Building the Three Pillars – Imaging in Early Phase Drug Development

Eugenii A Rabiner

[1]Imanova, Centre for Imaging Sciences, London, UK;
[2] Centre for Neuroimaging Sciences, Institute of Psychiatry, Kings College, London,

The development of novel medication for central nervous system (CNS) indications is facing increasing difficulties due to rising incremental costs of development. Attrition in the latter phases of development in unsustainable in the long term – due to the incremental costs of latter stage drug development. A particular point of failure in the drug development process is in the transition of drugs from Phase II “proof of concept” studies to Phase III “pivotal” studies. The conclusion to be drawn from this fact is that classical Phase and Phase IIa studies do not provide sufficient information to allow the early termination of unsuitable molecules. It has been argued that demonstration of tissue exposure, target engagement and pharmacological activity – the so called, Three Pillars of Drug Survival – in early phase studies, will enhance the probability of success of novel pharmaceuticals, thus minimising the prohibitive costs of late phase compound failure. Molecular and functional imaging methods have the ability to quantify brain penetration and target engagement, define the therapeutic dose and provide an indication of relevant pharmacodynamics activity in Phase I, at approximately the same time as the first-in-human single dose (FTIH-SD) safety and tolerability studies. Identification of the clinically relevant therapeutic dose range at this stage of development allows the reduction in the size of future phase II studies, and the early attrition of molecules which are not going to make it in late phase development.

I will present the methods allowing the estimation of target engagement and the optimization of therapeutic dose range for targets with existing PET ligands, as well as for compounds where no suitable molecular tools exist. Using real-world examples, I will demonstrate how the combination of functional and molecular imaging in adaptive design studies can be used to define biomarkers for brain disorders and provide utility for intelligent drug development.