Blood, sweat and toil all part of the job

Acclaimed scientist gets breakthrough from doing test on his own immune cells

Zeng Zeng

Q: Why are you won awards for your research on auto-immune diseases, which include rheumatoid arthritis and childhood diabetes? And last year, you were one of the world’s most highly cited scientists, according to Thomson Reuters’ report on the most influential scientific minds. But you originally wanted to be a medical missionary. How did you get started in science?

I’m from southern India and I studied medicine at the Christian Medical College in Vellore. After medical school, we had to serve a hospital, usually at a mission hospital, but I was given the opportunity to do my project research. At the time, young men came into the hospital with a damaged heart valve needing massive cardiac surgery. Normally, each valve damage is the consequence of a heart infection, but none of these patients had any evidence of such an infection. One of my professors told me – you’re a smart guy, go find out why this is happening to these people.

So I tested and did my research, and we found that a viral infection may trigger an immune reaction which attacks the heart valve. So I started thinking about auto-immune disease, and wondered if there was a common mechanism that underlies the different diseases.

I was 25 years old, and I did this calculation that if a busy doctor saw about 45 patients a day, and I worked until I was 75, I would see about 10,000 people. But if I could find a common mechanism for the autoimmune diseases, I could potentially help about 300 million people affected by the diseases.

Q: One of your first breakthroughs came in 1983 when you found that a type of white blood cell – T cells, which control the immune system – has channels that can be blocked to stop autoimmune diseases. Your own cells appeared on file to remove one of the conditions that made the disease. It’s an example of the prestigious scientific journal Nature. Can you tell us about the breakthrough?

I had an opportunity to do research in the United States to study autoimmune diseases. I met a guy called Professor Michael Calahan, who was studying proteins called channel ligand spines. He was using a new technique called the patch clamp which allows you to measure electrical currents carried by ions in and out of cells. But then, there was a weather phenomenon called El Nino which caused the waters of the Pacific Ocean to get really hot, and all of the spines disappeared. He had all this fancy technology and nothing to study.

We knew that when immune cells meet foreign invaders like bacteria and viruses, calcium and potassium ions go in and out of the cells, but we didn’t know how. I asked him to find the patch-clamping technique could be used to study immune cells.

I’ll always remember the day – May 24, 1983. When I asked him, I stuck myself with a needle and collected some immune cells, and we used his method to measure the electrical currents carried by ions in human immune cells.

That afternoon I saw his lab, for the first time, that immune cells had potassium channels opened. If blocked, we could prevent the cells from activating. In February 1984 we had a Nature paper, and cells from my blood were on the journal’s cover.

Q: You believe blocking some of those channels is a better way of curing autoimmune diseases? Auto-immune diseases can be stopped with immunosuppressant drugs, but those cause severe side effects because the drugs compromise the immune system’s function in protecting against infections and cancers.

There are about one trillion T cells in our bodies. At first they are naïve, but after they turn off the foreign invaders, some cells become central memory T cells that remember the specific invaders. When these central memory cells meet the same invader again, they reproduce to mount a faster and stronger immune response. But if repeatedly challenged, some of them become effectors memory T (TEM) cells instead, which are very aggressive and play a critical role in the development of autoimmune diseases. If TEM cells attack itself, you can get rheumatoid arthritis, if it happens in the pancreas, you can get Type 1 diabetes.

If we can control drugs to selectively block these TEM cells and block their uniqueness, we may be able to treat autoimmune diseases without compromising the rest of the immune system. That would be a significant advantage over existing therapies.

Q: You’ve found channels that can be targeted to treat obesity, diabetes, Glioblastoma disease, liver, kidney and lung fibrosis, which is the thickening and scarring of connective tissue. One of the drugs you’ve tested also had encouraging results against pneumonia, a skin disease, and a diagnosis of lung cancer.

The K+1.3 channel plays an important role in connective tissue, cells, macrophages, which ‘eat’ foreign invaders, and other cells. Our group developed TRAM-34, a drug which blocks this channel.

In animal studies, the drug effectively suppresses abdominal fat, a disease in which plaque builds up in arteries, the liver, kidneys and lungs, and it also reduces damage to the nervous system after a stroke.

You’ve had a lot of help from animals in your research. Can you elaborate?

I was thinking about how to design a drug that blocked the channel in a younger group. Dr Christine Beeton, sent me a scientific paper about how a 6-year-old girl in the United States, who had the autoimmune disease multiple sclerosis (MS), was helped by a scorpion.

Over a two-month period, all of her MS symptoms disappeared, and that lasted for two months. Dr Beeton added, ‘What if the scorpion venom was a K+1.3 channel? I really expected that to work, and not just with scorpions but also with venomous creatures.

While we were doing this, I was giving a talk in this medical centre, and Professor William Karm, came in and asked why I was so lost. He started collaborating, and with other investigators, discovered SRM-386.

Q: Your wife is a psychiatrist and was your classmates in medical school. What is this competition you have with her?

We share the same scientific background. She knows what it’s like for us. I have a PhD in biochemistry, but she’s been doing her MD in psychiatry.

I’ve published a bunch of papers but she’s never served as a professional person.

I keep telling him, ‘She, today, I’m telling you the joys of the work when your drug is approved and used for auto-immune diseases.’

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