

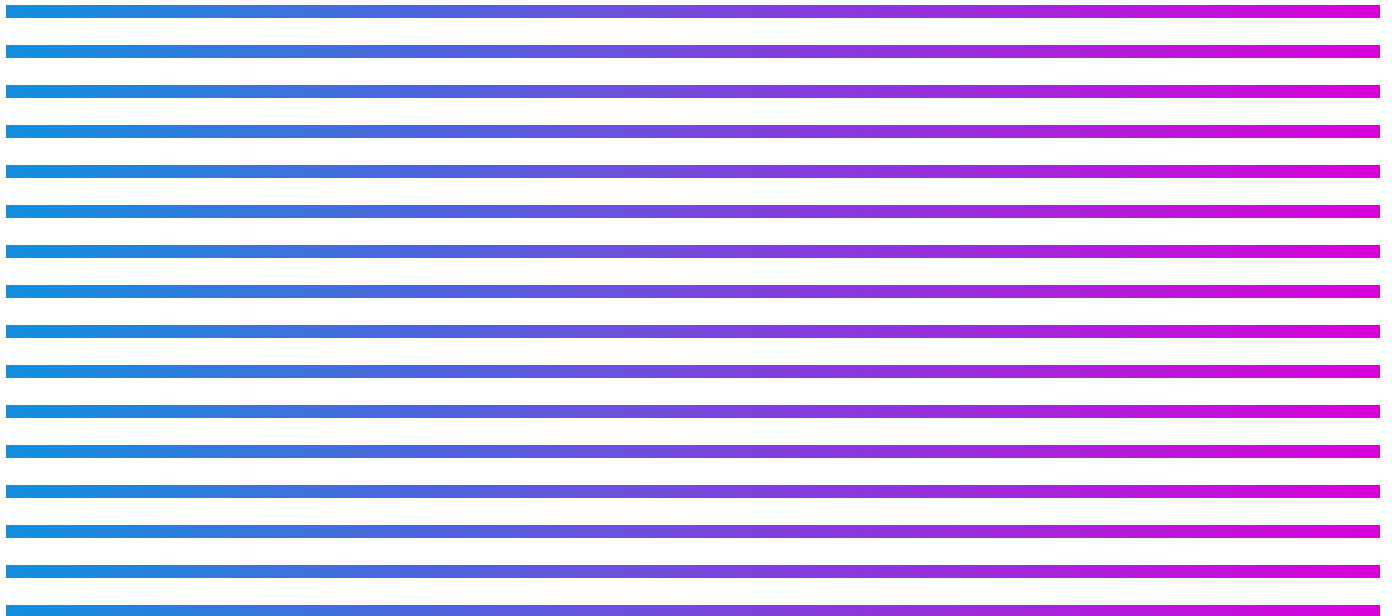


LEAPing into IPF Research: Analyzing CTGF's Therapeutic Failure and Guiding Future Strategies

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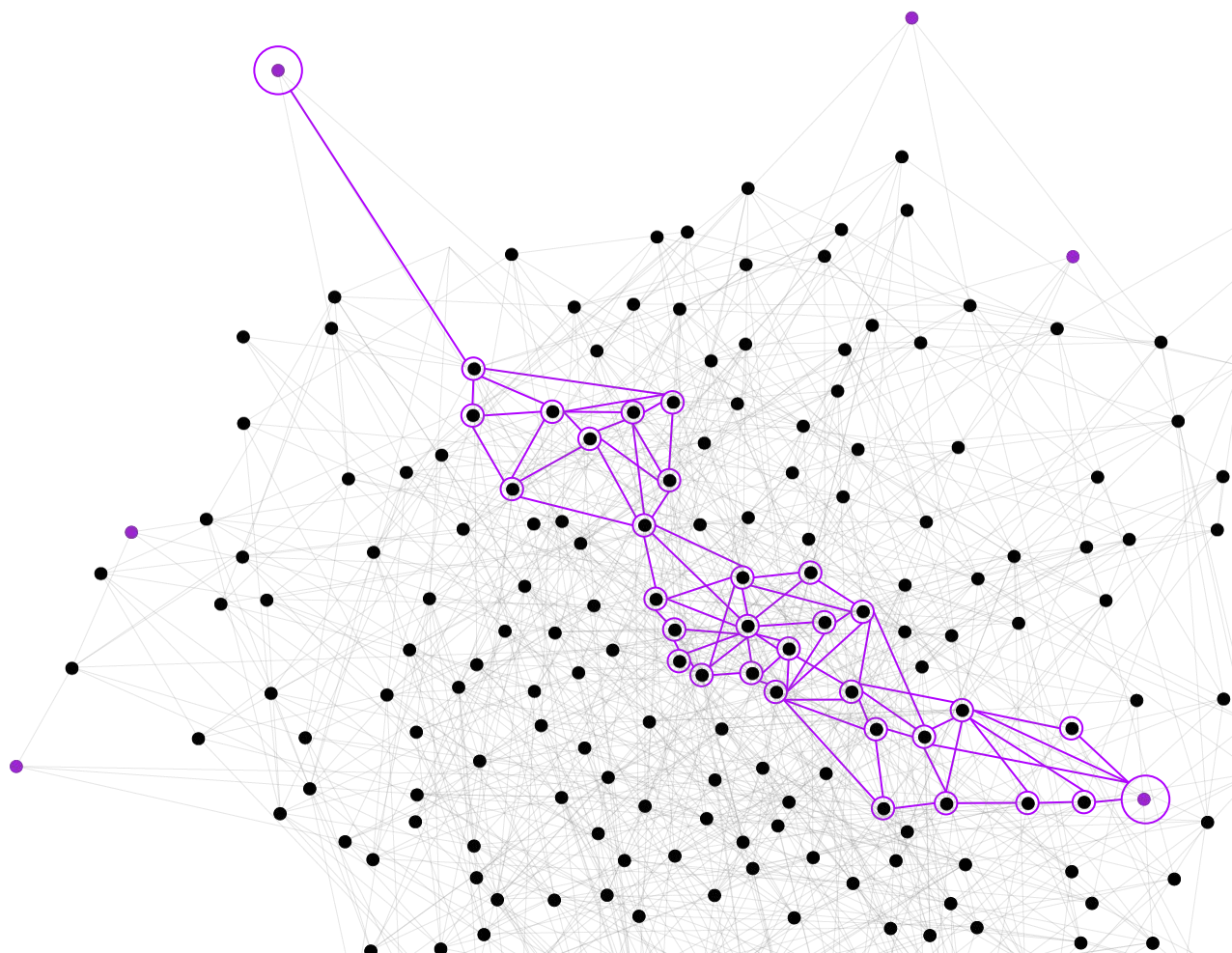


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LEAP Unravels Disease Biology

This report details the application of LEAP, BenchSci's agentic predictive knowledge graph technology, to examine the complex pathology of Idiopathic Pulmonary Fibrosis (IPF). Currently, only three therapies are approved for IPF, but these merely slow disease progression rather than halt or reverse it, underscoring the urgent need for new treatments. The accompanying analysis by LEAP dissects the biology of IPF and contextually assesses the recent Phase III clinical trial failure of the Connective Tissue Growth Factor (CTGF) inhibitor, pamrevlumab. Importantly, LEAP demonstrates that such a single-targeted approach is limited in a multifactorial disease, and subsequently identifies a novel, evidence-based hypothesis to enable a systems-based approach for the treatment of complex underlying disease pathologies.

Key Findings and LEAP-Driven Insights

Mapping IPF Complexity: Data drawn from more than 12,000 of the publications in LEAP's extensive corpus was used to identify over 6000 evidence-backed mechanisms that drive IPF. Synthesizing these into a single coherent system created a comprehensive knowledge map of IPF, which served as a foundation for subsequent contextual analysis of past failures and future opportunities. The IPF map revealed 68 key pathological processes that were classified into 8 key disease signatures.

Dissecting Therapeutic Failure: Contextually analyzing the effects of CTGF inhibition, using the IPF map revealed that it only impacted 35 of the 68 identified pathological processes. Crucially, key disease-driving themes, like cellular senescence and chronic inflammation, remained largely unaffected by CTGF inhibition, marking these as potential shortcomings with this treatment strategy.

Identifying Novel Opportunities: Analysis of the role of cellular senescence revealed it as a central and under-addressed pathology driving IPF. Discrete mechanisms uncovered by LEAP link cellular senescence to 55 of the 68 identified IPF pathological processes, mainly through components secreted by senescent cells.

Generating Actionable Hypotheses: LEAP's analysis identified cellular senescence as a critical therapeutic gap that is not targeted by CTGF inhibition. To address this gap, LEAP's hypothesis generation capabilities identified and ranked potential hypotheses for targeting senescence. Examples include, NOX4 as a well-established target, known to be selectively upregulated in senescent fibroblasts and the histone methyltransferase KMT2A (MLL1) as a novel, promising target predicted to disrupt senescence-driving signaling.

Accelerating Validation: LEAP also generated a complete, multi-step experimental design to validate individual hypotheses, such as the role of KMT2A in cellular senescence, thereby providing optimal strategies to test novel hypotheses.

A Systems-based Approach: This enhanced understanding of pamrevlumab's failure reframes the therapeutic challenge. The history of IPF drug development is marked by numerous failures, reflecting the field's focus on individual targets in a highly complex, interconnected disease. Analyzing these targets validates that a systems-based approach—one that targets multiple disease themes like fibrosis and cellular senescence simultaneously—is likely to yield more effective therapies.

Conclusions

Contextualizing the shortcomings of CTGF inhibition within the IPF map reframes the setback as a critical insight: single-target agents are likely insufficient for this multifactorial disease, and leave potential disease drivers unaddressed. Through this analysis, LEAP identified potential mechanisms of failure and suggested how to tackle those missing components to build a superior, systems-based strategy. The identification of actionable, evidence-backed hypotheses, complete with validation strategies, demonstrates LEAP's ability to not only understand complexity, but to also identify routes to acting on it.

Idiopathic Pulmonary Fibrosis (IPF)

IPF is a severe, progressive disease characterized by irreversible fibrosis of lung tissue, leading to shortness of breath, coughing and fatigue [1]. The exact cause remains unknown, and current therapeutic strategies are insufficient, merely slowing the disease rather than arresting progression or reversing existing scarring [2]. With a global prevalence of 5.8 cases per 100,000 people and a median survival of 3-5 years from diagnosis, there is an urgent unmet need for effective, disease-modifying treatments [3, 4].

Current Standard of Care

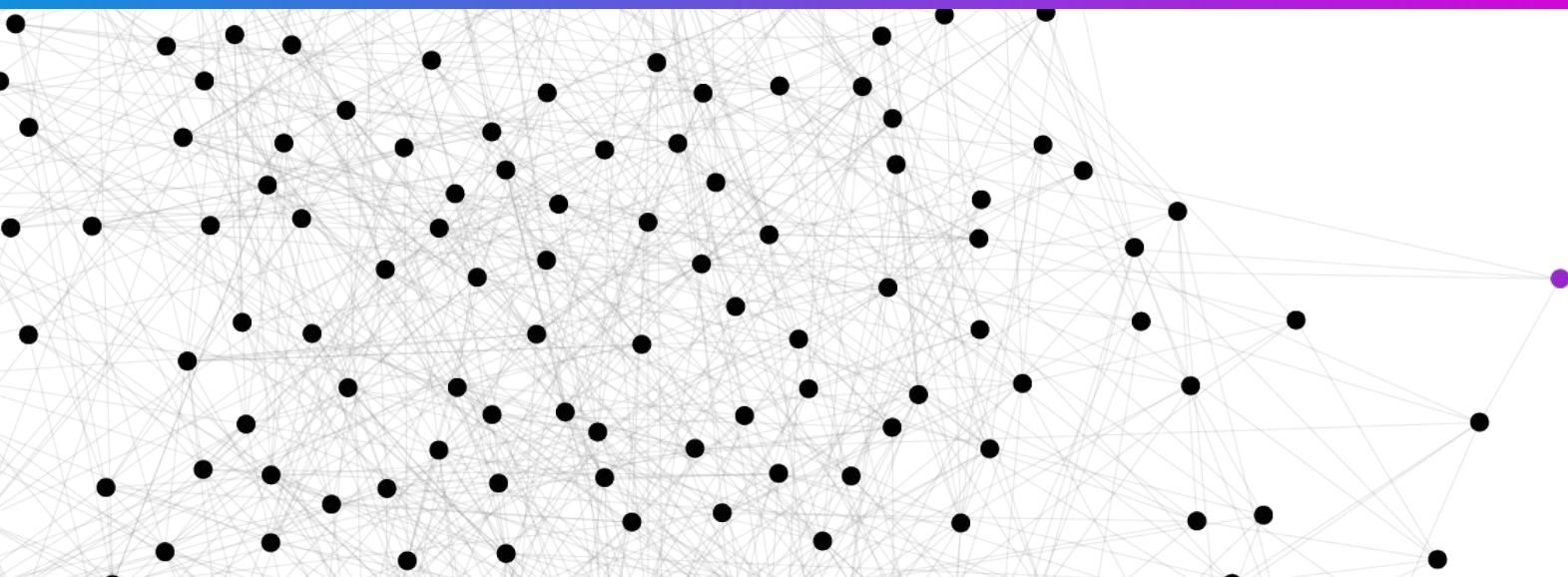
The pharmacological management of IPF currently revolves around three approved agents, namely nintedanib, pirfenidone, and the more recently approved nerandomilast, all of which predominantly target fibrosis and inflammation [1, 5, 6]. While these therapies slow the rate of lung function decline, they do not cure the disease, reverse existing scarring, or offer a meaningful impact on overall survival. Nintedanib and pirfenidone, the long-standing mainstays of treatment, target fibrotic pathways with only modest efficacy and are often associated with significant tolerability challenges and side effects [7]. The addition of nerandomilast, a PDE4B inhibitor with dual anti-fibrotic and immunomodulatory effects, offers a new mechanism of action, yet the fundamental challenge remains: current treatments only slow, but do not stop or reverse, this progressive and debilitating disease [8, 9].

Understanding Pamrevlumab Failure using LEAP

This case study aimed to apply BenchSci's agentic predictive knowledge graph technology, LEAP, to the analysis of a recent clinical trial failure. Pamrevlumab's is a connective tissue growth factor inhibitor that held promise for the treatment of IPF through Phase II trials, but ultimately fell short in Phase III [10]. With the large unmet therapeutic need for IPF, understanding failures such as this may enable identification of future opportunities.

Guided by LEAP, this analysis became a multi-step workflow:

- 1. Holistically understand IPF:** Identifying all of the mechanisms that drive IPF including effects on genes, proteins, cell types, signalling pathways and pathological processes.
- 2. Contextually analyze CTGF inhibition:** Using the identified mechanisms, determine the effects of CTGF inhibition, highlighting the pathologies it targets and those that it is unable to effectively target.
- 3. Identify novel hypotheses for potential therapeutic gaps:** Apply LEAP's ability to make connections across contexts and therapeutic areas to thread together mechanisms that hypothesise ways to tackle the gaps in a CTGF-centered approach.
- 4. Plan optimal experiments to validate novel hypotheses:** Generate experimental plans to test the entirety of selected hypotheses.



Unravelling Disease Pathology with LEAP

The scientific literature investigating IPF is growing by over 1400 papers a year, making the task of understanding and integrating this knowledge an overwhelming task. This challenge is compounded by tangential discoveries from alternative diseases and contexts that could also be relevant to IPF pathology and treatment. The profound complexity of IPF requires an analytical approach beyond human capacity. LEAP is designed to incorporate and connect the breadth of available scientific information to drive a large-scale understanding of complex diseases, such as IPF. LEAP's knowledge graph maps out connections between pairs of biological entities backed by published experimental data. These connections are threaded together in response to natural language queries to drive the identification of novel and evidence-backed disease mechanisms. The resulting mechanisms form the foundation from which LEAP can generate new therapeutic strategies to effectively target IPF disease pathology.

Mapping IPF Disease Biology with LEAP

In response to the query "What mechanisms drive IPF?", LEAP identified >6000 individual experimentally-backed mechanisms that provide a holistic overview of IPF disease pathology. This was then synthesized into a single comprehensive network (Figure 1), the foundation of which are individual pathology-associated biological mechanisms, including key components of IPF such as TGFβ and FGFR (Figure 1a). While each mechanism plays its own role, multiple mechanisms are aggregated into sub-networks (Figure 1b), which cumulatively form an unbiased, holistic network that serves as a foundational sub-graph for navigating IPF complexity (Figure 1c). By contextually probing this knowledge graph, it is possible to investigate past drug failures and predict future therapeutic opportunities in IPF.

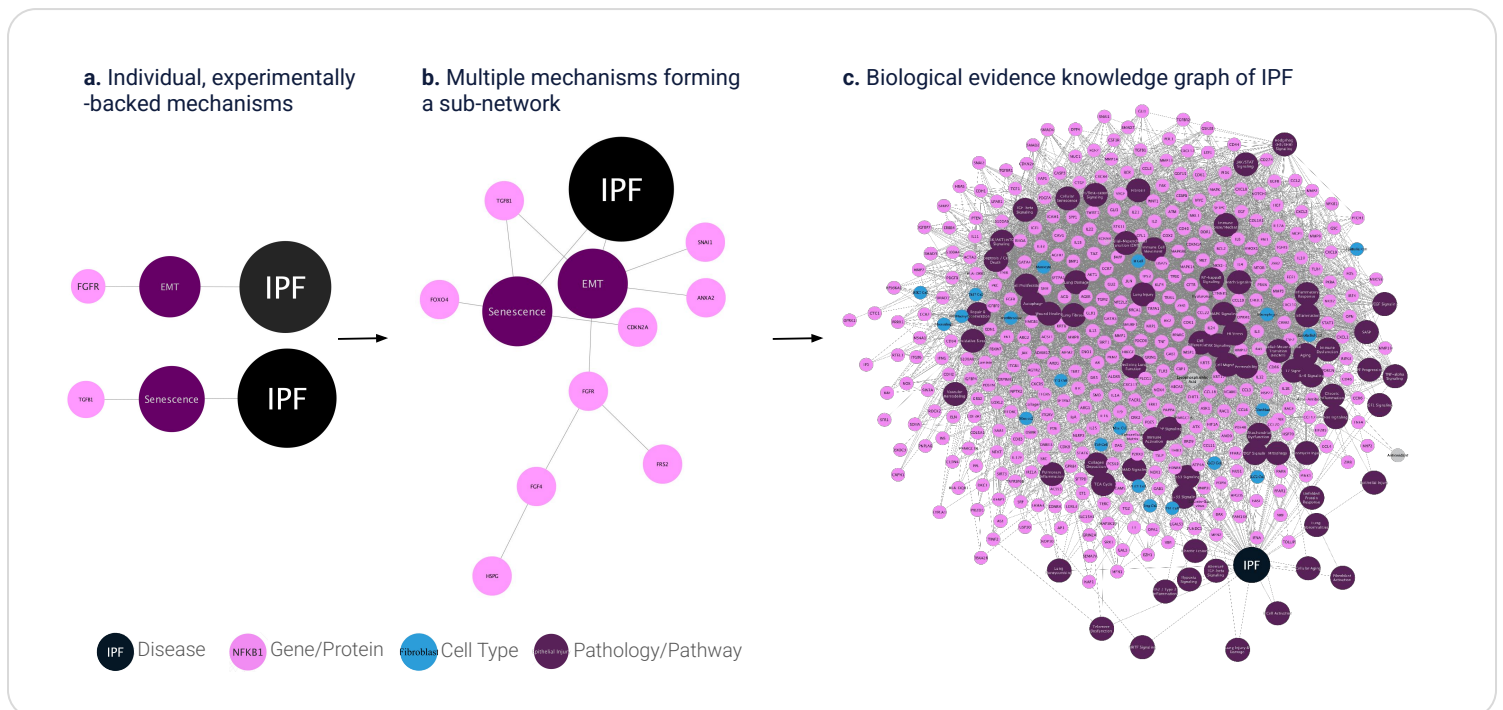


Figure 1. LEAP's isolated knowledge graph for IPF. This graph is systematically constructed by integrating individual, experimentally-backed mechanistic findings extracted from the scientific literature (a). The cumulative aggregation of these discrete findings progressively expands the network (b), which ultimately constitutes the comprehensive knowledge graph for IPF (c).

SECTION 2 | LEAP CASE STUDY

2.3 - LEAP's Insight into the Pathologies Driving IPF

Pathological Complexity of Idiopathic Pulmonary Fibrosis

By providing a deeper, evidence-based understanding of the biological contributors, the network generated by LEAP directly addresses the critical need to understand how biology manifests in clinical IPF. Analyzing the mechanisms shows that upstream genes, proteins and cell types converge through 68 pathological processes that are critical disease drivers in the network. These 68 pathological processes can be structured into 8 diseases signatures, including alveolar epithelial dysfunction, metabolic dysfunction, dysregulated growth pathways, epithelial-mesenchymal transition, fibroblast activation, chronic inflammation, pro-fibrotic signaling, and cellular senescence (Figure 2). Many of these core signatures are linked by shared pathological processes and individual mechanisms, but unique pathways also contribute to the formation of each. The resulting understanding of IPF pathology at multiple levels enables contextual investigation of therapeutic failures, like pamrevlumab, and identification of future hypotheses to pursue.

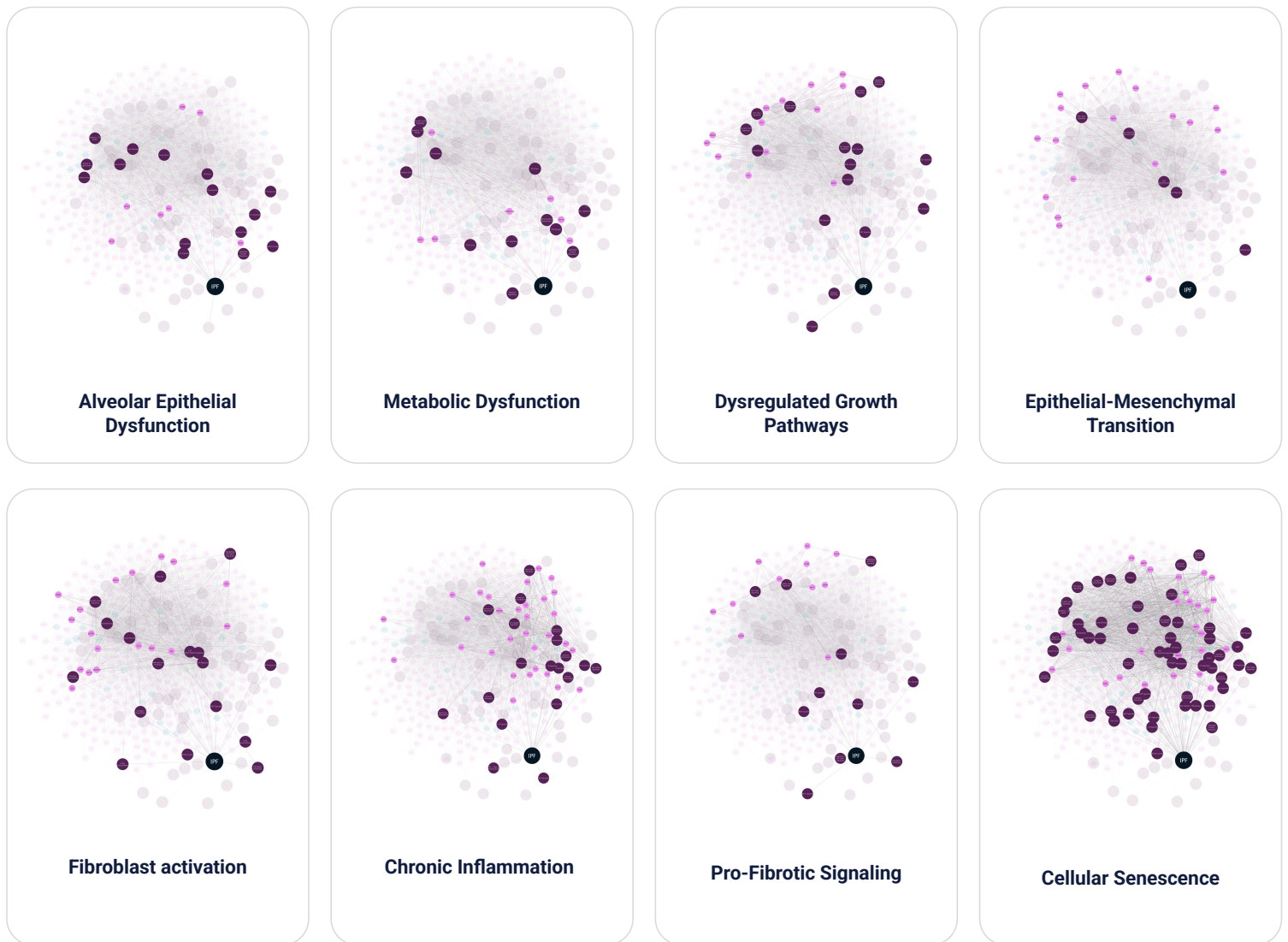


Figure 2. Schematic overview of the 8 disease signatures identified in IPF, represented as LEAP-generated knowledge graphs. The 68 identified pathological processes were grouped into 8 disease signatures with key upstream and downstream effects, determined by the LEAP mechanisms highlighted for each disease signatures to demonstrate the interplay between each.

IPF Disease NFKB1 Gene/Protein Cell Type Pathology/Pathway

Clinical Trial Setback: Assessing the Role of CTGF

Pamrevlumab is a monoclonal antibody that inhibits the pro-fibrotic glycoprotein, connective tissue growth factor (CTGF) [10]. Unexpectedly, it failed to meet primary and secondary endpoints in its Phase III trial (NCT04419558, NCT03955146) despite promising Phase II results (NCT01890265, NCT01262001) that corroborated its pre-clinical potential as an anti-fibrotic. The clinical failure of CTGF inhibition highlights the challenge of tackling IPF's complex interplay of pathologies.

A contextual analysis of CTGF inhibition within LEAP's understanding of IPF demonstrated that the CTGF inhibitor impacts only 35 of 68 (51%) identified pathological processes (Figure 3). While CTGF inhibition effectively targets pathways like fibroblast activation, EMT, and pro-fibrotic signaling, it leaves core disease signatures like chronic inflammation and cellular senescence largely unaffected (Figure 3b). Given the repeated failures of therapies targeting chronic inflammation [9, 11], the relatively uncharted territory of cellular senescence emerges as a promising avenue for future pursuit, either alone or in combination with anti-fibrotics.

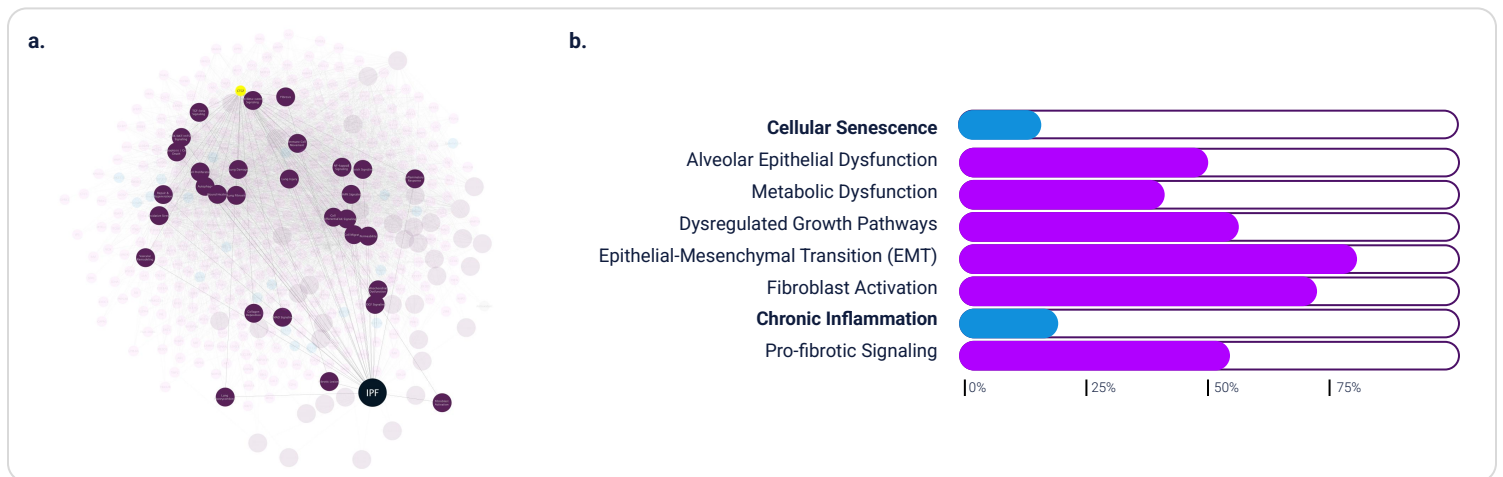


Figure 3. CTGF inhibition fails to fully mitigate all pathological processes in IPF. (a) LEAP-generated knowledge graph illustrating the subset of IPF processes susceptible to CTGF inhibition. (b) Proportional distribution of the pathological processes targeted by CTGF inhibition separated by pathogenic theme.

Cellular Senescence in IPF

Cellular senescence is a state of irreversible cell-cycle arrest triggered by various stressors. Although senescent cells cease proliferating, they remain metabolically active and undergo a significant phenotypic shift. This includes the development of the Senescence-Associated Secretory Phenotype (SASP), characterized by a complex secretome rich in pro-inflammatory cytokines and chemokines, growth factors, and proteases, which actively remodel the local tissue microenvironment and can drive pro-fibrotic and inflammatory disease signatures [12].

The insights generated by LEAP linked senescence to 55 of the 68 (81%) identified IPF pathological processes, primarily through secreted components (Figure 4). The depth of underlying connections between senescence and IPF marks this as a central driver of disease progression and indicates that therapies that don't tackle senescence are likely insufficient to effectively treat IPF. By leveraging this deep understanding of disease mechanisms and untargeted core disease signatures in IPF, LEAP's hypothesis generation capabilities next tackle the challenge of targeting areas of unmet therapeutic need.

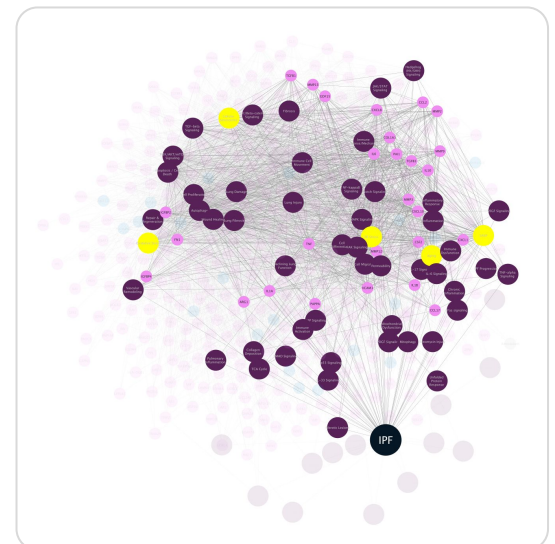


Figure 4. Cellular senescence is a significant component of IPF. LEAP-generated knowledge graph highlighting the 55 pathological processes linked to cellular senescence in IPF.

Translational Power of LEAP: Guiding IPF Therapy Post-Failure

Effective hypothesis generation is the creative driver of preclinical research, but critical insights are often fragmented across multiple resources. Integrating these insights is essential for fueling research advances. An additional commercial consideration is balancing confidence with novelty: Targets with extensive validation are low-risk but may only offer incremental therapeutic gains. Conversely, truly novel hypotheses offer breakthrough potential but are inherently high-risk, often lacking the strong evidential support needed to justify their pursuit. LEAP's ability to assess all possible hypotheses at scale, and provide metrics to inform this novelty-confidence axis, is key to its power for guiding future research effectively.

LEAP's analysis of IPF generated a variety of potential senescence-targeting mechanisms that spanned the spectrum from high confidence, well-established mechanisms, to those that are highly novel. Here, we explore two of these identified mechanisms, showcasing the trade-off between high confidence and high novelty in therapeutic (Figure 5). The first, a **high-confidence mechanism involving NOX4** (Hypothesis 1), scored highly on Relevance, Evidence, and Referencing, but low on Novelty, indicating a well-established mechanism. Specifically, LEAP's analysis shows that NOX4 is selectively upregulated in senescent fibroblasts, where its generation of reactive oxygen species (ROS) drives senescence [13-16]. Existing data in relevant contexts (including lung myofibroblasts) suggests that targeting NOX4 and thereby reducing pools of senescent cells may drive cells towards death. Further evidence supporting this hypothesis is provided by a recent Phase II clinical trial (NCT03865927), specifically targeting NOX1 and NOX4.

In contrast, LEAP additionally identified a **higher novelty mechanism involving the histone methyltransferase KMT2A (MLL1)** (Hypothesis 2). KMT2A catalyzes the histone modification H3K4me3, which then promotes the transcription of downstream genes like METTL3, driving cells towards senescence [17-23]. Therefore, targeting KMT2A's enzymatic activity may disrupt this cascade, blocking METTL3 expression and preventing senescence. The lack of a strong established connection to senescence, specifically in IPF, drives this mechanisms high novelty score, yet its connection to fibrosis and transcriptional targeting of key senescence regulators like METTL3 makes it a compelling hypothesis for further experimental investigation and validation.

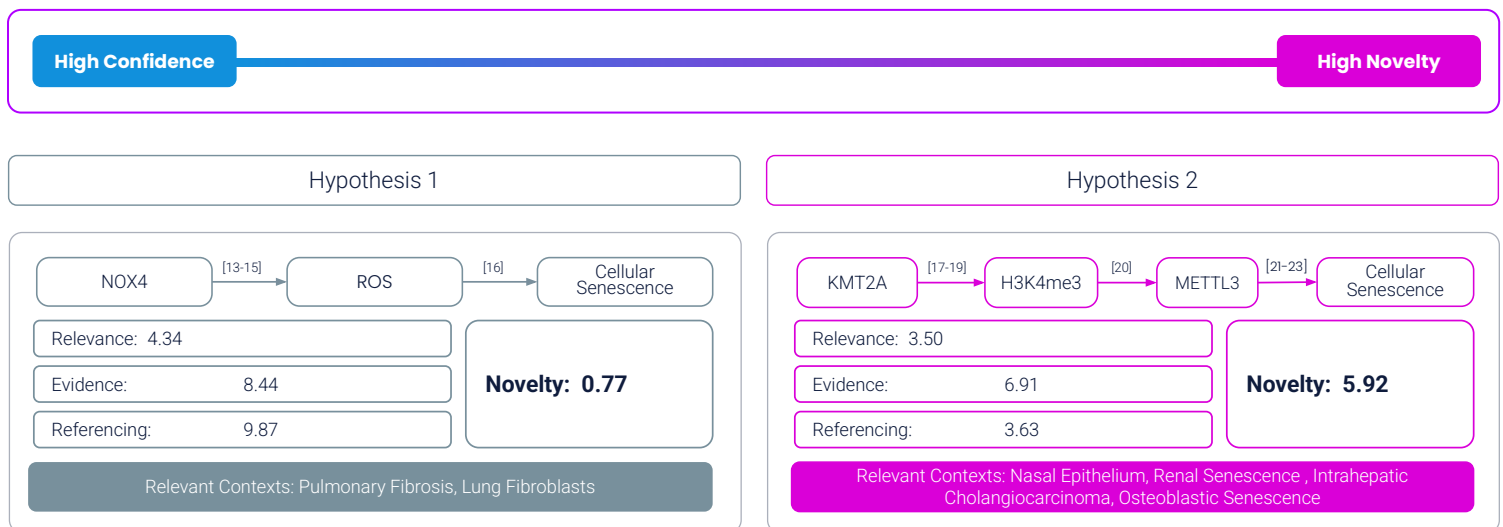


Figure 5. Schematic overview of the ranking of LEAP mechanisms. The LEAP ranking agent filters extensive query results by scoring each mechanism on four criteria: Relevance (mechanism-query alignment), Evidence (strength and quantity) and Referencing, which collectively indicate confidence in the hypothesis and are assessed alongside Novelty (indicates uniqueness of the mechanism). The high-confidence hypothesis 1 suggests NOX4 contributes to cellular senescence in pulmonary fibrosis through reactive oxygen species (ROS) production. In contrast, hypothesis 2 has higher novelty and proposes KMT2A catalyzes the histone modification H3K4me3 at the METTL3 gene, thereby activating its transcription and contributing to cellular senescence. The lower relevance score for hypothesis 2 is due to the lack of experimental evidence in an IPF context.

LEAP Supports Experimental Design for Hypothesis Validation

LEAP’s output extends beyond hypothesis generation; it produces a complete, actionable study design grounded in experimental evidence. The system proposes a series of experiments that rigorously test each component of a hypothesis as well as the mechanism as a whole. By analyzing experimental data captured from published figures using multimodal machine learning models, LEAP incorporates real experimental context into its study design recommendations. To assess the hypothesis that KMT2A drives cellular senescence in IPF, LEAP generated experiment details encompassing every aspect: the rationale, the appropriate experimental system (e.g., cell type), the specific positive and negative controls needed, and specific assays with their readouts (Figure 6). This automated generation of a complete, multi-step experimental design significantly accelerates the process of hypothesis validation in the research environment.

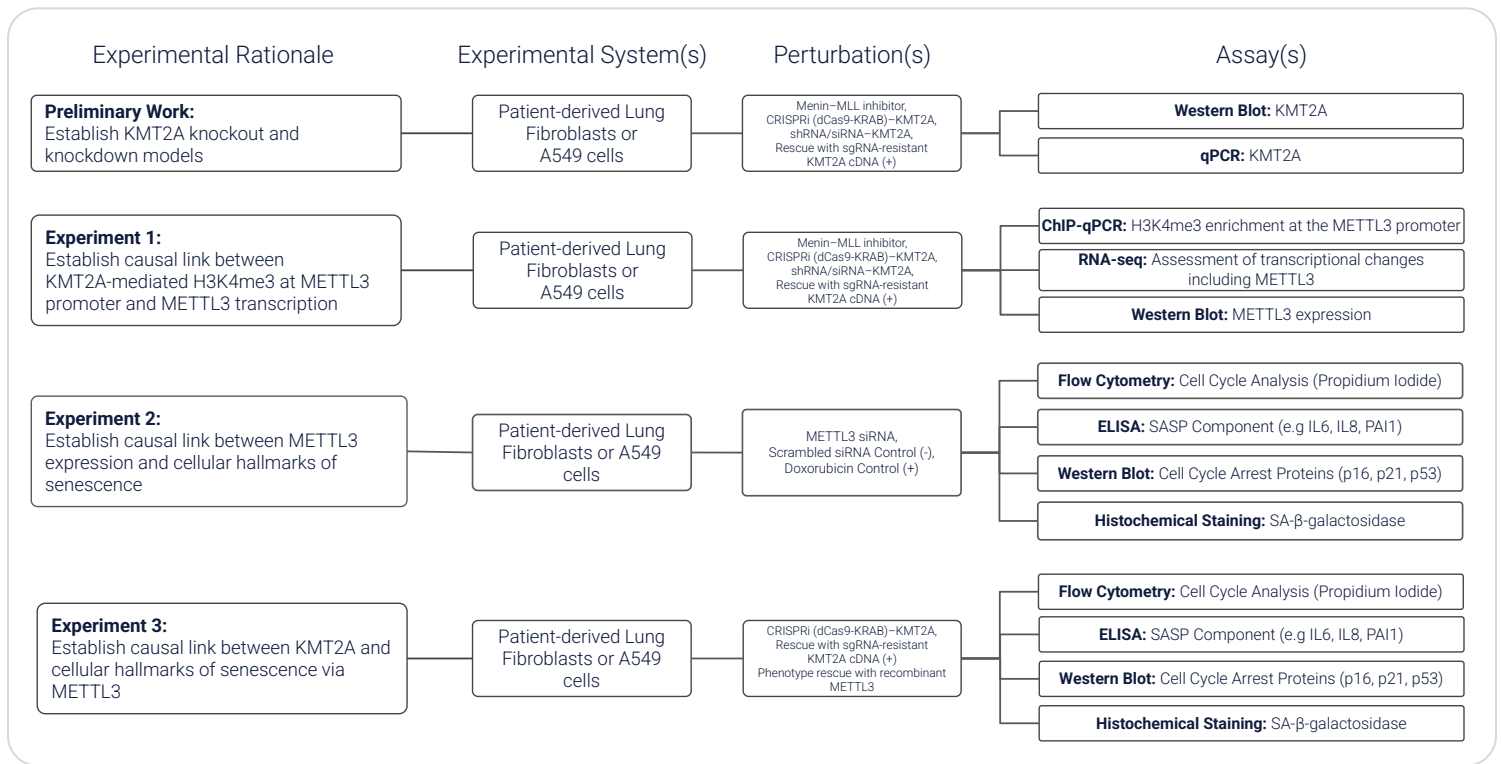


Figure 6. LEAP-generated study design for the KMT2A-METTL3-Senescence hypothesis. The experimental plan tests the hypothesis that KMT2A catalyzes the histone modification H3K4me3, leading to METTL3 transcription and subsequent cellular senescence in IPF lung fibroblasts. The study design outlines the required preliminary work (generation of *in vitro* KMT2A knockout/knockdown models) and proposes three critical validation steps: (i) linking KMT2A to METTL3 transcription and expression through H3K4me3, (ii) establishing METTL3’s causal role in senescence, and (iii) confirming the KMT2A causal link to senescence in lung fibroblast via METTL3.

Implications on Therapeutic Strategy in IPF

LEAP’s analysis, informed by an in-depth understanding of disease mechanisms and past therapeutic failures, strongly suggests that cellular senescence is a critical, under-addressed component of IPF pathology. Recognizing the interplay between heterogeneous disease components, LEAP strategically moves the field away from the ineffective single-target approach toward a systems-based approach, where IPF is treated as a combination of disease signatures. Current successful therapies apply this concept in a nonspecific manner (e.g., broad tyrosine kinase inhibition). By identifying key targets for each of the core IPF disease signatures, LEAP allows researchers to build a more effective, combination therapeutic strategy. The approach of mechanistically breaking down complex conditions is broadly applicable beyond IPF, with the potential to advance therapeutic strategies for other complex diseases.

The Therapeutic Landscape of IPF

Lack of Novel Therapeutics

To date, over 130 drugs targeting a wide variety of distinct molecular pathways have been evaluated in clinical trials as treatments for IPF [24]. These approaches have targeted various IPF disease signatures including fibrosis, inflammation, and immune dysregulation, via many different modalities. However, the multifactorial pathogenesis of IPF has hindered the success of these therapies and there have been many recent failures including pamrevlumab, bexotergast and TTI-101 [25].

Applying the same contextual analysis used to assess CTGF inhibition (Figure 3) to the 50 most well-characterized therapeutic targets (Figure 7) allowed us to broaden our understanding of the therapeutic landscape. This analysis showed that fibroblast activation and EMT are the most effectively targeted disease signatures, especially in comparison to chronic inflammation and cellular senescence. The current standard treatments, nintedanib and pirfenidone, have many targets including PDGFR, FGFR, VEGFR, TNF and TGFβ1. LEAP's analysis shows that this combination is able to modulate many of the observed pathologies (Figure 7), but this broad approach also contributes to the observed side effects and low tolerability in some patients [5, 7, 25]. Optimisation of pirfenidone to improve its tolerability is being explored, but this is unlikely to provide the step-change needed to dramatically impact patient outcomes [25]. Together this demonstrates that the shortcomings observed with CTGF inhibition are seen more broadly, with none of these individual targets able to specifically target the full breadth of the disease.

Implications on Therapeutic Strategy in IPF

Through LEAP's analysis of CTGF inhibition, cellular senescence was identified as a critical, under-addressed component of IPF pathology. Broadening that analysis demonstrated that even the best current therapies are unable to holistically tackle the disease with some components left untouched by all therapeutic approaches. This, therefore, suggests a strategic move away from these ineffective single-target approaches toward a systems-based approach where IPF is treated as a combination of pathologies. The most successful current therapies apply this concept in a non-specific manner (e.g., broad tyrosine kinase inhibition). However, through the identification of key targets for each of the core IPF disease signatures, LEAP can provide researchers with a strategy to find more effective, combination therapies.

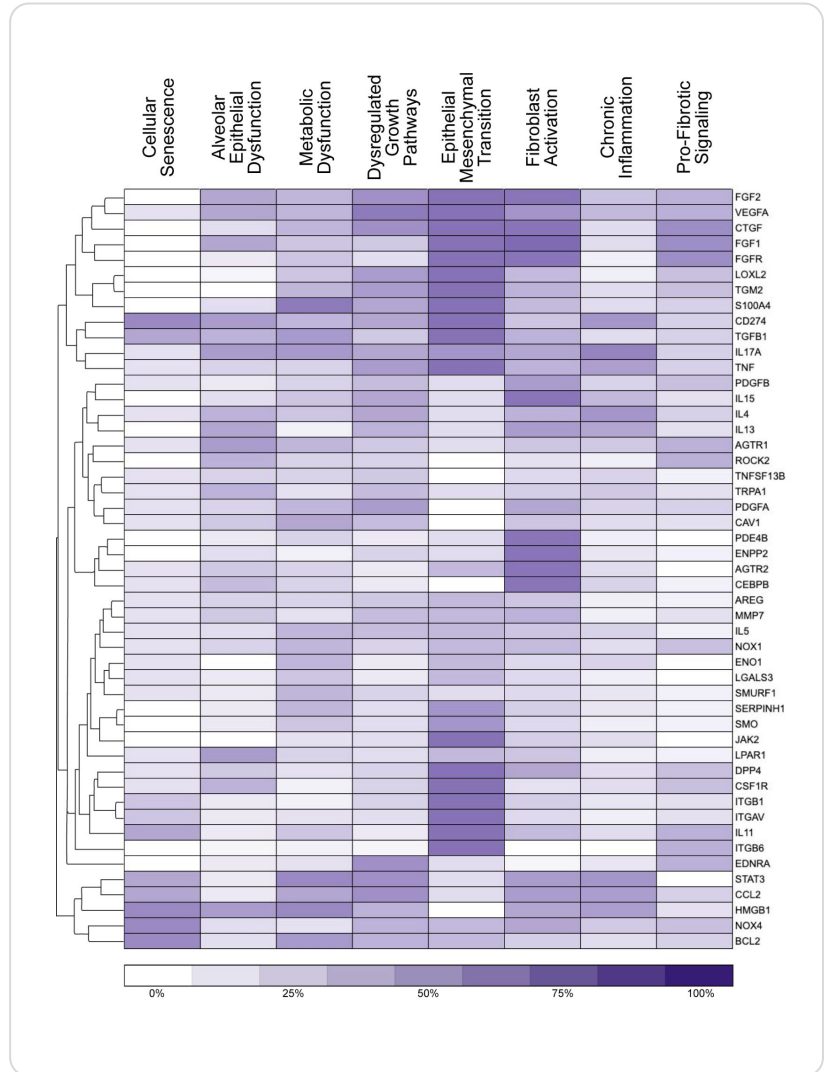


Figure 7. Heatmap illustrating the modulation of 8 IPF disease signatures by 50 therapeutic targets. Each cell quantifies the degree of modulation achieved by the targeted proteins evaluated in IPF clinical trials. Hierarchical clustering of targets was carried out using an unweighted pair group method with arithmetic means to enable visualisation of targets providing similar effects.

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