Scleroderma
RESEARCH FOUNDATION

SPRING MATCH

Summary Progress Report of Spring Research Challenge Projects: 2014-18

Below please find the 2019 SRF Spring Research Challenge progress report highlighting exciting advances in prior years' Challenge Projects.

SRF Research Program

The SRF Research Program fosters and sustains a community of collaborative and deeply committed researchers working to advance scleroderma research. We are diligent in our efforts to recruit scientific and clinical thought leaders to the field. Our research program is comprised of basic and translational research projects aimed at identifying relevant cell types and biological pathways in order to find points of therapeutic intervention, as well as large-scale projects that gather data from thousands of patients in order to better subtype scleroderma and target therapies (such as The GRASP Project and the CONQUER Registry). The SRF also has a long history of developing and enhancing Scleroderma Centers of Excellence. The SRF's esteemed Scientific Advisory Board ensures that our research program continues to be both focused and nimble. Our goal, and deepest hope, is to accelerate the SRF's ability to fund outstanding research in our search for a cure.

2014 Project: *Preventing and Reversing Fibrosis*

Hal Dietz, MD

Victor A. McKusick Professor of Genetics, Johns Hopkins University School of Medicine; Investigator, Howard Hughes Medical Institute

This groundbreaking project, originally published in *Nature*, made a key discovery that could have broad implications for future scleroderma therapies. SRF-funded investigator Dr. Hal Dietz and his team at Johns Hopkins demonstrated that modulating certain receptors that mediate the attachment between a cell and its surroundings can stop scleroderma's signature fibrosis (scarring) in a model of scleroderma and, more strikingly, established fibrosis can actually be reversed by the same agents. Investigating these biological pathways and how the immune system is stimulated in fibrosis will help scientists discover the underlying mechanism(s) driving scleroderma's onset and progression.

Update

- Dr. Dietz's research insights were the impetus for the creation of a venture-backed biotech company focused on fibrotic diseases, Blade Therapeutics, which has raised over $50M of venture capital funding.
- This research has identified additional therapeutic targets that potentially can be modulated as anti-fibrotic therapies.
- Blade Therapeutics plans to advance its lead drug candidate into clinical trials in 2019.

2015 Project: *Cancer and Scleroderma*

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Bert Vogelstein, MD
Clayton Professor of Oncology and Pathology, Johns Hopkins University; Investigator, Howard Hughes Medical Institute

Fred Wigley, MD
Martha McCrory Professor of Medicine, Associate Director of the Division of Rheumatology, Director of the Johns Hopkins Scleroderma Center, Johns Hopkins University

The results from this multi-year project were published in *Science* in 2014. In their initial findings, the Rosen, Vogelstein and Wigley groups identified the role of cancer as an initiator of autoimmunity in a group of scleroderma patients having autoantibodies against RNA polymerase III protein (RNApol3) and in whom cancer and scleroderma occurred within a two-year period.

Update

- Since the initial publication, the group has identified additional subgroups of scleroderma patients having a connection with cancer, including a subgroup of patients that have autoantibodies to an essential cell protein called RNPC3. This discovery has important clinical implications, and it provides insights into scleroderma disease processes.
- Together with Drs. Livia Casciola-Rosen and Ami Shah at Johns Hopkins, the group has several recent publications regarding the scleroderma-cancer link and how cancer risk varies for patients with different autoantibody profiles.
- Based on this SRF-supported research, the group recently received a 5-year NIH grant totaling over $2.0 million to expand their studies. The SRF continues to support additional research avenues related to this paradigm-shifting discovery.

2016 Project: *ATAC-seq Technology and Epigenetics of Scleroderma*

Howard Chang, MD, PhD
Virginia and D.K. Ludwig Professor of Cancer Genomics and of Genetics, Director, NIH Center of Excellence in Genomic Science: Center for Personal Dynamic Regulome, Stanford University; Investigator, Howard Hughes Medical Institute

Dr. Howard Chang and his colleagues at Stanford have developed a truly revolutionary technology, ATAC-seq, that enables analysis at the single cell level of the on/off status of every gene as well as the specific controls responsible for the gene's status. Thus, ATAC-seq analysis of cells from a patient can help researchers to understand the characteristics and behavior of any patient's cells and, importantly, how this may differ from normal cells. ATAC-seq not only reduces the cost and time required for this type of analysis, but also the technology allows researchers to sample living cells in real time from a small sample of blood or tissue, and it is a million-fold more sensitive than previous methods. This discovery has broad implications for investigating a number of diseases, including scleroderma. Dr. Chang's group is using ATAC-seq to examine why certain cells may deviate from normal behavior in scleroderma and to try to understand whether this happens more frequently in females, possibly leading to the preponderance of women among scleroderma patients.

Update

- Dr. Chang was recognized for his discovery of long noncoding RNAs and invention of genomic technologies, including ATAC-seq, with the 2018 National Academy of Sciences Award in Molecular Biology. The National Academy of Sciences Award in Molecular Biology has a rich history of honoring premier scientists making groundbreaking discoveries in science and medicine— fourteen prior recipients went on to become Nobel laureates.
- Dr. Chang is additionally working on a new genomics study focused on identical twin pairs (in which one twin has scleroderma and the other does not). This project takes advantage of the fact that identical twins have the same genes, but over their lifetimes, different environmental insults (such as illness, chemical exposures, etc.) alter their DNA in distinct ways. Dr. Chang will employ the ATAC-seq tool to explore these environmentally–induced changes to DNA in order to help pinpoint disease-causing biological pathways in scleroderma.

2017 Project: *Genome Research in African American Scleroderma Patients (GRASP)*

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Dan Kastner, MD, PhD
Scientific Director, Intramural Program at the National Human Genome Research Institute

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The GRASP Project is led by researchers at the National Human Genome Research Institute at the NIH, Johns Hopkins University and the University of California, San Francisco in partnership with the SRF and a consortium of clinicians from 21 additional major U.S. academic institutions. This large-scale project arose from a collaboration initiated at the annual SRF Scientific Workshop, and it aims to discover new genetic variants that may underlie the increased incidence and earlier age of onset of scleroderma in African Americans, as well as the predisposition for more severe clinical manifestations. GRASP will provide new insights into scleroderma-specific disease mechanisms that will hopefully lead to the identification of novel therapies for all patients.

Update

- First publication in *Medicine* described the clinical characteristics of the first 1,009 patients enrolled in the project, providing valuable information for clinicians treating African American patients.
- Initial findings were promising, with several novel candidate genes emerging out of the analysis and additional publications in press.
- The GRASP data has become a resource for the scleroderma research community, amplifying its value through numerous collaborations.

2018 Project: *The Scleroderma Lung Disease Trajectory Study*

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Scott Zeger, PhD
Professor, Johns Hopkins University Bloomberg School of Public Health

In the Scleroderma Lung Disease Trajectory Study, JHU researchers are analyzing long-term clinical data on thousands of patients collected over the past 30+ years at the Johns Hopkins Scleroderma Center and employing cutting-edge bioinformatics capabilities to identify additional scleroderma autoantibodies and more precisely define scleroderma subgroups. By improving our ability to identify and understand scleroderma subgroups, the Scleroderma Lung Disease Trajectory Study will be an important step toward more personalized medicine for scleroderma patients and improve our ability to conduct research studies and scleroderma clinical trials.

Update

- The group has developed valuable tools for clinicians and scientists to subset scleroderma patients based on their disease trajectories.
- The research group has developed novel measures of patients' multi-organ symptoms to improve clinical monitoring and established that these measures can predict future clinical events and, additionally, that they can be employed to guide treatment decisions.