Regulatory T Cells: Gatekeepers of Immune Control in Hematology SKK

Lisanne Schoutens, MD, MSc, and Charlotte K. Brierley, MD, PhD
Department of Haematology, Oxford University Hospitals, Oxford, UK

Excitement crackled around the Aula Medica at Karolinska Institute in Solna, Sweden, on a cold morning in December 2025 as an eager crowd of students, scientists, and members of the public vied for a coveted seat to the 2025 Nobel Prize lectures in physiology or medicine.

They were not disappointed. Nobel laureates Shimon Sakaguchi, MD, PhD, Mary Brunkow, PhD, and Fred Ramsdell, PhD, took the stage to recount the discovery of regulatory T cells (Tregs), a subset of T cells whose immunosuppressive powers have reshaped our understanding of self-tolerance and immune restraint and launched a new field of translational work aiming to modulate Treg activity for therapeutic purposes — across cancer, autoimmune disease, and transplantation.[1]

What Are Regulatory T Cells?

The immune system must strike a delicate balance: protecting the body against harmful foreign pathogens and cancer cells while sparing the body's own healthy tissues. In humans, adaptive immune recognition relies on highly specific B- and T-cell receptors, generated by stochastic recombination of gene segments to create a vast repertoire of antigen specificities. Inevitably, this random process gives rise to receptors that recognize "self-antigens." If left unrestrained, such self-reactive lymphocytes drive autoimmune disease, necessitating robust mechanisms to eliminate or suppress these cells.

One critical piece of the self-tolerance puzzle was the discovery of "central tolerance," whereby developing T cells with high affinity for tissue-specific antigens are eliminated from the thymus — a finding recognized by the Nobel prize in 1960. However, it soon became apparent that this process is incomplete — and some self-reactive cells escape thymic deletion. This observation pointed to the existence of additional mechanisms enforcing "peripheral" tolerance.

The identification of Tregs emerged from two converging lines of research in cellular immunology and molecular genetics. First, through cell fractionation and adoptive transfer experiments, Dr. Sakaguchi identified CD4+ CD25+ T cells as a specific cellular subset capable of preventing autoimmune disease in mice.[2] Subsequently, through meticulous sequencing efforts of multiple transgenic mice — with a phenotype that at the time was of dubious relevance to human disease — Drs. Brunkow and Ramsdell identified *FOXP3* as the critical gene underlying the development of a severe multisystem autoimmune disease phenotype in mice[2] and in humans.[4,5] The two discoveries were soon linked, revealing that FOXP3 is a transcription factor that drives the differentiation of naive CD4+ T cells into Tregs.[6,7]

Subsequent work elucidated the mechanisms by which Tregs exert their regulatory effects, including cell-cell contact,[8] secretion of suppressive cytokines,[9,10] and sequestration of interleukin-2 (IL-2), a critical growth factor for T cells.[11]

The Role of Tregs in Hematological Disease

The Nobel laureates' seminal discoveries laid the foundation for a rapidly expanding field focused on peripheral immune regulation. The body of work has revealed a host of diverse roles for Tregs in maintaining tissue homeostasis, modulating immune responses, and promoting tissue healing and repair.

Consistent with these functions, deficiencies in Treg number and/or function have been demonstrated in a range of autoimmune and inflammatory diseases, including immune thrombocytopenia.[12] Following allogeneic hematopoietic cell transplantation (allo-HCT), reduced numbers of Tregs in the gut correlated with increased severity of acute intestinal graft-versus-host disease (GVHD).[13] Supporting a causal role, studies in mouse models of allo-HCT demonstrated that enrichment of Tregs within the transplant suppressed GVHD while maintaining graft-versus-tumor effects.[14]

Conversely, increased numbers of Tregs in the cancer microenvironments may suppress antitumor immunity and promote disease progression. In B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia, Tregs have been shown to exert tumor-promoting effects by suppressing cytotoxic T-cell proliferation and production of interferon-gamma.[15] Successful outcomes to therapy were found to correlate with a reduction in Treg numbers.[16]

Therapeutic Applications

Building on an improved understanding of the central role of Tregs in regulating immune homeostasis, numerous strategies have been pursued to modulate Treg activity for therapeutic purposes. Broadly, these approaches fall into two categories: enhancing Treg number or function to suppress pathological (auto)immune responses, and depleting or inhibiting Tregs to boost antitumor immunity in cancer.

Early efforts to enhance Treg function focused on boosting endogenous Tregs — after observational studies linked lifestyle factors including diet, exercise, and the gut microbiome to Treg abundance.[17] Pharmacological strategies have centered on low-dose IL-2, exploiting the expression of the high-affinity IL-2 receptor alpha chain (CD25) on Tregs to preferentially promote their expansion. Achieving selectivity remains a challenge, due to the expression of CD25 on other immune cells (notably natural killer cells), as does the lack of antigen specificity of the expanded Tregs. So far, IL-2-based therapeutic strategies have not led to durable immune control.[18]

An alternative approach to harnessing the suppressive function of Tregs is to administer them as a cellular therapy. Multiple promising strategies have emerged, based on either isolating and expanding autologous (or, in the context of allo-HCT, allogeneic Tregs), or on reprogramming Tregs from total CD4+ T cells or pluripotent stem cells. These approaches can be supplemented with genetic engineering steps to enhance the antigen specificity of the Tregs (e.g., adding a chimeric antigen receptor [CAR] or a specific T-cell receptor) or to boost other desirable properties, such as efficacy, survival, or stability of the Tregs (Figure).

In a recently published phase III randomized controlled trial, an allogeneic T-cell immunotherapy product that combines induced Tregs with hematopoietic stem cells (Orca-T) showed superior chronic GVHD-free survival compared to conventional allogeneic stem cell transplantation. With a requirement for less immunosuppression with the Orca-T product, there was also a reduction in infectious complications and non-relapse mortality. This innovative approach could represent a major shift in the treatment paradigm for GVHD prevention.[19]

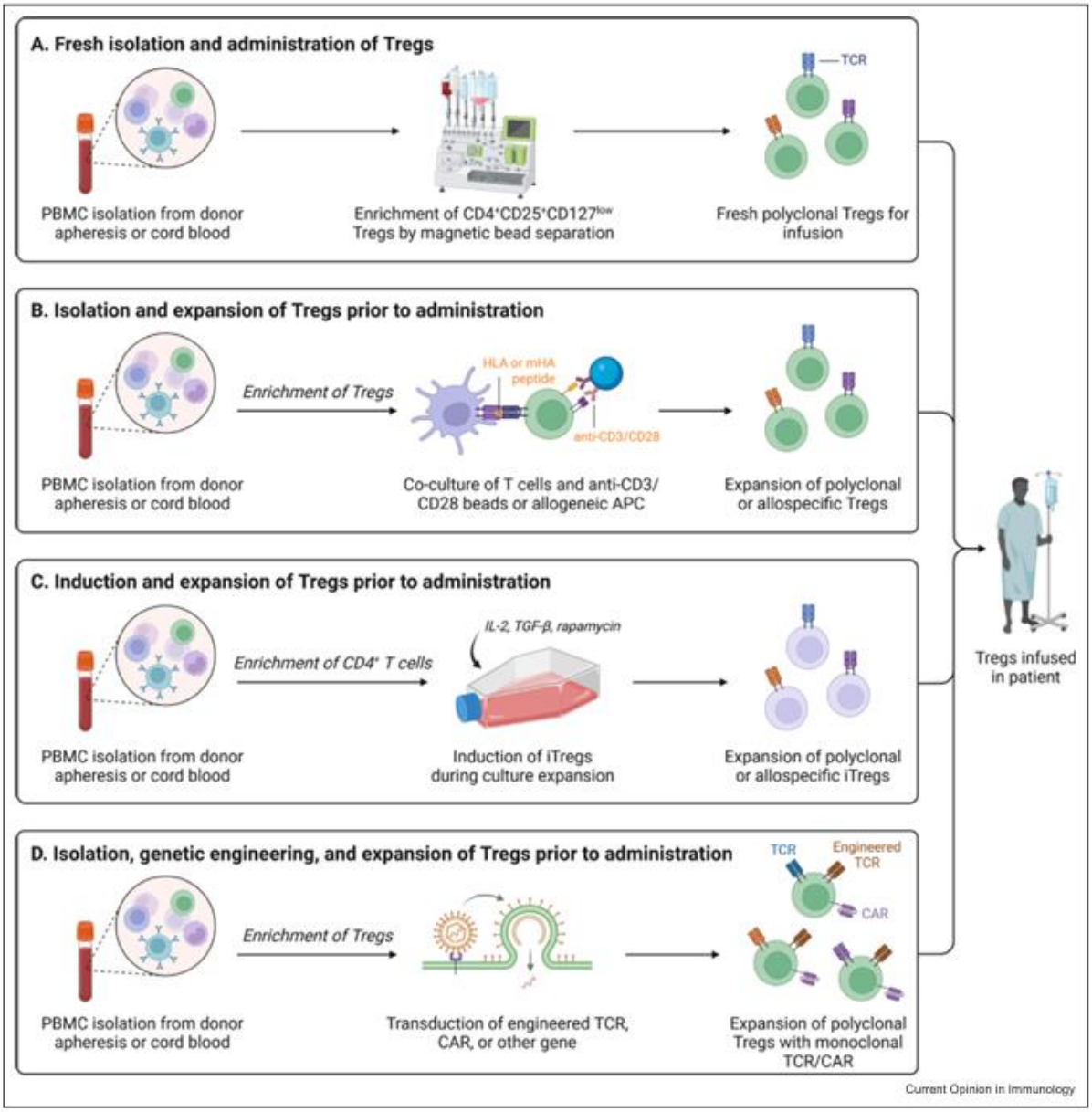
At ASH's 2025 annual meeting, data on the first in-human trial of engineered allogeneic CAR Tregs targeting CD6 (expressed on activated T cells) for the treatment of steroid-refractory GVHD demonstrated feasibility, a reasonable safety profile, and a partial response in the small number of patients tested.[20]

Conversely, in hematologic malignancies where Tregs contribute to immune evasion, therapies aim to deplete or functionally inhibit this population. Approaches include IL-2-toxin fusion proteins, CD25-targeting antibodies, or antisense oligonucleotides-targeting FOXP3. These strategies seek to relieve immunosuppression in the microenvironment, enabling host cytotoxic T-cell activity, and are being explored in clinical trials.[21]

Conclusion

Looking ahead, the therapeutic manipulation of Tregs in hematology is poised to transition from proof of concept to clinical application. Key challenges remain, including achieving antigen and tissue specificity, maintaining Treg stability in inflammatory environments, and treading the delicate balance of immune suppression and preservation of immune protection. As Dr. Brunkow acknowledged, the discovery of Tregs required "a bunch of different brains working together." The same will be true for the next phase of the field, as Treg-based therapies — poised for rapid evolution in the coming decade — are propelled by advances in cell engineering, synthetic receptor design, and cytokine platforms, alongside parallel innovations across immunology, stem cell transplantation, and clinical trial design.

Figure. Treg cellular therapy approaches in graft-versus-host disease



Abbreviations: APC, antigen-presenting cell; CAR, chimeric antigen receptor; GVHD, graft-versus-host disease; PBMC, peripheral blood mononuclear cell; TCR, T-cell receptor. Figure adapted from Bader, et al.[22]

1. *2025 Nobel Prize lectures in physiology or medicine*. YouTube. December 7, 2025. Accessed January 27, 2026. youtube.com/live/n1tfKu3e-_c
2. Sakaguchi S, Sakaguchi N, Asano M, et al. 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(3):1151-1164.
3. Brunkow ME, Jeffery EW, Hjerrild KA, 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(1):68-73.

4. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of *FOXP3*. *Nat Genet*. 2001;27(1):20-21.
5. Wildin RS, Ramsdell F, Peake J, et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. *Nat Genet*. 2001;27(1):18-20.
6. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science*. 2003;299(5609):1057-1061.
7. Khattri R, Cox T, Yasayko S-A, et al. An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nat Immunol*. 2003;4(4):337-342.
8. Wing K, Onishi Y, Prieto-Martin P, et al. CTLA-4 control over Foxp3+ regulatory T cell function. *Science*. 2008;322(5899):271-275.
9. Marie JC, Letterio JJ, Gavin M, et al. TGF-beta1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. *J Exp Med*. 2005;201(7):1061-1067.
10. Rubtsov YP, Rasmussen JP, Chi EY, et al. Regulatory T cell-derived interleukin-10 limits inflammation at environmental interfaces. *Immunity*. 2008;28(4):546-558.
11. Chinen T, Kannan AK, Levine AG, et al. An essential role for the IL-2 receptor in Treg cell function. *Nat Immunol*. 2016;17(11):1322-1333.
12. Nishimoto T, Kuwana M. CD4+CD25+Foxp3+ regulatory T cells in the pathophysiology of immune thrombocytopenia. *Semin Hematol*. 2013;50(Suppl 1):S43-S49.
13. Jarosch S, Köhlen J, Ghimire S, et al. Multimodal immune cell phenotyping in GI biopsies reveals microbiome-related T cell modulations in human GvHD. *Cell Rep Med*. 2023;4(7):101125.
14. Edinger M, Hoffmann P, Ermann J, et al. CD4+CD25+ regulatory T cells preserve graft-versus-tumor activity while inhibiting graft-versus-host disease after bone marrow transplantation. *Nat Med*. 2003;9(9):1144-1150.
15. Yang Z-Z, Novak AJ, Ziesmer SC, et al. Attenuation of CD8(+) T-cell function by CD4(+)CD25(+) regulatory T cells in B-cell non-Hodgkin's lymphoma. *Cancer Res*. 2006;66(20):10145-10152.
16. Maharaj K, Uriepero A, Sahakian E, et al. Regulatory T cells (Tregs) in lymphoid malignancies and the impact of novel therapies. *Front Immunol*. 2022;13:943354.
17. Wardell CM, Boardman DA, Levings MK. Harnessing the biology of regulatory T cells to treat disease. *Nat Rev Drug Discov*. 2025;24(2):93-111.
18. MacMillan ML, Hippen KL, McKenna DH, et al. First-in-human phase 1 trial of induced regulatory T cells for graft-versus-host disease prophylaxis in HLA-matched siblings. *Blood Adv*. 2021;5(5):1425-1436.
19. Meyer E, Salhotra A, Gandhi A, et al. Orca-T versus allogeneic hematopoietic stem cell transplantation (PRECISION-T): a multicenter, randomized phase 3 trial. *Blood*. Published online December 12, 2025. doi:10.1182/blood.2025031313.
20. Salhotra A, Wagner J, Yang D, et al. First-in-human trial of allogeneic CD6-CAR tregs in patients with chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Blood*. 2025;146(Suppl 1):276.
21. Kawai H, Ando K, Maruyama D, et al. Phase II study of E7777 in Japanese patients with relapsed/refractory peripheral and cutaneous T-cell lymphoma. *Cancer Sci*. 2021;112(6):2426-2435.

22. Bader CS, Meyer EH, Negrin RS. Regulatory T cell approaches for graft-versus-host disease prevention. *Curr Opin Immunol*. 2026;98:102685.

Disclosure Statement

The authors indicated no relevant conflicts of interest.