
Kaufmann
Protocol

WHY WE AGE AND HOW TO STOP IT

Dr. Sandra Kaufmann

Master's in Tropical Ecology and Evolutionary biology @ University of Connecticut

Medical School @ University of Maryland

Fellowship in Pediatric Anesthesia @ Johns Hopkins

Chief of Pediatric Anesthesia @ Joe DiMaggios Children's Hospital

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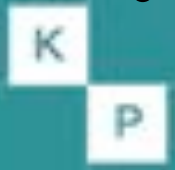
What the Protocol is Not

- It is not about diet and exercise
- It is not a treaty on weight loss
- It is not hormone replacement
- It is not just for older people
- Does not offer specific treatments for disease states

What the Protocol IS

- Comprehensive Interpretation of Cellular Aging
- All information is derived from **real science**
- Evidence is extrapolated from individual cells and animal models to the human form
- My theory is presented in a unique factory model
- Practical applications to decelerate the aging process



What is aging?

- “Aging is associated with a **generalized decline in all physiological functions, and between 30 and 70** we are likely to observe a 25-30% reduction on most functional capacities.” (Barbieri 2015)

- “...a **deterioration in the maintenance of homeostatic processes** over time leading to functional decline and increased risk of death and disease…” (Barzailai 2012)

- “Aging is a **complex multifactorial process of molecular and cellular decline** that affects tissue function over time, rendering organisms frail and susceptible to disease and death.” (Carmona 2016)

The Body as a Factory

- Company Operating Manual
- Energy source
- Pathways…Assembly lines
- Quality Control
- Security systems
- Work Force
- Waste Management

Analogy Applied to cells

- Company operating manual DNA
- Energy Source Mitochondria
- Pathways Pathways:

  AMPKinase, sirtuins, mTOR
- Quality control DNA and Protein

  repair mechanisms
- Security Immune system
- Workforce Individual cell

  requirements

Tenet 1: DNA

- Understand the science of DNA packaging
- Epigenetics
- Telomeres and telomerase

Epigenetics

Decoration or Methylation of DNA

Phosphates, acetyl groups or methylation of Histones

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Epigenetics

- Predictable pattern changes over time - Horvath clock
- Epigenetic Drift- more specific to the individual
    - Bee example
    - Foods and Agents that positively alter the epigenetic pattern

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Telomeres & Telomerase

- Positioned on the ends of DNA, once considered non-sense DNA
- Serve as protective caps
- Lose length with cell divisions and stresses
- High correlation between length of life and length of telomeres
- Telomerase, useful enzyme that increases the length in some cells, esp stem cells
- Over time: lose telomere length, and lose activity of telomerase

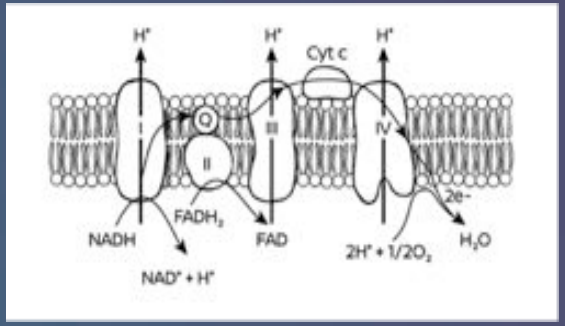
Tenet 2: Energy…..Mitochondria

- The Powerhouse of the cell
- Different numbers in different cell types
- Understand mitochondrial dynamics…fission and fusion

Mitochondria

- Functions via the Electron Transport Chain
- Byproduct of aerobic metabolism is radicalized Oxygen
- Lead to Mitochondrial Superoxide Theory of Aging
- Decline in endogenous scavengers over time; SOD, catalase, glutathione, etc
- Need for additional Free radical Scavengers
- Uncontrolled radicals cause increase in DNA, protein and lipid damage

Mitochondria



- Electron Transport Chain functions by passing electrons/ protons down chain to create gradient
- Rate limiting molecule over time is Nicotinamide adenine Dinucleotide or NAD/NADH
- Humans develop a severe deficiency of NAD with age
- Thus, energy production declines with aging

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Tenet 3: Aging Pathways

- Based on Caloric restriction
- Discovered SIRTUIN pathways
- AMP Kinase pathway
- MTOR pathway

Caloric Restriction

- Caloric restriction: a 20 to 50% caloric decrease from a standard diet
- Prolongs the mean and the maximum lifespan in dogs, rodents, worms, flies, fish and even yeast.

Caloric Restriction

"**Caloric restriction with adequate nutrition** is the only non-genetic, and the **most consistent non-pharmacological** intervention that **extends lifespan** in model organisms from yeast to mammals, and protects against the deterioration of biological functions, delaying or reducing the risk of many age-related diseases." (Testa 2014)

"Caloric restriction is by far the **most effective environmental manipulation** that can extend maximum lifespan in many different species." (Yuanyang 2011)

Sirtuins

- Silent Information Regulator gene
- Discovered in 2000
- Yeast that had additional copy of SIRT1, lived 30% longer
- NAD dependent genes and enzymes that sense environmental and nutritional stressors
- Activated Sirtuins:
  - Regulate the bodies metabolic and growth pathways
  - Trigger the transcription of specific proteins that enhance metabolic efficiency
  - Increase anti-oxidant pathways
  - Facilitates DNA damage repair

Sirtuins

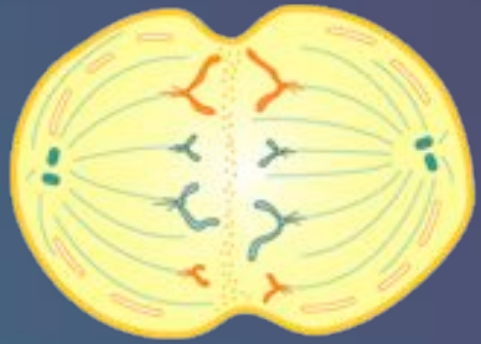
- Seven mammalian sirtuins

- SIRT 1:

  Located in the nucleus

  - Circadian rhythm regulation
  - Mitochondrial DNA transcription
  - Oxidative stress
  - Inflammatory pathways (NF-kB)
  - Sarcopenia

Sirtuin families



SIRT2:

Located in the cytoplasm and nucleus

Mitosis

cellular reorganization during cell replication and division

Known to affect histones @H4K16

...thus an epigenetic modifier

Sirtuin families

SIRT3:

Located in mitochondria

- Orchestrates mitochondrial function
- Increases production of superoxide dismutase
- Apoptosis (getting rid of useless dead cells)
- Effects brown fat expression
- Known to affect histones @ H3K9, H3K56

SIRT4:

Located in the mitochondria

TCA or Krebs cycle

SIRT5:

Located in the mitochondria

Uric Acid cycle

SIRT6:

Located in the nucleus

Controls inflammation through effects on NF-kB

Telomeric preservation

Prevents diet-induced obesity

DNA repair

Affects Histones H3K9, H3K56

SIRT7:

Located in the nucleus

Controls nucleolar maintenance during cellular stress

Sirtuins

- Decline with age
- NAD dependent…and NAD declines with age
- Artificially activate sirtuin gene family

Are there SIRT activators? Of course

AMP Kinase

- Adenosine Monophosphate-activated Protein Kinase
- Central regulator of cellular and organismal metabolism
- Plays a critical role in maintaining energy homeostasis
- Otherwise known as the **Metabolic Master Switch**
    - **Promotes catabolic mechanisms** that **generate ATP,** while simultaneously inhibiting anabolic systems that require ATP.

AMP Kinase

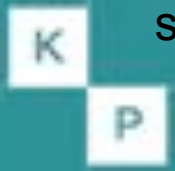
In order to **INCREASE ATP** production:

1) Increases cellular uptake of glucose

2) Increases glycolysis

3) Increases Fatty Acid Oxidation

4) Triggers the acute destruction of defective mitochondria while stimulating new mitochondria to be produced. (Autophagy)



AMP Kinase

In order to **DECREASE ATP** utilization

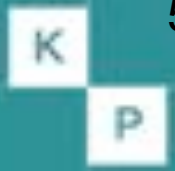
1) Decrease fatty acid synthesis

2) Decrease steroid synthesis

3) Decrease glycogen storage

4) Decrease protein production

5) Decrease cellular growth



What happens with the loss of AMP Kinase?

- Decrease in autophagy
- Increasing oxidative stress
- Increasing inflammation
- Increasing fat deposition
- Hyperglycemia

Are there AMP Kinase activators? Of course

mTOR: mechanistic target of Rapamycin

- mTOR is a serine/threonine protein kinase
- Senses the environment and promotes anabolic processes …its essential to the biosynthesis of proteins and lipids
- Get hyper-functioning of cells…contributes to high blood pressure, osteoporosis and hypercoagulability
- Pathway becomes obsolescent
- Blocking mTOR been shown to increase longevity…Rapamycin

Rapamycin

- First inhibitor of the mTOR complex 1 central regulator of RNA translation, cellular growth and metabolism

- Cancer treatment
  Renal cell CA, neuroendocrine tumors, some breast cancers, some leukemias, and lymphomas.

- Potent immunosuppressant after kidney transplant

- Drug-eluting cardiovascular stents

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Rapamycin- the positives

- Delay in stem cell loss
- Delay in cognitive decline
- Delayed heart failure
- Delayed liver degeneration
- Less tendon stiffening
- Less decline in physical activity
- Some aspects of cancer prevention

Rapamycin- the negatives

Side effects with doses from immune suppression:

- Immunosuppression
- Edema
- Mouth ulcers
- Alopecia
- Testicular function
- Fertility

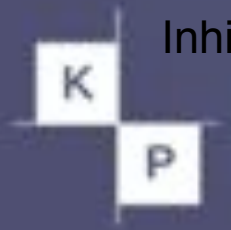
Even smaller doses

- Hippocampal neurons...memory
- Sarcopenia

*“Consolidation and reconsolidation of **fear memory, spacial memory, and modulation of auditory cortex-dependent memory** require activation of mTORCH1 and possibly mTORCH2.” (Bockaert)*

*In the hippocampus: “When mTORCH1 was inhibited by chronic intracerebral ventricular **infusion of rapamycin** the phosphorylation of mTOR substrates were also inhibit(ed) as well as the **learning-induced enhancement of protein synthesis and the acquisition of learning.**” (Garza-Lombo)*

*In the **Amygdala**: “It was found that rapamycin increases neuronal activity and anxiety-related behavior, **impairs both consolidation and reconsolidating of an auditory fear memory, and produces impairment of IA (inhibitory avoidance) memory**.” (Garza-Lombo)*



Inhibiting the mTOR system thus **may adversely effect long term memory**

Sarcopenia

“Patients taking rapamycin for more than 6 months for the treatment of renal cell carcinoma or paracrine neuroendocrine tumors demonstrated an **increase in sarcopenia**.” (Walter and Cox)

Tenet 4: Quality Control

- DNA: Four primary repair mechanisms
- Proteins: Four primary repair mechanisms
- Autophagy

DNA repair

- Single strand break: 5 - 10,000 per cell, per day
- Double strand breaks: 10 per cell, per day
- Errors in substitutions, deletions, strand crossing and linking
- Inclusively up to 10^5 DNA errors per cell/ per day

“Double-stranded breaks have been studied extensively and are known to **arise from ROS, gamma irradiation, mechanical stress,** defective telomere processing, chemotherapeutic drugs and replication fork collapse.” (Moehrle 2016)

DNA Repair Mechanisms

Step one:

- PARPs: Poly ADP-ribose polymerases
- an enzyme that deconstructs the NAD molecule, pieces together the ADP-riboses, and discards the nicotinamide

Step two:

1) Base excision repair (BER)
2) Nucleotide excision repair (NER)

3) Homogenous Recombination.
4) Non-homogenous recombination

How does DNA damage cause aging?

- DNA damage causes cells to become **senescent** or undergo apoptosis
- Senescence causes chronic inflammation
- DNA damage causes cancer

“Insufficient DNA repair mechanisms are also linked with **cardiovascular disease and neurodegeneration.** In specific, they play a role in such diseases as Alzheimer’s, Huntington's, and Parkinson’s.” (Panish 2015)

Tenet 5: Security systems

Immune system and Inflammatory cascade

Three main issues central to aging

- The body gets put in a chronic state of inflammation
- Infection risk rises
- Increase in cancers, especially in the cells that originate from bone marrow.

Chronic Inflammation

"The aging process is a **chronic smoldering oxidative and inflammatory stress** that leads to the **damage of cellular components,** including proteins, lipids, and DNA, contributing to the age-related decline of physiological functions." (Szarc 2015)

Inflammaging

Factors highly correlated to aging:
Interleukin-1, Interleukin-6, Interleukin-18, C-reactive protein (CRP), Tumor Necrosis Factor-alpha (TNF-a), serum Amyloid, Soluble vascular cell adhesion molecule-1 (sVCAM-1), and Monocyte chemoattractant protein-1(MCP-1).

Infection Risk

- Less robust cell production from **declining stem cells**
- Less efficacious macrophages, killer cells, and B cells
- Less response to vaccines with age

Tenet 6: Work Force

- Individual employees……Translates into individual cells

- Several determinants require needs
  - Cell life length
  - Mobility...circulate vs stationary

- Fast turnover cells require
  - Optimized stem cells
    - High nutrient availability

- Long lived cells require optimized niche and nutrient delivery

Individual cells

- Categorized by length of existence
  - Short lived…hours to days…

    live hard and die fast
  - Medium….years….goldilock cell
  - Long….entire lifespan

    Stem cells, neurons

Short- lived cells

- Originate from stem cells
- High nutrient requirement
- Don’t have waste or accumulation issues
- Don’t suffer DNA or protein error issues

Middle-aged cells

- Replaced every few years depending on tissue type
- Tend to be stationary, thus niche dependent
- Some issues with waste accumulation and damages

Long-lived cells

- Cells not replaced
- Protein and DNA damage accumulation
- Accumulation of waste products
- Can become senescent
- Mitochondrial dysfunction
- Prone to Epigenetic remodeling

Stem Cells

- Absolute number of viable stem cells decline with age
- Differentiation potential declines
- Compromised DNA repair mechanisms
- Decline in Telomerase activity
- Mitochondria dysfunction
- Prone to Epigenetic remodeling
- Niche dependent

Tenet 7: Waste Management

- Glucose precipitates AGEs and rAGEs
- Autophagy creates Lipofuscin
- Oxygen causes Free Radical formation

Advanced Glycation End products

- Result of Glucose and oxidative stress
- Non-Enzymatic, multi-step reaction
- Creates AGEs, ALEs, or DNA-AGEs

Do?

- Create inflammatory response
- Sticks to almost everything made of collagen/ structural integrity
- Lose protein or DNA function

Lipofuscin

- Byproduct of cellular recycling in the lysosomes
- Accumulations accurately age crustaceans
- Cause space occupying issues in long lived cells
- Prevents lysosomes from efficient recycling
- Get negative spiral of cell

Summation of Aging

- Company operating manual…DNA
- Energy Source…Mitochondria
- Pathways…Aging pathways, i.e. AMP Kinase, sirtuins, MTOR
- Quality control…DNA and Protein repair mechanisms
- Security…Immune system
- WorkForce…Individual cell requirements
- Waste Management…AGE’s, lipofuscin

your total 59	tenet 1	tenet 2	tenet 3	tenet 4	tenet 5	tenet 6	tenet 7
	DNA Alterations	Mitochondrial Failure	Aging Pathways	Quality Control	Immune System Failue	Individual Cell Needs	Waste Management
Molecular Agent	-	-	-	-	-	-	-
Astaxanthin	0	3	0	0	2	0	0
Carnosine	0	3	0	0	0	0	3
EGCG	2	2	1	2	1	1	2
Metacurcumin	2	3	1	0	3	0	3
Nicotinamide Riboside	0	3	3	3	0	0	0
Pterostilbene/Resveratrol	2	3	3	3	2	2	1
...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...
	6	17	8	8	8	3	9

Protocol Chart

Astaxanthin

0.3.0.0.2.0.0

(Kaufmann Rating Number)

xanthophyll carotenoid
3,3’-dihydroxy-beta,beta-carotene-4,4’-dione

Astaxanthin

- Substance made by a unicellular biflagellate, Haematococcus pluvialis, under stressful conditions
- Xanthophyll carotinoid
- Extremely red
- Responsible for most red found in and around water...salmon, crabs, lobster, roseate spoonbills

Astaxanthin
0.3.0.0.2.0.0

Tenet #2: Mitochondria

Powerful free radical scavenger and anti-oxidant

“It is well worth mentioning that astaxanthin can act as a safeguard against oxidative damage through various mechanisms, by **quenching of singlet oxygen**, **scavenging of radicals**, inhibiting lipid preoccupation, and **regulating gene expression** related to oxidative stress.” (Wu 2015)

Stimulates production of the endogenous antioxidant enzymes: catalase, superoxide dismutase, and peroxidase.

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Astaxanthin
0.3.0.0.2.0.0

Tenet# 5 Security/ Immune system

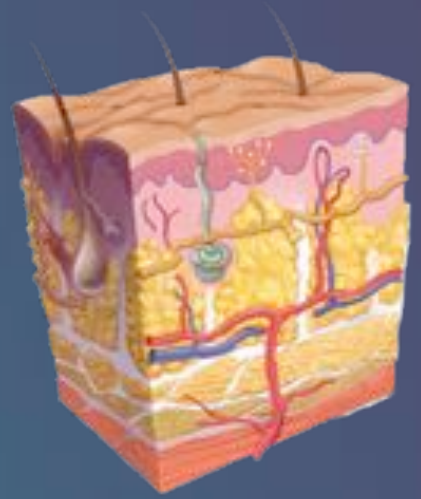
Reduces activation of NF-Kb, which then suppresses the production of IL-1B, IL-6 and TNF-a

Inhibits cyclooxygenase 2 (COX-2), prostaglandin E2, and C-Reactive Protein (CRP)

Astaxanthin Vision

In 2009, Japanese researchers administered 6 mg of astaxanthin daily to **middle aged people** (46-65) for **one** month. Remarkably, **60% of the subjects had visual improvements**, especially in the categories of “difficulty to see near objects,” “eye strain” and “blurred vision.” (Yuan and Kajita 2009)

Astaxanthin
Skin



In human cell lines, especially skin fibroblasts and melanocytes, astaxanthin was shown to **reduce DNA damage** that was precipitated by UVA radiation.

In human skin studies:
Topical astaxanthin demonstrated **improvements in crows feet, age spot size, elasticity, skin texture, and the moisture content of corneocytes.**

Astaxanthin Fitness

Prevents exercise related increases in Free Radicals

Decreases DNA and protein damage with exertion

Increases exercise capacity

Carnosine

0.3.0.0.0.0.3

KRN

L-histidine and B-alanine dipeptide

Carnosine
0.3.0.0.0.0.3

- Present in all muscle
- Identified in 1900 by a Russian scientist, V.S. Gulewitch
- The amino acids come from our diet
- Amount on the body varies with age and gender
- Men have more than women
- Youth have more than the aged

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Cool experiment

Senescent human fibroblast cells were put into a bath of carnosine

Very quickly, the old cells exhibited a rejuvenated appearance. But they didn't just look younger, they acted younger….the **senescent cells reverted to juvenile phenotypes**.

- If the carnosine was removed, the cells quickly became old again.
- If the carnosine was reintroduced, the transformation recurred.
- The **cells in carnosine lived longer AND better**
- Carnosine cells meanwhile had a **25% increase** in the ability to keep dividing.

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Carnosine

0.3.0.0.0.0.3

Tenet #2 Mitochondria

Reduces oxidative damage

Improves endogenous anti-oxidants

Restores depleted levels of glutathione

Increases the basal levels of superoxide dismutase

Carnosine
0.3.0.0.0.0.3

Tenet #7 Waste management

Blocks AGE formation

May actually reverse AGE formation; acts as a transglycating agent

“Carnosine was found to be effective already in the **first step of AGE formation** as well as by reversing glycated protein through a **transglycation** mechanism.” (Boldyrev 2013)

Hearing
Protects hearing from loud noises

Vision
Prevents presbyopia and cataract formation (via carnosine eye drops)

Skin
Improves quality of skin

	DNA Alterations	Mitochondria	Aging Pathways	Quality Control	The Security system	Individual Cell Needs	Waste Management	Total points
Aloe Vera	1	3	0	0	3	2	1	10
Alpha Lipoic Acid	2	3	1	0	2	2	1	11
Andrographolide	1	2	0	1	3	1	1	9
Apigenin	2	1	0	1	2	0	0	6
Astaxanthin	0	3	0	0	2	0	0	5
Astragalus	3	0	0	0	2	1	0	6
Carnosine	0	3	0	0	0	0	3	6
Chebulic Acid	0	2	0	0	2	1	3	8
Cistanche Deserticola	1	2	0	1	3	2	0	9
Curcumin	2	3	1	0	3	0	3	12
Delphinidin	1	3	0	1	2	0	0	7
Ecklonia Cava	0	2	2	2	2	2	1	11
EGCG	2	2	1	2	1	1	2	11
Ellagic Acid	1	2	2	0	2	0	1	8
Melatonin	2	2	1	2	2	2	0	11
Metformin	3	1	3	2	2	2	3	16
Nicotinamide Riboside	0	3	3	3	0	0	0	9
Naringenin	1	2	1	2	2	3	0	11
Polypodium	0	2	0	3	2	0	0	7
Pyridoxamine	0	0	0	0	0	0	3	3
Quercetin	0	3	1	2	2	2	0	10
Resveratrol/Ptero	2	3	3	3	2	2	1	16
Rosmarinic Acid/ LB	0	3	0	1	2	0	3	9
Sulfaphorane	3	2	0	1	0	2	0	8
Yerba Mate	0	2	2	2	2	0	2	10

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your total 59	tenet 1	tenet 2	tenet 3	tenet 4	tenet 5	tenet 6	tenet 7
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...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...
	6	17	8	8	8	3	9

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My subjects have experienced/ reported:

- Higher energy levels
- Decreased rates of infection/ URI’s
- Improved hair growth and color
- Improved skin quality
- Improved vision
- Weight loss
- Decreased joint pain/edema
- Improved sex life

How to choose a protocol

When choosing Regimen:

Age

Medical concerns

Goals

Age Issues

Physiology different from the age of 35 to 90+

At 35: DNA damage, epigenetic modifications

At 45: Loss of endogenous antioxidants, Sirtuin levels decline, fat levels increase, vision changes

At 90: No longer preventing…

Medical Conditions

Diabetes...

More glucose and oxidative stress… increased AGEs…..leads to elevated Blood Pressure, fragile skin, cataracts, early onset Metabolic Disease

Do?

Focus on molecular agents that reduce glucose levels, reduce AGE formation, and potentially lift the AGEs off of tissues

Goals

- Depends on Age of initiation
- Lifestyle choices (smoking, alcohol, exercise, overweight, etc)
- Degree of commitment to program

The Kaufmann Protocol: Why we Age and How to Stop it

Website: KaufmannProtocol.com

The App

Facebook: Sandra Kaufmann

Instagram: KaufmannAntiaging

Citations

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