Why it’s time to start human trials of medications that may slow aging

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Department of Biology
University of Alabama at Birmingham
American Federation for Aging Research
Some Good News:
Life Expectancy U.S.A.

<table>
<thead>
<tr>
<th>Year</th>
<th>Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1880</td>
<td>40</td>
</tr>
<tr>
<td>1900</td>
<td>50</td>
</tr>
<tr>
<td>1920</td>
<td>60</td>
</tr>
<tr>
<td>1940</td>
<td>70</td>
</tr>
<tr>
<td>1960</td>
<td>80</td>
</tr>
<tr>
<td>1980</td>
<td>90</td>
</tr>
<tr>
<td>2000</td>
<td>100</td>
</tr>
<tr>
<td>2020</td>
<td>110</td>
</tr>
<tr>
<td>2040</td>
<td>120</td>
</tr>
</tbody>
</table>

6.5 hours/day!

Japan
More good news:
Continuing to delay death in the 21st century

From Miniño, et al., 2002; Murphy, et al, 2013
Some bad news:
Consequences of delaying death in the 21st century

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>-50</td>
</tr>
<tr>
<td>Cancer</td>
<td>-20</td>
</tr>
<tr>
<td>COPD</td>
<td>-10</td>
</tr>
<tr>
<td>Flu/Pneumonia</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0</td>
</tr>
<tr>
<td>Nursing Homes</td>
<td>50</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>100</td>
</tr>
<tr>
<td>Stroke</td>
<td>150</td>
</tr>
<tr>
<td>Diabetes</td>
<td>200</td>
</tr>
</tbody>
</table>

Note: The Percent Change values are illustrative and do not represent actual data.
Impact of aging on major causes of death: Cancer

Percent Increase

- Smoking: 20%
- Alcohol: 10%
- Diet: 30%
- Infection: 8%
Impact of aging on major causes of death: Cancer

Percent Increase

0 1000 2000 3000 4000 5000 6000

Smoking Alcohol Diet Infection Aging

Cancer
Impact of aging on risk for heart disease

- Hypertension
- Smoking
- Cholesterol
- Diabetes
- Aging

Percent Increase

- Hypertension: 0
- Smoking: 0
- Cholesterol: 0
- Diabetes: 0
- Aging: 6000
Impact of aging on major causes of death:
Alzheimer’s disease
It’s not just death. It’s pain, quality of life, ...and healthcare costs

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Annual U.S. Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract removal</td>
<td>3,000,000</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>332,000</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>719,000</td>
</tr>
<tr>
<td>CA bypass</td>
<td>395,000</td>
</tr>
<tr>
<td>CA stent</td>
<td>454,000</td>
</tr>
<tr>
<td>Balloon angioplasty</td>
<td>500,000</td>
</tr>
</tbody>
</table>

various sources
And it’s not just the U.S. Aging = #1 threat to human health globally

<table>
<thead>
<tr>
<th>Rank as Cause of Death</th>
<th>Global</th>
<th>United States</th>
<th>East Asia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Disease</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cancer</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Lower Respiratory Infection</td>
<td>3</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Diarrheal</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malaria</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-term Birth Complications</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Road Accidents</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emphysema/bronchitis</td>
<td>10</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Aging kills and debilitates far more people than any other cause.
And aging is about to overwhelm us...

**Population: 1960 to 2050**

*(In millions)*

**Elderly**

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>16.6</td>
<td>20.0</td>
<td>25.6</td>
<td>31.1</td>
<td>34.7</td>
<td>39.4</td>
<td>53.2</td>
<td>69.4</td>
<td>75.2</td>
<td>78.9</td>
<td></td>
</tr>
</tbody>
</table>

**Oldest Old**

<table>
<thead>
<tr>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>1.4</td>
<td>2.2</td>
<td>3.0</td>
<td>4.3</td>
<td>5.7</td>
<td>6.5</td>
<td>8.5</td>
<td>13.6</td>
<td>18.2</td>
<td></td>
</tr>
</tbody>
</table>

Source: U.S. Bureau of the Census.
What can be done??

HEART
CANCER
ALZHEIMER’S
EMPHYSEMA
OSTEOPOROSIS
HEARING LOSS
DIABETES
What can be done??

HEART  CANCER  ALZHEIMER'S  EMPHYSEMA  OSTEOPOROSIS  HEARING LOSS  DIABETES
Some scientists have been studying this for years: Dietary Restriction (DR)
In many animals, DR improves many aspects of health

From McCarter, 1997
DR is not a general remedy for improved health
Known molecular *networks* contributing to aging

Source: Michael N. Hall Research group
Where are we now?

- Genes: Hundreds known, but a few major ones
- Diets: A handful (but more on the way)
- Medications: Some promising ones (but many more on the way)
- New research paradigms make human trials more feasible
This knowledge has led to...

NIA-supported Interventions Testing Program (ITP)
Key features of the ITP

• Experiments done in three independent laboratories (instant confirmation)
• Genetically variable mice used
• Results published in a timely fashion, whether positive or not
An incredible success rate so far

<table>
<thead>
<tr>
<th>Extends</th>
<th>Does not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (males only*)</td>
<td>NFP</td>
</tr>
<tr>
<td>NDGA (males only*)</td>
<td>CAPE</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>4-OH-PBN</td>
</tr>
<tr>
<td>17α-estradiol (males only*)</td>
<td>Enalapril maleate</td>
</tr>
<tr>
<td>Acarbose (males only*)</td>
<td>Simvastin</td>
</tr>
<tr>
<td></td>
<td>Resveratrol</td>
</tr>
<tr>
<td></td>
<td>Oxaloacetic acid</td>
</tr>
<tr>
<td></td>
<td>Green tea extract</td>
</tr>
<tr>
<td></td>
<td>Curcumin</td>
</tr>
<tr>
<td></td>
<td>Medium chain triglyceride oil</td>
</tr>
</tbody>
</table>

*so far
Drugs which mimic DR: Rapamycin
Current clinical uses of rapamycin (and its analogs)

1. Impregnated in coronary artery stents
2. Immunosuppressive cocktail for kidney transplants
3. Some cancer chemotherapy regimes
4. Treatment of chronic eczema
What Does Life-Extending Drug Mean for Humans?
By Laura Blue Thursday, Jul. 09, 2009

A natural compound used as an immunosuppressant in organ-transplant patients has been found to extend life in mice, according to a study published on July 8 in the journal *Nature Aging* mice that were given the substance, rapamycin, lived significantly longer than mice that didn’t get the drug: females that received rapamycin were 13% older at death and males 9% older.

Organ transplant drug extends life
WASHINGTON (AP) — A drug used to prevent the rejection of transplanted organs significantly increase the life span of older mice, researchers said Wednesday.

Two Mammals' Longevity Boosted
Transplant Drug Lengthens Lives of Mice, and Fewer Calories Benefit Monkeys
A study published Wednesday found that rapamycin, a drug used in organ transplants, increased the life span of mice by 9% to 14%, the first definitive case in which a chemical has been shown to extend the life span of normal mammals.

Easter Island drug makes Methuselah mice
PARIS (AFP) — A compound found in the soil of Easter Island stunningly boosts the lifespan of mice, enabling some to live more than 100 years old in human terms, researchers reported on Wednesday.
What was the big deal about rapamycin??

(1) Drug begun relatively late (60 years in human terms)
(2) Drug did many things in addition to extending life

Mouse Alzheimer’s disease

Caccamo, et al. (2010) JBC
Human flu vaccine response

Mannick, et al., 2014
Partial list of health effects of rapamycin (mostly in mice)

2. *Delays and slows Alzheimer’s disease* (Spilman, et al., 2010; Caccamo, et al., 2010)
3. Delays onset of progeria (Ramos, et al., 2012)
4. Delays normal cognitive aging, reduces anxiety & depression (Halloran, et al., 2012)
5. Prevents several cancer types (Sharp, et al., 2013; many others)
6. Prevents later-life heart dysfunction (Flynn, et al., 2013; Beutner, et al., 2012; Pakala, et al., 2005)
8. Prevents detrimental effects of senescent cells (Laberge, et al., 2015)
What have we learned from the rapamycin studies??

1. Potential aging-retarding medications can be effective even when started relatively late

2. Medications do exist (and others are in development) that can delay or alleviate a broad swathe of diseases and conditions of later life

3. Short-term (~ 5 year) human studies can be designed to evaluate the health impact of putative aging-retarding medications
Questions? Comments?
How to Die Young at a Very Old Age
Lifespan vs. Healthspan
(Mark Collins-Glenn)

Lifespan vs Healthspan

- Lifespan
- Onset of disease

Now

Target

Or even…

Nightmare scenario

Graph ©Mark Collins-Glenn Foundation
Appearance of all diseases in relationship to age

In press JAGS
Diseases include:
- Cancer
- Cardiovascular disease
- Diabetes mellitus
- Hypertension
- Dementia
- Osteoporosis

Medical cost ($) during the last 2 years of life:
- 60-70 Yo
- >100 Yo
Diabetes risk related to parental age at death
The Diabetes Prevention Program

Offspring of longer-lived parents had lower diabetes risk, independent of parental diabetes and DPP treatment

J Geron 2011; 66A:1211
Parental longevity associated with lower risk of Alzheimer's disease and memory decline. (Lipton, ... Barzilai etal J Am Geriatr Soc. 2010)
Genetics of human longevity
Can a study design depict the challenges of genetics of aging?

- Only ~1/10,000 individuals is 100 years old
  \((n\sim 600; 95-112; \text{LGP, LonGenity } n\sim 3,000)\)

- There is a remarkable family history of exceptional longevity in parents, siblings and offspring of “centenarians”

- **Hypothesis:**
  1) Perfect genome/environment
  2) Protective genes to assure human’s longevity
Cover of PLoS Biology April 2006
### Centenarians interaction with the environment

(n=477, 75% females)

<table>
<thead>
<tr>
<th>‘Environmental’ risk</th>
<th>Centenarians Men</th>
<th>Centenarians Women</th>
<th>NHANES1 Men</th>
<th>NHANES1 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over weight/obese:</td>
<td>48%</td>
<td>44%</td>
<td>• 55%</td>
<td>41%</td>
</tr>
<tr>
<td>Smoking:</td>
<td>60%</td>
<td>30%</td>
<td>• 75%</td>
<td>26%</td>
</tr>
<tr>
<td>Alcohol (daily):</td>
<td>24%</td>
<td>12%</td>
<td>• 22%</td>
<td>11%</td>
</tr>
<tr>
<td>Physical activity:</td>
<td>43%</td>
<td>47%</td>
<td>• 57%</td>
<td>44%</td>
</tr>
</tbody>
</table>

(Moderate: regular walking, bicycling, housework)

• Vegetarians: 2.6%

Swapnil Rajpathak and Jill Crandall

Do centenarians simply have perfect genome?

WGS of 44 centenarians:
ClinVar database ~15,000 pathogenic variants
A total of 227 autosomal and seven X-chromosomal coding SNVs.

- **Parkinson**- 2 mutations in L444P (GAB)
- **AD**- APOE, UBQLN2 (also ALS)
- **Other degenerative**- SEMA4A, RP1, FZD4, MYO1A, CYP1B1, VSX1, and WDR36
- **Neoplastic**- APC, BRCA1, RET, RNASEL, and STK11
- **Cardiac (dominant)**- ABCC9, ACTN2, ANK2, CACNA1C, JPH2, KCNE2, MYL2, and TMEM43
- **Other dominant**- 18 variants for autosomal-dominant diseases and 6 mutations for X-Chromosomal diseases
- **Other recessive**- 72 variants for recessive traits include four variants that have least one homozygous
- Similar prevalence of common SNPs for age-related disease
Trends of favorable longevity Genotypes/Allele
(All validated or have phenotype/function)

- ApoC3-CC
- CETP-VV
- ADIPOQ-del/del
- TSHr-G
Lipid gene (CETP VV) protects from cognitive and not only from cardiovascular aging.

Please respond to the following questions according to what your characteristics were like in most of your adulthood.

In general, how easygoing are you on a scale of 1 to 5 (1 = least; 5 = most)?

How optimistic are you on a scale of 1 to 5 (1- very pessimistic to 5- very optimistic)?

In general, do you consider yourself introverted or outgoing on a scale of 1 to 5?

Introverted 1 2 3 4 5 Outgoing

Is laughter a big part of your daily life?

Never 1 Rarely 2 Sometimes 3 Often 4

I express my feelings openly:

Never 1 Sometimes 2 Often 3 Always 4

I tend to bottle up my emotions:

Always 1 Often 2 Sometimes 3 Never 4

Domain 1, Positive Attitude Towards Life (PATL): Optimism, Easygoing, Laughter, & Outgoing
Domain 2, Emotional Expression (EE): Expressing Emotions Openly, & Not Bottling Up Emotions

Kaori Kato, Psy.D
The results of t-tests

To compare mean scores of personality traits in the current sample to the US population means

• Self-Report Group

  Lower Neuroticism  \( t(18) = -3.81, p < .01 \)
  Higher Extraversion  \( t(18) = 3.03, p < .01 \)
  Higher Agreeableness  \( t(18) = 3.82, p < .01 \)
  Higher Conscientiousness  \( t(18) = 2.42, p < .05 \)

• Informant-group

  Lower Neuroticism  \( t(25) = -2.24, p < .05 \)
  Higher Conscientiousness  \( t(25) = 2.88, p < .01 \)
  Higher Optimism  \( t(25) = 2.60, p < .05 \)

(Compared to a mixed age group)
Personality Outlook Profile Scale (POPS)
Participant Centenarian Questionnaire Longevity Genes Project
Albert Einstein College of Medicine


Cause-effect?
TAME (Targeting Aging with METformin)

• To show that multiple morbidities of aging can be targeted by metformin
• (FDA) To obtain a new indication for the delay of age-related morbidities.
• To provide a paradigm for studying other drugs targeting multiple morbidities of aging
• To apply the discoveries of geroscience as a powerful new tool for achieving primary prevention of multiple diseases.
Metformin targets multiple pathways of aging

Metformin regulates various cellular processes such as inflammation, cellular survival, stress defense, autophagy, and protein synthesis, ultimately impacting healthspan and longevity.
TAME: Targeting/taming Aging with METformin

- **Biology of Aging**: Metformin has age-delaying effects on nematodes and mice. Multi mechanisms possible.

- **Intervention in non-type 2 diabetes mellitus (T2DM)**: Metformin delays T2DM (DPP)

- **Intervention in T2DM**: Metformin delays CVD (UKPDS)

- **Association**: Metformin is associated with less cancer in patients with T2DM

- Early support that metformin may delay cognitive decline and AD.

- And:
Metformin decreases mortality in T2DM and in non-diabetics

Bannister et al. Diabetes, Obesity and Metabolism 2014.
**TAME: Targeting Aging with METformin**

**Inclusion Criteria**
- n~3000
- 65-79yo
- 14 centers

**Primary Prevention**
Persons with metabolic syndrome and/or Impaired Physical Function. (not CVD, Cancer, or Dementia).

**Secondary Intervention**
1 or 2 of CVD, Cancer, MCI present at baseline

**Double blind placebo control study**

**Time to clinical occurrence of composite outcome:**
MI, Stroke, CHF, revascularization, PAD, cancer, MCI or dementia, Death.

**Primary outcome**
Time to occurrence of composite outcome: Death, persistent severe difficulty or inability to walk ¼ mile or climb 10 steps, development of ADL limitation, MCI, or dementia transition

**Secondary outcome**
Time to onset of 14 age-related chronic health conditions (e.g. depression, osteoporosis, osteoarthritis), rate of acute events (e.g. falls, pneumonia), change in measures of function (gait speed, etc.), and quality of life measures (pain, sleep quality, fatigue)
Multi-morbidity Incidence: Rochester Epidemiology Project

Figure 2  Incidence rates (per 1000 person-years) of two chronic conditions (second condition in a dyad) and of three chronic conditions (third condition in a triad) in men and women separately (A and C), and stratified by ethnicity (B and D).

St Sauver JL et al. Risk of developing multimorbidity across all ages in a historical cohort study. BMJ Open 2015; 5:e006413
Summary

- Age = age-related disease
- There is a biology to aging—there is a target.
- Intervention has delayed aging in many species.
- Targeting aging in humans is a practical horizon for the next decade. (TAME)
- Personality cause/effect relationship to exceptional longevity needs to be determined.
TAME consortium:

- Steve Austad
- Nir Barzilai
- Morgan Canon
- Harvey Cohen
- Mark Collins
- Jill Crandall
- Mark Espeland
- Richard Faragher
- Jon Gelfond
- Tamara Harris
- Steve Kritchevsky
- George Kuchel
- Jamie Justice
- Brian Kennedy
- Jim Kirkland
- Anne Newman
- John Newman
- Michael Pollak
- Walter Rocca
- Felipe Sierra
- Stephanie Studenski
- Ella Temprosa
- Joe Verghese
- Jeannie Wei

Contributed to development

- Luigi Ferucci
- Eileen Crimmins
- Marcel Salive
- Jay Olshansky
- Caroline Blaum
- David Sinclair
- Rafa deCabo
- Sofiya Milman
- Stephanie Lederman

Efforts are sponsored by AFAR And Global Healthspan Policy Institute
psychometrically robust personality measure for centenarians

- Two domains of the POPS:
  - Positive Attitude Towards Life (PATL)
    - Optimism, Easygoing, Laughter, & Outgoing
  - Emotional Expression (EE)
    - Expressing Emotions Openly & Not Bottling Up Emotions

- Internal consistency: PATL, $\alpha = .65$, & EE, $\alpha = .62$.

- Concurrent Validity:
  - Self-Reports of Centenarians:
    - PATL x NEO-FFI Extraversion $r = .82$, $p < .001$
    - PATL x NEO-FFI Conscientiousness $r = .53$, $p < .05$
    - PATL x NEO-FFI Emotional Stability $r = .51$, $p < .05$
  - Informant Reports of Centenarians:
    - PATL x LOT-R Optimism $r = .75$, $p < .001$
    - PATL x NEO-FFI Extraversion $r = .70$, $p < .001$
    - PATL x NEO-FFI Emotional Stability $r = .66$, $p < .001$
    - EE x NEO-FFI Extraversion $r = .45$, $p < .05$