

Το ανοσοποιητικό σύστημα στην τρίτη ηλικία

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Διευθυντής, Κλινική Ρευματολογίας και κλινικής Ανοσολογίας, Παν. Θεσσαλίας

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Σύγκρουση Συμφερόντων σχετική με την Ομιλία: Καμία



Σύγκρουση Συμφερόντων μη σχετικές με την Ομιλία

ΚΆΛΥΨΗ ΣΥΜΜΕΤΟΧΗΣ: NOVARTIS

ΑΛΛΕΣ

Roche, Celgene, Genesis, Thermo Fisher, Menarini,
Inova, Medipan, Generic Assays, Elpen, Aenorasis, AID,
Biorad, Biolympus, CyBio, Diarect, IFT, Euclone,
Invitrogen-MabTech, Miltenyi, Novartis, Molecular
Probes, PeproTech, Gilead,

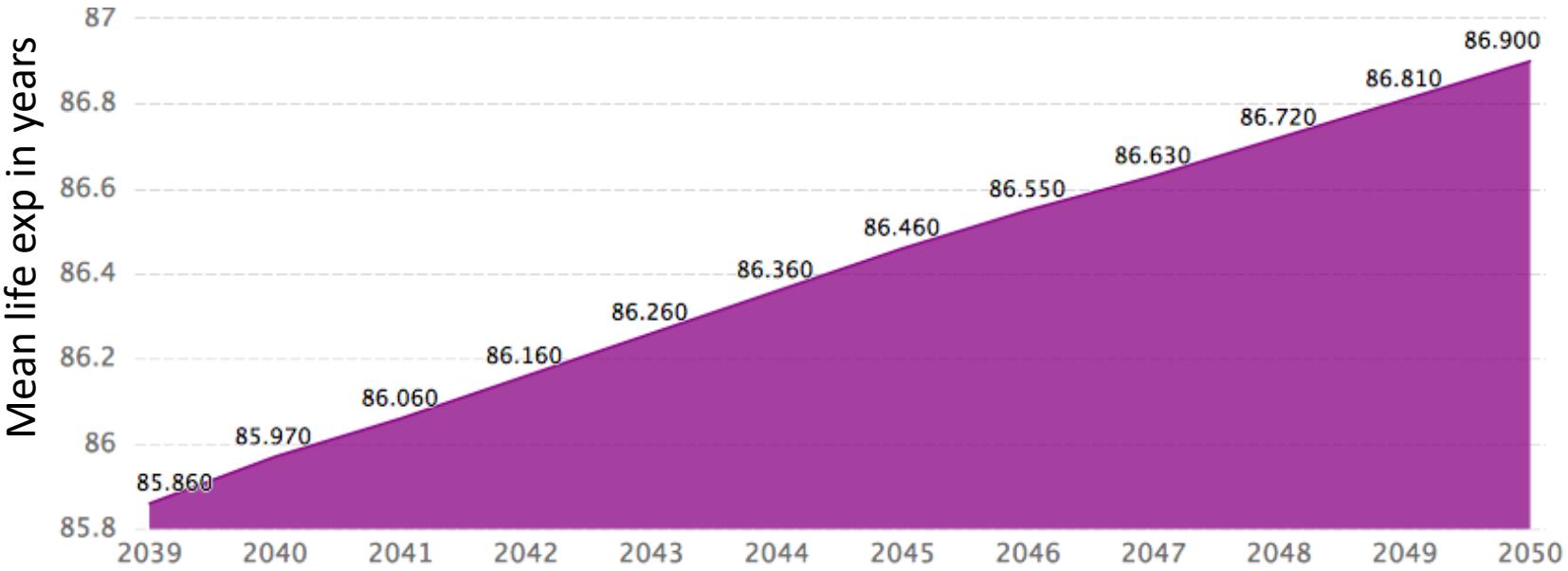


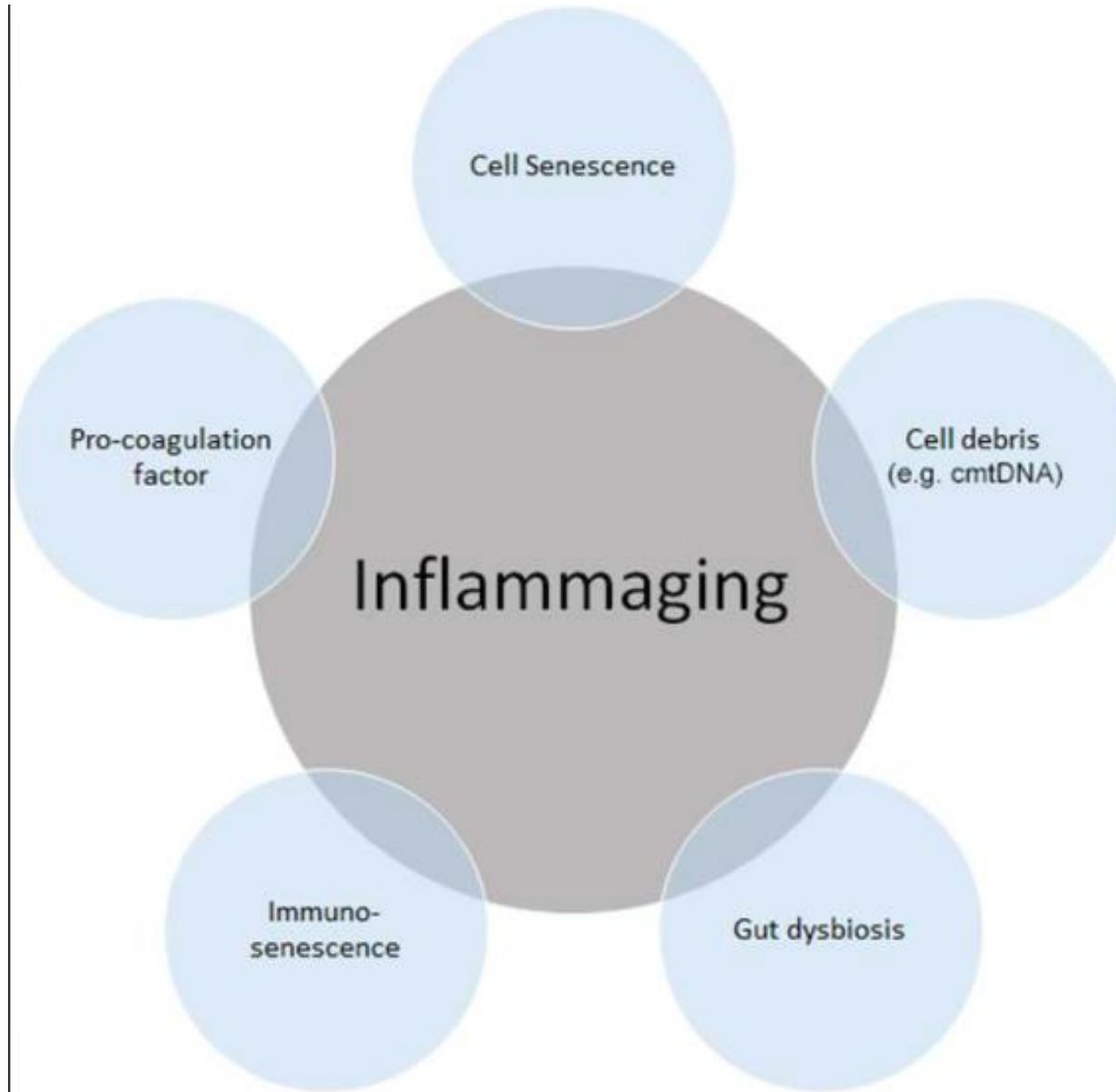
Το ανοσοποιητικό σύστημα στην τρίτη ηλικία A fair fight against diseases?

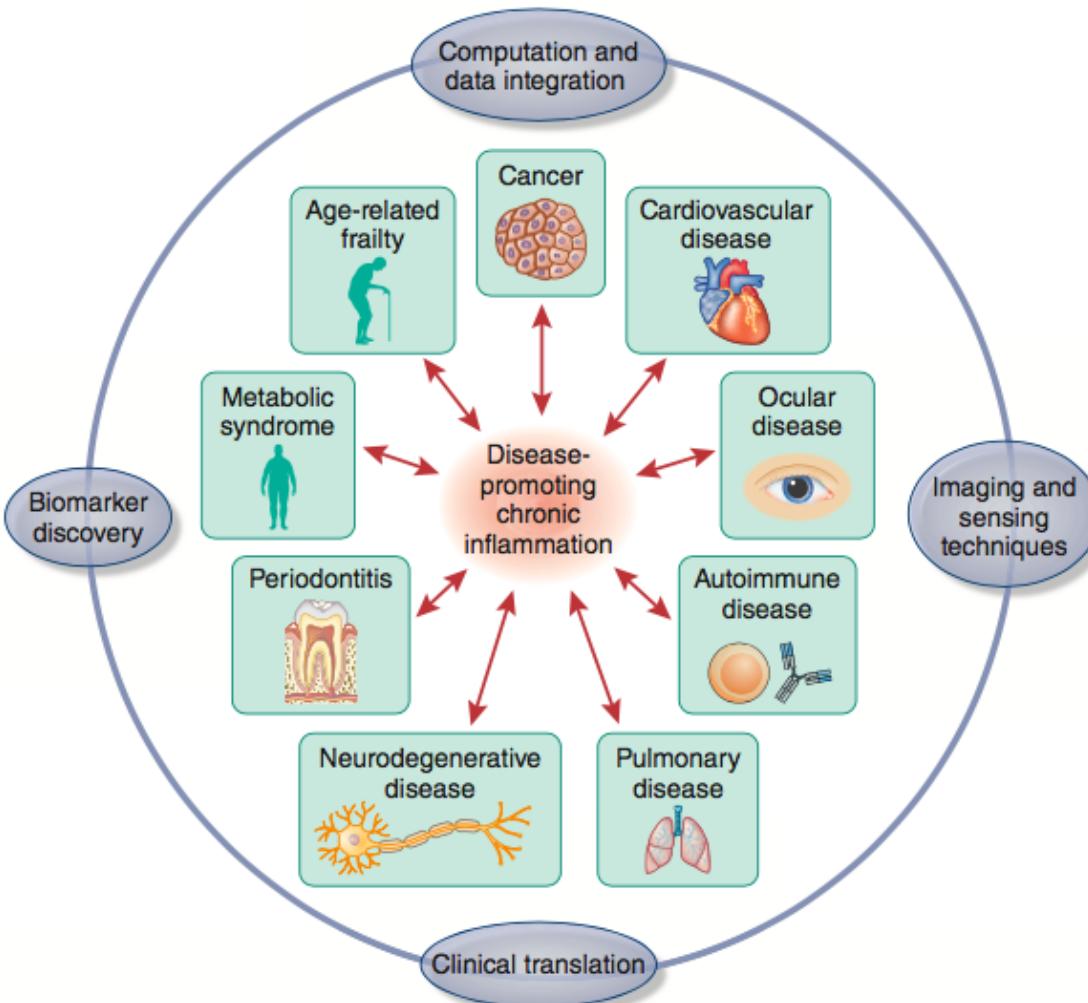
Ανοσογήρανση/ immunosenescence



Τι είναι η ανοσογήρανση;







Potential contributors and therapeutic targets:

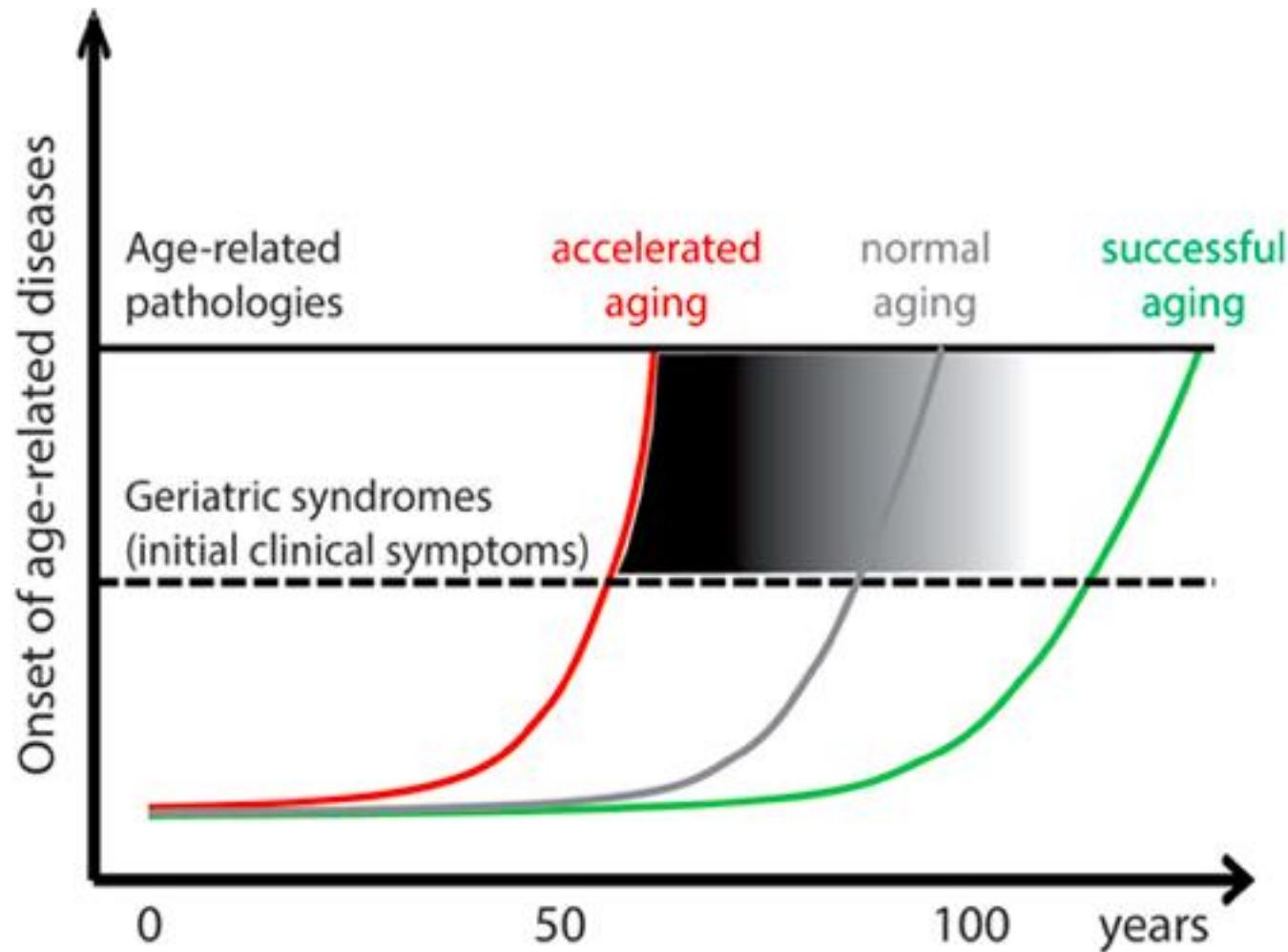
- Accumulation of senescent cells
- Unresolved infection
- Dysbiosis
- Activated microglia and macrophages
- Cytokine and chemokine dysregulation
- Imbalance between pro-inflammation mediators and pro-resolution mediators
- Gene mutations
- Epigenetic modifications
- Lifestyle risk factors

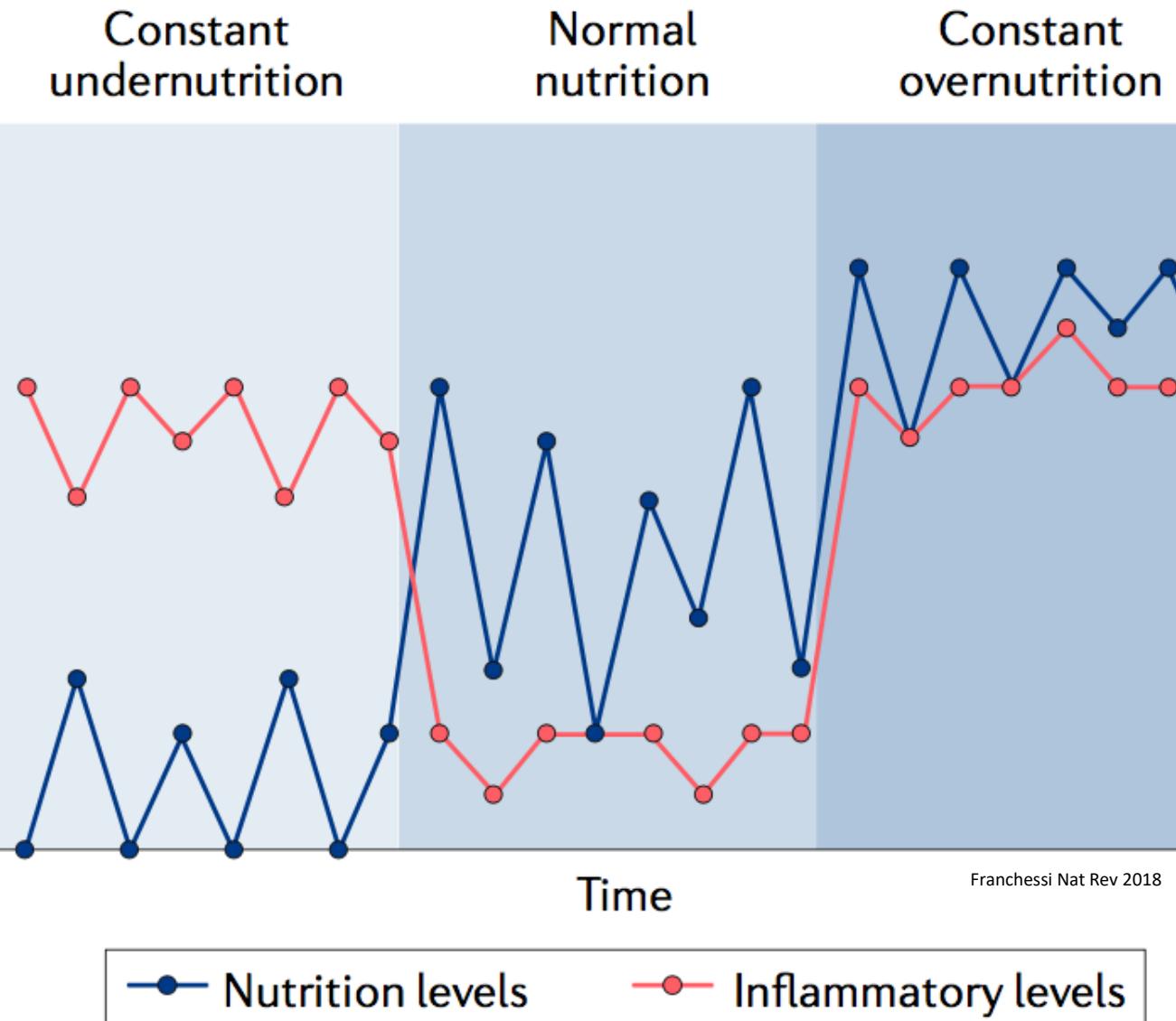
Debie Maizels/Springer Nature

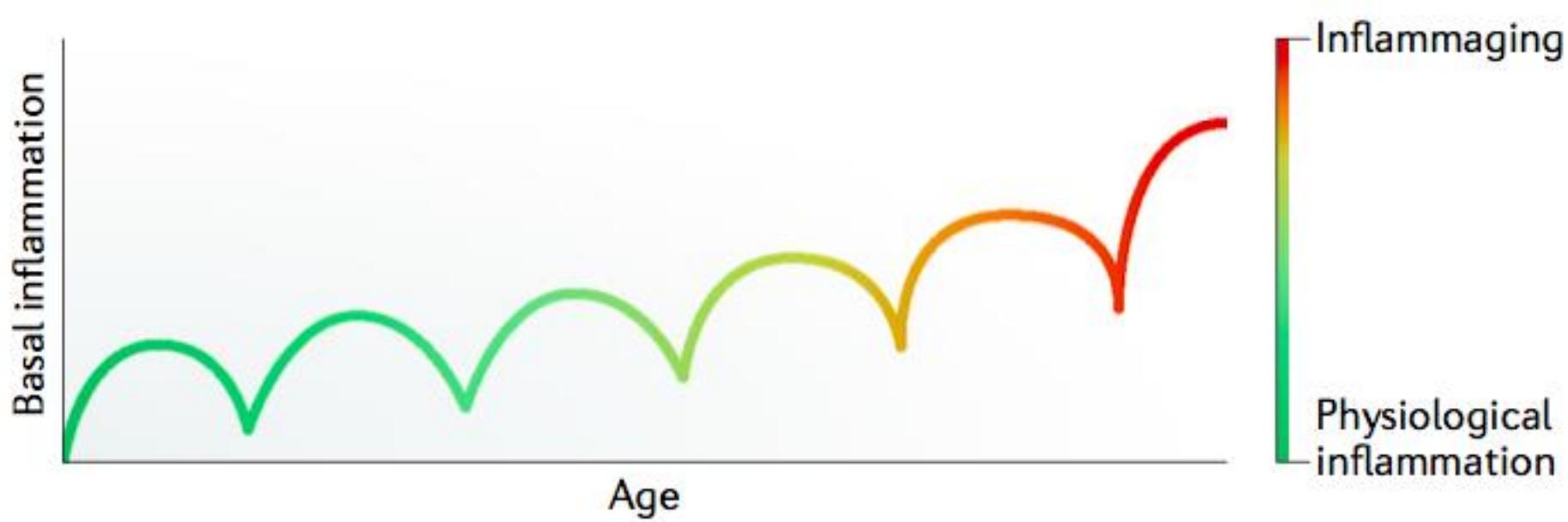


Geroscience

A



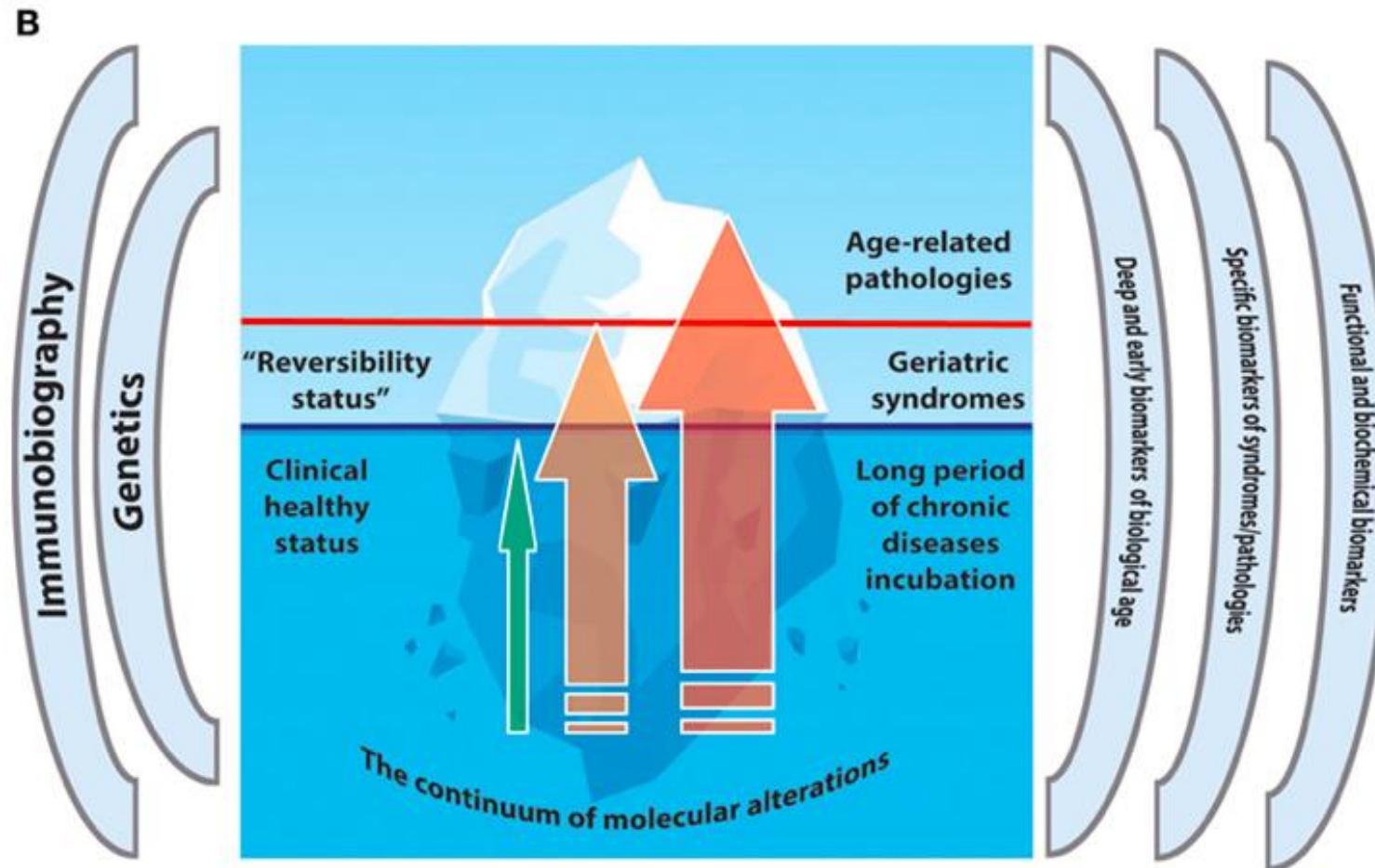


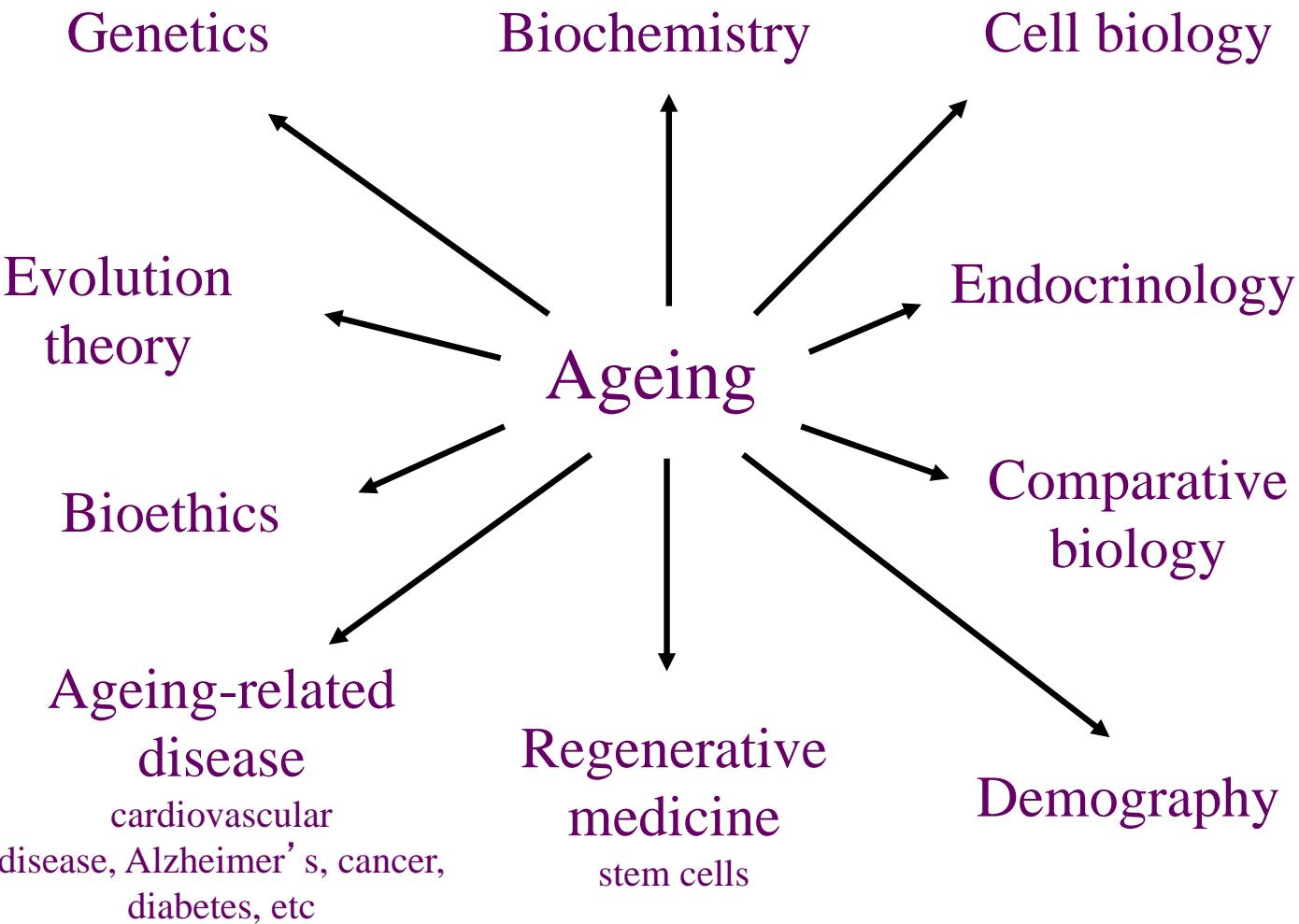


Franchetti Nat Rev 2018



Geroscience





1 important question about ageing

Comparative biology:

Maximum lifespans in mammals



3 years



59 years



122 years

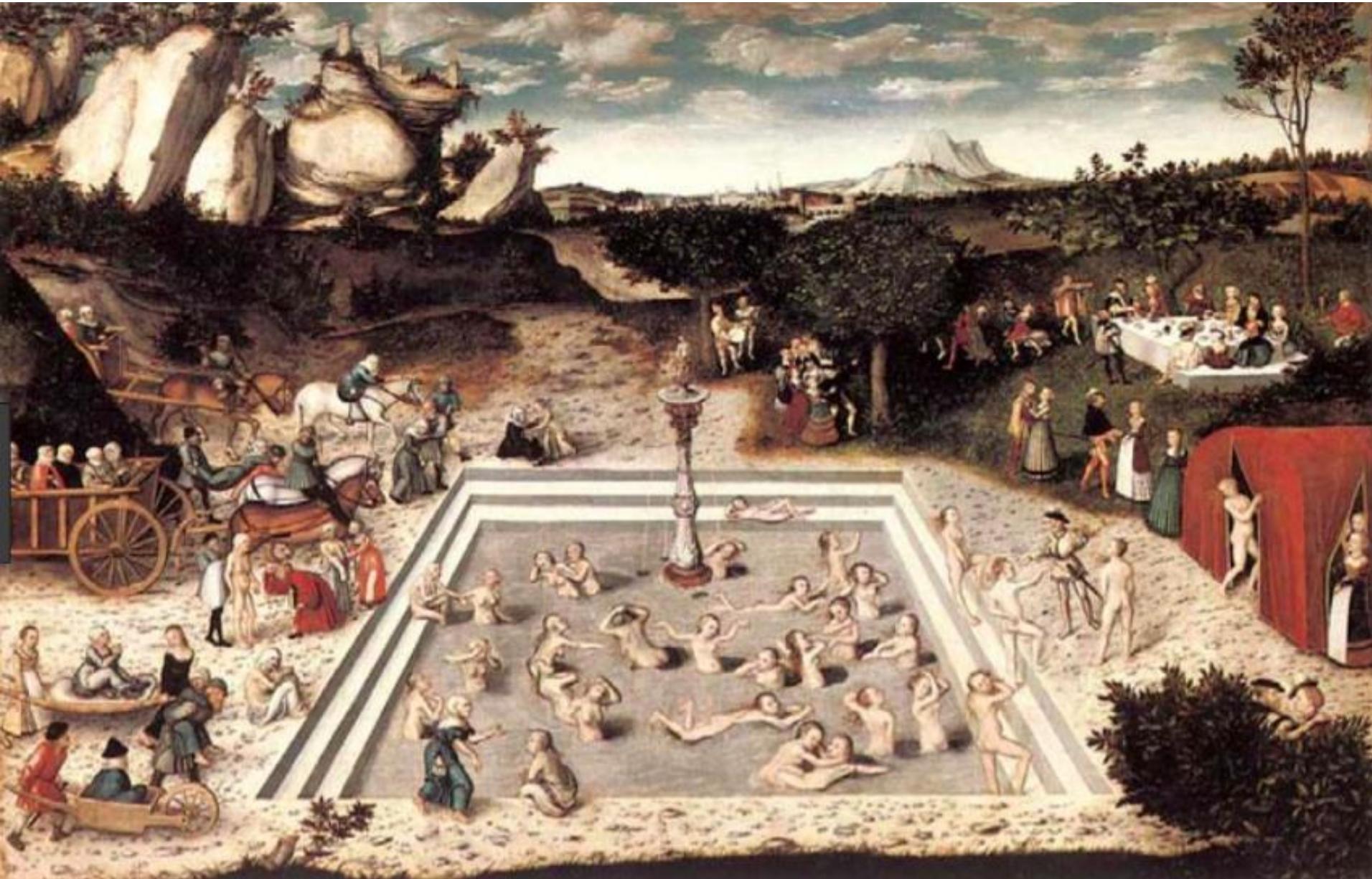


Pinus longaeva (Bristlecone pine) ~5000 years



Urticina felina (Dahlia anemone) Non ageing

Reversing human aging so far remains fiction



"Fountain of Youth" by Lucas Cranach

C. elegans

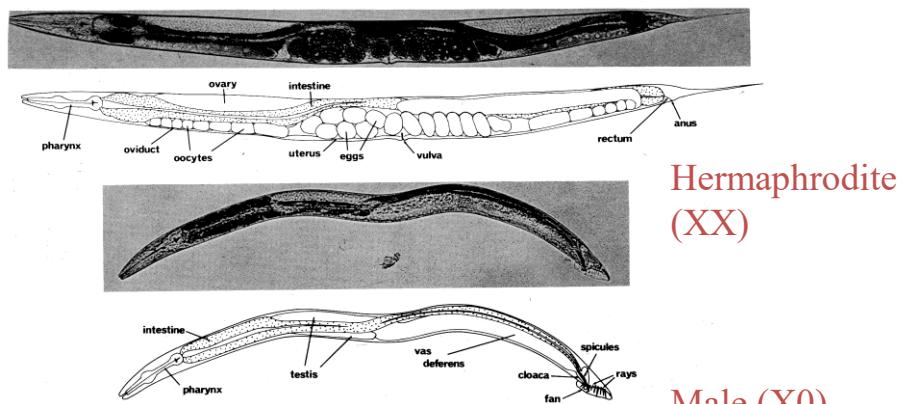
Kαινοραβδίτης ο κουμψός

A microbivorous terrestrial nematode, ~1.2 mm long

Genome: ~97,000,000 bases; ~19,000 genes

Signs of ageing

- Reduced fertility, feeding, movement
- Increased cuticular wrinkling (collagen cross linking)
- Increased protein carbonyl, mitochondrial DNA deletions, lipofuscin



Hermaphrodite
(XX)

Male (X0)



The hunt for lifespan mutants

Short lived or long lived?

Tom Johnson (1988): *age-1(hx546)* mutation

65% increase in mean lifespan

110% increase in maximum lifespan

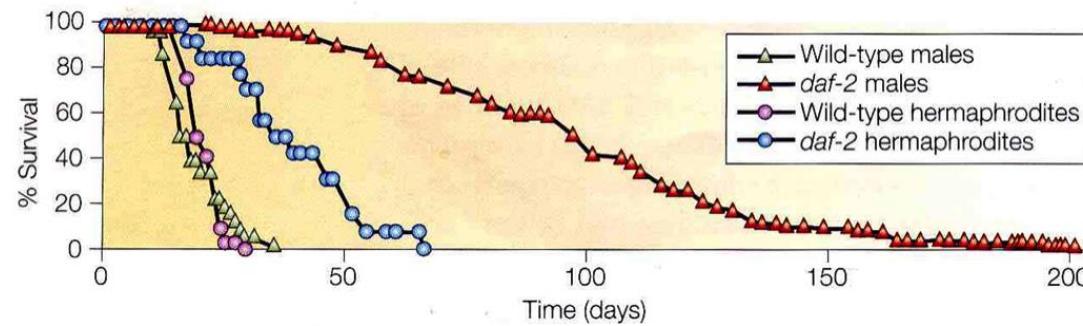
Remains youthful for longer



Tom Johnson



Cynthia Kenyon (1993): Mutations in *daf-2* greatly increase lifespan



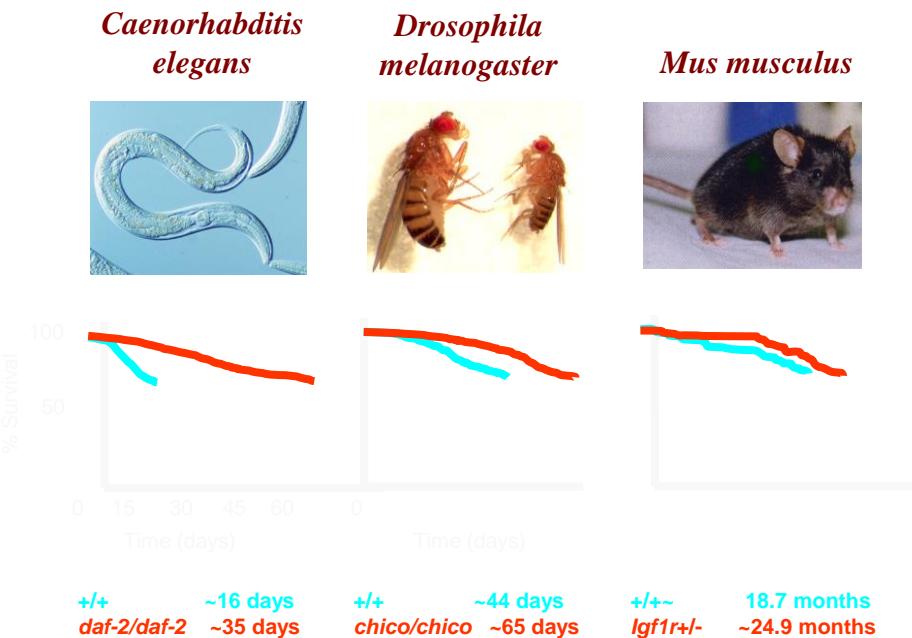
Cynthia Kenyon



- 2) Evolutionary biology: How/why does ageing evolve? How does it contribute to fitness?
- 3) Model organisms: Can aging be suppressed and lifespan increased?

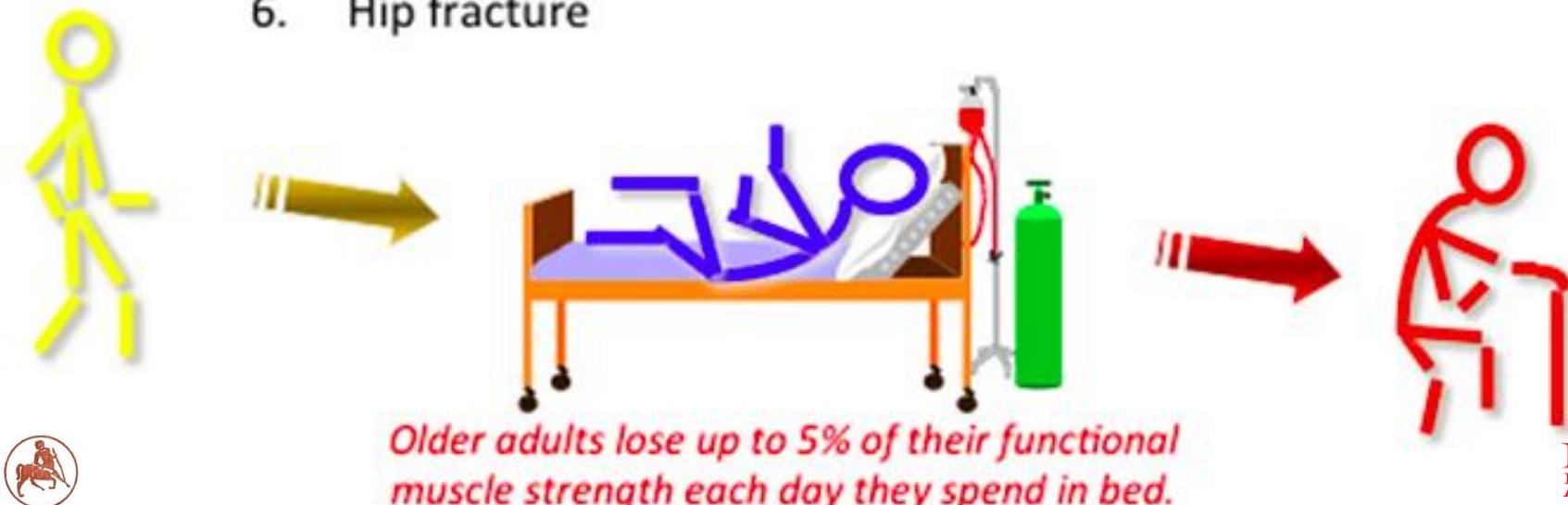
- Reduced insulin/IGF-1 signalling

- Caloric restriction



Ageing – Disability

- Leading causes of catastrophic disability
 1. Strokes
 2. CHF
 3. Pneumonia and influenza
 4. Ischemic heart disease
 5. Cancer
 6. Hip fracture



**Το ανοσοποιητικό σύστημα είναι
αποφασιστικός παράγοντας
διατήρησης της υγείας και της επιβίωσης
στην τρίτη ηλικία**

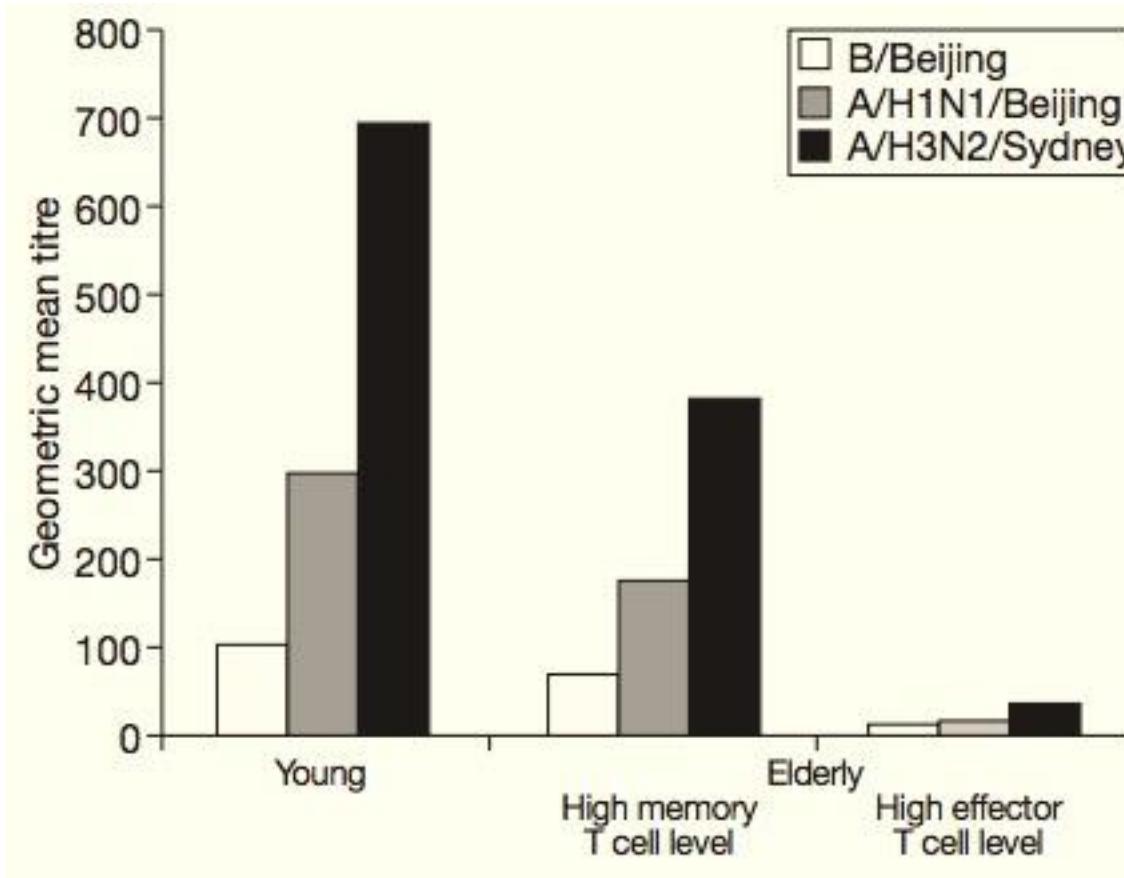


Τι είναι η Ανοσογήρανση;

1. Ασθένεια;
2. Φυσιολογική διαδικασία ή όχι;
3. Αναστρέψιμη ή μη;
4. Σε τί βαθμό και με τι μέσα;

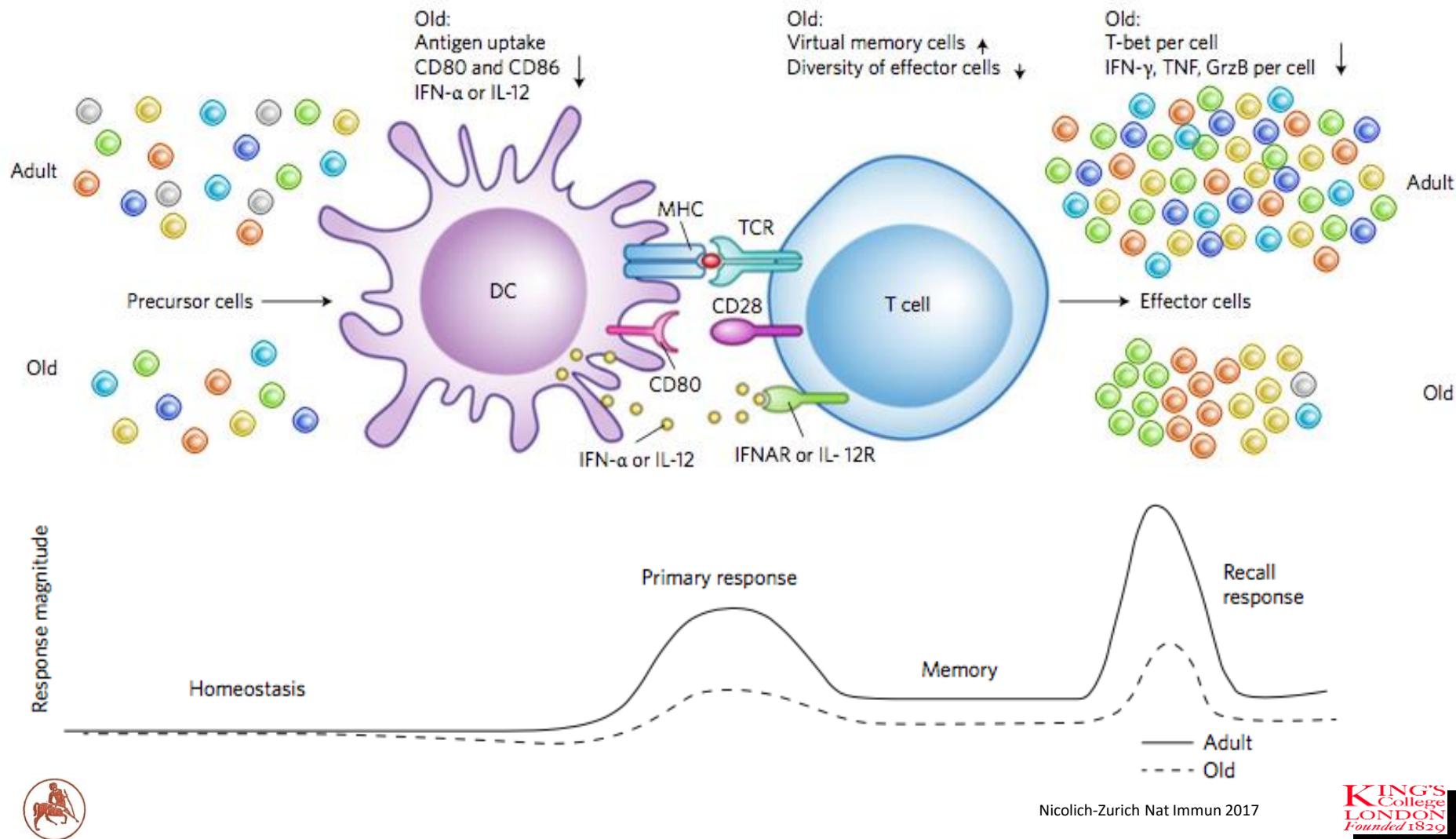


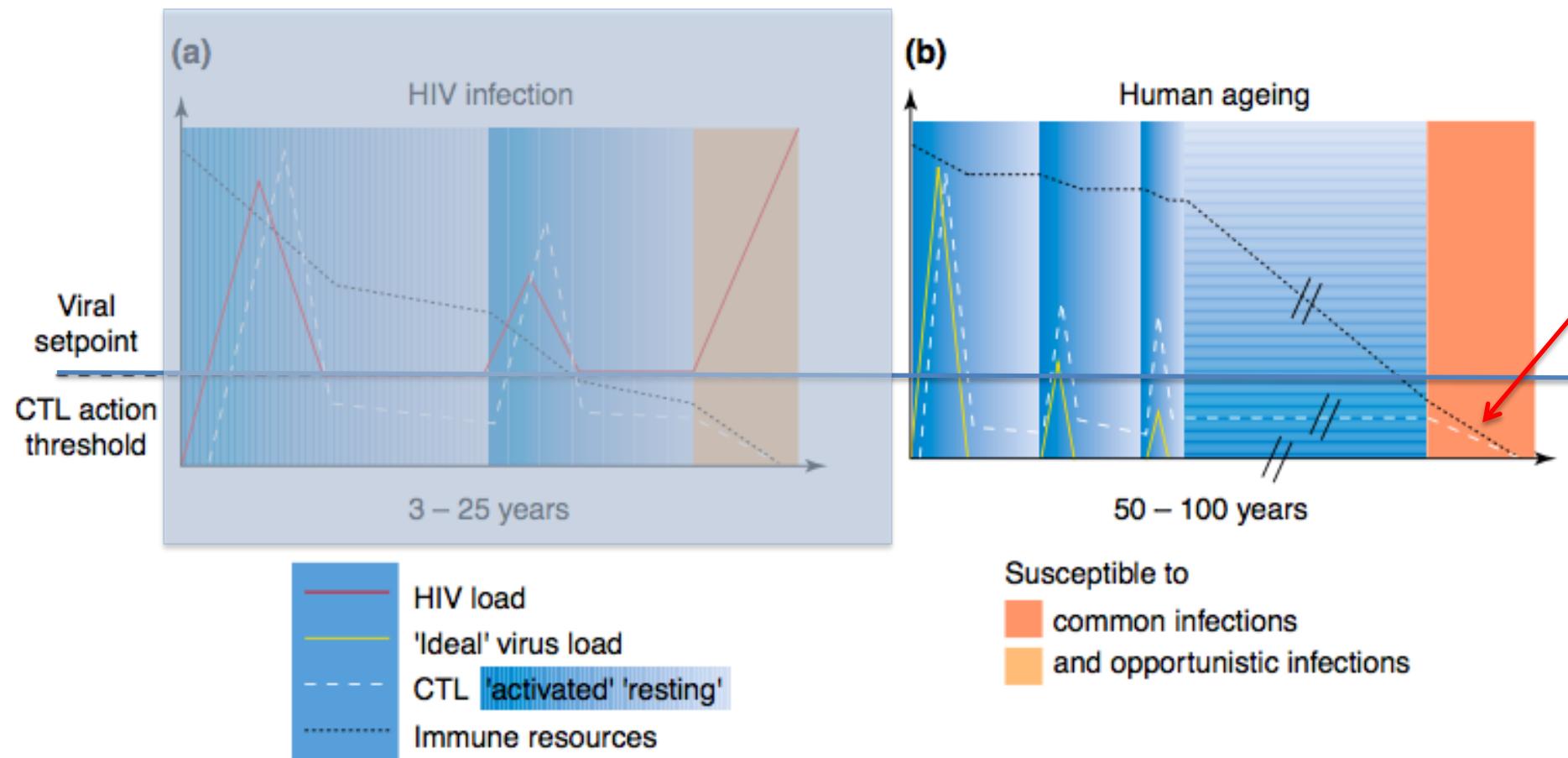
Lack of antibody production in old age

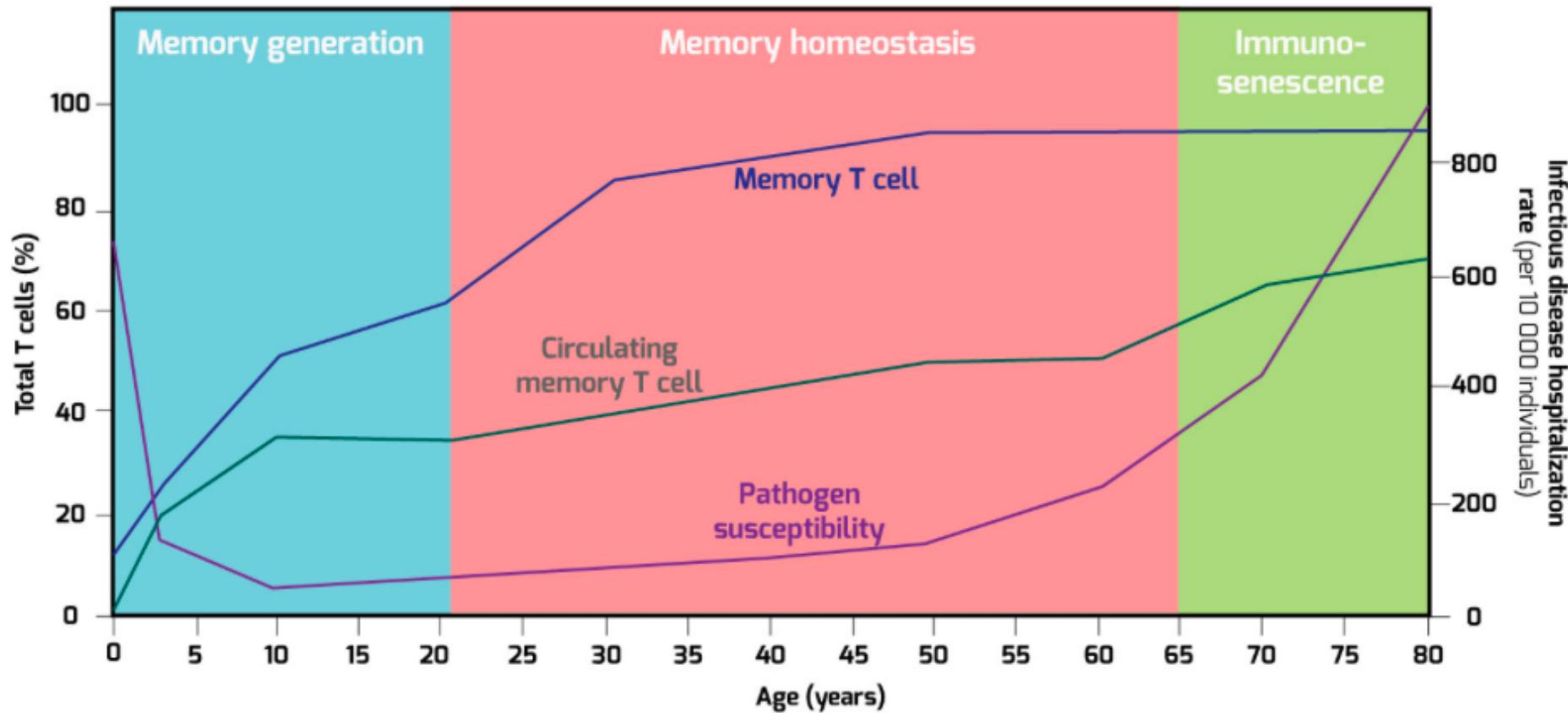


Saurwein-Teissl M J Immunol 2002







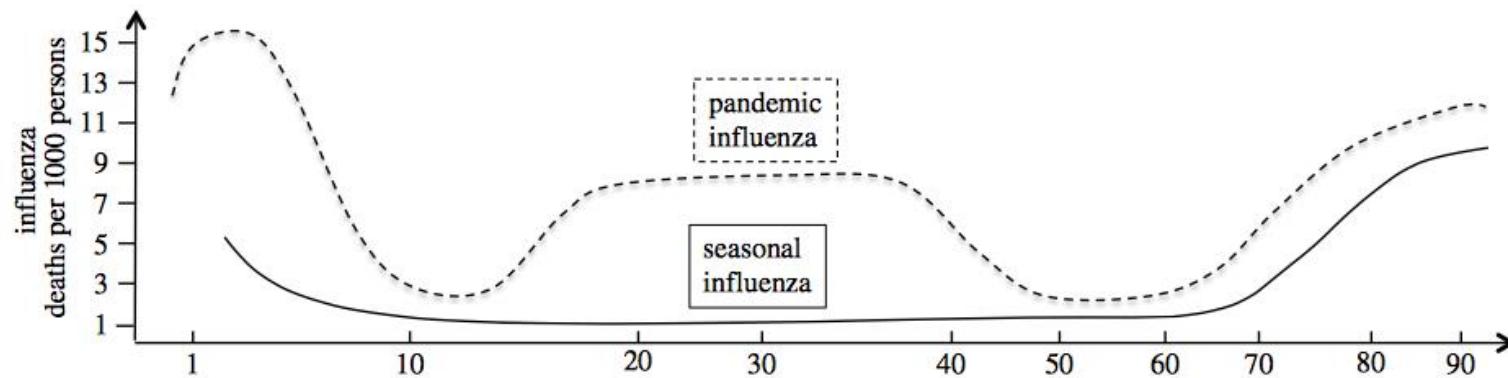




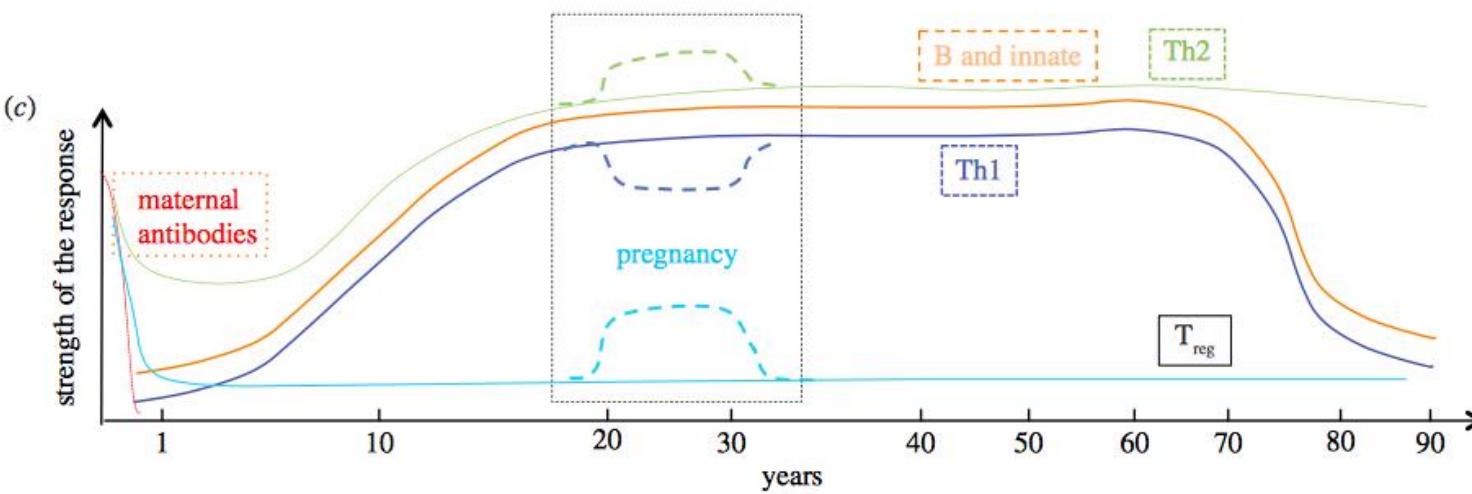
(a)



(b)

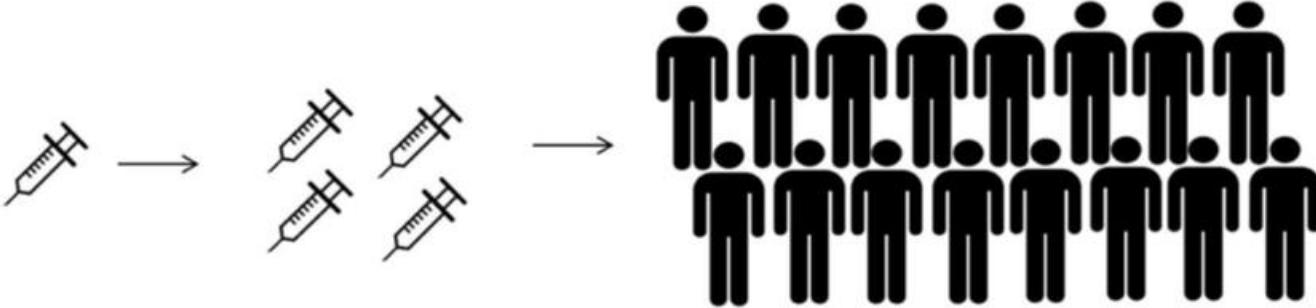


(c)

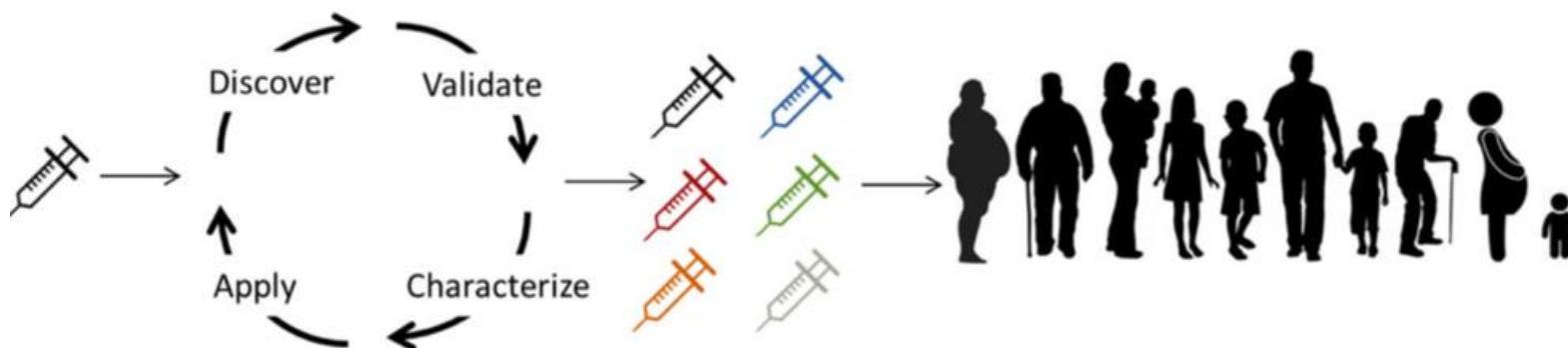


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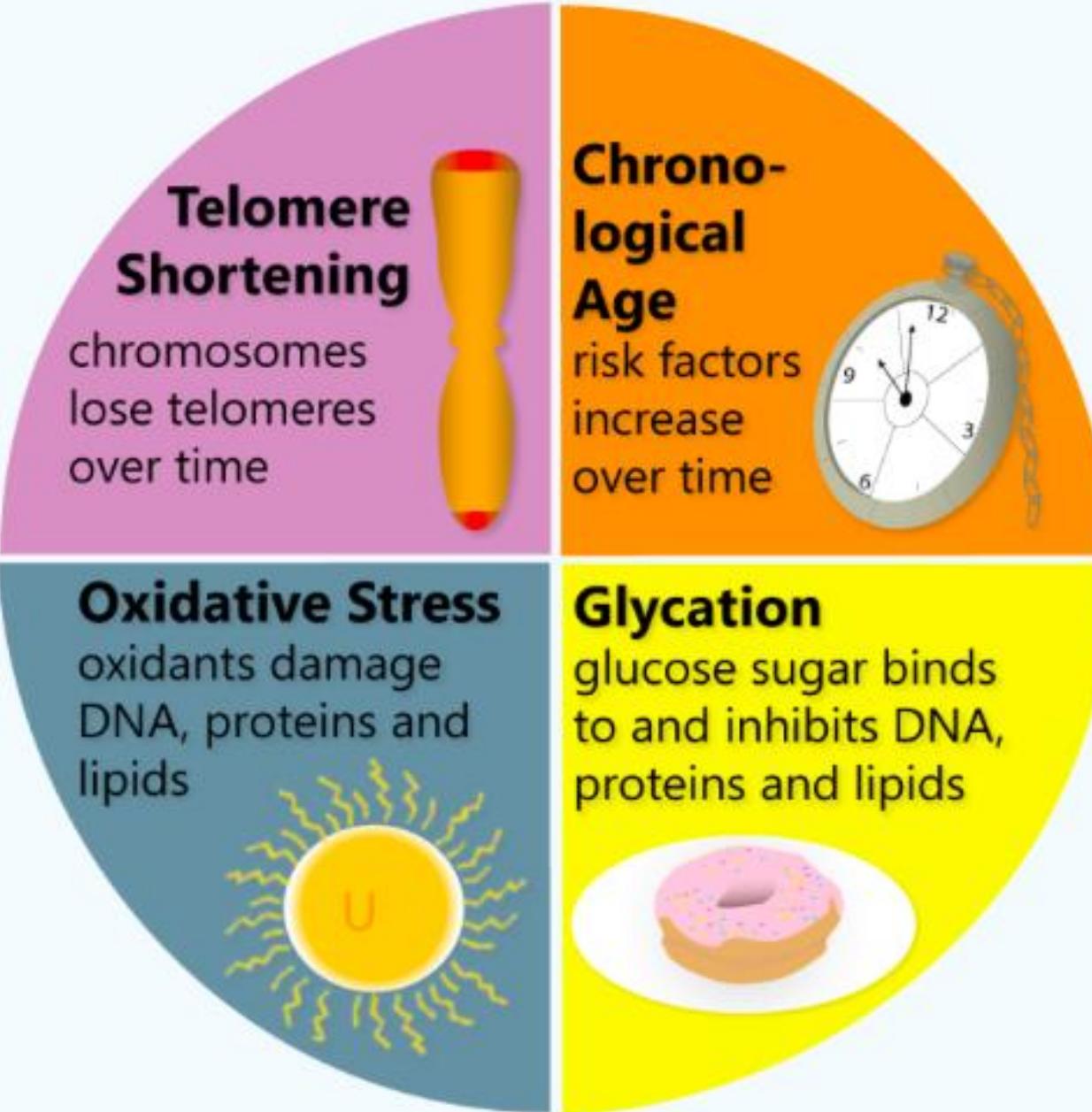
Empirical Vaccine Development (Isolate – Inactivate – Inject)



Personalized Vaccinology



SOME FACTORS IN AGING



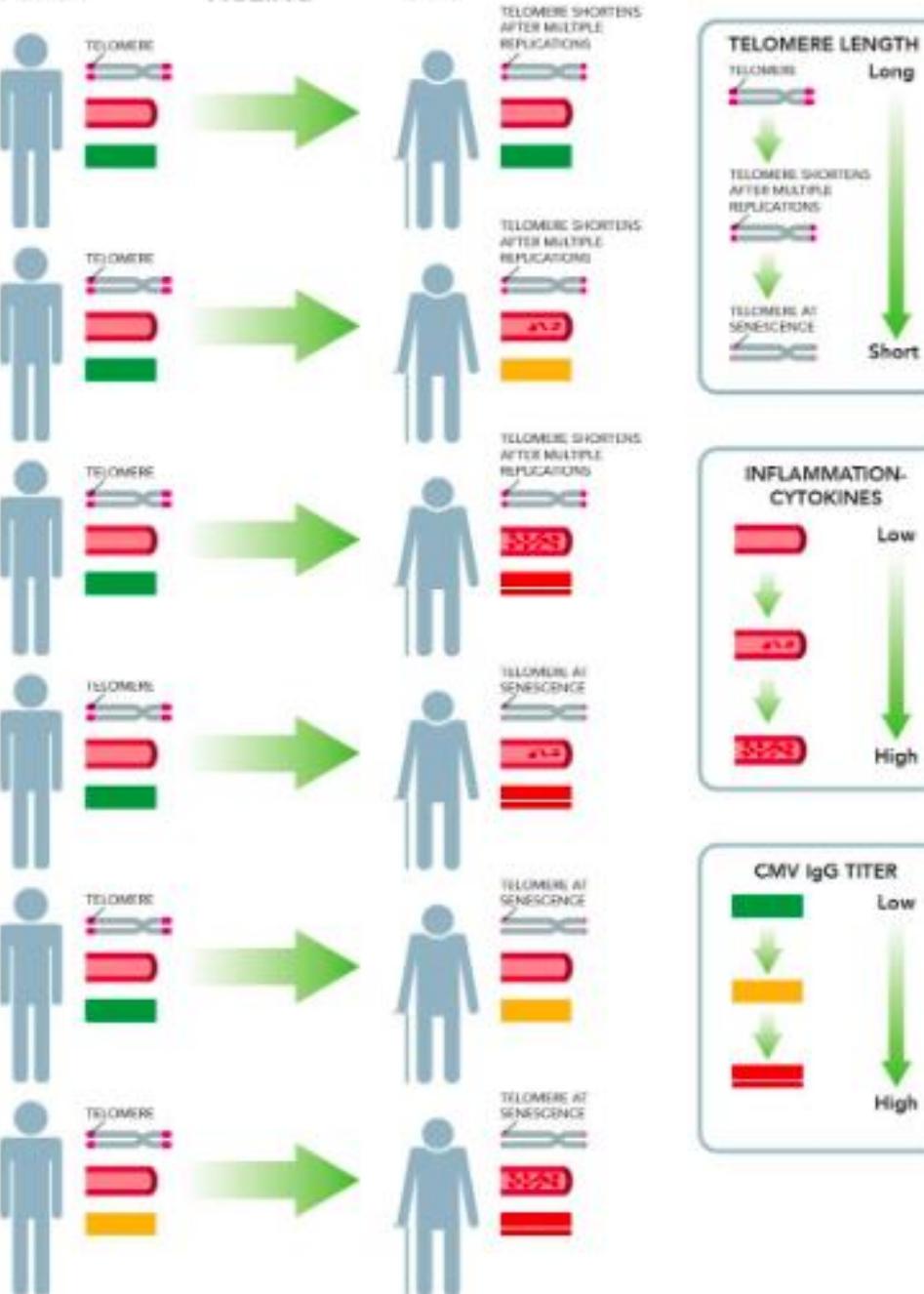


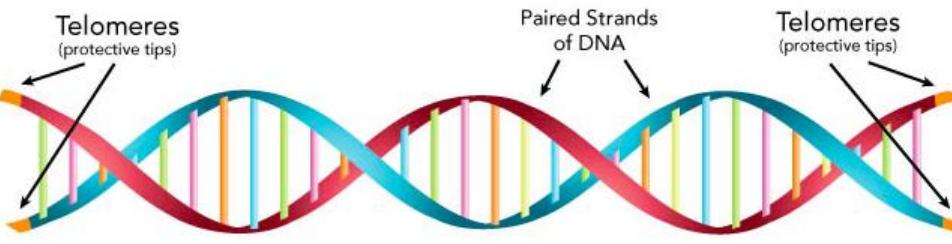
INDIVIDUALIZED AGE-ASSOCIATED CHANGES IN IMMUNE SYSTEM

YOUNG

AGEING

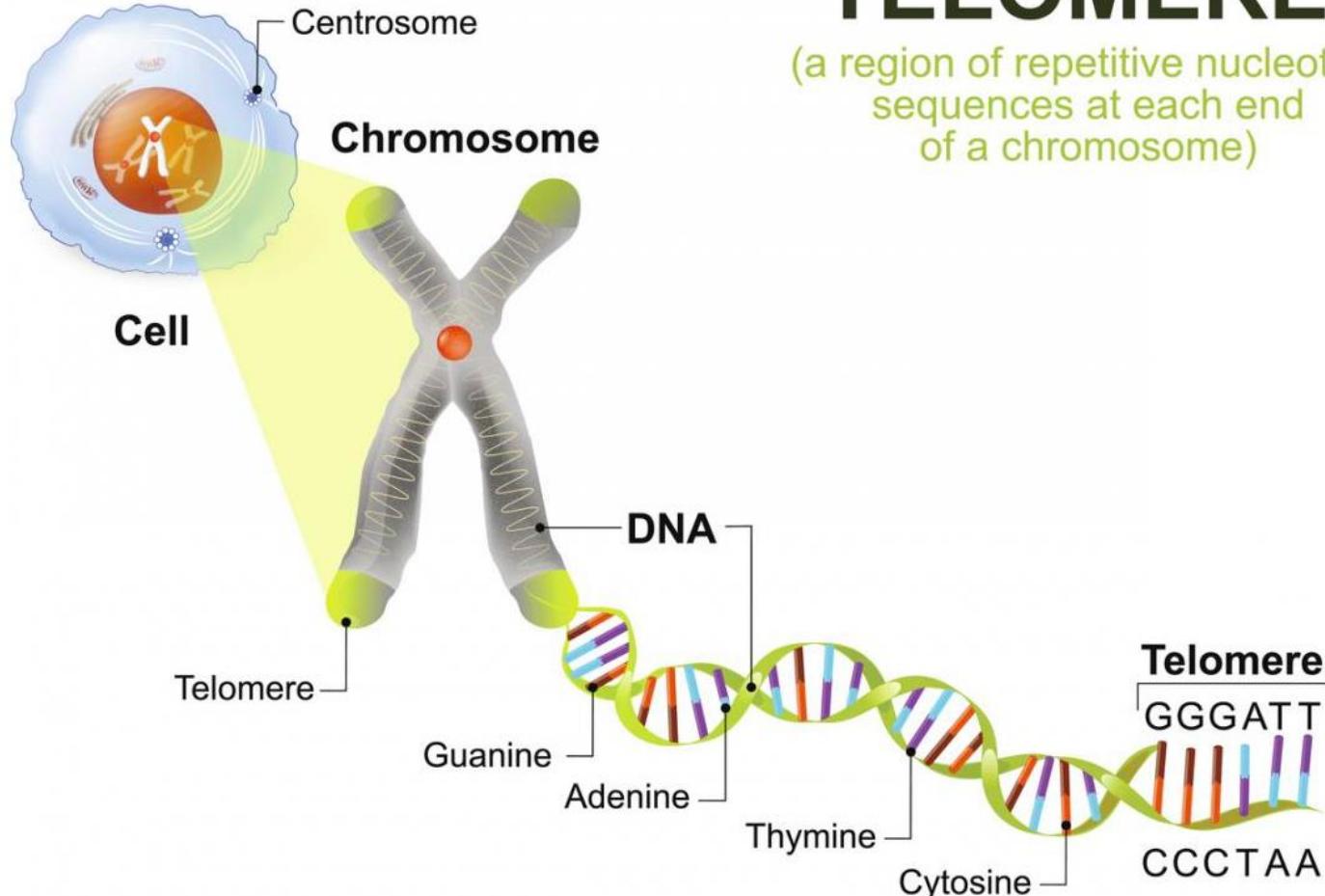
OLD



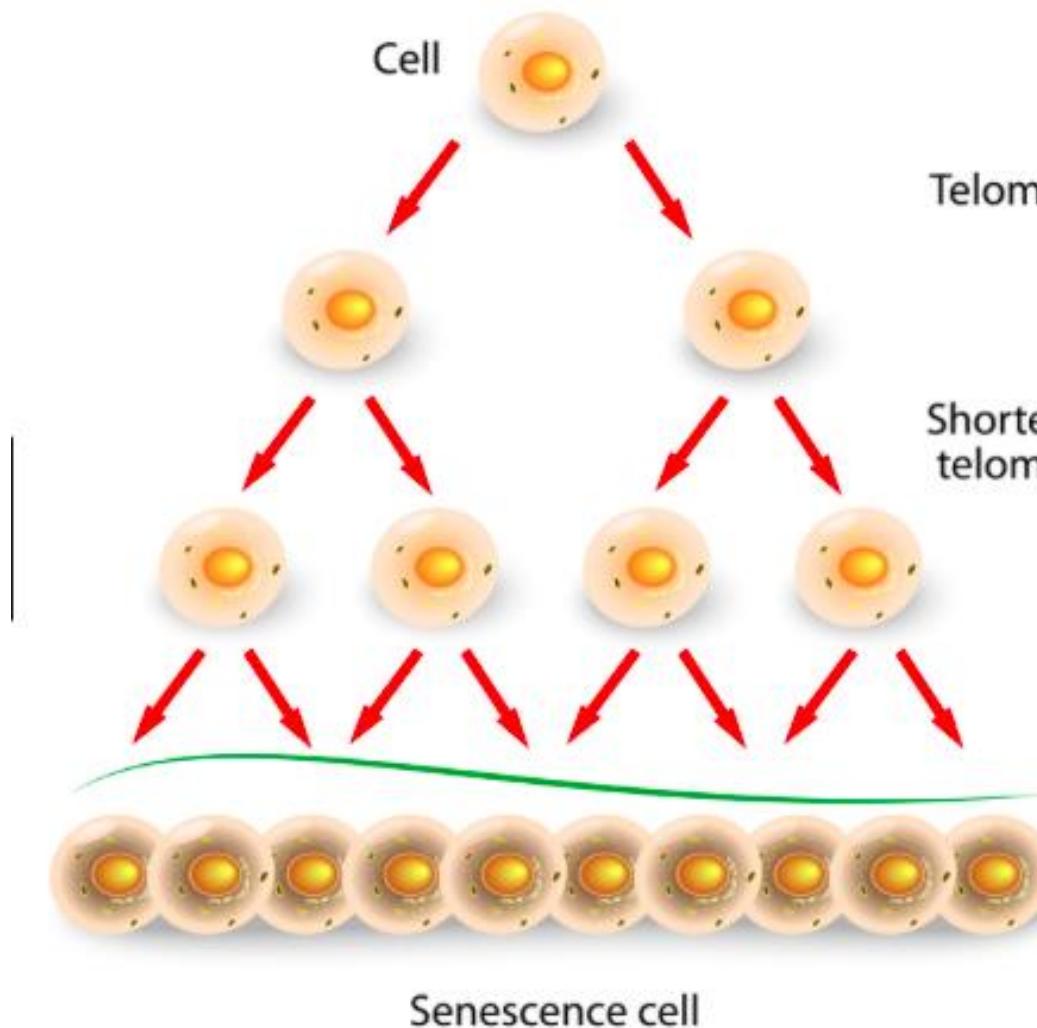


TELOMERE

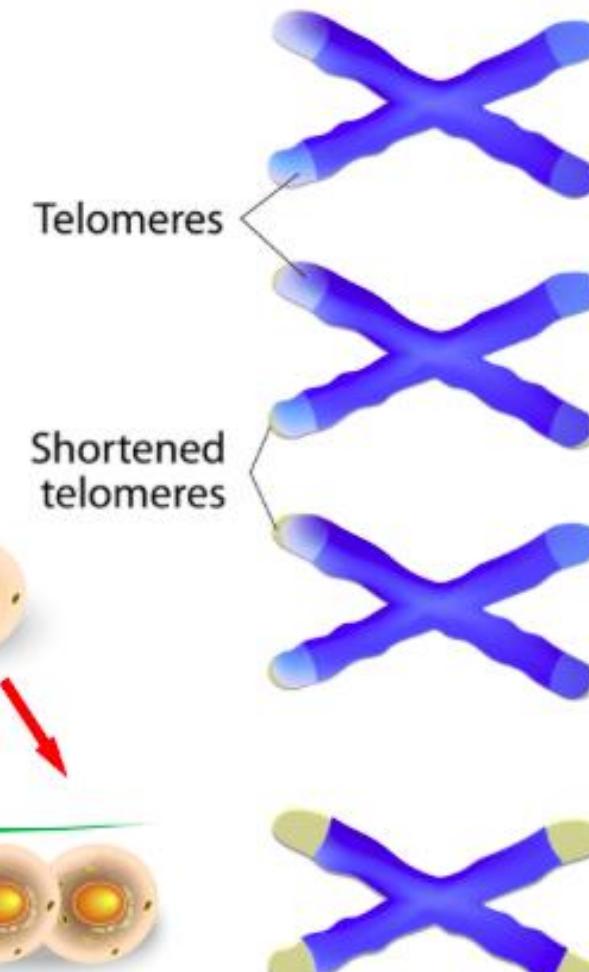
(a region of repetitive nucleotide sequences at each end of a chromosome)



Cell division

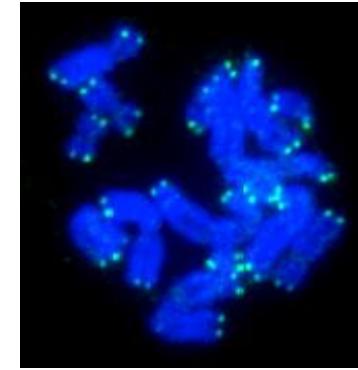
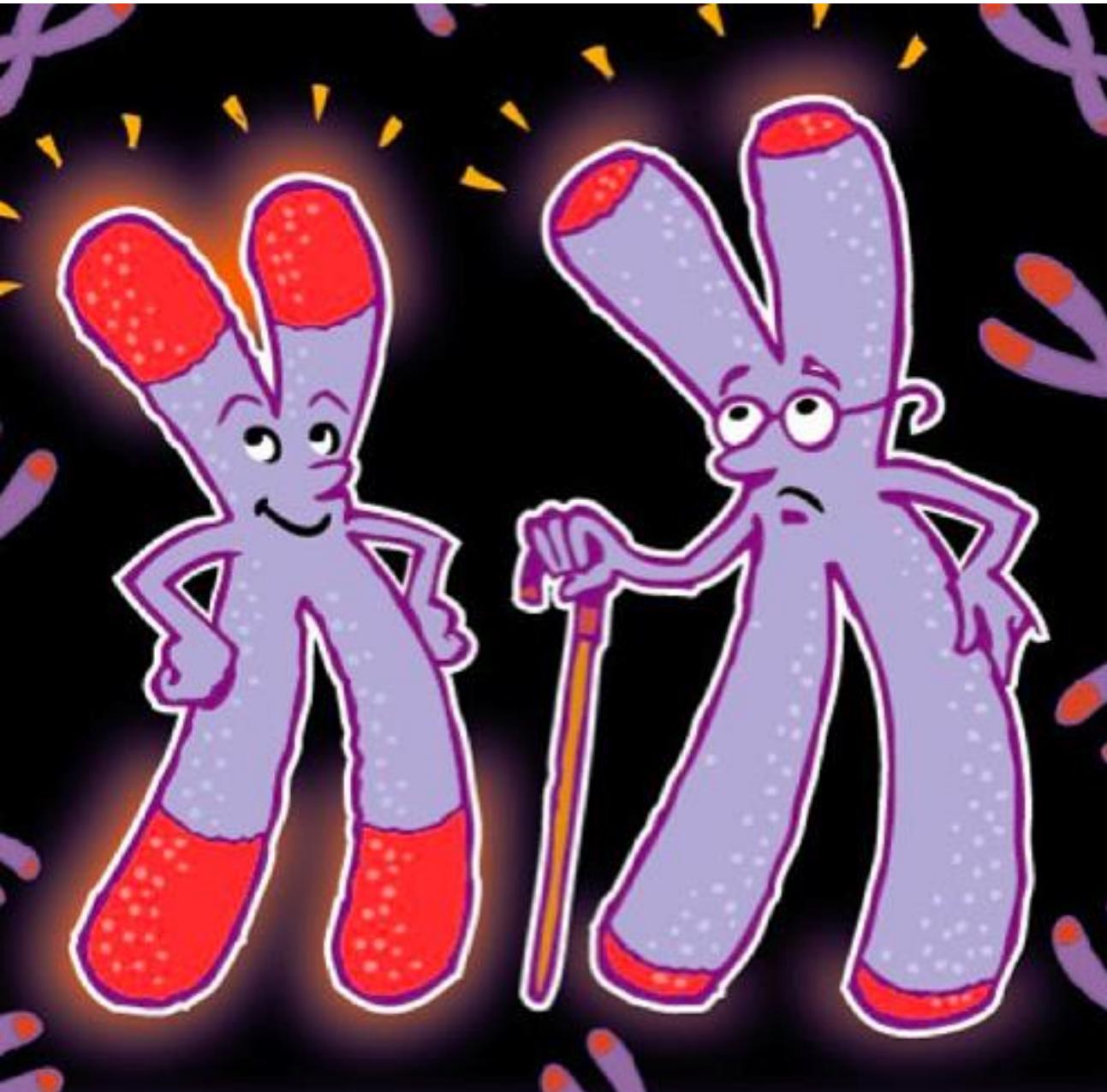


Chromosomes



Telomeres shorten,
cell division stops





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The Nobel Prize in Physiology or Medicine 2009

"for the discovery of how chromosomes are protected by telomeres and the enzyme telomerase"



Photo: Gerbil, Licensed by Attribution Share Alike 3.0

**Elizabeth H.
Blackburn**



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Carol W. Greider



Photo © Harvard Medical School

Jack W. Szostak



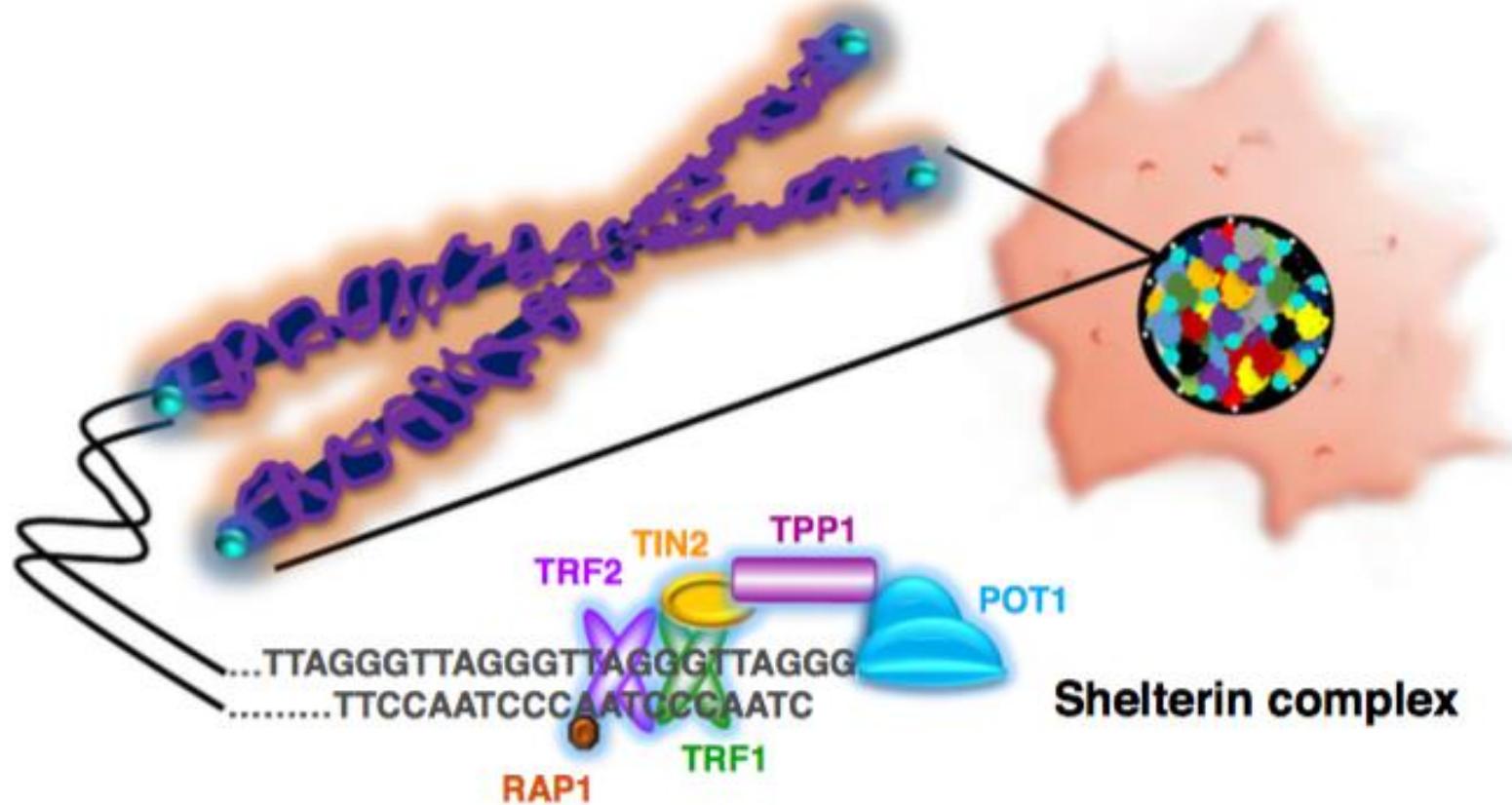
The Nobel Peace Prize 2009

"for his extraordinary efforts to strengthen international diplomacy and cooperation between peoples"



Barack Obama

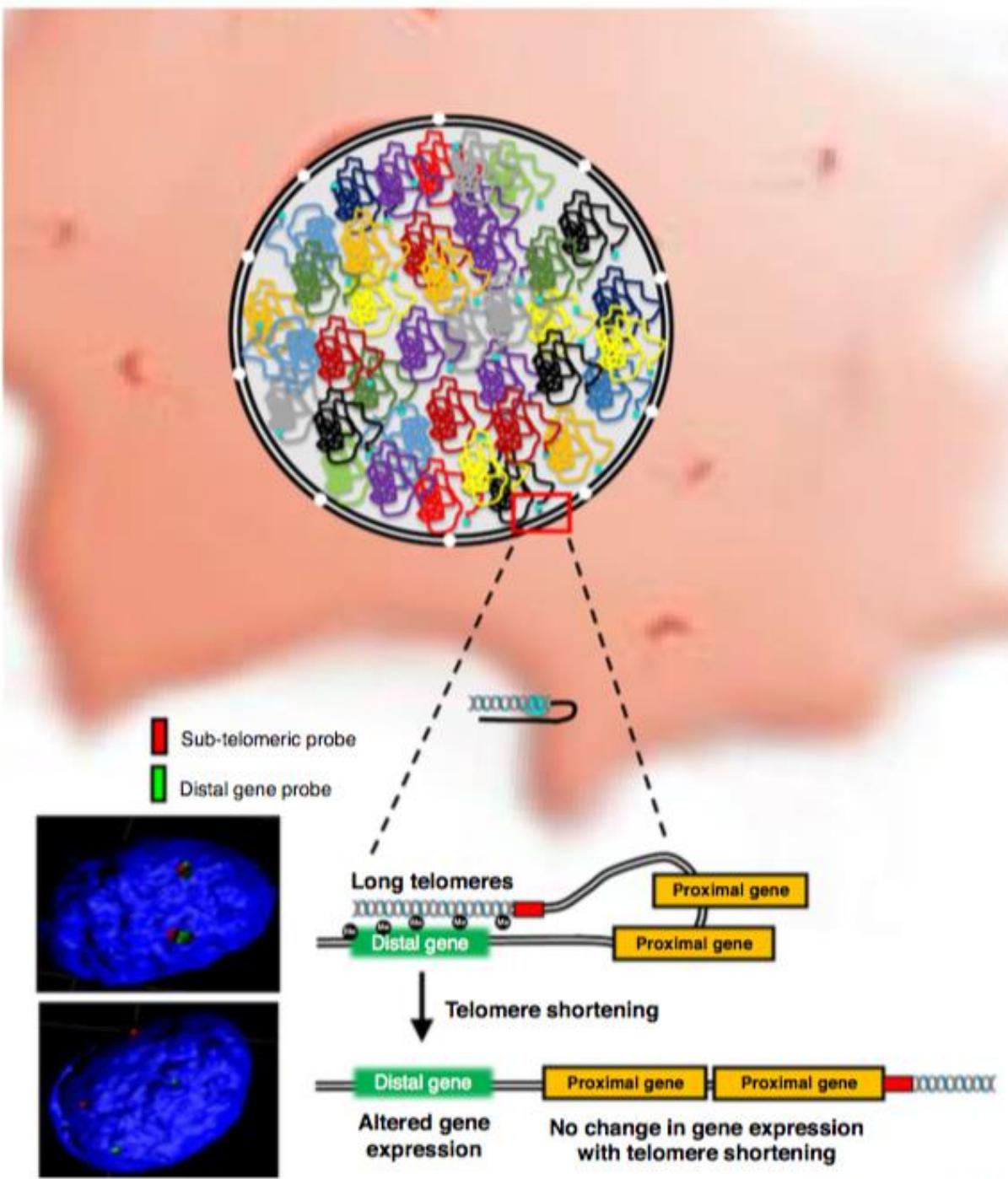




Shelterin complex

Current Opinion in Cell Biology







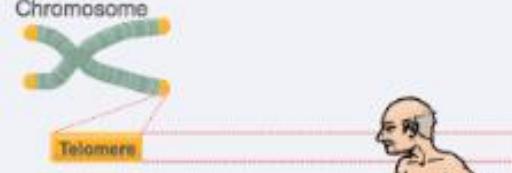
Telomere length of an infant.



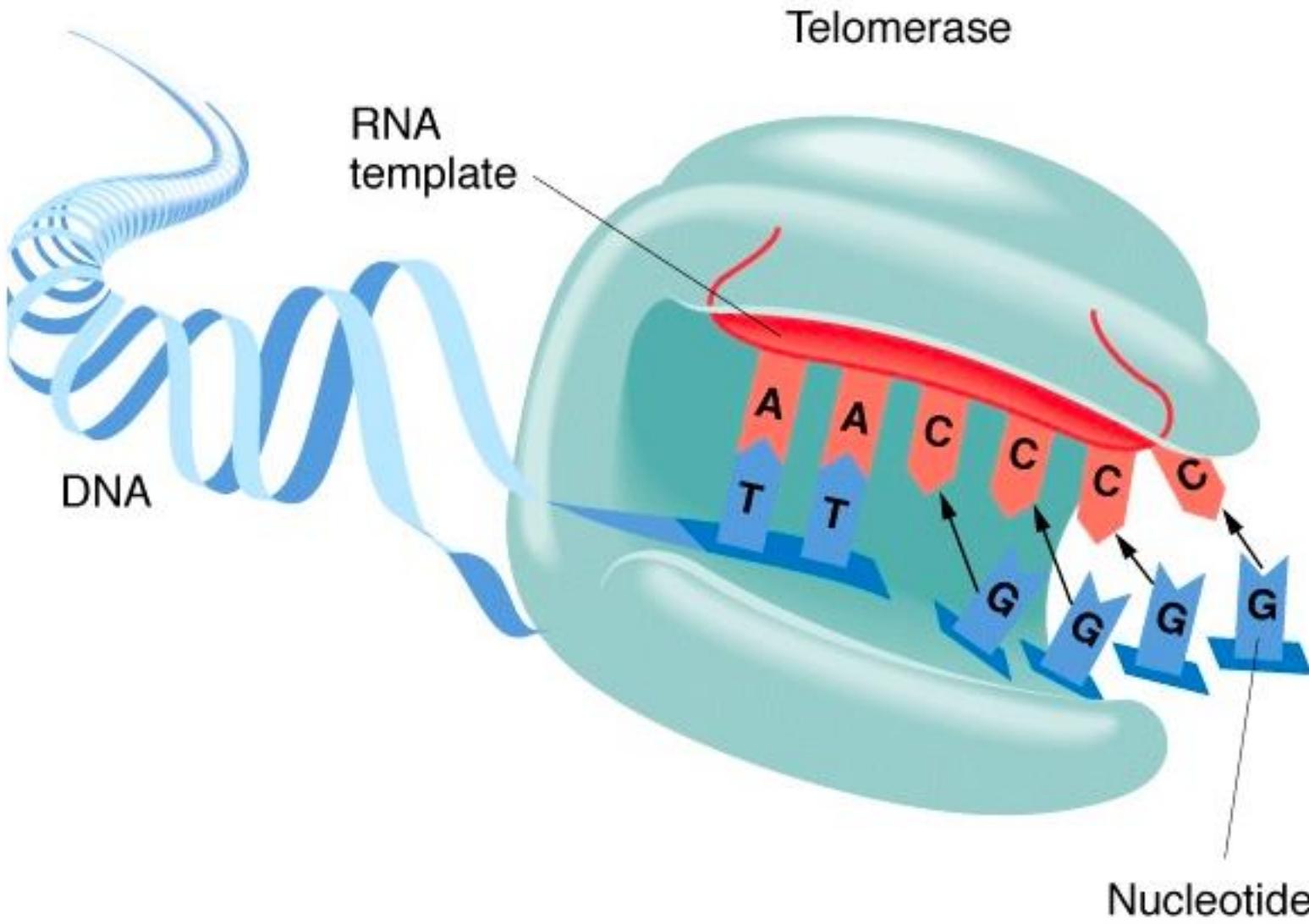
Telomere length of a teenager.

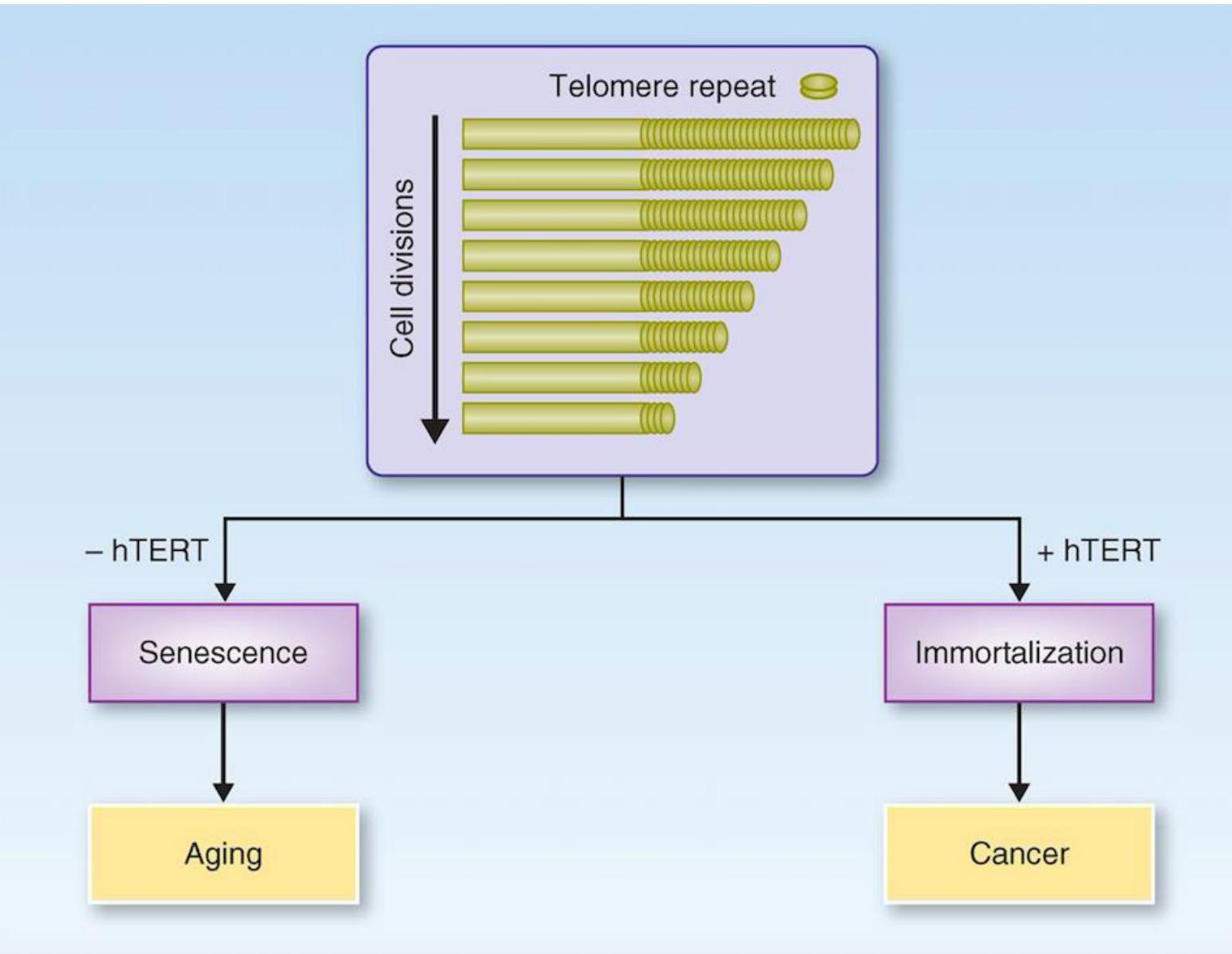


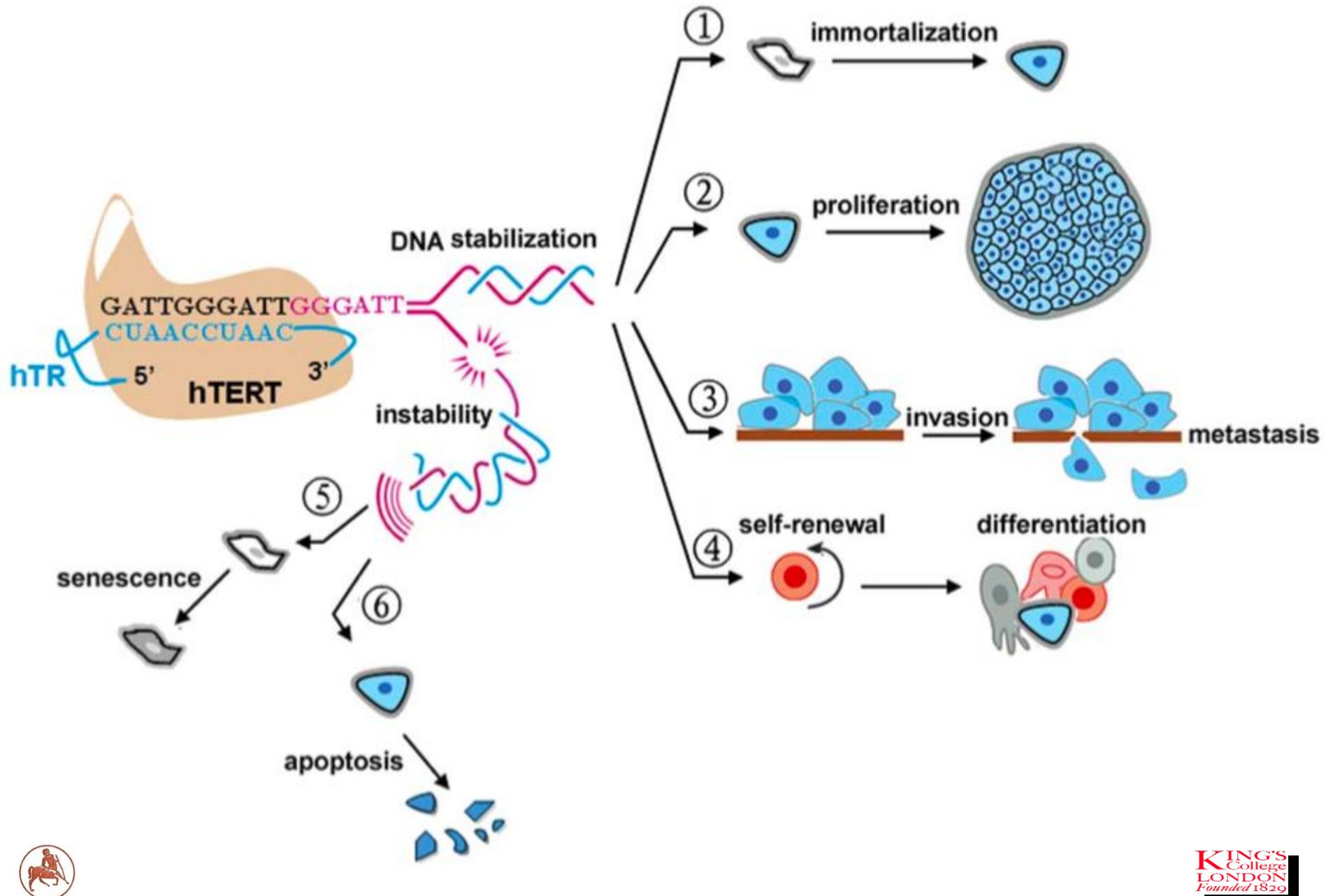
Telomere length of an adult.

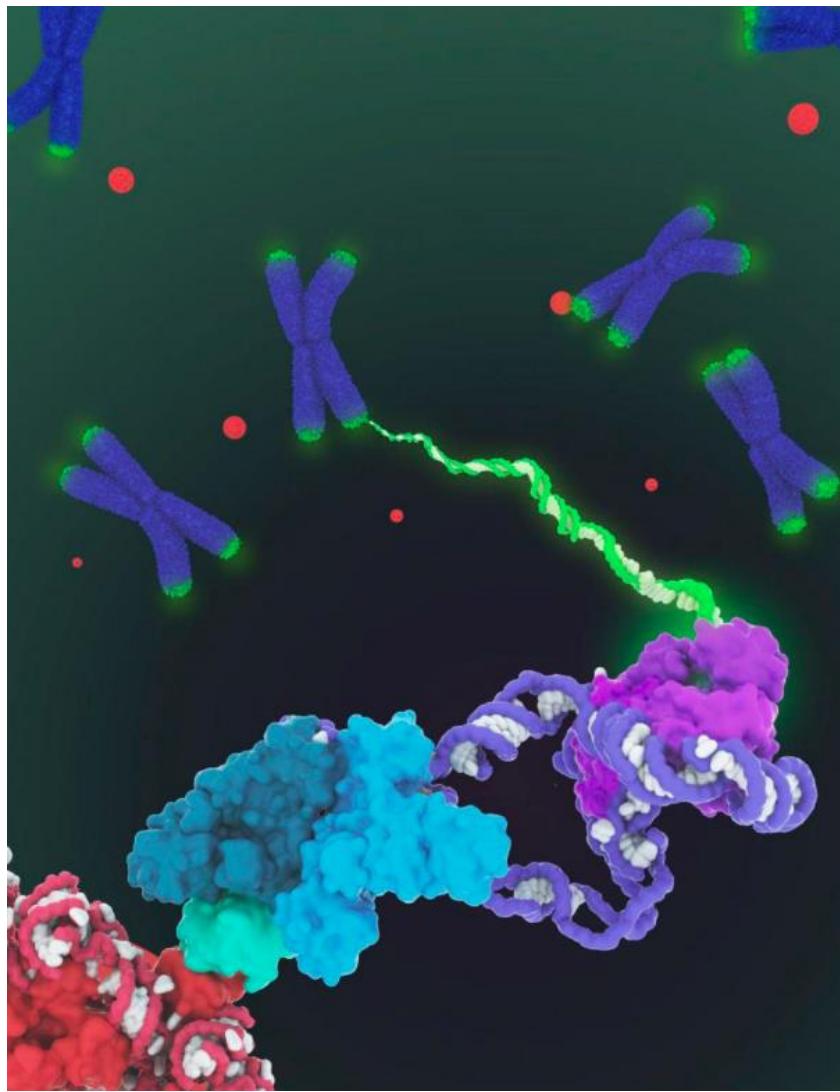


Telomere length of an elderly adult.









Nguyen Nature 2008

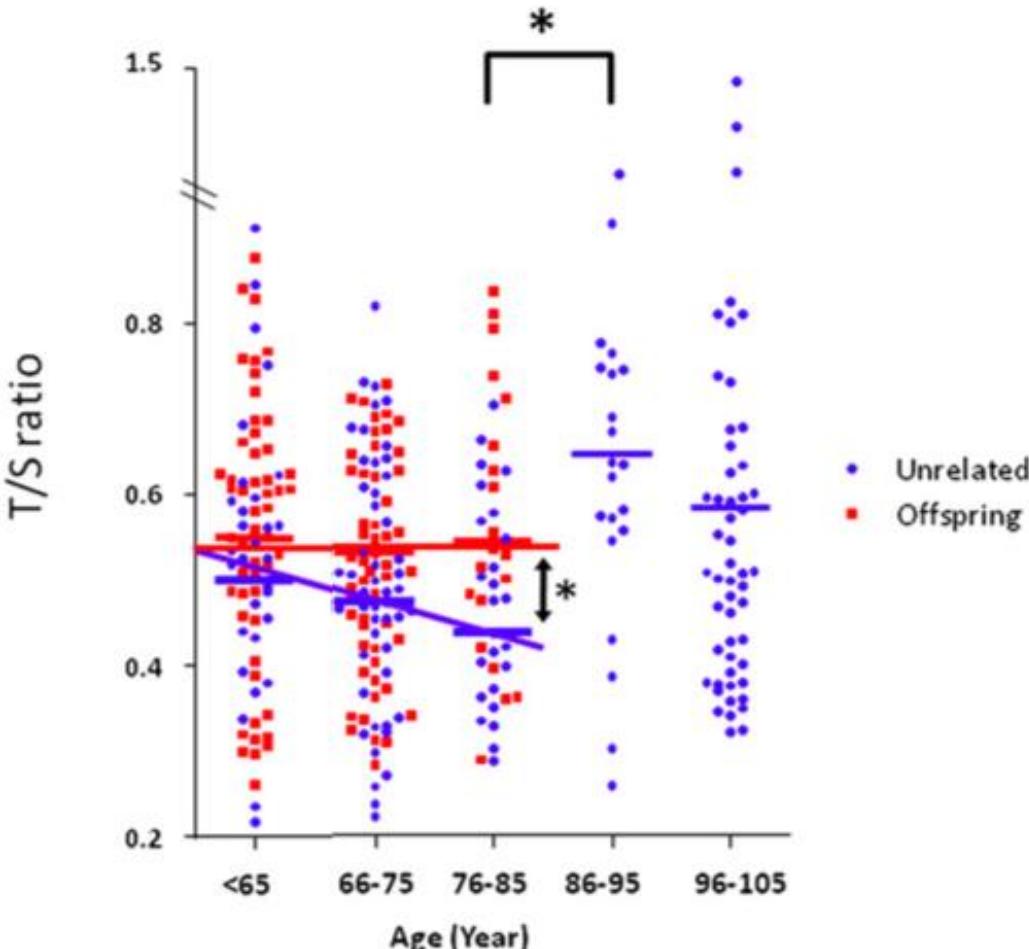


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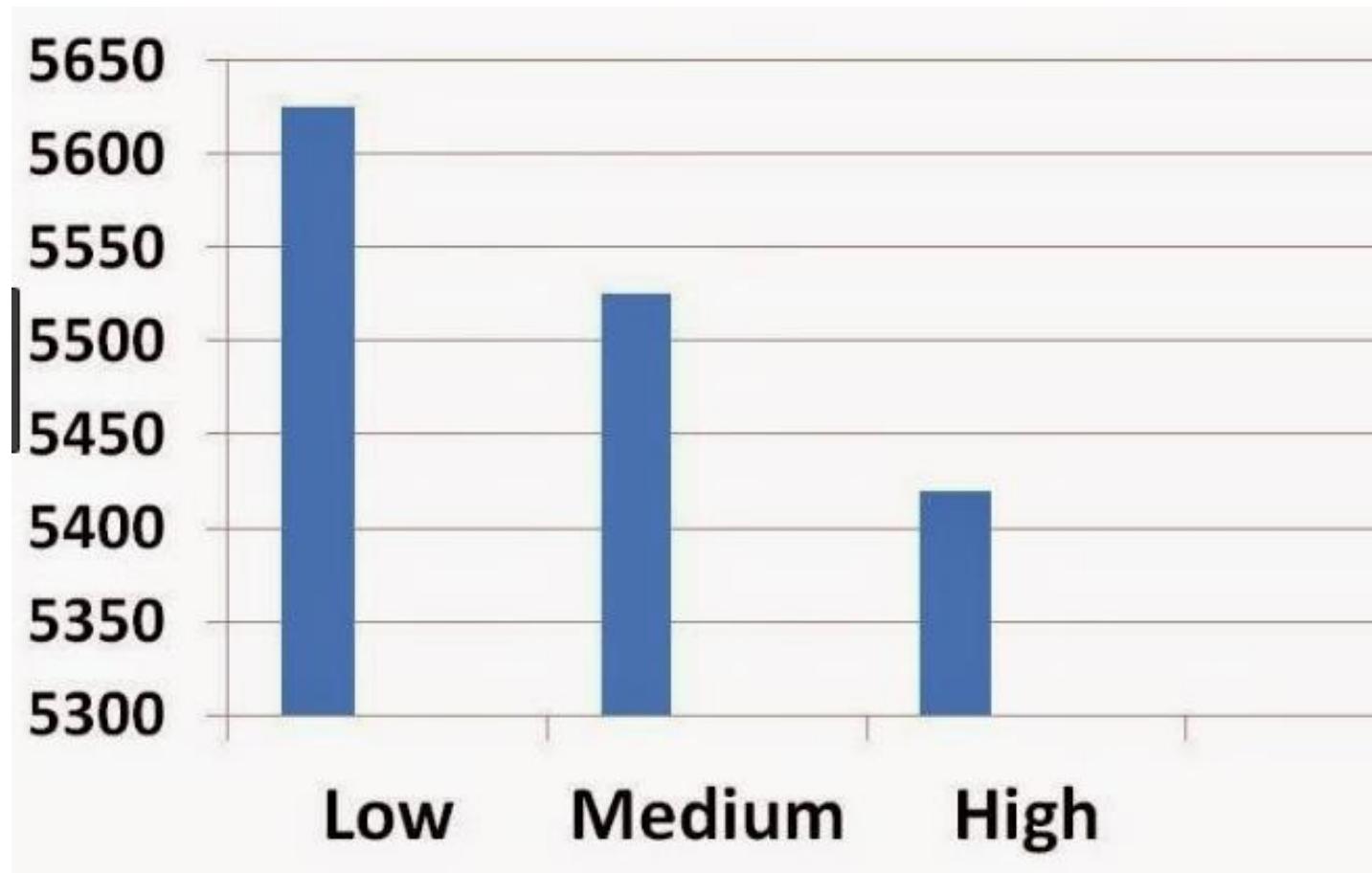
Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians

Gil Atzmon^{a,b,1,2}, Miook Cho^{a,1}, Richard M. Cawthon^c, Temuri Budagov^b, Micol Katz^b, Xiaoman Yang^b, Glenn Siegel^b, Aviv Bergman^d, Derek M. Huffman^{a,b}, Clyde B. Schechter^e, Woodring E. Wright^f, Jerry W. Shay^f, Nir Barzilai^{a,b}, Diddahally R. Govindaraju^g, and Yousin Suh^{a,b,2}

^aDepartments of Medicine and Genetics, Albert Einstein College of Medicine, Bronx, NY 10461; ^bInstitute for Aging Research, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY 10461; ^cDepartment of Human Genetics, University of Utah, Salt Lake City, UT 84112; ^dDepartment of



Τάση Περιπλάνησης του Εγκεφάλου vs Σύμπτυξης Τελομερών



Stand up for health—avoiding sedentary behaviour might lengthen your telomeres: secondary outcomes from a physical activity RCT in older people

Per Sjögren,¹ Rachel Fisher,² Lena Kallings,³ Ulrika Svenson,⁴ Göran Roos,⁴
Mai-Lis Hellénius⁵

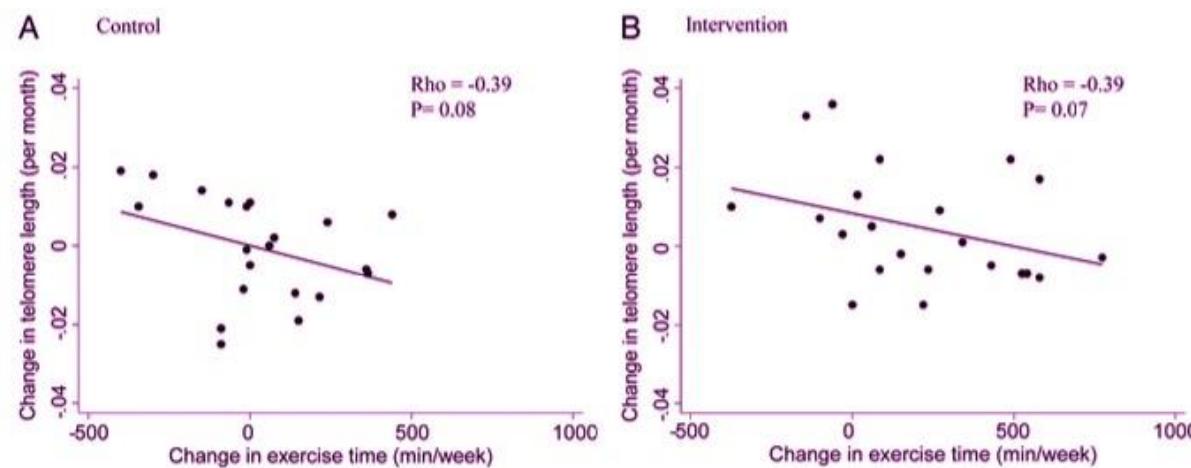
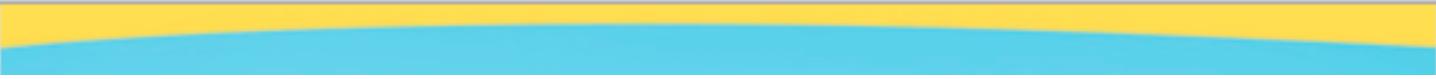


Figure 1 (A and B) Relationship between changes in telomere length (per month) and changes in exercise time of at least moderate intensity (min/week) over 6 months in individuals receiving minimal intervention (A, control, n=21) or individualised physical activity on prescription (B, intervention, n=21). Rho and p Values derived from Spearman rank correlation.





Shortened telomeres in individuals with abuse in alcohol consumption

Sofia Pavanello¹, Mirjam Hoxha², Laura Dioni², Pier Alberto Bertazzi², Rossella Snenghi³,
Alessandro Nalesso³, Santo Davide Ferrara³, Massimo Montisci³ and Andrea Baccarelli⁴

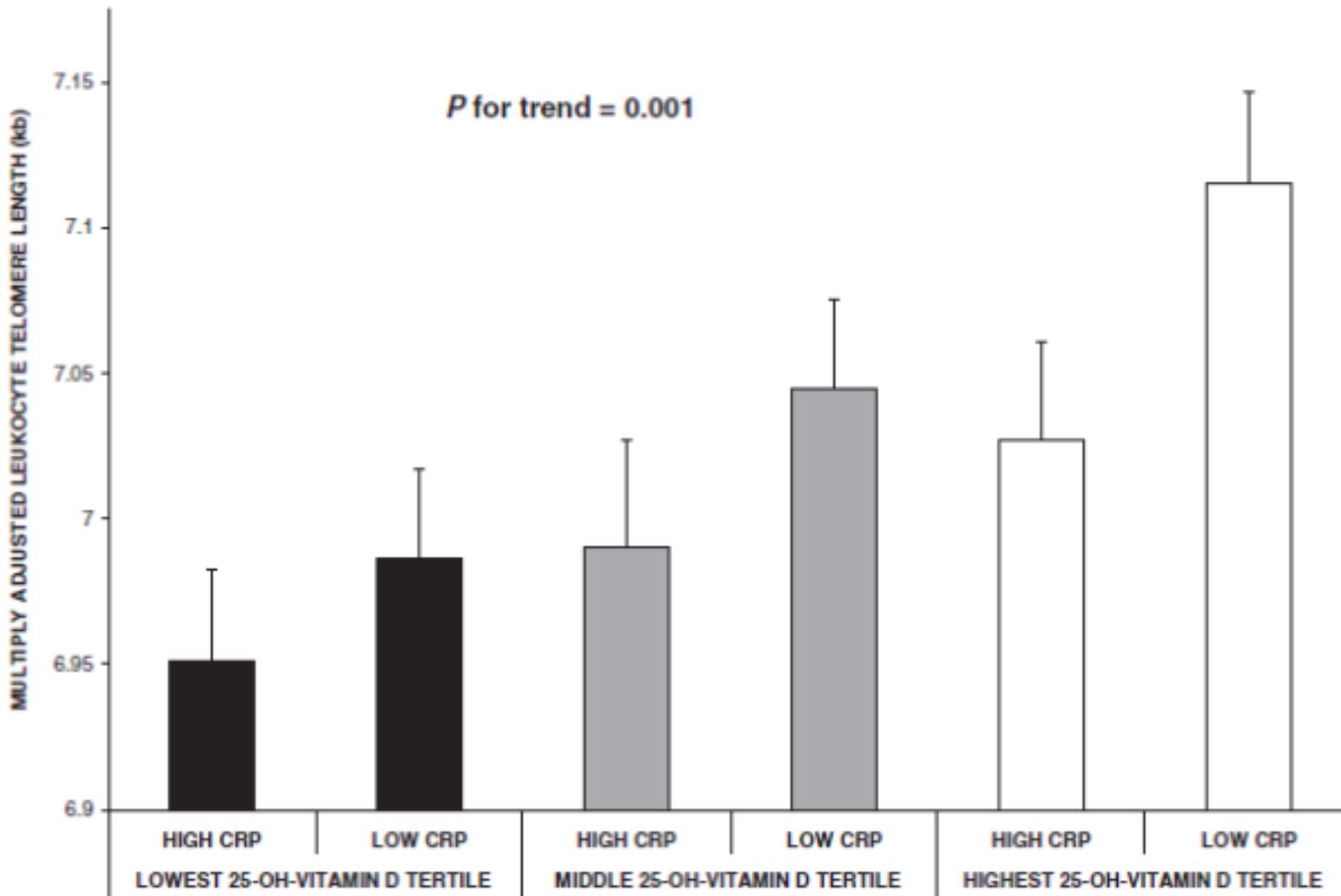
Table 2. Telomere length in alcohol abusers and controls

	Alcohol abusers	Controls	Statistics	
	n = 200	n = 257	p value Unadjusted	p-value Adjusted ²
Telomere length (T/S)				
Geometric mean (range) ¹	0.43 (0.20–1.11)	0.87 (0.30–4.84)	<0.0001	<0.0001
N (%) ≤ 5° percentile TL value of controls (0.38 T/S)	59 (30)	14(5)	<0.0001	0.0005

¹Unadjusted geometric means. Geometric means adjusted by age, BMI, current smoking, vegetables, and job at elevated risk of accident were 0.42 in alcohol abusers and 0.87 in controls. ²Adjusted by age, BMI, current smoking, vegetables, job at elevated risk of accident.



VITAMIN D AND TELOMERE LENGTH



Richards Am J Clin Nutr 2007



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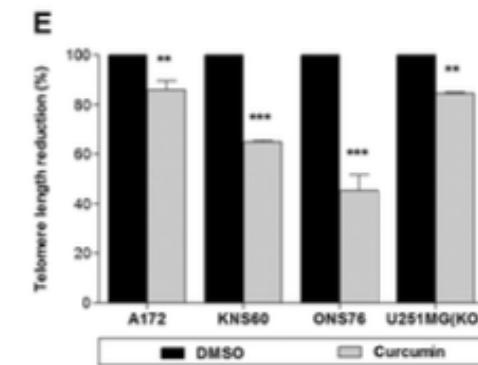
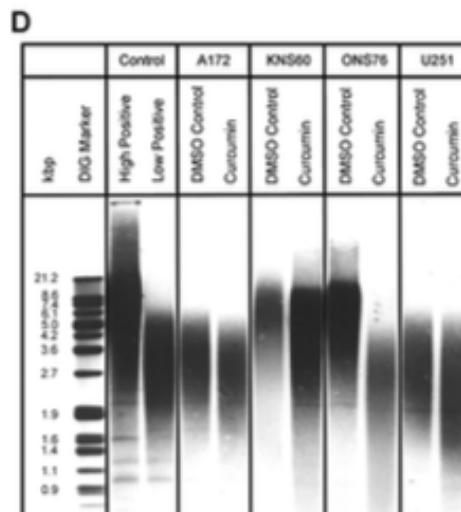
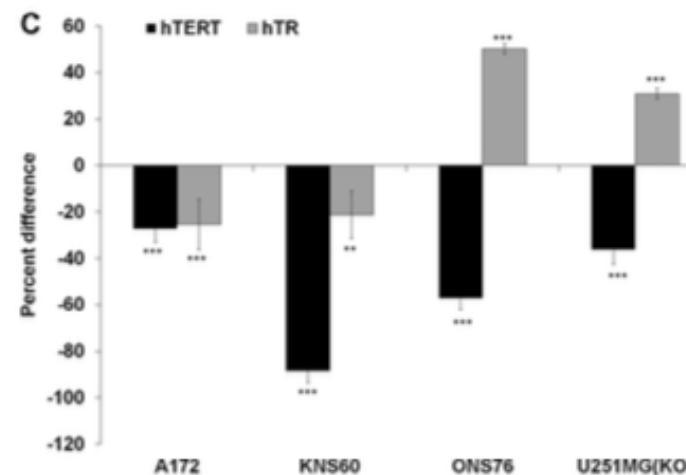
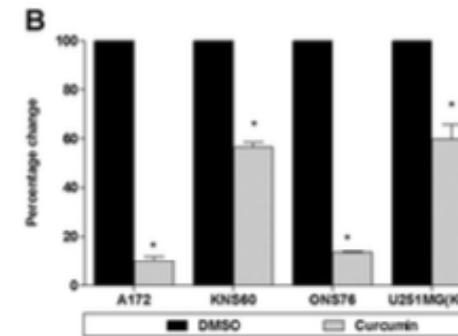
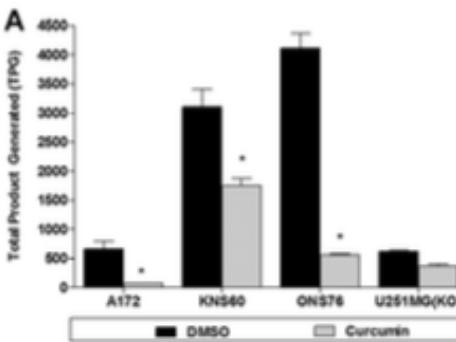
Curcumin Inhibits Telomerase and Induces Telomere Shortening and Apoptosis in Brain Tumour Cells

Aik Kia Khaw,¹ M. Pradeepa Hande,¹ Guruprasad Kalthur,^{1,2} and M. Prakash Hande^{1,*}

¹Genome Stability Laboratory, Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

²Department of Obstetrics and Gynaecology, Clinical Embryology, Kasturba Medical College, Manipal University, Manipal 576 104, India

³Tembusu College, National University of Singapore, Singapore 138598, Singapore

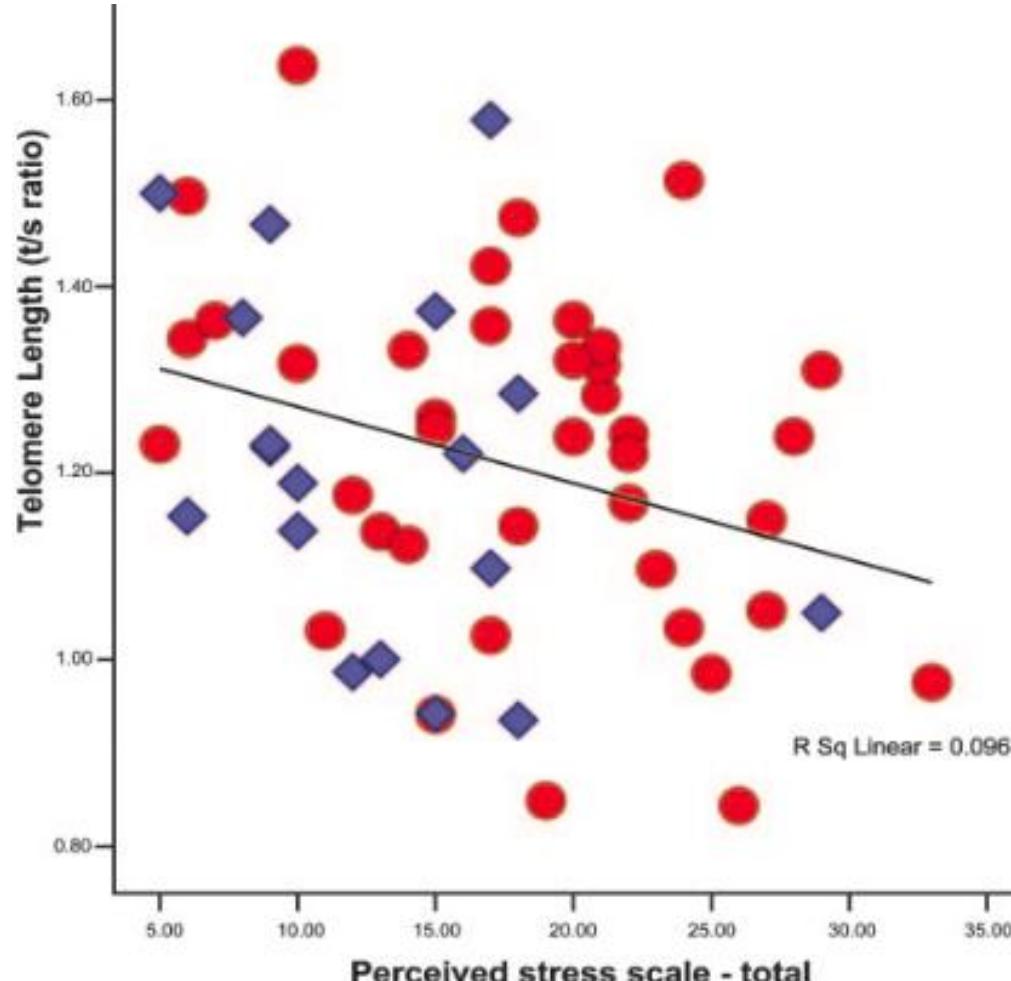


Accelerated telomere shortening in response to life stress

Elissa S. Epel*, Elizabeth H. Blackburn†, Jue Lin‡, Firdaus S. Dhabhar§, Nancy E. Adler*, Jason D. Morrow¶, and Richard M. Cawthon||

*Department of Psychiatry, University of California, 3333 California Street, Suite 465, San Francisco, CA 94143; †Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143; ‡Department of Oral Biology, College of Dentistry, and Department of Molecular Virology, Immunology, and Medical Genetics, College of Medicine, Ohio State University, Columbus, OH 43210; ¶Department of Medicine and Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232; and ||Department of Human Genetics, University of Utah, 15 North 2030 E Street, Room 2100, Salt Lake City, UT 84112

PNAS



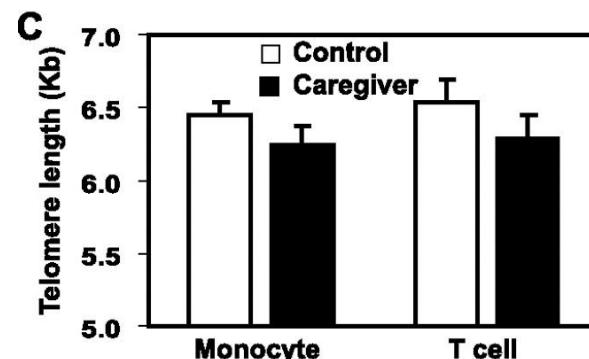
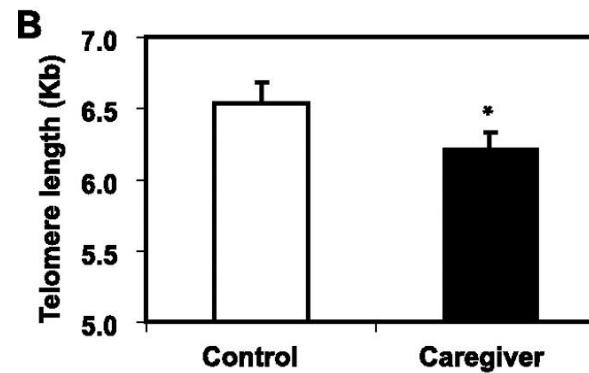
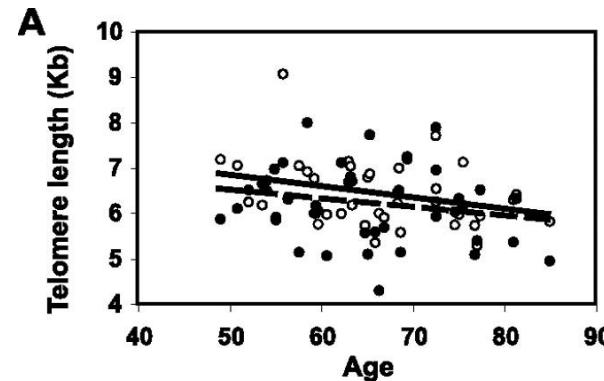
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Shortened telomere length of PBMC, T cells, and monocytes in Alzheimer's disease caregivers.

The Journal of Immunology

Accelerated Telomere Erosion Is Associated with a Declining Immune Function of Caregivers of Alzheimer's Disease Patients¹

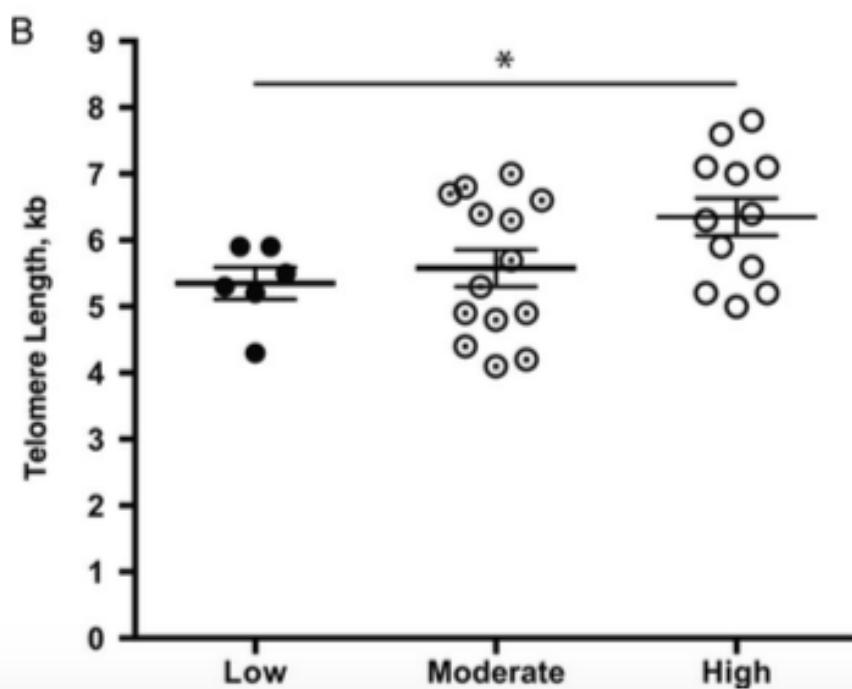
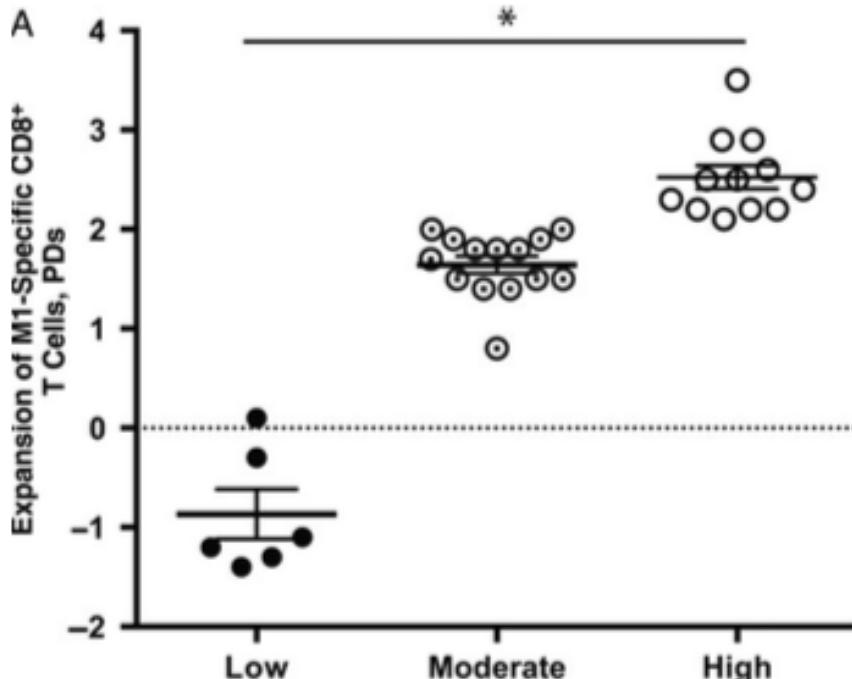
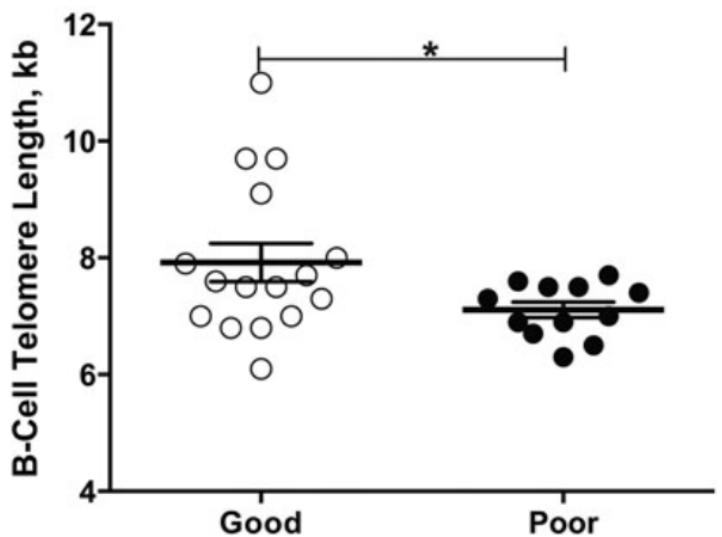
Amanda K. Damjanovic,* Yinhua Yang,* Ronald Glaser,^{2†§} Janice K. Kiecolt-Glaser,^{†‡¶}
Huy Nguyen,* Bryon Laskowski,^{†‡} Yixiao Zou,* David Q. Beversdorf,^{||}
and Nan-ping Weng^{2*}



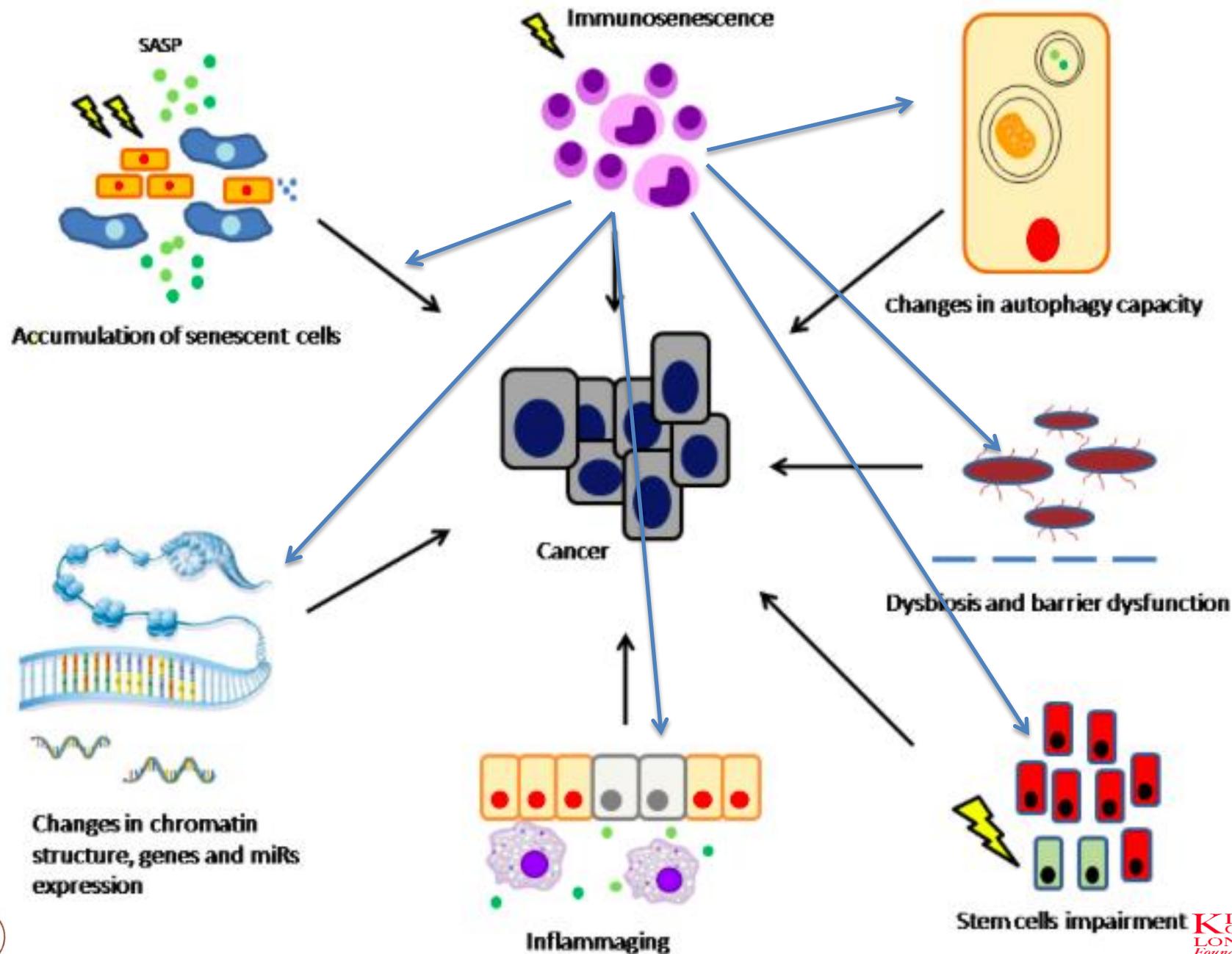
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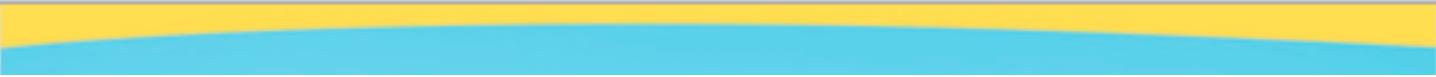
Telomere Length as an Indicator of the Robustness of B- and T-Cell Response to Influenza in Older Adults

Kevin Najarro,^{1,a} Huy Nguyen,^{1,a} Guobing Chen,¹ Mai Xu,¹ Sandy Alcorta,² Xu Yao,³ Linda Zukley,² E. Jeffrey Metter,² Thai Truong,¹ Yun Lin,¹ Huifen Li,³ Mathias Oelke,⁴ Xiyun Xu,⁵ Shari M. Ling,² Dan L. Longo,⁶ Jonathan Schneck,⁴ Sean Leng,³ Luigi Ferrucci,² and Nan-ping Weng¹



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R. Ferrara et al./Cancer Treatment Reviews 60 (2017) 60–68

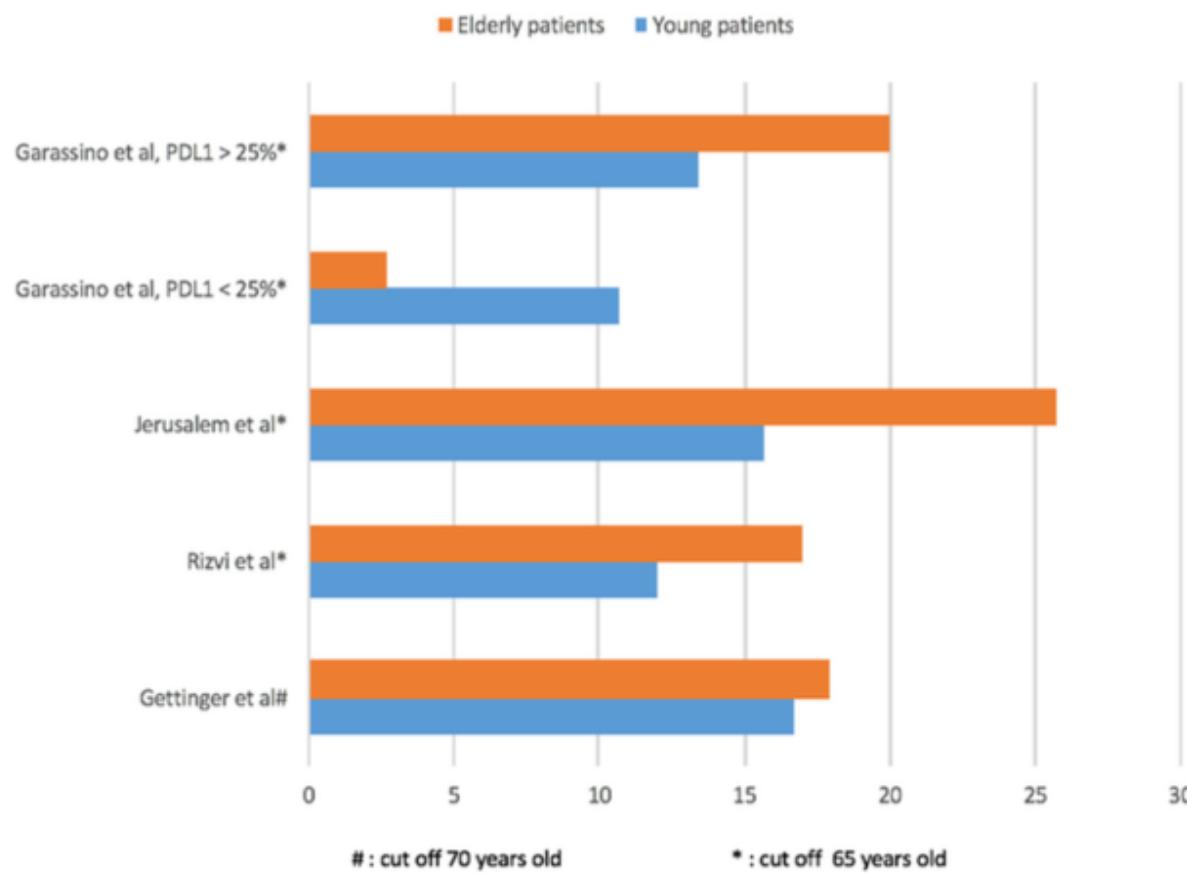
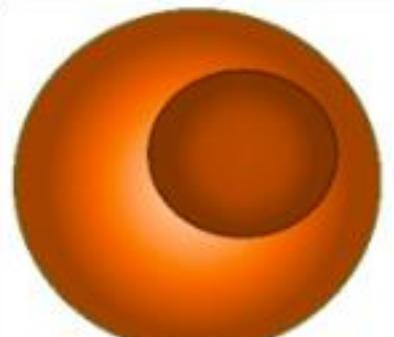


Fig. 1. ORR barplot stratified by age (cut-off: 65 years), from four phase I/II trials of anti PD-1/PD-L1 mAbs in advanced NSCLC.



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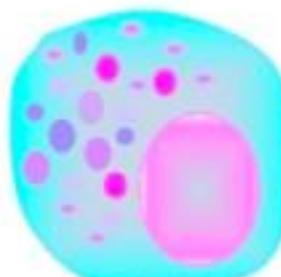
B lymphocyte

- Reduced development and numbers of naïve B cells
- Decreased diversity of B cell repertoires and B cell responses to new antigens



T lymphocyte

- Reduced development and numbers of naïve CD4⁺/CD8⁺ T cells
- Decline in CD4⁺ function and in CD8⁺ T cell cytotoxicity+proliferation
- Reduced generation of Th subsets



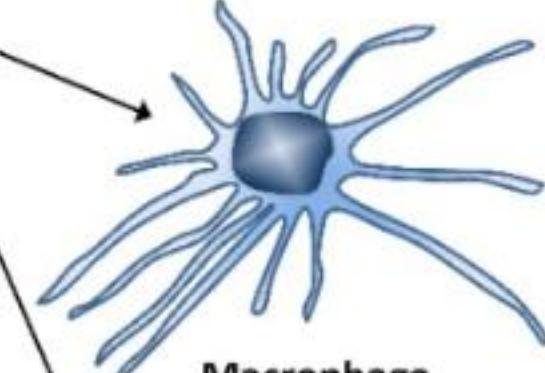
NK cell

- Reduced cytolytic potential and CD1 expression in NKT cells
- Decreased cytokine and chemokine production



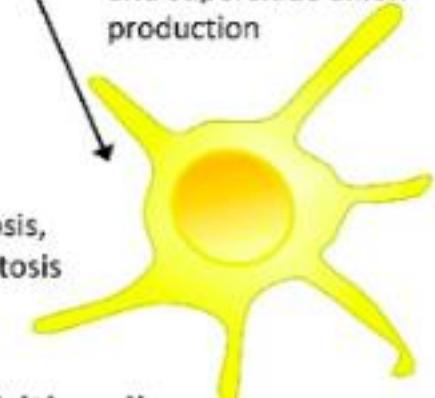
Neutrophils

- Decreased phagocytosis, chemotaxis and apoptosis function



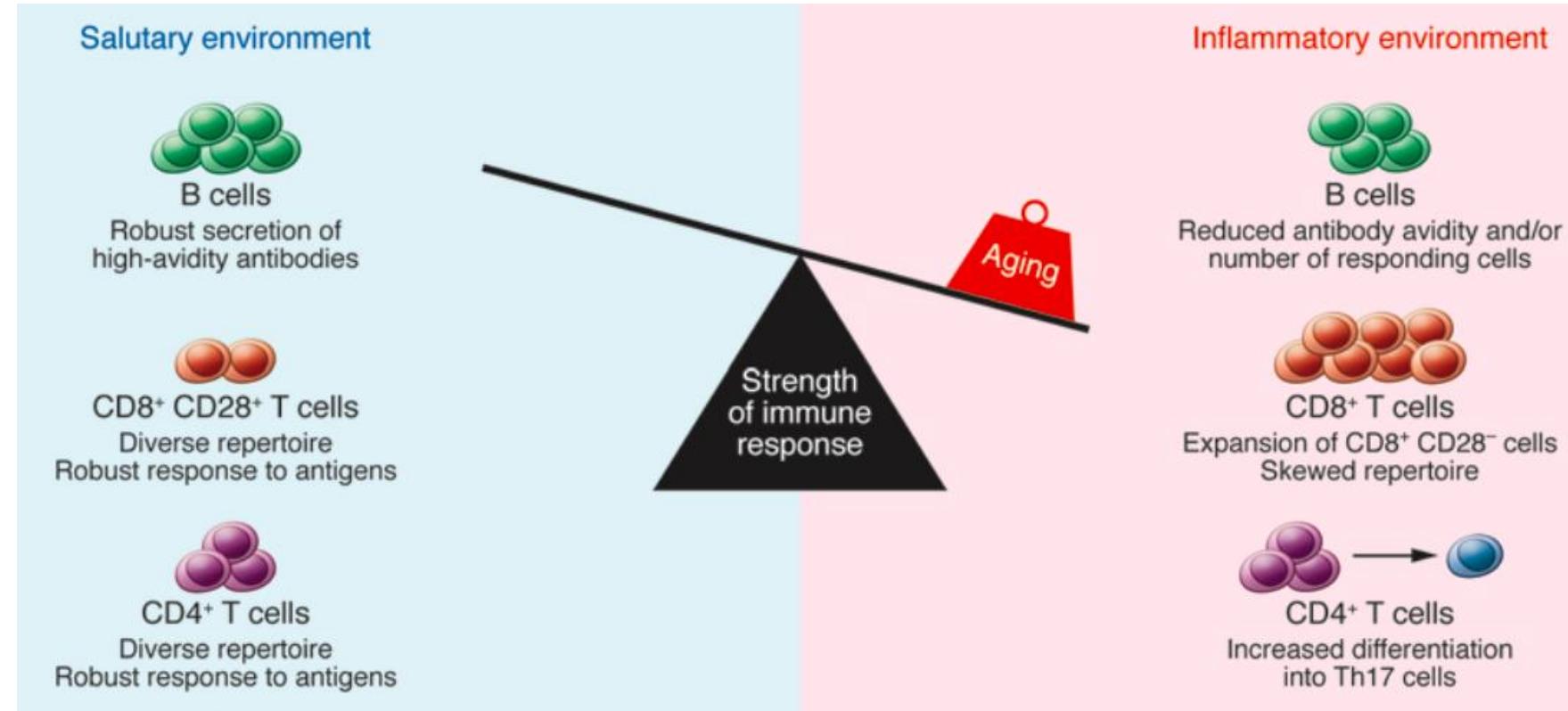
Macrophage

- Defective phagocytosis
- Decreased cytokine production, antigen presentation and superoxide anion production



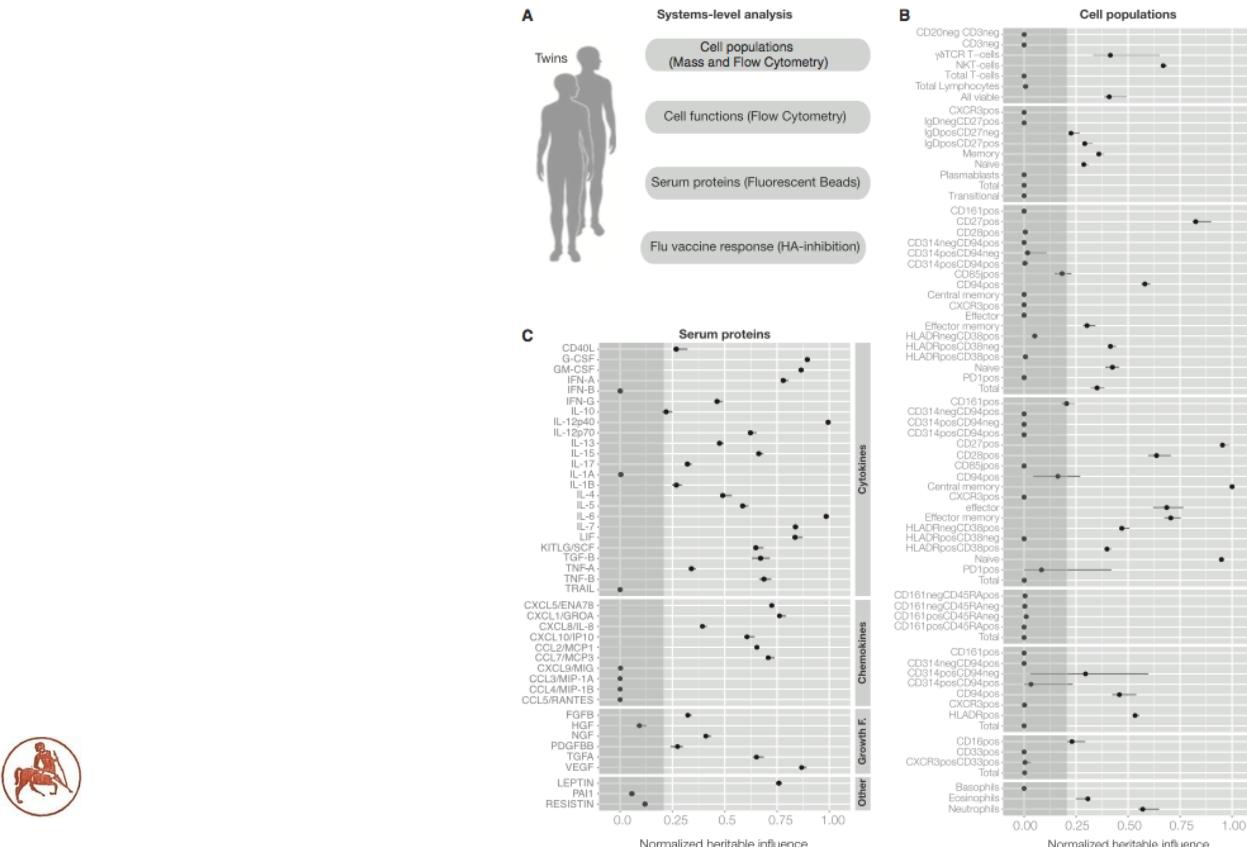
Dendritic cell

- Reduced IFN production and expression of CD25 and ICAM-1 in mature MODCs
- Reduction in lymphocyte cytotoxicity and greater migratory capacity of monocyte-macrophage derived APCs



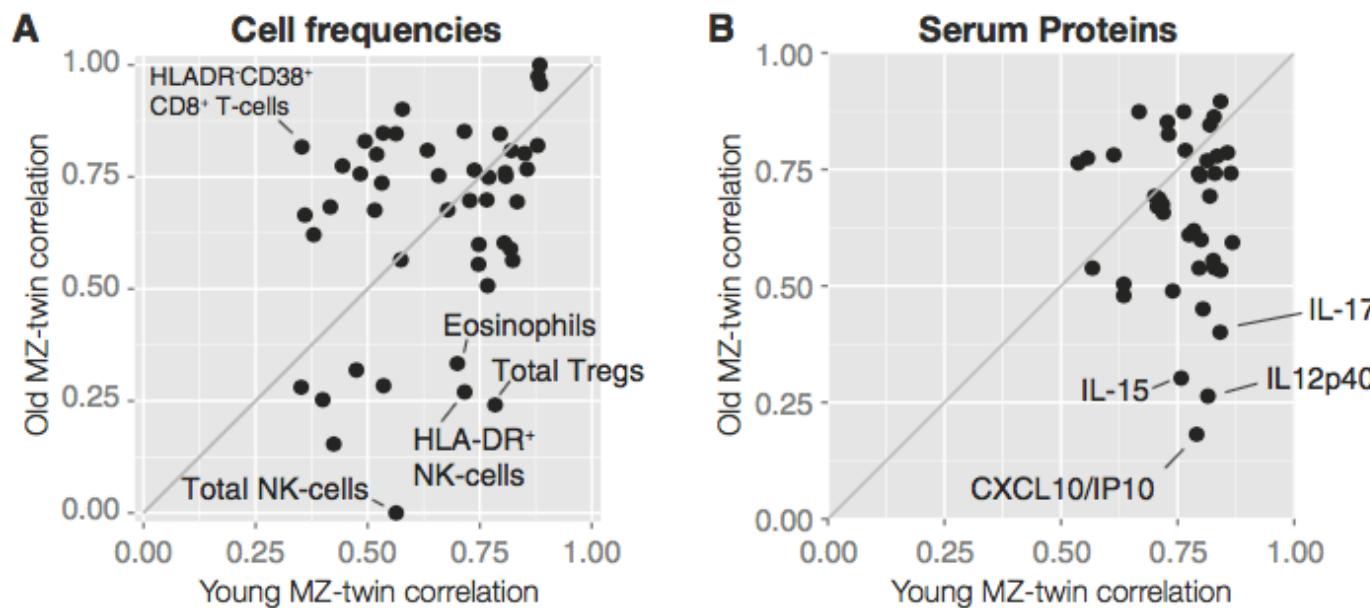
Variation in the Human Immune System Is Largely Driven by Non-Heritable Influences

Petter Brodin,^{1,2,3,11} Vladimir Jovic,^{4,11} Tianxiang Gao,⁴ Sanchita Bhattacharya,³ Cesar J. Lopez Angel,^{2,3} David Furman,^{2,3} Shai Shen-Orr,⁵ Cornelia L. Dekker,⁶ Gary E. Swan,⁷ Atul J. Butte,^{6,8} Holden T. Maecker,^{3,9} and Mark M. Davis^{2,3,10,*}



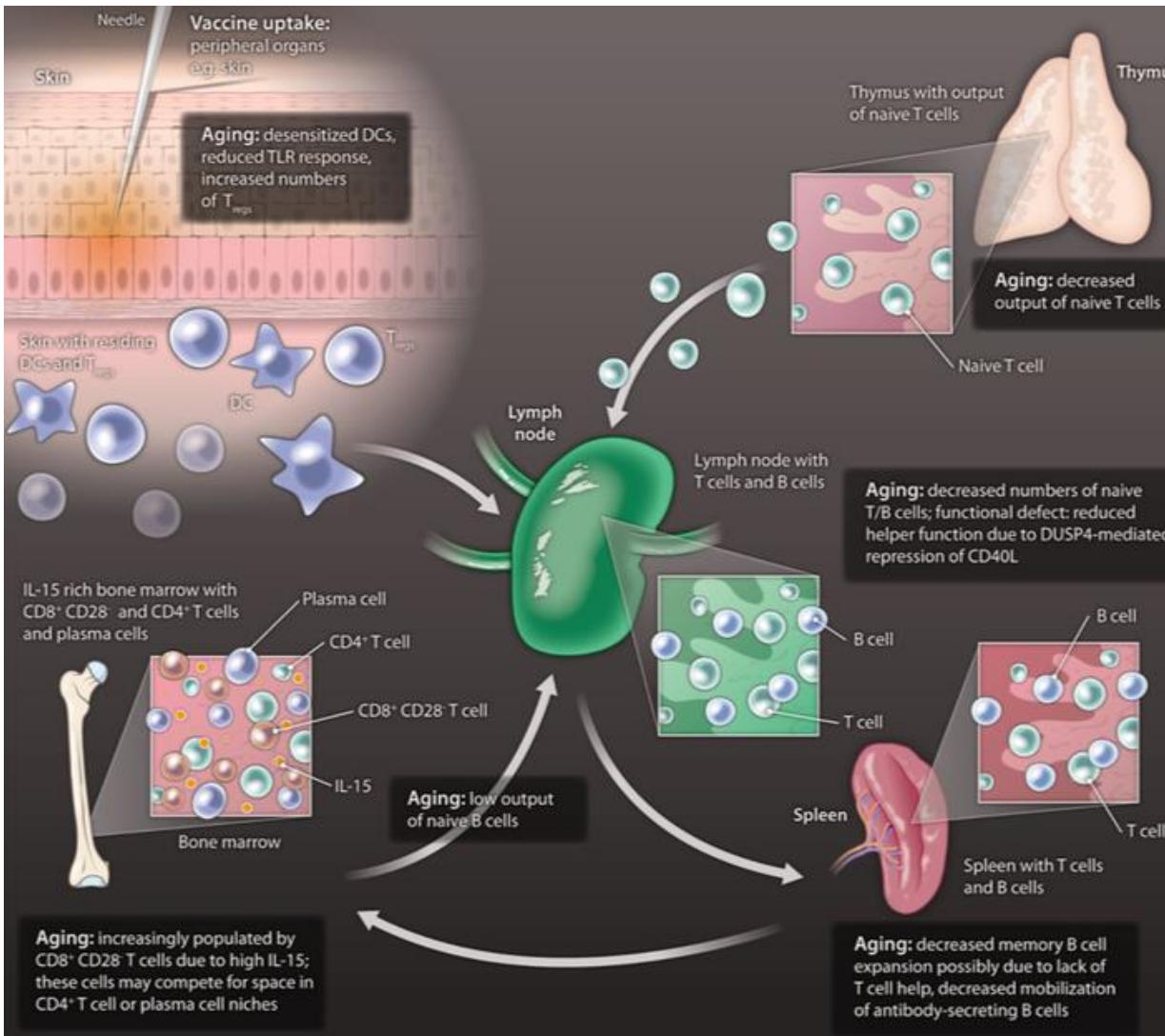
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The Gracefully Aging Immune System

Diana Boraschi,¹ M. Teresa Aguado,² Catherine Dutel,³ Jörg Goronzy,⁴ Jacques Louis,³ Beatrix Grubeck-Loebenstein,⁵ Rino Rappuoli,⁶ Giuseppe Del Giudice^{6*}

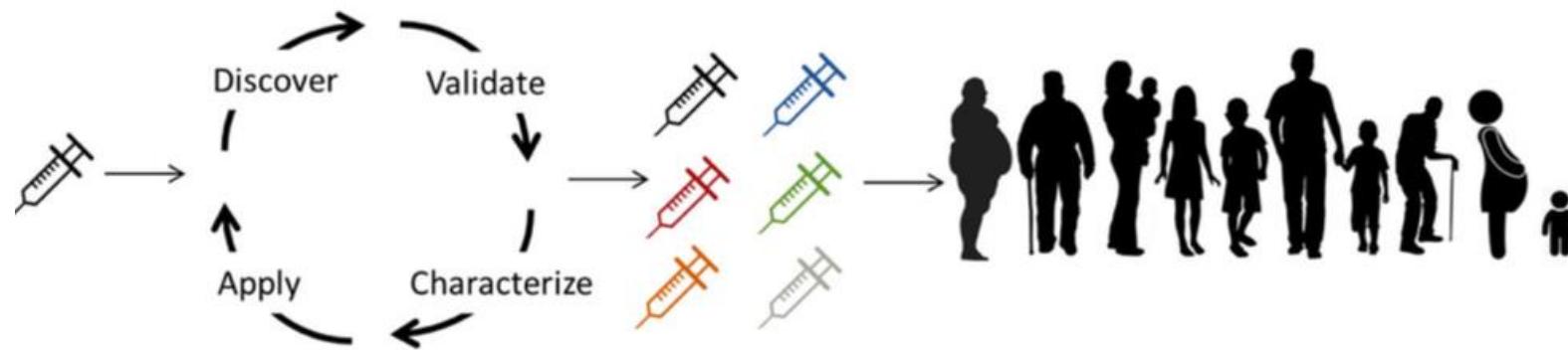


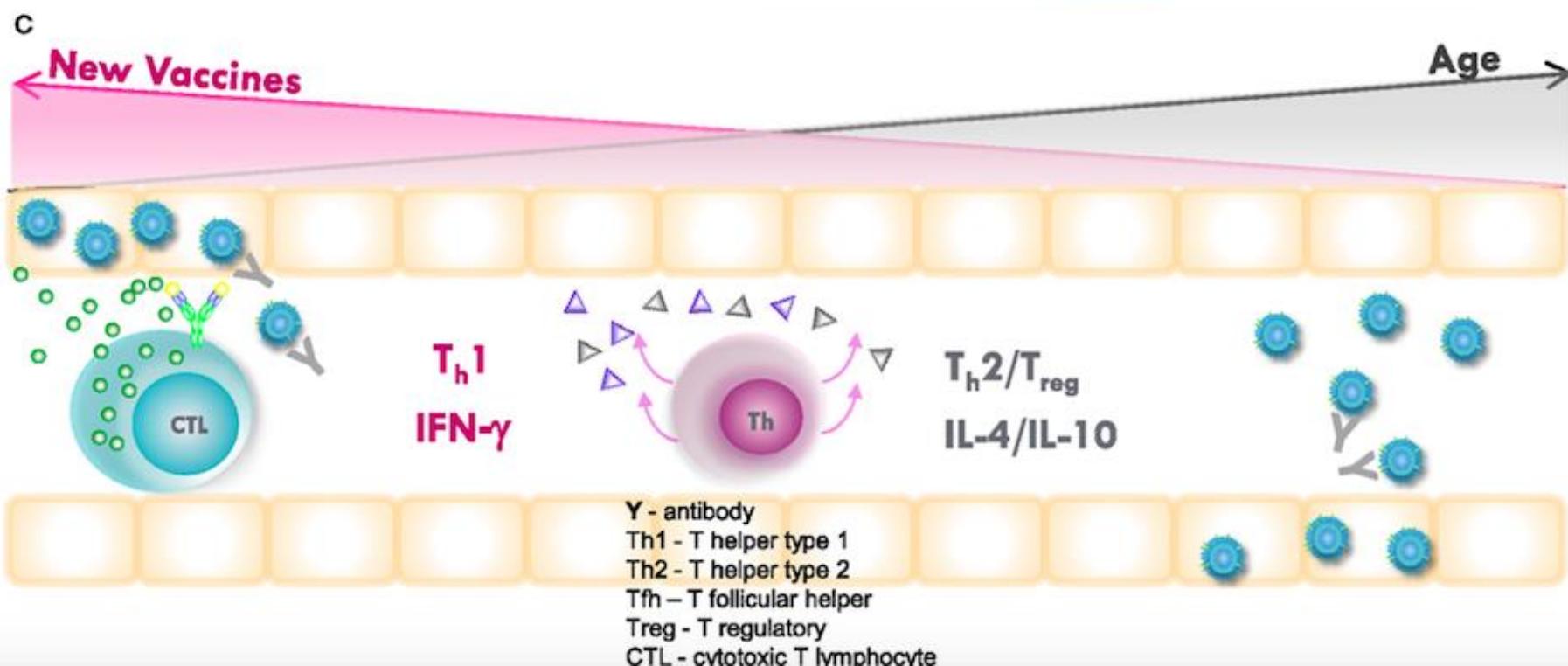
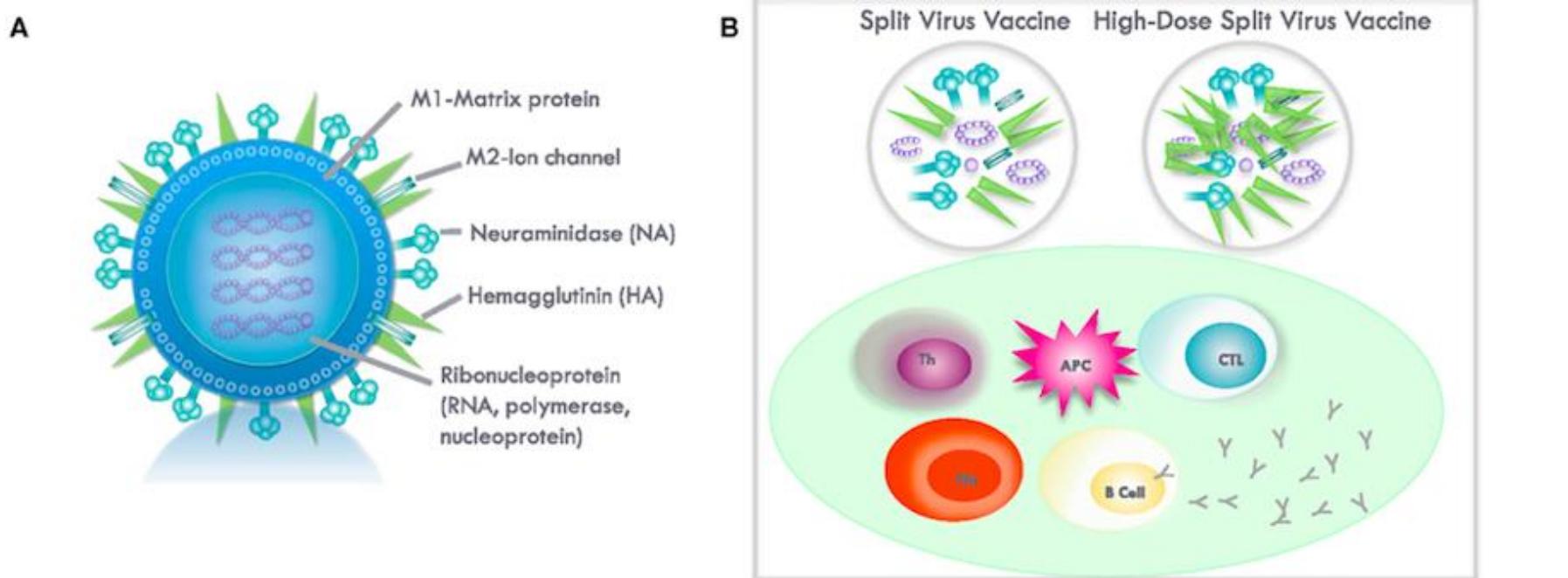
TAILORED VACCINES FOR THE ELDERLY

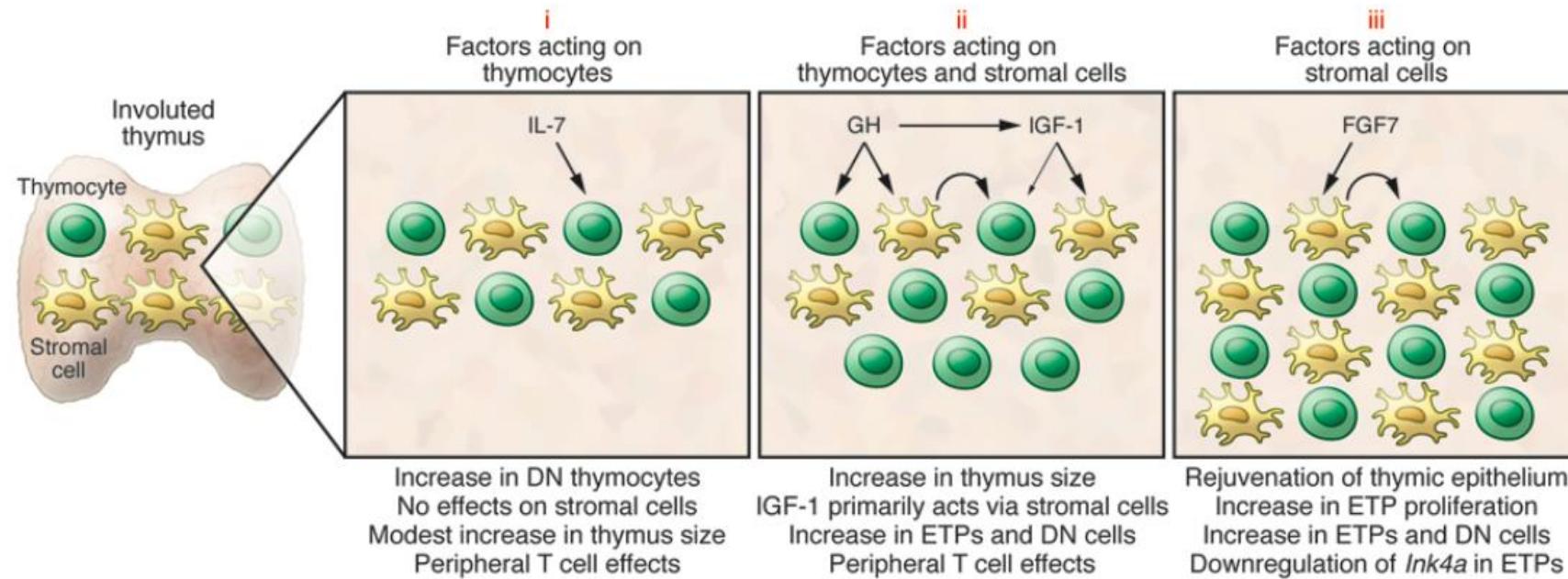
Adapting vaccination for the aging immune system

- Increasing dose
- Adjusting vaccine schedules
- Utilization of alternative routes

Personalized Vaccinology

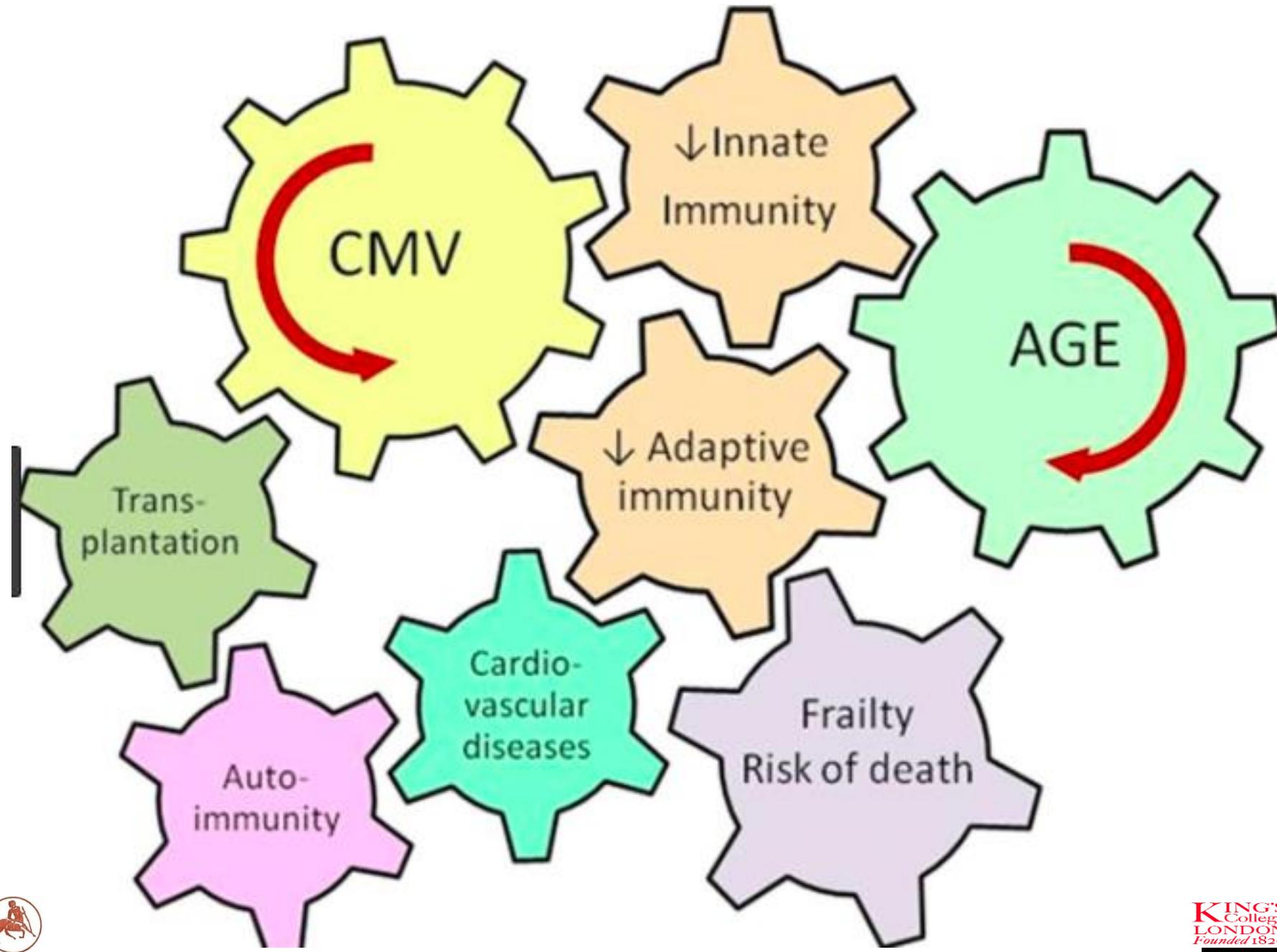


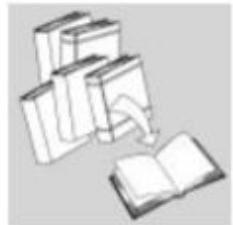




Montesino JCI 2013







Cytomegalovirus and human immunosenescence

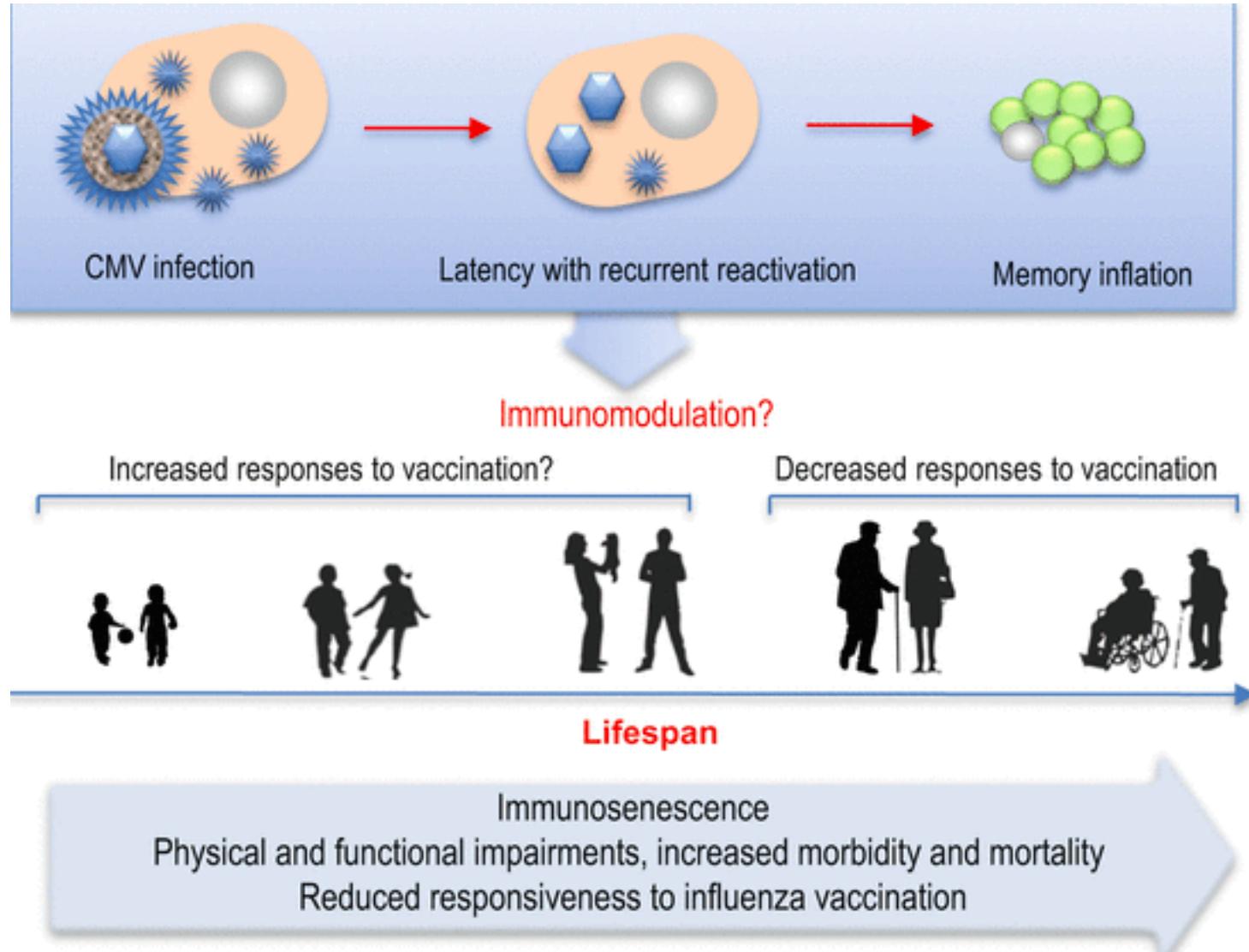
Graham Pawelec^{1*}, Evelyn Derhovanessian¹, Anis Larbi¹, Jan Strindhall² and Anders Wikby²

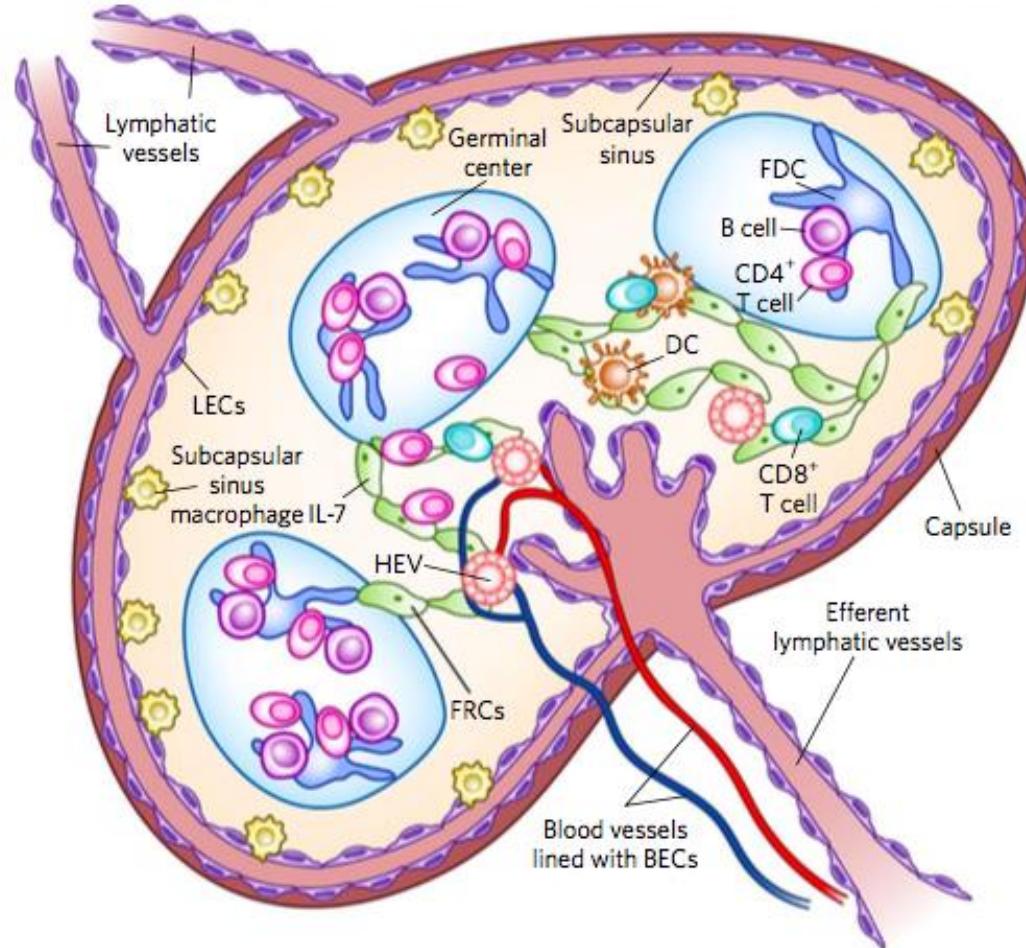
¹*Center for Medical Research, University of Tübingen Medical School, Tübingen, Germany*

²*Department of Natural Science and Biomedicine, School of Health Sciences, Jönköping University, Jönköping, Sweden*

Rev. Med. Virol. 2009; **19**: 47–56.
Published online 26 November 2008 in Wiley InterScience
(www.interscience.wiley.com)
DOI: 10.1002/rmv.598







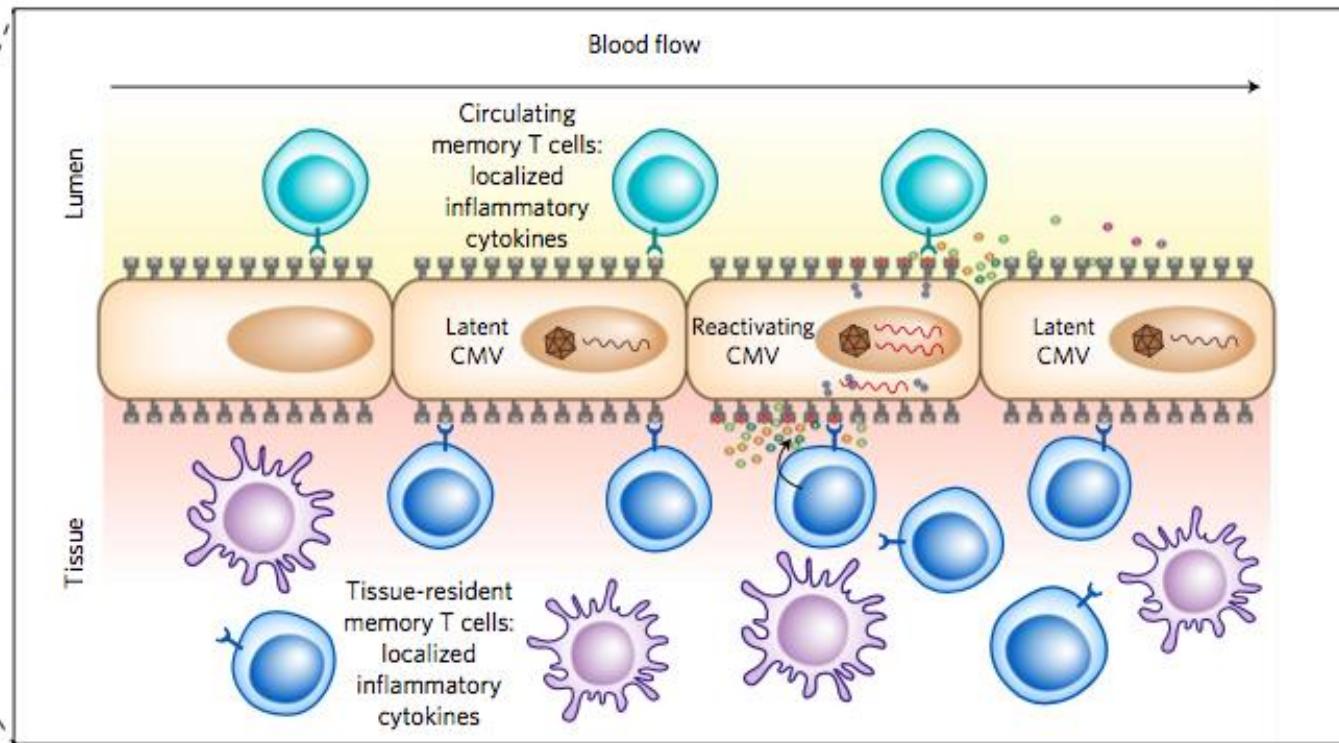
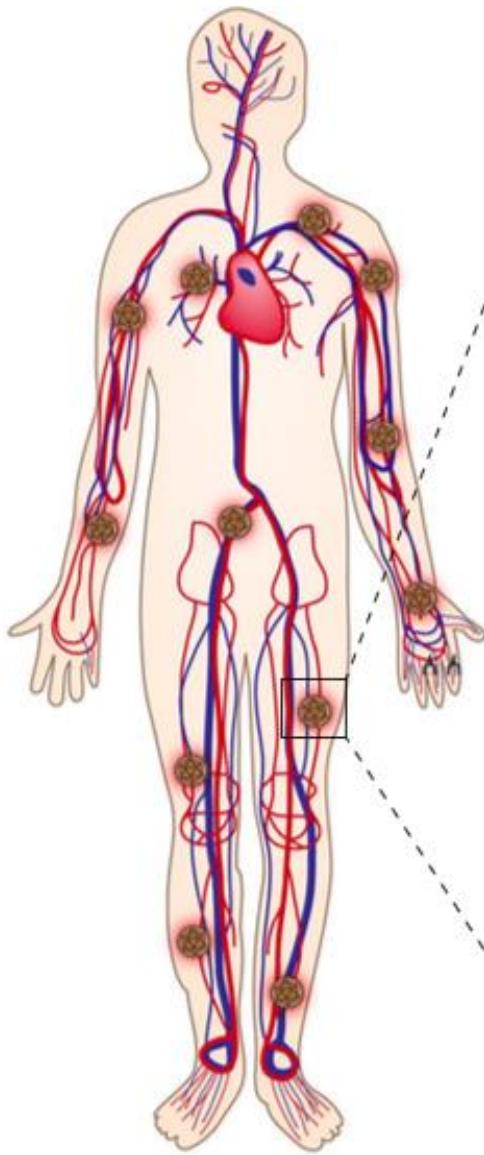
FRC
-Reduced and altered in aging LN (ref. 39)

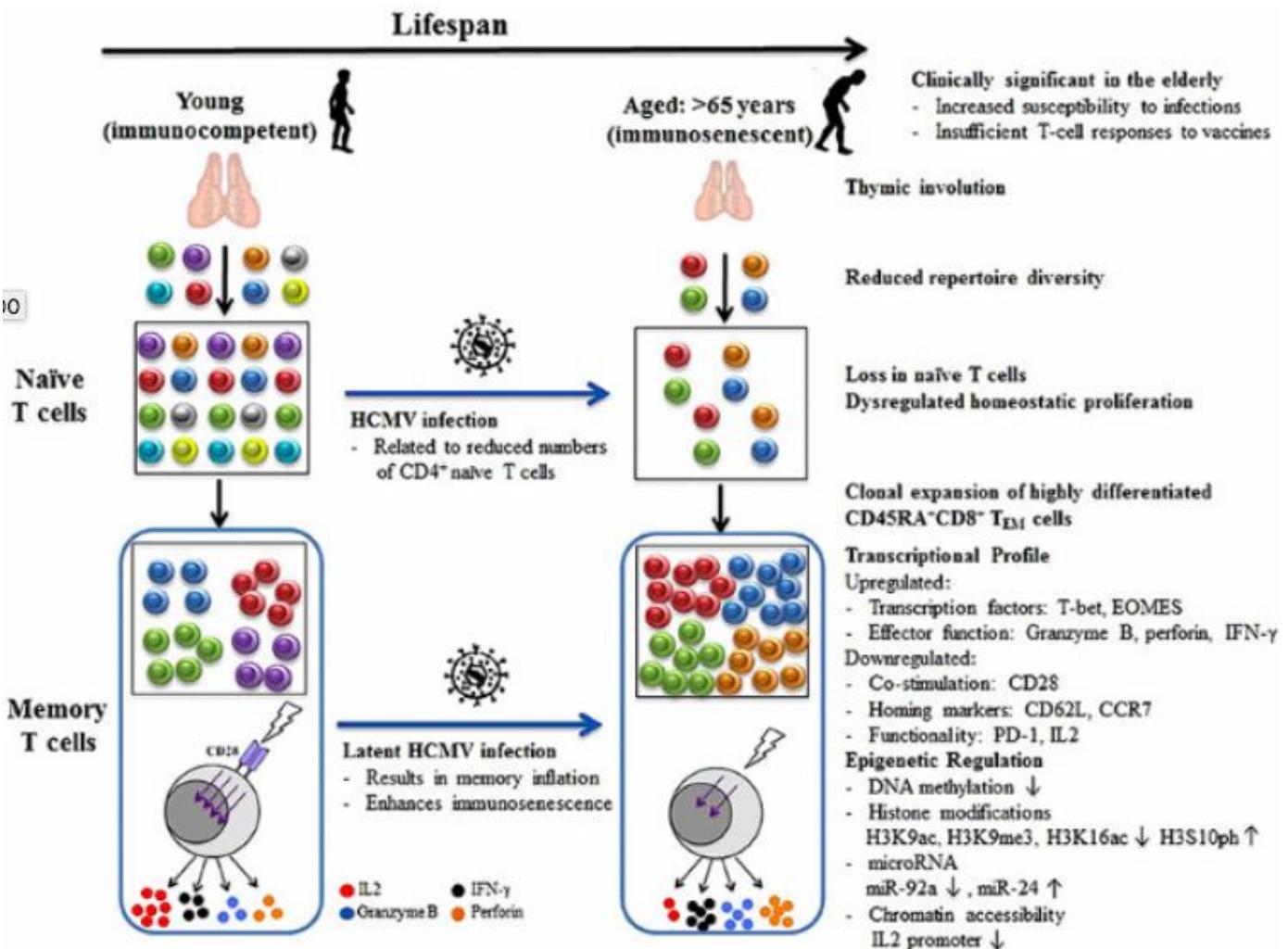
FDC
-Area decreased in aged mice (ref. 83)

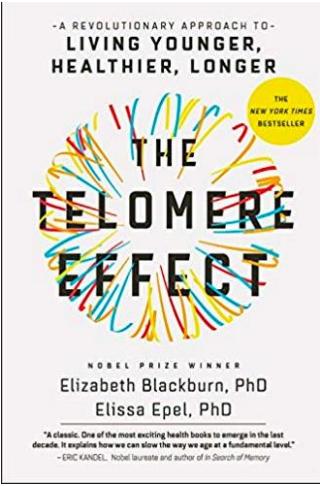
LECs
-LECs decrease numerically by 30-40% (H. Thompson, personal communication)

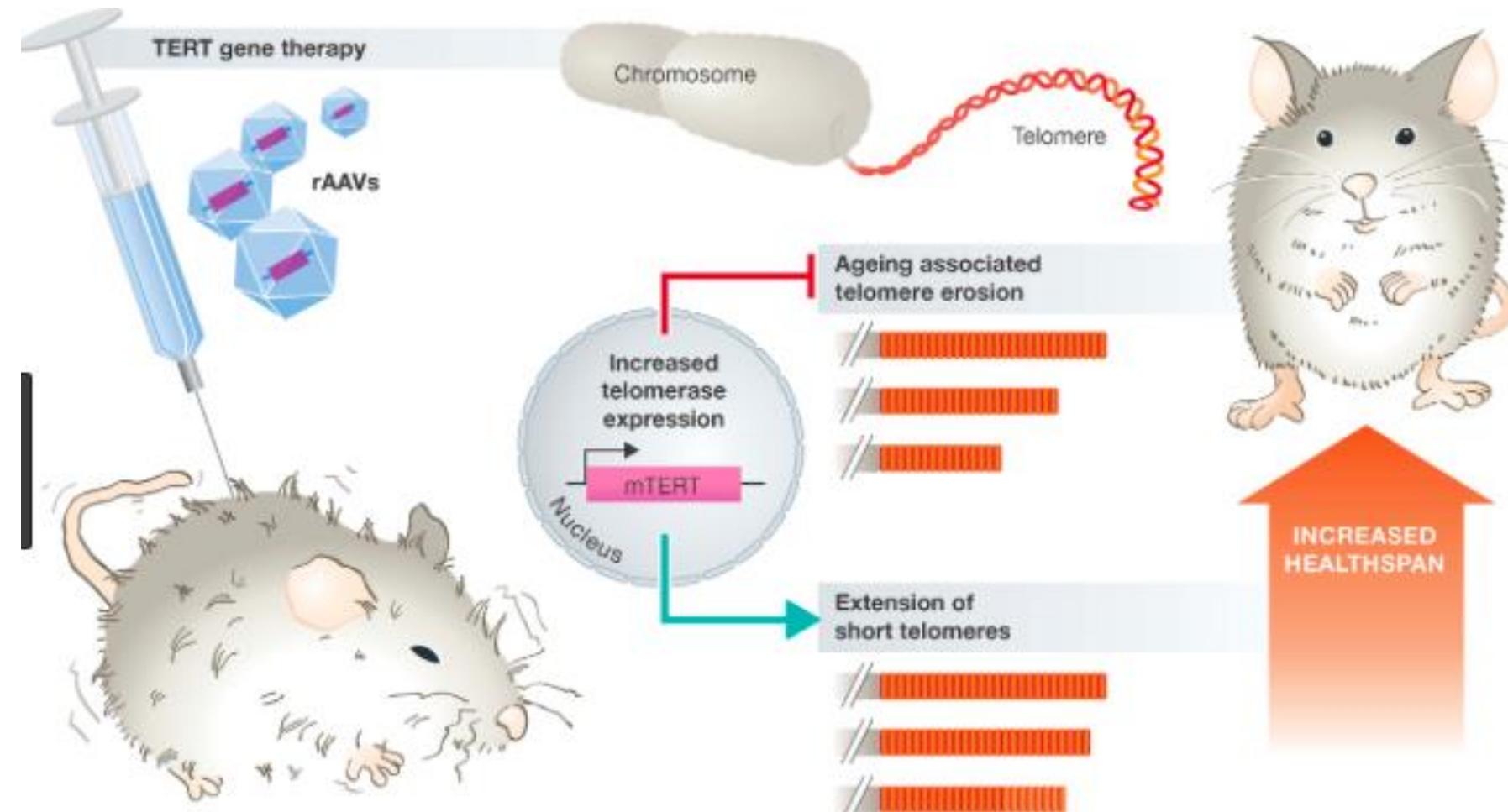
HEVs
-Impaired T cell diapedesis (ref. 49)











Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study

The Telomeres Mendelian Randomization Collaboration

JAMA Oncol 2017

Summary data were available for **35 cancers** and **48 non-neoplastic** diseases, corresponding to **420 081 cases** (median cases, 2526 per disease) and **1 093 105** controls (median, 6789 per disease)



Association Between Telomere Length and Risk of Cancer and Non-Neoplastic Diseases: A Mendelian Randomization Study

The Telomeres Mendelian Randomization Collaboration

Key Points

Question

What is the causal relevance of telomere length for risk of cancer and non-neoplastic diseases?

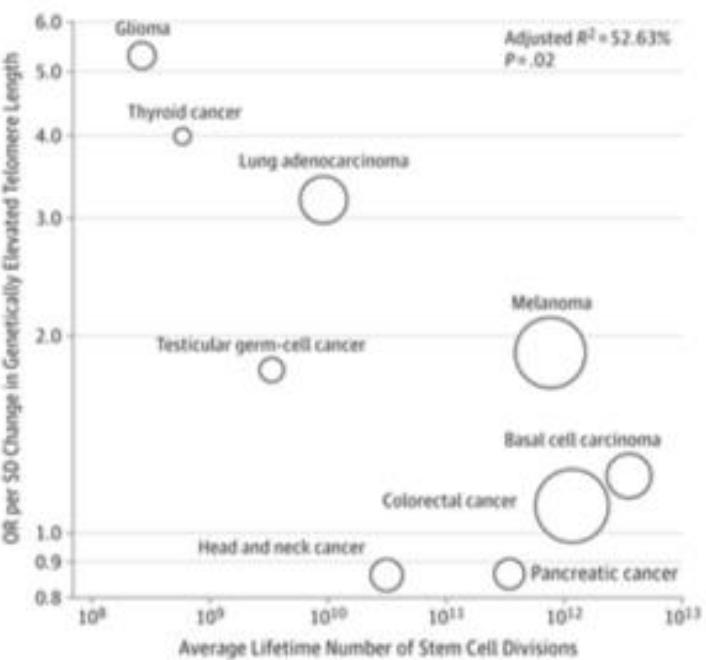
Findings

In this Mendelian randomization study, genetically longer telomeres were associated with higher odds of disease for 9 of 22 primary cancers tested but with reduced odds of disease for 6 of 32 primary non-neoplastic diseases, including cardiovascular diseases.

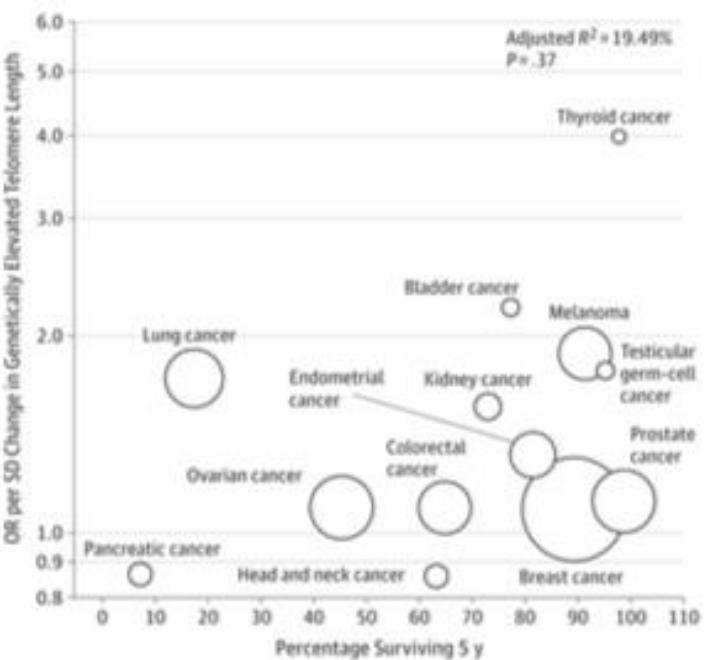
Meaning

It is likely that longer telomeres increase risk for several cancers but reduce risk for some non-neoplastic diseases, including cardiovascular diseases. This trade-off in risk should be carefully considered in any diagnostic, prognostic, or therapeutic applications based on telomere length.

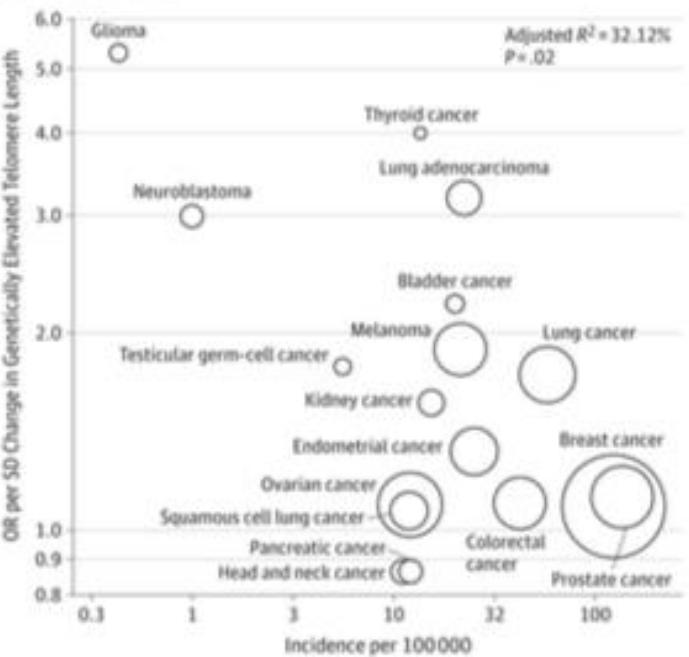
A Average lifetime number of stem cell divisions



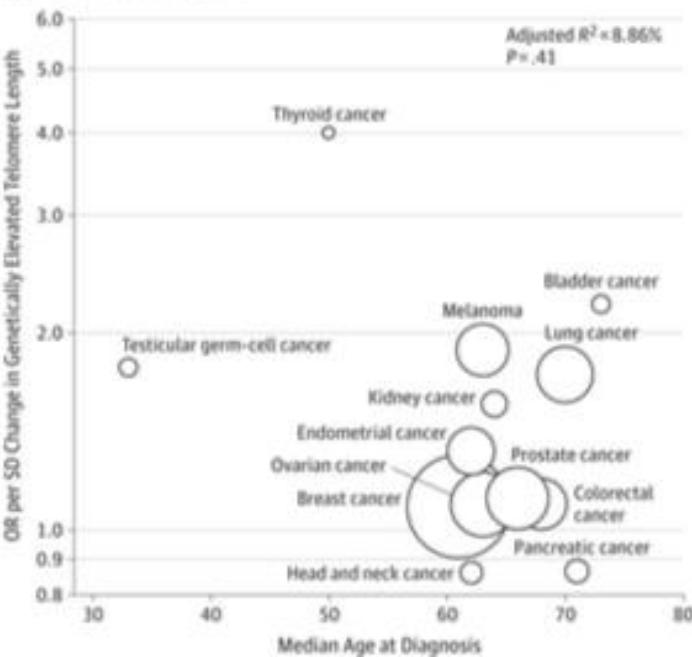
B Percentage surviving 5 y



C Cancer incidence



D Median age at diagnosis



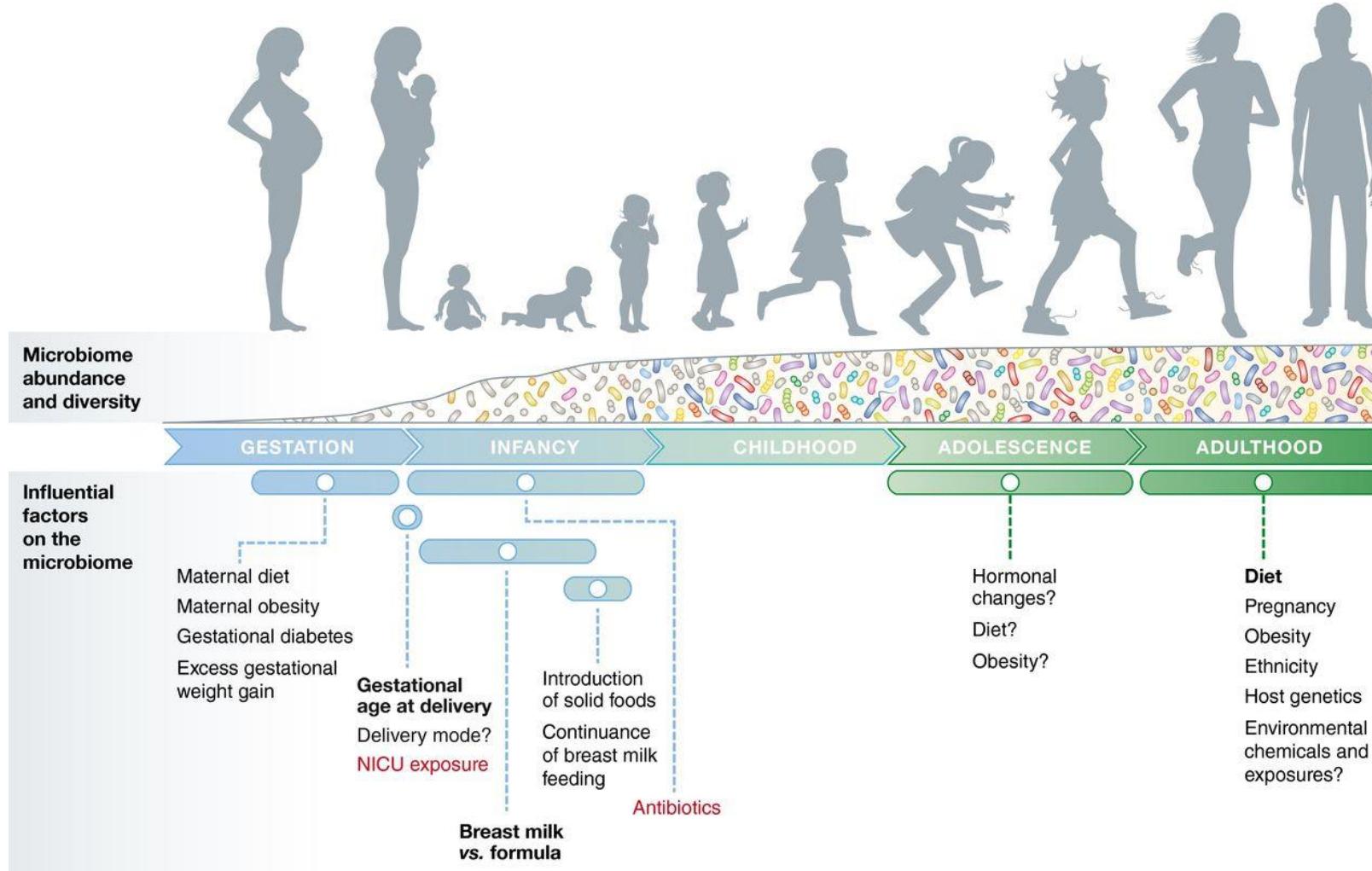
Το ανοσοποιητικό σύστημα στην τρίτη ηλικία

Σας ευχαριστώ



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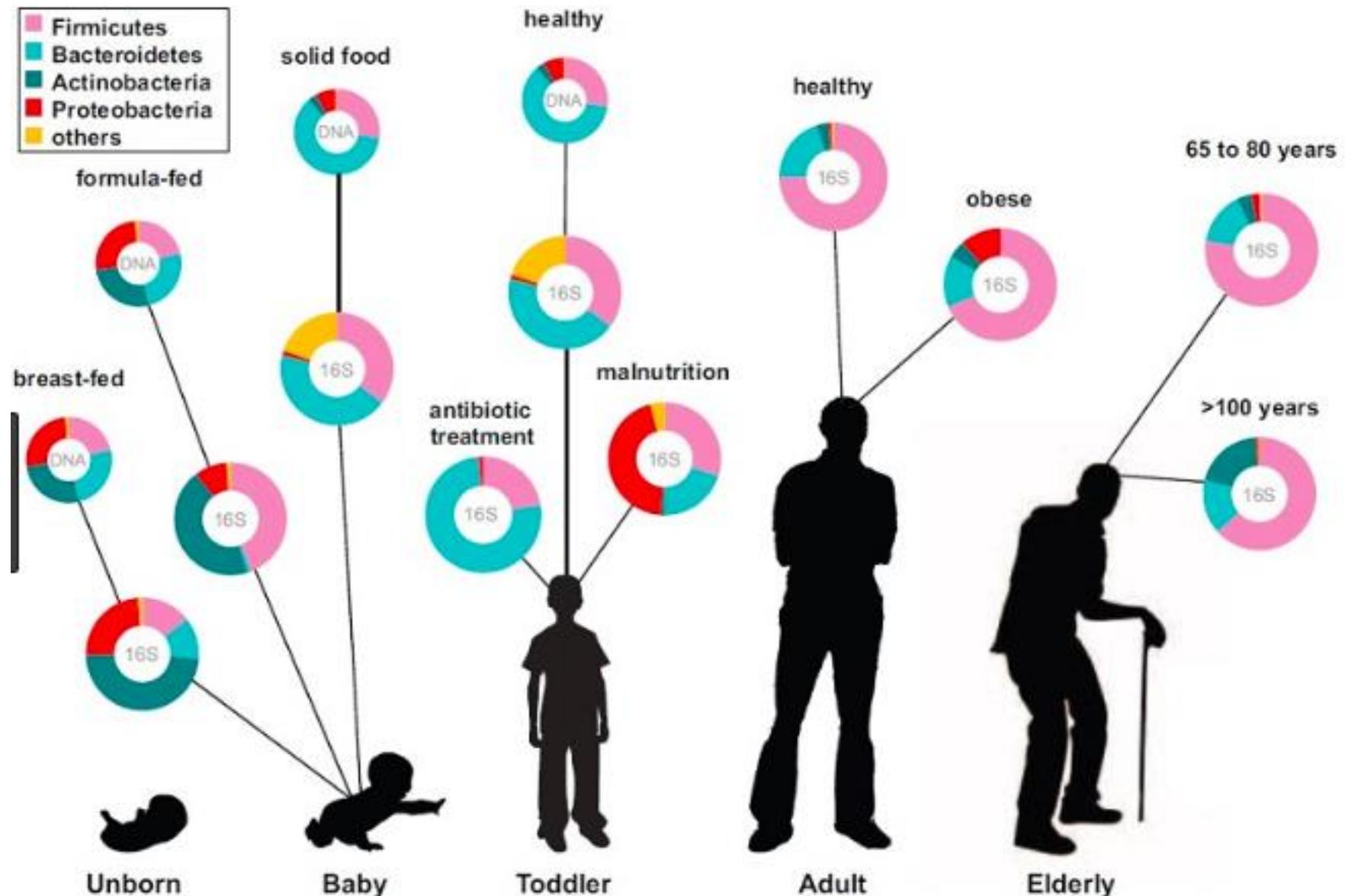
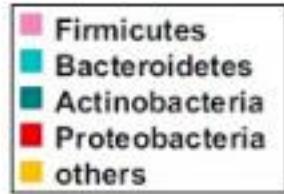
General composition of the maternal and infant microbiome in pregnancy and early life

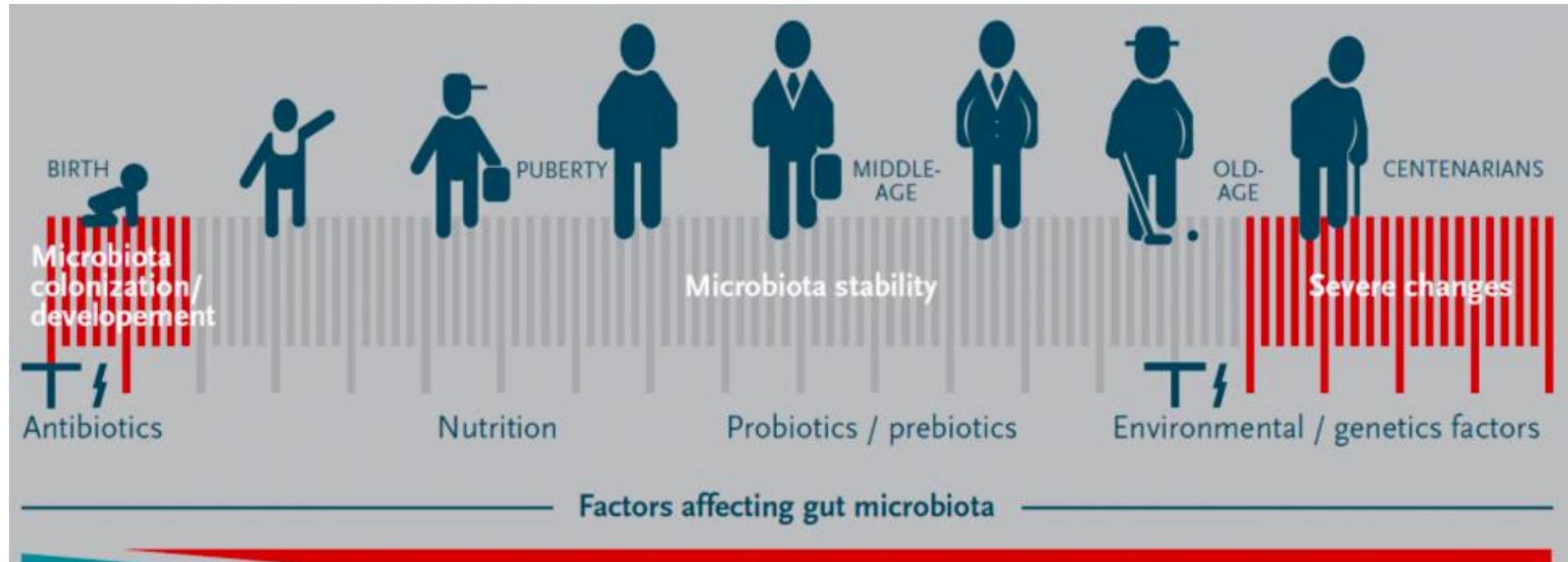


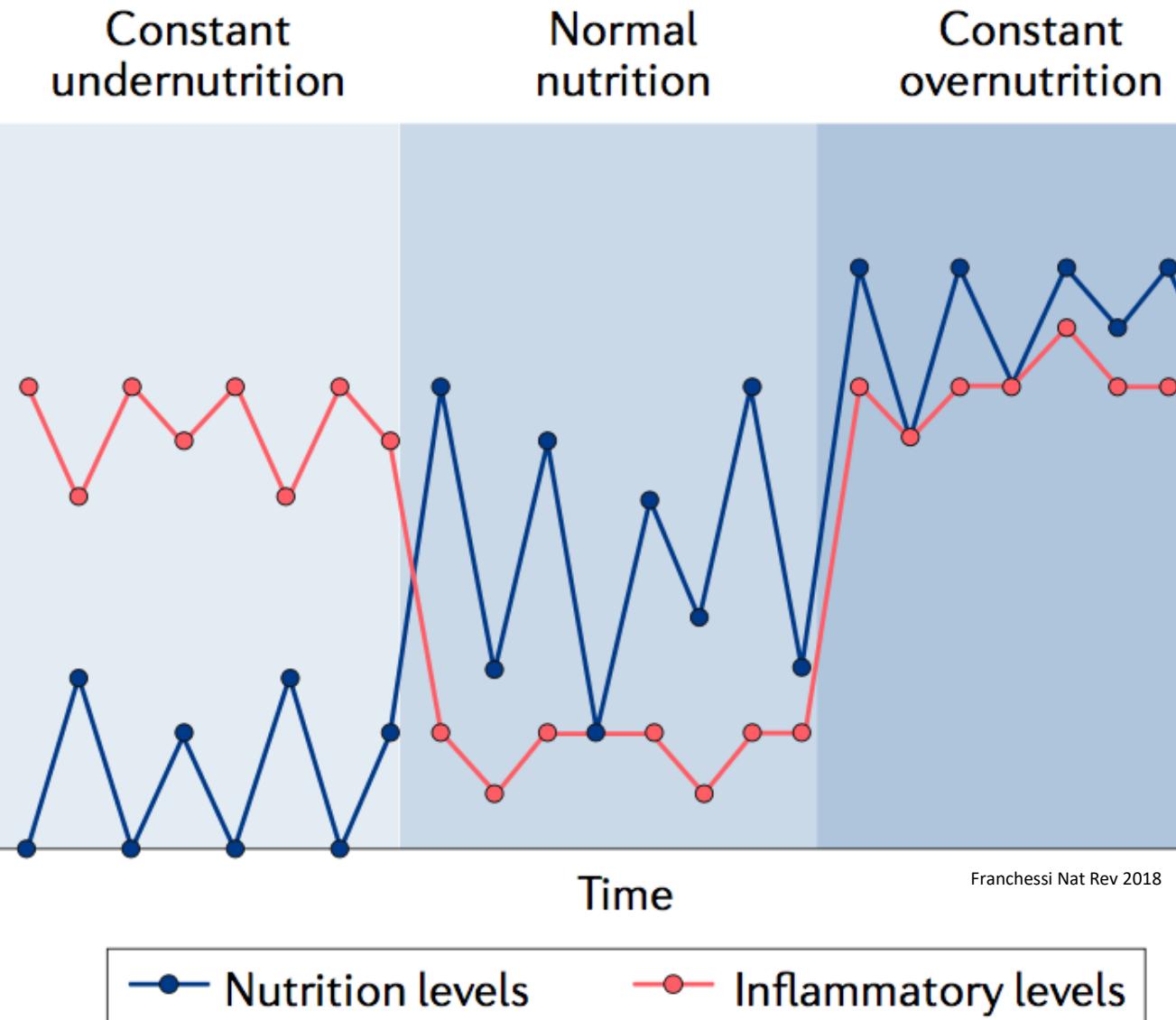
Kjersti Aagaard et al. EMBO Rep. 2016;17:1679-1684

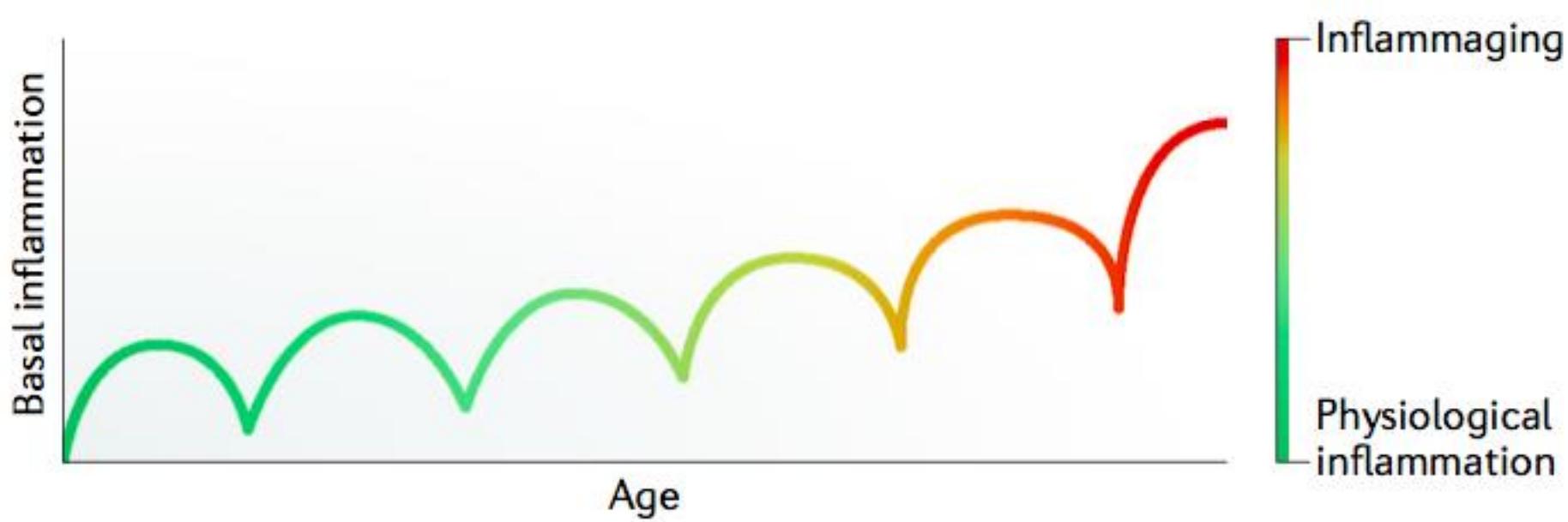


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