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

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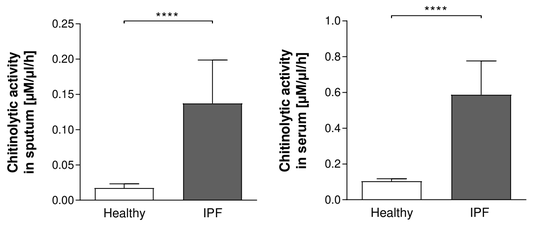
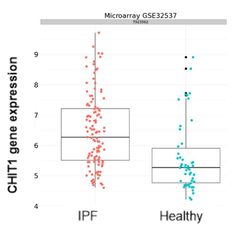
BACKGROUND

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.

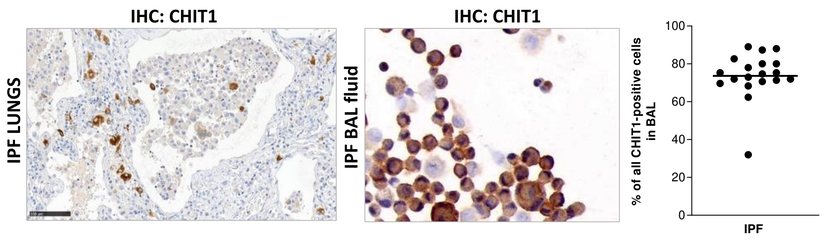
CHIT1 PROFILE IN IDIOPATHIC PULMONARY FIBROSIS (IPF)





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).**



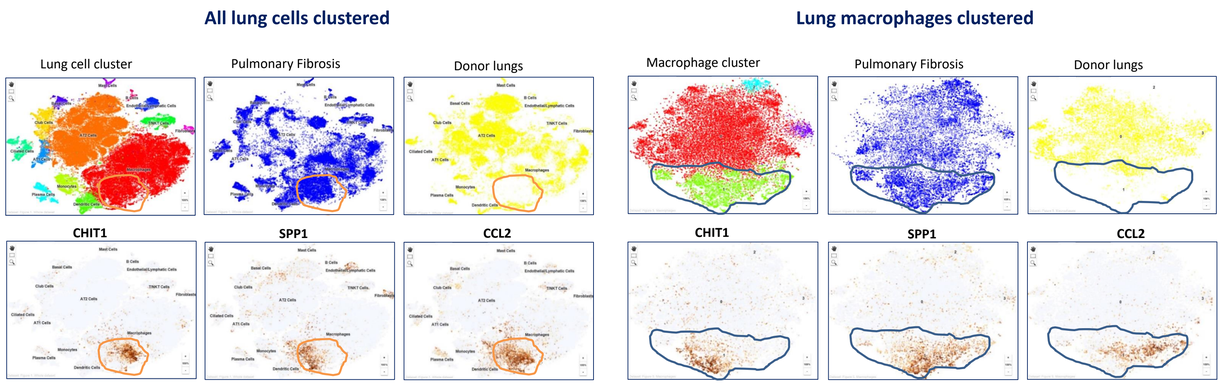
Moreover, CHIT1 is mostly localized in lung macrophages in IPF lungs.

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* 2019) 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 (nupulmonary.org/resources.)



CHIT1 expression was restricted to IPF lungs
Found only in pulmonary macrophages
CHIT1 coexpresses with SPP1 and CCL2 in IPF specific macrophages

CHIT1 is expressed exclusively in a subset of emerging fibrosis-specific macrophages
CHIT1 is one of most representative genes for this fibrotic macrophage population

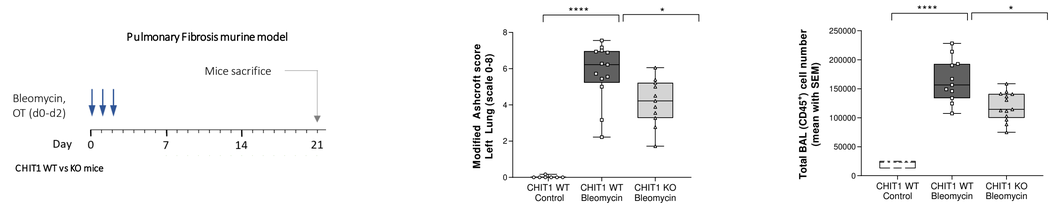
FINANCIAL SUPPORT

European Funds Smart Growth

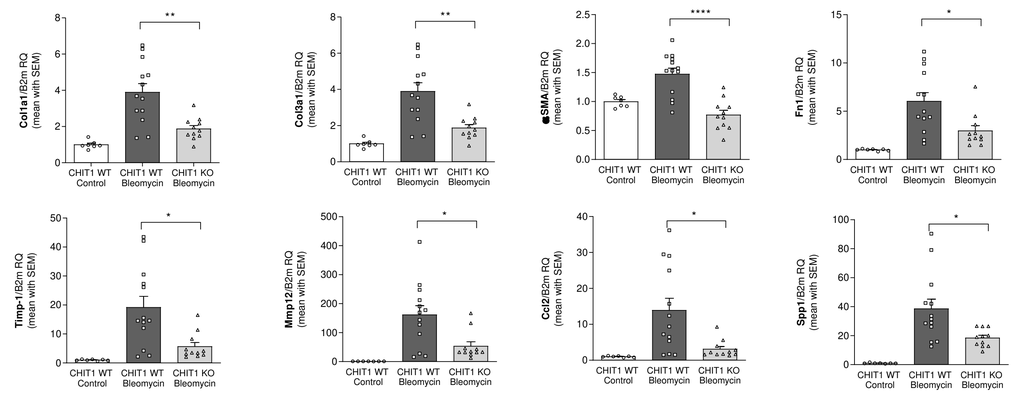
„ Development of a first-in-class small molecule drug candidate for treatment of idiopathic pulmonary fibrosis through chitotriosidase inhibition"

European Union
European Regional Development Fund

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.

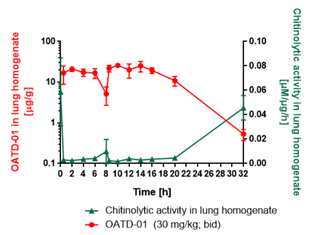


CHIT1 inactivation *in vivo* strongly decreased expression of multiple profibrotic genes in lungs as compared to CHIT1 WT mice; including Collagen 1 (**Col1a1**), Collagen 3 (**Col3a1**), alpha smooth muscle actin (**αSMA**), fibronectin 1 (**Fn1**), **Timp-1** and **Mmp12**. Moreover we observed that lack of CHIT1 significantly reduced osteopontin (**Spp1**) and the chemokine (C-C motif) ligand 2 (**Ccl2**), markers of profibrotic macrophages in human IPF.

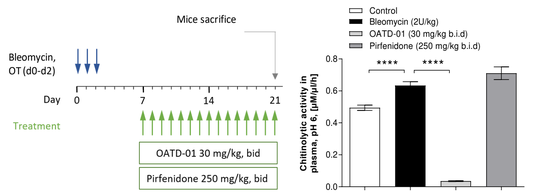
THERAPEUTIC EFFICACY OF OATD-01 IN BLEOMYCIN INDUCED PULMONARY FIBROSIS

OATD-01 activity		IC_{50}
Recombinant enzymes	hCHIT1	23.4 nM
	hAMCase	9.6 nM
	mCHIT1	27.5 nM
	mAMCase	7.9 nM
Human IPF samples	Serum	16 ± 4 nM
	Induced sputum	15.5 ± 0.7 nM
	BAL fluid	11 ± 10 nM

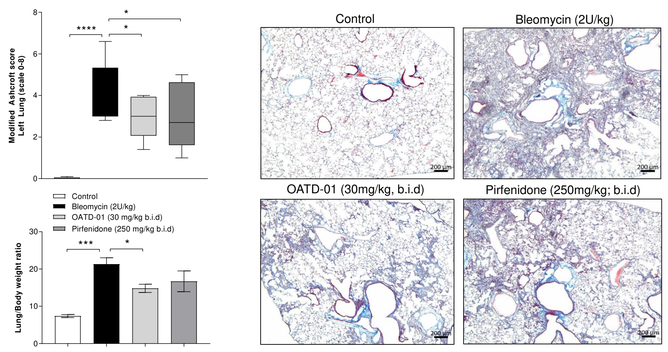
OATD-01 is a potent, CHIT1 small-molecule inhibitor, which strongly inhibited elevated chitinolytic activity in biological fluids collected from IPF patients.



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



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 Ib
- **ODD for IPF was granted by FDA in 2019**