Quantitative Prediction of Cisplatin-Induced Acute Kidney Injury Using RENAsym, a Mechanistic Quantitative Systems Toxicology Model, and Renal Proximal Tubule Epithelial Cell In vitro Assays

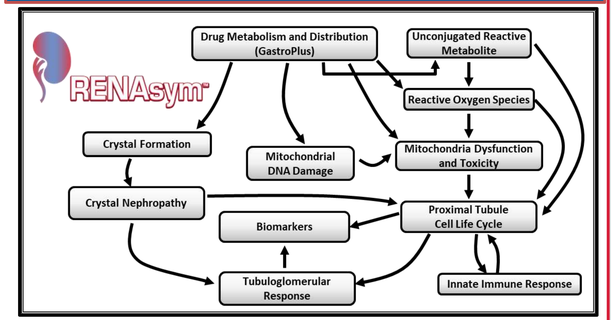
Yeshitila Gebremichael, Nader Hamzavi, Jeffrey L. Woodhead, Shailendra Tallapaka, Scott Q. Siler, and Brett A. Howell

DILIsym Services, Inc., a Simulations Plus company, Research Triangle Park, NC, USA

BACKGROUND

- Nephrotoxic drugs like cisplatin cause acute kidney injury (AKI) through complex cellular mechanisms that include mitochondrial dysfunction, oxidative stress, and immune mediated injury pathways.
- However, quantitative prediction of the underlying toxicity mechanisms remains a challenge.
- Quantitative system toxicology (QST) modeling offers a promise for quantitative description of toxicity mechanisms leading to drug-induced AKI.
- We developed a QST model of cisplatin induced AKI using in vitro assays to characterize key cellular injury mechanisms.

METHODS



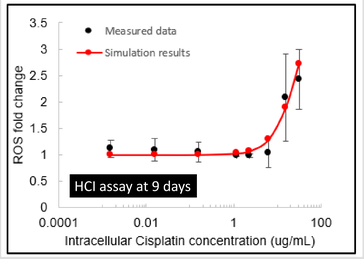
- We employed RENAsym®, a QST model of drug-induced acute kidney injury that is currently under development.
- RENAsym® represents aspects of renal proximal tubule epithelial cells (RPTECs), including cell life cycle, bioenergetics, drug-induced cell death pathways, and biomarker (αGST) responses.
- In vitro data related to cisplatin mitochondrial toxicity and oxidative stress generation were measured using RPTEC assays incubated with cisplatin (Cyprotex Inc.).
- To quantify cisplatin-induced mitochondrial dysfunction, oxygen consumption rate (OCR) was measured using the Seahorse XF analyzer. Cisplatin-induced oxidative stress was measured using high content imaging (HCI).

DILIsym Services

A SIMULATIONS PLUS COMPANY

Model Parametrization using *in vitro* Data

Oxidative Stress Parametrization

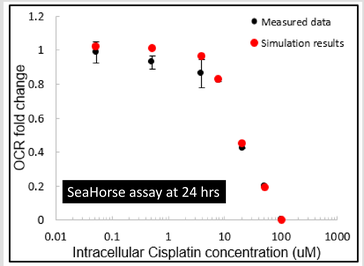


HCI assay measured by Cyprotex in RPTEC reveals significant cisplatin induced oxidative stress elevation after 9 days.

- The *in vitro* data was utilized to parameterize the oxidative stress (RNS/ROS) production and clearance of cisplatin.

Mechanism	Parameter	Unit	Cisplatin Value*
Oxidative Stress	Liver RNS/ROS production rate Vmax 4	1/hour	0.067
	Liver RNS/ROS production rate Km 4	µmol/L	57.68
	Liver RNS/ROS production rate Hill 4	Dimensionless	1.45
Mitochondrial Dysfunction	Coefficient for ETC Inhibition 3	µM	2.34
	Max inhibitory effect for ETC inhibition 3	Dimensionless	1.025

ETC Inhibition Parametrization

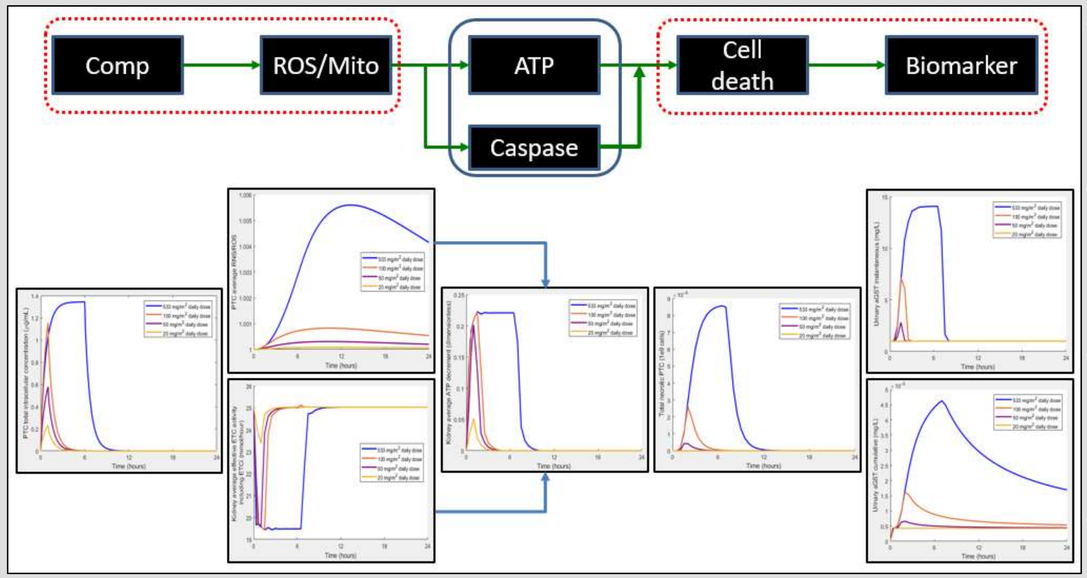


The Seahorse study shows substantial OCR decline at 24 hours, suggesting cisplatin-induced electron transport chain (ETC) inhibition.

- The OCR decline was fit using MITOsym, a model of *in vitro* mitochondrial bioenergetics [1].
- Rate constants for ETC inhibition from MITOsym were converted to RENAsym® parameters using a conversion factor.

Table: Summary of toxicity parameters for drug-induced mitochondrial dysfunction and oxidative stress production. The parameters were determined by fitting the *in vitro* data using MITOsym for mitochondrial dysfunction parametrization and RENAsym® for oxidative stress parametrization. These parameters were then incorporated in RENAsym® for predicting drug-induced AKI.

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.

- RENAsym® 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).

CONCLUSION

- Simulations predict dose-dependent cisplatin toxicity as quantified by elevations in αGST, a biomarker that marks RPTEC death.
- A simulated single high dose of 533 mg/m^2 i.v. cisplatin results in 14-fold change in αGST, while a simulated clinical dose of 100 mg/m^2 shows 7-fold increase.
- The 100 mg/m^2 result is in qualitative agreement with 3.4-fold change observed in a clinical study where patients administered 100 mg/m^2 i.v. cisplatin exhibited 20% incidence of AKI [3].
- RENAsym® shows promise in combining QST modeling and in vitro assay data to provide a unique tool for drug-induced AKI prediction.

REFERENCES

[1] Yang Y, et al. Pharm Res. 2015 Jun;32(6):1975–92.

[2] Kharasch ED, et al. Anesthesiology. 1998 Jun;88(6):1624-33.

[3] Ummer V, et al. International journal of Bioscience, Biochemistry and Bioinformatics. 2012 July; 2(4): 224-226

ACKNOWLEDGEMENTS

- Dr. Melissa Hallow and Dr. Zheng Dong
- This work was supported by the NIDDK of NIH grant R44DK118981.
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

cyprotex AN EVOTEC COMPANY

RENAsym®