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Programming Heart Cells to Heal

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As a boy in suburban Los Angeles, Mark Sussman's mother used to tell him that scientists saved more lives than physicians because they were the ones who developed the treatments that doctors used. He has taken her words to heart. By deploying a wide range of tools gathered throughout a diverse 25-year career, Sussman is pursuing novel ways to encourage the replacement and repair of damaged tissue in heart failure, the leading cause of hospitalization in the elderly.

After a postdoctoral fellowship in cytoskeletal biology, Sussman joined the molecular genetics laboratory of Larry Kedes, at the University of Southern California. There, he characterized the role of the tropomodulin, a protein that caps and regulates the length of actin fibers, in the heart.[1] In his first faculty position, at the Cincinnati Children's Hospital Medical Center, he created a transgenic mouse model of dilated cardiomyopathy resulting from the cardiac-specific overexpression of tropomodulin.[2]

Sussman's research in the area of signaling networks in the heart led to the discovery of the role of Pim-1 kinase as a mediator of cardiomyocyte survival and proliferation.[3] Using cells from patients with severe heart failure undergoing left ventricular assist device implantation, Sussman's laboratory at the San Diego State University Heart Research Institute recently demonstrated that stem cells engineered with Pim-1 kinase can enhance the repair of damaged myocardium.[4]

Mark Sussman

In a recent interview with *Circulation Research*, Sussman described how a successful career can be like a pinball machine: you ricochet from one thing to another, accumulating skills and ideas, and by making the most of each opportunity, end up doing something valuable that you never anticipated.

How Did You Get Interested in Science?

My father was an accountant who had little interest in science. On the contrary, my mother almost died of polio as a teenager and she always told me that the people who saved her life were the scientists, not the doctors—because the doctors would not have had anything to treat her with if it were not for the scientific research. We went to the museum every weekend, she would take me to the library and science-enrichment classes after school, and we would sit watching PBS (public broadcasting) shows about discovery and DNA and evolution. Although she never finished college, she was an educated person when it came to science and certainly had no shortage of opinions.

I had a little microscope from the age of 5 years, was fascinated by how the world was put together, and was always getting in trouble from my father for taking things apart as a little kid, radios, and TV sets, to figure out the way things worked. Eventually I came to the conclusion that one of the biggest puzzles I could try to figure out was how life worked. That is a mystery I could work on for the rest of my time on the planet without it ever getting old and never figuring it all out.

How Did You Pick Your College Major?

I started out at UC Davis as an animal science major, wanting to be a vet. I always loved animals and had crazy pets growing up such as (but not limited to) snakes, frogs, toads, Old World chameleons, parrots, piranhas, a cayman (little South American alligators), and dogs. My mother was incredibly indulgent with me having a miniature zoo in my bedroom; my father just tolerated it.

So I thought it would be really cool to be a vet, but in those days it was tougher to get into vet school than medical school, with <10% of the applicants getting accepted. So I started thinking about becoming a scientist and took some advanced science courses. Then, after being rejected from vet school, I decided to do a masters in Biology at Cal State University Northridge to see if I liked science, which turned out to be the best thing that could have happened to me.

I worked with the only immunologist in the department, who had not had a student in 20 years and did not really want one. I pestered him into accepting me to work in his laboratory, which he agreed to as long as he did not have to watch over me. I had a blast designing experiments, working independently, and rediscovering the love I had for science and asking questions nobody knew the answers to. Meanwhile, I was not having that much fun working at the vet clinic, realizing that you have to be part vet and part psychologist to figure out what the owners want and dealing with their issues. The pets were easy to work with, but some pet owners are truly crazy.

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That was a turning point for me. I realized my true calling was to do science and try to solve puzzles, so I applied to doctoral programs and was accepted to the University of Southern California with a full scholarship.

Did You Ever Consider Medical School?

I never wanted to go to medical school. I do not enjoy being around hospitals or sick people, and I hate to see humans bleed—especially me.

What Did You Study for Your PhD?

I worked in a viral immunology laboratory, studying a central nervous system infection in a mouse model of demyelinating disease.

How Does Your PhD Connect With Your Postdoc Studies?

There was absolutely no connection. One of the members of my PhD thesis committee told me that postdoc training would be the last chance for exposure to a totally unfamiliar research area and to expand the depth and breadth of my understanding. Trust me, he said, everything you learn will come back to you and you will need it. He was absolutely right.

In my postdoc I collected experiences in cell biology and cytoskeletal biology and signal transduction, and exposure to those areas helped build my career. I never would have ended up where I am today if I had stuck with viral immunology.

Would You Give the Same Advice to a Student Today?

There are upsides and downsides to focusing versus diversifying one's research background. These days you not only need to be well rounded but incredibly productive in terms of publication and establishing a track record, and your productivity does take a hit in the short run when you retrench in a unfamiliar area. But there is value in grabbing something totally different than what you know and incorporating that into who you are as a scientist at any stage of your career. To be successful you need to be constantly incorporating new ideas and reinventing yourself every few years.

I sit on a fellowship review panel and, when we evaluate postdoc candidates, one thing that weighs significantly is whether the applicant will gain new training and get new perspectives from the work they will be doing. If it is only incrementally different, that is considered a significant detriment.

How Did You Get Started Studying the Heart?

One word: serendipity. In my postdoc I had studied proteins involved in organizing the cytoskeleton, the fascinating interface between the cell and the outside world, where the cell needs to get cues about its environment and respond in the right way.

Then I took a research-track position in the hard-core molecular genetics laboratory of Larry Kedes at the University of Southern California, because I was convinced that the future would belong to scientists who could clone, build vectors, create expression vectors, and work with DNA. Kedes was an icon in the cloning world having characterized the actin promoter. I brought cell biology to his laboratory and he offered expertise for gene cloning and expression, and we agreed to teach each other.

When I arrived in the early 1990s, the first mass-produced Zeiss LSM1 confocal microscopes had just come on the market and the institution purchased one but nobody was using it. Because of my love of microscopes, I sat in front of it for hours playing around and learning the nuances. We were working on heart cells, so I started looking at them under the microscope. Then I created expression vectors to manipulate the cytoskeleton and came up with a project examining how muscle fibers are built in heart cells.

We published a series of articles and that gave me the keys I needed to unlock my first tenured faculty position at the Cincinnati Children's Hospital Medical Center.

What Made You Move to Cincinnati?

Jeff Robbins was at the beginning of putting together a group for Molecular Cardiovascular Biology. His group was at the epicenter for transgenic mouse production in the study of the heart. There, I could take my experience learning to clone, pick up some new skills, and move toward creating an animal model. We created one of the first mouse models of dilated cardiomyopathy, heart failure, published in 1998.

After mouse modeling for a few years, Robbins said during an annual review that it was time to reinvent myself and incorporate something new into my research program. I had been interested in signaling between the cytoskeleton (from my postdoc) and the nucleus. If we could understand how signals from the edge of the cell get telegraphed back to the nucleus and reprogram gene expression and change how the cell behaves, then maybe we could start programming the cell and telling it what to do from the outside-in. That idea led to a whole chunk of my career studying cell survival and ways to keep cells from dying. It seemed like a pretty obvious thing to ask: if heart failure occurs when cells die and you can keep them from dying, maybe the heart failure can be blunted and you can live longer.

We studied Akt (protein kinase B), a major cytoprotective molecule. Although lots of people recognized that Akt was important, they were activating it with nonphysiological maneuvers that did not really capture the normal way it worked. The contribution our laboratory made was to look at how the signal gets communicated into the nucleus of the cell and changes behavior. If you took cells in a laboratory dish and treated them with estrogen or insulin, Akt lit up and moved into the nucleus of the cell in ≈30 minutes. We studied the effects of nuclear-targeted Akt and uncovered a whole different biology and that became several National Institutes of Health grants and articles. That took my career in Cincinnati for a good 8 years and was part of the reinvention that Robbins was talking about.

Were You Glad to Return to California?

Cincinnati was a great place to raise a family. We moved there with 2 young kids and had another there. But my wife and I both grew up in suburban Los Angeles. At one point she said to me, "It looks like this science gig is working out, but would you do one thing for me? Don't let me die in Cincinnati."

I had been in San Diego before for my postdoc, and it gets in your blood. It is beautiful here all year long, and I wanted to live in a place where I could ride my bike along the ocean and think about solving research problems.

I had an offer from this wacky place, California State University San Diego, which had a vision to invest in advancing basic research. They had the ability to do things that a more rigid bureaucratic structure would not be able to do. I could be part of building something from the ground up instead of moving into an existing system—and that was why I chose to come here.

Some people said I would just end up surfing and my career would be over, but I do pretty well when given lots of room to

maneuver. This place gave me the opportunity to create my own program and it turned out to be incredibly successful. I got the first program project grant in the history of the Cal State system, in 2005, and built my laboratory up with undergrad and grad students. It was definitely the right move to make.

How Did You Get Started Working With Stem Cells?

As I was coming to California in 2003, at professional meetings, I started to hear reports about using stem cells in the heart: <1% survived a day, but they seemed to be helping. I thought if something good is happening, wouldn't it be much better if the cells stuck around for a week or a month? That fused together a lot of things I had worked on in my career and took me in a new direction—to engineer stem cells to enhance their regenerative potential with survival signaling mediated by Akt and Pim-1.

People continue to argue about whether the effect of stem cells is significant or not, but if we can agree that something is happening, maybe we could shift the debate toward how to make it more efficient. We recognized that stem cells responsible for repairing heart damage were dying along with the heart muscle cells. We began to modify cardiac stem cells with Pim-1 and found that it enhanced the activity of telomerase. After working with cell cultures, plus animal studies, we have begun working with hospitals to obtain chunks of heart tissue that are removed from people with severe heart failure during implantation of a left ventricular assist device. We wanted to work with the target population that desperately needs this therapy and have now shown that expressing Pim-1 in their stem cells enhances their regenerative potential.

We are also looking at the question of aging. The elderly, who are most likely to need this therapy, already come in with impaired ability to heal. So we are looking at how to turn back the clock and make the cells act like they did when you were young, so they will do a better job of healing you.

We are also exploring some creative ways of getting cells to talk to one another. Part of the problem is if you put in a lot of cells, and most are dead the next day, the few left are isolated, not communicating well with their environment and not understanding what to do. If we can make the environment more hospitable, and enhance cellular cross talk, they can better repair and blunt heart damage. It is like soldiers hitting the beach on D-Day: most are massacred when they show up and the few left are isolated from each other. Obviously, it is much better if we can figure out a way to keep the cells from being massacred and to enhance the initial engraftment and communication.

So You Think Stem Cells Will Be an Essential Part of the Fix for Heart Failure?

Absolutely. There are many controversies and questions, but it is important to keep in mind that the field is young. In the past 12 years, the heart has gone from being an organ thought to have no regenerative potential to an organ where people are finding all kinds of different stem cells in different locations with different properties—and no one has any idea which is the right one. And it is probably not just one, but a combination that works best.

It is a challenging time, however, with researchers putting in various types of stem cells with each camp lobbying that they have the right answer as they try to get grants or investors. It is a collision of fresh new science and a desperate unmet need for ways to attack the intractable problem of heart failure, for which we have no good treatments other than transplant.

Science evolves through debate and controversy and, after time, a shared understanding. Disagreements are not a bad thing, but when the conversation devolves into personal attacks we have crossed a dangerous threshold away from unbiased and impartial science into an "I am right and you are wrong" judgment that is destructive.

It is possible for 1 scientist to report an observation that is challenged by another researcher using different tools, with both being equally valid. The methodology and techniques are so complex that small changes can make big differences in outcomes. It is important to not become entrenched in rigid positions of who is wrong versus right, but instead to say I respect that's what you saw, but it is not what I saw. I like to believe that we can tolerate that disagreement and absorb that variation and respect each others' differences of opinion rather than debating right versus wrong or black versus white. We will appear more professional in the eyes of the public and federal agencies if we can agree to disagree in a mature and intelligent fashion.

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

I would like to cure heart failure and make heart transplants a thing of the past, but for right now I am just trying to take this little step of making regeneration work better.

How Hard Do You Work?

If you love something, is it that laborious? The things I have struggled the most with in my life are things I did not like doing, but I really like doing science. The hours are long and some people with a 9 to 5 job would think "that guy never stops." But it is not something I can turn off. Whether I am driving or in the shower, I am thinking about experiments or the results from the laboratory or literature. Researchers like me drop whatever we are doing in a heartbeat to talk about what is going on in the laboratory. I do not consider it work. It is part of who I am.

What Do You Do to Relax?

I like to get on my road bike and cycle up and down the coast, climbing hills and sweating. It is meditative, transcendent, and one of the times I can really be on my own instead of plugged into everyone else. For that period of time my mind can truly wander. Some of the best ideas I have had, and the coolest solutions to problems, have occurred when riding my bike. And although I do not do it often these days, but I also love to put music on the stereo and just space out listening to it. And there is still a little piece of me that likes to fix things, so I tinker around with my cars—fast cars.

Are Any of Your Family Scientists?

No. My wife was trained in clinical psychology at University of California, Los Angeles, but gave it up saying taking care of me and the kids is like a full-time clinical practice (and I think she is probably right!). My daughter, 24, has a masters in education and would love to teach middle-school English and History. My elder son, 21, is all about business, retail, computers, and technology—he thinks science is cool but would not do it for a living. My youngest son, 16, probably has the most interest. He loves science fiction, movies about space, and the Cosmos series. I used to find Post-Its in his room where he would write questions about the universe to remind himself to ponder them later—that is a little slice of me when I was growing up.

What Would You Tell a Young Person It Takes to Be Successful in Science?

The single most important thing is you really have to love what you are doing. Do not go into this career to get rich because most usually do not. You do not go in to get accolades and praise, because there is a huge amount of rejection and criticism. And these days you have to enjoy being around other people. There are a few scientists who manage to do their work in isolation, but science is more and more becoming a community-based, worldwide endeavor. You must be able to interface through social media and get on planes for face-to-face interaction with the other people who are doing what you do. There are lots of really smart people, much smarter than me, and I will never be a great scientist if I do it alone.

Go into science because you love the joy of discovery, the fun of being the first person to think of a question and answer it. It is still a rush. Although I get almost no time at the bench I get to live vicariously through my students and see their excitement and joy and passion.

Disclosures

None.

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