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Review

Oncology-Derived Strategies for Age-Related Diseases: Intersections of Oncogenesis, Senescence, and Immunity

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ABSTRACT: Growing evidence has highlighted that the same biological pathways implicated in oncogenesis also regulate the aging process, by influencing the organism's capacity to surveil and respond to cellular aberrations. Emerging therapeutic strategies, including senolytic agents, metabolic modulators and immunotherapies, not only hold promises for cancer treatment, but offer possibilities for mitigating the degenerative consequences of aging. This review seeks to integrate recent developments, provides insights into the overlapping molecular pathways that underlie both cancer and age-related disorders, while offering an in-depth exploration of the subtle dynamics in immune system, and explores how certain cancer therapies can be leveraged for managing age-related conditions. Furthermore, it illustrates the critical role of immune restoration as a therapeutic mechanism and examines the key considerations and potential pitfalls when adapting cancer treatments to age-related diseases.

Keywords: aging, immunotherapy, cellular senescence, oncology

Introduction

The past decade has seen a rapid increase in overlap between oncology and gerontology, with accumulating evidence suggesting that the physiological processes governing cancer and aging are deeply interwoven through shared molecular and cellular pathways. While senescence may halt the proliferation of damaged cells and thereby restrain early malignant transformation, its persistence contributes to both systemic deterioration and an increased predisposition to tumorigenesis. The dual role presents a paradox that has promoted research into the shared mechanisms of cancer biology and age-related pathologies.

The aging process is characterized by a gradual decline in physiological function. The 2013 "Hallmarks of Aging" identified 9 canonical domains (genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion and altered intercellular communication), while the 2023 update has expanded this list to 12 by adding disabled macroautophagy, chronic inflammation, and dysbiosis [1, 2].

The accumulation of senescent cells and their senescence-associated secretory phenotype (SASP) shift the microenvironment toward a pro-inflammatory state. While the activation of inflammatory cascades mobilizes immune cells to clear damaged or transformed cells, it simultaneously induces chronic inflammation and accelerates tissue degeneration [3]. Besides, the state of sustained immune activation ultimately impairs effective immune system, which in turn increases susceptibility to neoplastic transformation [4]. The delicate balance between surveillance and damage is harder to maintain in the setting of immunosenescence, where the functional capacity of immune cells diminishes with age, leading to impaired antigen recognition and reduced effective

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immune responses. The aging immune system not only fails to efficiently eliminate senescent or cancerous cells but may also be co-opted by tumors to achieve immune evasion [5].

As oncology has advanced, the impact of aging biology on cancer development and treatment response has become increasingly clear. Accumulation of senescent cells and the gradual decline of immune competence weaken tumor immunosurveillance and favor a more permissive, immunosuppressive microenvironment in older individuals, contributing to higher cancer incidence and poorer outcomes in late life [6]. As a matter of fact, many widely used cytotoxic anticancer drugs act on pathways that also regulate cellular senescence, partially because senescence programs and oncogenic transformation are driven by closely overlapping signalling networks [7]. Notably, the prototypical senolytic combination of dasatinib and quercetin has its origins in oncology: dasatinib is a tyrosine kinase inhibitor first approved for leukemia, and quercetin had long been studied for its anti-tumor and cytoprotective properties, before the two were repurposed together to selectively eliminate senescent cells [8].

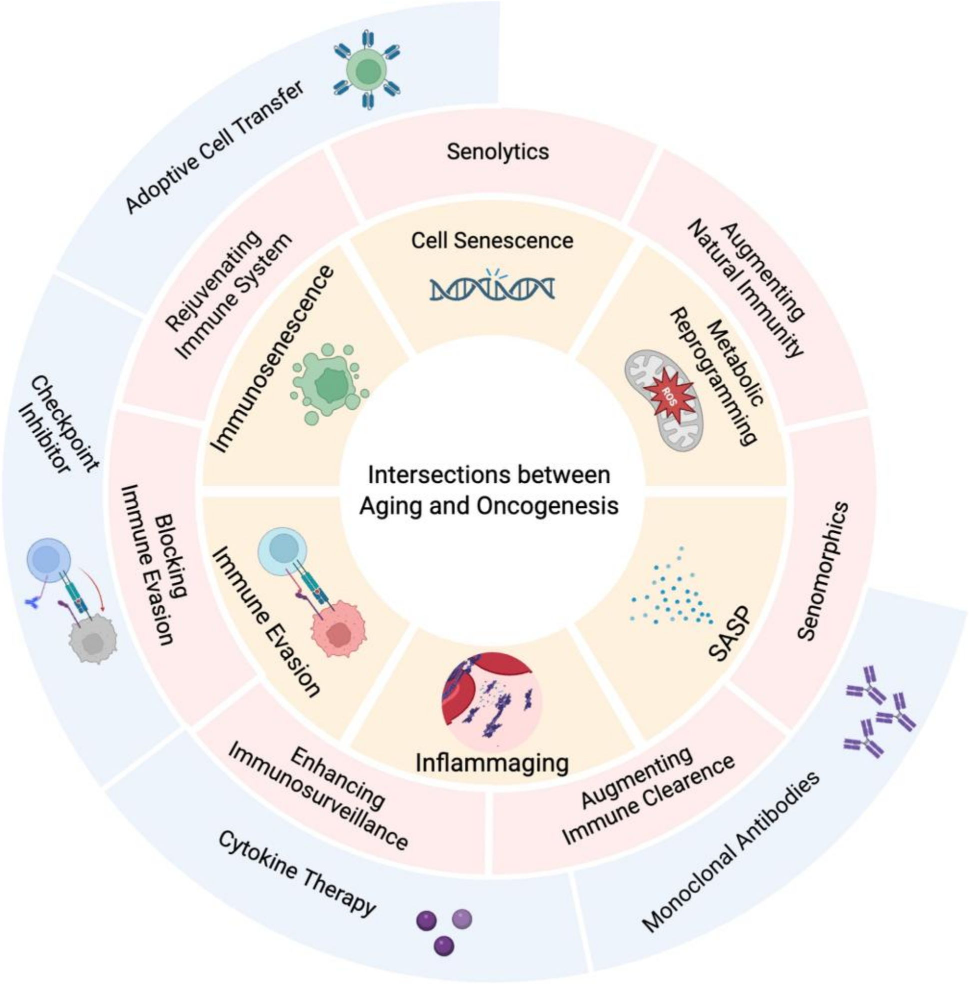

Figure 1. Intersections between aging and oncogenesis: mechanisms, therapeutic strategies, and translational immunotherapy. The conceptual overview summarizes the framework of this work. The inner ring depicts shared mechanisms of aging and oncogenesis, which the middle ring translates into intervention strategies (senolytics, senomorphics, metabolic regulators and immune rejuvenation). The outer semi-ring summarizes an oncology-derived immunotherapy toolbox that implements strategies of immune rejuvenation.

Advances in cancer immunotherapy (most notably immune checkpoint inhibitor [ICI], adoptive cell transfer, and cancer vaccines) have begun to extend into the realm of age-related diseases [9-12]. These therapies, originally designed to target specific antigens and reinvigorate exhausted immune responses, are now being repurposed to mitigate chronic inflammation, reverse tissue degeneration, and restore immune competence in age-related conditions. This work summarizes recent advances in application of cancer immunotherapies to age-related pathologies and discusses potential pitfalls and safety considerations that must be addressed as these interventions shift from treating malignancy to modulating age-related dysfunction. Figure 1 provides a conceptual overview of this work. Integrating mechanistic and clinical perspectives, we examine oncology-derived immunotherapies as candidate gerotherapeutics for non-malignant age-related diseases, a topic that has rarely been systematically addressed in earlier work.

Shared mechanisms

Cellular senescence

The intricate relationship between age-related diseases and cancer is rooted in gradual erosion of cellular homeostasis, with genomic instability serving as a fundamental driver. In healthy cells, precise DNA repair systems operate tirelessly to maintain genomic fidelity. Nevertheless, the cumulative burden of environmental insults and replicative stress leads to a progressive decline in these repair pathways. The deterioration results in either oncogenic transformation (triggered by the accumulation of mutations) or cellular senescence, a protective response that becomes increasingly prevalent with age and ultimately contributes to systemic decline.

Persistent activation of the DNA damage response (DDR) is a hallmark of senescent cells, where damage from telomere attrition, oxidative stress, or replication errors initiates a stable cell-cycle arrest [13]. DDR is initially protective, preventing the propagation of damaged DNA. However, chronic DDR signaling fuels tissue dysfunction and inflammation [14]. In principle, tumor cells commonly acquire mechanisms to bypass DDR checkpoints via mutations in key regulators such as tumor protein p53 (TP53) [15], ataxia telangiectasia mutated (ATM) [16], or breast cancer 1/2 (BRCA1/2) [17]. These alterations enable continued proliferation despite extensive genomic aberrations, promoting clonal evolution and tumor heterogeneity. Intriguingly, many early-stage cancers exhibit evidence of oncogene-induced senescence (OIS), in which hyperproliferative signals paradoxically activate DDR and cellular arrest. Accordingly, OIS is an anti-tumor barrier that must be overcome for full transformation [18]. Both aging and cancer engage DDR pathways as a stress-sensing and fate-determining network, yet the balance between repair, arrest, and evasion ultimately dictates divergent physiological outcomes. Strategies that restore efficient DNA repair may delay functional decline with age, while selective activation of DDR in tumor cells may re-sensitize them to genotoxic therapies.

The delicate balance between senescence and tumorigenesis is further complicated by the role of epigenetic modifications. DNA methylation patterns, histone modifications, and chromatin remodeling events—processes that are normally finely tuned—gradually become dysregulated over time [19]. The resulting “epigenetic drift” disrupts gene expression profiles essential for both normal cellular function and the ability to mount effective responses to stress. In cancer cells, similar epigenetic aberrations contribute to the silencing of tumor suppressor genes and the activation of oncogenic pathways, underscoring a striking parallel with the aging process [20, 21].

Metabolic reprogramming

A growing body of evidence highlights that cancer and aging, despite their opposing proliferative dynamics, share strikingly similar patterns of metabolic reprogramming. Both states undergo profound shifts in core metabolic circuits, including glucose, lipid, amino acid, and mitochondrial pathways, adapting cellular energy flux and biosynthesis to meet context-specific demands. In cancer, these alterations primarily support uncontrolled growth, enabling biomass accumulation and redox balance under proliferative stress. Meanwhile, aging, similar pathways are co-opted in response to cumulative damage, nutrient stress, and mitochondrial dysfunction, often leading to cellular senescence and functional decline.

Both cancer cells and senescent cells exhibit a shift toward aerobic glycolysis, known as the Warburg effect, despite their distinct proliferative capacities. This metabolic rewiring not merely supports ATP production but also modulates the cellular redox state and epigenetic landscape [22-25]. Lipid metabolism, particularly de novo fatty acid synthesis and altered β-oxidation, is a shared feature as well, contributing to membrane remodeling in tumors and lipotoxicity in aging tissues [26-29]. Moreover, there are overlapping metabolic signatures reflecting deterioration in aging and hyperactivation in cancer—opposite responses that can either drive dysfunction or promote survival, where the same pathways serve divergent purposes depending on the cellular environment and stressors involved. For instance, dysregulation of the tricarboxylic acid (TCA) cycle and electron transport chain are common to both contexts, fueling biosynthesis in cancer while driving reactive oxygen species (ROS) production and inflammatory signaling in aging [24, 30]. Table 1 summarizes overlapping metabolic features with consistent or divergent outcomes in aging and cancer.

Nutrient-sensing pathways such as AMP-activated protein kinase (AMPK)-mechanistic target of rapamycin (mTOR) act as metabolic hubs and link reprogramming events to immune function. Overactive mTOR signaling in aging organisms contributes to immunosenescence by promoting the differentiation of immune cells at the expense of regenerative capacity and by inhibiting autophagy [31-33]. In parallel, age-related declines in AMPK activity lead to excess mTOR activation and reduced autophagy and altered inflammatory signaling, exacerbating the senescent phenotype [34-36]. Chronic mTOR activation in aging T cells fosters the loss of naïve T-cell populations and the accumulation of dysfunctional, senescent-like memory cells, whereas in innate immune cells like macrophages, heightened mTOR/nuclear factor-κB (NF-κB) activity skews them toward a pro-inflammatory state [37, 38]. Activating AMPK promotes autophagy, mitigates pro-inflammatory effects, and helps to rejuvenate immune function by clearing damaged cellular components and dampening aberrant inflammasome activity. The AMPK activator metformin has been shown to enhance autophagy and normalize mitochondrial function in aged tissues, thereby reducing the SASP and systemic inflammation [36, 39].

Table 1. Metabolic reprogramming in cancer and aging.

Metabolic pathway	Role in cancer	Role in aging	Relationship	Key molecules/ enzymes	Reference
Glycolysis (Warburg effect)	Aerobic glycolysis supports biomass synthesis and rapid ATP production	Shift toward glycolysis in senescent cells; associated with mitochondrial decline	Aligned	GLUT1, HK2, PKM2, LDHA	[230-232]
TCA cycle and mitochondrial function	TCA intermediates diverted for biosynthesis; mitochondrial adaptation supports survival	Impaired TCA cycle and increased ROS production drive senescence and SASP	**Divergent**	IDH1/2, SDH, FH, PDH	[233-236]
Glutaminolysis	Glutamine used for TCA anaplerosis, nucleotide and NADPH synthesis	Reduced glutamine metabolism linked to impaired regeneration and nutrient sensing	**Divergent**	GLS1, ASCT2	[237, 238]
Lipid metabolism	Upregulated de novo lipogenesis supports membrane and signaling	Lipid accumulation and altered oxidation lead to lipotoxicity and inflammation	Aligned	FASN, ACC, SCD1, FAT/CD36	[239-241]
NAD^+ metabolism and sirtuins	Maintain DNA repair and survival via PARP and SIRT activation	NAD^+ depletion lowers SIRT activity, contributing to mitochondrial dysfunction and aging	**Divergent**	NAMPT, SIRT1/3, CD38	[242-244]
Redox metabolism and ROS regulation	Controlled ROS enhances proliferation and signaling; antioxidants limit toxicity	Excess ROS causes molecular damage, inflammation, and age-related decline	Biphasic	NRF2, GSH, SOD2, PRDXs	[235, 245, 246]
Autophagy and mTOR pathway	Autophagy modulated to manage metabolic stress; mTOR often hyperactive	Declined autophagy and persistent mTOR activity impair proteostasis and stem cell renewal	Mixed	AMPK, mTORC1, ULK1	[32, 247]

Abbreviations: GLUT1, glucose transporter 1; HK2, hexokinase 2; PKM2, pyruvate kinase M2; LDHA, lactate dehydrogenase A; IDH1/2, isocitrate dehydrogenase 1/2; SDH, succinate dehydrogenase; FH, fumarate hydratase; PDH, pyruvate dehydrogenase; NADPH, nicotinamide adenine dinucleotide phosphate; GLS1, glutaminase 1; ASCT2, alanine-serine-cysteine transporter 2; FASN, fatty acid synthase; ACC, acetyl-CoA carboxylase; SCD1, stearoyl-CoA desaturase 1; FAT, fatty-acid translocase; CD, cluster of differentiation; PARP, poly(ADP-ribose) polymerase; NAMPT, nicotinamide phosphoribosyltransferase; SIRT1/3, sirtuin 1/3; NRF2, nuclear factor erythroid 2 related factor 2; GSH, glutathione; SOD2, superoxide dismutase 2 (MnSOD); PRDXs, peroxiredoxins; mTORC1, mechanistic target of rapamycin complex 1; ULK1, Unc-51-like autophagy-activating kinase 1.

SASP and chronic inflammation

The cellular response to accumulated damage is embodied in the state of senescence. Senescent cells, characterized by an irreversible exit from the cell cycle, adopt a secretory phenotype that substantially alters their microenvironment. This senescence-associated secretory phenotype (SASP) is marked by the chronic release of inflammatory cytokines, chemokines, and proteases [14]. In some physiological processes, such as embryonic development and wound repair, the transient, programmed SASP (e.g., platelet-derived growth factor AA [PDGF-AA]) operates so that senescent cells are rapidly cleared and supports tissue remodeling. The response resolves once morphogenesis or repair is complete [40, 41]. On the contrary, persistent SASP in aged or chronically stressed tissues sustains low-grade inflammation and remodels the niche toward dysfunction and tumor promotion [42-44]. A comparable pro-inflammatory environment is commonly observed in tumors, where persistent inflammation and the dynamic crosstalk between malignant cells and stromal components not only fuel tumor progression but also promote the recruitment of immunosuppressive cells, thereby establishing a niche that facilitates immune escape. When persistently expressed, the pro-inflammatory and tissue-remodeling effects of SASP may shift the local microenvironment from protective to pro-tumorigenic [45].

Typically, persistent DDR signaling and cytosolic DNA sensing via the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) axis reinforce nuclear factor κB (NF-κB), interleukin-6 (IL-6), type I interferon and SASP components, thereby amplifying inflammation and contributing to tissue injury in aging [46-48].

Chemoattractants such as C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 1 (CXCL1) and IL-8 drive the infiltration of macrophages and neutrophils into senescent niches [45, 49]. While these immune cells can contribute to the clearance of senescent cells, their persistent recruitment in aging tissues is often maladaptive [50]. Chronically stimulated macrophages may shift toward an M2-like, tumor-supportive phenotype, while neutrophils promote local oxidative stress, angiogenesis, and even metastasis in cancer [50-52]. This creates a vicious cycle in which SASP-induced immune infiltration fails to eliminate senescent cells but instead reinforces inflammatory signaling and tissue damage.

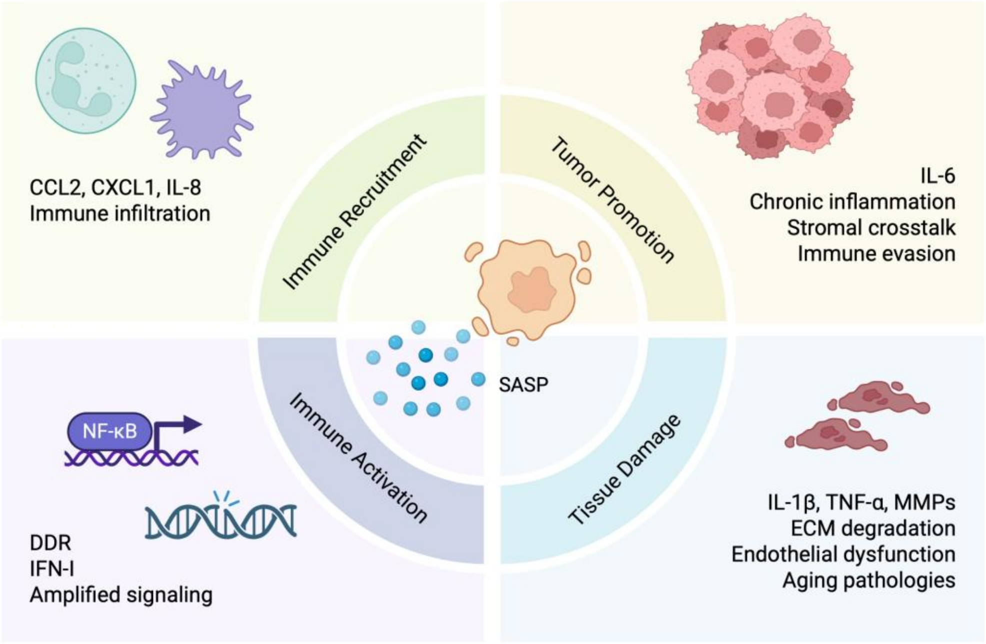

Figure 2. **Diverse pathological consequences of the senescence-associated secretory phenotype (SASP).** Senescent cells secrete a complex mixture of cytokines, chemokines, growth factors, and proteases collectively known as the SASP. These factors act through four major axes to remodel the tissue microenvironment. SASP-derived chemokines such as CCL2, CXCL1, and IL-8 promote infiltration of immune cells, including neutrophils and macrophages. Chronic inflammation and sustained IL-6 signaling foster stromal crosstalk and immune evasion, creating a tumor-supportive niche. Pro-inflammatory cytokines including IL-1β and TNF-α, along with matrix-degrading enzymes such as MMPs, contribute to endothelial dysfunction, extracellular matrix breakdown, and age-related pathologies. Persistent DNA damage responses (DDR) and cytoplasmic chromatin fragments activate signaling pathways such as NF-κB and cGAS-STING, enhancing type I interferon production and amplifying innate immune responses.

IL-6, IL-1β, and tumor necrosis factor-α (TNF-α) are critical mediators of autocrine and paracrine reinforcement of the senescent state. IL-6 and IL-1β synergistically activate NF-κB and transducer and activator of transcription 3 (STAT3) signaling, sustaining SASP expression and propagating senescence to neighboring cells (paracrine senescence) [53-55]. TNF-α further destabilizes tissue integrity by promoting endothelial dysfunction and matrix degradation [56, 57]. These cytokines are not only implicated in age-related pathologies such as sarcopenia [58, 59], insulin resistance [60], and neurodegeneration [61], but also contribute to immune evasion and therapy resistance in tumors [62, 63]. Overall, SASP is the central driver of diverse pathological consequences, including chronic immune activation, tissue damage and tumor promotion (Fig. 2)

Recent evidence highlights that certain SASP components are tissue specific [64]. For example, senescent colon fibroblasts under oxidative stress secrete growth differentiation factor 15 (GDF15) that promotes colon epithelial proliferation, migration, and invasion. Meanwhile, GDF15-rich SASP profiles skew the tumor microenvironment towards immunosuppression [65]. Tumor-derived GDF15 has been shown to block T cell recruitment and impair anti-tumor immunity [66].

Matrix metalloproteinases (MMPs) are core components and good examples of tissue- and context-specificity of the SASP. In fibrotic liver, senescent hepatic stellate cells upregulate matrix-degrading enzymes and thereby promote scar resolution, illustrating that senescent-associated MMPs can be tissue-protective in specific settings [67]. By contrast, in epithelial cancers, senescent stromal fibroblasts deploy MMPs with pro-tumor consequences—senescent cancer-associated fibroblasts secrete and activate MMP2, which disrupts cell-cell adhesion and drives keratinocyte invasion in a TGF-β-dependent manner, and blocking MMP2 abrogates these effects [68, 69]. Moreover, MMP3 secretion from senescent cells can induce epithelial-mesenchymal transition and genomic instability in epithelial cells [70]. In the crosstalk of idiopathic pulmonary fibrosis (IPF) and cancer, senescent fibroblasts secrete MMP1 that activate protease-activated receptor 1 (PAR1) and phosphoinositide 3-kinase (PI3K)-AKT (protein kinase B)-mTOR signaling in recipient tumor cells to promote non-small cell lung cancer (NSCLC) growth, and genetic or pharmacologic disruption of the MMP1-PAR1 axis blunts these phenotypes [71]. Collectively, both the constituents and downstream effects of the SASP depend on the inducer and the tissue context, and the SASP reprogramming could contribute to age-related tumor susceptibility.

Inflammaging

The chronic, low-grade inflammation observed in aging, termed parainflammation or inflammaging, is increasingly recognized as a systemic manifestation of persistent SASP signaling and immune dysregulation. Unlike classical inflammation, parainflammation lacks overt signs of infection or injury but features sustained expression of inflammatory mediators, altered tissue-resident immune populations, and metabolic reprogramming. In this state, senescent cells act as non-resolving inflammatory foci, impairing regeneration and promoting fibrosis, thereby linking aging to diseases such as osteoarthritis [72], cardiovascular disease [42], and cancer [45, 73]. The inability of the aging immune system to effectively clear senescent cells further perpetuate this pro-inflammatory loop.

There is a paradoxical coexistence of immune exhaustion and hyperactivity within the aging organism. While many immune cells exhibit features of senescence, others adopt a persistently activated state that contributes to tissue damage. Additionally, the regulatory networks become disrupted, leading to a “hypoactive yet hyperinflammatory” immune state where immune cells fail to clear pathological cells and harm normal tissue. This delicate interplay is mirrored in the tumor microenvironment, where cancer cells not merely evade immune surveillance but also actively manipulate immune cells to create a niche favorable for their own survival and growth. The low-grade inflammation in aging tissues parallels the tumor-promoting inflammation in malignant tissues, further emphasizing the shared molecular underpinnings of these pathologies.

Immune evasion

Senescent and malignant cells deploy similar mechanisms to evade immune surveillance, allowing their persistence in tissues despite immune recognition. A key feature of the immune escape is the upregulation of immune checkpoint molecules such as programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) [74, 75]. While their expression in tumor cells facilitates resistance to T cell-mediated cytotoxicity, senescent cells also exhibit increased PD-L1 expression, which has been implicated in suppressing T cell activity and promoting immune tolerance in aging tissues [9, 76]. The recruitment of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) creates a localized immunosuppressive environment. Both senescent and malignant cells secrete chemokines (e.g. CCL2 and CXCL12) that preferentially attract immune-regulatory cells, further dampening cytotoxic immune responses and enabling immune evasion [77, 78].

Loss of antigenicity and immunogenicity is another shared hallmark of immune escape in aging and cancer. Accumulation of epigenetic alterations, downregulation of histocompatibility complex (MHC) class I molecules, and altered proteasomal processing in senescent and tumor cells impair immune recognition by antigen-presenting cells and cytotoxic lymphocytes [79-81]. Immunological invisibility contributes to the failure of immunosurveillance in both contexts.

Moreover, senescent and malignant cells exploit immune-privileged niches, which are spatially confined tissue microenvironments with limited immune cell infiltration, such as hypoxic cores or fibrotic capsules in tumors [82]. Aging tissues, particularly those affected by fibrosis or chronic inflammation, may mimic such niches through extracellular matrix remodeling [83] and vascular dysfunction [84, 85], creating physical and biochemical barriers to immune cell entry. These shared mechanisms illustrate how senescent and tumor cells hinder immune access, not only through cell-intrinsic alterations but also by actively shaping their immunological micro-environment to avoid elimination.

Immunosenescence

Interwoven with inflammaging and immune evasion is the transformation of the immune system itself. Immunosenescence, defined by the gradual deterioration of immune competence, is a hallmark of aging. The transformation is characterized by the decline in the production of naive T cells due to thymic involution [86, 87], the expansion of memory and senescent T cell populations [88], the diminished capacity of natural killer (NK) cells [89] and a redistribution of other immune cell lineages [90]. The altered cytokine milieu in aged individuals, shaped by the SASP and chronic inflammation, further impairs immune cell function. The interplay between immunosenescence and chronic inflammation creates a self-perpetuating cycle, in which impaired immune function fuels further tissue damage and vice versa.

When it comes to malignancy, as the immune system's surveillance capacity wanes, the body becomes less adept at detecting and eliminating emerging neoplastic cells. Meanwhile, the immune system of an aging organism in many ways mirrors the tumor microenvironment in its inability to mount a robust, effective response against aberrant cells, which could be particularly detrimental. Therefore, strategies aimed at rejuvenating the immune system have emerged as a promising frontier in both oncology and geriatric medicine.

Oncology-derived senolytics and senomorphics

Cancer research has furnished an arsenal of small-molecule drugs that can be repurposed to selectively kill senescent cells (senolytics) or suppress their pathogenic secretions (senomorphics). Many senolytics target the same anti-apoptotic pathways that allow tumor cells to survive. For example, navitoclax (ABT-263), an inhibitor of B-cell lymphoma 2 (BCL-2) and B-cell lymphoma extra-large (BCL-xL) developed for leukemia, is one of the first senolytics identified [91-94]. In aged non-human primates, navitoclax reduced biomarkers of senescent cells and neuroinflammation, indicating brain penetrance and senolytic activity [95]. The dose-limiting thrombocytopenia in early clinical studies, which is consistent with the dependence of platelets on BCL-xL for survival [96-98], was markedly reduced by selective BCL-2 inhibitor thrombocytopenia and ABT-199 (Venclexta) has been approved for Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) [99, 100]. More recently, the selective BCL-xL proteolysis-targeting chimera (PROTAC) degraders exhibited potent activity with markedly reduced platelet toxicity and have advanced to in-human evaluation [101, 102]. Alternatively, the platelet toxicity can be reduced by conjugating navitoclax to a cleavable galactose moiety. This prodrug is preferentially activated by SA-β-gal within senescent cells [103]. The same strategy could be applied to duocarmycin, yielding Galactose-modified duocarmycin (GMD) [104]. Li et al. recently reported that senescence-specific killing compound 1 (SSK1), a β-galactosidase-targeted senolytic prodrug, selectively eliminated senescent chondrocytes, suppressed SASP factors, increased extracellular matrix (ECM) production and ameliorated preclinical post-traumatic osteoarthritis (OA) [105].

Dasatinib, a tyrosine kinase inhibitor approved for leukemia, in combination with the flavonoid quercetin (the D+Q cocktail), has also shown senolytic effects [8]. Notably, a pilot clinical trial in older individuals at risk for Alzheimer's disease (AD) found that a 12-week intermittent D+Q regimen was safe and associated with improved cognition (a+2 point Montreal Cognitive Assessment [MoCA] score in the most impaired participants). The regimen reduced systemic levels of TNF-α, a pro-inflammatory senescence-associated cytokine. These findings suggest D+Q can alleviate the neuroinflammatory burden in aging [106]. The senolytic acitivity of flavonoid fisetin has also been revealed and its optimized derivatives, CMS121 is under preclinical and early clinical pharmacology assessment (NCT05318040) [107, 108]. The FOXO4-derived D-retro-inverso peptide (FOXO4-DRI), which disrupts the FOXO4-p53 interaction, selectively eliminates senescent cells and mitigates chemo- and age- related dysfunction in mice [109]. FOXO4-DRI is also being explored in oncology contexts to clear therapy-induced senescent cells and is being deployed in "one-two punch" [73, 110, 111].

In addition to killing senescent cells, oncology-derived drugs can be used in sub-lethal ways to modulate senescent cell behavior. Janus kinase/signal transducer and activator of transcription (JAK/STAT) inhibitors like ruxolitinib (approved for myelofibrosis) have emerged as prototypical senomorphics. Ruxolitinib inhibits the SASP by blocking cytokine signaling, thereby alleviating the pro-inflammatory state without killing the cells [112]. In aged mice, ruxolitinib reduced systemic and adipose tissue inflammation and improved cardiac and lung function in models of age-related disease [113, 114].

The above applications illustrate how oncology-derived agents can be leveraged to eliminate senescent cells or suppress the SASP, helping restore tissue homeostasis and organ function in aging organisms. Nevertheless, clinical translation is limited by on- and off-target toxicity, low oral bioavailability and penetration problem. Besides, widely used senescence models such as IMR90 ER:HRAS^{G12V} human fibroblasts [115] and INK-ATTAC (p16^{Ink4a}-driven "Apoptosis Through Targeted Activation of Caspase") transgenic mice [116] sample only portions of the senescent landscape. As a result, conclusions tend to be inducer-contingent and tissue-specific. To date, no single biomarker or transgenic model universally identifies or encompasses senescent cells across tissues [117]. Recent progress has been made: Carver et al. recently confirmed in humans that plasma interleukin-23 receptor (IL-23R) levels increase with chronological age [118]. The IL-23/T helper 17 (Th17) axis was known for contributing to chronic, low-grade inflammation and barrier tissue pathology [119], and this research position IL-23R as a biomarker of "systemic senescent cell burden" rather than tissue-restricted senescence. The work also supports IL-23R as a candidate pharmacodynamic marker for future senolytic or senomorphic interventions in aging.

Table 2. Aging-directed strategies adapted from cancer therapeutics.

Therapy	Mechanism in cancer	Mechanism in aging	Gerotherapeutic evidence
Senolytics	Induce apoptosis in cancer cells	Induce apoptosis of senescent cells to reduce SASP and tissue damage	Preclinical
Senomorphics	Target inflammatory signaling in tumors to reduce cancer-related cachexia/inflammation	Suppress SASP and inflammatory secretions of senescent cells without killing them (modulate senescence phenotype)	Preclinical
Metabolic regulators	Curb malignant growth, expose metabolic vulnerabilities, and enhance responses to chemo-, radio- and immunotherapies	Modulate stress-sensing pathways, rebalance bioenergetics and inflammation, improve immune function	Validated
Cytokine therapies	Expand and activate effector T and NK cells to combat cancer	Augment diminished immune cell populations and function in elderly; restore thymopoiesis and NK activity	Preclinical
Bispecific engagers	Drive targeted cytotoxicity and overcome immune escape	Selectively eliminate pathologic senescent cells, remodel inflammatory-fibrotic microenvironments and minimize off-target toxicity	Preclinical
Immune checkpoint inhibitors	Block T cell inhibitory pathways to unleash anti-tumor T cells	Reinvigorate exhausted T/NK cells to clear senescent cells and improve immune surveillance in tissues	Preclinical
Monoclonal antibodies	Target tumor antigens or immunosuppressive factors	Target senescence markers and tag senescent cells, neutralize SASP cytokines or pro-aging factors	Preclinical
Adoptive cell therapies	Patient or donor immune cells engineered or expanded to attack tumors	Senolytic CAR-T or CAR-M cells engineered to recognize senescence markers and eliminate senescent cells; adoptive infusion of youthful immune cells	Preclinical
Therapeutic vaccines	Vaccines encoding tumor antigens or neoantigens to induce anti-tumor immune response	Vaccines against age-related antigens to induce immunity that clears or neutralizes pro-aging factors	Preclinical

Immune restoration

Innovations in oncology are now being applied to the rejuvenation of the aging immune system. Cancer immunotherapies encompass several classes of interventions, including ICI and other monoclonal antibodies, adoptive cell transfers, oncolytic vaccines and cytokine therapies, which have revolutionized cancer treatment by mobilizing the body's immune defenses. Aging is accompanied by the accumulation of senescent cells that secrete pro-inflammatory factors and evade immune clearance. By adapting oncology approaches to eliminate senescent cells, boost immune surveillance, and dampen inhibitory pathways, it may be possible to ameliorate multiple chronic diseases in parallel. In this section, we provide insights into how cancer immunotherapy paradigms are being translated into geriatric medicine. Table 2 summarizes aging-directed strategies adapted from cancer therapeutics and their mechanisms in cancer and aging, together with the current status of gerotherapeutic evidence. Most of these approaches remain in early-phase clinical trials or preclinical development in the context of aging and age-related diseases, as shown in Table 3.

Table 3. Clinical stage of senolytic strategies.

Intervention	Clinical stage	Clinical trial no.	Condition
Senolytics	D+Q Phase 2; fisetin Phase 2	NCT04685590 ongoing; NCT03430037 ongoing	AD; frailty and vascular cognitive impairment
Senomorphics	Preclinical	N/A	N/A
Metabolic regulators	Metformin Phase 3 and Phase 4; mTOR inhibitor Phase 2; NAD^+ precursor Phase 2	NCT02432287 completed; NCT04221750 ongoing; NCT04221750 ongoing; NCT04511416 ongoing; NCT04098666 ongoing; NCT02874924 completed; NCT04488601 completed; ACTRN12611001241921 completed; ACTRN12613001351707 completed; NCT05237687 ongoing; NCT05835999 ongoing; NCT02942888 completed; NCT06208527 ongoing; NCT03821623 ongoing; NCT05040321 ongoing	Aging and various age-related diseases
Cytokine therapies	GM-CSF Phase 2	NCT01409915 completed; NCT04902703 ongoing	AD
Immune checkpoint inhibitors	PD-1 blockade Phase 1	NCT05551741	AD
Monoclonal antibody	Approved: anti-Aβ; anti-RANKL, anti- sclerostin; anti VEGF-A; anti-PCSK9; anti-IL-6R	N/A	Approved for: AD[248, 249]; Osteoporosis[250, 251]; nAMD[252]; elevated LDL-C[253]; GCA[254]
Adoptive cell transfer	Preclinical	N/A	N/A
Senolytic vaccines	Anti-Tau vaccines Phase 2; anti-Amyloid vaccines Phase 2	NCT02579252 completed; NCT04445831 completed; NCT06544616 ongoing; NCT02551809 completed	AD

Clinical stage is defined for aging and age-related indications only; phases/approvals in other indications (e.g., oncology) are not counted here; for each treatment, the stage reflects the most advanced ongoing or completed trial; terminated studies are excluded from staging. Abbreviations: D+Q, dasatinib + quercetin; N/A, not applicable; RANKL, receptor activator of nuclear factor-κB ligand; VEGF-A, vascular endothelial growth factor A; nAMD, neovascular age-related macular degeneration; GCA, giant cell arteritis.

Augmenting natural immune clearance

The immune system naturally identifies and clears senescent or dysfunctional cells via surveillant NK cells, macrophages, and T cells. Aging, however, impairs immunosurveillance. Strategies to boost the body's innate clearance of senescent cells are therefore a priority. Preserving NK cell function has been highlighted in healthy aging, as NK cells target both senescent and malignant cells which upregulate stress ligands [10]. Adoptive transfer of ex vivo expanded NK cells is being explored as a means to bolster immune surveillance in older individuals, which could supply highly cytotoxic NK cells to an aging host, potentially clearing senescent cells that the endogenous aged NK pool fails to remove [120, 121].

Macrophage-mediated clearance of cell debris and apoptotic bodies is also impaired in aging, partly due to "don't-eat-me" signals on targets. Through blocking inhibitory signals and stimulating phagocytic capacity, colony-stimulating factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which have been approved in oncology to recover leukocytes after chemotherapy [122], help recruit and activate macrophages in tissues with heavy senescent cell burden [123]. In neurodegenerative disease, GM-CSF (sargramostim) has been tested with the rationale of activating microglia to clear amyloid [124]. Besides, there is evidence that simply improving the balance of immune cell subsets enhances clearance of senescent cells. For example, clearing senescent cytotoxic T ($CD8^+$ T) cells in adipose tissue leads to enhanced macrophage and T-cell function in mouse models [125]. Overall, by amplifying the innate immune mechanisms, a more powerful immune surveillance could naturally prune away senescent and premalignant cells before they accumulate.

Activating immune recognition pathways

Senescent cells persist partially because they exploit immune-ignorance: they escape immune detection or exist within immunosuppressive niches. Synthetic "adapter" molecules that make senescent cells more visible to immune cells have been developed, to activate innate and adaptive recognition pathways that label senescent cells. Targeting the spotlight molecule, a chimeric "adapter" peptide that binds urokinase plasminogen activator receptor (uPAR) and adds a polyanionic glutamate chain to the very cell-surface molecule, effectively opsonizing the senescent cell for NK cell adhesion and cytotoxicity. The chimeric peptide recruits immune effectors and physically crosslinks them to senescent cells, leading to immune-mediated senescent cell clearance in fibrotic liver, lung injury, and even natural aging models [126]. The "immunological conversion" strategy re-engages immune pathways by turning senescent cells from stealthy bystanders into immunogenic targets. By tagging senescent cells for recognition via synthetic peptides, bispecific engagers, and stimulation of pattern-recognition receptors [127], the immune system could be alerted and directed to remove cells and proteins driving age-related disease.

Blocking immune evasion mechanisms

Senescent cells have been shown to upregulate multiple inhibitory ligands that engage immune checkpoints on T cells, NK cells, and macrophages. For instance, senescent cells overexpress PD-L1, the ligand for PD-1, which can "turn off" cytotoxic $CD8^+$ T cells that might otherwise destroy them [76, 128]. They also display ligands that bind natural killer group 2A (NKG2A) and NKG2C on NK cells to inhibit their killing function [10, 80]. Furthermore, senescent cells can express "do not eat me" signals such as CD47 on their surface, engaging signal regulatory protein α (SIRPα) on macrophages to prevent phagocytosis, just as the malignant cells do [129-132]. These immune evasion tactics contribute to the accumulation of senescent cells with age, tipping the balance toward inflammation and tissue damage.

ICIs are being adapted for geriatric therapy. Preclinical studies have demonstrated that blocking PD-1/PD-L1 can improve senescent cell surveillance and ameliorate age-related phenotypes [9, 133]. IBC-Ab002, an Fc-modified anti-PD-L1 monoclonal antibody, is currently being evaluated in a first-in-human phase 1b trial in early AD (NCT05551741). The disialylated ganglioside (GD3) has been identified as a novel senescence-specific immune checkpoint. Senescent cells in various aging tissues upregulate GD3, which has been found to potently suppress NK cell immunosurveillance. Strikingly, an anti-GD3 monoclonal antibody treatment in mice has enabled immune clearance of $GD3^+$ senescent cells and has attenuated age-related pathologies like lung and liver fibrosis and bone loss, which establishes GD3 blockade as a gerotherapeutic strategy [134]. Similarly, experimental antibodies blocking CD47 (already in oncology trials) can relieve the brake on macrophages, allowing them to engulf senescent cells that used to escape phagocytosis [135-139]. By neutralizing these immune evasion signals, including PD-L1, CD47, GD3 and human leukocyte antigen E (HLA-E) [80], immune-evasion mechanisms of senescent cells are inhibited, allowing restoration of immune clearance. Importantly, ICI therapy must be carefully managed to avoid adverse effect including autoimmunity, yet they hold promise in breaking immune tolerance to deleterious aging cells.

Immunosurveillance-enhancing cytokines

Modulating cytokine levels offer opportunities to rejuvenate immune cell populations in the elderly. Cytokine therapies such as IL-2 and IL-15 infusion have been deployed to expand T cell and NK cell numbers in cancer. Similarly, boosting the production or signaling of cytokines that support lymphocyte development and survival represents a potential strategy to enhance immunosurveillance in aging. For example, supplementing IL-7, which is crucial for thymopoiesis and maintaining the naïve T cell pool, reverses thymic atrophy and increases T cell output and T cell receptor (TCR) diversity in older mice and middle-aged humans [140-142]. While complete thymic regeneration is challenging, IL-7 therapy could improve vaccine responses and immunocompetence.

The superagonists (e.g. ALT803) of IL-15, a key growth factor for NK cells and memory CD8$^+$ T cells, massively expand NK cell populations and enhance their cytotoxicity in cancer trials [143]. Intermittent low-dose IL-15 has been found to replenish the diminished NK cell pool [144] and holds the promise of bolstering the clearance of senescent cells or senescence-associated antigens. Cytokine-based interventions, including cytokine therapy and agents that recalibrate cytokine responses, enhance the surveillance and responsiveness of the aging immune system, making it more proficient at detecting and controlling emerging age-related diseases.

Rejuvenating aged immune system

Beyond targeting senescent cells or molecules, an important way of "immune restoration" is directly rejuvenating the aged immune cells themselves. With time, critical immune cell compartments (naïve T cells, NK cells and function of memory cells) decline. Approaches to restore a more youthful immune cell profile borrow ideas from regenerative medicine and cellular therapy. The strategies to reset the immune system, such as hematopoietic stem cell transplantation and partial reprogramming of immune cells, originate in oncology and transplant medicine. While a full bone marrow transplant is not a routine anti-aging therapy, milder analogues are being explored.

Circulating aged T cells can be re-expanded and "rejuvenated" ex vivo: With patients in their 60-70s achieving long-term remissions, Chimeric Antigen Receptor T cell (CAR-T) trials in older hematologic cancer patients have provided incidental evidence that aged T cells can be reinvigorated during the therapy process [145]. CAR-T manufacturing has shown that T cells from patients can be proliferated and activated to a vigorous state. Such ex vivo expansion could be used to generate autologous naïve or earlier-stage T cells for reinfusion. Researchers are developing *ex vivo* T memory stem cells, where a small number of a patient's T cells are driven back to a stem-like state and then expanded. These cells have robust proliferative capacity, essentially behaving like youthful T cells. For example, developmental cues bias CD8$^+$ T cells toward early-memory states through Wnt/β-catenin activation or pharmacologic AKT inhibition [146, 147]. Besides, T cells engineered to overexpress c-Jun or ablate nuclear receptor subfamily 4 group A (NR4A) become more resistant to exhaustion in mouse and human models [148, 149]. Constraining DNA methyltransferase 3A (DNMT3A)-dependent methylation or priming with low-dose decitabine epigenetically "resets" T cells and improves the efficacy of immunotherapy [150, 151].

In parallel, brief ex vivo exposure to IL-12/IL-15/IL-18 generates cytokine-induced memory-like (CIML) NK cells with durable antileukemia activity. CIML NK cells have shown robust antitumor responses in a human acute myeloid leukemia (AML) trail [152]. Together these oncology-derived playbooks enable functional rejuvenation of exhausted immune cells and the reconstitution of surveillance in older hosts (typically alongside vaccines or senolytics).

Metabolic regulators play a pivotal role in rejuvenating aged immune system. A low-dose mTOR inhibitor, which boosted T cell and myeloid function by modulating cytokine and growth factor signaling, improved the response of older volunteers to influenza vaccination and reduces overall infections [33]. Meanwhile, the AMPK activator metformin, backed by decades of clinical use in type 2 diabetes, is being repurposed in geroscience trials, the most advanced of which have reached phase 3/4 (Table 3). Importantly, impaired wound healing and wound-related infections have been reported in patients receiving rapamycin, whereas metformin use has been associated with rare but potentially fatal lactic acidosis in older or frail individuals, particularly in the presence of renal or cardiorespiratory impairment [153, 154]. Oxidized nicotinamide adenine dinucleotide (NAD$^+$) precursors, such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), have been shown to enhance the bioenergetics of aged lymphocytes, thereby improving their function [155-157], which is being tested in immunosenescent individuals [158, 159]. There is also intriguing research on partial cellular reprogramming with transient expression of Yamanaka factors to reverse epigenetic aging in cells including T cells [160], which raises the possibility of resetting the biological age of immune cells without altering their identity.

Targeting senescent immune cells is especially relevant for combatting immunosenescence and chronic inflammation. CD153 is a cell-surface receptor of the TNF family that marks senescent T cells in visceral fat. The CD153 senolytic vaccine elicits anti-CD153 antibodies that selectively deplete PD-1$^+$CD153$^+$ senescence-associated helper T (CD4$^+$ T) cells in obese mice via complement-dependent mechanisms, thereby reducing their osteopontin-rich SASP, alleviating adipose inflammation and improving glucose tolerance [125, 161]. Depleting exhausted or senescent NK cells could relieve competition for IL-15-limited homeostatic niches and reduce inhibitory signaling, thereby allowing fitter NK cells to expand and function more effectively [162, 163]. In summary, immune cell rejuvenation strategies include metabolic tuning, immune cell replacement or engineering, and senescent immune cell removal. Restored immunity not only fights external threats but is critical for surveying and repairing internal damage, thereby impacting overall aging.

Monoclonal antibodies targeting senescence-associated pathways

Monoclonal antibody (mAb) therapies directly target molecules and pathways implicated in aging and senescence by neutralizing pro-senescent or pro-inflammatory factors. Cell-surface proteins uniquely upregulated on senescent cells can be attacked by senescence-specific antibodies or antibody-drug conjugates (ADCs). Recent studies have identified candidates like β2 microglobulin (B2M) and Apolipoprotein D (ApoD) as senescence markers in certain tissues [164, 165]. A proof-of-concept ADC has been created by conjugating an anti-B2M antibody to a cytotoxic payload, which selectively bound senescent cells and eliminated about one-third of senescent cells in culture [166]. Similarly, an anti-ApoD ADC carrying a DNA synthesis inhibitor has been shown to selectively kill senescent fibroblasts in vitro and in vivo, improving tissue elasticity in aged mouse skin without harming young cells [165]. In early AD, mAbs that clear amyloid have shown clinical benefit: Lecanemab and donanemab have received United States Food and Drug Administration (FDA) approval after confirmatory Phase 3 trials demonstrated slowed cognitive decline, though its use is tempered by amyloid-related imaging abnormalities (ARIA) risk and monitoring needs [167, 168]. These strategies to clean up "aging debris" give a glimpse of a new precision medicine for age-related diseases.

The pro-inflammatory cytokine IL-1 is a component of the SASP and a known culprit in atherogenesis [169]. The mAb canakinumab (anti-IL-1β), originally developed for autoinflammatory diseases, was tested in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial on post-myocardial infarction patients (mean age ≈61 years). In the trial, canakinumab 150 mg quarterly reduced major adverse cardiovascular events (MACE) versus placebo, with concordant reductions in high-sensitivity C-reactive protein (hsCRP) and IL-6 and no effect on low-density lipoprotein cholesterol (LDL-C). These findings supported IL-1β as a therapeutic target in vascular aging, although increased fatal infections and lack of a consistent dose-response limited regulatory adoption [170, 171]. The lowering of IL-1β also coincidentally lowered the incidence of lung cancer—hinting that neutralizing SASP factors could reduce both cardiovascular and cancer risks in older adults [172]. IL-6 blockade (e.g. Ziltivekimab) lowers systemic inflammatory biomarkers in high-risk settings and holds promise for mitigating inflammaging and frailty in older adults [173, 174]. Anti-TNF-α agents, which has already been widely used in rheumatoid arthritis, could potentially be deployed to reduce chronic inflammation burden in the elderly [175]. However, infection risks in the elderly must be weighed [176]. Anti-oxidized LDL (OxLDL) antibodies can blunt foam-cell formation and slow atherogenesis in vivo [177]. Dipeptidyl peptidase-4 (DPP4, also known as CD26) is a promising target for metabolic syndrome, while anti-DPP4 antibodies are used primarily in oncology to date [178].

Aging remodels the splicing landscape through RNA-binding protein decline, epigenomic drift, and chronic stress signaling, yielding isoform-restricted extracellular epitopes that are scarce in young tissues. Such splice-variant neoantigens, including cryptic-exon insertions and age-biased domain truncations, represent a tractable class of targets for monoclonal antibodies, ADCs, and vaccine designs [179]. While this field is nascent, it offers a high-specificity approach complementary to traditional senescence antigens.

Redirecting CAR therapy to senescent cells

CAR-T cell therapy, a landmark in oncology, is now being repurposed as a "cellular senolytic" strategy. Normally, autologous CAR-T therapy involves collection of peripheral blood, T-cell isolation and activation, CAR transduction and expansion ex vivo, and reinfusion of the engineered cells after lymphodepletion (Fig. 3). CAR-T therapy offers a programmable, specific and durable approach to age-related diseases by recognizing surface markers of pathologic cells and wiping them out with high potency. Treatment of mice with anti-uPAR CAR-T cells selectively ablated senescent cells, which led to dramatic improvements in liver fibrosis and, in a cancer model, reduced tumor recurrence by clearing therapy-induced senescent cells [11]. Intriguingly, the follow-up study reported that mice receiving uPAR CAR-T cells showed enhanced glucose metabolism and physical fitness, with a lasting senolytic effect from a single infusion, suggesting that CAR-T cells could persist and provide long-term immune surveillance against senescent cells [180].

Senescent or stressed cells often upregulate ligands of NK cell receptor and evade immunity by engaging NKG2A/NKG2C [80]. CAR-T cells endowed with NKG2D have been shown in models of aging to efficiently eliminate senescent fibroblasts in vitro and clear senescent cells in vivo in naturally aged mice and in non-human primates, with no significant off-target toxicity observed [10]. This breakthrough in primates demonstrates the translational potential of CAR-T therapy for age-related indications.

Recent works position CAR-macrophages (CAR-M) as antifibrotic drugs for the injured heart: fibroblast activation protein-α (FAP)-targeted CAR-M cells, whether infused back as ex vivo engineered cells [181] or built in vivo via lipid-nanoparticle mRNA delivery [182], have reduced post–myocardial infarction (post-MI) cardiac fibrosis and have improved ventricular function, with benefits persisting and no evident toxicity, indicating a scalable platform for cardiac repair. Furthermore, in situ legumain engineering enhanced the phagolysosomal cargo degradation and efferocytosis of CAR-M, thereby restoring antifibrotic efficacy, shrinking infarct size, and further mitigating fibrosis after MI in mice, highlighting lysosomal tuning as a leverage point to potentiate CAR-M therapy for cardiac fibrosis [183].

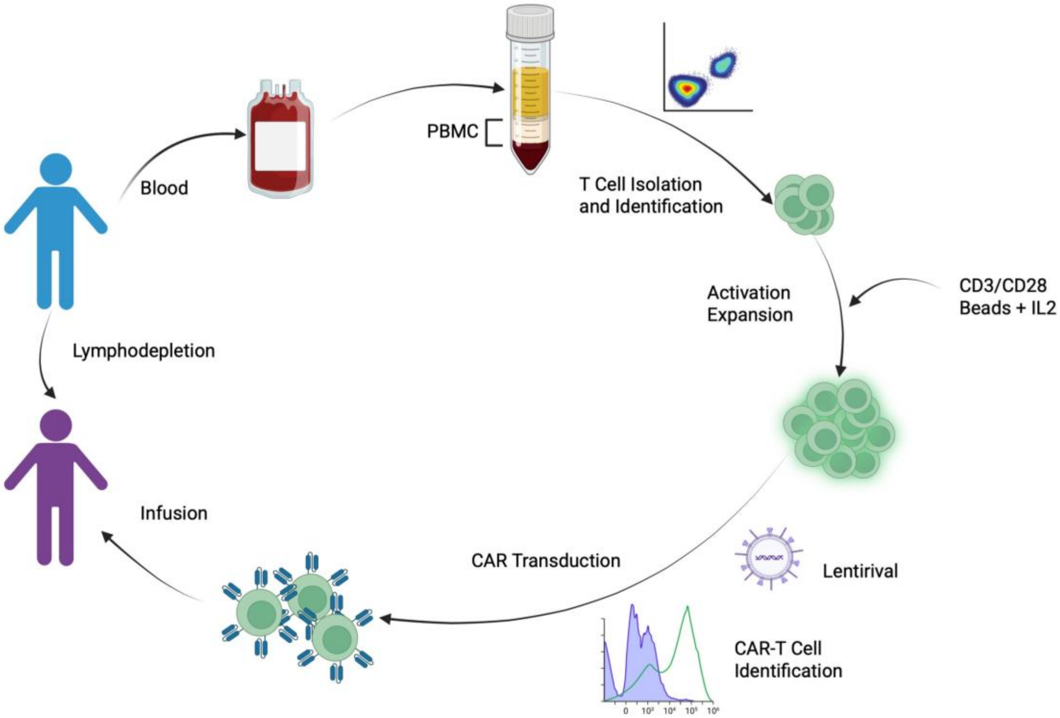

Figure 3. **Schematic representation of CAR-T procedure.** Peripheral blood is collected from the patient, and peripheral blood mononuclear cells (PBMCs) are isolated by density gradient centrifugation. T cells are further separated and identified by flow cytometry. Following activation and expansion with coated CD3/CD28 antibodies or artificial antigen-presenting cells (APCs) in the presence of IL-2, T cells are transduced with CAR constructs using viral (retrovirus or lentivirus) or non-viral (RNA or transposon) vectors. The resulting CAR-T cells are expanded in culture, re-activated, and amplified. Finally, the expanded CAR-T cells are infused back into the patient to exert anti-tumor effects.

The CAR therapy has been applied to neurodegenerative disorders, with the aim of clearing pathogenic proteins or re-establishing a normal immune milieu. In AD, the decline in microglial capacity to clear anti- amyloid-β (Aβ) is considered an important driver of pathological progression. Aβ CAR-M and CAR microglia markedly enhanced and selectively promoted phagocytic clearance of amyloid plaques in AD mouse models without overt toxicity, supporting the feasibility of engineering innate immune cells to restore Aβ clearance [184, 185]. In parallel, Aβ CAR-Tregs have been generated, which retain a stable regulatory phenotype, respond to Aβ, and suppress effector T-cell activation in vitro, consistent with in vivo data showing that Aβ-specific TCR-Tregs can attenuate amyloid burden and cognitive decline in amyloid precursor protein/presenilin-1 (APP/PS1) double-transgenic mice [186, 187].

Overall, CAR therapy portends a future where a patient could receive one-time cell therapy to clear harmful senescent accumulations and restore organ function. However, experience from oncology also underscores substantial safety and feasibility constraints. Approved CD19- and B-cell maturation antigen (BCMA)-directed CAR-T products can induce acute toxicities such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity, often requiring intensive monitoring and prompt intervention, and may lead to prolonged cytopenias, hypogammaglobulinemia and opportunistic infections in long-term survivors [188, 189]. These risks are particularly relevant in older or frail patients with reduced organ reserve. On the other hand, CAR-T applications in age-related, non-malignant indications may not require the same intensity of cell doses and in vivo expansion as refractory cancers, which could in principle mitigate toxicity, although this assumption remains to be tested systematically.

The problem of immune cell senescence needs to be addressed. Ex vivo expansion may not be a major limitation, but in vivo persistence and the downstream activation of endogenous immune responses may paradoxically narrow the therapeutic window for age-related diseases and immune restoration strategies [190, 191]. The high manufacturing complexity and cost of autologous CAR-T products further restrict their scalability for widespread use in age-related indications. Consequently, the application of CAR-based therapies to age-related diseases should be supported by rigorous preclinical studies in aged models, incorporation of safety switches and dose-adaptation strategies, and careful selection of high-risk populations rather than indiscriminate use in the general elderly population. In the future, universal allogeneic CAR-T platforms may reduce per-patient costs, but they remain in early development and introduce additional safety concerns [192].

Active immunization in aging

Therapeutic vaccines can be leveraged to target age-related pathologies. The glycoprotein non-metastatic melanoma protein B (GPNMB) is upregulated in senescent endothelial and bone cells. In obese mice on a high-fat diet, the GPNMB vaccine reduced the burden of $GPNMB^{high}$ senescent cells in adipose tissue, and improved glucose tolerance. In addition, vaccinating $ApoE^{-/-}$ mice against GPNMB led to fewer and smaller atherosclerotic plaques, improved the physical performance of middle-aged mice, and, more remarkably, extended median lifespan in a progeroid mouse model [12]. These outcomes suggest that prompting the immune system to selectively eliminate senescent cells can delay age-related degeneration and improve healthspan. However, as GPNMB preserves lysosomal integrity in senescent cells, indiscriminate targeting could disrupt lysosomal homeostasis in non-pathologic cells [193].

Researchers have been seeking to treat atherosclerosis with both active and tolerogenic immunization: active immunization against oxidation-specific epitopes to neutralize pro-atherogenic ligands [194, 195], and against proprotein convertase subtilisin/kexin type 9 (PCSK9) to lower LDL-C [196, 197], as well as induction of cellular immune tolerance to reduce vascular inflammation [198, 199]. Importantly, these vaccines are preclinical and the data were derived from mouse models of obesity and atherosclerosis, which only partially capture the heterogeneity, multimorbidity and long-term trajectory of human aging.

Vaccines against AD are being tested in human. Aβ candidates such as ACI-24.060 and UB-311 and anti-Tau vaccines such as AADvac1 and ACI-35.030/JNJ-2056 have generally demonstrated acceptable safety and have induced robust responses in early-phase clinical trials [200-203]. Notably, the first-generation AN1792 trial was terminated early because a subset of patients developed meningoencephalitis and other inflammatory complications, despite evidence of plaque reduction [204-206]. The failure prompted second-generation peptide and epitope vaccines with improved safety profiles, yet clear cognitive benefits have not been consistently demonstrated, and the risks of neuroinflammation and autoimmunity remain a central concern, particularly in older patients.

Challenges

Given the considerable risks that immunotherapies have revealed in real-world practice, their application in the context of aging has raised numerous concerns (Fig. 4). One of the foremost challenges in applying immunotherapies is still the risk of off-target effects. given the overlapping antigenic profiles of senescent and normal cells [180]. Besides, physiological forms of senescence (e.g., transient senescence in wound healing) must be spared [41]. Highly specific targeting is therefore crucial to prevent unintended cytotoxicity and preserve tissue integrity.

It remains a critical concern that the activation of immune responses should be balanced with the risk of precipitating autoimmunity or exacerbating inflammation. Although the reinvigoration of immune surveillance can promote the clearance of both and malignant cells, an unchecked or hyperactive immune response may lead to collateral tissue damage [207]. For example, the risk of CRS remains a significant concern in CAR-T cell applications, although early preclinical studies have demonstrated that senolytic CAR-T cells can effectively eliminate cells contributing to age-related dysfunction [208, 209]. Therefore, these approaches must be tempered by rigorous safety evaluations. Moreover, the altered cytokine milieu in aged individuals, often characterized by persistent low-grade inflammation, might predispose patients to exaggerated immune reactions [81]. Although cancer patients often display compromised or treatment-induced immune dysfunction that overlaps with features of immunosenescence, this state only partially mimic the chronic immune aging in older adults. Thus, extrapolations from oncology to age-related diseases should not be regarded as definitive. Dedicated aging-focused models that incorporate immunosenescence and multimorbidity, together with clinical trials enriched for aged individuals, are essential to validate immunotherapeutic efficacy and safety in truly aged immune systems. Elevated risks for adverse immune reactions and autoimmune complications that are not fully apparent in conventional trials might be entailed in older adults, which requires careful clinical monitoring.

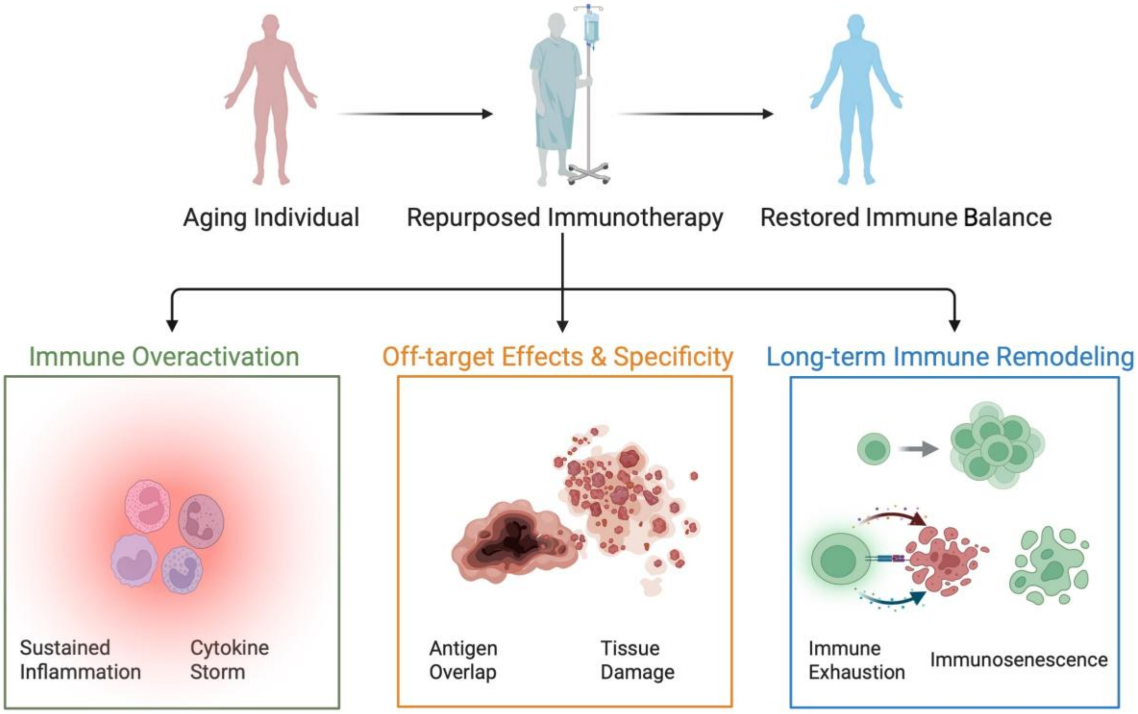

Figure 4. **Challenges in translating cancer immunotherapies to age-related diseases.** This schematic illustrates the major challenges associated with adapting cancer immunotherapies in aging populations. Immune Overactivation: Aging tissues are characterized by chronic low-grade inflammation, which increases susceptibility to immune overactivation. Manipulation of immune system may precipitate cytokine storm or systemic autoimmunity, necessitating cautious modulation. Off-target Effects & Specificity: The overlapping antigenic profiles between senescent and healthy cells raise the risk of unintended cytotoxicity and collateral tissue damage, especially in organs with pre-existing inflammatory or fibrotic changes. Long-term Immune Remodeling: Prolonged immune manipulation in the elderly may result in T cell exhaustion, immune senescence, or disrupted tissue repair mechanisms. These long-term consequences remain incompletely understood and highlight the importance of longitudinal safety monitoring.

Beyond the acute risks of immune hyperactivation, it's ambiguous whether immune restoration could be sustained over time without compromising tissue homeostasis [210, 211]. Durable benefit depends both on the removal of pathologic cells and the reconstitution of a balanced immune environment capable of efficient pathogen clearance and tissue repair.

There is a possibility that manipulating immune system leads to immune dysregulation over time. For example, prolonged PD-1 inhibition has been associated with autoimmune phenomena in cancer patients, and similar adverse effects could manifest in aged individuals who already contend with compromised immune regulation [81, 207]. Moreover, sustained interventions may carry risks of immune exhaustion, which underscores the importance of longitudinal studies to monitor the cumulative toxicity [212, 213]. The design of such studies is further complicated by the inherent variability in aging trajectories, necessitating personalized treatment regimens that account for individual differences in immune status, metabolic function, and genetic predispositions [214-216].

Treatment responses are highly heterogeneous across individuals. For example, females generally maintain stronger innate and adaptive immune responses across adulthood, whereas males show a more pronounced age-associated shift toward innate/pro-inflammatory programs and relative erosion of adaptive immunity in later life, which can reshape baseline inflammatory set-points and susceptibility to immune-mediated toxicities under immunomodulatory interventions [217]. Genetic ancestry can shape innate immune. In ex vivo studies, macrophages from individuals with greater African ancestry have shown stronger inflammatory transcriptional responses to pathogenic stimuli [218]. In addition, some populations have different hematologic baselines. For instance, the Duffy-null (ACKR1) variant is associated with lower baseline absolute neutrophil counts [219]. If uniform trial thresholds and Common Terminology Criteria for Adverse Events (CTCAE) grading are applied without considering these baseline differences, participants may be inappropriately excluded at screening or misclassified as having treatment-emergent neutropenia during follow-up.

In parallel, biological-age metrics can be used to quantify inter-individual variability in aging. For example, epigenetic age acceleration has been linked to frailty progression and higher levels of systemic inflammation in older adults. Accordingly, incorporating epigenetic age as a baseline covariate can support risk stratification [220, 221]. Moreover, pace-of-aging measures have shown sensitivity to interventions in geroscience trials. For instance, Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy (CALERIE) reported an association between caloric restriction and a slower DNA methylation–based pace of aging, suggesting that such metrics may serve as intermediate pharmacodynamic endpoints to help relate exposure to longer-term efficacy and safety signals [222].

Building on recent geroscience frameworks, one pragmatic approach is to stratify older participants using validated measures of frailty or biological age and to embed standardized panels of blood-based biomarkers into both eligibility criteria and longitudinal monitoring. For example, the Targeting Aging with Metformin (TAME) Biomarkers Workgroup has proposed a core set of circulating markers, including IL-6, TNFα receptors, CRP, GDF15, insulin-like growth factor 1 (IGF-1), cystatin C, N-terminal fragment of pro–B-type natriuretic peptide (NT-proBNP) and glycated hemoglobin A1c (HbA1c), as candidates for geroscience-guided trials, offering a structured template for capturing systemic inflammatory and metabolic risk in older adults [223]. Recent work has synthesized biomarkers of aging across frailty and age-associated disorders, highlighting panels of metabolic, inflammatory and cell-death related markers that capture systemic inflammaging and predict adverse outcomes in older adults [224]. In parallel, conceptual work on geroscience clinical endpoints emphasizes that biomarker panels and composite measures of biological age should be linked to hard health outcomes, rather than used as isolated surrogates, and that trial designs must balance feasibility with sufficient follow-up to detect clinically meaningful benefit [225, 226].

Agents repurposed for age-related indications have to navigate conventional, disease-focused approval pathways, because aging itself is not currently recognized as a treatable indication by major agencies such as the FDA and European Medicines Agency (EMA). Regulators therefore expect clear mechanistic justification, biomarker-anchored patient selection strategies and plans for long-term safety monitoring when high-cost immunotherapies are repurposed for non-malignant, chronic conditions. At the same time, there is considerable uncertainty about which clinical endpoints, trial durations and target populations are acceptable in multimorbid, frail older adults when interventions aim to modify aging biology rather than treat a single disease. In response, several groups have called for dedicated regulatory frameworks or adaptive approval pathways that can accommodate multi-domain functional endpoints and the distinctive risk-benefit profiles of aging interventions, which are essential to enable rigorous yet feasible evaluation of gerotherapeutics in older populations [215, 227].

Furthermore, the socioeconomic and ethical dimensions of repurposing cancer therapies for age-related diseases cannot be overlooked. The cost of advanced immunotherapies is significant, and their adoption in the aging population may pose challenges for healthcare systems [228, 229]. These financial pressures inevitably influence reimbursement and access; in practice, very expensive therapies are only funded for narrowly defined indications or for carefully selected patients.

It is vital that researchers remain vigilant to the complexities inherent in the aging process. The promise of harnessing cancer immunotherapies for age-related diseases comes with the ensuring that these interventions do not inadvertently accelerate deleterious processes or compromise the delicate balance of immune homeostasis. A nuanced appreciation of the mechanistic underpinnings, combined with a commitment to rigorous clinical validation, will be essential in translating these promising strategies into safe and effective treatments. With rapid progress, the integration of multidisciplinary expertise from molecular biology and immunology to clinical geriatrics and bioethics will play a pivotal role in shaping the future of therapeutic innovation.

Prospect

Repurposing cancer therapies for age-related diseases has generated considerable enthusiasm, but the current evidence base is not yet robust and many questions remain unresolved. Preclinical and early clinical observations suggest that oncology-derived interventions can be adapted to reduce senescent cell burden and enhance immune surveillance, with potential downstream effects on tissue repair and organ function. However, the signals are highly context dependent and have rarely been tested in truly aged, multimorbid populations. In gerotherapeutic practice, it’s essential to clarify which targets, dosing regimens and treatment windows are realistic in late life, and where the risk-benefit balance is acceptable.

A synthesis of insights from oncology, gerontology, and immunology will be needed to pave the way for translational medicine. Meanwhile, systems biology may help map the changing interactions between immune cells, tissue microenvironments and aging trajectories. Multi-biomarker panels that combine measures of senescent cell burden, inflammatory mediators and epigenetic signatures will support tailoring therapies, monitoring efficacy, and preempting adverse outcomes, thereby enabling more precise and personalized interventions.

Future work needs aging-relevant preclinical models that capture immune aging and common comorbidities. Adaptive clinical trials and long-term follow-up studies will be required to test durability, generalizability and real-world feasibility. A sequence of researches will be need to clear where, and for whom, oncology-derived immunotherapies can be safely and meaningfully repurposed for age-related conditions.

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Author contributions

Hao Li drafted the manuscript, and Xiaofen Wu critically revised the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest.

The authors declare no Conflicts of interest.

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