In vitro and in vivo antibacterial activity of novel dual bacterial DNA type II topoisomerase inhibitors (NBTIs)

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Quinolones are a successful class of antibiotics targeting bacterial DNA topoisomerases II enzymes. Following their extensive use, the incidence of resistance to these agents has rapidly increased justifying strong efforts to discover new scaffolds able to bind to novel pockets within these clinically validated bacterial targets. Such new agents, named NBTIs, should be also potentially able to overcome antimicrobial resistance to currently available quinolones. [D. Ehmann et al, 2014]

An in silico and in vitro screening program aimed to discover novel NBTIs led to the selection of six optimized hit compounds. In enzymatic assays all molecules showed a potent equivalent dual targeting activity against DNA gyrase and topoisomerase IV enzymes of both Staphylococcus aureus and Escherichia coli reference strains. Consistently, the compounds demonstrated a strong activity in S. aureus and E. coli susceptibility tests (MIC values ≤ 0.5 mg/L) and they maintained antimicrobial activity also against different Gram-positive and -negative reference species, including ciprofloxacin-resistant strains.

Subsequently the in vivo efficacy of one representative compound, named AL1, was investigated against the methicillin-resistant S. aureus strain 43484 in a murine peritonitis/sepsis model. [C. Vingsbo Lundberg et al, 2010]

Mice were inoculated intraperitoneally with MRSA-43484. At 1h after inoculation mice were treated subcutaneally with AL1 (60mg/kg) or vancomycin (80mg/kg) used as reference drug. At 4 hrs after treatment, blood and peritoneal fluid (PF) were sampled for Colony Forming Unit (CFU) determination.

AL1 caused a statistically significant ($p<0.05$) decrease in the number of CFUs in the peritoneal fluid compared to vehicle treated mice. CFUs were measured also in blood, where a slight but not significant reduction was also observed. Vancomycin, gave a statistically significant reduction of CFUs both in the peritoneal fluid ($p<0.001$) and in plasma ($p<0.001$) compared to vehicle group. Finally the plasma levels of AL1 were measured in treated animals at 4hrs from treatment and they resulted in an average concentration of 0.3 μg/ml, a value equal to the MIC (0.31 μg/ml) of AL1 vs. the MRSA strain 43484.

The results so far obtained prompt further studies to better elucidate the potential of these NBTI compounds for the treatment of severe infections caused by a wide range of bacterial pathogens and make them interesting candidates to develop a new broad spectrum antimicrobial agent.

References:

D. Ehmann et al (2014). Current opinion in Pharmacology; 18:76–83.

C. Vingsbo Lundberg et al (2010). J Antimicrob Chemother; 65: 981–985.