284 MWT-S00270, Selective Meprin β Inhibitor

Asset Overview

Product Type	Small Molecule
Indication	Fibrosis and kidney diseases (AKI)
Current Stage	Lead
Target(MoA)	Selective meprin β inhibitor
Brief Description	• Meprin is involved in cytokine activation and procollagen/collagen cleavage and meprin β is highly expressed in kidney epithelial cells • Relocalization of meprin β after toxic trigger brings the enzyme in contact with a number of substrates • Meprin KO mice are less susceptible to AKI and meprin inhibitors were able to reduce kidney injury in vivo to some extent. • MWT-270 is selective meprin β inhibitor and showed efficacy in an AKI animal model
Organization	Fraunhofer-Institut für Zelltherapie und Immunologie

Differentiation

□ **High degree of selectivity for treatment in the long-term**

- Human meprin is a member of the metzincin superfamily and correlates with matrix metalloproteinases and ADAMs
- ADAMs, especially ADAM10 is involved in different important cell biological functions such as, among others, neuronal signaling. Knock out of ADAM10 is lethal in mice
- MWT-S00270 (and all other compounds of this class) did not inhibit ADAM10 and ADAM17 up to 200μM concentration, i.e. concentrations far beyond any pharmacologically reasonable range
- First selective inhibitors & First in class potential

□ **Attractiveness in target indication, AKI**

- Currently there is no medication to treat AKI directly, only supporting therapies available
- Urgent medical need for new therapy approaches addressing the tissue-degrading AKI effects
- Prophylactic treatment to enlarge the therapeutic window for nephrotoxic drugs (chemotherapy, antibiotics etc.)

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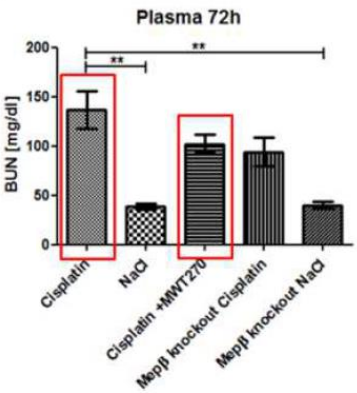
Key Data

Profiling of Lead MWT-S00270: No red flags detected yet

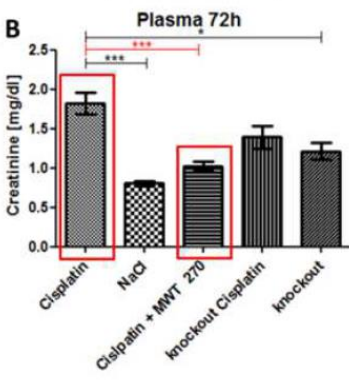
Parameter	Value	Parameter	Value
K_i Mep α [nM]	**10410 ± 999**	F_{abs} p.o. PK, rat, 5 mg/kg	13%
K_i Mep β [nM]	**18 ± 3**	C_{max} p.o. PK, rat, 5 mg/kg	0,335 mg/l
Sol [µM]	**> 200**	T_{max} p.o. PK, rat, 5 mg/kg	0,17 h
Viability SY-5Y [%]	**97 (@ 100µM)**	$T_{½}$ p.o. PK, rat, 5 mg/kg	5h
Viability Hep-G2 [%]	**97 (@ 100µM)**	V_D p.o. PK, rat, 5 mg/kg	49,5 ml
MMP2RA @ 200 µM [%]	**64**	F_{abs} i.p. PK, rat, 10 mg/kg	**83,9%**
MMP9RA @ 200 µM [%]	**74**	C_{max} i.p. PK, rat, 10 mg/kg	**6,46 mg/ml**
MMP13 RA @ 200 µM [%]	**78**	T_{max} i.p. PK, rat, 10 mg/kg	**0,12 h**
ADAM10 RA @ 200 µM [%]	**93**	$T_{½}$ i.p. PK, rat, 10 mg/kg	**1,98 h**
ADAM17 RA @ 200 µM [%]	**76**	V_D i.v. PK; rat, 3 mg/kg	**0,073 L**
PPB (mice plasma, 5µM cpd)	**82,2%**	$T_{½}$ i.v. PK; rat, 3 mg/kg	**2,5 h**
EC50 (cellular assay, APP, EC50	**2 µM**	F_{abs} i.p. PK, mouse, 10 mg/kg	**94%**
CYP2C9 Inhibition (% RA@25µM)	**94%**	C_{max} i.p. PK, mouse, 10 mg/kg	**29,81 mg/ml**
CYP3A4 Inhibition (% RA@25µM)	**93%**	T_{max} i.p. PK, mouse, 10 mg/kg	**0,13 h**

PoP study: Cisplatin-induced kidney failure in mice

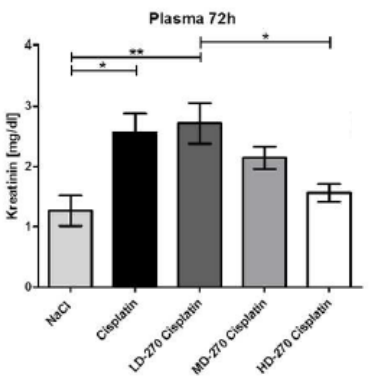
Blood Urea Nitrogen (BUN)



Creatinine



Dose-response-study, plasma creatinine



Dosage MWT-270: 50mg/kg i.p. every 12h, or 10/25/100 mg/kg; first dose 11h before cisplatin treatment
Dosage cisplatin: One dose i.p. 20mg/kg
NaCl: Control group

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Intellectual Property

Patent No.	KR 10-2018-0135002 A
Application Date	2017.04.18
Status	Application Pending
Country	US, EP, JP, KR, IN, CN, AU, CA

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