Challenge 1: A predictive *in vitro* screen for nephrotoxicity: from mice to men and back again

Surgery Questions and Answers

Cell lines:

Q. *Would you prefer a solution which uses HK-2 cells or a similar well established cell line or would you prefer a solution that uses a newer cell line?*
A. There are some draw backs of HK-2 cells – they are not representative of tubule cells. Newer cell lines might be better to use for this. Doesn't matter which cell line is used as long as it is predictive.

Q. *Would it be useful to use a panel of different human cell lines with different genotypes?*
A. Could be part of the proposal but we are more interested in getting a predictive assay and then we can incorporate different genotypes later. We need a single cell line that works before a panel of cell lines. We would prefer a realistic proposal that doesn't tick all the boxes rather than a completely unrealistic proposal that claims it will do everything.

Compounds:

Q. Can industry come up with a list of compounds for validation?
A. The industry Sponsor would advise the winning group on compound selection, however the applicants should also suggest which compounds to use in their application.

Q. *How many compounds would you like us to use to characterise the assay?*
A. 20 well characterised compounds would be great but if we could identify five important compounds to use that would be fine.

Q. Would you envisage screening thousands of compounds or only a few?
A. If the assay is quick and cheap then we could screen very large numbers of compounds but in practice it's more likely to be four or five – it depends on the cost and feasibility. An ideal assay would involve a 96 well plate with the four species next to each other, but that may not be possible. The main thing is that the assay needs to be predictive, even if it isn't high throughput.

Q. Will the sponsors be able to assist in obtaining supplies of compounds for which there is lots of data but which are no longer available?
A. We would help where this is practical, yes.

Current situation:

Q. Do you already have a standard assay that you run?
A. No

Q. *Will we have access to any assays you currently use?*
A. We don't use assays for kidney toxicity.

Q. Do you use genomic analysis of kidney tissue to find if specific pathways are switched on?
A: Yes, on a case by case basis to characterise a finding.

More detail on what is needed:

Q. How about a two tier system where the first tier is a screen of lots of compounds to identify those which are toxic in man and then a second tier to provide information on the mechanism involved in these?
A. Our feeling is that an assay capable of screening lots of compounds rapidly is less likely to be predictive. We would prefer an assay that is lower throughput but provides more information on mechanism.

Q. *Would you prefer a focus on more sophisticated endpoints?*
A: Not necessarily more sophisticated endpoints but we think some of the classical endpoints may be of less relevance (e.g it should not be another cytotox assay).

Q. Would you prefer a functional assay or a biochemical assay?
A. Predictive power is more important than the endpoint, but it is likely that any solution will need a combination of both (but data will speak).

Q. *How should we determine the endpoints?*
A. The project needs to address this. What would you measure? What is the best way to do this?

Q. *Would you prefer us to focus on acute kidney toxicity or chronic kidney toxicity?*
A. Either, or both if possible. Please indicate which you are planning to address.

Q. Would you prefer a high throughput assay or one that is not high throughput but gives insight into mechanism?
A. There might be a place for both. They have different places in the process and both could be valuable. The bottom line is that which ever type of assay it is it must work. High throughput is not a priority and there will always be a trade off. Our feeling is that a mechanistic assay might be more feasible.

Q. *Is there any role for in silico modelling in this challenge?*
A. We feel that the duration of this project is far too short for that unless you already have the data needed.

Different species:

Q. Why do you want to use all the species if ultimately you want results in humans?
A. To mimic how current animal testing is done. If we can do just human in three years then that would be great but we are sceptical that that will be possible.

Q. Will you be able to provide dog tissue?
This cannot be 100% confirmed at this point in time.

Do we need dog in the assay?
This would be very advantageous.

Validation:

Q. How should we define the predictivity of cell line, especially when using human cell lines?
A. By using compounds with established effects, possibly including failed compounds from industry. First step of the project is likely to be defining a list of compounds.

Q. *How would we make the test acceptable by regulatory bodies?*
A. The most important thing is that the test if useful for internal decision making. Regulatory use may come later if the test is adopted by industry.