PHASE III trials:
(and help is on the way..)

Relevance to targeting aging!
PHASE III Clinical Trial

- Preliminary evidence (phase I & II) suggesting safety/effectiveness of the agent/test article has been obtained.
- Expanded controlled and uncontrolled trials intended to gather additional information to evaluate the overall benefit-risk relationship and provide an adequate basis for physician labeling.
- Most often compares new agent/test article against commonly used agents/test articles.
- Driven by outcomes direct/indirect
- For most drugs in internal medicine use-thousands of patients.
Aging itself is the strongest risk factor for all age related diseases


Genetics and environment of the individual determine which disease occurs first

Deaths per 100,000 per year

- Heart disease
- Cancer
- Stroke
- Emphysema
- Pneumonia
- Diabetes
- Accidents
- Kidney disease
- Alzheimer’s
What is the evidence for success in the goal of delaying aging?

- Healthy lifespan has been extended in numerous animal models.
- Relevant drugs have been used in humans. (Metformin, Acarbose, Rapamycin....)
Metformin targets multiple pathways of aging

Barzilai N et al. Metformin as a Tool to Target Aging. Cell Metab. 2016 Jun 14;23(6):1060
TAME: Targeting 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:
Effect of metformin on neurodegeneration:
VA (n=433/6046 T2DM; ~63yo; 5.2 yr follow up)

HR metformin vs. Control:

Incidences ND was:
Metformin: 1.15/100 person year
Control: 2.79/100 person year

- Neurodegenerative disease: 0.686
- Dementia: 0.644
- Parkinson: 0.611

She Q., J et al: Abstract 72OR ADA -2016
# Metformin in Amnestic Mild Cognitive Impairment: Results of a Pilot Randomized Placebo Controlled Clinical Trial (n=80, 12 mo)

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Placebo</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>ADAS-Cog</strong></td>
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<tr>
<td>Baseline</td>
<td>12.0±4.0</td>
<td>14.6±6.1</td>
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<td>Last visit</td>
<td>12.1±3.8</td>
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<tr>
<td>Crude difference</td>
<td>0.0±3.3</td>
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<tr>
<td>Adjusted difference</td>
<td>−0.5±4.1</td>
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<tr>
<td><strong>Total recall SRT</strong></td>
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<tr>
<td>Baseline</td>
<td>34.2±7.9</td>
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<tr>
<td>Adjusted difference</td>
<td>9.5±6.1</td>
<td>5.4±6.1</td>
<td>0.05</td>
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</tbody>
</table>

PHASE IV Clinical Trial

• Post-marketing studies (after FDA approval and initial clinical use)
• to delineate additional information including the agent’s risks, benefits, comparative effectiveness, and optimal use.
• These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
Metformin decreases mortality in T2DM and in non-diabetics

Bannister et al Diabetes, Obesity and Metabolism 2014.
Why TAME?

• 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 next-generation drugs targeting multiple morbidities of aging

• To apply the discoveries of geroscience as a powerful new tool for achieving primary prevention of multiple diseases.
**TAME: Targeting Aging with METformin**

**Stratum 1: High Risk**
- Slow gait speed OR obesity plus hypertension and/or dyslipidemia (no CVD, cancer, or MCI/Dementia)

**Stratum 2: Positive History**
- 1 or 2 of CVD, Cancer, MCI present at baseline

**Inclusion Criteria**
- 3000 subjects
- 65-79 yo

**Primary Outcome**
- Time to new diagnosis of a composite component: CVD (MI, stroke, CHF, revascularization, PAD), cancer, MCI or dementia, death.

**Double blind placebo control study**

**Secondary Outcomes**
- Time to occurrence of composite functional outcome: Death, persistent severe difficulty or inability to walk ¼ mile or climb 10 steps, developing ADL limitation, transition to MCI/dementia
- Primary Composite + Type 2 diabetes mellitus (T2DM)

**Tertiary Outcomes**
- Accumulation rate 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!

• The biology of aging is the major underlying cause for age-related diseases!

• Aging can be targeted!

• Help is on the way and next generation will get better and better!
<table>
<thead>
<tr>
<th>Site</th>
<th>PI</th>
<th>Relevant NIH studies</th>
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<tbody>
<tr>
<td>Johns Hopkins</td>
<td>Sherita Golden, Larry Appel</td>
<td>DPPOS, CRIC, ASK</td>
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<td>U Alabama</td>
<td>Beth Lewis</td>
<td>WHI, ACCORD, Look AHEAD</td>
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<td>Albert Einstein</td>
<td>Jill Crandall, Nir Barzilai</td>
<td>DPPOS, GRADE, T-Trial</td>
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<td>LIFE, ENRGISE</td>
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<td>Vanita Aroda</td>
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<td>Wake Forest (*)</td>
<td>Steve Kritchevsky, Mark Espeland</td>
<td>Look AHEAD, LIFE, WHI</td>
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(*) Data coordinating center
Targeting Aging with MEtformin (TAME)
Executive team: Kritchevsky, Crandall, Espeland, Barzilai

- Steve Austad
- Nir Barzilai
- Morgan Canon
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- 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
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- Caroline Blaum
- David Sinclair
- Rafa deCabo
- Sofiya Milman
- Stephanie Lederman
- Odette van der Willik

Efforts so far are ponsored by AFAR
**A. Extending healthspan (Scenario 1)**

- **Function** vs **Time**
- **Disability/dependence threshold**

**B. Enhancing resilience (Scenario 2)**

- **Function** vs **Time**
- **Baseline**
- **Acute stressor**
- **Recovery**
- **Disability/dependence threshold**

- **Course with intervention that targets aging processes**
- **Natural Course**