New Leaders in Cardiovascular Science

Gerald W. Dorn II
Thinker, Teacher, Tinkerer

Karen Patterson

Cardiologist and molecular and cell biologist Gerald Dorn, MD, has built his research career crafting interesting questions and teaching himself techniques needed to find answers. Using approaches including genetic and physiological manipulation in animal models, development of mini-mouse technology to elucidate cardiac mysteries, and human genetics/genomics, Dorn is helping to unravel cellular and molecular mechanisms underlying cardiomyopathy and heart failure.1,2

Dorn, 57, is founding director of the Center for Pharmacogenomics at the Washington University in St. Louis School of Medicine, where he joined the faculty in 2008. As a teenager Dorn sped through high school, starting college two years early. He earned his medical degree and trained in internal medicine, pharmacology, and clinical and interventional cardiology at the Medical University of South Carolina (MUSC) in Charleston, where two key mentors sparked in him a passion for patient care and research. After a couple of years at the University of Texas Health Science Center at San Antonio, Dorn moved to the University of Cincinnati, where an American Heart Association Established Investigator Award kick-started his research program. From 1990 to 2008 Dorn rose through the ranks at Cincinnati, capitalizing on the institution’s strength in mouse cardiac transgenesis.

Dorn’s current interests include molecular mechanisms of cell death,3 microRNA regulation of cardiac genes,4 and mitochondrial dynamism5—work that has expanded to Parkinson’s disease. Building on an upbringing that valued lifelong growth, and drawing from his own broad experience, Dorn now leverages the holism of systems biology to fill in what he calls his field’s “infinitely large shades of gray.”

Describe Your Childhood.
My father was a career naval aviator. Whenever he moved, we moved. So I’m not really from anywhere. We spent a lot of time on both coasts. As a child I lived, in addition to the United States, in Puerto Rico, and spent three years in Japan during the Vietnam War. I have one younger sister.

When my father retired from the Navy, we moved back to his and my mother’s ancestral home, which is South Carolina. So I went to high school and college (Lander College) in a tiny little town called Greenwood, and then did all my medical training in Charleston.

What Did Your Mother Do?
Mother was a Navy pilot’s wife; that was her profession.

After we moved back to Greenwood, she went to college and got her bachelor’s degree, and then she went to Clemson and got a master’s degree in social work. She became director of the department of social services for many years in Greenwood.

And Your Dad?
He went to college at University of North Carolina and was in ROTC there, and that’s how he got introduced into the Navy. His final years in the Navy, he went to Pepperdine University and got a master’s degree in business administration. After we moved to Greenwood he got another master’s degree, in public administration, from the University of South Carolina.

Did Your Parents Encourage You as a Student, Or in the Sciences?
That was a natural proclivity. They tried to encourage me to sports, but I was a terrible baseball player. We found out later that might have been because I was severely nearsighted, and nobody suspected it.

What Influenced Your Path to Cardiovascular Research at MUSC?
At the time I was doing my training I had no intent to do research, no proclivity, and no talent. But I finished internal medicine, and because I had flirted with the idea of becoming a gastroenterologist before deciding on cardiology, I had a year before I started my cardiology training. During that year I got a job in the clinical pharmacology department.

The chairman of the department said, “By the way, we’ve got to identify a laboratory for you to go to.” That was a financial decision, to subsidize my salary off a training grant.
So I was forced to go to a laboratory, and I loved it. If somebody hadn’t made me to go to Perry Halushka’s laboratory in Charleston, I wouldn’t be able to spell “test tube.”

What Was Halushka Studying?
Perry (a cell and molecular pharmacologist) was an MD/PhD studying thromboxane receptors in platelets. This is the bioactive factor inhibited by aspirin. These were very early studies, what’s called grind-and-bind receptor pharmacology. Perry had invented a ligand that worked for this new receptor, and everybody in the laboratory was doing studies trying to characterize it.

What Made You Fall in Love With Research?
I liked being around the PhDs and the MD/PhDs. I viewed med school as not thinking, but just memorizing lists and structures and whatnot and regurgitating them. But when I went to the laboratory, there were people constantly trying to generate data that they had to interpret and then develop concepts that would explain them—it was constant thinking. It was about puzzle-solving. That was very refreshing.

I think the way medicine was taught at that time kind of dumbed people down because it was just rote memorization. For the record, the curricula have been vastly improved.

Did You Have Other Early Mentors?
I decided to be a cardiologist because of my exposure to a fabulous role model, Peter Gazes. He was the chief of cardiology in Charleston, and when I was a junior resident I did a rotation with him at the university hospital. His approach to cardiology was very scientific; his demeanor with the patients was very attentive and gentle. His teaching was personal. He was incredibly interested in all of these things he was doing, and basically I decided, “I want to be like him.”

Any Other Role Models?
(Harvard Medical School molecular geneticist Christine) “Kricket” Seidman expressed interest in my early work when she was a visiting professor (at Cincinnati), which inspired me to remain in academia during a period of difficulty in obtaining funding and publishing in quality journals. The following year I got my first R01. She remains my role model for the physician–scientist, Eric Olson (molecular biologist at University of Texas Southwestern Medical Center) is my role model as a pure investigator and in our field I think is the most effective communicator of his science.

Going on to University of Cincinnati, You Were There 18 Years.
Right. I was two years in San Antonio. The person who recruited me to San Antonio, Richard Walsh (cardiovascular physician-researcher, now at Case Western Reserve University), moved to, and then also hired me to, Cincinnati.

The other reason San Antonio’s important is it’s where I met my wife, Deborah Hauger, in the cath lab (in 1988).

What Was She Doing?
She was a cardiology fellow and I was a junior attending, and we were doing cases together.

What Were Your Highlights at Cincinnati?
I was moving up the clinical and academic administrative ladder. At the same time I learned how to do science. I taught myself a little protein chemistry and I spent some time with folks who introduced me to molecular biology.

Cardiac-specific transgenesis—the building of transgenic mice, in which you can manipulate genes in the heart—was a strength there. (Molecular biologist) Jeff Robbins had invented the alpha-myosin heavy chain promoter, which basically everyone now uses to build their mice. It was the essential reagent to permitting conditional gene expression in the heart.

Everybody with whom I was working was doing this kind of genetic manipulation in the heart, and I was studying platelets and vascular smooth muscle thromboxane receptors. One week in the laboratory—my tiny little lab of me and two other guys—I said, “We should make a mouse.” Literally that was the way we decided to do the experiment that has made my career.

We created a mouse called the G alpha q, or Gq, mouse, a very interesting mouse6,7 that has been quite useful for many laboratories in our field. It was a lucky thought.

What Findings Have Arisen From the Gq Mouse?
The Gq mouse is a model of cardiac hypertrophy, and we turned on the signaling pathway that is activated by (for example) adrenaline and angiotensin, but we just turned it on in the cells of the heart. Then the heart hypertrophied, and this constituted scientific proof of the neurohormonal hypothesis of heart failure, which was kind of a radical theory back then. The theory was that neurohormones circulating in your blood directly cause the heart to undergo hypertrophy, as opposed to (the idea that) they increase your blood pressure and the heart undergoes hypertrophy because your blood pressure is increased.

The other aspect of this was, I had these mice and they had hypertrophied hearts, and cardiac hypertrophy is something I see in the cath lab every day. But I could not interrogate the mouse with the expertise that I could interrogate humans. I wanted to get inside the mouse.

So in collaboration with other folks at Cincinnati, we began to engineer methods by which we could basically build little mouse cath labs and do the same type of clinical diagnostics that we were doing routinely in people. I turned out to be a pretty good engineer doing that.

What Insights Came of That?
First of all we had demonstrated that neurohormones—let’s just concentrate on angiotensin—that angiotensin is basically directly cardiotoxic. If you inhibit angiotensin, which is now done with ACE inhibitors, you can prevent hypertrophy independent of the effects on high blood pressure. They were already doing those clinical trials; we just helped to understand why.

Moreover, we determined that stimulation of this type of pathological hypertrophy directly led to cardiac failure, because the same genetic program that tells the cardiac myocyte to grow also predisposes it to die via apoptosis. So, we spent a number of years studying the mechanism of programmed cell death in these heart models.8
Where Did the Interest in Human Genetics Come In?
There was a very, very strong group at Cincinnati that included not only Jeff Robbins and Rick Walsh, but Steve Liggett (now at University of South Florida). Steve had an interest in beta-adrenergic receptors, the receptor for epinephrine and norepinephrine. One of his primary goals was to define polymorphisms of the beta adrenergic receptor that would alter human responses to heart failure, or to beta blockers used to treat heart failure.

Through my interaction with Steve I became interested in heart failure genetics. In a series of studies Steve and I built mice that expressed human mutations in the mouse heart, then evaluated how the mouse disease phenotypes compared to the human disease.\(^1^9\) If there was a good similarity—and there generally was—we could take the mice and drill down and understand the mechanism behind altered receptor function.

How Complex Is the Molecular Biology of Heart Failure, in Your Estimation, and How Much of This Do You Think Medical Science Understands?
We’ve got a pretty good feeling for the tip of the iceberg. Every time we think we understand something and it seems simple, then we drill down, we learn some more, and it becomes increasingly complex.

When I started doing science, I was convinced that reductionist biology would be how we understand everything—if we could disassemble systems into their constitutive parts and understand how each individual part interacts with each other part, we would understand how the whole thing works.

Over the last several years I’ve become more of a systems biologist, integrating not only physiology and biochemistry, but genetics, genomics, and pharmacology; this is much less deterministic. So it’s not so easy to say, “This causes this,” because usually there are lots of exceptions. The real way to approach this is more probabilistic: “If this happens then it is likely that this happens, but that’s conditional.”

Can I give you a specific example from our work? Through studying cardiac hypertrophy and then programmed cell death, we became interested in mitochondria, because mitochondria are important for apoptosis. We began to examine mitochondrial dynamism, how the organelles change by undergoing fusion and fission.

We discovered through gene manipulation in mice that if you prevent mitochondria from undergoing fusion, the mitochondria just accumulate and fill up the hearts. But, the mitochondria are abnormal and ultimately the hearts fail. Chasing that observation, we found that one of the mitochondrial fusion proteins was a critical factor in mitophagy, the process by which the cell kind of “vacuums up” damaged mitochondria. We made something of a splash by determining the molecular mechanism for this interaction.\(^1^0\)

We’ve now shown how the interaction between mitophagy and mitochondrial fusion, previously thought to be entirely separate, is essential to altering cardiac metabolism in the newborn heart. If you mess up this system, the newborn heart can’t change the food it prefers when it’s in the uterus to what it normally uses after birth. The hearts fail and the animals die.\(^1^1\)

It’s a completely unexpected story because now we’ve linked three processes previously considered completely independent—mitochondrial dynamism, mitophagy, and metabolic transformation involving mitochondrial biogenesis—and we find they’re working together.\(^1^2\) That’s the type of integrative systems approaches we think are especially revealing.

What Other Areas of Your Work Do You Think Are Promising?
We’re really excited about the mitochondrial work. It has relevance far beyond the heart. The factors we are studying are most important in the human condition in chronic neurological disease. We are developing mouse models of two neurological diseases—Parkinson’s disease, and Charcot Marie Tooth syndrome (type 2a).

We’ve learned a lot in the heart that we believe we can translate to the neurological system, not only in understanding the mechanism of disease, but we’ve created some small molecules that alter the processes we are studying and are getting ready to introduce them into mice.

What Are Your Most Fruitful Collaborations?
We’ve recently initiated a collaboration with Dan Kelly (now at Sanford Burnham Prebys Medical Discovery Institute). He was instrumental in bringing me here (to St. Louis). He’s a cardiac metabolism guy, and I’ve got an interest in mitochondria distinct from metabolism, so we have complementary skills.

I have a fabulous relationship with Rick Kitsis (of Albert Einstein College of Medicine). We’re beginning to make serious progress in the various aspects of mitochondrial biology that deal with cell death. There’s also Joan Heller Brown (University of California, San Diego pharmacologist) and Daria Mochly-Rosen (Stanford University chemical and systems biologist), who befriended me as a junior colleague in the 1990s, and with whom I continue to collaborate. They have not only been scientific partners, but are two of my dearest friends.

Do You Work Long Days?
I like to keep busy. This morning I was in the office well before 7, and I’ll work 10 or 11 hours. Basically I quit work when I get hungry because I don’t eat breakfast or lunch. So at some point I just need to go somewhere and get something to eat, and that marks the end of my day.

What Makes a Day Most Productive or Satisfying for You?
I like when something nice happens, whether you get a paper accepted or a good score on a grant. When I’m traveling I really like it when I’m either sitting in somebody’s office and we’re discussing something or I’m giving a speech to a group and we talk about something and then you can see they are understanding a new fact or concept.

I like to think, but I also like to teach. That’s what all those things have in common.

What Do You Do For Fun?
We have a house at the beach north of Charleston, and I like to sail. We do that a couple of times a year. And I have a farm near Cincinnati where my (four) horses live. I do all sorts of
noncognitive, outdoorsy things at the farm—I have tractors, I ride horses, I go fishing, I do farm maintenance.

Do You Have Any Favorite Books, Movies, or Music?

My wife would love to me to tell you how I like to go to the symphony and opera. I hate going to the symphony and opera—but I do frequently because she loves it.

I read all the time. When I am finished with work I’ll go home and have something to eat and because there’s nothing worth watching on TV, I’m likely to end up reading a book. I read lots of stuff: historical fiction, shoot-’em-up novels, airplane novels. It’s pretty diverse.

Describe Your Home Life.

My wife is a cardiologist in private practice. My daughter (Lisa) is now in the MD/PhD program at Ohio State. When we meet up it’s generally at our farm, which is centrally located to the places we live.

It’s pretty unremarkable.

What Is the Best Advice You Give to Your Daughter (Or to Students)?

Never give up.

Persistence is 90 percent of the battle. You don’t have to be a jerk, but if you think you’re right, keep plugging along. That’s really important in our business because Lord knows, dealing with rejection is what we do. You send in a paper; it gets rejected. You send in a grant; it gets rejected. You give a talk; somebody stands up and says you don’t know what you’re talking about.

I think in academics, if you don’t have an intrinsic sense of your own value and worth, you’re never going to make it; it’s a tough, Darwinian world.

Are There Lessons Your Career Taught You That You Wish You Knew When You Were Starting Out?

I’ve had a really fortunate run. I got to do interventional cardiology during the best possible time, when there were all sorts of tools, and before intracoronary stents became kind of the way to solve every problem. I have been and continue to be part of the research environment during the most interesting technological advances: I was playing in genomics, and next-generation sequencing exploded and made that easy for us; molecular biology has just exploded and made genetic manipulation in animals easy for us; systems biology is easier because computational power has increased.

It’s like a huge sandbox. It’s fun. Well, it’s not always fun—but it’s still amazing that people will pay me to do what I do.

References


