

A large, light gray, stylized graphic of a leaf or branch with several lobes, positioned on the left side of the slide.

# Senescence and Senolytics

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# Disclosures

- **Current funding**

The Irene Diamond Fund/AFAR Postdoctoral Transition Awards in Aging  
Startup funding from UConn Health

- **Other financial relationships**

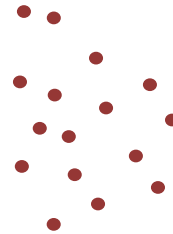
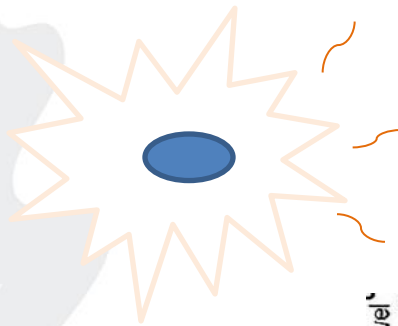
N/A

- **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

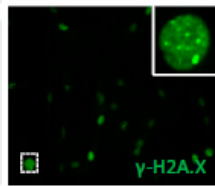
DNA damage  
Telomere dysfunction  
Mitochondrial defect  
Metabolic stress  
Oncogenic insult



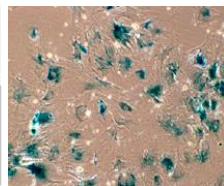
Senescence-associated secretory phenotype (SASP)

Proinflammatory cytokines,  
chemokines, proteases

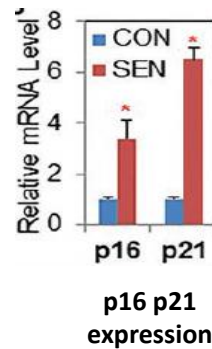
IL6, MCP1, IL8, GM-CSF, G-CSF, RANTES, IP-10, PAI-1, Activin A.....



DNA damage



Senescence-associated  
β-galactosidase  
activity

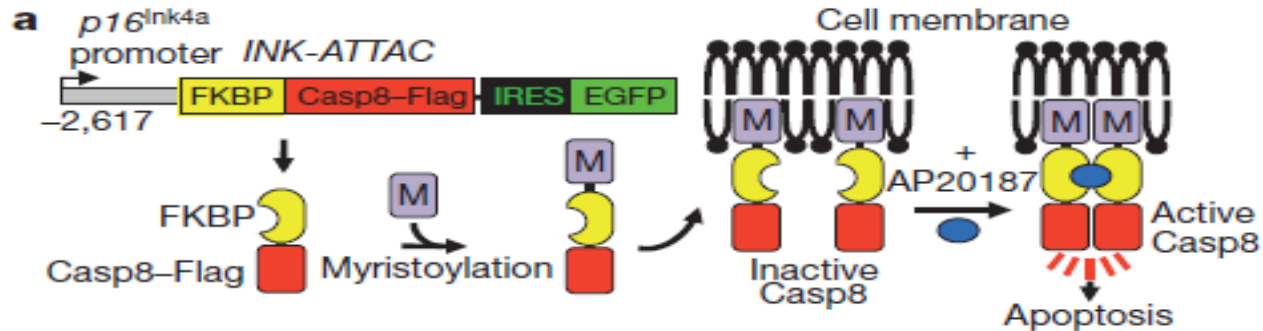


p16 p21  
expression

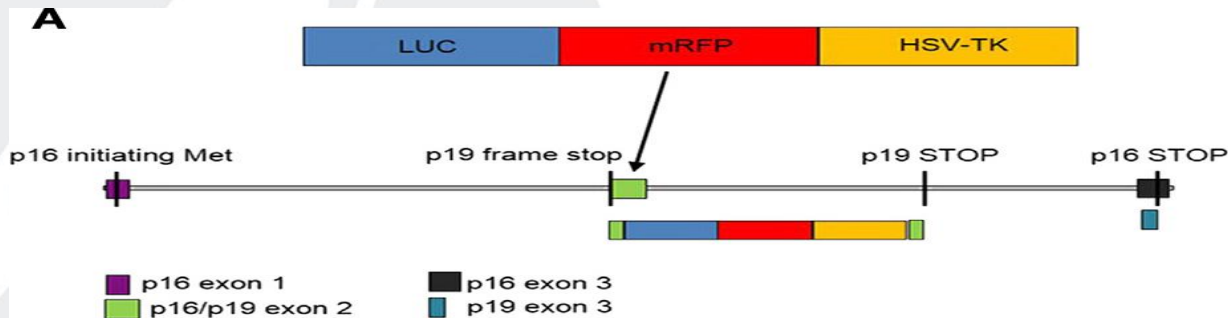
- Senescent cells accumulate with aging in a variety of tissues.

# Cellular senescence: *in vivo* models

## Genetic models



*INK-ATTAC*, Mayo Clinic

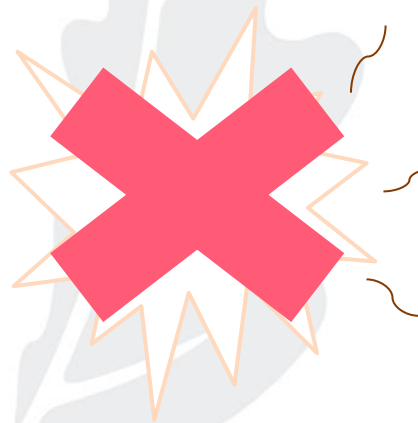


*p16-3MR*, Buck Institute

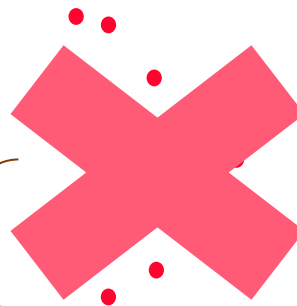
# Cellular senescence: *in vivo* models

## Translational approaches

Senolytic drugs



SASP inhibitors



Senescence-associated secretory phenotype (SASP)

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

**Dasatinib + Quercetin** Zhu, Y., et al. *Aging Cell* (2015)

Chang, J., et al. *Nat Med.* (2016)  
Zhu, Y., et al. *Aging Cell* (2016)

**Navitoclax (ABT263)**

**FOXO4 peptide**

Baar, M., et al. *Cell* (2017)

**Fisetin**

Zhu, Y., et al. *Aging* (2017)

**HSP90 inhibitor**

Fuhrmann-Stroissnigg, H., et al. *Nat Commu* (2017)

More...

**JAK inhibitor**

Xu, M., et al. *PNAS* (2015)

**Rapamycin**

Laberge, R., et al. *Nat Cell Biol* (2015)  
Herranz N., et al. *Nat Cell Biol* (2015)

**NFκB inhibitor**

**Metformin**

Moiseeve, O., et al. *Aging Cell* (2013)

**Glucocorticoid**

More...

## Brain

Bussian, T., et al. *Nature* (2018)  
Musí N., et al. *Aging cell* (2018)  
Ogrodnik, M., et al. *Cell Metab.* (2019)

## Eye

Miloudi K, O., et al. *Sci Transl Med.* 2016

## Heart and cardiovascular system

Childs, B., et al. *Science* (2016)  
Roos, C., et al. *Aging Cell* (2016)  
Baker, D, et al. *Nature* (2016)  
Anderson, R, et al. *EMBO J* (2019)

## Liver

Ogrodnik, M., et al.  
*Nat Commun.* (2017)

## Pancreatic $\beta$ cells

Helman, A., et al.  
*Nat Med.* (2016)

## Skin

Yosef, R., et al. *Nat Commun.* (2016)  
Baar, M., et al. *Cell* (2017)

## Adipose tissue

Xu, M., et al. *Elife* (2015)  
Baker, D, et al. *Nature* (2016)

## Lung

Yosef, R., et al. *Nat Commun.* (2016)  
Schafer, M., et al. *Nat Commun.* (2017)

## Physical dysfunction

Xu, M., et al. *PNAS* (2015)  
Xu, M., et al. *Nat Med.* (2018)

## Stem cell function

Xu, M., et al. *Elife* (2015)  
Chang, J., et al. *Nat Med* (2016)

## Cancer

Demaria, M., et al. *Cancer Discovery* (2017)

## Immune system

## Kidney

Baker, D, et al. *Nature* (2016)

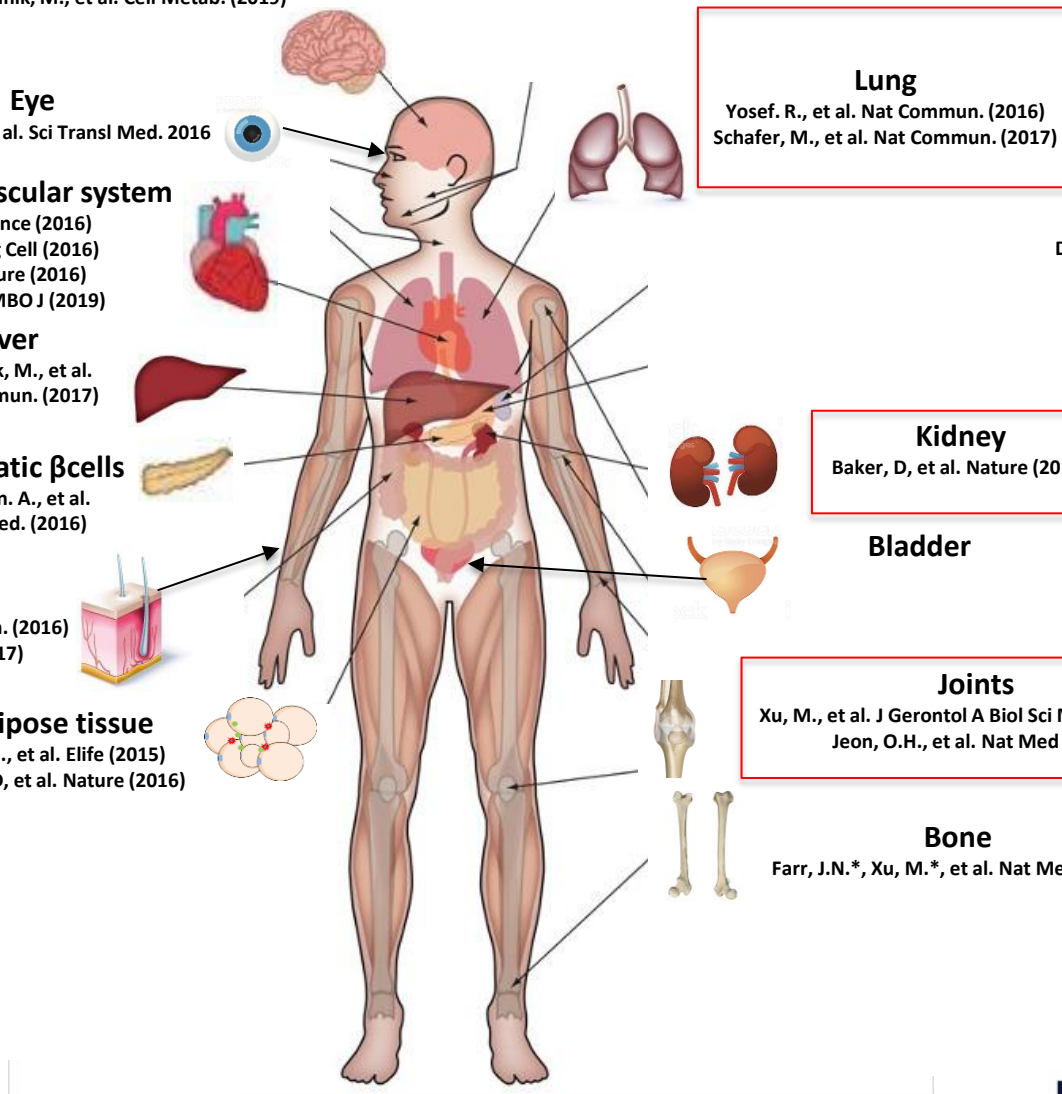
## Bladder

## Joints

Xu, M., et al. *J Gerontol A Biol Sci Med Sci.* (2016)  
Jeon, O.H., et al. *Nat Med* (2017)

## Bone

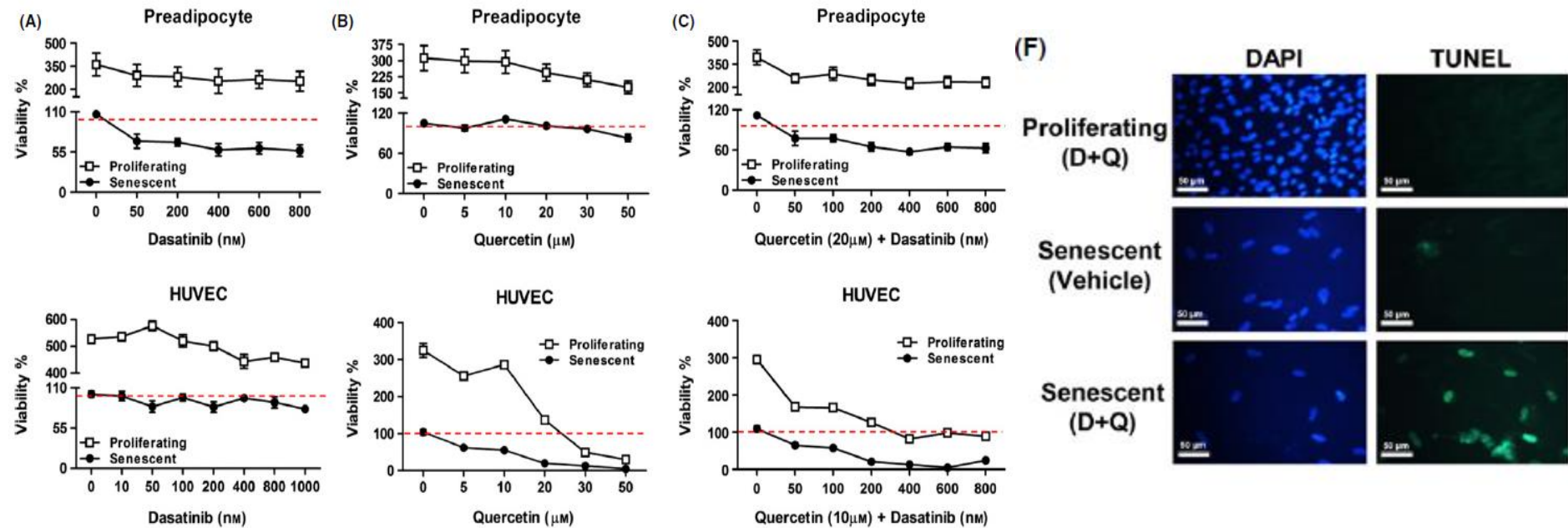
Farr, J.N.\*, Xu, M.\*, et al. *Nat Med.* (2017)



# Senolytic drugs

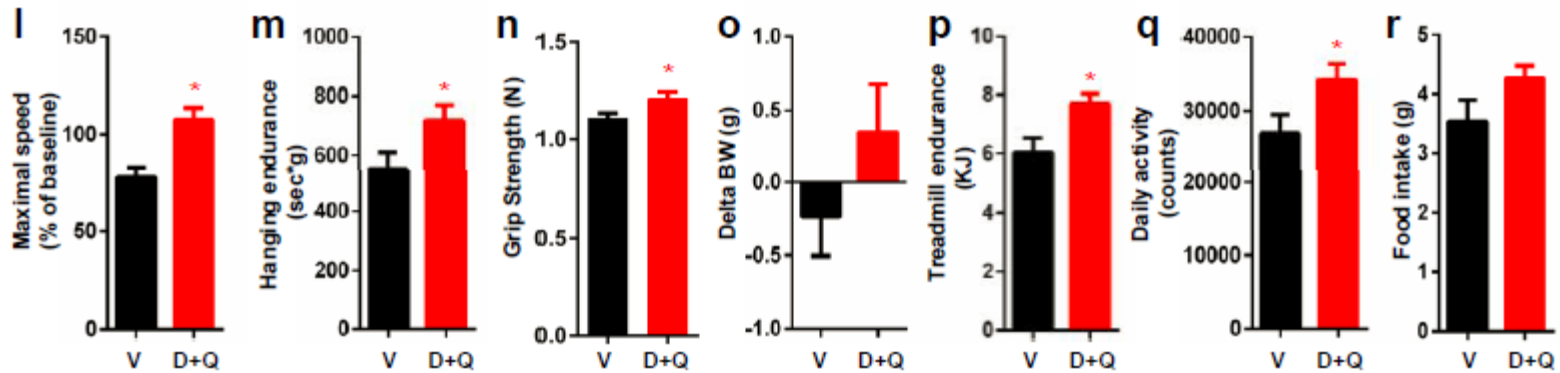
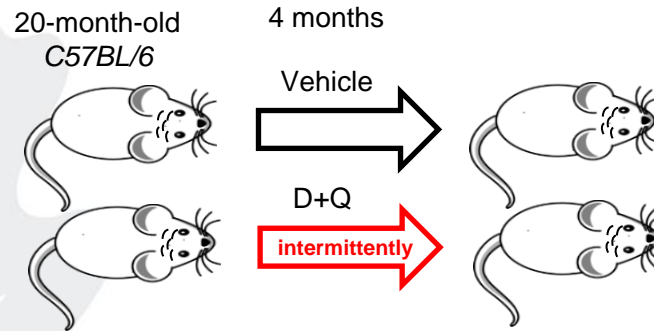
- Senolytics are drugs that selectively kill senescent cells.

Dasatinib (D) + Quercetin (Q)



Zhu, Y., et al. Aging Cell (2015)

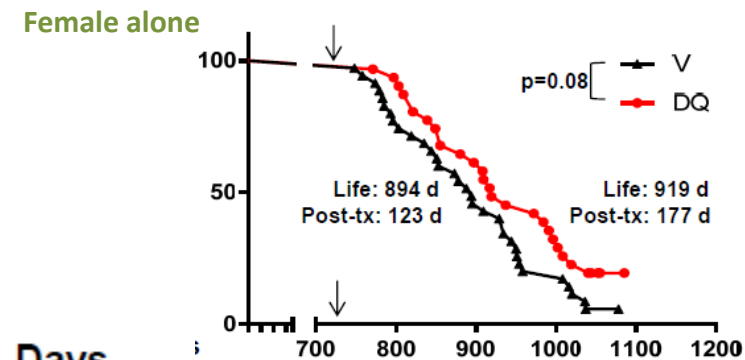
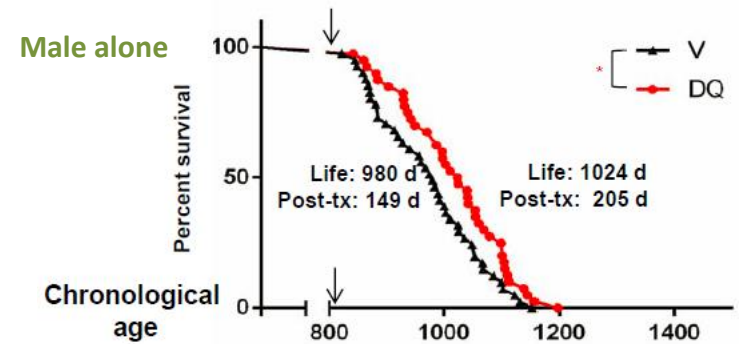
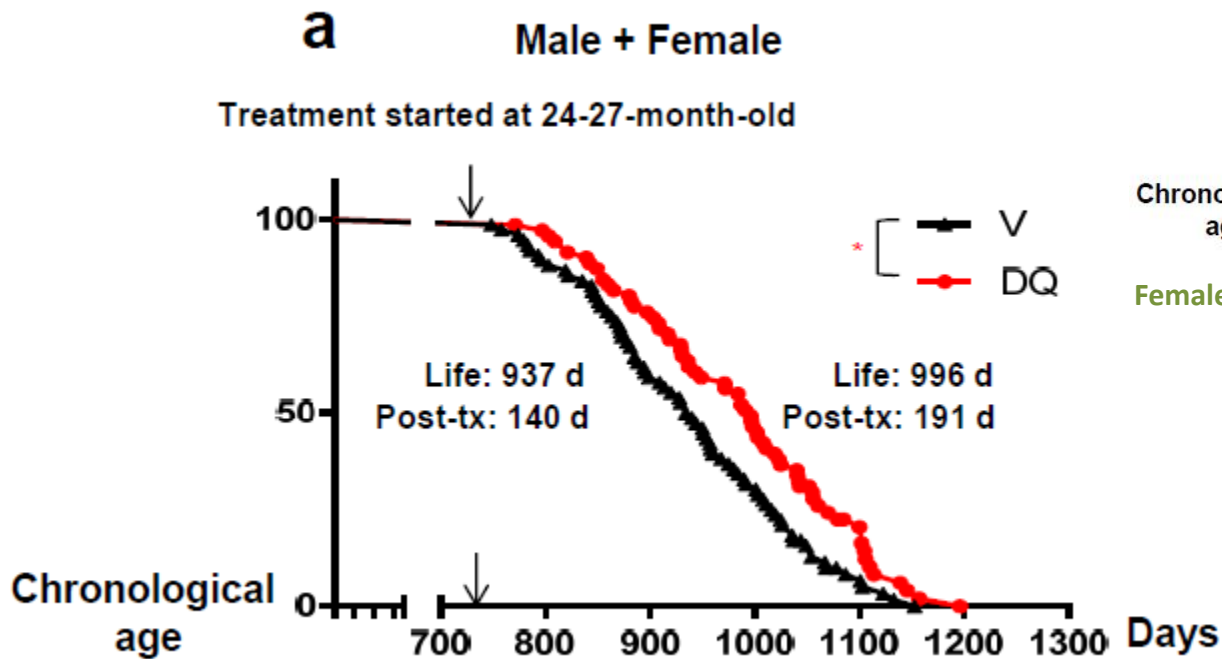
# Senolytics alleviate frailty in aged mice



Xu, M., et al. Nature Medicine (2018)

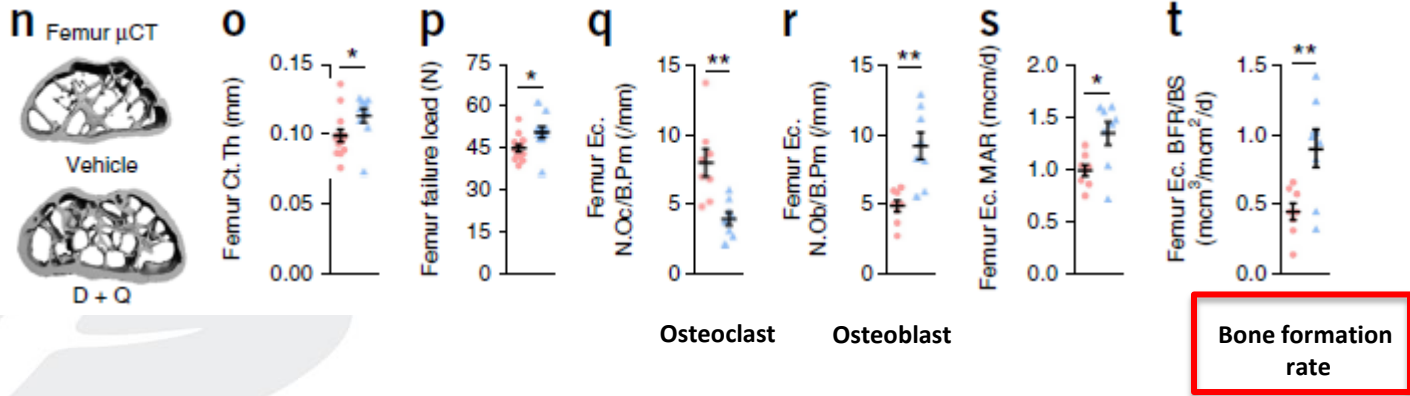
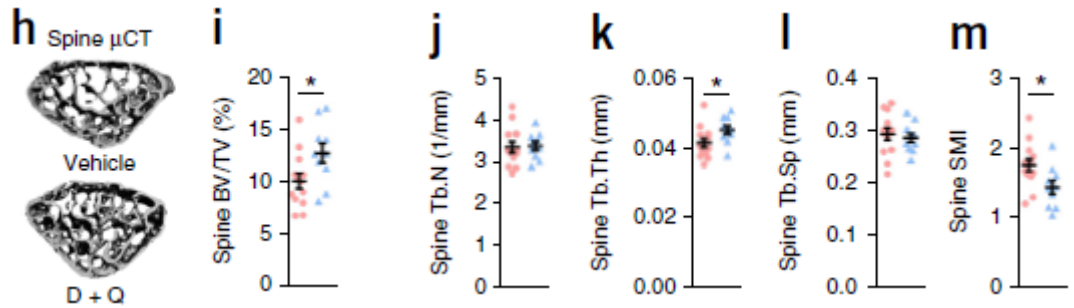
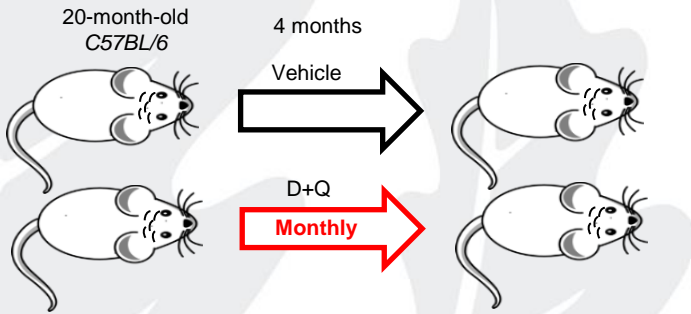


# Senolytics increase post-treatment lifespan



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

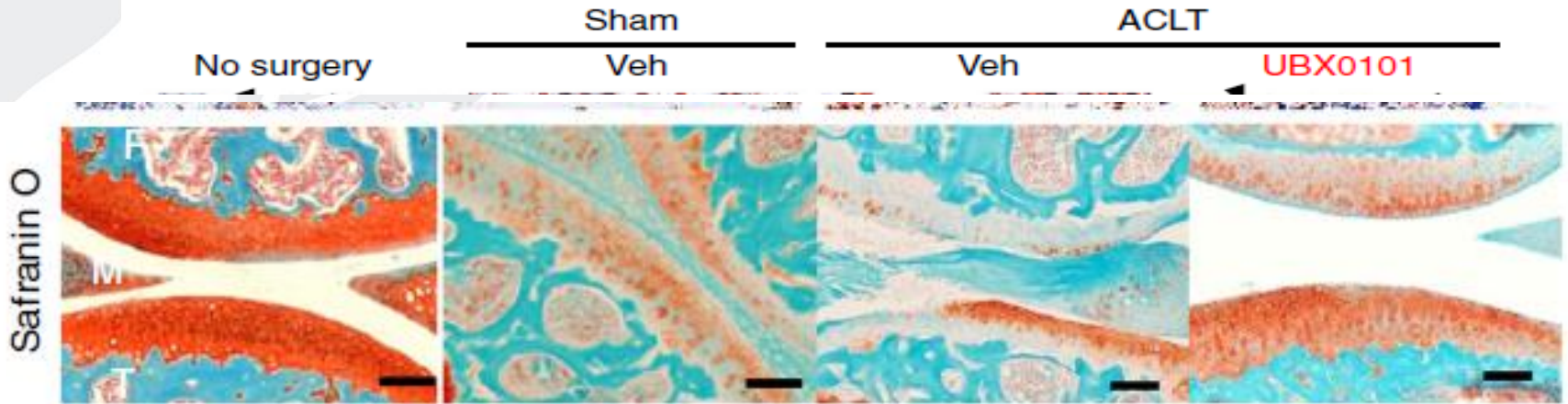
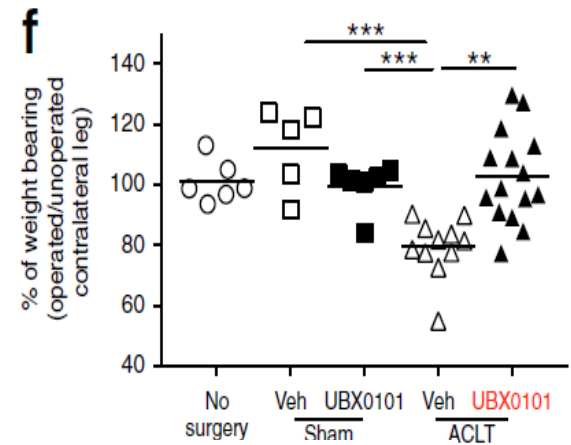
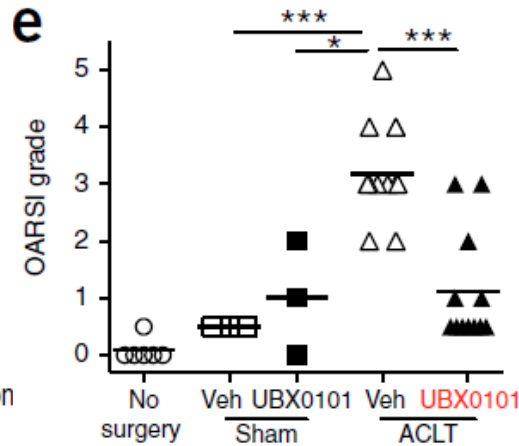
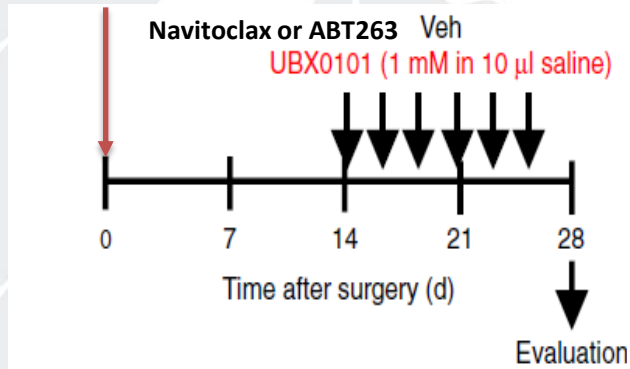
# Senolytics improve bone phenotypes



Farr, J.\*, Xu, M.\*, Weivoda, M\*. et al. Nature Medicine (2017)

# Senolytics attenuate post-traumatic osteoarthritis

Anterior cruciate ligament transection (ACLT)

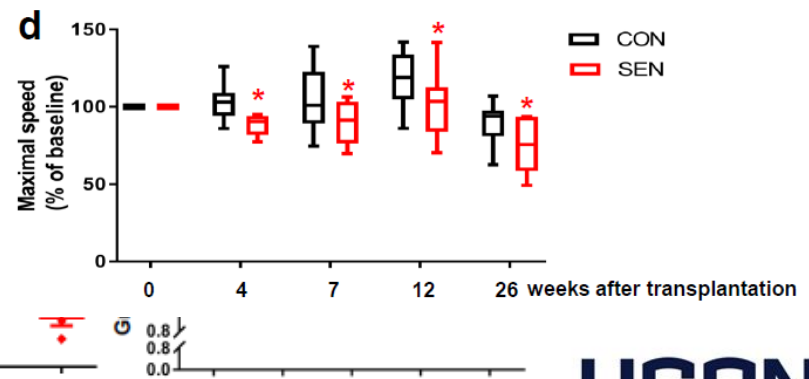
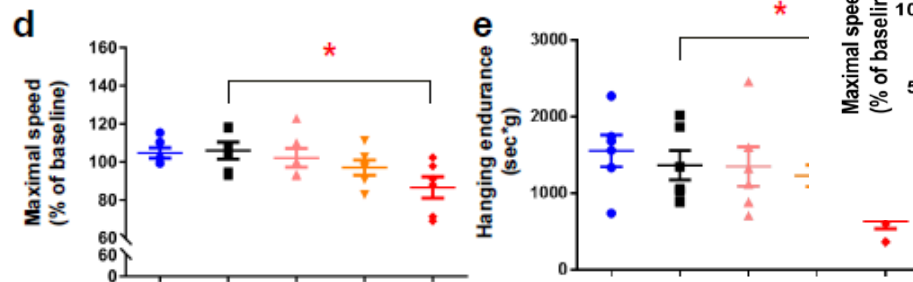
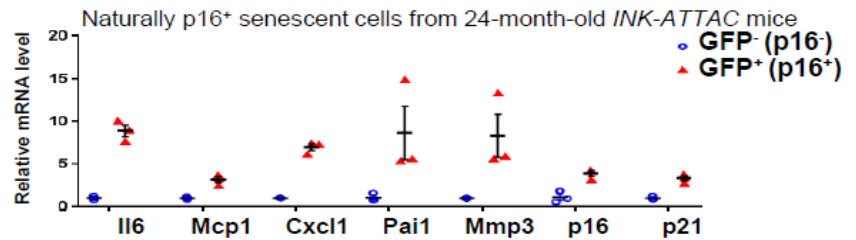
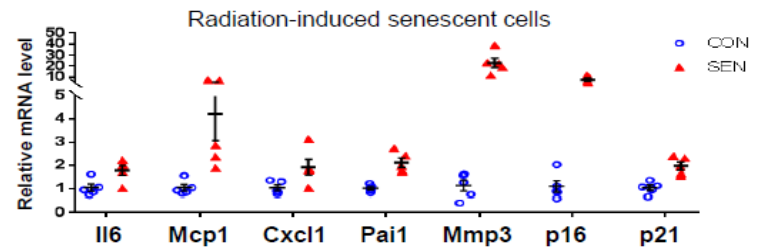
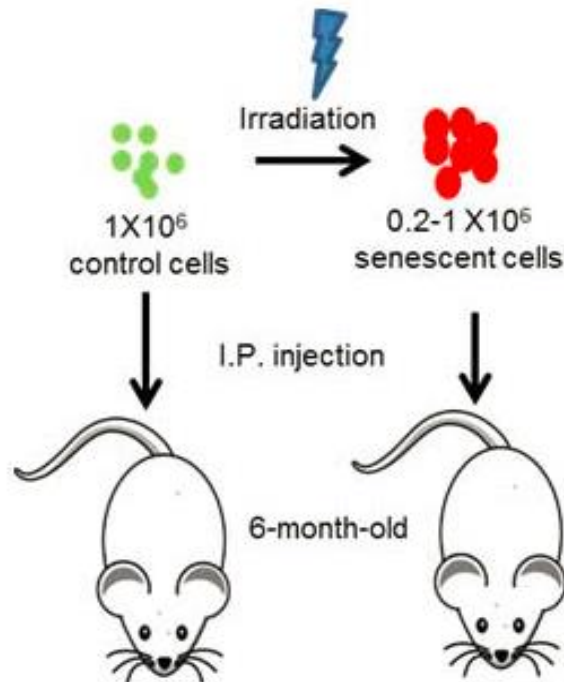


Jeon, O.H., et al. Nature Medicine (2017)

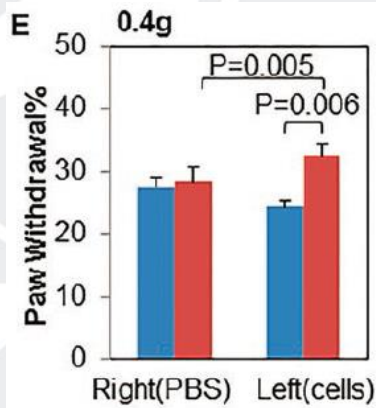
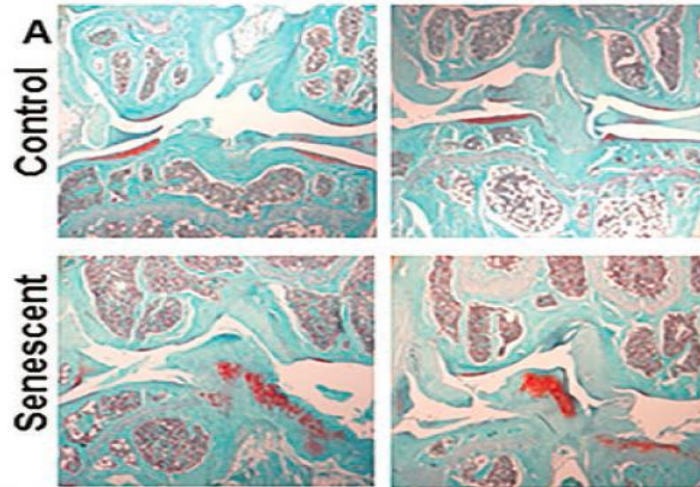
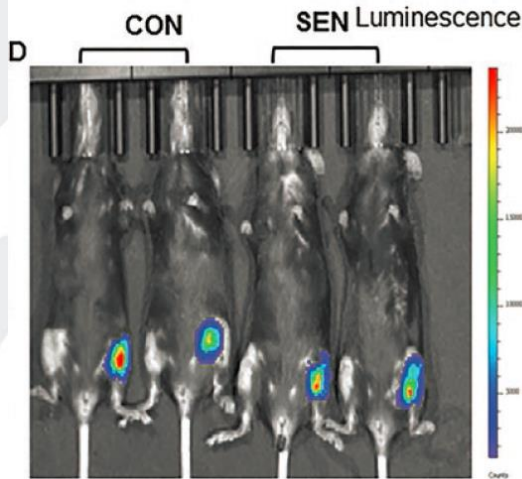
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# Senescent cell induce physical dysfunction in young mice

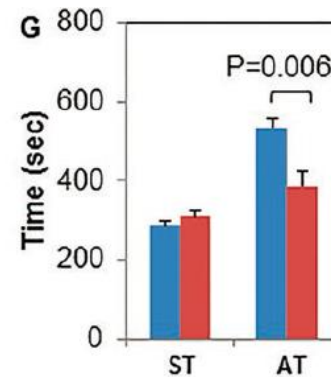
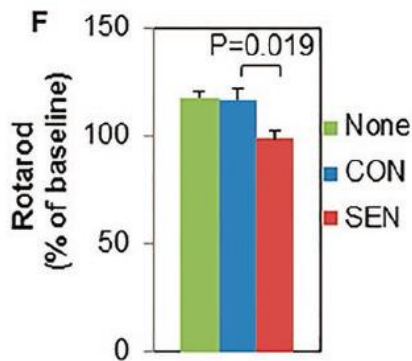
## Senescent cell transplantation model



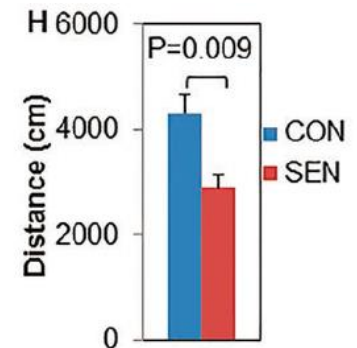
# Senescent cell induce osteoarthritis in young mice



Pain test



Function test



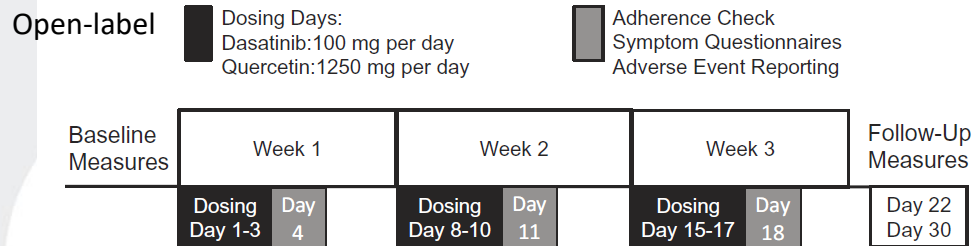
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# Ongoing clinical trials

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  $70.8 \pm 7.9$  years



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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