CHIT1 is a novel therapeutic target in IPF: anti-fibrotic efficacy of OATD-01, a potent and selective chitinase inhibitor, in the mouse model of pulmonary fibrosis

Barbara Dymek

I have no real or perceived conflicts of interest that relate to this presentation.

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CHIT1 - structure and function

Chitotriosidase (CHIT1) is a member of the GH18 family of chitinases which consists of enzymatically active hydrolases, CHIT1 and AMCase, and enzymatically non-active chitinase-like proteins (YKL-40, YKL-39, oviductin).

Evolutionary CHIT1 confers protection against chitin-containing pathogens. However, in humans, it has been implicated in pathology of multiple inflammatory and fibrotic diseases (IPF, sarcoidosis, COPD) where it is highly induced and associated with disease progression. The exact mode of action of CHIT1 remains to be elucidated.

CHIT1 protein structure

Faras F, 2015
Targeting CHIT1 in interstitial lung diseases: rationale

Human:
• CHIT1 gene expression is significantly upregulated in lungs of IPF patients as compared to healthy subjects. Data extracted from the study GSE32537 (IPF n=119; Control n=50). (Yang IV, 2013)
• CHIT1 activity is elevated in BAL and serum of patients with interstitial lung diseases e.g. IPF, systemic sclerosis-associated lung fibrosis and sarcoidosis. (Bargagli E, 2007, Lee CG, 2012)
• CHIT1 activity in serum of sarcoidosis patients correlates with a disease stage and clinical prognosis and is considered the best biomarker of disease progression. (Boot R, 2010)

Mouse:
• Lung fibrosis induced by bleomycin is enhanced in transgenic mice over-expressing CHIT1 and is reduced in CHIT1 knockout mice. (Lee CG, 2012)
CHIT1 activity is elevated in ILDs (IPF and sarcoidosis)

The analysis of chitinolytic activity in samples collected from patients demonstrate significantly increased chitinolytic activity in serum and in induced sputum in patients with IPF and sarcoidosis when compared to normal controls.

These results are in accordance with the published data.

In collaboration with Medical University of Warsaw
CHIT1 is expressed in macrophages and lymphocytes in BALf from IPF patients

77% of all BALf cells in IPF (n=8) express CHIT1. Cytological analysis demonstrated that macrophages (83% positive) and lymphocytes (51%) are the main cell subtypes expressing CHIT1.
OATD-01: the first chitinase inhibitor in clinical development

• OATD-01 is a highly potent, dual AMCase and CHIT1 small-molecule inhibitor with a nanomolar activity.

<table>
<thead>
<tr>
<th></th>
<th>hAMCase</th>
<th>hCHIT1</th>
<th>mAMCase</th>
<th>mCHIT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>OATD-01 IC$_{50}$ [nM]</td>
<td>9.2</td>
<td>23.4</td>
<td>7.8</td>
<td>27.5</td>
</tr>
</tbody>
</table>

• OATD-01 demonstrated a strong anti-inflammatory and anti-remodeling activity in animal models of airway inflammation induced by house dust mite (HDM)

• OATD-01 completed Phase Ia clinical studies (single ascending dose in healthy volunteers)
  o No serious adverse effects and no withdrawals due to AEs reported
  o Favorable PK profile, appropriate for oral, once-a-day dosing
  o Results presented at ERS congress (late-breaking abstract "Phase 1, first-in-human study of OATD-01, a dual chitinase inhibitor for the treatment of respiratory diseases", Sep 19th, 8:30)

• Enrolment for Phase Ib MAD study to start in Q4 2018
OATD-01 has a favorable pharmacokinetic profile in mice suitable for once- or twice-a-day oral dosing regimen in mice.

**OATD-01 Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Route</th>
<th>IV</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg/kg)</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>C0 or Cmax (mg/L)</td>
<td>3.97</td>
<td>3.42</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>n/a</td>
<td>2.0</td>
</tr>
<tr>
<td>CL (mL/min/kg)</td>
<td>5.8</td>
<td>n/a</td>
</tr>
<tr>
<td>Vss (L/kg)</td>
<td>1.01</td>
<td>n/a</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>2.09</td>
<td>1.88</td>
</tr>
<tr>
<td>Bioavailability (F%)</td>
<td>n/a</td>
<td>77%</td>
</tr>
</tbody>
</table>
CHIT1 is upregulated in the lungs in the bleomycin-induced pulmonary fibrosis model and localizes to fibrotic lesions.
OATD-01 administered once or twice a day led to a significant inhibition of chitinolytic activity (PD marker) in lung homogenates for 24h confirming the extended pharmacodynamic activity in lungs.
OATD-01 efficacy in lung fibrosis model: comparison with pirfenidone

- 21-day-long mouse model of pulmonary fibrosis induced by triple intranasal administrations of bleomycin
- Therapeutic scheme of treatment: oral bid administration of OATD-01 and pirfenidone starting at day 7
- Lung fibrosis assessed at day 21
OATD-01 efficacy in lung fibrosis model: comparison with pirfenidone

OATD-01 exhibited significant anti-fibrotic activity, comparable to pirfenidone, as assessed by the modified Ashcroft scale.
The significant reduction in Ashcroft score and in lung weight following OATD-01 administration was associated with suppression of the bleomycin-induced chitinolytic activity in plasma (4h after last dose) confirming target engagement.
OATD-01 efficacy in lung fibrosis model: comparison with nintedanib

- 21-day-long mouse model of pulmonary fibrosis induced by a single intratracheal administrations of bleomycin
- Therapeutic scheme of treatment starting at day 7; oral administration of OATD-01 and nintedanib once-a-day
- Lung fibrosis assessed at day 21
- Independent study – performed at CRO
OATD-01 efficacy in lung fibrosis model: comparison with nintedanib

OATD-01 dosed orally at 100 mg/kg qd demonstrated strong antifibrotic efficacy comparable to nintedanib

Significant, dose-dependent inhibition of chitinolytic activity in plasma was observed 24h after the last dose of OATD-01 confirming its extended PD activity.
➢ CHIT1 activity is elevated in serum and induced sputum of IPF patients and it is a potential novel therapeutic target in IPF

➢ OATD-01 is a potent, selective, orally active small-molecule inhibitor of chitinases that is currently in the phase I clinical trials

➢ OATD-01 demonstrated strong therapeutic efficacy, comparable to pirfenidone and nintedanib, in the bleomycin-induced mouse model of pulmonary fibrosis
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