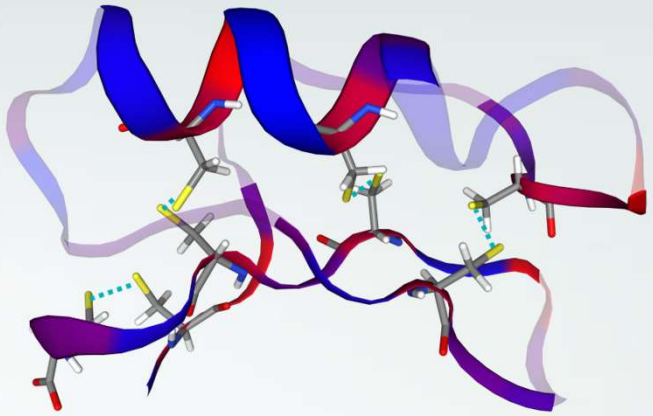
A4M | MEDICINE REDEFINED

MODULE II

PEPTIDE THERAPY CERTIFICATION



Peptide Bioregulators

Module II

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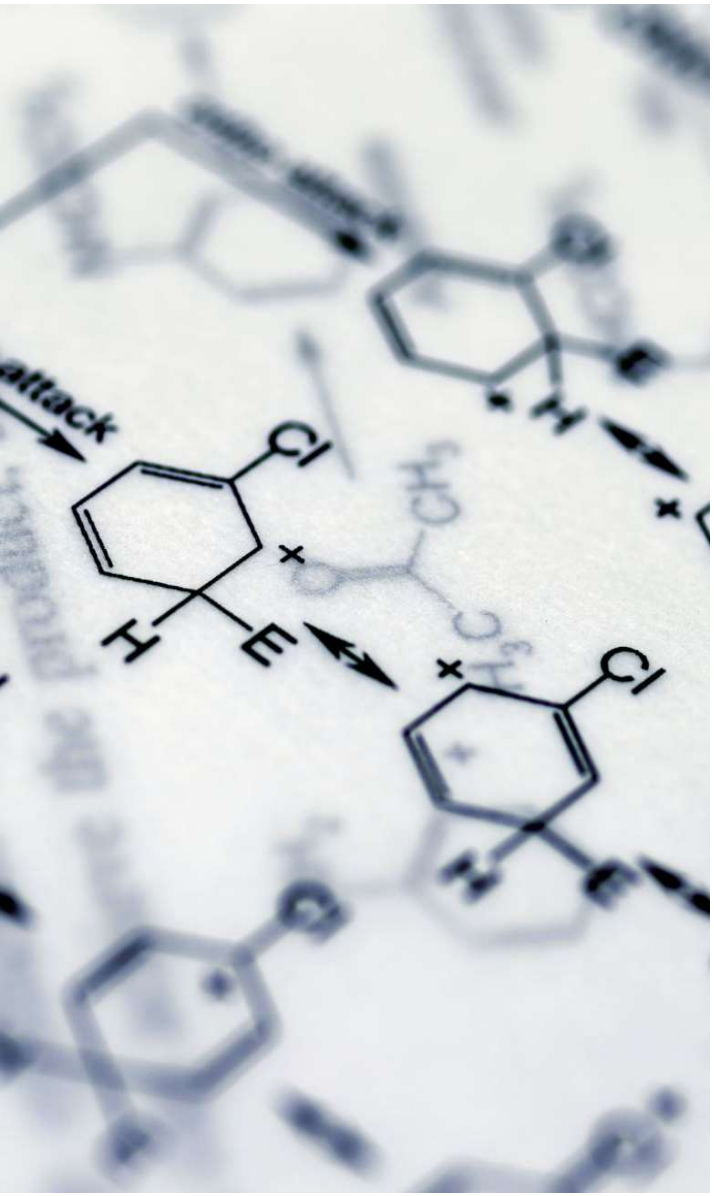
News..... March 2019

The Harvard Gazette

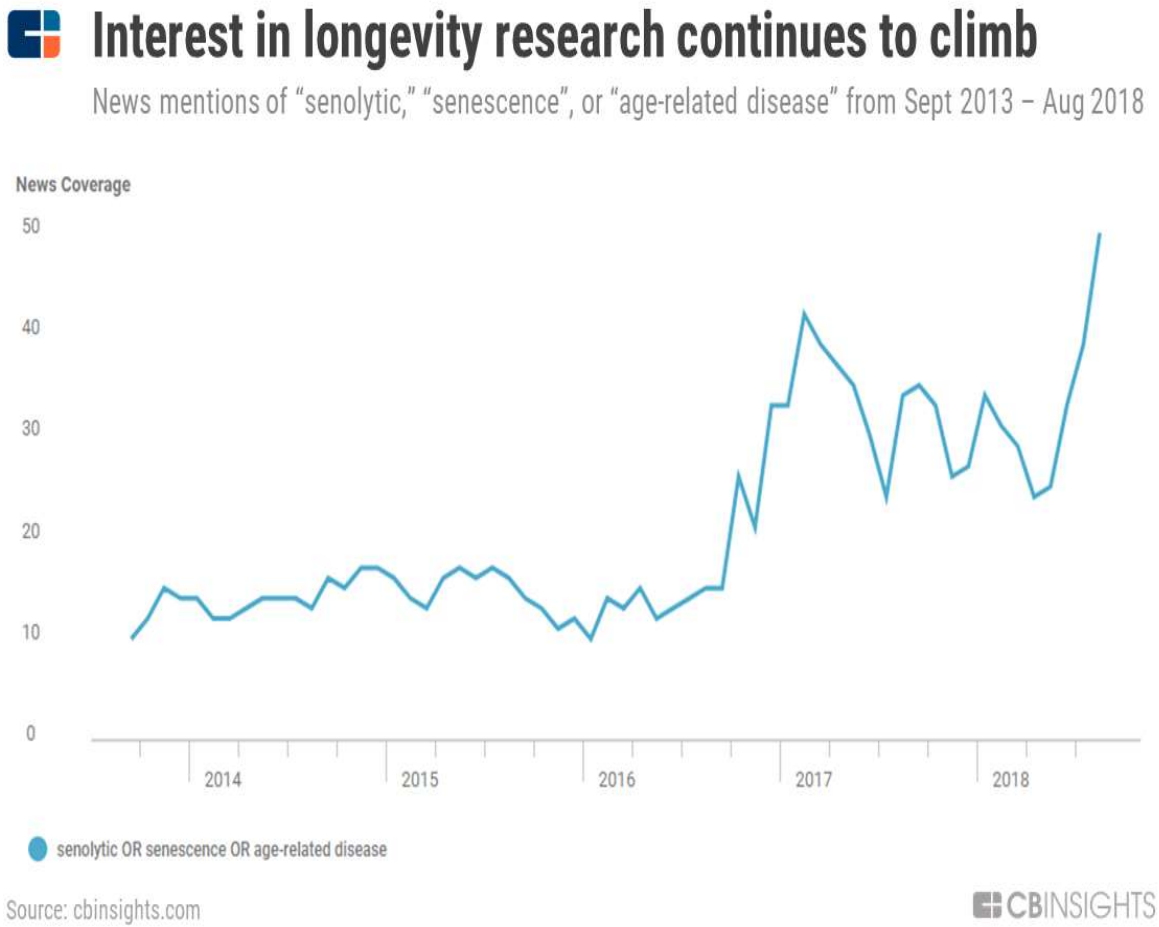
HEALTH & MEDICINE

Longevity and anti-aging research: 'Prime time for an impact on the globe'



Increasing Lifespan and Geroprotection

- The limit of human lifespan is 110-120 years
- Yet we only live to av. 75-80 years
- How can we increase those #s?
  - Systems biology approach to aging
  - Diet/Fasting
  - Exercise in moderation
  - Using senolytic supplements
  - **Peptidergic regulation of homeostasis**
    - Important in cellular aging
    - Promote postponing of division limit of human somatic cells

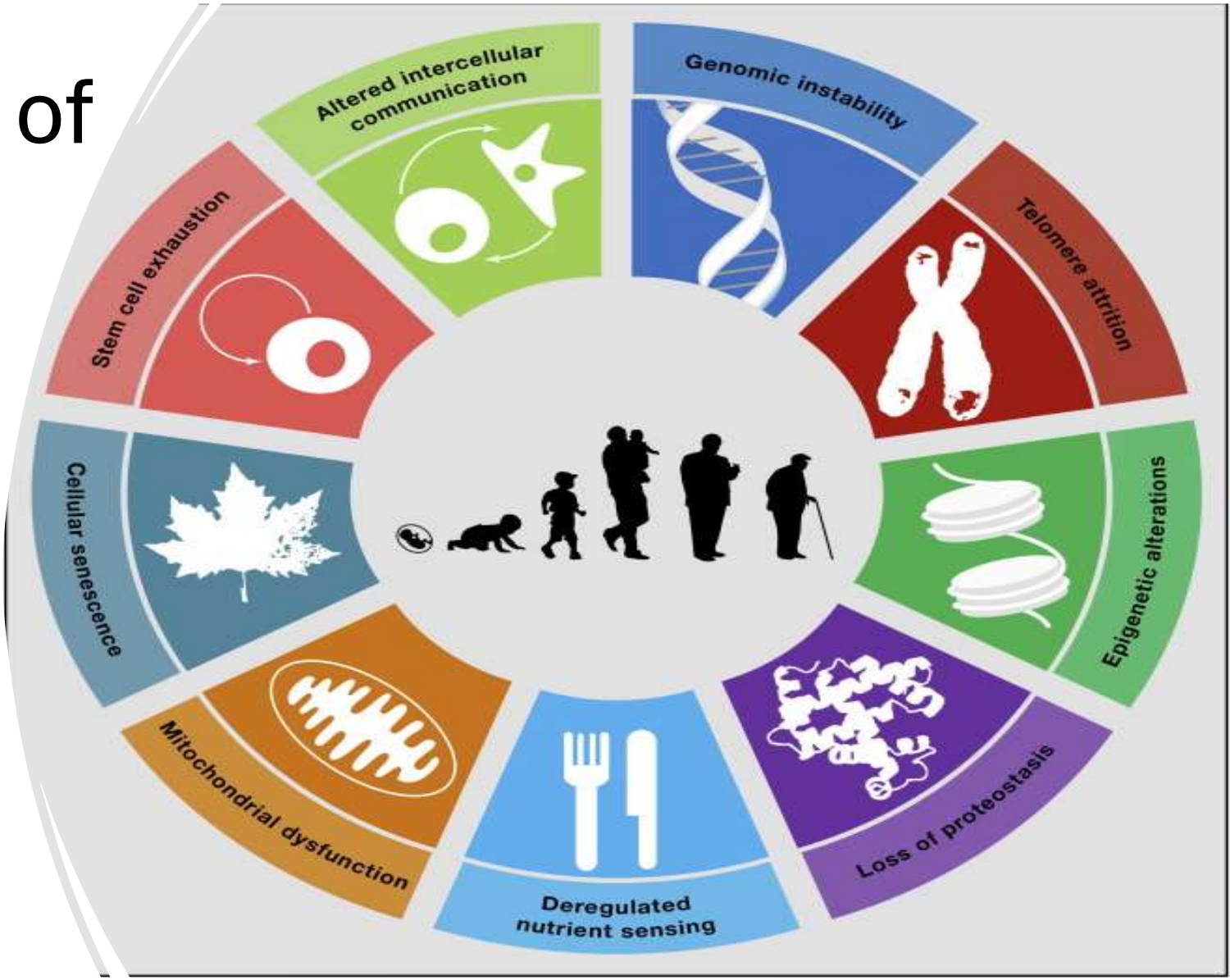


Anti-Aging Research On The Rise

Source: https://www.cbinsights.com/research/report/future-aging-technology-startups/

9 Hallmarks of Aging

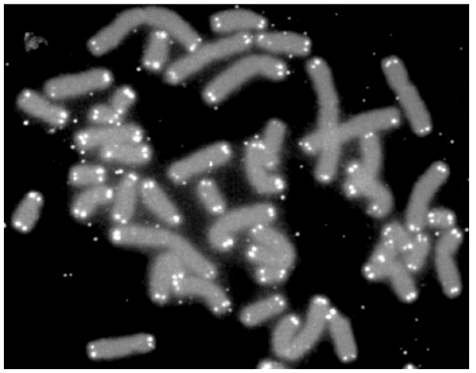
- Altered intercellular communication
- Genomic instability
- Telomere attrition
- Epigenetic alterations
- Loss of Proteostasis
- Deregulated nutrient sensing
- Mitochondrial dysfunction
- Cellular senescence
- Stem cell exhaustion



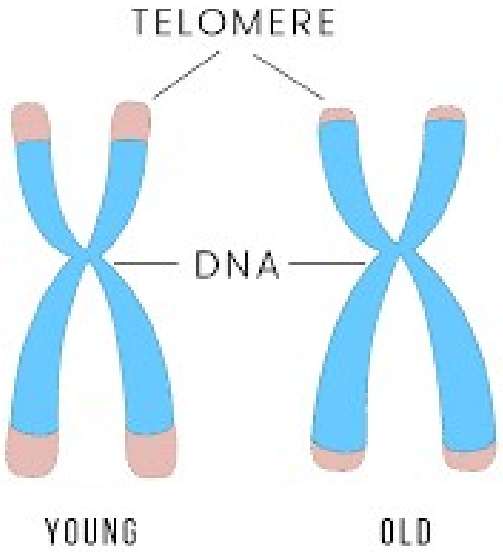
What's the Connecting Link?

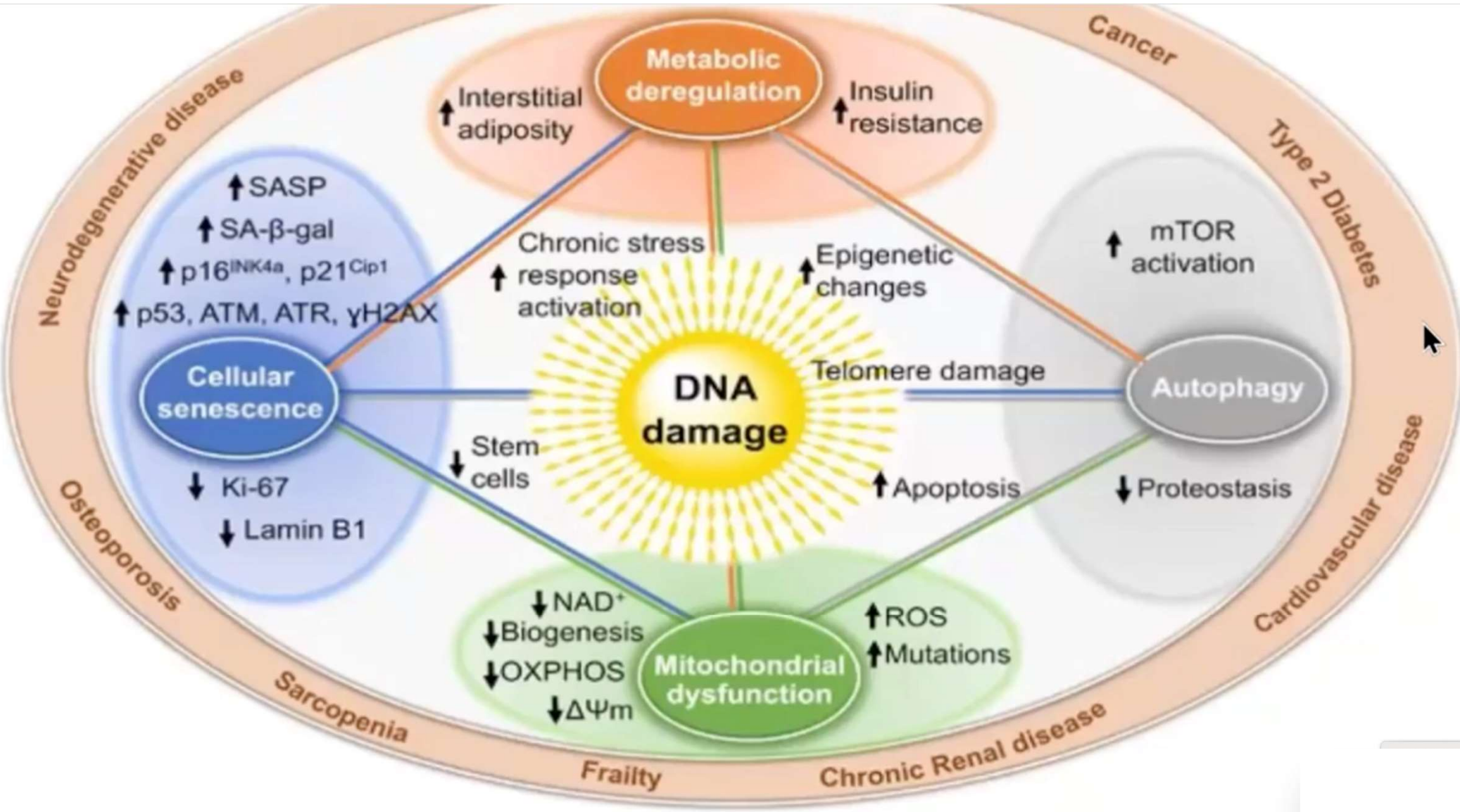
METAFLAMMATION

The Basics - What is a Telomere?



- Telomere is **a region of repetitive DNA sequences at the end of a chromosome**
- Telomeres protect the ends of chromosomes from becoming frayed or tangled
- In humans the telomere sequence is TTAGGG
- the sequence is usually repeated about 3,000 times and can reach up to 15,000 base pairs in length
- Telomeres shorten as you age
- Also high levels of oxidative stress can shorten telomeres
- Each time a cell divides, 25-200 bases are lost from the ends of the telomeres on each chromosome




Metabolic deregulation
Interstitial adiposity
Insulin resistance
SASP
SA-β-gal
p16INK4a, p21Cip1
p53, ATM, ATR, γH2AX
Cellular senescence
Ki-67
Lamin B1
Chronic stress response activation
Epigenetic changes
DNA damage
Telomere damage
Stem cells
mTOR activation
Autophagy
Apoptosis
Proteostasis
NAD+
Biogenesis
OXPHOS
ΔΨm
Mitochondrial dysfunction
ROS
Mutations
Neurodegenerative disease
Cancer
Type 2 Diabetes
Cardiovascular disease
Chronic Renal disease
Frailty
Sarcopenia
Osteoporosis

Telomeres and Aging Study

- 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
  - 8.54-fold higher mortality rate from infectious disease
- CONCLUSION: 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

Consequences

What Shortens Telomeres?

- Aging
- Chronic STRESS
- Rapid cellular division in response to infection
- Oxidative stress - ROS
- Lifestyle factors – poor diet, environmental exposures, lack of exercise
- Homocysteine / B6 deficiency – methylation issues
- Hormone deficiencies
- **Metaflammation**

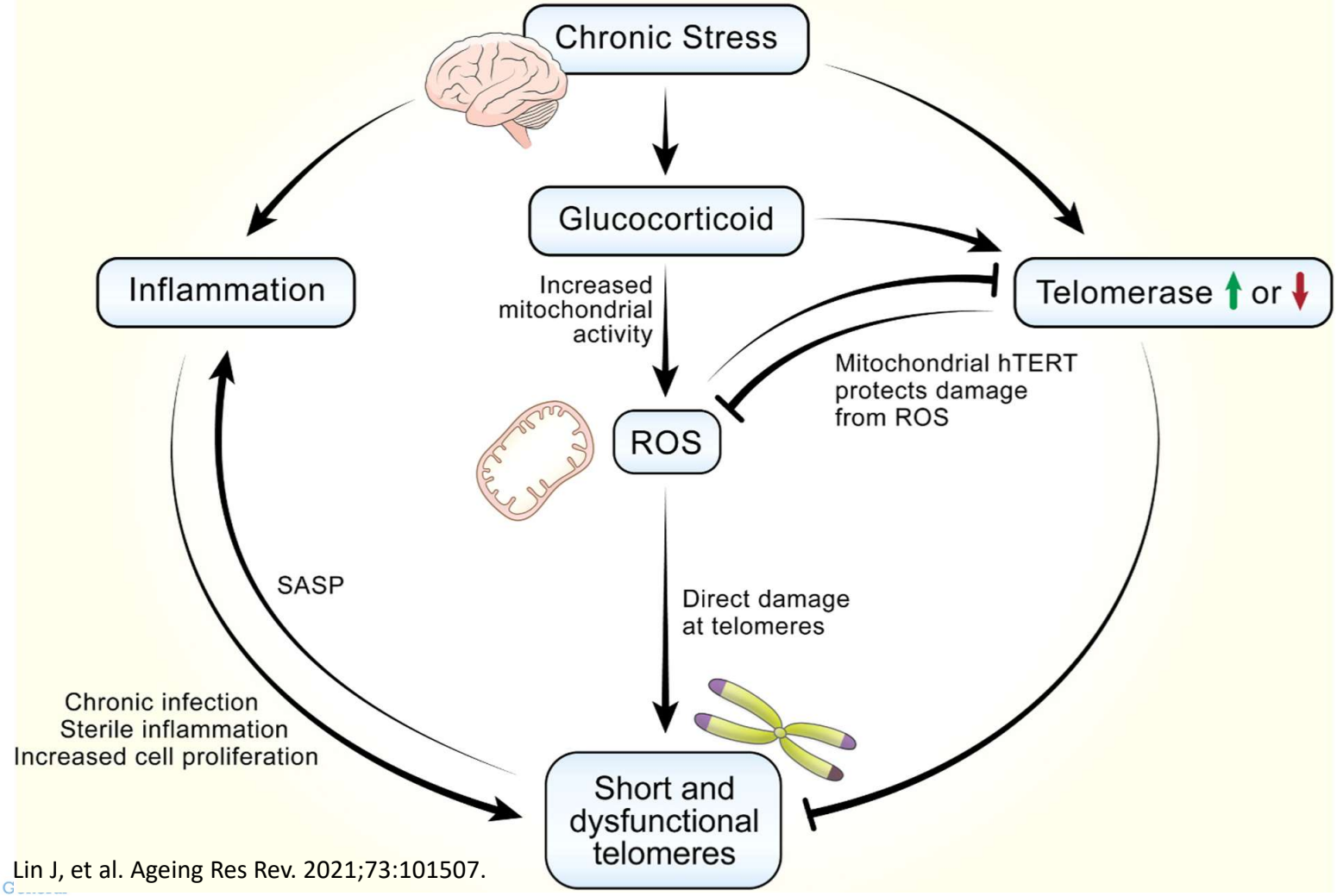
Zhang J, et al. Aging and the telomere connection: an intimate relationship with inflammation. Ageing Res Rev. 2016;25:55-69.

Stress Telomere Length Study

- 2017 study - Longitudinal Relationship Between Cortisol Responses to Mental Stress and Leukocyte Telomere Length
- N=400 healthy men/women ages 54-76
- Results: Cortisol responders had shorter telomeres and more rapid telomere attrition than nonresponders on follow-up
  - Controlled for age, sex, socioeconomic status, smoking, time of day of stress , and baseline telomere length
- The difference between cortisol responders and nonresponders was equivalent to approximately 2 years in aging

Steptoe A et al. J Clin Endocrinol Metab. 2017;102(3):962-971.

Chronic Stress and Telomeres



Lin J, et al. Ageing Res Rev. 2021;73:101507.

Obesity Telomere Length

- A large meta-analysis of 87 studies reported that higher body mass index (BMI) is significantly associated with shorter leukocyte telomere length (LTL)
- Each unit increase in BMI was associated with a -1.58×10^{-3} unit decrease in relative telomere length
  - Stronger effects in younger adults
- Base pairs were also decreased with increasing BMI
- Authors concluded a higher BMI is associated with shorter telomeres, especially in younger individuals

Gielen M, et al. Body mass index is negatively associated with telomere length: a collaborative cross-sectional meta-analysis of 87 observational studies. Am J Clin Nutr. 2018;108(3):453-75.

Homocysteine Telomere Length

- Elevated plasma homocysteine is a risk factor for vascular diseases
- Homocysteine-mediated increase in oxidative stress and inflammation
- Leukocyte telomere length (LTL) registers the cumulative oxidative stress and inflammation
- 2008 study n=1,319 healthy subjects
- Results: LTL was negatively correlated with plasma homocysteine levels
  - Adjustments made for smoking, obesity, physical activity, menopause, hormone replacement therapy use and creatinine clearance

Richards JB, et al. Homocysteine levels and leukocyte telomere length. Atherosclerosis. 2008;200(2):271-7.

Health Conditions Reported to Shorten Telomeres

- Diabetes
- Dyslipidemia
- HTN
- Atherosclerosis
- Stroke
- Obesity
- Neurodegenerative diseases
- Autoimmune conditions
- Coronary artery disease CAD
- MI myocardial infarction
- Colorectal CA
- Ovarian CA

Arsenis NC, et al. Oncotarget. 2017;8(27):45009-45019.

Telomeres, Aging and Inflammation

- In addition to telomere shortening and dysfunction - cells undergo senescence associated with inflammation
  - Hyperactivity of the transcription factor NF-κB
  - Overexpression of inflammatory cytokines
    - TNF-α, IL-6, and IFN-γ in circulating macrophages

- Major risk factors underlying aging and age-related diseases
  - Chronic inflammatory process
  - High oxidative stress

- Interdependence of Telomere shortening/dysfunction and metaflammation important in treatment of aging

Zhang J, et al. Aging and the telomere connection: an intimate relationship with inflammation. Ageing Res Rev. 2016;25:55-69.

Aging – Inflammation Study

- 2015 longitudinal study of Japanese semi-supercentenarians
- Revealed inflammation, not telomere length, predicts successful aging at an extremely advanced age
  - Chronic systemic inflammation had greater effect on mortality and loss of cognitive function in the centenarians
- Chronic inflammation MAJOR factor in aging process

Arai Y, et al. Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarian. EBioMedicine. 2015;2:1549-1558.

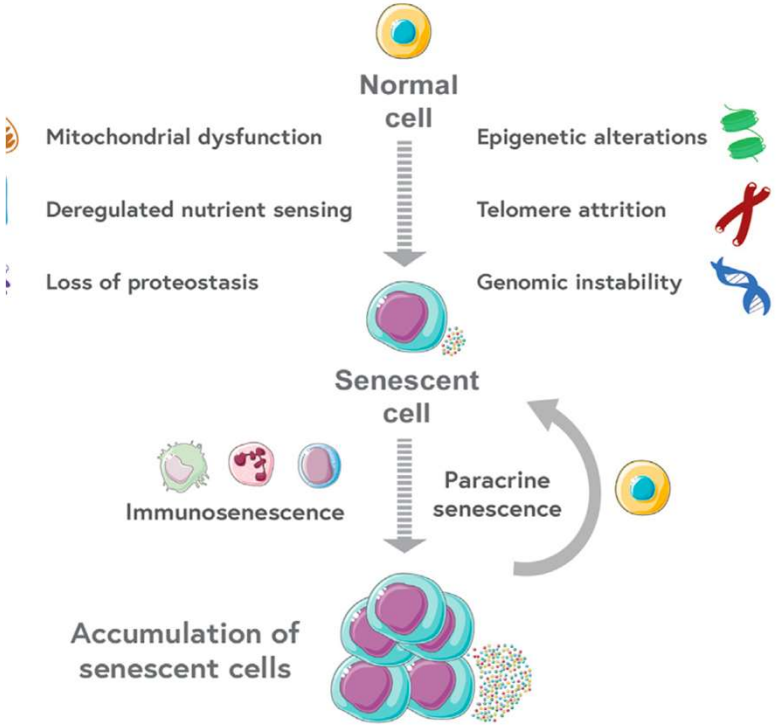
Fraternal Twins and Telomere Length

- 2007 study of elderly Danish twins
- Study analyzed 274 pairs of same-sex twins aged 73–94 years
- Follow-up spanning 9–10 years (1997–2007)
- During follow-up 204 pairs experienced the death of one or both co-twins
- Results: the co-twin with shorter telomeres was more likely to die first

Kappei D, et al. Telomere length inheritance and aging. Mechanisms of Ageing and Development. 2008;129(1-2):17-26.

Senescent Cells

- Cell cycle arrest and release of pro-inflammatory compounds with autocrine, paracrine and endocrine properties
  - DNA damage
  - Telomere shortening
  - Oncogene activation



- Some compounds produced by senescent cells have positive effects on the body
  - Called senescence-associated secretory phenotype (SASP)
  - Important in
    - Embryonic development
    - Childbirth
    - Wound healing

Schafer M, et al. SENESCENCE SECRETOME: BIOMARKERS OF BIOLOGICAL AGING AND POSTOPERATIVE OUTCOMES. Innov Aging. 2019;3(Suppl 1):S98.

How Do We EFFECTIVELY target DNA to Preserve Telomere Length to Increase Longevity?

PEPTIDE BIOREGULATORS

BIOLOGICAL AGE REVERSAL

Peptide Bioregulators

- Short peptides are 2-20 amino acids
- Peptide bioregulators = 2-4 amino acids
  - vs. regular peptides = 20 up to 100 AAs
- Discovered by Dr. Vladimir Khavinson in Russia ca. 1980s

Khavinson VK, Anisimov VN. Peptide regulation of aging: 35-year research experience. Bull Exp Biol Med. 2009 Jul;148(1):94-98.

History of Peptide Bioregulators

Soviet Union Military

Soviet Union Cosmonauts

Russian Use of Bioregulators

Dr. Khavinson in the middle

Peptide Bioregulators

- **Primal signaling molecules** that influence:
  - Cell signaling
  - Gene expression
  - Immune function/response
  - Metabolism
- Interacts with cellular DNA
- Helps the body restore and maintain homeostasis

Khavinson VK, Anisimov VN. Peptide regulation of aging: 35-year research experience. Bull Exp Biol Med. 2009 Jul;148(1):94-98.

Peptide Bioregulators

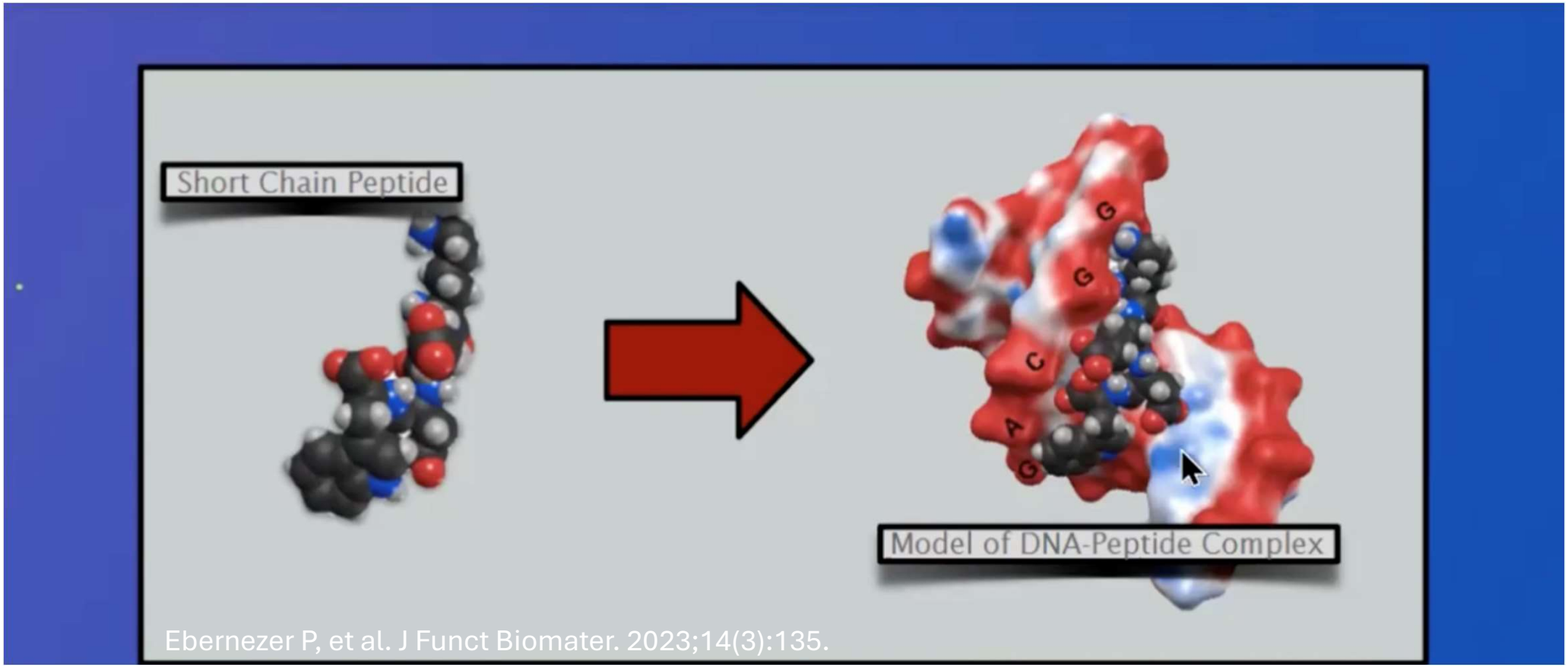
- Bioregulators don't bind to cell-surface receptors like other longer peptides

- Can penetrate the nuclei and nucleoli of cells and interact with the:
  - Nucleosome
  - Histone proteins
  - Both single- and double-stranded DNA

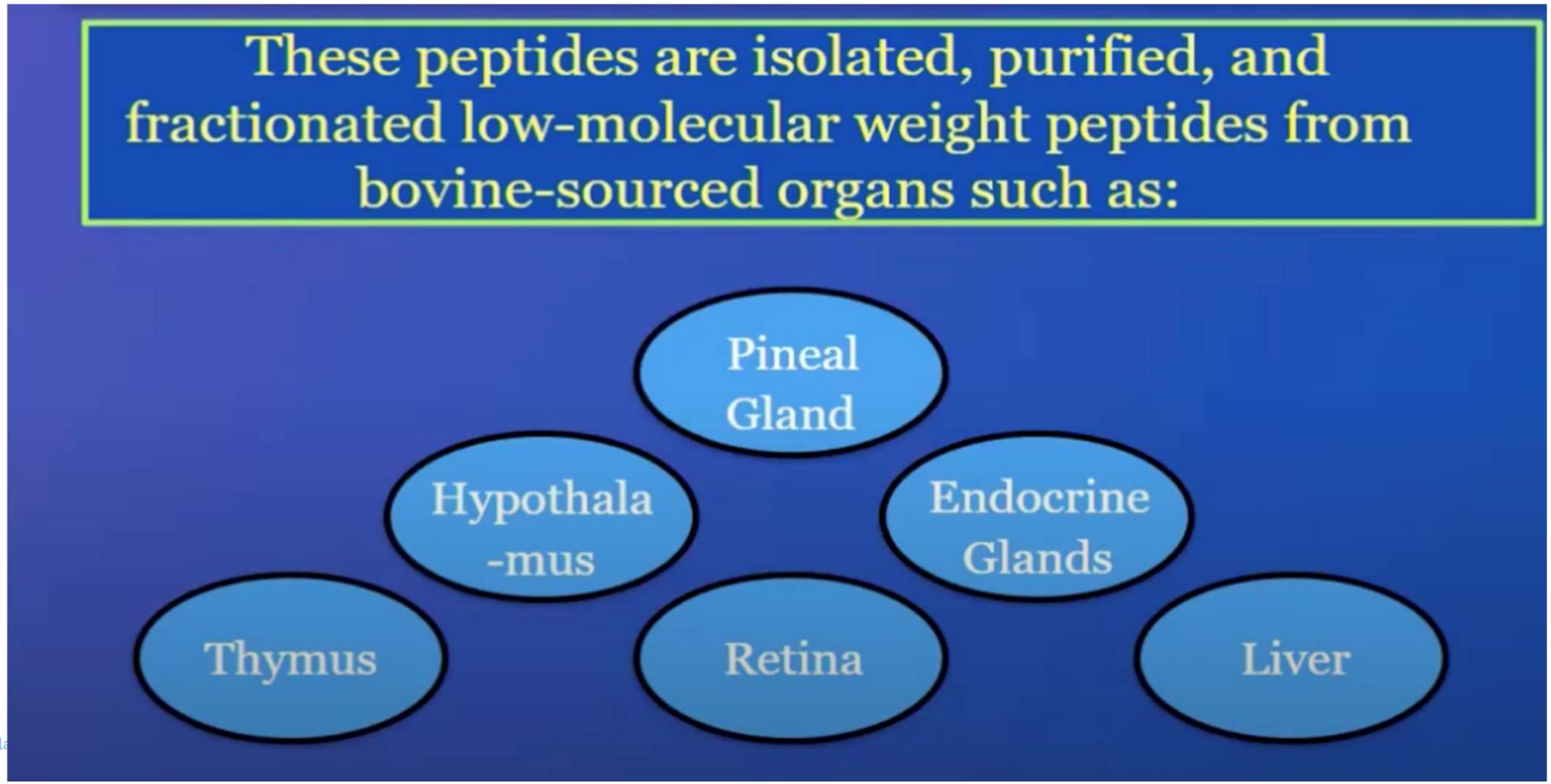
- Act as "gene switches"

Khavinson VK, Anisimov VN. Peptide regulation of aging: 35-year research experience. Bull Exp Biol Med. 2009 Jul;148(1):94-98.

Bioregulators will Lock into Specific Docking Sites in DNA and Activate Various Genes



Russian Bioregulators are Originally Extracted from Whole Food Sources



Bioregulators - Natural or Synthetic?

Available commercially as natural or synthetics

- Synthetic bioregulators - called cytogens
  - Have immediate impact but shorter half-life (1.5-2mo)
  - Used to initiate therapies – 20-30day tx

- Natural - called cytomaxes
  - Longer half-life
  - Use after synthetic
  - Used for maintenance tx - 2-3 months

- Treat patients w/ synthetic x 1 month then natural x 2-3 months, 2-3x annually

Khavinson VK, Anisimov VN. Peptide regulation of aging: 35-year research experience. Bull Exp Biol Med. 2009 Jul;148(1):94-98.

Bioregulator Dosages

- Remember Use synthetic 1st, then natural

- SubQ
  - 100-200mcg SubQ every 3 days x 5-15 d
  - Repeat 2x annually if needed

- Oral cap doses (10mg/cap):
  - 1 cap BID (20mg) x 20-30d
  - 2 caps BID (40mg) in complicated patients
  - Repeat 2-3x annually

- Sublingual liquid (0.1mg peptide/ml)
  - Sublingual peptides absorbed directly through the oral mucosa
  - Facilitates faster penetration of peptides and acceleration of effect
  - H2O is carrier – best refrigerated after opening
  - 5-6 drops (0.25-0.35ml), 3-4x daily 15 min before food
  - Tx 1 month, recommend repeat in 3-6 months

Bioregulator Dosages

- Bioregulators can be “stacked” – use more than 1 at a time therapeutically
  - Ex. For CVD patient, can use heart, blood vessel, kidney and brain bioregulators simultaneously for improved outcomes

Bioregulators Bottom Line

Using peptide bioregulators is reported to:

- Improve the quality of life
- Prolong active longevity
- Restore organs at the cellular level

Khavinson VK, et al. Peptide regulation of gene expression: a systematic review. Molecules. 2021;26:7053.

Bioregulators on the Market Target:

- Adrenal
- Bladder
- Blood Vessels
- Bone Marrow
- Cartilage
- CNS/Brain/pineal
- Heart
- Kidney
- Liver
- Lungs
- Muscle
- Ovary
- Pancreas
- Parathyroid gland
- Pineal gland
- Prostate
- Retina/Eyes
- GUT/Digestive system
- Testes
- Thymus/Immune
- Thyroid

Commonly Used **Synthetic** Bioregulators

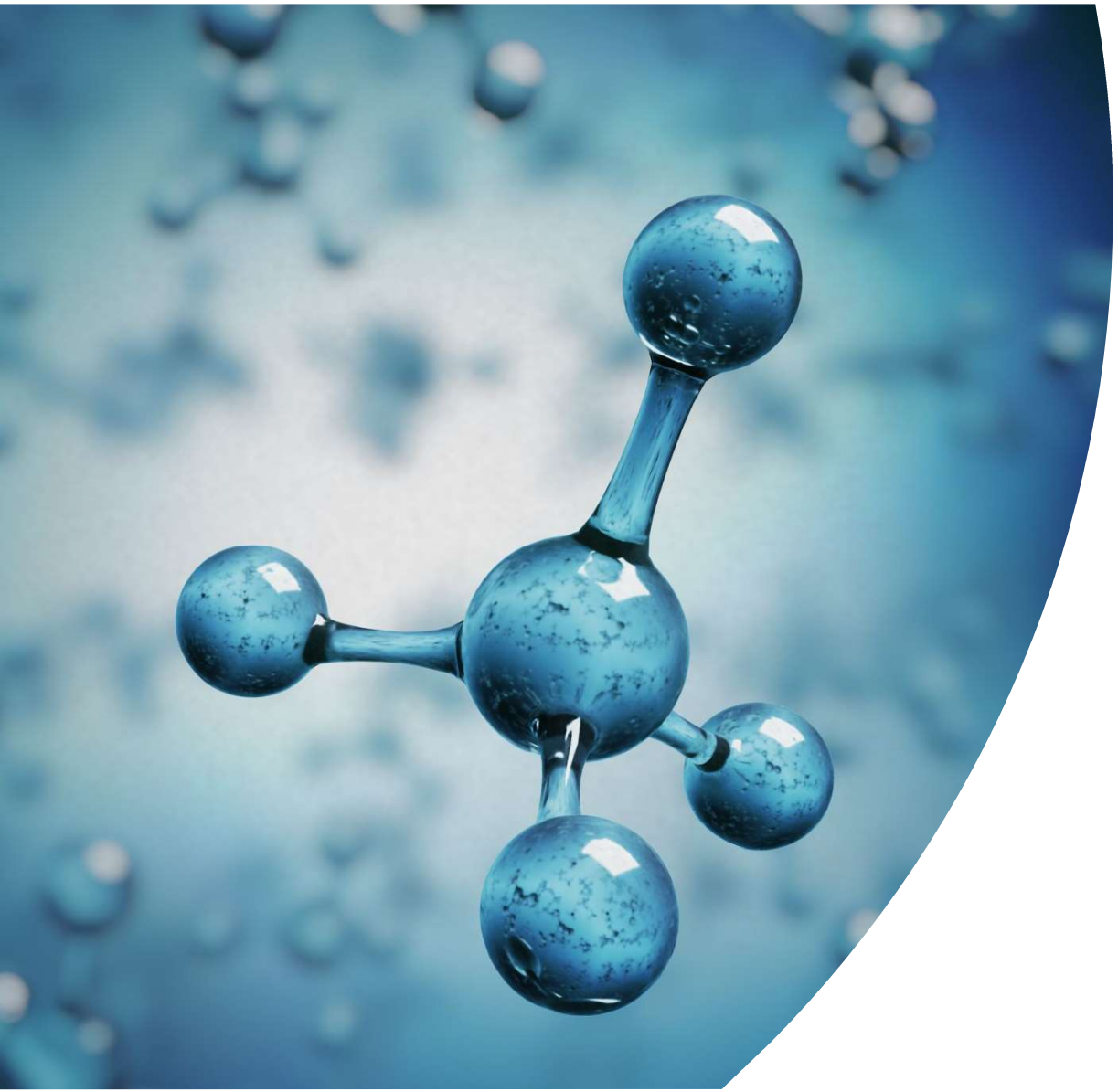
- Cytogen examples
  - Bronchogen – bronchial tubes/lung signaling
  - Cardiogen – heart/cardiovascular signaling
  - Cartalax – joints/cartilage signaling
  - Crystagen – immune signaling
  - Ovagen – liver signaling
  - Pancragen – pancreas signaling
  - Pinealon – brain signaling
  - Vesugen – blood vessel signaling
- Stacking example – Cardiogen + Vesugen + Pinealon
- Remember, synthetics are used as 1st line support x 1 month, then use natural bioregulators the next round

Commonly Used **Natural** Bioregulators

- Cytomax examples
  - Bonomarlot – bone signaling
  - Endoluten – neuroendocrine signaling
  - Glandokort – adrenal signaling
  - Pielotax – kidney signaling
  - Sigmur – joints/cartilage signaling
  - Suprefort – pancreas signaling
  - Thyreoge – thyroid signaling
  - Ventfort – blood vessel signaling
  - Chelohart – heart signaling

Injections

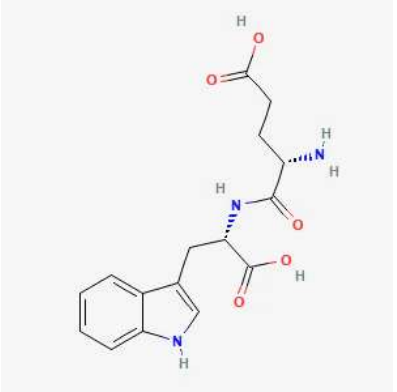
- **Peptide Bioregulator Injections**
  - There are also some injectable (SubQ) peptide bioregulators available for intensive treatments
- General dosage = 0.1-0.2ml (100-200mcg) SubQ every 3 days x 6-15 days
- Repeat twice annually
- Peptide bioregulators can be "**stacked**" based on symptoms presented
- Synergistic w/ conventional Rx therapy - no interactions



Bioregulator Examples and Studies

- from Russian literature

Thymagen and Thymalin



- Thymagen = aka. Thymogen and Vilon
  - Synthetic thymic dipeptide
  - Glu-Trp (L-glutamine/L-tryptophan)

- Thymalin = natural form from calf thymus
  - Also Glu-Trp

- Primary effects on thymus – immune support

Lunin SM, et al. Immunol Invest. 2008;37(8):858-70.

Thymagen/Thymalin

- Supports Th1/Th2 balance
- Enhances T cell maturation and differentiation
- Stimulates interferon
- Prevents overproduction of inflammatory cytokines – cytokine storm

Dardenne M, et al. Role of thymulin or its analogue as a new analgesic molecule. Ann NY Acad Sci. 2006;1088:153-63.

Thymagen/Thymalin

- Anti-inflammatory/analgesic activity
  - Acts directly on afferent nerve terminals through prostaglandin-E2 (PGE2)-dependent mechanisms
- Activates neutrophil chemotaxis and phagocytosis
- Applications for Thymagen include:
  - Chronic inflammatory conditions
  - Tissue repair disorders
  - Stress-induced immuno-depression
  - Optimization of cancer immuno-therapy, chemotherapy and radiotherapy
  - Age-related immune dysfunction

Vishal D, et al. Thymulin – a hope out of the box in COVID-19 disaster. World J Advance Healthcare Res. 2020;4(4):247-51.

Thymagen/Thymalin Dosage

- General dosages:
  - SubQ = 100-200mcg SubQ every 3 days x 15 days
  - Orally = 1 cap (10mg) BID x 20d or 2 caps (20mg) for more complicated pts.
  - Repeat several times annually
- Used for long-term thymic support and immune regulation
- Repeat at least twice annually for prevention
- Synergistic w/ conventional Rx therapy - no interactions

Thymalin Study

- **2014 human study -** 266 elderly subjects (60–74 yrs) with age-related immune decline

- **Design:** Controlled multi-year clinical observation

- **Results:**
  - Thymalin restored T-cell count and normalized CD4/CD8 ratio
  - 2-fold reduction in acute respiratory infections within 6 months
  - Improved leukocyte phagocytic activity and cytokine regulation (↑ IL-2, ↓ IL-6)
  - Reported 20–30 % reduction in mortality over 6 years versus controls

Khavinson VK et al. *Adv Gerontol*. 2014;4(4):346-361.

Thymalin Study

- **2023 study:** n= 60 patients with COPD/ARDS
- **Intervention:** Dipeptides KE and EW (active fragments of Thymalin)
- **Results:**
  - Decreased CRP and IL-1β by 35–40 %
  - Improved PaO_2 and oxygenation index within 10 days
  - Shorter hospital stay and improved immune cell recovery

Kuznik BI et al. *Bull Exp Biol Med*. 2023;158(1):159-163.

Thymalin Case Report

- Immunomodulation with Thymalin in COVID-19 related cytokine storm
- *P*opulation: 5 patients with severe viral pneumonia
- Dose: Thymalin 10 mg intramuscular daily × 10 days
- Results: Decreased inflammatory markers, improved recovery

Galvez J, et al. Am J Biomed Sci Res. 2020;10(6):1-4.

Thymagen Study

- **2018 study:** n=140 elderly subjects with mild cognitive decline
- **Results:**
  - Thymogen improved short-term memory, psychomotor performance, and mood scores
  - EEG showed normalization of alpha rhythm amplitude

Ryzhak GA et al. *Adv Gerontol.* 2018;31(3):460-466.

Pinealon

- Synthetic brain cortex tripeptide Glu-Asp-Arg
  - Glutamic acid (Glu), aspartic acid (Asp) and arginine (Arg)
- Natural form named Cortexin
- Geroprotective, antiaging bioregulator
- Crosses BBB readily
- Neuroprotective – decreases neuronal oxidative stress

Meshchaninov VN et al. Effect of synthetic peptides on aging of patients with chronic polymorbidity and organic brain syndrome of the central nervous system in remission. Adv Gerontol. 2015;28(3):439-444.

Pinealon

- Mitochondrial support
- May improve circadian rhythm – melatonin modulation
- Memory/cognitive support
- 1-2 caps daily (10-20mg) daily x 20 days (use 1-3 mo)
- SubQ 1 mg/day for a month should be good when repeated twice a year

Meshchaninov VN et al. Effect of synthetic peptides on aging of patients with chronic polymorbidity and organic brain syndrome of the central nervous system in remission. Adv Gerontol. 2015;28(3):439-444.

Epithalamin/Epitalon

- Epithalamin = natural pineal gland polypeptide
- Epitalon = synthetic pineal gland tripeptide
- **Telomerase activation & telomere elongation**
- Epigenetic modification

Khavinson V et al. Epithalamin increases life span and melatonin levels in elderly subjects. Neuro Endocrinol Lett. 2002;23(Suppl 3): 144–146.

Epithalamin/Epitalon

- Antioxidant & anti-aging effects
  - increase SOD, catalase, and glutathione peroxidase activity, reducing lipid peroxidation
- Neuroendocrine restoration
  - balances circadian rhythm and adaptogenic stress responses
- Melatonin regulation
  - Epithalamin (natural) = stronger response
- Immunomodulation
  - Enhances T-cell and cytokine balance in aging and chronic disease models

Khavinson V et al. Epithalamin increases life span and melatonin levels in elderly subjects. Neuro Endocrinol Lett. 2002;23(Suppl 3): 144–146.

2003 Study BIOGERONTOLOGY

Epithalon Peptide Induces Telomerase Activity and Telomere Elongation in Human Somatic Cells

V. Kh. Khavinson, I. E. Bondarev, and A. A. Butyugov

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 135, No. 6, pp. 692-695, June, 2003
Original article submitted April 24, 2003

Addition of Epithalon peptide in telomerase-negative human fetal fibroblast culture induced expression of the catalytical subunit, enzymatic activity of telomerase, and telomere elongation, which can be due to reactivation of telomerase gene in somatic cells and indicates the possibility of prolonging life span of a cell population and of the whole organism.

Key Words: *peptide; Epithalon; telomerase; telomeres; fibroblasts*

Epithalamin/Epitalon Studies

Study	Population	Outcome	Result
Khavinson et al (2003)	Elderly subjects	Longevity	1.6–2.0x lower mortality over 6–12 years
Khavinson et al (2001)	266 patients, aged 60–74	Immune function, sleep, lipid profile	Improved NK cell activity, sleep quality, lipid parameters
Anisimov et al (2004)	Animal models	Lifespan extension	Increased max lifespan by 25–31%
Khavinson et al (2011)	Elderly with CAD	Mortality and cardiac function	Reduced mortality and cardiovascular events over 6 years

Epithalamin Studies

- **1992 animal study**
  - **Model:** Aged rats
- **Results:**
  - Epithalamin extended mean lifespan by 25–30 %
  - Increased nighttime melatonin and antioxidant enzyme activity (SOD, catalase)
  - Reduced tumor incidence by 2-fold

Anisimov VN et al. *Ann N Y Acad Sci*. 1992;673:53-57.

Epithalamin Studies

- **2000 Human Cohort:** 266 older adults (60–89 yrs)
- **Results:**
  - Epithalamin normalized circadian cortisol/melatonin rhythms
    - Improved sleep quality
  - Improved immune status – increased NK cell activity
  - Reduced lipid peroxidation markers (MDA ↓ 40 %)
  - Improved cardiovascular indices and decreased total mortality (−44 % over 12 years)

Khavinson VK et al. *Biochemistry (Mosc)*. 2000;65(7):853-858.

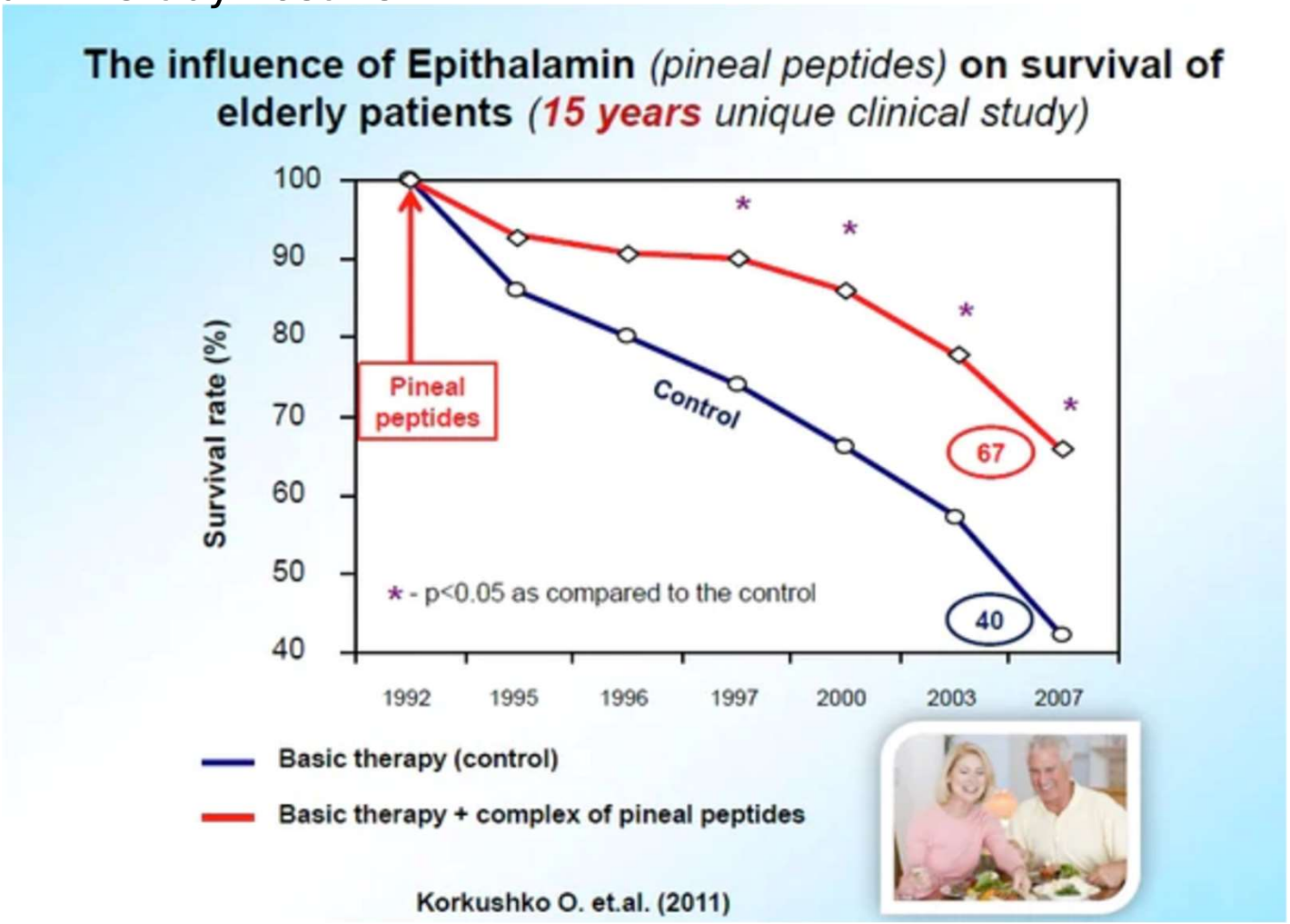
Epithalamin Studies

- **2013 Long-Term Study**
  - N= 19,731

- **Results:**
  - ↓ All-cause mortality
  - Better organ system function
  - Improved QOL

Khavinson VK, et al. Adv Gerontol. 2013;3(3):225-235.

2011 Epithalamin Study Results



Epithalamin Studies

- **2001 Study:**
  - **Model:** C3H/Sn mice
- **Results:**
  - Lifespan increase 31 % (female) and 16 % (male)
  - Tumor incidence reduced by 35 %
  - Melatonin restoration in aged pineal glands

Anisimov VN et al. *Exp Gerontol*. 2001;36(6):991-999.

Epithalamin + Thymalin for Cancer

- **2009 Study:** N= 266 elderly subjects followed 6–12 years
  - Administered a combined thymalin + epithalamin, 10mg each (IM or oral) x 10 days
  - Repeated annually
- **Results:** Combined natural thymic and pineal peptides reduced cancer incidence 2.0–2.3 × versus controls
- All-cause mortality decreased by 45 %
  - Participants who received both peptides annually showed the lowest mortality rates across all age groups
- Peak effect seen in ages 65–74

Khavinson VK et al. *Exp Oncol*. 2009;31(4):104-108.

Epithalamin + Thymalin for Cancer

- Thymalin normalized T-cell differentiation markers (↑ CD3+, CD4+)
- Epithalamin restored melatonin–cortisol rhythms and antioxidant enzyme activity (SOD, catalase)
- Synergistic use supported immune surveillance and endocrine balance

Khavinson VK et al. *Exp Oncol*. 2009;31(4):104-108.

Epithalamin/Epitalon Dosages Used in Studies

Form	Typical Dose	Route	Frequency
Epithalamin	10 mg IM daily × 10–20 days	Injectable	1–2 courses per year
Epitalon	5–10 mg SC/IM daily × 10–20 days	Injectable	1–2 courses per year
Oral (Epitalon bioregulator capsules)	10–20 mg/day × 10–20 days	Oral	Twice yearly (maintenance)

Comparative Summary

Aspect	Epithalamin	Epitalon
Natural vs Synthetic	Natural extract	Synthetic, pure analog
Consistency	Variable composition	Fully standardized
Research Basis	>40 years, multiple clinical trials	Confirmed in vitro, animal, and human studies
Safety	Excellent; used clinically in Russia	Excellent; human trials confirm tolerance
Key Focus	Pineal rejuvenation, melatonin normalization	Telomere and gene expression modulation
Availability	Limited (Russia)	Available as research peptide globally

Brain Bioregulators – Cerluten, Pinealon, Cortexin

- Cerluten = natural cerebral cortex peptide
- Pinealon = synthetic pineal glandular tissue tripeptide Glu-Asp-Arg (glutamic acid, aspartic acid, arginine)
- Cortexin - synthetic cerebral cortex peptide

Ryzhak GA et al. *Adv Gerontol.* 2018;31(3):460-466.

Brain Bioregulators – Pinealon

- **2018 Pinealon Study:** n= 90 elderly patients with mild cognitive impairment
  - 10mg/day x 20d

- **Results:**
  - Pinealon improved MMSE scores by +15 % after 20 days
  - Reduced anxiety/depression scores on HADS scale
  - EEG improvements in cortical connectivity

Ryzhak GA et al. *Adv Gerontol.* 2018;31(3):460-466.

Brain Bioregulators - Pinealon

- **2021 In-Vitro Study**

- **Mechanistic Review:**
  - Peptides Epitalon and Pinealon bind to promoter regions of ~700 genes
    - Regulat apoptosis, antioxidant defense, and circadian genes

  - DNA-peptide binding alters chromatin conformation, enabling selective transcription activation

Khavinson VK et al. *Front Genet*. 2021;12:676899.

Brain Bioregulators - Cerluten

- **2019 Cerluten Study**
  - **Population:** 40 patients post-stroke

- **Results:**
  - Cerluten + standard therapy improved cognitive recovery rate (MMSE + 18 %, $p<0.05$)

  - Enhanced regional cerebral blood flow by 22 % via Doppler data

Kamenskaya OV et al. *Bull Exp Biol Med*. 2019;167(1):133-136.

Brain Bioregulators - Cortexin

- **Design**: Randomized, controlled, multicenter; 3 arms
  - N = 189 adults (mean age ~64) with chronic cerebral ischemia I–II
- **Dose/Duration**: Cortexin IM 20 mg daily ×10 days vs IM 10 mg daily ×10 days vs basic therapy only; course repeated at 6 months
- **Main findings**:
  - Dose-response on overall neurologic impairment, asthenia, and sleep
  - Antioxidant effect in both dose groups
  - Antidepressant/anxiolytic effects modest and more evident after repeat course
  - Good tolerability

Fedin AI, et al. [Dose-dependent effects of cortexin in chronic cerebral ischemia (results of a multicenter randomized controlled study)]. Zh Nevrol Psikhiart IM S S Korsakova. 2018;118(9):35-42.

Brain Bioregulators - Cortexin

- **Design**: Multicenter, open-label (analysis subset from nationwide screening)
  - **N =** 500 subjects analyzed (out of ~50,000 screened) with stage II brain ischemia
  - Mean age ~64
- **Dose/Duration**: Cortexin IM 10 mg daily ×10 days
- **Main findings**:
  - Reduction/regression of focal neuro symptoms
  - Improvement in cognition and mood indices

Mashin VV, et al. [An open clinical trial of cortexin in treatment of brain ischemia]. Zh Nevrol Psikhiatr IM SS Korsakova. 2014;114(9):49-52.

Brain Bioregulators - Cortexin

- **Design**: Comparative clinical study with multiple dosing regimens alongside standard therapy (four groups)
  - N = 122 patients in acute/early recovery phase Acute hemispheric ischemic stroke

- **Dose/Duration**: Various Cortexin IM regimens including 20 mg/day ×10 days (one or two courses)
  - Also 30 mg/day divided 10+10+10 (two courses of 10 days separated by 10-day break)

- **Main findings**:
  - Most complete regression of neuro deficit in the **30 mg/day, two-course** group vs others

Belova LA, et al. [Efficacy of Korteksin in acute period of hemispheric ischemic stroke]. Zh Nevrol Psikhiatr IM SS Korsakova. 2018;118(7):30-34.

Brain Bioregulators - Cortexin

- **Design**: Multicenter, clinical-epidemiologic observational program
  - N = 979 outpatients with post-COVID syndrome
- **Dose/Duration**: Cortexin IM 10–20 mg daily ×10 days
- **Main findings**: Reported improvements in cognitive and asthenic symptoms; anxiolytic/antidepressant effects more pronounced with 20 mg

Putilina MV, et al. Zh Nevrol Psikhiatr IM SS Korsakova. 2022;122(1):84-90.

Vascular Peptides (Vesugen, Ventfort, Glandkort)

- Vesugen = synthesized tripeptide (Lys-Glu-Asp) lysine, glutamic acid, aspartic acid
  - Derived from active centers of vascular wall proteins
- Ventfort = natural vessel wall (aorta) peptide
- Glandkort = natural adrenal glandular peptides
- Used for endothelial repair, vascular aging, atherosclerosis, hypertension, stroke rehab, TBI

Khavinson VK et al. *Bull Exp Biol Med*. 2016;161(5):679-682.

Vascular Peptides - Vesugen

- Vesugen = synthesized tripeptide (Lys-Glu-Asp) lysine, glutamic acid, aspartic acid
  - Derived from active centers of vascular wall proteins

- 2016 study
  - N= 80 hypertensive patients, 55–70 yrs.
  - Administered Vesugen 20mg daily

- **Results:**
  - Vesugen improved endothelial NO-synthase activity by 30 %
  - Reduced plasma homocysteine (−20 %) and LDL oxidation markers
  - Improved retinal microcirculation indices by 15–18 %

Khavinson VK et al. *Bull Exp Biol Med*. 2016;161(5):679-682.

Vascular Bioregulators

- Mechanisms:
  - Modulates gene expression in endothelial cells
  - Reduces endothelial dysfunction and oxidative stress
  - Enhances synthesis of structural proteins like elastin and collagen in vascular walls
  - Supports angiogenesis and capillary repair
- 1-2 caps daily (10-20mg) daily x 20-30d
- SubQ – 2mg, 2-3x per week for 3-6 weeks
- 1-2x annually

Khavinson V, et al. Peptide regulation of aging: effect of peptide Vesugen on parameters of vascular wall in elderly patients. Bull Exp Biol Med. 2003;135(5):543-547.

Prostatilen Study

- Natural prostate tissue bioregulator - Supports prostate health
- Study n = 307 with chronic prostatitis ages 18-74
- Prostatilen administered 5-10mg IM daily
- Duration varied – many experienced benefits after 2-3 injections
- Maximal was 5-6 injections
- Results next slide

Tkachuk VN et al. The use of prostatilen in treating patients with chronic prostatitis. Urologiia i Nefrologiia. 1991; (1):3-6.

Prostatilen

- Authors reported symptom disappearance or attenuation occurred in 96.7% of patients
- Improvements were noted in:
  - Pain complaints
  - Diuresis (urine flow)
  - Sexual function
  - Sleep
  - Overall well-being
- Subjective improvements corresponded with objective laboratory and urodynamic data

Tkachuk VN et al. The use of prostatilen in treating patients with chronic prostatitis. Urologiia i Nefrologiia. 1991; (1):3-6.

Retinalamin – Water-Soluble Retinal Bioregulator

- 2018 study - efficiency of Retinoprotective Dry AMD Therapy with Neuroprotective Therapy: a Randomized Clinical Trials Meta-analysis
- **Retinalamin** used for **dry age-related macular degeneration (AMD)**
- Included 11 Russian studies
- Dose and length: retinalamin 5 mg IM per injection;
- Total dose 50 mg per course (10 injections)
- Courses were often **repeated at 3–6 months**

Erichev VP, Petrov SYu, Volzhanin AV. Ophthalmology in Russia. 2018;15(1):69-79.

Retinalamin – Water-Soluble Retinal Bioregulator

- Improved visual acuity
- Strongest effect persisted during the first 3 months
- Repeat courses at 3–6 months associated with additional improvement
- Also improved:
  - Perimetry (expanded visual fields, reduced central scotoma area)
  - OCT/ocular blood-flow metrics—generally showing positive trends that paralleled Visual Acuity change

Erichev VP, Petrov SYu, Volzhanin AV. Ophthalmology in Russia. 2018;15(1):69-79.

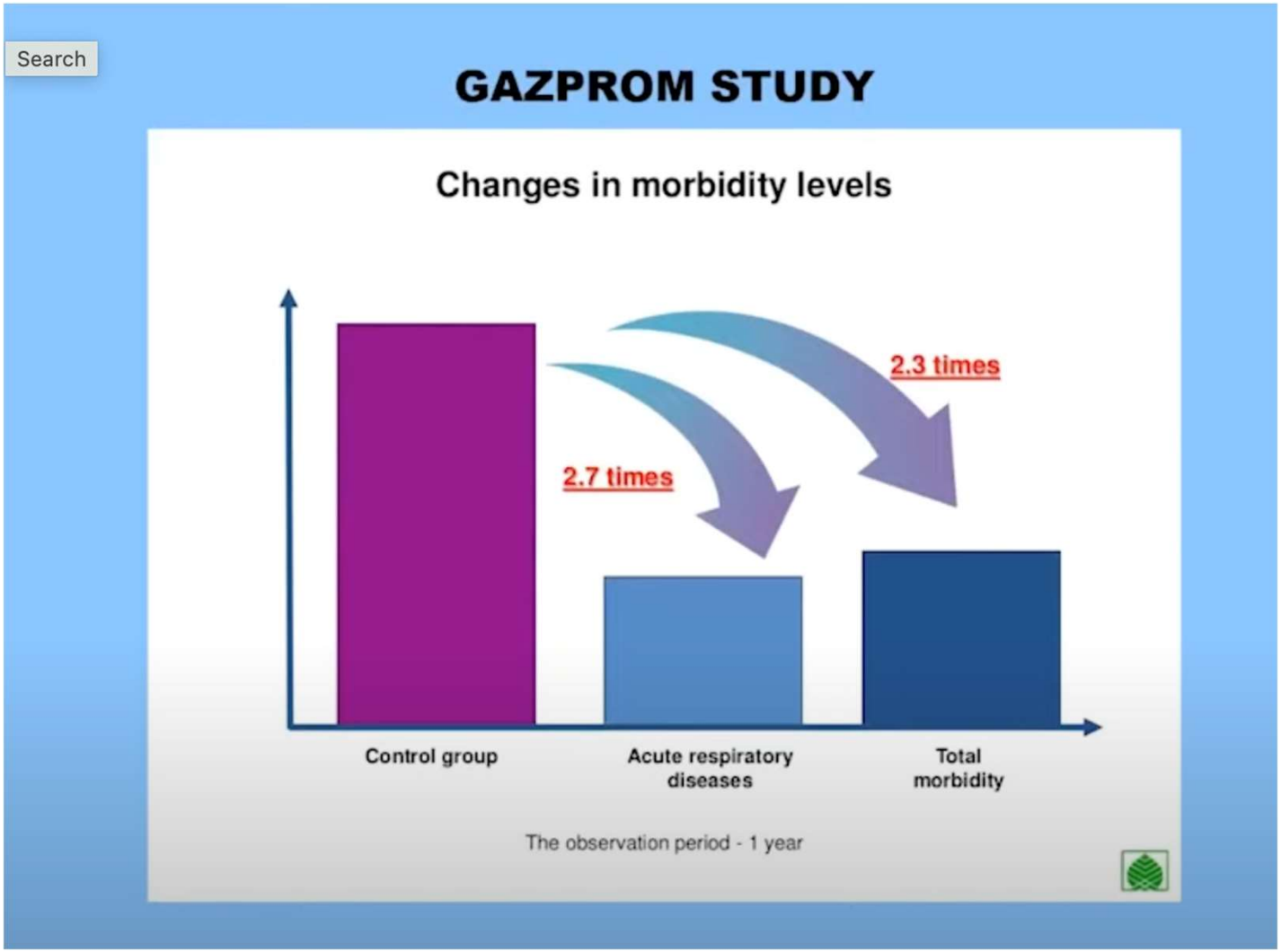
Gazprom Study

- Looked at the influence of bioregulators on morbidity in Gazprom Russian company employees
- This was during COVID-19 pandemic
- N = 14,192 employees (11,192 test group and 3,000 control) ages 35-60
- Each of test group received a complex of 6 bioregulators orally daily x 30d
  - Immune (Crystagen)
  - Brain (Pinealon)
  - Blood vessels (Vesugen)
  - Bronchi/Lung (Chonluten)
  - Liver (Ovagen)
  - Cartilage (Cartalax)
- Control group received muitivitamin/mineral orally x 30d

Khavinson VK, et al. Peptide regulation of gene expression: a systematic review. Molecules. 2021;26:7053.

Results

- Bioregulator group after 1 year was :
  - 2.7 x less likely to get an Acute respiratory disease when diagnosed w/ COVID
  - 2.3 x decreased morbidity



Khavinson VK, et al. Peptide regulation of gene expression: a systematic review. Molecules. 2021;26:7053.

Bioregulator Animal Studies

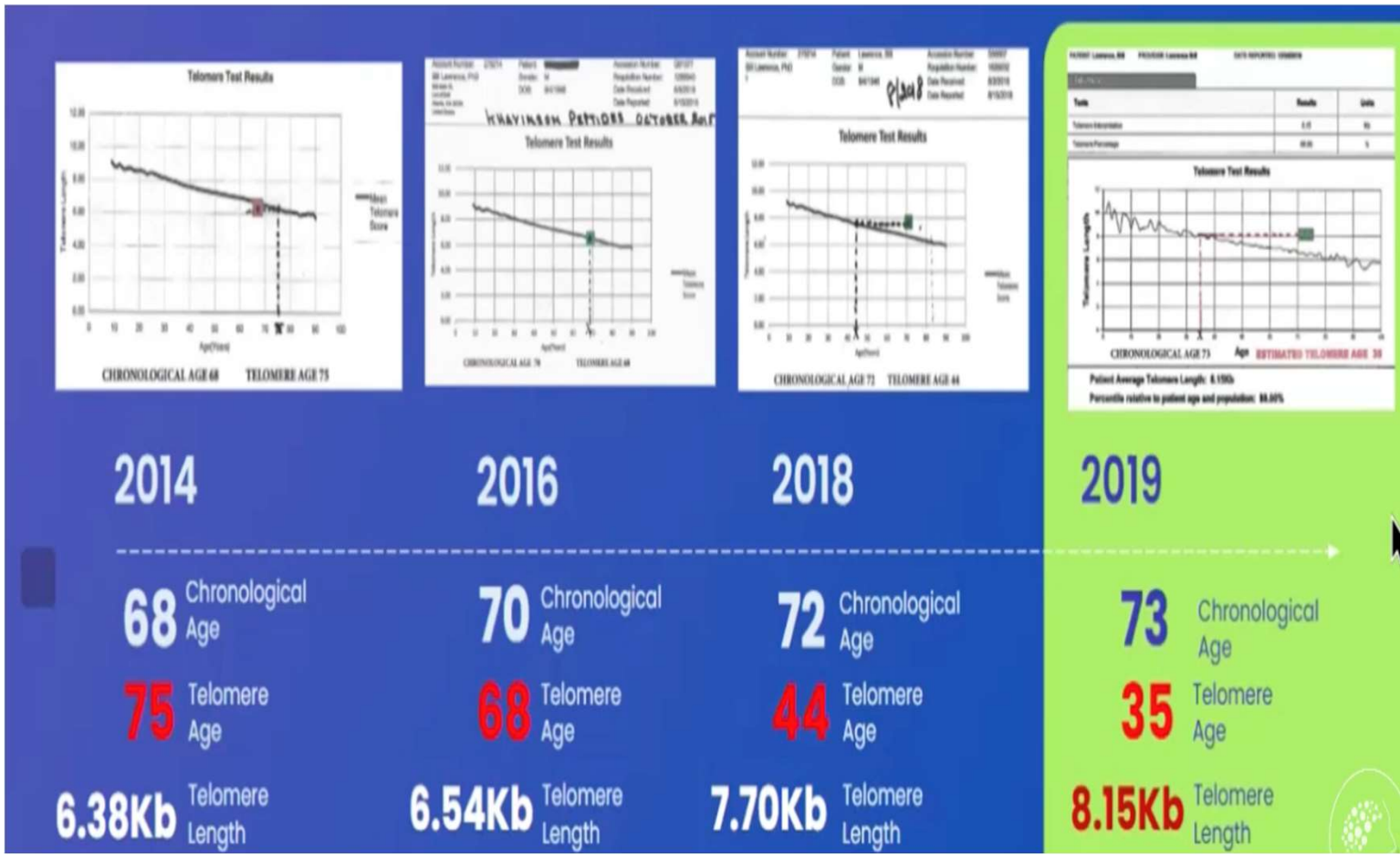
Biological Activity Increase	Publications
Protein synthesis in rat hepatocytes - by **39-173%**	*Khavinson V. Peptides and ageing. NEL (2002)*
Growth of animal **cells** by **22-42%**	*Khavinson V. Peptides and ageing. NEL (2002)*
The **amount** of heterochromatin in lymphocytes of elderly people by **42.4%**	*Khavinson V. et al. NEL (2003)*
The number of divisions of human cells - by **42.5%** and a **2.4-fold increase** in the average length of **telomeres**	*Khavinson V. et al. Bul. Exp. Biol. Med. (2004)*
Animal **lifespan - by 20-42.3%**	*Anisimov V., Khavinson V. Biogerontology (2010), Anisimov V. et al. Mech. Ageing Dev. (2001)*
3.1-fold decrease in **tumor incidence** in animals	*Anisimov V., Khavinson V. Biogerontology (2010)*

Khavinson VK, et al. Peptides of pineal gland and thymus prolong human life. Neuroendocrinol Lett. 2003;24(3-4):233-40.

Case Study: Telomere Age and Bioregulator Use

- Subject started taking bioregulators in 2015
- Bioregulators included:

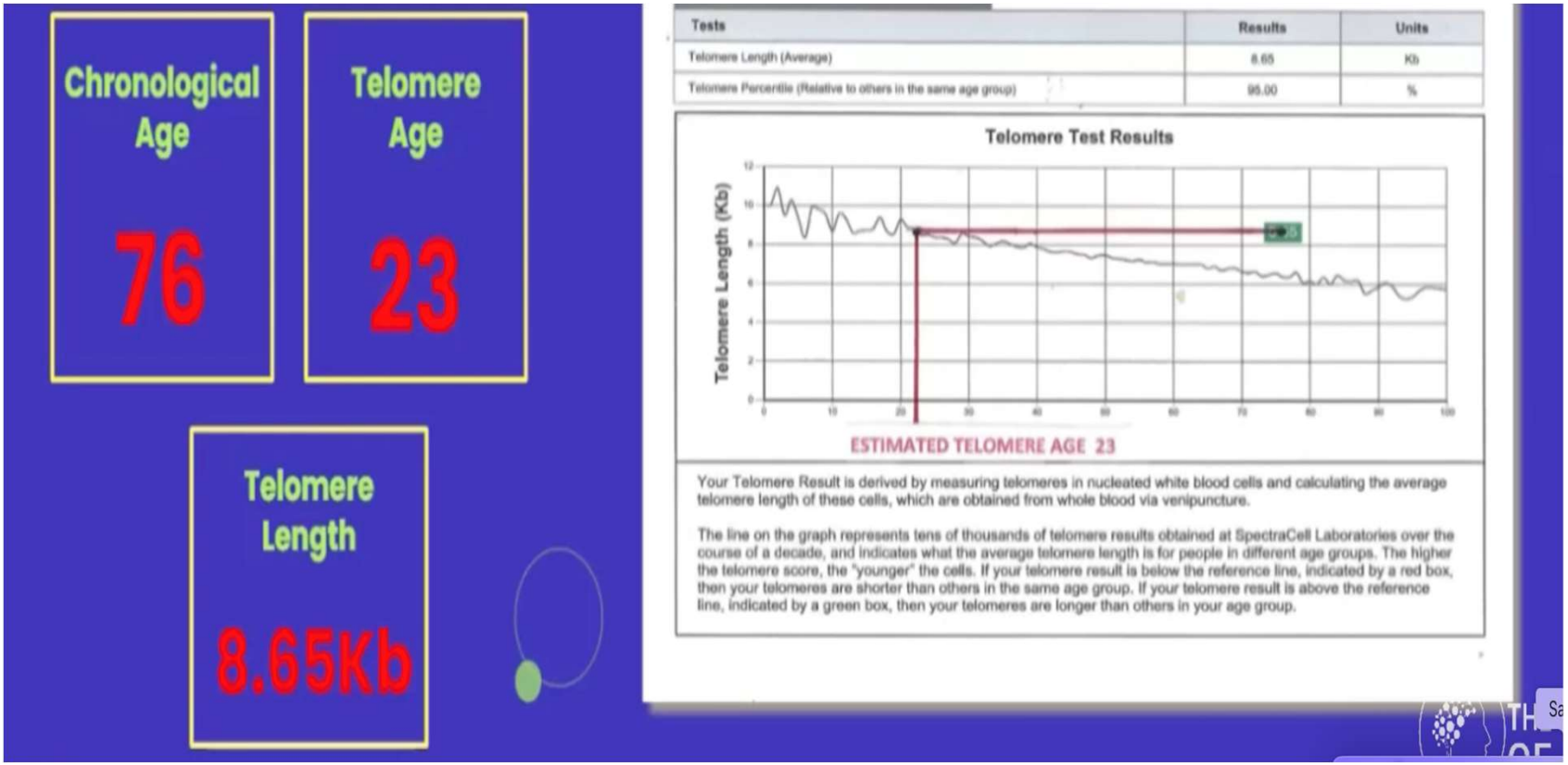
- Arterial System (Ventfort)
- CNS (Cerluten)
- Cartilage (Sigumir)
- Liver (Syetinorm)
- Pancreas (Suprefort)
- Pineal Gland (Endoluten)
- Thymus (Vladonix)



https://podofinquiry.com/2025/04/bioregulatory-peptides-bill-lawrence/

Telomere Age and Peptide Bioregulators

- Subject results in **2025** - still takes bio-regulators several x a year
- Pt has gone from telomere age of 75 to age 23 in 7 years using a 10d (20mg/d) course of bioregulators biannually



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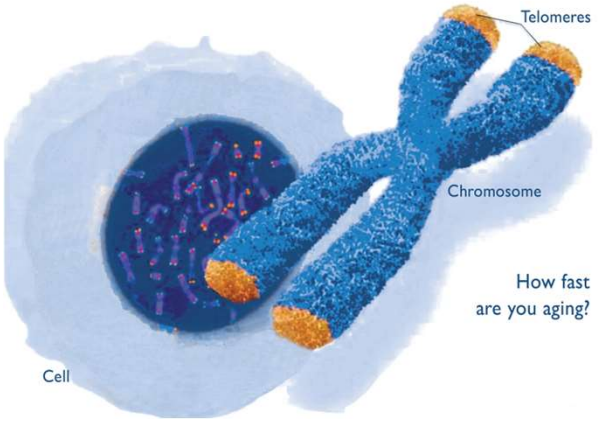
Study #2 – Telomere Length

- N= 124

- Each subject had a unique protocol of oral capsule bioregulators



- Rotated thru bioregulators over 3 years with each subject – 4-5 a month stacked

- Monthly regimen - 2 caps a day of each bioregulator x 10 days

- Telomere length tested

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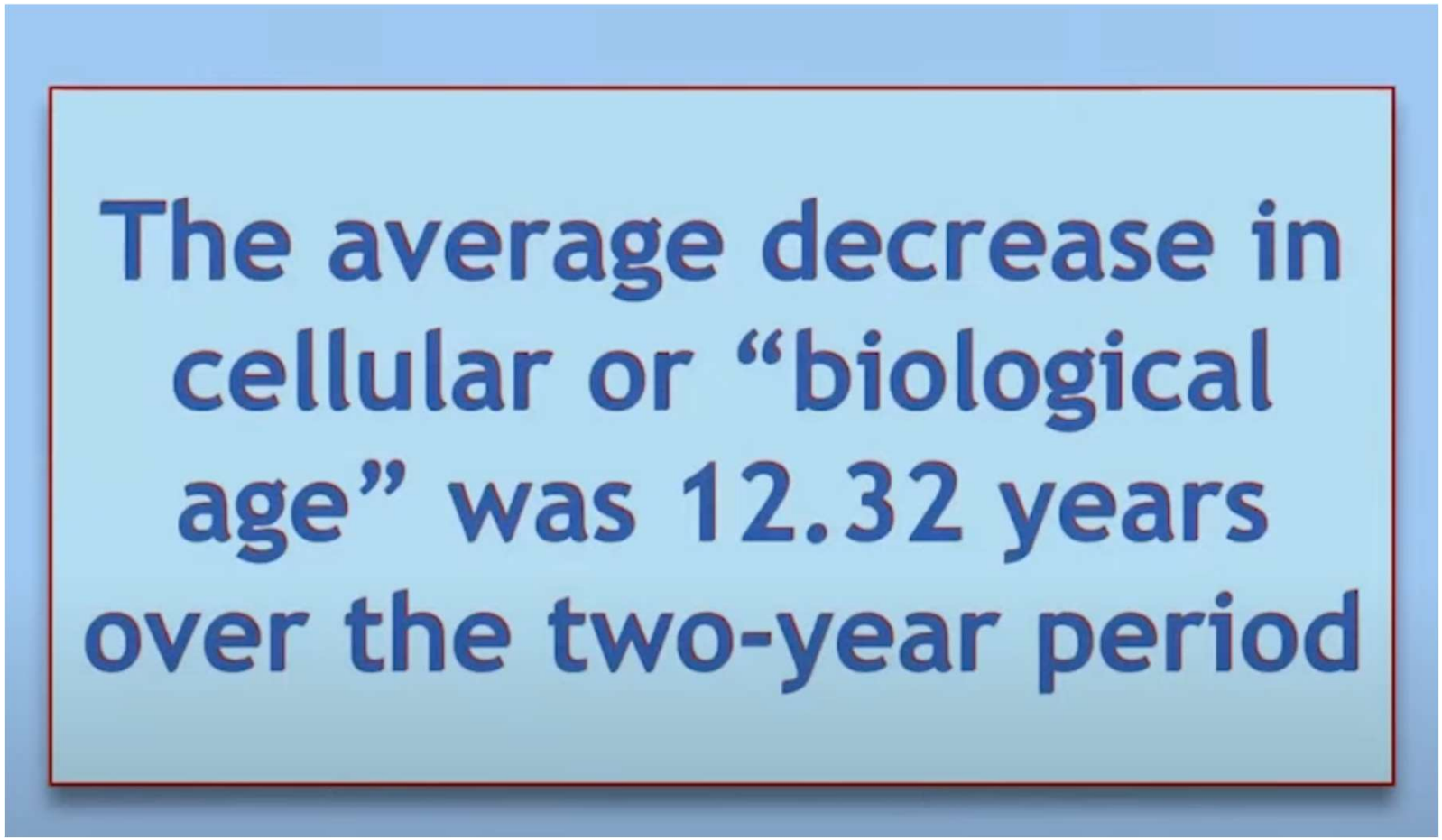
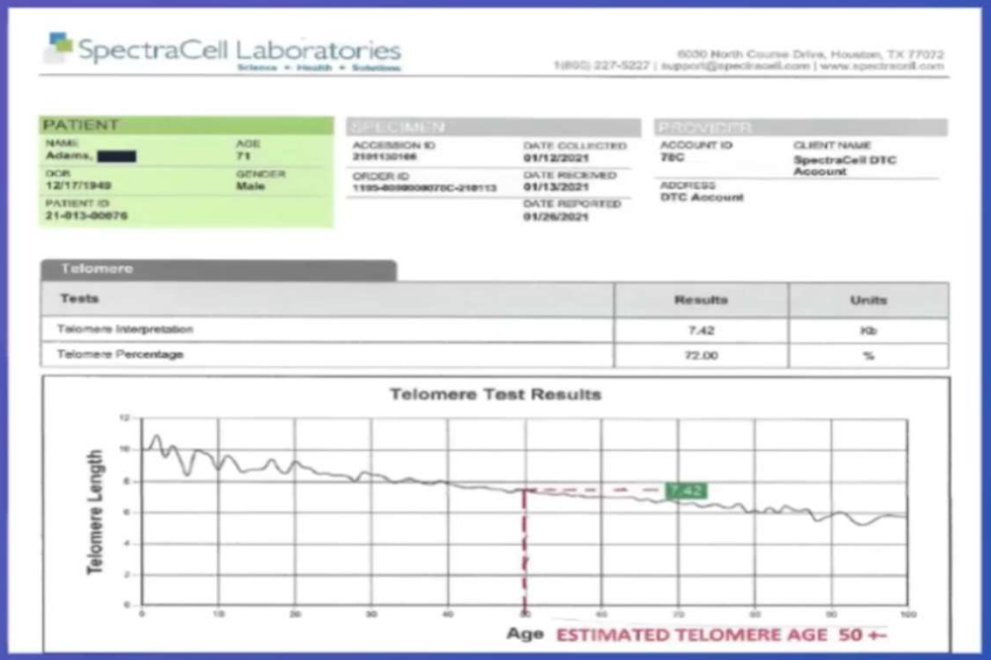
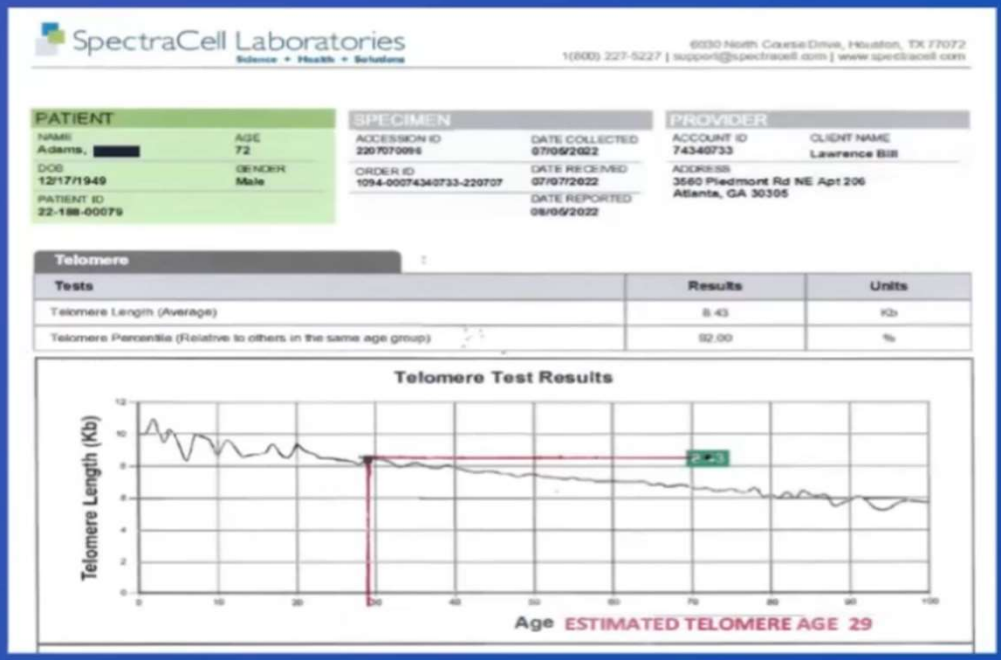


- Exceptional Result Example:
  71 y/o male



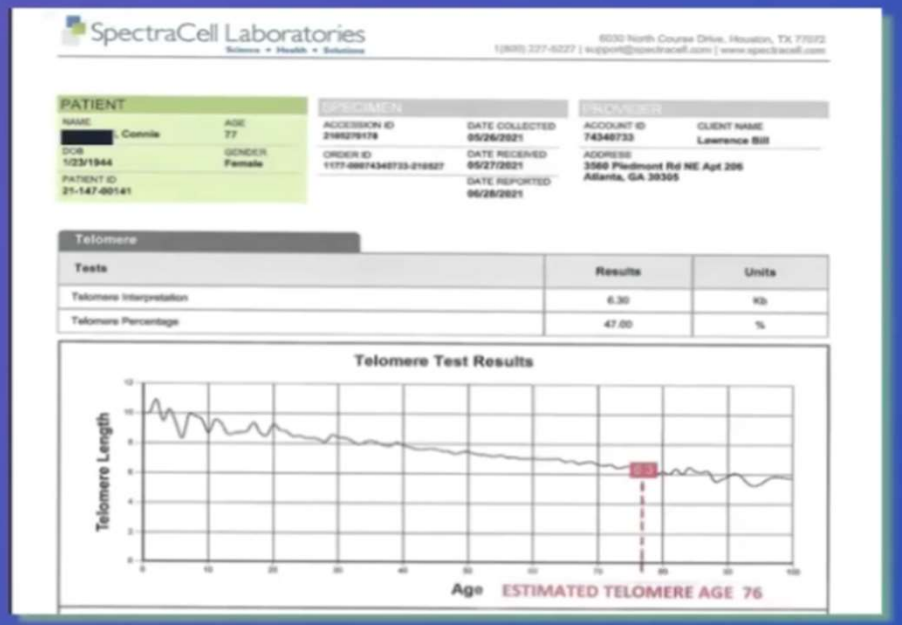


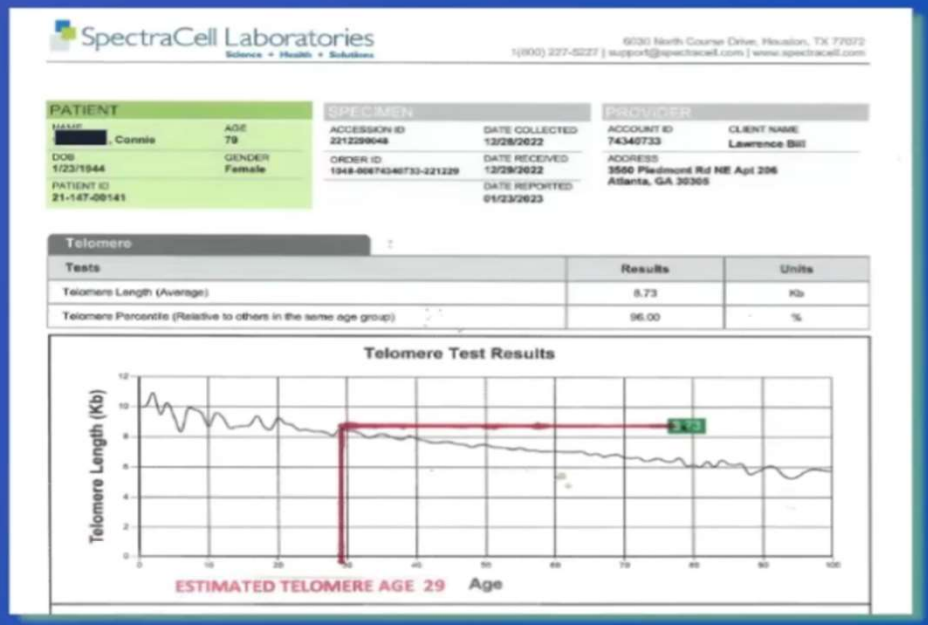
2021 Telomere Age 50

2022 Telomere Age 29

https://podcinquiry.com/2025/04/bioregulatory-peptides-bill-lawrence/

- Exceptional Result Example:
  70 y/o female





2021	Telomere Age	76

2023	Telomere Age	29

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