**Responses to Reviewers**

**Reviewer A.**

1. *A major problem of this review is the oversimplification and overstatement concerning the significance of telomere shortening and the potential of telomere-based therapy.*  The original manuscript described the biology of telomeres much more in detail, but it turned out to be too long and too complicated. Since the purpose of this manuscript is not to review the last 40 years of biogerontological research, but to comment on the modern landscape of telomerase-based gene therapy methods and to introduce the concept of the CSU model (focusing on the telomeric theory only), Dr. Fossel, who had assisted me during the process of the article organization, advised on cutting it short to and deliver only the most essential information. Knowing two versions of the article I can state that the final one serves as much clearer and straightforward piece of information. When it comes to overstating the significance of telomere shortening, I concur I did some dangerous oversimplified and concerning notions, which have been corrected and edited (highlighted passages).
2. Page 2: ‘hTERT (human telomerase reverse transcriptase) transcript” rather than “hTERT transcript (human telomerase reverse transcriptase)”. Ultimately, it is the telomerase activity more than hTERT mRNA expression that matters?  Mistake corrected.
3. Page 9: “recombined telomerase gene” – do you mean recombinant? Mistake corrected.
4. Figure 1: This diagram taken from ref 51 looks out of place, as there really is no explanation in the text. I linked the text to the diagram.

**Reviewer B.**

1. 1. There are four figures in this manuscript. Relation between figures and text is unclear. I agree, I did not link the proper passages with their complementary diagram representatives. After my corrections, it should be clear now which diagram serves which explanatory role.
2. 2. On page 2, third paragraph, all theories of aging are not related to cellular senescence. This paragraph should be rephrased. Very apt remark! I definitely rewrote the paragraph as it did not make sense in its original sounding.
3. 3. For Figure 1, environmental stresses such DNA damage and oxidative stress might affect telomere length but these stresses could induce cellular senescence directly in many cases. This figure gives the readers impression that all the stresses induce cellular senescence through telomere shortening. Please modify that point. Again, very accurate comment. Indeed, I added an explanatory sentence about the ambiguity of different factors having different effects on different cellular processes.
4. 4. On page 9, first paragraph, the author mentioned that there is no data on the relatedness between the telomere length maintenance (TLM) and cancer. Cancer cells maintain proper length of telomeres by expressing telomerase or activating ALT. It is obvious that telomere length maintenance is important for survival of cancer cells. This paragraph is misleading. I entirely agree! I made a factual mistake stating that there is no relatedness between the onset of cancer and telomeres shortening, whereas I originally meant that there is no negative implementation of the shortening telomeres on the process of cancerogenesis found (so far). Of course, the latter parts of the chapter explain that concept more in depth, but that initial mistake could be largely confusing. Mistake corrected.
5. On page 10, third paragraph, telomerase expression does not show any cancerous phenotype in many primary cultured cell lines even in some mouse models. However, the effect by telomerase expression might be different in genetic background or environment of individual. For example, cancer incidence increases by telomerase overexpression in some tumor suppressor null background in mouse. The author should mention this part more carefully. I could, but the status quo is this article is that we take into account only healthy somatic cells and place them against cancer cells in appropriate paragraphs; however, I agree that it would be beneficial to note that under different cellular/genomic circumstances, the simple Boolean expression/no-expression of telomerase would not hold true. Paragraph rewritten.
6. For Figure 4, it is better to explain more detail for Telomerase Therapy for Alzheimer’s disease in the text because this part is a main theme for this manuscript. I actually decided to delete the last figure due to its commercial theme and lack of scientific essence. However, I explained Telocyte’s approach in more details.
7. Dr. Michael Fossel is listed in Author’s contributions but is not in author list. Is Dr. Fossel a co-author? No, he is not. I changed that in Acknowledgements/Author Contribution sections; as far as Dr. Fossel guided the process of writing the article, he is not a co-author.
8. Reference #58 is missing. Reference added.