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Drug Development for Targets outside the Brain using Imaging

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Pharmaceutical industries are suffering for increasing attrition in the development of new drugs. Major limitations have been identified in poor ADMET characteristics (A=Absorption; D=distribution; M=Metabolism; E=Excretion; T=Toxicity) of drug candidates and increasing difficulties in translating preclinical data into clinical phases despite a massive number of tentative compounds.

Molecular imaging, in particular high sensitivity modalities like PET, is emerging as a powerful tool in the process of Drug Development & Research (DDR) also in anatomical regions outside the brain. Some technological achievements played a fundamental role to this purpose: the integration of PET data with anatomical information, in particular with hybrid machines (PET/CT), and the improvement of spatial and temporal resolution performances of PET scanners, including small animal scanners.

Use of radiotracers as primary end-points (labelled parent drug) or secondary end-points (radiopharmaceuticals reporting on drug action/effect) can be an added value in translational research to address early Proof-of-Concept demonstration and assessment of drug pharmacokinetics (PK) in humans (e.g. bioavailability, drug deposition). Indeed human microdosing coupled with high sensitive measurements (PET, mass spectrometry) is under assessment by major regulatory bodies to reduce attrition in DDR.

However, simple qualitative reading of images is not sufficient per se to address the complex and demanding field of DDR. A quite common perception of drug efficacy measurement by molecular imaging is represented by the use of PET/FDG to demonstrate tumour response to treatment. Although the answer may be of clinical value and used by the oncologist to draw conclusion on therapy, this is not sufficient to be a biomarker for a drug developer and would not be easily accepted by a Regulatory Agency. The outcome of the imaging procedure must be strictly related to the expected therapeutic effect: as a general rule PET measurements should be quantitative, dynamic and validated. This may be difficult to approach, in organs differing from the brain, where anatomical peculiarities and motion can make it very difficult. These issues will be elucidated through specific examples addressing:

- The importance of measuring the input function (either image-derived or deducted off-line via blood sampling) and its relation to PK measurements to assess both a tentative drug or the biochemical mechanisms underlying the physiological or pathophysiological process we want to unravel searching for therapeutic target or druggable compounds.
- A specific PET imaging application dealing with the liver, showing how multinuclide and multimodality experiments can be designed and integrated to address open issues in diabetes and metabolic disease.
- A measurement strategy for measuring the pharmacodynamic effects of cardiovascular drugs via myocardial blood flow and metabolism.

Finally, perspective applications of imaging in DDR, relating radiotracers and biochemical processes relevant to DDR (e.g. angiogenesis, apoptosis) will be reviewed and discussed in the perspective of Regulatory Bodies position and some examples of the use of Molecular Imaging to study drug formulation will be presented.

References

1. A.J.Atkinson et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin. Pharmacol. Ther. 2001; 69(3):89-95
2. S.A.G. Cherry. Use of Positron Emission Tomography in animal research. ILAR J. 2001; 42:219-232
3. M.Rudin,R.Weissleder. Molecular Imaging in drug discovery and development. Nature rev. Drug.Disc. 2003; 2: 123-131
4. G.J.Kelloff et al. The Progress and Promise of Molecular Imaging Probes in Oncologic Drug Development. Clin. Cancer Res. 2005; 11: 7967-7985