ACCSCIENCE PUBLISHING

Cell Aging & Regeneration

REVIEW ARTICLE

Advances in anti-aging strategies

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Abstract

Aging, once viewed as an inexorable decline, is now understood as a tractable, systems-level process, redefined by updated hallmarks and an emphasis on healthspan as the actionable endpoint. This review provides a stratified analysis of advances across lifestyle, pharmacological, cellular, and digital interventions, distinguishing clinically validated strategies from emerging experimental therapeutics. Multimodal lifestyle interventions, encompassing caloric moderation, circadian rhythm alignment, structured exercise, and social–cognitive engagement, target mitochondrial quality control, inflammaging, and neuroplasticity and demonstrate superior efficacy when combined. Pharmacologically, senescence-targeting agents, metabolic/NAD^+ boosters, and microbiome modulators show cross-tissue benefits in mammalian models and preliminary human trials, supporting the development of rational combinations guided by mechanism-specific biomarkers. In contrast to systemic prevention, cellular and factor-based approaches (e.g., partial epigenetic reprogramming) offer a regenerative paradigm aimed at tissue repair; however, these strategies remain largely preclinical, with key challenges persisting in safety, optimal dosing, and long-term durability. Concurrently, artificial intelligence-enabled wearables and molecular aging clocks provide reliable, continuous phenotyping to enrich trials and personalize interventions. To accelerate clinical validation, we recommend composite endpoints that couple molecular change with functional outcomes, adaptive designs, and inclusive enrollment to ensure generalizability. Finally, equitable delivery—via affordable interventions, digital platforms, and region-appropriate nutrition—will be essential as longevity science scales globally. Together, these strands define a pragmatic path from mechanism to medicine: multimodal, biomarker-driven, and ethically implemented to extend healthy lifespan.

Keywords: Anti-aging strategies; Geroprotective interventions; Biological aging hallmarks; Senolytics; Healthspan

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Citation: Yang X-F, Zhao R-C, Tong Y-W, *et al*. Advances in anti-aging strategies. *Cell Aging Regen*. doi: 10.36922/CAR025440003

Received: October 31, 2025

Revised: January 12, 2026

Accepted: July 3, 2026

Published online: July 20, 2026

1. Introduction

Over the past decade, aging has been reframed from an inevitable, organ-specific decline into a modifiable, systems-level process. This shift integrates molecular geroscience with clinical medicine, prioritizing upstream mechanisms that drive multimorbidity across the lifespan. The "hallmarks of aging" framework—comprising genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion, and altered intercellular communication—provides a unifying scaffold to organize causal biology and guide therapeutic strategies. A 2023 update emphasized crosstalk among hallmarks and highlighted immune dysfunction and microbiome changes as integral drivers of organismal aging, while a subsequent 2025 refinement recognized extracellular matrix changes and psychosocial isolation as hallmarks, underscoring how tissue mechanics and social environment intersect with cellular programs to shape aging.[1,2] Meanwhile, the objective has shifted from merely prolonging lifespan to extending healthspan—the period of life spent in functional, disease-free states—driven by both biological advances and a societal imperative to address the growing burden of multimorbidity.[3]

Recent progress has yielded a new generation of interventions that broadly fall into two complementary but distinct paradigms: geroscience, which aims to systematically slow the rate of aging to prevent multimorbidity, and regenerative medicine, which focuses on structurally repairing or replacing tissues that have already been damaged. We review these advances through a stratified evidentiary framework, moving from foundational lifestyle interventions supported by robust human randomized controlled trials (RCTs) to emerging pharmacotherapies and, finally, to exploratory cellular technologies (e.g., reprogramming) that, while promising in animal models, remain strictly preclinical.[4,5] Moreover, advances in digital phenotyping and artificial intelligence (AI) now allow for continuous, real-world assessment of mobility, sleep, and cognition, as well as the development of multimodal aging clocks that integrate molecular and behavioral data. These tools can personalize treatment regimens and detect therapeutic benefits at earlier stages.

In this review, we summarize the latest advances in main anti-aging strategies (Figure 1), with emphasis on conceptual innovation, translational progress, and emerging technologies. Our aim is to provide a systems-level perspective that informs both mechanistic inquiry and clinical application in human aging.

2. Pharmacological strategies targeting core mechanisms of aging

Pharmacological modulation of aging-related pathways represents a promising approach to delay biological aging, extend healthspan, and reduce the burden of aging-associated comorbidities, including neurodegeneration, cardiovascular disease, and sarcopenia. Compared to cell-based therapies or gene editing, small-molecule interventions offer distinct advantages: high oral bioavailability, precise dose titration, reversible effects, and scalability for widespread clinical use. These agents primarily act on evolutionarily conserved signaling networks that orchestrate metabolic homeostasis, proteostasis, mitochondrial function, and inflammatory regulation—core pillars of the "hallmarks of aging" framework (Figure 2).[6,7]

2.1. mTOR inhibitors

Rapamycin, a natural product first isolated from *Streptomyces hygroscopicus*, inhibits mechanistic target of rapamycin complex 1 (mTORC1) by binding to the FK506-binding protein 12 (FKBP12). Its longevity-promoting effects have been consistently validated across species, from yeast and *Drosophila* to genetically diverse mouse cohorts, including C57BL/6 and heterogeneous stock mice (with lifespan extensions of 10–25%).[8] In murine models, rapamycin not only extends survival but also reverses age-related pathologies: it attenuates cardiac hypertrophy by inhibiting mTORC1-mediated phosphorylation of forkhead box O3a (FOXO3a; a transcription factor that regulates cardiomyocyte survival)[9], improves cognitive function by enhancing hippocampal neurogenesis[10], mitigates periodontal tissue destruction via suppression of osteoclast activation[11], and rejuvenates T cell immunity by increasing naive T cell populations.[12]

Recent preclinical studies have demonstrated that intermittent rapamycin dosing, such as administration once every 5 days, mitigated glucose intolerance and reduced mTORC2 inhibition compared with more frequent dosing, thereby potentially preserving insulin sensitivity..[13] However, frequent and intermittent rapamycin-treated mice had impaired glucose tolerance and insulin sensitivity compared to vehicle-treated mice.

Clinically, the Phase II PEARL trial (NCT04348837) evaluated low-dose rapamycin (5–10 mg/week) in 114 healthy older adults. The study found that women in the 10 mg/week group experienced significant increases in lean muscle mass and reported lower pain levels, as measured by the 36-Item Short Form Survey. Participants receiving 5 mg/week reported improvements in emotional well-being and general health. These findings suggest that

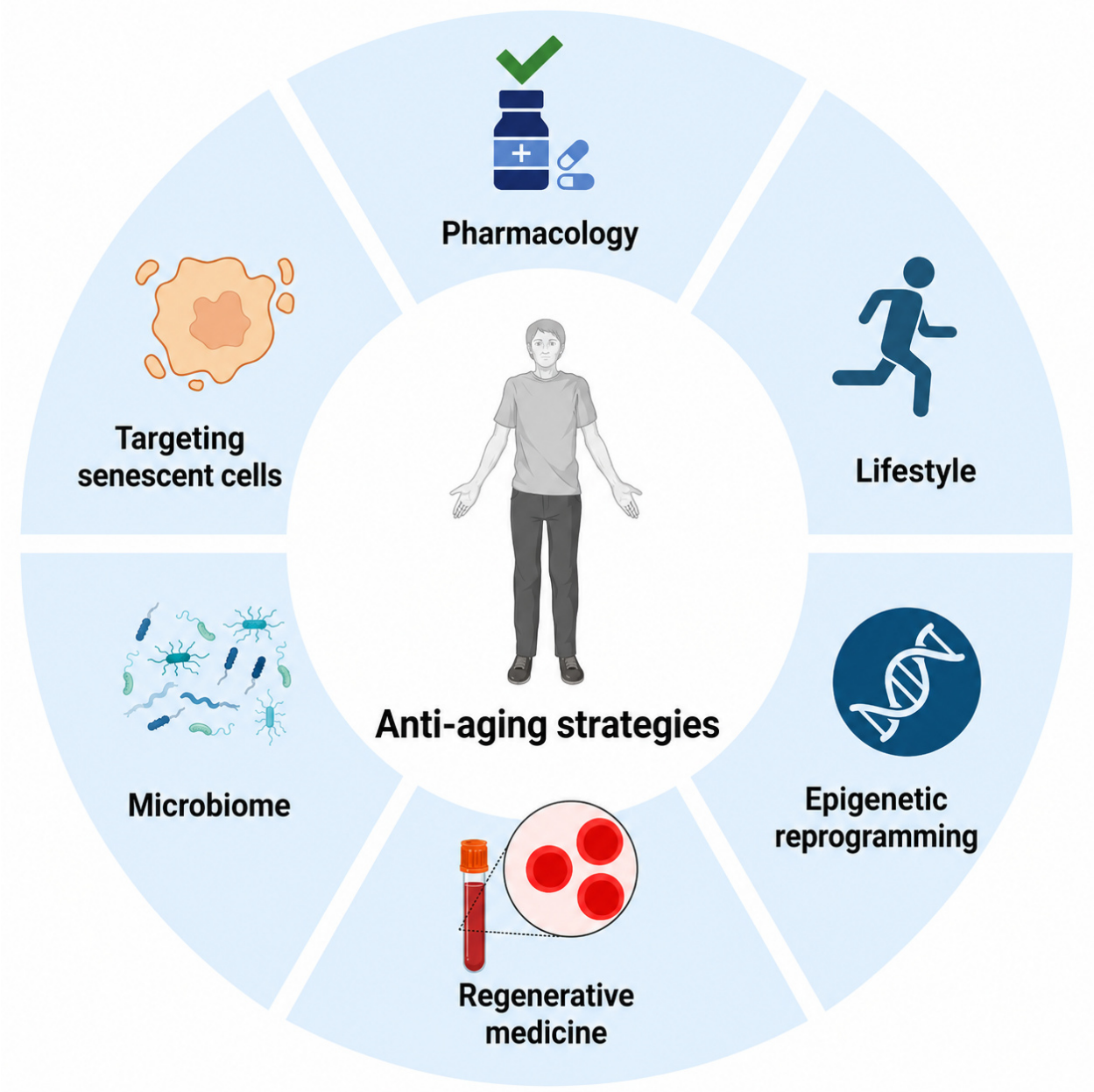

Figure 1. Summary of current anti-aging strategies

low-dose, intermittent rapamycin administration may improve physical and emotional well-being in older adults. Although intermittent rapamycin dosing reduces the severity of glucose intolerance compared to more frequent regimens, it does not eliminate the risk. Consequently, careful monitoring of glucose levels remains necessary during rapamycin therapy.[13]

Despite significant advances in the use of rapamycin for longevity, several critical challenges remain. First, tissue-specific effects must be addressed. For example, while mTORC1 inhibition in the brain enhances neurogenesis, it may inhibit muscle protein synthesis. This highlights the need for targeted delivery systems, such as lipid nanoparticles conjugated to transferrin receptors for brain-specific mTORC1 inhibition. Second, sex differences in rapamycin's effects have been observed. Female mice exhibit a greater lifespan extension compared to males, potentially due to estrogen-mediated regulation of FKBP5,

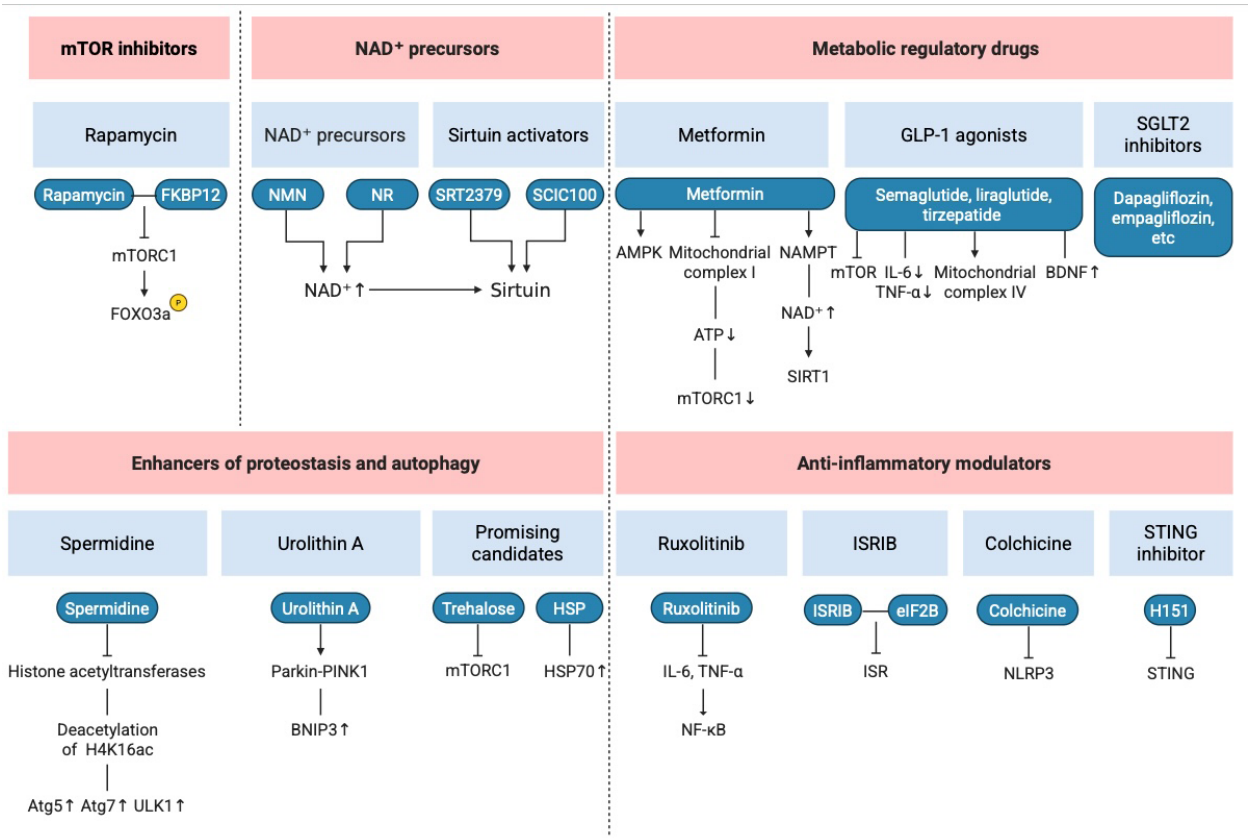

Figure 2. Mechanisms of anti-aging pharmacological strategies

a co-chaperone that modulates rapamycin's binding to mTOR. Third, balancing the longevity benefits of rapamycin with metabolic side effects is crucial. Combination therapy with glucagon-like peptide-1 (GLP-1) receptor agonists reverses rapamycin-induced glucose intolerance in mice, with improvements in pancreatic β-cell function and insulin sensitivity.[14] Finally, dual mTORC1/2 inhibitors, such as AZD2014, are under preclinical evaluation but have shown more severe lymphopenia compared to rapamycin, highlighting the need to establish their efficacy in aging models.

2.2. NAD⁺ precursors

Nicotinamide adenine dinucleotide (NAD^+) plays a crucial role in cellular processes such as redox reactions, DNA repair, and the regulation of sirtuins, which are involved in stress resistance and longevity. However, NAD^+ levels decline with aging, primarily due to three key mechanisms: reduced synthesis due to the downregulation of nicotinamide phosphoribosyltransferase (NAMPT), increased consumption by enzymes such as poly(ADP-ribose) polymerases (PARPs) during DNA repair, and enhanced degradation via CD38, an enzyme upregulated in aging tissues.[15] This decline in NAD^+ disrupts mitochondrial function, impairs oxidative phosphorylation, and contributes to genomic instability and is a hallmark of aging. Restoring NAD^+ levels through supplementation with NAD^+ precursors such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), as well as inhibiting NAD^+-degrading enzymes such as CD38, represents a promising strategy to mitigate the age-related declines and promote healthier cellular function.[16] These therapeutic approaches aim to preserve NAD^+ homeostasis, thereby alleviating age-related cellular dysfunctions.

Nicotinamide mononucleotide and NR are NAD^+ precursors that have attracted attention for their potential to restore NAD^+ levels and counteract age-related declines in physiological functions. Preclinical studies have shown promising results, while human clinical trials have provided further insights into their safety and efficacy. A randomized, double-blind, placebo-controlled study evaluated the safety of β-NMN administered orally at 1,250

mg per day for up to 4 weeks in healthy adults aged 20–65 years. The study found that β-NMN was safe and well-tolerated, with no severe adverse events observed and no significant changes in body composition, hematological, or biochemical parameters, suggesting that NMN supplementation does not negatively affect these measures. In another clinical trial, NR supplementation was assessed in individuals with peripheral artery disease and showed a 17.6 m improvement in the 6-min walk test at 6-month follow-up compared to placebo. Among participants with at least 75% adherence, the distance improved by 31.0 m, indicating a clinically significant effect. The study also reported that NR supplementation was well-tolerated with no serious adverse events.[17-19] These findings indicate that both NMN and NR supplementation are safe and well-tolerated, with NR showing potential benefits for improving physical performance in patients with peripheral artery disease.[20] Further large-scale, long-term studies are required to confirm their efficacy for promoting healthspan in the general population.

These inconsistent outcomes may stem from individual variations in NAD^+ metabolism, affected by factors such as gut microbiome composition[21], renal function, and tissue-specific transporter expression. For example, the solute carrier family 12 member 8 (Slc12a8) has been identified as a specific NMN transporter, with its expression regulated by NAD^+ levels and potentially influenced by factors including sirtuin 1 (SIRT1) activity.[22] Therefore, while NMN and NR supplementation show promise in preclinical studies, their effects in humans remain inconsistent and may be contingent upon individual metabolic profiles. Further research is necessary to elucidate the mechanisms underlying these variations and to determine optimal supplementation strategies for different populations.[23]

2.3. Metabolic regulatory drugs

Metabolic regulatory drugs have emerged as a cornerstone of anti-aging research. By modulating energy homeostasis, inflammation, and cellular repair pathways, these agents can delay biological aging and extend healthspan. Beyond the well-studied metformin, this class includes GLP-1 agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors—each with distinct mechanisms converging to mitigate aging-related metabolic dysfunction and tissue degeneration.

Metformin, a biguanide first approved for type 2 diabetes (T2D) in 1957, has attracted significant attention for its potential anti-aging effects. Its mechanisms of action are multifaceted: metformin activates AMP-activated protein kinase (AMPK), a key metabolic sensor that suppresses anabolic processes and promotes catabolic pathways, such as autophagy, which contribute to improved cellular maintenance and function.[24] By inhibiting mitochondrial complex I, metformin reduces ATP production and elevates the AMP/ATP ratio, thereby indirectly suppressing mTORC1, a regulator of cellular senescence.[25] Additionally, metformin modulates gut microbiota composition, increasing the abundance of beneficial bacteria, such as *Akkermansia muciniphila*, which enhances intestinal barrier function and reduces systemic inflammation.[26,27] Furthermore, metformin upregulates NAMPT, the rate-limiting enzyme in the NAD^+ salvage pathway, increasing NAD^+ levels to activate SIRT1, a deacetylase that helps preserve mitochondrial function and DNA repair.[28] The Targeting Aging with Metformin (TAME) trial, authorized by the Food and Drug Administration (FDA) in 2015, is a pivotal study designed to evaluate the effects of metformin on aging. It involves participants aged 65 to 79 and aims to assess whether metformin can delay the onset of age-related chronic diseases such as heart disease, cancer, and dementia.[29,30] In summary, while metformin shows promise as a geroprotective agent through various biological mechanisms, ongoing clinical trials such as TAME are essential to substantiate its efficacy in aging populations.

The agonists of the GLP-1 receptor—including semaglutide, liraglutide, and tirzepatide—have gained significant attention not only for their effectiveness in managing T2D and obesity but also for their potential anti-aging benefits. These agents act through multiple mechanisms beyond glucose regulation, contributing to overall metabolic health and potentially mitigating age-related decline.

One key mechanism involves enhancing mitochondrial function and reducing oxidative stress, which are key drivers of the aging process. Mitochondrial dysfunction and oxidative stress are central to cellular aging and the pathogenesis of age-related diseases. Studies suggest that GLP-1 receptor agonists can improve mitochondrial respiratory capacity, thereby reducing reactive oxygen species (ROS) production, which is typically elevated in aging tissues and contributes to aging-related damage. Another key mechanism is neuroprotection. Preclinical research has shown that these agents can reduce amyloid-β and tau protein accumulation, two pathological hallmarks of Alzheimer's disease, and upregulate brain-derived neurotrophic factor (BDNF), which is essential for neuronal survival and synaptic plasticity. Moreover, these drugs may reduce neuroinflammation, further contributing to their neuroprotective potential.[31]

Clinical evidence further supports the cognitive benefits of GLP-1 agonists. For example, studies suggest that these agents may delay the progression of dementia

in patients with T2D, a population that is at higher risk for cognitive decline due to insulin resistance and metabolic dysfunction. These effects, which include improvements in cognitive function and reductions in markers of neuroinflammation, underscore the potential for GLP-1 agonists to extend healthy brain aging.[32] Moreover, weight loss associated with GLP-1 agonist therapy reduces metabolic burden on critical tissues, such as the liver, pancreas, and joints, which are key drivers of aging-related decline. By promoting appetite suppression, GLP-1 receptor agonists help alleviate the inflammatory burden from excess adiposity, potentially leading to better long-term outcomes in age-related diseases.[33]

A particularly exciting area of research is combining metformin with GLP-1 agonists, which has shown synergistic benefits in preclinical studies. For example, in mice, the combination of metformin and semaglutide extended lifespan, surpassing that observed with either treatment alone. This effect is thought to be driven by enhanced autophagy and reduced mitochondrial dysfunction, both of which are critical processes for maintaining cellular health in aging. While GLP-1 receptor agonists have proven effective in managing metabolic disorders, their potential anti-aging effects offer an exciting avenue for future research. As clinical trials continue to explore these benefits, these agents may become a cornerstone of strategies aimed at extending healthspan and preventing age-related diseases.[34,35]

The inhibitors of SGLT2, such as dapagliflozin and empagliflozin, have emerged as promising anti-aging agents, building on their established benefits in managing T2D and cardiovascular diseases. Their benefits extend beyond glycemic control. Firstly, they reduce oxidative stress by upregulating antioxidant enzymes, such as superoxide dismutase 2 (SOD2), which is crucial for mitigating cellular aging and preventing age-related diseases.[36] Secondly, they improve endothelial function by increasing nitric oxide bioavailability, thus enhancing vascular health, a key concern in aging populations.[37] Furthermore, they modulate adipokine secretion, decreasing leptin and increasing adiponectin levels, thereby improving insulin sensitivity and metabolic health.[38] While clinical data on their specific anti-aging effects are still emerging, preclinical studies suggest that SGLT2 inhibitors could help preserve muscle mass and function, potentially alleviating sarcopenia in aging individuals.[39] In summary, SGLT2 inhibitors offer a multifaceted approach to promoting healthy aging through their effects on oxidative stress, endothelial function, adipokine secretion, and potentially muscle preservation. As research progresses, these agents may become important tools for extending healthspan and preventing age-related diseases.

Despite the great promise, the clinical application of metabolic regulatory drugs faces some challenges. Inter-individual variability plays a significant role in treatment outcomes. For example, the Pro12Ala polymorphism in the *PPARG* gene has been associated with altered responses to certain medications, including metformin, in specific populations.[40] Additionally, gut microbiome composition can influence the efficacy of GLP-1 receptor agonists, with certain microbial signatures correlating with better treatment responses. Gastrointestinal distress is a commonly reported side effect of metformin, affecting a significant proportion of patients.[41] Similarly, GLP-1 receptor agonists are associated with gastrointestinal side effects, including nausea, which can affect patient adherence.[42] To address these issues, novel formulations have been developed. Extended-release metformin has been shown to reduce gastrointestinal side effects compared with immediate-release metformin. Once-weekly GLP-1 receptor agonist injections have demonstrated improved adherence compared to daily dosing regimens.[43] Additionally, oral SGLT2 inhibitors have been introduced, offering a more convenient route of administration.

Future research should focus on validating the effects of these drugs in non-metabolic tissues, such as the brain and skeletal muscle, to fully understand their potential in anti-aging therapies. Moreover, optimizing personalized combination therapies and identifying biomarkers to guide drug selection will be essential in maximizing the benefits of metabolic regulators in aging care.

2.4. Enhancers of proteostasis and autophagy

Aging disrupts cellular proteostasis, the balance between protein synthesis, folding, and degradation, due to factors such as reduced autophagic flux, diminished expression of heat shock proteins (HSPs), and impaired function of the ubiquitin–proteasome system. This decline contributes to the accumulation of misfolded or aggregated proteins, including amyloid-β in Alzheimer's disease and α-synuclein in Parkinson's disease, as well as to the accumulation of damaged organelles, such as dysfunctional mitochondria.[44,45] These accumulations disrupt cellular homeostasis, leading to neurodegeneration, sarcopenia, and metabolic dysfunction. Consequently, pharmacological enhancers of autophagy and proteostasis are being explored as potential therapeutic strategies, with several candidates advancing to clinical trials.[46,47]

Spermidine, a naturally occurring polyamine found in foods such as wheat germ, soybeans, and fermented products, has attracted significant interest due to its potential to promote autophagy and modulate aging

processes. It functions by inhibiting acetyltransferases, such as p300, leading to the deacetylation of histone H4 at lysine 16 (H4K16ac) and thereby enhancing the expression of autophagy-related genes, including *Atg5*, *Atg7*, and *ULK1*.[48] Preclinical studies have shown that spermidine supplementation can extend lifespan in yeast, *Drosophila*, and mice, while also improving cellular functions, including mitochondrial health and stress resistance.[49] Additionally, spermidine has demonstrated neuroprotective effects in animal models of Alzheimer's disease, including reducing amyloid-β aggregation and mitigating neuroinflammation.[50,51] Human clinical trials have also explored its potential benefits in older adults, particularly those with cognitive decline, suggesting potential benefits for cognitive function and inflammatory status.[52] Despite these promising findings, further clinical studies are needed to confirm the long-term benefits and mechanisms of spermidine in aging and neurodegenerative diseases.

Urolithin A (UA), a microbial metabolite derived from ellagitannins found in pomegranates, strawberries, and walnuts, has been identified as a potent activator of mitophagy—the selective degradation of dysfunctional mitochondria. This process is primarily mediated through the PTEN-induced kinase 1 (PINK1)–Parkin pathway and is further supported by the upregulation of mitophagy receptors, such as BCL2 interacting protein 3 (BNIP3).[53] In preclinical studies, UA has demonstrated the ability to enhance mitochondrial function in muscle, increase muscle mass, and extend lifespan in animal models. These effects are attributed to the role of UA in promoting mitochondrial health and improving muscle function across various species. Regarding clinical applications, a trial (NCT06556706) is currently underway to evaluate the effect of UA supplementation on muscle strength and endurance in older adults with sarcopenia.[54] While specific outcomes from this trial are pending, previous studies have indicated that UA supplementation can improve muscle strength and exercise performance in older individuals.[55] One challenge with UA supplementation is its low oral bioavailability. To address this, lipid-based formulations have been developed to enhance absorption. For example, liposomal encapsulation methods have been shown to improve the stability and bioavailability of UA.[56]

Other promising candidates include trehalose, a disaccharide found in various organisms, which has been identified as a potent activator of autophagy through mechanisms independent of mTORC1.[57] It enhances the clearance of misfolded proteins and stabilizes protein structures, thereby preventing aggregation. In preclinical models, trehalose has demonstrated efficacy in reducing α-synuclein aggregation in Parkinson's disease and improving cognitive function in Alzheimer's disease models.[58] 17-Allylamino-17-demethoxygeldanamycin (17-AAG), an inhibitor of HSP90, has been shown to enhance proteostasis by upregulating HSP70, a chaperone that facilitates protein folding. Preclinical studies have indicated that 17-AAG can modulate protein quality control pathways, making it a candidate for therapeutic strategies in neurodegenerative diseases.[59] The antimalarial drug chloroquine, a classic autophagy inhibitor, was surprisingly found to extend median and maximum lifespan in middle-aged mice. This effect is attributed to a compensatory "hormetic" response involving proteasome inhibition and modulation of glycogen metabolism, suggesting that precise stress-induced induction of proteostatic networks may also yield geroprotective benefits.[60]

However, the development of autophagy enhancers faces challenges, including pleiotropic effects and a lack of tissue specificity. Excessive autophagy can lead to neuronal cell death, while insufficient activation may fail to clear toxic aggregates. Future efforts are focusing on tissue-targeted delivery systems, including nanoparticles conjugated to BDNF receptors, to achieve central nervous system (CNS)-specific autophagy activation. Additionally, the development of biomarkers, such as the circulating light chain (LC)3-II/I ratio, is underway to monitor autophagic flux in humans.[61]

2.5. Anti-inflammatory modulators

Inflammaging, a state of low-grade chronic inflammation associated with aging, is a key pathogenic process in age-related diseases, such as frailty, atherosclerosis, neurodegeneration, and cancer. It is driven by the accumulation of senescent cells, mitochondrial dysfunction, and gut dysbiosis.[62] The key molecular pathways include: (i) the nuclear factor kappa B (NF-κB) pathway, which regulates the expression of pro-inflammatory cytokines and is involved in numerous age-related diseases, including cancer and cardiovascular conditions[63]; (ii) the NLR family pyrin domain-containing protein 3 (NLRP3) inflammasome, a multi-protein complex that activates caspase-1 to mature pro-inflammatory cytokines sych as interleukin (IL)-1β and IL-18, playing a crucial role in immune and inflammation-related diseases such as arthritis and Alzheimer's disease[64]; and (iii) the integrated stress response (ISR), a signaling pathway activated by stressors that regulates cellular biosynthetic capacity, which becomes dysregulated with age.[65] Pharmacological targeting of these pathways has shown promise in preclinical and clinical studies, with strategies aiming to inhibit NF-κB, block NLRP3 activation, and modulate the ISR to alleviate chronic inflammation and associated

diseases.

Ruxolitinib, a Janus kinase 1/2 (JAK1/2) inhibitor, attenuates the senescence-associated secretory phenotype (SASP) by inhibiting JAK–signal transducer and activator of transcription (STAT) signaling and reducing pro-inflammatory cytokines, such as IL-6 and tumor necrosis factor alpha (TNF-α).[66] Preclinical studies have demonstrated its ability to improve various aging-related conditions, including reducing SASP in aged cells and enhancing hematopoietic function in mice by rejuvenating hematopoietic stem cells (HSCs) and reducing myeloid bias.[67] While its efficacy in age-related conditions is still under investigation, ruxolitinib has shown promise in preclinical models, improving cardiac function and reducing inflammation.[68,69] However, clinical trials exploring its effects on aging are limited, and further research is necessary to assess its long-term effects, optimal dosing, and safety profile in older adults. Studies focusing on its effect on HSC function and inflammaging are needed to define its long-term safety and efficacy.

Integrated stress response inhibitor (ISRIB) is a small molecule that targets the ISR by binding to eukaryotic initiation factor 2B (eIF2B), thereby restoring translational homeostasis. This modulation has shown promise in reversing age-related cognitive decline. In preclinical models, ISRIB has been demonstrated to improve synaptic plasticity, enhance learning and memory, and reduce amyloid-β accumulation in Alzheimer's disease models. These effects are attributed to ISRIB's ability to restore protein synthesis and alleviate stress-induced translational repression in neurons.[70] Recent studies have explored strategies to enhance the delivery of ISRIB across the blood–brain barrier (BBB). For example, conjugating ISRIB to transferrin receptor antibodies has been investigated to increase its brain penetration. Transferrin receptor-mediated transport at the BBB is elevated during early development and maintained across aging and in Alzheimer's mouse models, suggesting that this pathway can be leveraged to improve drug delivery to the brain.[71] However, specific data on the conjugation of ISRIB to transferrin receptor antibodies and its effect on BBB penetration are limited. While the potential of ISRIB in treating neurodegenerative diseases is promising, further research is needed to optimize its delivery mechanisms and assess its efficacy and safety in clinical settings.

Colchicine, an anti-inflammatory agent approved for gout and pericarditis, exerts its therapeutic effects by disrupting microtubule assembly—a mechanism that directly inhibits NLRP3 inflammasome activation. Recent studies have demonstrated that colchicine prevents the colocalization of NLRP3 inflammasome components, thereby reducing IL-1β secretion and alleviating inflammation associated with cardiovascular conditions. The 2024 COLCOT trial (n = 4,700 older adults with myocardial infarction) provided key evidence: over five years of treatment with colchicine (0.5 mg/day), the risk of age-related comorbidities (including heart failure hospitalization and stroke) was reduced by 22%, and all-cause mortality was lowered by 18%.[72]

In addition, the stimulator of interferon genes (STING) pathway has emerged as a novel target for addressing inflammaging. This pathway is activated by cytosolic DNA—such as that released from damaged mitochondria—and drives the production of type I interferons, which contribute to age-related systemic inflammation. Preclinical research has validated its therapeutic potential: the STING inhibitor H-151 reduced systemic inflammation and improved cognitive function by 30%—specifically, it decreased microglial levels, attenuated astrocyte immunoreactivity, and enhanced spatial memory in aged mice. A Phase I trial in healthy older adults will further evaluate the safety and anti-inflammatory effects of H-151.[73,74]

The development of anti-inflammatory therapies faces key challenges, particularly in balancing efficacy with immune competence. A meta-analysis indicated that treatment with oral JAK inhibitors was linked to a higher risk of infections compared to placebo across all indications.[75] Colchicine has been used in older adults for various conditions; while some studies have reported an increased risk of pneumonia associated with colchicine use, particularly in older patients, other research has found no significant increase in infection risk. Therefore, the evidence regarding colchicine's effects on infection risk in older adults remains inconclusive.[76] ISR is a critical cellular pathway that helps cells adapt to stress by regulating protein synthesis. Inhibition of the ISR has been shown to compromise cellular proteostasis restoration, potentially compromising the cell's adaptive capacity to physiological stress such as oxidative damage.[77]

Future research should prioritize the development of tissue-specific anti-inflammatory agents, including CNS-targeted NLRP3 inhibitors for neurodegeneration, and combination therapies that target multiple inflammaging pathways. For example, combining JAK1/2 inhibition with STING pathway inhibition may maximize efficacy while minimizing side effects. These strategies aim to enhance therapeutic outcomes by selectively modulating inflammatory pathways involved in aging-related diseases.

3. Strategies for targeting senescent cells

Cellular senescence is a stable, irreversible state of cell cycle arrest induced by various stressors, including DNA damage, oncogene activation, and mitochondrial dysfunction. While initially protective against tumorigenesis, the accumulation of senescent cells over time can contribute to the development of aging-related diseases. A hallmark of senescent cells is the SASP—a complex array of pro-inflammatory cytokines, growth factors, proteases, and extracellular vesicles (EVs). The composition and effects of SASP factors are context-dependent and influenced by the type of stressor and cell type involved. SASP can have both beneficial and detrimental effects on tissue homeostasis, influencing processes such as tissue repair, inflammation, and tumor progression.[78]

Recent advances in single-cell RNA sequencing (scRNA-seq) have illuminated the heterogeneity of senescent cells within tissues, revealing distinct subpopulations with unique SASP.[79] For example, studies have identified specific subsets of hepatic stellate cells and myofibroblasts in liver fibrosis, each exhibiting distinct transcriptional profiles and intercellular communications.[80] This cellular diversity underscores the complexity of targeting senescent cells therapeutically. Genetic ablation models have provided compelling evidence for the role of senescent cells in age-related pathologies. For example, the p16-CreERT2 DTR-tdTomato mouse model enables the inducible elimination of $p16^{iNK4a}$-positive senescent cells. In this model, removing these cells ameliorated hepatic steatosis and inflammation in a non-alcoholic steatohepatitis model, highlighting the detrimental effects of senescent cells on liver health. Beyond fibrosis, senescent cell accumulation has been implicated in other aging-related conditions. For example, senescent cells secrete factors that can dysregulate epigenetic modifiers in neighboring cells, exacerbating epigenetic drift.[81] Additionally, impaired autophagy—a hallmark of aging—fails to clear SASP components, amplifying inflammatory signaling.[82,83] Therefore, eliminating senescent cells is an important approach to delaying aging. Here, we introduce different methods for targeted elimination of senescent cells and their mechanisms of action (Figure 3).

3.1. Senolytics

Senolytic agents are small molecules, peptides, or drug combinations that selectively eliminate senescent cells by targeting their unique vulnerabilities, such as the upregulation of anti-apoptotic pathways, metabolic fragility, and lysosomal dysfunction. Unlike healthy cells, senescent cells often exhibit increased expression of anti-apoptotic proteins, such as B-cell lymphoma 2 (BCL-2), BCL-extra large (BCL-XL), and BCL-extra large related gene (BCL-W), which contribute to their resistance to apoptosis. These adaptations create therapeutic opportunities for selectively inducing cell death in senescent cells while sparing healthy cells.

A well-characterized class of senolytics targets BCL-2 family proteins.[84,85] Navitoclax (ABT-263), a potent inhibitor of BCL-2, BCL-XL, and BCL-W, has been shown to induce apoptosis in various senescent cell types, including human umbilical vein endothelial cells and lung fibroblasts. However, its clinical utility is limited by thrombocytopenia due to BCL-XL inhibition in platelets. To mitigate this, next-generation analogs, such as A-1155463, have been developed, exhibiting improved selectivity and reduced platelet toxicity. Studies have demonstrated that A-1155463 effectively clears senescent cells in models of pulmonary fibrosis, reversing collagen deposition and improving lung function.[86] Venetoclax (ABT-199), a selective BCL-2 inhibitor approved for chronic lymphocytic leukemia, also exhibits senolytic activity. In preclinical models, venetoclax reduced the burden of $p16^{iNK4a}$-positive senescent cells, enhanced HSC function, and improved tissue regeneration.[87]

Recent studies have identified the phosphoinositide 3-kinase (PI3K)/AKT/mTOR pathway as a critical survival mechanism in senescent cells, making it a promising target for senolytic therapies. Alpelisib, a PI3Kα-specific inhibitor approved for breast cancer, has been shown to disrupt this pathway in senescent cells by inhibiting the production of phosphatidylinositol 3,4,5-trisphosphate (PIP3), reducing AKT phosphorylation and mTOR activation. This disruption impairs senescent cells' ability to maintain redox homeostasis, resulting in ROS accumulation and subsequent apoptosis. In a mouse model of non-alcoholic fatty liver disease, alpelisib treatment led to a significant reduction in hepatic triglyceride content and improved insulin sensitivity, highlighting its potential as a senolytic agent.[88]

Another promising senolytic combination involves dasatinib, a multi-kinase inhibitor targeting Src, Abelson tyrosine-protein kinase (ABL), and PI3K pathways, in conjunction with quercetin, a natural flavonoid that inhibits BCL-2/BCL-XL interactions and depletes intracellular glutathione. This combination, known as D+Q, exerts a "double hit" on senescent cells: dasatinib inhibits PI3K/AKT signaling, while quercetin elevates oxidative stress by reducing glutathione, pushing senescent cells beyond their redox tolerance threshold. Studies have demonstrated that D+Q effectively reduces senescent cells in various tissues, including adipose tissue, liver, and skeletal muscle, and improves metabolic and cardiovascular functions in aged mice.[89] This reduction has been associated with

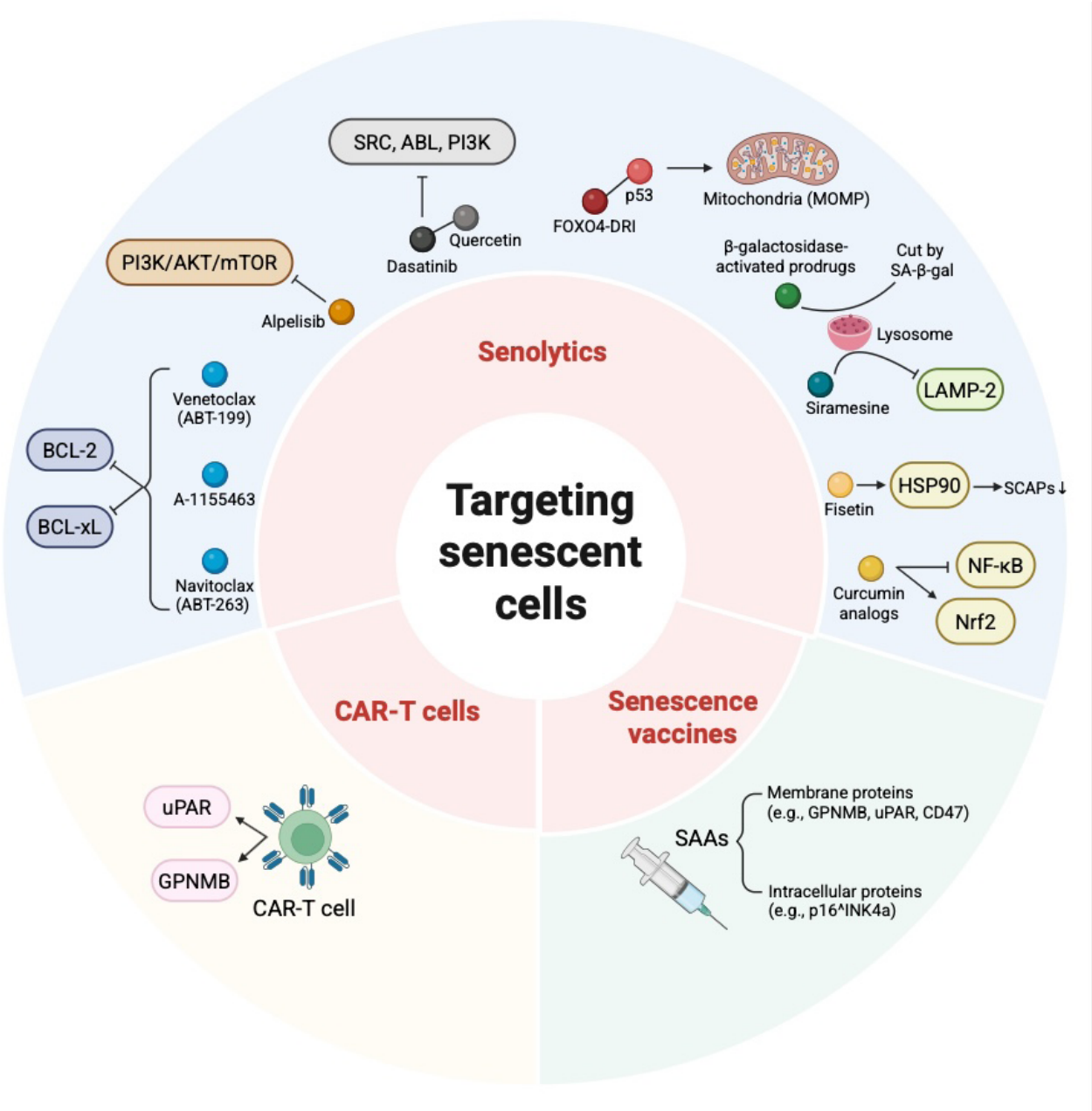

Figure 3. Mechanisms of targeting senescent cells

improvements in insulin sensitivity and cardiovascular function, as evidenced by enhanced glucose tolerance and left ventricular ejection fraction in aged mice.[90] In clinical settings, D+Q has shown potential benefits in older adults. While specific trials such as SOPHIA and INTERVENE are not available in the provided sources, other studies have reported improvements in physical function and strength among older populations. For example, a 12-week exercise and nutritional intervention significantly enhanced physical performance, grip strength, and quality of life among community-dwelling older adults.[91] Additionally, multi-component exercise programs have been shown to improve frailty and physical function in older adults.[92]

FOXO4–D-retro-inverso peptide (FOXO4-DRI) is a synthetic retro-inverso peptide designed to disrupt

the interaction between the FOXO4 transcription factor and the tumor suppressor protein p53. In senescent cells, FOXO4 binds to p53, preventing its translocation to the mitochondria and thereby inhibiting apoptosis. FOXO4-DRI competes with endogenous FOXO4 for p53 binding, promoting p53's mitochondrial localization and initiating programmed cell death in senescent cells.[93] Preclinical studies have demonstrated the efficacy of FOXO4-DRI in selectively eliminating senescent cells. For example, in vitro experiments using human chondrocytes expanded to population doubling level 9 (PDL9) showed that FOXO4-DRI treatment significantly reduced the proportion of senescent cells, as assessed by senescence-associated β-galactosidase (SA-β-gal) staining and gene expression analysis.[94] Additionally, in naturally aged mice, FOXO4-DRI administration improved testicular function by decreasing senescence markers and inflammatory cytokines, thereby enhancing testosterone secretion.[95]

Lysosome-targeted senolytics are an emerging class of therapies designed to selectively eliminate senescent cells by exploiting their elevated lysosomal activity and compromised membrane integrity. These agents typically utilize a cytotoxic payload conjugated to a substrate that is cleaved by SA-β-gal—a lysosomal enzyme upregulated in senescent cells. Upon cleavage, the active drug is released, inducing apoptosis specifically in senescent cells. One such agent, SSK1, has been shown to selectively kill senescent mouse and human cells, irrespective of the senescence inducers or cell types, highlighting its potential as a broad-spectrum senolytic.[96] Similarly, β-galactosidase-activated prodrugs, such as Gal-DOX (which conjugates doxorubicin to a galactose moiety), have demonstrated efficacy in targeting senescent cells. In a mouse model of pulmonary fibrosis, Gal-DOX was shown to clear a significant proportion of alveolar epithelial senescent cells, leading to improvements in lung function and reductions in collagen deposition.[97]

Another approach involves the use of lysosomotropic agents, such as siramesine, which disrupt lysosomal membrane integrity by inhibiting lysosome-associated membrane protein 2 (LAMP-2). This disruption increases lysosomal membrane permeability, leading to the release of cathepsins into the cytoplasm and activation of the intrinsic apoptotic pathway. In aged mice, treatment with siramesine reduced skeletal muscle SA-β-gal–positive senescent cells, enhanced muscle satellite cell activation, and increased muscle fiber cross-sectional area.[98]

Natural product-derived senolytics, such as fisetin and curcumin analogs, have garnered attention for their potential in targeting senescent cells with favorable safety profiles. Fisetin—a flavonoid found in various fruits and vegetables—has demonstrated senolytic activity by inducing apoptosis in senescent cells. Studies have shown that fisetin can reduce senescence markers in progeroid mice and human tissue explants, suggesting its potential to alleviate age-related pathologies. Additionally, fisetin has been reported to extend healthspan and lifespan in wild-type mice, even when treatment was initiated in aged animals.[99]

Curcumin analogs, such as EF24 and C66, have been developed to enhance the bioavailability and stability of curcumin while retaining its senolytic properties. These analogs have shown efficacy in preclinical models by reducing senescent cell burden and improving tissue function. For example, EF24 has been reported to induce apoptosis in senescent cells and to alleviate age-related conditions in animal models.[100] Similarly, C66 has demonstrated protective effects against diabetes-induced complications by modulating oxidative stress and inflammatory pathways.[101]

Despite significant progress in senolytic therapies, several translational challenges remain. Non-invasive biomarkers to accurately assess senescent cell burden are still lacking. Traditional markers, such as plasma IL-6 and peripheral blood mononuclear cell (PBMC) $p16^{iNK4a}$, are not specific to senescent cells. Nonetheless, recent studies have identified circulating EVs carrying glycoprotein non-metastatic melanoma protein B (GPNMB)—a senescence-associated antigen (SAA)—as a promising biomarker. These EV–GPNMB levels correlate with tissue senescent cell burden, offering a potential non-invasive monitoring tool.[102] Another challenge is the re-accumulation of senescent cells following treatment cessation, observed 6–9 months post-therapy in humans. This underscores the necessity for maintenance dosing strategies. One proposed approach is on-demand dosing guided by EV–GPNMB levels. Preclinical models have demonstrated that intermittent maintenance doses of D+Q can prevent senescent cell re-accumulation for up to 12 months.[103,104]

3.2. Senescence vaccines

Senolytic vaccines represent a promising therapeutic strategy that targets senescent cells by inducing immune responses against SAAs. These vaccines utilize antigens that are uniquely or highly expressed on senescent cells to elicit antigen-specific humoral and cellular immunity, thereby promoting the elimination of these dysfunctional cells.

The GPNMB protein has been identified as a prominent SAA. It is upregulated on various senescent cell types, including adipose tissue macrophages, osteocytes, and hepatic stellate cells. Studies have shown that GPNMB

expression correlates with senescent cell burden in human osteoarthritic joints, making it a potential target for senolytic vaccination. In preclinical models, immunization with GPNMB peptide vaccines has demonstrated efficacy in reducing senescent cell burden and ameliorating age-related pathologies. For example, Suda *et al.*[105] reported that immunizing aged mice with GPNMB peptide adjuvanted with monophosphoryl lipid A (MPLA) led to a significant reduction in senescent cell burden in white adipose tissue and liver, improved insulin sensitivity, and increased grip strength. These effects were mediated by GPNMB-specific $CD8^+$ T cells and natural killer (NK) cells via antibody-dependent cellular cytotoxicity.

Furthermore, a dendritic cell (DC)-based vaccine strategy involving GPNMB peptides fused with cationic proteins (GPNMB–CP) has been developed. This approach efficiently presents antigens to DCs, activating $CD8^+$ T cells and inducing potent anti-aging immunity. In both high-fat diet-induced and natural aging mouse models, GPNMB–CP–DC vaccination improved adipose tissue senescence and metabolic abnormalities, demonstrating resilience to the senescent environment of the organism.[106] Building on this framework, loads DCs ex vivo with SAA peptides (GPNMB, $p16^{iNK4a}$), which elicits stronger T cell responses than standalone peptide vaccines, enhancing senescent cell clearance in aged mice and highlighting the advantages of DC platforms.

Additionally, messenger RNA (mRNA)-based senolytic vaccines offer a scalable and rapid-production method: studies have shown that mRNA vaccines encoding GPNMB—encapsulated in pH-sensitive lipid nanoparticles—significantly reduce senescent cell burden, surpassing peptide vaccine efficacy. Moreover, targeting urokinase plasminogen activator receptor (uPAR; a prominent SAA expressed on senescent fibroblasts and lung myofibroblasts) has shown preclinical promise: uPAR-targeting chimeric antigen receptor T cells (CAR-T cells) effectively eliminate senescent cells and improve tissue homeostasis. To address challenges such as antigen heterogeneity and age-related immunosuppression, combinatorial therapies (e.g., senolytic vaccines paired with anti-programmed death-1 [PD-1] inhibitors) have been explored, further enhancing T-cell responses and senescent cell clearance. Despite these results, clinical translation challenges remain, including the need for specific biomarkers to monitor senescent cell burden and the development of tissue-specific delivery systems—addressing these will be key to successful human application of senolytic vaccines.[107]

3.3. Chimeric antigen receptor T cells

Chimeric antigen receptor T-cell therapies are emerging as a promising approach to selectively eliminate senescent cells. By engineering T cells to express receptors targeting SAAs, CAR-T cells combine the specificity of monoclonal antibodies with the cytotoxicity and persistence of T cells, offering a precise means of clearing senescent cells.

One such SAA is uPAR, which is upregulated on senescent cells. Studies have demonstrated that uPAR-targeted CAR-T cells can effectively deplete senescent cells across various tissues, leading to improvements in tissue function and fibrosis reversal. For example, in mouse models of liver fibrosis, a single intravenous infusion of uPAR–CAR-T cells reduced senescent hepatic stellate cells and reversed liver fibrosis, with improvements in liver enzyme levels.

To address the challenge of SAA heterogeneity, dual-specific CAR-T cells targeting both uPAR and GPNMB have been developed. These dual-target CAR-T cells have shown enhanced efficacy in eliminating senescent cells across multiple tissues (white adipose tissue, liver, and bone marrow) compared to single-target CAR-T cells. For CNS applications, CAR-T cells have been engineered with BBB-penetrating moieties, such as conjugation to transferrin receptor antibodies or cell-penetrating peptides, thereby increasing brain accumulation, enabling clearance of senescent microglia, and reducing amyloid-β plaque burden in Alzheimer's disease mouse models.[108]

Safety optimization remains a critical focus in the development of CAR-T cell therapies. Early preclinical models indicated that CAR-T cells could induce mild cytokine release syndrome due to T-cell activation. To mitigate this risk, the inducible caspase-9 suicide gene system has been employed: it allows rapid elimination of CAR-T cells within 24 h upon administration of the small molecule AP1903, which activates the iCasp9 homodimer and initiates apoptosis in the modified cells. Recent advancements include the development of "switchable" chimeric antigen receptor systems, in which CAR-T cell activity is controlled by a small-molecule inducer. This approach enables temporal regulation of senescent cell clearance, thereby modulating therapeutic activity without disrupting beneficial senescence processes.[109]

Allogeneic CAR-T cells—derived from healthy donors and engineered to reduce the risk of graft-versus-host disease (GVHD)—are also under investigation. These off-the-shelf products offer the advantage of scalability and reduced preparation time compared to autologous

therapies. Studies have shown that allogeneic CAR-T cells targeting SAAs can effectively reduce senescent cell burden in aged mice without inducing GVHD over extended periods.[110]

4. Lifestyle-based anti-aging strategies

While pharmacological agents targeting individual hallmarks have shown preclinical promise, lifestyle interventions remain the most accessible, cost-effective, and translationally robust approaches to extending healthspan. Unlike targeted drugs, lifestyle strategies simultaneously modulate multiple aging hallmarks via convergent molecular pathways, positioning them to counteract the systemic nature of aging. Here, we synthesize evidence across five core lifestyle domains, focusing on the specific molecular and cellular mechanisms underlying their anti-aging effects, integrating findings from preclinical models and human clinical trials.

4.1. Caloric restriction and fasting regimens

4.1.1. Caloric restriction

Caloric restriction (CR), defined as a 20–40% reduction in daily caloric intake without inducing malnutrition, has been extensively studied for its potential health benefits. The Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy (CALERIE) trial is a notable RCT that investigated the effects of moderate CR on various health parameters in humans. In this trial, 218 healthy, non-obese adults were randomized to either a 25% CR diet or an ad libitum control diet for two years. The results indicated that CR led to significant improvements in several cardiometabolic risk factors—specifically, participants in the CR group experienced reductions in fasting glucose, insulin resistance, and low-density lipoprotein cholesterol (LDL-C) levels. Additionally, CR was associated with decreased systolic and diastolic blood pressure, as well as reduced high-sensitivity C-reactive protein (CRP) levels, suggesting lower systemic inflammation.[111]

Beyond cardiometabolic benefits, the CALERIE trial also explored CR's effects on biological aging. Using the DunedinPACE epigenetic clock (which estimates the rate of aging from DNA methylation patterns), the study found that CR slowed aging by 2–3%. This reduction is equivalent to a 10–15% decrease in mortality risk, a benefit comparable to that of smoking cessation.[112]

One primary mechanism driving CR's effects is the suppression of mTORC1—a central regulator of cell growth and protein synthesis that is hyperactivated in aging. Inhibiting mTORC1 activates the UNC-51-like autophagy activating kinase 1 (ULK1)/autophagy-related gene 1 (ATG1) complex, initiating macroautophagy. This process involves lysosomal degradation of damaged proteins and organelles, restoring proteostasis and reducing toxic aggregate accumulation linked to neurodegeneration.[113] Additionally, CR elevates SIRT1, a NAD^+-dependent deacetylase. SIRT1 deacetylates and activates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which drives mitochondrial biogenesis by upregulating nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM). This SIRT1–PGC-1α axis enhances oxidative phosphorylation and reduces ROS production, thereby mitigating mitochondrial dysfunction.[114] Epigenetically, CR induces site-specific DNA methylation changes at loci encoding immune regulators and metabolic transcription factors, partially reversing age-associated epigenetic drift to mirror younger individuals' epigenetic signatures and preserve transcriptional homeostasis.

4.1.2. Intermittent fasting

In addition to CR, intermittent fasting (IF) has gained attention as a dietary approach that alternates eating and fasting periods. Various IF protocols—including alternate-day fasting (ADF), time-restricted eating (TRE), and the 5:2 regimen—have been studied for their effects on weight loss and metabolic health. Research indicates that IF can reduce weight and improve metabolic markers, but its long-term sustainability and effectiveness relative to continuous CR remain under investigation. Some studies suggest that IF may offer advantages in adherence and implementation, potentially leading to better long-term outcomes; however, more high-quality, long-term RCTs are needed to clarify its comparative benefits and risks versus CR.[115]

A systematic review and meta-analysis of RCTs involving over 1,200 participants showed IF delivers cardiometabolic benefits comparable to CR—including 15–20% lower homeostatic model assessment of insulin resistance (HOMA-IR) and 3–5 mmHg reduced systolic blood pressure—with significantly higher adherence rates.[116-118] Another study confirmed IF as an effective approach for long-term weight loss and improved cardiometabolic health in overweight or obese adults, while an RCT (101 overweight/obese adults with prediabetes) showed both ADF and 16:8 time-restricted fasting (16/8 TRF) reduced body weight, body mass index, and waist circumference versus a control group—with ADF yielding more significant weight and body mass index reductions than 16/8 TRF.[119]

Mechanistically, IF induces a metabolic switch from glucose to fatty acid and ketone body utilization, activating several adaptive pathways beneficial for metabolic health.[120,121] During fasting, reduced glucose availability and

increased ketone bodies activate AMPK. AMPK activation phosphorylates acetyl-CoA carboxylase (ACC) to reduce fatty acid synthesis and enhances mitochondrial function by phosphorylating PGC-1α. These effects mirror those of CR but are temporally linked to fasting cycles.[122] As an IF modality, TRE aligns food intake with circadian rhythms, thereby enhancing hepatic autophagy. Studies have shown that TRE increases the expression of autophagy-related proteins, such as ATG1 and ATG8a, facilitating the clearance of damaged cellular components and improving metabolic health. Fibroblast growth factor 21 (FGF21), a fasting-induced hormone, plays a crucial role in these processes. FGF21 is upregulated during fasting, acting on the liver to suppress lipogenesis and promote fatty acid oxidation.[123] It also activates the unfolded protein response to protect against endoplasmic reticulum stress and has been shown to enhance mitochondrial function via the AMPK and SIRT1 pathways.[124]

4.2. Dietary patterns

4.2.1. Plant-centered diets

The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets are plant-based dietary patterns rich in unsaturated fats (e.g., extra-virgin olive oil), whole grains, legumes, fatty fish (e.g., salmon, sardines), nuts, and colorful fruits and vegetables. The DASH diet additionally emphasizes reduced sodium intake (≤2,300 mg/day) to lower blood pressure. High adherence to these diets has been associated with a lowered risk of dementia and cardiovascular disease.

From an evidence-based perspective, a meta-analysis confirmed that adherence to the Mediterranean diet is linked to an 11–30% reduction in the risk of age-related cognitive disorders, including cognitive impairment, dementia, and Alzheimer's disease.[125] Similarly, a case-control study found that higher adherence to the DASH diet was significantly associated with a diminished risk of Alzheimer's disease.[126] For cardiovascular health, the Mediterranean diet has also been tied to a 30% lower incidence of cardiovascular conditions—including myocardial infarction, stroke, and cardiovascular death—in high-risk individuals.[127] These findings underscore the potential of these dietary patterns to promote cardiovascular health and reduce dementia risk.

Extra-virgin olive oil, a cornerstone of the Mediterranean diet, contains polyphenols (e.g., oleocanthal, hydroxytyrosol) that activate the nuclear factor erythroid 2-related factor 2 (NRF2)–antioxidant response element (ARE) pathway. This pathway's activation enhances the expression of antioxidant enzymes, such as SOD2 and catalase, mitigating oxidative stress—a key contributor to aging. Studies have shown that polyphenols in extra-virgin olive oil modulate cellular antioxidant responses through the NRF2–ARE pathway, leading to increased expression of phase II detoxifying enzymes and reduced oxidative damage.[128]

Fatty fish, rich in omega-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), activate the G protein-coupled receptor 120 (GPR120) on immune cells. This activation mediates potent anti-inflammatory effects by repressing macrophage-induced tissue inflammation, thereby enhancing insulin sensitivity and reducing systemic inflammation.[129] Beyond this anti-inflammatory effect, omega-3 fatty acids also inhibit the expression of genes involved in the NF-κB pathway, leading to decreased production of pro-inflammatory cytokines, such as TNF-α and IL-1β.[130]

The high fiber content of the Mediterranean and DASH diets—derived from whole grains and legumes—promotes the production of short-chain fatty acids (SCFAs) such as butyrate through fermentation by gut microbiota. SCFAs act as histone deacetylase (HDAC) inhibitors, increasing histone H3 acetylation at loci encoding tight junction proteins (e.g., occludin), thereby enhancing gut barrier function and reducing endotoxemia—a trigger of systemic inflammation. Beyond strengthening gut barrier function, SCFAs also activate the gut–brain axis via vagal nerve signaling, reducing hippocampal neuroinflammation and preserving cognitive function.[131]

4.2.2. Metabolic-switching diets

Metabolic-switching diets, such as the ketogenic diet (KD) and fasting-mimicking diet (FMD), aim to emulate the physiological effects of fasting while being more sustainable than prolonged CR.

The KD is a high-fat, very-low-carbohydrate regimen that induces ketosis—a metabolic state where the liver produces ketone bodies (e.g., β-hydroxybutyrate [BHB]) to provide energy when glucose is scarce. BHB serves not only as an energy source but also as a signaling molecule that enhances mitochondrial function and biogenesis via the PGC-1α–SIRT3–uncoupling protein 2 (UCP2) axis, improving cellular bioenergetics and reducing oxidative stress. Additionally, BHB upregulates BDNF in the hippocampus, activating the PI3K–AKT pathway, promoting neuroplasticity, and reducing neuronal apoptosis.[132,133] The KD also inhibits mTORC1, activating autophagy-related genes (e.g., *Atg5*, *Atg7*) that facilitate the clearance of damaged mitochondria and toxic proteins, supporting cellular maintenance and longevity.[134] However, while the KD offers therapeutic benefits, long-term use may lead to adverse effects, such as hyperlipidemia and

kidney stones—primarily due to dysregulated cholesterol metabolism and altered calcium excretion.[135,136] Therefore, close clinical supervision is essential, especially for individuals with preexisting comorbidities like chronic kidney disease.

The FMD approach is a low-calorie, low-protein, high-fat dietary regimen designed to mimic the physiological effects of fasting while providing essential nutrients. Clinical studies have demonstrated that periodic cycles of FMD can lead to reductions in biological age (as measured by the Horvath epigenetic clock), suggesting potential benefits for aging and disease risk.[137] Mechanistically, FMD influences several key pathways associated with aging and metabolism. By reducing intake of proteins and carbohydrates, FMD lowers levels of insulin-like growth factor 1 (IGF-1)—a hormone linked to aging and age-related diseases. This reduction in IGF-1 activity can activate the FOXO3 transcription factor, which promotes cellular repair and stress resistance.[138] Additionally, FMD has been shown to modulate the immune system. In clinical trials, participants undergoing FMD cycles exhibited changes in immune cell composition, including an increase in the lymphoid-to-myeloid ratio, suggesting a shift toward a more youthful immune profile.

4.3. Exercise

4.3.1. Molecular pathways of exercise-mediated geroprotection

Regular physical exercise engages conserved energy-sensing and remodeling programs that counter hallmarks of aging across tissues. In skeletal muscle, cellular energy stress activates AMPK, which interfaces with the PGC-1 family to coordinate transcription of nuclear-encoded mitochondrial genes and support mitonuclear communication; these signals upregulate effectors such as NRF1 and TFAM to expand mitochondrial content and oxidative capacity.[139,140] Beyond transcription, quality-control pathways are tuned by training: exercise regulates mitophagy to clear damaged organelles, maintaining mitochondrial fidelity and metabolic homeostasis.[141] Muscle also acts as an endocrine organ. During exercise bouts, IL-6 rises rapidly from contracting fibers and functions as a context-dependent "energy allocator," mobilizing substrates and shaping an anti-inflammatory milieu—an effect pattern distinct from chronic low-grade inflammation.[136]

Multi-tissue reviews further show that these myocellular and endocrine signals converge with adaptations in adipose tissue, liver, vasculature, and brain to improve systemic cardiometabolic resilience. At the genome–epigenome interface, training elicits rapid and durable remodeling: endurance programs reprogram chromatin and DNA methylation in human muscle, and population studies associate higher physical activity with slower DNA-methylation–based epigenetic aging.[142-144] By contrast, effects on leukocyte telomere length appear modest and heterogeneous overall: recent meta-analyses suggest small benefits, with some signal favoring high-intensity interval training, but results depend on program modality and duration.[145,146]

4.3.2. Exercise types and their unique anti-aging benefits

Exercise modalities vary in the biological pathway they engage, allowing clinicians to assemble personalized anti-aging prescriptions. Aerobic endurance training (e.g., brisk cycling and treadmill walking) chiefly targets the vasculature: meta-analyses of 12- to 16-week programs in older adults report 3–5% gains in flow-mediated dilation, coincident with higher endothelial nitric oxide synthase (eNOS) expression and sizeable reductions in CRP and TNF-α.[147] Rodent data extend these benefits to the brain, where voluntary swimming or running improves glymphatic exchange and accelerates amyloid-β clearance, a mechanism increasingly linked to exercise-related neuroprotection.[148]

Progressive resistance training supplies complementary musculoskeletal benefits. A 2022 meta-analysis found that 2–3 sessions per week for ≥12 weeks increased maximal strength by approximately 30% and produced modest yet significant gains in femoral-neck and lumbar spine bone mineral density, outcomes underpinned by acute mTORC1–p70S6K activation and sustained mechanical loading.[149,150]

High-intensity interval training (HIIT), typically 6–10 bouts of 30–90 s with brief recovery, compresses stimulus into 20-min sessions. A 2025 meta-analysis showed that HIIT elevated skeletal-muscle PGC-1α and citrate synthase activity more than volume-matched moderate exercise, while improving insulin sensitivity in adults ≥ 60 y.[151] Mechanistic work further demonstrated that the transient ROS burst during HIIT activates the PINK1–Parkin pathway, stimulating mitophagy and thereby improving mitochondrial quality in aged muscle.[152,153]

4.4. Sleep, stress management, and circadian

4.4.1. Sleep

Healthy adult sleep is now consensually defined as 7–9 h per night with preserved architecture—sufficient slow-wave sleep (SWS) for memory processing and rapid-eye-movement (REM) sleep for emotional regulation. Aging is accompanied by attenuated melatonin output and

a higher prevalence of conditions, such as obstructive sleep apnea and mood disorders, all of which erode sleep continuity and depth.[154] Large contemporary cohorts show that habitual short (<6 h) and long (>10 h) sleep are each associated with shorter leukocyte telomeres and a higher incidence of cardiometabolic disease and dementia, even after multivariable adjustment.[155,156]

Mechanistically, two systems appear pivotal. First, the glymphatic network is maximally active during SWS: astrocytic aquaporin-4 polarization enlarges the interstitial space, accelerating the clearance of amyloid-β and tau; experimental SWS reduction or total sleep loss impairs this flux and elevates cerebrospinal fluid amyloid within a single night.[157,158] Second, disrupted sleep destabilizes hypothalamic–pituitary–adrenal control; elevated night-time cortisol activates NF-κB, increases IL-6/TNF-α, and is linked to epigenetic-age acceleration and mitochondrial dysfunction.[159]

Interventions with proven benefit in older adults include: melatonin supplementation (1–3 mg 30 min before bedtime), which modestly lengthens SWS and improves subjective sleep quality with a favorable safety profile[160]; cognitive-behavioral therapy for insomnia (CBT-I), the guideline-endorsed first-line therapy that delivers durable gains in sleep efficiency, latency and fatigue—digital formats now broaden access for mobility-limited seniors[161]; and fundamental sleep-hygiene strategies, such as regular bed-wake schedules, evening blue-light restriction, and a cool (18–20 °C), quiet bedroom, which synergies with pharmacological or behavioral treatments. Together, maintaining adequate duration, protecting SWS, and correcting treatable sleep disorders represent tractable targets for slowing multiple biological aging clocks.

4.4.2. Chronic stress

Chronic psychosocial stress—whether rooted in loneliness, financial strain, or caregiving—emerges as a measurable accelerator of biological aging. A 2024 community-cohort analysis of >6,000 United States older adults found that cumulative psychosocial stressors were independently associated with a 28% higher odds of incident frailty over 4 years, after controlling for health behaviors and comorbidity.[162] At the molecular level, a prospective study of middle-aged women showed that caregiving-related stress predicted a nine-month decline in telomerase activity and impaired maintenance of leukocyte telomere length—a pathway consistent with accelerated cellular senescence. Mechanistically, sympathetic outflow during chronic stress elevates norepinephrine, which engages β-adrenergic receptors on macrophages to trigger protein kinase A (PKA)-dependent activation of the NLRP3 inflammasome and downstream IL-1β release, thereby fueling "inflammaging."[163,164] In parallel, sustained hypothalamic–pituitary–adrenal activation raises cortisol, a hormone that promotes oxidative DNA damage and NF-κB–driven cytokine production while downregulating telomerase reverse transcriptase, further linking stress to genomic and mitochondrial injury.[165]

Stress-management interventions can blunt these trajectories. A 2023 systematic review of 18 randomized trials reported small but significant improvements in telomere biology after mindfulness-based programs, especially when the practice lasted more than 8 weeks.[166] Complementary evidence shows that cognitive-behavioral therapy in chronically stressed adults reduces circulating IL-6 by ~15%, indicating a downshift in systemic inflammation.[167] Mind–body practices with gentle movement matter as well: a 2024 meta-analysis demonstrated that regular Tai Chi improves high-frequency heart rate variability, suggesting durable reductions in sympathetic dominance.[168] Taken together, observational and mechanistic data converge on a model in which chronic stress accelerates aging through neuro-immune crosstalk, while evidence-based behavioral therapies can meaningfully attenuate these effects.

4.4.3. Circadian alignment

The circadian clock—a cell-autonomous 24-h rhythm regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus—coordinates physiological processes, including sleep–wake cycles, hormone secretion (e.g., melatonin, insulin), and metabolic flux. Aging progressively dampens the amplitude and precision of the 24-h circadian system governed by the SCN. In two recent cohort studies that together followed >10,000 community-dwelling older adults, attenuated rest-activity rhythms or delayed acrophase predicted a 23–32% higher incidence of metabolic-syndrome components, cardiovascular events, and frailty within four years, even after adjusting for sleep duration, activity, and comorbidity.[169,170] Mechanistic work showed that aging-related loss of the core clock factor brain and muscle ARNT-like protein 1 (BMAL1) in vascular endothelium rewires hundreds of clock-controlled genes involved in lipid and glucose metabolism, thereby tilting the milieu toward dyslipidemia and insulin resistance.[171] Misalignment also lowers nuclear receptor subfamily 1 group D member 1 (REV-ERBα), a circadian locomotor output cycles kaput (CLOCK) output that normally represses NF-κB transcription; its decline removes a brake on innate immune signaling and amplifies low-grade inflammation.[172]

Three zeitgeber-based strategies show clinically relevant benefits. Morning bright-light therapy (~10,000 lux for

30 min within an hour of waking) enhanced circadian amplitude, improved subjective sleep and modestly stabilized daytime glucose excursions in older adults with T2D.[173] Early TRE, restricting all calories to an 8–10 h window aligned with the light phase, improved whole-body insulin sensitivity and reduced 24-h glucose variability in randomized crossover trials without necessitating weight loss.[174,175] Finally, maintaining regular bed- and wake-times throughout the week strengthens SCN output and reinforces peripheral clocks, amplifying the metabolic and inflammatory effects of light and feeding cues. Collectively, aligning behavioral signals—light, food, and sleep—with the endogenous clock emerges as a tractable lever to mitigate age-related metabolic and inflammatory burden.

4.5. Social engagement and cognitive activity

Maintaining robust social networks and engaging the mind every day form a complementary, evidence-based strategy for healthy aging. A 2023 meta-analysis of 90 prospective cohorts (2.2 million participants) showed that social isolation raises all-cause mortality by about one-third (pooled hazard ratio [HR] 1.32, 95% CI: 1.26–1.39).[176] Parallel longitudinal work across 28 European countries reported that participation in formal social activities—clubs, volunteering, and cultural groups—attenuated cognitive decline over a 4-year period among adults aged ≥70 years, with the greatest benefit in the oldest-old.[177] Mechanistically, social contact dampens stress biology: in a study of 542 community-dwelling seniors, greater perceived support and problem-focused coping were linked to flatter diurnal cortisol slopes and lower evening cortisol, pointing to a less activated hypothalamic–pituitary–adrenal axis.[178] Animal and translational data further show that socially enriched environments upregulate hippocampal BDNF and stimulate adult neurogenesis—molecular pathways that underpin synaptic plasticity and memory retention.[179]

Cognitive stimulation provides an additional layer of defense. In a 2025 Japanese cohort of socially frail older adults, high engagement in cognitively demanding hobbies was associated with a 38% lower five-year dementia incidence versus low engagement.[180] Structured programs amplify these benefits: a 2024 meta-analysis of 35 randomized trials found that computerized cognitive training produced moderate improvements in verbal and visual memory among people with mild cognitive impairment, indicating measurable neuroplastic gains.[181] Taken together, nurturing social ties reduces chronic stress and supports neurotrophic signaling, while regular intellectual challenges build cognitive reserve and slow pathological brain aging. Programs that combine community engagement with accessible digital or group-based cognitive training appear especially promising for older adults facing mobility or geographic barriers. Implementing such dual-pathway interventions could therefore yield outsized returns for longevity and late-life quality.

4.6. Synergy of lifestyle interventions

Mounting evidence indicates that single-domain lifestyle tweaks nudge only one or two hallmarks of aging, whereas carefully combined interventions interact biologically and deliver larger, system-wide gains. Mechanistic studies show that CR and endurance exercise converge on mitochondrial quality control: each stimulates PINK1–Parkin-mediated mitophagy, but together they amplify removal of damaged mitochondria and restore oxidative capacity more efficiently than either alone. In clinical settings, this synergy translates into functional benefit. The SPRINTT randomized trial (1,519 frail adults, mean age = 79 years) paired moderate physical activity with personalized nutritional counseling and reduced new mobility-disability events by 22% over ~2 years versus a health-education control.[182]

Circadian alignment adds a second layer: early TRE during the biological daytime improves glucose tolerance and lowers 24-h glycemic variability, effects that are blunted when the same menu is consumed late in the day.[183] Mediterranean-style foods rich in tryptophan further enhance evening melatonin secretion and deepen SWS, reinforcing the metabolic benefits of chrononutrition. Social and cognitive domains interact as well.[183] A 12-week "StrongerMemory" program showed that adding structured social engagement to computer-based cognitive exercises produced larger gains in episodic memory than cognitive training alone, paralleled by higher adherence and greater increases in plasma BDNF.[184] Videoconference-driven social connectedness trials report similar reductions in loneliness and depressive symptoms, suggesting that digital tools can overcome mobility barriers for many older adults.

Lastly, multidomain protocols knit these strands together. Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)-family studies, now replicated on four continents, combine Mediterranean diet guidance, aerobic/resistance exercise, cognitive training, and vascular risk coaching; pooled analyses show a ~25% slower composite cognitive decline over two years relative to usual care.[185] Collectively, the data support a "stacked" strategy: align light and meals with the body clock, pair calorie moderation with exercise, and embed both within socially and cognitively rich environments—an integrated recipe that tackles mitochondrial dysfunction, metabolic dysregulation, and

neuroinflammation in concert, extending healthspan more than any isolated fix.

Collectively, these clinically accessible interventions—including dietary modulation, exercise, sleep optimization, and selected metabolic or anti-inflammatory drugs—represent the most mature strategies for managing aging-related conditions and are summarized in Table 1.

5. Microbiome-based interventions to promote healthy aging

5.1. Probiotics, prebiotics, and postbiotics

Probiotics—live microorganisms that confer health benefits when administered in adequate amounts—have emerged as accessible, low-risk tools to counter age-related gut dysbiosis, with specific strains proving effective against inflammaging and immunosenescence. In an 8-week double-blind trial (n = 121), *Lacticaseibacillus rhamnosus* LM1019 significantly enhanced NK cell cytotoxicity in participants aged ≥ 40 years without safety concerns.[186] Among adults aged > 70 years, four weeks of *Lactiplantibacillus plantarum* HEAL9 lowered fecal calprotectin and trended toward reduced serum CRP, indicating attenuation of gut-driven inflammation.[187] Gut-barrier gains were corroborated in a 12-week Thai RCT of elders (60–75 years old): a multi-strain mix—*Lactobacillus paracasei* HII01, *Bifidobacterium breve*, and *Bifidobacterium longum*—improved intestinal permeability by ≈30% (lactulose:mannitol ratio) and raised high-density lipoprotein-cholesterol.[188] Beyond local effects, a 2024 systematic review of 14 probiotic RCTs in adults aged ≥60 years found a modest yet significant increase in antibody titers to influenza and pneumococcal vaccines, underscoring systemic immune benefits.[189] *A. muciniphila* is now recognized for geroprotective potential: a 12-week supplementation with pasteurized *A. muciniphila* (1×10^{10} cells/day) in overweight mid-life adults (mean age: 57 years) improved insulin sensitivity and lowered plasma lipopolysaccharide (LPS)-binding protein, a marker of metabolic endotoxaemia[190], and human trials targeting ≥65-year-old cohorts are underway. Molecular read-outs are equally encouraging; a 24-week multistrain intervention in older adults with T2D preserved leukocyte telomere length and reduced high-sensitivity CRP versus placebo.[191]

Prebiotics—non-digestible carbohydrates that selectively nourish beneficial gut microbes—complement probiotics by fostering a supportive microbial environment. Human trials over the past five years show that fermentable prebiotics can reshape the aging gut, with effects that reverberate through metabolism and immunity. In a randomized crossover trial, 15 g/day of chicory inulin for three weeks increased total fecal SCFA output by

Table 1. Existing and clinically validated interventions for aging-related conditions

Intervention	Specific strategy	Aging-related clinical indication	Mechanism
Dietary restriction	Caloric restriction	Obesity; metabolic syndrome	Inhibits mTORC1; activates autophagy; upregulates SIRT1–PGC-1α axis
Dietary patterns	Mediterranean diet	Cardiovascular disease (CVD) prevention; cognitive decline risk	Modulates NRF2–ARE antioxidant pathway; reduces systemic inflammation
	DASH diet	Hypertension; cardiovascular health	Reduces sodium load; enhances endothelial function
Physical exercise	Aerobic training	CVDs; metabolic health	Activates AMPK and PGC-1α; enhances mitochondrial biogenesis
	Resistance training	Sarcopenia; osteoporosis; frailty	Activates mTORC1–p70S6K signaling; mechanical loading improves bone density
Sleep & stress	CBT-I & sleep hygiene	Chronic insomnia; sleep fragmentation	Promotes glymphatic clearance of amyloid/tau; stabilizes HPA axis
Metabolic drugs	GLP-1 receptor agonists	Type 2 diabetes; obesity; CVD risk	Reduces oxidative stress; enhances neurotrophic factors
	SGLT2 inhibitors	Type 2 diabetes; heart failure; chronic kidney disease	Upregulates antioxidant enzymes; improves endothelial function
	Colchicine (low-dose)	Secondary CVD prevention; gout	Disrupts microtubule assembly to inhibit NLRP3 inflammasome activation

Abbreviations: AMPK: AMP-activated protein kinase; ARE: Antioxidant response element; CBT-I: Cognitive behavioral therapy for insomnia; DASH: Dietary Approaches to Stop Hypertension; GLP-1: Glucagon-like peptide-1; HPA: Hypothalamic–pituitary–adrenal; mTORC1: Mechanistic target of rapamycin complex 1; NLRP3: NOD-, LRR-, and pyrin domain-containing protein 3; NRF2: Nuclear factor erythroid 2-related factor 2; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; p70S6K: 70-kDa ribosomal protein S6 kinase; SGLT2: Sodium-glucose cotransporter 2; SIRT1: Sirtuin 1.

~35% in adults aged ≥70 years while preserving butyrate production, demonstrating that older microbiomes remain highly responsive to fructans.[192] A meta-analysis that pooled 24 inulin studies (median age: ≈64 years) reported small yet significant reductions in fasting glucose and HOMA-IR with ≥8 g/day, linking SCFA gains to better glycemic control.[193] Viscous fibers supply complementary benefits: oat β-glucan lowered post-prandial glucose and insulin by ~22% across 103 controlled meal trials, with the largest effects in older and diabetic cohorts.[194] Galacto-oligosaccharides (15 g/day, 3 weeks) increased fecal *Bifidobacterium* and dampened ex vivo IL-6 release in prefrail elders, suggesting anti-inflammatory potential.[195] Finally, fructan supplementation consistently expands *A. muciniphila*—a mucin-degrading bacterium enriched in centenarians and linked to improved metabolic homeostasis.[196]

Postbiotics—non-viable microbial molecules that reach the host intact—offer a shelf-stable route to many of the benefits attributed to live probiotics. The best-studied examples are the SCFAs butyrate and propionate: both enter colonocytes, inhibit class I/II HDACs, and tilt mucosal immunity toward a tolerogenic profile by expanding $FOXP3^+$ regulatory T cells and dampening NF-κB signaling. In aged brain models, oral microencapsulated sodium butyrate crossed the gut–brain axis, reducing hippocampal IL-1β/IL-6 by ~30% and restoring spatial memory performance in 5 × FAD mice (Morris water maze).[197] Human evidence remains preliminary but encouraging. In adults with active ulcerative colitis, 12-week sodium butyrate supplementation as an adjunct to standard therapy significantly reduced fecal calprotectin and serum high-sensitivity CRP, supporting its potential to attenuate both intestinal and systemic inflammation.[198,199] Postbiotic macromolecules are gaining traction as well. Purified exopolysaccharides from *Bifidobacterium adolescentis* reduced colonic IL-17 and restored tight-junction proteins in high-fat-diet–fed mice, indicating direct mucosal immunomodulation without viable cells. Meanwhile, nano-sized EVs released by *B. breve* carry surface adhesins that target intestinal and neural cells; in pre-clinical aging models, EV gavage tightened gut permeability and suppressed systemic TNF-α, offering a thermostable alternative to bacterial transplantation.[200] Observational data dovetail with these mechanistic findings: a higher habitual butyrate intake in United States adults aged ≥65 years correlates with better executive-function and verbal-fluency scores after multivariable adjustment.[201]

5.2. Dietary modulation of the microbiota

Diet is the most durable lever for sculpting the aging gut microbiome. In NU-AGE—a multicenter, 1-year intervention in 1,142 Europeans aged 65–79 years—high Mediterranean-diet adherence preserved α-diversity and expanded butyrate-producing taxa, such as *Roseburia* and *Faecalibacterium*, while parallel reductions in frailty and inflammatory markers occurred. A more recent Italian cohort confirmed the effects: older adults in the highest Mediterranean diet-score tertile harbored ~25% greater microbial richness and higher fecal SCFAs than Western-diet peers, trends that tracked with lower CRP and IL-6 over three years.[202] Mechanistic work explained why. Polyphenols in extra-virgin olive oil are biotransformed by gut bacteria into hydroxytyrosol and other phenolics that suppress pathobionts, while marine omega-3 fatty acids dampen epithelial NF-κB signaling, favoring colonization by commensals. Whole-grain β-glucans are fermented to butyrate, a key fuel for colonocytes and an anti-inflammatory HDAC inhibitor.[203]

Conversely, Western dietary patterns accelerate "microbiota aging." An exploratory cross-sectional study in 430 community-dwelling adults aged ≥65 years linked higher intakes of processed meat, refined grains, and added sugars to greater circulating levels of LPS-binding protein (a gut-permeability biomarker) and to an enrichment of pro-inflammatory Enterobacteriaceae. Experimental data indicate that such LPS leakage propagates systemic inflammation and cardiometabolic risk.

Precision nutrition now aims to harness these diet–microbiome links at the individual level. In an 18-week randomized trial, an app-based program that integrated metagenomic profiles with post-prandial glucose and triglyceride responses delivered personalized food scores; participants (mean age: 66 years) achieved a larger reduction in fasting glucose and triglycerides than controls receiving generic healthy-eating advice. A pilot study in T2D adults found that AI-guided diets informed by stool and blood metatranscriptomics lowered glycated hemoglobin (HbA1c) by 0.42% over eight weeks, quadrupling the improvement seen with United States Department of Agriculture-style counseling.[204] These programs typically boost fiber-degrading and SCFA-producing taxa that are missing in many older microbiomes, underscoring the value of "microbial gap filling."

5.3. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is being tested as a "reset button" for the aging gut: by transferring a complete, screened microbial community from a fit donor, it can re-seed taxa lost with age and re-establish metabolite networks that restrain inflammation and metabolic drift. Pre-clinical evidence is strong. Transplanting stool from young (3-month) to aged (24-month) mice consistently

improves functional phenotypes—restoring grip strength, lowering frailty scores, and normalizing body composition—while also rejuvenating hematopoietic and immune compartments; A 2023 study showed enhanced lymphoid output and reduced myeloid bias in aged recipients.[205] Benefits extend to metabolism: young-donor FMT improved insulin sensitivity and hepatic lipid handling in aged or obese models, tracking with higher colonic SCFA production.[206]

Early human data echo these signals, albeit in small cohorts. In a single-center, randomized pilot trial in metabolic-syndrome adults (mean age: ≈57 years), FMT from lean donors increased insulin-mediated glucose disposal by ~25% at 12 weeks relative to sham, alongside enrichment of *Akkermansia* and other SCFA producers. A phase-2 capsule study in frail elders (70–80 years) reported a 20% increase in gut α-diversity and an 18% decrease in serum IL-6 six weeks post-FMT, with no serious adverse events.[207] Although these gains are promising, engraftment—the proportion of donor strains that persist—appears lower in older adults than in younger recipients, potentially reflecting age-related barrier dysfunction and residual dysbiosis.

The 2024 American Gastroenterological Association guideline now mandates metagenomic screening of every donor sample to exclude latent pathogens, antibiotic-resistant genes, and engineered microbes—an especially critical safeguard for immunosenescent hosts.[208] Protocols to enhance engraftment are under study: short courses of antibiotics or bowel-prep "conditioning," targeted prebiotics, and repeated-dosing regimens are each being evaluated in registrational trials.[209] Long-term safety data are sparse; observational follow-up of FMT-treated patients for indications such as *Clostridioides difficile* infection will be essential to detect delayed effects on autoimmunity or opportunistic infection.

6. Epigenetic reprogramming

Partial epigenetic reprogramming has emerged as a powerful strategy to reverse cellular aging in vitro and in vivo. However, unlike lifestyle or metabolic interventions, which are clinically actionable today, this strategy represents a nascent frontier that faces significant translational hurdles (e.g., delivery vectors, oncogenic risk) and currently lacks human safety data.

6.1. Transcription factor-mediated partial reprogramming

Transcription factor-based partial reprogramming leverages cell-type-specific or pluripotency-associated transcription factors to directly modulate tissue-specific epigenetic regulatory networks, offering unparalleled specificity for targeting organ-specific aging phenotypes. The most rigorously validated transcription factor cocktail is OSK (Octamer-binding transcription factor 4 [Oct4], SRY-box transcription factor 2 [Sox2], Kruppel-like factor 4 [Klf4])—a truncated variant of the Yamanaka factor quartet (OSKM) that excludes the proto-oncogene c-Myc. This cocktail was first shown to delay progeroid pathology and improve tissue repair when induced cyclically in mice.[210] Subsequent retina work demonstrated that adeno-associated virus (AAV) delivery of OSK to adult retinal ganglion cells restores youthful DNA-methylation profiles and axon regeneration; genome-wide analyses revealed that OSK binding reopens chromatin at hundreds of "youth" loci related to mitochondrial biogenesis, DNA repair, and synaptic plasticity, while lowering repressive H3K27me3 marks—changes consistent with Switch/sucrose non-fermentable (SWI/SNF)-assisted chromatin remodeling observed in multi-tissue epigenomic maps of partially reprogrammed cells.[211] Importantly, systemic, doxycycline-tunable OSK gene therapy in extremely old (124-week) mice more than doubled remaining median lifespan and improved frailty indices without increased tumor incidence[212], supporting the safety advantage of dropping Myc. Emerging combinations aim to enhance tissue specificity: co-expression of Tet methylcytosine dioxygenase 1 (TET1) accelerates OSK-driven demethylation of retinal-identity genes, whereas OSK plus the cell-cycle factor FOXM1 activates DNA repair and antioxidant programs in aged skeletal muscle. Collectively, these studies position OSK-centered partial reprogramming as a tractable, tunable strategy for organ-focused epigenetic rejuvenation, now advancing toward first-in-human trials that couple inducible vectors with rigorous tumor-surveillance read-outs.

Targeted, cyclic partial reprogramming with the OSK cassette is now reproducibly rejuvenating multiple aged tissues in vivo. In the landmark study, AAV delivery of OSK into adult mouse retinal ganglion cells restored youthful DNA-methylation patterns, re-established *Pou4f2*/*Brn3b* transcription, promoted axon regrowth after optic-nerve crush, and preserved visual-evoked potentials in a glaucoma model; the effect was abrogated when TET1/2 demethylases were knocked out, highlighting active methylcytosine oxidation as a requirement.[213] Wang *et al.*[214] demonstrated that transient OSK expression in aged myofibers remodeled the satellite-cell niche, accelerated regeneration after injury, and restored contractile force, while follow-up work showed that adding the cell-cycle factor FOXM1 further amplified satellite-cell proliferation and myogenic gene expression, countering sarcopenia-like weakness.[215] A recent OSKM (full-factor) gene-therapy

study in 25-month-old rats lowered epigenetic-clock age in the hippocampus, increased BDNF, and improved Barnes-maze performance, suggesting that partial reprogramming can rescue cognitive function even in very old animals; transcriptional profiling indicated re-opening of youth-associated chromatin at DNA-repair and synaptic-plasticity loci.[216] Short OSK pulses delivered after myocardial infarction improved left-ventricular ejection fraction and reduced scar burden in adult mice, with benefits again dependent on TET-mediated demethylation. A unifying feature across these studies is the use of cyclic induction (2–4 days "ON", 5–10 days "OFF"), which limits factor exposure to the epigenetic-resetting window, avoids activation of pluripotency genes, such as *Nanog*, and eliminates teratoma risk observed with continuous expression.[215] Multi-omics analyses converged on two mechanisms: correction of age-skewed *CpG* methylation at senescence, metabolic, and lineage-fidelity genes, and SWI/SNF-assisted reopening of closed chromatin around pathways for mitochondrial biogenesis, DNA repair, and stress resistance.

6.2. Small molecule-mediated chemical reprogramming

Small-molecule or "chemical" reprogramming seeks to mimic transcription factor-driven epigenetic reset with drug-like compounds—an approach that sidesteps viral vectors, lowers production cost, and can be scaled for topical, oral, or systemic use. Four mechanistic classes now dominate the field:

(i) DNA-methyltransferase (DNMT) inhibitors. Brief exposure of chondrocytes to the cytidine analog 5-aza-2′-deoxycytidine (5-Aza) reversed senescence-associated DNA-methylation drift, restored colony-forming efficiency, and rejuvenated transcription of cartilage-maintenance genes, such as *SOX9*—findings that underpin current trials for osteoarthritic cartilage repair.[217]

(ii) HDAC inhibitors. The endogenous ketone body BHB and the FDA-approved drug vorinostat (SAHA) both increase the activation of H3K9ac/H3K27ac. BHB supplementation in aged mice dampened NLRP3–inflammasome signaling and improved cognitive scores, while SAHA blunted dexamethasone-induced myotube atrophy and partially restored fiber diameter—proof-of-concept for sarcopenia management.[218,219]

(iii) Histone methyltransferase inhibitors. Epigenetic "erasers" that block repressive marks are showing multi-organ promise: the enhancer of zeste homolog 2 (EZH2) inhibitor GSK126 protects hippocampal CA1 neurons by reducing H3K27me3 and apoptosis after ischemia, whereas a brain-penetrant G9a inhibitor (MS1262) reversed learning and memory deficits and lowered amyloid/tau load in several Alzheimer's disease mouse models.[220,221] EZH2 blockade has also been shown to revive β-cell identity and insulin secretion, suggesting utility in metabolic aging.

(iv) Retinoic acid receptor (RAR) agonists. The pan-RAR ligand 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB) enhances chromatin accessibility at developmental loci and, in human pluripotent stem cell models, steers mesodermal specification without growth factors[222]; pre-clinical work now pairs TTNPB with OSK protein or HDAC inhibitors to accelerate wound repair and skin-barrier rejuvenation.

Small-molecule "chemical reprogramming" now relies on cocktails that simultaneously target multiple epigenetic axes, producing rejuvenation signatures approaching those achieved with transcription-factor protocols, yet without introducing foreign genes. Yang *et al.*[223] first identified six-compound mixtures that, within a week, restored a youthful genome-wide transcriptomic profile and reversed transcriptomic aging clocks in human fibroblasts, while leaving cell identity intact. These findings were extended using a seven-component blend containing the RAR agonist TTNPB and the endogenous HDAC inhibitor valproic acid: multi-omics profiling showed broad reductions in biological age, re-engagement of mitochondrial oxidative phosphorylation, and improved membrane potential in mouse dermal fibroblasts.[224]

Domain-specific cocktails are emerging. In the nervous system, BHB alone acts as an HDAC inhibitor that blunts NLRP3–inflammasome activation and improves learning and memory in chemically aged mice, while pairing the EZH2 blocker GSK126 with DNMT inhibition reduces H3K27me3 accumulation, rescues hippocampal CA1 neurons after ischemia, and normalizes spatial memory.[225] Systemically administered HDAC1/2 inhibitors have likewise proved versatile: a two-week course in aged mice reset transcriptional aging signatures in liver, kidney, heart, and brain; reduced sterile inflammation; and improved muscle strength without overt toxicity.[226]

6.3. CRISPR-mediated targeted epigenetic reprogramming

Clustered regularly interspaced short palindromic repeats (CRISPR)-mediated targeted epigenetic reprogramming repurposes nuclease-dead CRISPR-associated protein 9 (dCas9) as a programmable landing pad for chromatin-modifying enzymes, allowing researchers to add, erase, or exchange specific epigenetic marks at virtually any genomic site without creating double-strand breaks. Pioneering

work by Hilton *et al.*[227] fused the acetyltransferase core of p300 to dCas9, showing that a single-guide RNA could deposit H3K27ac at promoters or enhancers and robustly activate otherwise silent genes. Complementary studies soon demonstrated the converse operation: Liu *et al.*[228] and Vojta *et al.*[229] attached the catalytic domain of TET1 to dCas9, achieving base-resolution DNA demethylation and sustained gene activation in human cells and pluripotent stem cells.

Additional modularity was introduced with dCas9 fusions to the Krüppel-associated box (KRAB) repressor, G9a, or the EZH2 methyltransferase domain, enabling locus-specific installation of H3K9me3 or H3K27me3 and long-term silencing.[227] These platforms collectively established that transcriptional states can be dialed up or down with single-base precision, and that "epigenetic edits" can remain mitotically stable long after the editor has disappeared from the nucleus. Multi-guide strategies have since scaled the approach to dozens of loci at once, and orthogonal Cas proteins now permit simultaneous writing of activating and repressive marks in the same cell, giving researchers granular control over promoter-enhancer hierarchies.

Therapeutic translation is proceeding rapidly. In the nervous system, AAV-packaged dCas9–KRAB was delivered to the mouse nucleus accumbent, selectively silencing cocaine-inducible genes and normalizing addiction-like behaviour.[230] Nuñez *et al.*[231] encoded a "programmable transcriptional memory" circuit in which dCas9 recruits KRAB and an Ezh2 fragment, thereby achieving heritable silencing of oncogenic drivers in dividing cells.

Outside the brain, epigenome editors have corrected metabolic disease alleles, rejuvenated senescent fibroblasts, and, through multiplexed enhancer acetylation, enhanced regenerative programs in injured muscle. Off-target profiling with chromatin immunoprecipitation sequencing (ChIP-seq) and whole-genome bisulfite sequencing consistently reveals fewer collateral changes than small-molecule chromatin drugs, underscoring the technology's specificity. Remaining hurdles include delivering the bulky dCas9 cargo to hard-to-reach tissues, mitigating pre-existing Cas9 immunity, and developing switchable or self-limiting expression cassettes to avoid chronic exposure; split-Cas9 vectors, lipid nanoparticles, and inducible degron tags are active areas of optimization. Nevertheless, the rapid march from single-locus proof-of-concept to multi-organ disease rescue suggests that CRISPR epigenome editing may soon provide clinicians with a way to rewrite the aging or diseased epigenome—repairing the regulatory code rather than the DNA sequence itself.

6.4. Lineage reprogramming

Lineage reprogramming—also called direct conversion—bypasses pluripotency and steers one somatic cell type directly into another by forcing new transcription factor circuits or microRNA (miRNA)/small-molecule programs onto the existing chromatin landscape. Pioneering work in 2010 showed that a triad of pioneer transcription factors (achaete-scute family bHLH transcription factor 1 [Ascl1]–POU class 3 homeobox 2 [Brn2]–myelin transcription factor 1-like [Myt1l]) was sufficient to turn mouse fibroblasts into action potential-firing induced neurons within days, establishing the principle that a minimal transcription factor "cocktail" can override lineage barriers without cell division.[232]

This paradigm rapidly spread to other tissues: cardiac fibroblasts transduced with GMT (GATA-binding protein 4 [Gata4]–myocyte enhancer factor 2C [Mef2c]–T-box transcription factor 5 [Tbx5]) converted into contractile, sarcomere-positive induced cardiomyocytes (iCMs) in vitro and, more strikingly, in vivo after myocardial infarction, where newly reprogrammed iCMs coupled electrically with host myocardium and reduced scar burden.[233] Parallel hepatic studies identified hepatocyte nuclear factor 4 alpha (HNF4α) with FOXA1/2/3 as potent drivers of fibroblast-to-hepatocyte conversion, generating hepatocyte-like cells that secreted albumin, performed cytochrome P450 detoxification, and rescued a mouse model of lethal liver failure.[234,235]

A common mechanistic theme across these successes is the deployment of pioneer factors—transcription factors that can bind nucleosomal DNA and pry open silent chromatin—followed by lineage "settler" factors that stabilize cell-specific transcriptional networks. Chromatin-accessibility assays show that pioneer binding triggers rapid gain of H3K27ac and loss of H3K27me3 at lineage enhancers, while single-cell RNA-seq reveals deterministic trajectories rather than stochastic passage through a pluripotent intermediate. Importantly, additional layers, such as miRNAs (e.g., miR-1/133) and small molecules (e.g., TGF-β or Wnt inhibitors), synergize with transcription factors to enhance efficiency, partially by repressing residual donor-cell identity and by modulating pro-reprogramming signaling nodes.[236,237]

Translational momentum is accelerating as lineage reprogramming moves into adult tissues in situ. In the brain, cortical astrocytes have been reprogrammed into subtype-specific neurons via the delivery of Neurogenic differentiation 1 (NeuroD1) or Ascl1–Brn2–Myt1l, restoring synaptic transmission in cortical injury models and improving motor behavior after striatal stroke when combined with doxycycline-inducible lentiviral vectors.

Cardiac studies now combine transcription factor cocktails with miRNA mimics or epigenetic modulators to achieve double-digit percentage conversion of resident fibroblasts into iCMs, leading to measurable improvements in ejection fraction within weeks.[233] Chemical-only protocols are emerging: a seven-compound regimen (including CHIR99021, RepSox, and forskolin) converts mouse fibroblasts into hepatocyte-like cells without genomic integration, offering a clinically attractive, non-viral route.[238]

Beyond currently validated approaches, several geroprotective interventions are being actively evaluated in clinical trials, including mTOR inhibitors, metformin, NAD^+ precursors, senolytics, mitophagy activators, polyamines, and mesenchymal stem cell (MSC)-based therapies (Table 2).

7. Regenerative medicine

Unlike pharmacological interventions that modulate metabolic pathways to preserve systemic function, regenerative medicine aims to restore the structural integrity of aged organs. This distinction dictates a shift in clinical evaluation: whereas geroscience relies on composite morbidity endpoints, regenerative therapies must demonstrate lesion-specific functional recovery (e.g., retinal integration and myocardial repair). Furthermore, given the invasive nature of cell delivery and potential immunogenicity, these interventions carry a distinct risk profile that necessitates rigorous safety monitoring beyond that of standard small-molecule prophylactics.

7.1. Stem cell-based interventions

7.1.1. Mesenchymal stem cells

Mesenchymal stem cells are increasingly regarded not primarily as replacement cells but rather as "drug factories," whose paracrine secretome—soluble cytokines, growth factors, and EVs—orchestrates immune modulation, angiogenesis, and matrix repair. However, the anti-inflammatory profile of the secretome erodes as MSCs age: senescent cultures accumulate ROS, upregulate SASP factors, such as IL-6 and TNF-α, and release fewer, miRNA-poor EVs. Multiple rejuvenation strategies, therefore, target senescence drivers rather than forcing terminal differentiation. Rapamycin restores autophagic flux and lowers SA-β-gal staining in placental-MSC sheets while preserving immunomodulatory potency[239]; antioxidants such as N-acetyl-L-cysteine blunt ROS-mediated DNA damage and delay growth arrest.[240]

Extracellular vesicles exhibit even greater potency. For example, small EVs enriched for miR-146a downregulate Src/NF-κB signaling, thereby dampening endothelial senescence and fostering angiogenesis in vitro, while engineered MSC-EVs overexpressing the same miRNA attenuate microglial activation and cognitive decline in Alzheimer's disease mouse models.[241,242] In metabolic aging models, intravenous young-MSC EVs reduce hepatic steatosis and improve insulin sensitivity—changes attributed to miRNA cargo that represses NLRP3 and rescues mitochondrial dynamics.[243] These cell-free data underpin the "exogenous restitution of MSC intercellular

Table 2. Interventions under clinical investigation

Intervention	Mechanism	Outcomes in trials
Rapamycin	mTORC1 inhibition	Prevent ovarian aging; improve lean muscle mass; periodontal health
Metformin	AMPK activation; mitochondrial complex I inhibition	Delay the onset of composite chronic diseases
NAD^+ precursors	NAD^+ repletion; sirtuin activation	Six-minute walking distance; improve motor functions; restore blood NAD^+
Senolytics	Senescent cell elimination	Physical function; stabilize lung functions; reduce SASP biomarkers
Mitophagy activators	Mitochondrial quality control	Muscle strength; endurance; mitochondrial respiratory capacity
Polyamines	Autophagy induction	Memory performance scores; reduce systolic blood pressure
Mesenchymal stem cell therapy	Paracrine signaling	Reduce frailty index; 6-minute walk distance; reduce joint pain

Abbreviations: AMPK: AMP-activated protein kinase; NAD^+: Nicotinamide adenine dinucleotide; mTORC1: Mechanistic target of rapamycin complex 1; SASP: Senescence-associated secretory phenotype.

signaling" concept, now edging into the clinic.

The most advanced product, allogeneic Lomecel-B, has cleared a Phase IIb frailty trial (NCT03169231): although final peer-reviewed efficacy analyses are pending, the study design targets 120 adults aged ≥ 70 years, with endpoints that include 6-min walk distance, grip strength, and inflammatory biomarkers under a National Institutes of Health (NIH)-monitored Investigational New Drug (IND) application.[244] Parallel first-in-human studies are testing inhaled or intrathecal MSC-EVs in neurodegeneration; an ongoing Phase I/II protocol (NCT04753302) has reported preliminary reductions in cerebrospinal fluid IL-1β and small Mini-Mental State Examination (MMSE) improvements after three months, echoing preclinical neuroprotective findings.

Mechanistically, rejuvenated or exogenous EVs activate the AMP–AMPK–SIRT1–PGC-1α axis, enhance mitochondrial respiration, reduce mitochondrial DNA lesions, and re-establish lymphoid output from aged HSCs—system-wide effects that situate MSC-derived paracrine products as versatile, low-immunogenic gerotherapeutics. Key challenges remain: scaling EV manufacture to clinical volumes, standardizing potency assays for heterogeneous secretomes, and ensuring long-term oncologic safety when telomerase or miRNA cargoes are overexpressed.

7.1.2. Hematopoietic stem cell transplantation

Hematopoietic aging features reduced lymphoid output, myeloid bias, and inflammation—driven partly by intrinsic changes in HSCs. Classic mouse studies demonstrated that aged HSC pools contain expanded myeloid-biased clones and diminished lymphoid potential; when transplanted, old HSCs generally retain myeloid-skewed differentiation even in young recipients, indicating substantial cell-intrinsic programming. Conversely, strategies that alter the aged stem cell compartment can rejuvenate immune features: depleting myeloid-biased HSCs in old mice shifts hematopoiesis toward youthful lymphopoiesis and improves primary and recall responses to viral challenge. Together, these data support the concept that modifying the composition or quality of the HSC pool—rather than relying on a single "youthful" niche signal—can partially reset immune function in late life.[245,246]

Translation to the clinic has emphasized safer conditioning and long-term genomic stability. In older adults, reduced-intensity regimens enable donor chimerism with acceptable non-relapse mortality, though GVHD remains a relevant risk. Non-genotoxic conditioning with anti-CD117 (c-Kit) approaches—now in early clinical experience and preclinical optimization—offers a path to minimize organ toxicity while permitting engraftment.[247,248] Post-transplant biology warrants caution: donor-derived cells can show epigenetic age acceleration within years after HSC transplantation and undergo early telomere shortening relative to expected aging trajectories, consistent with replicative stress during engraftment.[249]

Adjunct strategies under investigation include rational remodeling of the aged HSC pool and telomere-supportive interventions; while telomerase activators extend telomeres and health span in mice, their role around HSC transplantation in humans remains unproven.[250] Overall, the evidence supports a measured approach combining gentler conditioning, targeted HSC pool modulation, and rigorous genomic monitoring to mitigate immunosenescence without excessive toxicity.

7.1.3. Induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) enable the production of patient-specific cells from accessible tissues while avoiding embryo use and, in select settings, have shown initial clinical feasibility. In ophthalmology, the Rikagaku Kenkyūsho (RIKEN)/Center for iPS Cell Research and Application (CiRA) group generated autologous iPSC-derived retinal pigment epithelium sheets and performed the first-in-human transplant for neovascular age-related macular degeneration; detailed case reporting and follow-up imaging supported graft survival and an acceptable safety profile, while a second planned autologous case was halted after detecting genomic alterations—illustrating both promise and the need for stringent quality control.[251]

To expand beyond autologous use, current approaches combine human leukocyte antigen (HLA) pathway editing with pro-survival signals (e.g., *B2M*/*CIITA* deletion combined with CD47 expression, or HLA-G/programmed death ligand 1 [PD-L1] expression) to enable long-term survival of allogeneic iPSC derivatives in immunocompetent models, including non-human primates.[252] Parallel advances in reprogramming include CRISPR activation of endogenous pluripotency loci and miRNA-based strategies, which increase reprogramming efficiency and improve fidelity relative to exogenous factor overexpression.[253]

Preclinical pipelines are maturing for age-related organ failure. In large-animal heart injury models, human pluripotent stem cell-derived cardiomyocytes engraft, electrically couple, and improve function, supporting dose-intensive, Good Manufacturing Practice (GMP)-oriented manufacturing efforts that target ~10^9 cells per patient.[254,255] In Parkinson's disease, allogeneic

iPSC-derived dopaminergic progenitors have now entered—and recently reported—Phase I/II evaluation, demonstrating graft survival and no tumor formation with signals consistent with dopamine production.[256] For neurodegeneration more broadly, human neural stem cell grafts in APP/PS1 mice improve cognition through trophic mechanisms, such as BDNF, motivating analogous iPSC–neuron programs now in preclinical development.[257]

Meanwhile, genomic integrity and maturation remain key hurdles: iPSC derivation can select for or introduce mutations/copy-number variations that affect differentiation and safety, underscoring the need for deep single-cell quality control and release testing.[258,259] Collectively, these data support a measured path forward: refined immune-evasion edits, high-fidelity reprogramming, and scalable GMP bioprocessing are moving iPSC therapies toward broader clinical testing, with efficacy to be proven in adequately powered, randomized trials.

7.2. Circulating youth factors

Heterochronic parabiosis—the surgical joining of young and old mice—showed that circulating cues can modulate aging phenotypes across tissues: in classic work, exposure of old C57BL/6 mice to a young circulation restored Notch signaling and enhanced the proliferation of aged muscle satellite cells, demonstrating that progenitor activity is systemically regulated.[260]

In the brain, aged mice exposed to young blood or given young plasma exhibited enhanced hippocampal synaptic plasticity and improved performance in contextual fear conditioning and spatial learning; mechanistically, this was driven by activation of the cAMP response element-binding protein (CREB) pathway rather than a single "youth factor."[261,262] Complementing these "pro-youth" findings, earlier work showed that factors enriched in old blood—most notably the C-C motif chemokine ligand 11 (CCL11)/eotaxin—suppress adult neurogenesis and impair memory, underscoring that both pro- and anti-neurogenic signals circulate with age.[262] The cardiovascular effects remain contentious. An influential study reported that the TGF-β family member growth differentiation factor 11 (GDF11) declines with age and, when restored, reverses age-related cardiac hypertrophy in mice, but subsequent studies argued that commonly used assays lacked specificity and that GDF11 actually increases with age and inhibits skeletal-muscle regeneration; neutral commentaries and re-analyses highlight ongoing controversy rather than consensus.[263]

Transcending single-factor hypotheses, human umbilical cord plasma proteomics identified tissue-restricted candidates, such as tissue inhibitor of metalloproteinases 2 (TIMP2); systemic delivery of cord plasma (rich in TIMP2) rejuvenated hippocampal plasticity and improved memory in aged mice, emphasizing that different organs may respond to distinct circulating programs.[264] Translation to humans is at an early stage: a small, randomized/open-label Phase I study in mild-to-moderate Alzheimer's disease tested four weekly infusions of young fresh-frozen plasma and found the regimen safe and feasible, but it was not powered for efficacy—any clinical signals were exploratory and require larger, blinded trials.[265] More recently, attention has turned to plasma fractions such as small EVs. In mice, small EVs isolated from young plasma cross tissues and improve functional measures partly by enhancing mitochondrial energetics, and several groups report EV-mediated dampening of neuroinflammation (including NLRP3) in neurodegeneration models, although human trial data are not yet available.[266]

Finally, circulating metabolites may cooperate with proteins and EV cargo: the ketone body BHB functions as a signaling molecule that can influence inflammation and mitochondrial function, offering a plausible systemic mediator to test in conjunction with protein/EV interventions, but its role as a "youth factor" in parabiosis remains unproven.[267] Overall, the field supports a model in which composite, age-linked shifts in plasma proteins, EVs, and metabolites—rather than a single "silver bullet"—reshape tissue repair and neural plasticity; early human studies establish feasibility while definitive efficacy and dosing paradigms await rigorous randomized trials and precise biomarker-guided fractionation.

In contrast, a number of highly innovative interventions, such as partial reprogramming, senolytic vaccines, CAR-T cells, young plasma-derived factors, and FMT, remain largely preclinical and are summarized in Table 3.

8. Digital and AI-driven advances in anti-aging research

8.1. Integration of digital technologies in anti-aging strategies

Digital technologies have emerged as a foundational component of contemporary anti-aging strategies, enabling real-time biological monitoring. Wrist-worn photoplethysmography at the population scale shows that heart-rate variability declines with age across >8 million commercial-tracker users, illustrating the feasibility of passive, real-world monitoring.[268]

Speech captured remotely by smartphones is an emerging cognitive biomarker: AI systems analyzing

Table 3. Promising preclinical interventions

Intervention	Mechanism	Effects in animal models
Partial reprogramming	OSK/OSKM factors	Restore vision; reverse heart failure; extend lifespan in progeroid mice
Chemical reprogramming	Small molecule cocktails	Reverse transcriptomic age to youthful profiles in fibroblasts
CAR-T cells	Targeting uPAR or GPNMB antigens	Reverse liver fibrosis; reduce senescent cell burden in adipose tissue
Senolytic vaccines	Immunization against the GPNMB peptide	Reduce senescent cells; improve metabolism and motor function
Young plasma/factors	Systemic rejuvenation	Enhance hippocampal plasticity; improve memory and mitochondrial energetics
Fecal transplant	Microbiome remodeling	Rejuvenate hematopoietic stem cells; reduce frailty and myeloid bias
Chloroquine	Proteasome inhibition; autophagy modulation	Extend median and maximum lifespan in middle-aged mice

Abbreviations: CAR-T: Chimeric antigen receptor T cells; GPNMB: Glycoprotein nonmetastatic melanoma protein B; OSK: Octamer-binding transcription factor 4, SRY-box transcription factor 2, and Krüppel-like factor 4; OSKM: OSK and c-Myc; uPAR: Urokinase-type plasminogen activator receptor.

brief, scripted story-recall tasks discriminated amnestic mild cognitive impairment/mild Alzheimer's disease from amyloid-β positivity, and independent work links voice features to early cognitive impairment and AD biology, supporting the potential for remote screening rather than definitive diagnosis.[269,270] Computer vision applied to the eye provides another window on aging: the "retinal age gap" derived from fundus images predicts all-cause mortality risk in the United Kingdom Biobank, and retinal-image aging clocks show short-timescale sensitivity and genetic correlates, highlighting the retina as a practical biological-age sensor.[271] Sleep, a modifiable behavior with broad geroscience relevance, links digital readouts to molecular clocks: in a prospective pilot study, shorter and more irregular sleep was associated with accelerated DNA-methylation aging, motivating larger wearable-anchored studies.[272] Foundational work on "digital phenotyping" frames how to integrate multimodal streams from phones and wearables responsibly for health monitoring—issues of validation, bias, and privacy remain central as these tools move toward trials and care.[273] While small interventions suggest that lifestyle programs can modestly reduce epigenetic age, rigorous randomized evidence linking closed-loop, sensor-driven guidance to durable changes in biological-age clocks is still limited.[270]

Overall, converging evidence indicates that scalable, passively collected signals—cardiovascular dynamics, speech, retinal images, and sleep timing—can complement molecular biomarkers to stratify risk, enable remote follow-up, and generate actionable endpoints for geroscience trials, provided that models are clinically validated and embedded within ethical, privacy-preserving frameworks.

8.2. AI-powered biological aging clocks

Artificial intelligence-enabled "aging clocks" increasingly integrate molecular and phenotypic data to quantify biological aging beyond chronology. The foundational DNA methylation (DNAm) "epigenetic clock" showed that a 353-CpG signature estimates age across many human tissues with median errors of a few years, establishing methylomics as a robust substrate for biological age estimation.[274] Second-generation DNAm clocks link age to morbidity: DNAm PhenoAge, trained against a composite of clinical biomarkers, predicts all-cause mortality, functional decline, and disease risk better than earlier clocks.[275] DNAm GrimAge further incorporates DNAm surrogates of smoking pack-years and plasma proteins (e.g., cystatin C, TIMP-1), and its age-acceleration metric is strongly associated with time-to-death and incident coronary heart disease across large cohorts; an updated GrimAge v2 improves mortality and morbidity prediction.[276]

Beyond methylation, deep learning clocks trained on routine blood biochemistry provide practical, population-level inference of biological age and health risks, with models validated across multiple cohorts. Resolution is also advancing: single-cell epigenetic clocks (e.g., scAge, scEpiAge) infer age at the cellular level in mice and humans, enabling the mapping of cellular heterogeneity in aging tissues.[277] Image-based models are emerging in clinical contexts; notably, FaceAge—trained on facial photographs—adds prognostic value for cancer survival when combined with clinical covariates, underscoring that externally visible features can encode systemic aging signals.[278] Collectively, these clocks can stratify participants for geroscience trials, monitor responses to lifestyle or

pharmacologic interventions, and probe mechanisms that couple exposures (e.g., smoking) to accelerated biological aging—moving from descriptive biomarkers toward decision-support tools for extending healthspan.

However, a critical translational gap remains: these molecular clocks have not yet been validated by regulatory bodies (e.g., the FDA) as surrogate endpoints for clinical benefit. Consequently, their utility is currently limited to trial enrichment and hypothesis generation, rather than serving as standalone evidence of therapeutic efficacy.

8.3. AI-accelerated discovery of geroprotectors

Artificial intelligence is transforming geroprotector discovery by expediting hit identification, molecular optimization, and mechanism elucidation. Deep learning models—including graph neural networks, generative algorithms, and reinforcement learning—now enable virtual screening of ultra-large chemical libraries and the prediction of pharmacologically active compounds targeting aging mechanisms.[279,280]

In silico pioneering work demonstrated that AI-generated molecules could target senescence pathways; for example, their platform identified novel discoidin domain receptor 1 (DDR1) inhibitors with antifibrotic and pro-regenerative properties in aged tissues. AI-powered phenotypic screening and transcriptomic profiling by Recursion Pharmaceuticals and others have prioritized compounds modulating aging-relevant pathways, such as mTOR and sirtuins, and have accelerated preclinical pipelines.[281]

Moreover, AI-driven polypharmacology platforms facilitate rational combination therapies for complex aging phenotypes—for example, synergistic effects of senolytics and NAD^+ boosters are supported by multi-omics network analyses, though clinical translation is ongoing.[282] Molecular dynamics and AI-enabled target deconvolution have improved lead compound optimization and reduced preclinical cycle times, as exemplified by recent advances in SIRT1 and mTOR modulator design.[283] Several AI-discovered or AI-optimized geroprotectors are now in early-phase trials for age-related diseases, reflecting the field's rapid progress and translational potential.

9. Current challenges in translating anti-aging strategies

9.1. Complexity and heterogeneity of aging

Aging is a multifactorial, networked process spanning genomic instability, epigenetic change, proteostasis loss, mitochondrial dysfunction, cellular senescence, and altered intercellular communication—complicating translation from models to the clinic. Inter-individual variability further blurs signals: apolipoprotein E (APOE) ε4 is associated with a greater risk of cognitive decline and accelerated brain-aging phenotypes, though effects vary by cohort.[284,285] Environmental exposures can also shift biological-age readouts; multiple studies link air pollution (and related stressors) to DNAm age acceleration, with heterogeneity across clocks and populations.[286,287] Epigenetic clocks robustly track chronology and predict morbidity, yet their performance differs by ancestry and social factors, underscoring the need for calibration across diverse cohorts.[288] Early human senolytic trials (D+Q) demonstrated feasibility and mixed, small-sample functional signals—insufficient for broad efficacy claims.[289,290] Functional measures, such as handgrip strength, predict adverse outcomes and mortality but lack disease specificity, so they complement rather than replace molecular biomarkers in trial design.

9.2. Limitations of preclinical models

Preclinical models illuminate mechanisms but only partially mirror human aging. Mice differ immunologically (leukocyte subsets, receptors, cytokine pathways) and in lifespan/history, complicating translation; even genome-wide responses to inflammatory stress can diverge from humans, though this point is debated.[291,292] Non-human primates develop age-related amyloid-β pathology yet incompletely recapitulate full Alzheimer's disease-type lesions and progression. Standard laboratory housing and limited environmental stressors further narrow phenotypes versus human exposures.[293] "Humanized" mice improve immune readouts but still lack fully human lymphoid architecture and antibody responses.[294] Human organoids provide human genetics and cell types but generally lack vasculature, immune components, and systemic crosstalk, limiting maturation and inter-organ aging studies.[295] Furthermore, translation is challenged by the phenomenon of "evolutionary diminishing returns." As highlighted in recent analyses, the magnitude of lifespan extension from specific interventions tends to shrink as organismal complexity increases—from dramatic effects in lower invertebrates to modest gains in mammals.[296] This "complexity penalty" suggests that human homeostatic networks possess greater redundancy, buffering against single-target interventions and necessitating multimodal approaches.

9.3. Clinical trial design and regulatory barriers

Clinical translation is constrained by trial design and regulation: because regulators approve therapies for defined diseases rather than "aging" per se, geroscience trials typically target single indications or pre-specified

composites.[297] The TAME framework illustrates a feasible path—yet such endpoints raise costs and complexity.[298] Selecting outcomes remains challenging; recent consensus and methods papers emphasize aligning endpoints (e.g., incident multimorbidity, function, resilience) with mechanisms and feasibility.[299] Biomarkers can help, but epigenetic clocks—while predictive of morbidity—require calibration across ancestries, tissues, and laboratory platforms before routine regulatory use.[300] However, it is critical to distinguish this from the regulatory pathway for regenerative medicine, which typically targets established pathologies and necessitates mandatory structural and functional endpoints (e.g., visual acuity or ejection fraction) rather than preventative risk reduction. Future trial designs must adopt a "bridging strategy" that validates molecular biomarkers against mandatory functional outcomes. This is particularly critical for regenerative therapies, where molecular reversal is meaningless without demonstrated structural repair and functional recovery (e.g., improved grip strength or organ-specific metrics). Overall, geroscience trials must balance disease-based indications with composite outcomes and standardized biomarker strategies to gain regulatory traction.

9.4. Safety and ethical concerns

Anti-aging interventions raise distinct safety, equity, and privacy concerns. Pluripotent stem cell-derived products carry tumorigenicity risk, requiring stringent screening and release testing. Senescence has context-dependent benefits; therefore, indiscriminate senolysis could theoretically impair healing; early human senolytic trials are small and primarily establish feasibility.[289] Geroscience trial frameworks also flag access and equity issues for future therapies.[301] Meanwhile, wearable-enabled monitoring introduces privacy risks for older adults and health systems, underscoring the need for robust data-protection policies.[302]

10. Future perspectives

10.1. Integrative and personalized strategies

Because aging arises from interconnected hallmarks, most evidence supports multimodal rather than single-agent approaches. In mice, clearing senescent cells with senolytics improves physical function and healthspan[303], while strategies that raise NAD^+—such as inhibiting the age-related NADase CD38 or administering NAD^+ precursors—ameliorate metabolic and mitochondrial decline.[304] Together, these data motivate combination testing, though rigorous human efficacy evidence remains limited. In parallel, the gut microbiome shapes systemic inflammation and barrier integrity, with implications for responses to geroscience agents, supporting trials that pair host-targeted interventions with microbiome modulation.[305,306] For personalization, integrative models that fuse multi-omics (genome, epigenome, proteome/microbiome) with clinical data are being developed to stratify risk and align mechanisms with endpoints—the core vision of "precision geromedicine"—but require external validation and standardized biomarkers before guiding care.[2] Overall, an adaptive framework that combines senescence-targeting therapies, metabolic/NAD^+ support, lifestyle and microbiome interventions, and validated biomarkers/AI risk models is the most plausible path away from "one-size-fits-all" toward patient-centric geroscience.

10.2. Precision geroscience

Precision geroscience aims to tailor geroprotective strategies to an individual's biology by integrating multi-omics with clinically tractable endpoints. Single-cell and spatial profiling have begun to map tissue-specific aging programs and senescent niches[307]—for example, atlases that chart conserved inflammatory/fibrotic features of senescent cells across tissues and age-related senescence in the kidney[308]—informing concepts for tissue-targeted delivery (e.g., receptor-guided nanoparticles and liposomal senolytics), though these remain preclinical. Microbiome-informed interventions (including synthetic microbial communities) are being developed to modulate metabolism and inflammation, with human translation in progress. Telomere-directed approaches illustrate the spectrum from exploratory RCTs of small-molecule activators to gene-therapy studies in mice; clinical utility requires larger, controlled trials. Finally, multimodal machine learning frameworks that fuse genomics, epigenomics, proteomics, metabolomics, and clinical data are emerging to guide mechanism-aligned interventions, but need external validation and harmonized biomarkers before informing care pathways.

10.3. Advanced AI and digital health integration

Virtual, dynamically updated models of an individual are proposed to personalize intervention testing and trial design by integrating longitudinal clinical and multi-omic data, though clinical deployment is early and requires rigorous validation. In parallel, AI models applied to digital biomarkers from wearables (gait, activity patterns, cardiorespiratory signals) can flag emerging frailty and functional decline, supporting proactive care pathways.[309,310] Cytokine-sensing wearables and sweat biosensors illustrate the feasibility of tracking inflammation non-invasively, but translation into routine geriatrics requires standardization and outcome-linked studies.[311] For biological-age readouts, DunedinPACE and related DNA methylation

measures show high test–retest reliability and predict morbidity, disability, and mortality; they are promising for risk stratification and evaluating intervention effects, provided that platforms and cohorts are harmonized.[312] Taken together, AI-enabled digital twins plus validated digital/epigenetic biomarkers could optimize preclinical prioritization, enrich clinical trials, and individualize care—if supported by external validation, interoperable data pipelines, and robust privacy/ethics frameworks.

10.4. Translational multimodal clinical trials

Designing innovative, multimodal clinical trials is critical to accelerating the validation of anti-aging interventions. Over the past five years, anti-aging clinical trials have initially explored such innovative design ideas, with key information including their intervention models, endpoint settings, and design types summarized in Table 4. To validate geroscience interventions, trials should test

Table 4. Summary of clinical trials on anti-aging interventions in the past five years

Clinical trial no.	Interventions	Populations	Primary outcome
NCT05835999	Everolimus 0.5 mg/day or 5 mg/week vs. placebo	Adults 55–80 years	Safety and change in healthy aging biomarkers/phenotypes
NCT05237687	Low-dose sirolimus vs. placebo	Older adults	Functional decline prevention: Gait speed, grip strength, balance, body composition
NCT04742777	Sirolimus (rapamycin) vs. placebo	Older adults (70–95 years)	Muscle/Physical function metrics
NCT04488601	Intermittent low-dose rapamycin vs. placebo; 48 weeks, decentralized RCT	Adults without major comorbidity	Safety, body composition (DXA fat/lean mass), and healthspan proxies
ACTRN12624000790549	Rapamycin 6 mg/week + standardized exercise vs. placebo + exercise; 13 weeks	Adults (older), single-center, double-blind	Muscle strength/endurance adaptations with exercise training
NCT05836025	Low-dose rapamycin vs. placebo	Women at risk of ovarian aging	Markers of ovarian reserve/ovarian aging
NCT06208527	NR vs. placebo; ~52 weeks	Frail older adults; primary outcome: Gait speed	Functional decline, safety, and cognitive/biomarker exploratory
NCT04691986	NR vs. placebo; ~3 months	Healthy older adults (65–85 years)	Functional capacity
NCT05500170	NR vs. placebo	Older adults	Sleep quality and cognition outcomes
NCT06005350	NR 1,000 mg/day for 10 days	Adults	Extracellular NAD^+ in plasma
NCT06465602	Nicotinamide vs. placebo	Older adults at risk of disability	Physical performance measures
NCT05517122	Oral NAD^+ precursors vs. placebo	Adults, including older adult group	Blood NAD^+ levels and safety
NCT05698771	NR pharmacokinetic study	Adults	Blood & brain pharmacokinetics of NR/NAD
NCT05882214	NMN vs. placebo	Healthy adults	Metabolic response to alcohol
NCT04221750	Lifestyle + Metformin vs. Lifestyle + Placebo (~6 months)	Older veterans with obesity, community-dwelling	Frailty/Physical function, weight/body composition
NCT06185179	Metformin during 14-day recovery vs. placebo	Healthy older participants	Muscle recovery/strength after standardized stress
NCT03861767	Perioperative metformin (500–1,500 mg sustained release) vs. placebo	Adults undergoing major elective surgery	Hospital-free days at 90 days, perioperative resilience/frailty endpoints
NCT02570672	Metformin vs. placebo for 2 years	High-risk older adults ≥65 years	Prevention of frailty progression
NCT05786521	GLP-1 RA vs. standard care	Adults ≥65 with prediabetes or well-controlled T2D; overweight/obese	Physical function, DXA, aging biomarkers
NCT05302596	GLP-1 RA weekly semaglutide	Older adults with obesity	Body composition, weight, function

(*Cont'd...*)

Table 4. (*Continued*)

Clinical trial no.	Interventions	Populations	Primary outcome
NCT06811324	Open-label tirzepatide (GIP/GLP-1)	Older adults with obesity	Muscle mass/strength and vascular health
NCT05975528	SGLT2 inhibitor regimen	Adults with T2D; aging comorbidities/frailty focus	Frailty/Aging-related comorbidity outcomes
NCT05735886	Urolithin A vs. placebo (4–12 weeks)	Healthy adults (middle-aged/older)	Immune and mitochondrial function markers
NCT05921266	Urolithin A vs. placebo (8–12 weeks)	Middle-aged adults with metabolic syndrome features	Metabolic + Muscle/mitochondrial endpoints
NCT06274749	Urolithin A: Mitophagy activator vs. placebo	Adults ≥55 years	Glucose control and mitochondrial function
NCT05814705	Urolithin A + protein supplement vs. protein alone	Adults in the disuse/de-training model	Muscle function/recovery
NCT05459961	Oral spermidine supplementation	Adults	Metabolic response and polyamine profile
NCT07035626	Spermidine vs. placebo	Adults/Older adults	Prevention of cognitive decline
NCT06445569	Autophagy activator: KH-1	Healthy volunteers	Safety, pharmacokinetics/pharmacodynamics, and autophagy induction signals
NCT06025071	Colchicine: 0.5 mg qd vs. no intervention	Older adults 60–80 years with high hs-CRP, multivessel CAD	Inflammatory biomarkers and ischemic events
NCT06837623	Colchicine: low-dose anti-inflammatory therapy in HFpEF	Predominantly older HFpEF population	Inflammation load and cardiac function/exercise capacity
NCT05706389	Ca-AKG sustained-release vs. placebo	Middle-aged adults	Epigenetic age and inflammatory markers
NCT07114536	Ca-AKG sustained-release, Phase II vs. placebo	Healthy adults 40–60 years with elevated biological age	DNA methylation age reduction, inflammatory/metabolic exploratory endpoints
NCT05128331	Oral spermidine vs. placebo (includes exercise substudy)	Adults/Older adults	Metabolic, neural, cardiovascular markers and training response
NCT06186102	Spermidine: double-blinded RCT vs. placebo	Older adults (≥65 years) with coronary heart disease	Cardiometabolic risk, cognition, physical activity, QoL
NCT05422885	Dasatinib + Quercetin: intermittent dosing vs. usual care	Older adults	Safety, feasibility, aging biomarker signals
NCT06431932	Fisetin: intermittent oral dosing vs. placebo	Healthy volunteers & older multimorbid adults	Inflammation, SASP/senescence, aging biomarker panels
NCT06133634	Fisetin: intermittent dosing	Older adults	Vascular endothelial function, inflammatory markers
NCT06113016	Fisetin + structured exercise vs. exercise alone	Breast cancer survivors (≥55 years)	Prevention of frailty, physical function outcomes
NCT07195318	100 mg Fisetin daily vs. placebo	Adults focused on healthy aging	Anti-inflammatory effects, overall health metrics, safety
NCT06399809	Fisetin: intermittent dosing vs. placebo	Older adults with mobility impairment	Decrease senescent cell abundance, improve mobility
NCT06011798	UBX1325: repeat intravitreal dosing	Adults with diabetic macular edema	Vision outcomes (BCVA), durability vs. anti-VEGF
NCT04857996	UBX1325: Phase IIa proof-of-concept vs. sham	Adults with diabetic macular edema	Safety/pharmacokinetics, biological activity, vision function
NCT04537884	UBX1325: single intravitreal dose (Phase I)	Adults with diabetic macular edema	Safety/tolerability, pharmacokinetics

(*Cont'd...*)

Table 4. (***Continued***)

Clinical trial no.	Interventions	Populations	Primary outcome
NCT05976217	Venetoclax: oral	Idiopathic pulmonary fibrosis	Safety, antifibrotic/functional signals in aging-linked lung disease
NCT05698654	FMD ± Longevity diet: RCT	Adults	Body composition and aging-related health metrics
NCT06508255	TRE protocols with different eating windows	Adults/Older adults	Decision-making, brain activity
NCT05832086	Intermittent fasting using FMD (5 days/ month × 6 months) vs. usual diet	Adults receiving immunotherapy	Metabolic/Immune biomarker responses
NCT05732935	TRE: ~16-h fasting/day × 24 weeks vs. control	Adults at increased aging risk (includes cognition/fitness/ sleep assessments)	Feasibility, cognition, physical function, sleep, and metabolic markers
NCT05870982	Early TRE vs. Late TRE vs. Daily CR (52-week parallel RCT)	Adults with overweight/ obesity	Metabolic health and body composition over 1 year
NCT06019195	TRE adherence/Intermittent fasting protocol for brain health study	Adults, brain health cohort	Endothelial function, neurovascular coupling, cognition
NCT05997316	TRE (12-week feasibility)	Individuals with MCI	Feasibility/Acceptability, metabolic & psychological outcomes, cognition
NCT06429124	16:8 TRE (≥5 days/week, 12 weeks)	AD participants	Cognitive and metabolic outcomes, feasibility
NCT04962464	FMD + Calorie-mimetic supplement vs. Control (~3 months)	Healthy adults	Epigenetic aging (DNA methylation), metabolic markers
NCT06701968	Healthy Nordic diet vs. Habitual diet	Adults with subclinical atherosclerosis	Plaque volume, CAC, vascular inflammation
NCT05975723	MIND diet: Cluster-randomized, 12 months	Adults with MCI	Cognitive function over 1 year
NCT05921084	MIND diet + Lifestyle coaching vs. Usual care, 6 months	Adults with mild stroke/ vascular cognitive risk	Global cognition, executive function
NCT05236712	Mediterranean diet mHealth program (pilot RCT)	Older adults with frailty	Diet adherence, functional/healthspan signals
NCT06871384	Mediterranean diet + Non-alcoholic red wine vs. Control	Older adults at risk of cognitive and locomotor decline	Cognition and mobility outcomes
NCT06800027	SALSA: Tailored plant-forward healthy diet + Socialization (community setting)	Community-dwelling older adults	Diet quality, social function, health outcomes
NCT06055894	Plant-based diet vs. Dietary supplements: butyrate change study	Adults (including older adults)	Gut-derived SCFA as a metabolic/immune aging biomarker
NCT05777746	Online plant-based diet program vs. Usual care (12 weeks)	Adults with T2D	CVD risk markers (HbA1c, LDL-C, BP) relevant to healthy aging
NCT07220499	Whole-food plant-based diet to improve outcomes in older adults	Older adults and adults	All-cause outcomes, metabolic health
NCT05593939	Aerobic exercise: 150–300 min/week vs. TRE vs. NR vs. Control	Healthy older adults (≥65 years)	Aging biomarkers, cardiometabolic health
NCT06094413	Multicomponent training–community program	Older adults	Patient-reported outcomes, performance measures
NCT06845748	Structured exercise program	Older adults	Sarcopenia metrics: muscle mass/strength and physical performance
NCT04711785	Multicomponent physical training + Social/emotional support	Frail/Pre-frail older adults	Frailty index, cognition, mood, social connectedness

(*Cont'd...*)

Table 4. (***Continued***)

Clinical trial no.	Interventions	Populations	Primary outcome
NCT06940037	Supervised resistance training	Older adults	Molecular mechanisms underlying inter-individual variability in resistance training
NCT07048847	Supervised aerobic exercise	Adults (middle-aged/older)	Adipokines, myokines
NCT06809257	Aerobic exercise protocol	Adults with prediabetes	miR-126 expression dynamics
NCT05266976	Endurance vs. Resistance vs. Combined	Older veterans	Bone metabolism biomarkers (P1NP, CTX, osteocalcin, etc.)
NCT05053282	Endurance-trained cohort vs. Controls	Middle-aged to older adults (men)	Circadian rhythm, immune signatures, skeletal muscle aging pathways
NCT07212829	Structured exercise + Transcranial direct current stimulation vs. Exercise alone	Adults	BDNF expression, DNA methylation
NCT06732934	Multicomponent exercise program	Older adults ≥60 years	Telomere/Telomerase, stress-inflammation axes
NCT04103593	Center-based and remote exercise interventions	Older adults/Special cohorts	Blood aging biomarkers, inflammatory transcriptomic/epigenetic indicators
NCT06953648	HIIT: Remotely monitored, mobile-health–supported	Older adults	Cardiorespiratory fitness, physical function, remote scalability signals
NCT05542758	HIIT (total body HIIT; 12-week program)	Older adults	Aerobic capacity & functional performance, safety/tolerability in aging cohort
NCT05220670	HIIT intervals	Older adults at risk of sarcopenia	Sarcopenia metrics, oral microbiota shifts
NCT07035327	Resistance training + Cognitive dual-task vs. Conventional resistance (10 weeks)	Frail older adults with chronic musculoskeletal pain	Frailty status, cognition, pain, QoL
NCT07074639	Exergame (personalized cognitive-motor) vs. Otago (12 weeks)	Frail older adults	Physical & cognitive fall-risk factors, falls, QoL, activity
NCT05725668	Dual-task Tai Ji Quan vs. Standard Tai Ji Quan vs. Stretching	Older adults with MCI (65–95 yrs)	Falls incidence, cognition, dual-task gait
NCT05835297	Multicomponent exercise (strength + balance + endurance), nursing homes	Institutionalized ≥65 years	Falls prevention, SPPB & lower-limb function, feasibility in LTCFs
NCT06321263	Inspiratory muscle training vs. Peripheral muscle training + Aerobic	Older adults	Muscle strength, physical performance
NCT06882720	Otago + Strength training	Older adults with pre-frailty/ sarcopenia	Balance, strength, fall risk, QoL
NCT06650345	Aerobic exercise (cognitive aging focus)	Middle-aged and older adults	Cognitive function outcomes
NCT05513547	Daytime natural light exposure prescription + Physical activity increases	Adults	DLMO phase advance, circadian alignment, sleep/activity metrics
NCT05177055	Gradually advanced bright light therapy ± evening melatonin	Adults with DSWPD	Objective circadian phase correction, sleep quality, daytime function
NCT05226585	CBT-I	Middle-aged/Older adults (50–65 years)	Insomnia severity, daytime function, cognitive/emotional regulation pathways
NCT06329479	Multimodal non-pharmacological circadian intervention	Adults with circadian disruption	Rest-activity rhythm recovery, sleep, QoL
NCT02960776	Chronic mild sleep restriction	Young & older cohorts (2024 amendment adds 55–75 years with imaging/ cognition)	Cognitive function, brain atrophy/WMH, hormonal/metabolic mediators
NCT06267521	Closed-loop sleep-phase brain stimulation + Brief daily meditation	Adults	Sleep neurophysiology, cognition & emotional outcomes

(*Cont'd...*)

Table 4. (***Continued***)

Clinical trial no.	Interventions	Populations	Primary outcome
NCT04986904	Digital CBT-I: Effectiveness & implementation study	Adults with insomnia	Sleep outcomes, implementation signals relevant to population aging
NCT06696378	Melatonin supplementation	Older women (60–73 years)	Sleep/circadian metrics, cardiometabolic & body composition outcomes
NCT06583395	Intensive meditation retreat/mindfulness-based stress reduction	Adults (≥21 years) with chronic stress exposure	Epigenetic aging clocks, multi-omics stress/inflammation, physiological & emotional markers
NCT02977819	18-month meditation training vs. Active/wait-list controls	Healthy older adults (65–84 years)	Psychological well-being, brain structure/perfusion, cognition
NCT07033520	Online mindfulness-based cognitive therapy for stress and pain	Adults with elevated stress/pain	Stress-related symptom burden, physiological stress indicators
NCT05240495	Work-focused vs. Generic internet-based CBT for stress-related disorders	Adults with stress-related disorders	Functional health & stress outcomes, background notes, allostatic dysregulation
NCT04739696	Virtual stress-management psychoeducation for employed caregivers	Adult caregivers	Perceived stress, QoL; caregiver-related healthspan signals
NCT06864260	Environment/Behavioral prevention program targeting chronic stress & exposures	Adults	Allostatic load panel and stress biomarkers
NCT05422638	Race-Based Stress Trauma and Empowerment program	Adults with race-based chronic stress/trauma	Psychological health, protocol describes linkage to allostatic load
NCT05383690	Bright light therapy (morning) + Blue-light blocking (evening)	Adolescents/Young adults, mechanism relevant to circadian alignment	Circadian phase and sleep–wake alignment, alertness/cognitive outcomes
NCT06252571	Chronobiological treatment combining evening melatonin + Morning bright light	Adults with DSWPD	Circadian alignment, sleep timing/function
NCT06356337	Light exposure tracker device to improve circadian health	Adults	Circadian alignment metrics and sleep outcomes
NCT05382923	Treatments for simulated jet lag: Circadian adjustment comparison	Healthy adults	Circadian adjustment speed and alignment, performance/sleep outcomes
NCT05616819	Morning light exposure therapy (large-scale effectiveness)	Adults with misaligned sleep–wake patterns	Sleep–wake patterns improvement, circadian alignment
NCT07203196	Personalized circadian rhythm optimization plan	Adults	Circadian health composite, lifestyle-based alignment
NCT07207044	Factorial lifestyle synergy: Exercise training + TRF (16:8); arms: Exercise, TRF +TRF, control	Healthy older adults ≥65 years	Biological age, aging biomarker panel, metabolic/functional outcomes (52 weeks)
NCT03688126	Multidomain lifestyle: MIND-style diet + Moderate-to-vigorous physical exercise + Cognitive training/challenge + Social engagement + Cardiometabolic risk monitoring; Structured vs. Self-guided	Older adults at risk for cognitive decline	Global cognition composite, adherence/safety, healthspan-related risk factors
NCT05256199	FINGER-NL multidomain: Physical activity + Cognitive training + Cardiovascular risk management + Nutritional counseling + Sleep counseling + Stress management + Social activities	Dutch older adults 60–79 years at risk for cognitive decline	Change in cognition over 24 months, secondary: lifestyle/sleep/stress/social metrics
NCT05007353	SINGER multidomain: Dietary advice + Supervised exercise + Structured cognitive training + Vascular risk factor management; Structured vs. Self-guided	Older adults (60–80 years) at risk of dementia/frailty	Cognitive decline and physical frailty prevention, multidomain adherence/feasibility

(*Cont'd...*)

Table 4. (*Continued*)

Clinical trial no.	Interventions	Populations	Primary outcome
NCT04840030	CITA GO-ON: Multi-domain dementia-prevention strategies	Cognitively frail older adults	Global cognition, frailty/functional indices, prevention signals
NCT06492967	LatAm-FINGERS: Region-adapted multidomain lifestyle	Older adults at risk (Latin America network)	Cognitive composite and lifestyle risk reduction
NCT05886114	Multi-domain lifestyle intervention among aged adults	Older adults	Cognitive and functional outcomes, healthy aging indicators
NCT05735353	Sleep + Diet + Exercise combined lifestyle optimization	Older adults	Sleep quality/timing, cognitive & physical function, cardiometabolic risk markers
NCT05109169	MET-FINGER: Precision prevention combining FINGER 2.0 multidomain lifestyle + Metformin vs. Lifestyle alone	Older adults at risk for cognitive impairment/ disability	Cognitive function, disability, interaction on prevention
NCT06767410	Multi-domain healthy-aging program: Group physical activity + Cognitive activities + Social/choir practice	Older adults (healthy aging)	BDNF and functional outcomes
NCT06556706	Postbiotic: Urolithin A	Frail older adults (≥65 years)	Skeletal muscle mitochondrial quality/ function, strength & endurance
NCT05348694	Synbiotic: Probiotic blend + Prebiotic inulin	Postmenopausal women	Bone density/Bone health markers
NCT07073781	Probiotic: Lab4P consortium	Older adults	Cognition, metabolic & immune markers
NCT06670807	Probiotic: Lactobacillus plantarum DR7 formulation	MCI	Cognitive outcomes, gut–brain axis biomarkers
NCT05145881	Probiotic: *Bifidobacterium* + *Lactobacillus*	AD	Cognitive scales
NCT05943925	Probiotic composite	Older adults ≥60 years with AD/PD/DLB/FTD/MCI spectrum	Cognition/function and gut microbiome
NCT06834984	Synbiotic (Pre + Pro + Post): Ritual synbiotic	Adults	Gut health composite metrics
NCT05892627	Postbiotic: Heat-treated *Lactobacillus paracasei*	Middle-aged/Older adults (>50 years)	Cognitive task performance, EEG neurophysiology
NCT05013060	Postbiotic + Probiotic: Sodium butyrate + Probiotic blend	Adults	Gut symptoms, inflammation & microbiota shifts
NCT07110896	Postbiotic: Inactivated *Lactobacillus*	Adults	Immune/gut health outcomes
NCT05348642	Postbiotic: Pasteurized *Akkermansia muciniphila*	Adults with IBS	IBS symptom improvement, gut barrier/ inflammation
NCT05900609	High-fiber diet vs. Fermented-foods diet vs. Control	Adults	Gut microbiome diversity/composition, inflammation, lifestyle adherence
NCT05931562	Dietary intervention targeting the gut–brain axis	Healthy adults	Cognition & stress with linked gut microbiome changes
NCT06873204	Soluble arabinoxylan vs. Rice bran fiber vs. Control	Adults	Microbiome composition/diversity, SCFAs
NCT05195970	Walnut inclusion in the habitual diet	Adults	Colonic health, gut microbiome, inflammation/metabolic markers
NCT05917392	Fermented vegetables ± Polyphenol ± *Lactobacillus rhamnosus* GG	Adults	Gut microbiome, DNA damage/ inflammation markers
NCT04976959	High-fiber nutritional supplementation on top of habitual diet	Adults with PD	Gut bacteriome/virome/mycobiome, GI function/constipation

(*Cont'd...*)

Table 4. (***Continued***)

Clinical trial no.	Interventions	Populations	Primary outcome
NCT05239845	Prebiotic-rich dietary fiber and the sleep–gut–cognition/immune axis	Adults/Older adults	Sleep quality/timing, gut microbiome, cognition & immune measures
NCT05058131	Dietary fermentable fibers designed to enhance butyrate production	Adults (including middle-aged/older)	Gut barrier function, microbiome, inflammation & GI symptoms
NCT06911346	Plant-forward/Polyphenol-rich diet vs. Polyphenol supplement	Adults	Microbiome, metabolic/cardiovascular & inflammation markers
NCT06395324	Diverse foods rich in arabinose	Adults	Microbiome diversity/composition, feasibility & adherence
NCT05598112	Oral FMT capsules	Adults, healthy aging focus	Multi-domain healthy aging outcomes
NCT06920212	FMT	Adults with AD	Safety, cognitive outcomes, gut microbiota changes
ChiCTR2100043548	FMT capsules	MCI/Dementia spectrum	Cognition, safety, serum metabolomics and microbiome changes
NCT06063590	Allogeneic bone-marrow MSC	Sarcopenia	Muscle strength/mass/physical performance, safety
NCT04919135	MSC therapy	Older adults	Safety, preliminary efficacy, frailty indices
NCT05284604	Allogeneic MSC infusion	Older adults with age-related frailty	Safety/feasibility, frailty/physical function, QoL
NCT04914403	Umbilical-cord MSC dose-escalation	Frailty syndrome (60–85 years)	Safety, exploratory physical function/frailty scales
NCT06448052	Umbilical-cord MSC transplantation	Aging-related low vitality	Safety, efficacy, vitality/functional metrics
NCT07144072	MSC	Mild-to-moderate frailty in older adults	Phase I safety/tolerability
NCT05054894	Albumin-infused plasmapheresis	Age-related frailty	Frailty/physical function, safety/feasibility
NCT06079827	Therapeutic plasma exchange effect on RNA biomarkers	AD, adults/older adults	AD-linked circulating RNA biomarkers, exploratory cognition signals
NCT06234436	Plasma dilution + Plasma infusion to improve cognition	MCI	Cognition and blood-borne factors, safety
NCT05909709	Alocyte: Cord blood plasma + Mononuclear cells	Adults, dose escalation pilot	Safety/tolerability, exploratory functional & biomarker readouts
NCT04566757	Human umbilical cord blood plasma infusion	Age-related cognitive decline (65–85 years)	Cognitive measures in aging, safety

Abbreviations: AD: Alzheimer's disease; BCVA: Best-corrected visual acuity; BDNF: Brain-derived neurotrophic factor; BP: Blood pressure; Ca-AKG: Calcium alpha-ketoglutarate; CAD: Coronary artery disease; CAC: Coronary artery calcium; CBT-I: Cognitive behavioral therapy for insomnia; CVD: Cardiovascular disease; CTX: C-terminal telopeptide; DLB: Dementia with Lewy bodies; DLMO: Dim light melatonin onset; DSWPD: Delayed sleep–wake phase disorder; DXA: Dual-energy X-ray absorptiometry; EEG: Electroencephalography; FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability; FINGER-NL: FINGER–Netherlands; FMD: Fasting-mimicking diet; FMT: Fecal microbiota transplantation; FTD: Frontotemporal dementia; GIP: Glucose-dependent insulinotropic polypeptide; GLP-1 RA: Glucagon-like peptide-1 receptor agonist; GI: Gastrointestinal; HbA1c: Glycated hemoglobin; HFpEF: Heart failure with preserved ejection fraction; HIIT: High-intensity interval training; hs-CRP: High-sensitivity C-reactive protein; IBS: Irritable bowel syndrome; LatAm-FINGERS: Latin America FINGER; LTCF: Long-term care facility; MCI: Mild cognitive impairment; MIND: Mediterranean–DASH intervention for neurodegenerative delay; miR-126: MicroRNA-126; MSC: Mesenchymal stem cell; NAD+: Nicotinamide adenine dinucleotide; NMN: Nicotinamide mononucleotide; NR: Nicotinamide riboside; PD: Parkinson's disease; P1NP: Procollagen type I N-terminal propeptide; qd: Once daily; QoL: Quality of life; RCT: Randomized controlled trial; SALSA: Social activities and lifestyle support for aging; SASP: Senescence-associated secretory phenotype; SCFA: Short-chain fatty acid; SINGER: Study to Implement Geriatric Intervention and Evaluation for Neurocognitive Health; SGLT2: Sodium–glucose cotransporter 2; SPPB: Short Physical Performance Battery; T2D: Type 2 diabetes; TRE: Time-restricted eating; TRF: Time-restricted feeding; UBX1325: Small-molecule inhibitor of Bcl-xL targeting senescent cells; VEGF: Vascular endothelial growth factor; WMH: White matter hyperintensity.

combinations against composite endpoints that couple molecular and functional change. Consensus frameworks recommend pairing candidate biomarkers—such as blood inflammatory markers and DNA methylation measures—with clinically meaningful outcomes, including frailty indices and performance tests to balance sensitivity with real-world relevance.[298] Adaptive designs—pre-specified rules that modify randomization, dose, or arm selection as data accrue—can increase efficiency and ethical balance without sacrificing rigor when aligned with regulatory guidance.[313]

Finally, representation matters: method papers and roadmaps emphasize enrolling diverse older adults, using culturally appropriate measures, and reporting subgroup performance to ensure generalizability and equity.[314] Collectively, multimodal interventions, composite endpoints, adaptive methods, and inclusive enrollment provide a practical blueprint for translating geroscience from mechanism to medicine.

10.5. Global accessibility and health equity

Making longevity benefits globally accessible will require affordable interventions, digital delivery, and capacity building tailored to low- and middle-income country (LMIC) health systems. Preclinically, low-cost nutraceutical candidates such as fisetin exhibit senotherapeutic effects in mice, but human efficacy, dosing, and safety must be established before population-wide deployment.[315] Scalable mobile Health (mHealth) programs can extend nutrition and lifestyle counseling, with growing evidence of feasibility and behavior change in LMICs, though equity effects and long-term outcomes remain mixed—underscoring the need for careful design and evaluation.[315] WHO guidance on digital health emphasizes reaching vulnerable groups and protecting privacy, offering a policy framework for a responsible rollout.

Region-appropriate diets demonstrate that locally grounded nutrition can support metabolic and immune health without importing costly models.[316] On the diagnostics side, portable methylation and DNA assays hint at future lower-cost biomarker testing, but standardization and clinical qualification are prerequisites for routine use. Given that the majority of the world's older adults will live in LMICs by 2030, investments in workforce training, inclusive trials, and infrastructure are essential to ensure longevity science benefits all populations.[317]

11. Conclusion

The anti-aging strategies have progressed from theoretical inquiry to actionable translational science, shifting decisively from single-target fixes to integrative, patient-tailored strategies that reflect the multifactorial nature of aging. Synergistic combinations—spanning senescence-targeting agents, microbiome modulation, and regenerative approaches—are now guided by precision geroscience frameworks that integrate multi-omics profiling with tissue-resolved biomarkers and are augmented by AI tools, such as digital twins, and continuous wearable monitoring. Together, these advances show credible promise across preclinical models and early-phase trials for mitigating age-related decline. Progress will depend on coordinated action among scientists, clinicians, policymakers, and regulators, coupled with investment in scalable, cost-effective delivery systems and inclusive infrastructures. If achieved, this agenda could convert biological insight into routine care, extend healthspan, reduce the global burden of age-related morbidity, and ultimately redefine successful aging across diverse populations.

Acknowledgments

None.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 82125023 to Hui Xie, 82272562 and 82472523 to Zhen-Xing Wang) and the Science and Technology Innovation Program of Hunan Province (Grant No. 2023RC3075 to Zhen-Xing Wang).

Conflict of interest

Hui Xie serves as the Editor-in-Chief of this journal, but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. The authors declare no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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