

We thank the editor and the reviewers for reading and commenting on our manuscript to help us improve it.

Reviewer #1:

The manuscript "Stem Cells for Genitourinary Regenerative Medicine" is a review article on the use of stem cells in urology. At the beginning of the manuscript, general facts about anatomy, pathologies and current treatments of kidneys, bladder, ureters and urethra, as well as problems related to current treatments are given. Much of the manuscript is devoted to regenerative medicine strategies using stem cells for kidney, bladder, ureters and urethra. The widest space is given to the chapter "Adipose tissue as a source of therapeutic cells" in which the part "ASC-based therapies and tissue engineering approaches for treating urogenital-related diseases/pathologies" is especially widely covered. At the end of the article, a brief overview of the application of induced pluripotent stem cells and the self-assembly approach for genitourinary tissue engineering is given. A serious approach to this paper also presents a concluding section with concise perspectives and limitations in the use of stem cells. With a large number of references relevant to the field and appropriate by year, with two highly illustrative figures and four systematized tables, this review paper is exceptional for the field it deals with. Based on scientific quality and language quality, the manuscript should be accepted for publication in the submitted form.

We greatly thank the reviewer 1 for the very positive comments and appreciate his/her enthusiasm.

Reviewer #2:

Dear authors, we have read with interest your (long) manuscript. The review work is well presented and provides a clear overview of the topic of Regenerative Medicine applications for genitourinary therapy. Our main concern is that the manuscript is long and somehow difficult to follow.

We understand the concern of the reviewer 2, we significantly reduced the length of the manuscript. We reduced it from 10,750 to 8,926 words (-16.9%).

In our opinion, the objectives of the review should be re-written, and focused on the key elements presented. We hardly understand the purpose of the paragraph dealing with iPS. It brings more confusion than explanation (especially after explaining that ASC is a more easily accessible source of Stem Cells)

We removed the iPSC section and added a sentence to the end of the manuscript regarding the use of these cells, which is predicted to be more prominent in the field of urology in the coming years, and therefore is worth mentioning.

The wide section presenting Adipose derived cells makes sense if you consider clinical applications (you developed first the in vitro/in vivo use of BMSC; then explained that some clinical trials are on process with ASC). Our suggestion is to target Regenerative Medicine for Genitourinary Therapy/Applications/Purpose, as already clearly presented in the 'Introduction'. And remove the parts with iPS. Moreover, the title claims "Stem Cells for..." but, in fact, the manuscript is about Regenerative Medicine, and guides us towards to the problematic of Stem cells use (GMP conditions) and innovative Self Assembly Approach. And you also develop the concept of Secretome (as a therapeutics without cell grafting) A modification of the title would be interesting to enlighten the clinical targets.

We agree with the reviewer comment and have changed the title for “Considerations for the clinical use of Stem Cells in Genitourinary Regenerative Medicine”

The manuscript could be structured (reorganized) as: > Introduction 1/ Anatomy, Pathologies and Current Treatments (Kidney / Bladder / ureters and urethra) 2/ Regenerative Strategies Using Stem cells (introduced by your shorten paragraph "Stem Cell Sources for Urologic Regenerative Medicine") (Kidney / Bladder / ureters and urethra) 3/ Towards clinical Applications: a- Adipose Tissue as a source of Therapeutic Cells b- Self Assembly Approach > Conclusion & Perspectives : Considerations on the use of SC from various origins

We have reorganized the structure of the manuscript to comply with the reviewer’s suggestion.

Reviewer #3:

This is an interesting review including information about a up to date topic. Nevertheless the article needs to be shorten and reorganized.

As mentioned above for reviewer #2, the manuscript has been shorten by 16.9% and its structure has been reorganized.

In the abstract it should be included the main objective of the review. I think you should include Mesenchymal Stem Cells or Stem Cells as a key word.

We modified those sections accordingly.

It would be interesting to include the search algorithm that you use to do this review.

Used algorithms were mainly detailed in the table. Table 1: In vivo studies for regenerative medicine of urologic tissues (excluding studies using adipose tissue-derived stem cells) (words used in the PubMed research engine (National Library of Medicine): “urology” “regeneration” “reconstruction” “stem cells”); Table 2: ASC-based preclinical studies for treating urogenital related diseases/pathologies (2016-2021); Table3: Preclinical studies of urogenital related pathologies/disease using ASCs in tissue engineering (2016-2020); Table 4: Preclinical studies for treatment of urogenital related diseases using Dedifferentiated Fat (DFAT) cells

ANATOMY, PATHOLOGIES AND CURRENT TREATMENTS part could be deleted to avoid making the article too long. Maybe, you could include only the part of problems related to current treatments.

We think it is important to present the anatomy for people which are not familiar to these organs. Nevertheless, the reviewer’s comment is true and several paragraphs are too long. So we decided to eliminate the descriptions of the anatomy and to regroup them in a new figure (Figure 1). As suggested, we maintained the information pertaining to the challenges of current treatments.

STEM CELL SOURCES FOR UROLOGIC REGENERATIVE MEDICINE: A CONCISE OVERVIEW is too long and should be summarised in one short paragraph.

We consider this section is important in order to give an unbiased view of the stem cell types used for regenerative genitourinary medicine but we modified it for an easier reading it. We also significantly reduced the total length of the manuscript.

In the introduction you say that your review is focus on studies that have used mesenchymal stem/stromal cells isolated from adipose tissue. Nevertheless, in the Regenerative medicine for kidney you mainly provide information regarding bone marrow derived MSCs and other MSC. Why did you focus on AD-MSCs? I think you included several sources of MSCs and you could delete from the introduction that you focus on AD-MSCs and reorganize these sections.

It is true that many examples of SC uses are provided, including BM-MSC and urine-derived stem cells because advances made using these cells cannot be ignored. However,

we chose to focus on adipose tissue (ASCs and DFAT cells, to a lesser extent SVF) since ASCs have provided a huge amount of data in the field of urology recently and can be considered advanced candidates. As such, the Tables 2-4 provided for ASCs and DFAT studies are exhaustive for each organ, and type of therapies, for the years mentioned in the text. We believe it is best to keep this section separate from the previous section - describing selected seminal examples using other cell types-, in order to better guide the readers and to prevent event lengthier Tables than the ones presented considering the numerous studies that were included in our analysis.

The information explaining MSC secretome or MSC-conditioned medium should be provided in the introduction.

A sentence has been added in the introduction to this purpose.

The first three paragraph of ADIPOSE TISSUE AS A SOURCE OF THERAPEUTIC CELLS should be deleted or at least summarized. There are two approaches for obtaining stromal/stem cells from adipose tissue (Figure 2)... This paragraph and the next one should be also summarized.

The section about ASC has been shortened, keeping only the most relevant elements.

I don't think the INDUCED PLURIPOTENT STEM CELLS is necessary in this review. You could summarize this topic in one or two sentences.

We removed the iPSC section and added a sentence at the end of the manuscript regarding the use of these cells.

Table 2, 3 and 4. The first author's name should be included in the table in the first column or in the year column. Other option is to provide the reference number as in table 1. It would be interesting to include information regarding ongoing clinical.

We made sure both the reference number as well as first author's name and year are provided in Tables 2-4. We now use a format that allows viewing of the whole table in the page because some elements were already present in the document but did not readily appear to the readers.

6 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor: *1 Scientific quality: The manuscript describes a review of the stem cells for genitourinary regenerative medicine. The topic is within the scope of the WJSC. (1) Classification: Grade C, Grade B and Grade A; (2) Summary of the Peer-Review Report: This is an interesting review including information about a up to date topic. This review paper is exceptional for the field it deals with. However, the keywords, tables, review targets, etc. need to be modified. The questions raised by the reviewers should be answered; (3) Format: There are 4 tables and 2 figures; (4) References: A total of 279 references are cited, including 54 references published in the last 3 years; (5) Self-cited references: There are 5 self-cited reference; and (6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Grade B, Grade A and Grade A. 3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The study was supported by Fonds de Recherche du Québec-Santé (FRQS) (C.C.); the Canadian Urological Association (scholarship to S.B.); and the Canadian Institutes of Health Research. The topic has not previously been published in the WJSC. 5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);*

A document from the website of the CIHR has been joined.

(2) I found the authors did not provide the original figures. Please provide the Figures cited in the original manuscript in the form of PPT. All text can be edited, including A, B, arrows, etc. With respect to the reference to the Figure, determine if it is the original Figure, if not, please provide the source of the picture and the proof that the Figure has been authorized by the previous publisher or copyright owner to allow it to be redistributed;

Done figures are in a Powerpoint file and are fully editable.

(3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

We had download the World Journal of Stem Cells output style on EndNote website and correct this mistake.

(4) I found the authors did not write the “Conclusion” section. Please write the “Conclusion” section at the end of the main text;

Done

and (5) the author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

Please, see above the answer to the point (3)

6 Recommendation: Conditionally accepted.

(2) Company editor-in-chief: *I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.*