New Leaders in Cardiovascular Science

Walter J. Koch
Two Decades, One Mission

Karen Patterson

Temple University Professor and Chairman of Pharmacology Walter J. (“Wally”) Koch, PhD, has been on a career-long mission to elucidate molecular mechanisms of heart failure. Studying a family of kinases that regulate adrenergic receptors and other G protein-coupled receptors (GPCRs) in the heart, Koch has focused on one such kinase, GRK2, which at high levels impairs myocytes and promotes cell death.

Two decades of basic and preclinical work with GRK2 have put the 54-year-old Koch and his colleagues on the threshold of human trials using adeno-associated viral-mediated myocardial gene delivery to try to reverse heart failure. Koch has also shed new light on GRK5, including showing how this enzyme enters a heart cell’s nucleus, where it contributes to hypertrophy.

Koch, a native of Bryan, Ohio, first pursued his interest in science by following a friend’s path to pharmacy school at the University of Toledo. Koch earned his PhD in pharmacology and cell biophysics from the University of Cincinnati, completed a Howard Hughes Medical Institute fellowship at Duke University, joined the Duke faculty, and advanced to a tenured professor of surgery. In 2003 he moved to Philadelphia to launch Thomas Jefferson University’s Center for Translational Medicine, and in 2012 established the Center for Translational Medicine at Temple.

In 1995, when Koch started his own lab, he knew he wanted to be the “champion” of GRK2 in the heart and develop GRK2 inhibitors for heart failure. “Twenty years later,” he says in describing his journey, “we’re almost there.”

What Was Your Childhood Like?
My father was a truck driver, a World War II veteran. He hauled steel between Cleveland and Chicago, so he was not home during the week. My mom stayed home.

There were five kids; I’m the baby. I went to Catholic grade school and then to the public high school. There were seven of us in a house of about 1,000 square feet, (with) one bathroom. My four siblings and I remain close.

Were You Interested in Science as a Child?
I loved biology, I loved chemistry. When I was a junior in high school, I won the top prize in the Ohio state science fair.

What Was Your Project?
I took several name-brand cereals and I basically created our GI tract with acid. So I got all the cereals that said they were high in fiber, and I boiled away everything in acid and what’s left is fiber. Then I compared the cereals and which had the most fiber and which were accurate in their fiber count. I thought it was cool.

Then when I was a senior, I had the typical senioritis and I had the same project but did it with bread instead of cereal. I made it to districts and I got the same judge and he said, “Didn’t you do this last year?” (Laughs.) So I got nailed.

How Did You Find Your Career Path?
I worked in a lab a couple of summers (while at pharmacy school) and very naively I said I want to do drug research. I was clearly clueless on what drug research really was. I applied for graduate school, went to University of Cincinnati, in pharmacology, thinking that was the best program for me.
if I wanted to do drug research. Then slowly I learned what biomedical research was all about, and really took to the molecular side.

So I went to a lab that was on the cutting edge of cloning calcium channels in the cardiovascular system. This was in the mid-’80s, when molecular biology was taking off and cloning genes was the thing to do. I had a great mentor, Dr Arnold Schwartz, who was the chair (of pharmacology). That exposed me to high-pressure, high-impact science.

Then What?
Through my graduate studies I was reading papers about what was going on in molecular pharmacology. I read a paper in Science in 1988. The first author was Brian Kobilka; the last author was Robert Lefkowitz. It was the most exciting paper I’d ever read. There were the beta-adrenergic receptors and alpha-adrenergic receptors, and they coupled to different G proteins. In the mid-’80s those receptors were cloned by the Lefkowitz lab (at Duke). And this paper was about chimeric receptors, where basically you spliced one part of one receptor into the other and they delineated the area of the receptor responsible for the specific G protein coupling. Now you could do that study in a week. But back then it was a tour de force.

And I wanted to be a postdoc in the Lefkowitz lab. Fortunately because I was in a high-profile laboratory I had the opportunity to meet Dr Lefkowitz. When he came to Cincinnati for a meeting, I picked him up at the airport. We started talking and a year or so later I applied to his lab to be a postdoc, and was lucky that he offered me a Howard Hughes postdoctoral position.

It was a great opportunity. I had just gotten married and we left Cincinnati in January 1991 to go to Durham, NC.

I made the discovery in 1993 that has propelled my whole career. I was studying the kinase called βARK; GRK2 is now what it’s called. Then a paper came out in 1993 that showed this kinase was elevated in failing human hearts.1 I started reading that paper and got into some other papers, and it piqued my interest. Through our studying this kinase we found a way to inhibit it.

While I was still with Bob we made a mouse that had my inhibitor of this kinase. It was a peptide (βARKct) I developed in 1993–94. We made a transgenic mouse where only the cardiac cells expressed this peptide. And those mice had a phenotype that was out of this world. They had supercharged hearts.

That was published in Science in 1995.2 From that point on I wanted to test whether inhibiting GRK2 would be a heart failure therapy.

What Did You Achieve Next at Duke?
I was recruited by Dr David Sabiston, another great mentor of mine, the longtime chair of the Department of Surgery at Duke. He wanted to start a molecular cardiovascular laboratory, so I was in the right place at the right time.

I started my independent laboratory 20 years ago, (and) spent eight and a half years as faculty. One of the things I’m most proud of is I rose through the ranks from junior faculty to a tenured full professor in six years while at Duke, basically because I was able to get a lot of grants early and so built a very large lab in a short amount of time.

It was great to stay at Duke and continue talking to Bob Lefkowitz on a daily basis. I still call him a great friend and mentor. We just got a Program Project Grant renewed that’s headed by another friend of mine at Duke, Howard Rockman.

In 2003, I was persuaded to come to Philadelphia, so I went to Jefferson to start a very new center (the Center for Translational Medicine). Three and a half years ago we moved to Temple.

How Central Are G Protein-Coupled Receptor Kinases to the Development of Heart Failure?
I think GRK2 is a novel regulator of pathogenesis. I think it gets up-regulated and for some reason the heart can’t down-regulate it after it’s up-regulated.

The fight-or-flight response is basically when our body senses danger, the sympathetic nervous system pumps out (the neurohormones) adrenaline and noradrenaline, and that makes your heart beat fast, it makes it beat strong, it dilates your blood vessels, and it lets you run away. Heart failure is a disease where that system doesn’t work, and it wants to work because it recognizes that the heart, when it’s injured, has low cardiac output. To increase cardiac output, noradrenaline and adrenaline are released.

But when GRK2 is elevated, the heart doesn’t respond because the receptors are turned off. That creates this vicious cycle of neurohormonal bombardment of the heart. All the drugs right now are basically used to block that bombardment. But our data show that if you lower GRK2 you won’t need those drugs because the neurohormonal bombardment goes away, because now the heart can respond to those signals.

So we think GRK2 is very central. We’ve published a couple hundred papers almost, in all kinds of animal models, showing (what happens) when GRK2 is lower or inhibited.

How Does That Compare With GRK5?
As a postdoc in Bob’s lab I cloned GRK5 because I had this background in molecular biology and cloning, and we were looking at more of these kinases that may regulate GPCRs.

Several years ago we found that GRK5 goes to the nucleus of myocytes,3 which is a very unique property. We don’t think it’s there because there are receptors there. We found it had a very specific action promoting pathological gene transcription. So we’ve been studying that.

We also have some small-molecule inhibitors of GRK5 that I’m developing with Dr John Tesmer at the University of Michigan.

That’s in the early stages of whether that’s a true target. I think GRK2 is definitely a target.

Your Group Recently Reported Intriguing Results
Testing Paroxetine as a Therapy in Mice. What Led You to Paroxetine?
Dr Tesmer got a grant to screen for GRK2 inhibitors. The first library of compounds he screened was the (Food and Drug Administration) library, and got a very strong hit with paroxetine. Paroxetine is probably not a drug for (heart failure in) humans, but in mice we could give higher doses, and we found that it totally reversed heart failure. It was superior to beta blockers; it was due to GRK2 inhibition.
If you go back to our other mouse studies where we deleted the GRK2 gene after heart attack, the data are almost identical.

So now we have a small molecule, and we’re trying to build on that. Gene therapy, as much as I know it could work, is very hard to do, so I’d love to have a small molecule. The paroxetine study convinces me we’re on the right track.

Any Other Areas of Research That Are Really Enticing to You?

What I’m most excited about in the future is that, for both GRK2 and GRK5, these kinases have noncanonical actions,12,13 meaning they’re not just around to phosphorylate adrenergic receptors, or G protein-coupled receptors. GRK2, for example, is in mitochondria, and a large focus of my lab right now is to try to find out what it’s doing in mitochondria. It seems to localize to the mitochondria and produce cell death, but we also think it has a metabolic role.

What Have Been Your Most Fruitful Collaborations?

I’ve been working for over 20 years with Howard Rockman. We published several mouse models together. He’s been my longest collaborator and friend. Since moving to Philadelphia, I started working with (cardiovascular physiologist) Steve Houser. He’s a big reason why I moved from Jefferson to Temple.

Fortunately I have grants together with my closest friends, Steve Houser, and Jeff Molkentin (cardiovascular molecular biologist, of Cincinnati Children’s Hospital Medical Center), and this keeps science fun and fulfilling.

Do You Have Any Advice for Young Investigators? Sure! (Laughs.) I think the skill that’s needed the most for young people is to learn how to finish. A lot of people have a good idea, but you really need to learn how to finish that idea. What’s become evident in my trainees that’s different over the last decade or so is that they don’t keep their eye on the prize— and the prize is papers, right? Manuscripts are our only form of currency. Manuscripts get you a grant, which gets you a job, which gets you postdocs. So I think they need to focus on publishing more.

What Have Been the Key Ingredients in Your Own Research Success?

I think that I had good hands, and that’s important. Science is an art. You have to have some kind of technical skill, especially when you’re doing molecular biology and you’re doing cell biology, because the experiments have many steps and are very difficult. And I think I’ve also been lucky—not only in the projects and the results, but I was in the right place at the right time when Dr Sabiston at Duke wanted to start this new lab and new initiative in surgery, and after four years in Bob’s lab, I was ready to start my own lab.

How Important Is Hard Work in That Equation?

Hard work is very important. It goes without saying. I think in science it’s not necessarily the hours. If you’re very efficient, you don’t need to work 80 hours in the lab. But you have to work hard and be very dedicated.

What’s a Typical Workday Like for You?

I travel a lot, but when I’m in the ofﬁce my door is always open and I want people to bother me. I make a couple rounds a day in the lab, and we have weekly lab meetings. I’m an administrator too, so that takes some of my day, but not much. Most of the time I’m reading and writing, planning.

If You Had More Time in the Day, What Would You Do With It?

I would love to be back at the bench.

I would love to be involved in the molecular biology projects that we have going; I miss that. I really love molecular biology; I loved cloning.

What Are Your Favorite Ways to Relax?

I have two sons in high school, so I watch them in their endeavors. My older son does crew and rows on the Schuykill (River), and my younger son plays football and lacrosse. I love to play golf. That’s probably my Number One hobby.

I’m also a huge Cincinnati Reds fan.

Do Any Genres of Books/Film/Music Particularly Appeal to You?

I was a Harry Potter guy. I loved Harry Potter and everything about it, and I was on the Internet every day reading the fan sites, debating whether Dumbledore was really dead.

Right now I’m into Game of Thrones.

When and How Did You Meet Your Wife?

My wife (Macaira) was the manager of the medical school bookstore at the University of Cincinnati, and the bookstore was right across from the cafeteria. I was there every day; I went down for lunch. So I met her there. I asked her out for a date at the cash register in front of a lot of people, and then we started dating.

We’ve been married for 27 years. It’s going great.

What’s Been the Best Day of Your Life Up to This Point? (Laughs.) That’s a loaded question.

Let’s Split It Up—the Best Day Personally, and Then Scientiﬁcally.

I think the happiest I’ve been personally is probably when my wife agreed to go out with me, because she was the prettiest woman I’ve ever seen.

Professionally, there’s a lot of them, but I guess the day (in around 1997) that we got our first data in the βARKct mice where they rescued heart failure.14 That was a pretty amazing day. And that was the first of many.

References


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