Strategies and Challenges in Human Clinical Trials Targeting Aging

John Newman, MD, PhD
UCSF and Gladstone Institutes

newman@ucsf.edu
@GeriSciDoc
The Geroscience Hypothesis

Targeting **fundamental aging processes** might delay, prevent, alleviate, or reverse a **wide range** of diseases and conditions for which age is the primary non-modifiable risk factor.
Special Issue: Moving Geroscience into Uncharted Waters: Perspective

Strategies and Challenges in Clinical Trials Targeting Human Aging

John C. Newman,¹,* Sofiya Milman,²,³,* Shahrukh K. Hashmi,⁴ Steve N. Austad,⁵ James L. Kirkland,⁶ Jeffrey B. Halter⁷, and Nir Barzilai²,³

Frameworks for Proof-of-Concept Clinical Trials of Interventions That Target Fundamental Aging Processes

Jamie Justice,¹,* Jordan D. Miller,²,³,₄,* John C. Newman,⁵,* Shahrukh K. Hashmi,⁶ Jeffrey Halter,⁷ Steve N. Austad,⁸ Nir Barzilai,⁹,¹⁰ and James L. Kirkland³,⁴
Think Big
Study Patients
New Tools
Easy Mode
Think big

Do you want to lower cholesterol or do you want to change people’s lives?
Outcomes for aging interventions

Age-related Diseases:
T2DM, CAD, CKD, Alzheimer’s, Parkinson’s

Physiological Age

Age-related Changes:
Muscle loss, kidney function

Functional outcomes

Geriatric syndromes

Mortality
Scenarios for Clinical Trials of Aging

A. Extending Healthspan

- Course with intervention that targets aging process
- Natural course

Function

Time

Disability & Dependence

B. Enhancing Resilience

- Acute Stressor
- Baseline
- Recovery

Function

Time

Disability & Dependence
**A. Extending Healthspan**

- Course with intervention that targets aging process
- Natural course

**Scenarios for Clinical Trials of Aging**

- Slow/prevent the progressive decline with age
  - Long-term studies: years?
- Global outcomes representative of aging:
  - Multimorbidity
  - Geriatric syndromes
  - Functional decline
  - Multisystem effects

**Function**

- Disability & Dependence

**Time**
Scenarios for Clinical Trials of Aging

Improve the response to a stressor

May be short, with longer follow-up

Intensity of stressor:
  Immunization
  Wound healing
  Surgery/Chemotherapy

Planned vs. unplanned stressor

Pre-, peri-, or post-stressor intervention

Primary outcome related to the stressor, but global secondary outcomes

B. Enhancing Resilience

Function vs. Time

Disability & Dependence

Baseline

Acute Stressor

Recovery
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Don’t Study Spherical Cows
Don’t Study Spherical Cows
Study the patients you want to treat

Embrace heterogeneity!

Many elders are...old

Many elders are frail and/or have multiple chronic diseases

Age-related diseases occur in the context of aging

Age-related diseases occur in the context of other age-related diseases

A real-life, non-spherical older adult who strongly values her independence
Population Selection

- Incidence of disease/condition
- Likelihood of poor outcome
- Room to benefit
- Susceptibility to harms

Physiological age (age, frailty, multimorbidity...)

Seek your balance

Window of opportunity?

??
Samples, biomarkers, outcomes
Outcomes

How to “measure” aging?
Accumulation of diseases, syndromes, conditions
Decline in daily function: ADLs, IADLs, care settings
Decline in physiological function: gait speed, grip strength, etc.

Healthspan trials: Broad aging outcomes, but could some of these be added on to a trial targeting one specific disease/condition?

Resilience trials: Primary outcome is specific to stress, but should collect broad aging outcomes as well.

Any trial involving older adults: Where appropriate, could expand utility and extend results by collecting outcomes and samples broadly relevant to aging

- Longitudinal data collection as a salve for heterogeneity
- Long-term, low-touch follow-up could be very informative
- Development of validated biomarkers is an area for active investigation
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New tools for you?
## Interventions

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>Current Indication</th>
<th>Safety (adverse reactions)</th>
<th>Effect on Other Age-Related Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>✓</td>
<td>T2DM</td>
<td>+++ (diarrhea and GI upset)</td>
<td>Reduced risk of CVD, cancer, and dementia</td>
</tr>
<tr>
<td>Acarbose</td>
<td>✓</td>
<td>T2DM</td>
<td>+++ (flatulence and diarrhea)</td>
<td>Reduced risk of CVD and hypertension</td>
</tr>
<tr>
<td>Resveratrol/sirtuins&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>None</td>
<td>Limited data</td>
<td>No major studies</td>
</tr>
<tr>
<td>Rapamycin/rapalogs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>✓</td>
<td>Transplant, cancers&lt;sup&gt;c&lt;/sup&gt;</td>
<td>+ (hyperglycemia and oral ulcers)</td>
<td>Improved response to flu vaccine</td>
</tr>
<tr>
<td>ACEi/ARB</td>
<td>✓</td>
<td>Cardiovascular&lt;sup&gt;c&lt;/sup&gt;</td>
<td>++ (hypotension, hyperkalemia, and renal injury)</td>
<td>Reduced risk of cancer, cognitive decline, and dementia</td>
</tr>
<tr>
<td>Aspirin/salicylic acid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>✓</td>
<td>Many&lt;sup&gt;c&lt;/sup&gt;</td>
<td>++ (bleeding and GI ulcers)</td>
<td>Reduced risk of CVD and cancer</td>
</tr>
<tr>
<td>17-α-Estradiol</td>
<td>✓</td>
<td>Alopecia (Europe)</td>
<td>Limited data</td>
<td>No major studies</td>
</tr>
</tbody>
</table>

Dozens of drugs and other interventions are now known to extend healthspan and longevity in rodents. Several of these drugs are already FDA-approved and have human data suggestive of broad effects on aging.
Interventions

**Safety:** New drugs, and many approved drugs, will require safety testing in the targeted population.

**No panaceas:** Select drugs based on proposed mechanism. Not all drugs are likely to be helpful in all circumstances.

**Fit to study:** Risk of adverse effects and intensity of therapy should be proportionate to the duration and outcomes of the study.

**Combinations:** Multifactorial interventions may prove superior.

**Standard of care:** Leverage existing programs to provide infrastructure as well as comparisons (e.g. ACE units, Prehab clinics).
Outcomes

Regulatory agencies:

“Aging” is not an FDA indication

Registration indication is critical for new drugs, and preferable for repurposed drugs

Geroscience hypothesis: drugs will affect multiple diseases/conditions

The most impactful aspects of aging involve multiple pathophysologies

Solution: composite of existing outcomes, e.g. multiple diseases

Solution: Build evidence for adopting syndromes of aging as indications Multimorbidity, frailty, ADL/IADL functional decline, delirium immobility, cognitive decline, etc.
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Clinical Trial Kit

Background

Foreground
Accelerating Progress

Identifying new interventions:
- systematic expert review of literature/libraries
- standardized pre-clinical screening protocols
- partnering with e.g. NCATS Drug Repurposing Program

Shared library of templates:
- trial designs, IND applications, IRB proposals, DSMB designs
- all adapted to older adults and outcomes related to aging

Standardized, modular outcome toolkit:
- potentially applicable to ALL trials involving older adults
- physiological, functional, molecular measures
- natural history data needed!

National geroscience biobank
- diverse, uniquely enriched for multimorbidity, frailty, elderly
- helpful to ALL investigators studying an age-related disease or a disease in older adults
Geroscience Network for Aging-Related Proof of Concept Clinical Trials

- Expert Panel to Review FDA Approved Drugs
- Streamlined Pipeline for Repurposed Drugs
- Templates for Clinical Trials Designs
- Guides for Regulatory Compliance
- Aging-Related Outcomes “Toolkit”
- Central Geroscience Biobank
- Core Facilities for Biochemical Assays
- Specialized Centers for PoC Clinical Trials
Thank you!

newman@ucsf.edu

@AgingSciDoc