Dear editors,

Dear reviewers,

Thank you for your time to review our paper. We acknowledge that our paper might have some issues in conformity with the referees` comments. We have addressed them and revised the manuscript accordingly (with highlight).

We can see that some of the points are severely critical. However, we hope that the reviewers` requirements will be satisfied since we addressed them appropriately.

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision

Specific Comments to Authors: The Authors examined in this review the main challenges related to the therapeutic approach of pancreatic islets transplantation for the treatment of T1D.

- Thank you for the overall good evaluation of our paper.

The review is interesting but, in my opinion, does not take into consideration the following aspects:

- Authors mentioned the co-transplantation of pancreatic islets with mesenchymal stem cells just at the end of the review, and just as very brief point. I think that this part is worth of a more detailed examination, as well as the encapsulation option. Moreover, the co-treatment should be cite also in the core tip.

- Thanks for this valuable comment. A relevant paragraph and a core tip sentence was added in the manuscript. Since the topic is not related to MSCs, we limit to these inclusions based on your suggestions.

- In “introduction”, the Authors cite the possibility of an autologous transplantation of pancreatic islets; this is possible just when the pancreatectomy is necessary for other causes, different from diabetes, so I do not see the need to cite it. In addition, the yield of pancreatic islet isolation from the whole pancreas makes it very difficult to obtain from a single pancreas a number of islets sufficient to regulate glycaemia. Ik the authors would like to keep this part, they should be clearly stated that this option has several limits; otherwise I suggest erasing that point.

- Thanks for this point. We have addressed this comment by the following sentence: “While autologous islet transplantation has the advantage of being derived from the same patient, eliminating the risk of immune rejection, its widespread utilization is limited due to several drawbacks, including the need for pancreatectomy, which may have associated surgical risks, and the limited availability of functional islets from a single organ in patients with advanced disease.”

- Introduction: the Authors should explained the limits of exogenous insulin administration, to make clearer the improvement represented by pancreatic islet transplantation.

- Thank you for the great recommendation. The limitations of exogenous insulin administration are now explained:

Although exogenous insulin analogs are considered the primary treatment option for managing T1D, they cannot mimic the precise timing and dosing of physiological secretion of insulin by islets in response to hyperglycemia. Moreover, exogenous insulin therapy is associated with increased risk of severe side effects over time such as hypoglycemia, weight gain, lipodystrophy, etc.

- Type 2 diabetes could be treated with pancreatic islet transplantation, and there are several studies about it.

- Thanks for the suggestion. We have now removed the paragraph that addressed the T2DM since it is not a topic of interest for our concise review; thus, also removing reference 14.

- In “Islet transplantation procedure”, when the authors described the immunoisolation by encapsulation, they should at least mentioned some material used and its properties.

- We acknowledge the referee`s suggestion. We agree that providing more information on the material used for encapsulation would be helpful to the reader.
- We have added the following sentences: “Encapsulation of islets for immunoisolation involves the use of biocompatible materials that allow for efficient nutrient and oxygen exchange while also preventing immune cells from accessing the transplanted islets. Several biomaterials have been studied for this purpose, including alginate, agarose, and polyethylene glycol hydrogels. For example, alginate hydrogels are commonly used due to their biocompatibility, ease of fabrication, and ability to protect transplanted islets from the immune system.”

- The final point of “Immunological alterations in Type 1 diabetes” is very important, and it should be further face in discussion.

- Sure. This very important point was further discussed and the whole paragraph was edited to sound more comprehensive and complete: “Islet transplantation has been considered as a potential cure for type 1 diabetes by replacing the damaged beta cells. However, its effectiveness is dependent on the underlying cause of the disease. If T1D is considered as a result of a pancreatic dysfunction leading to the loss of beta

cells, then islet transplantation may be a viable option. However, if T1D is viewed as an autoimmune disorder, the presence of autoreactive T and B cells can lead to recurrence of the disease and limit the efficacy of transplantation. In such cases, alternative approaches such as immunomodulatory therapies, co-transplantation with immune cells, or encapsulation of islets can be explored to improve the success rate of islet transplantation."

- The authors should specify that the risk of teratoma development concerns just some kind of stem cells.

- We appreciate the reviewer's comment. To clarify, we have added the respected sentence: "Embryonic stem cells and induced pluripotent stem cells, have the potential to differentiate into all three germ layers and can form teratomas if not fully differentiated [Prokhorova et al.]. Theoretically, the presence of a few remaining undifferentiated pluripotent stem cells can cause undesirable teratomas after transplantation."

- More in general, the readability of the review would be enhanced by the add of some figures and overall of summary tables, i.e. for the different treatments. The layout of the table with clinical protocols should be checked.

- Thank you for the valuable comment, we completely agree. We formatted the table to make it more comprehensive and also add a figure on the techniques for graft survival – encapsulation and co-transplantation with SMCs.

Reviewer #2:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision

Specific Comments to Authors: Remarks to the author

The manuscript entitled " Islet transplantation - immunological challenges and current perspectives" has been reviewed. The work has been carefully carried out.

- Thank you for the valuable comments on our paper. We incorporated them to improve the quality of our paper.

A weakness of this paper is too long. The title of this paper refers to islet transplantation. Therefore, the description of diabetes in this manuscript should be minimized.

- Thank you for the critical note. Accordingly, we have revised and minimized this part of article; thus, also removing the references 32, 36-41; the references 28 and 29 were interchanged.

The main purpose of the paper is not clear.

Also, the content is not new.

- We modified the end of the introduction to make our goal clearer and concise. We agree with the referee that we do not present new data, our paper is a narrative review and we discuss the published papers in the topic so far. However, we also present the data critically, and made a summary in a table, thus, we believe that our paper contributes to the knowledge, especially after the revision.

The citation of the reference paper is inaccurate. For example, the paper describing the Edmonton protocol is also incorrect.

- Thank you for the critical note, we have thoroughly revised and corrected our references.

The description of islet isolation is also inaccurate.

- We corrected the issue, thank you for noticing the inaccuracy.

Minor

The references selected by the authors are not new.

- After searching in the major databases, such as Medline, Scopus, PubMed, we selected the most relevant and recent papers available.