Telomeres as Targets for Cancer and Aging

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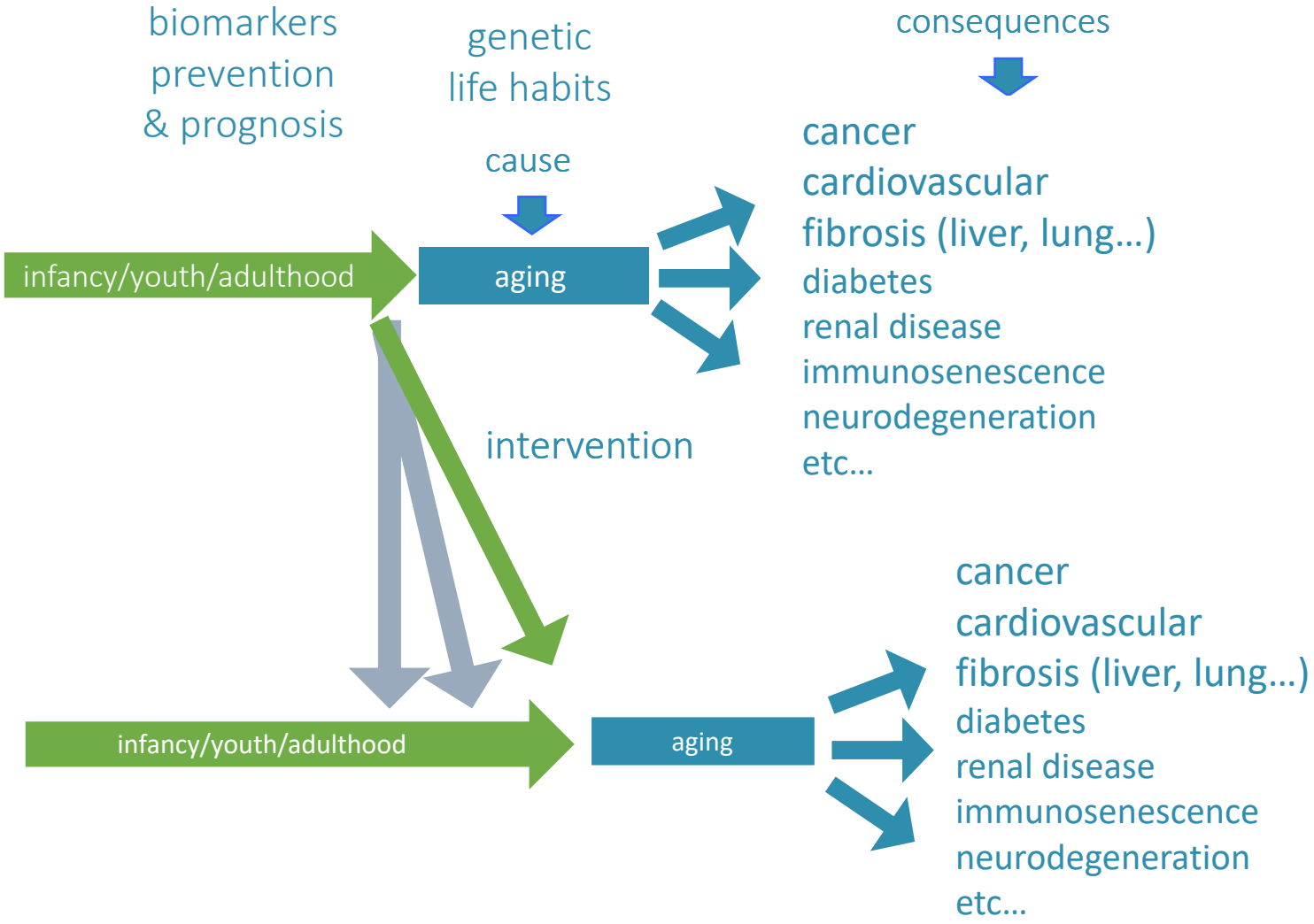
cnio stop cancer

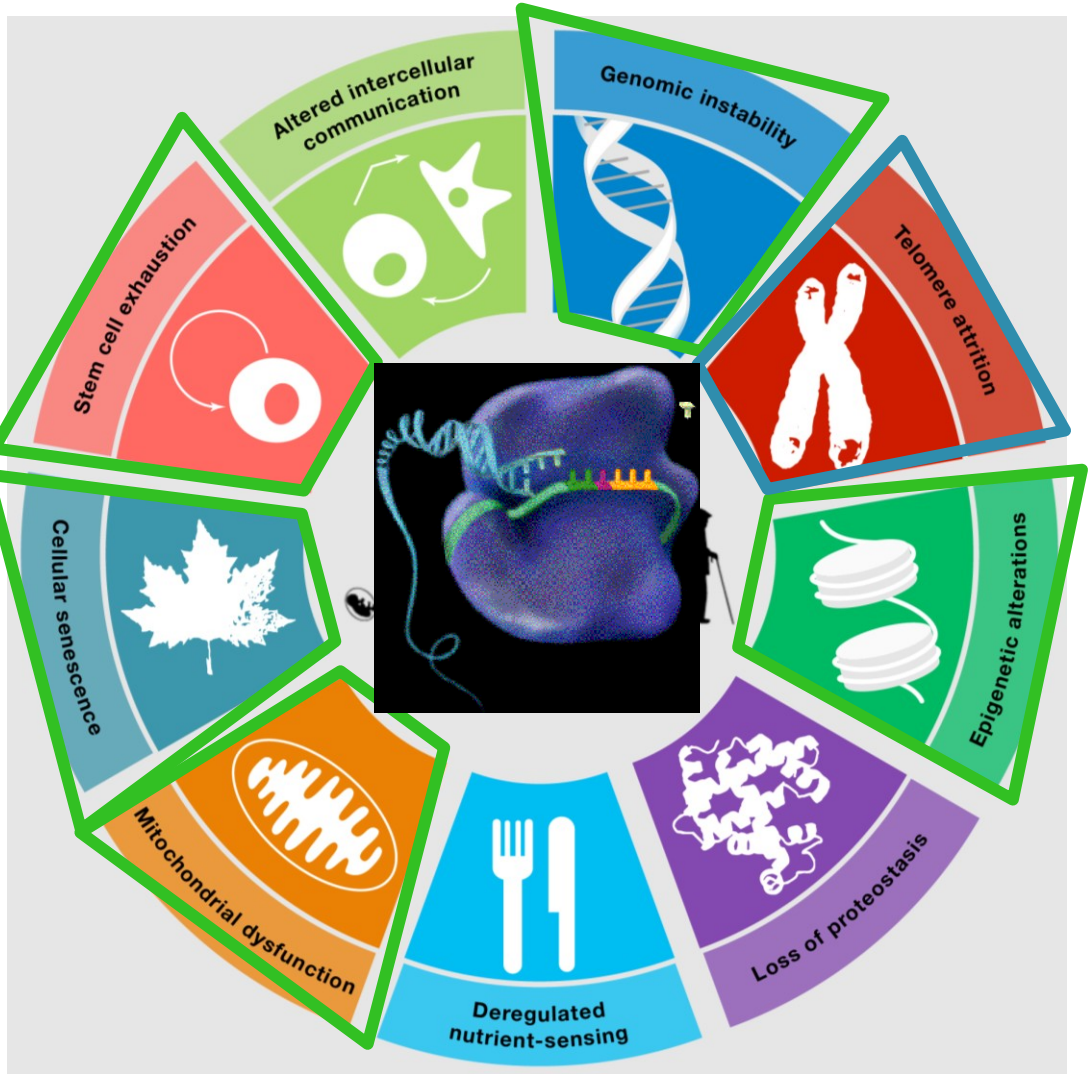
Targeting Telomeres in age-related diseases

(ie., pulmonary fibrosis)

Aging as the cause of disease

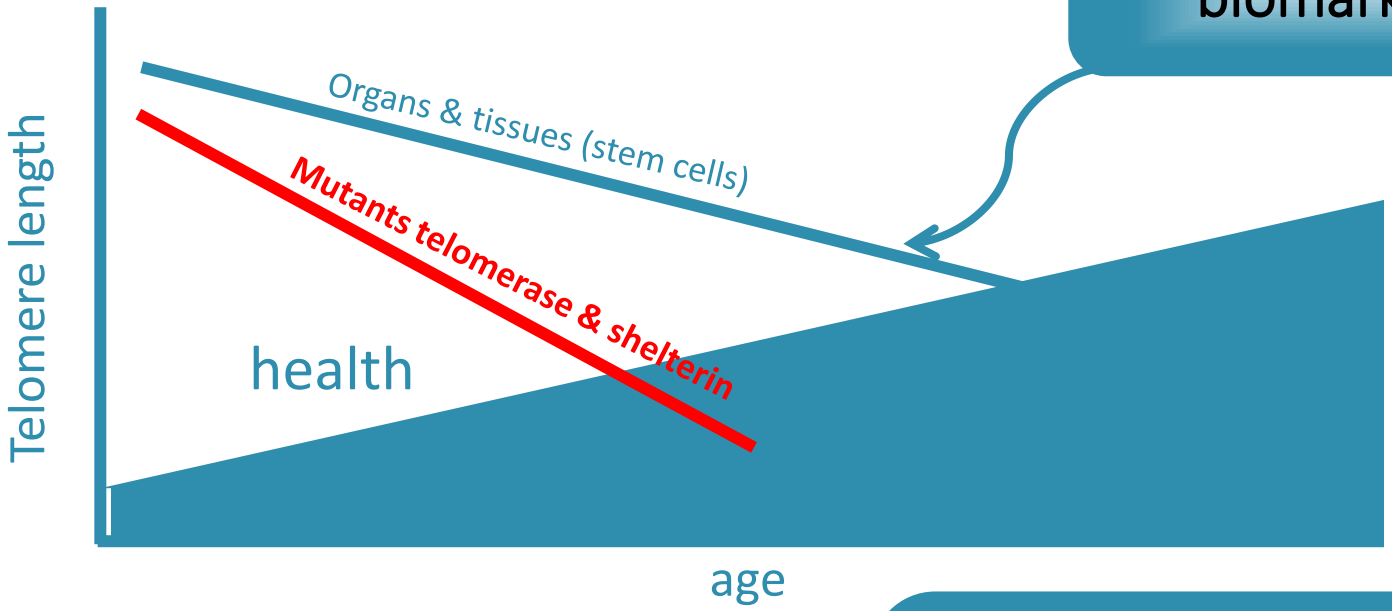


The Hallmarks of Aging



López-Otín, Blasco, Partridge, Serrano & Kremer, Cell (2013)

Telomeres, telomerase & disease



Telomere length: aging biomarker

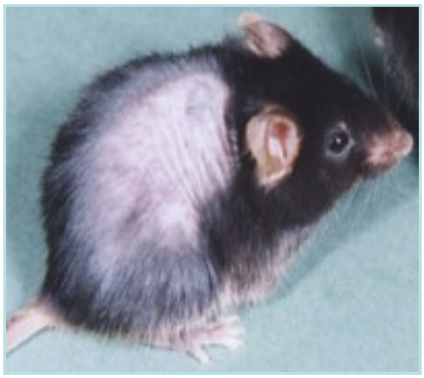
Cancer
(>95% activate telomerase)

Telomere syndromes
(mutations in telomerase)

Diskeratosis congenita
Aplastic anemia
Pulmonary & hepatic fibrosis

Validation of role of telomerase in cancer & aging

Terc$^{-/-}$ mice



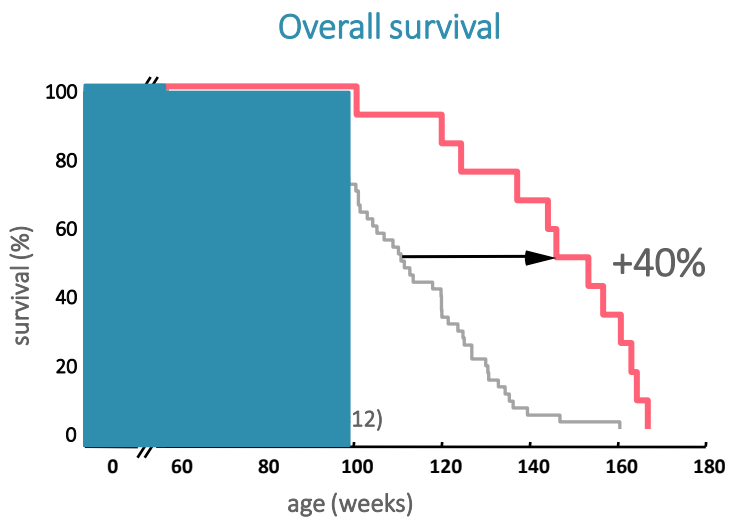
✓Premature loss of regenerative capacity of tissues (**stem cell mobilization defects**)

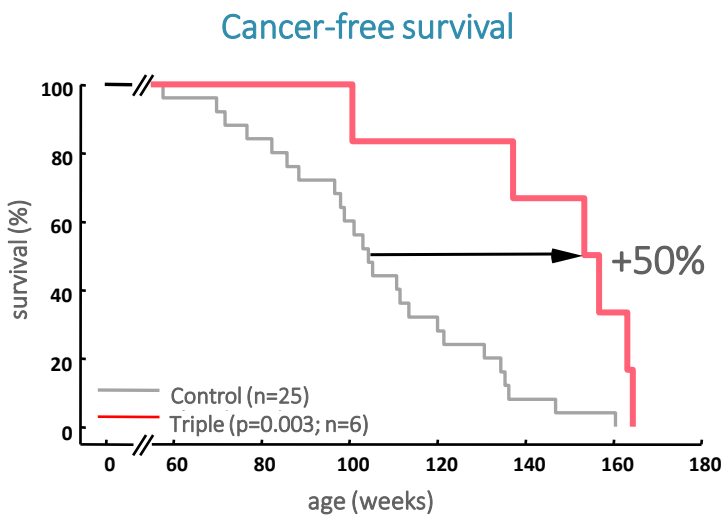
✓Anticipation of many **aging-associated pathologies (skin, gut, bone marrow etc)**

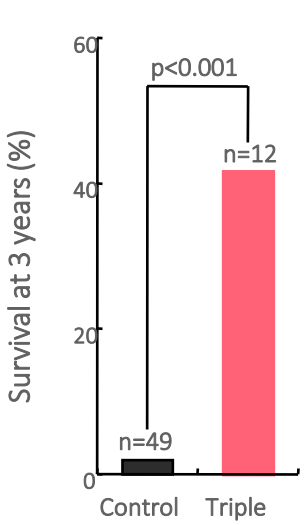
✓**Resistant to cancer in late generations** (when telomeres become short)

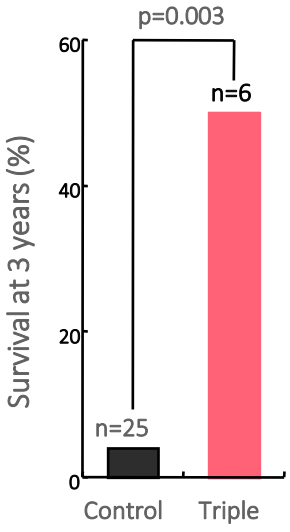
Blasco et al., Science (1995)
Blasco, Lee, et al., Cell (1997)
Lee, Blasco, et al., Nature (1998)
González-Suarez et al., Nat Genet (2000)
Flores et al., Science (2005)

Proof-of-concept that
TERT can delay aging





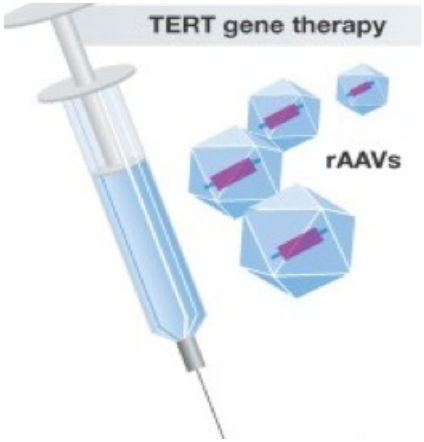


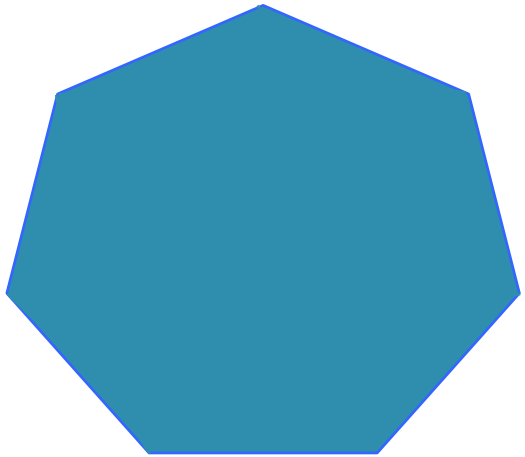


Tomás-Loba et al., Cell (2008)

Therapeutic strategy:

AAV9-TERT





✓ If aging is produced owing to **telomerase deficiency in adult life**, TERT delivery late in life (1-2 year old mice) should delay aging & diseases

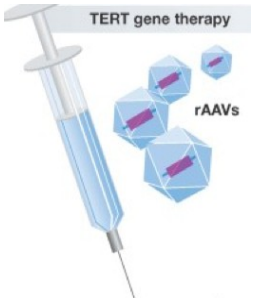
✓ We used **AAV gene therapy vectors**: non-integrative (TERT expression will be lost after a few cell divisions=**sufficient to elongate short telomeres** but not to induce cancer?), non-immunogenic, safe…

Bernades de Jesús et al., EMBO Mol Med (2012)

Proof-of-concept:

Efficacy AAV9-TERT

- ✓Improved glucose tolerance
- ✓Improved skin fitness
- ✓Less cognitive decline
- ✓Less osteoporosis
- ✓Improved neuromuscular
- ✓**Delayed cancer**
- ✓24% (1-yr) & 13% (2-yrs) increased survival

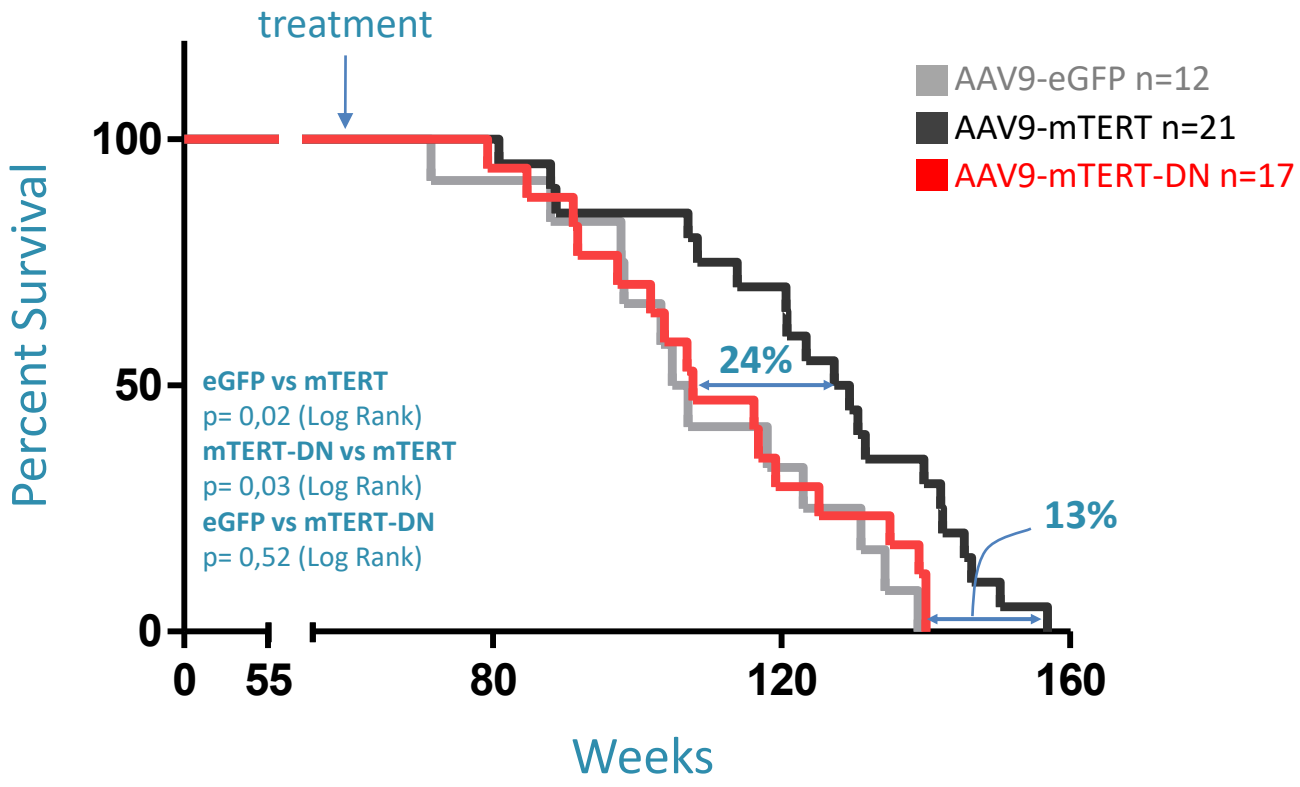


1 & 2 year-old mice

longer telomeres
lower DNA damage

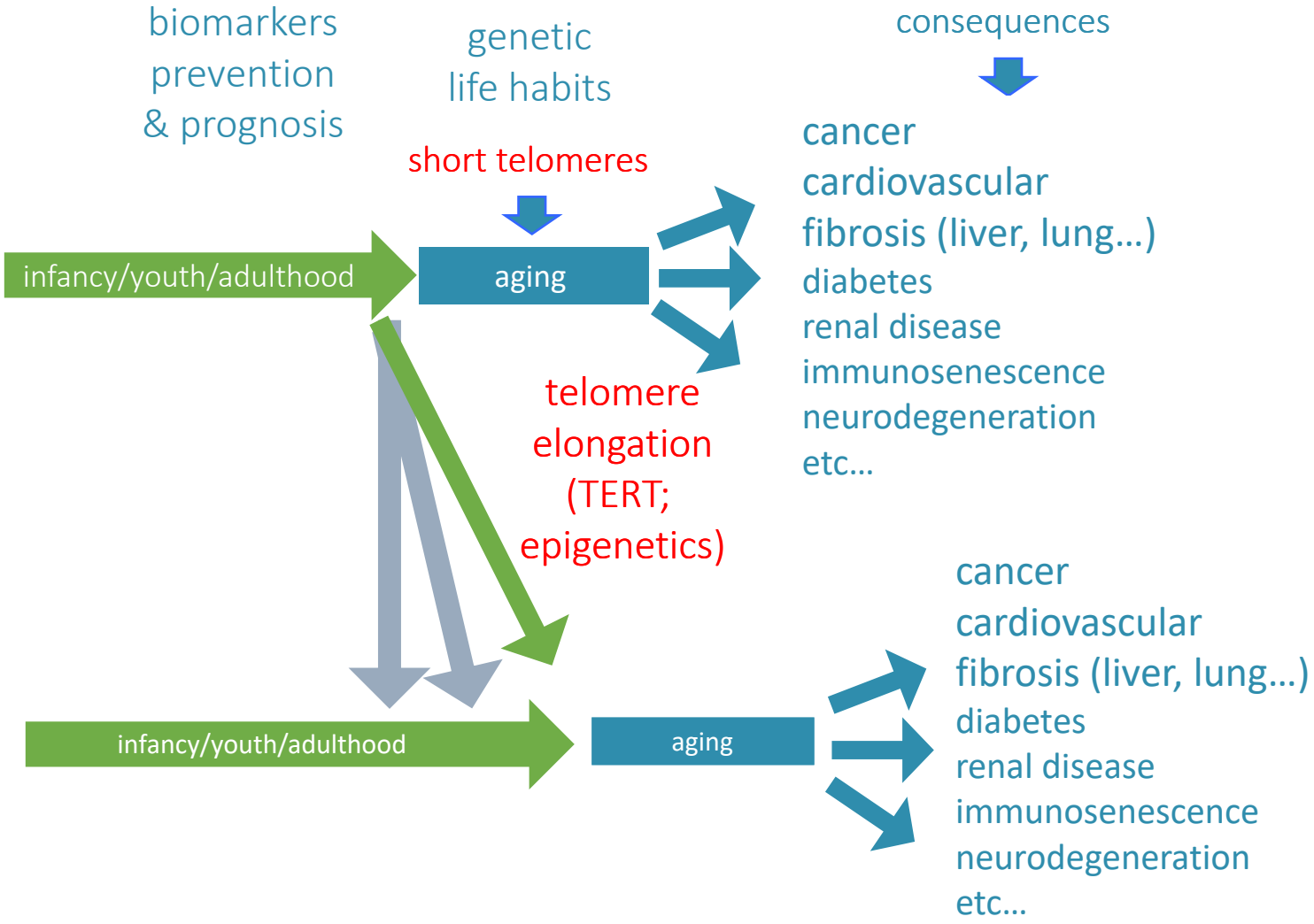
Bernades de Jesús et al., EMBO Mol Med (2012)

Life-extension requires TERT catalytic activity

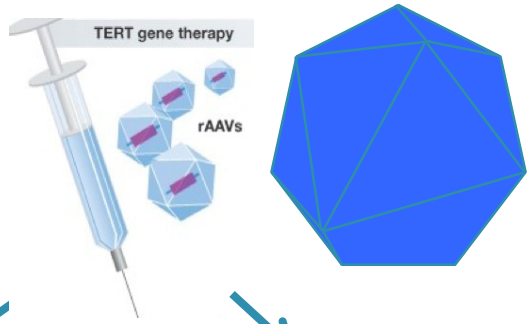


Bernades de Jesús et al., EMBO Mol Med (2012)

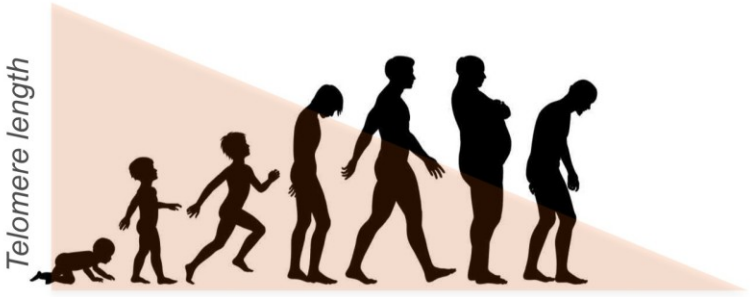
Short telomeres as cause of aging

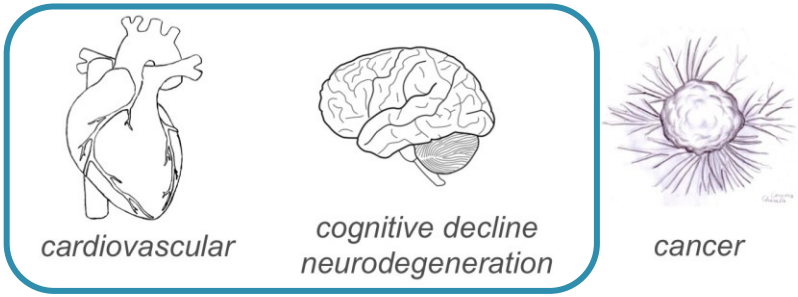


TERT Gene Therapy
To treat diseases

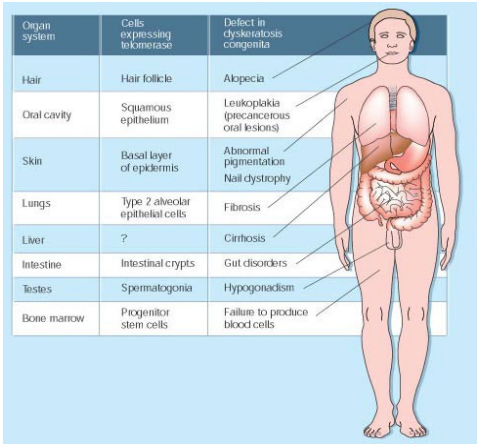


Age associated diseases

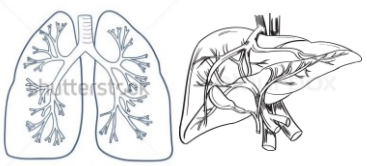




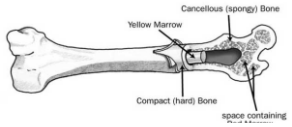
Telomere syndromes



Organ system	Cells expressing telomerase	Defect in dyskeratosis congenita
Hair	Hair follicle	Alopecia
Oral cavity	Squamous epithelium	Leukoplakia (precancerous oral lesions)
Skin	Basal layer of epidermis	Abnormal pigmentation Nail dystrophy
Lungs	Type 2 alveolar epithelial cells	Fibrosis
Liver	?	Cirrhosis
Intestine	Intestinal crypts	Gut disorders
Testes	Spermatogonia	Hypogonadism
Bone marrow	Progenitor stem cells	Failure to produce blood cells



lung & liver fibrosis

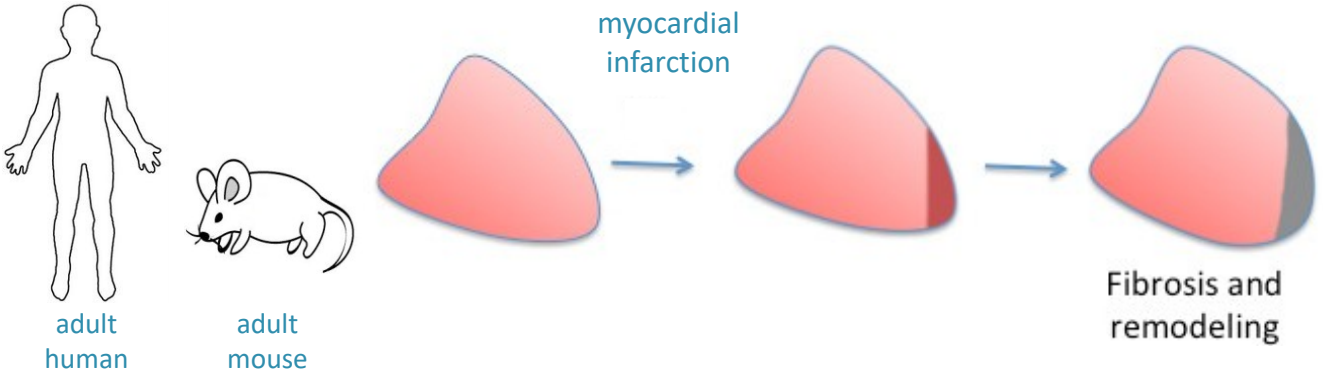


Bone marrow aplasia

Mutants for telomerase & shelterin
“extreme” telomere shortening

AAV9-TERT:

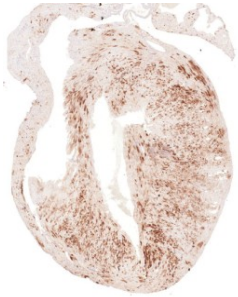
Heart infact



Telomerase is highly expressed the first week of life, then is downregulated (Blasco et al., Science, 1995)

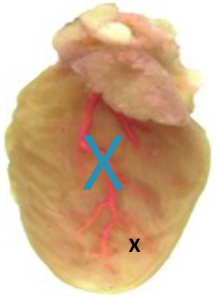
AAV9-TERT:

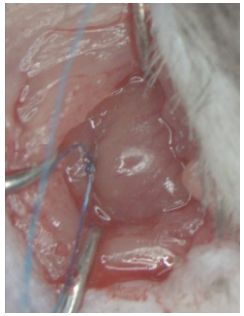
Heart infact



61% transduction
cardiomyocytes
(< 1% liver, brain)

AAV9-Tert





MI

no virus

Adult mice
(12 month old)

AAV9-empty

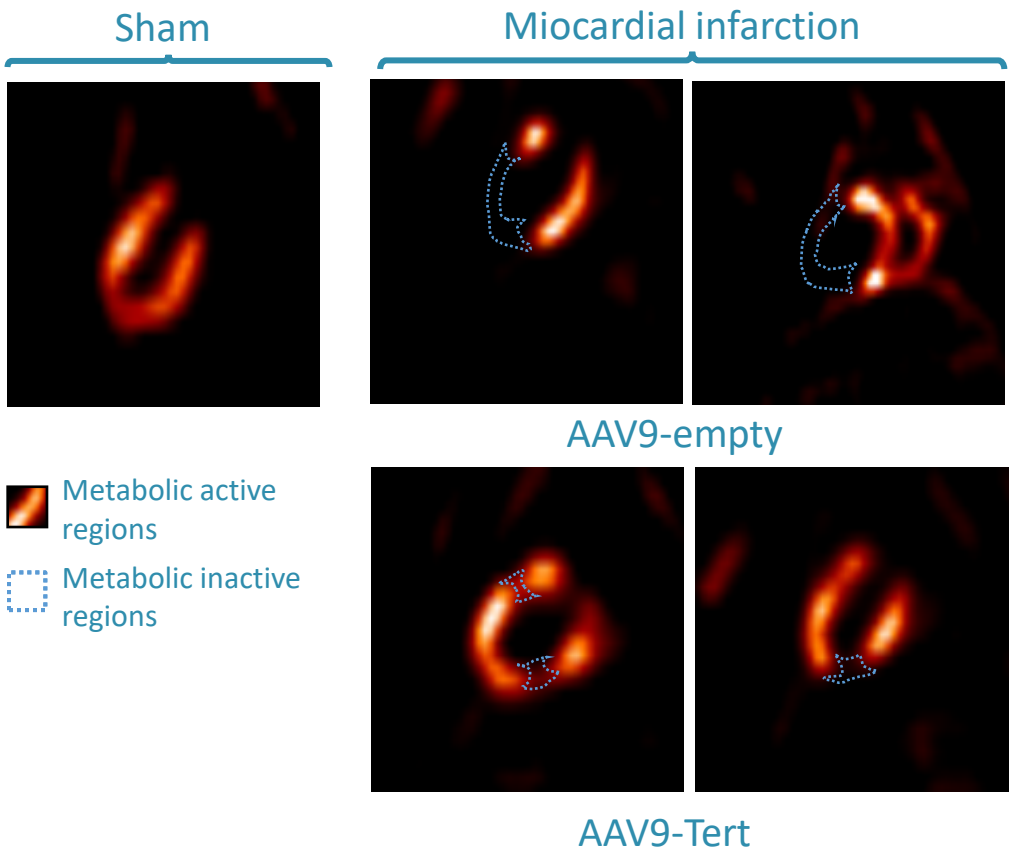
3-4
weeks

- ✓ Increased survival (17%)
- ✓ Improved cardiac function (PET, EC)
- ✓ Better metabolic parameters (urea)
- ✓ Less fibrotic scar
- ✓ Increased cardiomyocyte proliferation

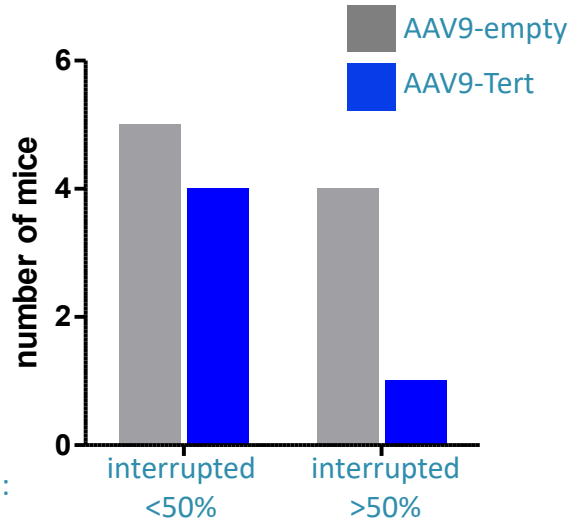
Bär et al. Nature Communications (2014)

AAV9-TERT:
Heart infact

PET imaging (glucose uptake by cardiomyocytes)



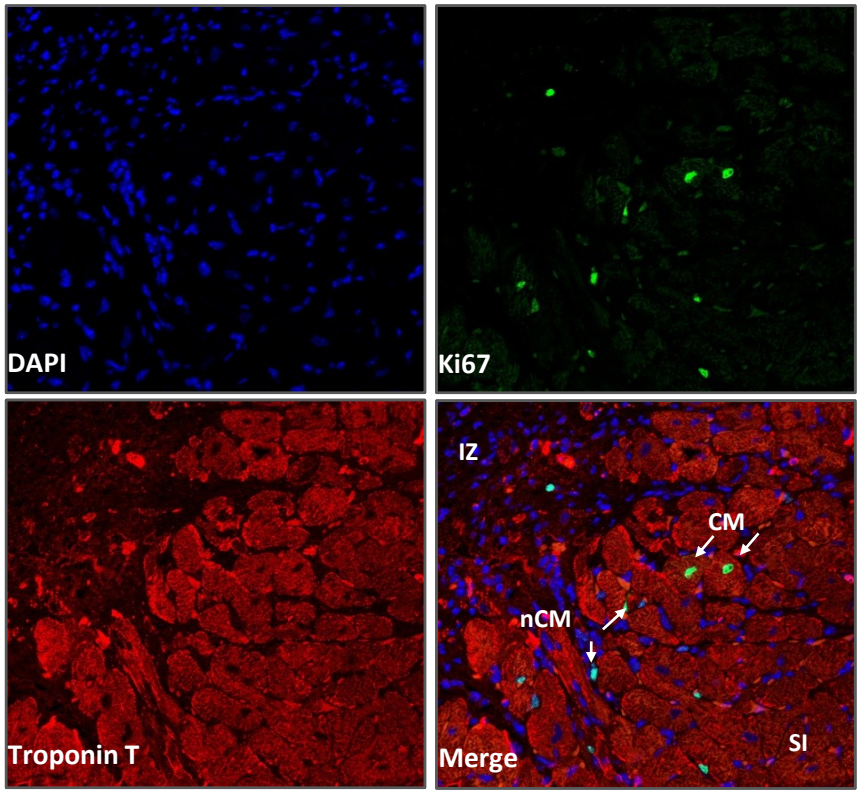
PET signal:

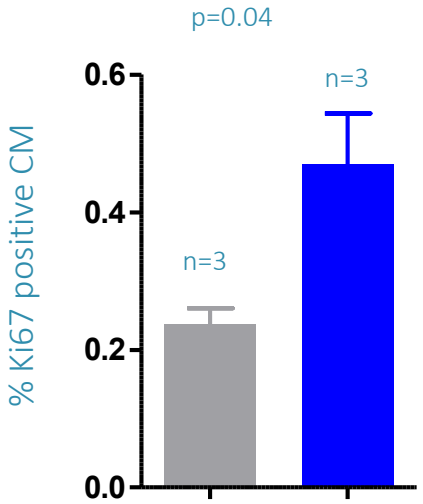


Bär et al. Nature Communications (2014)

AAV9-TERT induces Cardiomyocyte division

Ki67-positive cardiac myocytes in the infarct remote myocardium





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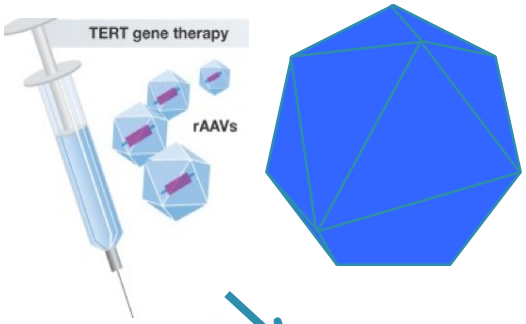

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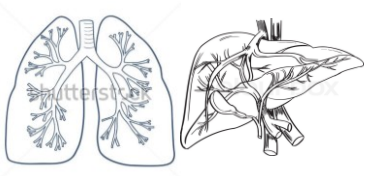
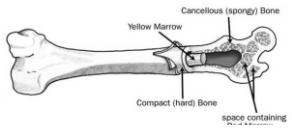


lung & liver fibrosis



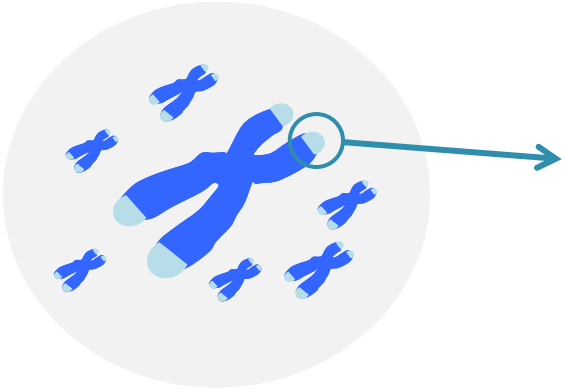
Bone marrow aplasia

Mutants for telomerase & shelterin
“extreme” telomere shortening

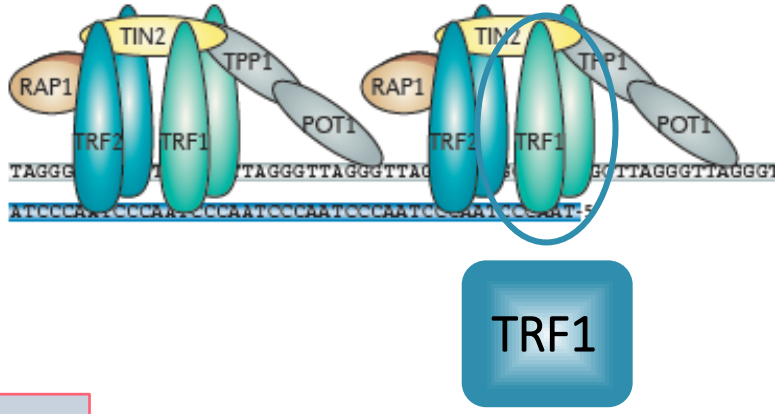
Mouse models

Telomere syndromes

Telomeres



Shelterin: the telomere protective complex



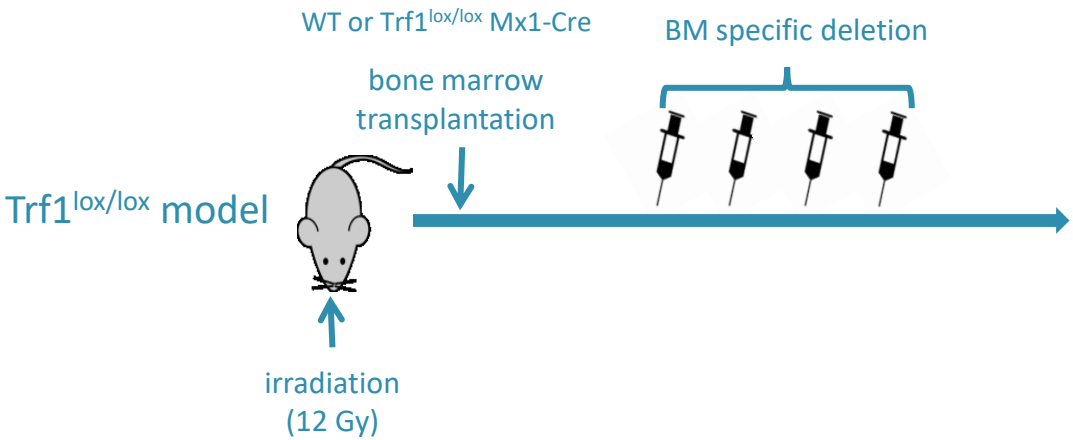
Telomere syndrome manifestations that overlap with human age-related phenotypes

High-turnover compartments	**Low-turnover compartments**
Hair graying	Idiopathic pulmonary fibrosis
Hair loss	Emphysema
Nail ridging	Liver fibrosis and cirrhosis
Periodontal disease	Impaired glucose tolerance
Thrombocytopenia	Defective insulin secretion
Decreased bone marrow cellularity	Insulin resistance
Immunosenescence	Osteoporosis
Gastrointestinal intraepithelial lymphocytosis	
Increased cancer risk	
Chemotherapy intolerance	

Martínez and Blasco. Nat. Rev. Cancer, 2011
Martínez et al., Genes & Dev, 2009
Tejera et al., Dev. Cell, 2010
Martínez et al., Nat Cell. Biol., 2011

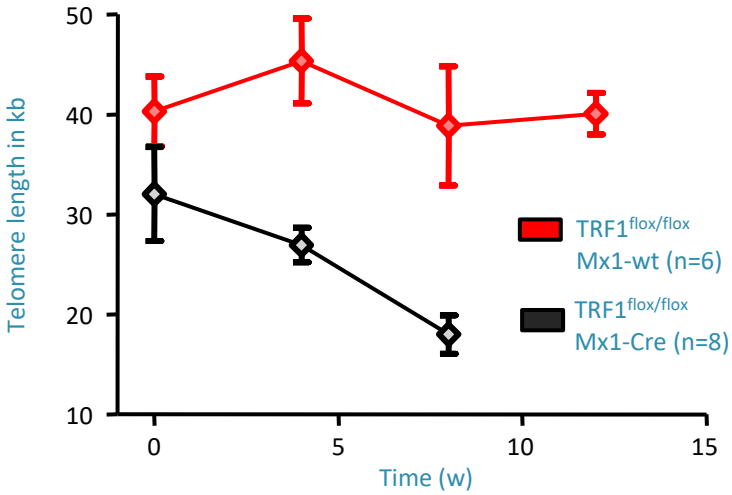
Mouse models

Aplastic anemia

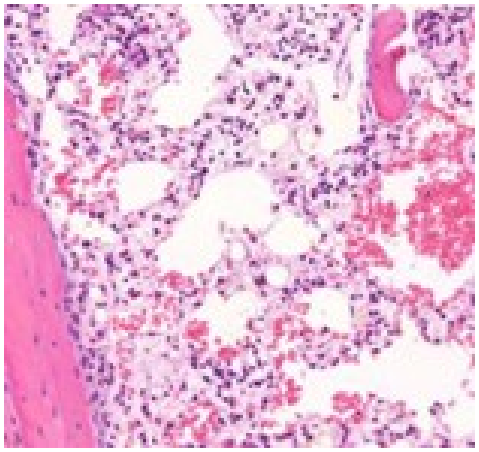


- ✓ Depletion of BM progenitor cells
- ✓ Compensatory proliferation SCs
- ✓ Induction of senescence (no apoptosis)
- ✓ Induction of rapid telomere shortening
- ✓ Full blown aplastic anemia

Rapid telomere shortening



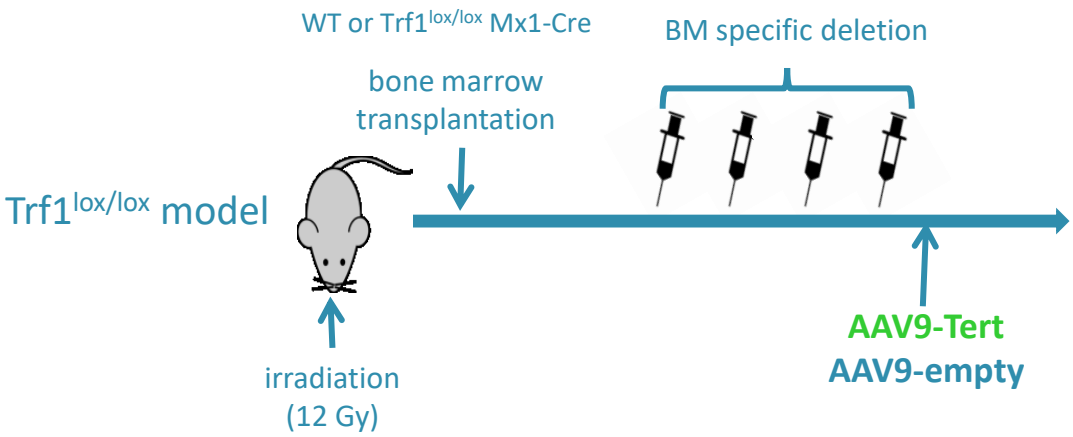
BM aplasia



Beier et al., Blood (2012)

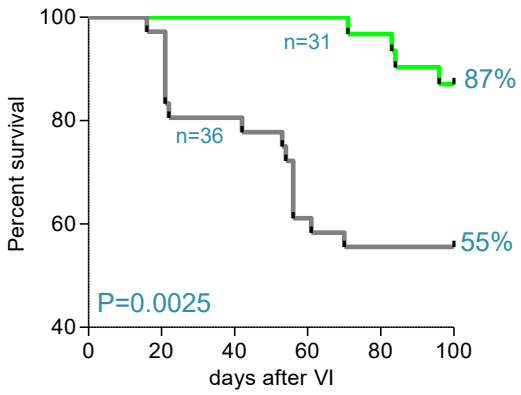
AAV9-TERT

Efficacy BM aplasia

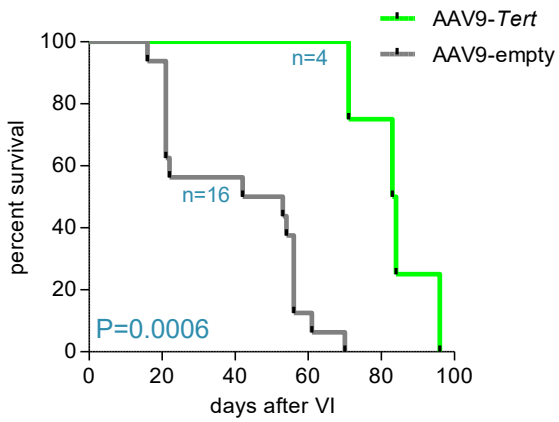


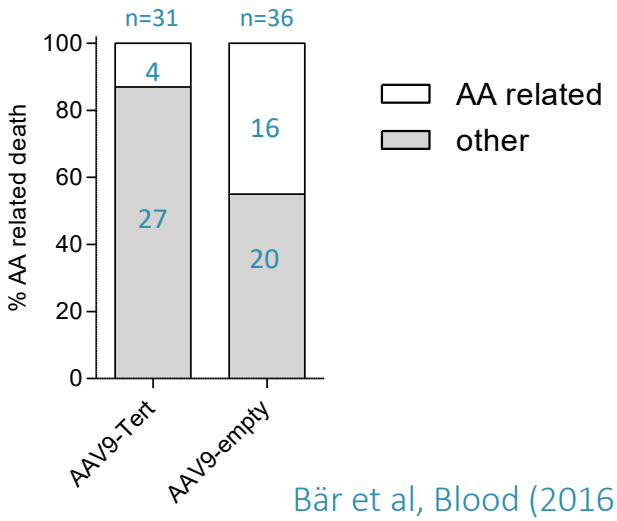
- ✓ Aplastic anemia
- ✓ Survival
- ✓ Blood counts
- ✓ Telomere length

Overall survival



AA-related deaths only



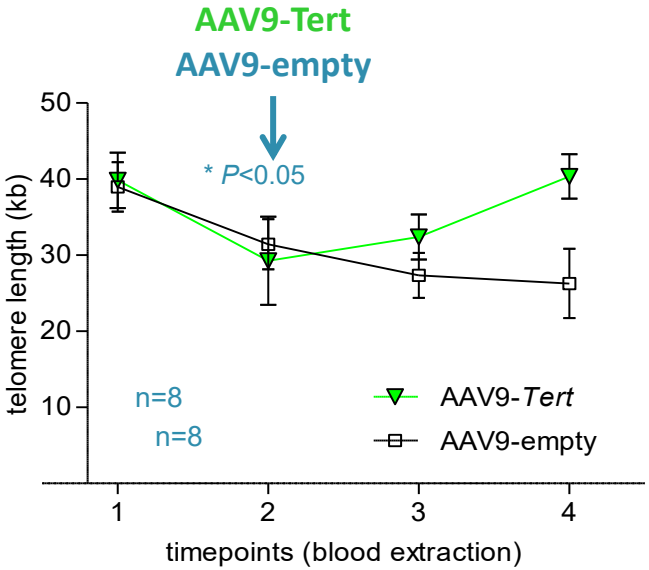


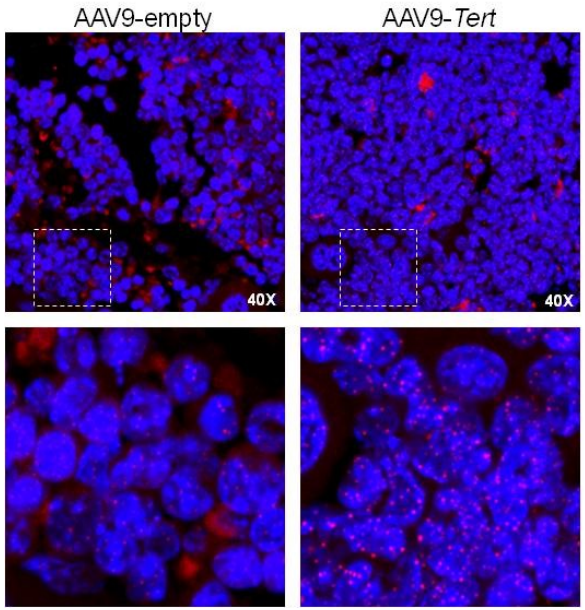
Bär et al, Blood (2016)

AAV9-TERT

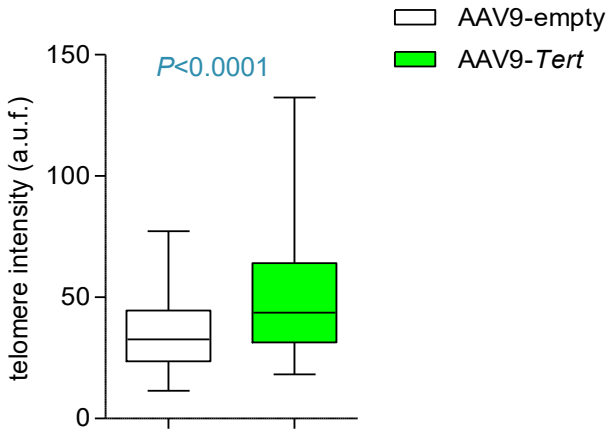
Efficacy BM aplasia

HT-QFISH blood





Q-FISH BM



Bär et al, Blood (2016)

Telomere Syndromes

Pulmonary fibrosis

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

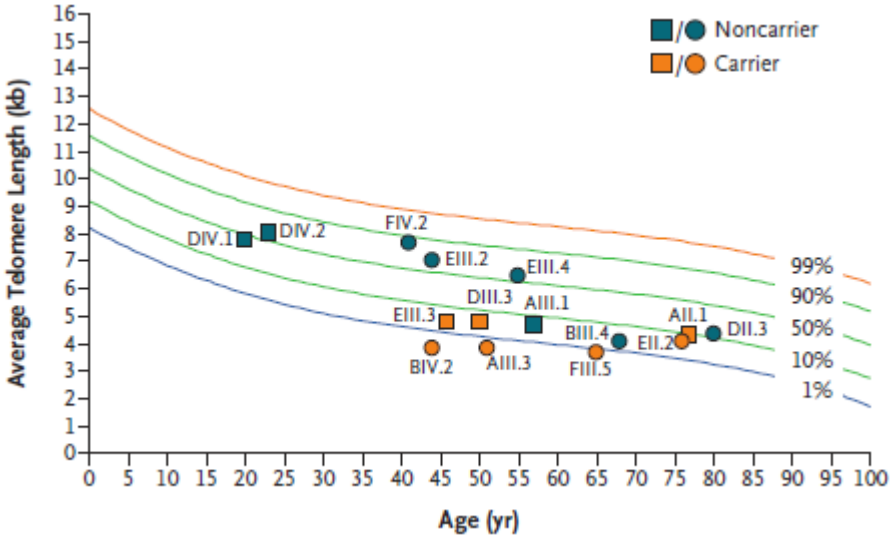
Telomerase Mutations in Families with Idiopathic Pulmonary Fibrosis

Mary Y. Armanios, M.D., Julian J.-L. Chen, Ph.D., Joy D. Cogan, Ph.D., Jonathan K. Alder, B.A., Roxann G. Ingersoll, B.S., Cheryl Markin, B.S., William E. Lawson, M.D., Mingyi Xie, B.S., Irma Vulto, B.S., John A. Phillips III, M.D., Peter M. Lansdorp, M.D., Ph.D., Carol W. Greider, Ph.D., and James E. Loyd, M.D.

PNAS PNAS PNAS

Short telomeres are a risk factor for idiopathic pulmonary fibrosis

Jonathan K. Alder*, Julian J.-L. Chen†‡, Lisa Lancaster§, Sonye Danoff§, Shu-chih Su‖, Joy D. Cogan**, Irma Vulto††, Mingyi Xie†, Xiaodong Qi†, Rubin M. Tuder‡†, John A. Phillips, III**, Peter M. Lansdorp‡‖§§, James E. Loyd§, and Mary Y. Armanios*¶¶



- ✓Age is a risk factor
- ✓Gender: more men than women affected
- ✓Cigarrette smoke, pollution & radiation are risk factors
- ✓8-20% of familial cases – 3%- have mutations in telomerase (Terc o Tert)

…and individuals with sporadic IPF also have shorter telomeres than healthy controls, even without mutations in TERT or TERC

Telomere Syndromes

Pulmonary fibrosis

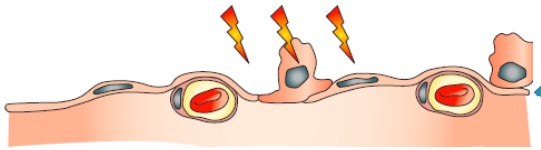
Telomere shortening

Pollution

Smoking

Radiation

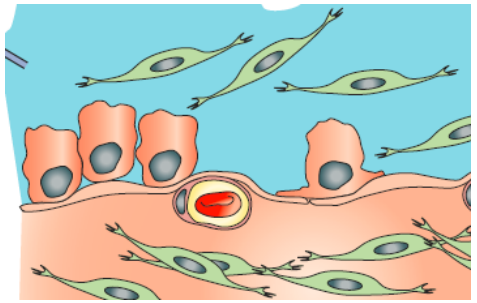
Injury in Alveolar Epithelial Cells



Senescence

Apoptosis

Immune response and fibroblast recruitment



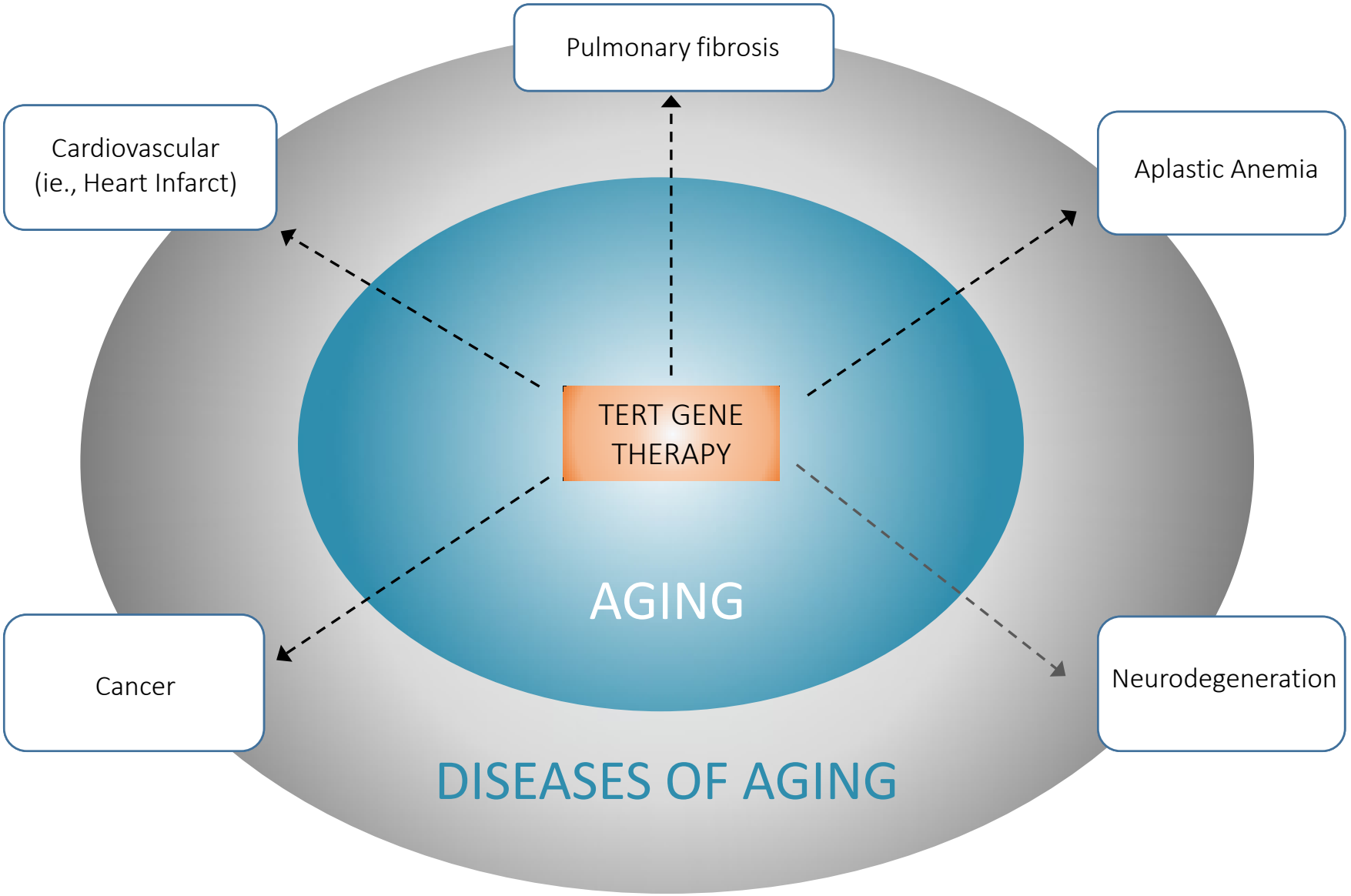
Impaired stem cell function
defective regeneration

Aberrant wound healing

Esbriet
(pirfenidone)
TGFβ blocker

fibrosis

TERT Gene Therapy



Funding (2012-2017)

cnio stop cancer

European Research Council

AXA Research Fund
Through research protection

fundación Lilly

SEVENTH FRAMEWORK PROGRAMME

worldwide cancer research

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