Dan Roden
Learn, Apply, Evolve

Karen Patterson

As a scientist, Dan Roden grew up as clinical electrophysiology did. Widely recognized for his research into mechanisms behind abnormal heart rhythms and drug responses, Roden was on the front lines in the 1980s and 1990s as new antiarrhythmic drugs were tested, the ability to use catheters to study drug actions evolved, and the speciality of clinical electrophysiology arose.

From his first publication, appearing in the *New England Journal of Medicine* in 1980, Roden set a tone for a career focused on variable action of antiarrhythmic therapies and genetic determinants of that variation. Much of his current work focuses on individual cardiac ion channel mutations and their role in variable responses to drug therapy, and applications of genomics to healthcare. Among his achievements, Roden is credited with developing the idea of reduced repolarization reserve leading to acquired long QT intervals and arrhythmias, and was one of the first to suggest that early afterdepolarizations cause long QT-related arrhythmias.

As leader of Vanderbilt University’s pharmacogenomics project PREDICT (Pharmacogenomic Resource for Enhanced Decisions in Care & Treatment)—which preemptively enhances individuals’ electronic medical records with personalized information about genetic variants that could guide drug therapy—Roden and colleagues have demonstrated multiple advantages of preemptive genotyping. Meanwhile Vanderbilt’s massive BioVU DNA bank, which includes ≈175 000 human DNA samples and which Roden pioneered and directs, is similarly showing the power of incorporating genomic data into electronic medical records, for research purposes.

Rodden, who initially flirted with a future in journalism, described to *Circulation Research* some of his interests beginning as a child of immigrants in Montreal and leading to not just 1 career as an investigator, but a series of interlinked careers—in clinical pharmacology, cellular electrophysiology, molecular genetics, and population science. The paradigm for his progress, he says, is to "learn something new, import it into what it is I do, and then ask interesting scientific questions."

Tell Me About Your Childhood

I grew up in a bilingual home, but not bilingual English-French, [rather] bilingual English and Czech. I spoke nothing but Czech until I was 3, and then I announced famously to my mother that cowboys don’t speak Czech, and from that moment on spoke English as my first language.

But I always understood Czech. If I wasn’t a physician and a cardiovascular person, I might be a language researcher. Because I think a really interesting question is how somebody can keep on understanding a language without absolutely being able to speak it.

I grew up on the English side of Montreal, but my parents being central Europeans from a small country were of the attitude that you ought to speak that other language as well, so in addition to studying French in school they had me go to French tutors after school and all of that. But what really helped me speak French was that I ended up working as a journalist for a while before I went to medical school, and when you’re a journalist and you call some labor union leader who speaks only French, you better speak French.

Was There Any Sort of Drive for You to be Educated, to Fulfill a Dream?

My parents I think are overachievers if that’s the right word. For example, English is their fourth language for both of them.

My father almost finished medical school when he was in Prague, but they left before he finished. So he, after a lot of struggling, got back into medical school in Queens in Kingston, Ontario, and basically did medical school all over again. He was in his early 30s when he graduated from medical school. He became a general practitioner. It’s fair to say that he was a model for me to do something in the biomedical sciences.

Talk About Your Journey to a Career in Medical Science

My attitude toward society when I was 20 years old was I wanted to do something with my life that will allow me to do sciencey kind of stuff and serve people. That was the overwhelming rationale for applying to medical school.

I told my father that I’m going to give it a month, and if I don’t like it, I’m going to go back to being a journalist. After a week, it was totally clear that it was like being in a completely foreign culture; I learned more in a week in medical school than I probably had as an undergraduate in 4 years, new anatomy things, new
concepts in histology, and all the things that I just found it fascinating. So I stuck with it.

How Did Your Interest in Clinical Pharmacology and Cardiology Arise?
I was one of those enthusiasts who after every rotation said, “You know, I could do this for my life.” I could do cardiology, I could do nephrology, I could do gastroenterology...

As I was doing my last year of medical residency I thought, I’m gravitating toward cardiology, but I had an elective in this thing called clinical pharmacology during my training. The clinical pharmacologists I worked with in Montreal were like super internists, and they were the guys everybody went to ask about drug interactions, to ask about what’s the dosing of this drug in kidney disease or in liver disease, pharmacokinetic kind of things, things that I thought every internist ought to be good at. And the people I worked with were pretty charismatic internists/clinical pharmacologists. So I thought, well, why don’t I train in that for a while? Because no matter what I end up doing that will be a good thing to have done.

I went to talk to one of the guys I worked with about where you could do this and he said the best place in the States is Vanderbilt. I then came down with a green card, my wife, and an 8-month-old baby for a 2-year fellowship in 1978, and I’ve been here ever since.

What Kept You at Vanderbilt?
I think it’s the real opportunity to grow the science that I’m really interested in doing.

The first thing that kept me there was the idea I would get to give new medicines to people and then record their electrocardiograms and record how many arrhythmias they had and all their vital signs, symptoms, and drug levels, analyzing all those data to make and write up a story like a newspaperman. It was all very exciting and learning biomedical science was something that I really, really enjoyed.

Vanderbilt, in particular in clinical pharmacology, had the structure at the time—which we don’t have anymore in science—that a young person could be mentored in an environment where they didn’t have to worry about their funding. If I needed something, the environment would provide it. The environment would grow me, the environment provided me opportunities to learn new things, to add skills to my skill set, to think critically.

I’ve been fortunate because over the course of the 1980s and 1990s when clinical electrophysiology emerged as a discipline of its own, I was there at the beginning administering these new drugs, thinking about how they work, and why they don’t work the same way in every patient.

You Were Focused on Arrhythmias From the Start of Your Career—Why?
I think there’s a particular phenotype of cardiologist who finds looking at the electrocardiogram, and trying to figure out what is wrong with the person’s rhythm, a particularly appealing intellectual exercise. I have encountered trainees in my career who will come to me and say, “I have this really interesting tracing. Could you look at it with me?” And I think, “That person’s going to be an arrhythmia doctor.”

Part of it is this precision of the electrocardiogram and the idea that you can look at this signal and infer what is happening at the whole heart and cellular levels and now at the genetic level. I find that tremendously appealing.

How Did Your Focus Develop on Cardiac Ion Channel Gene Expression?
It’s being lucky to be in the right place at the right time. I had trained [at Columbia University] in cellular electrophysiology, and when you did that in those days in animal tissues you record something called an action potential—and the action potential is the signal that integrates all the electric activity in a single cell over time. When the cell depolarizes, there’s a particular electric signature, and when the cell repolarizes there’s another electric signature. But the action potential itself is the result of the activity of many different ion currents that flow across the cell membrane at the same time.

The techniques to understand how that works in the heart, to dissect out the underlying ion currents, started to evolve rapidly in the 1980s. At Vanderbilt, we recruited a scientist [Luc Honderghem] to work on cellular electrophysiology. He knew how to measure ionic currents in heart cells; that was his passion. I basically came to work everyday in jeans and worked in his laboratory like a postdoctoral fellow; I was an associate professor at the time.

[Then] if you say to yourself “there’s variability in the underlying ionic currents—why is that?”—maybe the currents are products of different genes or maybe they’re expressed differently, concepts that are pretty familiar to all of us now but were pretty new back then. So if you want to start to answer [those] questions, the first thing you have to do is to learn how to clone the genes. So again I parked myself in the laboratory of a colleague, this time a junior colleague, from whom I learned the principles of molecular biology.

How Could This Area of Work Affect Medication Decisions for Individuals?
The most recent career evolution has been in what I would call population science. I had this idea, and I don’t claim that it was an original idea, [that it will be possible] within 10 or 20 years at the most to sequence every patient’s DNA, select the variants that are going to be important for that person’s health and drug responses, put those variants into their electronic medical record, and then develop tools to use that variant information when a particular drug is prescribed or when a particular procedure is contemplated. That was the vision 10 years ago.

To execute that vision, it seems to me obvious that you have to deliver care within an electronic medical record environment, and we have a very robust electronic medical record at Vanderbilt.

We started in 2003 to plan a DNA biobank as a way to study how to execute that vision. It took 3 and a half years to plan it, so in 2007 we started to collect our first sample.

Throughout Your Career, Who Were Your Key Mentors?
[When] I came to Vanderbilt, I worked for John Oates: my division director and then later my department chair in medicine. He’s just a superb, very knowledgeable scientist with great scientific taste in terms of picking the right questions, with a great depth of scientific knowledge about mechanisms of disease.

John’s major contribution to my career was to force me to think about questions: What’s the important question? What’s the underlying mechanism? Those are the kinds of questions you have to train yourself to ask. Not gee whiz, this is really cool… but gee whiz, why did that happen?
[Clinical pharmacologist] Ray Woosley was really my day-to-day mentor. I can’t say enough about the things he taught me. He was the one who took me from interested science guy to an investigator. He’s the one I saw every single day and pointed me in the right direction continuously.

The person I worked with [training in cellular electrophysiology] at Columbia was Brian Hoffman. He was chairman of the Department of Pharmacology there probably for 25 or 30 years, a really brilliant man, literally wrote the book on electrophysiology of the heart. I was fortunate to work for him at a time when I was really his only fellow. He devoted a huge amount of time to teaching me the fundamentals of cellular electrophysiology.

What Has Been the Biggest Success During the Course of Your Career?

The idea, for example, that repolarization of the heart is a complex system that relies on many, many, many different currents and other gene products to operate correctly and, therefore, has a lot of buffering capacity. And so a single genetic lesion might not do very much to a patient, or a single drug might not do very much to a patient. It is only when you get a drug and a genetic lesion and another common polymorphism and maybe a little bit of low potassium that people get really long QT intervals and arrhythmias.

The idea of reduced repolarization reserve is that there are people wandering around whose buffering capacity for tolerating insults like drugs or genetic lesions is less than the rest of us, sometimes for genetic reasons. And you don’t know about it until somebody gives them a drug or until their blood potassium goes down and then they’re the ones who get arrhythmias, not the rest of us.

I don’t think there’s anybody who ever has an idea that no one’s ever thought of before. So while I was one of the first to propose early afterdepolarizations as a cause of long QT-related arrhythmia or the idea of repolarization reserve, those thoughts came on the shoulders of lots of previous work by others. Those are ideas that have guided a lot of the research that I’ve done.

What Do You Tell Young Researchers in Your Laboratory About the Future of Science and Medicine?

Working with trainees, watching them mature scientifically and bring new thoughts to the lab, is one of the most gratifying parts of this career. If you read the news, it’s a depressing time, there’s not enough funding. But at the same time I tell them, (1) we have seen this before and (2) it’s a time of, what one of my colleagues once said, “insurmountable opportunity.” That’s a phrase I really like to use because it describes the fact that there are so many things that we are now in a position of being able to do that 10 years ago were just a pipe dream: sequencing a whole human genome for 3000 dollars. Come on, that’s amazing.

Is This the Best of Times for the Work You Are Doing? Or Would You Rather Be Doing This, Say, 50 Years From Now?

I think every era brings with it this arrogance that we are the only ones who know anything, and we fail to recognize that everything that we do builds on the shoulders of those who came before us. So this is the best of times, and 10 years from now it will be the best of times again. And I hope that continues.

What Do You Do for Fun Outside the Laboratory?

I’ve taken up golf. I am terrible, but boy, is it relaxing. We have 3 kids, a grandchild in Pittsburgh, and 2 grandchildren in Los Angeles. And my wife and I like to travel—so that takes up every spare moment. I wouldn’t be where I am without a family that has supported me.

What Sort of Reading Is on Your Bookshelf?

Right now I’m reading a detective novel about an Icelandic detective. Before that I was reading a series of detective novels about a Swedish detective. I find those Nordic detectives are all morose and they’re all really smart.

What Are Your Goals for the Next 5 Years?

I would like to see us deliver on this vision of genomically enabled medicine. I think that’s a doable thing. I’d like to see us figure out how to use large swaths of human genetic information to improve healthcare. I’d like to see us make discoveries in our biobank that are important for understanding variability in response to drugs. I’d like to see us use the kinds of resources that we’ve been building over the last 5 to 10 years at Vanderbilt and nationwide and worldwide in genome science to identify new drug targets that will be important and novel and improve human healthcare.

Disclosures

None.

References

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