Mechanistic Modeling of Kidney-Injury Molecule 1 (KIM-1) as a biomarker for Cisplatin-Induced Acute Kidney Injury

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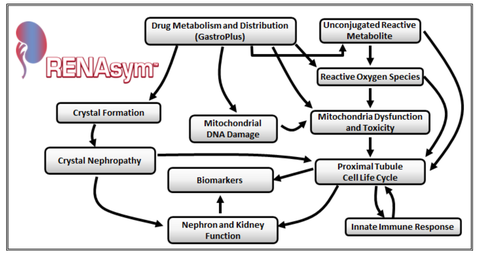
INTRODUCTION

- Kidney Injury Molecule 1 (KIM-1) is a specific and sensitive biomarker for drug-induced acute kidney injury (AKI) prediction
- Despite growing interest in clinical use of KIM-1 as a key biomarker for AKI diagnosis, a mechanistic model of KIM-1 that accurately predicts the kinetics of KIM-1 is still lacking.
- Unlike normal conditions where urinary Kim-1 is not detectable, it is significantly expressed during acute kidney injury. Kim-1 was detected at high levels in proliferating bromodeoxyuridine-positive and dedifferentiated vimentin-positive epithelial cells in regenerating proximal tubules (Ichimura 1998).
- We developed a mechanistic model of KIM-1 as part of a quantitative systems toxicology (QST) model to predict urinary KIM-1 in rats, mice and human treated with cisplatin.
- Our objective is to characterize cisplatin-induced injury of the renal proximal tubular epithelial cells (RPTEC) and biomarker responses using Kim-1 in vivo studies

METHODS

- A quantitative systems toxicology model, RENAsym™, recently developed for drug induced acute kidney injury by DILIsym Services. This model embodies key cellular injury mechanisms and renal hemodynamics.
- A mechanistic model of KIM-1 was developed within the framework of RENAsym™.
- The KIM-1 model represents the early shedding of KIM-1 arising from the loss of brush borders during sub-lethal injury of RPTEC followed by the marked expression of KIM-1 in dedifferentiated cells in regenerating proximal tubules.
- The model is integrated with the RENAsym to capture RPTEC injury and regeneration following toxic renal injury.

RENAsym QST Model



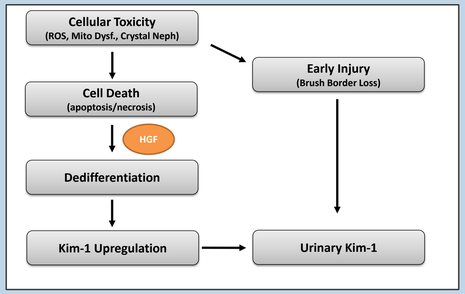
RESULTS

- Kim-1 is considered an inducible biomarker that significantly upregulated during AKI and released into the urine
- In our model, the production of Kim-1 mainly originates from upregulated Kim-1 in dedifferentiated cells and early shedding of Kim-1 comes from existing Kim-1

$$\text{Kim1 Excretion} = \text{Basal Kim1}\,(1) + \text{Exisiting Kim1}\,(2) + \text{Kim1 upregulation}\,(3) - \text{Kim1 shedding}$$

1. The basal Kim-1 production at steady state is set to be very low in line with the basal shedding rate of Kim-1 reported in control healthy individuals (Peters 2011)
2. Urinary Kim-1 is reported before dedifferentiation process begins, and it may be attributed to proximal tubule brush border loss
   - An existing level of Kim-1 is assumed to be sitting on PTCs and its shedding rate into the urine is determined based on ATP decrement
3. Kim-1 is markedly upregulated in regenerated PTCs and mechanistically linked with the flux of dedifferentiated cells in RENAsym
   - Increase in dedifferentiated cells is associated with increase in hepatocyte growth factor (HGF) following apoptotic or necrotic cellular death

Kim-1 Mechanistic Model



Model Calibration

- Calibration of model compares well to available preclinical and clinical data
  - A PBPK model built in GastrPlus9.8 to determine the kidney intracellular concentration of cisplatin and was further verified with clinical and preclinical data
  - Cisplatin exposure from PBPK model was combined with drug toxicity parameters obtained by parameterization of *in vitro* assay results in Renal Proximal Epithelial Tubular Cells (RPTEC) and translated from *in vitro* to *in vivo* for each species
  - Cumulative urinary Kim-1 was obtained from simulations and urinary Kim-1 fold change for every day was calculated, and calibrated Kim-1 timing/magnitude for cisplatin-mediated injury with preclinical/clinical data
  - Kim-1 model including upregulation rate constant for PTC dedifferentiated cells and early shedding rate constant were adjusted to recapitulate human, rat and mouse Kim-1 data

❑ **Rats**

- Rats treated with cisplatin at 2.5 mg/kg were simulated in RENAsym
- Simulation results show that the shedding of existing Kim-1 results in 20 fold-increase of urinary Kim-1 around day 4 (orange line)
- Urinary Kim-1 fold change peaks between day 5 and day 6 mainly due to Kim-1 upregulation
- The kinetics of urinary Kim-1 fold change from simulations agrees well with the observed Kim-1 profile (Gebremichael 2018 and Vaidya 2006)

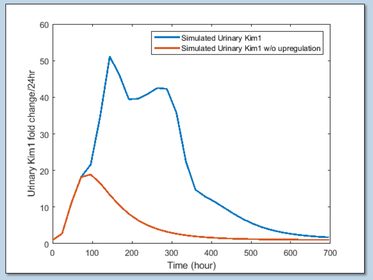
❑ **Humans**

- Humans treated with 4hr IV infusion of cisplatin at 75 mg/m2 were simulated in RENAsym
- Simulated urinary Kim1 fold change per 6hr well captures the observed urinary Kim-1 peak (Tekce 2015)

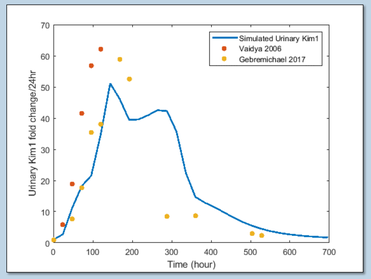
❑ **Mice**

- Mice treated with cisplatin at 20 mg/kg were simulated in RENAsym
- Simulated urinary Kim1 fold change per 24hr shows a good agreement with the peak in the observed data for mice treated at the same dose (Oh 2017)

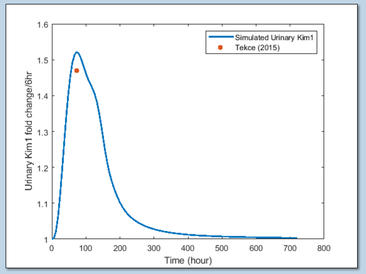
Rat cisplatin at 2.5 mg/kg



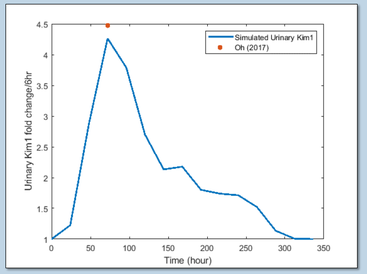
Rat cisplatin at 2.5 mg/kg



Human cisplatin at 75 mg/m2



Mouse cisplatin at 20 mg/kg



CONCLUSION

Developed a mechanistic model of urinary Kim-1 biomarker response to characterize cisplatin-mediated acute kidney injury

- Kim1 model recapitulate the Kim-1 profile in rats treated with cisplatin as well as the Kim-1 peak in humans and mice
- Kim-1 upregulation is determined to be the main contributor to urinary Kim-1 during AKI
- Using dedifferentiation as the driving signal for Kim-1 upregulation, the timing of predicted Kim-1 peak aligns with the clinical and preclinical data
- As dedifferentiation starts with a delay, we could capture the early increase in urinary Kim1 by assuming the shedding of existing Kim-1 sitting on PTCs

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