UNIVERSITY OF LIVERPOOL

Enterprise: Licensing & Ventures

NovlTex : A New Class of Novel Antibiotics

Screening of uncultured soil bacteria revealed teixobactin, a novel antibiotic with broad activity against multidrug esistant Gram-positive pathogens , including MRSA.

Teixobactin is an undecapeptide containing 5 non-canonical amino acids, including 4 D-amino acids and the cationic L-allo-enduracididin in a C-terminal depsi-cycle, rarely found in nature.

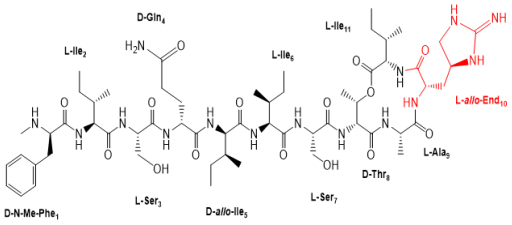
This binds to the highly conserved pyrophosphate motifs of lipid II and III in the bacterial cell causing disruption of the membrane and cell death.

That the targets are highly conserved lipids indicates that resistance is less likely to develop. Although in vivo studies suggest that teixobactin is a promising drug lead, its synthesis is challenging due to the enduracidine moiety. Natural Teixobactin is therefore unlikely to reach the clinic.

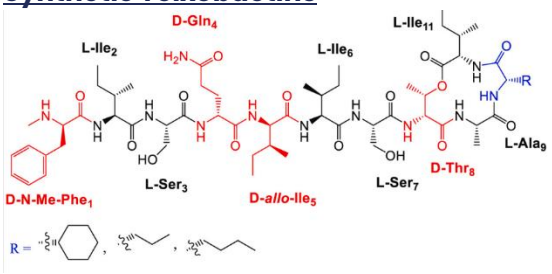
Technology

University of Liverpool has developed a library of synthetic Teixobactin analogues, eliminating the costly enduracididine cationic side chain (present in Novo29) with hydrophobic residues such as leucine. These molecules are easy to synthesise via microwave assisted coupling enabling solid phase peptide synthesis and single step purification.

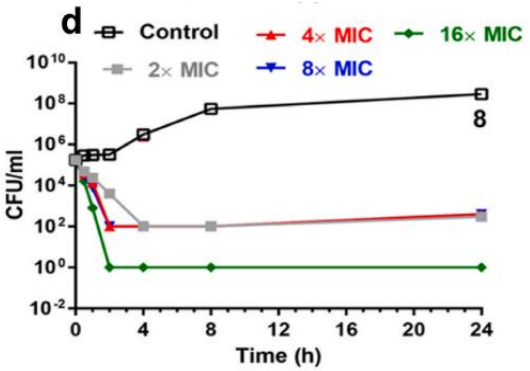
Natural Teixobactin



Synthetic Teixobactins

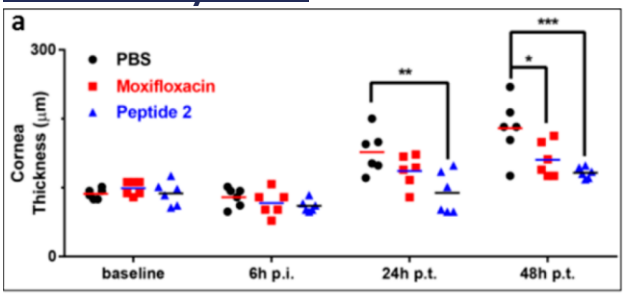


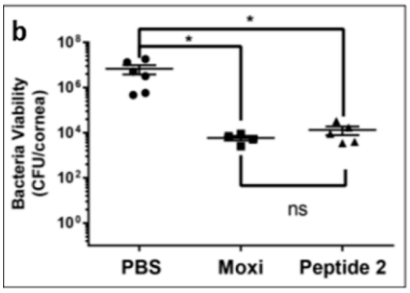
In Vitro Activity and SAR



Analogues have enhanced antibacterial activity against clinically relevant strains including MRSA and VRE. The SAR shows a correlation between number of carbons in the side-chain at position 10 and GM-MIC. Compounds containing a Chg10 substitution showed highly potent antibacterial activity against all bacteria tested with MIC values In the range of 0.0625–0.125 μg/mL and a GM-MIC of 0.07μmL. Analogue 12 exhibited lower MIC than the susceptibility cut of values for standard antibiotics when tested against MDR S. aureus and E faecium strains and achieved complete bactericidal activity within 6 hours, compared to 24 hours with Vancomycin

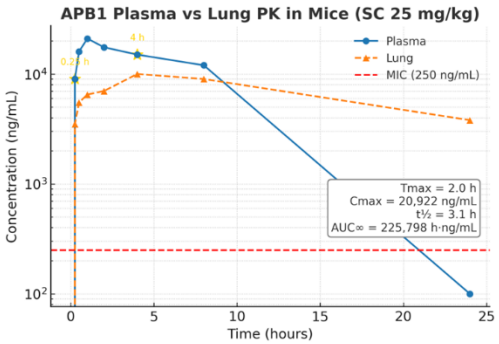
In Vivo Activity and PK





In Vivo activity is demonstrated in a mouse model of S. aureus induced keratitis . NovlTex halted progression of infection with activity comparable to moxifloxacin as determined by corneal thickness and bacterial viability. Similar activity was also demonstrated in a thigh implant model.

PK demonstrated plasma and lung levels above the MIC and good tolerability at 150mg/ml for 7 days



Benefits

- Scalable Synthesis
- Compound library for lead optimisation
- Highly conserved lipid target
- No detectable resistance at 20 passages
- Greater potency than Vancomycin or natural Teixobactin against MRSA and VRE
- Non-toxic to mammalian cells at 250µg/ml
- MIC less than 1 µg/ml.
- Efficacy in mouse keratitis model
- Efficacy in biofilm associated infection models
- Anti-inflammatory properties

Patents

Delivery agents in combination with Moenomycins
PCT/GB2015/052564
WO2016034894A3

New Antibacterial Products
PCT/GB2018/050605
Granted
EP18711656.1A
WO2018162922A1

New antibacterial products
NOVLTEX - A new class of antibiotic against MDR bacterial infections
Granted NP
PCT/GB2023/052905
WO2024100391A2

Teixobactins analogues as anti-biofilm agents
PCT/GB2024/051527
WO2024256834A1