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Imaging in Central Nervous System Drug Discovery

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The discovery and development of central nervous system (CNS) drugs is an extremely challenging process requiring large resources, timelines, and associated costs. The high risk of failure leads to high levels of risk. Over the past couple of decades PET imaging has become a central component of the CNS drug-development process, enabling decision-making in phase I studies, where early discharge of risk provides increased confidence to progress a candidate to more costly later phase testing at the right dose level or alternatively to kill a compound through failure to meet key criteria. The so called "3 pillars" of drug survival, namely; tissue exposure, target engagement, and pharmacologic activity, are particularly well suited for evaluation by PET imaging. This review introduces the process of CNS drug development before considering how PET imaging of the "3 pillars" has advanced to provide valuable tools for decision-making on the critical path of CNS drug development. Finally, we review the advances in PET science of biomarker development and analysis that enable sophisticated drug-development studies in man.
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Introduction

Central nervous system (CNS) drug discovery and development is a long and difficult process with the delivery of a successful new medicine taking approximately 10 years to complete from the initial identification of the disease and target biology through to the launch of an approved new molecular entity (NME). In addition, a lot of resource is consumed through high levels of attrition, for failed drugs that never overcome all the hurdles required to realize a viable CNS drug. These hurdles include appropriate safety, pharmacokinetics (PK), blood-brain barrier (BBB) penetration, target engagement, pharmacologic activity, and efficacy. Thus, vast costs and long timelines are associated with the approval of each NME—with more than $2 billion required to bring each NME to market, by current estimates.[1]

The drug discovery and development process can be broken down into a number of phases. After the identification of the putative biological target the process passes through a screen for compounds with the right properties (Fig. 1). This leads to libraries of compounds being generated that are then subsequently tested preclinically in vitro and in vivo, before a candidate compound is taken into human testing. In humans phase I (safety and tolerability), phase IIA (proof of concept and dose ranging), phase IIB (definitive dose finding), phase III (pivotal placebo-controlled trials and long-term safety) precede compound registration and approval by the relevant regulatory authorities. Postapproval phase IV studies are conducted (postmarketing surveillance studies). The size and cost of these studies increases throughout these phases, with costs increasing in proportion with increased sample sizes and safety monitoring requirements.

These exponentially rising costs make good decisions early in the process imperative to killing compounds that do not have the right characteristics for a successful drug as early as possible. For example, performing a phase III study with a compound that does not sufficiently engage the biological target is an easy way to waste the order of $100 million.

Direct assay of human brain tissues are extremely challenging, and thus historical approaches to CNS drug development

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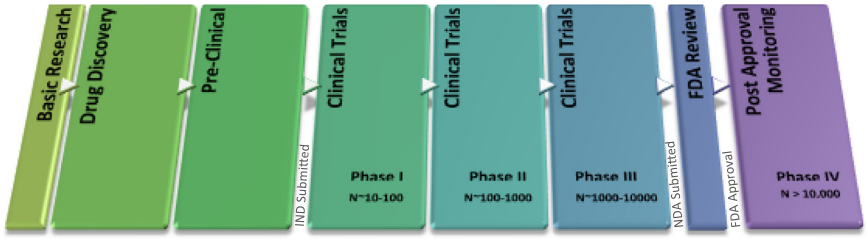

Figure 1 Phases in the drug discovery and development process.

relied heavily on peripheral PK and clinical measures. These lack direct quantitative information on the levels of brain exposure to the drug, target engagement, and pharmacological activity—the so-called 3 pillars of drug survival[2] (Fig. 2). These 3 pillars represent the hurdles that a candidate molecule must overcome to become a successful centrally acting drug. In a 2012 review of decision-making for 44 of its drug programs in phase II, Pfizer revealed that, in 43% of decisions, it was not able to conclude whether these 3 pillars had been met.[2] PET neuroimaging is unique in being able to provide a direct quantification of parameters central to the 3 pillars in the human brain in vivo, through the use of radiolabelled drugs or biomarkers.[1,3]

The first CNS PET studies looking at measuring target engagement of a drug were performed in the late 80s by Farde et al[4] who used [^{11}C]raclopride as a radiotracer to explore the target engagement of antipsychotics designed to interact with the dopamine D2 receptor. Such studies were first directly incorporated into the drug-development process in the early 90s.[5] This has led to PET target engagement (or occupancy) studies of novel drug candidates becoming de-rigeur in the past 2 decades, as big pharma has adopted this technology to provide confidence in brain penetration and rich dosing information from small human cohorts in phase 1 studies.[1,3,6] These studies deliver information on 2 of the 3 pillars in small cohorts (n = 6-12 subjects) in first time in human (FTIH) studies, providing an opportunity for a very early go-no-go decision in the development process.

Biodistribution studies, are ones where the drug candidate itself is directly radiolabelled, have also been performed.[7-9] These studies provide information on whether the drug access across the BBB and its concentration in brain tissue.

Measures of pharmacologic activity along with stratification for trial entry with imaging agents able to quantify levels of misfolded proteins such as Aβ and tau have provided important readouts for pharma in neurodegenerative diseases.[10]

This review focuses on PET measures of these 3 CNS drug survival pillars such as tissue exposure, target engagement, and pharmacologic activity as well as the methods of biomarker development and quantitative analysis that are critical for their application. In particular, we highlight the more recent evolution and sophistication of these approaches that have led to their increased value. We signify these recent innovations in sections identified with the "+" symbol.

Biodistribution

PET radiolabelling of a small molecule drug with either C11 and F18 allows for the introduction of an imaging tag without altering the properties of the drug compound itself. Subsequent intravenous injection of the labeled drug and careful quantitative analysis of the dynamic PET data allows for the direct measurement of the drugs concentration in brain tissue. Quantitative analysis involves the fitting of an appropriate tracer kinetic model to the data that partition the total signal

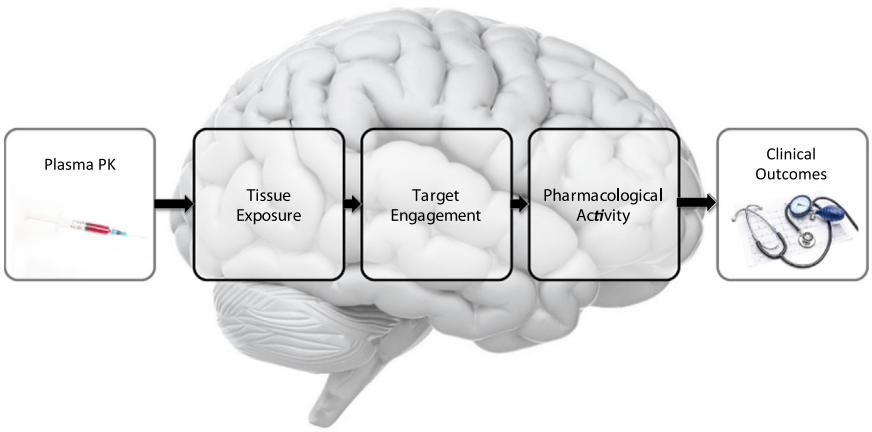

Figure 2 The three pillars of CNS drug survival that can be assayed with PET neuroimaging—tissue exposure, target engagement, and pharmacological activity.