Quantitative Systems Toxicology (QST) Modeling of Drug-Induced Acute Proximal Tubule Epithelial Cell Injury and Associated Renal Hemodynamic Responses

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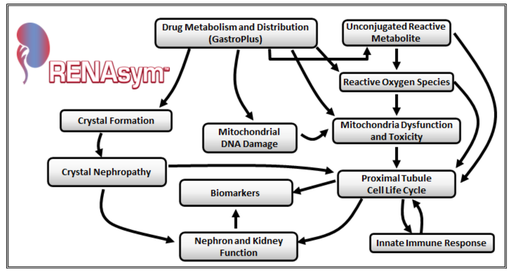
INTRODUCTION

- Renal proximal tubule epithelial cells (RPTEC) are vulnerable to drug-induced toxicities which often result in acute kidney injury (AKI).
- Drug toxic effects range from mild sub-lethal RPTEC injuries to cellular death via multiple cellular damage mechanisms. At the systems level, decline in glomerular filtration rate (GFR) is a common manifestation of AKI.
- The complexity of pathophysiological responses (cellular, neurohormonal, hemodynamic) that lead to impaired filtration pose a challenge for reliable prediction of AKI.
- QST modeling is a promising method for translating cellular-level renal damage to clinical manifestations of AKI.

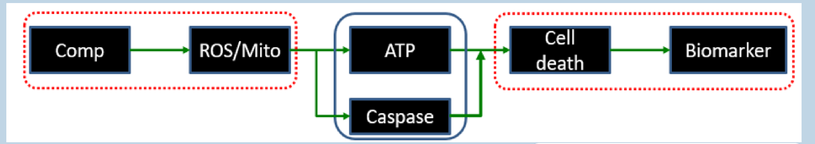
METHODS

- We developed RENAsym™, a QST model of drug-induced AKI that includes key cellular injury mechanisms and renal hemodynamic responses.
- At the cellular level, RENAsym represents RPTEC life cycle, bioenergetics, and immune responses to renal toxicity. In vitro assays were used to parameterize key cellular injury mechanisms.
- At the systems level, RENAsym model represents renal function and feedback mechanisms including tubuloglomerular feedback (TGF) and renin-angiotensin-aldosterone systems (RAAS).
- RENAsym was employed to characterize the renal hemodynamic responses of drug induced RPTEC injury in humans and rats treated with nephrotoxic drugs including cisplatin.

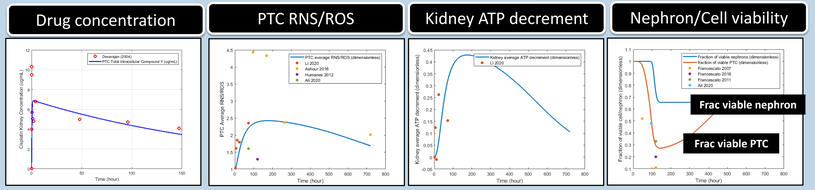


RESULTS

- The model quantitatively relates cellular injury and biomarker changes with renal hemodynamic responses.
- Nephrotoxic drugs such as cisplatin are used to assess drug-induced proximal tubule cell injury
- At the cellular level, urinary biomarkers such as KIM-1 and αGST were used to represent cellular injury (ROS/Mito dysfunction/Crystal nephropathy) and death following cisplatin exposure. RENAsym was able to capture the elevations in KIM-1 and αGST in rats treated with cisplatin.
- At the systemic level, functional biomarkers such as GFR and serum creatinine were used to represent the hemodynamic response of nephrotoxic drugs

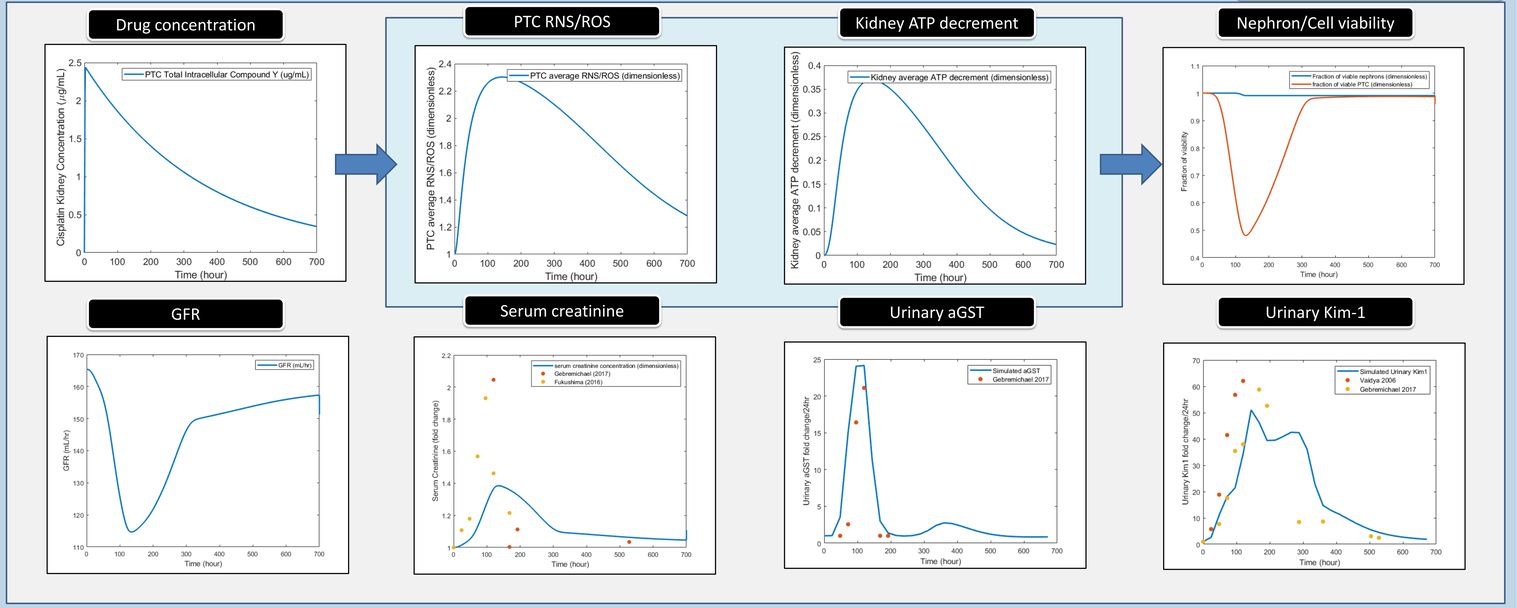


Rat cisplatin at 5 mg/kg



- Simulated rat cisplatin model compares well to the observed data for functional and urinary biomarkers at two different doses
  - Simulated viability at 2.5 mg/kg cisplatin in rats predicts a mild injury and recovery of PTC loss and GFR loss compared to 5 mg/kg cisplatin where PTC loss is not fully recovered representing a stronger injury
  - Functional biomarkers (e.g. serum creatinine) as well as urinary biomarkers (e.g. urinary aGST and Kim-1) are recapitulated for cisplatin-mediated injury in RENAsym

Rat cisplatin at 2.5 mg/kg



CONCLUSION

We developed a quantitative systems toxicology model of drug-induced acute kidney injury

- RENAsym represents kidney function at cellular and organ levels in healthy and pathologic states caused by toxic drug effects.
- RENAsym can predict clinical outcomes during AKI using functional and urinary biomarkers
- Different nephrotoxic drugs are represented in RENAsym, e.g. cisplatin, to describe drug induced cellular injury and subsequent hemodynamic changes.

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