During 36 years at Temple University in Philadelphia, Steven Houser has been a leader in advancing scientific understanding of heart function. All along, he’s been driven by a desire to understand his father’s fatal heart disease, and to contribute important insights to help future patients.

Houser and his collaborators—along with others in the field, he is quick to note—have shed light on numerous fundamental questions about how calcium regulates the beating of cardiomyocytes, including elucidating the details of calcium-induced calcium release.1,2 His research is probing calcium-dependent signaling pathways, aberrations in the hypertrophic, failing, or post-myocardial infarction heart,3–6 factors related to myocyte turnover,7 and potential treatment strategies including gene and stem cell therapy. Houser’s lab recently demonstrated that cortical bone-derived stem cells may be superior to cardiac stem cells in regenerating heart tissue after MI.8

Houser, 63, director of the Cardiovascular Research Center and chair of physiology at Temple, tells Circulation Research he’s never afraid to jump into a scientific argument9 and help inform the debate. His strategy is always fair and careful experimentation, with an emphasis on reproducible findings. “I think the results from my group have stood the test of time,” he says. “That’s one of the things I’m proudest of—that our work can be repeated.”

Let’s start with your childhood.

I grew up in New Jersey, in a little town called Magnolia, about 10 miles from Philadelphia, in suburban housing built primarily for soldiers returning after World War II. My dad had been in the service. [He] was a working guy. Mom stayed home, tried to keep me in line.

My dad worked for a company called Western Electric. He was a wireman. My mom ended up going to college when I started high school. To help pay my way through college, she went on to college and became a math teacher. I went to a little college called Eastern Baptist College.

I developed an interest in biomedical science while I was in college and applied to graduate school. I came to Temple, where I’ve been my whole life, it seems, academic life. I started in graduate school in the physiology department with an interest in neuroscience, and I started in a laboratory where I was studying synaptic transmission.

During that period my father had a major heart attack and ended up dying a few years later as a consequence of his heart attack. I decided to switch my thesis project to a project on basic cardiac electrophysiology. It was in the early days of cardiac electrophysiology.

When I finished my PhD—this was the late ’70s—I thought I needed more training in clinical topics so I could do translational science, which was what I really wanted to do. So I did my postdoctoral fellowship in the cardiology unit, again at Temple, and started projects related to cardiac hypertrophy and heart failure.

About your dad’s heart attack — what were the details?

My dad had an anterior wall myocardial infarction, which was never diagnosed actually, he never went into the hospital. He ended up in the hospital a few years later with heart failure, and it was at that time they realized he’d had a previous, very large myocardial infarction.

He had a ventricular aneurysm, and in those days there were not many options. It was the early days of surgery for those sorts of things. And before that became a serious option he died of an arrhythmia at age 51.

I went and studied as much as I could about myocardial infarction and post-myocardial infarction remodeling, and I concluded that we needed to understand more about the fundamental biology of the heart to figure out how it reacted to disease states. So I spent most of my early career, with many other folks in the field, defining how cardiac myocytes actually work.

We’ve made great progress over the last 30 years.

In what ways?

Back when I started [was] before the heyday of cardiac catheterization and really even the knowledge of how myocardial infarction takes place. We knew there was coronary disease, but we didn’t even know for sure in the early days whether the heart attack was caused by the vessel closing down over time from the disease, from atherosclerosis. Then it became clear mainly from autopsy studies that there were blood clots in these sites of people who had died of a heart attack.

Describe the evolution of your career.

When I started out, I was trying to understand fundamental aspects of cardiac contraction and cardiac electrical behavior, so
that eventually I could try to figure out why the heart didn’t contract properly in disease, and why electrical disturbances occurred in sick hearts.

Very early in my career, like within six months of starting my own independent lab, new techniques came out that really revolutionized my field, that I needed to learn if I was going to move my field forward. One was the isolation of single cells from heart tissue. Having the ability to have single muscle cells in a dish allowed investigators to perform novel experiments, and figure out how the heart cell worked in ways that we could never do before. The second technical advantage was there were these new ways to record electrical activity from single cells, called patch clamping. That let us learn about the electrical behavior of cardiac myocytes. The third technical advantage was people developed novel ways of measuring calcium within cardiac myocytes with dyes that would basically blink at you when the calcium concentration would go up and down.

So I spent 10 years of my life building apparatuses, learning how to make these measurements and making these measurements, and figuring how calcium was regulated in normal and diseased heart cells. It was great fun. And we literally revolutionized the field, not just my group, but my peer group of cardiac biologists.

After that, I started to focus my energies on mechanisms of cardiac dysfunction in disease, spent five to 10 years studying human heart failure, figured out a lot about why the failing human heart doesn’t work so well. When we finished all that, I decided I wanted to go and start to learn about how to repair hearts that had been damaged by ischemic insult. And I came to the conclusion that the reason that those hearts don’t do very well is that the ischemic event has killed too many cardiac myocytes, and the structure of the heart is abnormal, the number of myocytes is abnormal, and the function of the myocytes that are remaining is abnormal.

So how do you fix it? I started to think, as I use the experience I have, what can I do to potentially have impact to help people like my dad? And I concluded that just fixing the myocytes that survived the infarct was not going to be sufficient. Now that’s a hypothesis. I believe the way to really fix it is to replace the myocytes that were lost. And that’s when I started to teach myself about cardiac repair, cardiac regeneration, and stem cells. That’s what I’ve been doing for almost 10 years.

What would you consider your main contributions to the field?

My group was one of the first to really develop the ideas behind what’s called calcium-induced calcium release in the heart: How does calcium entry into a cardiac muscle cell regulate the contraction of the myocyte? It does it by regulating the release of calcium from a storage site called the sarcoplasmic reticulum. There were lots of competing hypotheses about how it works, and my group helped clearly show that the source of calcium to get this whole process going was through an ion channel called the L-type calcium channel.

Then we did all the nitty-gritty details. My group was one of the first to study diseased cardiac cells, and we showed there were abnormalities in the way these cells controlled and regulated their calcium concentration that were responsible for their contractile defects.

During the last 10 years, along with our cell therapeutic work we’re trying to do, we’ve been studying how calcium regulates cardiac hypertrophy—in collaboration with a number of groups.

Is that a big national or international effort?

No, it’s a few of us. My major collaborator in my calcium/hypertrophy story is Jeff Molkentin at the University of Cincinnati. Jeff is an absolute pro at making genetically modified mice; I think I’m a pro at making the calcium measurements in single cells, so we’ve had a nice collaboration, trying to figure out some of these pathways that regulate how cardiac muscle cells grow in normal hearts and in diseased hearts.

Anything else? Say, about stem cells?

I think my stem cell story is still immature, or we’re still learning. I’ve had to teach myself a whole new field. We’re developing a number of strategies to try to have stem cells engraft better within the damaged heart. We’re trying to develop strategies to induce more effective regeneration in the heart. But we’re not there yet. We have some mouse studies that have been published recently that are very interesting, but they’re very early.

What has kept you at Temple all this time?

It dates back to discussions with my father when he knew that he probably wasn’t going to live very much longer. I’m the only boy in the family, and he basically urged me to take care of my family. I can still hear him saying it, fair or unfair. And I’ve enjoyed every minute of staying here at Temple and taking care of my family.

I think maybe the thing I like about Temple the most: I love our students; they remind me of me. (Laughter) I think I can have a positive impact on our students. And the institution has allowed me to do whatever the heck I want to do, as long as I was productive. What a great job—you can do whatever you want day after day after day, within limits of course, especially now. I’m a senior administrator. But within my lab, I’ve been able to change my direction whenever I wanted to, as long as I can work hard and support the work that I want to try to do.

Of what you’re working on now, what do you think is most exciting?

We’re doing experiments with potential therapeutics. They’re not all cell therapies; some of them are gene therapies, [done] together with collaborators, or drug therapies. But the most exciting part is that we’re doing experiments that have the potential to lead to real therapeutics.

What are some of those?

We have two different stem cell types that we’re trying in an animal model. If either one of them shows to be sufficient to repair the heart after injury, we already have the intellectual property protected and would try to move forward and develop this into a clinical application.

We have a number of gene therapy projects ongoing, some with collaborators and some with just my group, where we’re trying to modify either the repair process itself by gene therapy vectors, or we’re trying to repair cells that are dysfunctional. When hearts get damaged obviously there’s a mechanism to repair the damage, but it usually produces scar. So we’re trying to develop ways to modify the repair so it includes regeneration rather than just scar formation. And we’re doing that with gene therapy vectors that are being developed by my collaborators, mainly by [Temple University colleague] Wally Koch and his group.

In an earlier-stage project, we’ve identified a new ion channel and it allows calcium to go through. They’re called transient receptor potential channels, TRP channels. These channels get expressed on the surface membrane of diseased heart cells, and they appear to contribute to the dysfunction you see in heart disease. We’re trying to develop therapeutics to modify these channels.
Where does the stem cell work fit in – is it just a piece of it all that has gotten more attention lately?
I would say yes. It’s about a third to a half of my lab. You know in theory, if you believe ischemic heart disease [is] a disease of myocyte death and that the reason the hearts don’t work properly is that too many of the cells have died, then certainly it makes logical sense that the therapeutics should be to replace those cells. It’s that simple idea that drives my desire to pursue stem cell therapies for heart disease.

The questions are, What types of cells are going to work? How do you deliver them? When do you deliver them? Do you deliver them in a naked form? Do you deliver them together with biomaterials that are being developed? There’s a whole, whole, whole laundry list of things that need to be explored.

What is the vision for patients in the future? When somebody has a heart attack, what do you see happening?
Standard of care now, if you can get them into the hospital quickly enough, you take them to the cardiac catheterization lab and try to open up that blood vessel. There’s still a region of their heart, though, that’s dead. A scar’s going to form and, over time, the heart’s going to develop dysfunction.

Best-case scenario, you develop something you can give to that patient while they’re in the hospital that’s going to repair their heart. It’s going to fix it so they don’t develop a scar, they don’t develop heart failure down the road, and they truly have a repaired myocardium.

You might as well dream big, right?

Who has really influenced your work?
Bill Barry is a cardiologist who was at Harvard and then at Utah who is now retired. He always was a source of sound advice for me. He had a big impact on me. He was about 10 to 15 years older than me and had been through what I was going through in my career and life. And I respected his judgment, and I always sought out his opinions, both scientifically and personally.

In the early ’90s, 1990, I did a one-year sabbatical. It was the only time I was away from Temple University. I was at UCSF, in the lab of Paul Simpson, cardiologist/scientist. And Paul tried his very best to teach me molecular biology. (Laughs.) I learned, and it had a major impact on my career. He’s a great scientist, one of the best scientists I’ve ever met. When Paul says it’s true, it’s true. I’ve mentioned the other two people I collaborate with the most, and that’s Jeff Molkentin and Wally Koch. They’re great collaborators and great friends, both.

Which opportunities are ripe for younger researchers? Where would you steer people?
I think the passion has to come from the person, not from me. I want people to pursue what they’re passionate about. That’s what the passion has to come from the person, not from me. So I give that advice all the time, and I got that advice a lot, because I got knocked down a lot when I was young—and still do. There’s negative feedback all throughout your academic life. You have to be willing to take it for what it is and use it to make you better. And if you do, you’ll get better.

What do you like to do in your down time?
I like to be with my family. I have a loving wife and two daughters, and I enjoy them immensely. My daughters are in college. They’re swimmers, so I go to watch their swim meets.

For myself, I like to play golf. I love to fish; I don’t get to fish very often, but when I have an opportunity, I do it. I love all types of fishing in all types of environments.

And I like to exercise. I ride bikes; I just do all sorts of aerobic work. I also do enough weight training to try to keep a little bit of lean body mass underneath the fat.

Now when I’m exercising, I’m usually thinking about experiments. (Laughs.)

What is the best advice anyone ever gave you, or the best advice you would give others early in their careers?
Something my father taught me and many other people teach their kids: When you get knocked down, get back up.
Science is a business with lots of negative feedback. Our papers get rejected, our grants get rejected, people say bad things about our ideas. So I tell people they have to be willing to get back up when they get knocked down, and to not let their life be defined by the way they got knocked down—let it be defined by the way they get back up.

I give that advice all the time, and I got that advice a lot, because I got knocked down a lot when I was young—and still do. There’s negative feedback all throughout your academic life. You have to be willing to take it for what it is and use it to make you better.

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None.

References

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