Idiopathic Pulmonary Fibrosis
Residual Unmet Need and Innovation

Idiopathic pulmonary fibrosis (IPF) is a non-neoplastic, chronic, progressive interstitial scarring of lungs which rapidly leads to respiratory failure and death. Its pathophysiology is not well understood but may occur due to an aberrant reparative response to repetitive alveolar epithelial injury in genetically susceptible ageing individuals. It is characterized by worsening cough, dyspnea, impaired quality of life (QoL), poor survival, and remains challenging to diagnose and manage. IPF is a diagnosis of exclusion and is based on the presence of a radiographic and/or histopathological pattern of usual interstitial pneumonia (UIP), in the absence of an alternate etiology for this pattern.

There are ~.25M IPF patients in the US, EU5, and Japan. More common in males, the median age of diagnosis is 65 years. The disease course is variable and unpredictable with ~50% mortality within 3-5 years of diagnosis. IPF is associated with multiple comorbidities such as coronary artery disease, pulmonary hypertension, emphysema, venous thromboembolic disease, lung cancer, gastroesophageal reflux disease, obstructive sleep apnea, diabetes mellitus, anxiety and depression.1-3 Two therapies – nintedanib and pirfenidone – are approved for mild-to-moderate IPF. They slow disease progression and have a beneficial effect on physiological deterioration of forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO) and progression free survival. These drugs do not reverse/stop lung fibrosis or provide a survival benefit. The only option for severe IPF is lung transplantation (LT), which may improve QoL and prolong survival.

Drug development in IPF continues to be challenging. Multiple assets including Simtuzumab (Gilead), Tralokinumab (AstraZeneca), GBT4404 (Global Blood Therapeutics), Lebrikizumab (Roche), SAR-156597 (Sanofi), Vismodegib (Roche), MK-7264 (Merck) and AEOL-10150 (Aeolus Pharmaceuticals) have either failed or been discontinued.2-4
<table>
<thead>
<tr>
<th>Asset</th>
<th>MoA</th>
<th>Company</th>
<th>Phase</th>
<th>Primary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART-123</td>
<td>Thrombin inhibitor</td>
<td>Asahi Kasei Pharma</td>
<td>III</td>
<td>Survival Rate</td>
</tr>
<tr>
<td>PRM-151</td>
<td>Fcγ receptors agonist</td>
<td>Promedior</td>
<td>III</td>
<td>Percent predicted change in FVC</td>
</tr>
<tr>
<td>Pamrevlumab</td>
<td>CTGF antagonist</td>
<td>FibroGen</td>
<td>III</td>
<td>Change in FVC</td>
</tr>
<tr>
<td>GLPG-1690</td>
<td>Autotaxin inhibitor</td>
<td>Galapagos</td>
<td>III</td>
<td>Rate of decline in FVC</td>
</tr>
<tr>
<td>PBI-4050</td>
<td>GPR40 stimulant + GPR84 inhibitor</td>
<td>ProMetic BioSciences</td>
<td>III</td>
<td>FVC</td>
</tr>
<tr>
<td>KD025</td>
<td>Rho-associated kinase 2 inhibitor</td>
<td>Kadmon Corporation</td>
<td>II</td>
<td>Change in FVC</td>
</tr>
<tr>
<td>Tipelukast</td>
<td>5-LO/LT+ PDE-3/4 + LOXL2 + TIMP-1 inhibitor</td>
<td>MediciNova</td>
<td>II</td>
<td>Change in FVC</td>
</tr>
<tr>
<td>TD-139</td>
<td>Galectin-3 antagonist</td>
<td>Galecto Biotech/BMS</td>
<td>II</td>
<td>Rate of decline in FVC</td>
</tr>
<tr>
<td>BG00011</td>
<td>Alpha v beta 6 integrin antagonist</td>
<td>Biogen</td>
<td>II</td>
<td>Rate of decline in FVC</td>
</tr>
<tr>
<td>GLPG-1205</td>
<td>GPR84 antagonist</td>
<td>Galapagos</td>
<td>II</td>
<td>Change in FVC</td>
</tr>
<tr>
<td>CC-90001</td>
<td>Mitogen-activated protein kinase 8 inhibitor</td>
<td>Celgene</td>
<td>II</td>
<td>Percent predicted change in FVC</td>
</tr>
<tr>
<td>Ianalumab</td>
<td>B-cell activator factor receptor antagonist</td>
<td>Novartis/MorphoSys</td>
<td>II</td>
<td>Change in FVC</td>
</tr>
<tr>
<td>TAS-115</td>
<td>Multi-kinase inhibitor</td>
<td>Taiho (Otsuka Holdings)</td>
<td>II</td>
<td>Change in FVC</td>
</tr>
</tbody>
</table>
Promising assets

- ART-123 (Thrombin inhibitor – Asahi Kasei Pharma) is currently in Phase III development in Japan and is the only asset that has shown reduction in mortality. In a non-randomized prospective, Phase II study for the treatment of acute exacerbation of IPF (AE-IPF), ART-123 demonstrated a statistically significant lower mortality rate of 36% at 90 days vs. 90% for the non-ART-123 group (Corticosteroid, Cyclophosphamide, Cyclosporine), (p = 0.023). The Phase III trial has been completed and results are awaited.

- KD025 (Rho-associated kinase 2 inhibitor – Kadmon Corporation), in a randomized, open-label, multicenter, Phase II study in IPF patients (NCT02688647), demonstrated a numerical decline in FVC of 50 mL at week 24 vs. a decline of 175 mL for patients receiving best supportive care.

- Pamrevlumab (CTGF antagonist – FibroGen), in a double-blind, placebo-controlled Phase II PRAISE study, (NCT01890265) demonstrated a statistically significant average decrease in FVC of 129 mL at week 48 vs. a decrease of 308 mL for placebo group (p = 0.0249).

Unmet needs in IPF

- **Effective and safe disease modifying therapies, especially for severe IPF**
  - Nintedanib and pirfenidone do not cure or reverse IPF
  - No approved drugs for severe IPF

- **Drugs to control cough**
  - Persistent cough is debilitating and refractory to standard antitussives

- **Drugs to prevent/reduce acute exacerbations (AE-IPF)**
  - AE-IPF occurs in ~20% of IPF patients and median survival after AE-IPF is 3-4 months

- **Validated diagnostic, prognostic, and predictive biomarkers specific to IPF**
  - ~50% of patients are initially misdiagnosed as symptoms may be similar to other respiratory diseases
  - Surgical lung biopsy is needed to confirm the diagnosis in patients with probable UIP/UIP indeterminate

- **Early diagnosis**, referral, and treatment improves outcomes, when lung function is still preserved

- **Significant impairment in quality of life due to:**
  - Fatigue, dyspnea, cough
  - Anxiety and depression
  - Pulmonary hypertension, COPD, lung cancer, ischemic heart disease, and gastro-esophageal reflux
  - Compromised exercise endurance and daily

**IPF is associated with a high mortality rate** - Median survival is 3-5 years
- Respiratory failure causes ~60% of deaths in IPF which may be attributed to AE-IPF (~30%), pneumonia (15%), or chronically progressive IPF (~10%)
- Cardiovascular causes result in ~20% of deaths and ~20% of IPF patients die due to other causes
- Only 5% of IPF patients receive a lung transplant, the only option for severe disease
  - Survival after LT is ~80% at 3 months, and 50% at 5 years
Innovation in IPF

**Combination therapies**

IPF has a rather complex pathogenesis. Multiple coactivated pathways interact and alveolar epithelial cells as well as fibroblasts are considered to be the key components responsible for the fibrosis. Combination therapies that target aberrant epithelial-mesenchymal cross talk, matrix deposition, and aberrant remodeling or highly pleiotropic drugs are likely to impact pulmonary fibrosis. Multiple pipeline assets such as PRM-151 ([Promedior](#)), PBI-4050 ([ProMetic Lifesciences](#)), GLPG 1205 and GLPG-1690 ([Galapagos](#)), and lanalumab ([Novartis/MorphoSys](#)) are being tested as add-on therapies to nintedanib or pirfenidone. Assets in development with pleiotropic effect include GKT831 ([GenKyoTex Suisse SA](#)), Tipelukast (5-LO/LT+ PDE-3/4 + LOXL2 + TIMP-1 inhibitor – [Medicinova](#)), Pemrevlumab (Connective tissue growth factor antagonist – [FibroGen](#)), and Ianalumab ([Novartis/MorphoSys](#)).

Multiple trials with combination protocols such as Lebrikizumab with pirfenidone; N-acetylcysteine (NAC) with pirfenidone; vismodegib with pirfenidone have either failed or been discontinued. Triple therapy with prednisone, azathioprine, and NAC has demonstrated harmful effects. Selection of combination therapies guided by genotype-stratified patient segments may be the way forward.\(^5\,10\,13\)

**Pharmacogenomics**

Personalized monotherapy approach based on individualized biomarkers, although appealing, may not have a desired impact on the fibrosis of IPF. However, such an approach could be utilized to combine highly specific therapies with pleiotropic drugs in add-on protocols. Novel strategies with pharmacogenomics include the use of NAC in MUC5b and TOLLIP genotypes. The potential benefit of NAC was observed in IPF patients with a specific TOLLIP genotype (TOLLIP rs3750920 TT) and not MUC5b genotype. Simultaneously, the study demonstrated harm in patients with TOLLIP CC genotype. Genotype-stratified prospective clinical trials could be considered among the future strategies to develop precision medicines for IPF patients.\(^5\,14\)

Unifying mechanism for fibrotic diseases

The pathophysiology of fibrotic diseases is not well-understood but transforming growth factor B (TGFβ), platelet-derived growth factor (PDGF), connective-tissue growth factor (CTGF), vasoactive peptide, integrin signaling, and increased tissue stiffness have been implicated. The fibrotic response is an important component of normal repair. Uncontrolled fibrotic response can lead to various fibrotic diseases.

It has been observed that these fibrotic disorders converge at the point of activation of the AP1 transcription factor c-JUN (a protein encoded by JUN gene in humans) in the pathologic fibroblasts. Induction of c-Jun in mice induces severe fibrosis in multiple organs and steatohepatosis, which is dependent on sustained c-Jun expression. c-Jun activates multiple signaling pathways in mice, including pAkt and CD47, which are also induced in human disease. αCD47 antibody treatment and VEGF or PI3K inhibition reverses c-Jun-mediated fibroses in vivo. These data suggest that c-JUN may be a central molecular mediator of most fibrotic conditions.

Wortmannin, a potent PI3K inhibitor, when systemically administered to mice that were induced to express c-Jun, resulted in complete suppression of bone marrow and skin fibrosis. Decreased proliferation of patient fibroblasts from fibrotic lungs after knockdown of c-JUN has also been observed. Activated c-Jun and Akt as well as upregulation of CD47 expression is observed in vivo in lungs with endstage fibrosis. Thus, c-Jun appears to be a key driver of organ fibrosis in most human fibrotic diseases. These observations may be used for preclinical evaluation of candidate antifibrotic therapies to develop common treatment strategies for various fibrotic diseases such as IPF, scleroderma, myelofibrosis, renal fibrosis, and NASH.\(^15\)

**Conclusion**

Efforts are underway to find a common link among the various fibrotic disorders, and the role of c-JUN activation in the propagation of fibrosis is a step in that direction. Even more encouraging is the reversal of fibrosis with...
inhibition of c-JUN. This may facilitate development of therapies that would arrest fibrosis regardless of the organ involvement. Drug development in IPF remains challenging and multiple trials either failed or were discontinued. Considering the high unmet need, drug development for this indication represents a key opportunity. The pipeline activity for IPF is robust with 16 assets in Phase I, 15 assets in Phase II and 5 assets in Phase III. If these assets are able to demonstrate significant efficacy, many more treatment options could be available in the near future. As multiple disease pathways are at work in IPF, a rational combination of therapies, likely to be effective in genetically predisposed individuals may be more successful than a monotherapy.

References

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15. Wernig G, et al., Unifying mechanism for different fibrotic diseases. PNA. 2017; 114(18): 4757-4762