

THINGS YOU NEED TO DO TO PURSUE RESEARCH

When Brad Margus graduated Harvard Business School, unlike most of his classmates who went on to careers on Wall Street or in consulting, he entered the business of leveraged buyouts and soon found himself running a shrimp processing company. It was then that he learned that two of his three sons had the rare disease Ataxia telangiectasia or A-T.

A-T is a genetic disease that causes progressive loss of muscle control, immune system problems, and a high rate of cancer. Children with A-T as toddlers wobble when they walk. Later they develop difficulty moving their eyes, their speech becomes slurred and they develop problems swallowing. The cerebellum of the brain suffers progressive degeneration that eventually leads to a loss of muscle control. Lung infections become common and about 30 percent develop cancer. Approximately 400 people in the United States have A-T.

When his sons were diagnosed, Margus, who was not trained in science, began to learn about molecular genetics. He eventually formed the A-T Children's Project and since has raised \$30 million to fund research, organize conferences, create a tissue bank, and do other work. In 2000, he left the food industry to launch Perlegen Sciences, which became a leader in analyzing genetic variation, discovering diagnostic markers for disease risks, as well as adverse drug effects. He later started Envoy Therapeutics to develop therapies to treat neurological diseases. Today he is founder and CEO of Exigence Neurosciences and a parent advocate.

During a presentation at the Global Genes 2015 RARE Patient Advocacy Summit, Margus discussed his experiences, what he's learned as a businessman interacting with scientists, and what rare disease groups can do to pursue a science agenda to address the challenges of a rare disease.

"I didn't know anything about how the government funds biomedical research—I really didn't care. I didn't know about the career scientists have and how publishing is important or how you have to get a post doc and serve your time as a lab rat before you become a big shot. I didn't know any of that stuff," said Margus, who said he learned to tell the difference between good scientists and bad ones and what motivated them. "I studied them. I also learned how science was funded, and how to raise money."

Margus said he launched the nonprofit A-T Children's Project to improve the lives of children with A-T and set out to raise money, something that was new to him. He had the added challenge of trying to raise money for a disease that few people have and a difficult name to pronounce. But he found strangers made a grassroots effort through events such as garage sales and sponsored runs to raise money for research.

"One thing I can say, although I wasn't trained at all, I think sometimes that has helped," he said. "It turns out you can get a lot in the world just by being a needy person and by saying to people I really need your help."

Margus laid out a range of efforts on the research front that his organization has pursued in order to accelerate A-T research.

RESEARCH GRANTS

The first way his organization has been able to orchestrate research is through grantmaking. As an example he pointed to the work the organization funded at Shiloh Lab in Tel Aviv, Israel, which identified the A-T gene.

SHARABLE SAMPLES

It turned out getting blood, tissue, cellular, and spinal fluid samples were a critical effort. At the time Margus began, there were two researchers that were gathering and working biological samples from children with A-T, but they didn't communicate with each other and had a monopoly on the samples. Margus reached out to a cell line bank at the Coriell Institute and had 100 families send samples, which they made available to any researcher in the world. "That completely changed the game," he said. "I didn't need to worry about people having to suck up to these two researchers."

ANTIBODIES THAT ACCURATELY IDENTIFY THE A-T PROTEIN

Antibodies are an example of a tool needed to determine where a protein is located in tissue and whether it is active, Margus said. Early on, some researchers made antibodies that weren't very specific. They detected the A-T protein, but also other proteins as well. That led to the publication of several bad research papers. "This is an example of one of those boring things that are not very sexy," he said, "but really critical to getting it right."

MODELS OF A-T IN OTHER ORGANISMS

Margus said researchers in A-T have worked with a variety of model organisms. Each model has its own benefits, but he said better models are needed. For instance, mice and pig models of the disease that were developed had the disease, but they didn't have any obvious neurological problems. When Margus went to see pigs that had been developed as an A-T model, the researchers had to spray paint them with a pink stripe to distinguish which pigs had the disease. "Here's a little tip for you: When they have to spray paint them to tell you which ones have A-T," he said, "It is not a very good model of the disease."

CHEMICAL TOOLS SUCH AS INHIBITORS OF THE A-T PROTEIN

Another example of tools needed for research is chemical tools. Margus said in the case of A-T, there are some compounds that have been developed to inhibit the A-T protein, which has been very useful.

SCIENTIFIC CONFERENCE AND WORKSHOPS

You can have huge conferences that are broadly focused and structure presentations and poster sessions or narrow workshops focused on a single topic. It's useful to bring together experts in the disease with experts in areas that involve similar biological disruptions in other diseases to develop new research strategies. The idea is to get people with different backgrounds to consider what's common in between these different diseases. The challenge is to get people to think out of the box and come up with breakthrough ideas.

SHARED DATA SETS

It is critical to have shared data sets. Margus said his organization wanted to look at all the all mutations observed in the A-T gene in A-T kids. One frustrating aspect of the disease is the wide variation of mutations in children with A-T, which makes carrier testing difficult. The organization set up a public database for gene expression profiling so researchers can share their work and others can look at it.

OBJECTIVE AND ACCURATE MEASURES FOR ASSESSING A-T KIDS

Another critical element is to have quantitative measurements for the disease so any clinician can tell if a drug is working. It's important that if a clinical trial is run in two different locations that the results are measured in the same way. You can provide a detailed description to clinicians on how to describe a child with A-T and get very different results. "It sounds simple," he said, "but actually it's tough."

BIOMARKERS

Biomarkers are measurable biological elements that can serve as a surrogate for the disease state. They can provide great value in determining the progression of the disease. Finding accurate biomarkers can provide insight into such things as whether a drug is providing benefit.

A SHAREABLE DATABASE

Margus' organization is working to gather health information about A-T kids worldwide who have been followed over time. This includes clinical data, such as medical records. The organization is planning on doing genetic sequencing of patients, and is exploring new sources of data, such as digital health technology to monitor things, such as movement disorders. "We want to make sure the database isn't owned by one consortium of researchers who have a private club and you have to get in their club to get access to their data," said Margus. "We want to make sure if there's a 14-year-old mathematics prodigy in India that has a great way of doing pattern recognition that we could share the data with him."

CLINICAL CENTERS WITH MULTIDISCIPLINARY EXPERTS

His organization helped set up clinical centers at institutions such as Johns Hopkins. This has allowed doctors to see hundreds of children with the disease and follow them over time, something that's critical for a disease where if a doctor sees a case, it would most likely be the only case he will ever see.

CLINICAL STUDIES OF LUNG PROBLEMS

Lung problems are the biggest cause of death in children with A-T so the organization has funded clinical research into lung functioning. It has also funded studies in swallowing and cognitive function to gain greater insight into A-T. Margus said it's important to think about an organization's mission in determining appropriate research, such as whether it is to find a cure, or improve the quality of life for patients with the disease.

BRAIN IMAGING STUDIES

Brain imaging studies have been a challenge. Resolutions have not been high enough to provide meaningful insight into the disease in terms of brain metabolism and circuitry with the disease, Margus said.

GENE SEQUENCING

Because there's a wide variability in the genetic mutation of children with A-T, the thought is that by looking at the genome broadly, researchers may uncover other places on the genome that affect the severity of impairment.

IMPROVING CAREGIVER UNDERSTANDING

This has had a huge impact, said Margus. He said at some of the best teaching hospitals he's seen misdiagnoses of A-T or distorted views on how to treat children with the disease. By working to improve caregiver understanding, he said "you get a lot of bang for the buck."

Two other points Margus stressed was the need to engage with industry and the need to get A-T families to provide samples for research and continue participating in research.

In the end, though, Margus said it's important that organizations be able to envision treatment.

"You can't just be funding research to learn things about the disease," he said. "You can keep learning things about the disease forever. You want to learn stuff that will get you somewhere."

CONTENT SPECIALIST

Brad Margus, Parent Advocate, Founder and Chairman, A-T Children's Project, Founder and CEO, Exigence Neurosciences

Brad Margus has recently founded Exigence Neurosciences, a new drug discovery company. In 2013, Margus started Genome Bridge, a non-profit subsidiary of the Broad Institute of Harvard and M.I.T., to build a computational platform for sharing genomic and clinical data. From 2009 to 2012, as co-founder and CEO of Envoy Therapeutics, Margus raised \$8 million from investors, discovered new compounds for brain diseases, and sold the company to a global pharmaceutical company for \$140 million.

From 2000 to 2007, Margus was co-founder and CEO of Perlegen Sciences, a leader in analyzing genetic variation. Concurrent with his business career, for the last 20 years, Margus has passionately worked as founder and volunteer President of the A-T Children's Project, a non-profit that orchestrates research on a rare, brutal, genetic disease — ataxia telangiectasia or "A-T" — that two of his sons have. A-T causes neurodegeneration, cancer and immune system problems. Margus also currently serves on the Boards of Second Genome, a microbiome company; Arvinas, a protein degradation and cancer company; and Cellular Research, a molecular biology tool company. In addition, Margus co-chairs the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) External Oversight Board at the National Institutes of Health.

Session Briefs, Summarized by Daniel Levine

Daniel Levine is an award-winning business journalist who has reported on the life sciences, economic development, and business policy issues throughout his 25-year career. Since 2011, he has served as the lead editor and writer of Burrill Media's acclaimed annual book on the biotech industry and hosts The Burrill Report's weekly podcast. His work has appeared in The New York Times, The Industry Standard, TheStreet.com, and other national publications. He also is the host of RARECast™ podcasts.