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Positron Emitting Tracers in Pre-Clinical Drug Development

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Abstract: Molecular imaging tools such as Positron Emission Tomography (PET) are increasingly being used in the drug development process. The unrivaled sensitivity of PET coupled with a solid experience in developing highly targeted molecular probes makes this technique a very valuable tool at all stages from pre-clinical development to the clinical phases. Positron emitting tracers allow us to measure, quantitatively, molecular processes and interactions between a candidate drug and its molecular targets. This information can save time and money by directing development towards the most promising compounds and excluding molecules with unfavorable properties that would otherwise only be recognized as failures in latter stages of the process. In this paper we review the application of positron emitting tracers in the pre-clinical stages of the drug development process in the areas of oncology, cardiology, neurosciences and inflammatory diseases. PET tracers provide an important support for drug development in the areas of: discovery of new drug targets, clarification of pathophysiology, identification of potential drug candidates and validation of drug effectiveness, as well as the evaluation of pharmacokinetic and pharmacodynamic parameters *in vivo*.

Keywords: Animal models, drug development, molecular imaging, PET, pre-clinical, radiopharmaceuticals.

INTRODUCTION

The discovery and development of new drugs is a long, costly and risky process. Despite all technological and scientific advances, the time and the cost involved have increased, and it now takes about 10-15 years and an estimated 1.0 to 2.0 billion USD until a new drug reaches the market [1-4]. For a new medicine to be approved, it must undergo several development phases in order to demonstrate quality, efficacy and safety. Following an initial phase of discovery, compounds are tested by a battery of pre-clinical tests (*in vitro* and *in vivo*) until they reach the clinical stages. These are divided in 3 Phases (I, II and III) that end, if successful, with the release of the product into the market. Recently, FDA has introduced a new pre-Phase I clinical stage called Phase 0 in order to speed up the development of new drugs into the market. In these studies, also called platform for deciding which molecules are most likely to succeed and which ones are not. Later, in early clinical development, the high sensitivity of PET, in the nano- to picomolar range, makes it ideal for Phase 0 microdosing studies. In those, valuable information regarding pharmacokinetic, bioavailability, biodistribution and targeting properties of new drugs, in a limited number of human volunteers, can be obtained. This information can be crucial to select only the most promising candidates for the lengthy and costly clinical phases. Also, in these clinical phases, positron emitting tracers can be used as imaging biomarkers that can, often quantitatively, assess the clinical efficacy of the drugs being tested and thus provide important tools for the assessment of clinical endpoints.

In this paper we revise the application of positron emitting tracers in the pre-clinical stages of the drug development