283 MWT-S-00001, inactivation of Gingipain Maturation for periodontitis treatment

Asset Overview

Product Type	Small molecule
Indication	Periodontitis
Current Stage	Lead optimization
Target(MoA)	Gingipains (proteases secreted by Porphyromonas gingivalis)
Brief Description	Periodontitis is one of the most abundant and neglected infectious diseases worldwide. Current Periodontitis drug market valued 347 million USD per year (CAGR 10.2 – 9.2 %). Gingipains are trypsin-like cysteine proteinases produced by Porphyromonas gingivalis, a major causative bacterium of adult periodontitis. It is suggested that gingipain inhibition by gingipain-specific inhibitors is a useful therapy for adult periodontitis caused by P. gingivalis infection.
Organization	Fraunhofer IZI

Differentiation

□ **Gingipain could be a valuable target in both chronic periodontitis and Alzheimer's disease.**

- Periodontitis-Inflammatory process caused by specific bacteria (Affects nearly 30% of the population worldwide). It increases the incidence of diabetes (nearly 11-times), Rheumatism and arthritis (nearly 6-times), and Alzheimer's disease
- Porphyromonas gingivalis is the "Key-Stone-Pathogen" in chronic periodontitis. A novel inhibitor is needed for selective targeting of periodontitis causing pathogens
- Recent studies showed that Porphyromonas gingivalis was identified in the brain of Alzheimer's disease patients. It suggests that gingipain inhibitors could be valuable for treating neurodegeneration in Alzheimer's disease as well as chronic periodontitis

□ **Improved selectivity by the structure-based modification of compounds**

- Department of Drug Design and Analytical Chemistry of Fraunhofer developed selective and local acting small molecules (MWT-S-00001) using computer chemistry and bioinformatics
- IP generation: SAR of different novel compound classes
- Porphyrin conjugates exhibit improved in vivo activity, further exploration of transport mechanisms necessary
- Additional structure-based compound optimization possible

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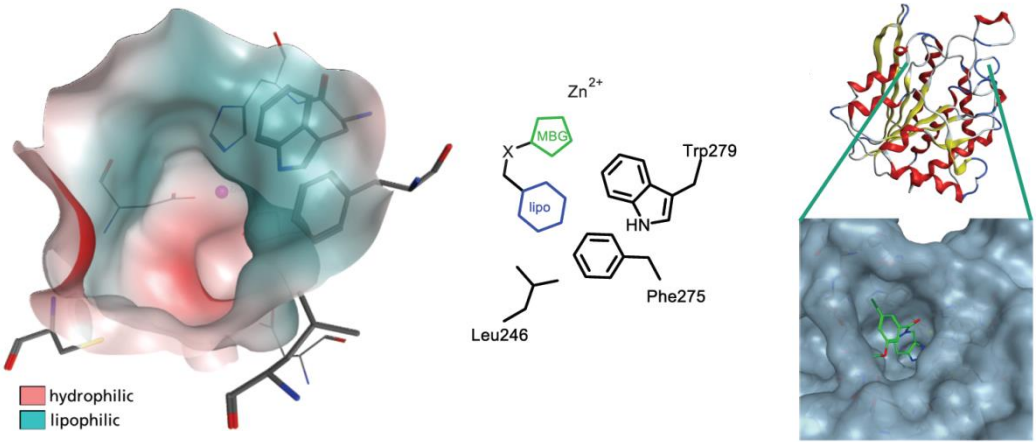
Key Data

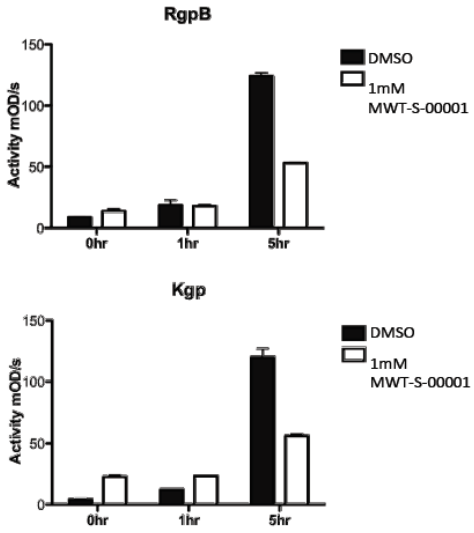
Inhibitor design strategy



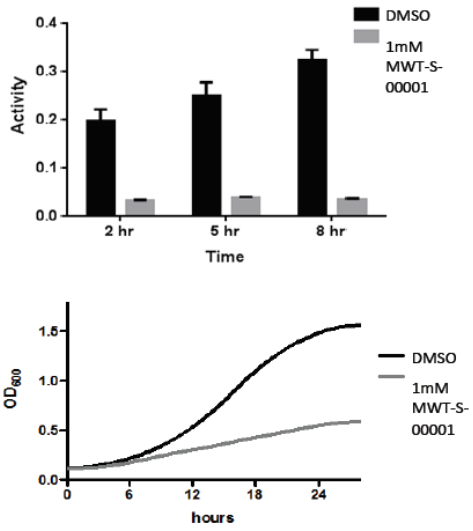
SAR of different novel compound classes IP generation. Porphyrin conjugates exhibit improved in vivo activity further exploration of transport mechanisms necessary.

Inhibition of gingipains by MWT-S-00001 (Proof of Principle in cell culture)

»MWT-S-00001«: secretion of gingipains



»MWT-S-00001«: growth inhibition



Enzyme inhibition leads to diminished secretion of virulence factors and growth inhibition of pathogens àcompound reaches bacterial site of action

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Improved activity and selectivity by modifying the uptake with conjugation

		Red Complex				Control	
Inhibitor (μM)	K_i (nM)	P.g. ATCC 33277 MIC (μM)	P.g. M5-1-2 MIC (μM)	T.f. ATCC 43037 MIC (μM)	P.i. ATCC 25611 MIC (μM)	S. g. ATCC 10558 MIC(μM)	A.a. ATCC 33384 MIC (μM)
CHX (%)	-	≤0.002	≤0.002	≤0.002	≤0.002	≤0.002	≤0.002
Doxy (mg/ml)	-	≤3.13	≤3.13	≤3.13	≤3.13	≤3.13	≤3.13
Bim-YYY-XXX	358	0.98	0.98	0.98	≤0.49	>2000	1000
Mtz-YYY-XXX		10 – 20[Lit]					

Red complex (a group of bacteria that are associated with severe forms of periodontal disease) includes Porphyromonas. MIC...minimal inhibitory concentration, CHX...chlorhexidine (antiseptic) Doxy...doxycycline (antibiotic), Mtz...metronidazol (conjugated antibiotic), Bim...benzimidazole (Inhibitor conjugated).

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Intellectual Property

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Country	

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