Telomere Dysfunction-Induced Senescence in Aging and Disease

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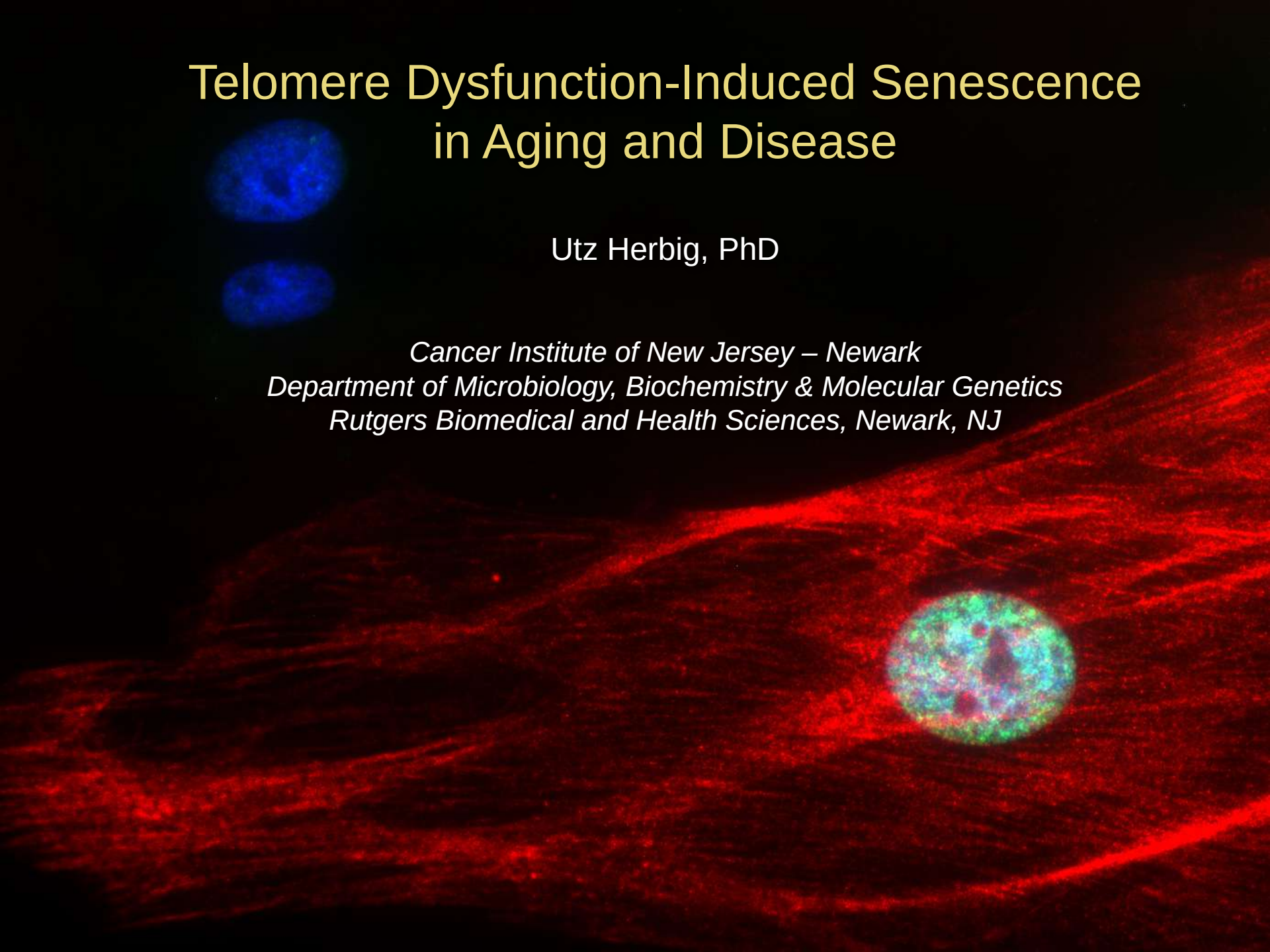
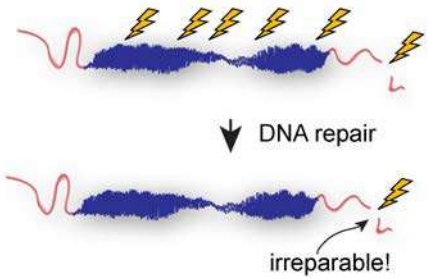


Cellular Senescence

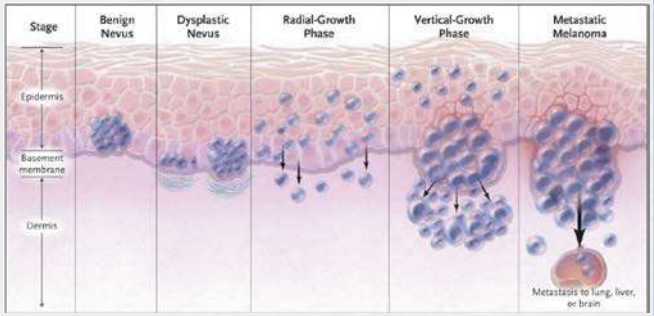
DNA Replication (Telomere Shortening)
Oncogenic Stress
DNA Damage
Oxidative Stress
Cytokines
Chromatin Changes
Developmental Cues
Mitochondrial Disturbances
Cell Reprograming
Cell-Cell Fusion



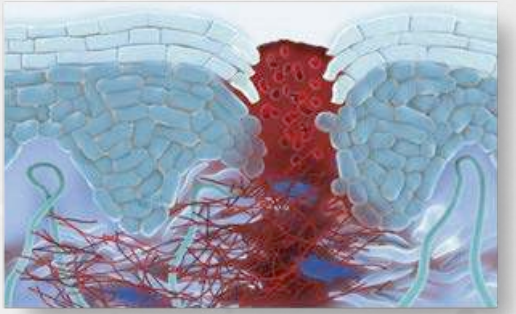
Human Diploid Fibroblasts

Biological Role of Cellular Senescence

Tumor Suppression
2005

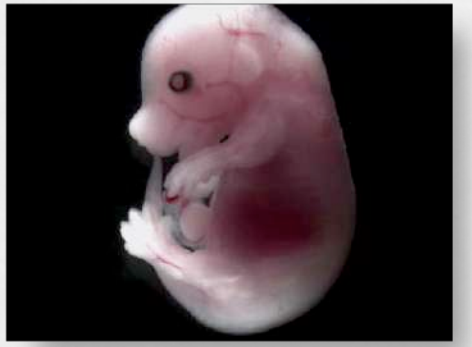


Wound Healing
2008



Aging
2011

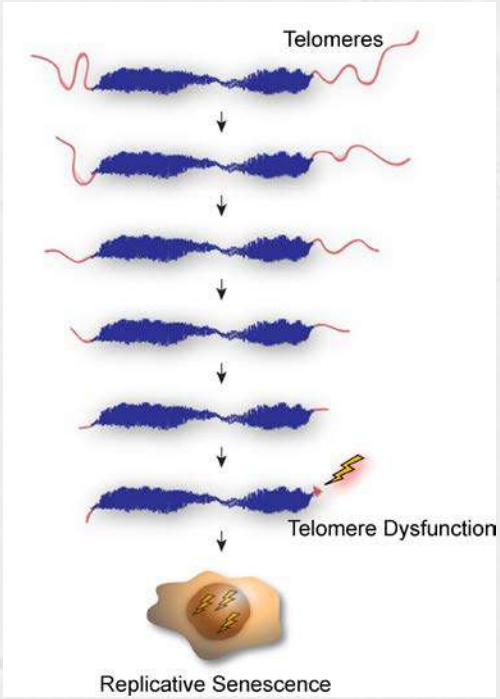
Embryonic Development
2013



Biological Role of Telomere Dysfunction-Induced Senescence - TDIS

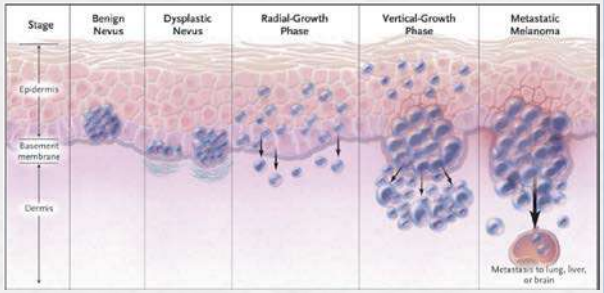
Aging

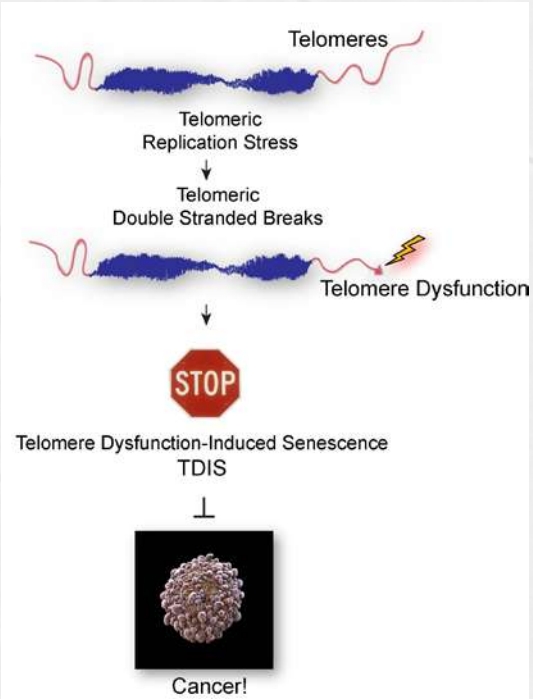
Herbig et al., 2006, Science



Tumor Suppression

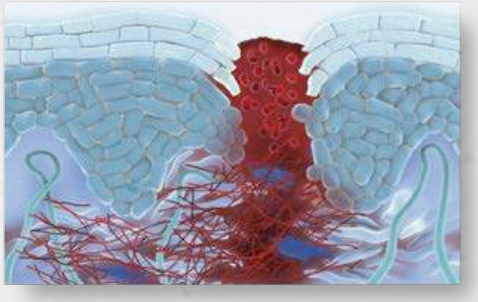
Suram et al., 2012, EMBO J

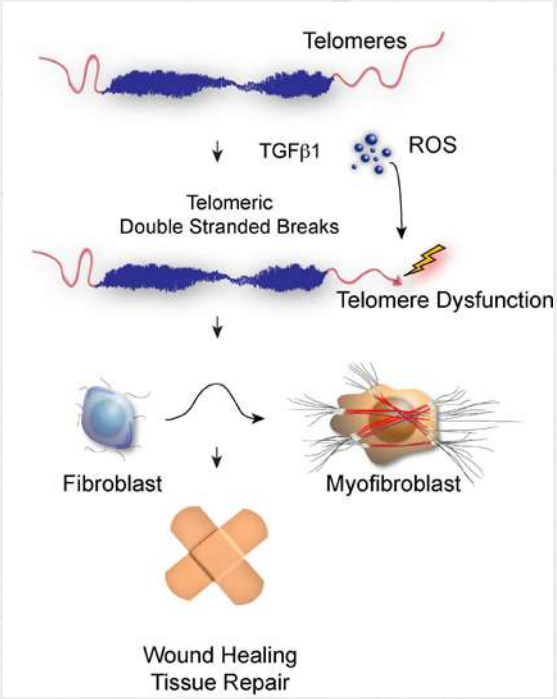




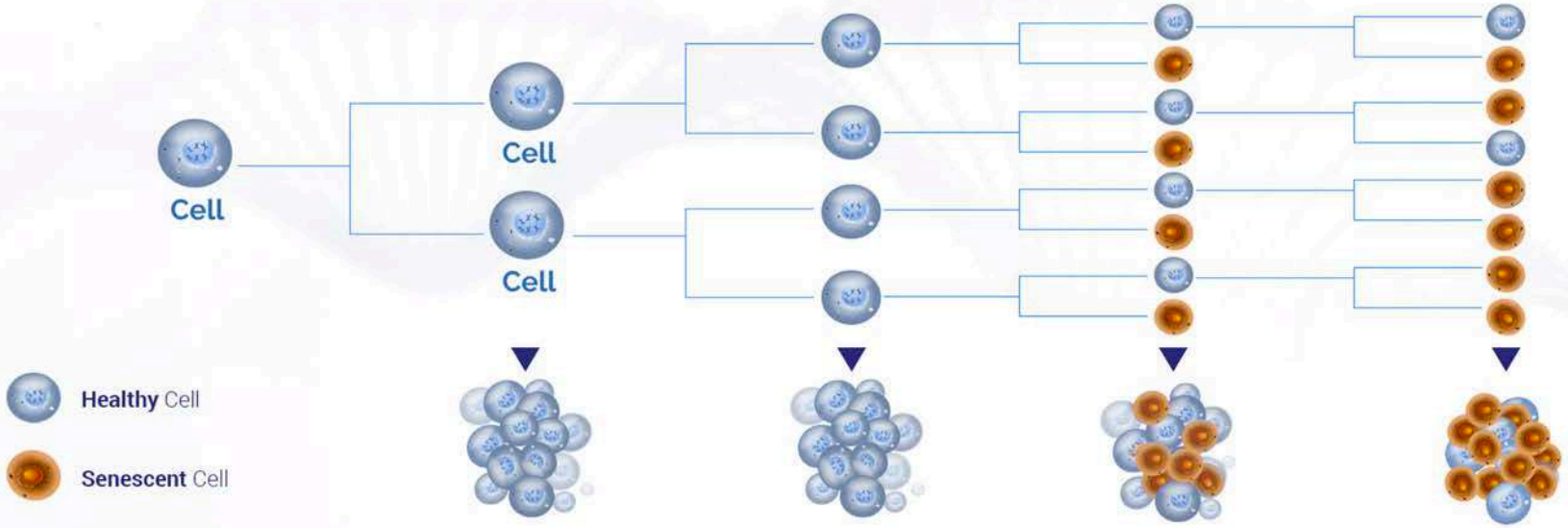
Wound Healing

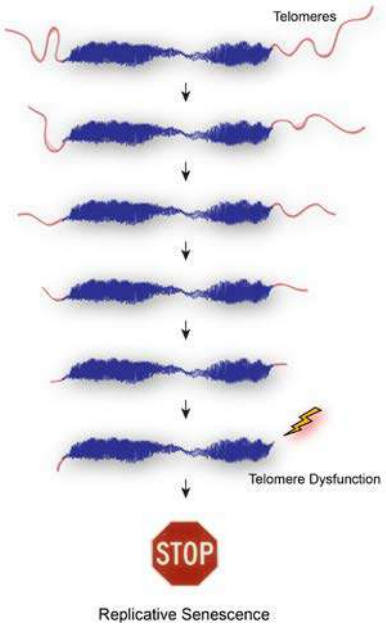
Razdan et al., 2018, Aging Cell

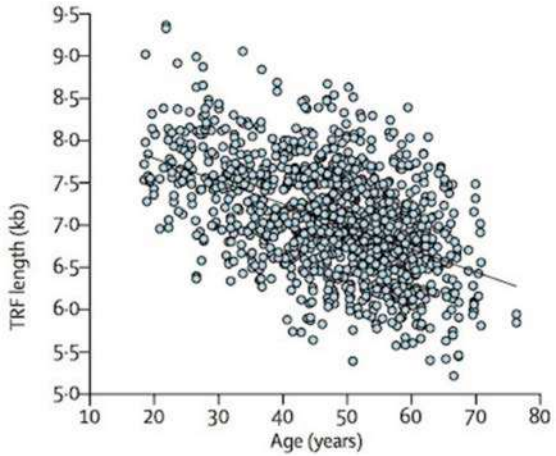




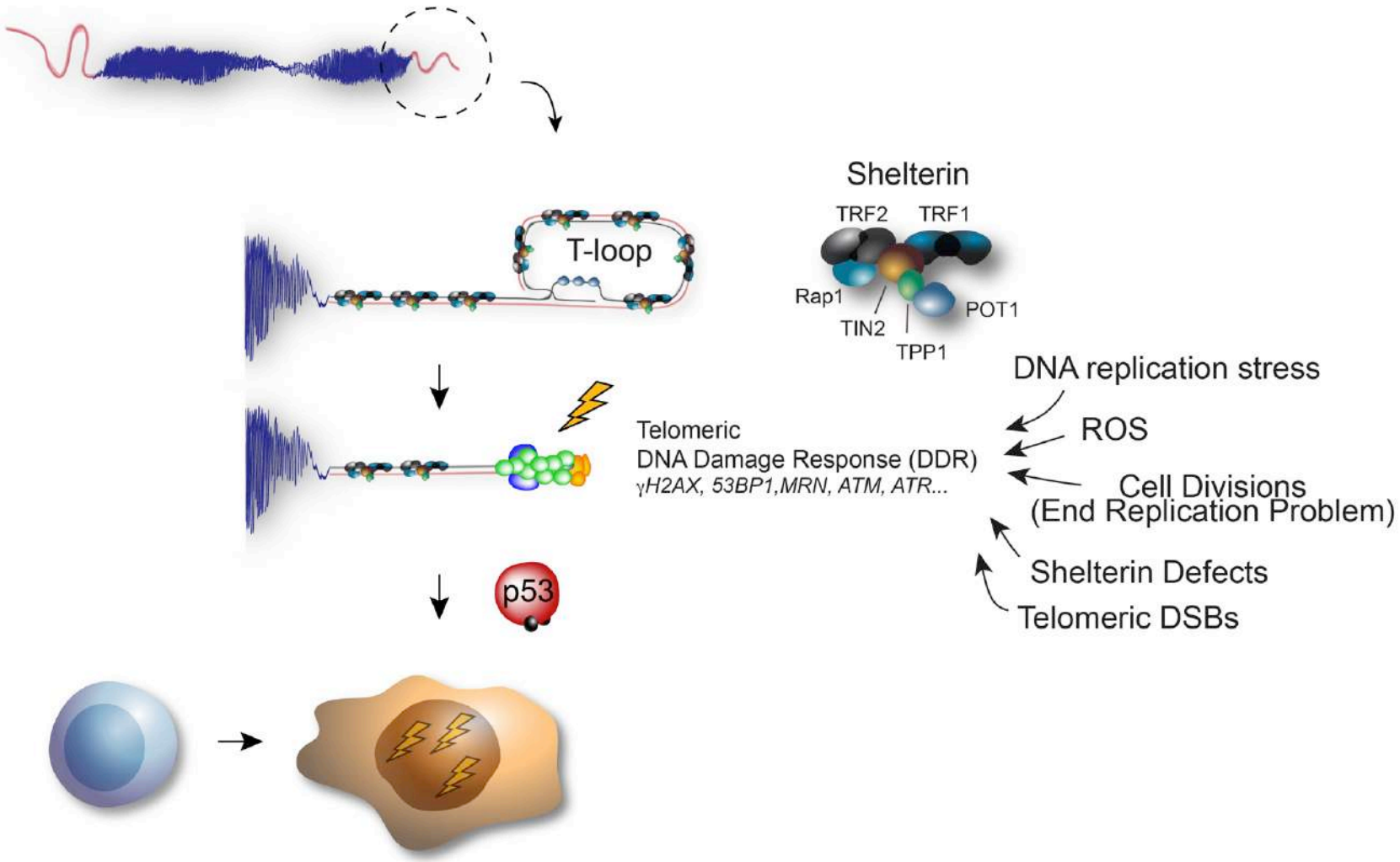
Cells Age and Undergo Replicative Senescence







Telomere Dysfunction-Induced Senescence

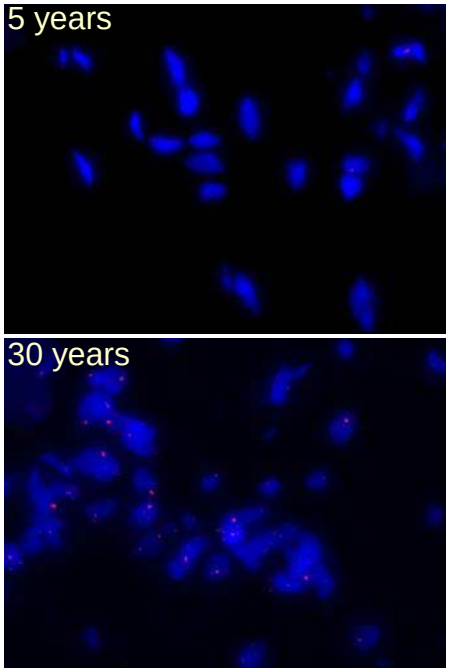


Telomere Dysfunction-Induced Senescence

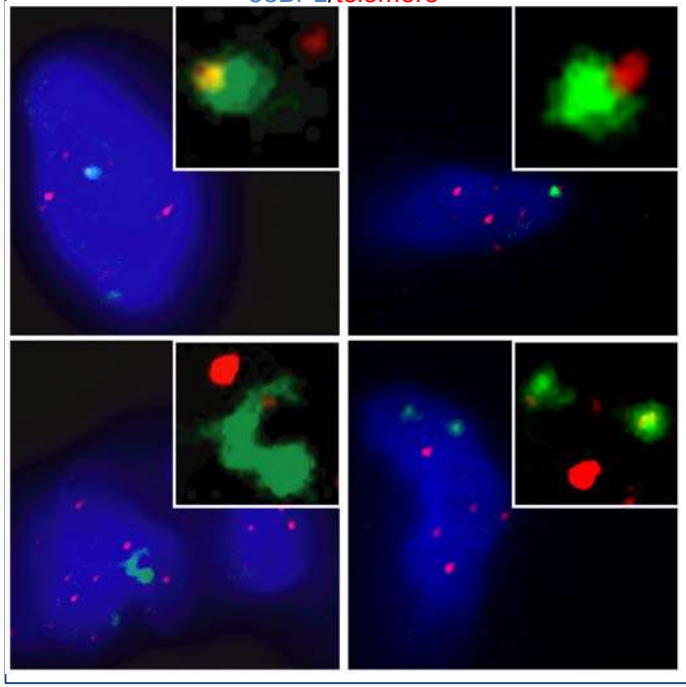
Telomere Dysfunction-Induced Senescence

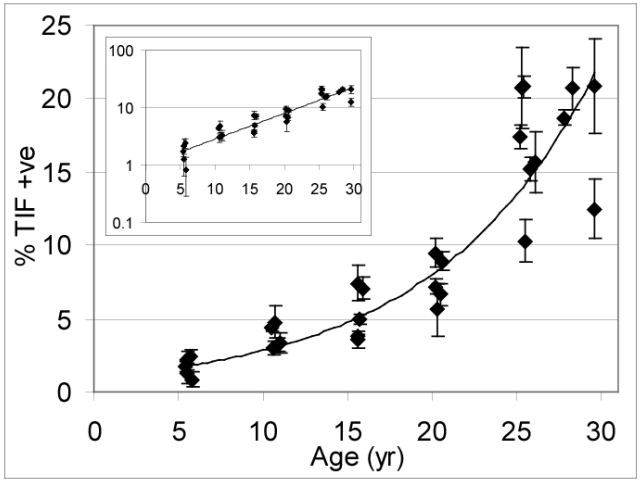
Fibroblasts
In
Dermal Tissue

53BP1/DAPI



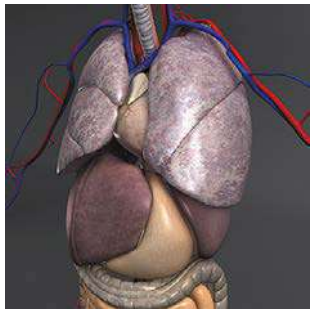
53BP1/telomere



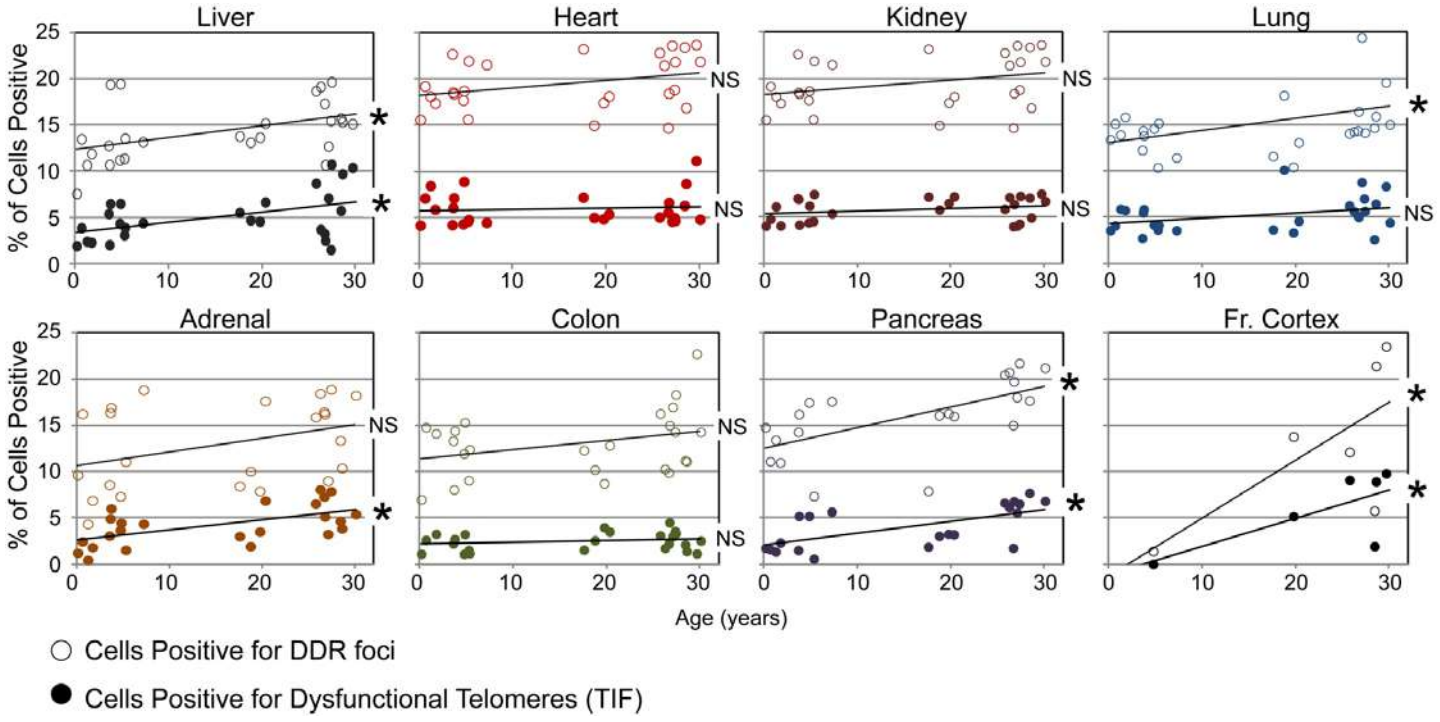


Herbig et al. Science (2006) 311:1257

Cells With Dysfunctional Telomeres Increase With Age

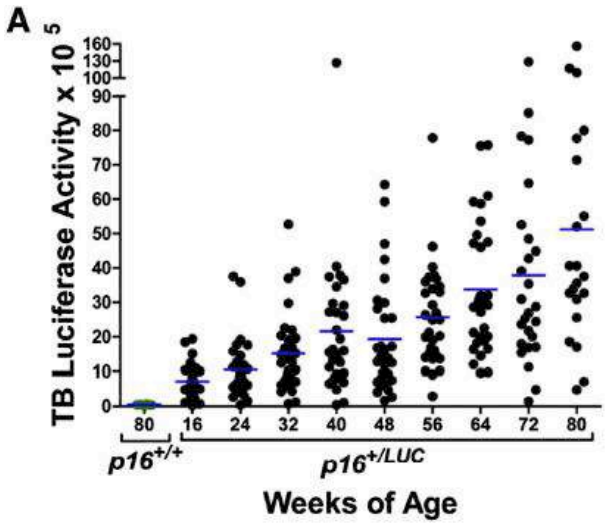


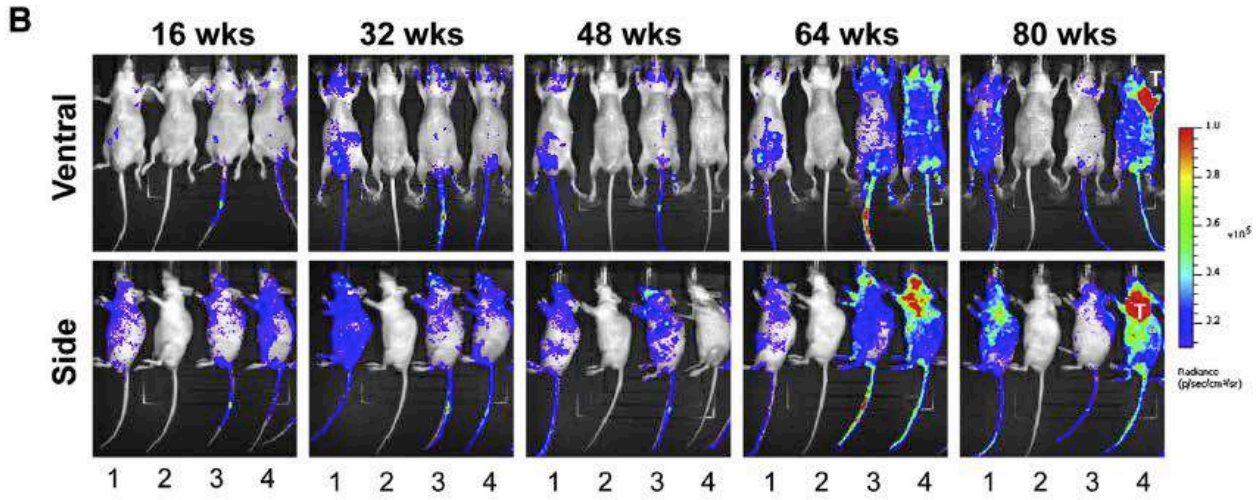
Skin (2-21%)
Liver (4-7%)
Heart
Kidney
Lung (fibroblasts,12-17%)
Adrenal Cortex (2-6%)
Colon (epithelium)
Pancreas (1-6%)
Brain (Frontal Cortex; 2-20%)



J. Kaplunov; unpublished

Mice Accumulate p16^{INK4a}-Senescent Cells With Advancing Age





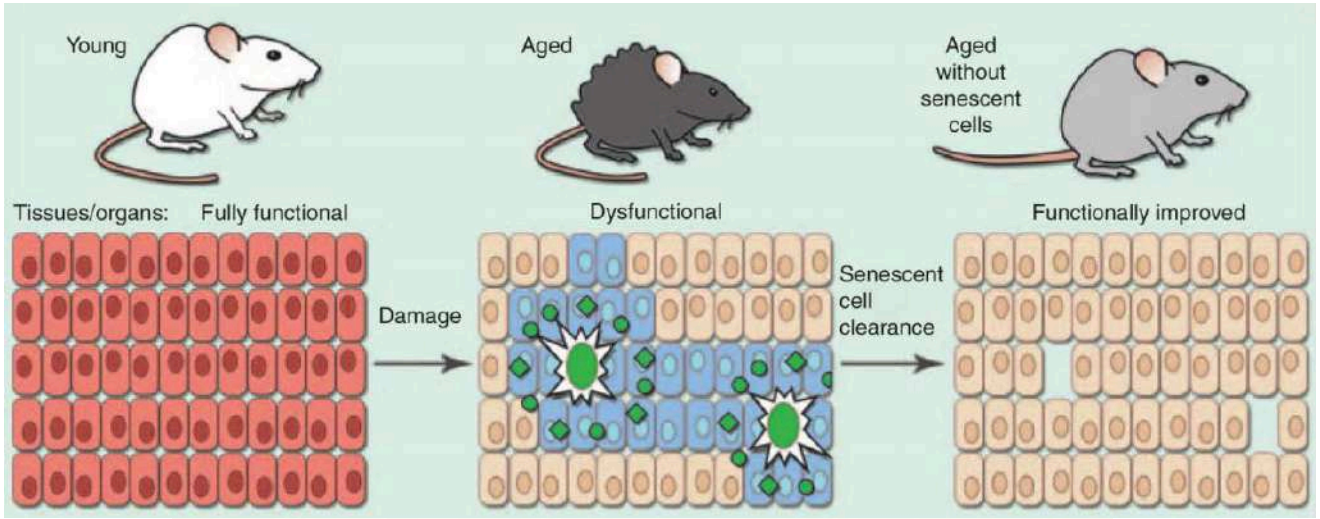
Burd et al., 2013. Cell 152: 340–351.

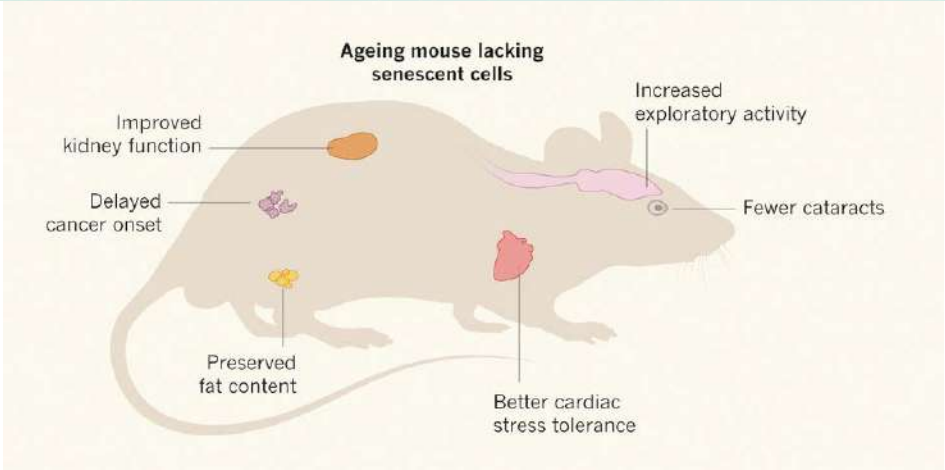
LETTER

doi:10.1038/nature10600

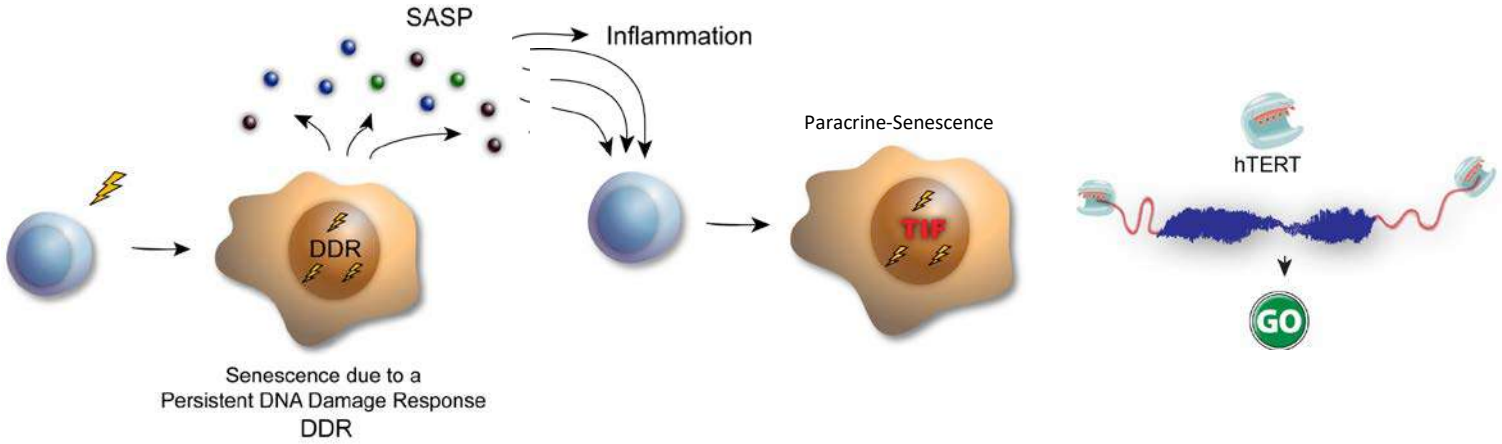
Clearance of p16^{Ink4a}–positive senescent cells delays ageing–associated disorders

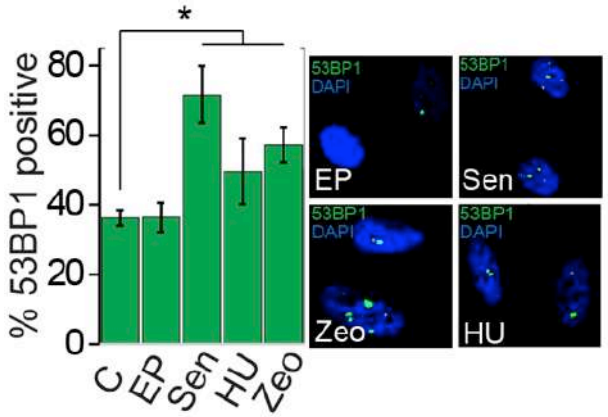
Darren J. Baker[1,2,3], Tobias Wijshake[1,4], Tamar Tchkonia[3], Nathan K. LeBrasseur[3,5], Bennett G. Childs[1], Bart van de Sluis[4], James L. Kirkland[3] & Jan M. van Deursen[1,2,3]

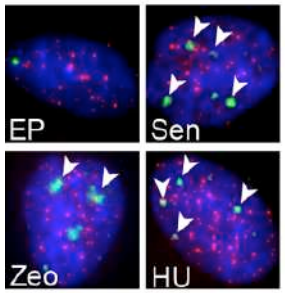


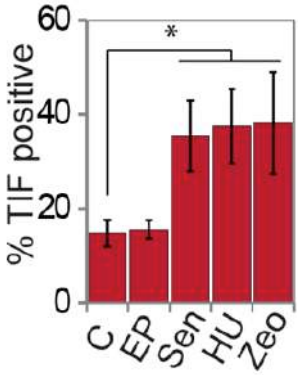


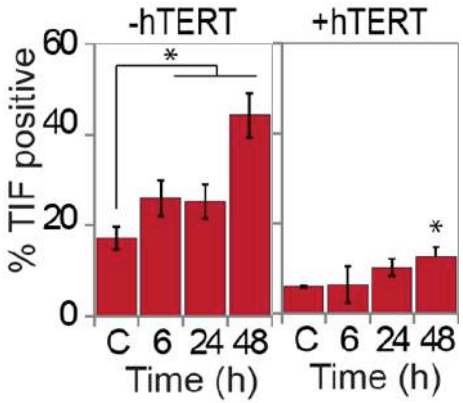
Senescence Associated Secretory Phenotype (SASP) Causes Telomere Dysfunction





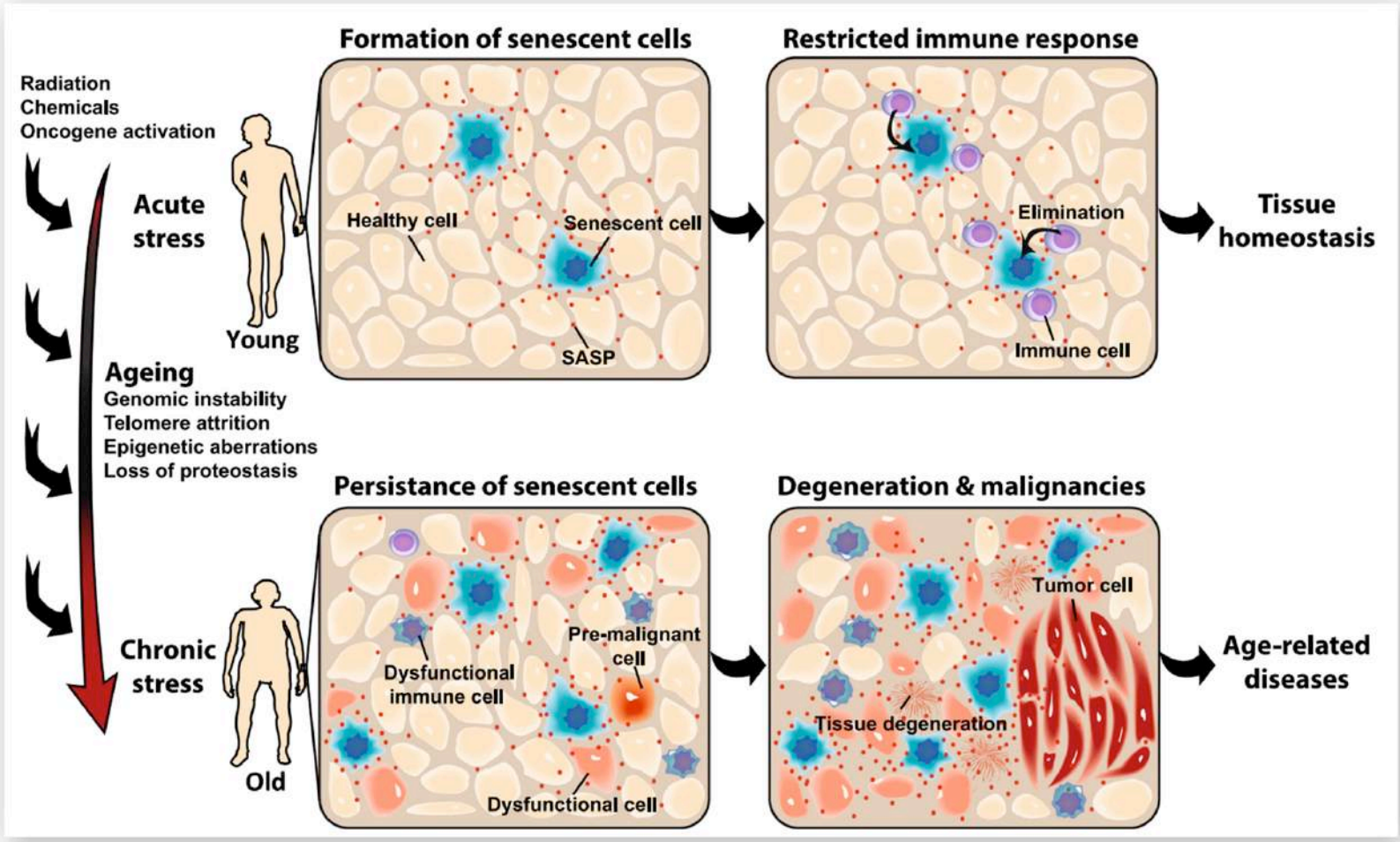






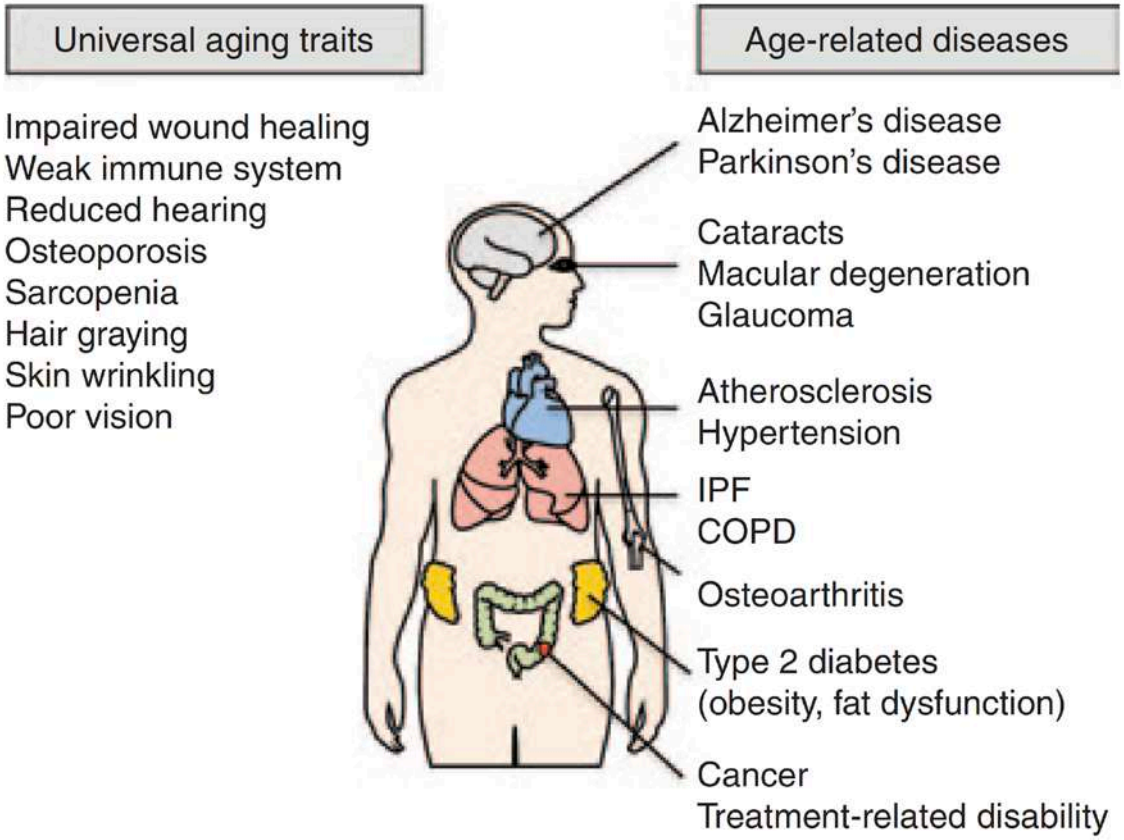
Razdan et al., 2018 Aging Cell

Senescence and Aging

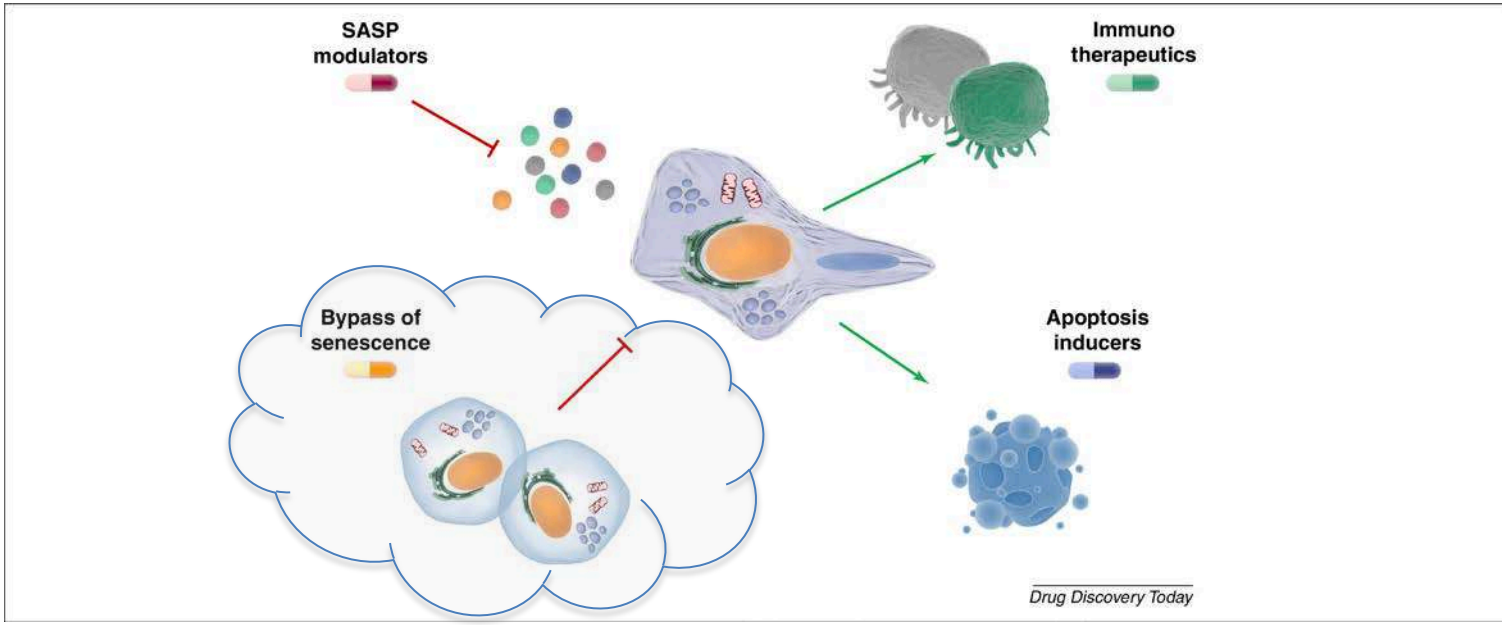


from Y. Ovadya & V. Krizhanovski; Biogerontology (2014) 15:627-642

The Accumulation of Senescent Cells Causes Aging and Age-Related Diseases



Senotherapeutic Strategies to Improve Healthy Aging



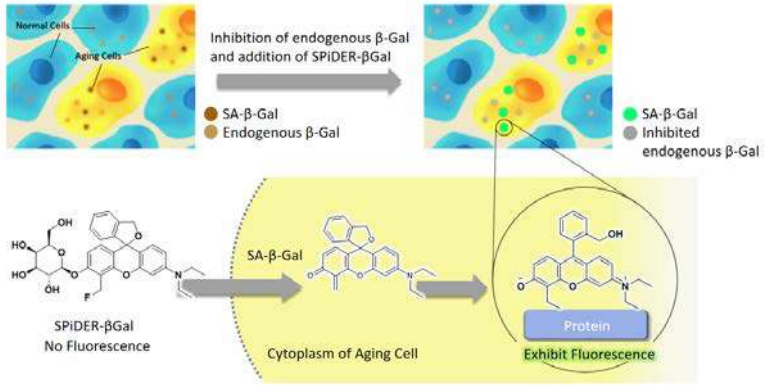
Our Current Research Efforts to Improve Healthy Aging

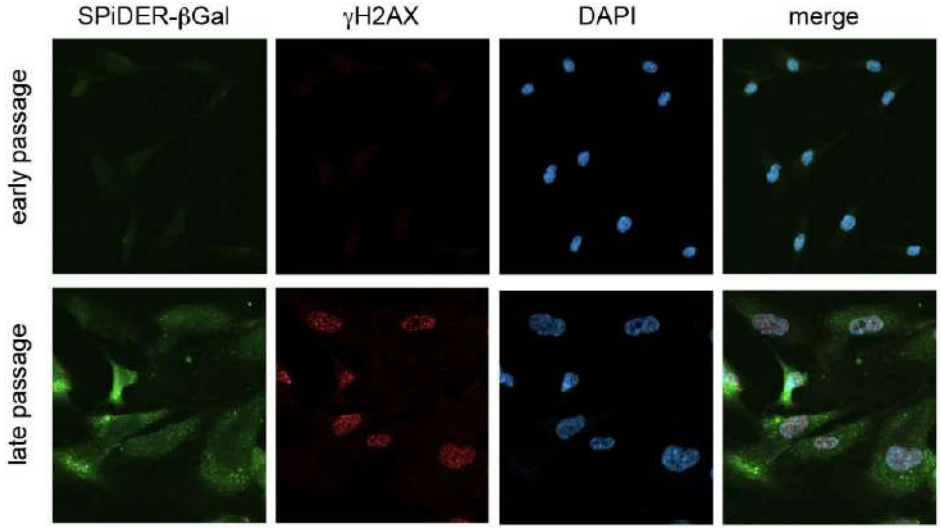
1. Improving the detection and characterization of senescent human cells *in tissue*
   Current techniques (TIF, SA-βGal, DDR-foci, SudanBlack, p16, p21, LaminB1, macroH2A…) are expensive, laborious, and time consuming. Separation of senescent cells from non-senescent cells is challenging

2. Rejuvenation of aged cells through pharmacological activation of hTERT expression
   In mice, hTERT gene therapy and TA-65 expression improves health-span and extends lifespan.

3. Inducing cellular plasticity by SASP factors
   In mice, SASP factors induce cellular plasticity and promote "stemness" of keratinocytes in a paracrine manner.

1. Improving the detection and characterization of senescent human cells in tissue

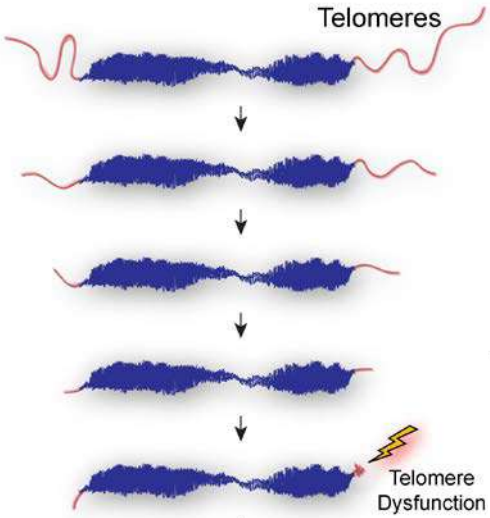




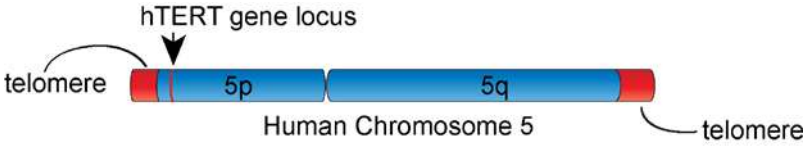
2. Rejuvenating Aging Cells

aged cell

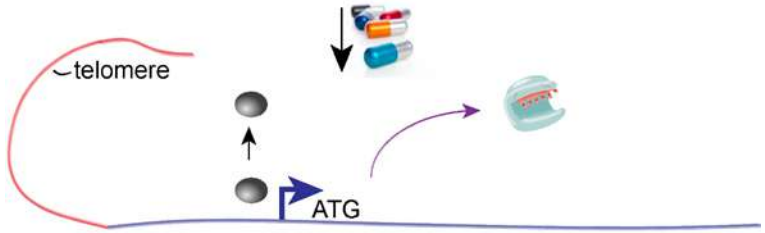
"young" cell



Aging?

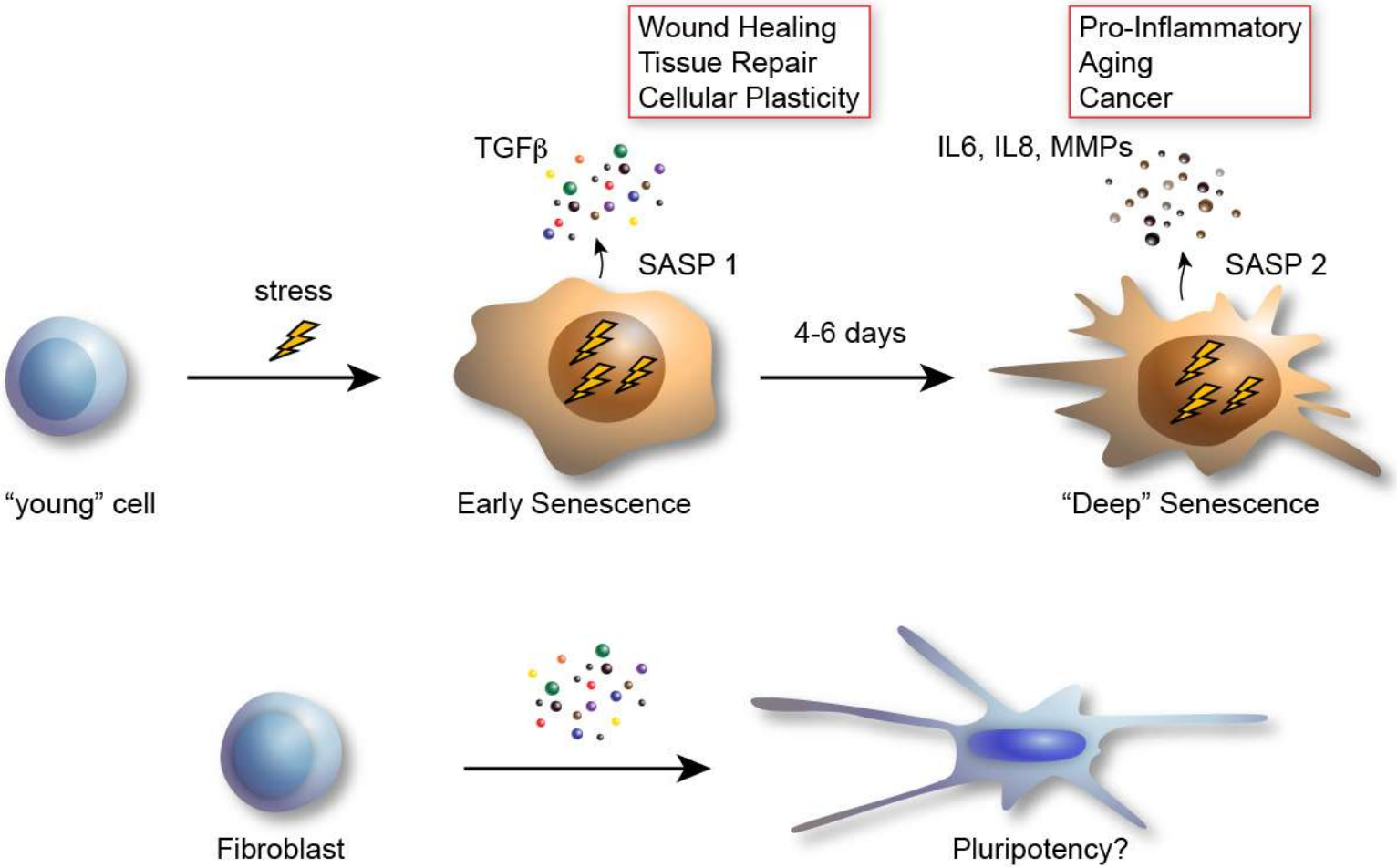


repressed hTERT promoter



active hTERT promoter

3. Inducing Cellular Plasticity



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NIH National Cancer Institute