Resilience and Frailty in Old Age: What Drives it?

Molecular/Genetic Level
Organ System Level

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Slow Walking
Unreliable
Unstable
Poor strength
Annoying
Lonely
Slow movement
Poor sleep
Needs Help
Wrinkled
Stooped
Poor Vision
Rigid
The Frailty CORE
Lost appetite
Belly fat
Breaks easily
Poor earing
Tired
Sagging skin
Multi-morbidity
Wide waist
Forgetful
Sad
Sick
Sedentary
Greying

Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 Managing Well – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.

4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have **more evident slowing**, and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail**.

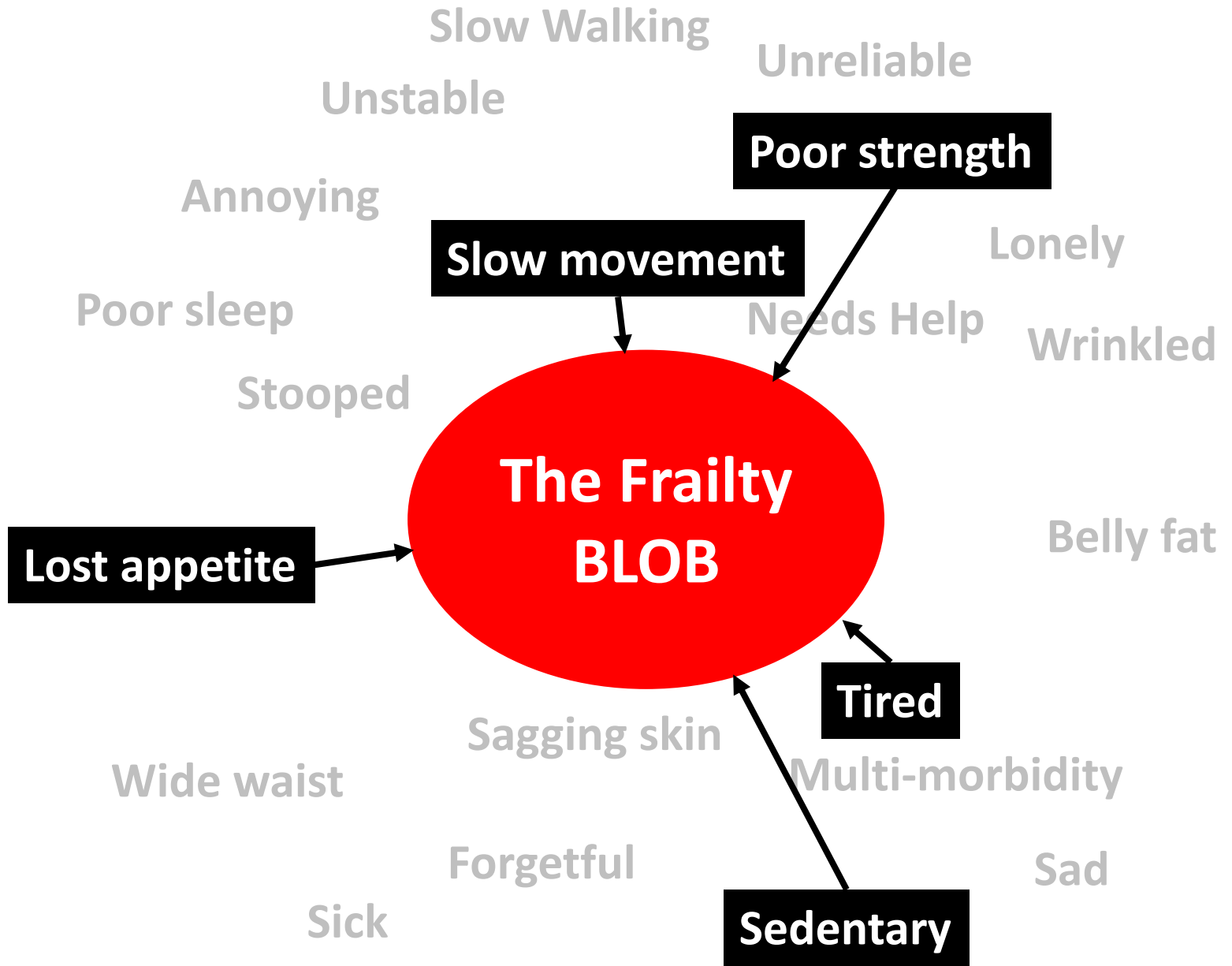## Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.
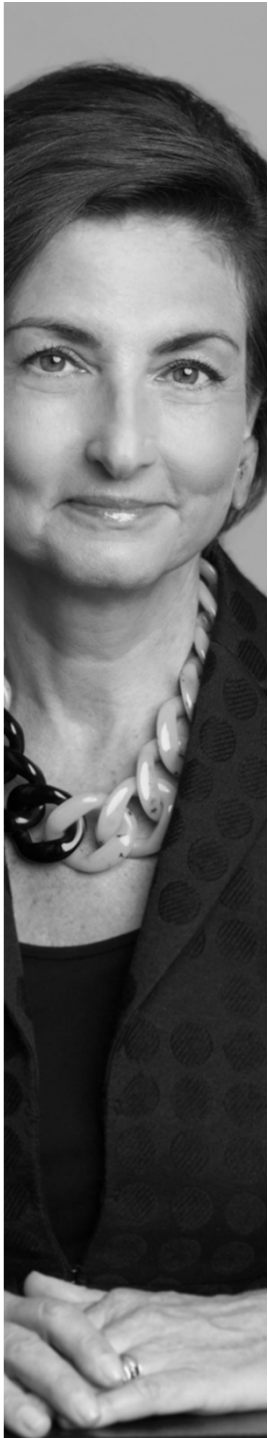
In **severe dementia**, they cannot do personal care without help.

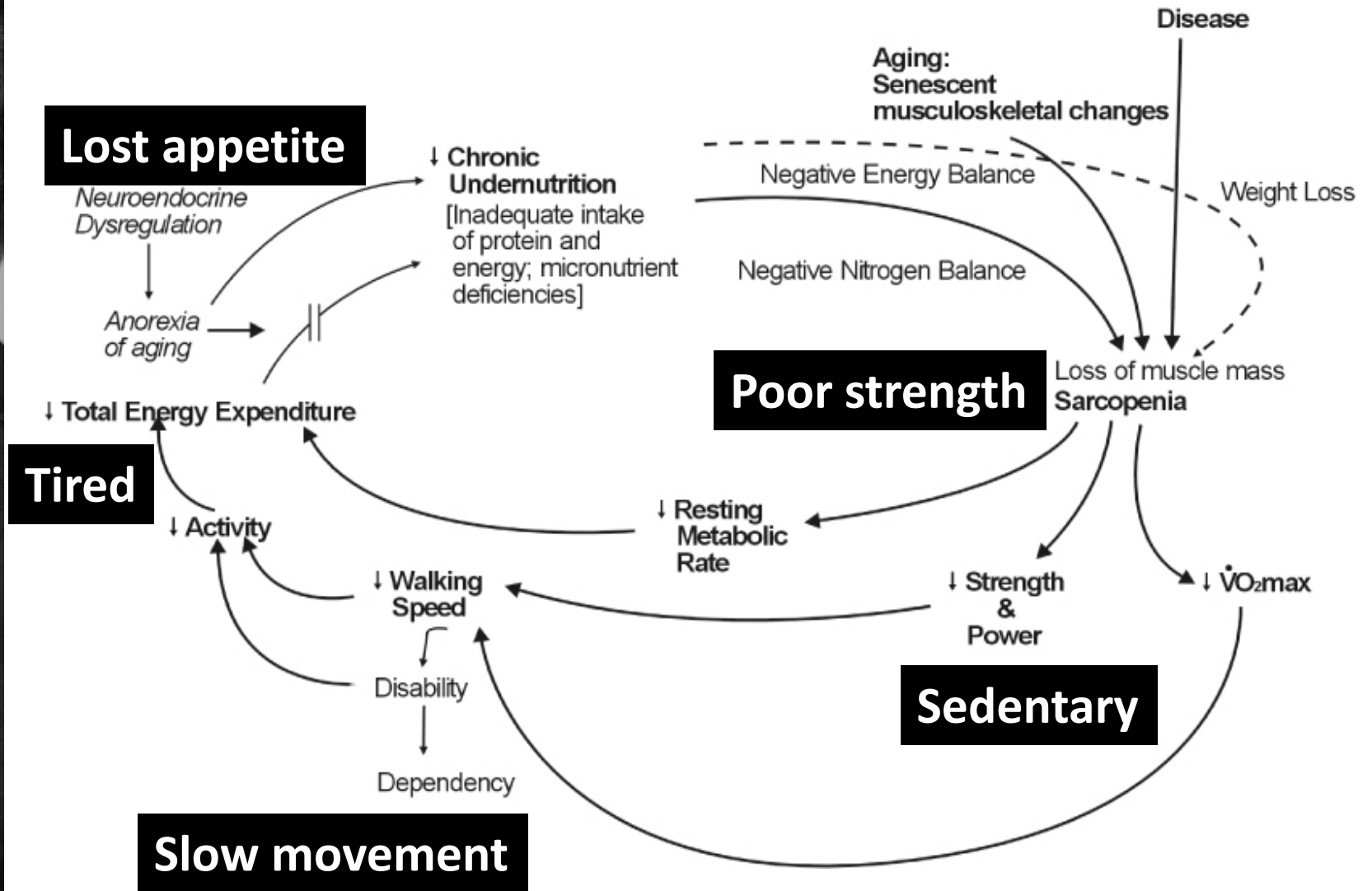* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.
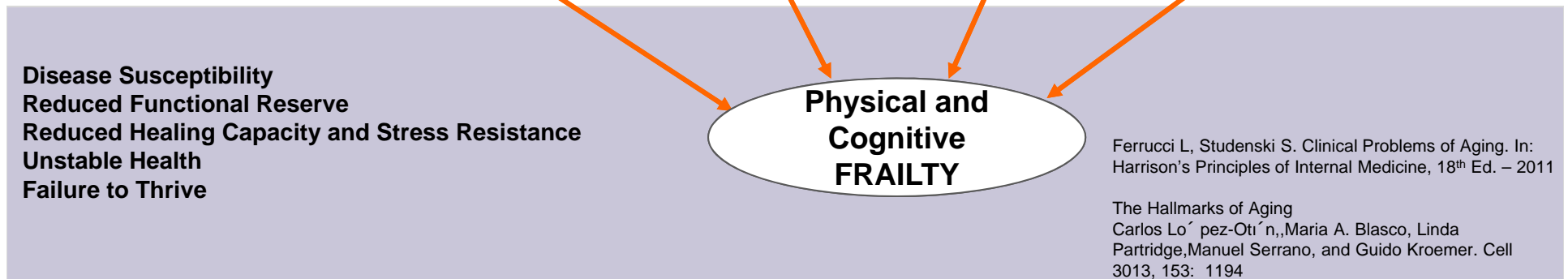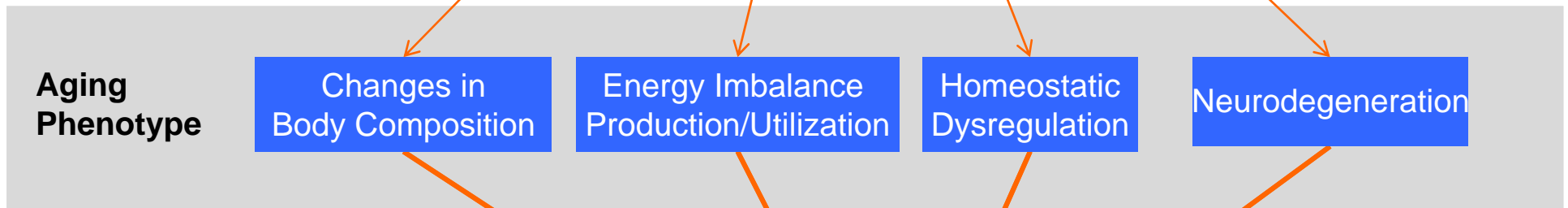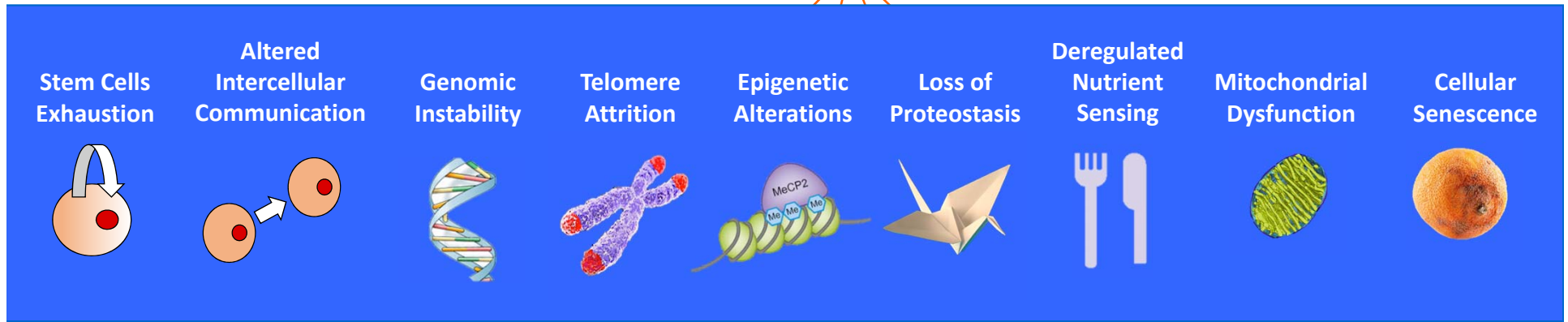
DALHOUSIE UNIVERSITY
Inspiring Minds

Slow Walking

Unreliable

Unstable

Poor strength

Annoying

Lonely

Slow movement

Poor sleep

Needs Help

Wrinkled

Stooped

The Frailty BLOB

Lost appetite

Belly fat

Tired

Sagging skin

Wide waist

Multi-morbidity

Forgetful

Sad

Sick

Sedentary

The Cycle of Frailty (one of the many versions)

Lost appetite

Tired

Poor strength

Sedentary

Slow movement

Neuroendocrine Dysregulation

↓ Chronic Undernutrition [Inadequate intake of protein and energy; micronutrient deficiencies]

Anorexia of aging

↓ Total Energy Expenditure

↓ Activity

Disability

Dependency

↓ Walking Speed

↓ Resting Metabolic Rate

Aging: Senescent musculoskeletal changes

Disease

Negative Energy Balance

Negative Nitrogen Balance

Weight Loss

Loss of muscle mass Sarcopenia

↓ Strength & Power

↓ $\dot{V}O_2max$

Fried LP et al.
Frailty in older adults: evidence for a phenotype.
J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.

What are the mechanisms by which aging and disease affect aging phenotypes and longevity?

AGING and DISEASES

Stem Cells Exhaustion	Altered Intercellular Communication	Genomic Instability	Telomere Attrition	Epigenetic Alterations	Loss of Proteostasis	Deregulated Nutrient Sensing	Mitochondrial Dysfunction	Cellular Senescence

Aging Phenotype

Changes in Body Composition

Energy Imbalance Production/Utilization

Homeostatic Dysregulation

Neurodegeneration

Disease Susceptibility
Reduced Functional Reserve
Reduced Healing Capacity and Stress Resistance
Unstable Health
Failure to Thrive

Physical and Cognitive FRAILTY

Ferrucci L, Studenski S. Clinical Problems of Aging. In: Harrison's Principles of Internal Medicine, 18th Ed. – 2011

The Hallmarks of Aging
Carlos Lo´ pez-Otı´n,,Maria A. Blasco, Linda Partridge,Manuel Serrano, and Guido Kroemer. Cell 3013, 153: 1194

Is the Biology of Aging at the Core Of Frailty?
Can This Hypothesis be Tested?

FRAILTY

- Loss of Proteostasis
- Deregulated Nutrient Sensing
- Epigenetic Alterations
- Mitochondrial Dysfunction
- Telomere Attrition
- Cellular Senescence
- Genomic Instability
- Stem Cells Exhaustion
- Altered Intercellular Communication
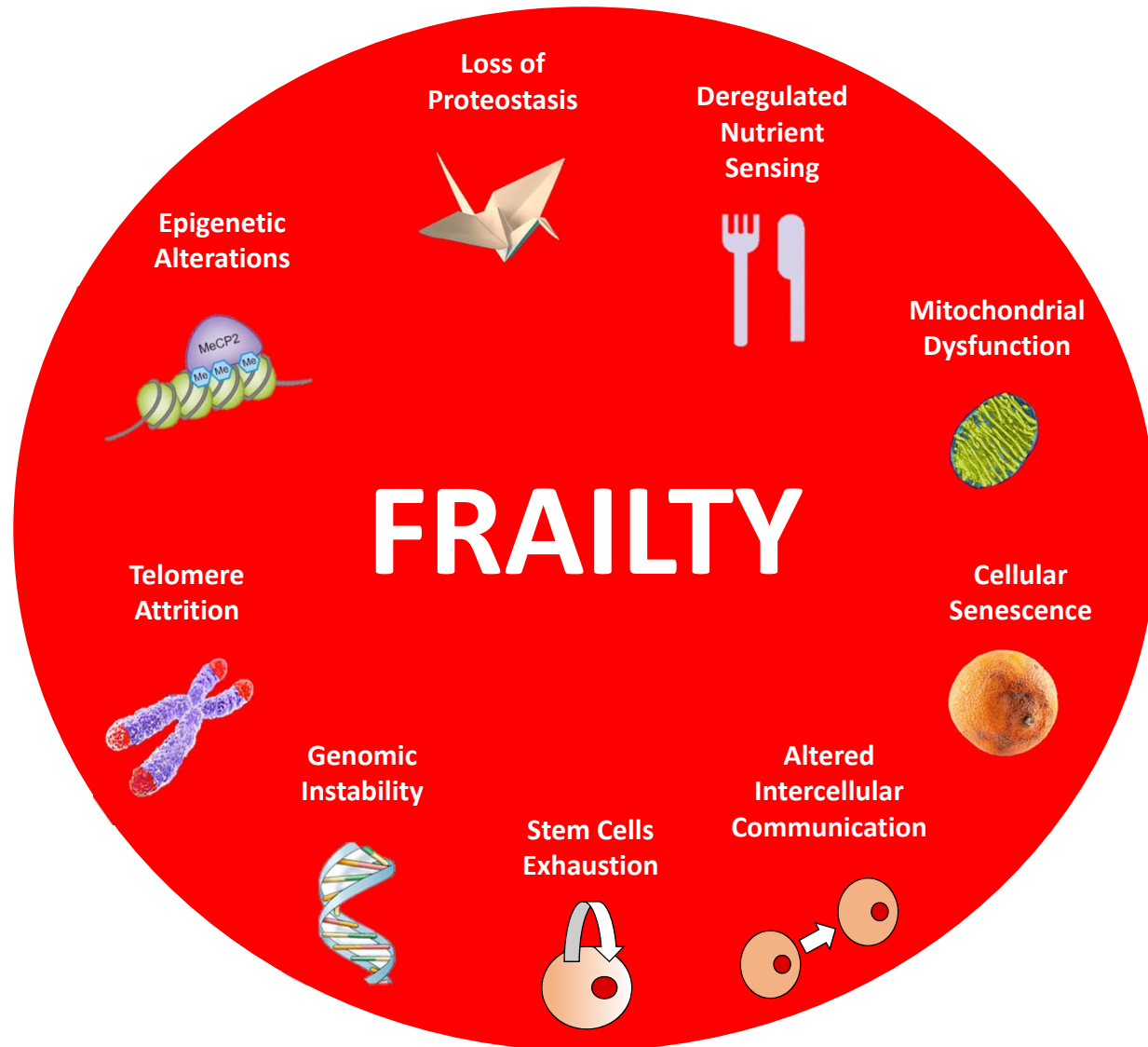
Is the Biology of Aging at the Core Of Frailty?
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Altered Intercellular Communication
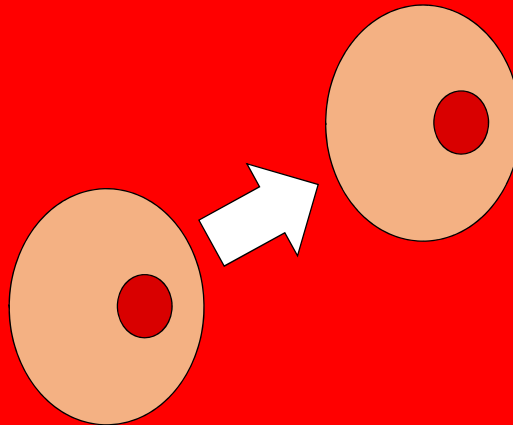
Genes up-regulated with aging
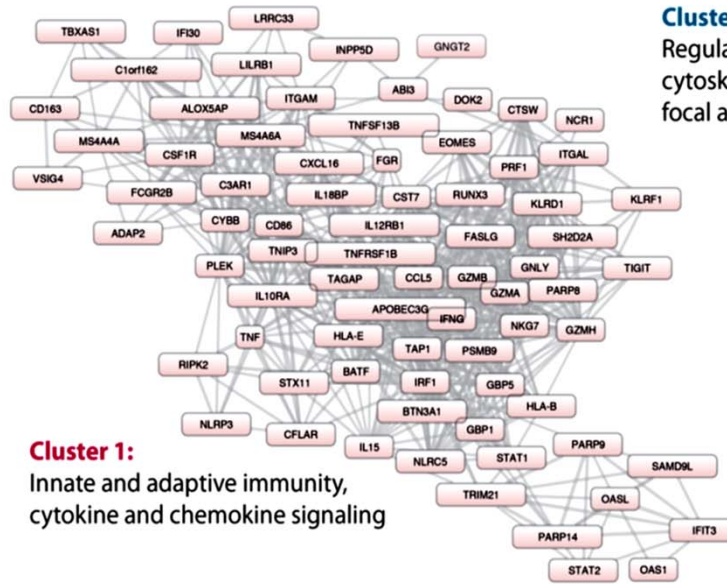
Cluster 1:
Innate and adaptive immunity, cytokine and chemokine signaling

Cluster 2:
Regulation of actin cytoskeleton, focal adhesion
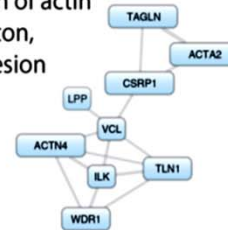
Cluster 3:
Fatty acid metabolism, peroxisome activity

Cluster 4:
Lysosome metabolism and glycosaminoglycan degradation
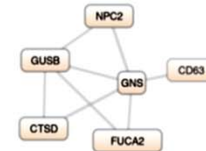
Aging is associated with up-regulation of immune function genes.

Transcriptome-wide meta-analysis of genes whose expression differs by age in 7,257 individuals of European ancestry. Findings replicated in another 8,009 individuals. 1,497 genes were differentially expressed with age. The major cluster of positively age-correlated genes (GeneNetwork pathway, 77 genes) was related to **innate and adaptive immunity, suggesting that dysregulation of the immune leading to a pro-inflammatory state is an hallmark of aging.**

Interleukin-6 Serum Levels Predict Incident Disability
A Case Cohort Study Nested in the EPESE

Walking

Probability of Mobility Disability

2.5 pg/ml

95% CI

Adjusted probability

95% CI

Ln (IL-6)
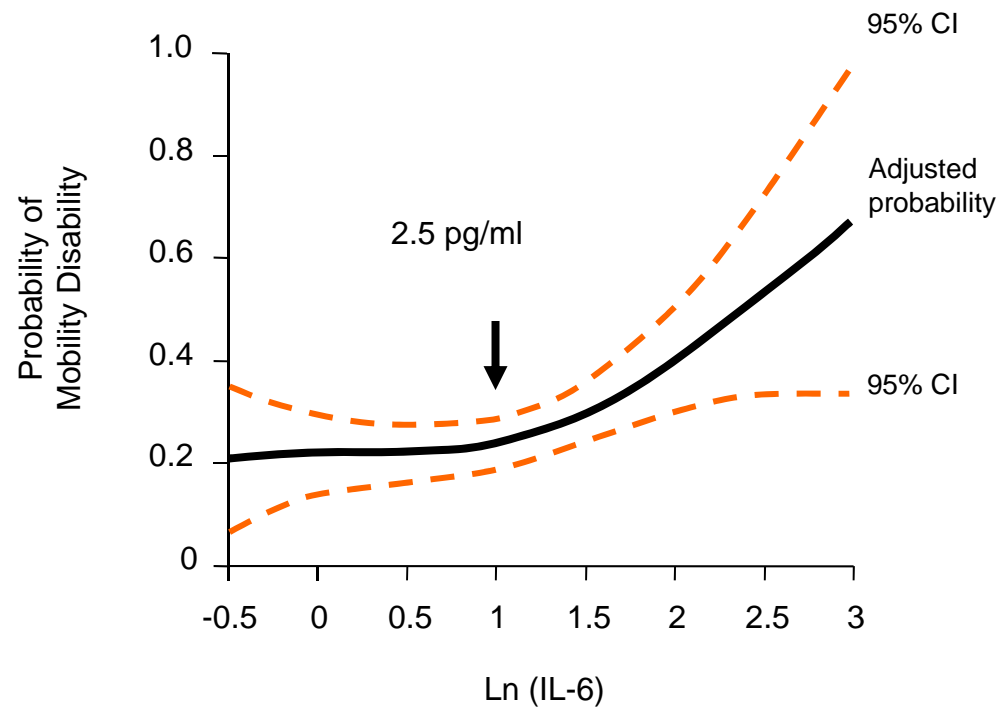
Ferrucci et al. *JAGS 1999;47: 639-44*

IL-6 is a Cross-Sectional and Longitudinal Predictor of Comorbidity
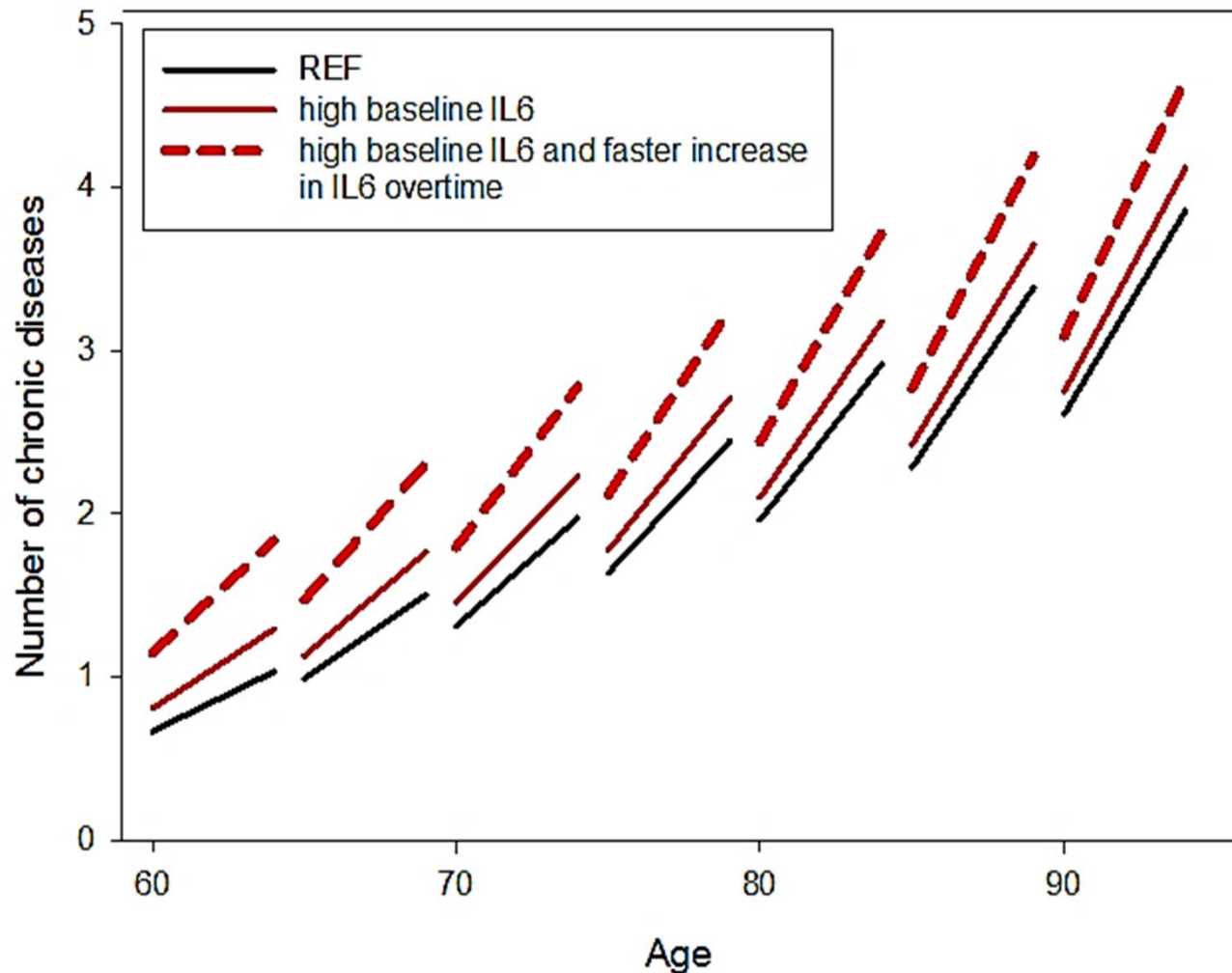
4. IL-6 as risk factor for multimorbidity.

A mild chronic pro-inflammatory state, characterized by high levels of IL-6, is a typical phenotype associated with older age and has been implicated in the pathogenesis of many age-related chronic diseases. In the InCHIANTI study (n=914, over 6-year follow-up) we demonstrated that IL-6 was a strong cross sectional and longitudinal correlate of multimorbidity, and increase in IL-6 over time independently predicted even higher increase in multimorbidity.

Systemic Effects of Localized Inflammation

Harmful stimuli:
- Damaged cells
- Irritant chemicals
- Pathogens

INFLAMMATION
attempts to remove damaged cells, irritants or pathogens

Effective
Eliminates the cause of inflammation

"Switch off" inflammation

Healing

Systemic Effects

G.I. System
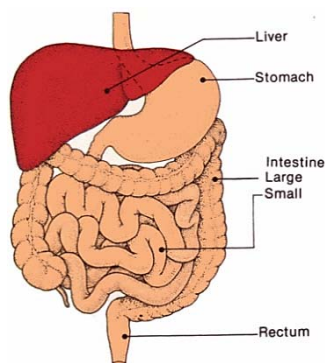
- Reduces food absorption
- Causes insulin resistance
- Stimulates glycogenolysis
- Down-regulates somatostain

Brain

- Activates microglia
- Inhibits Neurogenesis
- Down-regulates BDNF
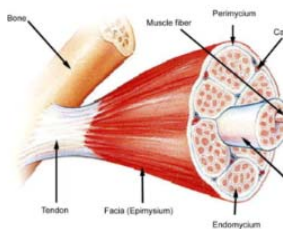
Muscle

- Inhibits muscle growth
- Down-regulates IGF-1 signaling

Bone
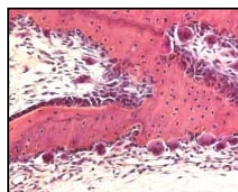
- Stimulates osteoclasts
- Down-regulates Osteocalcin

Bone Marrow
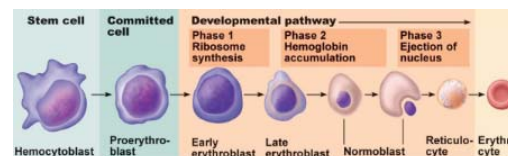
- Inhibits Hematopoiesis
- Down-regulates EPO signaling

Arteries

- Stimulates atherosclerosis
- Inhibit endothelial reactivity

Changes in basal gene expression in CD4$^+$ cells

cytapheresis

↓

PBMC

↓

CD4$^+$ T cells

↓

activation
(anti-CD3 0, 2, 4h)

RNA   protein

nuclear   cytoplasmic

microarray   immunoblot   mass spec.
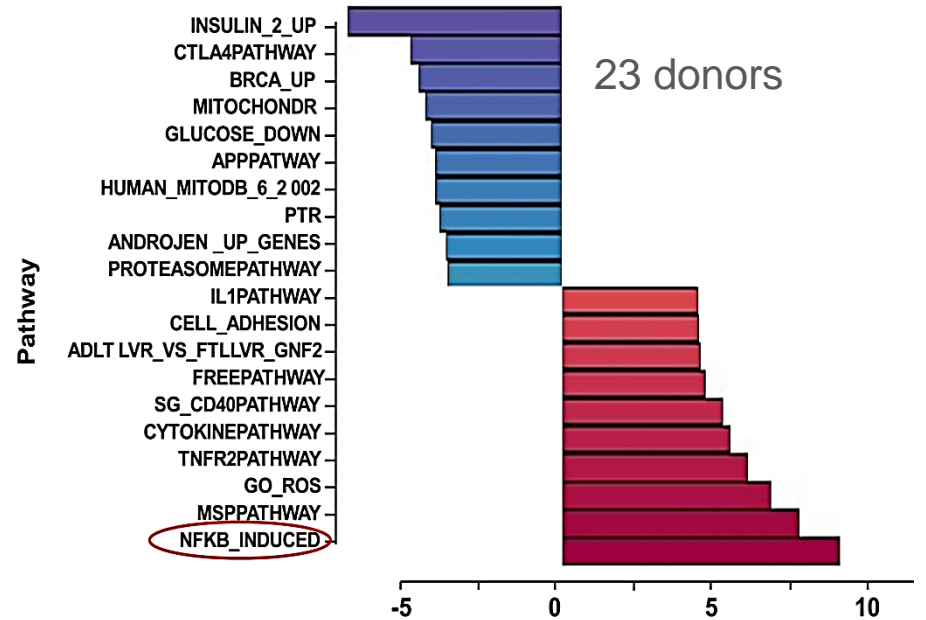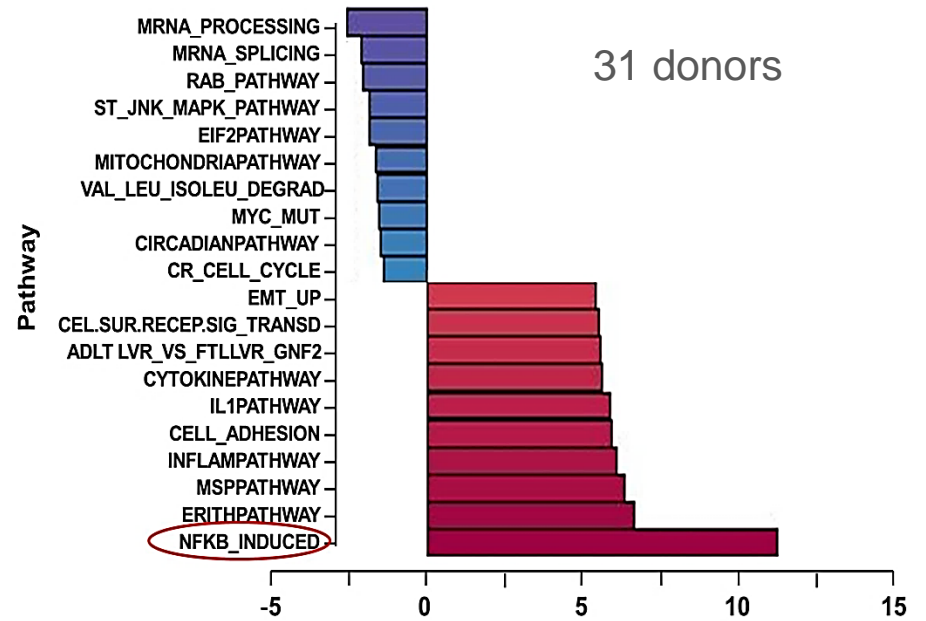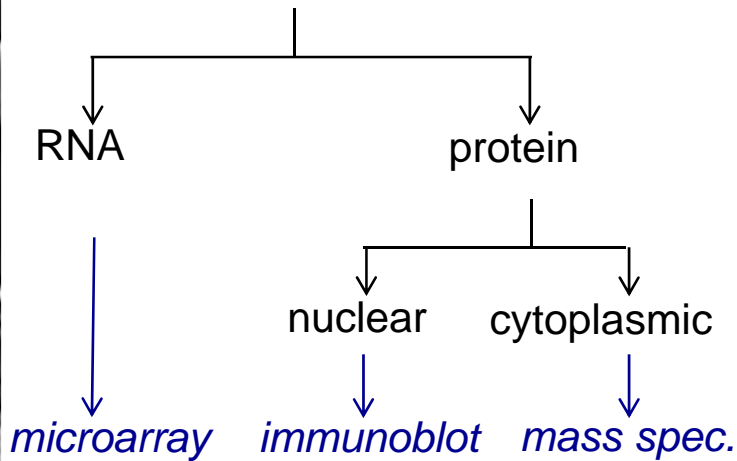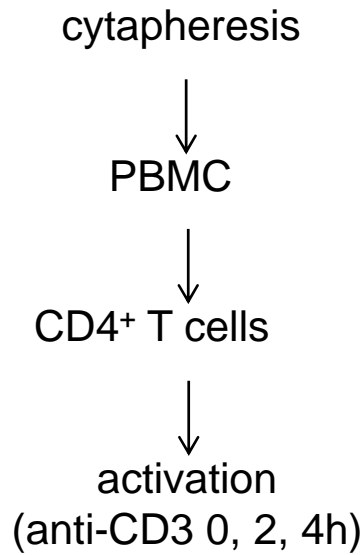
Cell-intrinsic activation of NF-κB target genes

Hypothesis: Effects of *in vivo* inflammatory milieu should be reflected in the gene expression pattern in freshly isolated cells compared to cells cultured *ex vivo*
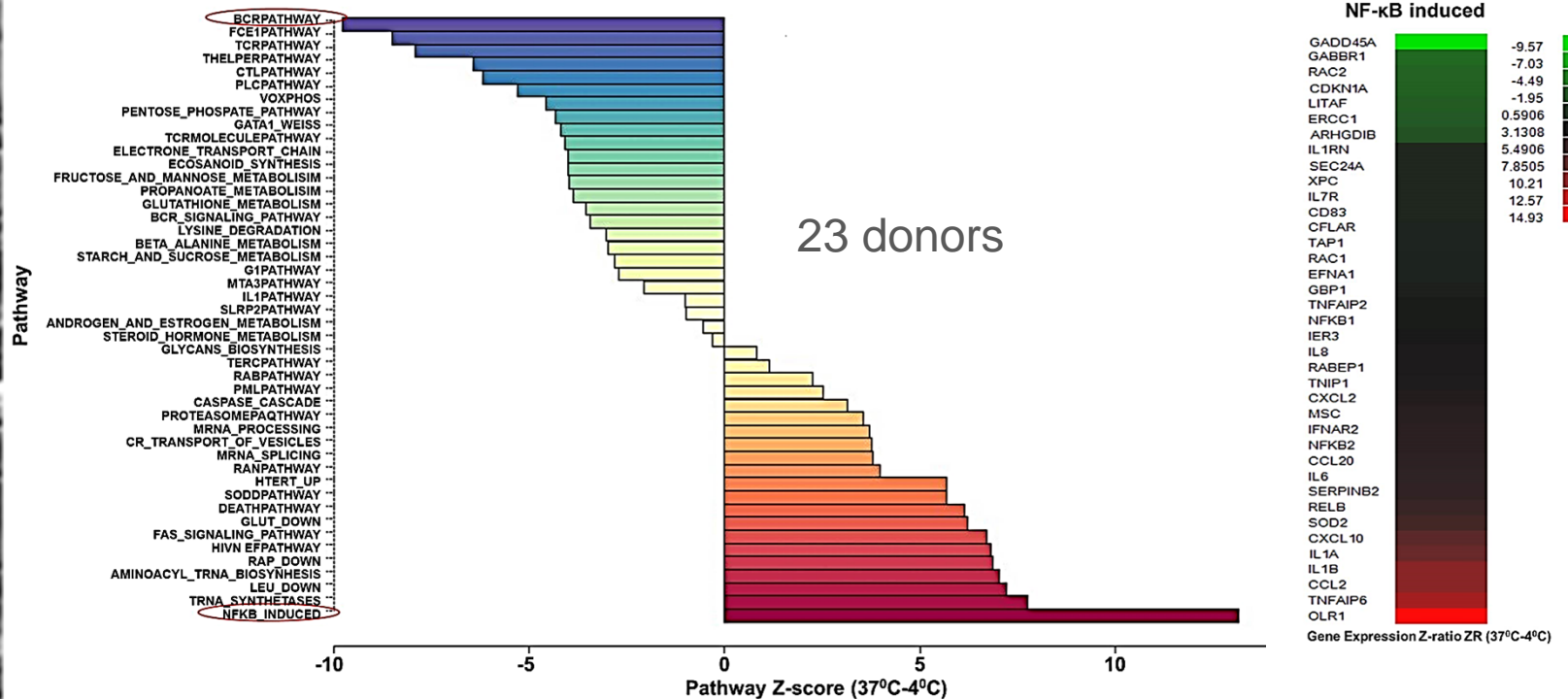
Elevated expression of putative NF-κB target genes is the consequence of metabolic activity

Proteomic analyses of age-associated changes in CD4$^+$ T cells

cytapheresis

↓

PBMC

↓

CD4$^+$ T cells

↓

activation
(anti-CD3 0, 2, 4h)

RNA   protein

nuclear   cytoplasmic

microarray   *immunoblot*   *mass spec.*
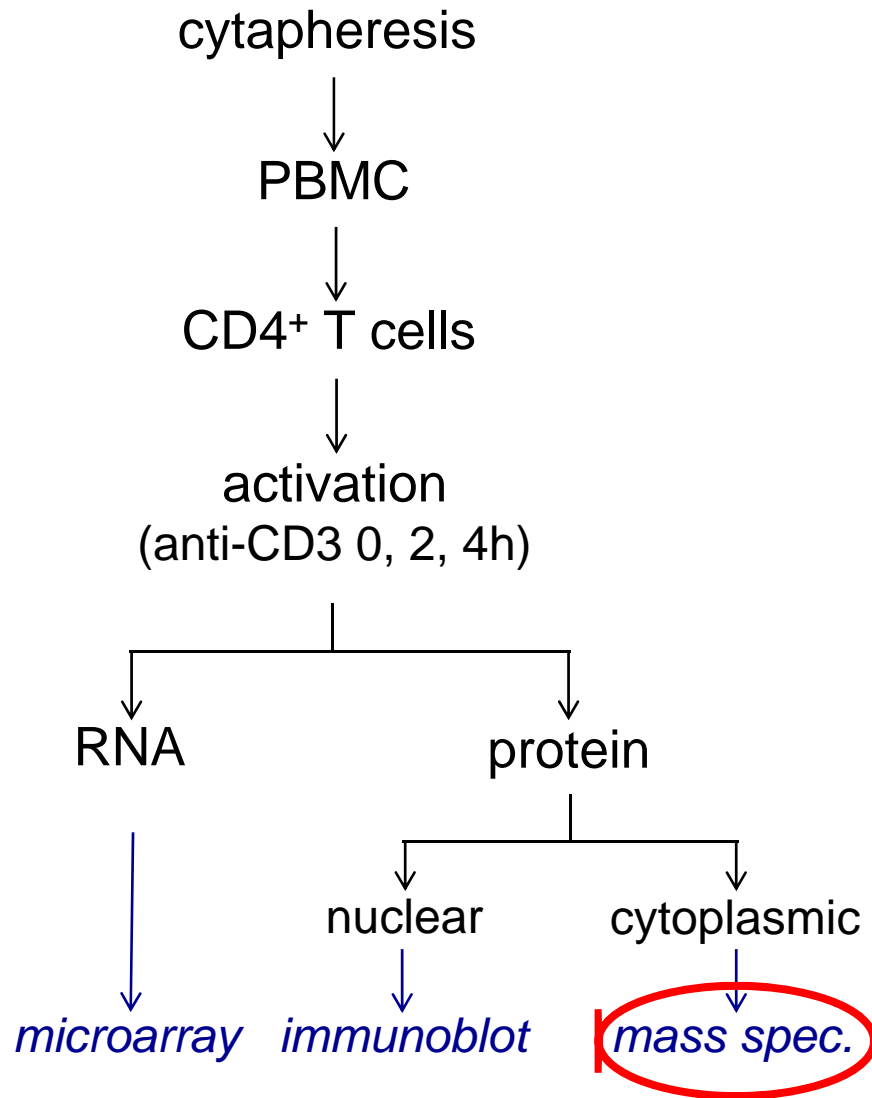
Protein quantitation by iTRAQ

iTRAQ 113 iTRAQ 114 iTRAQ 115 iTRAQ 116 iTRAQ 117 iTRAQ 118 iTRAQ 119 iTRAQ 121

↓

LC/MS/MS
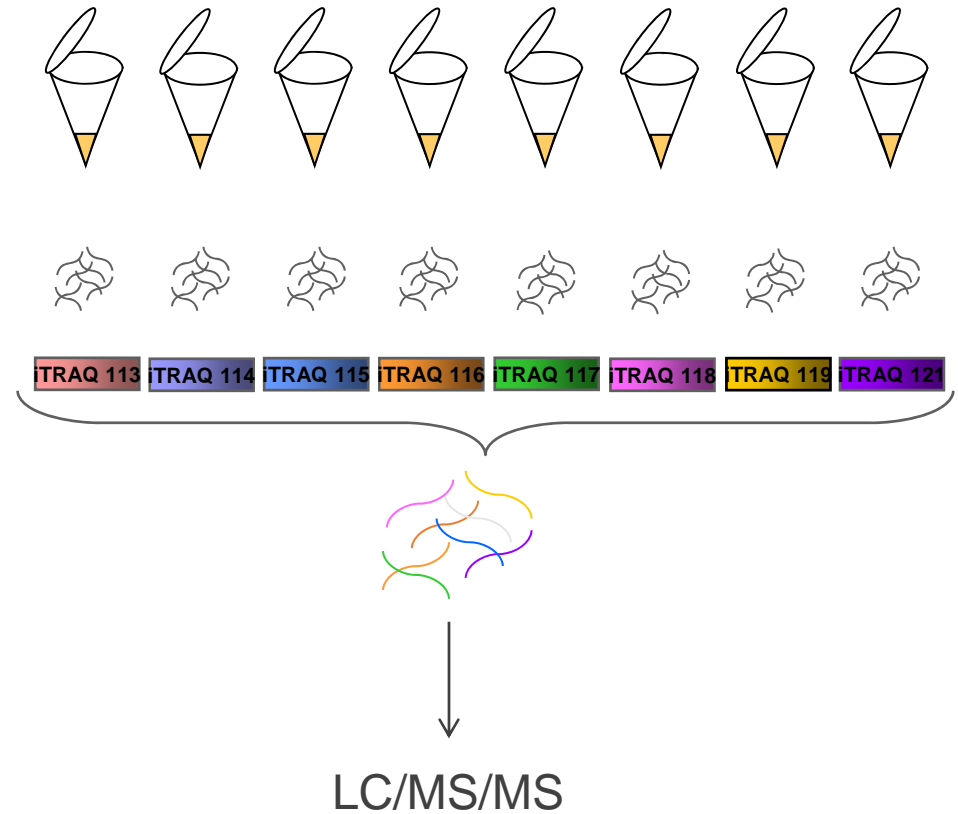
Experimental design

iTRAQ Reagents	iTRAQ 1 Sample #	Age	iTRAQ 2 Sample #	Age	iTRAQ 3 Sample #	Age	iTRAQ 4 Sample #	Age
113	ND340	30	ND617*	21	ND620	34	ND737	21
114	ND617*	21	ND620	34	ND617*	21	BL4906	70
115	BL1039	74	ND620	34	ND554	34	ND617*	21
116	BL531	75	BL4931	74	BL4855	70	ND620	34
117	BL1530	77	BL4943	73	BL4880	71	BL4941	71
118	BL4942	74	BL4926	73	BL4905	72	BL4924	72
119	BL4931	76	BL531	77	BL4939	73	ND394	70
121	BL4911	82	BL1193	68	BL4877	83	BL4929	76

4 young (20-34y)
18 old (68-83y)
ND617 used as control in each assay
ND620 repeated in 3 assays (tech control)
2 'old' repeats in independent assays

$\downarrow$

27 differentially expressed proteins between Y and O (>1.5x, p<0.05)

Pathways identified based on differential protein expression
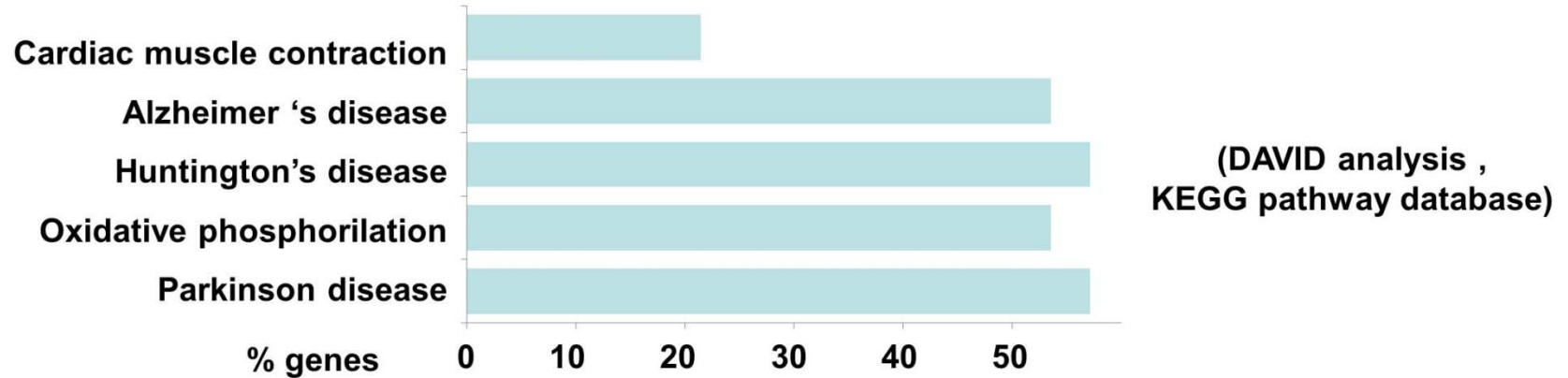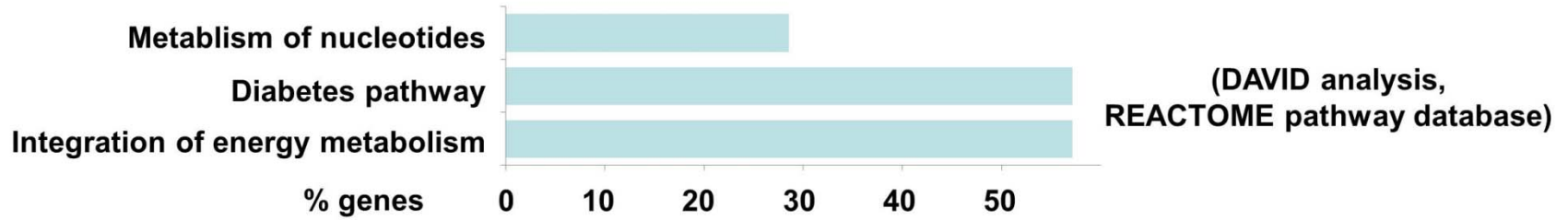
Multiple components of the mitochondrial electron transport chain are up-regulated in CD4$^+$T cells from older individuals
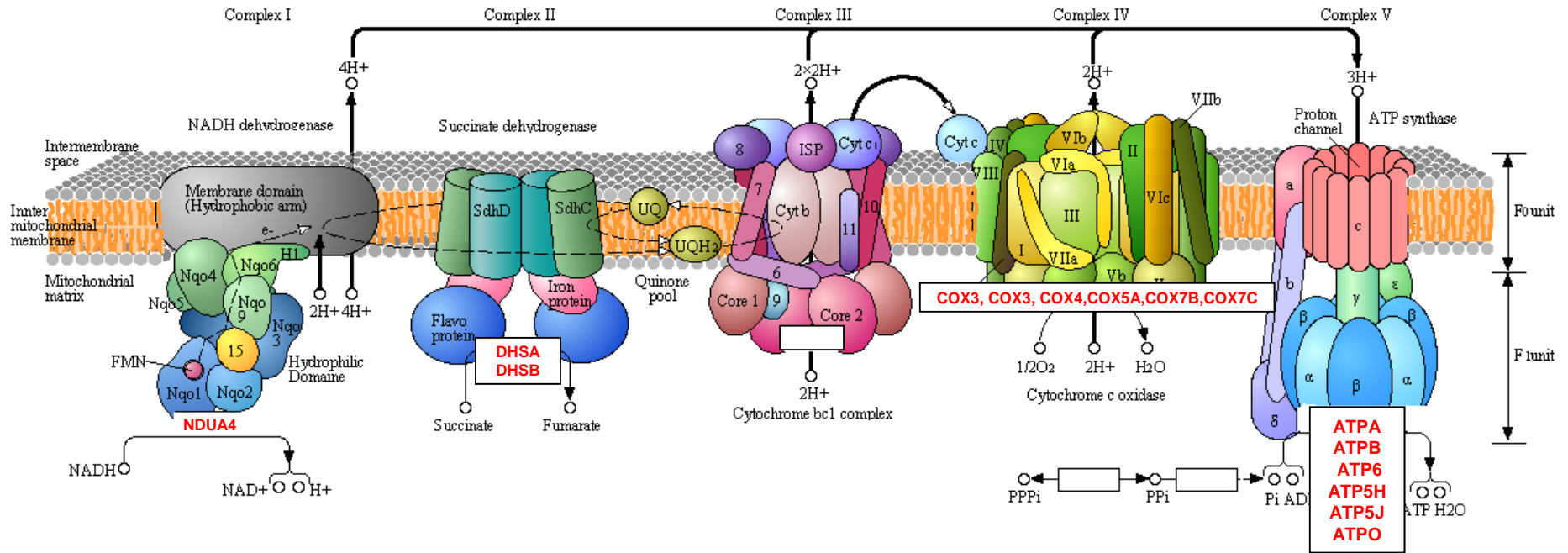
NADH dehdrogenase; NDUA4
Succinate dehdrogenase; SDHA, SDHB
Cytochrome c oxidase; COX3, COX3, COX4,COX5A,COX7B,COX7C
Type ATPase (Eukaryotes); ATPA, ATPB, ATP6, ATP5H, ATP5J, ATPO

Is the Biology of Aging at the Core Of Frailty?
Can This Hypothesis be Tested?

Energetics
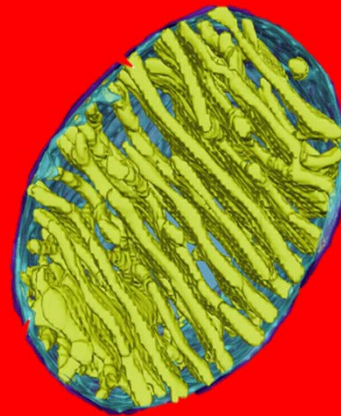
Age-dependent changes in mitochondrial morphology and volume are not predictors of lifespan
Saroj G. Regmi et al.
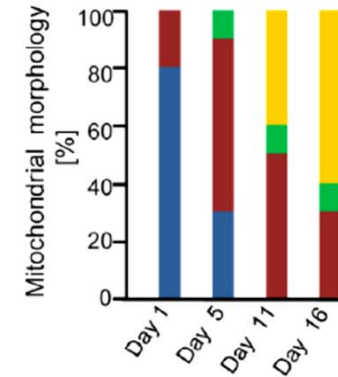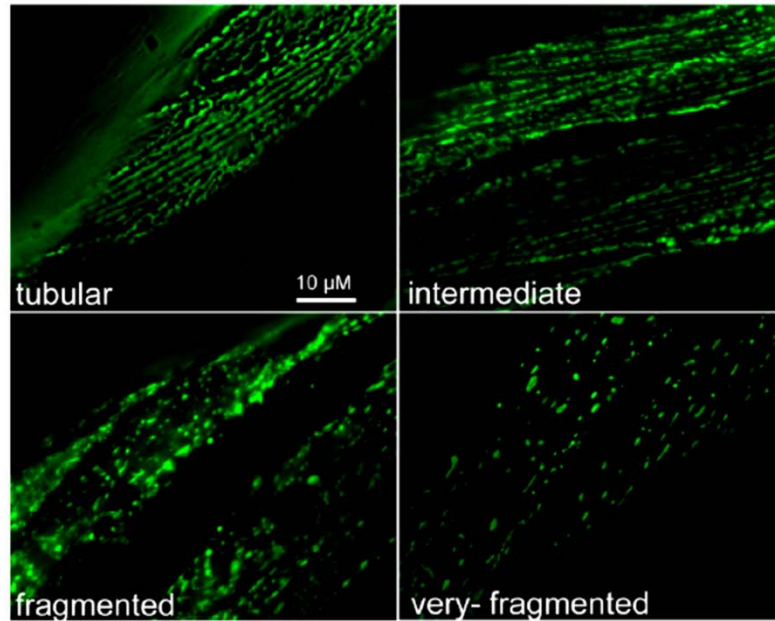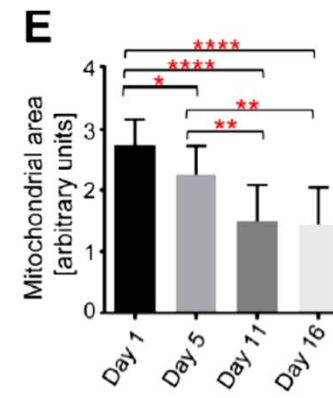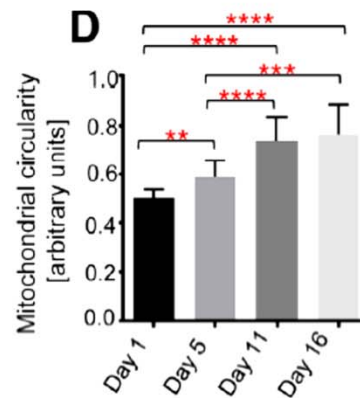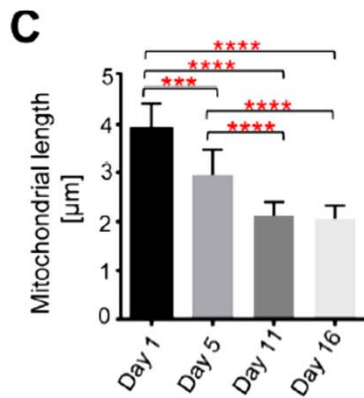
Age-dependent mitochondrial changes in C. elegans body wall muscle cells

Age Changes in Size and Number of Mitochondria of Human Hepatic Cells
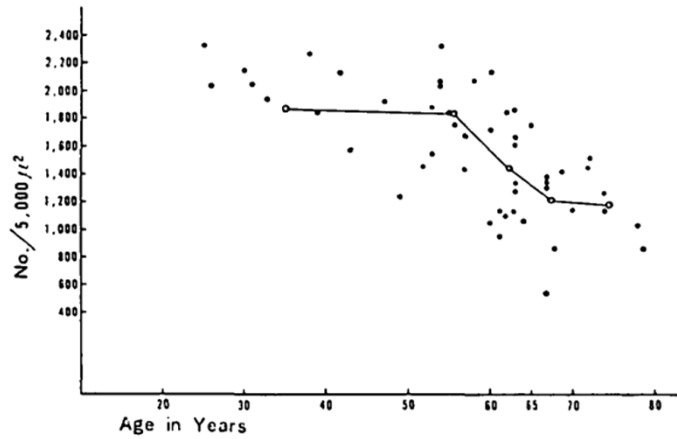
Fig. 1. Changes with age in number of mitochondria in a given area.
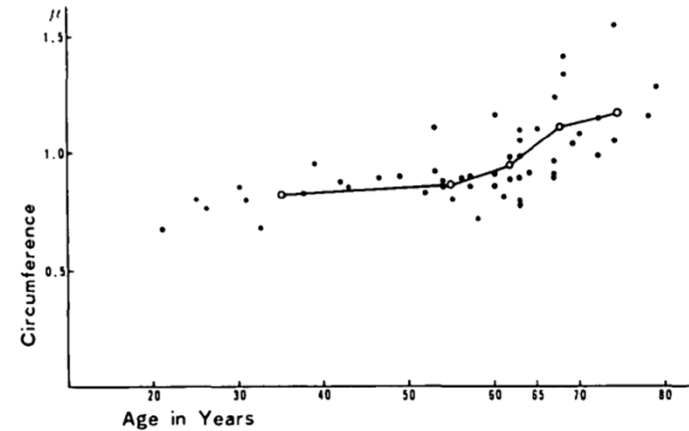
Fig. 3. Changes with age in circumference of mitochondria.
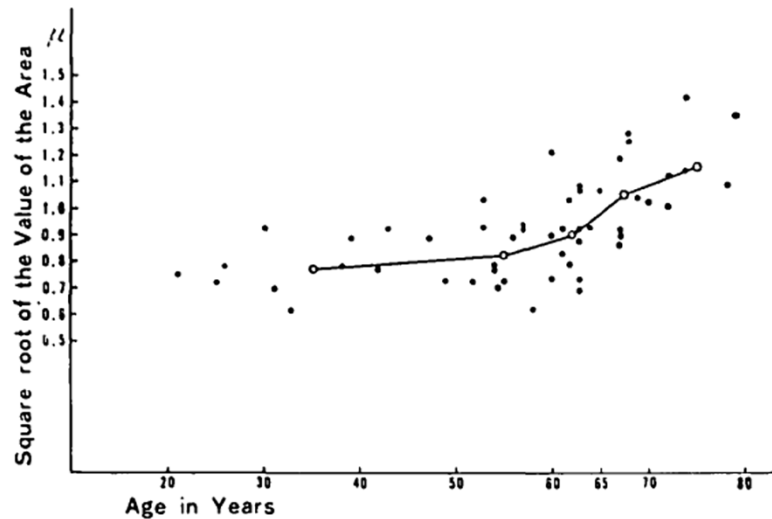
Fig. 2. Changes with age in size of mitochondria.
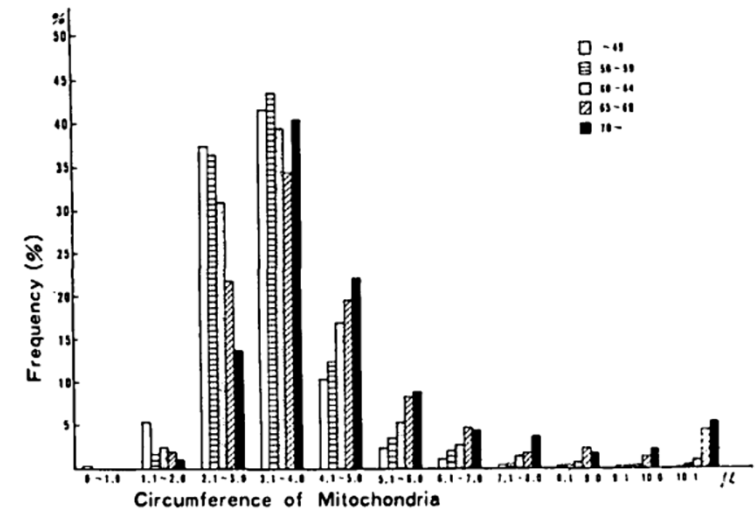
Fig. 4. Distribution pattern of circumference of mitochondria according to age.

P$_{31}$ MRS: Rate of Phosphocreatine Replenishment and Aging
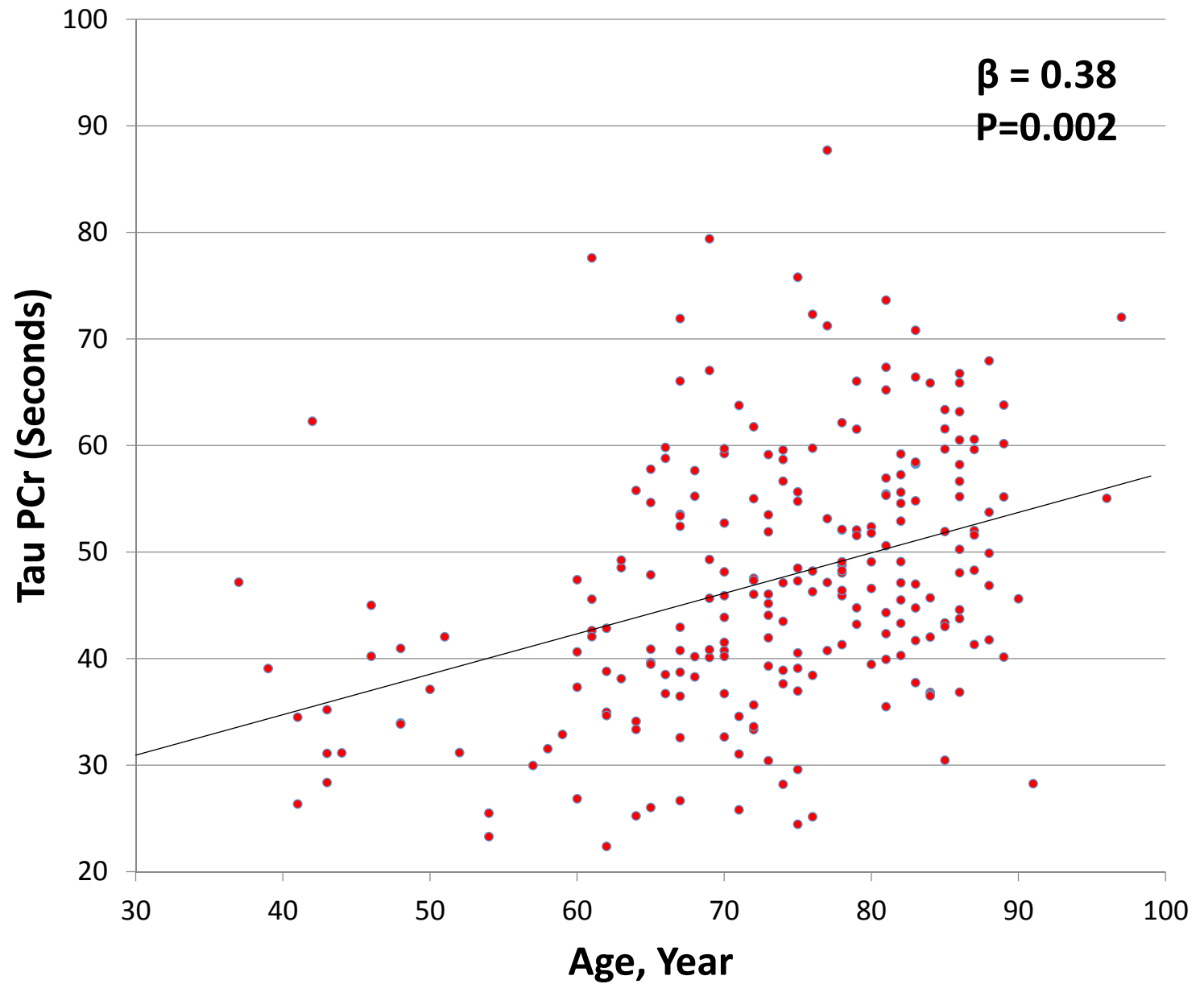
β = 0.38
P=0.002

Skeletal Muscle Mitochondrial Energetics Are Associated With Maximal Aerobic Capacity and Walking Speed in Older Adults. Paul M. Coen et al. *J Gerontol A Biol Sci Med Sci. 2013;68(4):447–455*
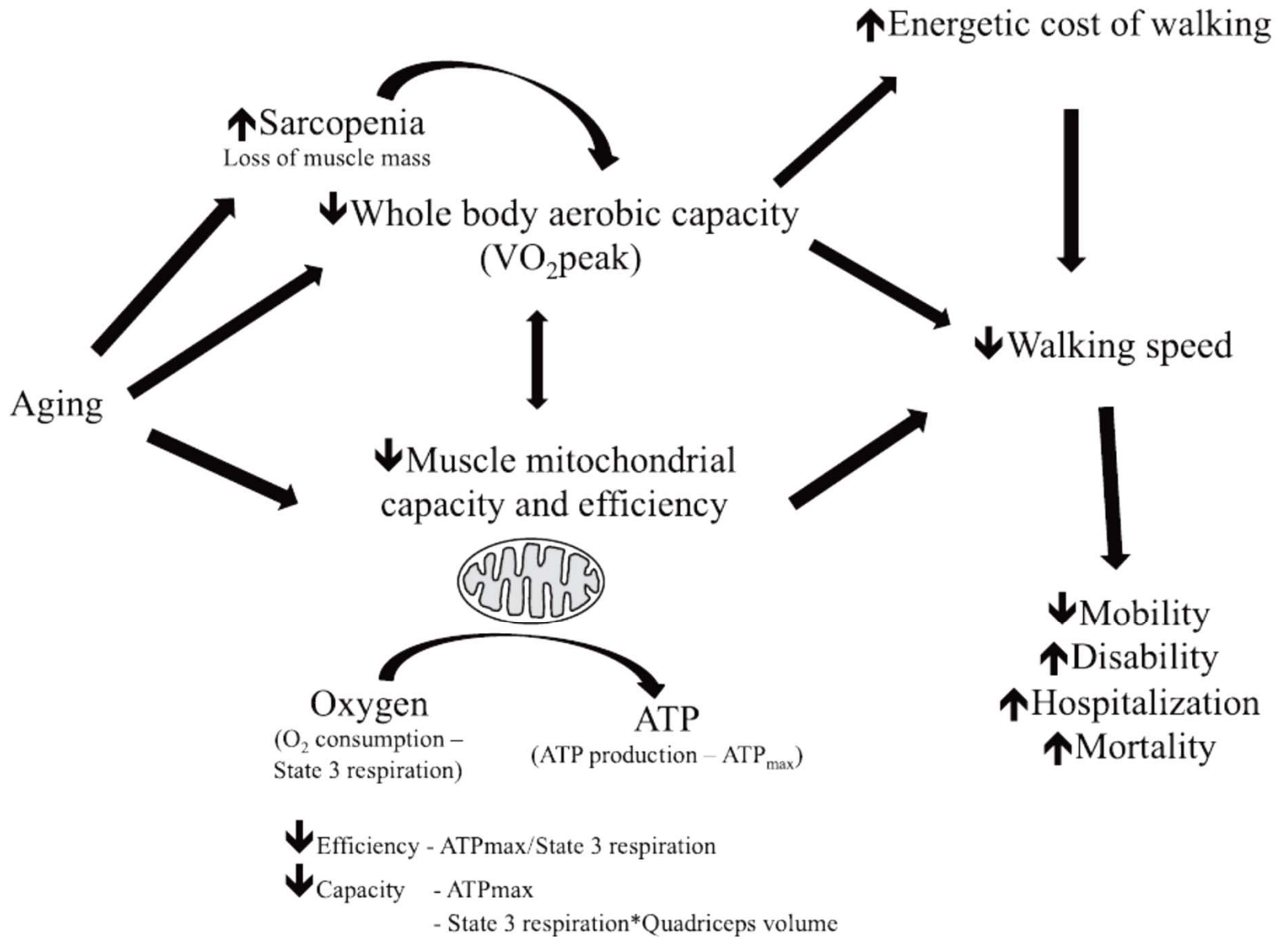
Skeletal Muscle Mitochondrial Energetics Are Associated With Maximal Aerobic Capacity and Walking Speed in Older Adults

Paul M. Coen et al. *J Gerontol A Biol Sci Med Sci. 2013;68(4):447–455*
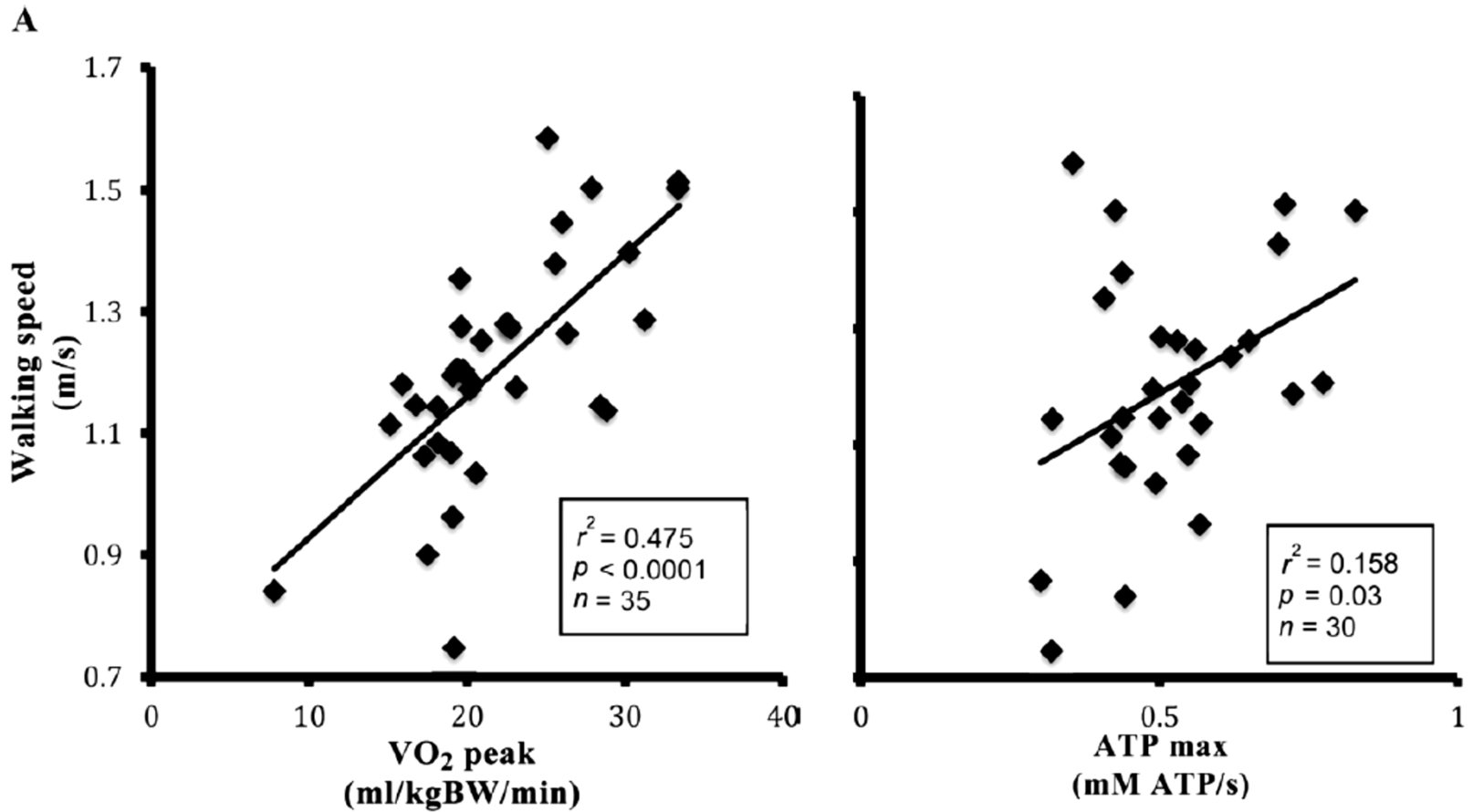
High Basal Metabolic Rate Is a Risk Factor for Mortality: The Baltimore Longitudinal Study of Aging
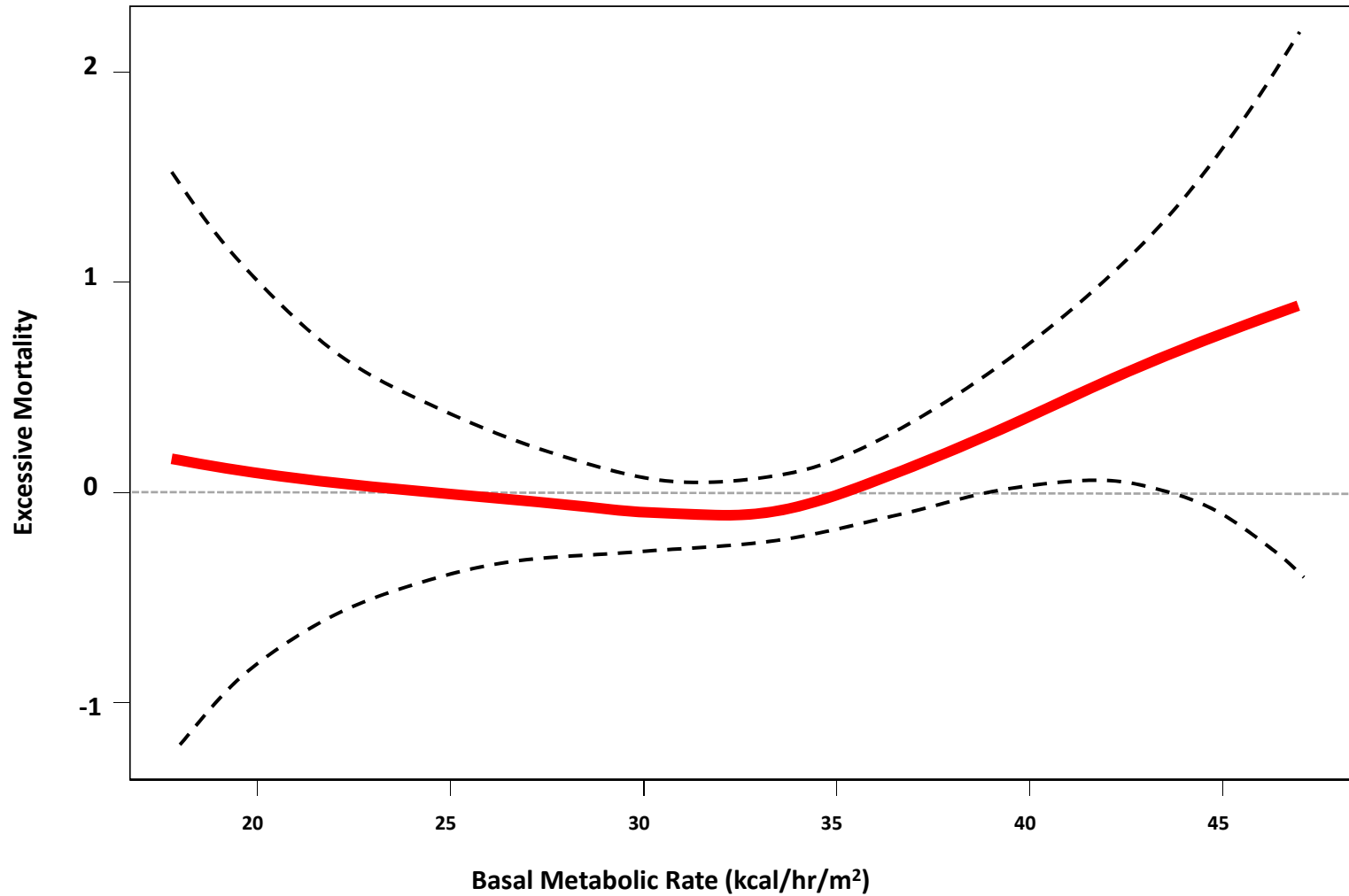
Multi-morbidity and Resting Metabolic Rate (RMR): longitudinal association
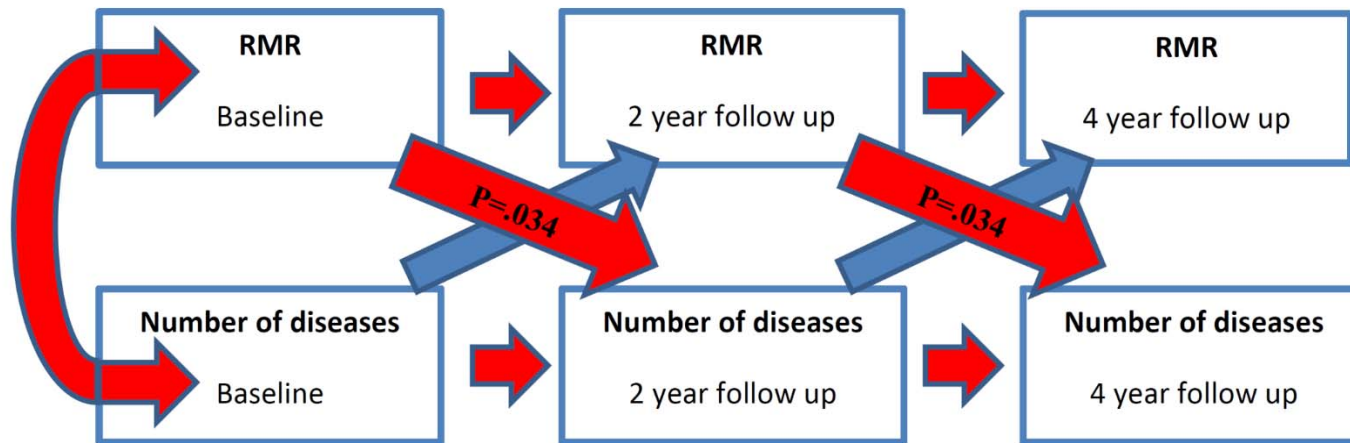
*adjusted for baseline age , sex, baseline total body lean mass and fat mass

BLSA (unpublished data)

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Epigenetic Alterations

MeCP2

Me Me Me
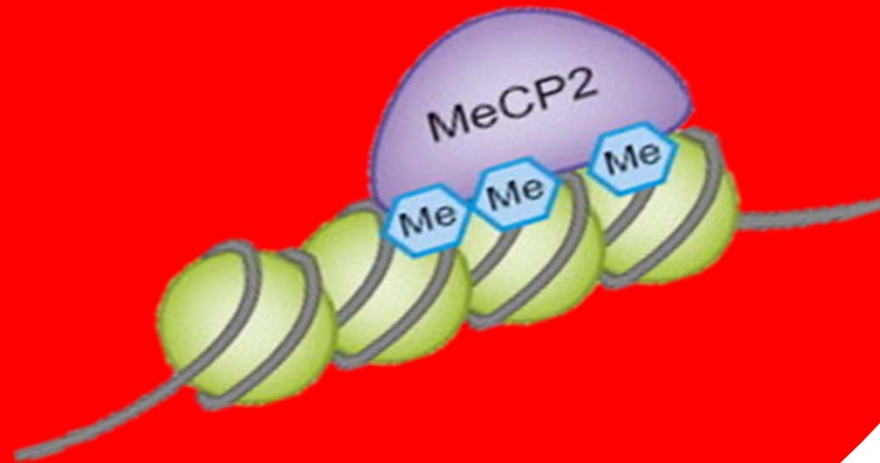
DNAm Age Correlates with Chronologic Age

cor=0.85, p<1e-200
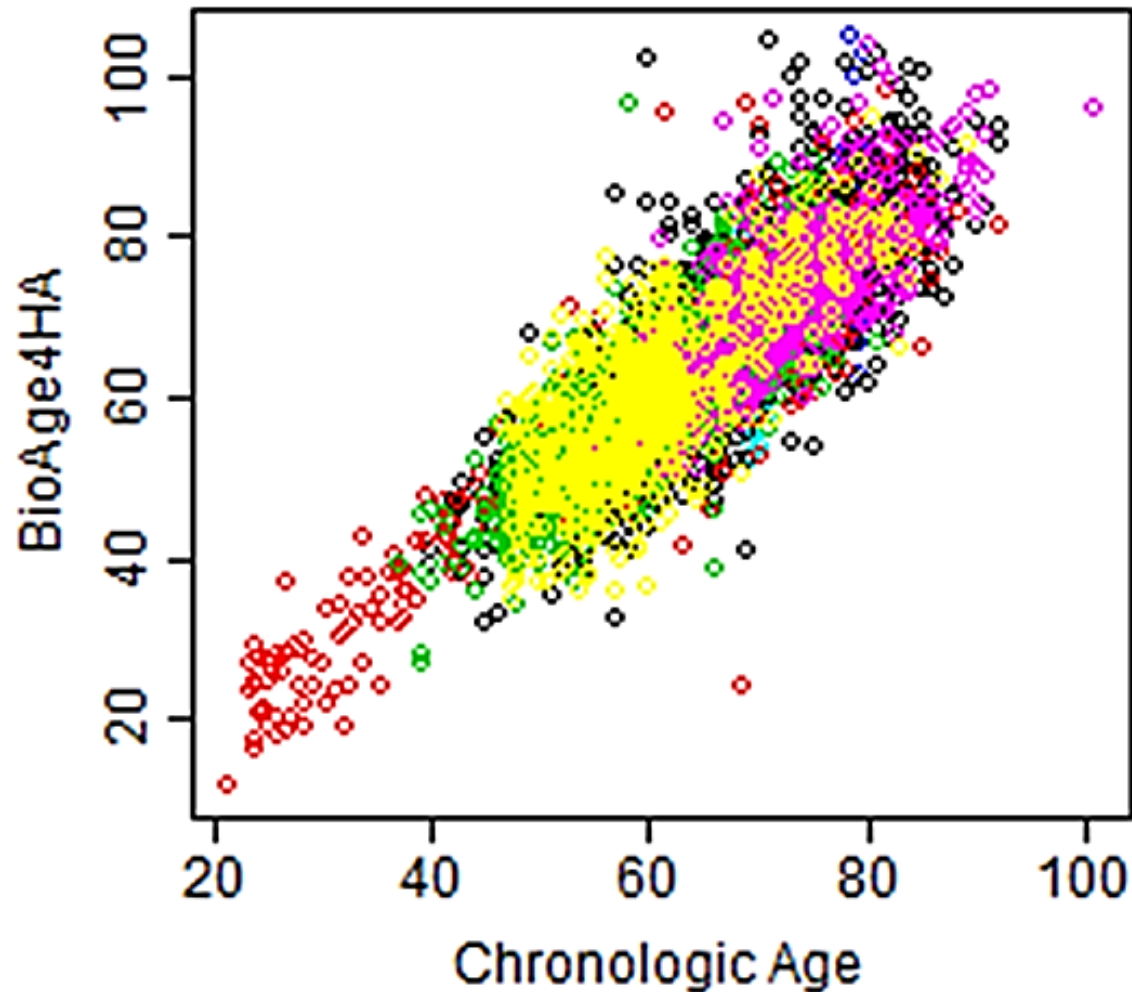
Ticking rate of the epigenetic clock
= rate of change of the average DNA meth levels
= rate of change of the red curve

B Training data cor=0.92, p<1e-200

C Test data cor=0.92, p<1e-200
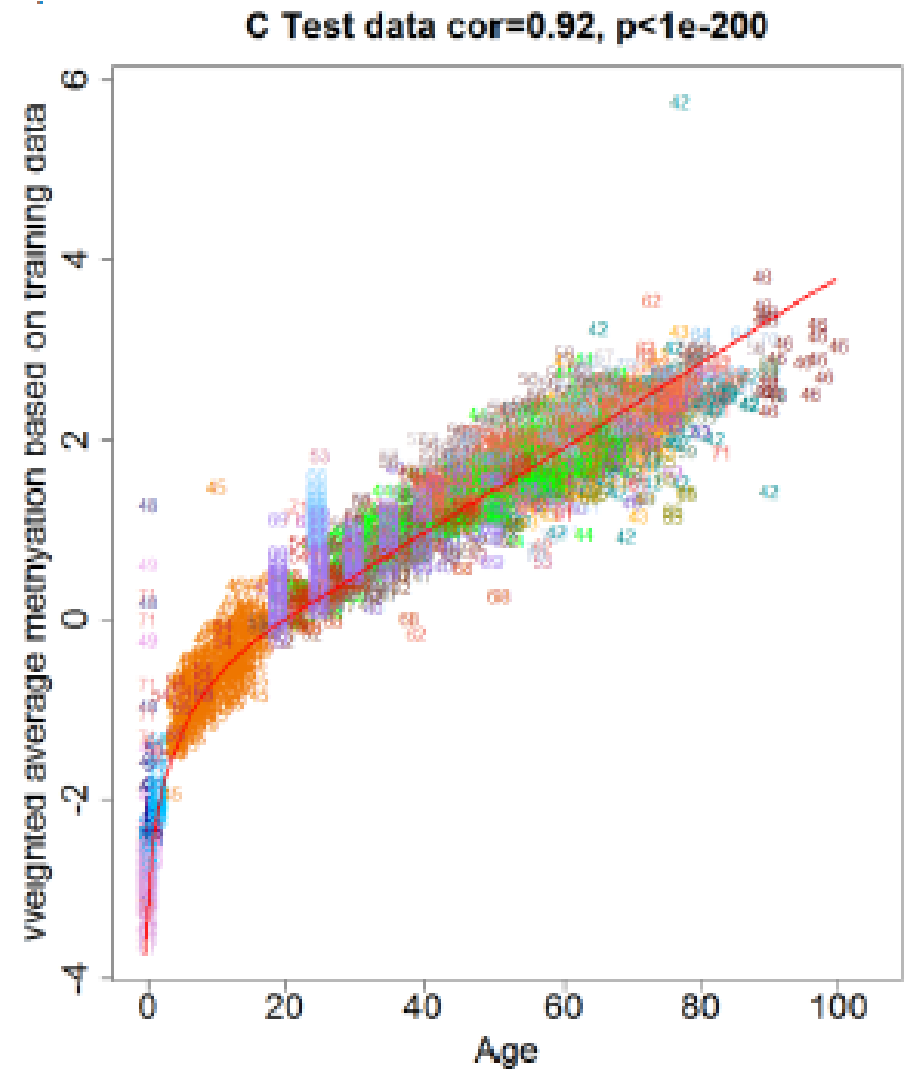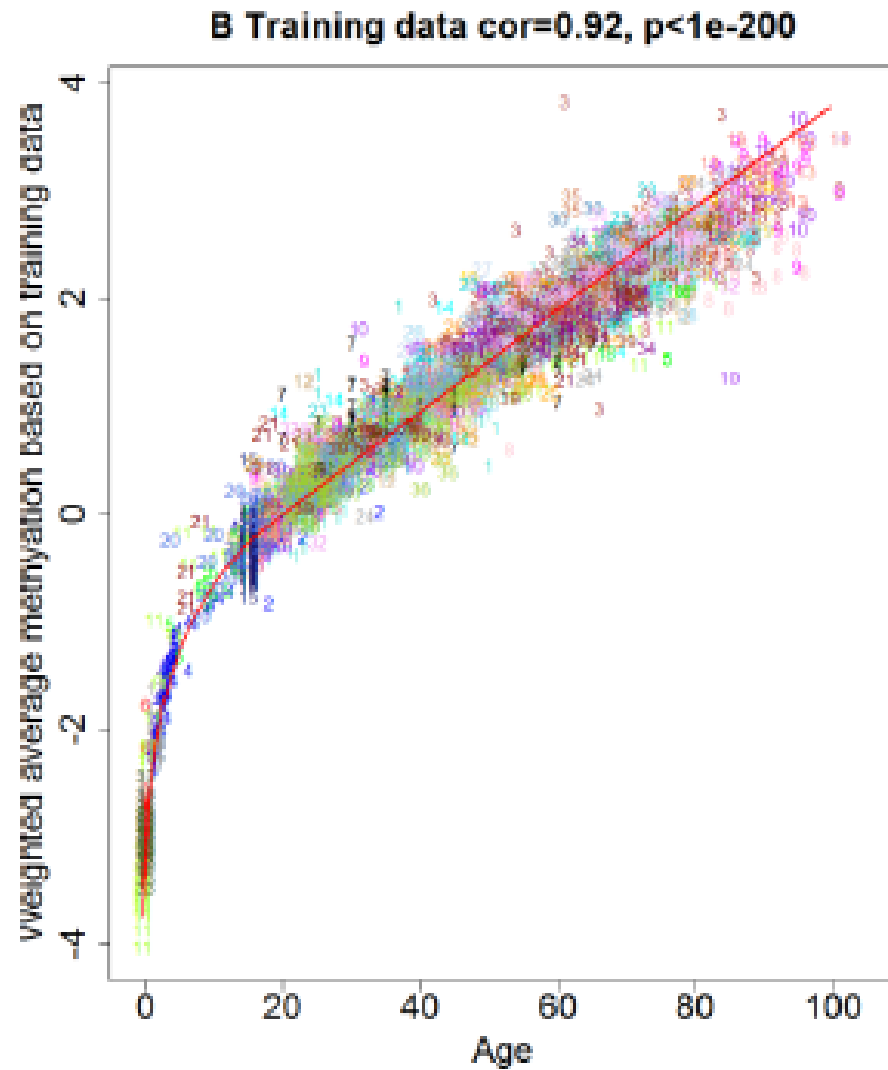
Chronologic vs DNAm Age
(test sets by tissue)
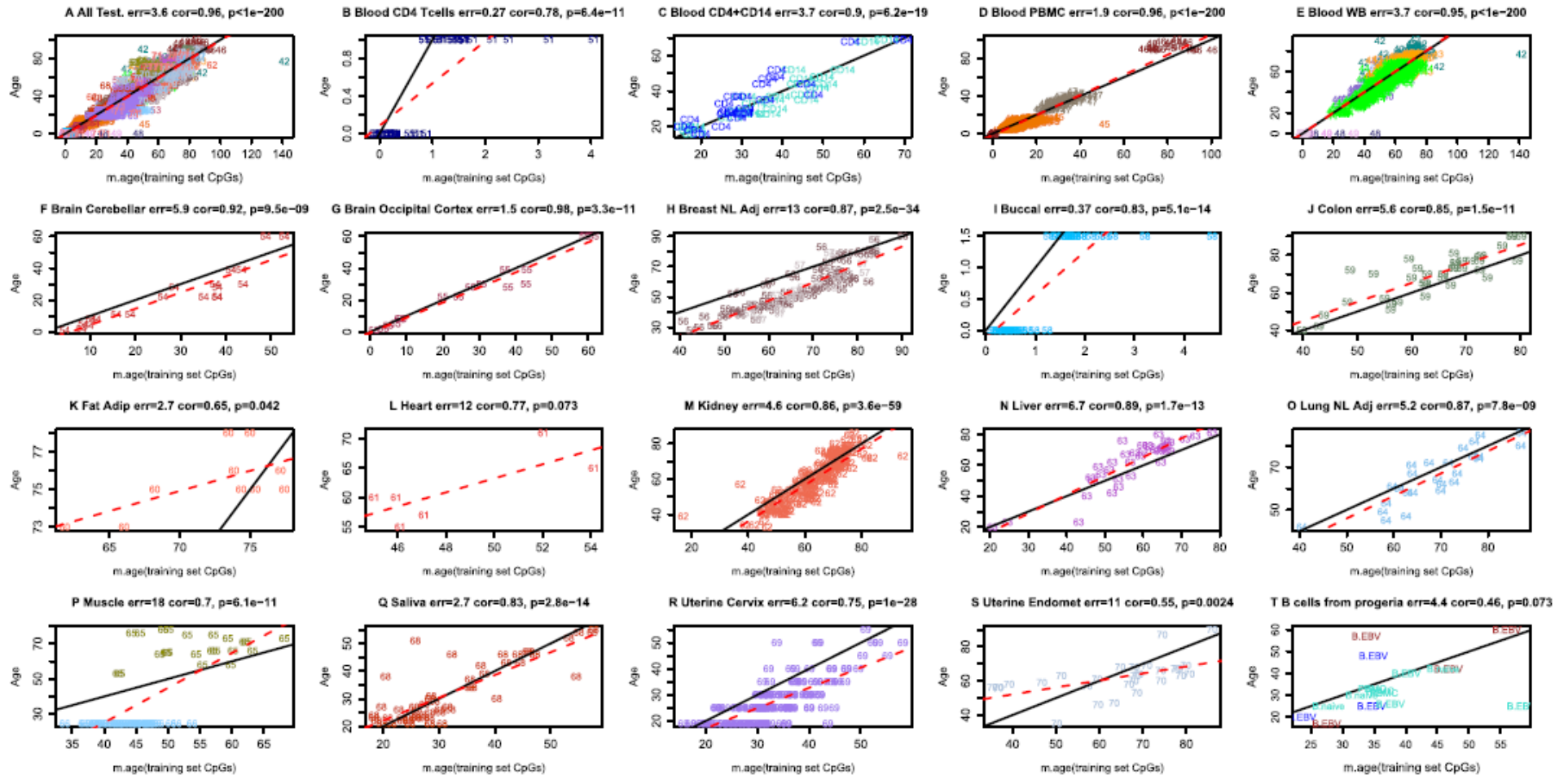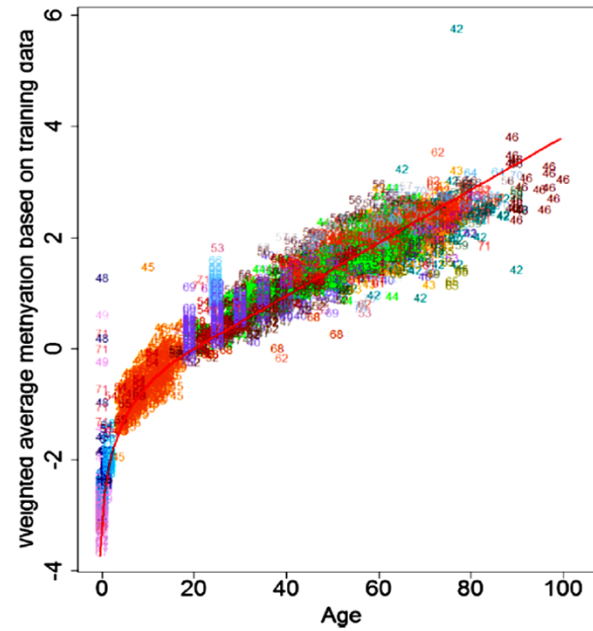
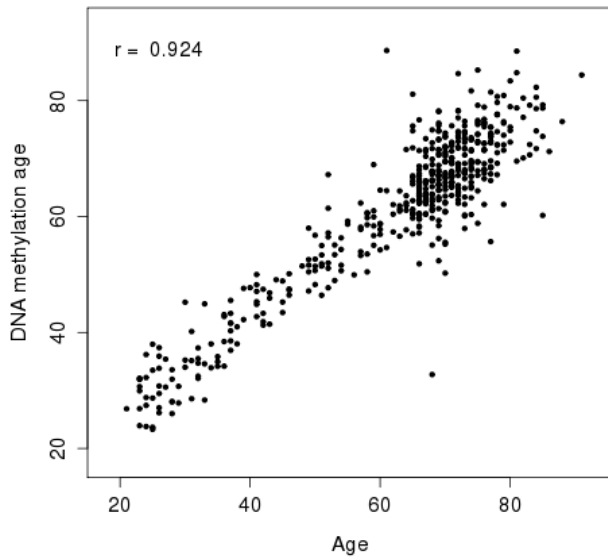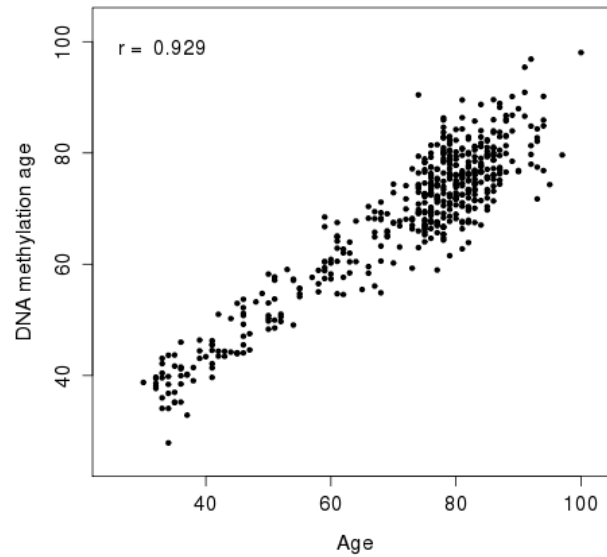# DNA methylation age of human tissues and cell types
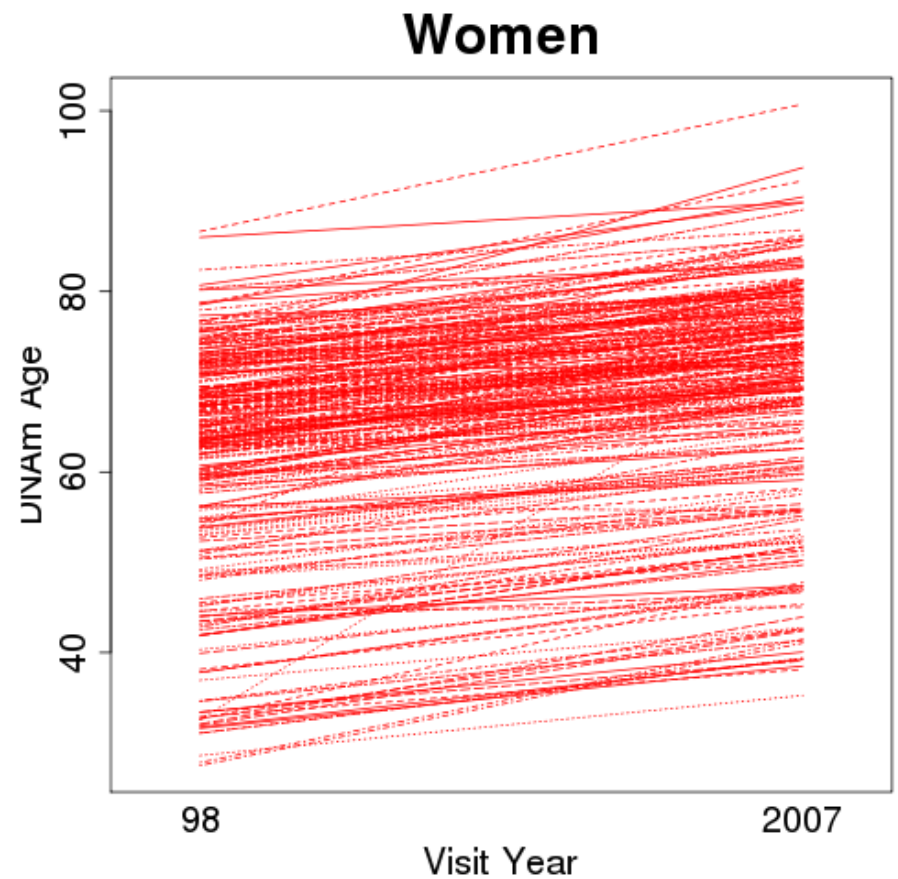## Steve Horvath at http://genomebiology.com//14/10/R115
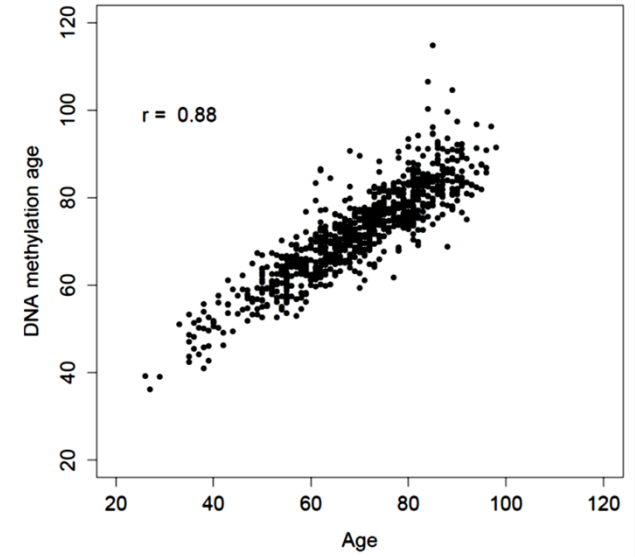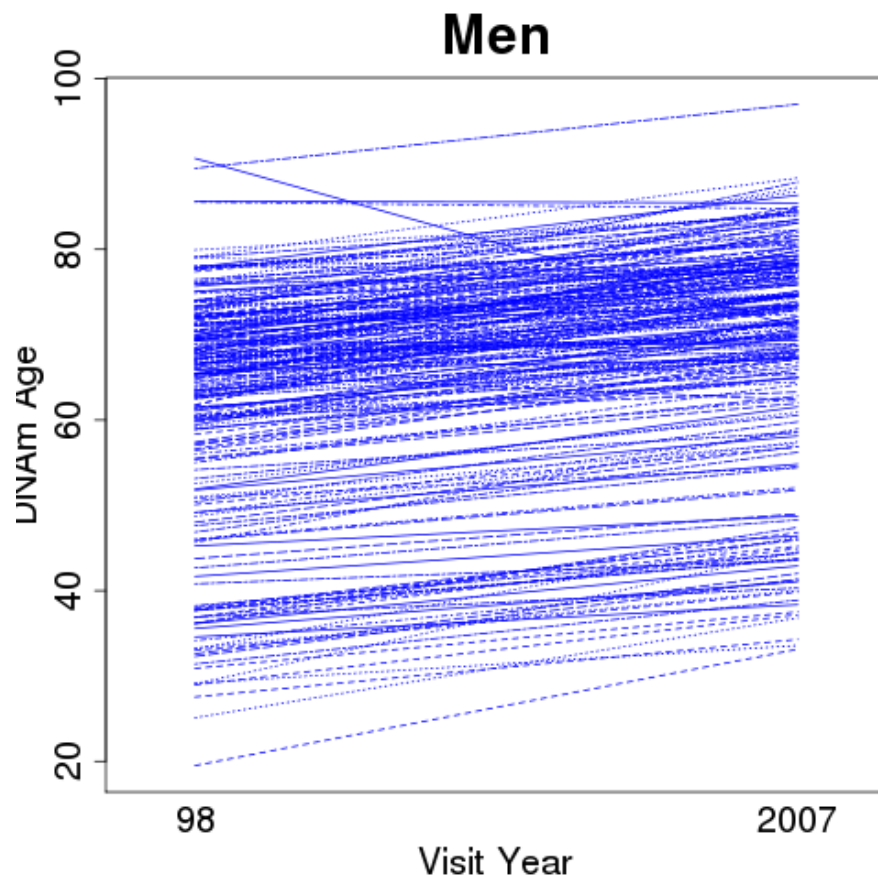
DNAm Age Tracks Chronologic Age Over a 9-year Period

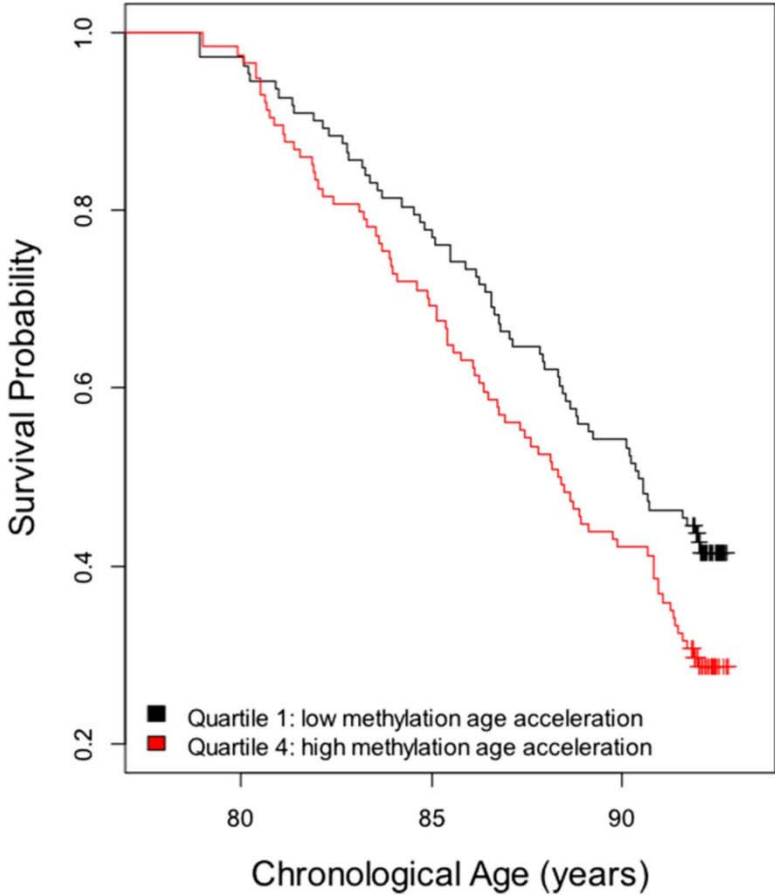# DNA methylation age of blood predicts all-cause mortality in later life

Riccardo E Marioni, Sonia Shah, Allan F McRae, Brian H Chen et al.
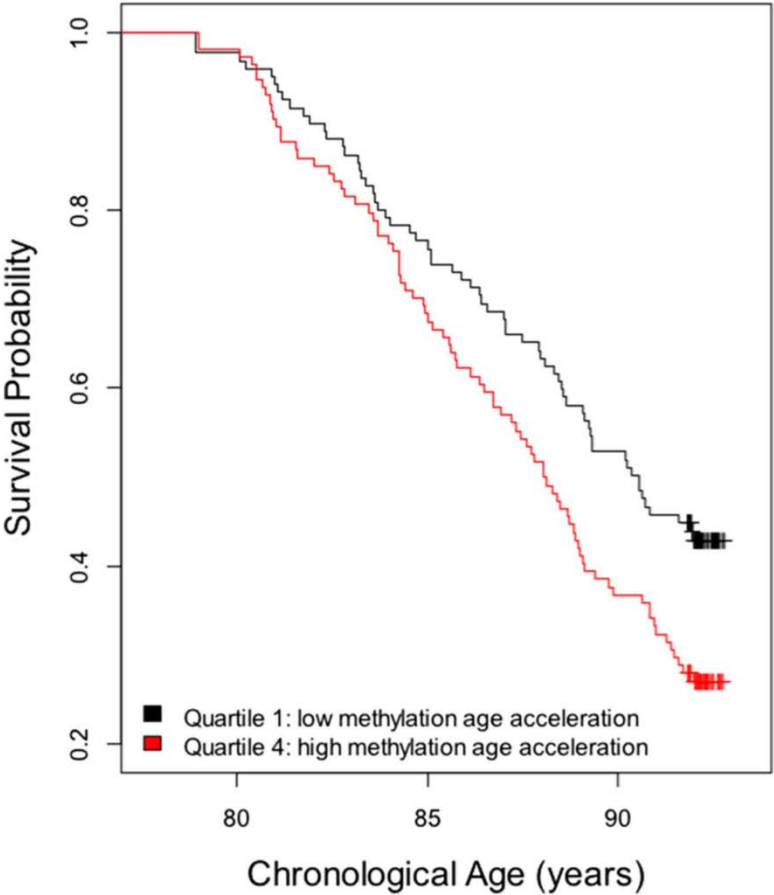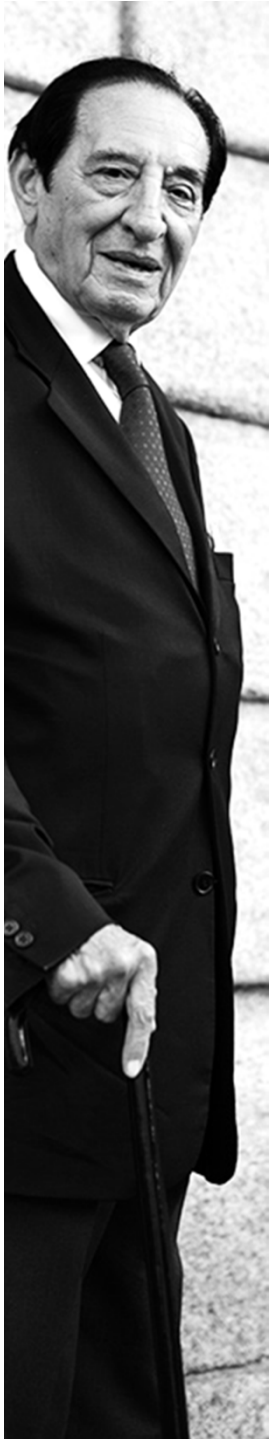
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Telomere
Attrition
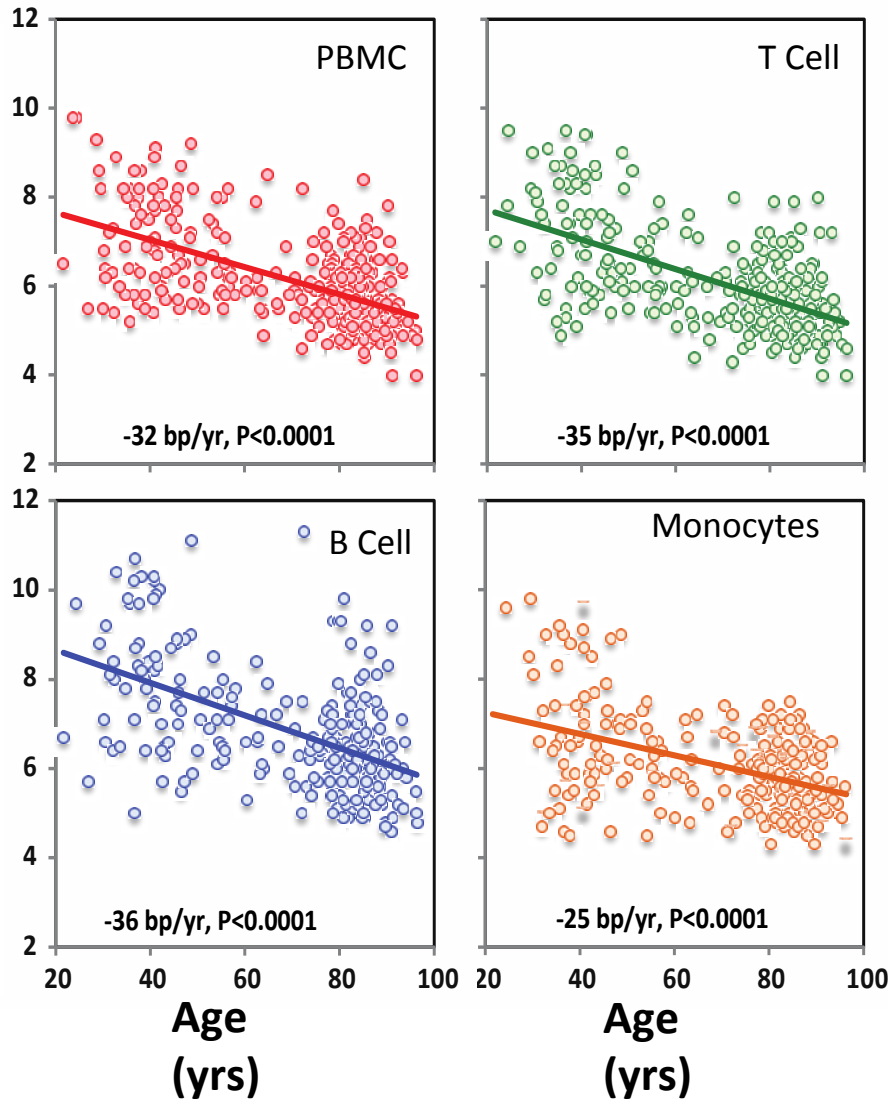
Telomere length declines with aging. Attrition of telomere length in peripheral blood mononuclear cells with age is documented from cross-sectional studies (left). Average decline in telomere length was recently confirmed in the Baltimore Longitudinal Study of Aging (below).
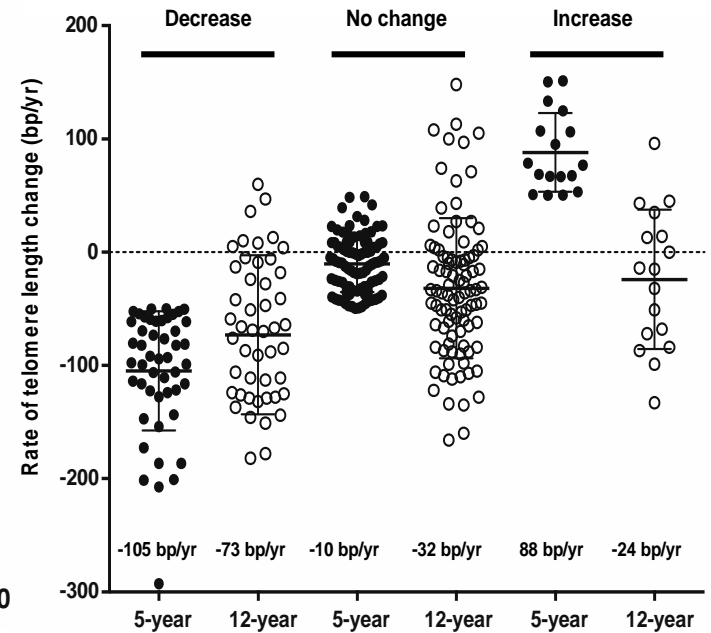
Telomere length vs. DNAm Age
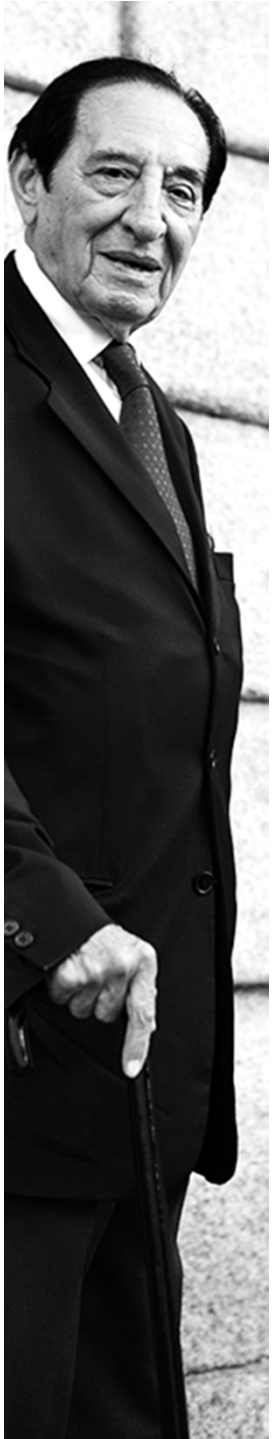
DNAm Age
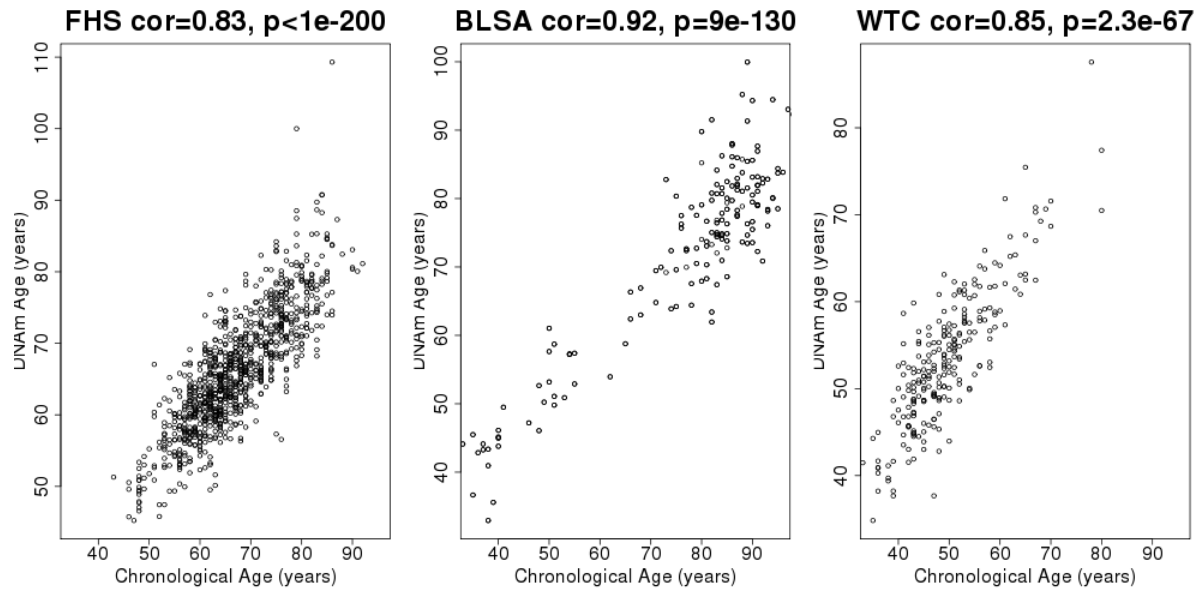
Telomere Length
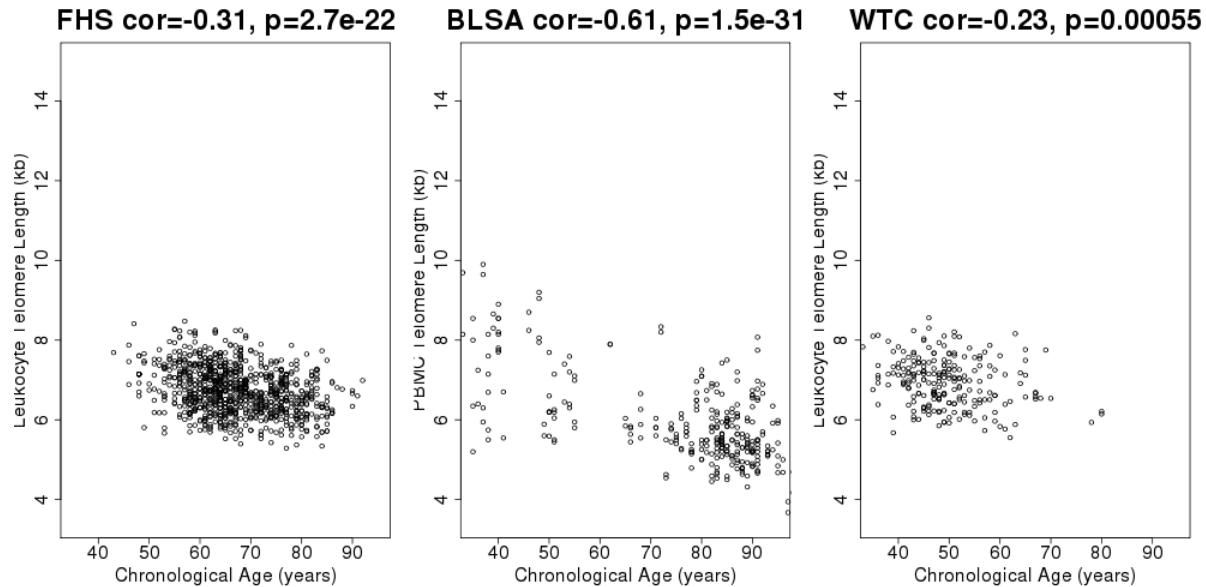
Is the Biology of Aging at the Core Of Frailty?
Can This Hypothesis be Tested?

Cellular Senescence

In 1961, L. Hayflick proposed that the limited lifespan of cells in culture represented the phenomenon of aging at the cellular level
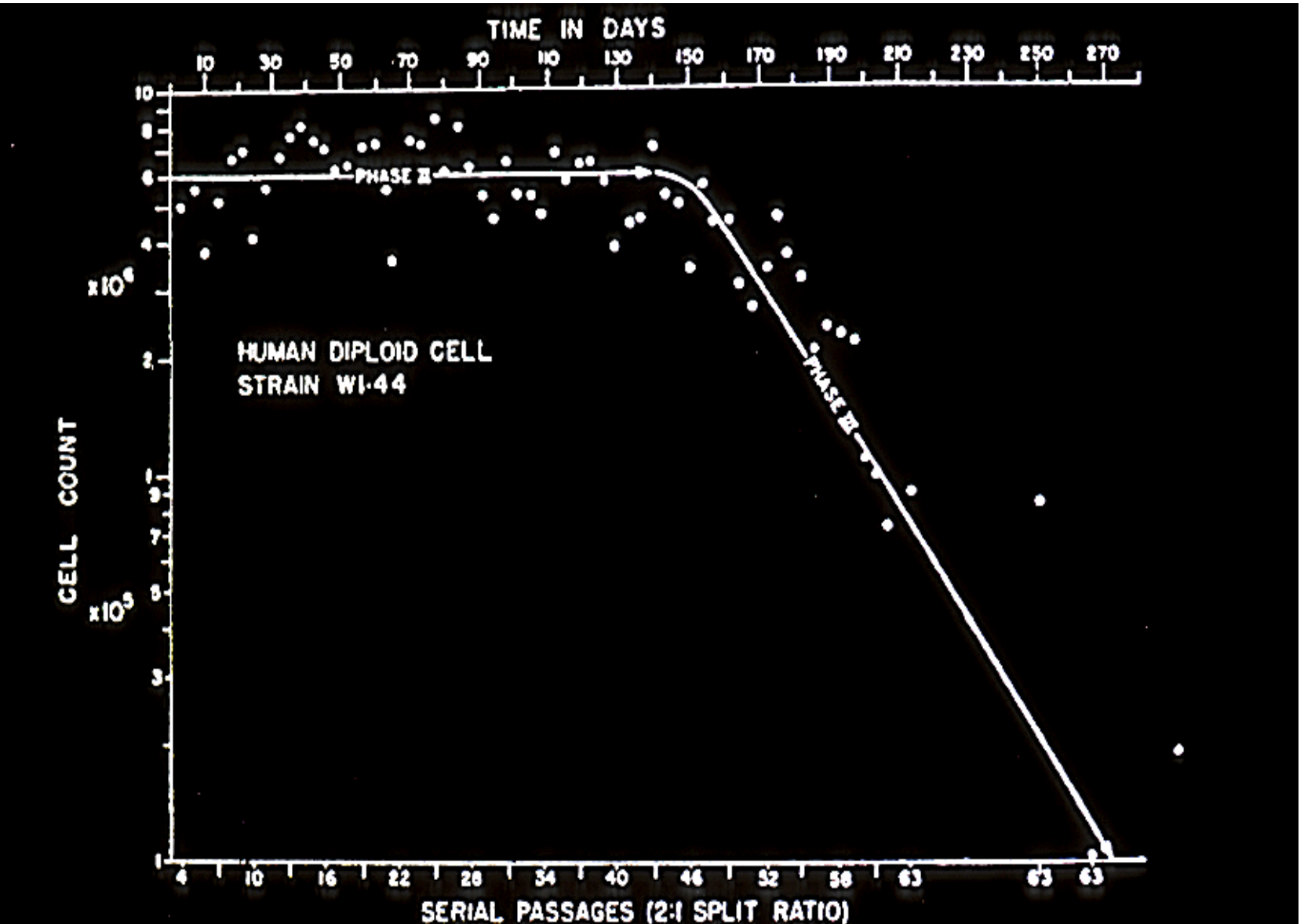
In 1998, it was conclusively demonstrated that replicative cell senescence is caused by telomere shortening
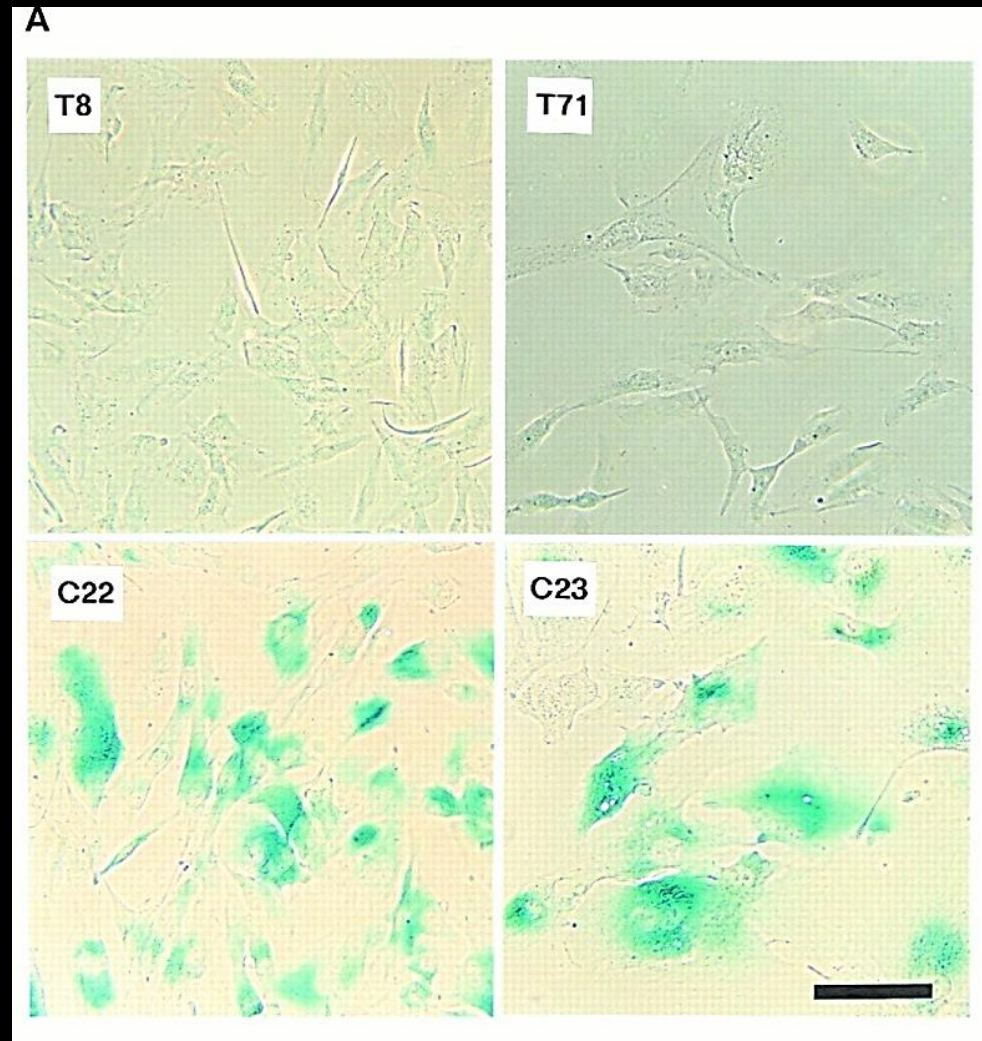
In these experiments, the authors introduced telomerase, and that was sufficient to abrogate cell senescence (as shown by lack of SA-bGal staining in the upper panels)

Telomere shortening is only one of many paths to cell senescence

Cell culture

Oxidative stress

Telomere dysfunction

DNA damage

Oncogene activation

HRAS → HRAS^V12

Cytotoxic drugs
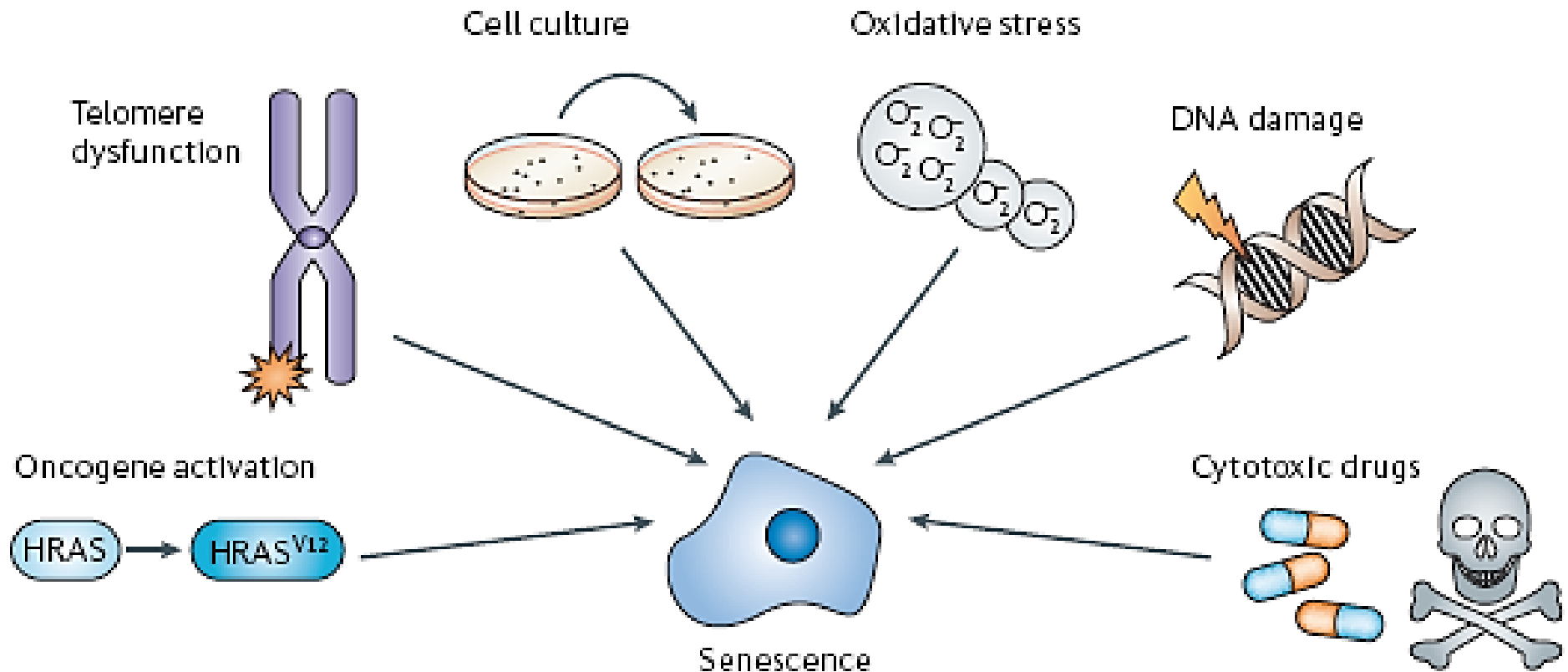
Senescence

Differentiated Cell Fates Under Stress
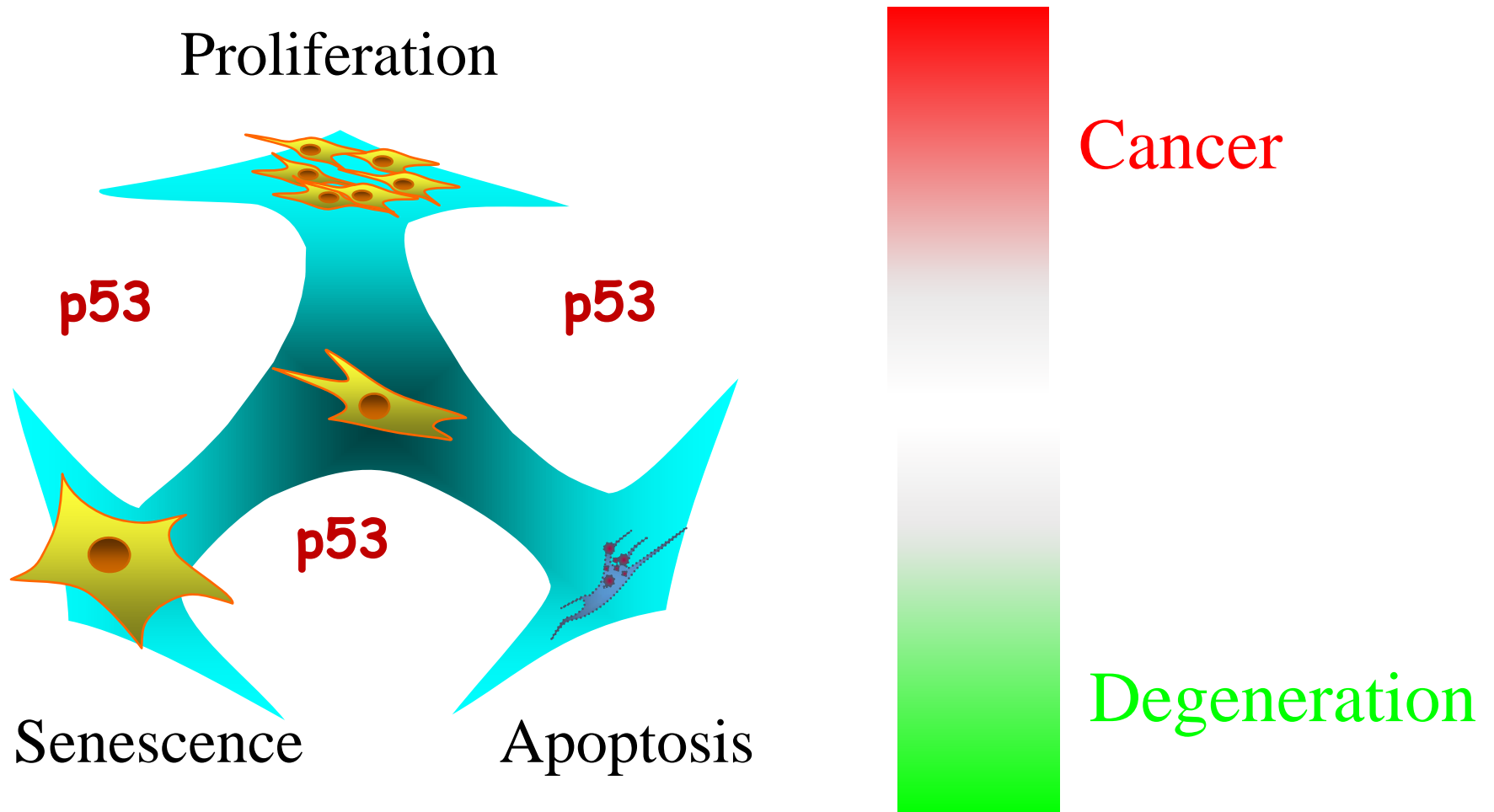
Do they exist in vivo?
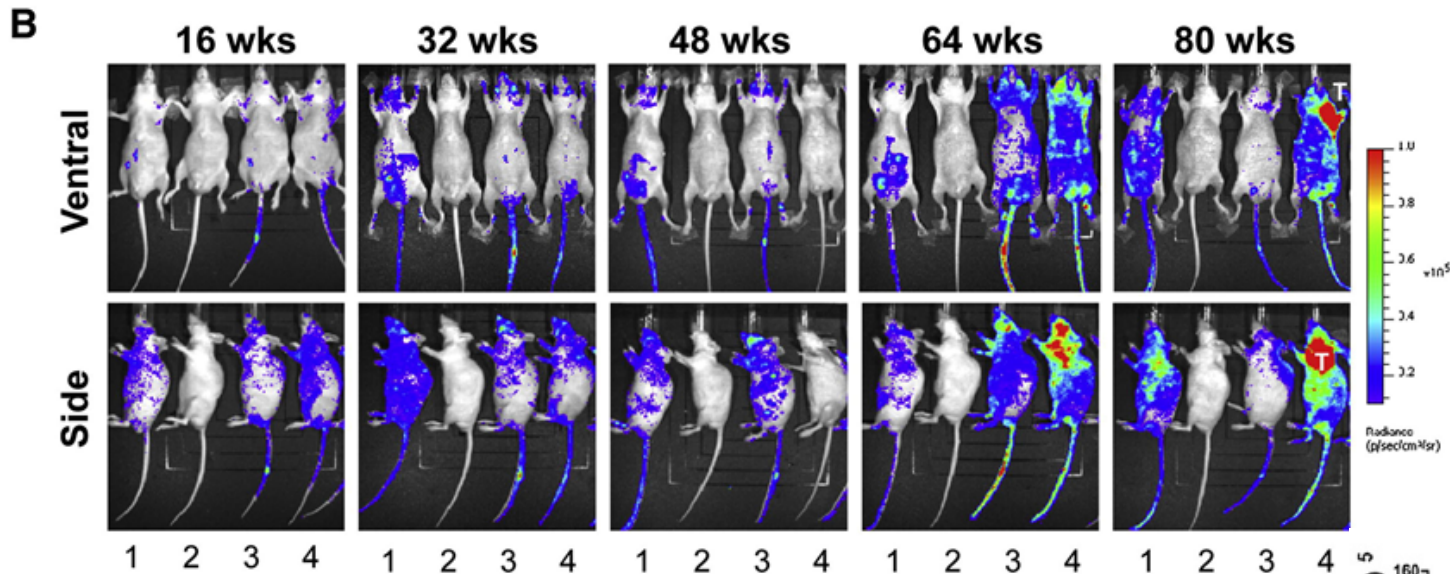
Monitoring Tumorigenesis and Senescence In Vivo with a $p16^{INK4a}$-Luciferase Model

Christin E. Burd,[1,2] Jessica A. Sorrentino,[2,3] Kelly S. Clark,[1,2] David B. Darr,[1,2] Janakiraman Krishnamurthy,[1,2] Allison M. Deal,[2] Nabeel Bardeesy,[4] Diego H. Castrillon,[5] David H. Beach,[6] and Norman E. Sharpless[1,2,*]
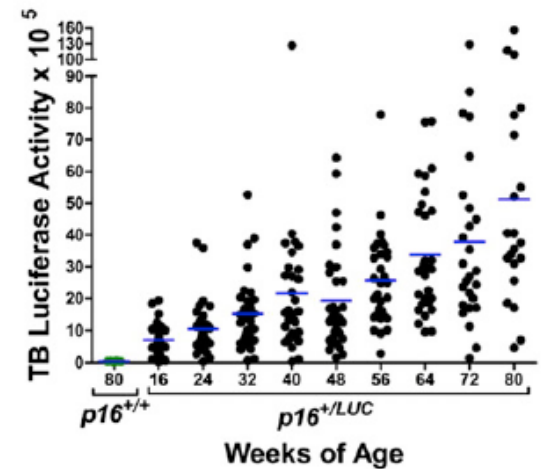
Burd et al. – Cell 152:340 (2013)

Chemotherapy-induced senescence *in vivo* (mice)
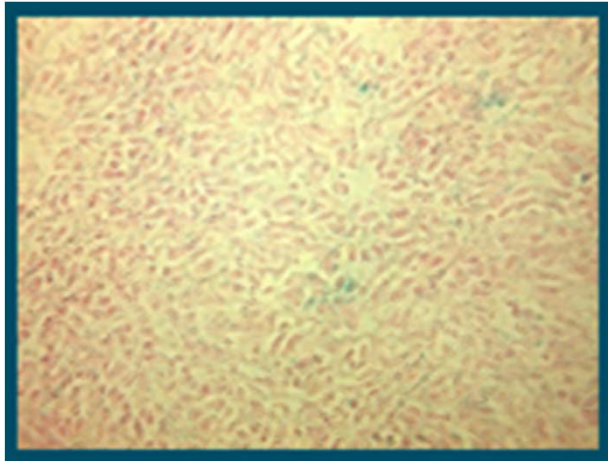
untreated
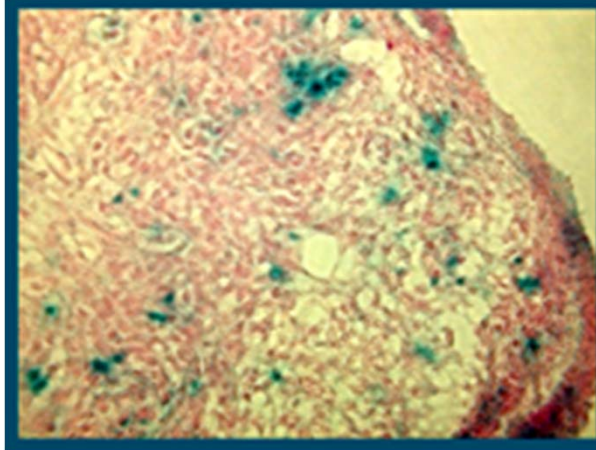
doxorubicin
0.05 mg/kg
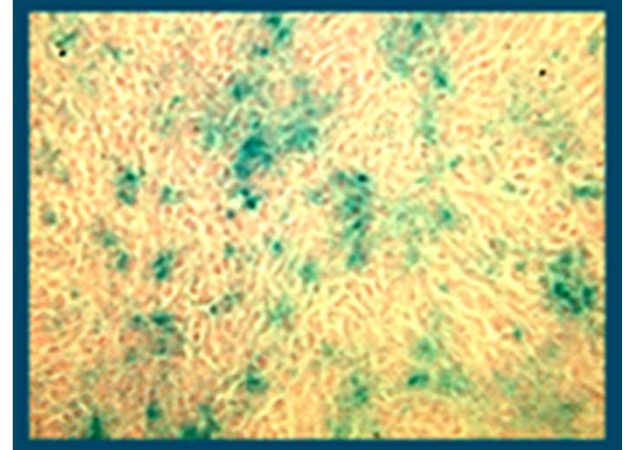
doxorubicin
0.2 mg/kg

HT1080 fibrosarcoma xenograft
Roninson et al., Drug Res. Updat. 4, 303, 2001

Senescent cells secrete a large number (and large amounts) of biologically active factors with the potential of affecting cellular physiology / responses in neighboring, non-senescent cells
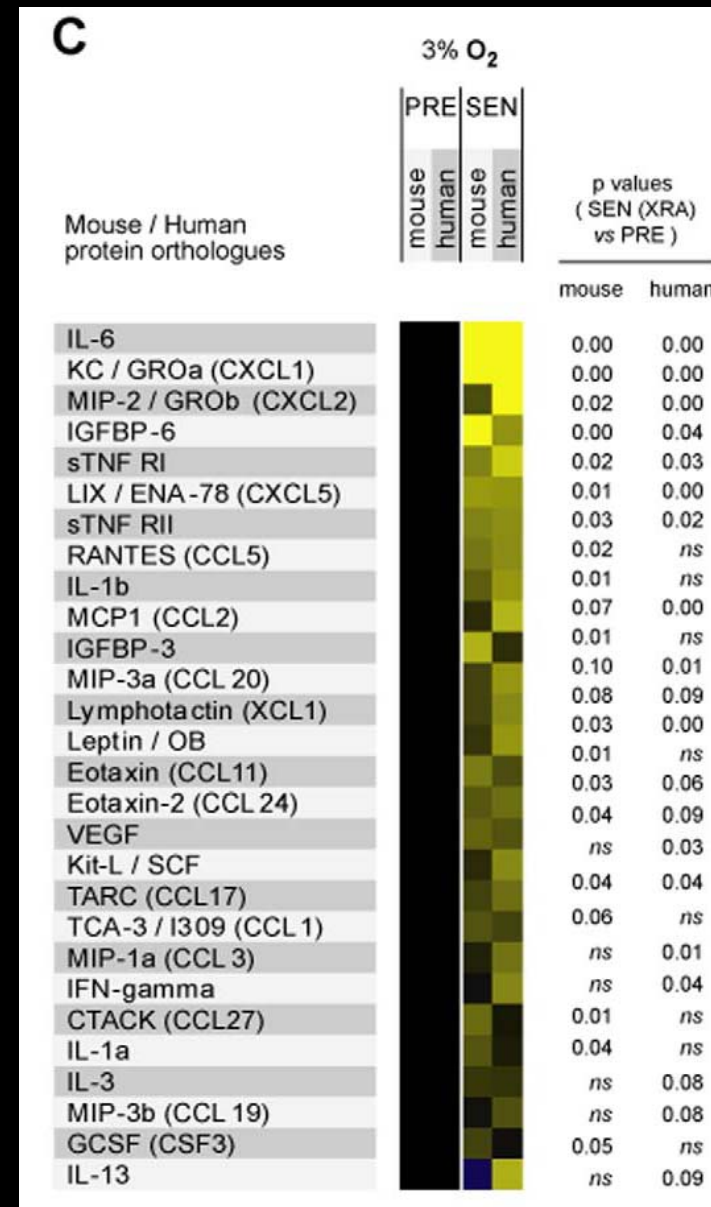
Purging Cells in Mice Is Found to Combat Aging Ills

Two 9-month-old mice from the study. The one on the right received the drug to eliminate senescent cells.

By NICHOLAS WADE
Published: November 2, 2011

In a potentially fundamental advance, researchers have opened up a novel approach to combating the effects of aging with the discovery that a special category of cells, known as senescent cells, are bad actors that promote the aging of the tissues. Cleansing the body of the

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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]
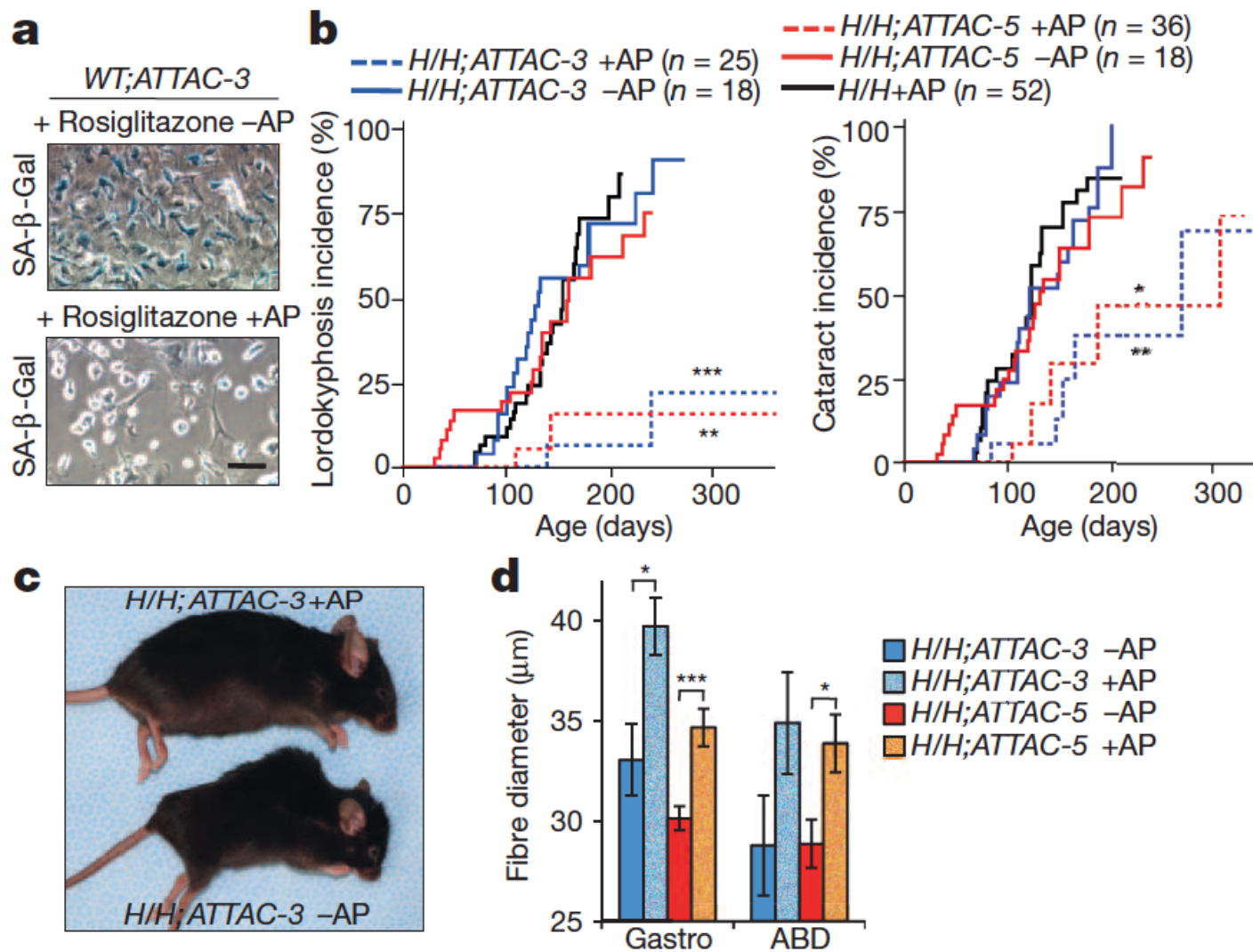
Expression of p16INK4a in peripheral blood T-cells is a biomarker of human aging

Yan Liu, Hanna K. Sanoff, Hyunsoon Cho, Christin E. Burd, Chad Torrice, Joseph G. Ibrahim, Nancy E. Thomas and Norman E. Sharpless.
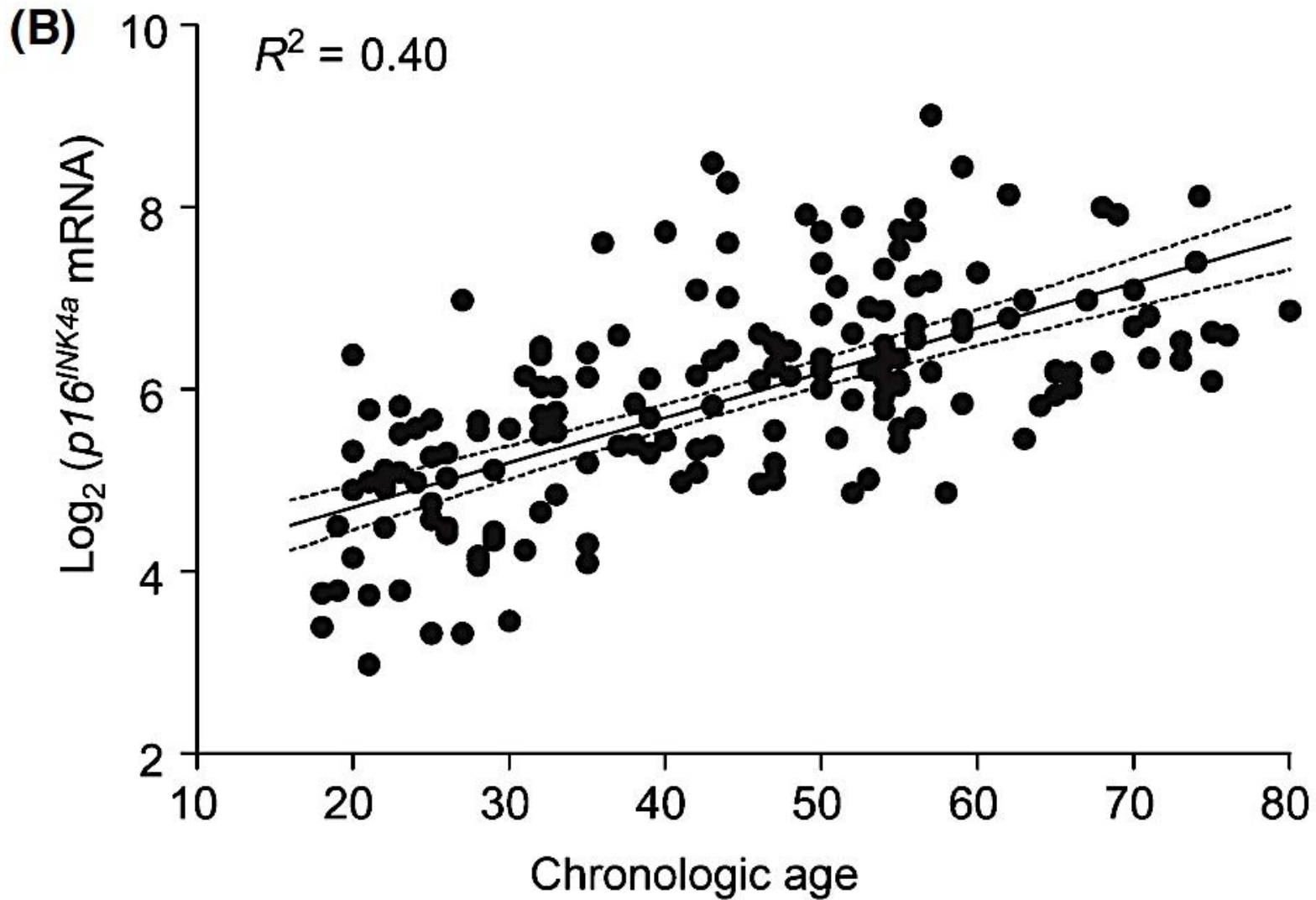
Is the Biology of Aging at the Core Of Frailty?
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Stem Cells Exhaustion

SATELLITE CELLS AND MYONUCLEI IN YOUNG AND ELDERLY WOMEN AND MEN

Fawzi Kadi et al. Muscle Nerve 29: 120–127, 2004
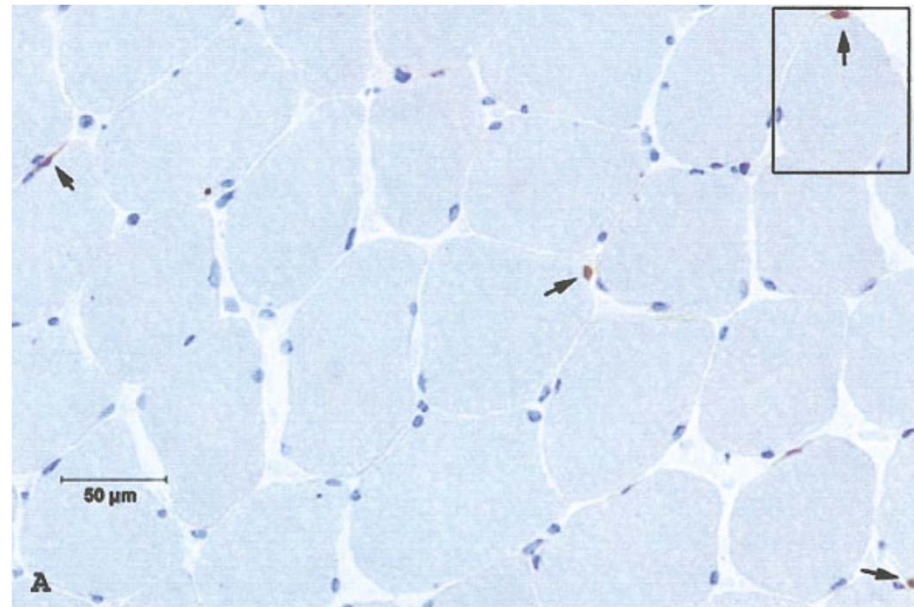
Table 2. Muscle fibers, satellite cells, and myonuclei in the tibialis anterior muscle of young and elderly women and men.

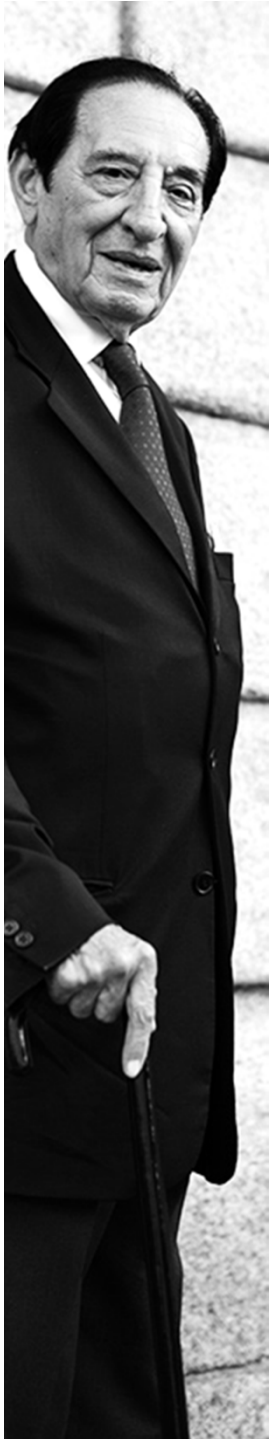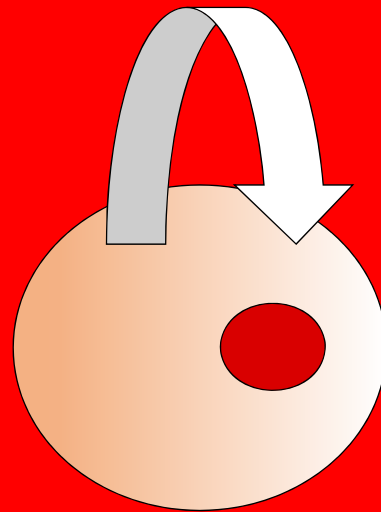|	Young		Elderly	
	Women (n = 16)	Men (n = 15)	Women (n = 14)	Men (n = 13)
No. of muscle fibers (f)	218 ± 12 (210–243)	212 ± 8 (192–223)	219 ± 12 (205–241)	210 ± 18 (171–236)
No. of satellite cells (s)	37 ± 10 (19–63)	40 ± 11 (24–58)	28 ± 8 (17–42)	25 ± 5 (13–35)
No. of myonuclei (m)	493 ± 72 (391–655)	545 ± 54 (461–627)	611 ± 61 (550–719)	664 ± 118 (481–844)
Total number of nuclei (s+m)	530 ± 73 (430–700)	585 ± 56 (505–683)	639 ± 62 (574–743)	639 ± 115 (468–818)
No. of satellite cells/muscle fiber (s/f)	0.17 ± 0.04 (0.09–0.28)	0.19 ± 0.05 (0.11–0.29)	0.13 ± 0.04 (0.08–0.20)	0.12 ± 0.03 (0.08–0.17)
No. of myonuclei/muscle fiber (m/f)	2.25 ± 0.27 (1.89–2.76)	2.57 ± 0.23 (2.28–2.97)	2.79 ± 0.196 (2.46–3.21)	3.16 ± 0.43 (2.37–4.04)
Relative number of satellite cells [s/(m + s) × 100] (%)	7.1 ± 1.9 (3.4–11.2)	6.9 ± 1.8 (4.4–11.2)	4.4 ± 1.3 (2.8–6.6)	3.9 ± 0.9 (2.7–5.7)

Values are presented as mean ± SD and range.

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Genomic Instability

CONSEQUENCES OF DNA DAMAGE

STRESS

Endogenous   Environmental

DNA Lesion

DNA REPAIR

SYSTEMS   UNREPAIRED
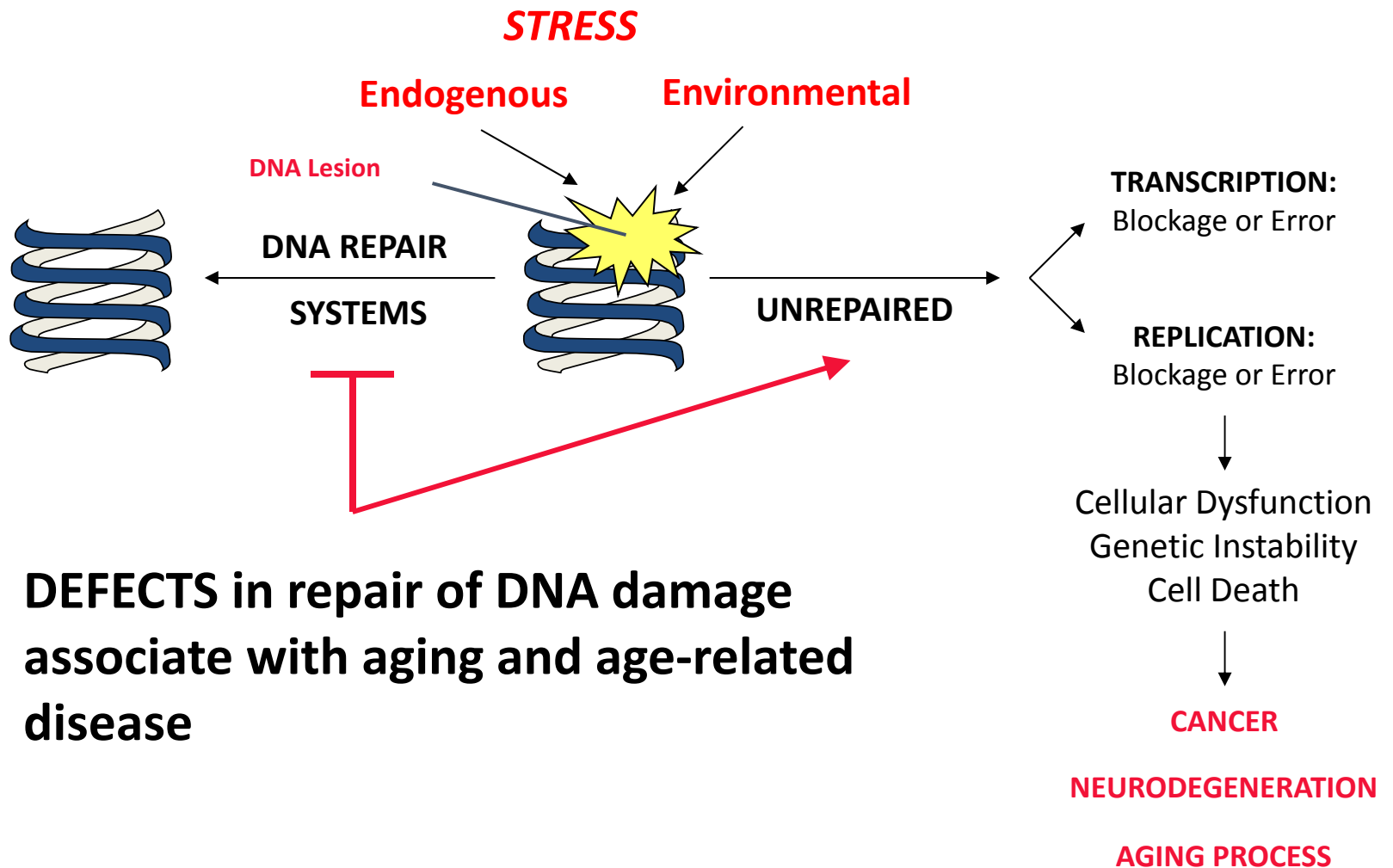
DEFECTS in repair of DNA damage associate with aging and age-related disease

TRANSCRIPTION:
Blockage or Error

REPLICATION:
Blockage or Error

Cellular Dysfunction
Genetic Instability
Cell Death

CANCER

NEURODEGENERATION

AGING PROCESS

Multiplexed DNA repair assays for multiple lesions and multiple doses via transcription inhibition and transcriptional mutagenesis

Zachary D. Nagel[a,b], Carrie M. Margulies[a,b], Isaac A. Chaim[a,b], Siobhan K. McRee[a,b], Patrizia Mazzucato[a,b], Anwaar Ahmad[a,b], Ryan P. Abo[a,b,c,d], Vincent L. Butty[a,b,c,d], Anthony L. Forget[a,b], and Leona D. Samson[a,b,c,d,1]
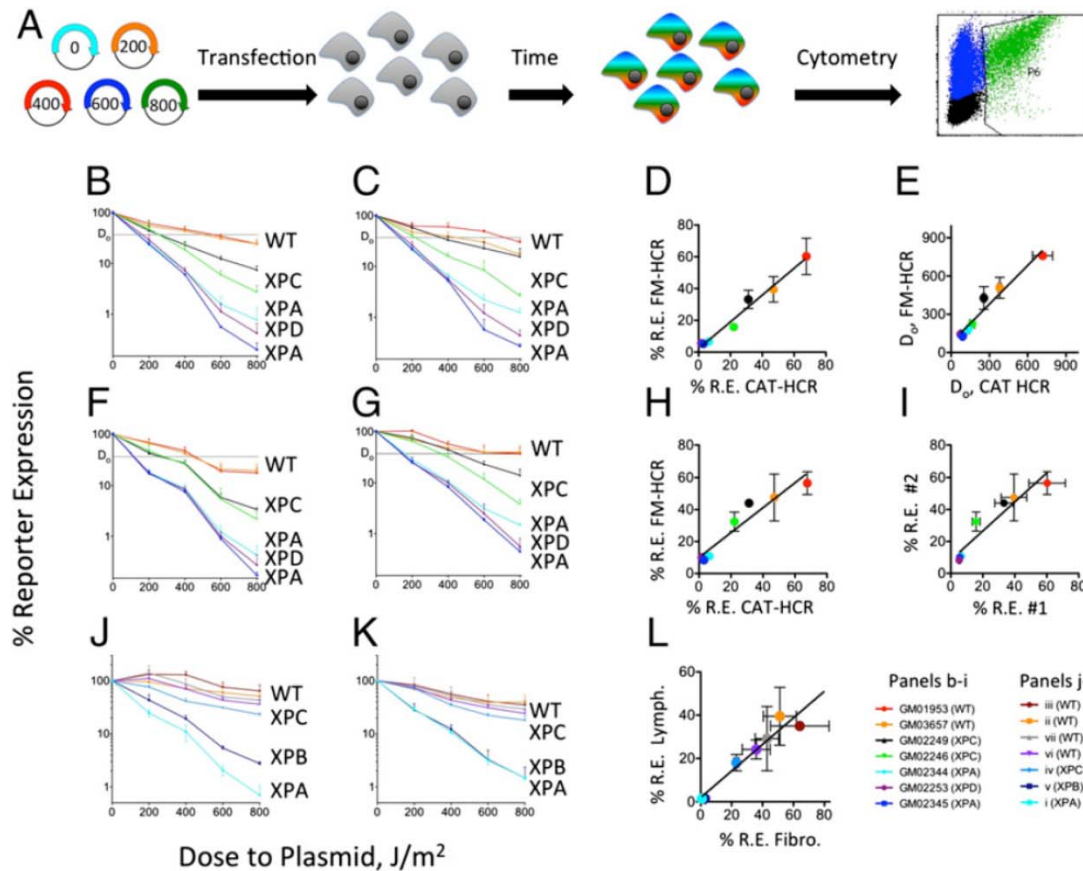
DNA lesions are introduced into fluorescent reporter plasmids in vitro. Numbers labeling the plasmids represent the dose (in joules per square meter) of UV radiation. Following treatment, plasmids were combined and cotransfected into cells. After 18 or 40 h incubation, cells were assayed for fluorescence by flow cytometry. Comparison of fluorescence signals with those from cells transfected with undamaged plasmids yields a dose–response curve.

The Green Ear by Gianni Rodari

One day as I took the train direct to *Capranica-Viterbo*
a man got on with an ear as green as an unripe tomato.
He wasn't exactly young at all, but rather somewhat older.
Except for his bright green ear, he was totally, totally in order.

I quickly moved and changed my seat
to study this phenomenon from head to feet.
"Sir," I said to him, "I see you've reached a certain age,
so why a green ear at this late stage?"

"Just say," he answered with courtesy, "that I've become quite old.
This ear is now the only thing left from my youth—if truth be told.
This ear, a child's ear, is used to help me grasp what I can—
those voices adults don't ever hear and will never understand.

I listen to what the birds say, to the words of all the trees.
I listen to the clouds that pass as well as the rocks and streams.
I understand the children when they say some things I hear,
those things that seem so strange to every grown-up's ear."

That's what he said. There with an ear as green as an unripe tomato
on the day that I took the train direct to *Capranica-Viterbo*.

Men with green ear
Miguel Lavino 2008 (UK)

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Can This Hypothesis be Tested?

Deregulated Nutrient Sensing

**Is the Biology of Aging at the Core Of Frailty?
Can This Hypothesis be Tested?**

Loss of
Proteostasis

Full performance

"Normal aging"

"Accelerated aging"

Frailty

Disability

Performance

Frailty time-window

Time (age)

Ferrucci L et al. Biomarkers of frailty in older persons.
J Endocrinol Invest 2002;25(10 Suppl):10-15