

SPECIAL ISSUE: Oral Regional Immune Mechanisms and Systemic Homeostasis

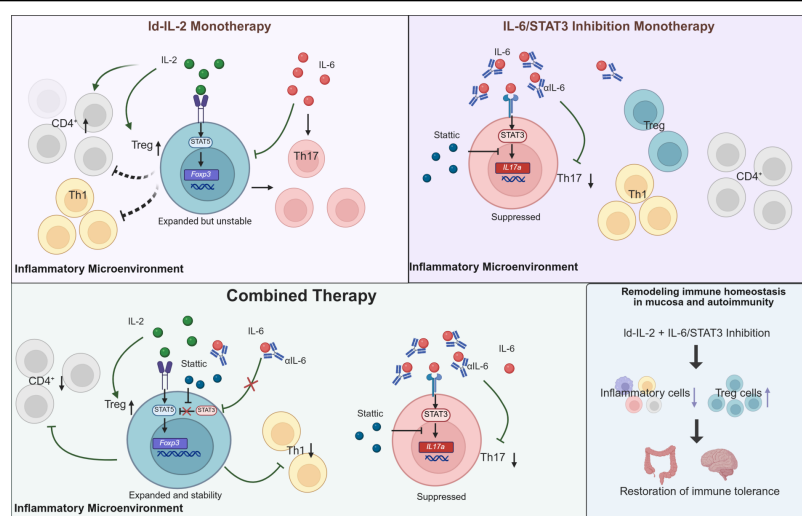
Remodeling immune homeostasis in mucosal inflammation and autoimmunity by combining low-dose IL-2 therapy and inhibition of IL-6/STAT3 signaling

Hao Cheng¹, Hantian Liang¹, Jianan Zhang¹, Zhenhong Li¹, Xiao Ma¹, and Dunfang Zhang¹ ✉¹ Department of Biotherapy, State Key Laboratory of Biotherapy and Cancer Center, Collaborative Innovation Center of Biotherapy, West China Hospital, Sichuan University, Chengdu, 610041, ChinaCite This: *Oral Sci Homeost Med*, 2026, 2, 9610052

Read Online

ABSTRACT: Targeting regulatory T (Treg) cells represents a promising strategy for reshaping peripheral immune homeostasis and treating inflammatory diseases, such as inflammatory bowel disease and multiple sclerosis. However, the two main strategies used for targeting Treg cells, which include adoptive Treg cell therapy and low-dose interleukin (IL)-2 treatment, have not achieved satisfactory clinical outcomes. Multiple studies have indicated that targeting Treg cells alone cannot effectively restore immune homeostasis. Here, we showed that the combination of low-dose IL-2 therapy and inhibition of IL-6/STAT3 signaling exhibits better therapeutic effects in the treatment of inflammatory bowel disease and experimental autoimmune encephalomyelitis. This combination therapy restored immune homeostasis and alleviated inflammation by significantly increasing Treg cells and suppressing effector T cells, such as T helper 1 and T helper 17 cells. Overall, our data indicate that the combination of low-dose IL-2 therapy and inhibition of IL-6/STAT3 signaling warrants further investigation as a means of remodeling immune homeostasis to treat mucosal inflammation and autoimmune disorders.

KEYWORDS: immune homeostasis, regulatory T cells, IL-2 therapy, IL-6 signaling inhibition, autoimmunity



1 Introduction

Immune homeostasis refers to the dynamic equilibrium between inflammatory responses and immune tolerance of the immune system. It ensures that the immune system can effectively identify and eliminate abnormal antigens, such as pathogens and damaged cells, while preventing excessive immune responses to the body's own tissues, symbiotic microorganisms, or harmless antigens, thereby avoiding tissue damage. A stable balance between regulatory T (Treg) and effector T (Teff) cells is important for maintaining immune homeostasis in the body^[1].

Inflammatory bowel disease (IBD) and autoimmune disorders (ADs) are characterized by disruptions in the balance between

regulatory and effector immune responses. The core mechanism involves impaired Treg cell function or excessive Teff cell activation, which ultimately leads to chronic inflammation and tissue damage. Recent preliminary successes of Treg cell-based therapies for IBD and ADs have confirmed that enhancing the number and function of Treg cells through exogenous means represents a promising therapeutic strategy for correcting immune imbalances and restoring tolerance^[2]. The emergence of low-dose interleukin (IL)-2 (Id-IL-2) therapy embodies this concept, as it aims to selectively expand and activate Treg cells to re-establish peripheral immune homeostasis. Although Id-IL-2 monotherapy has shown positive outcomes, its efficacy remains limited, with incomplete responses observed in some patients^[3]. These findings indicate that simply increasing the number of Treg cells often fails to effectively restore immune homeostasis.

In the inflammatory microenvironment, strong antigenic stimulation combined with pro-inflammatory cytokines, such as IL-6 and interferon-gamma (IFN- γ), can drive the loss of suppressive

Received: March 9, 2026; Revised: April 23, 2026

Accepted: May 7, 2026

✉ Address correspondence to Dunfang Zhang, izdf@163.com

function in Treg cells and even confer pro-inflammatory properties^[4]. In fact, targeting IL-6 signaling is also a potential approach for inhibiting IBD and ADs. However, clinical trials have shown that the use of an anti-IL-6 neutralizing antibody (αIL-6) alone does not achieve the ideal therapeutic effect in IBD and systemic lupus erythematosus^[5,6]. Therefore, we hypothesize that combining ld-IL-2 therapy with inhibition of IL-6 signaling may constitute a superior immunomodulatory strategy for improving therapeutic outcomes by more effectively restoring immune homeostasis. In the present study, we used two disease models, IBD and experimental autoimmune encephalomyelitis (EAE), to verify the efficacy of this strategy in restoring mucosal immune homeostasis and suppressing autoimmunity.

2 Materials and methods

2.1 Mice

All mouse lines had the C57BL/6J genetic background. CD45.1⁺ mice were obtained from The Jackson Laboratory (Bar Harbor, ME, USA), and C57BL/6 and *Rag1*^{−/−} mice obtained from Shanghai Model Organisms (Shanghai, China). All mice were housed in a specific pathogen-free animal facility at Sichuan University, with free access to food and water. All animal experimental procedures were reviewed and approved by the Animal Care and Use Committee of West China Hospital, Sichuan University (20211212A, 20220620002).

2.2 T cell-transfer model of IBD

Rag1^{−/−} mice (6–8-weeks-old) were intravenously injected with either 0.6×10^6 CD4⁺CD25[−]CD45RB^{hi} T cells isolated from the spleens of C57BL/6 mice or a co-transfer of the same T cell population along with 5×10^4 CD4⁺CD25⁺ Treg cells isolated from CD45.1 mouse spleens. The day of cell transfer was designated as Day 0. In the anti-IL-6 treatment group, mice received intraperitoneal injections of 100 µg anti-IL-6 antibody (MP5-20F3; Bio X Cell, Lebanon, NH, USA) every four days starting from Day 14 until the end of the experiment. For the ld-IL-2 treatment group, mice were administered 3 µg recombinant human IL-2 (100-21 C; PeproTech, Cranbury, NJ, USA) every two weeks starting on Day 14 until sacrifice. Body weight was measured every five days throughout the experimental period to monitor colitis development. After euthanasia, the colon, spleen, and mesenteric lymph nodes were collected for histopathological and immunological analyses.

2.3 Induction and assessment of EAE

EAE was induced in 8–10-weeks-old male mice via subcutaneous immunization. Specifically, the mice received a subcutaneous injection of 200 µg MOG_{35–55} peptide (163913-87-9; QYAOBIO, Shanghai, China) emulsified in a 1:1 mixture of phosphate-buffered saline and complete Freund's adjuvant supplemented with 2 mg/mL heat-inactivated *Mycobacterium tuberculosis* H37Ra (231141; Difco, Franklin Lakes, NJ, USA). Additionally, the mice were intraperitoneally administered 200 ng pertussis toxin (P7208; Sigma-Aldrich, St. Louis, MO, USA) on the day of immunization and 48 h later. The clinical signs of EAE were assessed daily and scored on a standardized 0–5 scale as follows: 0, no symptoms; 0.5, partial tail weakness; 1, tail paralysis; 1.5, mild gait instability; 2, hind limb paresis; 2.5, paralysis of one hind limb; 3, paralysis of

both hind limbs; 3.5, hind limb paralysis with mild forelimb weakness; 4, paralysis of one forelimb; 4.5, paralysis of both forelimbs; and 5, moribund or dead.

2.4 Preparation of central nervous system mononuclear cells

Brain and spinal cord tissues were harvested and meticulously minced with scissors. The tissue fragments were then subjected to enzymatic digestion for 30 min at 37°C using a solution containing collagenase IV (4 mg/mL) and DNase I (2 mg/mL). Subsequently, the digest was processed through a 70-µm cell strainer to obtain a single-cell suspension. Mononuclear cells were then isolated via density gradient centrifugation using a 30/70% Percoll gradient (GE Healthcare, Chicago, IL, USA).

2.5 Isolation of colonic lamina propria lymphocytes

Intraepithelial lymphocytes were separated using a magnetic stirrer in Dulbecco's Modified Eagle's medium containing 5% fetal bovine serum, dithiothreitol (5 mM), and ethylenediaminetetraacetic acid (1 mM). Subsequently, the remaining tissue fragments were subjected to a second enzymatic digestion in a solution containing 0.2 mg/mL Liberase TL (05401020001; Roche, Basel, Switzerland) and 0.5 mg/mL DNase I, with vigorous shaking at 37°C. The final digest was then filtered through a 70-µm cell strainer to obtain a single-cell suspension.

2.6 Flow cytometry

Dead cells were excluded via labeling with the Zombie Yellow Fixable Viability Kit (423104; BioLegend, San Diego, CA, USA). For surface marker analysis, cells were incubated with the appropriate fluorescent-conjugated antibodies at 4°C for 20 min. To detect cytokine expression, cells were stimulated with phorbol 12-myristate 13-acetate (5 ng/mL) and ionomycin (1 µg/mL) for 4 h in culture medium supplemented with GolgiStop (555029; BD Biosciences, San Jose, CA, USA). Subsequently, the cells were fixed and permeabilized using the Fixation/Permeabilization Solution Kit (554722; BD Biosciences) prior to antibody staining. For transcription factor analysis, the cells were fixed and permeabilized for 1 h with the Foxp3/Transcription Factor Staining Buffer Set (00-5523-00; Thermo Fisher Scientific, Waltham, MA, USA) before antibody staining.

2.7 Statistics and reproducibility

The mice were randomly assigned to different experimental groups, and two independent experiments conducted. Statistical analyses were performed using GraphPad Prism (v.8.4.1; GraphPad Software, San Diego, CA, USA). All results are presented as the mean ± standard error of the mean. Survival curves were analyzed using the log-rank test, whereas body weight curves were analyzed via two-way analysis of variance followed by Sidak's multiple-comparisons test; unpaired two-tailed Student's *t*-tests were applied for all remaining comparisons. A *p*-value <0.05 was considered statistically significant.

3 Results

We initially evaluated the combination therapy in a mouse model of T cell-mediated IBD. To demonstrate that the main mechanism of ld-IL-2 therapy involves the promotion of Treg cell expansion,

mice with IBD induced by T cell transfer were treated with ld-IL-2. The results showed that ld-IL-2 treatment alone not only failed to improve the condition but also resulted in a mortality rate higher than that of the untreated group (Fig. 1a). This confirmed that the therapeutic effect of IL-2 mainly depends on the expansion of Treg cells and highlighted the risk of IL-2-induced nontargeted activation of effector cells in exacerbating inflammation. Moreover, the combined ld-IL-2 and αIL-6 therapy had similar outcomes to those observed when using αIL-6 alone, showing only limited therapeutic effects and failing to effectively reduce the weight loss of mice or improve their colon pathological scores (Fig. 1b, 1c). These findings further confirm the importance of Treg cells in ld-IL-2 therapy. Meanwhile, the adoptive transfer of a small number of Treg cells alone, while capable of suppressing disease development, failed to support normal weight gain in the mice. In contrast, when Treg cells were combined with ld-IL-2 and αIL-6 therapy, this triple combination significantly reduced body weight loss compared to Treg cells alone, αIL-6 alone, or the ld-IL-2+αIL-6 group ($p < 0.05$ for each comparison) (Fig. 1b). Additionally, this combination group showed relatively normal crypt architecture and milder leukocyte infiltration (Fig. 1c).

This enhanced therapeutic efficacy was tightly associated with the profound remodeling of T cell subset balance within the tissue microenvironment. Flow cytometric analysis revealed that the

combined ld-IL-2 and αIL-6 therapy most potently suppressed the proportion of effector CD4⁺ T cells in colonic tissues while concomitantly elevating the frequency of total CD4⁺Foxp3⁺ Treg cells when Treg cells were present in the inflammatory microenvironment (Fig. 1d–1f). Notably, Treg cell therapy increased the frequency of CD4⁺IL-17A⁺ T (Th17) cells among the Teff cells (Fig. 1g, 1h). This observation aligns with our prior report demonstrating that Treg cells promote pathogenic Th17 cell differentiation under inflammatory conditions⁷. Importantly, the combined ld-IL-2 and αIL-6 therapy, together with Treg cell therapy, completely abrogated this adverse effect and achieved the most robust suppression of CD4⁺IFN-γ⁺ T (Th1) cells (Fig. 1i). These results demonstrate that the combined ld-IL-2 and αIL-6 therapy can achieve better therapeutic effects; however, similar to ld-IL-2 therapy alone, the combined therapy relies on Treg cell expansion in the inflammatory microenvironment.

As the modeling of IBD relies on the adoptive transfer of pro-inflammatory T cells without Treg cells, when conducting research on the combined ld-IL-2 and αIL-6 therapy, additional Treg cells need to be injected. In contrast to the IBD model, the EAE model retains an intact endogenous Treg pool. Therefore, when studying the therapeutic effects of the combined ld-IL-2 and αIL-6 therapy, no additional Treg cells need to be injected, making the findings more physiologically significant. To further evaluate whether the

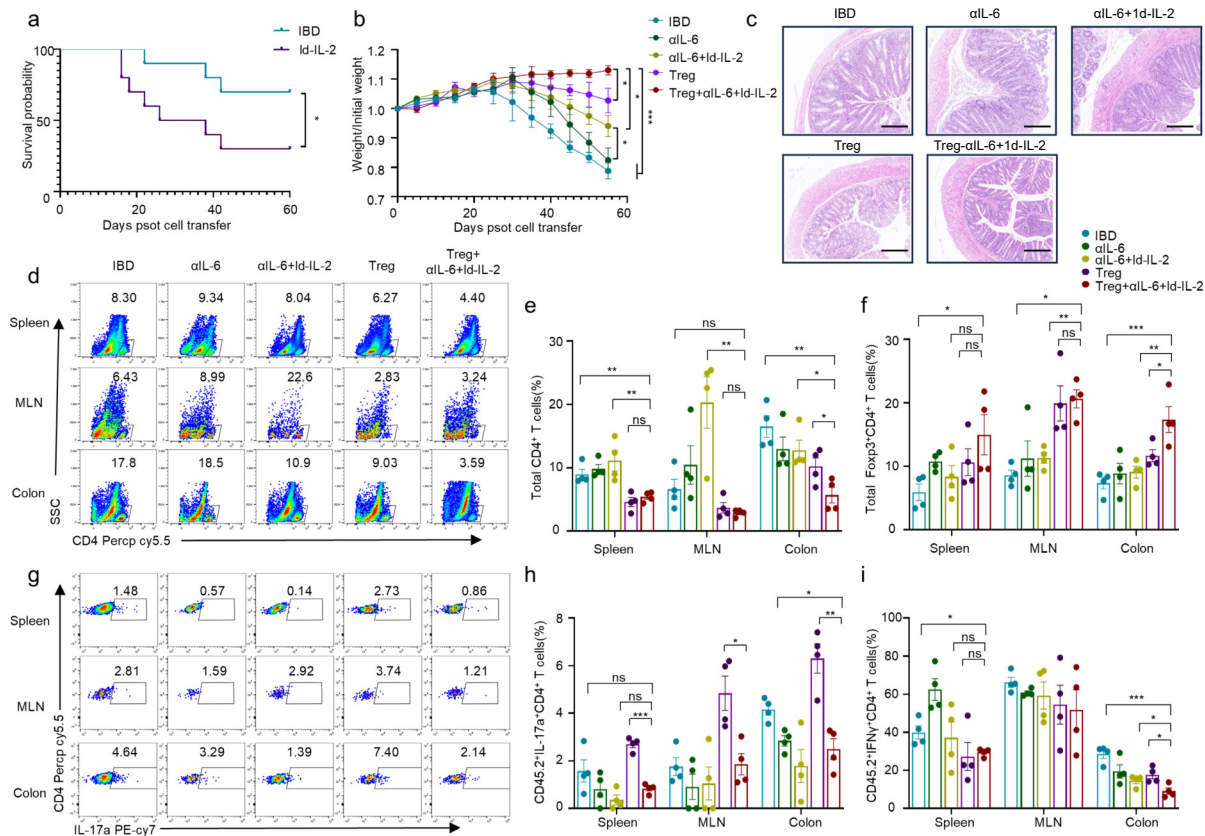


Figure 1 Combination of low-dose interleukin-2 (ld-IL-2) therapy and inhibition of IL-6 signaling remodels immune homeostasis in IBD. Therapeutic effects of ld-IL-2, IL-6 neutralizing antibody (αIL-6), adoptive regulatory T (Treg) cells, ld-IL-2+αIL-6, and Treg+ld-IL-2+αIL-6 therapies in mice with IBD. (a) Survival curves of *Rag1*^{-/-} mice after T cell transfer ($n = 10$), with data pooled from two independent experiments. (b) Body weight curves of *Rag1*^{-/-} mice after T cell transfer ($n = 4$); data are representative of two independent experiments. (c) Representative histological images of colonic sections derived from IBD mice. Scale bar, 500 μm. (d–i) Representative flow cytometry plots and bar graphs showing the frequencies of total CD4⁺ T cells (d, e), total CD4⁺Foxp3⁺ Treg cells (f), CD45.2⁺CD4⁺IL-17A⁺ T helper 17 (Th17) cells (g, h), and CD45.2⁺CD4⁺IFN-γ⁺ T helper 1 (Th1) cells (i) in the spleen, mesenteric lymph nodes (MLN), and colon tissues of the indicated mice ($n = 4$). Data are representative of two independent experiments. Data are presented as mean ± sem. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ns, not significant.

combined ld-IL-2 therapy and inhibition of IL-6 signaling could better restore immune tolerance, the EAE mice were treated with ld-IL-2 and Stattic, a small-molecule STAT3 inhibitor that can effectively cross the blood–brain barrier (Fig. 2a). Consistent with the findings in the IBD model, ld-IL-2 therapy alone had no impact on disease progression, and Stattic alone showed a partial therapeutic effect (Fig. 2b, 2c). The combination of ld-IL-2 and Stattic, however, resulted in the most significant improvement in clinical scores and the alleviation of inflammatory infiltration in the central nervous system (CNS) (Fig. 2b, 2c). Specifically, the combination group delayed disease onset to day 15, compared with day 11 in the EAE group and day 12 in both the ld-IL-2 alone and Stattic alone groups. Moreover, the peak clinical score was reduced to 0.5 in the combination group, versus 2 in the EAE group, 1.8 in the ld-IL-2 alone group, and 1.2 in the Stattic alone group.

Further analysis of CNS-infiltrating immune cells revealed that although ld-IL-2 monotherapy increased the proportion of Treg cells, it did not significantly reduce the number of CD45⁺ immune cells (Fig. 2d–2f). This suggests that in a highly inflammatory setting, a mere increase in Treg numbers may be insufficient to ensure their function, as their suppressive capacity may be compromised by the inflammatory microenvironment. In contrast, the combination of Stattic and ld-IL-2 not only synergistically promoted a higher Treg proportion but also more effectively reduced the total infiltration of CD45⁺ immune cells in the CNS

(Fig. 2d–2f). At the effector cell level, ld-IL-2 monotherapy partially reduced the proportion of Th1 cells but did not lower that of Th17 cells (Fig. 2g–2i), which may partly explain the lack of efficacy observed in some clinical trials of ld-IL-2 monotherapy⁸¹. In contrast, combination therapy significantly reduced the proportion of both Th17 and Th1 cells (Fig. 2g–2i), which corroborates our findings in the IBD model and collectively confirms the versatility of this strategy in suppressing the key pathogenic cells that drive autoimmune diseases across distinct tissues. Taken together, these data demonstrate that the combined ld-IL-2 therapy and inhibition of IL-6/STAT3 signaling has a better therapeutic effect.

4 Discussion

Our findings highlight the limitations of ld-IL-2 monotherapy and inhibition of IL-6 signaling. The failure of ld-IL-2 monotherapy in both disease models, coupled with its association with increased mortality in the IBD setting, echoes the clinical concerns of its potential off-target effects. Even at moderate doses, IL-2 promotes the expansion of other immune cell subsets, including CD4⁺ and CD8⁺ T eff and natural killer cells, a property attributed to pleiotropy⁸². While inhibition of IL-6 signaling as a monotherapy exhibits partial therapeutic efficacy, not all patients with autoimmune diseases derive benefits, as observed in clinical settings⁸³. Furthermore, higher doses of IL-6-targeting agents may

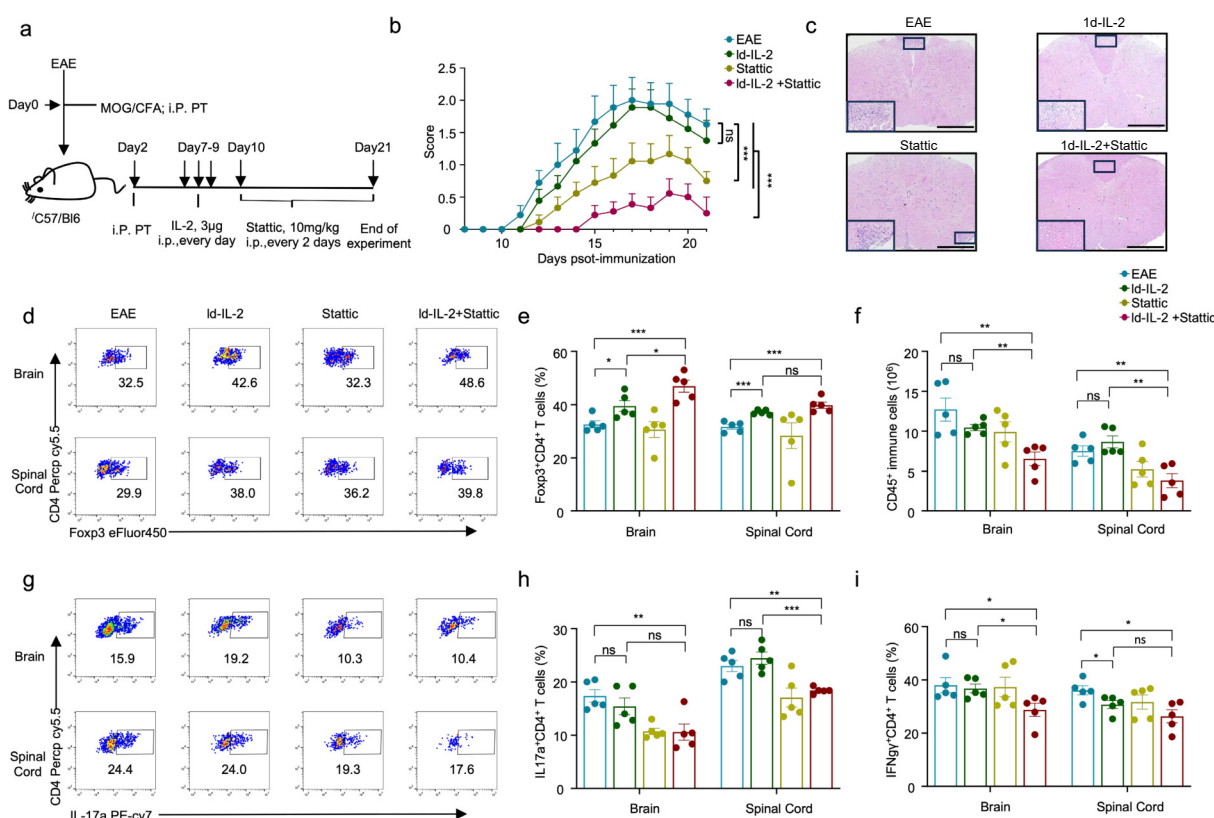


Figure 2 Combination of ld-IL-2 therapy and inhibition of STAT3 signaling remodels immune homeostasis in EAE. Therapeutic effects of ld-IL-2, Stattic, and ld-IL-2+Stattic therapies in mice with EAE. (a) Schematic diagram of EAE model establishment. (b) Clinical scores were monitored daily following immunization ($n = 9$), with data pooled from two independent experiments. (c) Representative histological images of spinal cord sections derived from EAE model mice. Scale bar, 500 μm . (d–i) Representative flow cytometry plots and bar graphs showing the frequencies of CD4⁺Foxp3⁺ Treg cells (d, e), total number of CD45⁺ immune cells (f), and frequencies of Th17 (g, h) and Th1 (i) cells in the brain and spinal cord tissues of the indicated mice ($n = 5$). Data are representative of two independent experiments. Data are presented as mean $\pm$ sem. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ns, not significant.

induce a range of adverse events, including pancreatitis and gastrointestinal perforation^[6].

The stability of Treg cells is also an important factor that limits the therapeutic effects of ld-IL-2 therapy. In an acute inflammatory microenvironment, Treg cells may lose Foxp3 expression and even transdifferentiate into Teff cells, thereby losing their anti-inflammatory capabilities^[9]. As the therapeutic effect of ld-IL-2 treatment relies on the expansion of Treg cells, the inflammatory microenvironment can also limit its efficacy. Abundant IL-6/STAT3 signaling in the inflammatory microenvironment has been shown to promote Foxp3 downregulation and compromise Treg identity and function^[10]. Our data validate that inhibition of IL-6/STAT3 signaling not only prevents Foxp3 downregulation and maintains Treg lineage stability but also directly abrogates Treg-induced pathogenic Th17 cell differentiation^[7]. Therefore, combining ld-IL-2 therapy with inhibition of IL-6 signaling is an ideal combination therapy strategy.

A notable advantage of combination therapy is that it enables superior therapeutic outcomes at lower drug doses. Notably, in both disease models employed in the present study, the inhibition of IL-6/STAT3 signaling was achieved using relatively low doses of the respective agents, which provided only modest therapeutic efficacy when applied alone. As ld-IL-2 therapy and IL-6 signaling inhibition act on distinct yet complementary nodes of the immunoregulatory network, their synergistic effects amplify their mutual therapeutic efficacy. This suggests that when compared with monotherapies that require higher doses of drugs to achieve optimal effects, combination therapy can attain equivalent or even superior immunomodulatory outcomes with lower doses of drugs while mitigating adverse events. Importantly, the improvements observed with the combination therapy, including reduced body weight loss, lower clinical scores, and suppression of Th1/Th17 responses, were statistically significant compared to each monotherapy.

Some limitations of this work should also be considered. The T cell transfer model of IBD requires exogenous Treg cell supplementation, which does not fully recapitulate the endogenous Treg cell pool present in human patients. In contrast, the EAE model retains endogenous Treg cells, yet neither animal model completely reflects the complexity of human IBD or multiple sclerosis. Therefore, the clinical translational value of our research results requires validation through clinical trials. Moreover, this study focused primarily on T cell immunity and did not examine how the combination therapy affects other immune cell subsets, such as NK cells or macrophages. Nevertheless, a recent clinical study demonstrated that low-dose IL-2 combined with tocilizumab (an IL-6 receptor blocker) is safe and effective in patients with rheumatoid arthritis, supporting the clinical feasibility of our proposed combination strategy of ld-IL-2 with IL-6/STAT3 inhibition^[11]. However, due to the limitations of peripheral blood sampling, that study only detected an increase in Treg cell numbers and did not observe direct suppression of Th1 or Th17 cells. Moreover, ld-IL-2 monotherapy even increased Th17 cell counts, yet the authors provided no explanation for this observation^[11]. In contrast, our study found that increased Treg cells in the inflammatory environment promote Th17 cell differentiation^[7]. Based on this finding, we adopted the combination strategy and performed flow cytometric analysis directly on inflamed tissues from IBD and EAE mouse models. Our results confirmed that the combination therapy achieves enhanced efficacy in both models

and elucidated its anti-inflammatory mechanism within the disease immune microenvironment.

In summary, our preclinical data suggest that combined ld-IL-2 therapy and inhibition of IL-6/STAT3 signaling may represent a potential immunotherapeutic approach for treating IBD and EAE. Distinct from broad immunosuppression or single-pathway modulation, this strategy shifts towards comprehensive immune reprogramming, aiming to re-establish immune homeostasis and treat inflammatory diseases by restoring peripheral immune tolerance.

Acknowledgements

This work was supported by the Sichuan Science and Technology Program (NO. 2026NSFSC0940), the National Natural Science Foundation of China (NO. 82171829), and the 1-3-5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (NO. ZYYC25010). D.Z. sincerely wants to commemorate Dr. Sang-A Park, who passed away suddenly in an auto accident in Bethesda, MD, USA.

Data available statement

All data supporting the findings of this study are available from the corresponding authors upon reasonable request.

Author contribution

H.C. designed and performed experiments, analyzed data, and drafted the manuscript. H.L., J.Z., Z.L., and X.M. performed experiments. D.Z. conceptualized, supervised and supported the whole study, designed experiments, analyzed data, and edited the manuscript. All authors have read and approved the final manuscript for publication.

Ethics approval and consent

All animal experimental procedures were reviewed and approved by the Animal Care and Use Committee of West China Hospital, Sichuan University (20211212A, 20220620002).

Consent for publication

All authors agree to publish.

Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article.

References

- [1] Zhang, D. F.; Chia, C.; Jiao, X.; et al. D-mannose induces regulatory T cells and suppresses immunopathology. *Nat. Med.* **2017**, *23*, 1036–1045.
- [2] Raffin, C.; Vo, L. T.; Bluestone, J. A. Treg cell-based therapies: Challenges and perspectives. *Nat. Rev. Immunol.* **2020**, *20*, 158–172.
- [3] He, J.; Zhang, R. J.; Shao, M.; et al. Efficacy and safety of low-dose IL-2 in the treatment of systemic lupus erythematosus: A randomised, double-blind, placebo-controlled trial. *Ann. Rheum. Dis.* **2020**, *79*, 141–149.
- [4] Cheru, N. T.; Osayame, Y.; Sumida, T. S. Breaking tolerance: An update of Treg dysfunction in autoimmunity. *Trends Immunol.* **2025**,

- 46, 611–613.
- [5] Wallace, D. J.; Strand, V.; Merrill, J. T.; et al. Efficacy and safety of an interleukin 6 monoclonal antibody for the treatment of systemic lupus erythematosus: A phase II dose-ranging randomised controlled trial. *Ann. Rheum. Dis.* **2017**, *76*, 534–542.
- [6] Choy, E. H.; De Benedetti, F.; Takeuchi, T.; et al. Translating IL-6 biology into effective treatments. *Nat. Rev. Rheumatol.* **2020**, *16*, 335–345.
- [7] Cheng, H.; Nan, F.; Ji, N.; et al. Regulatory T cell therapy promotes TGF- β and IL-6-dependent pro-inflammatory Th17 cell generation by reducing IL-2. *Nat. Commun.* **2025**, *16*, 7644.
- [8] He, J.; Zhang, X.; Wei, Y. B.; et al. Low-dose interleukin-2 treatment selectively modulates CD4⁺ T cell subsets in patients with systemic lupus erythematosus. *Nat. Med.* **2016**, *22*, 991–993.
- [9] Zhou, X. Y.; Bailey-Bucktrout, S. L.; Jeker, L. T.; et al. Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells *in vivo*. *Nat. Immunol.* **2009**, *10*, 1000–1007.
- [10] Komatsu, N.; Okamoto, K.; Sawa, S.; et al. Pathogenic conversion of Foxp3⁺ T cells into TH17 cells in autoimmune arthritis. *Nat. Med.* **2014**, *20*, 62–68.
- [11] Wang, J.; Zhang, S. X.; Chang, J. S.; et al. Low-dose IL-2 improved clinical symptoms by restoring reduced regulatory T cells in patients with refractory rheumatoid arthritis: A randomized controlled trial. *Front. Immunol.* **2022**, *13*, 947341.



Open Access This article is licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits reusers to distribute, remix, adapt, and build upon the material in any medium or format, so long as attribution is given to the original author(s) and the source, provide a link to the license, and indicate if changes were made. See <https://creativecommons.org/licenses/by/4.0/>

© The author(s) 2026. Published by Tsinghua University Press.