The aProximate™ in vitro renal proximal tubule cell model as a platform to investigate the renal uptake and nephrotoxic liability of biologics.

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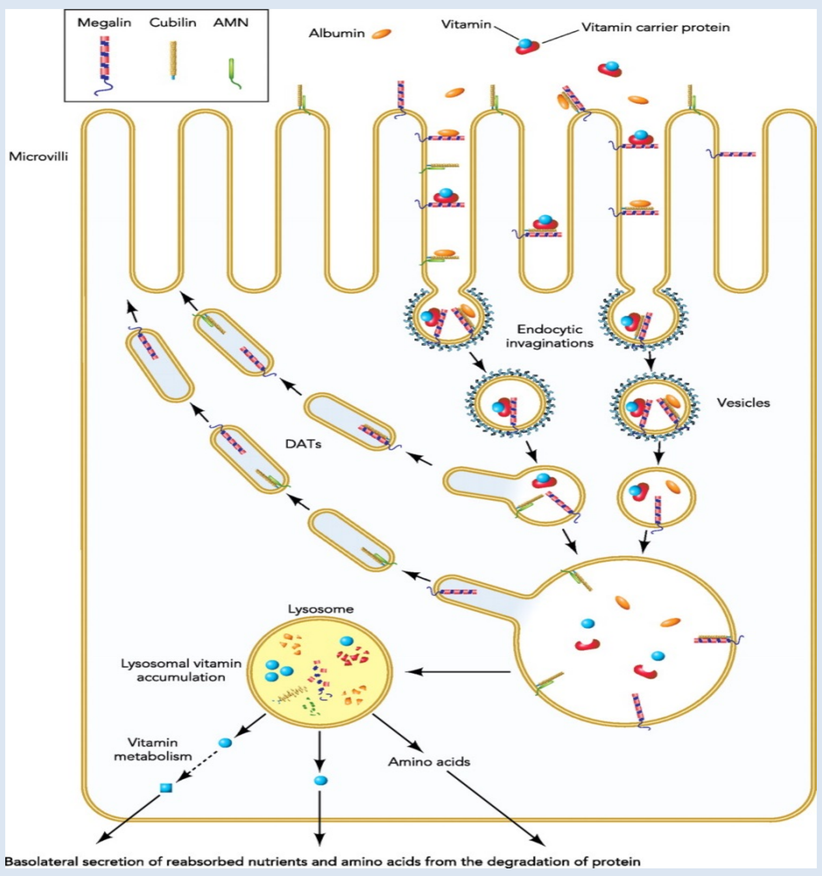
Introduction

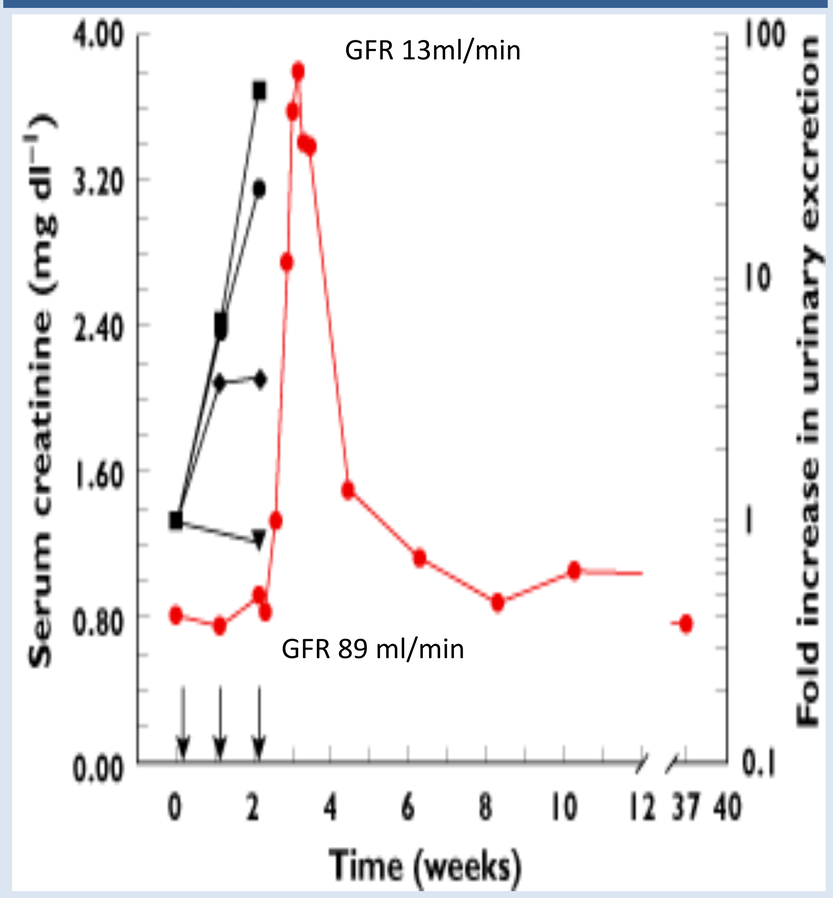
- Many biologics accumulate in the kidney and may cause unforeseen kidney injury
- Currently there is no in vitro platform that enables cross-species comparisons of drug transport or nephrotoxicity.
- Our innovative solution is to develop highly differentiated assay platforms using primary renal proximal tubule cells(PTCs) derived from key animal species to measure both drug transport and drug induced kidney injury a range of biomarkers across species
- Here we showcase data from our highly differentiated Human Primate proximal tubule model showing its utility in the study
- Of biolocics

Megalin- Cubulin mediates Renal Biologics Uptake



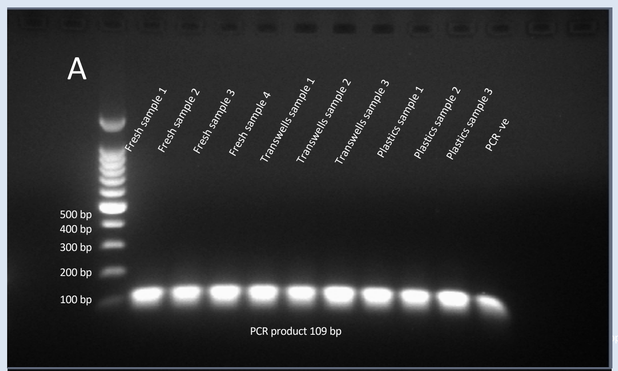
Basolateral secretion of reabsorbed nutrients and amino acids from the degradation of protein

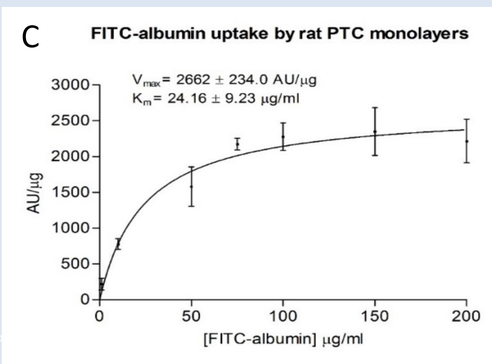
SPC-5001 Challenge resulted in nephrotoxicity in Man

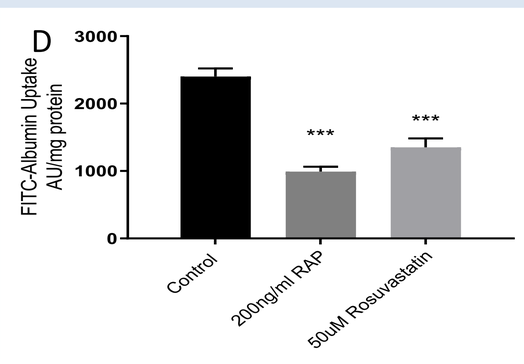


Data from van Poelgeest et al Am.J.Kid. Dis 62 (2013)

Albumin and siRNA Uptake by Megalin Cubulin

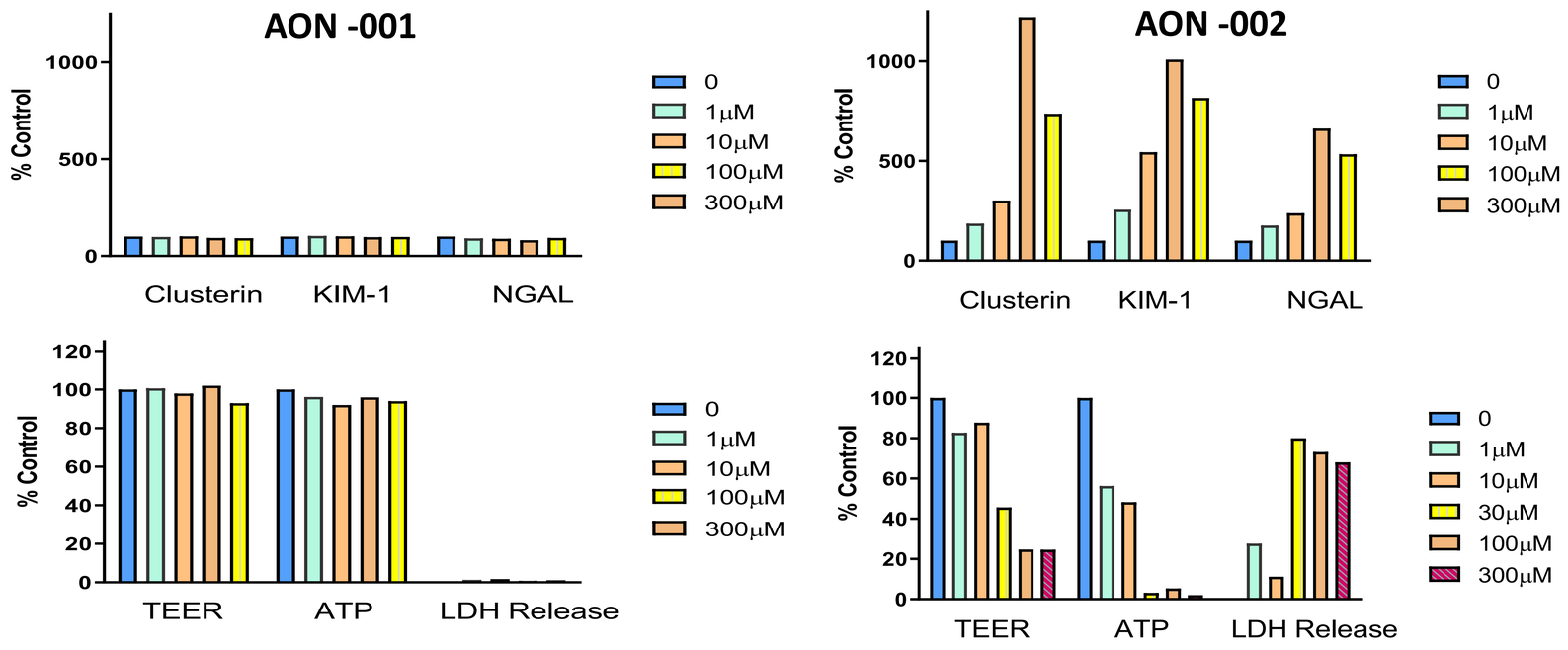




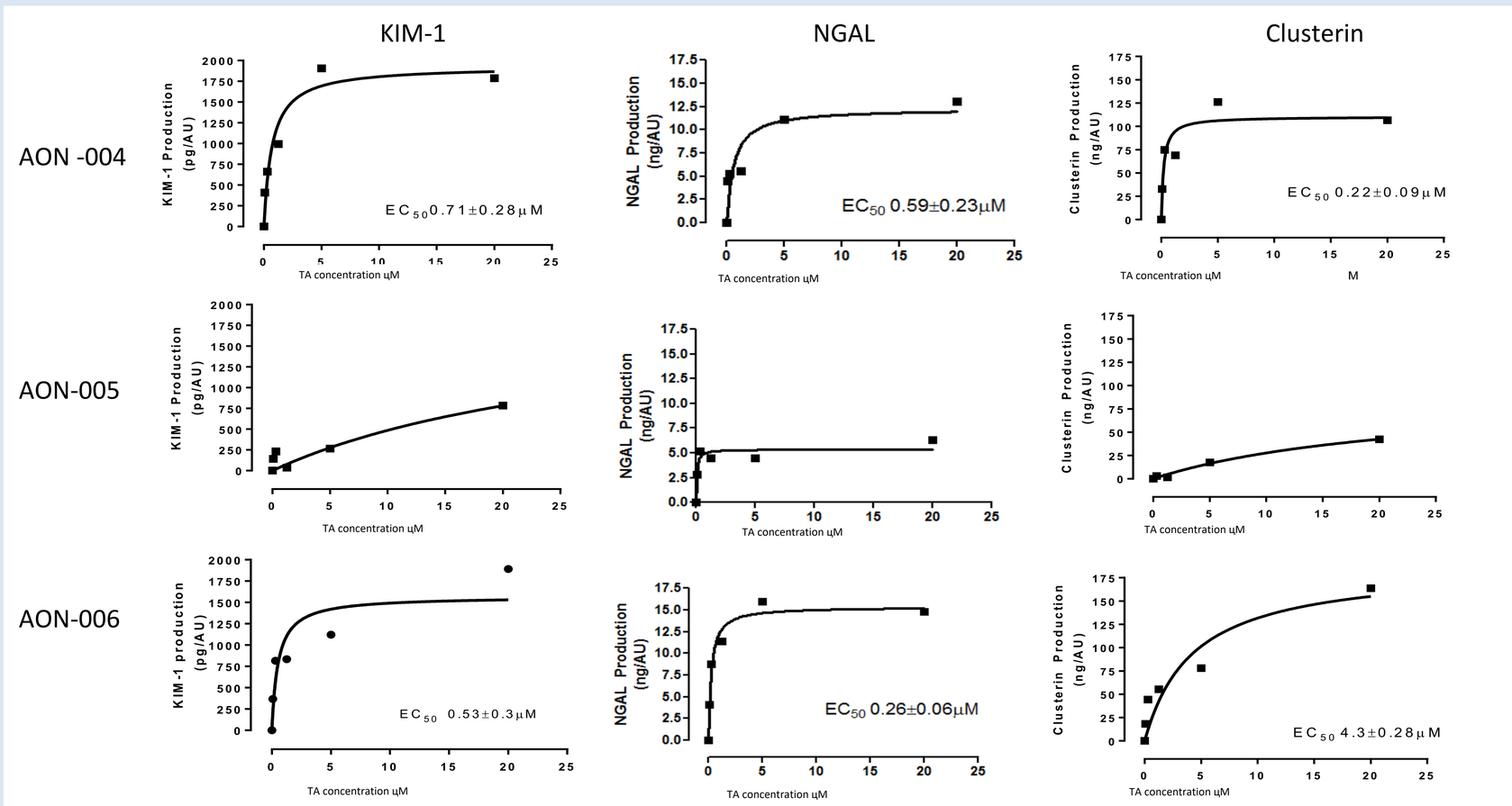


Megalin (A) and Cubulin (B) were expressed in rat PTC cell monolayers. Functional expression of Megalin-cubulin was demonstrated by showing saturable FITC-Alubumin uptake (C)) that was inbited by exposure to Rosuvastatin or RAP (D). Uptake of a labelled siRNA showed similar saturable uptake kinetics (E)) and uptake was significantly inhibited by Rosuvastatin or RAP

Biomarker Response to Antisense Oligonucucleotide Challenge



Comparison of challenge of human PTC cells to 72 hour exposure to 2 AONs. AON-001 had no effect on any markers of kidney injury. In contrast, AON-002 resulted in significant increases in all markers of kidney injury . Data n=6 from single kidney



Dose response curves generated from challenge of human PTC cells to 72 hour exposure to 3 AONs. AON-005 had no effect on any markers of kidney injury. In contrast, AON-004 and AON-006 resulted in significant increases in all markers of kidney injury with EC50 values in the nanomolar range. Data n=6 from single kidney

Conclusions

Human and rat proximal tubule cell monolayers retain a remarkable degree of differentiation and express a range of functional transporters and clinically relevant biomarkers of nephrotoxicity that are sensitive to nephrotoxin challenge over time. Human PTC monolayers show excellent potential as an in vitro predictive screening platform for biologics