NORTHWESTERN SCLERODERMA PROGRAM Bulletin

In this issue:

Does Broccoli Hold the Key to Halting Fibrosis?

In scleroderma, the immune system is working in overdrive. Cells begin to make collagen as if fixing an injury, but do not shut off like cells in a normal immune response. Instead, they continue to make collagen - resulting in fibrosis, or scarring, the hallmark of scleroderma. Fibrosis of the skin and lungs interferes with function, and causes stiff skin, joint contractures and breathing problems. Currently, there are no approved treatments to stop fibrosis. New research by a Northwestern team led by Jun Wei and John Varga in collaboration with scientists from the Baltimore biotech, Cureveda LLC, could lead to a ground- breaking treatment option based on a natural chemical found in broccoli. The study is supported by the National Institutes of Health (NIH).

The amazing Nrf2 pathway

Nrf2 is a protein normally present in every cell that helps the body's natural defenses. When activated, Nrf2 turns on anti-inflammatory, anti-oxidant and cell-protective proteins. Scientists recently discovered that broccoli is rich in sulforaphane, one of nature's strongest Nrf2 activators. Dr. Wei asked if this broccoli ingredient could be used to block scarring, and hence treat scleroderma, in mice.

New Nrf2 activator based on broccoli could halt fibrosis

Dr. Wei showed that Nrf2 activators can prevent or improve skin fibrosis in two different animal models. The new and exciting study builds on this discovery. The research focuses on VEDA-1209, a potent experimental Nrf2 activator. This compound, modeled after the broccoli substance sulforaphane, was recently discovered by scientists at Cureveda in Baltimore. Using skin biopsies collected from scleroderma patients, a team led by Dr. Wei and scientists from Cureveda will be evaluating Nrf2 levels, and testing VEDA-1209 as a potential anti fibrotic treatment.

Wishing You a Very Happy New Year from the Northwestern Scleroderma Program

Recent Research Breakthrough: Fibronectin and Fibrosis

A breakthrough discovery by Swati Bhattacharyya, PhD, Scientific Director of the Scleroderma Research Laboratories, identified a signaling pathway that may hold the key to stopping scarring (fibrosis) in some individuals. In her efforts to discover why fibrosis occurs, Bhattacharyya discovered that levels of a protein called fibronectin (FnEDA) were highly elevated in scleroderma patients and undetectable in healthy adults. FnEDA is a normal protein important for normal embryo development, but in adults its excess buildup appears to have harmful effects.

Does FnEDA lead to Fibrosis?

To test the theory that FnEDA is necessary for fibrosis, Bhattacharyya's team used a genetically engineered mouse that lacked the protein. The scientists found that these mutant mice were protected from fibrosis. Addition of FnEDA triggered an immune response in skin cells, leading to fibrosis. Furthermore, working together with scientists from the University of Michigan, Bhattacharyya's team discovered that fibrosis in the mice could be arrested by a small molecule used to block the immune response triggered by FnEDA.

Next Steps

The results of this high-impact study were published in the April 2014 issue of the journal, Science Translational Medicine. The study was supported by The National Institute of Arthritis and Musculoskeletal and Skin Disease Grants AR42309 and AR057216. The implications of this discovery are far-reaching, since they not only shed light on the role of FnEDA in scleroderma, but also open new doors for developing effective antifibrotic treatments. Studies along these lines are already underway.

From Bench Research to Clinical Trial...Stay Tuned!

A new clinical trial for the treatment of scleroderma skin diseases is slated to start at Northwestern in the Spring of 2015. Building on cutting edge research by members of the Northwestern Scleroderma Program, the trial will be evaluating a topical cream as a potential new treatment for the scarred skin and stiff joints. More information will be available soon.

Physician Profile: Darren Brenner, MD

After the skin, the gastrointestinal (GI) tract is the organ system most commonly affected in patients with scleroderma. Weakening of muscles in the GI tract can affect up to 90% of those with scleroderma. This causes the most common GI symptoms, such as acid reflux and difficulty swallowing. Even mild GI symptoms can significantly impact quality of life, making a gastroenterologist well versed in motility issues an important member of the team treating scleroderma.

A specialty in scleroderma was meant to be

After training under the motility experts at the University of Michigan, choosing scleroderma as one of his clinical specialties was a natural decision for Dr. Darren Brenner. It allows him to combine his long standing interest in critical care medicine with his passion for treating complex concurrent issues in multiple organ systems. He also enjoys working with patients that he finds inspiring for their commitment to understanding and treating the disorder.

Making a difference

Now, as director of Northwestern's GI Motility Lab, Dr. Brenner is able to use advanced motility tests and tools to improve patient care at Northwestern. "My ultimate goal is to reduce the patient's symptom burden and improve quality of life" says Dr. Brenner. "I have met and hope to continue to meet many wonderful people and their families. I hope to improve their quality of life whether by direct medical intervention, education, social awareness or advocacy on their behalf."

Clinician, educator and researcher

When not in clinic, Dr. Brenner dedicates his time to patient education and research. He has spoken at numerous patient education events, and is currently collaborating with Dr. Monique Hinchcliff in Rheumatology on a study looking at changes in gene expression in esophageal tissue taken from patients with scleroderma.

An Evening at Spiaggia

In a meaningful display of their partnership and mutual dedication to scleroderma research, Northwestern University Feinberg School of Medicine physician-researchers from the Northwestern Scleroderma Program joined with members of the Scleroderma Research Foundation (SRF) to host a presentation and dinner at Spiaggia in Chicago, Illinois.

Donors, Buddy and Sara Campbell (left), with Chef Tony Mantuano (right)

Funding to find a cure

Luke Evnin, PhD, chair of the Board of Directors at SRF, spoke to the importance of funding collaborative medical research aimed at improved therapies and a cure. John Varga, MD, John and Nancy Hughes Distinguished Professor of Rheumatology and director of the Northwestern Scleroderma Program, gave an overview of research being conducted at Feinberg, pointing out: "We are one of the innovation engines at Northwestern University, working to discover novel treatments for scleroderma that can be validated in preclinical studies and clinical trials, and delivering integrated personalized medicine—matching the right treatments to the right patients."

Results of a collaborative effort

John Pandolfino, MD, Hans Popper Professor and chief of the Division of Gastroenterology and Hepatology, introduced his clinical work involving pressure profiles and imaging in regards to reflux. "Because of our expertise in esophageal disease Dr. Hinchcliff, when looking at scleroderma's effects on swallowing, came to us so that we could help her to define different types of scleroderma esophageal disease on a clinical level."

Monique E. Hinchcliff, MD, MS, assistant professor of medicine-rheumatology, presented results of recent collaborative translational studies. Dr. Hinchcliff and gastroenterology researchers obtained esophageal biopsies from scleroderma patients and measured gene expression. They discovered that a subset of patients manifest inflammation while another subset demonstrate a proliferation gene expression signature. "Effective prevention and treatment strategies for esophageal disease in scleroderma will require obtaining a deeper understanding of the role that each of these (signatures) play in esophageal disease".

Generosity made the evening possible

The evening was made possible by celebrity chef Susan Feniger, a longtime friend of Sharon Monsky, founder of the SRF. On Top Chef Masters, Chef Feniger partnered with fellow celebrity chef, Tony Mantuano of Spiaggia Restaurant, to compete on behalf of SRF. This connection and Chef Mantuano's incredible generosity made this evening an extraordinary informational and gastronomical experience.

Through scientific collaboration and the philanthropic spirit of so many, much has been achieved in scleroderma research; however, much work remains to be done in order to continue to advance research and improve individualized patient care.

To learn more about Dr. Hinchcliff's groundbreaking esophageal research project and the ways in which you can support it, please contact Maureen Mizwicki at 312.503.1090 or m-mizwicki@northwestern.edu.

Clinical Trials Update: LOTUSS study complete

Lung disease remains the leading cause of death in patients with systemic sclerosis, and few treatment options exist. A team led by Dr. Jane Dematte, Professor and Co-director of the Northwestern Scleroderma Program, recently completed a clinical trial of pirfenidone, a new drug that could be added to the treatment arsenal for SSc. Pirfenidone recently received FDA approval as the first anti-fibrotic drug for the treatment of a form of lung disease called idiopathic pulmonary fibrosis.

Sponsored by InterMune, the LOTUSS study was a randomized, phase 2 study to evaluate the safety and tolerability of pirfenidone in patients with systemic sclerosis associated interstitial lung disease (SSc-ILD).

The study, conducted at 20 medical centers throughout North America and Europe, was completed in August 2014.

Approximately 60 patients with scleroderma enrolled, including 5 from Northwestern. Preliminary results indicated that the drug was safe and well tolerated, setting the stage for larger and more definite trials. With clinical trials like LOTUSS, the Northwestern Scleroderma Program hopes to introduce novel treatments for systemic sclerosis.

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

Scleroderma Investigator: Roberta Goncalves Marangoni, MD, PhD

For post-doctoral researcher Roberta Goncalves Marangoni, being an academic rhuematologist is truly in her blood: she is following in the footsteps of both her father and her grandfather, who was one of the first rheumatologists in Brazil.

Beginnings of her research career

Roberta started her research career while still in medical school. She travelled to Tufts University to find improved ways to diagnose Lyme disease. Her passion for research continued through her medical residency and fellowship at one of the top universities in Brazil, where she spent what free time she had visiting research labs and studying inflammation. She then completed a PhD training in Immunology.

Inspired by scleroderma research

Roberta's research turned to systemic sclerosis while studying a new animal model for the disease. Through her research, she became fascinated with the complexity of scleroderma and determined to continue to work on understanding the pathogenesis of the disease.

Current research focus

As an integral part of the scleroderma research team at Northwestern, Roberta's research focuses on the role fat metabolism plays in the development of fibrosis. She recently succeeded in developing a new genetically-engineered mouse that will afford unique insights into fibrosis, and where the scar-forming cells of the skin originate from. She just presented her preliminary results at the 2014 international Conference of the American College of Rheumatology in Boston. Her on-going research will be supported by a brand new research grant from the National Institutes of Health.

Most difficult part of her job

When asked what the most difficult part of her job is, Roberta answered,

"I love what I do. We have a team of very dedicated people and I have a wonderful mentor, both very important for a young researcher. For me, the most difficult part is knowing when to go home."

When she does find some free time, Roberta loves spending time with her family and hitting the ski slopes.

Favorite part of her job

Roberta loves a challenge, and she finds that in her job, every day is a new challenge. These challenges push her to work towards her goal: to find a piece of the puzzle that may lead to a cure for scleroderma.