THE SCIENCE OF CELLULAR SENESCENCE

UNITY Investor and Analyst Event

December 11, 2018

UNITY BIOTECHNOLOGY

INTRODUCTIONS AND OVERVIEW

Ned David, Ph.D.

Co-founder and President

UNITY BIOTECHNOLOGY

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This presentation and the accompanying oral commentary contain forward-looking statements, including: statements related to our understanding of cellular senescence and the role cellular senescence plays in diseases of aging; our expectations regarding the potential benefits, activity, effectiveness and safety of senolytic drug candidates; the status of our our preclinical, clinical and regulatory development plans and pipeline; our expectations with regard to the results of our clinical studies; and our expectations with regard to our ability to acquire, discover and develop additional drug candidates and advance such drug candidates into, and successfully complete, clinical studies. These statements involve substantial known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements in this presentation represent our views as of the date of this presentation. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should, therefore, not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this presentation.

For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to the business of the Company in general, see UNITY's most recently filed Quarterly Report on Form 10-Q for the quarter ended September 30, 2018, filed with the Securities and Exchange Commission on November 7, 2018, as well as other documents that may be filed by UNITY from time to time with the Securities and Exchange Commission.

This presentation concerns drug candidates that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration. They are currently limited by Federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

AGENDA

THE SCIENCE OF SENESCENCE

1 hour

Biology of senescence
Judy Campisi, Ph.D.

Link between senescence, aging and particular diseases of aging
Jan van Deursen, Ph.D.

UNITY AND SENESCENCE

40 min

Overview of UNITY's efforts to extend healthspan
Ned David, Ph.D.

UNITY's edge in optimizing senolytic development
Dan Marquess, D. Phil

The intersection of senolysis and oncology
Pedro Beltran, Ph.D.

30 min

Panel Q&A
Moderated by Keith Leonard

TODAY'S EXPERT SPEAKERS

JUDY CAMPISI, PH.D.

- Professor at the Buck Institute for Research on Aging
- Sr. Scientist at Lawrence Berkeley National Laboratory
- National Academy of Science elected member

JAN VAN DEURSEN, PH.D.

- Professor of Biochemistry and Biology at The Mayo Clinic
- Professor of Pediatrics at The Mayo Clinic

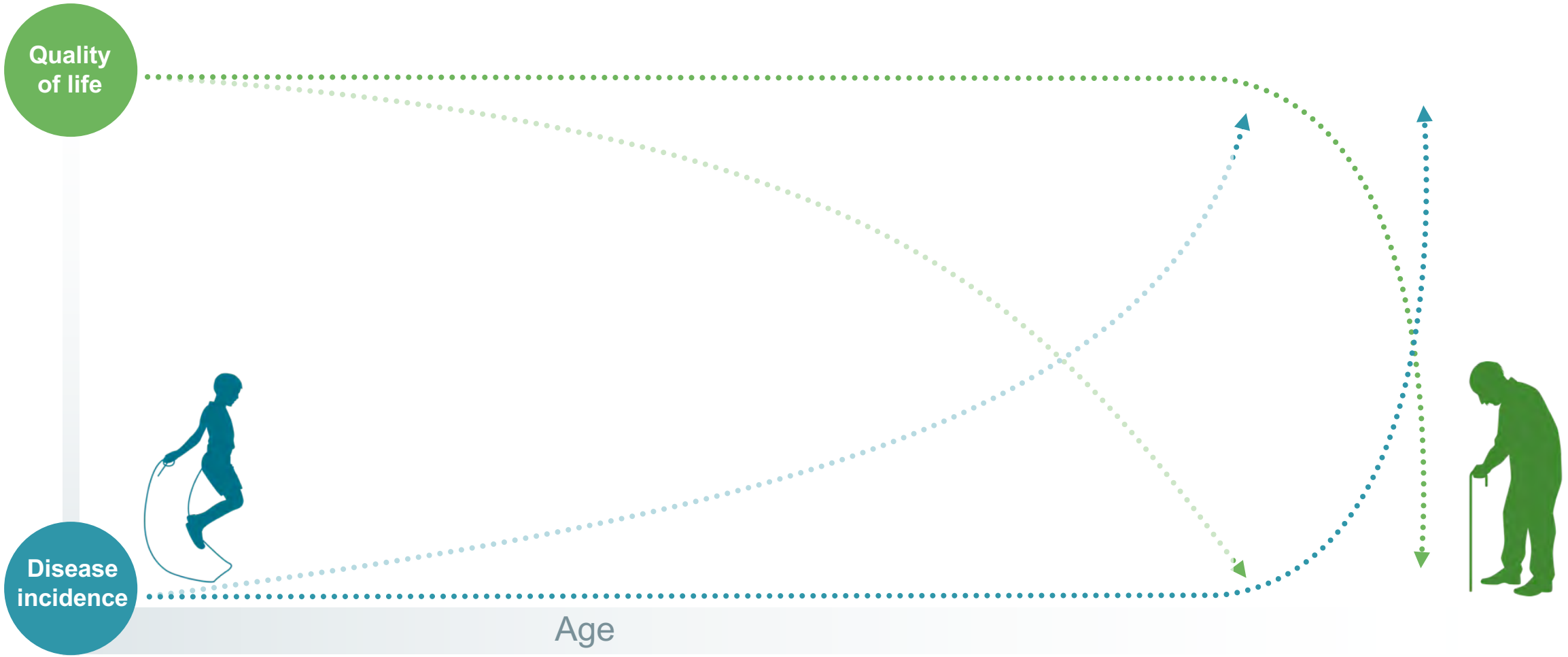
Health·span |helth' span| *noun*

The period of one's life unburdened by the diseases of aging

See also: anti-aging, healthy longevity

HEALTHSPAN

UNITY IS ADVANCING THERAPIES TO EXTEND HEALTHSPAN



AGING IS A FLEXIBLE, MALLEABLE THING

AGING HAS *KNOBS*

THESE *KNOBS* CAN BE TURNED

AGING IS A FLEXIBLE, MALLEABLE THING

Tiny shrew
<1 year

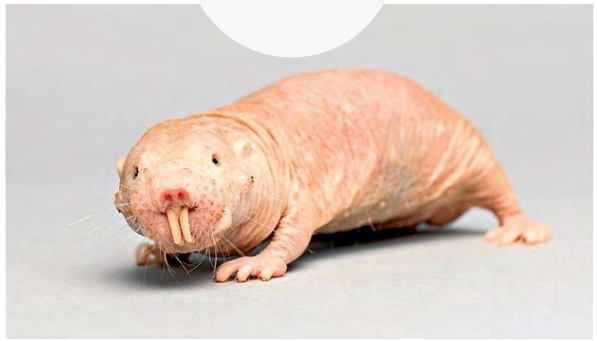
>200X

Bowhead whale
>200 years

AGING IS A FLEXIBLE, MALLEABLE THING

Field mouse
3 years

~11X



Naked mole rat
32 years

~12X

Brandt's bat
41 years

AGING HAS *KNOBS*

Rogina Blanka was able to extend a fly's lifespan by **2-fold** by creating a mutation in the *indy* gene

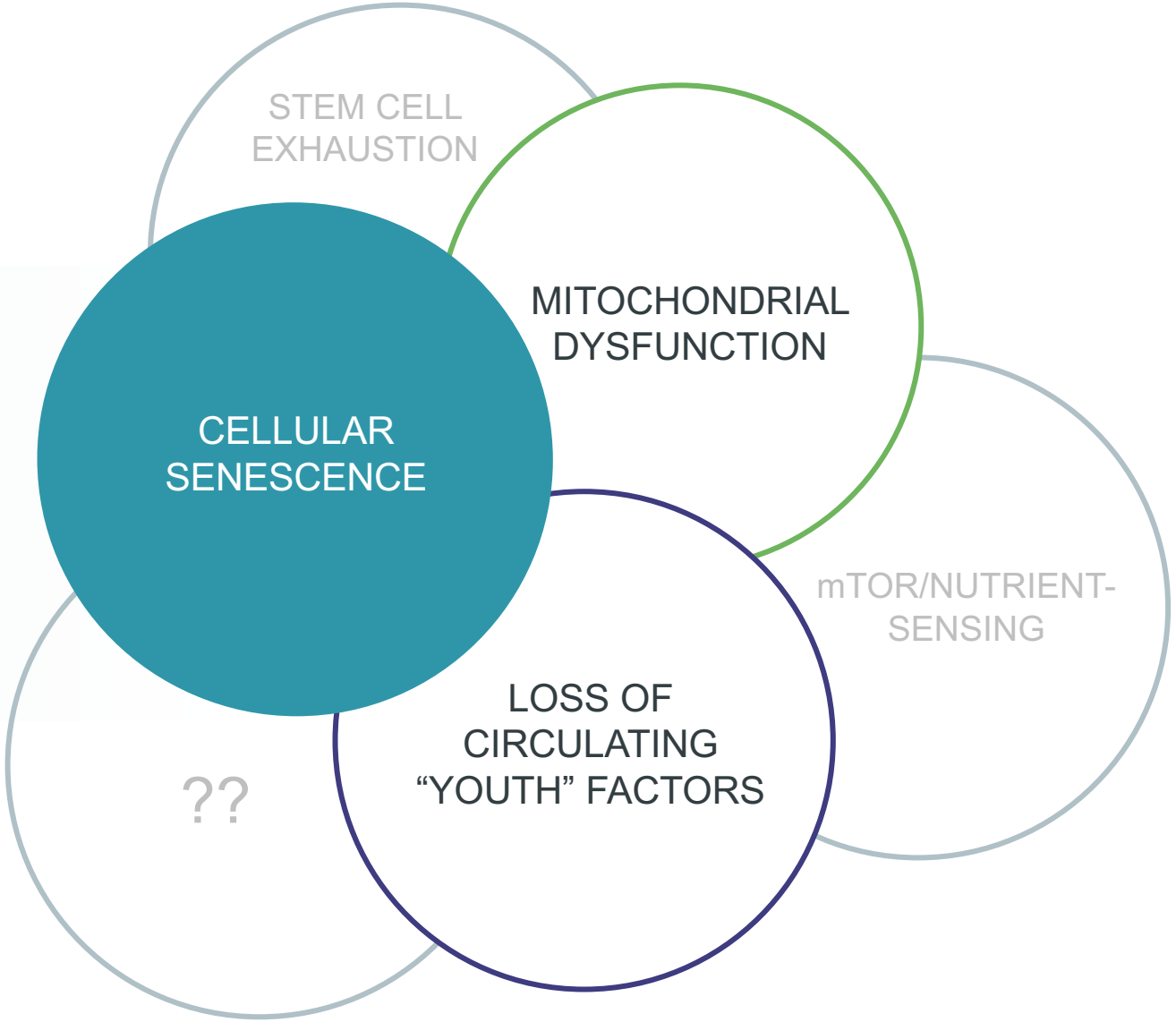
~2X

Andrzej Bartke was able to extend a mouse's lifespan by **2-fold** by mutating the growth hormone receptor gene and by restricting calorie intake

~2X

MULTIPLE MECHANISMS DRIVE AGING

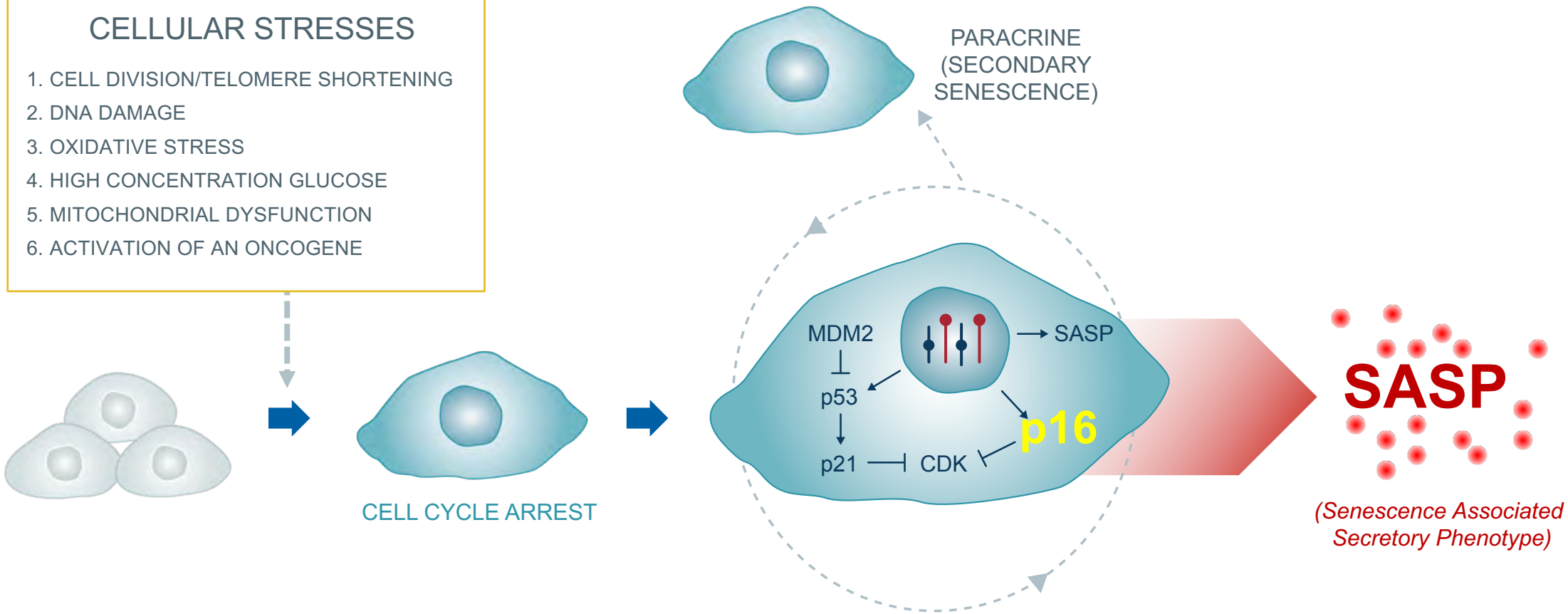
UNITY is pursuing multiple pathways to impact the aging process



CELLULAR STRESSES TRIGGER SENESCENCE

CELLULAR STRESSES

1. CELL DIVISION/TELOMERE SHORTENING
2. DNA DAMAGE
3. OXIDATIVE STRESS
4. HIGH CONCENTRATION GLUCOSE
5. MITOCHONDRIAL DYSFUNCTION
6. ACTIVATION OF AN ONCOGENE



PROLIFERATING CELLS | INITIATION OF SENESCENCE | STABILIZATION OF SENESCENCE

THE UNITY THERAPEUTIC PARADIGM

BIOLOGICAL STRESS

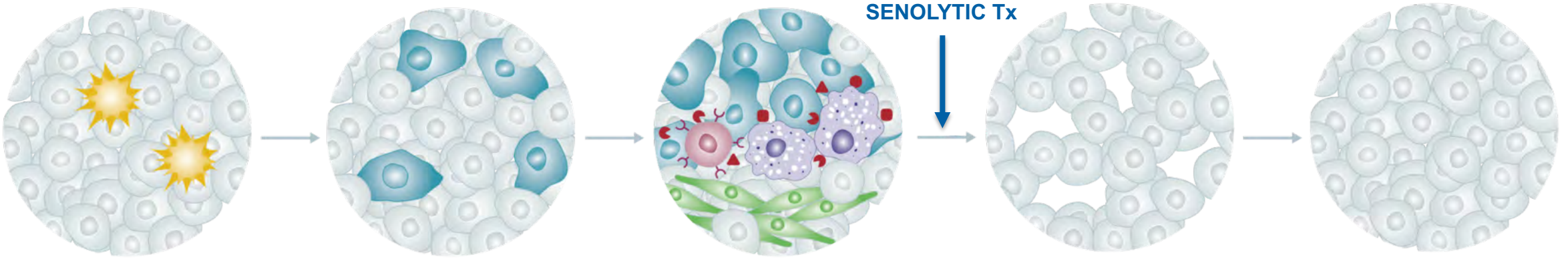
ACCUMULATION OF SENESCENT CELLS

SPREAD OF SENESCENCE AND INFLAMMATION

PERSISTENT DAMAGE, TISSUE DYSFUNCTION, AND DISEASE

UNITY THERAPEUTIC PARADIGM

ADMINISTER SENOLYTIC Tx



SnCs, INFLAMMATION, TISSUE DYSFUNCTION

CLEARANCE OF SnCs WITH SENOLYTIC Tx

REGENERATION AND RESTORATION OF FUNCTION

DISEASED TISSUE

FUNCTIONAL TISSUE

Functional Cell

Senescent Cell (SnC)

Cytokines, chemokines & matrix remodeling factors (SASP)

Macrophage

CD4+ T lymphocyte

Fibroblast

CELLULAR SENESCENCE: FROM BASIC BIOLOGY TO PHYSIOLOGY

Judy Campisi, Ph.D.
Buck Institute for Research on Aging
Lawrence Berkeley National Laboratory

UNITY BIOTECHNOLOGY

Buck Institute for Research on Aging

Cellular senescence: from basic biology to physiology

Lawrence Berkeley National Laboratory

In the beginning ….

Alexis Carrel

ON THE PERMANENT LIFE OF TISSUES OUTSIDE OF THE ORGANISM.
BY ALEXIS CARREL, M.D.
J Exp Med 15: 516-528

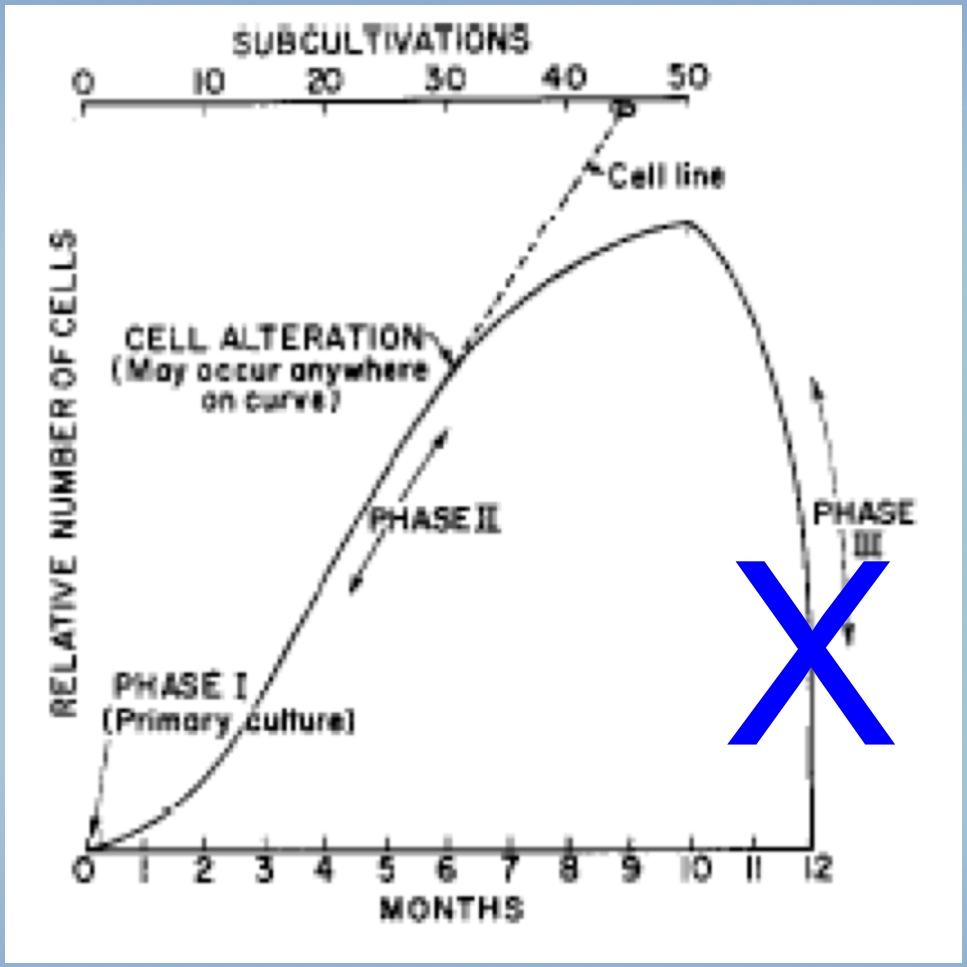
The true start ….

Leonard Hayflick

THE SERIAL CULTIYATION OF HUMAN DIPLOID CELL STRAINS
L. HAYFLICK and P. S. MOORHEAD
Wistar Institute of Anatomy and Biology, Philadelphia, Pa., (U.S.A.)
Exp Cell Res 25: 586-621, 1961

THE LIMITED IN VITRO LIFETIME OF HUMAN DIPLOID CELL STRAINS
L. HAYFLICK
The Wistar Institute of Anatomy and Biology, Philadelphia, Pa., U.S.A.
Exp Cell Res 37: 614-636, 1965

The Hayflick limit, as originally defined



Hayflick & Moorehead, 1961

not QUITE correct …..

Importantly, tumor cells don't do this!

So …. cellular senescence as a tumor suppressive mechanism?

YES!
Now validated by many mouse models and human patient data

BUT – a role in aging????

Cellular senescence, at first, a simple phenotype

Irreversible arrest of cell proliferation

Indeed, cell cycle inhibitors and tumor suppressor proteins, including $p16^{INK4a}$, showed increased expression in senescent cells

Curr Opin Genet Dev, 9, 22-30, 1999

The INK4A/ARF locus and its two gene products

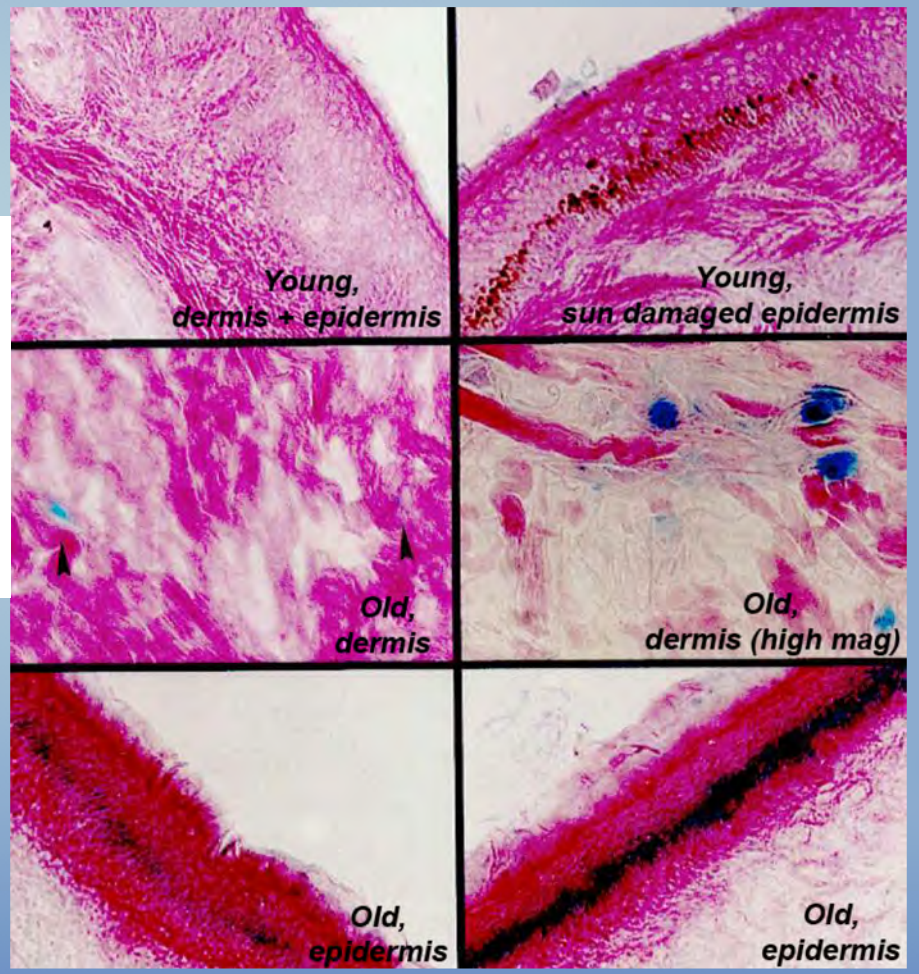
N E Sharpless, R A DePinho

Meanwhile, a serendipidous finding identified a senescent cell biomarker

SA-Bgal

and showed senescent cells increase with aging in human tissue:

Proc Natl Acad Sci 92: 9363-9367, 1995
A novel biomarker identifies senescent human cells in culture and in aging skin in vivo
Dimri G P, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano E E, Linskens M, Rubelj I, Pereira-Smith O M, Peacocke M, Campisi J



But …. many sporadic reports of altered gene/protein expression suggested something else was going on ….

Exp Cell Res 201:373-379 (1992)
Differential expression of metalloproteinase and tissue inhibitor of metalloproteinase genes in diploid human fibroblasts
Millis, A J T; Hoyle, M; McCue, H M; Martini, H

Proc. Nad. Acad. Sci. USA
Vol. 89, pp. 4683-4687, May 1992
Expression of interleukin 1-inducible genes and production of interleukin 1 by aging human fibroblasts
S. KUMAR, A. J. T. MILLIS, AND C. BAGLIONI*

Experimental Cell Research 205:396-403 (1993)
Enhanced expression of fibronectin during in vivo cellular aging of human vascular endothelial cells and skin fibroblasts
T KUMAZAKI, M KOBAYASHI, Y MITSUI

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 1559-1563, February 1994
Post-transcriptional regulation of interleukin la in various strains of young and senescent human umbilical vein endothelial cells
SUSAN GARFINKEL, SONDI BROWN, JORG H. M. WESSENDORF, AND THOMAS MACIAG

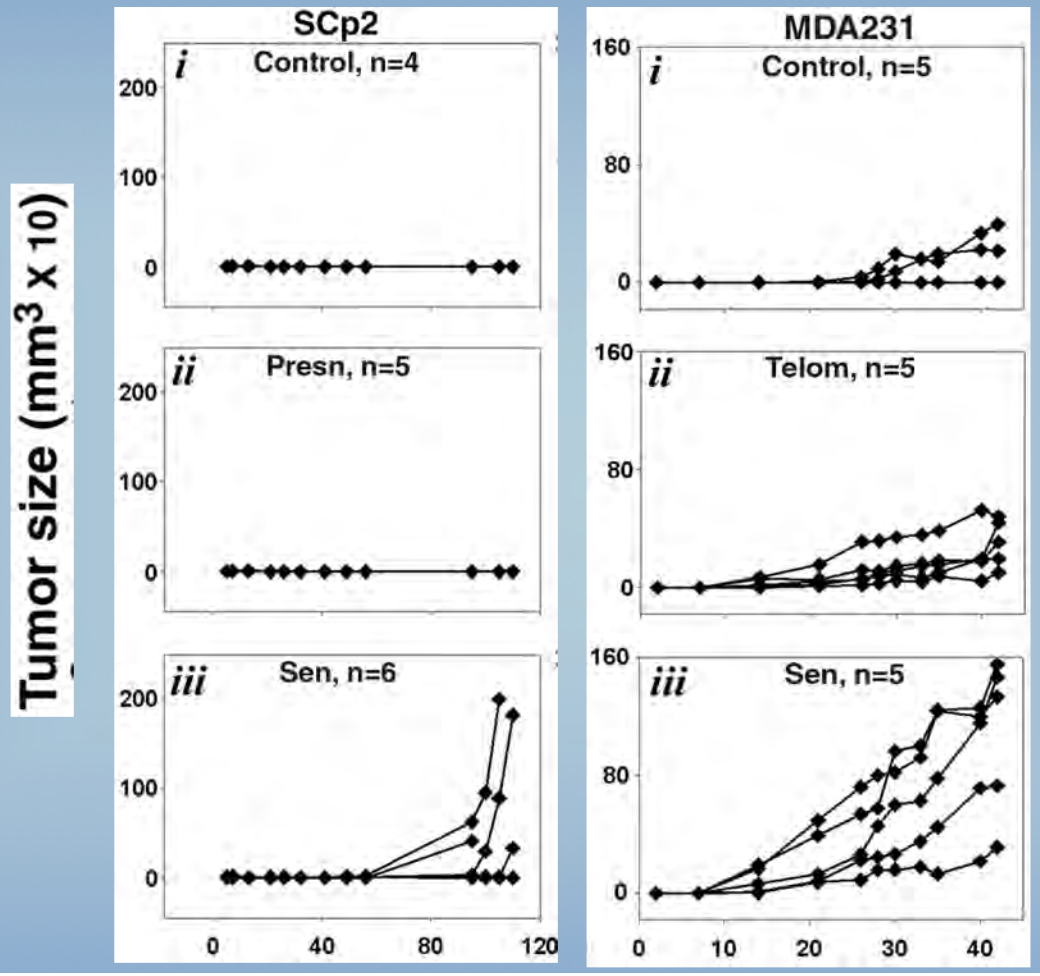
Experimental Cell Research 219: 304-308 (1995)
Senescence-dependent regulation of type 1 plasminogen activator inhibitor in human vascular endothelial cells
P COMI, R CHIARAMONTE, J A M MAIER

So maybe, just maybe, senescent cells DO have something to do with aging (but not due to arrested cell proliferation) ...

Cell, Vol. 84, 497–500, 1996
Replicative Senescence: An Old Lives' Tale?
Judith Campisi

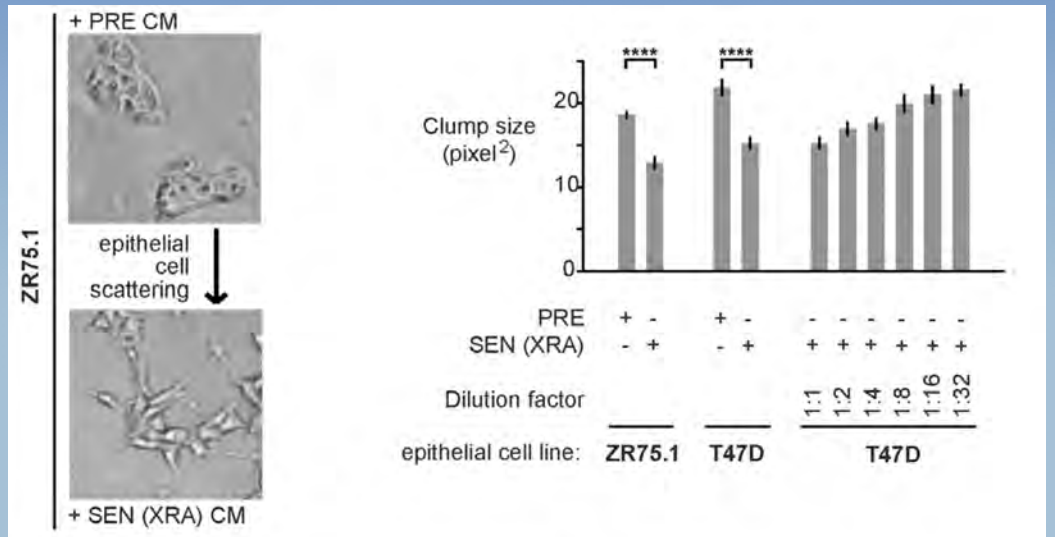
J Am Geriatric Soc 45: 1-6, 1997
Aging and cancer: The double-edged sword of replicative senescence
Judith Campisi

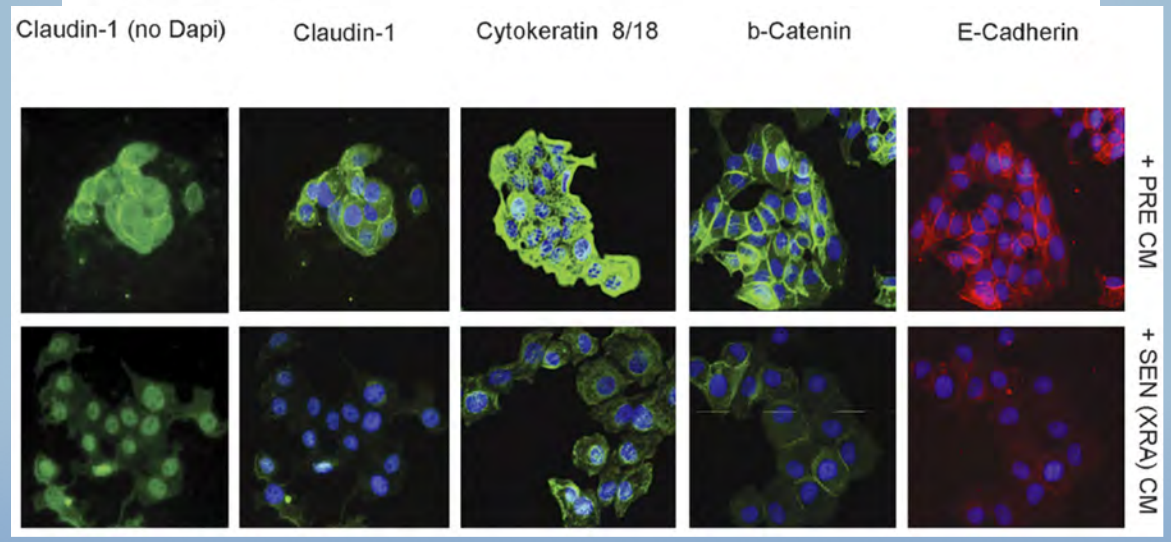
Senescent cells can influence neighboring cells ….



Proc Natl Acad Sci USA 98:12072-12077, 2001
Senescent fibroblasts promote epithelial cell growth
and tumorigenesis: A link between cancer and aging
Ana Krtolica*, Simona Parrinello*, Stephen Lockett*†, Pierre-Yves Desprez‡, and Judith Campisi* §

It's the secretions





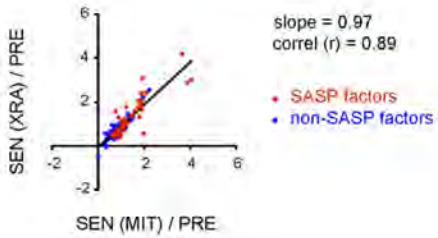
PLoS Biol 6, 2853-2868, 2008

Senescence-Associated Secretory Phenotypes Reveal Cell-Nonautonomous Functions of Oncogenic RAS and the p53 Tumor Suppressor

Jean-Philippe Coppe´ 1, Christopher K. Patil1[, Francis Rodier1,2[, Yu Sun3, Denise P. Mun˜ oz1,2, Joshua Goldstein1., Peter S. Nelson3, Pierre-Yves Desprez1,4, Judith Campisi

And it happens in vivo …

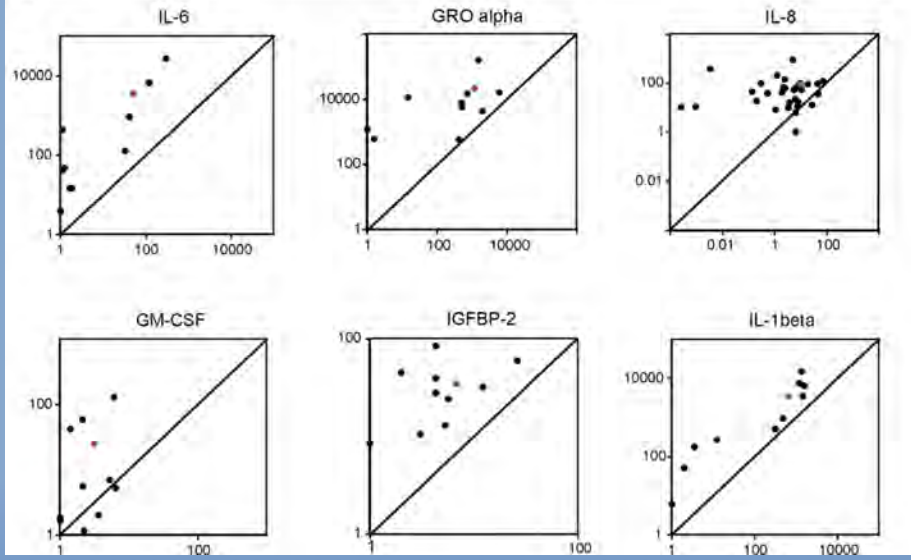
Correlation between factors secreted after XRA or MIT-induced senescence in epithelial cells



Correlation between SEN (XRA) and SEN (MIT) SASPs

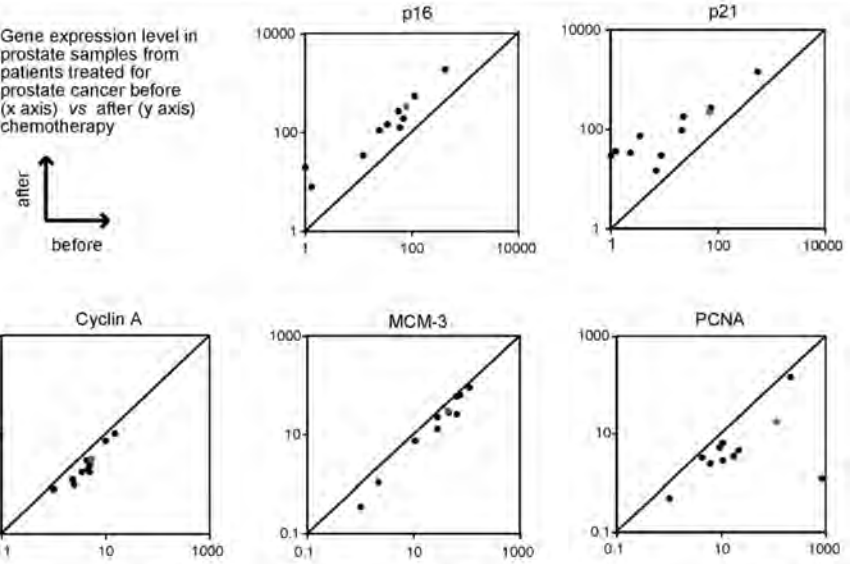
Cell line	correlation
BPH-1	0.70
RWPE-1	0.90
PC-3	0.88

SASP-associated genes

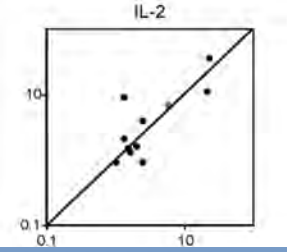


Proliferation-associated genes

Gene expression level in prostate samples from patients treated for prostate cancer before (x axis) *vs* after (y axis) chemotherapy



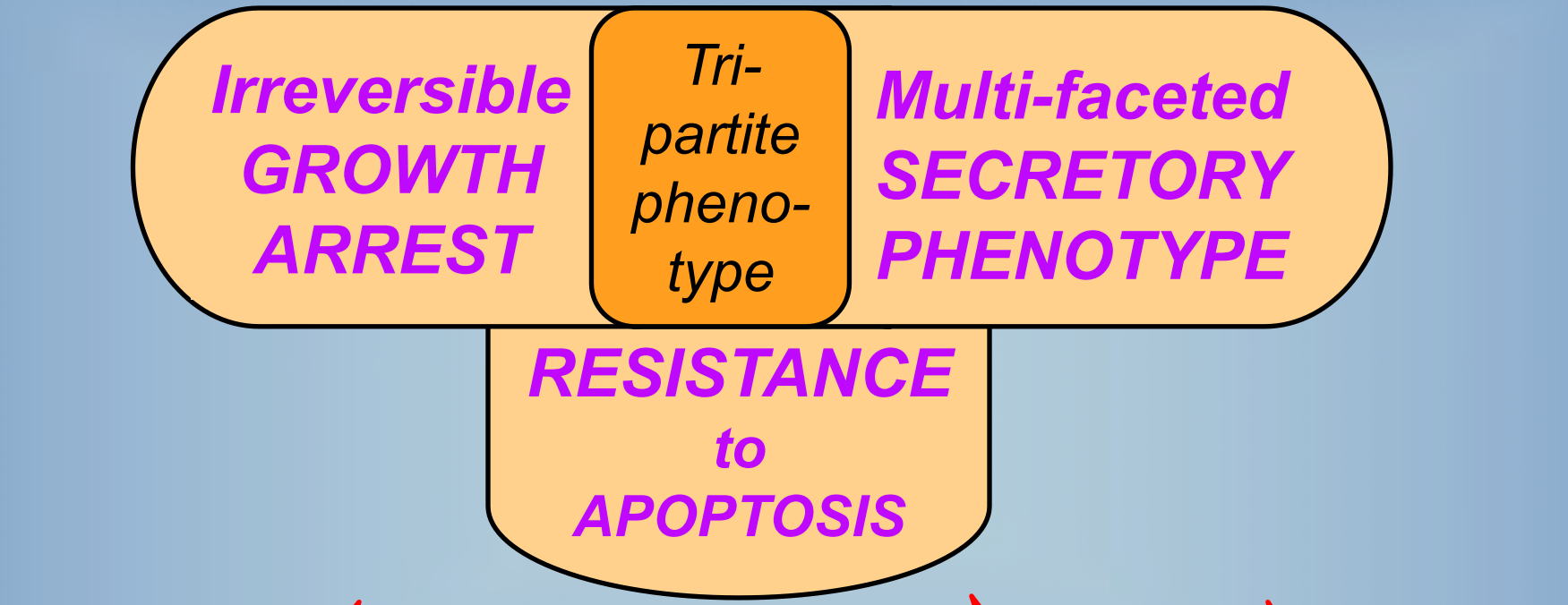
Non SASP-associated gene



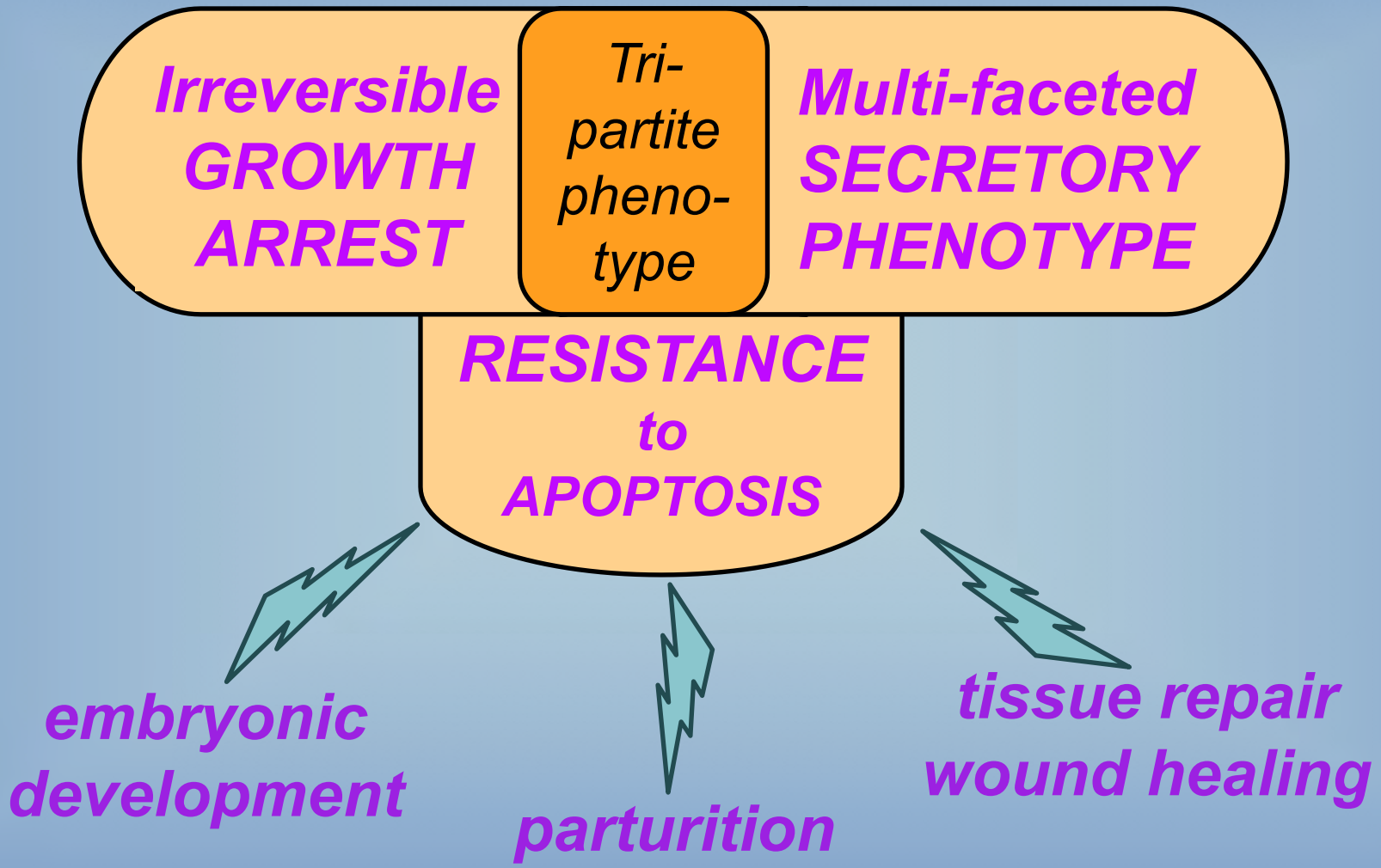
	post chemo-therapy	p values	number of patients
p16		< 0.01	10
p21		< 0.01	10
Cyclin A		< 0.01	10
MCM3		< 0.01	10
PCNA		< 0.05	10
IL-6		< 0.01	10
IL-8		< 0.01	30
GM-CSF		= 0.06	10
GRO alpha		< 0.01	10
IGFBP-2		< 0.01	10
IL-1 beta		< 0.01	10
IL-2		> 0.1	10

How best to view cellular senescence

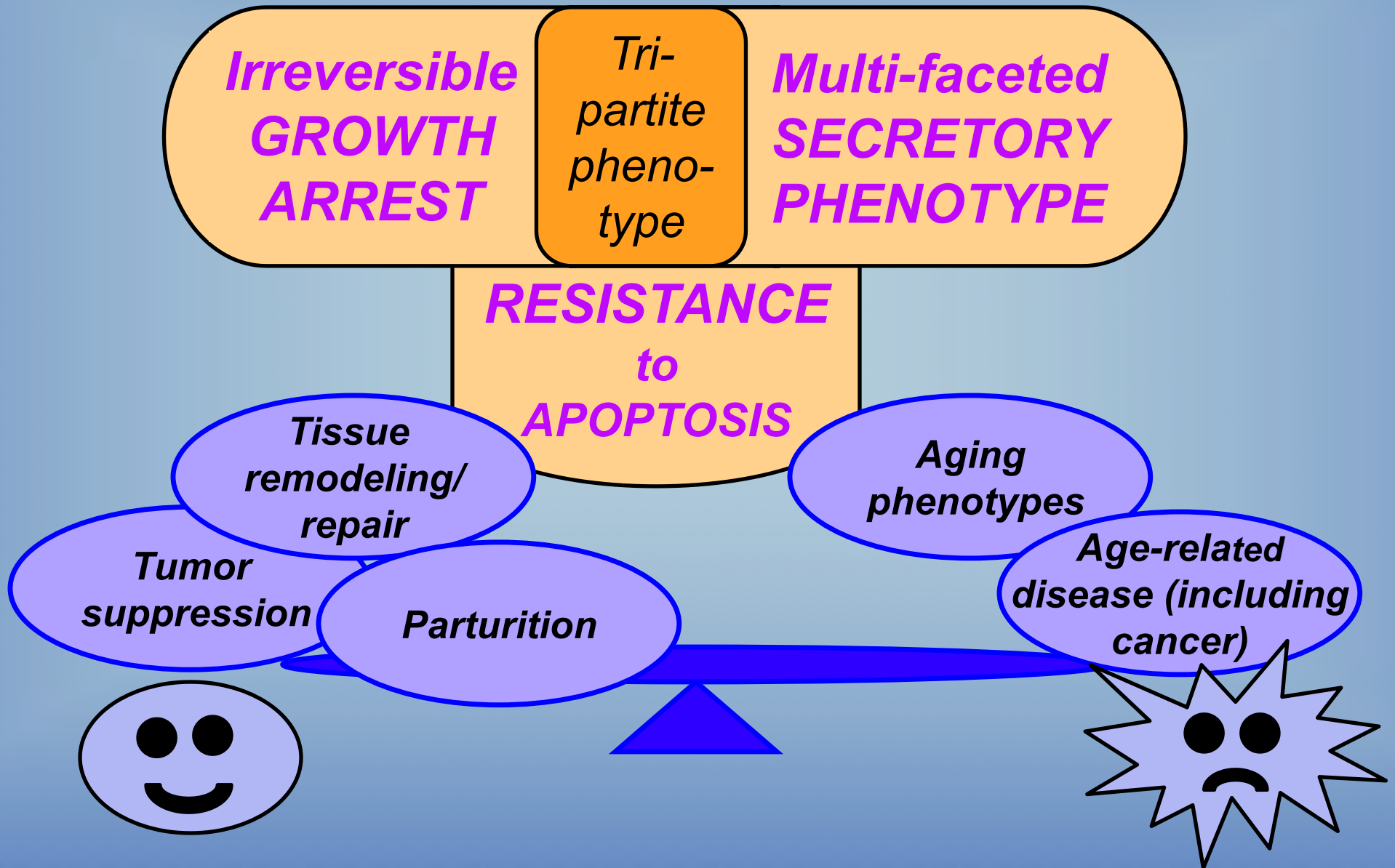
Cellular senescence, a complex stress response (including aging)



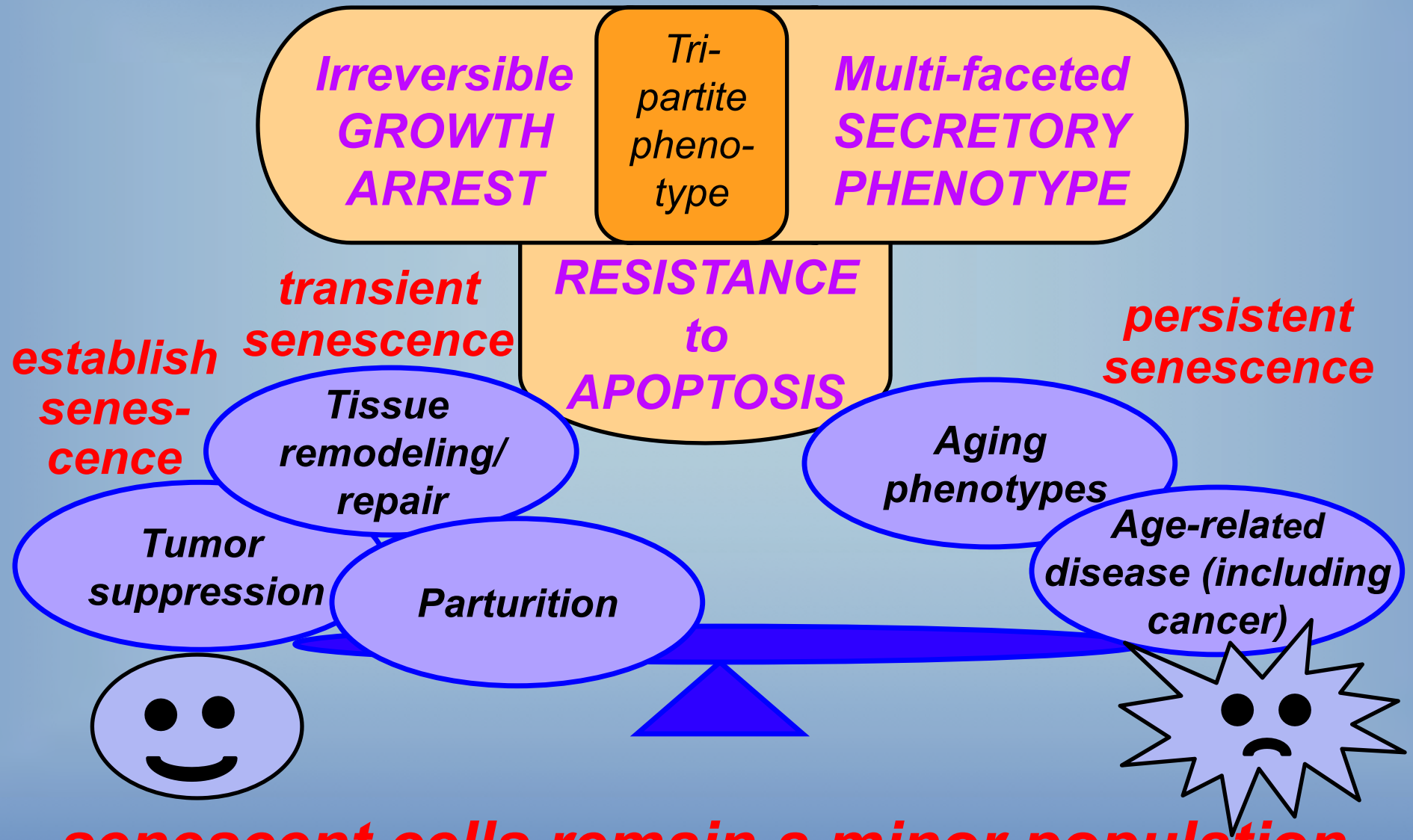
Cellular senescence, a physiological response



Cellular senescence, an evolutionary balancing act

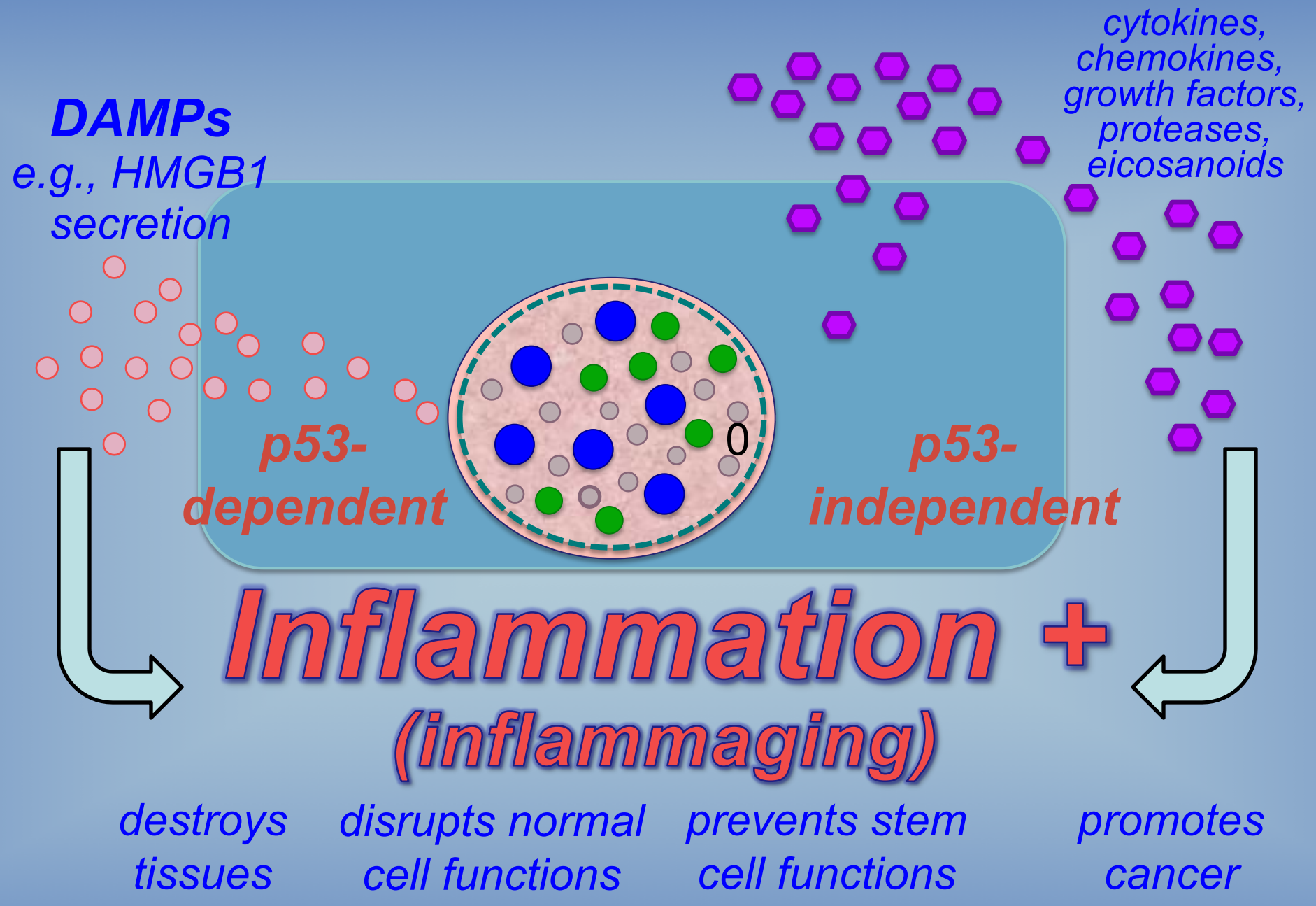


Cellular senescence, an evolutionary balancing act



senescent cells remain a minor population

How might senescent cells drive aging phenotypes and pathologies?


DAMPs
e.g., HMGB1
secretion
cytokines,
chemokines,
growth factors,
proteases,
eicosanoids
p53-
dependent
0
p53-
independent
Inflammation +
(inflammaging)
destroys
tissues
disrupts normal
cell functions
prevents stem
cell functions
promotes
cancer

DO senescent cells drive aging phenotypes and pathologies?

Two transgenic mouse models in which senescent cells can be eliminated by an otherwise benign drug

Small molecules that mimic the effects of the transgenes (senolytics)

Senescent cells cause or contribute to:

Alzheimer's@@ and Parkinson's disease*

*Atherosclerosis***

*Cardiovascular dysfunction**#*

*Cancer metastasis and recurrence****

*Chemotherapy (HAART) cardiotoxicity, blood clots, fatigue****

Cognitive decline/loss of neurogenesis

Diabetes

Myeloid→lymphoid skewing #

*Pulmonary fibrosis#**

Osteoarthritis ##

Osteoporosis ###

Sarcopenia/frailty

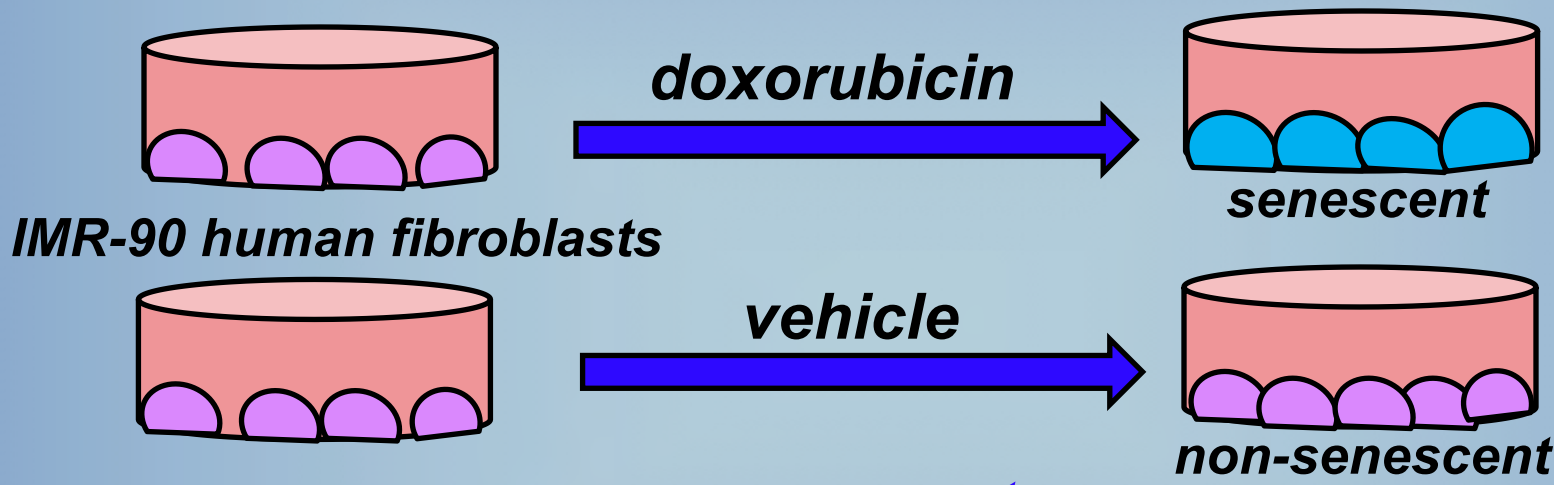
Wound healing, tissue regeneration @

**Chinta et al, Cell Reports, 2018; **Childs et al, Science, 2016; **#Baker et al, Nature, 2016; ***Demaria et al, 2017; #Chang et al, Nature Med, 2016; #*Schafer et al, Nature Comm, 2017; ##Jeon et al, Nature Med, 2017; ###Farr et al, Nature Med, 2017; @ Demaria et al, Dev Cell, 2014; @@Bussian et al, Nature, 2018*

New horizons?

Better understanding the complexity of senescent phenotypes in order to develop more specific small molecule interventions

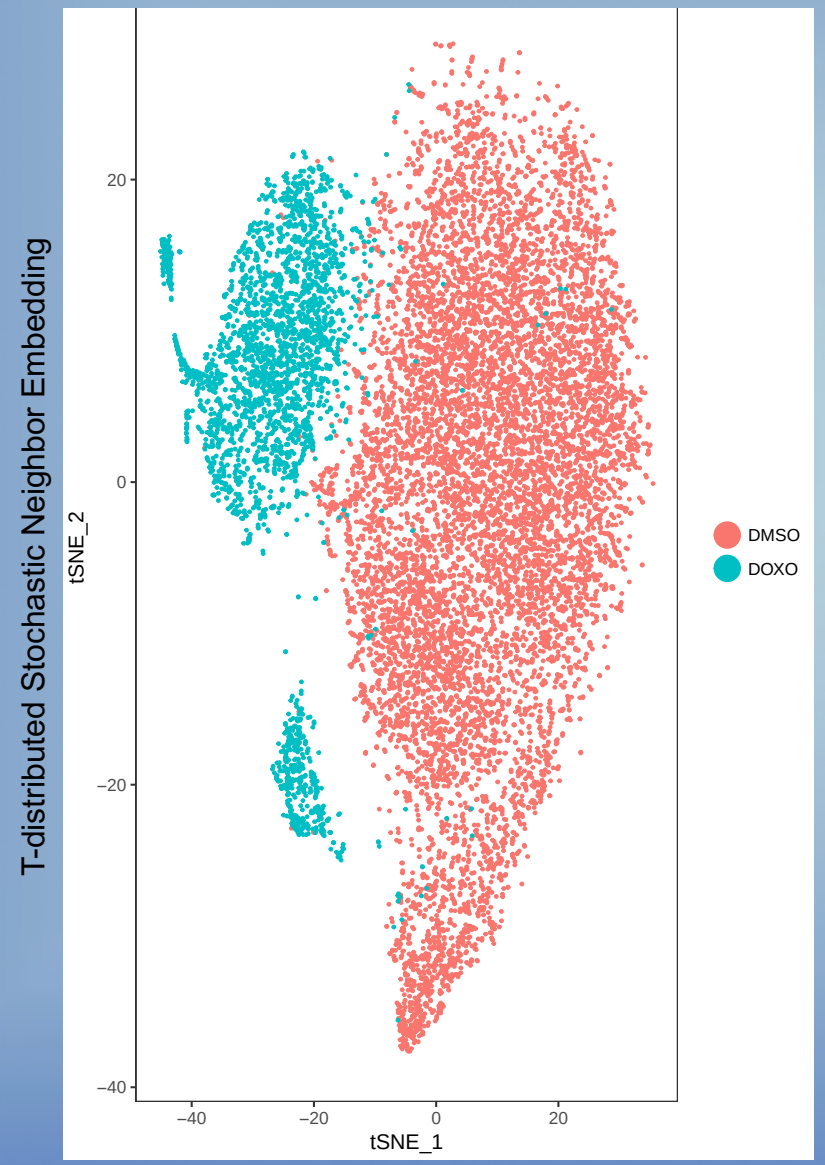
Senescent cells are surprisingly heterogeneous *(even in culture)*



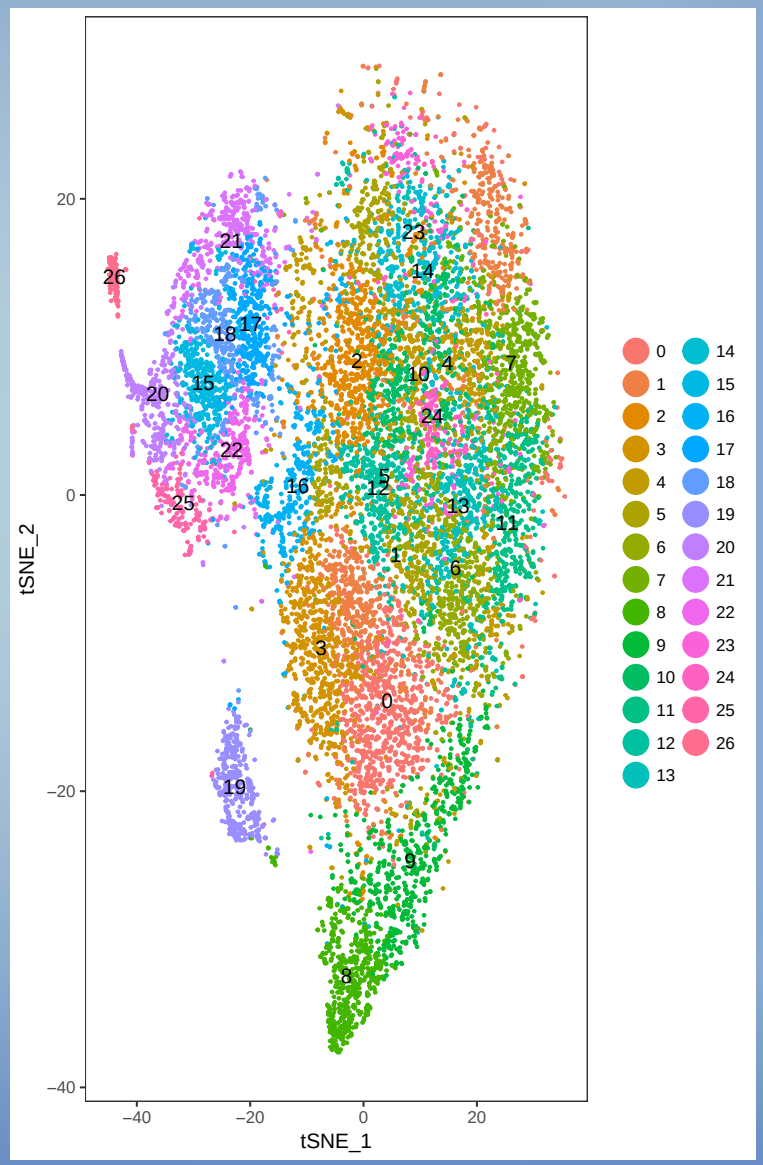
same genotype
same environment

SINGLE CELL TRANSCRIPTOME ANALYSIS

Senescent cells are surprisingly heterogeneous



Limbad, Melov, Clotios et al, unpublished



SUMMARY

Eliminating senescent cells:
An unprecedented opportunity
to extend health span

(not certain about life span)

Life span extension ….. humans??

I expect to die at 110,
shot by a jealous husband.

THANKS!

Present lab members

Nicholas Aguirre
Fatouma Alimirah
Natan Basisty
Ulises Castro
Albert Davalos
Jose Domingo-Lopez
Okhee Jeon
Chisaka Kuehnemann
Abhijit Kale
Clare Kim
Chandani Limbad
Christopher Wiley
Ying Zou

Past lab members

Christian Beausejour (Montreal U)
Marco Demaria (ERIBA)
Pierre Desprez (CA Pacific Med Cntr)
Peter de Keizer (Erasmus U)
Remi-Martin Laberge (Unity)
Francis Rodier (Montreal U)

Collaborators

PPG: Jan Vijg, Yousin Suh (Einstein); Jan Hoeijmakers (Erasmus); Paul Hasty (UTHSCSA)
Jennifer Elisseeff (Johns Hopkins U)
Claude LeSaux (UCSF); Pete Nelson (Fred Hutch)
Steve Yannone, Paul Yaswen, Cilla Cooper (LBNL)
Julie Andersen, Pankaj Kapahi, Simon Melov, Brad Gibson, Birgit Schilling, Arvind Ramachandran (Buck Inst)
Irina Conboy (UC Berkeley)
Eiji Hara, Naoko Ohtani (Osaka & Tokyo Universities)
Jan van Deursen, Jim Kirkland, Darren Baker (Mayo)
Daohong Zhou (U Florida))

LINK BETWEEN SENESCENCE, AGING AND DISEASES OF AGING

Jan van Deursen, Ph.D.
The Mayo Clinic

UNITY
BIOTECHNOLOGY

“THE GOLDEN DECAGE”

MAYO CLINIC

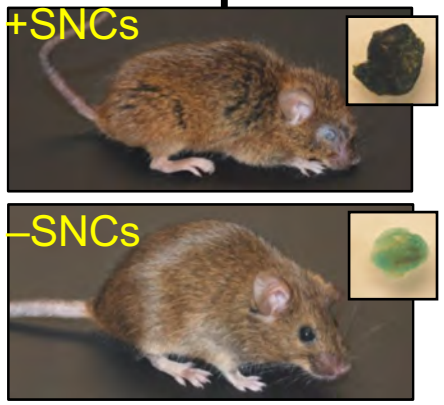
1999

T. Boveri (1914)

2004

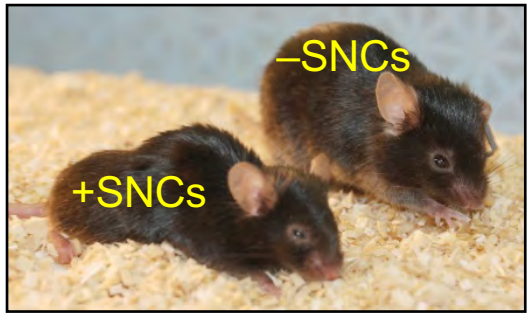
Nature Genetics 2004

2008



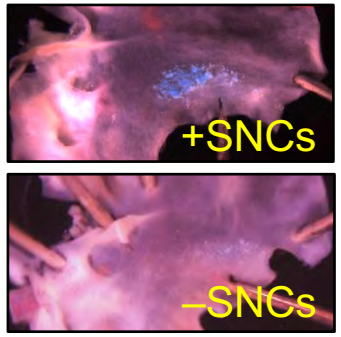
Nature Cell Biology 2008

2011

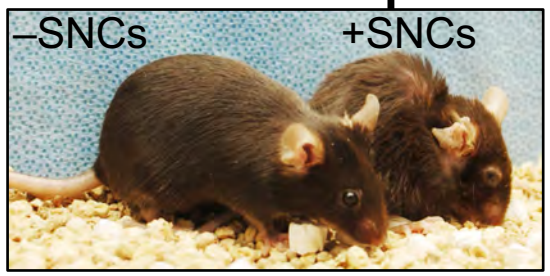


Nature 2011

2016

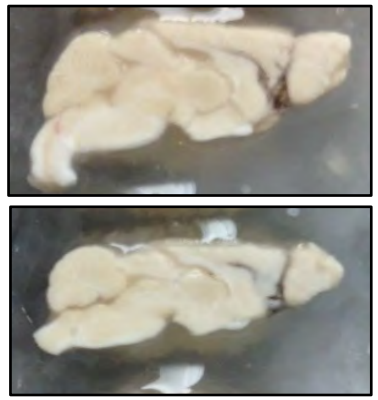


Science 2016

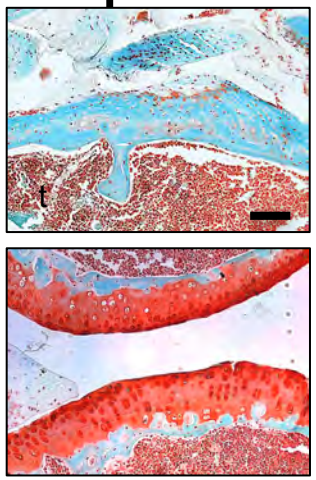


Nature 2016

2017 2018



Nature 2018

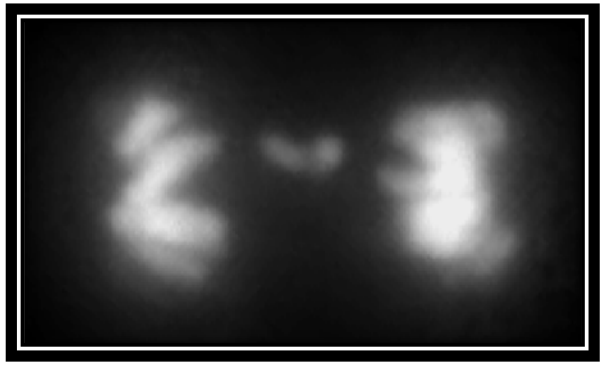


Nature Medicine 2017

SERENDIPITY

~~1999~~

T. Boveri
(1914)



Chromosome missegregation

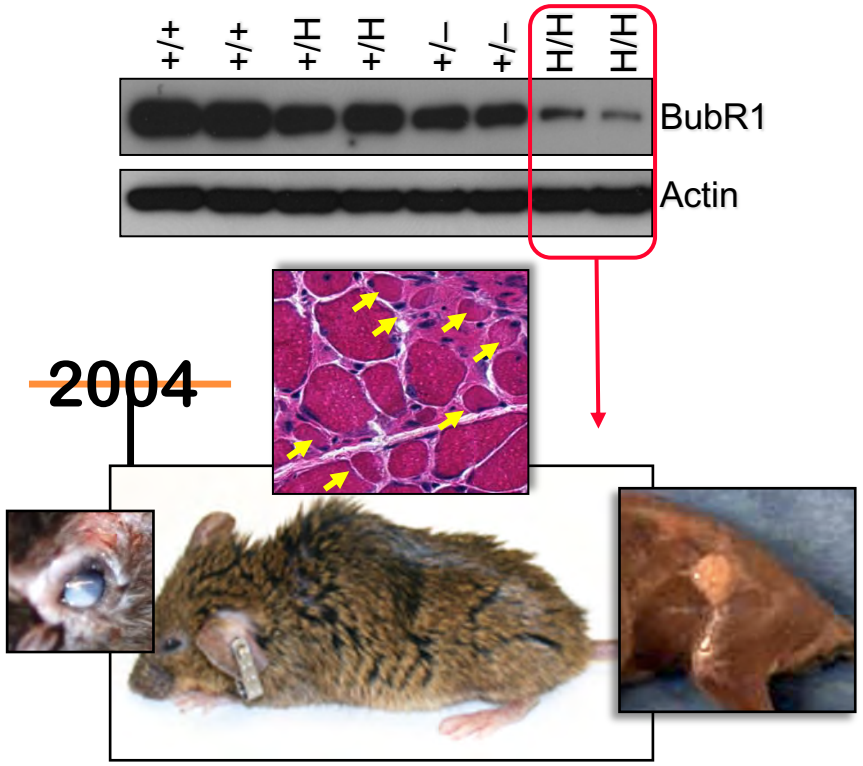
↓

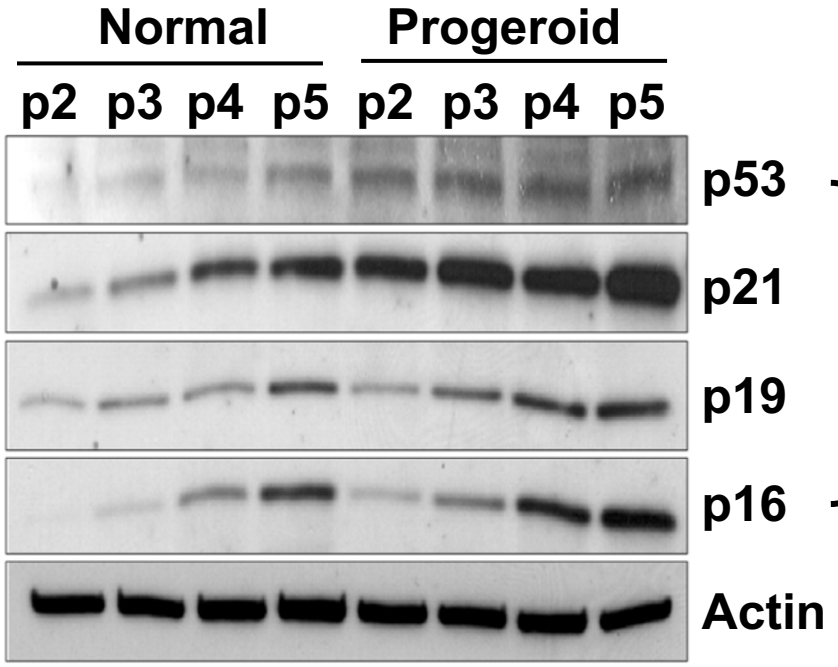
A hallmark of cancer

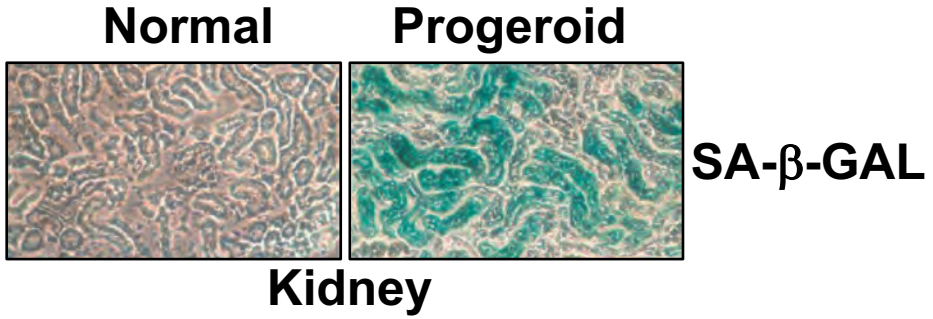
↓

Does it cause cancer?

A NEW ACCELERATED AGING SYNDROME

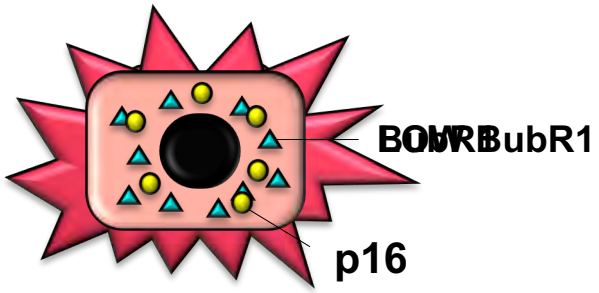






Baker et al., 2004 Nature Genetics

TESTING THE SENESCENCE THEORY OF AGING



Cellular senescence

↓

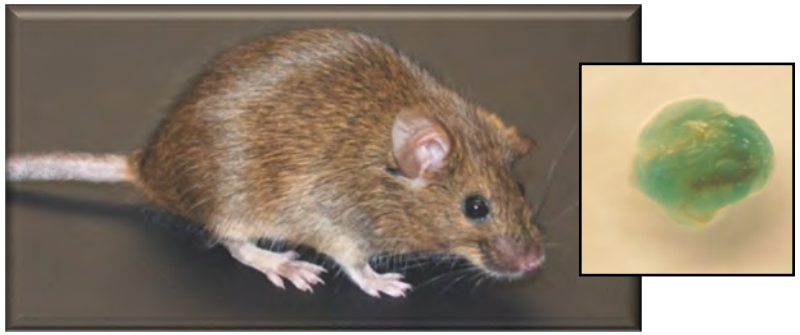
Aging pathologies

Sarcopenia
Cataracts
Fat loss

2008

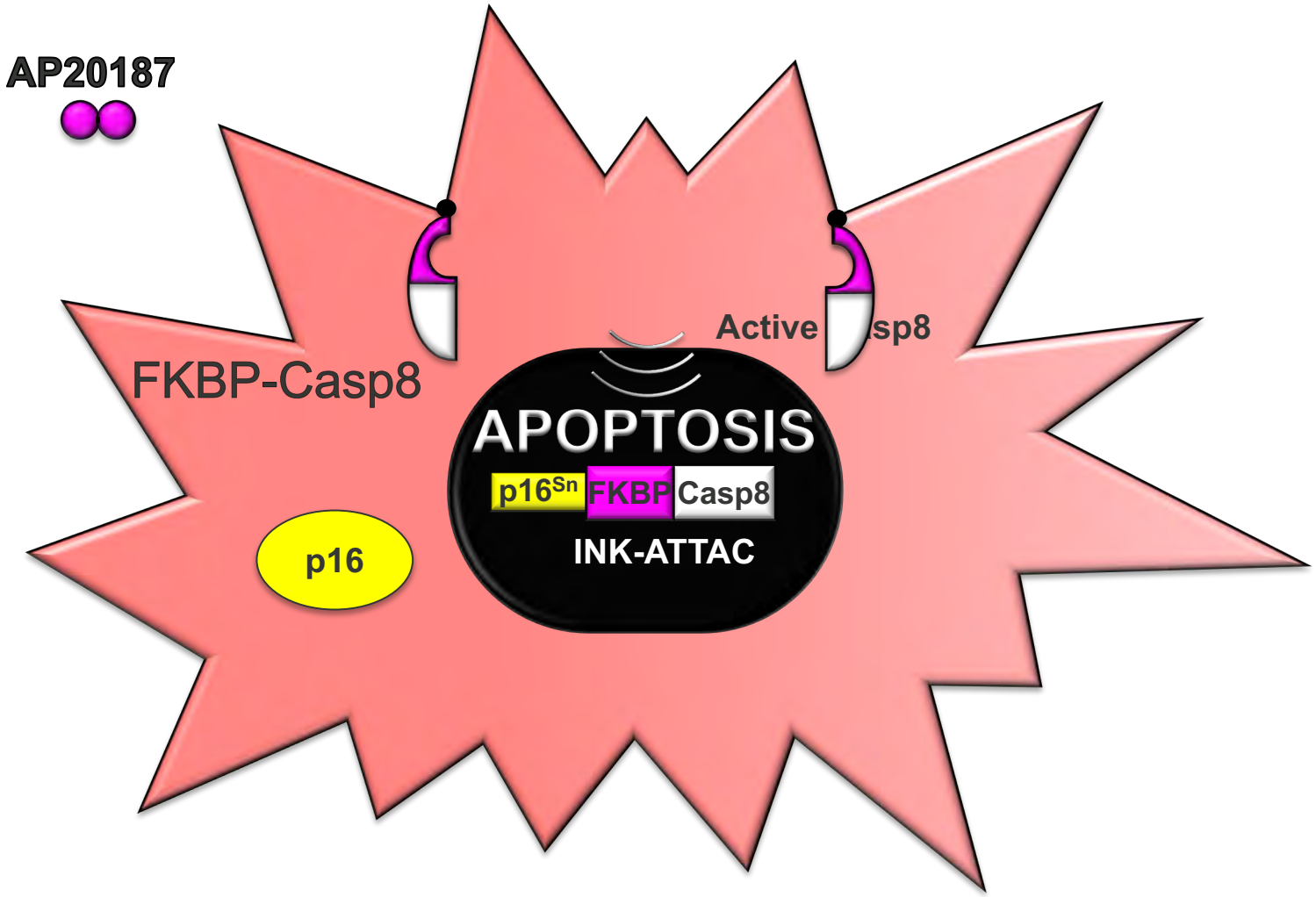
Progeroid mouse

Progeroid mouse without p16

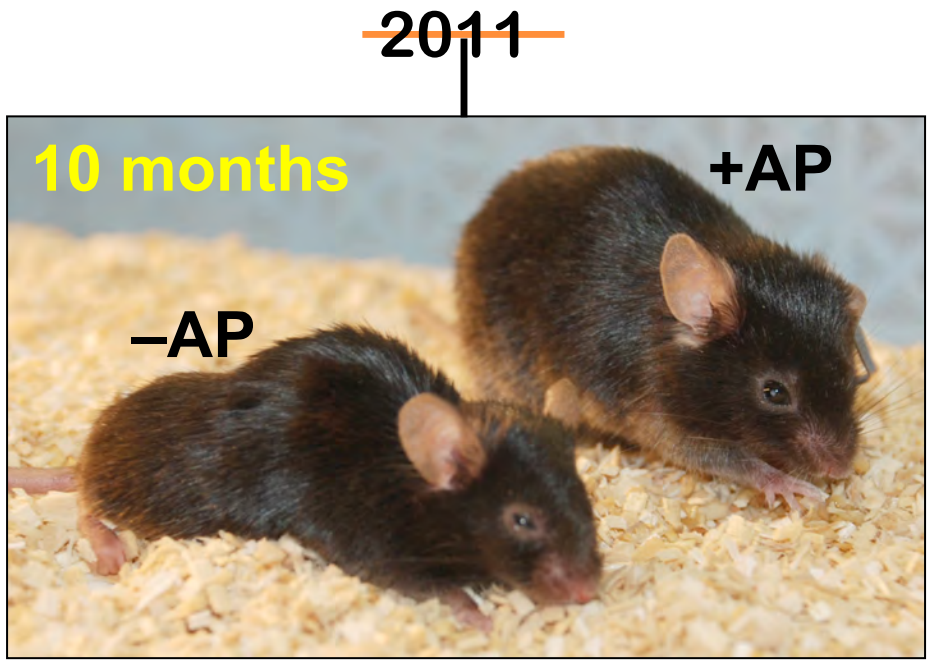


Baker et al., 2008 Nature Cell Biology

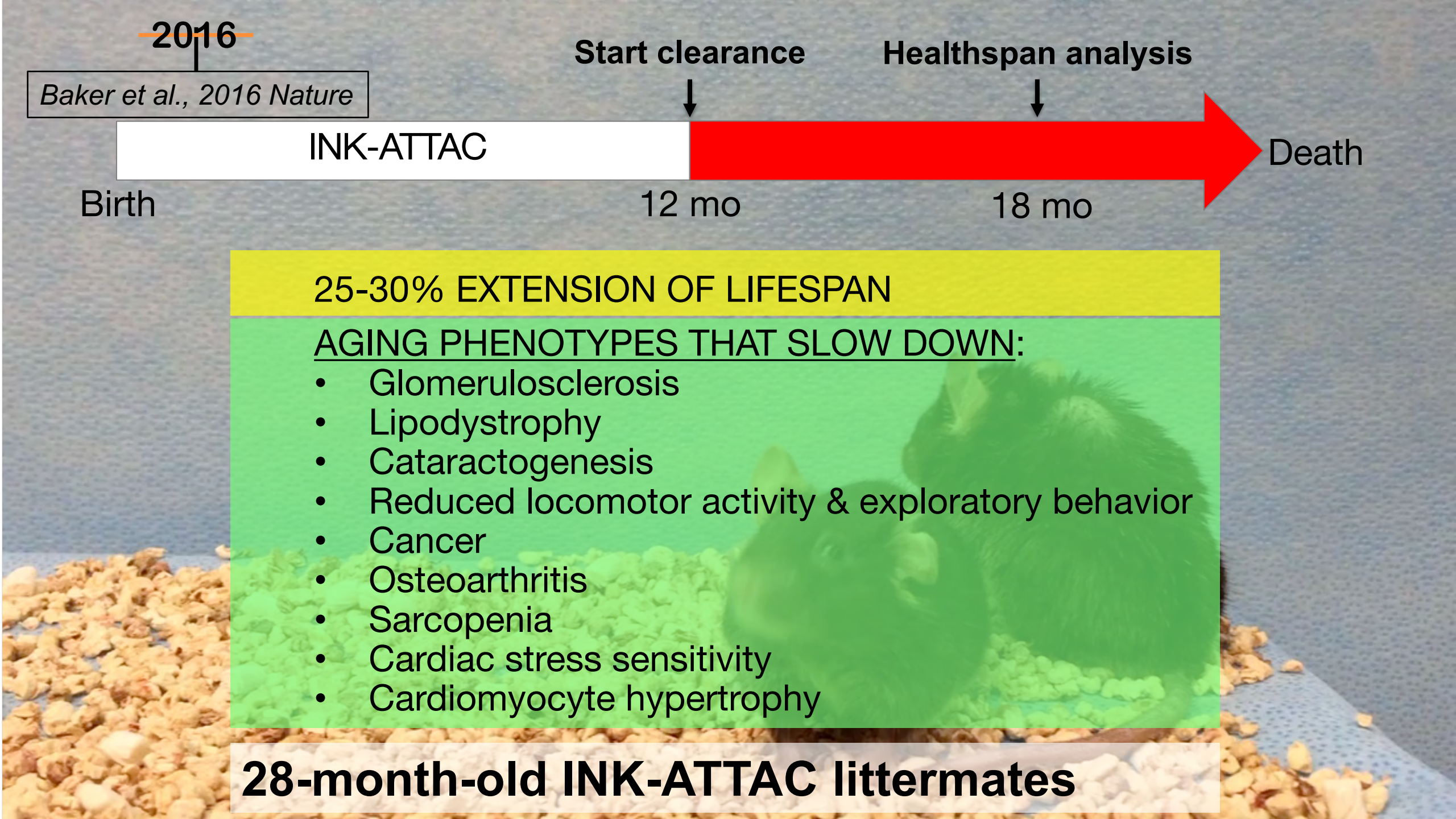
INK-ATTAC APPROACH



APPROACH VALIDATION

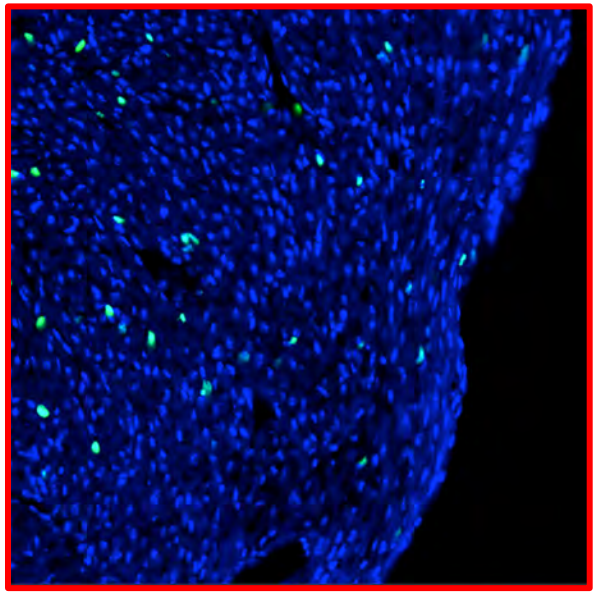


Baker et al., 2011 Nature

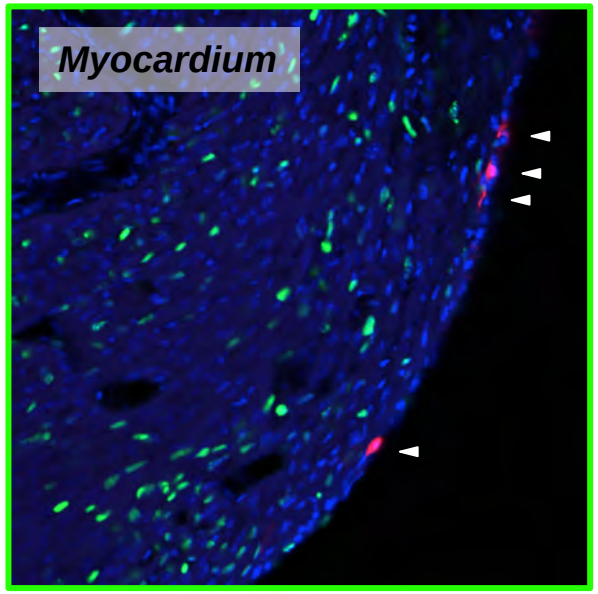

2016
Baker et al., 2016 Nature
Start clearance
Healthspan analysis
INK-ATTAC
Death
Birth
12 mo
18 mo
25-30% EXTENSION OF LIFESPAN
AGING PHENOTYPES THAT SLOW DOWN:
• Glomerulosclerosis
• Lipodystrophy
• Cataractogenesis
• Reduced locomotor activity & exploratory behavior
• Cancer
• Osteoarthritis
• Sarcopenia
• Cardiac stress sensitivity
• Cardiomyocyte hypertrophy
28-month-old INK-ATTAC littermates

REVERSE APPROACH

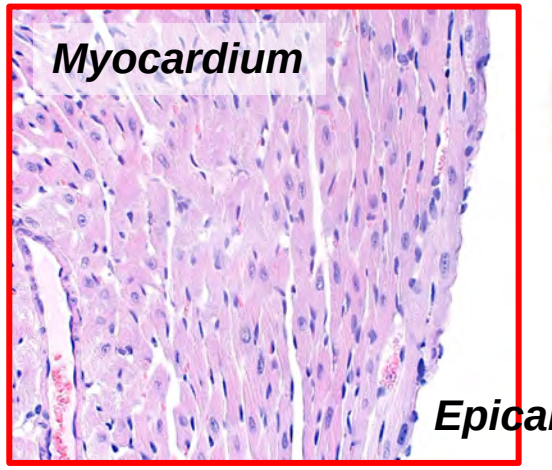
Control

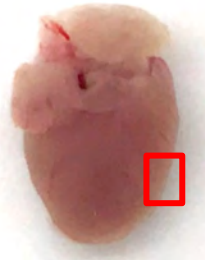


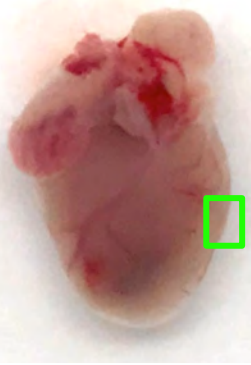
WT1-CreER^{T2};Ai14;LSL-Kras^{G12V}

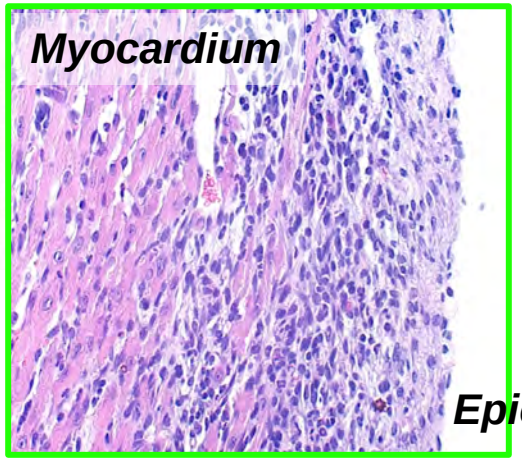


Epicardium
~1% Tom⁺ cells

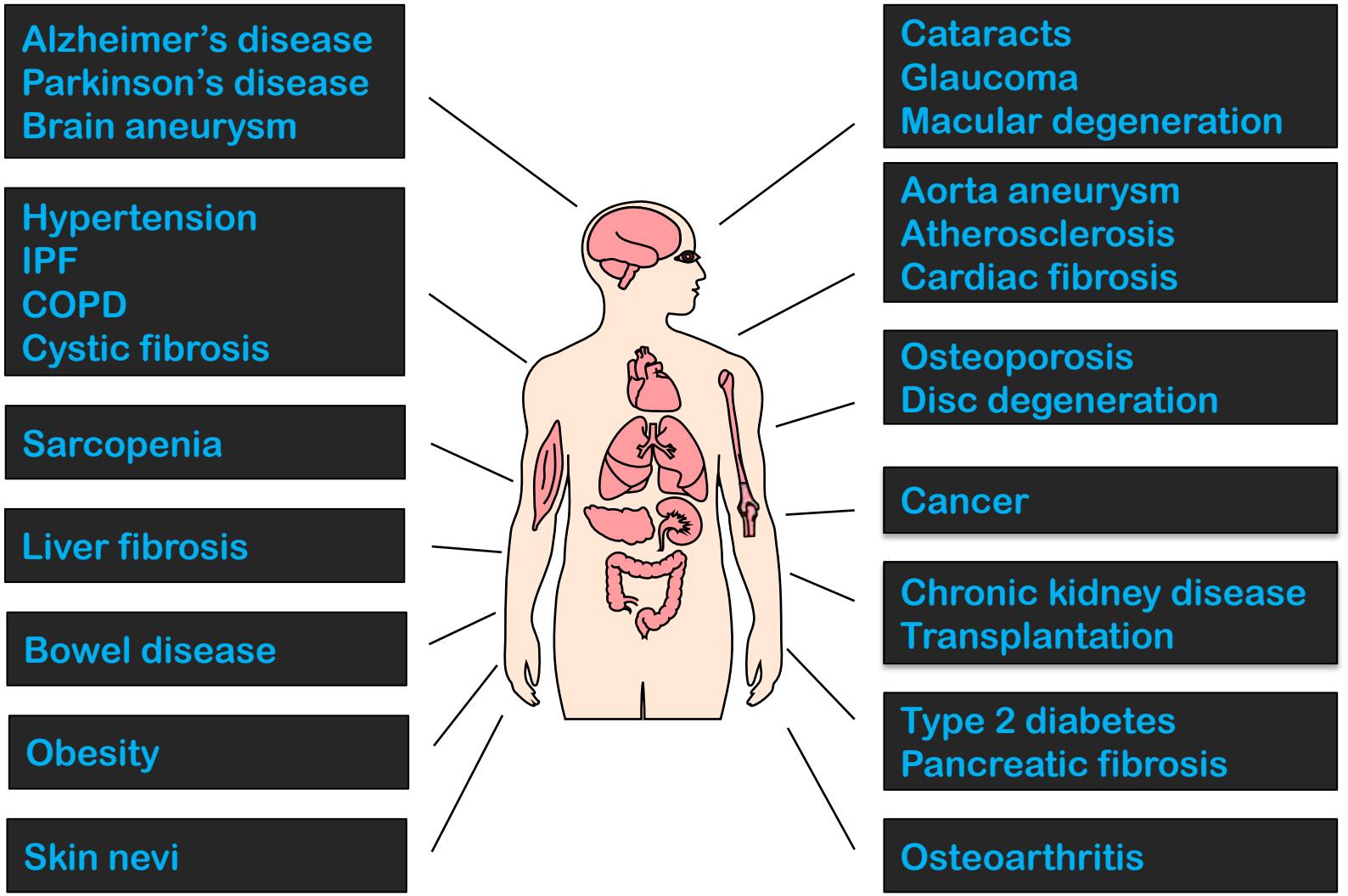








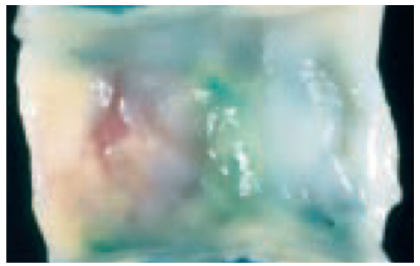
SNCs are implicated in numerous diseases



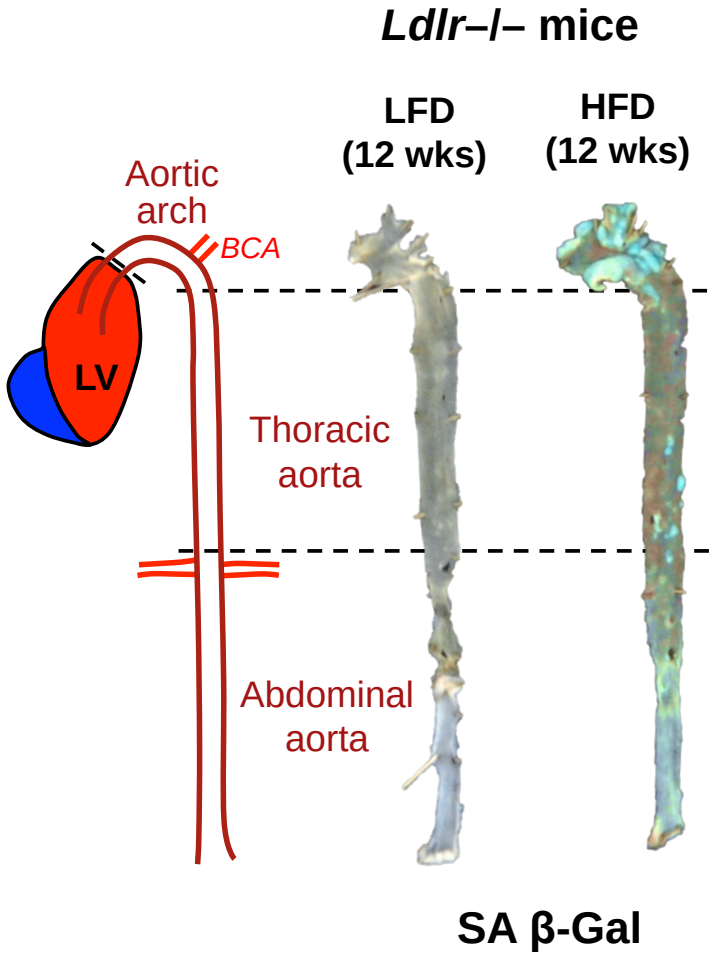
ATHEROSCLEROSIS

2016

SA-β-GAL stained atherosclerotic lesion

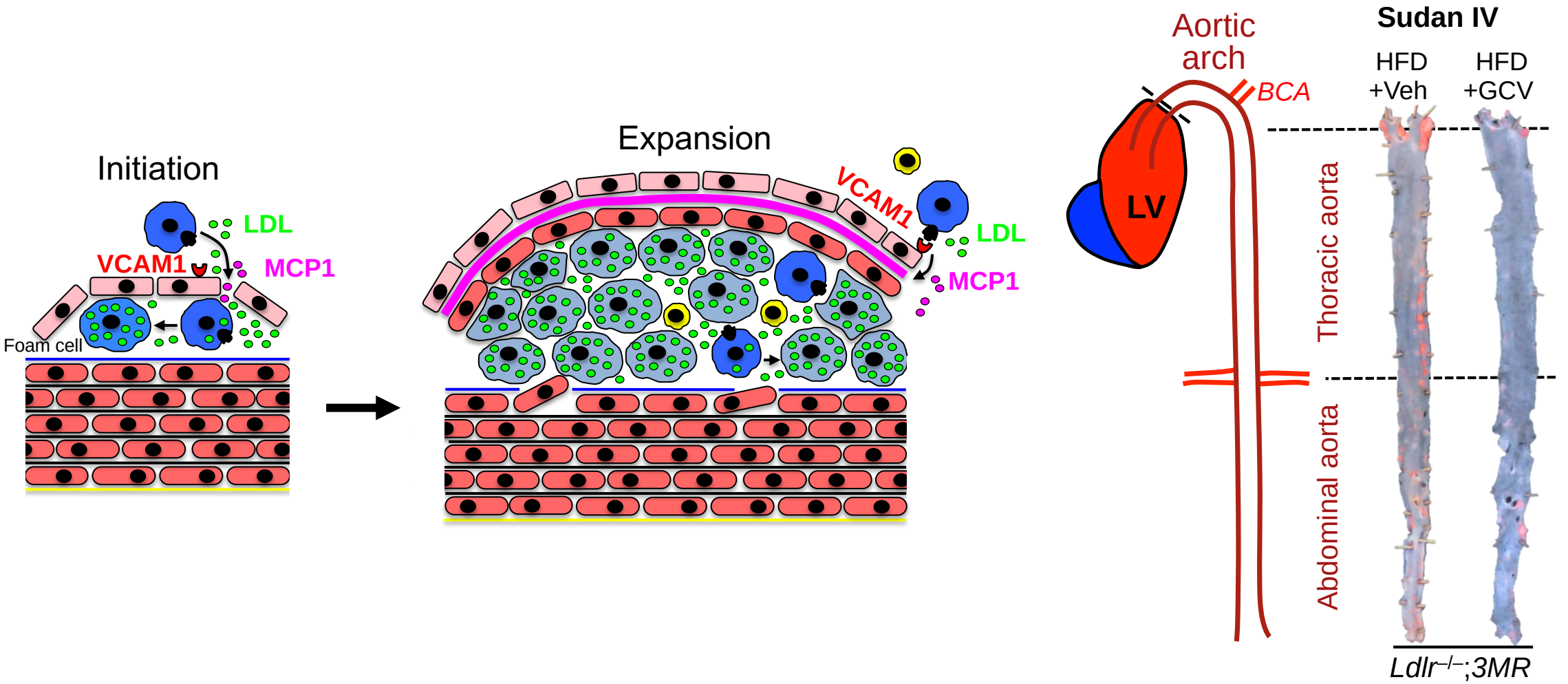


Minamino et al. 2002



Childs et al. Science 2016

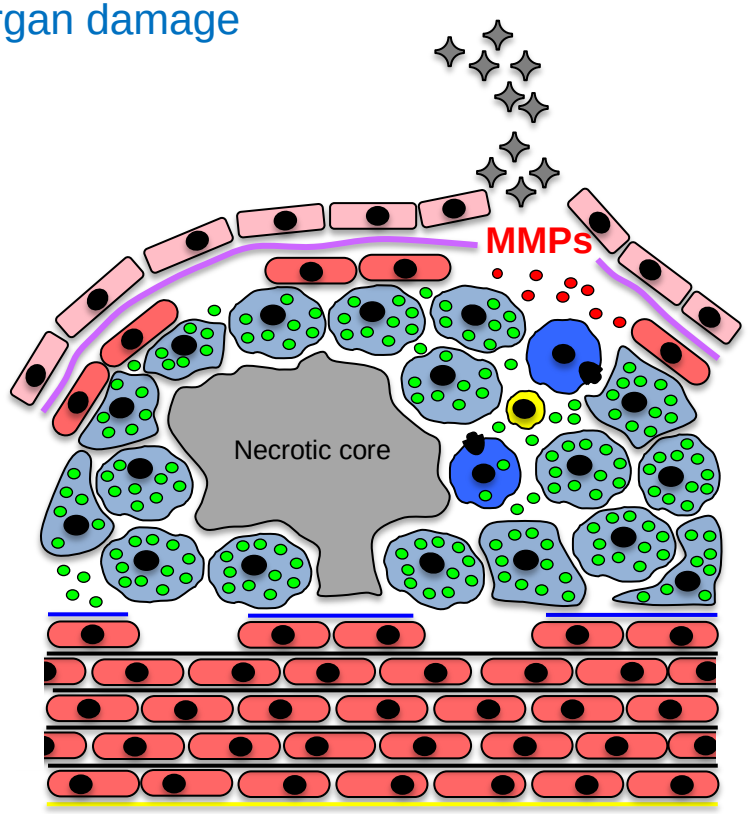
SENESCENCE DRIVES PLAQUE FORMATION

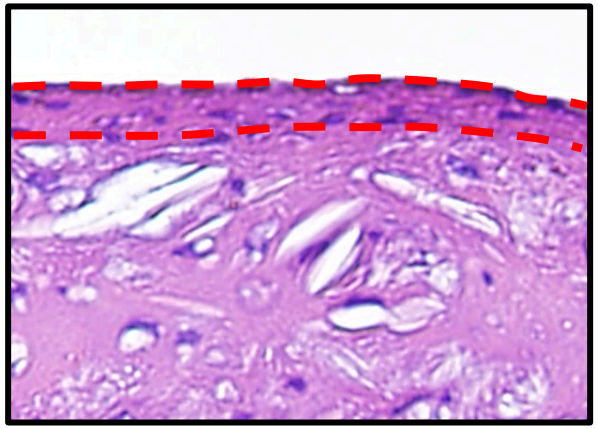


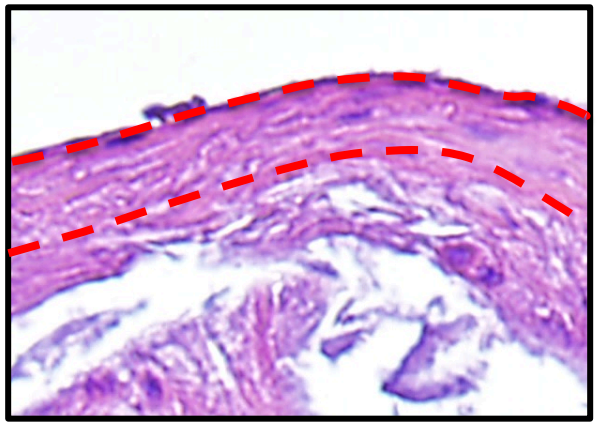
Childs et al. Science 2016

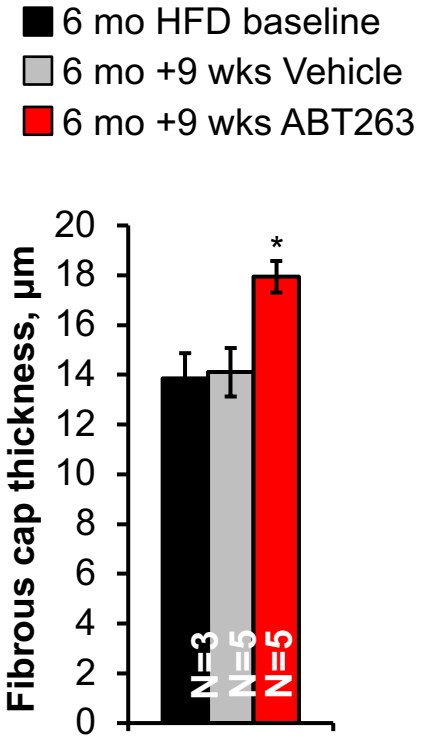
SENOLYSIS REVERSES PLAQUE MATURATION

- VSMC death
- Fibrous cap degradation (MMPs)
- Rupture + platelet aggregation
- End organ damage





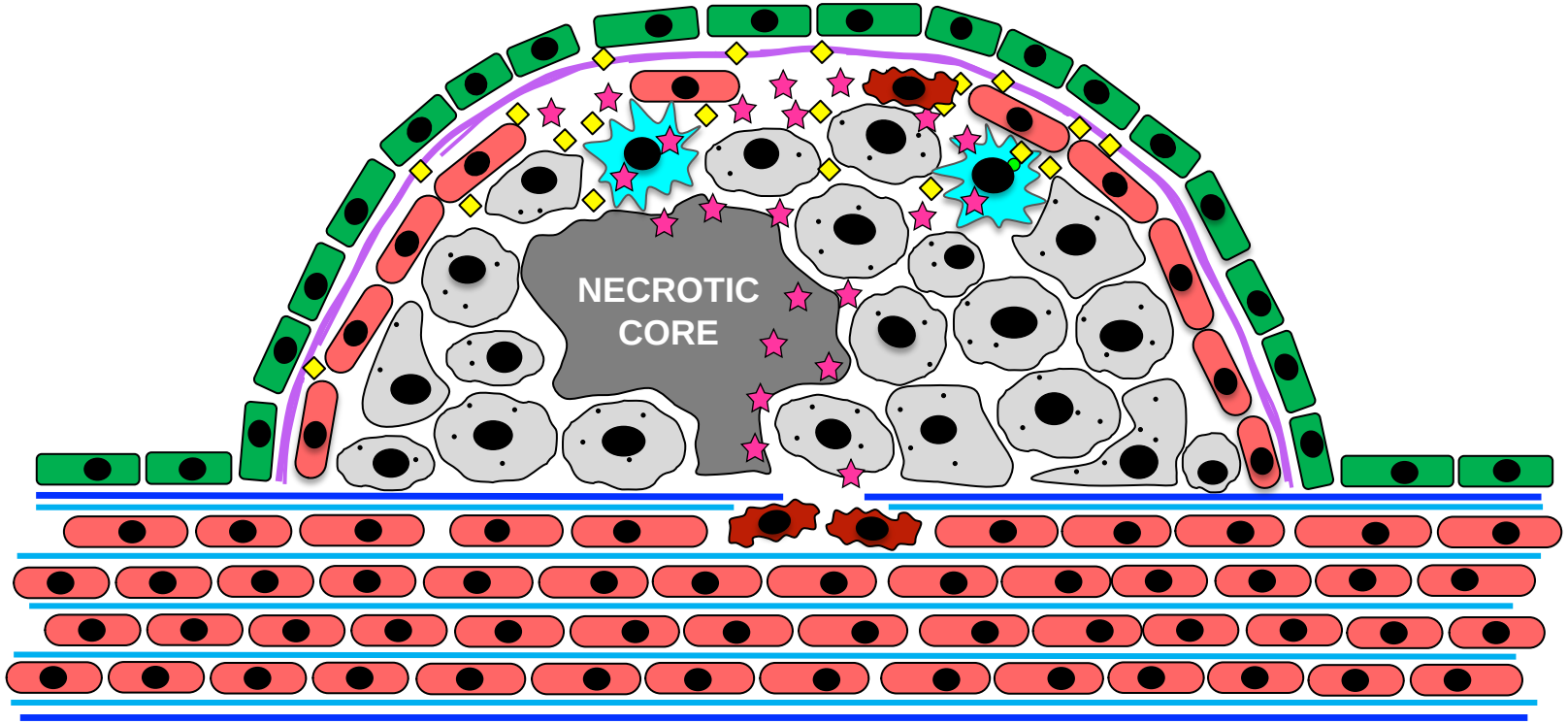




MODEL for plaque stabilization by senotherapy

SASP component(s) inhibiting VSMC proliferation/migration/activity, and/or promoting VSMC apoptosis

Proteolytic SASP component(s) (MMPs)



SNC clearance prevents age-related osteoarthritis

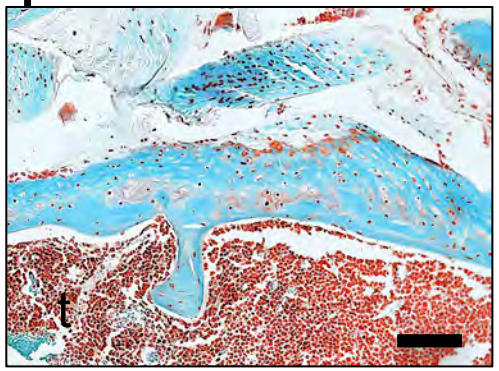
OA

- Degeneration of articular cartilage leading to pain and physical disability
- Senescent cells are found in the articular cartilage and the synovium

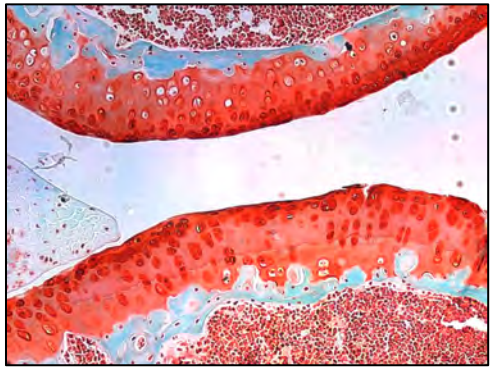
2017

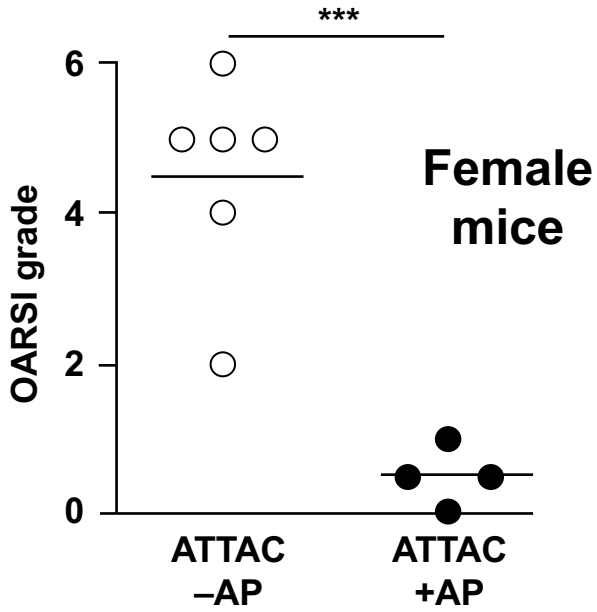
Safranin-O staining

ATTAC –AP



ATTAC +AP



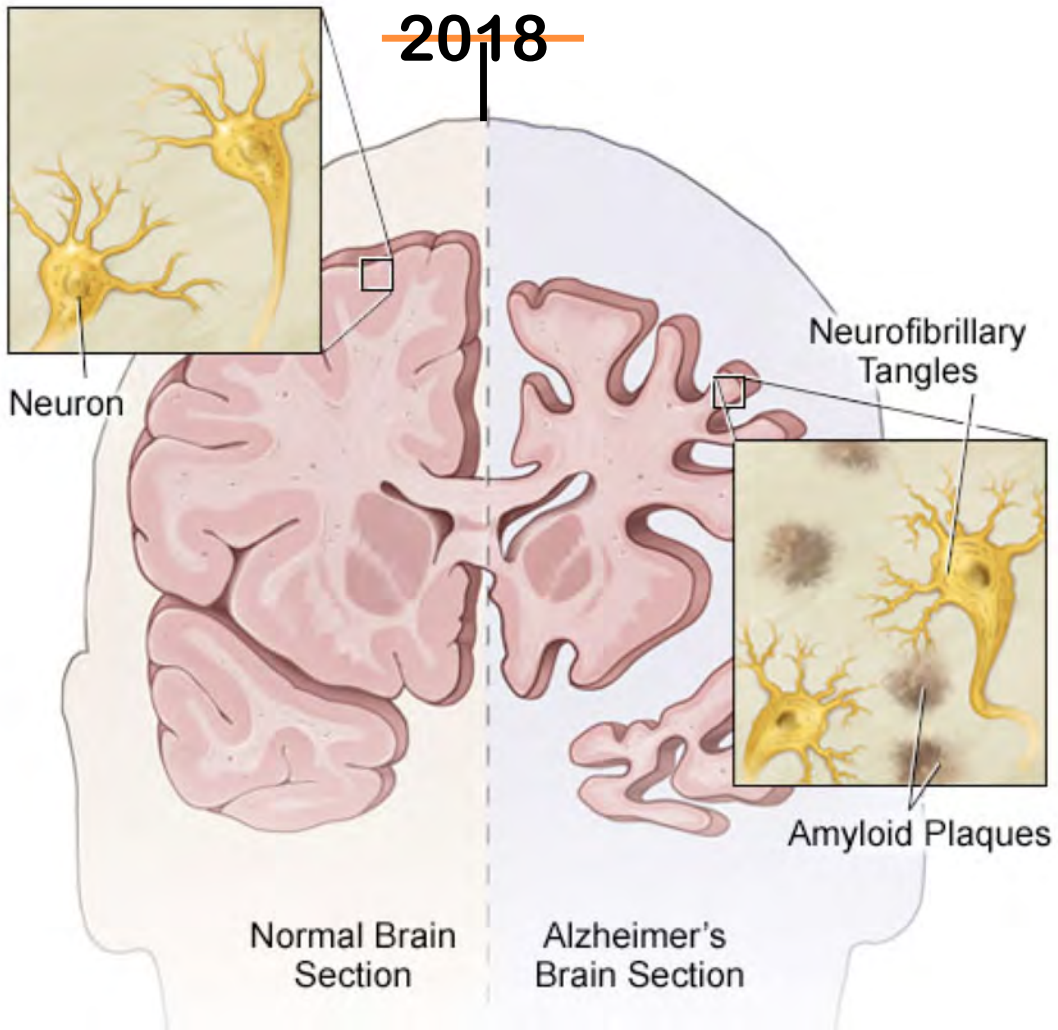


Anterior cruciate ligament transection (ACLT)

- Senescent cells are found in the articular cartilage and the synovium
- Clearance of senescent cells reduces pain and promotes cartilage formation

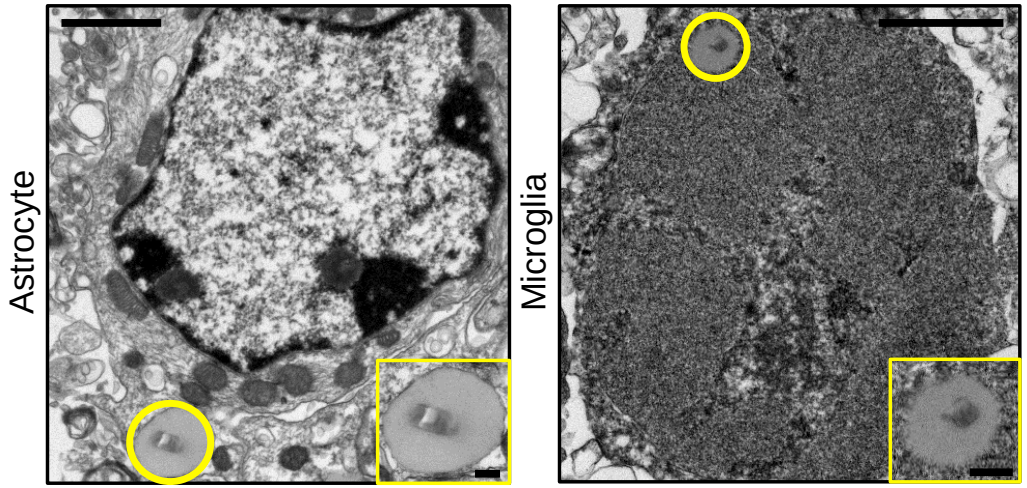
Okhee Jeon et al. Nature Medicine 2017

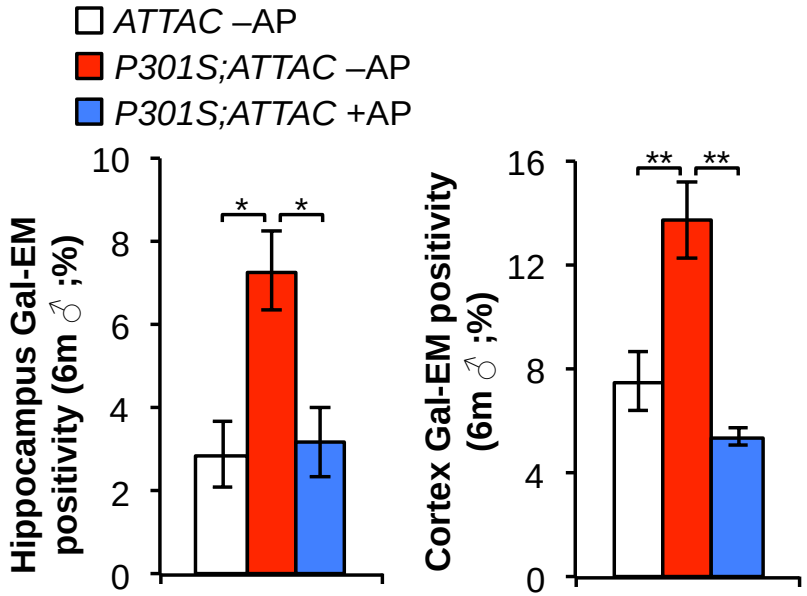
ALZHEIMER'S DISEASE



P301S mice

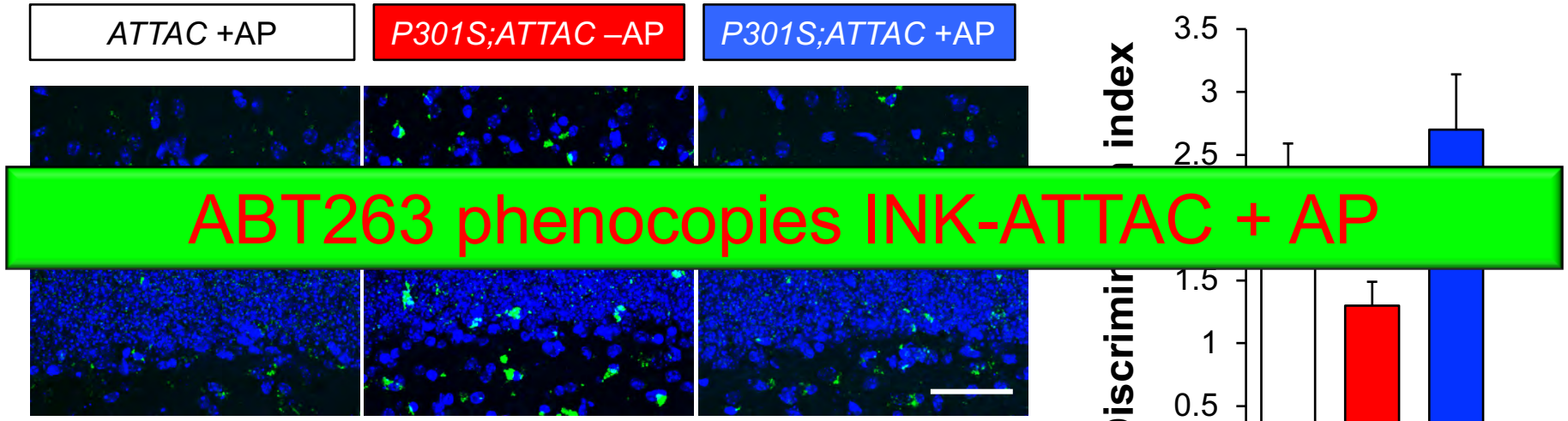
Senescent glial cells accumulate in the P301S AD model





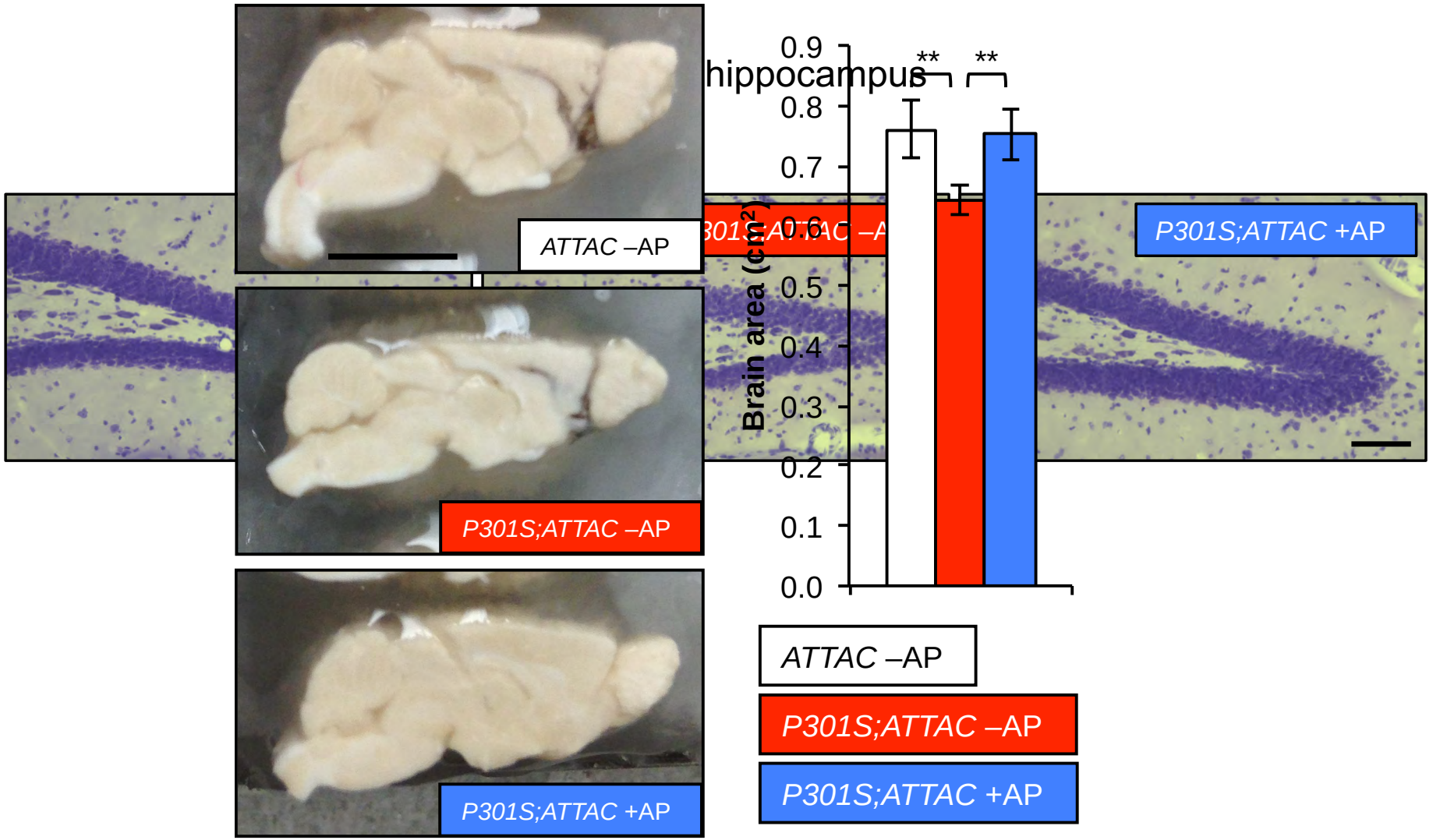
SNCs drive tangle formation and dementia

8-month-old hippocampus

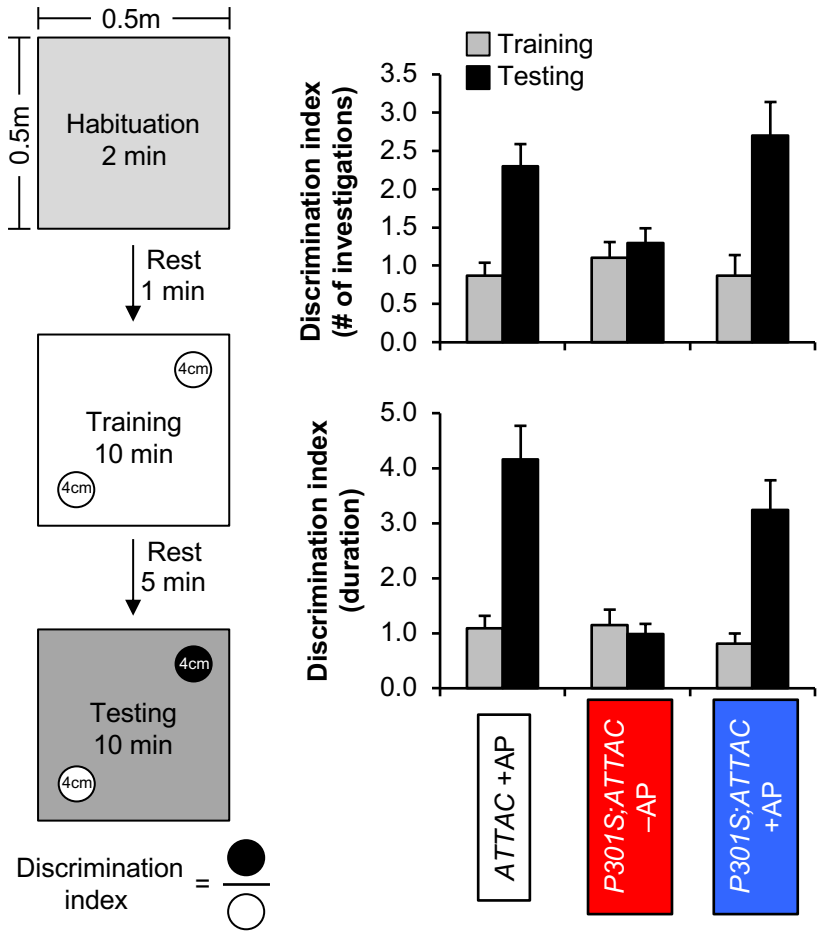


Blue – DAPI (nuclei)
Green – thioflavin S (neurofibrillary tangles)

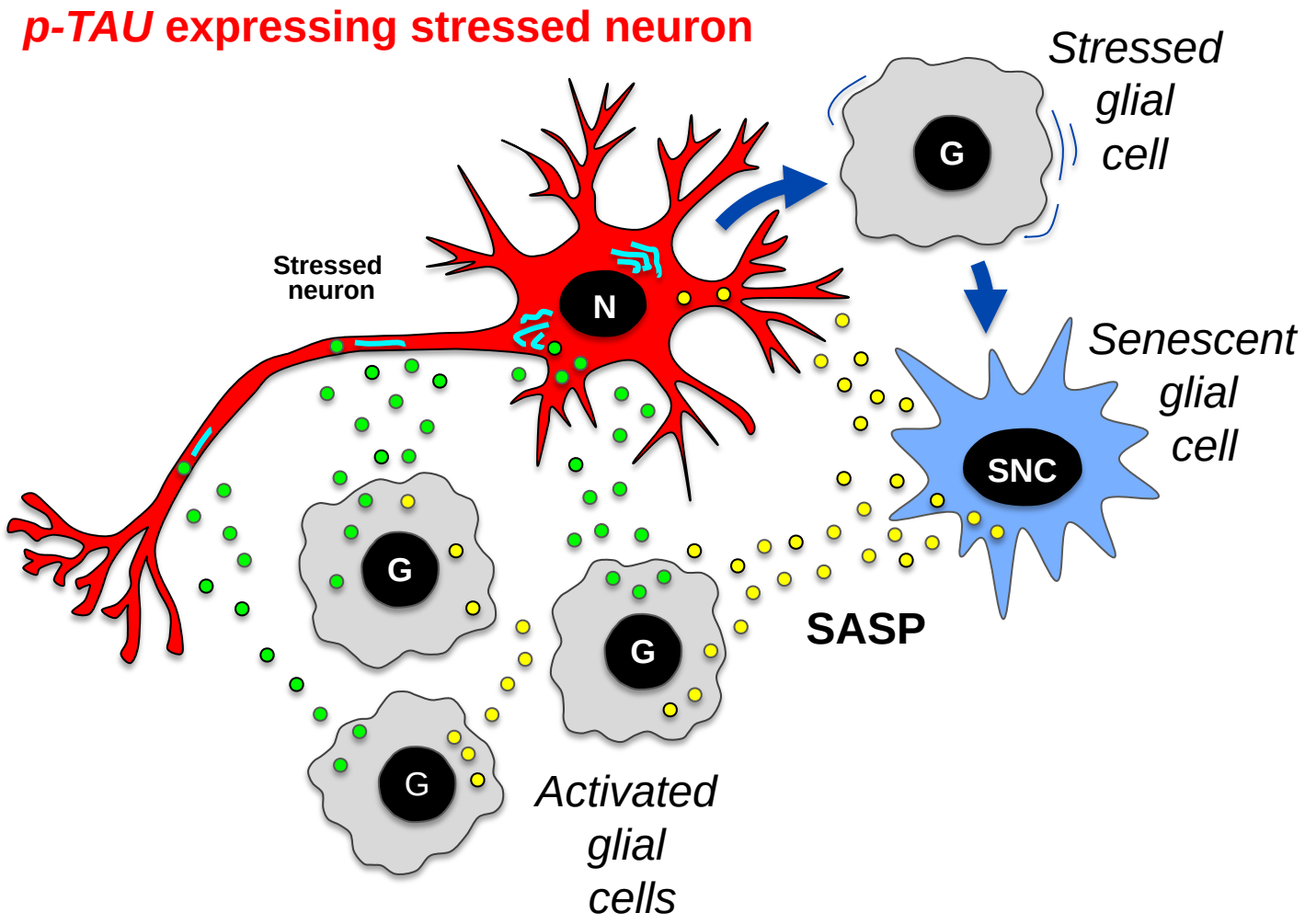
SNCs drive neurodegeneration



SENOLYSIS PREVENTS MEMORY LOSS



MODEL for preventing neuronal loss by senotherapy



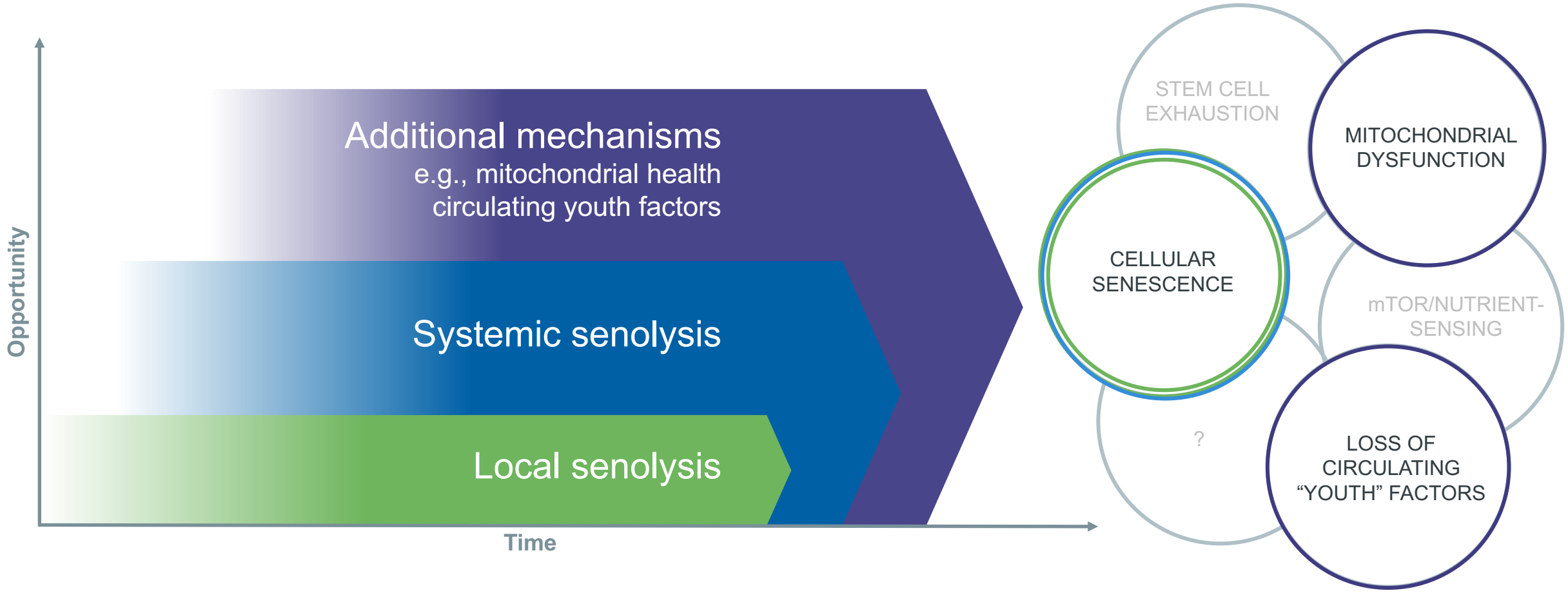
THERAPEUTIC APPROACHES TO AGING

Ned David, Ph.D.

UNITY BIOTECHNOLOGY

BROAD STRATEGY TO EXTEND HEALTHSPAN

Early effort in local senolytic therapy will expand to systemic senolytics and other mechanisms



UNITY plans to address multiple modalities to fully enable potential of age-related therapies

CELLULAR SENESCENCE

A history of our understanding

1910s

CONCEPT OF CELL DIVISION AS FINITE

1960s

DISCOVERY OF CELLULAR SENESCENCE

1990s

IDENTIFICATION OF SENESCENCE BIOMARKER

2000s

LINK TO AGING PHENOTYPES & IDENTIFICATION OF SASP

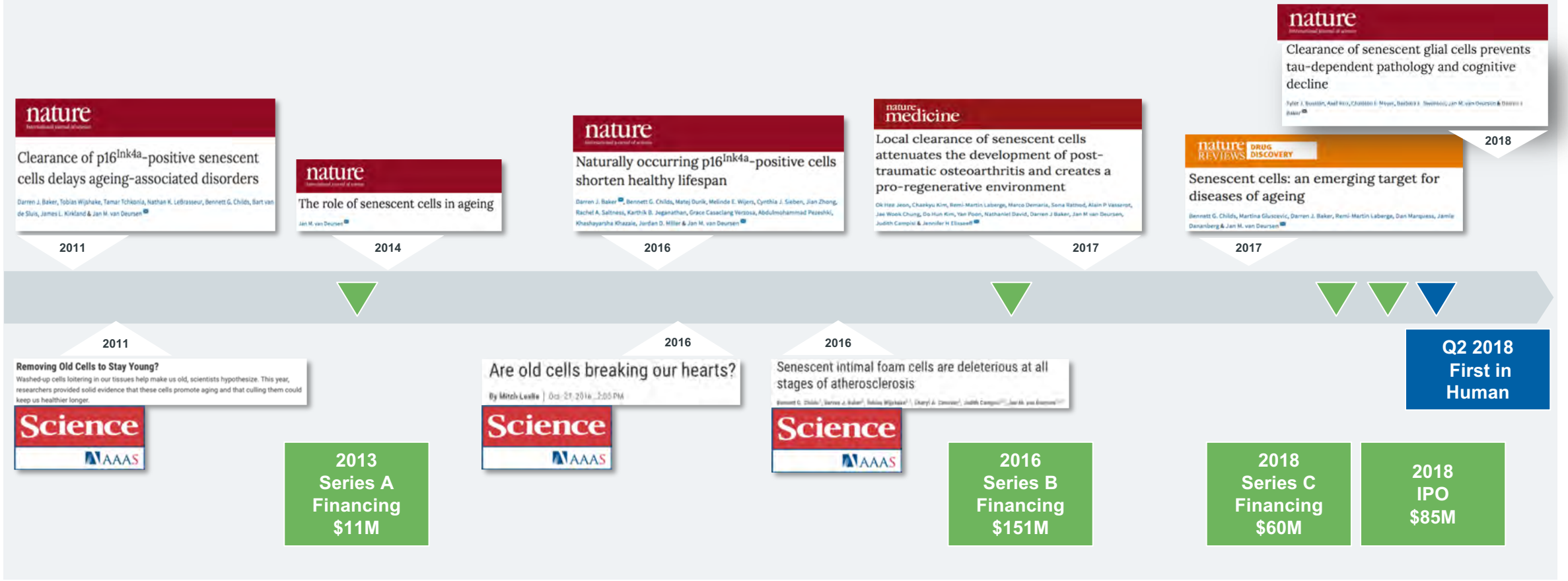
2010s

SENOLYSIS AS AN APPROACH TO TREAT DISEASES OF AGING

UNITY BIOTECHNOLOGY

UNITY: ESTABLISHING LEADERSHIP IN HEALTHSPAN

Robust funding for R&D with notice in prestigious scientific journals



THE UNITY THERAPEUTIC PARADIGM

BIOLOGICAL STRESS

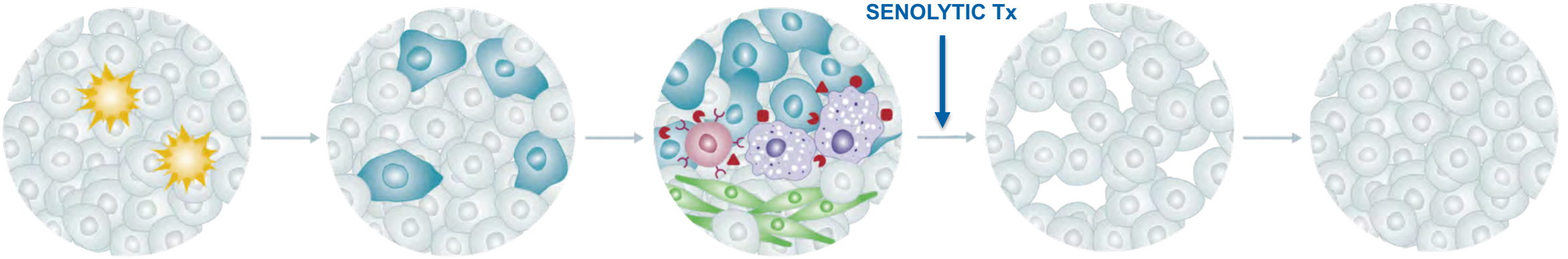
ACCUMULATION OF SENESCENT CELLS

SPREAD OF SENESCENCE AND INFLAMMATION

PERSISTENT DAMAGE, TISSUE DYSFUNCTION, AND DISEASE

UNITY THERAPEUTIC PARADIGM

ADMINISTER SENOLYTIC Tx



SnCs, INFLAMMATION, TISSUE DYSFUNCTION

CLEARANCE OF SnCs WITH SENOLYTIC Tx

REGENERATION AND RESTORATION OF FUNCTION

DISEASED TISSUE

FUNCTIONAL TISSUE

Functional Cell

Senescent Cell (SnC)

Cytokines, chemokines & matrix remodeling factors (SASP)

Macrophage

CD4+ T lymphocyte

Fibroblast

ADVANTAGES OF OUR APPROACH

1 TARGET THE ROOT CAUSE

- Selective elimination of SnCs & SASP
- Rather than inhibit a single disease factor, senolytics could inhibit many factors at once
- Targeting disease at its source

→ **A single medicine could remove many disease-causing factors**

2 INTERMITTENT DOSING

- After clearance, new SnCs may take months or years to re-accumulate
- Intermittent, instead of chronic, treatment

→ **Intermittent dosing may:**
- **Improve drug tolerability**
- **Improve patient adherence**

3 SnCs ACCUMULATE AT DISEASE SITES

- SnC accumulation may simplify indication selection
- Possible patient selection using senescence biomarkers
- Monitoring drug response by tracking reduction of senescence biomarkers

→ **Clustered SnCs may reveal treatable diseases**

4 RESTORE TISSUES TO A HEALTHY STATE

- Our belief that SnCs generally do not accumulate in young people suggests that accumulation is unnecessary for normal tissue function and that clearing them may be restorative

→ **Simple paradigm to restore tissues to a more youthful state**

UNITY PIPELINE

Broad therapeutic potential, addressing multiple mechanisms of aging

MANAGEMENT

An experienced team with a track record of success

KEITH LEONARD, MS, MBA
Chief Executive Officer

KYTHERA BIOPHARMACEUTICALS · ANACOR PHARMACEUTICALS · AMGEN

NATHANIEL DAVID, PHD
President

KYTHERA BIOPHARMACEUTICALS · ACHAOGEN · syrrx

DAN MARQUESS, D. PHIL
Chief Scientific Officer

Theravance · gsk

JAMIE DANANBERG, MD
Chief Medical Officer

Lilly · Takeda

BOB GOELTZ, CPA, MBA
Chief Financial Officer

CYTOMX THERAPEUTICS · ONYX PHARMACEUTICALS · AMGEN · Tularik

TAMMY TOMPKINS, JD
General Counsel

khosla ventures · AMYRIS

SUSIE LUNDEEN
SVP of People

KYTHERA BIOPHARMACEUTICALS · AMGEN

PEDRO BELTRAN, PHD
SVP of Biology

AMGEN

DOUG RICH, MBA
SVP, Operations

KYTHERA BIOPHARMACEUTICALS · AMGEN · Boehringer Ingelheim

CAMILLE LANDIS
SVP, Corporate Development

AFFYMAX · NAVIGANT CONSULTING · PiperJaffray · relypsa

UNITY'S EDGE IN DEVELOPING SENOLYTICS

Dan Marquess, D. Phil,
Chief Scientific Officer

UNITY BIOTECHNOLOGY

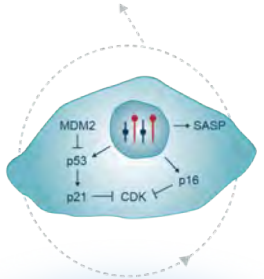
UNIQUE APPROACH TO CREATING SENOLYTIC MEDICINES

Diseases of aging

SnC disease hypothesis

Disease severity vs SnCs

CELL TYPE that becomes Sn



SENOLYSIS ATLAS: cell type *vs* mechanism

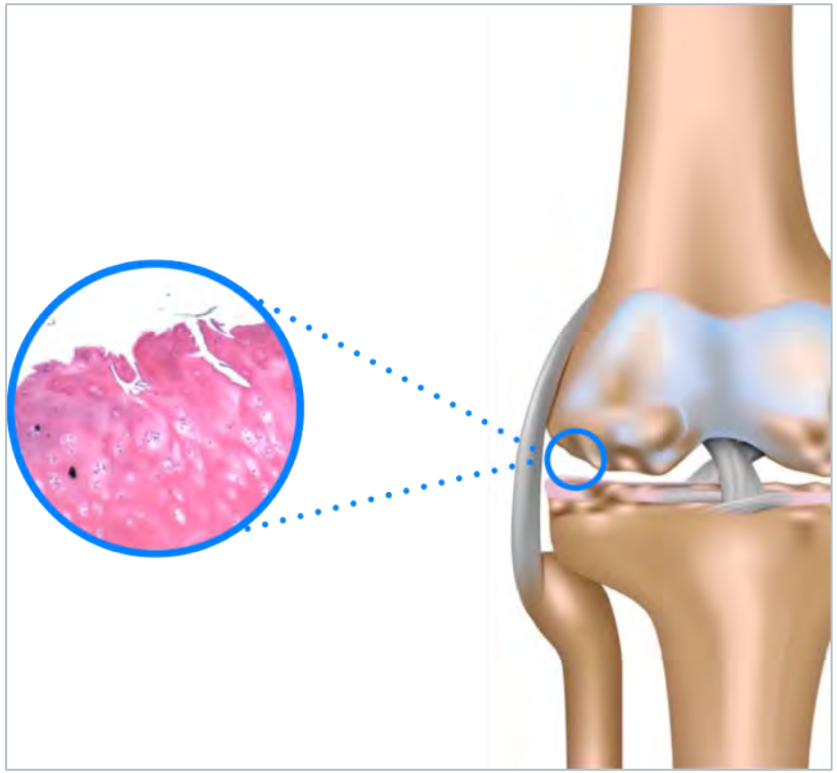
Senolytic discovery

Translational sciences

in vitro-in vivo efficacy

Integration of **SnC disease hypothesis** & senolytic discovery → unique insights

SENESCENCE DISEASE HYPOTHESIS: OSTEOARTHRITIS



Disease → pain, lack of mobility, joint replacement

disease symptoms

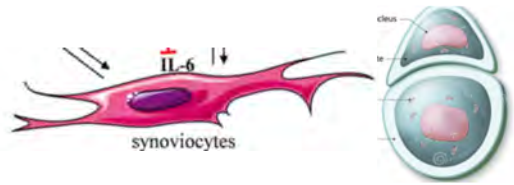
SASP → cartilage loss & inflammation of synovial membrane

INFLAMMATORY FACTORS

(MMP1, MMP3, MMP13, TNF-α, IL-1β, IL-6 prostaglandins)

senescence secretome

SnCs accumulate with age in knee tissue
(e.g., cartilage, synovial membrane)

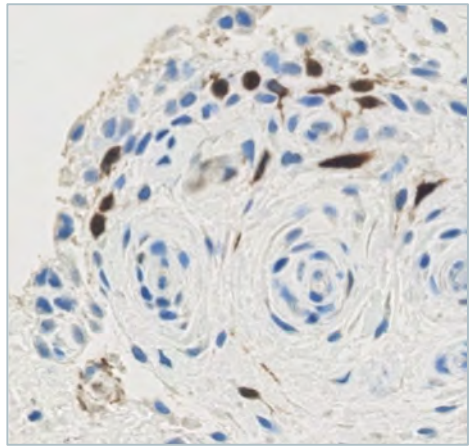


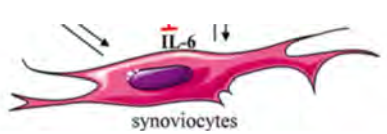
senescent cells

Identifies cell types for senolysis on a **disease by disease** basis

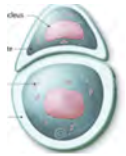
IDENTIFY SnC TYPES IN EACH DISEASE OF AGING

Joint disease *e.g.* OA



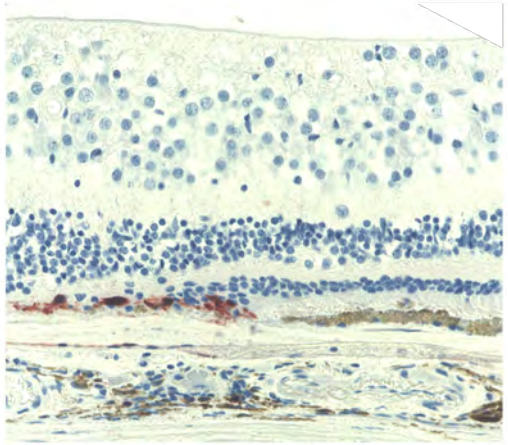


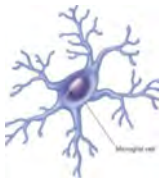
synoviocyte



chondrocyte

Retinopathies *e.g.* DR, AMD

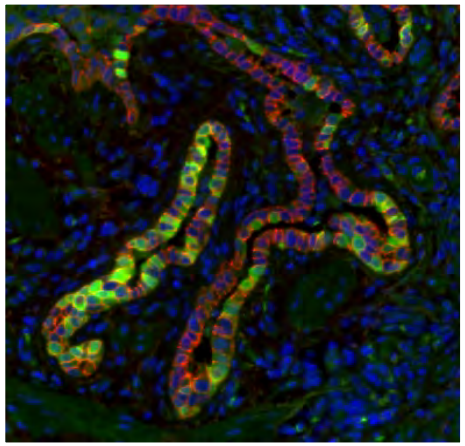


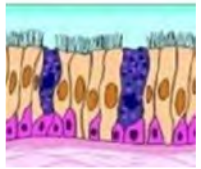


glial cell

retinal ganglion cell

Fibrotic lung disease *e.g.* IPF



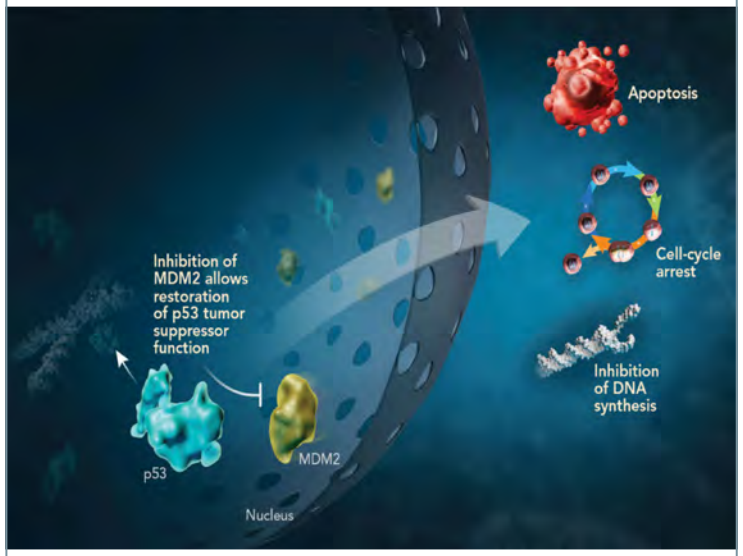


bronchial epithelial cells

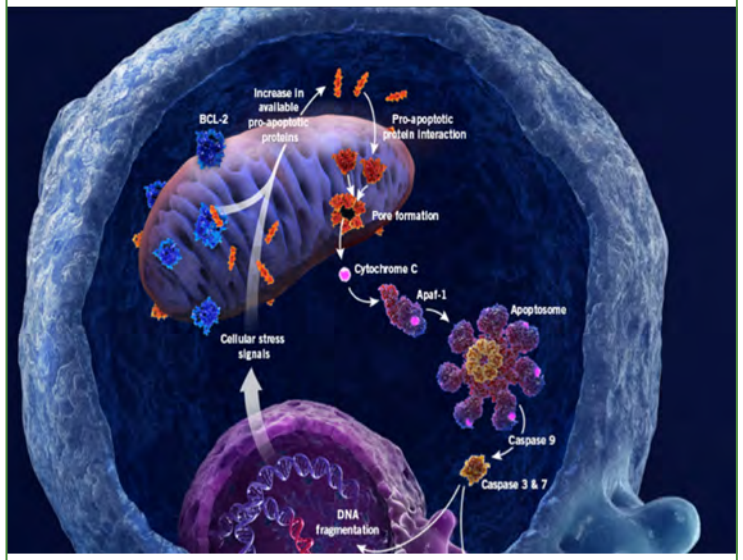
Definition of cell types causal to disease → evaluate senolytic efficacy

IDENTIFY & TARGET SnC SURVIVAL PATHWAYS

p53-MDM2 pathway



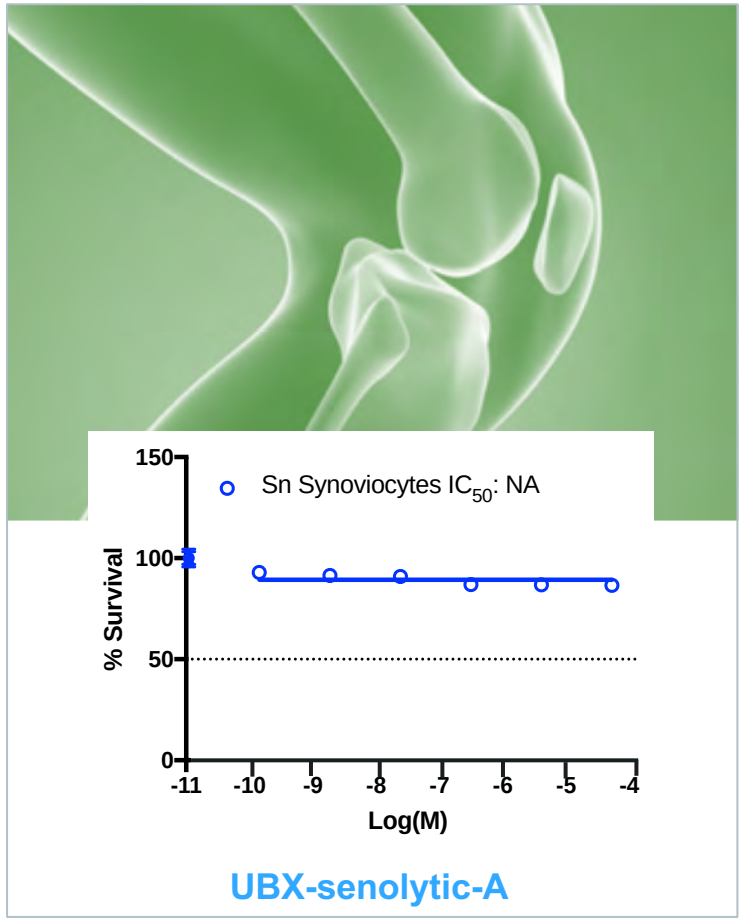
Bcl-2 pathway

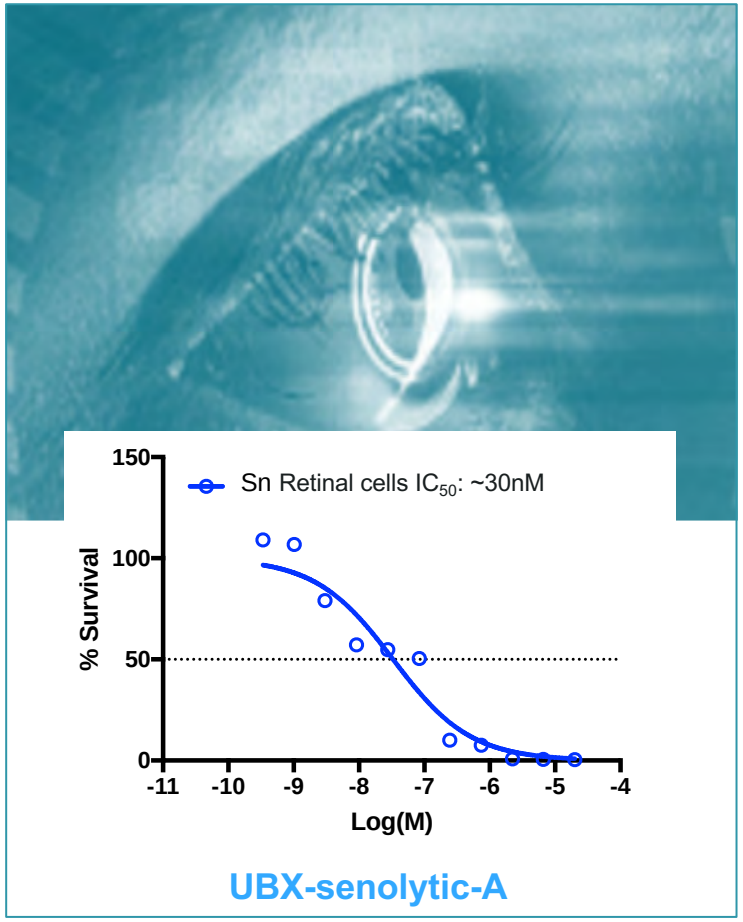


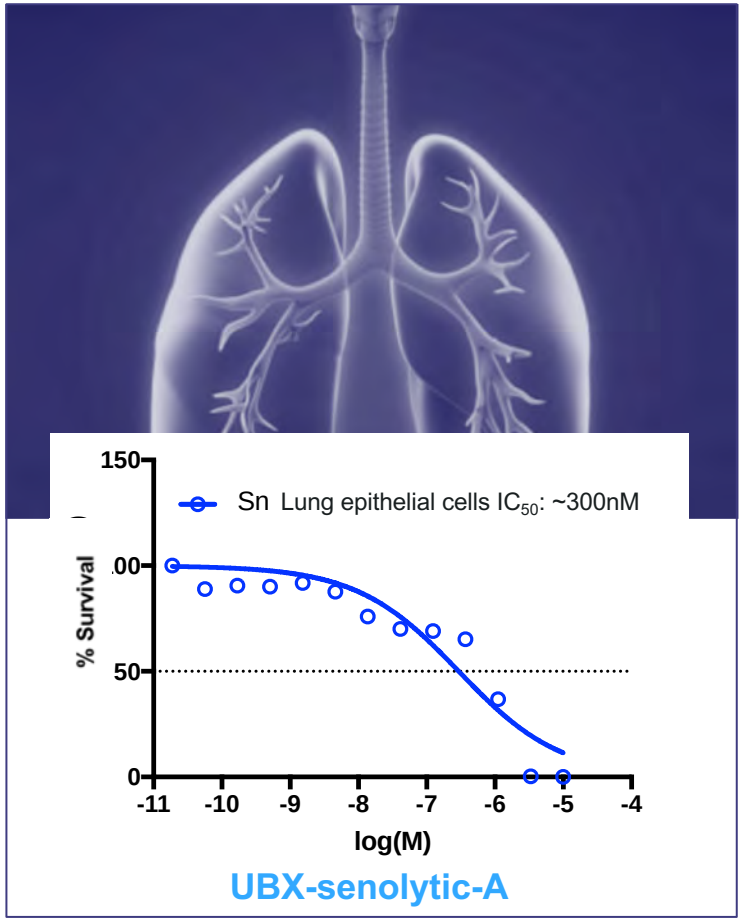
New pathways

Continue to search for & explore new mechanisms & modalities

SENOLYTIC POTENCY ACROSS DIFFERENT SnC TYPES

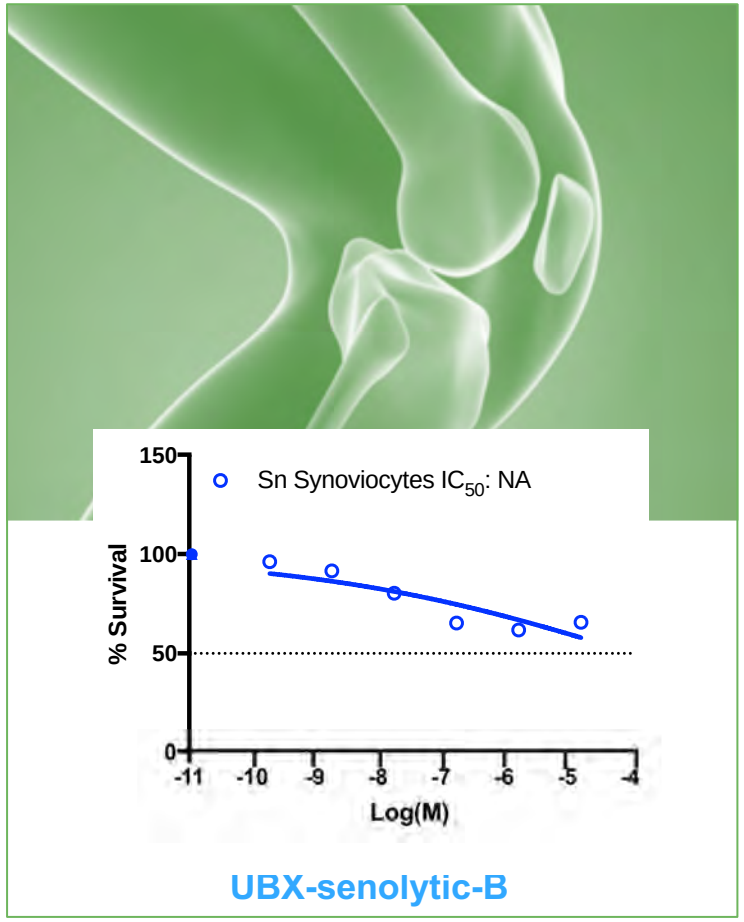




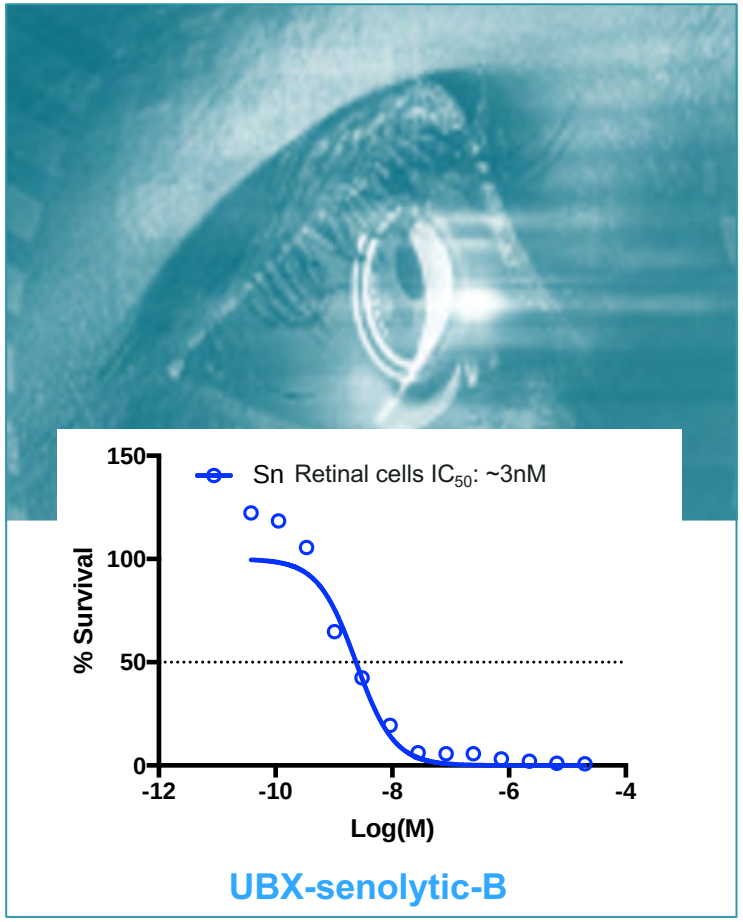


Combine insights on senolysis at different cell types → **compare mechanisms**

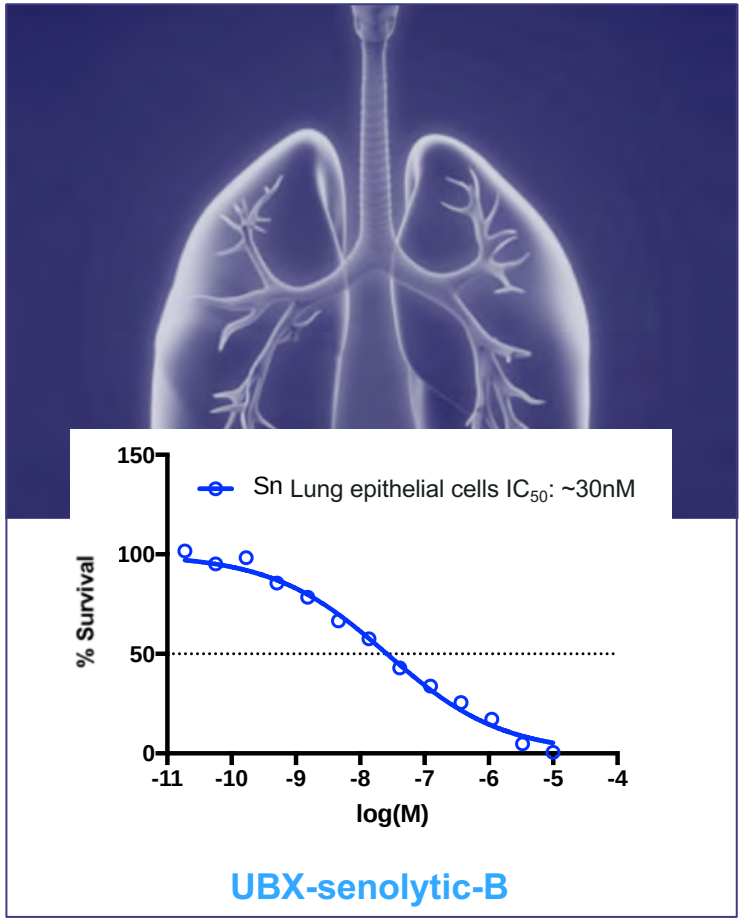
SENOLYSIS POTENCY FROM DIFFERENT MECHANISMS



UBX-senolytic-B



UBX-senolytic-B



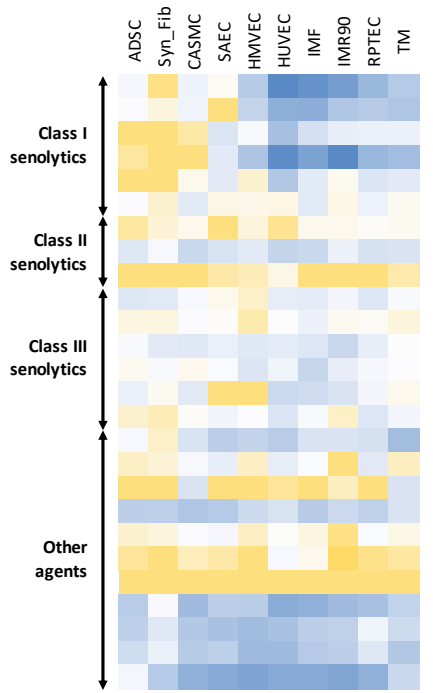
UBX-senolytic-B

Integrate insights on senolysis for mechanism & cell type → **ATLAS**

PROVIDES INSIGHTS TO ACCELERATE LATER PROGRAMS

Indication		Cell type	IC_{50}/nM	
			BCL	Novel
			UBX-A	UBX-B
	OA	Synoviocyte	>10^5	>10^5
	Eye	Retinal	30	3
	IPF	Epithelial	300	30

ATLAS



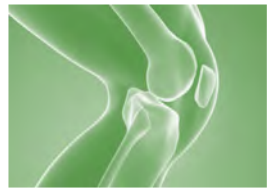
Catalog of cell-type survival pathways

Details which senolytics might eliminate SnC types

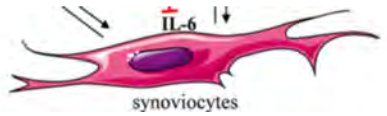
Opportunity to accelerate exploration of new indications

Creates further **insights** on how to eliminate SnCs in different tissues & diseases

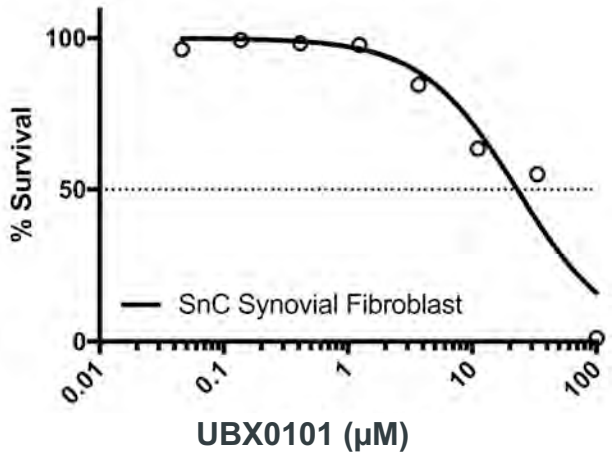
OA: PRE-CLINICAL *IN VITRO-IN VIVO* EFFICACY

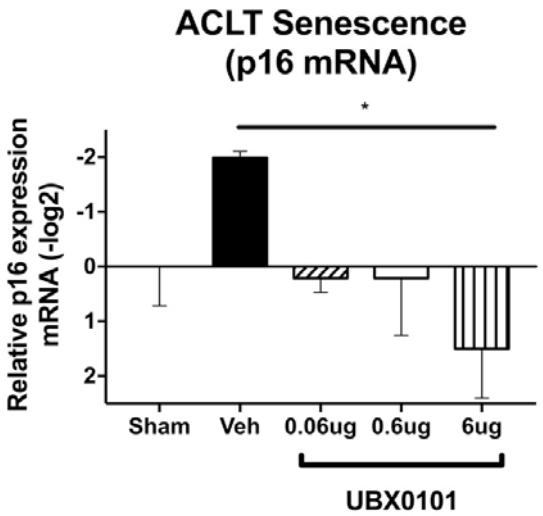


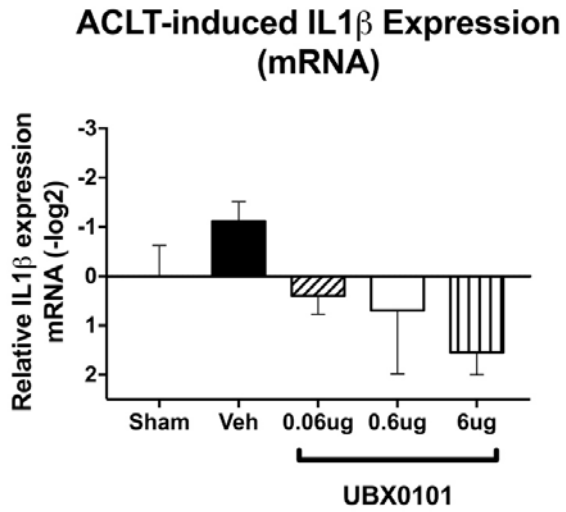
In vitro targeting → *in vivo* mechanism → *in vivo* efficacy



synoviocyte







Foundation for **translation to clinical studies** to create senolytic medicines

UNITY BIOTECHNOLOGY

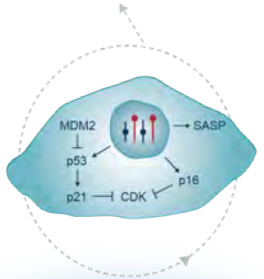
TRANSLATING SENOLYSIS INTO BENEFIT TO PATIENTS

Diseases of aging

SnC disease hypothesis

Disease severity vs SnCs

SnC cell type & SASP



ATLAS: cell type vs mechanism

Senolytic discovery

in vitro-in vivo efficacy

Translational sciences

Additional integration with other relevant therapeutic areas, *e.g.* **oncology**

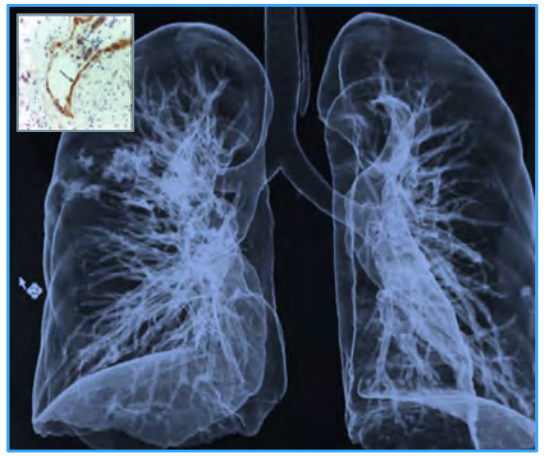
THE INTERSECTION OF SENOLYSIS AND ONCOLOGY

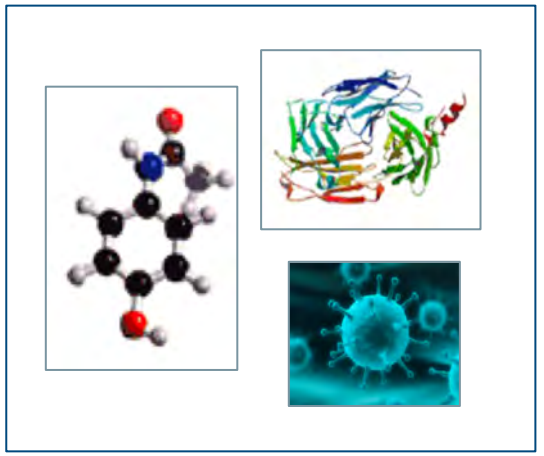
Pedro Beltran, Ph.D.,
Senior Vice President of Biology

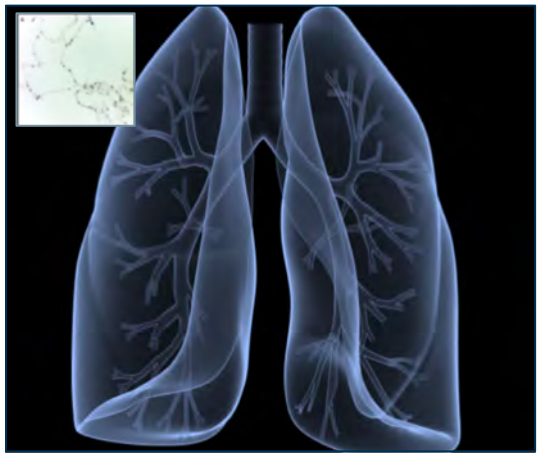
UNITY
BIOTECHNOLOGY

OUR STRATEGY

DETECT → DISCOVER → TARGET → REMOVE





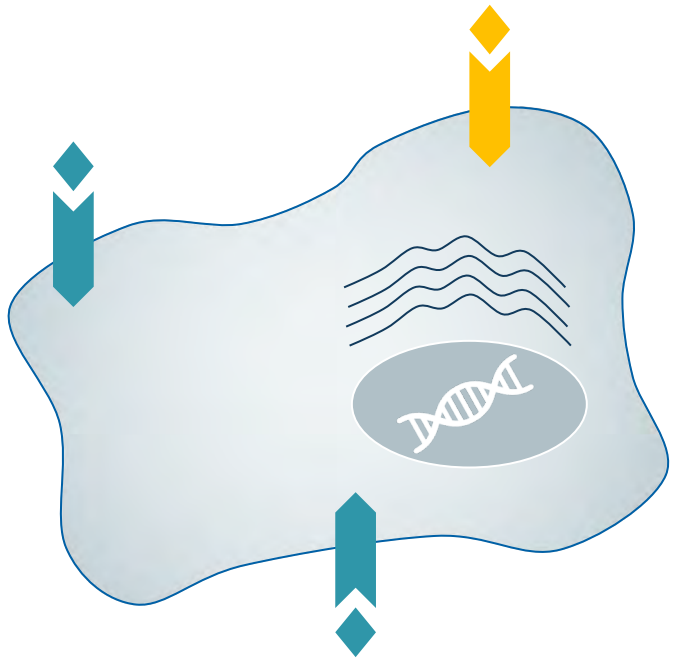


Oncology modalities and targets play a key role in senolytic development

TO ELIMINATE A CELL

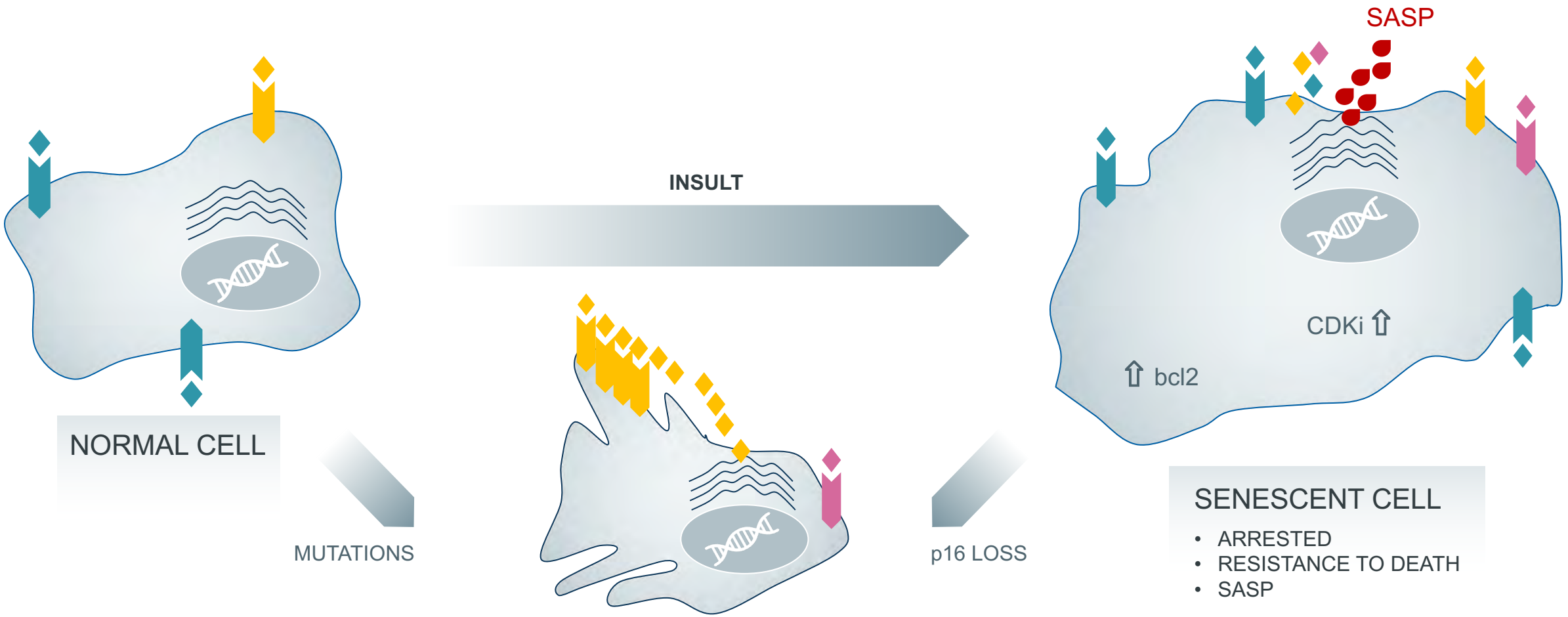
Normal, senescent or transformed

- DNA damaging
- Cytotoxics
- Radiation
- Apoptosis inducing
- Self-death MOAs
- Protein processing



- T cell cytotoxicity
- ADCC
- ADC
- Non-T cell immunotherapy
- Lytic virus
- Metabolic dependency

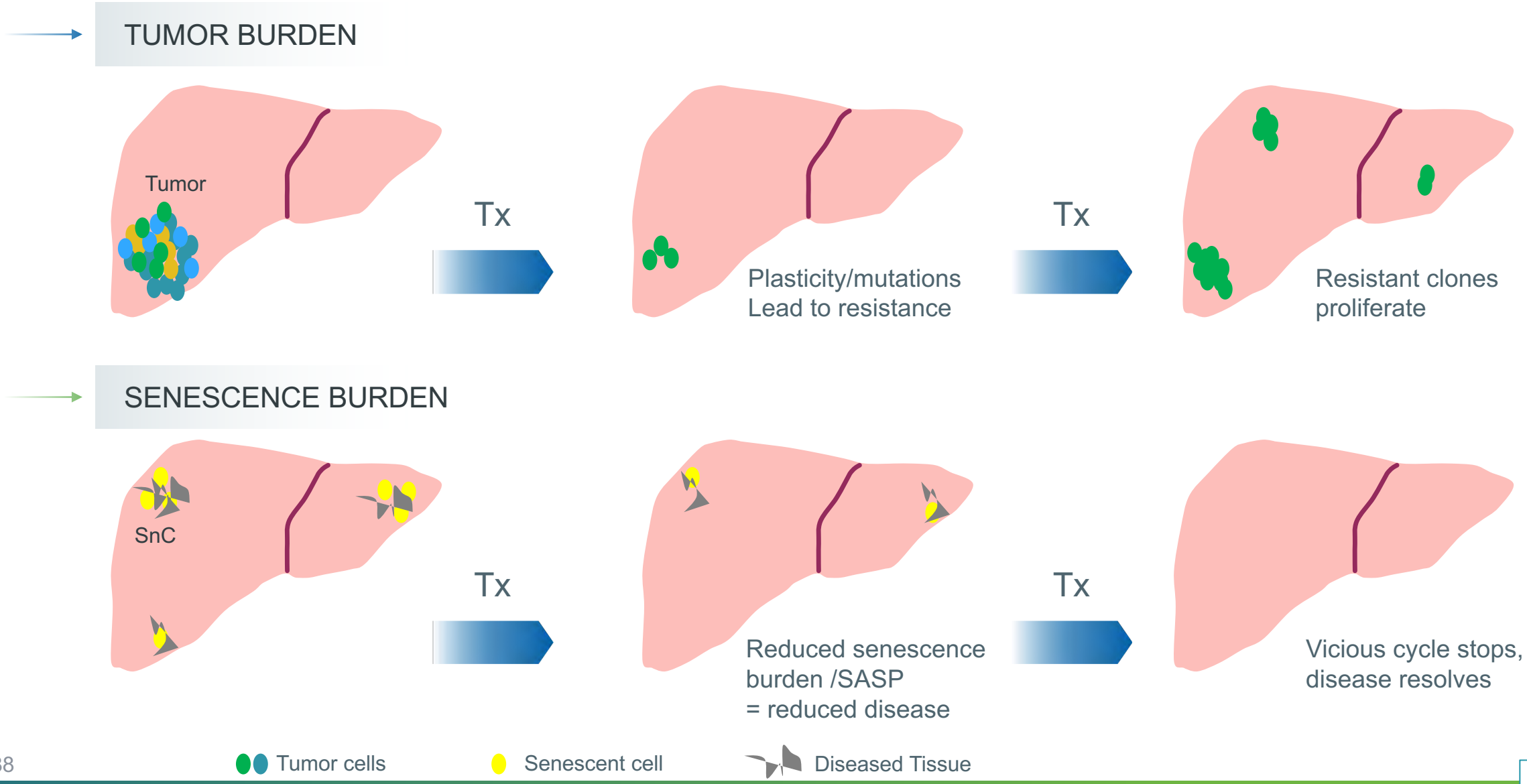
DIFFERENT PHENOTYPES, DISTINCT VULNERABILITIES



SENESCENCE BIOLOGY INSIGHTS GUIDE OUR BETS

	Transformed	Senescent
Proliferation/division	✓	●
Mutations/clonality	✓	●
Neoantigens/T-cells	✓	●
Apoptosis/self-death	✓	✓
Metabolic dependency	✓	✓
Non-T cell immmunotherapy	✓	✓
Protein synthesis	✓	✓
Lytic viruses	✓	✓

THE ISSUE OF RESISTANCE: NO PLASTICITY IN SnCs



LOCAL TO SYSTEMIC DELIVERY

SYSTEMIC DELIVERY

Senolytic MOA	Known Clinical SAEs
1	Neutropenia
2	Thrombocytopenia
3	Diarrhea
4	Anemia

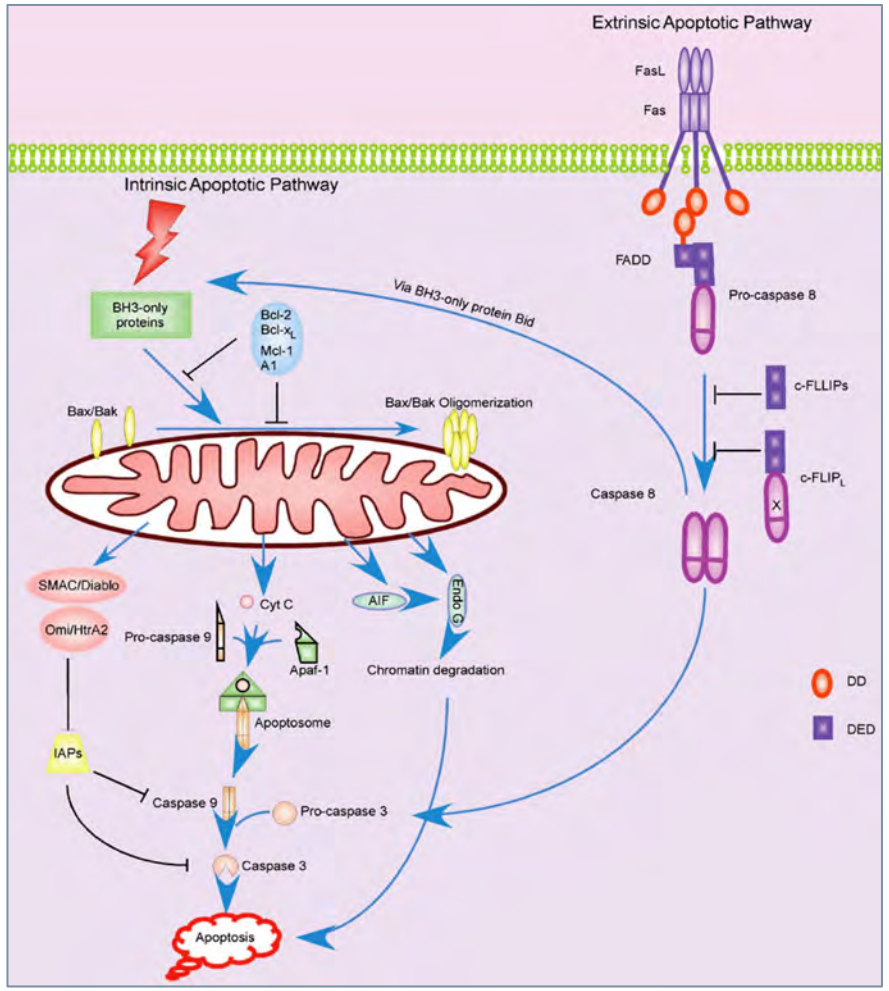
Common SAEs are a result of bone marrow and gut exposure

LOCAL DELIVERY & TARGETING

UBX Tx	Tissue : Plasma ratio
Lung (OA)	>400:1
Kidney (IV)	171:1
Eye (IVT)	>10,000:1
Liver (IV)	65:1

Rational drug design optimizes for senolytic activity and against systemic exposure

INTRINSIC/EXTRINSIC APOPTOTIC PATHWAYS

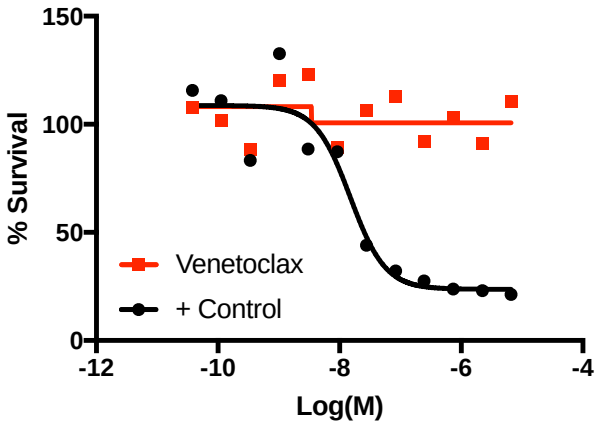


ORIGINAL ARTICLE

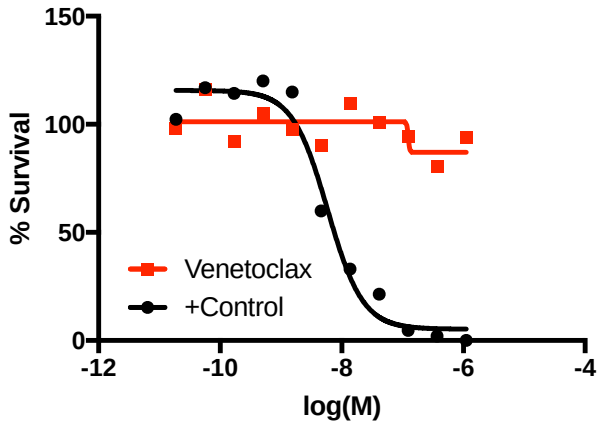
Venetoclax–Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukemia

J.F. Seymour, T.J. Kipps, B. Eichhorst, P. Hillmen, J. D'Rozario, S. Assouline, C. Owen, J. Gerecitano, T. Robak, J. De la Serna, U. Jaeger, G. Cartron, M. Montillo, R. Humerickhouse, E.A. Punnoose, Y. Li, M. Boyer, K. Humphrey, M. Mobasher, and A.P. Kater

Sn Retinal cells

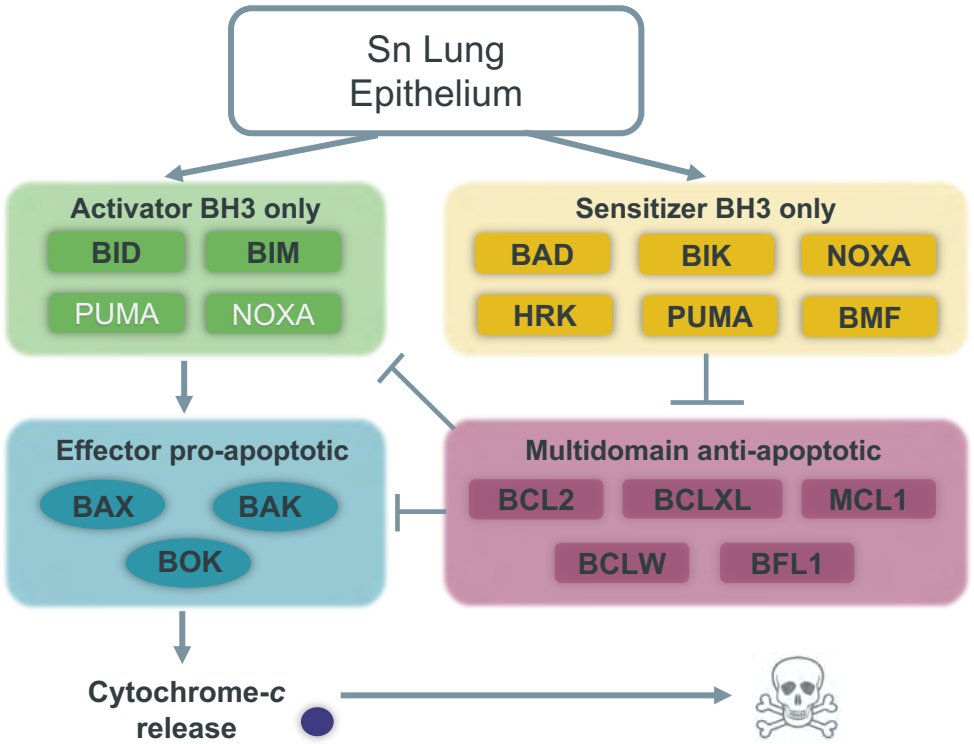


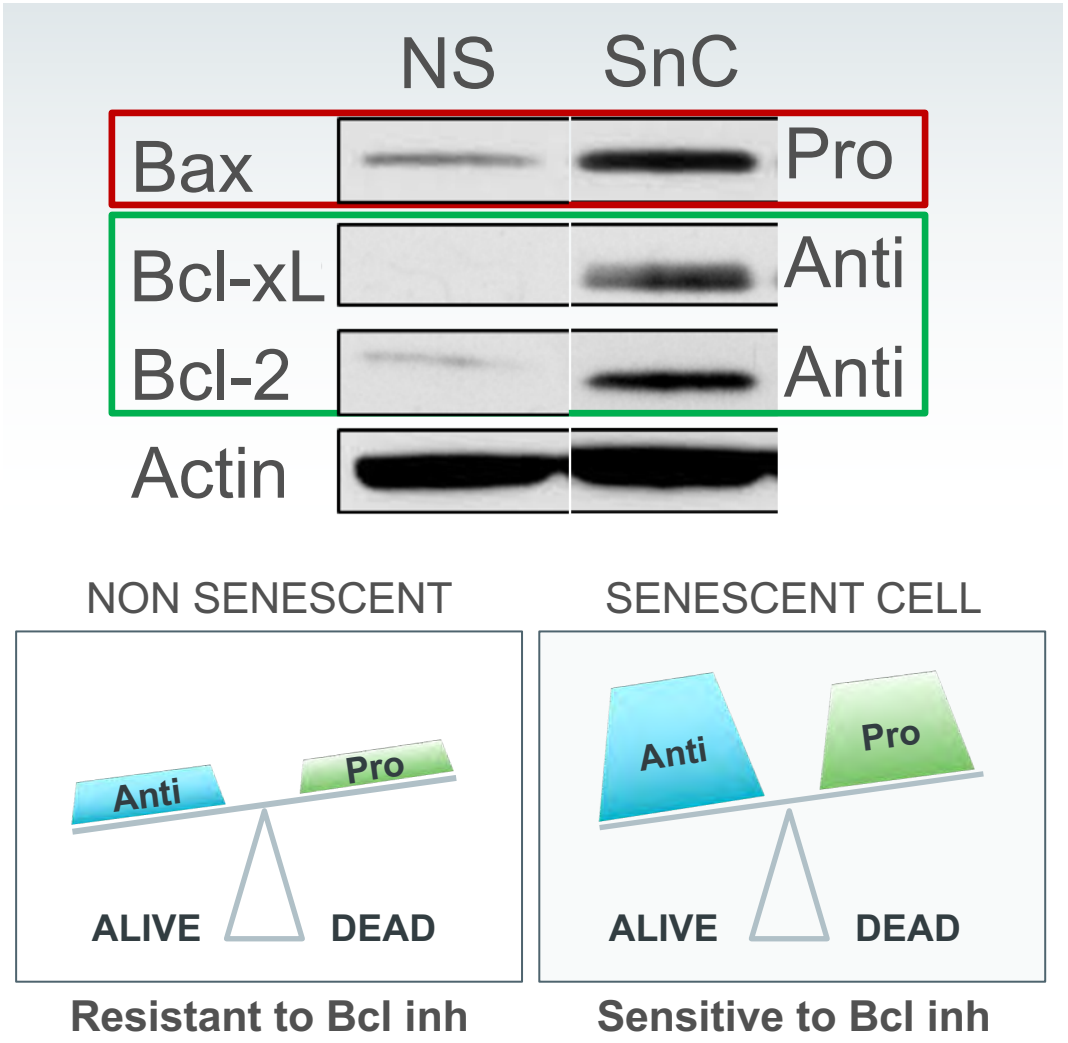
Sn Lung epithelial cells



RATIONAL SENOLYTIC DESIGN: FIT FOR INDICATION

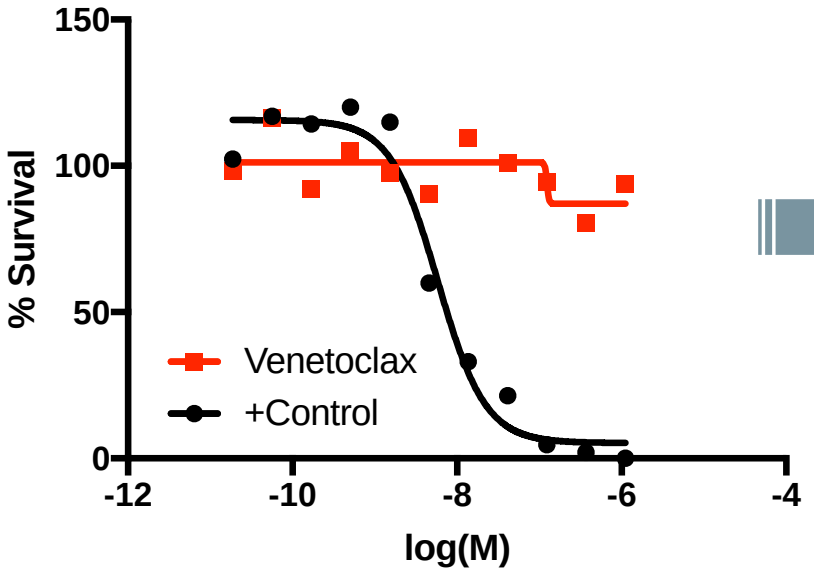
What are the players in senescent lung epithelial cells?



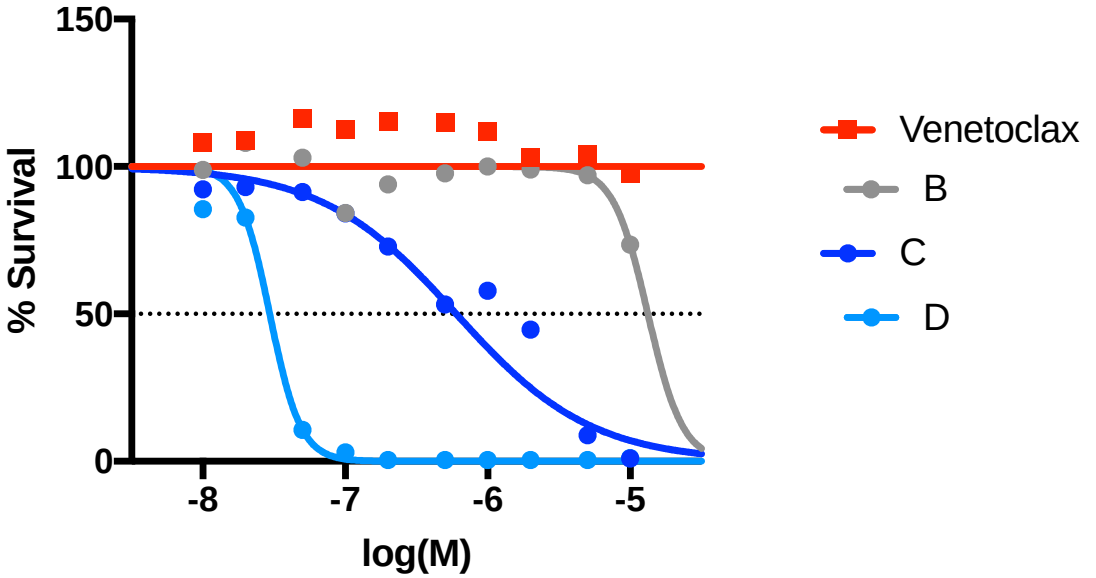


UNDERSTANDING PATHWAYS IN SnCs LEADS TO POTENT SENOLYTIC STRATEGIES

Sn HBE (Lung)



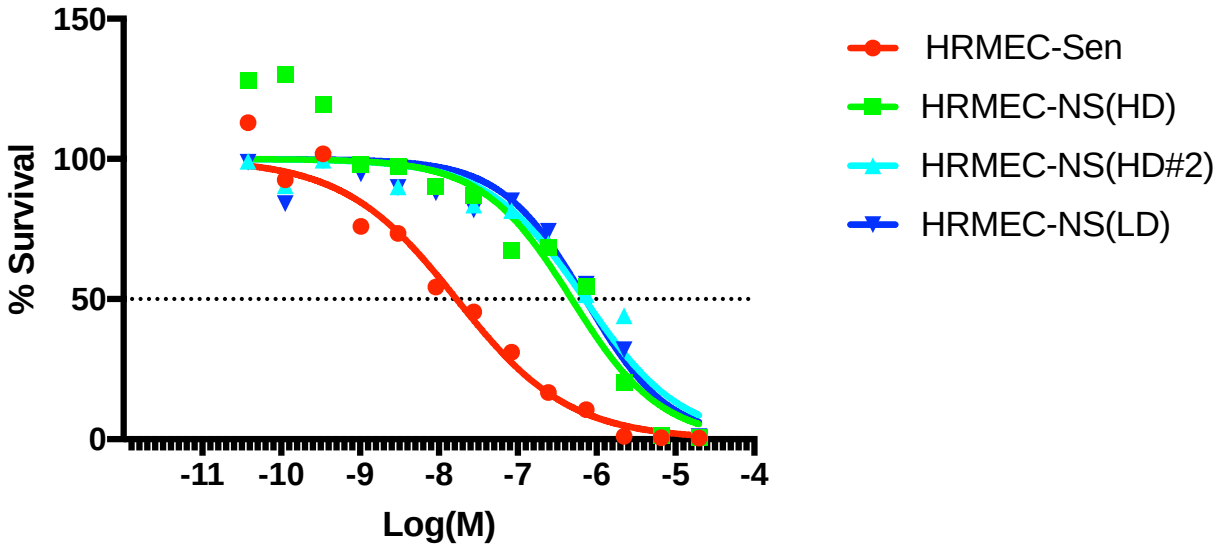
Sn HBE (Lung)



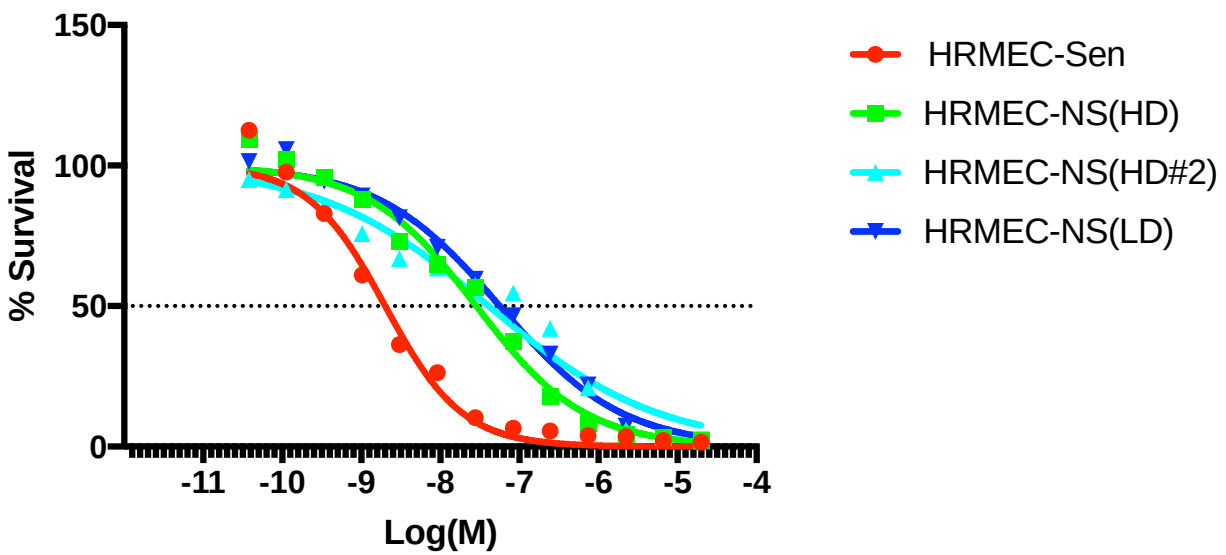
IS SELECTIVITY FOR A SENESCENT CELL POSSIBLE?

APOPTOSIS PATHWAYS

MOA#1



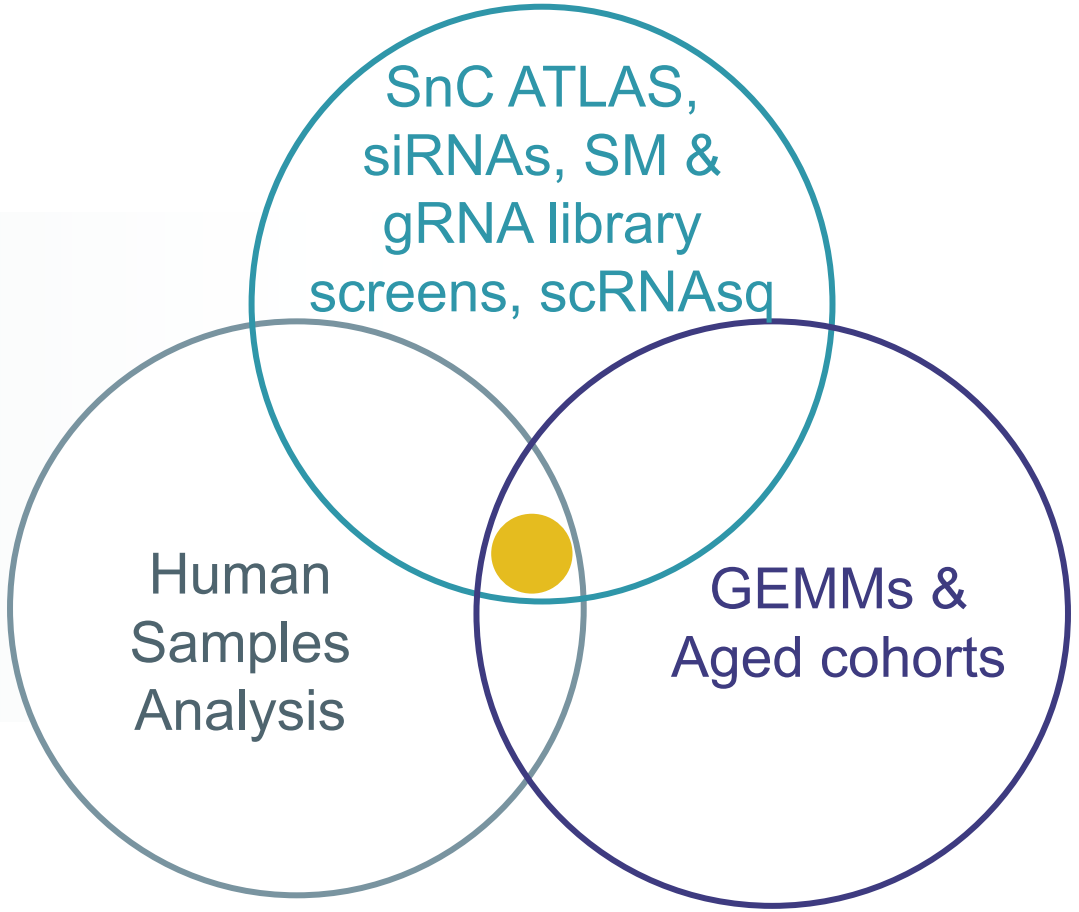
MOA#2



Specificity has not been achieved but 10-100 fold selectivity is possible

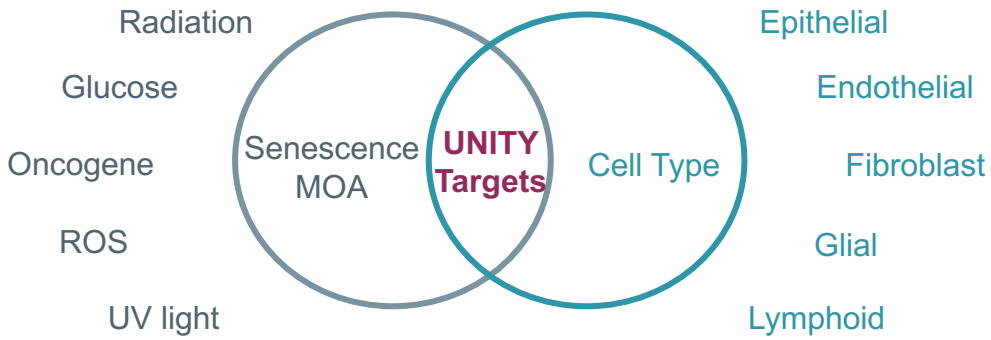
UNITY INSIGHTS IN SENESCENCE BIOLOGY LEAD TO NEW TARGET SPACE

Intersection delivers senescence targets

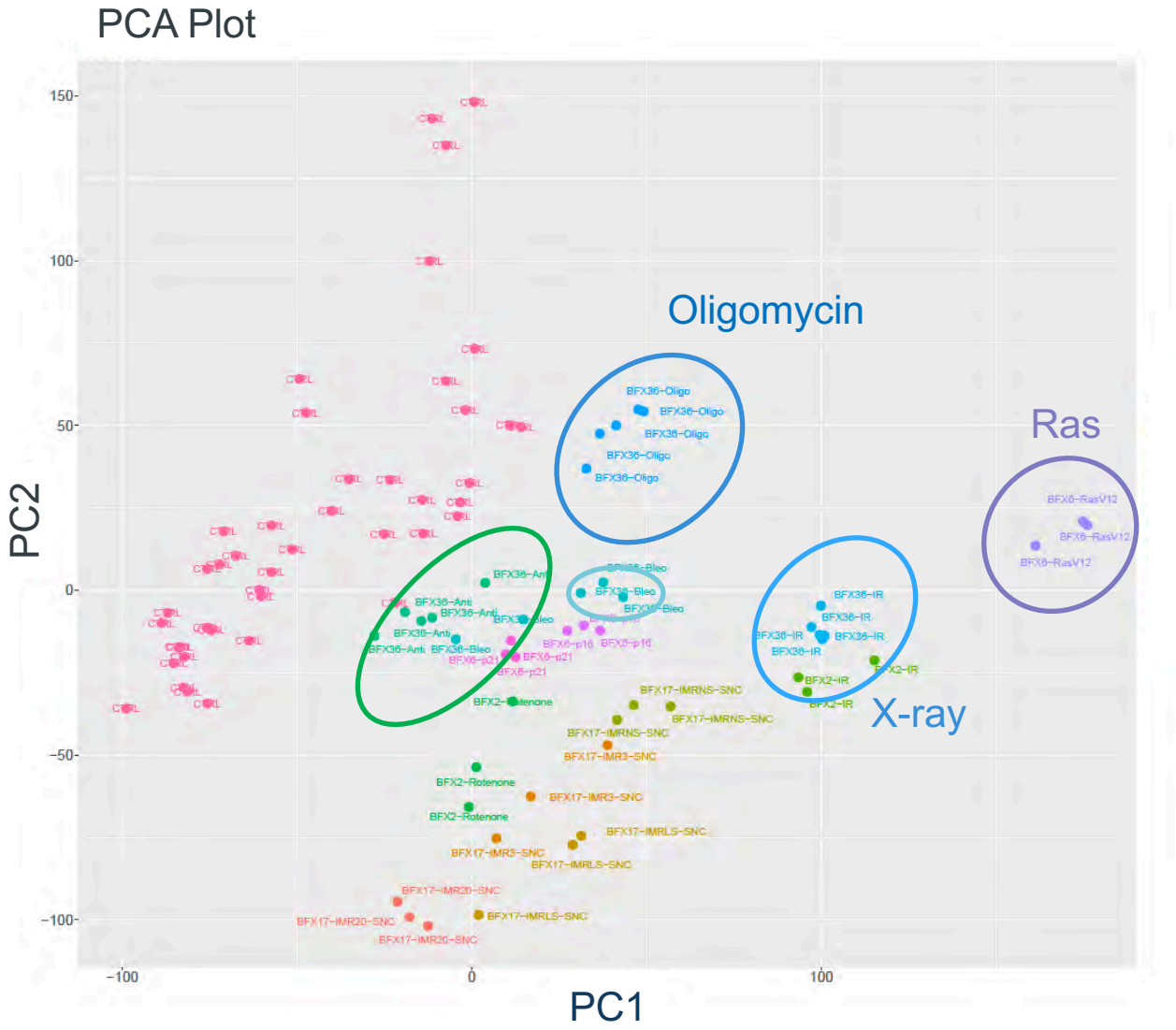


Success combines human, *in vitro* & *in vivo* platforms

GENE EXPRESSION PROFILE VARIES WITH Sn INDUCTION MECHANISM

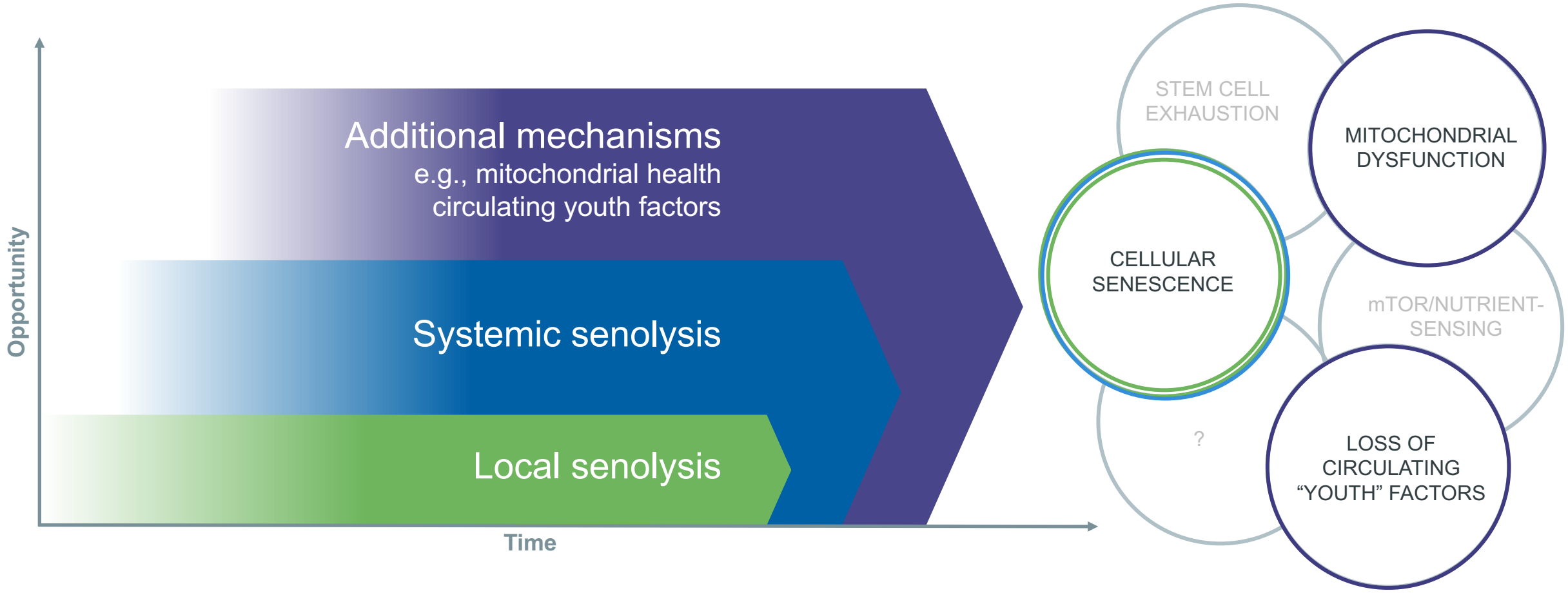


Need to pair mechanism with cell-type



BROAD STRATEGY TO EXTEND HEALTHSPAN

Early effort in local senolytic therapy will expand to systemic senolytics and other mechanisms



UNITY plans to address multiple modalities to fully enable potential of age-related therapies

UBX0101 SNAPSHOT + PANEL Q&A

Moderated by Keith Leonard,
Chairman and Chief Executive Officer

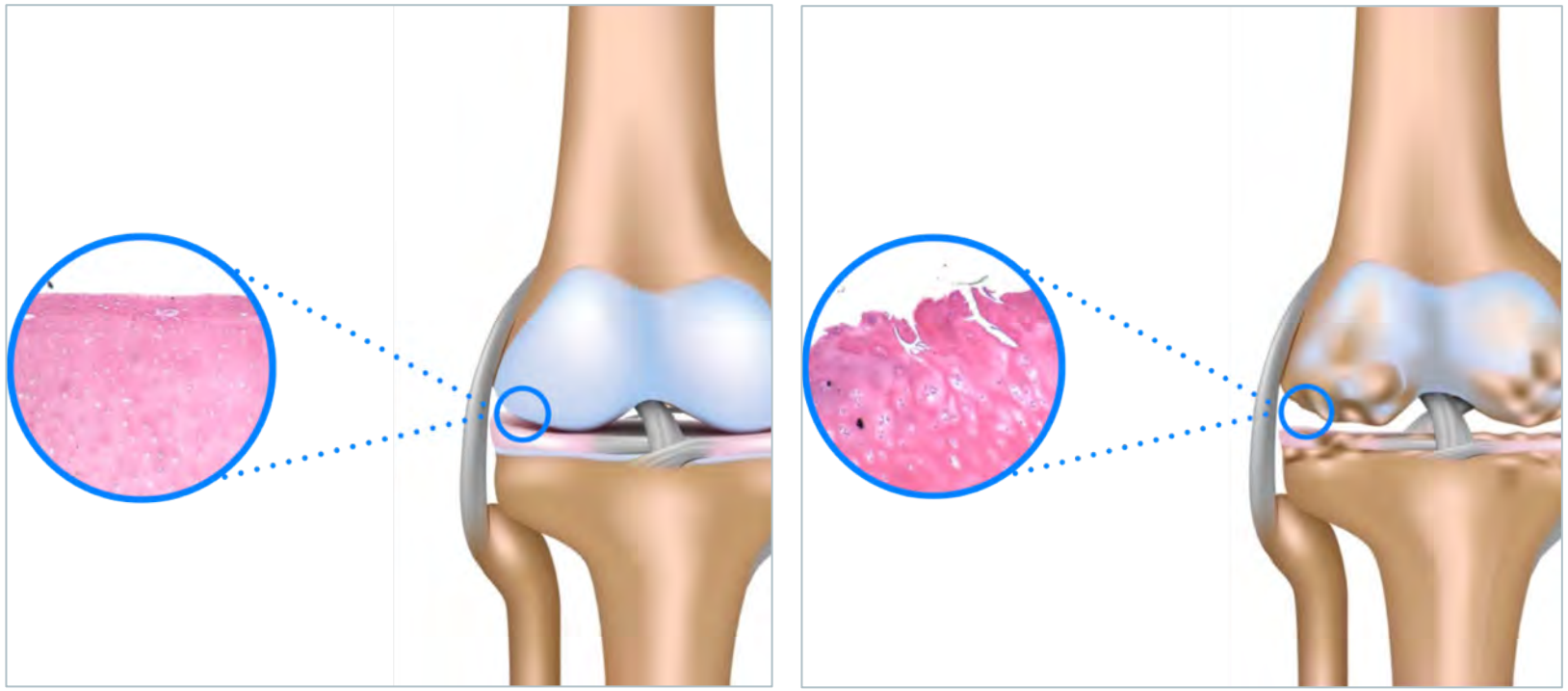
UNITY BIOTECHNOLOGY

UNITY PIPELINE

Broad therapeutic potential, addressing multiple mechanisms of aging

OSTEOARTHRITIS

A widespread disease; standard of care is pain mitigation or joint replacement

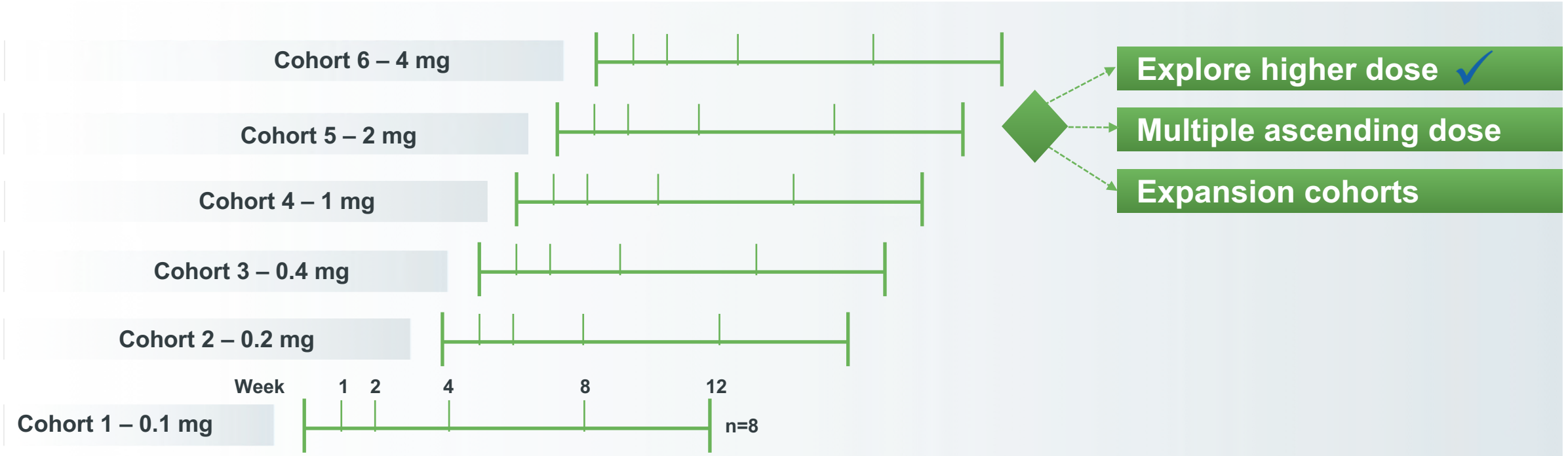


~10-15% of global population over 60 years of age

Aggregate annual expense associated with OA estimated at >$150B per year in US

Current treatments are NSAIDs, steroids, knee replacement, and acquiescence

UBX0101 PHASE 1 STUDY ENABLES OPTIONALITY



DESIGN

- Patients with OA, KL 1-4 + active synovial inflammation by MRI
- N=48
- Active to Placebo: 3:1
- Duration: 12 weeks
- Assessments: 1,2,4,8,12 weeks

MEASURES

- Safety
- Plasma PK
- Semi-quantitative assessment of synovitis by MRI
- 11-Point NRS pain assessment
- WOMAC-A (pain), WOMAC-B (function), & total WOMAC
- Synovial fluid SASP factors

PANEL Q&A

JUDY CAMPISI, PHD
The Buck Institute for Research on Aging
Lawrence Berkley National Laboratory

JAN VAN DEURSEN, PHD
The Mayo Clinic

DAN MARQUESS, D. PHIL
Chief Scientific Officer

NATHANIEL DAVID, PHD
Co-founder & President

PEDRO BELTRAN, PHD
SVP of Biology

MODERATED BY

KEITH LEONARD, MS, MBA
Chief Executive Officer

Health·span |helth' span| *noun*

The period of one's life unburdened by the diseases of aging

See also: anti-aging, healthy longevity

HEALTHSPAN