A4M | MEDICINE REDEFINED

## MODULE II

# PEPTIDE THERAPY CERTIFICATION

# The Impact of Peptides on Telomeres and Other Markers of Biological Aging


Presented by:

Gordon Crozier, DO FAARFM ABAARM

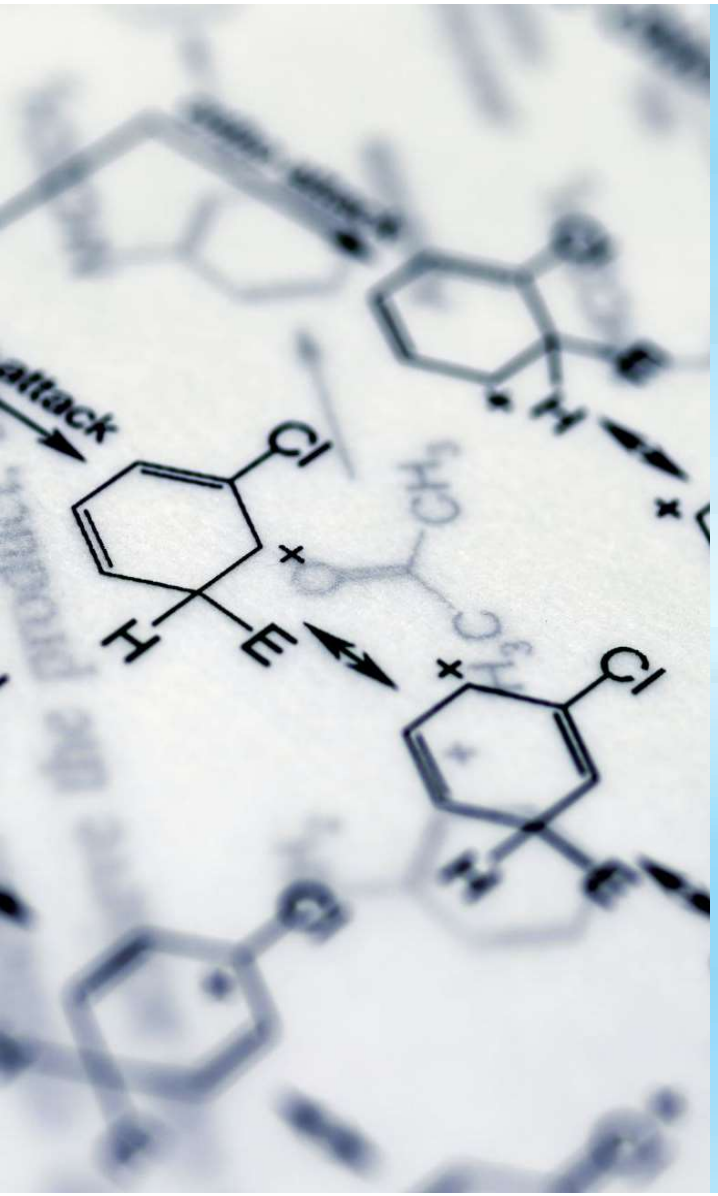
- Global Longevity Summit Chair
- Crozier Clinic Medical Director
- Miora Boca Raton Medical Director

# In the News..... March 2019

The Harvard Gazette

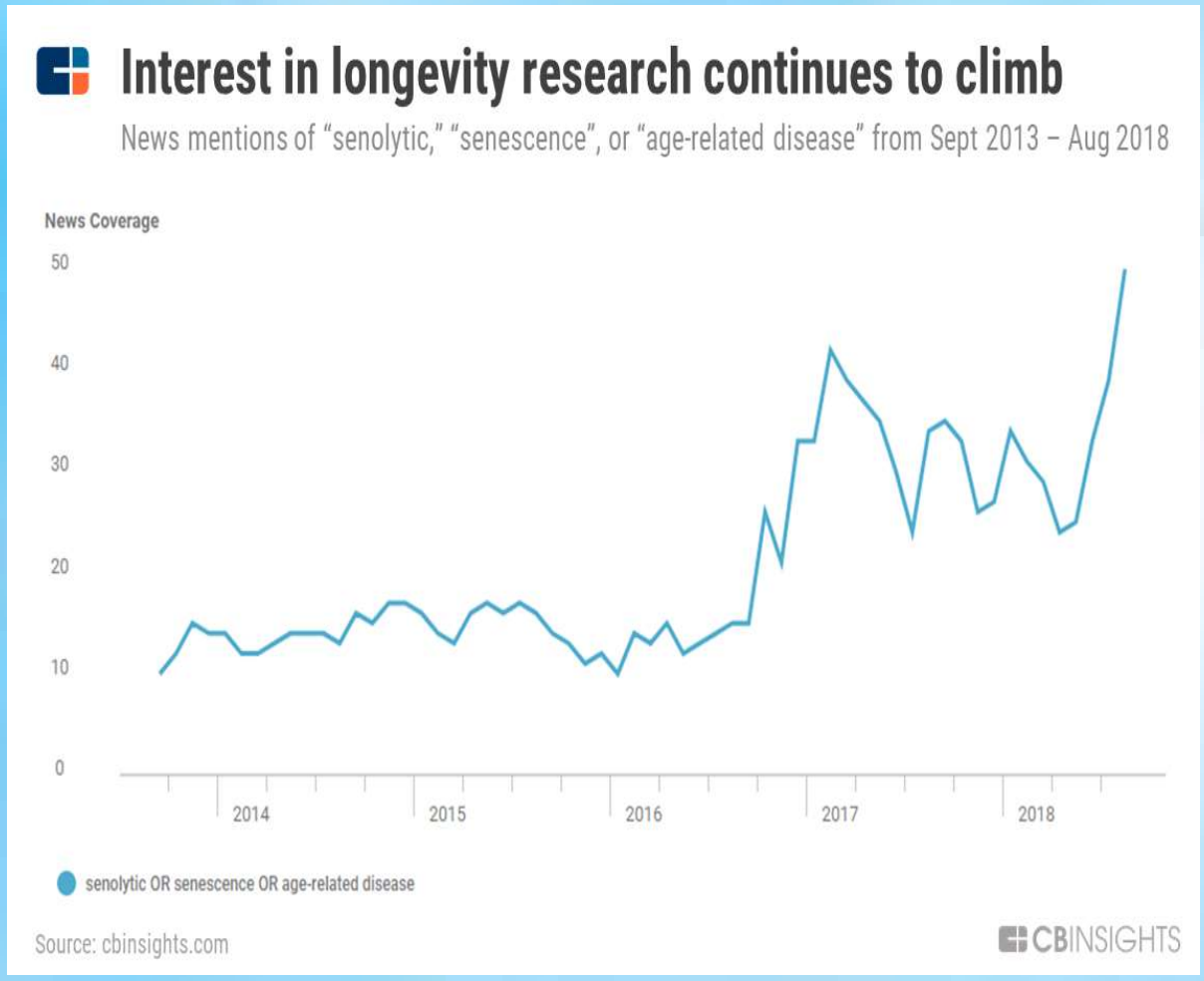
HEALTH & MEDICINE

## 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



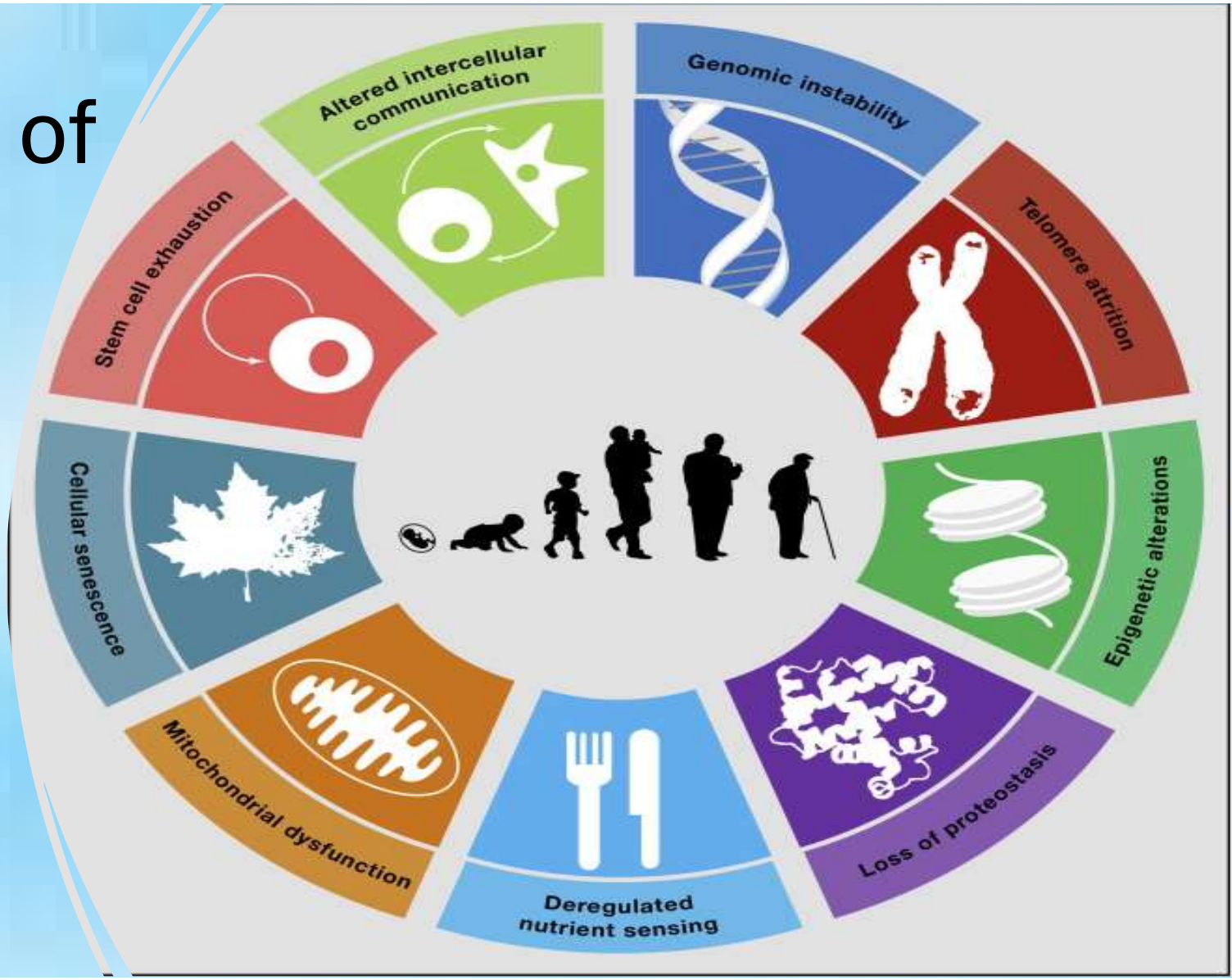

# Anti-Aging Research On The Rise



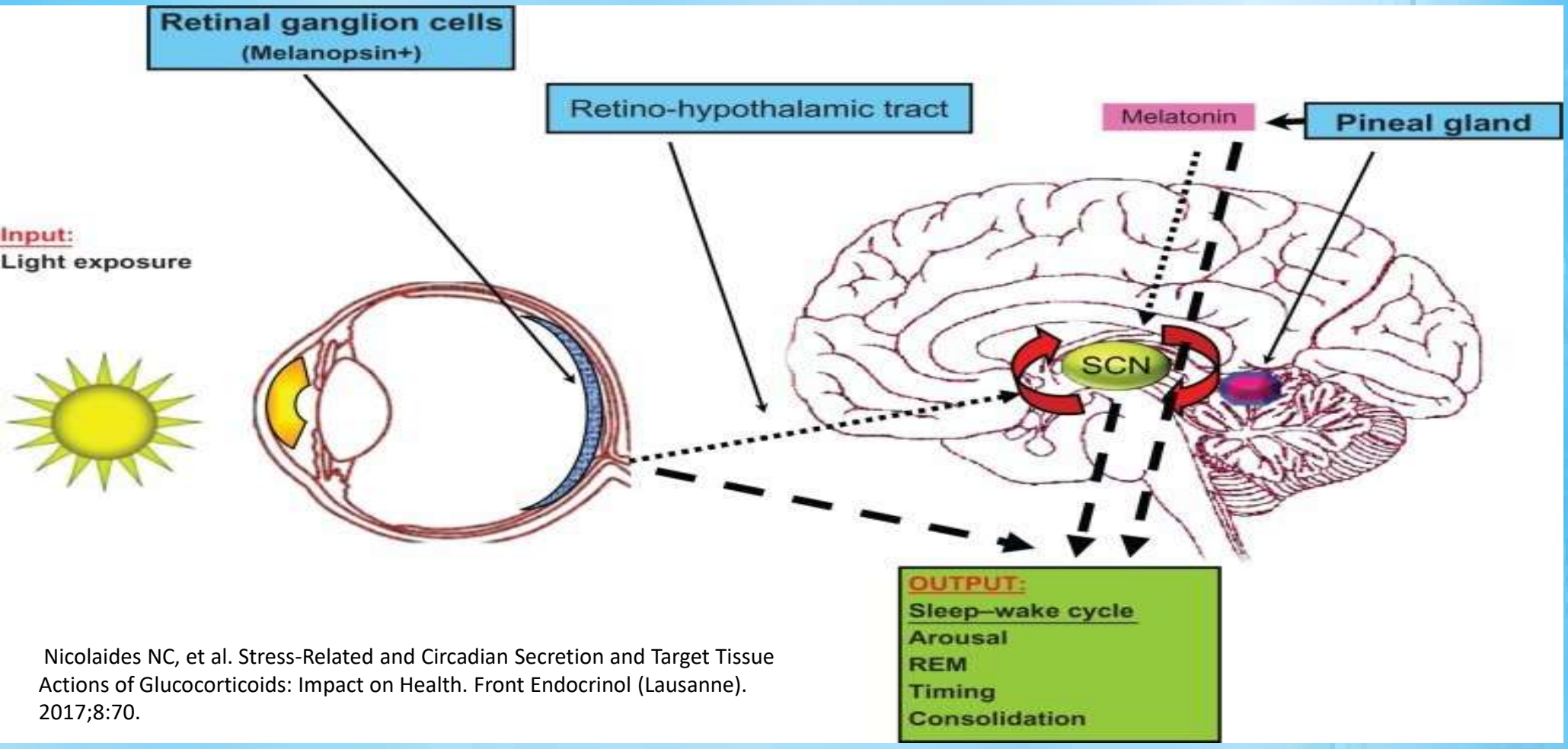
Source: https://www.cbinsights.com/research/report/future-aging-technology-startups/

# 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



# Master Clock SCN

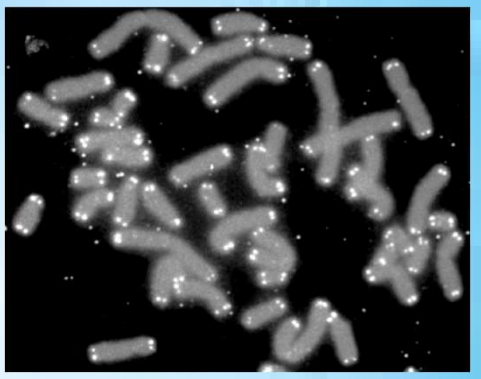



Nicolaides NC, et al. Stress-Related and Circadian Secretion and Target Tissue Actions of Glucocorticoids: Impact on Health. Front Endocrinol (Lausanne). 2017;8:70.

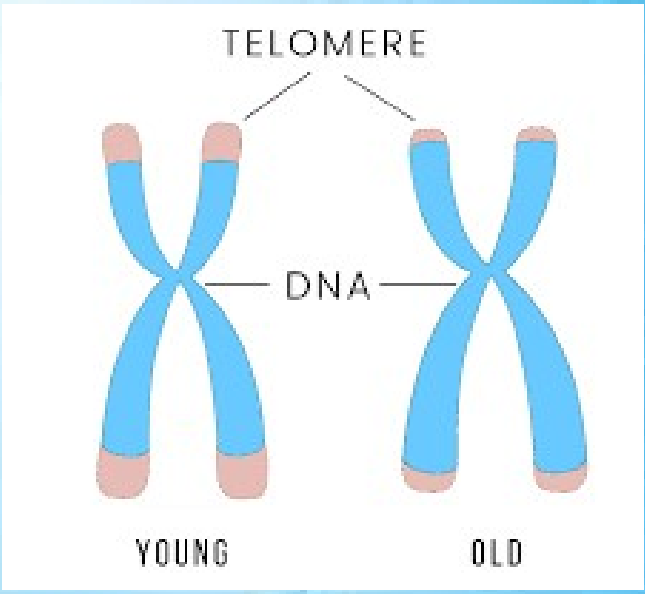
# What's the Missing Link?

# **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



# 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

# What Shortens Telomeres?

- Aging
- Rapid cellular division in response to infection
- Oxidative stress - ROS
- Lifestyle factors – diet, environmental exposures, exercise, stress reduction
- Homocysteine – 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.

# 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

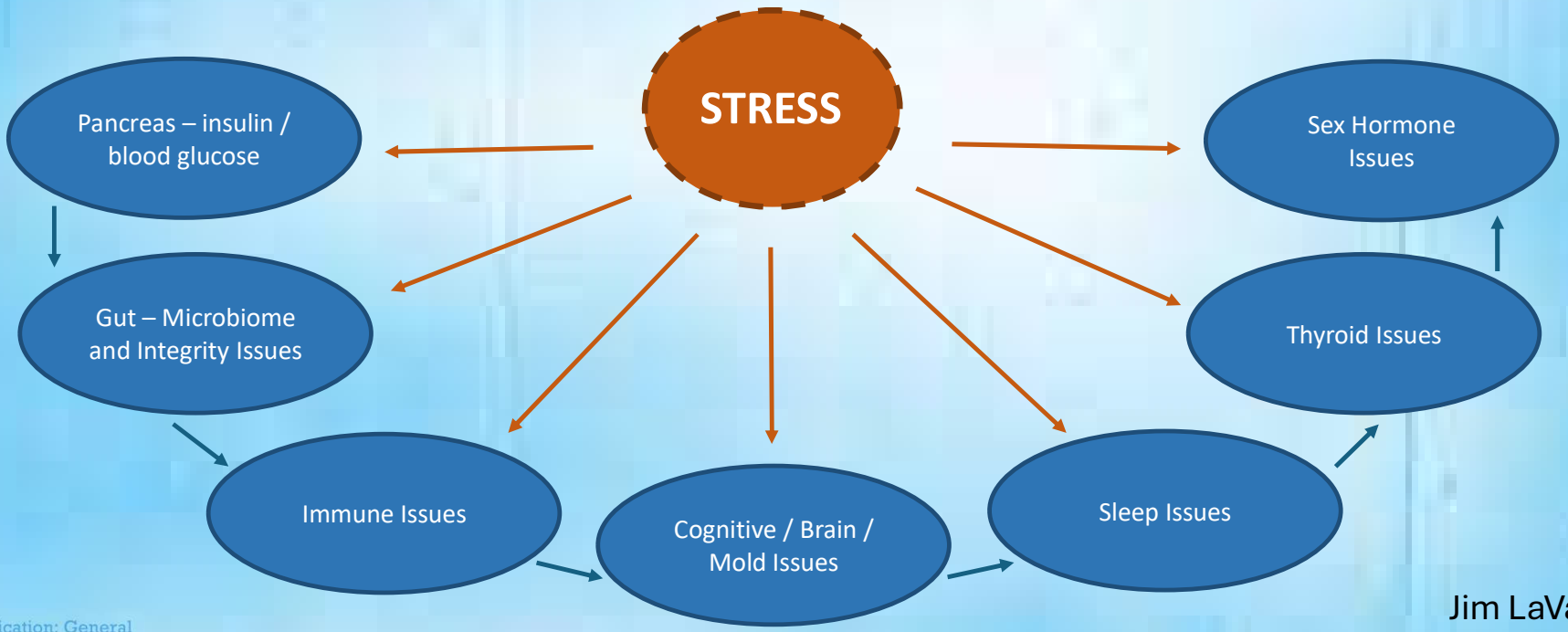
- 2015 longitudinal study of Japanese semi-supercentenarians
- Revealed inflammation, not telomere length, predicts successful aging at an extremely advanced age
  - Chronic systemic inflammation had greater effect on mortality and loss of cognitive function in the centenarians
- Chronic inflammation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

# How Do We EFFECTIVELY Preserve Telomere Length and Increase Longevity?

# Systems Biology Approach

Optimizing Inter-relationship of organ systems is important

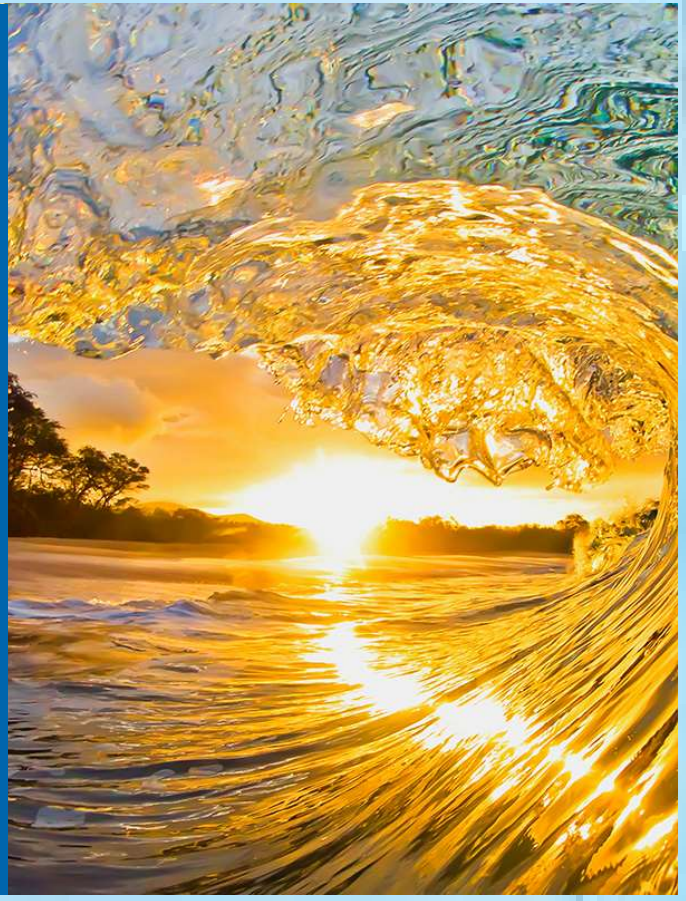





Jim LaValle @
jimlavallle.com

# METABOLISM

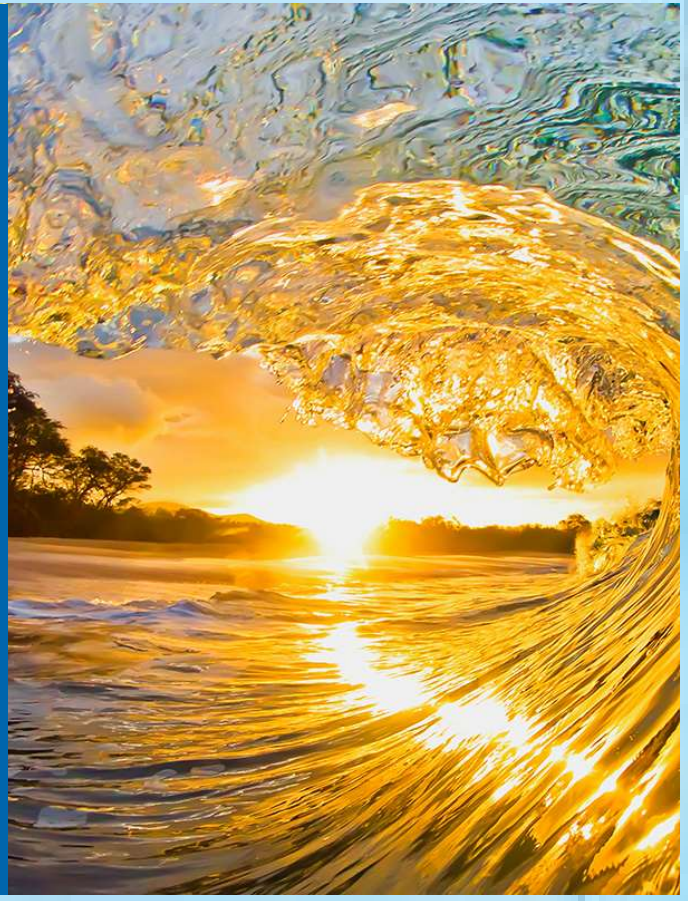
The sum total of all the chemical reactions **driving how you feel today** and creating the chemistry **moving you toward future health**.

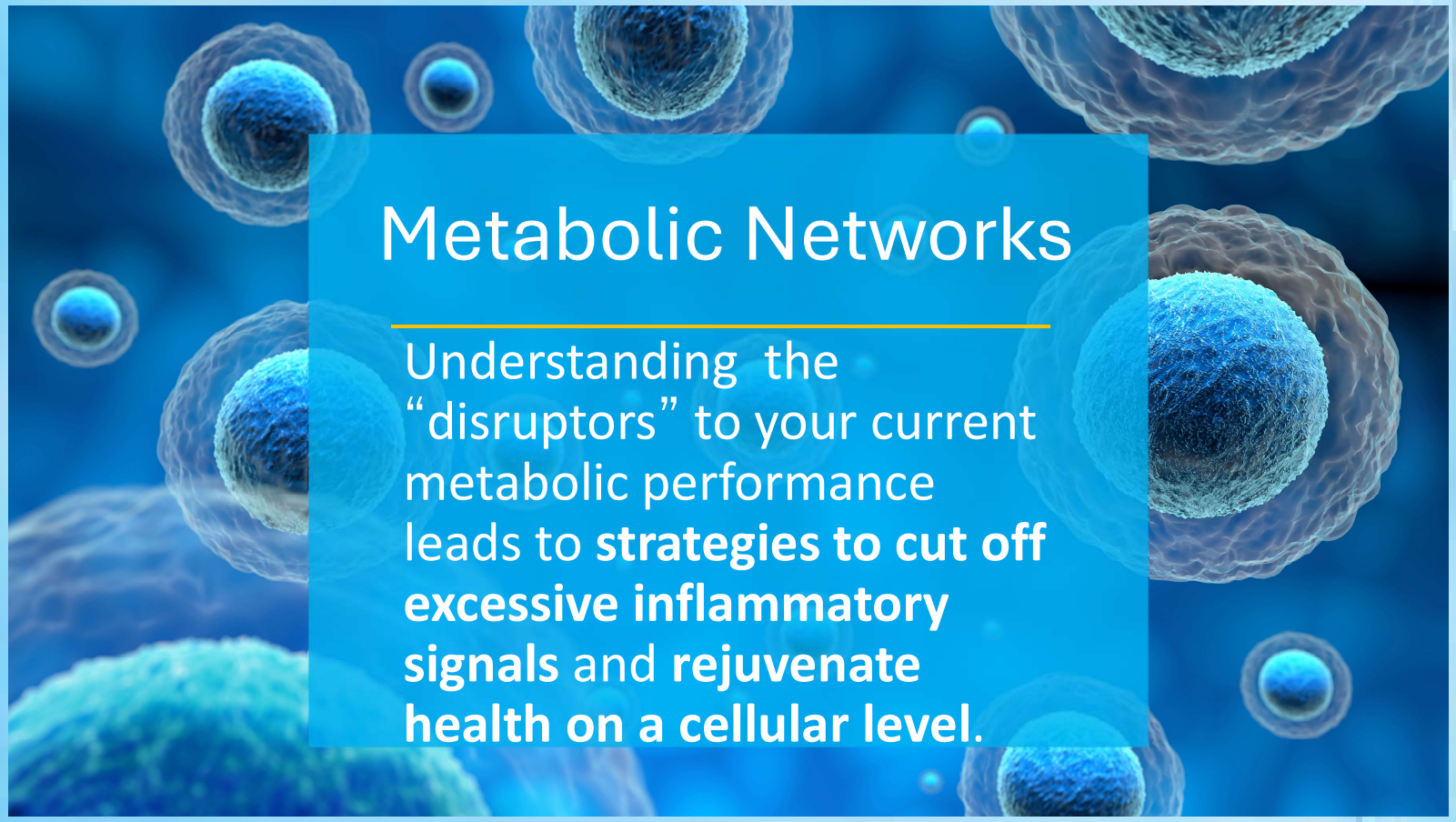


# METABOLISM

Directly under the influence of Global Metabolic Inflammatory Signaling =

**Metaflammation drives Metabolic Dysregulation**





# Metabolic Networks

Understanding the "disruptors" to your current metabolic performance leads to **strategies to cut off excessive inflammatory signals** and **rejuvenate health on a cellular level**.

Key Tenants of

# Aging, Performance and Vitality

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- GUT integrity and microbiome diversity
- Immune Balance
- Environmental Burden
- Individuality

# Metaflammation

- Also know as “Inflammaging” and metabolism induced inflammation
- Chronic low-grade inflammatory sequela
- Increases aging processes and metabolic signaling issues
- Caused by AND leads to “diabesity”:
  - Insulin resistance; type 2 diabetes
  - Obesity
  - Stress
  - Diet
  - LPS induced
  - Liver / kidney issues



Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

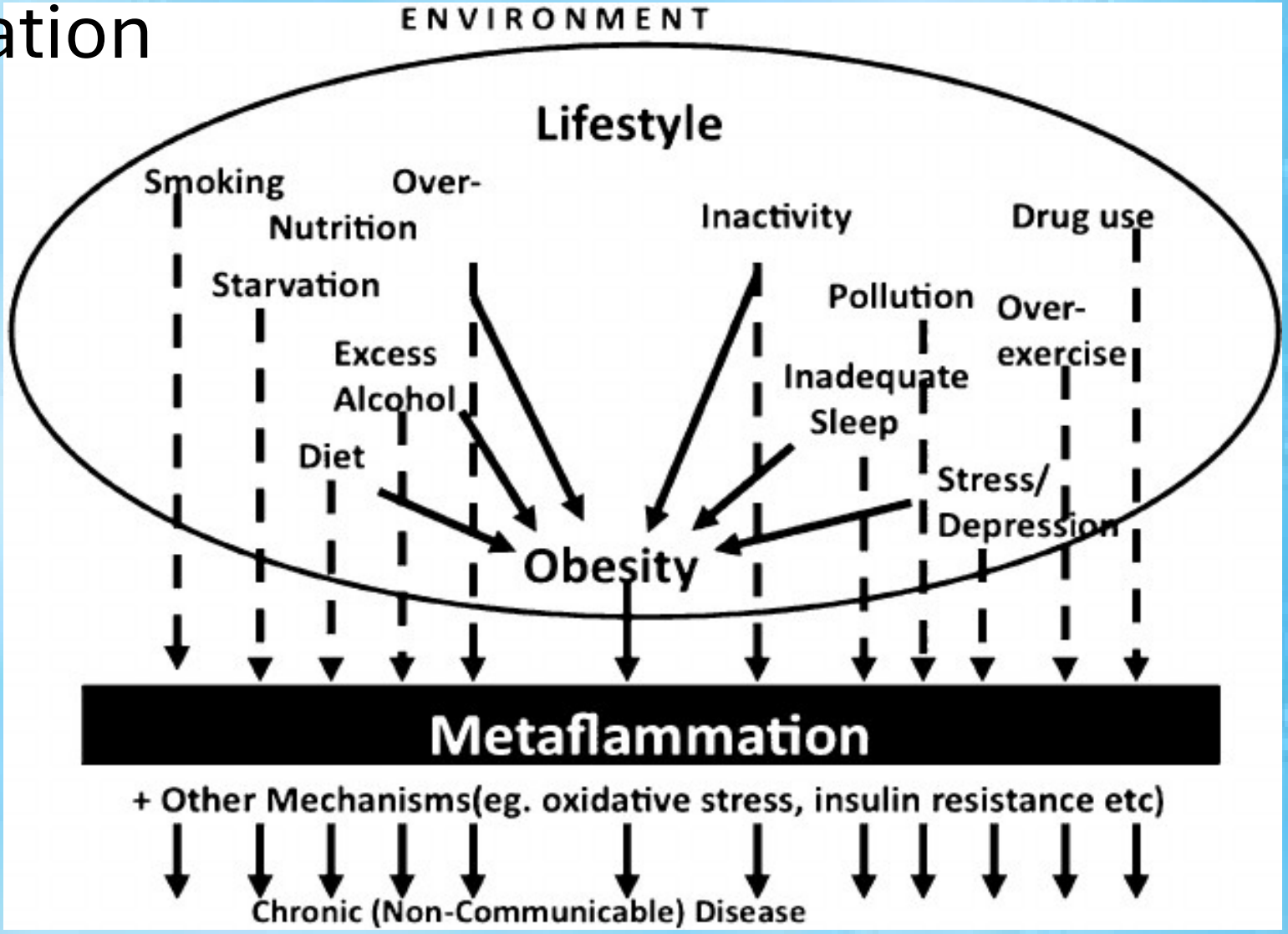
# Metaflammation – CoMorbid Conditions

- Altered methylation patterns
- Cardiovascular issues – lipid, vascular
- Hormonal imbalances
- Liver and kidney diseases
- Immune dysfunction
- Thyroid issues
- Fatigue
- Cognitive and mood problems
- Sarcopenia
- Osteoporosis
- Cancer
- Sleep problems



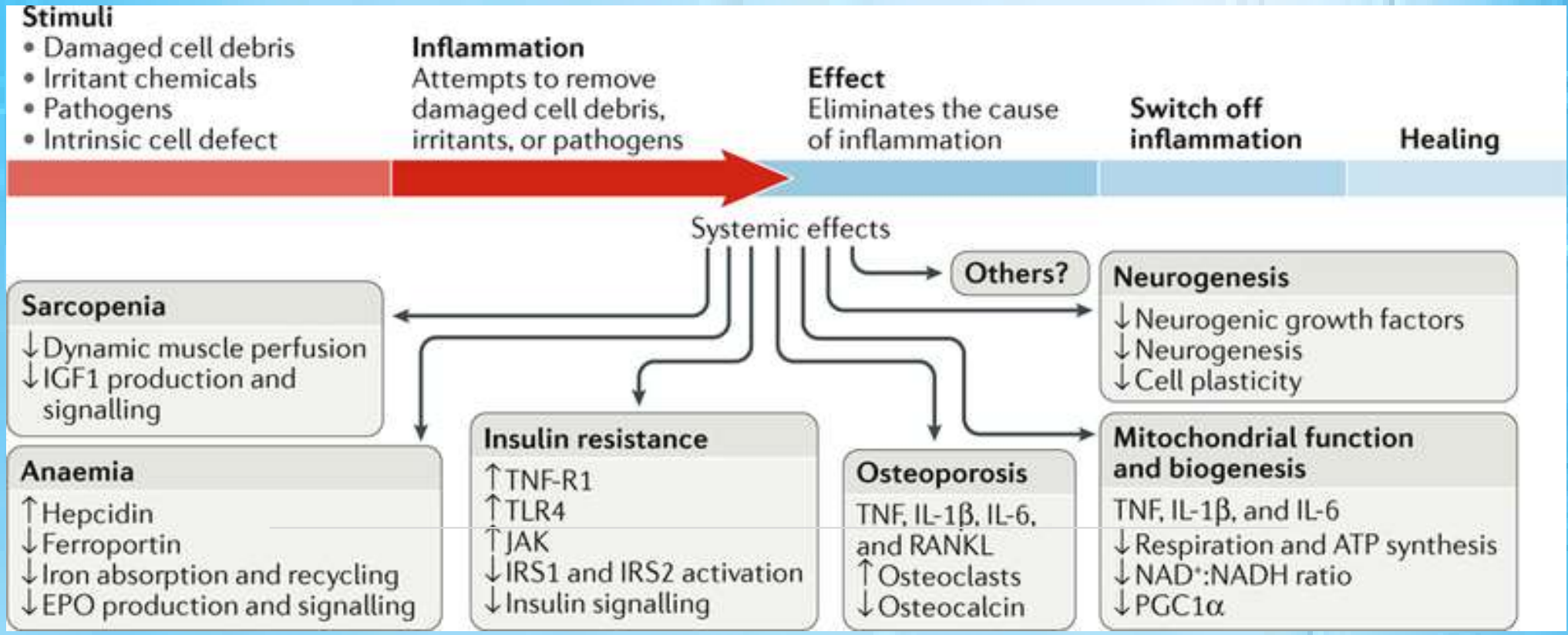
Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

# Metaflammation Constructs




Egger G, et al. Obesity Reviews. 2008;10(2):237-49.

# Metaflammation Induces Catabolic State




Ferruci L, et al. Inflammageing: chronic inflammation in ageing, cardiovascular disease and frailty. Nat Rev Cardiol. 2018;15(9):505-22.

# Metaflammation Pathophysiology

- Acute inflammation is a short-term defense response to injury
- Required for healing and tissue repair
- Resolution of acute inflammation should be terminated when no longer necessary to prevent tissue damage
- In a homeostatic model, pro-inflammatory response in balance with anti-inflammatory response
- Repeated stress, insult from dietary factors or injury to the body can lead to neuroendocrine dysregulation
- Results in prolong, chronic inflammation - metaflammation

Miller ES, et al. Chronic stress induces persistent low-grade inflammation. Am J Surg. 2019;218:677-683.

# Metaflammation Pathophysiology

- Chronic stress associated with persistent activation of HPA axis
- Leads to chronic release of stress hormones - glucocorticoids and catecholamines
- During chronic stress, activated polymorphonuclear cells (PMNs) release sIL-6Ra combines with IL-6 to activate endothelial cells
- Monocyte chemotactic protein-1 (MCP-1) are produced
- Stimulates monocyte recruitment
- Transition of neutrophil to mononuclear cell infiltrate is hallmark trait of chronic vs. acute inflammation



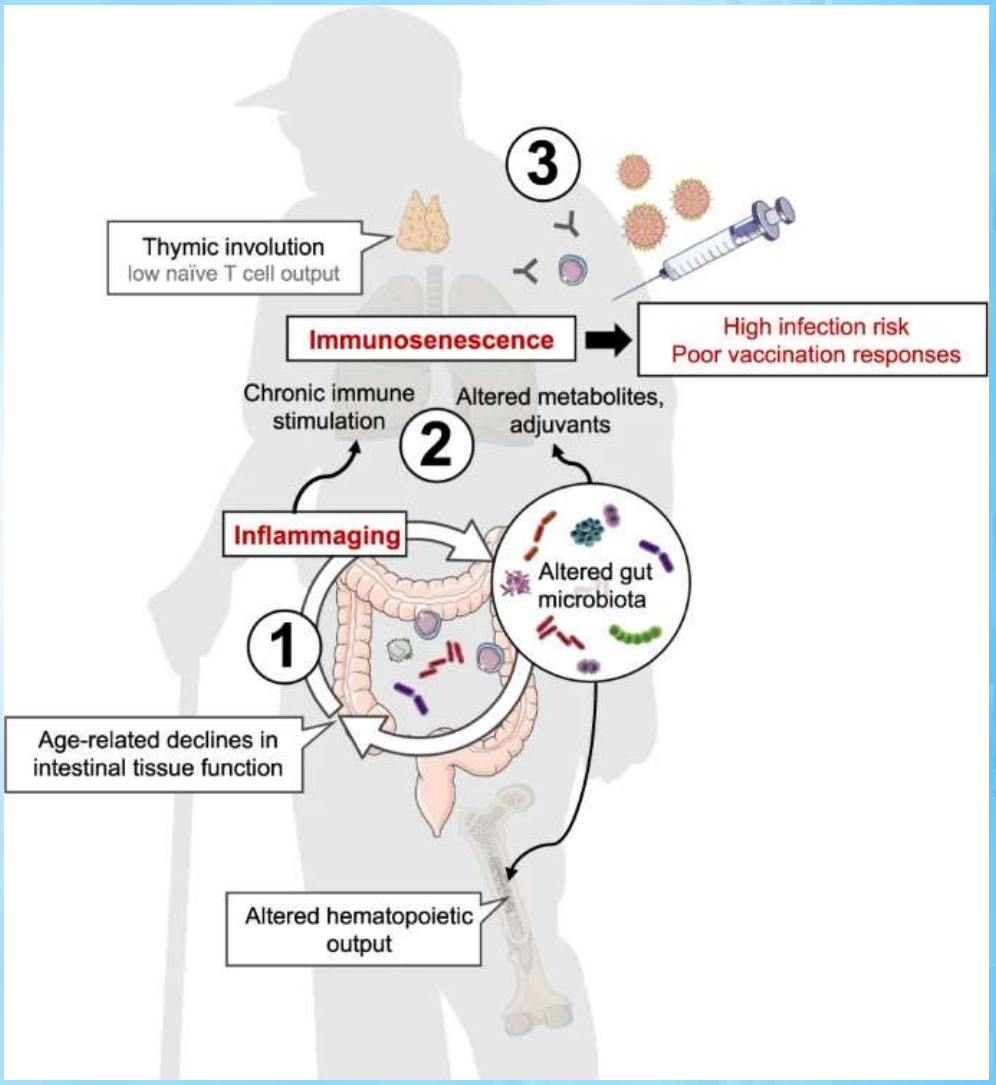
Miller ES, et al. Chronic stress induces persistent low-grade inflammation. Am J Surg. 2019;218:677-683.

# GUT and Aging

- Gut microbiota composition shifts with age
- Across the lifespan, and especially in old age, a diverse microbiome that produces anti-inflammatory metabolites – i.e. short-chain fatty acids – is reported to be associated with healthy aging

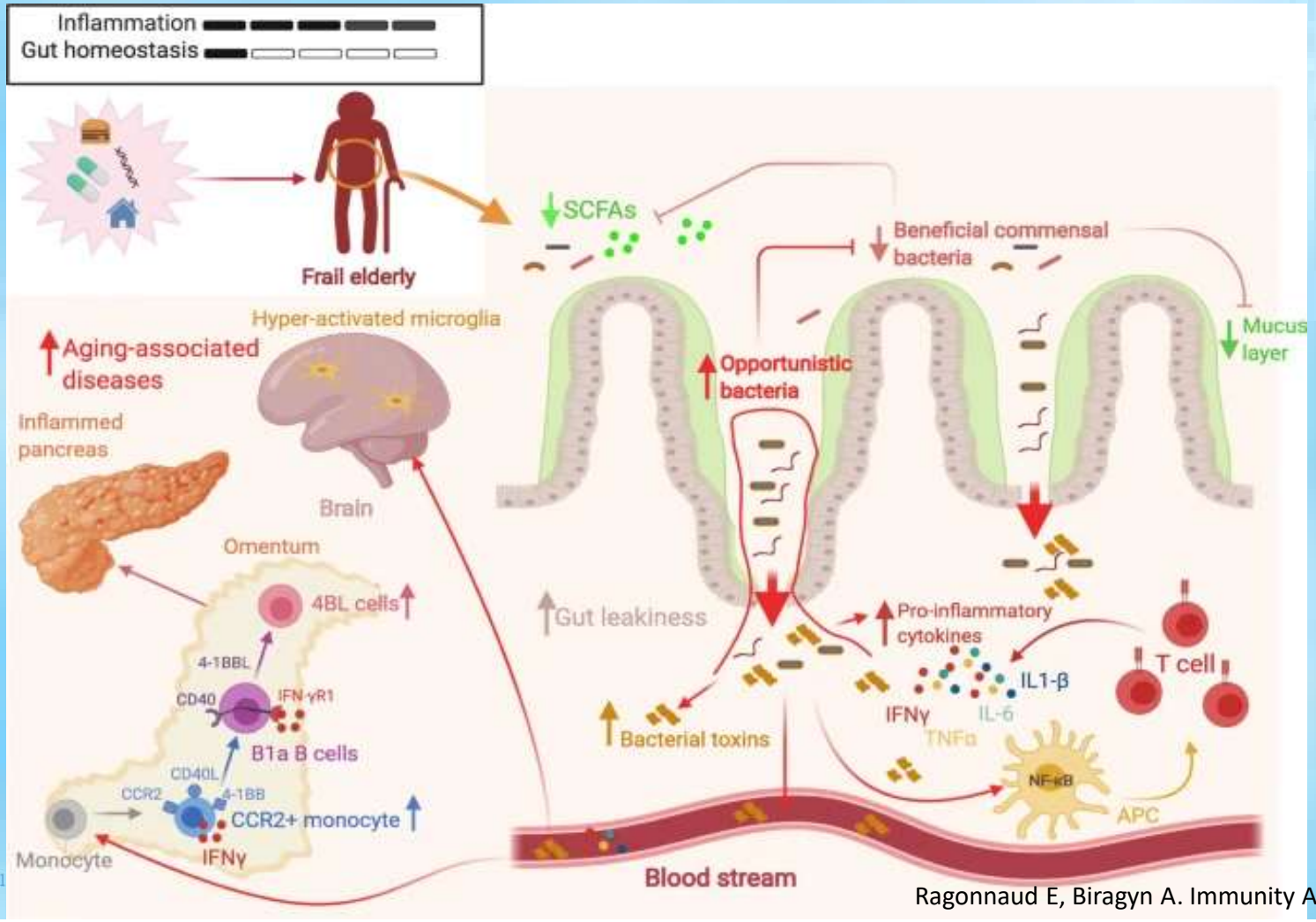
Bradley E. The human gut microbiome and aging. Gut Microbes. 2024;16(1):2359677.

# Age-related Changes in Gut Microbiome Fuels Inflammaging




Bosco N, Noti M. The aging gut microbiome and its impact on host immunity. Genes Immun. 2021;22:289-303.

# GUT Dysbiosis in Elderly Increases Disease Risk




Ragonnaud E, Biragyn A. Immunity Aging. 2021;18(1):2.

# GUT and Aging

- Summary of studies of microbiome and healthy aging

| Study Subjects | Microbiome Findings | Reference |
|---|---|---|
| Older adults 70–82 examining cohorts with and without underlying chronic disease | Higher abundance of *Akkermansia muciniphila* by 16s rRNA sequencing | Singh et al. (2019) |
| A subset of much larger cohorts comprising individuals 85 year and older living in the community | Unique microbiomes enriched in rare taxa by 16s rRNA sequencing and increased serum concentrations of microbial metabolites of aromatic amino acids | Wilmanski et al. (2021) |
| Comparison between older adults and centenarians | Increased abundance of metabolic pathways associated with tryptophan metabolism by metagenomic sequencing | Rampelli et al. (2013) |
| Comparisons between young adults and cohorts up to semisupercentenarians | Increased metabolic pathways associated with xenobiotic degradation, decreased pathways associated with carbohydrate metabolism by metagenomic sequencing in older cohorts | Rampelli et al. (2020) |
| Comparison between centenarians and young adults living in rural India | Higher bacterial richness and increase in *Prevotella* strains by 16s rRNA sequencing and higher concentration of neurotransmitter related metabolites in stool | Tuikhar et al. (2019) |
| Comparisons between young adults and cohorts up to semisupercentenarians | Increased abundance of *Christensenellaceae* and *Akkermansia* in the oldest cohort by 16s rRNA sequencing | Biagi et al. (2016) |



Bradley E. The human gut microbiome and aging. Gut Microbes. 2024;16(1):2359677.

# GUT As a Source of Metaflammation

- Sequencing analysis of the 16S rRNA gene reveals an association between the gut microbiota and inflammatory diseases
- Over-activation of immunity in GUT leads to increased production of inflammatory cytokines
- Leaky guy allows bacterial and toxins to enter bloodstream
- Leads to peripheral and central inflammation

Viera M, et al. Translocation of a gut probiont drives autoimmunity in mice and humans. Science. 2018;359(6380):1156-61

# Lipopolysaccharide - LPS

- LPS make up 75-80% of the material of the outer cell wall of gram negative bacteria
- 1 single cell death releases 1 million LPS molecules
- INFLAMMATORY
- Toll receptor-4 (TLR-4) is stimulated by LPS
- Increases GUT permeability
- Can be induced by:
  - STRESS
  - Ketogenic diets
  - Drugs such as ibuprofen
  - Overtraining
  - Binge drinking/chronic drinking
  - Poor foods
  - Others…


Bertani B, Ruiz N. Function and biogenesis of lipopolysaccharides. EcoSal Plus. 2018;8(1):

# LPS Effects

- ↑ Inflammatory response (TNFα and Il-6)
- ↑ WBC's
- ↑ MCP-1
- ↑ Transient HR
- ↑ Cortisol
- ↑ Autoimmunity
- ↑ Resistin
- ↑ Adipocyte inflammation

- ↓ Insulin sensitivity
- ↓ Thyroid function
- ↓ Alters tryptophan metabolism and increase quinolinic acid and kynurenine
- ↓ Melatonin
- ↓ Glutathione pool via increased ROS



Mohammad S, et al. Front Immunol. 2020;11:594150

# Gut-Derived Endotoxin and Telomere Length Attrition in Adults with and without Type 2 Diabetes

The findings from this study highlighted across all participants that circulating endotoxin ($r = -0.17$, $p = 0.01$) was inversely associated with TL, noting that endotoxin and triglycerides predicted 18% of the variance perceived in TL ($p < 0.001$). Further stratification of the participants according to T2DM status and sex highlighted that endotoxin significantly predicted 19% of the variance denoted in TL among male T2DM participants ($p = 0.007$), where TL was notably influenced. The influence on TL was not observed to be impacted by anti-T2DM medications, statins, or anti-hypertensive therapies. **TL attrition was inversely associated with circulating endotoxin levels independent of the presence of T2DM and other cardiometabolic factors, suggesting that low-grade chronic inflammation may trigger premature biological aging.**

Biomolecules 2021 https://doi.org/10.3390/biom11111693

# Zonulin and LPS levels in Centenarians

- Increased intestinal permeability is an important event leading to endotoxemia
- Gut microbiota lipopolysaccharide accelerates inflammaging
- Endotoxemia-induced inflammation has been associated with insulin resistance and atherosclerosis, ultimately increasing the risk of coronary heart disease
- 2018 study reported Disease-free centenarians had significantly lower levels of serum zonulin and lipopolysaccharide than young patients with acute myocardial infarction
  - They also had significantly lower concentrations of serum lipopolysaccharide than young healthy controls

Kim K, et al.. BMC Microbiol. 2016;16:9.

# Anti-Aging Research

- For each one year increase in the difference between chronological and epigenetic age:
  - There is a 6% increased risk of developing cancer within three years
  - And a 17%  increased risk of dying of cancer in the next five years

Jylhava J, et al. Biological Age Predictors. EBioMed. 2017;21:29-36.

# Back to the Question:

# How do We EFFECTIVELY Preserve Telomere Length and Increase Longevity?

# What Can You do From Lifestyle Perspective to Preserve Telomere Length?

EXERCISE !!

- Endurance Training but not resistance training lengthens telomeres
- 266 young inactive volunteers for 6 months
- 3 types training  endurance, high intensity interval and resistance
- 3 x 45-minute sessions a week

“Telomerase activity was increased two- to three-fold and telomere length was increased significantly in the endurance and high intensity training groups compared to the resistance and control groups.”

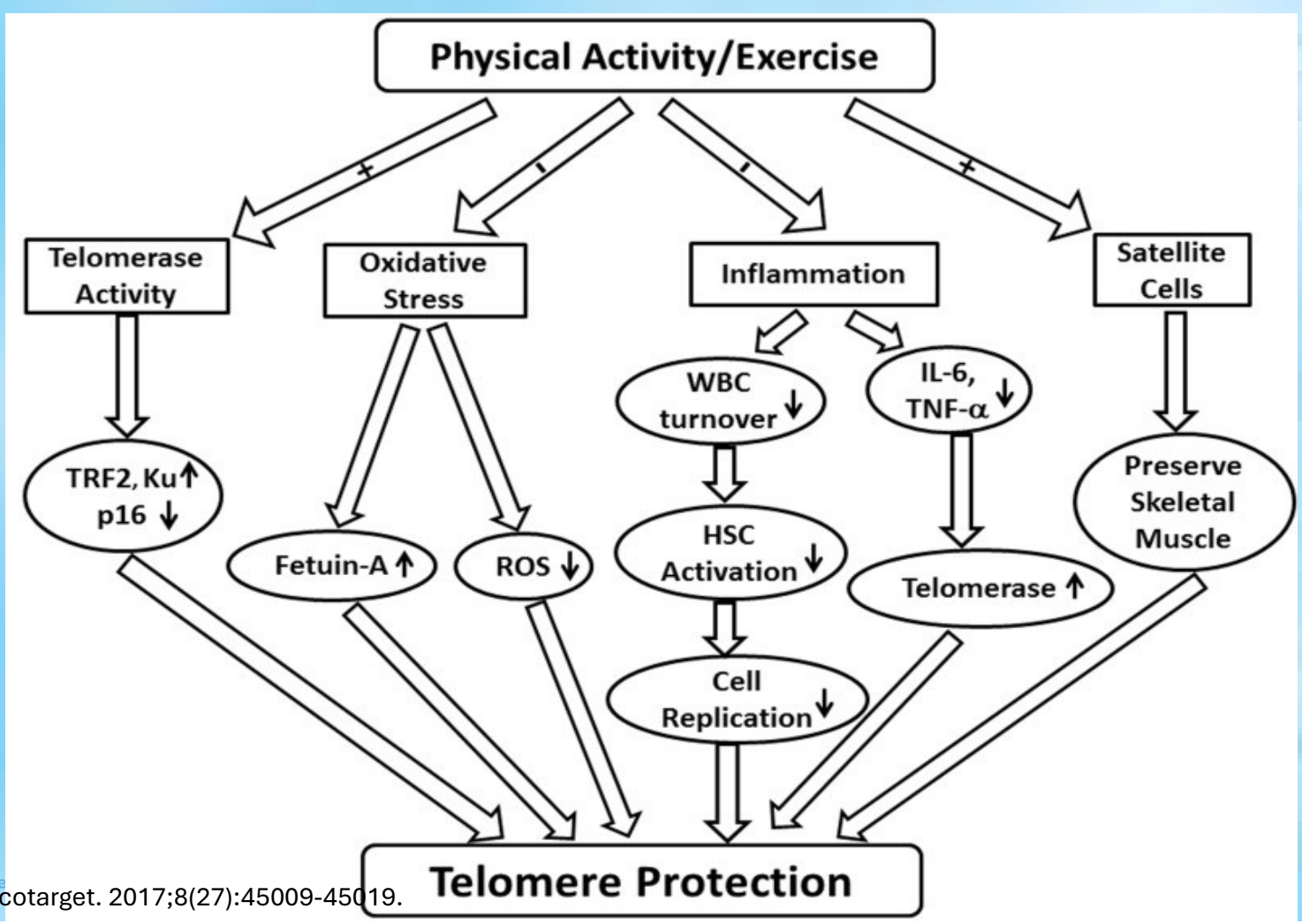
European Society of Cardiology  Nov 28 2018https://www.escardio.org/

# Exercise - Telomere Length

- 2017 cross-sectional study – n=5823 adults from NHANES 1999-2002 study
- Looking at physical activity (PA) effects on leucocyte telomere length (LTL)
- Adults with High activity were estimated to have a biologic aging advantage of 9 years over sedentary
- The difference in cellular aging between those with High and Low activity was also significant was 8.8 years
- 7.1 years between those with High and Moderate PA
- CONCLUSION: PA was significantly and meaningfully associated with telomere length in U.S. men and women.

Tucker LA. Physical activity and telomere length in US men and women: an NHANES investigation. Prvent Med. 2017;100:145-51.

# Potential Effects of Exercise on Telomere Length



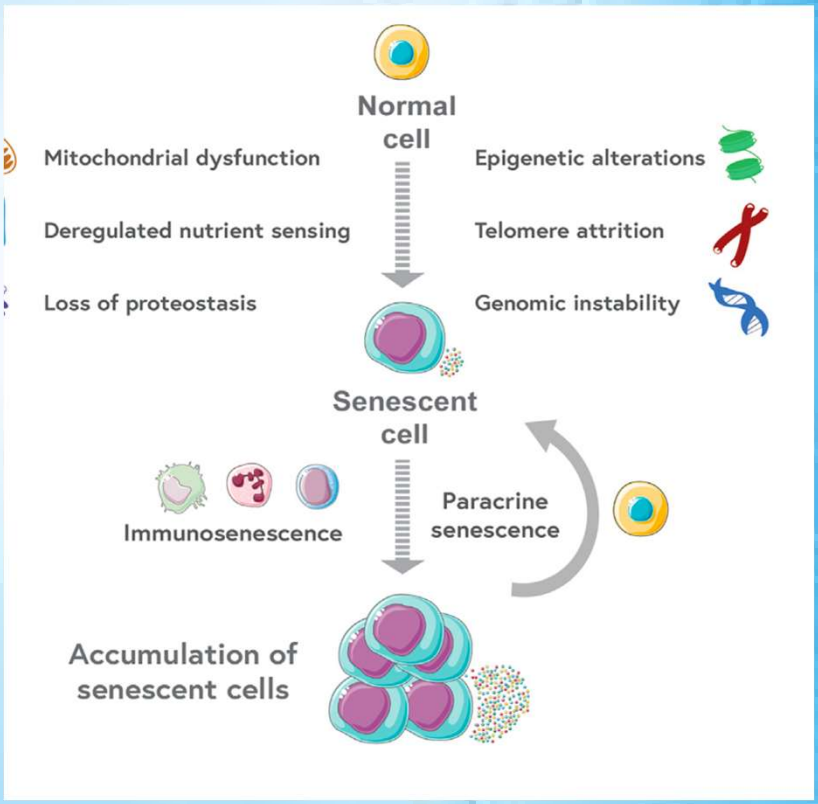



Arsenis NC, et al. Oncotarget. 2017;8(27):45009-45019.

# 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





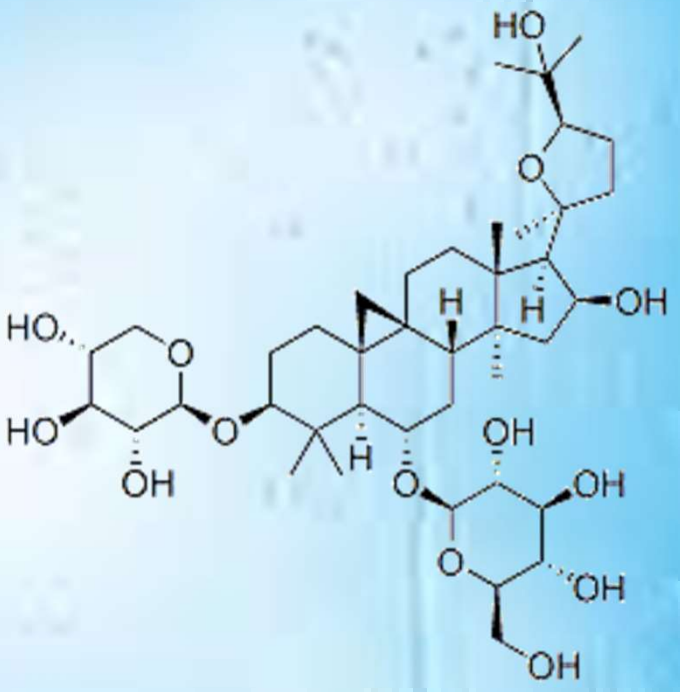

Schafer M, et al. SENESCENCE SECRETOME: BIOMARKERS OF BIOLOGICAL AGING AND POSTOPERATIVE OUTCOMES. Innov Aging. 2019;3(Suppl 1):S98.

# Senolytics

- Senolytic nutrients help clear senescent cells from the body
  - Theaflavins
  - Quercetin
  - Dihydroquercetin
  - Fisetin
  - Astragaloside IV
  - Pomegranate (urolithins)
  - Resveratrol
  - Thai ginseng - 4-5x more potent SIRT upregulation than resveratrol
  - Alpha GPC
  - PQQ
  - CoQ10
  - Rg3 ginsenoside
  - Nicotinamide Riboside NR
  - EGCG from green tea
  - Curcumin

# Astragaloside IV

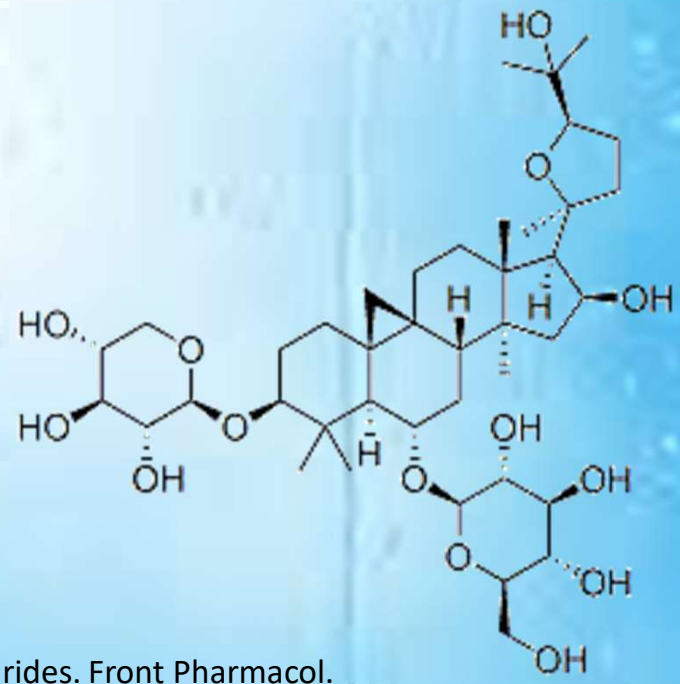
- Main bioactive phytocompound in *Astragalus membranaceus* root
- Traditional Chinese medicine
- Immunomodulatory
- Antiaging
  - Improves autophagy
  - **Increases telomere length**
    - Telomerase activator




- Zheng Y, et al. A review of the pharmacological action of astragalus polysaccharides. Front Pharmacol. 2020; https://doi.org/10.3389/fphar.2020.00349
- Salvador L, et al. A Natural Product Telomerase Activator Lengthens Telomeres in Humans: A Randomized, Double Blind, and Placebo Controlled Study. Rejuvination Res. 2016;19(6):478-84.

# Astragaloside IV

- Antioxidant
- Antiinflammatory
- Potent protective effect on:
  - Focal cerebral ischemia/reperfusion
  - Cardiovascular disease
  - Pulmonary disease
  - Liver fibrosis
  - Diabetic nephropathy
- 50mg QD-BID of 98% astragaloside IV






Zheng Y, et al. A review of the pharmacological action of astragalus polysaccharides. Front Pharmacol. 2020; https://doi.org/10.3389/fphar.2020.003497

# EGCG

- Epigallocatechin-3-gallate antioxidant compound found in Green tea
- Improves longevity in lab animals
- EGCG extended lifespan by reducing liver and kidney damage and improving age-associated inflammation and oxidative stress
- How? through the inhibition of NF-κB signaling by activating the longevity factors FoxO3a and SIRT1

Niu Y, et al. Aging Cell. 2013;12(6):1041-9.

# EGCG Mechanisms

- Neuroprotective
  - Decreases microglial inflammation
  - Improves adult neurogenesis in the hippocampus
- Immune supportive
  - Decreases proinflammatory cytokine release
  - Decreases inflammation
- Antiviral
  - EGCG binds to viral cell membrane
  - Represses the replication and transcription of virus

Bimonte S, et al. Drug Design, Development and Therapy. 2021;15:4447-54.

# EGCG

- Intake of EGCG is reported inversely associated with the risk of cardiovascular diseases
- Anxiolytic
  - Interaction with γ-aminobutyric acid (GABAA) receptors
  - EGCG may inhibit spontaneous excitatory synaptic transmission independently of GABA receptor activation
- Protects body from heavy metal-induced oxidative stress

Wang X, et al. Flavonoid intake and risk of CVD: A systematic review and meta-analysis of prospective cohort studies. Br. J. Nutr. 2014;111:1–11.
Zwolak I. Epigallocatechin Gallate for Management of Heavy Metal-Induced Oxidative Stress: Mechanisms of Action, Efficacy, and Concerns. Int J Molec Sci 2021;22:4027.

# EGCG Dosage

- 50-200mg BID
- 21mg oral liposomal , chew/swallow 1 QD-BID

Kim TE, et al. Effect of epigallocatechin-3-gallate major ingredient of green tea, on the pharmacokinetics of rosuvastatin in healthy volunteers. Drug Des Devel Ther. 2017;11:1409-16.

# Fisetin

- 3,3’,4’,7-tetrahydroxyflavone
- first record of fisetin as an isolate from Venetian sumac (*Rhus cotinus* L.) dates back to 1833
- Flavonoid found in fruits/veggies,  i.e. **strawberry (highest content)**, apple, persimmon, grape, onion, and cucumber
- Senolytic
  - Reported to induce apoptosis in aged human umbilical-vein endothelial cells
  - Mechanism of senescent-cell apoptosis related to its blocking on the PI3K/AKT pathway
  - mTOR blocked, autophagy activated

Khan N, et al. Fisetin: a dietary antioxidant for health promotion. Antioxid Redox Signal. 2013;19(2):151-62.

# Fisetin

- Anti-inflammatory/antioxidant
- Increases glutathione synthesis
- Reported to decrease risk of CHD and CVDs
- 100 mg daily
- Poorly orally absorbed – take w/ fat (ie fish oil) to increase absorption or use liposomal



Khan N, et al. Fisetin: a dietary antioxidant for health promotion. Antioxid Redox Signal. 2013;19(2):151-62.

# Curcuminoids from Turmeric (*Curcuma longa)*

- Anti-inflammatory/antioxidant
- Supports musculoskeletal system
- Joints/connective tissue support
- Helps improve flexibility and mobility
- Anti-aging support



Hewlings SJ, et al. Curcumin: a review of its effects on human health. Foods. 2017;6(10):92.

# Curcuminoids from Turmeric (*Curcuma longa)*

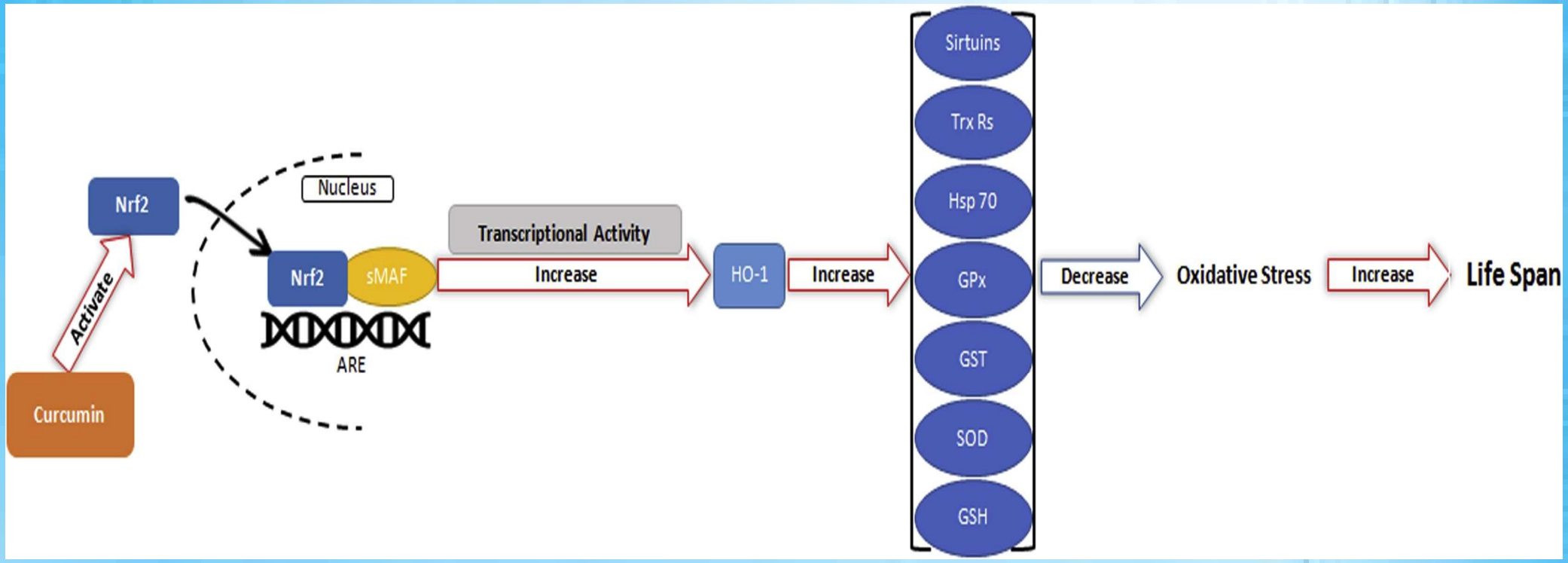
Mechanisms:

- Modulates cytokines – TNF-alpha, IL1, IL6
- Decreases oxidative stress via Nrf2-keap1 pathway
- Inhibits  nuclear factor-kappaB
- Inhibits Toll-like receptor 4-dependent signaling pathways
- Inhibits activation of a peroxisome proliferator-activated receptor-gamma pathway
- Decreases inflammasome signaling



Hewlings SJ, et al. Curcumin: a review of its effects on human health. Foods. 2017;6(10):92.

# Curcumin, Oxidative Stress Pathway and Lifespan




Zia A, et al. The role of curcumin in aging and senescence: molecular mechanisms. Biomedicine Pharmacotherapy. 2021;134:111119.

# Curcuminoids from Turmeric (*Curcuma longa)*

- Curcuminoids are poorly bioavailable
  - Not water soluble
  - 1st pass effect

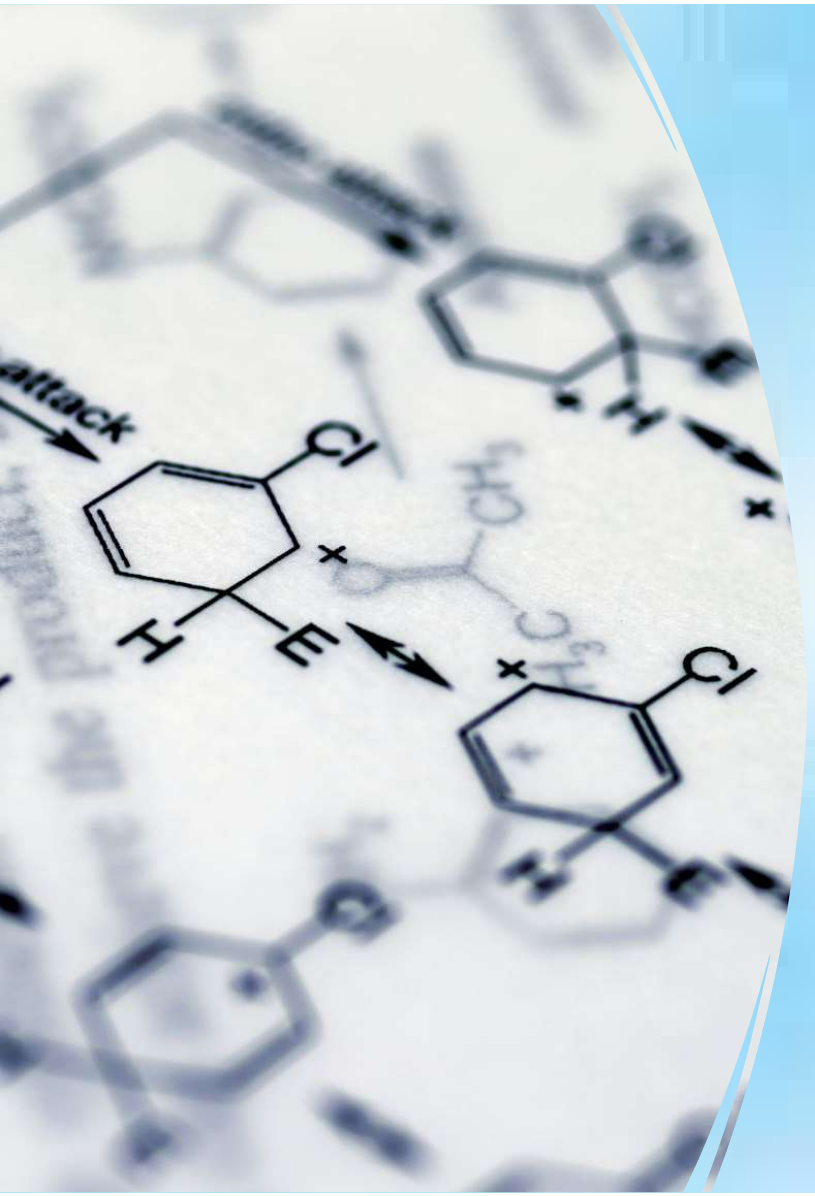
- White curcumin (tetrahydrocurcuminoids) oral liposomal
  - 50mcg/LPT
  - Chew/swallow 1 LPT BID
  - Improves bioavailability

Hewlings SJ, et al. Curcumin: a review of its effects on human health. Foods. 2017;6(10):92.

# Salidroside

- Salidroside major compound found in Rhodiola (*Rhodiola rosea*)
- Most studied phytochemical found in Rhodiola – with > 680 scientific studies on PubMed
- Improved oxygen uptake during exercise
- Improved VO2 max
- Improved energy/endurance
- Improved physical and mental performance
- Decreased mood disturbances
- Dose= oral liposomal salidroside 98% - 30mg per LPT, 2 times daily

Fintelmann V, Gruenwald J. Efficacy and tolerability of a Rhodiola rosea extract in adults with physical and cognitive deficiencies. Adv Ther. 2007 Jul-Aug;24(4):929-39.
Han J, et al. Therapeutic potential and molecular mechanisms of salidroside in ischemic diseases. Front Pharmacol. 2022;13:974775.



# Peptide and Aging Processes

- Peptides Can Support Aging Processes
  - Mitochondrial dysfunction
  - mTOR pathway
  - Insulin-like signaling (ILS) pathway
  - AMPK pathway
  - Decreased epigenetic alterations
    - Modifications in DNA methylation patterns, histones, and chromatin transformation
  - Sirtuin upregulation
  - Telomere lengthening
  - Inflammation signaling

# FOXO4-DRI (D-Retro-Inverso)

- FOXO4-DRI = Synthetic senolytic peptide
- Endogenous FOXO4 (forkhead box 04)
- Selectively induces apoptosis of senescent cells
- “Reversing” effects of aging
- Designed to block the interaction of FOXO4 with p53 protein
  - FOXO4 normally binds with P53 to induce cellular senescence

Le HH, et al. Molecular modelling of the FOXO4-TP53 interaction to design senolytic peptides for the elimination of senescent cancer cells. eBioMedicine. 2021;73:102646.

# FOXO4-DRI (D-Retro-Inverso)

- FOXO4-DRI allows for:
  - Elimination of senescent cells
  - Improved organ function
  - Decreased biological aging

- FOXO4-DRI impacts:
  - Insulin signaling
  - Cell cycle regulation
  - Oxidative stress signaling pathways
    - Including kidneys

Le HH, et al. Molecular modelling of the FOXO4-TP53 interaction to design senolytic peptides for the elimination of senescent cancer cells. eBioMedicine. 2021;73:102646.

# FOXO4-DRI

- FOXO4-DRI also reported in laboratory and human studies to:
  - Counteract Chemotherapy-Induced Senescence and Loss of Liver Function
  - Counteract Frailty and Loss of Renal Function- lab studies
  - Improve hair loss – lab studies

Baar, MP, et al. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. Cell. 2017;169:132–147.

# FOXO4-DRI Testosterone

- Alleviates age-related testosterone secretion insufficiency by targeting senescent cells

- FOXO4 expressed in human Leydig cells
  - its translocation to the nucleus in the elderly related to decreased testosterone synthesis

Zhang C, et al. FOXO4-DRI alleviates age-related testosterone secretion insufficiency by targeting senescent Leydig cells in aged mice. Aging (Albany NY). 2020;12(2):1272-84.

# FOXO4-DRI Dosage

- SubQ
  - 10mg/ml
  - 4 mg SQ every 3 days for 4-6 weeks
  - Repeat this cycle 1-3 times per year
- Well tolerated in recommended dosages
- Only use TFA free – trifluoroacetic acid

- Note: Noni fruit (Morinda citrifolia) reported to upregulate FOXO protein transcription factors; 500mg 2x daily std. 3-4% polysaccharides

Zhang C, et al. FOXO4-DRI alleviates age-related testosterone secretion insufficiency by targeting senescent Leydig cells in aged mice. Aging (Albany NY). 2020;12(2):1272-84.

# Thymulin

- Thymulin is zinc dependent nonapeptide
- Produced by thymic epithelial cells
- Endocrine-Immune modulatory
- Stimulates release of GH, PRL, LH, and FSH
- Prolactin can stimulate Thymulin synthesis and secretion through Prolactin-Thymulin axis
- Thymulin levels are low in immunodeficiency and autoimmune diseases

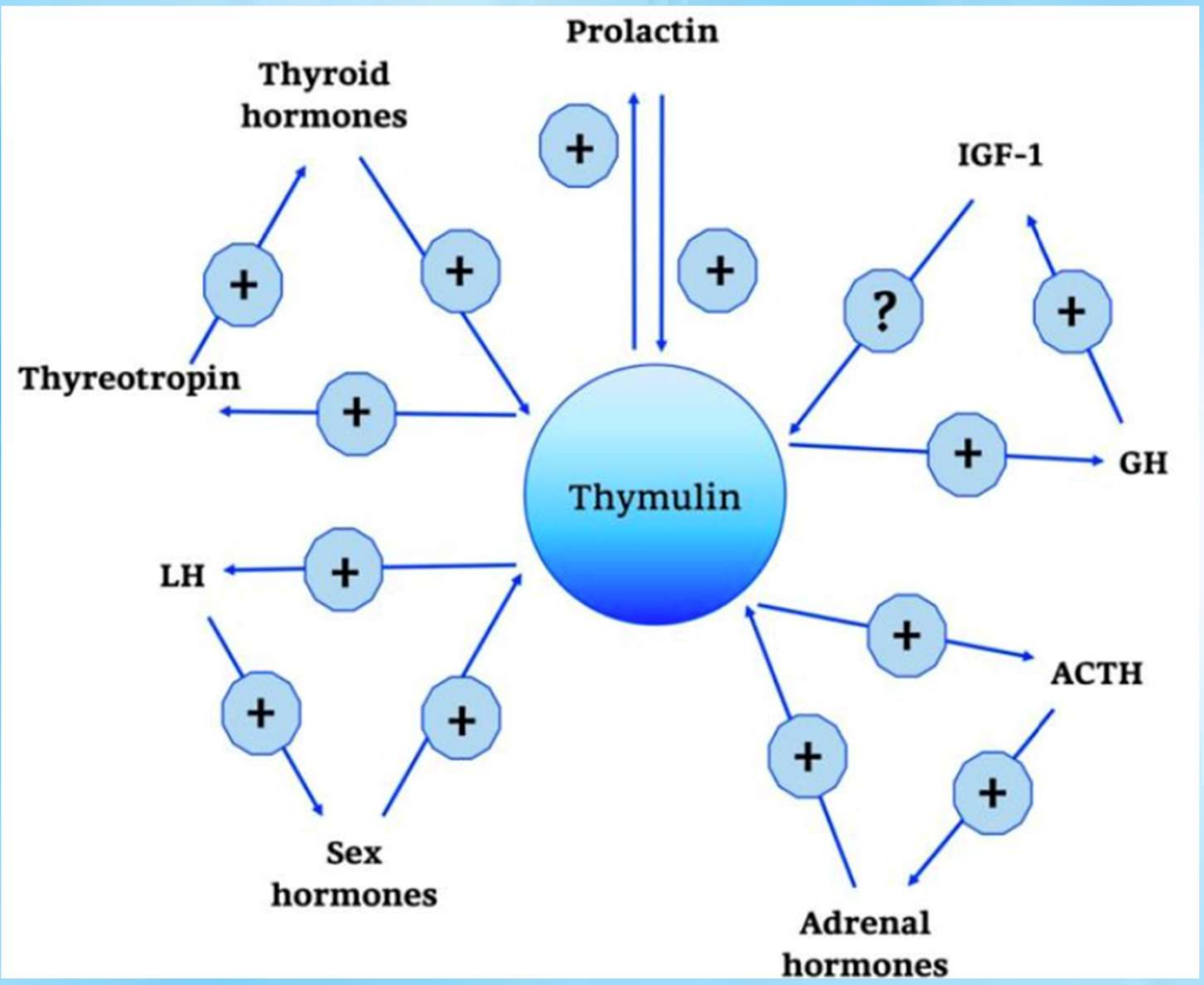
Lunin SM, et al. Thymulin, a thymic peptide, prevents the overproduction of pro-inflammatory cytokines and heat shock protein Hsp70 in inflammation-bearing mice. Immunol Invest. 2008;37(8):858-70.

# Thymulin vs. Thymalin

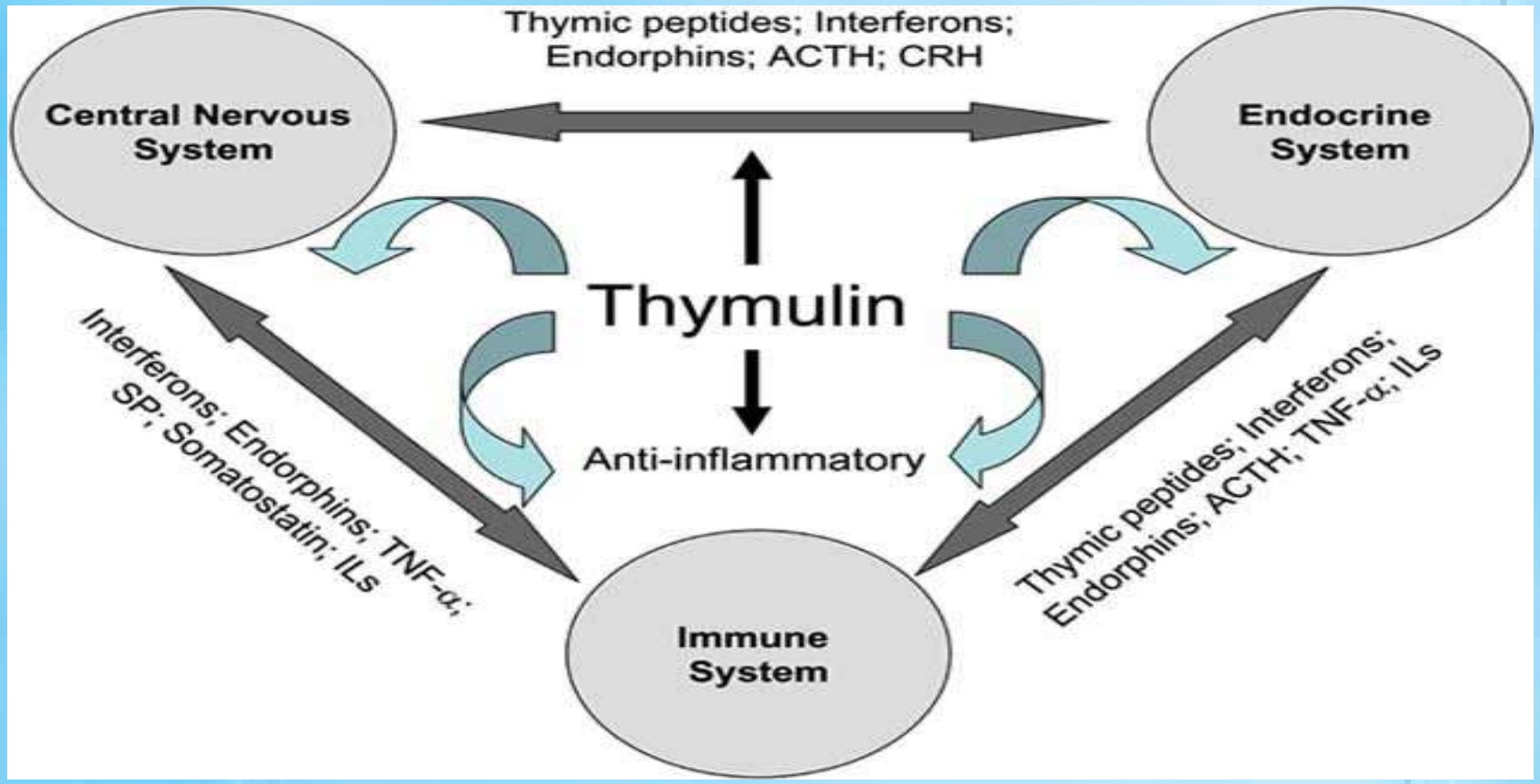
- Both immunomodulatory but different mechanisms
- Thymalin is much shorter peptide than **thymulin**
- Thymalin is a peptide bioregulator – 2 amino acids
- Thymalin is 1st peptide bioregulator discovered in 1981
- Thymalin helps regulate gene expression in the thymus
- **Thymulin** is a nonapeptide - H-Pyr-Ala-Lys-Ser-Gln-Gly-Gly-Ser-Asn-OH
- Thymulin is a signaling molecule
- Thymulin is produced by the thymus to support immunity after signal by thymalin

Lunin SM, et al. Thymulin, a thymic peptide, prevents the overproduction of pro-inflammatory cytokines and heat shock protein Hsp70 in inflammation-bearing mice. Immunol Invest. 2008;37(8):858-70.

# Thymulin – Multisystem Modulation




Lunin SM, et al. Thymulin, a thymic peptide, prevents the overproduction of pro-inflammatory cytokines and heat shock protein Hsp70 in inflammation-bearing mice. Immunol Invest. 2008;37(8):858-70.




Haddad JJ, et al. Thymulin: an emergin anti=inflammatory molecule. Curr Med Chem. 2005;4:333-38.

# Thymulin

- Supports Th1/Th2 balance
- Induces differentiation of T cells
- Enhances T cell function
- 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.

# Thymulin

- Anti-inflammatory/analgesic activity
  - acts directly on the afferent nerve terminals through prostaglandin-E2 (PGE2)-dependent mechanisms

- Most studies of Thymulin in humans conducted during 1980s in:
    - rheumatoid arthritis, multiple sclerosis, Di-george syndrome, nephrotic syndrome, immunodeficiency and SLE cases

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.

# Thymulin – Rheumatoid Arthritis Study

- 1987, 2 Double blind, randomized, placebo-controlled studies on Nonathymulin and rheumatoid arthritis
- Study #1 = 49 patients - study #2 = 30 patients
- Used 1mg, 5mg, 10mg/day SQ x 6 mo
- Significant clinical improvement as evaluated by the global assessment of all patients who entered the trials
- T cell improvement
- Nonathymulin 5 mg proved to be the most efficient dose
- Side Effects - 2 patients had SE's receiving 5mg daily
  - 1 patient – peripheral thrombocytopenia at month 3
  - 1 patient – vasculitis at month 5
  - Other SE's malaise, painful injection

Amor B, et al. Nonathymulin in rheumatoid arthritis: two double blind, placebo-controlled trials. Annals Rheu Dis. 1987;46:549-54.

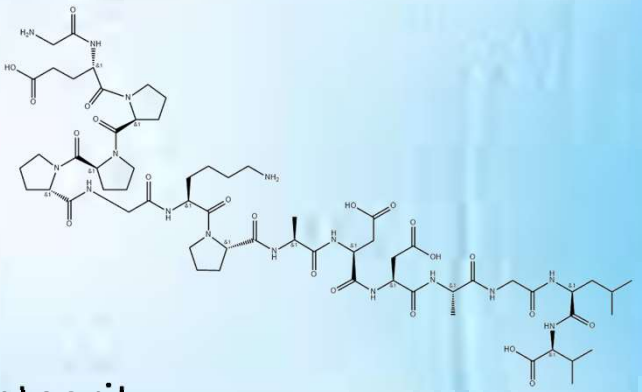
# Thymulin Dosage

- Thymulin has short t-1/2 = 30-60 min
- However, longer duration of drug effect on T lymphocytes (24-48 hour)
- Dosage :
  - **1 thymulin SQ daily for 2 weeks, then 1mg three times weekly x 4 months**
  - **May increase dosage to 5mg SQ in acute needs**
  - No documented side effects

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.

# GUT Peptide – BPC-157

- BPC-157 – body protection compound
  - GUT-BRAIN axis
  - Musculoskeletal/recovery support
  - Wound healing
- BPC normally found in gastric juices



- Gastric protection – helps maintain GI mucosal integrity
- Supports  connective tissues

Sikiric P, et al. Focus on ulcerative colitis: stable gastric pentadecapeptide BPC 157. Curr Med Chem. 2012;19(1):126-32.

# BPC 157

- Gastric protection
  - Antiulcer peptidergic agent
  - Cytoprotective
  - Nitric Oxide (NO) improvement
    - BPC 157 interacts with nitric oxide (NO)
    - system, both NOS-substrate (L-arginine) and NOS-blocker (L-NAME), including the regulation of a blood pressure
  - Helps improve GI mucosal integrity
  - Ulcerative colitis in lab studies
  - Decreases NSAID and alcohol gastric side effects



Sikiric P, et al. Focus on ulcerative colitis: stable gastric pentadecapeptide BPC 157. Curr Med Chem. 2012;19(1):126-32.

# BPC 157

- Wound healing
  - Reported to improve cell survival under heightened oxidative stress
  - Increases fibroblast migration and dispersal
  - Induces F-actin formation  in fibroblasts
  - Improves angiogenesis
  - Enhances vascular expression of  VEGFR2
  - Increases the extent of phosphorylation of paxillin and FAK proteins without affecting the amounts produced
- Used in deep skin burns, corneal injuries
- Injured muscle, tendon, ligament or bone
- Performance Recovery – WADA prohibited !



Duzel A, et al. Stable gastric pentadecapeptide BPC 157 in the treatment of colitis and ischemia and reperfuction in rates: new insights. World J Gastroenterol. 2017;23(48):8465-88.

# BPC 157

- **Neuroprotective**
  - Influences serotonergic,  dopaminergic, opioid and GABAergic systems
  - Improves nerve regeneration
  - Decreases neuroinflammation
  - May help in depression
  - Ameliorates alcohol withdrawal symptoms and opposes alcohol intoxication

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

# BPC 157

- **Cardioprotective**
  - May help regulate blood pressure
  - Nitric oxide improvement
  - BPC 157 rapidly and permanently counteracts the QTc prolongation induced by neuroleptics (such as haloperidol, fluphenazine, clozapine, olanzapine, quetiapine) and prokinetics

Strinic D, et al. BPC 157 counteracts QTc prolongatino induced by haloperidol, fluphenazine, clozapine, olanzapine, quetiapine, sulpiride and metoclopramide in rats. Life Sciences. 2017;186(1):66-79.

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des, 2014;20(7):1121-35.

# BPC 157 -Dosage

- Oral
  - 500mcg – 1.5mg daily x 30 days OR
  - 1mg troche sublingually QD x 30d
  - Oral liposomal tab (LPT) – 250mcg per LPT, chew and swallow 1 BID

  - Can Combine with KPV peptide

# BPC 157 -Dosage

- Note - Corticosteroids reported to reduce BPC-157's ability to heal
- Results can be spontaneous and improve over 2-4 weeks treatment
- Safe in recommended dosages
- As of 2023 - prohibited by WADA

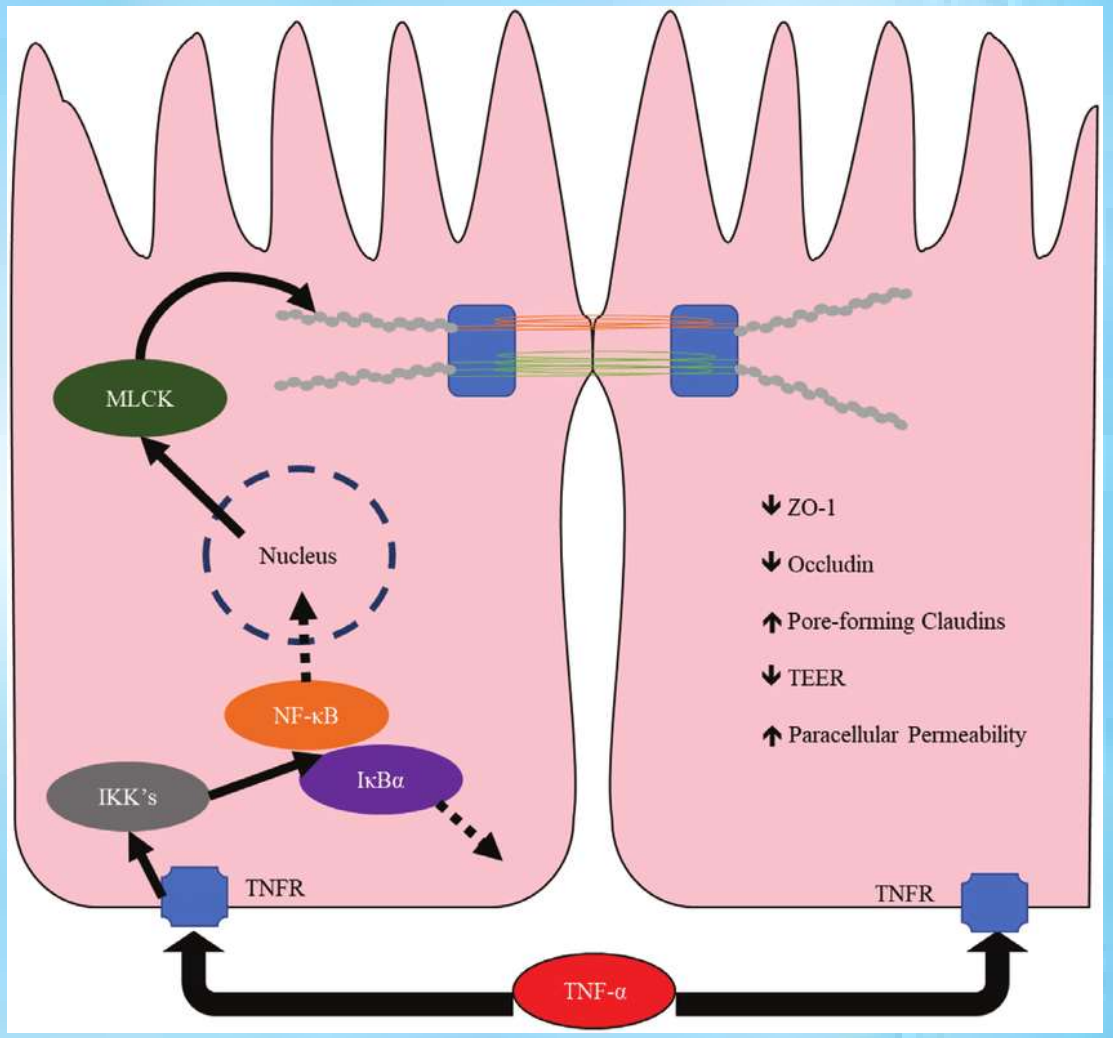
# KPV

- Synthetic analogue of alpha-melanocyte stimulating hormone
- 3 amino acids : Lys-Pro-Val
- **Anti-inflammatory peptide – metaflammation**
- GUT supportive
- Immune modulating
- Decreases the inflammatory response by inhibiting proinflammatory cytokine synthesis and secretion
- Potent TNF-alpha suppressor
- Reported to stop proinflammatory mechanisms in both intestinal epithelial cells and immune cells



Kannengiesser K, et al. Melanocortin-derived tripeptide KPV has anti-inflammatory potential in murine models of inflammatory bowel disease. Inflam Bowel Dis. 2008;14(3):324-31.

By regulating TNF-alpha, KPV helps restore tight junction function and helps prevent intestinal leakage




Kannengiesser K, et al. Melanocortin-derived tripeptide KPV has anti-inflammatory potential in murine models of inflammatory bowel disease. Inflam Bowel Dis. 2008;14(3):324-31.

# KPV

- Used in Inflammatory Bowel Diseases – Crohn's disease, Ulcerative Colitis
- Autoimmune potential
- Skin issues – psoriasis, eczema, dermatitis, ulcers, wound healing/scar formation
- Advantages over current therapeutics including infliximab (Remicade/Inflectra) and adalimumab (Humira)
  - KPV doesn’t form systemic antibodies like the PHARMA
  - Monoclonals have substantial potential SEs

Kannengiesser K, et al. Melanocortin-derived tripeptide KPV has anti-inflammatory potential in murine models of inflammatory bowel disease. Inflam Bowel Dis. 2008;14(3):324-31.

# KPV

- KPV's ability to target TNF-alpha in the GUT is unique
- KPV is a small molecule – can use orally, SubQ and transdermally
  - SubQ currently on FDA's Cat. 2 list
- Lack of pigmentary activity unlike alpha-MSH

- Dosage: orally 500mcg BID
- Addition of BPC-157 (500mcg) has synergistic healing effects on the GUT

Kannengiesser K, et al. Melanocortin-derived tripeptide KPV has anti-inflammatory potential in murine models of inflammatory bowel disease. Inflam Bowel Dis. 2008;14(3):324-31.

# Additional Biological Aging Markers

- Glucose/insulin
- Glycans
- IgG Glycosylation
- DNA methylation
- GAL-3

# Blood Glucose and Insulin

- Diabetes and impaired glucose tolerance affect a substantial proportion of older adults
- Diabetic population in US = 40% over 65 years
  - 20% 65 and older have diagnosis of T2D
  - Nearly that many are undiagnosed (approx. 16%)
- Accelerated aging is associated with elevated levels of both glucose and insulin
- Targeting healthy blood glucose and insulin are imperative for anti-aging protocols
- Aging increases the risk of T2D

www.CDC.org, Accessed Aug 2022.

# Leukocyte Telomere Length Independently Predicts 3-Year Diabetes Risk in a Longitudinal Study of Chinese Population

- 108 Non-diabetics  measure 3 yr follow up
- Baseline LTL (leucocyte telomere length)
- Mitochondrial DNA (MTDNACN)
- 8OHDG
- TNF alpha
- SOD

*"Cellular aging markers, including telomere length and mitochondrial function, as well as oxidative stress and inflammation markers influence each other and form a complex network, which is affected in diabetes.*

*Baseline LTL was found to be independently associated with the development of diabetes at the 3-year follow-up after the adjustment for mtDNAcn, markers of oxidative stress and inflammation, and conventional diabetes risk factors."*



Liu Y, et al. Oxid Med Cell Longev. 2020;2020:9256107.

SCIENTIFIC REPORTS
nature research

# Leukocyte telomere length is associated with elevated plasma glucose and HbA1c in young healthy men independent of birth weight

L. G. Grunnet, K. Pilgaard, [...], and C. Brøns

# GLUCOSE TARGET RANGES

- Fasting blood glucose
  - Alert Low = <65
  - Trending Low = 65-72
  - OPTIMAL = 73-89
  - Trending high = 90-99
  - Alert High = >99

- Postprandial
  - 1 hr Target = < 125
  - 2 hr target = < 95

# Insulin Ranges -Quest

- Range = 2 – 19.6 micro IU/ml
- Optimal = 3-9
- Trending hi = 9-19.6
- Hi = > 19.6

# Insulin Resistance Landmark Study

- 46,578 members of Kaiser Permanente Northwest
- FPG levels < 100 mg/dL (Jan '97-Dec 2000)
- No previous diagnosis of diabetes or impaired fasting glucose
- Subjects assigned to 1 of 4 categories (<85, 85-89, 90-94, or 95-99 mg/dL)
- Followed until developed diabetes, died, left the health plan, or until April 30, 2007
- Cox regression analysis--estimated risk of incident diabetes, adjusted for age, sex, body mass index, blood pressure, lipids, smoking, cardiovascular disease, and hypertension

Nichols GA, Hiller TA, Brown JB. Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis. Am J Med. 2008;121(6). 519-524.

# Study Results and Conclusions

- Every glucose rise of 1 point  above 84, was correlated with a 6% increased risk of developing Type 2 diabetes

- **Insulin resistance, which leads to Type 2 diabetes, is developing at least a decade before detection by traditional lab markers**

Nichols GA, Hiller TA, Brown JB. Normal Fasting Plasma Glucose and Risk of Type 2 Diabetes Diagnosis. Am J Med. 2008;121(6). 519-524.

# Fasting Plasma Glucose and T2D Risk – Updated Study

- 2022 long-term retrospective study
- N= 37,148 Japanese individuals w/ normal plasma glucose
- In 10 years, 1,028 patients developed T2D
- Cox regression analyses reveal:
  - **Risk for onset of T2D increased by 9.0 % per 1mg/dL increase in fasting plasma glucose from 90 – 99 mg/dL**

Munekawa C, et al. J Diabetes Invest. 2022;13:453-59.

# Bottom Line

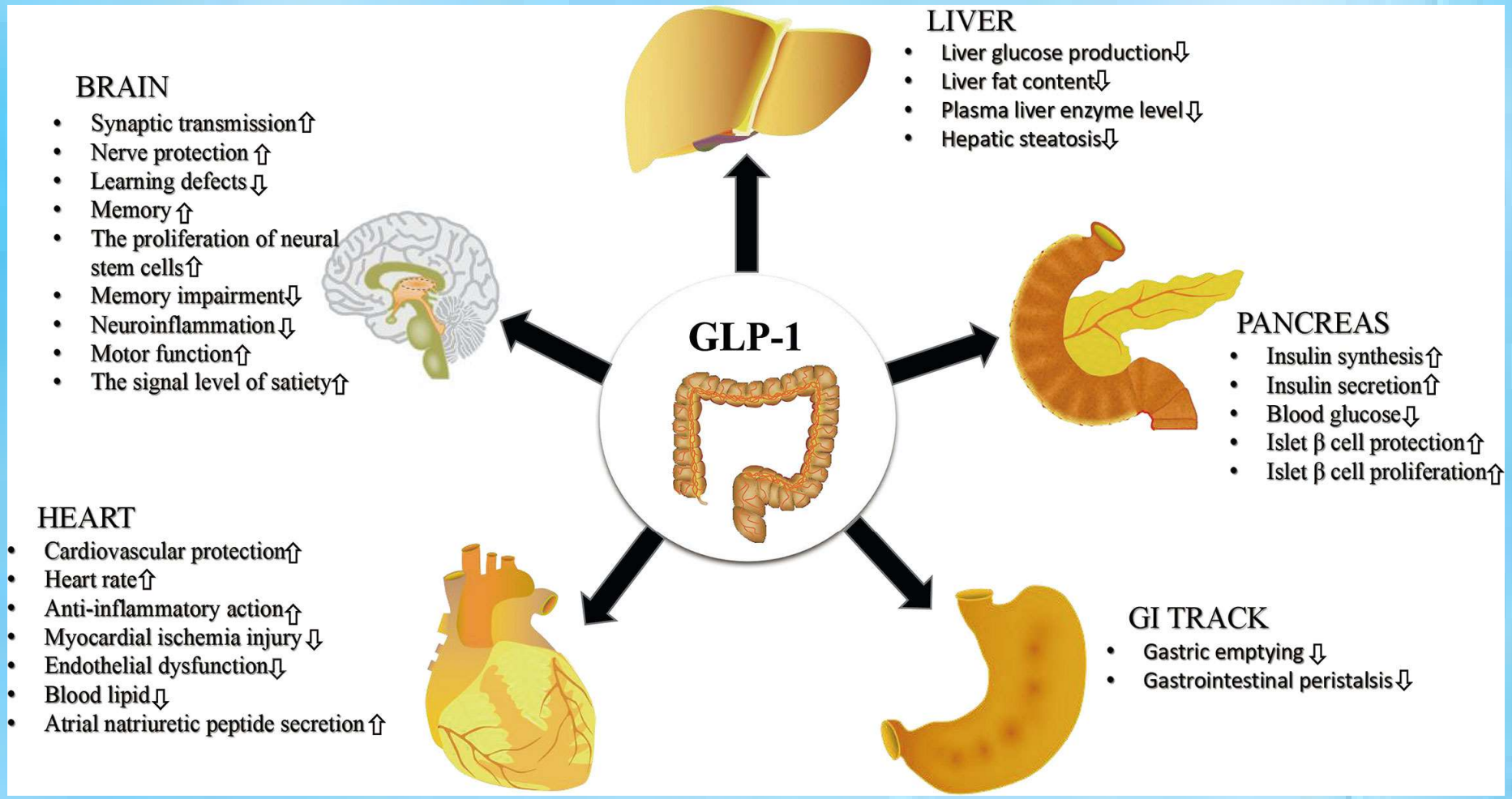
- RISK of T2D increases by 9 % for every point above 90mg/dL fasting plasma glucose

Munekawa C, et al. J Diabetes Invest. 2022;13:453-59.

# Glucagon-like peptide-1 Receptor Agonist (GLP-1 RA)

- Effects on multiple organ systems including pancreas, cardiovascular and renal
- Established efficacy and safety
- Individual GLP-1 RAs
  - Differences of molecular size, structure and duration of action provides differing pharmacodynamics and clinical effects
  - Degree of glycemic control
  - Weight loss abilities
  - Cardiovascular effects
  - Tolerability/Side Effects profiles

Cornell S. A review of GLP-1 receptor agonists in type 2 diabetes: A focus on the mechanism of action of once-weekly agents. J Clin Pharm Ther. 2020;45(Suppl1):17-27.





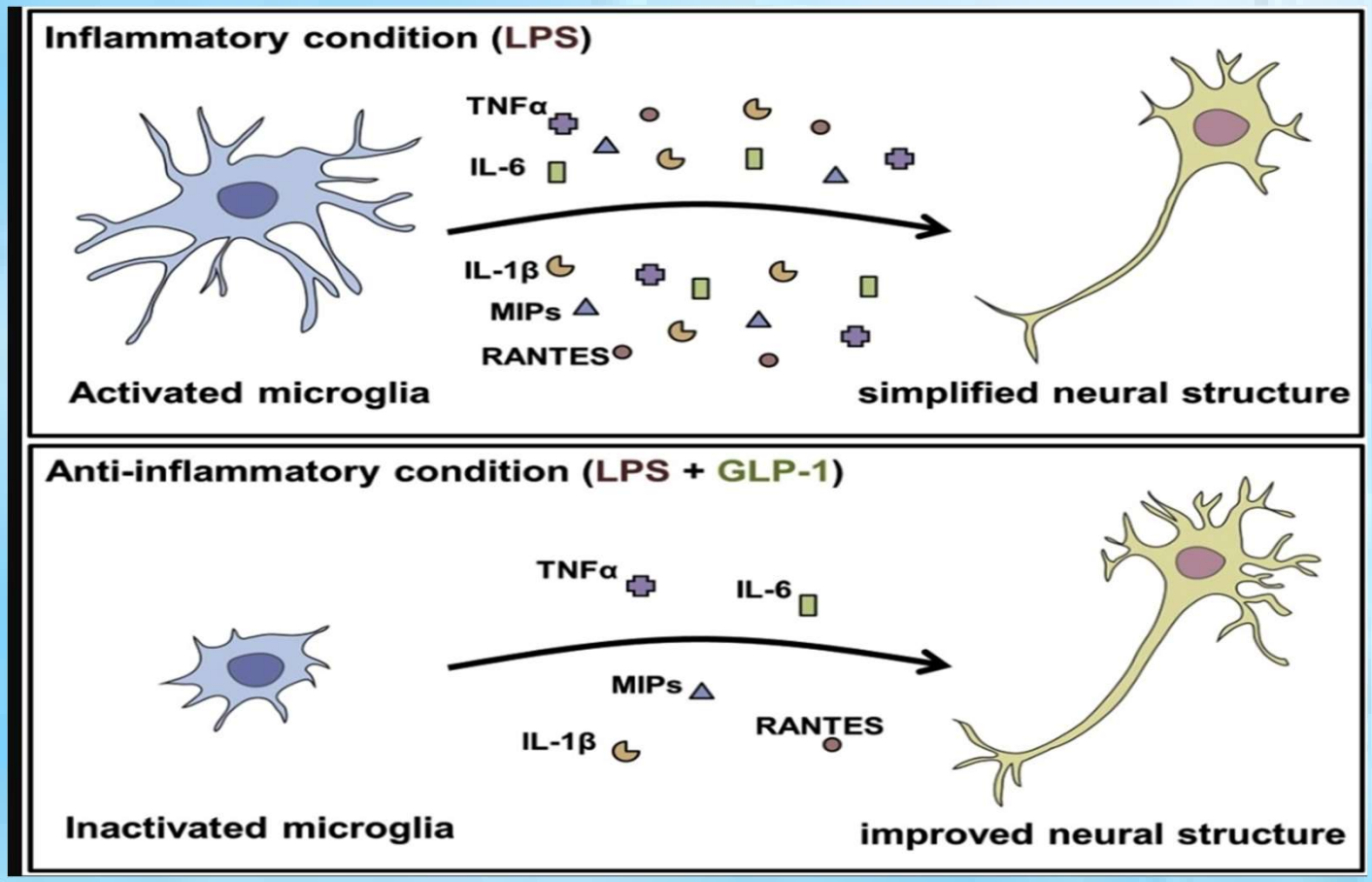

Zhao X, et al. GLP-1 receptor agonists: beyond their pancreatic effects. Front Endocrinol (Lausanne. 2021;12:721135

# New Research – GLP-1 and Neuroprotection

- GLP-1 reported to suppress neuroinflammation
- Brain and GUT derived GLP-1 activity (thru GUT/Brain axis)
- Inhibits lipopolysaccharide (LPS)-induced inflammation in microglia
- Suppresses tumor necrosis factor-alpha (TNF-α)-associated cytokines and chemokines in microglia
- Improves mitochondrial function and cell survival
- Improves neural structure
  - Enhanced neurite complexity = neurite length, number of neurites from soma, and secondary branches
  - Improved synaptic plasticity

Yoon G, et al. Glucagon-like-peptide-1 suppresses neuroinflammation and improves neural structure. Pharmacological Res. 2020;152:104615.

# GLP-1 Effect on Neuroinflammation






Yoon G, et al. Pharmacological Res. 2020;152:104615.

# New Research – GLP-1 and Neuroprotection

- Helps regulate memory
  - Activation of autophagy
  - Decreased neuroinflammation
  - Inhibits hippocampal neuronal loss
  - Inhibiting neuronal cell death
  - Promotes neurogenesis

- Brain derived GLP-1 also reported to improve glucose metabolism and insulin resistance in the brain

- Potential uses in Parkinson's and Alzheimer's



Yoon G, et al. Glucagon-like-peptide-1 suppresses neuroinflammation and improves neural structure. Pharmacological Res. 2020;152:104615.

# Semaglutide

- FDA approved GLP-1 agonist
- PHARMA:  Ozempic, Rybelsus, Wegovy
- Improves glycemic control via improved

Insulin secretion

- Improves weight loss

Wilding JPH, et al. Once weekly semaglutide in adults with overweight or obesity. NEJM. 2021;384(11):989.

# Semaglutide

- Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

- Also indicated to reduce risk of major adverse cardiovascular events (MACE) (eg, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in adults with T2DM and established cardiovascular disease

Wilding JPH, et al. Once weekly semaglutide in adults with overweight or obesity. NEJM. 2021;384(11):989.

# Semaglutide

**Benefits**

- Decrease in body fat
- Decrease in weight
- May suppress appetite
- Improved blood sugar regulation
- Insulin control
- Food craving reduction
- Beneficial effects on renal function

Wilding JPH, et al. Once weekly semaglutide in adults with overweight or obesity. NEJM. 2021;384(11):989.

# Semaglutide Lean Muscle Loss?

- 2024 study looked at 6 randomized clinical studies w/ 1,541 overweight or obese adults
- Significant weight reductions were observed primarily due to fat mass loss
- Lean mass remained stable in some cases, but notable reductions ranging from almost 0% - 40% of total weight reduction were observed in others
- Noteworthy decreases in lean mass were particularly evident in larger trials, yet proportion of lean mass relative to total body mass increased
  - Suggests a positive overall outcome

Bikou A, et al. A systematic review of the effect of semaglutide on lean mass: insights from clinical trials. Exp Opin Pharmacother. 2024;25(5):611-19.

# Semaglutide SEs/Contraindications

- Transient Side Effects – nausea, vomiting, diarrhea/constipation, abdominal pain; 7% semaglutide vs. 3.1% placebo
- Semaglutide reported in a dose dependent manner to cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in rats/mice
- Unknown how this translates to humans
- Manufacturer recommends contraindication in patients with a personal or family history of MTC and in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2).
- Recommend routine monitoring of serum calcitonin or use of thyroid ultrasound of uncertain value for early detection of MTC in patients receiving semaglutide.
- Suitable for combination with 1 or more antidiabetic medications

Wilding JPH, et al. Once weekly semaglutide in adults with overweight or obesity. NEJM. 2021;384(11):989.

# Semaglutide SubQ Dosage

SubQ

- *For T2D or pre-diabetes - SubQ*

- Start at 0.25 mg (250mcg) once weekly.
- After 4 weeks, increase the dose to 0.5 mg (500mcg) once weekly.
- If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly
- Administer once weekly at any time of day, with or without meals; semaglutide should not be administered daily.
- If a dose is missed administer within 5 days of missed dose
- Inject subcutaneously in the abdomen, thigh, or upper arm; rotate weekly
- Semaglutide injections should appear clear and colorless - Do not use semaglutide if particulate matter and coloration is seen.

- *For Weight Loss - SubQ*
- Start with 100mcg weekly
- If no nausea, increase 50mcg-100mcg weekly until 250-500mcg obtained or until clinical endpoints achieved (no > than 2500mcg [2.5mg] weekly).
- Final dosage is individual and depends on degree of weight loss needed and clinical presentation.
- Some individuals may require T2D and pre-diabetes dosages.

# Semaglutide Dosages - Oral

- Oral dosage (adult):
  - Initially 3 mg once a day for 30 days
  - Then increase to 7mg once daily for 30 days
  - Then 14 mg once a day target dosage if warranted
  - Swallow whole on an empty stomach, at least 30min before eating
  - No dosage adjustment in hepatic or renal impairment
- Oral semaglutide can be initiated 7 days after the last dose of injectable semaglutide administered
  - There is no equivalent dose of oral semaglutide for subcutaneous semaglutide 1 mg weekly per manufacturer
- Can add oral Vitamin B12 (500mcg-1mg) - reduces nausea and GI side effects

# Tirzepatide GIP/GLP-1

- Dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist
- 39 amino acids
- Approved for use in tx of T2D
  - Reduces HbA1c
  - Weight control
  - Improves cardiovascular risk factors

Frias JP, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. NEJM. 2021;285:503-15.

# Tirzepatide Dosage

- Mean half-life of ~5 days
  - Enables once-weekly dosing
- Available in six doses (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg)
- Lily autoinjector
- Side effects reported in at least 5% of patients:
  - nausea, diarrhea, decreased appetite, vomiting, constipation, indigestion (dyspepsia), and stomach (abdominal) pain
- BOX Warning regarding thyroid C-cell tumors
- Tirzepatide contraindicated in patients with:
  - a personal or family history of medullary thyroid carcinoma OR
  - In patients with Multiple Endocrine Neoplasia syndrome type 2

# Retatrutide (LY3437943)

- Phase III development
- Triple hormone receptor agonist for obesity
  - Glucose-dependent insulinotropic peptide receptor (GIPR) agonist
  - GLP-1 receptor agonist
  - Glucagon receptor (GCGR) agonist
- Induces lipolysis in adipocytes  > native GIP
- Delays gastric emptying
- Effective for weight management

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

# Retatrutide Dosage

| Doses | Initial Dose |
|---|---|
| 1 mg | 1 mg |
| 4 mg | 2 mg or 4 mg |
| 8 mg | 2 mg or 4 mg |
| 12 mg | 2 mg |

- Start with initial dose
- IF WEIGHT LOSS IS SATISFACTORY MAINTAIN DOSE
- increase dosage every other week to max dosage depending on tolerability
- 48 weeks total therapy
- T1/2 = 6 days – weekly dosing

Jastreboff AM, et al. N Engl J Med. 2023;389;514-26.

# TB006

- TB006 = experimental antibody-based drug targeting Gal-3
  - Blocks Gal-3 binding
  - Reduces Gal-3 protein aggregation and resulting inflammation
  - Improves cognitive performance

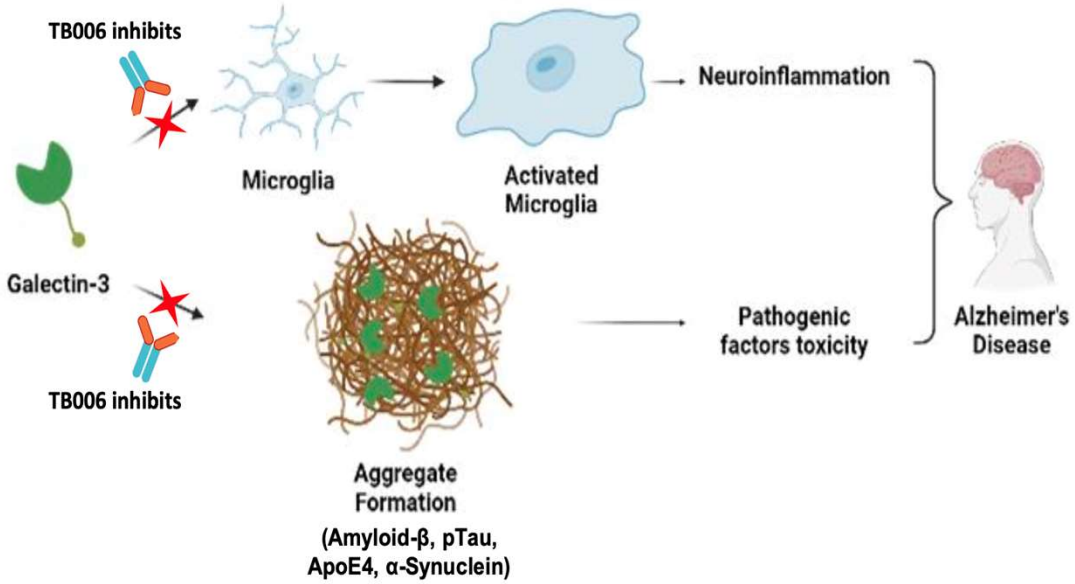
- Phase 1b/2a clinical trials are complete for use in dementias including Alzheimer's

Rasool S, et al. Alz Dementia. 2022;18(S10):DOI:10.1002/alz.060393

# TB006 and Alzheimer's Progression

## Proposed Mechanisms of Action for Alzheimer's Progression

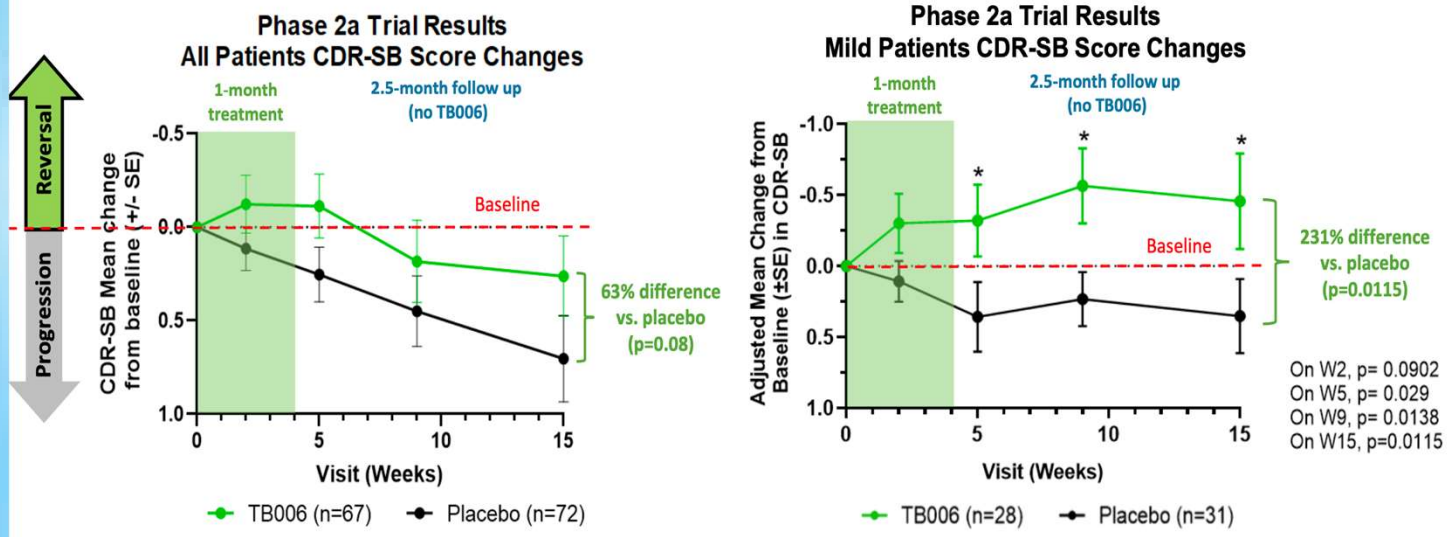
### Gal-3 regulates the neuroinflammatory response via microglia activation




### Gal-3 correlates with pathogenic factor toxicity via aggregation/oligomerization

# TB006 Phase 2a Study – 1 month

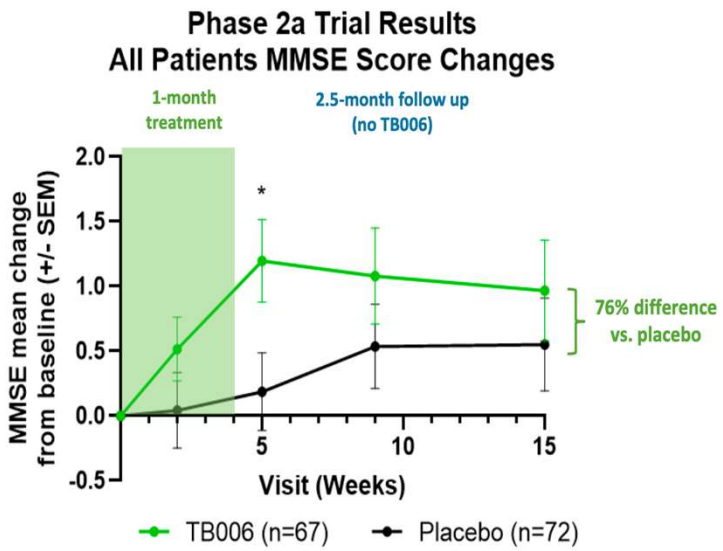
## Phase 2a: Significant Improvements in CDR-SB after One Month

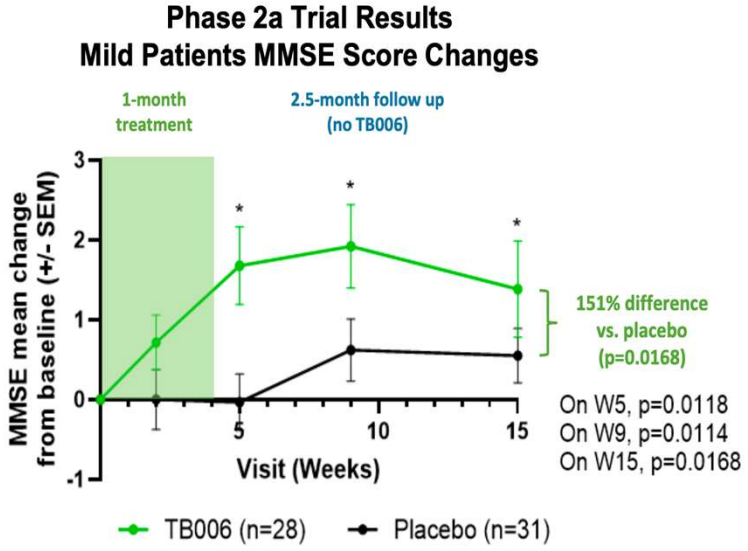



- Whole patient population included mild, moderate, and severe dementia (initial CDR-SB range 0.5 - 16)
- Signs of reversal observed in one month of treatment
- Statistically significant, sustained reversal and/or improvement in mild patients (231% difference by the end)

# TB006 Phase 2a Study – MMSE Improvements after 1 month

## Phase 2a: Significant Improvements in MMSE after One Month

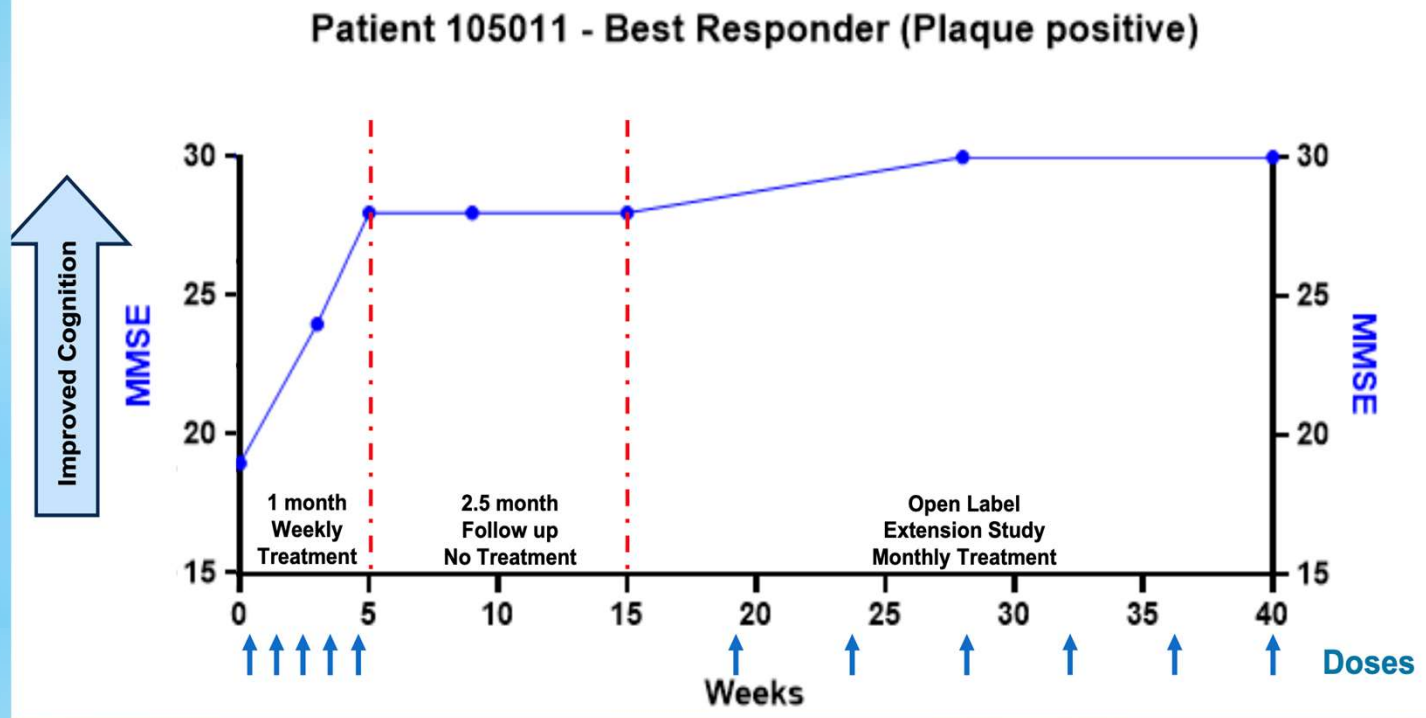



- Whole patient population included mild, moderate, and severe dementia (initial MMSE range 2 - 24)
- Statistically significant improvement observed in one month of treatment
- In mild patients, improvement in MMSE scores was maintained during the 2.5 month follow-up period

# TB006 Phase 2a Study – MMSE 6 months

## One Patient Improved MMSE from 19 to 30 in Six Months



# TB006 Phase 2a Study – Adverse Events

## TB006-related Adverse Events: Low Incidence, All Non-serious

### TB006-related Adverse Events From Phase 2a Trials

| Description | TB006 1000 mg/week dose (n=63) | Placebo (n=66) |
|---|---|---|
| Infusion-related reaction | 2 | 0 |
| Dizziness | 1 | 0 |
| Phlebitis | 1 | 0 |

- All reported TB006-related adverse events were non-serious
  - Resolved with little to no intervention
  - Many could be infusion-related
- No amyloid-related imaging abnormalities (ARIA) in phase 2a trials
- Over an average 8-month treatment period, 1 of 119 patients from Open Label Extension study had asymptomatic ARIA (incidence rate of 0.8%)

# ATX-304

- Increase fatty acid metabolism and lipolysis in adipose tissue and liver
- Increase energy expenditure and cause significant weight loss effects in diet-induced obese mice while increasing food intake
- Increase glucose uptake in target tissues such as skeletal and heart muscle to restore cellular energy balance
- Improve cardiovascular performance, increasing stroke volume and exercise endurance in aged mice

Steinberg GR, Hardie DG. New insights into activation and function of the AMPK. Nature Rev Mol Cell Biol. 2023;24:255-72.

# ATX-304

Potential Uses:

- Metabolic support – alternative to GLP-1s
  - Glucose homeostasis - Type 2 diabetes support
  - Weight management support
- Improved autophagy
- Cardiovascular support
- Improved microvascular perfusion in skeletal muscle
- Renal protection
- Decreased oxidative stress
- Pain/inflammation

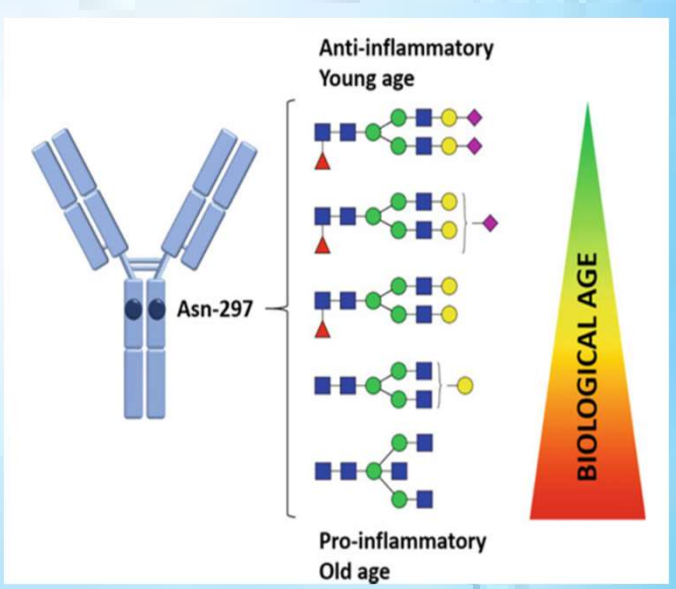
Steinberg GR, Hardie DG. New insights into activation and function of the AMPK. Nature Rev Mol Cell Biol. 2023;24:255-72.

# ATX-304

Dosage: 100mg orally daily for 4-6 weeks

# A Comprehensive Biological Age Test – Glycan Aging

- Science-based testing
- Reveals age of the **immune system and degree of inflammation present**
- Biological age is NOT a fixed variable
- Useful in:
  - Anti-aging therapies
  - Lifestyle improvement
  - Improving resiliency
  - Measuring and improving fitness recovery

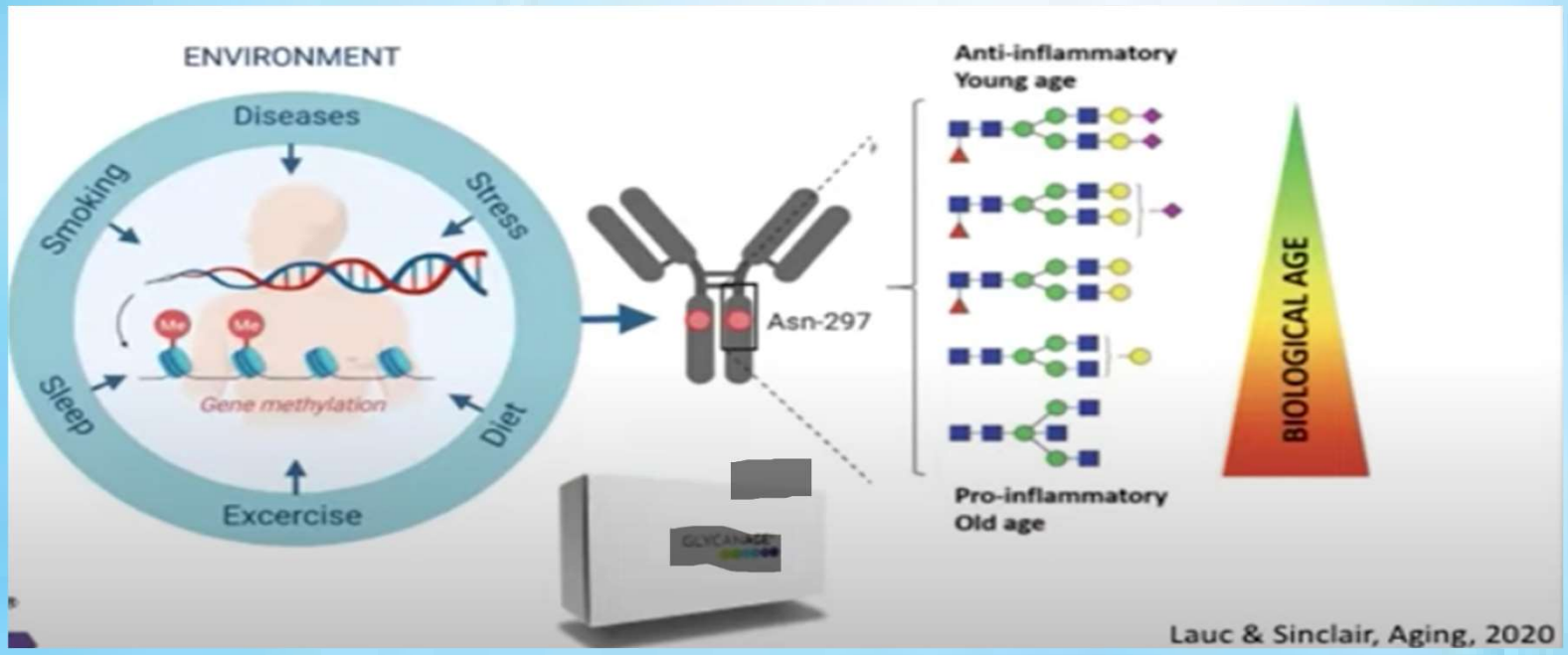


# Biological Aging and IgG Glycosylation

- Effects of aging on protein N-glycosylation used to determine biological age
- IgG measured in human serum or plasma
- Kristic and colleagues combined four European cohorts to study IgG glycosylation in aging
  - Results: Aging-Glycan Aging associated with lab variables such as fibrinogen, HbA1c, BMI, triglycerides and uric acid after correction for age and sex

Kristic J, et al. Glycans are a novel biomarker of chronological and biological ages.J. Gerontol. A Biol. Sci. Med. Sci. 2014; **69**: 779-789

# Testing IgG glycosylation quantifies functional effectors of aging that integrate genetic information, epigenetics and environmental factors



# Glycan Aging Testing Measures:

Ways to improve biological aging

- Impact of systems biology approach to aging
- Impact of dietary changes
- Impact of Exercise
  - Training and recovery impact
  - Impact of bodybuilding
- Impact of supplements – nutrients
- Impact of lifestyle changes
  - Stress control, job and home dynamics, sleeping habbits

Etc…