# Senolytics and Cellular Senescence: The Road to the Clinic

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## Abstract

Many ailments and diseases appear to have interrelated and fundamental ageing processes at their foundation. Cellular senescence is one such mechanism, which involves a cell cycle stop in response to harmful stimuli. Senescent cells can appear at any time during life and, due to the numerous proteins they secrete, can have detrimental impacts on tissue function if they are persistent. Interventions against persistent senescent cells that destroy tissue have been proven in preclinical models to postpone, stop, or even reverse a variety of diseases. Accordingly, the development of small-molecule senolytic medicines that specifically eliminate senescent cells has resulted in potential methods for the prevention or treatment of a variety of diseases and age-related problems in people. In this Review, we explain the rationale for using senescent cells as a therapeutic target for diseases affecting people of all ages and talk about the most promising methods for putting small-molecule senolytics and other senescence-targeting interventions into clinical practise, including recent and ongoing clinical trials.

**Keywords:** Cellular senescence • Senolytic medicines • Respiratory symptoms

## Introduction

The number of people who are older is rising gradually. By 2030, the World Health Organization (WHO) predicts that 1 individual in 6 individuals, or 2.1 billion people, would be older over 60. The majority of diseases that cause the majority of morbidity, death, and healthcare expenses in low-income, middle-income, and high-income nations are mostly predicted by chronological age. In children as well as adults, ageing can be accentuated at the etiologic sites of many acute and chronic disorders. In fact, essential ageing processes can start to take place even before conception, as is the case with older oocytes associated with Down syndrome. Cellular senescence is a key ageing mechanism that is receiving more and more attention. Senescent cells build up as people age and at the sites of many pathological conditions and diseases. Promising outcomes from preclinical investigations have aided transition to early-phase clinical trials testing the safety and efficacy of senolytics since the initial reports of senolytic medications in 2015, some of which have since been published. One important mechanism of ageing that is getting more attention is cellular senescence. As people age and at the locations of many clinical illnesses and diseases, senescent cells accumulate. Subsequently the initial reports of senolytic drugs in 2015, some of which have since been published, promising results from preclinical investigations have aided in the transition to early-phase clinical trials evaluating the safety and efficacy of senolytics. According to the Geroscience Hypothesis, several aspects of ageing, such as cellular senescence, tend to advance together and may be major factors in the pathophysiology of a number of diseases, aging-related dysfunction, and loss of resilience. The Geroscience Hypothesis is expanded upon by the Unitary Theory of Fundamental Aging Mechanisms, which asserts that therapies targeting one fundamental mechanism may also target the others. In experimental animal models of ageing and chronic diseases, interventions that target cellular senescence, for instance, have been shown to attenuate other fundamental ageing mechanisms, resulting in reduced inflammation, attenuated progenitor exhaustion, decreased fibrosis, and a partially restored microbiome. It is possible that multimorbidity could be reduced and health span increased by understanding and addressing cellular senescence and the other pillars of ageing rather than focusing on specific diseases that are downstream of fundamental ageing processes, with realisation of significant societal and financial benefits. In this Review, we examine the potential therapeutic value of senescent cells, the state of senolytic drug development, and the route to clinical implementation of senescent cell-targeting preventive and therapeutic approaches.

### Cellular Senescence

After serially subculturing human fibroblasts, Hayflick and Moorhead published the first study on cellular senescence in 1961. Senescent cells, which are basically in an irreversible cell cycle halt but are still alive, can build up with age, especially in more frail people, and in the locations of many pathologies in experimental animals and people across the lifespan. Numerous stressors, such as DNA damage, cancerous mutations or oncogene activation, mitochondrial dysfunction, reactive metabolites, hyperoxia or hypoxia, proteotoxic stress, extracellular signals, infections, mechanical or shear stresses that cause cell deformation, resistance exercise, and substances secreted by other senescent cells, can cause cells to become senescent. Numerous such stresses trigger DNA damage response signalling, the *p53/p21CIP1/WAF1*, the p16INK4a/retinoblastoma protein, as well as other pathways. This causes cell cycle arrest and the emergence of a Senescence-Associated Secretory Phenotype (SASP). Those senescent cells with a proapoptotic SASP can survive despite the cytotoxic microenvironment they produce by upregulating pro-survival and antiapoptotic pathways like SRC kinases, the PI3K-AKT signalling pathway, Heat Shock Protein (HSP) pathways, serpines, mitochondrial pathways, or apoptosis regulator *BCL-2*-related proteins.

### The senescent-associated secreted phenotype

Most cells going through senescence produce a SASP. This SASP includes pro-inflammatory, pro-apoptotic, and pro-fibrotic proteins in 30%–70% of senescent cells; some of these factors can induce previously unsenescent cells to become senescent both locally and at a distance in an endocrine manner. This proapoptotic SASP can have detrimental effects both locally and systemically due to senescent cell accumulation and persistence. Compared to proapoptotic, pro-inflammatory senescent cells, the remaining 30%–70% of senescent cells appear to include growth and other regenerative factors, which may reduce apoptosis, tissue damage, and fibrosis and even aid in tissue regeneration. Senescent cells can orchestrate tissue remodelling, trigger immune responses during infections or tissue injury, encourage parturition by releasing SASP factors, and promote clearance of those senescent cells with a pro-inflammatory SASP if they are transiently present. Immune cells can be drawn to, anchored to, and activated by both pro-apoptotic and pro-growth types of SASP.

### Adverse impacts of persistent, proapoptotic SASP-expressing senescent cells

Senescent cells typically appear to be eliminated by natural killer cells and other immune cell types days to weeks after they originate. Senescent cells, however, can build up if a threshold burden of them is exceeded, possibly because proapoptotic SASP-expressing senescent cells drive the paracrine and endocrine spread of senescence at a rate that outpaces immune clearance of already-existing and newly-formed senescent cells. Senescent cell burden may continue to rise after it crosses this threshold, boosting senescent cell accumulation in a feed-forward loop while also contributing to tissue degradation, the onset or progression of numerous diseases, age-related disorders, and immunological dysregulation. This sterile inflammatory state can cause nearby and far-off non-senescent cells, such as progenitor cells, to malfunction, impairing tissue function and reducing the ability to regenerate. In line with this, persistent senescent cells have been linked to diseases like extracellular matrix degradation, fibrosis, and insulin resistance in adipose tissue, reduced muscle hypertrophy after resistance exercise, and impaired fracture healing in older people, as well as to the promotion of malignant transformation.

Senescent cells' SASP is not constant; it can alter over time and differs based on the type of cells that underwent senescence and the method used to cause it. SASP factors are created and how much of them are present can be controlled by the intracellular and extracellular environment. The proapoptotic, pro-inflammatory properties of the SASP can be exacerbated by persistent senescent cells, which appear to be particularly receptive to external cues like

Damage-Associated Molecular Patterns (DAMPs) and Pathogen-Associated Molecular Patterns (PAMPs).

### Discovery and development of senolytic drugs

A hypothesis-driven, mechanism-based approach to drug development was used to find the first senolytic medications. It was assumed that these senescent cells rely on antiapoptotic, pro-survival pathways to prevent self-destruction because the 30%–70% of senescent cells with a proapoptotic, tissue-destructive SASP are themselves resistant to apoptosis. Senescent cells do exhibit overexpression of one or more Senescent Cell Antiapoptotic Pathways (SCAPs), according to the analysis of proteomic and transcriptome datasets. Similar to the mechanisms that shield some cancer cells, such as B cell lymphoma or chronic lymphocytic leukaemia cells, which also release tissue-destructive proapoptotic proteins but avoid going through apoptosis themselves, SCAP pathways protect specific cancer cells. 46 drugs that target SCAP pathways were found to be potentially senolytic by bioinformatic analysis. In order to accelerate the transition from the bench to the bedside, the first senolytic agents were purposefully chosen to be studied further because they: (1) target multiple SCAPs rather than using the conventional drug development strategy of one drug/one molecular target/one disease; (2) can be taken orally; (3) are natural products with well-known safety profiles; or are already approved by the US Food and Drug Administration (FDA) for other indications. High-throughput library screens and other techniques are increasingly being used to find second-generation senolytics. One strategy is based on the fact that many senescent cells have increased lysosomal mass and senescence-associated galactosidase activity; galacto-oligosaccharide-coated nanoparticles and galactosidase-activated prodrugs seem to kill at least some of these cells. Another strategy is based on the fact that some senescent cells have high levels of lysosomal activity, making them vulnerable to lysosomal ATPase inhibitors. At least some senescent cells rely on glutamine metabolism as a pH-buffering system because of ruptured lysosomal membranes; suppression of this metabolism makes the cells susceptible to death.

### SASP inhibitors

Another therapeutic strategy for treating cellular senescence-related phenotypes or disorders involves suppressing the SASP without destroying senescent cells. By blocking the Nuclear Factor (NF)-B transcription factor, the JAK-STAT signal transduction pathway, the serine/threonine protein kinase mTOR, targets of the mitochondrial complex-1 or complex-4, or other pathways involved in the induction and maintenance of the SASP. SASP inhibitors can either directly or indirectly reduce the SASP of senescent cells. Inhibitors of NF-B can lower pro-inflammatory SASP cytokines and chemokines both *in vitro* and *in vivo*.

## Conclusion

Senescent cell elimination has become a viable therapeutic approach for avoiding, postponing, or treating a variety of diseases and age-related dysfunction. Senolytics' promising preclinical results point to therapeutic and preventive options for postponing multimorbidity and lengthening life expectancy. While randomised controlled trials will determine the efficacy and safety of senolytic methods, immediate scientific and regulatory issues must be resolved if senolytics are to be employed in clinical settings. Finding dependable, sensitive, and specific gerodiagnostics—biomarkers that measure senescent cell abundance, the SASP, and senolysis as well as other pillars of ageing—should be a top focus. A possibility that needs to be experimentally tested and compared with predictive gerodiagnostics is the possibility of interventions modulating the SASP (including those that specifically upregulate or downregulate tissue-destructive factors versus growth factors) or topical senolytic agents, especially those that eliminate senescent cells with a proapoptotic SASP. Clinical advancement is hampered by the absence of WHO International Classification of Disease (ICD) codes for multimorbidity, sarcopenia, healthspan, or geriatric disorders. Such ICD codes would make it easier for the pharmaceutical sector to participate in regulatory approvals, epidemiological studies, the recording of conditions associated with basic ageing processes in hospital and insurance records, and physician and hospital reimbursement. To improve our understanding of basic ageing mechanisms and illness etiologies and to develop therapeutic options to lower multimorbidity and lengthen healthspan, it is necessary to look into any potential interdependencies among fundamental ageing mechanisms. One final word of caution is crucial. Although preclinical studies are encouraging, senolytics or SASP inhibitors should not be recommended for the over-the-counter or in clinical practise unless carefully controlled, rigorous clinical trials show their safety and effectiveness. While waiting for small-molecule senolytics to enter the clinic, findings from present and upcoming clinical studies will provide insightful information about the function of cellular senescence as a therapeutic target for age-related illnesses.

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