Objectives: To develop a quantitative systems pharmacology model of drug-induced renal injury that uses novel structural biomarkers to predict functional/pathophysiologic renal responses.

Methods: We employed a systems pharmacology model to predict pathophysiological responses to drug-induced proximal tubule (PT) injury. Cisplatin is a known nephrotoxicant that produces localized PT damage and is used as a test compound for the model. To inform the mathematical model, we utilized multiple urinary biomarker timecourse data (including KIM-1, uGST, albumin, glucose, urine volume, creatinine, etc.) from rats treated with cisplatin. Time profiles for biomarkers indicative of structural/cellular damage were used as input signals to the mathematical model (cf. Figure below).

Results: The time-course of urine biomarkers exhibited unique patterns that elucidated two groups of biomarkers with distinct timecourses: one group of expressed or up-regulated biomarkers with a broad peak at day 7, and another group of filtered and pre-formed biomarkers with a steep narrow peak at day 5. The two classes were hypothesized to represent distinct injury mechanisms and to reflect associated changes in PT function (water, sodium, glucose, albumin reabsorption). Under this hypothesis, uGST and KIM-1 timecourses were used to reflect changes in PT function in the model, and the model predicted the magnitude and timecourse of functional urinary biomarker responses including albumin and glucose. The sharp rise and decline exhibited by these biomarkers also correlated with qualitative histopathological data indicating the timecourse of necrosis and regeneration of PT epithelial cells.

Conclusion: The developed model quantifies changes in PT reabsorption and allows simulation of functional biomarkers based on measurement of two biomarkers (uGST and KIM-1) which represent distinct injury processes. Future work includes mapping drug-induced renal injury across additional tubular segments and the glomerulus. Such a model will facilitate benchmarking safety signals of new drugs, as well as translating to human injury in the setting of chronic kidney disease.