

Peer Review

# Review of: "The Future of Longevity Medicine: Repairing the Parts or Preserving the Whole? Holmes' Carriage as a Metaphor for Two Fundamentally Different Models of Aging"

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Dear Authors,

First of all, I would like to congratulate you on your efforts in writing a commentary on the current panorama of modern medicine regarding the understanding of human aging.

As a researcher, I agree that there is indeed a broad movement toward developing intervention plans for damage repair, which may subsequently result in life extension. It is worth recalling that the aging process itself fundamentally translates into overcoming stress events throughout life. In this sense, cells are capable of developing counteracting (anti-stress) mechanisms that ultimately contribute to micro-damage repair. Therefore, established interventions such as adequate nutrition, regular exercise, and sleep management are beneficial factors that can enhance the body's defense system.

Additionally, this paradigm is not new in its attempt to introduce the concept of "Healthspan" into clinical practice, which accounts for attaining more years lived in good health (healthy longevity). Currently, people are living—or seeking to live—longer; however, they do not adopt regular means (such as the aforementioned interventions) early enough to achieve extended years of life free from modern diseases. On the other hand, stressful lifestyles, increased sedentary time (reliance on motorized transport over walking or cycling), increased use of technology, and the consumption of ultra-processed

foods heavily contribute to cumulative cellular damage over time, even as individuals strive to advance their professional lives.

The article in question presents somewhat obvious ideas within an established theoretical model that makes logical sense. In my view, however, the manuscript fails to delve deeper and propose how medicine should evolve to prevent disease rather than merely treating existing damage. Furthermore, it lacks a solid foundation in key biological concepts that should be incorporated from specialized literature. Aging is a complex and heterogeneous process; thus, understanding the mechanisms leading to cellular failure, as well as those triggered by preventive interventions, remains an ongoing endeavor. Nevertheless, the interplay among these elements adds further complexity to this scenario. Even if clinicians and researchers know what needs to be done, biological individuality and gene-environment interactions (epigenetic factors) still require a better understanding.

Finally, I suggest omitting the topic of "Blue Zones" when addressing scientific matters, as it lacks rigorous study and relies heavily on empirical observations. Moreover, the framework popularized by the famous documentary appears to suffer from major flaws and biases, rendering the phenomenon highly questionable (<https://www.biorxiv.org/content/10.1101/704080v3.full>).

Therefore, I suggest respectfully rejecting the manuscript. I recommend that the authors incorporate additional literature to strengthen their proposal. Below, I provide a few suggestions:

- Kroemer et al., 2025

<https://doi.org/10.1016/j.cell.2025.03.011>

- López-Otín, Kroemer, 2021

<https://doi.org/10.1016/j.cell.2020.11.034>

- Furman et al., 2019

Chronic inflammation in the etiology of disease across the life span

- Franceschi et al., 2000

The network and the remodeling theories of aging: historical background and new perspectives

- **Franceschi, 1989**

Cell proliferation, cell death and aging

I remain at your disposal for any questions.

Best regards!

## **Declarations**

**Potential competing interests:** No potential competing interests to declare.