

## **Answer to Reviewer's comments**

### **Reviewer 1**

The author gives a succinct description of the recent advances in the field of osteoarthritis management. He presents details on the potential of the different modes of assisted surgery on offer today, and describes the recent advancements on the different modes of biologic joint reconstruction. This is a very interesting topic and it has been covered well, even though briefly.

Reply to the reviewer: Thank you for the kind comments and the comprehensive description of the work presented.

MAJOR POINTS This is an editorial that starts with the premise to provide a current and concise evidence to address the question of whether and when biologic joint reconstruction could replace joint arthroplasty. The author sets out by replacing this question with two new ones: How feasible is to claim today that biologic joint reconstruction will soon replace artificial joint arthroplasty? how soon can it be constituted in clinical practise. Firstly, question 2 is irrelevant if question 1 is negated. Secondly, the question is I think premature. The evidence we have so far and that the author presents in this editorial shows that there is not enough evidence to show long term efficacy of biological joint reconstruction. Therefore, I think the author needs to readdress the title and the main question of his editorial, perhaps to the one that he answered in the conclusions.

Reply to the reviewer: Thank you for the kind comments and concerns. Indeed, question 2 is depended on the answer to question 1. The goal of this editorial study is to highlight exactly what the reviewer is suggesting that there is not enough evidence yet to make suggestions. The reason I decided to structure the editorial on these questions is to provoke a reaction in relation to increasing suggestions from both the scientific community and industry that biologic joint reconstruction will be soon clinical applicable. This is why these questions are quoted.

B. Page 5, last paragraph, lines 7-9: MSCs exhibit a relatively safe profile, please explain safe in what respect?

Reply to the reviewer: Thank you for this comment. The exact safety profile was added accordingly.

“Another important step toward the extensive use of mesenchymal stem cells was the fact that they exhibit a relatively safe profile regarding toxicity, organ system adverse effects, infection, and malignancy.”

C. Page 6, paragraph 3, line 8 limitations that “cell homing” process has. They need to be stated briefly.

Reply to the reviewer: Thank you for this comment. The main limitations of cell homing were added accordingly

“However, it is important to accept the inherent limitations that “cell homing” process has, such as the inadequacy to differentiate in all different cell types and that cell homing is a delicate process that needs specific environmental requirement in order to be successful”

MINOR POINTS There are also a number of grammatical errors that we pinpoint below: Page 3, line 6: has initiated.. change to: has been initiated...

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 4, paragraph 2, line 5: ...its use have been... change to: its use has been...

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 4, last line: ...lacks or vessels... change to: ...lacks vessels...

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 6-7, More interestingly, ....over the last years. Please rewrite this sentence as it very badly written.

Reply to the reviewer: Thank you for this comment. This part was re- written.

Page 7, first paragraph last line: change “favors” to “favor”.

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 7, paragraph 2, line 4: change “One of the most ...” to “Two of the most...”.

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 7, paragraph 2, line 9: change “The use osteochondral...” to “The use of osteochondral...”

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 7, paragraph 3, line 4: change “...reconstruction to replace...” to “...reconstruction replacing...”

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

Page 8, paragraph 2, line 2: change "...prior joint replacement..." to "...prior to joint replacement..."

Reply to the reviewer: Thank you for this comment. This was changed accordingly.

## **Reviewer 2**

I congratulate with the author for the succinct but well focused work on biologic treatment of knee OA. The manuscript is ok and quite ready for publication. However I would highlight and expand some topics to let the reader understand more extensively some concept that could be not usual.

Reply to the reviewer: Thank you for the kind comments.

First, it seems that all the manuscript is focused on knee, therefore I would rephrase the title accordingly and revise the conclusions.

Reply to the reviewer: Thank you for your comment. The title was changed accordingly.

Secondly, I would expand and briefly explain the concept of KA, as the the navigation\robotic (how it works, which are the advantages on conventional TKA?)

Reply to the reviewer: Thank you for your comment. Additional data explaining the concept of KA TKA, navigation and robotic were added accordingly

Third, which are the stimuli for cell homing

Reply to the reviewer: Thank you for your comment. A sentence clarifying that additional knowledge and understanding of this mechanism and the stimuli involved was added.

"It is also of paramount importance to acquire a better understanding of the exact pathways that are activated during cell homing and of the stimuli that are involved in this process."

Fourth, i would also mention meniscal sustitution (allograft and prosthese) as could be considered a strategy to prevent OA or avoid metal resurfacing. You can refer to the following paper in this regard: "Unicompartmental osteoarthritis: an integrated biomechanical and biological approach as

alternative to metal resurfacing. Marcacci M, Zaffagnini S, Kon E, Marcheggiani Muccioli GM, Di Martino A, Di Matteo B, Bonanzinga T, Iacono F, Filardo G. Knee Surg Sports Traumatol Arthrosc. 2013 Nov;21(11):2509-17."

Reply to the reviewer: Thank you for your comment and suggestion. Clinical biological approaches, including meniscal transplantation, were also included in the relevant section

Lastly, I would present the results of each technique in a deep way: how are the improvement? pain reduction? increased survivorship? radiographic\MRI results?

Reply to the reviewer: Thank you for your comment. Additional details for each technique was added accordingly.

Conclusions: ok References: ok

Reply to the reviewer: Thank you for your comment.

### **Reviewer 3**

This is an interesting editorial about a topic of orthopaedics that will probably present important developments in the future.

Reply to the reviewer: Thank you for your comment.

Although the argument is covered satisfactory in terms of different models I would suggest further explanation on some of these. On page 3 the paragraph on "Kinematic aligned total knee replacement" should have an explanation of what this method involves and the same for the "Robotic technology in Orthopedics", "Navigation in TKR", "Biologic Growth Factors" and "Tissue engineering and regenerative medicine applications".

Reply to the reviewer: Thank you for your comment. Additional data explaining the concept, and more data were added for all techniques accordingly.

Furthermore some minor language and grammatical polishing i.e: 1. page 4: paragraph on "Robotic technology in Orthopedics" is not properly aligned

Reply to the reviewer: Thank you for your comment. This was changed accordingly.

2. page 6: effectiveness instead of ffectiveness.

Reply to the reviewer: Thank you for your comment. This was changed accordingly.

Finally in my opinion the questions: “How feasible is to claim today that biologic joint reconstruction will soon replace artificial joint arthroplasty?” “How soon these changes can be constituted in clinical practice?” should be modified accordingly to the manuscript conclusions. Probably the second question is premature.

Reply to the reviewer: Thank you for your comment. Indeed, question 2 is depended on the answer to question 1. The goal of this editorial study is to highlight exactly what the reviewer is suggesting that there is not enough evidence yet to make suggestions. The reason I decided to structure the editorial on these questions is to provoke a reaction in relation to increasing suggestions from both the scientific community and industry that biologic joint reconstruction will be soon clinical applicable.