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

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Kidney

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Introduction

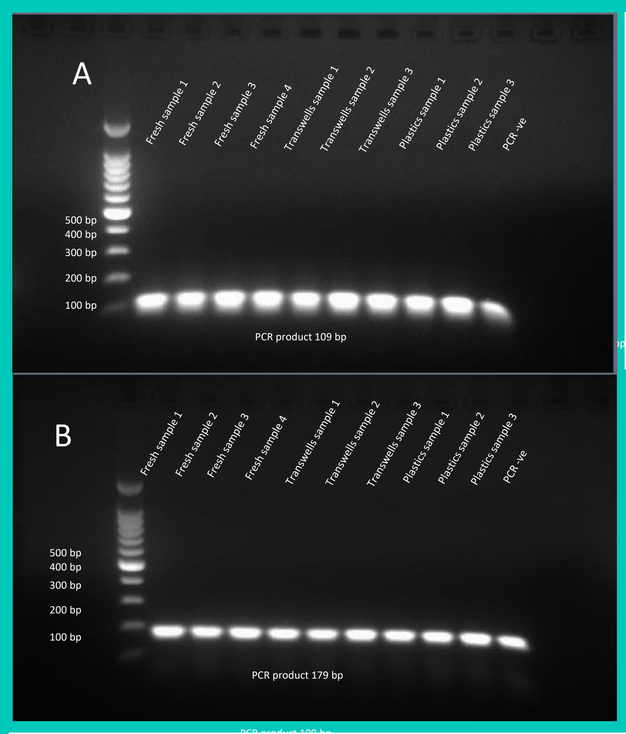
Many biologics accumulate in the kidney and may cause unforeseen kidney injury

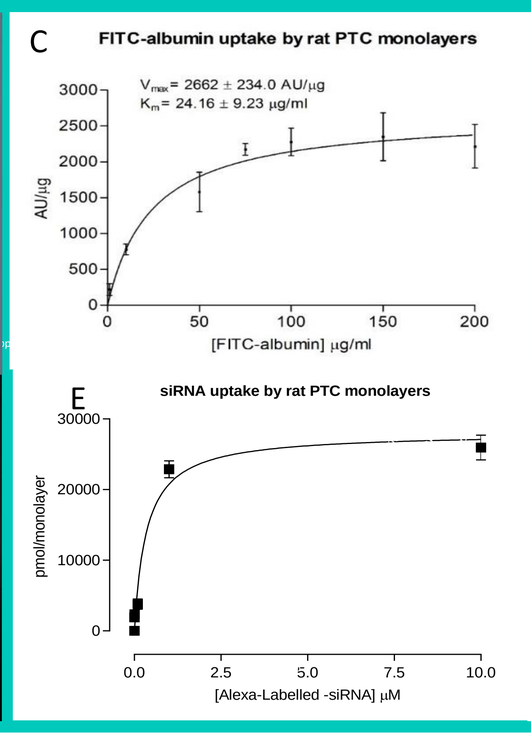
Currently there is no in vitro platform that enables cross-species comparisons of drug transport or nephrotoxicity.

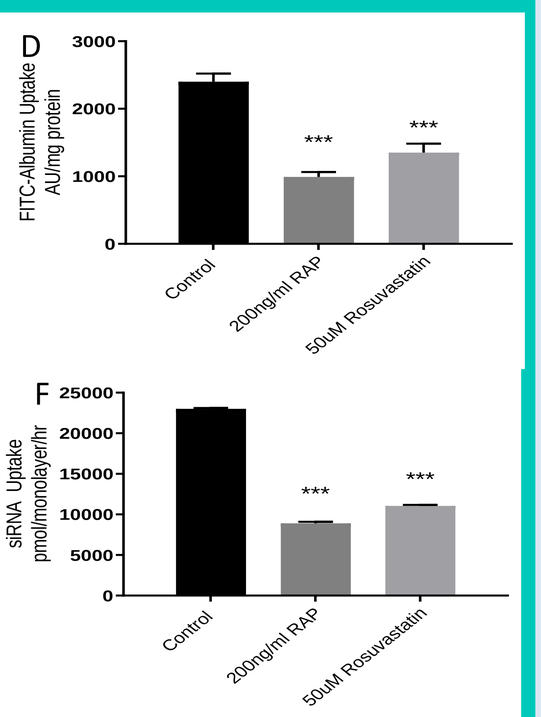
Our innovative solution is to develop highly differentiated assay platforms using primary renal proximal tubule cells(PTCs) derived from key animal species to measure both drug transport and drug induced kidney injury a range of biomarkers across species

Here we showcase data from our highly differentiated Human Primate proximal tubule model showing its utility in the study of biologics

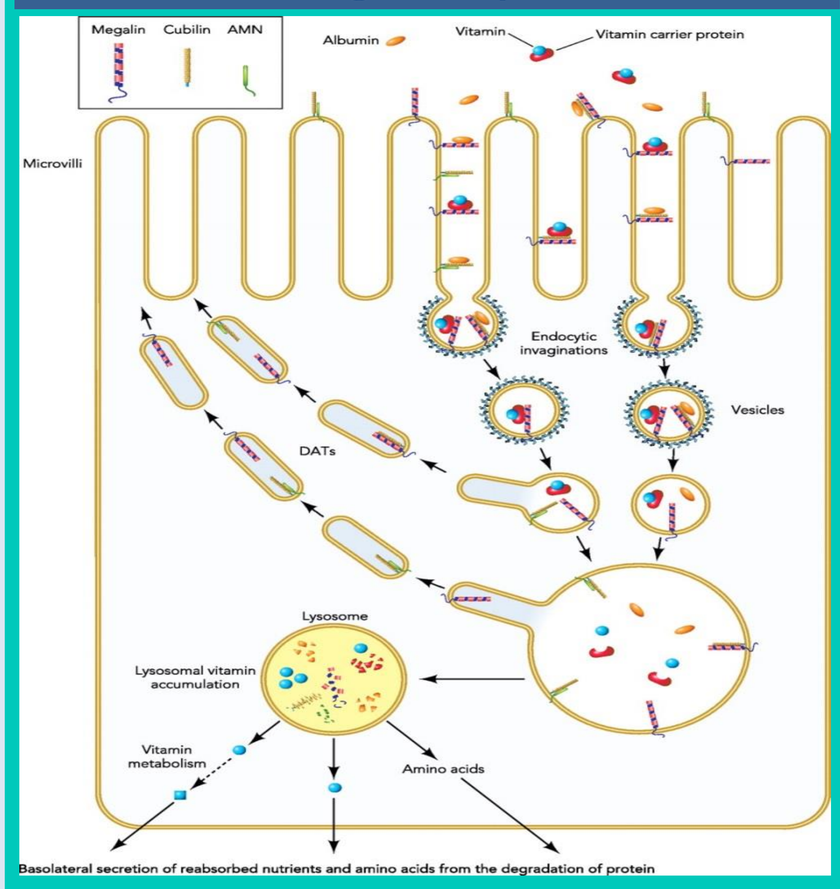
Albumin and siRNA Uptake by Megalin Cubulin





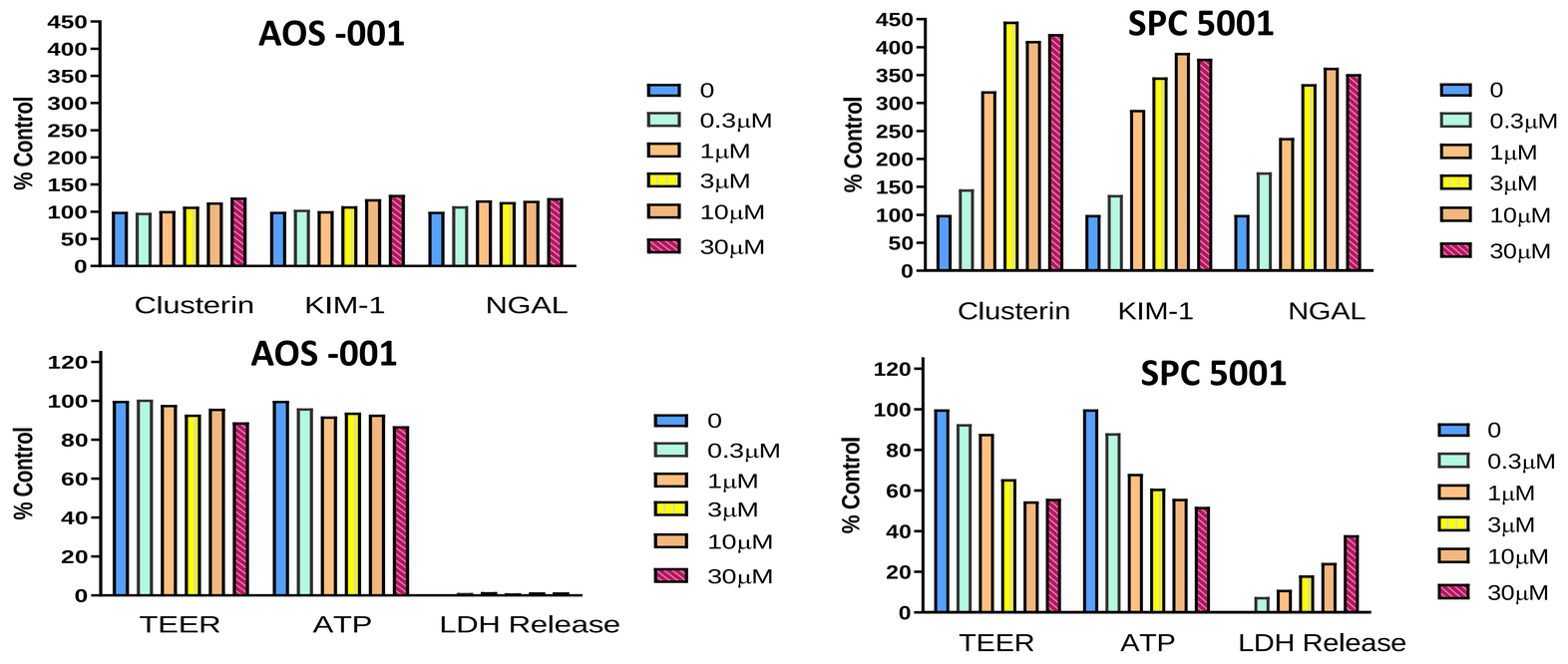


Megalin- Cubulin mediates Renal Biologics Uptake



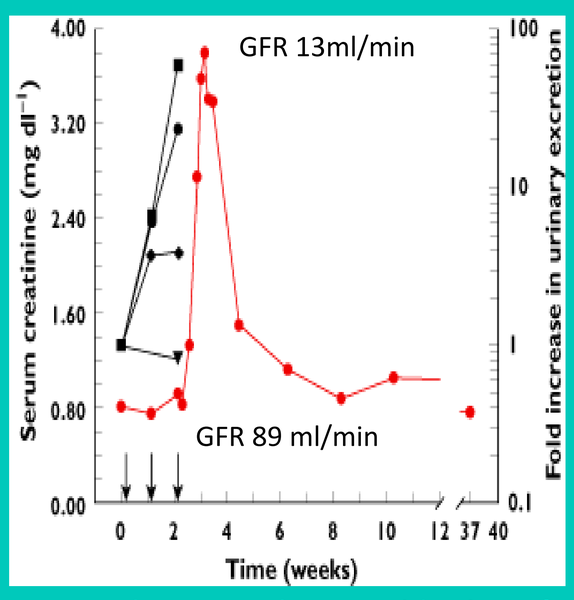
Megalin (A) and Cubulin (B) were expressed in rat PTC cell monolayers. Functional expression of Megalin-cubulin was demonstrated by showing saturable FITC-Albumin uptake (C)) that was inbited by exposure to Rosuvastatin or RAP (D). Uptake of a labelled siRNA showed similar saturable uptake kinetics (E))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

Biomarker Response to Antisense Oligonucucleotide Challenge



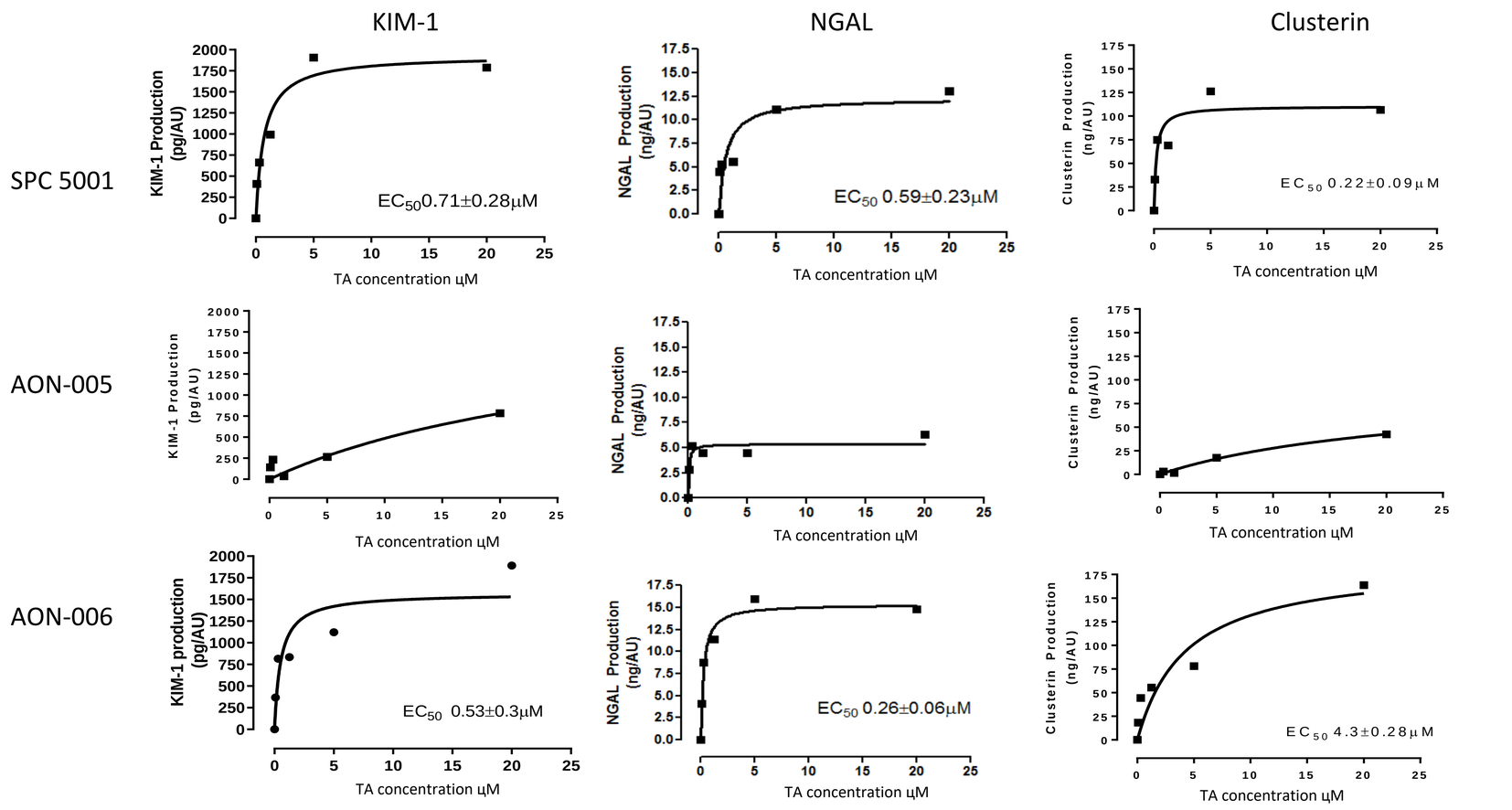
Comparison of challenge of human PTC cells to 72 hour exposure to 2 AOSs. AOS-001 had no effect on any markers of kidney injury. In contrast, SPC 5001 resulted in significant increases in all markers of kidney injury . Data n=6 from single kidney

SPC-5001 Challenge resulted in nephrotoxicity in Man



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

The anti sensense oligonucleotide SPC 5001 showed very limited liability in animal models. However, in human trials, SPC 5001 was shown to cause frank renal toxicity as measured by a rise in serum creatinine levels. The measurement of serum creatinine REPORTS renal damage. The use of biomarkers (which were only analysed after the event) clearly PREDICT that exposure to SPC 5001 was causing renal injury before the rise in serum creatinine was detected



Dose response curves generated from challenge of human PTC cells to 72 hour exposure to 3 AOSs. AOS-005 had no effect on any markers of kidney injury. In contrast, SPC 5001 and AOS-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