Positron Emission Tomography Imaging: A Quantitative Biomarker in CNS Drug Development

By: Yiyun Huang Ph.D. , Richard E. Carson Ph.D.

- Yale School of Medicine

Introduction

Drug development is a lengthy and costly endeavor. It is estimated that it costs close to one billion dollars to advance a single drug from discovery to the clinics [1]. This is a significant burden on the pharmaceutical industry, and in turn, on society as a whole, and may have contributed to the fact that despite the rapid advance in molecular biology in the last two decades and the identification of an increasing number of druggable targets, the number of approved drugs has been stagnant [2]. One way to contain the rising cost of drug development is to incorporate biomarkers and surrogate endpoints in drug discovery and development, as advocated in an FDA report entitled, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products [2]." The Biomarkers Definitions Working Group defined a biomarker as, "a characteristic that is objectively measured and evaluated as an indicator of normal biologic process, pathogenic process, or pharmacologic responses to a therapeutic intervention" and a surrogate endpoint as, "a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiological, therapeutic, pathophysiological or other scientific evidence," i.e., a subset of biomarkers [3]. Positron Emission Tomography (PET), as a non-invasive imaging technique that provides quantitative information about a drug target's distribution, its interaction with drug molecules and changes over time and upon therapeutic intervention, has been increasingly recognized as a powerful imaging modality that provides a specific and sensitive biomarker for drug development, especially the development of drugs targeting the central nervous system (CNS). This article provides an overview of how PET imaging can be used as an effective biomarker in CNS drug development, using examples in the literature and from our laboratory.

Basics of PET Imaging

PET imaging uses biologically active compounds labeled with positron-emitting radioisotopes such as carbon-11 (decay half-life of 20.4 min) or fluorine-18 (decay half-life of 109.8 min). The radiolabeled compounds (called radiotracers, or radiopharmaceuticals) are injected into a research subject lying in the scanner. These molecules can then reach the target tissues and interact with the target protein *in vivo*. Detection of these molecules occurs when the positron is emitted, collides with an electron and an annihilation event ensues that

by a pair of γ-detectors in the PET scanner (tomograph). The identification of these detectors provides the raw data for an image reconstruction algorithm to define the spatial distribution of the radiotracer. Dynamic acquisition of data over time and corrections for various physical factors in PET (e.g., random events, scatters, and deadtime) allow the quantitative measurements of the absolute concentration of the radiotracer in tissue over time in units of radioactivity concentration (Becquerels/mL). Alignment of PET images with structural information from Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) produces a map whereupon regions-of-interest can be defined anatomically to map the PET signals to any particular region. Application of appropriate mathematical models (tracer kinetic models) then extract from the PET data rate constants for the delivery, distribution and clearance of the radiotracer for quantification of the radiotracer's kinetic parameters *in vivo*.

Quantitative Modeling Analysis of PET Data

Tracer kinetic modeling has been used for over 50 years as a tool to measure the uptake, retention, and metabolism of radiotracers [4]. These modeling approaches depend upon the tracer assumption, i.e., that the mass concentration of the radiotracer is minute, and thus does not affect the saturation of any enzyme or the occupancy of any receptor or transporter (e.g., radiotracer concentration << K_D, the dissociation equilibrium constant of the radiotracer). In this case, the mathematics becomes "simple," i.e., linear, and compartment modeling approaches can be used [5]. In conventional tracer kinetic modeling, this approach involves measurement of tracer uptake and retention in blood and urine, allowing the production of models of the uptake in various body organs, even without direct measurement of the concentration in various organs.

In PET, many of the mathematical equations used are similar, but the structure of the model is different. Since the PET scanner can directly measure the radioactivity in the target organ of interest over time, we avoid the need for knowledge about the rest of the body by measuring (or inferring) the concentration of the radiotracer in the plasma. This curve of radioactivity concentration in the plasma over time, serves as the "input function" to the target organ and allows us to ignore the uptake and clearance of the radiotracer elsewhere. Thus, with the input function curve and each tissue time-activity curve (TAC), various compartment models are derived which can best fit these data [6]. Due to limits in statistical precision of the PET data, these models comprise either one- or two-tissue compartments. In addition, other simplified or graphical methods have been developed to extract the parameters, without definition of a specific model configuration [7,8]. Another important development was various methods to infer the input function, by use of the TAC in a "reference region," i.e., a region with no specific binding of the radiotracer [9-11]. This approach, once validated, avoids the need for measurement of the plasma input function that, in principle, should be acquired from arterial blood (since that is the supply source to the brain). A further complication of input function measurements is the need to correct the radioactivity measurements for the presence of radiolabeled metabolites.

For receptor-binding radiotracers, the kinetic modeling field has adopted standard nomenclature for the outcome measures from these kinetic analyses [12]. The two important terms are the volume of distribution (*VT*) and the binding potential (*BP*). The term V_T represents the radioactivity ratio, at equilibrium, between the tissue and the plasma; this ratio reflects the portion of a radiotracer that is bound specifically to the receptor, as well as free or non-specifically bound fractions (the latter two components are defined as non-displaceable). Since most PET studies are performed using bolus injection of a radiotracer, the modeling analysis predicts the equilibrium ratio from non-equilibrium condition (unless constant infusion is used for delivery of the radiotracer [13]). The binding potential, *BP*, is an equilibrium ratio of the concentration of specifically bound radiotracer to that in a reference fluid or region. Three versions of *BP* are used depending if the reference is free radiotracer in plasma (BP_F), total in plasma (BP_P), or the tissue non-displaceable component (BP_{ND}). The last measure, BP_{ND}, is most commonly used since only this form of the binding potential can be estimated using the reference region methods.

Receptor occupancy (RO) of a drug candidate at a target can then be measured quantitatively by comparing regional *BP* values at baseline to those measured following drug administration, i.e.,

$$RO = 100\frac{BP_{baseline} - BP_{drug}}{BP_{baseline}}$$

Then, RO can be compared to the plasma concentration of the drug (C) to estimate the IC_{50} value using classical receptor binding equations (see below for examples). Note that determination of *BP* requires the identification of a suitable reference region. However, RO can also be determined without a reference region from V_T values from multiple regions using the "occupancy plot" under the assumptions that RO and non-displaceable binding (V_{ND}, termed non-displaceable volume of distribution) are uniform across brain regions [14].

PET Imaging as a Biomarker in CNS Drug Development

PET imaging is functional and quantitative. It can provide quantitative measures of a radiotracer's behavior *in vivo* and extract from PET images biochemical information about the interaction of the radiotracer with the target protein. The applications of PET imaging in drug development includes the following four categories: 1) Detection of a drug's distribution and/or tissue kinetics if a drug molecule can be directly labeled with a positron-emitting radioisotope; 2) Validation of target engagement by the drug, or a proof-of-target study, to answer the question of whether the drug reaches and engages the desired target; 3) Target (receptor) occupancy study to relate a drug's dose with target occupancy, pharmacokinetic (PK) and pharmacodynamic (PD) parameters, or a proof-of-mechanism study, to answer the question of whether the drug interacts with the desired target at a level sufficient to produce the intended pharmacological effects; 4) Monitoring of a drug's treatment effect, or a proof-of-efficacy study, to answer the question of whether the drug alters the pathology of the disease being treated. It should be noted that all the above applications of PET imaging are not mutually exclusive. For example, depending on the design of the experiments, a single PET imaging study with related measurements may serve the dual purposes for proof-of-target and proof-of-mechanism.

Biodistribution of Drug Molecules

When a prospective drug molecule can be labeled with a PET radioisotope without changing the molecule's structure, PET provides a means to directly follow the drug molecule's delivery, distribution and clearance in the living body, and retention and kinetics in the tissue of interest over time. One example of such an application is in the case of BMS-181101, a putative antidepressant with a novel pharmacological profile as a serotonin reuptake inhibitor and an agonist at the serotonin 5-HT_{1A} and 5-HT_{1D} receptors. The compound was labeled with C-11 at the methoxy group on the pyrimidine ring. The C-11 labeled compound, [^{11}C]BMS-181101 (Figure 1), was shown to enter the brain. However, its delivery into the brain was dominated by blood flow and clearance from the brain was rapid, resulting in little retention in brain regions known to have high concentrations of serotonin receptors, even though clearance from plasma was relatively slow [15]. Due to the lack of sufficient retention and exposure in the brain demonstrated by PET imaging, further development of BMS-181101 as a novel antidepressant was terminated.

One related example is the biodistribution of triamcinolone acetonide (Figure 1), a steroid with anti-inflammatory property used in the treatment of rhinitis and asthma. Berridge et al. labeled the compound with C-11 and studied its distribution after inhalation. [^{11}C]Triamcinolone acetonide was shown to deposit in the targeted airway regions in a distal gradient from the trachea and bronchi to the lungs and clear slowly over time [16].

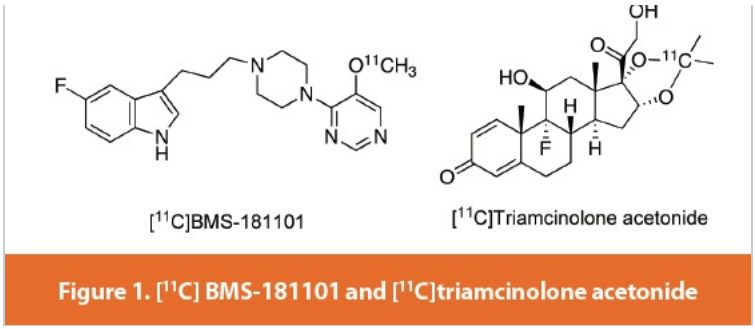

Figure 1. [^{11}C] BMS-181101 and [^{11}C]triamcinolone acetonide

Validation of Target Engagement

When a specific PET radiotracer is available for a target and a drug molecule is designed to engage with the same target to produce pharmacological effects, PET imaging can be used to validate engagement of the drug molecule with the target. For example, [^{11}C]P943 is a specific and selective radiotracer for the serotonin 5-HT$_{1B}$ receptor [17, 18]. CE-210,666 is a subtype-selective 5-HT$_{1B}$ receptor antagonist originally intended for the treatment of major depressive disorder (MDD). PET imaging with [^{11}C]P943 was used to study whether the drug binds to the 5-HT$_{1B}$ receptor *in vivo*. Oral doses of 5, 30 and 60 mg were given to three different groups of subjects. PET imaging with [^{11}C]P943 was performed on the High Resolution Research Tomograph (HRRT) at 3 and 24 h after the oral dose of the drug (the short half-life of C-11 permitted these repeat scans in each subject). As shown in Figure 2, the drug at a dose of 30 mg significantly reduced the binding of [^{11}C]P943, a demonstration that the drug and the radiotracer compete for the same binding sites in the human brain, thus validating the target of the drug as the serotonin 5-HT$_{1B}$ receptor.

Another example of target validation is for drug acting on the dopamine D$_3$ receptor using PET imaging with the radiotracer [^{11}C]PHNO [19]. Since [^{11}C]PHNO binds to both D$_2$ and D$_3$ receptors *in vivo* (albeit with different affinities) [20-22], and is thus not selective for D$_3$, brain regions where [^{11}C]PHNO binding is exclusively due to interaction with the D$_3$ receptors are used in this kind of study. Recent studies in humans indicated that [11C]PHNO signals in the dorsal striatum are due to D$_2$ binding, while signals in the substantia nigra are exclusively due to D$_3$ binding, and those in other brain regions, mixed D$_2$/D$_3$ binding [23,24]. Hence, binding competition of a drug with [^{11}C]PHNO in the substantia nigra is an indicator of target engagement by the drug at the dopamine D$_3$ receptor. In a PET imaging study with a putative D$_3$-selective antagonist, subjects were given an oral dose of the compound, and PET scans with [^{11}C]PHNO were performed at 2h and 24 h post-dosing, respectively. Figure 3 shows that at 2 h post-dosing, binding in the dorsal striatum was little changed, while that in the substantia nigra decreased significantly. By 24 h post-dosing, as the drug gradually cleared from the body, radiotracer binding in the substantia nigra was partially restored. Results from this PET imaging study demonstrated that the drug molecule indeed interacts with the dopamine D$_3$, but not D$_2$ receptor, in the human brain.

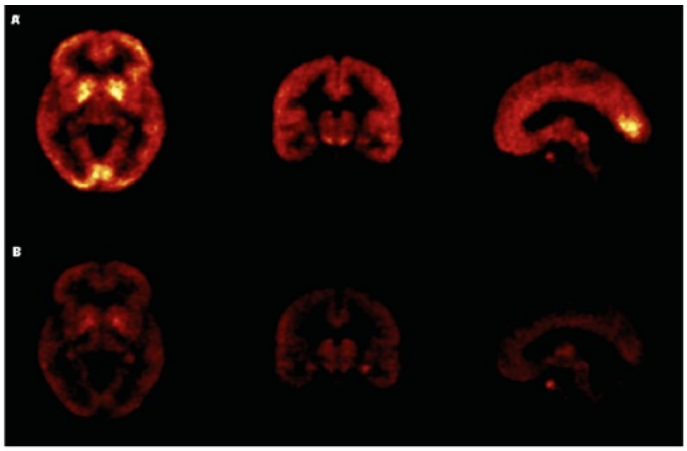

Figure 2. Average [^{11}C]P943 binding potential images. A. Transverse, sagittal, and coronal images of the baseline [^{11}C]P943 scan. B. Same slices of images from [^{11}C]P943 scan obtained 3 h after an oral dose of 30 mg CE-210666. All images are displayed on a common scale.

Study of Receptor Occupancy by Drug

Receptor occupancy studies provide a means to relate dosage of drug to the occupancy of target receptor by the drug in the brain, as described above. PET imaging is especially useful in this type of study, as it gives quantitative correlation of dosage with the level of target engagement. When coupled with measurement of drug concentrations in the plasma and other PK/PD parameters, this type of study can inform the relationship between a drug's dose, exposure in the circulation, level of receptor occupancy in the brain, and pharmacological response. Knowledge from this kind of study can be used to formulate key decisions in drug development. One clear example is to help design the dosing regimen for optimal therapeutic effects and minimal associated side effects. If a certain level of receptor occupancy is thought to be required for the intended pharmacological response and/or efficacy, inadequate occupancy level at the maximal tolerable dose (MTD) will pose a serious challenge to the further development of a drug, and clinical trials can be halted, thus saving drug development expense. On the other hand, adequate receptor occupancy without demonstrated clinical response will be cause to question/discount the mechanism of therapeutic action, as in the development of aprepitant (MK-869), a substance P/-neurokinin 1 (NK1) receptor antagonist, as antidepressant. In a phase III clinical trial incorporating PET imaging with the NK1 specific radiotracer [^{18}F]SPA-RQ [25], dose of aprepitant known to produce near saturation of NK1 receptor failed to generate antidepressant effect [26]. The conclusion, then, was that the concept of using neurokinin 1 receptor antagonists for the treatment of major depressive disorder was not valid.

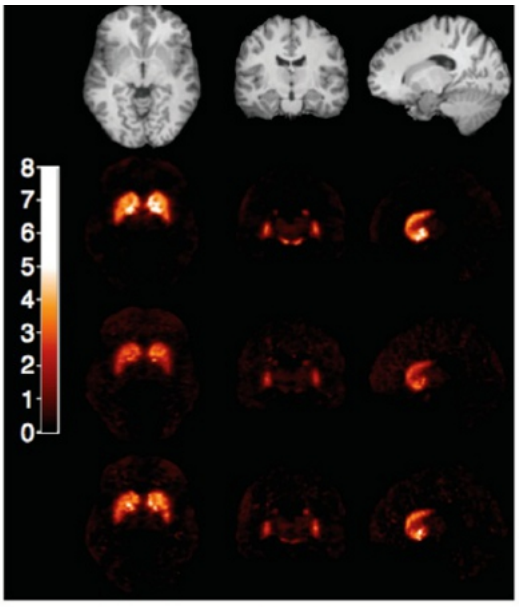

Figure 3. First row: MRI images. Second row: Baseline [^{11}]PHNO BP_{ND} images. Third row: [^{11}]PHNO BP_{ND} images 2 h post-dosing of a putative D_3-selective antagonist; Fourth row: [^{11}]PHNO BP_{ND} 24 h post-dosing.

The radiotracer [^{11}C]GR103545 is a selective kappa opioid ligand demonstrated to be suitable for imaging this receptor subtype in nonhuman primates [27]. Development of this radiotracer for PET imaging in humans was recently carried out in our laboratory [28,29]. After validation of this radiotracer in humans, it was used in a receptor occupancy study of PF-04455242. PF-04455242 is a selective kappa opioid receptor antagonist, with K_i of 3.0, 65 and *>4,000 $_n$M*, respectively, in radio-ligand binding assays *in vitro* using cloned human kappa, mu and delta receptors [30, 31]. In preclinical studies PF-04455242 was shown to exhibit antidepressant-like properties in several animal models of depression. In addition, preclinical and clinical experiments demonstrated that PF-04455242 inhibited the increase in plasma prolactin levels induced by the kappa agonist spiradoline, an indication of antidepressant efficacy [32]. In the receptor occupancy study, PF-04455242 was given to five healthy subjects at an oral dose of 30 mg and PET scans with [^{11}C]GR103545 were performed at 1.5 h (t_{max} for the drug) and 8 h (2 half-lives of the drug), respectively, post-dosing [33]. Venous blood samples were taken during the 2.5 h PET scan to measure the concentrations of PF-04455242 in the plasma. As there is no reference region for the radiotracer [^{11}C]GR103545, the occupancy plot method was used to calculate receptor occupancy (Figure 4) [14]. Averaged over the five subjects, PF-04455242 at a dose of 30 mg produced a mean kappa receptor occupancy of 50%, and mean *in vivo* IC_{50} was estimated at 48.6 ng/mL. In clinical PK/PD model, PF-04455242 plasma level of 39 ng/mL or higher was predicted to significantly reduce spiradoline-stimulated serum prolactin increase [32]. Hence, an occupancy level of 50% by kappa opioid receptor antagonist was predicted to have anti-depressant efficacy [33]. Even though the development of PF-04455242 was halted due to toxicology findings in animals exposed to the drug for three months, PET imaging with concurrent PK/PD measurements provided an important proof-of-mechanism study demonstrating the potential of kappa antagonists as efficacious antidepressants.

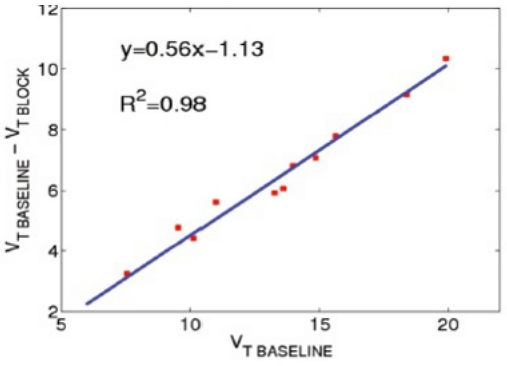

Figure 4. An occupancy plot, used to estimate kappa receptor occupancy by a 30 mg oral dose of PF-04455242 in a healthy male subject, measured at 1.5 h post-dosing with PET and [^{11}C]GR103545.

Treatment Monitoring

One important area of application for PET imaging biomarker is to monitor treatment outcome of disease-modifying therapeutic agents (proof-of-efficacy study). A prominent example is in the drug development for Alzheimer's Disease (AD). The hallmark of AD is the formation of insoluble plaques comprised primarily of the β-amyloid protein in the patients' brain (the β-amyloid cascade hypothesis) [34-36]. As such, one important theme for drug development for AD is to find compounds that can dissolve and clear the deposition of β-amyloid [37]. Over the years, a number of radiotracers for β-amyloid have been discovered, chief among them [^{11}C]PIB and [18F]AV-45 (Florbetapir) [38]. In clinical trials of anti-amyloid therapeutic agents targeted at the β-amyloid cascade, PET imaging with β-amyloid binding radiotracers can be used in two ways: 1) to select patients for the trials who present measurable β-amyloid load; and 2) to monitor the change in β-amyloid load over time, and thus, the efficacy of anti-amyloid therapeutic agents. In a recently published report, Rinne et al. used PET imaging with [^{11}C]PIB to monitor the treatment outcome of the anti-amyloid monoclonal antibody bapineuzumab. In a cohort of 26 Alzheimer's patients treated with the drug, significant reduction in β-amyloid load was detected in the brain at 78 weeks of drug therapy [39] . This is the first time an anti-amyloid therapeutic agent was shown, via PET imaging, to modify the pathology of Alzheimer's disease (proof-of-efficacy). Results from this study will certainly spur the use of PET imaging as a biomarker in similar clinical trials testing drugs targeted at the β-amyloid cascade. It also serves to further underscore the importance of this imaging modality in drug development.

Conclusion

Positron Emission Tomography, as a quantitative imaging modality, is an important tool in the development of drugs for CNS disorders. As illustrated above, PET imaging can be used to detect the distribution of drug **1**molecules in the body, to conduct proof-of-target, proof-of-mechanism and proof-of-efficacy studies. The value of this imaging modality has been increasingly recognized by the pharmaceutical companies, as evidenced by their entry into the radiotracer development area. It is expected that PET imaging will continue to have a substantial and growing impact on CNS drug development.

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Author Biographies

***Yiyun Huang, Ph.D.**, is an Associate Professor of Diagnostic Radiology, Yale University School of Medicine. He is a chemist experienced in the design and development of PET Imaging probes for CNS targets. Over the*

neurological and psychiatric disorders.

***Richard E. Carson, Ph.D.**, is a Professor of Diagnostic Radiology and Biomedical Engineering, Yale University. He is an expert in image processing and modeling analysis of PET data. His research focus is on the development and applications of new tracer kinetic modeling methods and algorithms and on PET image reconstruction and image quantification.*