



First evidence that senolytics are effective at decreasing senescent cells in humans

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The increasing life expectancy of the world population has become an economic and global public health problem. Increased life expectancy tracks with a higher incidence of multiple chronic conditions, despite unprecedented advances in prevention, diagnostics, and treatment. Ageing is the greatest risk factor for many life-threatening disorders, including cardiovascular disease, neurodegeneration and cancer.

Ageing in all tissues is associated with increased cellular senescence, a stress-response process whereby damaged cells exit the cell cycle permanently and produce a pro-inflammatory senescence-associated secretory phenotype (SASP). Moreover, senescent cells accumulate in multiple chronic diseases across the age range, like Obesity and Chronic Kidney Disease (CKD). Long-term persistence of senescent cells and their SASP disrupt tissue structure and function having deleterious paracrine and systemic effects causing fibrosis, inflammation, and a possible carcinogenic response. Remarkably, even a relatively low abundance of senescent cells (10–15% in aged primates) [1] is sufficient to cause tissue dysfunction [2].

Prof. James Kirkland and his team at Mayo Clinic have pioneered a new class of agents which eliminate senescent cells named 'senolytics' - from the words "senescence" and "lytic" - destroying. Through exploiting senescent cells' dependence on specific pro-survival pathways, senolytics transiently disable the pro-survival networks that defend senescent cells against their own apoptotic environment without affecting proliferating or quiescent, differentiated cells [3,4]. Senolytics thus far tested include dasatinib (D, a FDA-approved tyrosine kinase inhibitor), quercetin (Q, a flavonoid present in many fruits and vegetables), navitoclax, A1331852 and A1155463 (Bcl-2 pro-survival family inhibitors) and fistein (F, a flavonoid) [3].

Pre-clinical studies conducted in mice have shown senolytics eliminate senescent cells resulting in delaying, preventing or alleviating multiple age- and senescence-related conditions, including

frailty, cataracts, age-related osteoporosis, age-related muscle loss, radiation-induced damage, cardiac dysfunction, vascular dysfunction and calcification, pulmonary fibrosis, hepatic steatosis, metabolic syndrome, diabetes and dementia [3–5]. Overall, in mice, administration of senolytic agents and elimination of senescent cells have shown to improve physical function and extend health span and lifespan [2,6].

The results of the first-in-human, single-arm, open-label clinical trial of senolytics were published early this year in this Journal [7]. Subjects with idiopathic pulmonary fibrosis, a cellular senescence-driven fatal disease, showed significantly improved walking endurance, gait speed, chair rise test performance, and scores in the Short Physical Performance Battery 5 days after 9 doses of D + Q over 3 weeks [7]. Published recently in *EBioMedicine*, Kirkland and colleagues, demonstrate for the first time that a short (3 day) course of senolytics D + Q (D: 100 mg/day; Q: 500 mg twice daily) decrease senescent cells in humans with drug-controlled diabetes mellitus and CKD (age range 55–79 years old) [8]. In this ongoing clinical trial, whereby the effects of D + Q senolytic therapy on alleviating tissue dysfunction and disease progression in diabetes and chronic kidney disease (CKD) in humans are being tested, blood samples, adipose tissue and skin biopsies were taken before and 11 days after the short course of D + Q. Markers of senescent cells, p16^{INK4A}, p21^{CIP1} and SAβgal, were reduced by 35%, 17% and 62% in abdominal subcutaneous adipose tissue, respectively. Senescent cells attract, activate and anchor macrophages and a 28% decrease was found in CD68+ macrophages in adipose tissue following D + Q. The replicative potential of primary adipocyte progenitor cells, isolated from the adipose tissue, increased over time following D + Q. This increased replicative potential following senescent cell clearance using D + Q is like that seen with tissue-resident human cardiac progenitor cells *in vitro* [9]. In addition to adipose tissue, D + Q reduced p16^{INK4A}- and p21^{CIP1}-positive cells by 38% and 30% in the epidermal layer of the skin, respectively. Finally, key circulating SASP factors (IL-1α, -2, -6, and -9 and Matrix Metalloproteinases (MMP) -2, -9, and -12) were significantly lower 11 days after than before the 3 days of D + Q.

Senescent cells take weeks to over a month to form and acquire a SASP. The findings suggest that senolytics given intermittently in a 'hit-and-run' fashion, despite the elimination half-lives of D and Q being < 11 h, is effective at reducing senescent cell burden and could lessen side effects, which can occur when D is administered continuously. Further randomised, controlled clinical trials using different senolytics are underway or planned. For example, the Translational

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Geroscience Network, headed by the Kirkland team at the Mayo Clinic, will conduct senolytic clinical trials targeting fundamental aging mechanisms to extend healthspan and delay, prevent, or treat age- and cellular senescence-related conditions. The findings from these trials will not only determine the safety and efficacy of senolytics, but they could be transformative in the care and treatment of older adults and patients with multiple chronic diseases. However, despite these exciting preliminary translational developments in the senolytics field we should still err on the side of caution. There are many unanswered questions. As well as the unknown short- and long-term side effects of individual senolytics drugs, we need to understand which and how individual senescent cell types contribute to tissue dysfunction, are all cell types equally responsive to senolytics, could senolytics have detrimental effects in otherwise healthy cells, and could clearance of post-mitotic cells in organs with limited regenerative capacity like the heart and brain, lead to detrimental effects by interfering with tissue integrity.

Declaration of Competing Interest

The author declares no conflicts of interest.

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