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The discovery of Regulatory T Cells: a long journey toward immune balance and Nobel Prize

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The history of 2025 Nobel Prize in Physiology or Medicine is deeply rooted in the study of immunological tolerance, one of the cornerstones of modern immunology. The award was, indeed, conferred to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi in recognition of their ground-breaking contributions to elucidating how the immune system preserves peripheral self-tolerance, the capacity to distinguish and protect the body own tissues while effectively combating infections and malignant cells. Their pioneering studies identified the crucial role of regulatory T cells (Tregs) and the Forkhead box P3 gene (FOXP3) in maintaining immune homeostasis, profoundly reshaping our comprehension of immune regulation and opening new avenues for therapeutic strategies in autoimmune diseases, oncology, and organ transplantation [1, 2].

From the early days of the field, scientists understood that during central tolerance in the thymus, through the processes of positive and negative selection, the immune system eliminates autoreactive T cells. However, it soon became apparent that some lymphocytes could escape this central control, suggesting the need for a peripheral suppression mechanism capable of correcting such "errors" and preventing autoimmunity [3].

It was in this context that, in 1969, Nishizuka and Sakakura [4] first demonstrated the importance of thymus-derived cells in organ development and in preventing autoimmune diseases, through experiments involving thymectomy and thymus transplantation in newborn mice. Shortly thereafter, Gershon et al. [5] observed that certain thymic cells could suppress the antibody response, introducing the pioneering concept of "suppressor T cells". These discoveries unveiled a new level of immune regulation, in which T lymphocytes could directly modulate both humoral and cellular immune responses. However, specific markers and a molecular understanding of this suppression were still lacking.

A turning point came in 1995, when Sakaguchi et al. [6] identified CD25, the α-chain of the interleukin-2 (IL-2) receptor, as an essential marker for the function of suppressor T cells. This discovery laid the foundation for defining the modern Treg subset.

Five years later, Read et al. [7] demonstrated that cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) was highly expressed on $CD4^+CD25^+$ Tregs, functioning as a critical immune checkpoint molecule that prevents excessive immune activation, thereby elucidating a key mechanism of Treg-mediated immunosuppression. It was also established that the depletion of $CD4^{+}CD25^{+}$ T cells leads to autoimmune disease and hyperactivation of the immune system, further underscoring their role as guardians of immune homeostasis. On this basis, in 2001, Mary Brunkow and Fred Ramsdell [1, 8] discovered that mutations in the FOXP3 gene caused fatal autoimmune disease in mice. Investigating these mice, they found that this mutation blocked the generation of functional Tregs. Afterwards, they localised the FOXP3 gene to the X chromosome (Xp11.23–Xq13.3) and demonstrated that its mutation is responsible for the so-called IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome, a devastating congenital autoimmune disease [1, 8]. This discovery provided the molecular framework for understanding Treg biology and revealed how the immune system differentiates between self and foreign elements at the genetic level. Today, FOXP3 is recognized as one of the most critical transcriptional regulators in immunology, orchestrating a network of genes that curb inflammation and sustain immune equilibrium [3].

Further studies revealed that $CD4^{+}CD25^{+}$ T cells could lead to the conversion of $CD4^{+}CD25^{-}$ T cells into $CD4^{+}CD25^{+}$ regulatory cells, through the release of cytokines, like Transforming Growth Factor (TGF)-β and IL-2. Thus, the "educated" $CD4^{+}CD25^{+}$ regulatory cells become potent suppressor cells by mechanisms that require both cell contact (i.e., CTLA-4 expression) and TGF- β and IL-10 secretion. In subsequent years, the phenotypic characterisation of human Tregs expanded, including the expression of CTLA-4, the co-stimulatory molecule CD128, and the low expression of IL-7 receptor α-chain, CD127, all of which consolidated the immunological identity of Tregs [3, 9].

The discovery of regulatory T cells has profoundly transformed our understanding of the immune system, revealing it not as a purely defensive mechanism but as a dynamic network balancing activation and tolerance. Studies have shown that individuals with autoimmune disorders, such as type 1 diabetes, lupus, rheumatoid arthritis, and multiple sclerosis, often have too few Tregs in their blood or Tregs that fail to function properly. Early experiments in mice also demonstrated that Tregs hold great therapeutic potential for treating such diseases. In autoimmune disorders, researchers aim to restore Treg activity to prevent self-reactivity; in cancer, strategies target Tregs to boost anti-tumor responses; and in transplantation, Treg-based therapies seek to induce tolerance while minimizing immunosuppression. Several dozens of clinical trials worldwide stem from these insights, heralding treatments that fine-tune rather than merely suppress immunity [3, 10].

By uncovering how immune tolerance is maintained, the Nobel laureates established a conceptual shift in medicine, laying the groundwork for precision immunotherapy. For this reason, the 2025 Nobel Prize in Physiology or Medicine celebrates this extraordinary scientific achievement, the culmination of decades of research and visionary insight. From the mysterious "suppressor T cells" of the 1970s to today's well-defined $FOXP3^{+}$ regulatory T cells, this story stands as a shining example of how scientific curiosity and fundamental research can lead to breakthroughs that redefine the future of medicine.

Abbreviations

CTLA-4: cytotoxic T lymphocyte–associated antigen 4

FOXP3: Forkhead box P3 gene

IL: interleukin

TGF: transforming growth factor

Tregs: regulatory T cells

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Professor Calogero Caruso is the Editor-in-Chief of Exploration of Immunology. Dr. Anna Calabrò declares no conflicts of interest.

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