aProximate™

KIDNEY

Transporter and drug-drug interaction (DDI) studies

Overview

Newcells Biotech has developed and validated an *in vitro* pre-clinical assay for measurement of drug and xenobiotic transport in kidney proximal tubule cells.

The assays are available for measurement of drug flux and transporter mechanism in human, rat, mouse, dog and NHP formats.

The assay expresses all the major transporter proteins in a polarised apical and basolateral orientation. This allows the modelling and measurement of adsorption and excretion fluxes, net flux and steady-state intracellular drug levels.

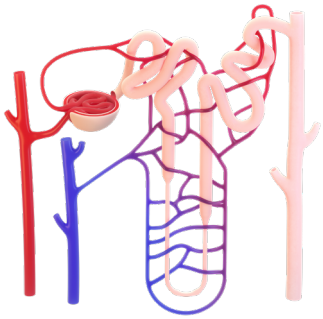
By the use of known inhibitors, the assay can be used to assess the major transporters for individual drugs as well as to understand drug-drug interactions.

Analysis requires radiolabelled substrate or bioanalytical approaches can be used.

Services and products

Newcells offer a full service for assessment of customers compounds carried out by our fully experienced scientists under the guidance of our Director of ADMET. We work with customers to design a study protocol that provides key data to support pre-clinical decisions.

In addition, we have developed the option for collaboration projects to ship plates to customers for in-house use.

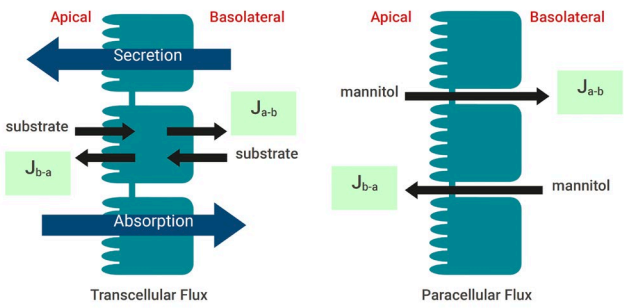


Applications

The measurement of drug kidney transporters has become increasingly important in drug discovery as the understanding has grown of their role in drug disposition in humans. The guidance from regulatory agencies is that if ≥25% of the absorbed dose is excreted unchanged in urine then in vitro studies on kidney transporters are recommended.

Widely used preclinical models of transport in the kidney are based on transfected human or animal cells which express a limited number of human renal transporters, and so do not accurately reflect the situation in vivo wherein the complex interplay between multiple transporters (determined by their relative protein expression and cellular localization) is key to the process of drug translocation. In contrast, the primary renal proximal tubule cell monolayer assay maintains the full complement and expression level of endogenous renal transporters, resulting in a more physiologically relevant, and therefore predictive, model of drug handling and nephrotoxicity in the clinical setting.

The assay has been developed and validated to measure small and large molecule transport including proteins, antibodies and oligonucleotides. The assay has been used in a wide range of study protocols for DMPK/ADME and DDI measurements.



Primary kidney proximal tubule cells are isolated and cultured on 24-well trans-well plates. The cells form a confluent monolayer polarised with tight junctions that allows the addition of test compounds to the apical or basal sides of the tubule. Experiments can be conducted using radiolabelled substrates or bioanalytical approaches. Using mannitol as a control substrate determines the level of paracellular flux which adjusts for non-transporter mediated flux. By the addition of known inhibitors or other compounds the assay allows identification of the primary transporters and drug-drug interactions.

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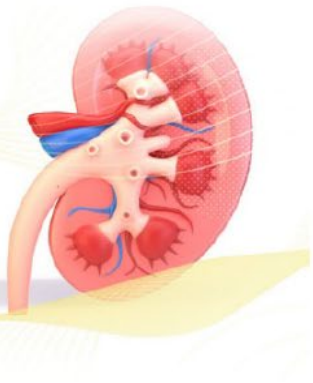
KIDNEY



Examples and Supporting Data

Metformin transport in Human PTCs

Monolayers of human kidney proximal tubule epithelia cells were treated with known inhibitors of the MATE and OCT transporters to confirm the mechanism of Metformin transport

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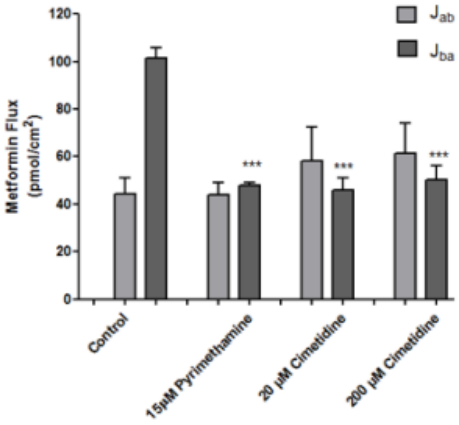
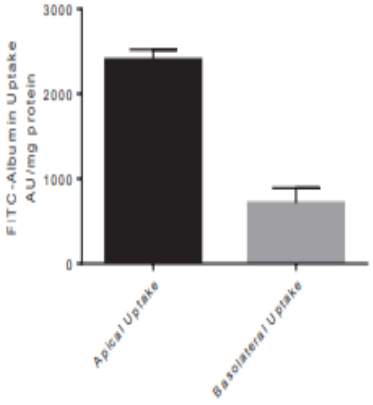
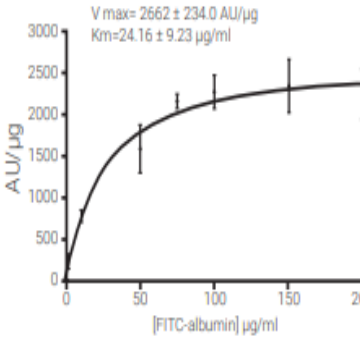
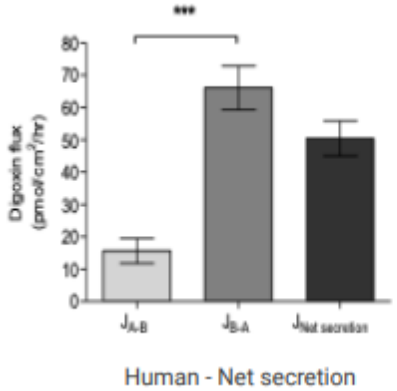




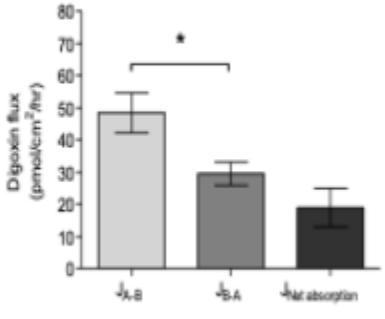


Investigation of cross-species drug handling - Digoxin

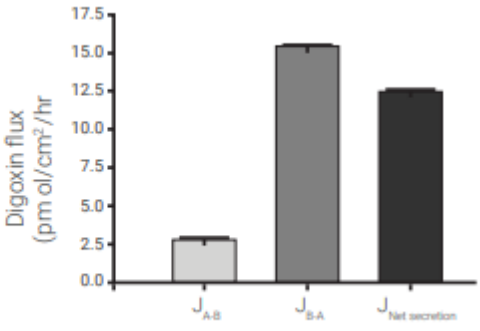
The assay was used to examine the net fluxes in human, rat and NHP kidney proximal tubule epithelia monolayers



Human - Net secretion



Rat - Net adsorption



NHP - Net secretion

References

Brown CDA, Sayer R, Windass AS, Haslam IS, De Broe ME, D'Haese PC, Verhulst A. Characterisation of human tubular cell monolayers as a model of proximal tubular xenobiotic handling. Toxicology and Applied Pharmacology 2008, 233(3), 428-438. Chung GW, Billington SF, Jenkinson SE, Brown CD. Drug transporters in the kidney. In: Nicholls G; Youdim K, ed. Drug Transporters : Volume 1: Role and Importance in ADME and Drug Development. Cambridge: Royal Society of Chemistry, 2016, pp.109-150.