# Is Aging Solvable?

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Slides available for download: www.optispan.life/khosla2023

#### Traditional medicine focuses on disease



Disorders

#### Aging is the greatest risk factor for disease





## Targeting aging is 21<sup>st</sup> Century Medicine



Slowing aging slows the progression of multiple age-associated diseases

#### Targeting aging is more effective than curing disease



Kaeberlein. Public Policy and Aging Report 2019.

# A few key concepts:



- Lifespan: Time from birth to death
- Healthspan: High functioning period of life (e.g. free from disease and disability)
- Geroscience: Biological mechanisms connecting aging with disease and disability

# The biology of aging is being solved...



#### **Hallmarks of Aging**

- Genomic instability
- Telomere shortening
- Epigenetic changes
- Loss of proteostasis
- Deregulated nutrient signaling
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion
- Altered cell-cell communication

## ...but we're far away from "solving aging"



Lopez-Otin et al., Cell. 2013 Jun 6;153(6):1194-217.



Hecataeus' Map (~500 BCE)

# We don't know what we don't know

- Field is mostly looking under the lamppost
- Focused on "hallmarks" and "clocks"
- Interventions have stagnated
  - Caloric restriction 1935





- We need bold strategies and new tools for massively highthroughput longevity discovery science
  - Ora Biomedical "Million molecule challenge"



https://orabiomedical.com/

## What do we know?

- Aging biology is real
- Aging biology is modifiable
- Modifying aging biology is more effective than reactive disease care
- Some key nodes in the aging network
  - mTOR, GH/IGF-1 axis, inflammatory signaling, senescent cells, mitochondrial function, epigenetic aging changes, etc.
- Some potentially "useful" therapies
  - rapamycin, senolytics, caloric restriction, autophagy activators, NAD boosters, etc.



## Where is hype ahead of reality?



#### Genetic Engineering & Biotechnology News Webinar (3/17/23)

https://www.genengnews.com/resources/gen-live/aging-separating-the-science-from-the-snake-oil/





- Anti-aging supplements
  - Many (like resveratrol) are pure snake oil
  - Some possibly have incremental effects: NAD, AKG, "autophagy boosters", NAC/GSH
  - Combinatorial effects?
- Biological aging clocks
- Epigenetic reprogramming

# Rapamycin: current best-in-class longevity drug



- Not a "miracle drug"
- FDA approved since 1999 (sirolimus)
- Most effective longevity drug to date
- Increases lifespan up to 30% in mice
- Works when started in middle age
- Appears to broadly delay or <u>reverse</u> aging phenotypes



Brain Heart **Kidney** Muscle Immune **Ovary** Skin **Oral cavity** Auditory Eye Intestine Bone

...

#### Transient rapamycin increases life expectancy

• Mice treated for 12 weeks beginning at 20 months of age



Length of treatment: 90 days Lifespan extension: 141 days

~2-3 years for 7 year old dog ~20 years for 50 year old woman

#### Will rapamycin work in the real world?

- 580 dog clinical trial of rapamycin (dogagingproject.org)
- Small human trials for periodontal disease, ovarian failure, dementia
- Self-reported data from off-label rapamycin users
  - https://link.springer.com/article/10.1007/s11357-023-00818-1
- There are more than a dozen good endpoints for rapamycin clinical trials, but somebody has to be willing to pay for them

#### Where will we be in 1-2 decades?

- No evidence aging can be "cured"
  - Immortality, "reversing aging", and "escape velocity" are science fiction; not impossible, but no data to support and lots of data to indicate we're not making any real progress in this direction
- We already know enough to intervene (weakly) in biological aging today
- I predict we'll be able to approach current "maximum" species lifespan for most people within two decades (~115 years)

#### Recapturing the lost decade



# The "longevity dividend"



# What should you do now?

- Invest in your health like it's your greatest asset
  - Don't die (Matt's Longevity Rule #1)
    - Baseline and preventative diagnostics
  - Find a good doc
  - Lifestyle matters (nutrition, exercise, sleep)
  - Educate yourself and identify credible sources of information
  - Consider risk/reward for things like rapamycin
    - Doing nothing has a cost
    - Traditional medicine is risk averse, reactive disease care



creating the toolkit for friction-free, science-based longevity medicine