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Integrating senotherapeutics into transplantation: liver reconditioning in an aging donor pool

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Our aging population is reshaping transplantation medicine. As demand for liver transplantation continues to rise, an aging donor pool presents unique challenges, with marginal organs becoming increasingly prevalent and representing a critical yet underexploited opportunity. Current selection criteria, such as chronological age, may not fully capture organ quality. A multidimensional approach that better reflects true biological aging is now more crucial than ever. Increasing evidence indicates that senescence, a hallmark of aging, influences multiple stages of transplantation, including organ procurement and preservation. Assessing senescence could provide an objective metric for evaluating organ quality. Importantly, senescence quantification could both define organ quality and guide interventions aimed at mitigating this phenomenon. This review explores the contribution of senescence to the transplant process and evaluates emerging opportunities for senescence-based assessment and therapeutic intervention. We also highlight the potential to integrate these strategies with *ex vivo* machine perfusion to quantify senescence burden, deliver targeted interventions, and functionally recondition marginal grafts, thereby expanding the donor pool and improving outcomes in an aging population.

KEYWORDS
aging, liver transplantation, machine perfusion, organ reconditioning, organ rejuvenation, senolytics, senescence

Introduction

A demographic shift is fundamentally altering healthcare systems and the landscape of organ donation and transplantation [1, 2]. Alongside this, the incidence of liver disease continues to rise as a leading cause of morbidity and mortality in the Western world [3–5]. Liver transplantation remains the only curative treatment for patients suffering from end-stage liver disease. Between 2015 and 2050, the proportion of the world's population aged over 60 years is expected to rise from 12% to 22% [6, 7]. Accordingly, donors over 60 account for more than one-third of all deceased-organ donations in the UK, Eurotransplant area, and the US, further aggravating organ scarcity and waiting list mortality [8–10]. In Europe and North America, the average age of organ donors has increased over recent decades [8–12], and in Scandinavia, it has already reached 61 years [13]. Despite growing demand and organ

scarcity, overall organ utilization remains suboptimal, with many older grafts being declined based on chronological age rather than age-related biological metrics [9, 14, 15].

Donor livers from individuals aged ≥65 years are typically categorized as expanded-criteria donors (ECDs). These grafts are associated with an increased risk of early allograft dysfunction (EAD) and inferior long-term outcomes, particularly in the presence of accompanying risk factors such as steatosis, prolonged ischemia, or donation after circulatory death (DCD) [16, 17]. Despite these concerns, ECD grafts represent a substantial yet underutilized source [14, 15, 18, 19] and recent studies highlight that donor age alone should not preclude transplantation [20–23]. Instead, biological aging (manifested through molecular and cellular alterations such as impaired proteostasis, mitochondrial dysfunction, stem cell exhaustion, altered intercellular communication, and senescence) could be considered a more robust metric to inform decision-making in the transplant process.

Although senescence represents only one component of this multifactorial process, causal evidence suggests that targeted elimination or modulation of senescence can delay aging-related decline and improve tissue function, underscoring its relevance for organ regeneration [24–26].

Growing evidence implicates senescence across various stages of the transplant process: from increased burden in aged donor livers and its transfer to recipients, to exacerbation during organ preservation and ischemia-reperfusion injury (IRI) [27–33]. To address these challenges, therapeutic innovations are required. *Ex vivo* machine perfusion (MP) technologies allow dynamic organ preservation while enabling metabolic assessment, and offer a platform for pharmacological interventions towards organ reconditioning [34, 35]. Several landmark studies have demonstrated that MP can recover marginal human livers, enabling successful transplantation [35–40]. In parallel, anti-senescent therapeutics (termed senotherapeutics) such as senolytic and senomorphic agents represent an emerging biologic strategy to target senescence and its deleterious effects [33, 41, 42]. Integrating senotherapeutic interventions into MP platforms offers the potential opportunity to recondition biologically aged, marginal liver grafts, enhance graft resilience, expand the donor pool, and improve transplant outcomes.

Chronological versus biological aging: redefining transplant criteria

Chronological age does not capture the functional status of tissues or organs. Biological aging, by contrast, reflects the progressive decline in tissue homeostasis, repair capacity, and metabolic function due to accumulating molecular and cellular damage [25, 43]. Although biological aging generally increases with chronological age, its rate and extent are strongly influenced by disease, underlying genetics and environmental stressors [25].

Biological aging encompasses multiple mechanisms including senescence, genomic instability, epigenetic alterations, proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis (thoroughly reviewed in [24, 43, 44]. Together, these processes reflect how cellular and molecular dysfunction accumulate over time driving organ decline.

Within this framework, senescence emerges as a key link between biological aging and functional tissue decline. Senescent cells (SnCs) accumulate with advancing age and pathological stress [45], impair regenerative capacity, and promote chronic inflammation through the SASP. Furthermore, clearance of SnCs delays aging phenotypes and improves tissue function [46–48]. Both lifestyle interventions (e.g., diet, exercise) and targeted interventions (e.g., senolytics, senomorphics) can reduce SnC accumulation and/or attenuate the SASP, indicating the modifiable nature of senescence [49–51].

Organ-specific data indicate that chronological age alone is a poor predictor of organ function. In kidney transplantation, expression of the senescence marker *CDKN2A* ($p16^{INK4a}$) predicts renal allograft dysfunction more accurately than donor age or telomere length [52]. Similarly, telomere attrition has been linked to poor survival in renal transplantation [53, 54]. Aged donor hearts exhibit increased SnC burden and inflammatory injury after transplantation, linking poor graft outcomes to biological aging [55]. In the liver, healthy hepatocytes and cholangiocytes show little age-related telomere shortening, whereas telomere dysfunction and accumulation of SnCs contribute to and increase with fibrosis [33, 56–61].

Collectively, these findings demonstrate that disease burden and tissue-intrinsic damage may drive biological aging beyond chronological aging [62–64]. This is particularly relevant in transplant medicine, where evidence indicates that biological age may better predict organ quality and long-term outcomes than chronological age [24, 65, 66]. Developing appropriate biomarkers for biological age could therefore refine the assessment of donor organ fitness [67].

Defining senescence

First described by Hayflick and Moorhead in 1961, senescence refers to a state of irreversible cell cycle arrest accompanied by phenotypic changes induced by stressors such as telomere shortening, DNA damage, oncogenic signaling, or oxidative stress [68]. SnCs remain metabolically active and influence the surrounding microenvironment through the secretion of pro-inflammatory cytokines, chemokines, and proteases collectively known as the SASP [69]. At the molecular level, senescence is orchestrated by multiple drivers, with p53/p21 and p16/retinoblastoma (RB) tumor suppressor pathways playing key roles [26, 70].

Abbreviations: CAR-T-cells, chimeric antigen receptor T cells; DBD, donation after brain death; DCD, donation after circulatory death; D + Q, dasatinib and quercetin; EAD, early allograft dysfunction; ECD, expanded criteria donation; IRI, ischemia reperfusion injury; MP, machine perfusion; MASLD, metabolic associated steatotic liver disease; NRP, normothermic regional perfusion; PET, positron emission tomography; SASP, senescence-associated secretory phenotype; SA-β-Gal, senescence-associated β-galactosidase; SCAP, senescent cell anti-apoptotic pathways; SCS, static cold storage; SnC(s), senescent cell(s); RB, retinoblastoma.

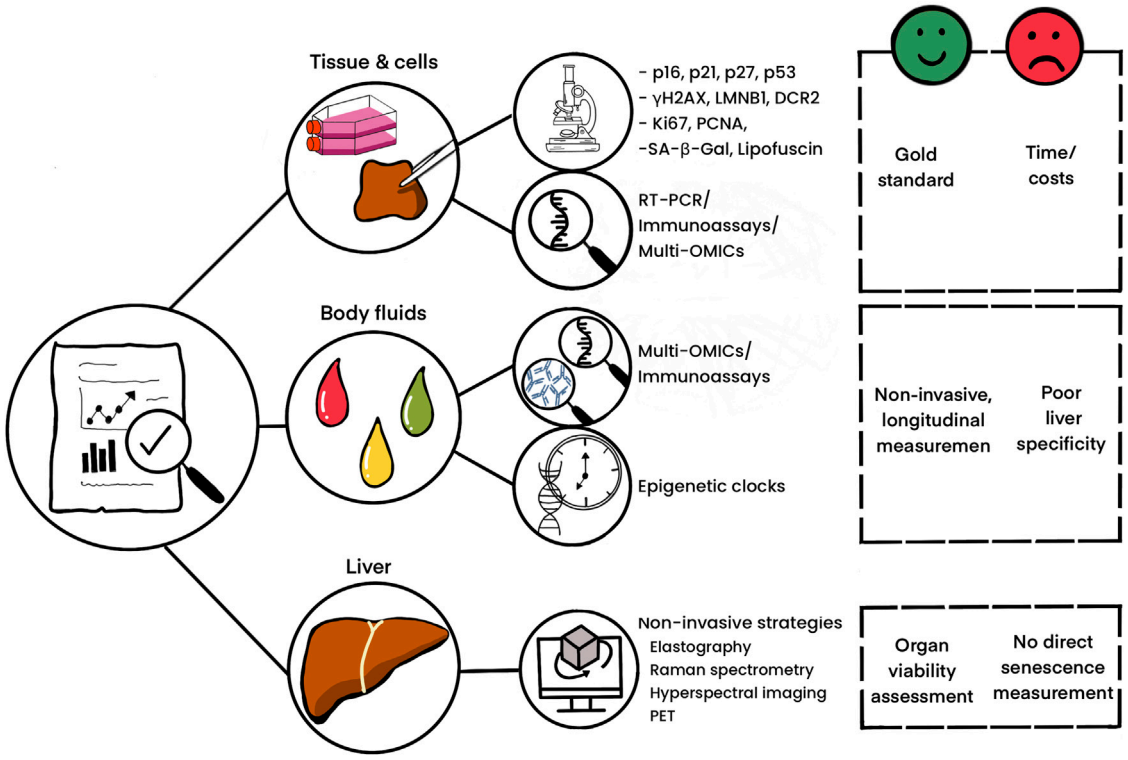

FIGURE 1
Assessment strategies for liver senescence in the setting of liver transplantation. Assessing senescence in liver grafts during liver transplantation requires complementary approaches. Given the heterogeneity of senescence and the lack of a universal biomarker, multiplex strategies are recommended, in line with the "minimum information for cellular senescence experimentation" (MICSE) framework [70]. In this setting, evaluation may include tissue sampling followed by staining protocols and multi-OMICS analyses, potentially combined with cell culture preparation, as well as the analysis of body fluids (e.g., blood, bile, perfusate, urine) and assessment of graft morphology. Each method offers specific advantages and limitations.

Senescence plays a critical role in maintaining tissue integrity, as acute senescence facilitates tissue repair and tumor suppression by halting the proliferation of damaged cells and engaging immune surveillance. However, with aging, chronic accumulation of SnCs promotes inflammation, fibrosis, and functional decline [45, 71–73]. Secreted SASP factors can induce paracrine senescence in neighboring cells and impair immune clearance, exacerbating tissue damage and reducing regenerative capacity [74, 75]. According to the threshold model of senescence, once a critical SnC burden is exceeded, SASP propagation together with inadequate immune clearance, drives accelerated biological aging [41, 64]. In transplantation, a young donor with comorbidities, such as advanced fibrosis, metabolic dysfunction (e.g., < high BMI), alcohol use or disorder, or drug-related injury, may already exceed this threshold and display a more pronounced aging-like phenotype than an older but biologically healthier donor. Assessing senescence could therefore help identify the "biological tipping point" between viable and marginal organs, supporting more precise donor selection.

Assessing liver senescence

Current efforts aim to define precise senescence-associated markers that capture the cellular and molecular alterations most relevant for *ex situ* reconditioning and graft viability [76].

Canonical senescence biomarkers include cell-cycle inhibitors $p16^{INK4a}$ and $p21^{CIP1}$, DNA damage markers (e.g., γH2AX and 53BP1 foci), and components of SASP (e.g., IL-6, IL-8, and MCP-1, among many others). Additional markers include senescence associated-β-galactosidase (SA-β-Gal) activity, telomere attrition, lipofuscin accumulation, increased anti-apoptotic BCL-2 expression and presence of DCR2 in cholangiocytes [45, 77–79].

Beyond individual markers, transcriptomic signatures are increasingly applied in experimental and translational transplant settings to capture senescence gene profile across tissues. Single cell sequencing and spatial transcriptomics enable high-resolution mapping of senescent and immune cell heterogeneity in aged or injured liver tissue [26, 33, 70, 78, 80–82]. Moreover, machine-learning-based analysis of histological sections enables automated senescence detection and may have utility in liver graft assessment [83–85] (Figure 1).

Currently no universal senescence marker exists for use in liver grafts and tissue-processing methods affect biomarker reliability [86, 87]. Biomarkers accessible via minimally invasive sampling would be ideal but must account for genetic and phenotypic heterogeneity.

Integrating multi-OMICs profiling and tissue architecture assessment into liver transplant could facilitate the identification of SnC populations amenable to interventions [79].

Targeting senescence in liver transplant

Senotherapeutics

The rationale for eliminating SnCs to restore tissue homeostasis emerged from observations that caloric restriction reduces SnC burden and extend health- and lifespan in mice [45]. Furthermore, selective clearance of SnCs delayed age-associated dysfunction in mice [46, 47]. Several approaches have emerged to eliminate SnCs and modulate their effects which can be grouped into the following categories, with Tables 1, 2 summarizing the relevant agents for liver applications.

Senolytics selectively eliminate SnCs.

SnCs persist within the tissue by activating senescent cell anti-apoptotic pathways (SCAPs), including BCL-2 (BCL-2, BCL-xL, BCL-w), PI3K-AKT signaling, SRC kinase–dependent survival pathways, and cell-cycle checkpoint-associated programs such as CDKN1A-linked signaling [107]. Multi-OMIC analysis has revealed that distinct SCAPs are upregulated across different SnC populations, highlighting the heterogeneity of their survival mechanisms. Senolytics exploit these SCAPs to tip the balance from senescence to apoptosis. Targeting key SCAP nodes using small interfering RNAs induced selective apoptosis in 30%–70% of SnCs while largely sparing non-SnCs [88]. Other senolytics target SnCs through alternative mechanisms, including ferroptosis and metabolic stress responses [90].

Early senolytic discovery followed a hypothesis-driven approach, focusing on natural compounds and repurposed drugs with established safety profiles [41, 88]. More recently, high-throughput screening has expanded the senolytic landscape, enabling the identification of second-generation senolytics with improved selectivity and potency [41, 51, 108].

Senoblockers inhibit upstream senescent drivers, and, unlike senolytics, prevent the formation of new SnCs.

Senoblockers act by interfering with key signaling pathways that induce senescence. These include p53/p21 and p16/Rb axes via selective targeting Hsp72, Bruton's tyrosine kinase, and the histone demethylase LSD1 among others [109].

Senomorphics (senostatics) do not eliminate SnCs but rather modulate their functional phenotype.

Senomorphics act primarily by suppressing the SASP pro-inflammatory signaling, targeting pathways such as NF-κB, JAK/STAT, mTORC1, p38, and MAPK signaling. Additional senomorphic strategies target mitochondrial complex-I or -IV, modulate NAD^+/NADH metabolism, or inhibit HSP90 [107, 110]. By exploiting these pathways, senomorphics attenuate the secretion of deleterious cytokines, chemokines, and proteases. By preserving SnCs while limiting inflammatory signaling, senomorphics help to maintain tissue integrity, prevent tumors, reduce senescence footprint and induce regeneration [41].

Immune-mediated clearance of SnCs seeks to enhance the physiological removal of SnCs.

This group includes multiple approaches including immune checkpoint inhibitors, senescence-targeted chimeric antigen receptor (CAR) T cells, vaccines or antibody-drug conjugates, which aim to increase SnC immunosurveillance [111–113].

Certain compounds may exert senomorphic or senolytic effects depending on dose, treatment duration or cellular context. For example, the flavonoid procyanidin C1 is senomorphic at low concentrations and senolytic at higher doses [100]. The translation of these concepts into clinical practice remains in its early stages. To date, human senolytic trial data are limited and predominantly based on Phase I/II studies, demonstrating that intermittent regimens are feasible and well-tolerated. The most studied regimen is oral dasatinib + quercetin (D + Q) for 3 consecutive days repeated in 3-week cycles (D 100 mg/day; Q 1,000–1,250 mg/day), with non-serious adverse events [114, 115]. A landmark Phase II randomized controlled trial demonstrated that response to D + Q is influenced by baseline SnC burden, with significant benefits in individuals with high $p16^{INK4}$ expression [116]. In addition, fisetin has been evaluated at 20 mg/kg/day for 3 consecutive days on an intermittent schedule (NCT04313634).

In liver disease, only one Phase I/II trial of D + Q in metabolic-associated steatotic liver disease (MASLD) has been initiated (NCT05506488) with outstanding results. Looking ahead, the senotherapeutic landscape is expected to expand rapidly.

Considering risks and limitations

Senotherapeutics offer potential benefits yet entail risks, varying across the different categories:

Senolytics reduce inflammation, tissue dysfunction, and propagation of secondary senescence [41]. This mechanism offers a conceptual advantage over senomorphics, allowing for intermittent, "hit-and-run" administration rather than continuous exposure. However, SnCs can exert beneficial physiological roles (e.g., tumor suppression, promoting wound healing, tissue remodeling and fibrosis resolution) [117, 118]. During wound healing, SNCs can promote closure through PDGF-AA secretion, and senolytic treatment during this period could compromise surgical site healing and anastomotic integrity [119]. Similarly, senescence functions as a tumor suppressor mechanism and prolonged SnC ablation may impair immune surveillance [113, 117, 118]. In the liver, senescence in endothelial cells (LSECs) is protective and compensatory and helps to maintain clearance of toxins during aging [120]. SnC ablation can therefore disrupt tissue homeostasis [32, 121–123]. Many senolytics work within a narrow therapeutic window and are cytotoxic at higher doses [124]. Therapeutic responses may vary according to biological context, sex [121] and senescence heterogeneity [122].

Senomorphics, preserve tissue homeostasis by retaining SnCs while mitigating their harmful effects. However, targeting specific pathways is challenging in a dynamic context where SnCs adaptively alter their SASP in response to the environment. For example, broad suppression of inflammatory mediators may result in off-target effects, including unintended inhibition of cytokine production by non-SnCs, potentially impairing necessary responses [107, 110, 113].

Senoblockers do not eliminate SnCs but prevent new SnC forming, potentially blocking senescent dependent tumor-suppressive functions. Therefore, their efficacy and safety remain to be established [109].

Immune-mediated strategies aim to enhance physiological SnC clearance but face several limitations: immunosenescence and age-related immune dysfunction can reduce the efficiency of SnC recognition and elimination, while the SASP may suppress

TABLE 1 Selected relevant senolytics and (pre-)clinical findings in the liver.

Agent	Mechanism of action	Pre/Clinical status	Key limitations	Ref.
Dasatinib	Inhibits SRC family kinases → suppressing multiple SCAPs	In combination with quercetin Preclinical: Promotes biliary regeneration in human liver explants and in murine models of cold storage Preservation of cilia morphology and biliary regeneration in human liver grafts Fibrosis suppression and SnCs elimination in murine MASLD model Reduction of hepatic steatosis in murine models Clinical: MASLD (NCT05506488, phase 1 + 2)	Heterogeneous cell-type–specific response; off-target effect and potential systemic toxicity, often combined with quercetin	[29, 30, 51, 88, 89]
Quercetin (natural flavonoid)	Inhibits PI3K/AKT signaling → BCL-2 family → apoptosis	Used in combination with dasatinib to target multiple SCAPs	Low bioavailability; variable potency, combination therapy for efficacy	[28, 29, 50, 90, 91]
ABT-737	BCL-2, BCL-xL, BCL-w Broad BCL-2 family inhibition → induction of mitochondrial apoptosis	Preclinical: Promotes biliary regeneration in murine models of cold storage Improved regenerative capacity following partial hepatectomy in a mouse model Preservation of cilia morphology and biliary regeneration in a mouse model of cholangiocyte senescence	Thrombocytopenia	[29, 32, 51, 91]
ABT-263 (navitoclax- orally bioavailable analog of ABT-737)	BCL-2, BCL-xL, BCL-w Broad BCL-2 family inhibition → induction of mitochondrial apoptosis	Preclinical: Promotes regeneration in acute-on-chronic liver failure in murine models Clinical: Solid tumors (NCT00887757, phase 1) Hepatocellular carcinoma (NCT02143401, phase 1)	Thrombocytopenia Neutropenia	[51, 92–95]
A-1331852	Selective BCL-xL inhibition → induction of mitochondrial apoptosis	Preclinical	Reduced effects of neutrophils - because not targeting BCL-2	[92]
A-1155463	Selective BCL-xL inhibition → induction of mitochondrial apoptosis	Preclinical	Reduced effects of neutrophils - because not targeting BCL-2	[51, 92]
Fisetin (natural compound)	Inhibits PI3K/AKT signaling → BCL-2 → apoptosis	Preclinical:Reduces oxidative stress in liver in senescence mouse models and extends lifespan Reduces inflammation and fibrosis in cholangiocytes senescence mouse model Clinical: Frail elderly syndrome (NCT03430037, NCT03675724) Aging (NCT04994561)	Low bioavailability, variable potency, potential interaction with warfarin; unclear selectivity	[92, 96–98]
FOXO4-DRI peptide	P53 nuclear exclusion in SnCs – cell-intrinsic apoptosis	Preclinical	Currently preclinical	[99]

(*Continued*)

TABLE 1 Continued

Agent	Mechanism of action	Pre/Clinical status	Key limitations	Ref.
Procyanidin C1 (natural compound)	Increased ROS production, mitochondria dysfunction	Preclinical: Depletion of SnCs and reduction of SASP and oxidative stress and increase in lifespan in mouse liver	Dose-dependent senomorphic or senolytic effects, high specificity and efficiency, safety	[100]
Piperlongumine	OXR1 degradation, increased ROS generation	Preclinical	Potentially synergistic with ABT-263, currently preclinical, unclear pharmacokinetics	[101]

Abbreviations: MASLD, metabolic dysfunction-associated steatotic liver disease; ROS, reactive oxygen species; SCAPs, senescent cell anti-apoptotic pathways; SnC(s), senescent cell(s).

TABLE 2 Selected relevant senomorphics and (pre-)clinical findings in the liver.

Agent	Mechanism of action	Pre/Clinical status	Key limitations	Ref.
Rapamycin everolimus, sirolimus, tacrolimus, RTB101	mTOR inhibitor → NF-κB → SASP suppression	Clinical: Approved for immunosuppression Multiple ongoing studies for aging-related indications	Immunosuppression at higher doses; may require continuous dosing	[102, 103]
Ruxolitinib	Inhibits JAK1/JAK2 → STAT3 signaling → suppress IL-6, IL-8 mediated SASP amplification	Preclinical Clinical: Approved for myelofibrosis, polycythemia vera, GvHD	Broad cytokine suppression; infection risk	[104]
Metformin	Mitochondrial complex I; AMPK → mTOR → NF-κB → SASP suppression	Clinical: Widely used, approved for T2DM. Targeting aging (TAME trial, NCT04245771)	Mild SASP modulation	[105, 106]

Abbreviations: GvHD, graft-versus-host disease; SASP, senescence-associated secretory phenotype; T2DM, type two diabetes mellitus.

immune surveillance. CAR-T cell mediated approaches risk off-target immune activation and tissue toxicity [90, 111, 112].

Combination strategies offer promising means to enhance efficacy while limiting toxicity. Combined D + Q treatment targets multiple SCAPs and demonstrates superior efficacy compared with treatment using dasatinib or quercetin alone [88]. Galacto-conjugation and β-galactosidase–activated prodrug strategies have been developed to further improve selectivity [123, 124]. Current evidence relies heavily on rodent data and fails to capture human heterogeneity. Natural compounds such as quercetin and fisetin have variable bioavailability and systemic endpoints are difficult to establish given the wide nature of senescence. The *ex vivo* MP scenario allows a uniquely controlled environment where the graft is isolated and senescence can be measured from biopsies, perfusate, or bile. Drugs delivered directly into the perfusion circuit bypass systemic limitations, allow higher local dosing, and provide a controlled, time-limited treatment window.

When, what and how: a biomarker-guided, senescence-targeted approach to liver transplantation

There are opportunities to detect and target SnCs during the stages of liver transplantation: donor pool, organ recovery, organ preservation (static cold storage (SCS) and MP), implantation and post-transplantation (Figure 2). Each timepoint offers benefits, logistical and ethical challenges [67, 125].

Donor pool

Strategic considerations for assessing and targeting senescence in the donor pool are summarized in Information Box 1 (Figure 3).

High SnC burden in donors can increase organ immunogenicity, exacerbate alloimmune responses, and ultimately compromise graft function and survival. Importantly, the increased SnCs burden is not limited to the donor organ itself. Emerging data suggest that SnCs can exert systemic, non-cell autonomous effects, propagating the senescent blueprint from graft to recipient, thereby contributing to post-transplant dysfunction. This is exemplified by the transfer of SnCs into young mice, which induces secondary senescence and pathological traits in distant tissues [126–129]. Consistently, cardiac transplantation from aged C57BL/6 donors into young recipients increases SnC burden and SASP across multiple recipient tissues, accompanied by impaired physical performance, and reduced cognitive function within 30 days post-transplantation [31]. Aging also activates profibrotic pathways in the liver, inducing senescence LSECs and increasing SASP, which promotes leukocyte adhesion and chronic inflammation [130]. This highlights the

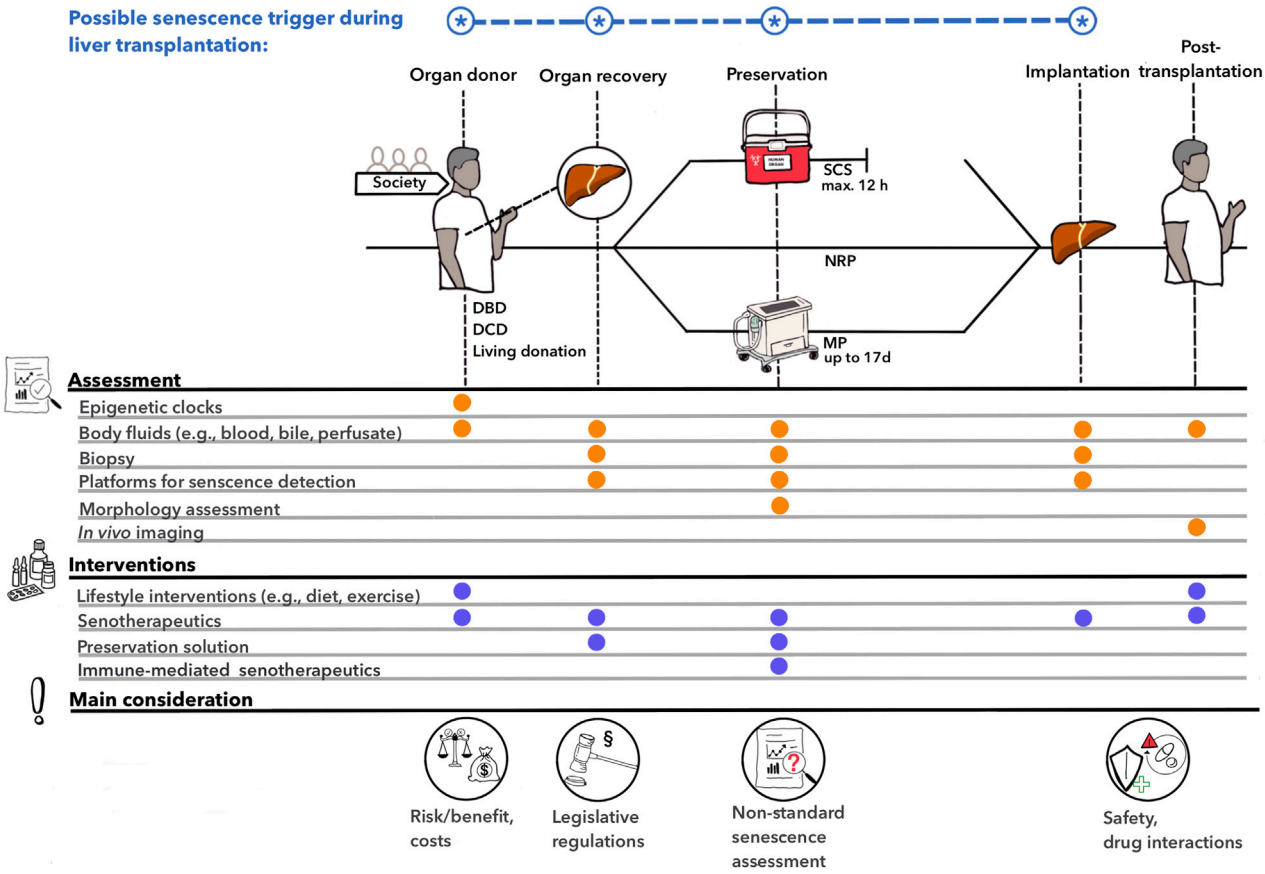

FIGURE 2
Integrating senescence assessment and targeting along the liver transplantation process. Distinct stages of the transplant process, from donor selection to post-transplant follow-up, provide opportunities for senescence assessment and therapeutic intervention. Senescence is known to be exacerbated at specific points along this pathway, while feasibility of these approaches depends on logistical and ethical considerations. Stage specific considerations are further detailed in Information Boxes 1–5 (Figures 3–7).

Donor pool

Assessing senescence in all potential donors is particularly challenging, if not impossible. Although assessing epigenetic clocks (157,158) or periodic liquid biopsies for SASP markers (77,80) would be feasible, this would require the implementation of large-scale logistical frameworks and significant economic investment to evaluate extensive cohorts. Beyond these practical considerations, such assessments carry substantial ethical and legal implications, including concerns related to consent, privacy, and the potential consequences of labeling individuals based on biological age or senescence markers.

Targeting senescence at a societal scale could confer multiple benefits, not only for transplant outcomes but also for population-level health. Lifestyle and pharmacological interventions (e.g., exercise, GLP-1 agonists, senolytics) may reduce SnC burden and improve overall health. Preclinical treatment with D+Q reduces levels of cell free mitochondrial DNA and prolongs graft survival in aged donor models (30,54,125,127), and ABT-737 reduces senescence and restores regeneration following partial hepatectomy (31). However, setting aside ethical considerations (given the unpredictable timing of organ availability) the practical implications of implementing such interventions at scale are immense. The logistical, economic, and regulatory demands render this approach, at present, largely unfeasible outside of a theoretical or "science-fiction" scenario.

FIGURE 3
Information Box 1| Assessing and targeting senescence in the donor pool. Conceptual approaches for evaluating and modulating senescence at the population level and in the donor prior to organ procurement.

Organ recovery

Assessing senescence at this stage may better reflect graft biological age than donor-level assessments, as procurement-related events (e.g., ischemia, mechanical stress) may rapidly induce or exacerbate underlaying senescence (28). This stage also benefits from direct availability of biological material (e.g., tissue biopsies, bile, and blood) enabling stainings, and multi-OMIC profiling.

However, due to the time-sensitive nature of organ procurement, most current tools for assessing senescence markers cannot be readily implemented. Rapid, point-of-procurement measurements using technologies such as lateral flows or electrochemical platforms detecting specific senescence signatures could help overcome this challenge. Adapting systems already used for organ assessment (e.g., portable blood gas analyser) may offer a practical solution.

Nonetheless, important limitations remain. The limited specificity of current senescence markers is a key concern, and large datasets will likely be required to identify markers that reliably reflect systemic SnC burden. Additionally, the optimal sampling site remains unclear, including whether assessment should be performed at systemic level (e.g., in blood) or directly within the graft (e.g., liver tissue, bile). Nonetheless, organ recovery phase may represent a critical decision point for senescence-informed stratification of liver grafts.

Targeting senescence during organ procurement must consider the type of donation, since the practical and ethical scope for intervention differs across donation settings.

- **Living donation** provides the longest and most controllable window, with donors undergoing comprehensive evaluation weeks or even months prior to the procedure. This would give sufficient time for lifestyle interventions (e.g., diet, exercise) and senotherapeutic administration (e.g., rapamycin, D+Q, metformin, etc.). Given the stringent safety standards currently applied to living donor selection, cautious and evidence-based use of senotherapeutic could, in the future, hold potential to modestly broaden selection criteria.
- Depending on donor type and legislative framework, pre-procurement ICU management may offer an opportunity for biomarker sampling and targeted approaches in **DBD** and certain **DCD** settings.

FIGURE 4
Information Box 2| Assessing and targeting senescence during organ recovery. Potential opportunities for senescence evaluation and intervention at the time of graft procurement.

context-dependent role of LSEC senescence: protective for toxin clearance but potentially harmful when excessive or chronic. In addition, hepatocellular senescence induces secondary senescence in other organs, exacerbating systemic inflammation and driving multi-organ dysfunction [131].

Organ recovery

Potential approaches for senescence assessment and targeting during organ recovery are outlined in Information Box 2 (Figure 4).

Importantly, the senescence landscape at this stage is also shaped by the type of donation. Compared with donations after brain death (DBD), DCD are subjected to warm ischemia prior to cold ischemia, which experimental evidence suggests may increase senescence [29, 30].

Conceptually, several strategies could be integrated into organ recovery, including single or repeated *in situ* graft flushing, delivery of senotherapeutics via regional perfusion circuits, or targeted bench flushing prior to preservation. Pilot studies incorporating quercetin and sucrose [102] or ABT-737 [29] to preservation solutions during SCS and perfusion models showed decrease SnC burden and enhanced regenerative capacity. However, because organs are routinely flushed with preservation solutions and exposed to various medications during standard procurement, concerns remain regarding drug interactions and reduced efficacy under hypothermic, metabolically suppressed conditions.

Alternatively, *in situ* normothermic regional perfusion (NRP), which partially restores circulation and metabolism, could create an additional window for senescence assessment and targeted intervention [132].

Organ preservation

Following procurement, the graft is fully isolated from both donor and recipient, allowing prolonged organ interventions under highly controlled conditions, offering a unique window for senescence evaluation, organ stratification and targeted therapies. Key opportunities for senescence evaluation and targeted intervention during organ preservation are presented in Information Box 3 (Figure 5).

- SCS elicits distinct, cell-type specific responses within the liver: hepatocytes predominantly undergo apoptosis, while cholangiocytes enter senescence with prolonged cold ischemic times [29]. This has been shown to directly alter/disrupt biliary architecture and impair liver regeneration, potentially affecting post-transplant outcomes. Mechanistically, DCR2 has been shown to play a pivotal role in the development of cholangiocyte senescence [29]. Moreover, prolonged ischemia

Organ preservation

Assessing senescence either during SCS or MP, unlike earlier transplantation stages, allows unrestricted access to the graft. Repeated longitudinal sampling of tissue, bile, perfusate also enable dynamic evaluation of senescence and response to inventions. However, clinical application during SCS is limited by time constraints, whereas MP permits flexible assessment for long-periods of time as well as therapeutic manipulation (34,132,133).

Looking ahead, integrating real-time senescence monitoring across procurement, SCS, and MP may help overcome these challenges. Bile-based biomarkers may offer a sensitive readout of cholangiocellular senescence and biliary viability. Such approaches could capture baseline senescence levels, assess the impact of preservation strategies, define optimal timing and duration of treatment, and support decisions regarding graft suitability for transplantation. Embedding Raman spectroscopy-based assessment or hyperspectral imaging into this step could provide alternative metrics (137,159).

Targeting senescence during SCS (where the graft's metabolism is greatly slowed and the lack of blood flow limits drug distribution), restricts any delivery to locally injected or flush-based interventions with uncertain tissue penetration. On the other hand, MP offers the most precise and controllable route for drug interventions. As discussed before, direct delivery of senotherapeutics to the graft enables high local drug concentrations without systemic exposure, allowing exploration of strategies such as senoblockers and immune-mediated senotherapeutics in a controlled setting. In MP, senotherapeutics could be delivered via the perfusate, or locally to the bile duct.

ABT-737 administered via portal vein during SCS and MP have been shown to reduce SnCs burden and restore regenerative potential in mice (28). Similarly, administration of D+Q to human grafts using a proof-of-concept MP results in similar outcomes with preservation of primary cilia and reduced levels of senescence (28,29). Therefore, targeting senescence at this stage represents a unique opportunity, building on the advantages discussed earlier. In particular, the ability to perform drug washout prior-to-implantation (using fresh perfusate flush-out or filter systems) offers an important safety advantage by minimizing residual drug exposure, especially given the uncertain toxicity profiles of many senotherapeutic agents.

FIGURE 5
Information Box 3| Assessing and targeting senescence during organ preservation. Experimental and therapeutic opportunities to evaluate and modulate senescence under controlled preservation conditions. This box highlights potential strategies to assess and target senescence during organ preservation.

shortens primary cilia in cholangiocytes (organelles essential for bile flow sensing) and triggers senescence [30]. These findings position organ preservation not merely as a passive holding period, but as an active biological phase during which senescence is induced, amplified, and potentially therapeutically reversible.

- MP offers an opportunity to maintain organs under near-physiological conditions, allowing longitudinal sampling before and after targeted interventions, supporting within-organ comparisons. Emerging approaches, including extended perfusion strategies [35, 133–135] and split-liver techniques [35], also open the possibility of using internal controls to simultaneously evaluate different senotherapeutics. Proof-of-concept studies for *ex vivo* senolytic delivery have shown feasibility in discarded human livers [29, 30] where left lateral segments were perfused with 5 mg/kg dasatinib and 50 mg/kg quercetin. However, systemic application in clinical MP remains in its early stages. Factors such as dosing relative to circuit volume, pharmacokinetics, tissue exposure, timing within the limited perfusion windows are still undefined. Unlike oral trials, perfusion may require single high-dose or repeated bolus strategies to achieve effective tissue concentrations. Perfusion temperature could also strongly influence efficacy. Hypothermia suppresses metabolism, potentially limiting drug uptake and apoptotic signaling, while normothermia preserves cellular activity [136] and could therefore support senolytic actions. Sub-nomorthermic approaches may offer a compromise, but establishing the optimal temperature, timing, and dosing will be essential to advance senotherapeutics in organ perfusion.

Implantation

At graft implantation, the preserved organ is revascularized and connected to the recipient's circulation. Although the graft remains physically accessible, opportunities for interventions are limited: prior to implantation and reperfusion, the organ is ischemic and unlikely to metabolize drugs, and after reperfusion, there is a risk of systemic exposure to any agents administered at this stage. However, IRI is an inherent component of implantation and it has been associated with SnC accumulation and impaired tissue repair, effects that may be reversible with senotherapeutic treatment [28, 137, 138]. Consistently, treatment of rats with rapamycin immediately after kidney transplantation led to reduced senescence and SASP response [139]. Evolving perspectives on senescence assessment and therapeutic targeting at the time of transplantation are detailed in Information Box 4 (Figure 6).

Implantation

Assessing senescence at this stage is theoretically feasible but time constrained. Early post-reperfusion sampling (e.g. biopsies, bile) can provide mechanistic insight, helping to distinguish pre-existing donor senescence from transplant-process associated senescence (e.g., IRI-mediated). However, longitudinal sampling is restricted (bleeding risks). Moreover, options to act on these findings are limited by perioperative immunosuppression and the risk of systemic drug interactions.

Targeting senescence at this stage would be conceptually limited to carefully timed, localized delivery during back-table preparation or early reperfusion. While a single bolus of senolytics or other senotherapeutics may be feasible, systemic interventions raise additional concerns, including potential drug interactions (e.g., with corticosteroids or immunosuppressants) and disruption of early repair processes and immune adaption.

FIGURE 6
Information Box 4| Assessing and targeting senescence during organ implantation. Considerations for senescence assessment and intervention at the time of graft implantation.

Post-transplant and Follow-up

Assessing senescence in the recipients would be largely limited to non-invasive sampling. Repeated post-transplant liver biopsies are rarely feasible, and longitudinal assessment would rely mainly on non-invasive surrogate measures. Blood-based markers, including circulating SASP factors, may not be graft-specific and may reflect systemic rather than liver-specific senescence (161). In addition, senescence-based assessments would need to be interpreted against the recipient's baseline senescence, to identify changes attributable to the graft. Interpretation could be further complicated by the recipient's medication, which may interfere with readouts and limit their reliability.

Emerging *in vivo* imaging approaches may overcome these limitations. Early clinical studies using SA-β-Gal-targeted positron emission tomography (PET) tracers demonstrated the feasibility of visualizing senescence-associated enzymatic activity in humans (162,163). Advances in probe design and imaging platforms may ultimately enable *in situ* assessment of senescence in transplanted grafts, although current near-infrared approaches remain experimental (164). Other strategies may include systemic assessment of renal-clearable fluorogenic probes in urine, which have been used experimentally to monitor senescence and responses to senolytics (165), offering a potential non-invasive approach for post-transplant monitoring.

Targeting senescence, systemically post transplantation could, in principle, reduce SnCs in both the graft and the recipient and attenuate early inflammatory and fibrogenic signaling and potentially lowering the risk of chronic allograft dysfunction. Senotherapeutics could be administered systemically (e.g., orally, intravenous) or delivered locally (e.g., endoscopic methods), depending on safety considerations.

However, systemic delivery carries substantial risks, including immune dysregulation, interactions with immunosuppressive regimens (66), and timing-dependent effects, as premature senescence ablation may impair adaptive repair, whereas delayed intervention may miss a critical therapeutic window (118,119,166).

FIGURE 7
Information Box 5| Assessing and targeting senescence post transplantation. Perspectives on senescence monitoring and modulation after transplantation within the context of immunosuppression.

Post-transplant and follow-up

This stage is crucial for monitoring rejection, optimizing immunosuppression and detecting complications [140]. It represents a phase in which graft-intrinsic biology intersects with recipient systemic factors and determines long-term outcomes. Practical considerations for evaluating and addressing senescence after transplantation are provided in Information Box 5 (Figure 7). SnCs contribute to sustained inflammatory and fibrogenic signaling in graft and recipient. Supporting evidence links senescent cholangiocytes to both acute cellular rejection and chronic rejection in liver transplant recipients and also implicates cholangiocyte senescence as a driver of EAD, long-term graft dysfunction and biliary complications [29, 59, 141–144].

Once maintenance immunosuppression is established, senolytic approaches may be less suitable, and senomorphic strategies may offer a safer alternative. Notably, commonly used immunosuppressive agents, including mTOR inhibitors, exhibit senomorphic properties, suggesting that partial senescence modulation may occur within existing regimes.

Drug-drug interactions remain a key concern [42]. For instance, dasatinib may enhance glucocorticoid-mediated T-cell suppression [145], potentially reducing the need for conventional

immunosuppressant but also increasing the risk of over-immunosuppression. Panobinostat may potentiate calcineurin inhibitors (e.g., tacrolimus, cyclosporine) [146], and flavonoids such as quercetin and fisetin may synergize with mTOR-inhibitors (e.g., rapamycin) [147, 148]. While these interactions could theoretically reduce overall drug exposure, they also increase the risk of excessive immunosuppression, opportunistic infection, and malignancy. Conversely, some interactions may be advantageous. For instance, mTOR inhibitors, already used for immunosuppression, possess senomorphic properties, suggesting that partial senescence modulation may be achievable within existing therapeutic regimens without additional agents. Careful dose optimization, immune monitoring, and phase-specific application will be essential.

Conclusion, challenges, and future directions

Assessing and targeting senescence may represent a paradigm-shifting approach in liver transplantation, potentially improving transplant outcomes and expanding the donor pool.

Adopting a senescence-centered perspective requires re-evaluation of long-standing donor selection criteria.

Chronological age, although widely used as a key selection criterion, may not fully capture organ quality, and alternative metrics (such as biological aging or SnCs burden) may warrant consideration. In this context, donor age can be reframed as a modifiable biological risk factor rather than a fixed contraindication.

Consistent with this view, senescence, a key driver of biological aging, compromises graft quality and propagates dysfunction to the recipient. As such, senescence represents a promising therapeutic target to improve transplant outcomes and expand the donor pool in an aging population [42, 149].

Shifting to biologically informed criteria underscores the need for reliable methods to quantitatively assess senescence in donor organs.

Clinical translation remains hindered by limited understanding of SnC heterogeneity, the lack of specific markers, potential interactions with immunosuppression, and unresolved ethical/regulatory questions. However, multi-OMIC approaches and emerging non-invasive assessment strategies are beginning to address these gaps [81, 150–154]. The field is advancing rapidly, offering great promise, but success will depend on robust safety assessment and the use of biomarkers to guide and monitor interventions. Importantly, distinct liver cell populations (e.g., hepatocytes, cholangiocytes, liver sinusoidal endothelial cells, stellate cells) exhibit different senescent phenotypes with diverse functional impact [130]. Targeting one population may improve certain aspects of organ function while impairing others. Overall, the relative contributions and the consequences of treating these cell types in transplantation remain poorly understood.

Assessing senescence offers a dual benefit: informing organ viability during transplantation and providing a framework to gauge the efficacy of targeted therapeutics. A validated, clinically applicable senescence marker is lacking. Nevertheless, multiple efforts are already underway to target, eliminate, or modulate senescence at different stages of the transplantation process, highlighting the dynamic and rapidly evolving nature of the field.

MP offers a unique platform to address many of these open questions, allowing *ex vivo* evaluation of senotherapeutics without exposing the recipient to systemic effects. Preclinical split-liver models may accelerate development, while early-phase clinical trials with biobanking strategies will be essential to build the evidence base. However, practical challenges must be addressed before routine use. MP itself already represents a substantial cost burden, with internal analyses from a single center reporting an additional ~10,000 EUR per liver perfusion [155]. Personal demands and institutional demands further compound these challenges. A feasible path forward may involve collaborative multicenter trials conducted at centers with established perfusion programs and research infrastructure already coexist, minimizing duplication of effort and distributing costs across institutions.

Integrating senotherapeutics into MP represents a promising yet evolving strategy to rejuvenate marginal grafts in an aging transplant landscape, with successful translation dependent on rigorous safety assessment and well-designed clinical trials [33, 117, 118].

In conclusion, targeting senescence for organ reconditioning raises the prospect of future organ-repair or rejuvenation centers, where marginal grafts could be biologically optimized before transplantation, requiring collaboration across the transplant community, standardized protocols, and rigorous clinical trials to assess benefits and risks.

Author contributions

MB: Conceptualization, Writing – Original Draft, Visualization, Review and Editing. HE: Review and Editing. HP: Review and Editing. RZ: Review and Editing. SF-G: Conceptualization, Writing, Review and Editing, Supervision. SF: Conceptualization, Funding acquisition, Review and Editing, Supervision.

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Conflict of interest

Author SF is a founder and director of the company Resolution Therapeutics.

The remaining author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Crimmins EM. Lifespan and healthspan: past, present, and promise. *Gerontologist* (2015) 55:901–11. doi:10.1093/geront/gnv130

2. Weimann A, Ahlert M, Seehofer D, Zieschang T, Schweda M. Old age and frailty in deceased organ transplantation and Allocation–A plea for geriatric assessment and prehabilitation. *Transpl Int* (2023) 36:11296. doi:10.3389/ti.2023.11296

3. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al. Burden of liver disease in Europe: epidemiology and analysis of risk factors to identify prevention policies. *J Hepatol* (2018) 69:718–35. doi:10.1016/j.jhep.2018.05.011

4. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol* (2019) 70:151–71. doi:10.1016/j.jhep.2018.09.014

5. Younossi ZM, Stepanova M, Younossi Y, Golabi P, Mishra A, Rafiq N, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. *Gut* (2020) 69:564–8. doi:10.1136/gutjnl-2019-318813

6. Busetta A, Bono F. Demographic aspects of aging. In: Pisani PB, Caruso C, editors. *Human Aging: From Cellular Mechanisms to Therapeutic Strategies*. London: Academic Press (2025). p. 13–34. doi:10.1016/B978-0-12-822569-1.00019-6

7. World Health Organization. *Ageing and Health* (2025). Available online at: https://www.who.int/news-room/fact-sheets/detail/ageing-and-health (Accessed December 17, 2025).

8. Israni AK, Zaun DA, Martinez A, Schaffhausen CR, Lozano C, McKinney WT, et al. OPTN/SRTR 2023 annual data report: deceased organ donation. *Am J Transpl* (2025) 25(Suppl. 1):S490–517. doi:10.1016/j.ajt.2025.01.026

9. Eurotransplant. *Annual report* (2024). Available online at: https://www.eurotransplant.org/statistics/annual-report (Accessed December 17, 2025).

10. NHS Blood and Transplant (NHSBT). *NHSBT Annual Report 2024/2025: Organ Donation Activity* (2025). Available online at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/36809/section-3-organ-donation-activity.pdf (Accessed December 17, 2025).

11. Bouzas CE, Sánchez Ibáñez J, Alvarez Vázquez M, Fernández García A, Mariño Rozados A, Ojea CM, et al. Organ donation in an aging population: the experience of the last 8 years in Galicia. *Transpl Proc* (2009) 41:2050–2. doi:10.1016/j.transproceed.2009.05.027

12. Scientific Registry of Transplant Recipients (SRTR). Liver-annual report chapter (2023). Available online at: https://srtr.transplant.hrsa.gov/ADR/Chapter?name=Liver&year=2023#fig:LIdeceased-don-age (Accessed December 17, 2025).

13. Scanditransplant. Annual report (2024). Available online at: https://www.scandiatransplant.org/resources/annual-report/Annual_Scandiatransplant_data_report_2024.pdf (Accessed December 17, 2025).

14. Messina M, Diena D, Dellepiane S, Guzzo G, Lo Sardo L, Fop F, et al. Long-term outcomes and discard rate of kidneys by decade of extended criteria donor age. *Clin J Am Soc Nephrol* (2017) 12:323–31. doi:10.2215/CJN.06550616

15. Chotkan KA, Kuiper MA, Alwayn IPJ, Heemskerk MBA, Braat AE, Jansen NE. Analysis of unused organ donors in the Netherlands: older donor age associated with higher risk of non-utilization. *Transpl Int* (2025) 38:14157. doi:10.3389/ti.2025.14157

16. Dayoub JC, Cortese F, Anžič A, Grum T, de Magalhães JP. The effects of donor age on organ transplants: a review and implications for aging research. *Exp Gerontol* (2018) 110:230–40. doi:10.1016/j.exger.2018.06.019

17. Moosburner S, Patel MS, Wang BK, Prasadh J, Öllinger R, Lurje G, et al. Multinational analysis of marginal liver grafts based on the eurotransplant extended donor criteria. *Ann Surg* (2024) 280:896–904. doi:10.1097/SLA.0000000000006491

18. Vodkin I, Kuo A. Extended criteria donors in liver transplantation. *Clin Liver Dis* (2017) 21:289–301. doi:10.1016/j.cld.2016.12.004

19. Azizieh Y, Westhaver LP, Badrudin D, Boudreau JE, Gala-Lopez BL. Changing liver utilization and discard rates in clinical transplantation in the *ex-vivo* machine preservation era. *Front Med Technol* (2023) 5:1079003. doi:10.3389/fmedt.2023.1079003

20. Roullet S, Defaye M, Quinart A, Adam JP, Chiche L, Laurent C, et al. Liver transplantation with old grafts: a ten-year experience. *Transpl Proc* (2017) 49:2135–43. doi:10.1016/j.transproceed.2017.07.012

21. Bezjak M, Stresec I, Kocman B, Jadrijević S, Filipec Kanizaj T, Antonijević M, et al. Influence of donor age on liver transplantation outcomes: a multivariate analysis and comparative study. *World J Gastrointest Surg* (2024) 16:331–44. doi:10.4240/wjgs.v16.i2.331

22. Vogel T, Szardenings C, Becker F, Jordan S, Katou S, Morgul H, et al. Viability assessment and transplantation of extended criteria donor liver grafts using normothermic machine perfusion. *Surgery* (2024) 176:934–41. doi:10.1016/j.surg.2024.05.025

23. Moein M, Bahreini A, Razavi A, Badie S, Coyle S, Abedini M, et al. A review of long-term outcomes of liver transplantation using extended criteria donors in the United States. *J Surg Res* (2025) 306:561–9. doi:10.1016/j.jss.2024.12.055

24. Lowsky DJ, Olshansky SJ, Bhattacharya J, Goldman DP. Heterogeneity in healthy aging. *J Gerontol A Biol Sci Med Sci* (2014) 69:640–9. doi:10.1093/gerona/glt162

25. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell* (2023) 186:243–78. doi:10.1016/j.cell.2022.11.001

26. Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. Cellular senescence: defining a path forward. *Cell* (2019) 179:813–27. doi:10.1016/j.cell.2019.10.005

27. Chen C, Zheng M, Hou H, Fang S, Chen L, Yang J, et al. Cellular senescence in ischemia/reperfusion injury. *Cell Death Discov* (2022) 8:420. doi:10.1038/s41420-022-01205-z

28. Mylonas KJ, O'Sullivan ED, Humphries D, Baird DP, Docherty MH, Neely SA, et al. Cellular senescence inhibits renal regeneration after injury in mice, with senolytic treatment promoting repair. *Sci Transl Med* (2021) 13:eabb0203. doi:10.1126/scitranslmed.abb0203

29. Ferreira-Gonzalez S, Man TY, Esser H, Aird R, Kilpatrick AM, Rodrigo-Torres D, et al. Senolytic treatment preserves biliary regenerative capacity lost through cellular senescence during cold storage. *Sci Transl Med* (2022) 14:eabj4375. doi:10.1126/scitranslmed.abj4375

30. Esser H, Kilpatrick AM, Man TY, Aird R, Rodrigo-Torres D, Buch ML, et al. Primary cilia as a targetable node between biliary injury, senescence and regeneration in liver transplantation. *J Hepatol* (2024) 81:1005–22.

31. Iske J, Roesel MJ, Martin F, Schroeter A, Matsunaga T, Maenosono R, et al. Transplanting old organs promotes senescence in young recipients. *Am J Transpl* (2024) 24:391–405. doi:10.1016/j.ajt.2023.10.013

32. Ritschka B, Knauer-Meyer T, Gonçalves DS, Mas A, Plassat JL, Durik M, et al. The senotherapeutic drug ABT-737 disrupts aberrant p21 expression to restore liver regeneration in adult mice. *Genes Dev* (2020) 34:489–94. doi:10.1101/gad.332643.119

33. Ferreira-Gonzalez S, Matsumoto T, Hara E, Forbes SJ. Senescence, aging and disease throughout the gastrointestinal system. *Gastroenterology* (2025) 169:1357–79. doi:10.1053/j.gastro.2025.06.010

34. Weissenbacher A, Vrakas G, Nasralla D, Ceresa CDL. The future of organ perfusion and re-conditioning. *Transpl Int* (2019) 32:586–97. doi:10.1111/tri.13441

35. Lau NS, McCaughan G, Ly M, Liu K, Crawford M, Pulitano C. Long-term machine perfusion of human split livers: a new model for regenerative and translational research. *Nat Commun* (2024) 15:9809. doi:10.1038/s41467-024-54024-4

36. Dries Sop den, Karimian N, Sutton ME, Westerkamp AC, Nijsten MWN, Gouw ASH, et al. *Ex vivo* normothermic machine perfusion and viability testing of discarded human donor livers. *Am J Transpl* (2013) 13:1327–35. doi:10.1111/ajt.12187

37. Nasralla D, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, et al. A randomized trial of normothermic preservation in liver transplantation. *Nature* (2018) 557:50–6. doi:10.1038/s41586-018-0047-9

38. Serifis N, Matheson R, Cloonan D, Rickert CG, Markmann JF, Coe TM. Machine perfusion of the liver: a review of clinical trials. *Front Surg* (2021) 8:625394. doi:10.3389/fsurg.2021.625394

39. Vogel T, Brockman JG, Quaglia A, Morovat A, Jassem W, Heaton ND, et al. The 24-hour normothermic machine perfusion of discarded human liver grafts. *Liver Transpl* (2017) 23:207–20. doi:10.1002/lt.24672

40. Ly M, Lau NS, Dennis C, Chen J, Risbey C, Tan S, et al. Long-term *ex situ* normothermic machine perfusion allows regeneration of human livers with severe bile duct injury. *Am J Transpl* (2025) 25:60–71. doi:10.1016/j.ajt.2024.07.019

41. Chaib S, Tchkonia T, Kirkland JL. Cellular senescence and senolytics: the path to the clinic. *Nat Med* (2022) 28:1556–68. doi:10.1038/s41591-022-01923-y

42. Matsunaga T, Roesel MJ, Schroeter A, Xiao Y, Zhou H, Tullius SG. Preserving and rejuvenating old organs for transplantation: novel treatments including the potential of senolytics. *Curr Opin Organ Transpl* (2022) 27:481–7. doi:10.1097/MOT.0000000000001019

43. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. *Cell* (2014) 159:709–13. doi:10.1016/j.cell.2014.10.039

44. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* (2013) 153:1194–217. doi:10.1016/j.cell.2013.05.039

45. Krishnamurthy J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su L, et al. Ink4a/Arf expression is a biomarker of aging. *J Clin Invest* (2004) 114:1299–307. doi:10.1172/JCI22475

46. Baker DJ, Wijshake T, Tchkonia T, LeBrasseur NK, Childs BG, van de Sluis B, et al. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. *Nature* (2011) 479:232–6. doi:10.1038/nature10600

47. Baker DJ, Childs BG, Durik M, Wijers ME, Sieben CJ, Zhong J, et al. Naturally occurring p16Ink4a-positive cells shorten healthy lifespan. *Nature* (2016) 530:184–9. doi:10.1038/nature16932

48. Tuttle CSL, Waaijer MEC, Slee-Valentijn MS, Stijnen T, Westendorp R, Maier AB. Cellular senescence and chronological age in various human tissues: a systematic review and meta-analysis. *Aging Cell* (2020) 19:e13083. doi:10.1111/acel.13083

49. Wiley CD, Campisi J. The metabolic roots of senescence: mechanisms and opportunities for intervention. *Nat Metab* (2021) 3:1290–301. doi:10.1038/s42255-021-00483-8

50. Zhang X, Englund DA, Aversa Z, Jachim SK, White TA, LeBrasseur NK. Exercise counters the age-related accumulation of senescent cells. *Exerc Sport Sci Rev* (2022) 50: 213–21. doi:10.1249/JES.0000000000000302

51. Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. *FEBS J* (2023) 290: 1362–83. doi:10.1111/febs.16350

52. Koppelstaetter C, Schratzberger G, Perco P, Hofer J, Mark W, Öllinger R, et al. Markers of cellular senescence in zero hour biopsies predict outcome in renal transplantation. *Aging Cell* (2008) 7:491–7. doi:10.1111/j.1474-9726.2008.00398.x

53. Braun H, Schmidt BMW, Raiss M, Baisantry A, Mircea-Constantin D, Wang S, et al. Cellular senescence limits regenerative capacity and allograft survival. *J Am Soc Nephrol JASN* (2012) 23:1467–73. doi:10.1681/ASN.2011100967

54. Domański L, Kłoda K, Kwiatkowska E, Borowiecka E, Safranow K, Drozd A, et al. Effect of delayed graft function, acute rejection and chronic allograft dysfunction on kidney allograft telomere length in patients after transplantation: a prospective cohort study. *BMC Nephrol* (2015) 16:23. doi:10.1186/s12882-015-0014-8

55. Iske J, Seyda M, Heinbokel T, Maenosono R, Minami K, Nian Y, et al. Senolytics prevent mt-DNA-induced inflammation and promote the survival of aged organs following transplantation. *Nat Commun* (2020) 11:4289. doi:10.1038/s41467-020-18039-x

56. Sasaki M, Ikeda H, Haga H, Manabe T, Nakanuma Y. Frequent cellular senescence in small bile ducts in primary biliary cirrhosis: a possible role in bile duct loss. *J Pathol* (2005) 205:451–9. doi:10.1002/path.1729

57. Meng L, Quezada M, Levine P, Han Y, McDaniel K, Zhou T, et al. Functional role of cellular senescence in biliary injury. *Am J Pathol* (2015) 185:602–9. doi:10.1016/j.ajpath.2014.10.027

58. Nakanuma Y, Sasaki M, Harada K. Autophagy and senescence in fibrosing cholangiopathies. *J Hepatol* (2015) 62:934–45. doi:10.1016/j.jhep.2014.11.027

59. Ferreira-Gonzalez S, Lu WY, Raven A, Dwyer B, Man TY, O'Duibhir E, et al. Paracrine cellular senescence exacerbates biliary injury and impairs regeneration. *Nat Commun* (2018) 9:1020. doi:10.1038/s41467-018-03299-5

60. Trussoni CE, O'Hara SP, LaRusso NF. Cellular senescence in the cholangiopathies: a driver of immunopathology and a novel therapeutic target. *Semin Immunopathol* (2022) 44:527–44. doi:10.1007/s00281-022-00909-9

61. Jalan-Sakrikar N, Anwar A, Yaqoob U, Gan C, Lagnado AB, Wixom AQ, et al. Telomere dysfunction promotes cholangiocyte senescence and biliary fibrosis in primary sclerosing cholangitis. *JCI Insight* (2023) 8:e170320. doi:10.1172/jci.insight.170320

62. Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. *J Hepatol* (2019) 70:745–58. doi:10.1016/j.jhep.2018.12.009

63. Allaire M, Gilgenkrantz H. The aged liver: beyond cellular senescence. *Clin Res Hepatol Gastroenterol* (2020) 44:6–11. doi:10.1016/j.clinre.2019.07.011

64. Chatterjee N, Sharma R, Kale PR, Trehanpati N, Ramakrishna G. Is the liver resilient to the process of ageing? *Ann Hepatol* (2025) 30:101580. doi:10.1016/j.aohep.2024.101580

65. Pavanello S, Campisi M, Fabozzo A, Cibin G, Tarzia V, Toscano G, et al. The biological age of the heart is consistently younger than chronological age. *Sci Rep* (2020) 10:10752. doi:10.1038/s41598-020-67622-1

66. Spinelli R, Baboota RK, Gogg S, Beguinot F, Blüher M, Nerstedt A, et al. Increased cell senescence in human metabolic disorders. *J Clin Invest* (2023) 133:e169922. doi:10.1172/JCI169922

67. Matsunaga T, Iske J, Andreas S, Azuma H, Zhou H, Tullius SG. The potential of senolytics in transplantation. *Mech Ageing Dev* (2021) 200:111582. doi:10.1016/j.mad.2021.111582

68. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. *Exp Cell Res* (1961) 25:585–621. doi:10.1016/0014-4827(61)90192-6

69. Acosta JC, Banito A, Wuestefeld T, Georgilis A, Janich P, Morton JP, et al. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. *Nat Cell Biol* (2013) 15:978–90. doi:10.1038/ncb2784

70. Ogrodnik M, Acosta JC, Adams PD, Fagagna F, Baker DJ, Bishop CL, et al. Guidelines for minimal information on cellular senescence experimentation *in vivo*. *Cell* (2024) 187:4150–75. doi:10.1016/j.cell.2024.05.059

71. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging: an evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* (2000) 908:244–54. doi:10.1111/j.1749-6632.2000.tb06651.x

72. Van Deursen MJ. The role of senescent cells in ageing. *Nature* (2014) 509:439–46. doi:10.1038/nature13193

73. Kirkland JL, Tchkonia T. Cellular senescence: a translational perspective. *EBioMedicine* (2017) 21:21–8. doi:10.1016/j.ebiom.2017.04.013

74. Muñoz-Espín D, Serrano M. Cellular senescence: from physiology to pathology. *Nat Rev Mol Cell Biol* (2014) 15:482–96. doi:10.1038/nrm3823

75. Childs BG, Gluscevic M, Baker DJ, Laberge RM, Marquess D, Dananberg J, et al. Senescent cells: an emerging target for diseases of ageing. *Nat Rev Drug Discov* (2017) 16: 718–35. doi:10.1038/nrd.2017.116

76. Javali PS, Kumar A, Sarkar S, Varshini RS, Mathew DJ, Thirumurugan K. Next-gen senotherapeutics: ai/ml-driven strategies for aging and age-related disorders. *Adv Pharmacol* (2025) 104:87–119. doi:10.1016/bs.apha.2025.01.017

77. González-Gualda E, Baker AG, Fruk L, Muñoz-Espín D. A guide to assessing cellular senescence *in vitro* and *in vivo*. *FEBS J* (2021) 288:56–80. doi:10.1111/febs.15570

78. Kohli J, Wang B, Brandenburg SM, Basisty N, Evangelou K, Varela-Eirin M, et al. Algorithmic assessment of cellular senescence in experimental and clinical specimens. *Nat Protoc* (2021) 16:2471–98. doi:10.1038/s41596-021-00505-5

79. Gurkar AU, Gerencser AA, Mora AL, Nelson AC, Zhang AR, Lagnado AB, et al. Spatial mapping of cellular senescence: emerging challenges and opportunities. *Nat Aging* (2023) 3:776–90. doi:10.1038/s43587-023-00446-6

80. Miller WC, Yousefzadeh MJ, Fisher J, Sarumi H, Kirchner V, Niedernhofer LJ, et al. A brief report on biomarkers of cellular senescence associated with liver frailty and length of stay in liver transplantation. *GeroScience* (2025) 47:5257–65. doi:10.1007/s11357-024-01482-9

81. Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, et al. A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLOS Biol* (2020) 18:e3000599. doi:10.1371/journal.pbio.3000599

82. Xu Y, Li Q, Jiao X. *Immunosenescence and Metabolic Reprogramming in MASLD: An Age-dependent Immunometabolic Vicious Cycle and Therapeutic Opportunities* (2025). doi:10.3389/fcell.2025.1650677

83. Kusumoto D, Seki T, Sawada H, Kunitomi A, Katsuki T, Kimura M, et al. Anti-senescent drug screening by deep learning-based morphology senescence scoring. *Nat Commun* (2021) 12:257. doi:10.1038/s41467-020-20213-0

84. v Heckenbach I, Mkrtchyan GV, Ezra MB, Bakula D, Madsen JS, Nielsen MH, et al. Nuclear morphology is a deep learning biomarker of cellular senescence. *Nat Aging* (2022) 2:742–55. doi:10.1038/s43587-022-00263-3

85. Duran I, Pombo J, Sun B, Gallage S, Kudo H, McHugh D, et al. Detection of senescence using machine learning algorithms based on nuclear features. *Nat Commun* (2024) 15:1041. doi:10.1038/s41467-024-45421-w

86. Kultima K, Sköld K, Borén M. Biomarkers of disease and post-mortem changes — heat stabilization, a necessary tool for measurement of protein regulation. *J Proteomics* (2011) 75:145–59. doi:10.1016/j.jprot.2011.06.009

87. Wang Y, Zhang Y, Hu W, Xie S, Gong CX, Iqbal K, et al. Rapid alteration of protein phosphorylation during postmortem: implication in the study of protein phosphorylation. *Sci Rep* (2015) 5:15709. doi:10.1038/srep15709

88. Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. The achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell* (2015) 14:644–58. doi:10.1111/acel.12344

89. Ogrodnik M, Miwa S, Tchkonia T, Tiniakos D, Wilson CL, Lahat A, et al. Cellular senescence drives age-dependent hepatic steatosis. *Nat Commun* (2017) 8:15691. doi:10.1038/ncomms15691

90. Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. *J Intern Med* (2020) 288:518–36. doi:10.1111/joim.13141

91. Yosef R, Pilpel N, Tokarsky-Amiel R, Biran A, Ovadya Y, Cohen S, et al. Directed elimination of senescent cells by inhibition of BCL-W and BCL-XL. *Nat Commun* (2016) 7:11190. doi:10.1038/ncomms11190

92. Zhu Y, Doornebal EJ, Pirtskhalava T, Giorgadze N, Wentworth M, Fuhrmann-Stroissnigg H, et al. New agents that target senescent cells: the flavone, fisetin, and the BCL-XL inhibitors, A1331852 and A1155463. *Aging* (2017) 9:955–63. doi:10.18632/aging.101202

93. Schoenwaelder SM, Jarman KE, Gardiner EE, Hua M, Qiao J, White MJ, et al. Bcl-XL–Inhibitory BH3 mimetics can induce a transient thrombocytopathy that undermines the hemostatic function of platelets. *Blood* (2011) 118:1663–74. doi:10.1182/blood-2011-04-347849

94. Cleary JM, Lima CMSR, Hurwitz HI, Montero AJ, Franklin C, Yang J, et al. A phase I clinical trial of navitoclax, a targeted high-affinity Bcl-2 family inhibitor, in combination with gemcitabine in patients with solid tumors. *Invest New Drugs* (2014) 32:937–45. doi:10.1007/s10637-014-0110-9

95. Gandhi L, Camidge DR, Oliveira MR, Bonomi P, Gandara D, Khaira D, et al. Phase I study of navitoclax (ABT-263), a novel Bcl-2 family inhibitor, in patients with small-cell lung cancer and other solid tumors. *J Clin Oncol* (2011) 29:909–16. doi:10.1200/JCO.2010.31.6208

96. Khan N, Syed DN, Ahmad N, Mukhtar H. Fisetin: a dietary antioxidant for health promotion. *Antioxid Redox Signal* (2013) 19:151–62. doi:10.1089/ars.2012.4901

97. Yousefzadeh MJ, Zhu Y, McGowan SJ, Angelini L, Fuhrmann-Stroissnigg H, Xu M, et al. Fisetin is a senotherapeutic that extends health and lifespan. *EBioMedicine* (2018) 36:18–28. doi:10.1016/j.ebiom.2018.09.015

98. Alsuraih M, O'Hara SP, Woodrum JE, Pirius NE, LaRusso NF. Genetic or pharmacological reduction of cholangiocyte senescence improves inflammation and

fibrosis in the Mdr2 -/- mouse. *JHEP Rep* (2021) 3:100250. doi:10.1016/j.jhepr.2021.100250

99. Baar MP, Brandt RMC, Putavet DA, Klein JDD, Derks KWJ, Bourgeois BRM, et al. Targeted apoptosis of senescent cells restores tissue homeostasis in response to chemotoxicity and aging. *Cell* (2017) 169:132–47.e16. doi:10.1016/j.cell.2017.02.031

100. Xu Q, Fu Q, Li Z, Liu H, Wang Y, Lin X, et al. The flavonoid procyanidin C1 has senotherapeutic activity and increases lifespan in mice. *Nat Metab* (2021) 3:1706–26. doi:10.1038/s42255-021-00491-8

101. Wang Y, Chang J, Liu X, Zhang X, Zhang S, Zhang X, et al. Discovery of piperlongumine as a potential novel lead for the development of senolytic agents. *Aging* (2016) 8:2915–26. doi:10.18632/aging.101100

102. Lee DJW, Kuerec AH, Maier AB. Targeting ageing with rapamycin and its derivatives in humans: a systematic review. *Lancet Healthy Longev* (2024) 5:e152–62. doi:10.1016/S2666-7568(23)00258-1

103. Mannick JB, Lamming DW. Targeting the biology of aging with mTOR inhibitors. *Nat Aging* (2023) 3:642–60. doi:10.1038/s43587-023-00416-y

104. Hao H, Liang W, Zhang S, Cai X, Yakefu A, Gao S, et al. Ruxolitinib delays nucleus pulposus cell senescence in rat intervertebral discs. *JOR SPINE* (2025) 8:e70044. doi:10.1002/jsp2.70044

105. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool to target aging. *Cell Metab* (2016) 23:1060–5. doi:10.1016/j.cmet.2016.05.011

106. American Federation for Aging Research. TAME-targeting aging with metformin (2025). Available online at: https://www.afar.org/tame-trial (Accessed December 17, 2025).

107. Suda M, Paul KH, Tripathi U, Minamino T, Tchkonia T, Kirkland JL. Targeting cell senescence and senolytics: novel interventions for age-related endocrine dysfunction. *Endocr Rev* (2024) 45:655–75. doi:10.1210/endrev/bnae010

108. Fuhrmann-Stroissnigg H, Ling YY, Zhao J, McGowan SJ, Zhu Y, Brooks RW, et al. Identification of HSP90 inhibitors as a novel class of senolytics. *Nat Commun* (2017) 8:422. doi:10.1038/s41467-017-00314-z

109. Dhokia V, Albati A, Smith H, Thomas G, Macip S. A second generation of senotherapies: the development of targeted senolytics, senoblockers and senoreversers for healthy ageing. *Biochem Soc Trans* (2024) 52:1661–71. doi:10.1042/BST20231066

110. Birch J, Gil J. Senescence and the SASP: many therapeutic avenues. *Genes Dev* (2020) 34:1565–76. doi:10.1101/gad.343129.120

111. Amor C, Feucht J, Leibold J, Ho YJ, Zhu C, Alonso-Curbelo D, et al. Senolytic CAR T cells reverse senescence-associated pathologies. *Nature* (2020) 583:127–32. doi:10.1038/s41586-020-2403-9

112. Wang TW, Johmura Y, Suzuki N, Omori S, Migita T, Yamaguchi K, et al. Blocking PD-L1–PD-1 improves senescence surveillance and ageing phenotypes. *Nature* (2022) 611:358–64. doi:10.1038/s41586-022-05388-4

113. McHugh D, Durán I, Gil J. Senescence as a therapeutic target in cancer and age-related diseases. *Nat Rev Drug Discov* (2025) 24:57–71. doi:10.1038/s41573-024-01074-4

114. Justice J, Nambiar A, Tchkonia T, LeBrasseur N, Pascual R, Hashmi S, et al. Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study. *EBioMedicine* (2019) 40:554–63. doi:10.1016/j.ebiom.2018.12.052

115. Nambiar A, Kellogg D, Justice J, Goros M, Gelfond J, Pascual R, et al. Senolytics dasatinib and quercetin in idiopathic pulmonary fibrosis: results of a phase I, single-blind, single-center, randomized, placebo-controlled pilot trial on feasibility and tolerability. *EBioMedicine* (2023) 90:104481. doi:10.1016/j.ebiom.2023.104481

116. Farr JN, Atkinson EJ, Achenbach SJ, Volkman TL, Tweed AJ, Vos SJ, et al. Effects of intermittent senolytic therapy on bone metabolism in postmenopausal women: a phase 2 randomized controlled trial. *Nat Med* (2024) 30:2605–12. doi:10.1038/s41591-024-03096-2

117. Grosse L, Wagner N, Emelyanov A, Molina C, Lacas-Gervais S, Wagner KD, et al. Defined p16High senescent cell types are indispensable for mouse healthspan. *Cell Metab* (2020) 32:87–99.e6. doi:10.1016/j.cmet.2020.05.002

118. Reyes NS, Krasilnikov M, Allen NC, Lee JY, Hyams B, Zhou M, et al. Sentinel p16INK4a+ cells in the basement membrane form a reparative niche in the lung. *Science* (2022) 378:192–201. doi:10.1126/science.abf3326

119. Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, et al. An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. *Dev Cell* (2014) 31:722–33. doi:10.1016/j.devcel.2014.11.012

120. Grosse L, Bulavin DV. LSEC model of aging. *Aging (Albany NY)* (2020) 12:11152–60. doi:10.18632/aging.103492

121. Fang Y, Medina D, Stockwell R, McFadden S, Quinn K, Peck MR, et al. Sexual dimorphic metabolic and cognitive responses of C57BL/6 mice to fisetin or dasatinib and quercetin cocktail oral treatment. *GeroScience* (2023) 45:2835–50. doi:10.1007/s11357-023-00843-0

122. Neri F, Zheng S, Watson M, Desprez PY, Gerencser AA, Campisi J, et al. Senescent cell heterogeneity and responses to senolytic treatment are related to cell cycle status during cell growth arrest. *Aging (Albany NY)* (2025) 17:2063–78. doi:10.18632/aging.206299

123. González-Gualda E, Pàez-Ribes M, Lozano-Torres B, Macias D, Wilson JR, González-López C, et al. Galacto-conjugation of navitoclax as an efficient strategy to increase senolytic specificity and reduce platelet toxicity. *Aging Cell* (2020) 19:e13142. doi:10.1111/acel.13142

124. Cai Y, Zhou H, Zhu Y, Sun Q, Ji Y, Xue A, et al. Elimination of senescent cells by β-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice. *Cell Res* (2020) 30:574–89. doi:10.1038/s41422-020-0314-9

125. Zhou H, Tullius SG. Targeting cellular senescence in organ transplantation. *Transplantation* (2023) 107:1413–5. doi:10.1097/TP.0000000000004552

126. Kim SR, Jiang K, Ferguson CM, Tang H, Chen X, Zhu X, et al. Transplanted senescent renal scattered tubular-like cells induce injury in the mouse kidney. *Am J Physiol Ren Physiol* (2020) 318:F1167–76. doi:10.1152/ajprenal.00535.2019

127. Xu M, Bradley EW, Weivoda MM, Hwang SM, Pirtskhalava T, Decklever T, et al. Transplanted senescent cells induce an osteoarthritis-like condition in mice. *J Gerontol A Biol Sci Med Sci* (2017) 72:780–5. doi:10.1093/gerona/glw154

128. Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, et al. Senolytics improve physical function and increase lifespan in old age. *Nat Med* (2018) 24:1246–56. doi:10.1038/s41591-018-0092-9

129. da Silva PFL, Ogrodnik M, Kucheryavenko O, Glibert J, Miwa S, Cameron K, et al. The bystander effect contributes to the accumulation of senescent cells *in vivo*. *Aging Cell* (2019) 18:e12848. doi:10.1111/acel.12848

130. Du K, Umbaugh DS, Ren N, Diehl AM. Cellular senescence in liver diseases: from molecular drivers to therapeutic targeting. *J Hepatol* (2026) 84:194–212. doi:10.1016/j.jhep.2025.08.021

131. Kiourtis C, Terradas-Terradas M, Gee LM, May S, Georgakopoulou A, Collins AL, et al. Hepatocellular senescence induces multi-organ senescence and dysfunction *via* TGFβ. *Nat Cell Biol* (2024) 26:2075–83. doi:10.1038/s41556-024-01543-3

132. Wall A, Gupta A, Testa G. Abdominal normothermic regional perfusion in the United States: current state and future directions. *Curr Opin Organ Transpl* (2024) 29:175–9. doi:10.1097/MOT.0000000000001144

133. Eshmuminov D, Becker D, Bautista Borrego L, Hefti M, Schuler MJ, Hagedorn C, et al. An integrated perfusion machine preserves injured human livers for 1 week. *Nat Biotechnol* (2020) 38:189–98. doi:10.1038/s41587-019-0374-x

134. Cillo U, Lonati C, Bertacco A, Magnini L, Battistin M, Borsetto L, et al. A proof-of-concept study in small and large animal models for coupling liver normothermic machine perfusion with mesenchymal stromal cell bioreactors. *Nat Commun* (2025) 16:283. doi:10.1038/s41467-024-55217-7

135. Clavien PA, Dutkowski P, Mueller M, Eshmuminov D, Bautista Borrego L, Weber A, et al. Transplantation of a human liver following 3 days of *ex situ* normothermic preservation. *Nat Biotechnol* (2022) 40:1610–6. doi:10.1038/s41587-022-01354-7

136. Wehrle CJ, Jiao C, Sun K, Zhang M, Fairchild RL, Miller C, et al. Machine perfusion in liver transplantation: recent advances and coming challenges. *Curr Opin Organ Transpl* (2024) 29:228–38. doi:10.1097/MOT.0000000000001150

137. Fodor M, Lanser L, Hofmann J, Otarashvili G, Pühringer M, Cardini B, et al. Hyperspectral imaging as a tool for viability assessment during normothermic machine perfusion of human livers: a proof of concept pilot study. *Transpl Int* (2022) 35:10355. doi:10.3389/ti.2022.10355

138. Kayumov M, Song Z, Martin F, Tsou S, Xiao Y, Zhou H, et al. The promise of organ rejuvenation to overcome the shortage in organ transplantation. *Nat Commun* (2025) 16:11259. doi:10.1038/s41467-025-66133-9

139. Hoff U, Markmann D, Thurn-Valassina D, Nieminen-Kelhä M, Erlangga Z, Schmitz J, et al. The mTOR inhibitor rapamycin protects from premature cellular senescence early after experimental kidney transplantation. *PLoS One* (2022) 17:e0266319. doi:10.1371/journal.pone.0266319

140. Neuberger J. Follow-up of liver transplant recipients. *Best Pract Res Clin Gastroenterol* (2020) 46:101682. doi:10.1016/j.bpg.2020.101682

141. Lunz JG, Contrucci S, Ruppert K, Murase N, Fung JJ, Starzl TE, et al. Replicative senescence of biliary epithelial cells precedes bile duct loss in chronic liver allograft rejection: increased expression of p21WAF1/Cip1 as a disease marker and the influence of immunosuppressive drugs. *Am J Pathol* (2001) 158:1379–90. doi:10.1016/S0002-9440(10)64089-8

142. Brain JG, Robertson H, Thompson E, Humphreys EH, Gardner A, Booth TA, et al. Biliary epithelial senescence and plasticity in acute cellular rejection. *Am J Transpl* (2013) 13:1688–702. doi:10.1111/ajt.12271

143. Rastogi A, Nigam N, Gayatri R, Bihari C, Pamecha V. Biliary epithelial senescence in cellular rejection following live donor liver transplantation. *J Clin Exp Hepatol* (2022) 12:1420–7. doi:10.1016/j.jceh.2022.08.004

144. Esser H, Jong IEM, Roos FM, Bogensperger C, Brunner SM, Cardini B, et al. Consensus classification of biliary complications after liver transplantation: guidelines from the BileducTx meeting. *Br J Surg* (2025) 112:znae321. doi:10.1093/bjs/znae321

145. Hmedat ANA, Doondeea J, Ebner D, Feller SM, Lewitzky M. The src family kinase inhibitor drug dasatinib and glucocorticoids display synergistic activity against tongue squamous cell carcinoma and reduce MET kinase activity. *Cell Commun Signal* (2025) 23:293. doi:10.1186/s12964-025-02129-8

146. Imai Y, Ohta E, Takeda S, Sunamura S, Ishibashi M, Tamura H, et al. Histone deacetylase inhibitor panobinostat induces calcineurin degradation in multiple myeloma. *JCI Insight* (2016) 1:e85061. doi:10.1172/jci.insight.85061

147. Schwartz A, Sutton SL, Middleton E. Quercetin inhibition of the induction and function of cytotoxic T lymphocytes. *Immunopharmacology* (1982) 4:125–38. doi:10.1016/0162-3109(82)90015-7

148. Song B, Guan S, Lu J, Chen Z, Huang G, Li G, et al. Suppressive effects of fisetin on mice T lymphocytes *in vitro* and *in vivo*. *J Surg Res* (2013) 185:399–409. doi:10.1016/j.jss.2013.05.093

149. Iske J, Matsunaga T, Zhou H, Tullius SG. Donor and recipient age-mismatches: the potential of transferring senescence. *Front Immunol* (2021) 12:671479. doi:10.3389/fimmu.2021.671479

150. Saul D, Kosinsky RL, Atkinson EJ, Doolittle ML, Zhang X, LeBrasseur NK, et al. A new gene set identifies senescent cells and predicts senescence-associated pathways across tissues. *Nat Commun* (2022) 13:4827. doi:10.1038/s41467-022-32552-1

151. Saul D, Jurk D, Doolittle ML, Kosinsky RL, Han Y, Zhang X, et al. Distinct senotypes in p16-and p21-positive cells across human and mouse aging tissues. *EMBO J* (2025) 44:7295–325. doi:10.1038/s44318-025-00601-2

152. Yang S, Liu C, Jiang M, Liu X, Geng L, Zhang Y, et al. A single-nucleus transcriptomic atlas of primate liver aging uncovers the pro-senescence role of SREBP2 in hepatocytes. *Protein Cell* (2023) 15:98–120. doi:10.1093/procel/pwad039

153. Yashaswini CN, Qin T, Bhattacharya D, Amor C, Lowe S, Lujambio A, et al. Phenotypes and ontogeny of senescent hepatic stellate cells in metabolic dysfunction-associated steatohepatitis. *J Hepatol* (2024) 81:207–17. doi:10.1016/j.jhep.2024.03.014

154. SenNet Consortium. NIH SenNet consortium to map senescent cells throughout the human lifespan to understand physiological health. *Nat Aging* (2022) 2:1100. doi:10.1038/s43587-022-00326-5

155. Ibrahim M, Dechantsreiter J, Müller PC, Finotti M, Kowal MR, Ngjelina J, et al. Machine perfusion in an ageing population - results from a German, national survey among transplant centers. *Transpl Int* (2025) 38:15681. doi:10.3389/ti.2025.15681

156. Kroemer G, Maier AB, Cuervo AM, Gladyshev VN, Ferrucci L, Gorbunova V, et al. From geroscience to precision geromedicine: understanding and managing aging. *Cell* (2025) 188:2043–62. doi:10.1016/j.cell.2025.03.01

157. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet* (2018) 19:371–84. doi:10.1038/s41576-018-0004-3

158. Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging* (2018) 10(4):573–91. doi:10.18632/aging.101414

159. Ember KJI, Hunt F, Jamieson LE, Hallett JM, Esser H, Kendall TJ, et al. Noninvasive detection of ischemic vascular damage in a pig model of liver donation after circulatory death. *Hepatology* (2021) 74:428–43. doi:10.1002/hep.31701

160. Dookun E, Walaszczyk A, Redgrave R, Palmowski P, Tual-Chalot S, Suwana A, et al. Clearance of senescent cells during cardiac ischemia–reperfusion injury improves recovery. *Aging Cell* (2020) 19:e13249. doi:10.1111/acel.13249

161. Farr JN, Monroe DG, Atkinson EJ, Froemming MN, Ruan M, LeBrasseur NK, et al. Characterization of human senescent cell biomarkers for clinical trials. *Aging Cell* (2025) 24:e14489. doi:10.1111/acel.14489

162. LaFougere C, Gueckel B, Dittmann H, Trautwein N, Hinterleitner M, Cotton J, et al. Abstract CT095: update: a phase 1/2, open-label study to assess safety, tolerability, biodistribution, radiation dosimetry and PET imaging characteristics of [18F]FPyGal in comparison to *in-vitro* diagnostic for the assessment of senescence in oncological patients (NCT04536454). *Cancer Res* (2023) 83(8_Suppl. ment):CT095. doi:10.1158/1538-7445.AM2023-CT095

163. Xiang X, Dong C, Zhou L, Liu J, Rabinowitz ZM, Zhang Y, et al. Novel PET imaging probe for quantitative detection of senescence *in vivo*. *J Med Chem* (2024) 67:5924–34. doi:10.1021/acs.jmedchem.4c00179

164. Liu J, Ma X, Cui C, Chen Z, Wang Y, Deenik PR, et al. Non-invasive NIR imaging of senescence *via in situ* labeling. *J Med Chem* (2021) 64:17969–78. doi:10.1021/acs.jmedchem.1c01313

165. Rojas-Vázquez S, Lozano-Torres B, García-Fernández A, Galiana I, Perez-Villalba A, Martí-Rodrigo P, et al. A renal clearable fluorogenic probe for *in vivo* β-galactosidase activity detection during aging and senolysis. *Nat Commun* (2024) 15:775. doi:10.1038/s41467-024-44903-1

166. Muñoz-Espín D, Cañamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, et al. Programmed cell senescence during mammalian embryonic development. *Cell* (2013) 155:1104–18. doi:10.1016/j.cell.2013.10.019