TA-65:

Immune optimization
Covid-19
Genome Protection
Mitochondrial Protection
What's new

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- Telomere/Telomerase Biology
  - DNA
  - Mitochondria
  - Cancer
  - Cardiovascular
  - TERT and TERC
  - Reversal of T cell senescence
  - T cells and Covid-19
- Connect the dots
  - Telomeres
  - Inflammation
  - Lifestyle, Nutrition, Exercise, Environmental toxicity
  - Hormones

- Medical Literature
  - CV
  - Brain
  - Immune
  - Does TA-65 activate telomerase and improve telomere length?
  - Peer reviewed Published studies using TA-65, animal and human
  - New current studies
- Clinical observations of TA-65 treatment
- Bottom Line
  - Should you and your patients take TA-65?

What causes the Hayflick limit?

- The **Hayflick limit:** The number of times a normal cell population will divide until cell division stops.
- The telomeres get shorter with each new cell division until they shorten to a critical length and cellular death, senescence or mutation result

Hayflick L et al. The serial cultivation of human diploid cell strains. *Exp Cell Res.* (1961).25(3):585–621.

Telomeres

- Region of repetitive nucleotide sequences (TTAGGG) at each end of the chromatid.
- Telomeres act as the cellular aging clock.
- Blackburn et al. Nobel Prize
- Telomere loss is a Major Cause of Cellular Aging, Inflammation and Mutation

Telomere Length Determines Cellular Age

Somatic cells

- Make up > 99% of the cells in the adult body
- Have little or no telomerase and telomeres shorten as we get older.

Telomere Length Shortening:

- **Conception**: Telomeres start out **15,000** base pairs (bp) long.
- By **Birth** the embryo has divided so many times that telomere length is down to **10,000 bp.**
- Over the rest of our lifetime, we lose another **5,000** to **7,000** bp**.**
- When telomere length gets to **3-5,000 bp,** the genome is no longer protected from mutations, the cell can no longer divide, becomes senescent, metabolism slows down, and the cell dies.
- Senescence-Associated Secretory Phenotype - inflammation

When telomeres become critically short
Loss of genome protection 3 bad options:

- Senescence
- Senescence associated secretory phenotype = SASP = Inflammation
- Genomic Instability: Mutation that can lead to malignancy

Telomeres are the Biological Clock of Aging

- Organs deteriorate as more and more of their cells die off or enter cellular senescence.
- Shortened telomeres impair immune function that might also increase cancer susceptibility
- Telomere length represents biological age as opposed to chronological age

Eisenberg DT. An evolutionary review of human telomere biology: the thrifty telomere hypothesis and notes on potential adaptive paternal effects. *Am J Hum Biol.2011. 2, 149-67*

Telomeres and Aging

- 143 normal unrelated individuals over the age of 60 years.
- Shorter telomeres in blood DNA had poorer survival
  - 3.18-fold higher mortality rate from heart disease (95% CI 1.36-7.45, p=0.0079)
  - 8.54-fold higher mortality rate from infectious disease (1.52-47.9, p=0.015).
- Telomere shortening in human beings contributes to mortality in many age-related diseases.

Cawthon RM et al. Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet*. 2003 Feb 1;361(9355):393-5.

The Impact of Telomere Shortening

- "Short telomeres are associated with increased risks for human bladder, head, neck, lung, and renal cell cancers"
- Fraternal twins with the shortest telomeres had a three times greater risk of death than their co-twins with the longest telomere measurements

Wu X et al. Telomere Dysfunction: A Potential Cancer Predisposition Factor (2003) *J National Cancer Inst*. 2003 Aug 20;95(16)1211-18.

Johansson, S et al. Telomere length predicts survival independent of genetic influences (2007) *Aging Cell*, 2007.

What shortens telomeres?

- Aging (except in immortal animals)
- Rapid cellular division in response to infection
- Oxidative stress
- Inflammation
- Lifestyle factors
- Homocysteine
- Hormone deficiencies

Telomerase

- Maintains the telomere length
- Promotes genomic integrity, proliferation, and lifespan
- Protects the mitochondria from oxidative stress
- Confers resistance to apoptosis
- **Important for the survival of non-mitotic, highly active cells such as neurons**

Grin Y et al. Telomerase activity in the various regions of mouse brain: non-radioactive telomerase repeat amplification protocol (TRAP) assay**.** *J Vis Exp*. 2014 Sep 2

To make telomeres longer…

- Activate ***Telomerase***
- Endogenous enzyme
- Stabilizes telomere length
- Adds DNA repeats (TTAGGG) onto the telomeric ends of the chromosomes
- Compensates for the erosion of telomeres when cells divide

Telomerase

E

Reverse

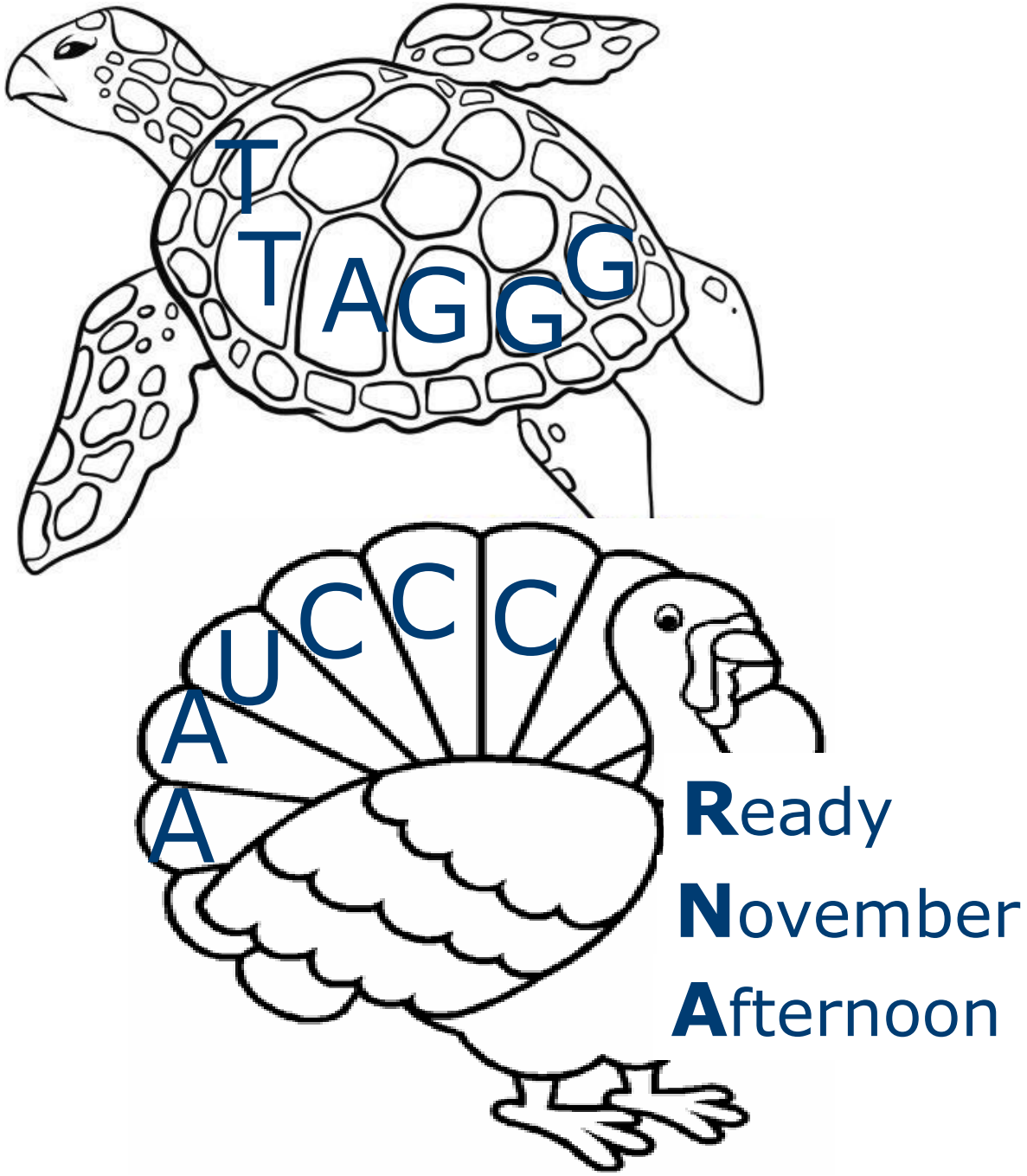
Transcriptase

Telomerase

E

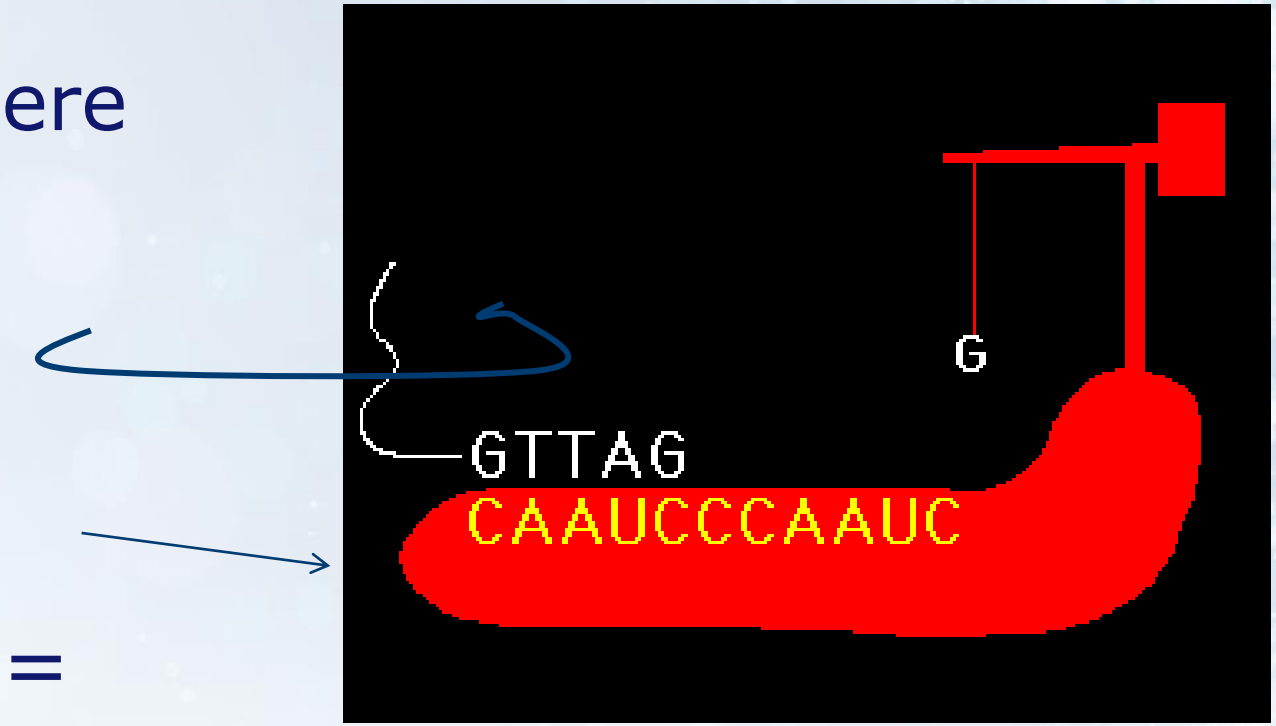
RNA

Component



Telomerase = TERT + TERC

Telomere



Telomerase reverse transcriptase- hTERT

hTERT

hTR = Template = *hTERC*

Telomerase is a “molecular motor” that adds new DNA bases (TTAGGG) onto the ends of telomeres

“Intelligent Antioxidant”

- Free radical damage is one of the fundamental causes of the degeneration of aging
- In preventive/regenerative medicine we attempt to control ROS with anti-oxidants, coenzyme Q 10, vitamin C, stimulating glutathione etc.
- Non-canonical actions
- Telomerase connection:
  - Shuttling of TERT from nucleus to mitochondria as needed.
  - If mitochondria are protected against free radicals there is more TERT to protect nucleus.
  - Increased oxidative stress shortens telomeres
  - Prevents vicious cycle

Astragalus

- Chinese medicine for more than 2,000 years for healing and diabetes
- Primary chemical constituent is cycloastragenol (CAG) (TAT2)
- Used as a tonic to improve:
  - Lungs
  - Adrenal glands
  - Gastrointestinal tract
  - Metabolism
  - Healing
  - Fatigue

Published Peer reviewed TA-65 papers

- Salvador L, et al. A Natural Product Telomerase Activator **Lengthens Telomeres in Humans:** A Randomized, Double Blind, and Placebo Controlled Study. *Rejuvenation Res*. 2016 Mar 30.

- Dow CT, Harley CB Evaluation of an oral telomerase activator for early **age-related macular degeneration** - a pilot study.. *Clin Ophthalmol*. 2016 Jan 28;10:243-9.

- Reichert S, Bize P, Arrivé M, Zahn S, Massemin S, Criscuolo Experimental increase in telomere length leads to **faster feather regeneration**. F. *Exp Gerontol*. 2014 Apr;52:36-8.

- Harley CB, Liu W, Flom PL, Raffaele JM. A natural product telomerase activator as part of a health maintenance program: **metabolic and cardiovascular** response. *Rejuvenation Res*. 2013 Oct;16(5):386-95.

- Molgora, B et al. Functional assessment of pharmacological telomerase activators in human T cells. *Cells*. 2013 Jan 14;2(1):57-66.

- Bernardes de Jesus B, Schneeberger K, Vera E, Tejera A, Harley CB, Blasco MA. The telomerase activator TA-65 **elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence.** *Aging Cell*. 2011 Aug;10(4):604-21.

- Harley CB, Liu W, Blasco M, Vera E, Andrews WH, Briggs LA, Raffaele JM. A natural product telomerase activator as part of a health maintenance program. *Rejuvenation Res*. 2011 Feb;14(1):45-56.

- Fernandez M et al. TA-65, A Telomerase Activator **improves Cardiovascular Markers** in Patients with Metabolic Syndrome. *Current Pharmaceutical Design*, 2018, 24, 1-7

- Kokubun T et al Telomerase Plays a Pivotal Role in **Collateral Growth Under Ischemia** by Suppressing Age-Induced Oxidative Stress, Expression of p53, and Pro-Apoptotic Proteins Collateral Growth Related to Telomerase.. *Int Heart J* 2019; 60: 736-745

- Eyolfon E et al. Sexually Dimorphic Behavioral and Genetic Outcomes Associated With Administration of TA65 (A Telomerase Activator) Following Repetitive **Traumatic Brain Injury**: A Pilot Study**.** *Front Neurol* . 2020 Feb 18;11:98.

Wan, T et al. Increased telomerase improves motor function and alpha-synuclein pathology in a transgenic mouse model of **Parkinson's disease** associated with enhanced autophagy. *Prog Neurobiol.* 2021 Apr; 199: 101953.

Maier, Rebecca et al. Telomerase Activation to Reverse Immunosenescence in Elderly Patients With **Acute Coronary Syndrome**: Protocol for a Randomized Pilot Trial**.** *JMIR Res Protoc.* 2020 Sep 23;9(9):e19456

Gunasekaran Singaravelu , Calvin B Harley , Joseph M Raffaele , Pratheesh Sudhakaran , Anitha Suram. Double-Blind, Placebo-Controlled, Randomized Clinical Trial Demonstrates **Telomerase Activator TA-65 Decreases Immunosenescent CD8+CD28- T** Cells in Humans. *OBM Geriatrics* 2021, volume 5, issue 2

Alshinnawy A et al. Astragalus *membranaceus* and *Punica granatum* alleviate infertility and kidney dysfunction induced by aging in male. Turk J Biol. (2020) 44: 166-175

TA-65 restored youthful levels of sperm function and kidney function in old rats

Ameera Saeed Alshinnawy. **Telomerase activator-65** and pomegranate peel **improved the health status of the liver in aged rats**; multi-targets involved. Iran J Basic Med Sci . 2021 Jun

Gabriele Saretzki. **Telomerase in Brain**: The New Kid on the Block and Its Role in Neurodegenerative Diseases *Biomedicines.* 2021 May.

Niloofar Ale-Agha. Mitochondrial Telomerase Reverse Transcriptase **Protects From Myocardial Ischemia/Reperfusion** Injury by Improving Complex I Composition and Function. 2021 Dec 2021 10.1161/*CirculationAHA*.

Dermochelys coriacea

Leatherback Sea Turtle

Virginia Plot et al. Telomeres, Age and Reproduction in a Long-Lived Reptile. Plos One. July 2012.Vol 7, Issue 7

It all fits together

- Everything we are trying to do for optimal health and quality of life has a telomere/telomerase connection
- Avoiding and controlling oxidative stress, Nrf2
- Nutrition
- Intermittent fasting
- Meditation
- Exercise
- Controlling Mental Stress, environmental toxicity, radiation exposure
- Optimizing hormones
- Optimizing Nitric Oxide (NO)
- Activate Telomerase

What Can Be Done To Keep Telomeres Long?

- Nutraceuticals
  - Kiecolt-Glaser JK et al. **Omega-3** fatty acids, oxidative stress, and leukocyte telomere length: A randomized controlled trial. *Brain Behav Immun*. 2013 Feb;28:16-24.
  - Lui M et al. **Resveratrol** protects against age-associated infertility in mice. *Hum Reprod*. 2013 Mar;28(3):707-17
  - Liu JJLiu et al. Plasma **Vitamin D** biomarkers and leukocyte telomere length. *Am J Epidemiol*. 2013 Jun 15;177(12) : 1411-7.
  - Zijian Xia et al. Telomerase: A Target for Therapeutic Effects of **Curcumin** and a Curcumin Derivative in Ab1-42 Insult In Vitro. *PLOS ONE* 1 July 2014.Volume 9. Issue 7
  - Richards JB et al. **Homocysteine** levels and leukocyte telomere length**.** *Atherosclerosis*. 2008 Oct.

- Garcia-Calzon S. et al. **Dietary total antioxidant** capacity is associated with leukocyte telomere length in a children and adolescent population. *Clinical Nutrition* 34 (2015) 694-699
- Bandi Hari Krishna et al. Association of Leukocyte Telomere Length with Oxidative Stress in **Yoga** Practitioners. *Journal of Clinical and Diagnostic Research*. 2015 Mar, Vol-9(3): CC01-CC03
- Werner C et al. Effects of physical **exercise** on myocardial telomere-regulating proteins, survival pathways, and apoptosis. *J Am Coll Cardiol*. 2008 Aug 5;52(6):470-82.
- Bijnens E et al. Lower placental telomere length may be attributed to **maternal residential traffic exposure**; a twin study. *Environ Int*.2015 Jun;79:1-7
- Laia Hernandez et al. **Aging and radiation**: bad companions. *Aging Cell* (2015) 14, pp153–161
- Marta Crous-Bou et al. **Mediterranean diet** and telomere length in Nurses' Health Study: population-based cohort study. *BMJ* 2014; 349
- Jacobs TL, Epel ES, Lin J, Blackburn E, Wolkowitz OM, Bridwell DA, Zanesco AP, Aichele SR, Sahdra BK, MacLean KA, King BG, Shaver PR, Rosenberg EL, Ferrer E, Wallace BA, Saron CD Intensive **meditation** training, immune cell telomerase activity, and psychological mediators. *Psychoneuroendocrinology*. 2011 Jun;36(5):664-81

Telomere Length-Depression

- Depression associated with shortened telomeres
- Shorter telomeres persist in individuals with lifetime depression
- CD8+ cytotoxic T cells and CD20+ B cells are particularly affected in depression.

Alexander Karabatsiakis et al. Telomere shortening in leukocyte subpopulations in depression. *BMC Psychiatry* 2014, 14:192

Telomerase Protects Brain

- Oxidative stress - important contributor to neurodegeneration associated with acute CNS injuries and diseases - spinal cord injury (SCI), traumatic brain injury (TBI), and ischemic stroke.
- Preventing DNA damage promotes neuronal survival and enhances **neurological recovery.**
- Telomerase is a novel therapeutic target in the treatment of **neurodegeneration**
- Modulates the neuronal response to both oxidative stress and DNA damage.

Smith JA et al. Oxidative stress, DNA damage, and the telomeric complex as therapeutic targets in acute neurodegeneration. *Neurochem Int*. 2013 Apr;62(5):764-75

TA-65 and TBI

- Children and adolescents have the highest rates of traumatic brain injury (TBI)
- Telomere length marker for outcomes in TBI
- TA-65 improved motor coordination and reduced depressive-like behavior in female rats with TBI
- In the healthy brain both glia and neurons are susceptible to significant telomere shortening.
- Glial cells because they are mitotic, and neurons (although post-mitotic) are excitable and exhibit higher metabolic rates leads to higher levels of oxidative stress

Eyolfon E et al. Sexually Dimorphic Behavioral and Genetic Outcomes Associated With Administration of TA65 (A Telomerase Activator) Following Repetitive Traumatic Brain Injury: A Pilot Study**.** *Front Neurol*. 2020 Feb 18;11:98.

Telomerase and Memory

- Adult hippocampus generates neurons throughout life
- Hippocampal TERT necessary for neuronal development throughout life
- “Non-canonical” action of TERT
- TERT based strategy for memory impairment needed

Zhou QG et al. Hippocampal TERT Regulates Spatial Memory Formation through Modulation of Neural Development. *Stem Cell Reports*. 2017 Jul 25

TA-65 and Parkinson's Disease

- Increased brain *TERT* expression
- Improvement of motor functions such as gait and motor coordination
- TA-65 resulted in a decrease of reactive oxygen species from brain mitochondria

- Wan, T et al. Increased telomerase improves motor function and alpha-synuclein pathology in a transgenic mouse model of Parkinson's disease associated with enhanced autophagy. *Prog Neurobiol*. 2021 Apr; 199: 101953.

TERT and Alzheimer's and Parkinson’s

- TERT in brain - benefit for the amelioration of brain aging and neurodegenerative diseases such as AD and PD.
- TA-65 discussed as therapy

Gabriele Saretzki.· Telomerase in Brain: The New Kid on the Block and Its Role in Neurodegenerative Diseases *Biomedicines*. 2021 May.

Optimized Hormones and Telomere Length

- Cen J et al. Anti-aging effect of **estrogen** on telomerase activity in ovariectomised rats--animal model for menopause**.** Gynecol Endocrinol. 2015
- Kaplan RC et al. **Insulin-like growth factors** and leukocyte telomere length: the cardiovascular health study. *J Gerontol A Biol Sci Med Sci*. 2009 Nov;64(11):1103-6
- Movérare-Skrtic S et al. Serum **insulin-like growth factor-1** concentration is associated with leukocyte telomere length in a population-based cohort of elderly men. *J Clin Endocrinol Metab*. 2009 Dec;94(12):5078-84.
- Rastmanesh, R. Potential of **melatonin** to treat or prevent age-related macular degeneration through stimulation of telomerase activity. *Med Hypotheses*. 2011 Jan;76(1):79-85.
- Rodrigo T. Calado et al. **Sex hormones**, acting on the *TERT* gene, increase telomerase activity in human primary hematopoietic cells. *Blood*. Sep 10, 2009; 114(11): 2236–2243

Telomeres and CVD

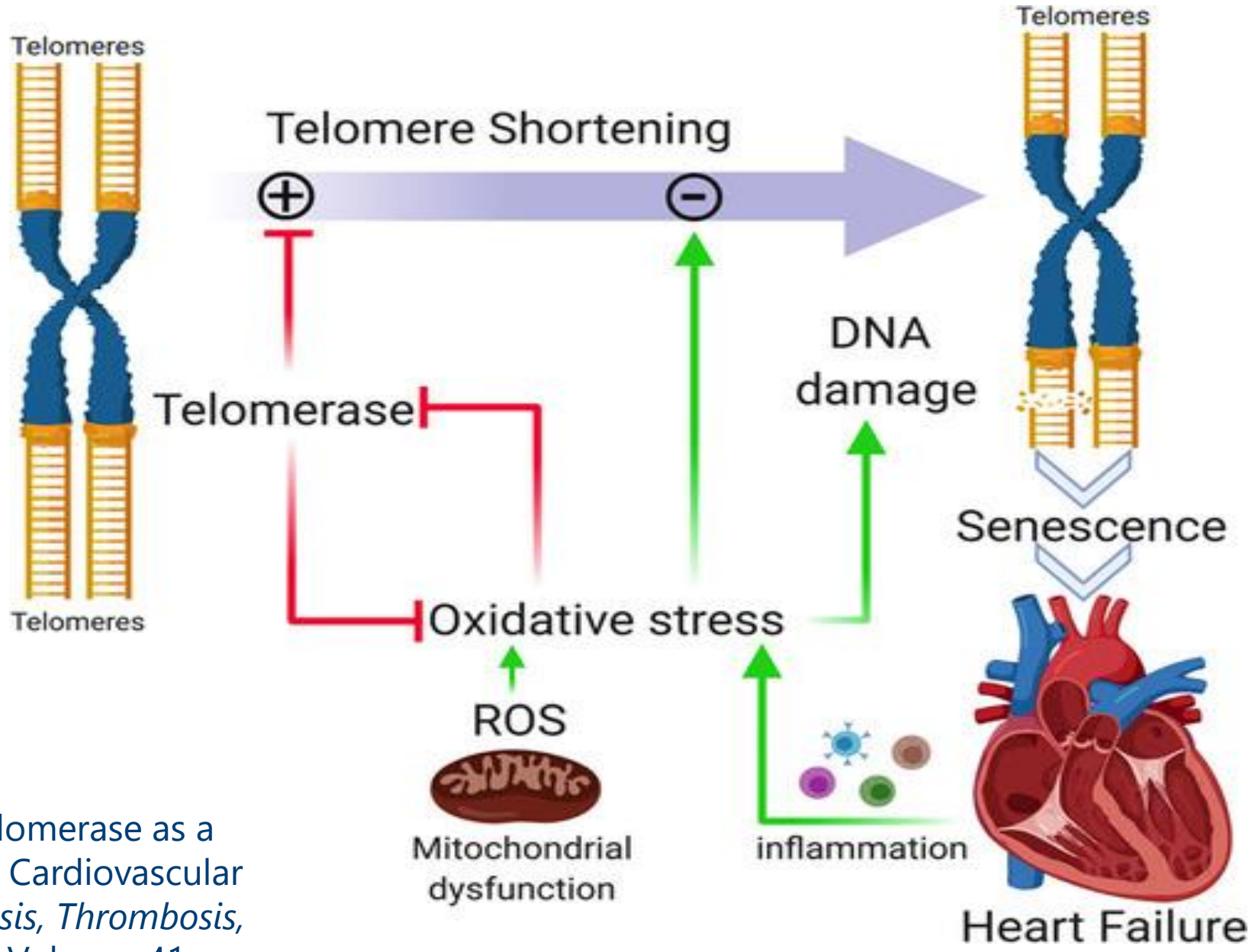
- Critically short telomeres lead to cellular senescence and apoptosis
- Contributes to the development of atherosclerosis and predispose to **plaque instability**
- LTL reflects the burden of oxidative stress and inflammation
- Effective biomarker for risk stratification for atherosclerosis and CVDs.
- Improving telomere length is a target for treating CVD

Yeh JK et al. Telomeres and Telomerase in Cardiovascular Diseases. *Genes (*Basel). 2016 Sep

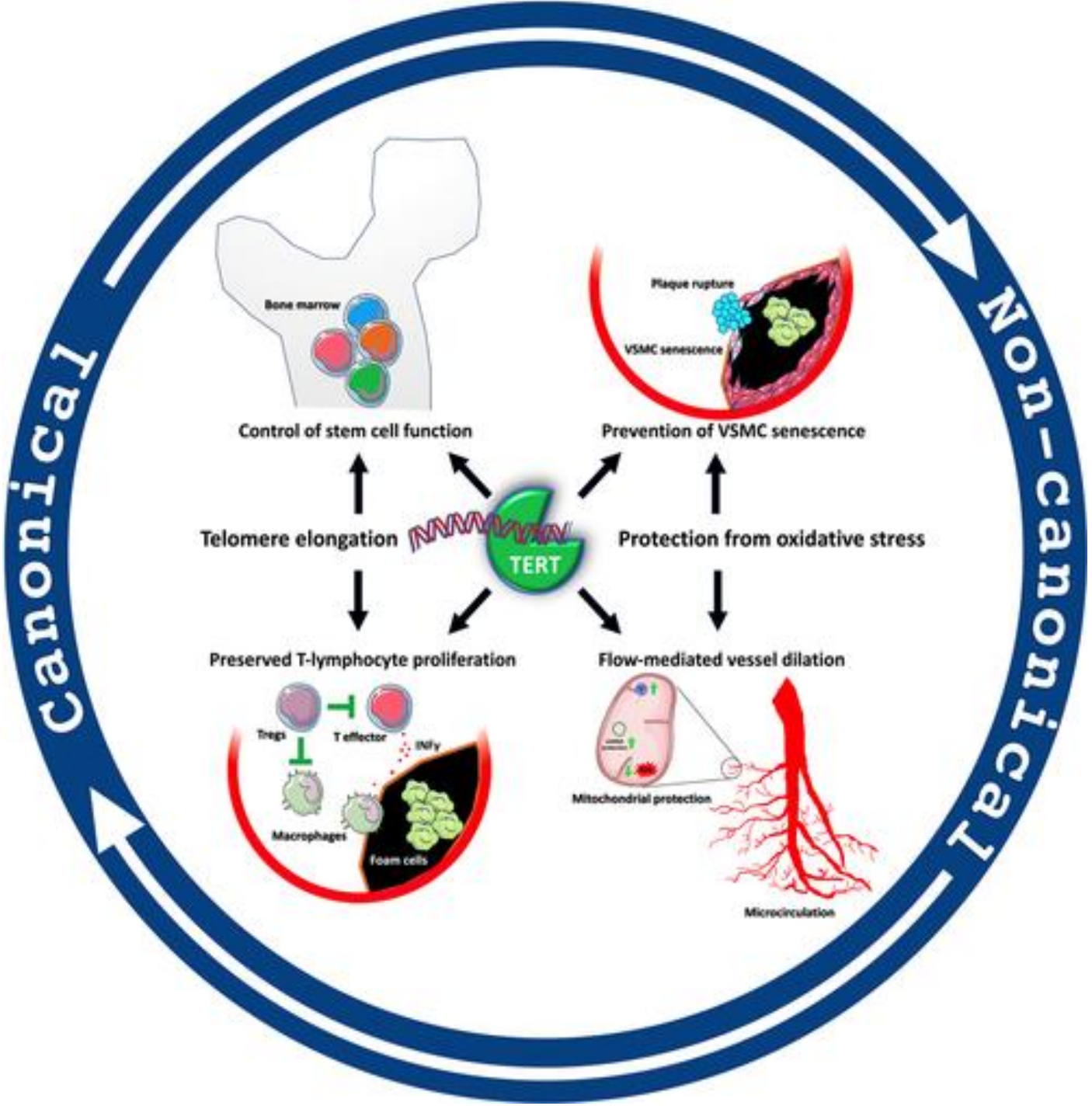
Telomerase and Atherosclerosis

- The atheroprotective role of mitochondrial TERT - antioxidative function and vascular cell regeneration.
- The noncanonical functions of TERT - beneficial in the treatment of cardiovascular aging and disease.

Jedrzej Hoffmann. Telomerase as a Therapeutic Target in Cardiovascular Disease, *Arteriosclerosis, Thrombosis, and Vascular Biology*. Volume: 41, Issue: 3, 2021



Jedrzej Hoffmann. Telomerase as a Therapeutic Target in Cardiovascular Disease, *Arteriosclerosis, Thrombosis, and Vascular Biology*. Volume: 41, Issue: 3, 2021



Jedrzej Hoffmann. Telomerase as a Therapeutic Target in Cardiovascular Disease, *Arteriosclerosis, Thrombosis, and Vascular Biology*. Volume: 41, Issue: 3, 2021

Clinical Implications of TA-65

- TA-65 increases TERT within the mitochondria
- Mitochondrial telomerase reverse transcriptase (TERT), not nuclear TERT, is cardioprotective against ischemia/reperfusion injury.
- Mitochondrial TERT protects cardiomyocytes from apoptosis, improves cardiac myofibroblast differentiation, and endothelial cell migration and vascularization.
- An increase in mitochondrial TERT levels, induced by treatment with TA-65, could be beneficial in ischemia/reperfusion injury.

Niloofar Ale-Agha. Mitochondrial Telomerase Reverse Transcriptase Protects From Myocardial Ischemia/Reperfusion Injury by Improving Complex I Composition and Function. Dec 2021 *Circulation AHA*.

TA-65 and immune function – Harley 2011

- 10-50 mg TA-65 12 months
- Multivitamin protocol
- Human study
- Reduction critically short telomeres
  - (<4 kbp) telomeres (p=0.037)
  - Decline in **senescent** Cytotoxic T cells p< .006 at 12 months
  - Increase in natural killer cells p < .0001 at 12 months
- Improved bone density
- Improved cytokine profile and decreased inflammation
- Lengthens critically short telomeres
- No adverse events

Harley CB et al. A natural product telomerase activator as part of a health maintenance program. *Rejuvenation Res*. 2011 Feb;14(1):45-56.

TA-65 and CV function – Harley 2013

- Multivitamin supplement plus TA-65 x 12 months
- Human study
- No significant change in diet or exercise
- Extensive lab testing
- BMD, Dexascan

Harley, C et al. A Natural Product Telomerase Activator as Part of a Health Maintenance Program: Metabolic and Cardiovascular Response. *Rejuvenation Research*. Volume 16, Number 5, 2013

TA-65 and Cardio-Metabolic function – Harley 2013

Fasting glucose	-3.72 mg/dl	p= 0.02
Insulin	-1.32 mIU/ml	p=0.01
Total cholesterol	-13.2mg/dl	p=.002
LDL cholesterol	-11.8 mg/dl	p=.002
Systolic/Diastolic	-17.8/-4.2	p=.007/.001
Homocysteine	-3.6 pmol/L	p=.001
BMD	+2% in spine	p=.003

Early AMD and TA-65 – Pilot study

- 1-year, double-blinded, placebo-controlled interventional study: TA-65 vs. placebo

Conclusion:

- TA 65 significantly improved the macular function of treatment subjects compared to controls
- "The treatment effect is due to **improved function of the retinal pigment epithelium** (RPE) due to reduced telomere attrition via telomerase activation."

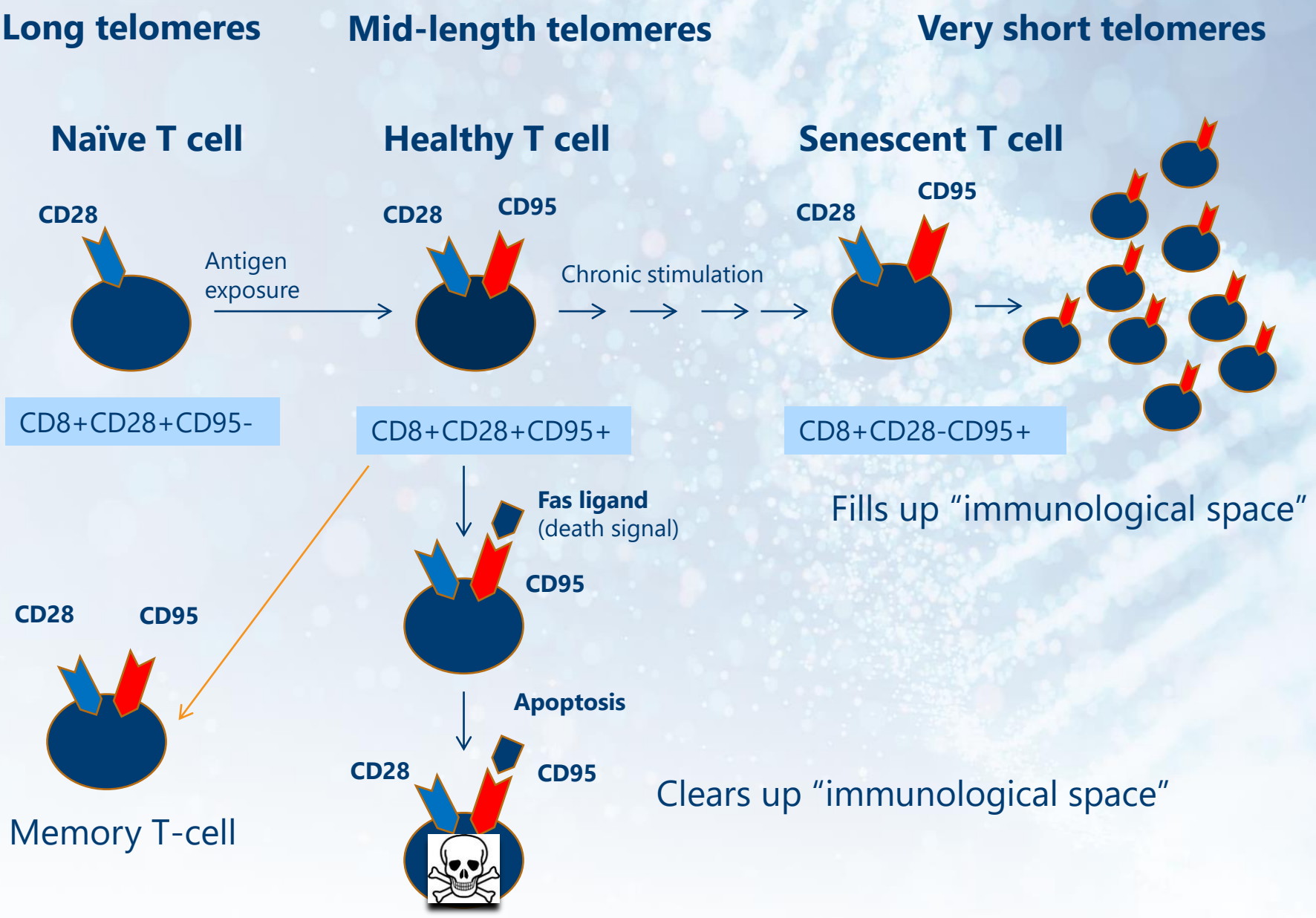
Dow, C and Harley, C. Evaluation of an oral telomerase activator for early age-related macular degeneration - a pilot study. *Clinical Ophthalmology*. 2016:10 243–249.

Antiviral

- Telomerase activator
  - Activates Telomerase
  - Retards telomere shortening
  - Increases proliferative potential
  - Enhances cytokine/chemokine production and antiviral activity
  - **Enhances antiviral functions of CD8 T cells**
  - **Short telomeres – increase risk of death from infection**

Fauce SR et al. Telomerase-based pharmacologic enhancement of antiviral function of human CD8+ T lymphocytes. *J Immunol*. 2008 Nov 15;181(10):7400-6.

Najarro K et al. Telomere Length as an Indicator of the Robustness of B- and T-cell Response to Influenza in Older Adults. *J Infect Dis*. 2015 Mar 31.



Courtesy - Joseph Raffaele MD

CD8+CD28- T cells

- Functional CD8+ cytotoxic T lymphocytes drive the adaptive immune response to cancer
- Downregulation of CD28 is a hallmark of senescent T cells, needed for activation of T cells
- Increased CD8+CD28- senescent populations present in solid and hematogenous tumors
- T cell senescence can be induced by several factors including aging, telomere damage, tumor-associated stress
- Senescent CD8+CD28− T cells display **immunosuppressive functions in cancer**
- Associated with **atherosclerosis and inflammation**

Huff W. et al. The Evolving Role of CD8+CD28- Immunosenescent T Cells in Cancer Immunology Int. *J. Mol. Sci*. 2019, 20, 281

Telomeres and COVID-19

- COVID-19 has increased morbidity and mortality in persons with underlying chronic diseases and those with a compromised immune system regardless of age.

- Aging hallmarks: immunosenescence, inflammation, genomic instability, mitochondrial dysfunction, epigenetic alterations and **telomere attrition**

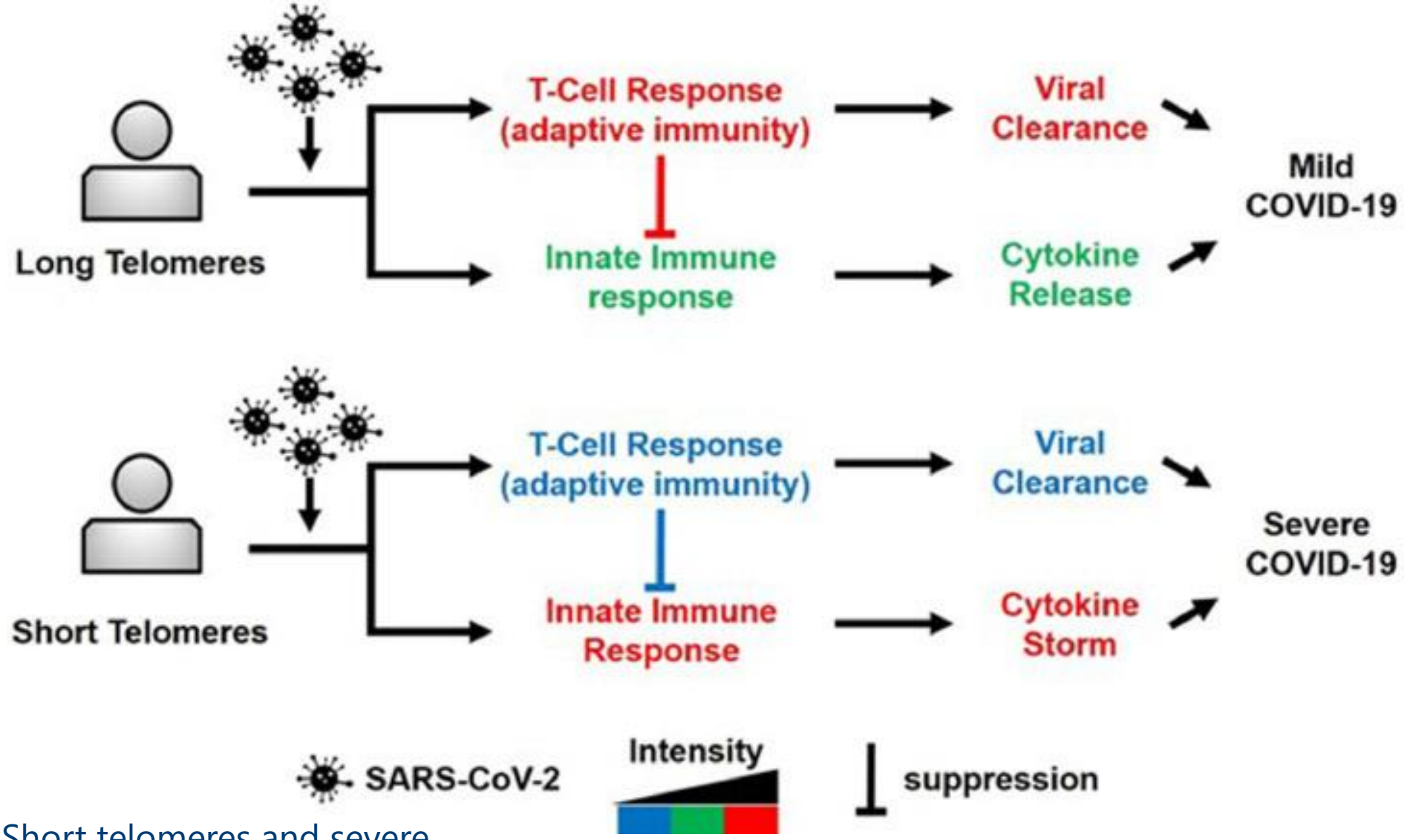
- Telomere attrition, with dysregulated innate and adaptive immune responses to viral infection contributes to the severe outcomes in older adults with COVID-19

Salimi S et al. COVID-19 and Crosstalk With the Hallmarks of Aging. *J Gerontol A biol Sci Med Sci*. 2020 Jun

Telomeres TA-65 and Covid-19

- Short telomere length identifies patients more likely to die from the SARS-CoV-2 infection, regardless of age
- **TA-65 is a potential intervention in COVID-19**
- "The telomerase activator **TA-65** augmented telomerase activity and elongated telomeres and activity and proliferation of T cells"
- "It was also shown to reduce the proportion of circulating senescent CD8+/CD28− T cells in humans"

Aviv A. Telomeres and COVID-19. *FASEB J.* 2020 Jun;34(6):7247-7252.



Abraham Aviv. Short telomeres and severe COVID-19: The connection conundrum. *EBioMedicine* 2021 Aug

Telomere Length and Covid-19

- 6775 adults with Covid-19
- LTL measurements performed **before** the SARS-CoV-2 pandemic.
- Shorter LTL is associated with higher risk of adverse COVID-19 outcomes, **independent of major risk factors** for COVID-19 including age,
- Effect on immune cell senescence
- This explains some of the heterogeneity in inter-individual response

- Wang et al. Shorter leukocyte telomere length is associated with adverse COVID-19 outcomes: A cohort in UK Biobank. *EBioMedicine* 70 (2021)

Telomere Length and Covid-19

Short Telomeres

COVID-19

PPCS (Long Covid) and Telomeres

- Persistent post-COVID-19 syndrome (PPCS) is common.
- In COVID-19 survivors, PPCS presents one or more symptoms:
  - Fatigue
  - Dyspnea
  - Memory loss
  - Sleep disorders
  - Difficulty concentrating
- Epigenetic alterations and **telomere shortening** are associated with the post-COVID-19 condition, particularly in younger patients (< 60 years).

Mongelli, Alessia et al. Evidence for Biological Age Acceleration and Telomere Shortening in COVID-19 Survivors. *Int. J. Mol. Sci.* 2021 June, 22, 6151

	COVID-19-Free	Post-COVID-19	*p*-Value
Samples (*n*)	144 (Male 66.0%; Female 34.0%)	117 (Male 60.7%; Female 39.3%)	
Chronological age (years)	62.48 ± 9.04	58.44 ± 14.66	Ns
Biological age (years)	63.81 ± 13.66	67.18 ± 10.86	Ns
Chronological vs. biological (*p*-value)	Ns	<0.0001	
DeltaAge (years) Ratio	3.68 ± 8.17 1	10.45 ± 7.29 2.84	<0.0001
DeltaAge distribution			
Decelerated (%)	12.8	0.9	
Normal (%)	39.0	22.5	
Accelerated (%)	48.2	76.6	
Telomere length (kb)	**10.67 ± 11.69**	**3.03 ± 2.39**	**<0.0001**
ACE2 expression (2^(-dct))	0.001390 ± 0.002298	0.0003801 ± 0.0004463	<0.0001

Mongelli, Alessia et al. Evidence for Biological Age Acceleration and Telomere Shortening in COVID-19 Survivors. *Int. J. Mol. Sci*. 2021 June, 22, 6151

Effect of TA-65 ® on Telomere Length in Humans

A Natural Product Telomerase Activator Lengthens Telomeres in Humans: A Randomized, Double Blind, and Placebo Controlled Study. Salvador L, et al. Rejuvenation Res. 2016 Mar 30.

- Randomized, double-blind, placebo-controlled study of 97 men and women (50-84 years old)- all CMV+
- First study to show statistically significant lengthening of telomeres ***in humans*** *(3, 6, 9, and 12 months)(p<.005)*

TA-65 ® Group
Increase in median telomere length

Time (months)	Increase in length (base pairs)
3 months	+384 (± 195) bp *
6 months	+158 (± 164) bp
9 months	+526 (± 167) bp *
12 months	+533 (± 183) bp *

Placebo Group
Decrease in median telomere length

Time (months)	Decrease in length (base pairs)
3 months	-24 (± 106) bp
6 months	none
9 months	-170 (± 106) bp *
12 months	-288 (± 101) bp *

* Statistically significant

TA-65 Decreases Immunosenescent CD8+CD28- T Cells in Humans
Primary Endpoint: Effect on Immuno-senescence

- N=500
- TA65 100 mg, 250 mg, 500 mg daily and 250 mg twice daily compared to placebo

Findings after 9 months:

- Senescent T cells decreased
- Naive T cells increased
- All p values for data. <.001
- Results independent of CMV status

Gunasekaran Singaravelu , Calvin B Harley , Joseph M Raffaele , Pratheesh Sudhakaran , Anitha Suram. Double-Blind, Placebo-Controlled, Randomized Clinical Trial Demonstrates Telomerase Activator TA-65 Decreases Immunosenescent CD8+CD28- T Cells in Humans. *OBM Geriatrics* 2021, volume 5, issue 2

TA-65 decreases senescent T cells (CD8+CD28-) in humans

Group	No. of Subjects	Baseline (mean ± SE) cells/μL	End of Study (mean ± SE) cells/μL	Change in mean*	% of change in mean	p value †
Placebo	72	123 ± 16	127 ± 22	+4	+3%	0.624
TA-65 (100 Units)	86	191 ± 17	167 ± 15	-24	-13%	<0.001
TA-65 (250 Units)	94	161 ± 15	138 ± 12	-24	-14%	<0.001
TA-65 (500 Units)	92	148 ± 15	129 ± 12	-18	-13%	<0.001
TA-65 (250 Units) b.i.d.	80	134 ± 18	117 ± 15	-17	-13%	<0.001

† *p* values <0.05 are indicated in red; p values are estimated by Student's *t*-test *Change in mean = End of study – baseline; SE = Standard error of mean

TA-65 decreases senescent T cells (CD8+CD28-) in humans

Group	No. of Subjects	Baseline (mean ± SE) cells/μL	End of Study (mean ± SE) cells/μL	Change in mean*	% of change in mean	p value †
Placebo	72	123 ± 16	127 ± 22	+4	+3%	0.624
TA-65 (all groups)	352	153 ± 7	136 ± 7	-17	-13%	<0.001

"No product related toxicity or serious adverse events (SAEs) were observed for this study."

† *p* values <0.05 are indicated in red; p values are estimated by Student's *t*-test *Change in mean = End of study – baseline; SE = Standard error of mean

Safe Over More Than 19 Years Of Studies

- Early safety studies done in the 1990's at California biotech company, Geron, before selling their telomerase activation technology and patents to TA Sciences.
- Safety studies began at T.A. Sciences in 2002
- In use by humans since 2007
- More than 20,000 people currently taking TA65®MD
- No reports of any significant adverse events

October 13, 2014
TA-65 "Generally Recognized As Safe"

BURDOCK GROUP
Consultants

Be It Known to All Interested Parties, That
Telomerase Activation Sciences, Inc.
Have Provided Substantive Data Leading to a Determination of
"Generally Recognized as Safe" (GRAS) Status of
TA-65®

According to the rights and privileges conferred in §201(s) (et seq.) of the Federal Food, Drug and Cosmetic Act, Experts, by virtue of their training and experience, have determined that the above mentioned substance, when produced in accordance with current Good Manufacturing Practice (cGMP), is safe under the intended conditions of use and is "Generally Recognized as Safe" (GRAS) by scientific procedures when used as a food ingredient in specific food categories at specified levels and for the purpose(s) indicated in the GRAS dossier, as approved by the GRAS Expert Panel.

Edward L. Carmines, Ph.D. - Expert Panelist — Date 10/6/14
Nancy J. Szabo, Ph.D. – Burdock Group Scientific Monographer — Date 03OCT2014
I. Glenn Sipes, Ph.D., Fellow ATS and AAAS - Expert Panelist — Date 10/7/14
George A. Burdock, Ph.D., DABT, FACN – President, Burdock Group — Date
John A. Thomas, Ph.D., D.A.T.S., F.A.C.T. - Expert Panelist — Date 10/8/14

GRAS

STATE OF FLORIDA
COUNTY OF ORANGE
Affirmed and subscribed before me this 13th day of October, 2014, by George A. Burdock, Ph.D., personally known to me.

Notary Public State of Florida
Gina Strollo Radcliff
My Commission EE026886
Expires 11/26/2014

TA 65: Telomeres, Health Span, Cancer

- Mice treated with TA 65 x 4 months
- Telomerase Activator stimulates telomerase activity and elongates short telomeres
- Significant decrease of very short telomeres (telomeres < 2, 3 and 4 Kb)
- Improved
  - Glucose tolerance
  - Epidermal thickness
  - Good hair day
  - Bone density
  - Higher hemoglobin
  - No increased cancer incidence

Bernardes de Jesus et al. The telomerase activator TA-65 elongates short telomeres and increases health span of adult/old mice without increasing cancer incidence. *Aging Cell.* 2011,10(4):604-2

Will Telomerase Activation Increase risk of Cancer?

- No
- Short telomeres increase cancer risk
  - Leukocyte telomere length in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiol Biomarkers Prev.* Aug 7

- Studies link short telomeres with cancer
  - Mucciardi G· et al. (bladder cancer)
  - Qu S et al., Carlson et al, Duggan et al. (breast cancer)

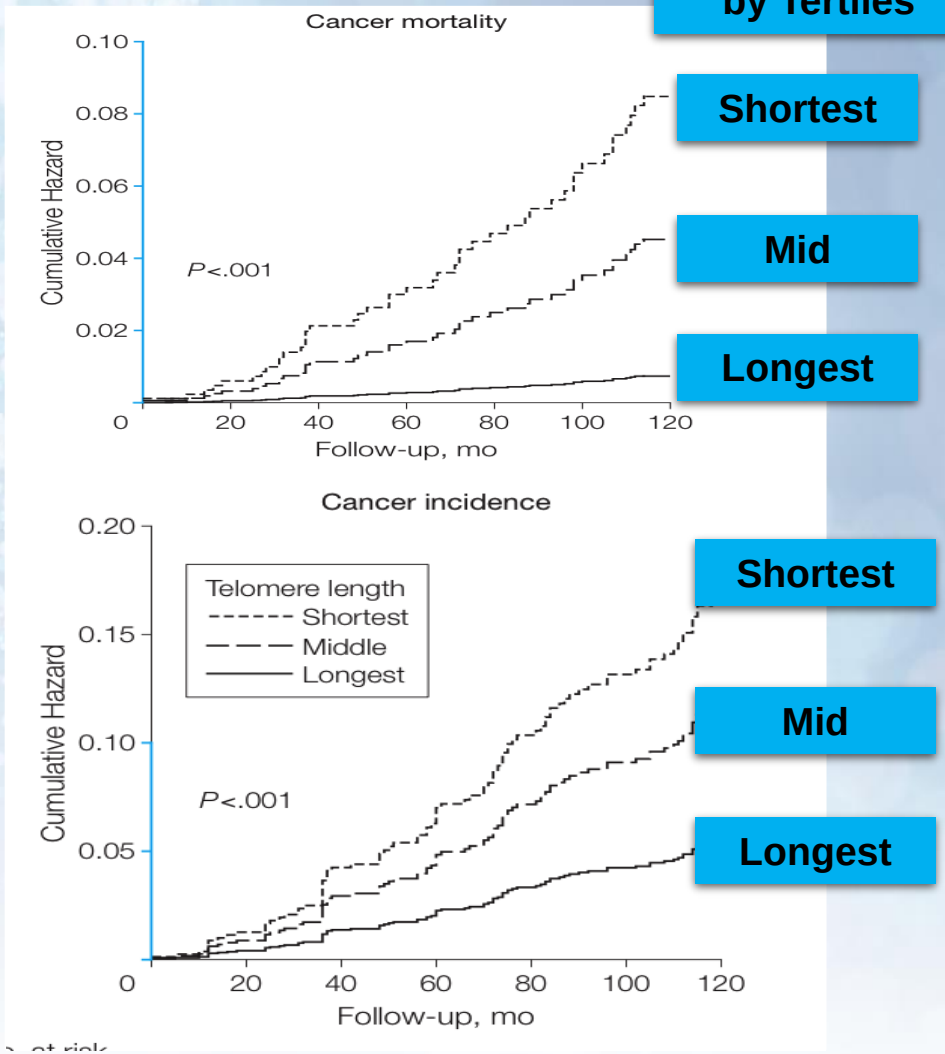
Telomerase and Cancer

- Telomerase is not an oncogene
- No studies suggest that telomerase induction causes cancer
- Germ cell line has been expressing telomerase for eons
- Cancer cells express telomerase
- Since cancer cells already express telomerase, telomerase activation is not a concern
- Cancer cells require multiple other properties not effected by telomerase
  - Loss of contact inhibition
  - Failure of apoptotic pathways
    - Loss of p53 pathway function
    - Loss of Retinoblastoma pathway (pRb)

Short Telomeres Predict Cancer Incidence & Death

Cancer

- 800 men, women, 45 to 84y, tracked 10 yrs
- 92 cases of incidence, 44 of mortality
- Shortest v. longest tertile hazard ratio
  - **3.1** cancer incidence
  - **11.1** cancer mortality



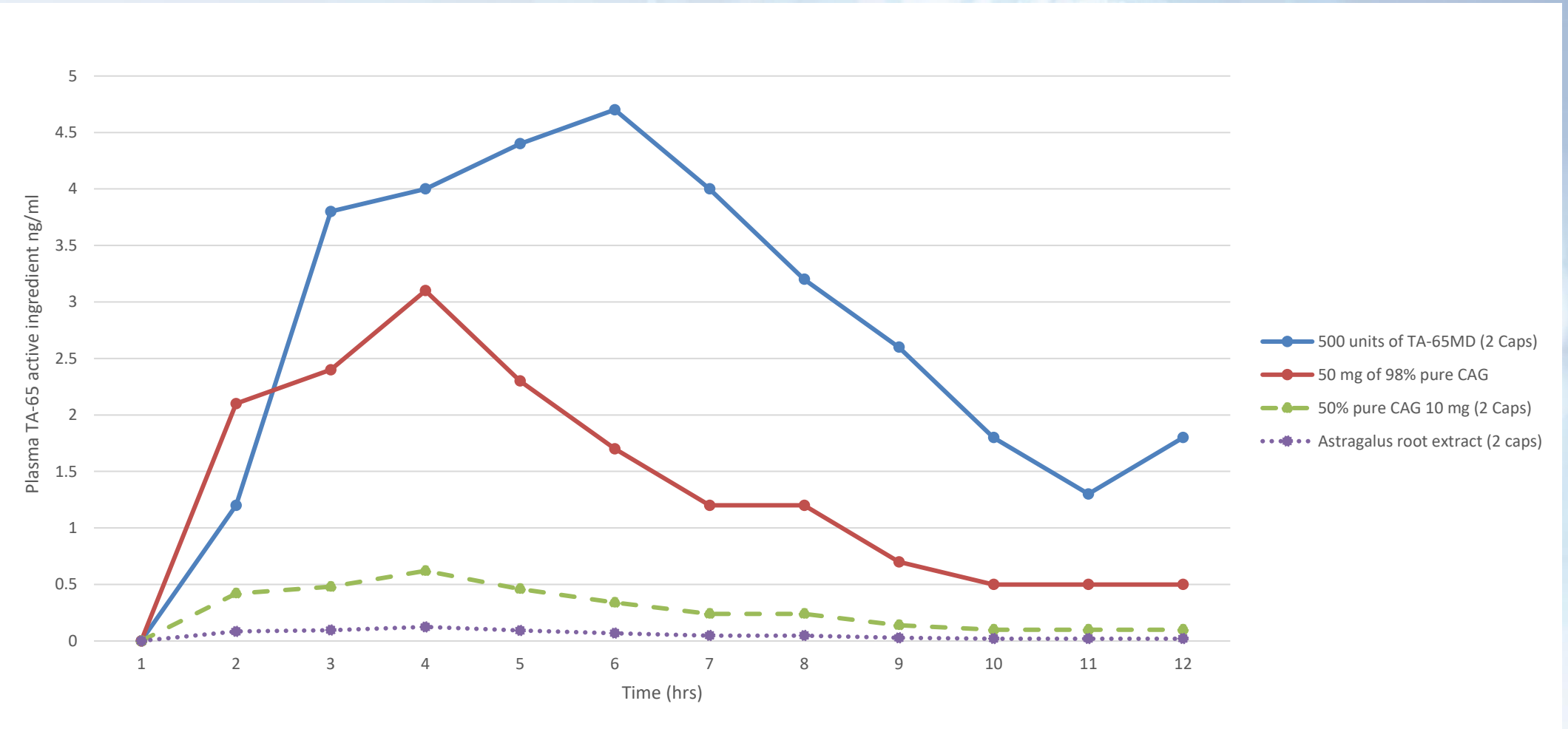
Willeit P et al. Telomere length and risk of incident cancer and cancer mortality. *JAMA*. 7,69-75 (2010)

Telomere length and Breast Cancer and all-cause Mortality

- Stage I to stage IIIA breast cancer survivors
- Followed 11 years
- Shorter telomeres
  - Increased Breast cancer mortality (HR = 3.03; 95% CI = 1.11 to 8.18)
  - Increased all cause mortality (HR = 2.38; 95% CI = 1.28 to 4.39)

Duggan C et al. Change in peripheral blood leukocyte telomere length and mortality in breast cancer survivors. *J Natl Cancer Inst*. 2014 Apr;106(4)

Bioavailability of TA-65MD



TA-65MD provides more than five times the bioavailability as compared to 98% pure CAG.

Anecdotal reports

- Skin
- Presbyopia- Vision improvement
- Energy
- Increased memory and attention
- Improved peripheral neuropathy
- Aerobic capacity
- Immune function
  - Less viral infections
  - Less basal cell skin cancer

- “I notice it will interfere with my sleep if I take it at night so I take one in the morning and one mid afternoon.. In conclusion I would say it gives me more energy.”
- “I stopped my amlodipine and my blood pressure is the same and is OK”
- “My fasting glucose has decreased from 110-120 to 90-105”
- “5 mg of Cialis works now where only 20 mg worked before with only change being addition of TA-65”
- “I can remember faces and names better”
- ”Finally something works for my ADD”

Telomerase Activation with TA-65

- Lengthens telomeres
- “Generally recognized as safe”
- Improves % critically short telomeres
- Protects Mitochondrial DNA as well as nuclear DNA
- Repair of tissue damage
- Improved Quality of Life
- Esthetic benefits –skin
- Improves immune markers, Restores CD8+28+ T cells from CD8+CD28-
- Improves metabolic biomarkers
- Improves AMD
- Improves function of non-mitotic tissues such as neurons and cardiac myocytes
- May lower cancer risks and protect against radiation
- **Synergistic with other anti-aging treatments such as Lifestyle, Intermittent fasting, Testosterone, Estrogen, Melatonin and Growth Hormone**

Why use TA-65?

- In preventive/regenerative medicine we want to optimize health and fitness for our patients and ourselves
- We want to use multiple modalities: Lifestyle, nutraceuticals, hormone optimization.
- Telomere optimization through TA-65 is a powerful addition of another approach to health and fitness.
- We have adequate data that TA-65 works to increase telomerase and lengthen telomeres and that it is safe.
- We have convincing data that TA-65 improves immune function in T cells
- Telomerase also protects us against inflammation, atherosclerosis, protects mitochondria and is necessary for optimal brain function

- We could wait 20 years for a prospective double-blind controlled outcome study but….
- We could use the information we have now to prevent the constant erosion of our telomeres, our DNA and our lives.