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

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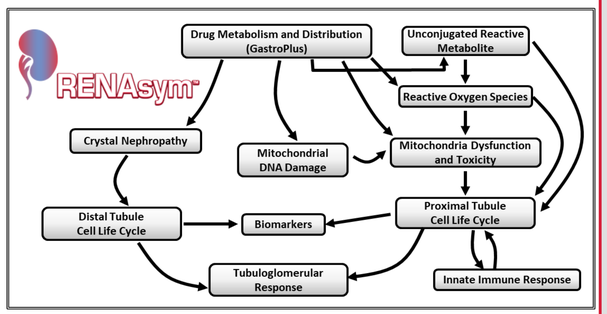
## BACKGROUND

- 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 (HCI) were used to quantify cisplatin-induced mitochondrial dysfunction and oxidative stress.

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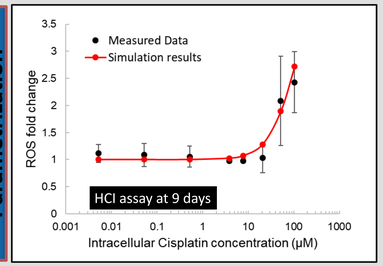
## Model Parametrization using *in vitro* Data

### Oxidative Stress Parametrization

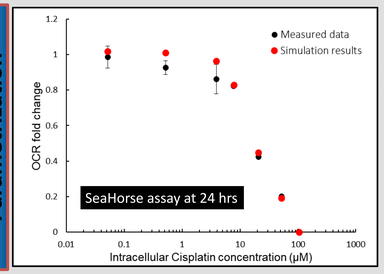



*In vitro* data measured by Cyprotex in RPTEC was utilized to parameterize the oxidative stress (RNS/ROS) production and clearance of cisplatin.

- HCI assay of RPTEC was used to measure an increase in cisplatin-induced reactive oxygen species.

| 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 | μM | 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

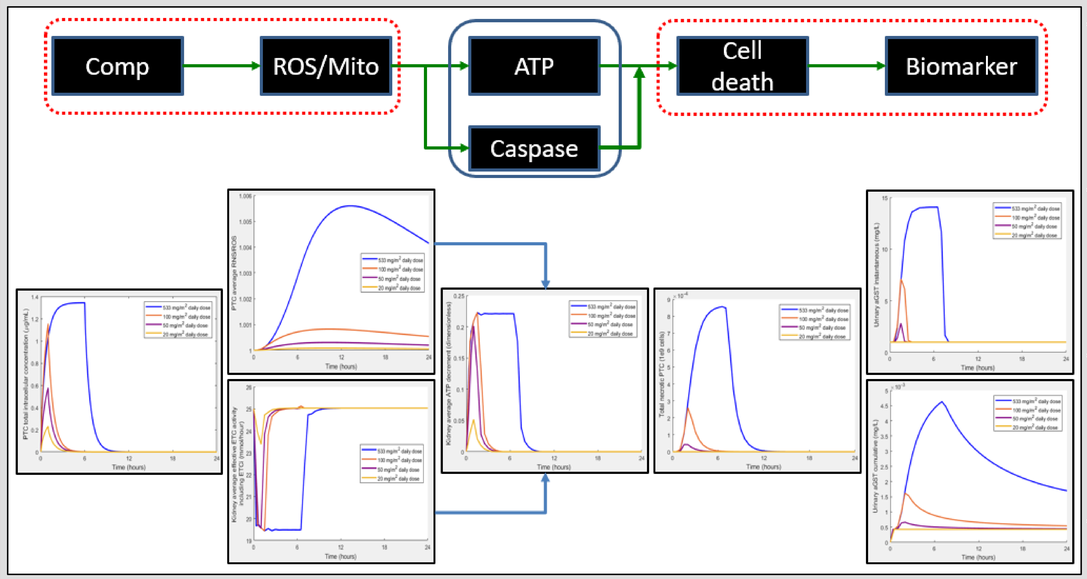



Oxygen consumption rate (OCR) decline measured using SeaHorse was fit using MITOsym, a model of in vitro mitochondrial bioenergetics (1).

- Rate constants for ETC inhibition from MITOsym were converted to 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).

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## 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.

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