CRACK IT

# Challenge 20: Metaboderm Surgery Q and As.

**Q. One of the deliverables is that we identify against known *in vivo* metabolism, but that is something that might not be known; if we see metabolites in the blood we don't know whether it is occurring in the skin, liver, kidney...**

A. The Sponsors understand that this will be difficult, but evidence that the model can measure known *in vivo* metabolites is important.

**Q. Have you considered how different formulations impact metabolism?**

A. Yes, when modelling penetration, the different formulations can pose a problem. Applicants would need to look at methods to address this. For example, imaging can show the location or form of the drug.

**Q. Which modes/routes of entry are the Sponsors interested in?**

A. All routes of entry. For example, even oral drugs can get to the skin and we want to be able to screen compounds that may not be suitable earlier in discovery.

**Q. Are you looking for specific approaches such as *in silico* / *in vitro* / *in vivo* imaging or a combination of techniques? Would expansion and/or validation of existing models be suitable or would completely new models be preferable?**

A. The Sponsors are open to different approaches, developing new methods or building on and improving existing ones. This may range from the development of a completely *in silico* method to use of *in vivo* imaging for skin penetration to help validate models that are developed.

**Q. The Sponsors will provide in-kind contributions. Do you have examples of cases where skin metabolism/bioavailability has been an issue? Would we have access to any data that we can use as a baseline to help the proof-of-concept in Phase I?**

A. There are very few examples in existence, but the Sponsors could share examples with the applicants, although formal in-kind contributions and high-level validation is not required in Phase I.

**Q. There are a number of enzymes that can predict the (metabolic) activity of certain compounds. Is there a known list of those involved in skin metabolism?**

A. Sponsors provided a list of some of these enzymes in the slide set. There are some reviews available in the literature with a list of phase I/II enzymes for skin metabolism and the differing responses in individuals (e.g. due to the mix of enzymes expressed).

**Q. The Sponsors (GSK) showed that there are already some good *in silico* models available, can the metabolism information just be added in to these existing models?**

A. There are several models that describe the dermal penetration of small molecules. These models include metabolism as a way to clear compounds from the skin but they do not track metabolites, do not predict the extent of the metabolism and do not predict the enzymes

responsible for the potential induction. We need to think how the current models can be adapted to predict what happens *in vivo*.

**Q. Is it possible to predict metabolism from currently available software?**

A. Yes – there is software that can predict liver metabolism from compound structure. This software could provide a starting point for predicting dermal metabolism.

**Q. The Sponsors mentioned the adverse outcome pathway (AOP) approach. Do the Sponsors want a focus on the whole pathway or just one part?**

A. This challenge is focussed on metabolism. The AOP would link the successful outcome of the challenge to being able to predict toxicity all *in silico*.

**Q. To develop the proof-of-concept in Phase 1, do we need to work with/interact with the Sponsors?**

A. In Phase 1 you will have access to the Sponsors, but there is no formal in-kind contribution at this stage.

**Q. Can we only interact with the Sponsors/NC3Rs once we have formed a team?**

A. No, you can contact the NC3Rs at any point during the process. We are happy to give advice, put you in touch with the Sponsors or let you know our thoughts on the team you are putting together.

**Q. Six months for Phase I is a very short time. What do the Sponsors expect us to achieve in this time?**

A. Sponsors are looking for proposals with evidence that applicants can achieve all the deliverables (ideally), or enough deliverables to provide confidence that the applicants can meet the Challenge. Applicants are encouraged to discuss their proposals with Sponsors to better understand if their approach would be considered appropriate.

**Q. Who should we email with questions?**

A. General questions can be sent to the NC3Rs. Questions regarding a specific Challenge can be sent to the Sponsors, but enquiries should be sent to ALL Sponsor parties for a particular Challenge. If preferred, please email the NC3Rs to introduce you to the Sponsors at CRACKITenquiries@nc3rs.org.uk.