



NORTHWESTERN SCLERODERMA PROGRAM

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A Northwestern research team in collaboration with Washington University has been awarded a transformational grant to advance research and treatment for scleroderma.

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Diagnosed with scleroderma at the age of 20, medical student Tiffany hasn't let her diagnosis slow her down. Now researching the genetics of scleroderma renal crisis, Tiffany hopes to help make a lasting contribution, and educate others with scleroderma.

Bulletin

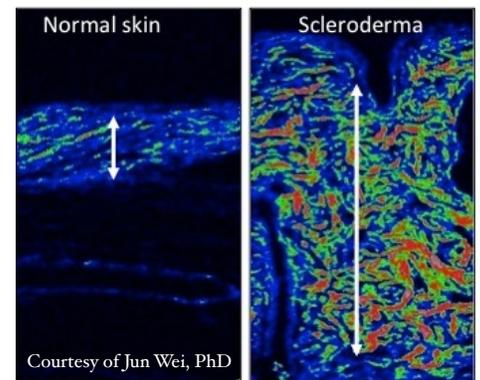
From Bench to Bedside: novel treatment based on Northwestern research enters first clinical trial

In an exciting development, a first-in-human clinical trial, based on laboratory discoveries by Northwestern investigators, was initiated a few months ago. The trial evaluates the safety and mechanism of a new drug to block the Wnt pathway.

Basic research leads to a new target: Wnt pathway

The Wnt pathway is a key regulator of embryo development, wound healing and hair cycle; and abnormal Wnt is a culprit in some cancers. Using cells and experimental mice, researchers from the Northwestern Scleroderma program, together with lung specialists Cara Gottardi and Anna Lam, discovered that the Wnt pathway also plays a pivotal role in scleroderma skin and lung fibrosis. The investigators then teamed up with the biotech Prism, and collaborators at Boston University and the Hospital for Special Surgery in New York, to explore a novel Wnt inhibitor as a potential treatment. Based on their research, supported by the Department of Defense and a gift from the Goldman family, the investigators predict that the new drug – which is used as a topical skin ointment – might normalize the scleroderma molecular profile in the skin, ultimately leading to tissue softening and disease regression.

Novel treatment and innovative study design: the way forward



Collagen (red and green areas), causing fibrosis in normal skin versus scleroderma skin

An innovative aspect of the clinical trial is that each patient serves as his/her own control. One arm is treated with the drug, while the other arm is treated with an inactive look-alike placebo, so each patient in the study gets treated with both active drug and placebo. Neither the patient nor the investigator knows which arm receives the active compound. According to John Varga MD, lead investigator at Northwestern, the results from this pilot study “should show clearly if the new drug is safe in scleroderma; and if it can normalize the misbehaving genes.”

Expecting exciting results

It is hoped that this innovative study will indicate drug efficacy without exposing the patient to potential systemic side effects. If successful, this trial might not only identify a promising new therapy, but should also pave the way for an entirely new and efficient way to evaluate anti-fibrotic drugs in the future.

Research Breakthrough: novel classification of scleroderma-related esophageal disease

Up to 90% of patients with scleroderma experience esophageal symptoms such as heart burn and trouble swallowing. Despite its frequency, little is known about how scleroderma-related esophageal disease develops.

First of its kind study

In a pioneering study, published July 2015 in *Arthritis and Research Therapy*, Dr. Monique Hinchcliff and her colleagues at Northwestern University and the Geisel School of Medicine at Dartmouth, made headway in the classification of scleroderma-related esophageal disease.

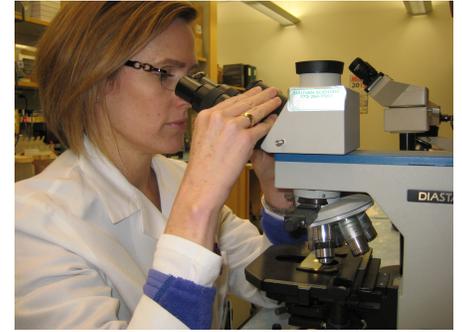
Identifying distinct subtypes

Using histological (study of tissue under the microscope) and gene expression analyses (study of which genes are 'turned on') on esophageal biopsies from scleroderma patients, the researchers identified two

specific gene expression signatures similar to those in skin. They call these inflammatory and proliferation signatures because the genes that were 'turned on' in patients were related to inflammation and cellular proliferation.

Classification leads to better therapies

Building upon previous research performed by Dr. Hinchcliff and colleagues showing that gene expression signatures in skin may accurately predict treatment response to a particular therapy, the identification of distinct subtypes in scleroderma-related esophageal dysfunction could be the first step in developing improved classification and ultimately better therapies for scleroderma esophageal disease. "We have known for a long time that simply treating patients with medicines to block acid suppression and life style modifications to



Dr. Hinchcliff examining an esophageal biopsy

prevent reflux is not sufficient. It may be that immune suppression and anti-proliferation medications are needed in order to halt disease progression in a meaningful way," says Hinchcliff.

Next Steps

Motivated by the exciting results of this study, follow-up studies are underway to determine if specific gene expression signatures are related to esophageal function and whether existing drugs can be repurposed to treat scleroderma esophageal disease.

Physician Profile: Benjamin Korman, MD



Dr. Benjamin Korman, MD is the newest physician-researcher to join Northwestern's Scleroderma Program.

Influenced by early experience

Many doctors go their entire career without seeing a patient with scleroderma. Dr. Korman's interest in scleroderma developed even before he knew he would be a rheumatologist. He recounts working with a patient with a scleroderma-like mixed connective tissue disease as a 3rd year medical student. He vividly remembers the feeling of helplessness that drove him to read as much as he could to

learn about scleroderma, and yet not having the ability to heal the patient because of the lack of available treatments and the poor understanding of the cause and nature of the disease.

Physician-researcher to make a tangible difference

Dr. Korman finds that being a physician-researcher in a field with so many unknowns, like scleroderma, lends the perfect opportunity to bridge the gaps in the treatment of the disease. Instead of feeling helpless, Dr. Korman now sees an opportunity to make a tangible difference.

Funding awarded for exciting research

Recently awarded a highly competitive NIH K12 award to

pursue his research interests, Dr. Korman is focusing on the relationship between fat and fibrosis. Having developed a mouse model to show that fat tissue plays a role in systemic sclerosis, Dr. Korman is now bringing his research to the clinic. He is measuring levels of circulating adipokines (cell signaling proteins made by fat cells) in serum samples collected from patients with scleroderma by the Northwestern Scleroderma Patient Registry. By correlating these levels with SSC complications such as lung disease, pulmonary hypertension, cardiac disease, and skin fibrosis, Dr. Korman hopes to find novel biomarkers that could help predict the complications that are likely to develop for each patient with scleroderma.

Care for Patients Near and Far

Betsy Hannig's scleroderma symptoms began in January 2006. After several misdiagnoses from physicians in her area and persistent uncertainty about the symptoms she was experiencing, Betsy was referred to Northwestern Scleroderma Program. That's when everything changed. She received her official diagnosis in November 2006—diffuse systemic sclerosis.

"I'm very happy that Betsy was referred to Northwestern, because she's received excellent care," said Martha Wiebers, Betsy's mother. "It's a bit of a trip to get to Chicago from Litchfield, but the quality of the care far outweighs the inconvenience."

Both Betsy and Martha credit the expert care Betsy has received to the overall excellence of the Northwestern Scleroderma Program—its faculty, breakthrough research, and state-of-the-art facilities.

"They know what's going on at Northwestern," said Betsy. "Instead of seeing just a couple of patients with scleroderma, the program sees thousands. This allows them to conduct research into the disease using their patient database."

Support for a Unique Program

Ever since her daughter's diagnosis,

Martha has been a committed philanthropic supporter of the Northwestern Scleroderma Program.

"Martha's philanthropic support has been invaluable by allowing us to run pilot experiments," said Dr. Varga. "The results from these initial efforts have led to a larger grant that will allow us to study individual variations in gene profile among patients with scleroderma. The new grant, called SPARC, enables us to use the most advanced molecular technology to study thousands of genes simultaneously. Our hope is that these studies will speed us toward 'precision medicine' so that we can use the most effective and safest drugs at the right time for each patient."

Bolstering Education in Scleroderma

An Illinois native, Martha worked as a public school teacher. "As a teacher, I understand the importance of education," said Martha. "And in the case of scleroderma, it is especially important."



Martha Wiebers (left) with her daughter Betsy Hannig

"I don't want other families to have to go through this," she continued. "At the start, our lack of knowledge about this disease was woeful. Rather than rely on internet research or word-of-mouth, I want other families to benefit from this great scleroderma research, care, and, hopefully one day, cure."

For more information about supporting the Northwestern Scleroderma Program, contact Maureen Mizwicki at 312-503-1090 or m-mizwicki@northwestern.edu. To make an online gift, visit wewill.northwestern.edu/rheum.

Northwestern Scleroderma Team Awarded First SPARC Grant

The Northwestern Scleroderma Program is among the first groups to be awarded a large grant from the Strategic Pharma Academic Research Consortium for Translational Medicine (SPARC).

Innovative Collaborations

The goal of SPARC is to advance research by creating unique opportunities for collaborative

research across academic centers and the pharmaceutical industry.

The research team will collaborate with a team at Washington University in St. Louis led by John Atkinson, MD, professor of Internal Medicine and Molecular Biology, and Elisha Roberson, PhD, instructor of Medicine.

From Basic Science to Improved Clinical Care

Patients with scleroderma and healthy controls will be recruited at Northwestern. The research team will use cutting-edge RNA/NextGen sequencing technology and advanced big data analysis to analyze blood and skin samples. These studies will allow the researchers to identify molecular signatures that could lead to more effective, personalized treatments for scleroderma.



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The Northwestern Scleroderma Program of Northwestern University's Feinberg School of Medicine is led by a multi-disciplinary team of dedicated clinicians and researchers. The Program is committed to provide comprehensive, state-of-the-art patient care and pursue clinical and laboratory research leading to innovative treatments for scleroderma. Our research is made possible through philanthropic support from individuals, grants from the National Institutes of Health, and private foundations.

Young Scleroderma Researcher: Tiffany Phanhdone



Diagnosed with scleroderma at the age of 20, medical school student Tiffany Phanhdone has a unique perspective on the disease. She understands the importance of being

an advocate for herself as a patient as well as the disease.

Patient and young researcher

Since her diagnosis, Tiffany has become active in scleroderma support groups, fundraising and spreading awareness. She has served

on the Associate Board of the Scleroderma Foundation of Greater Chicago. And now she is also researching the disease for a cure.

Tiffany's research on scleroderma renal crisis (SRC) was recently awarded a grant from the Rheumatology Research Foundation. Working with Drs. John Varga, Ben Korman and Cybele Ghossein, an expert in chronic kidney diseases, Tiffany will be targeting specific genes to determine their role in the development of SRC. Tiffany chose to study renal crisis because it is a rare yet potentially devastating complication of scleroderma. "I

hope my research helps physicians track SRC to determine if it will happen before it does happen. If you see it earlier, you can treat it earlier. I think this is an attainable goal."

Opportunity to educate other patients

As a scleroderma patient, budding physician, and now researcher, Tiffany finds that she has the unique opportunity to make important contributions to understanding scleroderma, and to educate others about the disease. She's excited to continue to learn more herself and pass on the knowledge to others with scleroderma.