

By Robert Halpern

Robert Halpern recently visited with John Varga to talk about scleroderma research, why it is important, what the state of scleroderma research is, and what the important questions might be in coming years. Here is what he learned.

The Scleroderma Program at Northwestern University's Feinberg School of Medicine includes several researcher-clinicians. Our visit started with Dr. Varga providing a tour of his laboratory facilities and he introduced me to members of the research team he has assembled.

At this time, Dr. Varga and his team are conducting research on the molecular level processes—and the roles of specific proteins—in causing collagen overproduction (which leads to fibrosis and scarring).

As a part of this work they are trying to identify the most likely cellular and molecular targets that might block these damaging processes. In his more clinically-oriented research, he is trying to identify the factors (known as biomarkers) that determine whether a person will or will not respond to a particular treatment.

The Funding Situation

Dr. Varga noted there is currently about \$10 million a year—at most—supporting scleroderma research in the United States. Though this sounds sizable, he pointed out this is a very small amount compared to what is available for other diseases with comparable frequency (such as multiple sclerosis, juvenile diabetes and ALS) and also for the general needs of scleroderma research.

This disease, he said, “is hugely underfunded,” noting that “there is a dire need for more funding if substantial progress is to occur in the near future.”

Over the years, the Scleroderma Foundation has worked diligently to raise the visibility of scleroderma among the general public, pharmaceutical industry, and government and elected officials, but in spite of this progress its profile remains low.

In addition, scleroderma is a difficult disease to describe and understand, especially in the simple terms needed to strike a chord with the public.

The National Institutes of Health is the main public funder of scleroderma research. Although attention to and funding for the disease has increased within the NIH in recent years, the funding climate for biomedical research has recently deteriorated “across the board.”



A Conversation With...

Chair of the Medical

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John Varga, M.D.

As Dr. Varga describes it, this deterioration puts scleroderma research in special jeopardy. Basically, the NIH puts prospective grants in related areas of research into a large pool, ranks them, and then funds them in descending priority until there is no money left.

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Since the total number of scleroderma research grants across the country is small, the loss of even a few grants, and elimination of even a few dedicated investigators, can have a big impact.”

“Seed Grants” Are Solid

Even though major grants are getting a little harder to come by, research funding through private organizations like the Scleroderma Foundation and the Scleroderma Research Foundation has been important in “seeding” research on the disease.

These grants have helped younger researchers get going and have supported the research programs of a few scleroderma centers around the country.

Dr. Varga says it is difficult to support the type of sustained laboratory and “translational” research that is critical to making progress in combating scleroderma using individual grants, secured one at a time.

While they can be very helpful supporting work on a specific issue or question, grants like these are unable to support the necessary accompanying infrastructure and typically “provide little leeway to explore anything totally innovative.”

Dr. Varga said he is beginning to believe the model that funds key research centers above and beyond individual research projects makes sense for scleroderma research. This approach provides greater stability, creating a foundation for a long-term program of research.

This allows for the development of the research infrastructure, and a

critical mass of researchers with overlapping interests and complementary strengths to be assembled in one setting. As an example of this, Dr. Varga mentioned the important role of “translational researchers,” who serve as a kind of bridge between basic research insights and novel treatment approaches.

Moreover, a regional scleroderma center is a source of pride, and a visible place for those seeking treatment.

The Questions We Face

Assuming the scleroderma community and its key researchers can raise adequate funds for research, Dr. Varga unfolded some of what he sees as the most important research questions we will face in coming years.

These are: the epidemiology of the disease; its pathogenesis (i.e., the sequence of events and processes leading to injury); and therapy.

Important epidemiological questions focus on the genetics of the disease, the criteria for defining it, different variants and their prevalence, whether scleroderma is best understood as one disease or more than one, sources of gender differences (women being far more commonly affected than men), and the role of environmental factors.

The questions surrounding issues of pathogenesis include links between the immunological, vascular and fibrotic components of the disease (e.g. the question of whether autoimmunity precedes vascular disease); the roles of particular types of cells in each of these areas; and insights from population genetics/family studies and gene array studies.

With respect to therapy, questions include what should be targeted (e.g. autoimmunity/tolerance, inflammation, vascular injury, fibrosis) at what stage of the disease, appropriate indicators of response to treatment, how early scleroderma can be diagnosed, and the individualizing

of therapy (including the role of biomarkers for distinguishing who will benefit from which therapies).

This list is very large. When asked to name priorities among these different areas and questions, Dr. Varga answered it is not possible to identify a small number of “right questions.”

He did say it is possible to prioritize among some of the strategies for improving understanding of the disease, noting as examples the importance of genetics/genomics and identification biomarkers, both of which would create new tools to use in research. But he believes, overall, a bottom-up approach with questions coming from researchers exploring different theories, pathways and understandings makes the most sense.

Reflections on the Day

Thinking back over the time spent with Dr. Varga, it is striking how, in research terms, the disease resembles an extremely complicated puzzle. Researchers and clinicians have found the right place for a number of pieces. Some connections have been made and the picture is just beginning to appear. This must be personally satisfying to be on the leading edge of research on an as yet partly understood disease.

It is impressive to see the enormous human and physical resources needed to address even a few of the many critical questions in scleroderma research.

It also seems that filling in this puzzle will require significantly greater support for research than \$10 million a year. That must be frustrating for researchers dedicated to identifying the cause of and cure for scleroderma.

Robert Halpern is a board member of the Greater Chicago Chapter of the Scleroderma Foundation.