WS7.1 Pre-clinical evaluation of novel antibiotic POL7001 against *Pseudomonas aeruginosa* in lung infection models

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Objectives: The discovery, development, and clinical exploitation of antibiotics with a new mode of action combined with efficient pulmonary drug delivery systems is a top priority in the battle against untreatable chronic infections in cystic fibrosis (CF) patients. POL7001 is a novel Protein Epitope Mimetic (PEM) antibiotic with potent activity against *Pseudomonas aeruginosa* (Pa) (Srinivas et al, Science 2010). POL7001 showed a potent in vitro activity against a large panel of Pa CF multi-drug resistant strains. To evaluate CF lung infections as potential clinical application, the therapeutic efficacy of POL7001 in mouse models was investigated.

Methods: Both Pa acute and chronic airway infection were established, and mice were treated by subcutaneous (s.c.) or pulmonary administrations (i.t.). Body weight, bacterial count and inflammation in lungs were evaluated at different time points. Comparison to clinically approved antibiotics was included.

Results: High antibacterial activity of POL7001, in particular after i.t. administration, was demonstrated. Leukocyte recruitment (in particular neutrophils) in the airways was reduced after POL7001 i.t. administration. Pharmacokinetic studies confirmed that POL7001 reached favorable concentrations in the lung after i.t. administration, with rather low systemic exposure.

Conclusion: The efficacy of POL7001 was superior to ciprofloxacin, one of the most effective clinically-approved antibiotics and used as an internal positive control in our pre-clinical studies. Based on these promising results, POL7001 was selected for further pre-clinical profiling.

WS7.2 Antibacterial activity of theta defensin (RTD-1) against clinical isolates of *Pseudomonas aeruginosa*

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Objectives: The macrocyclic peptide rhesus theta defensin-1 (RTD-1) exhibits broad-spectrum antibacterial and anti-inflammatory activities. The objective of this study was to investigate the therapeutic potential of RTD-1 for treatment of CF lung infections owing to chronic infection in CF patients. RTD-1 was tested against clinical strains of *P. aeruginosa* to evaluate the efficacy of RTD-1 against clinical isolates of *P. aeruginosa* in vitro and in vivo and compared to clinically approved antibiotics.

Methods: 

- **Clinical isolates**
  - Rationale: Isolates of *Pseudomonas aeruginosa* were obtained from patients in CF centers.
  - **In Vitro Assays**
    - Antimicrobial activity testing
    - Cytotoxicity determination
    - Antioxidant activity testing

Results: 

- **Antimicrobial Activity**: Fifty-six clinical isolates were tested against RTD-1 with a concentration-dependent effect, achieving complete kill within 1.5h at 4x MIC and a 2-log decrease within 15min at 64x MIC, with substantial minimal post-antibiotic effects.
- **Cytotoxicity**: Greater than 90% of RTD-1 was recovered intact following incubation in CF sputum. No cytotoxicity of CuFi cells was observed following exposure to RTD-1 for 24h.
- **Antioxidant Activity**: Greater than 90% of RTD-1 was recovered intact following incubation in CF sputum.

Conclusion: RTD-1 demonstrated potent antibacterial activity against clinical isolates of *P. aeruginosa* in CF patients.