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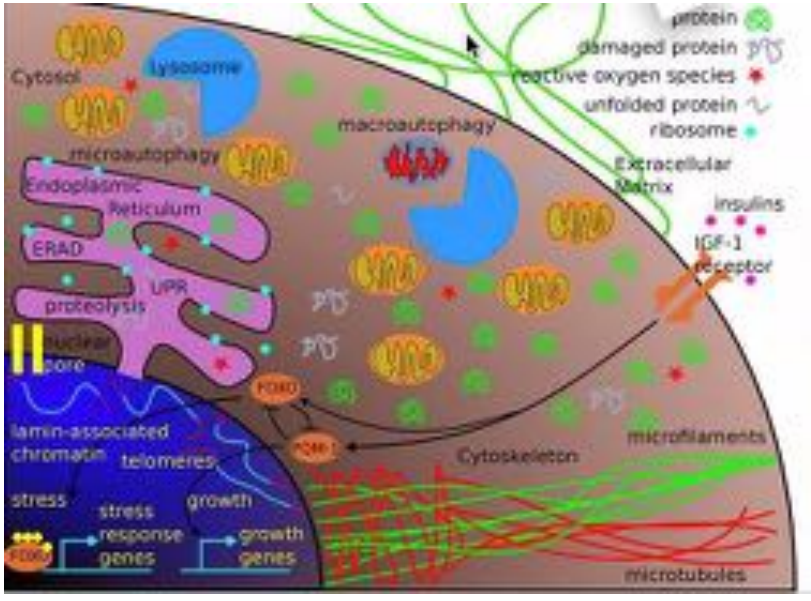
Synolytics The Science of Longevity

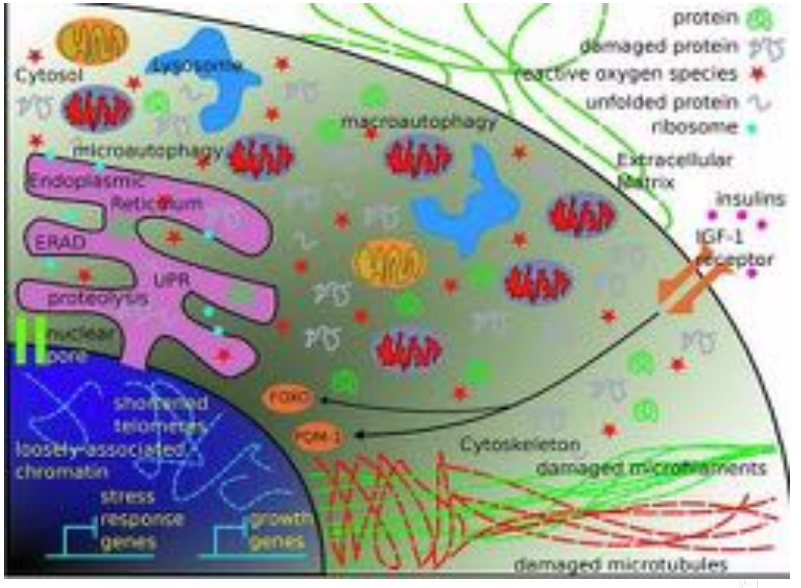
Joseph Cleaver MD

Cell Senescence

A. Young Cell



B. Old Cell



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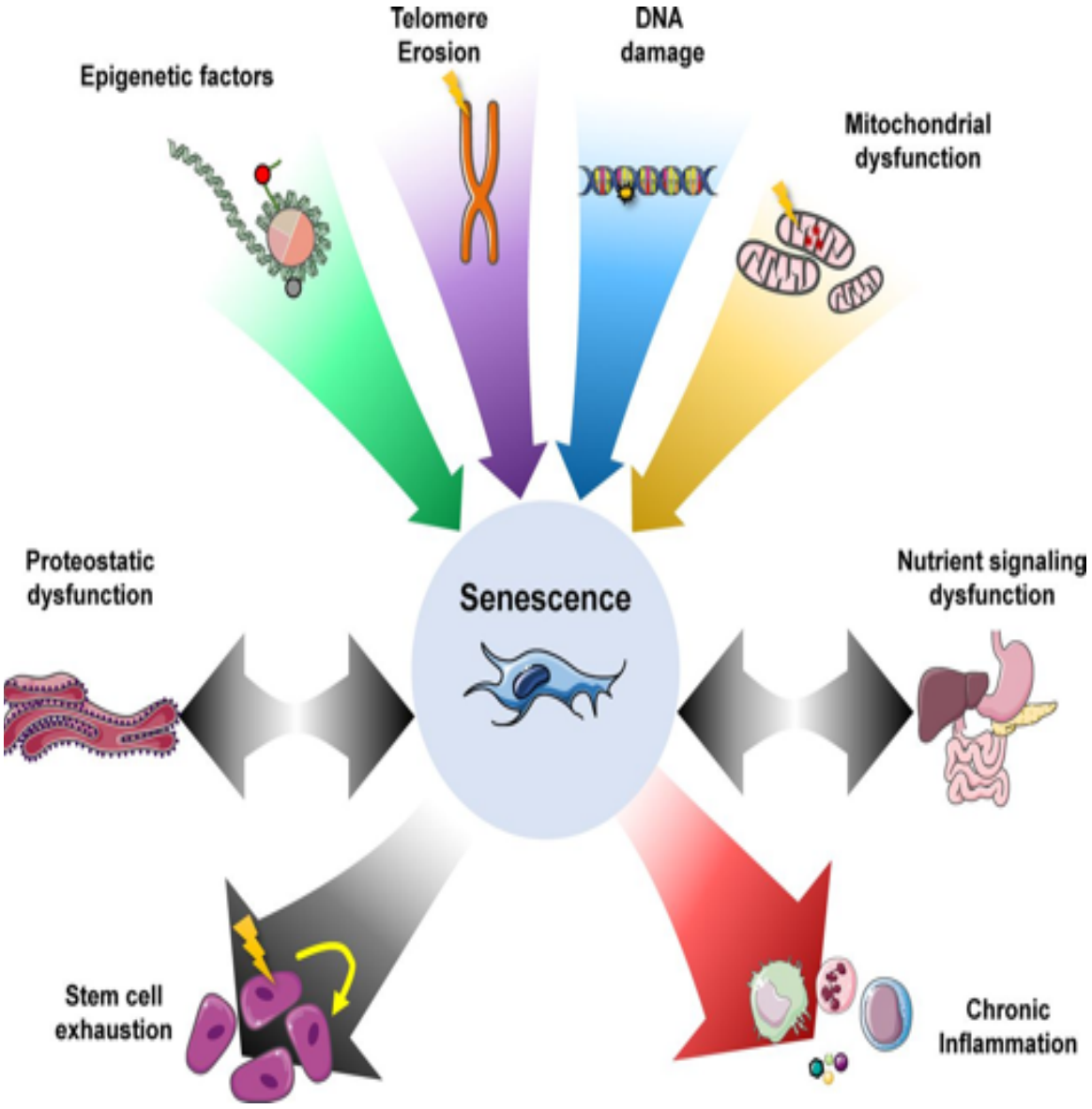
Cell Senescence



Stem cell exhaustion
Chronic inflammation

Senescence-associated secretory phenotype (SASP)

The two sides of senescence

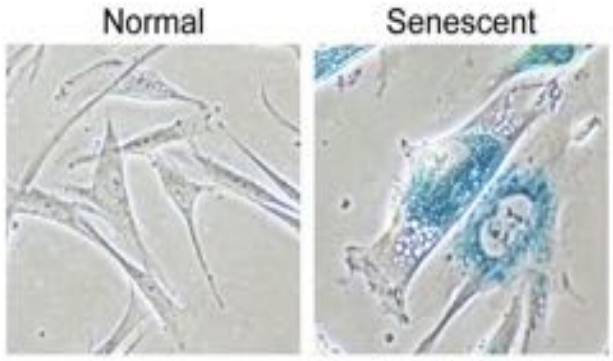
Irreversible Growth Arrest

- Cell autonomous tumor suppression

Inflammatory Secretory profile

- Alteration of the microenvironment
- Stimulation of malignancy phenotypes
- Global tissue degeneration

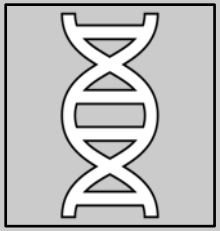
- √ Resistance to apoptosis
- √ Release inflammatory cytokines
- √ Regulated on IL-1
- √ NF-kB key Driven
- √ Alter and make toxic microenvironment to healthy cells including stem cells
- √ Cause malignant phenotypes



Cell Senescence

Diloreto R The cell biology of aging Mol Biology of the cell 205, Dec 15;26(25): 4524-4531

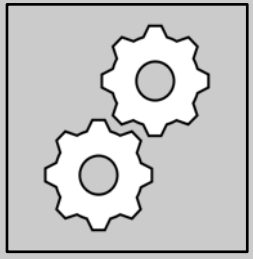
Mchugh, D (2017)Senescence and aging, The Journal of Cell Biology 217(1), 65-77



Occurs in response to stress driven by:

- **Proteostasis (protein misfolding),**
- **Genomic instability (DNA damage)**
- **Telomere erosion of aging.**

Senescence is also a **key player** in normal development and contributes to tissue homeostasis: ie; tissue repair



But, Senescent cells of aging display

- old defective mitochondria
- decreased mitophagy

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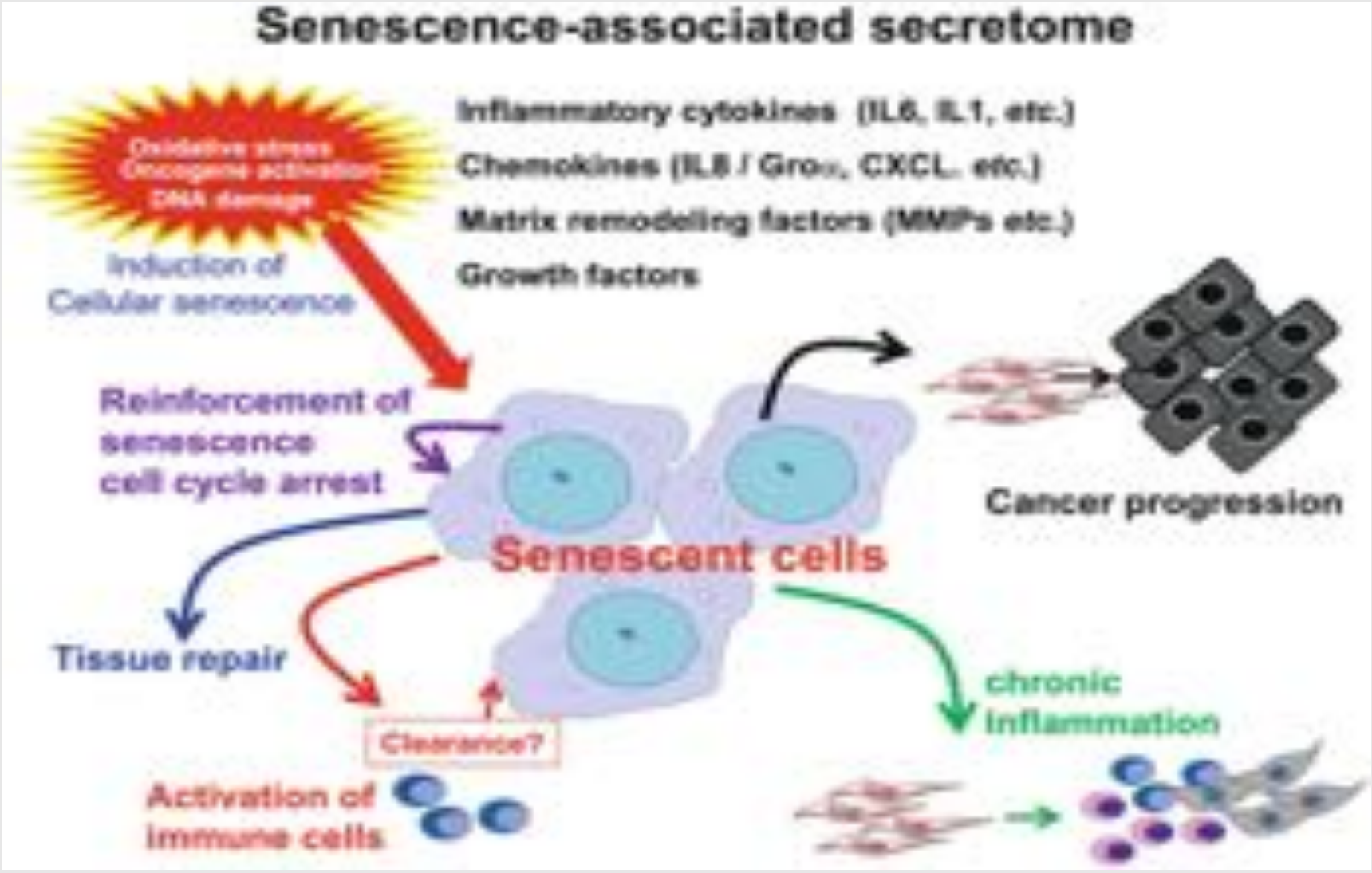
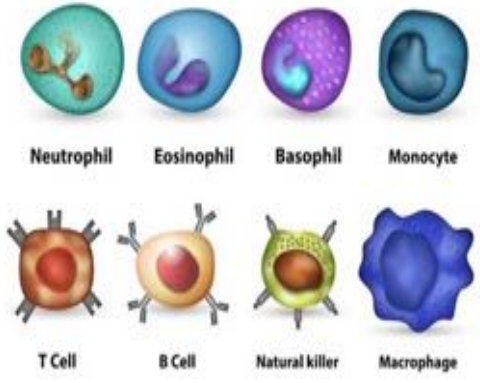
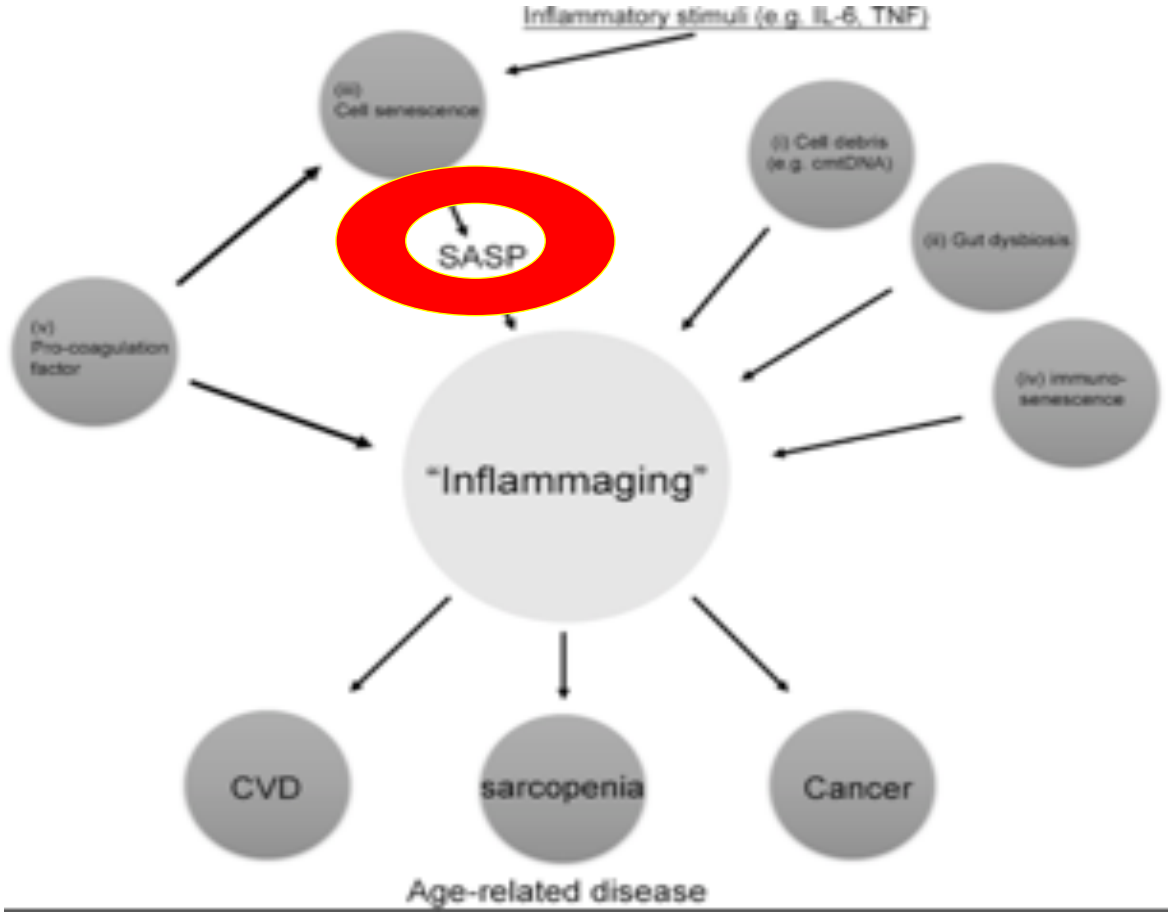
GOOD SENESCENCE AND BAD SENESCENCE



Inflammaging





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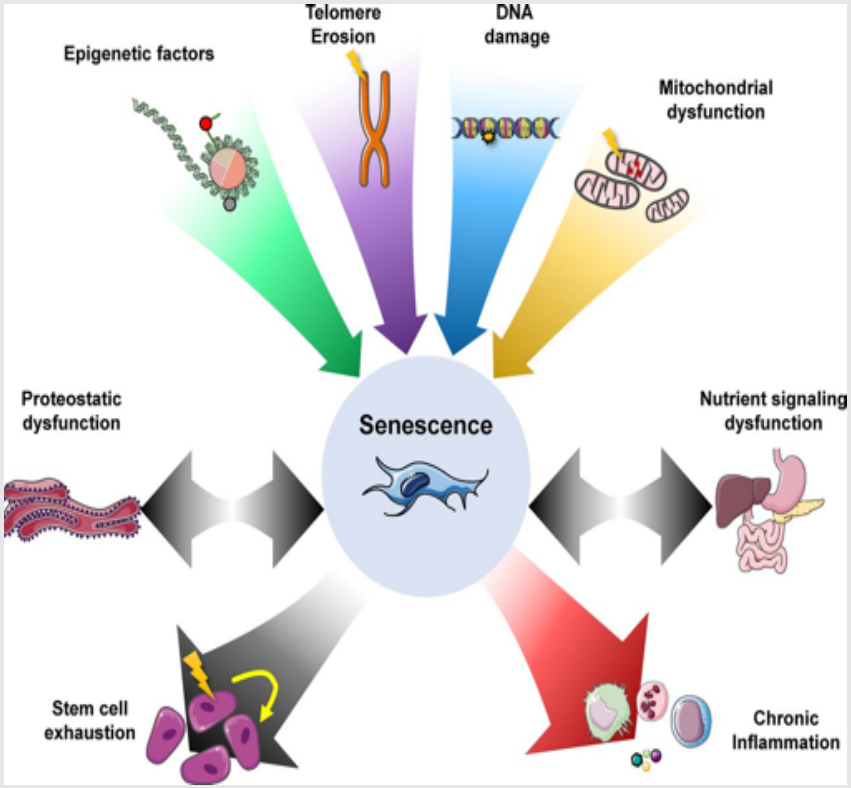
Longevity – healthy aging
Focus on Cell Senescence



Aging causes cell dysfunction in various systems in the body at various onsets and rates

- ***Resulting in:***
  - Cardiometabolic disease – DM II
  - Loss of brain function – dementia
  - Osteoporosis
  - Osteoarthritis
  - Cancers
  - Skin aging – wrinkles/sagging
  - Hair loss

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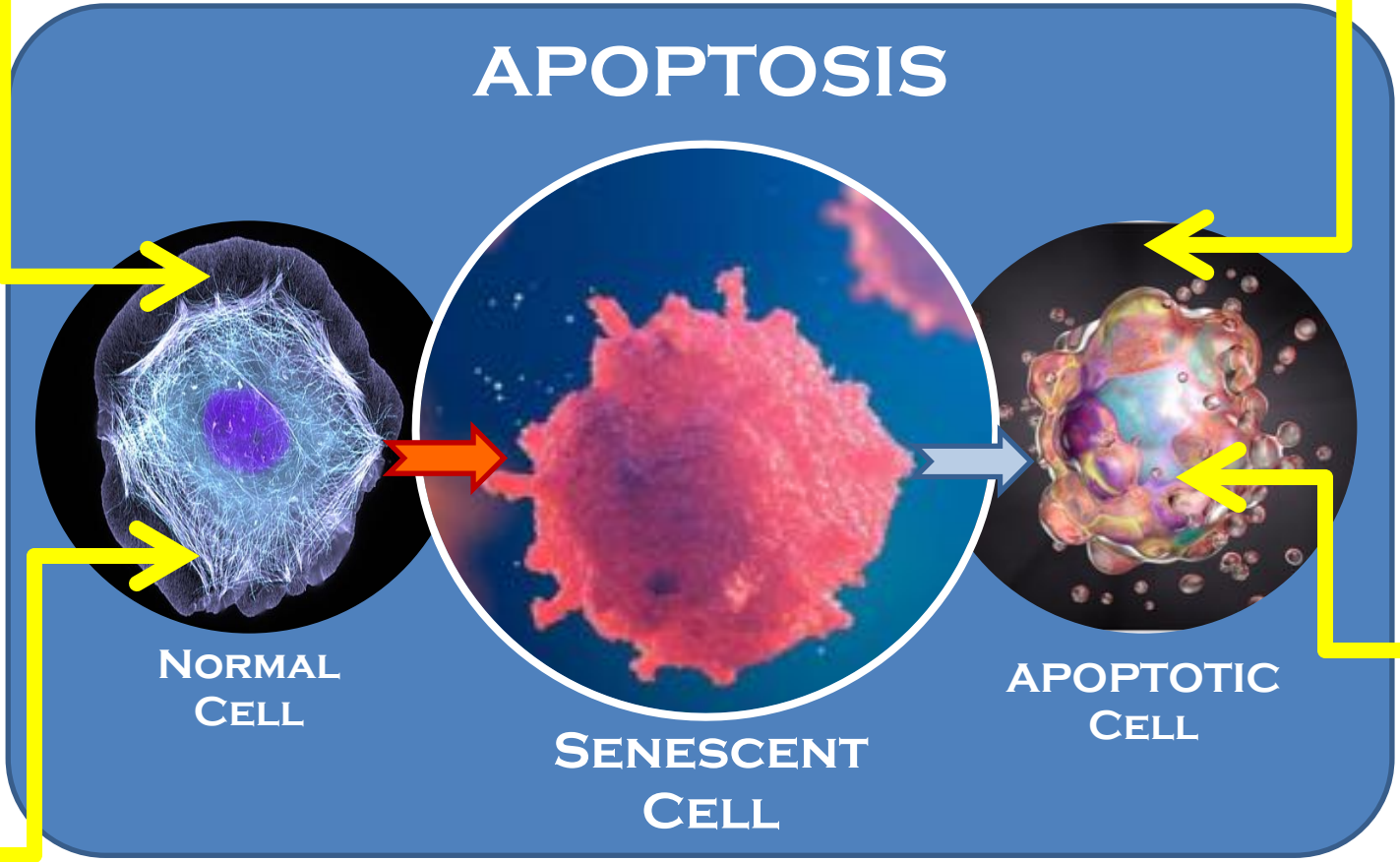
GEROTHERAPIES
Lifestyle, Mitochondrial
Telomeres, Peptides

Exercise
Sleep
Diet
Stress

ALA
MITOQ
Coq10
Carnitine
Curcumin
PQQ
Resveratrol

FOXO-4 DRI
CJC 1295/IPA
MOTSc
5 Amino 1 MQ
Thymosin B 4
Thymosin A 1
Liraglutide

Rapalogues
NAD+
Metformin
DHEA
ARBs



Exercise
Sleep
Diet
Stress

Quercetin
Fisetin
Apigenin
NAC
Green tea ext
Tocotrienols
Sulforaphane
Curcumin

Thymosin B4

Tasatinib?

INHIBIT SENESCENT CELL FORMATION

OPTIMIZE APOPTOSIS

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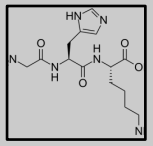
Longevity – healthy aging Focus on Cell Senescence

DIET: Intermittent Fasting and Fasting Mimicking.

Exercise: Timing and Type

Senolytic therapy: Target cells senescence



Senomorphic therapy: Target SASP

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FASTING IR and FMD

Longevity and weight loss

- Improve cell senescent state – autophagy – clears out SASP cells
- Metabolic health and improve insulin sensitivity
- Mitochondrial repair and biogenesis – energy – PGC-1a
- Improved REDOX – decrease inflammation
- Muscle health and anabolism
- Improve healthy aging and decrease premature aging
- Decrease cancer risk
- Decrease CV risk
- Improve body composition

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Intermittent fasting benefits

- ☑ Improved gut health – healthier Microbiome
- ☑ Converts WAT to BAT-thermogenesis
- ☑ Circadian rhythm and balance – better sleep and weight loss
- ☑ Decrease total energy intake
- ☑ Lowers somatomedin C (Igf-1) removing feedback inhibition of GH release
- ☑ Low protein modifies Igf-1 influence increases clearance

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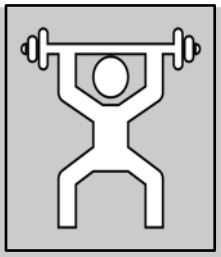
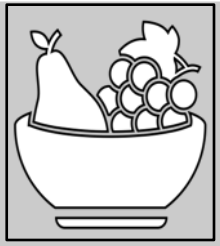
Intermittent Fasting

Less than 24 hours



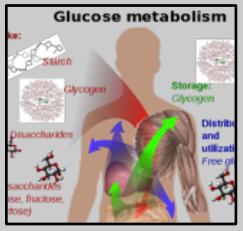
Body Composition :

decreased body fat



Eating habits improved

Adipose thermogenesis increased



Improved metabolism and Glucose metabolism

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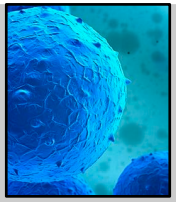
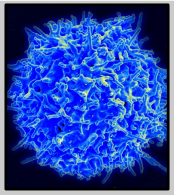
Extended fast 72 hours:

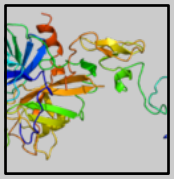
Key Longevity target



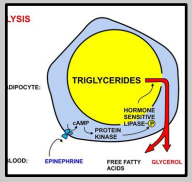
Stem Cell renewal



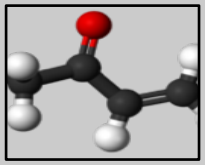
Decrease Igf-1-longer lifespan



Upregulate FOXO1- longevity signaling protein



Metabolic switch to fatty acid burning



Fat based/ketone body catabolism

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FASTING mimicking diet FMD

- 5 days consecutive a month x 3 months
- Decrease body fat, cholesterol, trigs, CRP
- Blood pressure, fasting glucose, Igf-1,
- Decrease mTOR
- Increase hematopoietic and
- Mesenchymal stem cells
- Brain – Increase neurogenesis
- Upregulates PGC-1a – mitochondrial
- Biogenesis
- Metabolic switch to fatty acid burning
- WAT to BAT – increase thermogenesis

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HDAC inhibition

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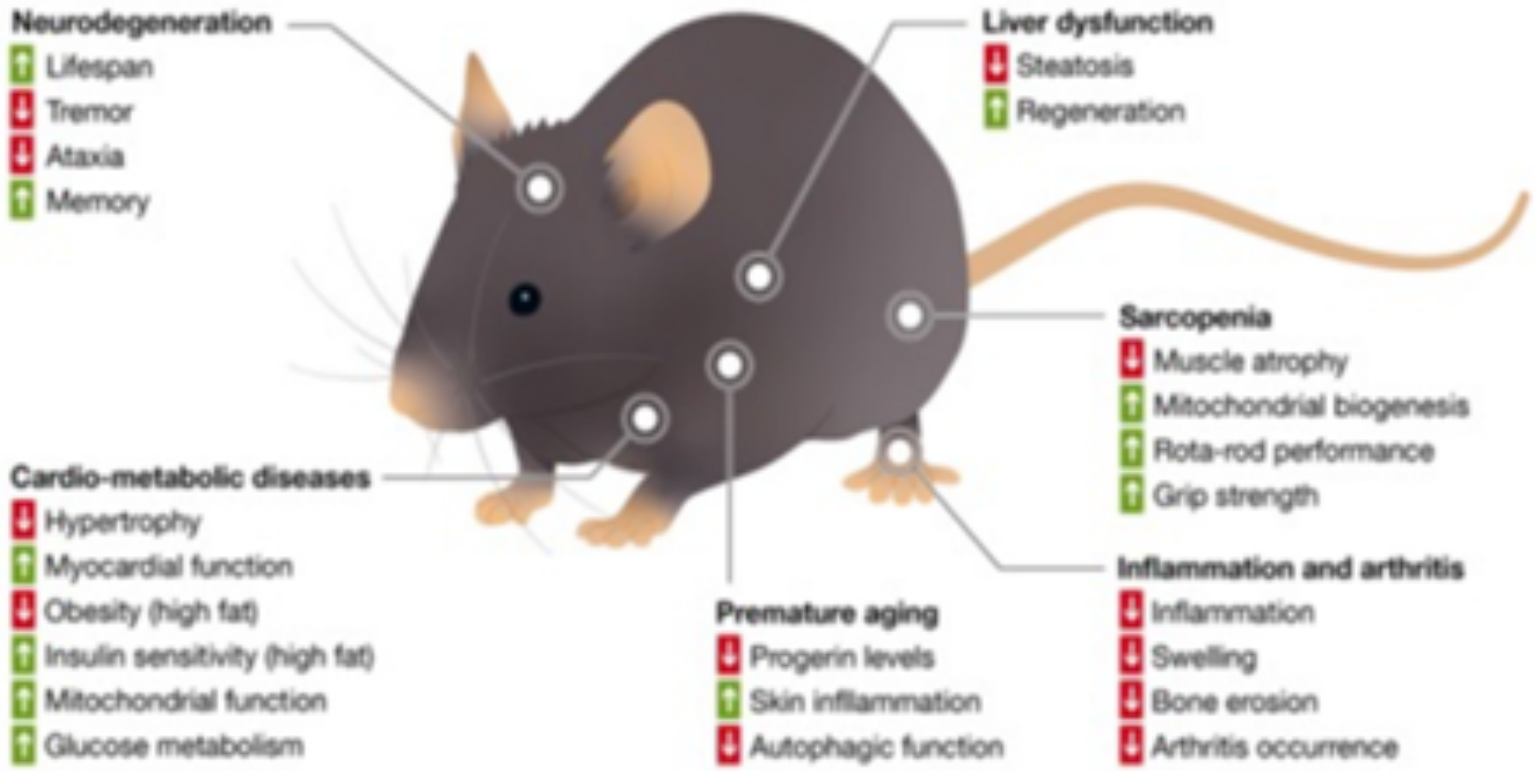
HDAC inhibition



Benefits of HDAC inhibitors in preclinical models

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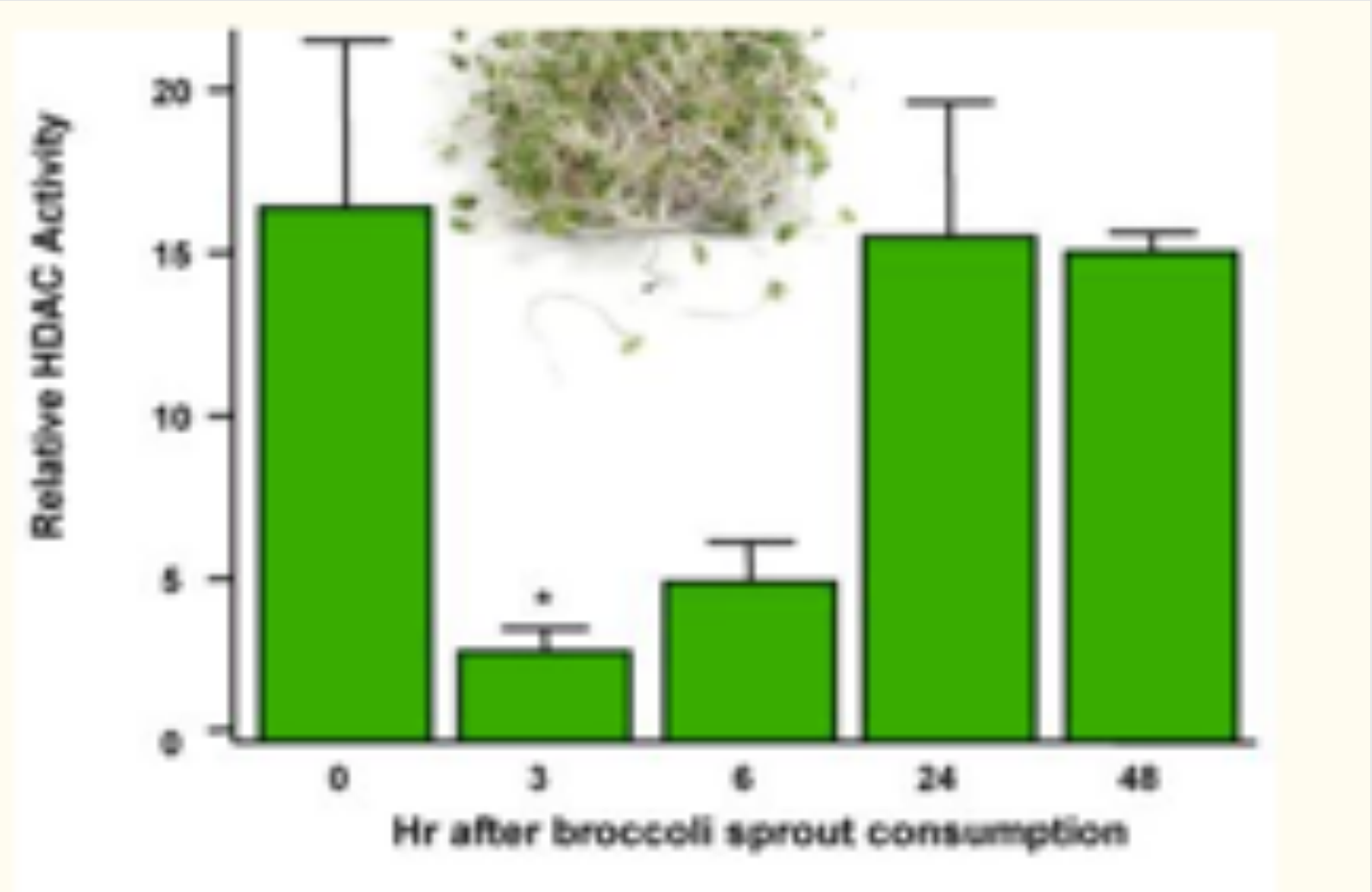
Selected HDAC inhibition

Properties of selected HDAC inhibitors

HDACi	HDAC1 IC_{50} (μM)	HDAC class specificity	Structural class	Lifespan extension
Valproic acid	171	I	Short-chain fatty acid	Worms (Evason *et al*, 2008)
Phenylbutyrate	162	I, II	Short-chain fatty acid	Flies (Kang *et al*, 2002)
Butyrate	175	I, II	Short-chain fatty acid	Flies (Zhao, 2005)
β-hydroxybutyrate (BHB)	5,300	I	Ketone body	Worms (Edwards *et al*, 2014)
Trichostatin A	0.017	I, II, IV	Hydroxamic acid	Flies (Tao *et al*, 2004)
Vorinostat (SAHA)	0.014	I, II, IV	Hydroxamic acid	Flies (McDonald *et al*, 2013)
Scriptaid	0.0064	I	Hydroxamic acid	NA
Apicidin	0.00030	I	Cyclic peptide	NA
MS-275 (Entinostat)	0.5	I	Benzamide	NA
Merck60	0.007	I	Benzamide	NA

Selected HDAC inhibition
Sulforaphane



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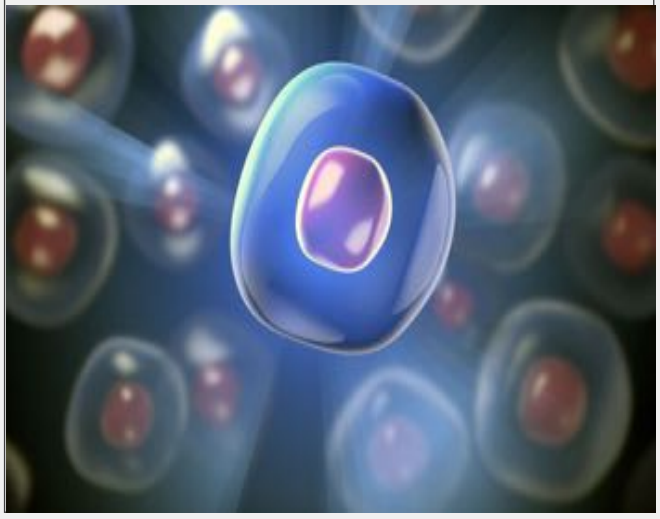
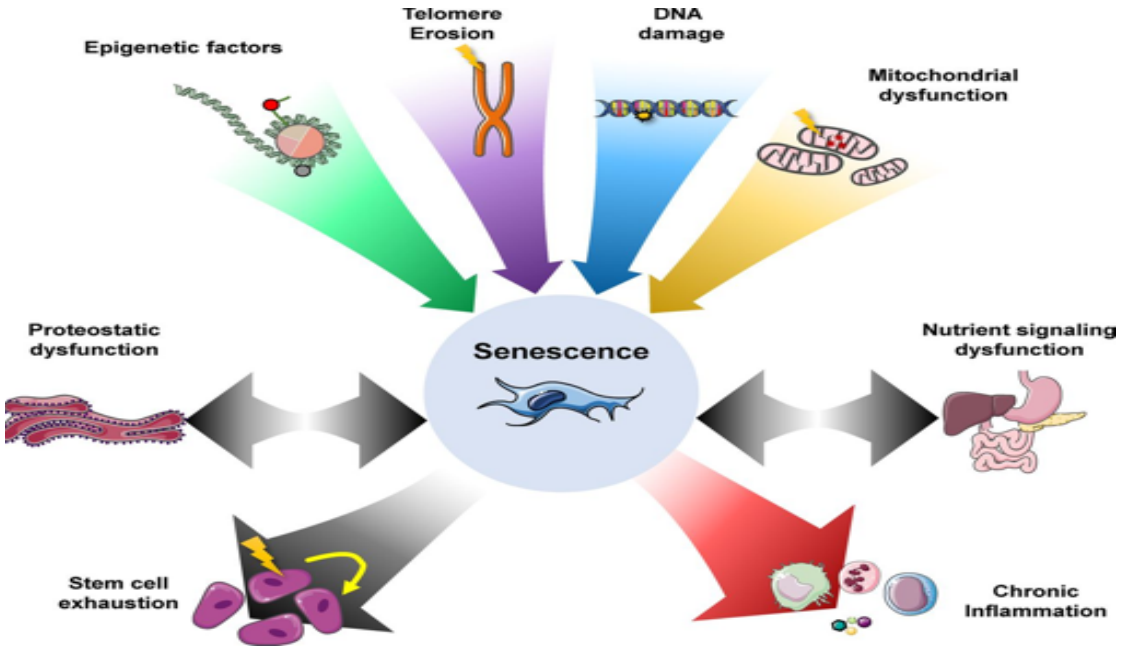
Cell Senescence Senolytic therapy





Modulate autophagy-apoptosis

- FOX04-DRI peptide (P53)

Decrease senescence

- Maximize Cell efficiency
- Mitochondrial optimization
- Decrease ROS
- Telomere erosion- slow, stop, reverse
- Immune modulation- NK cells

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SENOLYTIC Inhibitors

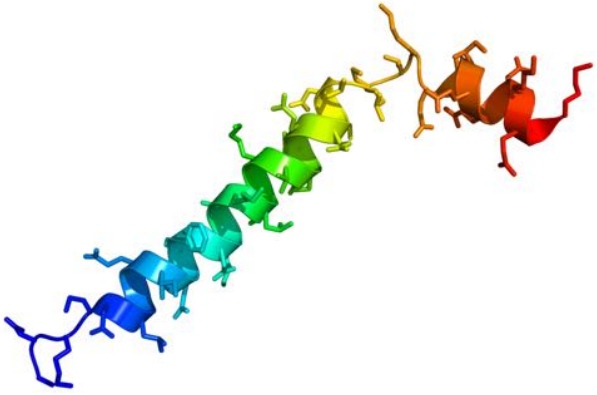
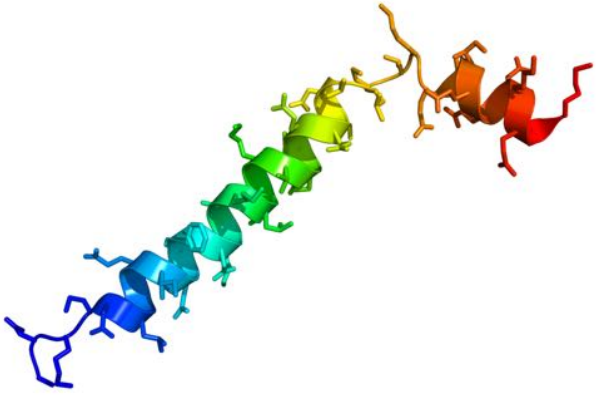


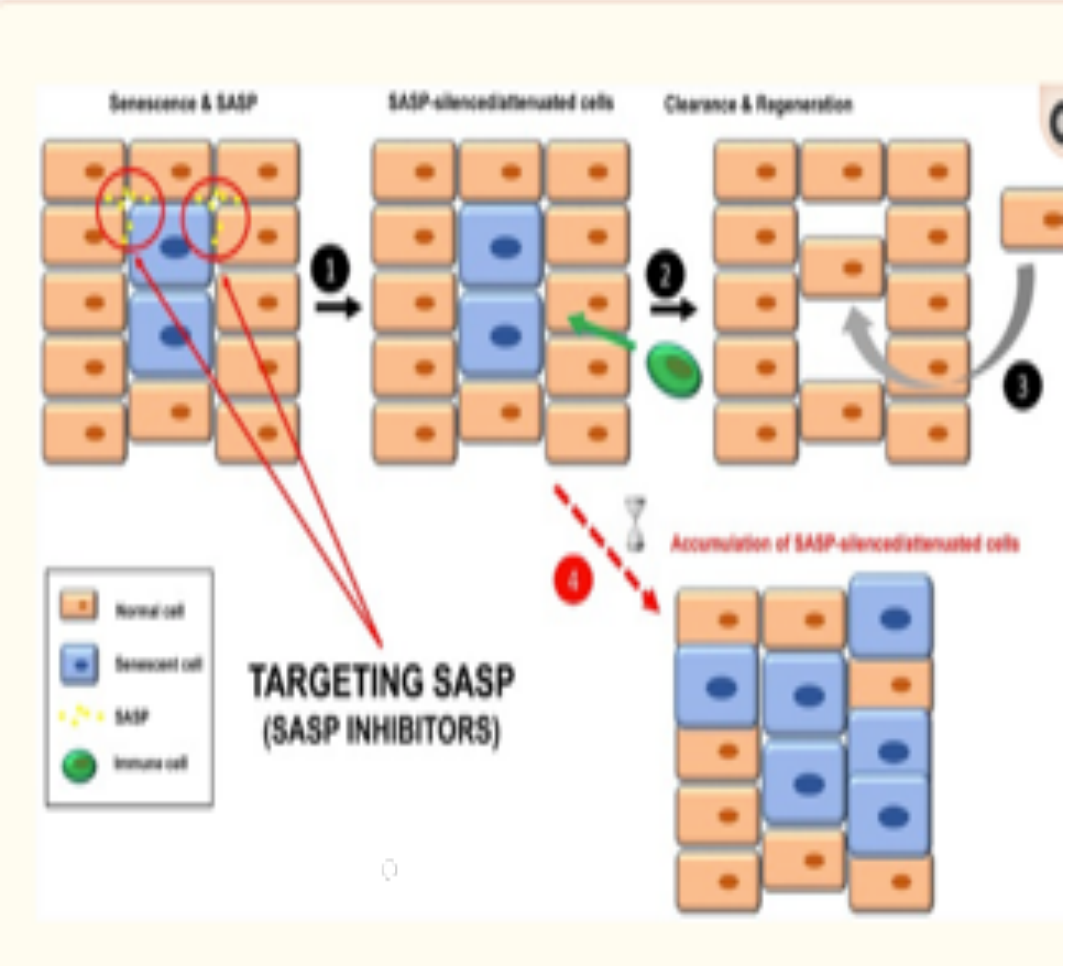
Table 1

List of senolytics and their targets.

Senolytic	Target/function	References
	Apoptosis	
Dasatinib (D)	Inhibitor EFNB*-dependent suppression of apoptosis	[51]
Quercetin (Q)	PI3K/AKT, BCL-2, p53, p21, Serpine	[51]
ABT 737	BCL-W and BCL-XL inhibitor	[52]
ABT 263 (Navitoclax; UBX0101)	BCL-2, BCL-XL and BCL-W inhibitors	[37, 53, 54]
A1331852, A1155463	BCL-XL	[55]
Fisetin	PI3K/AKT and ROS	[55]
FOXO4-related peptide (DRI)	Inhibitor of FOXO4-p53 interaction	[44]
Delivery options**		
Gal-encapsulated cytotoxics	SA-β-Gal	[42]

SASP Inhibitors





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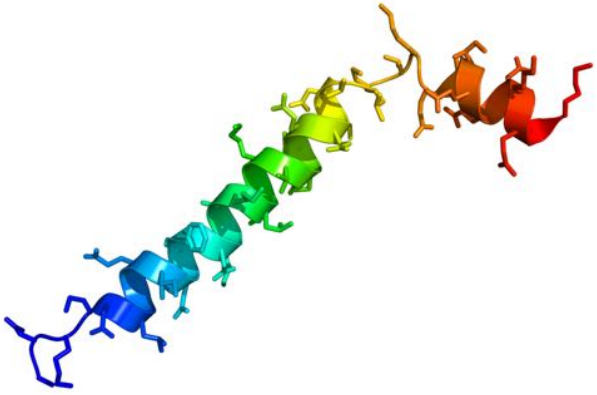
Specific SASP Inhibitors



List of senomorphics and their targets.

SASP inhibitor	Target/function*	References
SB 203580	p38 MAPK** inhibitor	([60] Reviewed by [123])
UR-135756, BIRB 796	p38 MAPK inhibitor	[61]
Resveratrol	NF-κB inhibitor (IκB-kinase inhibitor), AMPK and SIRT1 activator, others	[62–64]
Apigenin, Wogonin, Kaempferol	NF-κB inhibitors (IκB-zeta)	[65]
Metformin	Inhibition of IKK/NF-κB, mitochondrial electron tranport, mitochondrial GPDH, and KDM6A/UTX, AMPK activator, others	[66–70]
Cortisol/corticosterone	IL-1α/NF-κB pathway inhibitors	[71]
NDGA	ROS (free radical scavenger)	[72]
Rapamycin	mTOR inhibitor, membrane-bound IL-1A translation inhibition, prelamin A, 53BP1	[73] [74] [110]
Ruxolitinib	Inhibition of JAK1/2 and ROCK	[75, 76]

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Senolytic therapy

Add peptides to these

Free Radic Biol Med. Author manuscript; available in PMC 2012 Dec 15.
PMCID: PMC3232180
Published in final edited form as:
NIHMSID: NIHMS330450
Free Radic Biol Med. 2011 Dec 15; 51(12): 2150–2157.
PMID: 22019632
Published online 2011 Oct 6. doi: 10.1016/j.freeradbiomed.2011.09.037

Nitric oxide-cyclic GMP signaling in stem cell differentiation

Kalpana Mujoo,[*,1] Joshua S. Krumenacker,[2] and Ferid Murad[3]

Calorie Restriction Increases Muscle Mitochondrial Biogenesis in Healthy Humans

Anthony E. Civitarese[*], Stacy Carling, Leonie K. Heilbronn, Mathew H. Hulver, Barbara Ukropcova, Walter A. Deutsch, Steven R. Smith, Eric Ravussin for the CALERIE Pennington Team
Pennington Biomedical Research Center, Baton Rouge, Louisiana, United States of America

- Rapalogs
- Metformin
- Liraglutide-GLP-1
- NAD+
- DHEA

- ARBs
- Intermmittent fasting, FMD, ECR
- Nitric Oxide
- Acetyl Salicylic Acid
- Beta Hydroxy butyrate (BHB)

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Rapalogs

- mTOR is linked premature aging, cell senescence and shortened lifespan
- mTOR drives the irreversible geroconversion of senescence in mammals
- Rapalogs blocks the development of and conversion to cell senescence
- RAPAMYCIN in low doses 2 to 3 mg every two to three weeks decreases mTOR slows geroconversion and helps keep cell senescence in check
- Rapamycin is produced by bacterium streptomyces hygroscopicus found on Easter Island

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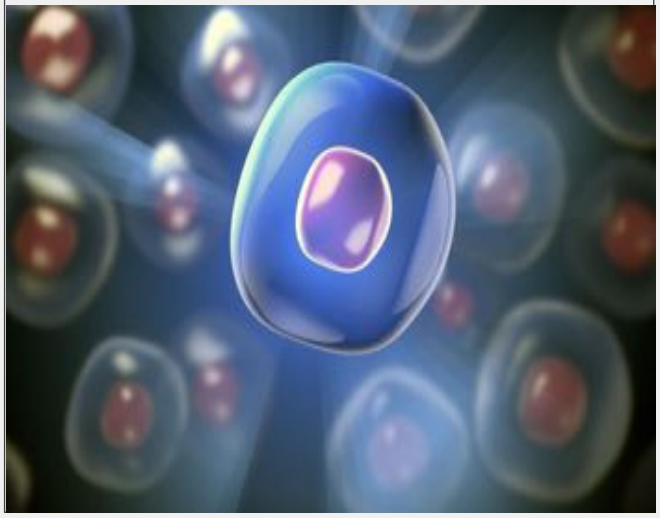
Peptides and Senolytic therapy



- Modulate apoptosis
- Improved B oxidation of Fat
- Improved TCA Cycle
- Improved Oxidative Phosphorylation
- Increased AMPK
- Increased PGC-1 alpha
- Increased PPAR - Gamma, Alpha
- Decreased TGF-Beta – improves hippocampal and skeletal muscle regeneration
- Increase GNRH through KISS1

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GHRH/GHRP and Senolytic therapy

Berlanga-Acosta, J., Abreu-Cruz, A., Barco Herrera, D. G., Mendoza-Marí, Y., Rodríguez-Ulloa, A., García-Ojalvo, A., ...

Guillén-Nieto, G. (2017). Synthetic Growth Hormone-Releasing Peptides (GHRPs): A Historical

Appraisal of the Evidences Supporting Their Cytoprotective Effects. Clinical Medicine Insights: Cardiology, 11, 117954681769455.

- Foundation for senolytic therapy and weight loss programs
- Preserves GH endocrine axis with physiologic release of HGH and upregulation of GH receptors
- No carbs or fats one hour before and one after administration
- Best windows of administration – fasted in am, post work out 90 minutes, and at bedtime

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GHRH/GHRP and Senolytic therapy

CJC 1295/Ipamoremin

Berlanga-Acosta, J., Abreu-Cruz, A., Barco Herrera, D. G., Mendoza-Marí, Y., Rodríguez-Ulloa, A., García-Ojalvo, A., ...

Guillén-Nieto, G. (2017). Synthetic Growth Hormone-Releasing Peptides (GHRPs): A Historical Appraisal of the Evidences Supporting Their Cytoprotective Effects. Clinical Medicine Insights: Cardiology, 11, 117954681769455.

- Increased Nfr-1
- upregulates TFAM
- Improved NAD+/NADH ratio
- Decreased IL-2, IL-6, Upregulation IL-10
- Blocks Nuclear transcription NF-KB leads to decreased IL-1Beta, IL-6, TNF-Alpha, IL-18.
- **Result -> improved cell efficiency – delayed senescence**

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GH
GHRH/GHRP

Reversal of epigenetic immunoscent trends in humans

TRIIM TRIAL

Reversal of epigenetic aging and immunosenescent trends in humans
G. FAHY sept 08, 2019 .

- Epigenetic "clocks" best at estimating biological clock
- Protocol age can be reversed in humans
- Regenerate the thymus
- Immuno-restoration
- Insulin mitigation

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HGH

GHRH/GHRP

Reversal of epigenetic immunoscent trends in humans

TRIIM TRIAL

Reversal of epigenetic aging and immunosenescent trends in humans
G. FAHY sept 08, 2019 .

- 61 to 65 yo healthy men
  - Age range of T - cell collapse – increased morality, cancer, infection, autoimmune, gen. inflammation, atherosclerosis
- Recombinant human growth hormone (rhGH)
  - 0.015 mg/kg 3 to 4 times a week
- DHEA – 50mg
- Metformin – 500mg daily
- Vit D and Zinc

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HGH

GHRH/GHRP

Reversal of epigenetic immunoscent trends in humans

TRIIM TRIAL

Reversal of epigenetic aging and immunosenescent trends in humans
G. FAHY sept 08, 2019 .

- Reversed epigenetic age 1.5 years after year one
- Update to 2.5 years age reversal
- CRP decreased
- MRI evidence of increased functional thymic volume
- Reduction of CD 38+ monocytes
- PSA reduced

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HGH

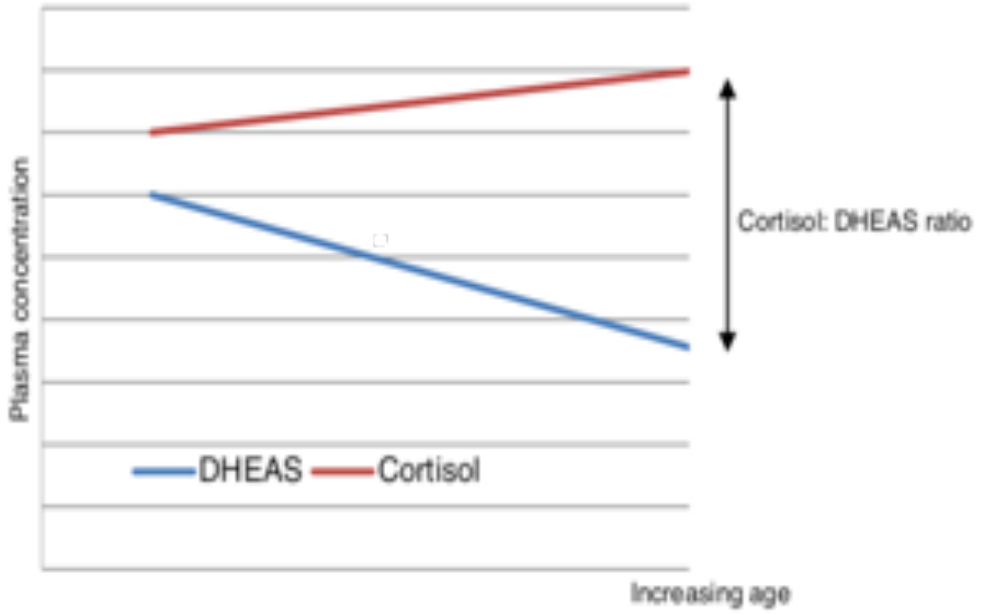
DHEA

Reversal of epigenetic immunoscent trends in humans

TRIIM TRIAL

Reversal of epigenetic aging and immunosenescent trends in humans
G. FAHY sept 08, 2019 .

- DHEA opposes cortisol
- Immunomodulator TH2
- Hippocampus - protects



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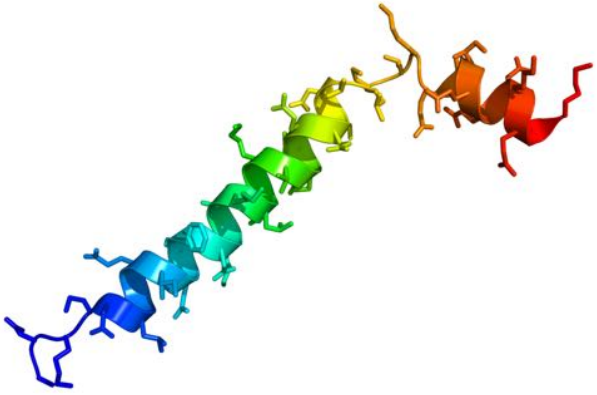
Improving immune system



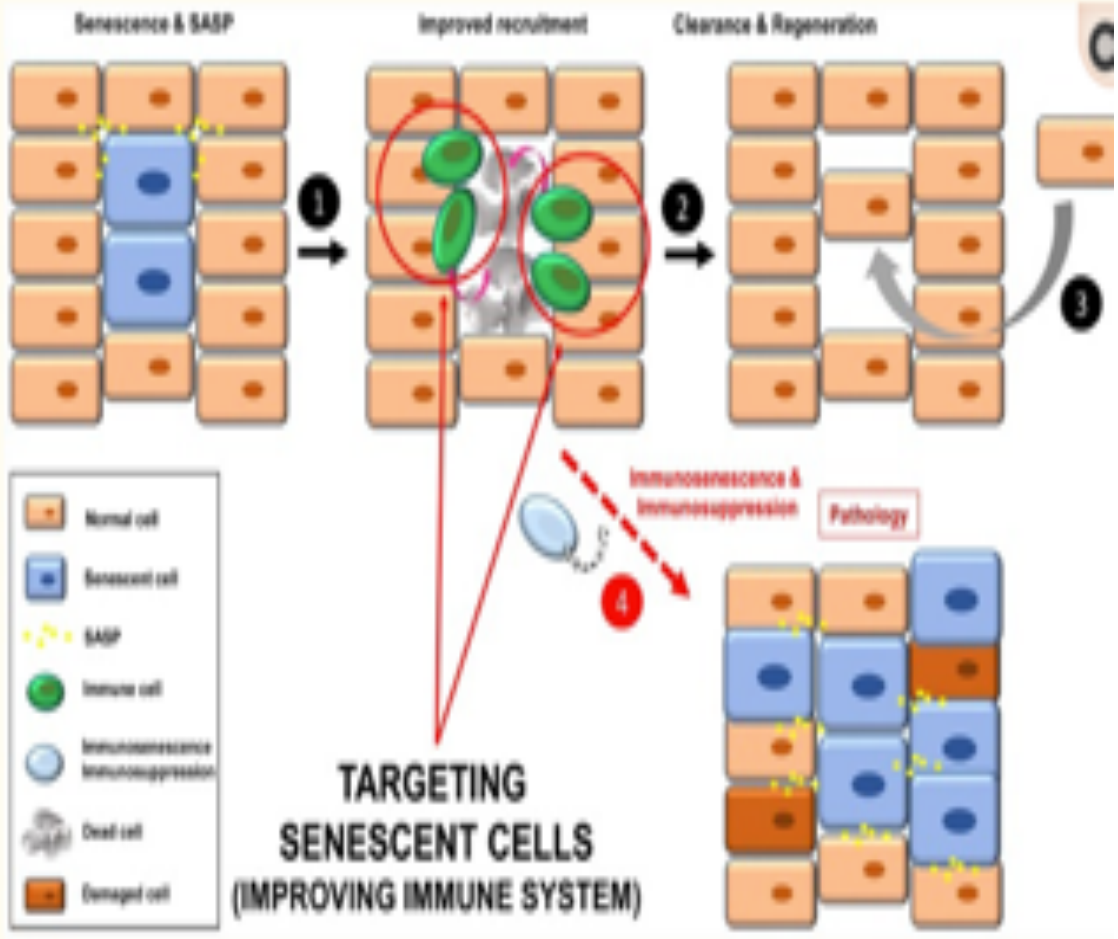


Figure 4

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Senescence Therapy Immune modulation and vigilance

Pica, F., Chimenti, M. S., Gaziano, R., Buè, C., Casalinuovo, I. A., Triggianese, P., ... Garaci, E. (2016). Serum thymosin α 1 levels in patients with chronic inflammatory autoimmune diseases. Clinical & Experimental Immunology, 186(1), 39–45

Goldstein, A. L., & Kleinman, H. K. (2015). Advances in the basic and clinical applications of thymosin β4. Expert Opinion on Biological Therapy, 15(sup1), 139–145.

Lee, C., Zeng, J., Drew, B. G., Sallam, T., Martin-Montalvo, A., Wan, J., ... Cohen, P. (2015). The Mitochondrial-Derived Peptide MOTS-c Promotes Metabolic Homeostasis and Reduces Obesity and Insulin Resistance. Cell Metabolism, 21(3), 443–454.

- Thymosin ALPHA -1 – immune modulation
- TB-4 – immune modulation

Mitochondrial peptides modulate mitochondrial function during cellular senescence , Su-Jeong Kim ,AGING 2018,Vol. 10, No. 6

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Thymosin alpha 1

- Discovered in 1960s by Goldstein,
- isolated from calf thymus
- Imbalance in thymosins identified in the etiology of autoimmune disease

12 Goldstein, A. Potential role for thymosin in the treatment of autoimmune disease. Annals of the New York Academy of Sciences. 1981 DEC;;177

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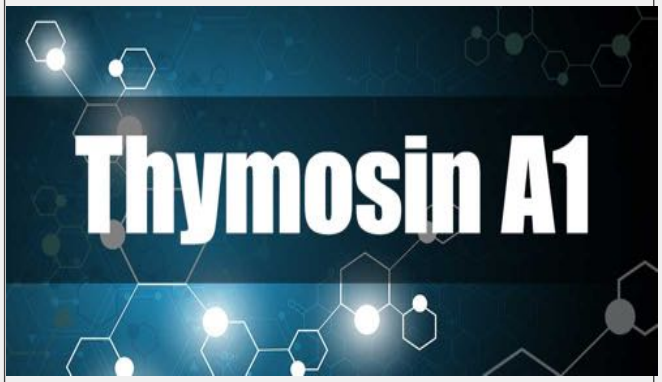
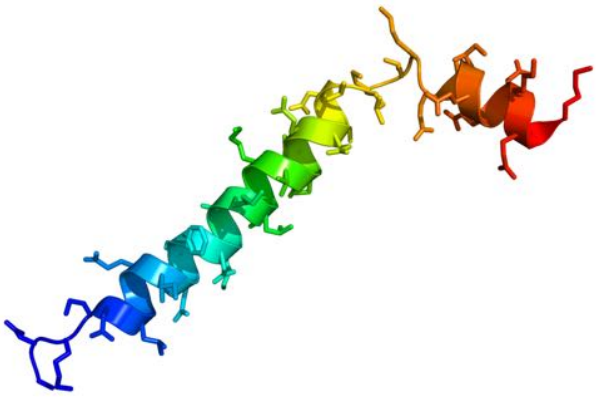


14 Romani, L. Thymosin alpha 1: an endogenous regulator of inflammation, immunity and tolerance. Ann N Y Acad Sci. 2007 Sep;1112:326-8.

- As levels decrease, typical symptoms of aging increase fatigue, loss of motivation and physical energy, increased pain soft tissue and joints, slow wound healing all linked to increased systemic inflammation ie; CRP, etc
- ***Key to senolytics***
  - Promotes Th-1 Th-2 balance to decrease autoimmune expression
  - Increase immuno-vigilance – inc NK cell activity
  - Inc T cells
  - Enhance immunotolerance – T reg cell amplification

Thymosin beta 4 TB4



- Promotes healthy cell growth
- ***Most abundant thymus peptide in body***
- Key to wound healing
- Activates stem cells
- Anti-inflammatory, antimicrobial
- Longevity –slows senescense
- immunomodulation

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GHKCu and gene expression

Int J Mol Sci. 2018 Jul; 19(7): 1987.
Published online 2018 Jul 7. doi: 10.3390/ijms19071987
PMCID: PMC6073405
PMID: 29986520

Regenerative and Protective Actions of the GHK-Cu Peptide in the Light of the New Gene Data

Loren Pickart and Anna Margolina*

Broad Institute of MIT and Harvard (Cambridge, MA, USA)

- Connectivity Map (2010)

Library of transcriptional responses to substances that modulate gene expression

Genome-wide effects of GHK

GHK-Cu is able to **up- and down-regulate a significant number of human genes.**

Connect biological effects of GHK-Cu and its effects on gene expression, to develop a more comprehensive view on GHK's mechanism of action

Most authors would attribute effects of GHK to its ability to bind copper ions.

GHKCu effects on gene expression

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Regenerative and Protective Actions of the GHK-Cu Peptide in the Light of the New Gene Data

Loren Pickart and Anna Margolina*

Estimate of number of genes affected by glycyl-L-histidyl-L-lysine (GHK)

Percent Change	Genes Stimulated	Genes Suppressed
50–99%	1569	583
100–199%	646	469
200–299%	227	196
300–599%	196	207
600–899%	39	47
900–1199%	8	7
1200% or more	2	4

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Ubiquitin proteasome system (UPS) by GHKCu

- Aging naturally causes accumulation of unfolded, misfolded, or aggregated proteins.
- UPS is tasked with removal of damaged or misfolded proteins.
- Proteasome activation by genetic means (GHKCu) retards aging.

DNA repair and GHKCu

- Normal metabolic activities and environmental factors such as UV light and radiation can cause DNA damage.

1000 and as many as 1 million individual molecular lesions per cell per day.

- Lack of sufficient DNA repair is considered a cause of cell senescence, programmed cell death, and unregulated cell division, which can lead to the formation of a tumor and cancer.

- GHK is stimulatory for DNA repair genes (47 stimulated, 5 suppressed) suggesting an increased DNA repair activity.

Insulin/ IGF1 and GHKCu

- The insulin/IGF-1-like receptor pathway
  - Cause of biological aging process.
- Insulin/IGF-1-like signaling is conserved from worms to humans.
- The gene expression data suggests that GHK suppresses this system as 6 of 9 of the affected insulin/IGF-1 genes are suppressed.
- Mutations that reduce insulin/IGF-1 signaling
  - decelerate the degenerative aging process and extend lifespan in many organisms, including mice and possibly humans.
- Reduced IGF-1 signaling is also thought to contribute to the "antiaging" effects of calorie restriction.

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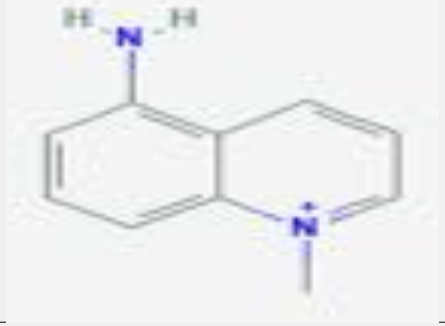
Aging and loss of hypothalamic GnRH gene expression



- *Hypothalmus is responsible for systemic aging and thus lifespan control*
- *Hypothalamic control of systemic aging. By activation of proinflammatory IKKβ/NFκB in hypothalamic microglia accelerates aging in mice*
- *Hypothalamic inflammation eventually causes various defects in regulatory functions and neurogenesis of the hypothalamus, and impairment of GnRH production.*
- *Ultimately, hypothalamic control of whole-body physiology is collectively compromised, contributing profoundly to the development of systemic aging.*
- *Through activating or inhibiting immune pathway IKKβ/NF-κB in the hypothalamus of mice, we were able to accelerate or decelerate aging process, leading to shortened or increased lifespan.*

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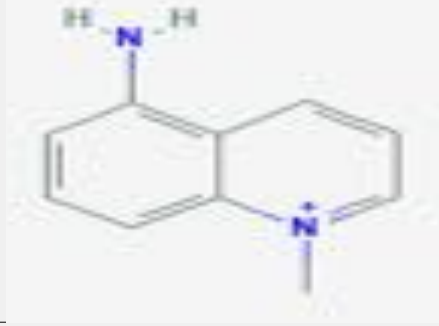
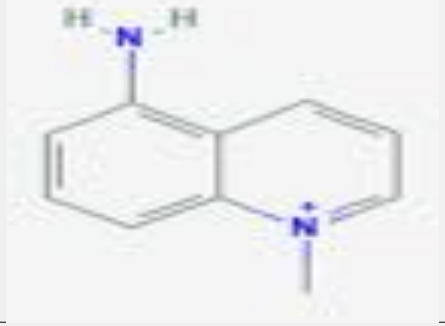
Aging and loss of hypothalamic GnRH gene expression



- *Hypothalmus is responsible for systemic aging and thus lifespan control*
- *Aging is associated with attenuation of hypothalamic GnRH gene expression.*
- *IKKβ/NFκB activation can strongly inhibit GnRH gene transcription, linked to aging-related GnRH decline.*
- *Therapeutically, GnRH treatment significantly reversed aging-impaired neurogenesis in the hypothalamus, hippocampus and other brain regions.*
- *GnRH therapy also leads to amelioration of various aging effects, including skin atrophy, muscle weakness, and bone loss.*

Aging and GnRH replacement



- *Hypothalmus is responsible for systemic aging and thus lifespan control*
- *Delivered GnRH into hypothalamic third-ventricle of old mice, and examined aging-related changes in brain cell biology. A striking observation was that*
- *GnRH promoted adult neurogenesis despite aging.*
- *Aging is characterized by diminished neurogenesis particularly in the hypothalamus and the hippocampus; however, this defect was substantially reversed by GnRH treatment*
- *GnRH travels within the brain to promote neurogenesis.*
- *Role of the brain controls whole-body physiology,*
- *The brain-wide neurogenesis induced by hypothalamic GnRH may provide an explanation regarding how the hypothalamus, a very small structure in the brain, could control systemic aging.*

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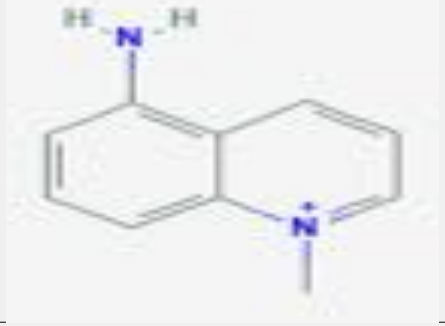
Kisspeptin peptide stimulates GnRH



- *Hypothalmus is responsible for systemic aging and thus lifespan control*
- *Kisspeptin, a hypothalamic peptide coded by the KiSS1 gene, is a novel neuromodulator that acts upstream of GnRH.*
- *sensitive to sex steroid feedback and metabolic cues.*
- *Kisspeptin is now recognized as a crucial regulator of the onset of puberty, the regulation of sex hormone-mediated secretion of gonadotrophins.*

Mitochondrial function and biogenesis

- MOTS-c – mitochondrial - insulin sensitivity – metabolic homeostasis

NAD+NADH (Reduced Nicotinamide Adenine Dinucleotide)

is the metabolically active form of Vitamin B3, also known as Niacin. NADH is essential for the production of cellular energy (ATP) from glucose and fat. Therefore, the more NADH a cell has available, the more energy it has available to operate with optimal efficiency.

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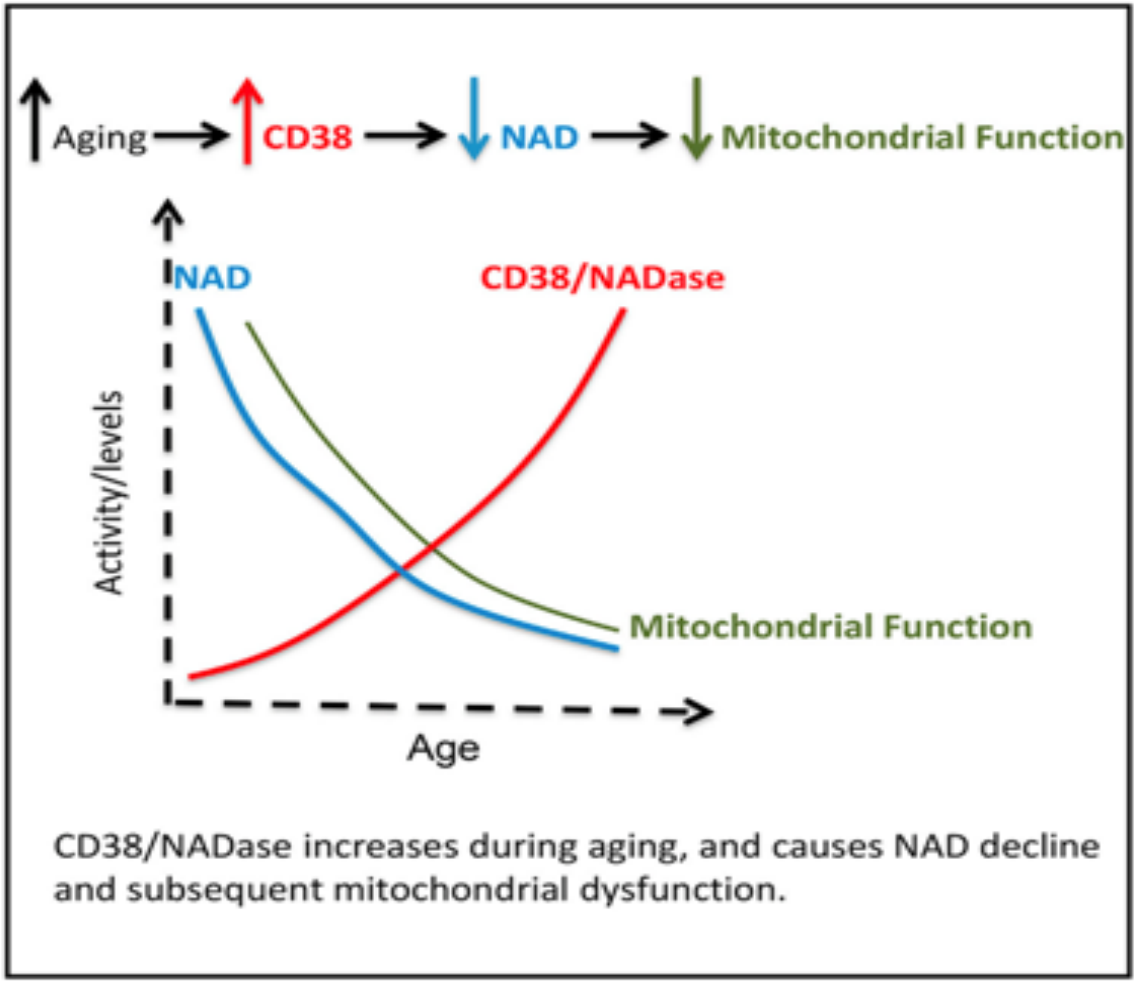
NAD+

Camacho-Pereira, J., Tarragó, M. G., Chini, C. C. S., Nin, V., Escande, C., Warner, G. M., … Chini, E. N. (2016). CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. Cell Metabolism, 23(6), 1127–113



CD38/NADase increases during aging, and causes NAD decline and subsequent mitochondrial dysfunction.

- *NAD declines with age*
- *CD38 enzyme increases with age destroying NAD+*
- *CD38 targets nicotinomide mononucleotide a precursor to NAD+*

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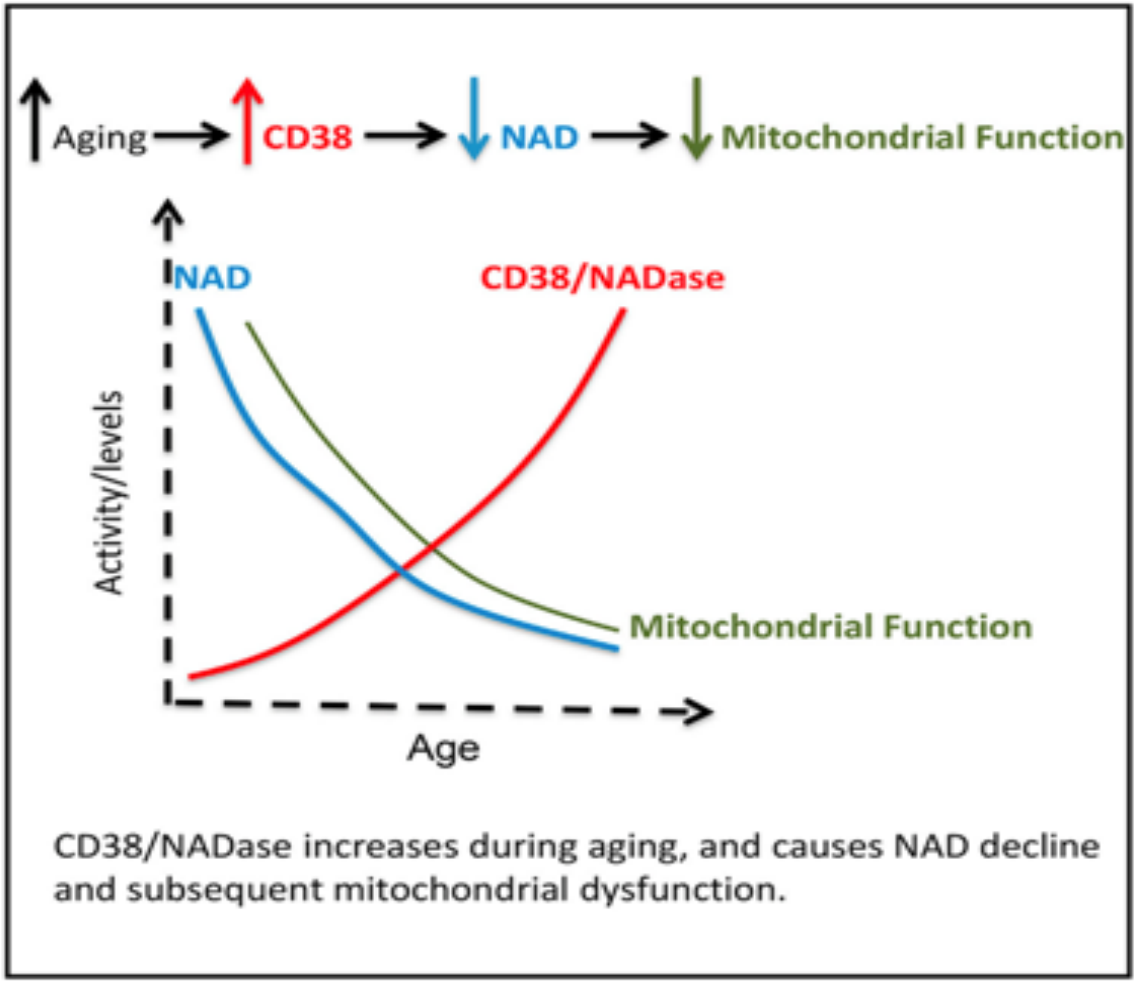
NAD+

Camacho-Pereira, J., Tarragó, M. G., Chini, C. C. S., Nin, V., Escande, C., Warner, G. M., … Chini, E. N. (2016). CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. Cell Metabolism, 23(6), 1127–113



CD38/NADase increases during aging, and causes NAD decline and subsequent mitochondrial dysfunction.

- *Natural flavones capable of reducing CD38 enzyme*
  - *Apigenin*
  - *Quercetin*
  - *Fisetin*
- *Natural senolytics to boot – kill senescent cells*

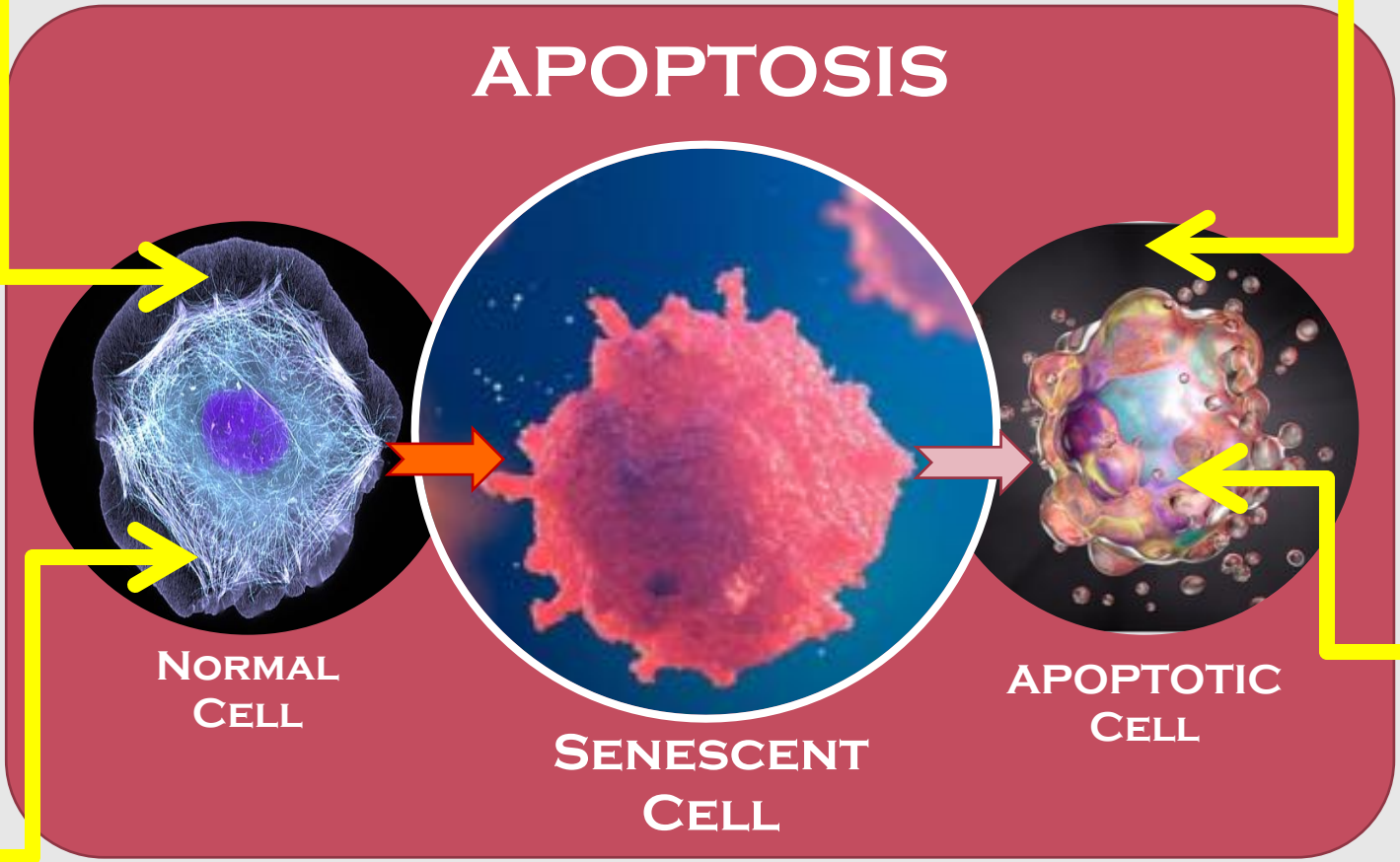
GEROTHERAPIES
Lifestyle, Mitochondrial
Telomeres, Peptides

Exercise
Sleep
Diet
Stress

ALA
MITOQ
Coq10
Carnitine
Curcumin
PQQ
Resveratrol

FOXO-4 DRI
CJC 1295/IPA
MOTSc
5 Amino 1 MQ
Thymosin B 4
Thymosin A 1
Liraglutide

Rapalogues
NAD+
Metformin
DHEA
ARBs



Exercise
Sleep
Diet
Stress

Quercetin
Fisetin
Apigenin
NAC
Green tea ext
Tocotrienols
Sulforaphane
Curcumin

Thymosin B4

Tasatinib?

INHIBIT SENESCENT CELL FORMATION

OPTIMIZE APOPTOSIS

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Treatment goals	peptides	dose	Benefits
Phase in	GHRP	50mcg bedtime	Well being, bone, sleep quality
Healthy aging	GHRH/GHRP	100mcg bedtime	Well being, bone, sleep, GH recep
Healthy aging/weight loss	GHRH/GHRP	100mcg morning 100mcg bedtime	Above addl fatty acid metabolism
Focus on fat loss	GHRH/GHRP	100mcg morning 100mcg 3 hours 100 mcg bedtime	Above addl fat loss enhance fasting
Muscle growth Anabolism	GHRH/GHRP BPC 157	100mcg morning 50 mcg x2 3 hrs 100mcg bedtime 600mcg split	Above GH receptor inc Improved recovery
Injury recovery	GHRH/GHRP BPC 157	100mcg morning 50mcg x 2 3 hrs 100mcg bedtime 600mcg split	Accelerated healing recovery

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