Dear Reviewers,

Thank you for the careful and detailed consideration of our manuscript "Regenerative medicine of pancreatic islets" by Irina Arutyunyan, Timur Fatkhudinov, Andrey Makarov, Andrey Elchaninov and Gennady Sukhikh.

We have thoroughly worked through the comments, and we are grateful for the opportunity to submit a revision; the corrections are highlighted for your convenience.

Reviewer #1:

Comment 1) Abstract is well written and introduces the reader within the topic. Maybe presenting information in shorter phrases and reducing text will be of benefit

Response to Comment 1) The Abstract has been edited as recommended.

Comment 2) In my personal opinion the word reimbursed needs to be changed as it is not reflecting properly the nuance intended (that is hormone replacement). Same goes with "incompensable" … trivial word corrector regarding the length and usage of verb in the phrase starting with " An interesting assumption"

Response to Comment 2) The corrections to the text have been made.

Comment 3) Maybe the reader will benefit a more schematic presentation of DM types and correlation with the situation of beta cells (a table, a schematic drawing?).

Response to Comment 3) A table 'Comparison of type 1, type 2 and surgically induced DM' has been added as Table 1.

Comment 4) Among the issues encountered with the so called bioartificial pancreas it would be worth to mention the challenges in executing insulin levels sensing implants that adjust insulin secretion to circulating glucose therefore avoiding both engineered islet exhaustion as well as hypoglycemic episode in transplanted hosts.

Response to Comment 4) The 'Tissue engineering of the pancreas' section has been supplemented with information on the implantable continuous glucose monitoring devices and the implantable insulin pumps.

Comment 5) There is a difference between attempting treating beta cell deficiency with non differentiated MSCs (which act, as authors themselves mention) as "medicinal signaling cells' with trophic effect (angiogenesis, anti-inflammatory and so on) and the transplantation of MSCs that have been differentiated to endodermic lineages that is in this case to beta cell progeny. There are non genetic modifying protocols for doing this, however the capability of such MSCs derived beta cells to engraft and function is still limited

Response to Comment 5) We totally agree with this point. Accordingly, the problem of the non-differentiated MSCs (and MSC-derived exosomes) transplantation is addressed in the 'Application of biologically active substances for the regulation of cell cycle in β-cells' section,

whereas the differentiation of MSCs into β-like cells is reviewed in the 'Stem/progenitor cell reprogramming' section, along with the non-genetically modifying protocols.

Comment 6) The manuscript contains generous information regarding existent clinical trials in the trade. A synthetic presentation of existent/ finished/ recruiting clinical trials (table) would help the reader to have an overview regarding this important aspect

Response to Comment 6) We attempted to survey the most breaking-through (in our opinion) clinical trials related to the topic of the article. These trials are highly dissimilar by their content and design, it would not be quite expedient to present the information as a table, especially since the examples of clinical trials were selected to supplement and illustrate specific sections of the review. The total number of clinical trials for DM treatment exceeds 15,000 and their comprehensive systematization is a big challenge in itself. As the status of a clinical trial (existent/ finished/ recruiting) is subject to changes over time, we suppose that indication of the status in a published article might be confusing; in any case, the indicated NCT provides a precise ID for updated reference.

Reviewer #2:

Comment 1) Page 10 "The second strategy implies creation of…specific expression of cognate receptors for toxins...". I think that the authors may explain this background/rationale better, otherwise non-experts would not be able to understand why such toxin receptors

Response to Comment 1) Appropriate explanatory information has been added to the section.

Comment 2) Page 8~ "Modeling the endocrine pancreas regeneration". It is great to know the details of b-cell ablation. However, I feel that "regeneration" part is downplayed in this section.

Response to Comment 2) We aimed at a proper representation of the variety of experimental models available today, for a reader interested in the topic of *Regenerative medicine of pancreatic islets* was able to choose the most suitable model for particular research.

Comment 3) I am just curious if adipose-derived stem cells or adipose-derived mesenchymal stem cells can be differentiated into pancreatic cells.

Response to Comment 3) Adipose-derived mesenchymal stem cells can be differentiated into β-like cells. Detailed consideration to this issue is given in several studies e.g. PMID: 19544426, 31109026, 31547868 (References 110, 111, 112, respectively). Information on the possibility of differentiation of MSCs derived from different tissue sources has been added to the text of the article.

All authors participated in drafting and subsequent critical revising of all versions of the manuscript for important intellectual content and way of presentation. The authors appreciate the

constructive suggestions of the reviewers. It is our sincere hope that this manuscript will now merit publication in World Journal of Gastroenterology.

With best regards,

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