Senescence and Senolytics

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  N/A

• Conflicts of interest
  Patents on senolytic drugs (PCT/US2016/041646, filed at the US Patent
  Office) are held by Mayo Clinic. I hold small shares of UNITY stock.
Cellular senescence

DNA damage
Telomere dysfunction
Mitochondrial defect
Metabolic stress
Oncogenic insult

Senescence-associated secretory phenotype (SASP)

Proinflammatory cytokines, chemokines, proteases

IL6, MCP1, IL8, GM-CSF, G-CSF, RANTES, IP-10, PAI-1, Activin A…….

• Senescent cells accumulate with aging in a variety of tissues.
Cellular senescence: *in vivo* models

**Genetic models**

*INK-ATTAC*, Mayo Clinic

*p16-3MR*, Buck Institute
Cellular senescence: *in vivo* models

**Senolytic drugs**
- Dasatinib + Quercetin
- Navitoclax (ABT263)
- FOXO4 peptide
- Fisetin
- HSP90 inhibitor
- More...

**SASP inhibitors**
- JAK inhibitor
- Rapamycin
- NFκB inhibitor
- Metformin
- Glucocorticoid
- More...

Translational approaches

Senescence-associated secretory phenotype (SASP)
- IL6, MCP1, IL8, GM-CSF, G-CSF, RANTES, IP-10, PAI-1, Activin A…….

References:
Liver

Brain

Heart and cardiovascular system

Liver

Pancreatic β cells

Eye

Skin

Adipose tissue

Bone

Joints

Stem cell function

Physical dysfunction

Cancer

Immune system
Senolytic drugs

- Senolytics are drugs that selectively kill senescent cells.

Dasatinib (D) + Quercetin (Q)

Senolytics alleviate frailty in aged mice

20-month-old C57BL/6

4 months

Vehicle

D+Q intermittently

Senolytics increase post-treatment lifespan

Treatment starting at 70-80 years of age increases 5-6 years of remaining lifespan in human.

Senolytics improve bone phenotypes

20-month-old C57BL/6
Vehicle
Monthly
D+Q

4 months

Osteoclast

Osteoblast

Bone formation rate

Senolytics attenuate post-traumatic osteoarthritis

Anterior cruciate ligament transection (ACLT)

Navitoclax or ABT263  Veh
UBX0101 (1 mM in 10 μl saline)

Time after surgery (d)

Evaluation

OARSI grade

% of weight bearing (operated/unoperated contralateral leg)

Senescent cell induce physical dysfunction in young mice

Senescent cell transplantation model

- Irradiation
- 1x10^6 control cells
- 0.2-1x10^6 senescent cells
- I.P. injection
- 6-month-old

Radiation-induced senescent cells

- Naturally p16^+ senescent cells from 24-month-old INK-ATTAC mice

Maximal speed (% of baseline)

Maximal Speed (sec^-1)

Senescent cell induce osteoarthritis in young mice

Ongoing clinical trials

D+Q  Idiopathic Pulmonary Fibrosis
D+Q  Chronic Kidney Disease
D+Q  Hematopoietic Stem Cell Transplant Survivors
UBX0101  Osteoarthritis

14 IPF patient (2 female) age 70.8±7.9 years

Open-label

- Dosing Days: Dasatinib: 100 mg per day, Quercetin: 1250 mg per day
- Adherence Check
- Symptom Questionnaires
- Adverse Event Reporting

Baseline Measures

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<tr>
<th>Week 1</th>
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<th>Follow-Up Measures</th>
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<tbody>
<tr>
<td>Dosing Day 1-3</td>
<td>Day 4</td>
<td>Dosing Day 8-10</td>
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<tr>
<td>Dosing Day 15-17</td>
<td>Day 18</td>
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Relatively safe (short-term)
Recapitulate findings in aged mice and IPF mice (physical function)

Only mild to moderate adverse events were reported (respiratory symptoms, skin irritation and gastrointestinal discomfort).

Physical function was significantly and clinically meaningfully improved (6-min walk distance, 4-m gait speed, and chair-stands time).

Pulmonary function, clinical chemistries, frailty index and reported health were unchanged.

Future studies

• Knowledge Gaps
  Biomarkers
  Long-term side effects from drugs and clearance of senescent cells
  Underlying mechanisms

• Research Opportunities
  Better understanding of naturally occurring senescent cells
  Develop next-generation senolytics
  Develop new animal models
  Combine senolytic drugs with other intervention
  Long-term clinical trials
Questions & Discussion

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