Overview

Idiopathic pulmonary fibrosis (IPF) is a type of chronic lung disease characterized by a progressive and irreversible decline in lung function. It is a progressive and ultimately fatal disease that causes scarring and thickening of the lung tissue leading to respiratory failure.

The causes of IPF remains unknown; however, some risk factors include cigarette smoking, gastroesophageal reflux, specific environmental exposures, viral infection and age. A genetic predisposition may also be a factor. (Drugs R D. 2018 Mar; 18(1): 19–25.

IPF is believed to be the result of an aberrant wound healing process including/involving abnormal and excessive deposition of collagen (fibrosis) in the pulmonary interstitium with minimal associated inflammation.

Treatments

In recent years both Pirfenidone and Nintedanib have been approved for use in multiple countries for treatment of IPF. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an orally administered drug with antifibrotic, anti-inflammatory, and antioxidant effects as shown in preclinical studies (Core Evid. 2016; 11: 11–22) Nintedanib is a tyrosine kinase inhibitor. Both drugs have been shown to slow idiopathic pulmonary fibrosis progression and have an acceptable tolerability profile.

Despite the moderate success of Pirfenidone and Nintedanib, additional treatment options are needed and lung fibrosis remains a major unmet medical need.
Pre-clinical Research

Bleomycin-induced pulmonary fibrosis has been a useful pre-clinical model in several species and is most prevalent in rodent models to evaluate potential prophylactic and therapeutic drugs for IPF. As a tissue injury and repair model of fibrosis, bleomycin (BLM) has contributed significantly to studies of the pathobiology of pulmonary fibrosis. The induction and progression of the disease in rodents is of a short duration, making it a practical model for evaluating test compounds in preclinical research. Major drawbacks for this model have been its mortality rate and inconsistency in the induction of the disease.

Creation of Customized, Client-Specific Study Designs in Mouse Model for IPF

- **Study animals:** C57B/L6
- **Fibrosis induction:** Clinical grade bleomycin instilled via oropharyngeal route or osmotic pump
- **Duration:** Two to five weeks
- **Treatment:** Test compounds and/or Pirfenidone as positive control
- **Route of administration:** Oral

**Endpoint Analyses**

**Standard Readouts**

- Body weight
- Survival
- Lung weight
- Leukocyte count in bronchoalveolar lavage (BAL)

**Fibrotic Readouts**

- Lung hydroxyproline
- Serum/BAL fluid (BALF) soluble mediators
- Lung FibropanelTM Gene expression
- Lung fixation for histology (H&E and trichrome staining at third party CRO)

**Lung Function Measurements**

- flexiVent™
- Hypoxia related parameters (Real-time)
- Whole-body plethysmography (Real-time)

**Changes in Body Weight, Lung Weight, and Total Leukocytes in BALF (Day 21 post-bleo)**

- Bleomycin instillation causes body weight loss and an increase in lung weight.
- Total leukocytes counts increase with bleomycin instillation.
- Pirfenidone treatment improves lung weight and total leukocytes counts.
**Case Study 1: Differential Analysis of Infiltrating Leukocytes from BAL Harvest plus Changes in Histology**

- Bleomycin instillation results in increased lung leukocyte counts on Day 21.
- In Bleomycin-induced animals, Pirfenidone decreases lung leukocyte counts by Day 21.
- Bleomycin instillation results in increased Ashcroft scores.
- In Bleomycin-instilled animals, improvement in lung pathology scores is observed upon Perfinidone treatment.

**Case Study 2: Changes in Lung Function in Bleomycin-Induced IPF**

- FlexiVent analysis demonstrates that bleomycin instillation results in increased resistance, increased elastance and decreased compliance.
- Bleomycin treatment results in decreased O2 saturation levels.
- Pirfenidone improves lung function.
**Case Study 3: Efficacy of a Small Molecule Compound in Bleomycin-Induced IPF**

- Therapeutic Study: Bleomycin on day 0 with compound treatment on days 7-21 (oral QD).
- Test compound reduces Bleomycin-induced increase in lung weights and leukocyte counts.

**Case Study 3: Consistency of Fibrotic Induction in Lungs from Multiple Studies**

- Histology is performed by outside specialists in a blinded manner.
- Highly reproducible and consistent fibrotic induction in lungs from multiple studies allows robust evaluation of candidate drugs.
Summary and Conclusion

Evaluation of new drugs, either small molecule or biologics requires robust and reliable re-clinical animal models. Aragen Bioscience has a portfolio of in vivo fibrosis models, we offer customised and high quality animal models with ex vivo readouts to support our clients anti-fibrosis drug development. The model described above has also been established in client-provided transgenic animals as well as in rats. In hundreds of studies over the course of a decade, we have evaluated the efficacy of small molecules and biologic test compounds in a variety of models, ultimately resulting in multiple INDs for our clients.

About Aragen Bioscience, Inc.

Aragen is a leading contract research organization based in the San Francisco Bay Area. Aragen Life Sciences offers a diverse set of In Vitro and In Vivo services for the discovery, characterization, activity assessment and early development of biologic and diagnostic products.

Our range of other fibrosis models:
- Lung fibrosis model in C57BL/6 mice
- Silica-induced lung fibrosis model in mice
- CCL4 induced liver fibrosis in mice
- Dermal fibrosis in a scleroderma mouse model
- TAA-induced liver fibrosis in rats
- The Unilateral Ureter Obstruction(UUO) model studies for kidney disease

To know more contact us at: info@aragen.com