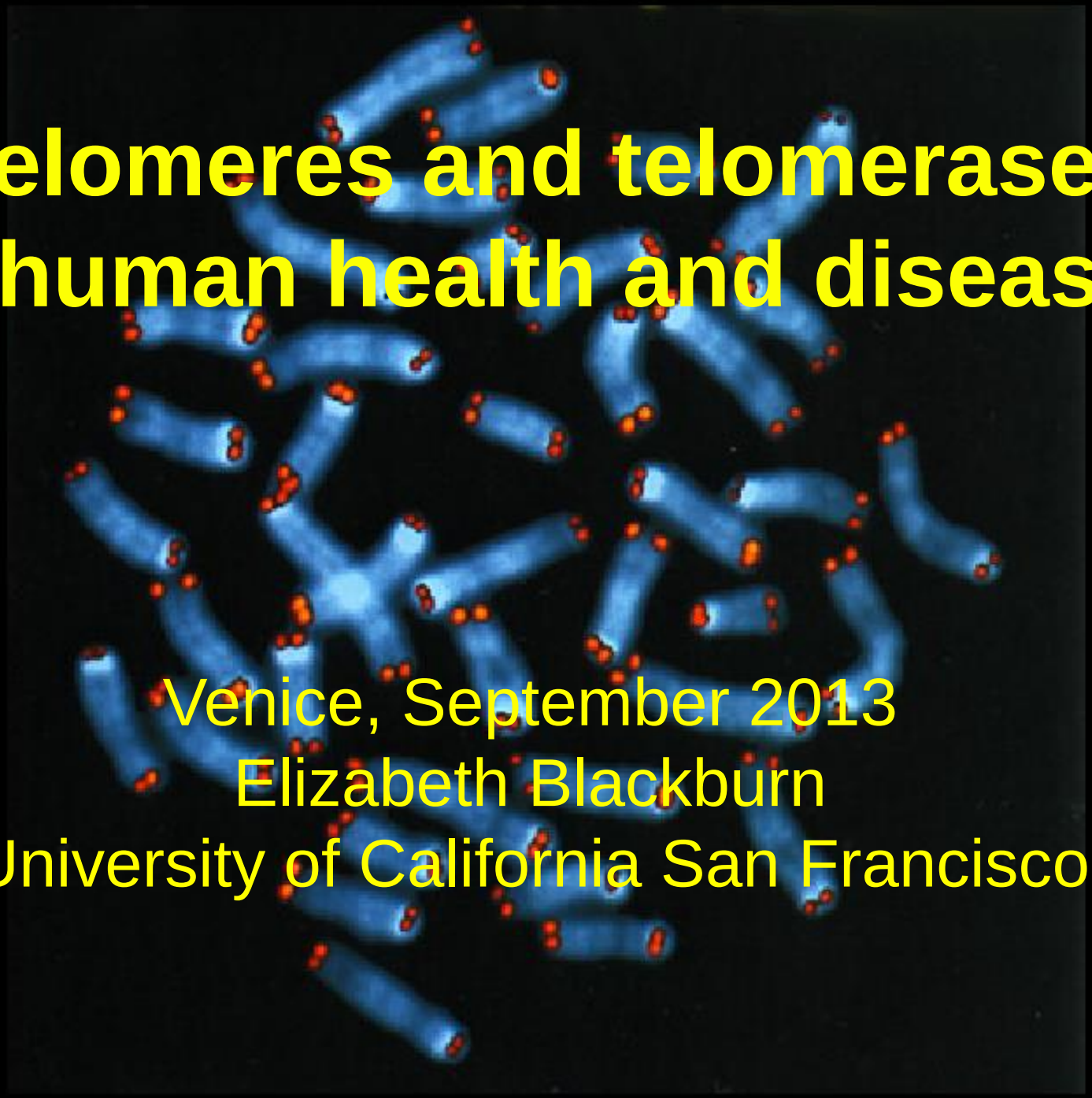
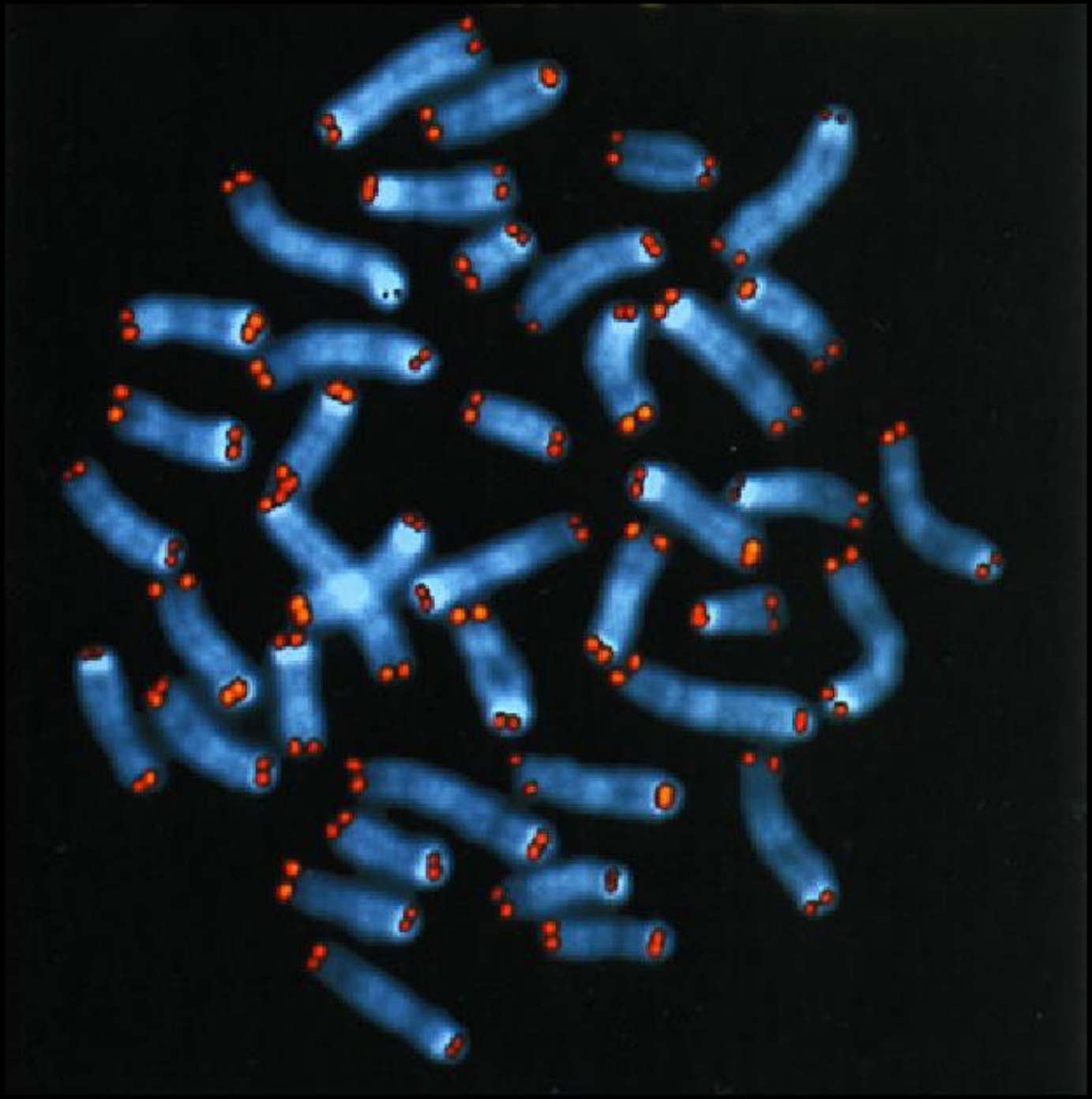
Telomeres and telomerase in human health and disease

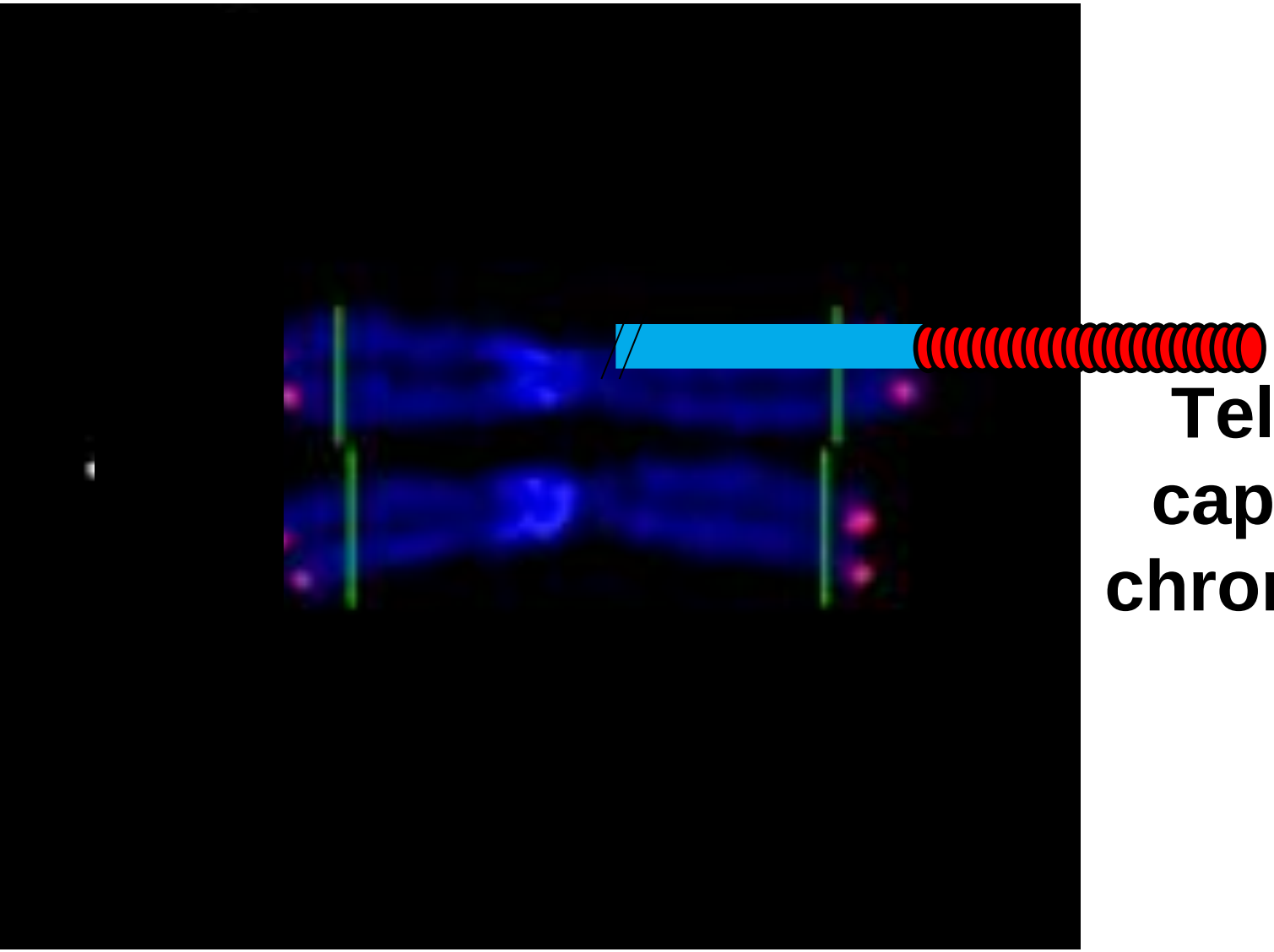


Venice, September 2013

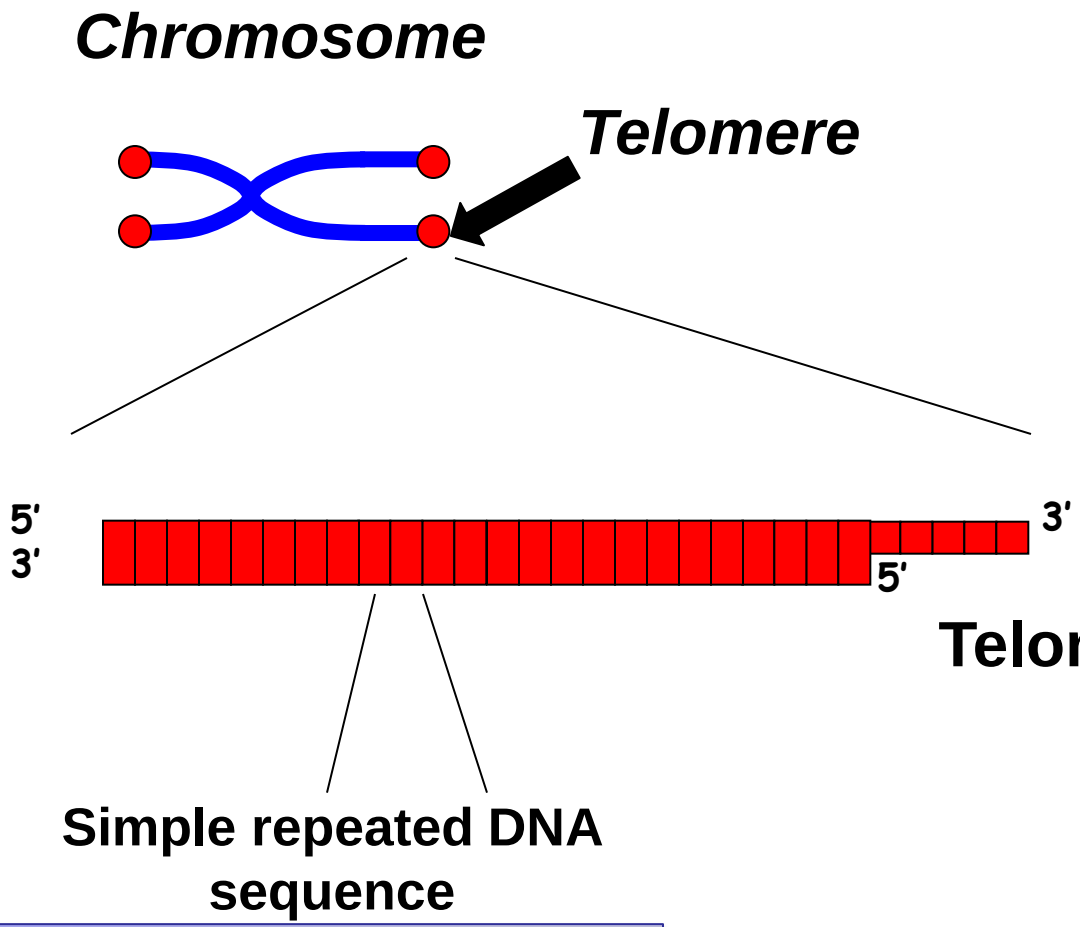
Elizabeth Blackburn
University of California San Francisco

What are telomeres and why should we care?





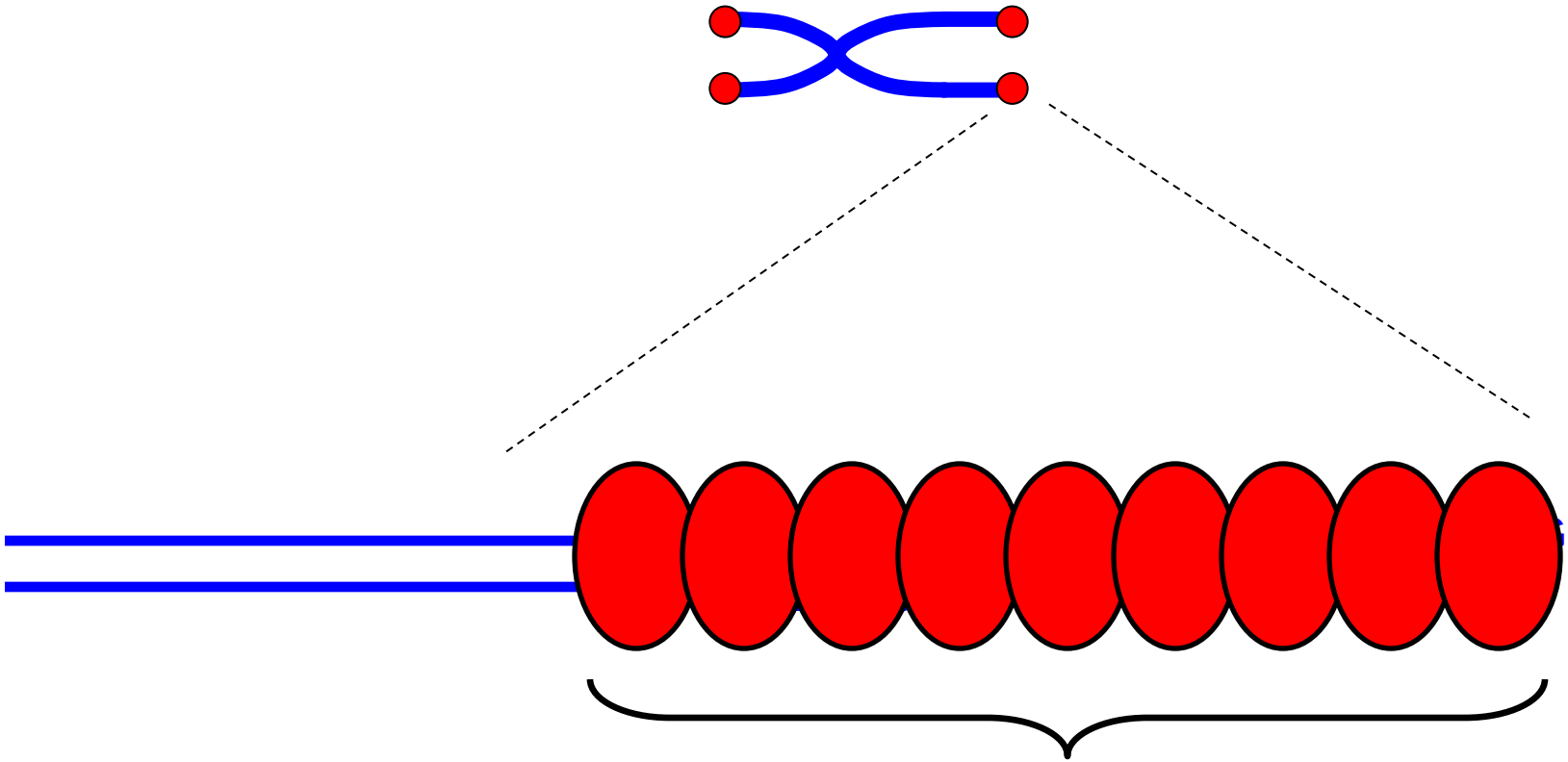
Telomeres cap ends of chromosomes



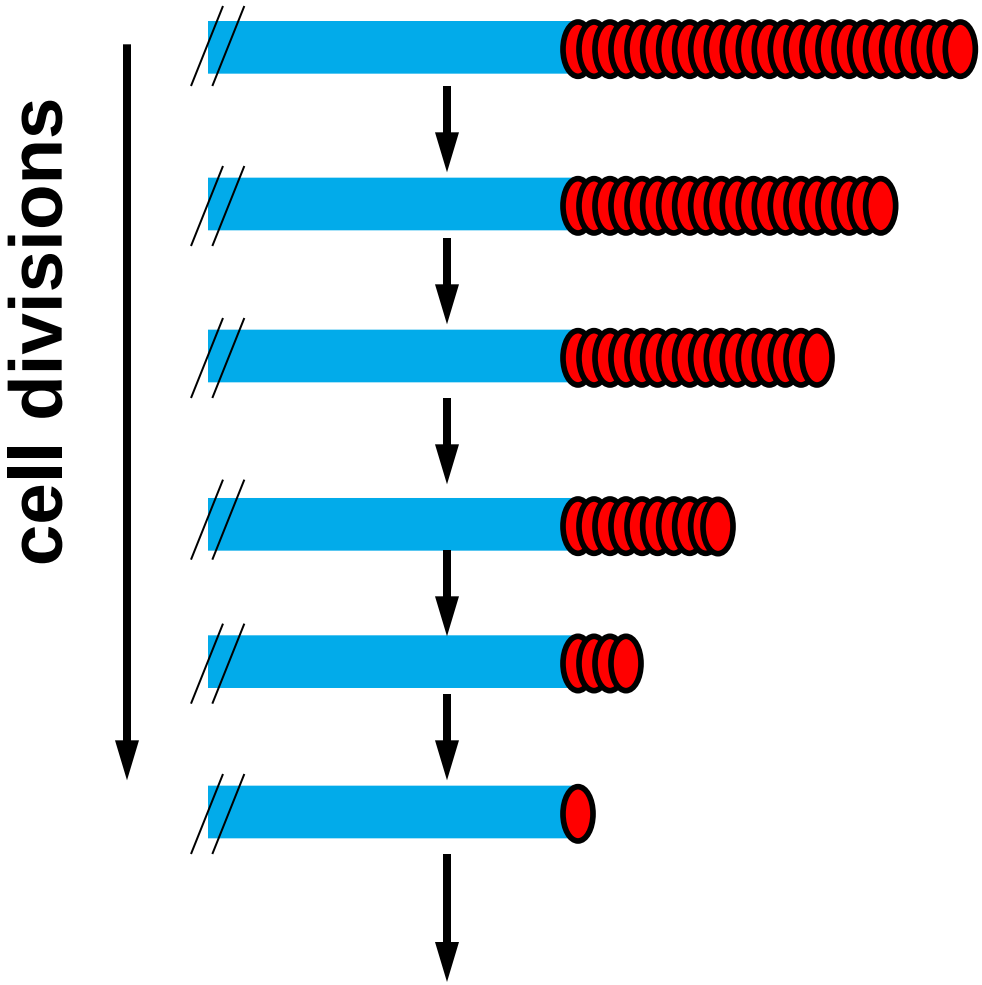
Telomeric DNA Structure

Blackburn and Gall, 1978

The Telomere – the protective cap at every chromosome end



Predicted, if DNA replication alone acts on DNA: Loss of DNA from the chromosome end



Eventual senescence

Watson, 1972, Olovnikov, 1971

DISCOVERY OF TELOMERASE

SYNTHETIC TELOMERE IN TEST TUBE

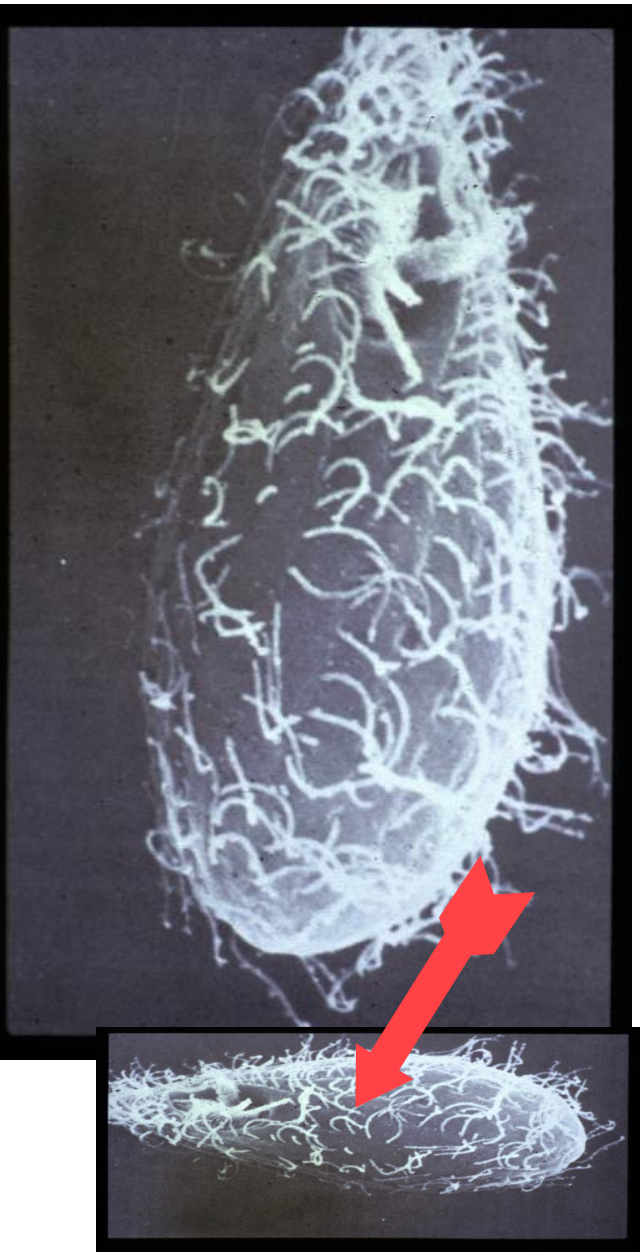
5' G G G G T T G G G G T T G G G G T T 3' OH

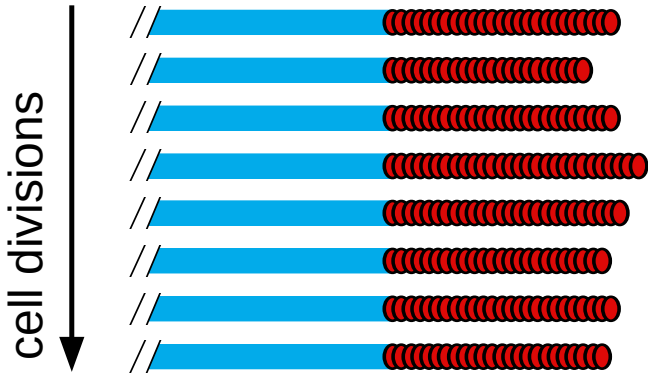
Tetrahymena cell extract
Mg++
dGTP + TTP

G G G G T T G G G G T T G G G G T T G G G G T T G G

Greider and Blackburn, 1985

Tetrahymena thermophila

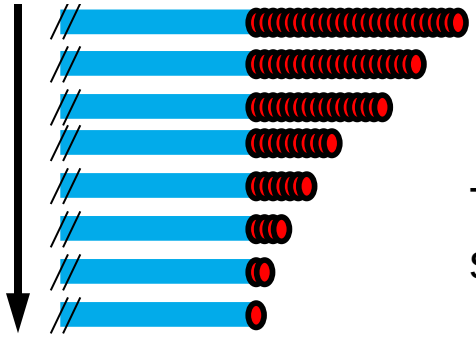




Telomeres replenished by telomerase

Cells are immortal

Plenty of telomerase



Genetically inactivate telomerase

Telomeres progressively shorten

Tetrahymena ceased divisions

They become “mortal”

Yu, Bradley, Attardi and Blackburn, 1990

“Immortal”

↓

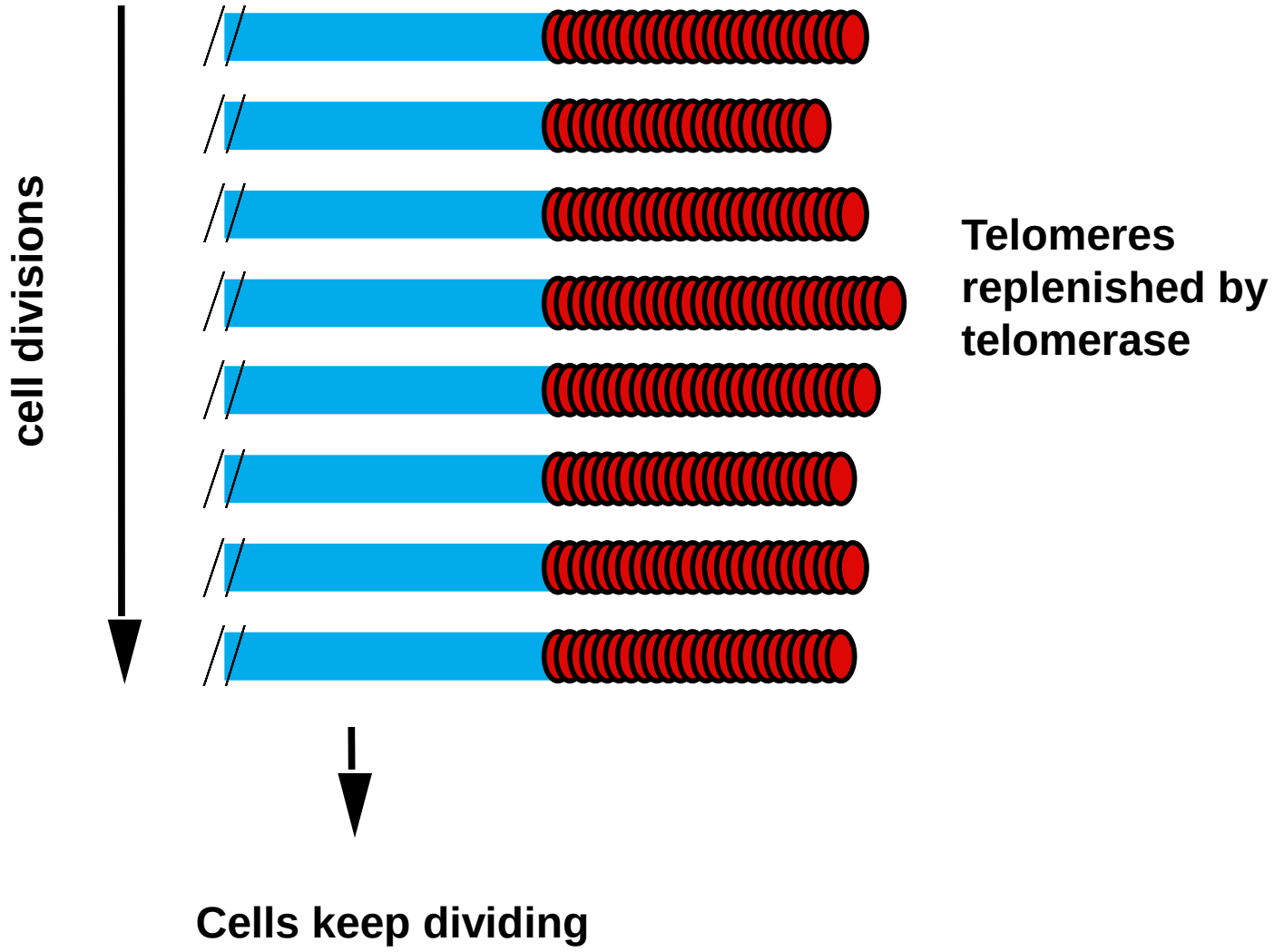
Mutate telomerase

↓

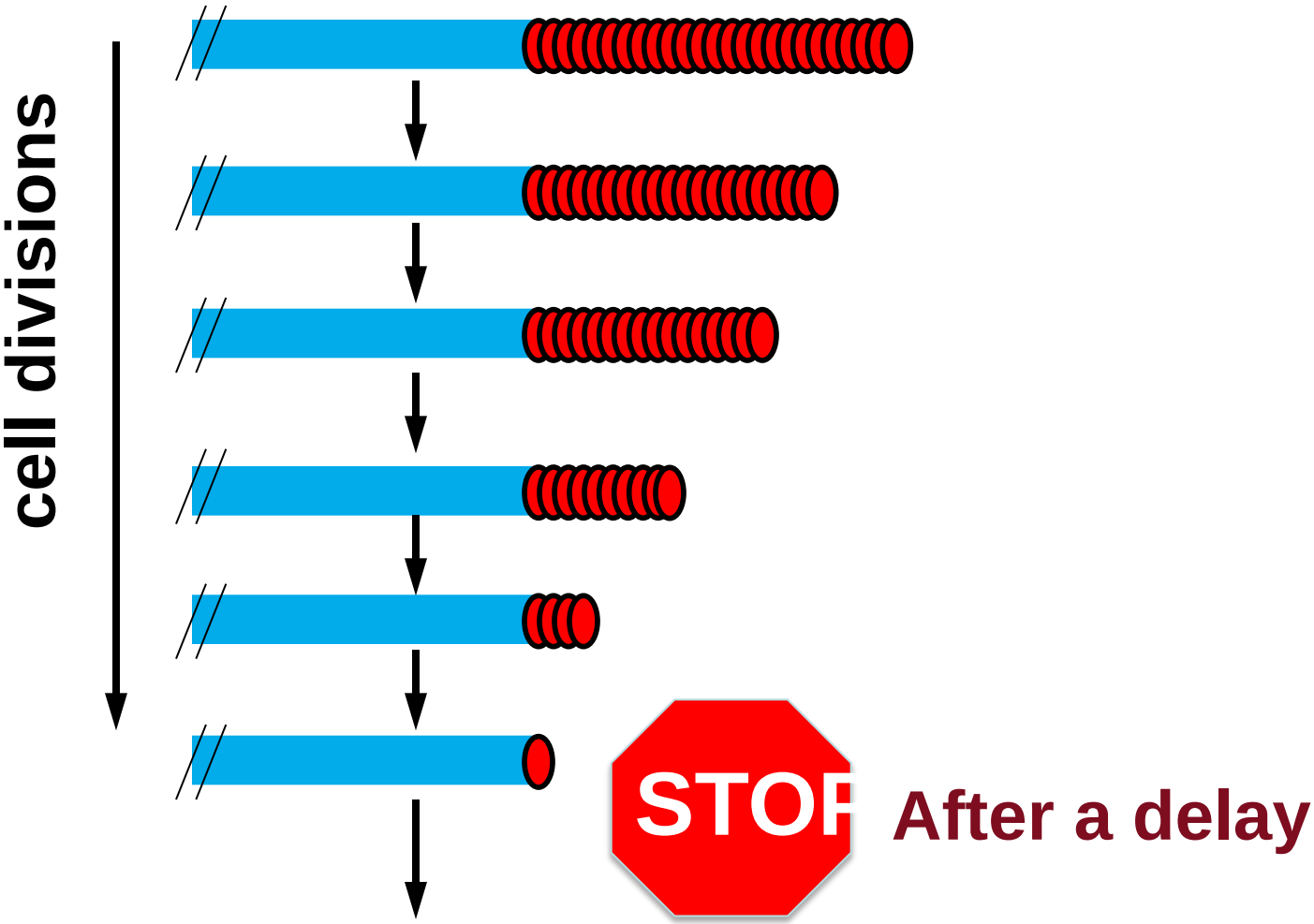
“Mortal”

Yu, Bradley, Attardi and Blackburn, 1990

Telomerase maintains the ends of chromosomes



Without telomerase



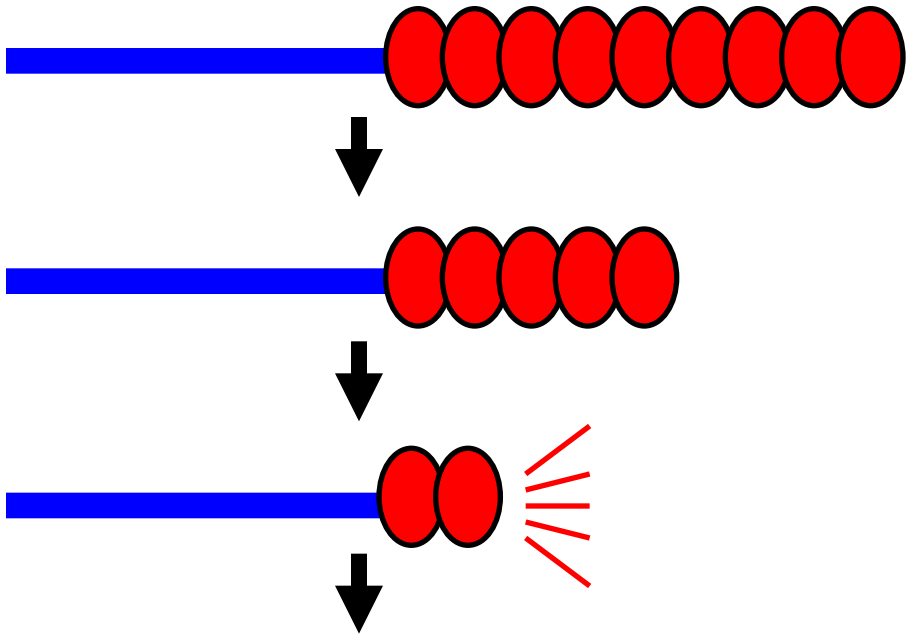
Senescence; cell malfunction; genomic instability

How do we age?

A multi-faceted process

- increased susceptibility to diseases

Many normal human cells have limiting or no telomerase and their telomeres shorten with age

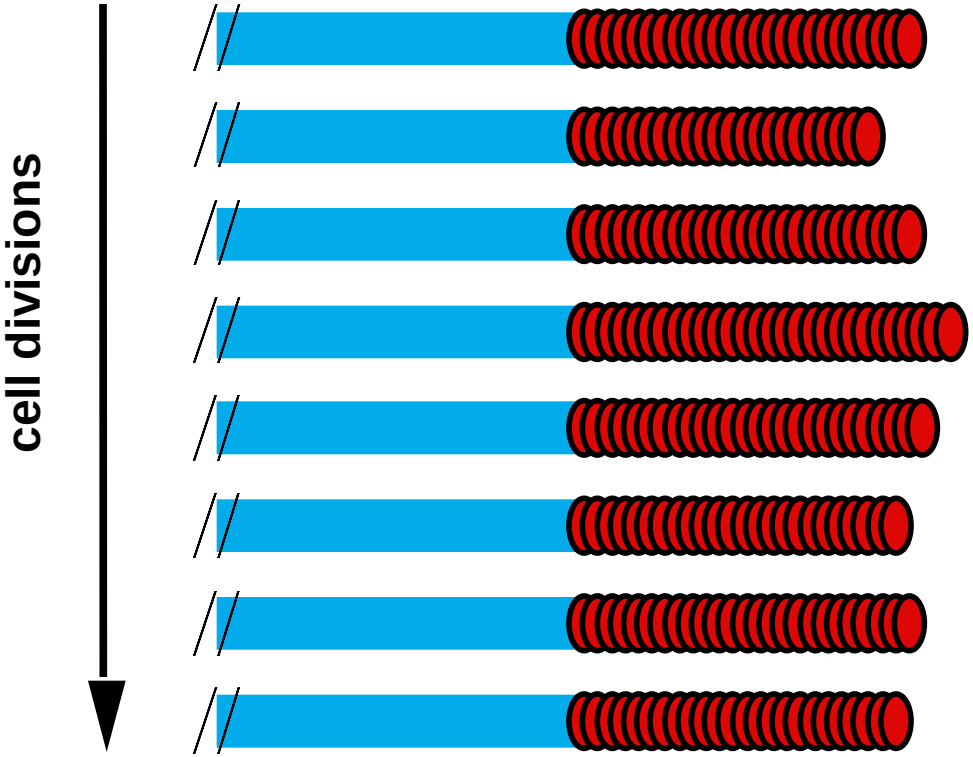


Senescence Death ?

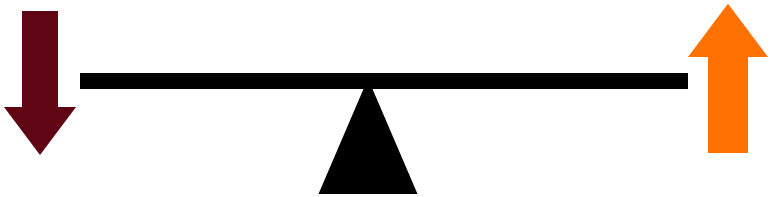
http://pebblez.com/pictures/soapstone/twisted-8in-candle-holders/candle-holders-9.jpg

WHAT CAN SAVE THE CELLS? <u>Telomerase:</u>

- **Active:** **stem cells, germ cells**
- **<u>Low/none</u>:** **many normal adult cell types**



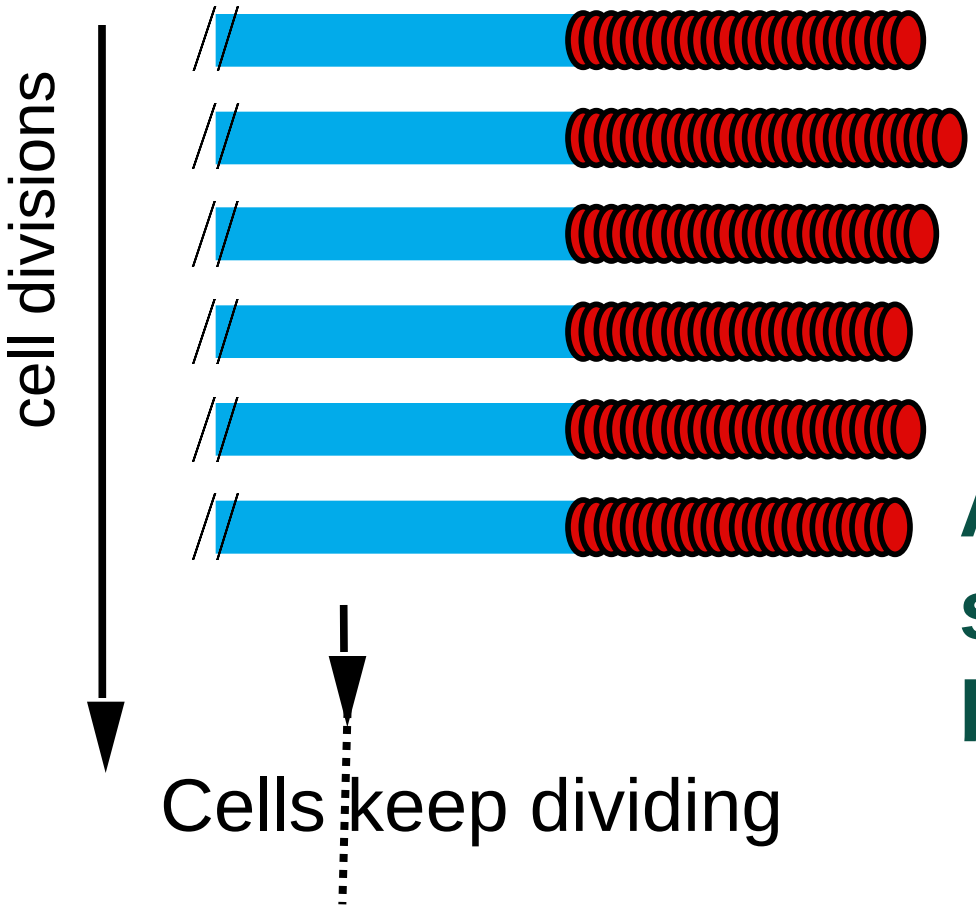
Plenty of telomerase:

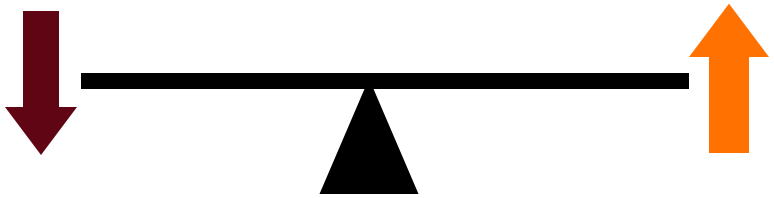


Addition and shortening stay balanced

Cells keep dividing

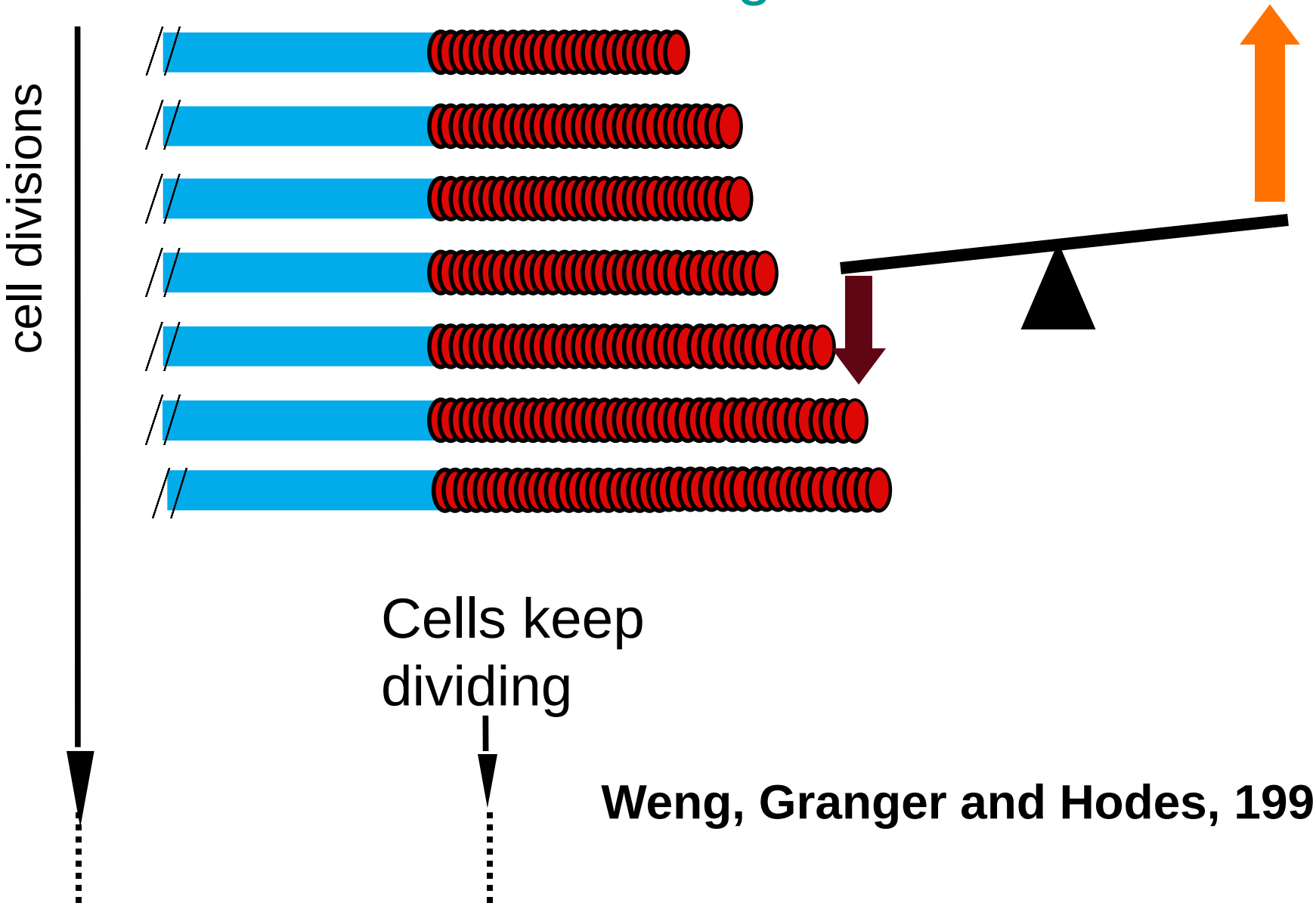
Plenty of telomerase:





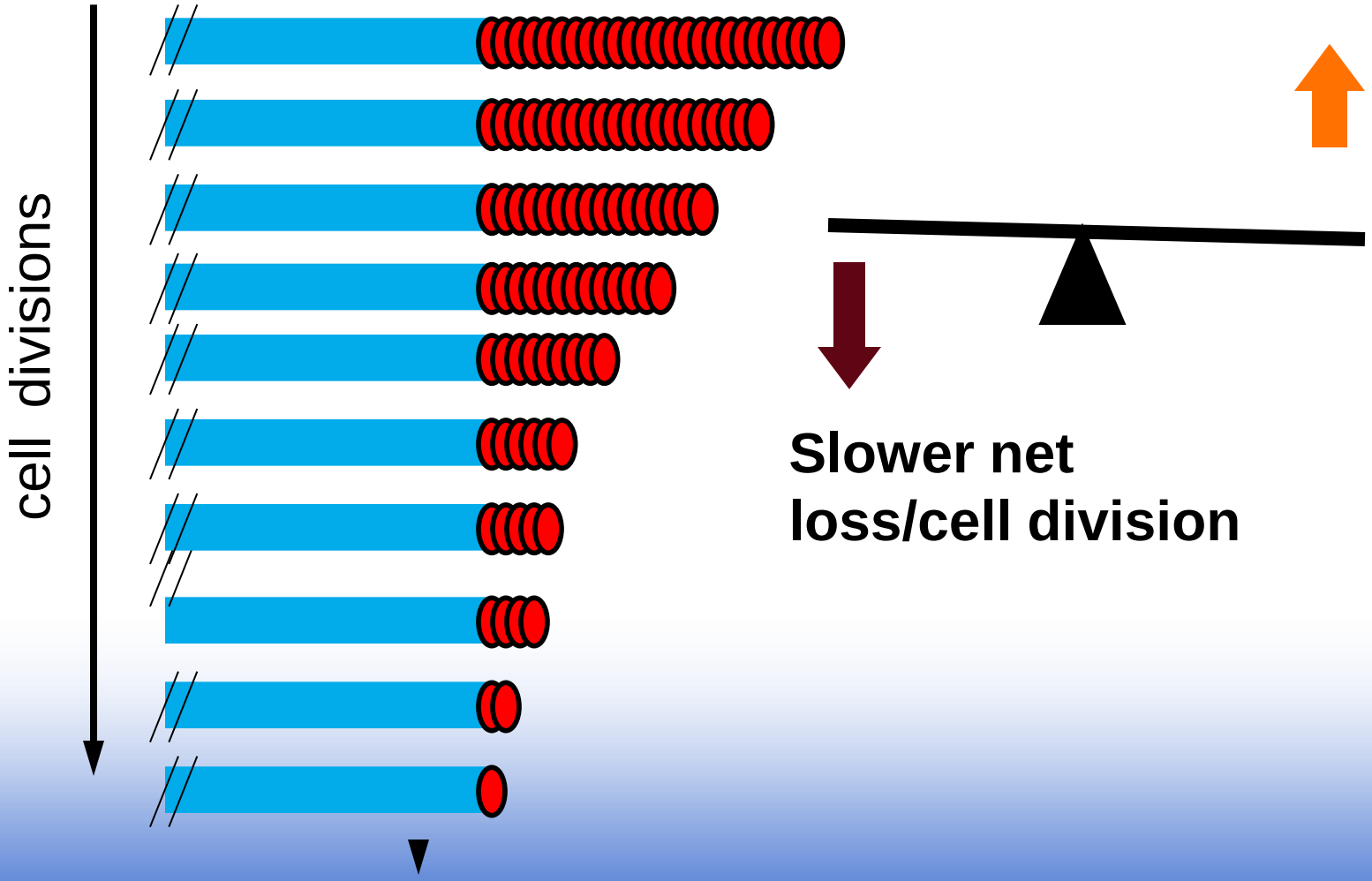
Addition and shortening stay balanced

Upregulated telomerase in humans: telomeres can grow in vivo



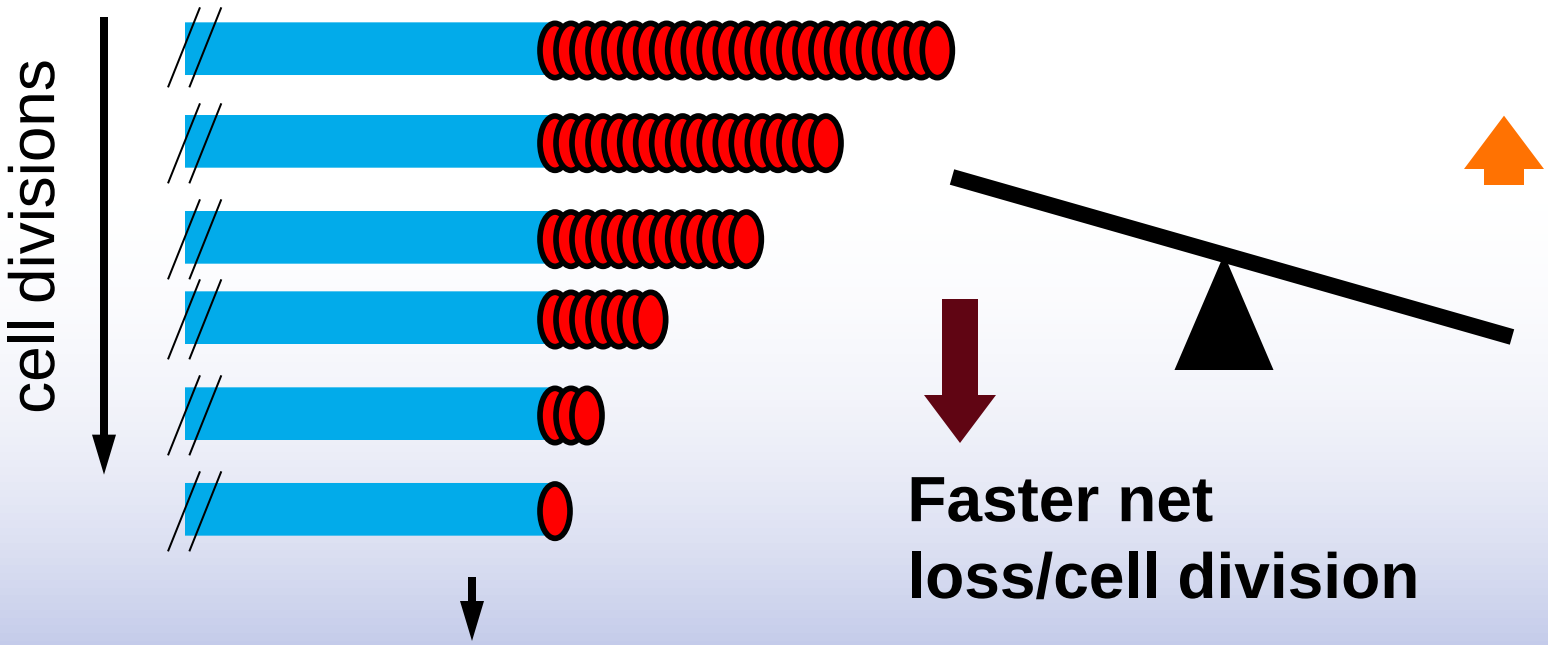
Weng, Granger and Hodes, 1997

Predicted, if some telomerase:
Slow loss of DNA from chromosome ends



Senescence/malfunction comes later

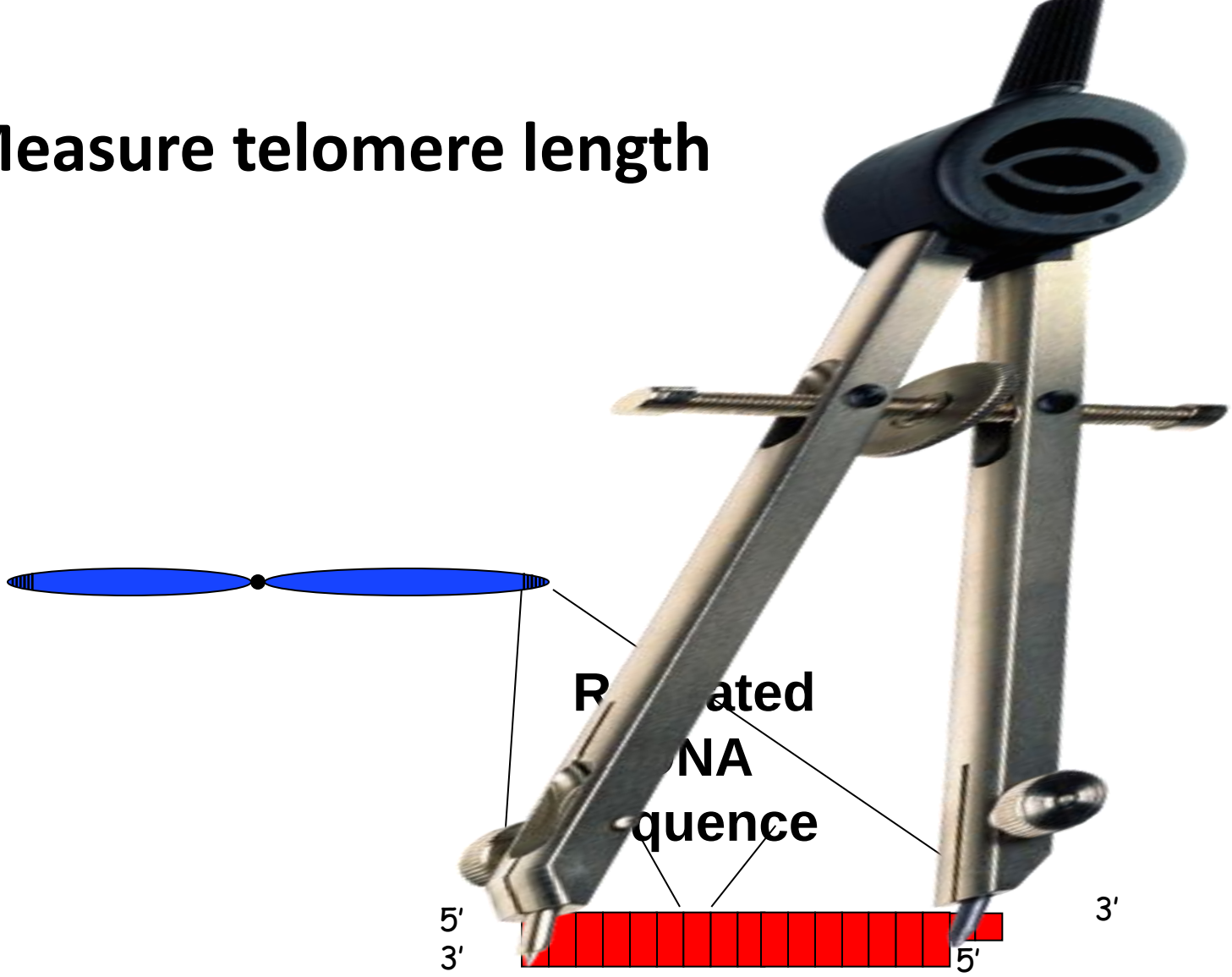
Predicted, if less telomerase:
Faster loss of DNA from chromosome ends



Senescence /malfunction sooner

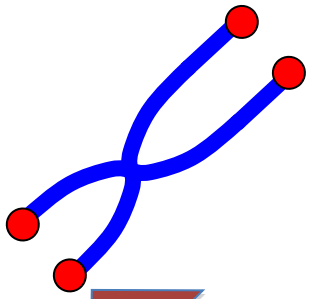
- genetic
- environment/life factors

Measure telomere length



Telomeric DNA

In the general population telomere shortness is associated with diseases

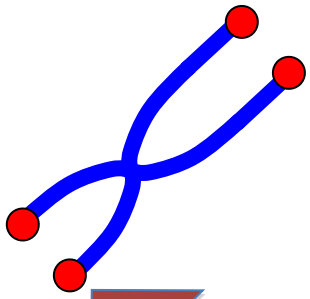


Shorter Telomeres

Impaired immune fn.
Cancers
Lung Disease
Heart disease
Diabetes
Vascular. dementia
Osteoarthritis
Risk factors eg smoking

After correcting
for age and multiple factors,
major common diseases of aging have been
linked to shorter telomeres in normal cells
(many independent studies and cohorts)

In general populations telomere shortness <u>precedes</u> the future onset of diseases of aging <u>and earlier mortality</u>



Shorter Telomeres

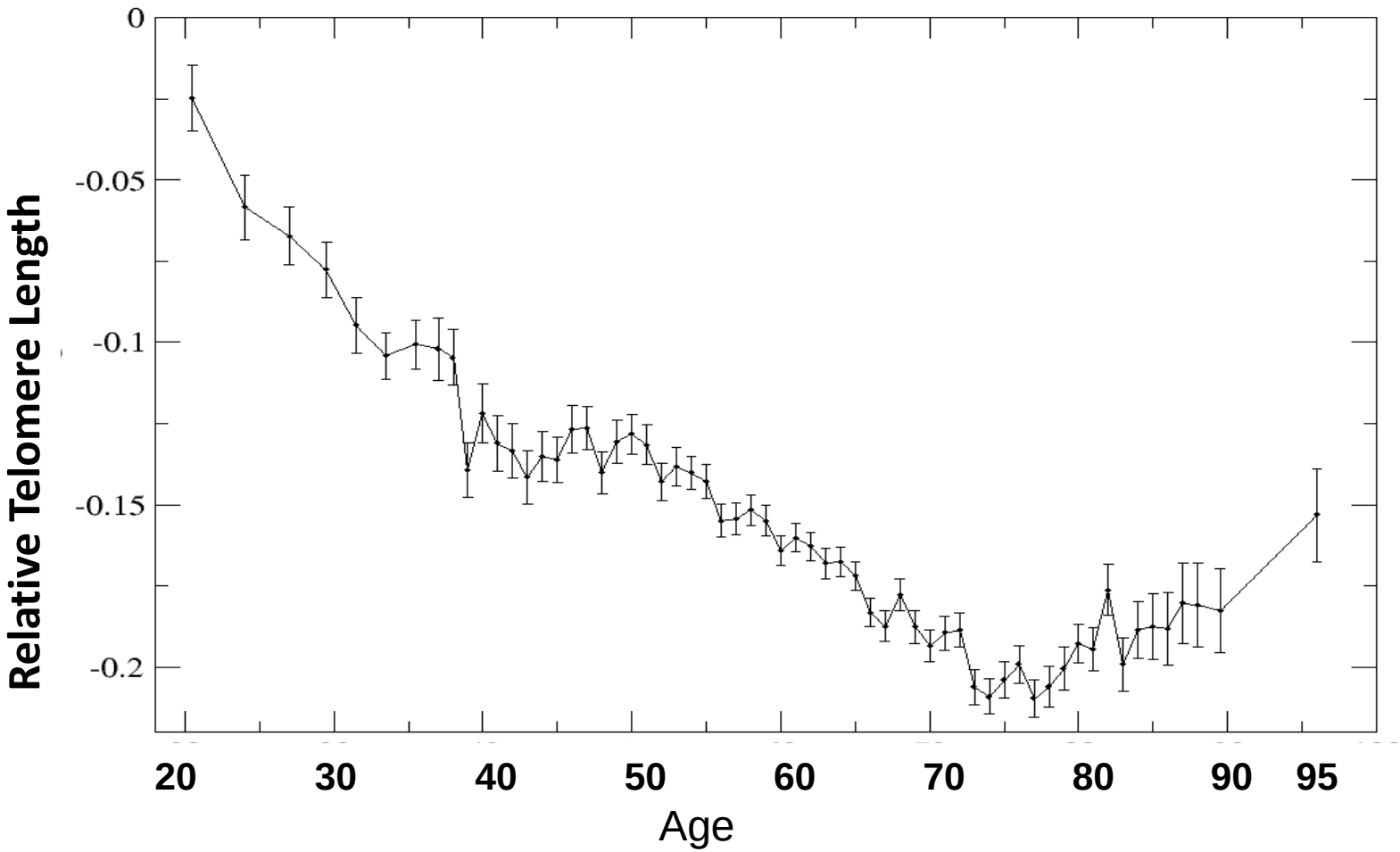
Earlier Mortality
Impaired immune fn.
Cancers
Lung Disease
Heart disease
Diabetes
Dementias

After correcting
for age and multiple factors,
major common diseases of aging are anticipated by
shorter telomeres in normal cells
(many independent studies and cohorts)

TELOMERE LENGTH AND MORTALITY

Cross sectional relationship of mean human telomere length with age. N = 100,000 people

Mean Telomere Length (cells in saliva). Error bars are 1 s.e. of mean

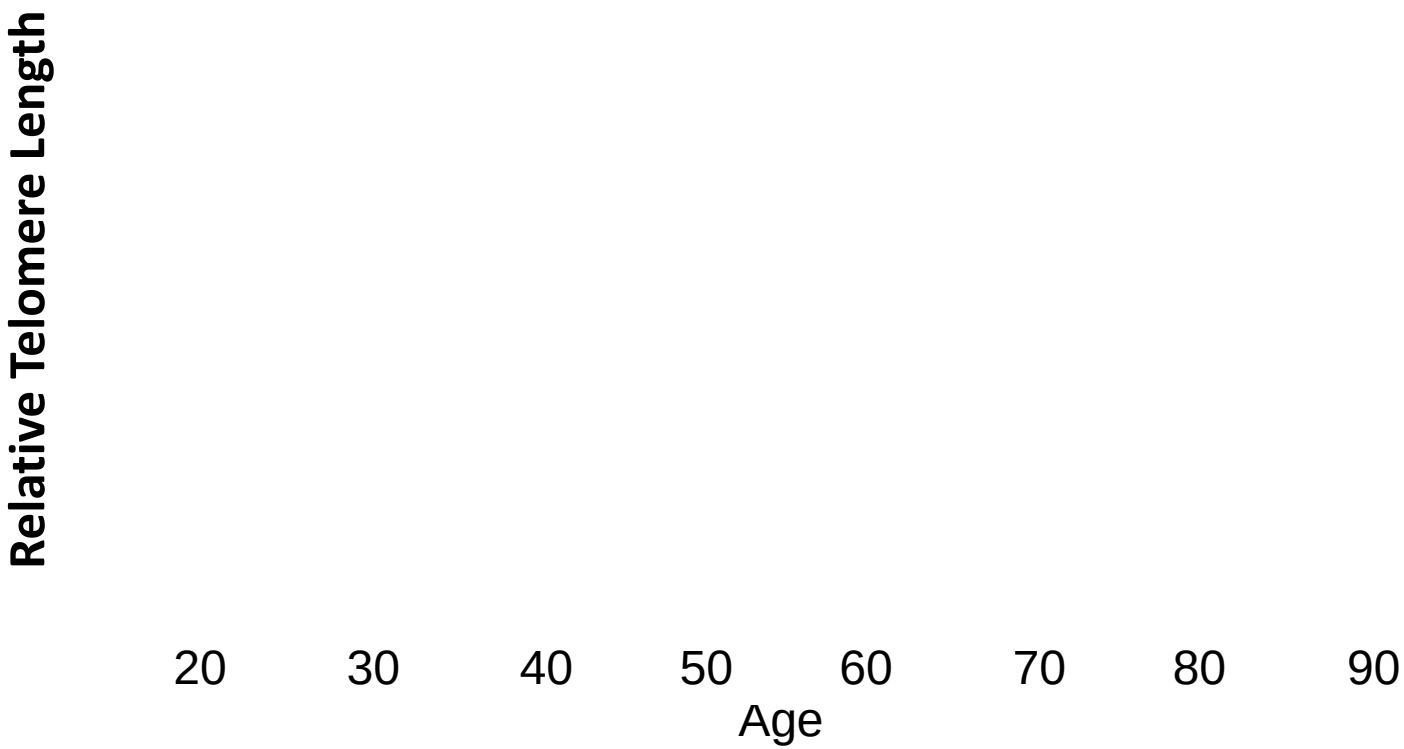


Kaiser Permanente Research Program in Genes, Environment and Health (RPGEH) Genetic Epidemiology Research on Aging (GERA) Cohort

Lapham, Kvale et al, unpubl.

Cross sectional relationship of mean human telomere length with age, separately for males and females.

Mean Telomere Length (cells in saliva). Error bars are 1 s.e. of mean



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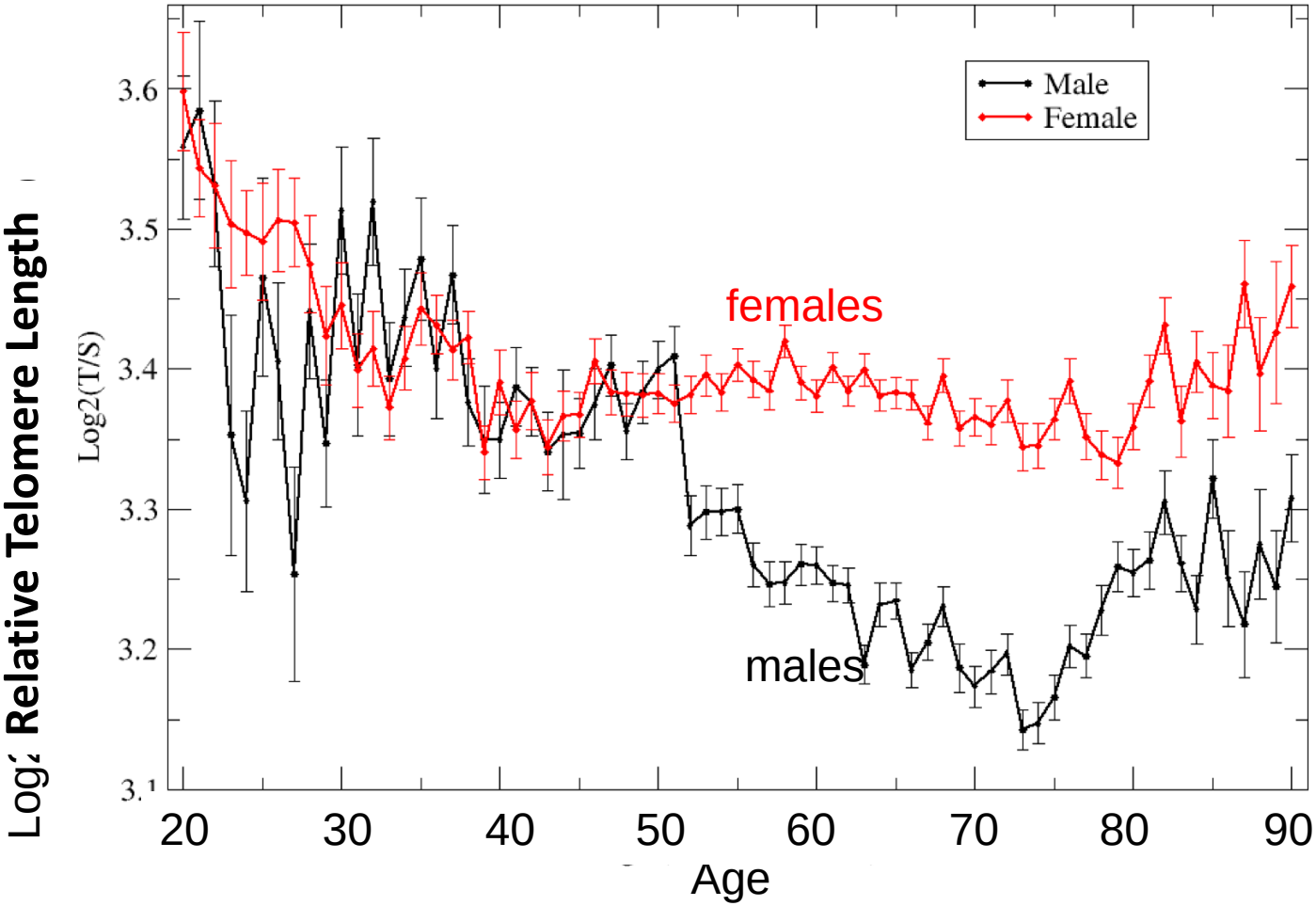


Kaiser Permanente Research Program in Genes, Environment and Health (RPGEH) Genetic Epidemiology Research on Aging (GERA) Cohort

Lapham, Kvale et al, unpubl.

Odds of all- causes mortality within 3 yrs of telomere measure

2009 2010 2011 2012

Telomere length at this time was measured (N= 100,000)

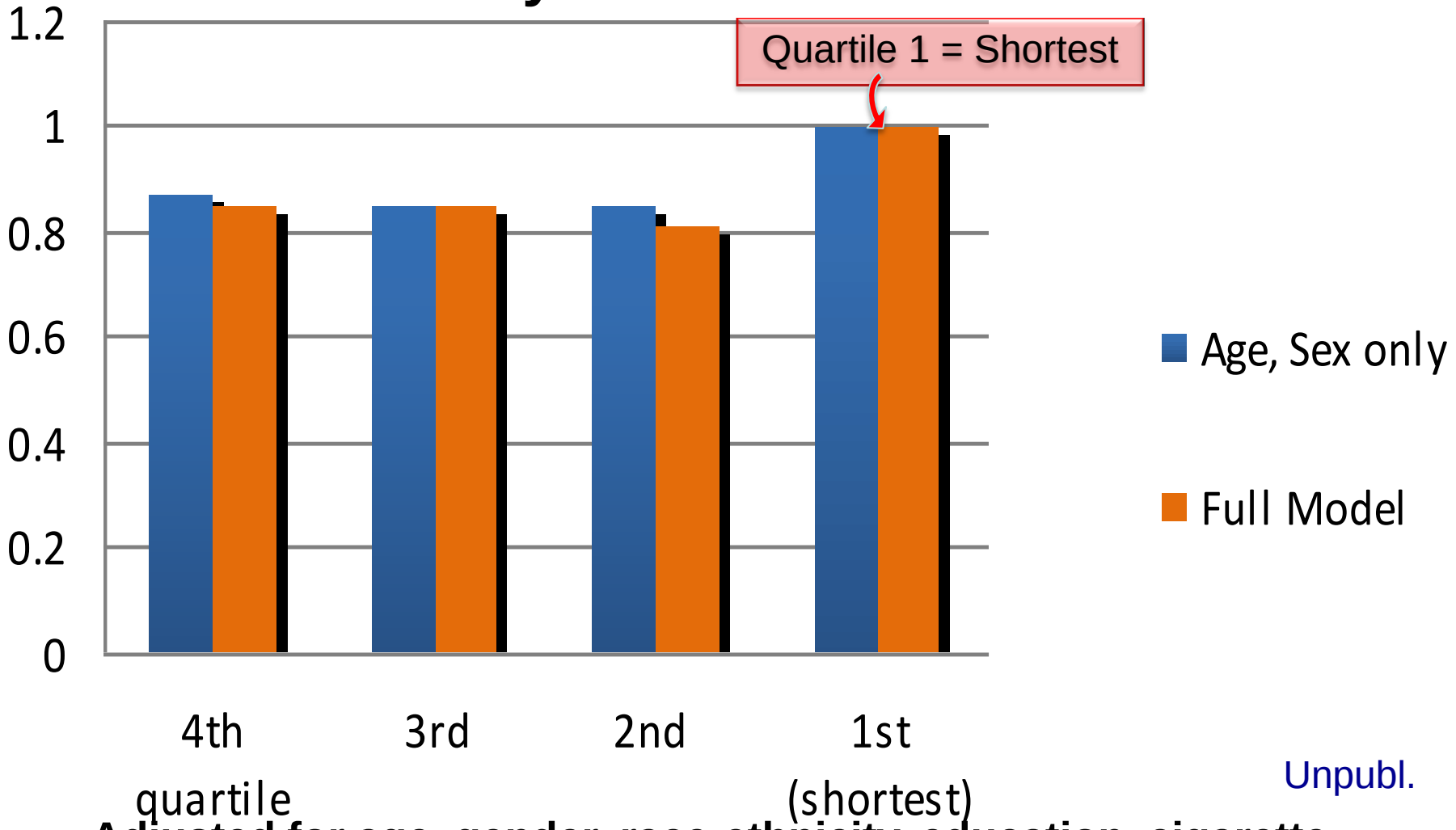
Who had died within the 3 years since telomere length measure (N= ~ 2,500)

Compare to
Mean Baseline Telomere Length

a Adjusted for age, gender, race-ethnicity, education, cigarette pack years, physical activity, alcohol drinks per week, and BMI

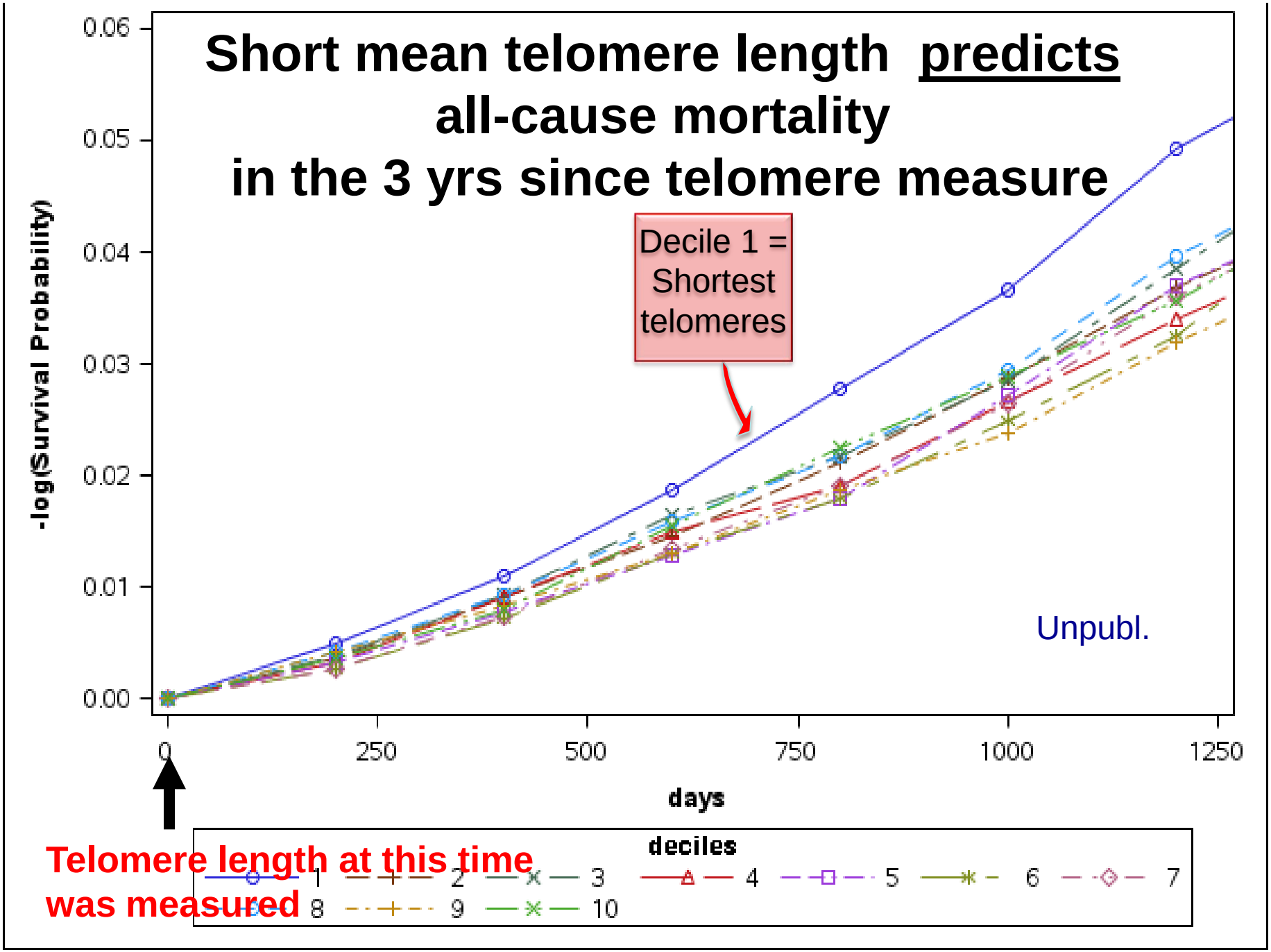
Unpubl.

Telomere shortness predicts all-cause mortality in the 3 yrs since telomere measure

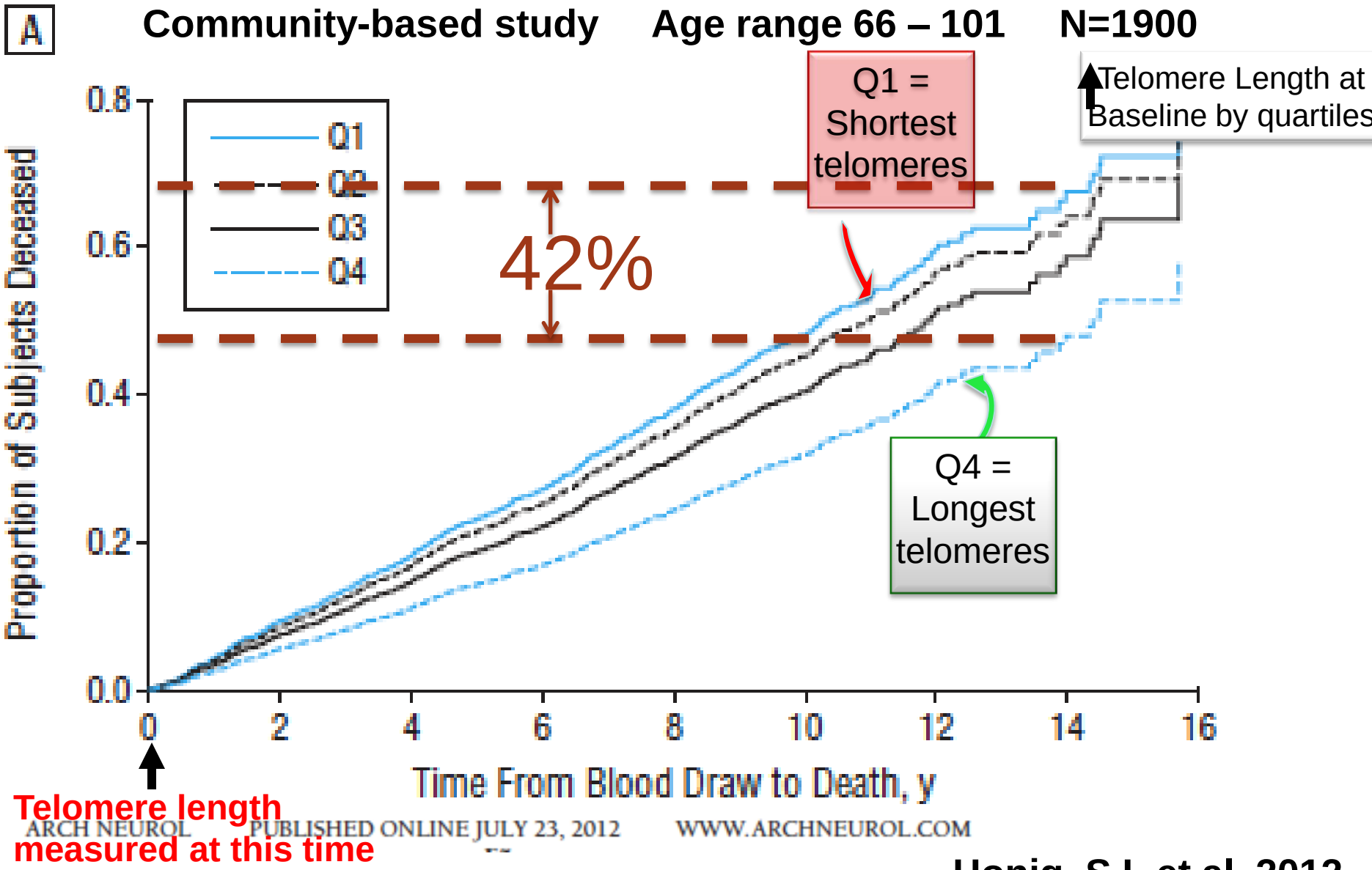


Unpubl.

[a] **Adjusted for age, gender, race-ethnicity, education, cigarette packyears, physical activity, alcohol drinks per week, and BMI**


Short mean telomere length predicts all-cause mortality in the 3 yrs since telomere measure
Decile 1 = Shortest telomeres
Unpubl.
-log(Survival Probability)
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
250
500
750
1000
1250
days
deciles
1
2
3
4
5
6
7
8
9
10
Telomere length at this time was measured

Short Mean Baseline Telomere Length in White Blood Cells Predicted All-causes Death



Honig, S.L et al. 2012

CAUSALITY

NON-GENETIC ***and*** ***GENETIC***

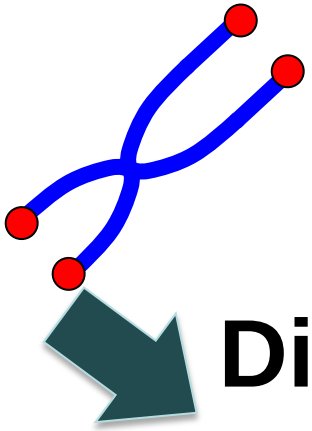
Environmental **Life events/behavior**

CAUSALITY

– Part 1

patterns of inheritance

Too-short Telomeres



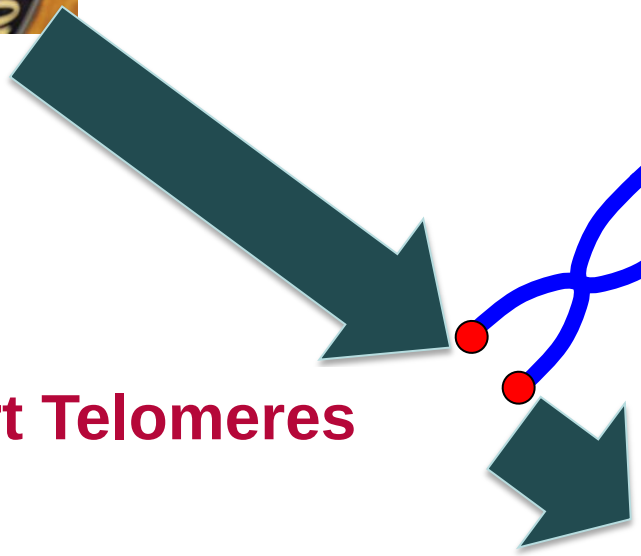
Disease impact

How do human beings respond if they have a mutation causing only half the usual telomerase level?

Lessons learned 1:

GENETICS tells us:

Lessons learned from
<u>Rare</u> Mutations in People's Telomerase Genes



Short Telomeres

Early death
Certain cancers
Immune system failure
Pulm. Fibrosis
Cirrhosis
Diabetes

GENETICS tells us:

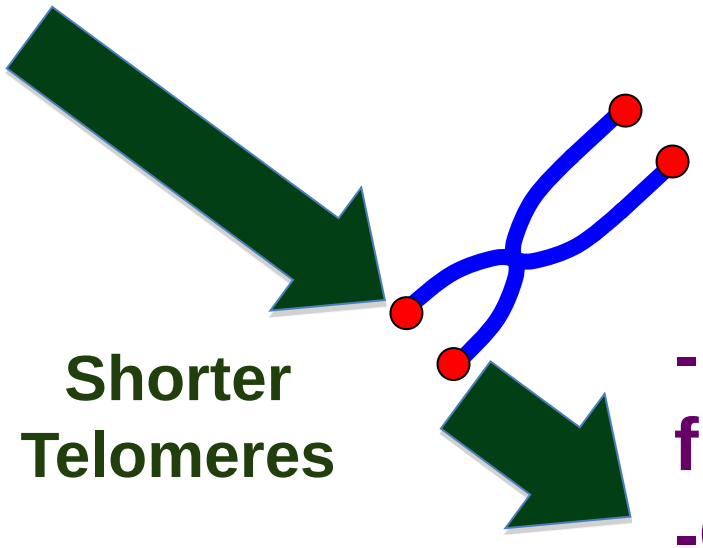
Just
2x too little
telomerase
causes some
cancers

Lessons learned 2:

GENETICS tells us:

Some COMMON variations in genes known to maintain telomeres - that can <u>cause</u> telomere shortness - <u>raise risks for common</u> diseases of aging.

COMMON variation in telomere/telomerase genes



Shorter Telomeres

e.g.
- Pulmonary fibrosis
-Coronary artery disease

Codd et al, 2013

Lessons learned 3:

GENETICS tells us:

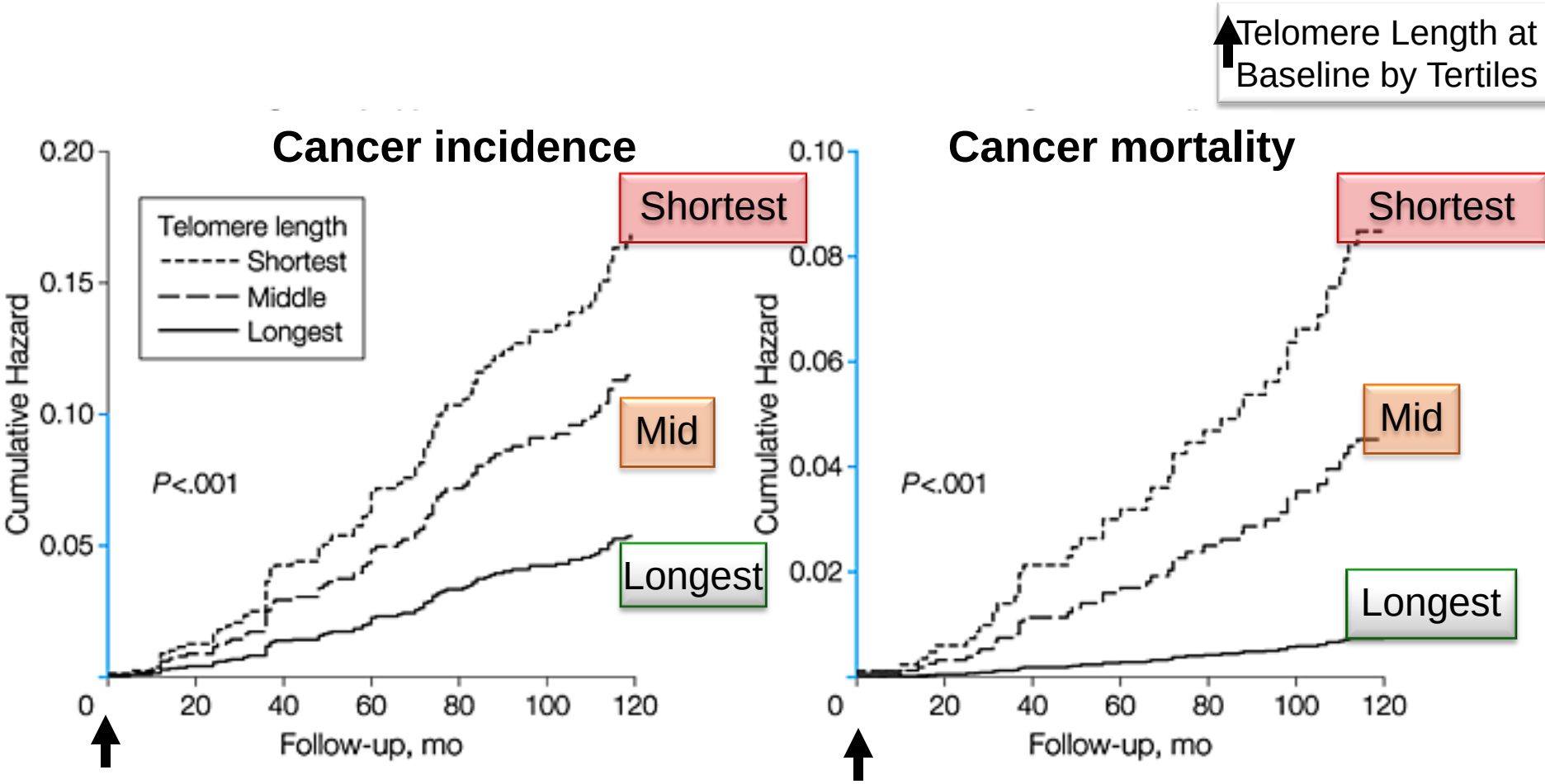
Other COMMON variations of genes known to maintain telomeres are especially likely to be in <u>centenarians</u>.

(Better maintenance of telomeres?)

COMMON variant SNPS – eg TERT, TERC, others

Deelen et al, 2011

Telomere shortness in White Blood Cells Predicts Future Cancer incidence and Cancer Mortality



Telomere length measured at this time

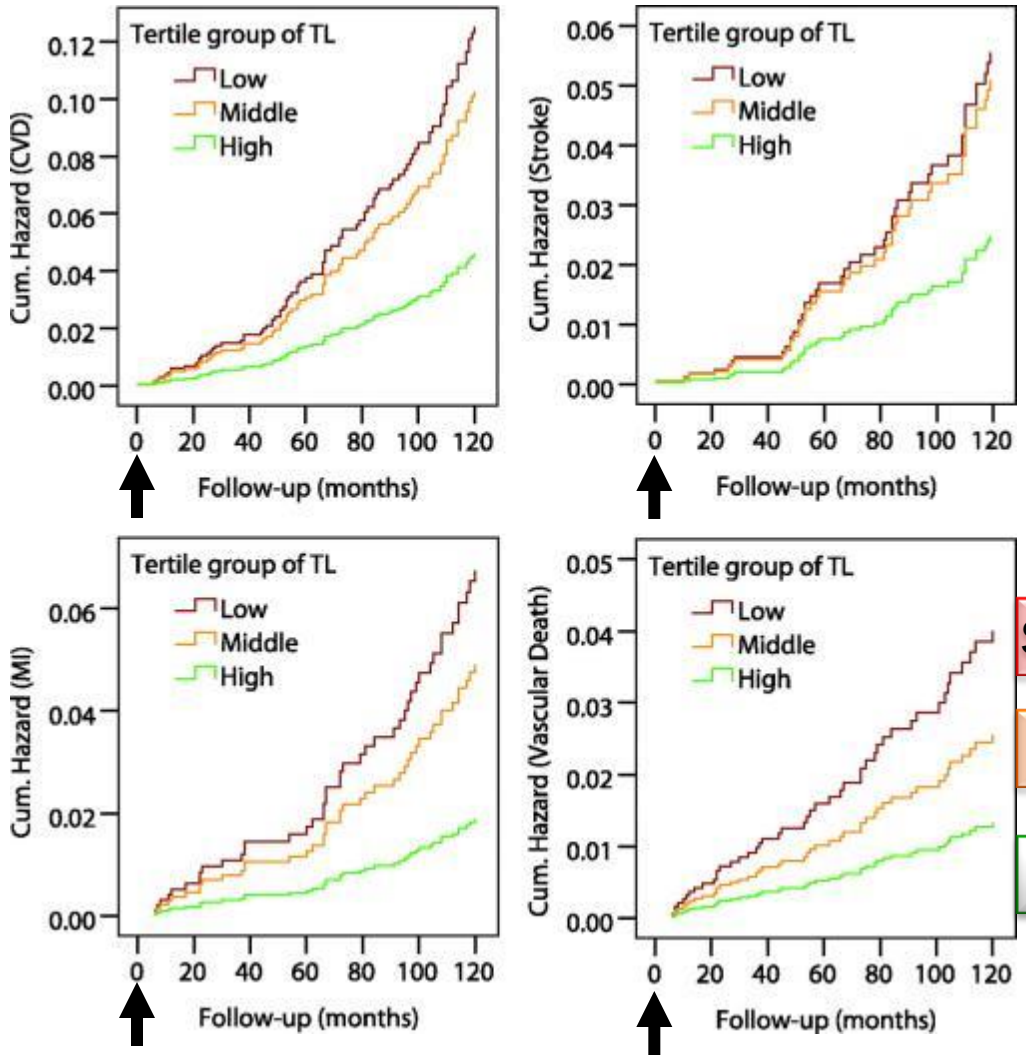
Willeit, P. et al. JAMA 2010;304:69-75

Cc

Short Telomere Length Predicts CVD

CVD

MI



Telomere Length at Baseline by Tertiles

Stroke

Vasc. Death

Shortest

Mid

Longest

Willeit P et al. Arterioscler Thromb Vasc Biol 2010;30:1649-1656

American Heart Association

Learn and Live

Lessons learned 4:

GENETICS tells us:

Just
2x too little
telomerase
causes cancers

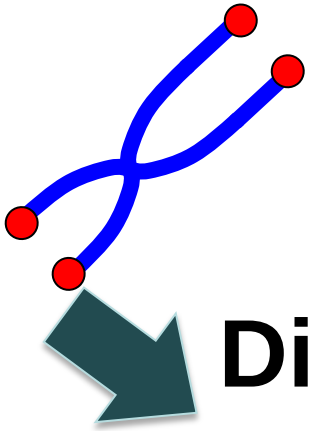
BUT
ALSO

Just 2x
too much
telomerase gene
expression
causes cancers

We live balanced on a knife-edge

GENETICS tells us:

Too-short Telomeres



Disease impact

NON-GENETIC ***and***

Environmental **Life events/behavior**

CAUSALITY – Part 2

WHAT CAN INFLUENCE TELOMERE MAINTENANCE IN HUMANS

?

A story from 2500 years ago: how stress accelerates aging

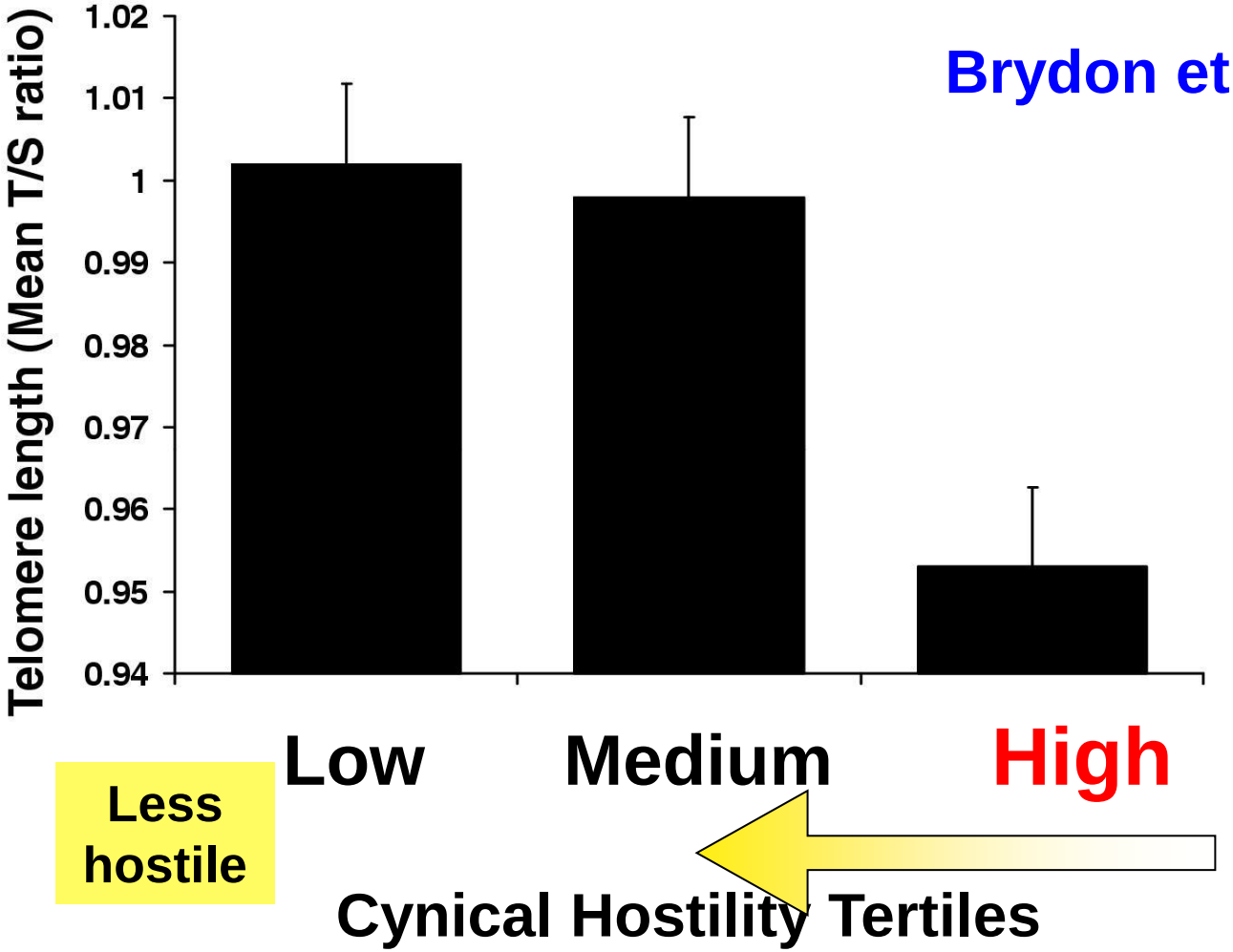

Chronic psychological stress
Disease Impact eg, heart disease

Stressors and Shortened Telomeres in Adults

- **Perceived stress** (Epel et al, 2004, Parks et al, 2009; Puterman 2010)
- **Caregiver stress** (Damjanovic, 2006; O' Donovan, 2011, Wolkowitz et al, 2011)
  - **- mothers of ill child**
  - **- dementia caregivers**
- **Major Depression** (Simon, 2006; Wolkowitz, 2011)
- **Former Domestic Abuse victim**

  (length of abuse) (Humphreys et al, 2011)

Cynical hostility level is associated with telomere shortness in the UK Whitehall Civil Servants Cohort



NON-GENETIC INFLUENCES

Factors in Earlier Life/Childhood are Associated with Persistent Effects on Telomere Shortness into Late Adult Life

1. Intrauterine maternal stress exposure (Entringer et al, 2011)

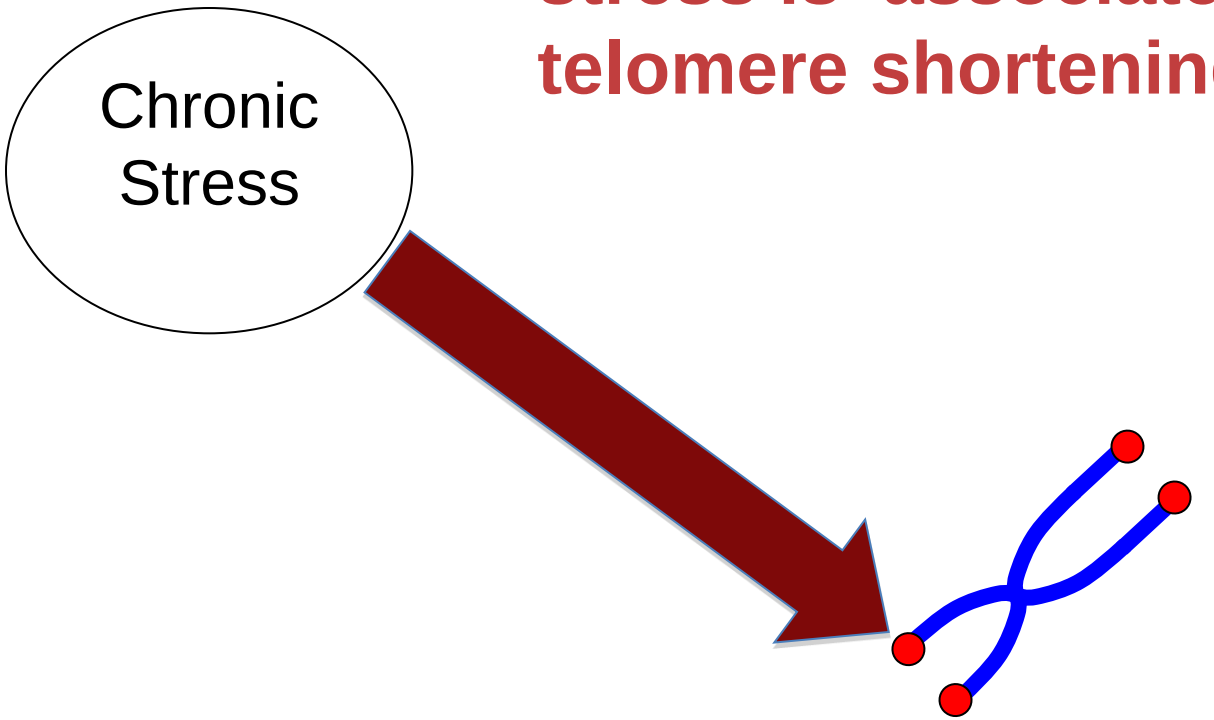
2. Cumulative exposure to childhood traumas (Tyrka, 2010, Kiecolt Glaser, 2011, Surtees, 2011)

3. Cumulative exposure to childhood traumatic events – in adults with PTSD (O'Donovan et al, 2011)

4. Low educational attainment (Steptoe et al, 2011; Lapham, Kvale, Risch, Shaefer, Blackburn, unpubl.)

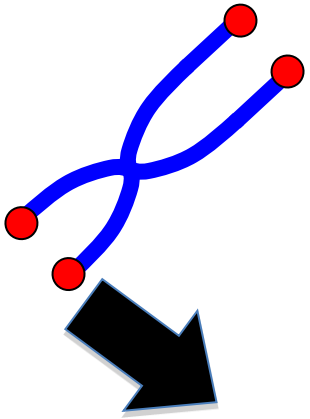
NON-GENETIC INFLUENCES

Chronic psychological stress is associated with telomere shortening



NON-GENETIC INFLUENCES

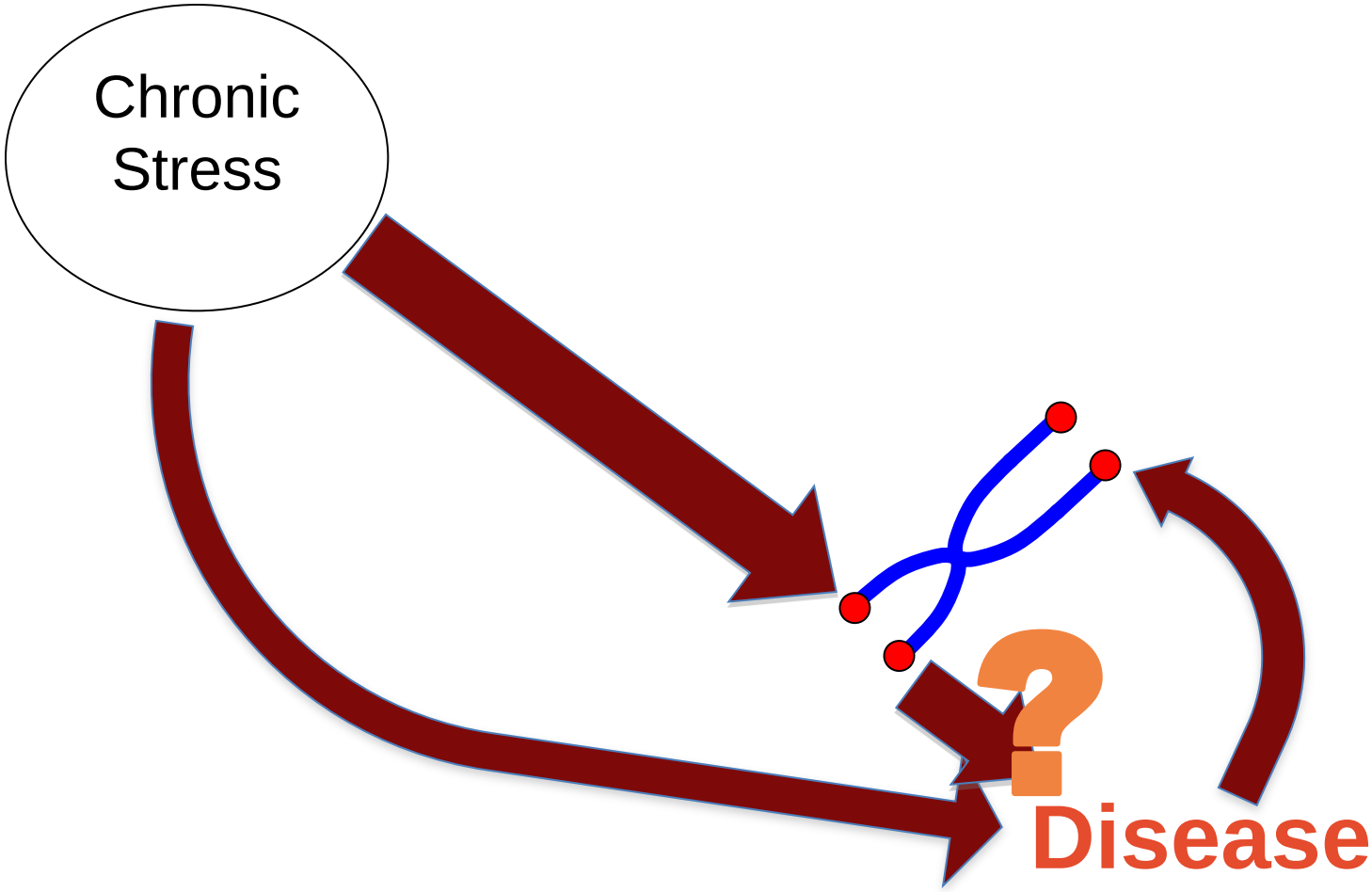
Shorter telomeres are associated with disease



Disease impact

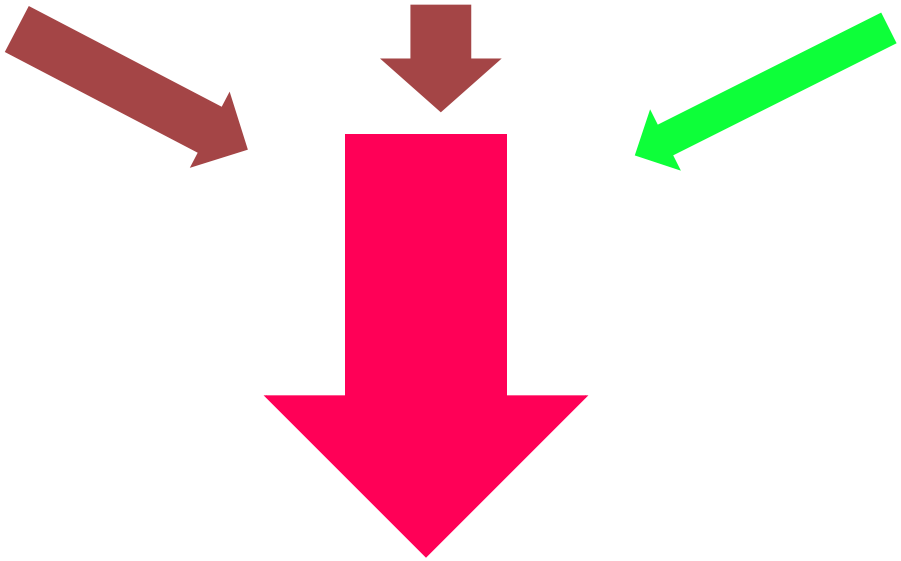
NON-GENETIC INFLUENCES

Connecting Chronic Psychological Stress, Telomeres and Disease Impact



NON-GENETIC ***and*** ***GENETIC***

Environmental **Life events/behavior**



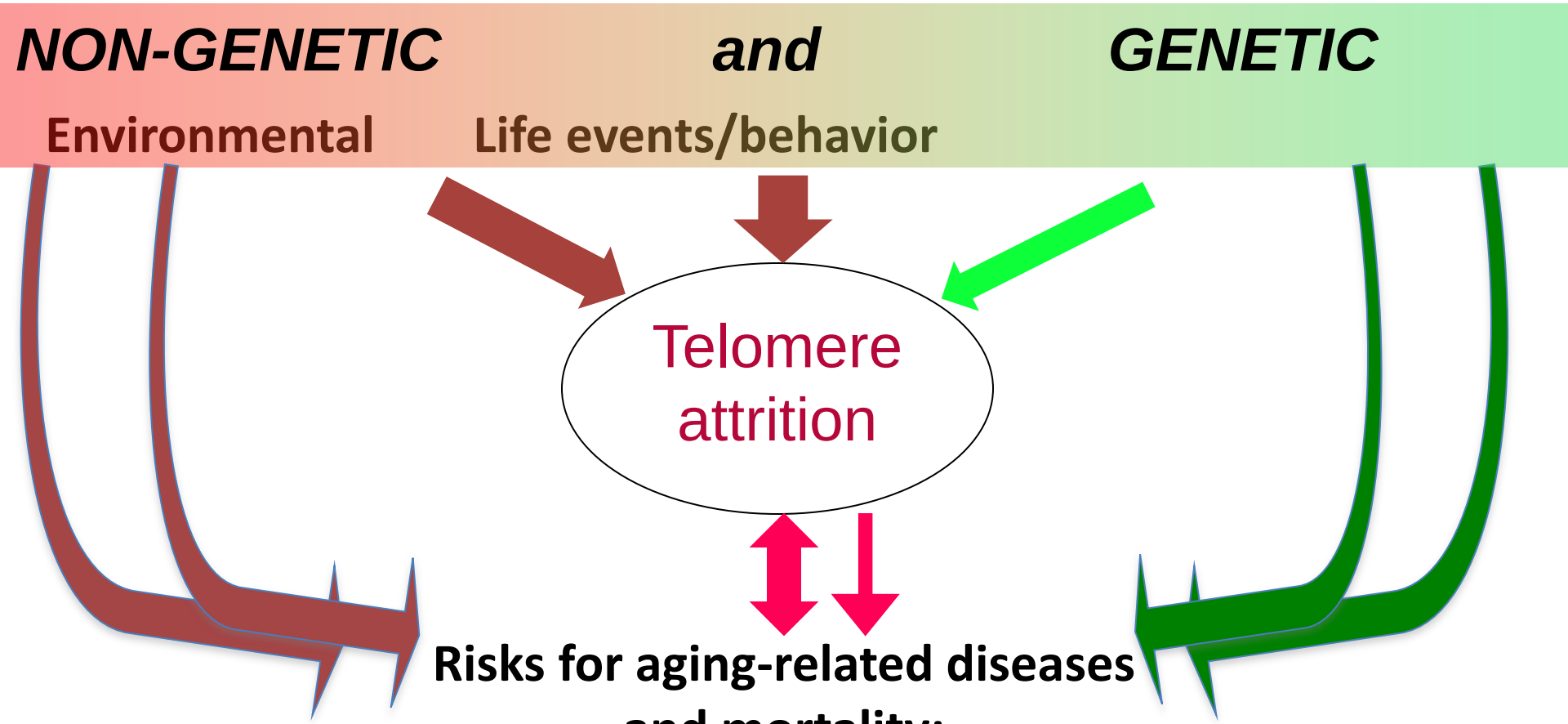
Risks for aging-related diseases and mortality:

Poor immune function

Cancers **Cardiovascular disease** **Diabetes**

Mental/cognitive disorders/depression

Telomere attrition: a stress-related, malleable biomarker for, and contributor to, aging-related diseases



Risks for aging-related diseases and mortality:

Poor immune function

Cancers **Cardiovascular disease** **Diabetes**

Mental/cognitive disorders/depression

The Future of Medicine:

Prevent, preempt and intercept Diseases.

Why Now?

Pre-disease

Advanced

Preempt

Treat

Advances in understanding disease etiology and biology and in clinic
options are giving us the ability to think about preventing and intercepting more diseases.

Telomere loss

Genes

Telomere upkeep

Adverse Childhood Events

Education

Chronic Stress

Exercise

Pessimism Hostility

Stress reduction

Disease risks

Health