Discovering new senolytic compounds for cancer therapy

- EU-OPENSCREEN-ERIC -

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Madrid, 4 julio 2023

ColladoLab
CELL SENESCENCE, CANCER AND AGING

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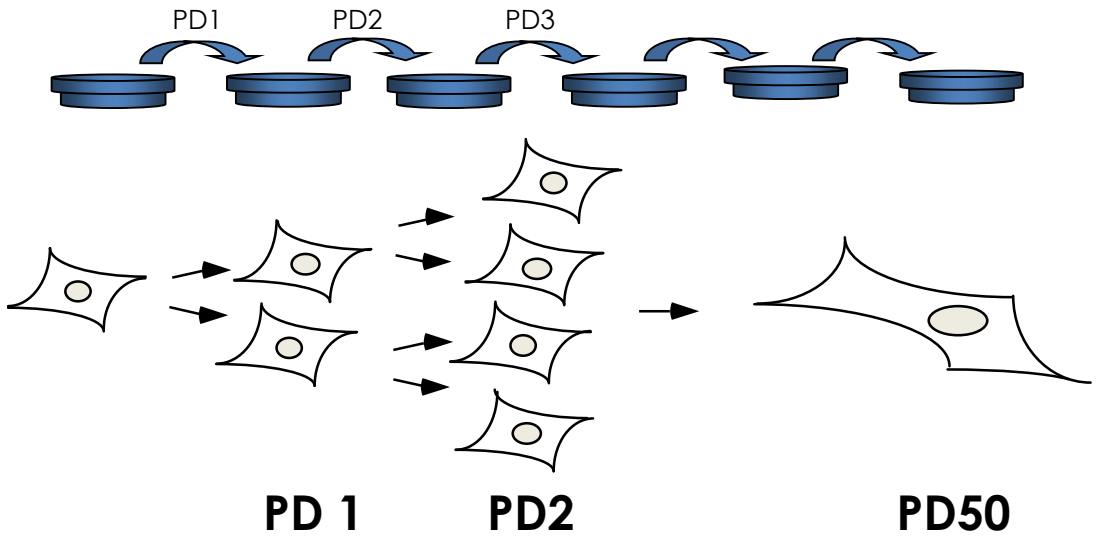
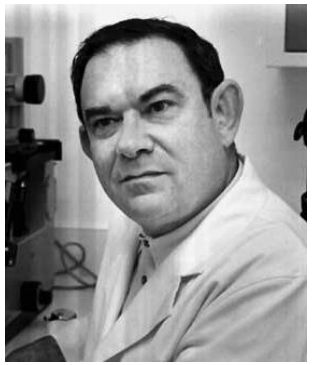
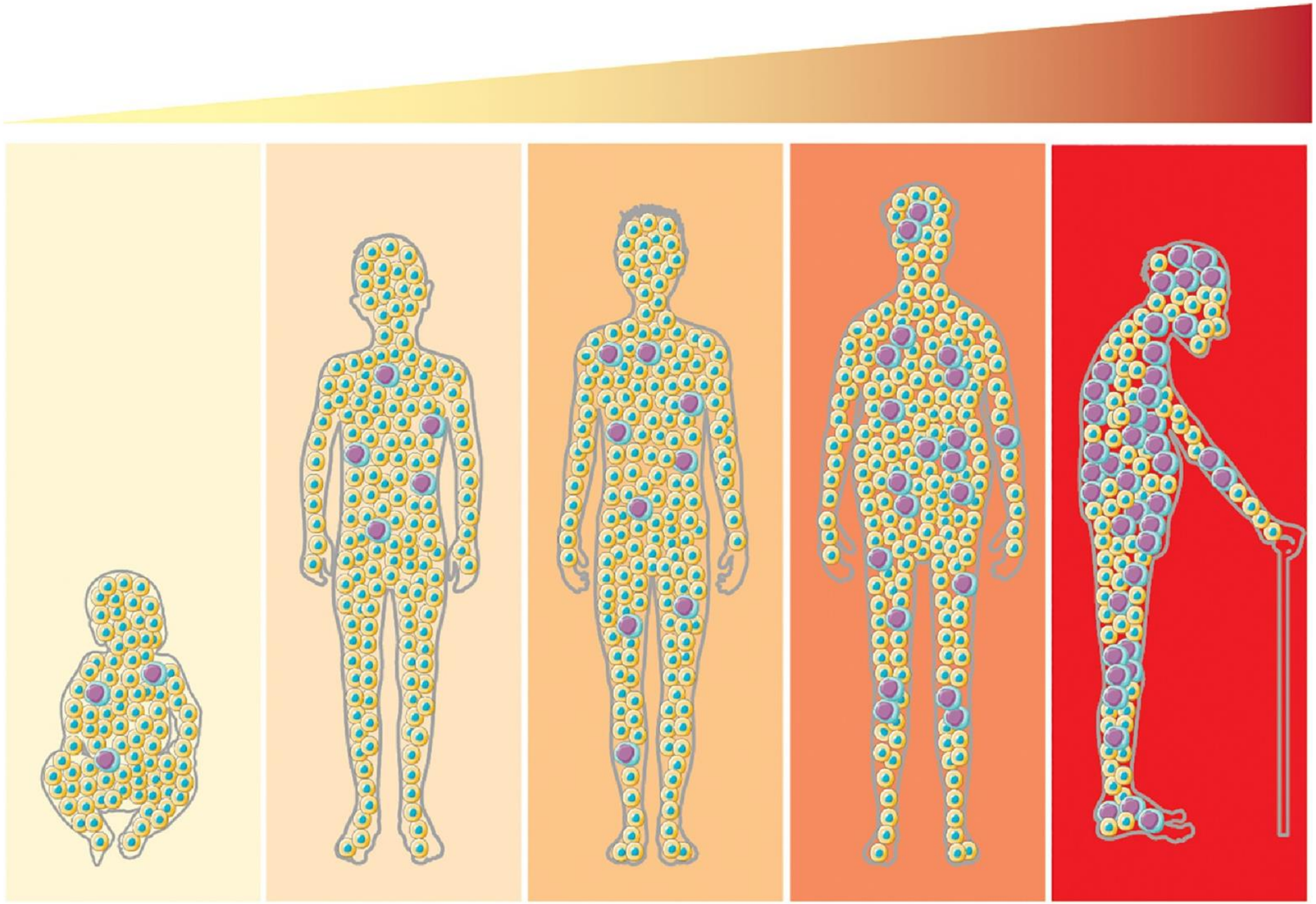
@ColladoLab

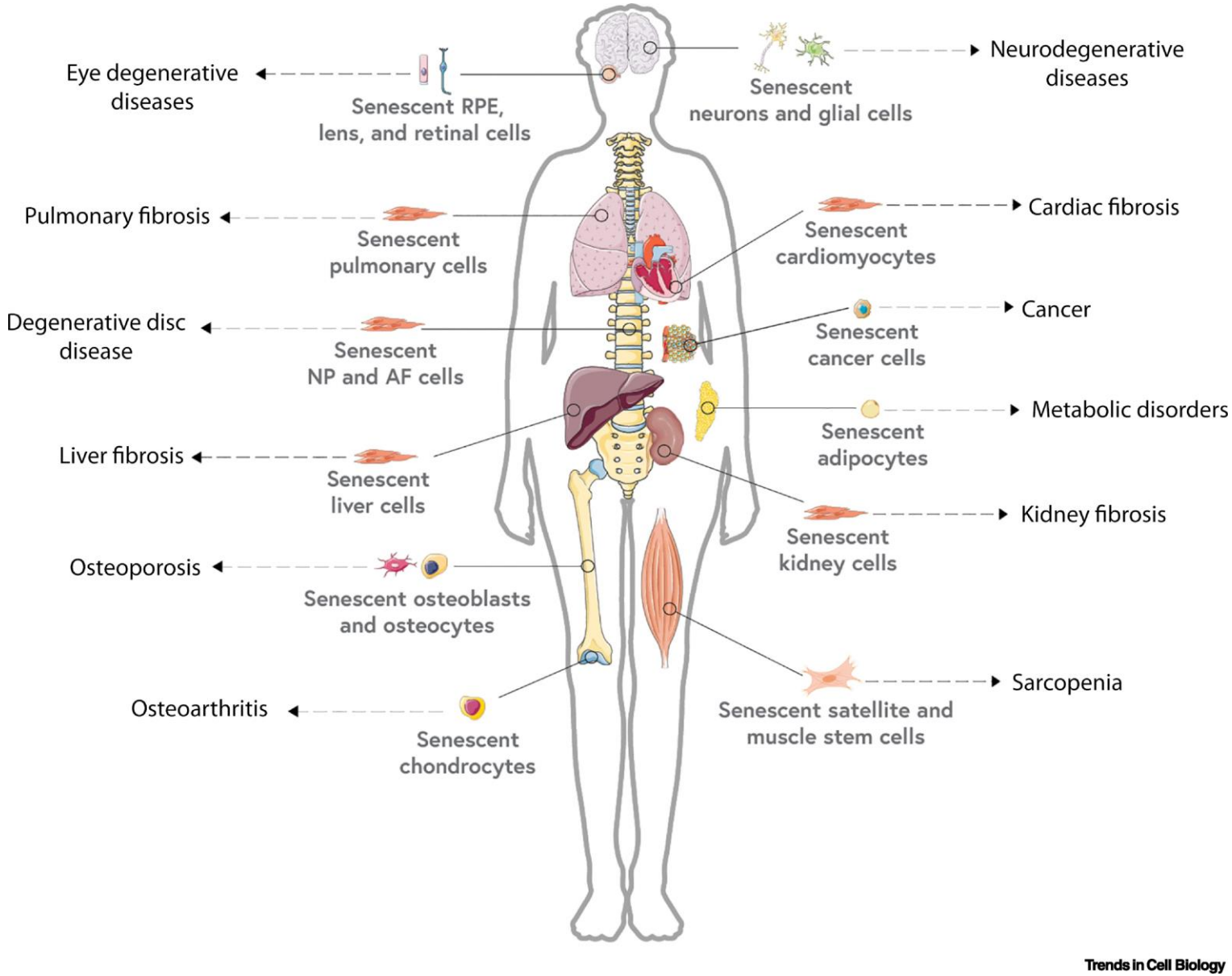
CELLULAR SENESCENCE





AGING???




Eye degenerative diseases
Senescent RPE, lens, and retinal cells
Neurodegenerative diseases
Senescent neurons and glial cells
Pulmonary fibrosis
Senescent pulmonary cells
Cardiac fibrosis
Senescent cardiomyocytes
Degenerative disc disease
Senescent NP and AF cells
Cancer
Senescent cancer cells
Metabolic disorders
Senescent adipocytes
Liver fibrosis
Senescent liver cells
Kidney fibrosis
Senescent kidney cells
Osteoporosis
Senescent osteoblasts and osteocytes
Osteoarthritis
Senescent chondrocytes
Sarcopenia
Senescent satellite and muscle stem cells
Trends in Cell Biology

WHAT HAPPENS IF WE GET RID OF THEM?

IT WORKS!!!

Darren Baker
Jan van Deursen
@Mayo Clinic

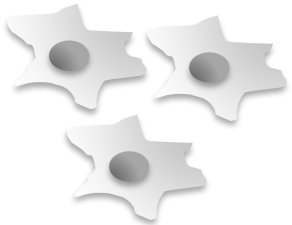
Marco Demaria
Judy Campisi
@Buck Institute

How could we get rid of senescence cells?

death

no effect

senescent cell



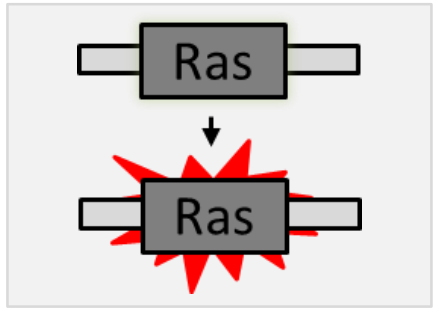
proliferating cell

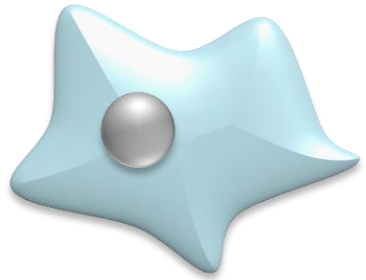
SENOLYTICS

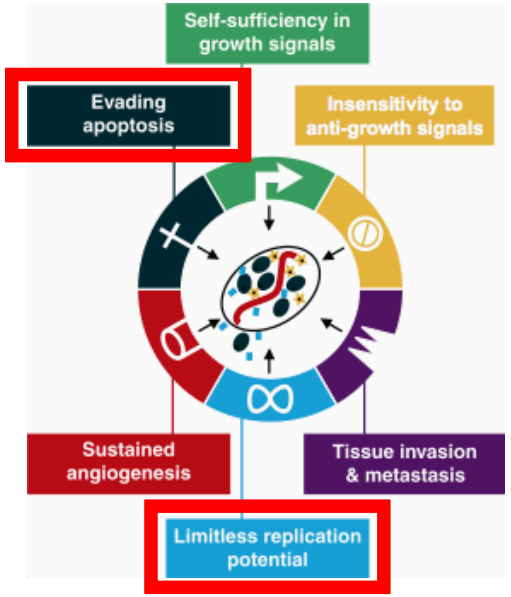
Human clinical trials (completed, ongoing, planned)

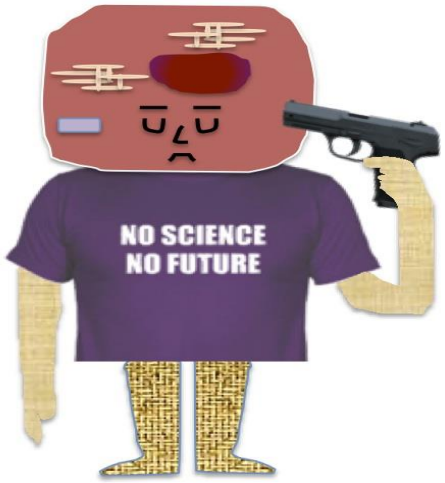
Study title	Senolytic	Study design	Identifier	Status
IPF	D + Q	Phase 1	NCT02874989	Completed[63]
chronic kidney disease	D + Q	Phase 2	NCT02848131	Current, preliminary report published[48]
Hematopoietic stem cell transplant	D + Q	Randomized	NCT02652052	Current
Alzheimer's disease	D + Q	Phase 1/2	NCT04785300	Current
Alzheimer's disease	D + Q	Phase 1/2 Phase 2	NCT04063124 and NCT04685590	Current
Alzheimer's disease	D + Q	Single-arm	Pending	Pending
frailty in adult survivors of childhood cancer	D + Q; F	Phase 2	NCT04733534	Current
skeletal health in older humans	D + Q; F	Phase 2	NCT04313634	Current
coronary artery by-pass surgery	Q	Phase 2	NCT04907253	Current
osteoarthritis	F	Phase 1/2	NCT04815902	Current
osteoarthritis	F	Phase 1/2	NCT04210986	Current
COVID-19	F	Phase 2	NCT04476953	Current
frailty, inflammation and related measures in older women	F	Phase 2	NCT03430037 and NCT03675724	Current
Diabitis and chronic kidney disease	F	Phase 2	NCT03325322	Current
COVID-19	F	Phase 2	NCT04771611	Current
COVID-19	F	Phase 2	NCT04537299	Current
osteoarthritis	F	Phase 1/2	NCT04770064	Current
platelet-rich plasma and losartan	F	Phase 1/2	NCT05025956	Current
osteoarthritis	UBX0101 (nutlin-3a or related)	Phase 2	NCT03513016 and NCT04349956	Completed; failed to achieve primary endpoint
osteoarthritis	UBX0101 (nutlin-3a or related)	Phase 1 Phase 2	NCT04229225 and NCT04129944	Current
diabetic macular edema or neovascular age-related macular degeneration	UBX1325 (N or related)	Phase 1 Phase 2	NCT04537884 and NCT04857996	Current

Oncogene activation





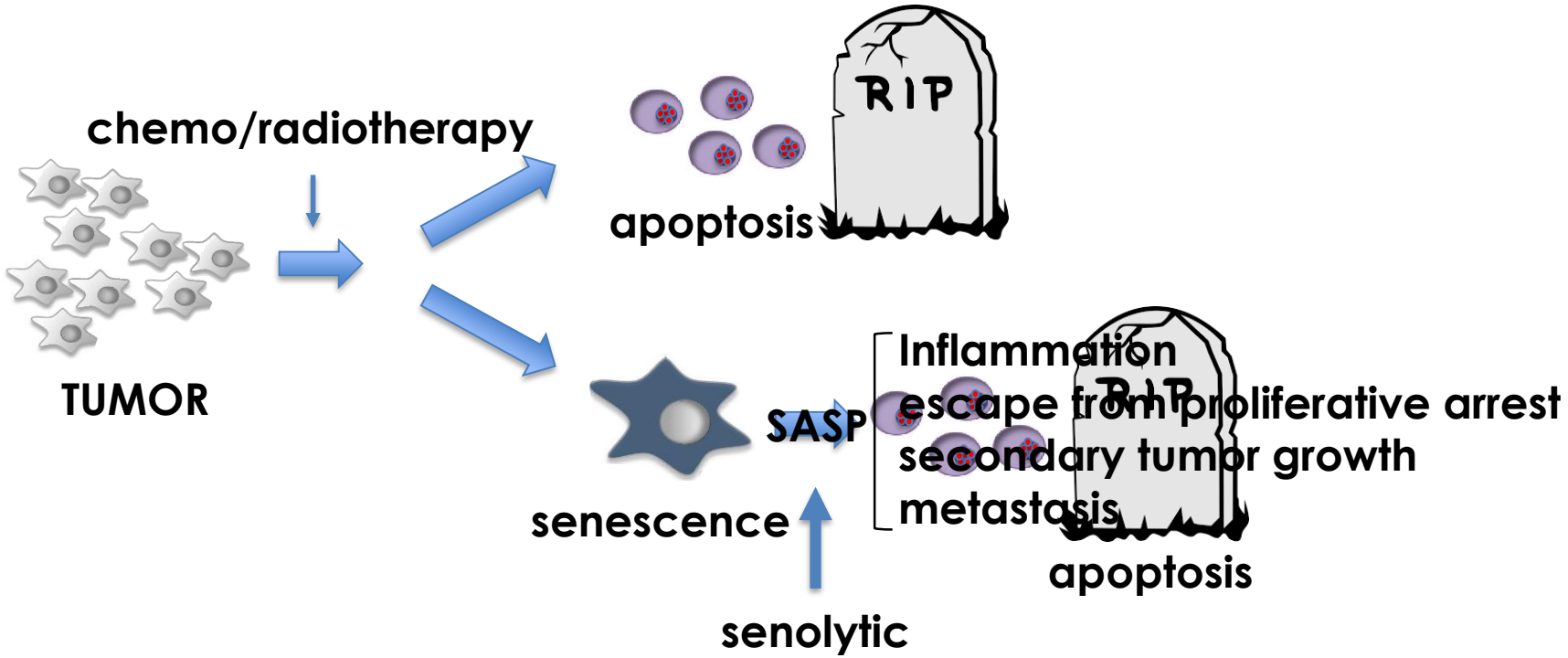




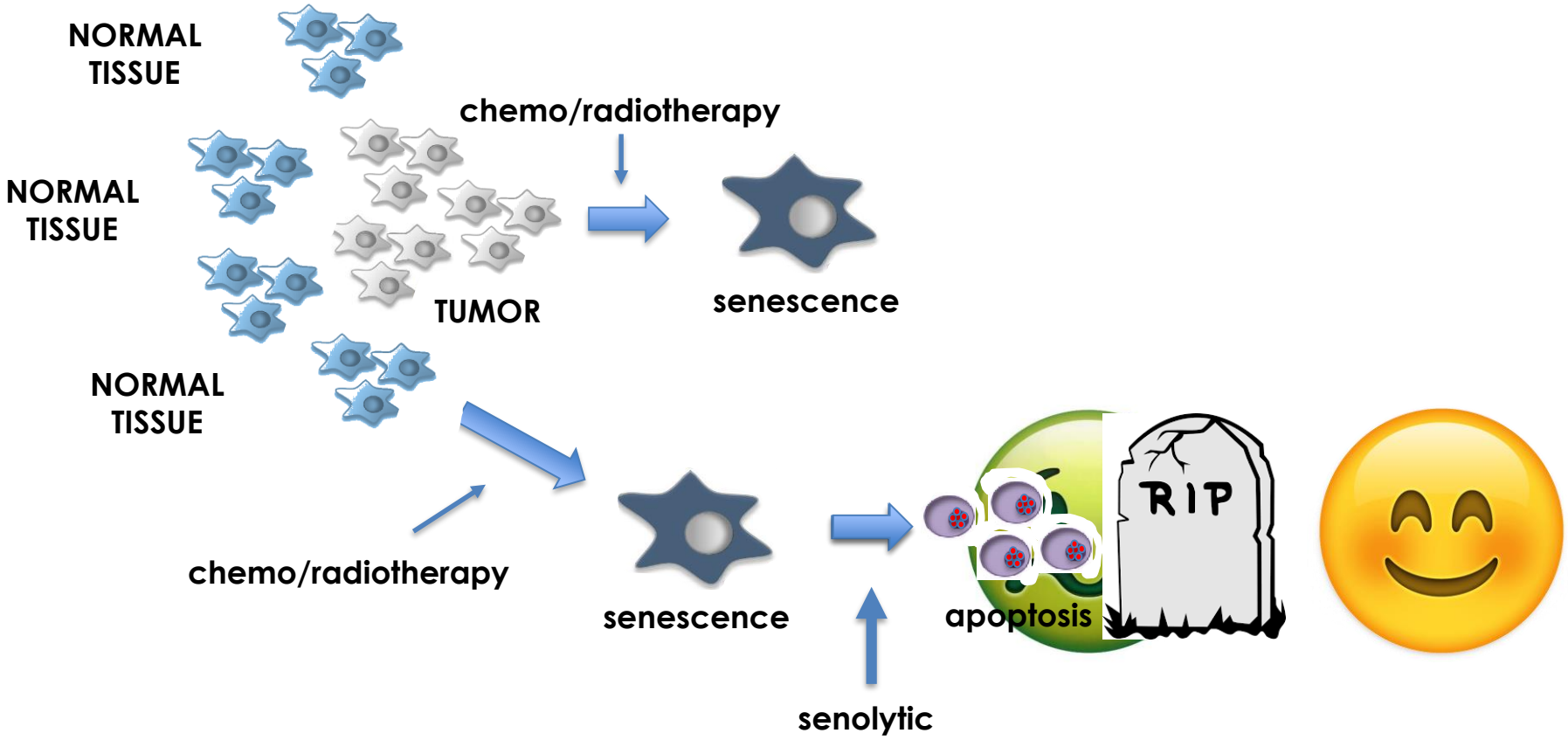
apoptosis

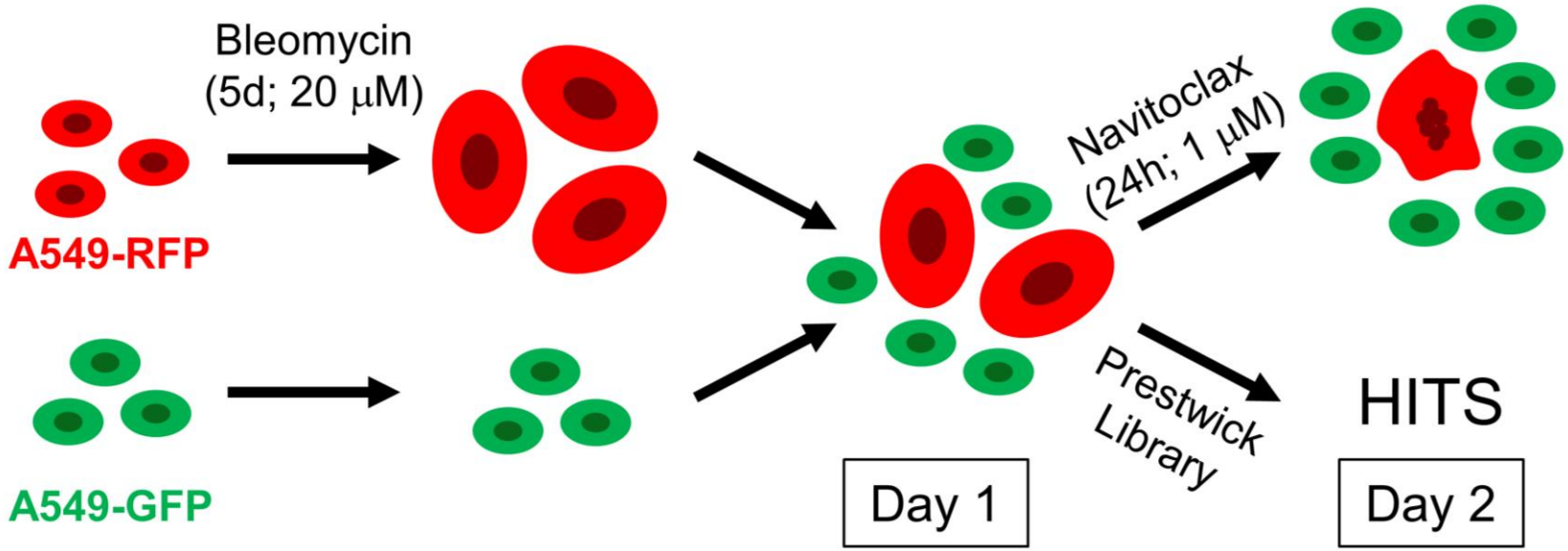
senescence

Senolytics in cancer treatment



Senolytics in cancer treatment

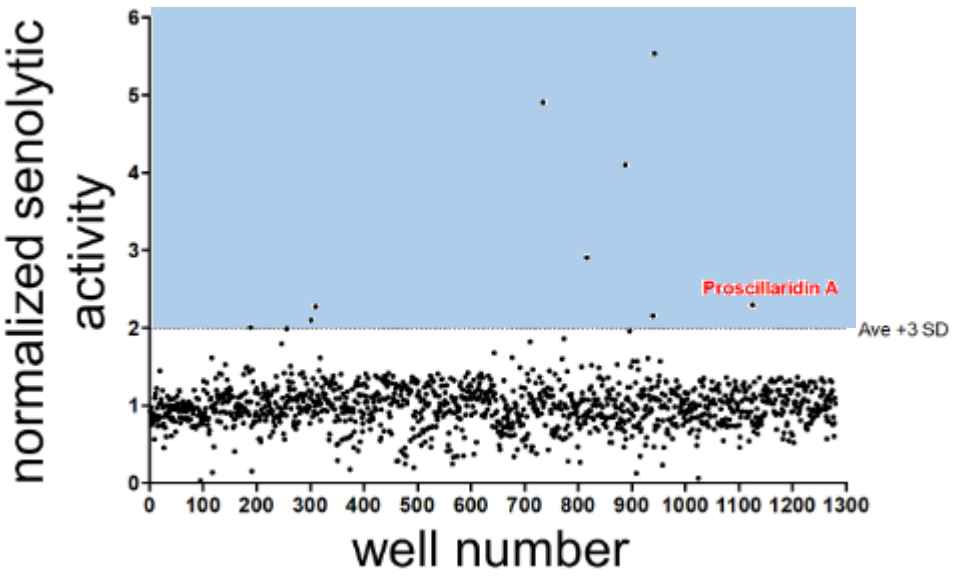




1280
Compounds

Operetta High-Content Imaging System

Mabel Loza

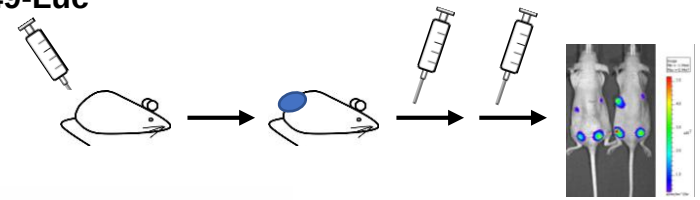


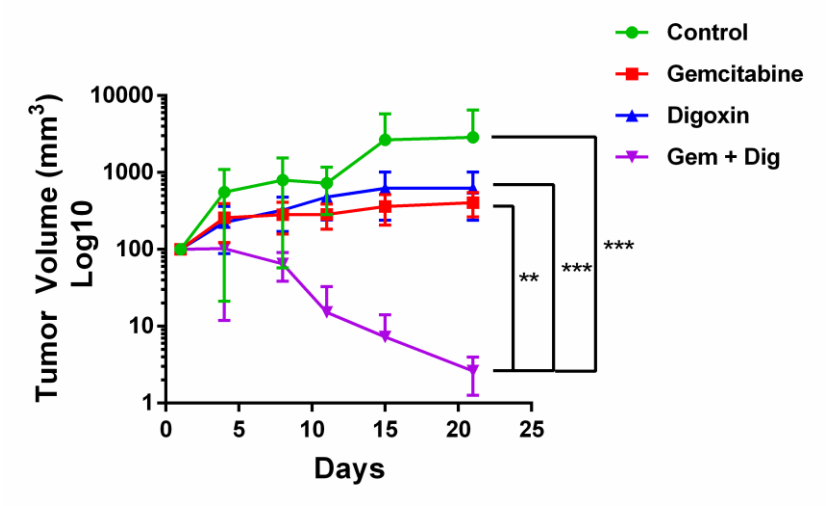
CARDIAC GLYCOSIDES FAMILY

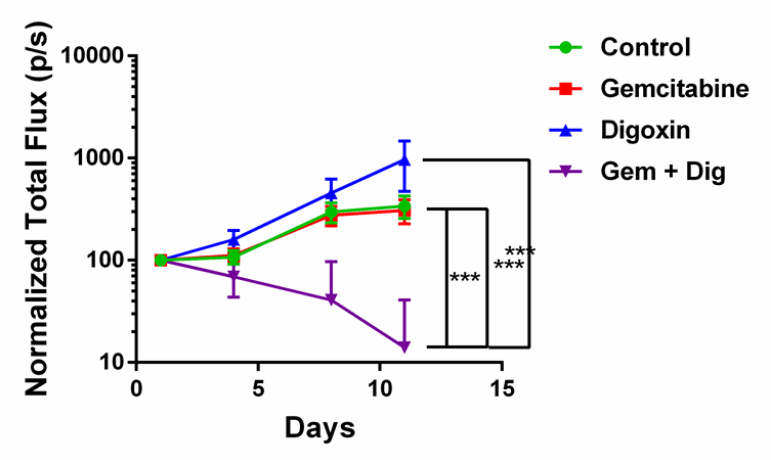
TUMOR XENOGRAFTS

- Gemcitabine: 25 mg/Kg SENOGENIC
- Digoxin: 2 mg/Kg SENOLYTIC
- Gem: 25mg/Kg + Dig: 2mg/Kg SENOGENIC+SENOLYTIC

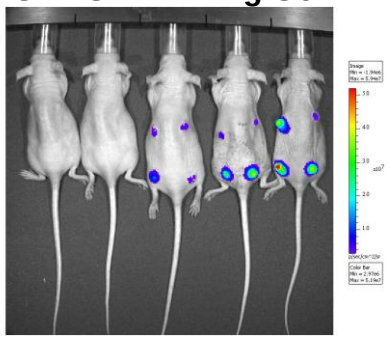
A549-Luc







G+D G+D NT Dig Gem



Senescence-based one-two punch strategy against cancer

senogenic

senolytic

NEW SENOLYTIC SCREENINGS

Jens Peter von Kries
Leibniz Forschungsinstitut für Molekulare Pharmakologie (FMP)
Berlín, Alemania

eu::openscreen

101024 compounds

- **Primary screen**
- screen of 287 compound plates (Bioactives and Commercials)
- single determination @10µM

1038 compounds

- **Selectivity screen**
- screen of 1038 primary active compounds
- triplicate determination @10µM
- parallel testing in senescent and proliferating cells
- identification of 64 compounds showing inhibition only in senescent cells

64 compounds

- **IC50 validation**
- concentration-dependent test of 64 compounds (1:2 dilution, start @40µM)
- triplicate determination
- test in senescent cells

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Leibniz Forschungsinstitut für
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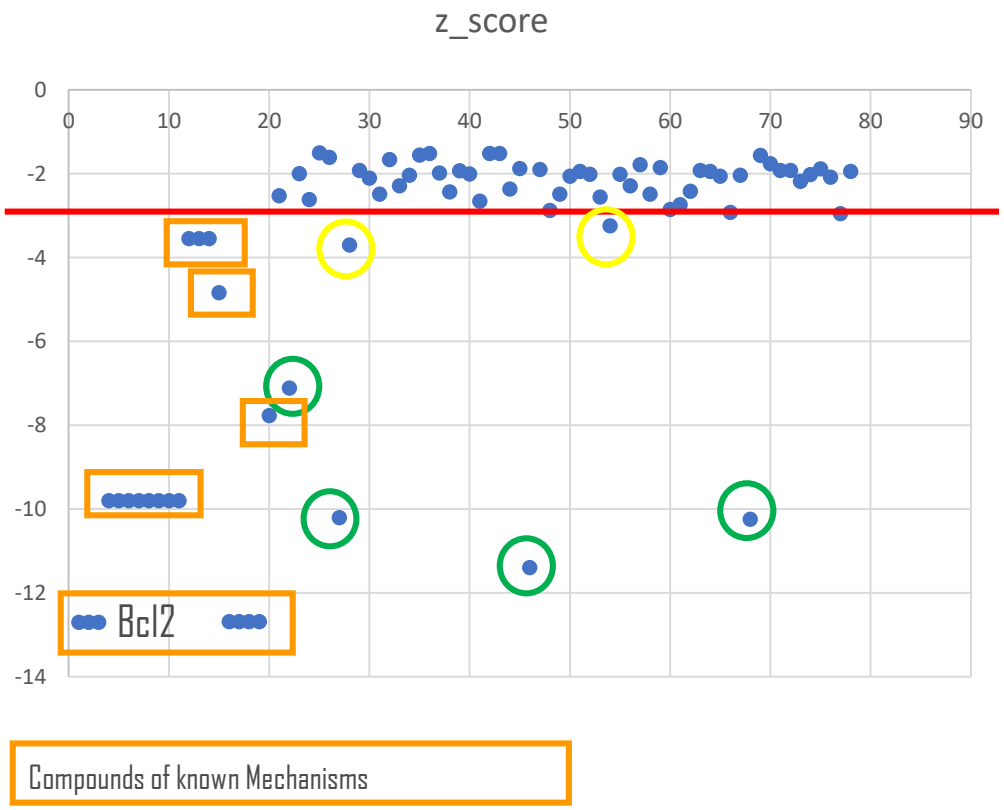
Berlín, Alemania



Patent registration pending

THANK YOU!!!

Cell Senescence, Cancer and Aging Lab

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Valentín Estévez
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Miguel Ángel Prados
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