Review

A Reflection on Theories of Aging

Wenbo Yu *

Posted Date: 2 March 2026

doi: 10.20944/preprints202603.0112.v1

Keywords: aging theory; entropy

 doi:10.20944/preprints202603.0112.v1

Review

A Reflection on Theories of Aging

Wenbo Yu [1,2,3]

[1] Centre for Cancer Biology, SA Pathology and Adelaide University, SA, Australia
[2] Cancer Clinical Trials Unit, Royal Adelaide Hospital, SA, Australia
[3] School of Medicine, Adelaide University, SA, Australia
* Correspondence: stanley.yu@adelaide.edu.au or stanley.yu@sa.gov.au

Abstract

Aging remains one of the most complex phenomena in biology, giving rise to a diverse range of theoretical frameworks aimed at elucidating its mechanisms. These theories often overlap, exhibiting both consistencies and contradictions, making it challenging to systematically categorize them. In this review, we revisit prominent aging theories from multiple perspectives. First, from the classical viewpoints of "wear-and-tear" and "programmed" aging, we introduce several foundational theories, including the oxidative damage family theories and information theory. We then examine these theories from an evolutionary perspective, which leads to the antagonistic pleiotropy (AP) theory and the hyperfunction theory. Following the mechanistic discussion, we consider several inclusive theories, including the "np" theory. Analogies are used throughout, and each section concludes with a philosophical reflection on the essence of aging. All discussions are centered on a fundamental question: "Is lifespan constrained by what nature does not pursue, or by what it fundamentally cannot achieve?" At least according to the "np" theory, an ultimate restriction stems from the information entropy. Finally, we highlight emerging rejuvenation strategies, which provide alternative lens to view aging theories. This review aims to inspire readers to think critically about current theories and to explore novel conceptual frameworks in the biology of aging.

Keywords: aging theory; entropy

Introduction

Aging, as a fundamental life process, is a fascinating and complex phenomenon that encompasses nearly all levels and aspects of biological systems [1]. Although efforts for centuries have been devoted to identifying a comprehensive theory of aging, it is likely—as in the study of social systems—that no single theory can account for all aspects of the process. Rather, theories can at best capture the principal drivers of aging. Theories that more effectively identify and elucidate these principal drivers are therefore more powerful. Importantly, robust theories should be compatible with proved molecular or cellular mechanisms.

Analogous to economics, the study of aging requires macro-level theories to explain the phenomenon, alongside micro-level theories to inform practical strategies. Constructing a single framework that neatly arranges all existing theories of aging is challenging, as different theories tend to focus on different layers of the aging process. Theories may support or include one another, or they may be partially overlapping yet partially exclusive. In this review, we aim to embed diverse theories of aging within a framework that facilitates understanding of their relationships. In addition, aging will be discussed from an evolutionary perspective, considering species-specific life-history and lifespan.

I. "Wear and Tear" or "Programmed"?

Aging is most intuitively approached from two conceptual frameworks: "wear and tear" versus "programmed". The *wear and tear theory* represents one of the earliest classes of aging theories [2].

 doi:10.20944/preprints202603.0112.v1

Biological organisms, much like mechanical systems, gradually deteriorate through use, with cumulative damage ultimately leading to functional decline and death. Life has been described as a self-maintaining system that counteracts entropy; thus, aging is seen as a progressive breakdown of this balance, resulting in systemic entropy increase [3,4]. The wear and tear theory suggests that systems wear out at genetic, cellular, or tissue levels, which ultimately results in aging.

As mentioned above, theories focus on different drivers. Different aging theories have emerged by attributing the primary drivers of this "entropy increase" to different microscopic mechanisms. At the genetic level, the *somatic mutation theory* suggests that aging results from the gradual accumulation of mutations that impair cellular function [5]. At the non-genetic level, there are cross-link theory [6], auto immune theory [7], Glycation theory [8], molecular inflammatory theory etc [9]. I'd like to discuss more about the highly influential family of oxidative damage theories. Denham Harman proposed the free radical theory of aging in 1956, which was recognized as a milestone in modern mechanistic aging research [10]. A free radical is defined as an unstable atom or molecule with an unpaired electron, often characterized as oxygen-derived and highly reactive. The free radical theory suggests that aging arises from the continual attack of these reactive species on biological macromolecules—such as DNA, proteins, and lipids—leading to the accumulation of stochastic and largely irreversible damage. This theory was further developed and refined as the oxidative damage theory, which provided mechanistic detail on how reactive oxygen species (ROS) induce molecular lesions, including oxidative DNA damage, protein carbonylation, and lipid peroxidation [11]. Mitochondria were identified as major sources and targets of oxidative damage, giving rise to the mitochondrial theory of aging as a distinct sub-theory [12,13]. However, comparative studies across species with widely divergent lifespans and life-history strategies indicate that oxidative damage can be effectively repaired or controlled over substantial portions of the lifespan. This raises a fundamental question: what ultimately shifts or disrupts this balance, sooner or later? Importantly, ROS, once viewed solely as deleterious free radicals, are now recognized as essential signaling molecules involved in cell proliferation, differentiation, immune defense, and homeostatic regulation. Dean P. Jones proposed the redox theory of aging, central to which is the concept of the redox network [14]. This network is defined as a complex, interconnected system of molecules, enzymes, and signaling pathways that mediate cellular oxidation–reduction reactions. Redox networks support critical biological processes including energy metabolism, protein trafficking, signal transduction, and immune defense. The redox network encompasses redox enzymes, reductants like glutathione and thioredoxin, and their regulatory nodes, forming hierarchical and dynamic structures that help maintain cellular redox balance. The accumulation of oxidative damage during aging reflects not merely increased ROS production, but a progressive decline in the regulatory capacity of the redox network itself. With advancing age, redox plasticity diminishes, genome–environment responsiveness weakens, and the network becomes increasingly rigid, ultimately compromising cellular and organismal resilience.

Having examined wear-and-tear theories of aging, exemplified by oxidative damage-based frameworks, a series of practical and theoretical questions naturally arise. From a practical standpoint, one may ask how oxidative damage can be counteracted to delay aging through medical intervention—an issue to be addressed in later sections of this review. From a theoretical perspective, more fundamental questions emerge: what is the ultimate cause of the redox network failing to maintain long-term homeostasis? Why are certain cell types particularly vulnerable to oxidative damage, whereas others display remarkable resistance? To what extent is oxidative damage reversible? Why do some species exhibit extremely short lifespans while others achieve exceptional longevity? And does an evolutionary pathway exist by which organisms could nearly perfectly offset oxidative damage, thereby dramatically extending lifespan?

These questions are not unique to redox-based theories but apply broadly to wear-and-tear models of aging. In this context, a profound question concerns intergenerational renewal: how does reproduction effectively reset accumulated wear and tear between generations? Furthermore, why is this effective resetting restricted to the intergenerational context and not achievable in fully

 doi:10.20944/preprints202603.0112.v1

developed individuals? These questions confront not only wear-and-tear theories but also many alternative frameworks of aging, and they will be revisited in subsequent discussion.

Let us discuss the programmed theory. Aging is invariably associated with the passage of time, which naturally inspired the idea that clock-like mechanisms might exert precise control. The programmed theory postulates that the aging of any species is genetically programmed to adapt its lifespan to its life history within an evolutionary framework [15,16]. It is evident that the lifespans of certain organisms are indeed highly programmatically controlled, with Caenorhabditis elegans being the most extensively studied example [17,18]. However, when considering higher organisms, the answer becomes less clear. Any discussion of "programming" first requires a clear understanding of what a program actually is. This places the issue at a critical intersection of semantics, philosophy, and biology. Here, we propose a working definition of a program as a specific way of limiting the range of possibility for natural events. Under this definition, a system may be regulated by *strong* or *weak* programs. Consider the following analogy: If a flock of sheep is released onto a grassland and left entirely to fend for itself, this situation can be defined as one in which no program exists. In contrast, suppose the sheep are confined in a pen with a corridor connecting it to a feeding area. At a fixed time each day, the gate of the pen opens, the sheep are driven through the corridor to the feeding area, fed by an automatic system, and then driven back along the same route. This arrangement may be regarded as a strong program. Between these two lies a weak program. For example, the gate of the pen may be opened at fixed times, allowing the sheep to enter the grassland freely. Whether the sheep choose to leave, whether grass is available, and whether they are adequately fed are all left to chance. Nevertheless, the very existence of the gate indicates that a program is still present, because the opening and closing of the gate limits the range of possibilities for natural events. Of course, a clock is required to control the gate; if the gate were instead designed to respond to ambient light, even the clock could be omitted from the system. Aging theories may also be classified into strong-program and weak-program models. For proponents of strong programmed theory, weak programs may not be recognized as "programs". Conversely, for advocates of non-programmed aging, even weak programs may still count as programs. Therefore, semantic sensitivity is essential when discussing programmed theories of aging. Strong programmed aging theories argue that aging is the result of deliberate biological design, whereby organisms are programmed to age and die close to the end of their life cycle, thereby removing themselves from ecological competition. However, in higher organisms—at least in homeothermic animals—this view is generally not accepted [19,20]. A hallmark of programmatic control is temporal precision. Early embryonic development is regulated with accuracy in minutes; the standard deviation (SD) of the entire gestational period is approximately 9 days, corresponding to about 3% of gestational length in humans. The SD of age at menarche is about 1.3 years, roughly 10% of the average age at onset [21,22]. In high-income countries, the SD of human life expectancy is approximately 15 years, accounting for nearly 20% of the mean lifespan. [23] The progressively increasing deviation across these life stages suggests that the direct influence of programmatic control diminishes over time. Programmatic control and wear-and-tear processes should therefore be viewed as two aspects of a complex phenomenon. Perhaps it is more accurate to state that biological programs did not *choose* aging and death; rather, they permit aging and death to happen.

If aging is a process coupled to time, then any programmed theory of aging must identify an aging clock and its underlying mechanisms. The most compelling micro-level evidence historically cited in support of programmed aging has been telomeres [24]. Telomere theory is attractive because it combines a clear molecular biological mechanism with clock-like properties, and it has therefore long been regarded as a promising candidate of the key to the puzzle of aging process. However, from a logical standpoint, the mere presence of clock-like character does not mean that this character is serving as the clock. To date, research has not established that telomeres function as a master clock governing the entire organism, nor even conclusively as the clock of a specific subsystem. Aging does not operate as a reaction chain from upstream to downstream but rather as a complex network. This represents a fundamental challenge faced by all aging theories: within a highly interconnected

 doi:10.20944/preprints202603.0112.v1

network, no single known micro-level mechanism is likely to serve as a universal master switch. The role of telomeres in aging is therefore multifaceted. Current evidence is insufficient to support telomeres as the sole or central regulator of aging. Instead, telomere-associated mechanisms are viewed as secondary or complementary contributors within a multicausal, multi-effector framework [25].

Advances in epigenetics have brought new insights into aging research. Epigenetic changes can themselves function as aging clocks, and related theories are currently developing at a great pace [26–29]. By statistically analyzing DNA methylation levels at large numbers of CpG sites, it is possible to measure an individual's chronological age. When DNA methylation data are integrated with clinical measures such as circulating protein levels, smoking status, and other variables—particularly through machine-learning approaches—predictions of all-cause mortality, chronic disease risk, and overall health status become substantially more accurate. Building on these epigenetic advances, David A. Sinclair has recently proposed the "information theory of aging" as a novel framework for understanding and potentially intervening in aging [30]. In this view, aging arises from the progressive loss of "youthful information" established during development, analogous to the loss or degradation of information in a communication system. The theory hypothesizes the existence of a cellular "biological observer" capable of storing, maintaining, and restoring youthful epigenetic information. Disruption of this system—through DNA damage, epigenetic alterations, changes in chromatin architecture, and dysregulation of transcription—leads to age-associated functional decline. On this basis, the author further argues that reversing epigenetic states, for example through partial cellular reprogramming, may restore a more youthful cellular state and thereby delay or even reverse aspects of aging. The core challenges remain the identification of the putative "observer" that stores youthful information and the elucidation of its underlying mechanisms. In addition, continued advances in gene-editing technologies, chemical interventions, and improved biomarkers are expected to facilitate the development of personalized and precision-based anti-aging therapies [31].

An important challenge remains concerning causality: are the epigenetic changes we observe a cause of aging, or merely its consequence? A recent study has shown that models based on the accumulation of stochastic variation can predict chronological age with remarkably high accuracy, including the ability to capture changes in biological age induced by lifespan-extending interventions such as caloric restriction and heterochronic parabiosis. The results suggest that the cumulative burden of stochastic changes alone may be sufficient to construct effective aging clocks, without requiring an explicit program of aging. At a more fundamental theoretical level, this work challenges the concept of programmed aging by proposing that the age-related signals captured by aging clocks may reflect statistical consequences of stochastic accumulation within biological systems, rather than the execution of a specific program [32].

II. Theories Beyond the Programmed Perspective

No single theory can fully account for all aspects of aging. Different theories often overlap in their explanatory scope, and many highly influential theories of aging cannot be readily classified into the traditional dichotomy of wear-and-tear versus programmed theories. This section briefly discusses several such frameworks. Importantly, beyond mechanistic explanations, the evolutionary shaping of aging constitutes another essential dimension for a comprehensive understanding of the phenomenon.

The disposable soma theory was proposed to bridge the gap between "programmed" theory and "wear and tear" theory, which suggests: since the wear and tear of soma, it has become increasingly expensive to maintain it. Nature decided to abandon the soma or shut down maintenance by programme [33,34]. Closely compatible with this framework is the theory of antagonistic pleiotropy (AP) [35]. This theory recognizes aging as a form of pathology, arguing that certain genes enhance survival or reproductive success early in life while exerting deleterious effects in later life, resulting in aging or age-associated diseases. Because natural selection acts predominantly on early-life fitness, such genes are nevertheless retained (a phenomenon known as

 doi:10.20944/preprints202603.0112.v1

the "selection shadow"). These theories share a common starting point: the acknowledgment of a finite lifespan and an even more limited reproductive window. This raises fundamental questions as to why natural selection cannot give rise to an unlimited reproductive period, and what microscopic mechanisms underlie the trade-off between reproduction and somatic maintenance. Blagosklonny has proposed the hyperfunction theory as a mechanistic foundation for AP and as fully compatible with the disposable soma theory. According to this view, aging does not arise from a primary loss of function, but rather from the continued operation of biological programs that are beneficial during development and early adulthood. When these programs persist into later life, they drive *excessive functional activity*, ultimately leading to pathological damage [36–39]. Blagosklonny rejects classical programmed aging theories, arguing instead that aging represents the continuation of developmental programs rather than their evolutionary purpose. He therefore characterizes aging-driving mechanisms as quasi-programs. This framework can be illustrated by examples such as: hypertension arising from excessive growth of vascular smooth muscle; prostatic hyperplasia resulting from sustained activation of growth-promoting signaling pathways; and osteoarthritis emerging from hyperfunctional cartilage metabolism.

mTOR-driven hyperfunction holds a central position within this theoretical framework [40]. mTOR (mammalian target of rapamycin) is a highly conserved protein kinase belonging to the serine/threonine kinase family. Its discovery dates back to the 1970s, when a compound later named rapamycin was isolated from soil bacteria on Rapa Nui (Easter Island). Structural characterization of rapamycin subsequently revealed potent immunosuppressive properties, leading to its clinical application in treatment of organ rejection, particularly in kidney transplantation, and as T-cell proliferation inhibitor. mTOR came into scientific field as the target of rapamycin, and subsequent studies demonstrated that mTOR senses and integrates a wide array of extracellular and intracellular signals to regulate cellular metabolism, survival, proliferation, autophagy, immune responses, and multiple aspects of cellular homeostasis. Further investigation revealed that mTOR exists in two major multiprotein complexes, mTORC1 and mTORC2, which are structurally and functionally distinct. This discovery has substantially advanced our understanding of cellular signal transduction and the mechanisms underlying diverse diseases. The hyperfunction theory suggests that mTOR remains inappropriately active later in life, driving cellular hyperfunctions that lead to age-related diseases. Rather than aging being caused by molecular damage alone, the theory suggests that the hyperactivation of mTOR causes cells and tissues to continue their growth and activity beyond the optimal point for longevity. Thus, mTOR-driven hyperfunction is central to the process of aging as a quasi-programmed continuation of development. It is important to note that when mTOR activity drives productive cell proliferation, harmful consequences do not accumulate. This explains why aging does not manifest during developmental stages. Only when development ceases does the failure to appropriately down-regulate these quasi-programs result in the gradual accumulation of deleterious effects.

These theories raise crucial questions: why cannot reproduction and somatic maintenance be simultaneously optimized? Empirically, reproduction is associated with substantial risk, and postnatal survival of offspring is often low, whereas maintaining an already mature organism generally requires fewer resources and incurs lower opportunity costs.

João Pedro de Magalhães employed an analogy of a carpet layer to explain the hyperfunction theory [41]. Here, I adopt and extend this analogy to clarify the relationships among different theories of aging. Consider the construction of a house: during the building phase, each worker performs a specific task in a coordinated manner, and the house is completed on schedule. This stage corresponds to individual development. If, after completion, the house ceases to be maintained, or if the maintenance rate is not sufficient to offset depreciation, this scenario reflects wear-and-tear theories of aging. If, once deterioration occurs, the workers receive instructions to dismantle the house, this corresponds to strong programmed theories. If the workers are instructed to cease or reduce maintenance, this reflects weak programmed theories. If the cost of maintaining the house increases over time to the point where it becomes more economical to construct a new one, this

 doi:10.20944/preprints202603.0112.v1

corresponds to the disposable soma theory. If the infrastructures of the building themselves later exert destructive effects—such as asbestos shedding, gas leaks, plumbing failures, or degraded electrical wiring causing fires—this exemplifies AP theory. Finally, if the workers continue to follow the original construction commands without ever receiving a stop signal—analogous to a carpet layer who *"ever-increasing layers of carpets will eventually prevent doors from opening, and ultimately, nobody will be able to get in or out of the house"*—this scenario captures the hyperfunction theory.

Following this analogy, a biological example can be considered: hair graying. According to strong programmed theories, hair graying is driven by an intrinsic aging program, potentially evolved to signal a decline in reproductive value. Weak programmed theories instead interpret hair graying as the consequence of a programmed cessation of eumelanin production at the cellular level. Wear-and-tear theories attribute the loss of pigmentation to cumulative cellular damage leading to melanocyte dysfunction or depletion. The disposable soma theory suggests that, once the reproductive period has come to an end, continued investment in the maintenance of follicular melanocytes is no longer selectively preferred. From the perspectives of AP and hyperfunction theory, melanogenesis itself constitutes a highly oxidative biochemical process, generating hydrogen peroxide (H_2O_2), which can damage mitochondria, induce mitochondrial DNA lesions, and promote further reactive oxygen species (ROS) accumulation [42]. Demographic studies demonstrate a remarkably broad distribution in the age of onset of hair graying, with a standard deviation of approximately 30% (32.9 ± 9.8 years), a pattern that is inconsistent with a strong programmed mechanism [43]. Mechanistic studies have revealed that hair graying stems from problems with how melanocyte stem cells maintain themselves within hair follicles, which also does not support strong programmed theory [44]. It remains difficult to determine whether hair graying more closely reflects a programmed shutdown of melanocyte stem cell activity or a process of wear and tear affecting the stem cell maintenance niche. Alternatively, one may still argue that the apparent wear and tear itself is driven by genes exhibiting AP or hyperfunction, thereby explaining aging through an underlying quasi-programmatic mechanism.

III. Evolutionary Perspective and Other General Theories

Let us now revisit previously discussed theories from an evolutionary perspective. Species exhibit substantial diversity in the aging process; nevertheless, aging appears to be universal among birds and mammals [45]. Accordingly, we narrow our discussion with homeothermic animals, with mammals serving as a representative group. Where are mammals positioned within the evolutionary landscape? The Disposable Soma theory, AP theory, and the Hyperfunction theory all emphasize the role of natural selection in shaping aging and lifespan, yet they impose no definitive evolutionary limits. Has evolution simply not yet arrived at more effective mechanisms to manage the deleterious consequences of hyperfunction? Alternatively, may there exist a higher-order constraint that renders such an outcome of longevity fundamentally impossible?

Although the wear-and-tear theory obeys the second law of thermodynamics, life is a negentropic phenomenon, constantly working to sustain order and resist entropy. The question, therefore, is not whether entropy can be resisted, but why such resistance cannot be sustained indefinitely. Programmed aging theories, by contrast, postulate the existence of an intrinsic biological clock. This raises a further question: could natural selection optimize such a clock, or even eliminate this constraint, thereby allowing certain species to achieve extreme longevity?

It has been observed that species lifespan follows several empirical patterns: species with higher individual survival rates in the wild tend to have longer intrinsic lifespans; species with larger brain volumes generally live longer; and phenomena such as the "grandmother effect" have also been documented [46–49]. Collectively, these findings suggest that natural selection is willing to invest resources in mature individuals, allowing them to survive longer and thereby increasing reproductive success. Longevity appears to be favored as long as the individual can withstand ecological and physiological challenges. In this sense, an extended lifespan is selectively favored when continued survival is feasible. This invites the ultimate question: what constraints, if any,

 doi:10.20944/preprints202603.0112.v1

fundamentally preclude the possibility of extreme longevity or even biological immortality? From the standpoint of the wear-and-tear theory, one might ask why a multicellular organism cannot resist systemic entropy increase for sufficiently long periods, given that the first living cells on Earth were able to sustain replication for approximately four billion years—demonstrating that cellular systems can, in principle, reconcile entropy increase indefinitely. From the standpoint of programmed aging, one might ask why natural selection has not rendered organisms capable of autonomous reprogramming. Many scientists believe that biological systems have the inherent ability to repair damage and replace defective cells, suggesting they are not necessarily destined to die [50]. For example, if a bone like the tibia undergoes aging, it is theoretically conceivable that the body could, similar to the process of pregnancy, initiate regeneration from a stem cell, erase aging signals, reset the epigenetic clock to age-zero, and develop a new bone in situ while resorbing and replacing the old one. Given that pregnancy is physiologically demanding and represents certain survival risks for an individual, conceiving a single bone within the lower leg might not pose a greater risk than pregnancy. At the very least, one cannot exclude the possibility that nature could evolve such a mechanism. Ultimately, the possible answers may come to: first, extreme longevity is possible but has not yet evolved; second, it is impossible due to more fundamental physical constraints.

We would like to discuss several particularly thought-provoking integrative theories of aging, including our own general theory. Gustavo Barja has proposed a model that integrates multiple established aging mechanisms into what he terms the Cell Aging Regulation System (CARS), a framework aligning closely with programmed aging theories [51]. According to this view, the essence of aging lies in the progressive dysregulation or alteration of multiple mechanisms driven by a nuclear-encoded regulatory system -CARS, ultimately leading to the gradual decline of cellular and organismal function. Barja argues that aging is not a random or irreversible process, but rather a dynamic system regulated by a genetic aging program, which coordinates a series of so-called "aging effectors". These "effectors" include mitochondrial reactive oxygen species (ROS) production, lipid unsaturation, autophagy, and DNA repair. Through metabolic and cellular-level changes, these effectors progressively reshape tissue physiology and ultimately culminate in organismal failure and death. This regulatory system is determined by genetic factors while remaining responsive to environmental signals, and thus can be regarded as a programmed, gene-driven biological process that has been selected through evolution as an optimization of life-history strategies. The introduction of CARS represents an attempt to unify previously disparate and seemingly independent theories of aging, reinterpreting them as a single, complex regulatory network. In this sense, CARS offers a more comprehensive framework for understanding the mechanisms of aging. However, the theory primarily reorganizes known mechanisms rather than addressing the fundamental nature of aging itself. Until the operational principles of CARS are fully elucidated, such a framework risks becoming excessively complex; and a theory that relies on complexity may not constitute a strong explanatory model, but rather an acknowledgment of the complexity of biological reality.

Michael D. West and colleagues have also proposed an integrative theory that provides a comprehensive account of aging based on AP theory [52]. In their work, the process of aging is understood as somatic cells progressively losing the capacity for unlimited replication and regeneration during development, which was named “somatic restriction”, with key mechanisms including telomerase silencing and telomere shortening, alterations in chromatin structure and its regulatory functions, and changes in the control of gene expression. The authors emphasize that these restrictive mechanisms may represent an evolutionarily shaped trade-off designed to prevent tumorigenesis and enhance individual survival. While limiting the proliferative potential of somatic cells protects the host from cancer, it leads to a gradual decline in tissue regenerative capacity, thereby contributing to aging.

One empirical observation can often be interpreted within different theoretical frameworks. For example, changes in chromatin structure: do they constitute an intrinsic biological clock themselves, act as a cause of cellular aging, or merely represent a consequence of the aging process? Similarly, the programmed restriction of somatic regeneration raises critical questions—does it reflect programmed

 doi:10.20944/preprints202603.0112.v1

aging, a deleterious side effect of otherwise beneficial genes, or does no program exist at all, with the observed phenomenon arising simply from the cumulative feedback of stochastic damage?

An intriguing paper draws an analogy between the diversity of aging mechanisms and the Danaids—the fifty daughters of Danaus in Greek mythology [53]. The Danaid theory emphasizes the complexity and inherent constraints of living systems, proposing that in many complex organisms, structural limitations of genetic, developmental, and metabolic networks render them inherently "unmaintainable," thereby inevitably leading to aging. While much of aging research seeks to identify principal drivers, the authors argue that results are determined by the combination of all causes. The essence of aging lies in the individual's inherent unmaintainability. The authors advocate for an emergent explanation of aging. As hierarchical complexity increases, the difficulty of maintenance grows exponentially, and systematic degradation cannot be fully described in terms of microscopic mechanisms but instead manifests as emergent phenomena. For example, the integration of epidermal cells, loose connective tissue—blood cells, body fluids—and the mechanical action of the heart gives rise to blood pressure as an "emergent" physiological phenomenon; none of the individual components alone can account for it. Similarly, dysregulation of the system cannot be attributed to any single mechanism; it should instead be understood as the emergent result of multi-system unmaintainability. The authors quoted the famous question posed by George Williams in 1957: "It is indeed remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed." [35] The author further asked: "Why is it that some organisms (species) seem incapable of doing inside their body what they are perfectly capable of doing outside their body: to create a perfectly healthy organism?" [53]

My colleagues and I have also proposed a general theory of aging, the "Nuts Poisoned" (np) theory [54]. This theory does not exclude any specific aging mechanism nor deny the existence of potential physical or physiological constraints. Rather, it aims to define the ultimate physical limits of lifespan and how species may evolve adaptations to these constraints. This theory was inspired from my experience with PCR in molecular biology work. In PCR, the accumulation of DNA mutations is unavoidable. To minimize this problem, one must not only employ high-fidelity polymerases but also carefully control the number of amplification cycles and finally perform single-clone selection and sequencing verification. From this, I realized that in any system, entropy inevitably increases, and only through selection at the single clonal level can the system be ultimately maintained. A tube of PCR product resembles a biological individual: no matter how optimized the system or how high the fidelity of the polymerase, the system gradually drifts toward disorder. Only through clonal selection—analogous to reproduction—can high-entropy molecules be eliminated. Based on this insight, we formulated the "np" theory, which suggests that aging is a manifestation of systemic entropy increase. We conceptualize three levels of organismal entropy: metabolic, structural, and informational entropy. Metabolic entropy must be continuously balanced and maintained by the organism, and structural entropy can ultimately be reconciled through proliferation. However, information entropy cannot be indefinitely maintained, representing the ultimate limitation of biological aging. The progressive accumulation of informational entropy within cells is referred to as the "poisoned nuts". Mathematically expressing the "np" model, "n" represents the number of active cells at a given time and "p" the average probability of cancer arising from entropy accumulation in a single cell at that given time; thus, the product of "n x p" represents the individual's overall risk at that moment. In response to Williams' question, the theory asserts: "Yes, fundamentally, information entropy can only be selected against, not maintained." Information entropy does not exclude information stored in proteins, RNA, or the epigenome; however, in essence, epigenomic information resembles software, whereas DNA information is like non-erasable information on a hard disk [30,55]. Our theory refers to the information change in DNA as the ultimate entropy increase.

Building on observations from cancer cases, we propose that the information entropy increase eventually disrupts cellular regulatory mechanisms, thereby releasing the primitive replicative drive

 doi:10.20944/preprints202603.0112.v1

of cells. This drive represents a system that evolved earlier than multicellular regulation, which can ultimately lead to cancer. Consequently, the total number of cells an organism can deploy throughout its lifespan represents a finite resource. Evolution has shaped how this resource is allocated, thereby determining the lifespan of a species. In species with low survival rates during their life history, lifespan is correspondingly short. When extended longevity becomes possible, natural selection can optimize metabolism and associated genes to provide a longer lifespan. Certain species with long post-reproductive lifespans—such as humans, elephants, and whales—possess additional longevity mechanisms involving slower cellular replication and the gradual release of limited cellular resources, thereby prolonging the aging process. If the total cellular resource is considered predetermined, the theory predicts observable phenomena that may appear counterintuitive. For example, a higher degree of aging at the cellular or tissue level may be associated with a longer lifespan, rather than the reverse. To summarize the "np" theory in three points: 1. The fundamental cause of aging is insufficient cellular replication; 2. Unlimited replication is impossible due to limits imposed by information entropy; 3. Clonal selection provides a solution for the maintenance of information entropy and species evolution.

As emphasized above, different theories of aging can sometimes become entangled in semantic disputes, making them difficult to falsify. Nevertheless, potential approaches exist to test the predictions of the "np" theory. Lifespan generally co-evolves with body size, which can invert causal interpretations across theories and render them unfalsifiable. However, if certain large-bodied species are selectively reduced to smaller, dwarfed forms, the "np" theory predicts that their limited total cellular resources can be allocated over a longer period, thereby extending lifespan. This phenomenon has already been observed in domesticated animals such as dogs and horses, where smaller breeds tend to live longer than larger breeds. Microbat species also demonstrate extended longevity [26]. The theory further predicts that if an organism's biological clock could be modified to slow the pace of cellular replication without altering the total number of cellular pool, one would observe the counterintuitive outcome of more pronounced aging phenotypes alongside a longer lifespan. The extreme longevity of naked mole-rats may be related to mutation-associated slowing of cellular rhythms [56,57]. Remarkably, naked mole-rats show little evidence of age-related deterioration in reproductive, physiological, or anatomical traits, yet they exhibit relatively high aging indices in certain physiological measures [58–60].

IV. Rejuvenation Practice

After discussing the major theories of aging, we now turn to the practical question: Can aging be delayed or even reversed? While theoretical frameworks are diverse, mechanistic interventions generally fall into three categories: targeting metabolism, maintenance, or the aging clock. This section will briefly discuss current rejuvenation strategies being explored under the guidance of scientific theory.

Targeting Metabolism

Caloric restriction (CR) suppresses growth signaling pathways, including insulin/IGF-1 and mTOR, while simultaneously activating stress-response and maintenance pathways such as AMPK and FOXO. This promotes autophagy and enhances DNA repair capacity. Experimental studies have demonstrated that CR can extend the lifespan in *C. elegans*, mice, and rhesus monkeys; however, its effects in humans remain uncertain [61,62]. Rapamycin is widely recognized as a prototype anti-aging drug due to its ability to systemically inhibit mTOR-driven growth/synthetic programs active during adulthood, thereby slowing or partially reversing functional aging [63]. Rapamycin has shown promise in extending lifespan and healthspan in animal models, but clinical evidence in humans remains limited and insufficient to confirm similar benefits [64,65]. Metformin, a classic anti-diabetic drug, has been widely investigated over the past decade as a potential anti-aging agent. Metformin inhibits mitochondrial complex I, reducing the ATP/AMP ratio and thereby activating AMPK. AMPK activation then suppresses mTORC1, reduces protein synthesis and excessive cellular proliferation,

 doi:10.20944/preprints202603.0112.v1

and enhances autophagy, promoting the clearance of damaged proteins and mitochondria. Large clinical trials are still ongoing, and definitive results have yet to be reported [66].

Targeting Metabolism and Maintenance

Nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) are precursors of NAD^+ (nicotinamide adenine dinucleotide), an essential coenzyme for the sirtuin family. Sirtuins mediate antioxidation, mitochondrial protection, DNA repair, and genomic stability. Supplementation with NAD^+ has been reported to improve mitochondrial function and energy metabolism, delay the accumulation of genomic instability, and enhance autophagy, thereby facilitating the clearance of senescent cells and protein aggregates [67]. As with many other interventions, these effects are robust in animal models but remain limited in humans [68]. Senolytics: Senescent cells (SnCs) are cells that have permanently exited the cell cycle but remain metabolically active. They secrete a range of factors—including pro-inflammatory cytokines such as IL-6 and TNF-α, chemokines, growth factors, and proteases—collectively termed the senescence-associated secretory phenotype (SASP) [69]. While SASP can be beneficial in the short term, aiding tissue repair, its chronic accumulation disrupts tissue microenvironments, promotes inflammation, and contributes to disease, making it a key target for anti-aging interventions. Senolytic agents, such as Dasatinib, Quercetin, Fisetin, and Navitoclax (ABT-263), selectively eliminate senescent cells to improve tissue health. However, widespread clinical application of these compounds faces challenges regarding safety, dose optimization, long-term effects, and effective targeting of senescent cells [70]

Targeting the Aging Clock

Stem cell therapies have long been regarded with great promise; however, they have also been associated with tumorigenic side effects [71,72]. Cellular reprogramming similarly carries the risk of tumor formation from dedifferentiated cells [73]. Thus, partial reprogramming has emerged as a major focus in current research [30,74]. By using specific transcription factors—such as OSK (Oct4, Sox2, and Klf4, associated with Yamanaka factors)—differentiated cells can undergo partial reprogramming, which restores youthful epigenetic information without fully reverting cells to a pluripotent embryonic stem cell state. This approach allows the reversal of age-associated epigenetic changes while maintaining cell identity and function. Partial reprogramming has been shown to significantly improve DNA methylation patterns, restore the expression of youthful genes, reduce DNA damage, and enhance mitochondrial function. Reprogramming can be achieved through both genetic and chemical approaches. Chemical reprogramming agents modulate the epigenetic landscape of cells; examples include histone deacetylase (HDAC) inhibitors, DNA methyltransferase inhibitors (e.g., 5-azacytidine, RG108), and TET enzyme activators (e.g., α-ketoglutarate), which regulate DNA methylation and histone modifications. These compounds do not rely on viral vectors and could be more readily translated into epigenetic rejuvenation applications, if proven effective. As discussed above, most interventions targeting metabolism and maintenance show measurable effects in laboratory models, but their efficacy in humans remains limited. This challenge often requires insights from integrative aging theories. Aging is a complex network process, and current interventions generally address only one or two mechanisms, thereby limiting their overall effectiveness. For example, the CARS theory suggests that many interventions—such as pharmacological agents or dietary restrictions—cannot comprehensively control the multiple mechanisms of aging, thus producing only partial effects [51]. According to the "np" theory, interventions targeting metabolism merely slow the accumulation of entropy in existing cells without addressing the underlying source of predetermined cell pool. This protective effect is particularly apparent in short-lived species: extending the lifespan of a mouse by six months represents a significant proportion of its life, whereas the same intervention in humans would be relatively insignificant. By analogy, metabolic protection merely slows the evaporation of water from a small pond without replenishing the fountain that feeds it.

 doi:10.20944/preprints202603.0112.v1

Stem cell therapies aim to address the source problem; however, practical challenges remain, including cell injection, homing, and controlled differentiation. Reprogramming aged stem cells faces similar obstacles. Moreover, an organism is likely controlled by multiple levels of aging clocks, including central and local clocks, and current knowledge has yet to elucidate how these clocks are coordinated [75]. From the perspective of the "np" theory, stem cell reprogramming therapies also have their limitations. Epigenetically reprogrammed stem cells address the "n" problem, providing a continuous source of cells, but they do not resolve the "p" problem – the chance of cancerization. Irreversible information entropy increase in DNA reflects degraded "water quality". Thus, the tumorigenic risk of stem cell therapy arises not only from dedifferentiation induced by reprogramming but also from preexisting irreversible changes in cellular information. Achieving safe stem cell reprogramming will require the development of techniques to identify stem cell colonies ex vivo, ensuring that they possess a genome perfect enough with minimal "p".

V. Conclusion

Promoting healthy aging represents a critical challenge at the intersection of medicine and social science. Practices aimed at extending lifespan and promoting rejuvenation may pose substantial complexities, both ethically and technologically [76]. Nevertheless, a robust theoretical framework for aging is indispensable for guiding such practices. A falsifiable theory of aging can not only inform intervention strategies but also clarify their ethical foundations. This article has provided a concise review of mainstream theories of aging, examining them through the lenses of wear and tear (entropy), programmed aging, as well as through the scope of evolutionary biology. At the mechanistic level, interventions designed to delay aging were discussed under three categories: metabolism, maintenance, and the aging clock. The theories explored here conceptually span a broad range and must be considered within their appropriate taxonomic context, that is, across the tree of life, species occupying different ecological niches face distinct constraints. The applicability of these theories can be considered at three distinct levels: All Species: Some theories, such as programmed aging, may apply universally, with different species evolving distinct programs in accordance with their life-history strategies. Endothermic Vertebrates: This level focuses on endothermic vertebrates, specifically birds and mammals, which constituted the primary scope of much of this discussion. While certain theories (e.g., AP theory) may not apply to plant lineages or so-called immortal species, but they appear to hold for warm-blooded vertebrates. The third level concerns our primary interest: humans. Ultimately, animal experiments must be interpreted in the context of human biology, as differences between humans and model organisms can significantly influence outcomes. According to the "np" theory, some species have not evolved advanced maintenance systems and consequently exhibit short lifespans (e.g., rodents), whereas humans, as longevity favored species, may rely on strategies such as reduced cellular pace to extend their lifespan. Therefore, observed clinical effects in short- and long-lived species should be interpreted with caution [77]. Throughout this article, philosophical reflections and conceptual syntheses of various theories have been provided, aiming to inspire further thought in the field of aging.

Reference

1. Lopez-Otin C, Blasco MA, Partridge L, Serrano M and Kroemer G. The hallmarks of aging. Cell. 2013; 153(6):1194-1217.
2. Strehler BL and Mildvan AS. General theory of mortality and aging. Science. 1960; 132(3418):14-21.
3. Schrodinger E. (1967). What is life? The Physical Aspect of the Living Cell. (Cambridge: Cambridge University Press).
4. Hayflick L. Entropy explains aging, genetic determinism explains longevity, and undefined terminology explains misunderstanding both. PLoS Genet. 2007; 3(12):e220.
5. Morley AA. The somatic mutation theory of ageing. Mutat Res. 1995; 338(1-6):19-23.

 doi:10.20944/preprints202603.0112.v1

6. Diggs J. (2008). The Cross-Linkage Theory of Aging. In: Loue SJD and Sajatovic M, eds. Encyclopedia of Aging and Public Health. (Boston, MA: Springer US), pp. 250-252.
7. Walford RL. The Immunologic Theory of Aging. Gerontologist. 1964; 4:195-197.
8. Suji G and Sivakami S. Glucose, glycation and aging. Biogerontology. 2004; 5(6):365-373.
9. Chung HY, Cesari M, Anton S, Marzetti E, Giovannini S, Seo AY, Carter C, Yu BP and Leeuwenburgh C. Molecular inflammation: underpinnings of aging and age-related diseases. Ageing Res Rev. 2009; 8(1):18-30.
10. Harman D. Aging: a theory based on free radical and radiation chemistry. J Gerontol. 1956; 11(3):298-300.
11. Michael T. Lin MFB. The oxidative damage theory of aging. Clinical Neuroscience Research. 2003; 2(5–6):305-315.
12. Loeb LA, Wallace DC and Martin GM. The mitochondrial theory of aging and its relationship to reactive oxygen species damage and somatic mtDNA mutations. Proc Natl Acad Sci U S A. 2005; 102(52):18769-18770.
13. Sohal RS, Mockett RJ and Orr WC. Mechanisms of aging: an appraisal of the oxidative stress hypothesis. Free Radic Biol Med. 2002; 33(5):575-586.
14. Jones DP. Redox theory of aging. Redox Biol. 2015; 5:71-79.
15. Davidovic M, Sevo G, Svorcan P, Milosevic DP, Despotovic N and Erceg P. Old age as a privilege of the "selfish ones". Aging Dis. 2010; 1(2):139-146.
16. Prinzinger R. Programmed ageing: the theory of maximal metabolic scope. How does the biological clock tick? EMBO Rep. 2005; 6 Spec No:S14-19.
17. Olsen A, Vantipalli MC and Lithgow GJ. Using Caenorhabditis elegans as a model for aging and age-related diseases. Ann N Y Acad Sci. 2006; 1067:120-128.
18. Son HG, Altintas O, Kim EJE, Kwon S and Lee SV. Age-dependent changes and biomarkers of aging in Caenorhabditis elegans. Aging Cell. 2019; 18(2):e12853.
19. de Magalhaes JP and Church GM. Genomes optimize reproduction: aging as a consequence of the developmental program. Physiology (Bethesda). 2005; 20:252-259.
20. Blagosklonny MV. Paradoxes of aging. Cell Cycle. 2007; 6(24):2997-3003.
21. Jukic AM, Baird DD, Weinberg CR, McConnaughey DR and Wilcox AJ. Length of human pregnancy and contributors to its natural variation. Hum Reprod. 2013; 28(10):2848-2855.
22. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J and Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev. 2003; 24(5):668-693.
23. Edwards RD. The Cost of Uncertain Life Span. J Popul Econ. 2008; w14093.
24. Shay JW. Telomeres and aging. Curr Opin Cell Biol. 2018; 52:1-7.
25. Stuart JA, Liang P, Luo X, Page MM, Gallagher EJ, Christoff CA and Robb EL. A comparative cellular and molecular biology of longevity database. Age (Dordr). 2013; 35(5):1937-1947.
26. Hannum G, Guinney J, Zhao L, Zhang L, Hughes G, Sadda S, Klotzle B, Bibikova M, Fan JB, Gao Y, Deconde R, Chen M, Rajapakse I, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell. 2013; 49(2):359-367.
27. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013; 14(10):R115.
28. Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, Hou L, Baccarelli AA, Stewart JD, Li Y, Whitsel EA, Wilson JG, Reiner AP, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY). 2018; 10(4):573-591.
29. Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, Raj K, Hou L, Baccarelli AA, Li Y, Stewart JD, Whitsel EA, Assimes TL, Ferrucci L, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY). 2019; 11(2):303-327.
30. Lu YR, Tian X and Sinclair DA. The Information Theory of Aging. Nat Aging. 2023; 3(12):1486-1499.
31. Yang JH, Petty CA, Dixon-McDougall T, Lopez MV, Tyshkovskiy A, Maybury-Lewis S, Tian X, Ibrahim N, Chen Z, Griffin PT, Arnold M, Li J, Martinez OA, et al. Chemically induced reprogramming to reverse cellular aging. Aging (Albany NY). 2023; 15(13):5966-5989.

 doi:10.20944/preprints202603.0112.v1

32. Meyer DH and Schumacher B. Aging clocks based on accumulating stochastic variation. Nat Aging. 2024; 4(6):871-885.
33. Drenos F and Kirkwood TB. Modelling the disposable soma theory of ageing. Mech Ageing Dev. 2005; 126(1):99-103.
34. Kirkwood TB. Evolution of ageing. Nature. 1977; 270(5635):301-304.
35. Williams GC. PLEIOTROPY, NATURAL SELECTION, AND THE EVOLUTION OF SENESCENCE. Evolution. 1957; 11(4):398-411.
36. Blagosklonny MV. Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle. 2006; 5(18):2087-2102.
37. Blagosklonny MV. Revisiting the antagonistic pleiotropy theory of aging: TOR-driven program and quasi-program. Cell Cycle. 2010; 9(16):3151-3156.
38. Blagosklonny MV. Aging is not programmed: genetic pseudo-program is a shadow of developmental growth. Cell Cycle. 2013; 12(24):3736-3742.
39. Blagosklonny MV. The hyperfunction theory of aging: three common misconceptions. Oncoscience. 2021; 8:103-107.
40. Panwar V, Singh A, Bhatt M, Tonk RK, Azizov S, Raza AS, Sengupta S, Kumar D and Garg M. Multifaceted role of mTOR (mammalian target of rapamycin) signaling pathway in human health and disease. Signal Transduct Target Ther. 2023; 8(1):375.
41. de Magalhaes JP. Programmatic features of aging originating in development: aging mechanisms beyond molecular damage? FASEB J. 2012; 26(12):4821-4826.
42. Munoz-Munoz JL, Garcia-Molina F, Varon R, Tudela J, Garcia-Canovas F and Rodriguez-Lopez JN. Generation of hydrogen peroxide in the melanin biosynthesis pathway. Biochim Biophys Acta. 2009; 1794(7):1017-1029.
43. Acer E, Arslantas D, Emiral GO, Unsal A, Atalay BI and Goktas S. Clinical and epidemiological characteristics and associated factors of hair graying: a population-based, cross-sectional study in Turkey. An Bras Dermatol. 2020; 95(4):439-446.
44. Nishimura EK, Granter SR and Fisher DE. Mechanisms of hair graying: incomplete melanocyte stem cell maintenance in the niche. Science. 2005; 307(5710):720-724.
45. Cohen AA. Aging across the tree of life: The importance of a comparative perspective for the use of animal models in aging. Biochim Biophys Acta Mol Basis Dis. 2018; 1864(9 Pt A):2680-2689.
46. Hawkes K. Grandmothers and the evolution of human longevity. Am J Hum Biol. 2003; 15(3):380-400.
47. Hofman MA. Energy metabolism, brain size and longevity in mammals. Q Rev Biol. 1983; 58(4):495-512.
48. Ricklefs RE. Life-history connections to rates of aging in terrestrial vertebrates. Proc Natl Acad Sci U S A. 2010; 107(22):10314-10319.
49. Turbill C and Ruf T. Senescence is more important in the natural lives of long- than short-lived mammals. PLoS One. 2010; 5(8):e12019.
50. Prinzinger R. Programmed ageing: the theory of maximal metabolic scope. How does the biological clock tick? EMBO Rep. 2005; 6 Spec No(Suppl 1):S14-19.
51. Barja G. Towards a unified mechanistic theory of aging. Exp Gerontol. 2019; 124:110627.
52. West MD, Sternberg H, Labat I, Janus J, Chapman KB, Malik NN, de Grey AD and Larocca D. Toward a unified theory of aging and regeneration. Regen Med. 2019; 14(9):867-886.
53. Wensink MJ and Cohen AA. The Danaid Theory of Aging. Front Cell Dev Biol. 2021; 9:671208.
54. Yu W, Gargett T and Du Z. A Poisson distribution-based general model of cancer rates and a cancer risk-dependent theory of aging. Aging (Albany NY). 2023; 15(17):8537-8551.
55. Orgel LE. The maintenance of the accuracy of protein synthesis and its relevance to ageing. Proc Natl Acad Sci U S A. 1963; 49(4):517-521.
56. Yamamura Y, Kawamura Y, Oiwa Y, Oka K, Onishi N, Saya H and Miura K. Isolation and characterization of neural stem/progenitor cells in the subventricular zone of the naked mole-rat brain. Inflamm Regen. 2021; 41(1):31.

 doi:10.20944/preprints202603.0112.v1

57. Montazid S, Bandyopadhyay S, Hart DW, Gao N, Johnson B, Thrumurthy SG, Penn DJ, Wernisch B, Bansal M, Altrock PM, Rost F, Gazinska P, Ziolkowski P, et al. Adult stem cell activity in naked mole rats for long-term tissue maintenance. Nat Commun. 2023; 14(1):8484.
58. Andziak B, O'Connor TP, Qi W, DeWaal EM, Pierce A, Chaudhuri AR, Van Remmen H and Buffenstein R. High oxidative damage levels in the longest-living rodent, the naked mole-rat. Aging Cell. 2006; 5(6):463-471.
59. De Waal EM, Liang H, Pierce A, Hamilton RT, Buffenstein R and Chaudhuri AR. Elevated protein carbonylation and oxidative stress do not affect protein structure and function in the long-living naked-mole rat: a proteomic approach. Biochem Biophys Res Commun. 2013; 434(4):815-819.
60. Takasugi M, Firsanov D, Tombline G, Ning H, Ablaeva J, Seluanov A and Gorbunova V. Naked mole-rat very-high-molecular-mass hyaluronan exhibits superior cytoprotective properties. Nat Commun. 2020; 11(1):2376.
61. Hultstrom M. Caloric restriction reduces age-related but not all-cause mortality. Acta Physiol (Oxf). 2015; 214(1):3-5.
62. Le Bourg E. Does Calorie Restriction in Primates Increase Lifespan? Revisiting Studies on Macaques (Macaca mulatta) and Mouse Lemurs (Microcebus murinus). Bioessays. 2018; 40(10):e1800111.
63. Miller RA, Harrison DE, Astle CM, Fernandez E, Flurkey K, Han M, Javors MA, Li X, Nadon NL, Nelson JF, Pletcher S, Salmon AB, Sharp ZD, et al. Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction. Aging Cell. 2014; 13(3):468-477.
64. Hands JM, Lustgarten MS, Frame LA and Rosen B. What is the clinical evidence to support off-label rapamycin therapy in healthy adults? Aging (Albany NY). 2025; 17(8):2079-2088.
65. Selvarani R, Mohammed S and Richardson A. Effect of rapamycin on aging and age-related diseases-past and future. Geroscience. 2021; 43(3):1135-1158.
66. Barzilai N, Crandall JP, Kritchevsky SB and Espeland MA. Metformin as a Tool to Target Aging. Cell Metab. 2016; 23(6):1060-1065.
67. Verdin E. NAD(+) in aging, metabolism, and neurodegeneration. Science. 2015; 350(6265):1208-1213.
68. Yamaguchi S, Irie J, Mitsuishi M, Uchino Y, Nakaya H, Takemura R, Inagaki E, Kosugi S, Okano H, Yasui M, Tsubota K, Hayashi K, Yoshino J, et al. Safety and efficacy of long-term nicotinamide mononucleotide supplementation on metabolism, sleep, and nicotinamide adenine dinucleotide biosynthesis in healthy, middle-aged Japanese men. Endocr J. 2024; 71(2):153-169.
69. Coppe JP, Patil CK, Rodier F, Sun Y, Munoz DP, Goldstein J, Nelson PS, Desprez PY and Campisi J. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008; 6(12):2853-2868.
70. Kirkland JL and Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020; 288(5):518-536.
71. Hatzistergos KE, Blum A, Ince T, Grichnik JM and Hare JM. What is the oncologic risk of stem cell treatment for heart disease? Circ Res. 2011; 108(11):1300-1303.
72. Meyer-Hermann M. Estimation of the cancer risk induced by therapies targeting stem cell replication and treatment recommendations. Sci Rep. 2018; 8(1):11776.
73. Abad M, Mosteiro L, Pantoja C, Canamero M, Rayon T, Ors I, Grana O, Megias D, Dominguez O, Martinez D, Manzanares M, Ortega S and Serrano M. Reprogramming in vivo produces teratomas and iPS cells with totipotency features. Nature. 2013; 502(7471):340-345.
74. de Magalhaes JP and Ocampo A. Cellular reprogramming and the rise of rejuvenation biotech. Trends Biotechnol. 2022; 40(6):639-642.
75. Jagota A, Khan ZA, Sharma SA and Priyanka. Multifaceted dynamics of circadian timing system influence aging and longevity. Biogerontology. 2025; 26(5):184.
76. Saliev T and Singh PB. Age reprogramming: Innovations and ethical considerations for prolonged longevity (Review). Biomed Rep. 2025; 22(6):96.
77. Kapadia CD, Williams N, Dawson KJ, Watson C, Yousefzadeh MJ, Le D, Nyamondo K, Kodavali S, Cagan A, Waldvogel S, Zhang X, De La Fuente J, Leongamornlert D, et al. Clonal dynamics and somatic evolution of haematopoiesis in mouse. Nature. 2025; 641(8063):681-689.

 doi:10.20944/preprints202603.0112.v1