The origins of tolerance: the 2025 Nobel prize in medicine

Talha Burki speaks with Fred Ramsdell, Mary Brunkow, and Shimon Sakaguchi about their Nobel-winning discoveries in peripheral immune tolerance.

Fred Ramsdell and his wife Laura O'Neill were camping on a hillside when the 2025 Nobel Prize in Physiology or Medicine was announced. "We try to spend all our free time in the mountains. On this occasion, we were in the high country in Wyoming, at about 8000 feet, a little east of Yellowstone National Park", said Ramsdell, Co-founder of Sonoma Biotherapeutics (San Francisco, CA, USA). There was no mobile phone coverage, so the Nobel Committee, or anyone else who wanted to reach the couple, could not get through.

Almost a full day had passed before Ramsdell and O'Neill decided to head out. They drove through Yellowstone, where they saw bison and antelope, crossed a little gateway town and finally reached somewhere within range of a mobile phone tower. "I was outside, walking the dogs, and Laura started yelling", Ramsdell told *The Lancet*. The thought occurred to him that they were in grizzly territory. "I was looking around thinking 'what is going on? Am I going to have to deal with a bear now?'", said Ramsdell. "Then Laura got out the car with a smile on her face and said 'you just won the Nobel Prize'. I said, 'no I didn't'. She said, 'I have 200 text messages that say otherwise'."

One of the first people Ramsdell telephoned was his former collaborator, long-term friend and co-laureate Mary Brunkow, Senior Program Manager at the Institute for Systems Biology (Seattle, WA, USA). Brunkow hung up on the Nobel Committee's first attempt to inform her of her victory. After all, it was an unfamiliar number and it was the middle of the night in Seattle. "I shut down the call and switched the phone to silent. I did start to think that the Nobels come out of Sweden and that was a Swedish number, but by then I was back to sleep", said Brunkow.

The third laureate is Shimon Sakaguchi, Distinguished Professor at the Immunology Frontier Research Center at the University of Osaka in Suita, Japan (the Nobel Committee did not have a problem catching up with him, at least). In a statement announcing the award on Oct 6, 2025, the Committee wrote that the winners were being recognised for "their groundbreaking discoveries concerning peripheral immune tolerance that prevents the immune system from harming the body". These discoveries have led to more than 200 clinical trials, opening a new field of research with implications for an enormous range of disorders.

> "'If you take out a certain population of T cells, you see autoimmunity, tissue destruction, and so on. This was a reliable phenomenon.'"

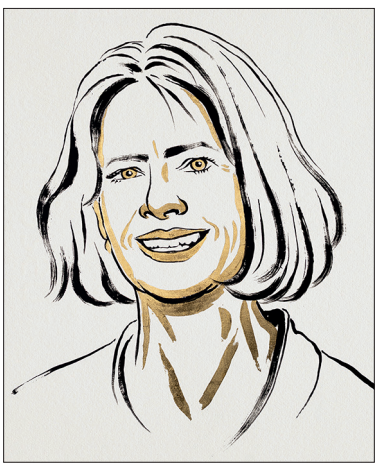
At the centre of the laureates' work is the question of how the body distinguishes between intruders and its own cells. There are two major types of T cell: helper T cells, which express the CD4 protein, and killer T cells, which express CD8. Helper T cells prowl for pathogens. When these cells find one, they alert the immune system, which mounts a defence. Killer T cells destroy infected cells and attack tumour cells.

T-cell receptors attach to fragments from antigens, such as viruses or bacteria, that appear on the surface of infected cells. The sheer quantity of T cells and their vast array of differently shaped receptors make it extremely difficult for any microbe to evade detection. But this raises the question of how the body protects itself from attack from the T cells—there are billions of T cells with receptors shaped to attach to the body's own tissues.

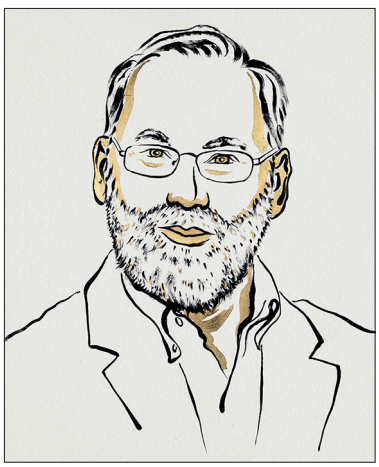
For many years, the answer was thought to lie exclusively in the thymus, which is where T cells mature. In a process known as central tolerance, the thymus eliminates T cells that would otherwise target the body. However, many researchers were convinced there was more to the story. They argued for the existence of a subset of immune cells they called suppressor T cells, which tackle dangerous T cells that made it through the thymus. But after some discouraging results, the field withered. "People thought that suppressor T-cell activity had been mapped to a particular region of the genome. When that region was sequenced, there was no gene there. A lot of immunologists walked away at that point. But not Shimon", said Ramsdell.

Sakaguchi was intrigued by an experiment that his colleagues at the Aichi Cancer Center Research Institute (Nagoya, Japan) had performed. They had found that if you remove the thymus from a 3-day-old mouse, its immune system goes into overdrive. The mouse develops all manner of autoimmune conditions. Sakaguchi isolated a group of mature CD4 T cells (ie, helper T cells) from healthy adult mice. He infused them into mice that had had their thymus removed. The T cells caused the mice to return to health.

In 1985, Sakaguchi published results showing that removing T cells from mice with normal immune systems caused the mice to develop autoimmune disease. His belief in suppressor T cells was cemented. "If you take out a certain population of T cells, you see autoimmunity, tissue



Mary Brunkow



Fred Ramsdell

Shimon Sakaguchi

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destruction, and so on. This was a reliable phenomenon. Whatever people may have said, I knew suppressor T cells were real", said Sakaguchi. By 1995, he had shown that by removing the 10% of CD4 T cells that also express the CD25 protein, you could induce autoimmune symptoms in mice. Transfer back that 10%, and the symptoms disappear. Sakaguchi had his suppressor T cells. He named them regulatory T cells, or Tregs.

Meanwhile, at Darwin Molecular Corporation, a small biotech company in Washington State, USA, Brunkow and Ramsdell were also dealing with diseased mice. They were investigating scurfy, a condition characterised by overactivation of the immune system. "We knew it was on the X chromosome, most likely a knockout mutation. There are lot of human conditions where you would like to be able to kick the immune system into gear. Perhaps this gene would represent a target", said Brunkow. They finally managed to narrow down the region to 20 potential genes.

"Today, you can go into GenBank and get the whole sequence. You would know what genes are there and you could even find out an awful lot about their function", said Brunkow. "Back then, we were dealing with unknowns, so we had to systematically sequence the region. With the help of bioinformatics approaches and the computational algorithms available at the time, we got there." It came down to a very small change in a gene that came to be known as *FOXP3*.

Brunkow and Ramsdell had come to suspect the same gene was linked to a rare human autoimmune condition called IPEX syndrome. The symptoms were similar to those associated with scurfy in mice, and the human IPEX locus was on the X chromosome. With the mouse *FOXP3* sequence in hand, Brunkow and Ramsdell were able to identify and sequence the equivalent human gene, and then show that patients with IPEX carry mutations in this gene. Sakaguchi later showed that *FOXP3* oversees the development of regulatory T cells.

For the team at Darwin Molecular, the findings were bittersweet. "We were looking for drug targets, and from that point of view, there was a little bit of disappointment when we realised that the protein the gene was coding for was most likely a DNA-binding transcription factor", explained Brunkow. "Transcription factors are challenging targets; they are located in the nucleus of the cell and they are really tough to get to." The site in Washington State where all this work took place was shuttered in 2003 and the staff laid off. Brunkow went into science writing and programme management.

Ramsdell has stayed in the field. Sonoma Biotherapeutics is developing cell therapies based on regulatory T cells. "Our focus is rheumatoid arthritis, but this technology has implications for diabetes, graft-versus-host disease and graft rejection, multiple sclerosis, and even things like ALS [amyotrophic lateral sclerosis], which is not fundamentally an autoimmune condition, but a lot of its pathology is caused by the immune response", said Ramsdell.

The principle is straightforward. For autoimmune conditions, the aim is to dampen the immune response. For other conditions, the aim is to do the opposite. "You reduce Tregs and you enhance the immune response. This is good if you want to attack a tumour or chronic infection. Maybe you can do this and reduce metastases. Or you might need to suppress the immune system, if it is overactive. Upregulation or downregulation, either way you can devise a strategy", said Sakaguchi.

Researchers are examining the possibility of engineering regulatory T cells to target specific proteins at sites of inflammation or in the brain. Perhaps the cells can be modified so that they recognise an antigen on a transplanted kidney and act as a guard. "There are endless possibilities", said Ramsdell. "Everything converged very nicely; the biology that Shimon had been doggedly studying and our ability to molecularly pin it all down just opened the floodgates."

Talha Burki