Regulatory T cells and Beyond: Shimon Sakaguchi's 2025 Nobel Prize in Physiology or Medicine

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ABSTRACT

The 2025 Nobel Prize in Physiology or Medicine, awarded to Shimon Sakaguchi, Mary Brunkow, and Fred Ramsdell, marks a defining milestone in modern immunology and the culmination of decades of inquiry into the mechanisms of immune tolerance. Sakaguchi has led a distinguished career in immunology, and his unwavering dedication to investigating the long-debated hypothesis of "suppressor T cells" culminated in the discovery of regulatory T (Treg) cells, which are specialised lymphocytes that maintain peripheral immune tolerance. Building on the early framework of central tolerance, his landmark 1995 study identified the $CD4^+CD25^+$ Treg cell subset as critical in preventing autoimmune pathology. Complementary work by Brunkow and Ramsdell subsequently identified the FOXP3 gene, which Sakaguchi later demonstrated encodes the master transcription factor defining Treg lineage specification, thereby revealing the genetic architecture of immune restraint.

The delineation of Treg biology has transformed both fundamental immunology and the therapeutic landscape, informing emerging strategies in autoimmunity, organ transplantation, and oncology. Ongoing clinical trials, including those exploring low-dose interleukin-2 (IL-2LD) therapy and chimeric antigen receptor T regulatory (CAR-Treg) cell engineering, highlight the promise of harnessing immune restraint while underscoring the complexity of safely translating these discoveries into clinical benefit. Persistent challenges remain in ensuring Treg cell lineage stability, optimising therapeutic windows, and elucidating the intricate molecular pathways governing suppression.

Sakaguchi's determination to pursue an idea once dismissed as artefactual exemplifies scientific rigour and intellectual courage. His discoveries have redefined the conceptual and therapeutic landscape of immunology, established Treg cells as a cornerstone of immune homeostasis, and opened new avenues for precision immunotherapy across a spectrum of diseases.

Keywords: CD4+CD25+ regulatory T cells, FOXP3-driven treg development, Peripheral immune tolerance mechanisms, Autoimmune disease suppression, Treg-targeted cancer therapy

Introduction

When the 2025 Nobel Prize in Physiology or Medicine was announced, many were perhaps reminded of Paul Ehrlich, the 1908 laureate who articulated the immune system's capacity to distinguish the "self" from the "non-self", thereby laying the groundwork for modern immunology. More than a century later, the question of how this delicate balance is maintained remains one of the field's most enduring challenges. In 2025, Shimon Sakaguchi, together with Mary Brunkow and Fred Ramsdell, was honoured for his groundbreaking discoveries on regulatory T cell–dependent peripheral immune tolerance.[1] Their work has revolutionised our understanding of immune restraint, paving the way for novel therapies that may alter the course of autoimmune disease, cancer, and beyond.

Sakaguchi was unconvinced by prevailing dogma, in which gaps in the existing theory of central immune tolerance were often dismissed. Yet he persisted, certain that a regulatory mechanism must exist. To fully appreciate this achievement, we must look not only at Sakaguchi's scientific journey, but also the challenges he overcame and what his discoveries mean for the future of medicine.

Biographical background

Immunologist Shimon Sakaguchi (Figure 1) was born on 19 January 1951 in Nagahama, Shiga Prefecture, Japan. He earned his medical degree from Kyoto University in 1976 and subsequently obtained his PhD there in 1982, during a period when immunology was rapidly evolving yet still riddled with unanswered questions. Between 1983 and 1987, he undertook postdoctoral studies at both Johns Hopkins University and Stanford University as a Lucille P. Markey Scholar and later served as an assistant professor in the Department of Immunology at the Scripps Research Institute.[2] He returned to Japan in 1991 and, following appointments at several leading institutes, his career advanced to the position of Distinguished Honorary

Fig 1 | Shimon Sakaguchi
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Professor at the Immunology Frontier Research Centre, Osaka University.[3] Over the decades, he has gained international recognition for his contributions to the field, including receipt of the prestigious Gairdner Foundation International Award in 2015 (Figure 2).

What he Discovered and Why it Matters

Sakaguchi's career is a testament to scientific perseverance. In the 1970s, the hypothesis concerning the existence of a distinct population of "suppressor T cells" remained contentious, largely due to a lack of reproducible experiments and definable molecular markers. The prevailing belief centred on the concept of "central immune tolerance", in which autoreactive T cells were eliminated from the thymus, and this alone was thought sufficient to prevent T cells from reacting against self-tissues. Early clues emerged when researchers observed that neonatal mice subjected to thymectomy developed profound lymphopenia followed by aggressive autoimmune diseases, hinting that thymus-derived lymphocytes were essential for preventing self-directed immune activation.[6] However, the identity and characteristics of these "suppressor" cells remained elusive. Throughout the 1970s and 1980s, mounting scepticism stalled progress, and the "suppressor" cell hypothesis was dismissed as a misleading artefact of early experimentation.

Fig 2 | Shimon Sakaguchi at the Gairdner Foundation International Award Ceremony, Toronto, Canada, on October 29, 2015
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Amid this uncertainty, Sakaguchi remained steadfast in his conviction that the immune system must possess a regulatory compartment, and he began his investigations in 1979. The breakthrough came in 1995, while he was at the Aichi Cancer Centre Research Institute in Japan, with the publication of his landmark paper "Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune disease", which identified a previously unrecognised subset of T lymphocytes defined by the $CD4^+CD25^+$ phenotype. This study demonstrated that depletion of these cells in experimental mice led to severe autoimmune diseases such as thyroiditis and polyarthritis.[7] The "brakes" of the immune system were revealed—the cells now known as regulatory T (Treg) cells.

Once the suppressive capacity of Treg cells was established, attention turned to the next question: what molecular mechanism underlies their development? The parallel contributions of co-laureates Mary Brunkow and Fred Ramsdell proved pivotal. Investigating the fatal autoimmune phenotype of the "scurfy" mouse strain, they identified FOXP3 as the causative gene and subsequently linked the absence of a functional FOXP3 gene in humans to the development of IPEX syndrome, a fatal disorder of immune dysregulation.[9,10] By revealing the genetic basis of Treg cell deficiency, their work laid the groundwork for dissecting the FOXP3 targetome. This is the network of genes regulated by FOXP3 that governs Treg cell development, lineage stability, and suppressive function, thereby establishing translational pipelines for human disease. Two years later in 2003, Sakaguchi's team demonstrated that FOXP3 encodes the transcription factor crucial for the development and function of Treg cells, publishing these findings in "Control of Regulatory T cell development by the transcription factor FOXP3".[11] This discovery was soon independently corroborated by Fontenot et al., who showed that FOXP3 programmes the development and suppressive function of $CD4^+CD25^+$ Treg cells, further establishing FOXP3 as the master regulator of immune tolerance.[12] Together, these findings defined the cellular and genetic framework of peripheral immune tolerance, firmly securing Treg cells as a cornerstone of modern immunology (Figure 3). The elucidation of Treg cell biology marked a turning point, bridging fundamental immunological theory with emerging avenues for therapeutic innovation.

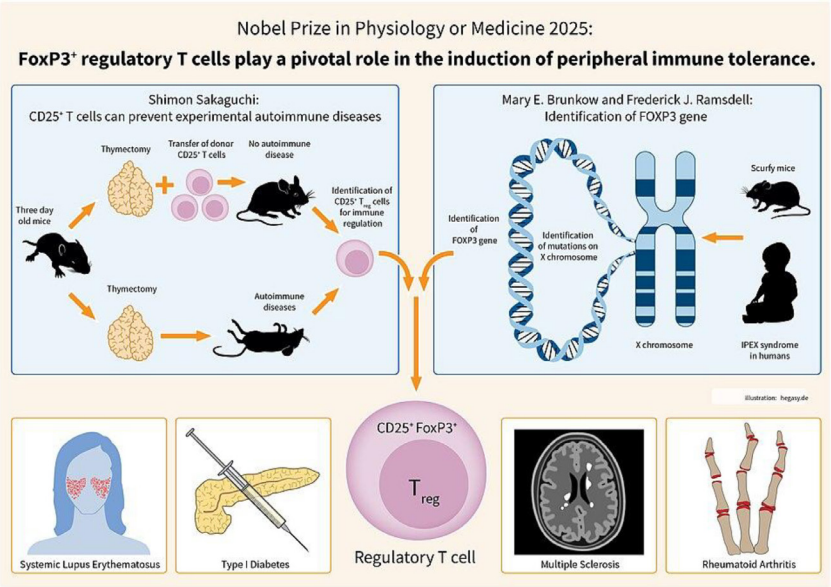

Fig 3 | FOXP3+ Treg cells play an important role in peripheral immune tolerance
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Implications and the Future

The journey from discovery to effective therapy is neither simple nor guaranteed. Following the announcement of the Nobel Prize, Sakaguchi expressed in an interview his hope that this research would inspire immunologists and clinicians to use Treg cells to "treat immunological diseases, control cancer immunity, or safer organ transplantation to prevent organ rejection".[13] Recent studies reveal that human Treg cells are phenotypically and functionally diverse, and a deeper understanding of their subset, ontogeny, and mechanism of suppression is essential to harness their therapeutic potential safely in autoimmune disease, transplantation, infection, and cancer.[14]

Although no Treg-based therapies have yet entered routine clinical practice, the field is advancing rapidly, with emerging clinical studies demonstrating the therapeutic potential of harnessing Treg cells. Notably, the MIROCALS trial investigated the use of low-dose interleukin-2 (IL-2LD) to selectively expand Treg cells in patients with amyotrophic lateral sclerosis (ALS) with the aim of improving survival. IL-2LD consistently increased circulating Treg cells and reduced inflammatory markers such as plasma CCL2. Adjusted analyses revealed a significant reduction in mortality among patients treated with IL-2LD after accounting for disease heterogeneity, underscoring the feasibility of immune modulation in neurodegenerative disease.[15]

In parallel, the engineering of Treg cells into chimeric antigen receptor T regulatory (CAR-Treg) cells represents an emerging approach to precisely suppress inflammation in targeted tissues.[16] Conversely, selectively disabling tumour-protective Treg cells could enhance anticancer immunity. Tumour-infiltrating regulatory T (TI-Treg) cells suppress antitumour responses and promote cancer progression, and recent studies have identified CCR8 as a molecule highly expressed on these TI-Treg cells. This discovery positions CCR8-targeted therapies as a promising strategy to enhance antitumour responses while minimising immune-related toxicity.[17]

Outlook

The discovery of Treg cells has fundamentally reshaped our understanding of immune tolerance, yet critical questions remain regarding their long-term stability and function. Concerns persist over Treg cell lineage plasticity, as some so-called "ex-Treg cells" may lose FOXP3 expression and acquire effector or pro-inflammatory phenotypes, posing risks to the safety and efficacy of adoptive Treg cell therapies.[18] The biology of tissue-resident Treg cells, such as GATA3$^+$ subsets in the skin and other organs, also remains incompletely understood, raising questions about how best to modulate these populations without disturbing systemic immune balance.[19]

In clinical translation, low-dose interleukin-2 (IL-2LD) therapy continues to show promise, yet its therapeutic window remains narrow and highly patient-specific, as excessive dosing risks activating effector T cells or natural killer cells.[20] Moreover, although pathways such as CTLA-4 are recognised as a key mediator of Treg-cell suppressive function, the full spectrum of its cellular and molecular mechanisms has yet to be elucidated.[21]

Together, these challenges highlight the delicate balance required to harness Treg cells for durable therapeutic benefit. Future advances will depend on integrating multi-omics profiling, in vivo imaging, and gene-editing technologies to map Treg cell dynamics across health and disease. As the field moves closer to clinical application, ethical oversight and global accessibility will be crucial in determining how these advances translate into meaningful patient benefit.

Conclusion

Sakaguchi's unwavering pursuit of a disregarded idea has reshaped fundamental immunology and opened therapeutic frontiers once thought unreachable. The 2025 Nobel Prize in Physiology or Medicine not only honours these breakthroughs but also reminds us that advances often come from those willing to go against the tide to look beyond established boundaries and to remain curious about what may yet be possible.

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