Geroscience

Aging

XP and Potential Therapeutics

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How we got here: an aging success story

[Graph showing a decrease in deaths per 100,000 people over age from 1900 to 2016, with a peak in deaths occurring later in life compared to earlier in the 20th century.]
Exponential increase in disease risk after 60

- osteoporosis
- cardiovascular disease
- neurodegenerative diseases
- osteoarthritis
- type II diabetes
- cancer
- macular degeneration
- intervertebral disc degeneration
- hearing loss
Most elderly individuals have >1 disease
Risk factors for heart disease

- Hypertension: 75%
- Cholesterol: 75%
- Smoking: 70%
- Diabetes: 48%
- Old age: 7500%
Geroscience: Treat aging biology

+ prevent, delay or ameliorate multiple debilitating, chronic degenerative diseases

+ avoid spending the rest of your life with “ologists”

+ avoid polypharmacy

+ reduce healthcare costs
Goal: increase healthspan, not lifespan

![Graph showing healthspan and lifespan relationship]

- Fitness axis
- Lifespan axis
- Compressing period of decline
Extension of Healthspan/Lifespan is feasible
What about aging can we therapeutically target?

Hallmarks of Aging

- Cellular senescence
- Adaptation to stress
- Macromolecular damage
- Epigenetics
- Inflammation
- Proteostasis
- Stem cells
- Metabolism

Kennedy et al. 2014. Cell
DNA damage drives aging

Hallmarks of Aging

- Cellular senescence
- Adaptation to stress
- Macromolecular damage (DNA damage)
- Epigenetics
- Inflammation
- Proteostasis
- Stem cells
- Metabolism
Available therapeutics that target >1 hallmark of aging

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hallmark of aging impacted</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSD1 inhibitors</td>
<td><strong>Epigenetics, senescence, inflammation</strong></td>
</tr>
<tr>
<td>Acarbose</td>
<td><strong>Inflammation, metabolism</strong></td>
</tr>
<tr>
<td>Rapamycin</td>
<td><strong>ROS &amp; DNA damage, autophagy, stem cells</strong></td>
</tr>
<tr>
<td></td>
<td><strong>inflammation, senescence, metabolism</strong></td>
</tr>
<tr>
<td>Canagliflozin</td>
<td><strong>Mitochondria, autophagy, metabolism</strong></td>
</tr>
<tr>
<td>Metformin</td>
<td><strong>ROS &amp; DNA damage, mitochondria, autophagy</strong></td>
</tr>
<tr>
<td></td>
<td><strong>inflammation, senescence, metabolism, stem cells</strong></td>
</tr>
<tr>
<td>Senolytics</td>
<td><strong>Senescence, inflammation, metabolism, stem cells</strong></td>
</tr>
<tr>
<td>Aspirin</td>
<td><strong>ROS &amp; DNA damage, autophagy, inflammation, senescence,</strong></td>
</tr>
<tr>
<td></td>
<td><strong>metabolism, epigenetics</strong></td>
</tr>
</tbody>
</table>
Senescent cells

**Senescence-associated secretory factors (SASP)**

**Triggers:**
- mitotic stress
- telomere erosion
- DNA damage
- epigenetic stress
- oxidative stress
- ER stress
- mitochondrial dysfunction
- proteotoxic stress
- nucleolar stress
- nutritional stress

- p16
- p21
- p53
- γH2AX
- Lamin B
- Senescence-associated β-galactosidase

Annual Rev Pharm Toxicol 2020
Senescent cells are pro-inflammatory
Senescent cell

A few bad apples can spoil a whole bushel

Damage tissue

A few senescent cells can cause inflammation and tissue destruction
# Senotherapeutics

## First-generation senolytics: hypothesis-driven, mechanism-based discovery

<table>
<thead>
<tr>
<th>Agent</th>
<th>Senomorphic</th>
<th>Cancer therapy</th>
<th>Natural product</th>
<th>XP mouse model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Quercetin</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Fisetin</td>
<td>✓</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Luteolin</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Curcumin</td>
<td>✓</td>
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<tr>
<td>Curcumin analog EF24</td>
<td>✓</td>
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<tr>
<td>Navitoclax (ABT263)</td>
<td>✓</td>
<td>✓</td>
<td></td>
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<tr>
<td>A1331852</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>A1155463</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Geldanamycin, tanespimycin, alvespimycin, and other HSP90 inhibitors</td>
<td>✓</td>
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<tr>
<td>Piperlongumine</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>FOXO4-related peptide</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutlin3a [although Nutlin3a can also cause senescence (87)]</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac glycosides such as ouabain, proscillaridin A, and digoxin</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>✓</td>
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</tbody>
</table>

## Second-generation senolytics: traditional and other drug discovery methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Senomorphic</th>
<th>Cancer therapy</th>
<th>Natural product</th>
<th>XP mouse model</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-throughput compound library screens</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Vaccines</td>
<td>✓</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Toxin-loaded nanoparticles preferentially lysed by Sncs</td>
<td>✓</td>
<td></td>
<td></td>
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<tr>
<td>Immunomodulators</td>
<td>✓</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cell-based therapies</td>
<td>✓</td>
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</tbody>
</table>
How senolytics are envisioned to work

Intermittent
Safe
Potent
Diseases in which senolytics work (in mice)

- Neuromuscular dysfunction
- Tauopathy (Alzheimer’s disease)
- Pulmonary fibrosis
- AV fistulae
- Steatosis
- Hepatic fibrosis
- Osteoporosis
- Osteoarthritis
- Atherosclerosis
- Kidney disease
- Cardiovascular disease
- Frailty
- COVID-19
- XP

2015  Senolytics first described
2018  First clinical trial
2021  >20 clinical trials
Senolytics improve physical function when administered in old age

Xu et al., Nat. Med., 2018
Senolytic Clinical Trials
Phase I/II underway or planned based on UMN/Mayo pre-clinical data

- Idiopathic pulmonary fibrosis (NCT028749819)
- Age-related osteoporosis (NCT04313634)
- Osteoarthritis (NCT04210986)
- Frailty (NCT03675724)
- Bone marrow transplant survivors (NCT02652052)
- Alzheimer’s disease (NCT0463124)
- Diabetic chronic kidney disease (NCT02848131)
- Childhood cancer survivors (NCT04733534)
- Improving outcomes after transplanting organs from old donors
- Reducing mortality in elderly Covid-19 patients (NCT04476953, NCT04537299, NCT04771611)
Laura’s team at work on the skin biopsies
# Biomarkers related to Hallmarks of Aging

<table>
<thead>
<tr>
<th>Hallmark of aging</th>
<th>Measure</th>
<th>Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial function</td>
<td>Cell mitochondrial content</td>
<td>Skin fibroblasts/keratinocytes - stain</td>
</tr>
<tr>
<td>Autophagy</td>
<td>p62 mRNA</td>
<td>PBMC - RNA qPCR</td>
</tr>
<tr>
<td>Metabolism</td>
<td>NAD+</td>
<td>Blood drop dip stick</td>
</tr>
<tr>
<td>ROS</td>
<td>4-HNE</td>
<td>PBMC protein lysate - ELISA</td>
</tr>
<tr>
<td>DNA damage</td>
<td>γH2AX foci and 8-oxo-dG</td>
<td>PBMC and skin fibroblasts/keratinocytes - stain</td>
</tr>
<tr>
<td>Inflammation</td>
<td>SASP</td>
<td>Plasma - ELISA</td>
</tr>
<tr>
<td>Senescence</td>
<td>SA-βGal</td>
<td>Skin fibroblasts/keratinocytes and PBMC - qPCR RNA</td>
</tr>
<tr>
<td>Stem cell function</td>
<td>Differentiation</td>
<td></td>
</tr>
<tr>
<td>Epigenetics</td>
<td>GrimAge clock</td>
<td>PBMC DNA</td>
</tr>
</tbody>
</table>