PO0103-3

Mechanistic Representation of Clusterin, a Damage Biomarker for Early Detection of Drug-Induced AKI

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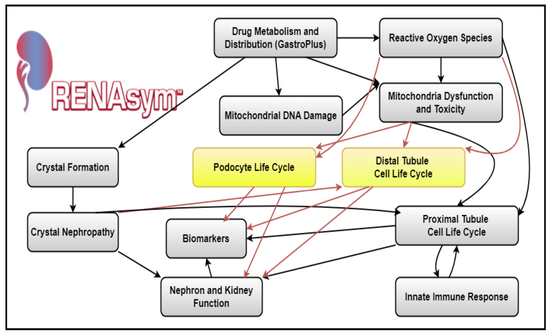
BACKGROUND: Novel biomarkers have the potential to address early diagnosis and timely intervention of acute kidney injury (AKI). To fully leverage the clinical potential of these biomarkers, a mechanistic understanding of the biological processes that lead to biomarker release is essential.

METHODS: We developed a mechanistic model of clusterin (CLU) within the framework of RENAsym, a QST model of drug-induced AKI that incorporates key cellular injury mechanism and renal hemodynamics. After cellular injury, clusterin gene is known to be upregulated. The clusterin model was used to predict urinary clusterin following cisplatin administration to rats in connection with necrosis and/or dedifferentiation of proximal tubular cells (PTC).



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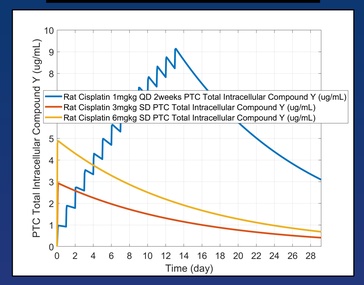
Quantitative systems toxicology modeling predicts the behavior of novel injury biomarkers following AKI

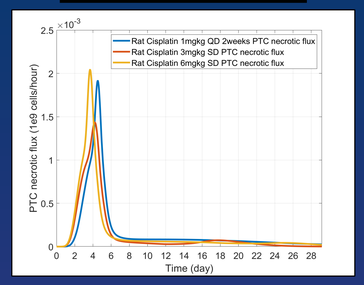
RESULTS:

- Simulated rats treated with single doses (3 mg/kg and 6 mg/kg) and daily dosing (1 mg/kg for two weeks) of cisplatin show that necrotic flux peaks around day 5, while dedifferentiation is predicted to peak 10 more days later.
- Literature data shows that urinary clustrin also peaks on day 5 (Gautier 2010, Vinken 2012, Pianta[1,2] 2017) consistent with necrosis peak time.

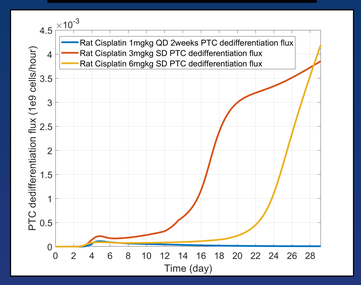
PTC Concentration



Necrotic flux

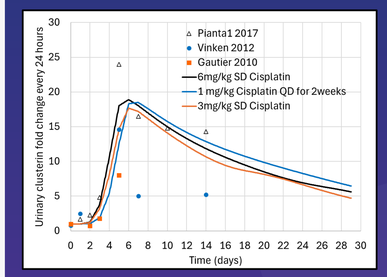


Dedifferentiation flux

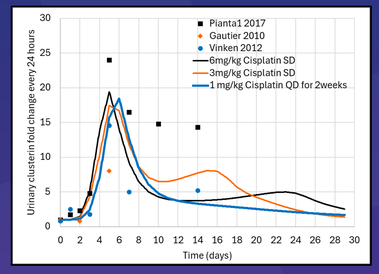


- Clusterin normalized by urinary creatinine shows a sustained presence in the urine after the peak and no return to baseline after one week.
- Urinary clusterin is closely represented up to day 5 in our model.
- Slow shedding rate or including dedifferentiation can predict a slow decay but neither are able to represent a sustained presence in the urine observed in normalized urinary clusterin.

CLU production connected with necrotic flux

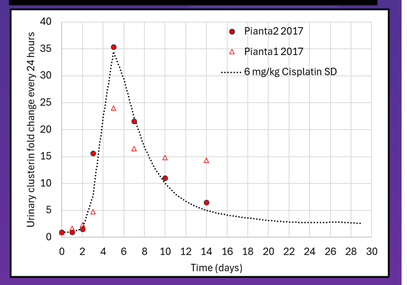


CLU production connected with necrotic and dedifferentiation flux



- In contrary to normalized creatinine, change of absolute amount of clusterin shows a natural decay (Pianta 2017[2]) which can be captured by only necrotic flux driving clusterin production and a proper shedding rate.

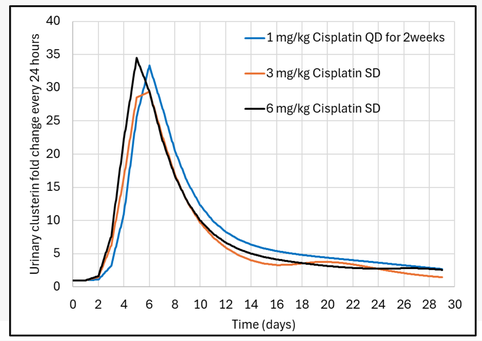
CLU production connected with necrotic flux using absolute amount of clusterin



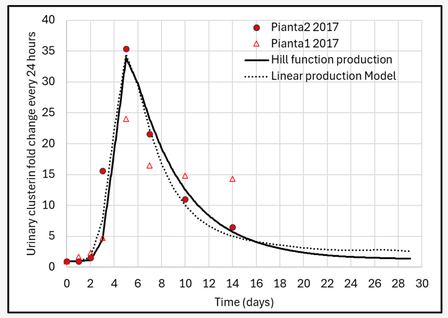
Tox Mechanisms → **PTC ATP Decrement** → **Cellular Death** → **Clusterin Production** → **Urinary Clusterin**

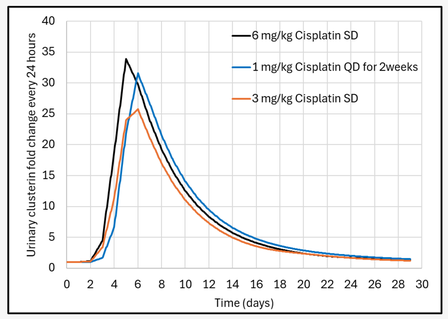
Vinken P et al. Toxicol Pathol. 2012;40(7):1049-1062.
Gautier JC et al. Toxicol Pathol. 2010;38(6), 943-56.
Pianta[1] TJ et al. Kidney Blood Press Res. 2017;42(1), 62-75. PMID: 28315878
Pianta[2] TJ et al. Toxicol Lett. 2017;268, 63-70. PMID: 28065798
Hidaka S et al. Cell Tissue Res. 2002;310(3), 289-96.

SUPPORTING FIGURES of LINEAR PRODUCTION MODEL: Urinary clusterin is predicted across two single doses and one daily dose of cisplatin but dose proportionality is not well represented.



FIGURES OF ALTERNATIVE Hill PRODUCTION MODEL: Like a linear production model, a Hill production model can represent clusterin kinetics. However, this model better predicts a dose-proportional response following cisplatin treatment.





Conclusion:

- This modeling informes that signals from necrotic tubular cells can predict the change of absolute magnitude of urinary clusterin.
- QST modeling enables prediction of behavior of novel kidney injury biomarkers following acute kidney injury.

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