

NORTHWESTERN SCLERODERMA PROGRAM

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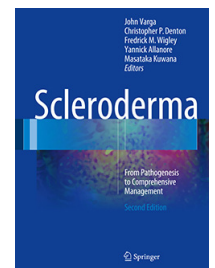
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Treatment of scleroderma lung disease: SLSII Results

The past year has seen intense scleroderma research activity at Northwestern, with multiple clinical trials underway or completed. One such trial is the recently completed Scleroderma Lung Study II (SLSII), the largest multicenter clinical trial of scleroderma lung disease to date. This pivotal study was sponsored by the National Institutes of Health (NIH), and at Northwestern was led by Drs. John Varga and Jane Dematte. This randomized study compared two treatments for scleroderma lung disease: mycophenolate mofetil (Cellcept) and oral cyclophosphamide (Cytoxan). The results showed that treatment with either improved lung function over 24 months, and was well tolerated. These findings substantiate the value of cyclophosphamide and mycophenolate mofetil in scleroderma lung disease. In addition, several newer drugs for lung disease, with potentially better safety and efficacy, are currently undergoing evaluation at Northwestern.

New Scleroderma Textbook Published

The second edition of **Scleroderma: From Pathogenesis to Comprehensive Management** was published recently. This major textbook, edited by John Varga, MD and international coeditors, presents a comprehensive and up-to-date view of the science and practice of scleroderma. The book includes chapters authored by leading specialists from around the world and members of the Northwestern Scleroderma Program, including Drs. Monique Hinchcliff, John Pandolfino, Amy Paller and Sanjiv Shah. The book is intended to be used as the major compendium of evolving knowledge on scleroderma and its treatment.



New clinical trials on the horizon

The Northwestern Scleroderma Program is participating in several exciting clinical trials for patients with early diffuse systemic sclerosis. For more information on research at the Northwestern Scleroderma Program please visit: <http://www.scleroderma.northwestern.edu/research/research-highlights.html>

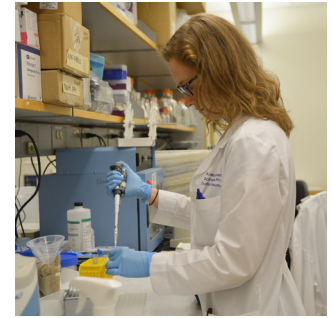
New tool predicts disease progression in scleroderma

Researchers at Northwestern Medicine along with those at the Stanford University School of Medicine and other institutions have designed a new diagnostic tool for scleroderma.

The standard measure of disease progression in scleroderma/systemic sclerosis (SSc) is the modified Rodnan skin score (mRSS). 17 areas of the patients' body are pinched and the thickness rated on a scale 0-3 with a maximum total score of 51. Despite careful training, different physicians evaluating the same patient may only agree 60-70% of the time, said co-lead author Dr. Monique Hinchcliff. A more precise measure has long been needed.

By measuring the activity in genes in skin samples (biopsies), the scientists were able to separate SSc patients from healthy control subjects. More importantly, the researchers identified 415 genes whose expression was associated with how severe a person's SSc skin disease had become. The researchers were able to use this gene-expression signature as the basis for a test, which they named the SSc Skin Severity Score, or 4S. The team then looked at existing data for a cohort of Northwestern patients who had repeated mRSS tests while undergoing treatment for SSc. When comparing the new 4S test to the mRSS test, the 4S test could distinguish patients who were improving from those who were not 12 months after their treatment began, whereas the mRSS test took up to 24 months to identify patient improvement.

Clinical trials, as opposed to retrospective studies looking at pre-existing data, are needed to validate the 4S test, the researchers said. But if it works as well as the researchers hope, clinicians may be able to evaluate patients' response to treatments much more quickly, so they can be switched to an alternative treatment that may work. The 4S test could also help advance the search for better



Monique Hinchcliff, MD (left) director of Translational Research and Co-Director of the Northwestern Scleroderma Program

Research coordinator Aileen Hoffmann, MS (right), processes serum samples in the Scleroderma research laboratory.

therapies. The study results also suggest that epidermal growth factor receptors (EGFR) may play an important role in the SSc in addition to its role in cancer susceptibility. In SSc, the study showed that EGFR is consistently upregulated (activated). Thus, drugs that have been approved by the FDA for treating EGFR-related conditions may turn out to be useful in treating patients with systemic sclerosis.

This study was published December 22, 2016 in JCI Insight. Researchers at the following institutions also contributed to the study: Dartmouth College, the University of California-San Francisco, the Hospital for Special Surgery, the University of Texas Health Science Center and the Veterans Affairs Palo Alto Health Care System.

The research was supported by the National Institutes of Health (grants 1U19AI109662, U19AI057229, U54AI117925, U01AI089859, 1R21AR068035 and K23AR059763), the Bill and Melinda Gates Foundation and the Scleroderma Research Foundation.



Featured Staff: Elisa Hoellerich, MMS, PA-C

The scleroderma team at Northwestern grew with the addition of Elisa Hoellerich. Elisa completed her Master of Medical Science degree at Yale University, and joined the Northwestern Scleroderma Program in 2015. Elisa is excited to be a part of a team that works directly with patients while at the same time carries out extensive patient-oriented research. She chose rheumatology as one of her elective rotations during her studies and was attracted to the challenges that come with treating patients with rheumatic disease. Her favorite part of the job is developing long-term relationships with patients in the program. The most challenging part of her job is dealing with insurance companies and logistics, since it takes away time she could be spending with her patients. During her undergraduate studies, Elisa worked as a research assistant and medical volunteer at a clinic in South Africa. Apart from work, Elisa has quite an obsession with her bulldog, enjoys traveling, and although originally from Barrington, IL, she likes to indulge in the many cultural and tourist attractions around Chicago.

Recap of Northwestern Scleroderma Program Patient Education Seminar

In collaboration with the Scleroderma Foundation Chicago Chapter, we held our annual Patient Education Conference on Saturday, October 15, 2016. About 100 people attended, including patients, caregivers, doctors, and other health professionals.

Presentations included an overview of a promising novel therapy called extracorporeal photopheresis (ECP) by Dr. Jaehyuk Choi, a dermatologist who recently joined the scleroderma team. Photopheresis is a procedure in which blood is taken from an IV, exposed to 8-MOP (the active ingredient in lime juice) and following exposure to UV light, returned to the body. This process stimulates T regulatory cells, which may help to dampen the immune response to autoimmune disease.

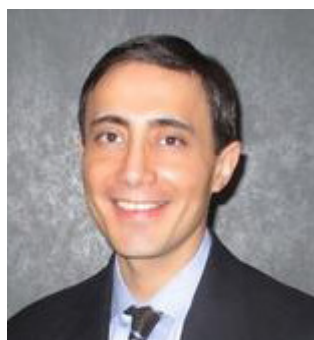
ECP has already been shown to help skin and joint involvement in scleroderma, and is used for a variety of skin conditions. The 5th Annual Walter Barr Keynote Presentation given by Dr. Shervin Assassi from the University of Texas-Houston, discussed the role of genetic studies in scleroderma. Additional sessions included research updates, erectile dysfunction, advice for caregivers, interstitial lung disease, pulmonary hypertension, and a patient panel. Most of the presentations can be found on the Scleroderma Foundation Chicago Chapter's YouTube channel at www.youtube.com/gcscleroderma. Please also visit the main website for additional resources: www.scleroderma.org/chicago and save the date for the next seminar, set for Saturday, October 14, 2017.

Fat grafting- toward regenerative therapy for scleroderma?

A new promising treatment involving autologous transplantation of stem cells from fat tissue, sometimes called "fat grafting," was recently evaluated in a clinical trial at Northwestern. The Northwestern team, led by Drs. Robert Galiano, Professor of Plastic Surgery and John Varga, Professor of Medicine, participated in the multi-center, randomized, placebo-controlled, double-blind study to evaluate whether the fat grafting treatment is safe and effective in scleroderma.

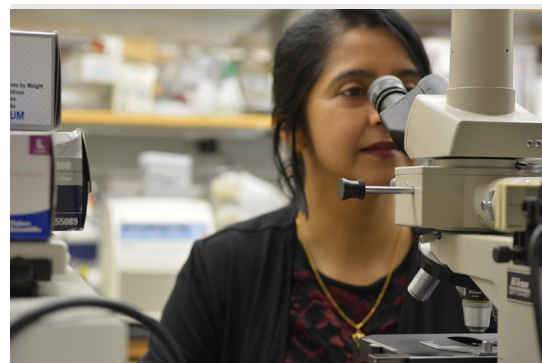
Here is how it works: after liposuction (removing some fat tissue from the patient), stem cells are isolated and prepared from the fat tissue, and these stem cells (or placebo) are then injected under the skin. The whole procedure is completed in a day, and is performed in the out-patient setting. Based on the basic research conducted by Drs. Jun Wei, Roberta Marangoni, and John Varga at the Northwestern Scleroderma

Research laboratory, the stem cells may help to reduce inflammation, form new blood vessels, and prevent skin fibrosis. A total of 88 scleroderma



Dr. Robert Galiano, Professor of Surgery

patients were enrolled nationally in the study. While final results will not be available until next year, the approach represents a significant advance in regenerative medicine to treat scleroderma organ damage.



Swati Bhattacharyya, PhD, Scientific Director of the Northwestern Scleroderma Research Laboratory and lead author in a study that discovered a molecule responsible for driving the excess scar buildup seen in fibrotic diseases like scleroderma

Mechanism behind chronic fibrosis discovered

In a recent study published in *Nature Communications*, Northwestern Scleroderma Program scientists led by Associate Professor Swati Bhattacharyya, PhD, discovered that a molecule called tenascin-C plays a pivotal role in driving the excess scar buildup found in fibrotic diseases such as scleroderma.

In this study, first author Swati Bhattacharyya and her team determined that levels of tenascin-C were significantly elevated in skin and lung samples from patients with scleroderma, suggesting that the molecule might be a biomarker of the disease. Follow-up studies in genetic animal-models of scleroderma showed that mice without tenascin-C did not develop chronic fibrosis. "We asked: How does the cell respond to this molecule? What is the sensor that tells the cell that there's too much tenascin-c?" co-author Varga explained. "We discovered that the sensor is the well-known immunoreceptor toll-like receptor 4 (TLR4), which is really exciting, because we have inhibitors that can block this receptor."

In ongoing research, the team is exploring novel compounds that can safely be given to patients to stop TLR4 from responding to tenascin-c and driving fibrosis. The investigators are also collaborating with cardiologists and neurologists to see how tenascin-c is involved in repair and scarring after heart attacks and spinal cord injuries. This study was supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases grants AR-42309 and K24 AR060297.

Patient Inspired to Connect through Research and Philanthropy

Six years ago, Julie Knost suddenly noticed a problem with her hands. Puffy and stiff, they made grasping objects difficult and performing simple tasks like preparing a meal frustrating for this once avid cook. An employment and discrimination attorney at Indiana University in Bloomington, Knost, 63, looked—and hoped—for a straightforward answer: “I thought it was maybe carpal tunnel.”

But then Knost’s symptoms worsened. In three months’ time, the skin on her face seemed extremely tight. A local rheumatologist offered a preliminary diagnosis of scleroderma. Fortunately, Knost’s rheumatologist had heard of John Varga, MD, John and Nancy Hughes Distinguished Professor of Rheumatology at the Northwestern Scleroderma Program—one of only a handful of such clinical and research programs in the country. Knost received an immediate referral.

While the disease has sapped her energy and limited her independence both at home and at work, Knost greatly appreciates the leading-edge care she receives through the program. “The doctors are not only great clinicians providing me with the latest therapies but also researchers who are spending their time in the lab looking for a cure,” she says.

“The program has truly given me a sense of place,” says Julie Knost (pictured). “Here, they know how to treat my disease. Here, there are other people like me who are being helped.”



“This unique relationship goes above and beyond the normal medical care you usually receive.”

For Knost, being actively involved in the Northwestern Scleroderma Program has given her an outlet

for overcoming the sense of isolation she sometimes feels as the only person she knows with the rare disease.

For example, she participates in the program’s research initiatives. Part of the scleroderma patient registry, she has contributed her tissue to the biobank and responded to research questionnaires. “Unlike with clinical trials and studies for more common diseases that can enroll hundreds of participants, there may be fewer than a dozen for a scleroderma study,” she explains. “Being involved in research allows me to help provide more data.” Knost also has supported the program through philanthropy because as a longtime employee of a university, she sees firsthand the impact of giving—no matter what the dollar figure. “I am by no means a big donor,” says Knost, “Even the smallest amount can make a difference.”

Giving to Scleroderma

Thank you for your interest in advancing Scleroderma care and research at Northwestern University Feinberg School of Medicine. The Scleroderma program and projects described in these pages is supported by funds from private philanthropy, government and institutional grants, and patient service revenue. While every source of funding is important, **private philanthropic support is especially vital to the success of our research and educational activities.** Over the years, the generosity of patients, friends and alumni has played a crucial role in attracting new faculty and initiating research. To make a gift to Feinberg’s Scleroderma program, please go to wewill.northwestern.edu/rheum. For more information on supporting the Scleroderma program, contact MaryPat Mauro at marypat.mauro@northwestern.edu or (312) 503-1090.

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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.