CRACK IT PREDART – Questions and Answers

Q: The challenge is focussing on replacing animal tests, are you looking for a specific set of requirements? For example, is it possible to also look at chicken up to two thirds gestation?

A: The goal is for the development of non-mammalian, non-vertebrate systems. The regulations may change on chickens and so current regulations on gestation periods may become obsolete. It may be possible to look at chickens up to two thirds gestation as a proof of concept study.

Q: What does medium throughput mean? What is an attractive cost?

A: Typically we mean 10 to 100 compounds. The new assay should be an improvement on current animal tests in terms of decision making times and costs.

Q: Will applicants get guidance from sponsors on understanding exposure concentrations?

A: We will share our data on this.

Q: How could a lower organism be more relevant to humans when higher species are not predictive? Wouldn't human stem cells be more relevant in terms of reproductive and development toxicity?

A: We're more interested in the toxicity pathways than which model organism is used. The objective is to look at which pathways are conserved across species. If we understand the pathways, we will be closer to predict what happens in human. Embryonic stem cells could indeed be the solution.

We are not interested in detecting teratogens. We are more concerned with detecting more subtle pathways which lead to a whole range of anomalies.

Q: What is it about systems that have been around for a long time, e.g. embryonic stem cells, that companies have not adopted them?

A: All these assays have been shown to give false negatives, which is a huge problem for companies.

Q: There is already a huge amount of literature on these models - why are you looking for a new model?

A: We are not looking for a new assay; the key is to bring existing models together.

Q: Are you solely looking for whether genes are up or down regulated?

A: Not just that but also the entire pathway.

Q: What criteria would you set for definitions of these pathways – is it the physiology involved in development or which chemicals perturb the pathways? Which is more important?

A: Both are important, for example, you could identify all the conserved pathways but find that not all are perturbed.

Q: What's the merit in comparing the data generated in these new systems to animal data instead of human data?

A: Realistically, these toxicity studies will not be carried out in humans. However, there is a lot of literature in humans that can be used for reference. If the pathways are conserved between lower species and rat and rabbit, it is likely to be relevant to humans. E.g. the dictyostelium can be used to identify SSRI but we don't believe that it suffers from depression. It does not have the human symptoms but the pathway is there.

Q: Are the key deliverables meant as a wish list or are they essential? Are you open to suggestions in terms of endpoints?

A: Some endpoints, such as ossification and organogenesis are essential and if your proposed test system could provide information on reproductive endpoints then that would be great. However this will be a two way dialogue so there is some flexibility.

Q: Are you looking for a solution just in bioinformatics or a combination of bioinformatics and experimental development?

A: For Phase 1 it may be possible to focus on a bioinformatics approach as there is considerable literature available and we will share data from the limited work we have done in this area. To meet Phase 2 deliverables further exploration will be needed.

Q: Do you have a list of top 10 pathways?

A: No – we're open for the agenda to be set by the identification of new pathways and new understanding.

Q: Do we need to involve regulators early on? Or will you take care of that?

A: There shouldn't be a need to involve regulators at this stage of development. The purpose of this Challenge is not to address regulatory requirements but to better detect toxic compounds early in development so that risky compounds can be killed before further animal testing.

Q: The regulators will have to be involved when you demonstrate that the test is 100% predictive of what happens in rat.

A: The development of a predictive system is not the end of the process. We will use it to provide an evidence base to support wider uptake by the industry which will in turn influence the regulators. Changing regulatory opinion is more of a long term goal.

Q: Would the new system be relevant to environmental toxicology as well?

A: Yes, and we work closely with colleagues in environmental safety. The very fact we are looking at pathways makes it a cross disciplinary approach.

Q: Is it a key aspect that the system becomes a consensus across industry?

A: Yes. Its strength would be that other people start using it, confirming that the results are reproducible and giving credibility to the system.

Q: A single process can be studied with one assay in one animal but other processes require a number of assays in other animals. Since you are looking for conserved pathways do you envisage needing a combination of assays?

A: Possibly – it depends whether all pathways are present in one lower organism or if several different organisms need to be used, which seems more likely. We need to see a dose response and this needs to be benchmarked to mammalian exposure. Mathematical modelling approaches may also form part of this.

Q: Are you interested in metabolites as well?

A: Yes - but also more than metabolites, we are interested in everything e.g. RNA, etc.

Contact the NC3Rs if you have further questions about this challenge and we can facilitate communication with the Sponsor.

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