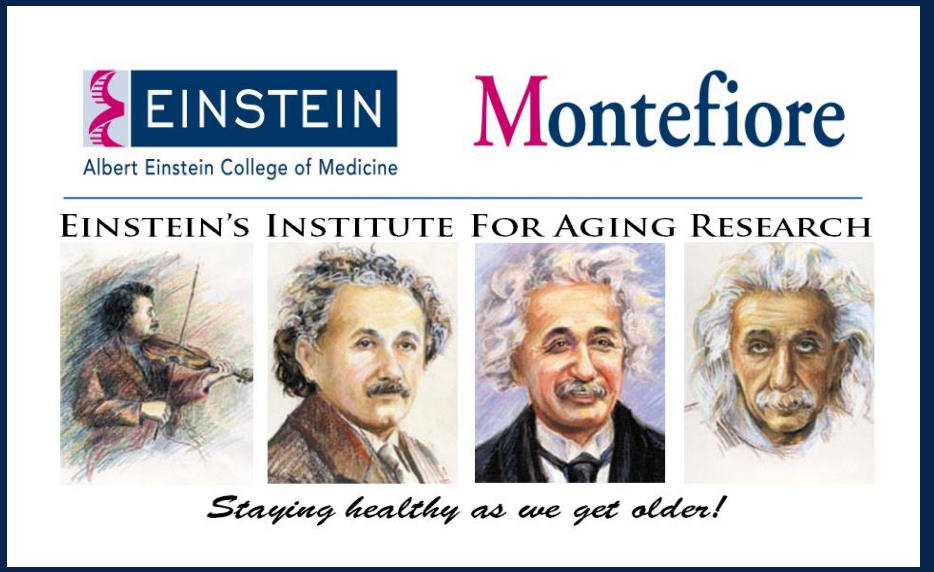


Nir Barzilai, M.D.
Professor of Medicine and Genetics
Director: Institute for Aging Research
PI: The E-Nathan Shock Center
The E-Glenn Center for the Biology of Human Aging

- **Mechanisms of Co-Development of Cancer and Cardiovascular Disease in an Aging Population**

The Geroscience View:

Age-related changes in key pathways that underlie both cancer and heart disease

Conflicts

Founder and on the Board of:

Founder and Medical/ Scientific Consultant

life

Biosciences

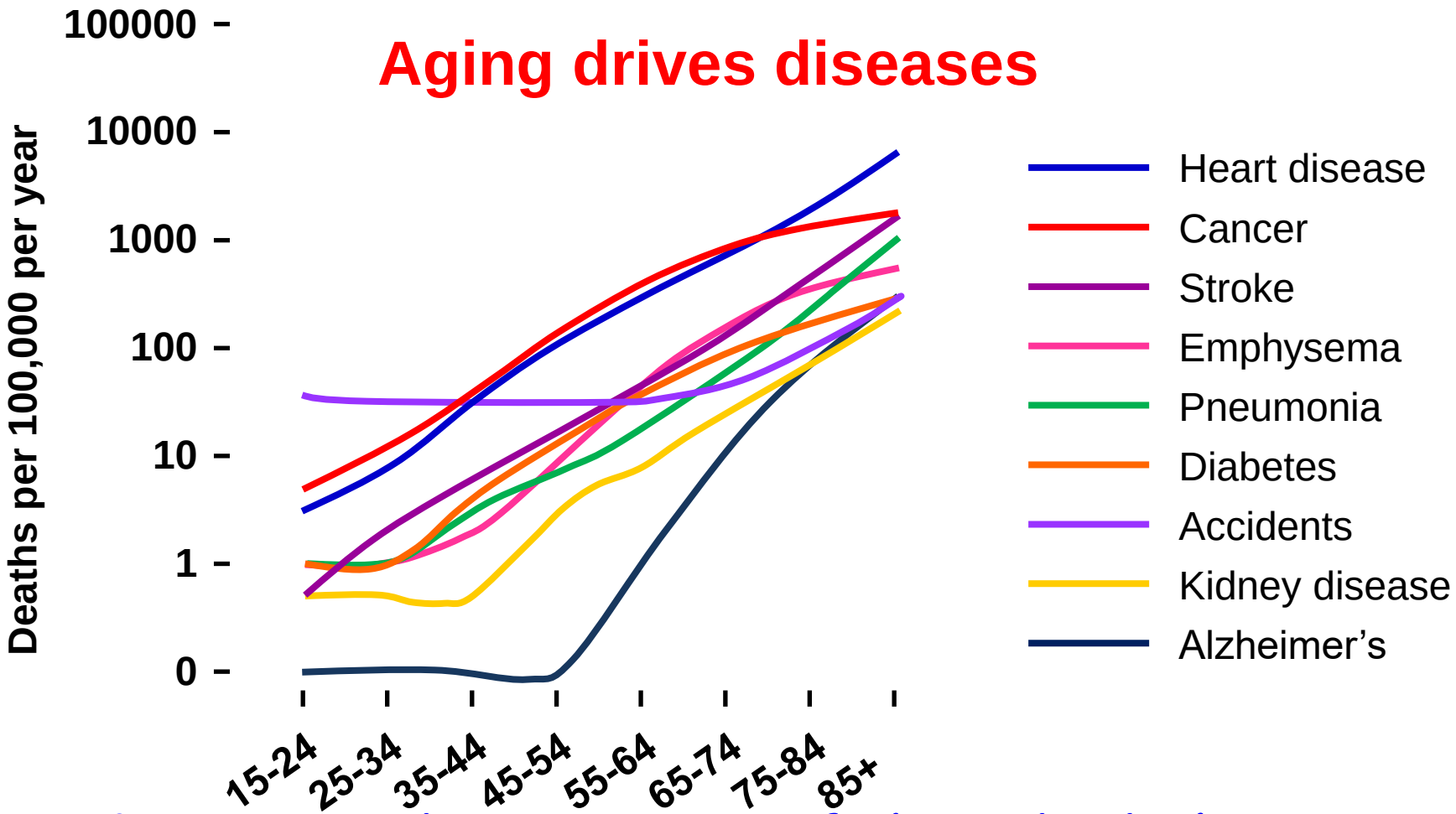
No conflict in this talk

Promise and challenges for Geroscience

- **Introduction to geroscience:**
- **Hallmarks of aging**
- **Gerotherapiutics (TAME)**
- **The immediate future of gerotherapiutics**

Aging itself is the strongest risk factor for all age related diseases

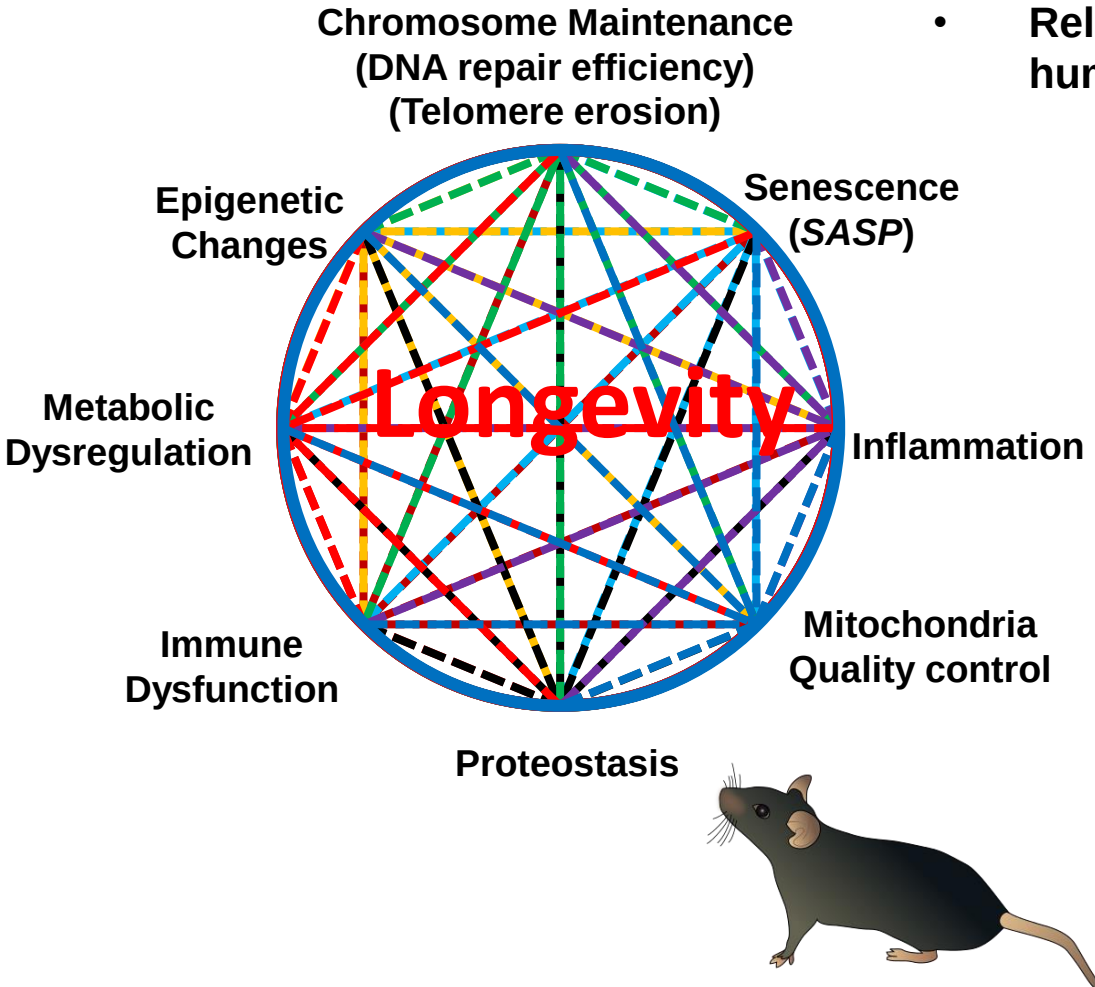
(The Milbank Quarterly, Vol. 80, No. 1, 2002 from 1997 U.S. Vital Statistics)



Genetics and environment of the individual determine which disease occurs first

Can we do something about aging?

Geroscience: Key to targeting aging



- **Healthy lifespan has been extended in numerous animal models.**
- **Relevant drugs have been used in humans. (Metformin, Rapamycin….)**

Can we do something about it?

Metformin Attenuates Biological Hallmarks of Aging

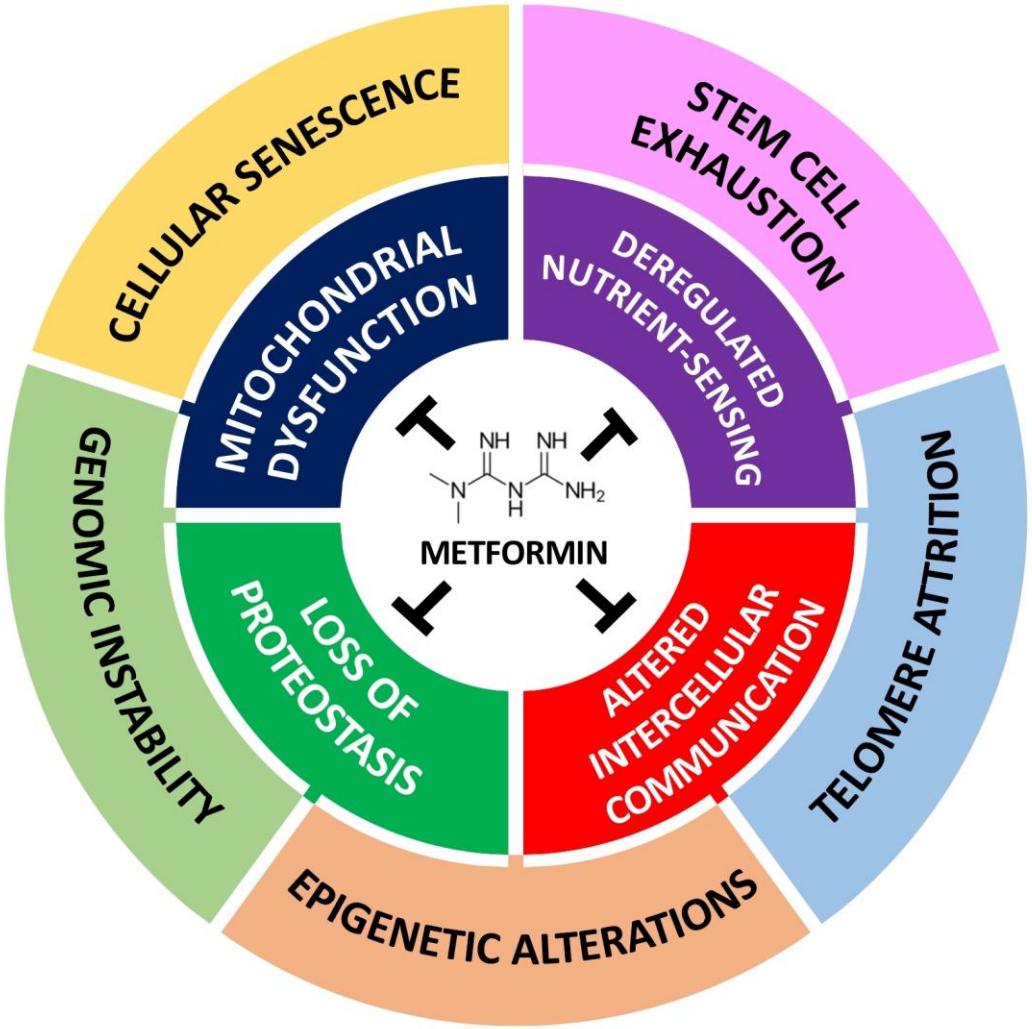
Its been used for 70 years and is safe!!!

It was used to prevent flu and malaria

Its generic and cheap

Metformin in clinical studies
Prevented, T2DM, CVD, AD/MCI
And mortality (Cancer)

TAME will show it targets aging



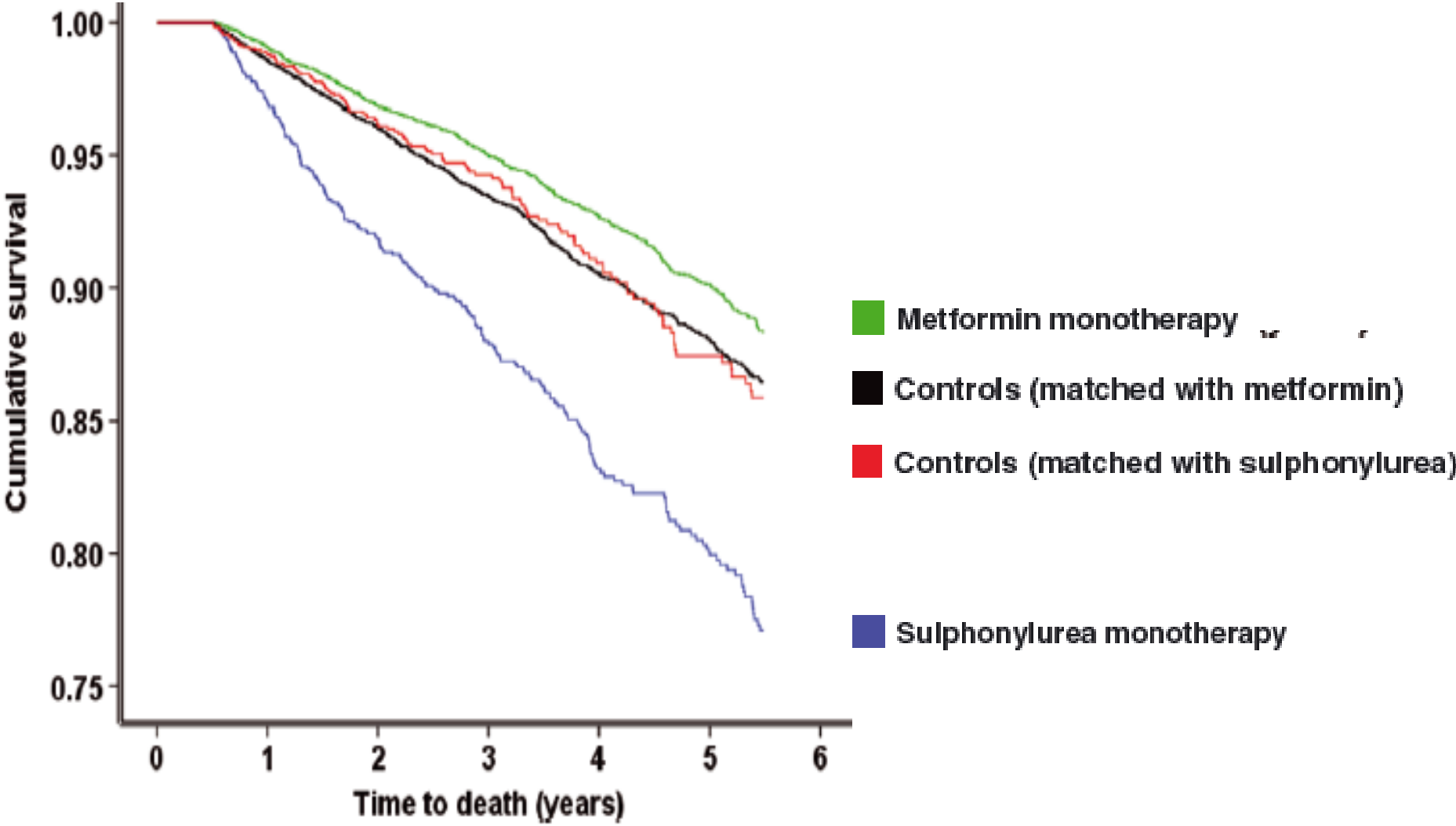
Kulkarni et al Cell Met 2020

Substantial effects of metformin on health-span in humans:

- **Intervention in non-type 2 diabetes mellitus (T2DM):** Metformin delays T2DM (DPP).
- **Intervention:** Metformin delays CVD (UKPDS) in T2DM.
- **Association:** Metformin is associated with less cancer in patients with T2DM.
- Metformin may delay cognitive decline and AD, even in non-T2DM.
- **Phase 4:** lower mortality in patients with T2DM on metformin compared with non-diabetics.

Metformin is a **tool** to target aging

Metformin decreases mortality in T2DM and in non-diabetics



Bannister e al Diabetes, Obesity and Metabolism 2014.

TAME study deign:

Age 65-80 AND
Gait speed 0.4-1 m/sec OR Age-related disease (CVD, cancer, MCI)

Inclusion Criteria

n = 3000

Double blind placebo-controlled trial

(Clinical) Time to incidence of any major age-related disease:

MI, stroke, cancer*, CHF, MCI/dementia, or death. FDA

Primary Outcome

(Biological) Change in metformin levels and biomarkers of aging and age-related diseases NIA. To provide convergent evidence of broad age-related effects while establishing a resource for innovation and discovery of emerging biomarkers.

If we could do more TAME-like studies....

Geroscience-guided repurposing of FDA-approved drugs for aging

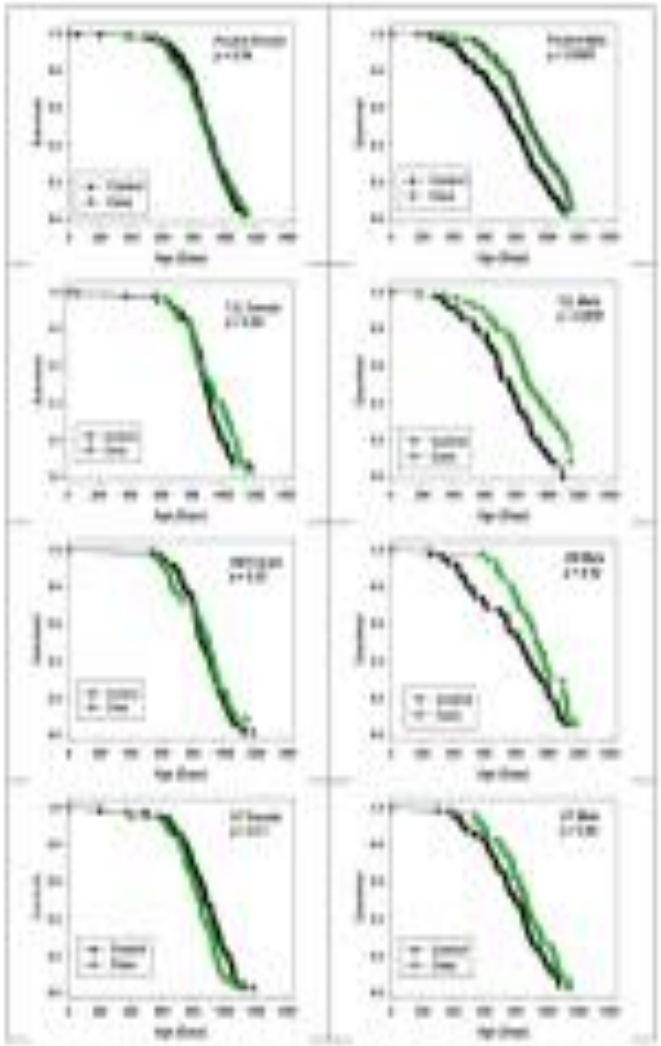
* Kulkarni A, *Aleksic S, Berger D, Kuchel G, Sierra F and Barzilai N

Gerotherapeutic (lifespan)	Hallmarks of aging	Preclinical healthspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT-2 inhibitors	2	2	2	3	3	**12**
Metformin	2	2	1	3	1	**9**
Rapamycin/rapalogues	2	2	2	3	0 (not assessed)	**9**
Acarbose	2	2	2	3	0 (not assessed)	**9**
ACEi/ARB	2	2	1	3	0	**8**
Dasatinib + (quercetin)	2	2	1	1	0 (not assessed)	**6**
Aspirin	2	2	2	0	0	**6**
Methylene blue	2	2	2	0 (not assessed)	0 (not assessed)	**6**
N-acetyl cysteine	0	2	2	0	0	**4**

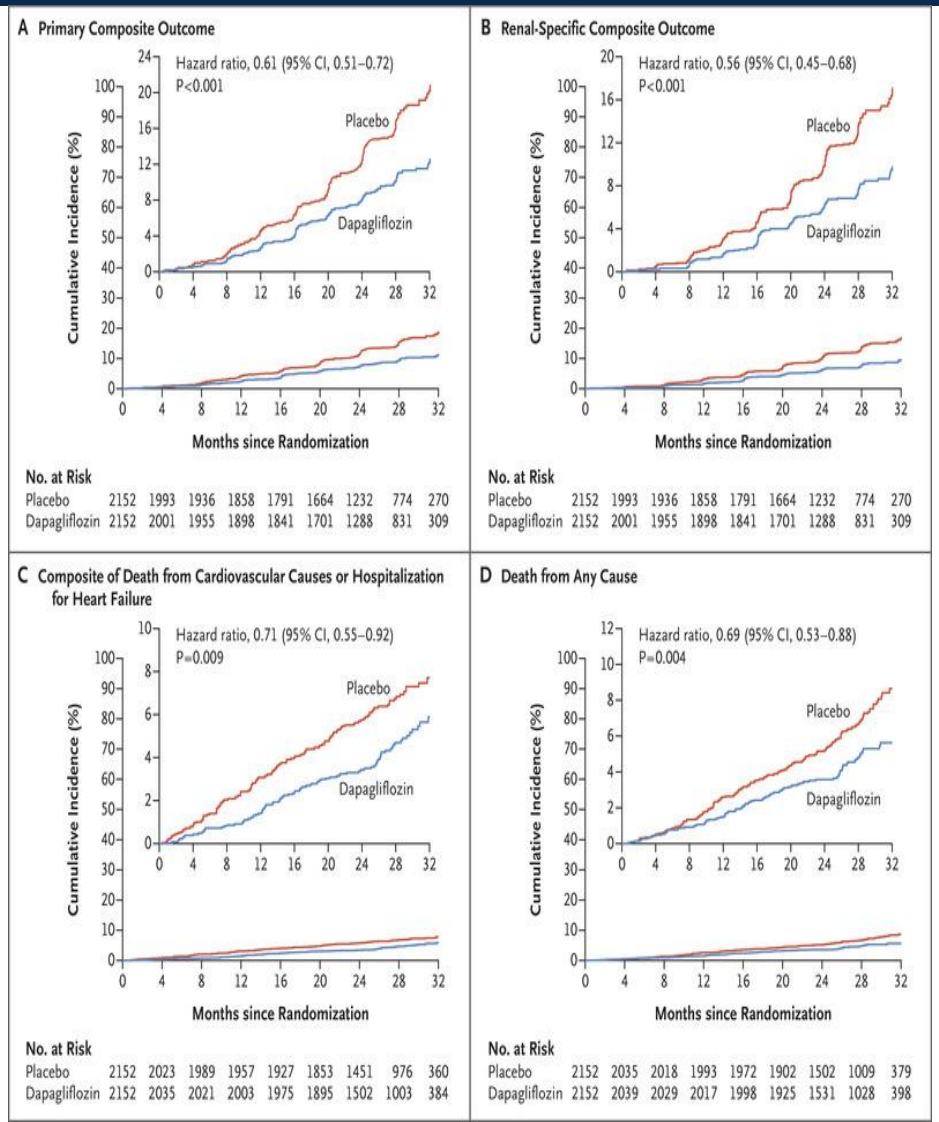
Preclinical points
Hallmarks >=3: 2, <3: 1
Healthspan increase: 2
Lifespan ITP: 2, non-ITP: 1

Human points
Healthspan RCT: 3, observational/open single arm: 1
Mortality RCT: 3, observational: 1

Canagliflozin extends lifespan in genetically heterogeneous male but not female mice
(Miller RA, JCI insight 10-20)



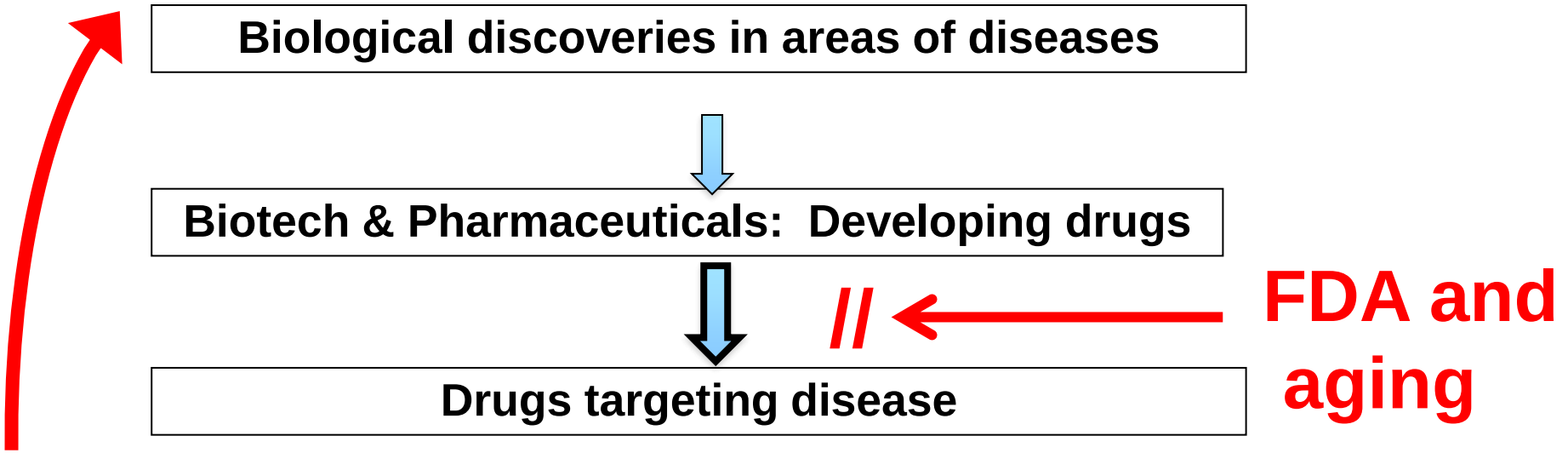
Dapagliflozin in patients with CKD
(Heerspink et at, NEJM October 8 2020)



Summary and challenges:

- **Geroscience: Treat aging and prevent cancer, CVD and much more!!!!**
- **Hallmarks of aging can be targeted and aging can be delayed**
- **Gerotherapiutics will demonstrate to the FDA that aging (age related diseases) is/are preventable**
- **More drugs for immediate future of gerotherapiutics**

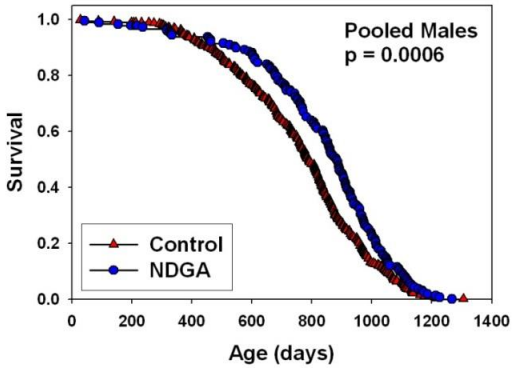
Challenges to translate our advance in understanding aging to humans?



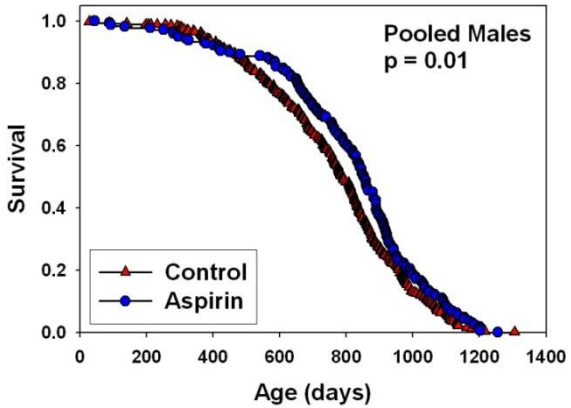
If diseases of aging are not recognized as preventable conditions:

1) Healthcare provider would not pay for their clients.
2) Pharmaceuticals will not develop other, better and combinati of drugs.

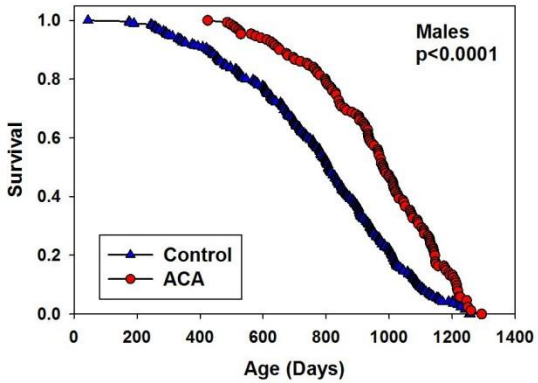
Intervention Testing Program (NIA)



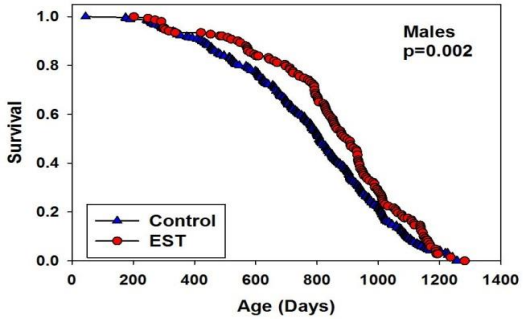
NDGA
(Nordihydroguiaretic acid)



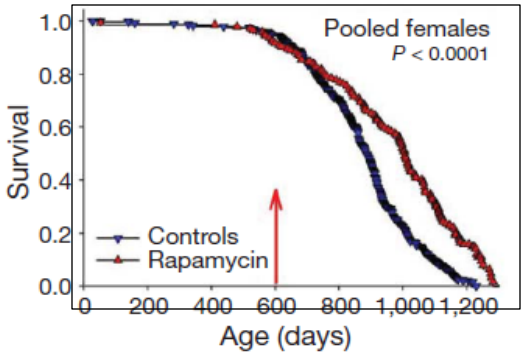
Aspirin



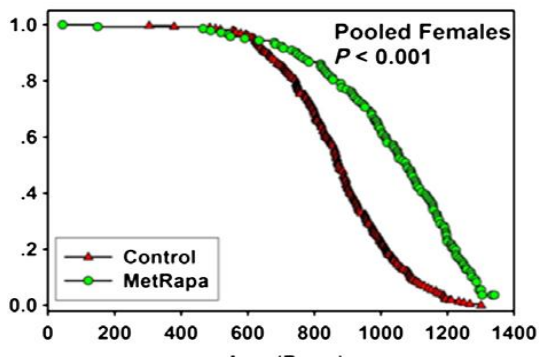
Acarbose



17-α estradiol

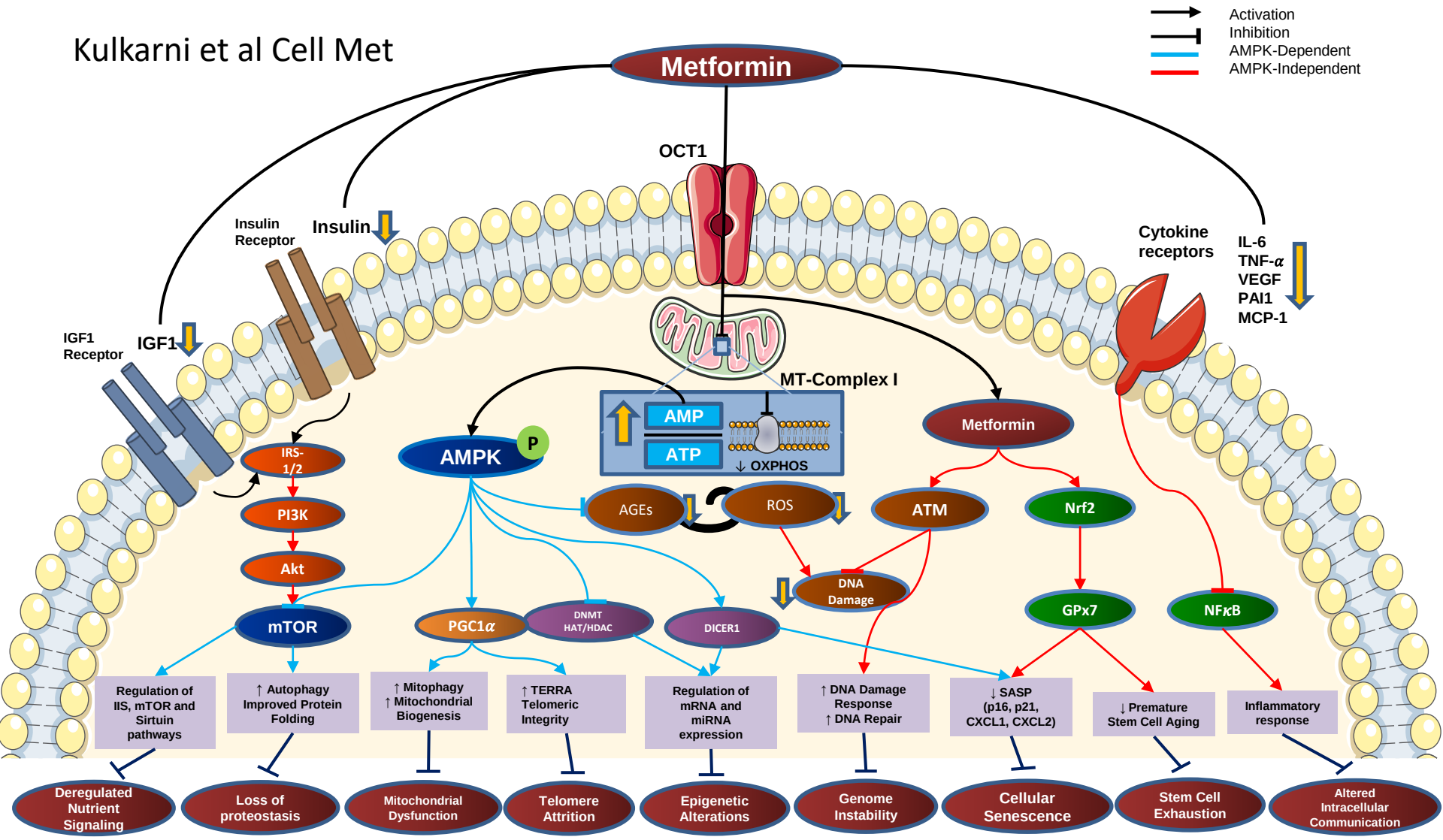


Rapamycin



Rapamycin+
metformin

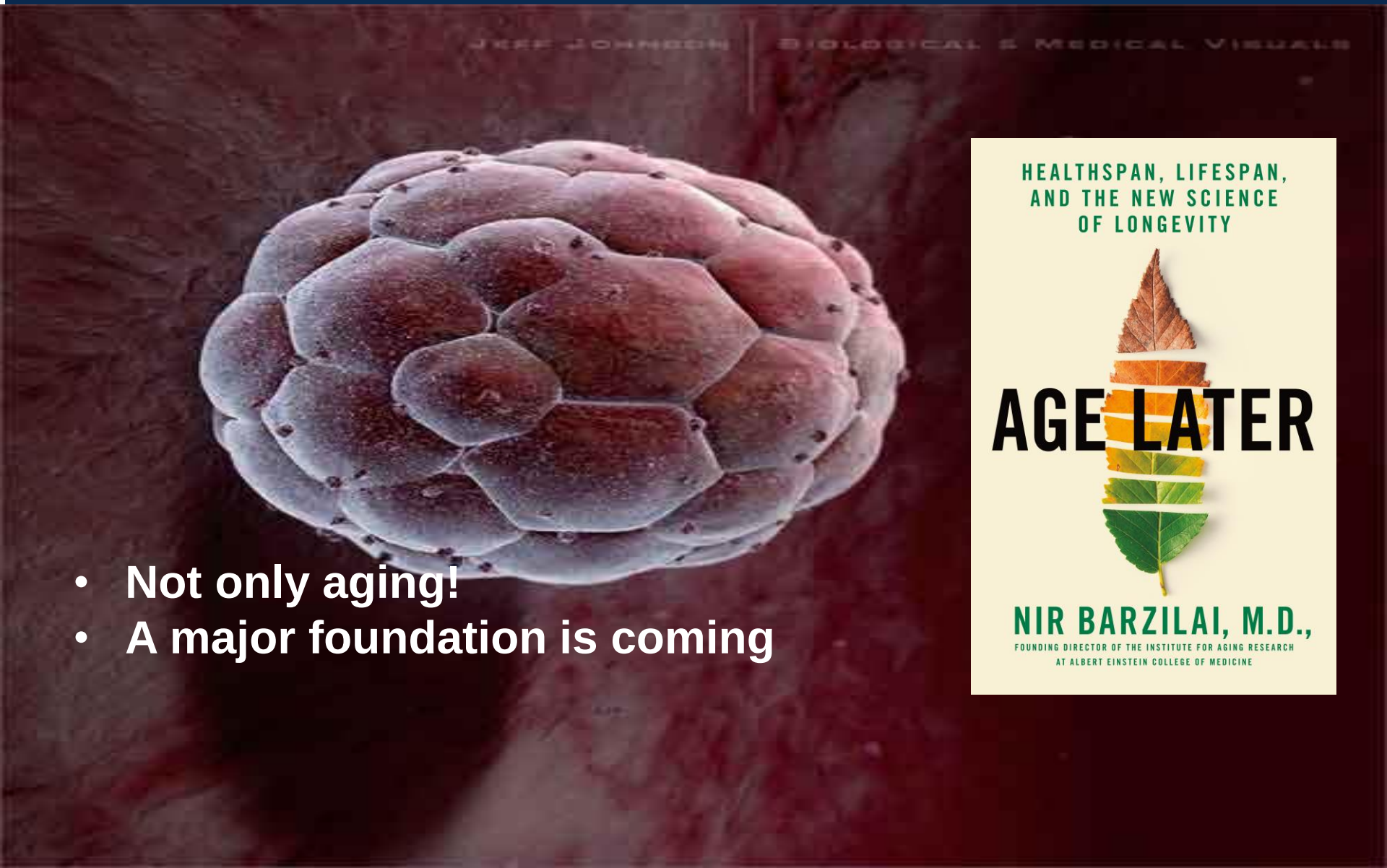
Metformin Attenuates Biological Hallmarks of Aging



Biological Hallmarks of Aging

Metformin extends lifespan and health span in animals. (683 papers in pubmed)

Blastocytes erase aging!



- Not only aging!
- A major foundation is coming