

**The revised manuscript has been re-reviewed. Please re-revise the manuscript according to the reviewers comments and update the Answering Reviewer document:**

Within the submitted document “64840-Answering-Reviewers-revision”, authors responded: All the modifications and suggestions highlighted by the reviewer is now incorporated in the revised version.

Thank you very much to reviewers for critically reviewing the manuscript and improving the quality.

Minor remarks: MSCs are not “fibroid-like cells”, but fibroblast-like cells. Corrections has been made.

Corrections has been made.

Spelling errors, such as: “chondroproginators” Spelling and typographical errors are corrected.

Unfortunately, many of the suggested corrections have not been incorporated in the revised version of the manuscript, moreover, new mistakes were created during this process, which is very disappointing!

Discussion and conclusions are improved, but that approach has not been applied throughout the whole manuscript.

Therefore, please find detailed list of my remarks related to the submitted “64840-Manuscript-File-revision” that need to be introduced into the final version of the manuscript:

We apologize for not improving the quality at desired level. However, in this revision we have improved the quality, and incorporated all the suggested corrections.

Abstract: Methodology MSCs were transfected with sox-9 and six-1 transfection factors Instead of - transfection factors, it should be - transcription factors

The correction has been made.

Result Isolated cells showed fibroid morphology Instead of - fibroid, it should be - -like fibroblast

The correction has been made.

Core tip: In this study, we highlighted that overexpression of Chondrogenic transcription factors in hUC-MSCs accelerated their differentiation potential into chondroprogenitor cells. Instead of – Chondrogenic, it should be – chondrogenic Instead of – chondroprogenitor, it should be - chondroprogenitor Instead of – The synergistic effect of sox9, and six1 transcription factors leads the MSCs to differentiate into chondrogenic cells in the basal medium produced the same effect as the chondro-induction medium. It should be – The synergistic effect of sox9 and six1 transcription factors lead the MSCs to differentiate into chondrogenic cells in the basal medium, which produced the same effect as the chondro-induction medium. *in vitro* - should be in Italic

The correction has been made.

INTRODUCTION Instead of – In the present study we hypothesized that if MSCs are preconditioned for overexpressing chondrogenic transcription factors six1, sox9 and their synergistic combination, and pre-differentiate MSCs into chondro-progenitor cell (CPCs), transplanted in the form of induced chondro-progenitor cell (iCPCs) into damage IVD, the disc can be regenerated and normal physiological function can be restored. It should be - In the present study we hypothesized that damaged IVD can be regenerated and its normal physiological function can be restored if MSCs are preconditioned by overexpressing chondrogenic transcription factors six1, sox9 or by their synergistic combination, as well as by MSCs pre-differentiated into chondro-progenitor cells (CPCs), transplanted into the damaged disc in the form of induced chondro-progenitor cells (iCPCs).

The correction has been made.

MATERIALS AND METHODS Transfection of Human Umbilical Cord-derived Mesenchymal Stem Cells (hUC-MSCs) by Electroporation Instead of – Each subset of transfected MSCs was cultured in a basic growth medium for 48 hours followed by incubation in a chondrogenic induction, and normal growth medium for day 21. It should be - Each subset of transfected MSCs was cultured in a basic growth medium for 48 hours, followed by incubation in a chondrogenic induction and normal growth medium for 21 days. Protein Expression Analysis Instead of - Normal MSCs and transfected MSCs cultured in the basal and chondro-induction medium for day 21... It should be - Normal MSCs and transfected MSCs cultured in the basal and chondro-induction

medium for 21 days... The same correction has to be introduced in the text that is part of the graphs within Figure 7. Instead of - at 21 day It should be - at day 21

The correction has been made.

RESULTS Isolation, Proliferation, and Characterization of MSCs from a Primary Culture of Human Umbilical Cord Tissue Instead of - Fibroid-like cells It should be - Fibroblast-like cells Characterization of Differentiated Transfected MSCs Instead of - The transfected cells completely lost their fibroid shape. It should be - The transfected cells completely lost their fibroblast-like shape. Instead of - called induce It should be - called induced Instead of - The fluorescent intensity was quantified and plotted and showed that MSCs transfected with sox-9, six-1, and the synergistic group expressed chondrogenic markers in 21 days of culturing in basal medium. The 21 days culturing of transfected MSCs in chondro-induction medium expressed chondrogenic markers sox-9 and six-1 as shown in figure 5. It should be - The fluorescent intensity was quantified and results showed that MSCs transfected with sox-9, six-1 and the synergistic group expressed chondrogenic markers following 21 days of culturing in the basal medium. Also, the 21 days culturing of transfected MSCs in chondro-induction medium lead to expression of chondrogenic markers sox-9 and six-1 as shown in figure 5. The second part of Figure 5 is missing in the submitted PowerPoint presentation!! Gene Expression Dynamics of Sox9 and Six1 Transfected MSCs Instead of - Expression of Sox9 has significantly up-regulated at 21 days post-transfection transfection in the basal medium... It should be - Expression of Sox9 has significantly up-regulated at 21 days post-transfection in the basal medium...

The correction has been made.

DISCUSSION Instead of - To analyzed It should be - To analyze Instead of - denerated disc It should be - degenerated disc

The correction has been made.