Conventional Approach: The targets being pursued by academic and pharmaceutical researchers include the following:

1. **Stem cell renewal:** mRNA therapeutics manipulating transcription factors to change cellular age;[1] Antisense Oligonucleotides (ASO) modulating gene expression[2]

2. **Telomerase Reverse Transcriptase (TERT):** ASO inhibiting DNA damage response (DDR) pathways lengthens telomeres (but are also important in DNA repair and preventing mutations; Telomerase Activating Compound (TAC) increased telomerase function 50-100%.[3]

3. **Reducing senescent cells:** Dasatinib/Quercetin inhibits ABL1 kinase increasing neural stem cells; ASO as per stem cells above.[4]

4. **Lysosomal metabolism:** AA-20 autophagy activator (non-mTOR pathway) decreases ferroptosis, increases AMP-K and a partial ATP synthase inhibitor. In C. elegans initiation at day 1 had 64% increased longevity, at day 7 increased 24%.

5. **Circadian rhythm and DNA replication**: in youth the majority of DNA replications occur at night, when there is the least oxidative stress and therefore fewer mutations. There is a decay in circadian communication in aging with higher rates of transcriptional errors and mutations. Time restricted eating in mice improved outcomes.[5]

6. **Microbiome and intestinal mucosal health**: in aging there is an increase in Goblet cells and Paneth cells with loss of intestinal stems cells and shift from anaerobic species to aerobic species leading to decrease in butyrate production. Stool transfers from young donors to older recipients are not maintained.[6]

Integrative Approach:

We can address all these targets with interventions now.

1. **Stem cell renewal:** Moderate intensity exercise (Zone 2 training) can trigger the release of stem cells from the bone marrow into the bloodstream, making them available for tissue repair in various parts of the body.[7]

2. **Telomerase Reverse Transcriptase (TERT):** Endurance exercise in Zone 2 (65-80% maximum heart rate). This also improves mitochondrial function and stimulates mitogenesis, fission/fusion responses. The Standard American Diet (SAD) diet has been associated with shortened telomeres.[8]

3. **Reducing senescent cells**: Fasting or a fasting mimicking diet (FMD) can increase autophagy through increased AMP-K and decreased mTOR activity thereby promoting quiescence and reducing senescence. A 12-week exercise program reduces circulating senescence biomarkers in older adults.[9]

4. **Lysosomal metabolism**: Oleoylethanolamide (OEA) is a signaling molecule that stimulates lipid catabolism. OEA is derived from oleic acid in olive oil. Time-restricted eating (TRE) initiates autophagy, a process where damaged cellular components are engulfed by membrane structures called autophagosomes, which then fuse with lysosomes to degrade the material for energy and building blocks.[10]

5. **Circadian rhythm and DNA replication:** TRE corrects/rescues muscle circadian functionality correcting metabolism.[11]

6. **Microbiome and intestinal mucosal health:** Exercise re-activates Notch signaling and shifts the transcriptional profile of the intestinal cells from old to younger. Exercise shifts the microbiome to a younger profile with butyrate induction and colon cancer reduction.[12]

Conventional Approach (continued):

7. **J-147 small molecule**: a modified version of curcumin, decreases ferroptosis, increases AMP-K, neuroprotectant, shown in mice to treat neurodegeneration and reverse aging.[13]

8**. The Yamanaka Factors OSKM:** Harvard's David Sinclair small molecules (CHIR99021, BIX01294, Valproate, Sodium butyrate, Foskolin) act in the following pathways:[14]

- **Histone deacetylase inhibitor**: allows DNA to be transcribed, changing our "epigenetics" leading to rejuvenation via reprogramming.
- **G9a histone methyltransferase inhibitor**: promotes formation of induced primordial stem cells (iPSCs) and controls epigenetic regulation of H3K9 methylation affecting cellular aging.
- **GSK3α/β inhibitor:** inducer of iPSCs and promoter of certain stem cell characteristics.
- **Increasing cAMP and AMP-Kinase activity:** increases autophagy, reduces inflammation, increases DNA repair and telomere length and mitochondrial biogenesis and mitophagy, inhibits mTOR pathway.

Exercise: Zone 2 versus Zone 5

- **Zone 2** training focuses on a heart rate zone where you can break a sweat while maintaining a conversation but with noticeable effort, aiming for a heart rate around 65-80% of your maximum heart rate, or a lactate level below 2 millimole per liter.
- **Zone 3** = 80-85% HRmax, zone 4 = 85-90%, zone 5 = 90-100%
- If using a treadmill: try a 15% incline at 3.0 to 3.4 miles per hour, adjusting to keep your heart rate in Zone 2.

Functional Medicine Approach (continued):

7. **J-147 small molecule:** Curcumin with pepperine in our diet.

8. **The Yamanaka Factors OSKM:** How to turn these on naturally.

- **Histone deacetylase inhibitor:** nutritional ketosis. Mediterranean Paleo diet with extra virgin olive oil, cruciferous and green leafy vegetables, nuts and seeds, berries and a healthy source of protein.[15]
- **G9a histone methyltransferase inhibitor**: berberine inhibits G9a as well as other histone modifying enzymes. Berberine lowers LDL and improves diabetes and turns on AMP-K through inhibition of complex 1 of the mitochondrial oxidative phosphorylation process.[16]
- **GSK3α/β inhibitor:** low dose lithium orotate 5 mg is an option for replenishing the lithium in our food supply, which is associated with less suicide, depression, cancer and dementia.[17]
- **Increasing cAMP and AMP-Kinase activity:** exercise, FMD, nutritional ketosis and berberine/metformin. Avoid excess nutrition that shuts down AMP-K and healing and promotes mTOR.[18]

- **Zone 5 (High Intensity Interval Training-HIIT)** has a target HR of 90-100% of maximum predicted heart rate (MPHR).
- **Calculating HRmax**: 220-age (but may overestimate in women and underestimate in men over 60 years).
    - **Men**: Tanaka Formula: HRmax = 206.9 – (0.67 x age)
    - **Women:** Gulati formula: 206 - (0.88 x age).
- **Weight training** is also important to address sarcopenia, balance issues and ability to continue activities of daily living, including mountain climbing as we approach 100 years of age. Farmer's carry is an easy exercise to incorporate.

Nutritional approaches

• **Mediterranean Diet:** a dietary pattern based on traditional foods consumed in countries bordering the Mediterranean Sea, such as Greece, Italy, and Spain. It emphasizes plant-based foods, such as fruits, vegetables, whole grains, and olive oil.

• **Time Restricted Eating (TRE):** early versus late eating-no difference in weight loss and adherence better with late versus early, duration of eating window of 4-8 hours, eating from noon-8 pm (8 hours) or from 4 pm-8 pm (4 hours).

• **Calorie Restriction (CR):** greater longevity in all non-clinical studies but concerns about sarcopenia and bone loss.

• **Fasting/Intermittent Fasting:**
  - **5:2 method:** Eating normally for 5 days a week and restricting calories to 500-600 on 2 non-consecutive days.
  - **Eat-stop-eat**: Fasting for 24 hours once or twice a week.
  - **Alternate-day fasting:** Fasting one day and eating normally the next.

• **Fasting Mimicking Diet (FMD):** The FMD is a 5-day diet high in unsaturated fats and low in overall calories, protein, and carbohydrates and is designed to mimic the effects of a water-only fast while still providing necessary nutrients and making it much easier for people to complete the fast. FMD promotes ketosis, as it involves a period of significantly reduced calorie and protein intake, which can lead the body to burn fat for energy, a process that results in ketone production.

• **Nutritional Ketosis:** The nutritional ketosis diet is a high-fat, low-carbohydrate diet that aims to induce ketosis, a metabolic state in which the body burns fat for energy instead of carbohydrates. Consume 70-80% of daily calories from fats, such as olive oil, avocado, fish oil, coconut oil, and nuts. Limit carbohydrate intake to 5-10% of daily calories, focusing on non-starchy green leafy and cruciferous vegetables, berries, and lower sugar fruits. Moderate Protein: Consume 10-20% of daily calories from protein sources like lean meats, fish, eggs, and Greek yogurt.

Points of interest

We are beginning to understand the underlying metabolic mechanisms for why what we eat and how we move can greatly impact on our health and the rate of our aging.

- **African Killifish:** the fish who do more “glass-surfing” and sleep better at night had greater longevity, as occurred with calorie restriction. Could these effects be epigenetic?
- **Improving our sleep hygiene** appears to reduce the risk of DNA replication errors leading to lower risk of mutations and possibly cancer. Disrupted sleep shortens lifespan and impacts wellness.
- **Exercise (Zone 2)** has multiple antiaging effects: increased stem cells, increased TERT, mitochondrial biogenesis, improved NK cell and overall immune function in surveillance for malignancy and infections.
- **Exercise** improves the microbiome and intestinal health as does our diet if we are avoiding the Standard American Diet. Younger type microbiome in older people.
- **Excess nutrition** decreases AMP-kinase function leading to greater inflammation, accumulation of misfolded proteins leading to neurodegeneration, decreased DNA repair, decreased mitochondrial biogenesis, disrupts circadian clocks, and increases mTOR function with accelerated aging through increased senescence and reduced proteostasis and autophagy. Does “Hunger equal Healing”?[19]
- **OSKM transgenic mice**: the OSKM factors are turned on for 2 days on and 5 days off, using a doxycycline genetic switch. This is done because the transgenic mice begin losing weight and dying on day 3 of the activated OSKM factors with many dying by day 5. So, some of the impact of the Yamanaka factors may be mediated through calorie restriction.

- Ketosis may explain many of the benefits of the SGLT2 inhibitors, which promote ketogenesis and inhibit ketone excretion.
- Calorie restriction may explain some of the benefits of the GLP-1 agonists.

Berberine

A yellow plant alkaloid, exerts its therapeutic effects through multiple mechanisms of action (MOA).

1. **Activation of AMP-activated Protein Kinase (AMPK)**:
Berberine activates AMPK, a key regulator of energy metabolism. AMPK activation promotes glucose uptake, fat burning, and insulin sensitivity, improving blood sugar control.[20]

2. Inhibition of Mitochondrial Respiratory Chain Complex I:
Berberine inhibits mitochondrial complex I, leading to increased production of reactive oxygen species (ROS). This oxidative stress triggers cellular adaptations that enhance insulin sensitivity and reduce inflammation.[21]

3. Regulation of Lipid Metabolism:
Berberine reduces cholesterol and triglyceride levels by inhibiting enzymes involved in lipid synthesis and promoting their breakdown. It also increases the expression of LDL receptors, leading to lower LDL (bad cholesterol) levels.[22]

4. Modulation of Gut Microbiota:
Berberine alters the composition of the gut microbiota by promoting the growth of beneficial bacteria and reducing the abundance of harmful bacteria. This modulation has been linked to improvements in metabolic health and immune function.[23]

5. Dosing of berberine: studies in diabetes have used 500 mg once or twice per day. Like metformin, berberine may reduce the training effect of exercise so it makes sense to take berberine with the evening meal. The ½ life is 3-4 hours but likely continues to work in the liver longer due to accumulation in the liver due to the avid hepatic uptake.[24]

Lithium and GSK3-beta[25]

- Lithium in drinking water, when examined in population studies comparing areas with higher versus lower lithium levels, is negatively linked with suicides, depression, lower AD mortality, as well as less obesity and type 2 diabetes, which are important risk factors for AD.[26]
- Lithium is a direct inhibitor of GSK3-beta.
- GSK3-beta is critical in dementia. It is the enzyme that hyper-phosphorylates Tau protein that leads to neurofibrillary tangles in Alzheimer's disease, as with Amyloid Beta pleated sheets.[27]
- A Brazilian study with 300 mcg per day that showed positive results for mild cognitive impairment, but this has not yet been confirmed by others.
- Another study used 400 mcg of lithium and saw increased scores for happiness, friendliness, energy, etc.
- The dose of lithium carbonate for bipolar disorder is 900 to 1800 mg per day, with blood levels of 0.8-1.2 mmol/L.
- The dosing in mild cognitive impairment studies had blood levels in the range of 0.25 - 0.5 mmol/L (60-70% lower than in bipolar disorder). This showed a slowing of cognitive decline over 4 years, and with follow up 8 years later the group that had taken lithium scored 25/30 on the Mini Mental Status Exam (MMSE), while those on placebo scored 18/25, even though neither group had continued lithium for those 8 years.
- The supplement dose is 1-5 mg per day of lithium orotate. It is thought that lithium may be an important essential mineral nutrient like zinc and copper.

Further Information: see GeorgeSteeleMD.com for further information including The Staying Healthy Handout, Health and Longevity 2.0, Lithium summary and other readings.

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