Update: Prospects for an Improved Healthspan and Lifespan

Feb. 2021

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We believe that while death is inevitable, aging need not be. This is important at the personal level and for our culture. Health care costs are coupled with the economic impact of society's loss of productivity from years of declining vigor.

- Judith Campisi, PhD, Professor, Buck Institute for Research on Aging, CA, on the founding of the Academy of Health and Lifespan Research (AHLR), Feb 2019 (https://www.ahlresearch.org/home)

Update: Prospects for an Improved Healthspan and Lifespan

- **Introduction to the machinery of aging, Nine Hallmarks**
- **COVID pandemic year: aging science and medicine disrupted (like everything else!)**
- **Biological Aging Clocks: A revolution in predicting Healthspan and Lifespan**
- **Cellular Senescence Hallmark: recent advances in research and pharmaceuticals development**
- **Epigenetic Alterations Hallmark: recent developments in slowing/reversing biological aging and promoting regeneration/rejuvenation of tissues**
- **Resources for further exploration of these and related developing stories**

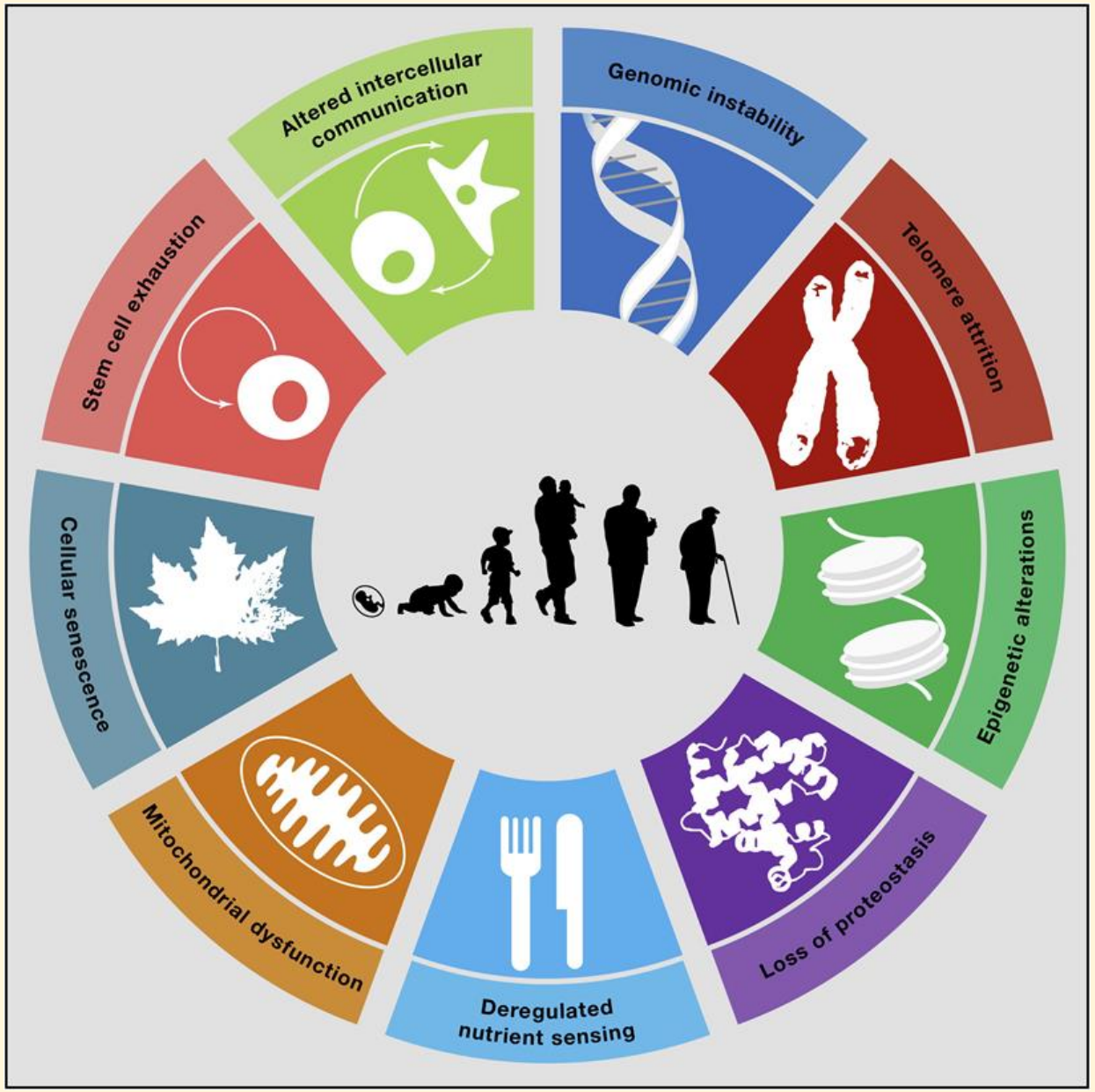
What is Aging?: Introduction & Nine Hallmarks

<u>Introduction:</u> Int. of Steven Austad, Scientific Director, Am. Federation for Aging Research, 8 m (https://vimeo.com/434123753)

<u>Hallmarks of Aging:</u> Cell-Level changes and "common denominators of aging" in mammals

Interdependencies between hallmarks in this complex system

Which are more fundamental, closer to root cause(s) of aging?



From: ***The Hallmarks of Aging***, Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, Guido Kroemer, *Cell* , Volume 153, Issue 6, Pages 1194-1217 (June 2013)

What are the Hallmarks of Aging?

Steven Austad, Director – Nathan Shock Center of Excellence in the Basic Biology of Aging, U of Alabama
(https://nathanshockcenters.org/biology-of-aging)

"The core underlying machinery of how our bodies age"

Epigenetic Alterations. Proteins and chemical tags, such as methyl groups, added on top of the genome DNA (without altering the genetic code) to regulate expression of different genes. Alterations during development differentiate cells in all our tissues and organs, and patterns of change continue through the entire lifespan. These can be influenced by lifestyle factors, including diet and exercise, and by pharmaceuticals.

Loss of Proteostasis. Maintenance of a specific mix of proteins of correct folded shape, for functionality, is essential to cell structure and function. Loss of precision control of protein folding with age leads to production, and possibly accumulation, of waste proteins. An example is Beta Amyloid accumulation in the brain during AD.

Deregulated Nutrient Sensing. Our bodies change modes of operation, either growth or maintenance-repair, according to the abundance of nutrition in our diet. A limited diet throttles back growth and extends lifespan.

What are the Hallmarks of Aging?
continued

Mitochondrial Dysfunction. Bacteria-like organelles produce the primary energy source of our cells, ATP, and some damaging oxidants as waste byproducts. Mitochondria can release excessive oxidants, outside of an optimal range, with advancing age. Mitochondria reproduce like bacteria, and may accumulate damaging mutations in their DNA with age. Mitochondrial health can be influenced by lifestyle factors.

Cellular Senescence. Attrition of telomeres and other damage may cause cells to stop dividing. If apoptosis (self destruction) fails, the cell may persist alive but dysfunctional, secreting disruptive signal molecules to its neighbors. This causes organ and tissue functioning to decline with age. Diet may modulate survival of senescent cells, and pharmaceuticals may soon provide powerful clinical tools to purge these cells and delay aging.

What are the Hallmarks of Aging?
continued

Stem Cell Exhaustion. Repair/regeneration of our body requires stem cell regulation within organs and tissues. Stem cells must be held in a healthy nonreplicating state until needed. With the advance of age maintenance of stem cells declines and repeated repair tasks may exhaust stem cell replication potential. Lifestyle (e.g. exercise) may promote stem cell maintenance, and signalling factors in the blood may cause stem cells to enter dormant or active states, characteristic of old age and youth, respectively. Stem cell exhaustion in old age is common in the blood-immune system and in skeletal muscles (sarcopenia).

Altered Intercellular Communication. Short range and long range molecular signaling between tissues changes with age. Our balance of hormones in the blood changes over lifespan, and inflammatory signals of damage may not be modulated properly by a declining immune system. Research into signalling molecules in the blood suggests optimization could improve the functioning of major organs, e.g. heart, and reduce the level of damaging inflammation. Optimization of major hormones for each stage of human life is a subject of ongoing research and debate in the popular media.

What are the Hallmarks of Aging?
continued

Genomic Instability. DNA in each cell accumulates damage daily. Fortunately, complex repair mechanisms handle nearly all of this. People born with genetic faults in DNA repair show signs of accelerated aging, so research has aimed to understand and restore DNA repair in the sick and elderly. Dietary restriction and composition, including forms of vitamin B3, seems able to improve DNA repair in older animals, and trials have begun to test their efficacy in humans.

Telomere Attrition. This is a specific kind of genomic instability at the free ends of our linear chromosomes, where many repeats of a special "DNA end" code shorten with each cell division until a critical short length triggers a halt to cell replication. Cells may then undergo apoptosis or become senescent, with the negative consequences noted above. Some stem cells and differentiated cells which are replaced frequently (e.g. the linings of the GI tract) partially make up for losses by prloducing an enzyme, telomerase, which lengthens short telomeres. Experiments with rodents show artificially induced telomerase expression alleviates some symptoms of aging (e.g. muscle weakness, coat condition and color deterioration) and extends lifespan, so translation to aging humans may be possible.

Healthspan and Lifespan Extension: Recent Developments in the Year of COVID19

- **Hospitals overwhelmed by elderly COVID patients, highlighted the disease vulnerabilities which grow dramatically with age. Potential novel clinical treatments entered the pandemic discussions**
  - **New level of interest in measuring and treating aging of the immune, pulmonary, cardiovascular, and other body systems**
  - **Treatment with variants of nutritional support known to normalize immune function (e.g. dietary Zn and oral or IV Vitamin D)**
- **Nonpandemic medical research and clinical trials have been delayed/halted/suspended**
  - **Resources sent home or redirected to immediate clinical needs**
  - **Aging research seminars and conferences have gone online**
- **The importance of lifestyle factors for maintaining health, including social engagement, diet, and exercise, have received prominent coverage in the media**
- **R&D on dietary supplements and pharmaceuticals targeting aging decline of function has accelerated and new products have been brought to market**

Healthspan and Lifespan Extension: Recent Developments in Prediction

- **Steve Horvath, UCLA, pioneered the development of biological aging clocks for many tissues (2013*) to predict longevity (lifespan) and probability of developing specific age-related diseases (healthspan)**
  - **Found species-specific patterns of epigenetic change, DNA methylation, characteristic of the chronological age of the organism, tissue, or cell.**
  - **Deviations from that general pattern of change by individuals, "age acceleration", were predictive of individual risk of death or disease.**
- **Subsequently, Horvath and others have developed improved or similar clocks for lifespan or disease risk based on**
  - **DNA methylation patterns, RNA's, and proteins present in cells.**
  - **Other clocks mix in or substitute conventional medical tests (e.g. fasting blood glucose, grip strength).**
  - **Skin and facial features have also been used to create clocks, and they show remarkable agreement with clocks based on biochemical characteristics alone.**

*Steve Horvath, 2013, DNA methylation age of human tissues and cell types, Genome Biology.

Healthspan and Lifespan Extension: Recent Developments in Prediction continued

- **The importance of biological age clocks is twofold:**
  - **Suggests feasibility of new health risk diagnostic tools, which applied to individuals, could help identify prescriptive therapies or lifestyle changes to reduce health risks, and, more importantly, measure the success of the prescription.**
  - **Facilitate the development of pharmaceuticals or other therapies for diseases using cell cultures and animal models. Epigenetic changes observed in a sample of affected patients, cells and animal models may be used to specify desirable epigenetic changes associated with risk reduction.**
- **2020 video talk by Rhonda Patrick, Ph D, introducing epigenetic age measurements, 3m45s: https://www.youtube.com/watch?v=_iI_U7lH8wc&t=8s**

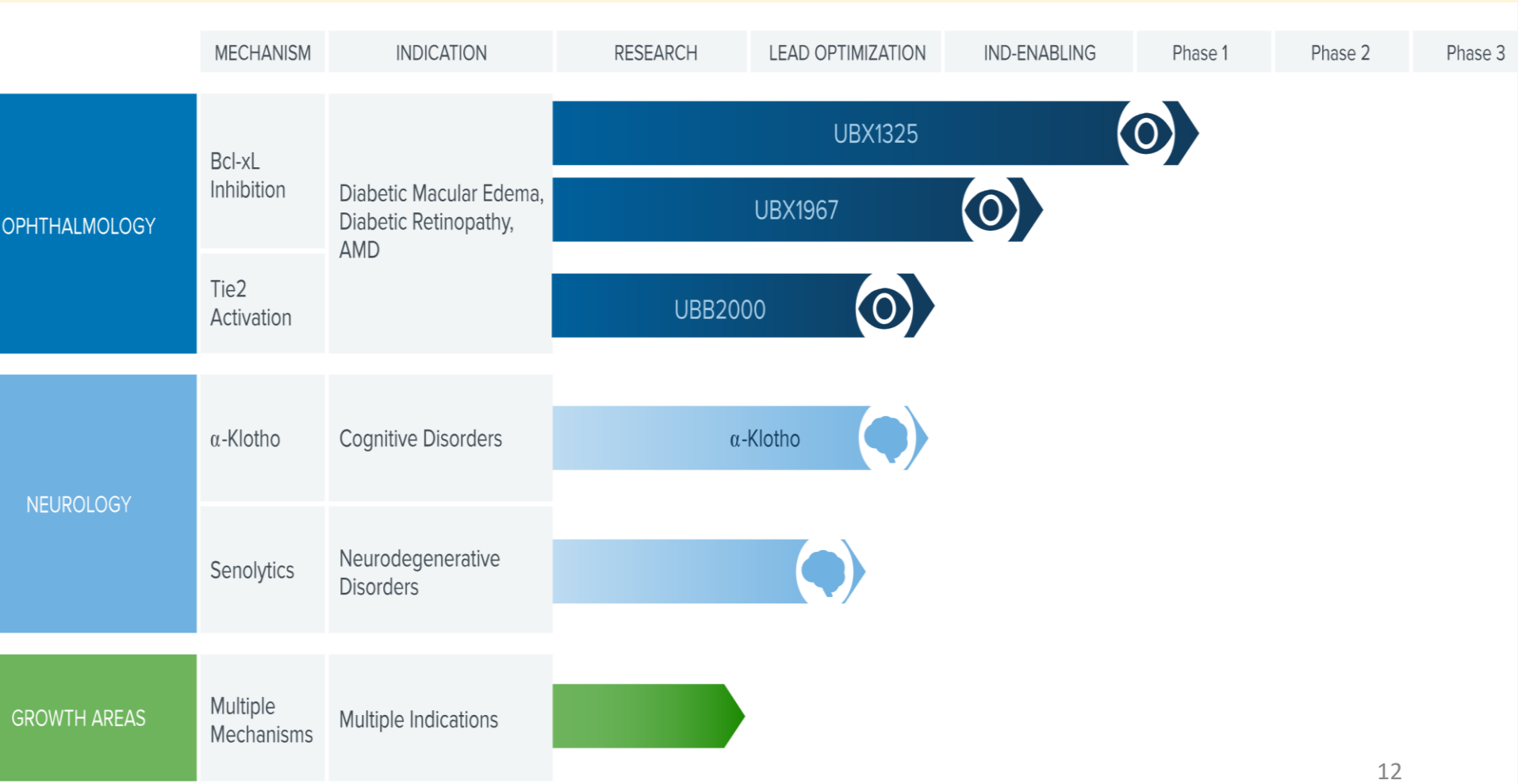
Healthspan and Lifespan Extension: Recent Developments in Aging Hallmarks Research

Cellular Senescence, a significant risk for age-related diseases including cardiovascular disease, cancer, and sarcopenia.

- **In June of 2019 Unity Biotechnology, arguably the leading pharmaceutical developer of senolytics, senescent cell destroyers, reported positive results of Phase 1 (safety level) trial of its first senolytic, UBX0101, targeted at osteoarthritis.**
- **In August of 2020 Unity reported the results of Phase 2 (efficacy level) trial of UBX0101. The treatment failed to meet the 12-week primary endpoint for reduction of pain. Unity halted all further work on UBX101, and refocused resources on UBX1325 for retinal disease.**
- **R&D of senolytics continues at numerous academic and pharmaceutical company labs. In August 2020 James Kirkland, senolytics pioneer at the Mayo Clinic, authored a review article, Senolytic drugs: from discovery to translation, in the J of Internal Med. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7405395/)**

UNITY Biotechnology Pipeline of Developmental Drugs, February 2021

(https://unitybiotechnology.com/pipeline/)



Healthspan and Lifespan Extension Recent Developments in Aging Hallmarks

Epigenetic Alterations:

Progress in reprogramming gene expression to a more youthful pattern in each tissue, leading to a more youthful state of health

- **In 2006 Shinya Yamanaka's lab at Kyoto U. published a revolutionary finding (later earning a Nobel Prize)**
  - **activation of only 4 genes, shorthand designated OSKM, was sufficient to reprogram skin cells (fibroblasts) back to a pluripotent stem cells which can give rise to all tissues in the body**
  - **raised the prospect of eventually growing youthful replacement tissues for the human body**
- **Over the next 12 years scientists found gene combinations to reprogram virtually any cell type to any other type without fully understanding the process**

Healthspan and Lifespan Extension Recent Developments: Epigenetic Alterations continued

- **Researchers at the Salk Institute have reprogrammed cells in the body with the aim of enabling regeneration of damaged/diseased/missing tissue**
- **The group of Juan Carlos Izpisua Belmonte has been conducting research on cell reprogramming in mice for several years:**
  - **2017: demonstrated relief from a progressive genetic disease, return to a youthful form, and erasure of cellular markers of aging without disrupting the epigenetic programming specific to individual tissues.**
  - **2018: demonstrated induction of wound healing by reprogramming exposed connective tissue, the first production of a major organ tissue, the skin, by reprogramming of another adjacent tissue**
  - **The reprogramming genes were engineered into a virus, which takes them into the cell membrane and activates them.**

Healthspan and Lifespan Extension Recent Developments: Epigenetic Alterations continued

David Sinclair's research group at Harvard and others authored a 2020 groundbreaking report, "Reprogramming to recover youthful epigenetic information and restore vision"
(https://www.nature.com/articles/s41586-020-2975-4)

- **Described a technique for youthful regeneration of retinal neurons by nudging the cells toward, but not into, a less differentiated state using Yamanaka factors plus enzymes for attaching/removing methyl groups (-CH_3) from DNA**
- **Yamanaka genes, along with a chemical on/off switch, were engineered into a virus to infect the retina of living mice**
- **Limited operation of the inserted genes promoted youthful regeneration of a crushed optic nerve and return of vision; vision lost due to mouse glaucoma or in the course of normal aging was also improved**
- **Another result was a more youthful neuron epigenome according to the methylation clocks developed by coauthor Steve Horvath, UCLA.**
- **In an excerpt from a 2019 interview by Rhonda Patrick, David Sinclair describes the above research briefly (5.5min): (https://www.youtube.com/watch?v=cr1iRlSPSTA)**

Resources for Further Exploration

- **Aging Clocks:**
  - **Introductory level talk by Steve Horvath in 2020 at TEDx Berkeley, 14.5 min: https://www.youtube.com/watch?v=LuQKXux8UlE**
  - **Recent 2020 talk by Steve Horvath in NUS Medicine lecture series Healthy Longevity, hosted by Prof. Brian Kennedy, a 1 hr. program: https://www.youtube.com/watch?v=w1cubSfCVbM**
  - **Recent research and review articles comparing clocks for accuracy, utility, and possible mechanisms of aging:**
    - **Z Liu, M E Levine, et al, 2020, Underlying features of epigenetic aging clocks in vivo and in vitro, Aging Cell**
    - **Wolfgang Wagner, 2017, Epigenetic aging clocks in mice and men, Genome Biology**
- **Talks on aging research interpreted for a broad audience**
  - **National University of Singapore (NUS) School of Medicine, webinar series Healthy Longevity (started late 2020 and now has 9 great recorded talks and counting), hosted by Prof. Brian Kennedy, formerly with the Buck Institute: https://medicine.nus.edu.sg/cet/healthy-longevity/ and on Youtube**
- **Talks and interviews on aging science and lifestyle, esp. nutrition**
  - **Rhonda Patrick, PhD website, Found My Fitness, https://www.foundmyfitness.com/, and Youtube channel**
- **Aging Research News**
  - **Lifespan.io provides aging science news, education, and opportunities to fund seed research projects: https://www.lifespan.io/**

Resources for Further Exploration

- **Critical Science-based Reviews of Lifestyle and Dietary Supplement Practices (frequent new developments in this arena, so you do need help here!) and other topics in health and aging**
  - **Dr. Brad Stanfield, MD (young physician in New Zealand) Youtube channel: https://www.youtube.com/channel/UCpcvPcHJVOkO9Qp79BOagTg**
  - **The Sheekey Science Show Youtube channel by an English biochemist and Ph.D. candidate at Cancer Research UK - Cambridge Institute. (p53 & senescence): https://www.youtube.com/c/TheSheekeyScienceShow/featured**
- **Recommended Books**
  - **Lifespan by David Sinclair**
  - **The Secret Language of Cells by Jon Lieff, MD (see also his WEB Blog on Searching for the Mind: https://jonlieffmd.com/blog)**
  - **Livewired by David Eagleman**
  - **The Cancer Code by Jason Fung, MD**
  - **Aging is a Group-Selected Adaptation by Josh Mitteldorf (and his science blog Aging Matters: https://joshmitteldorf.scienceblog.com/)**
  - **Breath by James Nestor**
- **Business Development News**
  - **Longevity Technology https://www.longevity.technology/**