13 Positron Emission Tomography Imaging as a Key Enabling Technology in Drug Development

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Abstract. The use of positron emission tomography (PET) in drug development has become more common in the pharmaceutical industry in recent years. One of the biggest challenges to gaining acceptance of this technology is for project teams to understand when to use PET. This chapter reviews the usage of PET in drug development in the context of target, mechanism and efficacy biomarkers. Examples are drawn from a number of therapeutic areas, but we also show that the relative penetration of this technology beyond CNS and oncology applications has been relatively small. However, with the increasing availability of PET

and development of novel radiotracers it is expected that the utilization will be much broader in future years, with the additional expectation that the use of PET as an efficacy biomarker will also become more evident.

13.1 Introduction

The goal of this manuscript is to describe how noninvasive imaging using positron emission tomography (PET) is positioned to significantly impact drug development. In order to best illustrate this opportunity, examples will be given in the context of a biomarker framework (Littman and Williams 2005) that deals with target, mechanism and efficacy applications. It will be clear from this paper that PET (as well as other noninvasive imaging modalities) can be applied at all stages of the pharmaceutical life-cycle.

One of the key challenges to achieving the optimal use of this technique is to ensure that project teams have clearly identified the questions that are faced at a particular juncture in the discovery and development paradigm. With this information in hand, technology groups can identify the range of potential solutions and find the optimal solution, while avoiding the problem of using technology for technology's sake.

13.2 Biomarker Definitions

There are three definitions of biomarker levels that are commonly used to describe the particular application of a biomarker:

1. Proof of Target (POT)
   In this category, techniques are used to confirm that the pharmaceutical candidate is reaching the desired target in order to confirm the pharmacological mechanism of action. A target biomarker will ideally be able to measure the level of pharmacological inhibition and the duration of action at the target site. In some cases it may be more limited in nature and simply confirm that the drug has reached the target site (for example, brain penetration or tumor uptake). Typically these types of studies are acute in nature and involve looking at changes within a subject from a baseline condition to one following dosing with the candidate pharmaceutical (either single dose or multi-dose).

Demonstration of POT is something that is ideally demonstrated as a part of a phase 1 clinical trial, and so typically examples of this technique are conducted in healthy volunteers.

2. Proof of Mechanism (POM)
   In this category we are looking to confirm that the candidate pharmaceutical is affecting a downstream component of the biochemical pathway related to target inhibition. This might be related to metabolism, flow, proliferation or one of many outcomes. Some mechanistic biomarkers can be evaluated in normal subjects, while others are restricted to patient populations (e.g., tumor effects, etc).
3. Proof of Efficacy (POE)
   Biomarkers of this category are of the highest value to a development program. Changes associated with these biomarkers will have been demonstrated to be directly linked to clinical outcome, and these changes will manifest ahead of the standard clinical response. It is conceivable that a POM biomarker could become an efficacy biomarker following rigorous qualification; examples of biomarkers in this situation will be discussed later. By default, efficacy biomarkers are restricted to a patient population and may require the use of large patient populations in multi-center studies, which raises the need for standardization in the technique and central data analysis.

As one progresses across this biomarker paradigm, it is clear that the rigor in, and cost of, validation of the biomarker increases dramatically for efficacy biomarkers. Target and mechanism biomarkers are likely to be used for internal go/no-go decision making, while *qualified* efficacy biomarkers will form a pivotal component of a regulatory submission package. However, it is likely that regulatory agencies will be interested in supplemental biomarker data to demonstrate that a novel therapeutic agent is able to elicit specific target- and mechanism-related changes.

13.3 PET as a Tool for Proof of Target

Historically the application of PET to drug development has its origins in the CNS therapeutic area. In the 1980s significant advances were made in the development of radiopharmaceuticals to target specific receptor

subtypes. Of those the dopamine D_2 receptor drew significant interest from the community and a number of candidate radiotracers were developed (Volkow et al. 1996). One of the earliest examples reported for receptor occupancy measurements using PET of a novel therapeutic candidate was for ziprasidone (CP-88,059–01); dose-dependent blockade of [^{11}C]raclopride was demonstrated in healthy male volunteers following oral administration of this pharmaceutical and 85% blockade was confirmed with the highest doses administered (Bench et al. 1993).

The typical paradigm used to measure receptor occupancy involves obtaining a baseline PET scan and magnetic resonance (MR) image (as an anatomic reference), the subject is then dosed with the experimental pharmaceutical (typically oral dosing) in either a single- or multi-dose regimen. A subsequent PET scan is obtained along with plasma pharmacokinetic (PK) samples to determine exposure levels of the experimental compound. From these data, receptor occupancy can be derived and a dose- or exposure-to-occupancy relationship obtained from a group of subjects. By addition of the third imaging session after discontinuation of dosing, one is also able to look at the central washout of the drug and compare this with the peripheral PK.

In the case of ziprasidone, temporal binding to striatal D_2 receptors was investigated and the measured binding potential was found to correlate significantly with the serum levels of ziprasidone (Bench et al. 1996). Since ziprasidone also had activity at the $5HT_2$ receptor, additional studies were conducted to investigate the time course of $5HT_2$ receptor occupancy following a single oral dose of ziprasidone using [^{18}F]septoperone, a $5HT_2$ selective radiopharmaceutical (Fischman et al. 1996).

Another more recent example using [^{11}C]raclopride to measure central receptor occupancy described studies of the antipsychotic drug aripiprazole (OPC 14597). In these studies, occupancy was measured (Yokoi et al. 2002) after 14 days of oral dosing and dose-dependent receptor occupancy ranged between 40% and 95%. This study highlights another key facet of target biomarkers; it is extremely important to link receptor occupancy with a clinical endpoint in order to fully comprehend the data. In this case the highest receptor occupancies were not accompanied by extrapyramidal side effects (common issue for dopamine-D_2 antagonism at high levels of occupancy). These data helped to build

confidence that aripiprazole was acting as a partial dopamine receptor agonist (Gründer and Wong 2003).

One of the most valuable contributions of PET-based target biomarkers is to provide sufficient data to confidently stop a research program early. Confirming that a molecule does not reach its target in sufficient concentrations to likely have a therapeutic effect can lead to significant savings by not advancing to a phase 2 "proof of concept" (POC) study; instead alternative chemical matter can be identified and brought forward to the clinic. On the other hand, if acceptable receptor occupancy levels are obtained and one has a negative POC outcome in phase 2, then a clear decision can be made that the underlying hypothesis for that therapeutic approach is invalid. A recent example of this has been highlighted by Merck in the development of NK1 antagonists (Hargreaves 2002), which have been successful in treating emesis, but have failed in other indications. By using PET ([^{18}F]FSPA-RQ) to demonstrate that adequate levels of target inhibition had been achieved, confidence was increased in terminating development for those indications.

13.4 PET as a Tool for Proof of Mechanism

[^{18}F]Fluorodeoxyglucose (FDG) is currently the most widely used diagnostic PET radiopharmaceutical; utilization of this radiotracer to stage and re-stage various cancers has grown enormously in recent years (Juweid and Cheson 2006). Technological advances have also helped to seed this growth; for example, the introduction of the combined PET/CT camera has revolutionized the ability to delineate metastatic disease. In recent years, a growing body of data has suggested that FDG-PET has the potential to monitor cancer therapy (Weber 2005). This has been driven by the need to identify biomarkers of response that occur sooner than reduction in tumor burden.

While FDG-related changes have been investigated in standard chemo- and radio-therapy regimens, a growing number of examples are emerging for novel targeted therapies, especially antiangiogenic agents. One of the most widely cited examples has been the treatment of patients with gastrointestinal tumors (GIST) using a receptor tyrosine kinase in-

hibitor, imatinib mesylate (Gleevec). Profound changes in FDG uptake were noted after a single cycle of therapy (Joensuu et al. 201); this effect has also been observed in other kinase inhibitors, such as sunitinib (SU011248, or Sutent) (Demetri et al. 2003). In both cases the manifestation of an early metabolic response ahead of clinical benefit helped to confirm that the drug was having an effect at the target site.

A key mechanistic feature of antiangiogenic or antivascular therapies is the direct effect on the tumor vasculature, which is unlikely to elicit immediate morphological changes within the tumor. Therefore, the ability to noninvasively monitor changes in *tumor* blood flow would clearly be of great value in exploratory development. Using PET, changes in tumor perfusion and specific measurements of tumor blood flow can be achieved using [^{15}O]water. The first reported use of this approach in a clinical trial was for the novel tubulin-binding inhibitor, combrestatin A4 phosphate (CA4P). In this phase 1 dose-escalation trial, subjects treated with CA4P demonstrated rapid changes in tissue perfusion demonstrating the immediate mechanistic interaction of this agent upon the tumor vasculature.

It is worthwhile digressing for a moment to mention another nonnuclear-based approach to study the effects of these types of interventions. Using diffusion contrast-enhanced MRI (dceMRI) one is able to monitor changes of two key parameters, K_{trans} and IAUC, which are hallmarks of perfusion and vascular permeability. In a recent phase 1 trail of AG-013736, a novel receptor tyrosine kinase inhibitor, this approach was used to show antivascular effects in subjects within 2 days of treatment (Liu et al. 2005).

Returning to FDG, it should be mentioned that as a mechanistic biomarker, a positive signal of target modulation is not limited to *decreases* in uptake of FDG. An example of increased uptake following therapeutic intervention has been shown in the treatment of metastatic breast cancer with tamoxifen (Moritmer et al. 2001). In this study increases in FDG uptake shortly after treatment with tamoxifen were associated with a good response to therapy and indicative of the mechanism-related hormonal flare associated with this therapy.

The examples highlighted in this section emphasize the value of mechanistic PET biomarkers across programs, which contrasts with target biomarkers whose utility is typically restricted to individual projects

or programs, due to the specific nature of the biomarker. Strategically, investment in the development of novel mechanistic biomarkers that have broad utility and can therefore be used for various therapeutic strategies is extremely useful from both economic and operational perspectives. There are a number of other PET radiotracers that are in development and likely to have a significant impact on cancer drug development in the future (Jager et al. 2005); these include markers of proliferation, hypoxia and apoptosis. In the meantime FDG continues to be evaluated in other therapeutic applications and has been demonstrated to be of great value in many areas including diabetes (Virtanen et al. 2003) and neurodegenerative diseases (Reiman et al. 2004).

13.5 PET as a Tool for Proof of Efficacy

The use of PET as a biomarker of efficacy has not fully been exploited, but it is quite likely that this will change in the near future. Since the qualification of an efficacy biomarker involves relatively large clinical trails, the costs of acquiring the PET data have been a barrier to progress. As an example we can return to the application of FDG in oncology, where data are needed to link the response in serial FDG images with an accepted clinical endpoint such as overall survival, or response as defined by RECIST. A number of small single-center trails have demonstrated that FDG-PET changes are correlated with clinical benefit in a number of cancers (Goerres et al. 2005), but the overall numbers of subjects studied have been too small to provide the statistical significance for qualification.

The issue of efficacy biomarker qualification is currently a major focus of the Food and Drug Administration (FDA) and forms a central component of the "Critical Path Initiative" (FDA 2005). This is occurring in collaboration with the National Cancer Institute (NCI) and their efforts (NCI 2006) in the Oncology Biomarker Qualification Initiative (OBQI). At the present time consortia are being assembled in order to conduct the first large-scale demonstration projects of FDG PET as a biomarker of efficacy. These initial projects will lay the groundwork for qualification of PET and other molecular imaging methods as efficacy biomarkers, by identifying and solving many of the questions related to multi-center

image acquisition and analysis. A central issue to this whole program is the need for standardization of the entire process.

13.6 PET as a Tool to Monitor Pharmacokinetics

One application of PET in drug development that is not adequately identified in this biomarker paradigm is the information obtained from simply radiolabeling the drug candidate itself. By administering a radiolabeled candidate, one is able to collect direct pharmacokinetic information about the compound itself and this is a fundamental premise of the microdosing concept (Lappin and Garner 2003). A few examples have been published which demonstrate the spectrum of questions that can be answered with this technique, ranging from monoclonal antibody distribution (Jayson et al. 2002) to the inhaled distribution of antiinflammatory steroids (Berridge et al. 2000).

13.7 The Role of Preclinical PET Imaging in Drug Discovery and Development

This document has focused on the clinical applications of PET in drug development. A significant effort is currently underway within the pharmaceutical industry to evaluate the value of preclinical PET imaging to address the biomarker questions outlined here. A number of companies have made significant internal investments into the technology, while others have entered into strategic alliances with diagnostic imaging companies or academic partners. The challenges of incorporating this technology into such a time-sensitive environment are enormous; however, some early indications of success have been reported (Hamill et al. 2005).

13.8 Conclusion

In this paper the application of PET imaging as a key enabling tool for drug development has been outlined. As can be seen, there are many opportunities for PET in this arena. It is anticipated that the utilization of

this and other noninvasive imaging technologies technology will grow rapidly in drug development in the years to come.

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