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Impact of Geroscience on Therapeutic Strategies for Older Adults With Cardiovascular Disease:

JACC Scientific Statement

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APPENDIX For the supplemental figure, please see the online version of this paper.

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Abstract

Geroscience posits that cardiovascular disease (CVD) and other chronic diseases result from progressive erosion of the effectiveness of homeostatic mechanisms that oppose age-related accumulation of molecular damage. This hypothetical common root to chronic diseases explains why patients with CVD are often affected by multimorbidity and frailty and why older age negatively affects CVD prognosis and treatment response. Gerotherapeutics enhance resilience mechanisms that counter age-related molecular damage to prevent chronic diseases, frailty, and disability, thereby extending healthspan. Here, we describe the main resilience mechanisms of mammalian aging, with a focus on how they can affect CVD pathophysiology. We next present novel gerotherapeutic approaches, some of which are already used in management of CVD, and explore their potential to transform care and management of CVD. The geroscience paradigm is gaining traction broadly in medical specialties, with potential to mitigate premature aging, reduce health care disparities, and improve population healthspan.

Keywords

frailty; geroscience; hallmarks; inflammation; multimorbidity

Aging and cardiovascular disease (CVD) are interconnected. As far back as the 15th century, Leonardo da Vinci (1452–1519) wrote: “vessels in the elderly restrict the transit of blood through thickening of the tunics.” Aging as a powerful risk factor for chronic disease and the population aging contribute to the expansion of CVD in the world population. There is evidence that chronic diseases result from the failure of mechanisms that oppose molecular damage with aging and that enhancing these mechanisms extends lifespan and healthspan. This research has led to the concept of geroscience,[1] which posits that therapeutics that target the fundamental mechanisms of aging (gerotherapeutics) delay or avert age-related chronic diseases and increase healthspan (Table 1). As CVD is the most prevalent cause of morbidity and mortality in the elderly, the hypothesis that the biology of aging contributes to CVD as well as other chronic diseases should interest cardiovascular clinicians for 3 main reasons.

First, although CVD prevalence and mortality fell in recent decades because of aggressive control of risk factors, geroscience-based therapies that target mechanisms upstream of CVD may enhance this trend, even in individuals free of CVD risk factors.

Second, by targeting the drivers of aging, gerotherapeutics might prevent or ameliorate comorbidities and frailty often present in patients with CVD and improve prognosis and overall health (Central Illustration).

Third, identification of individuals with accelerated aging may allow targeting the early stages of CVD and other development of disease, when gerotherapeutics may be more effective.

CVD, FRAILTY, MULTIMORBIDITY, AND CLINICAL COMPLEXITY AMONG OLDER ADULTS

Frailty is a state of exhausted functional reserve that is thought to be caused by a failure of the resilience mechanisms of aging.[2,3] Although many different definitions of frailty exist (Table 2), the syndrome of physical frailty is a distinctive high-risk clinical state characterized by 3 or more of 5 key criteria: weakness, slow walking speed, low physical activity, fatigue or exhaustion, and unintentional weight loss. Multimorbidity[4] is defined as 2 or more medical diseases or conditions that persist for >1 year. The erosion of resilience mechanisms with aging prevent or repair macromolecular and cellular damage leading to frailty, multimorbidity, and other geriatric syndromes. Resilience mechanisms decline faster in some individuals, causing them to develop multimorbidity and frailty earlier in life than the average population. CVD in older patients[5] typically develops in the context of frailty and multimorbidity,[6] with negative implication for prognosis and management complexity. Gerotherapeutics address CVD, frailty, and multimorbidity simultaneously.

CVD AND GERIATRIC SYNDROMES SHARE AGING HALLMARKS

The impairment of mechanisms that prevent damage accumulation with aging, referred to as the “hallmarks”[7] of aging, contributes to multimorbidity, frailty, and loss of physical and cognitive functions. Environmental stress and CVD risk factors,[8] such as obesity and smoking, accelerate the failure of these mechanisms (Central Illustration). Here we focus on aging resilience mechanisms that targeted by gerotherapeutics may both extend healthspan and reduce CVD (Figure 1).

GENOMIC DAMAGE.

DNA, the molecule that carries all genetic information, is continuously damaged and repaired throughout life. Insufficient or inaccurate DNA repair activity leads to corruption of the genetic code, generally referred to as “genomic instability.” The accumulation of DNA mutations or chromosome aberrations drives may cause cell death or senescence: 2 drivers of diseases and aging.[9] Mice with mutations that affect DNA repair proteins exhibit aging-like features including endothelial dysfunction, increased vascular stiffness, hypertension, and accumulation of senescent cells.[10] In humans, mutations of mitochondria DNA are associated with atherogenesis. Studies have shown a significant association of DNA damage and genomic instability with cancer, frailty, and unsuccessful aging.[11]

Clonal hematopoiesis of indeterminate potential (CHIP) reflects genomic instability. With aging, hematopoietic stem cells acquire somatic mutations in genes that promote the clonal expansion of myeloid cells. Mutated leukocytes occur at a frequency of 10% to 20% in individuals by age 70, with ≥2% of cells carrying a CHIP genetic variant associated with high risk of CVD, cancer, and mortality. Certain types of CHIP-related mutations accelerate atherosclerosis and cause activation of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome, a main inflammatory pathway that stimulates the production of interleukin (IL)-1β and IL-18 as well as apoptotic and pyroptotic cell death.[12] CHIP, because of mutations in DNA damage response genes, promotes peripheral

artery disease.[13] Aging-related loss of chromosome Y in some somatic cells, but not others (mosaicism), is the most commonly acquired mutation in the male genome and is associated with cancer, Alzheimer disease, and CVD.[14]

EPIGENETIC ALTERATIONS.

Epigenetic mechanisms regulate gene expression through chemical modifications of chromatin, particularly histone proteins that provide structural support to chromosomes, or changes in the superstructure of DNA. Methylation of DNA—specifically, the transfer of a methyl group to a cytosine in a cytosine-guanidine (CpG) sequence—is the most studied epigenetic mechanism in aging.[15]

An extensive literature connects DNA methylation with CVDs and other age-related health outcomes.[16] DNA from atherosclerotic plaques tends to be hypomethylated, with hypermethylation in regulatory regions of genes linked to atherosclerosis.[17] DNA methylation at specific CpG islands in circulating cells is associated with increased risk of CVD.[18] In the CARDIA (Coronary Artery Risk Development in Young Adults) study cohort, participants who maintained better CVD health with aging showed a slower change in GrimAge, an aggregate blood methylation-based biomarker that predicts healthspan and lifespan.[19] Epigenetic indexes (clocks) built from DNA methylation are associated with CVD, multimorbidity, and frailty. Methylation levels of specific histones (ie, H3K9 and H3K27) are significantly lower in smooth muscle cells and lymphocytes of patients with carotid artery stenosis than controls.[20]

LOSS OF PROTEOSTASIS.

Proteins are damaged throughout cells lives, and such damage can affect their architecture, functionality, and solubility. Protein aggregation and precipitation adversely affect their function. Protein folding guides exist (chaperones) that work in combination with the ubiquitin-proteasome system (eliminates misfolded proteins) and the lysosome-autophagy system (eliminates damaged organelles and pathogens) to ensure that proteins and organelles maintain their optimal structure and function. In a process called “autophagy,” large molecular aggregates and organelles are engulfed in vacuoles that are then fused with lysosomes: that is, intracellular sachets that contain enzymes that degrade the content of autophagic vacuoles. Mitophagy, a specialized form of autophagy, recycles damaged mitochondria. Defective mitophagy causes the persistence of fragmented, dysfunctional mitochondria that trigger inflammation and deranged energy metabolism in CVDs.[21]

During stress conditions, protein synthesis is suppressed to shift energy to active protein folding, and genes that support survival pathways and inflammation are overexpressed. Failure to reestablish protein homeostasis causes pathology, including in CVD and sarcopenia.[22,23] Accumulation of “toxic” proteins has been associated with endothelial and cardiomyocyte senescence, atrial fibrillation, cardiac hypertrophy, and cardiomyopathy.[24] Abnormal transthyretin amyloid folding contributes to cardiomyopathy and preserved ejection fraction heart failure (HF).[25] Impaired chaperone-mediated autophagy is also associated with the formation of atherosclerotic plaques.[26]

DEREGULATED NUTRIENT SENSING.

Cells sense energy availability to make decisions about growth, metabolism, and proliferation, and—in some cases—apoptosis and regulate autophagy, mitochondrial, and ribosomal biogenesis.[27] The phosphatidylinositol-3-kinase (PI3K)/AKT kinase (AKT)/ mammalian target of rapamycin (mTOR) pathway regulates signaling mechanisms that are central to such regulation. Altered mTOR signaling is involved in many age-associated diseases including restenosis after angioplasty, cardiac hypertrophy, HF, type 2 diabetes mellitus (T2DM) and obesity, neurodegenerative diseases, cancer, and immunosenescence. AMP-activated protein kinase (AMPK) detects a discrepancy between energy demand and availability caused by either mitochondrial dysfunction (eg, oxygen deprivation) or increased consumption (eg, during exercise). Activated AMPK increases energy production by stimulating mitochondrial biogenesis, fatty-acid oxidation, glycolysis, autophagy, angio-genesis, and nitric oxide bioavailability and by inhibiting biosynthetic processes such as gluconeo-genesis and protein synthesis. Abnormal AMPK signaling is associated with hypertension, atherosclerosis, stroke, obesity and diabetes.[28] Sirtuins, a family of nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylases or mono-adenosine diphosphate (ADP) ribosyltransferases, sense and activate several energy preserving pathways.[29]

MITOCHONDRIAL DYSFUNCTION.

Mitochondria generate most of the energy required for all biological processes including resilience mechanisms that combat aging. A decline of mitochondrial function occurs with aging and is a prominent characteristic of endothelial dysfunction, arterial stiffness, atherosclerosis, ischemia-reperfusion injury, hypertension, cardiac hypertrophy, diastolic dysfunction and HF, metabolic diseases (eg, T2DM and metabolic syndrome), and geriatric syndromes such as sarcopenia and frailty.[30,31] The release of reactive oxygen species (ROS), oxidized cardiolipin and mitochondrial DNA by damaged mitochondria, drive inflammation by triggering nuclear factor kappa light chain enhancer of activated B cells (NF-κB), NLRP3 inflammasome, and the cyclic guanosine monophosphate-adenosine monophosphate synthase with the adaptor stimulator of interferon genes (cGAS-STING) pathways and stimulate expression of proinflammatory cytokines such as IL-1, IL-6, IL-18, tumor necrosis factor (TNF)α, and Type-I interferons that contribute to a state of “inflammaging.”[32]

CELLULAR SENESCENCE.

Cellular senescence involves cell cycle arrest triggered by developmental and stress signals and is considered a cancer-suppression mechanism. Triggers of cellular senescence include irradiation, oxidative and genotoxic agents, epigenetic changes, perturbed proteostasis, mitochondrial dysfunction, and chemotherapeutic agents. Senescent cells change morphology, often express defining biomarkers, such as $p21^{WAF1/CIP1}$ and $p16^{INK4A}$, exhibit signs of persistent DNA damage response and show enhanced lysosomal activity. An important feature is the secretion of bioactive molecules, known as the senescence-associated secretory phenotype (SASP), which includes senescence triggers, proinflammatory cytokines (eg, IL-6), chemokines, proapoptotic factors, growth modulators,

angiogenic factors, proteases, bioactive lipids, extracellular matrix components, and metalloproteinases.[33]

Senescent cells accumulate with aging in multiple tissues, including the heart and vasculature,[34] and many SASP factors increase in the plasma of healthy individuals with aging.[35] Senescent cells contribute to pathology by obstructing tissue repair and regeneration. The SASP promotes chronic inflammation, paracrine spread of senescence, and support neoplastic transformation.[36] Senescent cells accumulate in several age-related diseases, such as atherosclerosis, diabetes, lung disease, Alzheimer disease, vascular dementia, and sarcopenia.[37,38] In humans, the accumulation of senescent cells in sub-cutaneous fat is associated with many age-related changes, including frailty.

The National Institutes of Health (NIH) Common Fund's Cellular Senescence Network Program (SenNet) aims to identify and characterize senescent cells throughout the body (including the heart) during aging and chronic diseases.[39]

STEM-CELL EXHAUSTION.

Stem cells maintain functionality of most tissues by replacing cells lost through wear and tear or injury. With aging, the renewal, proliferation, and differentiation capacity of stem cells decline, contributing to aging-associated disorders such as CVD. Some evidence suggests that circulating stem cells can enhance the regenerative capacity of multiple tissues, including those specific to the cardiovascular system.[40]

DYSBIOSIS.

Dysbiosis refers to the reduction of microbial diversity of the resident microbiome. The gut is the most studied microbiome in aging, and its changes have been connected to human pathologies, including cardiometabolic diseases. In healthy adults, the gut microbiome is extremely diverse, with Bacteroidetes and Firmicutes being the most prevalent phyla. With aging, the Firmicutes to Bacteroidetes ratio and the overall diversity of the microbiome declines, possibly because of the expansion of distinct groups of bacteria. These changes are associated with declining immunocompetence and a higher risk of diabetes mellitus, atherosclerosis, neurodegenerative and liver diseases, and frailty.[41,42] Dysbiosis of the gut microbiome impairs the integrity of the gut barrier, leading to leakage of bacteria and associated components into the circulation promoting chronic inflammation. Intestinal bacteria and the liver transform red meat components into trimethylamine N-oxide, whose blood level has been associated with CVD and CVD mortality.[43]

TELOMERE SHORTENING.

Telomeres are repetitive nucleotide sequences (TTAGGG) at the end of chromosomes that preserve chromosome integrity. In somatic cells, telomeric DNA is shortened at each cell division. The progressive shortening of telomeres in vitro causes a finite replicative lifespan, suggesting an important role in aging. Shorter telomeres in circulating leukocytes have been associated with higher risk of incident CVD such as myocardial infarction and stroke; however, other studies have failed to confirm such associations.[44,45] Despite much focus on

telomeres in aging, the relevance of telomere length as a marker of biological aging remains uncertain.

INFLAMMAGING

Inflammaging is the increase of proinflammatory molecules, such as IL-6 and c-reactive protein (CRP), with aging of and other in blood or tissues, paralleled by a blunted immune response to acute stimulation, such as vaccination. Consistent with the postulated interdependence between the mechanisms of aging, dysregulation of any reliance mechanisms of aging causes inflammation. For example, inflammation can be induced by dysfunction of mitochondria and defective mitophagy that leads to the release of oxidated cardiolipin and mitochondrial DNA, proteotoxicity that activates specific stress responses, or persistent DNA damage that activates responses that consume NAD^+. In addition, inflammation curtails the regenerative capacity of stem cells. Thus, inflammation is a collective biomarker of the failure of biological resilience against damage accumulation with aging.[46]

Inflammation participates in atherosclerosis and affects multiple CVDs including myocardiopathy, late-life valvular dysfunction, and HF. Higher blood inflammatory markers predict heart attacks, cerebrovascular events, peripheral artery diseases, as well as multimorbidity and a steeper increase of multimorbidity and frailty.[47] Finally, taming inflammation prevents cardiovascular events.

MEASURING BIOLOGICAL AGING

The geroscience hypothesis posits that slowing aging is maximally effective before the development of its clinical manifestations. Metrics of aging have been developed that combine various biomarkers and identify “fast aging” individuals and track the effect of interventions, such as antihypertensive medications, on the rate of aging.[48] Ideal “aging clocks” correlate with chronologic age yet discriminate individuals that are aging “faster” or “slower” biologically.

The epigenetic clocks pioneered by Hannum[49] and Horvath,[50] as a weighted average of DNA methylation at specific CpGs, correlate with chronologic age and identify diverse adverse health outcomes, including frailty, CVD, CVD mortality, and all-cause mortality. Recent platforms, such as DNAm PhenoAge and GrimAge, were developed using health outcomes and age for reference, whereas pace of aging calculated from the epigenome (DunedinPACE) was tuned on longitudinal data.[51] These DNA methylation-based tools also predict age-related outcomes, including CVD, with the most recent versions showing the highest reliability.

Aging clocks that use plasma proteomics can predict age-related outcomes with performances similar to those based on the methylome.[35,52] A recently developed inflammatory clock of aging (iAge) tracked multimorbidity, immune system aging, frailty, and cardiovascular aging, with the strongest contributor being the chemokine CXCL9, which is involved in cardiac aging, adverse cardiac remodeling, and poor vascular function.[53]

GEROSCIENCE-GUIDED THERAPEUTIC APPROACHES TO CVD

This section considers some of the most promising nonpharmacologic and pharmacologic gerotherapeutics for the treatment of CVD, citing research in humans whenever possible. Figure 2 highlights the association of aging hallmarks to CVD. Figure 3 highlights that gerotherapeutic interventions may lead to pleotropic effects that vary from one person to another. Given the rapid growth of geroscience and the absence of U.S. Food and Drug Administration (FDA)-approved clinical therapies, we have prioritized interventions meeting 4 criteria: robust biological rationale, rooted in sound geroscience principles, relevance to CVDs, and early-stage support in human studies.

NONPHARMACOLOGIC INTERVENTIONS

EXERCISE AND PHYSICAL ACTIVITY.

Physical activity prevents or ameliorates chronic diseases, including atherosclerosis, hypertension, diabetes, CVD, and sarcopenia[54,55]; this is not surprising, as physical activity enhances multiple resilience mechanisms and affects core mechanisms of aging.

The molecular mechanisms by which exercise improves health are complex and are currently being determined by the NIH-funded Molecular Transducers of Physical Activity Consortium (MoTrPAC).[56] In brief, acute aerobic exercise induces mild stress that increases the production ROS by mitochondria and triggers an inflammatory response, followed by a homeostatic response that enhances defense mechanisms. Aerobic exercise activates AMPK, sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1-α, and Ak strain transforming (AKT) signaling in skeletal and cardiac muscle, thereby promoting mitochondrial biogenesis.[57] Exercise also activates PI3-kinase, improving insulin and anabolic signaling (AKT/mTOR) in younger and older adults,[58,59] and stimulating cardiac cell proliferation.[57] Aerobic exercise reduces the SASP and improves production of nitric oxide and endothelial function, consequently lowering blood pressure and left ventricular load.[57,60,61] Aerobic exercise may also reduce NF-κB, receptor for advanced glycation end products, TNFα, nicotinamide adenine dinucleotide phosphate (NADPH), monocyte chemo-attractant protein-1, and inducible nitric oxide synthase, whereas the effect on IL-6 is uncertain.

Acute resistance exercise activates satellite cells, mTOR signaling, and muscle protein synthesis,[62] and long-term training improves hallmarks of senescence.[63] Resistance training induces muscle hypertrophy by activating mTOR signaling, muscle protein anabolism, and stimulating satellite cell proliferation and activation. The positive effects of resistance exercise are reduced but not eliminated in old age.[63]

DIET.

A balanced diet is essential to prevent and treat CVD, obesity, diabetes, and sarcopenia in older adults. More than 41% of older Americans are obese, and approximately one-third of them have T2DM, a disease that significantly increases the risk of CVD.[64,65] Diabetes and obesity accelerate aging and negatively affect most hallmarks of aging. Visceral adiposity promotes cellular senescence directly and through the production of adipokines

and inflammatory mediators.[66] In obese and overweight older individuals, weight loss lowers inflammatory biomarkers; improves glycemic control; and limits the risk of CVD, disability, and frailty. Adequate protein intake and resistance training should be part of any weight-loss regimen to mitigate lean mass loss and avoid disability and frailty.[67]

In animal models, caloric restriction (CR) in the absence of obesity is the most effective intervention at counteracting aging and promoting healthspan and increased longevity, eliciting positive effects on the core mechanisms of aging.[68] Preliminary data in younger humans from the CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) study suggest positive effects of CR on immune function, muscle quality, and cardiovascular risk profiles, as well as the ability to retard biological aging.[69] In obese and overweight persons and in persons with or without CVD—including older individuals—a CR diet has many benefits, including increased longevity.[70] In older persons with HF with preserved ejection fraction, CR improves function and quality of life.[71] CR remains controversial for nonobese older adults because of insufficient evidence and malnutrition concerns.

Intermittent fasting and time-restricted eating have been proposed as alternative dietary approaches to CR to increase adherence and reduce risks of malnutrition.[72] There is early evidence that intermittent fasting and time-restricted eating improve molecular markers of aging and cardiovascular risk factors[73,74] such as low-density lipoprotein (LDL) cholesterol and systolic and diastolic blood pressure.[75] A Mediterranean-type diet that includes a high proportion of fruit, vegetables, nuts, legumes, whole grains, fish, lean meats, moderate amounts dairy products, moderate intake of wine, and olive oil may reduce cardiovascular risk by limiting oxidative stress, inflammation, and LDL; improving insulin sensitivity and immune function; positively affecting the microbiome and genome stability[76]; and possibly inducing epigenetic rejuvenation.[77]

PHARMACOLOGIC INTERVENTIONS

The list of potential gerotherapeutic molecules grows every day, but their translation to clinical trials presents challenges that were recently addressed by the National Institute on Aging (NIA) Translational Geroscience Network (TGN).[78] More than 40 clinical trials are underway of pharmacologic, lifestyle, and nutraceutical interventions that target aging hallmarks.[79] Progress in the geroscience field has been hampered by the paucity of validated biomarkers that are easily measurable, reliably track biological aging,[80] and dependably respond to interventions. Authenticated “gerodiagnostics” are currently being pursued, based on data from the TGN clinical trials through the Facility for Geroscience Analysis. As aging mechanisms are interconnected, an intervention targeting a single hallmark likely affects other hallmarks with mechanistic pleiotropism (Figure 3).

NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD^+).

NAD^+ participates in DNA repair, mitochondrial biogenesis and function, and other facets of metabolism. NAD^+ levels decline with aging, and such a decline contributes to several chronic conditions, including CVD. Raising NAD^+ in mice improves both lifespan and healthspan and protects against vascular dysfunction and ischemic heart damage.[81] Human

studies testing the effectiveness of NAD precursors—such as niacinamide, nicotinamide mononucleotide, and nicotinamide riboside—in preventing or alleviating CVDs have recently begun. Early proof-of-concept clinical studies have shown good safety and tolerability of NAD precursors, with some studies showing improvement in muscle insulin sensitivity, blood pressure, and arterial compliance, as well as suppression of inflammatory activation of peripheral blood mononuclear cells from patients with HF.[82] Oral nicotinamide riboside raises NAD^+ and lowers biomarkers of neurodegenerative pathology in plasma extracellular vesicles enriched for neuronal origin.[83] These promising early-stage human findings require replication in larger clinical trials, and questions remain about the optimal target population(s), type of "NAD booster," dose regimens, length of treatment, and whether supplementation results in intracellular NAD^+ repletion.

SIRTUINS AND REVERATROL.

Resveratrol, a natural phenol, and phytoalexin, which is found in the skin of grapes, blueberries, raspberries, mulberries, and peanuts, are leading modulators of sirtuin mechanisms.[84] The presence of resveratrol in red wine has been proposed to explain the "French Paradox": that is, that France has an incidence of CVDs lower than expected based on their high consumption of saturated fats. Clinical trials with either resveratrol or phytoalexin have shown little effect on CVD,[85] although some benefits on blood pressure have been reported in subjects with diabetes.[86]

SENOLYTICS AND SENOMORPHICS.

Senolytic and senomorphic drugs may offset the deleterious effects of accumulation of senescent cells, thereby reducing CVD burden and mortality.[79] Senolytics eliminate 30% to 70% of senescent cells that are proapoptotic, proinflammatory, and tissue damaging.[87] Senolytics delay the onset; prevent, alleviate, or treat a range of age-associated disease features in cell culture models and animal experiments[79,88]; and selectively eliminate proinflammatory senescent cells in humans.[89]

First-generation senolytics include dasatinib, quercetin, fisetin, procyanidin C1, geldanamycin and related HSP-90 inhibitors, and navitoclax.[90–93] Dasatinib, approved for adult leukemias and lymphomas, inhibits tyrosine kinases and ephrin receptors. Both mesenchymal and endothelial cell effects are pertinent to posited CVD-reducing benefits. Dasatinib is mostly active on senescent mesenchymal cells. In contrast, quercetin and fisetin are plant flavonols that mainly target senescent endothelial cells such as cultured human umbilical vein endothelial cells. Genome-wide association studies suggest that flavonoid consumption associates strongly with extreme longevity. Like the plant flavonols, navitoclax and the BCL-2 family inhibitors—A1331852 and A1155463—target mostly senescent endothelial cells.[91,92] Dasatinib and quercetin used together are effective against a range of senescent mesenchymal and endothelial cells, including some senescent cell types that respond to neither alone.[94]

Studies have shown that senolytics enhance ejection fraction and vascular relaxation after nitroprus-side or acetylcholine administration in aged mice or $ApoE^{-/-}$ atherosclerotic mice fed a high fat diet[95]; reduce intimal calcification in high fat-fed $ApoE^{-/-}$ mice[95]; improve

brain small vessel perfusion in a 23-month-old Tau^{+} Alzheimer mouse model[96]; decrease vascular senescent cells in mice with chronic kidney disease[97]; and improve regenerative capacity of the aged heart by ablating senescent cardiac pro-genitor cells.[98] Elimination of senescent cells may slow down atherogenesis.[99,100]

Senomorphics inhibit release of SASP factors by senescent cells, suppressing or modulating their damaging effects.[79] First-line senomorphics include rapamycin, metformin, resveratrol, and related drugs such as sirolimus and aspirin. Although they all suppress the SASP in cell lines and animal models and have health effects that—in some cases—resemble those of senolytics, the precise mechanism of action is unknown.[101]

METABOLIC DRUG THERAPIES.

Several of the most promising gerotherapeutics are repurposed drugs originally developed as hypoglycemic agents for T2DM.[102] This is not surprising, as insulin-like growth factor (IGF) signaling is among the most deeply conserved and robustly validated mechanisms regulating aging. Insulin resistance and impaired glucose utilization are features of T2DM, among other diseases, and conditions of aging ranging from HF[103] to neurodegeneration[104] and frailty.[3,105] Emerging evidence of benefits for CVD and chronic kidney diseases (CKD) in patients without T2DM, together with contrary data for other hypoglycemic agents, such as insulin and sulfonylureas, supports the hypothesis that hypoglycemia is not solely responsible for the beneficial effects and that other aging mechanisms beyond nutrient signaling pathways are likely more significant.[106]

Metformin.—Metformin is widely used to treat T2DM[107] yet exerts beneficial effects on health well beyond a typical oral hypoglycemic.[108] Metformin alters energy metabolism of the cell by inhibiting mitochondrial complex I and activating AMPK. Independent of its effect on AMPK, metformin affects mitochondrial function, cellular senescence, proteostasis, and autophagy via mammalian target of rapamycin complex (mTORC1) inhibition, and chronic inflammation via NFκB inhibition.[108] The NIA Interventions Testing Program (ITP), which evaluates agents that extend lifespan or attenuate/delay age-related diseases by altering fundamental processes of aging, found that metformin increased mouse lifespan synergistically with rapamycin.[109]

In large observational studies, metformin reduced all-cause mortality of patients with diabetes compared with both nondiabetic patients and patients with diabetes not taking metformin,[110] including in subgroups with CKD, HF, or chronic liver disease.[111] Secondary analyses and observational studies in T2DM consistently found reduced mortality and improved cardiovascular outcomes, ranging from decreased HF hospitalizations and hypertension to reduced progression of aortic aneurysms, among patients taking metformin compared with alternatives.[112] A small interventional study found that metformin diminishes left ventricular hypertrophy in patients with coronary artery disease without diabetes.[113] Observational data also suggest, albeit less robustly, that metformin reduces cognitive decline[114] and cancer risk,[115] consistent with a broad gerotherapeutic effect.

The proposed TAME (Targeting Aging by Metformin) trial is the first randomized controlled trial (RCT) to test the geroscience hypothesis directly by examining whether a single agent

can slow the incidence of age-related multimorbidity in older adults.[106,116] Metformin was selected for this trial, as well as for the ongoing VA-IMPACT (Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular Outcomes Trial; NCT02915198), because of its safety profile and defined mechanism of action.[116]

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors prevent hyperglycemia by blocking reuptake of glomerular filtered glucose in the renal tubule, thereby promoting glycosuria. SGLT2 inhibitors likely have pleiotropic effects on CVD that are independent of glycosuria.[117] SGLT2 inhibitors received a high rank as gerotherapeutics in a systematic assessment of FDA-approved drugs based on published preclinical and clinical evidence.[102] Experimentally, SGLT2 inhibitors enhance autophagy in renal glomeruli, improve mitochondrial function, activate AMPK, improve calcium homeostasis in cardiomyocytes, inhibit NLRP3 inflammatory activation, and suppress mTORC1 activity.[102,118] Thus, by affecting global energy sensing, SGLT2 inhibitors promote a nutrient deprivation state that affects downstream, interconnected, aging mechanisms.[117] Consistent with SGLT2 inhibitors serving as nutrient-signaling gerotherapeutics, canagliflozin was reported to extend median male mouse lifespan by 14% in the ITP.[119]

Clinical use of SGLT2 inhibitors has expanded rapidly from T2DM to HF and CKD. SGLT2 inhibitors reduce CKD progression in patients with[120] or without[121] coexisting T2DM, reduce HF hospitalizations in patients with HF but not T2DM,[122] and reduce cardiovascular events in patients with T2DM.[123] SGLT2 inhibitors also reduce all-cause mortality in patients with T2DM, CKD,[121] or HF with reduced ejection fraction.[124]

Acarbose.—The α-glucosidase inhibitor acarbose impairs digestion of carbohydrates on the small intestine brush border and thereby reduces postprandial glucose absorption. It was among the first agents tested in the ITP, on the hypothesis that excessive postprandial hyperglycemia contributes to biological aging. Acarbose extends median lifespan in both male and female mice (by 22% and 5%, respectively)[125] and increases lifespan synergistically with rapamycin.[126] Acarbose likely functions as a nutrient-signaling regulator by modulating insulin/IGF pathways but might also interact with the proteostatic and epigenetic hallmarks of aging.[102]

In STOP-NIDDM (Study to Prevent Non-insulin Dependent Diabetes Mellitus), acarbose reduced the progression from impaired glucose tolerance to T2DM[127] and lowered the incidence of both hypertension and major cardiovascular events. Observational studies support a reduction in cardiovascular events in patients with T2DM treated with acarbose.[128] Although the more recent Acarbose Cardiovascular Evaluation trial in patients with both coronary artery disease and impaired glucose tolerance replicated the effect on prevention of diabetes,[129] the study found no difference in cardiovascular events or all-cause mortality, and a recent meta-analysis of trials involving administration of acarbose were inconclusive for cardiovascular events and all-cause mortality.[130] Overall, acarbose has strong preclinical data and a mechanistic basis as a gerotherapeutic but is comparatively understudied in the clinic compared with metformin and SLGT2 inhibitors.

GLP-1 agonists.—Similar to metformin and SGLT2 inhibitors, GLP-1 agonists improve insulin sensitivity and metabolic function and act as broad gerotherapeutics by interfering with the nutrient signaling mechanisms. Both preclinical and clinical evidence for GLP-1 agonists as gerotherapeutics are less well developed but are expanding rapidly.[131] In animal models, GLP-1 agonists reduce oxidative stress, improve mitochondrial function, inhibit cellular senescence, and modulate mTOR activity.[132]

Trials of GLP-1 agonists consistently report reductions in cardiovascular events and mortality in patients with T2DM,[133–135] and a few studies found improved secondary outcomes related to CKD as well.[133,135] In a Cochrane meta-analysis, GLP-1 agonists, as well as SGLT2 inhibitors but not dipeptidyl peptidase (DPP)-4 inhibitors, reduced cardiovascular events, cardiovascular mortality, and all-cause mortality in patients with both T2DM and CVD.[136] There are not yet similar data on GLP-1 targeting in patients without T2DM, and it is currently unknown whether these drugs positively affect other age-related outcomes.

Ketone body-related therapies.—Ketone bodies furnish energy that bypasses the insulin/glucose axis and provide a fat-derived, alternative substrate for cellular ATP generation. Thus, exogenously administered ketone bodies may help compensate for aging-or disease-related impairments in glucose utilization, as seen in neurodegenerative disease[104] or HF.[137] Ketone bodies affect several mechanisms of aging including reducing chronic inflammation via NLRP3 inhibition[138] and microbiome modulation[139]; regulating epigenetic modifications via histone deacetylase inhibition; preventing endothelial senescence by stabilizing an Oct4 RNA-binding protein; and enhancing stem-cell function.[140,141] Promoting endogenous ketogenesis via a carbohydrate-restricted ketogenic diet increased lifespan in 2 independent mouse studies.[142] However, the ketogenic small molecule 1,3-butanediol produced indeterminate results when tested in the ITP because of exceptionally reduced longevity in the control animals.[126]

The recent development of ketogenic small molecules enables ketone body administration without dietary changes. For example, acute ketone body administration improved cardiac hemodynamic measures in both patients with HF[143] and healthy adults.[144] Long-term studies are not yet completed, and ketone body therapies remain investigational for CVD.

TOR inhibitors.—TOR inhibition has garnered the most rigorous experimental support as a gerotherapeutic intervention, showing the most robust and reproducible effect of any pharmacologic agent in extending lifespan in animals. However, clinical trial data relevant to aging applications are at an earlier stage: for example compared with metformin and SGLT2 inhibitors. TOR emerged early as a critical nutrient-sensing complex that mediates the longevity benefits of CR.[145] TOR inhibition reduces protein synthesis and activates autophagy, whereas downstream effects include enhancement of many of the resilience mechanisms of aging.[145,146] The TOR inhibitor rapamycin was among the first drugs found to extend healthy lifespan in the ITP, in both male and female mice.[147] This lifespan extension was associated with reduced age-related changes in several tissues, including cardiac hypertrophy and other cardiovascular outcomes.[146] Replicative ITP studies showed a dose-dependent median lifespan extension of up to 23% in males and 26% in females,[148]

with efficacy starting as late as 20 months old (equivalent to approximately the seventh decade in humans),[149] and synergistic effects were observed with both metformin[109] and acarbose.[126] Preliminary findings of a rapamycin study show an improvement in age-related cardiac function in middle-aged companion dogs.[150]

TOR inhibitors such as sirolimus and everolimus are FDA approved as post-transplantation immuno-suppressants and as therapies for certain inherited disorders and cancers associated with TOR hyper-activation. However, the doses used for immuno-suppression or cancer therapy are 10-fold to 80-fold higher than those relevant to aging studies. This limitation is unlike the situation with metformin and SGLT2 inhibitors in which the doses for T2DM or CVD treatment resemble those required for geroprotection.

Anti-inflammatory therapies.—The CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) proved that inflammation participates causally in CVD pathogenesis. In CANTOS, neutralizing IL-1β with the monoclonal antibody canakinumab for over a median of 3.7 years in >10,000 patients reduced the risk of CVD events, especially in participants who showed a greater than median decline in the inflammatory markers CRP and IL-6. Canakinumab caused a small but statistically significant increase in infections,[151] consistent with the role of IL-6 in immunity. Exploratory results from CANTOS also revealed reduced lung cancer mortality,[152] anemia,[153] gout, hospitalizations for HF,[154] and replacements of the hip or knee.

The anti-inflammatory drug colchicine has shown effectiveness in prevention of secondary CVD. Among patients with recent myocardial infarctions, colchicine at a dose of 0.5 mg daily significantly lowered the risk of ischemic cardiovascular events. In a randomized trial involving patients with chronic coronary artery disease, colchicine also lowered the risk of cardiovascular events. Similar benefits of colchicine have been demonstrated for other CVDs as well.[155] Whether colchicine is effective against additional age-related outcomes is unknown. Anti-inflammatory benefits have also been associated with angiotensin receptor blockers, with decreased endothelial and vascular senescence.[156] Notably, other anti-inflammatory treatments were not very effective in preventing age-related outcomes. For example, low-dose weekly administration of methotrexate did not improve cardiovascular outcomes in a large trial.[157] In the Aspirin in Reducing Events in the Elderly trial, the daily administration of aspirin in healthy older adults did not lower all-cause mortality and had no substantial effect on the risk of mobility loss.

NOVEL BIOMARKERS FOR GUIDING RESEARCH FOR CVD IN RELATION TO AGING

Clinical trials that target the effects of biological aging on CVD would be maximally informative if biomarkers specific for each aging hallmark could be measured. However, the development of effective biomarkers is still a work in progress, with few being validated in humans and none having entered routine clinical use. The investigators for the TAME trial[80] evaluated the potential of 258 serum biomarkers using as criteria measurement reliability and feasibility; relevance to aging; ability to robustly predict all-cause mortality and clinical and functional outcomes; and responsiveness to the intervention. The final list generated

included IL-6, TNFα-receptor I or II, CRP, growth differentiation factor (GDF) 15, insulin, IGF1, cystatin C, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and hemoglobin A1c. These 9 biomarkers have now been incorporated into ongoing gerotherapeutic trials.

Another approach is to develop composite scores of biomarkers or "gerodiagnostics" rather than focusing on individual biomarkers. Such composite scores incorporate assays of multiple hallmarks of aging and appear to respond to interventions such as senolytics in humans.[158] Ideally, biomarkers of composite gerodiagnostic scores would not just reflect "biological age" but would predict age-related health outcomes independent of chronologic age; be measurable in body fluids such as urine, saliva, or blood; be inexpensive, reliable, and reproducible; and be sensitive to the effect(s) of geroscience interventions.

Research on biomarkers for use in clinical trials that target the mechanisms of aging and CVD has benefitted from technologic advances, such as proteomic methods that measure thousands of bio-molecules in blood and tissue samples. The ability to assess stored biospecimens with increasing numbers of markers permits continued expansion and refinement of candidates that may reveal "ideal" biomarkers that report on the state or function of the aging hallmarks. The TGN strives to standardize geroscience biomarker analyses across disparate clinical trials and provides a centralized biospecimen repository.[159] Similarly important, it strives to standardize clinical outcome measures that are relevant in aging such as activities of daily living and independent activities of daily living, gait speed, 6-minute walking test, short form physical battery, and frailty indices.[160]

THE TRANSFORMATIONAL IMPLICATIONS OF GEROSCIENCE-BASED CVD MANAGEMENT

Geroscience-based interventions are supposed to slow or delay aging-related chronic diseases (eg, CVD) and geriatric syndromes and improve general health.[78,161] However, this hypothesis requires rigorous testing on a large-scale RCT basis. Geroscience interventions may substantially affect social determinants of health (SDOH),[162] as income, wealth, and ZIP codes can powerfully predict longevity in the United States.[163] SDOH disparities manifest as increased rates of chronic diseases, such as CVD, as well as an earlier presentation of geriatric syndromes like falls and impairment of mobility. As SDOH disparities can strongly influence biological mechanisms of aging,[164] geroscience-based pharmacologic interventions that target prevention of CVD may prevent other SDOH-accelerated chronic diseases as well and with an earlier effect relative to individuals with favorable SDOH.

SUMMARY, GAPS, AND FUTURE DIRECTION

As we are faced with a growing aging population worldwide, gerotherapeutics have the ambitious goal of transforming health care. If we continue to intervene when pathology becomes clinically evident, we may only extend the period of life characterized by disease and disability but fail to extend healthspan: the period of life most enjoyable and productive. Success in promoting healthspan not only addresses the burden of aging on human life but may also come with enormous economic benefits. Compression of morbidity because

of gerotherapeutics is estimated to provide a $37 trillion per year return.[165] Medical practitioners focused on CVD, as well as other specialties, should strive to implement a more fundamental approach to prevent or mitigate multiple diseases, frailty, and other health impairments at all stages of life. Cardiovascular specialists have a privileged role in this process, as they have already embraced concepts of primary and secondary prevention, and cardiovascular conditions contribute enormously to the challenges of older age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS AND ACRONYMS

AMPK	AMP-activated protein kinase
CHIP	clonal hematopoiesis of indeterminate potential
CKD	chronic kidney disease
CpG	cytosine-guanidine sequence
CVD	cardiovascular disease
FDA	U.S. Food and Drug Administration
HF	heart failure
ITP	Interventions Testing Program
mTOR	mammalian target of rapamycin
mTORC1	mammalian target of rapamycin complex 1
NAD	nicotinamide adenine dinucleotide
NF-κB	nuclear factor kappa light chain enhancer of activated B cells
NLRP3	NACHT, LRR, and PYD domains-containing protein 3
SASP	secretory phenotype
SDOH	social determinants of health
SGLT2	sodium-glucose co-transporter 2
T2DM	type 2 diabetes mellitus
TGN	Translational Geroscience Network
TNF	tumor necrosis factor

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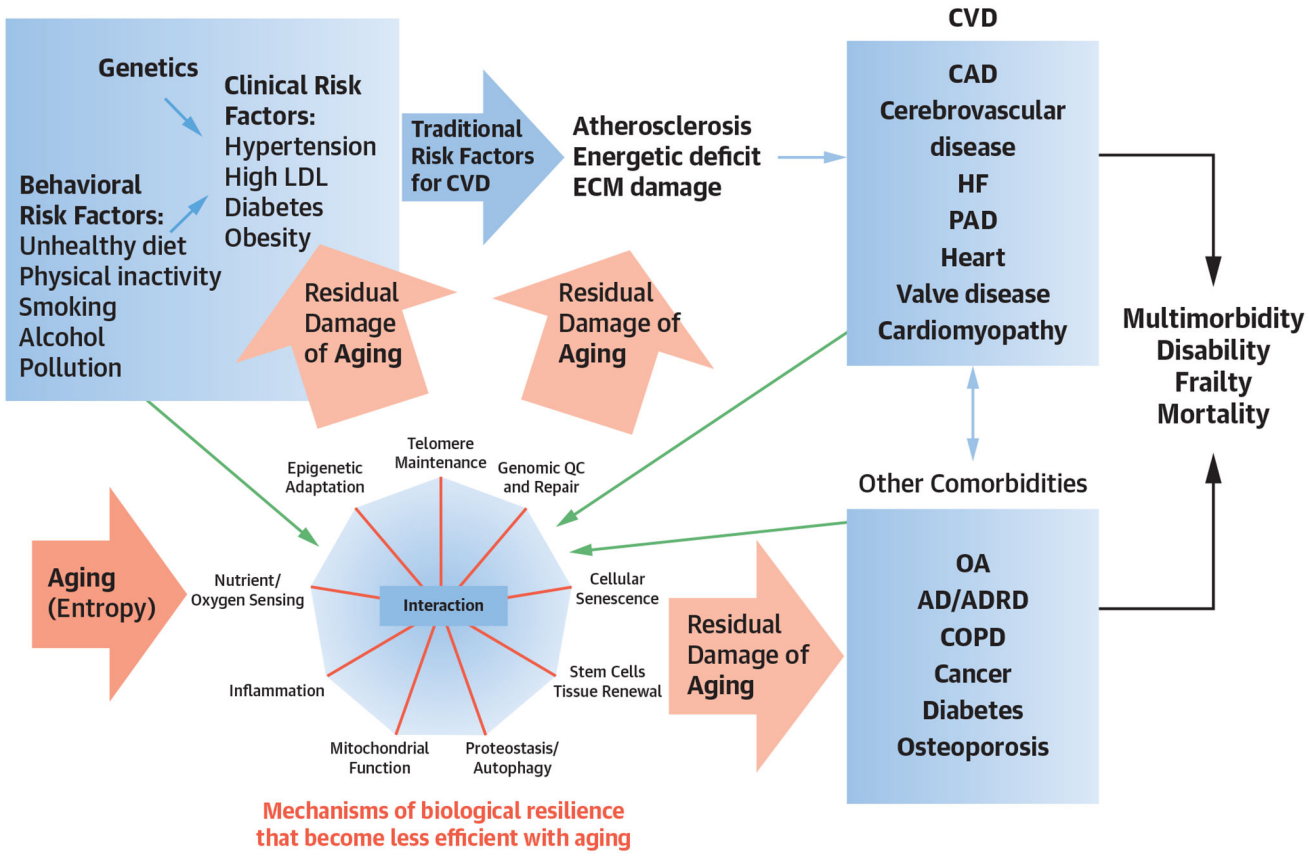
HIGHLIGHTS

- Reduced efficiency of mechanisms opposing age-related molecular damage increases susceptibility to cardiovascular disease.
- Key resilience mechanisms associated with aging have been identified as potential therapeutic targets.
- By targeting these mechanisms, geroscience could transform the diagnosis, prevention, treatment, and prognosis of cardiovascular disease in an aging population.



CENTRAL ILLUSTRATION.

The Geroscience Hypothesis in the Context of Cardiovascular Disease

Genetic predisposition and unhealthy behaviors (**blue arrows**) contribute to major CVD risk factors and CVD in older persons. Aging itself is associated with stochastic damage to molecules and organelles (**pink arrows**) and accelerates risks of CVD, as well as multimorbidity, frailty, disability, and premature death. Whereas resilience signifies capacity to repair or replace such damaged components, resilience often diminishes over time, especially amid behavioral risk factors (eg, unhealthy diet) and chronic diseases (**green arrows**). The geroscience hypothesis poses that enhancing resilience reduces the burden of CVD and other chronic diseases and related susceptibility to frailty and disability. AD/ADRD = Alzheimer disease and Alzheimer disease-related dementias; CAD = coronary heart disease; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; ECM = extracellular matrix; HF = heart failure; LDL = low-density lipoprotein; OA = osteoarthritis; PAD = peripheral arterial disease; QC = quality control.

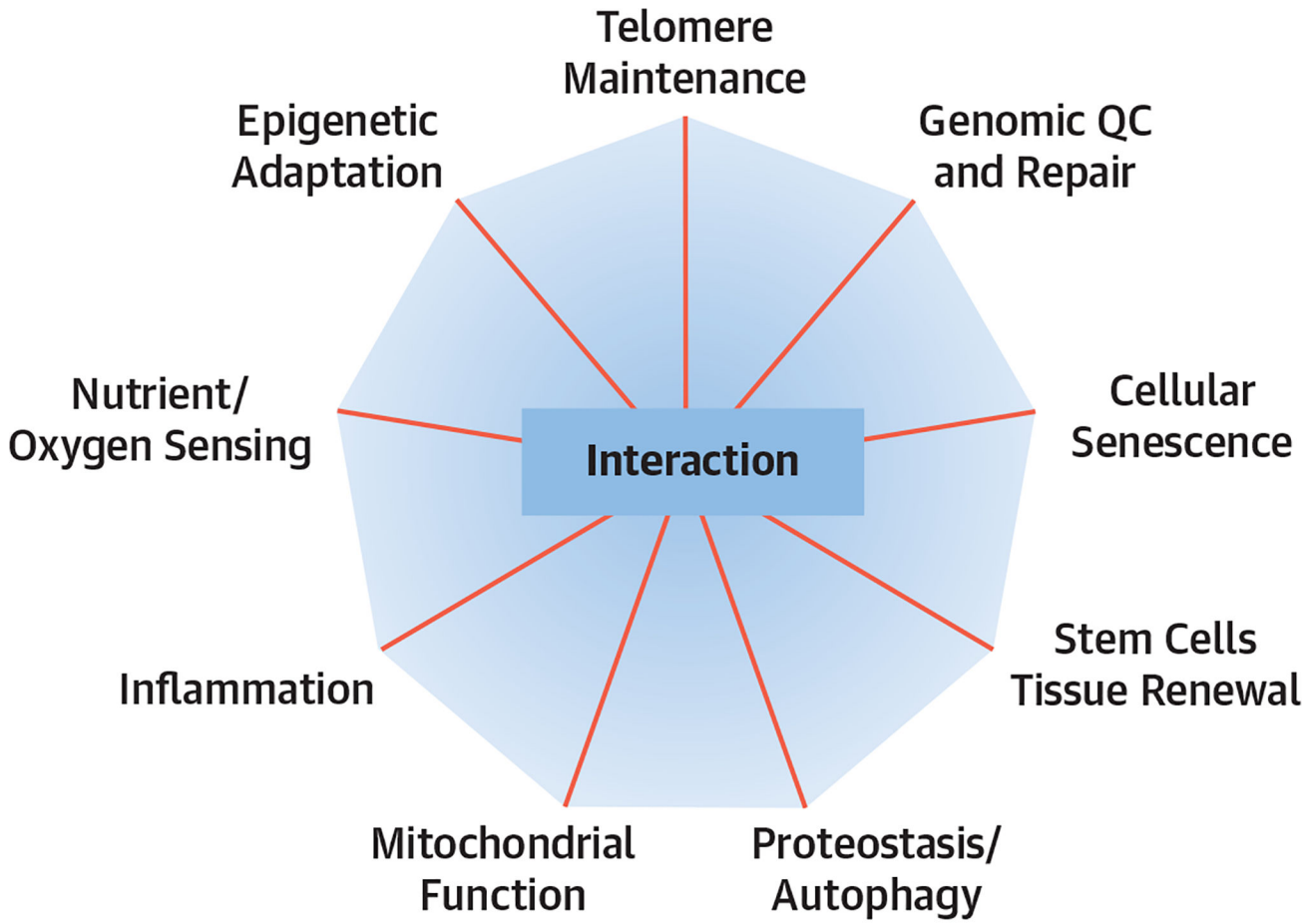


FIGURE 1.

The Hallmarks of Aging

Biological processes that become impaired with aging can be potentially targeted by gerotherapeutics. The intersecting lines depict how targeting each pillar can affect the others. QC = quality control.

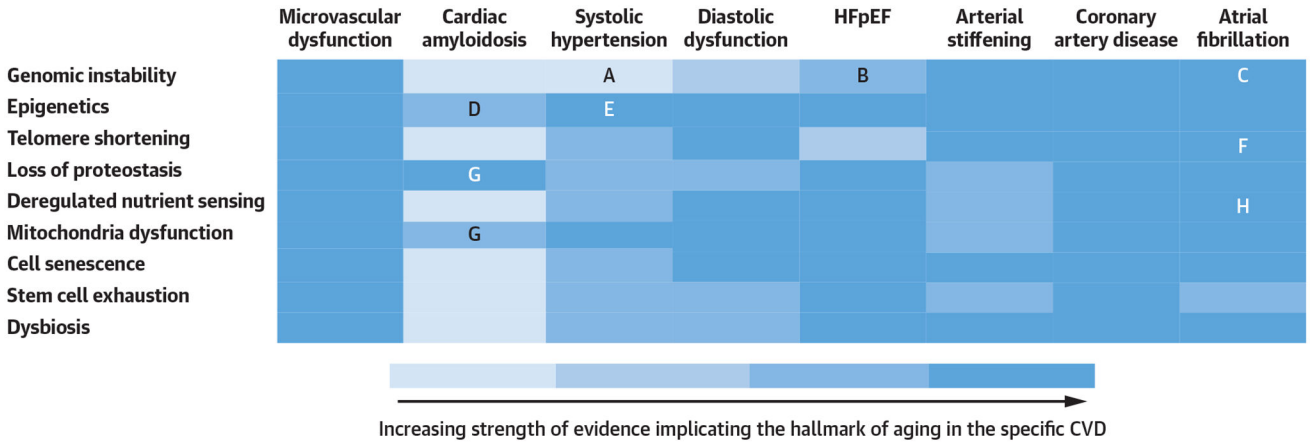


FIGURE 2.

Aging Hallmarks and Cardiovascular Disease

Heat map providing a visual representation of the strength of evidence in the literature implicating hallmarks of aging in cardiovascular disease (CVD). See Supplemental Figure 1 for added detail regarding the associated references. **A**, Genomic stability and systolic hypertension. **B**, Genomic stability and heart failure with preserved ejection fraction (HFpEF). **C**, Genomic instability and atrial fibrillation. **D**, Epigenetics and amyloid. **E**, Epigenetics and systolic hypertension. **F**, Telomere modification and atrial fibrillation. **G**, Loss of proteostasis, mitochondrial dysfunction, and amyloid. **H**, Deregulated nutrient sensing and atrial fibrillation.

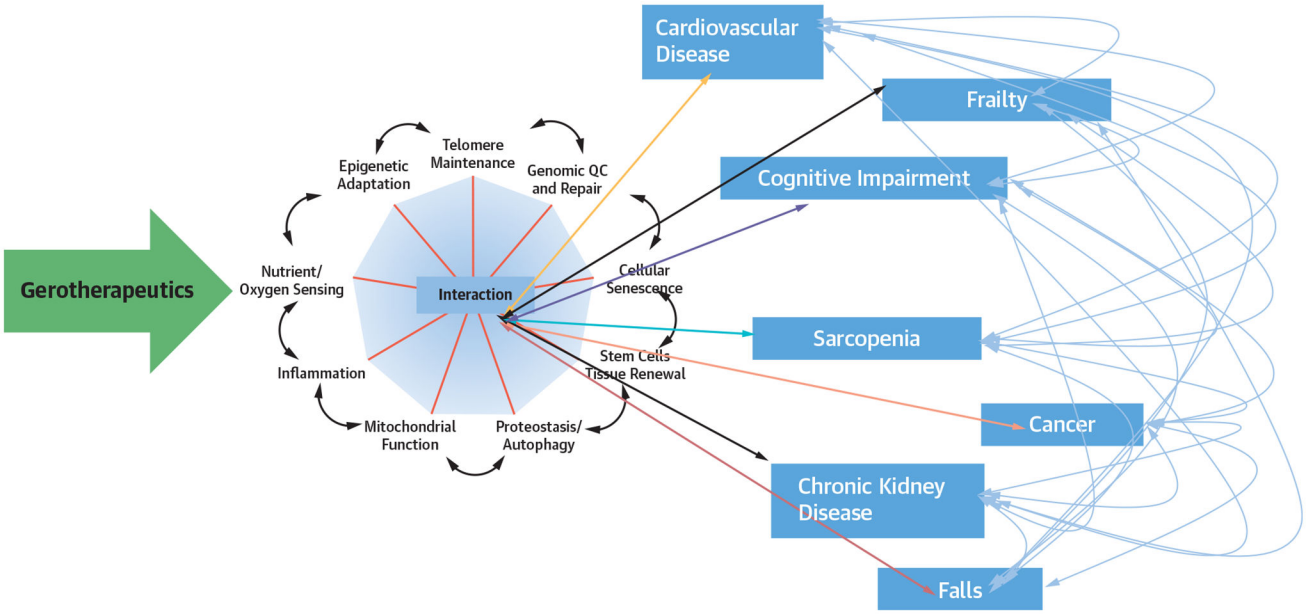


FIGURE 3.

Pleotropic Effects of Gerotherapeutics

Aging mechanisms are interconnected such that an intervention targeting a single hallmark of aging or multiple hallmarks of aging also exerts downstream effects on varied other hallmarks of aging. As a result of such interactions among varied biological hallmarks of aging, an intervention targeting a single hallmark can exert variable effects on multiple chronic diseases and geriatric syndromes. An ideal gerotherapeutic intervention moderates multiple hallmarks to prevent disease and geriatric conditions. QC = quality control.

TABLE 1

Glossary of Relevant Terms

Geroscience	Research focus premised on the concept that the physiology of aging plays a determinant role in chronic diseases as well as geriatric syndromes. Related assumptions are that are common therapeutic approaches to prolong life and moderate chronic diseases as well as geriatric syndromes.
Lifespan	Duration of life for a species or subgroup within a species.
Healthspan	Duration of life spent in good health, free from the chronic diseases and disabilities of aging.
Hallmarks of aging	Cellular biologic processes that are manifest with aging and that interact in various combinations within each adult to modify lifespan and healthspan.
Resilience	The intrinsic capacity to tolerate stresses including molecular, cellular, and systems mechanisms.
Geriatric syndrome	Health impairments that do not fit into discrete disease categories. Multimorbidity and frailty are common geriatric syndromes, with high prevalence in older adults with cardiovascular disease.

TABLE 2

Geriatric Syndromes

Geriatric Syndromes	Definition
Multimorbidity	≥2 chronic medical conditions[4]
Frailty	2 prevailing models • Fried phenotype[3,105]: ≥3 of the following 5 criteria: weight loss, exhaustion, low physical activity, slowness, weakness • Deficit index[166]
Falls	Episodes of sudden, involuntary transfer of body to the ground and at a lower level than the previous one
Cognitive impairment	Mild cognitive impairment (MCI): declining and disturbance of cognition, minimal impairment of complex activities, ability to perform regular daily functions, and absence of dementia Dementia: loss of cognitive functions of thinking, remembering, and reasoning to the extent that it interferes with doing everyday activities
Multisensory impairment	Loss of visual acuity, hearing, olfaction, taste, and tactile sensitivity that affect everyday functioning among older adults
Sarcopenia	Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality EWGSOP definition[167]: 3 criteria used for sarcopenia assessment: **1** Low muscle strength **2** Low muscle quality or quantity **3** Low physical performance Criterion 1 identifies probable sarcopenia, diagnosis is confirmed by criterion 2 and if all 3 criteria are met, severe sarcopenia is diagnosed
Polypharmacy	Use of ≥5 medications