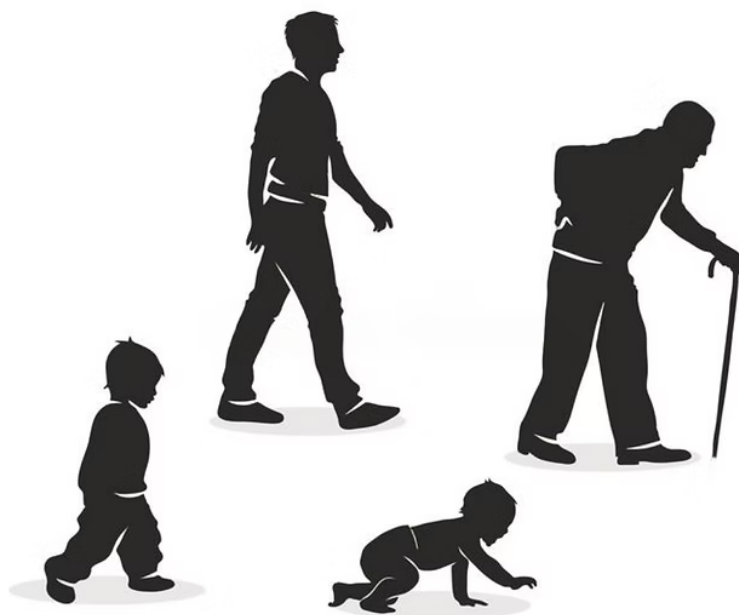




TARGETING AGING

Hassanali Bhimji, Marco Chamorro, Tina Su



Source: Dreamstime

Introduction

Aging is a natural process that occurs in all living organisms, except for a few simple plants, bacteria, and animals. Although the biological mechanisms of aging are not fully understood, research is underway to uncover these mechanisms. Human aging is believed to be based on a combination of genetic, lifestyle, and environmental factors. In this article, we will explore the leading theories on the biological basis of aging, the societal impact of aging, and current efforts to target aging.

Molecular Basis of Aging

One of the leading theories of aging is the telomeric theory of aging. Telomeres are repeating DNA sequences that prevent chromosome ends from fraying and sticking together. During each round of DNA replication, telomeres shorten by 30 to 200 base pairs. Smoking, lack of physical activity, obesity, stress, and pollution exposure have been shown to accelerate telomere shortening. Telomere shortening has been linked to several diseases, such as bone

cancer, prostate cancer, and heart disease. Longer telomeres have also been associated with a longer lifespan. Telomerase, an enzyme that adds bases to the ends of telomeres, has shown promise in reversing telomere shortening (NCBI [Telomeres, lifestyle, cancer, and aging]).

Another factor in aging is mitochondrial dysfunction, which occurs when mitochondria no longer function properly. This leads to a decrease in ATP production and an increase in the production of reactive oxygen species. Mitochondrial dysfunction is linked to several age-related health issues, including heart disease, neurodegenerative disorders, and cancer. It is also hypothesized to contribute to the aging process itself, as the decline in cellular energy production and increase in reactive oxygen species production can lead to cellular damage and dysfunction (NCBI [Mitochondrial Aging and Age-Related Dysfunction of Mitochondria]).

Telomere shortening and mitochondrial dysfunction are just a few of the many factors that drive aging. Although there are many complex pathways involved in aging, it is also essential to consider the societal impact of aging.

Social Impact of Aging

Aging has been a major issue in society for the past years. The current aging society is leading to an increase in long-term healthcare demand, shortage of workforce, and problems with old age social security.

The surge of elderly people needing healthcare creates a large economic expenditure. An average nursing home with a private room in California costs around \$11,000 per month, according to a study in 2020 (Comprehensive Advisor [How Much Does Long Term Care Really Cost in California]). With the current economic recession, many average American families are not able to afford such a room for one elderly relative. As life expectancy continues to grow, many families have four or more elderly members that need to be admitted into care centers. Many of these elderly people also have pre-existing health issues that require special professional medicare. Care centers with specialized nurses add more to the total expense of nursing homes. Therefore, the resolution of these elderly people becomes an economic burden for many young couples.

The aging population also reveals that the ratio of elderly people to young people has drastically increased. According to the World Health Organization, between 2015 and 2050, the population of elderly people aged 60 and above will almost double from 12% to 22% (WHO [Aging and Health]). Meanwhile, data collected from the National Center for Health Statistics shows a sharp decline of birth rates in recent years (WHO [Aging and Health]). The declining birth rates further creates a severe aging population. Many of the elderly people are unable to continue being active in the workforce due to physical health impairment, which leads to various labor shortages in the US. This shortage may lead to a higher inflation rate and a decrease in average household income. The lowered income will cause an increase in family economic burden which creates a vicious cycle

...which leads to an increase in family economic burden, which creates a vicious cycle.

An aging society also leads to an unstable old age income security. Currently, most seniors live with basic economic support from their retirement income. This minimal income is barely adequate or sometimes inadequate to cover an individual's basic needs (Economic Policy Institute [Financial Security of Elderly Americans at Risk]). Therefore, many people rely heavily on Social Security and Medicare. However, as the demand for Social Security increases overtime, the cost of these services will also increase. Furthermore, this increase will rise faster than the tax income for average American families because of the increased elderly population (NASI [How will Boomers Affect Social Security]). The society will not be able to afford supporting the elderly people.

To address these issues, many healthcare businesses are looking for resolutions to slow down the process of aging.

Targeting Aging

Unity Biotechnology

Unity Biotechnology, a Bay Area-based company, has developed a potent Bcl-xL inhibitor (UBX1325) currently in clinical trials to eliminate senescent cells in diabetic macular edema, age-related macular degeneration, and diabetic retinopathy (Unity Biotechnology [UBX1325]). Senescent cells have ceased to divide and have entered a state of permanent growth arrest, also known as senescence. These cells don't die when they should and release inflammatory cytokines, contributing to aging-related diseases. As the immune system becomes less efficient with age, senescent cells accumulate and damage neighboring, healthy cells (NIA [Does cellular senescence hold secrets for healthier aging?]). Their Phase 2 results show that targeting senescence may reduce the impact of aging:

- A single injection of UBX1325 led to a statistically significant and clinically relevant improvement in Best Corrected Visual Acuity of 7.6 ETDRS letters at 24 weeks compared to placebo treatment.
- UBX1325 maintained stabilization of the retinal structure, as measured by central subfield thickness at 24 weeks, as compared to worsening from baseline in placebo-treated patients.
- The proportion of rescue-free patients in the UBX1325-treated arm was 59.4% at 6 months after a single injection, compared to only 37.5% in the placebo-treated arm (Unity Biotechnology [Unity Biotechnology Announces Positive 24-week Data From Phase 2 Behold Study of Ubx1325 in Patients With Diabetic Macular Edema]).

Drug Discovery Lab at UCLA

Here at UCLA, Dr. Varghese John's Drug Discovery Lab is working to develop new small molecule compounds as therapeutics for Alzheimer's Disease (AD). AD is a progressive neurodegenerative disorder that affects memory, thinking, and behavior. It is the leading cause of dementia; its most significant risk factor is age (Alzheimer's Association [What is Alzheimer's Disease?]). Currently approved AD therapeutics (tacrine, donepezil, rivastigmine,

galantamine, and memantine) only provide unsustained symptomatic relief and do not stop disease progression. Dr. John's lab aims to change this by identifying new therapeutic targets and developing small-molecule drugs that can modulate novel targets. These include:

- **BACE Inhibitors:** Amyloid precursor protein (APP) is cleaved by the enzyme BACE, which produces A β , a protein that aggregates and damages neurons.
- **sAPP α Enhancers:** APP can be processed by an enzyme called ADAM10, which leads to the production of a neurotrophic protein called sAPP α . sAPP α reduces the production of A β and is needed for the normal functioning of the synapses between neurons.
- **APP-C31 Inhibitors:** In addition to BACE and ADAM10 cleavage, APP may be cleaved by an enzyme called a caspase to form a toxic molecule called APP-C31. APP-C31 formation is increased during early AD and is associated with inflammation.
- **SirT1 Enhancers:** SirT1 is a longevity determinant found in the brain and body that promotes healthy aging. It is found to be lower in the blood serum of AD patients.

Dr. John's lab has created a new chemical entity called DDL110, a small molecule that increases the sAPP α to A β ratio by interacting with two brain cell receptor pathways (crosses the blood-brain barrier). It was shown to have improved AD-like deficits to a greater degree than currently approved drugs in a mouse model and is now in clinical trials (John [Research]).

Bryan Johnson - Blueprint

Bryan Johnson, a 45-year-old Silicon Valley millionaire, has enlisted a team of over 30 doctors to monitor each of his organs and over 100 biomarkers to reverse his epigenetic age to 18 years old at the cost of **\$2 million per year**. His routine is available to follow on his website (<https://blueprint.bryanjohnson.co/>) and consists of reasonable protocols such as a skincare, workout, bedtime, and oral care routine, but also includes eating the same three optimized, vegan meals each day, 50 daily supplements, monthly blood tests, and more.

In 2021, he reduced his epigenetic age from 47 to 42, slowed his pace of aging by 28%, and achieved 50+ perfect biomarkers and 100+ biomarkers, indicating he is less than his chronological age and has the physical fitness of an 18-year-old (Johnson [Blueprint]).

While his methods may strike as biotech-infused snake oil and may sound extreme, Johnson is breaking ground in the field of longevity and is proving the effects that lifestyle can have on aging, or rather, on reversing aging.

