New Leaders in Cardiovascular Science

Jeffery Molkentin
Delves Into Cell Death

Ruth Williams

Jeffery Molkentin, a professor and Howard Hughes Medical Institute investigator at Cincinnati Children’s Hospital Medical Center, studies all aspects of heart and skeletal muscle cells—their growth, differentiation, replication, but most important of all, how they die.

Cellular death plays a prominent role in many human cardiac and skeletal muscle diseases. Thus, Molkentin’s quest is to identify the genes and pathways controlling cell death, curtail them, and minimize pathology. Among his most important contributions to the field was the discovery that necrosis is not the uncontrolled messy death it was once thought to be. He discovered, for example, that necrosis is regulated, in part, by cyclophilin D, a component of the mitochondrial pore, and that such mitochondrial-directed necrosis is a pathogenic process in both heart failure and muscular dystrophy.

Interestingly, Molkentin’s research into cell death began quite accidentally while he was carrying out studies into cardiac hypertrophy. As a postdoctoral researcher, and later in his own laboratory, Molkentin was part of a team that discovered that calcineurin is a potent promoter of cardiac hypertrophy, a rather controversial result at the time. It was Molkentin’s attempts to block calcineurin with a drug called cyclosporine that led down the unexpected path to cyclophilin D, the mitochondria, and necrosis.

In a recent interview with Circulation Research, Molkentin discussed his life, work, and the calcineurin controversy that plagued the start of his career. He said he kept his head during the backlash from senior cardiologists by being 100% confident in his work, a key requisite for any scientist starting their own laboratory.

Where Did You Grow Up?
I grew up in Milwaukee, Wisconsin. It is a wonderful little city, about 100 km north of Chicago. I lived there until I was 27. I completed my undergraduate degree at Marquette University, then my PhD at the Medical College of Wisconsin, right in the heart of Milwaukee.

What Was Family Life Like?
My parents were both blue-collar workers. My mother worked in a factory where they make lawn mower engines, and my dad was a millwright in the construction trade. They were simple folk who wanted my brother and me to do better than they did—go to college and become doctors or lawyers or whatever.

I was good at science in school. So there was a positive feedback. When you excel beyond other students at a subject, you recognize in yourself that it is something you are better at, so you push harder and are more inclined to keep working in that direction.

Even at an early age I had an aptitude that most other students did not. I also had a near-photographic memory—as a kid, at least. My memory is less stellar now.

This aptitude for science gave me the idea of making my parents proud by becoming a doctor. So I went to university to do premed, came out on top of the class, and got into the medical school at the University of Wisconsin. I did that for a semester and then—this is embarrassing—I dropped out.

Medical school was just more memorization and, at that point, I was completely burned out on that aspect of education. I wanted something more practical and scientific. So, I enrolled in a PhD program and never looked back and that is how I got my PhD in physiology.

How Did Your Parents Feel When You Dropped Out of Medical School?
They were very supportive. They ultimately just wanted what I wanted, and for me to be happy. And I was not happy in medical school.

What Did You Study for Your PhD?
I studied gene regulation at the Medical College of Wisconsin from 1990 to 1994, and my advisor was Bruce Markham. There I became really interested in the heart and gene regulation.

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You Moved to Texas at 27. That Is Quite a Change From Wisconsin
Yes, but I loved living in Texas. It was one of the highlights of my life so far. I went because I wanted to join Eric Olson’s laboratory. Back then he already had a reputation, but he was still young. I really felt like he was going places and obviously his career has just taken off since then.

What Did You Work on?
The first project I worked on was related to skeletal muscle myogenesis and then I started working on the cardiac side of things and made knockouts for 3 different GATA genes that are in the heart: GATA-4, -5, and -6. The work on GATA-4 resulted in a *Genes & Development* article and, later, a *Cell* article—when I discovered that GATA-4 was regulated by the NFAT–calcineurin pathway.

This Was the Article Showing the Link Between Calcineurin and Hypertrophy?
Yes. At first we did not even suspect that this was regulating hypertrophy, we just knew that NFAT and GATA-4 interacted and that calcineurin regulated NFAT, but when we turned this pathway on in the hearts of transgenic mice, it made the heart humongous: 2 to 3 times larger than normal.

I took those mice with me when I left Eric’s laboratory. And here is a funny story. It was back in 1997 and things were not as strict as they are now with shipping animals. The day I left Eric’s laboratory was a Friday and it was the day we euthanized the first calcineurin transgenic mouse. Eric was at my bench and we opened up the animal and the heart was literally 3 times larger than a normal heart. So, at the last minute, I said I have to take these mice, although I had already shipped all my previously approved mice. So I took 2 cages of the transgenic mice in my car! They were driven from Texas all the way to Cincinnati, and I had to keep my dog from constantly trying to get in the cages. If you did that now, you would get in so much trouble.

The Calcineurin Work Was Initially Controversial.
Tell Me About That
When we first published the calcineurin story, it generated a fair amount of controversy and even a bit of mean-spirited backlash. Here was an article from myself and Eric telling people about this new thing: 2 to 3 times larger than normal.

I set up my laboratory when I was 30, and my daughter was born when I was 31, so that was a really stressful period—having young kids is not always fun. It is stressful. You are constantly in the way of you, and the more pieces of you are parceled out.

Because of the backlash, there was a year or two where the right side of the controversy.

How Would You Advise Other Young Scientists Who Might Face Similar Resistance to Controversial Results?
It is really hard. You really do have to be confident that you are not basing the start of your career on something that is technically uncertain, because if you are wrong that could undermine your entire operation.

So I think my advice would be: just make sure what you are working on is important and that, if it is controversial, you are on the right side of the controversy.

Any Other Advice for Coping With Adversity?
I still never get used to an article being rejected or a grant being rejected. It still hurts. It really is the hardest part of this career, but it also defines the best scientists. If you can deal with the adversity, take the good from whatever the rejection was and build on it, that really is the heart of the scientific process.

After all, what does not kill you makes you stronger. So take ideas from the reviewers, and after initially licking your wounds, try to dig in and make it better. It is the only way to do this business.

Since the Calcineurin Work, Your Research Has Taken Many Different Routes. How Do You Juggle Them All?
I do not know. It is not unlike when I was a kid, my interest just evolves. It is all very interesting and if a new project comes up and it looks really interesting, I have always wanted to keep pushing in different directions to reduce complacency or boredom that would come from working on just one gene your whole career.

What DoYou Like to Do Outside the Laboratory?
I work out every day. I used to do competitive powerlifting. Not bodybuilding—do not write that—powerlifting is much more manly! I even set some state records. But now I do mostly running: half marathons, 10K events, things like that.

I get up at 4:30 AM, go to the gym at 5:00, work out from 5:00 to 6:30, and then I come to work. I am kind of a gym nut, so I lift weights and run every day. And whenever I travel, I make sure I can find a gym or that the hotel I am in has a good gym.

What Is Your Proudest Career Achievement?
I think the mitochondrial observations—the project related to cell death and mitochondria. I am proud of it because it is independent of anything I had done previously, not just an extension of my work from my PhD or postdoc training. That is rewarding.

But the calcineurin story was also rewarding because it was something that we did together. Eric is just a great mentor, and the conditions were just perfect to allow work to blossom the way it did. It also was rewarding because I developed a lot of it here in Cincinnati with my collaborators Jeff Robbins and Mark Sussman. So I am proud of that as well.
Some of the more recent stuff I am doing I am also really proud of. It is hard to pick one!

Tell Me About That Recent Stuff

One of the things I am really excited about is a whole new family of genes called thrombospondins and discovering what their true function is.

We found the genes during a screen—they are upregulated in the heart in response to injury. There are actually 5 genes, and it looks like all of them are induced after injury, but no one has ever really gone after them mechanistically to understand what they do, whether they are good or bad? I feel we are on the road to answering those questions, but I do not want to say too much, because some of it is not published.

Do You Have a Long-Term Dream for Your Research?

As well as heart diseases, my laboratory works on muscular dystrophy and I am particularly touched by how horrible that disease is. I do dream that the research we do could make a direct difference to the lives of these kids. That goes for heart failure too—trying to find potentially a new way of treating that—because it is such a prevalent disease.

So, a fruition of some of my life’s work would be to bring any of these concepts to the clinic and see if it helps patients. At the end of the day, if you were to look back at your career, it would be the one thing that you would be most proud of. Not that you published three, four, five hundred papers, but that you really did have an effect on people’s lives.

Disclosures

None.

References

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