Dear Editor,

Please find our responses to the reviewer's comments below. We thank the reviewer for his helpful and instructive commentary and believe the changes prescribed improve the quality of the manuscript substantially.

Reviewer #1:

COMMENT 1 and 2: In particular, the references used by the authors in the manuscript are often not recent in consideration of that the topic of the paper is constantly updated. 2. In particular, in the Introduction (page 6) an additional reference regarding evolving epidemiology should be cited (Wallace MC et al., Expert Rev Gastroenterol Hepatol. 2015, 9(6):765-79.

Response: We thank the reviewer for this comment. We have updated our references in the manuscript. In particular and as suggested by the reviewer we have added the reference of Wallace Mc et al., in the introduction. We have highlighted the references added in the references section.

COMMENT 3: The references (6,7) used for the description of the markers for the detection of the several stages of HCC are not completely appropriate to the context. On this regard, a more recent paper by Shreya Sengupta and Neehar D Parikh (Hepat Oncol. 2017 Oct; 4(4): 111–122) describes in exhaustive manner the most promising investigational biomarkers and their phase of discovery in HCC

We have made changes to the paragraph mentioning the detection of markers (page 6) and added the reference of Neehar D Parikh (Hepat Oncol. 2017 Oct; 4(4): 111–122) as per the reviewer recommendation (reference number 5).We have highlighted the references added in the references section.

COMMENT 4: Regarding the methods. Why the authors use specifically only HepG2 and PLC-PRF-5
HepG2/C3A/ HB-8065 and PLC-PRF-5/CRL-8024 were chosen specifically in this study for two reasons:
First, they are the only ATCC hepatocellular carcinoma cell lines available that secrete AFP, the other cell lines don't. Both cell lines secrete DCP too.

Second we wanted to choose two cells lines with different origin in order to compare results HepG2/C3A/ HB-8065 cell line was originated from a 15 years old adolescent male with no history of viral infection whereas PLC-PRF-5/CRL-8024 cells are infected with hepatitis B virus.

COMMENT 5: In the page 9 where the authors describe the microscope observation these is a mistake because authors describe a co-culture of ADMSCs with similar cells (probably the authors refer to HCC cell lines).

Response: We have reformulated our Material and methods in the section morphological observation indicating the cells lines used.

COMMENT 6: At page 10 where the authors describe treatment of cancer cells with ADMSCs CM the definition of CCM should be given.

Response: We have added the definition of CCM, page 10, which is Cancer Cell Media as it was mentioned earlier in page 8 in the paragraph cell lines and culture conditions.

COMMENT 7: The author s should explain the why for the choice of the following dilutions (1:1, 1:5, and 1:25) (referred to CMs).

Response: We appreciate the comment of the reviewer, we have changed the paragraph, page 10, indicating all the dilutions we have used in several experiments and our choice of the three dilutions *(1:1, 1:5, and 1:25).* All dilutions were significant in respect to cancer markers and morphology. After 1:25 dilution, no differences in results were observed (Data not shown). Thus, in all experiments ADMSCs CM were diluted at (1:1, 1:5 and 1:25).

COMMENT 8: In the results (page 15) the authors should report (referring to flow cytometry results) the numbers of SEM without indicate SEM.

We have reported the numbers of SEM without writing SEM. The word SEM was removed from the result section describing the characterization and differentiation of ADMSCs

COMMENT 9: In the results (page 15) (referring to co-culture experiments) it should be necessary to control the verb form ("reveals" and then "show" should be modified in the past form).

We thanks the reviewer for drawing out attention to this mistake. We have changed the verb reveal and show to the past tense.

COMMENT 10: In the figure 1 panel B it should be better to insert the panels B-a, B-b, B-c, B-d and B-e on a same line (indicating in the complex positive. In a similar way for the negative markers B-f ....to B-i. The images of differentiation panel C are too small. In addition the authors should indicate the bar and how many times the test of differentiation was repeated.

We have substantially improved and changed our figure and panels according to the reviewer suggestions. We indicated the number times differentiation was repeated n=4.

COMMENT 11: Figure 2, figure 3, figure 4, figure 5 and figure 6 panels are too small. It is difficult to analyze the data reported.

We have arranged the size of the figures as suggested by the reviewer.

COMMENT 12. In the discussion relative to the potential therapeutic effects of Adipose MSCs in different diseases the authors should indicate additional references (Saleh F, et al., Curr Stem Cell Res Ther. 2018; Brini AT, et al., Sci Rep. 2017, 29;7(1):9904).

We highly appreciate the reviewer comment. We have updated our references concerning the diseases involved in the therapeutic effects of Adipose MSCs (discussion page 19). We also added Additional references and paragraph on the effect of stem cells secretome on different types of cancer (page 20).

COMMENT 13: In the discussion regarding the interaction between MSCs and tumor the authors should consider the importance of the microenvironment that can modulate MSc role as well described in a paper "Tumor-educated mesenchymal stem cells promote pro-metastatic phenotype" by Hill BS, et al., Oncotarget. 2017, 14;8(42):73296-73311 that the authors should add in the discussion.

We have included in our discussions the role of microenvironment in the modulation of MSC roles. We have mentioned the paper by Hill BS et al, Oncotarget. 2017, 14;8(42):73296-73311

COMMENT 14: The authors should control the sentence at the end of page 21 (discussion).

We have changed the sentence concerning metalloproteinases in the discussion page 22

We hope our responses meet with the approval of the reviewer.