How can we slow down/reverse the process of aging?

Aging: Deterioration of cell function and performance leading to death. Cells, Nov 2019

I joined A4M (The American Academy of Anti-Aging) 18 years ago. Medical authorities at the time touted anti-aging medicine as a con or a fairytale but offered no solutions to the diseases plaguing geriatric patients. Geriatrics is a subspecialty that only offers ineffective bandaids to chronic issues, and yet doctors and patients alike were told that there was no other hope. Conventional medicine was failing then, and it still is, but anti-aging treatments have revolutionized care and come to the forefront of modern medicine.

As a doctor who observed life from the first breaths in the delivery room to the last ones in Hospice care and long term facilities, I have witnessed many patients hope for death in the face of the kind of pain and degradation that often comes with the last ten to twenty years of life. People who were dignified, joyful, and outgoing, wasting into tired shells. The mental toll of needing to be bathed, fed, and changed by caregivers can often match the physical strain of the disease. It becomes far too easy to lose hope. My mother has suffered a stroke, heart attack, renal failure, and memory loss, all common complications of old age. When I last facetimed her, I could tell she was already long gone, drifting away piece by piece. Her body and mind were both fighting a rising tide. This doesn't have to be the destination of every life well lived.

After joining A4M, I learned that there are ways to prevent these complications and live both longer and happier. Hormone replacement therapy is one of many ways to achieve that goal. After learning about genetics and genomics at Stanford, attending conferences from Precision medicine on a regular basis, and diving deep into the study of aging, I believe that we can treat the aging disease and all its complications. From memory loss to fragility, bone and muscle loss, poor vision, to cancer, all can be combated. One major idea about longevity is the reprogramming of cells to repair and replace the malfunctioning organs. The more cells divide as we age, the higher the probability of having more broken DNA pieces and therefore, more malfunctioning organs and cancer cell formation.

How we define a condition as a disease rather than as a natural part of life is greatly influenced by social and cultural standards. Some of the complications of aging such as Alzheimer's were once considered normal aging. Osteoporosis was recognized as a disease by WHO only in 1994. It was in 1998 that ageing was classified as a disease for the first time by Callahan and Topinkova.

There are currently five countries making efforts to stop and/or reverse the ageing process: The US, Australia, Singapore, Israel, and the UK. As well as these national endeavors, there are many private companies (mainly in the US) working towards the same goal. These include Samumed, Human Longevity, Cellularity, Blue Rock Therapeutics, Bioage labs, cellularity, Blue rock therapeutics, unity biotechnology, Alkahest, life bioscience, calico (google research), Elysium (NR), etc.

World Health Organization adds extension code for 'aging-related' via ICD-11:

"With the recent acceleration of the broad science of Juvenescence, it has now been conclusively proven that aging is itself a unitary disease and should be so categorized. July 2, 2018"
The Theories of Aging:

The desire to fight aging has a long history, and for good reasons. Aging is the main risk factor for many chronic degenerative diseases and cancer. It causes muscle and bone loss, brain atrophy, Alzheimer’s Disease, heart disease, dementia, diabetes, and more. The signs are clear: aging is a massive risk to our health, but the exact cause of this process is still up for debate.

The theories of aging include:

1. Senescence

   Increased senescent cell load in the body’s tissues is a major contributor to aging and age-related diseases. Senescent cells are those which have reached their maximum capacity to replicate. Although these cells are non-functioning, their presence in the body can cause inflammation and expedite degenerative processes in our tissues.

   Recently, a new class of drugs named “senolytics” were demonstrated to extend health span, reduce frailty and improve stem cell function in multiple murine models of aging (PMID: 28871086).

   Senolytics are agents that remove senescent cells, thus stopping tissue degeneration and aging complications. This allows tissues to regenerate, leading to the prevention, reversal, or delaying of age-related diseases.

   Over the last few years, many senolytic agents have been identified and tested on lab animals. There are ongoing human trials involving Metformin, Resveratrol, FOXO4-related peptides, a combination of dasatinib (chemotherapy agent to treat leukemia) and quercetin, Azithromycin and Roxithromycin, HSP90 inhibitors, navitoclax and TW-37, Fisetin (a natural polyphenol found in seaweed and strawberries), and piperlongumine (an extract of long pepper root), to name a few. Scientists are also currently developing safer, non-toxic chemotherapy-based agents that act as senolytics, including Rapamycin, Navitoclax and Dasatinib (PMID: 30006159). These have all shown potential to selectively kill senescent cells and decrease oxidative stress, and some are readily available to the public over the counter or through prescription.

   If these ongoing clinical trials prove the effectiveness of senolytic agents, they could bring hope to the wide range of patients suffering from severe, debilitating age-related diseases.

2. Cell division and Telomere lengths:

   A popular theory of how aging progresses involves the body’s telomeres, suggesting that the shortening of telomere length over the cycle of lifelong cell division causes the body to slow its regenerative processes and lead to aging. Although this theory of aging was remarkably popular when first introduced, its validity is debatable.

   Our cells contain a wide variety of telomere lengths naturally, and recent evidence has revealed that the correlation between telomere length and age-related complications in individuals is low (Müezzinler et al., 2013; Breitling et al., 2016; Marioni et al., 2016). This has led investigators to continue searching for other biomarkers that can be used in the prediction of age-related diseases with higher accuracy.

   The pill TA65, derived from chinese astragalus, was promoted as a method of stopping the shortening of telomere length and expanding life span, despite the fact that its effects were only studied in 6 patients. In the field of aging treatments, hyped-up medicines with little to no proven results are all too common.

   Despite the faults in this theory, telomere length may still be related to aging, even if not the direct cause. The process of aging results in multiple changes at both the molecular and cellular levels, including cellular senescence, telomere attrition, and epigenetic alterations.
(Lopezotin et al., 2013). Among these hallmarks, telomere length is a remarkable characteristic of aging and linked with age-related health status (Rizvi et al., 2015). The rate of shortening rather than the absolute telomere length may be a better predictor when it comes to connecting telomeres to the aging process. (Aging 2018, 10, 3397–3420)

3. Other Theories
Cellular damage has been the target of aging research for years, producing plenty of theories with varying levels of validity. For example, reactive oxygen species (ROS) are DNA damaging molecules shown to be widely linked to aging. Mutations in proteins that participate in free radical detoxification can also affect variation in aging and life span. As for genetic causes, the list is lengthy and complicated. There are 6 genetic diseases with identified genes involved in the accelerated aging process, each currently used by scientists to study the genetic aspect of aging. There are many genes identified as the genes of aging itself, and in order to make this article as simple as possible, we will avoid going into details in that regard.

These are only a small sample of the many theories on how aging progresses, but they all have the potential to propel the science of disease prevention to new heights if given plenty of research and review.

How to Measure Biological Aging:
There are two ways to measure aging, the first being a person’s chronological age, which is based on the date of birth. The second is referred to as biological age, which is the actual functionality and youthfulness of the body regardless of chronological age. Currently, the best measure of biological age is DNA methylation. Anyone can check their own methylated DNA by simply sending a buccal swab to qualified labs like Cygenia in Germany or Chronomics in London. Having this information can help individuals take personalized measures to ensure their health and longevity, including lifestyle changes and the use of certain supplements or medications.

Variables in the Speed of Aging:
Although the definitive cause of aging is up for debate, there are certain factors that have been proven to slow or accelerate the process. Cigarette smoking is observed to strongly drive mortality-associated predictive DNA methylation changes, alongside other health risks it causes. Drinking has been shown to affect methylation in a similar manner. Calorie restriction has been proven to slow the process of aging in numerous studies. Another study showed that a vitamin and antioxidant rich diet can promote methylation of DNA in type II Diabetes Mellitus. Those in middle age are likely to experience accelerated methylation change, although men are at higher risk than women. No matter your current age or lifestyle, understanding aging and its potential causes can help make decisions for lifelong wellbeing.
In this installment of our “slowing aging” series, we will be delving into various senolytic agents, which are supplements and drugs capable of treating aging and age-related diseases. However, senolytic agents are not the only approach patients can take to controlling their health. Activities that are proven to slow aging include:

1. Avoid exposure to agents and behaviors that accelerate DNA methylation and the process of aging, such as smoking, drinking alcohol, high sugar intake, etc.

2. Eating less through intermittent fasting and a healthy level of calorie restriction.

3. Engaging in regular exercise.

When daily activity isn’t enough to treat aging and its related issues on its own, senolytic agents such as these have been shown to help:

1. **NAD+** (Nicotinamide adenine dinucleotide): NAD+ is a coenzyme fundamental to producing cellular energy in the mitochondria, which are commonly referred to as “the powerhouses of the cells”. As we age, or in some cases due to disease, the body’s natural level of NAD+ production drops. Increasing a person’s level of NAD+ is one of many ways to slow down the process of aging and increase their energy. NAD+ can be supplemented through injection or oral supplements of its precursors, NR and NMN.

2. **Resveratrol**: A substance found in over 70 different commonplace plants such as grapes and berries, Resveratrol has been shown to possess anti-aging benefits. Plants produce resveratrol when under stress or exposed to bacteria and fungus, such as through fermentation. According to several studies, Resveratrol mimics the rejuvenating effects of calorie restriction. Resveratrol has also been shown to possess anticancer and antiviral effects. Studies show it is safe even when taken at a relatively high dose of 5 grams a day.

3. **Metformin**: Metformin, a drug extracted from French lilac to treat type two diabetes, has been in use in England since 1958 and in the United States since 1995. Recent studies have found that Metformin can also delay the process of aging by stimulating the AMPK pathway. The double-blinded TAME (targeting aging with Metformin) trial being sponsored by the American Federation for Aging Research (AFAR) is currently investigating the drug’s effectiveness as a senolytic agent, as are others currently in various stages of study. Although it has promise, patients should be aware of its potential to cause vitamin B deficiency. In my practice, I run genetic tests on various genes responsible for the methylation of vitamin Bs before prescribing Metformin as an anti-aging medication in order to supplement it properly with the most effective form of vitamin B; this could be either the standard form or the methylated form for specific patients who are genetically incapable to methylate it. In those who have kidney malfunction, it can cause lactic acidosis.

4. **Quercetin**: A chemical found in large amounts in apples and onions, Quercetin is proven to slow aging. Supplements are easily available to the public.

5. **Infrared Sauna**: This unique form of sauna works by stimulating the PNC1 gene, which increases NAD+ production naturally. These few senolytic agents are only a fraction of a rapidly expanding library currently under evaluation.
Other treatments have not been fully verified but show great potential for future application. These include:

1. **Klotho protein**: This protein shows potential to slow down the process of aging and treat age-related diseases when used as a therapeutic agent. Recently, a company named “Klotho Therapeutics” began research on the compound, although only on animal subjects for the time being. This is one of many labs currently investigating its potential. There are 3 different genetic variations for the gene regulating Klotho production in the body. As we age, our levels of Klotho drop and we become vulnerable to age-related diseases. Theoretically, if we increase the level of Klotho protein, we could potentially treat age-related diseases such as dementia, cancer, and kidney disease.

2. **Rapamycin** is another agent that can expand longevity by suppressing the mTORC1 gene, although all current forms are too hazardous to be used safely. Scientists are working to extract the beneficial values of Rapamycin in order to retain its anti-aging properties without the serious side effects it induces.

3. A specific **SIRT1 activator** that has been previously shown to cause life extension and betterment of metabolic impairments in mice fed a high-fat diet, but this method has not been verified in human trials.

4. More recently, it has been found that **SRT1720** supplementation can result in life span extension and delayed onset of age-associated metabolic diseases in mice fed a standard diet. Like its cousin treatment listed before, human trials for the drug have not yet begun.

5. **Exosomes**: As mentioned in my previous articles, the science of exosomes is in infancy. There are many potential treatment options utilizing exosomes derived from stem cells on the horizon. Currently, some companies provide commercial exosome products for IV infusion advertised as treatments for aging and age-related diseases as well as for cosmetic use. The FDA has no control or oversight on these products. These treatments are not FDA cleared or approved. I personally ordered samples of these products and sent them in for lab testing to determine their true components; the lab results exposed that one of the two companies tested was falsely selling salt and sugar solutions instead of exosomes. That company is still in business. If you decide to spend thousands of dollars on exosome treatment, make sure you get what you pay for.

A Parting Word: Many companies are currently working to discover cures for the disease of aging and its complications. It is quite possible to find a cure during our lifetime. The insights illustrated in this article are not definitive cures or treatments, only gateways to understanding the complicated world of ageing science.

*Please consult your physician before starting any medications or supplements.*