

The Search *for* a Cure

Since it was founded in 1998, the Scleroderma Foundation has devoted significant resources to funding research in hopes of finding new treatments and ultimately, the cure for scleroderma. Over the last 19 years, the Foundation has funded \$23 million in grants, which has been possible only through the generosity of donors who share the Foundation's commitment to the search for a cure. A goal we share with our donors is to fund and stimulate new research and ideas.

The research program is administered by the national office staff, and grants are approved by the Board of Directors. The foundation's Peer Review Research Committee is key to the program's success and reputation for rigorous review. The committee is composed of highly respected scleroderma medical experts who review, critique and rank all applications based on the National Institute of Health's ranking system. Only projects of significant scientific merit are funded.

Review criteria are highly disciplined and include the following:

- *Significance:* Does this study address an important issue related to systemic sclerosis?
- *Approach:* Are the design, methods and analyses appropriate and adequate?
- *Innovation:* Does the research represent new ideas and technologies?
- *Investigator:* Are reviewers properly trained and sufficiently experienced?
- *Environment:* Does the scientific environment contribute to its success?

The Scleroderma Foundation funds three different types of grants:

- *Early Career Investigator Grants* were designed for new investigators who hold faculty positions and wish to pursue careers in research related to scleroderma. This award is designed to mentor and encourage the next generation of researchers.



- *Established Investigator Grants* were created for promising, established investigators who wish to propose pilot studies with highly innovative themes related to the disease.
- *Multi-Center Collaborative Research Grants* were established to foster a more synergistic research community. This award supports two or more institutions to significantly enhance scleroderma research.

Three research grants are named in honor of individuals who have made major contributions to those affected by scleroderma:

- *The Marta Marx Fund for the Eradication of Scleroderma* was established by bequests from Ms. Marx and her brother, Rudolph Juhl. It is awarded annually to the researcher whose proposal achieves the highest score.
- *The Mark Flapan Award* is named in memory of the late psychologist and scleroderma patient.
- *The Marie Coyle Award* is named in honor of a founder of the Scleroderma Foundation who is also a scleroderma patient.
- *The Multi-Center Collaborative Grant* is funded by the generosity of the Kao Family Foundation.

We wish to acknowledge and thank the Scleroderma Foundation Tri-State Chapter for generously funding an additional research grant of \$150,000 through the foundation's Collaborative Research Grant Program.

The 2017 research grant awards honor the efforts of those who are making significant commitments to searching for a cure. The Scleroderma Foundation continues to foster and support education among scleroderma research programs internationally, and we are grateful to the donors who make this critical research program possible.

2017 Scleroderma Foundation Research Grant Awardees

SERGEI P. ATAMAS, M.D., PH.D. - BALTIMORE RESEARCH AND EDUCATION FOUNDATION



Project: Exploring the Antifibrotic Potential of SIRT7

Exaggerated deposition of scar tissue, also known as fibrosis, is a hallmark of scleroderma, and it is particularly dangerous when it occurs in the lungs. In other diseases, scarring can also be enhanced, especially in more aged patients. A current concept of scleroderma is that in this disease, the normal mechanisms of aging become activated prematurely, driving fibrosis. Recent research has shown that molecules known as sirtuins (SIRTs) are lost with age and that they may be lost in patients with scleroderma. There are seven different sirtuins, and most research is focused on SIRT1 and SIRT3. Our data reveal that a different sirtuin, SIRT7, may be involved in lung fibrosis in patients with scleroderma to an even greater extent than the other SIRTs. Moreover, we discovered that SIRT7 likely regulates fibrosis through mechanisms that are different from the action of other SIRTs. These observations make SIRT7 a unique and promising candidate for drug development, but the role of this molecule needs to be better understood. This project explores the mechanism of action of SIRT7 in fibroblasts from human lungs and in experimental mice. The results will lay the groundwork for future development of innovative therapies for patients with scleroderma.

ROBERT A. LAFYATIS, M.D. - UNIVERSITY OF PITTSBURGH



MARTA MARX FUND FOR THE ERADICATION OF SCLERODERMA

Project: Single Cell Transcription of Dermal Mesenchymal cells in Systemic Sclerosis

Fibrotic skin and lungs are major issues in the quality of life and in survival in patients with systemic sclerosis. Fibrosis is caused by cells, known as myofibroblasts, that produce collagen, a protein that scars the skin and lungs. We propose to apply a new technology called Drop-seq that will permit us to isolate individual cells from the skin and define the RNA molecules that encode the instructions for making collagen. Dropseq technology actually allows us to see levels of RNA encoding not just collagen, but all the ~20,000 genes active in cells. We will be able to see these RNA levels in not just the myofibroblasts, but also in other cells that may be contributing to the disease. By understanding the details of the different and unique RNA molecules made by these cells we will understand better what causes scarring in the skin of patients with systemic sclerosis. We hope that these insights into scarring in the skin will also be relevant to understanding scarring in the lungs. This understanding should also enable us insights into pathways that could be interrupted by drugs to block the scarring process.

AI P. LAM, M.D. - NORTHWESTERN UNIVERSITY**THE MARK FLAPAN AWARD****Project: Monocyte differentiation by Wnt/beta-catenin in signaling Systemic Sclerosis Interstitial Disease**

Systemic Sclerosis associated Interstitial Lung Disease (SSc-ILD) is a devastating disease due to abnormal repair of the lung tissue, leading to scarring. Wnt/ β -catenin is an important core pathway during normal human development and is abnormally altered in systemic sclerosis. Our lab was one of the first to link abnormal Wnt/ β -catenin pathway function to lung fibrosis. We demonstrated that genetic disruption of a key component of this pathway, Lrp5, is important in the process of lung scarring and that circulating white blood cells from pulmonary fibrosis patients showed abnormal high expression of Lrp5, correlating with worse disease outcome. Disruption of Lrp5/ β -catenin activity in mice affected differentiation of lung white blood cells called macrophages after lung injury, preventing proper healing. Macrophages, the most abundant immune cells in the lungs, are critical for fighting infection and clearing debris after lung injury. Our findings indicate that Wnt/ β -catenin signaling is important in maintaining macrophage maturation and function, which is an exciting new discovery. Our proposed studies will lead to the development of approaches to identify Systemic Sclerosis-ILD patients who are at risk for worsened prognosis and are most likely to benefit from Wnt/ β -catenin inhibitors that modify lung macrophage differentiation and resolve fibrosis.

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REBECCA LEE, M.D., M.S., PH.D. - MEDICAL UNIVERSITY OF SOUTH CAROLINA**Project: MSC Fate and Treatment of SSC: Modulation by Chemokine Receptor Antagonists**

When the skin (dermis) becomes thicker in scleroderma patients, the layer of fat below the skin becomes thinner. We believe that this is because there are precursor cells in the body (called MSCs) that are constantly faced with the choice of becoming dermis or fat and that in scleroderma, too many of the cells become dermis. Patients are already receiving experimental injections of MSCs grown from their own tissues with the hope that this will be beneficial. We think that this is a possible therapy, but that the MSCs need to be influenced to become fat and not dermis. We have determined that two pre-existing drugs (called MVC and AMD3100) developed to treat AIDS can influence MSCs to become fat and not dermis. In this proposal, we will work with MSCs in culture to understand the molecular mechanism through which MVC and AMD3100 act. We will also perform experiments in mice to determine whether when MSCs are influenced to become fat and not dermis, injection results in a very beneficial outcome. The results of these studies will be extremely beneficial for scleroderma patients if this approach reveals a novel effective therapy for the disease.

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THERESA LU, M.D., PH.D. - HOSPITAL FOR SPECIAL SURGERY



TRI-STATE CHAPTER RESEARCH GRANT

Project: Leptin receptor-expressing adipose-derived stromal cells as a putative skin-protective subpopulation

Scleroderma is a group of skin-fibrosing diseases for which there is no effective treatment. Adiposederived mesenchymal stromal/stem cells (ADSCs) reside in the fat under the skin. We have shown in scleroderma models that ADSCs die during fibrosis induction, suggesting that the loss of these regenerative and reparative cells contributes to fibrosis development. While ADSCs are maintained by unidentified mechanisms in normal skin, ADSCs remaining in fibrotic skin are maintained by dendritic cells and these ADSCs help preserve the function that is left in fibrotic skin. Supplying dendritic cell signals enhanced the survival and anti-fibrotic effects of therapeutically administered ADSCs. Thus, ADSCs have different mechanisms of survival in normal and fibrotic skin and have skin-protective functions during fibrosis induction, established fibrosis, and as a therapeutic modality. Our preliminary studies show that leptin receptor (LepR) marks an ADSC subpopulation that is preferentially lost with fibrosis induction, suggesting that LepR marks a skin-protective subpopulation. We will test the hypothesis that LepR+ ADSCs have skin-protective functions in fibrosis and are maintained by leptin and dendritic cells. Results will provide insights into the regulation and functions of ADSCs in skin fibrosis and suggest the strategy of enriching LepR+ cells to improve ADSC therapy for scleroderma.

BRADLEY A. MARON, M.D. - BRIGHAM AND WOMEN'S HOSPITAL



MARIE A. COYLE RESEARCH GRANT

Project: Endothelial exosomes regulate pulmonary vascular fibrosis in scleroderma

Pulmonary arterial hypertension is a major cause of hospitalization and death in patients affected by systemic sclerosis. Buildup of fibrous tissue, also known as collagen, in lung blood vessels is a hallmark feature of pulmonary arterial hypertension in systemic sclerosis. However, therapies to prevent or eliminate collagen in lung arteries do not exist currently. In this project, we use cutting edge mathematics, cell biology, and animal experiments to investigate the role of systemic sclerosis proteins that communicate between cells within lung arteries, increase collagen, and cause pulmonary arterial hypertension. Characterizing communication pathways between lung artery cells that regulate collagen is anticipated to identify novel treatment targets for improving clinical outcome of patients with pulmonary arterial hypertension in systemic sclerosis.

MONICA MUKHERJEE, M.D., M.P.H. - JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE



Project: Noninvasive Detection of Occult Right Ventricular Dysfunction in Systemic Sclerosis

Cardiac involvement in systemic sclerosis (SSc) patients is associated with high rates of morbidity and mortality, mostly due to the development of pulmonary hypertension and right-sided heart failure. Despite close monitoring, predicting cardiac involvement remains poor due to difficulties in imaging of the right heart. In this study, we seek to use novel noninvasive imaging techniques where we follow echocardiograms over time and apply a new

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method of measuring how segments of the right heart work to follow SSc patients for the development of right heart dysfunction. Identification of subclinical right ventricular dysfunction in SSc will have major clinical implications for the early detection and serial monitoring of right heart dysfunction and pulmonary hypertension. Further, utilizing novel imaging techniques of speckletracking echocardiography and stress imaging, we seek to understand how noninvasive parameters can be used to improve cardiovascular outcomes through the early detection of right ventricular myocardial dysfunction prior to the development of pulmonary hypertension.

MARIA TROJANOWSKA, PH.D. - BOSTON UNIVERSITY MEDICAL CENTER - THE KAO FAMILY FOUNDATION SCORE GRANT



THE KAO FAMILY FOUNDATION SCORE GRANT

Project: Preclinical assessment of dimethylfumarate (Tecfidera) as a novel therapeutic for SSC-PAH

Pulmonary arterial hypertension (PAH) is a life-threatening condition occurring primarily in patients with the limited form of scleroderma (lcSSc). Despite the existing treatment options, the disease remains poorly managed especially in patients with rapid progression and, therefore, there is a very high unmet need for alternative treatment options. This proposal seeks to lay the groundwork for an interventional study in SSc-PAH patients using the approved drug dimethylfumarate (Tecfidera®). We propose highly innovative studies to evaluate the therapeutic effects of DMF directly on pulmonary arteries derived from SSc patients undergoing lung transplant for end-stage PAH as well as in patient-derived cells (endothelial, smooth muscle and immune cells), representing the key cell types involved in development of PAH in parallel with in vivo novel mouse PAH models. This comprehensive and balanced analysis is possible through a powerful collaboration between the established scleroderma and pulmonary hypertension investigators at Boston University and the University of Pittsburgh with complementary resources and expertise in basic and translational clinical research.

PETER JOSEPH WERMUTH, PH.D. - THOMAS JEFFERSON UNIVERSITY



Project: Characterization of the molecular content and paracrine effects of profibrotic and antifibrotic microRNA in exosomes isolated from serum of Systemic Sclerosis

Systemic sclerosis (scleroderma, SSc) is a serious autoimmune disorder of unknown cause affecting the skin, internal organs and blood vessel walls. Three major factors may play a part SSc development: 1) small blood vessel damage and vessel wall fibrosis and thickening causing occlusion of small vessels in various organs, 2) prolonged immune system activation causing a build-up of immune cells (T-cells and macrophages) in affected tissues and 3) severe skin and organ fibrosis due to accumulation of excessive and abnormal scar tissue. Exosomes are small sacs of proteins, RNA or other cell contents surrounded by a membrane that are shed from most cells. This proposal seeks to identify molecular and functional differences between the exosomes found in the blood of normal donors and those found in the blood of donors with SSc or Raynaud Phenomenon that could be used as biomarkers to aid in the diagnosis of SSc or Raynaud Phenomenon and to analyze whether exosomes isolated from the serum of SSc patients can affect the normal fibroblasts that interact with them by rendering them similar to the diseased cells from SSc.