**Mechanism-based modelling to optimise piperacillin plus tobramycin combination dosage regimens against *Pseudomonas aeruginosa* for patients with altered pharmacokinetics**

Rajbharan Yadav1, Kate E. Rogers1,2, Phillip J. Bergen2, Jürgen B. Bulitta3, Carl M. J. Kirkpatrick2, Steven C. Wallis4, David L. Paterson4, Roger L. Nation1, Jeffrey Lipman5, Jason A. Roberts4,5,6 and Cornelia B. Landersdorfer1,2.

1Drug Delivery, Disposition and Dynamics, 2Centre for Medicine Use and Safety, Monash University, Parkville, VIC, Australia; 3Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, FL, USA; 4Centre for Clinical Research, 5Royal Brisbane and Women’s Hospital, 6School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia.

**Aims**: Augmented renal clearance (ARC) in critically-ill patients can result in suboptimal drug exposures and potential treatment failure. This study aimed to design optimised combination dosage regimens of piperacillin and tobramycin against a *Pseudomonas aeruginosa* (Pa) clinical isolate and evaluate them in the hollow-fibre infection model (HFIM) for the pharmacokinetics of patients with ARC.

**Methods**: We studied clinically relevant piperacillin and tobramycin concentrations, alone and in combinations in *in vitro* static concentration time-kills (SCTK), against a Pa clinical isolate at two inocula (105.7 and 107.5 CFU/mL) over 72h. Piperacillin and tobramycin combination regimens were optimised *via* mechanism-based modelling (MBM) of SCTK data. The importance sampling algorithm (pmethod=4) was used for simultaneous estimation of all PD parameters utilising parallelised S-ADAPT (version 1.57) facilitated by SADAPT-TRAN. The effects of optimised piperacillin (4g q4h, 0.5h infusion) plus tobramycin (5 mg/kg q24h, 7 mg/kg q24h and 10 mg/kg q48h as 0.5h infusions) regimens on bacterial killing and resistance was evaluated in the HFIM for patients with ARC (creatinine clearance 250 mL/min) over 8 days.

**Results**: In SCTKs, piperacillin plus tobramycin (except combinations with 8 mg/L tobramycin at low inoculum) achieved synergistic killing (≥2 log10 *vs.* the most active monotherapy at 48h and 72h) and prevented regrowth. The synergistic effect was modelled *via* a disruption of the bacterial outer membrane by tobramycin. Piperacillin monotherapy (4g every 4h) in the HFIM provided 2.4 log10 killing at 13h followed by rapid regrowth at 24h with resistance emergence. Tobramycin monotherapies displayed rapid initial killing (≥5 log10 at 13h) followed by extensive regrowth. As predicted by MBM, the piperacillin plus tobramycin dosage regimens were synergistic and provided ≥5 log10 killing with resistance suppression over 8 days in the HFIM.

**Conclusion**: Optimised piperacillin plus tobramycin regimens provided significant bacterial killing and suppressed resistance emergence as predicted by MBM, and therefore translated well from SCTK to the dynamic HFIM. This highlights the utility of MBM to select optimised regimens that maximise bacterial killing and minimise resistance emergence against Pa, an especially important finding given that Pa can rapidly develop MDR. Thus, these regimens are highly promising for effective and early treatment, even in the near-worst case scenario of ARC.