Title of Challenge

A predictive *in vitro* screen for nephrotoxicity: from mice to men and back again

Background

The kidney, together with liver and heart, is among the most important target organs for the detection of undesired adverse effects during drug development. Kidney toxicity accounts for 2% of drug attrition during preclinical studies and 19% in phase 3 (1). There is a clear need for experimental models to both predict as well as to investigate drug-induced toxicities in the kidney. In recent years, significant progress has been made in the establishment and qualification of kidney toxicity biomarkers in rodents and in their transferability to man (2). However, there are no well established *in vitro* assays available to investigate kidney toxicity.

The aim of this challenge is to establish *in vitro* predictive assays that can provide reliable nephrotoxicity assessment. Such assays would allow information from several toxicologically relevant species (e.g. mouse, rat and dog) and from human-derived cells to be obtained. *In vitro* assays will also help understand the mechanistic basis of nephrotoxicity in different chemical classes of drug. Such systems would also allow a direct comparison of compound effects in rodent, non-rodent (e.g. dog) and human-derived cellular systems aiding compound selection and design of preclinical studies, e.g. species selection and appropriate dosing regimes.

3Rs Benefits

Assessing the safety of drug candidates accounts for approximately 10-20% of the animals used in the drug discovery and development process. Improved *in vitro* assays for predicting nephrotoxicity will avoid drugs destined to fail in development being tested in animals, and where animals are used, improved information on the underlying mechanisms of toxicity will help refine study designs, including dosing regimes and species selection.

Need for collaboration

The kidney is a complex organ in terms of its multiple cell types and architecture. There are several kidney cell lines, mainly from the proximal tubule, that may provide a first indication of direct tubular toxicity. However, more complex systems such as co-cultures which include additional cell types and organotypical models need to be established, characterised and evaluated as possible test systems. The characterisation of such cell culture systems and the selection and establishment of suitable readouts require a diversity of expertise in the field of cellular and molecular assays (e.g. high content imaging, genomics, real-time read outs, etc). Collaboration between applicants with cell culture and assay expertise, and industry sponsors that can facilitate access to a selection of reference compounds with well characterized toxicological profiles derived from already performed *in vivo* experiments is essential. Technological expertise on the designated endpoints could be provided by both applicants and industry sponsors.

Overall objectives

To develop an *in vitro* cell-based model for the testing of nephrotoxicity that allows inter-species comparisons between toxicologically relevant species including rodents, non-rodents and man. The model should include both predictive and mechanistic aspects.

Key deliverables

- Identification and characterisation of appropriate cell types (cell lines and primary cells) to address kidney function;
- Establishment of appropriate endpoints for the detection of nephrotoxicity;
- Validation of the predictive performance of the assay by assessing a sufficient number of compounds and generating predictive statistical models with the obtained data;
- Demonstration that the model can provide mechanistic information on the underlying toxicological processes;
- Transfer of the assay(s) to industry standard platforms and initiating the process for formal validation (e.g. via ECVAM).

Industry sponsors

Roche, AstraZeneca and UCB

In-kind contributions

Projects of this nature require both toxicological expertise and availability of commercially available and proprietary compounds, as well as extensive analytical and instrumentation support. In-kind contributions from the pharmaceutical industry sponsors will include the provision of compound information and compounds for the assays being developed. In addition, access to instrumentation such as molecular biology platforms (e.g. microarrays), real-time read out (e.g. xCelligence), and high content imaging (HCI) platforms will be possible. Applicants could have access to these technologies at the site of the industry sponsor. The sponsor or the database-provider could perform the data analysis and models for the independent assessment of the model performance in terms of specificity and sensitivity.

Industry sponsor access to foreground Intellectual Property

The companies participation is conditional on a provision entitling them to use the results of the programme in their research and development (R&D) activities, in the form of a non-exclusive, royalty-free usage right on the results obtained under such project for the purpose of carrying out R&D activities for discovering novel commercial pharmaceuticals.

Duration

Up to three years

Budget

Up to £750,000 in total, inclusive of VAT where applicable

Funding Model

Although success in this project will require a multi-disciplinary approach, there are various ways in which this could be managed. It is unlikely that an applicant from a single organisation would be able to access all the required expertise and applications are therefore welcomed from consortia in which one organisation takes the lead (the Contractor) on behalf of the others (the Subcontractors).

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Keywords

Kidney, toxicity, organotypical, cultures, mechanistic, human, rodent, biomarkers.