Development of Quantitative Systems Toxicology Model to Predict Drug Induced Acute Kidney Injury via mtDNA Depletion Pathway

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ABSTRACT

Objective: Treatment of chronic viral infections like HIV, Hepatitis B etc., necessitates long-term administration of powerful antivirals like nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). Several NRTI's are primarily excreted renally and have been reported to cause nephrotoxicity. The observed toxicity is partially attributed to mitochondrial dysfunction caused by inhibition of mitochondrial DNA (mtDNA) synthesis[1]. We are developing a quantitative systems toxicology (QST) model called RENAsym® that can potentially predict drug-induced acute kidney injury (AKI) in humans and pre-clinical species by leveraging *in vitro* mechanistic toxicity data. The objective of this work is to develop a mechanistic model to represent drug-induced mtDNA depletion in proximal tubular cells and subsequent downstream toxic effects in the kidney.

Methods: The mtDNA depletion model was built within the mitochondrial dysfunction sub-model of RENAsym®. The current representation of kidney bioenergetics includes equations that describe mtDNA and electron transport chain (ETC) protein turnover, and substrate uptake and utilization by mitochondria to produce ATP. The model was parameterized based on human and rodent kidney bioenergetics data reported in literature. A physiologically based pharmacokinetic (PBPK) model including kidney exposure of IV administered adefovir was developed in GastroPlus™ 9.7 as an input for RENAsym. Toxicity parameter inputs into RENAsym for adefovir were derived from *in vitro* studies where changes in mtDNA content in primary human renal proximal tubule cells exposed to adefovir were measured using RT-PCR[2].

Results: Simulations in human at 3 mg/kg QD dosing for 40 weeks predicted a ~10% decrease in ATP level and minimal reduction in the fraction of viable PTCs. Sensitivity analysis indicated that a ~10-25% increase in either mtDNA destruction rate or kidney concentration of adefovir would predict significant nephrotoxicity (Fig. 6), which is well within the expected variability in pharmacokinetic and toxicological parameters. This qualitatively agrees with clinical observation of elevated serum creatinine in ~60% of patients treated with 120mg QD adefovir for 24 weeks[3].

Conclusions: A QST model of drug-induced mtDNA depletion and subsequent AKI has been constructed within RENAsym®. The model reasonably predicts adefovir-induced nephrotoxicity and shows promise in being a predictive tool for drug-induced AKI.

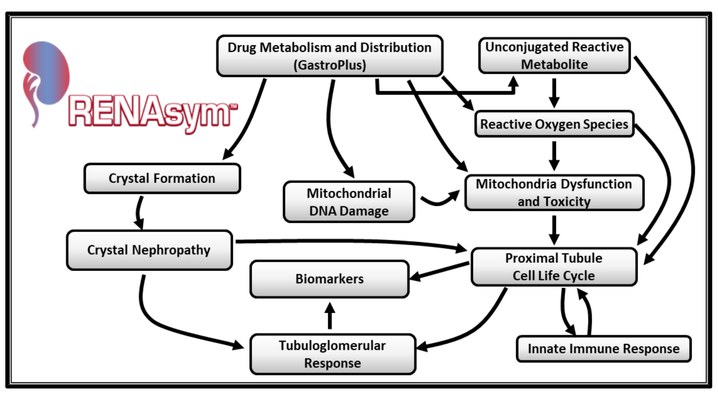

Figure 1 Overview of RENAsym model

DILIsym RENAsym IPFsym NAFLDsym

METHODS

- RENAsym, currently under development, is a QST model of drug induced AKI that integrates mechanistic *in vitro* data with *in vivo drug* exposure to predict nephrotoxicity.
- Mitochondrial dysfunction, oxidative stress and crystal nephropathy are represented within RENAsym as potential mechanisms of toxicity.
- Mitochondrial dysfunction sub-model in RENAsym representing proximal tubule cell bioenergetics and substrate utilization was adapted from DILIsym [4].
- PBPK model of adefovir was constructed in GastroPlus using data available in literature .
- Kidney concentration of adefovir predicted by PBPK model was used as input for toxicity simulations.
- *In vitro* data of adefovir induced mtDNA depletion in primary human PTECs was used to derive RENAsym parameters

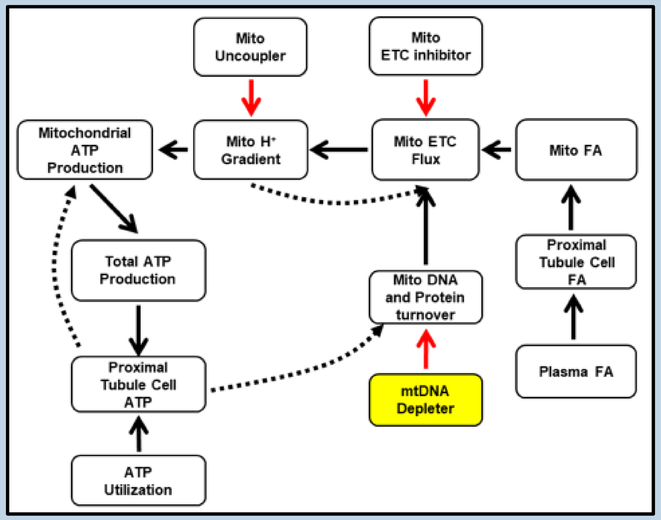

Figure 2 Summary of mitochondrial dysfunction sub-model in RENAsym

RESULTS

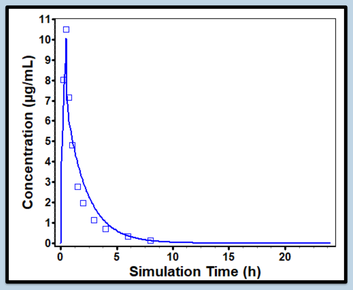

Figure 3. Simulated plasma profile of adefovir generally recapitulates clinical data

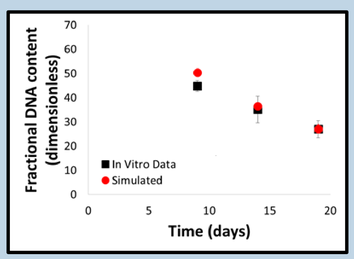

Figure 4. In vitro like conditions were reproduced in RENAsym and mtDNA destruction rate was optimized to fit experimental data

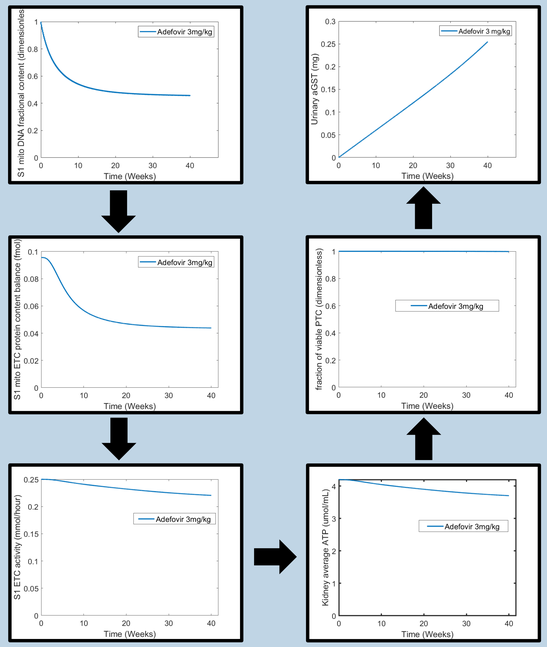

Figure 5. Simulation of adefovir at 3 mg/kg dose for 40 weeks predicted a modest decline in mtDNA/protein content, ETC activity and ATP that did not result in significant loss of PTCs or increase in urinary biomarker

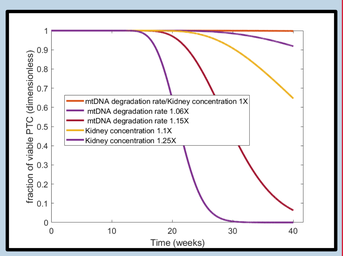

Figure 6. Sensitivity analysis indicated that small increase in either kidney concentration of adefovir or mtDNA destruction rate would predict significant nephrotoxicity which is within the expected variability.

CONCLUSION

- mtDNA depletion has been incorporated into the mitochondrial dysfunction sub-model of RENAsym.
- In the baseline simulated individual, model predicts decline in ATP but not PTC viability upon adefovir treatment.
- Sensitivity analysis indicates model is likely to predict toxicity in simulated populations.
- These results show that RENAsym shows promise in being a useful tool to predict drug induced AKI
- Model will be refined by collecting more in vitro data and representing more exemplar compounds.

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- 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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