Scleroderma Foundation 2019 Research Grant Awards

The Scleroderma Foundation leads the effort to ***discover*** the cause, ***understand*** the mechanism, and ***overcome*** scleroderma forever through its *Peer-Reviewed Grant Program* that follows the same merit-based system used by the National Institutes of Health (NIH). Additionally, the Foundation's *Early Career Investigator Workshop*, held every two years, provides up-and-coming scientists an opportunity to receive constructive feedback from leading scleroderma scientists.

The Foundation's leadership has been a contributing factor to the impressive growth in scleroderma research activity. Ongoing research has helped clarify and characterize the disease, which aids diagnosis and treatment. Innovative research has helped reduce mortality rates by identifying effective treatments, as in renal crisis. Basic science research is developing clues to genetic components and environmental factors of the disease. Fibrosis in scleroderma occurs in multiple organs, in contrast to other fibrotic diseases specific to a single organ. Scleroderma is a prototypic disease. An understanding of the broader impact of fibrosis in scleroderma could advance progress for all fibrotic diseases.

The Scleroderma Foundation's highly respected peer-review grant award process fosters quality science and attracts new investigators with seed money to develop data and test theories. As an example, the research careeers of world renowned scleroderma investigators **Dr. Maureen Mayes**, **Dr. John Varga**, and **Dr. Virginia Steen** started with Foundation funding, which also provides opportunities to established investigators to innovate.

The Scleroderma Foundation invests at least **$1 million** annually to fund approximately seven new multi-year projects, and has funded more than $20 million in scleroderma research projects over 21-year history. Investigations funded by the Foundation pursue leads in basic science investigations to discover the cause of the disease and to understand the disease processes, and in clinical research to they advance effectiveness of diagnostic, prognostic, and therapeutic methods and options.

The Foundation's primary areas of investigation: fibrosis, vascular system, and immune system. Trends in scleroderma research include single cell RNA sequencing, microbiome studies, repurposing existing FDA-approved medications, developing new therapies, and identifying biomarkers. The pipeline of potential treatments include antibodies blocking protein function to inhibit fibrosis; biomarkers that can predict patient response to specific medications; peptides (amino acids) affecting function of cells to impact fibrosis, vascular disease, or immune system; and synthetic compounds affecting function of cells to impact fibrosis, vascular disease, or immune system.

The Foundation's research grants are awarded in two categories. **New Investigators** are three-year awards given to test theories and develop data that in turn can form the basis of a larger NIH grant application. **Established Investigators** are two-year awards that provide funding to pursue innovative ideas. There are typically seven new awards each year that total $1 million dollars. In any given year, the Foundation is funding some 18 ongoing awards at different stages.

The Scleroderma Foundation is extremely pleased to announce the following seven awards for 2019. There are four established investigator awards and three new investigator awards. Each received high marks from the Peer-Review committee because they represent good scientific design and show promise for advancing the body of knowledge for scleroderma.

Primary Cilia: Finding the Missing Piece of the Puzzle for the Pathogenic Mechanism of Scleroderma

MARIA TEVES, M.S., Ph.D.,
Virginia Commonwealth University

Marta Marx Fund for the Eradication of Scleroderma

New Investigator $150,000, Three-Year Award

Systemic sclerosis (SSc) has a median survival of only 11 years and no effective treatment. It is estimated that 45% of all deaths are attributed to complications of fibrosis in multiple organs. Activation of specialized cells called myofibroblast represent the primary mechanism responsible for the pathogenesis of all forms of fibrosis. However, there is a gap in understanding how myofibroblast become activated and stay activated in SSc, hindering development of effective treatment. This proposal will investigate novel mechanisms that influence the activation of myofibroblast deriving in SSc. Results from this proposal will ultimately inform the development of entirely new approaches for fibrosis therapy. Additionally, a new cell-type specific spontaneous disease model for functional and translational studies of SSc will be generated, which will be useful for the scleroderma research community.

Role of EphB2 Receptor Tyrosine Kinase in Systemic Sclerosis

PATRICE N. MIMCHE, Ph.D.
University of Utah

Mark Flapan Award

New Investigator $150,000, Three-Year Award

Systemic sclerosis (SSc) is partly characterized by blood vessel damage and scarring of the skin and internal organs. The molecular factors responsible for the progression of this disease are incompletely understood. A feature of SSc is the exuberant deposition of extracellular matrix by activated fibroblasts. This proposal identifies the Eph receptors (Erythropoietin producing hepatocellular) specifically EphB2 and their corresponding Ephrin-B ligands as potential molecules responsible for the progression of fibrosis during SSc. Little is known about the role of EphB2 in SSc. This grant is designed to collect pilot data on the expression of soluble Ephrin-B ligands in patients with SSc (aim 1), identify the molecular mechanism of action of EphB2 during TGF-β signaling (aim 2), and to establish the ability of EphB2 to promote dermal fibrosis in vivo (aim 3). Our long-term goal is to validate EphB2 as a potential therapeutic target for the management of fibrosis during SSc.

Identifying the Mechanisms that Regulate Macrophage Activation in Systemic Sclerosis (SSc)

PATRICIA A. PIOLI, Ph.D.
Dartmouth College

Walter and Marie Coyle Research Grant

Established Investigator $150,000, Two-Year Award

Systemic sclerosis (SSc) is characterized by vascular injury, fibrosis, and inflammation, but little is known about the role that immune activation plays in disease development and/or progression. Our work has shown that white blood cells known as macrophages are activated in SSc and help induce fibrosis. However, the signals that cause SSc macrophage activation are unknown. We now demonstrate that soluble factors in SSc patients' plasma can cause macrophages from healthy control individuals to act like macrophages from SSc patients. Conversely, if SSc macrophages are cultured in healthy control plasma, they do not become activated. These results implicate soluble plasma-associated factors in SSc macrophage activation , and suggest that inhibition of these factors may ameliorate and/or eradicate fibrosis in SSc patients. Studies in this proposal will identify the signaling pathways and soluble mediators that induce SSc macrophage activation and will lay the foundation for development of targeted therapies for SSc.

Transcriptional Profiling of Inflammatory and Fibrotic Skin Signatures in Localized Scleroderma

KATHRYN S. TOROK, M.D.
University of Pittsburgh

Stephen I. Katz, M.D., Ph.D. Memorial Grant

Established Investigator $150,000, Two-Year Award

Inflammation occurs in active localized scleroderma (LS), a.k.a. morphea, skin lesions followed by fibrosis. LS is disfiguring and disabling especially if the disease begins during childhood and affects growth, resulting in reduced joint range of motion, uneven extremity size, and distorted facial features. Intervening during active LS is essential for minimizing fibrosis and long-term consequences for children. Identifying genes involved in inflammation and fibrosis using skin specimens may help us understand why LS occurs and help develop more effective therapies. This study utilizes innovative single cell RNA sequencing that will identify genes in individual cells turned on or off during LS inflammation or fibrosis in the skin. Findings will provide more insight into how LS develops and support development of more effective and targeted therapies, and improved outcomes in children and adults.

Understanding the Regulation of Procollagen Export from the ER During Fibrosis

CAROL ARTLETT, Ph.D.
Drexel University

Established Investigator $150,000, Two-Year Award

Scleroderma is a disease caused by the uncontrolled increase of collagen in the soft tissues. Its cause is unknown, and the progression of the disease is not well understood. Recently, we found more of the protein called TANGO1 SSc fibroblasts. This protein helps to control the export of procollagen out of a specialized organelle within the cell called the endoplasmic reticulum. The function of the endoplasmic reticulum is to fold the procollagen molecule properly and then to package it into parcel so that it can be secreted from the cell. It is a highly regulated process, which requires specific proteins. From our studies, we noted that the inhibition of two different pathways reduces collagen made by fibroblasts and we wonder if the two pathways are not as divergent as we originally thought. The goals of this application are to understand how these two different pathways contribute to collagen export from the endoplasmic reticulum in SSc and normal non-fibrotic fibroblasts. The results from these studies will help us to understand the process of fibrosis and may identify proteins that can be targeted to halt fibrosis.

Identification of Functional Regulatory Marks Involved in Monocyte Dysfunction in Scleroderma

PAULA RAMOS, Ph.D.
Medical University of South Carolina

New Investigator $150,000, Three-Year Award

Monocytes, a type of immune blood cell, are deregulated in scleroderma patients, showing elevated expression of several inflammatory genes. Nevertheless, the triggers responsible for their deregulation remain unclear. Epigenetic marks are DNA modifications that regulate gene expression. We believe that altered epigenetic marks in the monocytes from scleroderma patients are responsible for their elevated gene expression and deregulation. Specifically, we seek to investigate the role of one such mark, open chromatin, on monocyte deregulation in scleroderma patients. We will use state-of-the-art genomic approaches to identify altered chromatin marks and their effects on monocytes from scleroderma patients. Results from this study will contribute to a better understanding of the causes of scleroderma. Furthermore, the altered epigenetic marks identified in this study can become targets of novel approaches to regulate monocyte responses, which might lead to the development of novel therapeutic targets to control scleroderma.

The Role of Missense NCF1 Variant p.R90H in Scleroderma Pathogenesis

BETTY, P. TSAO, Ph.D.
Medical University of South Carolina

Established Investigator $150,000, Two-Year Award

Systemic sclerosis (SSc) is thought to develop in individuals who carry genetic risk factors upon environmental triggers. Our group has linked a single amino acid change in the gene NCF1 (p.R90H) resulting in reduced production of reactive oxygen species (ROS) to increased risk for the development of multiple autoimmune diseases. Here we propose to extend our genetic association between NCF1 variant and SSc in multiple ethnic populations, and to use a mouse model carrying the human risk gene variant to investigate the role of reduced ROS in scleroderma. We will compare the wild type and the homozygous risk gene littermates for the development of clinical manifestation of scleroderma in the presence of bleomycin, a cancer medication. The information gained from these experiments could help us understand underlying molecular and cellular mechanisms for the development of scleroderma that could lead to identify new druggable targets for treating scleroderma patients.