LETTER

REPLY TO UDROIU:

Interesting mathematical analysis of telomere shortening rate and life span

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We appreciate Udroiu's letter titled "On the correlation between telomere shortening rate and life span" (1). We acknowledge that our conclusion that "critical telomere shortening and the consequent onset of telomeric DNA damage and cellular senescence are a general determinant of species life span" in our recent publication (2) may not be the full story, but this conclusion does appear to be a fairly straightforward and logical explanation for our observations. We also understand that the same data can be analyzed using many different methods. We thought it was important to keep our mathematical analysis as simple and straightforward as possible to address the issue of whether there was any correlation at all between species life span and telomere shortening rate. Nevertheless, we find Udroiu's more sophisticated mathematical analysis interesting.

In part of Udroiu's analysis, the author mentions that he enriched the dataset with values taken from other published works. We want to caution that other publications measure the telomeres using different methods. A common method for measuring telomeres, for example, is a qPCR method. In our laboratory, we used the high-throughput quantitative fluorescence in situ hybridization method in all of the samples, in parallel, and this fact allows side-by-side comparisons of telomere length in different species. Thus, the best results may be obtained when using data acquired from the same laboratory method.

We also agree that the telomere length of leukocytes would not be the major determinant of life span if telomere shortening is indeed a cause of aging. However, the telomere length of leukocytes is a convenient and practical proxy for telomere length changes in the body with time, as Udroiu mentions.

Udroiu writes that, "In my view, it is not the reaching of a 'critical telomere length' that limits MLS, which would be 22 kb in a laboratory mouse (1), thus longer than in humans at birth." However, there are several issues to be aware of when thinking about mouse telomeres: The length of a critically short telomere in a laboratory mouse may be different from the length of a critically short telomere in a human, the length of the shortest telomeres rather than the average telomere length may be the more critical parameter (3–5), and the leukocyte telomere lengths are just a proxy measure for the telomere lengths of cells that may be much more important for the aging process.

The fact that Udroiu confirms our results using a much more sophisticated analysis and more stringent criteria, and even combines our data with data from other publications, is an interesting finding.

1 I. Udroiu, On the correlation between telomere shortening rate and life span. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 2248–2249 (2020).
2 K. Whittemore, E. Vera, E. Martínez-Nevado, C. Sanpera, M. A. Blasco, Telomere shortening rate predicts species life span. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 15122–15127 (2019).
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4 Z. Xu, K. D. Duc, D. Holcman, M. T. Teixeira, The length of the shortest telomere as the major determinant of the onset of replicative senescence. *Genetics* **194**, 847–857 (2013).
5 M. T. Hemann, M. A. Strong, L.-Y. Hao, C. W. Greider, The shortest telomere, not average telomere length, is critical for cell viability and chromosome stability. *Cell* **107**, 67–77 (2001).

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Author contributions: K.W. and M.A.B. designed research; K.W. performed research; K.W. analyzed data; and K.W. and M.A.B. wrote the paper.
The authors declare no competing interest.

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First published January 24, 2020.