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DISCOVERY-IN-CONTEXT REVIEW

Discovery, development, and future application of senolytics: theories and predictions

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Senescent cells accumulate with aging and at etiological sites of multiple diseases, including those accounting for most morbidity, mortality, and health costs. Senescent cells do not replicate, can release factors that cause tissue dysfunction, and yet remain viable. The discovery of senolytic drugs, agents that selectively eliminate senescent cells, created a new route for alleviating age-related dysfunction and diseases. As anticipated for agents targeting fundamental aging mechanisms that are 'root cause' contributors to multiple disorders, potential applications of senolytics are protean. We review the discovery of senolytics, strategies for translation into clinical application, and promising early signals from clinical trials.

Introduction

Aging is the leading risk factor for multiple serious chronic diseases and disabilities including dementias, cancers, cardiovascular diseases/atherosclerosis, lung diseases, osteoporosis, arthritis, diabetes/metabolic syndrome, renal failure, blindness, and frailty [1,2]. Although age-related chronic conditions are major drivers of morbidity, mortality, and health costs, most have been difficult to prevent or treat. The number of chronic conditions per individual increases with aging, leading to multimorbidity [3], offsetting potential gains from devising a treatment for any single age-related disorder [1,4]. Aging also predisposes to geriatric syndromes (including frailty, sarcopenia, immobility, falling, depression, mild cognitive impairment, incontinence, and weight loss [5]) and decreased physical resilience, resulting in failure to recover from stresses such as pneumonia, stroke, myocardial infarctions, dehydration, chemotherapy, surgery, or fractures [6–17]. Fundamental aging processes may be root cause contributors to all of these disorders, the Geroscience Hypothesis [18]. Among these fundamental aging mechanisms is cellular senescence.

Cellular senescence

Cellular senescence contributes to age-related dysfunction and multiple diseases throughout the lifespan. Senescent cells were discovered in 1961 [19] when serially subcultured human embryonic fibroblasts were shown to lose replicative capacity but remain viable. This prompted work to test whether aging leads to accumulation *in vivo* of presenescent cells, which have

Abbreviations
ATTAC, apoptosis through targeted activation of caspase 8; BCL-xL, B-cell lymphoma-extra large; D, dasatinib; DAMPs, damage-associated molecular patterns; DKD, diabetic kidney disease; IL, interleukin; INK4a, cyclin-dependent kinase inhibitor 2A; IPF, idiopathic pulmonary fibrosis; MAD cells, mesenchymal adipocyte-like default cells; PAMPs, pathogen-associated molecular patterns; Q, quercetin; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCAP, senescent cell anti-apoptotic pathway.

limited remaining replicative potential, and senescent cells, which cannot replicate but are metabolically active. In 1979, this was reported to be true for fibroblasts in skin biopsied from older than younger subjects [20] and in 1990, for primary fat cell progenitors (preadipocytes) cloned from adipose tissue of rats across the age spectrum that had been raised under controlled conditions [21]. Senescent cells appear at pathogenic sites of many major diseases, including Alzheimer's, cardiovascular diseases, osteoporosis, diabetes, renal disease, and cirrhosis [22,23].

There are no fully sensitive or specific markers for identifying senescent cells. These cells are generally large, may have high $p16^{INK4a}$ and/or p21 (but not always), and exhibit DNA damage foci, particularly in telomeres, senescence-associated distention of pericentromeric satellite DNA, and increased β-galactosidase activity [22]. Like cancer cells, senescent cells frequently are metabolically shifted from fatty acid utilization toward glycolysis, resulting in reactive oxygen species (ROS) generation, lipid accumulation, lipotoxicity, and dysdifferentiation into fat cell-like but insulin-resistant 'mesenchymal adipocyte-like default cells (MAD)' cells [24]. An example of such MAD cells is the pro-inflammatory, perilipin-expressing, lipid-laden senescent ependymal cells around the 3rd ventricle in obesity that contribute to neuroinflammation, failed brain microcirculation, impaired neurogenesis, and obesity-related neuropsychiatric dysfunction [25]. Senescent cells are resistant to death [26].

Senescence is essentially a cell fate, like differentiation, proliferation, apoptosis, and necrosis. External and internal signals can contribute to driving a cell into senescence. These are generally cell or tissue damage-related, including DNA alterations (dysfunctional telomeres, strand breaks, etc.), metabolic dysfunction (ROS, high glucose, bioactive lipids, mitochondrial dysfunction), protein alterations (aggregates, misfolding, failed autophagy), inflammatory signals, mechanical/shear stress, damage-associated molecular patterns (DAMPs) (extracellular nucleotides, etc.), pathogen-associated molecular patterns (PAMPs) (bacterial/fungal proteins, lipopolysaccharide, etc.), oncogenes, and mitogens (insulin-dependent growth factor-1, etc.). Once initiated, senescence takes weeks to over a month to become established through transcription factor cascades (that may, but do not always, include $p16^{INK4a}$/retinoblastoma protein and/or p53/p21), causing extensive changes in gene expression, histone modifications, altered organelle function (e.g., mitochondria, endoplasmic reticulum, nucleolus, nuclear envelope), and profound morphological and metabolic shifts [22,27].

Accumulation of senescent cells can cause local and systemic inflammation, tissue destruction, immune system inhibition, and stem and progenitor cell dysfunction due to their senescence-associated secretory phenotype (SASP) [22,28–31]. Generally, 30–70% of senescent cells develop a SASP comprising pro-inflammatory cytokines, chemokines, proteases, procoagulant factors, stem/progenitor cell 'poisons', growth factors, bioactive lipids (prostenoids, saturated ceramides, bradykines), miRNA's, noncoding but biologically active nucleotides, and microvesicles including exosomes. The SASP depends on the type of cell that became senescent, how senescence was induced, and its *milieu*. The SASP changes over time related to internal (e.g., transposons) and external (e.g., glucocorticoids, DAMPs, PAMPs, SASP inhibitors such as rapamycin) cues. PAMPs are particularly effective in exacerbating the SASP, perhaps accounting for severe debilitation in previously highly functioning elderly individuals with infections such as pneumonia, the 'Amplifier/Rheostat SASP Hypothesis'.

Likely due to their SASP, only a small number of senescent cells can cause considerable dysfunction. In preclinical experiments, transplanting senescent cells around the knee joints of young mice was sufficient to induce an osteoarthritis-like phenotype, while transplanting nonsenescent cells did not [32]. Transplanting 10^6 radiation- or chemotherapy-induced senescent autologous ear fibroblasts or syngeneic preadipocytes intraperitoneally into lean, adult mice, so that only 1/10 000 of all cells in the transplanted mice were senescent, induced impaired physical function and premature death due to early onset of the same age-related diseases that cause death in naturally aged mice [32]. When labeled senescent cells are transplanted intraperitoneally, they remained within the peritoneum, yet transplant recipients developed nonlabeled senescent cells in their limbs, demonstrating that senescence can spread from cell to cell, even at a distance [32].

Senescent cells are usually cleared by the immune system [33]. They can attract, activate, and anchor immune cells, including macrophages, dendritic cells, T lymphocytes, and neutrophils through such SASP chemokines as monocyte chemoattractant protein-1, regulated on activation, normal T cell expressed and secreted, and retinoic acid receptor responder-2, cytokines, such as interleukin (IL)-6, tumor necrosis factor-α, and possibly miRNAs and other factors [32–34]. However, above a threshold burden, senescent cells interfere with the immune system and its ability to remove them. For example, IL-6, a SASP component, interferes with macrophage migration, matrix

metalloproteinases can cleave FAS ligand and other immune cell surface proteins, and senescent cells can express 'don't eat me' signals [33].

The 'Threshold Theory of Senescent Cell Burden' holds that once senescent cell abundance is sufficient to cause spread of senescence that exceeds capacity of the immune system to keep up with clearing these cells, an accelerated aging-like state ensues [32,33]. Consistent with this, (a) the number of senescent cells that needs to be transplanted to cause frailty and limit healthspan is higher in middle-aged than old mice and in middle-aged lean than obese mice. Old and obese mice have more pre-existing senescent cells than middle-aged lean mice [32]; (b) Senescent cell abundance remains low in skin until early old age in humans, followed by an upward inflection in senescent cell burden in subjects who are in their late 60s through the mid-70s [35]. This precedes the age-related increase in multimorbidity [3] and (c) The lag between induction of senescence by chemotherapy and development of age-related morbidities is longer in childhood cancer survivors than adults who received higher chemotherapy doses in preparation for bone marrow transplants [36,37]. These findings support the hypothesis that there is a threshold above which senescent cell burden due to spread of senescence becomes self-amplifying that presages increased risk for senescence- and age-related phenotypes and diseases, perhaps contributing to age-related multimorbidity [3].

Cellular senescence leads to inflammation, fibrosis, DNA damage, mitochondrial dysfunction, ROS generation, NAD^+ depletion, protein aggregation, failed autophagy, lipotoxicity, and stem and progenitor cell dysfunction. In turn, cellular senescence can be caused by other fundamental aging processes, including DNA damage, low NAD^+, mitochondrial dysfunction, ROS, protein aggregates, and lipotoxicity. Thus, from our and others' data, fundamental aging processes appear to be interlinked, findings that led us to formulate a 'Unitary Theory of Fundamental Aging Processes', which posits that interventions, such as senolytics, targeting any one of these processes, such as cellular senescence, will affect many of the rest.

The discovery of senolytics

In 2004, Krishnamurthy *et al.* [38] showed delayed senescent cell accumulation in Ames dwarf mice with pituitary hormone deficiencies and calorically restricted mice, models with increased healthspan and lifespan. This was critical in prompting us to test the hypothesis that targeting senescent cells may alleviate multiple age-related disorders. Efforts to find senolytics, drugs that selectively eliminate senescent cells, began in 2004/2005, with initial attempts to create fusion proteins comprising a senescent cell surface-binding domain coupled to a toxin, high-throughput compound library screens for candidates that eliminate senescent but not nonsenescent cells, and other approaches. These traditional approaches were not initially successful, so we turned to a hypothesis-driven discovery paradigm to find the first 'senolytic' drugs [22,39,40] (Fig. 1). We asked how senescent cells expressing a SASP can survive, despite their own

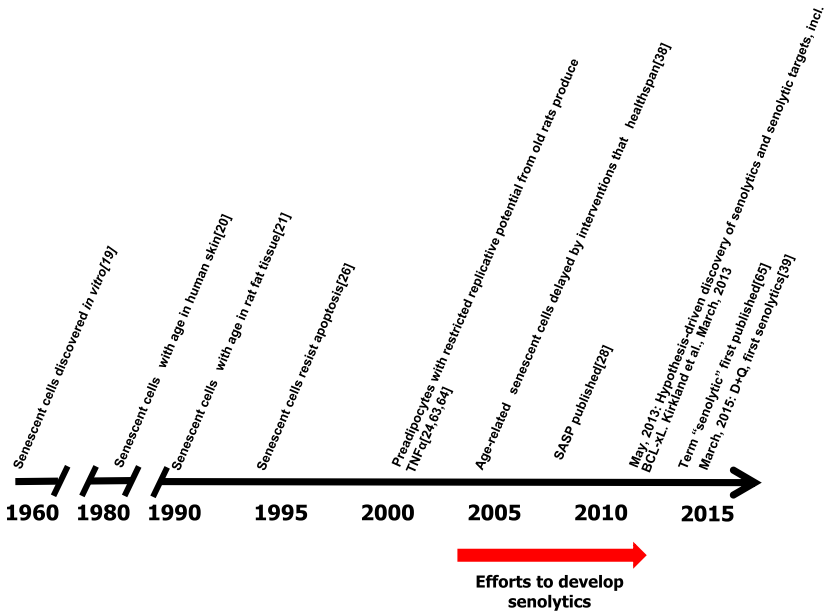

Fig. 1. Timeline for the discovery of senolytics. The discovery of senolytics began with the finding of senescent cells in 1961 by Hayflick and Moorehead [19] and was prompted by the finding of the J. Krishnamurthy group that interventions that increase healthspan also delay senescent cell accumulation [38]. Developing senolytics began before and independently from making or studying INK-ATTAC mice.

highly pro-apoptotic and metabolically distinct, potentially damaging *milieu* and so hypothesized: (a) Senescent cells can resist apoptotic stimuli, implying the existence of prosurvival/anti-apoptotic defenses against their own SASP and harsh metabolic internal state, and (b) in some respects, senescent cells are like cancer cells that do not divide, including apoptosis resistance and metabolic shifts [39].

Building upon bioinformatics data derived from proteomic and transcriptomic profiles of senescent *vs.* nonsenescent cells, we searched for senescent cell anti-apoptotic pathways (SCAPs). We identified several such potential SCAPs (ephrins/dependence receptors; PI3Kδ/Akt/metabolic; Bcl-2/B-cell lymphoma-extra large (Bcl-xl)/Bcl-w; p53/FOXO4a/p21/ serpine [PAI-1&2]; HIF-1α) [39] and then another, the HSP-90 pathway [41] (Fig. 2). We tested whether these SCAPs are essential for senescent cell survival by targeting nodes in the SCAP network using RNA interference in senescent *vs.* nonsenescent human primary preadipocytes and human umbilical vein endothelial cells. Of the 39 small-interfering RNA's targeting possible SCAPs, 17 selectively caused death of senescent cells. The patterns of SCAP pathways that prevent self-induced death of senescent human preadipocytes differed considerably from those required for senescent endothelial cell survival. For example, we found that senescent preadipocytes did not depend on BCL-2 family prosurvival proteins. Conversely, senescent endothelial cells depended on BCL-2 family members, particularly BCL-xL, compared to nonsenescent endothelial cells, plus components of the PI3 kinase and HIF-1α pathways. We tested drugs (*in vitro*) known to the target key SCAP network nodes and identified that dasatinib (D) and quercetin (Q) are senolytic [39]. D + Q was more effective than either alone. Based on our finding that BCL-xL is a SCAP network component [39], 10 months later we and others reported that navitoclax, a BCL-2 prosurvival pathway inhibitor, is senolytic in some but not all senescent cell types [42,43]. We found that fisetin, a flavonoid related to Q, is senolytic [40].

We intentionally selected particular drugs for further development from among those identified as being senolytic. We focused on drugs that: (a) were already US Food and Drug Administration-approved or were natural products with a history of safe human use, (b) could be administered orally, and (c) have a short

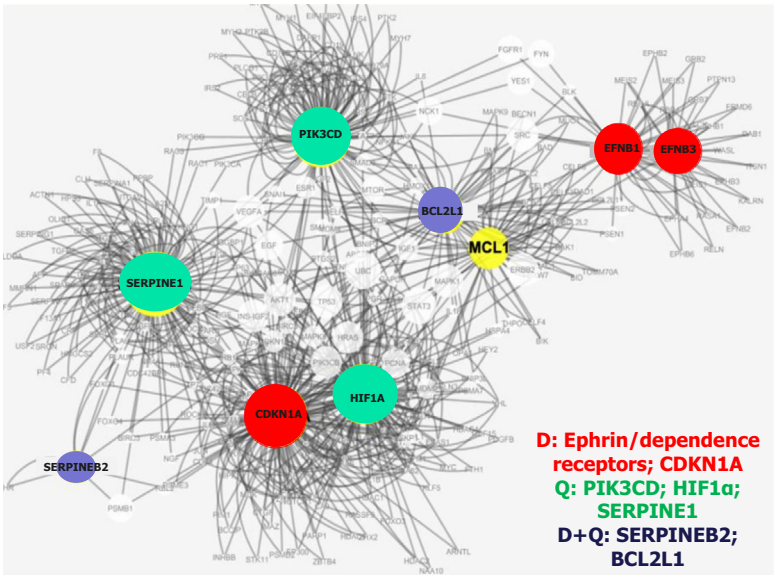

Fig. 2. SCAPs targeted by D plus Q. D + Q has targets across the entire SCAP network. Targeting a single molecule is not generally sufficient to promote apoptosis of many types of senescent cells. Agents that target a single molecule (e.g., BCL-2 inhibitors, such as navitoclax or A1331852) tend to have more off-target and side effects, resulting in unacceptable side effects than agents that act across multiple nodes of the SCAP network such as D + Q, which tend to have a more restricted side effect profile, less effect on nonsenescent cells, and more specificity in targeting senescent cells. D + Q were developed based on first delineating the SCAP network and then using computer-assisted approaches for selecting agents that act upon nodes across the SCAP network: Development of the first senolytics was entirely mechanism-based and did not involve random approaches such as high-throughput library screening [39,41]. [Copyright author].

half-life. D and Q met these criteria: D has been approved for clinical use since 2006 and Q is a natural product with a favorable safety profile, both are effective orally, and their elimination half-lives are < 11 h, meaning they are cleared from humans within 2 days.

The target of senolytics is senescent cells, not a single receptor, enzyme, or biochemical pathway. By targeting prosurvival networks instead of single molecules, specificity for senescent cells can be increased, side effect profiles flattened, and off-target effects on nonsenescent cells reduced. Drugs that have single or limited targets, such as navitoclax or nutlin-3a, have off-target apoptotic effects on multiple nonsenescent cell types, making them 'panolytic'. Navitoclax also eliminates a restricted range of senescent cells; for example, BCL-2 inhibitors are not senolytic against human adipocyte progenitors, one of the most abundant senescent cell types in aged humans or people with diabetes and obesity. The novel strategies for developing senolytics have more in common with approaches for developing antibiotics than the usual one-target/one-drug/one-disease drug development approach.

The first article about senolytics demonstrated D + Q reduces senescent cell burden in multiple tissues and improves function in naturally aged animals [39]. Since then, D + Q, fisetin, navitoclax, and other senolytics have been shown to alleviate multiple conditions. Among effects are: improved cardiac ejection fraction, fractional shortening, and regeneration in old mice, enhanced vascular reactivity in old mice, decreased vascular calcification and restored vascular reactivity in hypercholesterolemic, high fat-fed $ApoE^{-/-}$ mice, decreased loss of intervertebral disk glycosaminoglycans and spondylosis in progeroid $Ercc1^{-/\Delta}$ mice, decreased gait disturbance in mice following radiation damage to a leg and hematological dysfunction caused by whole body radiation, decreased age-related changes of skin, improved pulmonary function and reduced pulmonary fibrosis in mice with bleomycin-induced lung damage, a model of idiopathic pulmonary fibrosis (IPF), decreased liver fibrosis in $Mdr^{-/-}$ cirrhotic mice, decreased insulin resistance, hepatic steatosis, and renal dysfunction in high fat-fed mice, neuropsychiatric dysfunction and impaired neurogenesis in high fat-fed mice, neuroinflammation, impaired neurogenesis, microvascular impairment, and cognitive dysfunction in mouse models of dementia, age-related osteoporosis, uterine fibrosis, and frailty and physical dysfunction in naturally aged, progeroid, radiated, and senescent cell-transplanted young mice as well as increased healthspan and lifespan in old mice [22,32,34,39,43–50].

D + Q or F is effective if administered once every few weeks since they do not need to be continuously present to occupy a receptor or interfere with an enzyme, reducing off-target effects. Brief disruption of prosurvival pathways is sufficient to kill senescent cells in mouse and human cell cultures, *in vivo* in mice, and in human adipose explants freshly isolated from obese subjects [22,39,46,51]. In mice, monthly D + Q is as effective as daily administration to alleviate age-related osteoporosis [52], reducing potential side effects. These points, together with satisfying a modified set of Koch's postulates (Table 1), show that D + Q alleviates dysfunction by removing senescent cells, not other off-target mechanisms. Unlike microbes or cancer cells, since senescent cells do not divide, they are unlikely to acquire replication-dependent drug resistance.

In INK-apoptosis through targeted activation of caspase 8 (ATTAC) mice, administering the drug, AP20187, a viral FK506-binding protein-cross-linking

Table 1. Koch's postulates were used to prove causation in the case of infectious agents. Here we use modified Koch's postulates to prove that a candidate agent alleviates a condition because of senolytic effects.

Are candidate drugs truly senolytic for particular disorders? A modified Koch's postulates
To establish causality:
• Are senescent cells present in animals or humans with the disorder?
• Do individuals without senescent cells have the disorder?
• Is the disorder reproduced by inducing local accumulation of senescent cells (e.g., by transplanting senescent cells, focal irradiation, or tissue-specific genetic approaches)?
• Does removing these transplanted or induced senescent cells prevent or alleviate the disorder?
• Does targeting naturally occurring senescent cells alleviate the disorder?
• Does administering the potentially senolytic candidate have few or no effects related to the disorder being tested in individuals with few or no senescent cells (e.g., young mice)?
• Does the potentially senolytic candidate alleviate the condition if given intermittently, at intervals longer than the drugs' half-lives, since senescent cells can take 2–6 weeks to re-accumulate (at least in culture)? (In the case of D + Q, the drugs are as effective if administered monthly as continuously, at least in the case of age-related osteoporosis [52]).
• Does the candidate alleviate multiple age-related conditions? (If a candidate is truly senolytic and the Geroscience Hypothesis is true, it should alleviate multiple age- or chronic disease-related disorders).
So far, all of the above criteria appear to have been met in the cases of diabetes, frailty, and age-related osteoporosis and many for osteoarthritis and neurodegenerative diseases.

agent, activates the inducible, cell-killing ATTAC construct devised by P. Scherer's group [53], which is under the control of a $p16^{Ink4a}$ promoter element, resulting in elimination of highly $p16^{Ink4a}$-expressing cells. Results may be different from targeting only senescent cells, since some but not all highly $p16^{Ink4a}$-expressing cells are senescent and not every senescent cell has increased $p16^{Ink4a}$ expression [54]. On the other hand, senolytics remove senescent cells with a damaging SASP by transiently disabling defenses against their own SASP. Indeed, we began work on senolytics before and independently from planning INK-ATTAC mice. Discovery of senolytics neither depended on findings from INK-ATTAC mice nor involved their use. Likely because of the differences between cells targeted by senolytics from those targeted in INK-ATTAC mice, we observed differences between effects of removing senescent cells with senolytics and targeting highly $p16^{Ink4a}$-expressing cells in INK-ATTAC mice. For example, there is a more substantial effect of removing senescent cells with senolytics on restoring long-term survival after radiation than effects of removing highly $p16^{Ink4a}$-expressing cells from radiated INK-ATTAC mice (unpublished observations).

Strategies for translation

New paradigms are being developed and applied to take senolytics into clinical application, which will also likely be needed for other types of interventions that target 'root cause' fundamental aging processes [2,55–59]. Perhaps the closest analogy to strategies for translating senolytics into clinical application is that of antibiotics. Antibiotics or antibiotic combinations are usually developed to target a pathogen, rather than single molecular targets. In developing antibiotics, a range of infections, for example respiratory, urinary tract, and skin infections, are tested using candidate agents, rather than a single disease. Effects of antibiotics alone or in combination are tested. The same approach may be appropriate for effectively developing and translating senolytics into clinical application. The key drug targets are senescent cells and the networks that sustain them, not a single molecule, biochemical pathway, or receptor. Multiple senescent cell types, senescence-associated diseases, and combinations of senolytics need to be analyzed in translating senolytics into clinical application, unlike the traditional one-drug/one-target/one-disease approach for developing drugs that target a receptor, enzyme, or biochemical pathway.

Short- and long-term human side effects of senolytics are unknown. Therefore, balancing of potential risks to benefits is essential for devising ethical clinical trials strategies. It seems ethical to begin clinical studies for patients with serious cellular senescence-associated disorders in small safety/tolerability/early effectiveness trials, rather than proceeding to large preventive trials in healthier populations. As there is urgency to determining whether senolytic drugs are effective, conducting small trials across different serious conditions in parallel may show whether senolytics indeed alleviate age-related multimorbidity, a better way forward than conducting trials in series.

Early findings from the first of such trials have recently been reported. Interim results of a phase 1, open-label, clinical trial of D + Q for subjects with diabetic kidney disease (DKD) underway at Mayo (ClinicalTrials.gov Identifier: NCT02848131) showed a 3-day oral course of D + Q in nine subjects with DKD reduced adipose tissue senescent cell burden by 11 days after the last dose [60]. A composite score of 10 circulating SASP factors was significantly decreased 11 days after completing the 3-day D + Q intervention. This trial is continuing (goal = 30) to test effects of senolytics on adipose tissue and skin senescent cell abundance, blood and urine SASP factors, metabolic and renal function, inflammation, quality of life, safety (drug toxicity), and tolerability. No serious drug side effects have emerged so far. Evidence continues to show clearance of senescent cells. Each subject will be followed for 4 months after the single course of D + Q to provide data for a larger phase IIb randomized, placebo-controlled, double-blind trial of senolytics for DKD.

In the first study reported of senolytics, a pilot, open-label clinical trial in 14 patients with IPF, nine doses of oral D + Q over 3 weeks led to improved 6-min walk distance, walking speed, ability to rise from a chair, and short physical performance battery by 5 days after the final dose [61]. These results led to initiation of a phase IIb randomized, placebo-controlled, double-blind trial that is currently underway.

In preclinical studies, fisetin alleviated frailty in progeroid and naturally aged mice and extended median and maximum lifespan [51]. Frailty in elderly women is associated with senescent cell burden in adipose tissue biopsies [62]. Furthermore, senolytics alleviated frailty in the subjects in the IPF trial [58]. Therefore, a phase IIb double-blind, placebo-controlled clinical trial of fisetin to reduce senescent cell burden and alleviate frailty and inflammation, Alleviation of Frailty, Inflammation, and Related Measures in Older Women, has commenced (ClinicalTrials.gov Identifier: NCT03430037). Based on preclinical studies, open-label trials of intermittent D + Q for early stage,

symptomatic (Clinical Dementia Rating 1) tau$^+$ Alzheimer's disease to test safety, tolerability, target engagement, and early signals of effectiveness are beginning.

Along with the above clinical trials, other trials are underway or launching in the near future, including D + Q or fisetin for the accelerated aging-like state in bone marrow transplant survivors, age-related osteoporosis, and osteoarthritis. If these trials indicate safety and effectiveness, the next set will include trials for less serious age-related conditions, and after that, perhaps trials of senolytics to prevent diseases and dysfunction in at-risk patients with a demonstrated high senescent cell burden based on blood, saliva, urine, or other tests. For all these trials, sensitive/specific biomarkers need to be identified and optimized. Such biomarkers could be used for identifying asymptomatic patients who are at risk and selecting appropriate drugs to prevent progression to age-related diseases and dysfunction.

There is some question about the merits of local *vs.* systemic administration of senolytics. Conditions in which senescent cells are spread across multiple organs necessitate systemic administration. Local accumulations of senescent cells may also need to be treated systemically because senescence can spread [32]. Local administration does not guarantee the drug will remain in one place; for example, if osteoarthritis is sufficiently advanced to cause synovial breakdown, local injection is effectively systemic. Also, decreasing overall senescent cell burden below a threshold may decrease spread of senescence and allow the immune system to remove remaining senescent cells. If this 'Threshold Theory of Senescence' is correct, strategies that decrease overall senescent cell burden, rather than selectively targeting specific subtypes of senescent cells or only targeting localized senescent cells, would seem appropriate.

For each indication, preclinical and clinical studies will be necessary to optimize frequency of senolytic administration and identify the best senolytic agents or combinations for that indication and that particular patient. Furthermore, senolytic regimens might be synergistic with interventions that target other fundamental aging processes, such as metformin or NAD$^+$ precursors. It may be beneficial to select combinations based on results of blood, urine, saliva, biopsies, or other tests to determine the contribution of different fundamental aging processes within individuals, a personalized medicine approach. Perhaps combining interventions targeting fundamental aging processes, for example, senolytics, with conventional disease-specific interventions will be additive.

Conclusions

Senolytics may enhance healthspan and delay, prevent, or treat multiple chronic diseases, geriatric syndromes, and age-related declines in physical resilience, but this is not a certainty. More information about safety, tolerability, side effects, and target engagement (effectiveness in reducing senescent cell burden) in humans is needed. Severe, unanticipated side effects could emerge. Unfortunately, there has been premature excitement about senolytics along with efforts to sell them to the public, while safety and efficacy measures are still being evaluated. We are concerned about physicians prescribing senolytics or self-medication. At this juncture, we feel use of senolytic drugs should be confined to carefully monitored, controlled clinical trials.

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Conflict of interest

JLK, TT, and YZ have a financial interest related to this research. Patents on senolytic drugs are held by Mayo Clinic. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies. No conflicts of interest, financial or otherwise, are declared by EOWG.

Author contributions

EOWG and JLK wrote the manuscript with editorial assistance by YZ and TT.

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