Though it is important to help patients who have scleroderma improve their quality of life, our ultimate hope is that someday a cure will be found. The core of the Scleroderma Foundation’s mission is to find a cause and cure for this mysterious and devastating disease by funding encouraging research projects. While a cure remains elusive, research funded by the Foundation, other nonprofit organizations and government agencies has increased the medical community’s understanding of many aspects of the disease and led to the development of promising new therapies.

Since the beginning of the organization, the Scleroderma Foundation’s Research Grant Program has been modeled after the National Institutes of Health (NIH) peer review process. According to Tracey O. Sperry, the Foundation’s director of development and research, the grant program solicits proposals from a large pool of scientific talent from all around the world. Many individuals who receive funding from the Foundation go on to receive much larger and longer-term grants from the NIH and Department of Defense. The Scleroderma Foundation only funds proposals that have scientific merit. Numerous researchers who have received funding have published their results in leading medical journals and at major medical conferences. The Research Grant Program has earned a unique place in the field of scleroderma research and is widely respected by government health agencies. It serves as a model for other patient advocacy organizations.

For 2015, the Foundation is pleased to announce it has provided for the first time in its history more than $2 million to fund research projects.

For the 2015 regular research grant program, seven proposals received funding, including work by four new investigators.

The Multi-Center Collaborative Research Grant (SCORE) is newly established to support and enhance collaborations between two or more Scleroderma Centers to advance significant research on scleroderma. Two exceptional proposals received funding for 2015.

The following pages include summaries of this year’s grant award winners.

The Scleroderma Foundation remains committed to funding quality research projects and making finding a cure a top priority. We will continue this long-standing tradition of making research our single largest budgeted expense. We continue to fortify our role as the leading private funder of scleroderma research.

The Foundation extends its appreciation to the many researchers and clinicians who have made the research program possible and to the many individuals, corporations and Foundation chapters that have contributed to raising funds for the research grant program.

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2015 AWARD WINNERS

The Marta Marx Fund for the Eradication of Scleroderma

This award is funded by bequests from Marta Marx, who had scleroderma, and her brother Rudolph Juhl.

Principal Investigator: Janet Elizabeth Pope, M.D., PhD, University of Western Ontario

Title: Development of Systemic Sclerosis Subset Classification

Systemic sclerosis (SSc, scleroderma) is an autoimmune disease that attacks the body and causes hardening of tissues leading to organ failure and death. SSc is heterogeneous; an ability to classify patients within different subsets could help for prognosis, appropriate screening for complications and enrolment into clinical trials. Currently, studies select subjects who meet the definition of a particular subset using outdated definitions, so patients may erroneously be excluded from treatment. This proposal will use innovative methods through an international collaboration to develop new classification criteria to identify distinct subsets of SSc patients. Current subsets will be identified and tested on how they perform for separating patients. The strengths and limitations of existing SSc subset criteria will be determined, allowing for identification of areas of improvement. Novel methods will identify homogeneous subsets of SSc patients using immunologic and clinical data. Multicriteria decision analysis will determine distinct SSc subsets, which will be validated in SSc patients. The new subset criteria will be compared to ones previously published to determine if they better identify distinct groups. Future clinical studies will use the subset criteria and reference this work. Scleroderma experts will collaborate who have successfully published overall SSc criteria that are internationally endorsed.

The Mark Flapan Award

This award honors the late psychologist and scleroderma patient.

Principal Investigator: John Varga, M.D., Northwestern University

Title: Reduced Anti-aging Sirtuin in Ssc: Disease Biomarker and Therapeutic Target

Scarring (fibrosis) in systemic sclerosis (SSc) results in progressive skin and lung damage. The mechanisms underlying fibrosis in SSc remain poorly understood, and effective therapies are lacking. Accelerated aging may be an important factor that contributes to scarring in SSc. We recently observed that a protein called SIRT1 is reduced in skin biopsies from some individuals with SSc. We hypothesize that low SIRT1 expression and function in SSc contributes to tissue scarring and may be potential targets for treatment. To test this hypothesis, we will i) examine if reduced SIRT1 expression or function in patients with SSc is associated with disease complications, such as pulmonary fibrosis, or progressive disease in the skin and lungs; ii) evaluate the role of SIRT1 in experimental models of scleroderma using genetically-engineered mice; and iii) determine the effects and mechanism of action of a novel drug that activates SIRT1. These studies will fill important gaps in current knowledge. Moreover, our proposal is timely and relevant, as drugs to activate SIRT1 are currently in advanced stage clinical trials and might have a potential role in the treatment of SSc.
2015 AWARD WINNERS

The Linda Lee Wells Memorial Research Grant

This award honors the memory of Ms. Wells, who lost her battle with scleroderma in 2008. Always appreciative of the work and mission of the Scleroderma Foundation, she left the organization a significant legacy through a charitable remainder trust.

Principal Investigator: Stephen Mathai, M.D., Johns Hopkins School of Medicine

Title: Validation of the Tricuspid Annular Plane Systolic Excursion as an Outcome Measure 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. While there are new therapies for PAH, patients with PAH related to SSc (SSc-PAH) do not respond as robustly as patients with other forms of PAH. However, the “poorer” response in SSc-PAH may reflect limitations of the measures chosen to assess response. Patients with SSc have comorbidities that impact functional ability and survival, two measures of response that are currently used in therapy trials for PAH. Thus, we propose to examine a simple echocardiographic measure of heart function, the tricuspid annular plan systolic excursion (TAPSE) as a potential outcome measure in SSc-PAH. We have previously shown that TAPSE predicts survival in SSc-PAH. However, neither the responsiveness, whether TAPSE changes with therapy, nor the minimal important difference (MID; the smallest change in TAPSE associated with an important change for a patient) is known; these features are essential to validate an outcome measure. We anticipate that TAPSE will prove to be a valid outcome measure and thus should be used to assess response to therapies in SSc-PAH.

The Marie A. Coyle Research Grant

This award is given in honor of Mrs. Coyle in recognition of her 41 years of full-time volunteer service to the organization and to the scleroderma community. Mrs. Coyle is a founder of the Scleroderma Foundation and also established the Foundation’s Peer Review Research Program.

Principal Investigator: David Lagares, Ph.D., Massachusetts General Hospital

Title: Matrix Stiffness Gradients and Fibroblast Durotaxis in Scleroderma Fibrosis Progression

Fibrosis, or scarring, in scleroderma contributes heavily to the suffering and deaths caused by this disease. Improved understanding of the activities of the cells in the body that cause fibrosis is needed in order to find effective scleroderma therapies. Tissue stiffening, or hardening, has traditionally been thought to simply be a result of fibrosis. We have recently found, however, that this stiffness also contributes to the worsening of fibrosis – that is, this stiffness also causes fibrosis to progress. We have also found that increases in tissue stiffness are not uniform in all areas of fibrotic tissues, such as the skin of scleroderma patients. Rather, these tissues have “hotspots” of particularly high stiffness, surrounded by areas of lower stiffness – the stiffness of fibrotic tissues rises and falls in “peaks” and “valles.” We have now found that the high stiffness of these hotspots attracts the cells – called fibroblasts – that are responsible for the scarring of fibrotic tissues. In this project, we seek to understand how these stiffness peaks attract fibroblasts. We believe that increased understanding of this process of attraction will allow us to design therapies to block it, and prevent fibrosis in scleroderma from worsening.
Scleroderma (also known as systemic sclerosis, SSc) is a disease that is characterized by skin thickening and damage to internal organs. The cause for SSc is not known, but there is an association between SSc and exposure to environmental factors such as chemicals, which suggest that the environment that we live in may play a role in predisposition to SSc. The environment can affect cell function by modifying the program that controls gene activity (known as the epigenetic program). Methylation of DNA is one of the epigenetic mechanisms that control gene expression. In this study, we will focus on understanding what went wrong in DNA methylation profile in SSc in two important cell types that play a role in pathogenesis of SSc, the fibroblasts and endothelial cells. We will characterize the changes in DNA methylation profile in SSc, compare the profile of fibrotic and non-fibrotic skin, and most importantly examine the effects of oxidation on DNA methylation profile of healthy fibroblasts and endothelial cells. The data that we will obtain from this study will generate hypotheses about the cause of SSc and identify novel pathways that may be useful therapeutic targets or prevention strategies for SSc in the future.

Compared with the skin, relatively little attention is given to subcutaneous tissue in scleroderma research. Subcutaneous tissue is very important, however, as it normally allows the skin to move relative to tendons and muscles. When loose connective tissue becomes fibrotic, adhesions form between the skin and underlying tissues that impair their range of motion. Although physical therapies commonly prescribe stretching exercises in scleroderma, there has been little research so far on the effects of stretching and little scientific knowledge about what exactly happens to the tissues when they are stretched. Consequently, we do not have even the beginning of a solid foundation that would allow us to determine the correct “dose” of stretching in individual patients. Our research group has previously shown that subcutaneous tissue cells play an important role in relaxing the tissue and that these cells become impaired in a mouse model of scleroderma. We have also shown that stretching helps connective tissue remain mobile after an injury. In this project, we propose to apply this knowledge to an animal model of scleroderma with the long-term goal of understanding how stretching can help preserve the mobility of subcutaneous connective tissue in scleroderma patients.
ELIZABETH VOLKMANN, M.D., M.S.

Principal Investigator: Elizabeth Volkmann, M.D., M.S., UCLA

Title: Long-Term Morbidity and Mortality Outcomes in Systemic Sclerosis-Related Interstitial Lung Disease

The number one cause of death in patients with systemic sclerosis (SSc) is interstitial lung disease (ILD). The purpose of this study is to increase our understanding of treatment outcomes for patients with SSc-ILD. Specifically, we will compare long-term survival of patients enrolled in the Scleroderma Lung Study (SLS) II. SLS II is a large, nationwide study comparing cyclophosphamide versus mycophenolate for SSc-ILD. We will determine which medication has the best survival rate five years after starting the medication. We will also determine whether certain patient characteristics, such as race or gender, and/or specific blood tests are associated with worse long-term survival. Knowing which characteristics are associated with worse survival can help physicians identify patients in the greatest need of aggressive treatment for SSc-ILD. We will also collect information on long-term patient functioning and disability. Together, this information will help us understand which medication (cyclophosphamide or mycophenolate) leads to the best long-term survival and quality of life. While most clinical trials look at treatment effects one-to-two years after starting a medication, it is important to understand how these medications affect patients in the long run. This is the first study to compare the long-term effects of cyclophosphamide and mycophenolate for SSc-ILD.

MULTI-CENTER COLLABORATIVE RESEARCH GRANTS (SCORE)

KAO FAMILY FOUNDATION GRANT

Project Title: Molecular Profiling in Early Diffuse Systemic Sclerosis

Collaborators: University of Texas Health Science Center at Houston, Northwestern University, University of Utah, University of Michigan Ann Arbor

Principal Investigators: Shervin Assassi, M.D., M.S.; Monique Hinchcliff, M.D., M.S.; Tracy Frech, M.D., M.S.; Dinesh Khanna, M.D., M.S.

Systemic sclerosis (SSc) is divided into diffuse and limited subtypes. Patients with diffuse involvement have more severe disease and worse outcomes. Skin and lung involvements are two prominent SSc features, but their courses are highly variable. Some patients have rapidly progressive disease, while others experience mild and stable involvement. The currently available clinical information is not sufficient to predict the course of skin and lung involvement in diffuse SSc. Prospective Registry in Systemic Sclerosis (PRESS) is an unprecedented collaboration among 10 specialized SSc centers in the U.S. to study patients with early diffuse SSc for understanding the clinical and molecular features of this severe and active subtype of SSc. Novel molecular techniques like microarrays and protein profiling are important tools for understanding the molecular basis of diseases. These technologies can also be used to identify molecules that predict the course of disease and treatment response. The goal of this proposal is to use these novel technologies in the PRESS cohort for developing better predictors of skin and lung disease progression in diffuse SSc. Reliable molecular predictors can aid physicians in their clinical decisions and ultimately lead to monitoring and treatment regimens that are tailored based on the individual patient’s needs.

Project Title: Molecular Characterization of Multi-Organ Involvement in Patients With Systemic Sclerosis

Collaborators: Stanford School of Medicine, University of California San Francisco, Dartmouth School of Medicine

Principal Investigators: Lorinda Chung, M.D., M.S.; Paul Wolters, M.D.; Michael Whitfield, Ph.D.; Howard Chang, M.D., Ph.D.

Systemic sclerosis (SSc) is an autoimmune disease that leads to scarring in many organ systems including the skin, blood vessels, gastrointestinal tract, and the lungs. Each patient is different with respect to clinical findings and disease severity. Several molecules have been identified in single organ systems to be important in causing scar tissue to develop in that organ, but no studies have looked at multiple organ systems to identify molecules that are important in causing scarring throughout the body. Our group has developed cutting-edge technologies that will be used to identify common molecules in several organ systems from the same SSc patient. Our study will lead to groundbreaking findings by identifying markers in the skin or blood that can be used to monitor lung and gastrointestinal disease in patients with SSc. We will also identify molecules that can be targeted for the development of new therapies to control and potentially cure the scarring affecting all organ systems in patients with SSc.