2018 ANNUAL REPORT

Scleroderma
RESEARCH FOUNDATION

ADVOCATES FOR A CURE

The Scleroderma Research Foundation (SRF) is the nation's leading nonprofit investor in medical research to find improved therapies and a cure for scleroderma. Our progress is entirely dependent upon charitable gifts from generous people like you.

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Sharon L. Monsky, 1953-2002

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Dear Friends,

From basic research to pharmaceutical pursuit of novel drugs for scleroderma (and its associated organ-specific impact), 2018 has been an especially significant year for the scientific community. The progress of the SRF's funded programs has been particularly substantial, and we continue to have an impact that belies the size of our investment.

Our most noteworthy achievement this year has been the launch of CONQUER, a first-of-its-kind longitudinal registry that will collect and chart the trajectory of disease burden across thousands of scleroderma patients. CONQUER, which stands for "COllaborative National QUality and Efficacy Registry," recently began enrolling scleroderma patients through a network of 12 founding sites across the United States. The project aims to determine which disease features are associated with or predict outcomes, identify patients requiring early/aggressive intervention—as well as those to watch—and, among other goals, drive more personalized and effective therapy for patients. The enthusiasm across the research and clinical community for this effort is palpable. Not only will the resultant database be the gold standard, but the effort involved in assembling the network will in and of itself reap many benefits. We envision that this network will be the core for running trials to examine better therapeutic strategies, for example. We are seeking support from a wide range of sources, including a range of industry partners. Their willingness to participate has been gratifying, and the opportunity to build a public-private partnership is also an exciting extension of CONQUER. In short, I am confident that the results of such a widespread, comprehensive study will make a positive impact in the scleroderma research field.

CONQUER is not the only example of the collaborative, community-wide research that the SRF has funded and actively fostered: Funded Investigators Kastner, Wigley, and Boin have continued to advance the effort on Genome Research in African American Scleroderma Patients (GRASP). GRASP is a collaboration among 23 different scleroderma centers across the country and is anchored by DNA analysis at the National Human Genome Research Institute, and clinical data analysis at Johns Hopkins University School of Medicine. The project has sequenced DNA and collected clinical data on over 1300 African-American scleroderma patients. In the four years since we began GRASP, it has become a scleroderma community research resource, and is on track to substantially impact scleroderma research as it currently stands. A number of publications have already been released as a result of the study, including a clinical overview by Dr. Nadia Morgan, et. al.

Finally, the SRF's commitment to finding a cure encompasses not only funding the most promising scleroderma research, but also ensuring that that research is developed and turned into usable treatments and therapies for scleroderma patients. With that in mind, we are excited to announce that the drug derived from

the work of Dr. Hal Dietz on inhibiting, preventing, and even reversing fibrosis–which formed the basis of the biopharmaceutical company Blade Therapeutics–has entered into clinical trials and will begin dosing patients in phase 2 trials early in 2019. We remain extremely optimistic that Blade's efforts will prove out the novel disease mechanism identified by Dr. Dietz, who is funded by the SRF. If successful, the trial would lead to a new therapy, which we hope will be the first ever disease-modifying therapy.

The SRF is still a small team–in addition to our Board of Directors, Scientific Advisory Board, and Funded Investigators, our San Francisco office is comprised of five tireless employees who are committed to our efforts. We are small; but we are mighty. We have achieved so much with the help of our partners, volunteers, events, and, you, our generous donors. On behalf of all of us, I would like to thank you for all of your support–it is due to your contributions that we have arrived where we are today, and that we are able to continue to move onward and upward.

Sincerely,

Luke Evnin, PhD
Chairman

OUR MISSION
To Find, Fund, and Facilitate the Most Promising Scleroderma Research

The Scleroderma Research Foundation (SRF) is America's leading nonprofit investor in scleroderma research, and is laser-focused on finding a cu e for this rare and often deadly disease.

Because scleroderma affects fewer than 100,000 people in the U.S., it does not have the profile of other, better-known and more prevalent illnesses. But a cure for scleroderma may hold the key to cures and better outcomes for a host of other diseases.

In 1987, scleroderma patient Sharon Monsky founded the SRF with the belief that funding medical research was the best way to give hope to those living with the disease. For those who knew Sharon, it's no surprise that her passion, commitment, and ability to galvanize people toward a noble cause has gained continued momentum and success under the thoughtful leadership she inspired at the SRF. As Sharon once said, "I could organize a support group to help people in my community living with scleroderma or I could establish an organization that would bring the best of science and technology together in an effort to discover better treatments and a cure for people everywhere living with scleroderma. It wasn't easy, but I chose the latter." Though Sharon passed away from the complications of scleroderma in 2002, her mission and vision live on today.

The SRF research program seeks to deepen knowledge and understanding of this life-threatening condition, by facilitating research and collaboration among the world's top scientists and medical institutions. Funded projects are allocated in three broad categories: clinical, translational and basic research. While 20% of the SRF's budget is devoted to clinical endeavors, including developing and sustaining support for Clinical Centers of Excellence, 80% supports basic and translational research projects, such as developing more predictive animal models, biomarker development, defining relevant biological pathways, and the application of new technologies to better understand the underlying causes of scleroderma.

OUR VISION
A World Without Scleroderma

Sharon envisioned a future where those living with scleroderma would have access to new treatments, and ultimately, a cure. She proudly stated that the SRF was "in business to go out of business." Today, over 30 years later, we are accelerating our understanding of scleroderma through our innovative research program. Our focus on medical research enables gifted researchers and clinicians to explore promising ideas, share encouraging findings, and ta e us closer to our goal every day.

WE BELIEVE IN COLLABORATION
We Unite Both Exceptional Scientists and Sciences

Fostering collaboration is a core principle of the SRF. We unite exceptional scientists and clinicians across many disciplines in order to advance our understanding of scleroderma. We also partner with industry and academia, investigating scleroderma through a rigorous peer-reviewed research program. We believe that creating an environment that encourages open lines of communication within a multidisciplinary community maximizes efficie y, improves the quality of results, and leads to new avenues of exploration. Through our yearly Scientific Workshop, we bring together leading researchers in widely varying fields to discuss their work and move toward a cure for scleroderma.

WE PROMOTE DISCOVERY
Research is the Key

The SRF research program devotes the majority (84%) of its research budget to long-term fundamental discoveries in basic, translational, and clinical projects. The SRF actively recruits gifted scientists to work on scleroderma, seeks novel projects to fund, and encourages collaboration and leveraging of resources. To read about how Board Member and surgeon-physician Eric Kau thinks this will effect scleroderma treatment, turn to his feature on page 47.

WE ADVOCATE FOR COMPREHENSIVE CARE
Connecting Patients and Physicians with Clinical Excellence

Outside of the laboratory, SRF resources develop and sustain Scleroderma Centers of Excellence, where patients receive the most comprehensive care from clinicians specialized to treat scleroderma and its complications. Within these Centers, clinicians partner with front-line scientists to advance scleroderma research. The centers also advance the scleroderma Standards of Care, and are training grounds for the next generation of scleroderma clinicians.

ABOUT SCLERODERMA

One of the deadliest of all rheumatic disorders, scleroderma is chronic, complex and debilitating. Scleroderma begins as an autoimmune attack and eventually causes devastating fib osis or vascular damage. Depending on the subtype of illness (localized, linear, systemic limited, systemic diffus), scleroderma can damage multiple organ systems.

WHO DEVELOPS SCLERODERMA?

Anyone can develop scleroderma. Although it is generally more common in women, the disease affects people of any race, age or gender, anywhere in the world. The symptoms and severity of scleroderma vary greatly, and the course of the disease is often unpredictable. Because of its rarity, many healthcare professionals have little experience in recognizing its symptoms and confirming a diagnosis. One of the goals of the SRF is to bring greater awareness to the general public and educate health- care professionals to increase understanding.

WHO IS AT RISK?

The cause of scleroderma is still unknown, and there is likely no single risk factor. Scientists are working to understand what biological factors contribute to scleroderma pathogenesis. A number of scientific studies suggest that a combination of genetic and environmental factors may trigger the disease. The most striking statistics show that women in their childbearing years outnumber men with scleroderma by about four-to-one.

CAN SCLERODERMA BE TREATED?

There are a number of treatments available to address the various complications associated with scleroderma. None of these are a cure— they are designed to treat symptoms of the disease. Several different classes of drugs are currently approved, either in the U.S. or Europe, to treat these complications. The primary mission of the SRF is to find, fund, and facilitate the most promising research that will result in improved therapies, and ultimately a cure for patients.

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SCIENTIFIC ADVISORY BOARD

The individuals on the SRF's Scientific Advisory Board (SAB) are some of the world's most honored and distinguished scientists, and give their time and insights freely to the SRF's research endeavors. These renowned researchers guide the Foundation's research program, evaluate research proposals, and make funding recommendations.

Drawn from various medical fields–including genetics, autoimmunity, molecular biology, vascular biology, dermatology and inflamm tory disease–Scientific Advisory Board members' expertise and philosophy of collaboration drives the SRF research program forward by prompting the discovery of connections between different scientific fields and focuses. The magnitude of their combined depths of knowledge, coupled with an unwavering commitment to the mission, nurtures an environment where new questions are raised, probed and examined, catalyzing research that fosters progress towards a cure.

Each year, the SAB convenes and leads the SRF Scientific Workshop, which brings together thought leaders from diverse backgrounds, to exchange information and ideas. The results of this intensive work are new alliances and ideas that further develop the roadmap for vital research, which will lead to better treatments and ultimately to a cure for scleroderma.

Their deep personal commitment, independent judgment and ability to foster high-level scientific investigation is crucial to the SRF's vision: a future where those living with scleroderma have access to new treatments—and ultimately, a cure.

Bruce Alberts, PhD
Chairman of the Scientific Advisory Board
University of California San Francisco
President Emeritus, National Academy of Sciences

Dr. Alberts is recognized around the world for his work in the fields of bio-chemistry and molecular biology. As a scientist and educator, he served two terms as President of the National Academy of Sciences (NAS) (1993-2005), and was also Chairman of the National Research Council at the NAS. He is one of the original authors of *Molecular Biology of the Cell,* now in its sixth edition and the standard cell biology textbook in most universities. He served as Editor-in-chief of the leading scientific journal, *Science*, from 2009-2013. Now in his third decade of educating future scientists, he is the Chancellor's Leadership Chair in Biochemistry and Biophysics for Science and Education at the University of California, San Francisco (UCSF). Beginning in 2000 and through 2009, he served as the Co-Chair of the In-ter-Academy Council, an international organization established to provide scientific counsel to the world and governed by the presidents of 15 National Academies of Sciences. In 2009, Dr. Alberts was one of three leaders appointed to serve as the nation's first scientific envoy by then Secretary of State Hillary Clinton. In 2014, he was awarded the National Medal of Science by President Barack Obama. In 2016, he received the Lasker-Koshland Special Achievement Award in Medical Sciences for discoveries in DNA replication and leadership in science and education.
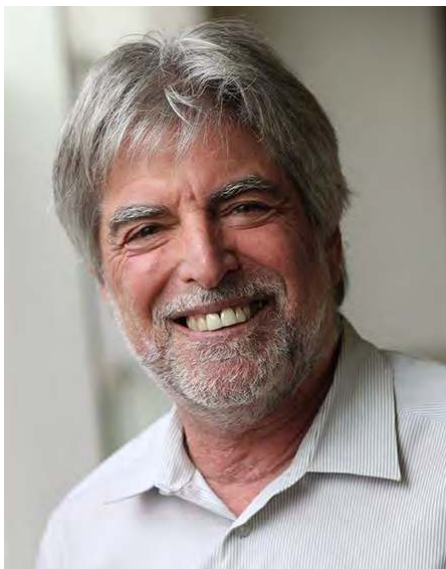
Jeffrey A. Bluestone, PhD
University of California, San Francisco

As an international scientist and leader in the field of immunotherapy, Dr. Bluestone has helped characterize the body's immune response on a molecular level, and has catalyzed recent progress in stem cell research, islet cell transplantation, and immune tolerance therapies—studies that have been translated into drugs to treat human disease. He joined the University of California, San Francisco (UCSF) faculty in 2000, and holds the A.W. and Mary Margaret Clausen Distinguished Professorship in Metabolism and Endocrinology. He is also Director of the Hormone Research Institute. In March 2010, he was appointed Executive Vice Chancellor and Provost to serve as Chief Academic Officer guiding the research and academic enterprise at UCSF, where he advanced the campus's priorities in collaboration with the Chancellor and campus leadership. Dr. Bluestone has also served as the director of the UCSF Diabetes Center, where he emphasized translating basic research in both type 1 and type 2 diabetes into improved patient therapies. He founded and directed the Immune Tolerance Network, a consortium of more than 1,000 of the world's leading scientific researchers and clinical specialists. In 2016, he was named President and CEO of the Parker Institute for Cancer Immunotherapy.

David Botstein, PhD
California Life Company (Calico)

Dr. Botstein is a renowned geneticist, educator, and pioneer of the Human Genome Project. He currently serves as the Chief Scientific Officer of Calico, a research and development biotech company established in 2013 by Google, with the goal of tackling the aging process. Dr. Botstein served as the Director of the Lewis–Sigler Institute for Integrative Genomics at Princeton University from 2003-2013, where he remains the Anthony B. Evnin Professor of Genomics. He was a professor and research scientist at the Massachusetts Institute of Technology for two decades, before joining Genentech as Vice President for Science, followed by the Stanford School of Medicine faculty, where he chaired the Department of Genetics. Dr. Botstein is known for his use of genetic methods to understand biological functions and systems. His pioneering insights into human gene mapping helped lay the foundation for the Human Genome Project more than 25 years ago. He has received numerous awards for his work on the Human Genome Project, including the Breakthrough Prize from the Life Sciences Foundation (2013), and the Albany Medical Center Prize in Medicine and Biomedical Research, often lauded as "America's Nobel," in 2010.

Dan Kastner, MD, PhD
National Human Genome Research Institute (NHGRI)

Dr. Kastner is Scientific Director of the Intramural Program at the National Human Genome Research Institute (NHGRI). His career has focused on using genetic and genomic strategies to understand inherited disorders of infla - mation. He continues the quest for genes underlying human disease by the development and application of advanced gene mapping and sequencing technologies. Prior to his NHGRI appointment, Dr. Kastner was Chief of the Laboratory of Clinical Investigation, Clinical Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and deputy director for Intramural Clinical Research at the National Institutes of Health (NIH). His lab focused on human genetic disorders of inflamm tion. He led an international consortium that identified the gene causing familial Mediterranean fever (FMF) in 1997. In 1999, Dr. Kastner's lab discovered mutations in a TNF-receptor responsible for causing a dominantly inherited periodic fever syndrome similar to FMF, a discovery that has led to the successful use of anti-TNF agents in the disorder. His team also established the association of STAT4 polymorphisms with several autoimmune diseases and is currently studying the genetics of Behçet's disease. Dr. Kastner is the recipient of the NIH Director's Award, the Paul Klemperer Award of the New York Academy of Medicine, the Lee C. Howley Prize for Research in Arthritis from the National Arthritis Foundation, and the NIAMS Mentoring Award. In October of 2018, he received the prestigious Service to America Award–popularly known as a "Sammie"–as the Federal Employee of the Year. He was honored for his lifetime achievements in researching genetic diseases, as well as for his conceptual contributions to the field of immunology.

Antony Rosen, MD
Johns Hopkins University

Dr. Rosen is Vice Dean for Research and Director of the Division of Rheumatology at the Johns Hopkins University School of Medicine. He also serves as Deputy Director of Medicine, the Mary Betty Stevens Professor of Medicine, and a Professor of Cell Biology and Pathology at Johns Hopkins. His expertise and research focuses on the mechanisms of autoimmune diseases, with particular emphasis on defining the role of autoantigens in rheumatic diseases such as scleroderma, lupus and arthritis. He has overseen a significa t expansion to the Division of Rheumatology at Johns Hopkins University, nearly doubling the faculty size. Dr. Rosen continues to be highly successful in recruiting and mentoring the next generation of clinical and translational investigators who are dedicating their careers to research that will provide new treatment options for patients living with rheumatic diseases. His recent landmark paper published in the leading journal *Science* provides evidence that certain cancer mutations may trigger scleroderma. In addition to his substantial research efforts, Dr. Rosen is a skilled clinician deeply committed to caring for his patients.

Bruce U. Wintroub, MD
University of California, San Francisco

Dr. Wintroub is a distinguished dermatologist and Vice Dean of Medicine at the University of California, San Francisco. At UCSF, he also serves as Chair of Dermatology, having joined UCSF from Harvard Medical School, where he was an Assistant Professor of Dermatology. His research projects have included pathogenesis of bullous (blistering) diseases, characterization of human mast cell enzymes, and use of photopheresis in cutaneous T-cell lymphoma, atopic dermatitis, and scleroderma. Dr. Wintroub is the Chairman of the Dermatology Foundation and is very active in promoting best practices and advances in healthcare delivery and management.

George Yancopoulos, MD, PhD
Regeneron Pharmaceuticals Inc.

Dr. Yancopoulos is Founding Scientist, President, and Chief Scientific Officer for Regeneron Pharmaceuticals, Inc. His scientific efforts have focused on growth factors, their mechanisms of action, and their role in a wide variety of diseases. His research group discovered the angiopoietins and the ephrins—new families of growth factors that help mediate growth of blood vessels and other cell types. Many of the discoveries of Dr. Yancopoulos and his research group have resulted in therapeutic candidates now in clinical trials, such as the VEGF-Trap^{TM} for cancer and blinding eye diseases, including AMD, and the IL-1 Trap^{TM} for inflamm tory diseases. His research group has additionally developed an innovative set of technology platforms that will greatly speed drug development. He has been recognized among the most highly cited scientists in the world, in a survey by the Institute for Scientific I formation.

2018-2019
FUNDED RESEARCH GRANTS

INVESTIGATOR	INSTITUTION	RESEARCH PROJECT
Franck Barrat, PhD | Senior Scientist **Eric Meffre, PhD** | Associate Professor of Immunobiology and Medicine	**Hospital for Special Surgery Yale School of Medicine**	Role of CXCR3 Agonists in the Generation of Autoreactive B cells in Scleroderma Patients
Livia Casciola-Rosen, PhD | Professor of Medicine **Ami Shah, MD, MHS** | Associate Professor of Medicine	**Johns Hopkins University School of Medicine**	Defining Novel Autoantibodies that are Probes of Cancer-Induced Autoimmunity and Risk in Scleroderma
Howard Chang, MD, PhD | Virginia and D. K. Ludwig Professor of Cancer and Genomics; Professor of Dermatology and of Genetics; Investigator, Howard Hughes Medical Institute	**Stanford University School of Medicine**	Gene Regulatory Mechanisms in Scleroderma Epigenetics of Sex Differences in Scleroderma Scleroderma Twin Study
Lorinda Chung, MD, MS | Associate Professor of Medicine **David Fiorentino, MD, PhD** | Associate Professor of Dermatology	**Stanford University School of Medicine**	Stanford Scleroderma Center of Excellence
Lorinda Chung, MD, MS | Associate Professor of Medicine **Paul Wolters, MD** | Professor of Medicine	**Stanford University School of Medicine, University of California, San Francisco**	Northern California Scleroderma Research Consortium
Erika Darrah, PhD | Assistant Professor in Medicine	**Johns Hopkins University School of Medicine**	Investigating X-chromosome-related Differences in Scleroderma
Erika Darrah, PhD | Assistant Professor in Medicine **Eleni Tiniakou, MD** | Instructor of Medicine	**Johns Hopkins University School of Medicine**	Naturally Presented Topoisomerase Epitopes in Scleroderma Patients with HLA-DPB1*13:01
Hal Dietz, MD | Victor A. McKusick Professor of Genetics and Medicine; Professor of Pediatrics; Investigator, Howard Hughes Medical Institute	**Johns Hopkins University School of Medicine**	Interrogation of the Pathogenesis of Stiff Skin Syndrome: A Congenital Form of Scleroderma
Benjamin Korman, MD | Assistant Professor of Medicine	**University of Rochester School of Medicine and Dentistry**	Assessment of the Complement Cascade as a Novel Biomarker, Genetic Risk Factor, and Treatment Target for Scleroderma-Associated Pulmonary Arterial Hypertension (SSc-PAH)
Zsuzsanna McMahan, MD | Assistant Professor of Medicine	**Johns Hopkins University School of Medicine**	Measuring and Objectively Characterizing Patterns of Gastrointestinal Dysmotility in Scleroderma
Zsuzsanna McMahan, MD | Assistant Professor of Medicine **Jay Pasricha, MD** | Director of the Johns Hopkins Center for Neurogastroenterology; Professor of Medicine	**Johns Hopkins University School of Medicine**	Identifying Autoantigens in Severe Gastrointestinal Disease
Ruslan Medzhitov, PhD | Sterling Professor of Immunobiology; Investigator, Howard Hughes Medical Institute	**Yale School of Medicine**	Macrophage-Stromal Cell Interactions in Tissue Homeostasis and Fibrosis
Dr. Kathryn Torok, MD | Assistant Professor of Medicine **Dr. Anne Stevens, MD, PhD** | Professor of Medicine	**Pittsburgh Children's Hospital Seattle Children's Research Institute**	Identification of Novel Pathogenic Genes in Juvenile Systemic Sclerosis
Gerlinde Wernig, MD | Assistant Professor of Pathology	**Stanford University School of Medicine**	Immune Checkpoint Inhibitors as Antifibrotic Therapy for Scleroderma
Michael L. Whitfield, PhD | Interim Chair and Professor of Biomedical Data Science; Professor of Molecular and Systems Biology	**Geisel School of Medicine at Dartmouth**	Molecular Subsets, Integrative Genomics and Tissue Models of Scleroderma
Fredrick Wigley, MD | Director, The Johns Hopkins Scleroderma Center; Martha McCrory Professor of Medicine	**Johns Hopkins University School of Medicine**	Johns Hopkins Scleroderma Center of Excellence
Fredrick Wigley, MD | Director, The Johns Hopkins Scleroderma Center; Martha McCrory Professor of Medicine **Francesco Boin, MD** | Director, UCSF Scleroderma Clinic; Professor of Medicine *In collaboration with* **Dan Kastner, MD, PhD** | Scientific Director of the Intramural Program at the National Human Genome Research Institute	**Johns Hopkins University School of Medicine University of California, San Francisco National Human Genome Research Institute**	Genome Research in African American Scleroderma Patients (The GRASP Project)
Scott Zeger, PhD | Professor of Biostatistics **Antony Rosen, MD** | Vice Dean for Research; Mary Betty Stevens Professor of Medicine **Livia Casciola-Rosen, PhD** | Professor of Medicine **Laura Hummers, MD, MPH** | Clinical Director, Division of Rheumatology, Associate Professor of Medicine **Fredrick Wigley, MD** | Director, The Johns Hopkins Scleroderma Center; Martha McCrory Professor of Medicine **Ami Shah, MD, MHS** | Associate Professor of Medicine	**Johns Hopkins University School of Medicine**	Scleroderma Lung Disease Trajectory Study

PROJECT PORTFOLIO

Research is the Key:
Projects Funded by SRF in 2018-2019

Each year, the SRF receives and evaluates applications for research projects that advance treatments, and ultimately a cure, for scleroderma. The process for determining which projects get funded is holistic. We ask numerous questions in considering projects for funding, such as: does this project answer a fundamental question about the scleroderma disease process? Would this project yield unique insights into targeting therapies to patients?

We also consider the investigator's potential contributions to the SRF research program with questions such as: would this project and investigator contribute unique and relevant cross-disciplinary insights to our understanding of scleroderma? Does the investigator have the appropriate skills, background and access to excellent mentorship, if needed, to accomplish the project goals? Will this investigator make a real effort to add to our community through collaboration and generous sharing of ideas or resources?

The SRF's focus on building a solid and integrated research platform leads us to consider other factors, including: would the project complement or balance the SRF's existing portfolio? Will this project build upon the SRF's previous research successes? Does this project allow us to leverage other expertise, assets, or outside funding to which we have access, or in some way create an opportunity to amplify the SRF's efforts?

All applicants, whether new or seeking continued funding, present their projects to the SRF's Scientific Advisory Board and other attendees at the annual SRF Workshop. There, assumptions are challenged, the project's relevance and limitations are probed, and constructive critique and collaborative discussion ensues.

It is worth noting that, at the end of the process, there are always worthy projects that SRF cannot fund, due to budgetary considerations. Our goal, and deepest hope, is to continue to expand the SRF's ability to fund great research in our search for a cure.

In the following pages, the 2018/19 SRF- funded investigators describe their research in their own words:

Role of CXCR3 Agonists in the Generation of Autoreactive B cells in Scleroderma Patients

Franck Barrat, PhD | Senior Scientist
Eric Meffre, PhD | Associate Professor of Immunobiology and Medicine

Hospital for Special Surgery
Yale School of Medicine

Project Overview

Dr. Barrat and Dr. Meff e: Scleroderma is a multisystem disorder characterized by vasculopathy, autoimmunity, inflamm tion, and fib osis. One of the hallmarks of scleroderma is the presence of autoantibodies and abnormalities of B cell function have been demonstrated in both animal models of scleroderma and in patients. We have shown that an important biomarker of scleroderma, called CXCL4, can inhibit a pathway that is critical for the elimination of the B cells that produce these autoantibodies. Our project addresses the following questions:

> How does CXCL4 impact B cell selection and activation?

> Is it possible to block or reverse its undesired effect?

First, we will use genomic approaches to identify genes whose expression is altered by CXCL4 in B cells; then focus on genes of interest, and test their expression in cells from scleroderma patients. Second, we will evaluate the effect of CXCL4 expression *in vivo* using a humanized mouse model in which a transplanted human immune system has developed in mice and is exposed (or not) to CXCR4. These studies may validate *in vivo* the observations obtained by the first approach. Finally, we will confirm or rule out the hypothesis that CXCL4 mediates its effect via its receptor (called CXCR3) using mice that lack CXCR3 expression.

Research Update

Over the past year, we have initiated work on all three parts of this project. We have identified genes associ ted with B cell activation that are regulated by CXCL4. We have additionally started to generate the tools required to test the impact of CXCL4 *in vivo* in humanized mice. Finally, we have completed the third aim of this project in that we have shown that, surprisingly, CXCR3 is not the receptor involved in mediating the effect of CXCL4. These initial findings are exciting, as they provide important insights into how CXCL4 controls B cell activation.

How this work will impact patients

Our ability to characterize the pathways controlled by CXCL4 in B cells in scleroderma patients may identify potential targets for drug development. Other potential benefits would be findin novel biomarkers to help predict disease evolution and select appropriate treatment.

Role of the Scleroderma Research Foundation

This is our first year as members of the SRF's research group. While both of us are trained immunologists, we value the input of researchers focused on scleroderma. The SRF is an incredible source of knowledge because the best investigators studying scleroderma are part of it. The SRF workshop was very impactful for us; we learned a lot about what others in field are investigating and how we can incorporate their discoveries into our own research. However, outside the pure academic aspect of this gathering, the general atmosphere both at the scientific sessions and at the more social gatherings is extremely valuable because all of us are dedicated to better understanding this devastating disease and developing new therapeutic strategies for scleroderma patients.

Defining Novel Autoantibodies that are Probes of Cancer-Induced Autoimmunity and Risk in Scleroderma

Livia Casciola-Rosen, PhD | Professor of Medicine
Ami Shah, MD, MHS | Associate Professor of Medicine

Johns Hopkins University School of Medicine

Project Overview

Dr. Casciola-Rosen and Dr. Shah: Emerging findings indicate that distinct subgroups of scleroderma patients have a high risk of cancer at the time scleroderma develops. These subgroups are marked by the presence of specific autoantibodies. We are now beginning to understand what the important autoantibodies are in this regard, and how they are associated with cancer risk. Our project aims to discover new scleroderma autoantibodies and disease patterns that predict either an increased or decreased risk of cancer developing in scleroderma.

Project Update

This year, we teamed up with colleagues in Engineering and Oncology at Johns Hopkins and performed studies that used autoantibodies as tools to investigate molecular events linking cancer and the development of autoimmunity in scleroderma. We showed that autoantibodies and scleroderma phenotype define subgroups of patients at higher or lower risk of getting cancer. These findings will ultimately facilitate development of personalized cancer screening guidelines. These studies were recently published in the *Annals of Rheumatic Diseases*. We are now extending these studies with SRF funding to investigate novel cancer detection strategies in patient subgroups that have a higher risk of cancer.

How this work will impact patients

Our proposed studies are designed to discover novel autoantibodies in two very specific subsets of scleroderma patients: those in which cancer is detected close in time (within fi e years) to the diagnosis of scleroderma, and those in which cancer is never detected. Defining antibodies that are specifical y associated with cancer detection close to the time of scleroderma onset will eventually enable clinicians to predict cancer risk when patients are first seen in a rheumatology clinic, and to guide cancer screening tests. New antibodies associated with cancer protection will give important information about the mechanism of disease and will help to design more effective treatments.

Role of the SclerodermaResearch Foundation

In addition to providing direct funding for this project, the SRF's long-standing support of the Johns Hopkins Scleroderma Center laid the groundwork for this project. Over many years, the SRF has provided funding that established and maintains the Johns Hopkins Scleroderma Center, enabling the establishment of a large repository of biospecimens from well-characterized scleroderma patients. Our studies looking for new antibodies are intimately linked with access to this serum bank, and could not be performed without it. This past year, we were successful in getting a RO1 grant funded from the National Institutes of Health for studies that directly arise out of and extend the work that was initiated with SRF support. We are extremely grateful to the SRF for their role in enabling this.

As researchers, we also look forward to the annual SRF Workshop, which provides a wonderful opportunity for interaction between funded and prospective researchers, and the Scientific Advisory Board. We always return from this meeting with renewed enthusiasm and commitment for continuing our studies that will further understanding of scleroderma, and improve treatment for patients.

Gene Regulatory Mechanisms in Scleroderma
Epigenetics of Sex Differences in Scleroderma
Scleroderma Twin Study

Howard Chang, MD, PhD | Virginia and D. K. Ludwig Professor of Cancer Genomics; Professor of Dermatology and of Genetics; Investigator, Howard Hughes Medical Institute

Stanford University School of Medicine

Project Overview

Dr. Chang: Scleroderma is a disease characterized by excess fib osis of skin and other organs, and the immune system is involved in triggering and sustaining this fib o-sis. My research is focused on how the genes involved in scleroderma are turned on or off. The control of these genes determines a cell's behavior, such as how active an immune cell may be or whether a fib oblast becomes activated to produce excess extracellular matrix, leading to fib osis. The gene control switches are like the command lines that run the cell's software, and we are working out how gene control is altered in scleroderma in order to detect and treat the disease at the most fundamental level.

Research Update

We have identified the gene switches that are different in scleroderma skin compared to normal skin. Because skin is a complex tissue composed of several types of cells, we have invested a lot of effort to understand which gene switches are changed in which cell types. We found that two cell types in skin have different gene switch activities in scleroderma patients in both fib otic skin and even in skin that still appears normal. Other cell types only show changes in gene switch activities in the fib otic skin. Because we can detect these different gene switch activities in "pre-fib otic" skin, we believe these results may yield insights into the cell types that initiate scleroderma. Our next steps are to understand how the gene switches that are changed in scleroderma affect their target genes, for example, by making the genes turn on too long or in response to the wrong stimuli.

We recently published our new technique for determining the exact gene(s) that are controlled by a particular switch (Mumbach et al. *Nature Genetics* 2017). Since many of the variations in DNA that have been associated with autoimmune diseases occur in these gene switches, we believe this new technique will greatly add to our knowledge about these diseases. Additionally, this technique will enhance the value of large-scale genomic projects (such as the GRASP Project) by improving our ability to interpret the data those projects generate.

How this work will impact patients

Insights about the cells and the specific gene switches that cause disease manifestations open new avenues for scleroderma diagnosis and treatment. For example, we are testing whether we can learn about tissue fib osis in different organs by analyzing gene switches in cells from the blood. If successful, such an approach would help patients monitor disease progression without invasive tissue biopsies. We are also asking whether insights about changes in gene switches in scleroderma can match patients to the therapies that target those genes. We hope this will make treatment strategies more rational and precise.

Epigenetics of Sex Differences in Scleroderma

Project Overview

Dr. Chang: The majority of patients with scleroderma are female, with women having an incidence four times that of men. Scleroderma in men, although rarer, can be a more aggressive form of the disease. Despite compelling epidemiological evidence of sex-related differences in the pathogenesis of the disease, there is very little consensus as to what is happening at the molecular

level. We are investigating "X chromosome inactivation," a female-specific cellular mechanism that silences one of the cell's two X chromosomes. The body's inefficit or incomplete silencing of the activity of one X chromosome in female cells (known as X chromosome inactivation escape), has been theorized to be involved in scleroderma and other autoimmune diseases. This project aims to build upon our finding of strong sex-related differences in gene regulation in T cells from scleroderma skin.

Research Update

Using a technique we developed called ATAC-seq, we have demonstrated marked differences in gene regulation in immune cells from males and females. We have discovered that the inactive X chromosome has many proteins associated with it that are autoantigens in systemic autoimmune diseases and we are investigating this connection to scleroderma and other autoimmune disorders. We are testing whether a male animal engineered to have a chromosome resembling the inactive X will experience female-level risk of autoimmunity.

Scleroderma Twin Study

Project Overview

Dr. Chang: Systemic sclerosis is challenging to study because it is rare and multifactorial. The conventional approach to medical study is to find a large number of subjects afflicted with a disease and to compare them to a large number of healthy controls. The hope is that, somehow, the average profil of patients and controls would balance each other out and reveal a disease-relevant signal. This approach has been applied to scleroderma with limited success because the small number of scleroderma patients and controls is often not suffici t to tease apart relevant disease-causing factors from inadvertent associations.

In this study, we are employing a new precision approach to understanding scleroderma pathogenesis. We are recruiting genetically identical twins where one twin has scleroderma and the other twin does not. Such "divergent twins" are uniquely informative because we have a perfect control for each patient—the same genes, same age, same household, so the small differences we find between the twins will hopefully pinpoint disease-relevant differences. Our experience with a more common disease, asthma, in divergent twins shows that this is a uniquely powerful approach to identify disease-relevant mechanisms. We estimate that the number of subjects needed for this twin approach is far less (perhaps by 100-fold) than conventionally designed studies. Our study involves three key components: (i) careful evaluation of the clinical findings of each twin pair; (ii) a new ultra-sensitive technology called ATAC-seq to map the functional differences in gene control from the blood cells of the twin pairs; and (iii) advanced bioinformatics methods to identify disease-relevant biomarkers and pathways.

Role of the Scleroderma Research Foundation

The SRF has played crucial roles in my research. They approached me a number of years ago about working on scleroderma and it is the reason my lab is working in this field. I have been continually impressed and moved by the dedication and vision of the people at the SRF. SRF supported me to take risks and apply the newest powerful technologies to scleroderma, and connected me with clinical investigators to bring these concepts to scleroderma patients.

The SRF is absolutely special because they seek out the best scientists and bring them in to work on scleroderma. The SRF creates a community that works together to tackle scleroderma. The Foundation brings not only money, but also organization and leadership to the search for a cure. I believe that SRF is the one of the most important engines of progress against this disease.

Stanford Scleroderma Center of Excellence

Lorinda Chung, MD, MS | Associate Professor of Medicine

David Fiorentino,MD, PhD | Associate Professor of Dermatology

Stanford University School of Medicine

Dr. Chung: The primary goal of the Stanford Scleroderma Center is to provide outstanding multi-specialty care for patients with scleroderma, with experts from Rheumatology, Dermatology, Pulmonology, Gastroenterology, Cardiology, Immunology, and Hand/Vascular Medicine working together to take care of each patient as a whole. At our Scleroderma Clinic, each patient is examined by a team, including physicians from Rheumatology, Dermatology, and Internal Medicine. We are also actively carrying out state-of-the-art research using tissue samples from patients with scleroderma and working with basic scientists to better understand what causes scleroderma, and to find markers in the skin or blood that can tell us which patients will go on to develop serious complications, like pulmonary arterial hypertension (PAH). In particular, we hope to develop a simple blood test to identify scleroderma patients who will ultimately develop PAH.

Research Update

We have collected a large number of blood samples from scleroderma patients who have developed PAH over time from Scleroderma Centers throughout the U.S. In collaboration with the Stanford Human Immune Monitoring Core, we are evaluating these blood samples for 62 different markers of immune dysfunction. Over the course of the year, we hope to identify the most promising blood markers of PAH in scleroderma patients. We will then confirm our results in a completely separate group of scleroderma patients.

How this work will impact patients PAH affects about 10% of patients with scleroderma. Luckily, over the past two decades, multiple treatments have been developed that are effective for the treatment of PAH. However, scleroderma patients tend to do worse than other patients with PAH, in part, because once the patients are found to have PAH, their disease is already very advanced. We hope to develop a simple blood test to identify, at the time of their initial clinic visit, scleroderma patients who will ultimately develop PAH. This will enable doctors to start effective treatments as early as possible to prevent the onset and progression of this potentially deadly complication.

Role of the Scleroderma Research Foundation

Without the support of the Scleroderma Research Foundation, support, we would not have been able to develop our large group of scleroderma patients who serve as the core of our translational and clinical research studies. In addition, the SRF has been instrumental in connecting us with other top scleroderma researchers both within our own institution as well as throughout the country. The annual SRF Workshop provides a perfect environment to share scientific ideas and brainstorm with new and old collaborators.

The SRF is a unique funding agency in that they support the development and growth of Centers of Excellence, as well as collaborative research groups such as our Northern California Scleroderma Research Consortium (Stanford and UCSF). They work hard to develop and sustain a close-knit community of researchers with a common goal to cure scleroderma.

Northern California Scleroderma Research Consortium

Lorinda Chung, MD, MS | Associate Professor of Medicine

Paul Wolters, MD | Professor of Medicine

Stanford University School of Medicine
University of California, San Francisco

Project Overview

The Northern California Scleroderma Research Consortium (NCSRC) consists of a group of investigators at UCSF and Stanford who collaborate on efforts to understand the clinical presentations of scleroderma patients and how they relate to disease pathogenesis.

Dr. Wolters: Work in my laboratory has focused on understanding the pathobiology of scleroderma-associated interstitial lung disease (SSc-ILD) and whether it shares biological mechanisms with idiopathic pulmonary fib osis (IPF), a genetically mediated, fib otic lung disease that affects older individuals. We have shown that IPF is driven by telomere dysfunction leading to premature aging in lung epithelial cells (Wolters, et al. *Lancet Resp Med* 2018).

Peripheral blood leukocyte telomere length (PBL-TL) correlates with loss of lung function and mortality in IPF patients, such that shorter telomeres are associated with poorer survival. Over the past year, we examined whether PBL-TL is similarly associated with outcomes in patients with SSc-ILD. Interestingly, we found that a subset of SSc-ILD patients have short telomeres in their lung epithelial cells. In addition, shorter PBL-TL is associated with greater loss of lung function (forced vital capacity) and progressive ILD in patients with SSc. These data suggest there is a subset of patients with SSc-ILD whose disease is driven by biological mechanisms (telomere dysfunction) commonly found in IPF patients. We are now in the process of validating these fin - ings in the Stanford arm of the NCSRC cohort. We are also investigating whether short telomeres are associated with other complications in scleroderma patients.

How this work will impact patients

Identifying clinical subtypes of patients with SSc-ILD advances understanding about variations in disease pathogenesis. This information can then be leveraged to develop therapies targeting specific disease subtypes. It is especially important to identify those SSc-ILD patients with pathologic drivers similar to IPF, as they may be more responsive to the recently approved anti-fib otic therapies for IPF patients.

Role of the Scleroderma Research Foundation

The SRF provides funding to support clinical coordinators and laboratory technicians who aid in patient recruitment, data and biological sample acquisition and processing, and molecular analyses for multiple collaborative projects of the NCSRC. The SRF also facilitates research meetings amongst the scleroderma investigators at UCSF and Stanford, which are essential to the success of the NCSRC.

Investigating X-chromosome-related Differences in Scleroderma

Erika Darrah, PhD | Assistant Professor of Medicine

Johns Hopkins University School of Medicine

Project Overview

Dr, Darrah: Scleroderma or systemic sclerosis (SSc) is a chronic autoimmune disease characterized by fib osis of the skin and internal organs, and marked by auto-antibodies to nuclear antigens. Like most autoimmune diseases, SSc disproportionately affects women with an estimated 4:1 female to male ratio. Many factors have been implicated in rendering females more susceptible to autoimmune diseases such as SSc, including the X chromosome itself, but the specific causes of this skewed gender susceptibility remain unknown.

An individual's susceptibility to autoimmunity appears to correlate with the number of X chromosomes that individual has. This concept is highlighted by the increased risk of autoimmune diseases among women and men with Klinefelter's syndrome. Klinefelter's syndrome is a rare genetic condition in which biological men have two X chromosomes. Large cohort studies have demonstrated a 14-fold increase in the prevalence of Klinefelter's syndrome among males with either Sjogren's syndrome or systemic lupus erythematosus compared to healthy males. In addition, there have been nine case reports of Klinefelter's syndrome co-occurring with SSc. This supports the hypothesis that qualities uniquely present in individuals with more than one X chromosome, rather than biological sex, may be important drivers of SSc development. We are taking a novel approach to investigating these qualities in scleroderma.

Naturally Presented Topoisomerase Epitopes in Scleroderma Patients with HLA-DPB1*13:01

Erika Darrah, PhD | Assistant Professor of Medicine
Eleni Tiniakou, MD | Instructor of Medicine

Johns Hopkins University School of Medicine

Project Overview

Dr. Darrah and Dr. Tiniakou: A group of patients with scleroderma (20-45%) makes immune responses against a protein normally present in the body called topoisomerase-I (Topo-I). Patients with these immune responses commonly have fib osis over a large portion of their skin, scar tissue in the lung, and a higher risk of death. While it is known that these immune responses develop, it is unknown why Topo-I is targeted in these patients or what parts of the Topo-I molecule are driving these responses. A genetic analysis was recently performed on blood samples from African American patients with scleroderma enrolled in the Genome Research in African American Scleroderma Patients (GRASP) cohort, through support from the SRF. Analysis of GRASP and patients from other demographic backgrounds has shown that immune responses to Topo-I are linked to a specific gene called HLA-DPB1*13:01. This gene encodes for a molecule that works by selecting "hot spots" within a protein to present to the immune system and triggering immune responses against the protein. The finding that this specific gene is found in patients with immune responses to Topo-I suggests that it may be involved in picking out the hot spots within the Topo-I protein that patients with scleroderma make immune responses against.

We have developed a technique to identify hot spots within proteins that become targets of the immune system in patients with scleroderma. Our study will use this new technique to identify the hot spots in Topo-I that are presented by HLA-DPB1*13:01 using white blood cells isolated from patients with scleroderma.

How this work will impact patients

The results of this study have the potential to unveil characteristics of the autoimmune response in a group of patients with severe scleroderma. In addition, it may pave the way for new tools for disease monitoring and diagnosis, as well as the development of treatments that specifical y block immune responses against Topo-I without knocking down other aspects of the immune system.

Role of the Scleroderma Research Foundation

The SRF has enabled us to translate into reality an idea that originated directly from the GRASP Project. We look forward to working with the SRF to unravel the immunologic role of this molecule in patients with scleroderma.

Interrogation of the Pathogenesis of Stiff Skin Syndrome: A Congenital Form of Scleroderma

Hal Dietz, MD | Victor A. McKusick Professor of Genetics and Medicine; Professor of Pediatrics; Investigator, Howard Hughes Medical Institute

Johns Hopkins University School of Medicine

Project Overview

Dr. Dietz: In broad terms, our lab has focused on the development of experimental models of scleroderma for use in exploring the events that trigger the onset and progression of tissue scarring (fib osis). Initially, we identified the gene underlying a rare inherited form of scleroderma called Stiff Skin Syndrome (SSS) and learned that manipulation of this gene in mice caused skin fib osis through activation of a specific type of immune system cell called a plasmacytoid dendritic cell (or pDC). We went on to show that manipulations that deplete pDCs or impair their function can prevent or even reverse fib osis in SSS mouse models.

In a second series of experiments, we have been studying the basic molecular changes that are required to stimulate certain types of cells to transition to an aggressive cell type, called myofib oblasts, that drives tissue fib osis. Importantly, we were able to implicate a specific family of enzymes (calpains), and even a specific enzyme within this family, in myofib oblast formation. Our work has shown that mice lacking this enzyme are remarkably resistant to various forms of fib osis – pointing toward a potentially powerful treatment strategy.

Recently, we have initiated studies of skin cells from patients with systemic sclerosis (SSc) to try to understand why they remain "activated" even after removal from the body. One plausible explanation for a permanently altered cellular program in patient cells relates to the body's ability to add stable marks to the DNA that essentially tell a given cell or cell type to ignore certain genes, but to drive other genes to produce proteins. Such marks are not inherited from our parents, but rather occur in response to various stimuli, including cellular stress and environmental cues. We are using a variety of methods to learn about the location and nature of these "epigenetic marks" that distinguish skin cells from patients with SSc from those derived from healthy controls. We are also exploring whether cells from patients with SSc can stimulate abnormal epigenetic marks when grafted onto mice. If so, this would allow the generation of a *bona fide* mouse model of SSc for use in treatment trials.

Research Update

Over the past year, we have been able to show that calpain inhibition can protect mice from fib osis of many different tissues and organs, now including the lungs, skin, liver and heart. We have recently extended this work to include mouse models of human genetic diseases that include a strong predisposition for fib osis. This work has formed the basis of a new biopharmaceutical company, called Blade Therapeutics. In partnership with Blade, we have demonstrated that a new medication has the ability to prevent a variety of forms of fibrosis in animal models, with a strong safety profile. Human studies are planned in the near future.

We have also identified specific genes that show altered epigenetic regulation in cells from patients with SSc. We have developed both genetic and pharmacologic strategies to either inhibit problematic genes that show excessive protein production or to prevent or even reverse the underlying abnormal epigenetic marks. In the process, we are learning about the environmental cues that can stimulate the onset of fib osis in scleroderma. Recently, we have shown that some of these treatment strategies have the ability to reverse fib osis in skin samples obtained from patients with SSc.

How this work will impact patients

All the work in our lab is very translationally focused, meaning that we are generating and testing hypotheses that have the potential to directly improve the length and/or quality of life for people with scleroderma. This relates to the development of drug strategies (e.g. inhibitors of pDCs or myofib oblasts), identific - tion of biomarkers (that point toward specific tissues or diseases that might be amenable to a given treatment or indicate how well a specific patient is responding to an intervention) or the creation of new and powerful experimental systems (e.g. cell culture or animal models of SSc) that can be used to develop, test or refin treatment strategies.

Role of the Scleroderma Research Foundation

In the SRF, I have found a new family of collaborators, mentors, critics (in a friendly and productive way) and partners. The annual SRF Workshop is a highlight of my professional year. My lab spends the next few months digesting and implementing new ideas and scientifi approaches. The SRF has facilitated every aspect of our work, including an exciting transition from a purely academic focus to a corporate endeavor – an essential event if we hope to bring powerful new treatments to patients. SRF funding has given our lab the ability to test new and exciting ideas and to recruit extremely talented young scientists to scleroderma research.

Assessment of the Complement Cascade as a Novel Biomarker, Genetic Risk Factor, and Treatment Target for Scleroderma-associated Pulmonary Arterial Hypertension (SSc-PAH)

Benjamin Korman, MD | Assistant Professor of Medicine - Allergy, Immunology, and Rheumatology

University of Rochester School of Medicine and Dentistry

Project Overview

Dr. Korman: Scleroderma patients are frequently affected by vascular complications, which include Raynaud's phenomenon, digital ulcers, cardiovascular disease, and pulmonary hypertension. Pulmonary arterial hypertension (PAH) is a type of high blood pressure that affects the arteries of the lungs and the right side of the heart. Scleroderma-associated PAH (SSc-PAH) is a severe vascular manifestation of scleroderma which currently has poor outcomes, is under-diagnosed, has no established biomarkers, and responds poorly to standard pulmonary hypertension medication.

We have recently shown that circulating levels of complement factor D are altered in patients with scleroderma and particularly in patients with pulmonary hypertension. Further characterization of patients with pulmonary hypertension and mouse models of pulmonary hypertension have shown additional abnormalities in certain parts of the complement cascade, an important part of the immune system that helps clear microbes and damaged cells. My lab is exploring the relevance of the complement cascade as a risk factor for developing pulmonary hypertension, a marker of disease onset and severity, and a potential treatment target. We will utilize large-scale genetic studies to evaluate variation in complement genes as a risk factor for SSc-PAH. We will perform serum and plasma studies to evaluate the utility of complement components and function-al assays as SSc biomarkers. To assess whether blocking complement may be an effective therapeutic strategy for treating SSc-PAH, we will use genetic and pharmacologic approaches to treat mice with pulmonary hypertension and abnormalities in lung complement.

How this work will impact patients

We hope to discover new biomarkers and genetic risk factors to identify, risk-stratify, and predict outcomes in patients with SSc-PAH. Moreover, in pre-clinical studies, this work will determine whether blocking parts of the complement cascade, an important part of the immune system, may serve as a novel treatment strategy for SSc-PAH. Our hope is that this work will lead to improved diagnosis, monitoring, and treatment of SSc-PAH.

Measuring and Objectively Characterizing Patterns of Gastrointestinal Dysmotility in Scleroderma

Zsuzsanna McMahan, MD | Assistant Professor of Medicine

Johns Hopkins University School of Medicine

Project Overview

Dr. McMahan: Though up to 90% of patients with scleroderma have GI dysmotility, heterogeneity exists among patients. Some patients have predominantly upper GI symptoms, while others have predominantly lower GI symptoms. The presence of various GI dysmotility patterns in scleroderma can complicate the management of patients and thus supports the need for systematic, quantitative assessment of GI subgroups. Understanding the differences among GI subgroups may also provide the insight into disease mechanisms.

The assessment of GI motility in patients with scleroderma has evolved in recent years. The use of a traditional, regionally-targeted motility study to assess one portion of the GI tract at a time (e.g. gastric emptying study) is inadequate in scleroderma, because co-existing dysfunction in other GI regions may be missed. GI symptoms are also not reliable, which increases the likelihood of incomplete assessments. Whole gut transit studies emerged to meet a clinical demand that could not be met by regionally-targeted GI studies. Both the scintigraphy-based whole gut transit and the wireless motility capsule were developed to assess transit from the esophagus to the colon, and are now validated and recommended by the American and European Neurogastroenterology and Motility Societies for this purpose. Scintigraphy is considered to be the most physiologic way to assess GI transit, because radiotracer is consumed within a meal. It is therefore an optimal approach to distinguish between GI dysmotility patterns among patients.

We hypothesize that distinct enteric neuromuscular pathways are important targets of the autoimmune response in scleroderma GI dysmotility, and that disruption of these pathways by immune-mediated damage leads to GI dysmotility. We will use the whole gut transit study to define homogenous SSc patient subsets with distinct motility patterns. We will also collect clinical and demographic information, validated GI patient-reported outcome measures, as well as patient serum along with these studies. These studies will establish a framework to ultimately study disease mechanism among clearly phenotyped SSc patient subsets.

How this work will impact patients:

This project will provide critical information to guide patient care. We have identified GI dysmotility patterns using the whole gut transit, which are not fully defined by clinical symptoms. Many of these patterns would have been missed using region-specific GI motility studies. The whole gut transit study provides the opportunity to objectively delineate GI dysmotility patterns from the esophagus to the colon, allowing for more precisely targeted therapies. We will also correlate symptoms of GI dysmotility with objectively measured patterns using a well-developed patient reported outcome measure.

The project will establish objectively-defined scleroderma-related GI dysmotility subsets. Interestingly, one scleroderma GI subgroup is characterized by delays in the foregut and hindgut (especially the proximal colon), which are regions where motility is predominantly controlled by the vagus nerve. This is the same pattern that we identified in patients with a form of autonomic dysfunction known as postural orthostatic tachycardia syndrome. This suggests that patterns of GI dysmotility in scleroderma may reflect dysfunction in important neural pathways. The clear delin-

eation of GI neuroanatomical patterns of dysmotility in scleroderma is an essential first step in determining whether GI subgroups are random or mechanistically related.

And final y, this project may also yield biomarkers for risk stratific tion and outcome prediction. In scleroderma, autoantibodies associate tightly with specific clinical phenotypes. For example, antibodies to topoisomerase-1 associate closely with interstitial lung disease, while antibodies to RNA polymerase 3 associate with renal crisis and rapidly progressive diffuse cutaneous disease. Interestingly, associations between scleroderma GI outcomes (e.g. gastroparesis) and autoantibodies are not well-defined, which is likely due to poorly defined GI subsets. Defining the associations between scleroderma autoantibodies (measured on all patients in the Johns Hopkins Scleroderma Center Database) and GI outcomes (measured by the whole gut transit study) may prove useful biomarkers for diagnosis and provide relevant information on specific GI risk in p tients.

Identifying Autoantigens in Severe Gastrointestinal Disease

Zsuzsanna McMahan, MD | Assistant Professor of Medicine
Jay Pasricha, MD | Director of the Johns Hopkins Center for Neurogastroenterology; Professor of Medicine
Johns Hopkins University School of Medicine

Project Overview & Recent Updates

Dr. McMahan and Dr. Pasricha: Gastrointestinal (GI) dysmotility is a common complication in systemic sclerosis (SSc), affecting over 90% of patients. Patients with SSc may have mild to severe GI symptoms, and dysmotility may be present anywhere from the esophagus through the colon. While it is recognized that the smooth muscle in the GI tract is weak in scleroderma, the reason why GI muscle weakness develops is poorly understood. We hypothesize that the smooth muscles cells (which control motility), enteric nerves (which stimulate muscle contraction), and/or the interstitial cells of Cajal (which facilitate communication between the nerves and muscles) are dysfunctional in SSc and this leads to decreased GI muscle strength and ultimately dysmotility. Using SSc patient serum to stain the longitudinal muscle and myenteric plexus in the GI tract (which is in charge of motility), we aim to identify and characterize novel proteins expressed in these cell populations that are targeted by the autoimmune response in patients with GI dysmotility.

Our preliminary data demonstrate that SSc sera bind distinct subsets of cells in the gut in 3 dominant patterns, which are not present when using normal control sera. In these studies we plan to explore whether proteins uniquely expressed in (or whose expression is highly enriched in) subsets of smooth muscle, and the interstitial cells of Cajal (ICC) are also targeted by scleroderma sera, and identify the distinct proteins in these cells that are recognized. Understanding the specifi mechanistic relationship between staining patterns and GI dysmotility will be a focus of future studies.

How this work will impact patients

These studies will delineate the specific cellular targets of scleroderma sera in the GI tract. Identifying clusters of patients with similar patterns of staining in the gut will allow for the creation of a strong framework upon which to explore expression of specific autoantigens in human tissue, perform functional studies in animal models, and apply novel therapies in clearly defined patient subsets. Because GI dysmotility affects the majority of patients with scleroderma, understanding disease mechanisms in the GI tract may provide insight into scleroderma disease pathogenesis and ultimately lead to new therapeutic strategies.

Role of the Scleroderma Research Foundation

Funding by organizations like the Scleroderma Research Foundation is critical. The SRF provides support for scleroderma research across the country and is also one of the primary supporters of the Johns Hopkins Scleroderma Center. They provide funding for cutting edge science and make it possible for investigators like us to continue to do research, even when governmental funding is low. We depend on the SRF to keep scientific p ogress moving forward.

Macrophage-Stromal Cell Interactions in Tissue Homeostasis and Fibrosis

Ruslan Medzhitov, PhD | Sterling Professor of Immunobiology; Investigator, Howard Hughes Medical Institute

Yale School of Medicine

Project Overview

Dr. Medzhitov: One of the hallmarks of scleroderma is fibrosis: the buildup of scar tissue that leads to thickening of the skin and, in extreme cases, causes the lungs and other organs to stiffen. That stiffening is responsible for much of the mortality caused by scleroderma. This scar tissue is made up of dense extracellular matrix (the proteins that form the normal scaffolding of any organ) that in scleroderma, is produced excessively. Fibroblasts are the main producers of extracellular matrix, but it is not known how that production is controlled. How is the extracellular matrix monitored to make sure that it does not go awry? We hypothesized that macrophages, immune cells that regulate other conditions within tissues, monitor the extracellular matrix to keep it in check.

We have shown that macrophages can sense the mechanical properties of the extracellular matrix, such as stiffness, and generate signals to control the production and remodeling of extracellular matrix by fib oblasts. We also found that fib oblasts monitor tissue properties to determine the optimal cell density. We are working to determine whether these control mechanisms are broken in scleroderma, leading to excessive production of extracellular matrix and the formation of scar tissue that causes suffering for scleroderma patients. Our goal is to determine, in detail, how macrophages and fib oblasts monitor the extracellular matrix and control each other's behavior, and what part of this circuit goes awry in scleroderma, so that we can help develop effective treatments that target that pathway.

How this work will impact patients

Our philosophy is that every disease is an abnormal version of some biological process and understanding the normal counterpart of disease is essential for the development of cures. Our work addresses these basic biological questions with the aim of identifying the key dysregulated steps so that they can be targeted with new therapeutics.

Role of the Scleroderma Research Foundation

The SRF has been instrumental in shaping and focusing my interest in scleroderma research. The annual SRF Workshop is one of my favorite scientific meetings. It provides invaluable opportunities for exchange of ideas and for fostering new collaborations. It has a unique atmosphere of scholarship and shared mission.

Identification of Novel Pathogenic Genes in Juvenile Systemic Sclerosis

Kathryn Torok, MD | Assistant Professor of Medicine
Anne Stevens, MD, PhD | Professor of Medicine
Pittsburgh Children's Hospital
Seattle Children's Research Institute

Project Overview

Dr. Torok and Dr. Stevens: Systemic sclerosis (SSc) affects about three in a million children, with an age of onset of 8 years. Children thus face a life-long risk for permanent organ damage and death from the infla-mation and fib osis of SSc. Understanding the genetic factors underlying a disease is an important step toward improved therapies and, potentially, a cure. Genetic background can also determine prognosis, as well as medication response and toxicity, guiding treatment choices. Although the etiology of scleroderma is undoubtedly multifactorial, past studies revealed genes that regulate immunity associated with adult SSc. However, we discovered that some genes associated with juvenile-onset SSc (jSSc) are different, just as a child's developing immune system is different. Thus, independent genetic studies focused on children with SSc are essential.

This study initiates a collaboration that leverages the extensive genetics experience and pipeline of SRF investigators Dan Kastner and Elaine Remmers at the National Human Genome Research Institute (NHGRI). Patients and their healthy family members are recruited at two of the largest pediatric rheumatology centers in the world (Children's Hospital of Pittsburgh and Seattle Children's Hospital). DNA from these individuals is sent to the NHGRI, where whole genome sequencing is performed with the aim of identifying novel candidate genes. Peripheral blood cells and plasma are also banked for future functional and expression studies that will be guided by the findings of the DNA sequence analysis.

How this work will impact patients

Because causative gene defects usually lead to onset of disease earlier in life, we hypothesize that a whole genome study of early-onset SSc will lead to identific tion of causative genes that cannot be identified in adult-onset populations. The results may lead to a better understanding of the molecular mechanisms of all kinds of scleroderma – localized, systemic, juvenile and adult.

Immune Checkpoint Inhibitors as Antifibrotic Therapy for Scleroderma

Gerlinde Wernig, MD | Assistant Professor of Pathology

Stanford University School of Medicine

Project Overview

Dr. Wernig: Scleroderma is a terrible and disfiguring disease; it mostly affects the skin and vasculature, but when it involves internal organs, the prognosis is quite poor. The disease is characterized by the onset of progressive scarring of yet unknown cause, and its underlying molecular mechanism is not well understood. There are no curative treatments other than bone marrow transplantation, which is associated with increased complications in these patients. We recently discovered that c-JUN is activated in fib oblasts in scleroderma patients and caused fibrosis reminiscent of scleroderma when induced in adult mice. This is a significa t observation, because it represents a non-chemical, purely genetic, inducible model of scleroderma and highlights one critical transcription factor at the core of a general fib otic response. In particular, two immune-regulatory proteins (checkpoint molecules) have stood out from our analyses in mice and patients. This is of particular interest because excellent reagents have already been developed by multiple pharmaceutical companies to target immune checkpoint molecules for cancer.

The main goal of our project now is to interrogate the role of immune checkpoint inhibitors in scleroderma and to determine whether they are safe and effective to use.

Role of the Scleroderma Research Foundation

The annual SRF Workshop in San Francisco is one of the best meetings in the field of fib osis; the scientific community assembled and connected through SRF and the spectrum and quality of research impresses me each time. Investigators are extremely collaborative and focused on innovating to find cures for scleroderma, and there is always new learning. Also, I met many of my current collaborators, including some of my mentors at the annual SRF Workshop. The SRF has become "THE Platform" for scientific innovations for scleroderma and they also foster academic and industry collaborations in an unprecedented way.

Molecular Subsets, Integrative Genomics and Tissue Models of Scleroderma

Michael L. Whitfield, PhD | Interim Chair and Professor
of Biomedical Data Science;
Professor of Molecular and Systems Biology
Geisel School of Medicine at Dartmouth

Project Overview

Dr. Whitfield: SRF-funded work from my lab has allowed us to understand the patient-to-patient and disease-stage variability seen in scleroderma, link this variability to disease progression and identify molecular mechanisms that results in fib osis of the skin, internal organ dysfunction (e.g.: GI symptoms), and pulmonary problems. My lab, with SRF support, has identified "molecular fingerpri ts" of scleroderma that determine where a patient is in their disease progression and allow us to identify drugs that may be useful in treating these patients. We have also linked these scleroderma disease states to model systems that we can use to better understand the disease. These include mouse models of disease in which we can test hypotheses, but more recently, we have developed three-dimensional skin-like tissues that resemble human scleroderma at a molecular level. These culture models are made using scleroderma or healthy control skin cells and reproduce many disease features (skin thickness and fib osis) that we observe in patients. Robust model systems allow us to test our hypotheses about how scleroderma progresses and what drives it—all critical parts of developing effective treatments.

A second major component of my lab is integrating the genomic data generated from my laboratory as well the vast amounts of genomic data available in the public domain, to better understand scleroderma pathogenesis. These analyses use bioinformatics, gene-gene networks and systems biology to understand how groups of genes act together (or against

each other) in scleroderma patients. We have been able to use these methods to generate a molecular model of scleroderma pathogenesis. We have been able to further show that the molecular processes that drive skin fib osis are likely the same processes that are driving disease in other organ systems (GI tract and lungs) of the body. We are now testing these hypotheses by analyzing data from multiple organs from single patients and asking if they show the same deregulated molecular processes. We are also performing molecular experiments in model systems to test our hypotheses. These data tell us that a common mechanism is likely driving disease across organs in scleroderma patients. Our goal is to target this fundamental mechanism therapeutically.

Finally, my lab is working to actively translate our findings from bench to the bedside. These studies have included development of molecular measures of disease severity that can be used in clinical trials, diagnostic markers that identify a patient's molecular state (i.e., which gene expression fi - gerprint is found in a patient), and final y, using our data to identify novel therapeutic targets and then establishing collaborative efforts to develop therapies against those targets. Our goal is to bring precision medicine efforts that are now becoming commonplace in cancer to scleroderma.

Project Update

We have developed multi-tissue networks that implicate cells of the innate immune system (such as alternatively-activated macrophages and dendritic cells) that we believe are driving scleroderma in skin and internal organs affected by the disease.   We have shown that these cells produce many of the molecules that have been implicated in driving scleroderma. Our network methods have also been used to

perform a meta-analysis of multiple scleroderma clinical trials and we have been able to use these methods to predict possible combination therapies. We are performing experiments in mouse models and in our model skin-equivalents to confirm that eliminating these cells prevents fib osis, something that has already been shown in other diseases such as kidney fib osis.

Diagnostic assays that we have developed (in part with SRF funding) are showing promise in our efforts to target therapies to particular patients. In a recent example, we identified patients in the Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial that were most and least likely to benefit from this lengthy and burdensome therapy. We analyzed gene expression data from the blood cells of these patients in the trial, and classified them into molecular subsets using a machine learning-based algorithm we developed over several years. We found that for one group of participants, called the 'normal-like group,' event-free survival did not differ between patients receiving transplant and patients receiving cyclophosphamide. In contrast, for participants in another group, called the 'fib oproliferative group,' the data showed a statistically significant improvement in event-free survival in patients receiving transplant as compared to patients receiving cyclophosphamide. This suggests that patients who fall into this group are more likely to benefit from stem cell transplant. This is an important finding because patients who fall into the fib oproliferative group tend not to respond to immunosuppressive therapy.

We have also implemented new efforts to develop novel therapeutics that can be used to treat scleroderma. These include efforts to target the cells driving scleroderma in collaboration with academic and industry partners. In particular, we are leveraging the methods pioneered in cancer immunotherapy at Dartmouth to develop immunotherapy for patients with scleroderma. We hope to combine our diagnostic assays and therapeutic targeting to develop a precision medicine strategy in scleroderma.

How this work will impact patients

Our work is providing a comprehensive molecular mechanism for scleroderma and demonstrating that a personalized medicine approach based on patient molecular subset will help us get patients to the most effective therapy, and also guide the development of better therapies. The active translation of our work from bench to bedside has resulted in our molecular subsets being actively used in scleroderma clinical trials around the country. Our methods are helping physicians interpret the outcomes of these clinical trials and identify the patients most likely to improve on a particular treatment, as we have shown in the stem-cell transplantation trials. Our network-based methods are now being used to interpret the molecular data from clinical trials so we can understand why some treatments work and some do not; we have also used these methods to predict combinations of drugs that may be most beneficia to scleroderma patients. We hope that our efforts to find new and improved therapies will ultimately benefit patients by developing drugs (or combinations of drugs) with greater effic y.

Role of the Scleroderma Research Foundation

I would not be working on scleroderma if it were not for the Scleroderma Research Foundation, and they are part of the reason that my entire lab now works on this disease. In recent years, this research has gone beyond me as an investigator and my laboratory at the Geisel School of Medicine at Dartmouth, as students and post-doctoral fellows that trained in my lab are now studying scleroderma in their own labs, have become the computational biology experts in rheumatology and fib otic disease, or are advocates for scleroderma in their own spheres of influen e. Most of these individuals attended SRF workshops, collaborated with SRF investigators, and had their work supported by grants we receive from the SRF. With these investments, the SRF is helping to build a community of young, talented investigators to advance scleroderma research.

The SRF has brought together some of the best scientific minds to think about this disease. In my opinion, there is no better "think tank" for scleroderma. The annual SRF Workshop provides a place and time for individuals to discuss the disease, trade their best ideas, and get expert advice from a Scientific Advisory Board that includes some of the best scientific minds in the world.

Johns Hopkins Scleroderma Center of Excellence

Fredrick Wigley, MD | Director, The Johns Hopkins Scleroderma Center; Martha McCrory Professor of Medicine

Johns Hopkins University School of Medicine

Project Overview

Dr. Wigley: The Johns Hopkins Scleroderma Center of Excellence now has seven full-time faculty members who evaluate and manage scleroderma patients referred to us from all over the world. Drs. Chris Mecoli and Julie Paik both also see patients with muscle diseases. All the faculty work as clinical-investigators. Members of the faculty take full advantage of the expertise at Johns Hopkins (JH) by utilizing superb specialists in other areas of medicine (skin, lung, heart, gastrointestinal tract, psychological, endocrine) and surgery (plastics, vascular, orthopedic) to help manage the complex care our patients require. We received about 350 new patient requests in 2018. The Center now has over 3,800 scleroderma patients in our research database; we evaluate and manage 10-11 new patients and 60-70 return scleroderma patients each operational week. This clinical practice remains fully integrated with our research and educational programs.

The Scleroderma Center has built a world-renowned framework for characterizing the breadth of scleroderma phenotypes, investigating underlying disease mechanisms and testing novel therapies for scleroderma. The cornerstone of this approach involves providing comprehensive, longitudinal patient care to scleroderma patients and, at the same time, prospectively collecting and storing clinical data and biological samples from patients. Coupling this exceptional data and sample resource to the discovery engine at Johns Hopkins has resulted in outstanding productivity.

Each of our faculty has a defined research focus and they interact to support the overall research activity.

Dr. Fredrick Wigley provides leadership and direction to the program. Dr. Laura Hummers continues to act as the JH site Principal Investigator (PI) for multiple clinical trials with pharmaceutical companies and investigator-initiated studies. Dr. Ami Shah recently discovered that cancer (many types) can be associated with and likely trigger the onset of scleroderma. Building on her work funded in part by the SRF, she now has NIH support to further investigate the interaction of cancer, autoimmunity and scleroderma. Drs. Hummers and Shah are the PIs for the CONQUER registry, a multicenter effort to develop a large cohort of scleroderma patients and clinical samples for collaborative research. Dr. Zsuzsanna McMahan is leading research to better understand the impact and cause of gastrointestinal disease among scleroderma patients. Dr. Julie Paik is classifying and studying the pathogenesis of scleroderma related muscle disease. Dr. Nadia Morgan is active in the Genome Research in African American Scleroderma Patients (GRASP) Project; a multicenter interactive program to understand why African Americans suffer a greater burden of scleroderma disease. Dr. Christopher Mecoli is investigating biomarkers that can better define disease activity and predict outcomes including treatment responses.

We continue several studies with Drs. Antony Rosen and Livia Casciola-Rosen and others to better understand how the immune system initiates and propagates the disease process as well as studies with Dr. Hal Dietz's lab investigating mechanisms of regulating tissue fib osis. All our faculty continue to collaborate with Dr. Scott Zeger, Professor of Biostatistics, with a goal of better predicting clinical outcomes by using our rich database and trajectory modeling. Our Center's research program continues to have exceptional momentum and is making major progress in understanding the disease process and novel treatments for this disease. The Educational Program also continues to be another major priority of

our Center, driven by a faculty known for their expertise both as clinical scientists and educators.

Role of the Scleroderma Research Foundation

The best way to understand how the SRF has played a key role in our program is to see the incredible growth of the Johns Hopkins Scleroderma Center. Several of our critical assets, such as our clinical database and biorepository, as well as the physicians, fellows, clinical coordinators and database managers who are so critical to our research efforts, have received long-standing support from the SRF. Our ability to conceive of and execute cutting-edge research depends on these assets and critical personnel. Further, the SRF has invested in projects that stem from the nuanced clinical observation and longitudinal care that is prized at our Center. Our program would not have the resources to fully operate without the support of the SRF. In fact, the funds provided by the SRF have made it possible for our faculty to get additional funding from the NIH and Department of Defense.

Scleroderma Lung Disease Trajectory Study

Scott Zeger, PhD | Professor of Biostatistics
Antony Rosen, MD | Vice Dean for Research; Mary Betty Stevens Professor of Medicine
Livia Casciola-Rosen, PhD | Professor of Medicine
Laura Hummers, MD, MPH | Clinical Director, Division of Rheumatology Associate Professor of Medicine
Fredrick Wigley, MD | Director, The Johns Hopkins Scleroderma Center; Martha McCrory Professor of Medicine
Ami Shah, MD, MHS | Associate Professor of Medicine

Johns Hopkins University School of Medicine

Project Overview

Dr. Rosen: Although scleroderma and other rheumatic diseases are quite heterogeneous in their presentation and disease course, recent studies underscore that these diseases can be effectively divided into much more homogeneous subgroups when relevant fil ers are applied. For example, the association of cancer and scleroderma appears highly variable in different studies. When the population is fil ered by the types

of autoantibodies each patient has, and by whether cancer and scleroderma appear clustered together in time, there is a striking clarific tion of the cancer-scleroderma association. This analysis reveals two clear subgroups within scleroderma - patients with anti-RNA polymerase III antibodies or patients lacking the three most frequent scleroderma autoantibodies (called CTP-negative). In these two groups, cancer and scleroderma are clustered in time, and carry a higher overall risk of cancer. Within the CTP-negative group, we were able to apply new measurement approaches to define novel antibodies associated with cancer. Such approaches are very valuable for their definition of diagnostic and prognostic tools, but particularly for their identific tion of novel pathways relevant to disease pathogenesis.

Many fil ers can potentially be applied to segregate disease into more homogeneous subgroups. The more closely related to biology, the more useful such fil ers will be. One of the most powerful indicators of disease biology is its trajectory over time, with different subgroups developing distinct complications at different rates. This integrated representation of forward and reverse pathways has great power to defin subgroups, measurements of their distinct states, and their underlying biological pathways. This project will combine the biostatistical expertise of Dr. Zeger and colleagues around defining disease trajectories, with the clinical expertise in scleroderma (Drs. Hummers, Shah and Wigley) in definin disease subgroups as well as the immunological expertise of

Drs. Rosen, Casciola-Rosen and colleagues to identify clinically relevant, biologically-driven subgroups in scleroderma.

From the Johns Hopkins (JH) clinical database, we are working to identify a group of scleroderma patients with well-defined skin disease and antibody status, and characterize each patient by their trajectory of lung function, heart and skin function (FVC, DLCO, RVSP, MRSS). We will externally validate our resulting trajectory measure by predicting key clinical events, including death. Then, among these patients, we will identify an appropriate group of cases (patients with a steep trajectories), plus a group of relevant control cases (patients lacking steep trajectories). We will use a novel antibody discovery approach to define whether novel autoantibody specificities are associated with either the cases or controls. In subsequent studies, we will also address whether genetic polymorphisms known to be associated with scleroderma susceptibility are enriched in the different trajectory subgroups.

Research Update

Phase 1 has been completed - the patient groups to be studied have been identified and the relevant clinical parameters have been meticulously collected. We have begun mathematical modeling and statistical analysis of these datasets. If our novel autoantibody measure ("signature") predicts whether the person is more likely to have a steep or shallow trajectory, clinicians will have an early indicator that can guide their therapeutic strategy by balancing treatment benefits and risks. It may also point toward a mechanism that can be targeted to produce novel therapies. We are also exploring adding numerous additional measures to differentiate between clinically distinct trajectories.

We are grateful to the SRF for funding this project, and are excited to share new data with our colleagues at the next SRF Workshop.

grasp

GENOME RESEARCH IN AFRICAN AMERICAN SCLERODERMA PATIENTS

Genome Research in African American Scleroderma Patients (The GRASP Project)

Fredrick Wigley, MD | Director, The Johns Hopkins Scleroderma Center; Martha McCrory Professor of Medicine
Francesco Boin, MD | Professor of Medicine; Director, UCSF Scleroderma Center

In collaboration with **Dan Kastner, MD, PhD** | Scientific Director of the Intramural Program of the National Human Genome Research Institute

Johns Hopkins University School of Medicine
University of California, San Francisco
National Human Genome Research Institute

Project Overview

Dr. Wigley and Dr. Boin: There is evidence that racial differences exist in the susceptibility to and severity of scleroderma. African Americans have a higher age-specific incidence and prevalence of scleroderma compared to European Americans. In addition, the incidence of severe scleroderma-associated interstitial lung disease (SSc-ILD) and pulmonary hypertension (high blood pressure between the heart and lung; a life-threatening complication in scleroderma) is also reported to be higher in this ethnic group compared to others. As a result, African Americans affected by scleroderma experience greater disease severity and, as a consequence, worse disease burden as measured by morbidity and mortality. Socioeconomic factors and impaired access to health care do not fully account for the predilection of African American scleroderma patients to poor health outcomes. To date, attempts to elucidate the factors influencing increased disease severity have been hindered by the relatively small size of studied African American scleroderma cohorts.

The Genome Research in African American Scleroderma Patients (GRASP) Project was established to enhance our understanding of the clinical manifestations of scleroderma in African Americans and to perform genomic analyses with the aim of identifying key factors contributing to the onset and severity of their disease. In order to achieve these goals, a large cohort of African American scleroderma patients has been gathered and clinical data as well as DNA samples have been collected from all enrolled patients.

The GRASP cohort currently consists of more than 1,300 extensively evaluated African American scleroderma patients enrolled from 23 participating US academic centers. This is the largest multicenter cohort of African American scleroderma patients ever studied. GRASP's comprehensive clinical database and its significa t size are enabling important informative analyses. In our initial phase, these have included a careful characterization of the relevant clinical features and the analysis of the specific repertoire of autoantibodies presented by African American patients. Results from our study confirm and clearly emphasize the unique and severe disease burden of scleroderma in African Americans and highlight key factors associated with clinically relevant disease outcomes.

The GRASP consortium is now working to define how variation in the DNA across the genome of African American patients may affect the expression of scleroderma. Subtle and rare differences between the DNA makeup of African Americans who have scleroderma and African Americans not affected by the disease or other ethnic populations may explain their increased risk of developing scleroderma as well as the particular array of severe clinical manifestations. Consistent with the underlying assumptions of the project, GRASP investigators have found that certain African ancestry-derived genetic variants increase the risk of scleroderma in the modern-day African American population.

How this work will impact patients

One of the challenges of caring and managing a complex multisystem disease like scleroderma is to be able to define not only its stage of activity or progression, but also to predict with precision the future course of the disease. We know that scleroderma does not follow one well-defined path in everyone; rather, each patient is unique and affected by a highly variable combination of disease manifestations. This heterogeneous disease expression (mild in some and severe in others) requires a deeper understanding in order to enable physicians to provide the best treatment for individual patients. We hope that the GRASP Project will provide novel insights into the genetic and biological basis for the unique disease expression observed in African Americans. The discovery of specific genes or segments of the genome strongly associated with particular clinical manifestations will allow clinicians to identify early on individuals at risk for certain outcomes, to follow them closely, and to intervene with more targeted therapies at the appropriate moment in the disease course.

The GRASP Project clearly will broaden our understanding of scleroderma and help us to deliver more effective care to African Americans affected by this condition. We are confide t that the discoveries prompted by GRASP will have a major impact also for patients of other racial backgrounds. In fact, variations of genes critical for the development of scleroderma and its specific disease manifestations could be shared across different ethnicities and help us to decipher with greater precision the fundamental biological processes that cause scleroderma to occur and progress.

Role of the Scleroderma Research Foundation

The SRF has been instrumental to the development of the GRASP Project since the very beginning. It was during an annual SRF Workshop, that Drs. Wigley and Kastner envisioned an interactive, multi-center project to study from a genetic standpoint why African Americans are affected by scleroderma more frequently and with greater severity. The strong partnership with the GRASP leadership and the continued financia support provided by the SRF has enabled the participation of a large number of academic centers in the GRASP consortium. Moreover, the SRF has provided the perfect framework for GRASP: an environment that encourages brainstorming, formulation of ambitious research goals, and streamlined collaboration among leaders in the field   f scleroderma research and clinical care.

The SRF has a unique philosophy and method of supporting scleroderma research and related programs. In fact, the SRF has steered away from the traditional format of providing research funding. While the door for applications is always open for anybody to apply, their approach is first to proactively search for and identify the most talented researchers (even those who are not directly working on scleroderma) as well as the most outstanding clinical programs and invite them to formulate relevant research proposals. This process of seeking the very best talent has driven over the years the creation of a very robust and comprehensive research program. The SRF is also unique among funding organizations in how they decide whom to support and how to use their funds. The SRF has a gifted professional leadership that is knowledgeable about the disease, biology and research; and it has an incredibly talented, dedicated, and independent Scientific Advisory Board that provides guidance regarding the best research programs and proposals to support. Through this process, the SRF has built a highly successful research network and community of investigators that is making a difference and will continue to bring about important new discoveries.

CONQUER

The Scleroderma Research Foundation Launches a Groundbreaking Registry

CONQUER is a national, multi-center, longitudinal patient registry and biosample repository that will enable sophisticated studies ranging from genetics to biomarkers, and will transform our understanding of scleroderma.

THE CONQUER REGISTRY
The What and Why of a Registry

Scleroderma can manifest in many different ways: some patients have fib otic skin diease; other have lung disease, heart disease, or gastrointestinal disease; still others have many affected organs. Similarly, scleroderma patients need and are treated with many different therapies that span from more passive approaches that involve monitoring the disease coupled with symptomatic therapy, all the way to aggressive therapy aimed at modifying their underlying disease, such as chemotherapeutic immune system resetting coupled with autologous stem cell rescue. Why is there so much variabilitiy in disease presentation? Why is it so difficul to predict an individual patient's disease course? What is the right therapy for any one patient? What is the range of outcomes that patient might expect?

Understanding these differences and answering these questions will require tracking and collecting data on the health status, disease complications, treatments and outcomes of many patients over many years. The Scleroderma Research Foundation began developing the CONQUER Registry in 2013 with the goal of enrolling a large group of patients and building a powerful database that tracks their disease. Data will be collected at normal clinic visits–ultimately for thousands of patients–over many years.

Because scleroderma is highly variable in its presentation, we need better ways to classify patients into more clearly defined subgroups in order to understand the course of their disease progression and more successfully target medications for their treatment. However, this subgrouping can only be achieved through studying large numbers of patients over relatively long periods of time—allowing patterns

to be detected. The data amassed in the CONQUER Registry will allow researchers to refine disease subgroups and track therapeutic interventions and patient outcomes for various subgroups with the aim of enabling more precise and tailored care for patients. The data will also enable the development of improved outcome measures and more refined clinical trial designs.

Due to the rarity of scleroderma, a broad consortium of scleroderma centers is required to enroll a sufficitly large patient population in a short period of time and a concerted and dedicated effort is required to assemble a sufficitly comprehensive dataset to enable these deeper insights into the disease.

Steps toward CONQUER

International scleroderma groups have launched large observational studies in Europe; however, these do not necessarily reflect the .S. scleroderma patient population and, in any case, these studies have constraints that limit their utility.

In 2011, a group of collaborative clinicians across the nation and including most of the major U.S. scleroderma centers launched a pilot effort called the Prospective Registry of Early Systemic Sclerosis (PRESS) registry. Ultimately this effort enrolled almost 200 patients and laid some of the groundwork for the more ambitious and comprehensive effort that is CONQUER. The SRF, appreciative of the spirit and progress of the PRESS group, approached the investigators with a proposal to partner on the larger effort that it had envisioned. This new effort, a partnership of the SRF and the participating academic Scleroderma Centers, will create a much larger-scale registry and amass a broader and highly informative cohort of ear-

ly-stage scleroderma patients in the U.S. This collaborative effort, initially among 12 of the largest scleroderma centers in the U.S., was named CONQUER (an acronym for **CO**llaborative, **N**ational **QU**ality and **E**ffic y **R**egistry for Tracking Disease Progression in Systemic Sclerosis (scleroderma) Patients).

Transforming Research and Patient Care

As a longitudinal registry, CONQUER will be a groundbreaking platform for advancing research and care. It will ultimately enable researchers to:

> Determine whether certain disease features are associated with or predict clinical and patient-reported outcomes (short-term and long-term).

> Identify patients who require early and aggressive intervention and patients who can be closely monitored and treated as needed.

> Evaluate the response to therapeutic agents and to combinations of therapeutic agents outside of the clinical trial setting.

> Develop insights into drug toxicities that are unique to scleroderma patients and more precisely to patients with specific co-morbidities or disease features (e.g.: underlying heart disease due to pulmonary vascular disease).

> Track and understand patient satisfaction with the current Standard of Care.

> Collect biological samples for future analyses (e.g.: genetic factors contributing to disease or markers in blood that might predict disease worsening).

> Establish and support a collaborative network for scleroderma investigators in the U.S.

> Support the critical infrastructure for future scleroderma studies, including trials for novel therapeutics.

Dr. Luke Evnin, PhD, (Chairman of the SRF), who has led the SRF's effort to create the CONQUER Registry and briefly discussed the registry in his earlier letter, notes, "the CONQUER Registry was conceived not only to be the gold standard for data on patient outcomes, but also as a platform for novel drug trials and the development of new methods to measure outcomes. Additionally, we see the CONQUER Registry enabling biopharmaceutical companies to effectively engage the scleroderma clinical community as financia sponsors, intellectual partners, and technology providers. Many benefits to the scleroderma research community will fl w from this effort, but ultimately it is about driving toward more personalized and effective therapy for patients."

CONQUER Community Members

Patients

Participation in the CONQUER Registry enables patients to make a critical contribution to improving scleroderma care and therapies for all patients with minimal personal impact.

Patients 18 years of age and older, who meet the 2013 ACR/EULAR classific tion criteria for systemic sclerosis and who are less than fi e years from onset of first non-Raynaud's phenomenon symptom attributed to systemic sclerosis are eligible to be enrolled in CONQUER.

CONQUER Institutions and Principal Investigators

The institutions listed below are the founding sites participating in the CONQUER Registry and the investigators comprise the current CONQUER consortium. Other expert sites will be added over time, with several additional sites to be added in 2019.

INSTITUTION	PRINCIPAL INVESTIGATOR
Columbia University	Elana Bernstein, MD, MSc
George Washington University	Victoria Shanmugam, MD, FACP, FACR
Georgetown University	Virginia Steen, MD
Hospital for Special Surgery	Jessica Gordon, MD
Johns Hopkins University	Ami Shah, MD, MHS Laura Hummers, MD, ScM
Mass General Hospital	Flavia Castelino, MD
Medical University of South Carolina	Faye Hant, DO, MSCR
Northwestern University	Chase Correia, MD
Stanford University	Lorinda Chung, MD, MS
University of Michigan	Dinesh Khanna, MBBS
The University of Texas Health Science Center at Houston	Shervin Assassi, MD, MS
University of Utah	Tracy Frech, MD, MS

Database and Biorepository

All clinical data collected for CONQUER will be entered into a National Institute of Health (NIH)-sponsored RedCap database, a secure web-based application designed to support data for research studies. Led by John Van Buren, PhD, a team at the Data Coordinating Center (DCC) at the University of Utah School of Medicine will provide data coordination and management services for the CONQUER Registry. The DCC has extensive experience working with national research networks and will take an active role in ensuring data quality.

The Biorepository Center at the University of Texas Health Science Center at Houston will provide processing, storage and man-

agement services for the biological samples of the CONQUER Registry as it does for a variety of national research networks.

The Scleroderma Research Foundation

The Scleroderma Research Foundation is the lead sponsor and founding partner of the academic investigators in CONQUER Registry. The SRF actively works with the investigators to shape the formation, activities and capabilities of the registry. The SRF independently funds the registry and secures outside sources of funding and other technological capabilities for the registry.

Industrial Partners

Boehringer Ingelheim is a Founding Partner of CONQUER and Actelion (a Janssen Pharmaceutical company of J&J) is a Silver Partner of the CONQUER Registry.

"We're so appreciative of the support of our industrial partners and for their financia and intellectual contributions to the CONQUER Registry," says Dr. Evnin. "Boehringer Ingelheim joined the effort at inception and, in addition to being the Founding Sponsor of CONQUER, they have generously shared their knowledge and experience with respect to creating a successful registry. Actelion has also generously stepped up as a Silver Sponsor." The SRF will continue to secure private funding and expects to engage the NIH to provide additional support.

The launch of the CONQUER Registry in 2018 was a pivotal accomplishment for the SRF. Initial funding has been secured (which includes a portion of the Betty Benedict bequest, see page 60), and after many months of contract negotiations and working to secure IRB approvals at twelve institutions, the consortium has enrolled its first 100 patients. Dr. Evnin adds, "We're on our way. For the scleroderma research community, the CONQUER Registry will be an incredible resource and a platform for collaboration and progress."

For more information about the CONQUER Registry, see www.conquerssc.org.

ERIC KAU

SRF Board Member
Connected to the Cause

Eric Kau

SRF Board Member Dr. Eric Kau Discusses Why He Joined the SRF and the Future He Sees for the Foundation

Dr. Eric Kau, SRF board member and urologist, is currently Clinical Assistant Professor of Urology at the Keck School of Medicine of the University of Southern California (USC), and Director of the USC Institute of Urology–Arcadia. He remembers when a family member was diagnosed with scleroderma. His first reaction was to learn as much as he could about this deadly autoimmune disorder. "Even in medical school," he explains, "I don't remember spending a lot of time on scleroderma."

So how did Dr. Kau find his place as board member of the nation's leading investor in scleroderma research? How did he become part of the team of superheroes that leads the Scleroderma Research Foundation? Arguably, by tackling every situation–good or bad–that has come his way with a relentless curiosity and desire to learn.

Kau was born in Nashville, Tennessee, as the child of immigrant Taiwanese/Chinese parents. Kau's father had come to the United States for his PhD at Vanderbilt, and subsequently moved to New York, England, and eventually Delaware, where he completed the majority of his pre-college studies. After finishing his undergraduate program a year early, Eric took a gap year in Taiwan to improve his Chinese language skills before starting medical school. Early on in his education, Kau had decided that he wanted to help and take care of people, so becoming a doctor seemed like a natural choice. "The real decision," he explains, "was choosing a specialty."

Urology had appealed to him for a number of reasons: first, because it involved using both his skills as a surgeon and as a physician. Typically, doctors either take the route of surgery or medicine– urology, however, is different. "The interesting thing about urology is that it's a combination of both," says Kau, "We have to see our patients for issues that are both medical and surgical." The second reason for Kau's choice in specialty was the high-tech aspect of the field. Urologists regularly use lasers and perform laparoscopic and robotic surgeries. These surgeries are minimally invasive, but still require significant skill on the part of the surgeon–in this regard, Kau's excitement comes across. "It was a lot of hours, and very little sleep, not much of a social life. But you know, you learn–I was very fortunate, I got to train with a lot of people who are world leaders in their field." After six years of residency at NYU following medical school, Kau found himself as a fellow at Cedars Sinai Medical Center in Los Angeles, relocating him to his current home in Southern California.

The SRF's dedication to research and the information on www.srfcure.org was what initially drew him to the organization. After becoming a board member, he began attending scleroderma-focused conferences in order to become as well-versed as possible about the disease. What he saw at these conferences– namely the SRF Scientific Workshop – was inspirational.

"These researchers are legends," he says about the SRF's Scientific Advisory Board and the researchers who spoke at the event, "They've done such a remarkable job. It's hard not to learn, given all the opportunities the SRF has created for researcher collaboration." Then, he notes, "In medical school, Fred Wigley is the doctor you *dream* you should be. He is the one you want to be. He is incredibly patient, and always at the service of his patients."

Kau enthusiastically describes the SRF-funded research projects, noting that they're making headway in the right direction. "We have some of the brightest minds in the world working in partnership with the SRF in trying to meet our goal of finding a cure. The future is very promising."

He finds the trajectory modeling project, which is headed by investigators Antony Rosen, Livia Casciola-Rosen, and Scott Zeger, to be one of the most exciting SRF-funded research initiative–and he explains that, in a way, the project is how his love of sports and medicine have intersected. "Akin to PECOTA, which is a system for forecasting performance for Major League Baseball players, you can incorporate physical attributes, production metrics, etc, and compare similar players historically to predict performance. It's the same idea in trajectory modeling: you find "similar" patients, and you see how the disease is going to manifest in those patients." These types of research projects are symbolic of the kind of energy in the scleroderma research field today, which Kau believes is a result of Chairman Luke Evnin and Volunteer President Deann Wright's leadership. He is also in awe of the seemingly life-long dedication of fellow board members Bob Saget and Susan Feniger.

Kau notes that people are still waiting for a clinical breakthrough for scleroderma; that, even with all the exciting new discoveries coming out of SRF's research, there's still more to be done, a cure to be reached. But the question that must inevitably be asked is, how should people cope until then?

"Well, support is important." He says, "Patients need others who support the cause, which is why we have fundraising events where we get people from all walks of life to come." But more importantly, in his years as a physician to people of all shapes, sizes, and backgrounds, he's noticed that the most important aspect of patient care is retaining a desire to learn. Research is the key, and Kau, considering what his responsibility is as a doctor, family member of a patient, and SRF board member, explains that he feels as though he needs to continue to educate himself about this disease.

Kau's commitment to learning supports and encourages the SRF and the scleroderma research community to continue to strive for a cure–and for a constant and tireless intellectual curiosity.

Research is the key, and Kau, considering what his responsibility is as a doctor, family member of a patient, and SRF board member, feels as though he needs to continue to educate himself on the disease.

COOL
COMEDY
HOT
CUISINE

Cool Comedy-Hot Cuisine:
A walk through the ages
from 1987 . . . until today!

ROBIN WILLIAMS | 1987

JOHN CANDY | 1993

SHARON MONSKY & LEA THOMPSON | 1997

DENIS MILLER | 1996
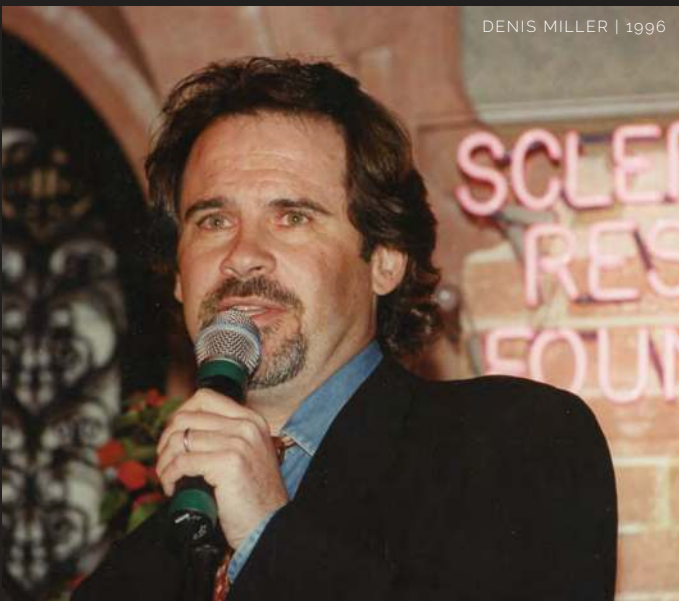
BILL FENIGER, BOB COSTAS, DERRICK FENIGER | 1998

DANA DELANY | 2001

SUSAN FENIGER | 2002

SUSIE ESSMAN | 2007

TRAIN | 2005

BOB SAGET & ATTENDEES | 2008

ELIZABETH FALKNER
& GILBERT GOTTFRIED | 2017

ADAM DURITZ, MARY-KATE OLSEN, BOB SAGET, JOHN OLIVER, GEORGE LOPEZ | 2017

MARY SUE MILLIKEN & SUSAN FENIGER | 2017

BOB SAGET & KELLY RIZZO | 2017

ADAM DURITZ | 2017

CAROLINES | 2017

Nearly 100,000 U.S. patients will benefit

GEORGE LOPEZ | 2017

LUKE EVNIN | 2017

EMILY HINDERER

26.2 Miles Closer to a Cure

Emily Hinderer, Scleroderma Patient, Runs the Chicago Marathon to Fundraise for the SRF

When Emily Hinderer ran her first marathon as a senior in college, she did not know what would lie ahead. She did not know what a long, hard, slog the 26.2 miles would be, did not know the emotional and physical toll that the distance would have on her body, and certainly did not know she would ever want to do it again. According to Emily, "It was terrible. It could not have gone worse." Somehow, though, Emily kept coming back to the running course, rain or shine, until her fifth marathon–the Bank of America Chicago Marathon of 2018– when a scleroderma diagnosis three years prior dictated that this would be her last race. But Emily is a marathoner through and through, and in her usual fashion, she decided to go out with a bang: by fundraising for the Scleroderma Research Foundation.

Emily's story is an unusual one: the third of nine siblings, she grew up in southwest suburbs of Chicago in a big, bustling, physically active family. "I have an older sister who has four kids, and so her oldest is fi e or six years younger than my younger brother. So my youngest brother is closer in age to his nephew than he is to me," Emily explains. With such an active family, it's no surprise that Emily became a runner and athlete; she started running during her first year of college. After a friend introduced her to the idea of distance running, she was hooked. "I thought, that is totally what I want to do. I want to run the marathon. I had never done a distance race –I had never even run a 5K. I didn't know how

it was going to go, but I thought, I'm going to do it and train for it." She ran her first full marathon her senior year of college. Running, and especially marathoning, made her a stronger, braver person–after a number of races, she went on to become an Ironman triathlete. Of that race, she says, "I loved it."

Shortly after completing an Ironman, however, Emily started noticing some odd symptoms that had arisen during training, but that she had assumed were a result of the strenuous exercise. "My legs were so sore, my arms were so painful–no one could touch me, or give me a hug, and my parents final y said 'Yeah,

something's wrong. You need to go to the doctor." Emily put off going to the doctor, hoping the symptoms would go away–when they wouldn't however, she went to her primary care physician. "I went in and basically laughed to the doctor. I said, 'Hi, I have the weirdest symptoms.'" Emily's doctor listened to what she told him, and ran a series of blood tests that eventually pointed towards a scleroderma diagnosis.

The road to diagnosis for Emily was pretty quick, compared to that of other patients–her sister, a nurse, immediately told her that her blood test results confirmed scleroderma, and her doctor was relatively quick

to confirm the diagnosis. Emily knew what the disease was by chance–she'd had a distant aunt who had passed away from the condition, and a friend whose mother had had to make serious changes in her lifestyle to accommodate the autoimmune disorder. "I was officia y told the diagnosis on a Thursday," says Emily, "Friday night I came home and I remember we had a Christmas tree up–and I just remember laying on the couch crying, and staring at the Christmas tree. I then went to bed, and woke up Saturday morning, and thought, you know what? I'm done. This is what it is, and I need to pick myself up and make the best of it. Just take it one day at a time." Diagnoses for three other autoimmune disorders, as well as epilepsy, were quick to follow, and for three years, she didn't run as often or as long as she had in the past. But Emily never gave up "I thought to myself, I'm going to use the talents that I already have to raise awareness–not just for scleroderma, but about everything I have going on. So it just became my mission to raise awareness and make a difference." Emily says staying active in this domain has helped her process and cope with her diagnosis. "It's been really cool and uplifting, for me to know that I'm making a difference," she explains, "because how can we find a cure for scleroderma if nobody knows about it?"

Ultimately, the Chicago Marathon of October 2018 was momentous for a number of reasons. "It was super bittersweet," says Emily, "It was terrible weather here–rainy and misty and cold, which, when you have Raynaud's, isn't great. But I felt pretty good for the whole thing." Emily, as well as her family, knew this would

be her last race–but it was also the first 26.2 mile run she'd undertaken since her diagnosis, and finishing it meant a lot to Emily, her father and sister, who were also running the race, the team she had assembled and trained with, and ultimately, the extended scleroderma community. Emily remembers a moment in the middle of the race when a race volunteer, seeing her SRF shirt, thanked her for running for the SRF, because her mother had scleroderma. "I was flabbe gasted by the fact that she was thanking me," she remembers, recalling the emotional moment, "and the fact that somebody else had it." Emily also remembers a particularly poignant moment at the end of the race: "I just thought, 'Oh my god. I'm doing it. I'm actually doing it.'"

Emily, her family, and her team proudly finished the ra e.

Being a long-distance runner and triathlete has taught Emily about more than just physical endurance–it has strengthened her mind and patience too. "I don't give up," she says, "And when you get that diagnosis, you can't give up either." When asked what she would do now, Emily responded, "I don't know yet, I'm open to suggestions." After a brief pause, however, she says, "But I'm going to do something."

EMPLOYER MATCHED GIFTS

We salute each individual who discusses the possibility of matching a personal gift made to the SRF with their employer. We also celebrate the leaders of the organizations who have made a commitment to stand by those employees, and thereby doubled their efforts to find a cu e for scleroderma.

The following organizations have generally matched contributions made by their employees:

Actelion Pharmaceuticals US, Inc.

ADP

Air Products & Chemicals, Inc.

Allstate Giving Campaign

American Endowment Foundation

American Express Charitable Fund

AT&T Employee Giving Campaign

Bank of America Foundation (Matching Gift Program)

Chevron Humankind Matching Gift Program

Give With Liberty Employee Donations

Good Done Great

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JK Group - Trustee for CA, Inc.

JP Morgan Chase Foundation

Los Alamos National Laboratory

Marathon Petroleum Matching Gift Program

The Merck Foundation

Microsoft Matching Gifts Program

Morgan Stanley

PG&E Corporation Campaign for the Community

QVC

Travelers Community Connections

Truist

UnitedHealth Group

PLANNING FOR A CURE

Betty Benedict

Wellesley Alumna Betty "Busybee" Benedict Leaves A Considerable Portion of Her Estate to the SRF In Planned Giving

Betty Benedict, nee Zahn and who called herself "Busybee," spent her life living up to her nickname by being active in the communities she was a part of and contributing to the causes she championed. When deciding where to bequeath her assets, Betty may have reflec ed on the legacy she left behind through her active life, and wondered where she could do the greatest good beyond her lifetime. In consulting with Dr. James Seibold, a scleroderma expert and her physician, Betty found the answer with the Scleroderma Research Foundation. Given her focus on having a longterm impact, Betty generously bequeathed a significa t portion of her estate to the SRF. Through her planned giving, she continued her tradition of setting out to impact as much as she could in the world: the SRF has set aside a large part of her bequest to support the CONQUER Registry, which will, as it develops, lead to the creation of a gold-standard database of information about patients and the trajectory of their disease. The other portion of her estate will support the Foundation's pursuit of fundamental scleroderma research projects.

Betty's early years were spent at Grover Cleveland High School in Caldwell, New Jersey, where she developed her scientific interests. After graduating in 1950, Betty attended Wellesley College, where she majored in Chemistry, applying her academic interests to practical pursuits, like making lipsticks for her friends at the Wellesley Lab. The friendships–though perhaps not the lipsticks–remained strong long after her undergraduate years, after which she became a laboratory assistant and analytical control chemist. Even after she left Wellesley, she was a strong supporter of the university.

At the age of 25, Betty married fellow scientist Joseph T. Benedict. In contrast to Betty's reserve, Joe was a romantic; nonetheless, they bonded over intellectual pursuits in the arts, sciences, literature, and travel. They took on the world, living in Switzerland early on in their marriage. Upon return to the US later, Betty continued to further her education, earning a Master's in Library Sciences from Rutgers University in 1968, and an MBA from Fairleigh Dickinson University's School of Business in 1980. She was named in the Who's Who of American Women, and inducted in the Delta Mu Delta National Honors Society in Business Administration.

Even after Joe's death, Betty remained active and gregarious, both physically through tennis and in her career. She met her dear friend, Bob James, at a friend's house over dinner. After his passing, she inherited his family: two daughters, a son, their respective spouses, and seven grandchildren. Her memory lives on not only with those loved ones, but with the many she helped as well–including the patients across the scleroderma community that the SRF serves.

Betty's story and her contribution to the Scleroderma Research Foundation are examples of the many ways in which "Busybee" made a splash in the world, and how her legacy will continue beyond her lifetime. Betty's donation brings the SRF another step closer to a cure, and empowers the Foundation's research initiatives. With her help, the fig t goes on, and her legacy continues through the SRF and the CONQUER Registry.

WELLESLEY COLLEGE, MASSACHUSETTS - BETTY'S BELOVED ALMA MATTER

THE SRF LEGACY SOCIETY

When Sharon Monsky founded the Scleroderma Research Foundation, she wanted her contributions to advance the care and health of scleroderma patients long after she was gone.

The SRF Legacy Society honors this noble goal by providing an opportunity for individuals who would like to support the Foundation through a will, trust, designation, or other planned gift, to do so. Reflecting the thoughtful planning involved in making a bequest, planned gifts are often among the most generous and impactful donations we receive. The SRF Legacy Society allows us to appropriately thank donors who have included the SRF in their estate throughout their lives, and who have chosen to support our future beyond their lifetimes.

Involvement in the Legacy Society gives contributors the opportunity to enjoy the company of others who want to make a lasting gift to the scleroderma community, and inspires others to look to the future and consider leaving a gift that will impact the SRF research program for years to come.

If you have included the Scleroderma Research Foundation in your will or another planned gift, please let us know, so that we may honor you as a member of the SRF Legacy Society.

For more information, please call the SRF at 800.441.2873 or email :
Alex Gonzalez,
Director of Development at
alexg@sclerodermaresearch.org

SRF FOUNDER SHARON MONSKY AT AGE 16

Estate of Maria Anargyros

Estate of Harold E. Aust

Sylvia Marie Becherer Revocable Trust

Estate of Betty Z. Benedict

Estate of Teresa W. Duggan

Karen Fraley 2005 Family Trust

Marie C. Kronman Charitable Lead Annuity

Trust of Margaret R. Lee Irrevocable Trust

Estate of Janice Lowry

La Verne B. McCrory

Estate of Neal McGuire

Martha L. McHenry

Estate of Ramelle Ferer Monsky

Neptune Family Trust

Estate of Jerome T. Osborne, Sr.

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Anne D. Ramsier Family Trust

Dolly Saget

Mary Scott Trust

Cheryl E. Shea

Robert H. Shutan Trust

James Simon Family Trust

Estate of Helen I. Steffanu

Clinton Ternstrom

FINANCIAL INFORMATION

*SCLERODERMA RESEARCH & EDUCATION COMPRISE **84%** OF SRF EXPENSES*

Expenses: 05.01.2017 - 04.30.2018

STATEMENT OF FINANCIAL POSITION

ASSETS	2017	2018
Cash and Cash Equivalents	991,765	528,383
Investments	2,213,308	3,166,067
Other Current Assets	57,850	28,196
Contributions Receivable	396,351	157,5948
TOTAL ASSETS	**3,659,274**	**5,298,594**

LIABILITIES AND NET ASSETS
Liabilities

	2017	2018
Accounts Payable	13,640	32,415
Other Current Liabilities	42,735	19,512
Research Grants Payable	110,000	0
TOTAL LIABILITIES	**166,375**	**51,927**
NET ASSETS	**3,512,265**	**5,266,873**
TOTAL LIABILITIES & NET ASSETS	**3,678,640**	**5,318,800**

RESEARCH		FUNDRAISING	
69.10%	15%	7.5%	8.3%
	EDUCATION	MANAGEMENT & GENERAL	
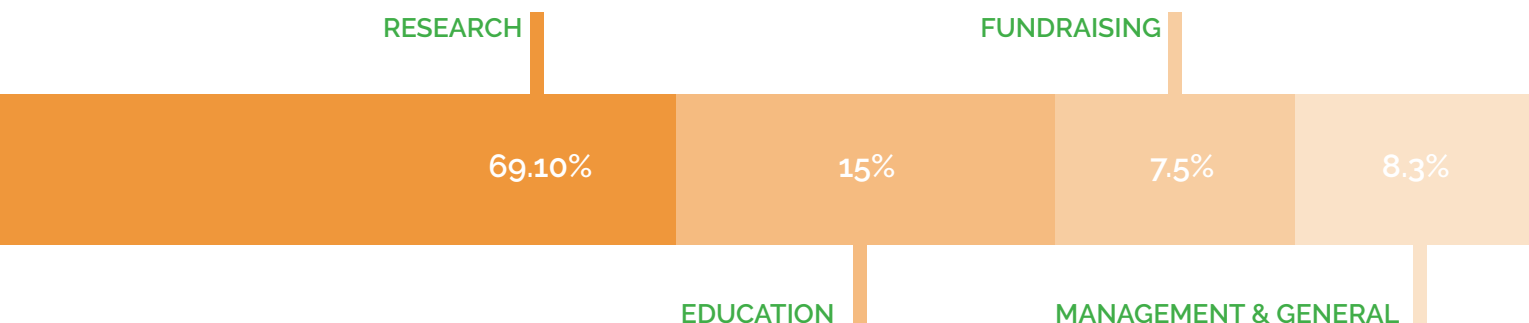
STATEMENT OF ACTIVITIES & CHANGES IN NET ASSETS

SUPPORT AND REVENUE	2017	2018
Support	2,825,476	4,632,995
Other Income	163,896	124,269
TOTAL SUPPORT & REVENUE	**2,989,372**	**4,760,064**

EXPENSES

	2017	2018
Research	1,794,632	1,769,853
Education	376,313	452,040
Fundraising	189,598	226,366
Management and General	167,093	249,078
TOTAL EXPENSES	**2,527,636**	**3,005,456**
Increase in Net Assets	461,736	1,754,608
Net Assets, Beginning of Year	3,050,529	3,512,265
Net Assets, End of Year	3,512,265	5,266,873

Thank you!

The SRF has seen tremendous growth during the last 30 years, and we are closer to a cure than ever before.

Our success and continued progress in driving discovery forward depends upon charitable gifts. Your generous support propels our work into the future, and ultimately we will end scleroderma together.

We are deeply grateful to the many individuals, companies, and foundations whose support at every level helps to fund lifesaving medical research.

The following pages acknowledge those who contributed $250 or more during the Foundation's Fiscal Year ending April 30, 2018.

$50,000+

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Boehringer Ingelheim Pharmaceuticals Inc.

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Mr. Joseph Hulston

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AKS Family Foundation

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We express our deepest sympathy to the families and friends of the following people in whose memory gifts were made during our fiscal year.

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