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## Debate on human aging and lifespan

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### Summary

The issue of human lifespan has long been a matter of controversy among scientists. In spite of the recent claim by Dong et al that human lifespan is limited to 115 years, with the mounting improvements in biotechnology and scientific understanding of aging, we may be confident that aging will slow down over the course of the current century extending human longevity much longer than 115 years.

#### Authors' Biosketch

Mohammad Rafi received his PhD in Animal Biology from the University of Montpellier, France, in 1970. He taught Cell and Molecular Biology for over 17 years at the School of Science, Tabriz University, Iran, where he also served as Chair of the Department of Animal Biology. He is currently a Professor of Neurology in the Department of Neurology with a joint appointment in the Department of Neurosciences at Thomas Jefferson University in Philadelphia, USA. Though he has worked on several lysosomal storage diseases, his main research interest is gene therapy of neurodegenerative disorders using animal models of globoid cell leukodystrophy (Krabbe disease). With successful AAVrh10-mediated treatment of murine and canine models, his research is moving towards the treatment trials of human patients.



Abass Alavi, MD is a distinguished professor in the Department of Radiology at the Hospital of the University of Pennsylvania (Philadelphia). Professor Alavi is known for his exceptional achievements in the field of PET as well as the structural imaging with MR and CT, including groundbreaking studies in cardiovascular diseases, neurologic disorders, and inflammation. He was awarded two honorary degrees from the European universities in 2016. Each was presented in the recognition of his great contributions to the molecular and structural imaging over the past 45 years. In May 2016, he received an honorary doctorate of medicine from the Medical University of Gdansk (Poland) at a ceremony hosted by the rector of the university, Dr. Janusz Morys (MD, Ph.D.) who highlighted Prof. Alavi's excellent contributions to PET imaging that changed the direction of the diagnosis of diseases. In October 2016, Dr. Alavi was rewarded with an honorary doctor of medical sciences degree from the University of Southern Denmark (Odense) in a ceremony of the 50th anniversary of the university in the attendance of Queen Margrethe II of Denmark. In the celebration, Dr. Alavi's outstanding contributions to the nuclear medicine and clinical molecular imaging were highly remarked. Professor Alavi has mentored and trained a large number of physicians and scientists in the United States, Europe, South America, and Asia. Dr. Alavi is a researcher of the highest international reputation - one of a kind in his class. With his unique background and education, he possesses the characteristics and qualities of a true polymath. He has been and remains to be the driving force behind the spread of knowledge about and the application of molecular imaging technology for the benefit of patients and society. Dr. Alavi was born in 1938 in Tabriz, a city in the Azerbaijani region of Iran. After becoming a physician, he moved to the United States in 1966 to advance his education in a science-based specialty. Together with chemists at Brookhaven National Laboratory (Upton, NY), Dr. Alavi, David Kuhl (MD) and Martin Reivich (MD) introduced <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG). Through this collaboration, in 1976, Dr. Alavi was the first to administer <sup>18</sup>F-FDG to a human subject, producing tomographic images of the brain by means of a handmade Single-photon emission computed tomography (SPECT) device and planar whole-body images with a rectilinear scanner. His group pioneered the positron-emission tomography (PET) imaging of the normal brain and disorders (e.g., dementia, stroke, glioma, schizophrenia, and brain trauma). Professor Alavi has published over 1,000 articles in scholarly and high-impact journals. He is among the most cited physician/scientists in the United States, with current annual citations of 3,000 and citation indices of 50,000. Previously, Dr. Alavi has been recognized with honorary degrees from the University of Bologna (Italy), the University of the Sciences (Philadelphia, PA), and the Universities of Shiraz and Tabriz (Iran). He is a past recipient of the De Hevesy and Cassen awards from the Society of Nuclear Medicine and Molecular Imaging (SNMMI). He plays a central role in the establishment of the Aging Research Institute at Tabriz University of Medical Sciences in Iran. Prof. Alavi serves on the editorial board of several international journals, including *BioImpacts*.



In a paper entitled “Evidence for a limit to human lifespan” by Dong et al that was published in *Nature* Vol. 538 (October 13, 2016),<sup>1</sup> the authors concluded that human lifespan is limited to 115 years and the probability of a lifetime exceeding 125 in any given year is less than 1 in 10000. After about 8 months, the topic is now up for debate again. Five brief communications from different research groups have appeared in *Nature* Vol. 546 (June 29, 2017),<sup>2-6</sup> all disagreeing with the paper's

conclusion that the human lifespan is limited to 115 years. The critics have analyzed the paper from different viewpoints. The arguments focus primarily on different aspects of the statistical analysis, the limited availability of data, the splitting of the study period into two ranges (1968–1994 and 1995–2006), the failure to collect and verify the lifespan of extremely long-lived individuals, and the disregard for possible other trajectories. However, the authors of the paper have rejected all of these critics in



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different rebuttal letters (*Nature* Vol. 546) and defended their conclusion of a human lifespan limited to 115 years.

The issue of human lifespan has long been a matter of controversy among scientists. According to Olshansky and Carnes,<sup>7</sup> there are three opposing viewpoints on human longevity, those of “Futurists,” “Optimists,” and “Realists.”

Futurists believe in the continuous extension of human life with no limitation. They rely on forthcoming improvements in different biotechnological domains that will dramatically transform the landscape of human aging and longevity toward a physical immortality and eternal youth.

Optimists believe that the existing increase in life expectancy, which began during the last century, will continue its linear increase at about 2.5 years per decade. Optimists, too, rely on biomedical technologies not currently available and do not foresee any limit to a continuous increase in life expectancy.

Realists, however, argue that human lifespan is biologically determined and that continuous increase in life expectancy is, practically, implausible. They believe that there are many factors interfering with the duration of human life, as well as with the lifespans of other organisms. Aging, itself, is a fact that, according to existing scientific knowledge, cannot be stopped or reversed. It may be slowed down, but it is unlikely to have a perceptible impact on life expectancy. Therefore, Realists believe in the existence of a life boundary that is like a warranty period or expiration date, limiting lifespan and, hence, longevity.<sup>7</sup>

There is no doubt that, due to scientific advances in biotechnology and medicine, human life expectancy has increased during the last century. According to the National Institute on Aging, while the average life expectancy for babies born in 1900 was only 47 years, it rose to 79 years in 1998. Meanwhile, the title for the longest life recorded in human history belongs to the French woman Jeanne Calment, who lived 122 years (1875-1997).<sup>8</sup> It is also notable that the upward course in life expectancy has slowed down during the current century. While the precise limit to human longevity is arguable, based on the current state of our medical and biomedical knowledge, some limit or range of limit is necessary. Therefore, human immortality and eternal life, as supported by Futurists, appears to be out of the question. Clearly, the study done by Dong et al.<sup>1</sup> suffers from restricted sample availability. A more realistic evaluation of human longevity requires not only a longer study duration, which would, in turn, provide an increased sample size but also a carefully designed study plan and data analyzing strategy.

The increase in life expectancy during the last century was mostly due to improvements in public health and achievements in declining early age mortalities. In the future, the escalation in human lifespan will depend on healthier lifestyles and the availability of improved biomedical advances and biotechnologies. With scientific interventions and environmental improvements, we may be confident that aging will slow down over the course of

the current century.

Aging may be inevitable, but the rate of aging may not be so if we recognize the causes of aging. What appears to play a more influential role in limiting lifespan is the progressive accumulation of molecular damage inside the cells. While any kind of structural and molecular damage may profoundly affect cell function and accelerate the aging process, damage to DNA structure, because of its vital role in life, has been a focal point, giving rise to the “DNA damage theory of aging.” Both mitochondrial and nuclear DNA damage lead to the development of pathological conditions that accelerate aging and senescence. Fortunately, our cells are equipped with mechanisms that can efficiently repair these damages. However, over time, some of these repair mechanisms may fail or their function may be blocked by other molecules. Therefore, damaged DNA will remain unrepaired and, as time goes on, accumulate, disturbing cell function and affecting lifespan.

One of the DNA repair pathways relies on the restoration activity of “poly-adenosine diphosphate-ribose-polymerase 1” (PARP1). The repair function of this enzyme can be inhibited by another protein called “deleted in breast cancer 1” (DBC1). The DBC1 gene was originally found to be deleted in some breast cancer cells.<sup>9</sup> This protein seems to be involved in the regulation of cancer cell energy metabolism.<sup>10</sup> A recent study by Li et al.<sup>11</sup> has revealed that both PARP1 and the oxidized form of “nicotinamide adenine dinucleotide” (NAD<sup>+</sup>) compete with each other in binding to the DBC1 protein, therefore, keeping PARP1 unblocked and capable of DNA repair.

Experiments conducted in old mice,<sup>11</sup> have shown that age-related DNA damage diminishes when the cellular level of NAD<sup>+</sup> is increased. The outcome of these experiments suggests that as NAD<sup>+</sup> levels decline with age, fewer NAD<sup>+</sup> molecules are available to prevent DBC1 binding PARP1. Therefore, unblocked DBC1 will bind PARP1 and damaged DNA will remain unrepaired. The accumulation of the unrepaired DNA, over time, will gradually paralyze cell function. In an increased abundance of NAD<sup>+</sup>, the harmful action of DBC1 will be stopped and DNA repair with PARP1 will continue slowing down the aging process.

Another study just published in *Nature* (July 26, 2017)<sup>12</sup> demonstrates the role of renewed neuro-stem cells (NSCs) in the hypothalamic region of the mouse brain. While the pivotal role of the hypothalamus in whole body aging was shown previously,<sup>13</sup> in this study the authors demonstrated that besides the known neurogenesis role of the hypothalamic NSCs, these cells contribute greatly in the production of exosomal microRNAs (miRNAs) in the cerebrospinal fluid. These exosomes, which are linked to the neuro-stem cell function, and therefore, to whole body aging, can be produced from the cultured hypothalamic NSCs and delivered to the brain hypothalamic area. While the exosomal miRNAs production declines during aging, their increased level in the treated mice leads to slow down the aging process.<sup>12</sup>

Given the crucial biological differences between mice and humans, the applicability of these treatments in humans and their positive results remain to be seen. In the best case of scenario, expecting an increase in average life expectancy for young generations of about 100 years and longevity over 125 years appears to be reasonable.

#### Competing interests

The author declares no competing interests.

#### Ethical approval

There is none to be declared.

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