The discovery of Treg cells and what they mean for the future of immunology

Shimon Sakaguchi obtained an MD in 1976 and a PhD in 1982 from Kyoto University, Japan, where he was trained as a pathologist and immunologist. After performing postdoctoral studies at Johns Hopkins University and Stanford University as a Lucille P. Markey Scholar, he served as an assistant professor in the Department of Immunology at the Scripps Research Institute. He returned to Japan in 1991 and continued his immunology research at RIKEN Institute as an investigator of the Japan Science and Technology Agency and subsequently as the head of the Department of Immunopathology at Tokyo Metropolitan Institute of Gerontology, Tokyo. From 1998 to 2011, he was a professor and the chairman of the Department of Experimental Pathology, Institute for Frontier Medical Sciences at Kyoto University and served as the director of the institute for several years. In 2011, his lab moved to Osaka University and he assumed the current position as university distinguished professor of Osaka University.

In 1995, he discovered "Treg cells," which are said to be the last major immunological discovery. He has received many national and international awards, including the Order of Culture, for outstanding contributions to Japanese culture (2019), and the Robert Koch Award (2020).

Professor Shimon Sakaguchi, MD, PhD
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When Shimon Sakaguchi was a medical school student, he became intrigued by the paradoxical nature of the immune system: while it primarily protects the body by attacking foreign substances, in some cases it can overreact and start attacking normal cells and constituents of the body, causing autoimmune diseases. "I thought that if this paradoxical phenomenon of the immune response was resolved, a universal principle behind autoimmune disease would be revealed," he says. The immune system works in concert with a variety of cell populations, including regulatory T cells, or Treg cells, which were discovered by Professor Sakaguchi and play a central role in suppressing excessive or misguided immune responses such as autoimmune disease. We asked him about his journey that led to the discovery of Treg cells, and what applications they may have in future medical treatment of autoimmune and other diseases.

How did you become involved in the field of immunology?

"I enrolled in a postgraduate program in 1977, and many of the researchers at that time were tackling the issue of how the immune system differentiated normal from foreign cells," he remembers. While there were several theories, he was most interested in the one that hypothesized that self-reactive lymphocytes are always present in the body, but they are usually suppressed from responding. When that delicate balance is interrupted, an autoimmune disorder develops. "This theory was the most unpopular among immunologists," he said, "but I strongly supported it based on some experiments performed in mice. But to prove this, I needed to clearly define the unknown T cells that suppress immune responses."

What questions were you trying to answer with your research?

While working as a postgraduate, he came across a research paper from the Aichi Cancer Center in Nagoya that caught his attention. “The paper described that removing the thymus from normal mice 3 days after birth resulted in an autoimmune inflammation that resembled human autoimmune disease in various organs.” The thymus, an organ responsible for producing T cells, is crucial to a functioning immune system. “They thought that if the T cells disappeared, the overall immune response would be reduced; however, the result was the opposite, and a strong immune response occurred in those mice who had their thymus removed,” recalls Professor Sakaguchi. Intrigued, he dropped out of his postgraduate program and joined the Aichi Cancer Center as a research student. Once there, he and his team “confirmed that transplanting lymphocytes from normal mice to mice without a thymus could reduce autoimmune reactions, and that removing subpopulations of T cells from the transplanted lymphocytes did not suppress these reactions.” He became convinced that there were unknown T cells in the mice that were suppressing these autoimmune reactions, but there was still a large overlap between these immune-suppressing T cells and helper T cells. He knew that they would need to be narrowed down with more specific markers.

At the same time, another research group in Japan drew worldwide attention with their proposal of so-called “suppressor T cells.” Professor Sakaguchi was skeptical. “The immune-suppressing T cells that I’d seen were CD4-positive subpopulations. Their T cells were CD8-positive and were only observed under special conditions, so they were different from the cells I was capturing.” However, because both were T cells, they were often conflated with each other. In 1983, Professor Sakaguchi decided to leave Japan and move to the US. “I was very fortunate to meet with researchers who provided me with the monoclonal antibodies against markers of immune cells that were valuable at the time,” he said. “We tried many markers to select cell populations while also demonstrating the presence of cells that suppress immunity in normal mice. Finally, CD25-positive cells constituting approximately 10% of CD4-positive T cells were found. CD25 is a high-affinity receptor of IL-2 that promotes T cell proliferation and turned out to be an important molecule in the inhibitory mechanism in immune response.” These findings were published in 1995, almost 20 years after the start of his research. In 2000, after successful replications by other researchers and recognition at academic conferences, Professor Sakaguchi and his team named these cells “regulatory T cells,” or “Treg cells.”

That was not the end of his discoveries. When IPEX syndrome, an extremely rare monogenic disease that causes severe immunological disorders including autoimmune disease, allergy, and inflammatory bowel disease (IBD), was linked to a gene called *Foxp3*, Professor Sakaguchi and his team examined the relationship between *Foxp3* and Treg cells to try to understand how multiple symptoms and autoimmune issues could be caused by an abnormality in one gene. “We were able to functionally convert normal T cells into Treg cells by expressing *Foxp3* on normal T cells. We reported that this gene is the master gene of Treg cells, and that Treg function is impaired due to abnormalities in the *Foxp3* gene, causing various immune abnormalities,” he said. “Treg cells are the link between the gene and human diseases.”

What are your hopes for the future of the field of immunology?

“I would like to use the results of our basic research to treat and prevent diseases that affect so many people; for example, allergies, autoimmune diseases, and cancer,” said Professor Sakaguchi. “The immune system is flexible and finely balanced, and we believe that it’s possible to control immune responses by slightly adjusting this balance.”

His goal is to harness the power of the immune cells that exist naturally in our bodies to fight disease, rather than relying on surgery or drugs. “By using the antigen specificity of Treg cells,” he said, “we are considering a treatment method that precisely suppresses the immune response against self cells and tissues or transplanted non-self cells. It will not affect the immune response that attacks viruses and pathogens.” This treatment could be applied to the fields of treating autoimmune disease, allergy, IBD, organ transplantation, and cancer.

There is still work to be done when it comes to utilizing this method in cancer treatment. Activation of the immune response via immune-checkpoint inhibitors has already been utilized, but the response remains limited. “Because Treg cells are also involved in the immune suppression of anti-cancer immune responses, it is possible that a higher therapeutic effect could be achieved by precisely releasing only the inhibitory mechanism on cancer tissues,” he said. “We are working on the next generation of cancer treatment and the development of new cancer preventive measures.”

How have Applied Biosystems technologies helped you in your research?

Professor Sakaguchi utilizes Applied Biosystems™ products including the Applied Biosystems™ 3500 Genetic Analyzer and QuantStudio™ 3 Real-Time PCR System in his laboratory. Having worked on such a specialized research topic for more than 40 years, he understands the importance of keeping up with new technology. “Actively incorporating technical advancements widens the range of research,” he said, pointing out that the identification of *Foxp3* as the causative gene for IPEX syndrome would not have been possible without major advances in genetic analysis technology. “The use of genomic information is now more essential for human research than ever. Genomic analysis provides unbiased information that complements our experimental approach.”

What is some advice you would give other researchers?

Dr. Sakaguchi understands the struggle of being a scientist in a novel or unpopular field better than most. “When I started my study, research on immunosuppressive cells was not popular. We were isolated and unpopular in academic societies.” But having seen the phenomenon of these experiments on mice, he knew that it was important to continue. Despite what others may think at the time, persistence and a passion for answers are key ingredients in scientific success.

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