

NUARS NEWSLETTER



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Highlights in this issue:

- Announcement of new faculty member, Elisa Rhew, MD.
- Report on the development of Northwestern's Scleroderma Program

CUTTING-EDGE NORTHWESTERN PROGRAM OFFERS NEW HOPE FOR SCLERODERMA PATIENTS

The Northwestern Scleroderma Program is a new initiative in the Feinberg School of Medicine's Rheumatology Division. The primary aims of this unique program, headed by John Varga, M.D., are to build on the intellectual and material resources of Northwestern to accelerate scleroderma research, and to help discover new treatments. Clinicians and scientists from different departments have come together to work in the Scleroderma Program to achieve these shared aims.

What Is Scleroderma?

Scleroderma is a chronic disease of unknown cause that affects 300,000 people in the United States, most frequently young to middle-aged women. Scleroderma currently has no cure, and 10-year survival for the aggressive form is less than 50 percent. Because its symptoms vary, its complications affect multiple organs, and its clinical course is unpredictable, the evaluation and care of patients with scleroderma presents an extraordinary challenge. Furthermore, by the time of diagnosis, some patients are in an advanced stage of disease, with extensive skin, lung, gut, and joint involvement. At this stage, damage to the target organs may be irreversible.

Clinical Features—The most common first sign is Raynaud's phenomenon, or spasm of the blood vessels of the fingers and toes. With cold exposure or emotional stress, the fingers turn white, dark blue (cyanosis), then red. Spasm



Dr. John Varga (right) and his scleroderma research team pause to enjoy a Summer afternoon on the grounds of Northwestern University's Chicago campus

of the blood vessels is due to increased levels of proteins that cause blood vessel constriction. Over time, sustained elevation of these proteins leads to injury of the blood vessel lining. At this stage, vasospasm is no longer reversible and can result in soft tissue and bone loss at the fingertips.

The clinical hallmark of scleroderma is hard skin ("scleroderma" from the Greek scleros [hard] and derma [skin]). Under the microscope, the involved skin looks like scar tissue. Some patients have hard skin only on the fingers or face, whereas in others, the arms, chest, and legs are all involved. Many patients with scleroderma develop (*cont'd on page 3*)

NUARS NEWSFLASHES

Jennifer Weber, Research Project Coordinator for Dr. Ramsey-Goldman, joined the NUARS team in March 2005. This Chicago native has a degree in Biology from the University of New Mexico. When not working on Lupus research projects, Jennifer enjoys relieving stress by attending music concerts. Welcome, Jennifer!

Best wishes to **Dr. Darcy Majka**, Instructor of Medicine, on the birth of her new baby daughter, Elizabeth Clare. Mother, father Rich, and big sister Anna are all doing fine.

Welcome to **Dr. Kumi Inazaki**, new post-doctoral trainee in Dr. John Varga's laboratory. Kumi attended Juntendo University School of Medicine in Tokyo and worked as a pediatrician at a general hospital in the Japanese countryside prior to joining Northwestern. She is a native of Tokyo and enjoys motorcycle riding, inline skating on Chicago's lakefront, books, and movies.

Congratulations to rheumatology trainees **Drs.**

Sakeba Issa and Pin Lin on receipt of their new training grant awards from the National Institutes of Health. These prestigious awards, called F32 National Research Service Awards, will go a long way in supporting their training to become the next generation of rheumatologists.

We are pleased to announce that this year's **Scleroderma Foundation Forum** will be held right here at Northwestern on Saturday, October 22nd. This annual event, which will feature lectures on Scleroderma from Drs. John Varga and Walter Barr from NUARS and Dr. Jane DeMatte from Northwestern's Pulmonary Division, is free and open to the public. If you wish to attend, please RSVP with Ann Peterson at the Scleroderma Foundation by calling 312-922-3532.

The NUARS/Rheumatology office has a new administrative assistant. **Kelly Thompson** holds a degree in English from DePaul University. She joins our central office staff after working for the law school at the University of Texas, Austin. This new mother enjoys literature, kayaking, and spending time with her three-month old daughter, Maggie.



A BONE TO PICK: RICHARD POPE, M.D. NUARS DIRECTOR

I am pleased to announce the arrival of a new faculty member to the NUARS team, Dr. Elisa Rhew. Dr. Rhew joins our faculty after a three-year training fellowship here at Northwestern. Dr. Rhew was one of our most successful fellows and was able to secure not only a prestigious F32 training grant from the NIH, but was also awarded two additional grants, one from the Arthritis Foundation and another from the Northwestern Memorial Foundation. Dr. Rhew works closely with Dr. Rosalind Ramsey-Goldman and her Lupus research team. Please join me in welcoming Dr. Rhew to the faculty.

As former fellow Elisa Rhew joins the Northwestern faculty, I am pleased to welcome two new fellows into our training program, Drs. Siddharth Tambar and Arthur Mandelin. Dr. Tambar is a graduate of Northwestern's own residency program and was highly regarded by all our NUARS faculty while a resident at Northwestern. He received his MD degree from SUNY Upstate Medical University and is interested in pursuing research in psoriatic arthritis. Dr. Mandelin, our second new trainee, joins us following residency at Lutheran General Hospital, Park Ridge, IL. Dr. Mandelin, who holds both an MS degree in applied physiology and a PhD in biochemistry and molecular biology, received his MD degree from Finch University of Health Sciences/The Chicago Medical School. He plans to do research work in rheumatoid arthritis.

The cover story in this edition of the NUARS newsletter was written by Dr. John Varga. We introduced you to Dr. Varga in our Winter 2005 edition as a new faculty member. Dr. Varga is working to establish a world-class program in research and clinical care at Northwestern to battle scleroderma. Dr. Varga's program is off to a great start as he works to change the lives of those afflicted with scleroderma. I hope you will enjoy reading about his progress in our cover story.

Regards,

MULTIDISCIPLINARY CLINICAL RESEARCH IN RHEUMATOLOGY (MCRC) UPDATE

- Dr. Rosalind Ramsey-Goldman was recently named Program Director of Northwestern's General Clinical Research Center (GCRC). This federally-funded center provides resources for safe, cutting edge patient-oriented research for scientists across Northwestern's campus.
- We have begun preparations for the renewal of our MCRC grant. We are excited about the new potential research projects that our faculty have proposed and we hope to send our renewal application in February 2006.
- Congratulations to MCRC Methodology Core Director Rowland Chang on receipt of his new research grant: "Physical Activity Management for Clients of Arthritis" from the National Institute of Arthritis and Musculoskeletal Diseases.

NORTHWESTERN SCLERODERMA PROGRAM (CONT'D)

(*cont'd from page 1*) severe complications. Problems in the esophagus are very frequent, manifested by heartburn, and difficulty swallowing. When the entire intestinal tract is involved, weight loss and malnutrition can occur.

Currently, the most severe complications affect the lung in two distinct forms: interstitial lung disease, or ILD, and pulmonary arterial hypertension, or PAH. In ILD, scarring affects the lung itself, causing difficulty with breathing. Initially, the problem is recognized only with tests, such as CT scans and pulmonary function studies; with time, shortness of breath develops. The other main respiratory complication is PAH, which is like Raynaud's of the blood vessels in the lung. Because it tends to be progressive and no effective treatments were available until recently, PAH was a dreaded complication of scleroderma.

By its very nature, scleroderma is a multisystem disease with variable manifestations. Optimal care therefore requires the coordinated efforts of medical specialists experienced with scleroderma. Furthermore, management must be individualized to meet the unique needs of each patient. A major goal of the Northwestern Scleroderma Program is to provide integrated care addressing all aspects of the disease. The input of specialists with

expertise in the various facets of scleroderma, the availability of state-of-the-art imaging technologies, and the superb clinical facilities of Northwestern Memorial Hospital, ensure the best outcome for patients with scleroderma.

The Scleroderma Challenge—The complexity of scleroderma is due to its association with widespread blood vessel damage, autoimmunity (when the immune system attacks the body), and scarring affecting multiple organs. Because scleroderma is relatively uncommon, there are only a handful of specialized scleroderma centers in the U.S. There are no effective disease-modifying drugs, steroids may be contraindicated, and, until recently, no treatment of scleroderma had been approved by the Food and Drug Administration. Fortunately, the past five years have seen substantial progress in scleroderma therapy, and in understanding its molecular basis.

Scleroderma Research at Northwestern—To build on this progress, the Northwestern Scleroderma Program brings together an expert team of clinical and laboratory researchers to “hone in” on the specific abnormalities that cause scleroderma. Broadly speaking, scleroderma research at Northwestern falls into two categories: basic laboratory research and clinical/translational research. The

efforts in these two interlinked categories are closely coordinated to ensure rapid translation of discoveries from the bench to the bedside and back.

Exciting New Insights: Laboratory Research

The hallmark of scleroderma, scarring or fibrosis in the skin and vital organs, interferes with their function and leads to the clinical complications. Scar tissue is composed of a large protein called collagen. While collagen is a normal component of all tissues, excess accumulation causes fibrosis in scleroderma. The main source of collagen is a cell called fibroblast, and activation of fibroblasts results in collagen overproduction.

How and why are fibroblasts activated in scleroderma?

To answer this vital question, the Varga Lab has studied fibroblast cells obtained from scleroderma patients or healthy volunteers. The studies have yielded several surprising and highly significant findings: first, that scleroderma fibroblasts appear to be activated; second, some fibroblasts change into muscle-like cells called myofibroblasts; third, that a protein called transforming growth factor- β (TGF β) is essential for fibroblast activation; and finally, several compounds can specifically block fibroblast activation. Some of these are already in use for diseases such as diabetes and leukemia,

whereas others could be developed into drugs in the future. Our studies have identified over a dozen cellular proteins whose suppression could prevent fibroblast activation and “normalize” scleroderma fibroblasts. We are now trying to identify all the molecules and cellular pathways that contribute to scar formation, with the goal of developing interventions that selectively and efficiently block their functions.

Mouse models are vital tools—Another major goal of our research is to develop animal models of scleroderma. To date, the lack of a mouse model that mimics the human disease has slowed down the discovery of new treatments. We are evaluating several models (genetic mutations and chemically induced) to determine their similarity to scleroderma, to gain new insights into the mechanism of disease, and to evaluate the effectiveness of novel treatments. Discoveries emerging from these pre-clinical studies will serve as springboards for clinical trials.

Clinical and Translational Scleroderma Research

Hand-in-hand with laboratory research, clinical investigation is also moving ahead. A major focus is the evaluation of innovative treatments. New drugs and interventions must undergo rigorous testing to determine their safety as well as their effectiveness. This is performed under strict ethical and (*cont'd on page 4*)

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NORTHWESTERN SCLERODERMA PROGRAM (CONT'D)

(cont'd from page 3) institutional guidelines, within the framework of randomized controlled trials. Such studies are generally carried out in collaboration with other centers, and can take up to a year or longer. An important goal of clinical research is to identify and characterize the factors ("biomarkers") that determine if a person will or will not respond to a treatment. Biomarkers include genetic variations, protein levels, or the activation of blood cells. Because biomarkers will be vital tools for taking the guesswork out of clinical decision-making, current clinical trials include collection of blood, DNA, and other patient material for analysis. A long-term goal of our research is to correlate biomarkers with patient outcomes.

These research efforts are intimately linked to patient care. The guiding philosophy of the program is "bench-to-bedside." In order to facilitate translation of cutting-edge research discoveries into the highest level of patient care, our clinical team, representing a variety of medical specialties, interacts with our researchers. Regular conferences provide a forum for sharing the latest developments and exchanging information. In addition, the Northwestern Scleroderma Program is integrated into nationwide research efforts, including the Scleroderma Clinical Trials Consortium and the National Institutes of Health-funded Scleroderma Lung Study.

Goals of the Northwestern Scleroderma Program:

- Provide integrated medical care (multidisciplinary clinical team)
- Trials of novel drugs and therapies
- Clinical and translational research (bench-to-bedside)
- Educate patients, and physicians, about prognosis in the diagnosis and therapy of scleroderma

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