• 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:

CohBar Inc.

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


Aging drives diseases

Genetics and environment of the individual determine which disease occurs first

- Heart disease
- Cancer
- Stroke
- Emphysema
- Pneumonia
- Diabetes
- Accidents
- Kidney disease
- Alzheimer’s
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

- It's been used for 70 years and is safe!!!
- It was used to prevent flu and malaria
- It's 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
n = 3000
Double blind placebo-controlled trial

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

Primary Outcome
(Clinical) Time to incidence of any major age-related disease:
MI, stroke, cancer*, CHF, MCI/dementia, or death. FDA

(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

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

**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 al, 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
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 combination of drugs.
Intervention Testing Program (NIA)

- NDGA (Nordihydroguiaretic acid)
- Aspirin
- Acarbose
- 17-α estradiol
- Rapamycin
- Rapamycin + metformin
Metformin Attenuates Biological Hallmarks of Aging

Kulkarni et al Cell Met

Metformin extends lifespan and health span in animals. (683 papers in pubmed)
Blastocytes erase aging!

- Not only aging!
- A major foundation is coming