

Cellular Senescence in the Cardio-Diabetes-Renal Continuum: Biology, Therapy, and Clinical Translation

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Cellular senescence is a complex, multifaceted biological state defined by essentially irreversible cell-cycle arrest in response to various stresses including telomere shortening, DNA damage, oncogene activation, and metabolic derangements (Calcinotto et al., 2019; Xiong et al., 2019). Although initially recognised as an important tumour-suppressive mechanism limiting uncontrolled proliferation, senescent cells persist as metabolically active entities producing a distinctive senescence-associated secretory phenotype (SASP) composed of pro-inflammatory cytokines, chemokines, growth factors, and matrix-remodelling enzymes that significantly alter tissue microenvironments (Calcinotto et al., 2019; Suda et al., 2024). This SASP fuels chronic low-grade inflammation, fibrogenesis, and progressive tissue dysfunction, processes which have emerged as central drivers of ageing and numerous chronic diseases encompassing atherosclerosis, heart failure, type 2 diabetes, and chronic kidney disease (Boccardi et al., 2024; Katsuomi et al., 2018; Spinelli et al., 2023).

The dual nature of senescence—beneficial in tumour suppression and tissue repair but detrimental when senescent cells accumulate and evade clearance—poses challenges and opportunities for therapeutic development. Cellular senescence arises via converging molecular pathways principally involving the p53–p21 and p16INK4a–Rb axes that enforce stable growth arrest (Calcinotto et al., 2019). Epigenetic and chromatin changes further stabilize this phenotype, whose heterogeneity reflects distinct stressors, tissue contexts, and temporal dynamics (Suda et al., 2024; Chandra et al., 2022). The SASP evolves over time from signals that promote immune-mediated clearance to pro-fibrotic, matrix-remodelling profiles that exacerbate chronic disease (Boccardi et al., 2024).

Within metabolic tissues, senescence is intimately linked to obesity and insulin resistance, where senescent adipose cells secrete inflammatory mediators that perpetuate metabolic dysfunction and vascular damage (Matsubayashi et al., 2023). Experimental models demonstrate that clearing senescent cells improves insulin sensitivity and reduces complications such as steatosis and neurocognitive deficits (Ogrodnik et al., 2017; Ogrodnik et al., 2019). Senescence also drives vascular aging via endothelial and smooth muscle dysfunction, contributing to arterial stiffness, plaque instability, and impaired myocardial function typical of heart failure with preserved ejection fraction (Katsumi et al., 2018; Suda et al., 2024). The kidney is a paradigmatic target of senescence, with accelerated senescence of tubular, endothelial, mesangial, and podocyte populations in diabetic kidney disease (Xiong et al., 2019; Wei et al., 2025). These senescent cells produce pro-fibrotic SASP factors, linking cellular ageing mechanistically to progression of renal failure and vascular comorbidities.

The centrality of senescence in cardio-metabolic-renal disease has spurred interest in novel therapeutic classes—senolytics that selectively eliminate senescent cells, and senomorphics that modulate the SASP. Early preclinical studies demonstrate that senolytics improve cardiac and renal function, reduce fibrosis, and extend health span in model organisms (Baker et al., 2011; Kirkland, 2020). Early human pilot trials employ intermittent dosing of agents such as dasatinib plus quercetin to achieve sustained senescent cell clearance with promising safety and feasibility (Hickson et al., 2019). Integration of Seno therapeutics into complex cardio-diabetes-renal care paradigms is an

evolving frontier, requiring biomarker-driven patient selection, careful safety monitoring, and ethical stewardship.

This chapter reviews the biology of cellular senescence, molecular heterogeneity, metabolic implications, vascular and renal contributions, and the emerging clinical translation of senolytic and senomorphic therapies. We explore trial design, biomarker development, safety, pharmacology, and pragmatic implementation issues, concluding with perspectives on how senescence-informed medicine could radically reshape care and outcomes across the cardio-diabetes-renal continuum.

Molecular Pathways and Heterogeneity of Senescent Cells

Senescence induction converges on the activation of cell-cycle inhibitors p53–p21 and p16INK4a–Rb, enforcing a durable G1 arrest that halts proliferation despite persistent stress (Calcinotto et al., 2019). Triggers include DNA damage responses mediated by ATM/ATR kinases, telomere shortening, oncogenic RAS activation, and oxidative stress, which remodel chromatin architecture via formation of senescence-associated heterochromatin foci and global epigenetic changes (Xiong et al., 2019). This transcriptional reprogramming stabilizes the cell-cycle arrest and fuels SASP production.

Notably, senescent cells are heterogeneous, shaped by the nature and duration of stress, tissue type, and microenvironmental cues (Suda et al., 2024). p21-expressing senescent cells may accelerate pathological marrow changes seen in radiation-induced osteoporosis, while selectively ablating p16-expressing cells fails to fully recapitulate effects, highlighting functional specialization (Chandra et al., 2022). In obesity and diabetes, synergistic dysfunction of insulin-signalling, mitochondrial biogenesis, iron metabolism, and autophagy promotes senescence in adipocytes, hepatocytes and renal tubular cells (Spinelli et al., 2023; Wei et al., 2025).

The SASP is temporally dynamic: early senescence promotes immune clearance via growth-arrest signals and chemokines, while chronic senescence supports fibrosis, angiogenesis, and extracellular matrix remodelling (Boccardi et al., 2024). p21-driven secretomes recruit immune effectors for immunosurveillance, whereas persistent p16-dominant senescent populations become deleterious sentinel cells in ageing tissues (Sturm Lechner et al., 2021). Understanding this heterogeneity is critical as indiscriminate senolytic removal may compromise beneficial senescent subsets or destabilize vulnerable tissue structures like atherosclerotic plaques (Is Senolytic Therapy in CVD, 2025).

Senescence, Metabolism, and Obesity

Metabolically active tissues are highly susceptible to senescence given their exposure to nutrient overload, lipid flux, and reactive oxygen species. Obesity induces accumulation of senescent adipocyte precursors and stromal cells exhibiting impaired differentiation capacity, altered adipokine profiles, and a robust SASP comprised of pro-inflammatory cytokines such as IL-6 and MCP-1 (Matsubayashi et al., 2023). These inflammatory milieu components attract macrophages, promoting crown-like structures that sustain low-grade chronic inflammation, exacerbating insulin resistance and endothelial dysfunction (Matsubayashi et al., 2023).

Preclinical models validate these mechanisms where genetic or pharmacologic senescent cell clearance in adipose tissue improves systemic glucose tolerance and insulin sensitivity, alongside reduced hepatic steatosis (Ogrodnik et al., 2017; Matsubayashi et al., 2023). Senescence in adipose tissue and brain also mediates neurobehavioral effects including anxiety and impaired neurogenesis (Ogrodnik et al., 2019). This last finding has implications for cardio-diabetes-renal medicine, as neuropsychiatric status influences lifestyle adherence and risk factor control.

Human studies demonstrate early senescence of adipose-derived mesenchymal stromal cells, with diminished regenerative potential and inflammatory secretome that may impair microvascular repair in heart, kidney and peripheral tissues (Conley et al., 2020). Clinical cohorts with metabolic syndrome and diabetes show increased expression of senescence markers in multiple tissues, substantiating its role within human metabolic disease beyond experimental models (Spinelli et al., 2023).

Cardiovascular and Renal Senescence in Cardio-Metabolic Disease

Senescence within the cardiovascular system is evident across endothelial cells, vascular smooth muscle cells (VSMCs), fibroblasts and cardiomyocytes. Age-related and metabolic stress accelerate endothelial senescence leading to reduced nitric oxide availability, enhanced adhesion molecule expression, and a prothrombotic, proinflammatory state that promotes atherosclerosis initiation and progression (Katsumi et al., 2018; Suda et al., 2024).

Senescent VSMCs contribute to arterial stiffness and vascular calcification via diminished contractility, increased matrix metalloproteinase secretion, and osteogenic differentiation (Katsumi et al., 2018). These cells accumulate in plaques; while elimination of senescent foam cells reduces plaque size, excessive VSMC clearance may destabilize plaques by thinning the fibrous cap, increasing rupture risk (Is Senolytic Therapy in CVD, 2025).

In myocardial tissue, aged or stressed cardiomyocytes and fibroblasts display SASP-mediated promotion of fibrosis and adverse remodelling—mechanisms central to heart failure with preserved ejection fraction (HFpEF) common among aged diabetics and CKD patients (Suda et al., 2024). Genetic senescent cell clearance in animal models improves diastolic function and vascular responsiveness, evidencing causality (Is Senolytic Therapy in CVD, 2025).

Renally, diabetic kidney disease exemplifies a condition driven by complex senescence pathways in tubular epithelia, podocytes, mesangial and endothelial cells (Xiong et al., 2019; Wei et al., 2025). These cells undergo senescence induced by hyperglycaemia-related oxidative stress, mitochondrial dysfunction and renin-angiotensin-aldosterone system activation, releasing SASP factors (e.g., IL-6, TGF- β) that promote fibrosis, atrophy and capillary rarefaction creating a vicious cycle (Xiong et al., 2019). Senescence burden in CKD heightens cardiovascular risk by promoting systemic frailty and vascular calcification, linking renal and cardiac ageing mechanistically (Goligorsky, 2020).

Senolytic and Senomorphic Therapeutic Strategies

Given the central role of senescent cells in driving cardio-diabetes-renal disease, targeted therapies aiming to eliminate (senolytics) or modulate (senomorphics) these cells have emerged. Senolytics exploit senescent cells' reliance on anti-apoptotic pathways ("SCAPs") to selectively induce apoptosis (Kirkland and Tychonian, 2020). Navitoclax, an early senolytic targeting BCL-2 family proteins, clears senescent cardiovascular cells but causes thrombocytopenia limiting chronic use (Rad et al., 2024). Dasatinib plus quercetin (D+Q) is a widely studied oral combination with broad, cell-type complementary activity and demonstration of prolonged benefits on cardiac and vascular function in mice with a practical "hit-and-run" dosing strategy (Zhu et al., 2015; Anderson et al., 2019).

Fisetin, a plant flavonoid with senolytic and senomorphic actions, modulates inflammatory signalling pathways, reduces early adipogenesis and has shown metabolic benefits in obese models with good tolerability, making it a candidate for human trials (Jung et al., 2013; Rad et al., 2024). Other emerging senolytics with improved specificity and reduced toxicity are in development, as are senomorphics—agents moderating SASP and inflammation without killing cells, including mTOR and JAK-STAT inhibitors (Raffaele et al., 2022).

Notably, established cardio-metabolic drugs such as SGLT2 inhibitors and GLP-1 receptor agonists exhibit senomorphic effects by improving mitochondrial function and reducing oxidative stress (Yesilyurt-Dirican et al., 2025), suggesting synergy in combined therapeutic regimens.

Clinical Trial Design and Biomarkers for Senolytics

Translation of senolytics into clinic mandates carefully designed trials, especially in older, multimorbid cardio-diabetes-renal patients. Intermittent dosing regimens optimize durable senescent cell clearance while minimizing chronic side effects (Kirkland and Tychonian, 2020). Early-phase human trials of D+Q across pulmonary fibrosis, early dementia, and diabetic kidney disease have demonstrated feasibility and reductions in senescent cell markers (Justice et al., 2019; Hickson et al., 2019).

Biomarkers permitting patient stratification and therapeutic monitoring include p16INK4a and p21 expression in peripheral blood and tissues, inflammatory SASP factors (IL-6, TNF- α , MMPs), telomere length, and epigenetic ageing clocks (Raffaele et al., 2022; Wei et al., 2025). Renal senescence markers correlate with disease severity, supporting mechanistic and prognostic significance (Xiong et al., 2019).

Composite biomarker panels integrating transcriptomics, metabolomics and imaging (arterial stiffness, coronary calcium, fibrosis MRI) promise improved precision for enrolment and outcome prediction (Luo et al., 2024). Clinical trial endpoints will combine organ-specific functional measures (eGFR slope, vascular indices) with geriatric assessments including frailty and quality of life (Suda et al., 2024).

Safety, Drug Interactions, and Ethical Considerations

Senolytics' clinical development is challenged foremost by safety concerns. Agents like navitoclax cause dose-limiting cytopenias; even D+Q and fisetin carry risks of off-target kinase inhibition, drug interactions (notably with antiplatelets and anticoagulants), and immune or endothelial perturbations (Kirkland and Tychonian, 2020; Rad et al., 2024). Theoretical risks include impaired wound healing, interference with tumor surveillance, increased infection risk and destabilization of plaques or scar tissue (Is Senolytic Therapy in CVD, 2025).

CDR patients' frequent polypharmacy elevates interaction risk. Dasatinib metabolized by CYP enzymes interacts with statins, direct oral anticoagulants and immunosuppressants, while flavonoids impact hepatic metabolism and platelet function (Rad et al., 2024).

Ethical considerations address prioritizing treatment allocation, especially in resource-limited settings, balancing benefits with unknown long-term risks, and preventing premature off-label use without sufficient evidence (Raffaele et al., 2022). Clear clinical guidelines, pharmacovigilance, and educational initiatives will be essential.

Integration into Cardio-Diabetes-Renal Care and Future Perspectives

Pending positive efficacy and safety data, senolytics and senomorphics will complement—not replace—standard therapies in CDR care. Rational sequencing in type 2 diabetes with CKD may involve metformin, SGLT2 inhibitors, RAAS blockade, then GLP-1 receptor agonists or non-steroidal MRAs, with intermittent senolytic pulses for patients exhibiting high senescence markers and rapid progression (Wei et al., 2025). In HFpEF, senotherapies target myocardial and vascular senescent cells to reduce fibrosis and improve function (Suda et al., 2024). In advanced atherosclerosis, more conservative approaches favour senomorphics to preserve plaque stability.

Emerging concepts include combination serotherapy pairing senolytics with immune-based approaches such as vaccines or CAR-T cells targeting senescent cell antigens, though these remain experimental and costly.

Conceptually, the assimilation of senescence biomarkers into clinical risk assessment could reframe disease management to address biological ageing rather than solely pathological endpoints. This promises individualized therapy intensity to preserve functional reserve and health span.

Conclusion:

The burgeoning field of cellular senescence biology offers transformative potential for understanding and treating the synergistic diseases comprising the cardio-diabetes-renal continuum. Once considered a purely cancer-suppressive adaptation, senescence is now recognized as a critical driver of age-related chronic conditions through persistent senescent cell accumulation and SASP-mediated tissue dysfunction.

Cardio-metabolic organs—heart, kidney, vasculature, and metabolic tissues—show distinct yet interlinked patterns of senescent cell burden, all contributing to progressive insulin resistance, vascular stiffness, fibrosis, and decline in organ function. This mechanistic insight elevates senescence as a strategic therapeutic target in a population where current therapies incompletely halt progression and morbidity remains high.

Preclinical and emerging clinical data support senolytic strategies to selectively remove senescent cells or senomorphic agents to modulate their harmful secretome. Early human trials have validated feasibility, short-term safety, and promising biomarker reductions in diabetic kidney disease and other conditions. These advances enable unprecedented biological age-directed therapy beyond conventionally monitored clinical metrics.

However, translating serotherapy into routine cardio-diabetes-renal practice entails challenges. Safety concerns, especially regarding haematological toxicity and drug interactions, require rigorous pharmacovigilance and carefully selected patient populations. Efficacy endpoints must reflect not only organ function but also geriatric outcomes like frailty, cognition, and quality of life to justify therapy in complex multimorbidity. Ethical frameworks are essential to equitably allocate therapies and guard against overenthusiastic off-label use.

Integrating senolytics into current standards will likely involve adjunctive, biomarker-guided, intermittent “hit-and-run” regimens in high-risk patients already receiving comprehensive metabolic, haemodynamic and lipid control. The long-term vision is an era of “senescence-informed” medicine, where biological age guides personalized prevention and treatment to extend health span as well as lifespan.

Such a paradigm shift transcends traditional disease silos, approaching cardio-metabolic diseases as manifestations of an integrated ageing network. Preservation of cellular and tissue integrity across heart, kidney and metabolism may redefine therapeutic goals—focusing on functional reserve and resilience rather than isolated endpoints.

In conclusion, cellular senescence research offers deep mechanistic understanding and a novel therapeutic frontier with far-reaching potential. Ongoing clinical trials, biomarker development, and translational science will shape how senotherapies complement existing care to improve survival, function and quality of life for patients with diabetes, kidney disease, heart failure and their overlap. The promise of delaying or reversing biological ageing heralds a transformative future for cardio-diabetes-renal medicine, provided safety, efficacy, equity and ethical stewardship guide its clinical adoption.

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