**The intersection of biotechnology and anti-Aging: Pioneering the future of youthful**

**living**

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**ABSTRACT**

This chapter explores the exciting overlap between biotechnology and anti-aging research. It overviews the aging process, delves into the cellular and molecular mechanisms involved, and introduces revolutionary biotechnological advancements such as gene editing and regenerative medicine. The chapter also examines the ethical considerations surrounding life extension and discusses potential societal implications. Ultimately, it highlights the transformative potential of biotechnology in reshaping the future of youthful living and outlines future research directions in the field.

**Keywords**- Rejuvenation; longevity; Aging process; Cellular mechanisms; Molecular mechanisms; gene editing; Regenerative medicine; Ethical considerations; Life extension; Societal implications.

**I. INTRODUCTION**

In a world where advancements in biotechnology are rapidly transforming scientific frontiers, pursuing extended and enhanced youthful living has become a subject of great interest and intrigue. The intersection of biotechnology and anti-aging represents a promising avenue for revolutionizing our understanding of aging and exploring innovative approaches to rejuvenation and longevity. The journey begins with an overview of the aging process, elucidating the complex interplay of genetic, environmental, and lifestyle factors contributing to cellular damage and functional decline over time. By understanding the intricacies of aging, we can better appreciate the challenges and opportunities that lie ahead in our pursuit of prolonged youthfulness. Building upon this foundation, the chapter explores the cellular and molecular mechanisms of aging, diving deep into the role of telomeres, DNA damage, cellular senescence, and epigenetic modifications. Understanding these mechanisms sheds light on the fundamental aspects of aging and paves the way for targeted interventions and therapeutic strategies. The advent of biotechnology has propelled anti-aging research into new realms of possibility. This chapter showcases the revolutionary advancements in gene editing, stem cell therapies, tissue engineering, and regenerative medicine that hold tremendous potential for rejuvenating aging tissues, reversing age-related diseases, and enhancing overall health span. While the promises of biotechnology in anti-aging are captivating, addressing the ethical considerations accompanying these developments is crucial. The chapter discusses the ethical boundaries of manipulating human biology, ensuring equitable access to life-extension technologies, and navigating the potential societal implications of extended longevity. This chapter aims to explore the dynamic interplay between biotechnology and anti-aging research, uncovering the cutting-edge scientific breakthroughs, revolutionary therapies, and ethical considerations that shape the future of youthful living. By delving into the underlying mechanisms of aging and unveiling the transformative potential of biotechnology, this chapter sets out to paint a comprehensive picture of the groundbreaking advancements in this field.

**II. THE AGING PROCESS: AN OVERVIEW**

Aging refers to a natural and progressive change that occurs in the human body or any living body over time. It combines complex phenomena like genetic, environmental and lifestyle factors. As it is a universal process it can manifest differently in different individuals [1]. Some key aspects associated with it are cellular and molecular changes, physiological changes, cognitive decline, hormonal changes, immune function, lifestyle factors, genetic factors. While ageing is a natural process, it is essential to remember that it does not always result in bad health or a worse quality of life. Adopting good behaviors and getting the right medical treatment can promote healthy ageing and reduce age-related problems. A number of things can affect how quickly one ages [2].

*A. Genetic, Environmental, and Lifestyle Factors*

A.1. Genetic factors

*Genetic predisposition:* Some people may carry genes linked to longer lifespans and better health as they age. Understanding genetic influences can aid in risk assessment and direct individualized anti-aging strategies [3].

*Telomeres:* Cellular ageing is influenced by telomeres, the protective caps at the ends of chromosomes [4]. Anti-aging research is interested in preserving telomere length or reducing their shortening [5].

*Single Nucleotide Polymorphisms (SNPs):* Changes in certain genes (SNPs) can affect how the body metabolizes nutrition, reacts to stimuli from the environment [6], and controls inflammation, which can have an impact on how old you are [7].

A.2. Environmental factors

*UV rays:* Prolonged sun exposure has been shown to hasten the ageing process of the skin, causing wrinkles, age spots, and other skin damage [8]. These effects can be minimized by wearing protective clothes and sunscreen [9].

*Pollution:* Particulate matter and airborne toxins are examples of environmental pollutants that may accelerate the ageing process by causing inflammation and oxidative stress [10].

*Lifestyle choices:* Bad habits like smoking and drinking too much alcohol can have an adverse impact on general health and accelerate the ageing process [11], [12] .

A.3. Lifestyle factors

Diet: An antioxidant-rich, vitamin- and mineral-rich diet helps maintain cellular health and fight oxidative stress linked to ageing [13], [14].

*Exercise:* Regular physical exercise helps preserve cardiovascular health [15], [16], bone density [17], and muscular mass [18]. Additionally, it might boost circulation and general well-being [19].

Sleep: Cellular repair, cognitive function, and hormone control depend on getting enough good sleep [20], vital for healthy aging [21].

*Management of stress:* Long-term stress damages cells and affects hormones, speeding up aging. It might be advantageous to practice stress-reduction practices like mindfulness and meditation [22].

*B. Telomeres: Guardians of Cellular Aging*

The distinctive DNA-protein structures known as telomeres, which are present at both ends of each chromosome, shield the genome from inter-chromosomal fusion, unneeded recombination, and nucleolytic breakdown [5]. Telomeres are consequently essential for protecting the data in our genome. Each time a cell divides, a little telomeric DNA is lost as part of the regular cellular process [23]. Senescence and/or apoptosis occur in the cell when the length of the telomeres exceeds a crucial threshold. It shortens with age and rate of telomere shortening may indicate the pace of aging, shortening can accelerate due to certain lifestyle factors including smoking, obesity, lack of exercise, and intake of unhealthy diets, which can result in sickness and/or premature mortality [24]. Numerous age-related health issues, including coronary heart disease, heart failure, diabetes, elevated cancer risk, and osteoporosis, have an earlier beginning when telomere shortening is present [25].

*C. DNA Damage and Repair*

According to this theory, unrepaired DNA damage contributes to genomic instability and ageing. Age-associated DNA damage may consist of DNA breaks, cross-links, and changed bases (such as oxidative lesions), however it is yet unclear which particular DNA lesions cause ageing [26]. This hypothesis fits into a larger idea that ageing is caused by a widespread loss of molecular integrity. In light of this, it has been postulated that natural selection has helped humans preserve ideal biomolecular fidelity throughout the height of our reproductive capacity. Genomic maintenance has been compared to a double-edged sword [27]since mutations can occur when DNA damage from external and endogenous causes is not completely repaired. These mutations cause evolution through natural selection in germline cells. These mutations may speed up ageing in multicellular animals' somatic cells [28].

*D. Cellular Senescence: Implications in Aging*

Senescence of cells can result from stochastic damaging events. One of the primary causes of aging is now recognized to be the senescence-related cellular stress response [29]. This idea is supported by fibroblasts from progeroid disease patients who typically exhibit accelerated senescence. On the other hand, the oxidative damage that causes growth arrest in vitro is unaffected by fibroblasts from long-lived Snell dwarf mice. Due to the development of the senescence-associated secretory phenotype, which affects the cellular milieu, senescent cells now seem to play a significant role in the aging process [30]. This trait of senescent cells is reportedly a reaction to genotoxic stress. Senescent cells build up in various tissues throughout time, indicating that they develop more quickly than they degrade or are eliminated. Another crucial anticancer process is the cellular stress response associated with senescence. In fact, the tumor suppressor p53 is crucial for controlling the processes that lead to DNA repair, apoptosis, and senescence [31]. It has been suggested that the senescence response may contain antagonistically pleiotropic characteristics since data suggests that senescence causes both degenerative and hyperplasic diseases. Senescence thus is another example of how poor homeostasis underlies aging. It should be noted that germ cells and ESCs do not age; this is an example of germline evasion of faulty homeostasis [32].

*E. Epigenetic Modifications and Aging*

Epigenetic modifications play a significant role in the aging process. Epigenetics refers to changes in gene expression that do not involve alterations to the underlying DNA sequence. Instead, epigenetic modifications involve chemical modifications to DNA and its associated proteins, such as histones, which can influence how genes are turned on or off [33].

E.1. Several key epigenetic mechanisms have been implicated in aging

*DNA Methylation*: DNA methylation involves adding a methyl group to specific DNA sequences. As we age, patterns of DNA methylation can change, leading to alterations in gene expression. Some genes become more methylated, leading to decreased expression, while others become less methylated, potentially increasing expression. Changes in DNA methylation can affect processes like cellular differentiation and response to stress [34].

*Histone Modifications:* Histones are proteins that help package DNA into a compact cell structure. Various chemical modifications to histones, such as acetylation and methylation, can influence how tightly DNA is wrapped around them. Changes in histone modifications can affect gene accessibility and expression, potentially impacting aging-related processes [35].

*Non-Coding RNAs*: Non-coding RNAs, such as microRNAs and long non-coding RNAs, play roles in gene regulation. They can interfere with translating messenger RNAs (mRNAs) into proteins or influence chromatin structure. Dysregulation of non-coding RNAs has been associated with aging-related diseases and processes.

Chromatin Remodeling: Chromatin remodeling complexes are responsible for altering the structure of chromatin, thereby influencing gene accessibility. Chromatin structure changes can affect transcription factors' ability to bind to DNA and regulate gene expression [36].

Both genetic and environmental factors influence epigenetic modifications. While some epigenetic changes occur naturally with age, external factors such as diet, stress, exercise, exposure to toxins, and lifestyle choices can also impact epigenetic patterns. These changes can contribute to cellular senescence, inflammation, and other processes associated with aging and age-related diseases [37].

**III. CELLULAR AND MOLECULAR MECHANISMS OF AGING**

Aging is a complex and multifaceted process involving genetic, cellular, and molecular changes over time. While our understanding of the mechanisms underlying aging is still evolving, several key cellular and molecular processes have been identified as contributing to the aging process (Fig 1). Here are some of the important cellular and molecular mechanisms of aging:

*Genetic Factors:* Genetic predisposition plays a significant role in determining how individuals age. Genetic mutations and variations can influence the rate of aging, susceptibility to age-related diseases, and overall lifespan. Epigenetic changes, which involve modifications to the DNA and its associated proteins without altering the underlying genetic code, also contribute to aging by affecting gene expression and cellular function [38].

*Telomere Shortening:* Telomeres are the protective caps at the ends of chromosomes, and they shorten with each cell division. When telomeres become critically short, cells can enter a state of senescence (permanent growth arrest) or undergo apoptosis (cell death). Telomere shortening is considered a hallmark of cellular aging and is associated with various age-related diseases [5].

*Cellular Senescence:* Cellular senescence refers to the state in which cells lose their ability to divide and function properly. Senescent cells accumulate in tissues over time and secrete various molecules, collectively known as the senescence-associated secretory phenotype (SASP), which can promote inflammation and tissue dysfunction, contributing to aging and age-related diseases [32].

*Mitochondrial Dysfunction:* Mitochondria are the energy-producing organelles within cells. Over time, mitochondrial function can decline, leading to reduced energy production, increased reactive oxygen species (ROS) production, and cellular damage. Mitochondrial dysfunction is linked to various age-related conditions, including neurodegenerative diseases and cardiovascular disorders [39].

*Protein Homeostasis (Proteostasis) Decline*: Maintaining proper protein folding and degradation is essential for cellular function [40]. As cells age, they may struggle to maintain protein homeostasis, leading to the accumulation of misfolded or aggregated proteins. This can contribute to the development of diseases such as Alzheimer's and Parkinson's [41].

*Inflammation:* Chronic low-level inflammation, often called inflammation, is a hallmark of aging. It involves the persistent activation of the immune system, which can contribute to tissue damage and the progression of age-related diseases [36].

*Autophagy Decline:* Autophagy is a cellular process that removes damaged or dysfunctional cellular components. As cells age, their ability to perform efficient autophagy may decline, accumulating cellular debris and contributing to aging-related problems [42].

*Hormonal Changes:* Changes in hormone levels, such as a decline in sex hormones (e.g., estrogen and testosterone), can impact various physiological processes and contribute to age-related changes in tissues and organs [43].

*DNA Damage and Repair:* Over time, cells accumulate DNA damage due to various factors, including environmental stressors and normal metabolic processes. Efficient DNA repair mechanisms help maintain genomic integrity, but as cells age, these repair processes can become less effective, leading to the accumulation of mutations and potentially contributing to aging and cancer [28].

*Oxidative Stress:* Oxidative stress occurs when there is an imbalance between the production of ROS and the body's ability to neutralize them with antioxidants. Excessive oxidative stress can damage cellular components, including lipids, proteins, and DNA, and contribute to aging and age-related diseases [39].

These cellular and molecular mechanisms are interconnected and can influence each other, contributing to the complex process of aging. Researchers continue to study these mechanisms to better understand how they interact and how interventions might be developed to promote healthy aging and mitigate age-related diseases.



**Figure 1. Hallmarks of aging**

**IV. BIOTECHNOLOGY AND ANTI-AGING: REVOLUTIONARY ADVANCEMENTS**

*A. Gene Editing: Precision Tools for Rejuvenation*

Gene editing could be a precision tool for addressing the biological processes underlying aging. While the quest for eternal youth remains a distant goal, gene editing technologies hold promise for mitigating some of the effects of aging and age-related diseases. Targeting Senescence: Cellular senescence is when cells cease to divide and accumulate with age. These senescent cells can contribute to tissue inflammation and dysfunction. Researchers are exploring gene editing techniques to selectively eliminate or modify these cells, potentially restoring tissue function and delaying age-related decline [44].

*DNA Repair:* Accumulated DNA damage over a lifetime is a key contributor to aging and age-related diseases. Gene editing technologies could be used to repair specific DNA lesions, reducing the burden of mutations and enhancing cellular function [26].

*Telomere Extension:* Telomeres, which protect the ends of chromosomes, shorten with each cell division. Eventually, critically short telomeres lead to cellular senescence. Gene editing might offer a way to extend telomeres, allowing cells to divide more times before reaching a senescent state [45].

*Epigenetic Modifications:* Epigenetic changes, alterations in gene expression without changes in the DNA sequence, play a role in aging. Gene editing could revert or adjust these epigenetic marks to restore more youthful gene expression profiles [38].

*Mitochondrial Health:* Mitochondria, the cellular powerhouses, decline in function with age, contributing to various age-related diseases. Gene editing could potentially target genes related to mitochondrial health, enhancing their function and delaying cellular decline [39].

*Age-Related Disease Treatment:* Gene editing could correct genetic mutations predisposing individuals to age-related diseases such as Alzheimer's, heart disease, and diabetes. The risk of developing these conditions could be reduced by editing these disease-associated genes [46].

*Immunosenescence Reversal*: The aging immune system becomes less efficient at fighting infections and cancer [47]. Gene editing could help restore immune cell function, enhancing the body's ability to protect itself against diseases [48].

*Lifespan Extension:* While directly extending the human lifespan is complex and controversial, gene editing could contribute to overall health span extension—increasing the period of life spent in good health. This would involve targeting genes and pathways associated with age-related diseases and deterioration [49].

*B. Stem Cell Therapies: Restoring Youthful Potential*

In general, cells deteriorate and finally die through apoptosis when the number of cell divisions surpasses the Hayflick limit. Adult stem cells are in charge of these procedures in various tissues, replacing dead cells to preserve normal tissue function and healing wounds. Therefore, adult stem cells are essential for preventing the aging of tissues and organs and postponing the onset of old age. Adult stem cells, however, may experience cellular senescence and apoptosis as they age. Adult stem cells do exhibit senescence-specific characteristics during the expansion and culture processes, such as morphological alterations, reduced proliferative activity, and imbalanced biological activities [50].

The capacity of adult stem cells to replenish most tissues in multicellular animals to regenerate and self-renew decreases with aging. The accumulation of DNA mutations, telomere attrition, apoptosis, and senescence may contribute to stem-cell reserves' exhaustion with aging. Loss of functioning stem cells may be especially sensitive in organs like bone marrow, the intestines, and others that proliferate a lot. As a result, an organism's tissues do not age equally. It has been proposed that the tissue-dependent poor balance between stem cell self-renewal and differentiation is the overall cause of the reduction in stem cell pools [51].

*C. Tissue Engineering: Regenerating Aging Tissues*

Tissue engineering is a multidisciplinary field that combines principles of biology, engineering, and medicine to develop strategies for regenerating or repairing damaged tissues and organs. In the context of aging, tissue engineering aims to address the age-related decline in tissue function by creating artificial tissues or promoting the regeneration of native tissues. Scaffold bases approaches in tissue engineering involve the creation of a scaffold, a 3-D structure that mimics the extracellular matrix of the target tissue. This scaffold provides a framework for cells to attach, grow and differentiate. In the case of aging tissues, scaffolds can be designed to support the regeneration f deteriorating tissues, such as cartilage, bone, and cell [52].

*Cell Seeding and Culture:* Cells are seeded onto the scaffold and cultured in a controlled environment that mimics the conditions required for tissue growth [53]. This includes providing nutrients, oxygen, and mechanical cues to encourage cell proliferation and differentiation [54].

*Bioreactors and Mechanical Stimulation:* Applying mechanical forces, such as stretching or compression, to the developing tissue can enhance cell alignment, tissue maturation, and overall functionality. Bioreactors are devices that provide dynamic culture conditions, such as fluid flow or mechanical loading, to improve tissue development [55].

*Biochemical Signaling:* Growth factors, cytokines, and other biochemical cues are often used to promote specific cell behaviors, such as differentiation into the desired cell type or the secretion of specific extracellular matrix components [56].

*Vascularization:* Establishing a functional blood supply is crucial for sustaining the growth and survival of large tissue constructs. Techniques such as pre-vascularization, where blood vessels are engineered before implantation, help ensure proper nutrient and oxygen delivery to the regenerated tissue [57].

*Implantation and Integration:* Once the tissue is developed in the lab, it can be implanted into the patient's body. The success of integration depends on factors such as immune response, tissue compatibility, and the ability of the regenerating tissue to form connections with the host tissue [58].

*Monitoring and Long-Term Assessment:* After implantation, the regenerated tissue's performance and integration with the host tissue need to be monitored over time [59]. This may involve various imaging techniques and functional assessments to ensure proper tissue function and longevity [60].

Tissue engineering holds great potential for regenerating aging tissues, such as damaged cartilage, bone, muscle, skin, and even entire organs. While significant progress has been made in the field, challenges remain, such as achieving proper tissue vascularization, long-term stability, and avoiding immune rejection. As technology and our understanding of tissue biology continue to advance, tissue engineering approaches have the potential to revolutionize the treatment of age-related tissue degeneration and improve the quality of life for aging individuals [61].

**V. ETHICAL CONSIDERATIONS IN BIOTECHNOLOGY AND ANTI-AGING**

*A. Access and Equity in Life Extension Technologies*

As new anti-aging technologies are developed, ensuring equitable access to these treatments becomes paramount. There should be efforts to prevent these treatments from becoming available only to a privileged few, thereby exacerbating social inequalities [62].

*B. Ethical Boundaries of Manipulating Human Biology*

*Informed Consent:* Any medical or biotechnological intervention, including anti-aging treatments, must ensure that individuals provide fully informed consent. This means they understand the risks, benefits, and potential outcomes of the treatment and are able to make an autonomous decision. It's essential to avoid exploiting vulnerable individuals or misleading them about the true nature of the intervention [63].

*Safety and Efficacy*: Thorough testing and validation of anti-aging interventions are crucial. Treatments should be backed by rigorous scientific research, clinical trials, and evidence-based results to ensure their safety and efficacy.

*Long-Term Effects:* Anti-aging interventions might have long-term effects that are not fully understood at the outset. Ethical considerations involve ongoing monitoring and research to assess the potential risks and benefits of these treatments over extended periods.

*Quality of Life vs. Quantity of Life*: Biotechnological interventions in anti-aging raise questions about the balance between extending lifespan and improving the quality of life. Prolonging life without addressing age-related health issues could lead to prolonged suffering, which should be carefully considered.

*Interference with Natural Processes:* Some argue that anti-aging interventions interfere with the natural aging process, potentially disrupting the cycle of life and death. Ethical debates arise about whether it is appropriate for humans to manipulate the aging process.

*Unintended Consequences:* Biotechnological interventions can sometimes have unintended consequences, both at the individual and societal levels. Ethical considerations involve anticipating and mitigating these potential outcomes.

*Identity and Existential Considerations:* Prolonging life significantly could lead to profound questions about personal identity, relationships, and the meaning of life. Ethical discussions should encompass these existential considerations.

*Regulation and Oversight:* Robust regulatory frameworks are needed to ensure that anti-aging interventions are appropriately tested, evaluated, and monitored. Regulatory bodies should be equipped to adapt to the rapid pace of biotechnological advancements.

*Transparency and Accountability:* Researchers, developers, and practitioners should maintain transparency in their work, sharing both successes and failures, to foster accountability and trust within the scientific and broader communities.

*C. Socio-Economic Implications of Life Extension*

The potential for life extension through biotechnological interventions has significant socio-economic implications that need careful consideration. As we explore these implications, it's important to acknowledge the complex interplay between technology, ethics, and society [64].

*Cost and Resource Allocation:* Developing and implementing anti-aging interventions can be resource-intensive. Decisions must be made about allocating limited resources to balance the pursuit of anti-aging technologies with other pressing healthcare needs.

*Cultural and Religious Perspectives:* Different cultures and religions have diverse views on aging, life, and death. Ethical considerations should respect and incorporate these perspectives in developing and implementing anti-aging technologies.

*Increased Healthcare Costs:* While life extension technologies could lead to healthier and longer lives, they might also increase healthcare costs. Older individuals often require more medical care, and extending their lifespan could strain healthcare systems and resources.

*Pension and Retirement Systems*: Longer lifespans could impact pension and retirement systems. If people live significantly longer, there might be a need to reconsider retirement ages, pension plans, and other social safety net programs to ensure financial sustainability.

**VI. THE FUTURE OF YOUTHFUL LIVING: TRANSFORMATIVE POTENTIAL**

*A. Reshaping the Future of Health and Vitality*

Reshaping the future of health and vitality in aging requires a concerted effort from individuals, communities, governments, and the private sector. By combining scientific advancements with compassionate care, inclusive policies, and a commitment to lifelong well-being, we can create a future where people can age gracefully while maintaining their health, vitality, and dignity. It includes Preventive Healthcare, Personalized Medicine, Digital Health and Telemedicine, Cognitive Health, Social Support and Community Engagement, Interdisciplinary Collaboration Health Literacy and Education, Long-Term Care Innovation: Ethical Considerations: Policy and Advocacy, Economic Planning and Workforce Adaptation, Public Awareness and Attitude Shifts, Research and Innovation, Global Collaboration [65].

*B. Promising Avenues for Biotechnology and Anti-Aging*

Promising avenues for biotechnology and anti-aging research offer exciting possibilities for extending human lifespan, enhancing health span (the period of life spent in good health), and improving overall quality of life. Collaboration among scientists, healthcare professionals, policymakers, and ethicists is essential to ensure responsible and ethical development of promising avenues. While challenges and ethical considerations exist, ongoing research and innovation hold the potential to reshape our understanding of aging and significantly improve the health and well-being of aging populations [66].

**VII. CONCLUSION**

The intersection of biotechnology and anti-aging research holds immense potential for transforming the future of youthful living. By understanding the intricacies of the aging process and leveraging revolutionary biotechnological advancements, such as gene editing and regenerative medicine, we can envision a future were rejuvenation and extended health span is within reach. However, ethical considerations must guide our exploration of life extension, ensuring equitable access and thoughtful examination of the societal implications. Moving forward, continued research and development in biotechnology and anti-aging will pave the way for a society where individuals can enjoy enhanced vitality and well-being throughout their lives.

**REFERENCE**

[1] B. Flint and P. Tadi, “Physiology, Aging,” in *StatPearls*, Treasure Island (FL): StatPearls Publishing, 2023. Accessed: Aug. 17, 2023. [Online]. Available: http://www.ncbi.nlm.nih.gov/books/NBK556106/

[2] C. Franceschi *et al.*, “The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates,” *Front. Med.*, vol. 5, p. 61, Mar. 2018, doi: 10.3389/fmed.2018.00061.

[3] S. Rodríguez-Rodero, J. L. Fernández-Morera, E. Menéndez-Torre, V. Calvanese, A. F. Fernández, and M. F. Fraga, “Aging genetics and aging,” *Aging Dis*, vol. 2, no. 3, pp. 186–195, Jun. 2011.

[4] R. J. O’Sullivan and J. Karlseder, “Telomeres: protecting chromosomes against genome instability,” *Nat Rev Mol Cell Biol*, vol. 11, no. 3, pp. 171–181, Mar. 2010, doi: 10.1038/nrm2848.

[5] M. A. Shammas, “Telomeres, lifestyle, cancer, and aging:,” *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 14, no. 1, pp. 28–34, Jan. 2011, doi: 10.1097/MCO.0b013e32834121b1.

[6] X. Wang, D. Tomso, X. Liu, and D. Bell, “Single nucleotide polymorphism in transcriptional regulatory regions and expression of environmentally responsive genes,” *Toxicology and Applied Pharmacology*, vol. 207, no. 2, pp. 84–90, Sep. 2005, doi: 10.1016/j.taap.2004.09.024.

[7] M. Chen and W. Chen, “Single-nucleotide polymorphisms in medical nutritional weight loss: Challenges and future directions,” *Journal of Translational Internal Medicine*, vol. 10, no. 1, pp. 1–4, Apr. 2022, doi: 10.2478/jtim-2022-0002.

[8] A. Amaro-Ortiz, B. Yan, and J. D’Orazio, “Ultraviolet Radiation, Aging and the Skin: Prevention of Damage by Topical cAMP Manipulation,” *Molecules*, vol. 19, no. 5, pp. 6202–6219, May 2014, doi: 10.3390/molecules19056202.

[9] S. Shanbhag, A. Nayak, R. Narayan, and U. Y. Nayak, “Anti-aging and Sunscreens: Paradigm Shift in Cosmetics,” *Adv Pharm Bull*, vol. 9, no. 3, pp. 348–359, Aug. 2019, doi: 10.15171/apb.2019.042.

[10] A. Amaro-Ortiz, B. Yan, and J. D’Orazio, “Ultraviolet Radiation, Aging and the Skin: Prevention of Damage by Topical cAMP Manipulation,” *Molecules*, vol. 19, no. 5, pp. 6202–6219, May 2014, doi: 10.3390/molecules19056202.

[11] G. D. Goodman *et al.*, “Impact of Smoking and Alcohol Use on Facial Aging in Women: Results of a Large Multinational, Multiracial, Cross-sectional Survey,” *J Clin Aesthet Dermatol*, vol. 12, no. 8, pp. 28–39, Aug. 2019.

[12] A. Villiers-Tuthill, A. Copley, H. McGee, and K. Morgan, “The relationship of tobacco and alcohol use with ageing self-perceptions in older people in Ireland,” *BMC Public Health*, vol. 16, no. 1, p. 627, Dec. 2016, doi: 10.1186/s12889-016-3158-y.

[13] B. L. Tan, M. E. Norhaizan, W.-P.-P. Liew, and H. Sulaiman Rahman, “Antioxidant and Oxidative Stress: A Mutual Interplay in Age-Related Diseases,” *Front. Pharmacol.*, vol. 9, p. 1162, Oct. 2018, doi: 10.3389/fphar.2018.01162.

[14] V. Lobo, A. Patil, A. Phatak, and N. Chandra, “Free radicals, antioxidants and functional foods: Impact on human health,” *Phcog Rev*, vol. 4, no. 8, p. 118, 2010, doi: 10.4103/0973-7847.70902.

[15] K. Pinckard, K. K. Baskin, and K. I. Stanford, “Effects of Exercise to Improve Cardiovascular Health,” *Front. Cardiovasc. Med.*, vol. 6, p. 69, Jun. 2019, doi: 10.3389/fcvm.2019.00069.

[16] M. A. Nystoriak and A. Bhatnagar, “Cardiovascular Effects and Benefits of Exercise,” *Front. Cardiovasc. Med.*, vol. 5, p. 135, Sep. 2018, doi: 10.3389/fcvm.2018.00135.

[17] M. G. Benedetti, G. Furlini, A. Zati, and G. Letizia Mauro, “The Effectiveness of Physical Exercise on Bone Density in Osteoporotic Patients,” *BioMed Research International*, vol. 2018, pp. 1–10, Dec. 2018, doi: 10.1155/2018/4840531.

[18] G. Distefano and B. H. Goodpaster, “Effects of Exercise and Aging on Skeletal Muscle,” *Cold Spring Harb Perspect Med*, vol. 8, no. 3, p. a029785, Mar. 2018, doi: 10.1101/cshperspect.a029785.

[19] D. E. R. Warburton, C. W. Nicol, and S. S. D. Bredin, “Health benefits of physical activity: the evidence,” *CMAJ*, vol. 174, no. 6, pp. 801–809, Mar. 2006, doi: 10.1503/cmaj.051351.

[20] P. Alhola and P. Polo-Kantola, “Sleep deprivation: Impact on cognitive performance,” *Neuropsychiatr Dis Treat*, vol. 3, no. 5, pp. 553–567, 2007.

[21] L. Xie *et al.*, “Sleep drives metabolite clearance from the adult brain,” *Science*, vol. 342, no. 6156, pp. 373–377, Oct. 2013, doi: 10.1126/science.1241224.

[22] A. Brunet *et al.*, “Stress-Dependent Regulation of FOXO Transcription Factors by the SIRT1 Deacetylase,” *Science*, vol. 303, no. 5666, pp. 2011–2015, Mar. 2004, doi: 10.1126/science.1094637.

[23] T. S. Gopenath, S. Shreshtha, and K. M. Basalingappa, “Telomerase reactivation for anti-aging,” in *Anti-Aging Drug Discovery on the Basis of Hallmarks of Aging*, Elsevier, 2022, pp. 113–125. doi: 10.1016/B978-0-323-90235-9.00005-7.

[24] M. Jaskelioff *et al.*, “Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice,” *Nature*, vol. 469, no. 7328, pp. 102–106, Jan. 2011, doi: 10.1038/nature09603.

[25] H.-J. Gruber, M. D. Semeraro, W. Renner, and M. Herrmann, “Telomeres and Age-Related Diseases,” *Biomedicines*, vol. 9, no. 10, p. 1335, Sep. 2021, doi: 10.3390/biomedicines9101335.

[26] S. Maynard, E. F. Fang, M. Scheibye-Knudsen, D. L. Croteau, and V. A. Bohr, “DNA Damage, DNA Repair, Aging, and Neurodegeneration,” *Cold Spring Harb Perspect Med*, vol. 5, no. 10, p. a025130, Oct. 2015, doi: 10.1101/cshperspect.a025130.

[27] J. Vijg, “Aging genomes: A necessary evil in the logic of life: Prospects & Overviews,” *BioEssays*, vol. 36, no. 3, pp. 282–292, Mar. 2014, doi: 10.1002/bies.201300127.

[28] Y. Zhao, M. Simon, A. Seluanov, and V. Gorbunova, “DNA damage and repair in age-related inflammation,” *Nat Rev Immunol*, vol. 23, no. 2, pp. 75–89, Feb. 2023, doi: 10.1038/s41577-022-00751-y.

[29] D. McHugh and J. Gil, “Senescence and aging: Causes, consequences, and therapeutic avenues,” *Journal of Cell Biology*, vol. 217, no. 1, pp. 65–77, Jan. 2018, doi: 10.1083/jcb.201708092.

[30] J. M. Van Deursen, “The role of senescent cells in ageing,” *Nature*, vol. 509, no. 7501, pp. 439–446, May 2014, doi: 10.1038/nature13193.

[31] E. O. Wissler Gerdes *et al.*, “Cellular senescence in aging and age-related diseases: Implications for neurodegenerative diseases,” in *International Review of Neurobiology*, Elsevier, 2020, pp. 203–234. doi: 10.1016/bs.irn.2020.03.019.

[32] A. Mylonas and A. O’Loghlen, “Cellular Senescence and Ageing: Mechanisms and Interventions,” *Front. Aging*, vol. 3, p. 866718, Mar. 2022, doi: 10.3389/fragi.2022.866718.

[33] P. Caiafa, T. Guastafierro, and M. Zampieri, “Epigenetics: poly(ADP‐ribosyl)ation of PARP‐1 regulates genomic methylation patterns,” *FASEB j.*, vol. 23, no. 3, pp. 672–678, Mar. 2009, doi: 10.1096/fj.08-123265.

[34] K. D. Robertson, “DNA methylation and human disease,” *Nat Rev Genet*, vol. 6, no. 8, pp. 597–610, Aug. 2005, doi: 10.1038/nrg1655.

[35] J. L. Miller and P. A. Grant, “The Role of DNA Methylation and Histone Modifications in Transcriptional Regulation in Humans,” in *Epigenetics: Development and Disease*, T. K. Kundu, Ed., in Subcellular Biochemistry, vol. 61. Dordrecht: Springer Netherlands, 2013, pp. 289–317. doi: 10.1007/978-94-007-4525-4\_13.

[36] E. Della Bella, J. Koch, and K. Baerenfaller, “Translation and emerging functions of non‐coding RNAs in inflammation and immunity,” *Allergy*, vol. 77, no. 7, pp. 2025–2037, Jul. 2022, doi: 10.1111/all.15234.

[37] J. A. Alegría-Torres, A. Baccarelli, and V. Bollati, “Epigenetics and lifestyle,” *Epigenomics*, vol. 3, no. 3, pp. 267–277, Jun. 2011, doi: 10.2217/epi.11.22.

[38] D. Saul and R. L. Kosinsky, “Epigenetics of Aging and Aging-Associated Diseases,” *IJMS*, vol. 22, no. 1, p. 401, Jan. 2021, doi: 10.3390/ijms22010401.

[39] J. S. Bhatti, G. K. Bhatti, and P. H. Reddy, “Mitochondrial dysfunction and oxidative stress in metabolic disorders — A step towards mitochondria based therapeutic strategies,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1863, no. 5, pp. 1066–1077, May 2017, doi: 10.1016/j.bbadis.2016.11.010.

[40] Š. Lehtonen, T.-M. Sonninen, S. Wojciechowski, G. Goldsteins, and J. Koistinaho, “Dysfunction of Cellular Proteostasis in Parkinson’s Disease,” *Front. Neurosci.*, vol. 13, p. 457, May 2019, doi: 10.3389/fnins.2019.00457.

[41] D. W. Anderson, K. A. Bradbury, and J. S. Schneider, “Neuroprotection in Parkinson models varies with toxin administration protocol,” *European Journal of Neuroscience*, vol. 24, no. 11, pp. 3174–3182, Dec. 2006, doi: 10.1111/j.1460-9568.2006.05192.x.

[42] S. Y. Cheon, H. Kim, D. C. Rubinsztein, and J. E. Lee, “Autophagy, Cellular Aging and Age-related Human Diseases,” *Exp Neurobiol*, vol. 28, no. 6, pp. 643–657, Dec. 2019, doi: 10.5607/en.2019.28.6.643.

[43] M. W. Pataky, W. F. Young, and K. S. Nair, “Hormonal and Metabolic Changes of Aging and the Influence of Lifestyle Modifications,” *Mayo Clinic Proceedings*, vol. 96, no. 3, pp. 788–814, Mar. 2021, doi: 10.1016/j.mayocp.2020.07.033.

[44] S. Saeed *et al.*, “Genome Editing Technology: A New Frontier for the Treatment and Prevention of Cardiovascular Diseases,” *Current Problems in Cardiology*, vol. 48, no. 7, p. 101692, Jul. 2023, doi: 10.1016/j.cpcardiol.2023.101692.

[45] M. Lulkiewicz, J. Bajsert, P. Kopczynski, W. Barczak, and B. Rubis, “Telomere length: how the length makes a difference,” *Mol Biol Rep*, vol. 47, no. 9, pp. 7181–7188, Sep. 2020, doi: 10.1007/s11033-020-05551-y.

[46] A. Caobi *et al.*, “The Impact of CRISPR-Cas9 on Age-related Disorders: From Pathology to Therapy,” *Aging and disease*, vol. 11, no. 4, p. 895, 2020, doi: 10.14336/AD.2019.0927.

[47] N. A. Duggal, “Reversing the immune ageing clock: lifestyle modifications and pharmacological interventions,” *Biogerontology*, vol. 19, no. 6, pp. 481–496, Dec. 2018, doi: 10.1007/s10522-018-9771-7.

[48] Y. Wang, C. Dong, Y. Han, Z. Gu, and C. Sun, “Immunosenescence, aging and successful aging,” *Front. Immunol.*, vol. 13, p. 942796, Aug. 2022, doi: 10.3389/fimmu.2022.942796.

[49] M. Tosato, V. Zamboni, A. Ferrini, and M. Cesari, “The aging process and potential interventions to extend life expectancy,” *Clin Interv Aging*, vol. 2, no. 3, pp. 401–412, 2007.

[50] T. A. Rando and T. Wyss-Coray, “Stem Cells as Vehicles for Youthful Regeneration of Aged Tissues,” *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, vol. 69, no. Suppl 1, pp. S39–S42, Jun. 2014, doi: 10.1093/gerona/glu043.

[51] N. Rosenthal, “Youthful prospects for human stem‐cell therapy: In another few decades, revised attitudes towards stem cells could lead to disease prevention and life extension,” *EMBO Reports*, vol. 6, no. S1, Jul. 2005, doi: 10.1038/sj.embor.7400427.

[52] M. Khorraminejad-Shirazi, M. Dorvash, A. Estedlal, A. H. Hoveidaei, M. Mazloomrezaei, and P. Mosaddeghi, “Aging: A cell source limiting factor in tissue engineering,” *WJSC*, vol. 11, no. 10, pp. 787–802, Oct. 2019, doi: 10.4252/wjsc.v11.i10.787.

[53] M. P. Nikolova and M. S. Chavali, “Recent advances in biomaterials for 3D scaffolds: A review,” *Bioactive Materials*, vol. 4, pp. 271–292, Dec. 2019, doi: 10.1016/j.bioactmat.2019.10.005.

[54] B. P. Chan and K. W. Leong, “Scaffolding in tissue engineering: general approaches and tissue-specific considerations,” *Eur Spine J*, vol. 17, no. S4, pp. 467–479, Dec. 2008, doi: 10.1007/s00586-008-0745-3.

[55] C. Selden and B. Fuller, “Role of Bioreactor Technology in Tissue Engineering for Clinical Use and Therapeutic Target Design,” *Bioengineering*, vol. 5, no. 2, p. 32, Apr. 2018, doi: 10.3390/bioengineering5020032.

[56] K. C. Clause and T. H. Barker, “Extracellular matrix signaling in morphogenesis and repair,” *Current Opinion in Biotechnology*, vol. 24, no. 5, pp. 830–833, Oct. 2013, doi: 10.1016/j.copbio.2013.04.011.

[57] M. Lovett, K. Lee, A. Edwards, and D. L. Kaplan, “Vascularization Strategies for Tissue Engineering,” *Tissue Engineering Part B: Reviews*, vol. 15, no. 3, pp. 353–370, Sep. 2009, doi: 10.1089/ten.teb.2009.0085.

[58] A. Carnicer-Lombarte, S.-T. Chen, G. G. Malliaras, and D. G. Barone, “Foreign Body Reaction to Implanted Biomaterials and Its Impact in Nerve Neuroprosthetics,” *Front. Bioeng. Biotechnol.*, vol. 9, p. 622524, Apr. 2021, doi: 10.3389/fbioe.2021.622524.

[59] M. Willadsen, M. Chaise, I. Yarovoy, A. Q. Zhang, and N. Parashurama, “Engineering molecular imaging strategies for regenerative medicine,” *Bioengineering & Translational Medicine*, vol. 3, no. 3, pp. 232–255, Sep. 2018, doi: 10.1002/btm2.10114.

[60] D. B. Berry, E. K. Englund, S. Chen, L. R. Frank, and S. R. Ward, “Medical imaging of tissue engineering and regenerative medicine constructs,” *Biomater. Sci.*, vol. 9, no. 2, pp. 301–314, 2021, doi: 10.1039/D0BM00705F.

[61] D. Bakula *et al.*, “Latest advances in aging research and drug discovery,” *Aging*, vol. 11, no. 22, pp. 9971–9981, Nov. 2019, doi: 10.18632/aging.102487.

[62] J. C. Lucke, D. Herbert, B. Partridge, and W. D. Hall, “Anticipating the use of life extension technologies: Possible pointers from the adoption of assisted reproductive technologies,” *EMBO Reports*, vol. 11, no. 5, pp. 334–338, May 2010, doi: 10.1038/embor.2010.48.

[63] M. Araki and T. Ishii, “International regulatory landscape and integration of corrective genome editing into in vitro fertilization,” *Reprod Biol Endocrinol*, vol. 12, no. 1, p. 108, 2014, doi: 10.1186/1477-7827-12-108.

[64] A. Klaassen-van den Berg Jeths and J. A. van Langen, “[2 scenarios on extension of life. Various social consequences of a higher life expectancy],” *Tijdschr Gerontol Geriatr*, vol. 21, no. 5, pp. 217–221, Oct. 1990.

[65] D. W. Edington, A. B. Schultz, J. S. Pitts, and A. Camilleri, “The Future of Health Promotion in the 21st Century: A Focus on the Working Population,” *American Journal of Lifestyle Medicine*, vol. 10, no. 4, pp. 242–252, Jul. 2016, doi: 10.1177/1559827615605789.

[66] E. C. Hadley, E. G. Lakatta, M. Morrison-Bogorad, H. R. Warner, and R. J. Hodes, “The Future of Aging Therapies,” *Cell*, vol. 120, no. 4, pp. 557–567, Feb. 2005, doi: 10.1016/j.cell.2005.01.030.