CRACK IT Solutions

Development of *in vitro* cross species renal proximal tubule DMPK and drug safety platforms

We are looking for a collaboration with the pharmaceutical or biotechnology sector to develop and validate primary cell cultures for inter-species comparisons of renal toxicity between toxicologically relevant species and man. The current animal testing regime for drug molecules in late development pipelines is poorly predictive of 'first in man' toxicity. Renal issues account for around 25% of failures and there is a lack of good robust and predictive renal cell models.

What could your solution be used for?

We have developed primary cultures of proximal tubule cells grown as monolayers on permeable filter supports (aProximate™). These renal models remain differentiated and provide for the first time models which allow both a mechanistic and predictive understanding of drug transporters and drug-drug interactions to better predict the potential of a compound to induce renal toxicity in humans.

Need for collaboration

Primary cell models are currently leading edge but in order to realise its full potential as an accurate 'predictor' of renal toxicity and help accelerate drug development, we are seeking partners to work with us on one or more of the following research proposals to:

- Further validate the primary renal model (aProximate™) of renal tubular function by collaborating in the generation of *in vitro* to *in vivo* correlations for both renal drug clearance and measures of renal toxicity utilising compounds/established drugs for which good *in vivo* data of renal toxicity or renal clearance is established.
- Validate parallel rodent/dog species primary proximal tubule models to fill knowledge gaps and address the 3Rs, with the goal of reducing animal studies with a robust *in vitro* model. The input of industry partners is requested to direct and focus the research towards their requirements in a drug development setting. For example; multiple species monolayers on a single assay plate would allow simple rapid and accurate determination of species to species variation.
- Develop methods of cryogenic preservation that would allow cells to be stored until required. This would have the following positive benefits: (i) it would maximise use of scarce donor tissue; and (ii) pooling of cells removes batch to batch variation and importantly monolayer production would become independent of availability of donor tissue ensuring an uninterrupted supply of human cell monolayers.
- We are also keen to investigate whether growing cells in 3D-culture provides further differentiation and functional expression of properties of native tissue than achieved growing cells on permeable filter supports (2.5D cultures).

3Rs impact assessment

Assessing the safety of drug candidates accounts for approximately 10-20% of the animals used in the drug discovery and development process. Identifying compounds destined to fail in humans due to nephrotoxicity early in the drug discovery process using more predictive *in vitro* assays will avoid drugs destined to fail in development being tested in animals. These systems may also help to refine animal studies where they are still required by providing more information on the underlying mechanisms of toxicity and therefore the potential for the use of lower doses and earlier endpoints.

To find out more or to connect with the technology developer contact crackitenquiries@nc3rs.org.uk

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