

as in imaging technology. Molecular-genetic imaging provides visualization in space and time of normal as well as abnormal cellular processes at a molecular or genetic level. Three different noninvasive, in vivo imaging technologies have developed more or less in parallel: 1) magnetic resonance imaging; 2) nuclear imaging (PET and gamma camera); 3) optical imaging of small animals. However, it is the convergence of these disciplines that is at the heart of this success story; it is the wellspring for further advances and has provided the opportunity to address new research questions. Three different imaging strategies are described: 1) "direct molecular imaging", whereby the resultant image of probe localization and magnitude (image intensity) is directly related to its interaction with the target molecule. "Indirect molecular imaging" is a little more complex in that it may involve multiple components. One example of indirect imaging is "reporter imaging", which involves a complimentary "reporter gene" and a "reporter probe". The "reporter gene" product can be an enzyme that converts a "reporter probe" to a metabolite that is selectively trapped within transduced cells. Alternatively, the reporter gene product can be a receptor or transporter that "irreversibly traps" the probe in transduced cells. Indirect reporter imaging paradigms are widely used in molecular imaging and will be discussed in greater detail. "Surrogate" imaging can be used to reflect down-stream effects of one or more endogenous molecular/genetic processes. This latter approach is particularly attractive for potential translation into clinical studies in the near-term, because established radiopharmaceuticals and imaging paradigms that are already in the clinic are used. The development of versatile and sensitive imaging paradigms that do not require tissue samples will be of considerable value and can be used for monitoring molecular-genetic and cellular processes in animal models of human disease, as well as for studies in human subjects in the future. Non-invasive imaging of molecular-genetic and cellular processes will complement established ex vivo molecular-biological assays that require tissue sampling, and would provide a spatial as well as a temporal dimension to our understanding of various diseases. For a recent review, see: Blasberg RG, Tjuvajev JG. *J Clin Invest.* 111(11):1620-9, 2003.

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Developments in MRI and MRS for biological/functional imaging

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Magnetic Resonance Imaging (MRI), often combined with i.v. contrast agents, is widely used in anticancer drug trials. Recently, "functional MRI" methods have been developed and this term is now applied to several very different techniques. In oncology, the main functional technique is Dynamic Contrast Enhanced MRI (DCE-MRI), in which blood flow and the permeability of the tumour neovasculature are assessed by monitoring the pharmacokinetics of standard Gd-based contrast agents. To obtain physiologically-meaningful parameters (e.g. Tofts' K_{trans}) one must deconvolve the highly non-linear arterial input function (AIF) from the tumour uptake curve. Measuring the AIF is difficult in the rodent tumour models that are used both for laboratory evaluation of antivasular drugs and for developing methods for monitoring human trials, mainly because of the small blood vessels. We will report a novel method for obtaining an AIF from the rat-tail vessels during the acquisition of a tumour uptake curve, allowing calculation of K_{trans} and other parameters.

Magnetic Resonance Spectroscopy (MRS), uniquely, gives non-invasive measurements of the chemical constituents of body tissues. It has been slow to achieve acceptance in routine medicine, but modern instruments now allow an MR spectrum to be taken in a few minutes during an MRI examination. 1H MRS of the brain is the most extensively developed method, and brain tumours have been found to have reproducibly different spectra that permit both diagnosis and grading. However, few radiologists or oncologists have the skills required to interpret such spectra. The EU INTERPRET project (<http://carbon.uab.es/INTERPRET/>), a four-country collaboration led by Prof Carlos Arus, has developed a Decision Support System (DSS) to enable clinicians to diagnose and grade brain tumours. It compares each unknown spectrum with a database of several hundred spectra from tumours and other intracerebral lesions, in each of which the diagnosis has been carefully validated. As well as performing computer-based pattern recognition analysis on an unknown spectrum, the DSS allows the operator to review difficult or ambiguous spectra by studying their associated images and clinical data in comparison with any cases in the database.

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Prioritising PK/PD endpoints for molecular imaging

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Studies of pharmacokinetics (PK, what the body does to the drug) and pharmacodynamics (PD, what the drug does to the body) are an essential component of drug discovery and development. Defining the precise relationship between PK and PD is critical. It is especially important to establish a pharmacological 'audit trail' that links all of the essential parameters of drug action, from the molecular target to the clinical effects. The pharmacological audit trail allows us to answer two critical questions: 1) How much gets there? and 2) What does it do? During drug discovery, it is essential that PK/PD properties are optimised, so that the best compound can be selected for clinical development. Furthermore, as part of contemporary mechanistic, hypothesis-testing clinical trials, the pharmacological PK/PD audit trail facilitates rational decision making. However PK/PD endpoints frequently require invasive sampling of body fluids and tissues. Non-invasive molecular measurements, eg using MRS/MRI or PET, are therefore very attractive. This presentation will highlight the need for PK/PD endpoints in modern drug design and development. The value of PK/PD endpoints will be illustrated, and the importance of non-invasive molecular and functional imaging in drug development will be highlighted. Examples will include the use of PK/PD endpoints in the development of molecular therapeutic drugs such as the Hsp90 inhibitor 17AAG as well as the development of SR4554 as a non-invasive probe for the detection of tumour hypoxia. Because resources are inevitably limiting, PK/PD endpoints must be prioritised. This involves making a choice between PD endpoints that measure whether a specific molecular target (eg a particular kinase) has been inhibited and those that detect whether an entire biochemical pathway (eg the Ras or PI3 kinase pathways) or biological effect (eg apoptosis or angiogenesis) has been modulated. The advantages and disadvantages of each will be described.

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Target identification labelling for molecular imaging

Abstract not received.

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Clinical molecular imaging in oncology drug development and radiotherapy

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In vivo molecular imaging is an emerging discipline that is of importance to the development of anti-cancer therapies. 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. PET uses positron emitting radionuclides to label molecules, which can then be imaged in vivo. The inherent sensitivity 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. 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. 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. In radiotherapy molecular imaging has potential for quantitating the biological phenotype and thus defining the Biological Target Volume (BTV). There is potential here to define areas for boost treatment and to assess response to therapy. 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.