

What Are Senolytics?

Senolytics are compounds that selectively destroy **senescent cells**.

Senescent cells accumulate with normal aging and:

- ▶ Impede Organ Function
 - ▶ Create Chronic Inflammation
 - ▶ Emit Protein-Destroying Enzymes
 - ▶ Shorten Healthy Lifespan
-

Removing Senescent Cells Confers Healthy Longevity

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Removing Senescent Cells Confers Healthy Longevity

Senolytics Extend Healthy Lifespan

Preclinical (rodent) model shows **dasatinib + quercetin**:

- Improve frailty symptoms (gait, grip strength)
- Enhance coat color appearance
- Improve cardiac/arterial function
- Reduce tremors and urinary incontinence
- Decrease osteoporosis
- Increase exercise endurance
- Improve kidney/liver pathologic age scores
- Extend healthy lifespan

Does anyone NOT want these benefits?

Scientific Discovery and the Future of Medicine

Aging, Cell Senescence, and Chronic Disease: Emerging Therapeutic Strategies

“...many human pathologic conditions are associated with the presence of **senescent cells**.”

“Interventions aimed at **eliminating** those **senescent cells**, commonly called **senolytic**, have also been shown to improve health and extend life in various mouse disease models.

“If senolytics are shown to be safe and effective in humans, they could transform care of older adults and patients with multiple chronic diseases.”

“It’s looking like very old mice are able to substantially improve their health span, reduce or delay age-related diseases and increase their survival.”

They calculated that if only **one** in **7,000** to **15,000** cells is **senescent**, then age-related problems in physical function started to appear in the mice.

Like a **contagion**, senescent cells seem to pass on their **accelerated aging** abilities to healthy cells by releasing a number of factors that can cause tissues such as muscle to deteriorate.

Mice given senescent cells and the **senolytic** compounds **lived 36% longer** than animals with senescent cell transplants that were **not** given the drugs.

This drug cocktail reduced signs of age-related diseases and extended life in mice and human cells

“Group led by **Mayo Clinic** anti-aging researcher James Kirkland not only offers a clear look at the power of senescent cells to drive the aging process, but also a pharmaceutical cocktail that, in mice at least, can slow and even reverse it.

Compared to mice who aged normally, those who started getting the dasatinib-quercetin cocktail at an age equivalent to **75 to 90 years in humans** ended up living roughly **36% longer**, and with better **physical function**.

In human cells in a test tube and in mice bearing human senescent cells, the dasatinib-quercetin cocktail showed equally promising results, targeting senescent cells while leaving other cells intact.

Aging...is beginning to look more and more like a disease — and a treatable one at that.

This is not a place for self-experimentation,” Kirkland said. “Until safety trials are completed, he added, “we don’t know what’s going to happen.”

Delay = Death

Experts Tell Us to Wait...

“...patients should be advised not to self-medicate with senolytic agents or other drugs that target fundamental aging processes in the expectation that conditions alleviated in mice will be alleviated in people. Senolytics represent a new potential treatment approach, and the adverse effects of these therapies remain to be elucidated.”

January 7, 2019

Mayo Clinic, Wake Forest, and University of Texas Sciences Center

First Human Senolytic Findings Published

“Researchers have published findings from a safety and feasibility clinical trial on the removal of senescent cells from a small group of patients with pulmonary fibrosis.

The researchers used a drug called a senolytic -- dasatinib plus quercetin, an open-label drug, to clear the senescent cells.”

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Research paper

Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study

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ABSTRACT

Background: Cellular senescence is a key mechanism that drives age-related diseases, but has yet to be targeted therapeutically in humans. Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal cellular senescence-associated disease. Selectively ablating senescent cells using dasatinib plus quercetin (DQ) alleviates IPF-related dysfunction in bleomycin-administered mice.
Methods: A two-center, open-label study of intermittent DQ (D:100 mg/day, Q:1250 mg/day, three-days/week over three-weeks) was conducted in participants with IPF (n = 14) to evaluate feasibility of implementing a senolytic intervention. The primary endpoints were retention rates and completion rates for planned clinical assessments. Secondary endpoints were safety and change in functional and reported health measures. Associations with the senescence-associated secretory phenotype (SASP) were explored.
Findings: Fourteen patients with stable IPF were recruited. The retention rate was 100% with no DQ discontinuation; planned clinical assessments were complete in 13/14 participants. One serious adverse event was reported. Non-serious events were primarily mild-moderate, with respiratory symptoms (n = 16 total events), skin irritation/bruising (n = 14), and gastrointestinal discomfort (n = 12) being most frequent. Physical function evaluated as 6-min walk distance, 4-m gait speed, and chair-stands time was significantly and clinically-meaningfully improved (p < .05). Pulmonary function, clinical chemistries, frailty index (FI-LAB), and reported health were unchanged. DQ effects on circulating SASP factors were inconclusive, but correlations were observed between change in function and change in SASP-related matrix-remodeling proteins, microRNAs, and pro-inflammatory cytokines (23/48 markers r ≥ 0.50).
Interpretation: Our first-in-humans open-label pilot supports study feasibility and provides initial evidence that senolytics may alleviate physical dysfunction in IPF, warranting evaluation of DQ in larger randomized controlled trials for senescence-related diseases.
ClinicalTrials.gov identifier: NCT02874989 (posted 2016–2018).
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Senescent cells secrete toxic Senescence-associated secretory phenotype (SASP)

SASP accelerates aging by:

- Recruiting inflammatory immune cells,
- Damaging extracellular matrix
- Inducing fibrosis
- Inhibiting stem cell function

<https://science.sciencemag.org/content/364/6441/636.full>



Show Senescent cells Promote Cancer

Senescence-associated secretory phenotype (SASP)

“Can stimulate neoplastic cell growth, tumor angiogenesis, and metastasis, thereby promoting development of late-life cancers.”

<https://science.sciencemag.org/content/364/6441/636.full>



Anti-Cancer Properties of Senolytics

“Indeed, elimination of senescent cells with aging attenuates tumor formation in mice, raising the possibility that senolysis might be an effective strategy to treat cancer.”

<https://science.sciencemag.org/content/364/6441/636.full>



Stark Example of Extreme Age Delay

Mouse to the right underwent senolytic therapy at mid-age:



Normal aged mouse has characteristic **bent-spine**, **cataracts**, and loss of **coat fur** (hair).

Same aged mouse from **senolytic**-treated group appears outwardly **younger** and healthy.

<https://www.cnbc.com/2018/08/29/-jeff-bezos-is-backing-this-scientist-who-is-working-on-a-cure-for-aging.html>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845101/>

Lifespan Increase in Senolytic-Treated Mice

This finding may indicate that **humans** scheduled to die at **age 80** may live to **age 100** in relatively good health...using this one intervention.

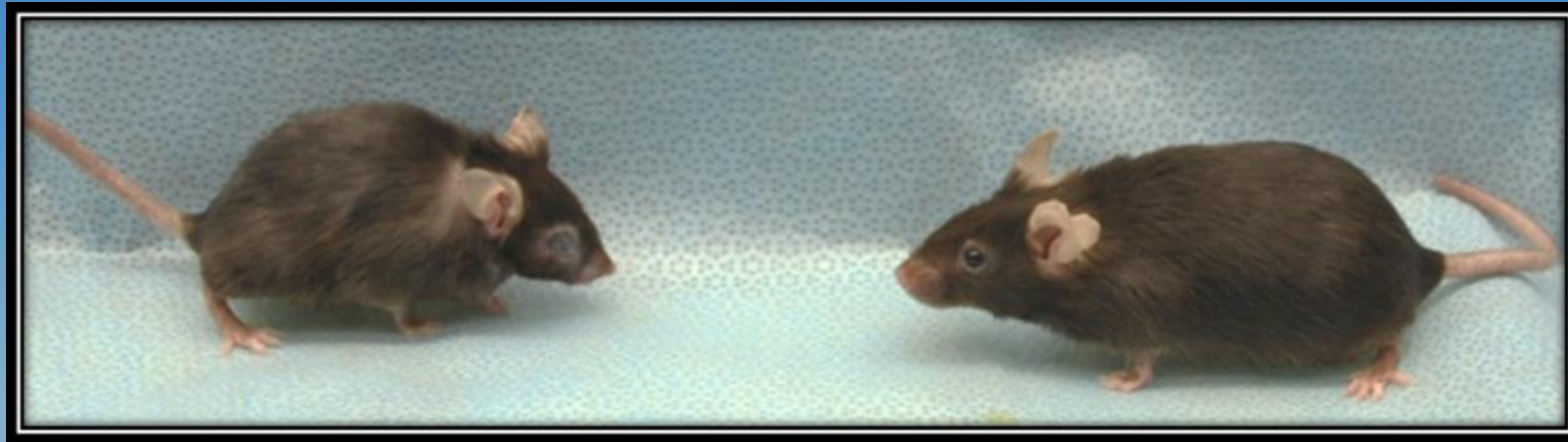


- ❑ Mouse on the left suffers from a bent spine, cataracts, loss of coat fur.
- ❑ Mouse on the right (senescent cells removed) shows delayed outward aging.
- ❑ Internal measures show improved organ function in senolytic-treated group.

Median lifespans increased **24%** to **27%**

Mayo Clinic study demonstrates improved organ function when **Senescent Cells** are removed

- ✓ Improved kidney function.
- ✓ Hearts more resilient to stress.
- ✓ Extended lifespans.

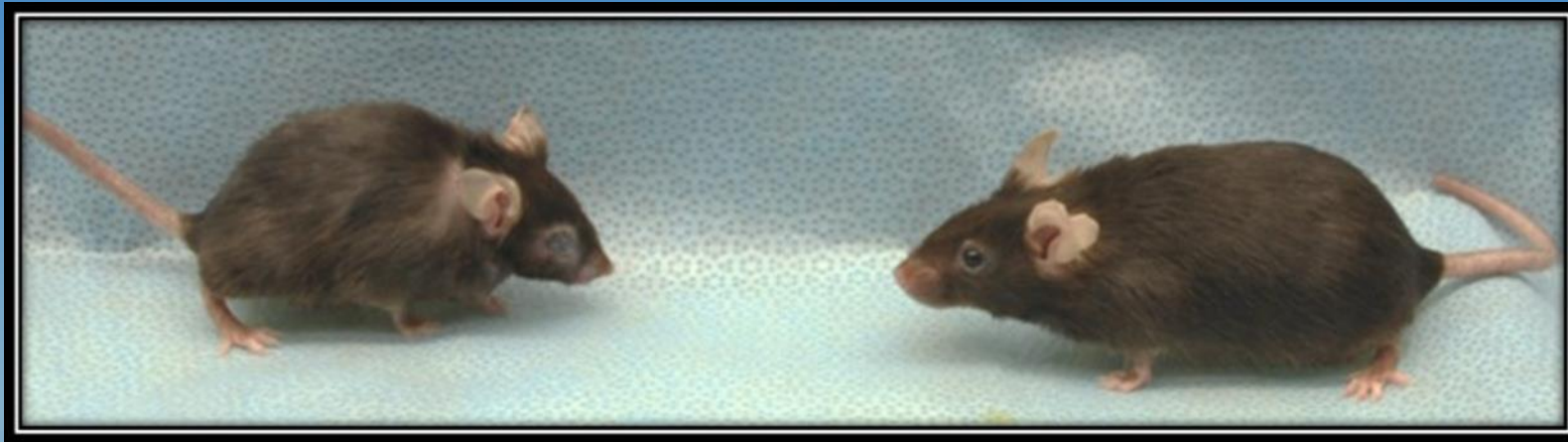


Elderly control mouse
(normal aging)

Elderly senolytic-
treated mouse
(delayed aging)

Jeff Bezos Funds Company to Bring Senolytic Drugs to Market

- ❑ Company capitalized with \$300 million---Market cap near \$700 million today.
- ❑ Investors include Pay-Pal co-founder Peter Thiel.
- ❑ Company objective is to enable people to age free of disease.
- ❑ Strategy is to purge people of senescent cells.
- ❑ Osteoarthritis is first disease being targeted in Phase 1 clinical trial.



Many Silicon Valley Billionaires Are Funding Anti-Aging Research

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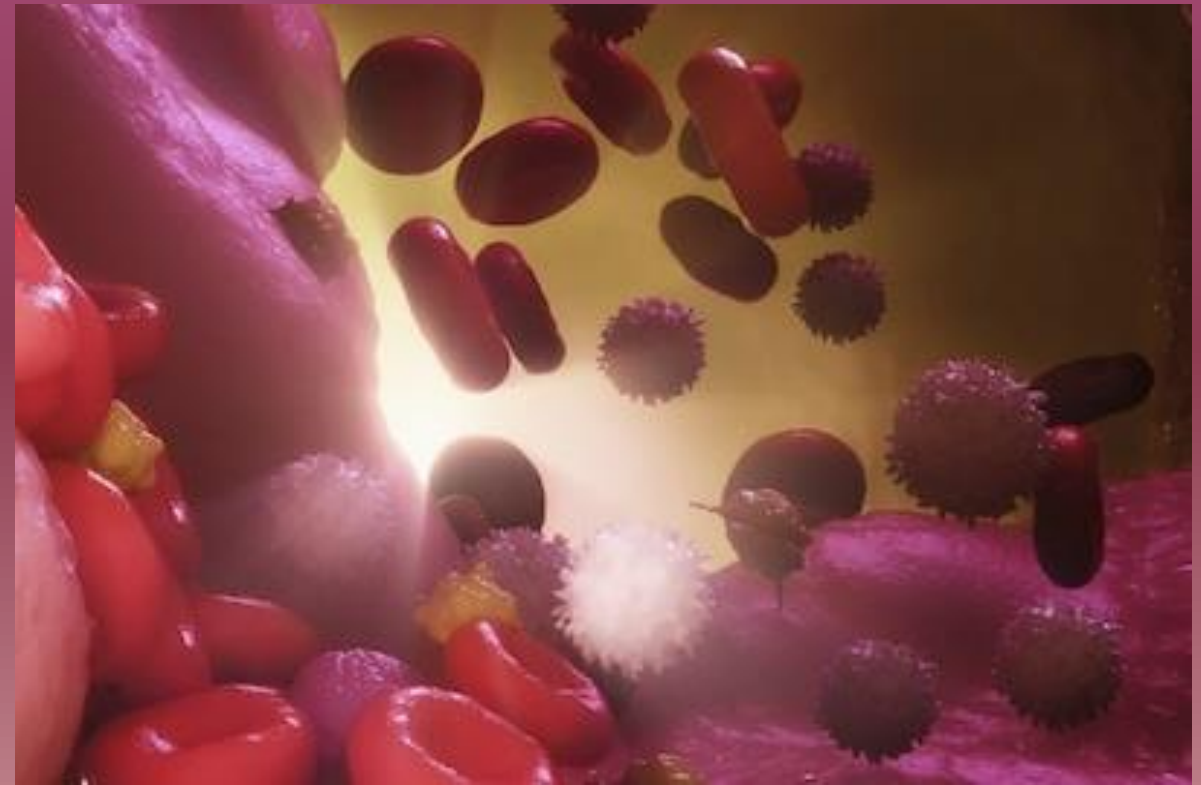
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Drug to clear 'zombie cells' from body could be first anti-aging treatment after 'impressive' human trial

“A drug to fight aging may finally be on the horizon after the first trial in humans showed ‘impressive’ results.”

“The treatment clears out dead cells even when the immune system no longer can.”



“Previously animal studies have shown that removing these cells reverses the aging process, extends lifespan, and restores lost youth”

“Now for the first time scientists in the US have shown improvements in humans using a drug that sweeps away the defunct cells.”

The treatment protocol in this study consisted of **dasatinib** and **quercetin**

Dr. James Kirkland of Mayo Clinic:

“This is like a glimmer that it might actually work. The results were impressive.

All 14 (humans) got better in their functional ability.”

Removal of 'zombie cells' alleviates causes of diabetes in obese mice

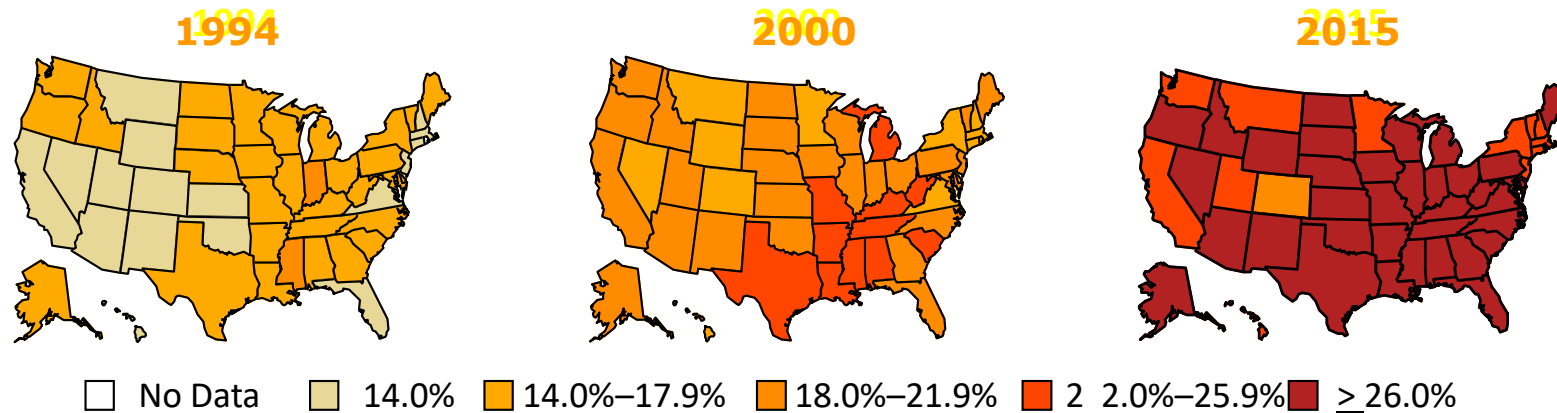
Selective removal of senescent cells:

- ☐ Reduced glucose levels
- ☐ Improved insulin sensitivity
- ☐ Decline in inflammatory factors
- ☐ Return to normal fat cell function
- ☐ Improved kidney & heart function

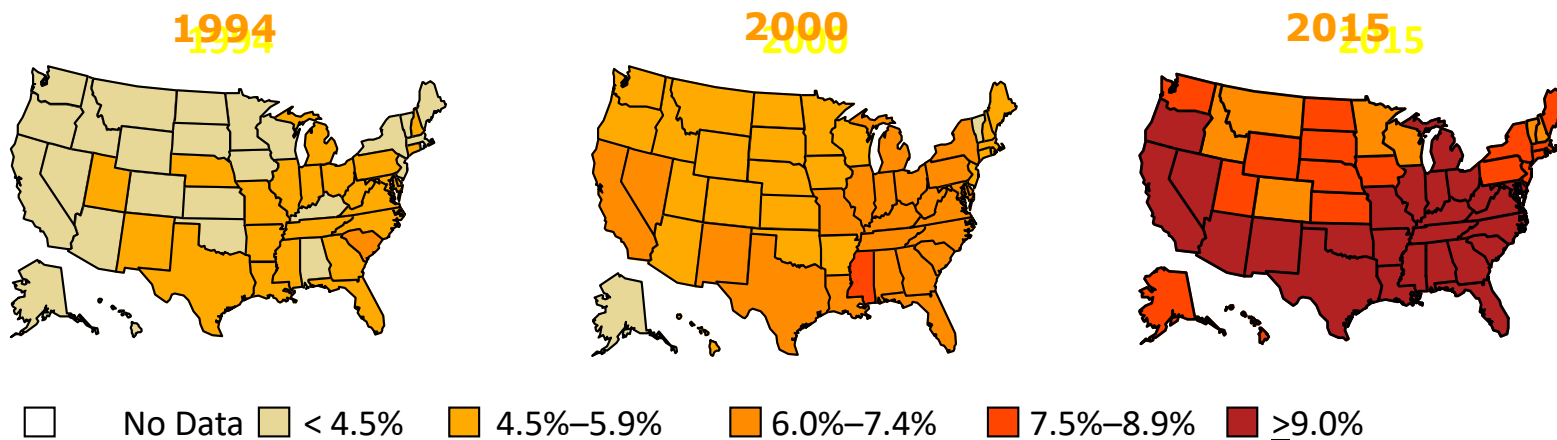


Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity



Diabetes



CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/data>



Aged-senescent cells contribute to impaired heart regeneration

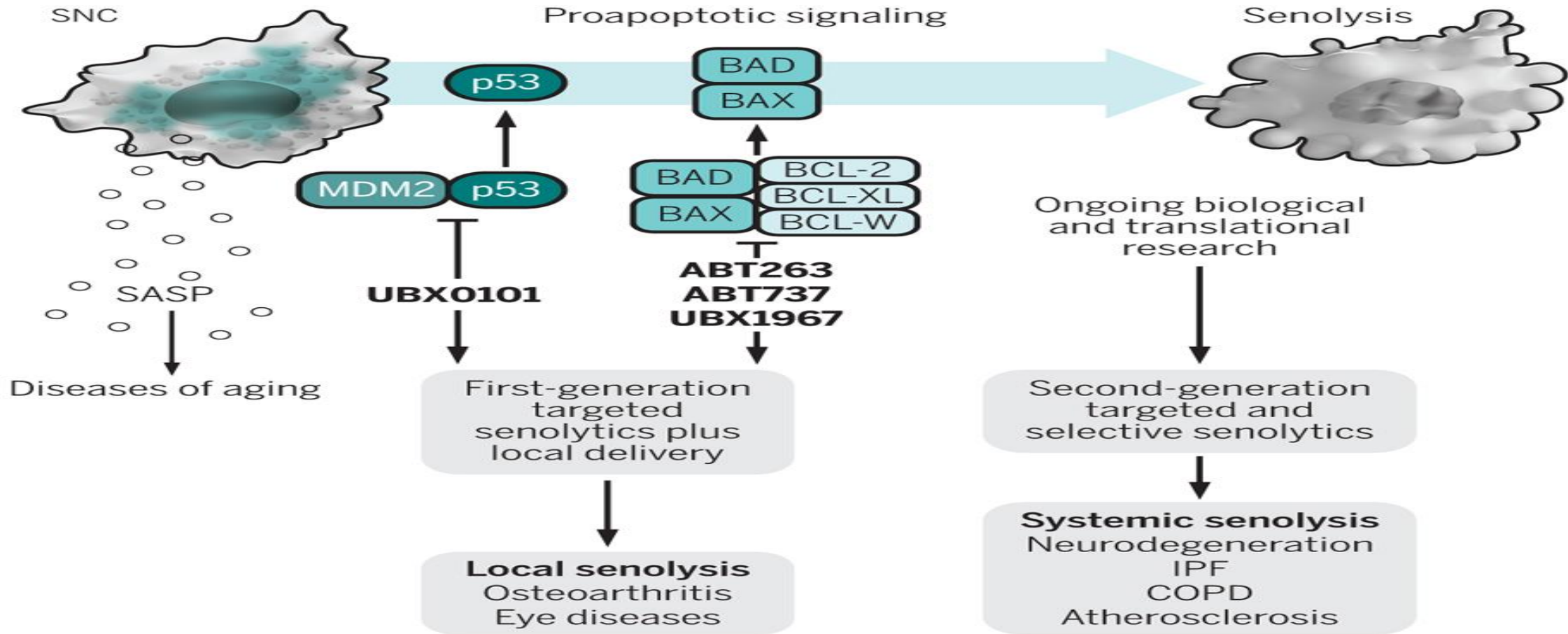
Fiona C. Lewis-McDougall¹ | Prashant J. Ruchaya¹ | Eva Domenjo-Vila¹ | Tze Shin Teoh¹ | Larissa Prata² | Beverley J. Cottle¹ | James E. Clark³ | Prakash P. Punjabi⁴ | Wael Awad⁵ | Daniele Torella⁶ | Tamara Tchkonja² | James L. Kirkland² | Georgina M. Ellison-Hughes¹

“Aging leads to increased cellular senescence and is associated with **decreased potency of tissue-specific stem/progenitor cells**.

Here, we have done an extensive analysis of cardiac progenitor cells isolated from human subjects with cardiovascular disease, aged 32–86 years...In aged subjects (>70 years old), over **half of cardiac progenitor cells are senescent...**”

Senolytic therapies for optimized aging

Senescent cells (SNCs) resist apoptosis by activating prosurvival pathways and inhibiting proapoptotic pathways.



First-generation senolytics

Drugs developed to target key components of prosurvival pathways eliminate SNCs and thereby the SASP that drives diseases of aging.

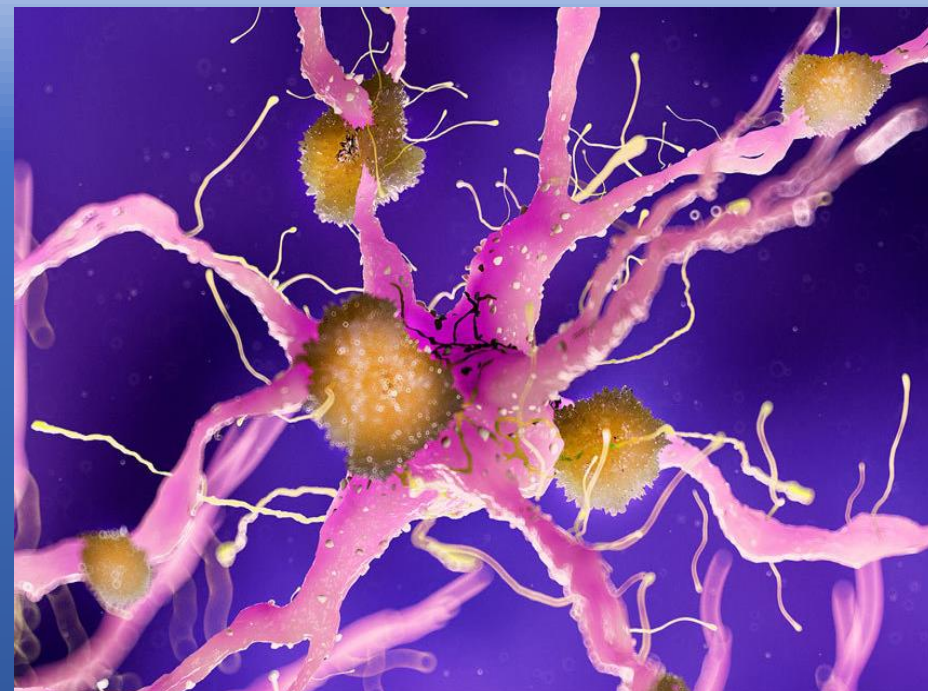
BAD, BCL-2—associated agonist of cell death; BAX, BCL2-associated X; BCL-2, B cell lymphoma 2; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; SASP, senescence-associated secretory phenotype.

Second-generation senolytics

Development of selective senolytics that safely and effectively eliminate SNCs upon systemic administration awaits further understanding of SNCs.

Senolytics Effective in Mouse Model of Alzheimer's

“National Institute on Aging Intramural Research Program added substantial proof that **senolytics**, the golden child of anti-aging drugs, rescue memory loss in Alzheimer's disease, at least in mice genetically engineered to accumulate amyloid clumps in their brains.”



“Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model”

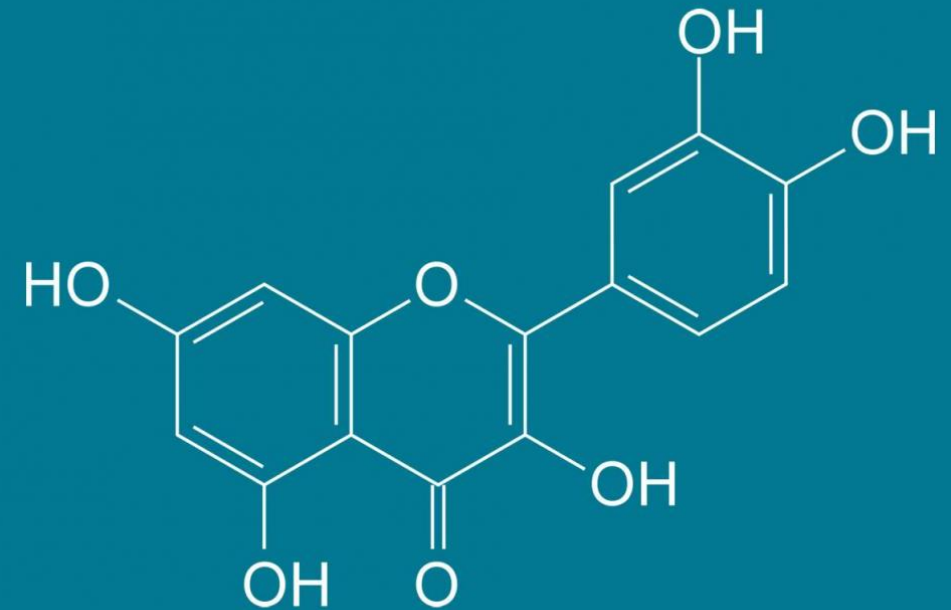
Senolytics: Dasatinib + Quercetin

“The team squirted the drug cocktail (dasatinib and quercetin) into their Alzheimer’s mice once a week for 11 weeks.”

“Positive results came fast: the mice’s beta-amyloid levels dropped within three months.”

“...the treated mice also had fewer senescent cells in their hippocampus, the brain’s main memory center, and navigated complex water mazes better than their peers.”

- QUERCETIN & DASATINIB -



Senolytics Restore Memory

“In a series of memory tests, the treated mice regained their ability to learn and memorize complex mazes.”

Conclusions from study:

“Our findings pave the way for future preclinical and clinical studies that will test the hypothesis that senolytic therapies can ... preserve brain function in [Alzheimer’s] and other age-related neurodegenerative disorders,”



Initial Data Reported **Human Senolytic Study** RAADFest-Sept 21, 2018

Two doses of **dasatinib** + **quercetin** in osteoarthritis patients:

- ✓ 82% of subjects see relief of osteoarthritis pain + improved joint function
- ✓ Most subjects want to re-dose (after 6 months) to see better results
- ✓ Waiting for follow-up results of MRI scans of joints & aging biomarkers

(Most study subjects had severe bone-on-bone osteoarthritis.)

Senolytic Dose Schedule

One **quercetin + dasatinib** dose once a week for **two weeks** only (two total doses)

Quercetin

25 mg per kilogram of body weight is approximately:

100 pounds = 1,125 mg

165 pounds = 1,875 mg

220 pounds = 2,500 mg

275 pounds = 3,000 mg

330 pounds = 3,750 mg

Dasatinib

2.5 mg per kilogram of body weight is approximately:

100 pounds = 112 mg

165 pounds = 187 mg

220 pounds = 250 mg

275 pounds = 305 mg

330 pounds = 375 mg

Take first dose of quercetin/dasatinib (preferably on empty stomach) then repeat same dose one week later.
(May repeat this protocol in 6-12 months, or sooner as your doctor may direct.)

Possible side effects include: Mild flu symptoms, diarrhea, headache, fatigue for 12-24 hours.

Caution: Take in presence of qualified medical doctor in case of severe allergic reaction.

Do not engage in strenuous exercise during or for one week after the dosing schedule.

What Age Should Dasatinib Therapy Begin?

Typical people accumulate significant **senescent cell** burdens around **age 60**

Senescent cell burdens may occur earlier in **obese middle-aged** individuals.

Dasatinib + quercetin may ideally be initiated by most people around **age 60**

Obese individuals may initiate dasatinib + quercetin around **age 40-45**.

Take first dose of quercetin/dasatinib (preferably on empty stomach) then repeat same dose one week later.
(May repeat this protocol in 6-12 months, or sooner as your doctor may direct.)

Possible side effects include: Mild flu symptoms, diarrhea, headache, fatigue for 12-24 hours.

Caution: Take in presence of qualified medical doctor in case of severe allergic reaction.

Do not engage in strenuous exercise during or for one week after the dosing schedule.

How to Obtain Dasatinib

Four tablets cost \$2,200 in United States

Provides two doses (160 mg each dose) to be taken one week apart for *only* two consecutive weeks.

(Doctor's prescription needed in either

Dasatinib

Potency Verified by Independent Assay

HPLC (high-performance liquid chromatography) testing of a Lucius Lucidas (dasatinib) 50 mg tablet purchased from Bonhoa, and a Sprycel dasatinib (Bristol-Myers Squibb) 60 mg tablet purchased from the Indian pharmacy Vea Impex against a generic (known) quality of dasatinib acquired from Sigma (CAS: 302962-49-8), and Sprycel dasatinib (Bristol-Myers Squibb) 20 mg from a US pharmacy.



UNITY BIOTECHNOLOGY

“A Senolytic Drug Company”

EXPANDS ONGOING PHASE 1 STUDY TO FURTHER EVALUATE SENESCENT CELL FACTORS IN OSTEOARTHRITIS

“We are encouraged by the safety and tolerability observed to date in this first study of a **senolytic drug** in patients with **osteoarthritis**. It is that experience in patients that gives us the confidence to initiate Part B at the highest evaluated dose.”

UNITY Biotechnology, Inc. is a company developing therapeutics to extend healthspan by slowing, halting or reversing diseases of aging using a patented senolytic compound.