CHARACTERIZATION OF CISPLATIN TOXICITY IN aPROXIMATE™
HUMAN PROXIMAL TUBULE CELL MONOLAYERS

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Introduction

- Around 50% of preclinical toxicity screens fail to predict subsequent toxicity in vivo.
- This leads to significant attrition of drug molecules during drug development.
- Understanding nephrotoxicity has been hampered by the lack of good renal model.
- Here we demonstrate the utility of the aProximate human proximal tubule cell (PTC) monolayers as an in vitro tool to investigate nephrotoxicity using clinically relevant biomarkers NGAL, KIM-1 and clusterin.

Methods

- Kidney decapsulated and cortex dissected and minced
- Collagenase digest
- Digested tissue passed through cell strainer separate via density gradients
- Tubular cell retrieved and cultured on Transwell inserts

- PTCs were isolated from human kidneys as described in Figure 1, and cultured onto Transwell inserts.
- Confluent monolayers were treated with nephrotoxins.
- Transepithelial electrical resistance (TEERs) were measured, in addition to cell viability using an Real time Glom™ assay
- Culture media was collected from both apical and basolateral compartments and analysed for biomarkers using an ELISA approach.

Biomarkers are released in to the apical media in a concentration dependent manner

Response of Apoptosis Signalling Pathways in Human PTCs to Cisplatin Challenge

- Levels of all 3 clinically relevant biomarkers KIM-1, NGAL, and clusterin increased within response to challenge with a range cisplatin concentrations.
- Importantly, as in vivo, biomarker release was predominately across the apical membrane than across the basolateral membrane (Figure 3, 4 & 5).

Conclusion

In summary, aProximate™ human proximal tubule cell monolayers retain a remarkable degree of differentiation, express clinically relevant biomarkers of nephrotoxicity and signalling pathways that translate to an appropriate response to cisplatin challenge. aProximate™ human proximal tubule cell monolayers show excellent potential as an in vitro predictive human toxicology screening platform during the drug development process.