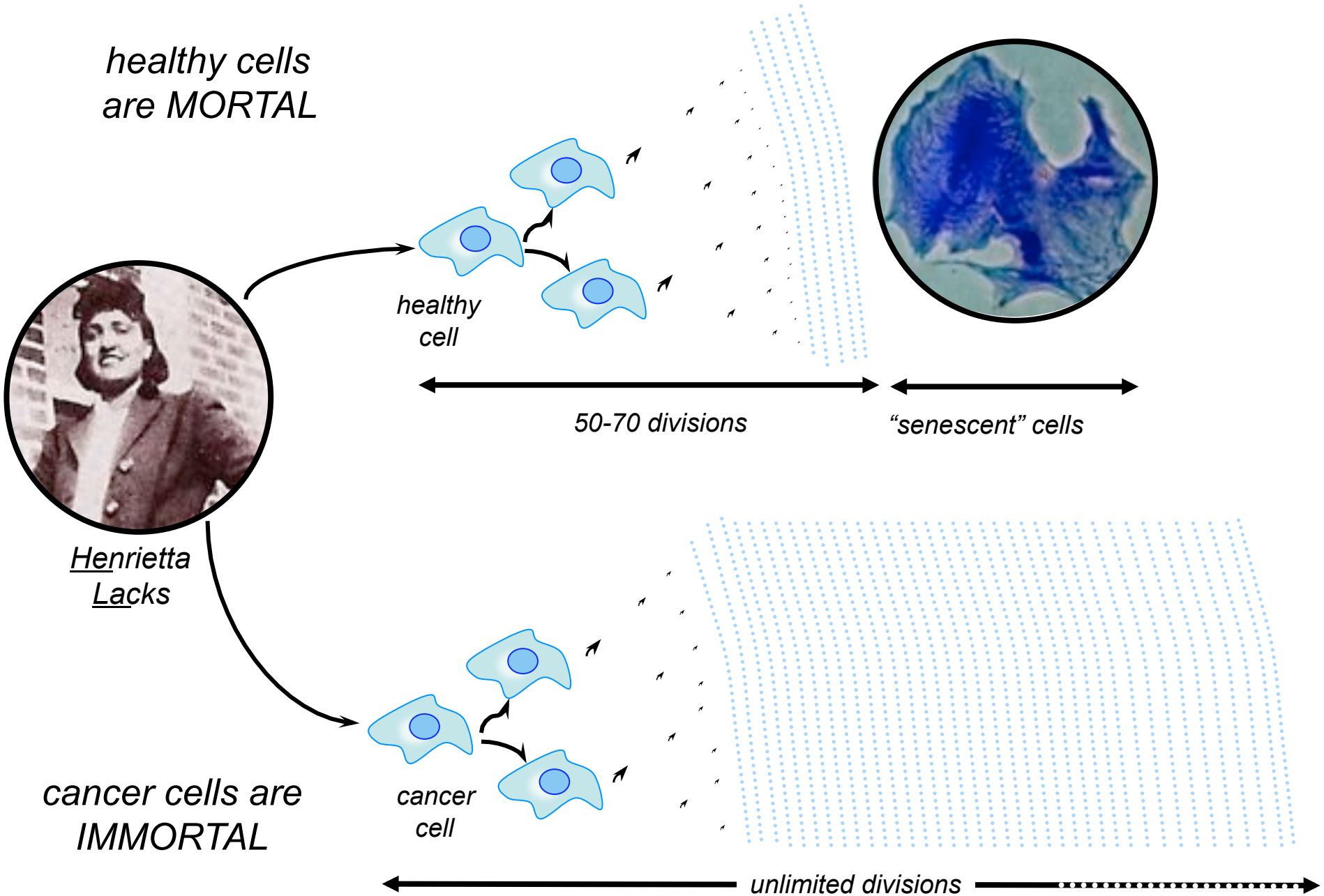
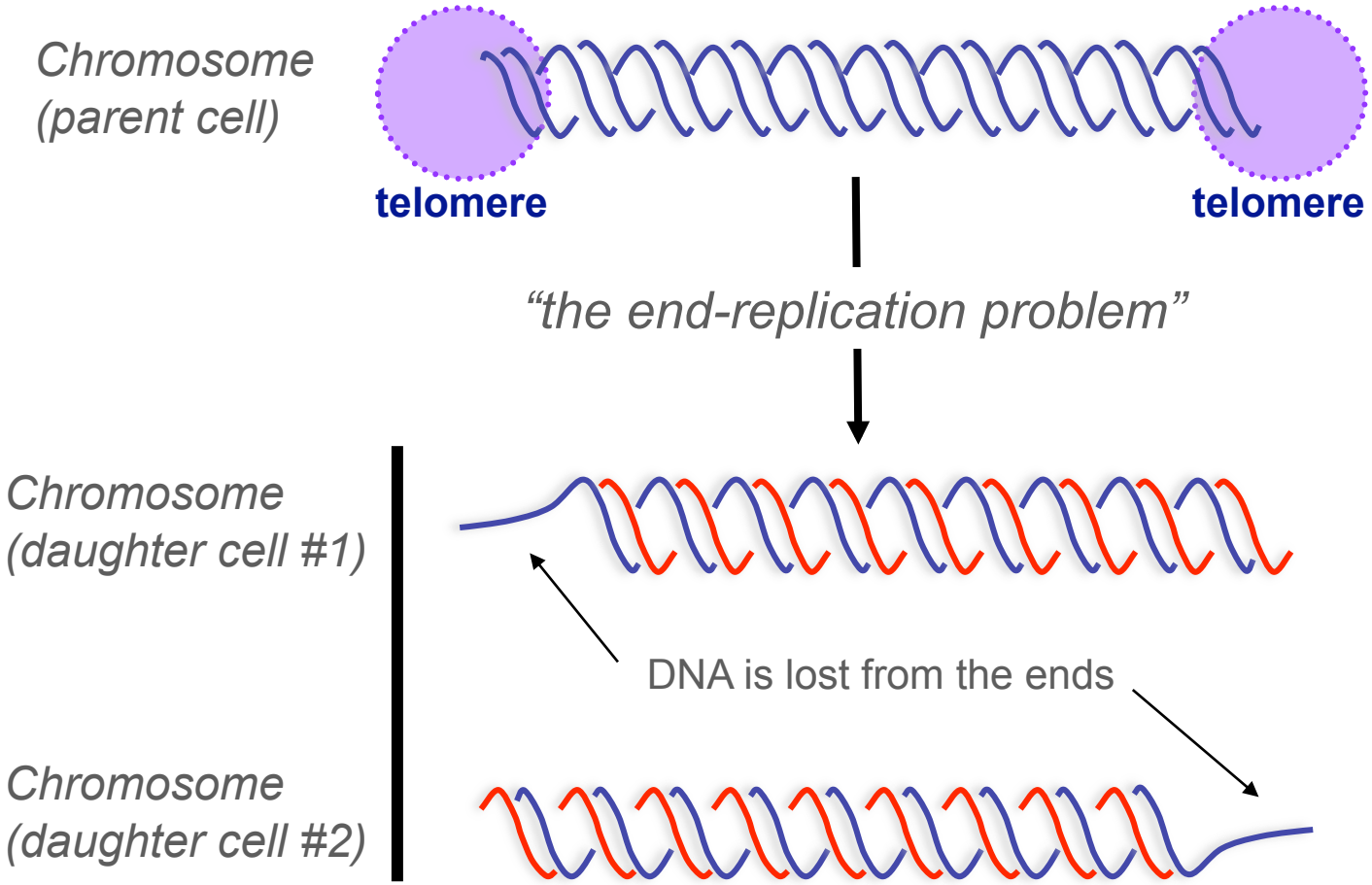
Telomeres & telomerase as therapeutic targets

Fighting cancer and aging

Maria A. Blasco´s team, CNIO, Madrid


healthy cells are MORTAL
healthy cell
50-70 divisions
"senescent" cells
Henrietta Lacks
cancer cells are IMMORTAL
cancer cell
unlimited divisions

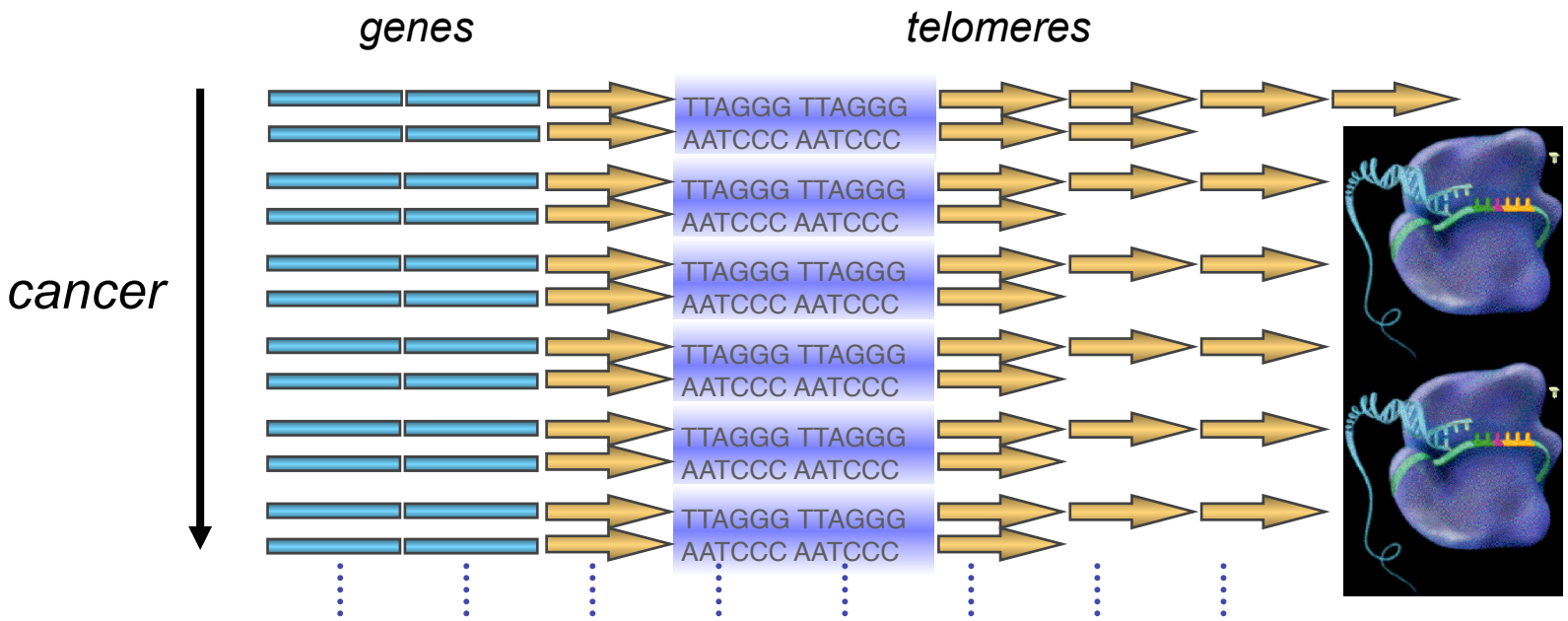
Telomeres are lost everytime that a cell divides



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 …

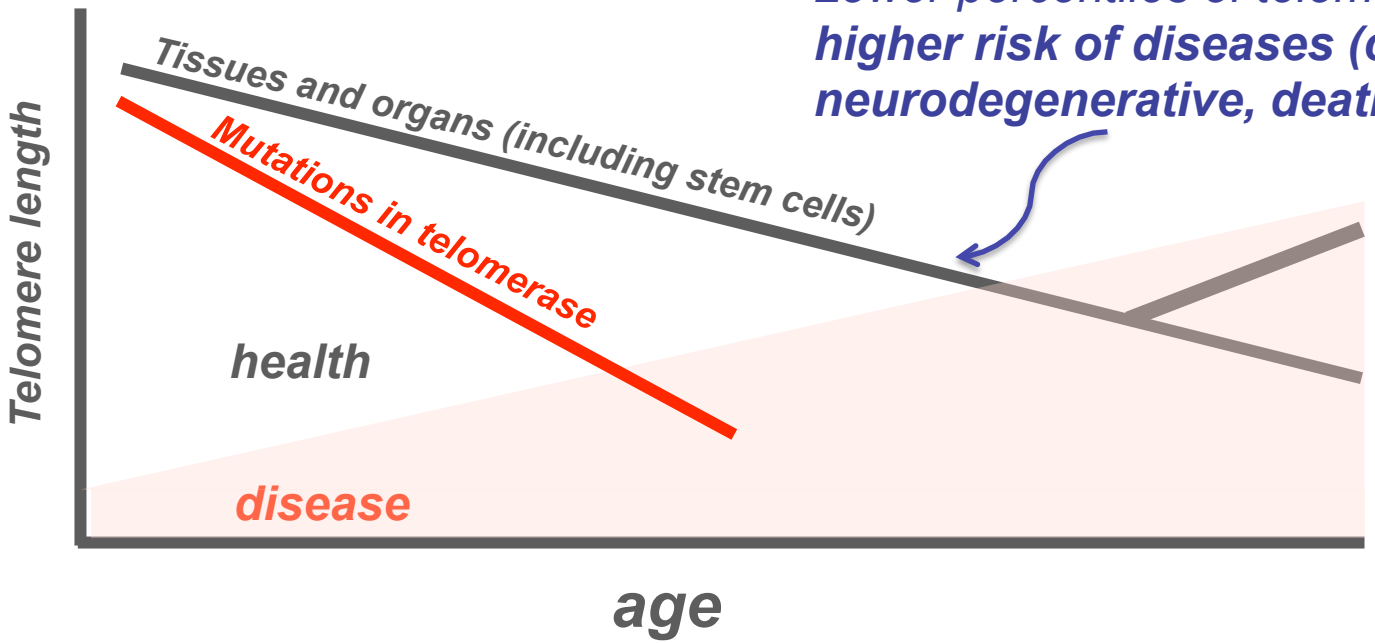
Cancer cells manage to reactivate telomerase, thus escaping the mortal fate of adult cells and becoming immortal.



Telomeres, telomerase and aging

*Telomere length=**Biomarker** of aging?*

Lower percentiles of telomere length=
higher risk of diseases (cardiovascular, neurodegenerative, death by infections)



Human pathologies due to telomerase defects

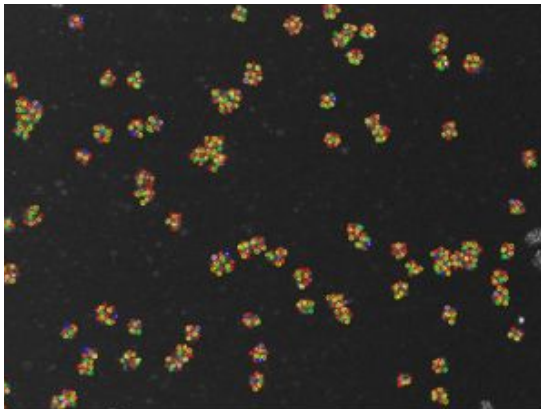
dysqueratosis congenita (DKC1, Terc)
aplastic anemia (Terc, Tert)
idiophatic pulmonary fibrosis (Terc, Tert)

loss of the regenerative capacity of the skin lungs, bone marrow…

Telomere length as a BIOMARKER of aging & health status

A very accurate technology for telomere length measurement

LIFE LENGTH



Canela et al., *PNAS* (2007)

Telomere length measurements for individuals

Life Length´s partnership with:

LABCO Quality Diagnostics

sistemas genómicos

CENEGENICS medical institute

Age Diagnostic Laboratories
Dedicated to the anti-aging practitioner

Telomere length measurements for individuals

LIFE LENGTH

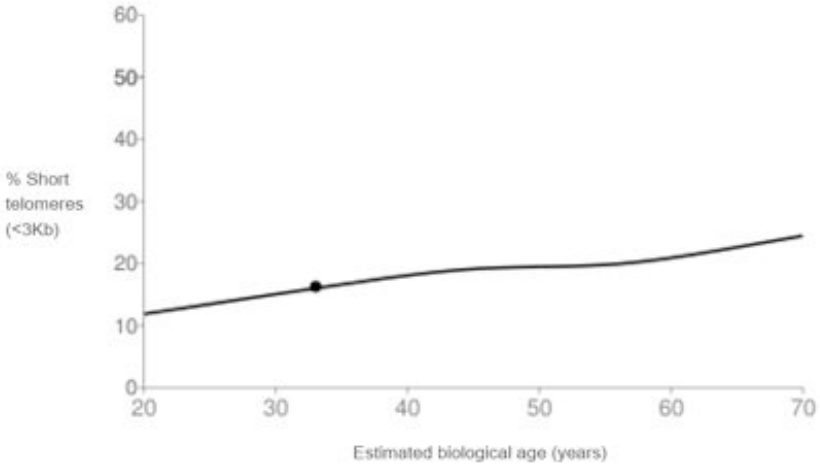
RESULTS REPORT

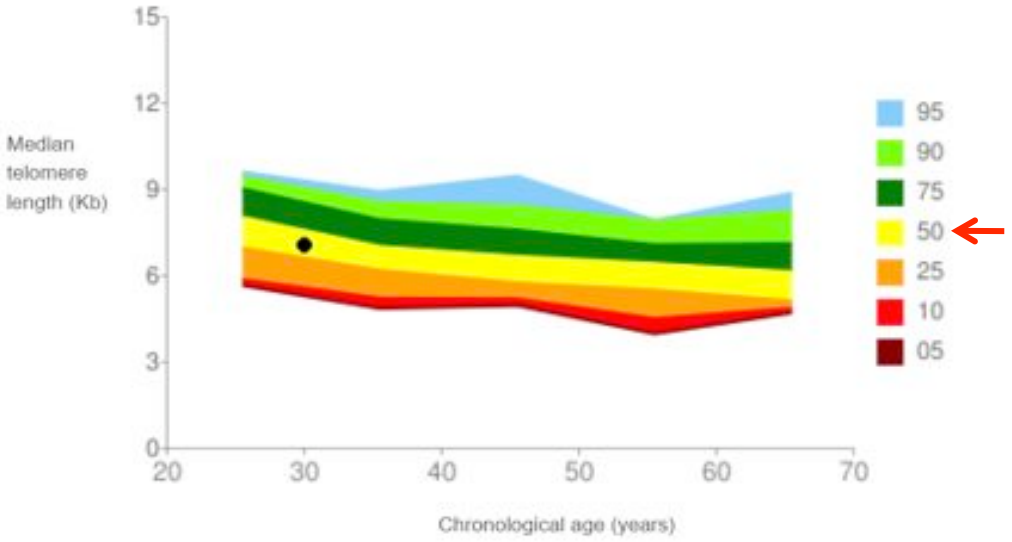
SAMPLE CODE: 66-048

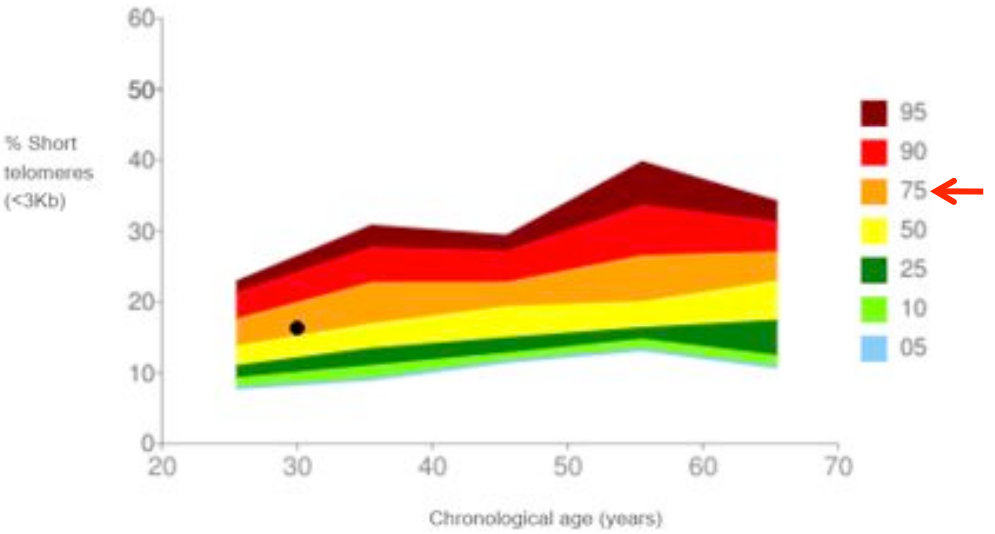
Percentage of short telomeres - General analysis

Percentage of short telomeres (<3Kb) 16.07

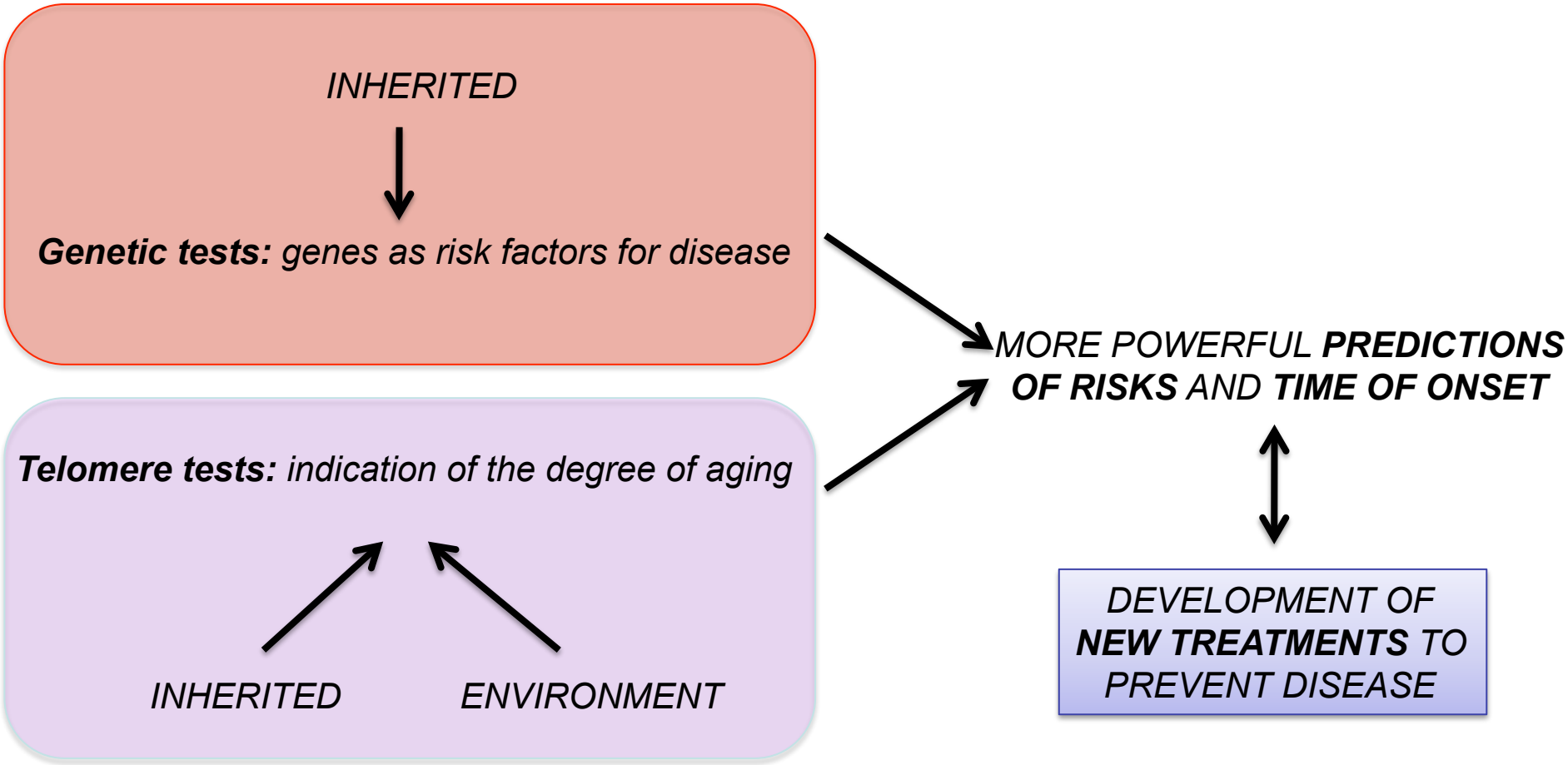
Estimated biological age (years) 33.2







A NEW ERA in medicine?: Personalized & preventive medicine



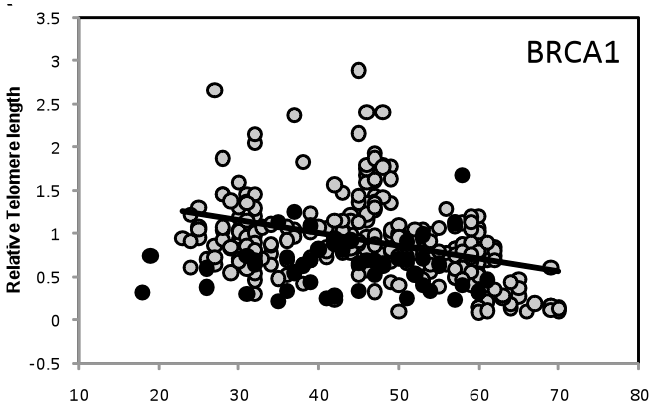
 # aging is the highest risk factor for all diseases

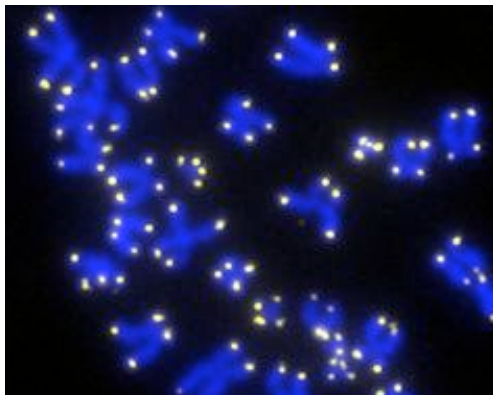
 # telomere length integrates both inheritance & environmental factors

More powerfull tools to predict risk factors and develop new treatments

***Breast cancer**: Familial breast & ovarian cancer*

BRCA1/BRCA2





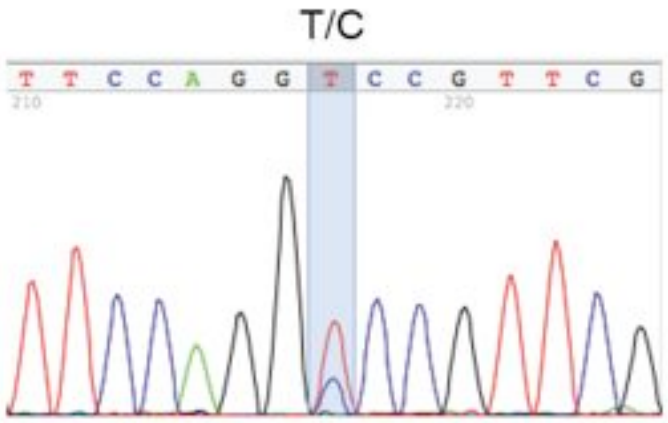
Martínez-Delgado et al., PLoS Genetics, 2011

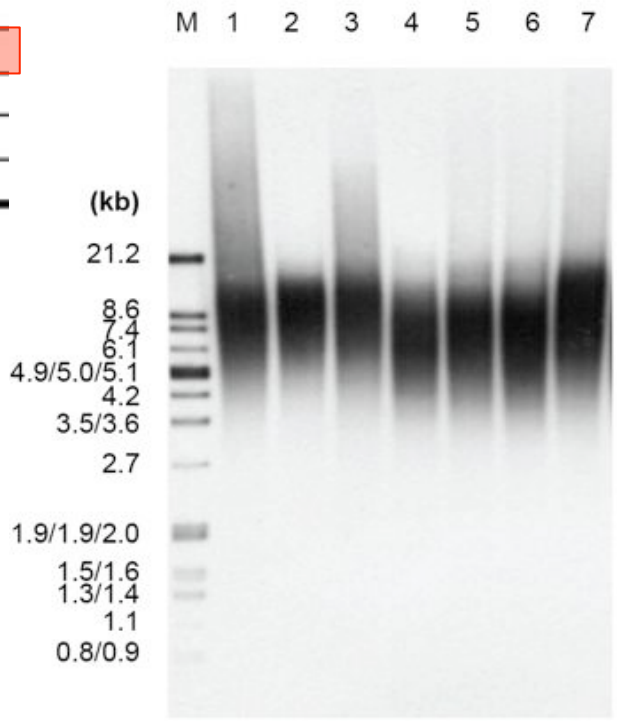
Martínez-Delgado et al., J. Medical Genetics, 2012 (ovarian)

Personal Omics prolifing and telomere length for Michael Snyder

High Interest Disease-Associated Rare Variants.

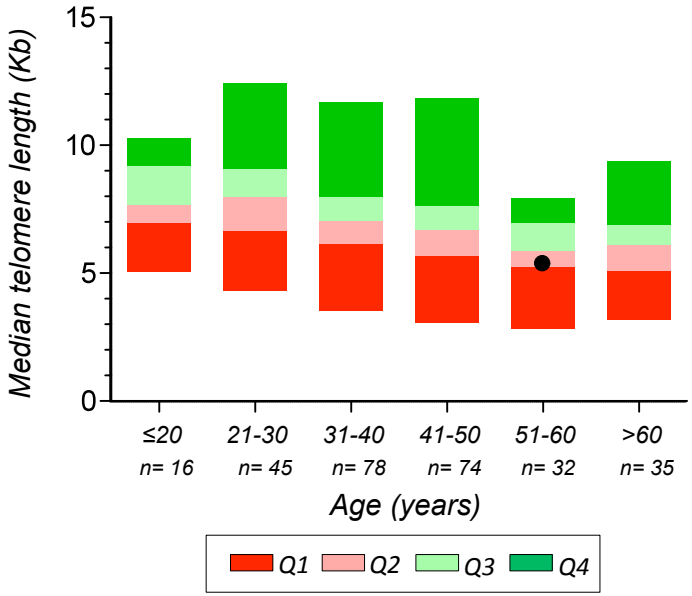
Gene ID	Position	Genotype	OMIM_disease
SERPINA1	14:94844947	C/T	Emphysema due to AAT deficiency
TERT	5:1294397	C/T	Aplastic anemia
KCNJ11	11:17409571	T/T	Type 2 diabetes
GCKR	2:27730939	T/T	Hypertriglyceridemia
NUP54	4:77055431	G/A	



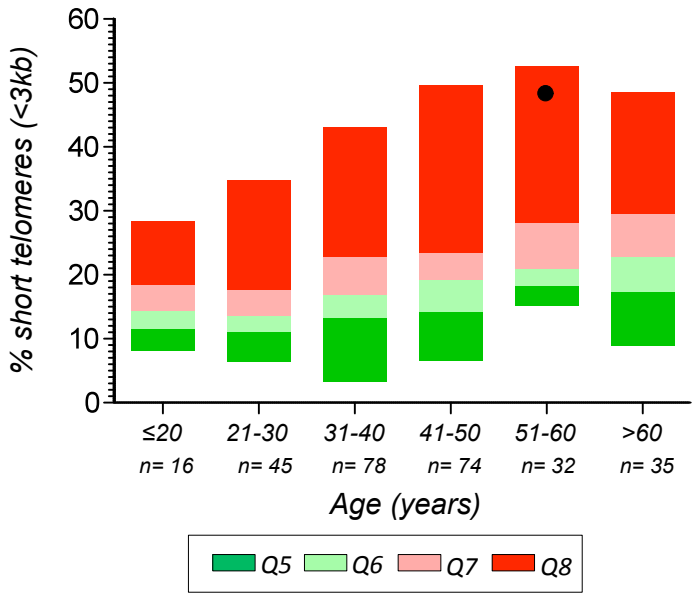


Chen et al., Cell, (March 15th 2012)

Snyder´s TERT mutation associated to increased abundance of short telomeres



Current age (years)	***55***
Predicted age (years)	***76***



Current age (years)	***55***
Predicted age (years)	***101***

Chen et al., Cell, (March 15th 2012)

The role of telomerase in chromosome stability, cancer & aging

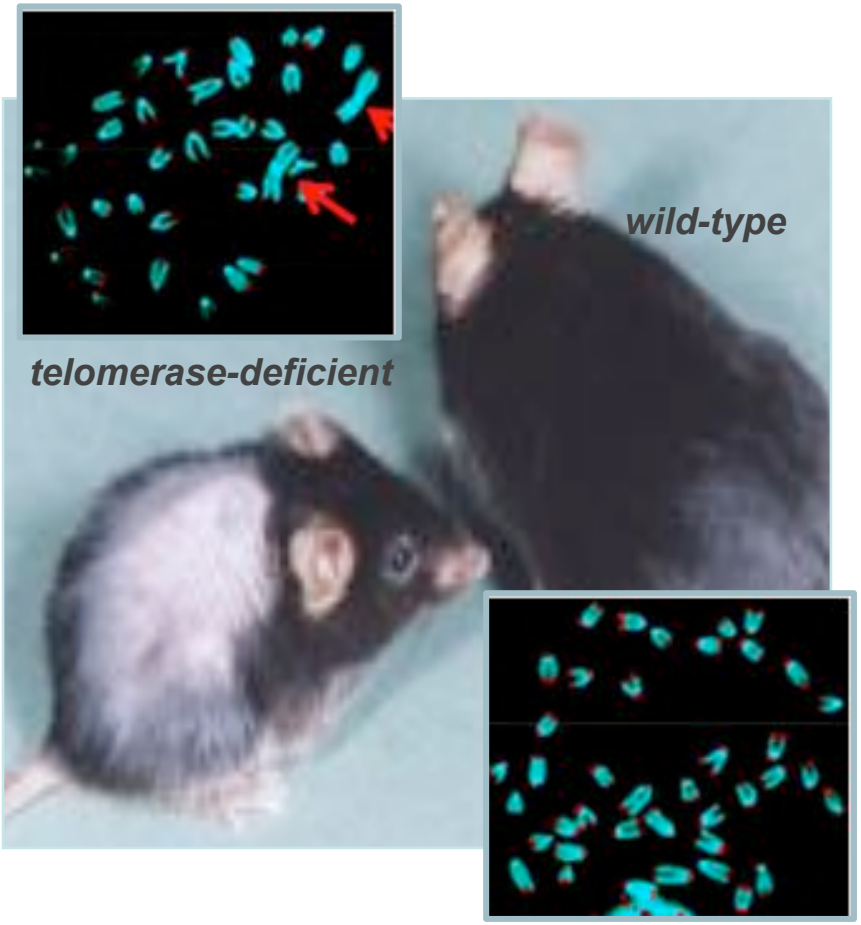
Telomerase-deficient mice (Terc$^{-/-}$):

decreased regenerative capacity
due to stem cell dysfunction

less cancer

Super-telomerase mice (K5-Tert):

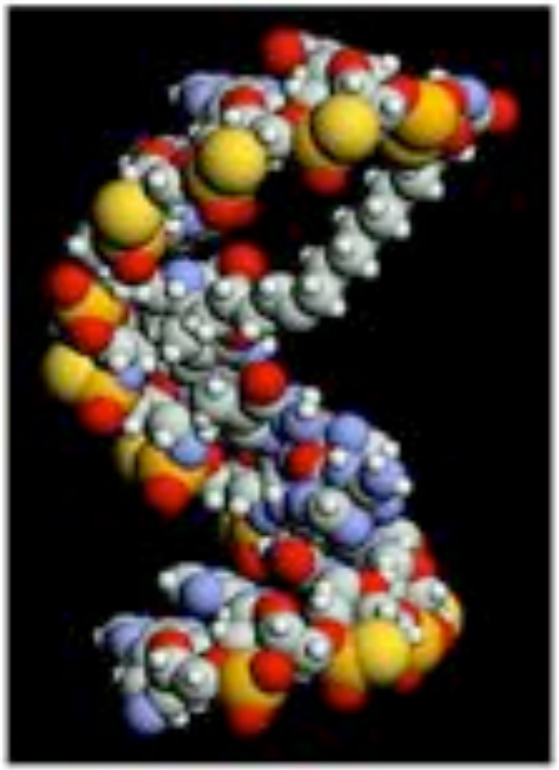
better tissue fitness
slightly more cancer



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)

Telomerase as an anti-cancer target (Imetelstat)

geron



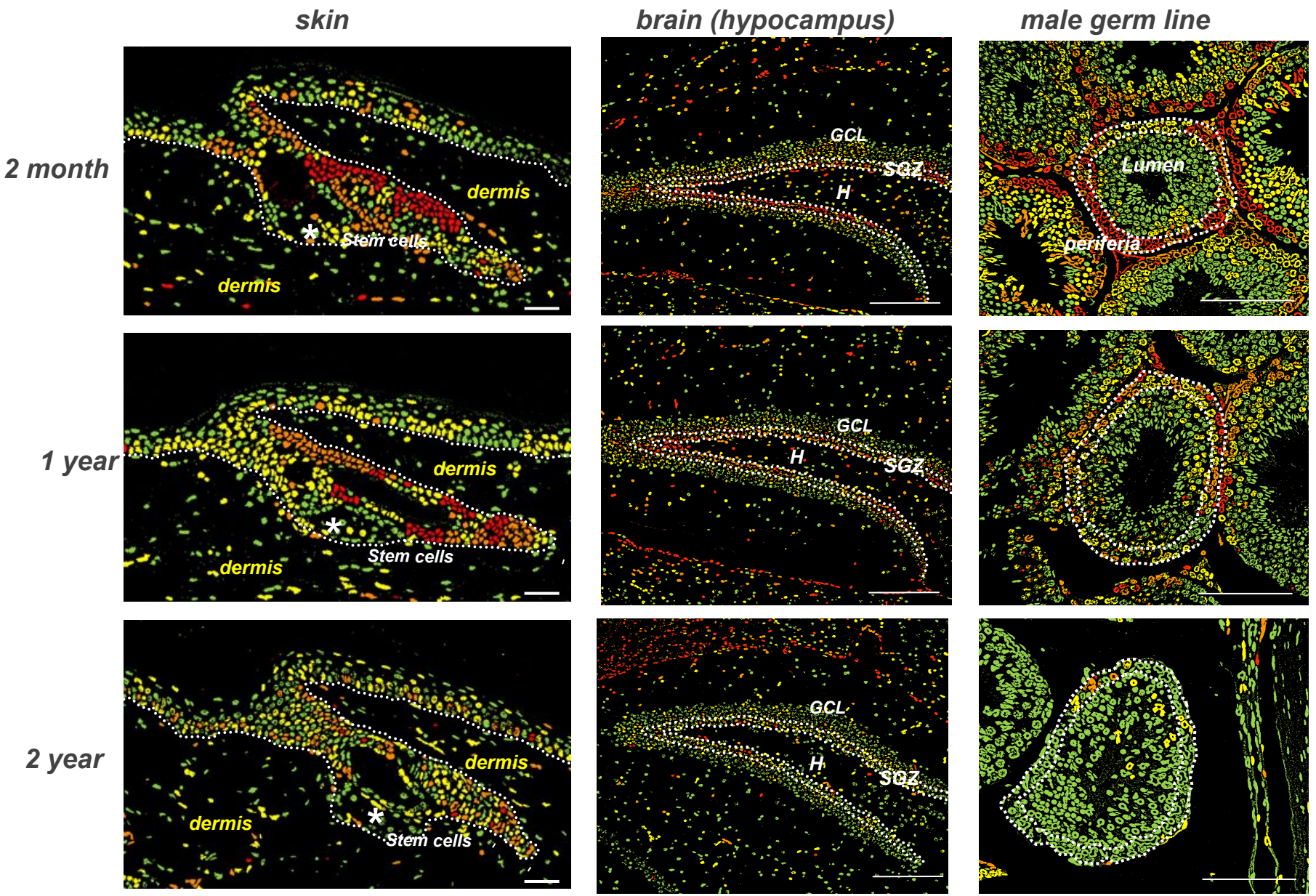
GRN163L Molecule

Phase II
Clinical trials
(breast, lung, prostate etc)

Can telomerase

increase health span?

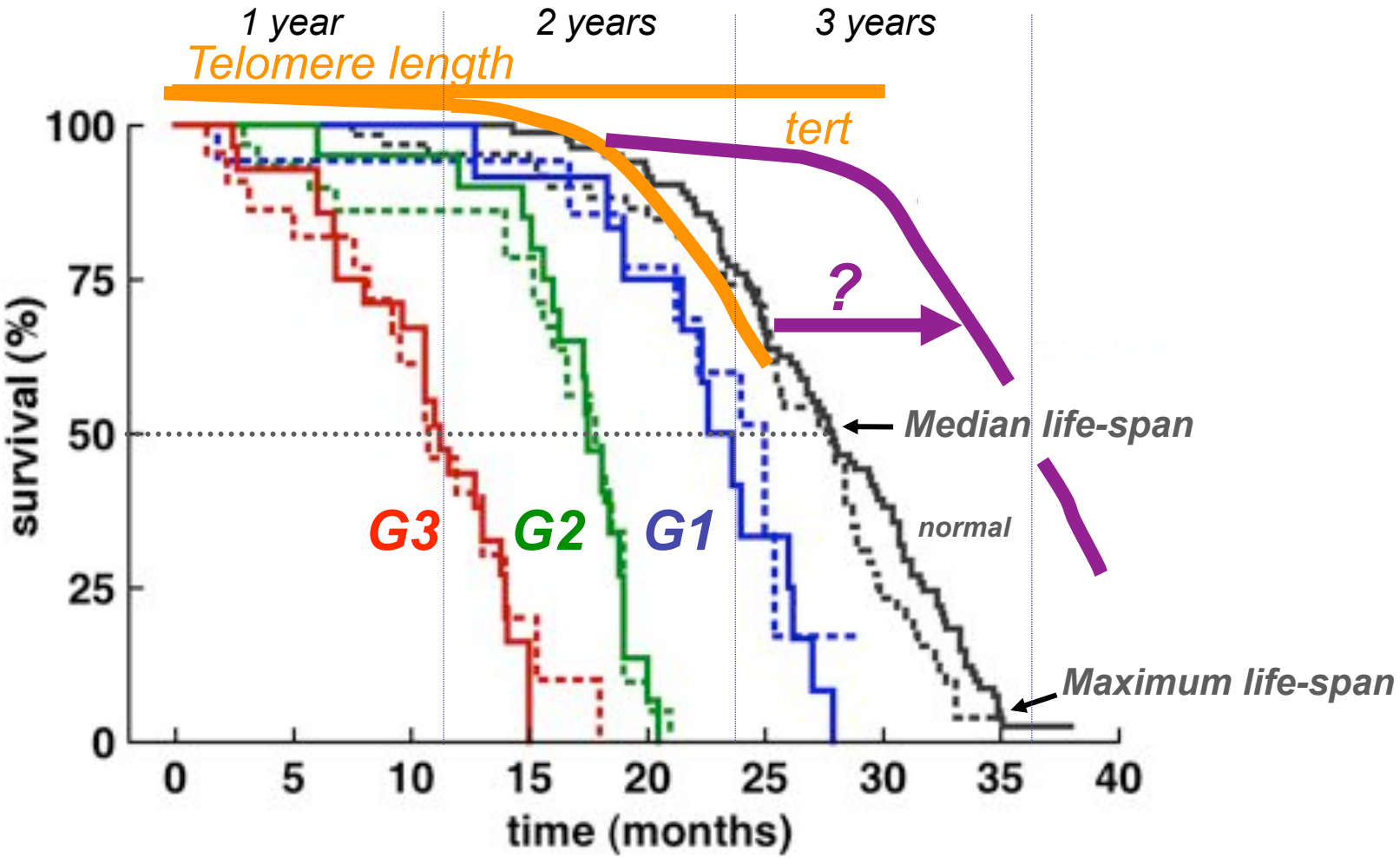
Mice are born with long telomeres but suffer telomere shortening with aging



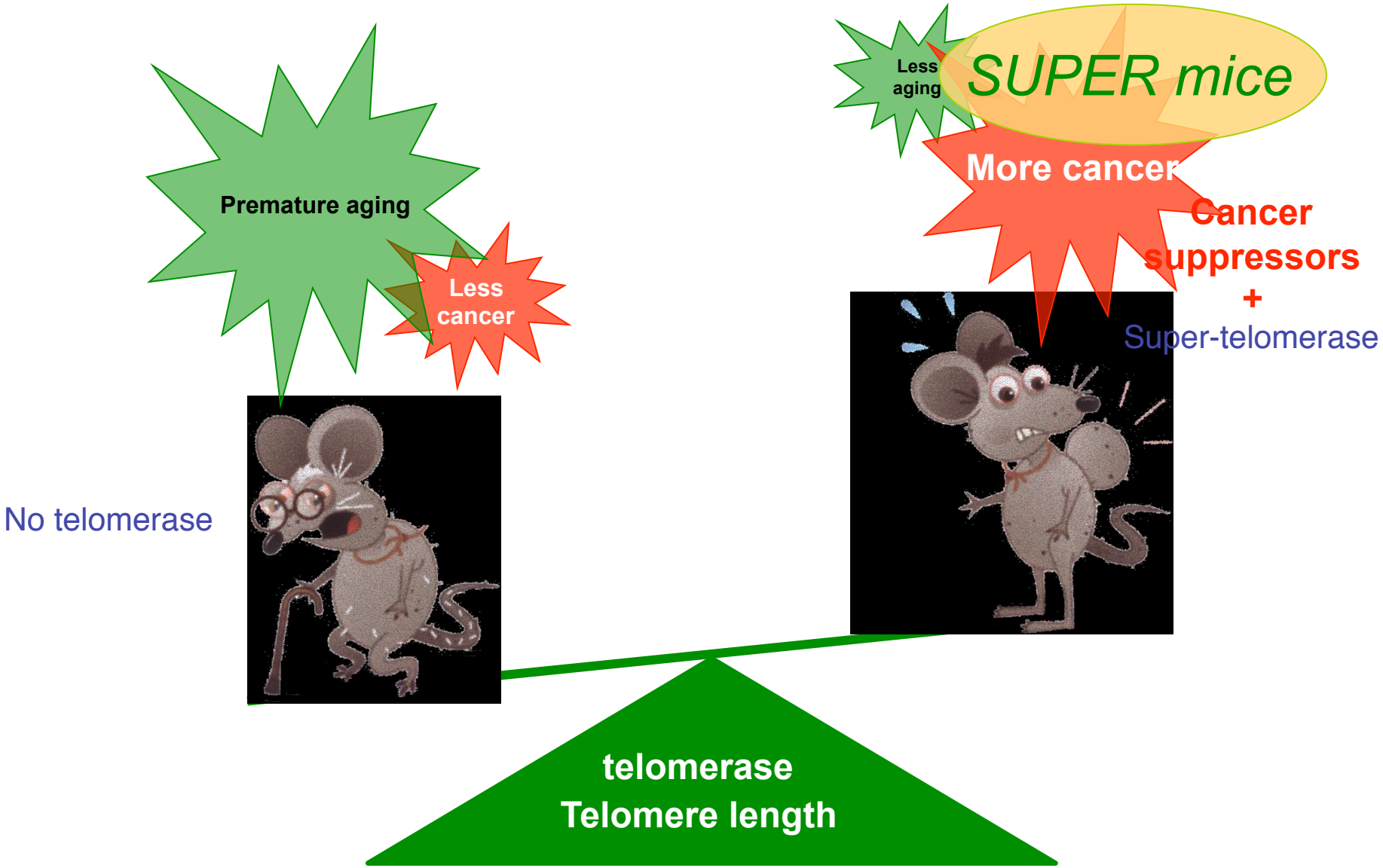
Telomapping technique

Flores et al., Genes and Dev (2008)

Telomerase is rate-limiting for mouse longevity



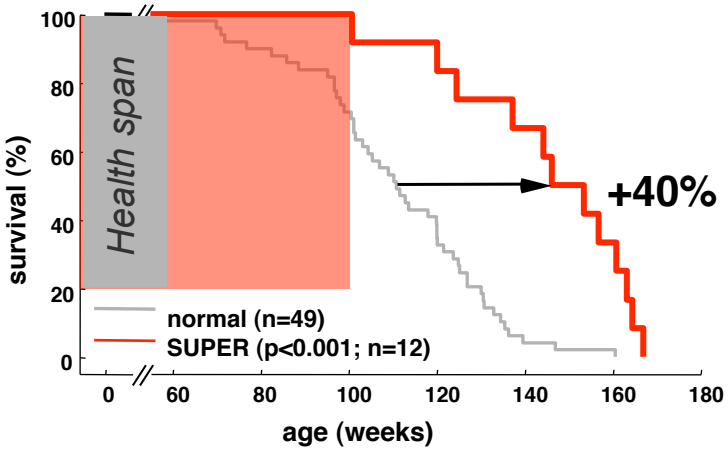
García-Cao et al., EMBO Rep, (2006)
Flores et al., Genes & Dev, (2008)

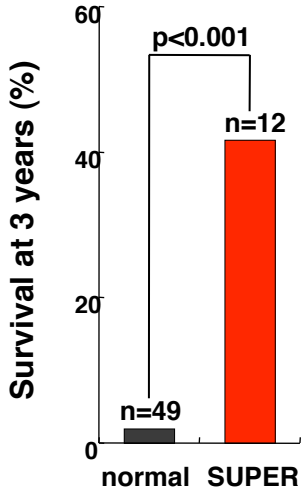


Gonzalez-Suarez et al., Oncogene (2004)

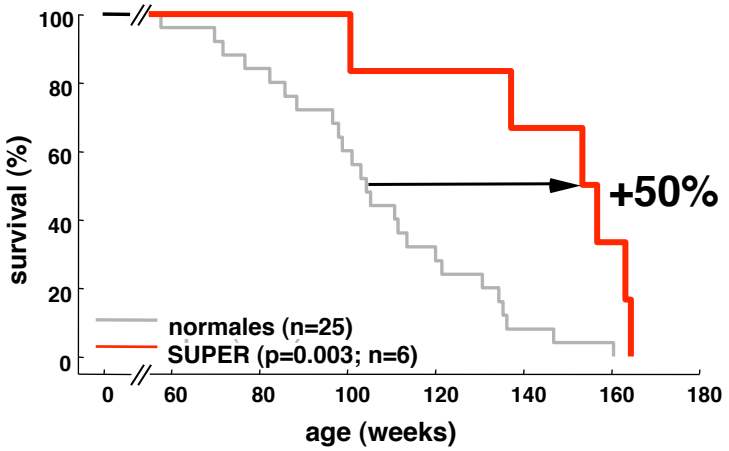
Increased "health span" & longevity in SUPER mice

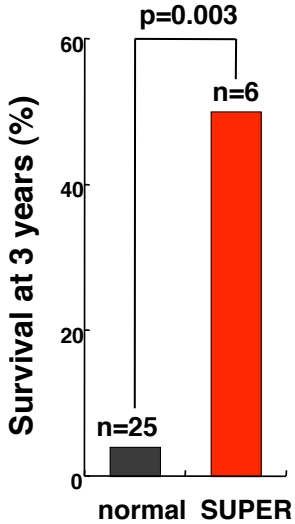
Overall survival





Cancer-free survival

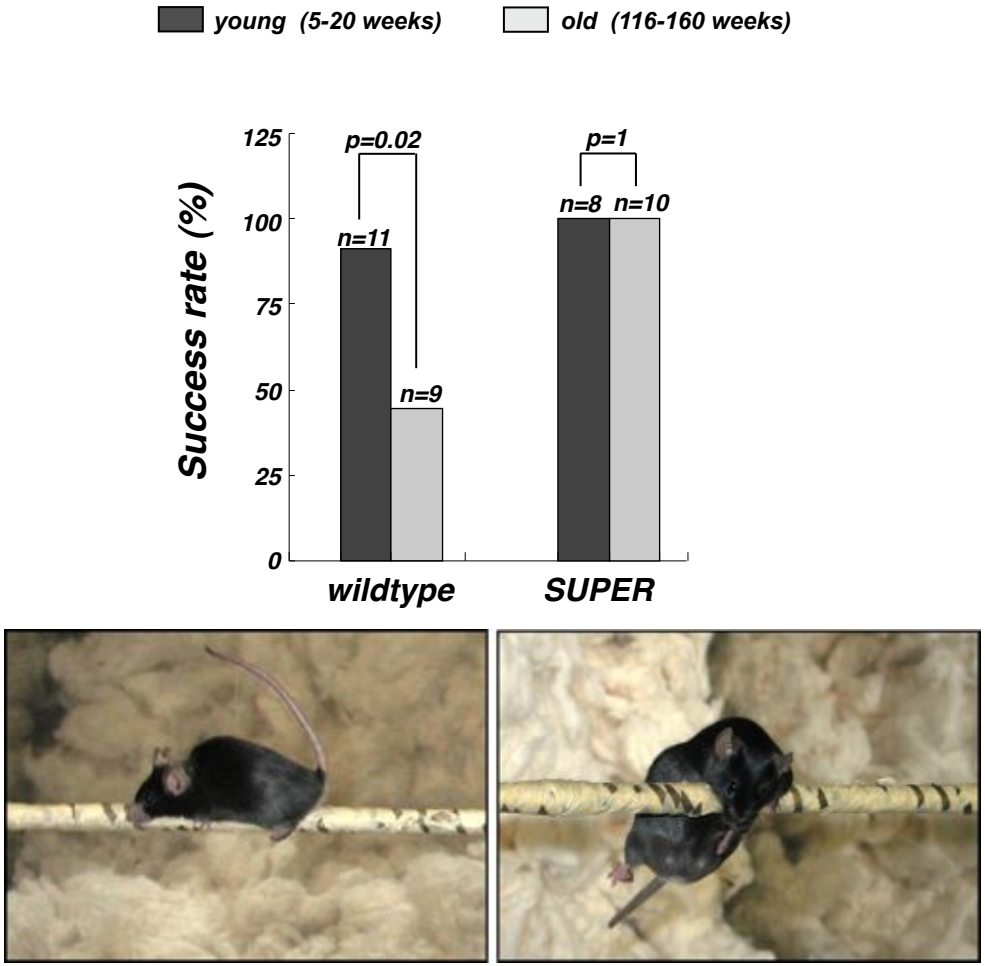




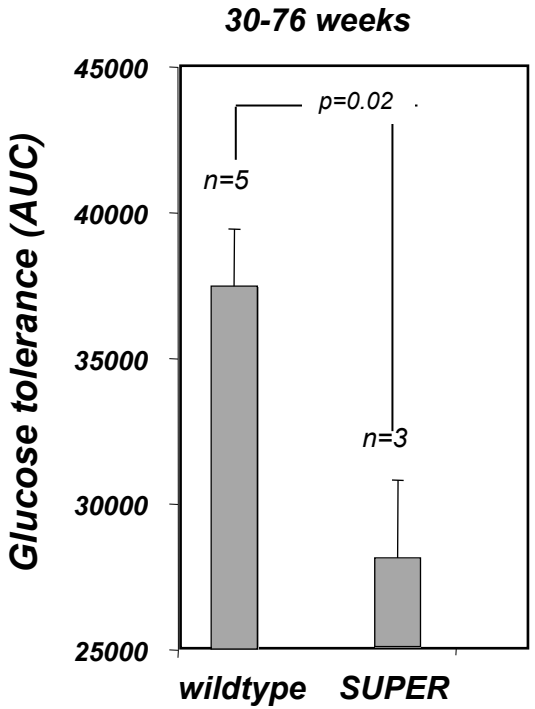
Tomás-Loba et al., Cell (2008)

Improved health late in life in SUPER mice

Improved neuromuscular fitness

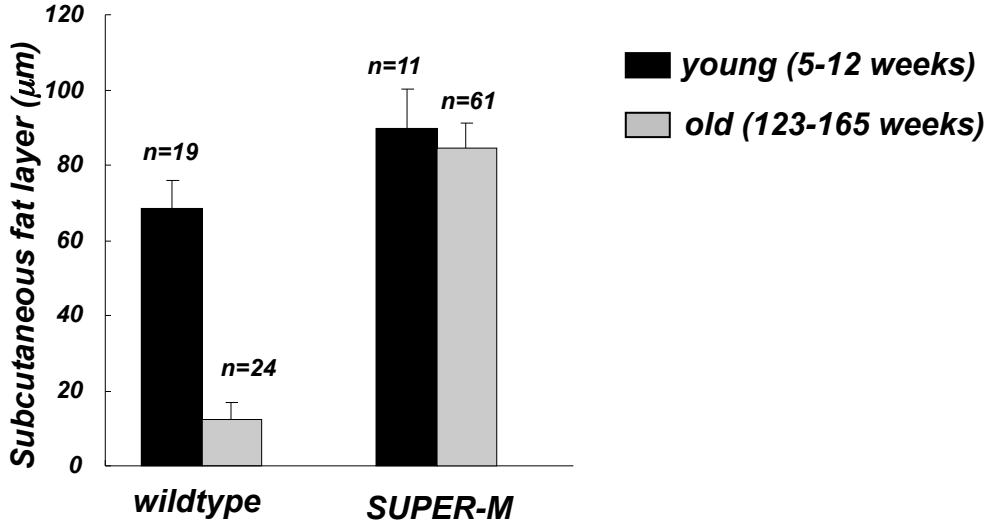


Improved glucose tolerance



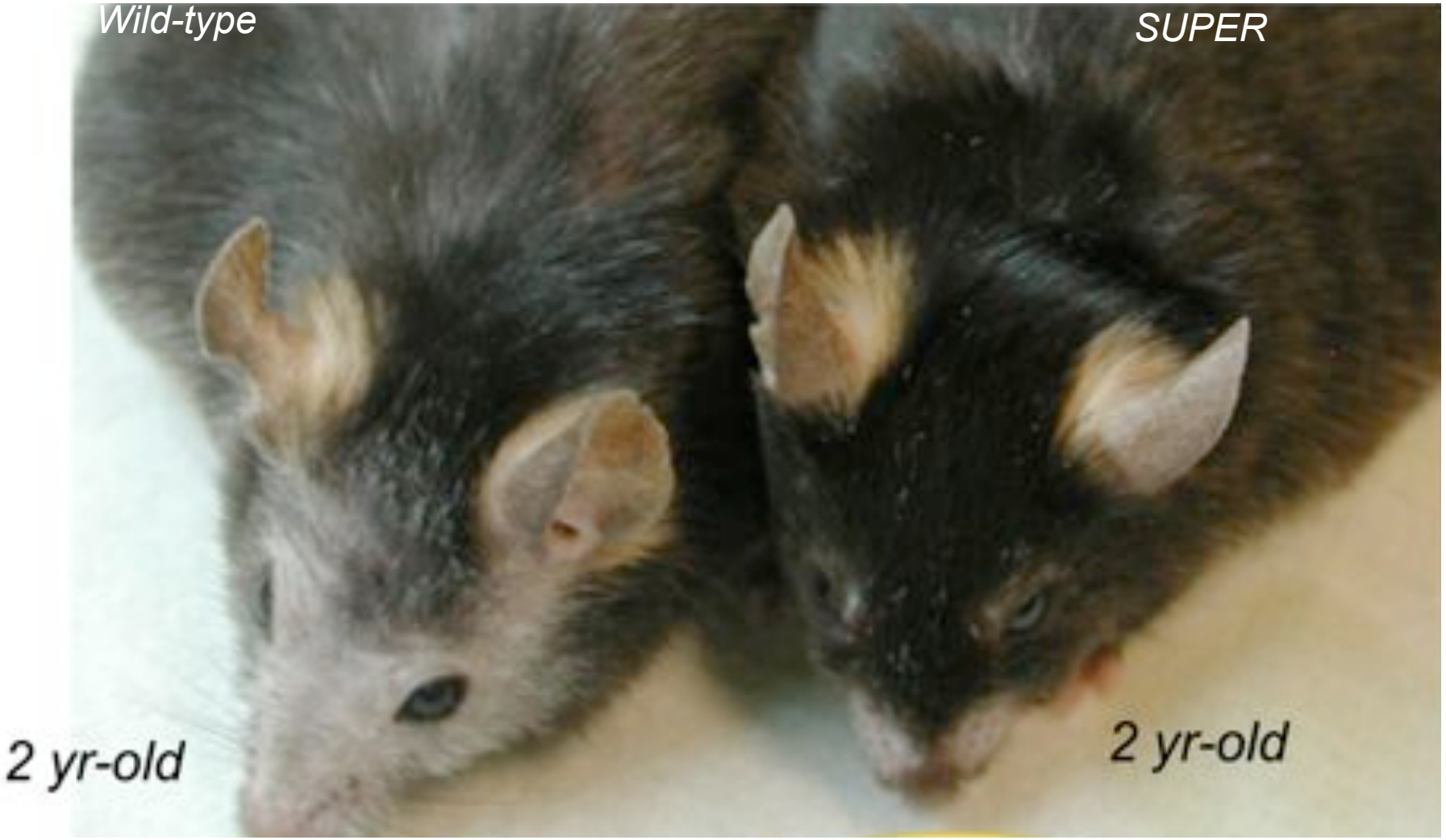
Tomás-Loba et al., Cell (2008)

Less skin aging in SUPER-M mice



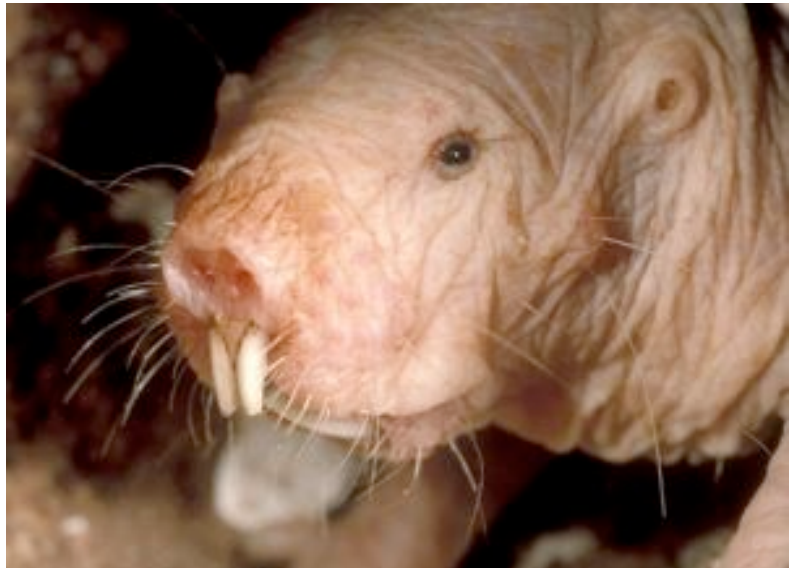
Tomás et al., Cell (2008)

Defeating aging with telomerase



Tomás-Loba et al, Cell (2008)

The naked mole rat does it!



The longest lived rodent (>30 years old)

Size of a mouse

LETTER

doi:10.1038/nature10533

Genome sequencing reveals insights into physiology and longevity of the naked mole rat

 # constitutive expression of telomerase
 # increased cancer resistance

Therapeutic strategies

Can TERT "treatment" delay aging without increasing cancer?

A gene therapy of aging

(Adeno associated viruses, AAV9)

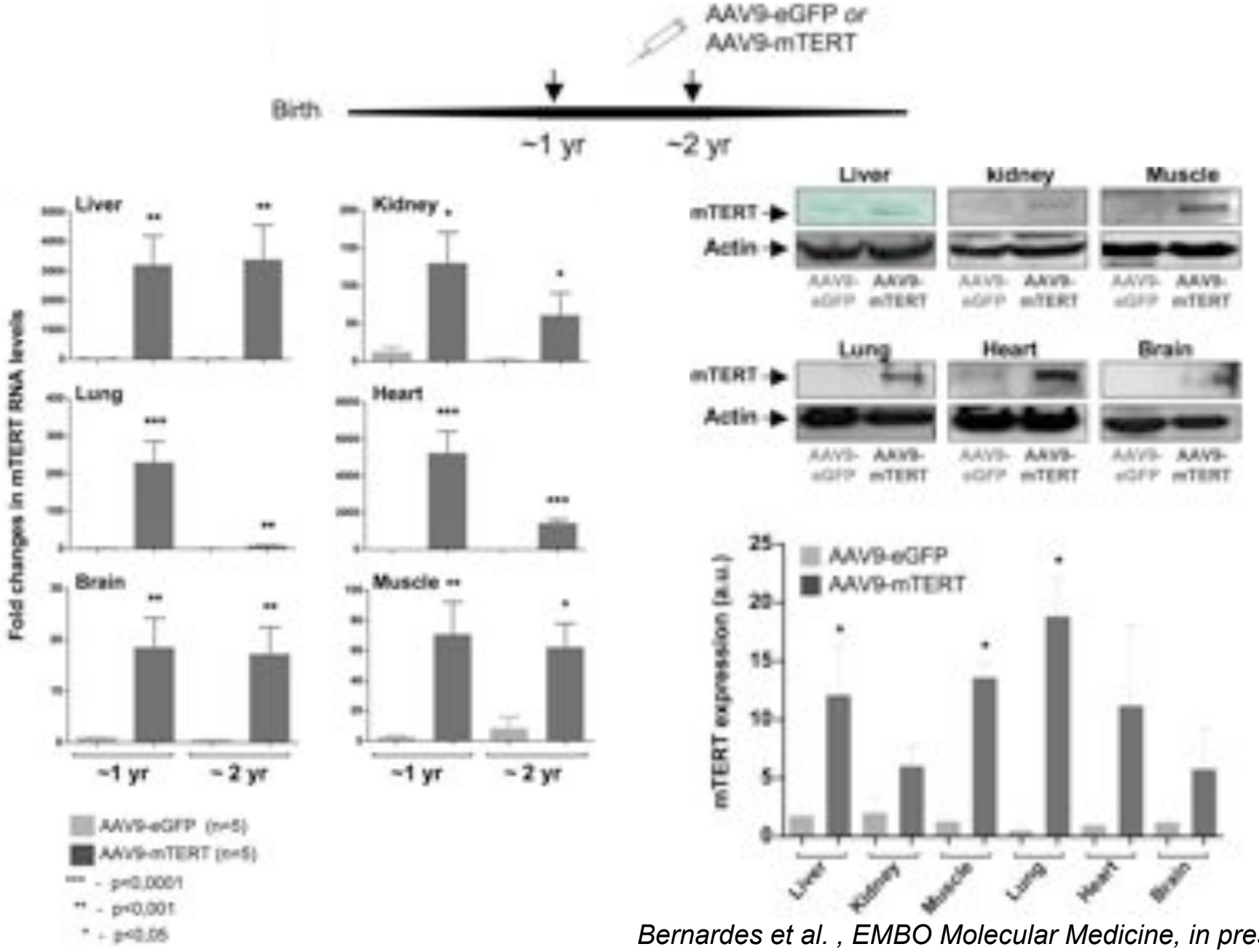
Current clinical trials with Adeno Associated Viruses

Table 1 | **Summary of clinical trials using AAV gene transfer**

Disease	Transgene product	Serotype	Route of administration	Clinical trial	ClinicalTrials.gov identifier	Refs
AAV clinical trials for inherited diseases						
α1 antitrypsin deficiency	α1 antitrypsin	AAV2	Intramuscular	Phase I/II	NCT00377416	101,102
		AAV1			NCT00430768	
Batten's disease	CLN2	AAV2	Direct intracranial administration	Phase I	NCT00151216	90
		AAVrh10			NCT01161576	
Canavan's disease	Aspartoacylase	AAV2	Direct intracranial administration	Phase I	NA	89
Cystic fibrosis	CFTR	AAV2	Direct instillation to maxillary sinus, bronchoscopy to right lower lobe, aerosol to whole lung	Phase I/II	NCT00004533	154–158
Haemophilia B	Factor IX	AAV2	Intramuscular	Phase I/II	NCT00076557	36,39
			Hepatic		NCT00515710	
		AAV8	Intravenous		NCT00979238	
LPL deficiency	LPL	AAV1	Intramuscular	Phase I/II	NCT01109498, NCT00891306	12,103,116
Pompe's disease	GAA	AAV1	Series of intradiaphragmatic injections	Phase I/II	NCT00976352	NA (unpublished)
Muscular dystrophy: Duchenne	Microdystrophin	AAV1–AAV2 hybrid	Intramuscular	Phase I	NCT00428935	97
Muscular dystrophy: limb girdle	α-sarcoglycan	AAV1	Two to six separate injections into the selected muscle	Phase I	NCT00494195	95,96
AAV clinical trials for acquired diseases						
Severe heart failure	SERCA2a	AAV1	Antegrade epicardial coronary artery infusion	Phase I/II	NCT00454818	159
		AAV6			NCT00534703	
Parkinson's disease	AADC	AAV2	Intracranial	Phase I/II	NCT00229736	64,65
	GAD				NCT00643890, NCT00195143, NCT01301573	66,69
	Neutrophin				NCT00252850, NCT00985517, NCT00400634	67,68
Age-related macular degeneration	sFLT01	AAV2	Intravitreal injection	Phase I	NCT01024998	NA (unpublished)
Rheumatoid arthritis	TNFR-Fc	AAV2	Intra-articular	Phase I	NCT00617032, NCT00126724	160–162

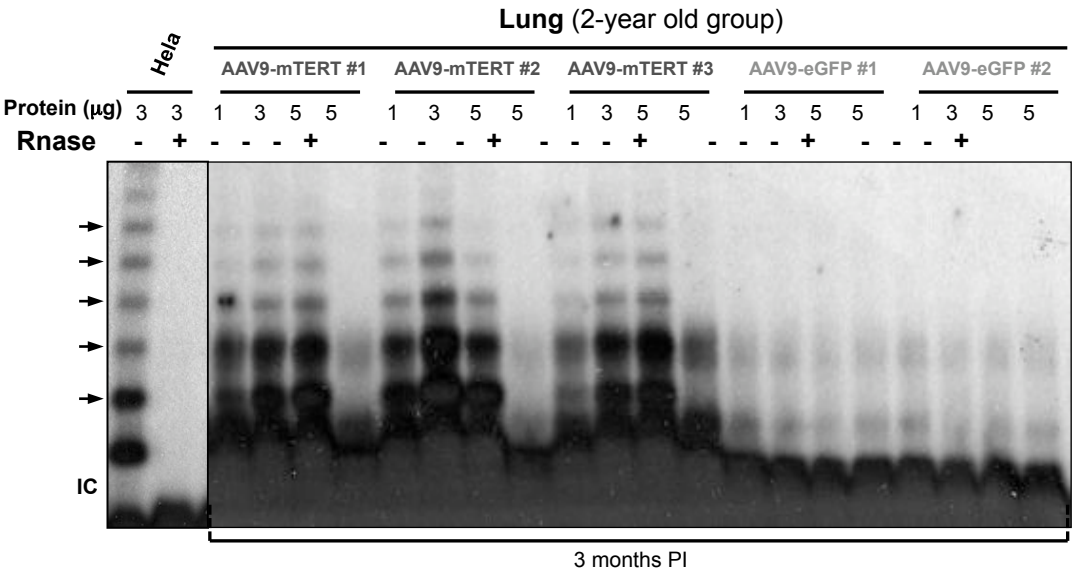
Mingozzi and High, Nature Reviews Genetics, 2011

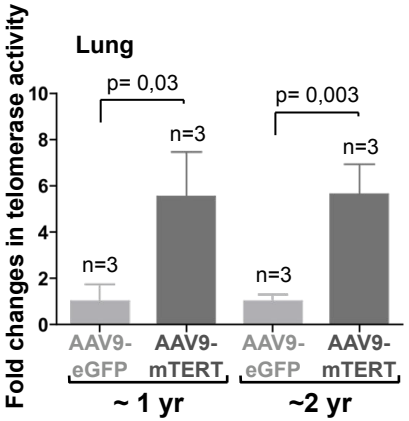
A Gene Therapy of Aging: AAV9-TERT treatment



Bernardes et al. , EMBO Molecular Medicine, in press

AAV9-TERT treatment increases telomerase activity in tissues



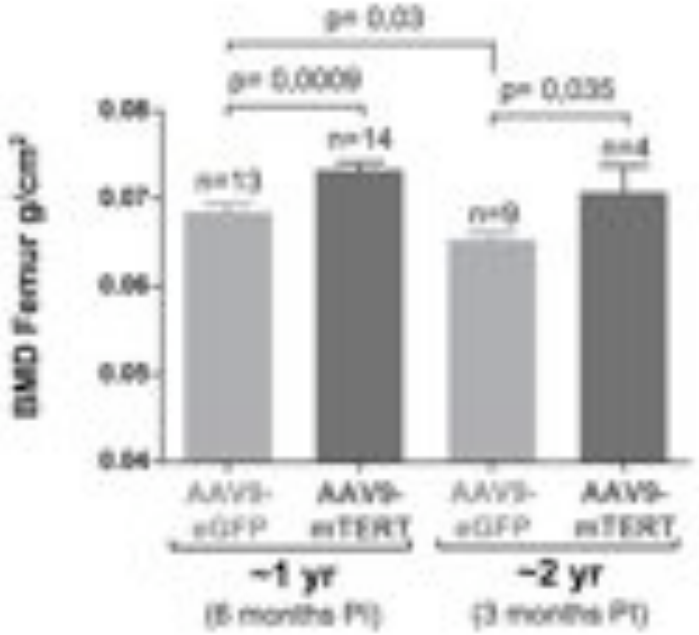


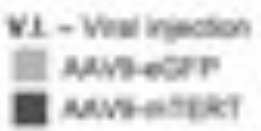
Some cases of pulmonary fibrosis caused by telomerase mutations

Bernardes et al. , EMBO Molecular Medicine, in press

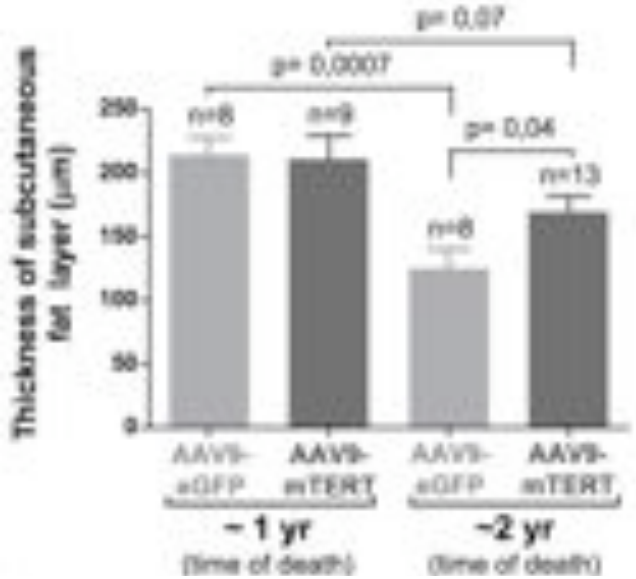
AAV9-TERT treatment improves healthspan in 1 & 2 year old mice

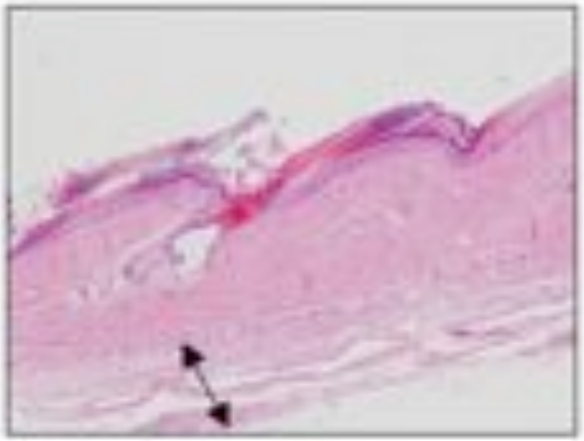
bone density





subcutaneous fat layer

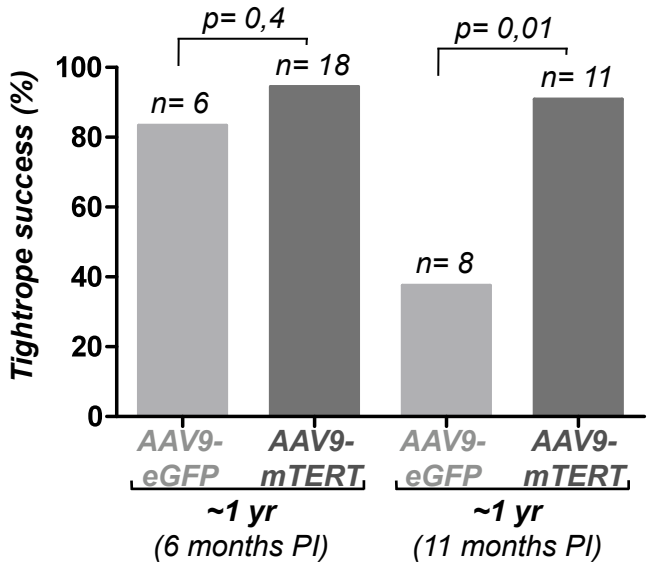




AAV9-mTERT

Bernardes et al. , EMBO Molecular Medicine, in press

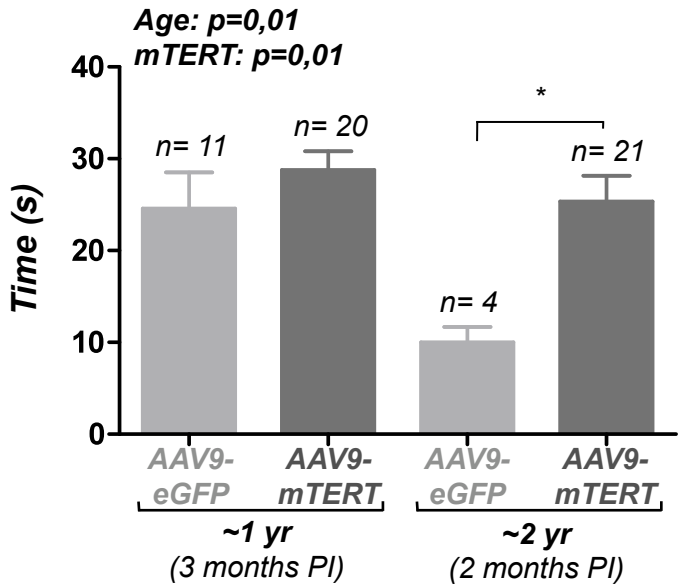
AAV9-mTERT treatment late in life improves neuromuscular coordination



Bernardes et al. , EMBO Molecular Medicine, in press

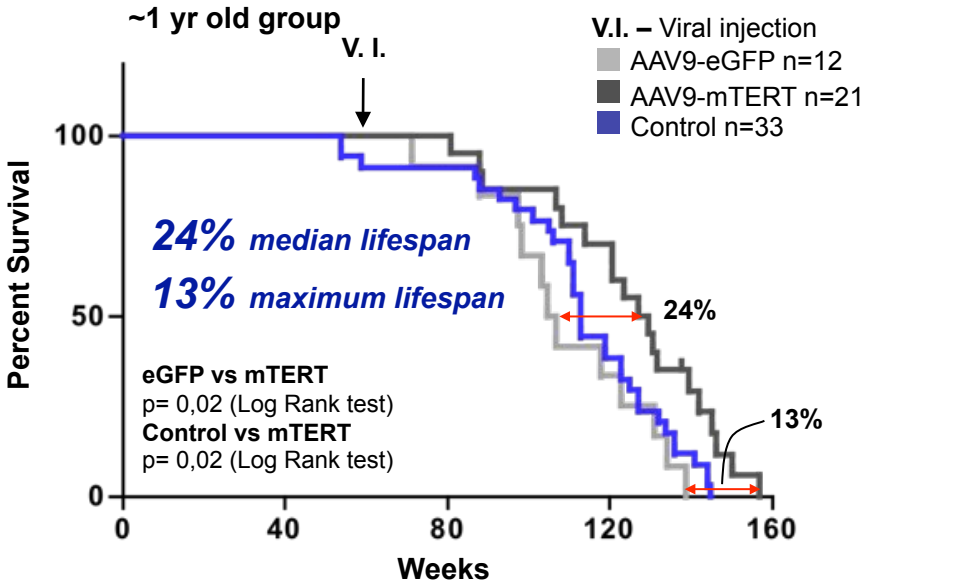
AAV9-mTERT treatment late in life improves Rota-Rod test performance

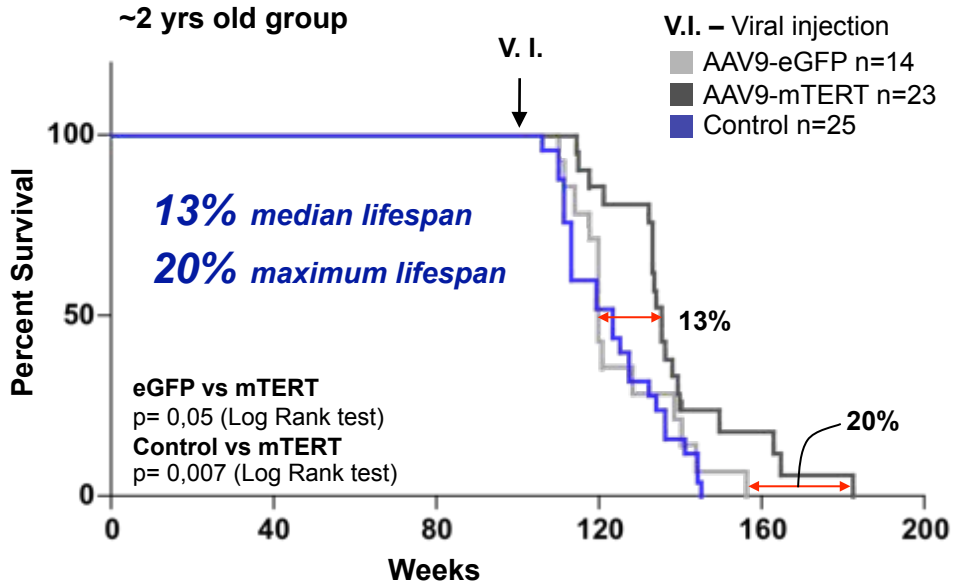
Rota-Rod test



Bernardes et al. , EMBO Molecular Medicine, in press

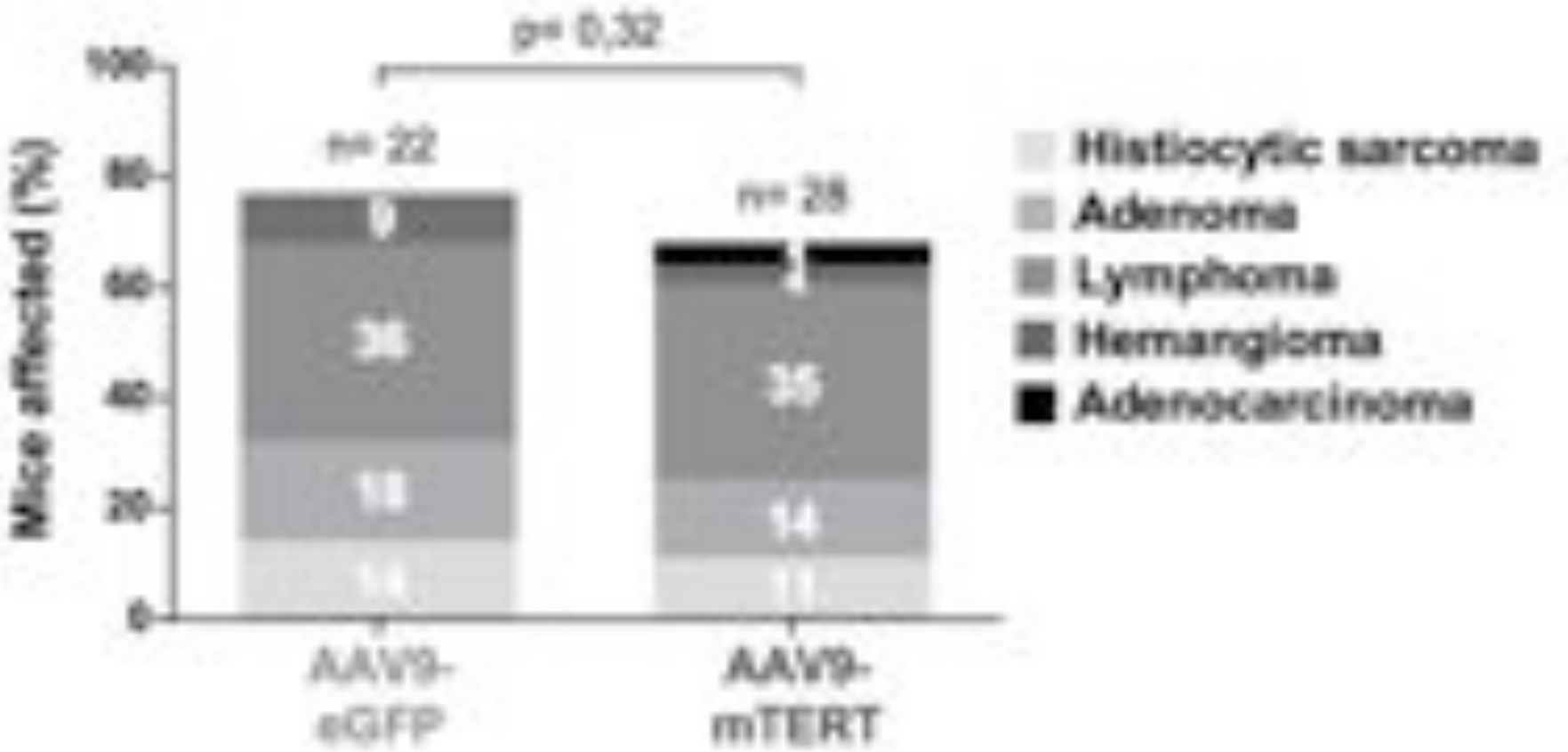
A single AAV9-mTERT treatment late extends mouse lifespan





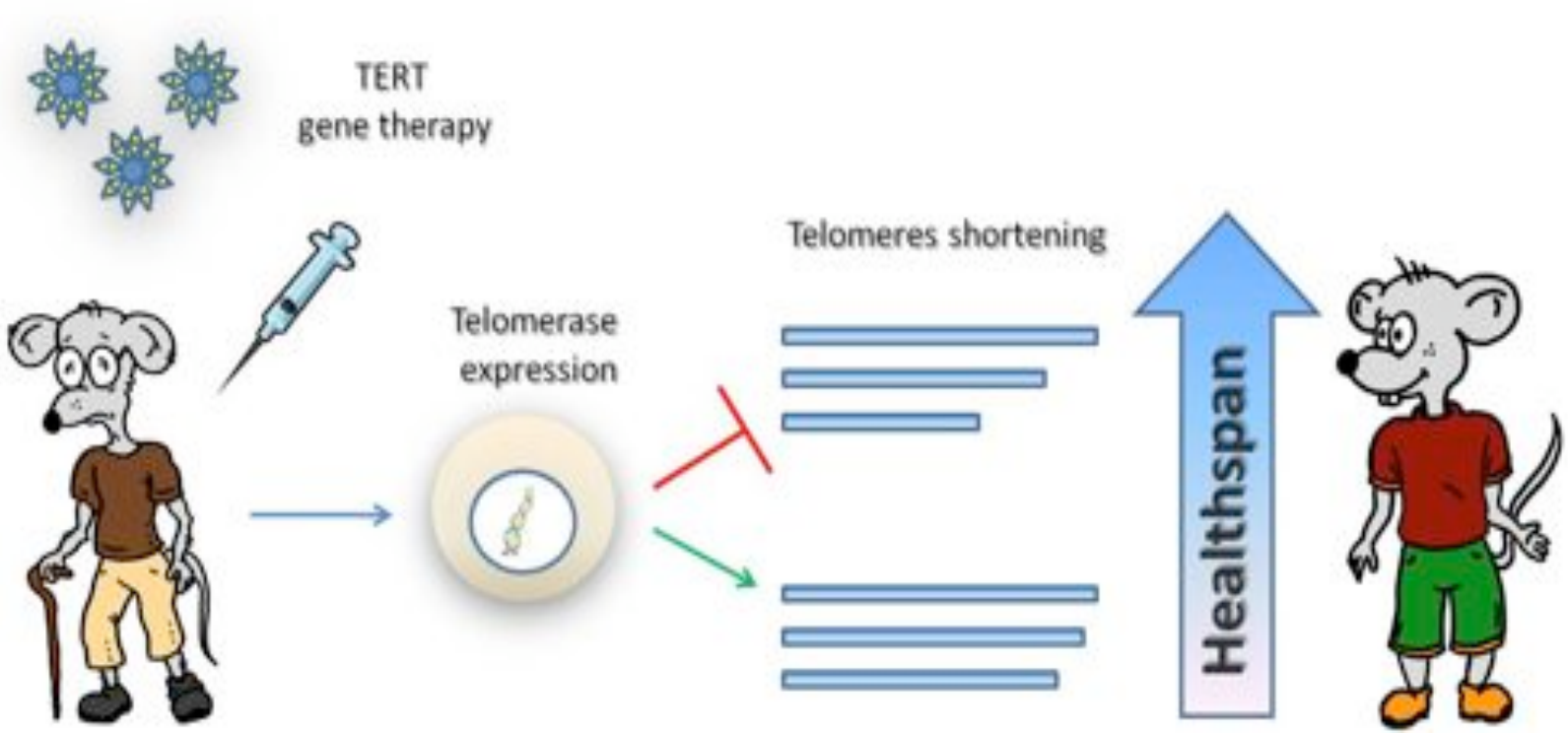
Bernardes et al. , EMBO Molecular Medicine, in press

AAV9-TERT treatment late in life does not increase cancer



Bernardes et al. , EMBO Molecular Medicine, in press

Telomerase activation-based therapy to increase healthspan & longevity



Commentary in:
Boccardi & Herbig, EMBO Molecular Medicine, in press

Telomeres & Telomerase Group, CNIO, Madrid, Spain