BRIEF OF THE SCIENTIFIC ADVISORY BOARD ON:

THE BIOLOGY OF AGING[1]

Scientific Advisory Board

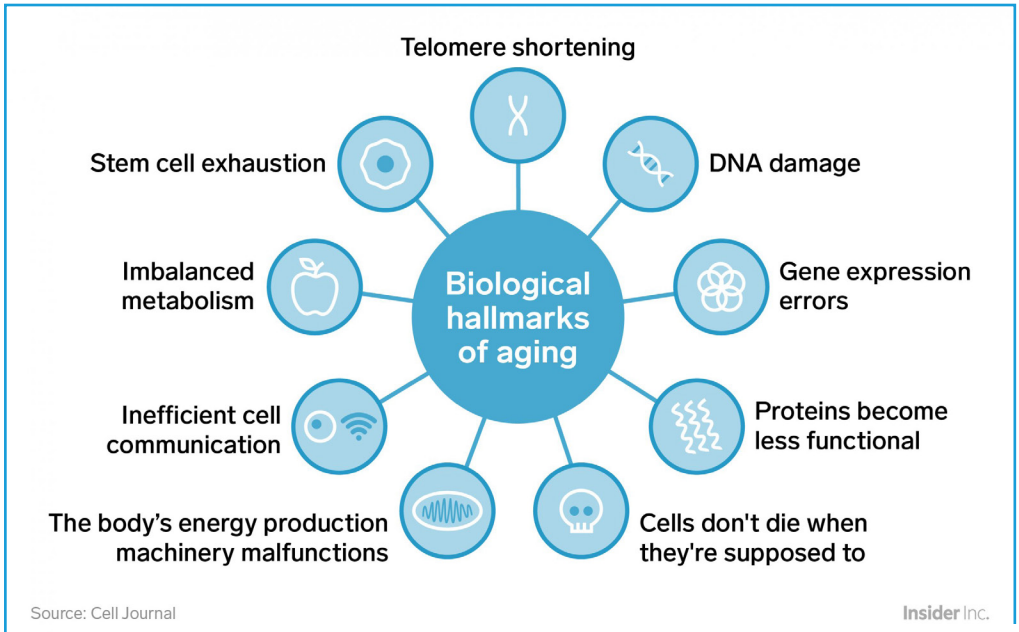
WHAT IS AGING?

In biological terms, aging refers to declines in function, decreased capacity to recover from such stresses as wounds or infections, and increased susceptibility to disease and death over time.[2] Aging results from genetic, environmental, social and other factors that manifest differently in each person. In biological terms, age is associated with:

Molecular and cellular processes: The accumulation of damage at the molecular and cellular level is one of the primary causes of aging. Over time, cells undergo "senescence," gradually losing their ability to replicate and function properly. An accumulation of DNA mutations, stress, and/or a decline in DNA repair mechanisms can lead to instability and decline in a human's genomic stability. Telomere shortening – the gradual loss of the protective caps on the end of chromosomes – or telomere dysfunction is one of the main causes for cells to enter senescence. Loss of proteostasis – the ability of proteins to maintain quality and fold correctly – can contribute to multiple disorders and diseases including Alzheimer's.

Genetics and epigenetics: Our genetic code regulates all cellular functions and our susceptibility to diseases, playing an important role in aging. Over time, chance mutations in our genome predispose humans to diseases such as cancer, and increase our chance of suffering heart attacks. Our genes are regulated by epigenetic processes (for example, DNA methylation and histone modifications) that can deteriorate with aging. As a result, epigenetic clocks are a potential measure a person's biological age and risk of mortality.[3] Large-scale genome studies have identified genetic predispositions to longevity; for example, human variation in the apolipoprotein gene are a major factor in aging, and can help control the risk of diseases like Alzheimer's.[4]

Systemic biomarkers: At the level of the human body, the functional decline of tissues and organs can be used to measure aging. Blood-based biomarkers (e.g. glucose and cholesterol levels) have been found to be highly correlated with disease and death. Similarly, changing metabolic functions, hormone production, and organ degeneration are all well-established markers of aging.[5]



Biological Processes of Aging

Inflammation and the immune system: Low-grade inflammation that occurs as part of the aging process is referred to as "inflammaging."[6] Resulting from a range of factors like cellular senescence, oxidation, stress, and accumulation of molecular damage, inflammaging contributes to degenerative disorders, cardiovascular disease, and cancers. Over time, the weakening of immune system response places older people at greater risk of disease and death.

Taken together, these approaches offer an increasingly accurate understanding of the complex and interrelated fundamental aging processes that are root-cause contributors to multiple disorders and diseases across the lifespan.

WHAT IS "GEROSCIENCE"?

Around the world, people are living longer. By 2030, 1 in 6 people will be aged 65 or older, with numbers steadily increasing until 2050.[7] But longer lifespans are not equaled by improved "health span" (the period of life spent in good health), meaning that more people are living for longer periods of time with impaired cognitive functions, chronic diseases and other ailments.[8] Indeed, the gap between health span and lifespan is increasing around the world.[9] The enormous social and economic costs of this trend have driven a significant growth in biological research on aging, referred to as "biogerontology," "gerontology" or "geroscience."[10]

In general terms, geroscience aims to discover ways to target fundamental human aging mechanisms and to delay, prevent, alleviate, or treat multiple disorders and diseases linked to these aging processes.[11] Geroscience involves: (1) altering or tracking the **biological mechanisms** of aging; (2) **pharmacological** treatment of age-related diseases; (3) **dietary** approaches to increase healthspan and delay, prevent, or treat age-related dysfunction and diseases; and (4) **surgical** approaches such as organ replacement, bionic augmentation, and tissue regeneration.[12] Geroscience has not only uncovered new ways of measuring progression of aging processes (for example, epigenetic clocks), but also suggested lifestyle changes and investigated possible gene editing and pharmacological manipulations to delay aging.[13]

Appreciating the important roles that social and environmental factors play in aging, this brief focuses on recent developments in the biological and medical approaches.

RECENT DEVELOPMENTS AND BREAKTHROUGHS

Major advances in the fields of genetics in the past 25 years have fueled optimism that geroscience could eventually slow or even suspend human aging processes. Discoveries of genes linked to longevity, enzymes involved in DNA repair, drugs that can regulate cellular function (e.g., mTOR inhibitors), and the effects of dietary interventions on the lifespan of animals under laboratory conditions have led some scientists to speculate that aging itself may be at least partially biologically controllable.[14]

This optimism has driven a dramatic increase in investment in gerontology, with hundreds of millions of dollars being offered annually as prizes for breakthroughs in aging, and major national investments in research facilities.[15] Some scientists have criticized the field as overly optimistic, driven more by a desire to attract large-scale funding than demonstrated application to human beings.[16] Separating the hype from the reality is one of the major challenges in assessing the current field of geroscience.

Based on consultations with a wide range of experts in the field, the most important developments in recent years include:

Senolytic drugs: Many of our cells undergo a process called cellular senescence over time, contributing to age-related diseases and death. Senolytic drugs selectively eradicate these senescent cells, preventing their build-up in our body's systems and potentially warding off a number of disorders and diseases. Clinical trials on the application of senolytic drugs for diabetes, Alzheimer's disease, age-related osteoporosis, eye disease, and cancer have shown some promise. However, these studies have also highlighted the need for a deeper biological understanding of cellular senescence and its role in disease progression,[17] particularly since this process plays a vital role in development and wound earlier in life.[18]

Epigenetic reprogramming: Many organisms, including mammals, lose genetic and epigenetic information over time as our cells and DNA age, leading to massive changes in gene expression. A recent study in DNA regulation and sequencing in mice has suggested that this loss of information could be halted or even reversed.[19] While still only in animal trials, the potential for new therapeutic approaches to age-related diseases and lengthened healthspans is significant.

Base editing: The genetic mutation behind Hutchinson-Gilford progeria syndrome causes rapid aging symptoms in children, including osteoporosis, balding, and premature death. Inspired by CRISPR's success in gene-editing, a recent single base-editing technique was able to correct the mutation in mice. If successful in humans, base editing holds the

promise of pinpointing and eradicating some of the most important age-related diseases.[20] Indeed, a recent study at University of California San Diego pinpointed a single genetic mutation that can create a "cascade" of changes across the genome, potentially causing far more of the aging process than previously thought. This discovery suggests that our ability to make genetic modifications to the aging process might be more difficult than previously assumed.[21]

What emerges from a survey of the field is that the biology of aging remains a fundamental mystery. Theories abound, exciting findings are continuously reported, but no widely accepted concept of aging has yet emerged. Across many fields, artificial intelligence (AI) is accelerating progress in geroscience and could have a major impact, including in our understanding of the main mechanisms of aging.[22] For example, machine learning has improved our ability to estimate many biomarkers of aging,[23] radically improved drug discovery,[24] and has revolutionized the prediction of protein folding processes that are at the heart of much of aging research.[25]

However, many of these breakthrough areas are only now emerging. The exciting advances in geroscience have shown us how complex aging processes are biologically and how they predispose to diseases and death. This has moved us closer to the discovery of concrete ways of targeting aging processes, from lifestyle changes to possibly drugs or genetic manipulations.

CONSIDERATIONS

Geroscience has enormous implications, not only for the health sector, but also for our global economy and sustainable development goals. Some of the most important considerations include:

Social and economic burdens: Substantially extending human lifespans would mean a larger, older population (and potentially relatively smaller working-age population), which could place enormous burdens on already strained social and health systems as well as on economic growth and development. If lifespans are not accompanied by preserved function and improved healthspans, this could lead to the collapse of some public health systems.[26] As such, the economic benefits of targeting aging and extending healthspans are potentially enormous.[27] In this context, the scientific community is increasingly advocating for balanced approaches that ensure sufficient focus on healthspan, prevention, and a care economy for aging populations.

Environmental considerations: The increase in the intensity and frequency of climate events, heat and pollution will intersect with an ageing population requiring greater response and care.[28] Polluted environments – particularly air pollution – can increase the cumulative risks for older persons.[29] Growth in global population and age would also contribute to greater energy use, adding to global warming. Building a better scientific understanding of the links between environmental risks and age will be an important global health priority.

Public knowledge and awareness: Much research is focused narrowly on quickly developing often complex avenues to counteract aging. This can lead to major investments in the latest alleged breakthrough, but not necessarily a deeper understanding of how biological advancement can benefit humanity as a whole. Public understanding is largely inhibited by the highly technical nature of the research, and also to the tendency of some geroscientists to "hype" findings to attract funding. Here, a growing number of scientists have called for greater transparency, clear communication of scientific advancements, the importance of holistic approaches to extend healthspan, and improved understanding of potential avenues to prevent, delay, or manage age-related disorders.

Inequalities: The overwhelming bulk of geroscience is conducted in the global North, with large companies focusing efforts on more affluent populations. This is likely to lead to widening global health inequalities if emerging therapies and treatments are only available in developed regions, or tailored to specific groups living in developed countries. Equitable development of geroscience, reduced barriers to access, and capacity-building in the global South could help to prepare middle- and low-income countries for major demographic transitions that will take place over the coming decade. It is also worth highlighting a well-established gender bias in health research, where women-specific issues are often overlooked – highlighting the need for geroscience to account for gender-specific aging pathways, for example, the anti-aging effects of hormone replacement therapy.[30]

Dual-use of geroscience: As with any health research, the possibility of military application poses some risks. In some scenarios, therapies to combat fatigue or increase cognitive abilities could be employed to create more robust soldiers. In others, treatments to reverse or slow aging could be manipulated to create diseases or aging acceleration. While these remain highly speculative for now, there is a growing call for scientific forums and normative guardrails for the safe development of geroscience to be put in place.

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1 This brief represents the views of the independent scientists on the Scientific Advisory Board. It does not necessarily reflect the UN's position or those of network institutions. Mention of a commercial company or product in this document does not imply endorsement by the UN or the authors. The use of information from this document for publicity or advertising is not permitted. Trademark names and symbols are used in an editorial fashion with no intention on infringement of trademark or copyright laws. The Board is deeply grateful for the expert views offered by Nir Barzilai, Rafael de Cabo, Kaare Christensen, Collin Ewald, Evandro F. Fang, David Gems, Christian Enrique Gonzalez Billault, Vera Gorbunova, Verena Haage, Glenda Halliday, Eva Hoffmann, Steve Horvath, Gerard Karsenty, James Kirkland, Valter D. Longo, Joao Pedro Magalhaes, Suresh Rattan, Bjoern Schumacher, David Sinclair, Reisa Sperling, Deborah Toiber and Jan Vijg.

2 It is worth noting that Aging processes can begin at or before conception. For example, Down syndrome (trisomy 21) occurs in the mother's oocyte even before conception and leads to accelerated cellular senescence, even in utero, and earlier death from multiple disorders and diseases, such as Alzheimer's and many blood cancers, than others in their children. Progeroid syndromes that are accelerated with accelerated biological aging processes begin in childhood. Pre-eclampsia in mothers during pregnancy results in accelerated development of diabetes, cardiovascular disorders, and dementias. Treatment of children with chemotherapy or radiation can cause an accelerated aging-like state, with death in their 30's from multiple chronic diseases. The WHO ICD 11 classification for multimorbidity and other syndromes is "impaired intrinsic capacity". This effectively replaces "aging", which was removed from ICD 8 because a 6 year old is older than a 4 year old.

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