CRACK IT ProBE IT – Questions and Answers

Q: How do you know that the probe will not effect distribution of the macromolecule?

A: Following administration of the molecule it will be broken down so we are always looking at subsets of the breakdown products. It is always a risk that the probe will affect biodistribution however, because of the size of the molecules we are targeting with this challenge we expect it to be less of an issue than for small molecules. We need to understand what the half life of the probe is and also the pharmacodynamics of both the probe and the molecule. Ideally we would not be altering the biodistribution or pharmacokinetics of the molecule, but if we were we would need to understand how to compensate for that in our measurements.

Q: Would single slices through specific organs be sufficient or do you need images of the whole animal? E.g. if we could get the whole liver in one plane would that satisfy your requirements.

A: This is dependent on the disease type. However, we are more likely to need the whole organ system rather than a slice. For example if we are looking at idiopathic pulmonary fibrosis (IPF) and a patch of fibrosis in the lung we need to see we are getting the molecule to the right place in the lung.

Q: What do you mean by single modality?

A: This is one imaging platform that could provide both efficacy and distribution readouts within a single animal without too much disruption to the animal.

Q: What are the specifications for wavelengths of the probe?

A: Water absorbs at around 800+nm so if you get to about 900 then you get lots of water absorption and at lower wavelengths there is too much interference and background noise. Therefore ideally the wavelength would be about 700 to 800 (+)nm.

Q: You focus on rodent models of disease and biodistribution; have you thought of assessing biodistribution in invertebrates first as these are transparent? This information could be used to inform and refine the vertebrate studies.

A: The use of other systems is dependent on how relevant they are to the rodent. The regulatory safety and toxicity studies would have to be carried out in the rodent so we would like to know the biodistribution profile in the rodent before starting these studies.

Q: How relevant is it to have a probe system that translates from mouse to man so that you can use the same reporter?

A: Ideally, it would be good to use the same system, however, the aim of this challenge is to assess 12-20 molecules in candidate selection to choose 4-5 to take through to the next stage of development rather than finding probes that translate to the clinic. The focus of this challenge is early development rather than clinical translation.

Q: What is the resolution you want to achieve?

A: This is dependent on the organ system that we are interested in. In the range of about 100 ums would be compatible with MRI.

Q: For a biodistribution readout are you looking at the sum of all pixels in the kidney? Therefore, looking in the range of about 1mm?

A: 1mm would be satisfactory but not ideal. Less would be better. For instance, if we want to deliver to a metastases then the area we are targeting would be less than 1mm.

Q: Are you more interested in the development of new probes or the development of an instrument to detect a probe?

A: We are aware that systems do already exist but the issues are; the level of penetration, types of monitoring, sensitivity, depth and accurate 3D representation. We want to be able to differentiate between a molecule that has a relative distribution of 50% in the kidney and one that has 30-40% for instance. The system needs to be 3D, whole body and rapid. So, we are interested in a whole system to do this.

Q: In phase 1 is the focus on probes or imaging technology? For instance if someone could show that they can get whole body resolution with an image but without a probe would you be interested in that?

A: We are open to applications that show advances in imaging technology to address the issues described in phase 1. If the way to approach this challenge is to deliver in the other order where the technology comes in the first phase and the probes in phase 2 we would be willing to consider this. We can also put groups together that have been successful in phase 1 to apply for phase 2. E.g. if one group provided proof of concept for probe design and another group advanced imaging technology, together this would make a strong application for phase 2.

Q: What are your priorities for cost verses accuracy?

A: It needs to be a balance. We want to image a number of animals to see dose response in, for instance, ten different molecules so we need a cheap and quick method to do this. We need data within 24/48 hours.

Q: Would you prefer the technology to be in house or could a contract research organisation carry out the research externally?

A: The business model is not important. We would be willing to consider either.

Q: Do you have any specific imaging system that you would like to work with the probe?

A: Any commercially available imaging system would be fine.

Q: If we could target to one organ would you be interested in that? E.g. the brain?

A: It has to be the whole body because we need to understand the relative distribution in the key organs e.g. the liver, kidney and heart to predict the risk of toxicity. We need as much if not more information on off-target distribution as on-target as sometimes this is more important for safety assessment.

Q: Is it therefore important to decipher on-target vs. off-target biodistribution?

A: Yes, as it gives us information to go back to the biologist/chemist to alter the structure of the molecule and produce appropriate domains.

Q: Would a biological reporter be useful?

A: It depends what it is and how it impacts on the cost. For instance, luciferase can be expensive to licence and therefore would be a problem to increase throughput. It is more likely that we would only make this investment in committed programmes rather than early development and candidate selection.

Q: What about a probe that could be switched on or off depending on where it is in the body?

A: It depends whether you mean on and off depending on distribution or engagement. Our primary aim is to determine biodistribution and our secondary aim is to figure out what that biodistribution means. For example, if you could report on binding then that would be interesting.

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

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