Acknowledgements This study was supported by the Agency for Innovation by Science and Technology in Flanders through the ‘SAFEPEDDRUG’ project (IWT/SBO 130033; IWT 141427).

REFERENCE

O-37 A HUMAN PROXIMAL TUBULAR EPITHELIAL CELL MODEL TO EXPLORE A KNOWLEDGE GAP ON NEONATAL DRUG DISPOSITION
1Raaijmakers*, 2Reda, 2Van Donst, 2Pauwels, 2Allegaert, 4Masereeuw, 4Van den Heuvel, 1Levchenko, 1Arcilio. 1KU Leuven, LEUVEN, Belgium; 2University hospital Leuven, LEUVEN, Belgium; 2Utrecht University, UTRECHT, Netherlands
10.1136/archdischild-2017-esdppp.36

Background Finding the right drug-dosage for neonates is still a medical challenge. Up to now, neonatal doses are extrapolated from adult and children doses. However, there are differences between neonatal and adult kidney physiology that should be put into consideration, especially when it comes to active drug metabolism. Studying renal drug clearances in neonates is limited by the lack of reliable human cell models. Our aim was to illustrate the feasibility to develop an in vitro model for neonatal proximal tubule epithelial cells (nPTECs) for studying renal drug clearances at this age.

Method nPTECs were isolated from urine samples of neonates of different gestational age (GA) and conditionally immortalised using a temperature sensitive SV40T antigen and human telomerase hTERT. The cell clones were characterised on gene expression level for PTECs markers such as P-glycoprotein (P-gp), aquaporin1 (AQP1), and organic cation transport protein 2 (OCT2). In addition, protein expression and functional assessment were per-formed for P-gp and OCT2.

Results We established 101 clonal cell lines of cinPTECs derived from neonatal urine. Gene expression analysis confirmed the expression of the PTECs markers (P-gp, AQP1, and OCT2), similar to the expression in the adult control ciPTECs. P-gp was expressed in cinPTECs from the different gestational ages and exhibited similar functionality as the adult derived ciPTECs. In contrast, OCT2 functionality was significantly lower in the cinPTECs cell lines compared to the adult ciPTECs.

Conclusion We demonstrate the feasibility of culturing cinPTECs expressing mature ciPTECs markers with high efficiency out of the urine samples of neonates. The cell model presented here can serve as a valuable tool to study proximal tubule physiology and pharmacology in new-borns. In addition, we demonstrate the physiological differences between the neonatal and adult kidney, which puts emphasis on the importance of studying drug pharmacokinetics in neonatal models instead of extrapolating from adult models.

O-38 PREVENTING AMINOGLYCOSIDE-INDUCED NEPHROTOXICITY USING STATINS: AN EXAMPLE OF BENCH-TO-BEDSIDE RESEARCH
1McWilliam, 1Antoine, 2Smyth, 1Pirmohamed. 1University of Liverpool, LIVERPOOL, UK; 2University College London, LONDON, UK
10.1136/archdischild-2017-esdppp.37

Background Megalin-mediated endocytosis is the princi-pal pathway for the accumulation of aminoglycosides in proximal tubule epithelial cells, resulting in kidney toxicity. Activation of this pathway depends on intermediates derived from mevalonate, the product of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reduction, catalysed by HMG-CoA reductase. We hypothesised that inhibition of HMG-CoA reductase by statins would reduce uptake of aminoglycosides in the proximal tubule, leading to a re-duction in toxicity. This has previously been demonstrated in vitro. We tested this in two in vivo models.

Methods Sprague Dawley rats, (n=4/group) received in-traperi-toneal (IP) dosing with saline (control), gentamicin (200 mg/kg/day), rosvastatin (40 mg/kg/day), or gentami-cin and rosu-vastatin for 9 days. Nephrotoxicity was measured using urin ary N-Acetyl-β-d-glucosaminidase (NAG) and kidney injury molecule-1 (kim-1) on urine samples collected within 24 hours after the final dose. Male Hartley guinea pigs (n=6/group) received IP dosing with saline (control), gentamicin (100 mg/kg/day), statin, or combined gentami-cin and statin (simvastatin or rosvastatin, 0.4 to 40 mg/kg/day) for 9 days. Nephrotoxicity was measured using serum creatinine and blood urea nitrogen (BUN) on urine samples collected within 24 hours after the final dose.

Results In rats co-administered rosvastatin and gentami-cin, urinary concentrations of NAG and kim-1 were signifi-cantly lower than for gentamicin alone (p<0.01). In guinea pigs, rosvastatin reduced gentamicin-induced nephro-toxicity in a dose-dependent manner: doses of 0.4, 4 and 40mg/kg/day led to 46% (p<0.01), 81% (p<0.0001), and 83% (p<0.0001) reductions, respectively, in serum creati-nine compared to ani-mals receiving gentamicin only. Similar results were seen with BUN. The minimum effective dose to prevent toxicity was 0.97/mg/kg/day. Using a dose scaling algorithm this equates to a dose of 10mg/day in children. Simvastatin did not protect the kidney from gentamicin-in-duced nephrotoxicity. The results from the in vitro and in vivo animal studies led to the design of a phase IIa multi-centre, randomised, controlled clinical trial (RCT) in children with cystic fibrosis receiving clini-cally indicated treatment with aminoglycosides, where co-treatment with rosvastatin (10mg) will be compared with current standard of care.

Conclusion Rosuvastatin inhibits gentamicin-induced nephro-toxicity in both rat and guinea pig models; in the latter, at therapeutic doses used in humans. This led to an RCT in chil-dren which has just completed recruitment. This bench-to-bedside translational research showcases the exciting area of drug repurposing with potential for signifi-cant patient benefit.

REFERENCES

O-38 THE INFLUENCE OF BODY COMPOSITION ON PAEDIATRIC DRUG DOSING
AI-Sallami. University of Otago, DUNEDIN, New Zealand
10.1136/archdischild-2017-esdppp.38
O-37 Preventing aminoglycoside-induced nephrotoxicity using statins: an example of bench-to-bedside research
McWilliam, Antoine, Smyth and Pirmohamed

Arch Dis Child 2017 102: A17
doi: 10.1136/archdischild-2017-esdppp.37