

**Dear Editor-in-Chief,**

Here we submit the revised version of our manuscript, entitled "Issues and opportunities of stem cell therapy in autoimmune diseases" for publication in your honored journal, World Journal of Stem Cells.

**Here are our answers to the Reviewers.**

**Dear Reviewer #00609371:**

Thank you for your useful comments and suggestions.

Here are our answers to your comments:

Ad major concern 1.:

Whereas there is a lot of misunderstanding and misinformation in the literature, in the first part of our aim was to write an overview regarding the classification, origin, and mode of therapeutic effect of stem cells. From this point of view, cancer stem cells and induced-pluripotent stem cells should also be included.

There are more possibilities of the use of stem cells than mentioned in our manuscript. The main modes of the use of stem cells are the followings:

- drug research and toxicity studies;
- development and gene regulation studies;
- genetic modification of laboratory and farm animals: production and propagation of transgenic animals;
- tissue engineering and cell replacement for therapeutic purposes

For tissue engineering, adult stem cells can be seeded on synthetic or nature-derived scaffolds and differentiated towards a desired phenotype by combinations of appropriate composition, architecture, mechanical properties and physicochemical properties of the scaffolds, appropriate composition of the cell culture media, and appropriate mechanical and/ or electromagnetic stimulation. For cell therapies, stem cells can be directly applied to damaged tissues, or they can be used in the form of extracellular vesicles, containing bioactive molecules produced by these cells in an autocrine manner, particularly growth factors and immunomodulatory molecules.

In the "Therapeutic use of stem cells" part, we focused on such modalities that can be useful in autoimmune diseases.

For clarity, we have indicated the intention of each chapter.

Ad major concern 2.:

As to date, studies regarding stem cell therapy of autoimmune disorders are only available with hematopoietic and mesenchymal stem cells, we could only focus on their therapeutic applications.

Ad major concern 3.:

We tried to summarize the challenges and opportunities of stem cells and stem cell therapy based on the following classification: 1. stem cells; 2. stem cell therapeutic modalities; and 3. stem cell therapy of autoimmune diseases. The stem cell type related challenges, side effects and opportunities are discussed in the "Types of stem cells" paragraph. The "pros and cons" of different clinical stem cell applications are discussed in "Therapeutic use of stem cells" section. The special concerns about the discussed autoimmune diseases are summarized in "Stem cells therapy in autoimmune diseases" chapter.

Ad minor concern 1.:

Table 1. summarizes the indication of stem cell transplantation in autoimmune and autoinflammatory diseases according the latest guidelines of European Bone Marrow Transplantation Recommendation 2017. This table also clearly indicates that there is still little clinical experience of stem cell therapy in autoimmune diseases. That is why we believe it is not uninformative.

Ad minor concern 2.: "inner node" had been corrected to "inner mass".

Ad minor concern 3.: The English language of the manuscript had been revised again by a native English-speaking editor (Anika Scott).

**Dear Reviewer #02446101:**

Thank you for your positive suggestion regarding the acceptance of our manuscript for publication.

**Dear Reviewer #03370303:**

Thank you for your comment on our manuscript.

The suggested language correction had been corrected.

All the changes and modifications of the revised manuscript are highlighted by yellow color.

We hope that the revised version of our manuscript is now suitable for publication in World Journal of Stem Cells.

Yours Sincerely,

Ferenc Sipos MD, PhD