Rajat Gupta

A Scientist in Doctor's Clothing

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Rajat Gupta is a postdoctoral research fellow in the laboratory of Sekar Kathiresan at the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard in Boston. He studies the genetics of coronary artery disease, examining the biological mechanisms by which certain genetic variants confer risk.[1–4] Gupta also teaches medical students at Harvard Medical School and is a practicing cardiologist at the Massachusetts General Hospital in Boston.

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Becoming a doctor had been Gupta's dream since childhood, he told *Circulation Research* in a recent phone conversation. He grew up in a small town in central Michigan called Okemos, which Gupta fondly describes as a block of ice, and spent his spare time either ice-skating or escaping the cold in the local library. He would plow through books ravenously, memorizing facts and figures, teaching himself human anatomy and imagining that one day he would serve the people of his local community as their physician. But then, around the time that Gupta was heading off to university to study medicine, his childhood plan started to shift. He read an inspiring magazine article about a physician who was also a scientist and realized that there was an alternative way to tackle health problems and disease.

How Did Your Research Interests Develop?

As soon as I arrived at the University of Michigan as an undergraduate studying biochemistry, I started to look for research opportunities. I e-mailed as many laboratories as I could find, asking if they would be willing to take someone with zero experience. As a result, I started working nights and weekends in the rheumatology laboratory of David Fox.

I worked alongside a great postdoctoral fellow from Japan, Yoshi Morita, essentially as his technician, and he taught me how to perform experiments. He was very meticulous and had high standards. I just loved working with him. That experience really changed my course from wanting to be a community doctor to wanting to be a scientist who addresses medical questions.

So How Did You Achieve That New Goal?

I went to the University of Pennsylvania for medical school because it had a very strong research focus. During my rotations, I got the sense that probably the sickest patients were those who had suffered a heart attack or who had heart failure. They needed a whole team of people working on them. Cardiology, therefore, seemed to offer the sort of team-based care of the sickest patients that appealed to me.

When I was looking for residency positions, I again searched for programs that emphasized research. I opted for Massachusetts General Hospital in Boston for my internal medicine residency and the Brigham and Women's for a cardiology fellowship. There, I worked with Sekar Kathiresan who was designing large-scale genetic studies to find new risk factors for cardiovascular disease. I decided I wanted to be part of that effort and have worked in the Kathiresan Laboratory ever since

What Have Been the High Points of Your Career So Far?

The first highlight for me was when I was working in David Fox's laboratory as a college student. I was looking at how two different cytokines— interleukin 12 and 23 (IL-12 and IL-23)—interacted. I did a simple PCR (polymerase chain reaction) and found that when IL-12 increased, IL-23 went down. I showed the results to Yoshi and he said, "Wow. These two cytokines regulate each other and you and I are the only two people in the world who know that." I thought that was really incredible—to have done an experiment that created knowledge that did not previously exist. I still get goose bumps thinking about that moment and how much fun it was.

The second high point was coming to Boston as a resident and attending medical and population genetics conferences at the Broad Institute. The conferences were like an open forum where people presented unpublished work and there was a great deal of debate and discussion. Before that, I had been doing clinical

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training for six years, but at these conferences, I felt like I was using a different muscle or a different part of my brain. I remember thinking that I wanted to one day present my own work at such a conference. I knew it was the environment I wanted to be in.

So Did Your First Presentation Feel as Good as You Had Hoped?

No. Ha ha. In my postdoc, I actually struggled a bit. I was studying a DNA variant associated with coronary artery disease trying to figure out the biological mechanism, and we made a lot of assumptions about how it might work, most of which turned out to be incorrect. It took about three years for me to figure out that I was moving in the wrong direction, so that was a frustrating time.

I would give presentations at laboratory meetings or small conferences but never felt that I was advancing the conversation much because my results were not robust or even reproducible in some cases. It was tough, not only because of the science not going well but because I started to doubt whether I was cut out for this field and started to second-guess decisions I had made about what projects to work on or how much time to devote to certain things.

Ultimately, I had to take a step back and rethink the problem. Fortunately, we were able to figure out that this variant works in a different way than we expected and actually regulates endothelin 1. The findings have now been published in *Cell*,[1] so finally the frustrations turned into success.

What Did You Learn From This Dark Period?

For me, I learned that I do enjoy this work, and even when things were bleak, I did not really seriously think about stopping. So, I guess the experience has prepared me for when an inevitable downturn happens again: I will be able to feel more confident that I really do want to be a scientist.

The other thing I learned was that when you do not have good data, it is even more important than usual to engage with colleagues and collaborators and discuss your findings because that is what can get the creative process going. Instead of going into a shell, I learned to be more focused on conversation and collaboration. It is important although it is difficult.

Also, when I was going through this tough period, my first daughter was born, which was obviously the happiest day of my life. So that put things in perspective and made it a lot easier to temper a difficult career moment.

How Important Is Hard Work to Your Success?

I often think back to my father who is possibly the hardest working person I have ever met and who believed that any problem could be overcome by hard work. I definitely learned that from him. Even now, when things seem difficult, I think that I should go back to that instinct and just work harder and things will improve.

Hard work does not necessarily mean tasks at hand, it also means, for example, reading widely. I have found that the people who I admire the most for their intelligence and creativity in science are those that read voraciously. My mentor, Dr Kathiresan, is exceptionally well read. I try to copy that trait.

What Do You Like to Do Outside the Laboratory?

I enjoy playing tennis, but one of my biggest passions is reading. I love to read about different places around the world, places that I may never experience myself but that through a book I can get to know.

Nowadays, with my two daughters, I like to find books that can capture their imaginations too. I probably visit the public library two or three times a week.

Do You Have Ambitions to Be Running Your Own Laboratory?

Absolutely. That is the next challenge for me. I am starting to look for opportunities where I can study the genetics of vascular disease in an independent direction. I currently have a career development award from the National Institutes of Health (NIH) that I have four years left on. And this year, I am applying for as many grants as I can. By the end of the five years, the idea is that I should already be independent. That is the crossroad I am at now.

What Advice Do You Have for Younger Scientists?

They should cherish the opportunity they have to be curious. It really is a privilege to have a job where your only tasks are to be curious, to learn as much as possible, and to somehow contribute a little bit to a field that has been around for hundreds of years.

I would say that if that is fundamentally enjoyable to you, then every bump along the way can seem smaller. And if you are driven by that curiosity, then things like reading broadly, asking questions, finding mentors, and persisting through tough times will come naturally.

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