What caused you to enter this field?

I came to Vanderbilt to study something called clinical pharmacology, which is the science of why people don't respond to drugs in exactly the same way – some people have great reactions, some people have no reaction, and some people have really terrible reactions. I got interested in the genetics of drug response, and then, along the way, I got interested in heart rhythm regulating drugs. A number of drugs that were in investigation at the time looked like they caused drug-induced Long QT Syndrome. So I've had an interest in understanding the mechanisms of drug-induced Long QT Syndrome since the beginning. And we got interested in potassium channels as drug targets early on – we were involved in some of the early cloning of potassium channels – and then understanding how drugs interact with potassium channels, and other ion channels. That was the 1980s and first half of the 1990s.

We were aware of congenital LQTS, and I followed a couple of patients. But at the time when we followed them, we weren't attuned to thinking about the genetics. We would occasionally ask people to make sure their family members would come in and be seen. We didn't have much in the way of therapies to offer people short of beta blockers, which sometimes work and sometimes don't. Defibrillators were becoming a thing, but they weren't really widely used, except in very ill patients. And then, in the mid 1990s, the identification of the first of the disease genes in congenital LQTS opened up the idea that we could screen families using genetics, we could identify specific mutations in the families we had followed. We had a couple of publications early on of identifying the mutation in a family with congenital LQTS, and understanding how these mutations affect ion channel function.

We created a genetic arrhythmia enterprise that sees patients that has genetic counselors and trainees involved, and sees a large number of patients with congenital LQTS and other diseases as well. We have a very active, busy genetic arrhythmia clinic. You need a lot of expertise to take optimal care of these patients, and you have to have a big arrhythmia team around you. I'm very fortunate that I have a team of people around me.

I came in through the backdoor, through drug-induced LQTS, but because we had the background in pharmacogenetics, and then ion channel biology and genetics, we got into this pretty early.

What are you most excited about in current research?

We're pretty good at identifying and recognizing patients with manifest genetic diseases. General cardiologists are quite familiar with the idea that if you have somebody whose QT interval is 530, and no other obvious cause, then they probably have congenital LQTS. What we're not so good at is identifying patients who are at risk for unusual drug responses, or who are at risk but don't have any clear phenotype that you can identify from an ECG or something else.

We're in an era now where people are going to get a lot more genetic testing. We're going to find a lot more carriers of pathogenic or likely pathogenic variants. And we won't yet know what to do with them, so that's the next major challenge. One challenge is to figure out which variants are pathogenic, and a second challenge is to figure out, among those variants that are pathogenic, what determines penetrance. You can have the variant that really misbehaves in a cellular system, yet never confers a phenotype in a patient. And why that happens is actually not very clear. So the hope is that we'll use things like polygenic risk scores or studying biology in pluripotent stem cells and cardiomyocytes from induced pluripotent stem cells to understand what it is about the biologic context in which a variant exists that makes it particularly deleterious or particularly benign. So that's the big challenge.

We continue to identify new diseases, and I hope that doesn't ever go away, but the new diseases we identify get rarer and rarer. At least at the beginning – every rare disease is rare when you identify the first case. The challenge and excitement is seeing a variant – often obtained by whole genome sequencing or whole exome sequencing – seeing a variant and deciding whether it's pathogenic, and then deciding how to determine penetrance of those pathogenic variants.

We have to be very careful, because we run the risk of labelling something benign when it's not, but we also run a huge risk of labelling something pathogenic in a person who will never have a problem because of that variant, because they have a protective polygenic risk score or the variant we think is pathogenic is not. We have to be careful on both sides – so the science has to go forward in a rigorous way.

What's a patient story that sticks with you?

A young woman diagnosed as a child because of a death of an older sibling had a manifest phenotype on her electrocardiogram. We established the diagnosis by genetic testing and instituted appropriate medical therapy. When she was an adolescent, her mother decided she was not very compliant with her medications (she wasn't), and was the same age as the sibling who had died so she asked us to implant an ICD. We spend a lot of time agonizing over that and did implant. The defibrillator has gone off three times now and the patient is in her 30s. The first time was for a lead fracture, and she had to get the system extracted and replaced. The second time was ten years after the initial device implant when the device rescued her from an episode of ventricular fibrillation. And the third time was six years later, when she was pregnant, and had a second lead fracture. Managing a lead fracture during a pregnancy is a painful thing, because you don't want to extract the system because of radiation exposure. She ended up having a life vest for the duration of her pregnancy. After she delivered, she had the system revised. She's now on her third or fourth defibrillator.

A second story involves two young women, both freshmen in college. One of them had a syncopal event, and was brought to the hospital confused, so they thought she'd had a seizure. Her EEG was normal, and she was sitting in the hospital (with a long QT) being worked up when she had a 3-minute episode of Torsades. She got chest compressions and was about to be

cardioverted when it stopped by itself. The second was also a freshman in college, had a witnessed syncopal event and was brought to the hospital. They said she probably wasn't eating enough. She went home and had an unwitnessed syncope event and went to the hospital again. They hospitalized her overnight and she had long episodes of Torsades.

Complicated situation for both of them, but both of them, for a variety of reasons, ended up with defibrillators. Every patient is different, and the discussion around an 18-year-old in college getting a defibrillator is not just about medical stuff – but all the other things that person has to think about in their life. We have to counsel them about fever and about certain medications. Every patient needs a personalized approached.

How and why are you involved with the SADS Foundation?

I've gone to several SADS family conferences, and I think that those are incredibly important – to hear the stories, and to tell people that they're not alone, and to counsel people on best practices to avoid those awful, catastrophic outcomes. And I've helped with some of the webinars. SADS has an excellent set of leadership. At one of the conferences, I talked to a physician and a family, and we generated some phenotyping because of that, and we generated a mouse because of that, and IPS cells because of that one conversation. It's so important for people to know they're not alone, and that we're working on these problems.