Reviewer 3

The review covers modern trends in the use of Induced pluripotent stem cells in Spinal cord injury. Fundamental and applied aspects of this treatment and diagnostic technique are analyzed. The review is quite complete and covers all the main aspects of this issue. However, there are a number of shortcomings in the format of presentation of the material, which, in my opinion, do not allow publishing this review in the presented form.

We sincerely appreciate your thorough review and constructive feedback on our manuscript. Your comments have provided valuable guidance for improving the depth and clarity of our discussion. Below, we address each point and outline the corresponding revisions made. Please also see our revised manuscript, where the revised sections are highlighted in blue for your reference.

Comment 1: The main drawback is too superficial a description of the provided main areas of application of these cells. Each paragraph from the sections provides only general data on certain aspects of cell therapy. In my opinion, firstly, it is necessary to indicate how this or that direction of differentiation of pluripotent stem cells is implemented. Secondly, in each of the sections it is advisable to provide at least one example of restoration of functional indicators.

Authors' response to reviewer 1: We appreciate this suggestion and have significantly expanded the discussion on the differentiation strategies of pluripotent stem cells, including transcription factors, signaling pathways, and culture conditions used to direct their lineage specification. Additionally, we have now provided specific examples of functional recovery in preclinical models and early clinical trials, detailing improvements in motor function, sensory recovery, and neuroregeneration.

Comment 2: The disadvantages and difficulties in the use of this therapy are described very superficially. In particular, I consider it necessary to provide examples of complications such as malignancy, immune reactions, and to more fully substantiate their possible causes and methods of prevention.

Authors' response to reviewer 2: We have elaborated on the key challenges associated with iPSC-based therapies, including tumorigenicity, immune rejection, and ethical considerations. The revised section now provides specific case studies and experimental findings that illustrate these risks, along with strategies to mitigate them, such as genome editing, immune-compatible iPSC lines, and controlled differentiation techniques.

Comment 3: In the section on clinical trials, it is advisable to provide data on the largest studies with reference to official sources, as well as intermediate results. Indicate whether there are completed studies and guidelines for this method of therapy.

Authors' response to reviewer 3: We appreciate this valuable suggestion and have enhanced the clinical research section by including specific examples and details of larger-scale clinical studies. We now reference notable clinical trials, such as those conducted by Nagoshi and Okano (2018), highlighting the feasibility, preliminary outcomes, and safety profiles of autologous iPSC-derived neural progenitor cells for SCI treatment. Additionally, we clarified the current status of completed trials, discussed available interim results, and addressed the existence of guidelines or consensus recommendations regarding the clinical use of iPSC-derived therapies for SCI. These additions significantly improve the section by providing concrete evidence of clinical progress and clarify the current state of translational research in this field.

Comment 4: It is advisable to create a separate section or describe in more detail in one of the existing sections the methods for obtaining these cells from humans.

Authors' response to reviewer 4: We appreciate the reviewer's suggestion to provide a more detailed description of the methods for obtaining iPSCs from human somatic cells. To address this, we have added a dedicated subsection (5.2 Generation and Validation of Human iPSCs) that comprehensively describes the reprogramming methods used to generate iPSCs from human cells. This section outlines commonly used approaches, including integrating and non-integrating viral vectors (e.g., retrovirus, lentivirus, Sendai virus), as well as non-viral and chemical-based reprogramming techniques. Furthermore, we have detailed the selection criteria for somatic cell sources (e.g., fibroblasts, peripheral blood mononuclear cells) and discussed essential validation steps such as pluripotency marker assessment, genomic stability analysis, and differentiation capacity evaluation. These additions provide a clearer understanding of the methodologies involved in generating clinically applicable iPSCs and enhance the completeness of our manuscript.

Comment 5: The authors say that today there are no uniform approaches to assessing functional results. In this regard, it is advisable to describe which indicators there is agreement on, and which are debatable.

Authors' response to reviewer 5: We appreciate the reviewer's comment on functional recovery assessment in SCI research. In response, we have revised the Functional Recovery section to clarify widely accepted and debated indicators. We now highlight electrophysiological recordings and hindlimb locomotor scoring systems (e.g., BBB scale in rodents) as standard preclinical tools, while noting their limitations in clinical translation. Additionally, we discuss clinical assessment methods, including ISNCSCI and ASIA Impairment Scale (AIS), as well as advanced imaging techniques (e.g., DTI, fMRI) for monitoring neural recovery. These revisions enhance clarity on standardized and evolving assessment approaches.