DISCOVERY OF AN ADVANCED DUAL CHITINASE INHIBITOR OAT-870: A NEW POTENTIAL THERAPEUTIC IN THERAPY OF LUNG DISEASES

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INTRODUCTION
Chitotriosidase (CHIT1) and acidic mammalian chitinase (AMCase) are the enzymatically active chitinases. They belong to the family of glycosidases including several chitinase-like proteins (CLPs) which lack the ability to degrade chitin⁴.

It has been shown that elevated CHIT1 levels and activity were found in the plasma and bronchoalveolar lavage (BAL) fluid from patients suffering from orphan lung diseases (i.e., idiopathic pulmonary fibrosis—IPF or sarcoidosis)⁴.

Given these observations we decided to design and prepare small-molecule chitinase inhibitors which would constitute a new class of orally administered therapeutics targeting the aforementioned lung diseases. Modification of the previously discovered in our laboratory OAT-870 led us to discovery of a potent dual chitinase inhibitor OAT-870⁴.

STRUCTURAL ACTIVITY RELATIONSHIP STUDY
Cyclisation to 3-substituted pyrrolidine

Replacement of piperidine with more polar ring

SYNTHESIS OF OAT-870

OAT-870 is a potent dual AMCase and CHIT1 inhibitor with very good pharmacokinetic profile. Significant anti-inflammatory effect in HDM-induced airway inflammation model in mice was observed when dosing once daily (50 mg/kg).

Flow cytometry analysis of total infiltrating leukocyte numbers in BAL recovered from mice challenged with PBS or HDM with or without OAT-870 (50 mg/kg; IP; qd) or after dexamethasone (10 mg/kg, IP, qd) dosed in therapeutic regimen was performed.

Oral administration of OAT-870 exhibited a significant reduction (37 %) of CD45-positive leukocytes influx into the lungs.

CONCLUSIONS

OAT-870 is a potential dual AMCase and CHIT1 inhibitor with very good pharmacokinetic profile. Significant anti-inflammatory effect in HDM-induced airway inflammation model in mice was observed when dosing once daily (50 mg/kg).

Together with OAT-177 (selective mAMCase) and OAT-2068 (selective mCHIT1) OAT-870 constitutes a unique set of potent inhibitors which can be used as valuable tool compounds for the studies concerning the role chitases in various pathologies.

Further profiling revealed no genotoxicity in the AMES test, but data from the CEREP Diversity panel (including 72 binding and 27 enzyme assays) indicated dopamine transporter (DAT) as a significant off-target (95% inhibition at 10⁻⁵ M). These results led us to discovery of compound OATD-01—a first-in-class chitinase inhibitor currently in clinical trials (see Poster MEDI 272).

ACKNOWLEDGEMENTS

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