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**Title:** Current advances in using tolerogenic dendritic cells as a therapeutic alternative in the treatment of type 1 diabetes

**Authors:** William de Jesús Ríos-Ríos, Sorely Adelina Sosa-Luis, Honorio Torres-Aguilar

Dear Editor,

We have read thoroughly all the reviewer comments with the constructive criticism which we do respect for the perfection of the manuscript.

We have taken all comments into consideration and we answered the questions and revised the text accordingly (all changes are highlighted in red letters in the reviewed manuscript).

I am herewith attaching the revised manuscript and the point-to-point replies to the reviewers.

With my best regards,

Honorio Torres-Aguilar

#### **REVIEWER #1**

In this paper, the authors have reviewed the recent progress in using tolerogenic dendritic cells as a therapeutic alternative in the treatment of type 1 diabetes. Overall, the review is informative and well prepared. I have some suggestions to revise the manuscript. -Introduction section. It's too long and someone could not focus on the main topic. Please condense the main content and move some content to the subsequent section. -Page 15. In the section, it has been shown that "TolDC-based phase I clinical trials for the treatment of T1D patients are currently ongoing or have already been completed". However, only one phase I clinical trial was described in the section. It is confusing. Please add the other trials and describe the progress. - "Perspective obtained from clinical trials with the use of tolDCs for T1D therapy." In order to better describe the current status and prospects of tolDCs for T1D therapy, I suggested that the section be divided into two subsections: i. Clinical trials with good progress but limitations and barriers. ii. Perspectives for T1D therapy. -Conclusion section should be concise and clear. Please shorten the section.

Suggestions:

1. Condensation of introduction.

**ANSWER: Following up the pertinent reviewer suggestion, the introduction paragraph was modified to focus on the main topic (highlighted in red letters).**

2. In the section, it has been shown that “TolDC-based phase I clinical trials for the treatment of T1D patients are currently ongoing or have already been completed”. However, only one phase I clinical trial was described in the section.

**ANSWER: Attending the reviewer suggestion, the authors have considered excluding the statement to avoid similar confusion, and the following paragraph was modified attending the next suggestion.**

3. Suggestion to divide the section “perspective obtained from clinical trials with the use of tolDC for T1D therapy”

**ANSWER: Author thanks for the reviewer accurate observation in order to better describe the current status and prospects. The section was divided and modified to clarify the content (highlighted in red letters the individual sections).**

4. Shortening of conclusion section.

**ANSWER: Attending the reviewer's suggestion, the conclusion was modified more concisely and clearly (highlighted in red letters).**

## **REVIEWER #2**

The authors did very well on the literature review involving tolerogenic dendritic cells for treatment of autoimmune diabetes mellitus. The manuscript is well written and pictures and table are informative. I have no major concerns about this review manuscript. However, the process of clinical use of cell therapy such as this should be mentioned as well in terms of, for instance, good clinical practicing and relevant instruments that are acceptably used that conform international standards for cell therapy, etc., which will be useful for the audience both scientists and clinicians for the long-term in many aspects including considerations on procedures and expert personnel, management and investment policy related to the laboratory procedure.

**ANSWER:** The authors appreciate the reviewer's motivating words and have considered them to improve the manuscript's quality.

Suggestion:

1. Mention the process of clinical use of cell therapy.

**ANSWER:** Following up the pertinent reviewer suggestion, the next paragraphs and corresponding references were included (Highlighted in red letters):

In this study, the procedures, equipment, and facilities comply with recommendations and are approved by the FDA, and no toxicity or adverse effects associated with the tolDC therapy were reported. Hence with FDA and IRB (Institutional Review Board) approval, a new phase 2 study was started; pp:15

It is worth mentioning that the clinical trials described are carried out according to the standards for effector immune cells regulated by the FACT (foundation for the accreditation of cellular therapy) [ 71]: pp:16

Here, the safety and viability of autologous tolDCs loaded with proinsulin peptide "C19-A3" (PIpepTolDC) in new-onset T1D patients is evaluated, being C19-A3, a pharmaceutical product regulated by FDA.; pp:16

#### **ADDITIONAL INCLUDED REFERENCE**

71 FACT standards for immune effector cells [cited 10 February 2021]. Available from: <http://www.factwebsite.org/iecstandards/>.