To Academic Editor:

Dear Dr. Fang-Fang Ji,
Dear reviewers,

Thank you very much for the careful evaluation of our manuscript. We corrected the manuscript according to your suggestions. Here is our point-by-point response to your and the reviewer's comments. The revised manuscript is attached: the supplemented and corrected text in the manuscript is marked by blue highlighting:

Reviewer 1.
1. "However, the review is overall very uneven and unfocused on the proposed subject which is mesenchymal stem cells and natural poly(3-hydroxyalkanoates). To extrapolate some reactions observed in vivo in mammalian tissues with these materials, the authors give examples of naturally occurring functions of in many organisms, but the link and conclusions raised from these observations are not clearly drawn. The manuscript could gain by organizing in it in defined sections with appropriate section titles":
To emphasize the topic of the review we changed the title of the manuscript to read: "The effect of poly(3-hydroxyalkanoates) as natural polymers on mesenchymal stem cells". We believe indeed that the properties (e.g. biological activity) of PHAs associated with their natural functions are closely related to their effect on MSCs.
In order to accommodate these comments and to clarify the association between natural functions of PHAs and their effect on MSCs the paper was virtually disassembled and compiled again in a more acceptable manner. Now the main text is organized in 4 chapters, the main chapters 2 and 3 are structured each to 5 subsections with appropriate titles. In Chapter 3 (from 3.1 to 3.5 subsections) we describe in detail the different aspects of PHA biological activity concerning their effect on MSCs. And now we show separately the association of such aspects of PHA biological activity with the appropriate aspects of their natural functions.
Unfortunately, this very interesting problem is studied very poorly. There is very fragmentary information and this information is really irregular. For example, only 3 year ago it was shown that PHA oligomers have antioxidant properties (p. 12, ref. 85). But I can't find a study about the role of these properties in biocompatibility or biological activity of PHAs. Maybe this is one of the main reasons of PHA biocompatibility, especially, with stem cells. This is an unexplored problem. While oxidant stress plays a significant role in MSCs growth and differentiation. But if PHAs have their antioxidant properties as their natural functions, e.g. in bacterial cells (as it is shown in ref. 85), it can explain the mechanism of interaction of PHAs with stem cells. And this is an absolutely unexplored problem. The same is with the piezoelectric properties of PHAs, their antimicrobial activity, etc. And the main purpose of our review is to draw the attention of the scientific community to these unstudied scientific fields. These suggestions was added to text (p. 12-13).

2. "The discussion/conclusion is merely a summary of what was exposed extensively in the main text body".
We rebuild the text in such a way that the discussion now is given in section 2 (in separate subsections) on the appropriate relevant issue. In fact, the discussion is also a review of studies of different types of PHA biological activity, which may be related to the interaction of polymers with cells that was described in the section 2.

3. "Perhaps a discussion on how the authors think these problems/events can be solved or adapted to better achieve potential therapies would be welcome".
To take into account this comment we added the following text (p. 18) immediately before Conclusions section: "A better understanding of the mechanisms of interaction of PHAs with

MSCs is the key to developing new therapeutic agents based on them. For example, if PHB causes the osteogenic differentiation through activation of some receptor of MSCs and PHBHHx causes the chondrogenic differentiation of MSCs through activation of another receptor of MSCs, the medical devices based on PHB should be developed specifically for bone regeneration and medical devices based on PHBHHx – specifically for cartilage regeneration. But if the osteogenic differentiation of MSCs is caused by the main product of PHAs biodegradation – 3-hydroxybutyrate, and chondrogenic differentiation of MSCs is caused by some kind of microstructure of PHBHHx medical devices, it's better to use any type of PHAs depending on their physicochemical properties (the strength and flexibility of PHB and PHBHHX differ greatly) for bone regeneration and medical devices based on any type of PHAs with desired microstructure - for cartilage regeneration. At the first case of receptor-mediated induction of MSCs differentiation, it can be connected with the similar receptor-mediated action of bacteria-origin PHAs when bacteria interact with each other or with the cells of the host organism that can help to discover mechanisms of PHAs action regarding signal functions and binding with receptors of PHB oligomers. At the second case, the bone regeneration process is mediated by internal product of lipid metabolism - 3-hydroxybutyrate and connected with mechanisms of its metabolism. Maybe, in this case, it's better to regulate 3-hydroxybutyrate metabolism to improve bone regeneration. The same is with the microstructure of PHAs devices because in this case, it's necessary to find the specific structural element regulating chondrogenic MSCs differentiation independent of the type of biomaterial at all.
Moreover, a deeper understanding interaction of PHAs with MSCs in relation to natural functions of these biopolymers can help to develop novel types of medical devices and pharmaceutical formulations based on them: medical devices with selective osteoinductive or chondroinductive activity and desired regenerative activity, prebiotics that promote regenerative activity of the intestinal wall through modulation of microbiota and stimulation of intestine progenitor stem cells, substrates for MSC cultivation in bioreactors, formulations for sustained delivery of drugs with biopolymer-compatible natural bioactivity, experimental model systems for MSC cultivation for drug testing, or therapeutic tissue-engineered systems simultaneously containing probiotic bacteria and MSCs as active ingredients for treatment of gastrointestinal system diseases".

Reviewer 2.
4. "However, the manuscript requires an intensive revision before it can be recommended for a publication. The major concern is that the manuscript contains too much information, which is not directly related to the topic of review."
To emphasize the topic of the review we changed the title of the manuscript to read: "The effect of poly(3-hydroxyalkanoates) as natural polymers on mesenchymal stem cells". We believe indeed that the properties (e.g. biological activity) of PHAs associated with their natural functions are closely related to their effect on MSCs. To clarify the association between natural functions of PHAs and their effect on MSCs the paper was virtually disassembled and compiled again in a more acceptable manner. Now the main text is organized in 4 sections, the main sections 2 and 3 are structured each to 5 subsections with appropriate titles. In section 3 (from 3.1 to 3.5 subsections) we describe in detail the different aspects of PHA biological activity concerning their effect on MSCs. And now we show separately the association of such aspects of PHA biological activity with the appropriate aspects of their natural functions.

5. "1. Introduction section is too long and can be shortened by about half."
We shortened the Introduction section as far as possible.

6. “2. Chapter 2. Here the main question of review (as suggested by title) is considered. However, it is not clear why do Authors included studies on MG-63 cells, human osteoblasts etc? The aim of the review is the effect of PHAs on MSCs and Authors need to follow this aim.”
The studies on MG-63 cells and human osteoblasts were removed from the review. However, the mention of the study of osteogenic differentiation of mouse MC3T3-E1 preosteoblast cells caused by 3-hydroxybutyrate (not PHB) (see p.13, ref. 90) is necessary to explain one of the possible mechanisms of the effect of PHAs on MSCs, because I can’t find the study about the effect of 3-hydroxybutyrate directly on MSCs. And to logically connect these data with all other I had to leave also the study about the influence of PHB-HV on mouse MC3T3-E1 preosteoblast cells (p. 24, ref. 19) adding the phrase: “It should be noted that PHAs enhanced osteogenic differentiation of both MSCs and exactly this cell line of preosteoblast cells” (p. 13). In addition, in early studies (the 90s, early 00s), “osteoblasts” are usually understood to mean exactly MSCs, since the method of their isolation is the same.

7. “Furthermore, this section needs to be more structured, to show the effect of PHAs on the different aspects of MSCs physiology like proliferation, osteogenic, adipogenic, chondrogenic differentiation. In the current version, presentation is quite chaotic and unclear for the readers”
Now the main text is organized in 4 sections, the main sections 2 and 3 are structured each to 5 subsections with appropriate titles. We added the information about proliferation and osteogenic, adipogenic, chondrogenic, neurogenic, endotheliogenic, and epidermogenic differentiation in Table 1 with appropriated titles and in the main text of Section 2.

8. “3. Chapter 3. Most information presented in this chapter is not directly related to the topic of Review. There are several paragraphs, which do not touch the topic of MSCs at all. All information, which is not related to the topic must be skipped or at least substantially shortened.”
Some information in the Charter 3 was shortened. And the other text was organized in 5 subsections: from 3.1 to 3.5 with appropriate titles. In Chapter 3 (from subsections 3.1 to 3.5), we describe in detail the different aspects of PHAs biological activity concerning their effect on MSCs. And now we show separately the association of such aspects of PHAs biological activity with the appropriate aspects of their natural functions.
To emphasize the topic of the review we changed the title of the manuscript to read: “The effect of poly(3-hydroxyalkanoates) as natural polymers on mesenchymal stem cells”. We believe indeed that the properties (e.g. biological activity) of PHAs associated with their natural functions are closely related to their effect on MSCs.

Reviewer 3.
I am very pleased that our research was interesting to you.

Comments from Academic Editor:

1. “A short running title of less than 6 words should be provided”.
We added a short running title: “Effect of natural PHAs on MSCs”.

2. “The approved grant application form(s) will be released online together with the manuscript in order for readers to obtain more information about the study and to increase the likelihood of subsequent citation. Our purpose of publishing the approved grant application form(s) is to promote efficient academic communication, accelerate scientific progress in the related field, and improve productive sharing of research ideas. In addition, a copy of the full approved grant application form(s), consisting of the information section and body section, should be provided to the BPG in PDF format.”
We attached the copy of selected pages (that are not confidential) of approved grant agreement.

3. “Please offer the audio core tip, the requriment are as follows:
In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:
Acceptable file formats: .mp3, .wav, or .aiff
Maximum file size: 10 MB
To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS”.
We attached the audio core tip.

4. “Repeat with ref 20, please revise. Thank you.” “Repeat with ref 33, please revise. Thank you.”
The repeated references were removed. The list of references was corrected and supplemented according to comments of reviewers.

5. English editing.
The manuscript was sent to Springer Nature Publishing Group Language Editing as recommended in the Guidelines for manuscript preparation. The certificate is attached. The corrections in English editing are not market in order to avoid confusion of text perception.

Best regards,
Bonartsev Anton, PhD
Faculty of Biology, Moscow State University

As pointed out by Reviewer 1 - 3. “Perhaps a discussion on how the authors think these problems/events can be solved or adapted to better achieve potential therapies would be welcome.” In the revision, the authors argued “that PHA oligomers have antioxidant properties (p. 12, ref. 85). But I can’t find a study about the role of these properties in biocompatibility or biological activity of PHAs. Maybe this is one of the main reasons for PHA biocompatibility, especially with stem cells. This is an unexplored problem. While oxidant stress plays a significant role in MSCs growth and differentiation.” Too much text to get their point across to the reader. Ideally, they should use schematic diagrams to show such impacts with their own speculation. Another example, “The same is with the piezoelectric properties of PHAs, their antimicrobial activity, etc. And the main purpose of our review is to draw the attention of the scientific community to these unstudied scientific fields.” Again, they should use schematic diagrams to show such impacts with their thoughts. As pointed out by Reviewer 1 - “2. “The discussion/conclusion is merely a summary of what was exposed extensively in the main text body.” Ideally, the Conclusion is from the authors, not merely citing the literature, offering their insight into a new direction. The revised section was written like discussion, not the conclusion. Overall, it is of great interest, and their choice of the topic shows their taste of the field. It can become a most-frequently-cited review if they can come up with schematic diagrams revealing their vision toward future research. Specific comments: About 50 locations in the body of text should be revised to enhance the clarity and the logic flow as shown in tracking. (A separated email with the attachment was sent to the WJSC editorial office).

Answer: Thank you very much for the additional time for the revision of our manuscript. I made the revision and send you the revised version of the manuscript with my correction accordingly the comments of editor-in-chief (the manuscript in .doc is attached in this letter - in the journal submission system I can't attach the revised manuscript). The corrections are blue highlighting and made in review mode. We made a schematic diagram to illustrate our speculations - Figure 1 (see last page 51). The conclusion section was corrected according to the remark.