Regulatory T cells in neurological disorders and tissue regeneration: Mechanisms of action and therapeutic potentials

Jing Jie[1, 2, #], Xiaomin Yao[1, #], Hui Deng[1], Yuxiang Zhou[1, #], Xingyu Jiang[1], Xiu Dai[1, *], Yumin Yang[1, *], Pengxiang Yang[1, *]

https://doi.org/10.4103/NRR.NRR-D-24-01363

Date of submission: November 9, 2024

Date of decision: November 11, 2024

Date of acceptance: February 11, 2025

Date of web publication: June 19, 2025

From the Contents

Abstract

Regulatory T cells, a subset of $CD4^+$ T cells, play a critical role in maintaining immune tolerance and tissue homeostasis due to their potent immunosuppressive properties. Recent advances in research have highlighted the important therapeutic potential of Tregs in neurological diseases and tissue repair, emphasizing their multifaceted roles in immune regulation. This review aims to summarize and analyze the mechanisms of action and therapeutic potential of Tregs in relation to neurological diseases and neural regeneration. Beyond their classical immune-regulatory functions, emerging evidence points to non-immune mechanisms of regulatory T cells, particularly their interactions with stem cells and other non-immune cells. These interactions contribute to optimizing the repair microenvironment and promoting tissue repair and nerve regeneration, positioning non-immune pathways as a promising direction for future research. By modulating immune and non-immune cells, including neurons and glia within neural tissues, Tregs have demonstrated remarkable efficacy in enhancing regeneration in the central and peripheral nervous systems. Preclinical studies have revealed that Treg cells interact with neurons, glial cells, and other neural components to mitigate inflammatory damage and support functional recovery. Current mechanistic studies show that Tregs can significantly promote neural repair and functional recovery by regulating inflammatory responses and the local immune microenvironment. However, research on the mechanistic roles of regulatory T cells in other diseases remains limited, highlighting substantial gaps and opportunities for exploration in this field. Laboratory and clinical studies have further advanced the application of regulatory T cells. Technical advances have enabled efficient isolation, *ex vivo* expansion and functionalization, and adoptive transfer of regulatory T cells, with efficacy validated in animal models. Innovative strategies, including gene editing, cell-free technologies, biomaterial-based recruitment, and *in situ* delivery have expanded the therapeutic potential of regulatory T cells. Gene editing enables precise functional optimization, while biomaterial and *in situ* delivery technologies enhance their accumulation and efficacy at target sites. These advancements not only improve the immune-regulatory capacity of regulatory T cells but also significantly enhance their role in tissue repair. By leveraging the pivotal and diverse functions of Tregs in immune modulation and tissue repair, regulatory T cells–based therapies may lead to transformative breakthroughs in the treatment of neurological diseases.

Key Words: demyelinating diseases; gene editing; immune regulation; immune tolerance; neural regeneration; neurological diseases; non-immune mechanisms; regulatory T cells; stem cells; stroke; tissue homeostasis; tissue repair

Introduction

The global population affected by neurological dysfunctions due to acute injuries, chronic diseases, or aging is steadily increasing, posing a great burden on healthcare systems, families, and societies (Li et al., 2018; Yang et al., 2023c; Gao et al., 2024). Historically, the nervous and immune systems were considered distinct domains, primarily due to the presence of the blood–brain barrier (BBB) and the blood–spinal cord barrier (BSCB) (Ning et al., 2024; Wang and Bai, 2025). However, in the last decades numerous studies have challenged this century-old concept of central nervous system (CNS) immune privilege, revealing a significant overlap between the CNS and the peripheral immune system (Castellani et al., 2023; Peng et al., 2024). Despite the restriction imposed by the BBB and BSCB to the passage of toxins, large molecules, and cells into the CNS (Yin et al., 2025), neuroimmune interactions are becoming increasingly evident at the tissue, cellular, and molecular levels (Louveau et al., 2015; Hu et al., 2018). It is now clear that the CNS operates under continuous immune surveillance and regulation, and that a close intertwining exists between lymphatic vessels and peripheral nerves (Alves de Lima et al., 2020; Badimon et al., 2020).

The complexity of neurological disorders and the limited regenerative capacity of the nervous tissue present central challenges in medicine. Researchers widely acknowledge that precisely regulating the immune system can effectively resolve inflammation and restore the structure and homeostasis of neural tissue (Feng et al., 2022; Yang et al., 2023a; Holl et al., 2024). Conversely, excessive or unregulated immune responses may exacerbate damage, leading to fibrosis and scar formation, which hinder the self-repair capacity of injured sites (Asboth et al., 2018; Adusei et al., 2021; Wang et al., 2023b). Therefore, there is an urgent need to deepen our understanding of the immune mechanisms underlying neurological disorders and tissue repair. This knowledge is essential for designing effective therapies aimed at counteracting the pathological processes that lead to organ dysfunction, promoting nerve regeneration, and enhance tissue repair.

[1]Key Laboratory of Neuroregeneration of Jiangsu Province and Ministry of Education, Co-Innovation Center of Neuroregeneration, NMPA Key Laboratory for Research and Evaluation of Tissue Engineering Technology Products, Nantong University, Nantong, Jiangsu Province, China; [2]Department of Clinical Laboratory, The Second Affiliated Hospital of Nantong University, Nantong, Jiangsu Province, China

*__Correspondence to:__ Pengxiang Yang, PhD, yangpengxiang@ntu.edu.cn or yangpengxiang@163.com; Yumin Yang, PhD, yangym@ntu.edu.cn; Xiu Dai, PhD, dx0821@ntu.edu.cn.
https://orcid.org/0000-0003-2777-7533 (Pengxiang Yang); https://orcid.org/0000-0002-7390-5842 (Yumin Yang); https://orcid.org/0000-0002-2527-0539 (Xiu Dai)
#These authors contributed equally to this work and share first authorship.

Funding: *This work was supported by the National Natural Science Foundation of China, Nos. 32271389, 31900987 (both to PY); the Natural Science Foundation of Jiangsu Province, No. BK20230608 (to JJ).*

How to cite this article: *Jie J, Yao X, Deng H, Zhou Y, Jiang X, Dai X, Yang Y, Yang P (2026) Regulatory T cells in neurological disorders and tissue regeneration: Mechanisms of action and therapeutic potentials. Neural Regen Res 21(4):1277-1291.*

Immune sentinel cells, such as dendritic cells, macrophages, fibroblasts, and peripherally derived T cells in peripheral tissues, and microglia in the CNS, play a dual role in maintaining immune balance and disrupting immune homeostasis, offering new possibilities for mitigating tissue damage and promoting the repair of the neurovascular unit (Ousman and Kubes, 2012; McGettrick, 2021). In this context, $CD4^+Foxp3^+$ regulatory T cells (Tregs), as key immune regulators, are indispensable for maintaining immune homeostasis through the precise modulation of immune responses (Savage et al., 2020; Dikiy and Rudensky, 2023). Developmental defects in Tregs can lead to severe and potentially fatal inflammatory disorders, such as immunodeficient endocrinopathies, enteropathy, and X-linked syndrome (Li et al., 2018; Attias et al., 2019; Becker et al., 2024; de la Fuente et al., 2024).

Tregs not only alleviate inflammation and facilitate debris clearance following neurological diseases and injuries but also exhibit unique neuroregenerative functions, as revealed by recent studies. These functions include myelin repair, induction of stem cell proliferation, neurovascular remodeling, and the restoration of regenerated neural circuits (Korn, 2023; Liston et al., 2023; Ho et al., 2024). Importantly, these regenerative roles are distinct from the immunosuppressive mechanisms typically associated with these cells, indicating that Tregs regulate neurological disorders and tissue repair through multiple pathways. In most scenarios of injury repair, immunosuppressive and regenerative mechanisms likely operate concurrently (Cohen et al., 2024; Ho et al., 2024; Loffredo et al., 2024).

This review comprehensively explores the multifaceted roles of Tregs in diseases and tissue injury, focusing particularly on their immunological and non-immunological mechanisms in neurological disorders and tissue repair. Additionally, we discuss recent preclinical research advances in adoptive Treg therapy for treating neurological diseases and nerve injury, highlighting their immense potential as therapeutic tools. Furthermore, we summarize various strategies aimed at enhancing the reparative properties of Tregs, including genetic engineering, cell-free technologies, biomaterial-based recruitment and conversion, and *in situ* localized delivery. These innovative approaches hold promise for effectively halting or reversing the progression of neurological disorders and promoting neural tissue regeneration and functional recovery. These strategies lay in turn a critical foundation for the development of next-generation cell therapies and therapeutic agents, providing novel directions for basic research and clinical applications.

Literature Search Strategy

A comprehensive literature search was conducted using the PubMed database, focusing on publications from 2000 to 2024. The search terms included "Treg cells," "regulatory T cells," "immune regulation," "neural repair," "neuroinflammation," "tissue regeneration," "cell therapy," "gene engineering," "biomaterials," and "local delivery," as well as specific terms related to both the immunological and non-immunological mechanisms of Treg cells in disease and tissue injury. These terms were carefully selected to include the broad spectrum of Treg cell functions, their roles in neurological disorders and tissue repair, and the development of innovative therapeutic strategies. Data extracted from the selected articles included study design, experimental models, therapeutic approaches, and key findings relevant to the roles of Treg cells in immune regulation and tissue regeneration. A detailed narrative synthesis approach was used to integrate findings from experimental studies, preclinical research, and previous review articles, providing a comprehensive overview of Treg cell functions, their therapeutic potential, and emerging engineering strategies.Particular attention was given to synthesizing information on the immunological and non-immunological pathways of Treg cells, highlighting their complex roles in the progression and recovery from neurological diseases, as well as innovative methods such as gene engineering, biomaterial-based recruitment, and local delivery systems.

Origin, Characteristics, and Mechanisms of Action of Regulatory T Cells

Origin and characteristics of Tregs

Tregs are a critical subset of T cells within the immune system, primarily responsible for maintaining immune homeostasis (Tiemessen et al., 2007; Zhang et al., 2017; Zhu et al., 2022). They play a broad role in various physiological and pathological processes, including infection, inflammation, tissue repair, and transplantation rejection. Additionally, Tregs are involved in regulating responses to bacterial and viral infections, autoimmune diseases, and cancer (Shanley et al., 2021; Zhong et al., 2022; Gao et al., 2024). Based on their developmental pathways and characteristics, Tregs can be divided into two categories: natural Tregs (nTregs) and induced Tregs (iTregs) (Dittmer et al., 2018; Attias et al., 2019). nTregs develop in the thymus and are characterized by the expression of CD4, CD25, and forkhead box p3 (Foxp3). These cells acquire their immunoregulatory functions upon exposure to specific antigens during thymic development, and exert their effects by secreting cytokines such as interleukin (IL)-10, IL-35, and transforming growth factor-β (TGF-β) (Burns et al., 2020). The IL-2/signal transducer and activator of transcription-5 (STAT5) signaling axis plays a pivotal role in the induction of Foxp3 and the stability of Tregs (Mao et al., 2019; Xie et al., 2023). Other critical molecules, such as Helios and GATA binding protein 3 (GATA3), also contribute to the maintenance of the suppressive functions of nTregs, particularly under inflammatory conditions (Ramanan et al., 2023). The interaction of thymic stromal cells and antigen-presenting cells with developing T cells provides essential signals, including costimulatory molecules and cytokines, that are vital for Treg lineage commitment (Yi et al., 2019). In contrast, iTregs are derived from conventional $CD4^+$ T cells in peripheral tissues upon antigen stimulation and in the presence of specific cytokines such as TGF-β and IL-10 (Joetham et al., 2020). iTregs can be further subdivided into T regulatory-1 (TR1) and T-helper-3 (TH3) cells, depending on the inducing factors. TR1 cells are $CD4^+Foxp3^-$ and primarily mediate immunosuppression through the secretion of IL-10, while TH3 cells are $CD4^+Foxp3^+$ and primarily regulate immune responses via TGF-β secretion (Adusei et al., 2021; Hu et al., 2021b). The differentiation of iTregs is notably influenced by the local microenvironment, including the presence of retinoic acid and microbial-derived metabolites such as short-chain fatty acids (Smith et al., 2013; Jang et al., 2023). These factors enhance the stability and function of iTregs by epigenetically modifying Foxp3 expression and maintaining chromatin accessibility in regulatory regions (Wang et al., 2018).

Tregs are characterized by high expression of CD25 (the IL-2 receptor α chain) and the transcription factor Foxp3, while exhibiting low or undetectable levels of CD127 (the IL-7 receptor α chain). These markers are essential for the identification and characterization of Tregs (Tiemessen et al., 2007; Hu et al., 2018; Korn, 2023). Among them, Foxp3 is considered a key regulatory factor for maintaining the function and stability of Tregs, with its expression levels being closely correlated with the immunosuppressive capabilities of these cells (Attias et al., 2019; Honaker et al., 2020; Ho et al., 2024). Additionally, activated Tregs express CD134, which further enhances their functional stability (Queiroz-Glauss et al., 2022).

Tregs also express various inhibitory molecules and receptors, including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed cell death protein 1 (PD-1), lymphocyte activation gene-3 (LAG-3), and Helios, all of which play major roles in regulating their immunosuppressive functions. Furthermore, surface expression of the ectonucleotidases CD39 and CD73, which metabolize extracellular ATP into adenosine, further strengthens the immunosuppressive effects of Tregs (Wang et al., 2022; Liston et al., 2023; Becker et al., 2024). The dynamic regulation of Tregs by external factors such as cytokines, tissue-derived signals, and microbial components significantly affects their phenotypic plasticity and functional specialization. For instance, IL-33 has been shown to enhance Treg-mediated tissue repair functions, while pro-inflammatory cytokines such as IL-6 can destabilize Tregs and impair their immunosuppressive abilities (Arpaia et al., 2015; Yan et al., 2021). Understanding these regulatory mechanisms is crucial for developing therapeutic applications that target Tregs.

Roles of regulatory T cells in disease

The roles of Tregs in autoimmune diseases, infectious diseases, and chronic inflammation have been extensively studied (Sakaguchi et al., 2020). Tregs primarily function to regulate immune homeostasis and maintain self-tolerance (Zhong et al., 2022; Ho et al., 2024). Dysfunction and reduced numbers of Tregs are closely associated with the onset and progression of autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis, and systemic lupus erythematosus (Dombrowski et al., 2017; Li et al., 2018; Honaker et al., 2020). Clinical studies indicate that in patients with MS, decreased Treg numbers and impaired suppressive functions contribute to disease relapse and progression (Raphael et al., 2015; Shi et al., 2023a). Similarly, in rheumatoid

arthritis, synovial fluid from inflamed joints has been found to contain Tregs with reduced Foxp3 expression, suggesting that an inflammatory microenvironment drives their dysfunction (Jiang et al., 2021). Research has demonstrated that the immunosuppressive function of Tregs relies on sustained expression of Foxp3. Accordingly, Foxp3 loss of function or depletion of Tregs can lead to severe autoimmune diseases (Hu et al., 2018; Korn, 2023). Notably, Hu et al. (2021b) reported that restoring Foxp3 expression in mice can rebalance immune activation, suppress tissue inflammation, and reverse fatal autoimmune disease. Previously, Worthington et al. (2015) had reported that effector Tregs inhibit pathogenic T-cell responses by expressing integrin αvβ8, which activates latent TGF-β. Under conditions of active inflammation, the lack of integrin αvβ8, significantly weakens Tregs' suppressive effects.

Tregs play a crucial role in regulating the intensity of immune responses in infectious diseases, helping to prevent tissue damage caused by excessive immune reactions (Amaya-Uribe et al., 2019). For instance, during viral infections such as from human immunodeficiency virus, Tregs modulate immune responses to control inflammation and limit tissue damage. However, excessive Treg activity can suppress antiviral immunity, potentially leading to chronic infection (Méndez-Lagares et al., 2012; López-Abente et al., 2016). In cases of infectious lung injury, Tregs can respond to inflammatory cytokines such as IL-18 or IL-33 by secreting the tissue repair factor amphiregulin (AREG), thereby directly contributing to tissue repair. This function operates independently of their classical T-cell receptor-mediated immunosuppressive effects (Arpaia et al., 2015). A clinical study in patients with sepsis-induced acute respiratory distress syndrome showed that elevated levels of Tregs expressing IL-10 and AREG correlated with improved lung function recovery and reduced fibrosis (Halter et al., 2020). In the context of chronic inflammation, Tregs modulate cytokine networks to prevent persistent inflammation from damaging tissues. Langston et al. (2023) demonstrated that in a chronic inflammation model induced by exercise, Tregs protect from metabolic disorders and mitochondrial dysfunction by suppressing excessive interferon-γ production. Their study showed also that mice lacking Tregs exhibit significantly reduced benefits from exercise. Additional studies on obesity-related chronic inflammation have highlighted the tissue-specific heterogeneity of Tregs. For example, Tregs residing in visceral adipose tissue exhibit unique transcriptomic profiles compared to their counterparts in lymphoid tissues, enabling them to adapt to the metabolic and inflammatory signals of their microenvironment (Cipolletta et al., 2015; Zhu et al., 2017). Although the critical role of Tregs in various diseases is well recognized, precisely regulating their numbers and functions under pathological conditions remains a major challenge and a focus of current research. For instance, in cancer, tumor-resident Tregs can promote immune evasion, while in autoimmune diseases, restoring Treg numbers and functions is essential for maintaining immune tolerance.

Studies employing single-cell RNA sequencing (scRNA-seq) technology revealed the functional and phenotypic heterogeneity of Tregs across different tissues and disease states, highlighting their context-specific roles (Zemmour et al., 2018; Miragaia et al., 2019; Luo et al., 2021). However, existing research on the regulatory mechanisms of Tregs primarily focuses on their immunological functions, while their roles in tissue repair and regeneration remain largely unexamined. This gap may stem from the overlap and intersection of immunoregulatory and tissue repair/regeneration pathways. Therefore, studies aimed at distinguishing immunological from non-immunological pathways are crucial for a deeper understanding of the mechanisms by which Tregs contribute to tissue repair and regeneration.

Roles of regulatory T cells in tissue regeneration

Since the first report in 2009 suggesting the participation of Tregs in tissue repair, research on their regenerative functions has steadily grown (Loffredo et al., 2024). These cells include lymphoid tissue Tregs and tissue-resident Tregs found in non-lymphoid tissues. The latter play critical roles in the repair and regeneration of various tissues, such as muscle, heart, hair follicles, and nerves (Li et al., 2018; Ito et al., 2019; Loffredo et al., 2024). Tissue-resident Tregs exhibit high expression of tissue-specific transcription factors, which equip them with effective tissue-protective and reparative functions. For instance, in the visceral adipose tissue of obese individuals, resident Tregs are gradually depleted, contributing to chronic inflammation and metabolic dysfunction (Lee and Lee, 2014). In contrast, Tregs in muscle tissue express high levels of IL-6 receptor (IL-6R), which is critical for modulating local inflammation and promoting repair. However, the use of IL-6R antibodies in systemic inflammatory diseases often leads to side effects such as muscle weakness, highlighting the tissue-specific regulatory mechanisms of Tregs (Wang et al., 2022). Although the brain has traditionally been considered an immune-privileged site, studies have confirmed in mice and humans the presence of T cells, including Tregs, in the meninges and within the brain parenchyma (Pasciuto et al., 2020; Marin-Rodero et al., 2025). Genetic analyses showed that compared to peripheral Tregs, brain-resident Tregs express genes that are more closely associated with the nervous system. For example, they exhibit high levels of AREG, which directly contributes to the repair of damaged neural tissues (Korn, 2023; Liston et al., 2023). This area of research is a key focus of this review and will be discussed in detail in subsequent sections.

Beyond their role in regulating immune responses, Tregs can protect stem cell niches from inflammatory activity or directly signal to non-immune cells and/or stem cells (Fujisaki et al., 2011; Cohen et al., 2024). This signaling represents a new function and regenerative mechanism of Tregs. In the liver, for example, Tregs interact with hepatic stellate cells to regulate fibrosis, while in the lungs, they promote alveolar epithelial repair during injury through TGF-β and AREG signaling pathways (Dial et al., 2017; Wen et al., 2017).

Stem cells, with their capabilities for self-renewal and multipotent differentiation, are essential drivers of tissue regeneration and repair. By differentiating into specific cell types or secreting reparative bioactive factors, stem cells can repair damaged tissues, replace injured cells, and promote tissue regeneration (Xuan et al., 2018; Li et al., 2022). In recent years, the interaction between stem cells and specific microenvironments has been the focus of intense research. Among these interactions, the regulation of stem cells by Tregs has been recognized as a novel mechanism of regeneration, distinct from traditional immune responses. For instance, Tregs can enhance the secretion of IL-10 by macrophages in the bone marrow, promoting the recovery of hematopoietic stem cells following irradiation (Fujisaki et al., 2011). Similarly, during cardiac injury, Tregs have been shown to support the survival and differentiation of cardiac stem cells through paracrine effects mediated by IGF-1 and other factors (Wang et al., 2022). Although research in this area is still in its early stages, substantial progress has been achieved in certain tissues, providing new insights and promising implications for exploring regeneration in others, including neural tissue. For example, studies by M.D. Rosenblum's research team demonstrated the critical role of Tregs in epidermal regeneration. They showed that skin-resident Tregs localize preferentially around hair follicles, sustaining their growth and renewal by promoting the activation and differentiation of hair follicle stem cells (HFSCs) through the Notch ligand JAG1 signaling pathway (Ali et al., 2017). In a subsequent study, they investigated the regulatory role of Tregs in the repair of skin injury. Their findings indicated that Tregs suppress the secretion of chemokine C–X–C motif ligand-5 (CXCL5) by keratinocytes, limiting the recruitment of T-helper 17 (Th17) cells and neutrophils. This negative modulation of the local inflammatory environment facilitates the differentiation of HFSCs into epithelial cells, thereby restoring the skin barrier. Accordingly, they showed that depletion of Tregs prevents skin wound healing by inhibiting HFSC differentiation (Mathur et al., 2019). More recently, Luan et al. (2024) revealed the mechanism by which HFSCs operate under inflammatory conditions during wound healing. Their research showed that HFSCs that migrate to the wound site promote the local expansion of Tregs by activating CD80, forming a protective immunoregulatory network that prevents excessive neutrophil accumulation and supports epithelialization and wound healing.

At the same time, by modulating Treg cell functions, stem cells exhibit broad application prospects in the regeneration of various tissues, including nerves, blood vessels, muscles, and bones (Hu et al., 2018; Li et al., 2018; Shanley et al., 2021). Research has shown that during tissue repair, stem cells induce the generation of Tregs, partly relying on their ability to promote the production of cytokines such as IL-10 and TGF-β by macrophages (Qi et al., 2018). In the nervous system, Tregs support neural repair by regulating the balance between pro-inflammatory and anti-inflammatory factors. Wang et al. (2020) reported that human Wharton's jelly-derived mesenchymal

stem cells (MSCs) promote sciatic nerve regeneration and functional recovery by inducing Treg expansion. Depletion of Tregs significantly impaired this repair effect, while supplementation with Tregs accelerated neural functional recovery (Wang et al., 2020). Dombrowski et al. (2017) demonstrated that Tregs directly promote the differentiation of oligodendrocyte precursor cells (OPCs) in demyelinating diseases, highlighting their crucial role in remyelination and neural repair (Dombrowski et al., 2017). The pivotal role of Tregs in regulating neurological diseases and promoting tissue regeneration is summarized in **Figure 1**.

In bone and vascular regeneration, Tregs regulate stem cell functions and promote osteogenesis and angiogenesis through their exosomes. Chen et al. (2022a) demonstrated that Treg-derived exosomes enriched with miR-142-3p accelerate fracture healing and bone remodeling via the TGFBR1/SMAD2 pathway. Another study showed that Tregs modulate the angiogenic properties of endothelial progenitor cells during vascular repair through the production of vascular endothelial growth factor (VEGF) (Loffredo et al., 2024). In summary, Tregs show significant potential in regenerative medicine through different mechanisms of action operating in diverse tissue types. This capability offers a promising, flexible basis for the development of novel therapeutic strategies based on Tregs.

Molecular mechanisms underlying regulatory T cell function

The immunosuppressive functions of Tregs are mediated by diverse and complex mechanisms, which include classical immunoregulatory pathways, tissue-specific mechanisms, and emerging interactions with stem cells (Georgiev et al., 2019). Classical mechanisms of Treg-mediated immunosuppression involve contact-dependent inhibition, secretion of inhibitory cytokines, metabolic competition, and direct cytotoxic effects (Tiemessen et al., 2007; Dombrowski et al., 2017; Attias et al., 2019). One of the most significant mechanisms is direct cell-to-cell contact, where inhibitory receptors on the surface of Tregs (such as CTLA-4 and PD-1) bind to CD80/86 on antigen-presenting cells such as dendritic cells, B cells, and macrophages. This interaction suppresses the maturation of these cells and prevents the activation of effector T cells (Yang et al., 2018, 2019; Jie et al., 2022). For instance, CTLA-4 not only competes with CD28 for binding to CD80/86 but also actively removes CD80/86 from the surface of dendritic cells through trans-endocytosis. This process prevents full dendritic cell activation, thereby reducing T-cell activation in the microenvironment (Marangoni et al., 2021). Additionally, Tregs express Lag-3, which binds to major histocompatibility complex class II molecules on antigen-presenting cells, further inhibiting their activity. As mentioned, Tregs also secrete inhibitory cytokines, such as IL-10, TGF-β, and IL-35, to regulate the functions of effector T cells, natural killer cells, and dendritic cells, thereby diminishing their activity (Muscella et al., 2019; Almanan et al., 2020; Yang et al., 2024). These cytokines not only suppress inflammatory responses but also promote the differentiation of induced Tregs in inflamed tissues, enhancing their regulatory capacity. Metabolic competition operates primarily in two ways. First, Tregs, which express high levels of CD25, compete with effector T cells for IL-2, limiting their proliferation. IL-2 is critical for T-cell survival, and its depletion creates an unfavorable microenvironment for effector T cells while supporting Treg expansion. Second, Tregs express ectonucleotidases CD39 and CD73 on their surface, which produce adenosine from ATP. ADP binds to A2A receptors on effector T cells, inhibiting their activation, proliferation, and cytokine production. Furthermore, Tregs modulate the metabolic environment by altering glucose and lipid metabolism, effectively depriving effector cells of essential nutrients and further limiting their function. Adding another layer of complexity to Treg-mediated regulation, emerging studies have highlighted the role of Treg-derived extracellular vesicles (EVs) in modulating metabolic pathways in target cells. Moreover, Tregs enhance their immunosuppressive effects by secreting perforin and granzyme, which can directly kill effector T cells (Silva et al., 2019; Yang et al., 2021a, b; Jung et al., 2022; Jang et al., 2024). In summary, Tregs use a combination of mechanisms to maintain immune homeostasis and prevent excessive immune activation, thereby playing a central role in immune regulation (Becker et al., 2024; Loffredo et al., 2024).

In addition to classical suppressive mechanisms, Tregs exhibit tissue-specific regulatory characteristics. For example, in skin tissue, Tregs protect HFSCs from immune damage through non-CTLA-4-dependent mechanisms, such as the IL-2 signaling pathway (Cohen et al., 2024b). Furthermore, as discussed previously, Tregs optimize the local inflammatory microenvironment by suppressing the secretion of CXCL5, which reduces the recruitment of neutrophils and Th17 cells, thereby promoting hair regeneration and skin barrier repair (Mathur et al., 2019). In neural tissue, Tregs alleviate neuroinflammation by regulating the balance between pro-inflammatory and anti-inflammatory factors. They also enhance neuronal repair capabilities, facilitating axon regeneration (Dombrowski et al., 2017). In cardiac tissue, Tregs secrete cytokines such as IL-10 and promote macrophage-mediated clearance of necrotic cells, which reduces inflammation and fibrosis during myocardial injury (Xia et al., 2024). A growing understanding of the mechanisms governing Treg functions, along with emerging evidence of substantial crosstalk between Tregs and stem cells, offers new perspectives on the therapeutic potential of Tregs in tissue repair (**Figure 1**).

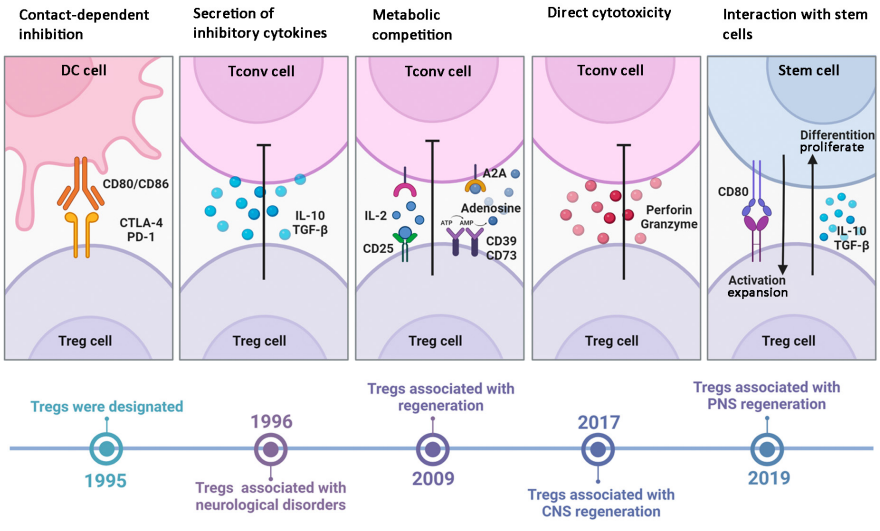

Figure 1 | **Mechanisms and milestones of Treg cells in neurological diseases and regeneration.**
Treg cells exert their immunoregulatory functions through multiple pathways. First, they directly interact with DCs to mediate cell-to-cell interactions. Second, Treg cells release inhibitory cytokines that suppress the functions of various immune cells. Additionally, they inhibit effector T cell activity through competitive suppression. Furthermore, Treg cells secrete perforin and granzyme, which further suppress effector T cell functions and help maintain the balance of the immune microenvironment. Simultaneously, Treg cells promote the proliferation and differentiation of stem cells, creating a favorable microenvironment for stem cell activity. Created with BioRender.com. CNS: Central nervous system; CTLA-4: cytotoxic T lymphocyte associate protein-4; DC: dendritic cells; IL-10: interleukin-10; IL-2: interleukin-2; PD-1: programmed death 1; PNS: peripheral nervous system; Tconv: conventional T cells; TGF-β: transforming growth factor-β; Tregs/Treg cells: regulatory T cells.

Roles of Tregs in Neurological Diseases and Neural Regeneration

The human nervous system is anatomically divided into two parts: the CNS, which includes the brain and spinal cord, and the peripheral nervous system (PNS), encompassing all neural structures outside the CNS (Louveau et al., 2015; Wang et al., 2019; Varadarajan et al., 2022). The CNS integrates sensory input from the body, generates coordinated motor outputs, and serves as the neural substrate for learning and memory (Hong et al., 2017; Zhang et al., 2020). While the brain was long considered an immune-privileged organ, it is now evident that immune cells, including Tregs, can access the brain, particularly during disease and injury (Adusei et al., 2021; Korn, 2023). The BBB and the BSCB are critical for maintaining the stability of the CNS microenvironment. These barriers function not only as physical obstructions but also as dynamic regulatory interfaces that finely control the passage of molecules and cells. Composed of tightly connected endothelial

cells, pericytes, astrocytes, and the basement membrane, the BBB and BSCB are endowed with tight junctions and adherens junctions between endothelial cells that serve to strictly regulate barrier permeability. This ensures that only specific nutrients, oxygen, and metabolic waste products can pass through, maintaining homeostasis within the microenvironment of the nervous system (Badimon et al., 2020; Zhang et al., 2020; Mahmoudi et al., 2024). This barrier function prevents the entry of blood-borne pathogens, toxins, and inflammatory mediators into the brain and spinal cord while regulating the transport of neurotransmitters, hormones, and other signaling molecules to ensure proper neural function. Under healthy conditions, the BBB and BSCB effectively isolate the CNS from the peripheral immune system; however, this isolation is not absolute. During disease and injury, immune cells can traverse these barriers and infiltrate the CNS.

In the brain microenvironment, Tregs exhibit transient residency characteristics, displaying specific phenotypes adapted to the neural environment during their brief stay in brain tissue. The Tregs population in the brain is dynamically renewed, with cells continuously replaced by newly recruited Tregs. Although their presence typically lasts only a few weeks, this transient residency can be prolonged through secondary in situ antigen recognition, enhancing their capacity for immunoregulation and tissue repair (Liston et al., 2023). Following neural injury, mechanical forces can directly damage the vasculature at the injury site, leading to the disruption of the BBB/BSCB, even in areas distant from the primary lesion (primary injury). Vascular contents, including macrophages and lymphocytes, infiltrate neural tissues through the compromised barrier, interacting with inflammatory mediators and triggering inflammatory responses. This exacerbates barrier permeability, further destabilizing the local microenvironment (secondary injury) (Feng et al., 2022; Liston et al., 2023; Yang et al., 2023a; Jerome et al., 2024; Lu et al., 2024; Zhao et al., 2024). The critical role of Tregs in neural injury repair makes them essential for understanding and promoting neural regeneration. The actions of Tregs on the nervous system are summarized in **Figure 2**.

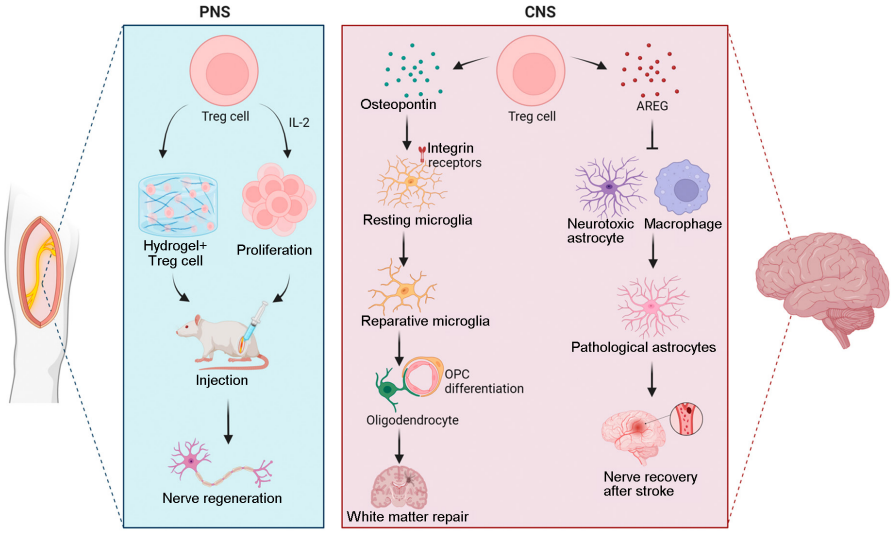

Figure 2 | **Role of Treg cells in neurological disorders and tissue regeneration.**
Treg cells play critical roles in various nerve injury environments. In the CNS, Treg cells support nerve injury recovery and regeneration by releasing cytokines and proteins that modulate the phenotypes of glial cells and immune cells. In the peripheral nervous system, Treg cells can be combined with biomaterials or cytokines and delivered via *in situ* injection to treat peripheral nerve injuries. These approaches help regulate inflammatory responses and promote axonal regeneration, significantly contributing to injury repair. Created with BioRender.com. AREG: Amphiregulin; CNS: central nervous system; IL-2: interleukin-2; OPC: oligodendrocyte precursor cells; PNS: peripheral nervous system; Treg cell: regulatory T cell.

Roles of regulatory T cells in stroke and neurodegenerative disorders

Stroke

Ischemic stroke, commonly referred to as cerebral infarction, is a cerebrovascular disease primarily caused by the interruption or insufficiency of blood supply to the brain. This results in damage or necrosis of brain tissue due to a lack of oxygen and nutrients. As a prevalent type of stroke, ischemic stroke can rapidly worsen, causing direct and severe damage to brain tissue and leading to neurological deficits that pose a serious threat to patient survival and quality of life. Prompt treatment to restore blood flow is critical for preventing further damage and reducing mortality and disability rates in ischemic stroke patients. The role of Tregs in the brain has been extensively studied using the middle cerebral artery occlusion (MCAO) ischemic stroke model. This model is typically established through the intraluminal suture method, which involves a surgical procedure to expose the carotid artery system in mice. A suture is inserted into the common or external carotid artery and advanced to the origin of the middle cerebral artery, mechanically blocking blood flow to induce transient cerebral ischemia. After a defined duration of ischemia (e.g., 60 minutes), the suture is slowly removed to restore blood flow and achieve reperfusion. Using the MCAO model, Wang et al. (2015) uncovered the direct effects of Treg-derived IL-10 on neurogenesis in the subventricular zone. Their research revealed that following MCAO surgery, injection of activated Tregs into the left lateral ventricle promoted the proliferation of the Mash1$^+$ neural stem cell population, an effect negated by administration of anti-IL-10 antibodies. In a seminal study, Ito et al. (2019) first reported that Tregs massively accumulate in the brain during the later stages of MCAO, promoting neural recovery in chronic ischemic brain injury. Their study found that although brain-resident Tregs share similarities with Tregs from other tissues, they exhibit unique gene expression profiles related to the nervous system. On further analysis, the proliferation of brain-resident Tregs was shown to depend on IL-2, IL-33, serotonin, and T-cell receptor recognition, while their migration into the brain is driven by the chemokines CCL1 and CCL20. It was further demonstrated that Tregs contribute to neural recovery by suppressing the proliferation of neurotoxic astrocytes and microglia by producing AREG, a low-affinity ligand for EGFR, which blocks the IL-6/STAT3 signaling pathway in those cells (Ito et al., 2019). Using also the MCAO stroke model, Shi et al. (2021) further demonstrated that Tregs infiltrate brain tissue between 1 to 5 weeks from stroke onset. Depletion of Tregs reduced oligodendrocyte generation, impaired white matter repair, and hindered post-stroke functional recovery. Mechanistically, Treg-derived osteopontin interacted with integrin receptors on microglia, enhancing their reparative activity and promoting oligodendrocyte generation and white matter repair. Increasing Treg cell numbers through IL-2 antibody complexes improved white matter integrity and facilitated long-term neurological recovery (Shi et al., 2021). These findings highlight Tregs as critical targets for neural repair during stroke recovery.

Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory decline, cognitive impairment, and behavioral changes. Hallmark pathological features of the disease include the abnormal deposition of amyloid-beta (Aβ) plaques in the brain, neurofibrillary tangles within neurons, and chronic neuroinflammation mediated by activated microglia and reactive astrocytes. These pathological changes lead to the gradual loss of neurons, particularly in the hippocampus and cerebral cortex, which are critical regions for memory and cognition. Using APPPS1 mice to model AD pathology, Dansokho et al. (2016) performed intraperitoneal injection of anti-CD25 monoclonal antibodies and low-dose IL-2 treatment to deplete and expand, respectively, Tregs. Their study found that compared to a control group with non-depleted Tregs, the Treg-depleted group exhibited a significant reduction in the number of activated microglia migrating toward Aβ deposits and demonstrated early cognitive impairment. In contrast, low-dose IL-2 treatment significantly increased the number of Iba1$^+$ and CD68$^+$ microglia associated with plaques, promoting their aggregation toward Aβ deposits and thereby restoring cognitive function in the mice. These findings suggest that Tregs play a crucial role in AD pathogenesis and can significantly influence pathology and cognitive function by modulating microglial reactivity. In another study, Stym-Popper et al. (2023) found that Tregs can limit the functional differentiation of plaque-

associated reactive astrocytes into the neurotoxic C3+A1 subpopulation, thereby alleviating harmful neuroinflammation in AD-like pathology. This finding suggests the key role of Tregs in regulating neuroinflammation, indicating that they not only influence microglial reactivity but also regulate the functional differentiation of astrocytes, further mitigating neuroinflammation. Yang et al. (2022) intravenously administered Aβ-specific Tregs ($Aβ^+$ Tregs) into 3×Tg-AD mice to investigate their effect on the pathological process of AD. The study found that following the adoptive transfer of $Aβ^+$ Tregs, the accumulation of Aβ plaques in the hippocampus of AD mice was significantly reduced. Notably, upon early treatment, $Aβ^+$ Tregs significantly inhibited the phosphorylation levels of tau protein. Furthermore, adoptive transfer of $Aβ^+$ Tregs markedly reduced the upregulation of Iba1 in AD mice, indicating effective suppression of reactive microglia (Yang et al., 2022). These results demonstrate that Tregs alleviate neuroinflammation in AD and highlight their therapeutic potential to treat this prevalent neurodegenerative disease.

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the gradual loss of dopamine-producing neurons in the brain. A recent study reported that following repetitive transcranial magnetic stimulation, improvements in motor dysfunction in patients with PD are closely associated with increased numbers of peripheral Tregs (Xie et al., 2024a). Further animal experiments indicated that repetitive transcranial magnetic stimulation alleviates neuroinflammation by increasing the number of peripheral Tregs, thereby helping to improve motor function (Xie et al., 2024a). In the 6-hydroxy-dopamine mouse model of PD, Xie et al. (2024b) found that calcitriol inhibited T-cell infiltration in the midbrain by promoting the expansion of Tregs, which reduced the release of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6). This process improved the inflammatory microenvironment in the brain, suppressed the polarization of microglia toward the pro-inflammatory M1 phenotype, and promoted the survival of dopaminergic neurons. In research addressing cell therapy for PD, Park et al. (2023) reported that co-transplantation of autologous Tregs significantly improved the survival rate of transplanted midbrain dopaminergic precursor cells. By inhibiting acute neuroinflammation and immune cell infiltration caused by needle injury, Treg co-transplantation alleviated early post-transplantation death of dopaminergic neurons. Furthermore, Treg co-transplantation not only reduced graft volume, but also increased the proportion of dopaminergic neurons within the graft. Addressing this phenomenon, the research team concluded that Tregs inhibit excessive proliferation of transplanted cells by secreting immune-regulatory factors such as TGF-β1, thereby optimizing transplantation outcomes.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons. Sheean et al. (2018) reported a negative correlation between Treg levels in peripheral blood and ALS progression rate in ALS patients. Experimenting on SOD1G93A transgenic mice, they further showed that treatment with an IL-2/IL-2 monoclonal antibody complex (IL-2c) increased the proportion of circulating Tregs and induced the expansion of effector ($GITR^+$, $CTLA4^+$, $ICOS^+$) Tregs with immunosuppressive functions. This was correlated with a significant reduction in the activation of astrocytes and microglia, slowed disease progression, and prolonged survival. Using the same ALS mouse model, Beers et al. (2011) had previously reported that in the early stages of ALS, Tregs exert a neuroprotective effect by secreting IL-4, which inhibits the neurotoxic phenotype of microglia (characterized by NOX2 expression) while promoting a protective M2 phenotype. These findings indicate that Tregs play an important regulatory role in the pathological process of ALS, particularly in its early stages. By modulating the phenotype of microglia, Tregs can slow the progression of ALS, highlighting new potential targets for treatment.

Demyelinating diseases

Myelin is a protective structure that ensheaths neuronal axons, playing a crucial role in safeguarding neurons and accelerating nerve signal transmission. In the CNS, myelin is formed by oligodendrocytes, while in the PNS, it is produced by Schwann cells. Loss or damage to myelin disrupts nerve signal conduction, leading to neurological dysfunction and the development of demyelinating diseases. Tregs have been shown to play a pivotal role in myelin regeneration, which is essential for preventing neurodegeneration associated with conditions such as MS. Using demyelination models induced by lysophosphatidylcholine (in the spinal cord) and cuprizone (in the corpus callosum), D.C. Fitzgerald's research team investigated the effects of Tregs on neuronal myelin regeneration. In both models, depletion of Tregs severely impaired the differentiation of OPCs and subsequent myelin regeneration. Conversely, myelin regeneration was restored after adoptive transfer of Tregs. The study also identified cellular communication network factor 3 (CCN3) as a potential mediator through which Tregs promote OPC differentiation in several co-culture models (Dombrowski et al., 2017). However, subsequent research suggested that Treg-derived CCN3 might not directly signal to OPCs (Dittmer et al., 2018).

The efficiency of myelin regeneration declines with age. In a recent study, the same research group demonstrated that aged Tregs exhibit an inherent decline in their ability to promote oligodendrocyte differentiation and myelin formation (de la Fuente et al., 2024). However, this regenerative capacity can be restored by exposure to a young systemic environment. Additionally, the referred study identified melanoma cell adhesion molecule 1 (MCAM1) and integrin α2 (ITGA2) as candidate factors mediating Treg-driven oligodendrocyte differentiation. The expression levels of these factors also decline with age, highlighting their potential as therapeutic targets for enhancing myelin regeneration associated with aging and neurodegenerative conditions.

Roles of regulatory T cells in peripheral nerve injury

The PNS includes all neural structures outside the spinal cord and cranial meninges, excluding the olfactory and optic nerves, which connect directly to the brain. In the PNS, somatic nerves are distributed throughout the body surface, skeleton, and skeletal muscles, whereas visceral nerves are associated with internal organs, blood vessels, smooth muscles, and glands. Most peripheral nerves are mixed, containing sensory, motor, sympathetic, and parasympathetic fibers, all of which are encased in connective tissue membranes along with blood vessels and lymphatic vessels (Cattin et al., 2015; Wang et al., 2019; Li et al., 2022; Zhao et al., 2024). Compared to the CNS, the PNS exhibits fewer restrictions on immune responses. Consequently, T-cell accumulation in injured sciatic nerves is significantly greater than in injured optic nerves, and T lymphocyte infiltration closely correlates with increased expression of major histocompatibility complex class II antigens (Adusei et al., 2021). The protective role of Tregs in the PNS is primarily attributed to their immunosuppressive functions. In mouse experiments, Hu et al. (2021a) demonstrated that low-dose IL-2 significantly increased the proportion of Tregs in injured sciatic nerves. Moreover, the combined administration of low-dose IL-2 and adoptive Treg transfer effectively alleviated punctate hyperalgesia and dynamic allodynia following sciatic nerve injury.

For peripheral nerve injuries exceeding the critical gap length, bridging grafts are required to promote nerve regeneration. While autologous graft transplantation provides the best results, allogeneic grafts from immunologically incompatible donors also offer an efficient bridging method; however, the high costs and health risks associated with systemic immunosuppression therapy pose major challenges. Santos Roballo et al. (2019) developed a novel strategy that encapsulates Tregs in biodegradable polyethylene glycol (PEG)-based norbornene hydrogels, serving as localized immunosuppressive agents. When injected around allogeneic nerve grafts, Tregs are gradually released from the hydrogel over 14 days, infiltrating the graft, suppressing host immune responses, and promoting nerve regeneration. Notably, the outcomes were comparable to those achieved with autografts. This approach to localized immunosuppression circumvents the risks associated with systemic immunosuppression, providing an effective new method for treating segmental peripheral nerve defects (Santos Roballo et al., 2019). Although current research on Tregs in peripheral nerve injury is relatively limited, their demonstrated role in promoting neural repair and regeneration in CNS injuries suggests that these cells may also play a similarly critical role in the PNS.

Clinical Application Potential of Regulatory T Cells

***In vitro* regulatory T cell culture and expansion**

Tregs are crucial for establishing fundamental tolerance mechanisms that mitigate immune responses, offering promising therapeutic potential for treating neurological autoimmune diseases and promoting the regeneration of damaged tissues through adoptive therapy. Tregs are typically generated by the combined action of TGF-β and IL-2, along with stimulation signals from CD3 and CD28 (Shi et al., 2021; Zhong et al., 2022;

Jang et al., 2024). Obtaining a large number of high-purity Tregs is essential for initiating adoptive transfer therapies. This process involves selecting appropriate Treg sources and determining effective isolation and culture methods. In murine experiments, Tregs are commonly derived from splenic tissue, although inguinal or axillary lymph nodes are also used in some cases. For clinical applications, human Tregs are typically isolated from autologous peripheral blood, while ongoing research is exploring non-autologous sources such as umbilical cord blood or pediatric thymus tissue (Ferreira et al., 2019). Following isolation, Tregs are purified using common methods, including cell sorting via flow cytometry or magnetic bead separation. Fluorescence-activated cell sorting offers higher cell purity and reduced sorting time, making it suitable for large-scale isolation. Magnetic-activated cell sorting yields higher cell viability, is simpler to operate, and is more appropriate for sorting smaller quantities of cells (Azimi et al., 2016). Both methods produce cells that are effective for downstream applications, with comparable outcomes. Isolated Tregs are typically identified using flow cytometry to assess cell surface markers, with CD4, CD25, and Foxp3 being the most commonly used. **Table 1** summarizes the characteristics of these isolation methods.

Current research aims to develop innovative therapies that enhance the function of endogenous Tregs *in vivo* through the use of cytokines and small-molecule drugs. It also investigates the adoptive transfer of *ex vivo* cultured Tregs in autoimmune environments to promote immune regulation. However, adoptive cell therapies employing *ex vivo* cultured Tregs encounter significant challenges, including insufficient purity, unstable activity, and potential shifts in phenotype or functional loss following expansion (Li et al., 2018; Attias et al., 2019; Jie et al., 2022). In this regard, a study found that the molecular weight of hyaluronic acid specifically upregulates certain transcription factors that are crucial for maintaining the Treg phenotype (Bollyky et al., 2007). More recently, Shi et al. (2023b) demonstrated that the induction of human Tregs is influenced by the ability of T cells to sense the mechanical stiffness of the substrate. On polyacrylamide gels, Treg induction was highly sensitive to the elastic modulus of the substrate, with higher levels of induction observed as the material's stiffness increased. ScRNA-seq analysis revealed that Treg induction on stiffer substrates was associated with upregulation of oxidative phosphorylation. Inhibiting ATP synthase significantly reduced Treg induction rates and eliminated the differences observed between gels of varying stiffness. Conversely, activating AMP-activated protein kinase enhanced Treg induction on softer substrates but had no effect on stiffer substrates. These findings thus revealed that Treg induction is mechanosensitive and reliant on oxidative phosphorylation (Shi et al., 2023b), suggesting new strategies to enhance the therapeutic potential of Tregs in cellular immunotherapy, especially in the fields of biomedical engineering and neural regeneration.

Table 1 | **Methods for the separation of regulatory T cells**

Item	Magnetic bead sorting	Flow separation
Separation purity	Lower	Higher
Sorting activity	Higher	Lower
Technical difficulty	Lower, easy to operate	Higher, complexities in machine programming

Adoptive transfer of regulatory T cells

Following brain injury, Tregs can suppress adaptive immune responses and mitigate glial reactions that lead to neuronal damage, while also directly facilitating various repair and regeneration processes (Liston et al., 2023). Depletion of Tregs results in uncontrolled inflammation, tissue damage, and cell death, and these features can be rescued to some extent by the supplementation of exogenous Tregs. Shi et al. (2021) demonstrated that in the setting of experimental stroke, selective depletion of Tregs leads to reduced oligodendrocyte generation, impairs white matter repair, and hinders functional recovery. Conversely, increasing Treg numbers improves white matter integrity and promotes long-term neurological recovery, highlighting Tregs as critical targets for neural repair in stroke rehabilitation. Wang et al. (2015) injected Tregs into the left lateral ventricle of mice following transient MCAO and found that the proliferation of $Mash1^+$ neural stem cells in the subventricular zone was significantly increased. This effect was abrogated by the application of anti-IL-10 antibodies. In another study, $CD4^+Foxp3^+$ Tregs were isolated from Foxp3-GFP mice and administered via tail vein injection to $CD3e^{-/-}$ mice on day 5 post-stroke (Ito et al., 2019). The adoptively transferred Tregs facilitated neural recovery by interfering with IL-6/STAT3 signaling in astrocytes and microglia via AREG/EFGR signaling, promoting the production of IL-6, which facilitated neural recovery.

Dombrowski et al. (2017) evaluated the role of Tregs in myelin regeneration using FoxP3-DTR knock-in mice, which express the human diphtheria toxin (DT) receptor under the control of the Foxp3 promoter. In FoxP3-DTR mice with DT-induced Treg depletion, intraperitoneal injection of DT-insensitive Tregs (purified from wild-type mice) 24 hours prior to lysophosphatidylcholine-induced spinal cord white matter demyelination effectively restored myelin regeneration. Recently, another study showed that treatment with Tregs derived from young mice reversed myelin damage associated with aging and alleviated negative effects linked to the functional decline of Tregs in older mice (de la Fuente et al., 2024). Overall, these findings indicate that the adoptive transfer of Tregs holds significant therapeutic potential in demyelinating disorders.

Substantial evidence supports the neuroprotective role of Tregs in neurodegenerative disorders (Machhi et al., 2020). The innate and adaptive immune responses of the host influence the early and long-term survival of midbrain dopaminergic neuron grafts, a plausible approach to PD treatment. Park et al. (2023) showed that co-transplanting stem cells with Tregs can modulate immune responses, significantly protect midbrain dopaminergic neurons, and enhance the efficacy and safety of cell replacement therapies for neurodegenerative diseases such as PD (Park et al., 2023). In the early stages following sciatic nerve injury, adoptively transferred lymphocytes migrate to the injury site, releasing pro-inflammatory cytokines that promote Wallerian degeneration, thereby accelerating debris clearance and axonal regeneration (Bombeiro et al., 2020). Hu et al. (2021a) investigated the role of Tregs in alleviating mechanical hypersensitivity and dynamic allodynia resulting from nerve injury. They found that low-dose IL-2 treatment or the adoptive transfer of Tregs significantly alleviated punctate and dynamic allodynia, suggesting that these cells may serve as a potential therapeutic target for pain related to nerve injury.

Effective clinical translation of the obvious potential of Tregs in managing neurological autoimmune diseases and preventing graft rejection requires further optimization of therapeutic strategies. Key challenges include producing these cells in sufficient quantities while ensuring consistent genotypic and phenotypic stability for therapeutic applications. Santos Roballo et al. (2019) developed an innovative approach for localized immunosuppression that involves a single application of Tregs encapsulated in biodegradable PEG-based hydrogels. This procedure was shown to prevent systemic immunosuppression and promote nerve regeneration in recipient rats. Zhang et al. (2023b) designed a perforated microneedle with a core-shell structure that exhibits excellent mechanical performance and a spacious encapsulation cavity to support Treg viability. Additionally, the adjustable channels in the microneedle facilitated cell migration. This strategy successfully achieved percutaneous delivery of Tregs, providing a more efficient way to deliver local cell-based therapies (**Table 2**).

Advancements in clinical research on Tregs

In recent years, a growing number of clinical studies investigated the potential of Tregs in disease treatment, particularly in the realms of autoimmune disease and cancer therapy. In comparison, research on Treg-based therapies for neurological disorders has developed relatively slowly, but is quickly emerging as a focal research point. Several studies indicated that Tregs possess unique and significant therapeutic potential in neurological disorders by modulating neuroinflammation, neurodegeneration, and various pathophysiological processes associated with autoimmunity (Machhi et al., 2020). Clinical trials targeting neurological diseases such as AD, MS, ALS, and PD have gradually been initiated. These studies have explored the safety and efficacy of treatments that involve activating endogenous Tregs through low-dose IL-2 injections or the direct transfer of *ex vivo* expanded autologous Tregs. In these trials, Tregs have shown multifaceted effects, including the regulation of neuroinflammation, the alleviation of immune-mediated neuronal damage, and the promotion of tissue repair. **Table 3** presents a summary of current clinical studies on Treg cell therapy for neurological disorders, illustrating various disease models, therapeutic strategies, and metrics for evaluating efficacy.

Table 2 | **Comparative analysis of studies using Treg cell adoptive transfer in neurological diseases**

Animal model	Formulation type	Injection site	Route	Dosage and frequency	Reference
MCAO	Treg cells	Tail vein	Injection	2×10^6 Treg cells 6 h after MCAO surgery	Shi et al., 2021
MCAO	Treg cells	Tail vein	Injection	1×10^6 Treg cells on d 5	Liston et al., 2023
MCAO	Treg cells	Lateral ventricle	Injection	1×10^5 Treg cells on d 1 after MCAO surgery	Wang et al., 2015
Demyelination model	Treg cells	Intraperitoneal	Injection	1×10^6 Treg cells	Dombrowski et al., 2017
Parkinson's disease	C4-mDAPs+Treg cells	Striatum of the brain	Injection	1×10^5 mDAPs + 1×10^4–10^5 Treg cells (mDAPs: differentiated from human iPSCs)	Park et al., 2023
SNI unilateral nerve injury model	Treg cells	Tail vein	Injection	1×10^6 Treg cell administration 3 wk after SNI surgery	Hu et al., 2021a

iPSCs: Induced pluripotent stem cells; MACO: middle cerebral artery occlusion; mDAPs: midbrain dopamine precursor cells; SNI: spared nerve injury; Treg cell: regulatory T cell.

Table 3 | **Ongoing clinical trials for neurological diseases involving Treg cells (https://clinicaltrials.gov/)**

ID	Sponsor	Disease	Enrollment (*n*)	Strategy	Phase/Status
NCT05468073	Centre Hospitalier St Ann	Alzheimer's disease	45	Low-dose IL-2 injection	Phase 2
NCT06096090	The Methodist Hospital Research Institute	Alzheimer's disease	40	Low-dose IL-2 injection	Phase 2
NCT05016427	VTBIO Co. LTD	Alzheimer's disease	12	Low- and high-dose Treg cells (VT301) injection	Phase 1
NCT03865017	VTBIO Co. LTD	Alzheimer's disease	20	Autologous Treg cells (GB301) injection	Phase 1 Phase 2
NCT06671236	Novabio Therapeutics	Neurodegenerative diseases	12	Autologous human polyclonal Treg cells (NP001) injection	Phase 1
NCT05245344	Neuromed IRCC	Relapsing-remitting multiple sclerosis, neuromyelitis optica spectrum disorder	154	Evaluate the effect of ozanimod on the proliferation, metabolism, and function of Treg cells	Unknown
NCT04220190	Rapa Therapeutics LLC	Amyotrophic lateral sclerosis	41	Autologous Treg/Th2 cells (RAPA-501) injection	Phase2 Phase 3
NCT04055623	The Methodist Hospital Research Institute	Amyotrophic lateral sclerosis	12	Autologous Treg cells infusion + IL-2 injection	Phase 2
NCT05695521	Cellenkos, Inc.	Amyotrophic Lateral Sclerosis	66	Neurotropic, allogeneic, umbilical cord blood derived Treg (CK0803) injection	Phase 1
NCT03039673	Centre Hospitalier Universitaire de Nimes	Amyotrophic Lateral Sclerosis	304	Low-dose IL-2 injection	Phase 2
NCT06169176	Rapa Therapeutics LLC	Amyotrophic Lateral Sclerosis	Unknown	Autologous hybrid Treg/Th2 cell (RAPA-501) injection	Unknown

IL-2: Interleukin-2; Treg cells: regulatory T cells.

Engineered Tregs for Disease Treatment and Tissue Regeneration

Engineering T cells is a cutting-edge biotechnological approach aimed at enhancing their therapeutic potential through genetic editing, molecular modifications, and chemical alterations (Chen et al., 2022b; Lim, 2022; Wang et al., 2023c). Wang et al. (2022) used genetic editing techniques, such as the CRISPR/Cas9 system, to precisely modify the T-cell genome, thereby enhancing specific immune functions. Additionally, molecular modifications, including the addition of functional molecules (e.g., chimeric antigen receptors; CARs) to the cell surface, provide T cells with improved targeting specificity and efficacy in treating tumors and autoimmune diseases (Guo et al., 2022; Zhu et al., 2022; Foss et al., 2023). Chemical modifications enhance the stability and activity of Treg cell membranes through the use of chemical crosslinkers or small-molecule drugs, thereby improving cell survival, prolonging therapeutic effects, and enhancing efficacy (Jin et al., 2023; Wang et al., 2023c). This section focuses on four key aspects: the genetic engineering of Tregs, acellular engineering strategies for Tregs, in situ recruitment and activation of endogenous Tregs, and the delivery of immunomodulators to convert effector T cells into Tregs (**Figure 3**).

Genetic editing is commonly applied to enhance Tregs' immunosuppressive functions, while physical or chemical modifications achieve non-genetic functional enhancements. Specific regulatory factors or biomaterials can induce the recruitment and activation of endogenous Tregs *in vivo*, and the design of precision delivery systems can facilitate the conversion of effector T cells into Tregs, stabilizing and enhancing their functionality (Tajima et al., 2015; Ishihara et al., 2018). These multidimensional engineering strategies significantly improve the effector functions of Tregs and their adaptability to complex inflammatory microenvironments. They also enhance long-term survival *in vivo* and provide novel approaches for clinical applications in autoimmune diseases, cancer immunotherapy, and tissue engineering (Li et al., 2018; Loffredo et al., 2024). Notably, the integration of Tregs with biomaterials further drives technological innovation and expands their applications, paving the way for breakthroughs in tissue engineering and regenerative medicine development (Ho et al., 2024; Wang et al., 2024b).

Genetically engineered regulatory T cells

Genetic engineering of T cells has recently emerged as a major topic in the fields of bioengineering and immunotherapy (Shrestha et al., 2020; Zhao et al., 2024). By endowing T cells with new functions or enhancing specific characteristics, this approach enables precise treatment for a variety of diseases (Foss et al., 2023). In the context of tissue regeneration, engineered T cells hold great potential for modulating the immune microenvironment following tissue damage (Tang et al., 2018). For instance, after neural injury, the local microenvironment often exhibits excessive inflammation and a lack of sufficient signals for tissue repair. Engineered T cells can promote nerve regeneration and functional recovery by secreting specific neurotrophic factors or modulating immune responses (Yang et al., 2023a; Gao et al., 2024). Currently, enhancing or regulating the key transcription factor Foxp3 through genetic engineering is a primary approach for precisely modifying Treg functions and treating autoimmune diseases (Georgiev et al., 2019; Korn, 2023). Honaker et al. (2020) used homologous directed repair technology to insert a potent enhancer/promoter combination near the first exon of the Foxp3 gene in Tregs. This approach overcomes the limitations of epigenetic silencing, enabling stable and sustained expression of Foxp3. The engineered Tregs exhibited typical inhibitory markers and significantly enhanced immunoregulatory functions, demonstrating great potential in treating diseases such as type 1 diabetes and rheumatoid arthritis.

In another study, Thatte et al. (2023) developed an ionizable lipid nanoparticle platform for the efficient delivery of Foxp3 mRNA into $CD4^+$ T cells, converting them into $Foxp3^+$ T cells with a temporary immunosuppressive phenotype (Thatte et al., 2023). This non-permanent genomic modification effectively suppressed the excessive proliferation of effector T cells within a short period, achieving flexible immune regulation suitable for treating acute graft-versus-host disease or inflammatory disorders. These two Foxp3-engineering strategies offer long-term and short-term immune regulation options, demonstrating the immense potential of genetic engineering in immunoregulation and laying a solid foundation for the development of personalized immunotherapy.

NEURAL REGENERATION RESEARCH
www.nrronline.org

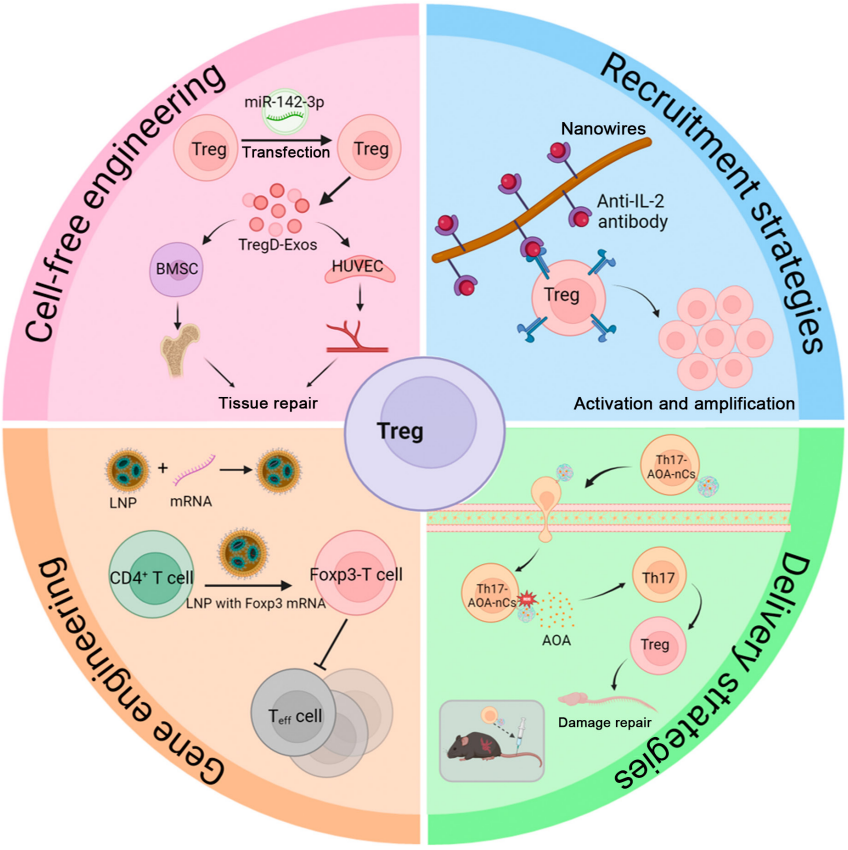

Figure 3 | **Advances in engineered Tregs for neurological diseases and neural regeneration.**
The figure summarizes four key aspects of Treg engineering: genetically modified Tregs, cell-free engineering strategies for Tregs, in situ recruitment and activation of endogenous Tregs, and the delivery of immunomodulators to transform effector T cells into Tregs. Created with BioRender.com. AOA: (Aminooxy)-acetic acid; AOA-nCs: (aminooxy)-acetic acid-nanocapsules; BMSC: bone marrow stromal cells; HUVEC: human umbilical vein endothelial cells; LNP: lipid nanoparticle; Th17: T-helper cell 17; Treg: regulatory T cell; TregD-Exos: Treg-derived exosomes.

Gene-editing tools such as CRISPR-Cas9 have significantly enhanced the precision of T-cell engineering. By knocking out genes associated with inflammatory responses or overexpressing genes that support neural regeneration, dual-function engineered T cells can be customized to effectively suppress inflammation while promoting tissue repair. Wang et al. (2022) used CRISPR/dCas9 nanoparticle technology to program Tregs *in situ*, successfully preventing excessive inflammatory responses following the transplantation of small-diameter tissue-engineered vascular grafts and promoting neural regeneration. In rat experiments, the edited Tregs upregulated the *TET2* gene, reduced the proportion of $CCR2^+$ macrophages, and modulated IL-6 levels, maintaining them within a range favorable for neural regeneration. This strategy significantly improved vascular integrity and long-term patency, achieving near-normal vascular regeneration and immune homeostasis after 3 months. These results demonstrate the great potential of Treg genetic reprogramming for tissue regeneration and immune regulation. Another promising immunoregulatory strategy is the design of CAR-Tregs. By expressing CARs that target specific antigens on T cells, these engineered cells can precisely regulate immune responses. D. W. Scott's research team developed a CAR analog, the B-cell targeting antibody receptor (BAR), which targets the protein antigen ovalbumin and uses the CD28-CD3ζ signaling domain to regulate the activity of B cells and mast cells. In an anaphylaxis mouse model, OVA-BAR Tregs effectively suppressed allergic reactions, providing basic evidence of possible clinical protection against severe allergic reactions in IgE-sensitized individuals (Abdeladhim et al., 2019). Building on this foundation, CAR-Treg applications might be further extended to the field of neural regeneration by targeting neural tissue-specific antigens to localize at sites of nerve injury. These CAR-Tregs could secrete anti-inflammatory cytokines (such as IL-10 and TGF-β), suppress overactivated immune responses, and reduce damage caused by inflammatory mediators to neurons and myelin. Additionally, these cells could release neurotrophic factors (such as brain-derived neurotrophic factor) or interact with glial cells to promote axonal regeneration and myelin repair. Through their diverse applications in immune regulation and tissue repair, CAR-Tregs hold immense potential for precise therapies for a variety of complex diseases, offering innovative directions for clinical development.

A cutting-edge approach in the field of neural regeneration involves the use of Treg-biomaterial composite systems. These systems encapsulate genetically engineered Tregs within biodegradable biomaterials, providing novel therapeutic strategies for repairing neural tissues (Bollyky et al., 2007). The biomaterials not only function as scaffolds to support neural tissue repair but also enhance the local microenvironment by controlling the release of bioactive factors (Santos Roballo et al., 2019). The engineered Tregs express specific chemokines or surface adhesion molecules, facilitating interaction with regenerating nerve fibers and surrounding matrices, which accelerates the reconstruction of neural networks (Hu et al., 2018; Jie et al., 2022). In summary, the genetic engineering of Tregs, when combined with biomaterials, nanotechnology, and high-throughput gene editing techniques, holds significant promise for developing more precise and efficient Treg-based therapeutic strategies. This multidisciplinary collaboration offers innovative solutions for addressing complex diseases, including central and peripheral nerve injuries.

Cell-free Treg engineering strategies

EVs, particularly exosomes, are emerging as critical tools in tissue repair, immune regulation, and regenerative medicine, representing key components of cell-free engineering strategies (Ullah et al., 2021; Fan et al., 2024). These small vesicles, typically ranging from 30 to 150 nm in diameter, are released into the extracellular matrix when multivesicular bodies fuse with the cell membrane (Li et al., 2021d). Rich in biologically active molecules—including proteins, lipids, and nucleic acids such as mRNA and miRNA—exosomes not only reflect the characteristics of their parent cells but can also be delivered to specific cells or tissues, thereby modulating the functions of recipient cells (Kalluri, 2024). Exosomes derived from Tregs are particularly enriched with various anti-inflammatory molecules and factors, enabling them to suppress the activity of effector T cells and promote tissue-specific immune tolerance (Zhang et al., 2023a; Li et al., 2024). For example, Treg-derived exosomes containing miR-142-3p, when delivered to bone marrow MSCs and human umbilical vein endothelial cells, significantly enhance osteogenesis and angiogenesis. Specifically, miR-142-3p promotes osteogenic differentiation of bone marrow MSCs via the TGFBR1/SMAD2 signaling pathway while simultaneously enhancing the proliferation, migration, and angiogenesis of human umbilical vein endothelial cells, thus accelerating bone repair *in vivo* (Chen et al., 2022a). These naturally secreted nanoscale particles play a vital role in intercellular communication, and their unique properties position them as ideal carriers and effectors for cell-free therapies (Krishnan et al., 2023; Wang et al., 2023a; Zhang et al., 2024).

The advantages of exosome applications stem from their natural biocompatibility and low immunogenicity (Wallen et al., 2022). Moreover, through genetic engineering or chemical modifications, it is possible to construct artificially designed bioactive molecules, synthetic materials, or delivery systems that can regulate cellular behavior and immune responses *in vivo*, without the need for live cells. The core concept of this strategy is to precisely regulate biological and physical signals within the microenvironment, stimulating the repair potential of innate cells while avoiding the complexities and risks associated with cell-based therapies (Veerman et al., 2019; Zhou et al., 2020; Fan et al., 2024). For instance, Tian et al. (2021) developed a nanomedicine that combines Treg-derived exosomes with an anti-

VEGF drug. This system exploits the activity of matrix metalloproteinases in inflammatory lesions to enable the precise release of Treg-derived exosomes and an antiangiogenic drug, thereby suppressing inflammatory responses and VEGF activity. This innovative approach suggested that by carefully controlling drug release and combining the immunoregulatory effects of Treg cell-derived exosomes, it is possible to effectively intervene in pathological processes, such as ocular neovascular diseases, to optimize therapeutic outcomes. Cheng et al. (2022) used a biomaterial engineering strategy to design carriers or scaffolds for delivering secreted protein acidic and cysteine rich (Sparc)-overexpressing Treg-derived EVs, creating a composite hydrogel system. This system responds to specific biomarkers in infarcted areas, such as CXCR2, pH, H_2O_2, and MMP9, enabling targeted EV release. As a result, it reduces myocardial damage, promotes collagen synthesis, and suppresses pro-inflammatory factors such as IL-1, IL-6, and TNF-α, significantly improving cardiac function following acute myocardial infarction. Building on the immunosuppressive functions of Tregs, Li et al. (2021b) devised an innovative biomimetic immunoregulatory strategy by coating poly(lactic-co-glycolic acid) nanoparticles with Treg cell membranes. This approach addresses the impairment of Treg cell function in inflammatory environments such as chronic periodontitis. By preserving the natural immunoregulatory properties of Treg cell membranes, this biomimetic membrane technology effectively targets inflammation sites and modulates the local immune microenvironment, facilitating efficient inflammation control and tissue repair. In summary, cell-free engineering strategies based on Treg-derived exosomes, Treg membranes, and biomimetic nanoparticles have broadened the potential applications of Tregs in inflammation regulation, tissue regeneration, and immune balance, demonstrating significant advantages for treating complex diseases (Zhang et al., 2021b; Zeng et al., 2023). Compared to cell-based therapies, these strategies bypass the technical challenges of cell sourcing, cultivation, and storage, while offering more flexible solutions through modular design (Yang et al., 2023b). With the ongoing integration of synthetic biology, materials science, and nanotechnology, cell-free engineering is poised to become a cornerstone of precision therapy and regenerative medicine, providing groundbreaking opportunities for treating neurological diseases and advancing tissue regeneration (Rau et al., 2021; Liu et al., 2022).

In situ recruitment and activation of endogenous regulatory T cells

In situ recruitment and activation of endogenous Tregs is an innovative strategy to modulate the local immune microenvironment (Zhang et al., 2022). A notable characteristic of Tregs is the persistent expression of CD25, the alpha chain of the trimeric high-affinity IL-2 receptor. Through selective binding to IL-2, Tregs can be preferentially activated to exert immune regulation, a critical goal in the treatment of autoimmune diseases (Attias et al., 2019; Ho et al., 2024). Building on this property, Shi et al. (2021) demonstrated that the administration of IL-2 antibody complexes significantly increased the number of Tregs and improved long-term recovery after stroke. However, the narrow therapeutic window and short half-life of IL-2 limit its broader clinical application. To address this issue, Zhang et al. (2021a) introduced azido amino acids at specific positions in the IL-2 molecule and orthogonally conjugated them with PEG groups via copper-free click chemistry, significantly enhancing the pharmacokinetics and half-life of IL-2. Following subcutaneous injection, PEGylated IL-2 exhibited a high degree of selectivity in binding to the trimeric IL-2R across a broad dosage range, persistently inducing Treg activation and expansion. In mouse models of inflammatory diseases and graft-versus-host disease, PEGylated IL-2 significantly improved therapeutic outcomes while preserving the host's immune defense against viral infections.

Although systemic cytokine injection can effectively activate the immune system, it may also unwantedly activate immune cells in non-target tissues, leading to toxicity and limiting its clinical application (Quijano-Rubio et al., 2022). To address this issue, Zamecnik et al. (2020) proposed an innovative strategy involving the design of a high-aspect-ratio polycaprolactone nanowire system. These nanowires can form complexes with cytokine-binding antibodies and self-assemble into a porous matrix after subcutaneous injection. This system can remain *in vivo* for several weeks, eliciting minimal foreign body reactions and effectively resisting clearance. By combining them with the anti-IL-2 antibody JES6-1, these nanowires can capture endogenous IL-2 and selectively activate tissue-resident Tregs. This approach successfully rebalanced the local immune environment in autoimmune disease models involving wild-type and transgenic mice, shifting it toward a Treg-mediated suppressive phenotype (Zamecnik et al., 2020; Zhong et al., 2022). This strategy not only optimizes the pharmacokinetics of the drug but also enhances Treg functions locally, thereby avoiding the side effects associated with systemic immune responses.

Unlike traditional systemic immunoregulatory approaches, *in situ* recruitment strategies achieve localized immune balance by selectively activating endogenous Tregs that reside in or migrate to the target site. The core of this strategy lies in leveraging biomaterials or drug delivery systems to optimize the local microenvironment, thereby inducing the recruitment, activation, and functional enhancement of Tregs (Ishihara et al., 2017; Gaharwar et al., 2020). However, while current strategies have demonstrated significant efficacy in Treg recruitment and activation, they do not specifically target Tregs in a particular tissue but instead act systemically or across all tissues (Becker et al., 2024). This limitation underscores the challenges for future clinical translation, particularly in achieving precise regulation of Tregs within specific tissues or immune environments. Future research focusing on developing strategies that can specifically target particular tissues or immune microenvironments is necessary to enhance therapeutic specificity and safety while minimizing unintended immune responses.

Delivery of immunomodulators for regulatory T cell conversion

Drug delivery systems offer great potential for improving therapeutic efficiency and reducing side effects, particularly in the treatment of complex health conditions such as autoimmune diseases (Foss et al., 2023; Mahmoudi et al., 2024). In recent years, research on Treg conversion and functional regulation has highlighted the significant potential of immunomodulators, conversion inducers, and innovative immune-homeostatic particles as drug delivery strategies.

Aminooxy-acetic acid (AOA) is a promising transdifferentiation inducer that promotes the expression of Foxp3 by inhibiting pyridoxal 5′-phosphate-dependent transaminases and reducing the methylation of the Foxp3 locus, thereby inducing the conversion of Th17 cells into Tregs. However, the inability of AOA to cross the BBB limits its application in treating neurodegenerative conditions such as MS. To address this challenge, Shi et al. (2023a) developed an innovative "Trojan horse" drug delivery strategy using Th17 cells. By employing nanocapsule technology, AOA was conjugated to Th17 cells and intravenously administered into MS model mice. These nanocapsules successfully crossed the BBB and released AOA in a pro-oxidant environment, inducing the conversion of Th17 cells into Tregs to significantly reduce inflammation and exert immune regulation in MS mice.

In another study focusing on Treg-mediated immunoregulation, efficient targeted delivery of the immunomodulatory drug fingolimod to draining lymph nodes was achieved through the design of CaCO3/CaP/heparin hybrid nanoparticles modified with a CCL21-specific aptamer. This strategy significantly enhanced the local accumulation of the drug and effectively reduced the incidence of long-term complications in a heart transplantation mouse model by promoting the generation of endogenous Tregs and decreasing the proportion of effector T cells (Che et al., 2022). This approach improved therapeutic specificity through precise delivery, avoiding the side effects of traditional systemic immunosuppression. Chen et al. (2021) developed an immune-homeostatic microparticle system by combining mesoporous silica nanoparticles with polymer microspheres, providing a multifunctional delivery platform. This system utilized monocyte chemoattractant protein-1 (MCP-1) to induce T-cell migration to inflammation sites, while Fas ligand immobilized on the surface of the microparticles triggered apoptosis of activated T cells. Following the phagocytosis of these cells by macrophages, large amounts of TGF-β were produced, further promoting Treg differentiation (Chen et al., 2021).

The aforementioned studies demonstrate the significant potential of innovative drug delivery strategies that combine nanotechnology and bioengineering to target and regulate Treg differentiation and function. By integrating drug release and delivery with specific immune microenvironments, these technologies not only enhance therapeutic efficacy but also

reduce the side effects associated with systemic immunosuppression. However, these strategies still face numerous challenges in terms of clinical translation, such as the controllability of delivery systems, targeting specificity, and drug stability (Rong et al., 2020; Shan and Wu, 2024). Future research should focus on developing more precise and efficient delivery technologies tailored to the characteristics of immune microenvironments in diseased or injured tissues. This approach will help accelerate the translation of these promising technologies from the laboratory to the clinic.

Limitations

This review comprehensively covers relevant research on the multifaceted roles of Tregs in diseases and tissue injury, with a particular focus on their immunological and non-immunological mechanisms in neurological disorders and tissue repair. However, we acknowledge some limitations in this review. First, research in this field remains relatively scarce, limiting the breadth of analysis and highlighting the necessity for further exploration. Second, distinguishing between the immunological and non-immunological pathways of Tregs in experimental models poses a major challenge, as these mechanisms often overlap and interact in complex ways. Third, the technical complexity associated with studying neurological models, particularly those focusing on the brain and other CNS structures, remains a substantial hurdle. In the context of spinal cord research, exploration in this area remains limited, resulting in a significant gap in our understanding of the mechanisms underlying Treg-mediated spinal repair. Fourth, despite advancements in the field, many mechanisms, particularly those bridging the immunological and non-immunological functions of Tregs, remain unclear. Further targeted and comprehensive research to address these gaps will help establish a robust foundation for biomedical engineering applications in regenerative medicine.

Discussion and Future Perspectives

In recent years, the role of the immune system in tissue repair and regeneration has garnered significant attention in the field of regenerative medicine. However, our understanding of the mechanisms by which the immune system—particularly specific immune cell subsets—regulates the tissue healing process remains limited (Adusei et al., 2021; Wang et al., 2023c, 2024a). Tregs present a promising avenue for research focusing on the treatment of neurological conditions, immune-related diseases, and tissue regeneration (Arpaia et al., 2015; Liston et al., 2023; Loffredo et al., 2024).

In this review, we first introduce the multifaceted roles of Tregs in diseases and tissue injury, encompassing traditional immunological functions and emerging non-immunological mechanisms. As part of their well-characterized immunological functions, Tregs suppress the activation and proliferation of effector T cells by secreting anti-inflammatory cytokines, thereby reducing excessive immune responses against pathogens or self-antigens. Furthermore, Tregs play a critical role in establishing central and peripheral tolerance by regulating the development of self-reactive T cells in the thymus and promoting immune tolerance to non-pathogenic antigens in the periphery, which helps prevent autoimmune diseases (Savage et al., 2020; Dikiy and Rudensky, 2023).

In addition to regulating T cells, Tregs influence B-cell antibody production and memory formation through cytokine secretion and cell-to-cell contact mechanisms. They also modulate the functions of innate immune cells, such as macrophages, neutrophils, and natural killer cells, further balancing immune responses (Sakaguchi et al., 2020; Ho et al., 2024). Through these multilayered immunoregulatory mechanisms, Tregs play a central role in suppressing inflammation, maintaining tissue homeostasis, and promoting repair under pathological conditions.

This review summarizes the non-immunological pathways of Tregs, emphasizing their critical roles in interacting with stem cells during immune regulation and neural tissue repair. Tregs and stem cells work together to maintain tissue homeostasis and promote regeneration through complex intercellular signaling networks. In the stem cell microenvironment, Tregs secrete anti-inflammatory cytokines that suppress local inflammation, reduce immune-mediated damage to stem cells, and protect their survival and function (Loffredo et al., 2024). Additionally, Tregs release pro-regenerative signals that enhance the proliferation, differentiation, and functionality of stem cells, thereby supporting tissue regeneration (Qi et al., 2018). At the same time, exosomes or factors derived from stem cells can regulate Treg metabolism and signaling pathways, improving their migration and function in injured tissues (Chen et al., 2022a). These synergistic interactions between Tregs and stem cells offer novel mechanistic insights into immune regulation and tissue repair, providing a solid foundation for developing regenerative medicine and cell-based therapies that leverage the potential of both cell types. However, several key questions regarding their mechanisms of action remain unresolved. For instance, it is unclear whether Treg-mediated immunosuppression and tissue repair require the cooperation of innate immune cells. It is uncertain also whether these processes depend on specific antigens, whether there are functional differences and interrelationships between tissue-resident Treg cells in the nervous system and peripheral Tregs, and what the optimal therapeutic window is for Treg-mediated repair. As research into the repair mechanisms of Tregs advances, addressing these challenges will enhance our understanding and establish a robust theoretical foundation for Treg-based therapies.

To achieve success in future personalized cell therapies for neurological diseases and tissue regeneration, therapeutic strategies must be scalable, demonstrate appropriate efficacy, and provide long-lasting effects without causing significant adverse events. Current adoptive cell transfer strategies have shown promise in treating neurological disorders and promoting regeneration across a variety of neurodegenerative diseases, autoimmune conditions, and age-related regenerative impairments. However, several barriers continue to limit the clinical therapeutic potential of Tregs (Li et al., 2021a, c; Wu et al., 2022; Liu et al., 2023). Under good manufacturing practice conditions, Tregs can be expanded *ex vivo* to generate sufficient quantities for clinical applications. This approach addresses challenges such as their survival and persistence *in vivo*, the stability of their functional phenotype, and the selective engagement or inhibition of antigen-specific responses in specific disease contexts (Hickey et al., 2019; Foss et al., 2023; Eckman et al., 2024). Despite these challenges, we remain cautiously optimistic about the prospects of utilizing Treg cells to slow or even reverse the progression of neurological diseases, especially given the notable successes of passive cell therapies in various other conditions.

The integration of biomaterials into immunoregulatory therapies has the potential to revolutionize tissue engineering and regenerative medicine (Gaharwar et al., 2020). Current strategies for modulating immune cell responses primarily focus on targeting pro-inflammatory or anti-inflammatory activities within the tissue microenvironment, particularly by suppressing the inflammatory activity of immune cells to promote healing and tissue regeneration. By incorporating biomaterials into these therapeutic designs, it is possible to achieve localized delivery of cytokines and other molecules that target inflammatory processes while precisely controlling their release kinetics (Gaharwar et al., 2020; Wu et al., 2022; Wang et al., 2023c). In regenerative therapies and biomaterial implants, greater attention must be paid to the role of Treg cells. Progress has already been made in modulating Treg cell activity, providing a robust theoretical foundation for designing biomaterials that support immune responses. Beyond existing biological approaches, such as genetic engineering and cell-free therapies, modifications to material properties through physical and chemical techniques (e.g., size, shape, surface characteristics) can also directly influence the therapeutic efficacy of Treg cells (Chaudhuri et al., 2020; Yuan et al., 2021; Shi et al., 2023b). Future immunoregulatory therapies may further leverage these biomaterial properties, particularly in controlling the delivery of cytokines, chemokines, and other regulatory factors, thereby demonstrating greater potential in fine-tuning immune responses (Eppler and Jewell, 2019; Madhusudanan et al., 2020; Li et al., 2021c; Lou and Mooney, 2022). In the field of tissue repair and immune engineering, a major future challenge will be to strike a balance between encouraging beneficial immune responses and ensuring that immunoregulatory technologies harmoniously integrate with the native tissue microenvironment. This integration is essential for modifying immune responses and supporting tissue regeneration. Overall, the role of Treg cells in the nervous system and the development of related therapeutic strategies open up an exciting new avenue of research in Treg cell medicine. This research will deepen our understanding of repair mechanisms and advance the development of cell therapies, ultimately leading to precise cellular drug therapies.

Author contributions: *Manuscript conceptualization: JJ, YY, and PY. Literature search: JJ, XY, YZ, HD, XJ, PY, and XD. Writing-original draft: JJ. Writing-review & editing: JJ and PY. Funding acquisition: JJ and PY. Illustration: XY and YZ. Data collection: XY, YZ, HD, XJ, and XD. Supervision: YY and PY. Approval of final manuscript: All authors.*
Conflicts of interest: *The authors declare no conflicts of interest.*
Data availability statement: *Not applicable.*

References

Abdeladhim M, Zhang AH, Kropp LE, Lindrose AR, Venkatesha SH, Mitre E, Scott DW (2019) Engineered ovalbumin-expressing regulatory T cells protect against anaphylaxis in ovalbumin-sensitized mice. Clin Immunol 207:49-54.

Adusei KM, Ngo TB, Sadtler K (2021) T lymphocytes as critical mediators in tissue regeneration, fibrosis, and the foreign body response. Acta Biomater 133:17-33.

Ali N, et al. (2017) Regulatory T cells in skin facilitate epithelial stem cell differentiation. Cell 169:1119-1129. e1111.

Almanan M, Raynor J, Ogunsulire I, Malyshkina A, Mukherjee S, Hummel SA, Ingram JT, Saini A, Xie MM, Alenghat T, Way SS, Deepe GS, Divanovic S, Singh H, Miraldi E, Zajac AJ, Dent AL, Hölscher C, Chougnet C, Hildeman DA (2020) IL-10–producing Tfh cells accumulate with age and link inflammation with age-related immune suppression. Sci Adv 6:eabb0806.

Alves de Lima K, Rustenhoven J, Kipnis J (2020) Meningeal immunity and its function in maintenance of the central nervous system in health and disease. Annu Rev Immunol 38:597-620.

Amaya-Uribe L, Rojas M, Azizi G, Anaya JM, Gershwin ME (2019) Primary immunodeficiency and autoimmunity: A comprehensive review. J Autoimmun 99:52-72.

Arpaia N, Green JA, Moltedo B, Arvey A, Hemmers S, Yuan S, Treuting PM, Rudensky AY (2015) A distinct function of regulatory T cells in tissue protection. Cell 162:1078-1089.

Asboth L, Friedli L, Beauparlant J, Martinez-Gonzalez C, Anil S, Rey E, Baud L, Pidpruzhnykova G, Anderson MA, Shkorbatova P, Batti L, Pagès S, Kreider J, Schneider BL, Barraud Q, Courtine G (2018) Cortico–reticulo–spinal circuit reorganization enables functional recovery after severe spinal cord contusion. Nat Neurosci 21:576-588.

Attias M, Al-Aubodah T, Piccirillo CA (2019) Mechanisms of human FoxP3+ Treg cell development and function in health and disease. Clin Exp Immunol 197:36-51.

Azimi M, Aslani S, Mortezagholi S, Salek A, Javan MR, Rezaiemanesh A, Ghaedi M, Gholamzad M, Salehi E (2016) Identification, isolation, and functional assay of regulatory T cells. Immunol Invest 45:584-602.

Badimon A, et al. (2020) Negative feedback control of neuronal activity by microglia. Nature 586:417-423.

Becker M, Dirschl SM, Scherm MG, Serr I, Daniel C (2024) Niche-specific control of tissue function by regulatory T cells—current challenges and perspectives for targeting metabolic disease. Cell Metab 36:229-239.

Beers DR, Henkel JS, Zhao W, Wang J, Huang A, Wen S, Liao B, Appel SH (2011) Endogenous regulatory T lymphocytes ameliorate amyotrophic lateral sclerosis in mice and correlate with disease progression in patients with amyotrophic lateral sclerosis. Brain 134:1293-1314.

Bollyky PL, Lord JD, Masewicz SA, Evanko SP, Buckner JH, Wight TN, Nepom GT (2007) Cutting edge: high molecular weight hyaluronan promotes the suppressive effects of CD4+CD25+ regulatory T cells. J Immunol 179:744-747.

Bombeiro AL, Lima BHdM, Bonfanti AP, Oliveira ALRd (2020) Improved mouse sciatic nerve regeneration following lymphocyte cell therapy. Mol Immunol 121:81-91.

Burns JC, Hsieh LE, Kumar J, Behnamfar N, Shimizu C, Sivilay N, Tremoulet AH, Franco A (2020) Characterization of circulating immune cells in acute Kawasaki disease suggests exposure to different antigens. Clin Exp Immunol 202:263-272.

Castellani G, Croese T, Peralta Ramos JM, Schwartz M (2023) Transforming the understanding of brain immunity. Science 380:eabo7649.

Cattin A-L, Burden Jemima J, Van Emmenis L, Mackenzie Francesca E, Hoving Julian JA, Garcia Calavia N, Guo Y, McLaughlin M, Rosenberg Laura H, Quereda V, Jamecna D, Napoli I, Parrinello S, Enver T, Ruhrberg C, Lloyd Alison C (2015) Macrophage-induced blood vessels guide schwann cell-mediated regeneration of peripheral nerves. Cell 162:1127-1139.

Chaudhuri O, Cooper-White J, Janmey PA, Mooney DJ, Shenoy VB (2020) Effects of extracellular matrix viscoelasticity on cellular behaviour. Nature 584:535-546.

Che YJ, Ren XH, Wang ZW, Wu Q, Xing K, Zhang M, Xu C, Han D, Yuan S, Zheng SH, Chen YY, Liao XR, Shi F, Zhong XH, Cai X, Cheng SX (2022) Lymph-node-targeted drug delivery for effective immunomodulation to prolong the long-term survival after heart transplantation. Adv Mater 35:e2207227.

Chen L, Xiong Y, Hu Y, Yu C, Liu G (2022a) Regulatory T cell-exosomal miR-142-3p promotes angiogenesis and osteogenesis via TGFBR1/SMAD2 inhibition to accelerate fracture repair. Chem Eng J. 427:131419.

Chen X, Yang X, Yuan P, Jin R, Bao L, Qiu X, Liu S, Liu T, Gooding JJ, Chen W, Liu G, Bai Y, Liu S, Jin Y (2021) Modular immune-homeostatic microparticles promote immune tolerance in mouse autoimmune models. Sci Transl Med 13:eaaw9668.

Chen Y, Qin D, Zou J, Li X, Guo XD, Tang Y, Liu C, Chen W, Kong N, Zhang CY, Tao W (2022b) Living leukocyte-based drug delivery systems. Adv Mater 35:e2207787.

Cheng P, Cheng L, Han H, Li J, Ma C, Huang H, Zhou J, Feng J, Huang Y, Lv Y, Huang H, Wang Y, Hou L, Chen Y, Li G (2022) A pH/H2O2/MMP9 time-response gel system with sparchigh tregs derived extracellular vesicles promote recovery after acute myocardial infarction. Adv Healthc Mater 11:e2200971.

Chung CL, Mak MK, Hallett M (2020) Transcranial magnetic stimulation promotes gait training in Parkinson disease. Ann Neurol 88:933-945.

Cipolletta D, Cohen P, Spiegelman BM, Benoist C, Mathis D (2015) Appearance and disappearance of the mRNA signature characteristic of Treg cells in visceral adipose tissue: age, diet, and PPARγ effects. Proc Natl Acad Sci U S A 112:482-487.

Cohen JN, Gouirand V, Macon CE, Lowe MM, Boothby IC, Moreau JM, Gratz IK, Stoecklinger A, Weaver CT, Sharpe AH, Ricardo-Gonzalez RR, Rosenblum MD (2024) Regulatory T cells in skin mediate immune privilege of the hair follicle stem cell niche. Sci Immunol 9:eadh0152.

Dansokho C, Ait Ahmed D, Aid S, Toly-Ndour C, Chaigneau T, Calle V, Cagnard N, Holzenberger M, Piaggio E, Aucouturier P, Dorothée G (2016) Regulatory T cells delay disease progression in Alzheimer-like pathology. Brain 139:1237-1251.

de la Fuente AG, et al. (2024). Nat Commun 15:1870.

Dial CF, Tune MK, Doerschuk CM, Mock JR (2017) Foxp3(+) regulatory t cell expression of keratinocyte growth factor enhances lung epithelial proliferation. Am J Respir Cell Mol Biol 57:162-173.

Dikiy S, Rudensky AY (2023) Principles of regulatory T cell function. Immunity 56:240-255.

Dittmer M, Young A, O'Hagan T, Eleftheriadis G, Bankhead P, Dombrowski Y, Medina RJ, Fitzgerald DC (2018) Characterization of a murine mixed neuron-glia model and cellular responses to regulatory T cell-derived factors. Mol Brain 11:25.

Dombrowski Y, et al. (2017) Regulatory T cells promote myelin regeneration in the central nervous system. Nat Neurosci 20:674-680.

Eckman N, Nejatfard A, Cavet R, Grosskopf AK, Appel EA (2024) Biomaterials to enhance adoptive cell therapy. Nat Rev Bioeng 2:408-424.

Eppler HB, Jewell CM (2019) Biomaterials as tools to decode immunity. Adv Mater 32:e1903367.

Fan MH, Pi JK, Zou CY, Jiang YL, Li QJ, Zhang XZ, Xing F, Nie R, Han C, Xie HQ (2024) Hydrogel-exosome system in tissue engineering: a promising therapeutic strategy. Bioact Mater 38:1-30.

Feng Y, Peng Y, Jie J, Yang Y, Yang P (2022) The immune microenvironment and tissue engineering strategies for spinal cord regeneration. Front Cell Neurosci 16:969002.

Ferreira LMR, Muller YD, Bluestone JA, Tang Q (2019) Next-generation regulatory T cell therapy. Nat Rev Drug Discov 18:749-769.

Foss DV, Muldoon JJ, Nguyen DN, Carr D, Sahu SU, Hunsinger JM, Wyman SK, Krishnappa N, Mendonsa R, Schanzer EV, Shy BR, Vykunta VS, Allain V, Li Z, Marson A, Eyquem J, Wilson RC (2023) Peptide-mediated delivery of CRISPR enzymes for the efficient editing of primary human lymphocytes. Nat Biomed Eng 7:647-660.

Fujisaki J, Wu J, Carlson AL, Silberstein L, Putheti P, Larocca R, Gao W, Saito TI, Lo Celso C, Tsuyuzaki H, Sato T, Côté D, Sykes M, Strom TB, Scadden DT, Lin CP (2011) In vivo imaging of Treg cells providing immune privilege to the haematopoietic stem-cell niche. Nature 474:216-219.

Gaharwar AK, Singh I, Khademhosseini A (2020) Engineered biomaterials for in situ tissue regeneration. Nat Rev Mater 5:686-705.

Gao W, Kim MW, Dykstra T, Du S, Boskovic P, Lichti CF, Ruiz-Cardozo MA, Gu X, Weizman Shapira T, Rustenhoven J, Molina C, Smirnov I, Merbl Y, Ray WZ, Kipnis J (2024) Engineered T cell therapy for central nervous system injury. Nature 634:693-701.

Georgiev P, Charbonnier LM, Chatila TA (2019) Regulatory T cells: the many faces of Foxp3. J Clin Immunol 39:623-640.

Guo Q, Chen C, Wu Z, Zhang W, Wang L, Yu J, Li L, Zhang J, Duan Y (2022) Engineered PD-1/TIGIT dual-activating cell-membrane nanoparticles with dexamethasone act synergistically to shape the effector T cell/Treg balance and alleviate systemic lupus erythematosus. Biomaterials 285:121517.

Halter S, Aimade L, Barbié M, Brisson H, Rouby JJ, Langeron O, Klatzmann D, Rosenzwajg M, Monsel A (2020) T regulatory cells activation and distribution are modified in critically ill patients with acute respiratory distress syndrome: a prospective single-centre observational study. Anaesth Crit Care Pain Med 39:35-44.

Hickey JW, Dong Y, Chung JW, Salathe SF, Pruitt HC, Li X, Chang C, Fraser AK, Bessell CA, Ewald AJ, Gerecht S, Mao HQ, Schneck JP (2019) Engineering an Artificial T-Cell Stimulating Matrix for Immunotherapy. Adv Mater 31:e1807359.

Ho P, Cahir-McFarland E, Fontenot JD, Lodie T, Nada A, Tang Q, Turka LA, Bluestone JA (2024) Harnessing regulatory T cells to establish immune tolerance. Sci Transl Med 16:eadm8859.

Holl D, Hau WF, Julien A, Banitalebi S, Kalkitsas J, Savant S, Llorens-Bobadilla E, Herault Y, Pavlovic G, Amiry-Moghaddam M, Dias DO, Göritz C (2024) Distinct origin and region-dependent contribution of stromal fibroblasts to fibrosis following traumatic injury in mice. Nat Neurosci 27:1285-1298.

Honaker Y, Hubbard N, Xiang Y, Fisher L, Hagin D, Sommer K, Song Y, Yang SJ, Lopez C, Tappen T, Dam EM, Khan I, Hale M, Buckner JH, Scharenberg AM, Torgerson TR, Rawlings DJ (2020) Gene editing to induce FOXP3 expression in human CD4+T cells leads to a stable regulatory phenotype and function. Sci Transl Med 12:eaay6422.

Hong LTA, Kim YM, Park HH, Hwang DH, Cui Y, Lee EM, Yahn S, Lee JK, Song SC, Kim BG (2017) An injectable hydrogel enhances tissue repair after spinal cord injury by promoting extracellular matrix remodeling. Nat Commun 8:533.

Hu R, Zhang J, Liu X, Huang D, Cao YQ (2021a) Low-dose interleukin-2 and regulatory T cell treatments attenuate punctate and dynamic mechanical allodynia in a mouse model of sciatic nerve injury. J Pain Res 14:893-906.

Hu W, Wang ZM, Feng Y, Schizas M, Hoyos BE, van der Veeken J, Verter JG, Bou-Puerto R, Rudensky AY (2021b) Regulatory T cells function in established systemic inflammation and reverse fatal autoimmunity. Nat Immunol 22:1163-1174.

Hu X, Leak RK, Thomson AW, Yu F, Xia Y, Wechsler LR, Chen J (2018) Promises and limitations of immune cell-based therapies in neurological disorders. Nat Rev Neurol 14:559-568.

Ishihara J, Fukunaga K, Ishihara A, Larsson HM, Potin L, Hosseinchi P, Galliverti G, Swartz MA, Hubbell JA (2017) Matrix-binding checkpoint immunotherapies enhance antitumor efficacy and reduce adverse events. Sci Transl Med 9:eaan0401.

Ishihara J, Ishihara A, Potin L, Hosseinchi P, Fukunaga K, Damo M, Gajewski TF, Swartz MA, Hubbell JA (2018) Improving efficacy and safety of agonistic anti-CD40 antibody through extracellular matrix affinity. Mol Cancer Ther 17:2399-2411.

Ito M, Komai K, Mise-Omata S, Iizuka-Koga M, Noguchi Y, Kondo T, Sakai R, Matsuo K, Nakayama T, Yoshie O, Nakatsukasa H, Chikuma S, Shichita T, Yoshimura A (2019) Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. Nature 565:246-250.

Jang JY, Kim HW, Yan JJ, Kang TK, Lee WB, Kim BS, Yang J (2024) Interleukin-2/anti-interleukin-2 immune complex attenuates cold ischemia-reperfusion injury after kidney transplantation by increasing renal regulatory T cells. Clin Transl Med 14:e1631.

Jang YS, Park SH, Kang SG, Lee JS, Ko HJ, Kim PH (2023) Combined treatment with TGF-β1, retinoic acid, and lactoferrin robustly generate inducible Tregs (iTregs) against high affinity ligand. Immune Netw 23:e37.

Jerome AD, Sas AR, Wang Y, Hammond LA, Wen J, Atkinson JR, Webb A, Liu T, Segal BM (2024) Cytokine polarized, alternatively activated bone marrow neutrophils drive axon regeneration. Nat Immunol 25:957-968.

Jiang Q, Yang G, Liu Q, Wang S, Cui D (2021) Function and role of regulatory T cells in rheumatoid arthritis. Front Immunol 12:626193.

Jie J, Mao D, Cao J, Feng P, Yang P (2022) Customized multifunctional peptide hydrogel scaffolds for CAR-T-cell rapid proliferation and solid tumor immunotherapy. ACS Appl Mater Interfaces 14:37514-37527.

Jin Y, Tang Z, Shang S, Chen Y, Han G, Song M, Zhou J, Zhang H, Ding Y (2023) A nanodisc-paved biobridge facilitates stem cell membrane fusogenicity for intracerebral shuttling and bystander effects. Adv Mater 35:e2302367.

Joetham A, Schedel M, Ning F, Wang M, Takeda K, Gelfand EW (2020) Dichotomous role of TGF-β controls inducible regulatory T-cell fate in allergic airway disease through Smad3 and TGF-β-activated kinase 1. J Allergy Clin Immunol 145:933-946.e4.

Jung D, Shin S, Kang SM, Jung I, Ryu S, Noh S, Choi SJ, Jeong J, Lee BY, Kim KS, Kim CS, Yoon JH, Lee CH, Bucher F, Kim YN, Im SH, Song BJ, Yea K, Baek MC (2022) Reprogramming of T cell-derived small extracellular vesicles using IL2 surface engineering induces potent anti-cancer effects through miRNA delivery. J Extracell Vesicles 11:e12287.

Kalluri R (2024) The biology and function of extracellular vesicles in immune response and immunity. Immunity 57:1752-1768.

Korn T (2023) Foxp3+ regulatory T cells in the central nervous system and other nonlymphoid tissues. Eur J Immunol 53:e2250227.

Krishnan N, Peng FX, Mohapatra A, Fang RH, Zhang L (2023) Genetically engineered cellular nanoparticles for biomedical applications. Biomaterials 296:122065.

Langston PK, Sun Y, Ryback BA, Mueller AL, Spiegelman BM, Benoist C, Mathis D (2023) Regulatory T cells shield muscle mitochondria from interferon-γ–mediated damage to promote the beneficial effects of exercise. Sci Immunol 8:eadi5377.

Lee BC, Lee J (2014) Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. Biochim Biophys Acta 1842:446-462.

Li C, Qi Y, Zhang Y, Chen Y, Feng J, Zhang X (2021a) Artificial engineering of immune cells for improved immunotherapy. Adv Nanobiomed Res 1:2000081.

Li J, Tan J, Martino MM, Lui KO (2018) Regulatory T-cells: potential regulator of tissue repair and regeneration. Front Immunol 9:585.

Li S, Wang L, Gu Y, Lin L, Liu J (2021b) Biomimetic immunomodulation by crosstalk with nanoparticulate regulatory T cells. Matter. doi:10.1016/j.matt.2021.08.015

Li S, Li W, Wu X, Zhang B, Liu L, Yin L (2024) Immune cell-derived extracellular vesicles for precision therapy of inflammatory-related diseases. J Control Release 368:533-547.

Li X, Shou Y, Tay A (2021c) Hydrogels for engineering the immune system. Adv Nanobiomed Res 1:2000073.

Li X, Guan Y, Li C, Zhang T, Meng F, Zhang J, Li J, Chen S, Wang Q, Wang Y, Peng J, Tang J (2022) Immunomodulatory effects of mesenchymal stem cells in peripheral nerve injury. Stem Cell Res Ther 13:18.

Li YJ, Wu JY, Liu J, Xu W, Qiu X, Huang S, Hu XB, Xiang DX (2021d) Artificial exosomes for translational nanomedicine. J Nanobiotechnology 19:242.

Lim WA (2022) The emerging era of cell engineering: Harnessing the modularity of cells to program complex biological function. Science 378:848-852.

Liston A, Pasciuto E, Fitzgerald DC, Yshii L (2023) Brain regulatory T cells. Nat Rev Immunol 24:326-337.

Liu W, Xu B, Zhao S, Han S, Quan R, Liu W, Ji C, Chen B, Xiao Z, Yin M, Yin Y, Dai J, Zhao Y (2023) Spinal cord tissue engineering via covalent interaction between biomaterials and cells. Sci Adv 9:eade8829.

Liu Z, Tong H, Li J, Wang L, Fan X, Song H, Yang M, Wang H, Jiang X, Zhou X, Yuan H, Wang Y (2022) Low-stiffness hydrogels promote peripheral nerve regeneration through the rapid release of exosomes. Front Bioeng Biotechnol 10:922570.

Loffredo LF, Savage TM, Ringham OR, Arpaia N (2024) Treg–tissue cell interactions in repair and regeneration. J Exp Med 221:e20231244.

López-Abente J, Correa-Rocha R, Pion M (2016) Functional mechanisms of treg in the context of HIV infection and the janus face of immune suppression. Front Immunol 7:192.

Lou J, Mooney DJ (2022) Chemical strategies to engineer hydrogels for cell culture. Nat Rev Chem 6:726-744.

Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J (2015) Structural and functional features of central nervous system lymphatic vessels. Nature 523:337-341.

Lu YZ, Nayer B, Singh SK, Alshoubaki YK, Yuan E, Park AJ, Maruyama K, Akira S, Martino MM (2024) CGRP sensory neurons promote tissue healing via neutrophils and macrophages. Nature 628:604-611.

Luan J, Truong C, Vuchkovska A, Guo W, Good J, Liu B, Gang A, Infarinato N, Stewart K, Polak L, Pasolli HA, Andretta E, Rudensky AY, Fuchs E, Miao Y (2024) CD80 on skin stem cells promotes local expansion of regulatory T cells upon injury to orchestrate repair within an inflammatory environment. Immunity 57:1071-1086.e7.

Luo Y, et al. (2021) Single-cell transcriptomic analysis reveals disparate effector differentiation pathways in human Treg compartment. Nat Commun 12:3913.

Machhi J, Kevadiya BD, Muhammad IK, Herskovitz J, Olson KE, Mosley RL, Gendelman HE (2020) Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. Mol Neurodegener 15:32.

Madhusudanan P, Raju G, Shankarappa S (2020) Hydrogel systems and their role in neural tissue engineering. J R Soc Interface 17:20190505.

Mahmoudi N, Wang Y, Moriarty N, Ahmed NY, Dehorter N, Lisowski L, Harvey AR, Parish CL, Williams RJ, Nisbet DR (2024) Neuronal replenishment via hydrogel-rationed delivery of reprogramming factors. ACS Nano 18:3597-3613.

Mao QF, Shang-Guan ZF, Chen HL, Huang K (2019) Immunoregulatory role of IL-2/STAT5/CD4+CD25+Foxp3 Treg pathway in the pathogenesis of chronic osteomyelitis. Ann Transl Med 7:384.

Marangoni F, Zhakyp A, Corsini M, Geels SN, Carrizosa E, Thelen M, Mani V, Prüßmann JN, Warner RD, Ozga AJ, Di Pilato M, Othy S, Mempel TR (2021) Expansion of tumor-associated Treg cells upon disruption of a CTLA-4-dependent feedback loop. Cell 184:3998-4015.e3919.

Marin-Rodero M, Cintado E, Walker AJ, Jayewickreme T, Pinho-Ribeiro FA, Richardson Q, Jackson R, Chiu IM, Benoist C, Stevens B, Trejo JL, Mathis D (2025) The meninges host a distinct compartment of regulatory T cells that preserves brain homeostasis. Sci Immunol 10:eadu2910.

Mathur AN, Zirak B, Boothby IC, Tan M, Cohen JN, Mauro TM, Mehta P, Lowe MM, Abbas AK, Ali N, Rosenblum MD (2019) Treg-cell control of a CXCL5-IL-17 inflammatory axis promotes hair-follicle-stem-cell differentiation during skin-barrier repair. Immunity 50:655-667.e4.

McGettrick HM (2021) Bridging the gap-Immune cells that can repair nerves. Cell Mol Immunol 18:784-786.

Méndez-Lagares G, Pozo-Balado MM, Genebat M, García Pergañeda A, Leal M, Pacheco YM (2012) Severe immune dysregulation affects CD4$^+$CD25(hi)FoxP3$^+$ regulatory T cells in HIV-infected patients with low-level CD4 T-cell repopulation despite suppressive highly active antiretroviral therapy. J Infect Dis 205:1501-1509.

Miragaia RJ, Gomes T, Chomka A, Jardine L, Riedel A, Hegazy AN, Whibley N, Tucci A, Chen X, Lindeman I, Emerton G, Krausgruber T, Shields J, Haniffa M, Powrie F, Teichmann SA (2019) Single-cell transcriptomics of regulatory t cells reveals trajectories of tissue adaptation. Immunity 50:493-504.e7.

Muscella A, Vetrugno C, Cossa LG, Marsigliante S (2019) TGF-β1 activates RSC96 Schwann cells migration and invasion through MMP-2 and MMP-9 activities. J Neurochem 153:525-538.

Ning W, Lv S, Wang Q, Xu Y (2024) The pivotal role of microglia in injury and the prognosis of subarachnoid hemorrhage. Neural Regen Res 20:1829-1848.

Park TY, Jeon J, Lee N, Kim J, Song B, Kim JH, Lee SK, Liu D, Cha Y, Kim M, Leblanc P, Herrington TM, Carter BS, Schweitzer JS, Kim KS (2023) Co-transplantation of autologous Treg cells in a cell therapy for Parkinson's disease. Nature 619:606-615.

Pasciuto E, et al. (2020) Microglia Require CD4 T cells to complete the fetal-to-adult transition. Cell 182:625-640.e24.

Peng B, Rao Y, Wang Y, Duan S, Qi H, Yang J, Zhang H (2024) Immunology reshapes neuroscience, and neuroscience reshapes immunology. Fundam Res 4:199-200.

Qi K, Li N, Zhang Z, Melino G (2018) Tissue regeneration: the crosstalk between mesenchymal stem cells and immune response. Cell Immunol 326:86-93.

Queiroz-Glauss CP, Vieira MS, Gonçalves-Pereira MH, Almeida SS, Freire RH, Gomes MA, Alvarez-Leite JI, Santiago HC (2022) Helminth infection modulates number and function of adipose tissue Tregs in high fat diet-induced obesity. PLoS Negl Trop Dis 16:e0010105.

Quijano-Rubio A, Bhuiyan AM, Yang H, Leung I, Bello E, Ali LR, Zhangxu K, Perkins J, Chun JH, Wang W, Lajoie MJ, Ravichandran R, Kuo YH, Dougan SK, Riddell SR, Spangler JB, Dougan M, Silva DA, Baker D (2023) A split, conditionally active mimetic of IL-2 reduces the toxicity of systemic cytokine therapy. Nat Biotechnol 41:532-540.

Ousman SS, Kubes P (2012) Immune surveillance in the central nervous system. Nat Neurosci 15:1096-101.

Ramanan D, Chowdhary K, Candéias SM, Sassone-Corsi M, Gelineau A, Mathis D, Benoist C (2023) Homeostatic, repertoire and transcriptional relationships between colon T regulatory cell subsets. Proc Natl Acad Sci U S A 120:e2311566120.

Raphael I, Nalawade S, Eagar TN, Forsthuber TG (2015) T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine 74:5-17.

Rau CS, Kuo PJ, Wu SC, Huang LH, Lu TH, Wu YC, Wu CJ, Lin CW, Tsai CW, Hsieh CH (2021) Enhanced nerve regeneration by exosomes secreted by adipose-derived stem cells with or without FK506 stimulation. Int J Mol Sci 22:8545.

Rong L, Lei Q, Zhang XZ (2020) Recent advances on peptide-based theranostic nanomaterials. View 1:20200050.

Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K, Ohkura N (2020) Regulatory T cells and human disease. Annu Rev Immunol 38:541-566.

Santos Roballo KC, Dhungana S, Jiang Z, Oakey J, Bushman JS (2019) Localized delivery of immunosuppressive regulatory T cells to peripheral nerve allografts promotes regeneration of branched segmental defects. Biomaterials 209:1-9.

Savage PA, Klawon DEJ, Miller CH (2020) Regulatory T cell development. Annu Rev Immunol 38:421-453.

Shan BH, Wu FG (2024) Hydrogel-based growth factor delivery platforms: strategies and recent advances. Adv Mater 36:e2210707.

Shanley LC, Mahon OR, Kelly DJ, Dunne A (2021) Harnessing the innate and adaptive immune system for tissue repair and regeneration: Considering more than macrophages. Acta Biomater 133:208-221.

Sheean RK, McKay FC, Cretney E, Bye CR, Perera ND, Tomas D, Weston RA, Scheller KJ, Djouma E, Menon P, Schibeci SD, Marmash N, Yerbury JJ, Nutt SL, Booth DR, Stewart GJ, Kiernan MC, Vucic S, Turner BJ (2018) Association of regulatory T-cell expansion with progression of amyotrophic lateral sclerosis: a study of humans and a transgenic mouse model. JAMA Neurol 75:681-689.

Shi C, Zhang J, Wang H, Chen C, Han M, Gao L, Tang C, Sun P, Zhao X, Guo F, Wang Z, Abdalla M, Yang Z, Liu Y, Li A, Zhang C, Jiang X (2023a) Trojan horse nanocapsule enabled in situ modulation of the phenotypic conversion of Th17 cells to treg cells for the treatment of multiple sclerosis in mice. Adv Mater 35:e2210262.

Shi H, Chi H (2019) Metabolic control of treg cell stability, plasticity, and tissue-specific heterogeneity. Front Immunol 10:2716.

Shi L, Lim JY, Kam LC (2023b) Substrate stiffness enhances human regulatory T cell induction and metabolism. Biomaterials 292:121928.

Shrestha B, Zhang Y, Yu B, Li G, Boucher JC, Beatty NJ, Tsai HC, Wang X, Mishra A, Sweet K, Lancet JE, Kelley L, Davila ML (2020) Generation of antitumor T cells for adoptive cell therapy with artificial antigen presenting cells. J Immunother 43:79-88.

Silva DA, et al. (2019) De novo design of potent and selective mimics of IL-2 and IL-15. Nature 565:186-191.

Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science 341:569-573.

Stym-Popper G, Matta K, Chaigneau T, Rupra R, Demetriou A, Fouquet S, Dansokho C, Toly-Ndour C, Dorothée G (2023) Regulatory T cells decrease C3-positive reactive astrocytes in Alzheimer-like pathology. J Neuroinflammation 20:64.

Tajima A, Liu W, Pradhan I, Bertera S, Bagia C, Trucco M, Meng WS, Fan Y (2015) Bioengineering mini functional thymic units with EAK16-II/EAKIIH6 self-assembling hydrogel. Clin Immunol 160:82-89.

Tang L, Zheng Y, Melo MB, Mabardi L, Castano AP, Xie YQ, Li N, Kudchodkar SB, Wong HC, Jeng EK, Maus MV, Irvine DJ (2018) Enhancing T cell therapy through TCR-signaling-responsive nanoparticle drug delivery. Nat Biotechnol 36:707-716.

Thatte AS, Hamilton AG, Nachod BE, Mukalel AJ, Billingsley MM, Palanki R, Swingle KL, Mitchell MJ (2023) mRNA lipid nanoparticles for ex vivo engineering of immunosuppressive T cells for autoimmunity Therapies. Nano Lett 23:10179-10188.

Tian Y, Zhang F, Qiu Y, Wang S, Li F, Zhao J, Pan C, Tao Y, Yu D, Wei W (2021) Reduction of choroidal neovascularization via cleavable VEGF antibodies conjugated to exosomes derived from regulatory T cells. Nat Biomed Eng 5:968-982.

Tiemessen MM, Jagger AL, Evans HG, van Herwijnen MJC, John S, Taams LS (2007) CD4+CD25+Foxp3+regulatory T cells induce alternative activation of human monocytes/macrophages. Proc Natl Acad Sci U S A 104:19446-19451.

Ullah M, Kodam SP, Mu Q, Akbar A (2021) Microbubbles versus extracellular vesicles as therapeutic cargo for targeting drug delivery. ACS Nano15:3612-3620.

Varadarajan SG, Hunyara JL, Hamilton NR, Kolodkin AL, Huberman AD (2022) Central nervous system regeneration. Cell 185:77-94.

Veerman RE, Güçlüler Akpinar G, Eldh M, Gabrielsson S (2019) Immune cell-derived extracellular vesicles - functions and therapeutic applications. Trends Mol Med 25:382-394.

Wallen M, Aqil F, Kandimalla R, Jeyabalan J, Auwardt S, Tyagi N, Schultz DJ, Spencer W, Gupta RC (2022) A model system for antiviral siRNA therapeutics using exosome-based delivery. Mol Ther Nucleic Acids 29:691-704.

Wang AYL, Loh CYY, Shen HH, Hsieh SY, Wang IK, Lee CM, Lin CH (2020) Human Wharton's jelly mesenchymal stem cell-mediated sciatic nerve recovery is associated with the upregulation of regulatory T cells. Int J Mol Sci 21:6310.

Wang J, Xie L, Yang C, Ren C, Zhou K, Wang B, Zhang Z, Wang Y, Jin K, Yang GY (2015) Activated regulatory T cell regulates neural stem cell proliferation in the subventricular zone of normal and ischemic mouse brain through interleukin 10. Front Cell Neurosci 9:361.

Wang J, Wang M, Jiang N, Ding S, Peng Q, Zheng L (2023a) Emerging chemical engineering of exosomes as "bioscaffolds" in diagnostics and therapeutics. Genes Dis 10:1494-1512.

Wang J, Liu X, Wang Y, Zhang Y, Gao R, Gao Y, Kong P, Huangfu Y, Zhang C, Feng Z, Huang P, Yang P, Wang W (2024a) Pro-regenerative glycopeptide hydrogel activates type 2 immune response for wound healing via macrophage-T cell crosstalk. Adv Funct Mater 34:2307711.

Wang M, Chen F, Wang J, Zeng Z, Yang Q, Shao S (2018) Th17 and Treg lymphocytes in obesity and Type 2 diabetic patients. Clin Immunol 197:77-85.

Wang R, Wu XX, Tian Z, Hu T, Cai C, Wu GP, Jiang GB, Liu B (2023b) Sustained release of hydrogen sulfide from anisotropic ferrofluid hydrogel for the repair of spinal cord injury. Bioact Mater 23:118-128.

Wang R, Bai J (2024) Pharmacological interventions targeting the microcirculation following traumatic spinal cord injury. Neural Regen Res 19:35-42.

Wang S, Yao Y, Song L, Zhai Z, Li S, Wang Z, Shen L, Zhu Y, Liu W, Gao C (2024b) ROS-responsive drug-releasing injectable microgels for ameliorating myocardial infarction. Biomaterials 307:122534.

Wang Y, Chang F, Liu P, Peng J, Han GH, Ding X, Wei S, Gao G, Huang K (2019) Role of macrophages in peripheral nerve injury and repair. Neural Regen Res 14: 1335-1342.

Wang Y, Xue F, Li Y, Lin L, Wang Y, Zhao S, Zhao X, Liu Y, Tan J, Li G, Xiao H, Yan J, Tian H, Liu M, Zhang Q, Ba Z, He L, Zhao W, Zhu C, Zeng W (2022) Programming of regulatory t cells in situ for nerve regeneration and long-term patency of vascular grafts. Research 2022:9826426.

Wang Y, Li Z, Mo F, Chen-Mayfield TJ, Saini A, LaMere AM, Hu Q (2023c) Chemically engineering cells for precision medicine. Chem Soc Rev 52:1068-1102.

Wen J, Zhou Y, Wang J, Chen J, Yan W, Wu J, Yan J, Zhou K, Xiao Y, Wang Y, Xia Q, Cai W (2017) Interactions between Th1 cells and Tregs affect regulation of hepatic fibrosis in biliary atresia through the IFN-γ/STAT1 pathway. Cell Death Differ 24:997-1006.

Worthington John J, Kelly A, Smedley C, Bauché D, Campbell S, Marie Julien C, Travis Mark A (2015) Integrin αvβ8-mediated TGF-β activation by effector regulatory T cells is essential for suppression of T-cell-mediated inflammation. Immunity 42:903-915.

Wu Y, Liu Y, Wang T, Jiang Q, Xu F, Liu Z (2022) Living cell for drug delivery. Eng Regen 3:131-148.

Xia Y, Gao D, Wang X, Liu B, Shan X, Sun Y, Ma D (2024) Role of Treg cell subsets in cardiovascular disease pathogenesis and potential therapeutic targets. Front Immunol 15:1331609.

Xie F, Shen B, Luo Y, Zhou H, Xie Z, Zhu S, Wei X, Chang Z, Zhu Z, Ding C, Jin K, Yang C, Batzu L, Chaudhuri KR, Chan LL, Tan EK, Wang Q (2024a) Repetitive transcranial magnetic stimulation alleviates motor impairment in Parkinson's disease: association with peripheral inflammatory regulatory T-cells and SYT6. Mol Neurodegener 19:80.

Xie Y, Jin C, Sang H, Liu W, Wang J (2023) Ivermectin protects against experimental autoimmune encephalomyelitis in mice by modulating the Th17/Treg balance involved in the IL-2/STAT5 pathway. Inflammation 46:1626-1638.

Xie Y, Chen L, Chen J, Chen Y (2024b) Calcitriol restrains microglial M1 polarization and alleviates dopaminergic degeneration in hemiparkinsonian mice by boosting regulatory T-cell expansion. Brain Behav 14:e3373.

Xuan K, Li B, Guo H, Sun W, Kou X, He X, Zhang Y, Sun J, Liu A, Liao L, Liu S, Liu W, Hu C, Shi S, Jin Y (2018) Deciduous autologous tooth stem cells regenerate dental pulp after implantation into injured teeth. Sci Transl Med 10:eaaf3227.

Yan Y, Ramanan D, Rozenberg M, McGovern K, Rastelli D, Vijaykumar B, Yaghi O, Voisin T, Mosaheb M, Chiu I, Itzkovitz S, Rao M, Mathis D, Benoist C (2021) Interleukin-6 produced by enteric neurons regulates the number and phenotype of microbe-responsive regulatory T cells in the gut. Immunity 54:499-513. e495.

Yang H, et al. (2022) Adoptive therapy with amyloid-β specific regulatory T cells alleviates Alzheimer's disease. Theranostics 12:7668-7680.

Yang L, Cao J, Du Y, Zhang X, Hong W, Peng B, Wu J, Weng Q, Wang J, Gao J (2024) Initial IL-10 production dominates the therapy of mesenchymal stem cell scaffold in spinal cord injury. Theranostics 14:879-891.

Yang P, Song H, Qin Y, Huang P, Zhang C, Kong D, Wang W (2018) Engineering dendritic-cell-based vaccines and PD-1 blockade in self-assembled peptide nanofibrous hydrogel to amplify antitumor T-cell immunity. Nano Lett 18:4377-4385.

Yang P, Song H, Feng Z, Wang C, Huang P, Zhang C, Kong D, Wang W (2019) Synthetic, Supramolecular, and Self-Adjuvanting CD8+ T-Cell Epitope Vaccine Increases the Therapeutic Antitumor Immunity. Adv Ther 2:1900010.

Yang P, Cao X, Cai H, Feng P, Chen X, Zhu Y, Yang Y, An W, Yang Y, Jie J (2021a) The exosomes derived from CAR-T cell efficiently target mesothelin and reduce triple-negative breast cancer growth. Cell Immunol 360:104262.

Yang P, Peng Y, Feng Y, Xu Z, Feng P, Cao J, Chen Y, Chen X, Cao X, Yang Y, Jie J (2021b) Immune cell-derived extracellular vesicle-new strategies in cancer immunotherapy. Front Immunol 12:771551.

Yang P, Peng Y, Dai X, Jie J, Kong D, Gu X, Yang Y (2023a) Bionic peptide scaffold in situ polarization and recruitment of M2 macrophages to promote peripheral nerve regeneration. Bioact Mater 30:85-97.

Yang Q, Su S, Liu S, Yang S, Xu J, Zhong Y, Yang Y, Tian L, Tan Z, Wang J, Yu Z, Shi Z, Liang F (2023b) Exosomes-loaded electroconductive nerve dressing for nerve regeneration and pain relief against diabetic peripheral nerve injury. Bioact Mater 26:194-215.

Yang X, Qi Y, Wang C, Zwang TJ, Rommelfanger NJ, Hong G, Lieber CM (2023c) Laminin-coated electronic scaffolds with vascular topography for tracking and promoting the migration of brain cells after injury. Nat Biomed Eng 7:1282-1292.

Yi J, Jung J, Hong SW, Lee JY, Han D, Kim KS, Sprent J, Surh CD (2019) Unregulated antigen-presenting cell activation by T cells breaks self tolerance. Proc Natl Acad Sci U S A 116:1007-1016.

Yin W, Ma H, Qu Y, Ren J, Sun Y, Guo ZN, Yang Y (2024) Exosomes: the next-generation therapeutic platform for ischemic stroke. Neural Regen Res 20:1221-1235.

Yuan DJ, Shi L, Kam LC (2021) Biphasic response of T cell activation to substrate stiffness. Biomaterials 273:120797.

Zamecnik CR, Levy ES, Lowe MM, Zirak B, Rosenblum MD, Desai TA (2020) An injectable cytokine trap for local treatment of autoimmune disease. Biomaterials 230:119626.

Zemmour D, Zilionis R, Kiner E, Klein AM, Mathis D, Benoist C (2018) Single-cell gene expression reveals a landscape of regulatory T cell phenotypes shaped by the TCR. Nat Immunol 19:291-301.

Zeng J, Gu C, Sun Y, Chen X (2023) Engineering of M2 macrophages-derived exosomes via click chemistry for spinal cord injury repair. Adv Healthc Mater 12:e2203391.

Zhang B, et al. (2021a) Site-specific PEGylation of interleukin-2 enhances immunosuppression via the sustained activation of regulatory T cells. Nat Biomed Eng 5:1288-1305.

Zhang C, Li D, Hu H, Wang Z, An J, Gao Z, Zhang K, Mei X, Wu C, Tian H (2021b) Engineered extracellular vesicles derived from primary M2 macrophages with anti-inflammatory and neuroprotective properties for the treatment of spinal cord injury. J Nanobiotechnology 19:373.

Zhang D, Chia C, Jiao X, Jin W, Kasagi S, Wu R, Konkel JE, Nakatsukasa H, Zanvit P, Goldberg N, Chen Q, Sun L, Chen ZJ, Chen W (2017) D-mannose induces regulatory T cells and suppresses immunopathology. Nat Med 23:1036-1045.

Zhang L, et al. (2022) Programmable bispecific nano-immunoengager that captures T cells and reprograms tumor microenvironment. Nano Lett22:6866-6876.

Zhang Q, Jeppesen DK, Higginbotham JN, Franklin JL, Coffey RJ (2023a) Comprehensive isolation of extracellular vesicles and nanoparticles. Nat Protoc 18:1462-1487.

Zhang S, Kim B, Zhu X, Gui X, Wang Y, Lan Z, Prabhu P, Fond K, Wang A, Guo F (2020) Glial type specific regulation of CNS angiogenesis by HIFα-activated different signaling pathways. Nat Commun 11:2027.

Zhang W, Chen Y, Zhao Z, Zheng H, Wang S, Liao Z, Sheng T, Zhao S, Hou W, Yu X, He F, Yu J, Zhang Y, Gu Z (2023b) Adoptive Treg therapy with metabolic intervention via perforated microneedles ameliorates psoriasis syndrome. Sci Adv 9:eadg6007.

Zhang W, Wan Z, Qu D, Sun W, Zhang L, Liang Y, Pan L, Jiang H, Ye Z, Wei M, Yuan L, Yang G, Jin F (2024) Profibrogenic macrophage-targeted delivery of mitochondrial protector via exosome formula for alleviating pulmonary fibrosis. Bioact Mater 32:488-501.

Zhang ZT, Zhang DY, Xie K, Wang CJ, Xu F (2021c) Luteolin activates Tregs to promote IL-10 expression and alleviating caspase-11-dependent pyroptosis in sepsis-induced lung injury. Int Immunopharmacol 99:107914.

Zhao X, Deng H, Feng Y, Wang Y, Yao X, Ma Y, Zhang L, Jie J, Yang P, Yang Y (2024) Immune-cell-mediated tissue engineering strategies for peripheral nerve injury and regeneration. J Mater Chem B 12:2217-2235.

Zhong JX, Raghavan P, Desai TA (2022) Harnessing biomaterials for immunomodulatory-driven tissue engineering. Regen Eng Transl Med 9:224-239.

Zhou X, Xie F, Wang L, Zhang L, Zhang S, Fang M, Zhou F (2020) The function and clinical application of extracellular vesicles in innate immune regulation. Cell Mol Immunol 17:323-334.

Zhu F, Wang A, Li Y, Liang R, Li D, Li B (2017) Adipose tissue-resident regulatory T cells. Adv Exp Med Biol 1011:153-162.

Zhu I, Liu R, Garcia JM, Hyrenius-Wittsten A, Piraner DI, Alavi J, Israni DV, Liu B, Khalil AS, Roybal KT (2022) Modular design of synthetic receptors for programmed gene regulation in cell therapies. Cell 185:1431-1443. e16.

C-Editor: Zhao M; S-Editors: Wang J, Li CH; L-Editor: Song LP; T-Editor: Jia Y