special Feature

SCLERODERMA RESEARCH

There is no cure for scleroderma…yet. For more than 20 years, the Scleroderma Foundation and its predecessors have fostered the careers of promising scientists and experienced investigators by funding their innovative research to discover the underlying cause, to understand the disease mechanism, to overcome the disabling symptoms, and to repair damaged tissue. Ultimately, a cure for scleroderma means doing all four. Pursuing that goal creates hope for the more than 300,000 individuals in the U.S.A. who have scleroderma, and for their families.

Attracting new, talented researchers has been a signature success of the Scleroderma Foundation throughout our history. The most noted researchers, Dr. Varga and Dr. Mayes, launched their careers with funding from the Scleroderma Foundation. Ironically, we are now losing experienced researchers to other areas of scientific investigation because of insufficient funding to sustain their scleroderma work. Even so, this is an exciting time for scleroderma research because there are so many promising avenues of study.

According to **Carol Feghali-Bostwick,Ph.D.**, one of the hallmarks of scleroderma is fibrosis. "Scleroderma is a multi-system disease where fibrosis can affect multiple organs at once. There are other diseases that are characterized by fibrosis of one organ at a time. Therefore, since fibrosis in scleroderma affects multiple organs, we consider scleroderma as a prototypic disease and solving the fibrosis puzzle in scleroderma will have broad impact on multiple other diseases as well." Scleroderma research has received increased interest from the pharmaceutical industry because of its impact on other diseases.

"Scleroderma is a rare disease, and funding for scleroderma research through traditional public channels, such as the National Institutes of Health (NIH), is more limited than for other diseases with larger populations," said **Virginia Steen, M.D.**, chair of the Foundation's Medical and Scientific Advisory Board. "The gap in available funding creates a far less promising environment for up and coming scientists. Receiving grants is the only way to establish and maintain a successful laboratory. It's only natural that researchers tend to follow the path of study that offers readily available dollars," said Steen.

The Foundation's *Research Grant Funding Program* has earned high respect by medical researchers and by government health agencies such as the NIH. The program is administered by the Scleroderma Foundation's Board of Directors and staff, and is guided by the Foundation's *Peer Research Review Committee* that is composed of scleroderma experts from around the country. They determine which proposals will be funded each year by reading, critiquing, and ranking all applications based on scientific merit using an unbiased and fair review process similar to that of the NIH.

Research funded by the Scleroderma Foundation is laying the building blocks of knowledge in successive courses to create pathways to the cure. Scientific research follows a time-tested process that checks itself and produces reliable results. It is necessarily methodical; however, no one who has scleroderma can afford to wait for the steady march of progress to conclude. History teaches us that the answers are out there. It's only a matter of time and resources before they are found. The only way to increase the speed of medical research is to do more of it. And, to accomplish that we need to raise a dramatically larger sum of money.

Great strides have been made over the last two decades, because of generous donors and dedicated investigators. These achievements are only the groundwork for far more promising studies. Without greater funding, recent successes might lie dormant for years before other researchers choose to continue that avenue of investigation. Some notable achievements include:

- *Since 2000, there have been 12,550 papers published in scleroderma research.*
- *The classification of systemic sclerosis in 1980 and in 2013 dramatically aided diagnosis and changed the way physicians treated patients.*
- *Development of better therapies and treatments that have reduced mortalities*

- *Understanding the balance between genetic and environmental factors*

The Scleroderma Foundation is very proud to announce its 2018 grant awards. On the following pages, we present summaries of the seven projects selected by the Peer Review Committee based on scientific merit. These remarkable investigations cover a range of subjects that will advance our knowledge of the disease mechanism, our understanding of the underlying causes of scleroderma, tools for doctors to use to treat symptoms more effectively, and potential new treatments.

Research topics include utilizing a new MRI technique to improve care by predicting the pace of lung scarring (fibrosis). Trying to understand the cause of the disease by determining how healthy skin cells turn into skin lesions. Developing data to form a basis for a future clinical trial of a potential treatment for lung fibrosis (scarring). Examining the interaction between infection and the immune system to discover new approaches to curing systemic sclerosis. Investigating the potential for treating scleroderma using nanoparticle therapy. And, laying groundwork to establish a standard for occupational therapy treatment of systemic sclerosis to improve movement of hands and arms.

Please join us in congratulating the grantees and wishing them great success in their work. We look forward to reading reporting on their progress and will keep you apprised of results.

Above and beyond the standard allocation of monies to research, Scleroderma Foundation chapters make voluntary pledges to the research effort thanks to the generosity of their donors.

CHAPTER VOLUNTARY RESEARCH FUND
2018 Grant Cycle Pledges

Delaware Valley:	$30,000
Georgia:	$40,000
Greater Chicago:	$110,000
Greater Washington, DC:	$5,000
Michigan:	$10,000
Minnesota:	$36,000
Missouri:	$17,000
New England:	$100,000
Ohio:	$55,000
Oklahoma:	$7,000
Oregon:	$32,000
Rocky Mountain:	$15,000
South Carolina:	$6,000
Southeast Florida:	$5,000
Southern California:	$26,201
Tennessee:	$8,000
Texas Bluebonnet:	$8,500
Tri-State:	$75,000
Washington Evergreen:	$15,000
TOTAL:	$600,701

2018 Research Grant Awardees

Sydney Butler Montesi, M.D.

SYDNEY BUTLER MONTESI, M.D., Massachusetts General Hospital
The Marta Marx Fund for the Eradication of Scleroderma

Project: Using Lung MRI to Assess Disease Activity in Scleroderma-Associated Interstitial Lung Disease
Interstitial Lung Disease occurs commonly in patients with scleroderma causing scarring in the lungs and shortness of breath. Lung scarring is the leading cause of death in scleroderma; however, how rapidly the scarring progresses varies greatly from person to person. We have developed a new type of MRI (Magnetic Resonance Imaging) scan that we believe will enable physicians to predict how rapidly lung scarring will progress in an individual patient. The goal of this project is test the ability of this MRI scan to predict the pace of lung scar progression in patients with scleroderma and hopefully improve their care.

2018 Research Grant Awardees

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RAFAEL CONTRERAS-GALINDO, PH.D., University of Michigan
The Mark Flapan Award

Project: Centromere Dysfunction in Scleroderma Fibroblasts

Patients with scleroderma produce antibodies that interact with the centromeres, the middle region of each chromosome. Centromere antibodies then could negatively affect chromosome function in scleroderma patients. We have seen that skin fibroblasts, the type of cell that thickens the skin in scleroderma lesions, have centromere defects and have abnormal numbers of chromosomes. This proposal will investigate the role of centromere defects in the development of skin and other organ lesions. Understanding how healthy skin cells turn into skin lesions is important to ascertaining the cause of scleroderma and to finding a cure to treat this devastating disease.

Rafael Contreras-Galindo, PH.D.

Giuseppina Alessandra Farina, M.D., Ph.D., Boston University
The Marie Coyle Award

Project: The Role of EBV in Monocyte Activation in Scleroderma Vasculopathy and Fibrosis

The mechanism that sustains the inflammation/fibrosis process in systemic sclerosis (SSc) is still unknown. We recently found that Epstein-Barr virus (EBV) is activated in SSc patients with increased expression of viral lytic-genes in peripheral blood mononuclear cells (PBMCs) and skin, suggesting that the active form of EBV infection (EBV replication) is ongoing in SSc. We hypothesize that EBV active infection in monocytes might directly contribute to the inflammatory and fibrotic process in SSc. Specifically, we think that distinct EBV viral component might activate SSc monocytes and contribute to the inflammation, while selected EBV-lytic genes might induce a strong profibrotic gene response in infected cells. We feel that understanding the interaction between EBV infection and scleroderma monocytes will shed a light on SSc pathogenesis and will help guide emerging new approaches to finding a cure for SSc patients.

Giuseppina Alessandra Farina, M.D., Ph.D.

DAN XU, Ph.D., Northwestern University

Project: A Novel Therapy for Scleroderma Using Biodegradable Nanoparticles

The proposed studies are designed to determine the clinical significance of MARCO expression by inflammatory monocytes and macrophages in lesional skin biopsies of scleroderma patients, as well as evaluating the effects and determining the mechanisms of carboxylated poly (lactic-co-glycolic acid) (PLGA) nanoparticle therapy that targets MARCO+ inflammatory monocytes and macrophages on the solution of skin fibrosis using mouse models of scleroderma. This work should provide critical pre-clinical information relevant to the translation and clinical testing of the PLGA nanoparticle platform for the treatment of scleroderma.

Dan Xu, Ph.D.

Richard M. Silver, M.D.

RICHARD M. SILVER, M.D., Medical University of South Carolina

Project: Antifibrotic Effects of Dabigatran in Scleroderma Patients

Fibrosis or scarring of the lung is one of the major complications in scleroderma. When lung fibrosis is severe, patients experience shortness of breath and may require supplemental oxygen. The mechanisms leading to lung fibrosis are not well understood, but studies suggest that the clotting factor thrombin may be an important factor. In studies conducted in our laboratory we have shown that a drug that blocks thrombin can improve lung fibrosis in an experimental animal model. Currently, we are testing the safety and tolerability of one such drug, dabigatran etexilate (ClinicalTrials.gov Identifier NCT02426229). We now propose to study the fibroblast cells and tissues obtained from patients before and after treatment with dabigatran etexilate in order to elucidate the anti-fibrotic effects and mechanisms of action of this drug, which is already FDA-approved for other indications. The results of the proposed studies will provide further rationale for a future clinical trial of thrombin blockade in scleroderma patients with lung fibrosis.

Matthew Robert Lammi, M.D., M.S.C.R.

MATTHEW ROBERT LAMMI, M.D., M.S.C.R.
Louisiana State University Health Sciences Center

Project: Novel Screening Strategy for Systemic Sclerosis-associated Pulmonary Hypertension Incorporating Endothelial Biomarkers

Pulmonary hypertension, an increase in pressure in the lung blood vessels, is the second leading cause of death in scleroderma. Despite efforts at early detection, it is usually discovered when the disease is very advanced. Therefore, we need better tests so that we can diagnose and treat earlier. One new strategy that we will investigate is whether blood tests that tell us about blood vessel damage (tested before and after exercise) can be used to identify scleroderma patients with pulmonary hypertension. If we are successful, this could lead to earlier identification of this devastating complication of scleroderma, hopefully improving health outcomes.

Susan Lynn Murphy, Sc.D., O.T.R.

SUSAN LYNN MURPHY, SC.D., O.T.R. University of Michigan

Project: Occupational Therapy Versus Home Exercise to Increase Upper Extremity Function in Individuals with Systemic Sclerosis: A Pilot Randomized Controlled Trial

Systemic sclerosis commonly causes skin tightening and restricts hand and arm movements critical to carrying out daily activities. Occupational therapy can improve hand and arm function; however, there is no standard evidence-based occupational therapy treatment for systemic sclerosis. Thus there is a critical need to test evidence-based strategies to advance occupational therapy treatment. This pilot randomized clinical trial tests an eight-week intervention involving in-person sessions plus home exercise via computer app compared to a condition of only home exercise via app. The long term goal is to improve consistency and quality of occupational therapy treatment for systemic sclerosis.