

Advances and challenges in cancer immunotherapy targeting regulatory T cells

Elena M. George ^{1*}, Octavia L.Ersoy ², Askeyf Y. Taemriu ³

¹ Phd Student, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, 40-055 Katowice, Poland. Email: Elenageorgemmd@sum.edu.pl

² Department of Pharmacy, Faculty of Medicine and Pharmacy, Virginia Commonwealth University VCU, Richmond, VA 23284, USA. Email: octaviadersoy@umw.edu.pl

³ Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, , 410073 Oradea, Romania. Email: Askeytaiidmdn@uroadea.ro

* Corresponding Author: Elena M. George, Elenageorgemmd@sum.edu.pl

DOI: <https://doi.org/10.64440/IBNSINA/SINA0015>

ARTICLE INFO

Article history

Received Jan 25, 2026

Revised Jan 27, 2026

Accepted Feb 24, 2026

Keywords

T cells;

Cancer Immunotherapy;

Immunotherapy;

Therapy development

ABSTRACT

Regulatory T cells (Tregs) are important mediators of immune tolerance, but represent a major barrier to effective antitumor immunity in the tumor microenvironment (TME). Accumulating evidence indicates that intratumoral Treg enrichment is associated with immune evasion, tumor progression, and resistance to immunotherapy in many malignancies. This review systematically examines current strategies targeting Tregs in cancer, including antibody-mediated depletion (anti-CD25, anti-CTLA-4), immune checkpoint modulation, inhibition of Treg trafficking, and metabolic reprogramming approaches.

We analyze mechanistic insights underlying Treg stability and suppressive function, including FOXP3-dependent transcriptional regulation, IL-2/STAT5 signaling, PI3K-Akt-mTOR pathway, and CD39/CD73-mediated adenosine production. Furthermore, we evaluate preclinical findings and emerging clinical data, highlighting the therapeutic efficacy, limitations, and immune-related side effects associated with Treg-targeted interventions.

Although selective Treg modulation has proven promise for improving antitumor responses, systemic depletion poses giant dangers for immune dysregulation and autoimmunity. Therefore, future techniques should prioritize spatially limited and functionally precise targeting inside TME. Advances in single-cell sequencing, metabolic profiling, and precision immunotherapy structures offer new possibilities to refine Treg-focused cures and enhance medical results.

Collectively, this evaluate gives a comprehensive mechanistic and translational framework for know-how Treg biology in most cancers and descriptions future directions for the development of safer and extra effective immunotherapeutic techniques.

This is an open-access article under the [CC-BY-SA](https://creativecommons.org/licenses/by-sa/4.0/) license.



1. Introduction

CD4⁺CD25⁺FOXP3⁺ T cells, phenotypically known as regulatory T cells (Tregs), play a central role in maintaining immune tolerance and immunological homeostasis. These cells serve as crucial modulators of immune responses through the inhibition of uncontrolled or misdirected immune activation. Their suppressive role may be mediated via direct cell-to-cellular interaction in addition to the secretion of inhibitory cytokines, particularly interleukin-10 and reworking growth factor-beta (TGF-beta). By these properties, Tregs block the potential of autoimmune responses to prevail and contribute to immune homeostasis. The differentiation, focalization, and suppressive function of Tregs are very tightly regulated through only a few signaling pathways, e. g. the IL, 2/STAT5 and PI3K, Akt, mTOR pathways. Moreover, epigenetic regulatory mechanisms play an important role in maintaining high FOXP3 expression and thus stable lineage commitment.

On the one hand, Tregs have a protective role against autoimmunity. On the other hand, they might also have detrimental effects in the context of cancer. Inside the tumor microenvironment (TME), tumor, infiltrating Tregs contribute to tumor cells escaping immune control by suppressing the antitumor immune response. They inhibit the activity and infiltration of cytotoxic CD8 T, cells, interact with antigen, presenting cells (APCs), and promote a highly immunosuppressive environment. Mechanistically, this suppression is through pathways such as inhibition of CTLA, IV, mediated costimulatory signaling and production of adenosine by CD39/CD73 enzymatic activity. A growing number of clinical and translational studies show that high levels of intratumoral Tregs often correlate with poor prognosis in several types of cancers. This correlation highlights the significant role of Tregs in tumor progression.

This study through an assessment of those factors sets out to find present gaps in the understanding and to extend the knowledge of the ways that limitations of Treg biology and immunotherapy can be eliminated. Therefore, this paper is more than just a conceptual review of the literature. It is a call to action for research and development, challenging both researchers and clinicians to discover new pathways that might lead to more therapeutic choices and better results for cancer patients treated with the current cancer immunotherapy approach.

2. Methodology

This examination was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta, Analyses (PRISMA 2020) guidelines.

A methodical and thorough study retrieval plan was implemented in the four major online databases: PubMed, Scopus, Web of Science, and Embase. The dates for studies considered for inclusion are from January 2018 to February 2026.

In order to guarantee the most extensive coverage of the relevant literature, predefined key terms along with combinations thereof were used. Terms were the following: "regulatory T cells", "Tregs", "cancer immunotherapy", "tumor microenvironment", "FOXP3", "immune checkpoint inhibitor" and "Treg depletion method". Boolean operators (AND/OR) were used to build and precisely modify the search queries.

Studies were taken into consideration eligible inside the occasion that they met the subsequent inclusion standards: (1) peer-reviewed unique research articles or systematic reviews; (2) investigations addressing the organic function of Tregs in most cancers; (3) studies comparing therapeutic strategies especially focused on Tregs; and (four) courses available in English. Exclusion requirements comprised: (1) case reviews and convention abstracts; (2) studies unrelated to oncology; and (3) articles for which full-textual content versions have been not reachable.

The preliminary database search diagnosed 742 statistics. After disposing of 198 reproduction entries, 544 articles remained for call and abstract screening. Of those, 312 were excluded due to lack of relevance to oncology or absence of recognition on Treg-targeted interventions. The closing 232 entire-text articles had been assessed for eligibility. Following sure evaluation, 118 research satisfied the predefined inclusion standards and had been in the end protected in the qualitative synthesis.

For every covered study, statistics had been systematically extracted concerning study format, tumor type, molecular dreams, recovery technique, clinical degree, treatment reaction outcomes, and stated immune-related detrimental sports. To enhance methodological rigor and reduce choice bias, look at screening and eligibility evaluation have been completed independently by means of reviewers.

The specified have a look at selection manner, dependent in step with PRISMA 2020 recommendations, is illustrated in Figure 1.

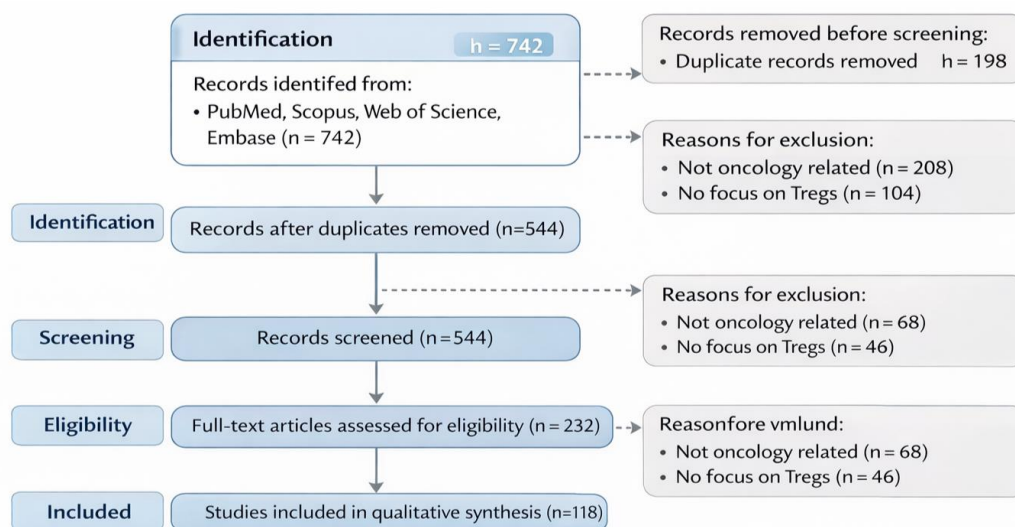


Figure 1. PRISMA Flow Diagram of Study Selection.

A total of 742 records were identified through database searching, and 198 duplicates were removed. Following title and abstract screening of 544 records, studies meeting the predefined eligibility criteria were assessed in full text, resulting in 118 articles included in the final qualitative synthesis.

3. Literature Review

Regulatory T cells, often known as Tregs, are an exceptionally small and distinctive population of CD4 T cells that play a vital role in the immune system by keeping immune tolerance and preventing uncontrolled inflammatory reactions [7]. These cells are mainly identified by the expression of the FOXP3 transcription factor, and they carry out their suppressive activities through a range of mechanisms, including the secretion of inhibitory cytokines, the employment of inhibitory receptors, and the competition for metabolic substrates, etc. Besides that, Tregs are not only essential for the maintenance of immune homeostasis under normal physiological conditions but also their functional change is most noticeably the case with cancers, particularly in the tumor microenvironment (TME) [8].

Numerous studies have shown that tumor, infiltrating Tregs may be more effective in their suppressive activity than those in the peripheral circulation. This heightened suppressive capability is mainly due to the sustained expression of FOXP3, the increased levels of CTLA-4, the very active CD39/CD73 enzymatic functions and the ability to adapt to the hypoxic and metabolically limited tumor conditions [9, 10].

Due to these adaptations, Tregs not only can survive in the tumor microenvironment but also they can efficiently suppress the cytotoxic T lymphocytes (CTLs) mediated anti, tumor immune response.

Recent research have highlighted the heterogeneity of intratumoral Tregs, indicating that extraordinary subsets can also vary in their contribution to tumor improvement and resistance to remedy [11,12]. Moreover, Tregs do no longer act in isolation; they have interaction closely with extremely good immune cells, which incorporates dendritic cells, tumor-associated macrophages, and exhausted CD8⁺ T cells. Together, those interactions installation a coordinated immunosuppressive network that would notably lessen the effectiveness of immunotherapeutic interventions [13].

Preclinical investigations centered on Tregs have showed that selective depletion or useful reprogramming of these cells can decorate antitumor immune responses [14–16]. However, translating the ones findings into medical workout stays tough, in large component due to troubles about disrupting systemic immune tolerance. Consequently, contemporary-day research efforts are directed in the direction of identifying tumor-specific markers, metabolic dependencies, and chemokine-mediated trafficking pathways that would allow for additional unique and localized recovery centered on [17–19].

Overall, the GIFT literature emphasizes that Treg characteristic in cancer is rather context-established and dynamically regulated. Deep mechanistic expertise of their stability, plasticity and spatial distribution in tumors is critical for the rational improvement of most most cancers immunotherapies inside the subsequent technology.

4. Treg Cell Targeting Strategies

Immune regulatory cells (Tregs) are at the center stage of the battle against cancer and are in a complicated and sensitive position. Being the silent watchmen of the immune system, these cells have turned into one of the principal priorities of immunotherapeutic studies [14]. Some researchers have shown that attacking Tregs can be a potent and effective way of boosting the body in fighting against tumors in the recent decades [15]. But what can we do to get our work fruitfully directed to these cells?

In targeting Tregs, there are various approaches that can be used and perhaps these approaches would form the interface between science and practice. The use of antibodies is one of the most conspicuous of these strategies, the development of polyclonal antibodies such as CD25 and CTLA-4 receptors on the surface of Tregs. Inhibiting such receptors, we can weaken the preventive effect of such cells, thereby enabling the immune system to be more effective in fighting cancer cells [16]. As an illustration, antibodies that bind with CD25 have been experimented and they have been found to decrease the population of Tregs in tumors, thereby boosting the immune response [17].

But that is not all about innovation. Emerging tendencies are the immune stimulators, e.g., immune checkpoint inhibitors. These medications are effective by releasing the immunity system so that it can combat tumors in a better manner [18]. The effect of anti-immunosuppressive cell combination such as PD-1 and CTLA-4 inhibition can be improved in immunodefense against Tregs cells. Therefore, there is a concerted effort to have a fine delivery of the balance between the different forces of the immune system [19].

Although this is not a perfect solution, the present strategy is to target Tregs. Tissue type regulatory (Treg) cells are not the only focus of these strategies. While it is true that by destroying or inhibiting Treg cells we may improve the anti-tumor immune response, in the process we also may see the induction of autoimmunity and in turn autoimmune disease [20]. This issue is more complex than it at first appears – the issue of that fine line between enhancing anti-tumor activity of the immune system and at the same time preserving health of the immune system is a very complex issue that requires in depth study.

An opportunity on this admire gives the proposed path of motion, which is the pursuit of the so-referred to as immunomodulation. These techniques intention to redefine the function of Treg cells, now not their complete eradication. By turning into privy to the unique mechanisms that manage the pastime of Treg cell devices, we will be able to calculate how such gadgets can carry out their ordinary functions towards tumors with out compromising the immune device [21]. Such procedures may additionally contain manipulation and manipulation of cells in laboratories and subsequent reintroduction of cells into the body in progressed combos that can lead to a higher compromise between the potential of the immune machine to fight cancer and fitness in popular [22].

Today, there is a large possibility in Treg cell focused on. But pursuing safe and powerful strategies requires staying power and innovation. What we're doing is more than taking steps towards new treatments, we are trying to understand the very complicated photo of the immune gadget's interplay with cancer. As studies progresses, we look toward a destiny in which immunotherapy becomes greater precise and effective, which in turn raises the bar for what we can assume to see in the fight towards most cancers. Ultimately, targeting Treg cells

is not only a therapy we are pursuing, however a new way of wondering that rewrites the history of the fight against cancer in a brand new and innovative light.

Table 1. Summary of Major Treg-Targeting Strategies in Cancer Immunotherapy

Strategy	Target Molecule	Mechanism of Action	Clinical Status	Major Limitation
Anti-CD25 antibodies	CD25	Depletion of Tregs	Phase I/II	Off-target effector T cell depletion
Anti-CTLA-4	CTLA-4	Checkpoint inhibition and Treg reduction	Approved	Immune-related adverse events
Anti-PD-1/PD-L1 combinations	PD-1/PD-L1	Immune activation and partial Treg modulation	Approved	Resistance mechanisms
CCR4 antagonists	CCR4	Inhibition of Treg trafficking to tumors	Clinical trials	Limited specificity
Metabolic targeting	mTOR, lipid metabolism	Disruption of Treg metabolic adaptation	Preclinical	Systemic toxicity risk

The multifaceted role of regulatory T cells in the tumor microenvironment, including their suppressive mechanisms, metabolic adaptations, and contribution to tumor progression, is summarized in Figure 2.

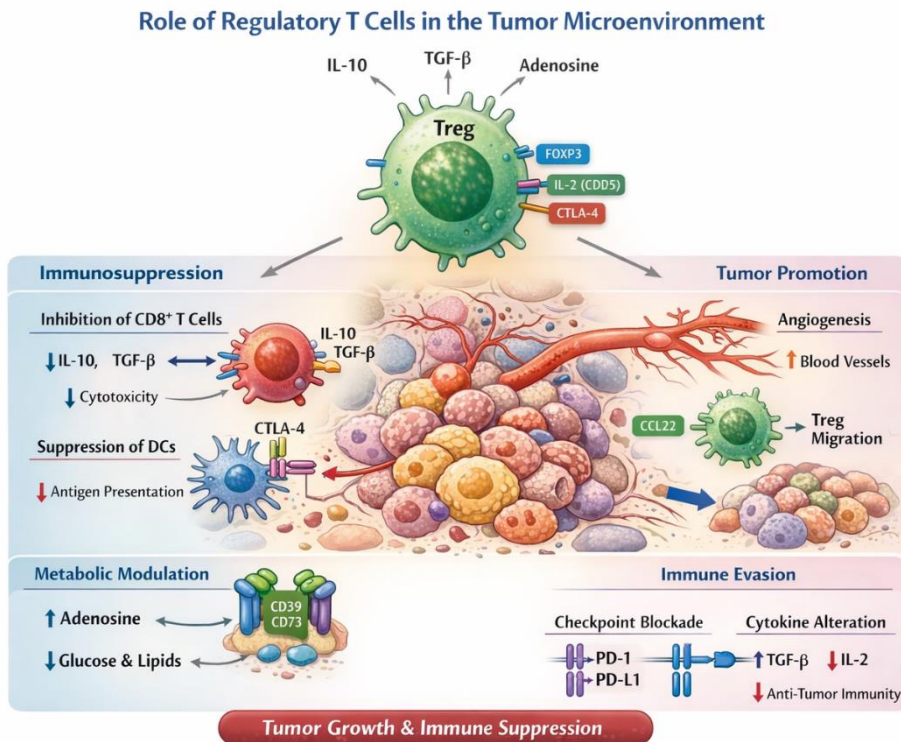


Figure 2. Role of Regulatory T Cells in the Tumor Microenvironment (TME).

Regulatory T cells (Tregs) contribute to tumor immune evasion through several mechanisms, including suppression of CD8⁺ cytotoxic T cells through IL-10 and TGF-β secretion, CTLA-4-mediated inhibition of antigen-presenting cells, and metabolic modulation through CD39/CD73-dependent adenosine production.

Tregs also promote angiogenesis and tumor progression by shaping an immunosuppressive microenvironment. In addition, checkpoint pathways such as PD-1/PD-L1 interactions further amplify immune dysfunction. Together, these mechanisms support tumor growth and resistance to immunotherapy.

5. Reviewing the Research Literature

The immune regulatory cells (Tregs) are crucial inside the global of scientific studies as they're of use in knowledge many procedures in biology, mainly in terms of improving efficiency of immunotherapies towards tumors [23]. An overview of the literature on the targeting of those cells suggests the past studies and the lesson found out as a way of achieving understanding, providing the gaps in knowledge that needed to be filled by means of non-stop research. The research in this trouble is various and gives a range of consequences and specific critiques, and this sphere is controversial and exciting.

The genesis of this examine is traceable to Treg cells which had been discovered and became famous due to their impact in ensuring homeostasis of the immune system. Early studies aimed at exploring the underlying biological techniques of such cells and their negative effect at the immune procedure against tumor [24]. Several sorts of Treg cells are defined including those of thymus manufacturing and that of peripheral tissue manufacturing. Each of those kinds has its very own peculiarities and features and this complicates the process of knowing it [25].

An analysis of literature on attacking Treg cells shows that there is a lot of progress inside the examination of innovative strategies. Indicatively, latest studies have hired sure antibodies towards those cells in preclinical models to show that it is effective in up-regulating immune baseline [26]. Immune stimulators were also hired in inducing an anti-tumor response and those processes have been found to have proper effects in initial trials [27].

Nevertheless, there are challenges in those research. It has been tested that the use of Treg cells must be completed with carefulness because a negative outcome will end result to the immune imbalance which could reason immunodeficiency or maybe autoimmune illnesses. Thus, the conclusions of the beyond research allow concluding that the position of the Treg cells calls for a more profound and thorough investigation, which necessitates rigorous studies and interdisciplinary efforts. Even though the topic of this vicinity is increasingly gaining attention, there are still gaps inside the knowledge. The troubles related to the practical heterogeneity of immune levers and their interactions in cancer situations continue to be unexplored [28].

These gaps also are research opportunities, due to the fact illuminating to a greater certain information of the mechanism of motion of the Treg cells might be a move to come up with viable and powerful treatment plans [29]. In the cease, this literature review on the targeting of Treg cells gives a enough review of research advances, which replicate the troubles which might be experienced by way of scientists and specialists. This description highlights the reality that collaboration and integration of simple and medical research is the key to reaching a main breakthrough within the field. More perception into these cells will useful resource in creating new possibilities of finding various and effective remedy methods, for you to make

a contribution to advancing the have a look at of immunology and introduction of extra green tactics to combat most cancers.

6. Results and Discussion

A growing number of studies are showing that regulatory T cells (Tregs) act as the key coordinators of immune suppression inside the tumor microenvironment, mediating their effects through secret molecular, metabolic, and cell communication pathways. In fact, rather than merely functioning as passive inhibitory lymphocytes, intratumoral Tregs acquire a special phenotype characterized by maintained FOXP3 expression, elevated CTLA, 4 levels, and metabolic alterations that support their survival in hypoxic, nutrient, limited conditions.

At the mechanistic level, Tregs limit effector T, cell responses through multiple complementary pathways. These consist of the release of IL, 10 and TGF, CTLA, 4 mediated downregulation of CD80/CD86 on antigen, presenting cells, and the generation of immunosuppressive adenosine via CD39/CD73 ectonucleotidase activity. Altogether, these mechanisms dampen cytotoxic CD8 T, cell function and hinder effective antigen presentation. Meanwhile, tumor, derived factors such as lactate buildup, altered lipid availability, and local cytokine gradients additionally support the metabolic reprogramming of Tregs, thus strengthening the stability of their suppressive phenotype.

Therapeutic strategies that focus primarily on Tregs have produced very different results, with the treatment selectivity and tumor context being the main reasons for the variations. Techniques that are mainly based on anti, CD25 mediated depletion can reduce Treg frequency, but may accidentally get rid of activated effector T cells as well. It has been shown that anti, CTLA, 4 therapy could be a method to partially deplete Tregs within the tumor by antibody, based cell cytotoxicity; however, immune, related negative effects are still a major medical challenge. Combination methods that include PD, 1/PD, L1 blockade along with Treg, targeting interventions have improved response rates significantly in high, quality malignancies, although resistance is still a problem.

Another frequently discussed concept is that positive modulation of Tregs, instead of their total systemic depletion, could be a more balanced and therefore a less harmful way of healing.

Methods that rely on localizing the action to within the tumor microenvironment, breaking up Treg, specific metabolic dependencies, or interfering with chemokine, mediated trafficking pathways, such as the CCR4/CCL22 axis, can also help to raise antitumor immunity while maintaining systemic immune tolerance.

Despite the incredible progress, a lot of key questions are still hanging there. The diversity of tumor, infiltrating Tregs, their helpful plasticity under inflammatory pressure, and their crosstalk with other immunosuppressive populations, such as tumor, associated macrophages, need to be further explored. Next, generation that integrates single, cell transcriptomic, epigenetic profiling, and spatial immunophenotyping can be very helpful in tuning recovery accuracy. In general, today's evidence supports the design of Treg, targeting immunotherapy approaches that can be mechanistically explained and customized to tumor, specific scenarios. The main challenge is to achieve a fine balance between potent immune

activation and the maintenance of immune tolerance in order to secure a long, lasting and stable clinical benefit.

6.1. Challenges and Opportunities

Indeed, we're seeing amazing development at the front of focused on Treg cell therapy in most cancers remedy, however the destiny isn't always so simple. These difficulties are not most effective related to technical obstacles, however also to the complicated organic interactions among specific immune cells, which require a higher understanding. Although Treg cells are suppressors of the immune tool, they may be still part of the immune system. This duality highlights the importance of the want for an incredible balance among stimulating the immune device to combat maximum cancers cells and preserving the Treg cells' shielding skills.

In terms of Treg cells we face great issues with regard to their adverse effects. In the cancer fight we may think that which is best is to go after or reduce the number of these cells. What we may not count on is that this will cause unacceptable immune responses which in turn bring about autoimmune disease. Also, we must pay to attention to the way in which we go about specific treatments in a smart way and see to it that the immune system is able to put tumors on notice but also not go overboard. It is very much a fact that we need to study the dynamics of Treg cells more. An example of this is how the environment around them, that is the chemicals or other cell activities, play a role in their function? Answers to such questions will put us in a position to come up with new tools that improve present treatments. The better we research these interactions the better we will do at to find out new safe and effective targeted therapies.

The opportunities to develop and grow are, in addition to the challenges, very high. New opportunities are being presented by the current technologies, including genomics and gene editing. With such technologies, we would be able to come up with more specific strategies that would attack Treg cells. What would happen should we be able to alter the functioning of these cells rather than do away with them? It may result in an optimal balance that will improve the effectiveness of the treatment without impairing the immune health of the patient.

The healing of such opportunities will be a radical change in the fight against cancer. Immunotherapy is in a phase of crossroad whereby new opportunities are arising and it can be changed. As what we are seeing in the present research, we can invest in the development of the inhibitory drugs that would be capable of attacking Treg cells and at the same time safeguard against adverse effects. It is not so much about finding solutions, but reconsidering the way we value the immune system in its entirety. Having studied its sophisticated dynamics, we assume that the increase of the immune reaction in a moderated manner entails such drastic measures. These problems are not going to fade away, yet these opportunities will help to seek innovative solutions that can change the future of immunotherapy. The desire to know Treg cells in and out and investigate new opportunities of their application will allow us to make the treatments more efficient and can become the groundwork of a new era of healthcare.

To sum up, the study of regulatory T (Treg) cells is a massive slice of the whole endeavor to enhance cancer immunotherapy, yet it does not represent the ultimate answer. On the contrary, challenges related to Treg biology continue to be a source of scientific curiosity and

a driving force for innovation. The advancement of this field is a reflection of a much broader commitment in the clinical and pharmaceutical sectors to develop more effective and durable cancer treatments. New findings in several fields of biomedical research are giving us promising chances to improve and expand healing strategies.

Clinical translation of Treg, centered interventions has yielded inconsistent outcomes across different tumor types. For example, anti, CTLA, 4 therapy has generated complete and lasting clinical responses in melanoma and renal cell carcinoma, partly through Fc, mediated depletion of intratumoral Tregs. However, the high rate of grade 3/4 immune, related adverse events still poses a major problem. Agents targeting CCR4 have demonstrated the capability to selectively deplete tumor, infiltrating Tregs in early, phase clinical trials; nonetheless, their long, term effect on survival outcomes remains to be confirmed. Also, new metabolic interventions such as combining PI3K, inhibition and lipid metabolism modulation are currently under clinical investigation and may potentially enhance the effectiveness of therapy.

Collectively, these observations spotlight that remedy achievement seems to rely extra on accomplishing intratumoral specificity than on giant systemic depletion of Tregs. Refining this stability amongst centered immune activation and upkeep of peripheral tolerance stays a applicable goal in the persisted evolution of Treg-directed cancer immunotherapy.

7. Future Therapeutic Framework for Precision Treg Modulation

Future immunotherapeutic strategies should transition from broad systemic depletion of Tregs toward more precise modulation within the tumor microenvironment. A next-generation therapeutic framework may be built upon three complementary pillars:

1. **Spatial targeting:** Development of tumor-restricted delivery systems or highly specific antibodies designed to selectively eliminate or modulate intratumoral Tregs while preserving peripheral immune tolerance.
2. **Metabolic reprogramming:** Interference with key metabolic pathways that sustain Treg suppressive function—such as lipid uptake and adenosine-generating mechanisms—to destabilize their immunosuppressive phenotype within tumors.
3. **Context-specific checkpoint integration:** Strategic combination of PD-1/PD-L1 blockade with selective Treg modulation to counteract adaptive resistance pathways and enhance antitumor immune responses.

The integration of advanced technologies, including single-cell transcriptomics, spatial immunophenotyping, and AI-guided biomarker stratification, may further enable individualized therapeutic optimization. Collectively, this precision-oriented approach reflects a conceptual shift in Treg-directed immunotherapy, with the potential to improve both safety profiles and durability of clinical responses.

Conclusion

Regulatory T cells (Tregs) are very instrumental in mediating immune suppression inside the tumor microenvironment; thus, they represent a major obstacle to the effective immunotherapy of the majority of cancers. The data gathered in this review show that the presence of intratumoral Tregs is one of the mechanisms that cancer cells manage to evade the immune system, at the molecular, cellular, and metabolic levels, and these mechanisms are coordinated. While therapeutic interventions targeting these cells look very promising, their clinical application remains limited due to the issues of systemic immune tolerance and treatment, related toxicity. A farther step in Treg, targeted immunotherapy will rely on mechanistically aware, spatially selective interventions, which will probably be functional modulation it through, instead of indiscriminate depletion. The combination of single, cell technologies, metabolic profiling, and biomarker, driven patient stratification might be the key to therapeutic precision and long, term sustainability.

In the end, advancements in this field necessitate the translation of innate understanding into treatment, contexts aiming at balancing efficacious immune activation along with immune homeostasis restoration. Reaching this harmony may also be capable of increasing the response rates while at the same time, reducing the risks of adverse effects most patients experience due to the current immunotherapeutic interventions.

Author Contribution: All authors contributed equally to the main contributor to this paper. All authors read and approved the final paper.

Funding: Please add: “This research received no external funding”.

Conflicts of Interest: “The authors declare no conflict of interest.”.

References

- [1] C. J. Imianowski, Q. Chen, C. J. Workman, & D. A. Vignali. 2025. “Regulatory T cells in the tumour microenvironment,” *Nature Reviews Cancer*, vol. 25(9), pp. 703–722, <https://www.nature.com/articles/s41568-025-00832-9>.
- [2] Y. Pan, H. Zhou, Z. Sun, Y. Zhu, Z. Zhang, J. Han, & Wang, Q. Regulatory . 2025. “T cells in solid tumor immunotherapy: effect, mechanism and clinical application,” *Cell death & disease*, vol. 16(1), pp. 277, <https://www.nature.com/articles/s41419-025-07544-w>.
- [3] C. M. Wardell, D. A. Boardman, & M. K. Levings. 2025. “Harnessing the biology of regulatory T cells to treat disease,” *Nature Reviews Drug Discovery*. vol. 24(2), pp. 93–111. <https://www.nature.com/articles/s41573-024-01089-x>.
- [4] R. Singh, P. Srivastava, & P. P. Manna, 2024. “Evaluation of regulatory T-cells in cancer immunotherapy: therapeutic relevance of immune checkpoint inhibition,” *Medical Oncology*, vol. 41(2), pp. 59. <https://link.springer.com/article/10.1007/s12032-023-02289-y>.
- [5] T. S. Sumida, N. T. Cheri, & D. A. Hafler, 2024. “The regulation and differentiation of regulatory T cells and their dysfunction in autoimmune diseases,” *Nature Reviews Immunology*. vol. 24(7), pp. 503–517. <https://www.nature.com/articles/s41577-024-00994-x>.

- [6] Y. Li, C. Zhang, A. Jiang, A. Lin, Z. Liu, X. Cheng, & P. Luo, 2024. "Potential anti-tumor effects of regulatory T cells in the tumor microenvironment: a review," *Journal of Translational Medicine*, 22(1), 293. <https://link.springer.com/article/10.1186/s12967-024-05104-y>.
- [7] M. Singer, A. M. Elsayed, & M. I. Husseiny, 2024. "Regulatory T-cells: the face-off of the immune balance," *Frontiers in Bioscience-Landmark*, vol. 29(11), pp. 377. <https://escholarship.org/uc/item/8qq3z40x>.
- [8] Y. Wang, J. Li, S. Nakahata, & H. Iha, 2024. "Complex role of regulatory T cells (Tregs) in the tumor microenvironment: their molecular mechanisms and bidirectional effects on cancer progression," *International journal of molecular sciences*, vol. 25(13), pp. 7346, <https://www.mdpi.com/1422-0067/25/13/7346>.
- [9] Z. Shaopeng, Z. Yang, F. Yuan, H. Chen, & Q. Zhengjun, 2024. "Regulation of regulatory T cells and tumor-associated macrophages in gastric cancer tumor microenvironment," *Cancer Medicine*, vol. 13(2), pp. e6959, <https://onlinelibrary.wiley.com/doi/full/10.1002/cam4.6959>.
- [10] M. Kondo, S. Kumagai, & H. Nishikawa, 2024. "Metabolic advantages of regulatory T cells dictated by cancer cells," *International immunology*, vol. 36(2), pp. 75–86. <https://academic.oup.com/intimm/article/36/2/75/7317563>.
- [11] A. Zhang, T. Fan, Y. Liu, G. Yu, C. Li, & Z. Jiang, 2024. "Regulatory T cells in immune checkpoint blockade antitumor therapy," *Molecular cancer*, vol. 23(1), pp. 251. <https://link.springer.com/article/10.1186/s12943-024-02156-y>.
- [12] S. Ma, R. Sandhoff, X. Luo, F. Shang, Q. Shi, Z. Li, & G. Cui. 2024. "Serine enrichment in tumors promotes regulatory T cell accumulation through sphinganine-mediated regulation of c-Fos," *Science immunology*, vol. 9(94), pp. eadg8817, 2024, <https://www.science.org/doi/abs/10.1126/sciimmunol.adg8817>.
- [13] S. Vilbois, Y. Xu, & P. C. Ho. 2024. "Metabolic interplay: tumor macrophages and regulatory T cells," *Trends in cancer*, vol. 10(3), pp. 242–255. [https://www.cell.com/trends/cancer/abstract/S2405-8033\(23\)00238-8](https://www.cell.com/trends/cancer/abstract/S2405-8033(23)00238-8).
- [14] L. Y. Cao, Y. Zhao, Y. Chen, P. Ma, J. C. Xie, X. M. Pan, & L. L. Xie, 2025. "CAR-T cell therapy clinical trials: global progress, challenges, and future directions from ClinicalTrials.gov insights," *Frontiers in Immunology*, vol. 16, pp. 1583116. <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2025.1583116/full>.
- [15] J. Ge, X. Yin, & L. Chen, 2024. "Regulatory T cells: masterminds of immune equilibrium and future therapeutic innovations," *Frontiers in immunology*, vol. 15, pp. 1457189. <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1457189/full>.
- [16] M. Navarrete, C. Costoya, F. Galvez-Cancino, K. S. Peggs, A. Marabelle, & S. A. Quezada, 2025. "Regulatory T Cell Depletion in Cancer: Challenges, Opportunities, and Future Directions for Antibody Development," *Annual Review of Medicine*, 77. <https://www.annualreviews.org/content/journals/10.1146/annurev-med-043024-123559>.
- [17] Fatafteh, O. H. 2024. PD-1 expression ratio on the T cell surface in Jordanian acute and chronic brucellosis: Consequences for immune depletion and disease development. *Ibn Sina Journal of Medical Science, Health & Pharmacy*, 2(12). https://ibn-sina-journal-of-medical-sciences.jo/details_paper/48
- [18] M. Attias, & C. A. Piccirillo. 2026. "The impact of Foxp3+ regulatory T-cells on CD8+ T-cell dysfunction in tumour microenvironments and responses to immune checkpoint inhibitors," *British Journal of Pharmacology*, vol. 183(6), pp. 1250–1270, <https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.16313>.
- [19] Y. Shan, T. Xie, Y. Sun, Z. Lu, W. Topatana, S. Juengpanich, & M. Chen. 2024. "Lipid metabolism in tumor-infiltrating regulatory T cells: perspective to precision immunotherapy," *Biomarker research*, vol. 12(1), pp. 41. <https://link.springer.com/article/10.1186/s40364-024-00588-8>.

-
- [20] D. Y. Honing, R. M. Luiten, & T. R. Matos. 2024. "Regulatory T cell dysfunction in autoimmune diseases," *International Journal of Molecular Sciences*, vol. 25(13), pp. 7171, <https://www.mdpi.com/1422-0067/25/13/7171>.
- [21] P. Shi, Y. Yu, H. Xie, X. Yin, X. Chen, Y. Zhao, & H. Zhao. 2025. "Recent advances in regulatory immune cells: exploring the world beyond Tregs," *Frontiers in Immunology*, 16, 1530301. <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2025.1530301/full>.
- [22] D. Zou, X. C. Li, & W. Chen. 2025. "Beyond T-cell subsets: stemness and adaptation redefining immunity and immunotherapy," *Cellular & Molecular Immunology*, vol. 22(9), pp. 957–974, <https://www.nature.com/articles/s41423-025-01321-7>.
- [23] P. Spiliopoulou, P. Kaur, T. Hammett, G. Di Conza, & M. Lahn, 2024. "Targeting T regulatory (Treg) cells in immunotherapy-resistant cancers," *Cancer Drug Resistance*, vol. 7, pp. 2, <https://pmc.ncbi.nlm.nih.gov/articles/PMC10838381/>.
- [24] S. J. Zheng. 2024. Immune regulation. "In *Veterinary Molecular Immunology*," Singapore: Springer Nature Singapore, pp. 205–217. https://link.springer.com/chapter/10.1007/978-981-99-8929-4_9.
- [25] K. M. Ashby, & K. A. Hogquist. 2024. "A guide to thymic selection of T cells," *Nature Reviews Immunology*, vol. 24(2), pp. 103–117. <https://www.nature.com/articles/s41577-023-00911-8>.
- [26] L. Wang, Y. Liang, C. Zhao, P. Ma, S. Zeng, D. Ju, & Y. Shi. 2025. "Regulatory T cells in homeostasis and disease: molecular mechanisms and therapeutic potential," *Signal Transduction and Targeted Therapy*, vol. 10(1), pp. 345. <https://www.nature.com/articles/s41392-025-02326-4>.
- [27] Y. Zong, K. Deng, & W. P. Chong. 2024. "Regulation of Treg cells by cytokine signaling and co-stimulatory molecules," *Frontiers in immunology*, vol. 15, pp. 1387975. <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2024.1387975/full>.
- [28] C. Brescia, S. Audia, A. Pugliano, F. Scaglione, R. Iuliano, F. Trapasso, & R. Amato. 2024. "Metabolic drives affecting Th17/Treg gene expression changes and differentiation: impact on immune-microenvironment regulation," *Apmis*, vol. 132(12), pp. 1026–1045, <https://onlinelibrary.wiley.com/doi/full/10.1111/apm.13378>.
- [29] R. Zi, X. Zhao, L. Liu, Y. Wang, R. Zhang, Z. Bian, & Y. Dong. 2025. "Metabolic-Immune Suppression Mediated by the SIRT1-CX3CL1 Axis Induces Functional Enhancement of Regulatory T Cells in Colorectal Carcinoma," *Advanced Science*, vol. 12(17), pp. 2404734, <https://advanced.onlinelibrary.wiley.com/doi/full/10.1002/advs.202404734>.