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

**Nader Hamzavi**, Yeshitila Gebremichaelb, Jeffrey L. Woodheada, Sergey Ernakov, and Brett A. Howella

aDILLsym Services Division, Simulations Plus company, Research Triangle Park, NC, bValo Health, Boston, MA, cDaichi Sankyo, Inc, Hayward, CA

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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 bromatic-endothine- 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 DILLsym Services. This model embodies key cellular 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.

**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 coming from existing Kim-1.

**Model Calibration**

- Calibration of model compares well to available preclinical and clinical data.
- A PBPK model built in GastroPlus®8.0 to determine the kidney intracellular concentration of cisplatin 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.

**CONCLUSION**

- Developed a mechanistic model of urinary Kim-1 biomarker response to characterize cisplatin-mediated acute kidney injury.
- Kim-1 model recapitulates 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 Kim-1 by assuming the shedding of existing Kim-1 sitting on PTCs.

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**REFERENCES**


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