**Editorial**

# Nobel Prize awarded for the discovery of *Foxp3*-Directed 'Immune Policing' by Tregs

The Nobel Prize in Physiology or Medicine for 2025 was awarded to Mary Elizabeth Brunkow, Fred Ramsdell, and Shimon Sakaguchi for their original discoveries on peripheral immune tolerance, a key protective mechanism against autoimmunity. Mary E. Brunkow is a Senior Program Manager at the Institute for Systems Biology in Seattle, USA. Fred Ramsdell serves as a Scientific Advisor at Sonoma Biotherapeutics in San Francisco, USA. Shimon Sakaguchi is a distinguished Professor at the Immunology Frontier Research Centre at Osaka University, Japan. The laureates identified the immune system's "security guards," the Regulatory T cells or Tregs, as well as the *Foxp3* gene that controls their development and function. Their work explains how immune tolerance to the body's own tissues is established, and its far-reaching implications for autoimmune disease, cancer, and transplantation, offering significant therapeutic potential.

The body is protected against infections by immune responses. Meanwhile, the immune system avoids attacking the body's own tissues or antigens through immune tolerance. The word immune tolerance is meant to describe the process by which immune cells are rendered unresponsive to self-antigens, thereby preventing damage to healthy tissues. The immune tolerance includes two key mechanisms: Central tolerance and Peripheral tolerance.

*Central tolerance* is the first line of defence against self-reactivity. It eliminates self-reactive lymphocytes during their development in primary lymphoid organs namely, the thymus in the case of T cells and the bone marrow for B cells. This process involves negative selection, in which self-reactive lymphocytes are removed by apoptosis.

*Peripheral tolerance*, on the other hand serves as the second line of defence, acting as a 'backup mechanism' to control any self-reactive lymphocytes that escape central tolerance. The secondary lymphoid organs and peripheral tissues, such as lymph nodes are the primary centres of peripheral tolerance. Peripheral tolerance is achieved through several mechanisms, including anergy (functional inactivation), clonal deletion, and suppression by Tregs. Together, these peripheral mechanisms form a subtle but vital system that prevents the immune response from attacking the very tissues it is meant to protect.

Immune responses must be tightly regulated, as uncontrolled activity can lead to tissue damage and autoimmune disease. For many years, it was believed that immune tolerance was accomplished primarily through the elimination of harmful immune cells in the thymus *i.e.,* through the central tolerance. Sakaguchi showed that the immune system is more complex than previously understood. He identified, for the first time, a previously unknown class of immune cells: *Regulatory T cells (Tregs).* These cells protect the body from autoimmune diseases. Experiments in mice showed the role of Tregs in controlling autoimmunity: depletion of these cells led to disease, while restoration brought the animals back to health. Six years later, Mary Brunkow and Fred Ramsdell reported that a particular mouse strain was unusually prone to autoimmune disease. In 2001, they found that this vulnerability was linked to a gene first called *scurfin*, later renamed *Foxp3*. A mutation in *Foxp3* prevented the development of Tregs, leading to a fatal autoimmune disorder. Around the same time, they showed that mutations in the corresponding human *Foxp3* gene cause a severe autoimmune disorder known as IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome, providing direct evidence that immune regulation by Tregs is mediated by this gene. It was Sakaguchi's group that brought together various threads from decades of research and provided a clear,

unified picture of how the immune system protects itself from self-destruction by autoimmunity, by recruiting Tregs, whose development and function, in turn, are governed by the *Foxp3* gene.

The Tregs monitor other immune cells and ensure the protection of own tissues by activating the peripheral tolerance mechanism. The identification of Tregs thus provides an explanation as to how the immune system protects the body's own tissues and how the failure of this mechanism leads to autoimmune diseases such as type 1 diabetes and lupus. In immunology, the field of peripheral tolerance has recently gained significant attention, paving the way for new medical treatments for cancer and autoimmune diseases. Recent advancements in this field may enhance the success of organ transplantation, and several of the newly proposed therapeutic approaches are already undergoing clinical trials.

The Nobel Committee praised the laureates "for filling a major conceptual gap in medicine." Their findings clarified the delicate balance between immune activation and immune tolerance, providing a scientific foundation for new forms of therapy. Today, researchers are exploring ways to use Tregs to treat autoimmune diseases and prevent organ rejection subsequent to transplantation. Reinforcing the Treg population is expected to mitigate harmful immune activation in autoimmune conditions. Similarly, improved graft acceptance may be achieved by infusing engineered Tregs. Conversely, employing the opposite strategy, *i.e.,* reducing Treg activity, may be beneficial in cancer treatment. This approach is important because Tregs infiltrate the tumour microenvironment (TME), where they suppress the anti-tumour activity of effector T cells, thereby facilitating tumour immune evasion and progression. Accordingly, current therapeutic strategies seek to counter Treg-mediated immunosuppression by selectively depleting, inhibiting, or reprogramming tumour-associated Tregs into less suppressive or pro-inflammatory cells. These strategies are expected to enhance local anti-tumour immunity without triggering autoimmunity.

More than 200 clinical trials have been reported worldwide employing mechanisms involving Tregs and *Foxp3.* However, such approaches require great caution, as the outcome between activation and suppression of Treg activity is extremely delicate. Excessive strengthening of immune tolerance could leave patients vulnerable to infections; while weakening it too much may trigger new autoimmune responses. Achieving precision will be of paramount importance in future therapies, relying on inventions that allow for the careful modulation of the immune system rather than its complete suppression or activation.

The individual contributions of each of the three Nobel laureates in this discovery of peripheral tolerance are noteworthy, and together they provided fundamental insights into the mechanisms of autoimmunity. Mary Brunkow and Fred Ramsdell have been credited with identifying the gene *Foxp3***,** a discovery that formed the basis of modern regulatory T-cell biology. Working on a fatal autoimmune disorder "scurfy" in mouse, they found that this condition was linked to mutation in Foxp3 gene. It was then revealed that mutations in the human counterpart of the mouse *Foxp3* gene, result in a severe autoimmune disorder known as IPEX syndrome. Ramsdell has also played a key role in translating basic immunological research into clinical applications at Sonoma Biotherapeutics. Sakaguchi is a pioneer with a long and distinguished career in the field of immunological self-regulation. He identified the Tregs, and demonstrated that they are essential for maintaining immune tolerance or the normal state in which the immune system is prevented from attacking the body's own cells. He is also associated with identifying the role of the *Foxp3* gene and integrating various pieces of evidence related to Tregs and *Foxp3*, establishing that the development and function of Tregs are governed by the *Foxp3* gene. These discoveries have opened an entirely new field of research in immunology, the peripheral tolerance, enabling novel therapeutic approaches in medicine, particularly for

treating autoimmune diseases and cancer, as well as enhancing the success of organ transplantation. The editorial team of EBIOZ congratulates all three researchers on being awarded the Nobel Prize.

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