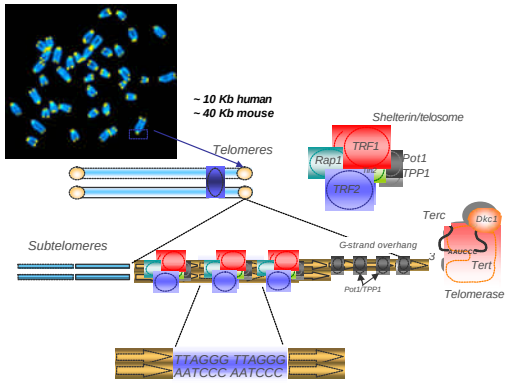
Los telomeros, arma de doble filo: cancer y envejecimiento

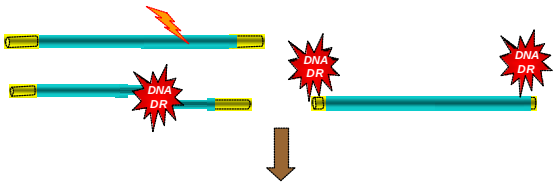
Paula Martínez
CNIO, Madrid

Telomeres protect chromosome ends from DNA repair and degradation



from Blasco, Nature Rev Genet, 2007

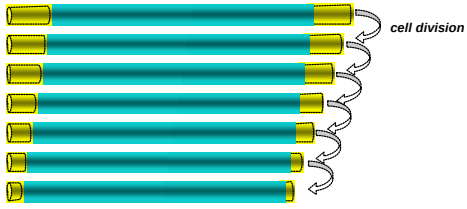
Telomeres are essential for chromosome stability by distinguishing chromosome ends from DNA breaks



Cell cycle arrest
Senescence
Apoptosis

The end replication problem

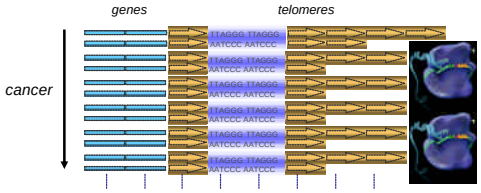
pérdida de material genético con la duplicación celular

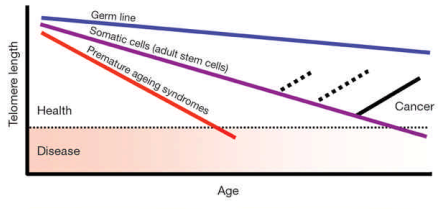


An embryonary gene known as telomerase is able to elongate telomeres to compensate excessive telomere loss during embryo development.

This gene, telomerase, is silenced after birth … however …

Cancer cells manage to reactivate telomerase, thus escaping the mortal fate of adult cells and becoming immortal.





Factors that accelerate telomere loss:
Perceived stress
Smoking
Obesity

Premature ageing syndromes:
Ataxia telangiectasia (*ATM*)
Werner syndrome (*WRN*)
Bloom syndrome (*BLM*)
Dyskeratosis congenita (*DKC1*, *TERC*)
Aplastic anaemia (*TERC*, *TERT*)
Fanconi anaemia (Fanc genes)
Nijmegen breakage syndrome (*NBN*)

Role of telomerase in adult stem cells and extension of lifespan by telomerase

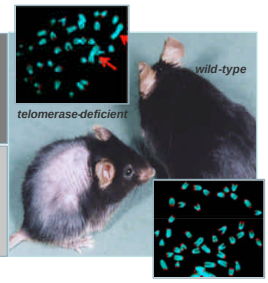
Flores et al., Science, 2005
Flores et al., G&D, 2008
Tomas-Loba et al., Cell, 2008

The role of telomerase in chromosome protection, cancer & aging

Telomerase-deficient mice ($Terc^{-/-}$):

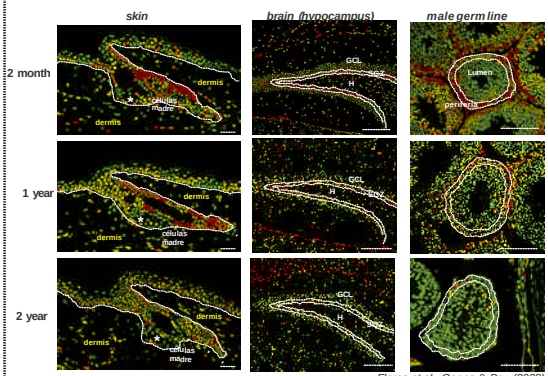
decreased regenerative capacity due to stem cell dysfunction

less cancer



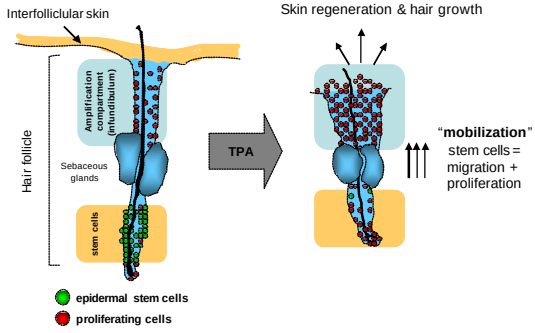
Blasco et al., *Science* (1995)
Blasco et al., *Cell* (1997)
Lee, Blasco, et al., *Nature* (1998)
González-Suarez et al., *Nat Genet* (2000)
González-Suarez et al., *EMBO J.* (2001)
Flores et al., *Science* (2005)

Stem cells suffer telomere shortening with aging

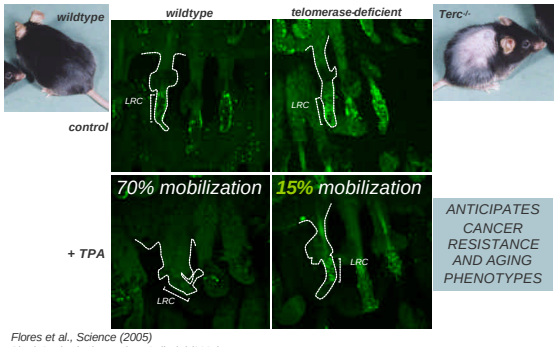


Flores et al., Genes & Dev (2008)

Epidermal stem cells

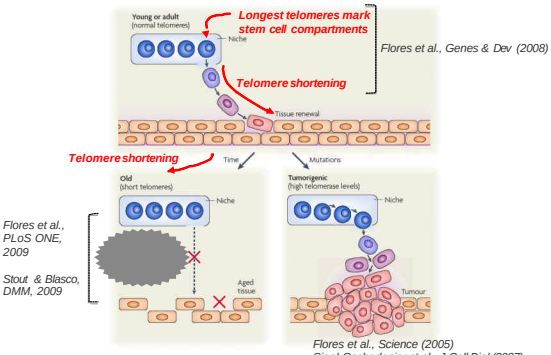


Short telomeres impair adult stem cell function



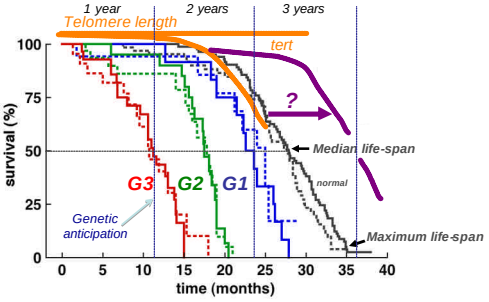
Flores et al., Science (2005)
Siegl-Cachedenier et al., J Cell Biol (2007)

A telomere-based model for cancer and aging

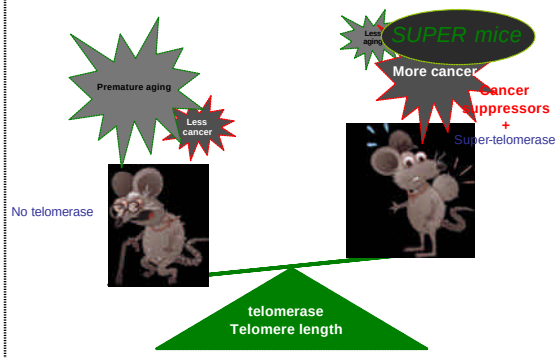


Flores et al., Science (2005)
Siegl-Cachedenier et al., J Cell Biol (2007)
Serrano & Blasco, Nat Rev Mol Cell Biol (2007)

Telomerase is rate-limiting for mouse longevity

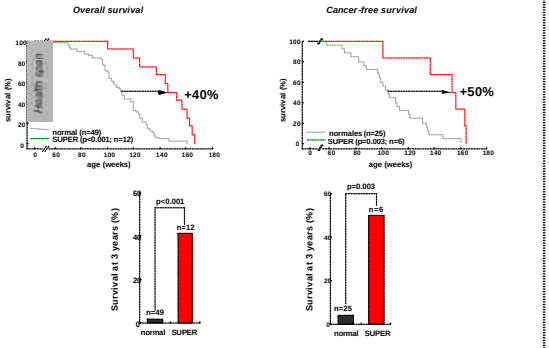


García-Cao et al., EMBO Rep (2006)



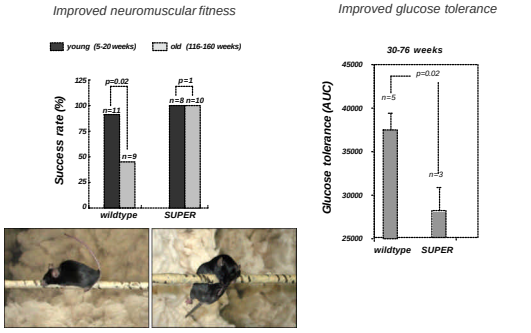
Gonzalez-Suarez et al., Oncogene (2004)

Increased "health span" & longevity in SUPER mice



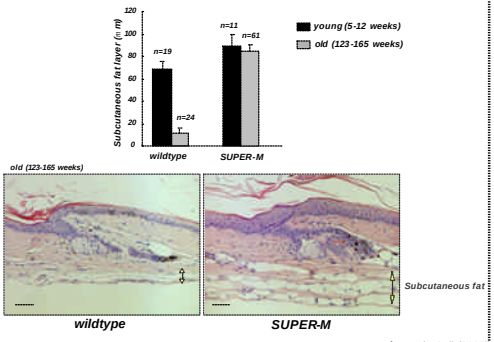
Tomás-Loba et al., Cell (2008)

Improved health late in life in SUPER mice



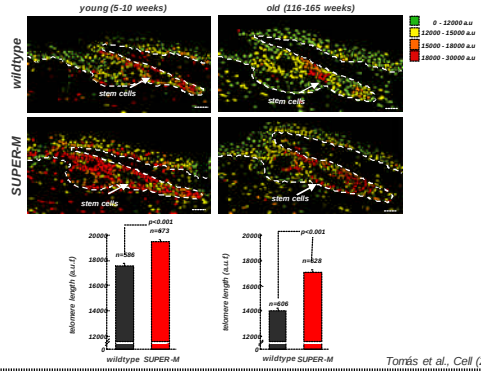
Tomás-Loba et al., Cell (2008)

Less skin aging in SUPER-M mice

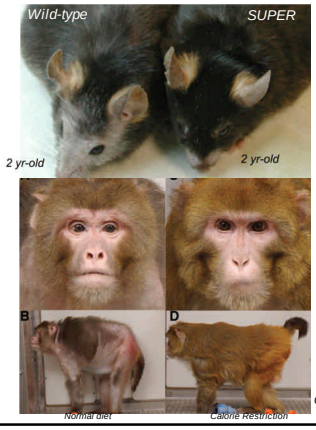


Tomás et al., Cell (2008)

Longer telomeres in SUPER-M mice at old age



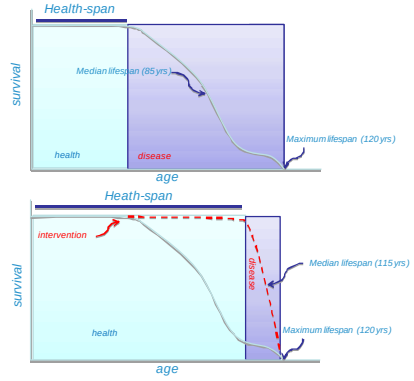
Tomás et al., Cell (2008)



Tomás-Loba et al, Cell (2008)

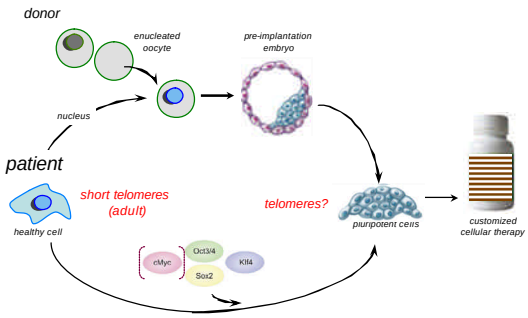
Colman et al, Science (2009)

...in humans?



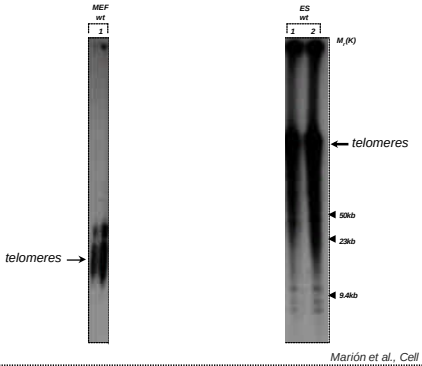
Telomere rejuvenation

re-programming "à la Dolly" (1997)



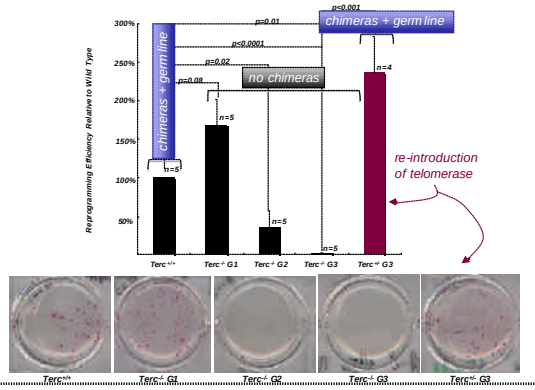
re-programming "à la Yamanaka" (2006)

Telomere elongation by telomerase in iPS cells

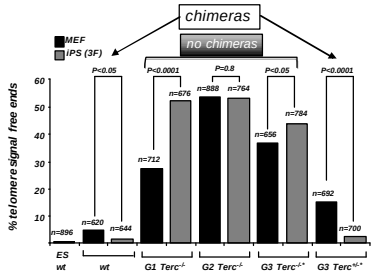


Marión et al., Cell Stem Cell (2009)

Absence of telomerase decreases the efficiency and quality of reprogramming

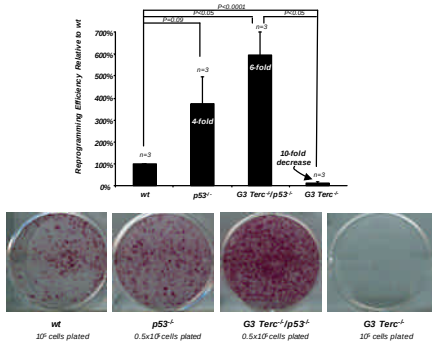


Telomerase-deficient iPS cells have telomere damage



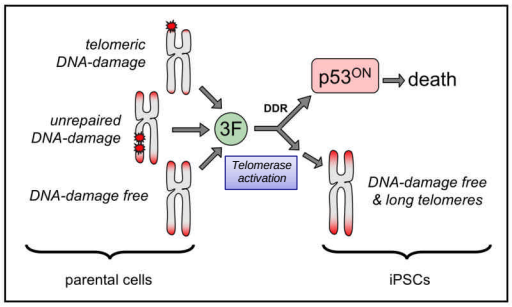
Marión et al., Cell Stem Cell, 2009

p53 is a key factor limiting reprogramming of suboptimal cells



Marión et al., Nature (2009)

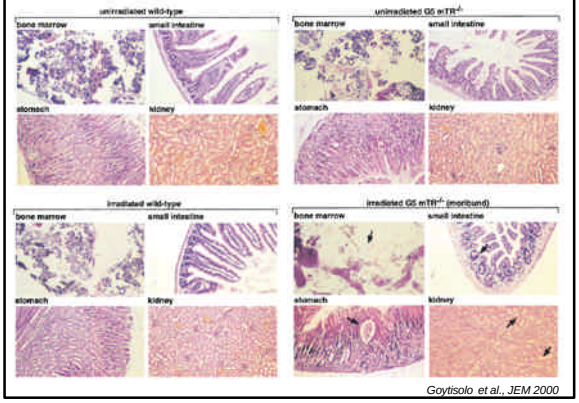
Reprogramming checkpoints



Marión et al., Nature (2009)

Telomeres and Ionizing radiation

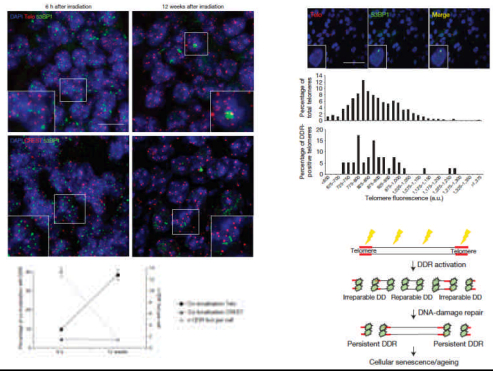
Short telomeres results in hypersensitivity to ionizing radiation



Goytisolo et al., JEM 2000

Ionizing radiation induces persistent DDR at telomeres independently of their length

Fumagalli et al, Nature Cell Biology, 2012

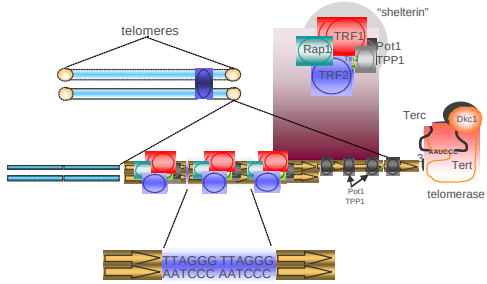


shelterins

The importance of cancelling the DDR at chromosome ends for cancer & aging

conditional knock-out mice for Shelterin proteins

Shelterin: the protein complex that protects chromosome ends

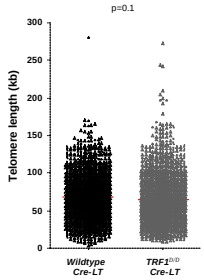


Tin2 mutations and TRF1 genetic variants in dyskeratosis congenita & aplastic anemia (Savage, 2006; 2008; Walne, 2008)
epithelial abnormalities are a hallmark of these rare diseases (skin hyperpigmentation, nail dystrophy, oral leukoplakia)

$TRF1^{D/D}$ MICES

Martínez et al., Genes & Dev., 2009

TRF1 deletion in MEF does not lead to telomere length changes

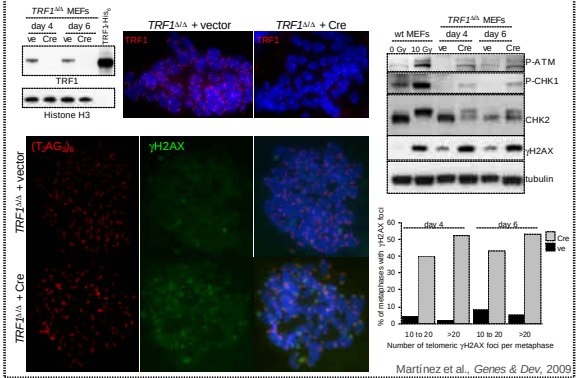


Wildtype-Cre-LT
Number of telomeres = 1887
Number of metaphases = 7
Mean length ± SD = 68.5 ± 28.9 kb

$TRF1^{D/D}$ –Cre LT
Number of telomeres = 1622
Number of metaphases = 6
Mean length ± SD = 65.3 ± 33.4 kb

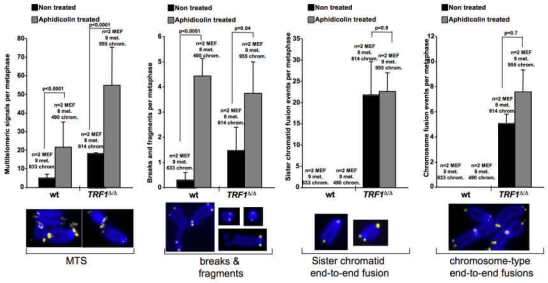
Martínez et al., *Genes & Dev*, 2009

TRF1 abrogation leads to an ATM/ATR-dependent DDR at chromosome ends

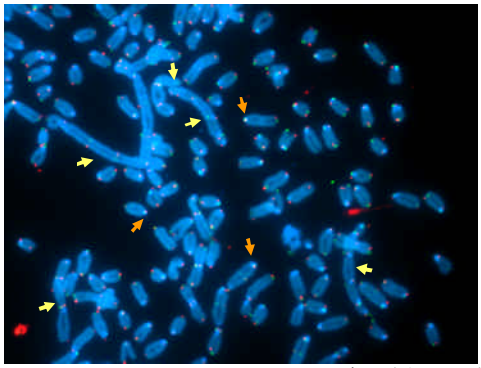


Martínez et al., *Genes & Dev*, 2009

TRF1 depleted telomeres are prone to replication fork stalling & breakage

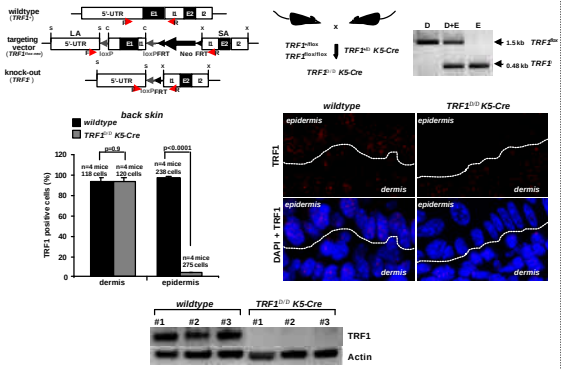


Massive telomere end-to-end fusions & fragility in the absence of TRF1

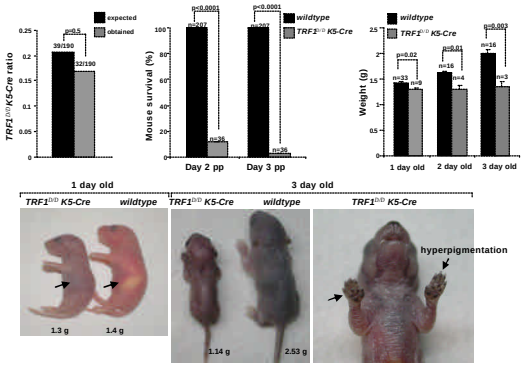


Martínez et al., Genes & Dev (2009)

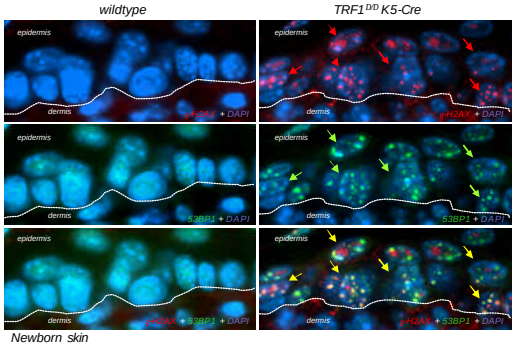
Generation of a epidermis-specific TRF1 knock out mouse



Perinatal lethality & skin hyperpigmentation in TRF1$^{D/D}$ K5-Cre mice



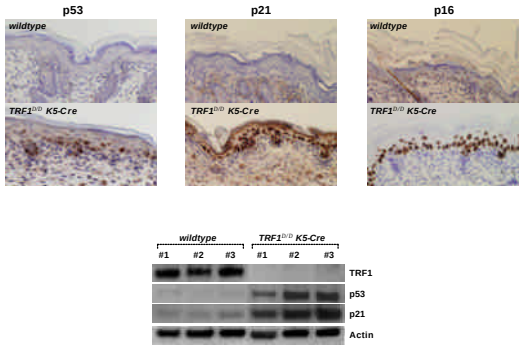
Persistent DNA damage-signaling in the epidermis of TRF1$^{D/D}$ K5-Cre mice



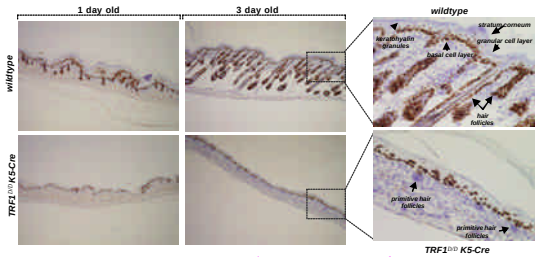
Newborn skin

Martínez et al., Genes & Dev (2009)

Increased cell cycle inhibitors in TRF1 knock out mice



Severe skin morphogenesis defects in TRF1$^{D/D}$ K5-Cre mice



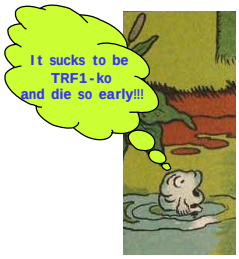
Reduced skin thickness

Reduced of skin stratification

Lack of hair follicle development

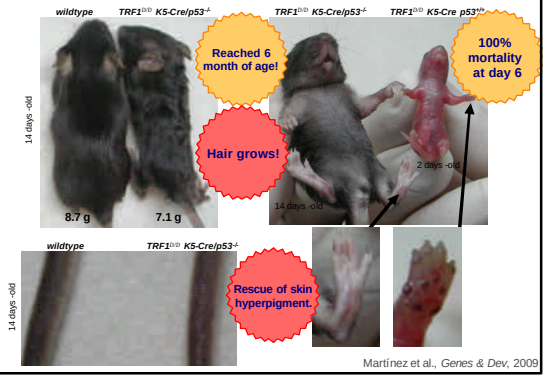
NO hair follicles & sebaceous glands

Lack of K15^{+} cells
Lack of Sox9^{+} cells at HB



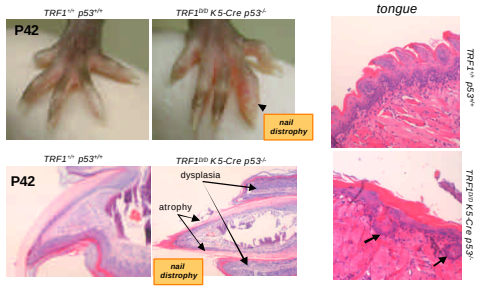
TRF1$^{D/D}$ p53$^{-/-}$ mice cancer & aging

p53 deficiency rescues survival and stem cell impairment in TRF1$^{D/D}$ K5-Cre mice



Martínez et al., *Genes & Dev*, 2009

Longer-lived TRF1/p53 DKO mice show "human" telomere pathologies

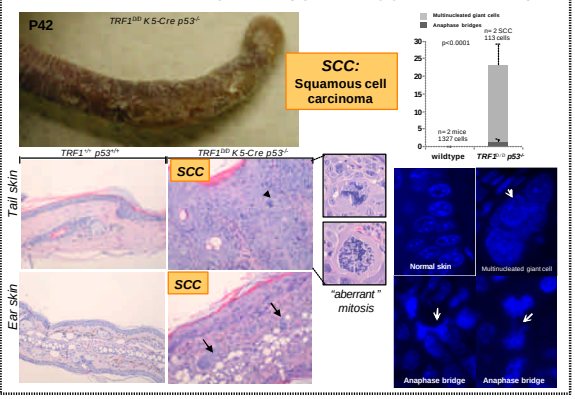


Nail abnormalities
(atrophic and irregular nail plate, dysplastic epithelium)

Oral leukoplakia
(hyperplasia, hyperkeratosis, dermis invasion)

Martínez et al., *Genes & Dev*, 2009

TRF1 acts as a tumor supressor by preventing genomic instability



Why is this of relevance?

 # First mouse models for telomere-induced aging in the absence of telomere shortening

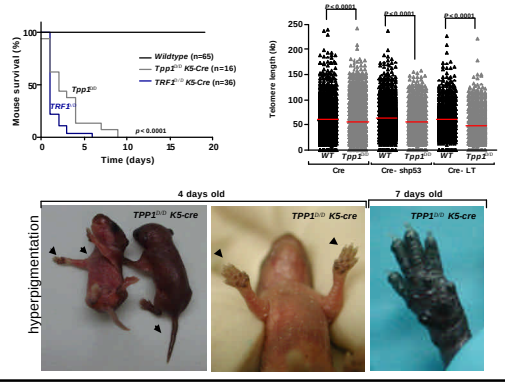
 # they show that telomere uncapping and increased telomere fragility impact on cancer in the absence telomere shortening

 # suggests a new class of telomere diseases produced by telomere dysfuction in the presence of long telomeres

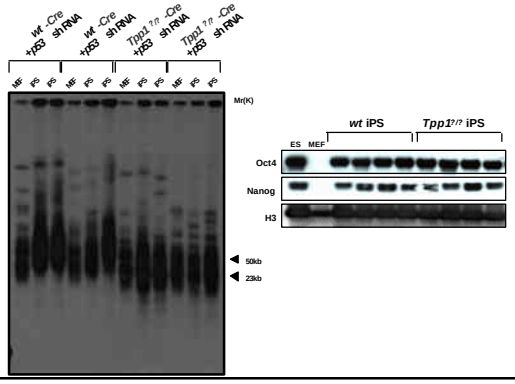
$Tpp1^{D/D}$ MICE

Tejera/Stagno d´Alcontres et al.
Dev. Cell, 2010

Reduced survival & increased skin hyperpigmentation & telomere shortening in $Tpp1^{D/D}$ K5-Cre mice

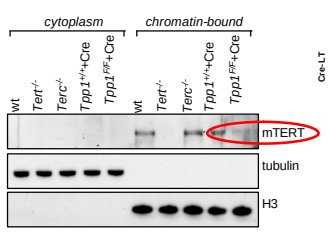


Telomeres do not elongate in $Tpp1^{-/-}$ iPS cells

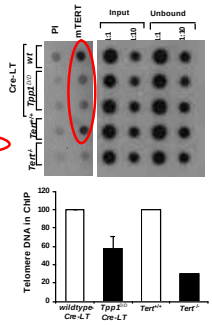


TPP1 recruits TERT to chromatin

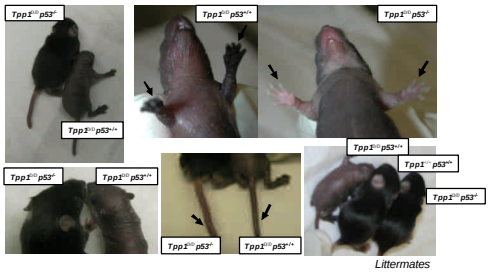
Chromatin fractionation assay



ChIP assay

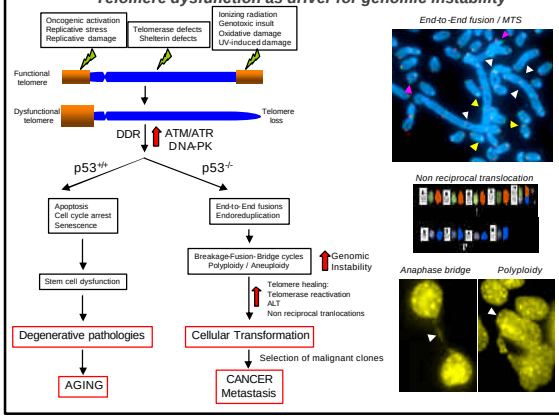


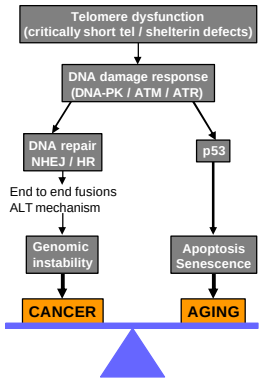
p53 mediates proliferative defects and skin hyperpigmentation in Tpp1 mice



No impact on cancer!!

Telomere dysfunction as driver for genomic instability





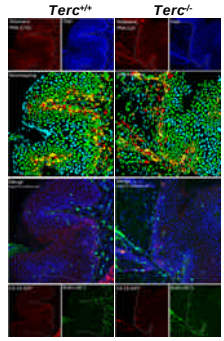
Towards medical applications

Telomere length analysis in hyperplasic lesions (preneoplasic) and in human skin carcinomas

Telomere length decreases during hiperplasic development (precancerous lesions)

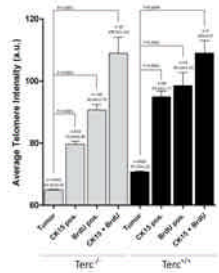
Telomere length increases during malignat transformation (carcinomas)

Telomere length decreases during papilloma development in WT and Terc$^{-/-}$ mice



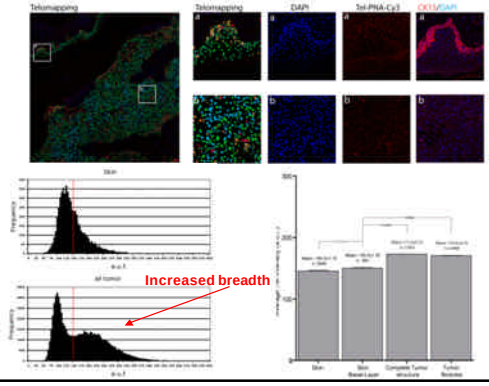
Longer telomeres in wt papillomas than in *Terc*$^{-/-}$

Putative cancer stem cells (BrdU LRC + CK15 positive cells) have the longest telomeres



Telomere length in human squasmous cell carcinomas (SCC)

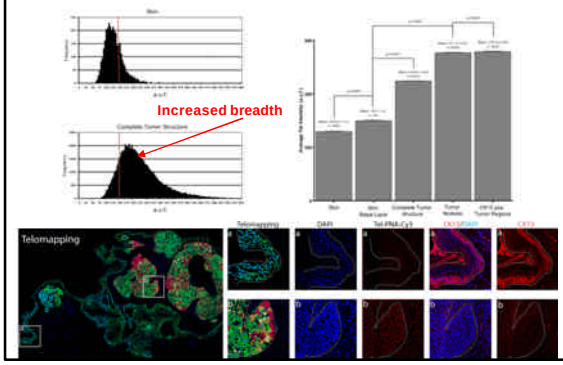
Telomere length increases during neoplasic transformation



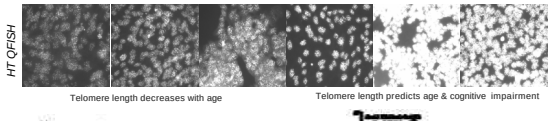
Telomere length in human basal cell carcinomas (BCC)

Telomere length increases more drastically in the most agresive tumors

Longer telomeres in BCC as compared to SCC

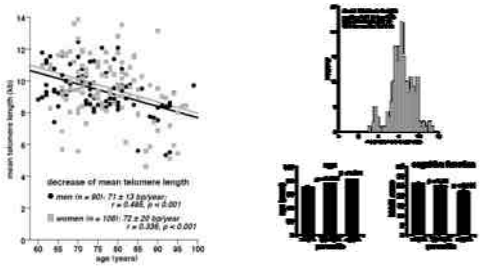


Telomere length as a biomarker of biological age & health status



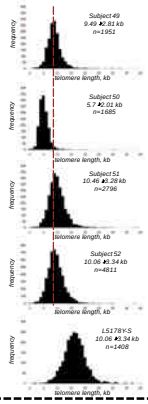
Telomere length decreases with age

Telomere length predicts age & cognitive impairment



Canela et al., *PNAS* (2007)

Telomere length as a diagnosis tool



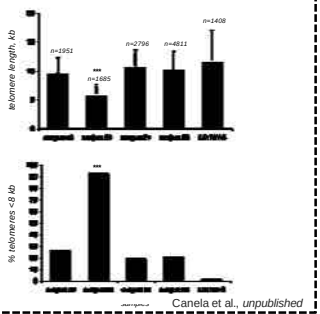
Subject 49- Male 02/02/78 healthy

Subject 50- Male 22/09/77 medular aplasia, TERC mut

Subject 51- Male 17/05/78 healthy

Subject 52- Male 06/06/78 healthy

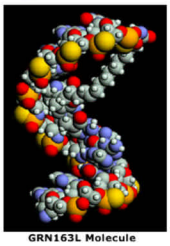
Hospital Vall d Hebrón



Canela et al., *unpublished*

Telomerase as an anti-cancer target

geron



GRN163L Molecule

ClinicalTrials.gov

Linking patients to medical research

Safety and Dose Study of GRN163L Administered Weekly to Treat Patients With Chronic Lymphocytic Leukemia (CLL)

This study is currently recruiting patients.

Sponsored by: Geron Corporation

Information provided by: Geron Corporation

ClinicalTrials.gov Identifier: NCT00124189

Purpose

The purpose of this study is to determine the safety and maximum tolerated dose of GRN163L in treating patients with refractory or relapsed chronic lymphocytic leukemia (CLL).

Condition	Intervention	Phase
Lymphocytic Leukemia, Chronic	Drug: GRN163L	Phase 1 Phase 2

Telomerase activation to extend longevity and "health-span"

The Telomeres & Telomerase Group, M.Blasco's team

The Spanish National Research Cancer Centre (CNIO), Madrid