CRACK IT

ProBE IT: Determining the *in vivo* biodistribution Properties of Biological Entities through the use of advanced Imaging Techniques

Probe IT aims to:

- Generate probes with increased sensitivity, quantifiable readouts and broad applicability for macromolecules;
- Develop a streamlined imaging platform that would allow rapid, non-invasive 3D assessment of macromolecule distribution across a range of therapeutic areas and tissues;
- Advance methods to combine biodistribution with efficacy readouts.

BACKGROUND

The proportion of new biological drugs in development is continuing to increase due to good probabilities of clinical success (12% for biologics versus 7% for small-molecule drugs), higher peak sales and perceived lack of generic competition[1,2]. This class of drugs includes macromolecules such as antibodies and oligonucleotides that present unique challenges in candidate drug selection. To improve efficacy, detect toxicity and reduce drug attrition, it is essential to understand the biodistribution properties of these macromolecules early in development to ensure they are being delivered to the intended site of action. Linking biodistribution to disease progression through the use of efficacy biomarkers also provides greater confidence in predicting the ultimate success of the molecule.

PET imaging can be used to determine biodistribution information for drug candidates and has clear advantages when looking at small molecules where a single atom can be exchanged for a radioactive ligand without changing the intrinsic properties of the molecule. Currently, there are no routinely available and accessible techniques to allow whole body distribution of larger macromolecules to be measured over a longitudinal timeframe of several days within a single animal. Traditionally, animals are dosed with the drug candidate and biodistribution is subsequently assessed using *ex vivo* techniques which have a considerable impact on the total number of animals required to gain accurate information on a time course. There are scientific and practical limitations associated with current assessments including the number of animals required, the difficulty in obtaining precise profiles of biodistribution patterns within an animal, the inability to visualise biodistribution in 3D and the need to remove and analyse each individual organ to obtain a profile.

The aim of this Challenge is to develop a sensitive, non-invasive imaging technology to accurately detect and quantify a range of macromolecules in a variety of tissues and link this information to efficacy. If *in vivo* efficacy imaging biomarkers could be linked to

Sponsor
GlaxoSmithKline

Budget per project
Phase 1: Up to £100,000 inc. VAT where applicable

Phase 2: Up to £750,000 inc. VAT where applicable

Key words
Biodistribution, biologicals, efficacy, imaging

SBRI Government challenges. Ideas from business. Innovative solutions.

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understanding biodistribution within the same animal a powerful paradigm would be realised for biological drug development using fewer animals. Emerging technologies using optical probes in the near infra red (NIR) range such as FRET, which can give information on distribution and potentially conjugation to a receptor, as well as FLIM which provides information on the local chemical environment of the molecule, are potentially of use to this Challenge[3,4]. However, these are not currently adequate to link biodistribution to efficacy.

3Rs BENEFITS

- The development of imaging tools for routine biodistribution studies would reduce animal use by at least 85%. This could be reduced even further if biodistribution can be linked with non-invasive efficacy readouts within the same animal.
- Linking biodistribution to efficacy will enable more precise measurements to be made allowing earlier stages of disease to be detected that better reflect the clinical situation and reducing the severity of the animal studies (refinement).
- The impact could potentially span many therapeutic areas including oncology, neurodegenerative diseases and diseases that affect the kidney, lung, liver and heart where targeted therapy is the main goal. Earlier efficacy or safety observations, together with biodistribution profiles, may also provide earlier decision points on whether to progress compounds therefore reducing the length of these studies.
- Decisions on whether a macromolecule should be progressed will also be made earlier, resulting in fewer candidate drugs that may be dropped later in development entering regulatory safety and toxicity studies. This is particularly important for antibodies, where often the only relevant species for toxicology studies is the non-human primate.

NEED FOR COLLABORATION

This Challenge includes (i) technological development of probes that can be routinely attached to a wide range of molecules, (ii) improvement of probe properties to maximise resolution and sensitivity, and (iii) advanced imaging technologies for accurate quantification of biodistribution. The multi-disciplinary nature means that expertise from a number of different sectors will be needed to provide a solution and input from sectors that are not normally associated with the biosciences such as chemists and engineers will be critical.

OVERALL AIM

Development of a sensitive, non-invasive, single imaging modality, through the combination of existing or development of new techniques, to define biodistribution of macromolecules *in vivo* and enable better predictions of efficacy.

KEY DELIVERABLES

Phase 1

Demonstrate technology to produce a panel of probes including antibodies and oligonucleotides

Phase 2

Generate a panel of probes with the following characteristics:

- Improved sensitivity to allow deep tissue imaging;
- Limited effect on pharmacokinetics of macromolecule;
- Wide applicability across therapeutic areas and macromolecule type;
- Simple chemistry for conjugation;
- Appropriate cost to enable access to a wide range of sectors/users;
- Absolute quantification across a range of tissues (e.g. brain, tumour, liver and kidney).

Prototype for detecting macromolecule biodistribution using the probes developed in 1 that:

- Enables 3D visualisation;
- Is rapid (ideally <1 minute for whole animal assessment);
- Is non-invasive;
- Uses non-anaesthetised animals;
- Detects receptor binding.

Prototype for a multi imaging modality platform to allow efficient efficacy and biodistribution readouts

Other considerations

- Potential for automation of image analysis;
- Use of appropriate image analysis software, either existing or development of specific software for the purpose.

IN-KIND CONTRIBUTIONS

Phase 1

- Advice on initial macromolecules to demonstrate/validate probe conjugation
- Guidance on probe characteristics and industry requirements

Phase 2

- Panel of macromolecules to assess conjugation;
- Expertise in wide range of disease areas and relevant efficacy readouts;
- Assessment of prototypes;
- *In vivo* validation

REFERENCES

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