Buck Institute for Research on Aging

01 August, 2017

Research Advisory Committee on Gulf War Veteran's Illnesses

Senescent cells and aging

Lawrence Berkeley National Laboratory

Disclosure:

I am a scientific co-founder of UNITY Biotechnology

Aging = susceptibility to (chronic) disease

not a coincidence! caused by basic aging process(es)

Neurodegeneration, memory loss

Osteoporosis

Macular degeneration, hearing loss

Heart disease

Vascular disease

Sarcopenia, frailty

Diabetes, metabolic syndrome

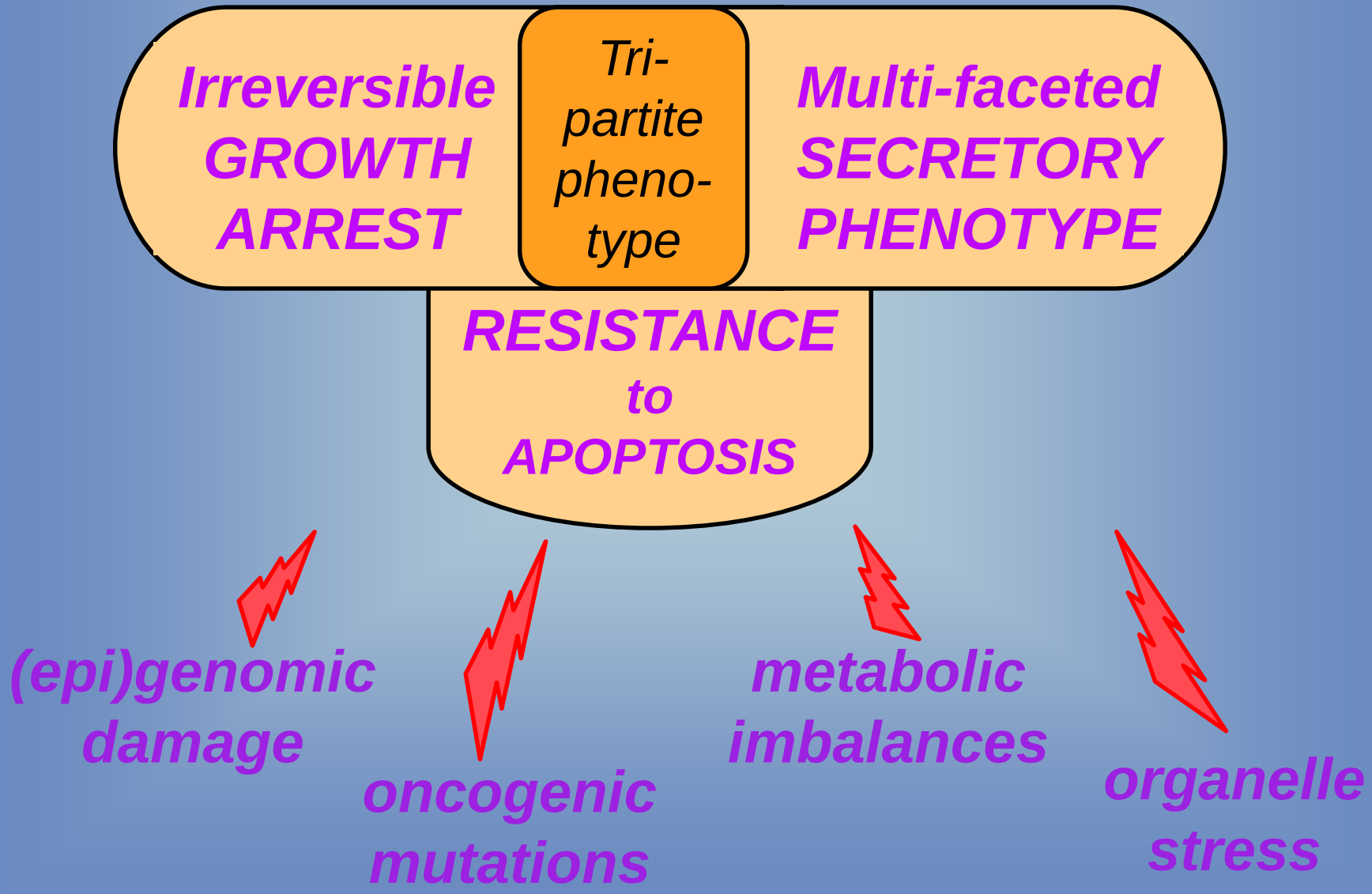
Decreased lung, kidney, etc function

CANCER

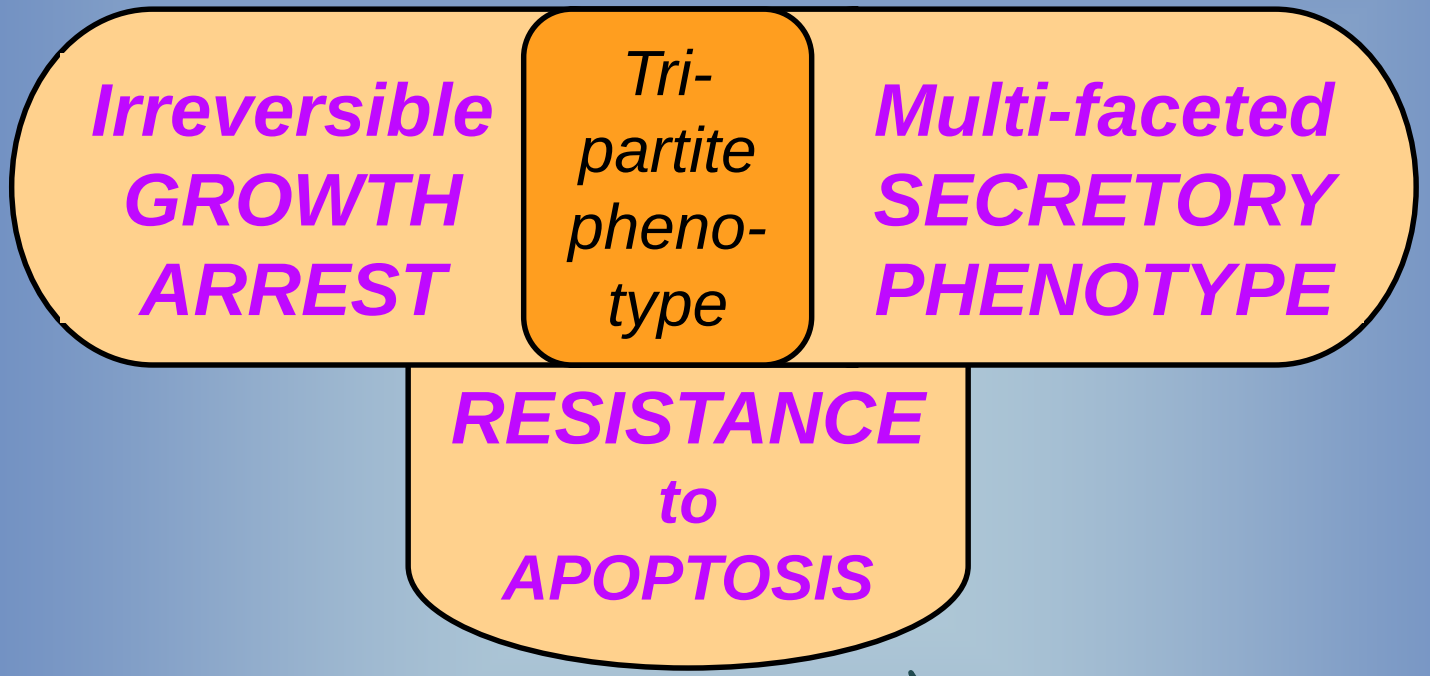
Cellular senescence: a candidate basic aging process

What is cellular senescence?

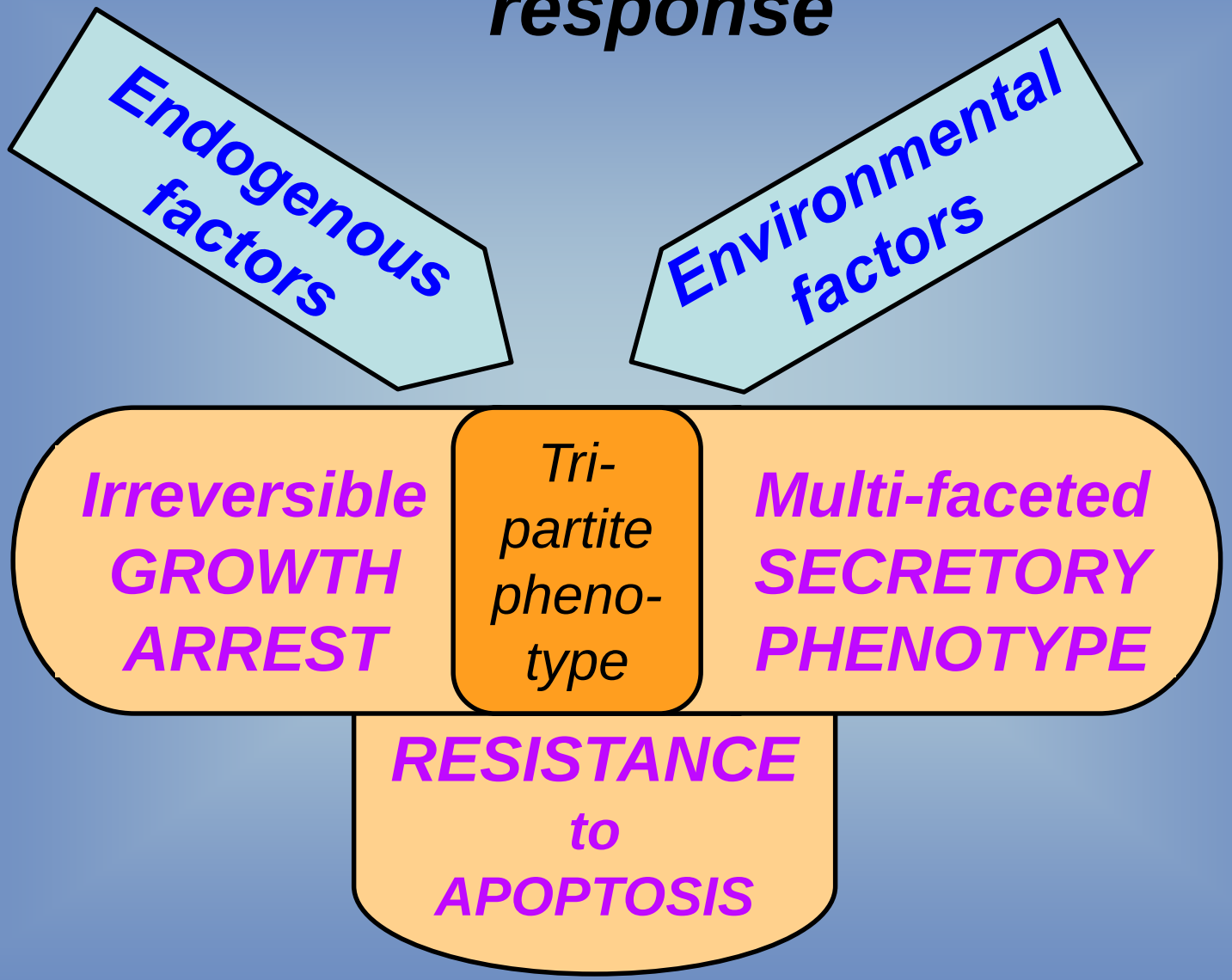
Cellular senescence, a complex stress response



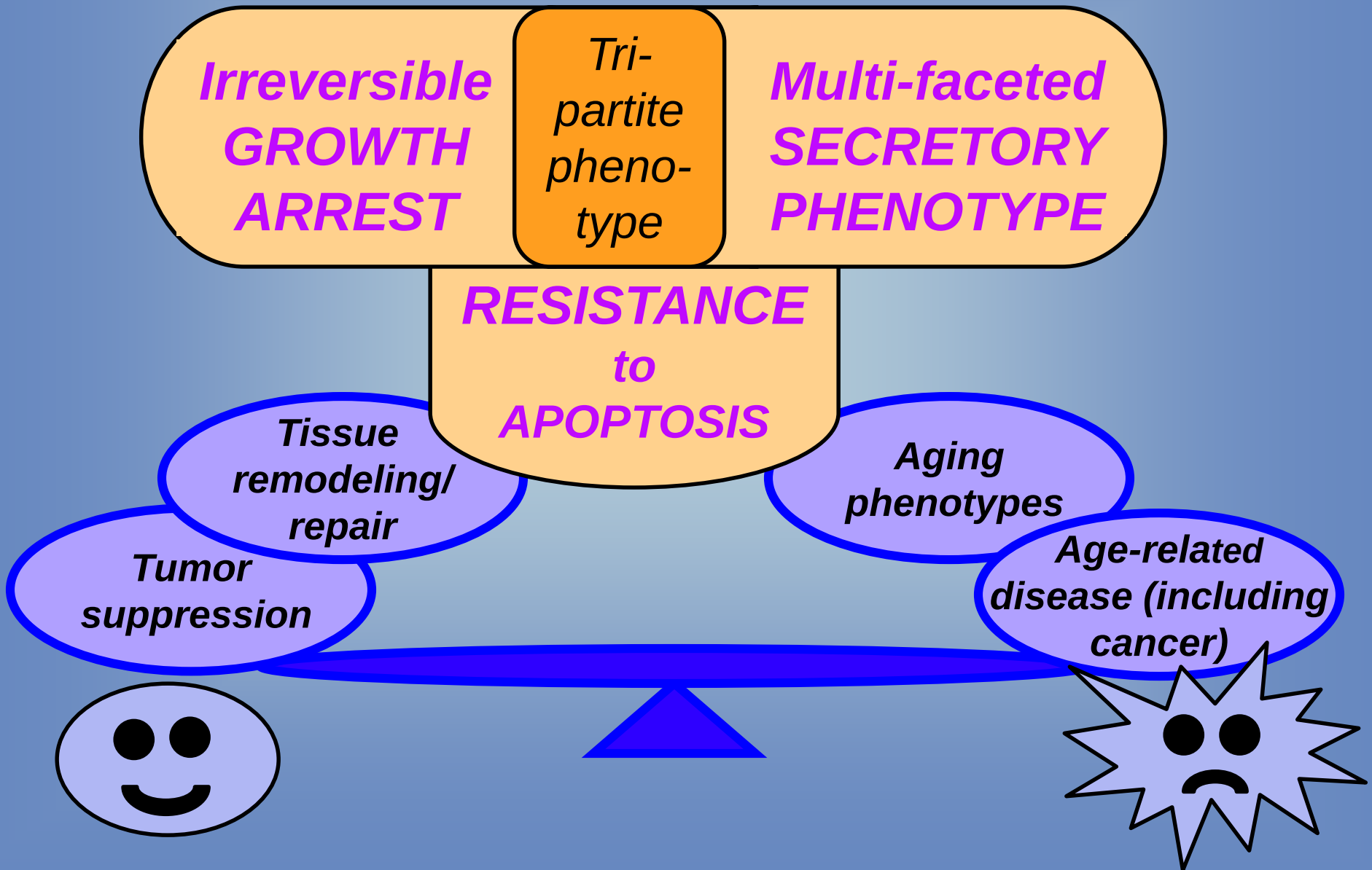
Cellular senescence, a physiological response



Cellular senescence, a complex stress response

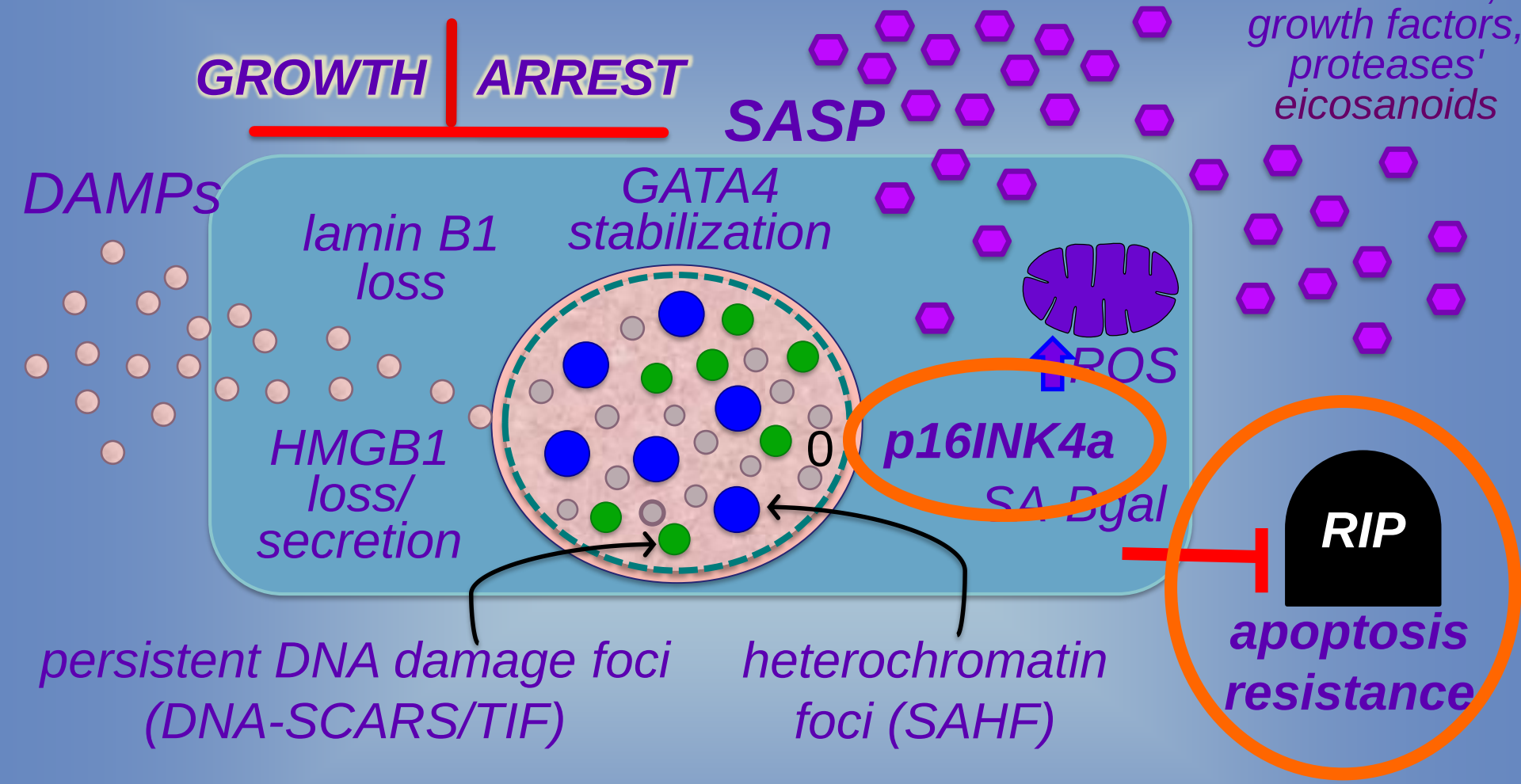


Cellular senescence, an evolutionary balancing act



How are senescent cells defined?

What defines a senescent cell?



ps – there are no senescence-SPECIFIC markers

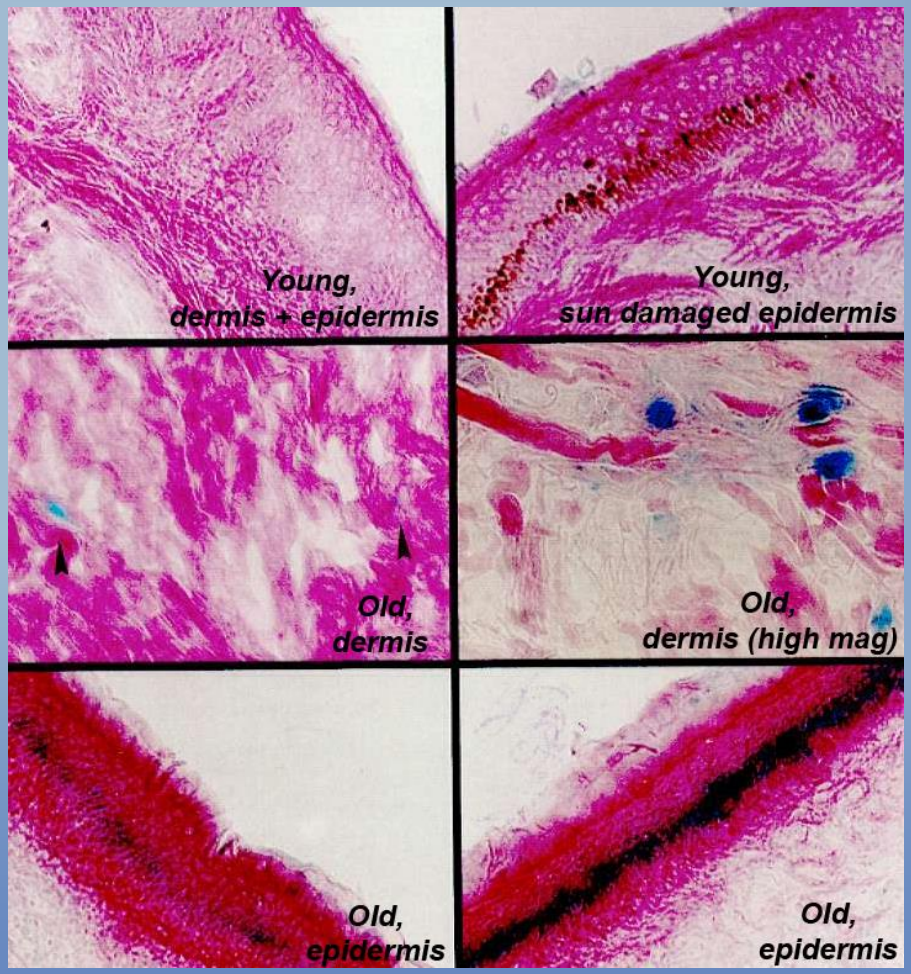
Dimri, PNAS, 1995; Beausejour, EMBO J, 2003; Narita, Cell, 2003; Rodier, Nature Cell, 2009; Rodier, J Cell Sci, 2011; Freund, Mol Cell Biol, 2012; Kang, Science, 2015; Wiley, unpublished

When and where do senescent cells occur?

Senescent cells increase with age in many tissues

Human, non-human primates, rodents, zebrafish
skin, retina, liver, spleen, aorta, kidney, lung, etc.

SA-Bgal staining, human skin



young

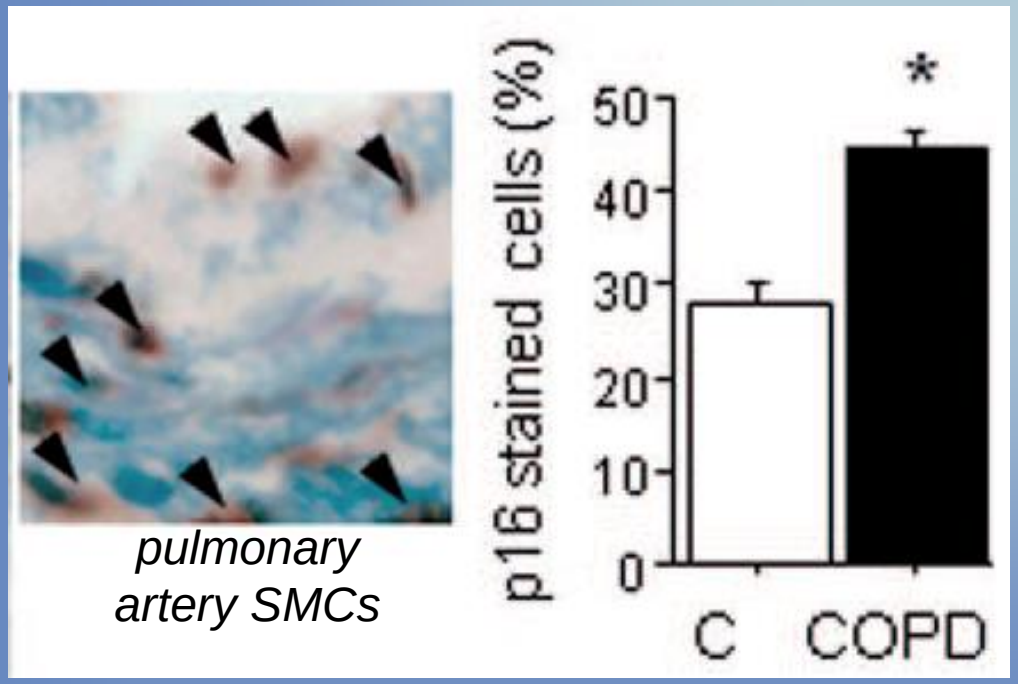
old

old

Dimri et al., PNAS, 1995

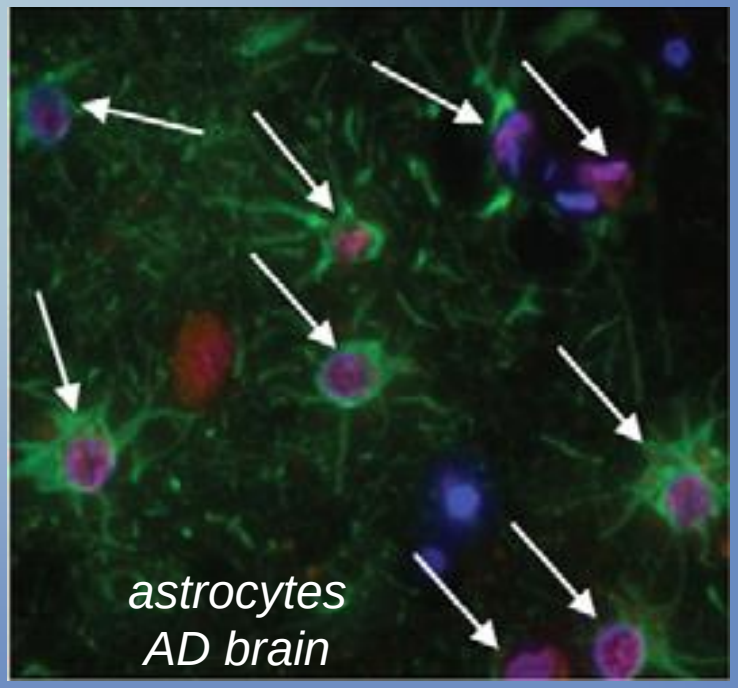
Senescent cells are present at sites of many age-related pathologies

Venous ulcers, atherosclerotic plaques, arthritic joints, COPD, visceral fat, AD brain, etc
Benign prostatic hyperplasia, pre-neoplastic lesions



pulmonary artery SMCs

Noureddine et al., Circulation, 2011



astrocytes AD brain

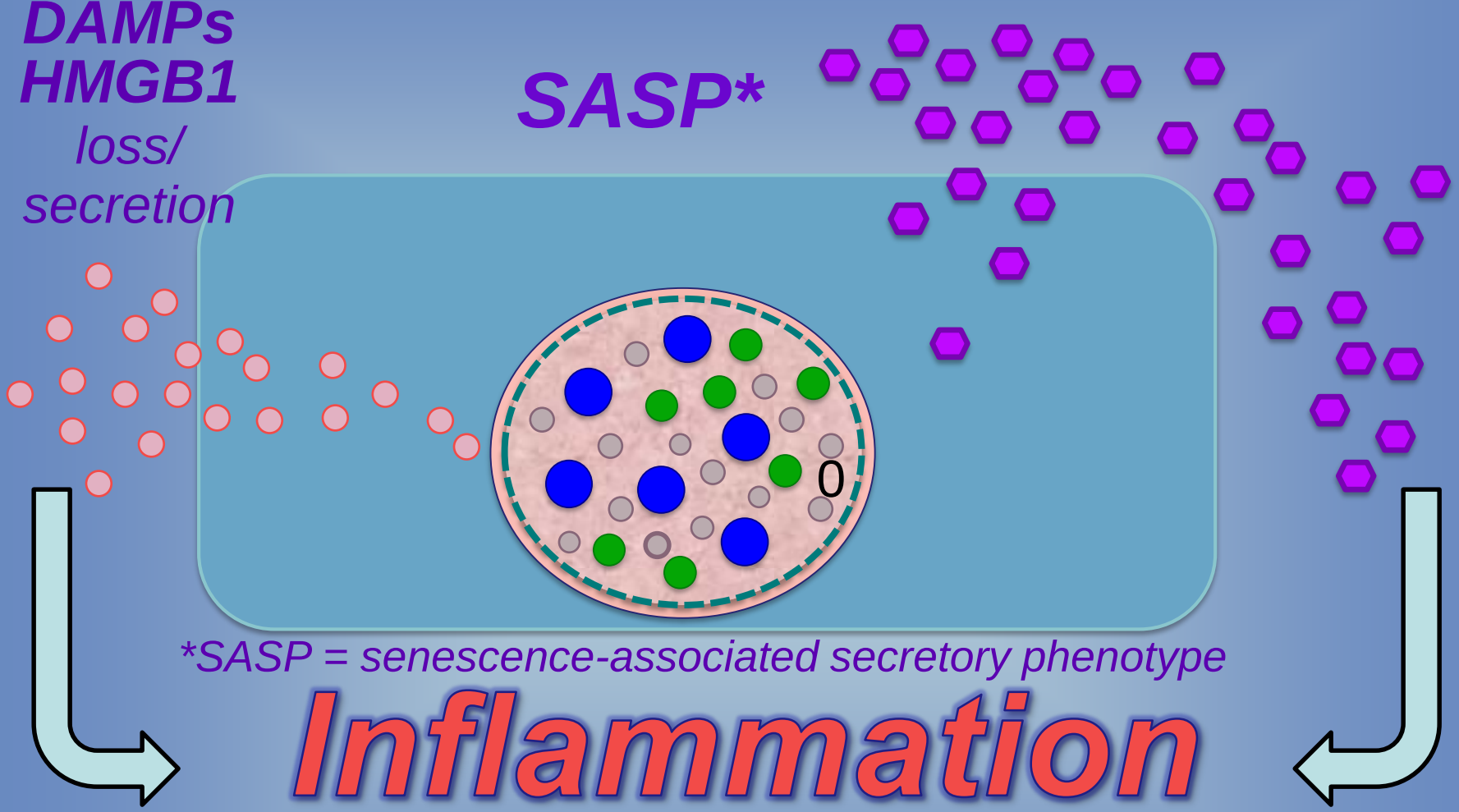
Bhat et al, 2012, PLoS One 7:e45069.

Senescent cells ….

Present at the right time and place to drive aging and multiple age-related diseases

How do senescent cells drive aging?
DO senescent cells drive aging?

How might they do it?



**SASP = senescence-associated secretory phenotype*

Inflammation

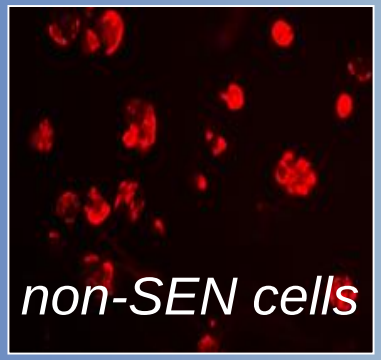
destroys tissues

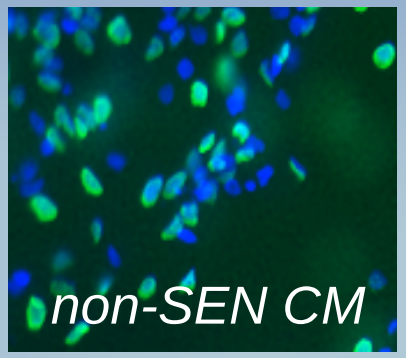
disrupts normal cell/tissue functions

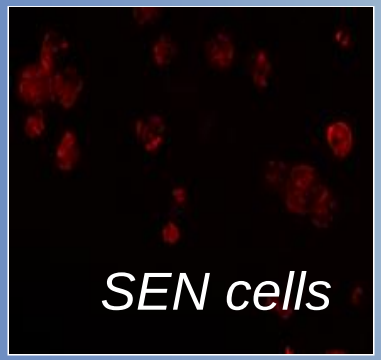
prevents stem cell functions

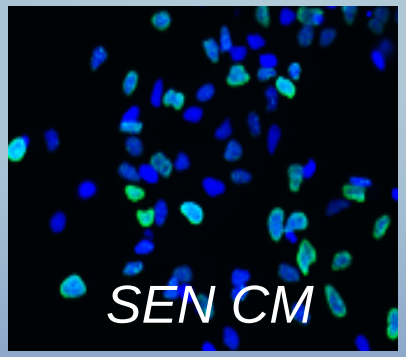
promotes cancer

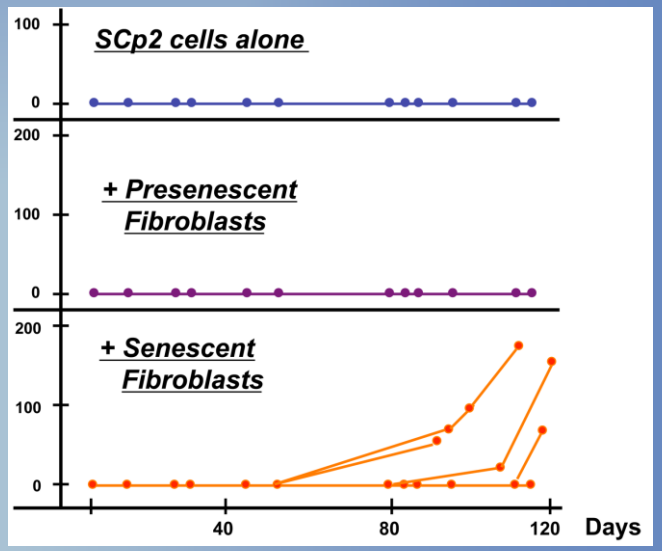
Senescent cells have potent paracrine activities on normal, premalignant and malignant cells

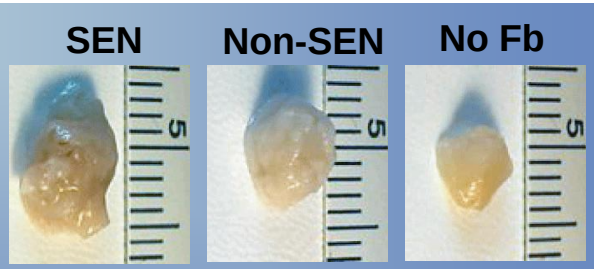










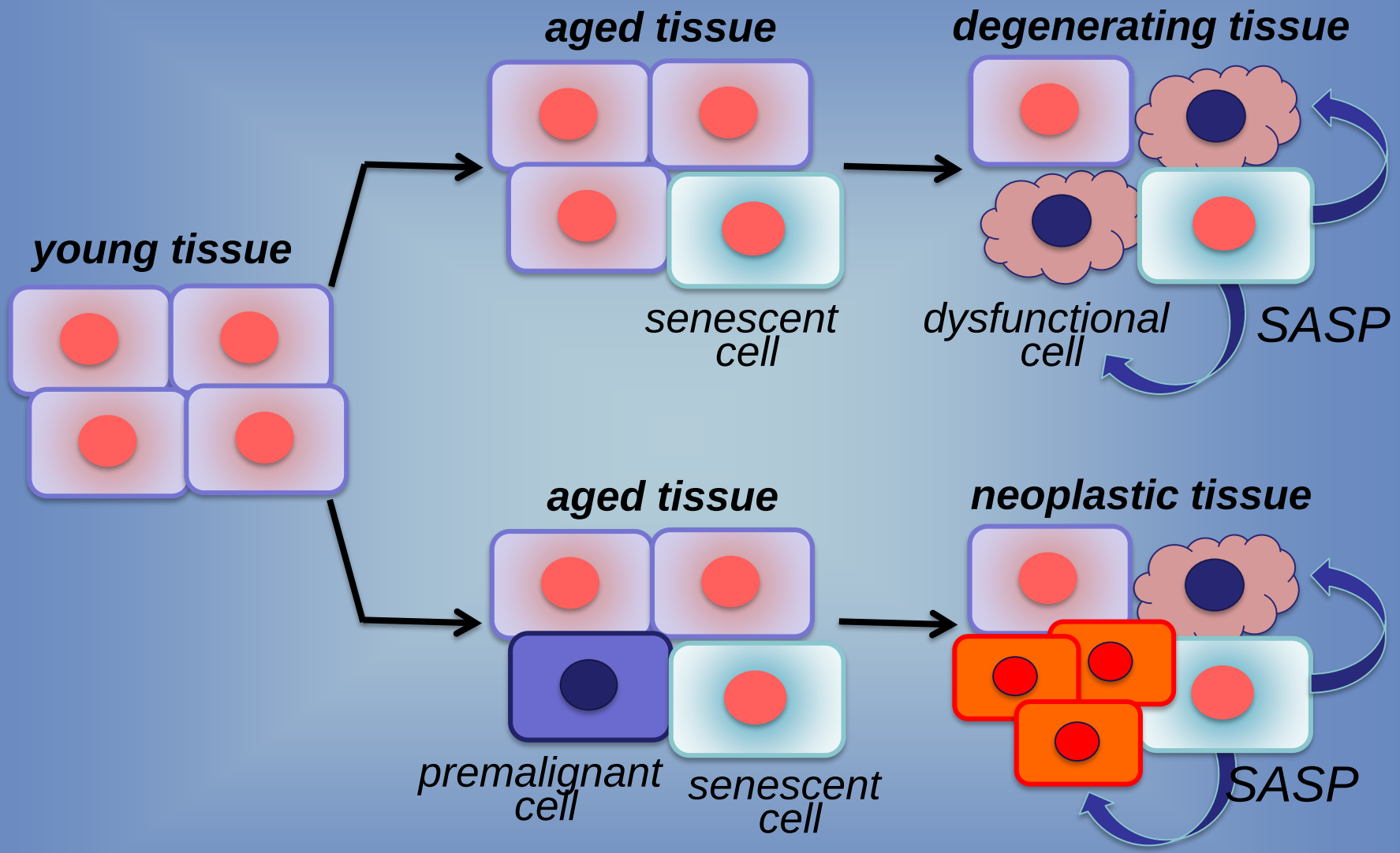


disrupt normal structures, functions

disrupt stem cell functions

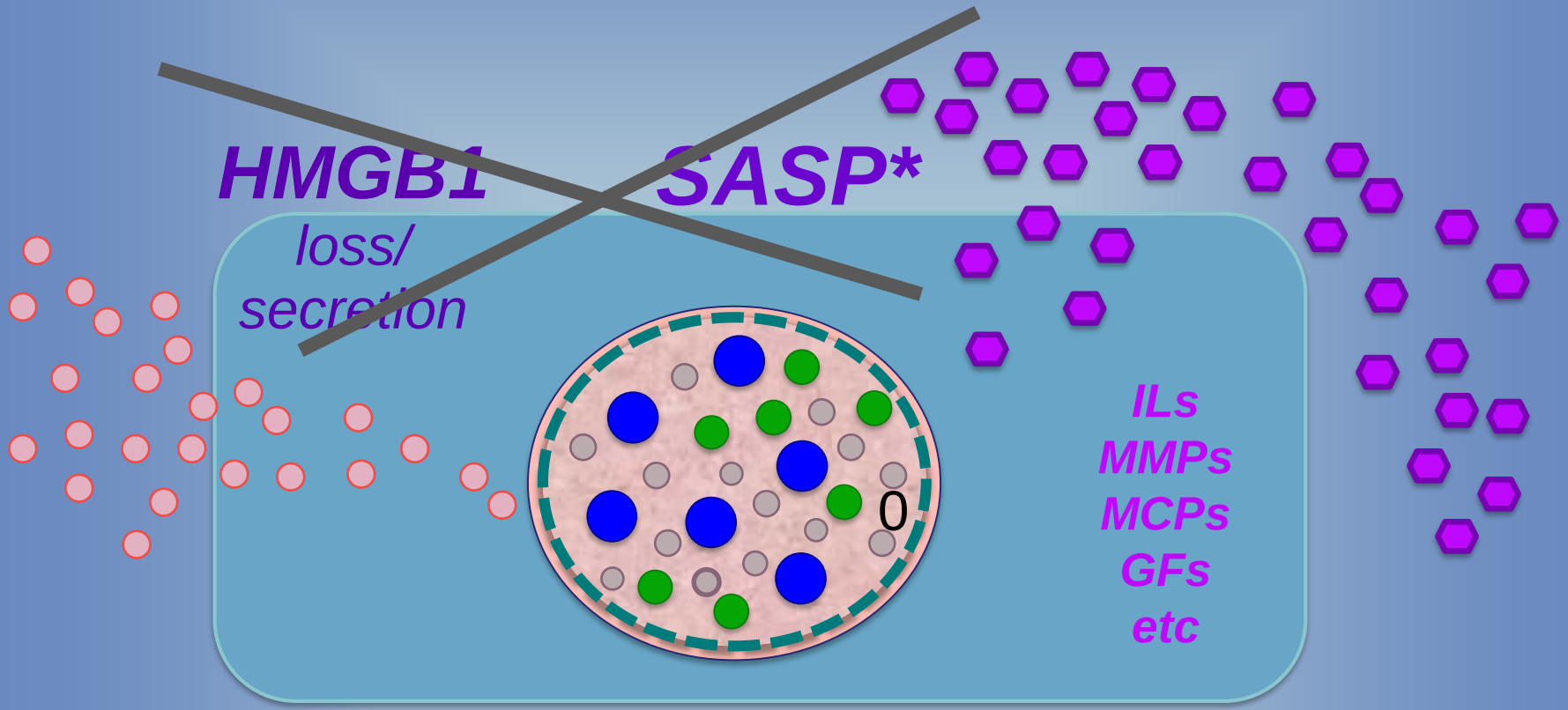
promote malignant phenotypes

Parrinello et al, J Cell Sci, 2005; Chintar et al, unpublished collaboration with Andersen lab; Krtolica et al, PNAS, 2001; Coppe et al, PLoS One, 2010


young tissue
aged tissue
senescent cell
degenerating tissue
dysfunctional cell
SASP
aged tissue
premalignant cell
senescent cell
neoplastic tissue
SASP

Are you depressed yet?

Strategies to combat aging phenotypes and pathologies fueled by senescent cells



Suppress secretory phenotype

What are the pathways and molecules that drive the secretory phenotype?

(three pathways relevant to cancer and aging)

The DNA Damage Response (DDR) pathway

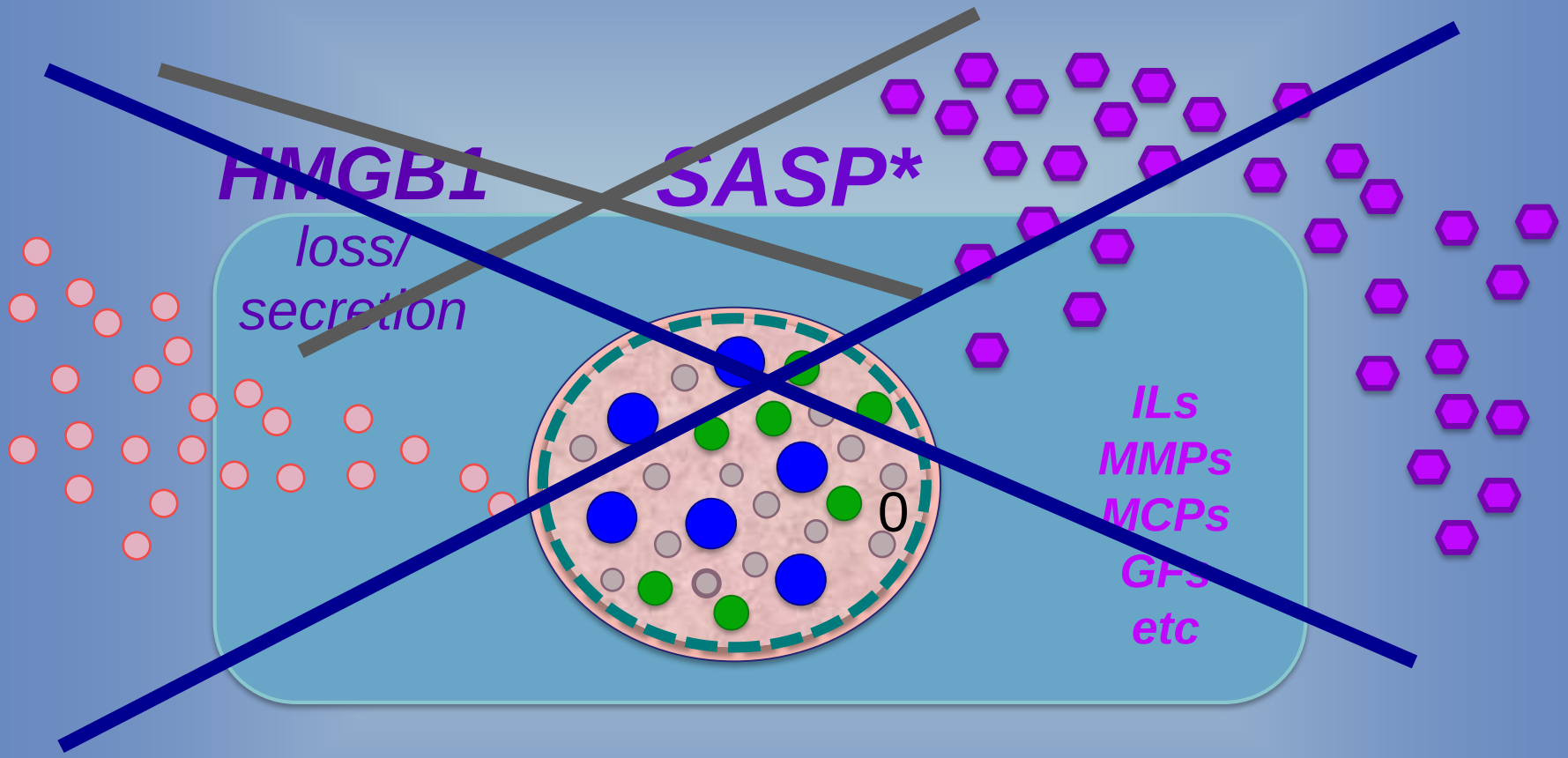
The p38MAPK-NF-kB pathway

The mTOR pathway

These are important pathways that are required for tissue homeostasis

Drugs that suppress the SASP require continuous dosing (a safe drug?)

Strategies to combat aging phenotypes and pathologies fueled by senescent cells



Suppress secretory phenotype

Kill/eliminate senescent cells

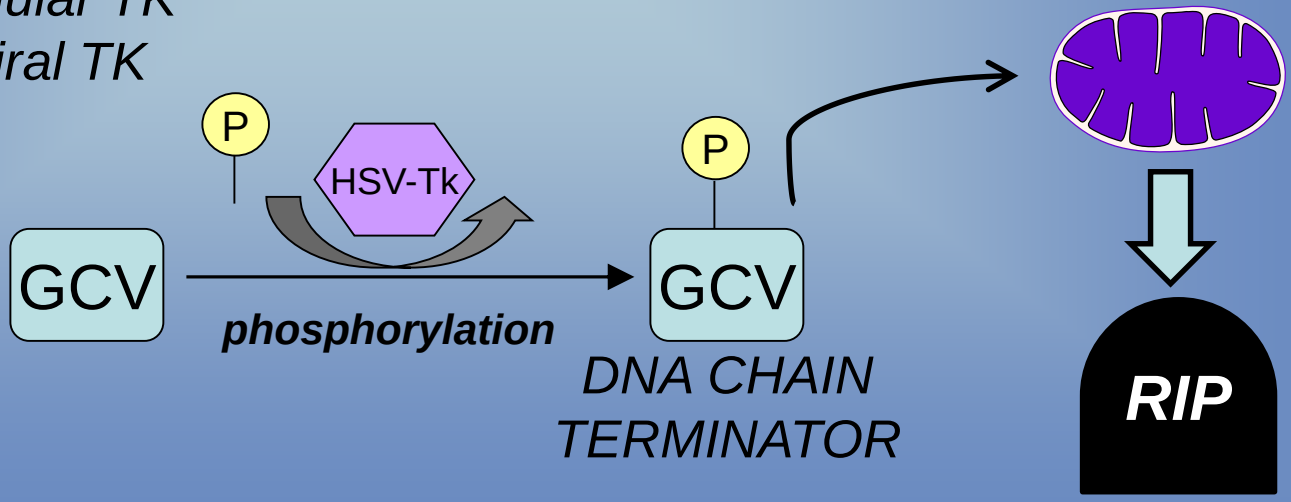
p16-3MR (tri-modal reporter) mice

BAC containing murine INK4a locus inserted into mouse genome

3MR knock-in: downstream of p16^{INK4a} promoter + inactivation of p14ARF
Mice have normal (diploid) copies of p16 and p14 genes

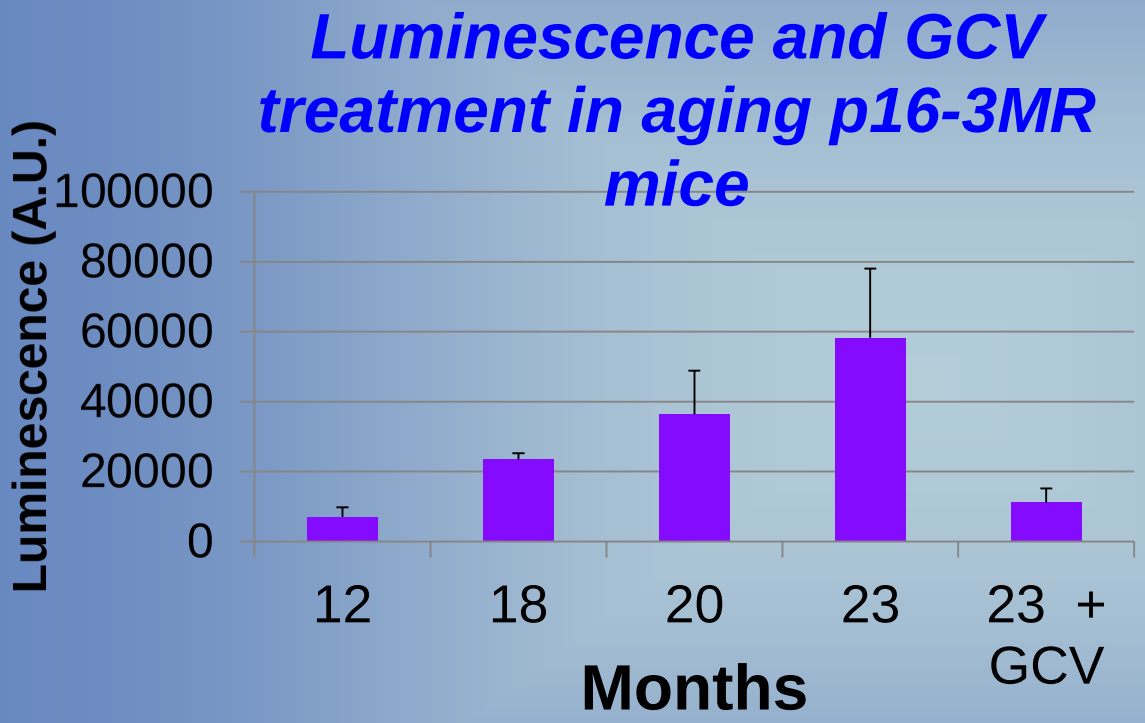
3MR: renilla luciferase; modified red fluorescent protein; herpes simplex virus thymidine kinase

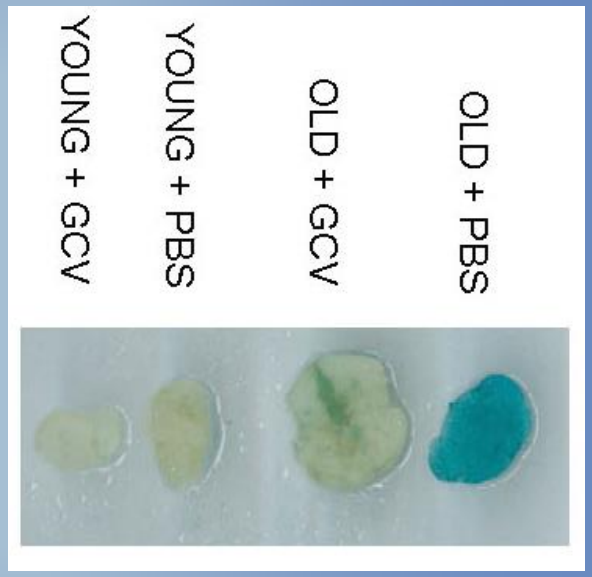
GCV = gancyclovir
Low affinity for cellular TK
High affinity for viral TK



Demaria et al, Dev Cell, 2014; Laberge et al, CDD

Senescent cells can be eliminated from naturally aged mice





parallel age-related increase in endogenous p16INK4a, 3MR, IL-6, etc; all reduced by GCV treatment

Senescent cells …..

Alzheimer's and Parkinson's disease

Atherosclerosis

Cardiovascular dysfunction

Cancer metastasis and recurrence

Chemotherapy (HAART) cardiotoxicity, fatigue

Cognitive decline/loss of neurogenesis

Diabetes

Myeloid→lymphoid skewing

Osteoarthritis

Sarcopenia/frailty

Wound healing, tissue regeneration

** published; * unpublished*

Cellular senescence

Adverse effects of chemotherapy

Parkinson's disease and brain aging

Injury-induced osteoarthritis

Wound healing

Many cancer + other therapies → DNA damage

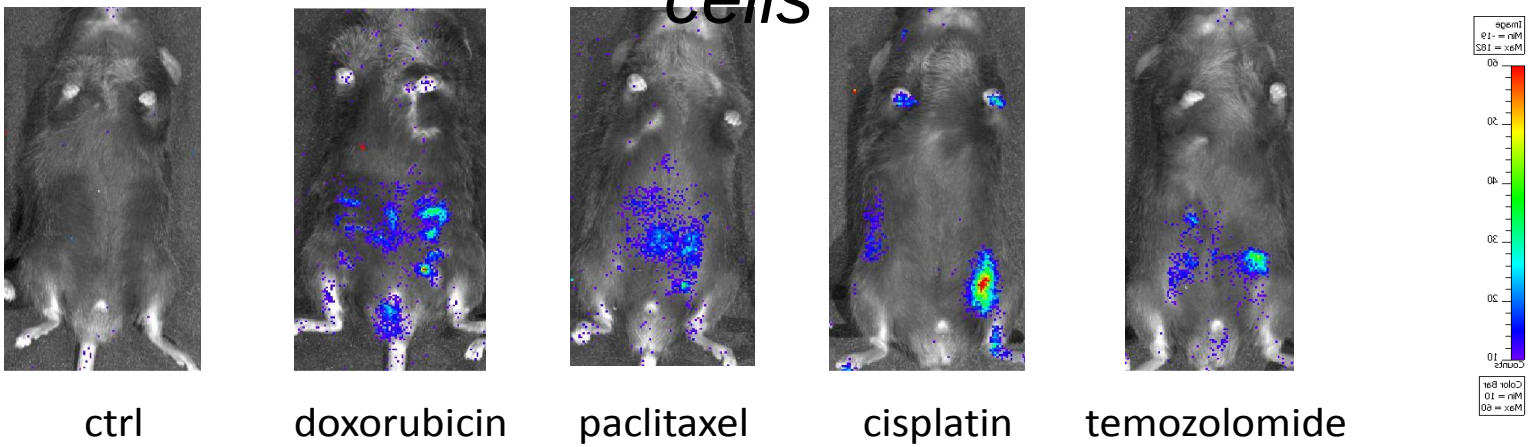
DNA damage → senescence/SASP

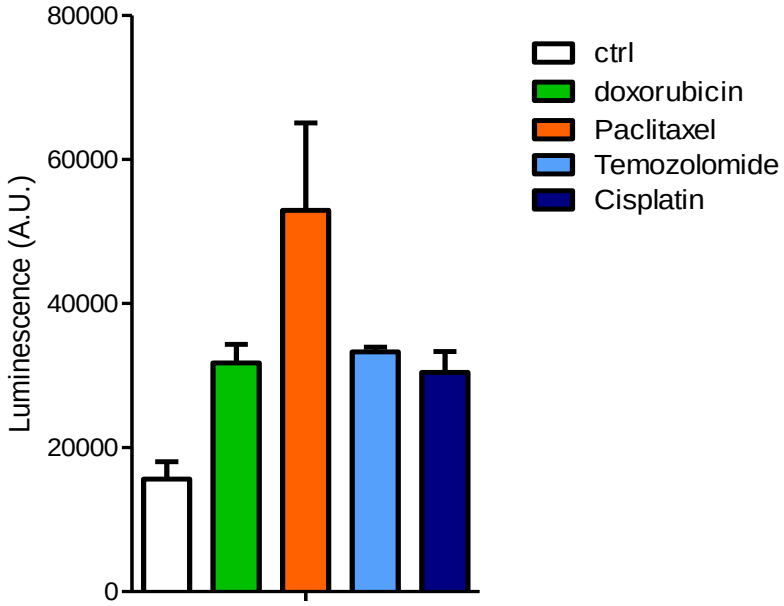
DNA damaging therapies → long- and short-term adverse side effects

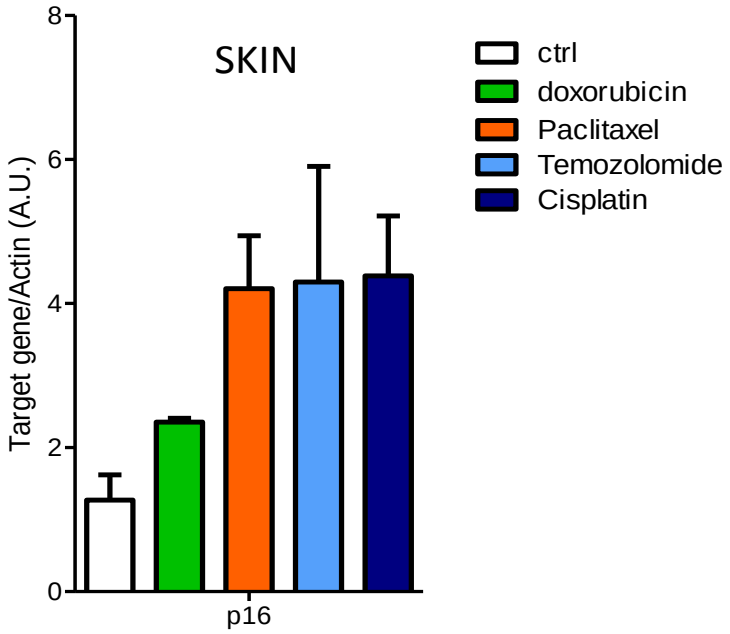
"Among adult survivors of childhood cancer, the prevalence of adverse health outcomes was high ….. medical assessment identified a substantial number of previously undiagnosed problems that are more prevalent in an older population."

Clinical ascertainment of health outcomes among adults treated for childhood cancer
Hudson et al, JAMA, 2013

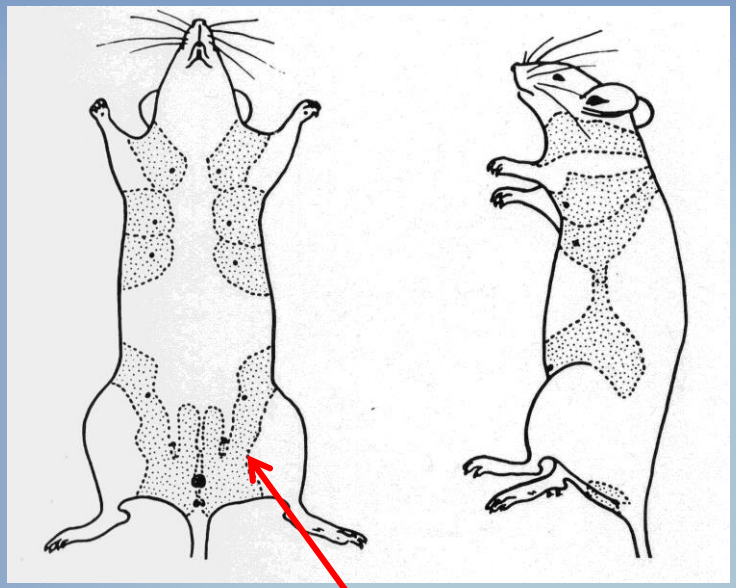
DNA damaging therapies → persistent senescent cells

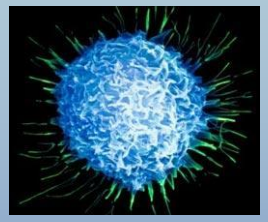






Senescent cells promote metastases MMTV-PyMT breast cancer

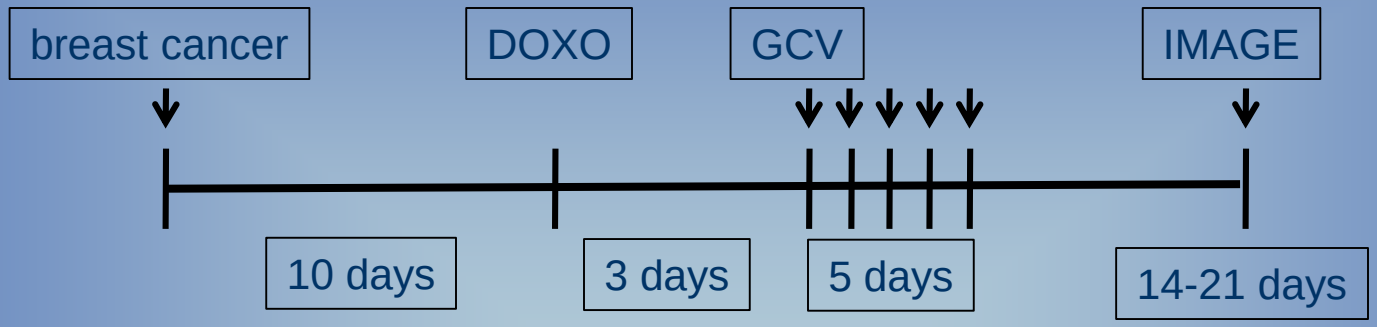




MMTV-PyMT cells expressing firefly luciferase

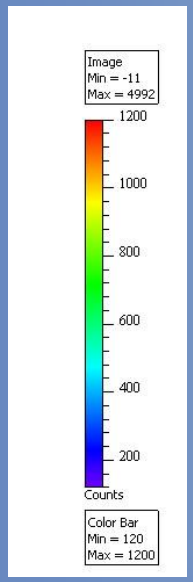
Inject into inguinal mammary fat pad → multifocal mammary adenocarcinomas + lung/liver metastases

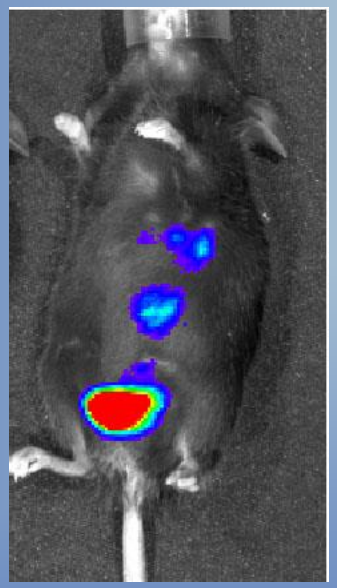
Senescent cells promote metastases in mice with breast cancer

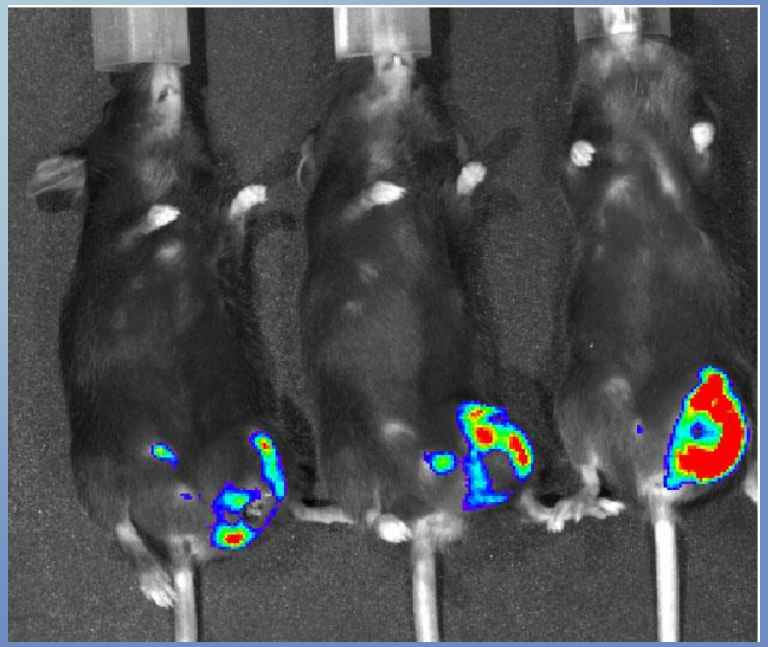


Control

GCV

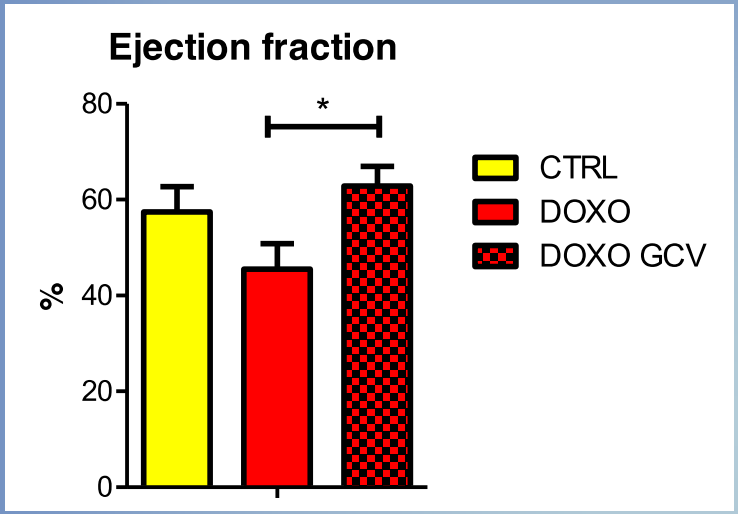


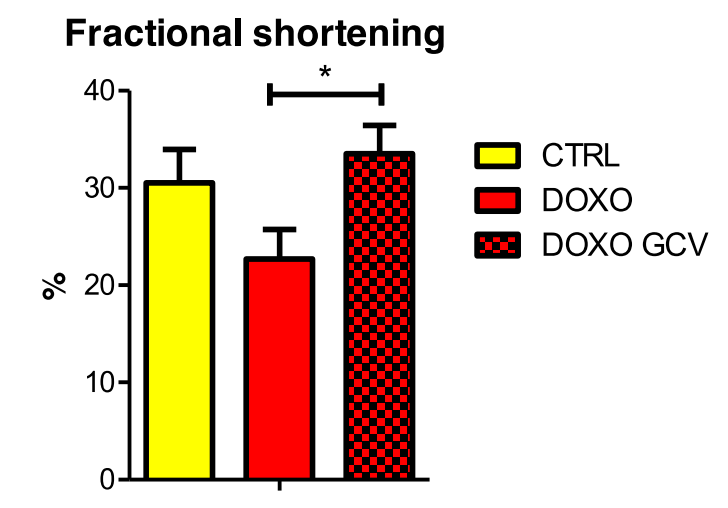


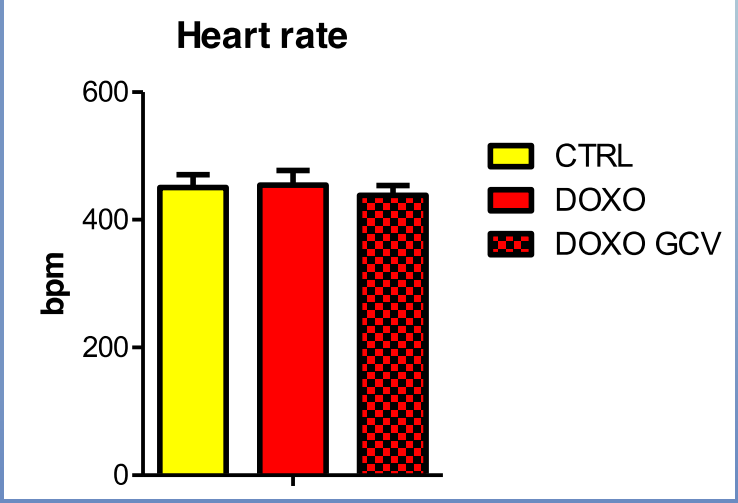


Cardiotoxicity often limits chemotherapy

Senescent cells contribute to chemotherapy-induced cardiotoxicity





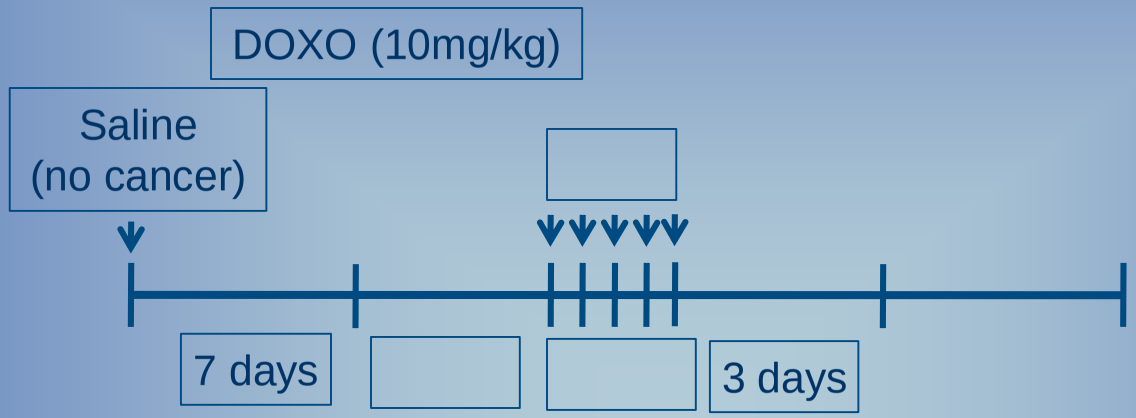


21 days post-doxo

No effect 7 days post

Chemotherapy-induced loss of activity (fatigue?)

Mice without breast cancer treated with chemotherapy (doxorubicin)



Metabolic cages

Behavior: mice + chemotherapy (no cancer)

EFODA			
TFODA			
DWART			
TWART			
WHEEL			
IHOME			
THOME			
LLNGE			
SLNGE			

Interaction with food hopper A (significant uptake found)
Interaction with food hopper A (no significant uptake)
Interaction with water dispenser (significant uptake found)
Interaction with water dispenser (no significant uptake)
Interaction with wheel (>= 1 revolution)
Entered habitat (stable mass reading)
Interaction with habitat (no stable mass reading)
Long lounge (> 60 sec, no non-XY sensor interactions)
Short lounge (5 - 60 sec, no non-XY sensor interactions)

% Total time

*p-value: *<0.05; **<0.01; ***<0.001*

N=5

Measurements at night

Demaria et al, in progress

Cellular senescence

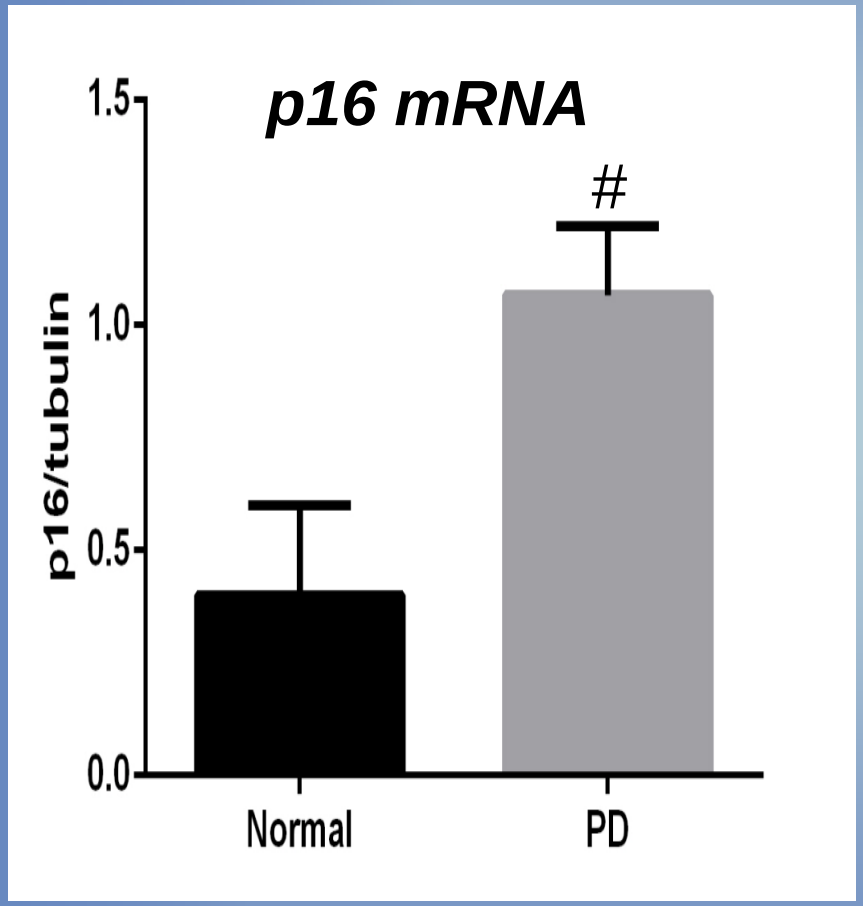
Adverse effects of chemotherapy

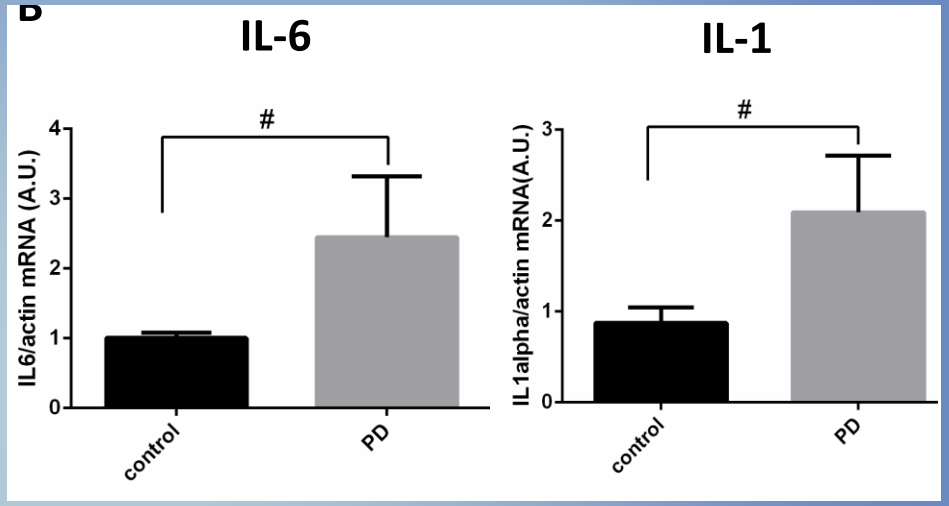
Parkinson's disease and brain aging

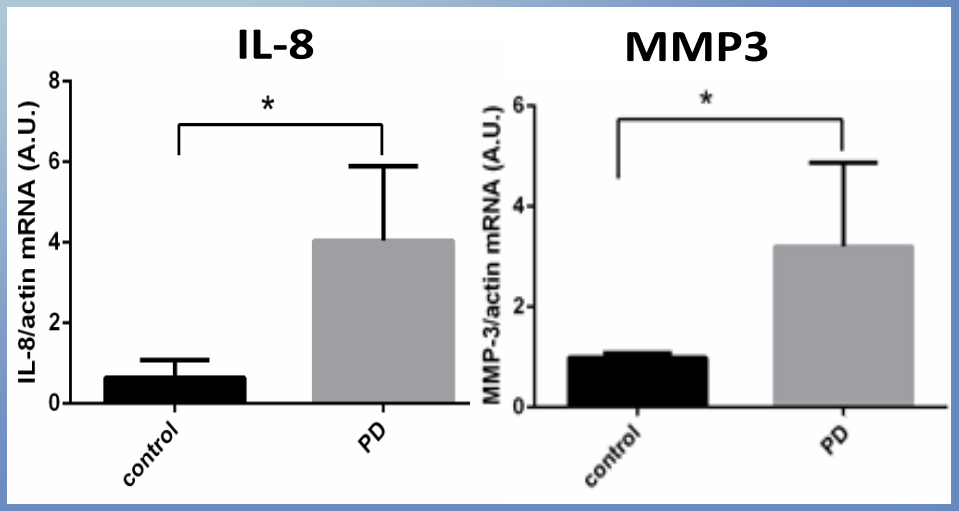
Injury-induced osteoarthritis

Wound healing

Senescence marker p16^{INK4a} increases in brains of human PD patients







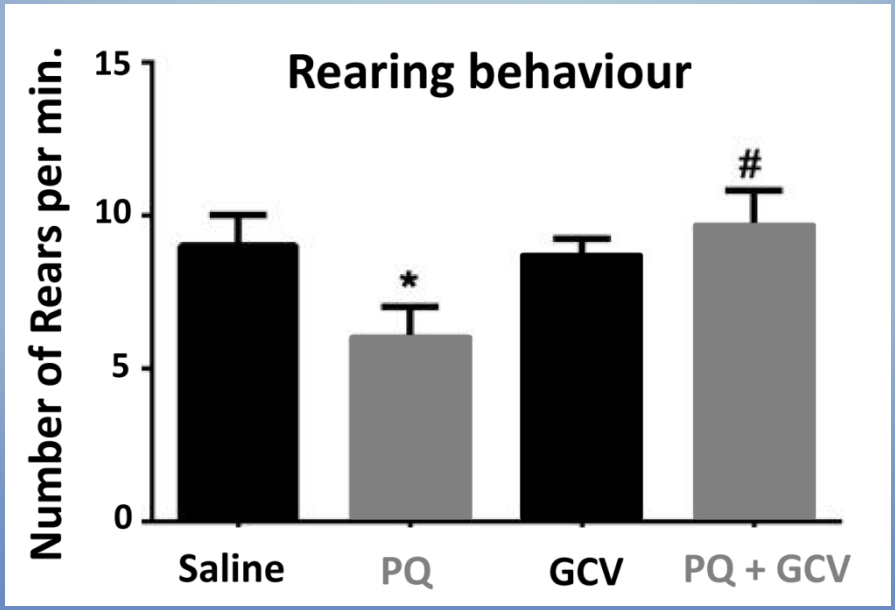
Chintar, Demaria, Andersen et al; unpublished

Paraquat (PQ) causes Parkinson's disease in mice and humans

PQ causes astrocytes to undergo senescence

Chinta et al, submitted

PQ reduces motor neuron function; restored by GCV



Cellular senescence

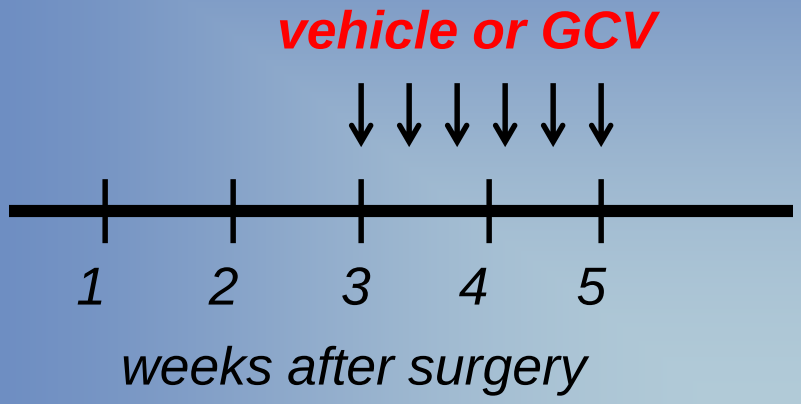
Adverse effects of chemotherapy

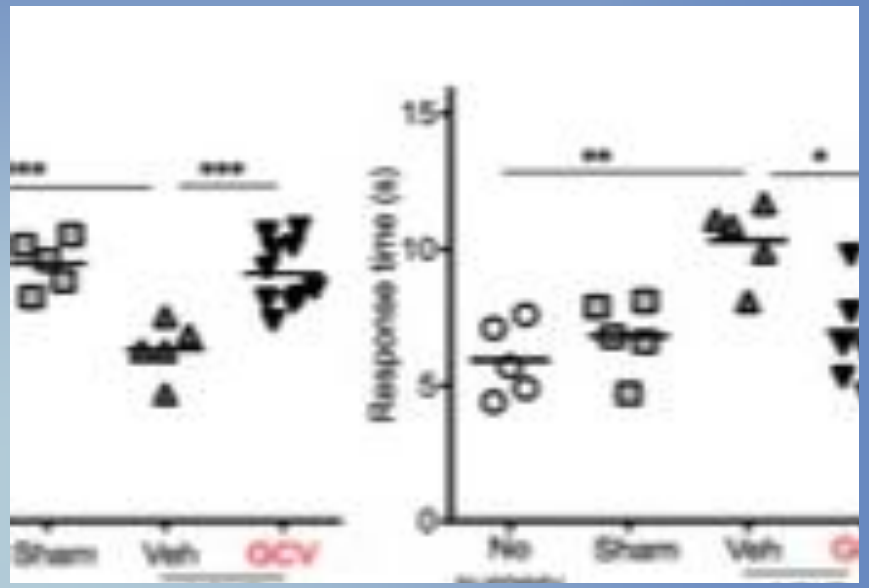
Parkinson's disease and brain aging

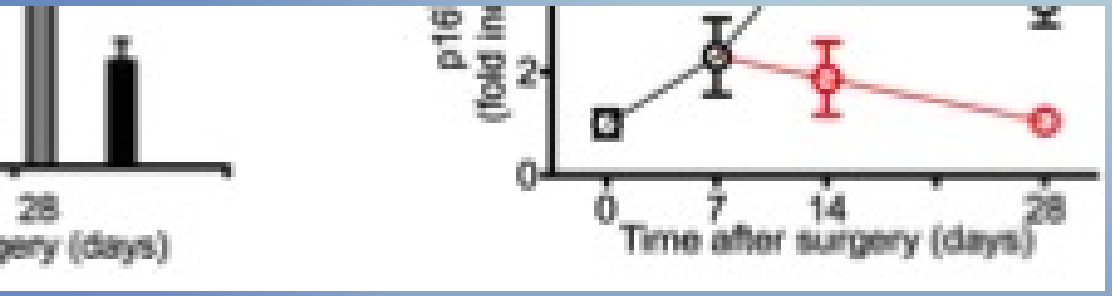
Injury-induced osteoarthritis

Wound healing

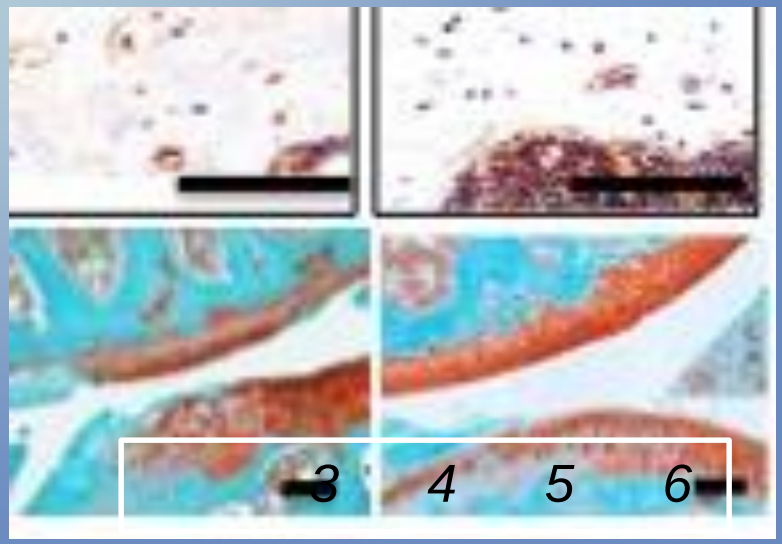
Surgical cut in anterior cruciate ligament





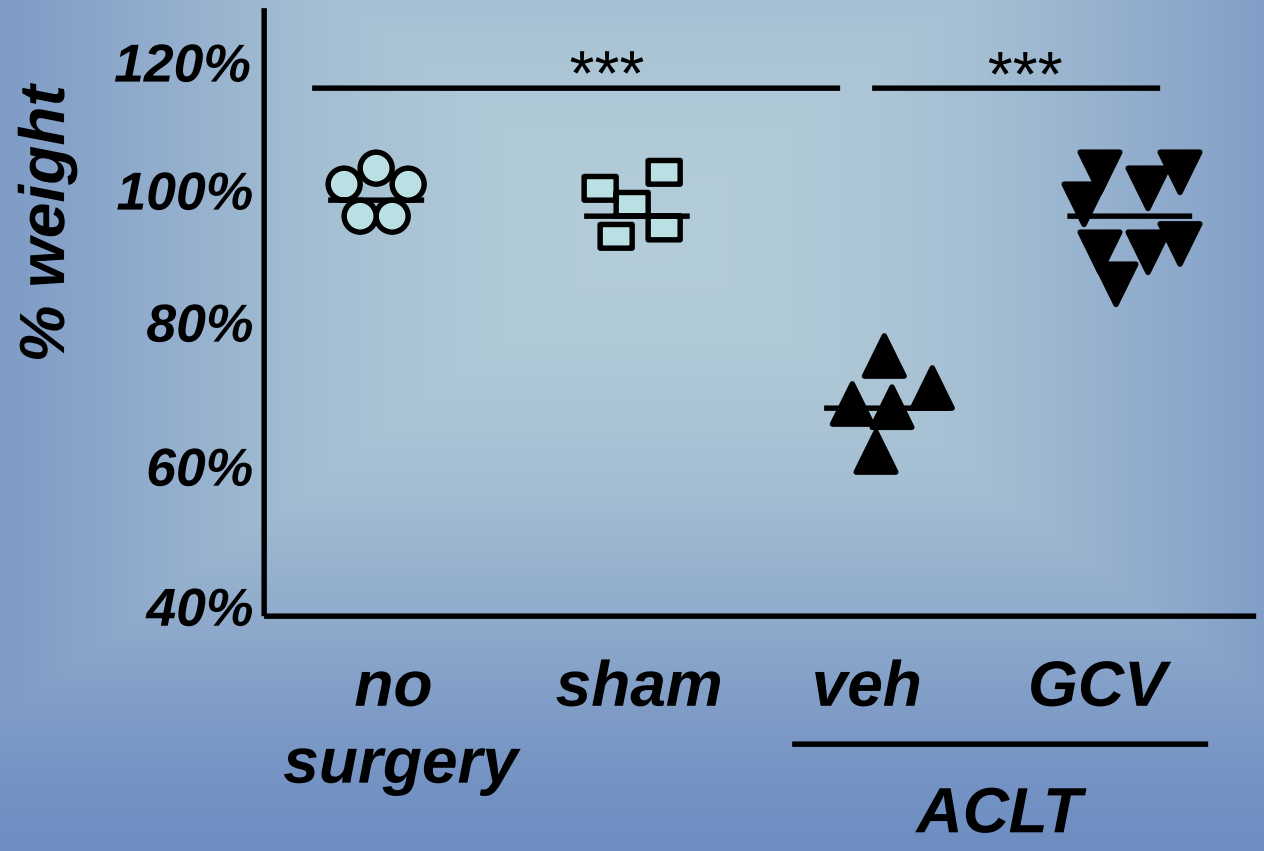


sham *vehicle* *GCV*

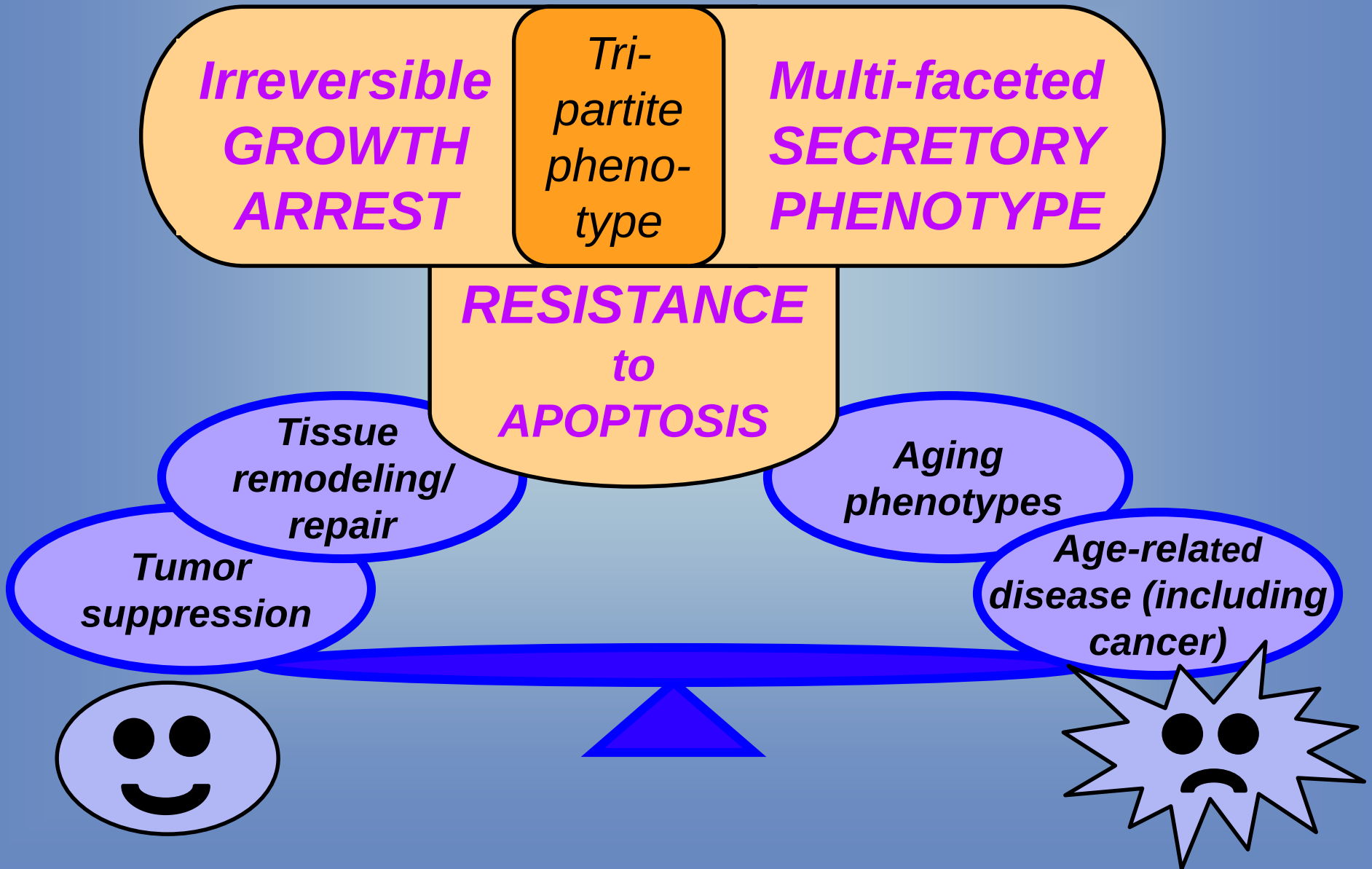


Jeon, Elisseeff; unpublished

Surgical cut in anterior cruciate ligament: eliminating senescent cells restores function



Cellular senescence, an evolutionary balancing act *(why did the SASP evolve?)*



Cellular senescence

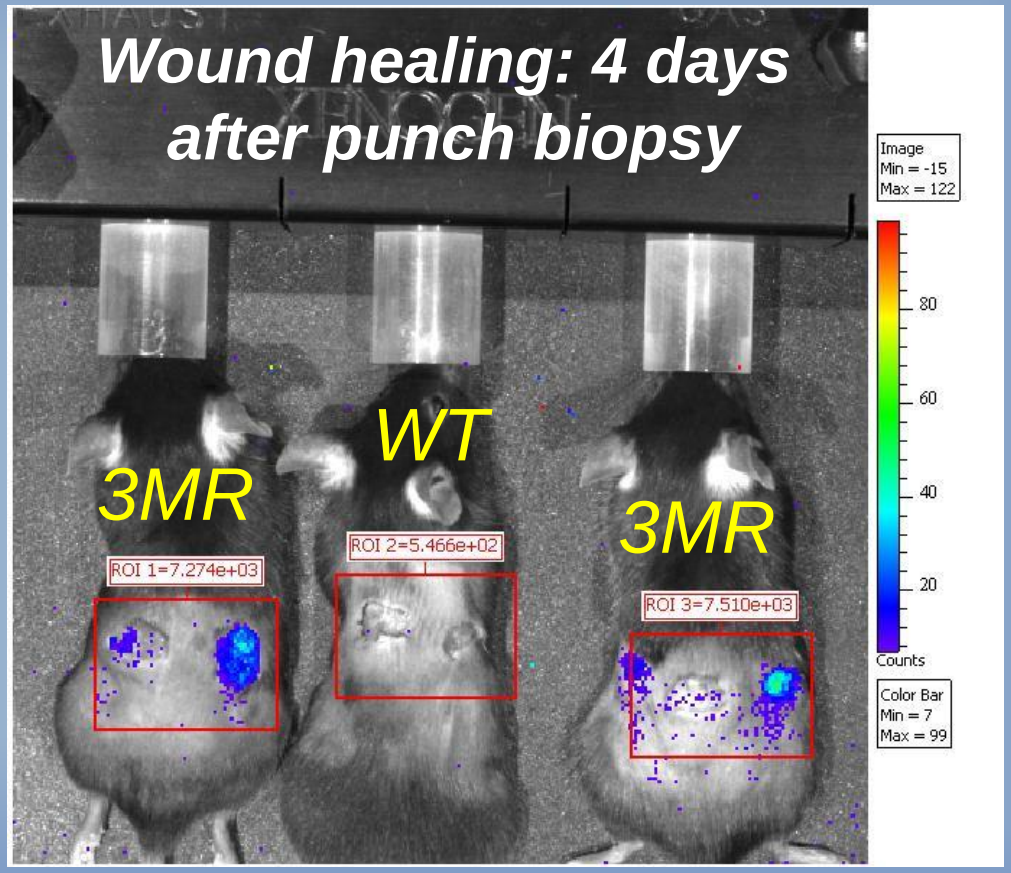
Adverse effects of chemotherapy

Parkinson's disease and brain aging

Injury-induced osteoarthritis

Wound healing

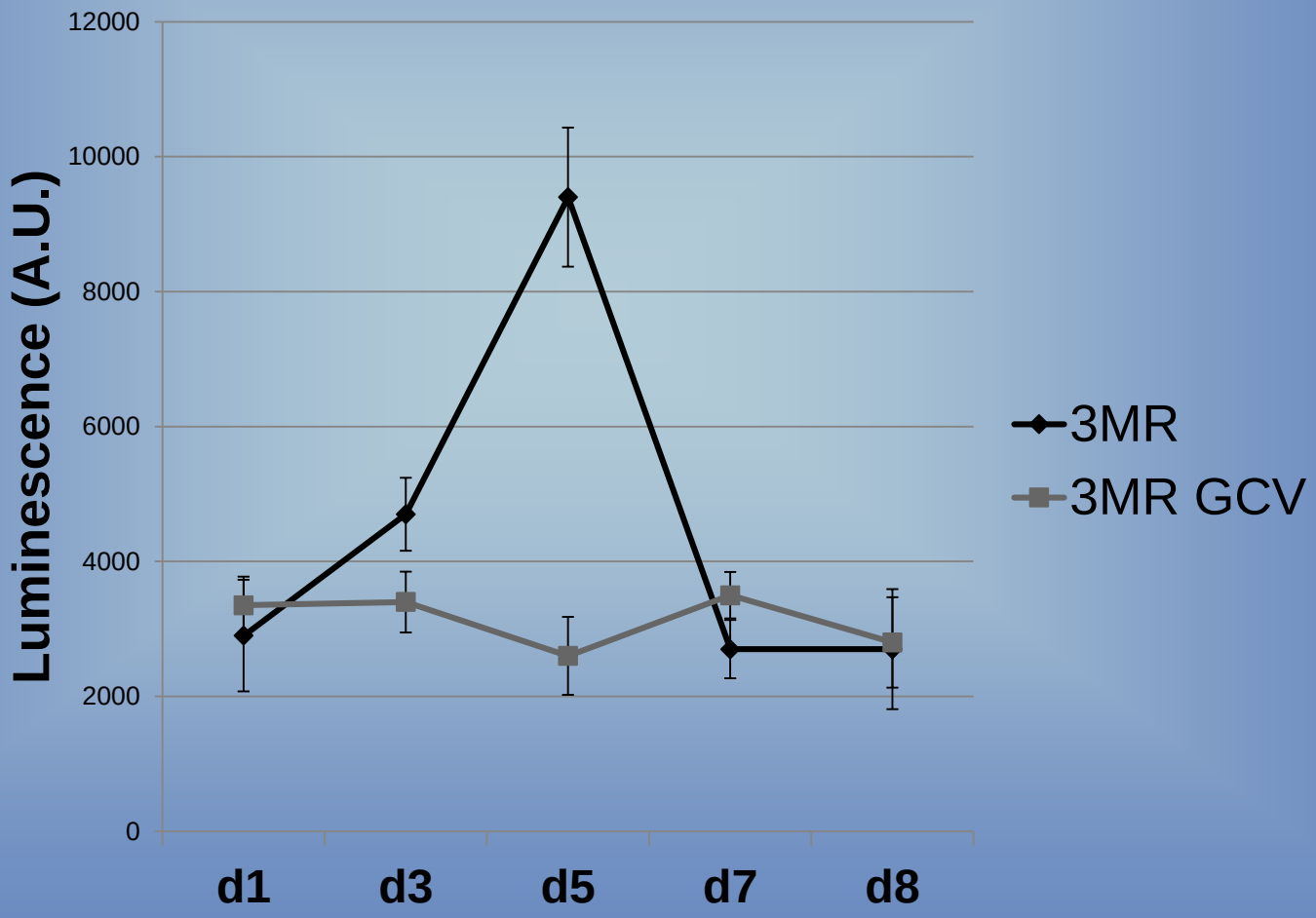
Cellular senescence is induced during wound healing



Induction of $p16^{INK4a}$, 3MR, IL-6 expression

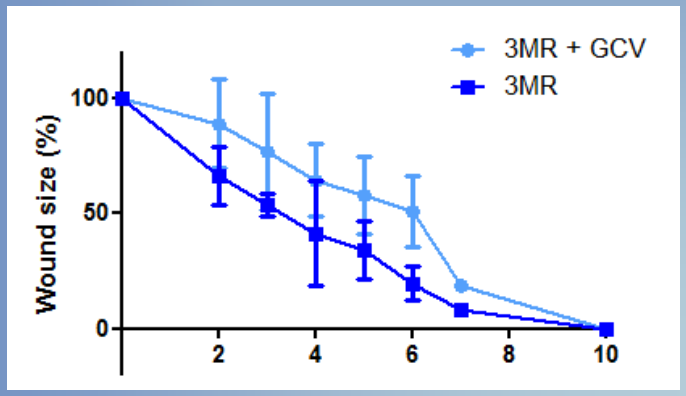
Demaria et al,Dev Cell, 2014

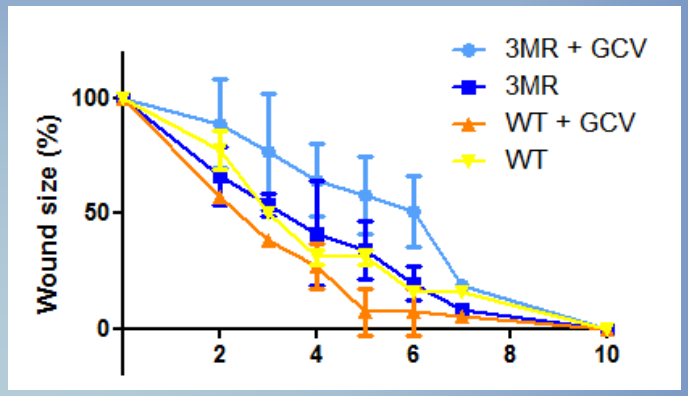
Senescent cells are present transiently during wound healing

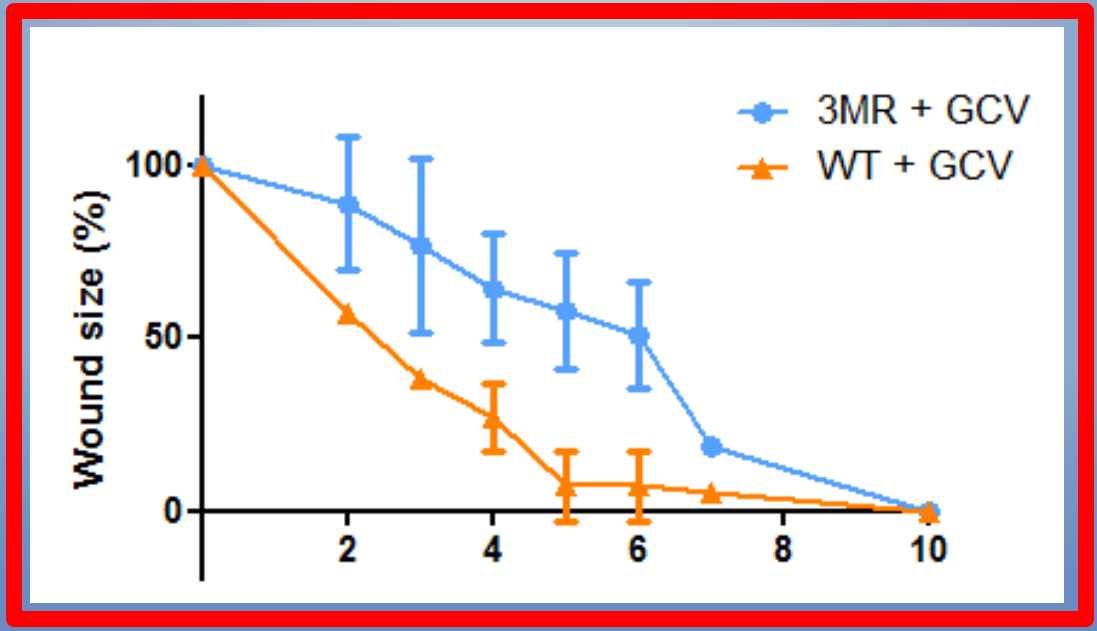


WOUND HEALING IS RETARDED BY ELIMINATING SENESCENT CELLS

GCV 0-5 days after biopsy

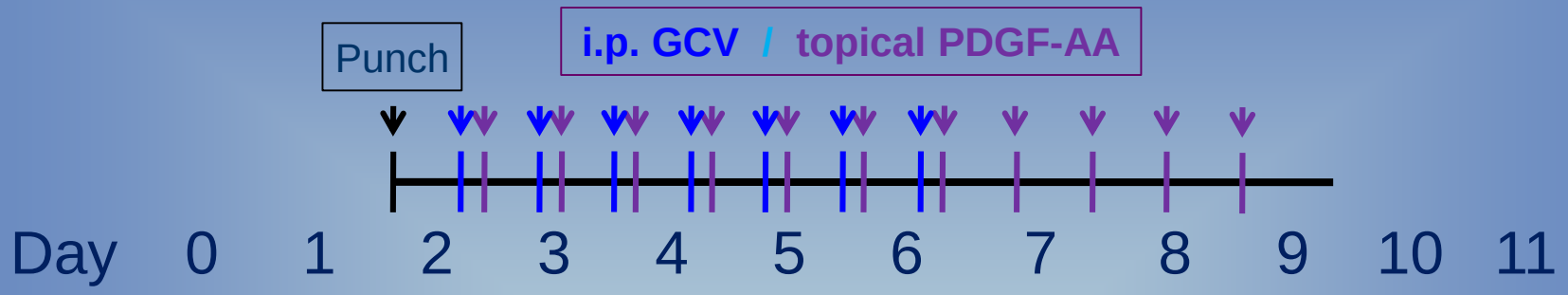


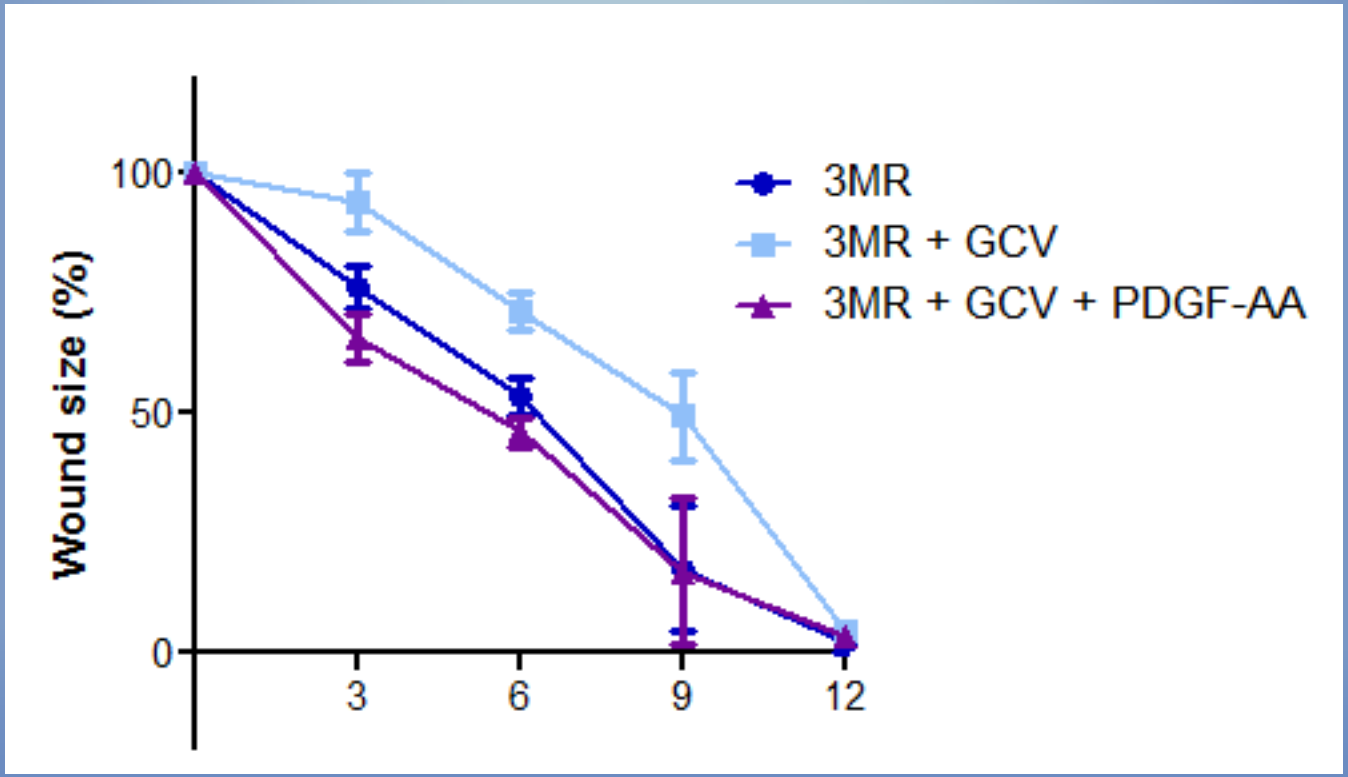




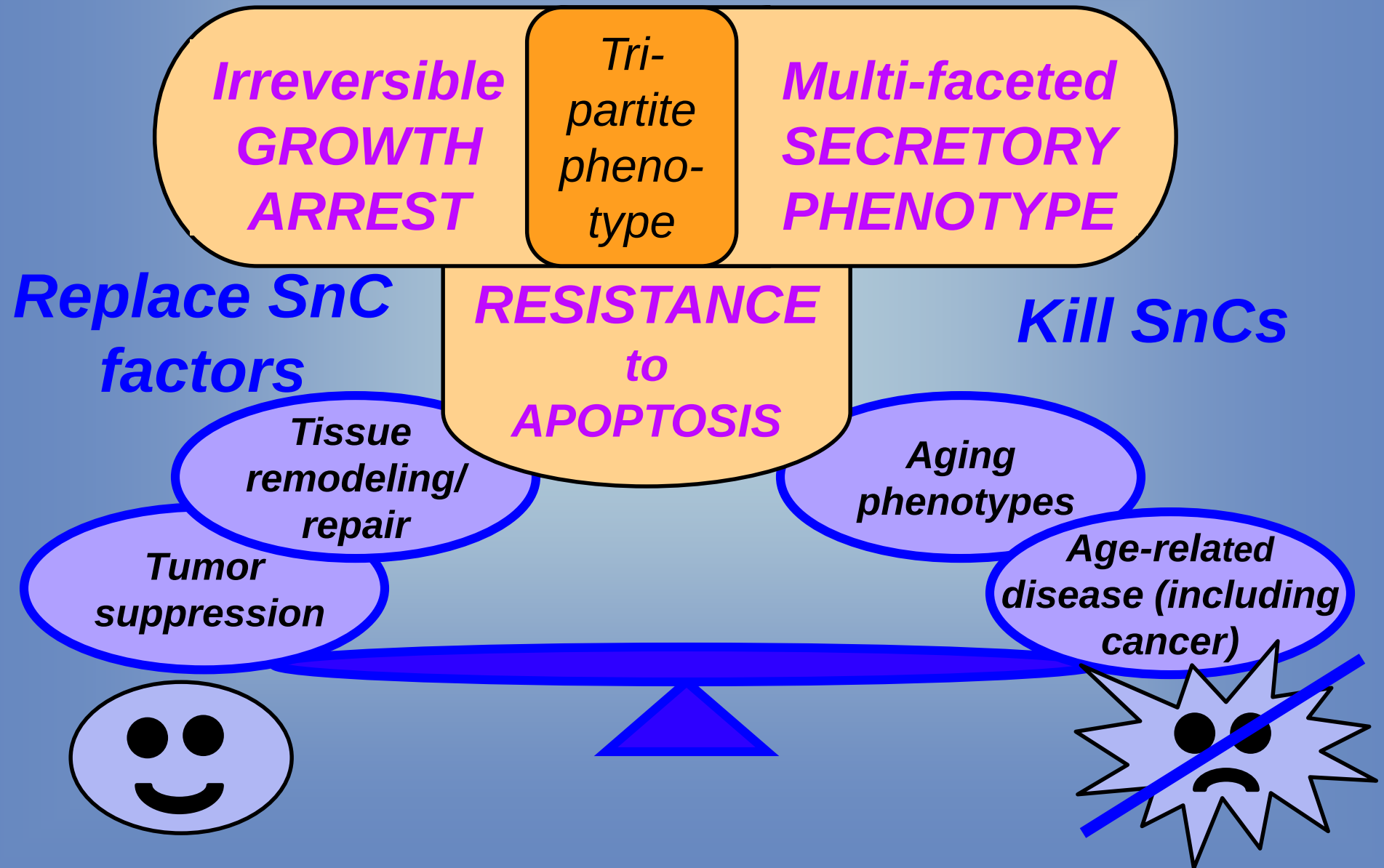
female mice

Topical PDGF-AA topical rescues slow wound healing in GCV-treated 3MR mice

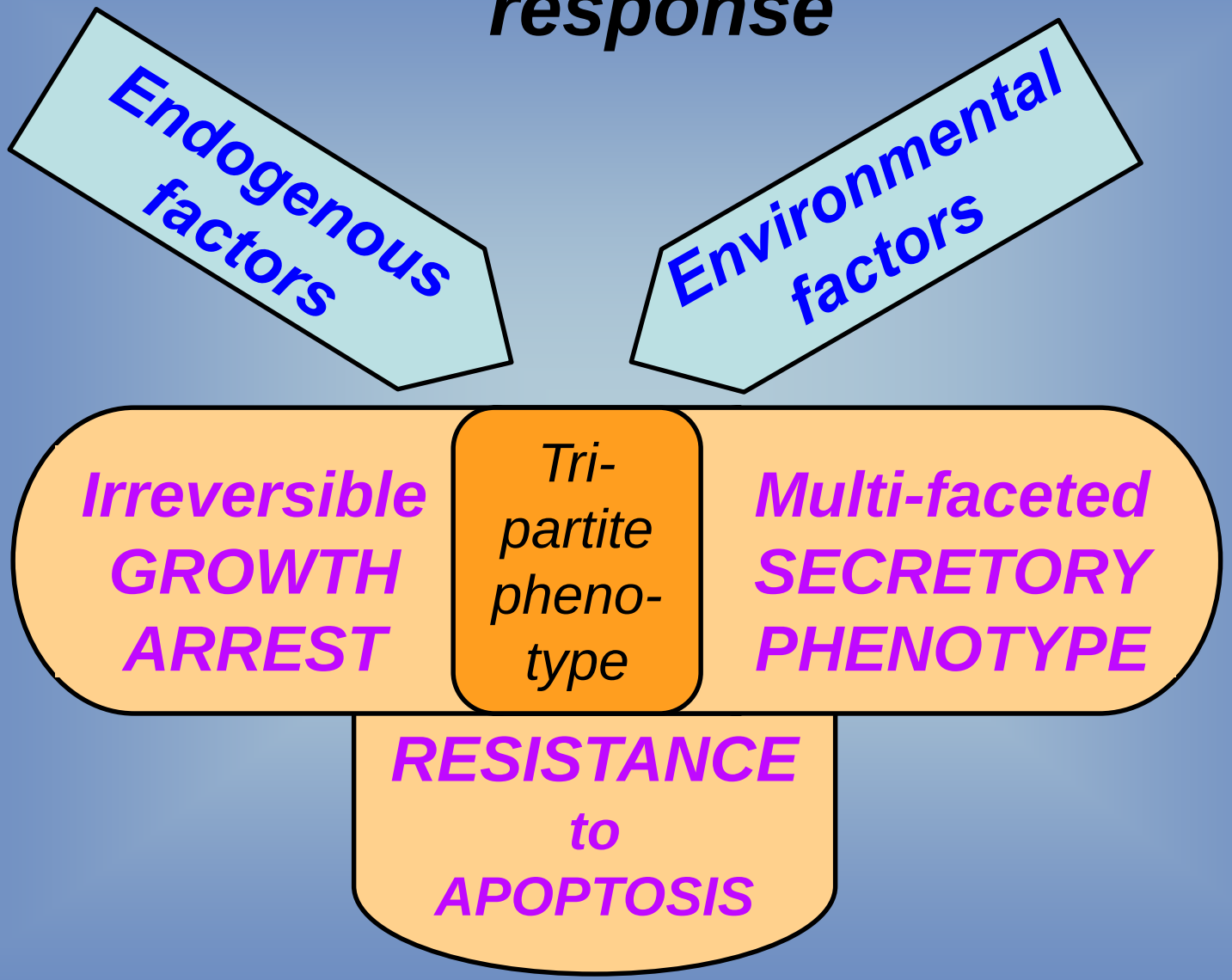




Cellular senescence, an evolutionary balancing act



Cellular senescence, a complex stress response



THANKS!

Present lab members

Nick Aguirre
Fatouma Alimirah
Nate Basisty
Albert Davalos
Jose Domingo-Lopez
Chisaka Kuehnemann
Abhijit Kale
Clare Kim
Chandani Limbad
Su Liu
Kevin Perrott
Chris Wiley
Ying Zou

Past lab members

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

Collaborators

PPG: Jan Vijg, Yousin Suh (Einstein); Jan Hoeijmakers (Erasmus); Paul Hasty (UTHSCSA)
PPG: Jim Kirkland, Jan van Deursen, Tamara Tchkonia, Darren Baker, Nathan LeBrasseur (Mayo), Yuji Ikeno (UTHSCSA), Rich Miller (U MI)
Jennifer Elisseeff (Johns Hopkins U)
Pete Nelson (Fred Hutch)
Steve Yannone, Paul Yaswen, Cilla Cooper (LBNL)
Julie Andersen, Pankaj Kapahi, Simon Melov, Brad Gibson, Arvind Ramachandran, Birgit Schilling (Buck Inst)
Eiji Hara, Naoko Ohtani (Osaka U, Tokyo U)