Molecular imaging: what picture does it paint for future oncology?

'Molecular imaging in humans is an emerging new discipline with huge potential in anti-cancer drug development.'

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In vivo molecular imaging is an emerging discipline that is of importance to the development of anti-cancer therapies. As anti-cancer strategies become more directed towards a defined molecular target, we need information that is relevant to humans about whether the molecular target is expressed, the selectivity and binding of the compound for that target, and the effects of such an interaction. Real-time information is required and molecular imaging technology looks set to provide this. This editorial first defines molecular imaging and how it can help drug development (Box 1), and then highlights how the key areas of probe development and the leadership of multidisciplinary molecular imaging groups need to be optimized.

What is molecular imaging?

Molecular imaging uses new and emerging quantitative functional imaging technology to look at molecular pathways. Technologies encompassed within molecular imaging include optical, magnetic resonance and nuclear medicine techniques. Positron emission tomography (PET) is the most sensitive and specific technique for imaging molecular pathways *in vivo* in humans [1]. PET uses positron emitting radionuclides to label molecules, which can then be imaged *in vivo*. The inherent sentisitivity and specificity of PET is the major strength of this technique. Indeed, PET can image molecular interactions and pathways, providing quantitative kinetic information down to sub-picomolar levels.

Generally, the isotopes used are short-lived. Once the molecule is labelled, it is injected into the patient. The positrons that are emitted from the isotopes then interact locally with negatively charged electrons and emit what is called annihilating radiation. This radiation is detected by an external ring of detectors. It is the timing and position of the detection that indicates the position of the molecule in time and space. Images can then be constructed tomographically, and regional time activities can be derived. The kinetic data produced provide information about the biological activity of the molecule.

Molecular imaging in oncology for drug development

Molecular imaging can provide pharmacokinetic, pharmacodynamic and mechanistic information. Use of the technique in early clinical trials can: (1) provide information on optimum biological dose and PK/PD relationships; (2) identify tumours containing specific molecular targets; and (3) provide *in vivo* pharmacodynamic evaluation of compounds. Its use can also be extended to general physiological questions; for example, regarding vascular physiology and *in vivo* pharmacokinetics [2].

The promise of molecular imaging

The promise of molecular imaging is huge. To be able to track the kinetics of a molecule at sub-picomolar levels in humans is an astonishing feat. However, many methodological challenges remain. Not least of these is developing and directing multi-disciplinary groups with the range of expertise needed (from innovative radiochemistry through to pre-clinical pharmacology and molecular biology, to medical physics and mathematical modelling). Few such groups exist internationally and so progress for the molecular imaging technique has been slow.

What is needed to bring this field on?

Methodological investment is needed and Pharma need to get involved. Two key areas that need attention if the use of PET for translational research in oncology is to be advanced are expanded in the following sections. These are the development of more-specific imaging probes and of clinical research-led directorships of the multi-disciplinary PET-based molecular imaging groups.

More-specific ligands and tracers for in vivo *molecular imaging in oncology*

The major challenge to realizing the potential of molecular imaging for translational clinical research and drug development is to overcome the lack of specific tracers and ligands

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Box 1. Information required by the drug industry

Molecular imaging provides information *in vivo* in humans:
- Is the drug hitting the target?
- Is the target expressed in an accessible way?
- What are the timing and magnitude of such molecular interactions?
- Does this molecular interaction have the desired downstream effect?

Advantages of knowing this information early *in vivo* in humans:
- Speed of drug development.
- Stopping compounds early if they prove not to have the desired mechanism.
- *In vivo* target validation.
- Identification of new targets.

available for *in vivo* imaging. Here, the problem is often not one of specificity for the molecular interaction or pathway, but rather of background owing to non-specific binding *in vivo*, peripheral metabolism and/or poor penetration across endothelial barriers. The following are proposed strategies to develop new probes for molecular imaging:

- To discover molecular imaging probes that are of generic value for a range of drug developmental studies. These would include *in vivo* assays of molecular interactions and pathways that are sufficiently cancer-specific to be of use as therapeutic targets. Such probes could provide therapeutically relevant functional measures of disease status and, hence, assays of potential responsiveness. They would also provide endpoints of pharmacodynamic responses. Systems already in place for cancer include the imaging of proliferation and its relevance to anti-proliferative agents, blood flow and its relevance to anti-vascular agents, and gene expression with relevance to gene therapy.
- To derive a consensus on which are the most promising therapeutic targets for oncology, for which tracers and ligands should be developed. The discovery of useful probes for *in vivo* imaging is high risk because of the background problems already described. Hence, it is essential to define the molecular interactions and pathways that, if imaged *in vivo*, would provide the maximum information to help drug development. Consequently, it is important that opinion leaders in the field of cancer therapeutics define areas in which imaging could make the biggest contribution.
- To encourage collaborations between clinical science-led academic PET centres and the pharmaceutical industry so that the risk is shared in discovering, developing, validating and exploiting new, more-specific probes for molecular imaging. This should generate partnerships in which the whole promises to be greater than the sum of the parts. Both partners share common interests of using molecular imaging for translational research through *in vivo* studies of tissue patho–physiology, expression, accessibility of therapeutic targets, pharmacokinetics and pharmacodynamics. Academia would bring the infrastructure, the know-how of developing and applying PET methodology in the clinical scientific setting, and the practice of formulating clinical research questions and paradigms to the partnership. By contrast, the pharmaceutical industry would provide the molecules and the know-how of refining these to be target-specific.
- To develop *in vitro* tissue assays of the biochemical, metabolic and physiological properties that determine levels of non-specific binding, peripheral metabolism and endothelial penetration. Once developed, these assays need to be coupled to those of specificity for the molecular target or pathway to be imaged. The next logical stage would be to integrate such assays within systems of combinatorial chemistry and high-throughput screening. From the data sets emerging from this high level of screening, it should be possible to use bioinformatic techniques to begin to understand the scientific basis of what makes a good ligand or tracer for *in vivo* molecular imaging. This is an especially attractive proposition as, at present, it is not well understood, and it might lead to *in silico* mining of existing databases of molecular structures for new imaging probes [3].
- To derive a practical regulatory means for introducing tracer molecules into oncology patients for the first time. With increasing regulations being associated with the administration of new pharmaceutical agents into humans, there are major hurdles and time restraints associated with introducing new imaging agents. This is despite the facts that the volunteering cancer patients being studied often have a limited life expectancy, and that the mass of tracer material administered is typically <1 μg. A recent report proposes guidelines for introducing novel tracer molecules into cancer patients to parallel drug development. These are based on experience gained in the UK in this area and, in essence, argue for only single species toxicology tests before administration into humans [4]. This approach is in line with that adopted in the UK several years ago for accelerating the use of new anti-cancer agents in Phase I and II patient trials.

The leadership of a molecular imaging centre

For a centre whose remit is one of translational research for the development of new therapeutic agents and

involves proof-of-concept studies in cancer patients, a clinical science-led directorship held by an academic oncologist is favoured. Here, the role is one of providing:

- An in house, clinical research programme focusing on the development and application of PET methodology for generic patho–physiological studies in oncology.
- A clinical scientific overview of the major research questions in oncology that could be addressed with PET-based molecular imaging.
- Close collegial links between referring oncologists and clinical trialists.
- A conduit between the centre and external groups that are active in basic cancer therapeutic studies, from both academia and the pharmaceutical industry.
- A consensus of common clinical research goals towards which the methodological groups of the centre can aim while still advancing their own areas in a generic form.
- Cross-fertilization between the respective developmental and operational groups, within the framework of the centre's common clinical scientific goals
- Links with national and international networks concerned with translational studies in oncology.
- An overarching authority that can adjudicate on the priorities, logistics, regulatory and ethical issues associated with in-house multidisciplinary activities involving both patient volunteer studies and external collaborations from academia and industry.
- Balanced judgements, from a neutral position, on the appointments of non-clinical scientists to provide strengths in their own areas as well as to perform as team players.

Conclusion

Molecular imaging has the potential to revolutionize, streamline and accelerate drug development in oncology. In this post-genomic era, the functions of the massive repertoire of emerging molecular targets will need to be quantified *in vivo* to effect rational drug development. We still need developments in methodology, with multidisciplinary groups and Pharma sharing the risk. The development of new ligands and tracers and, to define future goals, clinical science-led multidisciplinary groups, will be crucial to this development.

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