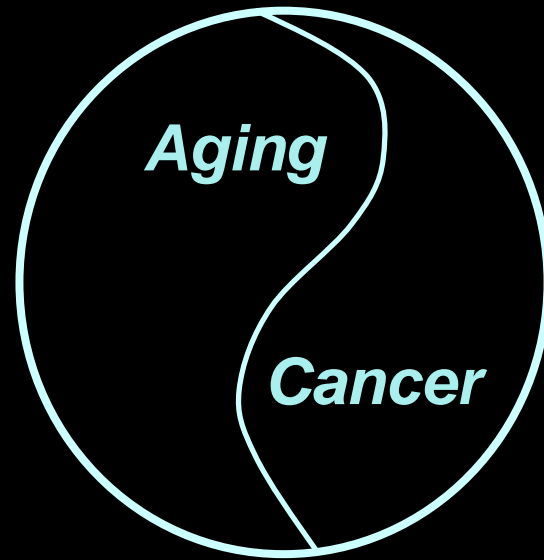


Aging and Cancer:

Rival Demons?



Aging and Cancer are Biological Linked

**Understanding Aging is
Key to Understanding Cancer**

Cancer is linked to aging

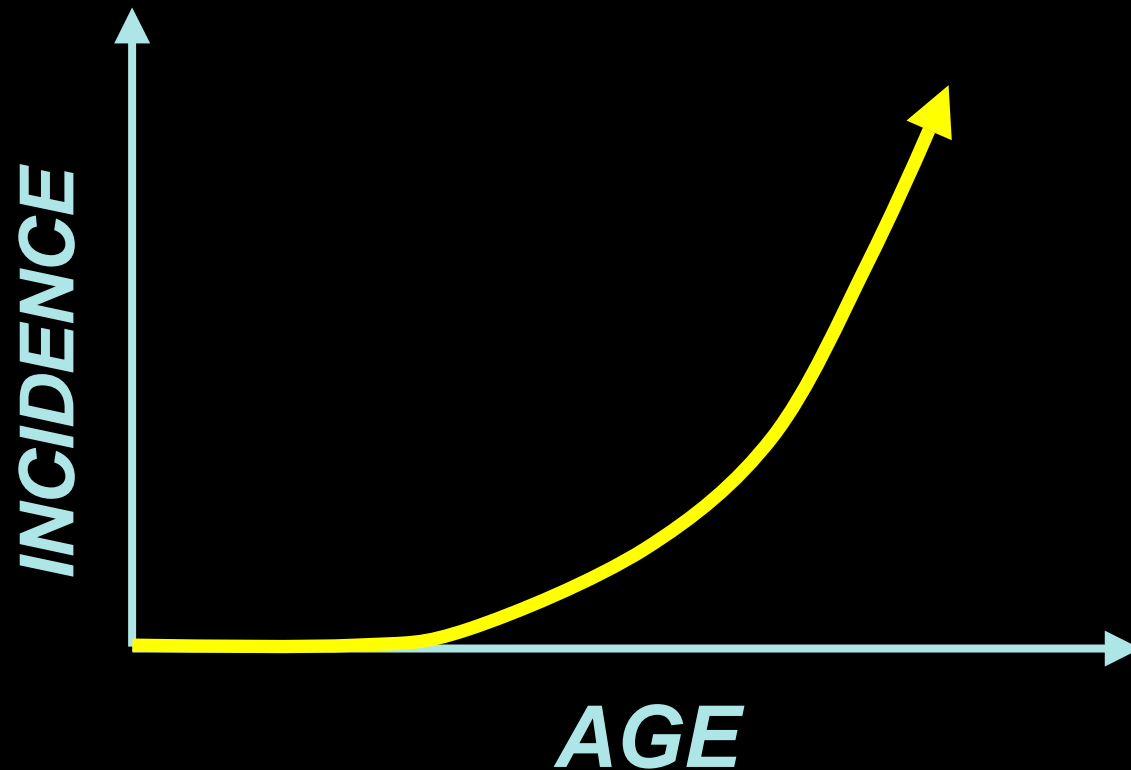
What is cancer?

What causes cancer?

What limits cancer?

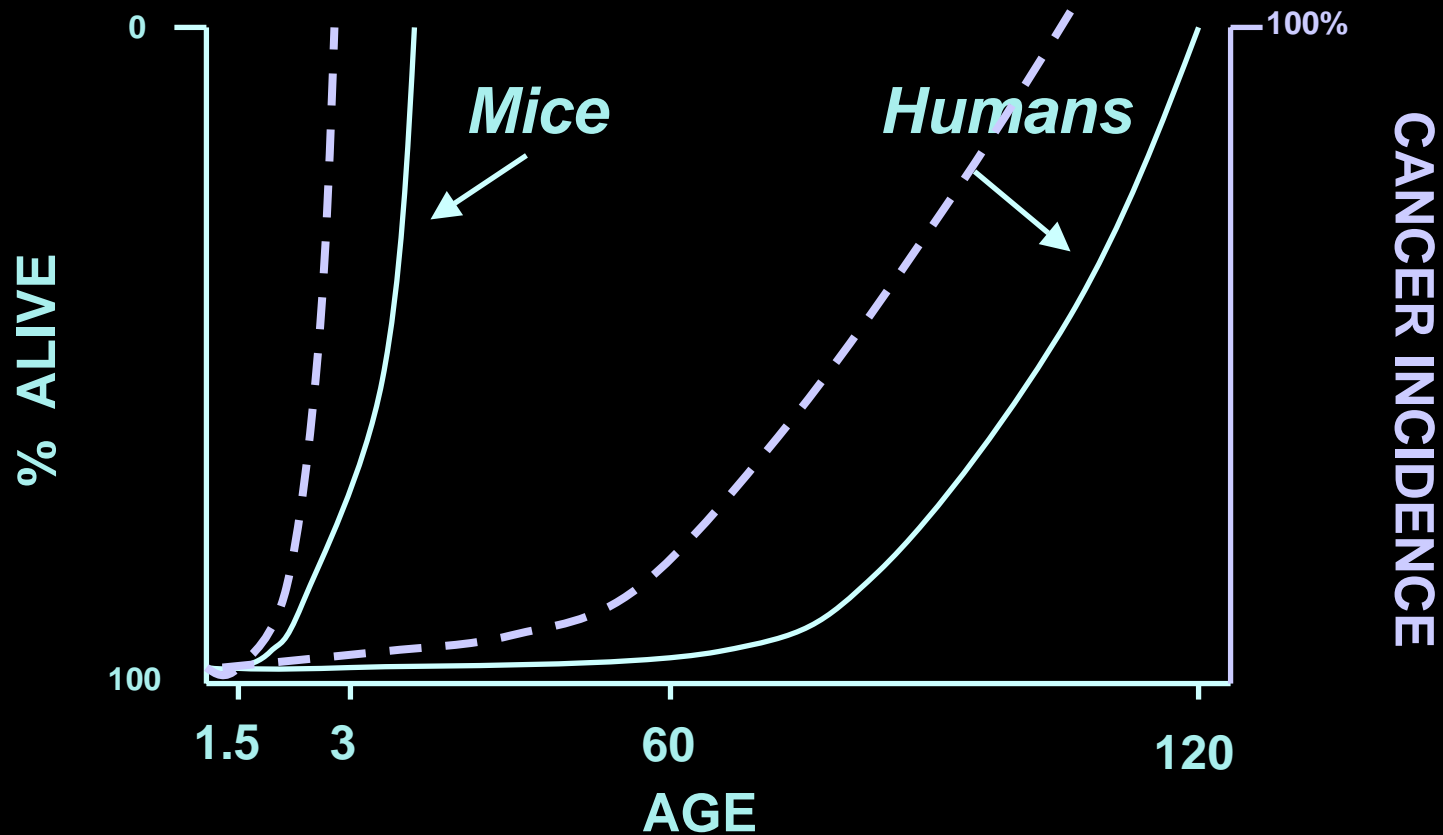
How are cancer and aging linked?

Cancer Rises Exponentially with Age



*Age is the largest single risk factor
Incidence vs mortality
Similar to other age-related diseases*

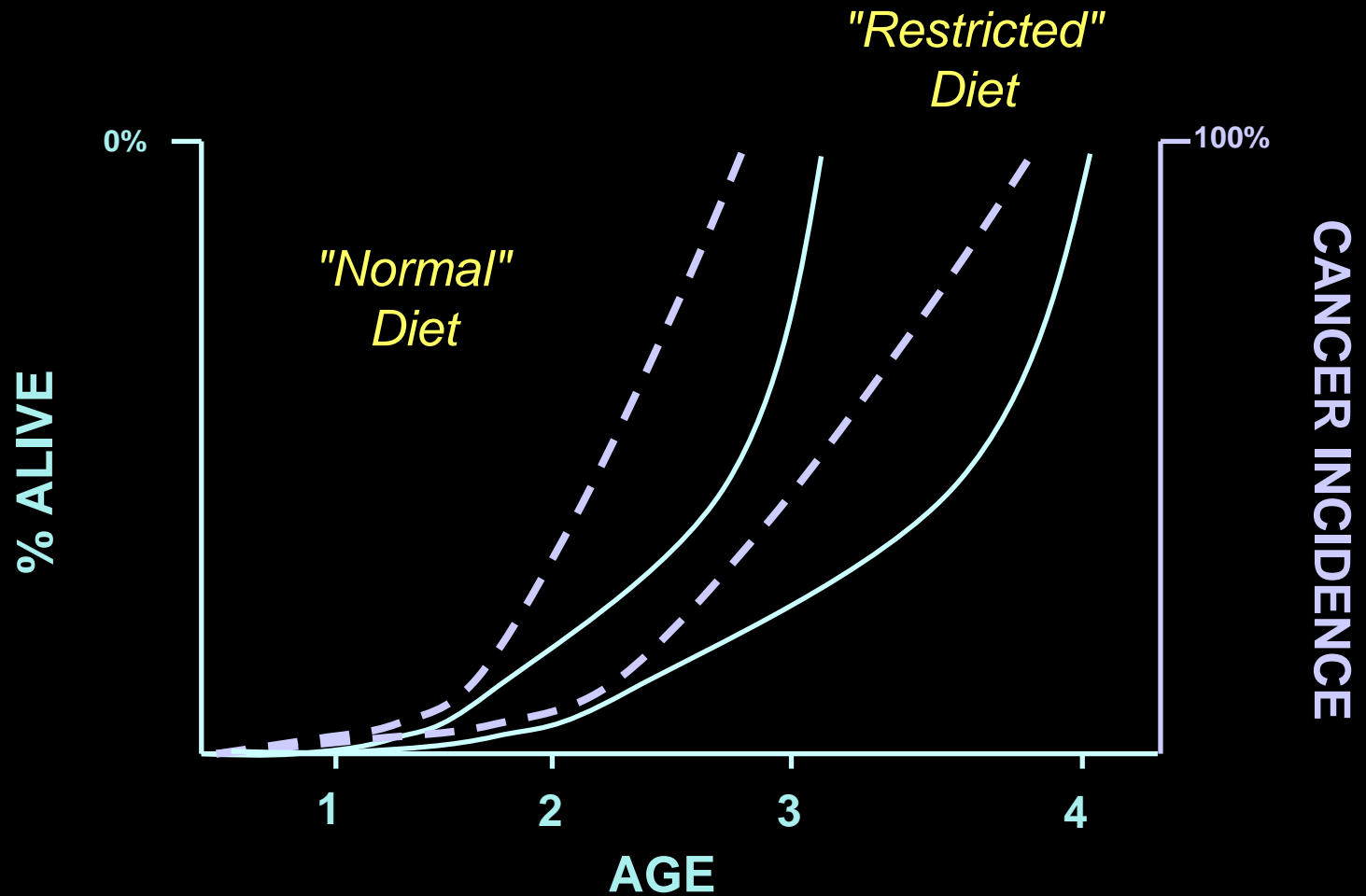
Cancer Incidence Scales with Life Span



Mice and Humans are ~ 97% Genetically Similar

Postponed Aging Delays Cancer

Mice



***The RATE at which cancer increases
is proportional to the RATE of aging***

Cancer is linked to aging

What is cancer?

What causes cancer?

What limits cancer?

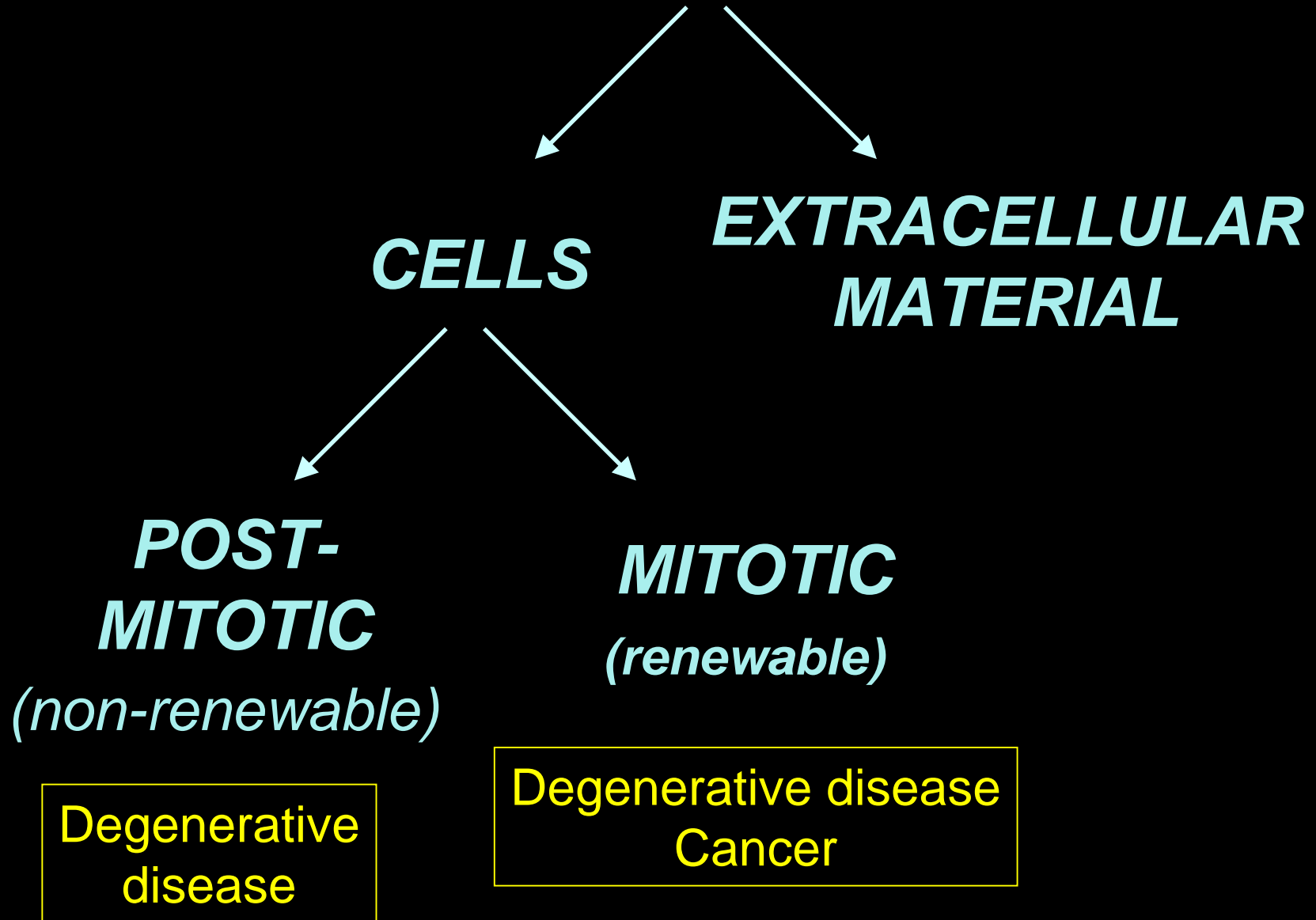
How are cancer and aging linked?

Cancer is an abnormal mass (tumor),
resulting from cell proliferation,
that has the potential to kill the organism

Cancer is much more than cell proliferation

***CANCER ARISES FROM
RENEWABLE TISSUES***

Composition of Complex Organisms



Five Characteristics of Malignant Cells

*Loss of growth control, including avoidance of senescence (**neoplasia**) **

*Avoidance of cell death (**apoptosis resistance**) **

*Stimulation of blood vessel formation (**angiogenesis**)*

*Invasion into surrounding tissue (**invasion**)*

*Ability to colonize distal tissues (**metastasis**)*

Loss of growth control
(neoplasia)

Inappropriate cell division

Unlimited cell division potential
(cellular senescence; replicative immortality)

Activation of growth promoting genes
[oncogenes]

Inactivation of growth inhibitory genes
[tumor suppressor genes]

Avoidance of Apoptosis
(cell death)

***Resistance to physiological
"death" signals***

***Resistance to damage-induced
death signals
(survival of cells with genomic instability)***

***Activation of growth promoting genes
[oncogenes]***

***Inactivation of growth inhibitory genes
[tumor suppressor genes]***

Cancer is linked to aging

What is cancer?

What causes cancer?

What limits cancer?

How are cancer and aging linked?

***Cancer cells acquire
malignant properties through
de novo somatic mutations
(activation of oncogenes or
inactivation of tumor suppressor genes)***

***Cancer cells also require
a tissue microenvironment that
permits the growth and survival of
mutant cells***

***(disruption of normal tissue
structure and function)***

Mutations accumulate throughout life

Potentially oncogenic mutations are present even in young apparently normal tissues

Tissue structure changes throughout life

Young tissues are often structurally distinguishable from middle-aged and old tissues

If mutations and tissue structure change throughout life, why then do we not get cancer more often?

Cancer is linked to aging

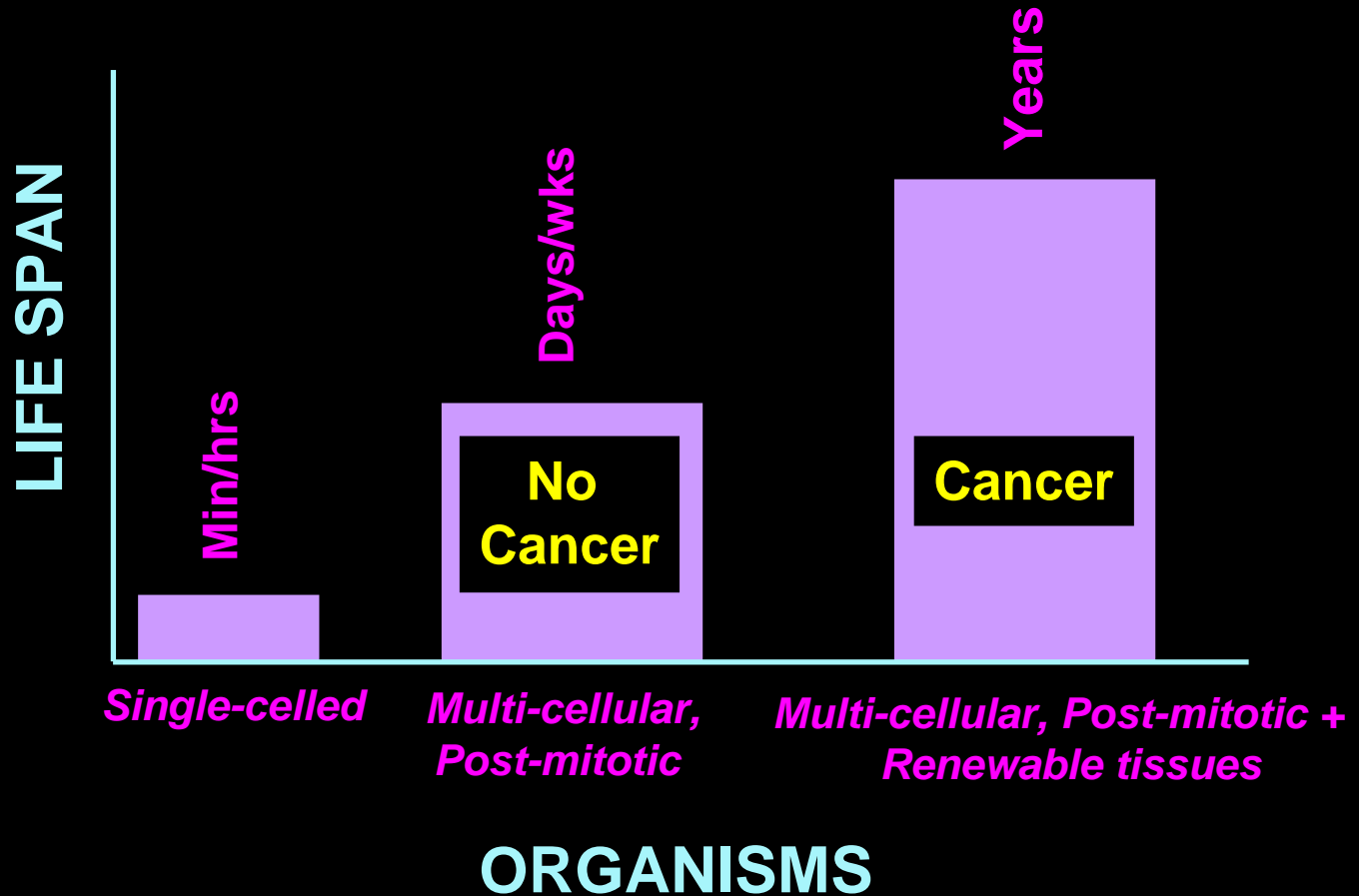
What is cancer?

What causes cancer?

What limits cancer?

How are cancer and aging linked?

Evolution of Long-Lived, Complex Organisms



CELL DIVISION IS RISKY!!

Risky business of CELL DIVISION

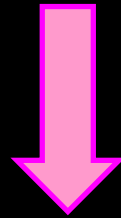
3 billion bp DNA:

**Unpackaged
(loss of protection)**

**Replicated
(fidelity; repair)**

Mutation Fixation

**Organisms with renewable tissues
had to evolve mechanisms
to prevent cancer**



Tumor Suppressor Genes

Two Classes of Tumor Suppressor Genes

- ***CARETAKERS -- act on the genome***

Damage prevention and repair

- ***GATEKEEPERS -- act on cells***

Apoptosis - eliminates potential cancer cells

Cellular senescence - prevents their growth

Apoptosis Suppresses Cancer

- Cancer cells frequently acquire mutations that inhibit cells from sensing or processing physiological death signals
- Mutations that dampen the apoptotic response greatly increases susceptibility to cancer
- Apoptosis is controlled by the two most powerful tumor suppressor pathways (p53 and pRB)

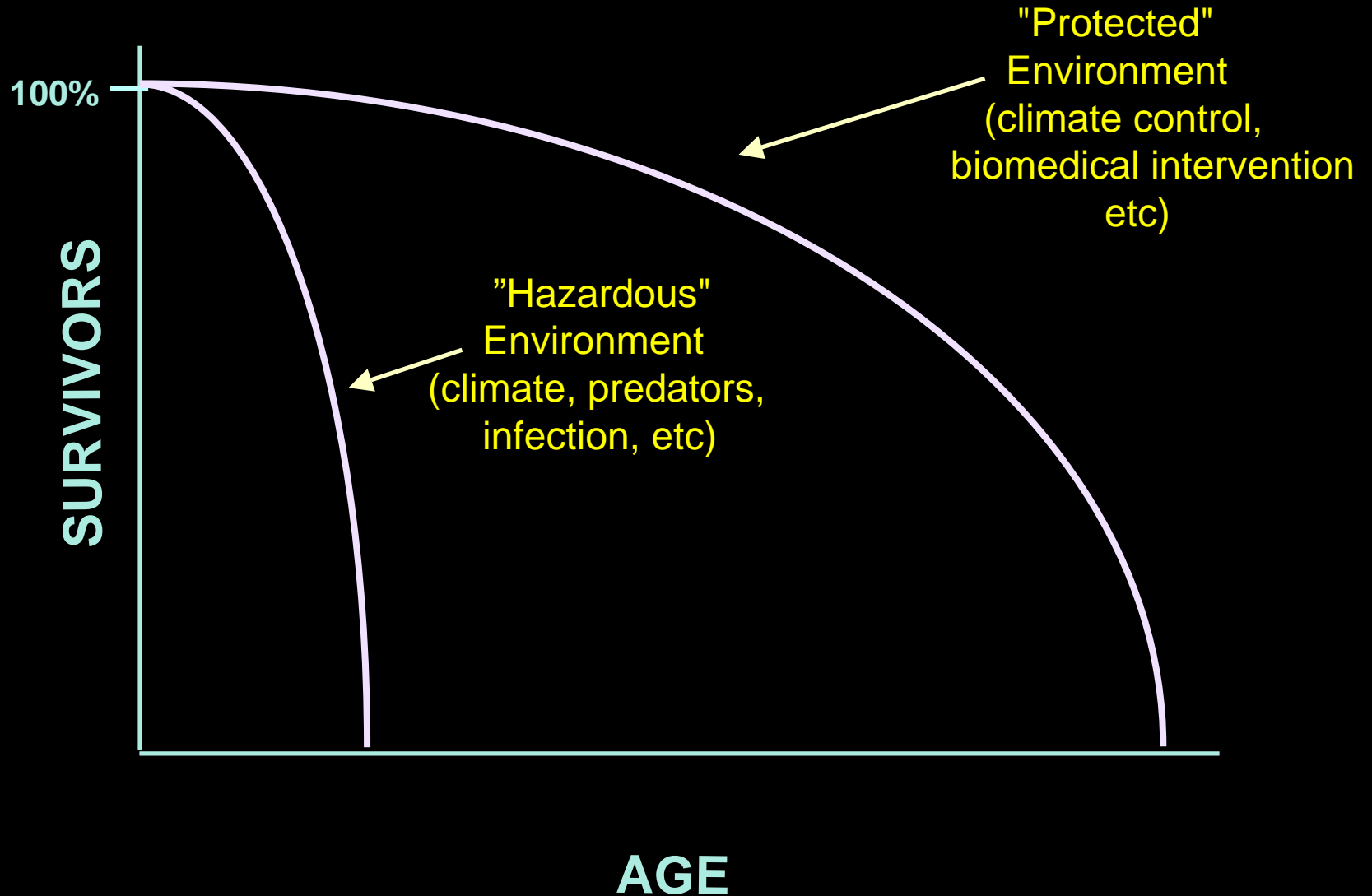
Cellular Senescence Suppresses Cancer

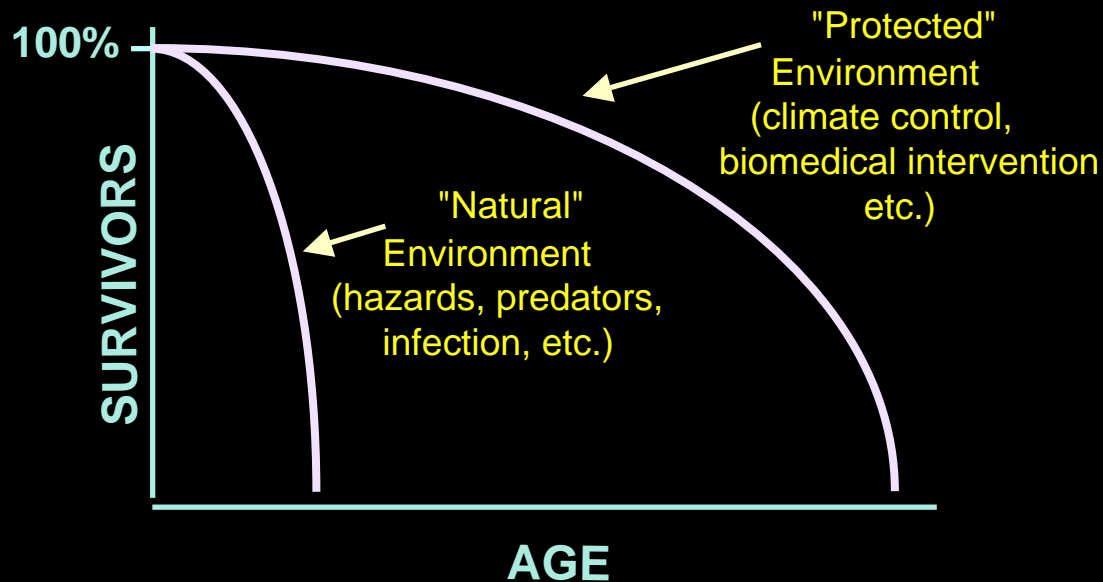
- Cancer cells frequently acquire mutations that abrogate the senescence response
- Mutations that dampen the senescence response greatly increases susceptibility to cancer
- Cellular senescence is controlled by the two most powerful tumor suppressor pathways (p53 and pRB)

***Caretaker tumor suppressor genes are
longevity assurance genes***

***Gatekeeper tumor suppressor genes can be
antagonistically pleiotropic***

Aging before cell phones





Mutation Accumulation ("*bad*" genes can persist)

Antagonistic Pleiotropy

(*what's good for you when you're young can be bad for you when you're old*)

*Why might gatekeeper tumor suppressors --
be antagonistically pleiotropic??*

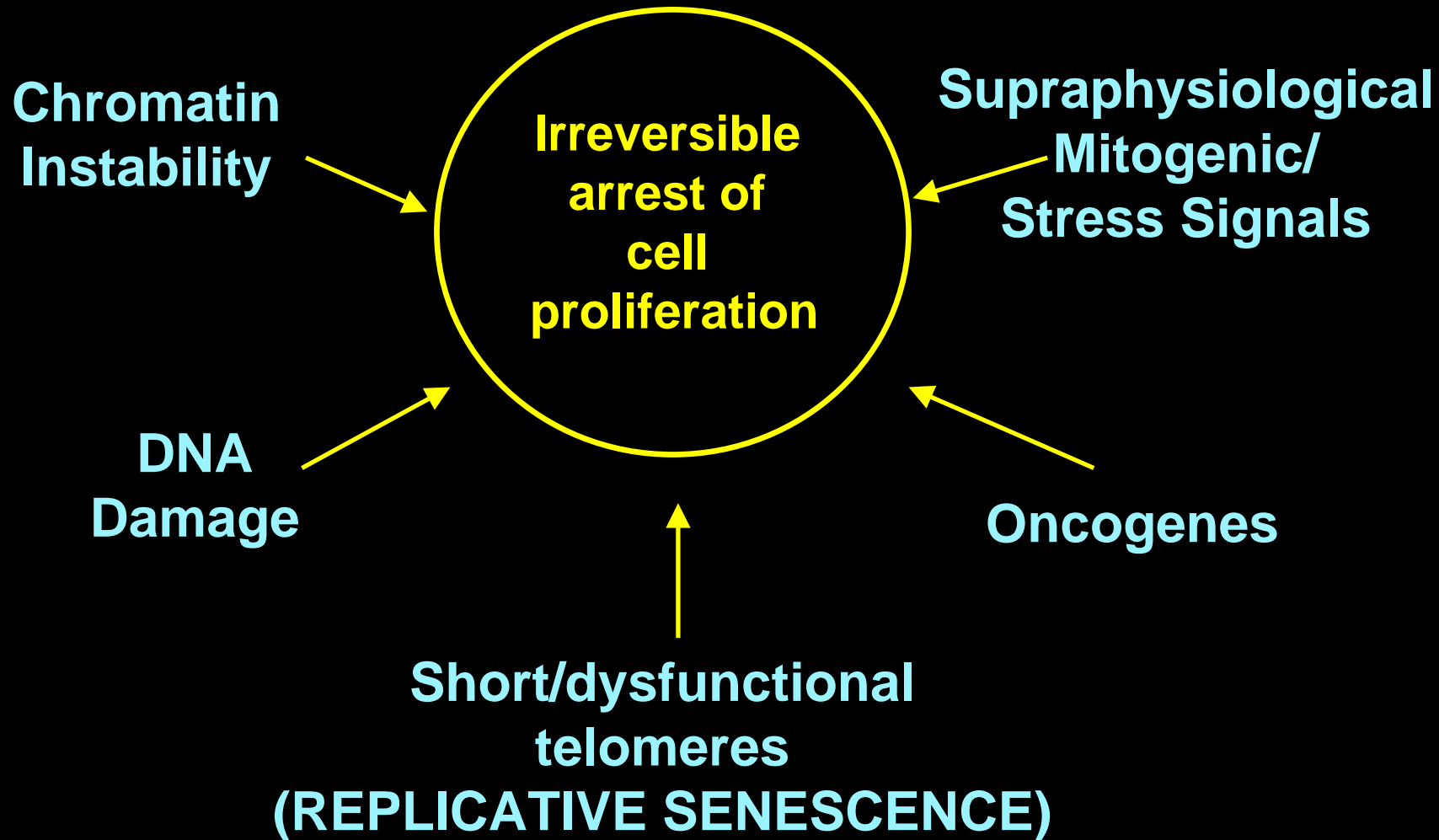
APOPTOSIS -- *culls defective cells.....
but deplete tissues of cells*

CELLULAR SENESCENCE -- *arrests
proliferation of defective cells
but senescent cells are dysfunctional*

***Testing the hypothesis that gatekeeper
tumor suppressors are
antagonistically pleiotropic:***

Cellular senescence

Cellular Senescence: Arrests Cell Proliferation In response to Potential Cancer-Causing Events



The Senescent Phenotype is Not Simply an Arrest of Cell Proliferation



The senescent phenotype:
Altered pattern of gene expression

Cell cycle regulation

Cell structure

Metabolism

Biologically active secreted molecules

Proteinases

Cytokines

Growth factors

Secreted molecules upregulated by the senescence response

Proteinases/regulators

MMP-1
MMP-3
Elastase
TIMP-2
PAI-1



Alter tissue structure

Growth Factors/regulators

EGF
Heregulin
IGFBP-3
IGFBP-4



Alter cell proliferation

Cytokines

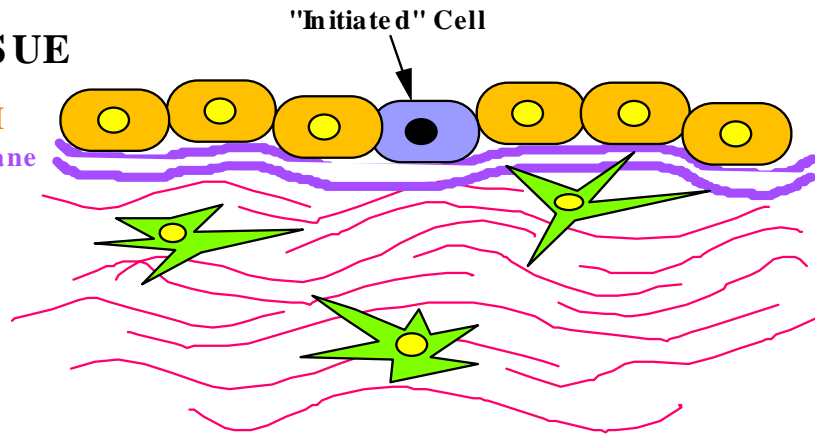
TGF- β
IL-1
IL-6
GRO(KC)
MIP-1



Alter cell motility, inflammation

YOUNG TISSUE

EPITHELIUM
Basement Membrane

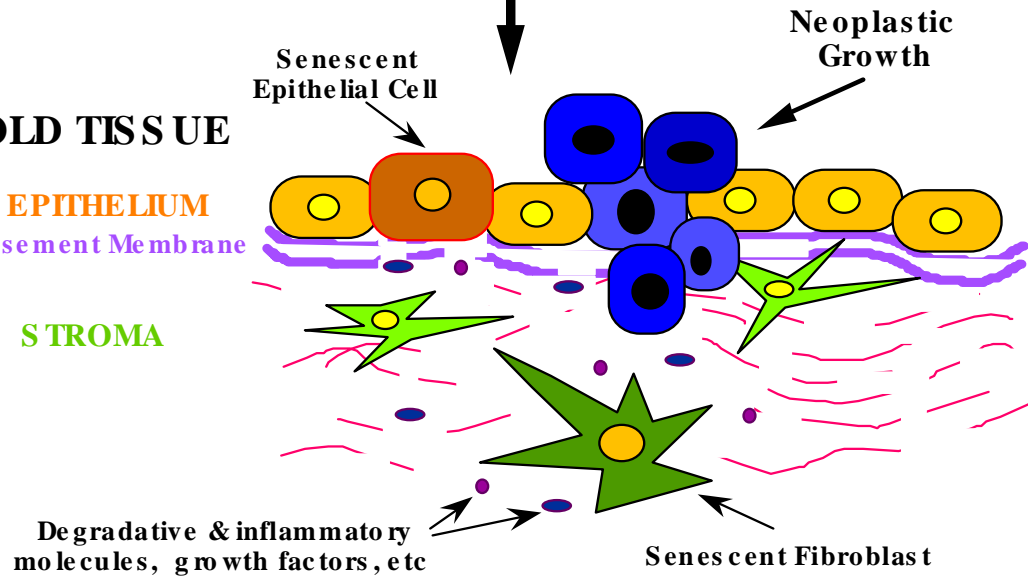


AGING ?

OLD TISSUE

EPITHELIUM
Basement Membrane

STROMA



Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do senescent cells exist and accumulate with age in vivo?

Goberdhan Dimri

Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith O, Peacocke M, Campisi J
(1995) **Proc Natl Acad Sci USA** 92: 9363-9367

Senescent Cells Accumulate In Vivo

With Increasing Age

Skin

Retina

Liver

Spleen

At Sites of Age-Related Pathology

Venous ulcers

Atherosclerotic plaques

Benign prostatic hyperplasia

Preneoplastic hepatic lesions

Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do gatekeeper tumor suppressor genes accelerate aging?

***Larry Donehower
Heide Scrabble***

Tyner et al., p53 mutant mice that display early aging-associated phenotypes. Nature 415:45 (2002)

Maier et al., Modulation of mammalian life span by the short form of p53. Genes Dev 18: 306 (2004)

p53 -
a quintessential gatekeeper tumor suppressor gene

Transcription factor

(activation and repression of multiple target genes)

Binds DNA as a tetramer

(Donehower/Scrabble mutant/short forms thought to assemble mixed tetramers)

Mixed tetramers “hyperactive”

(hyper-transcriptional activation and/or repression, or altered spectrum of target genes)

“Hyperactive” p53

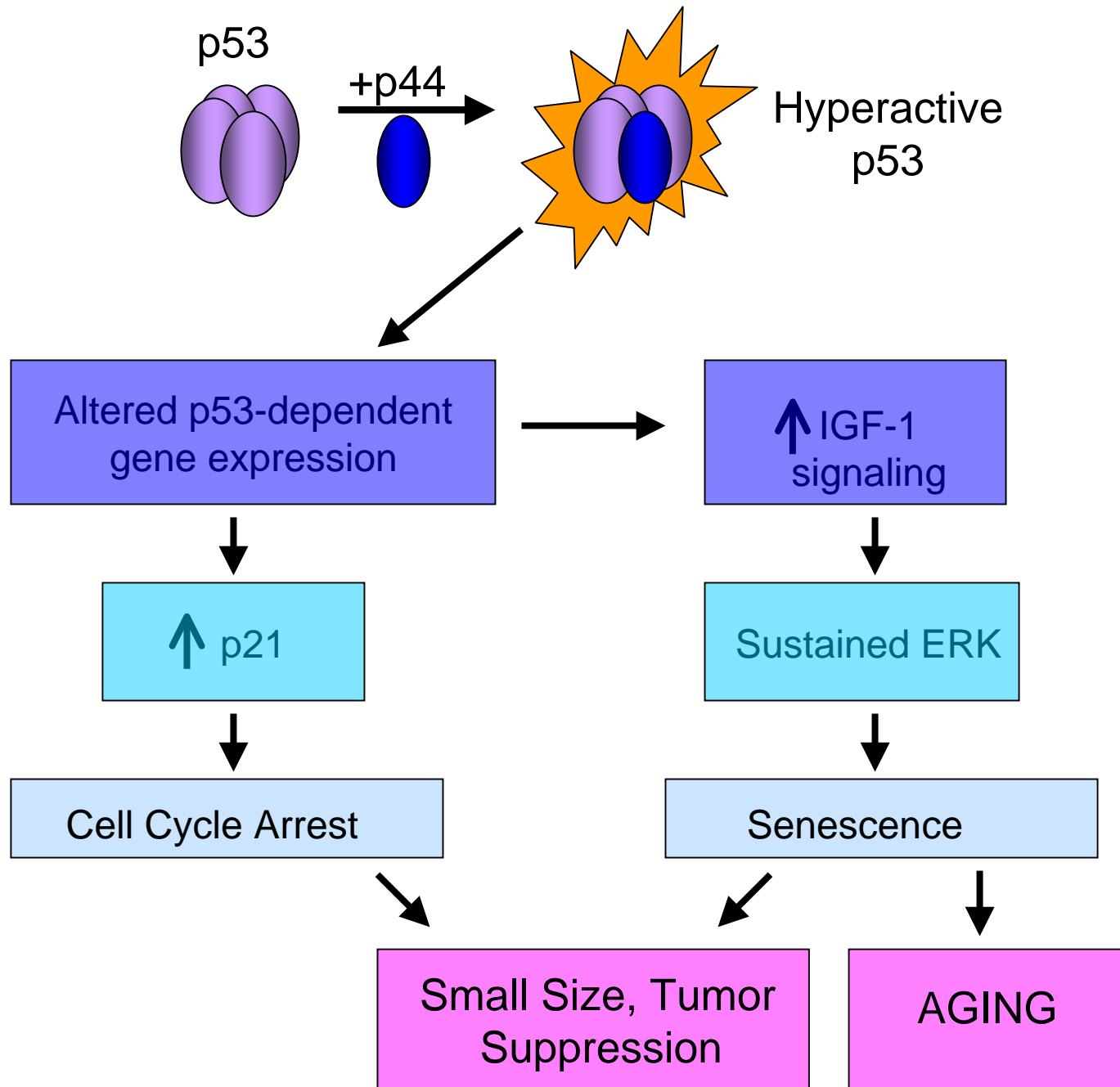
***Donehower mouse: cancer-free but
prematurely aged!***

***Enhanced apoptotic response to damage
(published)***

***More senescent cells in tissues of mutant mice
(unpublished)***

***Scrabble mouse: small size, cancer-free but
prematurely aged!***

***Enhanced senescence owing to supraphysiological
IGF-1 signaling
(unpublished)***



Testing the hypothesis that cellular senescence is antagonistically pleiotropic

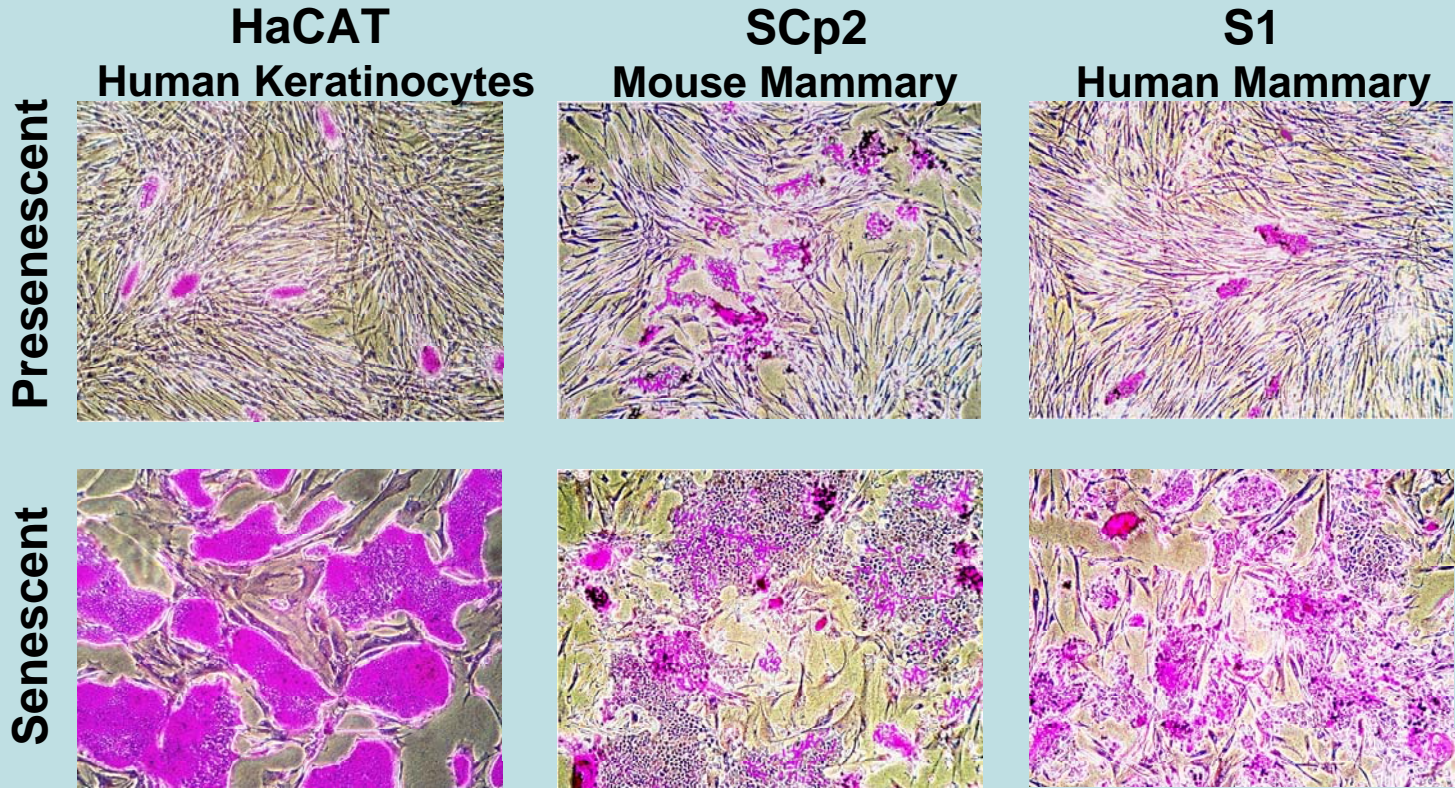
***Do senescent cells facilitate age-related pathology?
(CANCER)***

***Ana Krtolica
Simona Parrinello***

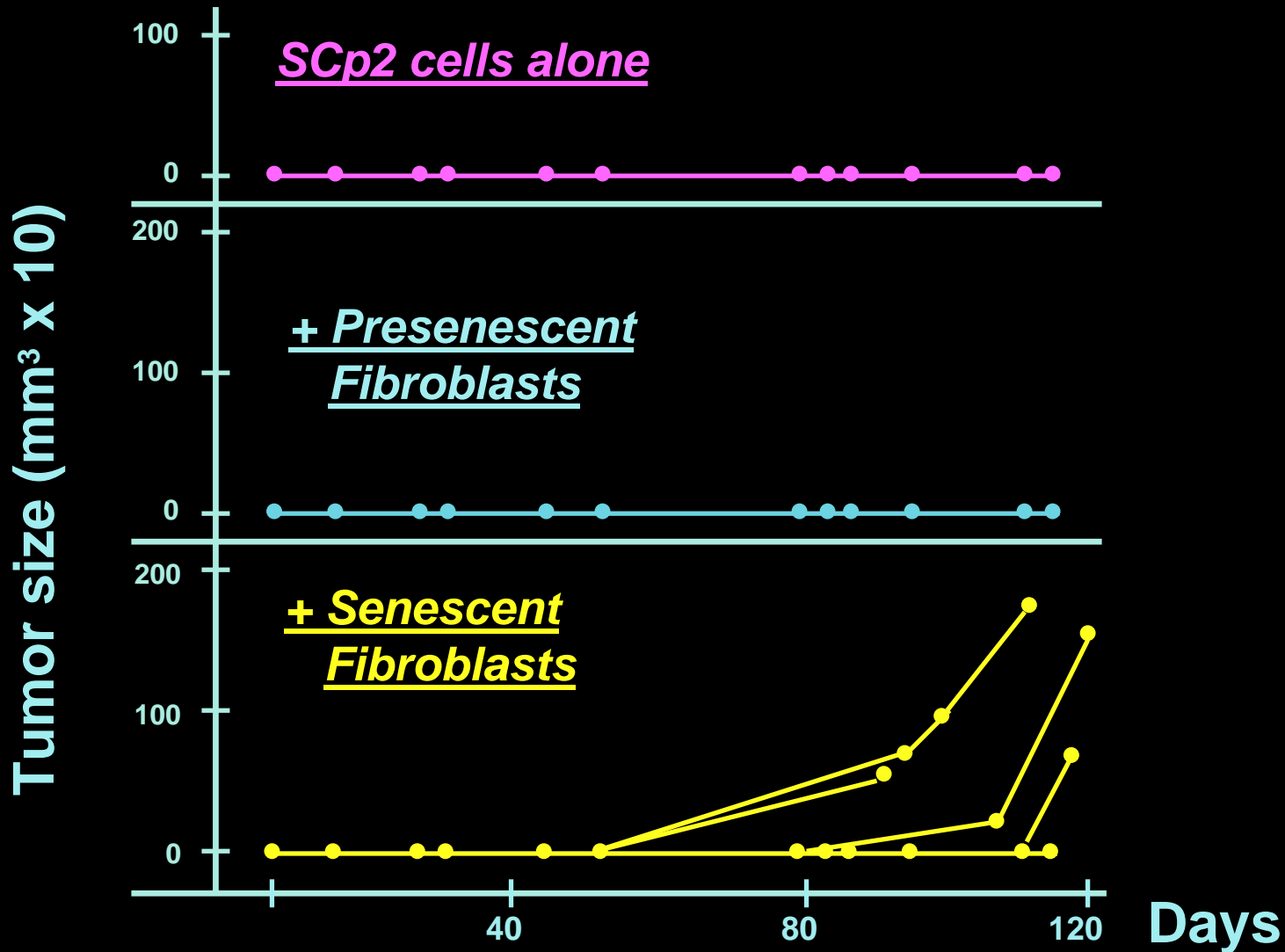
Krtolica A, Parrinello S, Lockett S, Desprez P, Campisi J
(2001) *Proc Natl Acad Sci USA* 98: 12072-12077

**Senescent Fibroblasts Stimulate the Proliferation of
Premalignant Epithelial Cells**

Human Fibroblasts (WI-38)



Senescent Fibroblasts Stimulate Tumorigenesis of Premalignant Epithelial Cells In Vivo



Testing the hypothesis that cellular senescence is antagonistically pleiotropic

Do senescent cells disrupt normal tissue function?

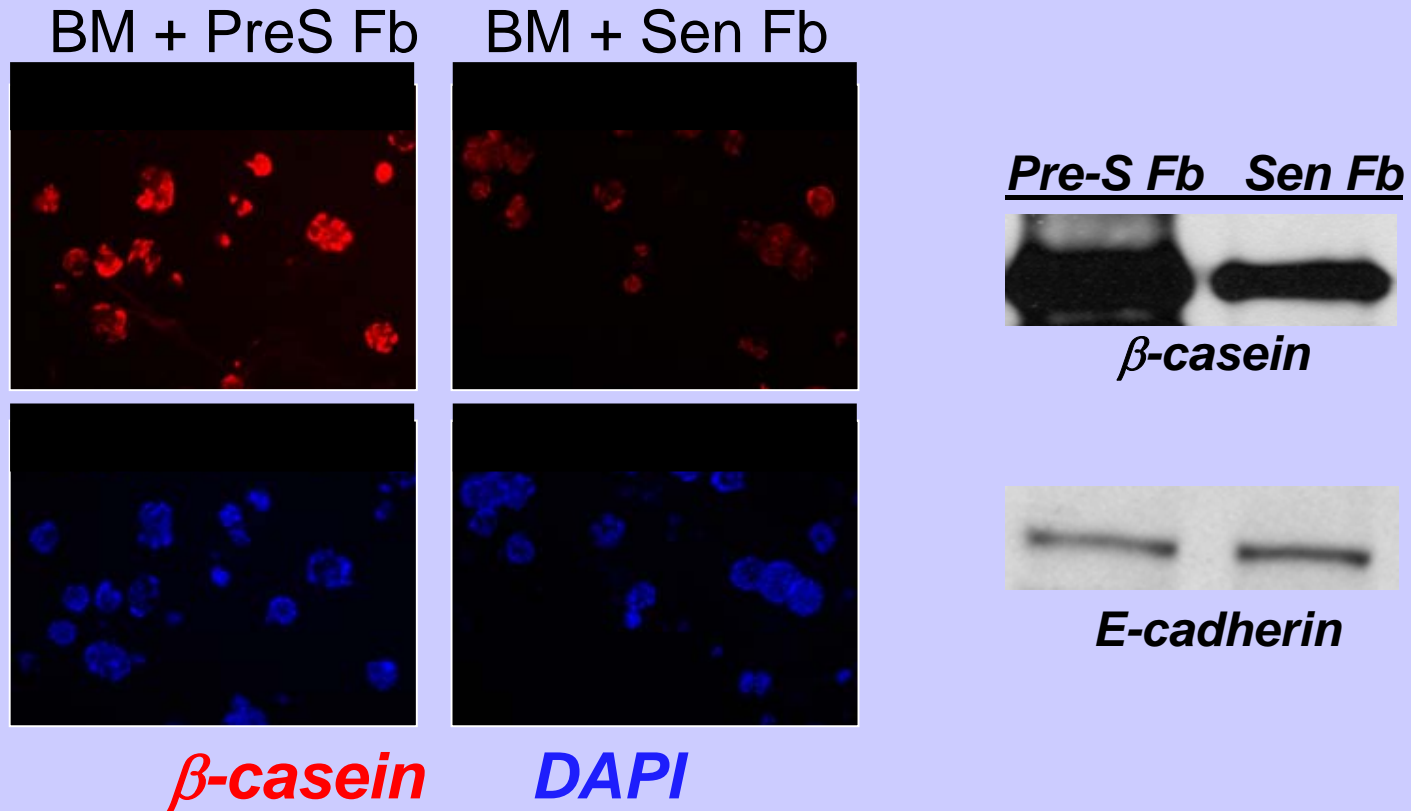
Simona Parrinello
Ana Krtolica
Jean-Philippe Coppe

***Three dimensional cultures to study
tissue structure and function:***

***Human and mouse mammary epithelial cells
organize into physiological alveoli when
cultured with appropriate components in 3D***

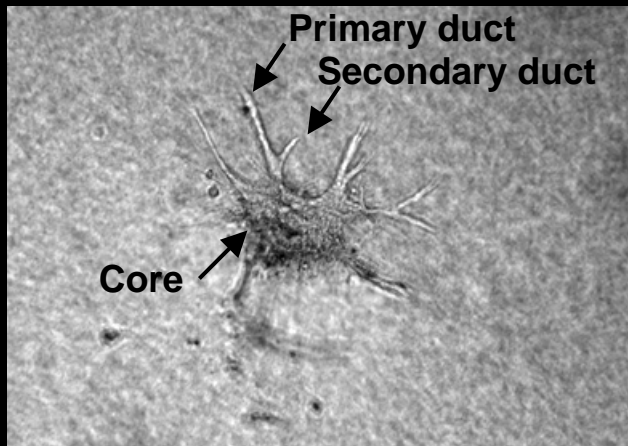
***Morphological organization
Functional differentiation***

Senescent fibroblasts inhibit morphological and functional differentiation

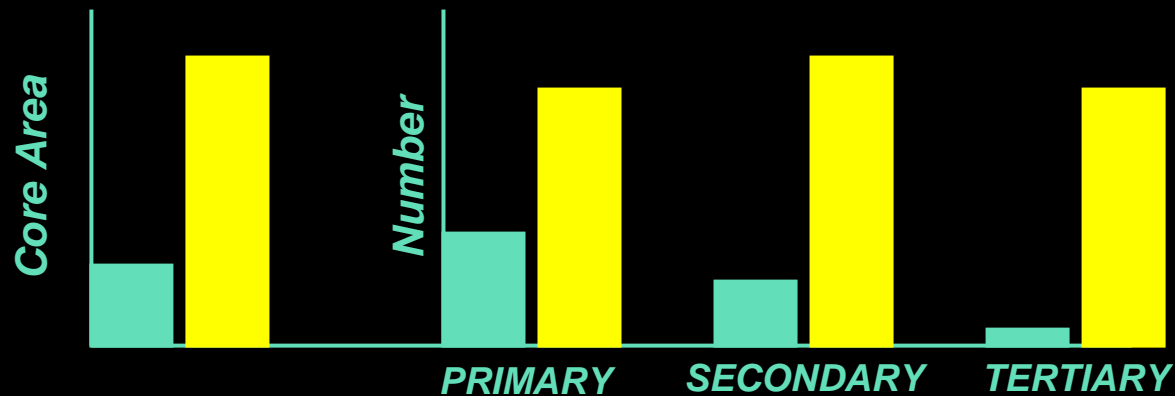
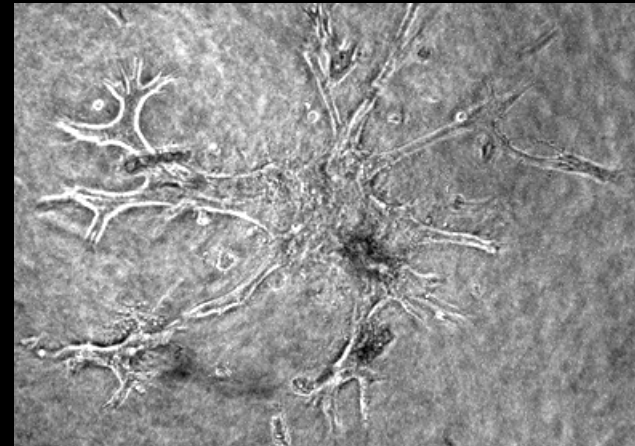


Senescent fibroblasts derange mammary morphogenesis

Presenescent fibroblasts



Senescent fibroblasts



Cellular senescence, a tumor suppressor mechanism, prevents cancer early in life.

Late in life, accumulation of senescent cells can disrupt normal tissue structure and function.

Accumulated senescent cells may synergize with accumulated mutations to promote cancer and age-related tissue dysfunction.

Can senescent phenotypes be reversed?

Christian Beausejour, Ana Krtolica, Francesco Galimi, Masashi Narita,
Scott Lowe, Paul Yaswen

(2003) EMBO J 22: 4212-4222

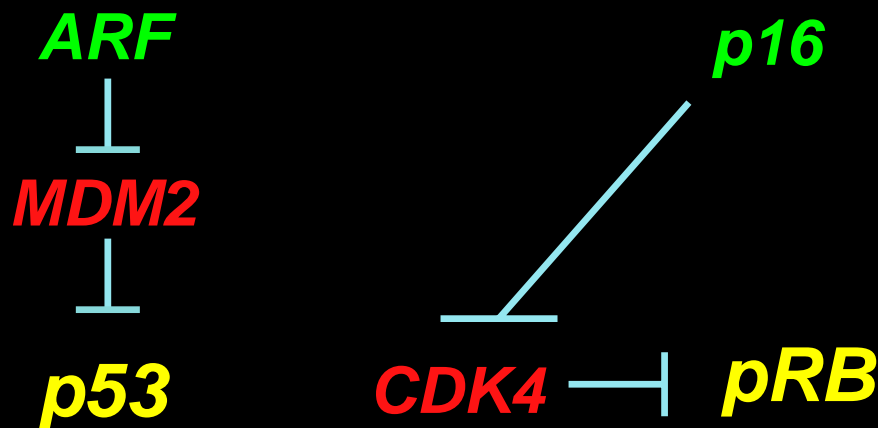
Lentiviruses ---> high-efficiency expression of genes in senescent cells

Lenti-GSE (inactivates p53)

Lenti-CDK4m (inactivates pRB)

Lenti-p16 (activates pRB)

Lenti-p16(RNAi) (inactivates pRB)



***Replicatively
Senescent***

WI-38

(fetal lung fb)

***Replicatively
Senescent***

BJ

(foreskin fb)

+ Lenti-GSE (inactivate p53)

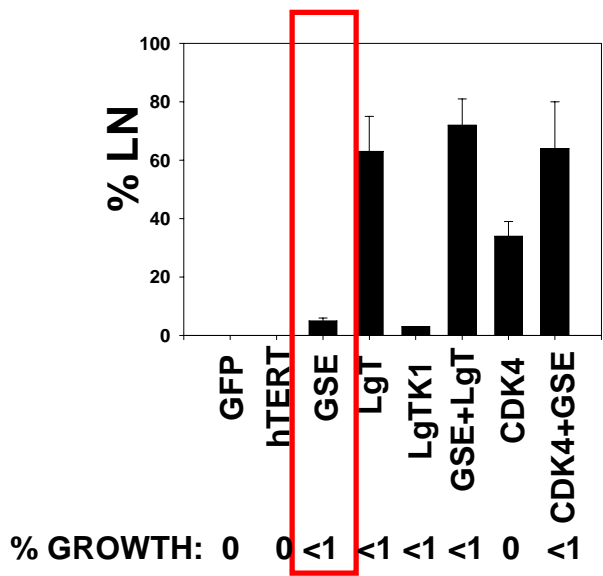


No proliferation

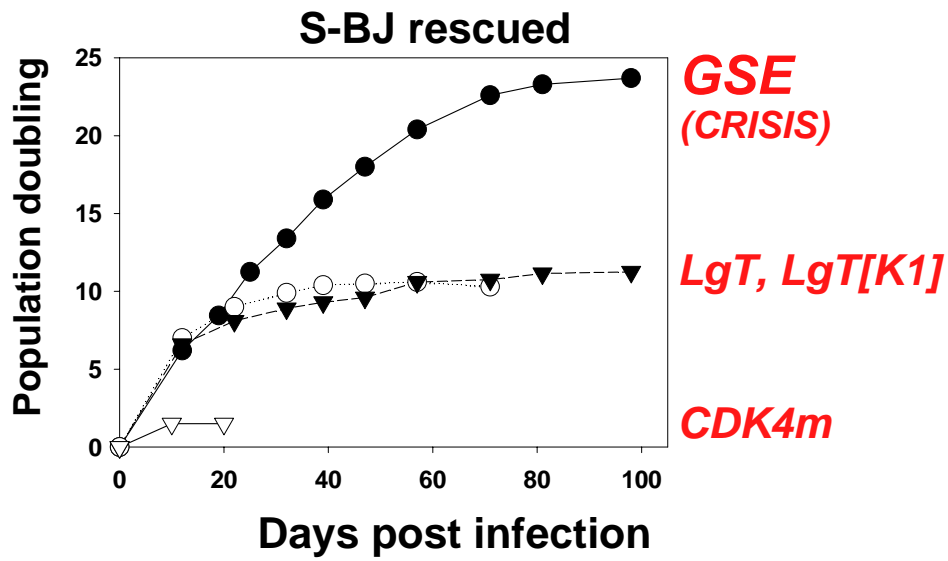
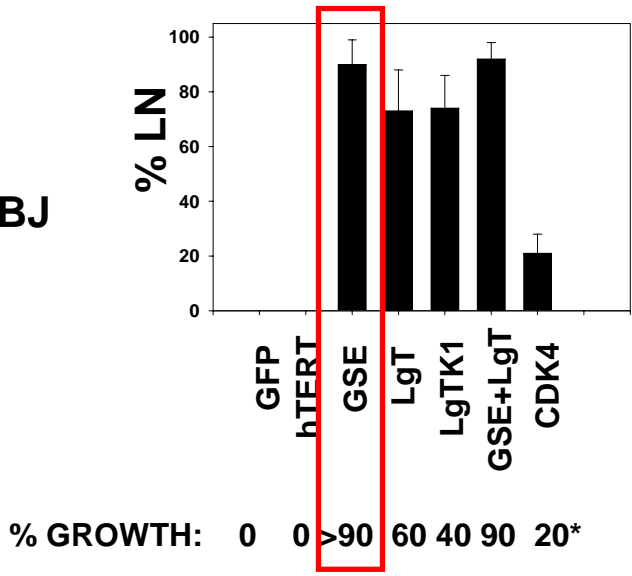


20 Doublings

S-WI



S-BJ



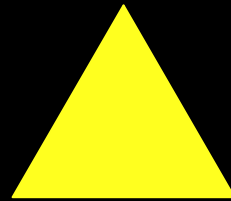
On the horizon

- *Molecular strategies to eliminate (or reverse the phenotype of) senescent cells*
- *Cell based therapies (stem cells) to replace senescent cells or cells lost through apoptosis in degenerated tissues*

Aging and Tumor Suppression

Aging Phenotypes

Cancer



**Gatekeeper
Tumor Suppressors**

***Can tumor suppression and aging
be uncoupled??***

Jean Philippe Coppe
Joshua Goldstein
Ana Krtolica
Francis Rodier
Simona Parinello

Christian Beausejour - Sangamo
Pierre Desprez -CPMC
Goberdhan Dimri - NW U

Francesco Galimi/Inder Verma - Salk
Steve Lockett - LBNL/NCI
Masa Narita/Scott Lowe - CSH
Enrique Samper/Simon Melov - Buck
Carlos Ortiz de Solorano - LBNL
Paul Yaswen - LBNL