

INTRODUCTION TO MOLECULAR IMAGING

The medical industry, including the pharmaceutical, biotechnology components and clinical practice has recognized the importance of using molecular imaging biomarkers, especially PET biomarkers, as tools for predicting the outcomes in drug development for diagnosing early stage disease and for the following of treatment.

The Food and Drug Administration (FDA), the National Institute of Health (NIH) and many international organizations have recognized the importance of using biomarkers and expanding the use of biomarkers in medicine. The completion of the sequencing of the human genome is now approximately six years old and many new insights in the human body have been gained from this monumental accomplishment.

Modern system biology has taught us that genotypic understanding must be expanded to include the non-hereditary information or the phenotypic information about disease. As a result of the need for new tools and approaches, acceleration in the development of new treatment drugs has not occurred. Instead, there has been a recognized deceleration in the drug development process with the advent of more personalized drugs. The development cost of a new drug now exceeds \$1 billion resulting in a steady decrease in new molecular entity (NME) output. The problem is clearly defined in the FDA white paper - Innovation Stagnation - Challenge and Opportunity on the Critical Path to New Medical Products. The white paper suggests in-vivo molecular imaging as an important tool for drug development but, also points out some of the technology problems of making this tool available. The opportunity and problem is well defined in the following FDA quote: Opportunity: "Imaging Technologies, such as molecular imaging tools used as measures of drug absorption and distribution may provide powerful insights into the distribution, binding and other biological effects of pharmaceutical but, their predictive value needs further study and evaluation. New imaging technologies will ultimately contribute important biomarkers and surrogate endpoints. How soon these new tools will be available for use will depend on the effort invested in developing them specifically for this purpose."



Following this FDA paper a follow up paper was published in Clinical Pharmacology and Therapeutics entitled "Paving the Critical Path: How can Clinical Pharmacology Help Achieve the Vision?". In this very important paper six critical paths are identified for improving the effectiveness of drug development. Molecular Imaging will contribute significantly to the following three of the six critical paths.

- Taking responsibility for optimal dosing
- Identifying biomarkers as potential diagnostic test
- Using therapeutic drug monitoring to individualize dosing

In a commentary paper in Clinical Pharmacology and Therapeutics the concept of biomarkers and the preferred definition is presented: "Biological Marker (biomarker): A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."

Clinically, PET can be used to diagnose or stage all cancers with more than 2 million scans being performed in the US this year. Depending on the cancer type, PET changes the treatment of the disease from 30 percent to as high as 60 percent of the cases. A typical PET image is shown in Figure 1 illustrating a staging case for head and neck cancer.

The result of patients being properly treated is cited by Annual Report to the Nation on the Status of Cancer, 1973-1999(4) as one of three reasons death from cancer in the US has been declining for the past few years.

There are several classes of biomarkers including in-vitro, as well as, the in-vivo markers. This discussion focuses on PET radio-labeled biomarkers because of the important characteristics of such markers. PET biomarkers are labeled with positron emitting radioisotopes, including nitrogen, oxygen, carbon and fluorine, primarily which are short lived elements (2 minutes to 110 minutes). They normally do not interfere with the tagged molecule and present minimal pharmacological effects in humans.

PET imaging is quantitative and can measure rapid pharmacokinetics in animals from a small mouse to larger primates including humans. An important paper in the current Clinical Pharmacology and Therapeutics: Molecular Imaging as a Tool for Personalized and Targeted Anticancer Therapy" outlines the concept of using molecular imaging in drug development as well as in diagnosis of disease and in the following of treatment of disease. The author concludes that "No toolbox will be complete without the capability to perform an imaging assessment of a drug's effectiveness in an individual patient or in particular patient population".

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