Journal title: **World Journal of Stem Cells**

Manuscript NO: **46623**

Title: **Mesenchymal stem cells for cartilage regeneration in dogs.**

Dear members of the Editorial Board

Thank you for valuable comments by the editor and the reviewers. We appreciate the time and effort you have dedicated to providing valuable feedback on ways to strengthen our paper. Based on the comments, we have rewritten the manuscript and added figures. We believe the revised paper has been much improved.

The original comments of the referees and our responses are as follows:

Response for reviewer #1

Reviewer's comment:

This review summarizes current knowledge concerning canine MSCs. The title is consistent with the main subject of the manuscript, the abstract and key words reflect the main topics of the entire text. The review is informative and helpful. Tables capture information concisely and are illustrative of the paper contents. The paper cites the relevant and important references. The manuscript is well written, and the literature data is discussed well. I suggest to accept the manuscript with no specific comments.

Author's response:

Thank you for your high appraisal on this review. Your comments are very encouraging for me. We hope this review will provide beneficial information for researchers of canine MSCs.

Response for reviewer #2:

Reviewer's comment 1:

In this manuscript, the authors summarize the current knowledge of mesenchymal stem cells (MSCs) from dogs, including in vitro characteristics, and in vivo cartilage regenerative potential and therapeutic effects for naturally developed osteoarthritis (OA). Dogs have distinctive characteristics compared to other laboratory animal species in that they share an OA pathology with humans. Dogs in actual conditions of OA can serve as vulnerable translational animal models for human medicine in terms of the use of MSCs. In cartilage repair, MSCs are a promising therapeutic agent due to their self-renewal capacity, ability to differentiate into cartilage, potential for trophic factor production, and capacity for immunomodulation. There are still many problems in the application of MSCs in dogs, including ethical issues and difficulty of effect measurement. Regulations and guidelines for MSCs should be established in the future, and standardized methods for MSC usage would provide more unified and reliable results from the studies. More data on MSC characteristics and their use as an OA treatment in dogs will be needed, and they must be meaningful for the improvement of cartilage repair treatment in both human and veterinary medicine. The objective of this study is clear, however, some issues should be addressed by authors prior to the consideration for publication.

Author's response 1:

We wish to express our deep appreciation for your insightful comments, which have helped us to make significant improvements in the paper. In this revised manuscript, we have addressed all the concerns raised in the original manuscript.

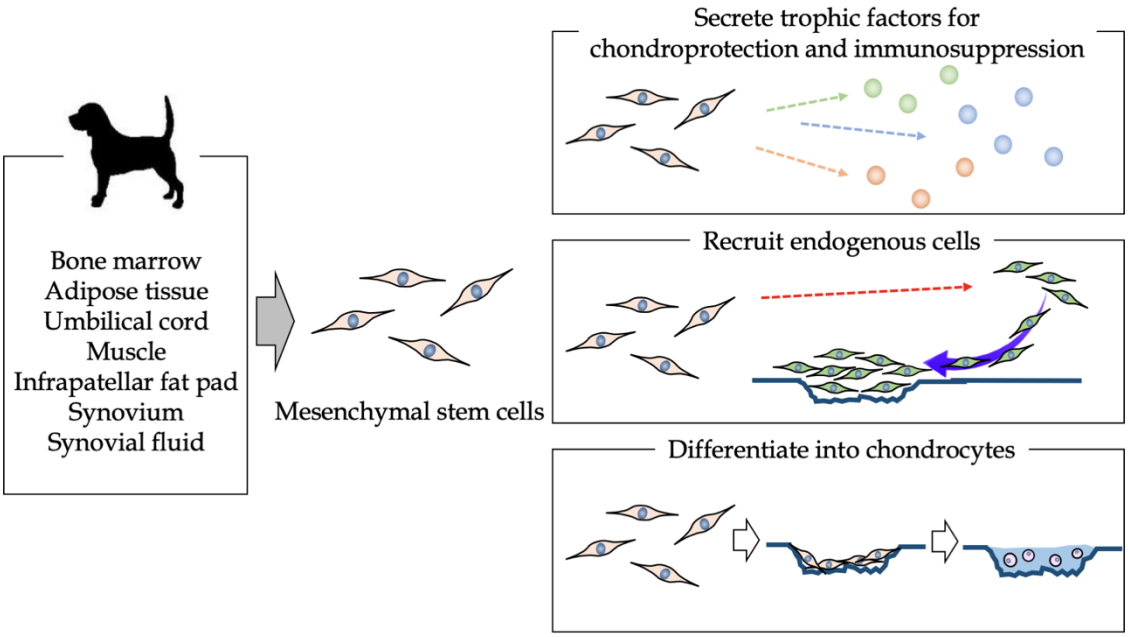
Reviewer's comment 2:

A schematic showing the main content of the text should be added.

Author's response 2:

Thank you for your suggestion. We have added a schematic representation (Figure 1) to the manuscript. (Page 6, Line 120)

"This review summarizes the *in vitro* data, preclinical *in vivo* studies, and clinical studies involving the use of MSCs for cartilage regeneration in dogs (Figure 1)."



Reviewer's comment 3:

On Page 16, "However, one report showed a decrease in the effects of cMSCs between 30 and 90 days after the cMSC injection.", the injection is intravenous or intra-articular?

Author's response 3:

We are sorry for the insufficient description. The injection is intra-articular. We added the word "intra-articular" to the relevant part of the manuscript. (Page 17, Line 379)

"However, one report showed a decrease in the effects of cMSCs between 30 and 90 days after the cMSC intraarticular injection."

Reviewer's comment 4:

The references are too old, it would be better to be replaced by more references of the latest three years, for example, Stem Cells International 2015, 2015, 10; Journal of Materials Chemistry B 2018, 6 (47), 7822-7833; Acta Biomaterialia 2018, 73, 103-111.

Author's response 4:

We agree with you and substitute the references which are too old except those which are not substitutable.

Reviewer's comment 5:

The sections should have Figures, not just tables.

Author's response 5:

In response to this comment, we have added Figure 2 for the section 2 "The importance of studies on cartilage repair in dogs" (Page 7, Line 151) and Figure 4 for the section 4 "*In vivo* study of cartilage regeneration with cMSCs" (Page 14, Line 353).

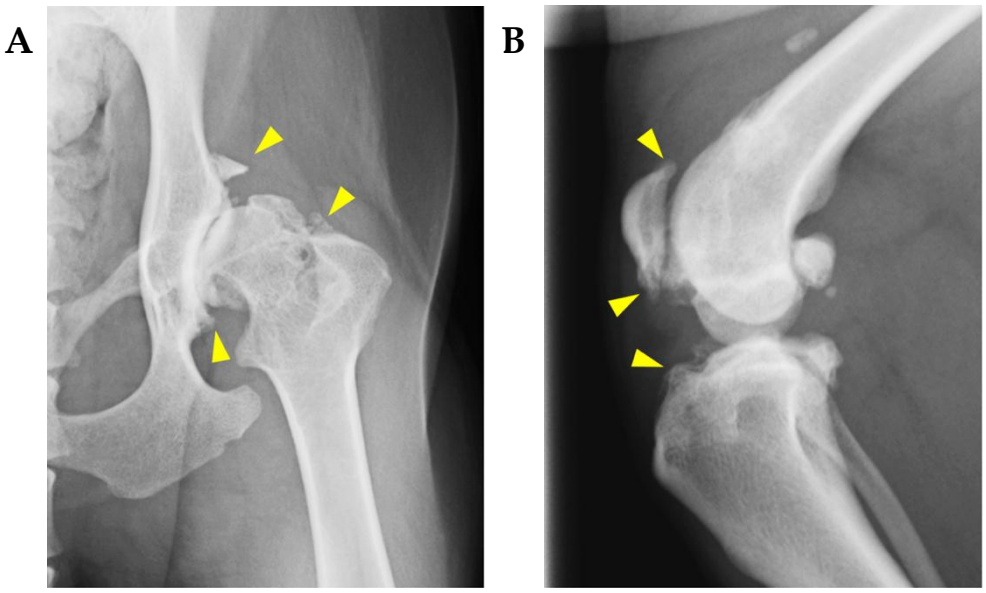


Figure 2 Radiographic findings of osteoarthritis (OA) in dogs.

A: A radiographic image of the hip joint in an 8 years-old Labrador retriever suffering from OA which resulted from hip dysplasia. B: A radiographic image of the stifle joint in a 4 years-old Shiba suffering from OA which resulted from cranial cruciate ligament rupture. Yellow arrowheads: osteophytes.

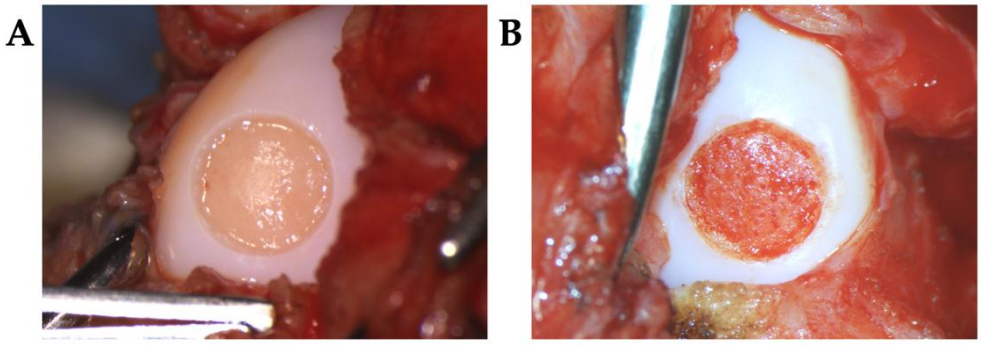


Figure 4 Cartilage defect models in dog stifle joints.

A: A macroscopic image of a partial-thickness cartilage defect model in a dog stifle joint. B: A macroscopic image of a full-thickness cartilage defect model in a dog stifle joint.

Reviewer's comment 6:

The full name of the first appeared abbreviations should be stated, such as "FGF".

Author's response 6:

We have corrected the relevant part of the manuscript as follows (Page10, Line 200);

"These findings suggest that the optimal culture conditions for cMSCs should be reconsidered; for instance, the inclusion of supplemental growth factors, such as fibroblast growth factor-2 (FGF-2), could increase the proliferation ability of cMSCs[61]."

Reviewer's comment 7:

Some references are incorrectly formatted, please check.

Author's response 7:

Thank you for your indication. We have corrected the format of references.

Reviewer's comment 8:

The resolution of all the figures in the manuscript should be improved.

Author's response 6:

Thank you for your indication. We substitute the figures to those with high resolution (Figure 3).