· Editorial ·

The 2025 Nobel Prize in Physiology or Medicine: a milestone in peripheral

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Immune tolerance research

The 2025 Nobel Prize in Physiology or Medicine has been awarded to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi for their groundbreaking contributions to the field of peripheral immune tolerance. Their discoveries related to regulatory T cells (Tregs) and the *FOXP3* gene have fundamentally transformed our understanding of how the immune system distinguishes between foreign invaders and the body's own tissues, opening new avenues for the treatment of autoimmune diseases and other immune-related disorders.

The immune system's delicate balancing act

The human immune system performs a complex and delicate balancing act. It must be robust enough to defend against pathogenic threats while remaining sufficiently restrained to avoid attacking the body's own tissues. When this balance is disrupted, autoimmune diseases, such as rheumatoid arthritis, type 1 diabetes, and multiple sclerosis, can arise.

Historically, scientists believed that the thymus, the primary site of immune cell maturation, eliminated self-reactive cells through a process known as central tolerance, primarily through negative selection of T cells. However, this mechanism is imperfect, and many self-reactive immune cells escape into the periphery, necessitating a secondary line of defense.

Shimon Sakaguchi's breakthrough: identifying functional Treg subsets

In 1995, Shimon Sakaguchi made a pivotal breakthrough in the study of immune tolerance. At the time, the prevailing view centered on central tolerance in the thymus as the sole driver of immune tolerance, even though earlier concepts of "suppressive T cells" (proposed in the 1970s–1980s, e.g., by Robert Gershon) had existed but lacked clear molecular markers for validation.

Sakaguchi's research challenged this paradigm by identifying a subset of immune cells expressing CD25 (IL2 receptor α chain) that exert a stable immunosuppressive function [1,2]. These cells, later termed regulatory T cells (Tregs), provided definitive evidence of peripheral immune tolerance and fundamentally altered our understanding of immune regulation.

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Brunkow and Ramsdell's Contribution: revealing the role of the *FOXP3* Gene

In 2001, Mary E. Brunkow and Fred Ramsdell made another critical discovery [3]. They identified that a specific strain of mice (known as "scurfy mice") was highly susceptible to autoimmune disease because of a variation in the Foxp3 gene.

Their work was complemented by a simultaneous study from Richard Siegel's team at the U.S. National Institutes of Health, which independently identified FOXP3 as the causative gene for IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome in humans. Together, these parallel discoveries revealed the central role of FOXP3 in immune regulation, providing a molecular basis for understanding how Tregs function.

Sakaguchi's integration: linking *FOXP3* to regulatory T Cells

In 2003, Sakaguchi bridged these discoveries by demonstrating that FOXP3 is the master transcription factor that controls the differentiation, stability, and immunosuppressive function of regulatory T cells.

These cells act as immune sentinels, monitoring other immune cells to ensure that the immune system remains tolerant to the body's own tissues. This integration not only completed the theoretical framework of peripheral immune tolerance but also laid the groundwork for developing Treg-based therapies.

The laureates' careers and contributions

Shimon Sakaguchi

Born in Japan in 1951, Shimon Sakaguchi earned his Ph.D. from Kyoto University in 1983. He is currently an honorary professor at the Immunology Frontier Research Center at Osaka University.

His latest research focuses on the differentiation and functional regulation of regulatory T cells, particularly the regulatory mechanisms of the master transcription factor, *FOXP3*. Using cutting-edge techniques, such as genome-wide CRISPR knockout screening and single-cell Perturb-icCITE-seq, he has systematically explored the gene regulatory networks induced by *FOXP3* [4]. His work has provided critical theoretical support for immunotherapy and continues to shape the field of immunology.

Mary E. Brunkow

Born in the United States in 1961, Mary E. Brunkow earned her Ph.D. from Princeton University. She conducted her Nobel Prize-winning research on *FOXP3* while working in the research and development department of the biotech company UCB in Bothell, Washington.

She is a co-author of a seminal 2001 paper in Nature Genetics that identified the scurfy gene product, initially named scurfin and later renamed *FOXP3* [3]. Currently, she is a senior project manager at the Institute for Systems Biology in Seattle. In an interview with the Nobel Foundation, she expressed her deep honor at being recognized for work that has significantly shaped her career and advanced the field of immunology.

Fred Ramsdell

Born in the United States in 1960, Fred Ramsdell earned his Ph.D. from the University of California, Los Angeles in 1987. He has been a driving force in both basic research and the biotech industry, translating immunological discoveries into clinical applications.

Currently, he is a scientific advisor at Sonoma Biothera-

peutics in San Francisco, where he focuses on exploring immune modulation and developing innovative therapies for autoimmune diseases and cancer. His work exemplifies the critical role of interdisciplinary collaboration in advancing medical science.

The awarding of the 2025 Nobel Prize in Physiology or Medicine to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi is a testament to their extraordinary contributions to immunology and to the profound impact of their discoveries on human health. Their work has fundamentally reshaped our understanding of immune tolerance, providing critical insights into how the immune system maintains balance and prevents autoimmune diseases.

The identification of functional Treg subsets, the *FOXP3* gene, and their molecular interconnection has opened new frontiers in both basic science and clinical medicine. These discoveries have paved the way for innovative therapies targeting autoimmune diseases, cancer, and organ transplantation. For instance, Treg-based therapies—such as ex vivo expansion of autologous Tregs for type 1 diabetes and gene-editing-mediated *FOXP3* repair for IPEX syndrome—are now being explored in clinical trials, offering hope to patients with conditions such as multiple sclerosis and graft-versus-host disease.

Moreover, their research has catalyzed interdisciplinary collaboration, bridging immunology, molecular biology, and genetics. Technologies, such as CRISPR-Cas9 and single-cell sequencing, have been employed to further unravel the complexities of Treg function and *FOXP3* regulation, accelerating the development of precision medicine.

The Nobel Committee's decision to honor Brunkow, Ramsdell, and Sakaguchi underscores the transformative power of fundamental research. Their journey from basic discovery to clinical application exemplifies how curiosity-driven science can yield profound societal benefits. Their work reminds us that breakthroughs often emerge from decades of persistence and collaboration, and that the pursuit of knowledge is essential for addressing humanity's greatest health challenges.

As we look to the future, the legacy of their discoveries will continue to inspire and guide the next generation of scientists. Advances in Treg biology hold the promise of more effective and targeted treatments, potentially revolutionizing the management of immune-related disorders. The 2025 Nobel Prize in Physiology or Medicine not only celebrates the awardees achievements but also reaffirms the vital role of immunology in shaping the future of medicine. Their contributions will undoubtedly continue to benefit patients worldwide, bringing us closer to a healthier and more resilient global community.

References

[1] Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M. 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 diseases. J Immunol. 1995 (155):1151-1164.

[2] Asano M, Toda M, Sakaguchi N, Sakaguchi S. Autoimmune disease as a consequence of developmental abnormality of a T cell subpopulation. J Exp Med. 1996 (184):387-396.

[3] Brunkow ME, Jeffery EW, Hjerrild KA, Paeper B, Clark LB, Yasayko SA, et al. Disruption of a new forkhead/winged-helix protein, scurfin, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet. 2001 (27):68-73.

[4] Chen KY, Kibayashi T, Giguelay A, Hata M, Nakajima S, Mikami N, et al. Genome-wide CRISPR screen in human T cells reveals regulators of FOXP3. Nature. 2025 (642):191-200.