



Scleroderma
RESEARCH FOUNDATION

YEAR-END UPDATE 2016

Founded in 1987 with a
passionate commitment that lives on:
**to use the power of
collaborative medical research
to advance a cure.**

hereditary, making it amenable to genetic analysis. Dietz was especially intrigued because he suspected SSS might arise from mutations in fibrillin-1 (the same protein that is affected in Marfan Syndrome).

While most forms of systemic sclerosis are associated with minimal hereditary risk, the Choctaw Native Americans have a higher incidence of scleroderma than the general U.S. population, indicating that they may be susceptible to a form of systemic sclerosis that has a stronger genetic component. Interestingly, the form of scleroderma found in the Choctaw population has been associated with a mutation in the regulatory regions of the fibrillin-1 gene. This evidence provided additional support for the idea that studying SSS might illuminate molecular pathways involved in systemic sclerosis.

Dietz and his team worked aggressively to confirm the genetic cause of SSS.

“There are perhaps fifteen families, total, that have SSS,” said Dietz. “But we were able to use some of the most powerful scientific tools available in order to understand that disease and its causes.”

Their research pinpointed the genetic mutation responsible for SSS, in the gene for fibrillin-1. Their findings, published in *Science and Translational Medicine* in 2010, seemed a watershed moment.

The fibrillin-1 protein plays a role in other connective tissue disorders, such as Beals Syndrome and Marfan Syndrome. In some types of tissues, including skin, fibrillin-1 constitutes part of the scaffolding for cells that holds tissue together and communicates with cells. The particular genetic changes in fibrillin-1 in SSS impair the protein’s ability to make contact with the cells through bridging molecules called integrins.

In SSS, and perhaps in scleroderma, the researchers postulated, the cells in the skin lose their ability to attach to the extracellular matrix (through fibrillin-1) and to sense their surroundings. Those cells then activate and stimulate an immune response causing surrounding cells to produce excessive amounts of collagen in the skin. The findings were a crucial first step toward halting the merciless progression of fibrosis in scleroderma.

Building a Better Model

“Scleroderma has, for years, been a frustrating and mysterious disease to study,” said Dietz. “People can show no obvious signs of the disease, and then within a year, have catastrophic consequences.”

Among some of the more frustrating elements of studying scleroderma is the heterogeneity of the disease. Scleroderma, like other complex, adult-onset autoimmune diseases, had proven resistant to the development of animal models, due to weak hereditary links and the uncertain etiology, which makes it difficult to recreate a disease process in a model system. Also, the fact that the disease can present in many different ways and with different levels of severity further confounds development of a single model.

Dietz, however, was convinced that having identified the genetic cause of fibrosis in SSS, he could create a mouse model that would be informative for scleroderma. Subsequently, his team was successful in developing transgenic mice with SSS and this model has allowed them to tease out how the molecular defect caused by the mutation in fibrillin-1 leads to fibrosis. They found that SSS created a condition that impaired fibrillin’s interaction with integrins. And, as separate

proof of this insight, animal models that were manipulated to express artificially low levels of integrins never developed fibrosis (i.e. they were protected).

They then found that blocking certain integrins, or activating others suppressed the inflammatory response that preceded fibrosis and even turned off the production of collagen, the key protein that is over-expressed in scleroderma. The team tested their fibrillin-1 pathway blocking and activating compounds on cultured skin cells from scleroderma patients and saw the same results. Their subsequent research has identified many components in the pathway that interact to initiate and sustain fibrosis. Thus, the first and one of the most complicated parts of finding a potential treatment for scleroderma’s signature fibrosis — identifying the mechanism for how fibrosis develops — may be beginning to crack open.

“Indeed, it would seem that the study of a very rare disorder has informed the study of scleroderma,” said Dietz.

Building a Company, Building a Drug

The work done by Dietz and his team has paved the way for the next phase in the evolution of the discovery, the development of potential therapies. In 2015, Dietz took a giant leap toward translating his research into treatments with the formation of a biotech company, Blade Therapeutics. To do this, Dietz turned to SRF Chairman Dr. Luke Evin to help get it done. Evin, a scleroderma patient and co-founder of the life sciences venture capital firm MPM Capital, knew Dietz and his fibrosis work very well.

With MPM leading the way, a number of highly respected life science investors, including Deerfield, Osage, Novartis, Pfizer, Inc., and Bristol-Myers Squibb, saw value in moving the research forward. Blade Therapeutics has raised more than \$50 million in two venture financings, an exceptional amount for an early-stage biotechnology company.

Armed with the cutting edge research provided by Dietz, Blade’s focus is to discover potential drugs against therapeutic targets that are critical to the fibrotic process and advance them into clinical development. With several potential leads already identified, Blade will now be tasked with narrowing the field to a promising drug compound. This is no small task. “Going in, we thought that fibrosis couldn’t be reversed,” said Dietz. “While I can’t overestimate my excitement, getting this eventually to patients is the goal.”

The SRF as an Essential Partner

The SRF’s strategy of finding, funding, and facilitating the most promising, highest quality research, and fostering the community of scientists to tackle the problems presented by scleroderma has, with Dietz, Blade Therapeutics, and his fibrosis research, provided reasons for optimism.

“The SRF has been a critical, essential partner,” said Dietz. “Scientists need a community to form and check ideas, and we need funding. The SRF Scientific Advisory Board nudged and sometimes shoved us into some very important new directions in the research.”

The direction is promising and we look forward to what the future holds. “I’m proud of the funding of Hal’s work,” said Evin. “It was catalyzing, and it is the foundation of a promising company that we are all proud to be playing a role in.”



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