Basic reporting

The manuscript "CD4+CD25+ regulatory T cell therapy in neurological autoimmune diseases" demonstrates clear, unambiguous, and professional English throughout. The authors have effectively improved the language quality in response to previous comments, including appropriate terminology refinements such as replacing "extended half-life" with "prolonged persistence" (line 587).

Literature references are comprehensive and up-to-date, providing sufficient field background and context. The authors have successfully incorporated additional relevant studies as suggested, notably those discussing indirect therapeutic regulation of Tregs (lines 415-423). With 194 articles selected through exhaustive PubMed database searching (as stated in the Survey methodology section), the reference list constitutes a thorough foundation for this review.

The article structure is well-organized. The figures effectively illustrate key concepts, particularly the mechanisms of Treg function (Figure 3) and differentiation pathways (Figure 2), which aid considerably in understanding complex immunological processes. Tables summarize preclinical and clinical studies appropriately.

This review demonstrates broad and cross-disciplinary interest, bridging immunology and neurology, and clearly falls within the scope of PeerJ. The timely nature of this review is justified by recent advances in Treg therapy for autoimmune diseases and the lack of a comprehensive review specifically focusing on neurological applications.

The Introduction adequately introduces the subject, clearly defining neurological autoimmune diseases and establishing the relevance of CD4+CD25+ Tregs in this context. It effectively communicates that the intended audience includes neuroscientists, bioengineers, and neurologists seeking to understand current and potential Treg therapies (lines 96-100). The motivation—to elucidate therapeutic options for patients with currently incurable conditions—is clearly articulated.

Experimental design

The article content aligns well with PeerJ's Aims and Scope, focusing on the intersection of immunology and neurology. The investigation is rigorous, as evidenced by the systematic approach to the literature review described in the Survey methodology section.

The authors have transparently described their methodology and approach to literature selection, including database search and quality assessment criteria (lines 103-107). This methodology allows for replication of the review process.

The Survey Methodology is consistent with comprehensive, unbiased coverage of the subject. The authors' selection of 194 articles through exhaustive PubMed database searching with specific subject terms provides appropriate breadth, while their exclusion of "publications of inferior quality or redundant content" indicates attention to quality control.

Sources are adequately cited throughout, with appropriate quotations or paraphrasing. The authors have been diligent in attributing ideas and findings to their original sources.

The review is organized logically into coherent sections and subsections. The progression from basic Treg biology (development, migration, function) to pathological roles in specific diseases to therapeutic approaches (in vivo expansion, adoptive transfer, disease-specific applications) to challenges creates a natural flow that enhances comprehension of this complex topic.

Validity of the findings

This manuscript will contribute to the literature by synthesizing current knowledge on Treg therapy, specifically for neurological autoimmune conditions. The conclusions are well-stated and appropriately limited to supporting results from the literature reviewed. The authors have maintained scientific integrity by acknowledging both the therapeutic potential and the significant challenges of Treg-based approaches.

Overall, this manuscript presents a well-developed and supported argument that meets the goals established in the Introduction. The authors have successfully addressed how Tregs develop, function, and can be therapeutically manipulated in neurological autoimmune diseases, fulfilling their stated aim to "elucidate the current state of Treg therapy" (line 97).

The Conclusion effectively identifies unresolved questions and future directions. The authors specifically note that "the challenge of obtaining a sufficient number of antigen-specific Tregs with stable functionality and prolonged persistence remains a significant obstacle" (lines 586-588) and that "issues regarding the safety of Tregs therapy warrant further in-depth investigation" (lines 588-589). These statements appropriately guide future research efforts.

Additional comments

This revised manuscript represents a scientifically robust review of CD4+CD25+ regulatory T cell therapy in neurological autoimmune diseases. The authors have demonstrated good responsiveness to previous reviews, substantially enhancing the manuscript's scientific depth and clinical relevance through targeted additions and revisions.

Particularly commendable are:

The newly added "Migration and residency of CD4+CD25+ Tregs" section, which elucidates the unique characteristics of brain-resident Tregs

The expanded discussion of Tregs' role in specific neurological autoimmune conditions

The comprehensive "Side effects and challenges" section balances therapeutic optimism with a realistic assessment of current limitations.