Considering the vast and increasing costs demanded by R&D today, it is not surprising that a growing number of experts are starting to apply PET imaging early in the development process, with the aim of avoiding late-stage failures by gaining more information on target engagement and downstream target response.

Studies have shown a steady decline in pharmaceutical R&D productivity over recent decades. The inexorable increasing cost of drug development has not been rewarded with an associated growth in the number of new drugs receiving marketing authorisation from governing bodies such as the FDA and EMA. A study from the Tufts Center for the Study of Drug Development (CSDD) in 2014 puts the cost of developing a prescription pharmaceutical at $2.6 billion (1). Taking into account inflation, this represents a rise of 145% over the estimate made by the CSDD in 2003.

The steep rise in costs comes despite growing efforts to bring greater efficiency to pharmaceutical R&D, and can be largely attributed to the cost of developing late-stage failures. Thus, it is ever-more important for drug companies to address some of these issues, including major R&D restructuring, the creation of entrepreneurial development units and a focus on translational medicine. One encouraging outcome from this activity has been an increased focus on the use of biomarkers to help gain an early indication of drug activity in both healthy volunteer and patient studies.

Traditionally, biomarkers have been thought of as measurable physiological responses, such as fluctuations in blood pressure or changes in the level of a protein related to the disease state.

Why, What and When to Image

Keywords
- Clinically validated biomarkers
- Positron emission tomography
- Experimental medicine
- First-in-human studies
- Biomathematical modelling
- Magnetic resonance imaging

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While these approaches are relatively cheap and can be implemented along the development process, validation can be lengthy and the results subject to variability. The pharma industry requires new, clinically validated biomarkers that give early information in humans.

**Three Pillars of Drug Survival**

In 2011, Morgan et al at Pfizer published a paper in which they analysed the success and failure of compounds in their pipeline when transitioning from Phase 2 to Phase 3 (2). In this publication, scientists were able to identify that drugs were most likely to make a successful transition if they already had evidence of drug distribution to the target tissue, interaction with the drug target within the tolerable range, and some evidence of a downstream pharmacological effect. These three tenets have become known as the ‘three pillars of drug survival’.

An increasing number of experts believe that the questions concerning these three pillars can often be answered by the timely use of imaging and, in particular, the use of positron emission tomography (PET) (3). Molecular PET imaging uses high energy radiolabelled compounds, which emit measurable signals to study target biology in vivo in either preclinical species or in the clinic.

Questions about drug distribution to a target tissue can be answered by applying the radiolabel to the compound being tested. This technique provides useful but limited information and requires labelling of the drug, which is not always practicable. Far richer information on drug target interaction can be measured by developing a radiolabelled tool compound or ligand that binds competitively at the receptor target with the drug of interest. Alternatively, downstream pharmacology can be measured using a ligand that detects changes in the biochemical pathways of a cell, such as energy metabolism.

By applying PET imaging in early clinical development, often in parallel with the first-in-human trials, it is possible to determine the drug distribution, target interaction and downstream pharmacology. Such data can be used to provide dosing information for proof-of-concept studies, which has been demonstrated to reduce both cost and time in early-stage development. However, to ensure that imaging does not impact the critical path, it is important to commence biomarker development as soon as possible, preferably at the same time as lead compound selection.

**Imaging Biomarkers**

Given the undoubted value of PET imaging to drug development, there are surprisingly few validated PET ligands available, and most of these are used in late-stage development trials on patients. In order to support first-in-human studies against novel targets, it is necessary to start planning biomarker development during the drug discovery phase.

PET ligand development has many similarities to that of drug development, and often a suitable candidate can be identified from the compound library used for selection. Like the drug, the PET ligand should be selective for the target of interest and have a high affinity. On the other hand, a shorter half-life is more appropriate for a PET ligand than for most drugs and, because the PET ligand is administered as a microdose, toxicity is generally not an issue. Additionally, a PET ligand can be administered intravenously, thus intestinal absorption will not prove problematic. These factors mean that development of a novel PET ligand – selected from an existing compound series – takes around 18 months to clinical validation, compared with the 10-14 years that it takes to develop a novel pharmaceutical.

With appropriate data on target and compound properties, *in silico* biomathematical modelling can be used to predict the behaviour of potential ligands and rank them...
In terms of likely success before the determination of labelling feasibility and routes of synthesis, PET radioisotopes typically have short half-lives, so it is important that the label is added during the final synthetic stage.

The next step is designed to evaluate the performance of the selected PET ligand candidate in a suitable preclinical species, and will generally involve the quantification of the magnitude of the displaceable signal, as well as an estimate of the reproducibility of its measurements.

Before the PET ligand can be used in the clinical setting, a single dose toxicity study should be performed, as outlined in the ICH M3 guidelines for preclinical safety testing. In parallel, while the toxicity study is being performed, the synthesis of the PET ligand must be implemented to Good Manufacturing Practice (GMP) standards.

**Case in Point**

A recent trial on a drug candidate targeting the Adenosine A2A receptor for treatment of neurological disorders, carried out by biotechnology company Vernalis and imaging company Imanova (4), demonstrates very...
clearly how imaging can be used to provide early information in humans, and reduce both the cost and time of entering proof-of-concept studies. In this instance, a suitable PET ligand, [11C]SCH4424, had already been reported, but needed to be implemented at Imanova to a GMP standard. This introduction was carried out alongside the preclinical development and study planning, ensuring that the ligand was available for use with an adaptive protocol to determine receptor occupancy once the test drug was in the clinic.

Using an adaptive trial design, the PET analysis was carried out in parallel with the single ascending dose (SAD) study, in order to relate occupancy at the A2A receptor in the brain with drug dose and plasma concentration. Each subject underwent three PET scans: at baseline; three hours after dosing with the drug; and at 23 hours after drug dosing (see Figure 3). For each dose, A2A receptor occupancy was calculated for two plasma drug levels. Magnetic resonance imaging (MRI) of volunteers was also used for anatomical reference.

The data generated clearly demonstrates the relationship between plasma concentration and receptor occupancy in the central nervous system (CNS), showing that the drug crosses the blood brain barrier and interacts with the target receptor (see Figure 4). Using this information, Vernalis was able to take the drug into further development. Importantly, the quantitative data generated from imaging was used to determine the dose to be used in patient studies for efficacy, thus reducing the number of doses to be tested.

This study clearly demonstrates the value imaging can add to aid a number of critical decisions. In this way, imaging holds the key to considerably reducing time and costs of drug development overall.

**Beyond the CNS**

Although the benefits of imaging and the valuable data it can provide is becoming increasingly clear, it remains an underutilised tool in the drug development arena, in part due to its strong association with diagnostics and CNS research.

In addition, broad application of PET imaging is constrained by the lack of sufficient imaging biomarkers. The creation of novel ligands needs to be structured and timely to ensure it does not impact the critical path of drug development. Thus, it can be used most effectively when a PET imaging strategy is considered as part of the discovery process.

Novel PET imaging agents and applications can be developed in a broad range of therapeutic targets, including autoimmune diseases and inflammation, fibrosis and oncology. Furthermore, it can prove very useful to work collaboratively with industry and academia to identify and develop future applications.

By raising awareness of the applications of imaging within the debate about R&D productivity, there is an opportunity to transform the drug development process. Drugs that do not interact sufficiently with their target in the clinic can be dropped from further development, allowing drug developers to focus resources on compounds that are likely to be successful. In addition, the information gained from a timely and well-designed PET imaging study can be used to make decisions about further development, such as drug dose – saving both money and time.

References


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