Review

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What Is Aging, and How Can We Defeat It?

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Review

What Is Aging, and How Can We Defeat It?

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Key points

- Aging is a combination of stochastic and non-stochastic processes; the latter are shaped by evolutionary mechanisms, such as AROCM.
- Almost all chronic age-associated diseases show significant links to one or more hallmarks of aging.
- Senolytics are a promising strategy for eliminating senescent cells and should be further developed into next-generation, safer solutions; monoclonal antibodies may help eliminate specific detrimental cell types (e.g., pathogenic T-cell clones) and molecules (e.g., DAMP-related factors like HMGB1).
- Many well-known interventions – from caloric restriction and exercise to NMN, metformin, GLP-1 agonists, and OSK – activate pre-existing homeostatic and repair mechanisms and should be integrated into multimodal aging therapies.
- Genome and epigenome editors offer tremendous potential for preventing or delaying aging-related dysfunction, though current CRISPR-based platforms will likely be superseded by next-generation systems.
- Cell, tissue, and organ replacement strategies hold nearly unlimited potential for lifespan extension, although they are still in their infancy.
- Machine learning tools, including aging clocks, and AI agentic systems should be leveraged to understand aging biology, discover novel therapies, and enable personalized, precise, longevity-oriented medicine.

Abstract

Aging is not an immutable fate but a malleable biological process driven by interconnected molecular, cellular, and systemic failures. While modern medicine excels at managing acute conditions, it largely fails to address the root cause of most chronic diseases – aging itself. In this review, I synthesize current evidence that aging arises from the interplay of stochastic damage and evolutionarily shaped regulatory programs (exemplified by conserved parameters such as AROCM) and manifests through the hallmarks of aging, including genomic instability, proteostatic collapse, mitochondrial dysfunction, cellular senescence, and inflammaging, ultimately driving chronic disease across organ systems. I argue that defeating aging requires a strategic shift from symptom palliation to restoration of youthful function, achieved through three synergistic pillars: (1) elimination of damage (e.g., senolytics, monoclonal antibodies against pathogenic immune clones or DAMPs), (2) reactivation of endogenous repair mechanisms (e.g., caloric restriction, metformin, GLP-1 agonists, transient OSK expression), and (3) cell, tissue, and organ replacement (e.g., stem cell–derived islets, *FOXO3*-enhanced MSCs). I highlight evolutionary insights from long-lived species, the centrality of chronic inflammation and fibrosis in age-related disease, and the transformative role of AI: from multi-omic aging clocks to agentic systems for target discovery and personalized longevity medicine. The tools to initiate this paradigm shift are already emerging; what is needed now is scientific rigor, interdisciplinary integration, and a collective commitment to treating aging as the fundamental driver of human morbidity and mortality.

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Why Aging is a Fundamental Driver of Human Suffering and Why it is so Hard to Deal With

Today, representatives of our species live longer and healthier than at any time in history. Thanks to vaccination, the later introduction of antibiotics, and now the emerging victories over cancer, aging may become the next frontier our minds are poised to overcome [1,2].

Yet progress in this field seems stalled, and not only due to lack of funding or understanding, but because aging is fundamentally different from infectious diseases or cancer. By its nature, aging is a systemic degenerative process, not caused by a single hostile agent, but by a progressive, body-wide loss of function – observable in the brain, immune system, skeletal muscles, cardiovascular system, and virtually every organ [3,4].

The bad news is that modern medicine remains poorly equipped to address such degenerative and chronic conditions. It often focuses on masking symptoms rather than achieving true recovery or eradication of the underlying pathology. Thus, addressing aging requires answering two intertwined questions: how to genuinely cure chronic disease – and how to defeat aging itself [5,6].

How difficult it will be to defeat aging is, in fact, inscribed in the very architecture of our gene regulatory networks. A recent large-scale epigenomic atlas across 17 human tissues demonstrated that perturbing the majority of age-associated co-methylation modules, representing core gene networks, exacerbates rather than ameliorates aging signatures. Only a handful of modules, such as those linked to NAD^+ salvage metabolism, showed resilience to intervention. This underscores a sobering truth: effective anti-aging strategies must be exquisitely precise, because in most cases, blunt manipulation does more harm than good [7].

Why aging is harmful is becoming increasingly obvious, yet human psychology remains reluctant to acknowledge it as a treatable condition. Common objections come from various domains: religious beliefs ("this is how God made it"), demographic fears ("the planet is overpopulated!"), or concerns about stagnation ("we'll run out of new ideas").

In reality, many polytheistic and especially Abrahamic religions developed the concept of "life after death" as a psychological coping mechanism for mortality – anxiety so profound it echoes in the existential verses of Omar Khayyam [8,9]. Not all traditions reject longevity: in Daoism, for example, longevity and harmony with nature are central virtues, giving rise to practices like Qigong [10].

The demographic argument now seems increasingly outdated: more and more countries face severe economic strain due to aging populations, with no viable solutions in sight [11,12]. Similarly, the fear of intellectual stagnation ignores a key fact: cognitive rigidity is itself a hallmark of brain aging [13].

Most striking, however, is this contradiction: people universally condemn cancer, Alzheimer's, and heart attacks as evils, and wish them on no one – yet normalize the very process that causes them all: aging, often even refusing to recognize it as a disease [14]. Beneath all

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objections to fighting aging lies a single, deep-seated belief: "It's impossible: no one has succeeded before."

Meanwhile, aging imposes a substantial burden on individuals, healthcare systems, and economies worldwide. But today, for the first time in history, we possess unprecedented data, tools, and biological insight. The question is no longer whether we can defeat aging, but when.

And so, evidence supports the view that: targeting the biological mechanisms of aging represents a viable and urgent strategy to extend healthspan, and potentially lifespan, with growing evidence supporting its feasibility [15].

What Causes Aging: Stochasticity or Programme?

If aging exerts profoundly detrimental effects across biological systems, what is its fundamental cause? This question remains one of the hottest debates in biogerontology, and to date, no single consensus theory of aging exists.

What is widely accepted, however, is the "Hallmarks of Aging" framework, though it is more phenomenological than causal. In brief, aging is characterized by a set of interconnected changes, grouped into three categories. Primary hallmarks, which arise intrinsically and may act as initial drivers: (1) genomic instability, (2) telomere attrition, (3) epigenetic alterations, (4) loss of proteostasis, and (5) disabled macroautophagy. Antagonistic hallmarks, which emerge as compensatory responses to primary damage but become harmful over time: (6) cellular senescence, (7) mitochondrial dysfunction, and (8) deregulated nutrient-sensing. Integrative hallmarks, which result from the interplay of the above and reflect systemic collapse: (9) chronic inflammation, also referred as inflammaging, (10) stem cell exhaustion, (11) altered intercellular communication, and (12) microbiome dysbiosis [16].

I will explore these mechanisms in detail later. For now, I ask: what is the root cause of aging? Two opposing views dominate the field: purely stochastic damage versus an evolutionarily shaped program. Increasingly, however, scientists converge on a middle ground: aging is quasi-stochastic: a blend of random molecular decay and regulated biological responses.

Indeed, aging can be seen as a biological manifestation of the second law of thermodynamics: complex living systems maintain order by exporting entropy to their environment, but over time, they accumulate internal entropy, gradually losing the ability to preserve structural and functional integrity.

This manifests at multiple levels. Somatic mutations accumulate stochastically across the genome [17]. Chromatin architecture, exquisitely organized in youth, becomes increasingly disordered with age: global loss of DNA methylation and histone marks coexists with focal heterochromatinization, such as senescence-associated heterochromatin foci (SAHF) [18]. This epigenetic drift disrupts transcriptional fidelity, derepresses endogenous retroviruses and transposable elements, and fuels genomic instability, inflammation, and cancer risk [19,20].

At the tissue level, aged cells lose their differentiated identity. Meanwhile, the extracellular matrix stiffens due to random non-enzymatic cross-links (e.g., advanced glycation end-products, or AGEs), which not only reduce tissue elasticity but also mechanically induce senescence-like phenotypes in neighboring cells – this all gives rise to the extracellular matrix (ECM) theory of aging [21,22].

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At first glance, these processes appear purely stochastic, yet biological programs actively modulate them. For instance, FOXO3, a key regulator of chromatin stability and stress resistance, declines with age but functions as a potent anti-aging safeguard, as demonstrated in arteries, lungs, and skeletal muscle [23–25]. SIRT6, an NAD^+-dependent deacylase, orchestrates genomic integrity, suppresses LINE1 retrotransposons, and enhances DNA repair; its overexpression extends lifespan in mice and it is evolutionarily more efficient in long-lived species, while some rare *SIRT6* variants exist in human centenarians [26–30]. Klotho, a circulating anti-aging hormone, represses insulin/IGF-1 and Wnt signaling, protects against fibrosis and vascular calcification, and its deficiency recapitulates accelerated aging [31–33]. Polycomb complexes (PRC1/2), by maintaining repression of developmental genes, buffer epigenetic drift; their age-related dysfunction underlies the loss of cellular identity [34–37]. This suggests that numerous regulatory networks embedded in our biology may shape the trajectory of aging.

Supporting this view, a recent study from Vadim Gladyshev's lab disentangled stochastic and programmed components of aging: while some age-related gene expression changes are tissue-specific and random, others are highly concordant across cell types and organs, implying systemic regulation [38].

Likewise, work from Andrew Teschendorff's group showed that, despite the presence of stochastic noise, the core signature of biological aging is largely non-stochastic – with the notable exception of pre-cancerous and cancerous tissues, where randomness dominates [39].

Evolutionary Regulators of Aging

If a biological programme of aging exists, what is it, and who are its main players? As in the previous section, such regulation likely operates at multiple levels, beginning with chromatin integrity.

For mammals, the AROCM (Average Rate of Change in Methylation), calculated across a conserved set of 552 CpG sites located in polycomb-repressed bivalent promoter regions (BivProm2+), robustly predicts species maximum lifespan, according to work by Steve Horvath and the Mammalian Methylation Consortium. These CpGs serve as a biomarker of epigenetic drift: they are hypomethylated in youth and gain methylation with age. Crucially, a lower AROCM (reflecting slower age-related methylation gain and better maintenance of the youthful epigenetic state) correlates strongly with greater longevity, spanning from short-lived rodents to exceptionally long-lived whales and bats. In essence, species with the slowest epigenetic "drift" at these developmentally silenced loci tend to live the longest [40].

Beyond epigenetics, other phenomenological patterns of animal longevity reveal evolutionary adaptations. For example, elephants and whales, despite their vast cell numbers (and thus high cancer risk under Peto's paradox), rarely develop tumors.

Elephants resolve Peto's paradox through a remarkable expansion of the *TP53* locus, harboring one canonical copy and 19 transcribed retrogenes (*TP53RTGs*). Although these retrogenes lack DNA-binding domains and do not function as classical transcription factors, they enhance p53 signaling and promote a hypersensitive apoptotic response to DNA damage, effectively eliminating potentially malignant cells before they can proliferate [41,42].

In contrast, cetaceans such as bowhead and other long-lived whales lack *TP53* amplification but instead rely on a multi-layered tumor suppression strategy. This includes positive selection

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and lineage-specific duplications in key apoptosis regulators (e.g., *CASP3*, *APAF1*, *TP73*) and potent inhibitors of angiogenesis (e.g., *SERPINE1*, *CD82*, *TSC2*) [43]. Critically, bowhead whale cells also exhibit uniquely high-fidelity DNA repair: they resolve double-strand breaks and mismatch lesions with exceptional efficiency and accuracy, mediated in part by elevated levels of CIRBP and its downstream effector RPA2, which together enhance genomic stability without eliminating damaged cells via apoptosis [44].

According to the research in the Gorbunova and Seluanov laboratory, he naked mole-rat, a longevity icon, possesses a unique hyaluronan-rich extracellular matrix that confers cancer resistance [45] – and even mice expressing naked mole-rat hyaluronic acid synthase 2 gene (*nmrHas2*) had lower tissue inflammation and cancer incidence [46]. Moreover, an evolutionarily altered cGAS protein in this species lacks the suppressive function seen in humans and mice, instead enhancing homologous recombination repair and delaying aging through prolonged chromatin retention after DNA damage [47].

Spalax galili (the blind mole rat), another long-lived rodent, does not accumulate clonal expansions of T- and B-lymphocytes with age – unlike humans, whose immune senescence drives chronic "inflammaging" [48].

Early in their evolution, Neoaves acquired a loss-of-function *KEAP1* mutation that constitutively activates NRF2, enhancing antioxidant defense and neutralizing the high ROS from their elevated metabolism, decoupling intense metabolic activity from oxidative damage and enabling unusually long lifespans [49].

Longevity is also shaped at the physiological level. Neoteny, the retention of juvenile traits into adulthood, appears tightly linked to extended lifespan [50]. The axolotl, a neotenic salamander, remains in a larval-like state (with external gills and delayed metamorphosis due to impaired thyroxine signaling) and shows negligible senescence for most of its 13-year lifespan [51–53]. Naked mole-rats resemble hairless, earless newborn mice (a neotenic phenotype), and their mitochondria retain biophysical properties typical of neonatal, not adult, rodents [54,55]. Even humans are neotenic: compared to other great apes, we have flatter faces, smaller canines, reduced sexual dimorphism, and weaker musculature – traits that emerged alongside extended lifespans and complex social structures (including pair bonding) [54,56]. Indeed, among hominids, humans are among the longest-lived, despite not being the largest.

Conversely, lifespan can also shorten during evolution, often due to relaxed selection or inbreeding. In domestic dogs, large breeds live significantly shorter lives than small ones, primarily due to body size–related aging acceleration. However, within breeds, higher individual inbreeding coefficients are associated with reduced lifespan, and purebred status itself (vs. mixed ancestry) explains 46% of lifespan variation after accounting for body size, highlighting the fitness cost of recent inbreeding and loss of heterozygosity [57,58]. Even more extreme is the case of annual killifish (*Nothobranchius* spp.), which inhabit temporary African pools. Their life history is compressed into a few months: they mature rapidly, reproduce, and die, while their embryos enter diapause to survive the dry season. Even in captivity, they rarely exceed 12–14 months. This short lifespan stems from evolutionary trade-offs: massive expansion of transposable elements, degradation of DNA repair pathways, and loss of genomic maintenance systems – essentially, they've "given up" on longevity [59–61].

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What can we conclude? Evolution has already shaped *Homo sapiens* into one of Earth's longest-lived species. But nature has also equipped other organisms with extraordinary longevity mechanisms, from epigenetic stability to cancer resistance and neotenic physiology. Rather than developing entirely novel paradigms, current efforts can build upon evolutionarily conserved longevity mechanisms observed across species. If we combine them with radical technologies, from epigenetic reprogramming to organ replacement, to extend healthspan beyond evolutionary limits.

Aging Cell Physiology

During aging, profound alterations occur within every cell, many of which are captured by the "Hallmarks of Aging" framework. While a full discussion would require a dedicated review, I focus here on several key cellular processes.

Nuclear Dysfunction

The nucleus is among the first compartments affected. DNA damage, from both endogenous sources (e.g., replication errors, ROS) or exogenous insults (UV, alkylating agents), triggers the DNA damage response (DDR). Initially protective (activating repair and halting cell cycle to prevent oncogenesis), DDR becomes chronically activated in aged cells, driving a senescent phenotype characterized by sustained expression of p21 and other cell cycle inhibitors [62].

A major endogenous trigger of DDR is telomere attrition. Because eukaryotic chromosomes are linear, their ends are capped by telomeres – nucleoprotein structures that prevent recognition as double-strand breaks (DSBs). With each cell division, telomeres shorten; once critically eroded, they mimic DSBs, leading to persistent DDR activation and irreversible cell cycle arrest [63].

Beyond mutations, epigenomic drift is a hallmark of aging nuclei. Global loss of DNA methylation and histone marks reduces chromatin compaction, leading to: (1) increased transcriptional noise (leaky expression of silenced genes), (2) derepression of transposable elements, fueling inflammation and genomic instability, (3) loss of cellular identity, as lineage-specific gene expression programs blur [64,65].

Paradoxically, focal hypermethylation also occurs, often at promoters of tumor suppressor or developmental genes, which forms senescence-associated heterochromatin foci (SAHF), which may be adaptive (e.g., silencing oncogenes) or maladaptive [18,66].

Cytoplasmic and Proteostatic Collapse

Nuclear dysfunction propagates to the cytoplasm. Mutated or truncated mRNAs (from genomic or splicing errors) produce misfolded proteins. Simultaneously, altered gene expression disrupts stoichiometry of multi-subunit complexes (e.g., ribosomes, proteasomes), further impairing protein homeostasis [67,68].

In healthy young cells, misfolded proteins are either refolded by chaperones (foldases) like HSP70/HSP90, or degraded via the ubiquitin–proteasome system (UPS) or autophagy–lysosome pathway (ALP). All these systems (foldases, UPS, ALP) are highly energy-consuming and thus rely on ATP [69].

But in aging, ATP becomes scarce (see below), crippling these systems. Cells resort to ATP-independent "holdases" (e.g., small HSPs, like HSP27) that sequester aggregates, leading to

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lipofuscin accumulation in long-lived post-mitotic cells (e.g., cardiomyocytes, retinal pigment epithelium) [69].

Critically, impaired macroautophagy affects not only proteins but also organelles. Damaged mitochondria, which produce excess ROS and generate little ATP, are normally cleared by mitophagy, but this process falters with age, creating a vicious cycle [70].

Autophagy is regulated by several nutrient-sensing pathways, such as mTOR (activated by nutrients/energy), which suppresses autophagy, and AMPK (activated by starvation), which promotes it and antagonizes mTOR. This explains why caloric restriction, rapamycin (mTOR inhibitor), and metformin (AMPK activator) enhance proteostasis and extend healthspan [71].

Mitochondrial Decline

Mitochondria suffer a double vulnerability: their DNA lacks protective histones and is located in close proximity to the electron transport chain (ETC), where reactive oxygen species (ROS) production is highest, making mtDNA highly susceptible to mutations. These mutations impair the function of ETC proteins, rendering them even less efficient. As a result, mitochondria produce more ROS and less ATP, creating a vicious cycle. The situation is further aggravated by ROS-mediated oxidation of membrane lipids, which compromises mitochondrial integrity [70].

Additionally, NAD^+ levels decline with age due to reduced synthesis and increased consumption, particularly by PARP during the DNA damage response (DDR), leading to reduced sirtuin activity and further impairment of ETC function [72].

In fact, some mitochondria remain relatively intact in aged cells. However, because autophagy, especially mitophagy, is impaired with age, a large fraction of mitochondria accumulate damage and become dysfunctional [70].

The result is a triad of hallmarks in aged cells: reduced ATP output, increased ROS leakage, and oxidized membrane lipids [70].

Senescence and Inflammaging

Faced with cumulative stress – from genome, mitochondria, proteome, and extracellular matrix – cells often enter senescence, which is characterized by irreversible cell cycle arrest (via p16/Rb and p53/p21), but at the same time resistance to apoptosis (via upregulation of BCL-2 family anti-apoptotic proteins) [73].

Their true danger lies in the senescence-associated secretory phenotype (SASP): a cocktail of pro-inflammatory cytokines (IL-6, IL-8, TNF-α), chemokines, and matrix metalloproteinases. SASP acts as a damage-associated molecular pattern (DAMP), inducing paracrine senescence in neighboring cells – hence the "zombie cell" analogy [73].

Over time, SASP drives chronic, low-grade inflammation ("inflammaging"), which impairs stem cell function, disrupts tissue regeneration, alters host–microbiome crosstalk, which finally integrates all hallmarks of aging into a systemic collapse [73].

Normally, immune cells clear senescent cells, but immunosenescence with age cripples this surveillance, allowing senescent cells to accumulate and amplify the damage [74,75]…

How Aging Affects Major Organ Systems

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Taking into consideration all general cell aging mechanisms listed in the section above, I will briefly look at how this all ends with the well-known age-associated diseases of particular organ systems that we all know, and why aging is indeed their fundamental reason [76].

Just before delving into the details, a recent perspective introduced a quantitative framework linking age-related diseases to the hallmarks of aging and found the strongest alignment for type 2 diabetes, followed by idiopathic pulmonary fibrosis, Parkinson's disease, and rheumatoid arthritis [77].

Brain

The brain is probably the most complicated organ in our body, constituting as many as 86 billion cells [78]. Main brain cells, neurons, are long-living with very low neurogenesis in some zones in adults, but their function becomes impaired in the elderly. Two main reasons in their biology underlie this: first, neurons rely very heavily on energy due to the need for membrane potential maintenance, and energy becomes scarce because of mitochondrial dysfunction [79]. Second, neurodegenerations are a dramatic illustration of how harmful proteostasis stress may be: beta-amyloid plaques and tau protein neurofibrillary tangles, alpha-synuclein, and TDP-43 and SOD1 are thought to be the most important players in Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), respectively [80].

What may be even more important is chronic inflammation in the neural tissue. The key players here are astrocytes (going into the A1 state), microglia (M1-like), and T-lymphocytes, particularly Th1 and Th17 types [81–83]. T-lymphocytes, according to recent research from the Brunet group, are particularly deleterious, as they foster brain aging the most – namely via IFN-γ signaling [84].

A crucial and often underestimated factor in age-related cognitive decline and neurodegenerative diseases is the increasing permeability of blood vessels and the blood-brain barrier (BBB). This occurs for several reasons, including a decrease in the expression of genes encoding tight junction proteins (such as ZO-1, occludin, claudin) [85] and a selective death of M-pericytes, which are responsible for supporting the extracellular matrix [86].

What drives this inflammation, which is so wicked and exacerbates the effects of protein aggregates? The factors include the inflamed state of the whole body (including the brain itself), maladaptive responses of glial cells to protein aggregates, increased blood–brain barrier permeability (so that T cells may enter, while brain antigens can leak out and trigger immunity), impaired gut–brain axis signaling, and the debated role of viral infections such as HSV-1 [87–89].

Cardiovascular System, Lungs, and Skeletal Muscles

Cardiovascular diseases (CVD) remain the leading cause of death worldwide. This group includes atherosclerosis-related conditions such as hypertension, myocardial infarction, stroke, and acute coronary syndrome, primarily affecting blood vessels, as well as heart-specific disorders like cardiac insufficiency, arrhythmias, and bradycardia [90].

The key deleterious processes in blood vessels involve cholesterol deposition in the vessel wall, followed by maladaptive responses of macrophages that infiltrate to clear it but instead become pro-inflammatory foam cells. Additional contributors include vascular calcification and extracellular matrix (ECM) stiffening [91]. Among ECM-related pathways, SPP1–CD44 signaling

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is particularly harmful, promoting inflammation and fibrosis [92]. On the protective side, FOXO3 (a stress-resistance transcription factor) declines in aged endothelial cells, as does nitric oxide (NO) production, impairing vasodilation and vascular homeostasis [23].

As for the heart, major age-related changes include fibrosis (driven by factors such as WWP2) and chronic inflammation [93,94]. Cardiomyocytes become hypertrophied yet decrease in number due to limited regenerative capacity. The gene encoding FOXP1, a transcriptional regulator that maintains cardiac identity and function, shows reduced expression with age, contributing to functional decline [95].

Lungs are tightly interconnected with the cardiovascular system, and their aging contributes to conditions such as chronic obstructive pulmonary disease (COPD), one of the leading causes of death worldwide, as well as idiopathic pulmonary fibrosis (IPF) and increased susceptibility to severe pneumonias. The underlying mechanisms include enlargement of alveoli, loss of elastic recoil, and impaired mucociliary clearance [96,97].

As for skeletal muscles, they share several physiological features with the heart. Inflammation and fibrosis also occur in aged muscle tissue, and together with impaired regenerative capacity and intracellular lipid accumulation, they drive sarcopenia, a condition characterized by reduced muscle mass, declining physical strength, and increased risk of disability [98]. Interestingly, *FOXO3* in myotubes also serves as a key homeostasis regulator, whose expression is gradually lost during aging [25].

Immune System

Immune system aging is probably one of the most important aspects of organismal aging, because it dramatically affects all other organ systems and impairs the body's ability to eliminate precancerous, cancerous, and senescent cells [99,100].

At the population level, a shift toward a higher myeloid-to-lymphoid cell ratio occurs. This results from chronic inflammatory signaling, which biases hematopoietic stem cells toward myeloid lineage commitment. Myeloid cells belong to the innate immune system, which is less "clever" than adaptive immunity and more prone to drive nonspecific inflammation rather than precise responses, further fueling the vicious cycle of inflammaging [101,102].

Within the lymphoid lineage, profound changes also take place. Thymic involution with age drastically reduces the production of new naïve T cells in elderly individuals [103]. Meanwhile, memory T cells specific to a very limited set of antigens – often from chronic viral infections like cytomegalovirus or Epstein-Barr virus – become dominant. In some cases, individual clones expand to represent more than 1% of all T lymphocytes, which is excessive given the normal diversity of the T-cell repertoire. These expanded clones not only pour fuel on the fire of chronic inflammation but also suppress the maturation of new naïve T cells and occupy their niches [104–107]. Notably, as has been discussed earlier, the long-lived rodent *Spalax* does not exhibit this pathological clonal expansion [48].

With age, the immune system also accumulates errors and begins to attack self-antigens as tolerance mechanisms break down. This is why immune aging shares more features with autoimmune disorders and hypersensitivity reactions than is commonly appreciated [108,109].

Yet paradoxically, this same chronically activated and dysregulated immune system becomes largely ineffective in the elderly, against both infectious agents and cancers. This state is

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known as immunosenescence, and it explains why older adults face significantly higher risks from infections such as COVID-19 [110].

Stomach, Intestine, Microbiome, Liver, and Pancreas

Some of the most important age-related changes occur in the gastrointestinal (GI) system and associated organs, disrupting interactions with the gut microbiome and triggering systemic effects in blood and distant tissues [111].

In the aged stomach, hypoacidity (reduced HCl secretion) develops alongside decreased pepsin synthesis. This is often linked to Helicobacter pylori infection and gastric mucosal atrophy, leading to impaired protein digestion, a factor that exacerbates sarcopenia [112,113].

In the intestine, the mucosa also deteriorates, and, most critically, synthesis of tight junction proteins (e.g., occludin) declines, resulting in "leaky gut" (increased intestinal permeability) [114–116]. This coincides with dramatic shifts in the gut microbiome: overall diversity drops, with a notable loss of *Akkermansia muciniphila* (a key symbiont that strengthens the epithelial barrier) and SCFA-producing genera such as *Faecalibacterium*, *Roseburia*, and *Eubacterium*. Simultaneously, potentially pathogenic *Proteobacteria* expand [117–119]. Combined with weakened local immune surveillance and tolerance mechanisms, this dysbiosis fuels chronic inflammation, both locally in the gut and systemically across other organs [120].

The aging liver undergoes progressive structural and functional decline. Hepatocytes become enlarged and increasingly polyploid, while liver sinusoidal endothelial cells lose their fenestrations, a process known as pseudocapillarization, which impairs the exchange of metabolites, lipoproteins, and insulin between blood and hepatocytes. This directly contributes to hepatic insulin resistance and age-related type 2 diabetes. Concurrently, mitochondrial dysfunction, reduced autophagy, and accumulation of lipofuscin and fat (even in non-obese individuals) lead to steatosis and diminished detoxification capacity [121–123]. A recent study in aged monkeys further showed that *SREBP2* (a master regulator of cholesterol biosynthesis) is upregulated in the aging liver, driving hypercholesterolemia and accelerating liver aging itself [124].

The exocrine pancreas also experiences significant age-related remodeling. Acinar cells atrophy, and fatty infiltration (pancreatic lipomatosis) increases, reducing secretion of digestive enzymes such as amylase, lipase, and trypsin. This exocrine pancreatic insufficiency further compromises nutrient absorption, especially of proteins and lipids, amplifying the risk of malnutrition and sarcopenia [125,126]. In the endocrine compartment, aging drives degeneration of pancreatic β-cells, marked by a heightened unfolded protein response, accumulation of protein aggregates, and β-cell-specific upregulation of the ER chaperone HSP90B1, which impairs glucose-stimulated insulin secretion. Together, these changes disrupt proteostasis, cause functional decline, and ultimately contribute to impaired glucose tolerance and type 2 diabetes [127,128].

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Other Organs

Kidneys. With age, nephron mass declines, accompanied by glomerulosclerosis and interstitial fibrosis. Impaired autophagy in podocytes and tubular cells leads to accumulation of damaged DNA and ROS, resulting in reduced glomerular filtration rate, predisposing to chronic kidney disease and heightened vulnerability to acute kidney injury [129,130].

Bones. Osteoblast activity wanes due to attenuated Wnt/β-catenin signaling and AGE-mediated collagen cross-linking, driving osteoporosis. In postmenopausal women, estrogen loss unleashes RANKL, causing a surge in osteoclast-mediated resorption, culminating in hip and vertebral fractures [131,132].

Male reproductive system. Leydig cells show reduced expression of *INSL3* and *LHCGR*, leading to age-related testosterone decline (late-onset hypogonadism), which exacerbates sarcopenia and osteoporosis. Concurrently, senescent cell accumulation in prostatic stroma and chronic inflammation fuel benign prostatic hyperplasia and increase prostate adenocarcinoma risk [133,134].

Female reproductive system. Ovarian reserve depletion stems from accumulated double-strand DNA breaks and mitochondrial dysfunction in oocytes, culminating in menopause. The resulting estradiol drop disrupts the RANKL/OPG balance, accelerating bone loss, while also causing vaginal epithelial atrophy and genitourinary syndrome of menopause [135,136].

Skin. Dermal thinning and wrinkling arise from suppressed TGF-β/Smad signaling and senescent fibroblasts, reducing COL1A1 and elastin production. Combined with DNA damage in keratinocytes and NAD^+ decline, this impairs wound healing and elevates squamous cell carcinoma risk [137,138].

Cancer Risks and Beyond

Aging is the major risk factor for nearly all cancers, probably excluding only juvenile forms. This occurs due to a combination of factors. Most obviously, cells accumulate mutations over time, and if such a cell evades death, it may eventually give rise to cancer. As I have already discussed, the immune system, whose primary role includes cancer surveillance, becomes increasingly ineffective with age. Moreover, a chronically inflamed environment provides an ideal niche for pre-cancerous and cancerous cells to thrive. Additional contributors include VEGF secretion by senescent cells, extracellular matrix (ECM) remodeling, and age-related microbiome alterations, all of which further fuel tumor initiation and progression [100,139].

Thus, as we can see, aging lies at the core of almost every major human disease. If we truly want to develop effective treatments, we must adopt a holistic perspective – and place aging itself at the center of our therapeutic strategy.

What Technologies Could be Used to Fight Aging

Given the deep interconnections between aging, chronic inflammation, fibrosis, and age-related diseases, the next critical question is: what tools do we already have, or will soon have, to intervene?

Today, the most effective lifespan-extending interventions remain deceptively simple: caloric restriction (CR) and regular exercise act as powerful rejuvenating therapies, alongside sufficient sleep, stress reduction, sunlight exposure, and a nutrient-rich diet [140]. Yet, as powerful as they

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are, they are not enough to halt aging. Here, I focus on the concrete therapeutic tools already in our arsenal, and those emerging on the near horizon.

Small Molecules

Small molecules represent the oldest and still dominant class of therapeutics, accounting for over half of all approved drugs. Despite the rise of biologics, gene therapies, and cell-based approaches, big pharma is now returning to small molecules – a trend highlighted by Alex Zhavoronkov in recent LinkedIn posts. Their advantages are clear: (1) the most easy tissue delivery, especially compared to gene therapies, (2) often orally bioavailable (no injections needed) (3) relatively inexpensive to manufacture, (4) target and off-target effects can be predicted with increasing accuracy using molecular docking and machine learning [141–144].

This category includes several well-known "pro-longevity" candidates: rapamycin, an mTOR inhibitor that extends lifespan and healthspan in model organisms, but in humans, its immunosuppressive side effects limit chronic use [145]. Skulachev ions (SkQ1), mitochondria-targeted antioxidants designed to neutralize ROS; however, their systemic efficacy in humans remains modest [146,147].

Metformin and NMN represent particularly promising candidates for near-term clinical translation, given their safety profiles, mechanistic rationale, and ongoing trials. Metformin, initially an anti-diabetic drug, activates AMPK, enhances autophagy, and antagonizes mTOR signaling, while NMN serves as a precursor to NAD^+, a coenzyme that declines sharply with age and is essential for mitochondrial and DNA repair functions. Both are already in clinical trials for aging-related outcomes (e.g., TAME and MILES trials for metformin) [148–153].

But the real game-changers may come from precision small molecules that block specific pathological drivers. For example, Insilico Medicine identified TNIK as a master regulator of fibrosis and developed INS018_055 (Rentositib), a TNIK inhibitor now in trials for idiopathic pulmonary fibrosis and kidney fibrosis [154,155], while the Petretto lab has pinpointed WWP2 as another promising target in heart and kidney fibrosis [94,156]. At the same time Insilico has also unveiled ISM8969, a potent NLRP3 inflammasome inhibitor, designed for CNS inflammatory disorders like Parkinson's disease [157]. Evidence supports that NLRP3 inhibitors could have a far broader impact, since the NLRP3 inflammasome is a central hub of inflammaging, one of the core pillars of aging itself [158].

Ultimately, no single molecule will be a silver bullet. But a rational combination, boosting autophagy, restoring NAD^+, suppressing chronic inflammation, halting fibrosis, already offers a credible, near-term path toward significantly extended healthspan.

Antibodies

This class of therapeutics emerged relatively recently but has already proven highly effective in treating many chronic diseases, often in combination with other agents.

The best-known examples are immune checkpoint inhibitors used in cancer immunotherapy, such as pembrolizumab and nivolumab. These antibodies block the interaction between PD-L1 (expressed on cancer cells as a "don't eat me" signal) and PD-1 (its receptor on T cells), thereby restoring anti-tumor immunity [159].

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Beyond oncology, monoclonal antibodies have achieved remarkable success in autoimmune disorders. For instance, Tribuvia (senprutug), developed by Russian scientists Sergey Lukyanov and Dmitry Chudakov in collaboration with BIOCAD, targets the TRBV9+ T-cell receptor of a pathogenic T-cell clone responsible for ankylosing spondylitis (Bekhterev's disease), leading to its selective elimination. This breakthrough was made possible by years of high-throughput TCR sequencing, which identified the disease-driving clone. This approach could be expanded in the future towards other autoimmune disorders [160–162]. Notably, Chudakov has proposed in his interview that similar approaches could be used to eliminate hyperexpanded, pro-inflammatory T-cell clones that accumulate with age, a key driver of inflammaging [163]. If so, antibodies may become a precision tool against immune aging itself.

Antibodies are also highly effective in allergic diseases. A combination of omalizumab (anti-IgE), dupilumab (anti-IL-4Rα), and mepolizumab (anti-IL-5) acts at multiple levels: omalizumab reduces cell-bound IgE, dupilumab blocks Th2 signaling to B cells via the IL4/13-IL-4Rα axis, while mepolizumab inhibits eosinophil and basophil activation via IL-5. Together, they disrupt the allergic cascade more comprehensively than any single agent. However, in clinics dual combinations are more widespread [164–166].

In cardiovascular disease (CVD), Repatha (evolocumab), an antibody against PCSK9, enhances hepatic clearance of LDL cholesterol by preventing PCSK9-mediated degradation of LDL receptors, significantly lowering circulating LDL levels [167].

Most recently, Lecanemab (Leqembi) and Donanemab (Kisunla) received FDA approval for Alzheimer's disease. Both target amyloid-β (Aβ) aggregates in the brain and promote their clearance by microglia. While effective in slowing cognitive decline, they carry risks – most notably amyloid-related imaging abnormalities (ARIA), including brain edema [168–171].

Overall, monoclonal antibodies excel when the goal is to eliminate a specific pathological cell population, block extracellular signaling, or neutralize a harmful soluble or membrane-bound molecule.

They are highly potent and generally well-tolerated, though limitations remain: (1) targets must be extracellular or cell-surface exposed, (2) manufacturing is complex and costly, (3) administration typically requires injections or infusions, (4) and there's a risk of anti-drug immune responses [172,173].

Looking ahead, antibodies could be engineered to target: (1) SASP (senescence-associated secretory phenotype) factors, (2) potential pro-aging proteins identified in plasma proteomic studies (e.g., by Tony Wyss-Coray [174], or (3) detrimental inter-tissue signaling pathways that drive systemic aging; (4) pathogenic immune clones, in particular, represent a promising frontier.

Regardless of the specific approach, monoclonal antibodies are already among our most powerful weapons, not just against disease, but against aging itself.

mRNA, Oligonucleotides, and siRNA

mRNA vaccines entered mainstream medicine during the COVID-19 pandemic, thanks to Pfizer–BioNTech's Comirnaty and Moderna's Spikevax. They elicit potent and durable immune responses – a breakthrough that earned the 2023 Nobel Prize in Physiology or Medicine [175–177]. Beyond infectious disease, this platform is now being applied to cancer immunotherapy, with mRNA vaccines in development for melanoma and non-small cell lung cancer [178–181].

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In the context of aging, tolerogenic vaccines (both protein- and mRNA-based), designed not to activate, but to silence or reprogram the immune system, hold particular promise for autoimmune and chronic inflammatory conditions, which are central to inflammaging [182–184].

Oligonucleotides and siRNA represent another powerful class of gene-targeting therapeutics. They work by binding to specific mRNA transcripts, thereby blocking translation or triggering mRNA degradation. Among the most compelling examples are pelacarsen (an antisense oligonucleotide, Novartis), and lepodisiran (an siRNA, Eli Lilly), both currently in Phase 3 clinical trials [185–188]. They target the *LPA* gene, whose product, lipoprotein(a), is a major independent genetic risk factor for atherosclerosis and thrombosis. Elevated Lp(a) affects ~20% of the population, yet no effective therapies existed until now, largely because Lp(a) is structurally similar to plasminogen, with predictable consequences [189–191].

In brief,If we want to temporarily express a gene (e.g., a pro-longevity factor like *FOXO3*) without altering the genome, mRNA delivery is a viable option. If we aim to knock down a harmful gene, antisense oligonucleotides or siRNA offer precise, reversible control. The main challenge for both approaches remains efficient intracellular delivery, since these molecules must reach the cytoplasm to function [192].

Genomic and Epigenomic Editors

Genome and epigenome editing are among the most transformative technologies in modern biomedicine. Early tools like zinc finger nucleases (ZFNs) and TALENs used engineered protein domains to recognize and cleave specific DNA sequences. Today, however, CRISPR/Cas systems dominate the field, leveraging guide RNA (gRNA) for programmable targeting [193,194].

Beyond standard CRISPR nucleases, its daughter technologies offer greater precision and safety: base editors fuse a nickase Cas9 (D10A or H840A mutant) to a deaminase enzyme, enabling direct C•G→T•A or A•T→G•C conversions without double-strand breaks [195,196]. Epigenome editors use catalytically dead Cas9 (dCas9) or dCas12 fused to epigenetic effectors (e.g., DNMT3A, TET1, p300), allowing reversible, tunable control of gene expression, which is ideal for modulating aging pathways like FOXO3, SIRT1, or NF-κB [197,198].

While CRISPR's applications are vast, I focus here on its potential against aging. For blood vessels, key genetic risk factors, such as PCSK9 (which regulates LDL receptor degradation) and LPA (encoding lipoprotein(a), a major independent risk factor for atherosclerosis), can be permanently inactivated, not just transiently suppressed by antibodies or RNAi. Companies are already advancing this vision: Verve Therapeutics is developing VERVE-102, a base editor that introduces a premature stop codon in PCSK9, leading to lifelong LDL reduction [199,200]. Scribe Therapeutics is advancing STX-1200 to knockout LPA [201] and STX-1150 to epigenetically silence PCSK9 [202]. Critically, the liver, the primary target for these therapies, is among the most accessible organs for in vivo gene editing, supporting optimistic forecasts for clinical translation [203].

Despite their promise, all nuclease-based platforms face major hurdles. One is about delivery: only adeno-associated viruses (AAVs) offer reasonable tissue specificity and safety, but their cargo capacity is limited, and pre-existing immunity is common. The blood–brain barrier (BBB) makes CNS targeting especially difficult; even successful delivery risks neuroinflammation or edema. Additional challenges include off-target edits, reduced on-target efficiency (especially in

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high-fidelity variants), PAM sequence constraints, and immune responses to bacterial Cas proteins [204,205].

A potential paradigm shift may come from de novo protein design. Recently, David Baker's lab used AI-driven protein folding to generate ultra-compact DNA-binding proteins (~55–60 amino acids vs. 1,368 in SpCas9). These "mini-Cas" analogs are: small enough for non-viral delivery (e.g., LNPs), non-immunogenic (human-like sequence), and highly specific, with tunable binding affinity [206].

In my view, CRISPR/Cas, while revolutionary today, will likely be superseded by this new generation of AI-designed genomic and epigenomic editors. Ultimately, two strategies will be essential in the fight against aging: (1) permanent removal of detrimental alleles (e.g., *PCSK9*, *LPA*, *APOE4*) via precise genome editing, and (2) dynamic, reversible reprogramming of gene networks via epigenome editing – restoring youthful expression patterns without altering the genomic sequence. Together, they form a powerful toolkit for precision geroscience.

We will separately discuss cell therapies and tissue engineering in the next section - probably, some of the most promising approaches, yet in the very beginning of their development.

To summarize, aging is an extremely complex process, and only a multimodal approach, rather than a single therapeutic intervention, can drive a true revolution.

Main Approaches to Fight Aging

Given that we have discussed in the previous section the tools available against age-related dysfunctions, let us now classify them into several logical approaches. While alternative taxonomies exist, we highlight three major strategies: (1) eliminating hostile agents, (2) stimulating the body's intrinsic rejuvenation capacity, and (3) cell, tissue, and organ replacement.

Eliminating Hostile Agents

When this approach is mentioned, the first targets that come to mind are pre-cancerous/cancerous cells and senescent cells. Leaving oncology to specialists, senescent cells are already primed for death: their survival hinges solely on the hyperexpression of anti-apoptotic proteins, which constitutes their Achilles' heel.

This insight gave rise to senolytics – compounds designed to selectively eliminate senescent cells while sparing healthy ones. Examples include dasatinib, quercetin, fesitin, and navitoclax. In practice, however, these first-generation agents exhibit significant toxicity: fatigue, gastrointestinal and hematological side effects, and thrombocytopenia, among others. Many scientists rightly criticize these drawbacks, but the approach itself is sound; what deserves scrutiny is the current pharmacological implementation [207–210].

A ray of hope comes from a recent study by the Rando lab: a combination of ABT-199 (a navitoclax analog with weaker senolytic activity) and birinapant (an anti-cancer drug that mimics the pro-apoptotic protein SMAC) achieved potent senolytic effects without inducing thrombocytopenia [211]. Such rationally designed combinations may pave the way for safer, more effective clearance of senescent cells in aging and chronic disease.

It is also a vital strategy to target specific age-related pathologies driven by senescent cell accumulation, particularly those with a strong inflammatory component – rather than positioning senolytics as broad anti-aging agents. Recently, senolytics had success in treating animal models

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neurodegenerations, via eliminating senescent-like neurons, astrocytes, and microglia [212,213], while senolytic treatment reduces pain and senescence burden in human intervertebral disc tissue and preclinical models of low back pain [214–216]. Senolytics also have high potential in treating lung fibrosis [217–219], CVD [220,221], type 2 diabetes [222–224], postmenopause bone loss [225], and so on.

Beyond senescent cells, pathogenic immune clones (such as the age-expanded T lymphocytes discussed earlier) also represent valid targets for elimination. In fact, detrimental cell populations have been identified across multiple tissues. For instance, the Deep Dixit group recently described $CD38^{+}CD169^{-}CD11c^{-}$ age-associated macrophages and dysfunctional adipose ILC2 cells, both pro-inflammatory and tissue-disruptive, making them prime candidates for selective removal [226,227].

Not only cells, but also harmful molecules, can be targeted. Obvious examples include SASP factors that fuel chronic inflammation. A key case in point is HMGB1, a nuclear protein involved in DNA architecture that, when released extracellularly, acts as a damage-associated molecular pattern (DAMP) and induces senescence in neighboring cells. Critically, its activity depends on redox state: the reduced form is potently pro-senescent, whereas the oxidized form is inert. This makes HMGB1 a compelling therapeutic target, either through neutralization or forced oxidation, to disrupt paracrine SASP signaling and halt the spread of senescence [228].

Equally promising are cross-tissue signaling axes, such as the MIF–CD74 pathway uncovered by the Kellis lab: MIF is secreted by fibro-adipogenic progenitors in skeletal muscle, binds to CD74 on myeloid cells in white adipose tissue, and drives adipose inflammation – a process that declines with exercise [229]. Why not pharmacologically block this, and other similarly vicious, circuits?

Stimulating the Body's Intrinsic Rejuvenation Capacity

Our body possesses more regenerative capacity than it normally uses. Many of the most promising interventions do not invent something entirely new – they reactivate pro-longevity mechanisms already embedded in our biology.

The simplest examples are caloric restriction (CR), rapamycin, and metformin. Our cells can degrade protein aggregates and damaged mitochondria via autophagy, but they rarely operate at full capacity. Physiological challenges (like fasting) or pharmaceuticals can safely enhance this intrinsic cleanup system [230,231]. Similarly, supplementing with NAD^{+} precursors (e.g., NMN), currently in clinical trials, helps restore normal cellular metabolism by boosting sirtuin activity [232,233].

GLP-1 receptor agonists, initially developed for diabetes and obesity, demonstrate broad geroprotective effects by suppressing chronic inflammation, oxidative stress, and cellular senescence – core hallmarks of aging [234]. Preclinical studies show they reverse brain aging signatures and reduce Alzheimer's-related gene expression [235], while clinical trials are now evaluating their impact on physical function and molecular aging biomarkers in older adults [236]. Their multimodal action across metabolic, cardiovascular, and neurodegenerative pathways positions GLP-1 agonists as leading candidates for healthspan extension [237,238].

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The same principle applies to DNA repair, which can be enhanced by lifestyle factors (e.g., high-quality sleep) or pharmacological agents, thereby reducing senescence signaling and cancer risk.

Exercise is another well-established rejuvenating intervention. In skeletal muscle, for instance, it acts through the SPP1–CD44 axis, which modulates the stem cell niche and promotes regeneration, as recently shown by the Rando and Brunet labs [239]. Could we pharmacologically mimic this pathway (specifically in muscle, not systemically) to treat sarcopenia?

One of the most actively debated strategies is transient expression of Yamanaka factors: the cocktail of *Oct4*, *Sox2*, *c-Myc*, and *Klf4* (OSKM). Despite concerns about carcinogenicity, recent studies from the Belmonte group demonstrate that short-term, cyclic induction is generally safe, even with long-term use in mice [240]. Even safer is the OSK combination (without c-Myc), which retains efficacy while minimizing tumorigenic risk. Controlled OSK exposure restores chromatin integrity, activates tissue-resident stem cells (e.g., in muscle), and, counterintuitively, triggers apoptosis in cancer cells: once their epigenome is reset, they recognize irreparable genomic damage and self-destruct, according to recent David Sinclair's and Tao Cheng's research [241–243]. Since OSK delivery currently requires gene therapy (a major hurdle), the Sinclair lab is developing small molecules that mimic OSK activity [244]. While this approach remains high-risk and demands precise control, we believe it holds strong potential for partial, targeted rejuvenation, once proven safe in humans.

Another controversial but intriguing avenue is the "young blood" effect. Heterochronic parabiosis experiments show that joining the circulatory systems of young and old mice partially rejuvenates the old while accelerating aging in the young (compared to isochronic pairs) [245,246]. This inspired practices like young plasma transfusions (e.g., by Bryan Johnson), widely criticized as unscientific and potentially harmful (transfusion itself is a physiological stressor). Moreover, no significant results were achieved in clinical trials by the commercial company Ambrosia [247], which were widely criticized for flawed methodology. This was followed by a strong 2019 FDA warning against such unproven "young blood" practices, leading Ambrosia to cease treatments [248,249]. Furthermore, a trial involving young fresh frozen plasma infusions for Alzheimer's patients showed no significant improvement in cognition [250,251]. On the other hand, a separate study exploring umbilical cord plasma concentrate in elderly individuals showed potential in affecting some biomarkers related to aging, though the researchers emphasized that these results are highly preliminary [252]. And despite all this, the underlying idea may hold merit: what specific factors in young blood drive rejuvenation? If we identify these proteins, metabolites, or extracellular vesicles, they could become components of a rational, cell-free rejuvenation therapy.

In general, the first two strategies – elimination of damage and activation of repair – are deeply intertwined. Take microglia: in response to beta-amyloid, they can launch either a damaging inflammatory program or an adaptive, phagocytic one (driven by GPNMB and lysosomal clearance) [253–255]. If we block the harmful pathway, will cells default to the protective one? If we remove chronic stressors like senescent cells, will the body's innate healing capacity rebound more fully? Likely, yes. And if we carefully combine both strategies, we may shift human healthspan toward its biological ceiling of 120–150 years [256].

But what if we want more?

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Cell, Tissue, and Organ Replacement

Cell, tissue, and organ replacement holds near-unlimited potential for extending both healthspan and lifespan, potentially enabling biological immortality. The main limitation is that most approaches remain preclinical or early clinical, with only a few validated applications.

Probably the most widely used cell therapy today is CAR-T cells, which fuse an antibody-derived targeting domain with T-cell receptor signaling components to selectively eliminate tumor cells [257,258]. Beyond oncology, CAR-T and TCR-T cells (T cells engineered with antigen-specific receptors) are now being explored for autoimmune disorders [259]. Importantly, it is not only conventional $CD8^+$ cytotoxic and $CD4^+$ helper T cells that can be engineered: CAR/TCR-Tregs (regulatory T cells) can be designed to induce antigen-specific immune tolerance [260,261]. Such cells could potentially suppress autoimmune-like processes in aging, including chronic inflammation driven by self-reactive clones.

Equally promising is immune system replacement. As discussed above, aging drastically reduces naïve T-cell production, partly due to age-associated clonal expansions and inflammaging, and partly due to thymic involution [103,262]. Recent studies show that *FOXN1* overexpression (in mice) [263,264] or IL-22 administration can partially restore thymic architecture and naïve T-cell output [265]; bioengineered thymic organoids are also emerging [266]. Replacement is not limited to adaptive immunity: innate immune cells, such as ILC2s, can also be replenished [227]. Critically, this should be coupled with the clearance of old, senescent, and chronically inflamed immune cells.

What is already used in clinics is skin and corneal epithelia – autologous or allogeneic sheets derived from stem or progenitor cells. These are standard care for severe burns, chronic ulcers, and corneal injuries, with decades of safety data [267–270]. In the context of aging, they hold clear potential for age-impaired wound healing, where delayed re-epithelialization, reduced growth factor secretion, and chronic inflammation impede recovery [271].

Also in high demand are cartilage and bone grafts. Engineered cartilage, often from chondrocytes or MSCs seeded on biodegradable scaffolds, is used for nasal and auricular reconstruction and is being tested for focal osteoarthritic lesions [272,273]. Bone substitutes, including 3D-printed ceramic or collagen-based matrices loaded with osteoprogenitors, are increasingly deployed in orthopedics and dentistry to treat osteoporotic fractures and non-unions [274,275]. Both tissues are highly relevant to aging: cartilage loss drives osteoarthritis, while age-related declines in osteoblast function and matrix mineralization underlie fragility fractures [276,277].

One of the most encouraging success stories is currently unfolding in diabetes therapy. Clinical trials have demonstrated that stem cell–derived islets (SC-islets) – pancreatic β-like cells differentiated from human pluripotent stem cells – can restore glucose-responsive insulin secretion in both type 1 [278–280] and advanced type 2 diabetes [281,282]. In multiple studies, patients achieved insulin independence for over a year, with near-normal HbA1c and time-in-range metrics [283,284]. Both autologous (patient-specific iPSC-derived) and allogeneic approaches are being explored, but the latter are considered more scalable. To overcome the need for systemic immunosuppression, scientists are developing several advanced strategies. These include the use of encapsulation devices (e.g., ViaCyte's PEC-Direct/Encap, now under Vertex) to protect grafts [285,286]. Another major effort involves engineering hypoimmunogenic SC-

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islets, for example by knocking out *B2M* (to eliminate HLA class I) and *CIITA* (to suppress HLA class II), which have shown promise in preclinical models for evading T-cell and NK-cell rejection [287–290]. This represents one of the clearest proofs that chronic metabolic disease can be eradicated, not just managed, by fully restoring endogenous insulin regulation.

Very promising is neuronal replacement for neurodegenerative conditions – to my view, perhaps the only way to truly restore function in a dying brain. Antibody-based therapies (e.g., lecanemab, donanemab) and emerging anti-neuroinflammatory strategies slow decline but do not halt or reverse neuronal loss [291]. In contrast, iPSC-derived dopaminergic neurons are already in clinical trials for Parkinson's disease (e.g., by BlueRock Therapeutics and Kyoto University), with grafts showing survival, integration, and motor improvement at 2 years [292–294]. For Alzheimer's, cortical and cholinergic neurons derived from iPSCs are in preclinical development, aiming to replace lost circuitry in the entorhinal cortex and basal forebrain [295]. Unlike symptomatic approaches, neuronal replacement targets the core pathology: irreversible cell loss.

Very promising, minimally invasive, and still underutilized is microbiome replacement. Fecal microbiota transplantation (FMT) not only cures recurrent *C. difficile* infection but also reverses age-associated dysbiosis in preclinical models, restoring SCFA production, gut barrier integrity, and systemic immune tone [296]. Engineered consortia (e.g., VE303 by Vedanta Biosciences) containing defined *Clostridia* strains induce colonic Tregs and suppress inflammaging [297–299]. In aged mice, FMT from young donors improves cognitive performance, reduces microglial activation, and extends healthspan – effects linked to bile acid and tryptophan metabolite shifts [300,301]. Human trials are now exploring precision microbiota therapeutics for sarcopenia and frailty treatment [302].

Conceptually intriguing work has emerged from China, where the Liu Guang-Hui lab, in collaboration with Belmonte, leveraged extensive single-cell profiling of aged cynomolgus monkeys (*Macaca fascicularis*) to pinpoint FOXO3 as a central anti-aging regulator. They engineered mesenchymal stem cells (MSCs) carrying a gain-of-function *FOXO3* mutation, which, upon transplantation, induced robust systemic rejuvenation with no significant adverse effects. Wild-type MSCs provided modest benefit, but far less pronounced. The effect was largely mediated by exosome-dependent signaling, not direct engraftment [303].

What's next? The main bottleneck in engineering complex organs (such as the heart, lungs, or kidneys) is achieving functional vascularization and innervation. In large organoids, cells in the core rapidly undergo necrosis due to hypoxia and poor metabolite exchange [304,305]. Additional hurdles include the trade-off between autologous approaches (patient-derived iPSCs: low immunogenicity but high cost and complex QC) and allogeneic hypoimmunogenic iPSC platforms (e.g., with B2M/CIITA knockout), which are now entering clinical development [306].

Once these barriers are overcome, and we can reliably replace aged or failing organs, we may finally confront the ultimate question: how long can a fully repaired human live?

But What If We are to Act Right Now?

I will end this section with a sobering reality.

Some individuals are, or soon will be, facing imminent death (e.g., from terminal cancer), and one more technology, albeit controversial and unproven, offers a speculative lifeline:

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cryonics. In this procedure, the body (or brain) is preserved at –196°C in liquid nitrogen after perfusion with cryoprotective agents designed to minimize ice crystal formation and reduce cellular damage [307].

The good news: vitrification (ice-free glass-like solidification) has enabled successful recovery of functionality in small tissues and organisms, including nematodes (*Caenorhabditis elegans*), mammalian retinas, and even whole pig kidneys, which were later transplanted and functioned ex vivo [308–311].

The bad news: no complex mammal, let alone a human, has ever been revived after cryopreservation. Current protocols typically begin hours after legal death, during which ischemic damage and imperfect CPA perfusion may already compromise neural integrity [312].

In my view, no known law of physics forbids future revival, if sufficient structural information (especially in the brain's connectome) is preserved. The real question is whether today's cryonics protocols preserve enough fine-scale neural architecture to retain identity and memory. To answer this, we need systematic, high-resolution comparisons of brain ultrastructure before and after vitrification – ideally using connectomics [313].

Encouragingly, the FlyWire Consortium and Google recently mapped the full synaptic-resolution connectome of the adult *Drosophila melanogaster* brain, a milestone that demonstrates our growing capacity to image, store, and analyze neural wiring at scale [314]. A lot of progress is needed to move from the fruit fly brain to the human one, but this is the first step.

While cryonics remains a high-risk, long-shot bet, it may one day serve as a bridge to future rejuvenation technologies, if we can prove that "you" are still there in the frozen brain.

Aging Clocks

How can we quantify aging to assess how biologically "young" or "old" an individual is, irrespective of chronological age, or to measure the efficacy of anti-aging therapies? For this, multiple aging clocks have been developed. They estimate biological age as an integrative metric of organismal state: if it exceeds chronological age, the individual is at higher risk of serious illness or death; if it is lower, the opposite holds true. Today, aging clocks exist for numerous tissues and species, working with data ranging from clinical blood tests to single-cell RNA-seq.

The era of aging clocks began with Steve Horvath, who in 2013 introduced the first multi-tissue DNA methylation clock. Like most clocks today, it uses an elastic net regression model based on methylation levels at 353 CpG sites [315]. This was followed by other first-generation clocks such as Hannum (71 CpGs) [316] and Zhang (514 CpGs) – one of the most accurate models for predicting chronological age to date [317].

However, these first-generation models face the "biomarker paradox": the more precisely they predict chronological age, the less they reflect health status or disease risk. Many CpG sites in these clocks correlate strongly with age but weakly with pathology. Returning to the stochasticity question, clocks like Horvath's and Zhang's are largely driven by stochastically drifting CpGs, unlike second-generation clocks such as PhenoAge [39,318].

Second-generation clocks answer not "How old am I?" but "How much time do I have until death, cancer, or a cardiovascular event?" Many CpGs in these models show modest age correlation but strong association with clinical outcomes. According to the ComputAgeBench

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study by the Ekaterina Khrameeva's group, PhenoAgeV2 [319] is currently the strongest predictor, followed by GrimAgeV1 [320], PhenoAgeV1 [318], and GrimAgeV2 [321,322].

Moreover, the Mammalian Methylation Consortium has recently developed pan-tissue, pan-mammalian epigenetic clocks applicable to 185 species. These clocks are built on evolutionarily conserved CpG sites, highly enriched in polycomb-repressed developmental loci, that form the molecular backbone of cross-species aging biomarkers and underpin the AROCM framework [323].

Not all clocks rely on DNA methylation. In fact, they can be built from any biomedical data modality. The Wyss-Coray group recently developed plasma proteome clocks, capturing both systemic aging signals and organ-specific proteins from 11 major organ systems [174]. The Kennedy and Gruber groups created DoliClock, a lipidome-based brain aging clock [324], as well as PCAge and LinAge2, designed for routine clinical data [325,326]. The Anne Brunet lab built cell type–specific clocks for the brain: separate models for neuroblasts, astrocytes, oligodendrocytes, and microglia [327]. And the Vadim Gladyshev lab recently introduced ScAge, an aging clock for single-cell data [328].

We must understand that aging clocks are not just diagnostic tools or risk predictors – they can reveal causal drivers of aging. Genes, proteins, or metabolites that strongly increase predicted age may themselves be active contributors to aging and thus valid therapeutic targets. This insight underpins Insilico Medicine's Precious1GPT, Precious2GPT, and Precious3GPT clock models, which use transformer-based models to identify such targets [329–331].

Finally, we must remember that not all age-related changes are harmful. Some are adaptive responses to damage, and blocking them could worsen outcomes. To distinguish between the two, Gladyshev and Horvath recently developed DamAge (measuring detrimental alterations) and AdaptAge (measuring protective or compensatory changes) – a crucial step toward precision geroscience [332].

The Power of AI in Aging Research and Drug Development

To comprehend and ultimately defeat a complex process like biological aging, we don't need to be alchemists, but our science must be data-driven. Fortunately, thanks to trends like Moore's Law, more data is generated every year. AI tools can now ingest numerous datasets and read millions of scientific papers to uncover patterns invisible to humans, and thus drive real breakthroughs.

One of the brightest examples of AI in biopharmaceutical innovation is Insilico Medicine, led by Alex Zhavoronkov. They've built a complete end-to-end pipeline that has already yielded a strong portfolio of novel small molecules. In brief, PandaOmics identifies therapeutic targets by integrating multi-omics and biomedical literature [333], Chemistry42 designs small-molecule inhibitors and predicts their properties (e.g., target binding, toxicity) [334], and inClinico forecasts clinical trial outcomes to avoid costly failures [335].

Equally transformative is the work of the Manolis Kellis lab, which harnesses machine learning to comprehend the regulation of the human genome in aging and disease. Just some examples of their work includes Hydra, an interpretable deep generative model for robust annotation of single-cell omics data [336]; scCLIP, a multimodal contrastive learning framework that aligns chromatin accessibility and gene expression across tissues [337]; SPATIA, a spatially

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aware foundation model that unifies cellular morphology, transcriptomics, and tissue architecture [338]; Procyon, a multimodal protein language model that predicts functional phenotypes across the proteome [339]; and Epilogos, an information-theoretic browser for navigating epigenomic landscapes across thousands of samples [340].

Such AI solutions will be transformative across virtually every area of research and development. They are not replacements for scientists – they are force multipliers, accelerating discovery and enabling us to tackle the systemic complexity of aging with unprecedented precision.

AI Tools as Assistants in Personalized Medicine

AI tools must also be integrated into clinical medicine, and for compelling reasons [341].

First, a typical doctor–patient consultation lasts only 15 to 30 minutes – far too little time to thoroughly assess an individual's full medical history, lifestyle, and risk profile. In some settings, such as pre-shift medical checks for miners, it can be even shorter [342,343].

Second, no single physician or scientist can keep up with the entire body of biomedical literature, especially when dealing with rare or complex cases. An AI agent, however, can instantly access and synthesize millions of publications, ensuring no relevant evidence is overlooked [344,345].

Third, computer vision algorithms can outperform humans in specific diagnostic tasks, serving as powerful assistants that reduce medical error. A prime example is the use of AI in dermatology, where algorithms now routinely distinguish benign nevi from melanomas with high accuracy [346,347]. Another one is IRA Labs, a Skolkovo-based startup that analyzes CT scans to detect pathologies, automating routine radiological workflows with precision [348].

AI also excels at interpreting genomic data. By analyzing a patient's sequencing results, it can highlight clinically relevant variants and guide decision-making – a major step toward precision medicine. In some cases, AI even helps stratify patients for targeted therapies. For instance, Neuron23, in collaboration with QIAGEN, developed NEU-411, a small-molecule inhibitor of LRRK2, a kinase linked to vesicle trafficking, inflammation, and increased Parkinson's disease risk in certain genetic variants. Since NEU-411 is effective only against specific LRRK2 forms, an ML-based tool is used to identify likely responders based on the patient's *LRRK2* gene sequence [349,350].

Moreover, omics-based diagnostics are enabling ultra-early disease detection. For example, aberrant methylation of the *SEPT9* gene is already used as a blood-based biomarker for colorectal cancer screening [351,352]. In neurodegeneration, although not "pure" omics, companies like ToxGenSolutions and DiamiR, along with the NeuroMiR project, are developing miRNA-based panels that can detect Alzheimer's disease 5–6 years before symptom onset – far earlier than current blood tests for Aβ40/42 (which offer only 1–2 years of lead time) [353–357]. As such tools enter clinical practice, AI will become indispensable for interpreting their complex outputs.

Finally, AI agents can serve as personal health companions, acting as psychotherapists (in high demand today), nutritionists, fitness coaches, and even life mentors, all tailored to an individual's biology and behavior [358].

The future belongs to integrated health ecosystems that fuse scientific, genomic, clinical, and psychological data, empowering both doctors and patients to understand, prevent, and

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ultimately cure disease. Some great examples of such complex ecosystems include Tempus [359], Luria Health [360], and numerous other platforms.

Conclusions

In 2025, we are witnessing a tectonic shift in how society perceives aging, and not as an immutable fate, but as a modifiable biological process. Yet biogerontology remains marginalized, even ridiculed, by parts of the scientific establishment. This is not merely due to inertia or dogma; it is also a consequence of overhyped claims that outpace evidence. Premature promises of "curing aging tomorrow" erode public trust – a tragedy for those of us committed to rigorous, data-driven science.

The pragmatic path forward begins not with abstract longevity fantasies, but with concrete, high-burden chronic diseases, particularly those rooted in inflammaging and fibrosis: atherosclerosis, type 2 diabetes, Alzheimer's disease, and autoimmune conditions. We must move beyond the palliative mindset of "managing symptoms" and instead aim to restore tissues to a functional, youthful reference state, whether we call it rejuvenation, repair, or simply cure.

Critically, the same interventions can serve dual roles: prevention and reversal. Caloric restriction and exercise lay the foundation; next-generation tools: senolytics, metformin, GLP-1 agonists, and emerging gene and cell therapies like anti-LPA editing or *FOXO3*-augmented MSCs – offer far greater precision. But their true power emerges only when we reframe our intent: not just "treating disease X," but "delaying systemic aging" or "rejuvenating organ system Y." This conceptual shift is essential: it aligns clinical practice with geroscience and unlocks regulatory, funding, and public support pathways.

As AI and machine learning mature, they will increasingly guide this effort: identifying causal drivers of aging, predicting individual responses to interventions, and integrating multi-omics data into personalized health strategies. The future belongs not to miracle cures, but to precision restoration, grounded in biology and scaled by technology.

If our generations commit to this mission enough, not with hype, but with humility, rigor, and vision, we may not only extend healthspan for future generations, but ourselves live as long as biology and the laws of physics allow.

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