

# Treating Idiopathic Pulmonary Fibrosis with Senotherapeutics

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# Abstract

## **Medical Problem:**

Idiopathic pulmonary fibrosis (IPF) is an age-related, progressive, fibrotic lung disease with high mortality, affecting 1-3 million people globally. Current antifibrotic therapies slow disease progression but cannot reverse fibrosis, carry significant side effects, and are costly. IPF disproportionately affects older males and exhibits disparities in diagnosis and treatment access, especially in low-resource regions, underscoring a clear need for innovative therapies targeting underlying pathogenic mechanisms, notably cellular senescence.

## **Scientific/Clinical/Technical Innovation:**

Senotherapeutics, including senolytics and senomorphics, represent a promising novel therapeutic strategy. Senolytics selectively induce apoptosis of senescent cells, while senomorphics suppress detrimental inflammatory and fibrotic signaling (SASP). Preclinical studies indicate improved lung function and reduced fibrosis in animal models. Early human trials using dasatinib and quercetin showed feasibility and improved physical function, highlighting the potential of senotherapeutics to significantly impact IPF treatment paradigms through combination therapies or targeted application strategies.

## **Ethical, Economic and Healthcare considerations:**

Ethically, introducing senotherapeutics raises issues of informed consent, especially in elderly patients, balancing risks of tumor suppression loss versus potential therapeutic benefits. Justice demands addressing underrepresentation in clinical trials and equitable access. Economically, while upfront drug costs may increase, reduced hospitalizations and improved patient outcomes could offer significant cost savings. Healthcare integration requires clinician training, protocol revisions, robust biomarker monitoring, patient education, and supportive policy frameworks from regulatory authorities.

## **Translational Status, Perspectives, Conclusion:**

Senotherapeutics have moved from promising preclinical studies to initial clinical validation, demonstrating safety and functional benefits. Significant gaps remain in understanding optimal patient selection, dosing, long-term safety, and efficacy. Large randomized clinical trials are essential to establish clear clinical benefits. Ultimately, senotherapeutics offer transformative potential, shifting IPF management from palliation toward meaningful disease modification, contingent upon overcoming translational, ethical, and economic challenges, thereby greatly enhancing quality of life for IPF patients.

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# Current Medical Problem

## Epidemiology – Prevalence & Incidence

Idiopathic pulmonary fibrosis (IPF) is a rare disease with prevalence and incidence varying by region. Recent systematic reviews estimate the incidence of IPF to range from roughly 1 to 13 new cases per 100,000 persons per year globally and the prevalence from 3 to 45 per 100,000 persons, with the highest rates reported in North America, lower rates reported in Europe, with even lower reported rates in Asia and South America (1-3). See figure 1 below. Overall, IPF affects on the order of 1-3 million people globally, and most studies indicate that incidence has been increasing over time (2). This rise may be attributed to better awareness and diagnosis, but it also suggests a growing public health burden.

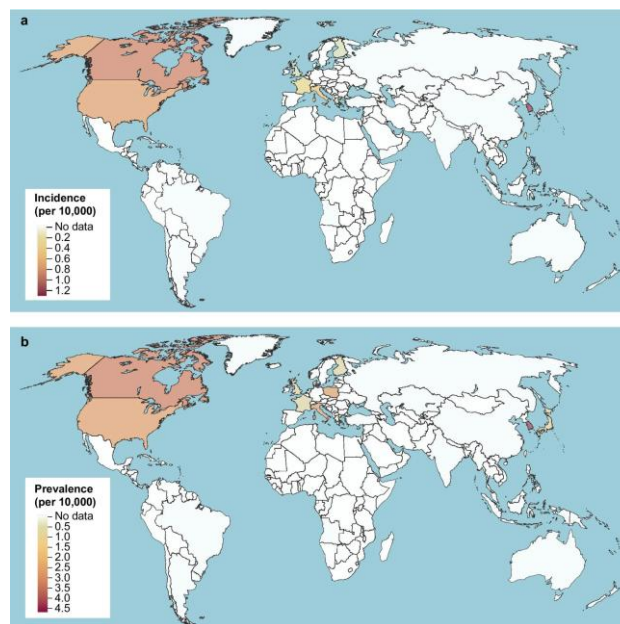


Figure 1: Global heat maps of IPF incidence and prevalence. Reproduced from Maher et al. (2021)

## Survival and Mortality

IPF is a progressive, life-threatening lung disease with a notably high mortality. Approximately half of patients die within 5 years of diagnosis (4). In untreated patients, the median survival has historically been only about 2-3 years (3). A recent meta-analysis reported 3-year and 5-year survival rates of just 61.8% and 45.6% respectively (5). This poor prognosis persists despite the advent of antifibrotic therapies (pirfenidone and nintedanib), although there is some evidence that these therapies have made improvements. Notably, there was no significant improvement in IPF survival prior to

2010, but in the 2010s (after antifibrotic therapies became available) 3-year survival saw a modest increase to 67% (4).

Mortality data show that IPF is an increasing cause of death. Age-standardised mortality rates range from 0.5 up to 12 per 100,000 per year and many countries in Europe have seen rising IPF mortality (4). Even with current therapies, IPF remains a lethal condition and deaths from IPF contribute significantly to the worldwide mortality of respiratory diseases.

### Demographic and Diversity Factors (Age, Sex, & Ethnicity)

IPF primarily affects older adults and is rare before mid-adulthood. The median age at diagnosis is approximately 65-70 years and incidence rises sharply with age (5). Most patients are diagnosed in the sixth or seventh decade of life and the highest mortality rates are seen in those above 75 years of age (6). IPF is predominantly seen in males (7). Possible explanations include differences in occupational exposures and smoking history as well as hormonal or genetic factors, though the reasons are not fully understood (7).

Data on racial and ethnic disparities in IPF are limited as most epidemiologic studies come from Western countries with predominantly Caucasian populations. However, there is evidence indicating important disparities in disease presentation and outcomes among different ethnic groups. In the United States, for example, African-American patients with pulmonary fibrosis tend to be diagnosed at a significantly younger age (mean ~ 58 years) compared to Caucasian patients (mean ~ 69 years) (8). African-American patients are also younger at first hospitalization, lung transplant and death than Caucasian patients (8). Additionally, some historical data suggest that Hispanic Americans were more likely and African-Americans less likely, to have IPF listed as cause of death compared to Caucasian Americans (9). This could reflect differences in either disease prevalence or diagnosis, or both. In general, IPF has been studied mostly in Caucasian populations and there is a need for more global data. Patients from different ethnicities may face different disease trajectories due to varying environmental exposure or access to care, which highlights the importance of understanding and addressing these disparities (8).

### Socio-Economic & Healthcare Burden

IPF represents a substantial economic burden due to both direct medical costs and indirect costs such as loss of work productivity. Studies in high-income countries have shown that annual healthcare costs for an IPF patient are 2-4 times higher than for an average person as denoted by the healthcare expenditure per capita (10). Other studies, that include all medical expenses have found even larger figures. For example, one study

in the U.S. reported mean all-cause annual health costs of \$ 59,000 per IPF patient (11). It is estimated that IPF costs the U.S. healthcare system over \$3 billion annually in direct medical expenses excluding the cost of drugs (12). Hospitalizations, acute exacerbations and end-of-life care contribute heavily to these costs. Indirect costs are harder to quantify especially since many patients are retired, but there are patients that may suffer lost income and all patients require social support from family or caregivers as the disease progresses. Overall, the economic impact of IPF on a per-patient basis is comparable to or exceeding that of many cancers (2). The economic burden is expected to grow as populations age and thus presents a challenge for healthcare systems worldwide.

### Limitations of Current Therapies

In the 2010s there was a paradigm shift in the treatment of IPF with the approval of two antifibrotic drugs, pirfenidone and nintedanib. These medications were the first to show efficacy in slowing the decline of lung function in IPF. However, their benefits are limited since they do not represent a cure for the disease. These therapies only slow disease progression but do not halt or reverse the fibrosis (3). As a result, despite treatment, many patients continue to experience deteriorating lung function and ultimately pass away from the disease. Lung transplantation remains the only option that comes close to a curative intervention but is only an option for a small minority of patients, typically those who are younger and otherwise healthy (3). Thus, most patients need to rely on antifibrotic therapy along with palliative care.

Both pirfenidone and nintedanib have well-documented side effects that can impact tolerability. Gastrointestinal side effects are extremely common, for instance, diarrhea is the most frequently reported adverse effect of both medications (13). Pirfenidone often causes nausea, anorexia, and a rash, whereas nintedanib tends to cause nausea and liver enzyme elevations. These side effects can have a large impact on patients as evidenced by a study where over half of patients had to discontinue antifibrotic therapy within a couple of years. Specifically, 64% of patients on nintedanib and 54% on pirfenidone discontinued treatment (14). Such high rates underscore the challenge of these therapies as even among those who tolerate the medication, dose reductions and supportive medications such as antidiarrheals are frequently needed.

Another impactful limitation is the cost and access to these medications. In the U.S. antifibrotic drugs cost around \$100,000 per patient per year (15). In many countries, access to pirfenidone or nintedanib is restricted or delayed due to cost-effectiveness considerations and as a result, not all eligible patients even receive this therapy. Only about 25-65% of IPF patients end up receiving antifibrotic therapy (16, 17). This was attributed to a combination of patient comorbidities, patient or physician preference, and

reimbursement issues. While antifibrotic therapy represents an advance in the treatment of IPF, the high cost, side effects and limited efficacy reveal the need for better therapeutic options.

## Global Disparities in Diagnosis & Access to Care

There are notable global disparities in the diagnosis and management of IPF. Firstly, there are gaps in epidemiological data and a likely underdiagnosis in many regions. As shown in figure 1, in many regions such as Africa, South Asia and South America there is a lack of data on IPF incidence and prevalence (3). This underscores the need for more research in these regions. IPF diagnosis requires high-resolution CT scans and specialized multi-disciplinary evaluation which may not be readily available in low-resource settings. Consequently, IPF may be misdiagnosed as other lung diseases in countries with a low awareness of IPF. Even in high-income countries, the diagnosis of IPF is often delayed, on average by 2 to 4 years from the onset of symptoms (17). This may be because early symptoms (dry cough, dyspnea) are nonspecific and can be attributed to more common conditions. A delayed diagnosis means that many patients present with advanced fibrosis, further limiting their treatment options.

There are also disparities in access to treatment. In high-income countries, specialized clinics and antifibrotic therapies are more available compared to lower-income countries. Within Central and Eastern Europe, for instance, a registry found that in some countries fewer than 50% of newly diagnosed IPF patients received antifibrotic treatment (16). In the U.S. African-Americans are less likely to receive antifibrotic therapy than white Americans which indicates an inequity in treatment beyond just regional differences (9).

Another aspect is the availability of lung transplantation. Such transplants are mostly performed in high-income countries so many countries have essentially no access to this potential life-saving intervention. Moreover, other specialized care such as oxygen therapy, pulmonary rehabilitation and palliative care differs across national healthcare systems. All these differences contribute to unequal outcomes.

# Knowledge Gaps in Fundamental and Clinical Understanding

## Fundamental Pathogenesis

IPF is a progressive, irreversible fibrosing interstitial lung disease of unknown cause. Clinically, IPF presents with chronic exertional dyspnea and dry cough. On high-resolution CT a usual interstitial pneumonia pattern can be observed with reticular opacities, honeycombing cysts, and fibroblastic foci (18).

## Core Molecular Mechanisms

IPF is thought to result from repetitive microscopic lung injuries to the alveolar epithelium with abnormal wound healing. This leads to a cycle of epithelial cell dysfunction, chronic inflammation, and fibroblast activation with extracellular matrix (ECM) deposition (18). Several key mechanisms have been implicated in IPF pathogenesis:

### Telomere Attrition and Genomic Instability

Telomere dysfunction is a prominent feature of IPF. Many patients, especially those with familial IPF, show mutations in telomere-maintenance genes such as TERT, TERC, PARN or RTEL1 as well as abnormally short telomeres (19). Telomere shortening in alveolar type II epithelial cells cause them to undergo senescence or apoptosis, thereby decreasing the regenerative capacity of the epithelium. This dysfunction is thought to promote a persistent pro-fibrotic environment. Senescent cells secrete inflammatory and profibrotic mediators, the Senescence Associated Secretory Phenotype (SASP). The SASP can recruit immune cells and activate TGF- $\beta$  signaling (20). The downstream consequence is collagen deposition and fibrosis. This often starts in the subpleural spaces with a characteristic progression from the periphery to the center. However, the precise mechanisms by which telomere defects provoke IPF are not fully understood (20).

### Mitochondrial Dysfunction and Oxidative Stress

Senescent and damaged cells often exhibit impaired mitochondrial function, leading to excessive reactive oxygen species (ROS) production. IPF lung tissues show evidence of elevated mitochondrial ROS and altered mitochondrial DNA homeostasis, along with deficient mitophagy (21). For example, loss of the PINK1/Parkin mitophagy pathway in alveolar epithelial cells causes accumulation of dysfunctional, swollen mitochondria and increases susceptibility to lung fibrosis in mice (21). Mitochondrial dysfunction in IPF is often linked to telomere attrition and endoplasmic reticulum stress, which suggests interplay between multiple age-related stressors. A gap in the literature remains in determining the causality of whether ROS from mitochondria drives the injury or if it is a consequence of another injury trigger.

### Epithelial-Mesenchymal Transition (EMT)

Injury to alveolar epithelial cells can also induce them to acquire features of the mesenchyme in a process called EMT. In IPF, epithelial cells in areas of fibrosis often show upregulation of mesenchymal markers and mediators such as Wnt signaling and PAI-1 (21). This suggests that some fibroblasts may be derived from alveolar epithelium that has undergone EMT. EMT can be provoked by TGF- $\beta$ 1 signaling, impaired autophagy and other chronic stress pathways (21). However, the actual contribution of EMT remains



unclear. Lineage-tracing studies in animal models have reported conflicted results with some showing that a subset of alveolar type II cells transition into mesenchymal cells, whereas others find minimal evidence for EMT fibroblasts. Clarifying the extent of EMT in IPF pathogenesis could open therapeutic avenues, such as those that target Wnt/  $\beta$ -catenin pathways.

## Celular Senescence and SASP

IPF is often described as a disease of accelerated lung aging. Celular senescence, a permanent cell-cycle arrest, is one of the hallmarks of aging (22). Senescence markers are highly expressed in IPF lungs with increased senescence-associated  $\beta$ -galactosidase activity in alveolar epithelial cells and fibroblasts within fibrotic lesions (18). One study found that senescent cells were present in all IPF lung samples but absent in healthy lung controls (19), which implies that cell senescence plays a prominent role in IPF. The SASP includes cytokines (e.g. IL-6, IL-1 $\beta$ ), chemokines, growth factors (e.g. TGF- $\beta$ , VEGF) and proteases. The SAPS can act in a paracrine manner to induce injury. In IPF, senescent fibroblasts stimulate collagen production and matrix remodeling, thereby driving fibrosis in the local environment (18). Senescent cells also upregulate survival pathways that make them resistant to apoptosis, allowing them to survive. Together, this creates a vicious cycle of persistent tissue injury and remodeling. However, there are still unknown factors that influence the role of senescence in IPF. For instance, senescence has shown anti-proliferative and tumour suppression qualities and can even aid in wound healing (23). Some studies in liver fibrosis suggest that inducing senescence in stellate cells can even limit fibrosis (24). The question remains why the immune system fails to clear senescent cells in IPF. The mechanisms by which senescent cells persist and drive fibrosis are not yet fully understood which has direct implications for the therapy as discussed below.

## Fundamental Knowledge Gaps

Despite advances in elucidating the mechanisms above, the origin of IPF, as the same suggests, remains idiopathic. The initial triggers that start the pathogenesis are not defined. It is hypothesized that repetitive injuries such as microaspirations, viral infections, air pollution etc., lead to accelerated aging in the lungs but no concrete biomarkers have been defined (18). Moreover, the interplay between genetic risk factor and environmental exposures is poorly understood. Genetic risk factors such as MUC5B promotor polymorphism (which increases mucous secretion) make one more susceptible to IPF but only a subset of people with this genetic variant progress to IPF (21). Additionally, the mechanisms of fibrosis progression and resolution are not yet clear. For instance, in healthy individuals or young animals, lung injury does not lead to permanent fibrosis, suggesting mechanisms that can limit fibrosis which are absent or impaired in

IPF. Identifying why fibrosis becomes self-sustaining in IPF is a major gap in the current knowledge (18). Finally, as explained above, the role of cellular senescence is still unclear as it is not known how senescent cells interact with inflammatory pathways and how senescence in multiple cell types differs and manifests itself in IPF (21).

## Clinical Knowledge Gaps

Beyond the mechanistic uncertainties outlined above, several clinical challenges exist in IPF management. Firstly, under-representation of women and non-white patients. Trials of antifibrotics have a skew toward white males (25). This raises concerns about equity and safety and efficacy in underrepresented groups. Secondly, the long-term safety and efficacy of pirfenidone and nintedanib are lacking (26). While they were both approved for use in the treatment of IPF, follow-up data beyond 5 years is limited and discontinuation due to the aforementioned side effects, remains high (27). Thirdly, there is a lack for robust, validated biomarkers for early diagnosis, disease staging and treatment response. Most clinical trials rely on forced vital capacity (FCV) and diffusing capacity for carbon monoxide (DLCO), which may miss subtle improvements in function or early fibrosis progression (28, 29). Additionally, many circulating markers of senescence are not yet clinically validated (30). Lastly, clinical endpoints fail to capture disease burden beyond the lungs such as physical frailty, reduced mobility and overall quality of life (31). Broader and more patient-centric outcome measures are needed to evaluate the holistic benefit.

# Advancement Fundamental Understanding; Evidence Clinical Translation

## Rationale: Cellular senescence in IPF

As stated above, IPF is an age-related lung disease characterized by accumulation of senescent cells in the lungs. Multiple cell types in IPF lungs (especially alveolar epithelial cells and fibroblasts) show markers of senescence, such as p16<sup>INK4a</sup> and p21<sup>Cip1/Waf1</sup>, expressed at higher levels than healthy age-matched controls, in which some were even absent (32, 33). In fact, p16 positive senescent cell clusters, which are senescent epithelial cells overlying fibroblast foci, are largely specific to IPF and correlate with worse pulmonary function and survival (33). These senescent cells secrete a pro-fibrotic, pro-inflammatory SASP. Key SASP factors implicated in fibrosis include interleukins (IL-1 $\beta$ , IL-6, IL-8), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), chemokines (e.g. CCL2/MCP-1), matrix metalloproteinases (MMPs), and TGF- $\beta$  which recruit immune cells and lead to increased ECM deposition. This creates a cycle of inflammation and fibroblast activation that drives progressive fibrosis. Collectively, these observations indicate that

IPF lungs are burdened by senescent cells that drive the disease progression, and removing or altering these cells can mitigate fibrosis (34). This justifies the targeting of senescent cells as a viable strategy in the management of IPF.

## Classes of Senotherapeutics

Senotherapeutics are interventions that target cellular senescence. They fall into two broad classes: senolytics and senomorphics (32). Senolytics, are agents that can selectively induce apoptosis of senescent cells by disabling certain pathways, the so-called Senescent Cell Anti-apoptotic Pathways (SCAPS). Senescent cells develop resistance to apoptosis by upregulating these SCAPS. Examples of such pathways include BCL-2/BCL-x<sub>L</sub>, PI3K/AKT, and NF-κB signaling (35). The earliest discovered senolytics, dasatinib + quercetin (D+B) exploit kinase inhibition (dasatinib) and BCL-2/oxidative stress modulation (quercetin) to trigger caspase-mediated death of senescent cells (36).

In contrast, senomorphics are compounds that suppress the SASP or reprogram senescent cells without inducing apoptosis. These compounds aim to 'morph' senescent cells into a less deleterious state.

Typical targets include inhibiting mTOR, which dampens SASP translation via rapamycin/everolimus. Another pathway, JAK/STAT, involved in the interleukin signaling in senescent cells can be inhibited via ruxolitinib. Another approach is to activate NF-κB via metformin or resveratrol to improve cell longevity and resilience (18).

Senolytics are usually given intermittently, in a so-called 'hit-and-run' dosing regimen, to limit off-target toxicity (37). This idea is based on the short half-lives of drugs like D+Q (11 hours) and that periodic clearance of senescent cells is sufficient while limiting toxicity to normal tissues and giving time to recover (38). Senomorphics, on the other hand, require continuous or pulsed chronic dosing to maintain the suppression of the SASP. Senotherapeutics might be used in a combination, a continuously given senomorphic and an intermittently given senolytic (38).

## Candidate Drugs & Mode of Action

Several senotherapeutic drugs have shown promise in preclinical models of pulmonary fibrosis.

### *Rapamycin/Everolimus (mTOR inhibitors)*

These inhibit the mTOR kinase, a central regulator of protein synthesis and SASP. In senescent cells, mTOR drives the translation of IL-1α and other SASP factors. Rapamycin thus decreases SASP output. Specifically, rapamycin prevented the loss of epithelial E-cadherin and a rise of mesenchymal markers (fibronectin, α-SMA) in bleomycin-treated mice, indicating it blocked alveolar epithelial–mesenchymal transition (EMT) and fibrosis

progression (18). A small pilot trial in IPF patients demonstrated acceptable safety of low-dose rapamycin (sirolimus) and showed a reduction in circulating fibrogenic cells (39).

### *Metformin*

Best known as an AMPK-activating antidiabetic drug, metformin activates AMPK which, in turn, downregulates mTOR/AKT, thereby reducing SASP production and oxidative stress. In bleomycin-mice, metformin protected against fibrosis by lower levels of TGF- $\beta$ 1 and collagen deposition. It even restored lung histology and antioxidant defenses in one study (40). Clinically, metformin's impact on IPF is still under investigation. One retrospective study noted that IPF patients with diabetes on metformin had slower disease progression (41). Other studies found no significant effect on key outcomes (42). Nonetheless, metformin has an established safety profile and is not only SASP-suppressing but also contains antioxidant and anti-inflammatory properties which makes it an appealing candidate (41).

### *Resveratrol*

Resveratrol is a natural polyphenol which activates sirtuin (SIRT1) pathways and has anti-inflammatory and antioxidant effects. In vitro models show that resveratrol can delay cellular senescence and reduce SASP cytokine release deacetylating the RelA/p65 subunit of NF- $\kappa$ B. Resveratrol administration in rats alleviated bleomycin-induced lung fibrosis, as evidenced by reduced alveolar inflammation, less collagen accumulation, and preservation of lung architecture (43). It also suppressed hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), which is often upregulated in fibrotic lung regions. Although the rapid metabolism of resveratrol is an issue, its safety profile is good. A small pilot in rheumatoid lung fibrosis showed improved exercise tolerance with resveratrol therapy (44)

### *Other novel agents*

Examples of other innovative senotherapeutics include BET-inhibitors such as JQ1, JAK-STAT inhibitors such as ruxolitinib or baricitinib, FOXO4-DRI peptides and most notably BCL-xL PROTACs (35, 45-47). The latter are proteolysis-targeting chimeras designed to degrade the anti-apoptotic protein BCL-xL in senescent cells (48). Though not tested in IPF models, such PROTACs could enable safe senolytic therapy in humans.

## **Pre-clinical Evidence**

Multiple studies support the idea that targeting senescence can be beneficial in IPF. IPF is considered a disease of aging, so researchers have examined whether clearing senescent cells in normal aged lungs has positive effects. In a landmark study, Hashimoto *et al.* used a transgenic "suicide gene" model (INK-ATTAC mice) to ablate p16<sup>Ink4a</sup>-positive

senescent cells in healthy older mice (49). Clearing senescent cells in these aged mice resulted in improved lung compliance, elasticity, and exercise endurance, effectively rejuvenating the lungs and improving lung function. This provided proof that senescent cells actively contribute to age-related lung dysfunction, and that their removal can restore function. It laid the groundwork for senolytics as a therapy for lung health.

The bleomycin injury mouse model of IPF causes lung fibrosis that mimics many features of IPF, especially when injury occurs in older mice (50). Studies have found that bleomycin-treated lungs accumulate senescent cells (both epithelial and myofibroblasts) during the fibrotic phase. These senescent cells then appear to impede the resolution of fibrosis (51). The anti-fibrotic potential of senotherapeutics has therefore been explored primarily in the bleomycin mouse model. In one study, treating fibrotic mice with a transgenic approach to remove senescent cells led to faster resolution of fibrosis. In a 2017 study, D+Q was administered to mice after bleomycin injury. The senolytic treatment selectively eliminated senescent fibroblasts and significantly improved lung function and exercise capacity in the fibrotic mice (18). Importantly, although senolytic therapy did not dramatically erase the existing collagen scars in the short term, the treated mice had better pulmonary mechanics and overall health than the untreated fibrotic controls. This suggests that even without fully reversing fibrosis, removing senescent cells can stabilize and even improve functional outcomes. Another study demonstrated that D+Q reduced fibrosis burden and improved survival in bleomycin-injured mice by impeding the SCAP of senescent cells (21). Beyond D+Q, other agents have shown promise in preclinical models such as the FOXO4-DRI peptide which disrupts a SCAP and was able to clear senescent cells in vivo. These successes at the preclinical stage provide a strong rationale for researching senotherapeutics in humans.

## Completed Clinical Trials

In the attempt to translate these findings to humans, researchers have begun testing senolytic therapies in IPF patients. The first-in-human pilot study of senolytics in IPF was reported in 2019 ((38)). In this open-label trial, 14 patients with stable, mild-to-moderate IPF were given oral dastinib (100 mg/day) and quercetin (1250 mg/day) 3 consecutive days per week for 3 weeks. Key findings include feasibility and safety as 100% of patients completed the 3-week program with no discontinuations. The treatment was well-tolerated with only mild to moderate adverse events such as a cough, transient skin rashes, bruising and gastrointestinal upset. Only one serious adverse event occurred, possibly unrelated. Standard blood tests and liver and kidney function tests showed no adverse changes. Functional outcomes showed a notable improvement in physical performance. The 6-minute walk distance (6MWD) increased by an average of 21.5 meters, the gait-speed in a 4-meter walk test improved and the time to rise from a chair

also improved. The changes were both statistically and clinically meaningful. Patients self-reported better physical health status. Perhaps expected for such a short trial, pulmonary function tests such as forced vital capacity (FVC) and gas diffusion remained stable which can be regarded as a positive given the usual trajectory of IPF. Firm conclusion cannot be drawn from such a short pilot, but functional, physical improvements in most subjects hint to tangible benefits.

The study also looked at circulating SASP factors and other biomarkers. Although the results were exploratory, there were indications that some pro-inflammatory SASP proteins and matrix remodeling factors decreased after treatment or showed correlations between their reduction and the functional improvements. For example, levels of certain matrix metalloproteinases and inflammatory cytokines changed in a manner consistent with reduced senescent cell burden. One notable finding was an increase in serum GDF15, a marker associated with senescence clearance, which the authors interpreted as a systemic response of senescent cell clearance.

Following the open-label study, a more rigorous randomized controlled trial (RCT) was conducted. In 2022-2023, a phase 1, single-centre, placebo-controlled trial whereby 12 IPF patients were randomized 1:1 to D+Q versus a placebo with identical dosing (52). The primary goal was to further evaluate safety and feasibility. The results were consistent with the pilot. The D+Q was well tolerated with no significant differences in adverse events compared to placebo. All participants completed the full dosing schedule without dose reduction. This trial did not assess efficacy on lung function. There were trends that suggested some improvements in frailty indices and reduction in circulating PAI-1 compared to placebo but the authors await larger trials to conclude the efficacy. The conclusion of the authors was that intermittently dosed D+Q is feasible in IPF patients and does not pose major safety issues.

The results from the clinical trials indicate that senotherapeutic therapy for IPF appears to be safe and feasible and justify larger phase 2 trials to examine lung-function endpoints and determine optimal dosing.

## Safety

Initial human studies have seen acceptable safety but only in the short term. Available human data from the aforementioned pilot study had less than 4 weeks of D+Q exposure in around 30 total IPF patients (38). The most common adverse effects were mild. These include a cough, transient skin rashes, and gastrointestinal discomfort. However, larger trials are needed to fully characterize safety. Theoretical toxicities remain a concern. Senolytic drugs often target pathways also important in normal cells; for example, navitoclax is notorious for on-target platelet apoptosis, causing

thrombocytopenia (48). Another consideration is oncologic risk as senescent cells sometimes play beneficial roles in tumour suppression (53). Long-term use will require monitoring for malignancies.

## Dosing

As noted, most studies that demonstrated sustained senescent-cell clearance did so with an intermittent pulsing dosing regimen (38). Future senolytic protocols may use even shorter pulses such as a single 3 day cycle every 3 weeks since many senolytics have rapid clearance and their benefit is in triggering a one-time apoptotic event in senescent cells (37). For senomorphics, continuous low-dose schedules are hypothesized to optimally maintain SASP suppression. An alternative route being explored in the delivery is via inhalation, to concentrate drugs in the lungs and reduce systemic exposure, and this could potentially improve their efficacy (32). The aforementioned combination of senolytics and senomorphics or senotherapeutics with an antifibrotic drug could be viable and highly effective but raises the need to monitor toxicities and overlapping immunosuppression.

## Biomarker Development

A major challenge in measuring senescence burden and treatment response is the pursuit of finding optimal biomarkers. Circulating SASP factors such as pro-inflammatory cytokines like IL-6, IL-8, and GRO- $\alpha$ , as well as matrix-modifying proteins (MMP-7, TIMP-1, PAI-1), are often elevated in IPF serum and might reflect senescent cell activity (38). In the D+Q trial, an exploratory panel of 48 SASP-related markers was assessed. Individuals with the greatest functional improvements showed corresponding declines in certain SASP proteins and microRNAs (38). Another interesting biomarker is the anti-aging protein Klotho. IPF is associated with reduced circulating Klotho levels, presumably due to senescence in Klotho-expressing cells. Remarkably, a recent study found that senolytic therapy increased urinary Klotho excretion in IPF patients (54). This supports the idea that Klotho upregulation could be a positive marker of senolytic effect. Researchers are also developing imaging biomarkers. For instance, PET tracers that target senescent cell markers. Preclinical PET studies have shown uptake in fibrotic, senescent-rich areas, which can aid in noninvasive monitoring (55).

## Predicted Impact on Fibrosis Cascade

Integrating the above mechanistic and translational data suggest that senotherapeutics have the potential to intervene at multiple points in the IPF fibrotic cascade. Using senomorphics in the early phase of the disease to dampen the fibrogenic environment, then deploying senolytics in a later stage to remove senescent cells could be an effective therapeutic strategy. Administering a senomorphic such as rapamycin could reduce SASP



cytokines, thereby reducing the activation of fibroblasts and differentiation to myofibroblasts. This might slow the initial fibrosis and essentially buy time to preserve more functional lung tissue. As fibrosis progresses, senescent fibroblasts accumulate and signal chronic wound-healing. At this stage, a senolytic could be introduced to clear these senescent cells, thereby stopping the fibrotic loop (18, 21).

Combining senolytics with existing antifibrotics might, in theory, both remove the pro-fibrotic driver (SASP) and block TGF- $\beta$ -stimulated collagen synthesis, thereby producing synergistic benefits. Antifibrotics mainly target fibroblast proliferation and differentiation pathways, whereas senotherapeutics target the cellular aging aspect of disease. The two approaches should be complementary. For example, nintedanib's inhibition of tyrosine kinases might slow the generation of new senescent fibroblasts, and interestingly nintedanib itself can induce death of senescent fibroblasts via STAT3 blockade (35). Meanwhile, a senolytic drug could eliminate the existing pool of senescent cells that nintedanib cannot affect.

If upcoming phase 2 or phase 3 trials confirm a reduction in FVC decline and improved frailty or quality of life (QoL) indices without major toxicity, senotherapeutics could redefine IPF management by transforming it from progressive, fatal, lung scarring into a controllable chronic condition more akin to other age-related diseases. Translational hurdles such as targeted delivery, long-term safety and biomarker validation still remain but there is a clear mechanistic rationale and early human proof-of-concept.

## Challenges

However, despite this promise, several hurdles must be overcome. First, patient selection and timing need to be refined. Some IPF patients have a high burden of senescent cells (especially those with telomere-mediated disease or very advanced fibrosis), while others might have more immune-driven fibrosis. Identifying "senescence-high" patients via biomarkers via high plasma PAI-1 or low Klotho levels could help those most likely to respond (21). Moreover, determining the optimal window for intervention is crucial. Starting senomorphic therapy too late, when irreversible honeycomb cysts have formed, may yield little benefit, whereas starting too early might carry unnecessary risk. Secondly, safety in a frail population remains a concern. IPF patients are often elderly with comorbidities. Adding a senolytic could worsen immune function. An optimized or even personalized dosing regimen will be needed to avoid toxicity. Thirdly, there are challenges in drug delivery. Fibrotic lungs have poor perfusion, so systemic drugs may not penetrate fibrotic foci. Inhaled senotherapeutics could help but for some drugs such as dasatinib, or navitoclax, inhalation is technically challenging and will require innovation in aerosol formulations. Fourthly, measuring efficacy is difficult. Reliable biomarkers will be needed to confirm efficacy in Phase II trials. Fifthly, the cost and



complexity of combining therapies might be high. Layering therapies increases the burden in terms of polypharmacy and monitoring. Demonstrating additional benefit will be necessary to justify this in practice.

## Ethical Aspects

### *Autonomy*

IPF predominantly affects older adults, raising unique ethical considerations. Many IPF patients may face cognitive or sensory challenges that complicate truly informed consent for novel senotherapeutic therapies. Extra effort is needed to ensure patients (and families) understand the experimental nature, potential risks, and uncertain benefits of senolytic or “anti-aging” drugs in IPF (56). Respecting patient autonomy means providing clear information and avoiding therapeutic misconception, while also considering that some patients might prefer letting physicians make decisions for them due to the complexity of the disease and interventions (56). Decisions surrounding palliative care and advance directives are also important in IPF given its poor prognosis, so introducing an experimental senotherapeutic must align with the patient’s wishes.

### *Beneficence & Non-maleficence*

Cellular senescence has a dual role. It promotes aging and disease yet also aids in tumor suppression and tissue repair. Eliminating senescent cells could, in theory, impair these beneficial defenses. Preclinical studies indicate that interfering with senescence triggers can increase cancer risk, whereas clearing already-senescent cells may delay cancer development (57). This highlights a duty of non-maleficence. Senolytic trials should start in conditions where the alternative treatments are suboptimal to justify the risks (58). IPF does fit this criterion, it is a lethal disease with limited therapies, making it an ethically suitable situation to test senolytics. However, monitoring long-term safety is required as off-target effects are not fully known. Researchers have a beneficence obligation to maximize potential benefit such as choosing dosing to reduce toxicity, while minimizing harm and to halt trials if unexpected safety issues emerge (58).

### *Justice*

The development and deployment of senotherapeutics for IPF must address equity in access and representation. Current IPF therapies already show disparities, for instance, African-American patients in the U.S. are only about half as likely as Caucasian patients to receive antifibrotic treatment (59). Likewise, women and racial minorities have been under-represented in IPF clinical trials. A meta-analysis found that 77% of trial participants were white and less than 1% were black (60). Such under-representation can skew safety and efficacy data. Ethically, senotherapeutic trials should proactively

recruit a diverse IPF population to ensure findings generalize across genders and ethnicities. Achieving justice also means ensuring affordability and availability of new therapies. If senolytics are approved, high cost could exacerbate disparities. This is a recurring concern in geroscience, namely equitable access to longevity interventions (61). Policymakers and clinicians will need to strive for fair allocation, for instance, through insurance coverage or patient assistance programs, in order to prevent that the benefits of senotherapeutics only are received by certain patients.

## Economic Aspects

IPF imposes a substantial economic burden per patient even before any new senotherapeutics are added. In the United States, all-cause medical costs for an IPF patient average around \$60,000 per year in 2011 (11). In Europe, costs are similarly high. A Spanish consensus study estimated annual IPF management costs ranging from €11,500 per patient (stable disease) up to €57,800 in rapidly progressing cases (62). These estimates include routine care, but not include the price of new senotherapeutic drugs.

The introduction of senotherapeutics would add to this cost. If repurposed drugs like dasatinib and quercetin are used, the incremental cost might initially be relatively low. Dasatinib as a cancer drug is expensive but senolytic dosing is intermittent and shorter-term. The two approved anti-fibrotic drugs (pirfenidone and nintedanib) each cost on the order of \$100,000 per year in the US market (15). Even in countries with price controls, this is a significant annual cost with ~\$36,000 in the UK and ~\$29,000 in Belgium for just one of these drugs. The affordability concern is acute since many IPF patients are retired and public payers or insurers would bear most of the cost.

Cost-effectiveness analyses (CEA) are critical to determine if these added costs are justified by health gains (measured in quality-adjusted life years, QALYs). Pirfenidone and nintedanib have very high incremental cost-effectiveness ratios (ICERs). One U.S. study found an ICER of approximately \$1.6 million per QALY gained for nintedanib versus supportive care (15). This is far above the willingness-to-pay threshold of \$100,000.

For senotherapeutics, no published cost-effectiveness models exist yet. But If a senolytic is used in addition to antifibrotics, the combined cost could approach \$150k per year, necessitating a very large clinical benefit to be cost-effective. If, alternatively, senotherapeutics eventually reduce or even replace reliance on other treatments, there could be major cost savings. For example, if a senolytic delays the need for costly lung transplant or hospitalization. Savings would come via preserved lung function which translates to fewer acute exacerbations and hospital stays as each IPF hospitalization

averages >\$17,000 (63). One modeling study suggested that reducing IPF progression could cut annual follow-up and hospitalization costs substantially (15). If lung function decline is reduced, the avoided costs of ICU stays, and mechanical ventilation might (partially) offset costs of treatment.

On a macroeconomic scale, the impact of IPF is notable despite the fact that it is a rare disease. One could argue that IPF prevalence is rising with aging populations, which means the combined costs could grow substantially. In contrast, if senotherapeutics improve survival and/or quality of life, there are economic benefits in terms of increased quality-adjusted life years and reduced need for end-of-life care. Although most IPF patients retired, preserving their functional independence could reduce caregiver burden.

To measure cost-effectiveness, senotherapeutics could be assigned a cost per QALY. Health insurers will need to consider financing or limit use to patients most likely to benefit to manage the financial impact of novel senotherapeutic therapies. Nonetheless, if senotherapeutics show improved survival or function, the value may justify higher spending.

## Implementation in Healthcare

Integrating senotherapeutics into IPF management will require a complex approach within healthcare organizations. This includes personnel education and new protocols. Clinical staff will need training on senotherapeutic mechanisms. Physicians must understand the rationale, evidence and use of such drugs. Medical education programs and updated IPF treatment guidelines can help spread this knowledge.

Given the potential risks, healthcare organizations will need to establish monitoring plans for patients on senotherapeutics. This may include baseline screening and periodic checks during treatment. For example, if using dasatinib+quercetin (D+Q), monthly blood counts and liver tests might be done during and after the dosing period to catch any toxicity. Clinicians should monitor infections or impaired wound healing, or other immune abnormalities. Hospitals will need to track adverse events and feed this data back to regulatory authorities. In addition, because these drugs are novel, long-term follow-up of treated patients, even after treatment has ended, should be done to observe any late effects. This could be done via patient registries (58).

New biomarkers might be required to better monitor efficacy and safety. New innovations in imaging can also assist such as the aforementioned PET tracers, that highlight senescent cells in the lungs. Implementation is facilitated if regulatory bodies support early access. The FDA and EMA have mechanisms (Fast Track, Breakthrough Therapy, PRIME, etc.) that can expedite drug approval for serious diseases like IPF. For instance,

nintedanib was granted Fast Track and Priority Review by the FDA. A promising senotherapeutic may also receive an expedited roll-out. A similar scheme in Europe, the PRIME scheme from the EMA exists.

Some patients may seek compassionate use of senotherapeutics. Hospital review boards and expanded access protocols need to evaluate such requests ethically and coordinate with manufacturers. Once approved, health technology assessments (HTA) agencies such as NICE in the UK, CADTH in Canada need to decide on reimbursement. Their evaluations could determine if the therapy is covered by insurance.

Health insurers may require documents on IPF progression or failure of standard therapy before covering the costs. Therefore, clinicians will need to inform themselves about these processes to be able to submit evidence to the insurers. Implementing senotherapeutics also would involve educating patients. This includes creating patient information brochures, discussions surrounding informed consent and patient support groups. This would involve discussions with patient advocacy groups.

## Synthesis/Perspectives/Conclusions

The research on senotherapeutics in IPF is still in its infancy but it has progressed from fundamental research to early clinical trials. At the preclinical level, multiple studies linked cellular senescence to pulmonary fibrosis. Senescent cells accumulate in IPF lungs and actively contribute to fibrogenesis by secreting a SASP. In mouse models of lung fibrosis, clearing senescent cells has shown to reduce fibrosis and improve lung function. This proof-of-concept laid the groundwork for human trials. The first human study was a small open-label pilot which showed feasibility and physical benefits as participants showed improvements in 6MWD and gait speed among others. Although this was not an RCT, the study provided evidence that senolytics might improve physical function in IPF patients with limited adverse events. Building on this, a recent RCT in 2023 confirmed the safety of senolytic therapy in IPF. All treated patients completed the dosing regimen without toxicity and only mild side effects.

In general, the clinical evidence is limited but acceptable safety and some functional improvements have been observed. The strength in the evidence lies in the confirmation of the hypothesis that accelerated cellular senescence is a driver of IPF and senotherapeutic therapies can act on this senescence. However, until Phase II or Phase III clinical trials, any efficacy in the clinic remains unclear. It is not yet understood whether clearing senescent cells can reduce mortality. The current studies were too small and too short. A larger, longer-duration trial is therefore needed.

Another question is which senescent cells are most important in IPF. Senolytics such as D+Q target broadly but perhaps more specific approaches such as PROTACs which can be aimed at specific cell types has a higher efficacy and/or safety. The optimal dosing schedule is also still an unanswered question. Moreover, patient selection is perhaps an important factor as only a subset of IPF patients could respond extremely well while another subset might not experience a good response. Current studies lack diversity in patient populations to even begin answering this question. Another uncertainty lies in how senotherapeutics might interact in a combination therapy, as in a senomorphic and a senolytic or a antifibrotic and a senotherapeutic. Would combining have synergistic effects as hypothesized above or would this increase toxicity? Finally, as stated earlier, there is a risk of malignancy due to the tumour suppression by senescent cells which needs careful surveillance.

In the coming years, senotherapeutics will likely remain in the research domain. Until results from late-phase clinical trials become available, it is unlikely that senotherapeutics will become a standard-of-care in IPF. If upcoming research reports positive outcomes in terms of efficacy and safety, there could be accelerated approval and adoption in the clinic. In the near term, senotherapeutics will probably be offered mainly through clinical trials until patients and patient advocacy groups show an interest. Advances in senotherapeutics in other domains besides lung disease, such as in liver disease could accelerate enthusiasm in senotherapeutics in general.

To ensure equitable access to senotherapeutics, policymakers should involve themselves in discussions surrounding diversity, ethics and pricing to mitigate the risk of high costs and unequal access. The advent of senotherapeutics marks a new chapter in IPF management. The scientific rationale is strong and early studies have opened the door to the possibility that the disease progression can be altered.

Nonetheless, significant work remains in translating this into a widely adopted therapy. Ethically, patient welfare, informed choice, autonomy and equity are important. Economically, stakeholders must collaborate to ensure cost does not become a barrier to a potential life-saving innovation. Practically, healthcare organizations need to prepare if such therapies need to be integrated in their current care, which requires collaboration and education. The results from upcoming trials will decide whether there is a paradigm shift in the treatment of IPF or perhaps just an increase in our understanding of IPF pathology. The hope is that in the future there will be better options for a patient diagnosed with IPF. A treatment that can turn IPF from a progressive terminal illness into a more manageable chronic condition would be of immense value to those patients.

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