Chitotriosidase Inhibitor OATD-01 as a Potential Therapeutic Agent for Treatment of Inflamatory and Fibrotic Diseases

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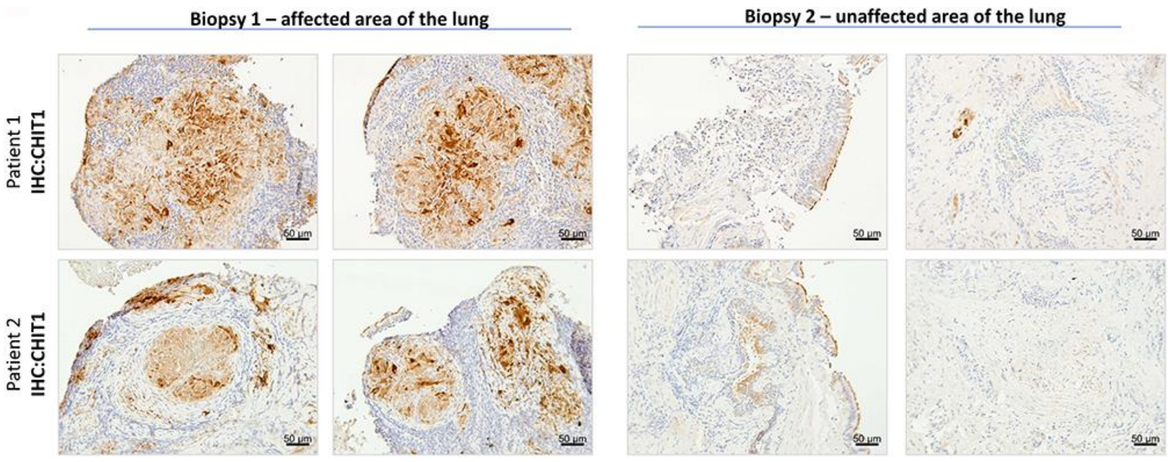
Therapeutic target

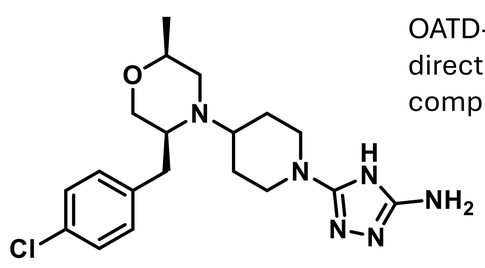
Chitinase-1 (CHIT1) is an activated macrophage-specific enzyme implicated in pathology of several disorders where chronic inflammation leads to tissue remodelling. CHIT1 expression and activity correlates with severity and progression of many of these disorders. Specifically in lung sarcoidosis for which multicenter, randomized, double-blinded PoC Phase II study „KITE" is currently conducted.



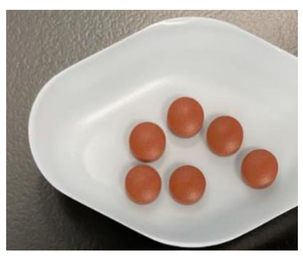
Pathological macrophages are a source of CHIT1 in lung sarcoidosis.
J Inflamm Res. 2022 Sep 29;15:5621-5634.

OATD-01 – first-in-class CHIT1 inhibitor

ın vivo efficacy of OATD-01 was demonstrated in several models of inflammatory diseases such as chronic and acute asthma, inflammatory bowel disease, idiopathic pulmonary fibrosis, and MASH. Importantly, data from in vivo studies showed that OATD-01, administered in the therapeutic mode, demonstrated efficacy in a process of fibrosis reversal. OATD-01 has been so far administered to 129 healthy volunteers, as single (up to 600 mg) or multiple (up to 50 mg/day) doses, in four Phase 1 clinical studies (two dose escalation and two drug-drug interaction studies). At doses of 25 to 50 mg/day, at steady-state, the total time with the inhibition of the plasma chitinolytic activity of >80% was maintained for 24h.



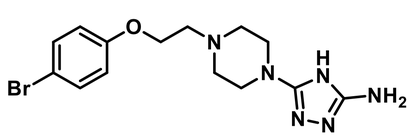
OATD-01 is a once-a-day, direct compression tablet for compliance and ease of use



25 mg FC tablets

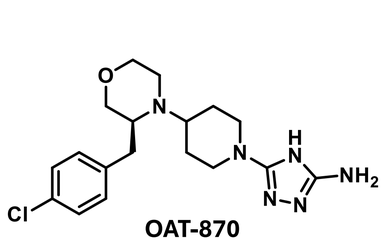
SAR Study

In the course of our program over 2500 compounds have been designed and synthesized, starting from Wyeth-1 and resulting in OAT-870 as our advanced lead compound. Further optimization of drug-like properties and selectivity of OAT-870 yielded a clinical candidate OATD-01. The compound bears an additional methyl group at the morpholine ring, which abrogated undesired off-target activity towards dopamine transporter (DAT).



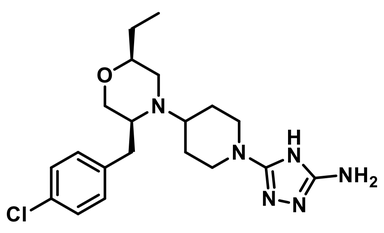
Wyeth-1
Starting point

hAMCase	IC_{50} = 5.4 µM
hCHIT1	IC_{50} = 6.8 µM
mAMCase	IC_{50} = 2.3 µM
Mchit1	IC_{50} = 19.7 µM

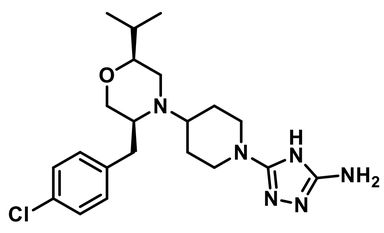


OAT-870

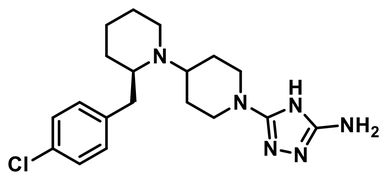
hAMCase	IC_{50} = 24 nM
hCHIT1	IC_{50} = 47 nM
mAMCase	IC_{50} = 20 nM
mCHIT1	IC_{50} = 77 nM
DAT	94% inh. at 10 mM



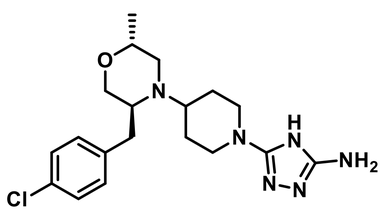
hAMCase	IC_{50} = 54 nM
hCHIT1	IC_{50} = 14 nM
mAMCase	IC_{50} = 1 nM
mCHIT1	IC_{50} = 14 nM



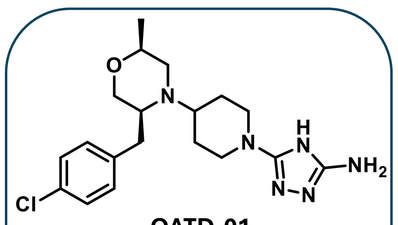
hAMCase	IC_{50} = 3 nM
hCHIT1	IC_{50} = 18 nM
mAMCase	IC_{50} = 2 nM
mCHIT1	IC_{50} = 19 nM
DAT	34% inh. at 10 mM



hAMCase	IC_{50} = 23 nM
hCHIT1	IC_{50} = 52 nM
mAMCase	IC_{50} = 111 nM
mCHIT1	IC_{50} = 87 nM



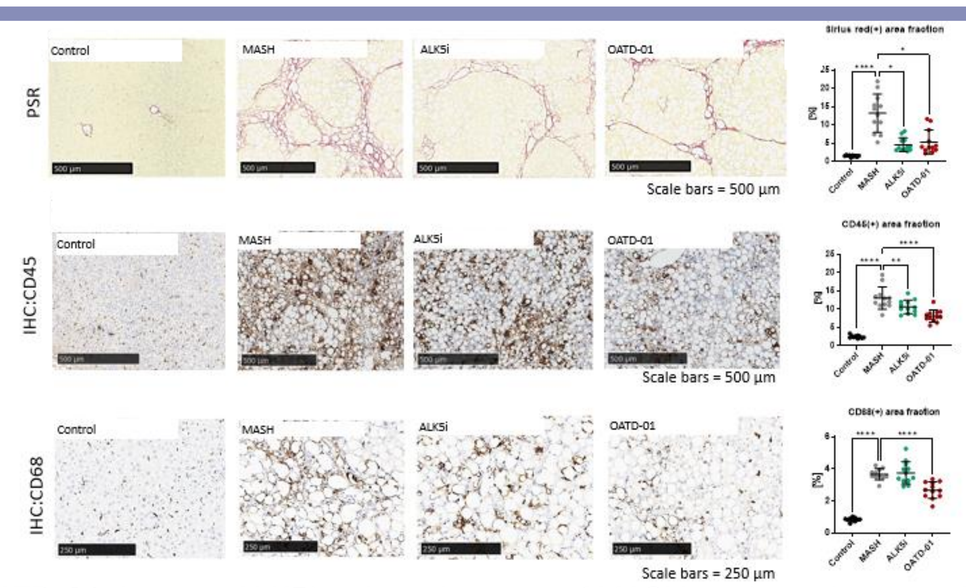
hAMCase	IC_{50} = 826 nM
hCHIT1	IC_{50} = 5100 nM
mAMCase	IC_{50} = 1000 nM
mCHIT1	IC_{50} = 6400 nM



OATD-01

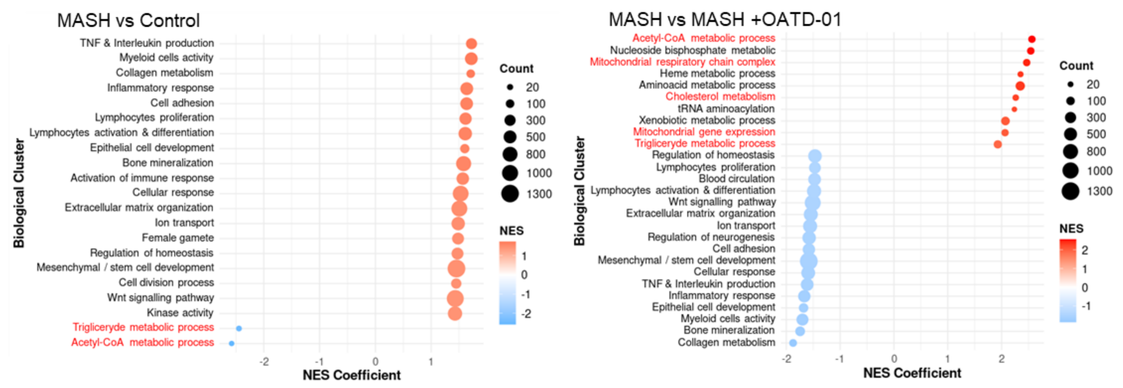
hAMCase	IC_{50} = 9 nM
hCHIT1	IC_{50} = 23 nM
mAMCase	IC_{50} = 8 nM
mCHIT1	IC_{50} = 28 nM
DAT	IA

OATD-01 demonstrates efficacy in MASH model

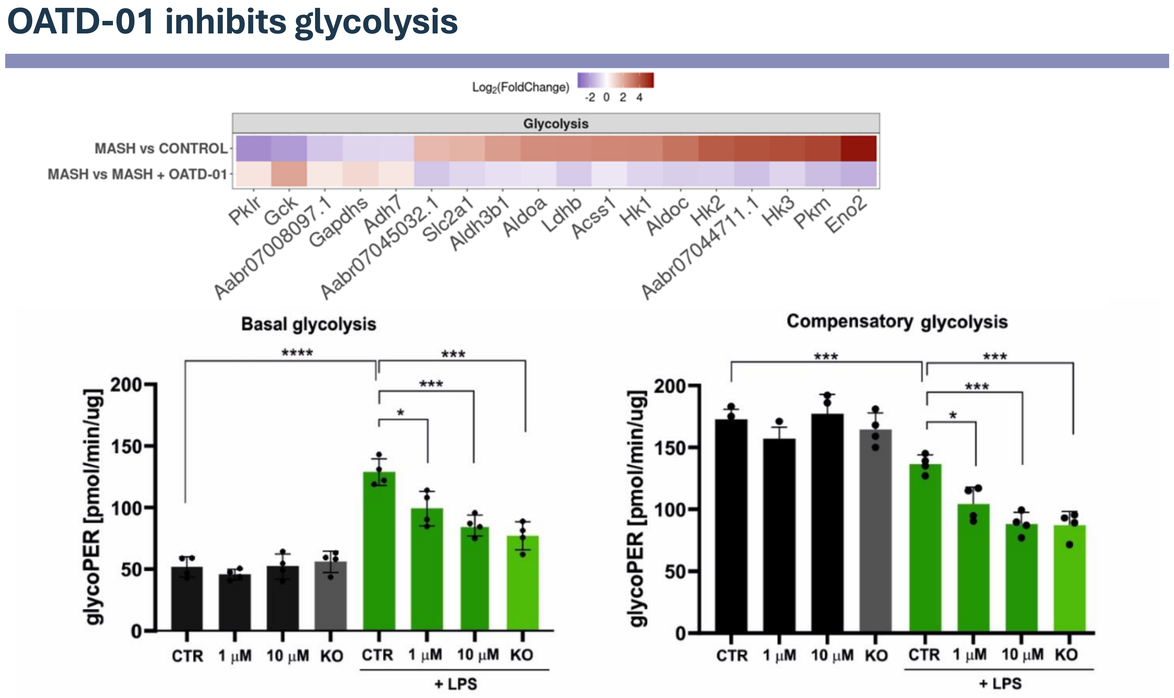


OATD-01, but not ALK5i reduced numer of MASH-activated macrophages

Most OATD-01-regulated processes involve metabolism

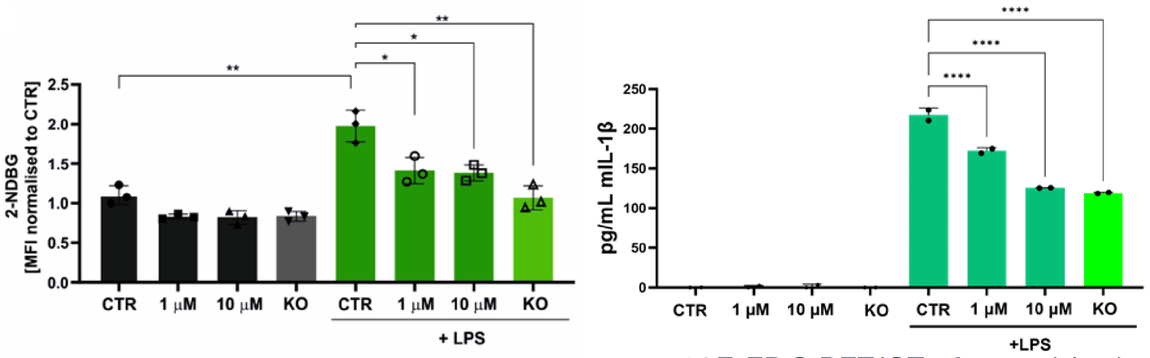


OATD-01 inhibits glycolysis



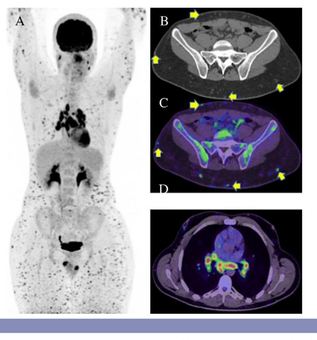
OATD-01 reduces glycolysis in 48h LPS-stimulated BMDMs

OATD-01 inhibits glucose uptake and IL-1β production



18F-FDG PET/CT of sarcoidosis

Primary endpoint in the study will be [18F]FDG-PET/CT.
Study population involves male and female subjects with active pulmonary sarcoidosis, treatment-naïve or currently untreated, no recruitment cap.



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Studies were supported by project: "„ Development of a first-in-class small molecule drug candidate for treatment of idiopathic pulmonary fibrosis through chitotriosidase inhibition" (POIR.01.01.01-00-0551/15), cofinanced by the European Union in the framework of European Funds Smart Growth and European Regional Development Fund.

European Funds Smart Growth
European Union European Regional Development Fund

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European Funds Smart Growth
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The National Centre for Research and Development

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THE KITE STUDY