New Generation Antimicrobials Developed Using Efflux Resistance Breaker (ERB) Technology

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Background: King's College London and UKHSA have developed a novel approach to reduce efflux liability in different antibiotic and antifungal classes, based on advanced structural modelling, identification of "efflux-resistance breaker" pharmacophores and detailed understanding of efflux liability in multidrug resistant pathogens. This technology allows development of antimicrobials that are less susceptible to efflux and do not require the use of additional efflux pump inhibitors.

Methods: Computational tools including Biovia Discovery Studio and Amber v16.0 were used for optimisation of the ERB fragments. The fragments were linked to fluoroquinolone and 4-oxoquinolizine pharmacophores using solution phase chemistry. Minimum inhibitory concentration (MIC) values were determined using the microdilution broth method. A gel-based assay was used to determine the IC_{50} against DNA gyrase. The oral and IV pharmacokinetics study and thigh infection model employing MRSA strains were carried out by contract research organisations, Evotec and Eurofin.

Results: The ERB-fluoroquinolones and ERB-4-oxoquinolizine show notably better activity compared to fluoroquinolones and parent 4-oxoquinolizines in a variety of MDR bacteria with up to a 512-fold reduction in MIC (MIC_{90} 0.03 to 2 µg/mL). The lead compounds, KSN-L22 and KSN-BL-7 showed MICs of 0.03 to 0.5 µg/mL against MRSA, 0.03 to 2 µg/mL against *Acinetobacter baumannii*, 0.03 to 2 µg/mL against *Escherichia coli* and 0.25 to 4 µg/mL against *Klebsiella pneumoniae* strains. The ERB-fluoroquinolones work by inhibiting both wild type and mutant (GyrA S84L) DNA gyrases (IC_{50} ~3.8 µg/mL). The lead compounds showed *in vivo* efficacy in a thigh infection model with 5-log reduction of bacterial load at both 20 and 50 mg/Kg oral dose levels and excellent oral and iv PK/PD profiles. The compounds did not show any toxicity at 1200 mg/Kg/day in mice. The off-target toxicity screen did not reveal any issues, including the hERG channel, and the compounds do not induce or inhibit Cytochrome p450 enzymes.

Conclusion: ERB-antibiotics has the potential to revive the use of several classes of current antibiotics. A pre-clinical candidate, KSN-BL-7, against MDR Gram-positive bacteria, and a pre-clinical candidate, KSN-L22, with broad-spectrum activity has been identified and has been licensed to a biotech to imitate a clinical development programme against *Neisseria Gonorrhoea*.