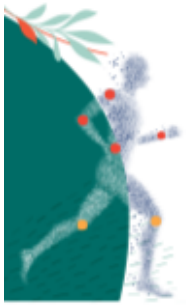
Γήρανση και αλλαγές στην ανοσιακή απόκριση: Ποια η σημασία τους στις ρευματικές παθήσεις;

Δημήτριος Π. Μπόγδανος,
Καθηγητής Παθολογίας και Αυτοάνοσων Νοσημάτων,
Διευθυντής Τομέα Παθολογίας,
Διευθυντής, Κλινική Ρευματολογίας και κλινικής Ανοσολογίας, Παν. Θεσσαλίας
Vis. Professor, Division of Transplantation Immunology and Mucosal Biology, King's College London, UK



Εαρινές ημέρες Ρευματολογίας

13-15 Μαΐου 2022

Xenia Poros Image Hotel

ΠΟΡΟΣ

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INSTITUTE OF RHEUMATIC & AUTOIMMUNE DISEASES

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4th POLYTHEMATIC Panhellenic Congress of Autoimmune Diseases, Rheumatology and Clinical Immunology

9-11 Σεπτεμβρίου 2022

Λευκάδα

9-11 September 2022

Lefkada

Save the date

Σύγκρουση Συμφερόντων σχετική με την Ομιλία: Καμία

Σύγκρουση Συμφερόντων **μη σχετικές** με την Ομιλία:

ΚΆΛΥΨΗ ΣΥΜΜΕΤΟΧΗΣ: NOVARTIS
ΜΕΤΑΦΟΡΙΚΑ: ELPEN

ΑΛΛΕΣ ΜΗ ΣΧΕΤΙΖΟΜΕΝΕΣ
BiOlympus, Genesis, Thermo Fisher, Menarini, Inova, Hospital Line, Pfizer, Medipan, Generic Assays, Elpen, Euroimmun, Aenorasis, AID, Biorad, CyBio, Diarect, IFT, Euclone, Invitrogen-MabTech, Miltenyi, Novartis, Molecular Probes, PeproTech, Gilead, Werfen, Roche, Celgene, Boehringer, Demo, Amgen, Lilly, Abbvie, Janssen, Cooper, Faran, MSD, UCB, GSK

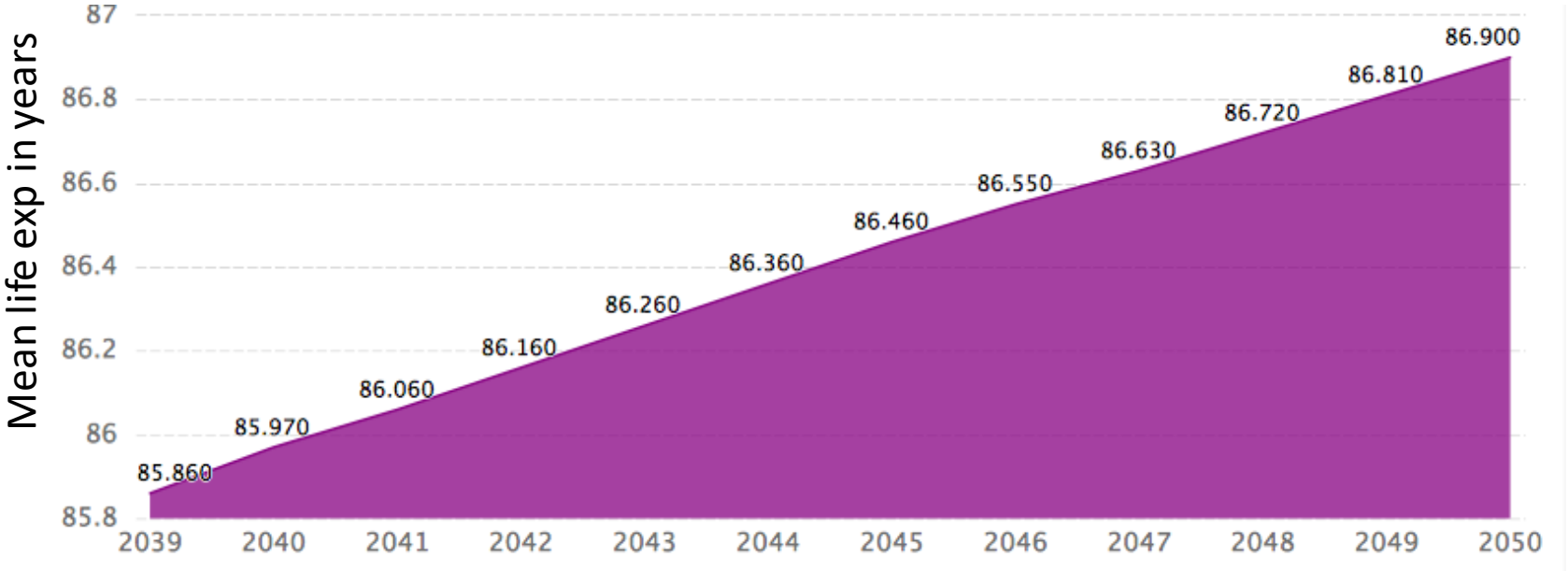
Το ανοσοποιητικό σύστημα είναι αποφασιστικός παράγοντας

διατήρησης της υγείας και της επιβίωσης στην τρίτη ηλικία

Το ανοσοποιητικό σύστημα στην τρίτη ηλικία

Ανοσογήρανση/ immunosenescence

Τι είναι η ανοσογήρανση;

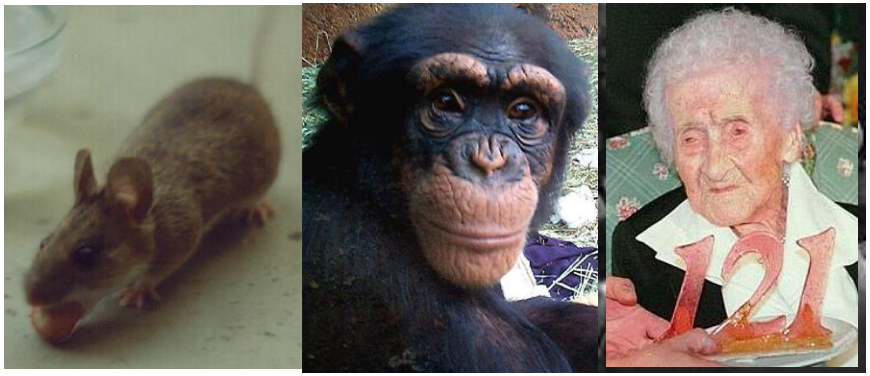


ELSTAT Life Expectancy: at Birth:
Females from 2006 to 2050 in the chart:

`Γιατί γερνάμε;

Comparative biology:

Maximum lifespans in mammals



3 years | 59 years | 122 years

Pinus longaeva (Bristlecone pine) ~4853 years

Urticina felina (Dahlia anemone) Non ageing

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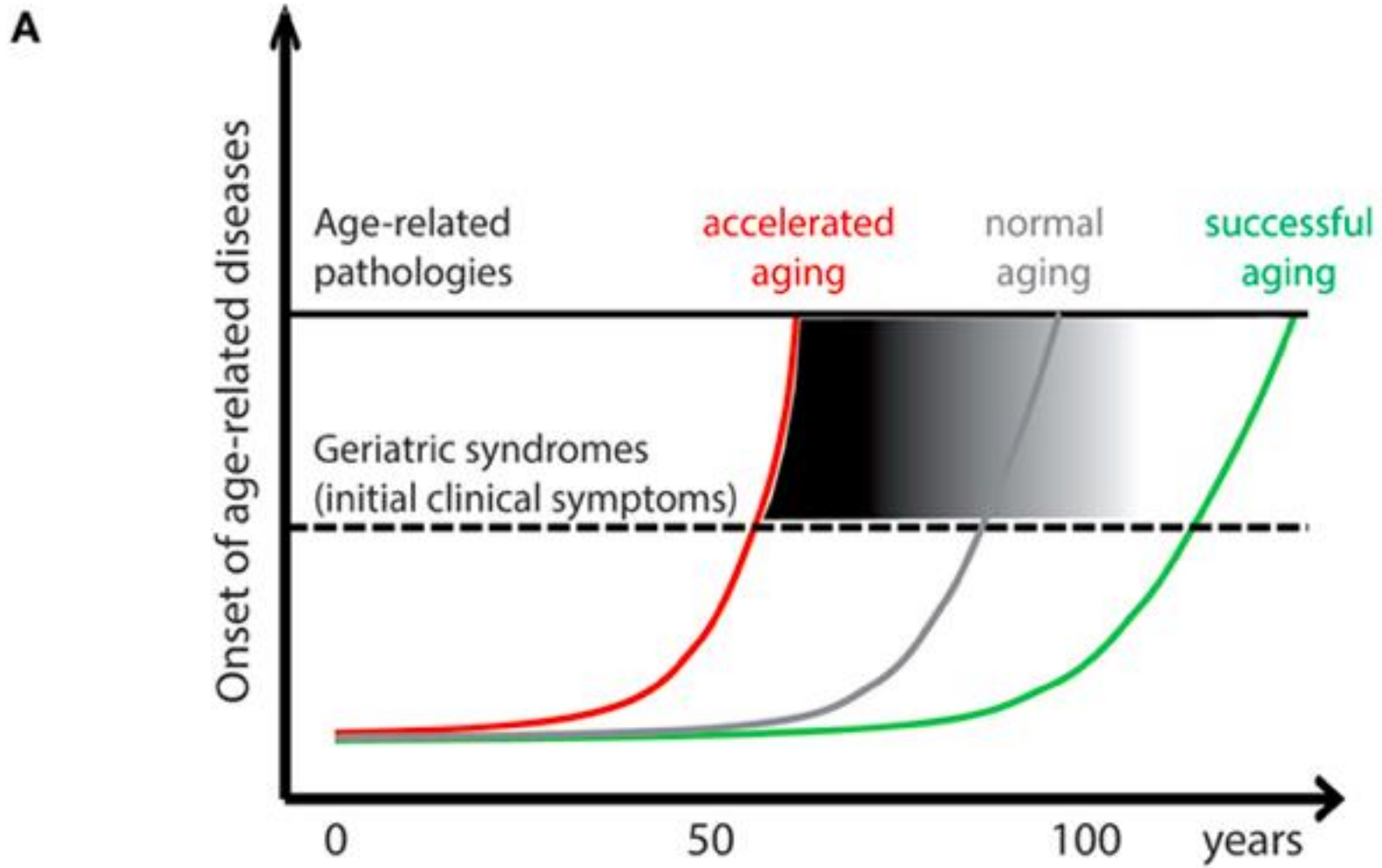
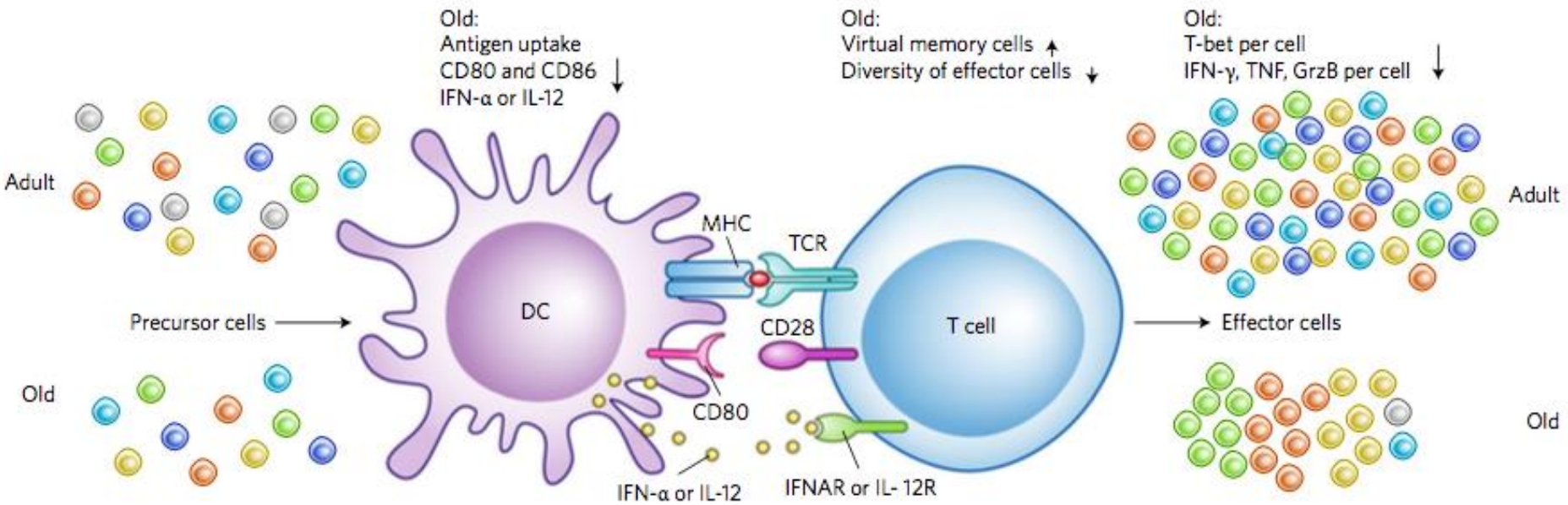
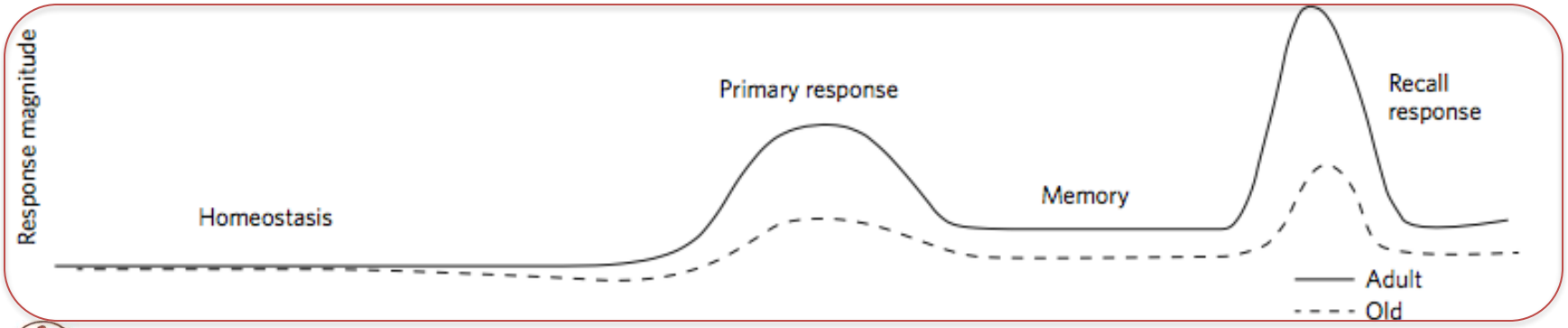
Τι είναι η Ανοσογήρανση;

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

Γήρανση


A
Onset of age-related diseases
Age-related pathologies
accelerated aging
normal aging
successful aging
Geriatric syndromes (initial clinical symptoms)
0
50
100
years



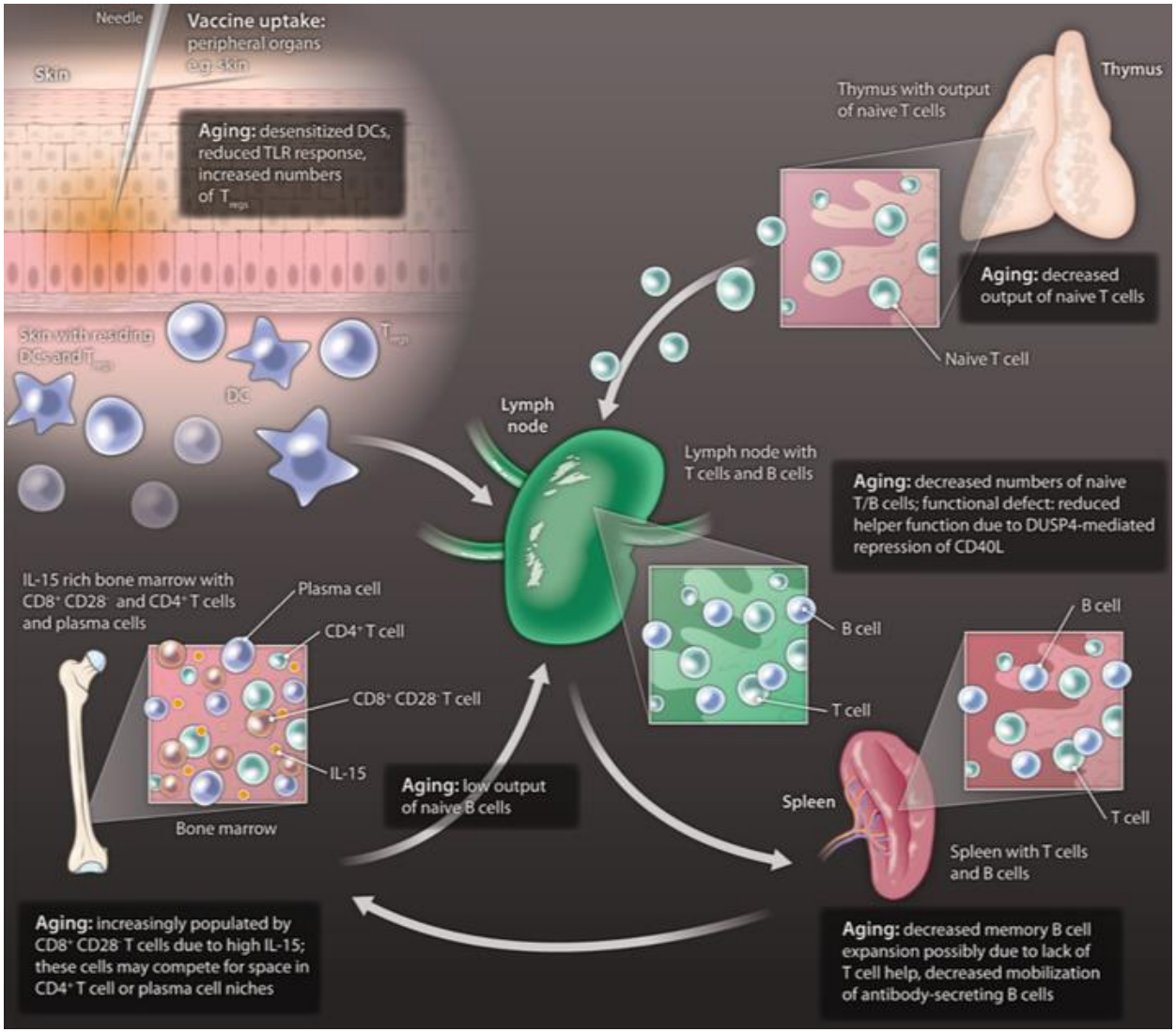


Nicolich-Zurich Nat Immun 2017

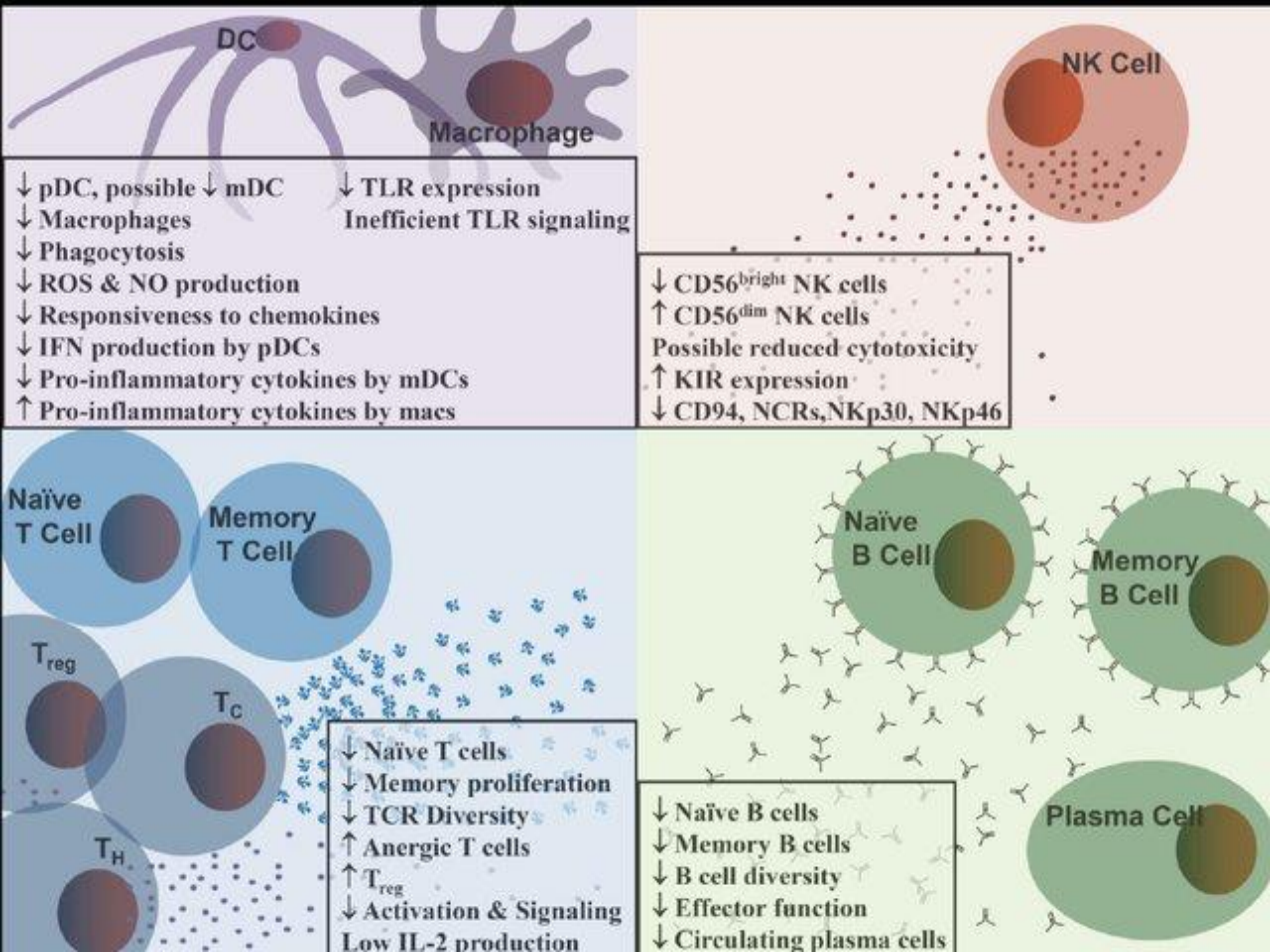
AGING

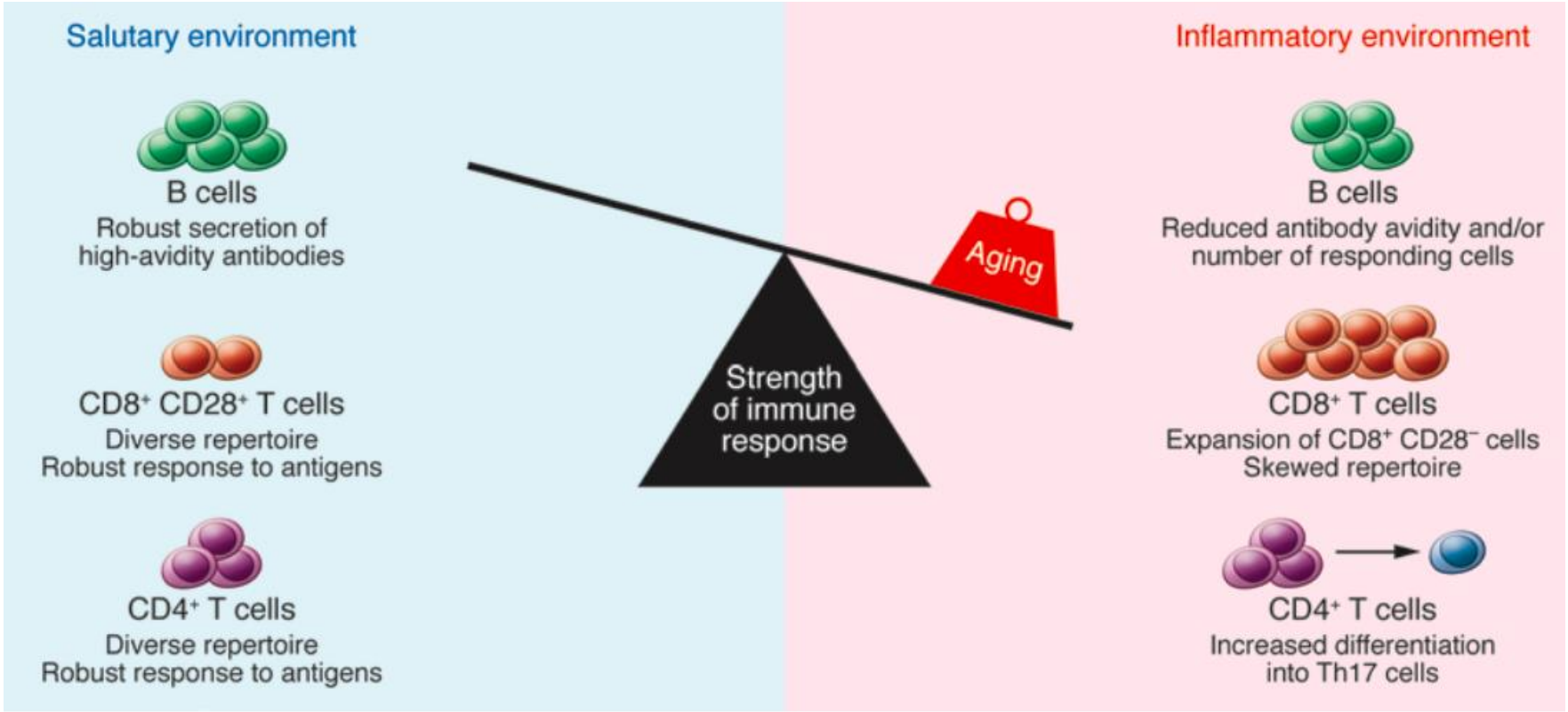
The Gracefully Aging Immune System

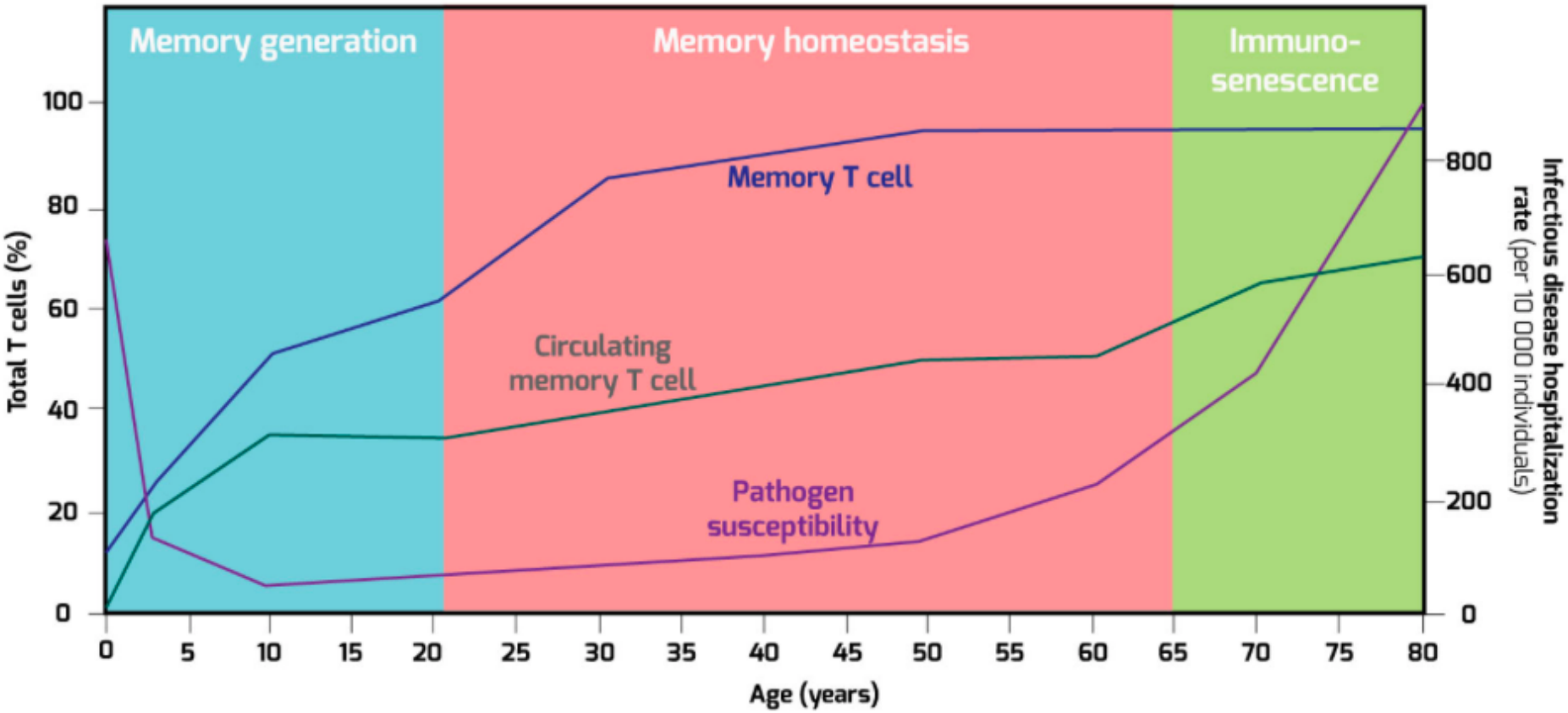
Diana Boraschi,[1] M. Teresa Aguado,[2] Catherine Dutel,[3] Jörg Goronzy,[4] Jacques Louis,[3] Beatrix Grubeck-Loebenstein,[5] Rino Rappuoli,[6] Giuseppe Del Giudice[6]*



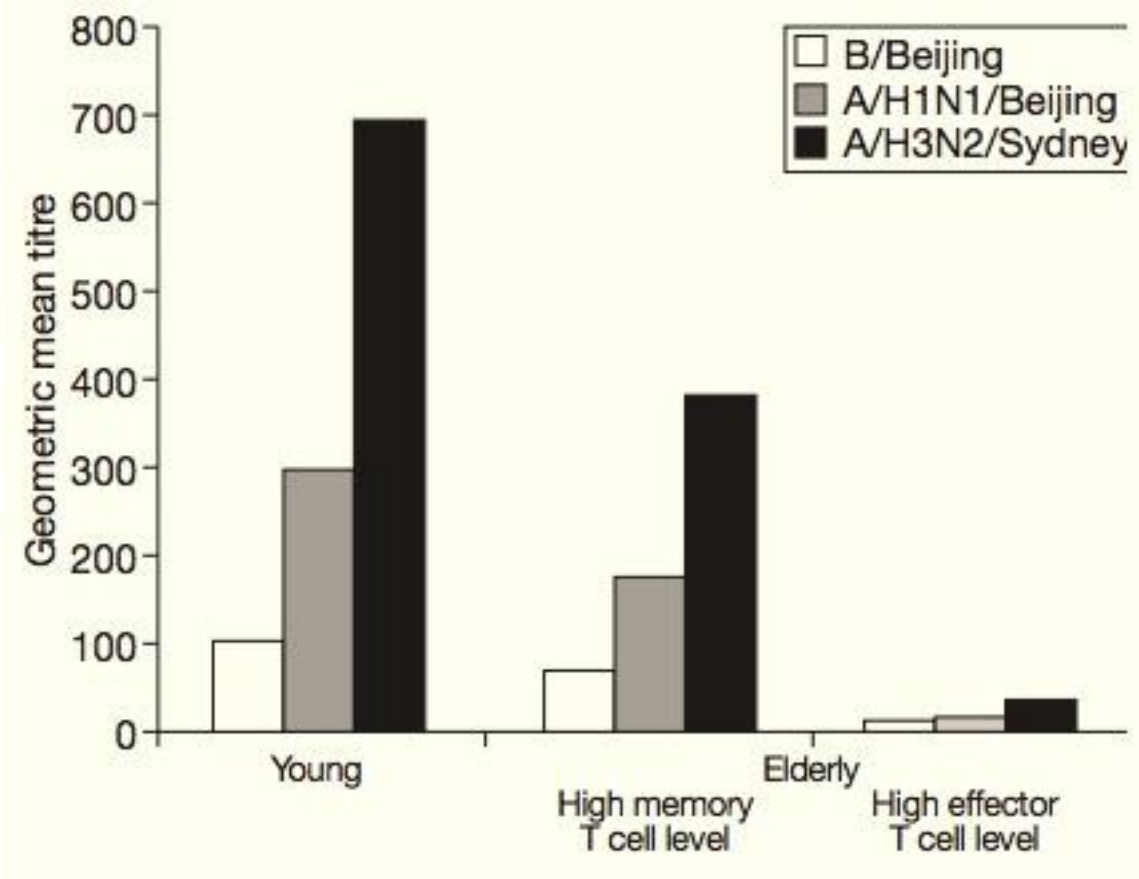
Montesino JCI 2013


DC
Macrophage
↓ pDC, possible ↓ mDC
↓ Macrophages
↓ Phagocytosis
↓ ROS & NO production
↓ Responsiveness to chemokines
↓ IFN production by pDCs
↓ Pro-inflammatory cytokines by mDCs
↑ Pro-inflammatory cytokines by macs
↓ TLR expression
Inefficient TLR signaling
NK Cell
↓ CD56bright NK cells
↑ CD56dim NK cells
Possible reduced cytotoxicity
↑ KIR expression
↓ CD94, NCRs,NKp30, NKp46
Naïve T Cell
Memory T Cell
Treg
TC
TH
↓ Naïve T cells
↓ Memory proliferation
↓ TCR Diversity
↑ Anergic T cells
↑ Treg
↓ Activation & Signaling
Low IL-2 production
Naïve B Cell
Memory B Cell
Plasma Cell
↓ Naïve B cells
↓ Memory B cells
↓ B cell diversity
↓ Effector function
↓ Circulating plasma cells


Salutary environment
B cells
Robust secretion of high-avidity antibodies
CD8+ CD28+ T cells
Diverse repertoire
Robust response to antigens
CD4+ T cells
Diverse repertoire
Robust response to antigens
Aging
Strength of immune response
Inflammatory environment
B cells
Reduced antibody avidity and/or number of responding cells
CD8+ T cells
Expansion of CD8+ CD28− cells
Skewed repertoire
CD4+ T cells
Increased differentiation into Th17 cells

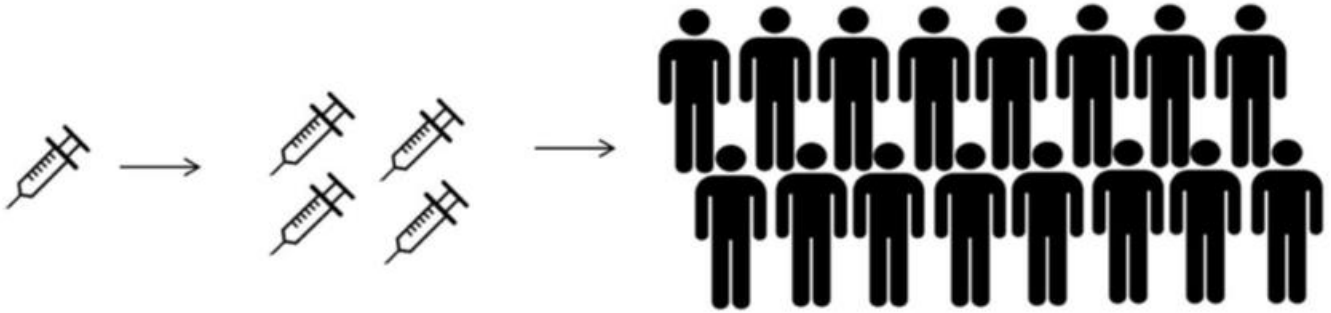

Memory generation
Memory homeostasis
Immuno-
senescence
Memory T cell
Circulating
memory T cell
Pathogen
susceptibility
Total T cells (%)
Infectious disease hospitalization
rate (per 10 000 individuals)
Age (years)
0
20
40
60
80
100
0
200
400
600
800
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80

Lack of anti-inffuenza body production in older age

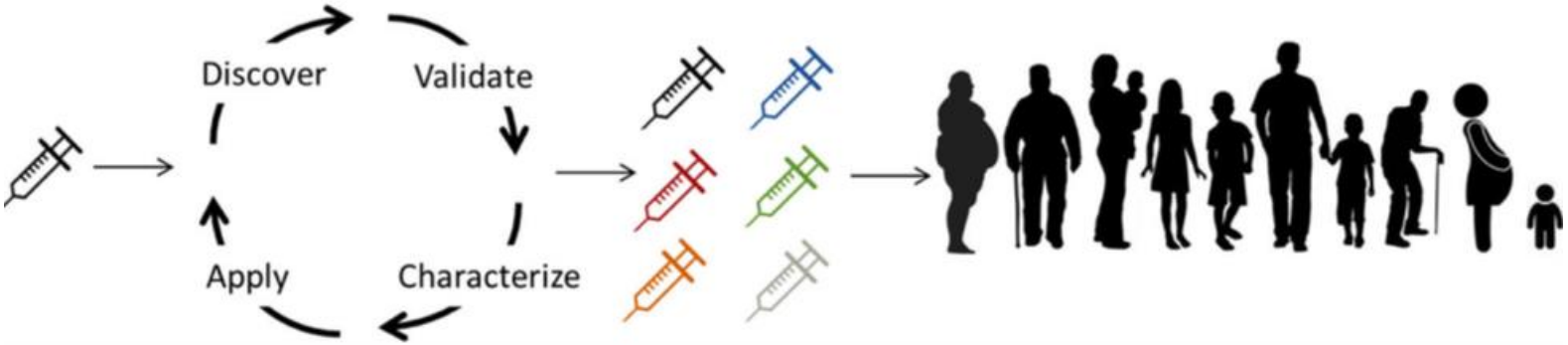


Saurwein-Teissl M J Immunol 2002

Empirical Vaccine Development
(Isolate – Inactivate – Inject)

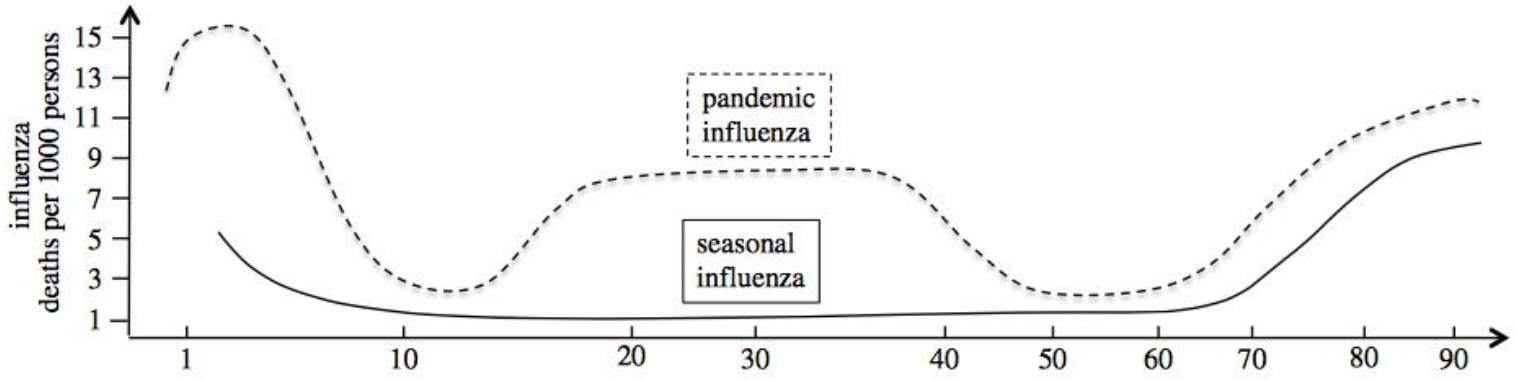


Personalized Vaccinology

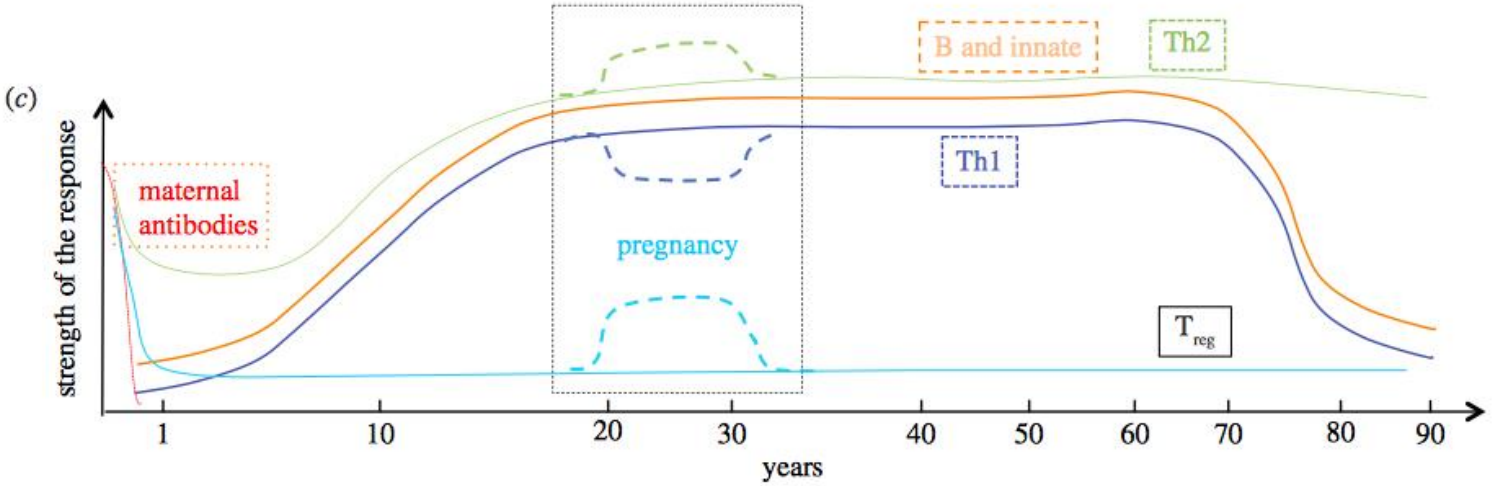


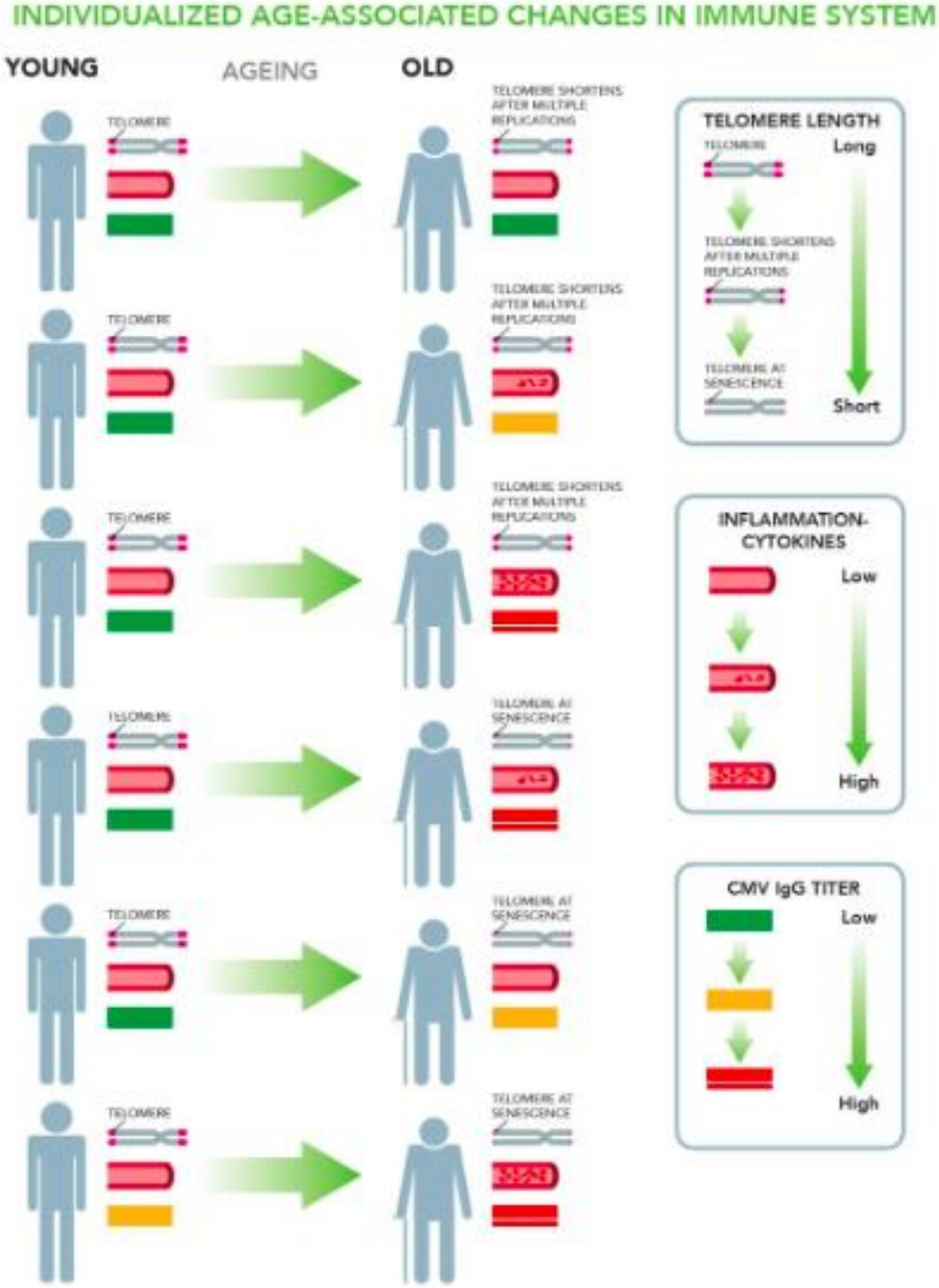
(a)

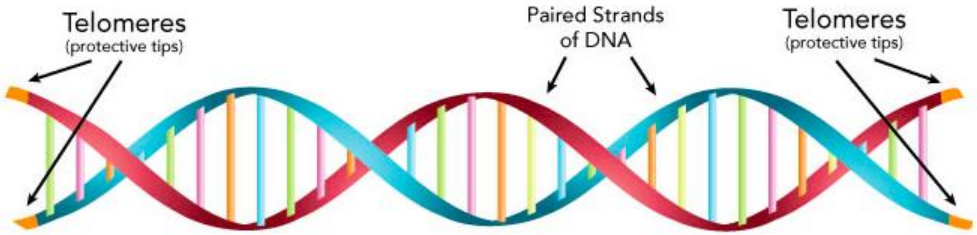
(b)


influenza deaths per 1000 persons
15
13
11
9
7
5
3
1
pandemic influenza
seasonal influenza
1
10
20
30
40
50
60
70
80
90

(c)

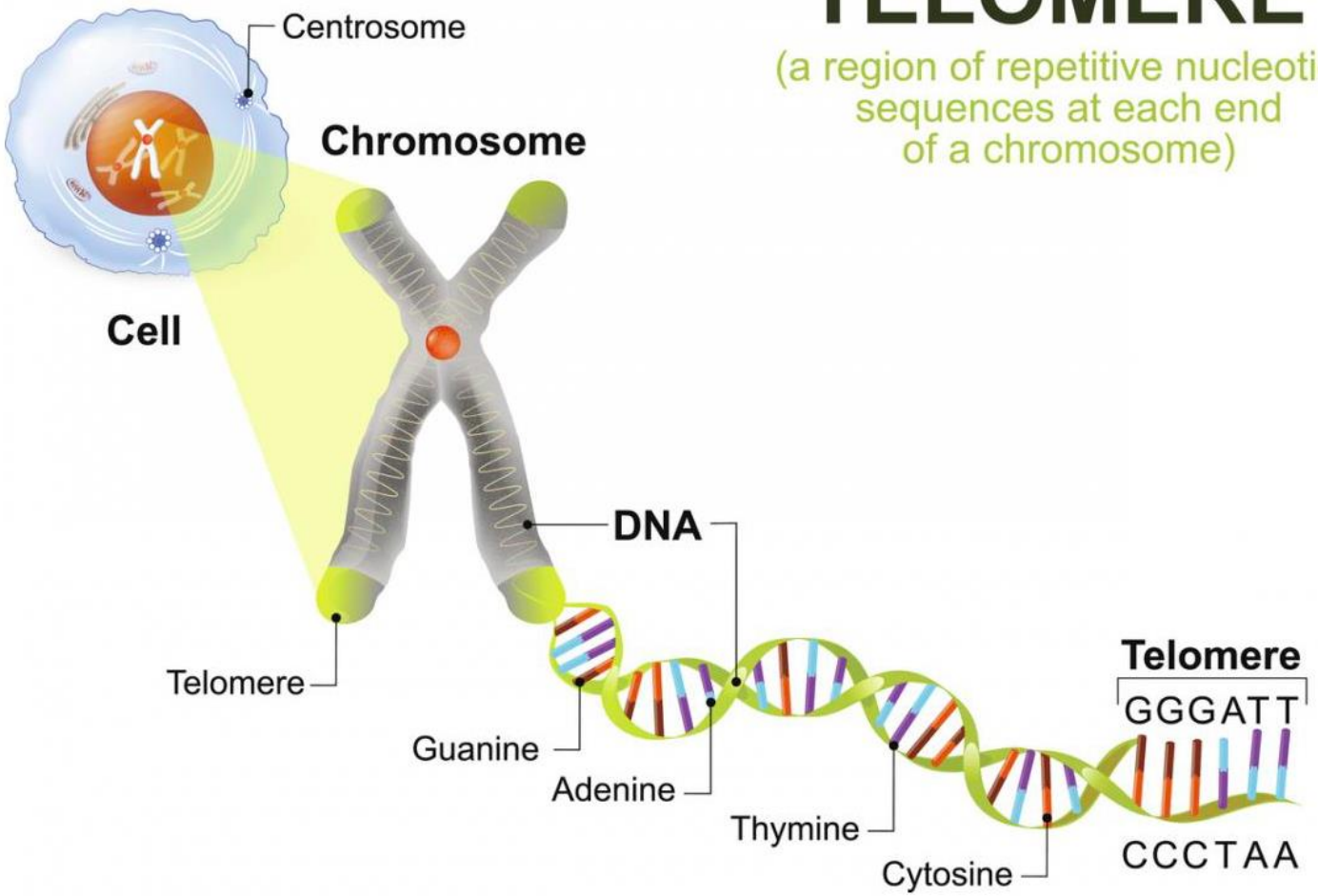

strength of the response
maternal antibodies
pregnancy
B and innate
Th2
Th1
T reg
1
10
20
30
40
50
60
70
80
90
years

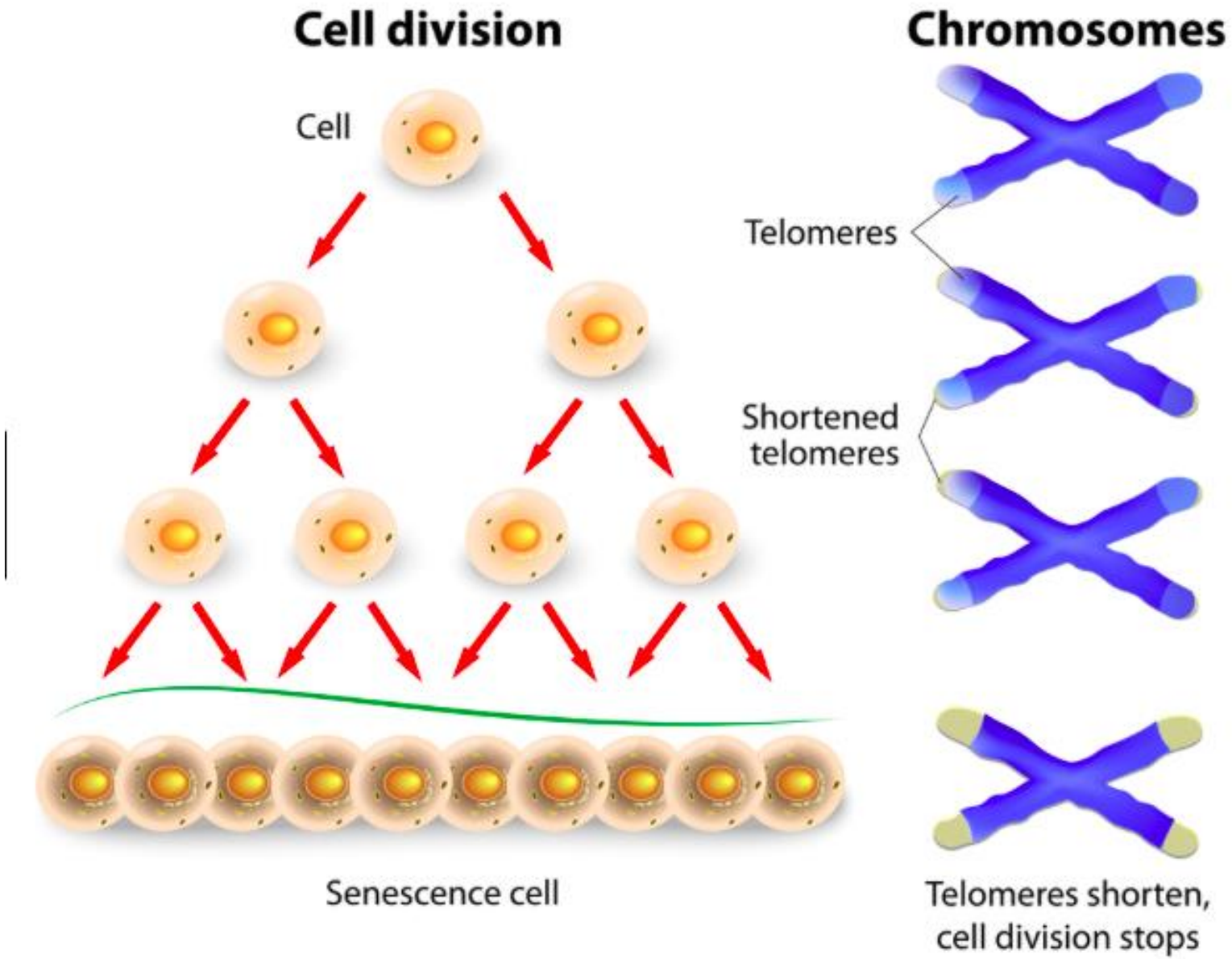

INDIVIDUALIZED AGE-ASSOCIATED CHANGES IN IMMUNE SYSTEM
YOUNG
AGEING
OLD
TELOMERE
TELOMERE SHORTENS AFTER MULTIPLE REPLICATIONS
TELOMERE AT SENESCENCE
TELOMERE LENGTH
Long
Short
INFLAMMATION-CYTOKINES
Low
High
CMV IgG TITER
Low
High



TELOMERE

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




Cell division
Chromosomes
Cell
Telomeres
Shortened telomeres
Senescence cell
Telomeres shorten, cell division stops

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

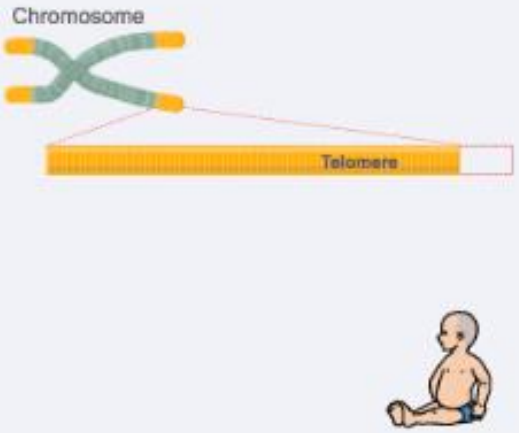
Elizabeth H. Blackburn

Photo: Gerbil, Licensed by Attribution Share Alike 3.0

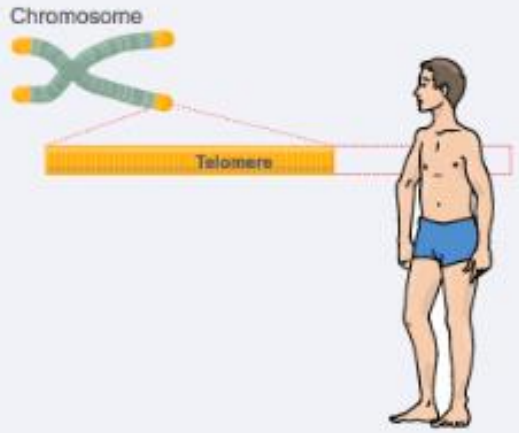
Carol W. Greider

Photo © Harvard Medical School

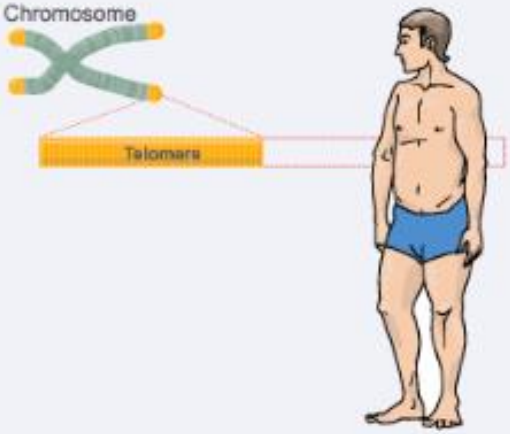
Jack W. Szostak



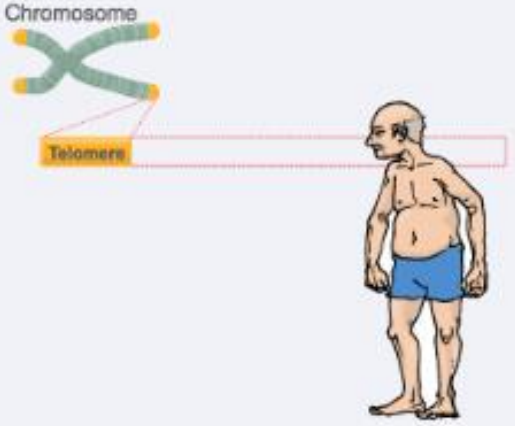
Telomere length of an infant.



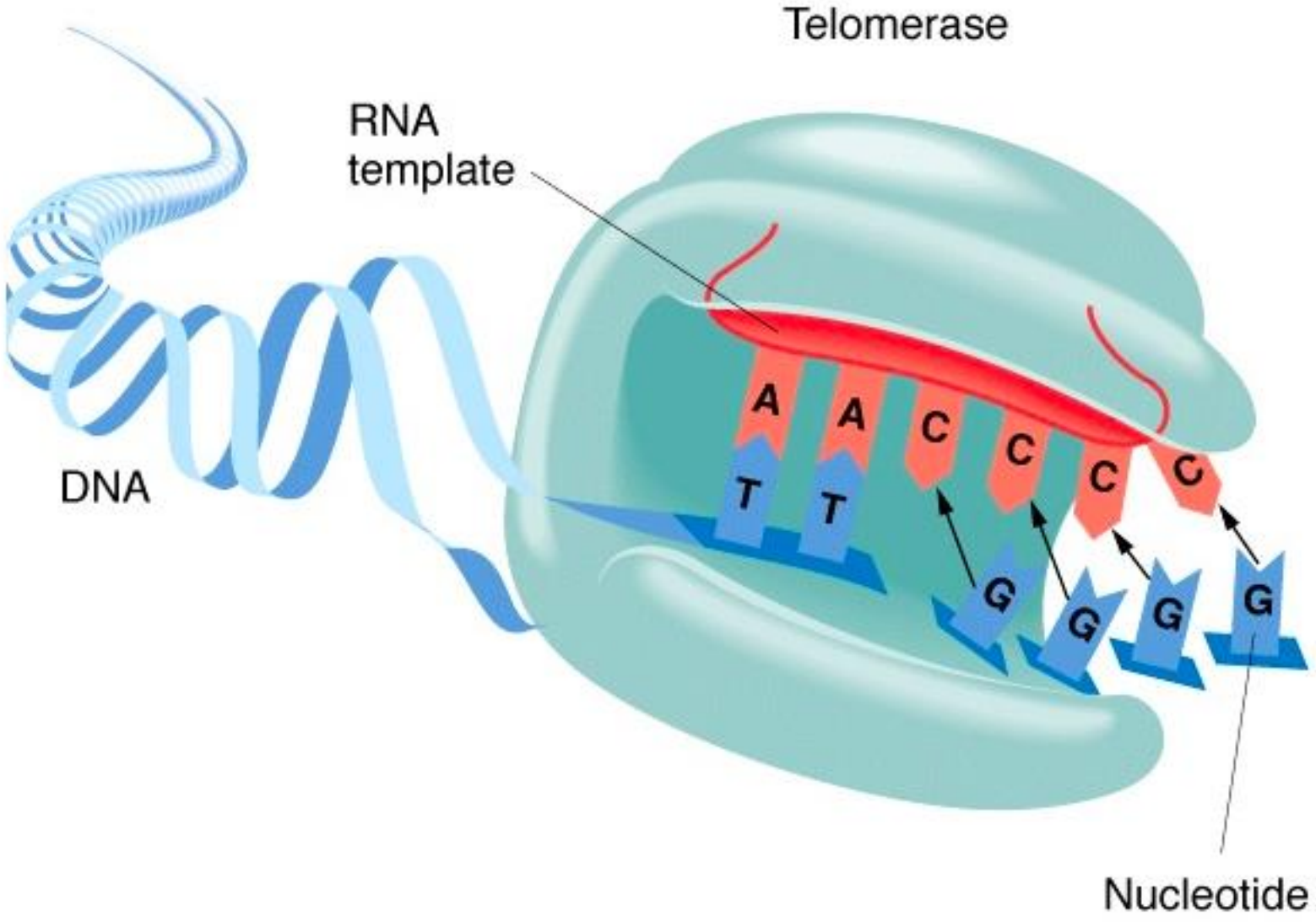
Telomere length of a teenager.

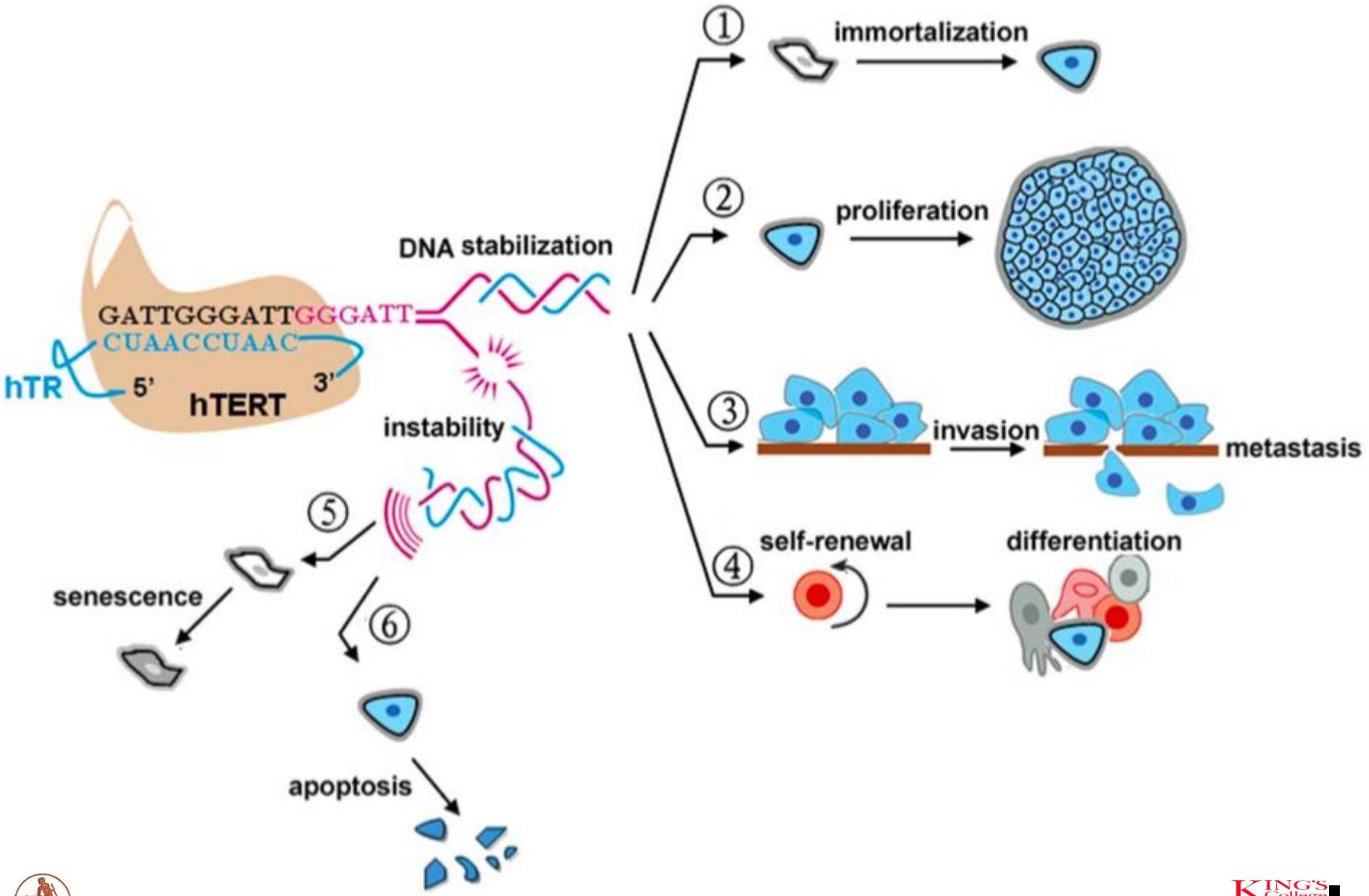


Telomere length of an adult.



Telomere length of an elderly adult.


Telomerase
RNA
template
DNA
A
A
C
C
C
C
T
T
G
G
G
G
Nucleotide


GATTGGGATTGGGATT
CUAACCUAAC
hTR
5'
3'
hTERT
DNA stabilization
instability
1
immortalization
2
proliferation
3
invasion
metastasis
4
self-renewal
differentiation
5
senescence
6
apoptosis

The NASA twins study: The Kelly Brothers

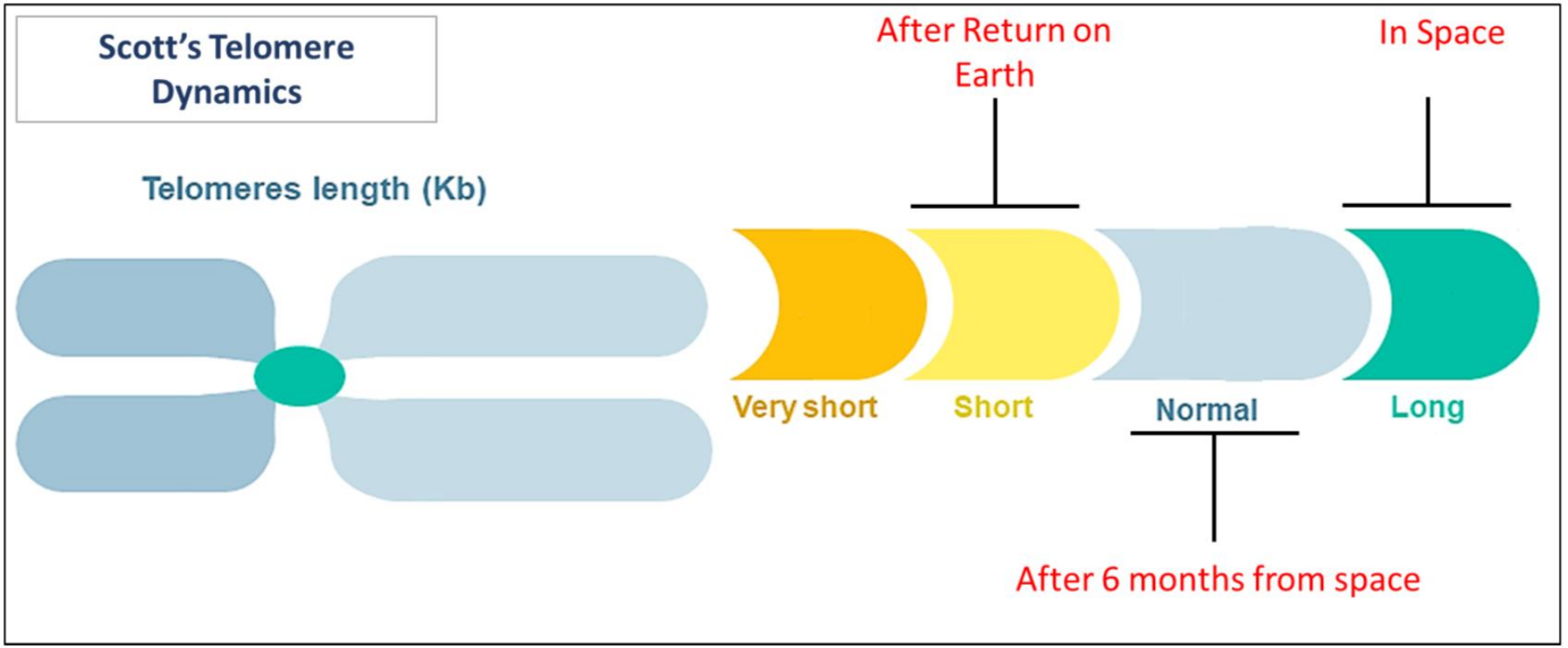
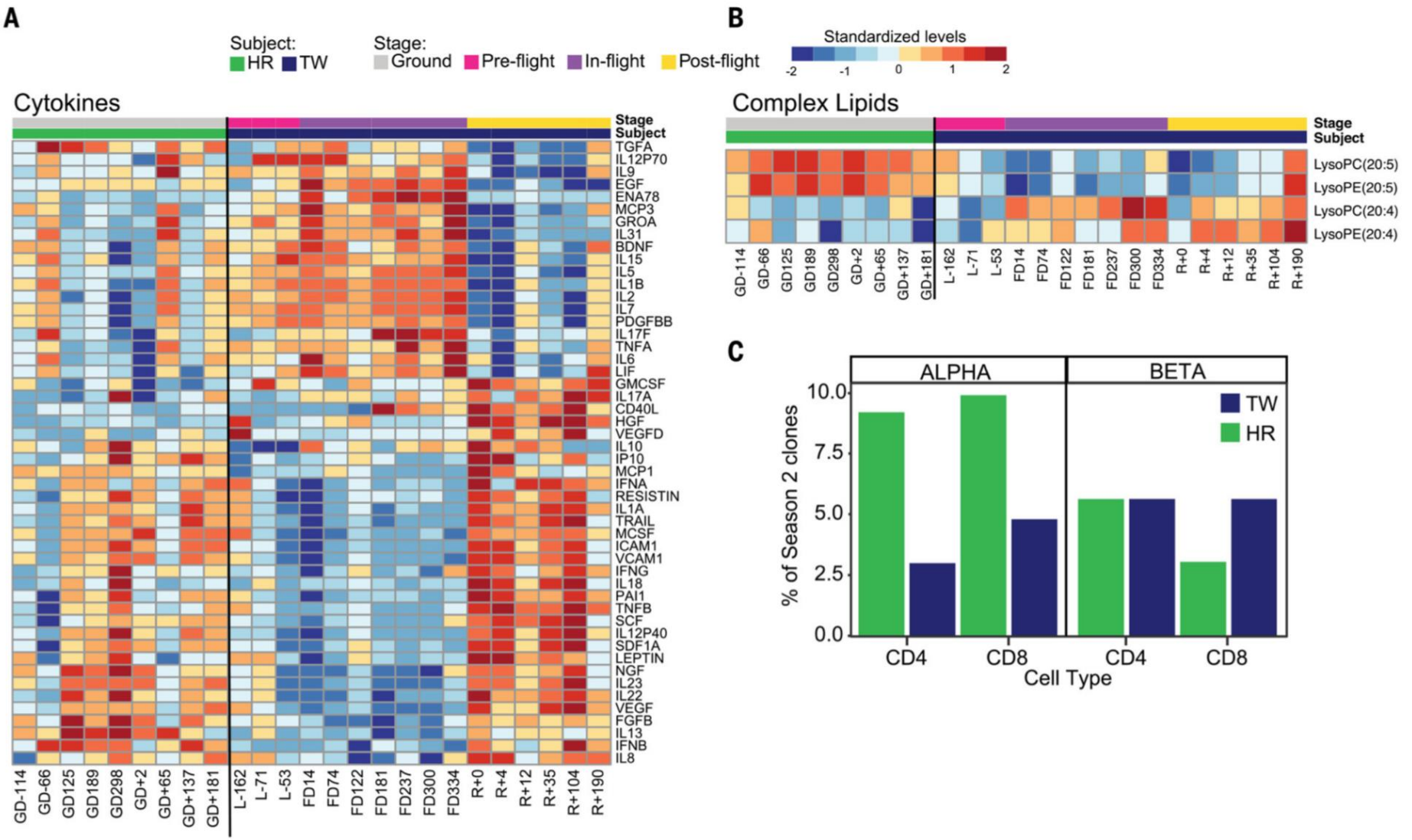


Figure 1. Telomere dynamics in space and Earth.

Published in final edited form as:
Science. 2019 April 12; 364(6436): . doi:10.1126/science.aau8650.

The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight



BJSM Online First, published on September 3, 2014 as 10.1136/bjsports-2013-093342

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 Hellénius[5]

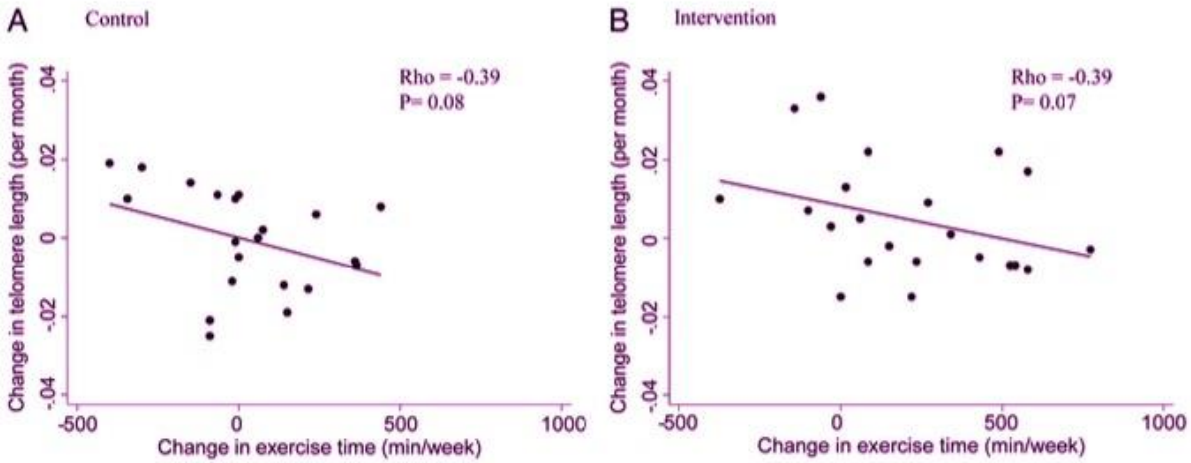


Figure 1 (A and B) Relationship between changes in telomere length (per month) and changes in exercise time of at least moderate intensity (min/week) over 6 months in individuals receiving minimal intervention (A, control, n=21) or individualised physical activity on prescription (B, intervention, n=21).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

uicc
global cancer control

IJC
International Journal of Cancer

Shortened telomeres in individuals with abuse in alcohol consumption

Sofia Pavanello[1], Mirjam Hoxha[2], Laura Dioni[2], Pier Alberto Bertazzi[2], Rossella Snenghi[3], Alessandro Nalesso[3], Santo Davide Ferrara[3], Massimo Montisci[3] and Andrea Baccarelli[4]

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

[1]Unadjusted 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. [2]Adjusted by age, BMI, current smoking, vegetables, job at elevated risk of accident.

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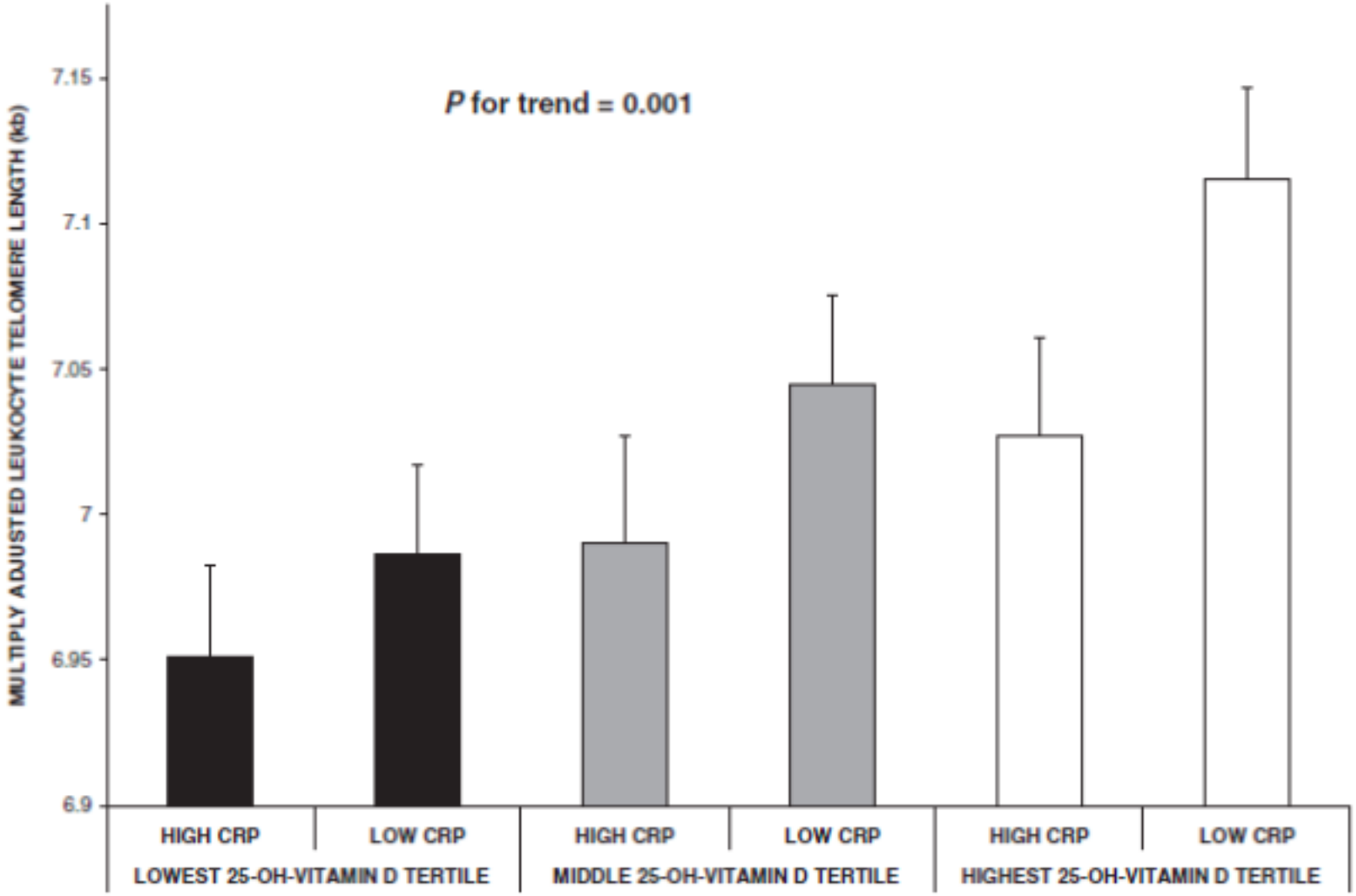
VITAMIN D AND TELOMERE LENGTH



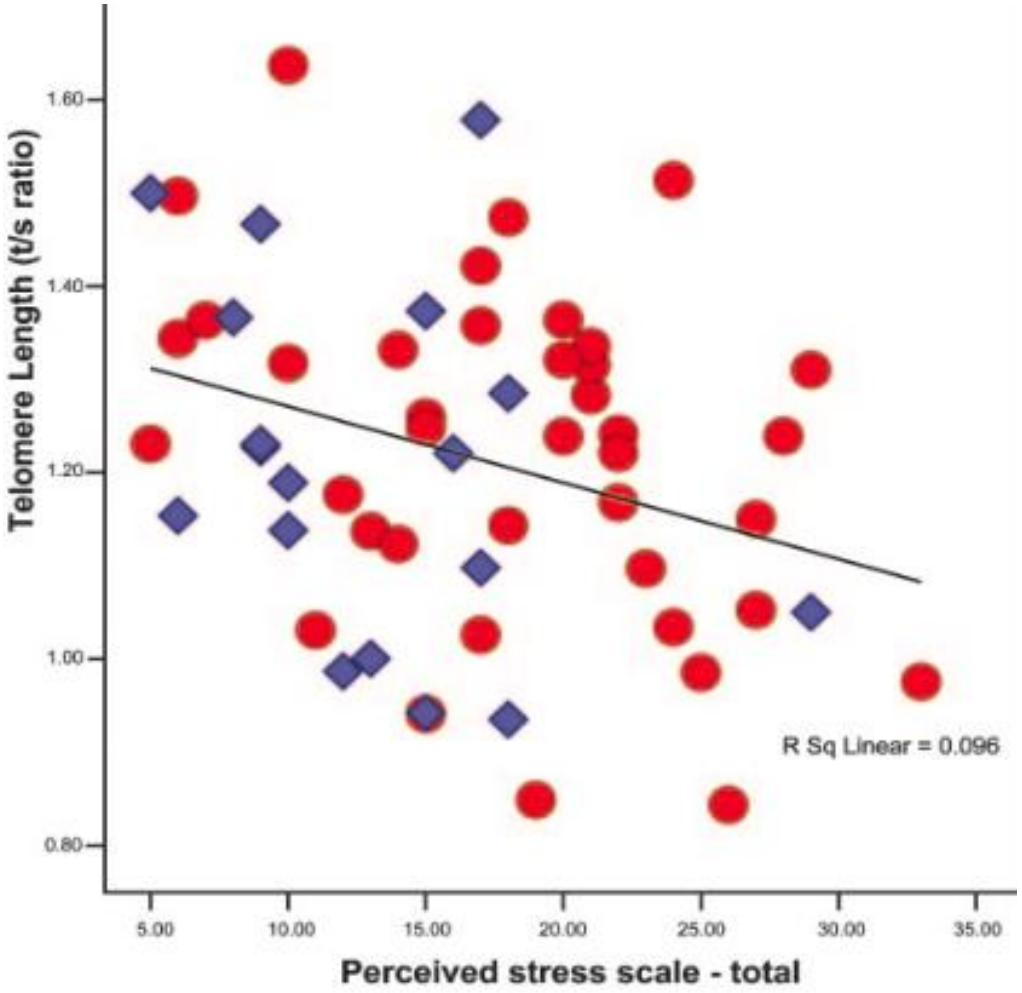
Richards Am J Clin Nutr 2007

PNAS

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



ARTICLE
Journal of Cellular Biochemistry 114:1257–1270 (2013)

Journal of Cellular Biochemistry

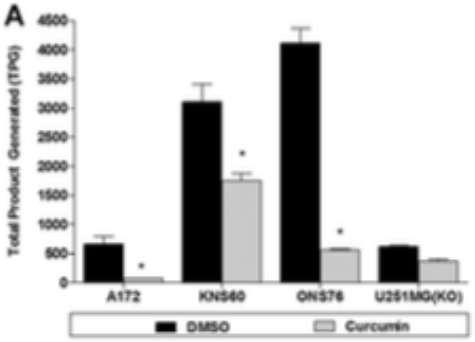
Curcumin Inhibits Telomerase and Induces Telomere Shortening and Apoptosis in Brain Tumour Cells

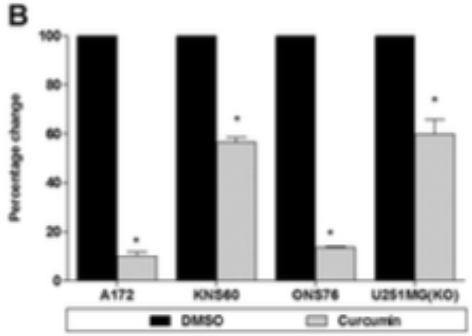
Aik Kia Khaw,[1] M. Pradeepa Hande,[1] Guruprasad Kalthur,[1,2] and M. Prakash Hande[1,3]*

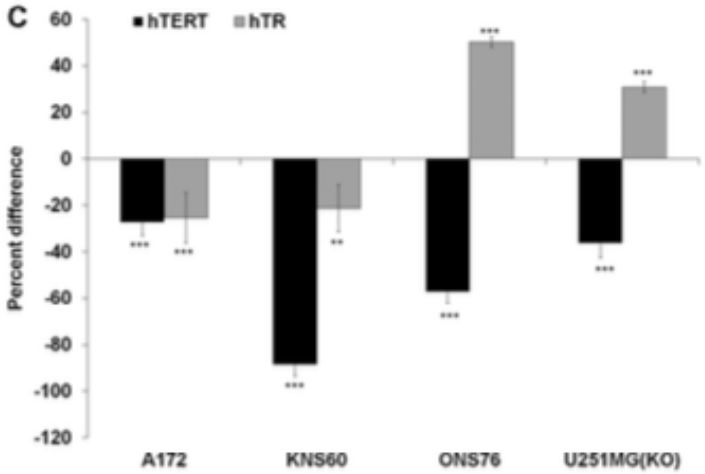
[1] Genome Stability Laboratory, Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore

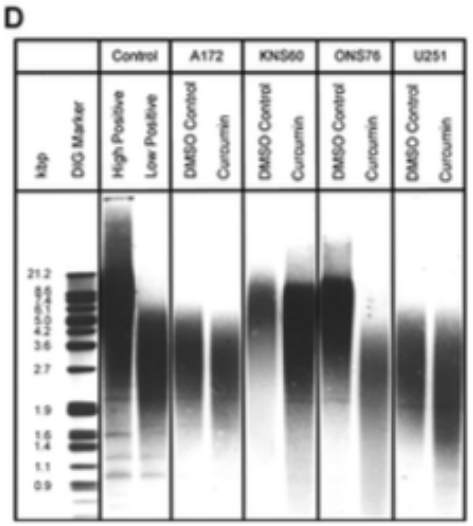
[2] Department of Obstetrics and Gynaecology, Clinical Embryology, Kasturba Medical College, Manipal University, Manipal 576 104, India

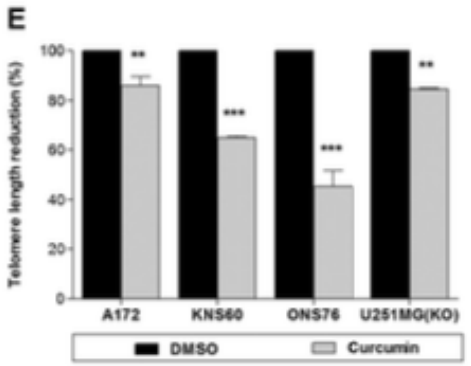
[3] Tembusu College, National University of Singapore, Singapore 138598, Singapore





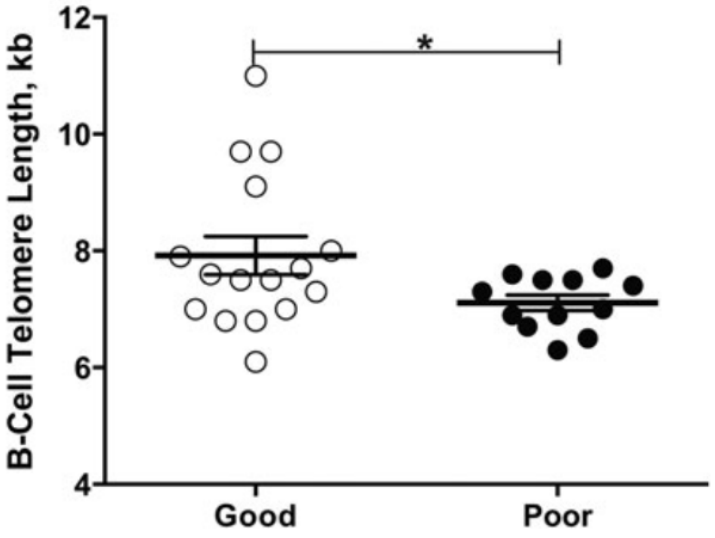


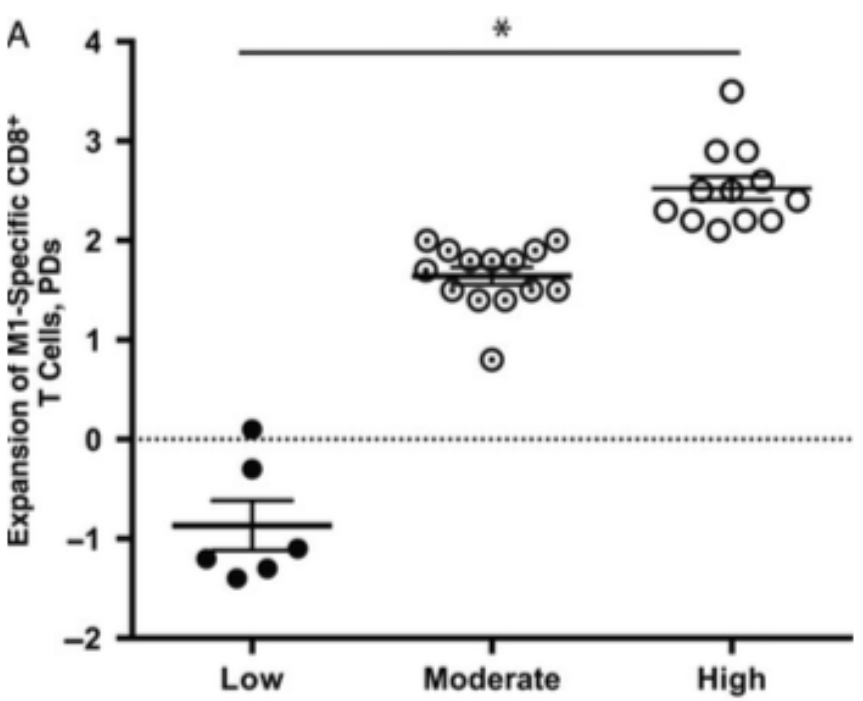


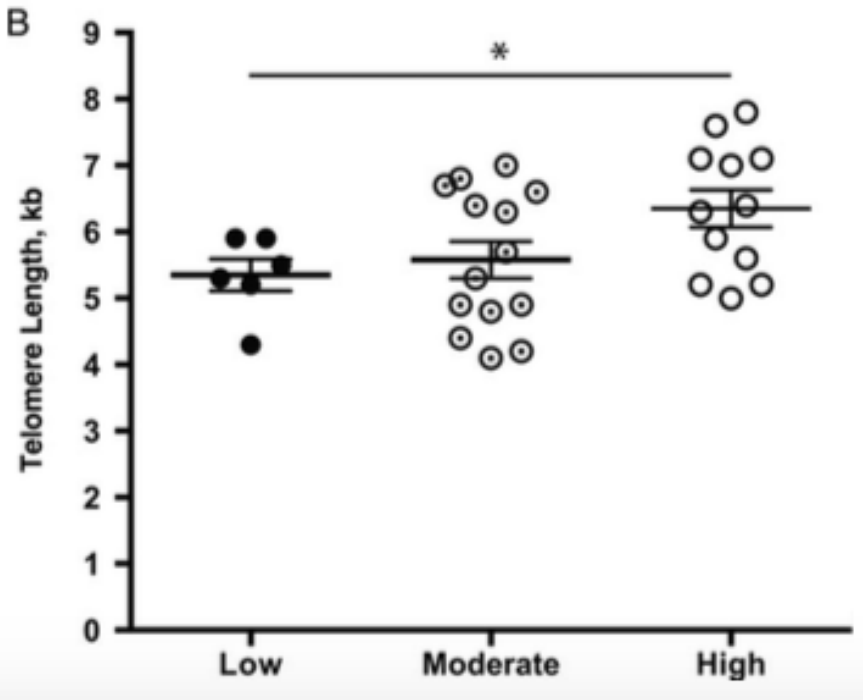


Telomere Length as an Indicator of the Robustness of B- and T-Cell Response to Influenza in Older Adults

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] Xiyan Xu,[5] Shari M. Ling,[2] Dan L. Longo,[6] Jonathan Schneck,[4] Sean Leng,[3] Luigi Ferrucci,[2] and Nan-ping Weng[1]







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

Reviews in Medical Virology

REVIEW

Cytomegalovirus and human immunosenescence

Graham Pawelec[1]*, Evelyna Derhovanessian[1], Anis Larbi[1], Jan Strindhall[2] and Anders Wikby[2]

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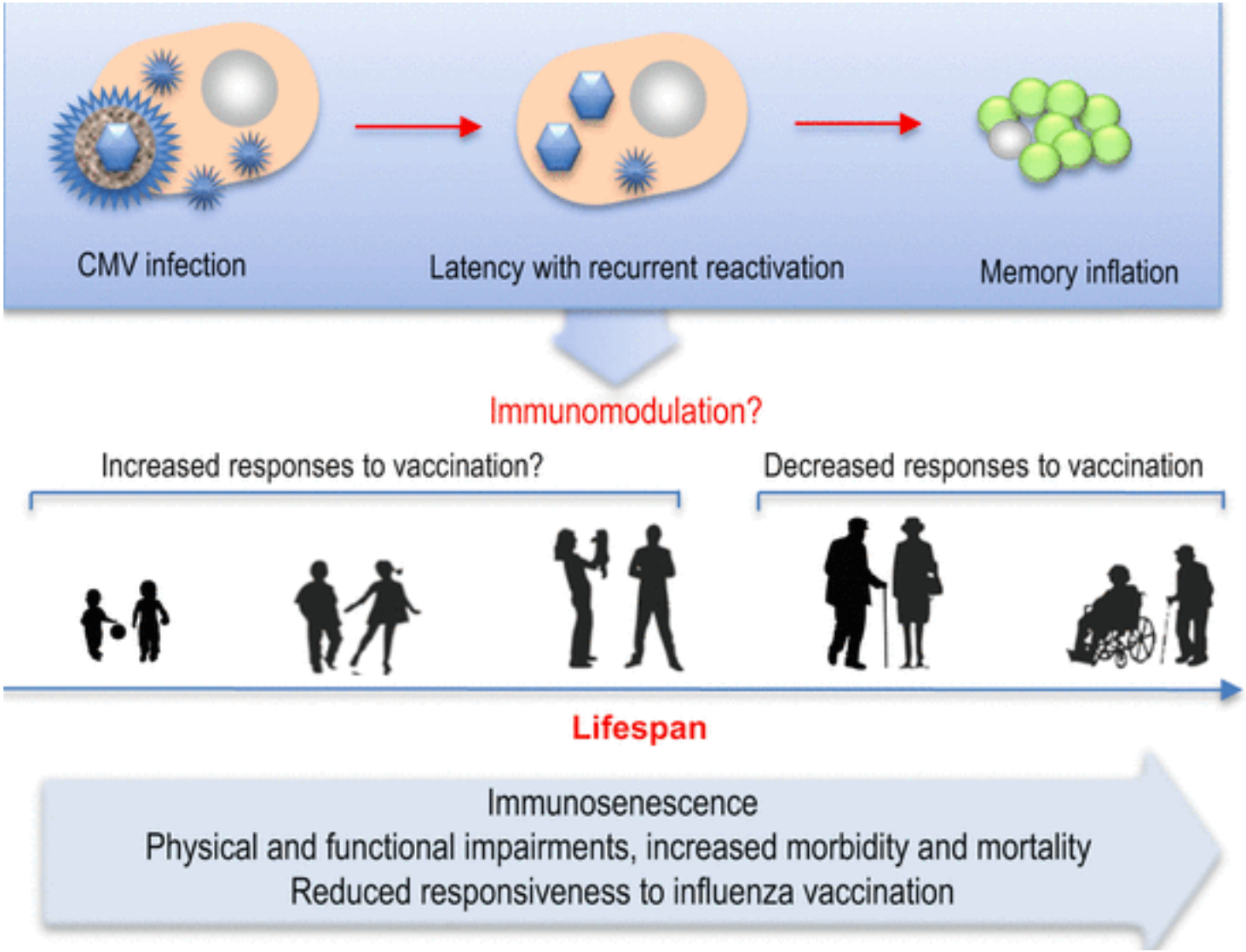
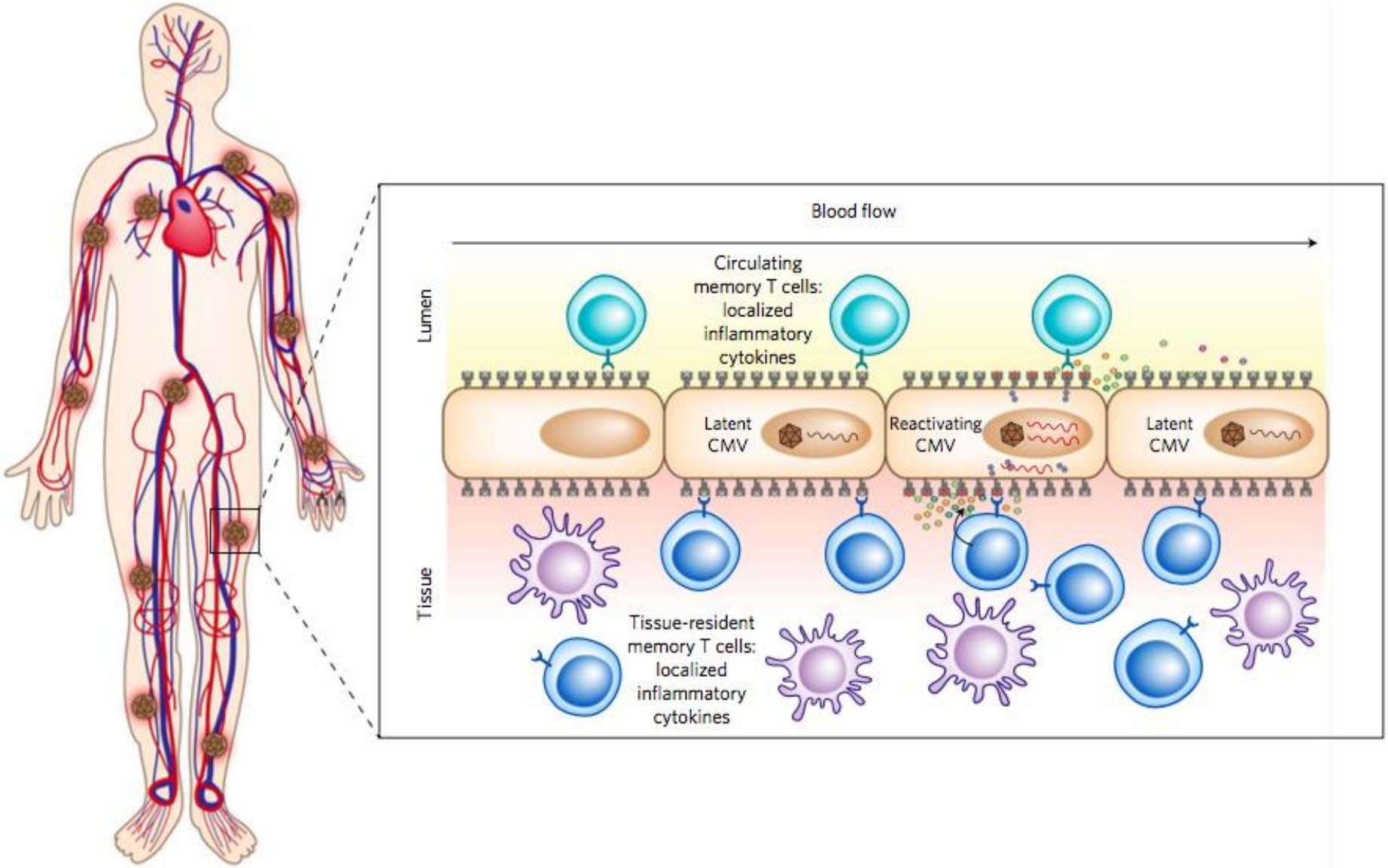
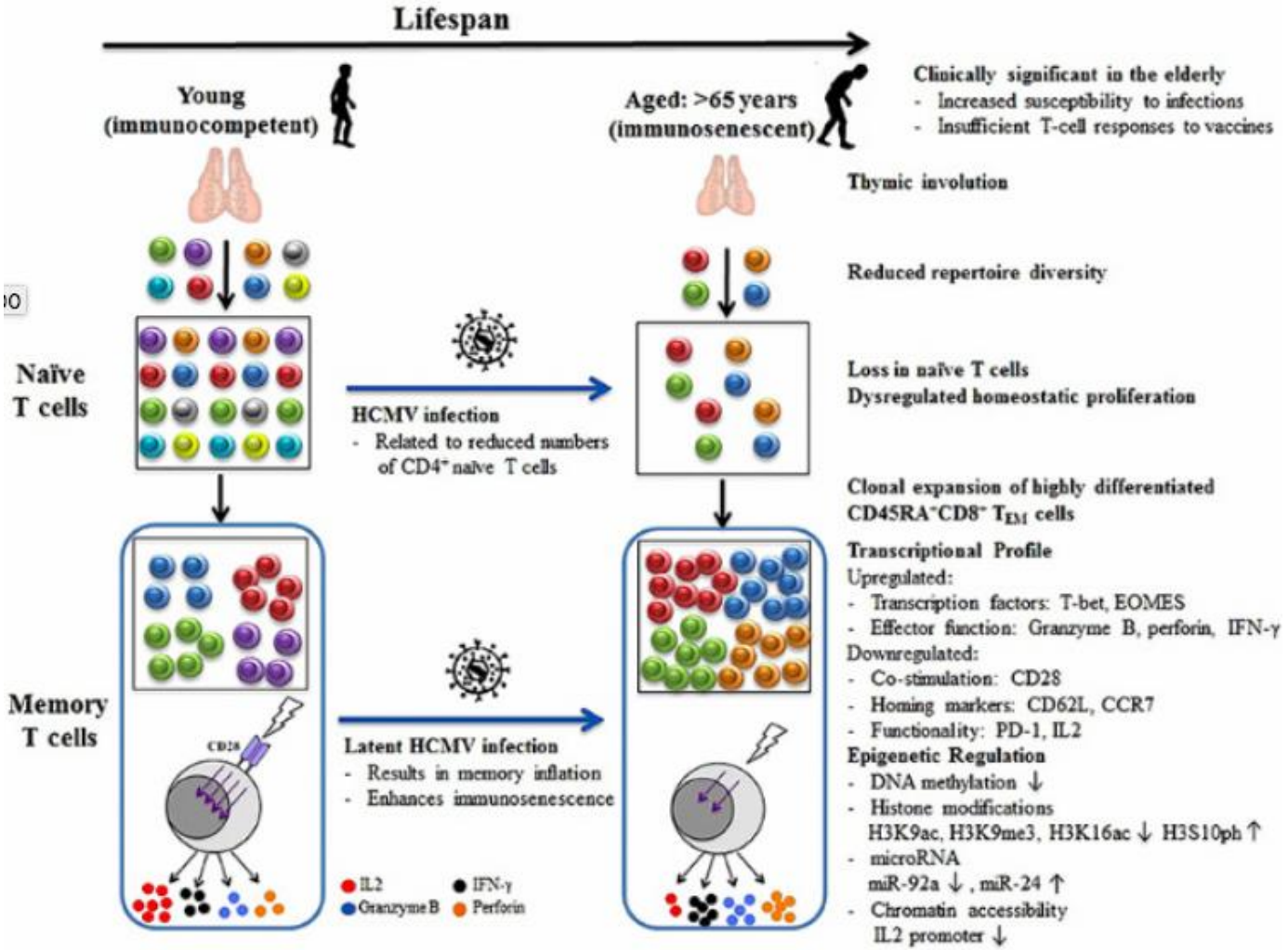
[2]*Department of Natural Science and Biomedicine, School of Health Sciences, Jönköping University, Jönköping, Sweden*


CMV infection
Latency with recurrent reactivation
Memory inflation
Immunomodulation?
Increased responses to vaccination?
Decreased responses to vaccination
Lifespan
Immunosenescence
Physical and functional impairments, increased morbidity and mortality
Reduced responsiveness to influenza vaccination


Blood flow
Lumen
Tissue
Circulating memory T cells: localized inflammatory cytokines
Latent CMV
Reactivating CMV
Latent CMV
Tissue-resident memory T cells: localized inflammatory cytokines


Lifespan
Young
(immunocompetent)
Aged: >65 years
(immunosenescent)
Clinically significant in the elderly
- Increased susceptibility to infections
- Insufficient T-cell responses to vaccines
Thymic involution
Reduced repertoire diversity
Naïve
T cells
HCMV infection
- Related to reduced numbers of CD4+ naïve T cells
Loss in naïve T cells
Dysregulated homeostatic proliferation
Clonal expansion of highly differentiated CD45RA+CD8+ TEM cells
Memory
T cells
CD28
Latent HCMV infection
- Results in memory inflation
- Enhances immunosenescence
IL2
IFN-γ
Granzyme B
Perforin
Transcriptional Profile
Upregulated:
- Transcription factors: T-bet, EOMES
- Effector function: Granzyme B, perforin, IFN-γ
Downregulated:
- Co-stimulation: CD28
- Homing markers: CD62L, CCR7
- Functionality: PD-1, IL2
Epigenetic Regulation
- DNA methylation ↓
- Histone modifications
H3K9ac, H3K9me3, H3K16ac ↓ H3S10ph ↑
- microRNA
miR-92a ↓, miR-24 ↑
- Chromatin accessibility
IL2 promoter ↓

Premature telomeric loss in rheumatoid arthritis is genetically determined and involves both myeloid and lymphoid cell lineages

Stefan O. Schönland[†], Consuelo Lopez[†‡], Thomas Widmann[†‡], Julia Zimmer[†], Ewa Bryl[†], Jörg J. Goronzy[†§], and Cornelia M. Weyand[†§¶]

PNAS | November 11, 2003 | vol. 100 | no. 23 | 13471–13476

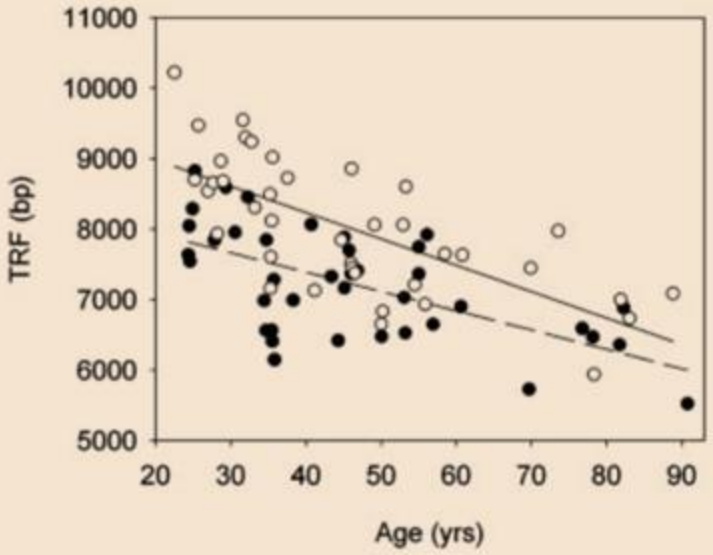


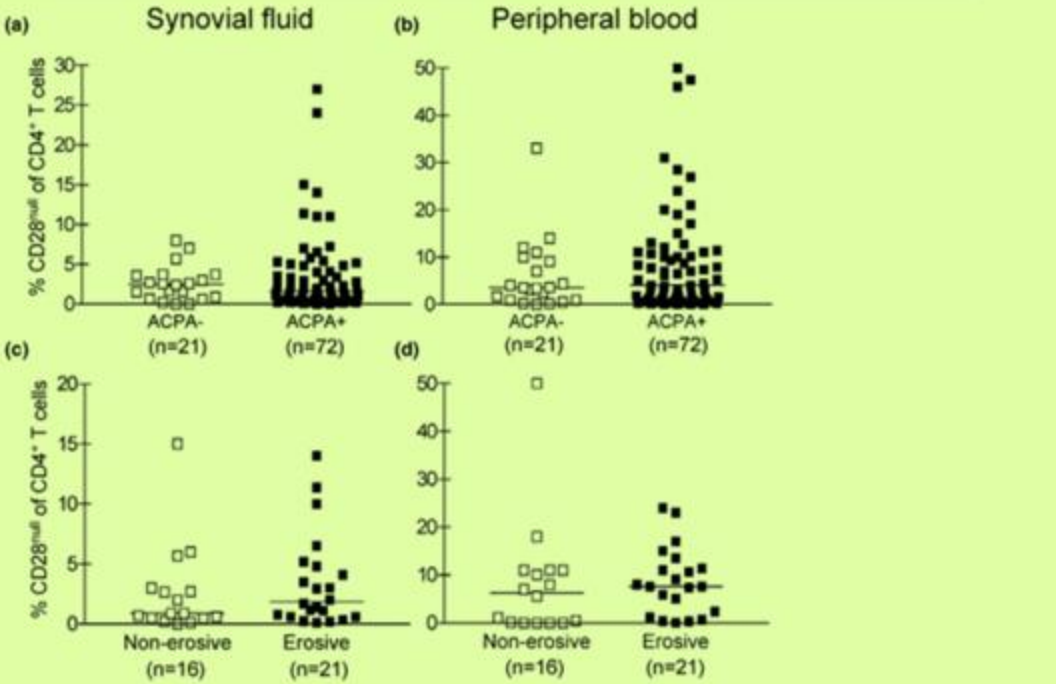
Fig. 3. Premature telomeric erosion in granulocytes of HLA-DR4$^+$ donors. TRF lengths were measured in granulocytes from 39 HLA-DR4$^+$ (●) and 39 HLA-DR4$^-$ (○) donors. The age dependency of telomeric loss in both cohorts is indicated by regression lines (dashed line, HLA-DR4$^+$; solid line, HLA-DR4$^-$). Granulocytes from HLA-DR4$^+$ donors had significantly shorter telomeres (P = 0.004). The annual loss during adult life did not differ significantly (P = 0.24).

Research article

Open Access

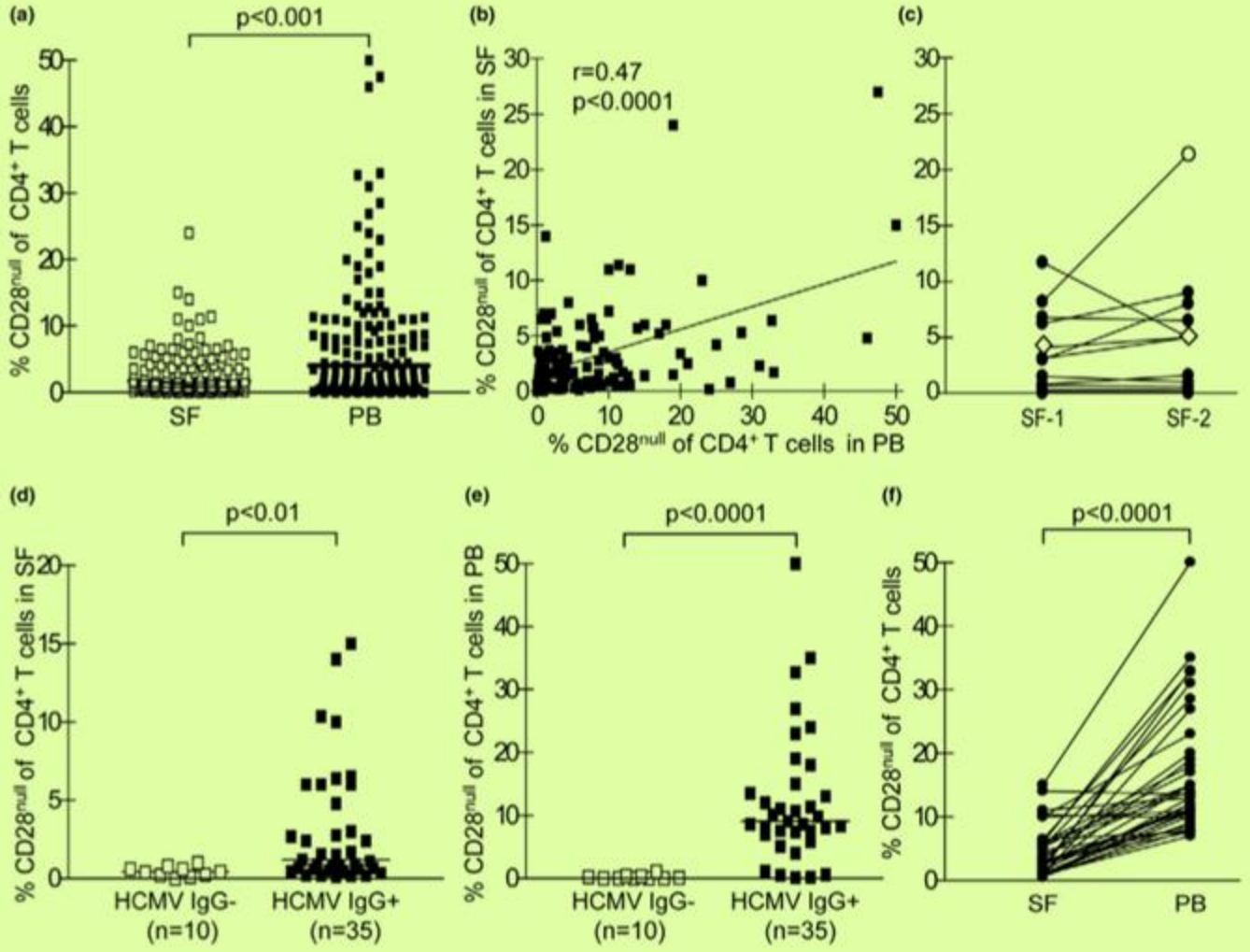
Skewed distribution of proinflammatory CD4+CD28null T cells in rheumatoid arthritis

Andreas ER Fasth[1], Omri Snir[1], Anna AT Johansson[1], Birgitta Nordmark[1], Afsar Rahbar[2], Erik af Klint[1], Niklas K Björkström[3], Ann-Kristin Ulfgren[1], Ronald F van Vollenhoven[1], Vivianne Malmström[1]* and Christina Trollmo[1]*



CD4+CD28null T cells do not associate with erosive disease. Frequency of CD4+CD28null T cells in paired samples of synovial fluid (left column) and peripheral blood (right column) from **(a), (b)** patients seronegative (ACPA-) and seropositive (ACPA+) for anti-citrullinated peptide/protein antibodies, and **(c), (d)** patients with or without erosive disease.

Figure 2



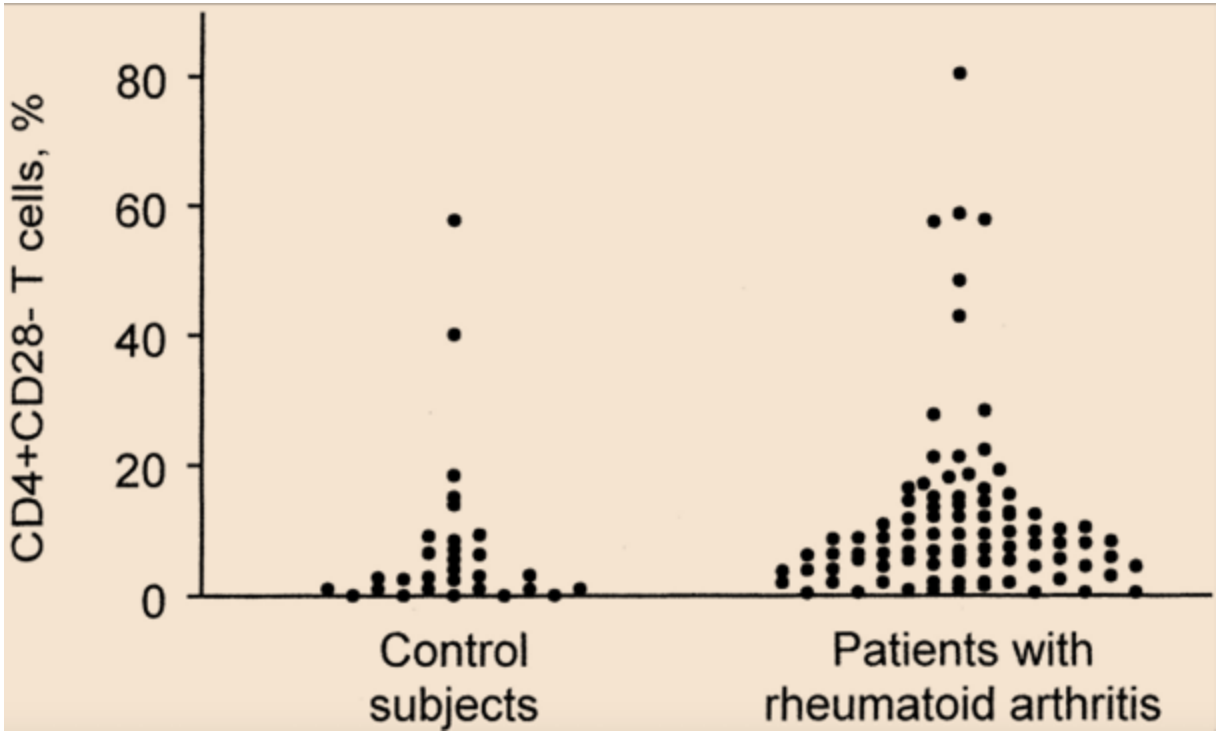
Skewed distribution of $CD4^+CD28^{null}$ T cells in synovial fluid and peripheral blood. **(a)** Paired samples of synovial fluid (SF) and peripheral blood (PB) from 128 rheumatoid arthritis patients were compared for the frequency of $CD4^+CD28^{null}$ T cells by flow cytometry. **(b)** Frequencies of $CD4^+CD28^{null}$ T cells in SF tend to be higher in patients with large populations in PB. **(c)** Comparison of the frequency of $CD4^+CD28^{null}$ T cells in SF from two different synovial compartments. Open circle, elbow; open squares, shoulder joints. Frequencies of $CD4^+CD28^{null}$ T cells in **(d)** SF and **(e)** PB in patients seronegative and seropositive for human cytomegalovirus (HCMV). **(f)** Frequencies of $CD4^+CD28^{null}$ T cells in paired PB and SF of patients seropositive for HCMV.

Circulation
Volume 109, Issue 22, 8 June 2004; Pages 2744-2748
https://doi.org/10.1161/01.CIR.0000131450.66017.B3

CLINICAL INVESTIGATION AND REPORTS

CD4+CD28– T Lymphocytes Contribute to Early Atherosclerotic Damage in Rheumatoid Arthritis Patients

Roberto Gerli, MD, Giuseppe Schillaci, MD, Andrea Giordano, MD, Elena Bartoloni Bocci, MD, Onelia Bistoni, BiolSc, Gaetano Vaudo, MD, Simona Marchesi, MD, Matteo Pirro, MD, Federica Ragni, MD, Yehuda Shoenfeld, MD, FRCP, and Elmo Mannarino, MD



frontiers in Immunology

ORIGINAL RESEARCH
published: 20 March 2017
doi: 10.3389/fimmu.2017.00280

Novel Senescent Regulatory T-Cell Subset with Impaired Suppressive Function in Rheumatoid Arthritis

Johannes Fessler[1], Andrea Raicht[2], Rusmir Husic[1], Anja Ficjan[1], Christine Schwarz[2], Christina Duftner[1], Wolfgang Schwinger[2], Winfried B. Graninger[1], Martin H. Stradner[1] and Christian Dejaco[1,3]*

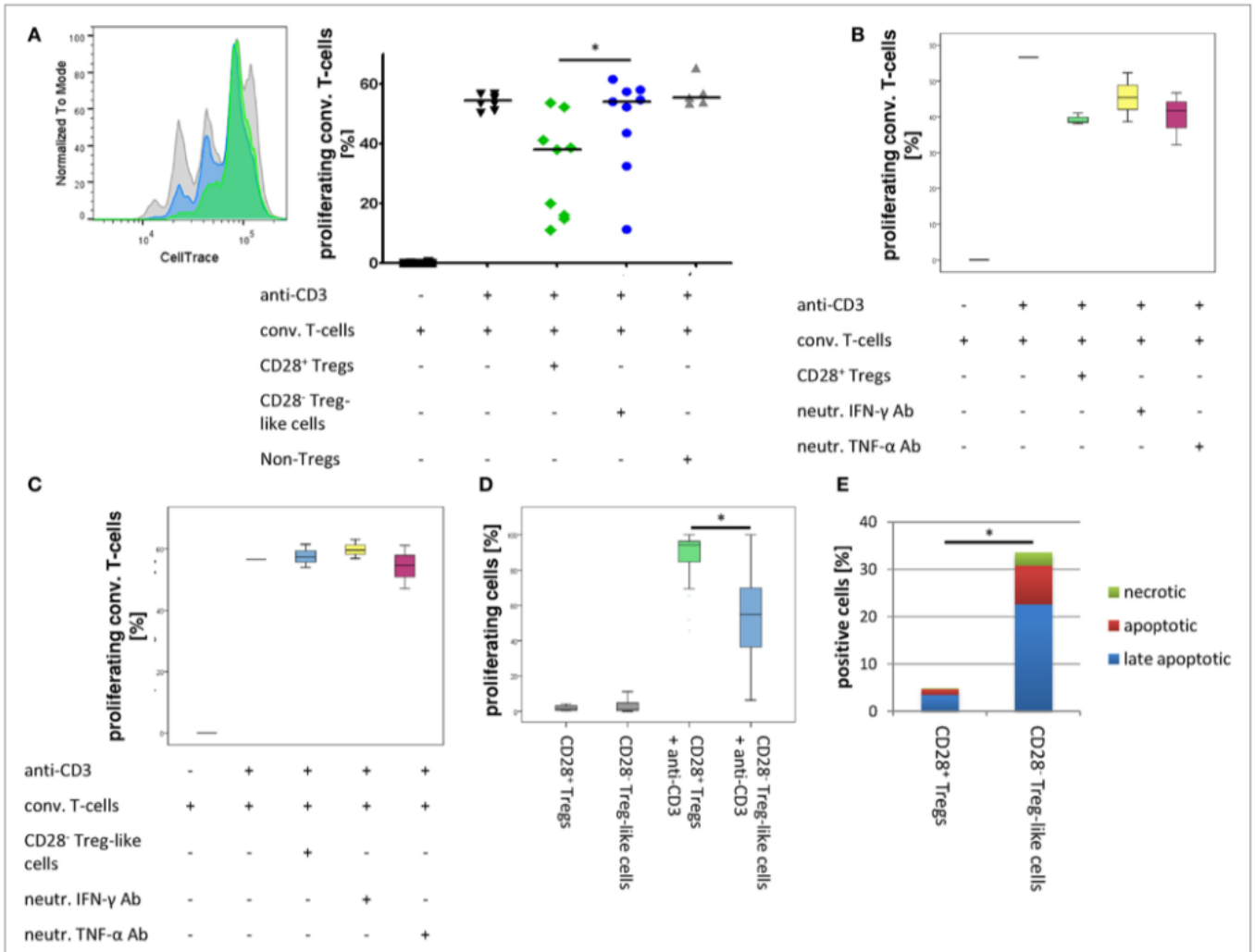


FIGURE 5 | CD28⁻ regulatory T-cells (Tregs)-like cells show reduced suppressive capacity. Graphs show **(A)** representative histograms and box plots of *in vitro* suppression assays with CD28⁺ Tregs (green), CD28⁻ Treg-like cells (blue), as well as conventional T-cells (gray) of nine rheumatoid arthritis patients, **(B)** box plots of *in vitro* suppression assays with CD28⁺ Tregs (green) as well as **(C)** CD28⁻ Treg-like cells (blue) in the presence of neutralizing ab to IFN-γ (yellow) or TNF-α (pink); **(D)** proliferative potential of CD28⁺ Tregs (green) and CD28⁻ Treg-like cells (blue) following stimulation with anti-CD3; and **(E)** apoptotic (green), late apoptotic (blue), as well as necrotic (red) cells. Mann–Whitney *U* test was used to assess differences between groups. *$p < 0.05$.

D

proliferating cells [%]
0
20
40
60
80
100
*
CD28+ Tregs
CD28- Treg-like cells
CD28+ Tregs + anti-CD3
CD28- Treg-like cells + anti-CD3

Το ανοσοποιητικό σύστημα στην τρίτη ηλικία

Σας ευχαριστώ