Although stiffening of the lungs is the leading cause of death in scleroderma and is more common and severe in African Americans than Caucasians, little is known about the cause(s) of this major health disparity. We find that African Americans may be predisposed toward developing scleroderma because white blood cells called monocytes from normal, healthy African Americans exhibit features associated only with monocytes from scleroderma patients in the Caucasian population. These features are the lack of a protein called caveolin-1 and the resulting enhanced ability of the cells to move toward a source of a protein called CXCL12. The movement of blood cells toward CXCL12 in scleroderma patients results in the inflammation and stiffening of damaged lung tissue.

These observations suggest that African Americans are predisposed to scleroderma due to the low level of caveolin-1 in their monocytes, and that restoring caveolin-1 using a drug we call CSD will be beneficial to scleroderma patients, particularly African Americans. We will test this idea by evaluating the effects of restoring caveolin-1 function in monocytes from African Americans and of depleting caveolin-1 from Caucasian monocytes.

**The Marta Marx Fund Eradication of Scleroderma Award**

Elena Tourkina, Ph.D., Medical University of South Carolina  
**Title of Project:** Caveolin-1 Deficiency Predisposes African Americans in SSc ILD

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**The Mark Flapan Award**

Ai (Anna) P. Lam, M.D., Northwestern Feinberg School of Medicine  
**Name of Project:** Selective Inhibition of Wnt/β-catenin Signaling as Novel Therapeutic Target for Systemic Sclerosis-Related Pulmonary Fibrosis

Systemic sclerosis is a progressive disease that causes fibrosis in the skin and other organs of the body. Presently, lung fibrosis is a major cause of morbidity and mortality for patients with systemic sclerosis. However, there is no effective treatment for pulmonary fibrosis. Emerging evidence indicates that embryonic development pathways may be implicated in fibrogenesis, in particular the Wnt/β-catenin pathway, which is critical in normal development and homeostasis.

Data from our lab indicates that this pathway is important in lung healing after injury. We hypothesize that abnormal Wnt/β-catenin signaling drives fibroblasts to become inappropriately activated. Thus, we propose to develop a transgenic mouse in which expression of the specific inhibitor of β-catenin signaling, ICAT, can be induced in fibroblasts after treatment with a chemical that causes pulmonary fibrosis.

In this proposal, we also will demonstrate the efficacy of a novel compound inhibitor of β-catenin signaling in the treatment of pulmonary fibrosis in mice. The results from this proposal will provide not only critical insights regarding the fundamental mechanisms of pulmonary fibrogenesis but also will provide the evidence to pursue the use of a novel Wnt/β-catenin compound for treating systemic sclerosis fibrotic lung disease.

**The Walter A. Coyle Memorial Grant by the New England Scleroderma Foundation Chapter**

Flavia V. Castelino, M.D., Massachusetts General Hospital  
**Name of Project:** Role of Lysophosphatidic Acid and Its Receptor LPA1 in Scleroderma Dermal Fibrosis

Our long-term goal is to study the underlying cause for skin thickening, or fibrosis in scleroderma. The research goal is to study whether natural chemicals in the body, called lysophospholipids, contribute to fibrosis in scleroderma.

We plan to study the natural chemical, lysophosphatidic acid (LPA) and its receptor, LPA1 (the molecule on cells that recognizes and responds to LPA), to determine how this pathway drives skin thickening in scleroderma. We will evaluate how this pathway interacts with transforming growth factor-β (TGF-β) another key natural chemical that has been implicated in the development of fibrosis in scleroderma. Additionally, we will look at the levels of these mediators of fibrosis in the blood and skin of scleroderma patients.
Eric Lorne Greidinger, M.D., Miller School of Medicine University of Miami
Name of Project: Antigenic Targets of Autoimmunity-Associated Raynaud Phenomenon

In scleroderma patients, the fingers and toes become overly sensitive to the cold, and patients develop frostbite-like pain and even gangrene. This process, Raynaud Phenomenon (RP), occurs in several autoimmune conditions but to date has not itself been shown to be due to the immune system.

Using mice, we have developed evidence that certain antibodies are capable of inducing a Raynaud-like condition. We have characterized these antibodies and found that they recognize and kill blood vessel lining cells. We find similar antibodies in patients who have RP, and we have shown that patients are also able to induce Raynaud-like lesions in our mice. We have now identified what we hypothesize is a specific target of these antibodies, a protein called K10.

To test whether these antibodies can cause RP, we propose to see whether monoclonal anti-K10 antibodies also induce the Raynaud’s when injected into mice. Second, we propose to measure anti-K10 antibodies in patients’ blood and show that the patients with RP are the ones who have these antibodies. Worse RP occurs with higher antibody levels.

Heidi Jacobe, M.D., University of Texas at Dallas
Name of Project: Something New Under the Sun: A Randomized, Double Blinded, Controlled Trial of UVA1 Phototherapy in Localized Scleroderma

Localized scleroderma (LS), or morphea, causes skin hardening. Patients with LS have itching, pain, decreased limb growth or inability to move their joints. Only one treatment regimen has proven benefit in LS, the immunosuppressive medications methotrexate and prednisone. Both have significant side effects. In our University of Texas Southwestern Morphea Registry, with more than 300 patients, only 23 percent are candidates for methotrexate and prednisone. Other, safer treatment options are needed.

Similar to published reports, we have noted significant improvement in LS after UVA1 phototherapy. UVA1 phototherapy avoids the side effects of immune suppressive medications. However, there are no randomized, controlled trials investigating UVA1 phototherapy. Our center, the only one that houses a federally funded registry for LS patients and an established UVA1 phototherapy center, is uniquely poised to conduct this trial.

We propose a randomized, controlled, blinded trial to determine the effect of UVA1 phototherapy in LS. We will also characterize the changes in the skin before and after treatment via microarray technology to determine the molecular basis of response to UVA1 phototherapy. This will provide a much-needed therapeutic option for patients with LS and lay groundwork for further research.

Thomas M. Ruenger, M.D., Ph.D., Boston University
Name of Project: Intracellular Degradation of Collagen in Scleroderma

A main symptom of scleroderma is skin hardening. The exact pathogenesis of this skin hardening remains unknown, but is thought to result from an imbalance between production and removal of proteins (mainly collagen) between cells. The current understanding of mechanisms by which collagen is removed from the space between cells focuses on protein-cleaving enzymes (proteases) that cells secrete into the space between them.

We recently identified a novel pathway in which cells internalize collagen and then degrade it. Our observation that several patients that were treated with an inhibitor of the intracellular protease cathepsin K developed morphea (circumscribed scleroderma) indicates that a disruption of collagen-degradation within cells can indeed increase the protein content in the space outside of cells. We propose that a disruption of intracellular degradation of extracellular collagen can result in skin hardening and that induction of this process can counteract and/or reverse it. Furthermore, we also aim to identify small molecules that can induce cathepsin K, as a first step to develop a new therapeutic avenue to reverse skin hardening in scleroderma.
Other Research Grant Recipients

Richard M. Silver, M.D., Medical University of South Carolina
Name of Project: Molecular Basis for Therapeutic Interventions in SSc-ILD by Inhibition of Thrombin

Scleroderma-associated interstitial lung disease (SSc-ILD) is an irreversible and progressive disease process with unresolved pathogenesis and inadequate responsiveness to currently available therapies that may lead to respiratory failure and death. We recently demonstrated that a direct thrombin inhibitor, dabigatran etexilate, has marked anti-fibrotic effects in a mouse model of ILD and merits consideration as a potential drug for the treatment of SSc-ILD. However, the mechanisms underlying the anti-fibrotic effects of thrombin inhibition remain obscure.

The goal of this project is to provide the molecular basis for a novel therapeutic intervention in SSc-ILD based upon the inhibition of thrombin and thrombin-induced signaling pathways. The completion of our project will help clarify how early lung injury in scleroderma patients followed by thrombin activation leads to the development of pulmonary fibrosis. Furthermore, it will provide fundamental, preclinical information about the feasibility and efficacy of a novel direct thrombin inhibitor, dabigatran etexilate, as a new therapeutic approach for the treatment of SSc-ILD. A better understanding of the mechanisms underpinning thrombin inhibition may ultimately lead to more effective and safer means of treatment for patients with SSc-ILD.

Barbara D. Smith, B.S., M.A., Ph.D., Boston University School of Medicine
Name of Project: Collagen Regulation in Systemic Sclerosis

Fibrosis, or excessive scarring, is a progressive deposition of excess collagen-rich extracellular matrix produced by activated myofibroblasts. This fibrosis occurs in scleroderma, leading to organ failure with no effective therapy. During progression of fibrosis, fibroblasts are activated and become myofibroblasts that continue to divide and produce excess amounts of collagen-rich extracellular matrix.

Based on our preliminary data, we hypothesize that a protein called myocardin-related transcription factor A (MRTFA) plays a central role in activation and perpetuation of myofibroblast deposition of collagen in SSC. The specific aims are to investigate the function of MRTFA in normal and SSC fibroblasts by adding more MRTFA to cells or depleting the active MRTFA and to examine the mechanism by which MRTFA alters collagen expression.

New Research Grant Encourages Collaboration

The Scleroderma Foundation’s National Board of Directors approved a new research grant initiative to enhance its ongoing commitment to scleroderma research. The “Multi-Center Collaborative Research Grant” would support and enhance collaboration between two or more scleroderma centers. Fostering greater collaboration between experts and institutions will help to advance research by bringing talented experts together to share knowledge and leverage the strengths of multiple centers and facilities.

Scleroderma centers must meet the following guidelines to be eligible for funding:

- Demonstrate expertise in scleroderma including clinical and lab-based research.
- Conduct clinical trials in scleroderma.
- Conduct educational activities about scleroderma and provide information about the advances in care and treatments of the disease to health care professionals and the public.

The Foundation hopes to launch this new research grant opportunity next year as an addition to its current peer-review research program. We are working with the Foundation’s Medical Advisory Board to finalize the proposal, application and review process. If you would like to learn more about this or other research funded by the Scleroderma Foundation, or if you wish to support research, please contact Robert Riggs at rriggs@scleroderma.org, or call the Foundation at (800) 722-4673.