**Chitotriosidase (CHIT1) as a Novel Therapeutic Target in Idiopathic Pulmonary Fibrosis (IPF)**

Chitotriosidase (CHIT1) and Acidic Mammalian Chitinase (AMCase) are enzymatically active chitinases, which have been implicated in the pathology of chronic interstitial lung diseases (ILDs) e.g., IPF, COPD, sarcoidosis and others. CHIT1 has been reported to be the main chitinase present in the human lungs - both its expression and activity are strongly induced in patients with ILDs and often correlate with disease stage and progression. Genetic and pharmacological studies in animal models of chronic lung diseases confirmed a critical role of CHIT1 in lung remodeling and fibrosis. Together, the clinical and preclinical data suggest that pharmacological inhibition of CHIT1 might represent a novel therapeutic approach in IPF. In this context, we have developed OATD-01, the first-in-class, potent chitinase inhibitor, currently in phase 1 clinical trials.

**CHIT1 PROFILE IN IDIOPATHIC PULMONARY FIBROSIS (IPF)**

Chitinolytic activity in serum and induced sputum samples (n = 16) is significantly increased as compared to healthy controls (n = 30).

CHIT1 was reported to be significantly upregulated in IPF lungs (n = 119) vs. healthy lungs (n = 50) (Fan L. et al. Mediators Inflamm. 2017, Microarray ID: GSE32537).

Moreover, CHIT1 is mostly localized in lung macrophages in IPF lungs. Overall, 78% of all BALf cells were positive for CHIT1 in IPF patients (n = 10). Cytological analysis showed that the main subtype of CHIT1-positive cells in BALf are macrophages (83%) positive cells in IPF.

**CHIT1 EXPRESSION IS SPECIFIC TO PRO-FIBROTIC MACROPHAGES IN IPF LUNGS**

Single cell RNA sequencing of donor vs. IPF lungs

Reyfman PA et al. (AJRCCM 2018) identified a distinct, novel population of profibrotic alveolar macrophages exclusively in patients with pulmonary fibrosis. We interrogated publicly available web-based tool to determine CHIT1 expression in donor vs IPF lungs [nuipulmonary.org/resources]

**ROLE OF CHIT1 DEFICIENCY IN PULMONARY FIBROSIS IN MICE**

CHIT1 wild-type (WT) and knockout (KO) mice (n = 12) were subjected to bleomycin injury via the orotracheal instillation (0.25 U/kg, d0-d2). CHIT1 deficiency significantly reduced lung fibrosis, as assessed by the modified Ashcroft scoring system. This correlated with a reduction of the infiltration of CD45-positive myeloid cells as compared to the CHIT1 WT animals administered with bleomycin.

**THERAPEUTIC EFFICACY OF OATD-01 IN BLEOMYCIN INDUCED PULMONARY FIBROSIS**

OATD-01 administered in a therapeutic regimen, from day 7 after the first bleomycin dose, produced a strong pharmacodynamic effect in plasma.

OATD-01 has favorable PK/PD profile in mice after oral dosing. Selected scheme of treatment provided full target inhibition (chitinolytic activity) for 20h after a single dose.

OATD-01 significantly reduced lung fibrosis, comparably to pirfenidone, as assessed by the modified Ashcroft scoring system (n=12). This correlated with a significant reduction of the lung to body weight ratio.

**CONCLUSIONS**

- Elevated CHIT1 activity in IPF patients
- CHIT1 is expressed in pro-fibrotic, IPF-specific macrophages in lungs
- CHIT1 deficiency reduced pulmonary fibrosis in mice
- OATD-01, a potent, oral CHIT1 inhibitor reduced lung fibrosis comparably to pirfenidone in the mouse model of IPF
- OATD-01 currently in clinical phase Ia
- ODD for IPF was granted by FDA in 2019