**Quantitative Systems Toxicology Modeling of Cisplatin Nephrotoxicity Using in vitro Assays of Proximal Tubule Epithelial Cells for Mechanistic Toxicity Pathways**

**BACKGROUND**
- Cisplatin-induced nephrotoxicity results in acute kidney injury (AKI) and is caused by various cellular mechanisms, including mitochondrial dysfunction, oxidative stress, and others.
- AKI mechanisms of cisplatin and several other nephrotoxic drugs remain incompletely understood.
- Quantitative system toxicology (QST) offers promise for better understanding of drug induced AKI through mechanistic representation of the underlying toxicity pathways.
- We developed a QST model of cisplatin induced AKI using in vitro assay data to characterize injury pathways.

**METHODS**
- We employed RENAsym®, a QST model of drug-induced acute kidney injury that is currently under development.
- RENAsym® represents aspects of renal proximal tubule epithelial cells (RPTCs), including cell life cycle, bioenergetics, drug-induced cell death pathways, and biomarker (αGST) responses.
- For mechanistic representation of cisplatin induced AKI, we analyzed data from a 2D in vitro assay (measured by Cyprotex, Inc.) of RPTEC.
- Seahorse XF analyzer and high content imaging (HCl) were used to quantify cisplatin-induced mitochondrial dysfunction and oxidative stress.

**Model Parametrization using in vitro Data**
- In vitro data measured by Cyprotex in RPTEC was utilized to parameterize the oxidative stress (RNS/ROS) production and clearance of cisplatin.
- HCl assay of RPTEC was used to measure an increase in cisplatin-induced reactive oxygen species.
- Oxygen consumption rate (OCR) decline measured using SeaHorse was fit using MITOsym, a model of in vitro mitochondrial bioenergetics (1).
- Rate constants for ETC inhibition from MITOsym were converted to RENAym® parameters using a conversion factor.

**Simulation Predictions for dose dependent responses of cisplatin exposure**
- Simulations based on RPTEC in vitro toxicity assay show cisplatin-induced toxicity that is dominated by ETC inhibition.
- RENAym® is designed to integrate drug exposure, in vitro toxicity, and kidney physiology to predict drug-induced AKI.
- Urinary biomarkers offer early detection of AKI. Model predicts αGST as a key biomarker that signals cellular death.
- The figure shows the intermediate mechanistic pathways that link between drug exposure and biomarker responses.
- The relation between cell death and αGST is parameterized using literature data (2).

**REFERENCES**

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