

# **Update: Prospects for an Improved Healthspan and Lifespan**

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**Karl Blasius**

# **Healthspan and Lifespan Extension: Progress Update, Refocusing on the Basics**

**With the easing of the COVID Pandemic we can focus again on the common life-threatening diseases for which age is the greatest risk factor:**

- **cardiovascular disease, including stroke and heart attack,**
- **neurological diseases (e.g. dementias),**
- **insulin resistance (including T2 diabetes and its complications), and**
- **cancer.**

# **Healthspan and Lifespan Extension: Progress Update, Outline**

**Today's focus is on three developments in healthspan research and clinical practice:**

- 1. Refinements to the observed components of aging, the Hallmarks of Aging, a framework for research into the biochemical mechanisms of aging**
- 2. Illustrative scientific advances in specific Hallmarks in basic science and clinical treatments**
- 3. A renewed clinical focus on lifestyle basics, food and physical activity, for addressing multiple Hallmarks.**

# What is Aging?: Its Hallmarks have been reassessed from nine to twelve

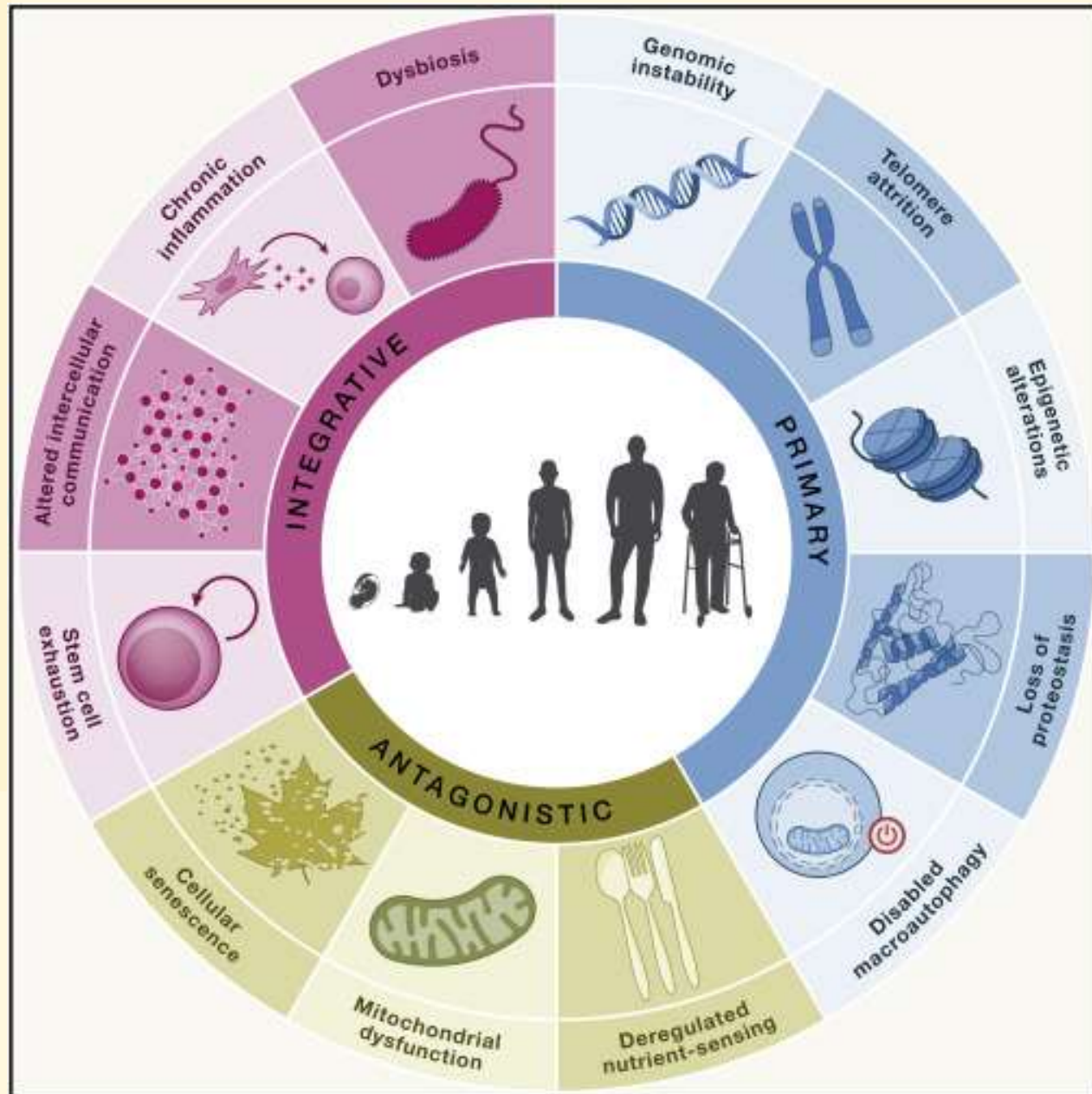
Cell-Level changes associated with aging, or “common denominators of aging” in mammals

Initially recognized to be incomplete. Now rethought to add: the aging microbiome (Dysbiosis), disabled macroautophagy, and chronic inflammation.

Hallmarks are found to be organized into networks.

*The Hallmarks of Aging*, Carlos López-Otín, Maria A. Blasco, Linda Partridge, Manuel Serrano, Guido Kroemer, *Cell*, Vol 153, 2013.

*Hallmarks of aging: An expanding universe*, same authors, *Cell*, Vol 186, 2023.



# Hallmarks and Aging Research Methodology

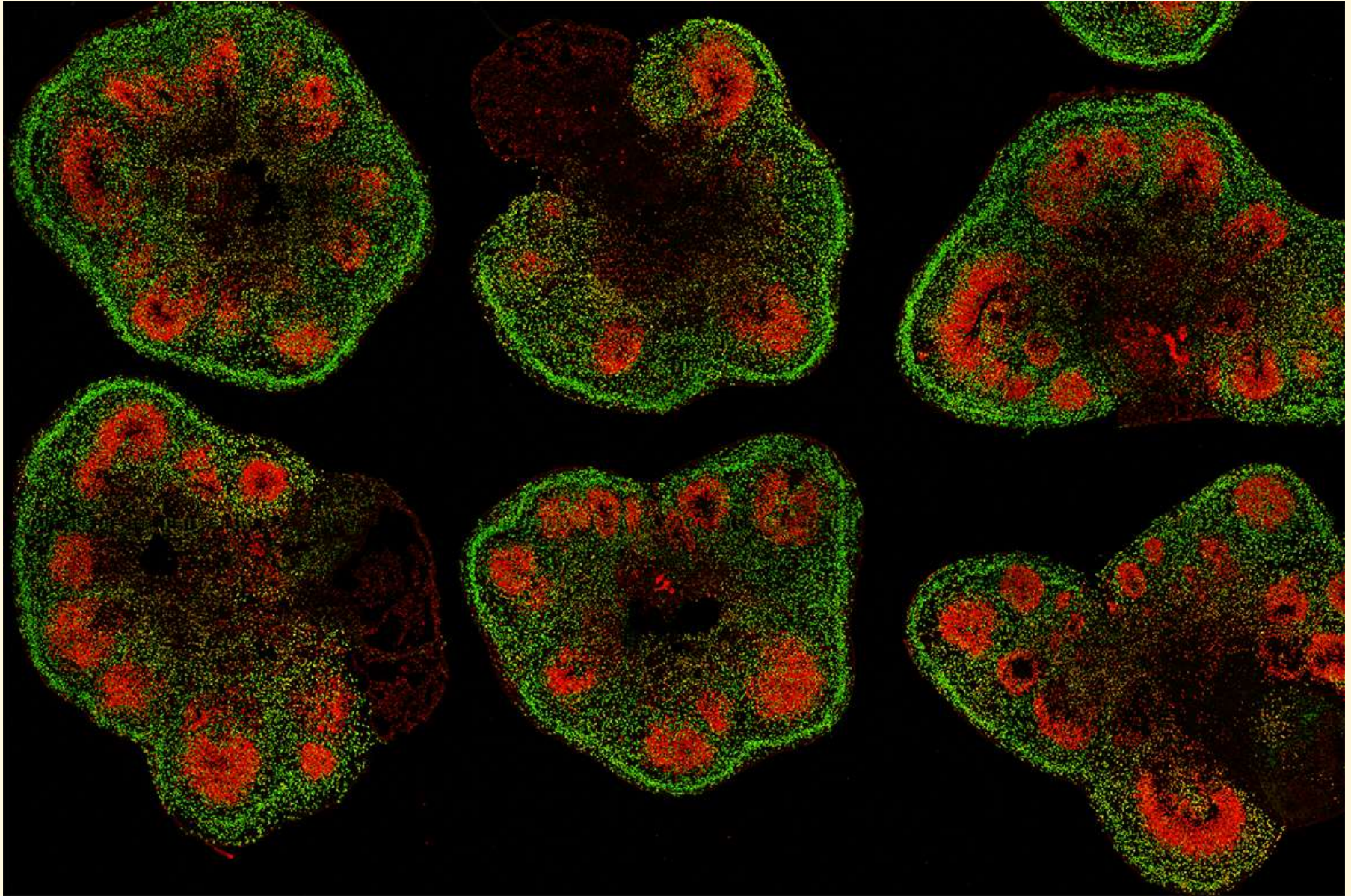
- **Three categories of Hallmark**
  1. **Primary: observed changes with underlying mechanisms thought to be fundamental to aging**
  2. **Antagonistic: changes which seem to be adaptive responses to more fundamental negative changes with age (e.g. cellular senescence blocking cancers)**
  3. **Integrative: changes traceable to multiple other Hallmarks and their mechanisms**
- **Research often starts with the Hallmarks of Aging**
  - **screen to select candidate natural substances, drugs, and other interventions/therapies for Hallmark(s), then**
  - **validate/compare effects in cell cultures, model lab organisms, and then human trials.**
- **This methodology is used in commercial and academic research to target one or more of the Hallmarks.**

# **Aging Research Motivation and Recent Progress**

- **Motivations for Aging R&D** are financial (investors, governments, and individuals), a desire to shorten the period of suffering from severe disabilities at the end-of-life, and curiosity about how life works.
- **Recent successes**
  - **Stem cell Exhaustion:** Lab study of the potential use of cultured stem cells, in the form of brain organoids, to repair brain damage after injury from accident, stroke, or surgery
  - **Chronic Inflammation:** Pilot clinical trial results published for an individualized screening approach to the treatment of Mild Cognitive Impairment (middle stage of Alzheimer's)



# Aging Research Recent Progress: Brain Organoids



**Slices of brain organoids (Hajime Ozaki, Watanabe lab/UCI)**

Week 8 mini-brain organoids with neural stem cells seen in red and cortical neurons seen in green. The layered arrangement of these cells in the organoids resembles the natural architecture of the developing brain.

# **Stem cell Exhaustion Countered to Repair Brain Injury in a Lab Animal Model**

- A group at the Perelman School of Medicine, U Penn, published an investigation\* of the feasibility of using cultured brain stem cells to repair brain damage.**
- Organoids are miniature model organs, exhibiting some functionality, which have been cultured in vitro from induced Pluripotent Stem Cells (iPSCs). Brain organoids, transplanted into an injured brain, might integrate as functional tissue, restoring lost function.**

**\* D Jgamadze, H I Chen, et al., 2023, Structural and functional integration of human forebrain organoids with the injured adult rat visual system, *Cell Stem Cell*.**



# **Stem cell Exhaustion Countered to Repair Brain Injury in a Lab Animal Model**

- **In a step toward testing this hypothesis Jgamadze et al. transplanted human brain organoids into damaged visual cortices of rats and investigated their integration and functionality. They found:**
  - **At 3 months the transplanted tissue had acquired functional blood vessels, grown in size, and integrated synapses with host neurons.**
  - **Neurons within the organoid were found to be responsive to light stimuli in the rat's visual field, a step in functional integration of graft and host.**
  - **A successful first step requiring follow-up with work to overcome transplant rejection and test the potential for more complete vision restoration.**

# **Chronic Inflammation Controlled to Reverse Cognitive Decline in MCI Stage Alzheimer's Disease**

- **A pilot study\* of 25 patients has been published testing a precision medicine personalized approach to the treatment of MCI.**
- **Over 9 months there were statistically significant improvements in**
  - **cognitive assessment (MoCA) scores ( $p < 0.001$ ),**
  - **CNS Vital Signs Neurocognitive Index (NCI) ( $p < 0.001$ ), and**
  - **Alzheimer's Questionnaire Change scores ( $p < 0.01$ ).**

\* K Toups, DE Bredesen, et al., 2022, Precision Medicine Approach to Alzheimer's Disease: Successful Pilot Project, *J Alzheimer's Disease*.

# **Chronic Inflammation Controlled to Reverse Cognitive Decline in MCI Stage Alzheimer's Disease**

- **Significant improvements over 9 mo. were also seen in serum biochemical tests Hs-CRP (inflammation), Hemoglobin A1c (blood sugar), TG:HDL, Homocysteine (CVD risk), and Vitamin D.**
- **Comparison of the results to historical controls**
  - **no such broad cognitive improvements have been observed previously,**
  - **support the general approach in a larger randomized controlled clinical trial (planned to start 2023)**

# **Chronic Inflammation Controlled to Reverse Cognitive Decline in MCI Stage Alzheimer's Disease**

- **Treatment protocol of personalized precision medicine involved identifying and addressing potentially MCI contributory factors for each patient with the intention of:**
  - **restoring insulin sensitivity**
  - **improving hyperlipidemia**
  - **resolving inflammation**
  - **treating pathogens**
  - **optimizing energetic support to the brain (oxygen, blood flow, ketones, mitochondria)**
  - **Optimizing trophic factors (hormones, nutrients, growth factors)**
  - **Treat autoimmunity**
  - **Detoxify, if applicable**

# **Dr. Dale Bredeesen describes the Pilot Project and its Results**

- **Lessons from the First Clinical Trial to Reverse Cognitive Decline, August 2022, 1h16m (excerpt 13m51s to 26m15s: Theories of Alzheimer's and The Clinical Trial)**

**<https://www.youtube.com/watch?v=rp-sEZsuQPA>**

**From the Apollo Health Youtube channel description:**

**“Unlike other trials, which have only managed to slow disease progression slightly at best, 84% of participants in Dr. Bredeesen’s trial experienced improvements in their cognition, with the average leaping from the 38th to 63rd percentile — a 65.7% improvement. There were also measurable improvements in brain volume and wellbeing assessments.”**



# Adjusting Lifestyle to Address Hallmarks of Aging

Longevity clinicians and researchers seem to be focusing again on physical activity and nutrition.

- The positive values of regular physical activity are supported by extensive research. Notable is a 2022 review article (J Raffin, et al., *Sedentary behavior and the biological hallmarks of aging, Ageing Res Rev.*), which summarizes current knowledge of the negative effects of sedentary behavior on all 9 original Hallmarks.
- The common geriatric condition of sarcopenia, weakness and declining muscle mass, increases the incidence of fall injuries typically requiring sedentary convalescence, and in turn leading to rapid deterioration of health.
- To slow aging, build strength, and avoid accidents requires physical activity plus adequate dietary protein to support mass-neutral or -positive turnover of muscle tissue. However,
  - The amount and timing of protein meals to cause muscle building is a matter of debate,
  - As is the optimal proportion of time we should keep our bodies in growth mode, as opposed to repair mode (mTOR switching).

# Adjusting Diet and Exercise to Address Hallmarks of Aging

**Prof. Stuart Phillips and Dr. Rhonda Patrick of FoundMyFitness discuss these issues in an excerpt from a long discussion: [On Building Muscle with Resistance Exercise](https://www.youtube.com/watch?v=r8DSpOd0NZc), YouTube, June 2022, 1h50m (excerpt 40s to 24m)**  
**<https://www.youtube.com/watch?v=r8DSpOd0NZc>**

- **From the interview description:**

**“Stuart Phillips, PhD, is a professor of kinesiology at McMaster University in Hamilton, Ontario, Canada, where he also serves as the director of the Physical Activity Centre of Excellence. His research centers on the roles exercise and nutrition play in influencing human skeletal muscle protein turnover and how these lifestyle factors influence body composition, especially as we age.”**

# Adjusting Lifestyle to Address Hallmarks of Aging

**Brad Stanfield, MD of New Zealand, discusses the use of protein powders to help achieve our nutrition goals for general health and building/maintaining strength: How Protein Powder is Transforming Aging - Human Study, YouTube, August 2022, 3m58s:**

**<https://www.youtube.com/watch?v=UchD-EVQQpw>**

**From the interview description:**

**“Most of us aren’t getting enough protein and this is an issue because higher protein intakes are associated with a longer lifespan according to a 2020 British Medical Journal meta-analysis”**

**<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7374797/>**.

# Adjusting Lifestyle to Address Hallmarks of Aging, An Amazingly Easy Prescription

Jessie Inchauspe, mathematician and biochemist by training, has written Glucose Revolution (Simon & Schuster, 2022), a practical guide to human metabolism of glucose (mostly from dietary sugar and starch)

- inspired by her personal experience monitoring her own blood glucose levels. She offers simple tips to reduce glucose spikes while eating your preferred diet, and thereby reducing risks of developing obesity, insulin resistance, Type 2 Diabetes, and all their complications.
- The UK health research organization ZOE interviewed Jessie in July of 2022: How to control blood sugar spikes, YouTube, 47m8s (short excerpt 0-2m40s): <https://www.youtube.com/watch?v=PrvSLtRLDg0>

# In Summary

- **Dramatic breakthroughs and promising research advances continue as investment by government, charities, and private enterprises are fueling R&D into the diseases of aging.**
- **Small scale research and clinical practice is again emphasizing the necessity of building optimal health on a foundation of physical activity plus adequate but not excessive basic nutrients, particularly protein**
- **This presentation has provided an introduction to some key resources which I hope you find useful for designing your personalized path to improved health as we age together**
- **The most positive news is that there are numerous and diverse free sources of expertise on healthy aging available for our personal research**



# Healthspan and Lifespan Extension Recent Developments: More Information

- **What I'm Reading**

- **The Switch (2019) by James W Clement, lawyer and entrepreneur turned research scientist, known best for The Supercentenarian Research Study started in 2010 with Prof George Church of Harvard Medical School; turning mTOR on and off, growth and cleaning house, respectively, to optimize health throughout life**
- **Darwin's Spectre (1998) by Michael R Rose, Prof Evolutionary Biology, UCI; Darwin's legacy of insights which are the foundations of biology**
- **Entangled Life (2022) by Merlin Sheldrake, biologist (tropical ecology) and writer; the pivotal role of fungi in the evolution and maintenance of life on Earth**
- **Eat to Beat Disease (2019) by William W Li, MD known for research on the role of angiogenesis in disease, particularly in cancer; building a healthy diet around the foods you enjoy to avoid and treat disease**

# Healthspan and Lifespan Extension Recent Developments: More Information 2

## What I'm watching/listening to:

- ZOE Youtube streams of original research, lectures, and interviews on science of nutrition and public health from the UK: <https://www.youtube.com/@joinZOE/streams>
  - “ZOE is a healthcare science company using data-driven research to tackle the world’s health issues. Our approach combines artificial intelligence, digital technologies, and collaboration with leading scientists around the world.” Co-Founder is Prof Tim Spector MD OBE, Kings College London.
- FoundMyFitnessYoutube streams on the science of nutrition and biology of aging, lectures and interviews by Rhonda Patrick, PhD:  
<https://www.youtube.com/@FoundMyFitness/featured>
- Peter Attia, MD Youtube streams (many interviews) and The Drive podcast:  
<https://www.youtube.com/@PeterAttiaMD/playlists>
  - “Peter Attia is a physician focused on the applied science of longevity, dealing extensively with nutritional interventions, exercise physiology, sleep physiology, emotional and mental health, and pharmacology” to increase lifespan while improving healthspan.
- Huberman Lab YouTube streams (interviews and lectures) by Prof Andrew Huberman (neurobiology and ophthalmology) Stanford U:  
<https://www.youtube.com/@hubermanlab/featured>
  - “discusses neuroscience and science-based tools, including how our brain and its connections with the organs of our body control our perceptions, our behaviors, and our health, as well as existing and emerging tools for measuring and changing how our nervous system works.”

# More Information

## Other Ongoing Sources of Information

- <https://longevity.technology/> for news of commercial ventures and relevant research
- <https://www.lifespan.io/> for “aging research news, crowdfunding and advocacy”

## Hallmarks of Aging

- T Schmauck-Medina, et al., 2022, New Hallmarks of ageing: a 2022 Copenhagen ageing meeting summary, *Ageing* 14:16. <https://www.aging-us.com/article/204248/text>

## Stem cell therapy

- Recent progress at UCLA and UCI in culturing consistent quality brain organoids: [https://www.cell.com/stem-cell-reports/pdfExtended/S2213-6711\(22\)00422-2](https://www.cell.com/stem-cell-reports/pdfExtended/S2213-6711(22)00422-2)

## Exercise and Diet

- Why strength & stability are essential for longevity | Peter Attia, M.D. & Beth Lewis [https://www.youtube.com/watch?v=aYzWHsWz\\_Oo&t=26s](https://www.youtube.com/watch?v=aYzWHsWz_Oo&t=26s)
- New book on longevity medicine, Outlive, by Peter Attia due March 28, 2023: <https://peterattiamd.com/outlive/>