ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26mar1137

Targeting FOXP3+ regulatory T cells: Divergent Strategies in Cancer Immunotherapy and Transplantation

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Publication Date: 2026/03/24

Abstract: Tregs, or FOXP3 regulatory T cells, help maintain the balance of the immune system by preventing unnecessary or potentially harmful immune responses. They are essential for preserving immune tolerance, but the outcomes differ based on the illness. Tregs frequently accumulate in large quantities in cancer, especially in inflammatory tumor environments, where they inhibit the activity of cytotoxic immune cells that would kill cancer cells. Tumors can grow, evade immune control, and resist treatment in a safe environment created by this suppression. As a result, the focus of cancer treatments is shifting increasingly toward reducing or modulating the activity of Tregs within tumors. This can be done by using antibodies to kill Tregs, blocking chemokine signals, targeting their metabolism, using antisense techniques, or using methods that only work inside the tumor. Transplantation, on the different hand, is dependent on raising Treg activity to help the body accept organs to organ donors. Scientists are researching into ways to promote long-term graft tolerance while reducing off the need for broad immunosuppressive drugs. These include expanding Tregs outside the body, stabilizing them, or engineering them with specific TCRs or CARs. Both fields use different strategies, but they both have problems like keeping FOXP3 stable, making sure safety without lowering overall immunity, and making sure targeting is accurate.

Keywords: *FOXP3⁺ regulatory T cells, Immune Tolerance, Cytotoxic, Chemokine Signals, Graft Tolerance.*

How to Cite: Naveen Thalari; Yenumula Lavanya Lahari; Dr. Nizamuddin N. D.; Neelam Amrutha; Dr. Govardhan M. (2026) Targeting FOXP3+ regulatory T cells: Divergent Strategies in Cancer Immunotherapy and Transplantation.
International Journal of Innovative Science and Research Technology, 11(3), 1910-1915.
https://doi.org/10.38124/ijisrt/26mar1137

I. INTRODUCTION & BIOLOGICAL RATIONALE

FOXP3⁺ regulatory T cells (Tregs) sit at the heart of immune balance. This becomes obvious when FOXP3 is lost—both humans and mice rapidly develop overwhelming inflammation, underscoring how essential this transcription factor is for immune control [1,21]. What keeps a Treg stable is not FOXP3 alone, but a larger program it coordinates: demethylation of the TSDR region, and steady expression of molecules such as CTLA-4, CD25, IL-10, and TGF-β, all of which allow these cells to suppress unwanted immune activity [4,19]. Some Tregs originate in the thymus and enforce central tolerance, while others develop later in the periphery after encountering antigens in tissues [8]. Once they migrate into specific environments, especially tumors, they change again—tumor-resident Tregs often express higher levels of inhibitory receptors, shift their metabolism, and are recruited through chemokine pathways involving CCR4 and CCR8 [2,4,7]. These adaptations protect tissues

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during normal inflammation, yet in cancer they can unfortunately dampen effective antitumor immunity. Many solid tumors rich in FOXP3⁺ Tregs show weaker CD8⁺ T-cell responses and worse clinical outcomes. However, in some breast and gastrointestinal cancers, abundant Tregs simply reflect a generally inflamed tumor environment and are associated with better prognosis [7,16]. In transplantation, Tregs play a more clearly beneficial role. Their stability—maintained through continuous FOXP3 expression and resistance to inflammatory stress—limits harmful allo-reactive T-cell responses and supports long-term graft health [5,9,14]. Therapeutic use of Tregs has advanced quickly: polyclonal Tregs, alloantigen-specific Tregs, and CAR-modified Tregs have each shown promise in protecting grafts while reducing the need for broad immunosuppressive drugs [5,9,11]. Improvements in CAR design, chemokine receptor engineering, and metabolic tuning continue to strengthen the persistence and stability of these cells after transfer [9,17,18]. In parallel, drugs such as low-dose IL-2 or rapamycin help encourage the body's own Tregs without deeply suppressing the rest of the immune system [14,23]. FOXP3 itself remains the anchor of Treg identity. It works alongside partners like Helios, IRF4, and BATF to secure a suppressive transcriptional state, even when the surrounding environment is inflammatory or nutrient-poor [27,35]. When FOXP3 is disrupted—by cytokines, metabolic stress, or epigenetic instability—Tregs can shift into harmful IL-17– or IFN-γ–producing cells, a phenomenon known as Treg instability [21,34]. This makes FOXP3 maintenance a critical priority for any adoptive Treg or CAR-Treg therapy [5,9,31]. Despite aiming for opposite outcomes—enhancing Treg function in transplantation versus limiting it in cancer—both fields face overlapping challenges. Keeping Tregs stable and ensuring antigen specificity remain two of the biggest hurdles. Broad Treg depletion in cancer risks triggering autoimmunity, while excessive Treg expansion in transplant settings can weaken infection control or tumor surveillance [7,11,30]. Local tissue conditions, such as the hypoxic nature of tumors or the injury associated with graft reperfusion, further shape how Tregs behave and how long they remain functional [4,7,12,23]. Clinical progress also depends on overcoming practical issues: generating consistent GMP-grade Tregs, minimizing off-target activity of biologics, and improving methods for tracking these cells once they are infused [9,11,13,15,22,27,31]. Even so, emerging technologies—from spatial transcriptomics to FOXP3-stability engineering, nanoparticle delivery systems, and next-generation CAR-Treg designs—continue to push the field forward [13,15,22,31,32,35].

II. STRATEGIES AGAINST FOXP3⁺ TREGS IN CANCER IMMUNOTHERAPY

In cancer, the therapeutic aim is to selectively weaken or remove FOXP3⁺ Tregs within the tumour microenvironment (TME) while preserving systemic tolerance.[1,4,8] Major strategy classes include targeted depletion, FOXP3 destabilization, blocking Treg trafficking, and engineered delivery systems. Antibody-based depletion remains a major strategy for reducing tumour Tregs. Because Tregs express high levels of CD25, early anti-CD25 antibodies were used to eliminate them, although activated effector T cells can also transiently express CD25, limiting selectivity [2,4,7]. New Fc-engineered anti-CD25 antibodies focus ADCC more strongly within tumours while sparing peripheral effector cells [15,30]. CCR4-targeting antibodies such as mogamulizumab further enhance selectivity for tumour-homing Tregs [2]. Checkpoint molecules enriched on intratumoural Tregs, including CTLA-4, PD-1, TIGIT, and LAG-3, can also be targeted with Fc-competent antibodies to both deplete Tregs and reinvigorate exhausted CD8⁺ T cells [4,8,15]. Strengths include rapid TME reshaping and synergy with checkpoint blockade, while risks involve autoimmune toxicity and compensatory recruitment pathways [7,21]. Treg suppression can also be weakened by disrupting FOXP3. Antisense oligonucleotides that alter FOXP3 expression, along with epigenetic and metabolic modulators, diminish Treg stability under tumour-specific stress conditions [1,4,7,14]. This avoids global Treg loss but demands strict tumour-focused delivery to prevent systemic FOXP3 impairment. Another approach prevents Treg entry into tumours by blocking chemokine axes such as CCL17/CCL22–CCR4 and CCR8, limiting continual Treg recruitment while preserving systemic tolerance [2,4,7]. This can enhance effector activity and pair well with checkpoint therapy, though resident Tregs remain and tumours may bypass the inhibited pathways [7,16,22]. More targeted platforms include CAR-T or CAR-NK cells engineered to recognize Treg-associated antigens, bispecific engagers that redirect cytotoxic cells toward intratumoural Tregs, and nanoparticles delivering FOXP3-modulating agents directly to the TME [3,13,15,25,30,31]. These approaches offer high specificity but carry risks such as antigen escape, off-tumour toxicity, and immune reactions to engineered cells [17,18]. Because Tregs maintain systemic tolerance, all Treg-directed therapies require careful safety monitoring. Autoimmune events such as colitis, dermatitis, and thyroid dysfunction arise when systemic Tregs are inadvertently depleted [7,14]. Biomarkers—including cytokines, autoantibodies, TSDR methylation, and TCR repertoire changes—are increasingly used to detect early toxicity [22,27]. Combination strategies and safety-switch technologies aim to maximize antitumour activity while limiting systemic risk [3,8,12,13,30,31].

III. STRATEGIES TO EXPAND OR STABILIZE FOXP3⁺ TREGS IN TRANSPLANTATION

In transplantation, the aim is opposite to cancer: boost and stabilize FOXP3⁺ Tregs so they can suppress alloimmunity and maintain long-term graft tolerance.

A. Adoptive Transfer of Tregs

Polyclonal Tregs are easy to expand and safe, but donor-specific and antigen-specific Tregs are more powerful and precise. CAR-Tregs engineered to recognize donor antigens/HLA show better homing, stronger FOXP3 stability, and superior graft protection. In xenotransplant models, SLA-specific CAR-Tregs preserve their phenotype and extend graft survival. They can also trigger infectious tolerance, especially when paired with CD154 blockade.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26mar1137

- Strengths: high potency, reduced drug-based immunosuppression, potential long-term tolerance.
- Risks: complex manufacturing, FOXP3 instability, unwanted broad immunosuppression with polyclonal cells.

B. In Vivo Expansion & Support

Low-dose IL-2 selectively boosts Tregs because they express high-affinity IL-2 receptors. Engineered IL-2 variants increase this selectivity even more. Rapamycin promotes Treg survival by inhibiting effector T-cell metabolism while supporting Treg oxidative pathways. Other methods include tolerogenic DCs, nanoparticle cytokine delivery, and vectors that induce FOXP3 or generate CAR-Tregs inside the body.

- Strengths: avoids ex vivo cell processing, supports natural Treg renewal.
- Risks: over-suppression of immunity; expansion of unstable Treg subsets.

C. Stability, Trafficking & Persistence

Treg lineage stability can be threatened by inflammation; solutions include gene editing, Helios reinforcement, and stability-enhanced CAR designs. Trafficking is improved using chemokine receptors like CCR7, CXCR3, CCR4, directing Tregs to the graft and draining lymph nodes. Persistence is tracked using TCR sequencing, FOXP3-TSDR methylation, single-cell profiling, and new Treg-targeted imaging tools.

- Strengths: long-lasting, graft-localized tolerance.
- Risks: unstable Tregs can become pathogenic; poor trafficking reduces efficacy.

D. Safety, Monitoring & Translation

Too much regulation increases infection and cancer risk; too little FOXP3 stability risks Treg→effector conversion. Clinical translation demands monitoring of lineage fidelity, cytokines, metabolism, and early signs of infection or autoimmunity.Combining Tregs with costimulation blockade or rapamycin improves stability and reduces immunosuppressive drug load—as seen in the ONE Study. Safety switches, inducible circuits, and real-time imaging help control CAR-Treg therapies.GMP production requires high purity, strong FOXP3 stability, and avoiding contaminating effector cells.

- Strengths: controlled, durable tolerance with less dependence on drugs.
- Risks: logistical complexity; long-term engraftment risks still being defined.

IV. EMERGING TRENDS AND FUTURE DIRECTIONS

➢ *Biomarkers and Imaging*

Spatial transcriptomics, single-cell Treg clonotyping, and PET tracers now enable real-time mapping of FOXP3$^+$ Tregs within tumours or grafts, revealing their stability, trafficking routes, and interaction with effector cells.[20–22] These tools provide next-generation biomarkers to optimize Treg-modulating therapies and predict responses with unprecedented precision.[20–22]

➢ *Localized/Context-Specific Modulation*

Nanoparticles, antibody–drug/RNA conjugates, and inducible systems deliver Treg-modulating agents directly to tumour or graft sites, limiting systemic toxicity.[23] Optogenetic and photo-activatable platforms add spatial–temporal control, enabling precise modification of FOXP3$^+$ Tregs while preserving systemic immune balance.[24]

➢ *Switchable/Safety Control Systems*

Engineered ON/OFF switches and suicide genes provide reversible control of Treg-directed agents or CAR-Tregs, allowing rapid shutdown during toxicity.[25,26] These safety circuits enhance clinical feasibility by minimizing risks of autoimmunity, infection, or graft dysfunction during aggressive FOXP3-targeted interventions.[25,26]

➢ *Combined Regimens*

Treg depletion or destabilization can sensitize tumours to checkpoint inhibitors, vaccines, and adoptive T-cell therapies, converting immunologically “cold” tumours into responsive ones.[27] In transplantation, combining Treg therapy with low-intensity immunosuppression or tolerogenic conditioning promotes durable, antigen-specific graft acceptance.[28]

➢ *In Vivo Programming and Gene Editing*

Vector-mediated FOXP3 stabilization, in situ CAR-Treg generation, and CRISPR-based editing of endogenous Tregs may bypass ex vivo manufacturing barriers.[29] Inducible promoters enable dynamic control of FOXP3 or CAR expression, offering scalable, programmable tolerance strategies.[29]

➢ *Cross-Disciplinary Lessons*

Cancer immunotherapy and transplantation increasingly exchange technologies such as targeted delivery systems, safety switches, and high-resolution biomarker platforms.[30] These shared innovations accelerate progress in tuning FOXP3$^+$ Treg activity for either antitumour immunity or stable transplant tolerance.[30]

V. BENEFITS AND BARRIERS TO IMPLEMENTATION OF THE FOXP3 T CELLS THERAPY IN BOTH CANCER IMMUNOTHERAPY AND ORGAN TRANSPLANTATION

➢ *Therapeutic Benefits in Cancer Immunotherapy*

Targeted disruption of intratumoural FOXP3$^+$ Tregs enhances CD8$^+$ T-cell infiltration, improves dendritic-cell activation, and markedly boosts responses to checkpoint inhibitors.[2,4,7,15] Strategies such as CCR4 blockade, metabolic interference, and bispecific platforms selectively thin Treg networks within the TME while maintaining systemic tolerance.[13,25,30] These approaches are

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26mar1137

especially effective in Treg-rich tumours where suppression heavily limits antitumour immunity.

➢ *Therapeutic Benefits in Organ Transplantation*

Enhancing FOXP3$^+$ Tregs—via adoptive transfer, donor-specific expansion, or CAR-Treg engineering—promotes graft acceptance and reduces reliance on chronic immunosuppression.[5,9,17,18] In vivo methods such as low-dose IL-2, mTOR modulation, and tolerogenic conditioning further reinforce endogenous Treg populations and stabilize alloimmune control.[14,23,37] Together, these strategies offer a biologically precise route toward operational tolerance.

➢ *Barriers to Implementation Across Both Fields*

- *Lineage Stability*

Maintaining durable FOXP3 expression is essential; inflammatory stress or epigenetic disruption can convert Tregs into pathogenic effector-like cells, undermining both cancer and transplant outcomes.[21,32,34]

- *Specificity and Targeted Delivery*

Insufficient tumour selectivity risks autoimmune toxicity, while poor graft-specific targeting may weaken antiviral and antitumour immunity in transplant recipients.[7,12,15,25] CAR-Tregs improve precision but require careful antigen selection.

- *Safety and Immune Balance*

Over-depletion of Tregs may expose latent autoimmunity, whereas excessive expansion increases infection and malignancy risk, demanding tight therapeutic windows and real-time monitoring.[11,40]

- *Manufacturing and Regulatory Barriers*

Clinical-grade Treg products require GMP-compliant expansion, stringent purity, and validated FOXP3 stability assays—constraints that currently limit large-scale deployment.[9,31,40]

- *Monitoring Persistence and in Vivo Function*

Reliable tracking remains limited; advanced tools such as TCR sequencing, TSDR methylation assays, single-cell profiling, and PET tracers are improving insights but are not yet broadly available.[22,27,38]

VI. DISCUSSION

FOXP3$^+$ regulatory T cells (Tregs) represent one of the most context-dependent immune lineages in modern immunotherapy. Their behaviour shifts dramatically depending on microenvironmental cues, metabolic constraints, and FOXP3 stability, generating opposite clinical implications in cancer and organ transplantation. This review shows how these dual roles—Treg attenuation in cancer versus Treg reinforcement in transplantation—share common mechanistic bottlenecks and translational challenges. Tumours often create hypoxic, inflammatory, and metabolically restrictive niches that enhance Treg survival and suppressive potency, enabling immune escape by inhibiting CD8$^+$ T-cell function and dendritic cell activation [1,4,7,15]. In contrast, similar stability-promoting cues support Tregs in transplantation, where they restrain allo-reactive responses and promote long-term graft acceptance [5,9,17]. Central to both settings is FOXP3 stability: inflammatory cytokines and epigenetic disruption can drive Treg instability, resulting in IL-17$^+$ or IFN-γ$^+$ effector-like conversion, with detrimental consequences in either disease context [21,32,34]. Spatial distribution further influences Treg function. In triple-negative breast cancer, high intratumoural FOXP3$^+$ Tregs—not stromal Tregs—were associated with improved survival and co-enrichment of CD8$^+$ and CD20$^+$ populations, reflecting an immune-active rather than suppressive microenvironment [43]. This overturns the traditional assumption that Tregs uniformly worsen outcomes in solid tumours and reinforces the importance of spatially resolved immune profiling. Across both fields, targeting specificity remains a central challenge. In cancer, therapeutic success depends on selectively depleting or disabling intratumoural Tregs while sparing systemic pools to avoid autoimmune toxicity [7,15]. Chemokine-receptor blockade, Fc-engineered antibodies, compartment-restricted drug conjugates, and nanoparticle-based delivery systems have emerged to enhance tumour precision [13,23,30]. In transplantation, specificity must be directed toward donor antigens to preserve host defence against infection and malignancy [12,25]. TCR-engineered Tregs and CAR-Tregs provide this targeted approach but introduce additional concerns regarding FOXP3 stability, off-target recognition, and long-term persistence [3,17,18]. Safety constraints continue to shape therapeutic design. In cancer, aggressive Treg depletion risks triggering systemic autoimmunity, while in transplantation, extensive Treg expansion may impair tumour surveillance or increase susceptibility to infections [11,40]. Inducible ON/OFF circuits, suicide genes, and drug-regulated control systems provide essential safeguards for next-generation engineered Treg therapies [13,17,26]. Translation remains limited by manufacturing and monitoring challenges. GMP-grade Treg production requires stable FOXP3 expression, validated TSDR demethylation, and high-purity expansion protocols [9,31,40]. After infusion, tracking Treg persistence, trafficking, and phenotype is still technologically demanding; advances in TCR repertoire sequencing, single-cell analysis, PET tracers, and spatial transcriptomics are beginning to address these gaps [20–22,27,38]. Despite these hurdles, progress is rapid. Cross-disciplinary insights—such as applying CAR-engineering concepts from oncology to transplantation, or adapting tumour-immunology imaging tools for graft monitoring—are accelerating innovation. Deeper understanding of Treg metabolic programming, tissue adaptation, and epigenetic anchoring continues to open more refined therapeutic windows [31,35,41]. Overall, FOXP3$^+$ T-cell modulation remains a promising yet complex frontier. In cancer, strategic Treg attenuation may enhance checkpoint inhibitor responses and restore cytotoxic immunity. In transplantation, boosting or stabilizing Tregs offers a realistic path toward reducing long-term pharmacologic immunosuppression and achieving operational tolerance. Future progress will depend on

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26mar1137

improving precision targeting, enhancing lineage stability, integrating safety switches, and expanding scalable manufacturing capabilities. Finally, although FOXP3⁺ Treg therapies hold immense clinical potential, global accessibility remains limited. High production and engineering costs — similar to CAR-T cell therapy, which currently exceeds ₹31 lakh in India [44] — present major barriers for low- and middle-income populations. Expansion of local manufacturing, decentralised platforms, and India-specific clinical trials will be essential to ensure equitable access as the field moves toward broader clinical adoption.

VII. CONCLUSION

FOXP3⁺ regulatory T cells sit at the intersection of two opposing immunological goals: their depletion is essential for unleashing antitumor immunity, while their reinforcement is critical for achieving transplant tolerance. In cancer, selective targeting of tumour-infiltrating Tregs—through chemokine-guided depletion, functional reprogramming, or localized delivery—has emerged as a strategy to overcome suppressive tumour niches and enhance the effectiveness of immunotherapy. In transplantation, antigen-specific and CAR-engineered Tregs offer a precise way to stabilize immune regulation, protect grafts, and reduce dependence on long-term immunosuppression.Across both settings, challenges such as FOXP3 stability, lineage fidelity, targeted delivery, and scalable manufacturing continue to shape therapeutic progress. Yet advances in synthetic immunology, gene editing, single-cell profiling, and precision tracking technologies are rapidly closing these gaps. Together, these insights underscore that FOXP3⁺ Tregs are not simply suppressive cells but context-dependent modulators of immune fate—barriers to effective cancer immunity and key facilitators of durable transplant tolerance. This duality defines FOXP3-targeted therapy as a transformative and increasingly achievable frontier in modern immunomedicine.

- *Abbreviations and Acronyms*

CAR-Tregs – Chimeric Antigen Receptor Regulatory T Cells; CCR – C-C Motif Chemokine Receptor; CCL – C-C Motif Chemokine Ligand ;CTLA-4 – Cytotoxic T-Lymphocyte Antigen-4; FOXP3 – Forkhead Box Protein P3; IL-2Rα – Interleukin-2 Receptor Alpha; mAb – Monoclonal Antibody; mTOR – Mammalian Target of Rapamycin; PD-1 – Programmed Death-1; PD-L1 – Programmed Death Ligand-1; TCR – T-Cell Receptor; TGF-β – Transforming Growth Factor-Beta; TME – Tumour Microenvironment; Tregs – Regulatory T Cells; TSDR – Treg-Specific Demethylated Region.

ACKNOWLEDGMENT

The authors acknowledge the support of Dr. B. V. Ramana, Professor & Principal of Dr. K. V. Subba Reddy Institute of Pharmacy, for providing a conducive academic environment for the successful completion of this review. The authors extend their gratitude to the Professor & Heads of the Department of Pharmacy Practice, Dr. M. Sri Ramachandra, for their guidance and encouragement. We sincerely acknowledge and express our gratitude to all the authors whose previous research and review works on this topic have significantly contributed to the available literature and provided valuable data for our review.

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