



## Commentary

## Ageing as a druggable process: Moving forward



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Senescent cells (SCs) are emerging as major drivers of the ageing process. During the last decade, the removal of highly p16-expressing SCs has been shown to foster a longer lifespan and healthspan in different mouse models [1]. In addition, an accumulation of SCs has been observed in various age-related diseases (ARD)s, e.g. atherosclerosis, type 2 diabetes, and osteoarthritis [2]. SCs may promote ageing and ARDs development through the secretion of pro-inflammatory, profibrotic, and other soluble factors, collectively termed SASP, i.e. the senescence-associated secretory phenotype. The SASP can promote tissue deterioration and fuel inflamm-ageing, the chronic, progressive state of low-grade inflammation observed during ageing [3]. Indeed, the removal of SCs is associated with a lower inflammatory burden in different organs [1].

In 2015, the group headed by Kirkland showed that SCs could be selectively killed by interfering with specific pro-survival pathways exploited by these cells to survive the pro-inflammatory milieu they live in. These small molecules, termed senolytics, promote SCs death *in vitro* and their clearance *in vivo* [4]. While many senolytics are being developed [5], the first effective approach combines quercetin (Q), a natural flavonol that inhibits PI3K and other kinases, with dasatinib (D), a chemotherapeutic that inhibits multiple tyrosine kinases [4]. This D + Q cocktail alleviated a plethora of ageing-associated phenotypes in mice, including pulmonary fibrosis and physical dysfunction [6,7]. Worth mentioning, intermittent treatment was applied to obtain such effects, possibly limiting the toxicity associated with the continuous use of these compounds, especially D.

In *EBioMedicine*, the same group presents preliminary results of the first approach translating the use of senolytics into clinical settings [8]. At present, regulatory agencies do not consider ageing as a pharmacologically treatable nor preventable disease. Also, long-term endpoints (e.g. lifespan) for clinical trials targeting the ageing process are impossible to study [9]. Thus, senolytics must be tested in a specific disease where SCs play a large role. Considering the solid preclinical data in a mouse model of bleomycin-induced lung injury [6], Kirkland and colleagues selected 14 patients with idiopathic pulmonary fibrosis (IPF) to test the feasibility and toxicity of a therapeutic scheme of treatment with the senolytic cocktail D + Q in the first-in-human, pilot study. Patients were assigned to receive D:100 mg/day and Q:1250 mg/day, three-days/week over a three weeks period. The primary endpoints were retention rates and completion rates for planned clinical

assessments. Secondary endpoints were safety and change in functional and reported health measures. Associations with the SASP were also explored. There was no control arm and treatments were administered in addition to the standard of care. The retention rate was 100% and one serious adverse event was reported. Functional parameters assessing pulmonary function were unchanged. However, treatment with the senolytic cocktail was associated with an improved physical function, as measured with 6-minute walk distance (6MWD), 4-meter gait speed, and 5-repeated chair-stand times. This effect was evident 5 days after the last dose of D + Q (when both drugs had been completely eliminated) and observed changes were statistically associated with the modulation of major SASP factors, e.g. IL-6, supporting the notion that SCs clearance can have enduring beneficial effects without requiring the continued presence of senolytic drugs. While these findings should be taken with caution, especially considering the small sample size, the large range of outcomes investigated, and the absence of a placebo arm, these data represent the first tangible demonstration of a long-lasting effect of senolytics in humans. Notably, no improvements in 6MWD have been observed in the control arms of previous larger IPF drug trials [8].

These results indicate that a senolytic intervention in humans is feasible, opening a number of questions. First, the outcomes strictly related to IPF (i.e. measures of lung function) were unchanged. This could be due to the short duration of the intervention, the small sample size, the heterogeneity and complexity of IPF etiopathogenesis, the role played by SCs in human IPF, and the lack of clearance of SCs by this cocktail in the lungs (e.g. due to insufficient dosage or an inefficient drug distribution in the lungs), among other reasons. The clearance of SCs is of particular importance since it deals with the rationale that has prompted the use of this cocktail. On the other hand, exploring the amount of SCs within the lungs before and after the intervention by performing repeated biopsies is not ethical and often not feasible. Thus, a range of surrogate, plasmatic biomarkers of SC burden have been probed, e.g. microRNAs and pro-inflammatory cytokines secreted by SCs. Unfortunately, none of the molecules released by SCs is exclusive to the senescence status, thus limiting the interpretation of the results [3]. Indeed, IL-6 decreased in a subset of patients, but the amelioration was not significant when considering the whole group of subjects [8]. While a variability among patients in drugs response (e.g. depending on the initial SC burden) can only be speculated at this stage, these data suggest that there is an urgent need to identify a reliable panel of easily accessible biomarkers tracking the load of SCs, in order to test the efficacy of senolytic and other anti-ageing interventions [10]. Once

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available, many more questions could be eventually answered. For instance, can senolytics be considered a class or specific molecules are effective for particular ARDs? Do they have side effects associated with the physiological role of senescence? Which conditions benefit from their use? How long the effect of SCs removal lasts? [9] Future research will address these points. However, the observation that the senolytic cocktail D + Q has an acceptable toxicity in IPF patients, coupled with the intriguing results showing an improvement in physical function, encourages the design of larger, randomized, placebo-controlled trials exploring the effect of senolytics (even beyond D + Q, in case of proven safety) on multiple but specific endpoints in humans affected by IPF, as well as in patients with other ARDs where SCs are emerging as relevant drivers [9].

Translation from preclinical models to humans is often hampered by a number of obstacles. In this case, the complexity of the ageing process and the dogma that each disease must be treated as a stand-alone entity, instead of targeting a biological phenomenon underlying multiple phenotypes, render the application of new discoveries even more challenging. These preliminary data pave the way to move forward and begin to consider ageing a druggable condition.

#### Conflicts of interest

I have no competing interests.

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