P1448

Abstract (poster session)

In vitro potency of novel tetracyclines against Pseudomonas aeruginosa and other major Gram-negative pathogens

W. O'Brien, C. Fyfe, T. Grossman, C. Chen, R. Clark, Y. Deng, M. He, D. Hunt, C. Sun, X. Xiao, J. Sutcliffe* (Watertown, US)

Objectives: To discover novel tetracyclines with enhanced Pseudomonas aeruginosa activity while maintaining in vitro activity against other important gram-negative pathogens. Methods: The guidances and breakpoints of the Clinical Laboratory Standards Institute were used to determine the susceptibility of new compounds and comparators in microtiter-based cation-supplemented Mueller Hinton broth or in time-kill assays using 5 milliliter cultures. In the case of tigecycline, FDA breakpoints (if available) were used. In vitro potency against Escherichia coli DH10B strains genetically engineered to express tet(A), tet(B), tet(K), tet(M), tet(X) or blaNDM-1 was assessed. Compounds were also assessed for mechanism of action (MOA) using a coupled transcription/translation assay (TnT) fueled with S30 ribosomal extracts from either Escherichia coli or P. aeruginosa. Results: Ten novel scaffolds were found that produced compounds with MICs against P. aeruginosa PA01 of 2-4 mcg/ml and MIC90 values of 8-16 mcg/ml against recent clinical isolates (n=76). The MIC50/90 ranges against a separate panel of P. aeruginosa isolates from cystic fibrosis patients were 4-8/8-16 mcg/ml. In vitro activity against panels of Acinetobacter baumannii and extended-spectrum beta-lactamase producing Klebsiella pneumoniae and E. coli was also retained by many compounds, with MIC50/90 values of <=0.25/1 mcg/ml and comparator MIC90 values of >=32 mcg/ml for tetracycline, ceftriaxone, imipenem, levofloxacin, gentamicin, tobramycin for P. aeruginosa, Enterobacteriaceae and A. baumanii. Two compounds were profiled in 24-hour time-kill studies using 4 isolates of P. aeruginosa and generally found to be bactericidal at 4-8x the MIC. The new scaffolds retained activity against strains expressing genes encoding tetracycline-specific efflux pumps (Tet(A), Tet(B), Tet(K)), a ribosomal protection mechanism (Tet(M)), and a monooxygenase that inactivates tetracyclines (Tet(X)). The compounds inhibited protein synthesis in both TnT assays, with IC50 values 5-10x lower than conventional tetracyclines (1-2 uM). Conclusions: This is the first report of novel tetracyclines with improved potency against contemporary P. aeruginosa isolates. These compounds retain activity against other major gram-negative pathogens and merit additional work to advance into development.