CRACK IT

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

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ProBE IT - Aims

•Generate NIR probes with increased sensitivity, quantifiable readouts and broad applicability for macromolecules.

•Develop a streamlined imaging platform that would allow rapid, non-invasive, whole body 3D assessment of macromolecule distribution across a range of therapeutic areas and tissues

•Advance methods to combine biodistribution with efficacy readouts to maximise the 3Rs.

Background

•The proportion of biologicals as opposed to small molecules as therapeutic agents is rapidly increasing.

•These biologicals include macromolecules that are protein derived (therapeutic proteins and antibodies), and potentially nucleic acid derived (oligonucleotides).

•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 that they are being delivered to the intended site of action.

•In addition it is vitally important to determine relative pharmacology compared to distribution profiles of these molecules.

Background

•Gold standard techniques such as PET and SPECT are currently being used but remain highly expensive and inaccesable the majority.

•Due to the complexity, expense and organisation required for setting up such studies this technique is not universally accessible to a vast majority of labs for routine assessment.

- •Large macromolecules may also present particular difficulties when radiolabelling is required.

•However, large macromolecules unlike small molecules may be suited to a different approach where conjugation with a small ‘reporting’ probe such as NIR agents would be possible.

•This may allow routine biodistribution assessments to be made longitudinally within the same animal using non-invasive and non-ionising forms of imaging.

•If biodistribution could then be linked using imaging techniques to assess efficacy then a powerful paradigm would exist that would significantly reduce the total number of animals required.

3Rs Benefit

•The development of imaging tools for routine biodistribution studies would reduce animal use significantly. This could be reduced even further if biodistribution can be linked with non-invasive efficacy readouts within the same animal (REDUCTION)

•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.

Current position

- Imaging is becoming an important tool for determining efficacy, toxicity and biodistribution due to the non-invasive nature (refinement), translatability to the clinic and the reduction in the total number of animals required per study.
- Expensive techniques such as PET and SPECT do exist and are employed but not routinely.
- The use of NIR probes could play an important role in understanding the relative distribution of large macromolecules.
- NIR probes are beginning to become more accessible and showing promise with regard to sensitivity.

However

- Further improvements in probes would allow better sensitivity and hence more accurate quantitation, providing ease of use across a wide range of test macromolecules.
- Improved 3D data generation is required that is quick and has minimal impact on animal welfare.
- Seamless multi-imaging platforms to allow efficacy and distribution assessments.
- Improved image handling and analysis packages for automated assessments.

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.

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

  - Prototype for detecting macromolecule biodistribution using the probes developed in phase 1 that:
    a. Enables 3D visualisation;
    b. Is rapid (ideally <1 minute for whole animal assessment);
    c. Is non-invasive;
    d. Potentially uses non-anaesthetised animals;
    e. detects receptor binding.
    f. Allow efficient efficacy and biodistribution readouts

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