Recent Advances in Pharmacology of Senotherapeutics: A Review

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ABSTRACT

Cellular senescence, a hallmark of ageing, is characterised by irreversible proliferative arrest and the secretion of inflammatory mediators that influence tissue microenvironments. While senescence is protective in development, wound healing, and tumour suppression, the chronic accumulation of senescent cells accelerates inflammation, fibrosis, and organ dysfunction. Senotherapeutics, a novel pharmacological class that encompasses Senolytics and Senomorphics, aims to selectively eliminate senescent cells or suppress their harmful secretory activity. This review, based on seminar discussions and recent literature, outlines the mechanisms of senescence, associated biomarkers, links to chronic diseases, and current advances in Senotherapeutic strategies. Preclinical evidence and early clinical studies suggest their potential to extend health span in humans and animals.

Keywords: Ageing, Cellular senescence, SASP, Senolytics, Senomorphics, Senotherapeutics, Geroscience, Pharmacology

INTRODUCTION

Ageing is a complex biological process marked by progressive functional decline, increased disease susceptibility, and reduced resilience to stressors. The conceptual framework of the “hallmarks of ageing” highlights interconnected processes such as genomic instability, telomere attrition, mitochondrial dysfunction, and stem cell exhaustion (Lopez-Otin *et al.*, 2013). Among these, cellular senescence has emerged as a central mechanism (Baker *et al.*, 2011)

The geroscience hypothesis proposes that targeting fundamental ageing mechanisms such as senescence can delay multiple chronic disorders simultaneously (Kirkland & Tchkonia, 2020). This paradigm has led to the development of senotherapeutics—agents that selectively target senescent cells or modulate their pathological effects (Zhang *et al.*, 2023).

Senescence is defined as a state of stable cell-cycle arrest, usually mediated by p16^INK4a^, p21^CIP1/WAF1^, and p53 pathways, accompanied by persistent metabolic activity and secretion of the senescence-associated secretory phenotype (SASP) (Aratani & Nakanishi, 2023). While short-term senescence contributes to tumour suppression and tissue repair, chronic persistence of senescent cells is linked to inflammaging, tissue degeneration, and age-related pathologies (Raffaele & Vinciguerra, 2022).

Molecular Basis of Cellular Senescence

Cellular senescence is primarily regulated through the p53–p21 and p16^INK4a^–Rb pathways in response to DNA damage, oxidative stress, and mitochondrial dysfunction (Han *et al.*, 2024). Senescent cells secrete a complex array of cytokines, chemokines, proteases, and growth factors known as SASP, which promote chronic inflammation, fibrosis, and tissue degeneration (Muthamil *et al.*, 2024). Recent guidelines emphasise multi-marker strategies for accurate in vivo detection of senescence due to its heterogeneous nature (Ogrodnik *et al.*, 2024).

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Markers of Senescence

Because senescence is a multifactorial process, its detection requires a panel of markers rather than a single indicator. Commonly used features include:

- **Morphological changes**: flattened, enlarged cell shape with altered chromatin architecture.
- **Biochemical markers**: senescence-associated β-galactosidase (SA-β-gal) activity at pH 6.
- **Molecular indicators**: upregulation of p16^INK4a^, p21, and DNA damage foci marked by γ-H2AX.
- **Nuclear changes**: reduction of Lamin B1 expression.
- **Secretory profile**: elevated SASP factors such as IL-6, IL-8, TNF-α, and matrix metalloproteinases (Aratani & Nakanishi, 2023).

These markers are used in combination to identify senescent cells in tissues and experimental models.

Role of Senescence in Age-Related Disorders

Progressive accumulation of senescent cells contributes significantly to the pathogenesis of multiple chronic diseases:

- **Cardiovascular diseases:** vascular stiffening, atherosclerosis, myocardial fibrosis
- **Neurodegenerative disorders:** exacerbation of neuroinflammation in Alzheimer's and Parkinson's disease
- **Metabolic disorders:** insulin resistance and type 2 diabetes
- **Cancer:** SASP-mediated tumour promotion and metastasis
- **Fibrotic diseases:** pulmonary fibrosis, chronic kidney disease, and liver cirrhosis (Aratani & Nakanishi, 2023).

Induction and Detection of Senescence

Senescence may arise from diverse stimuli, including:

- **Replicative exhaustion** due to telomere attrition.
- **Oncogene-induced senescence**, triggered by abnormal Ras or Myc activity.
- **DNA damage**, caused by oxidative stress, ionising radiation, or chemotherapy.
- **Mitochondrial dysfunction** and metabolic stress (López-Otín *et al*., 2013).

Detection techniques range from histochemical assays (SA-β-gal staining) and flow cytometry for cell cycle inhibitors to molecular profiling of SASP-related gene expression (Raffaele & Vinciguerra, 2022).

Senescence and Age-Related Diseases

Senescent cell accumulation contributes to a variety of chronic disorders:

- **Cardiovascular diseases**: vascular stiffness, atherosclerotic lesion development, and myocardial fibrosis.
- **Neurodegenerative disorders**: astrocyte and microglial senescence exacerbate neuroinflammation in Alzheimer's and Parkinson's disease.

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- **Metabolic dysfunction**: adipose tissue senescence promotes insulin resistance and type 2 diabetes.
- **Cancer**: while senescence halts tumour initiation, chronic SASP supports tumour progression and metastasis.
- **Fibrosis**: senescent fibroblasts are implicated in idiopathic pulmonary fibrosis, chronic kidney disease, and cirrhosis (Aratani & Nakanishi, 2023).

Senotherapeutic Strategies

Senolytics: Senolytic drugs selectively induce apoptosis in senescent cells by targeting pro-survival signalling pathways, including the BCL-2/BCL-XL and PI3K/AKT networks (Lelarg *et al.*, 2024). Prominent examples include:

- **Dasatinib** (tyrosine kinase inhibitor) and **quercetin** (flavonoid), often used in combination to clear multiple senescent cell types (Zhu *et al.*, 2015) & (Xu *et al.*, 2018).
- **Fisetin**, a natural flavonoid with broad Senolytic activity.
- **Navitoclax (ABT-263)**, a BCL-2 family inhibitor with clinical promise but limited by thrombocytopenia.
- **FOXO4-DRI peptide**, which disrupts FOXO4–p53 interaction to trigger senescent cell apoptosis (Aratani & Nakanishi, 2023).

Senomorphics

Senomorphics reprogram senescent cells to reduce SASP without killing them. Notable agents include:

- **Rapamycin**, which inhibits mTOR to suppress SASP factor synthesis.
- **Metformin**, which activates AMPK to reduce oxidative stress and inflammation.
- **JAK inhibitors** such as ruxolitinib, which dampen IL-6–STAT3 signalling and SASP output (Matsubayashi *et al.*, 2023; Alqahtani *et al.*, 2025).

Evidence from Preclinical and Clinical Studies

Preclinical animal models demonstrate broad therapeutic effects:

- **Metabolic diseases**: Dasatinib–Quercetin reduced adipose senescence and improved Insulin sensitivity.
- **Cardiovascular health**: Senolytics improved vascular elasticity and reduced hypertrophy.
- **Neurodegeneration**: clearance of senescent astrocytes improved cognition and attenuated tau pathology.
- **Fibrotic diseases**: Senolytics alleviated pulmonary, renal, and hepatic fibrosis (Raffaele & Vinciguerra, 2022).

Early human studies show promise. In idiopathic pulmonary fibrosis and diabetic kidney disease, Dasatinib–Quercetin improved physical function and lowered senescence biomarkers (Justice *et al.*, 2019; The Lancet Healthy Longevity, 2022). However, larger controlled trials are required to validate efficacy and safety.

Veterinary Relevance: In Veterinary medicine, Senotherapeutics could be applied to extend the healthy lifespan of companion animals and improve productivity in livestock. It could be helpful in companion animal research; studies in dogs and cats are exploring the potential of Senotherapeutics to address age-related conditions. Common in pets, including arthritis and kidney diseases. Dogs and cats develop osteoarthritis, heart failure, and neurodegenerative conditions similar to humans, suggesting translational potential (Guelfi *et al.*, 2024).

Companion animals provide valuable transitional models for human application, as they develop many age-related conditions naturally in a shared environment with humans (Simon *et al.*, 2024). This offers advantages over traditional laboratory animal studies. Market potential it has, the clinical trial landscape for senotherapeutics has rapidly expanded since 2018. Nonetheless, Veterinary-specific Pharmacokinetic and Toxicological studies are scarce, and further research is essential.

Challenges and Future Directions

Key challenges include:

- **Safety and specificity**: avoiding off-target effects such as thrombocytopenia with Navitoclax.
- **Heterogeneity of senescent cells**: requiring tissue-specific or cell-type–selective approaches.
- **Optimal dosing regimens**: intermittent "hit-and-run" dosing may reduce toxicity.
- **Translational gaps**: moving from preclinical models to clinical and Veterinary practice (Raffaele & Vinciguerra, 2022).

Future directions should focus on combination therapies, precision delivery systems, and integration with regenerative medicine strategies. Future research should prioritise precision Senotherapeutics, targeted delivery platforms, and combination strategies integrating regenerative medicine.

CONCLUSION

Senotherapeutics offers a transformative approach to the pharmacology of ageing by selectively eliminating or reprogramming senescent cells and represents a paradigm shift in pharmacology by targeting ageing itself. With emerging veterinary and human translational evidence, Senotherapy may soon become a cornerstone of preventive and therapeutic strategies in veterinary medicine. While early evidence demonstrates potential in treating chronic human and animal diseases, optimising safety, efficacy, and translational feasibility remains essential. Continued research is expected to establish senotherapeutics as an integral component of future healthcare and veterinary practice. Senotherapeutics holds remarkable promise for preventing and treating chronic degenerative disorders in both humans and animals. Continued translational research will be pivotal in establishing these agents as cornerstone interventions in longevity medicine.

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