PET's benefit

shining a light on human disease

As the experience and advances in PET imaging grows, so does the belief that this technology can have a key role to play in ushering in an era of personalised medicine while also offering an enormous contribution in reducing the attrition rates in the pharma industry as a whole.

By Dr Jean-Luc Vanderheyden

Highly valued for its ability to detect and stage cancers and for its nascent role in identifying Alzheimer's disease and other neurological functions, Positron Emission Tomography (PET) has demonstrated its broad ranging applicability at the earliest stages of therapeutic drug development in preclinical and clinical testing, and now, as a reimbursed, cost-effective procedure of molecular imaging. With continuing advances in PET technology, this imaging technique is poised for growth and is positioned to become an indispensable tool at the lab bench and in the daily practice of medicine. PET provides a non-invasive, safe means of looking inside the body. It allows understanding of normal physiology and that of diseases, while evaluating the effects of existing or experimental drugs. It offers the potential to bridge the gap between basic biological research, animal studies and human trials, to expedite new drug development, to identify safer and more effective therapeutic agents, to diagnose pre-symptomatic disease and to select appropriate patient populations for clinical testing and drug treatment.

To foster the goals of translational medicine – defined as the development and application of new technologies where the emphasis is on early patient testing and evaluation, PET can contribute critical information that will shorten the path from animal testing to the bedside.

PET offers unique capabilities and advantages for pharmaceutical R&D. It enables quantitative, *in vivo* activity interrogation within tissues throughout the body. PET provides information on biochemical and physiological processes that complements morphological information.

Pioneers of clinical PET imaging research at centres such as Hammersmith Hospital, London and Uppsala University, Sweden (now part of GE Healthcare's commercial imaging network) have facilitated the growth of PET tracers now widely used in the early stages of drug development to confirm drug performance at the molecular level to understand the biological basis of disease, to validate and refine drug targets, to evaluate surrogate endpoints of disease activity, and to assess the pharmacokinetics and pharmacodynamics (PK/PD) of drug candidates in animal studies and early stage human trials. Specifically, PET could be used for the rapid quantitation of response to multiple permutations of drug combinations and dose strengths in a range of disease types.

In clinical testing, PET is playing a valuable role in demonstrating whether a test compound reaches and interacts with its intended target, documenting its physiologic effects in a small number of

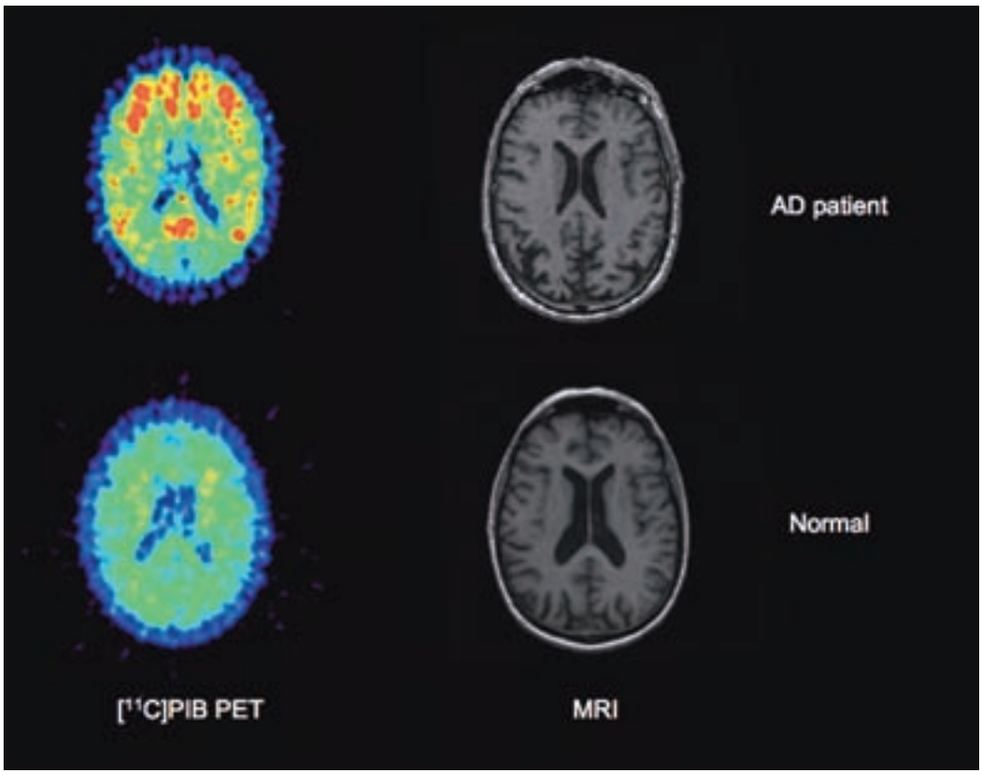

Figure 1
Earlier detection of Alzheimer's disease could enable the use of safer and more effective therapies to slow or halt disease progression

patients, assessing its dose-related ADME properties, and predicting the safety profile and potential side reactions and toxicities of a drug. Radiolabelled drugs are used in microdosing studies to gather information related to drug occupancy, as researchers cannot rely on clinical manifestations of drug activity. For example, a drug may saturate the target without achieving a clinical effect, or, alternatively, it may be unable to reach an effective concentration without producing intolerable side-effects and toxicity. Using a PET tracer, the binding of aprepitant (EMEND, Merck) to brain NK1 receptors was quantified by measuring blockade of binding of the PET tracer to NK1 receptors in the corpus striatum. Nearly complete brain NK1-receptor blockade provided maximum antiemetic efficacy of aprepitant in humans. The PET study was the basis for the FDA approval of the EMEND dose. If the therapeutic window that spans the two extremes is too narrow, a company may decide to abandon a project or reassess the chemical structure of the drug candidate. Therefore, the use of PET has provided drug development teams with the information needed to make these types of decisions earlier in the process, as early as Phase I clinical testing.

In preparation for late stage trials, PET can help the pharmaceutical industry with information-driven patient selection by identifying individuals and sub-populations in whom a drug is more likely to be effective, safe, and well tolerated. This could tip the balance in favour of successful trial outcomes and, in so doing, perhaps may entice companies to invest in R&D targeting of rare and historically more difficult diseases. PET also supports the development of linked diagnostics/therapeutics designed to identify appropriate patients for treatment. In fact, the FDA and other regulatory agencies are encouraging companies to include more high quality imaging data through the submission of Exploratory INDs.

Beyond the surface

The main priorities of the Pharma industry, which is under mounting pressure to improve productivity and reduce the cost of drug development, are threefold:

- To discover effective compounds with novel mechanisms of action.
- To move these compounds more rapidly through the developmental pipeline and fail ill-fated drugs as early as possible.
- To improve the odds for successful clinical trial

outcomes and minimise the possibility of late-stage and post-marketing product failures due to poor efficacy or unanticipated toxicity.

In other words, the ultimate goal is to accelerate and improve the efficiency of drug discovery and development.

The emerging recognition that imaging techniques have value across the spectrum of drug development is highlighted by improved technology and labelling methods, reduced cost of and greater access to instrumentation. In the future, the synergies realised when PET is used in combination with other imaging techniques and with novel types of biomarkers now in development will further drive interest in this evolving technology.

In neurology, examples of the power and commercial potential of molecular imaging for diagnostic applications include DaTSCAN™ (GE Healthcare), a SPECT imaging agent approved for use in Europe that binds to dopamine transporters on neurons in specific brain regions to detect neuronal degeneration. It can be used to differentiate between Parkinson's disease-related dementia and other forms of dementia, such as Lewy body disease, helping physicians select the most appropriate drug therapy for individual patients. Pittsburgh Compound B (PiB), developed at the University of Pittsburgh in collaboration with researchers at Uppsala University in Sweden, is

A PET primer

Positron Emission Tomography (PET) involves the *in vivo* detection of radiation produced by the emission of positrons from the decay of a radioactive substance. In biomedical research and clinical applications, the result of a PET scan are images and input functions that depict, over the time of the study, the biochemical activity, tissue function, or blood flow, for example, by following the distribution and kinetics of radiolabelled molecules. PET does not replace, but rather is complementary to other techniques for structural imaging, including x-ray, computed tomography (CT), and magnetic resonance imaging (MRI). In fact, most PET instruments currently on the market are combined PET/CT scanners that enable non-invasive imaging of both structural and physiological processes. The scans can be performed in the same session and with the subject in the same position, enhancing correlation of the biochemical findings on PET with the anatomical results of the CT scan. PET may be able to detect cellular and tissue changes indicative of disease even before anatomic changes become evident.

Commonly used positron-emitting radionuclides include isotopes of carbon, oxygen, fluorine, rubidium and gallium, ^{11}C, ^{15}O, ^{18}F, ^{82}Rb and ^{68}Ga. These are typically produced by a cyclotron, or, in the case of ^{82}Rb and ^{68}Ga, by generators. A chemical synthesis is usually needed to prepare the radiotracer molecule from the radioactive starting material. These tracers can be used as ligands for specific receptor subtypes (eg Dopamine D2, Serotonin 5-HT1A, α_v/β_3 integrin receptor), as transporters (such as [^{11}C]McN5652, [^{11}C]DASB for Serotonin), or enzyme substrates (eg 6-FDOPA for the AADC enzyme). These labelled molecules are typically injected intravenously. Since the chemical strategy is to replace ^{11}C or ^{18}F for carbon, fluoride or hydrogen in endogenous compounds, their incorporation does not usually alter the size or structure of the resulting radiolabelled tracers.

As each radioisotope decays, it emits a positron, which, on encountering an electron, is annihilated, producing a pair of high energy gamma photons (511 keV) that travel away from each other in opposite directions. When colliding with the detector of the PET scanner, the signal is amplified and after reiterative reconstruction and computation, the instrument translates into an image that depicts the location in the body or target tissue where the source of energy originated. The image can be represented in a scale ranging from black to white, or in variations in colour or brightness. Depending on the radiotracer used and the physiologic process or event being imaged, these variations may correlate to different levels of metabolic activity, blood flow, concentrations of drug compound, receptor activation or enzymatic activity, or presence of a target molecule.

For example, ^{18}F labelling of glucose to produce the radiotracer fluorodeoxyglucose, or FDG, is commonly used in the diagnosis, staging and restaging of many cancers. Glucose is taken up by tissues such as the heart, muscle and brain cells, for energy production, but because cancerous cells are more rapidly dividing and metabolising glucose, tumour tissue will accumulate more FDG over a given time period and will produce a brighter image on PET scanning. Once taken up by a cell, FDG is phosphorylated by a hexokinase, trapping it within the cell. Thus, the FDG accumulates and remains in the cell as it decays, making it an excellent radiotracer for imaging tissues with high glucose uptake.

^{18}F has the added advantage of having a relatively long half-life of 110 minutes. The half-lives of other commonly used radioisotopes are 68, 20, 2 minutes and 75 seconds for ^{68}Ga, ^{11}C, ^{15}O and ^{82}Rb, respectively, which offer both challenges and benefits. The main challenge in working with radioisotopes with short half-lives is that less time is available between radiotracer production, its conversion in a chemical entity and its use. This necessitates close proximity between the cyclotron, the radiochemistry laboratory and the camera. If ^{15}O and ^{82}Rb are uses 'as is', ^{11}C is capable of interrogating a multitude of metabolic pathways, but commercialising ^{11}C and other shorter-lived isotopes will require much faster technologies for producing unit doses in 'ready-to-inject' form. Miniaturisation and microfluidics are likely part of the answer.

being evaluated in clinical studies for its ability to detect amyloid plaque in the brains of patients with pre-symptomatic Alzheimer's disease. Earlier detection of Alzheimer's disease could enable the use of safer and more effective therapies to slow or halt disease progression (**Figure 1**).

In oncology, the use of radioactive glucose (FDG **– see sidebar, A PET primer**) has allowed the rapid expansion of PET. It is now widely used and reimbursed in the US for diagnosis, initial staging and restaging of many cancers, and was recently accepted for the monitoring of breast cancer treatment and in cancer radiation therapy planning. An example of how PET can be applied in oncology drug development emphasises the critical distinction between structural and functional imaging. After treating a test animal or patient with an anticancer agent it is common practice to evaluate the size of the tumour for shrinkage several weeks after treatment. Often, though, tumours may exhibit no change in size on structural imaging, yet an assessment of tumour cell function using FDG may reveal that its cellular metabolism is no longer upregulated, implying that drug treatment has stopped tumour growth. PET can also be used to distinguish between correlates of cell proliferation (using FLT), hypoxia (using F-MISO) and apoptosis (using Annexin-V), differentiating between the ability of a drug either to down-regulate proliferative activity, induce apoptosis or reflect the Oxygen level of a cell. A new agent undergoing clinical trials, F-Angio, is a radiolabelled RGD peptide with high affinity for the α_v/β_3 integrin receptor present on the surface of the neovasculature of tumours. It is tested for the detection of cancer metastasis and the aggressiveness of a tumour based on its angiogenic activity, and possibly may serve as a biomarker for the response to chemotherapy of metastatic cancers.

In cardiology, patients at high risk for coronary heart disease and heart failure can benefit from imaging procedures looking at the density and activity of adrenergic receptors with MIBG, whose imbalance may predispose patients to heart failure, thus detecting early stage disease that may be more amenable to prophylactic and therapeutic interventions.

PET: present and future

The use of imaging techniques such as PET has more often been applied after identification of a drug target to study target expression and distribution in specific tissues. However, the emerging focus on personalised medicine is changing how Pharma formulates its development strategy. Rather than focusing on a disease, companies are beginning to define projects in terms of specific targets. For Gleevec (Novartis), for example, the target is not CML, but rather *bcr-abl* expressing CML. The target defines the disease. Similarly, in the area of CNS disorders, the basis of a project may not be Alzheimer's disease or Parkinson's disease, but rather targets that represent the disease pathology. This new perspective places a great deal of importance on biomarker development and creates abundant opportunities for the application of PET. It also necessitates the development of novel radiotracers that can be used for target validation, the stratification of subpopulations within a disease area, and patient selection for clinical trials.

Today, high-performance chemistry with dedicated equipment has firmly established F-18 as a PET diagnostics mainstay. New tracer production also continues to simplify. The next advance is software-controlled synthesis using versatile chemistry platforms composed of pre-loaded cGMP cassettes. As chemistries and methods for radiolabelling drug compounds improve, PET will be able to make an even more valuable contribution to drug development.

As illustrated in the examples provided here, PET offers unique advantages for drug development, clinical diagnostics and patient management. It is a non-invasive, quantitative tool for imaging human physiology, detecting disease and measuring biochemical changes associated with pathology or drug treatment. Advances in genomics and proteomics leading to new *in vitro* diagnostic tests will stratify populations into 'risk groups' that may benefit from imaging. PET technology and the emerging recognition by the pharmaceutical industry of the valuable role that molecular imaging can play throughout drug discovery and development, will continue to expand the growing interest in PET. As experience with PET increases, so will the knowledge that this imaging tool can contribute to earlier diagnoses and earlier interventions, with data-driven decisions regarding drug targets and drug compounds as well as patient selection for drug testing and drug treatment, and that it has a key role to play in ushering in an era of personalised medicine.

Advantages of PET

A notable benefit of PET is the ability to administer a radiotracer repeatedly in the same subject over a short time period. This facilitates time course studies and baseline versus drug treatment assessments without the need to account for inter-subject variability. In animal studies, subjects can serve as their own controls, thereby improving the statistical quality of the data and reducing the

Exploiting the power of PET

PET can answer the following questions in early drug development:

- Can a drug reach its intended target?
- Does it sufficiently bind the primary target?
- Does its interaction with the primary target affect one or more biochemical/signalling pathways?
- Is the drug's impact on cell or organ physiology relevant to a therapeutic effect?
- Does the drug interact with or affect other off-target tissues or organs?
- Can the drug be delivered to the target efficiently and can therapeutic levels be achieved?

As a biochemical and physiologic modelling tool, PET imaging is able to generate data related to tissue perfusion, target binding and cellular and sub-cellular drug distribution. The technology can be used to detect a variety of changes in the local environment:

- Including changes in oxygen and flow.
- In vascular and cellular permeability and cellular transport.
- In cell proliferation (DNA replication), gene expression, and protein production.
- In surface proteins and receptor systems.
- And in enzyme-driven intra and extra-cellular processes such as coagulation, inflammation and extra-cellular matrix metabolism.

number of animals needed for a study. Furthermore, PET allows researchers to determine the impact of treatment on a target tissue without having to wait for the animal to die.

In humans, PET offers particular advantages for assessing the impact of CNS drugs, as samples of brain tissue can only be evaluated post mortem. In oncology, key criteria for evaluating drug effects and establishing treatment protocols include the length of time a drug exerts a therapeutic effect and the time until maximum effect is achieved. These parameters are difficult to determine using traditional biomarkers, and tumour biopsies only provide a view of the effects of a drug at a single time point. PET enables direct imaging of the target tissue, repeat assessments and quantitative data output.

Above all, PET is a rather safe imaging technique. The high specific activities of positron emitting tracers (typically greater than 1 Ci/micromole), means that subjects are administered with radiolabelled drug compounds at sub-pharmacological doses (typically <10 nmol). This has particular advantages for drug development, as information about tissue kinetics, regional distribution and target occupancy can be acquired with only small amounts of drug. This may allow for the study of trace doses of a compound in humans earlier in the drug development process and contribute to earlier decision making on whether to pursue a particular drug candidate. DDW

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