

Everything You Wanted to Know about MR-PET: **PET-MR in Drug Research**
Alex de Crespigny decrespigny.alex@gene.com

This presentation is aimed at investigators at academic centers and imaging scientists working in the biotechnology/pharmaceutical industry who are considering the use of hybrid PET/MRI scanners in clinical trials of novel therapeutics. Following the presentation, the audience should be better able to decide in what disease areas and in what types of studies this new hybrid technology could be advantageous, now and in the future, compared to sequential PET and MRI scans.

Broadly speaking, imaging is used in two ways in clinical drug development. Routine clinical imaging is often used to gauge response to therapy; for example CT scans to monitor tumor size or MRI to track brain lesions in multiple sclerosis (MS) patients. Increasingly, advanced imaging techniques are being used in early phase drug trials to help improve decision making, and this is where hybrid PET/MRI scanners are most likely to first have an impact. Due to the smaller size of phase I (safety) or phase II (initial proof-of-concept) trials of novel therapeutics, the feasibility of using advanced and novel imaging technology is much greater than in pivotal phase III studies. The two major disease areas where PET is currently used in novel drug evaluation are oncology and neuroscience. In oncology, the reduced radiation exposure of a PET/MRI scan is of secondary importance to the logistical benefit of two evaluations in one visit (for patients already subjected to many hospital visits for drug infusions, blood and tissue sampling, etc.). Semi-quantitative ¹⁸F-fluoro-deoxyglucose (FDG) PET has been widely used to detect pharmacodynamic activity (i.e. an effect on the drugs intended pathway) of novel targeted cancer drugs and diffusion MRI has been evaluated at many centers for the same purpose. Additional applications include patient selection (e.g. screening for metabolically active lesions) and an earlier or more sensitive measure of drug efficacy (i.e. killing tumor cells). While images from sequential FDG-PET/DW-MRI can already be combined for brain studies (with the caveat that scans would often be acquired on different days with possibly differing drug effects) fusing such data is much more challenging for tumors in the body, as seen in the vast majority of early phase oncology trials, where inter-scan motion can be highly problematic for sequential imaging exams. Another application area for PET/MRI in oncology may be for drugs targeting tumor angiogenesis, where imaging PET tracers that bind to tumor microvasculature complements perfusion and permeability information from DCE-MRI.

Similar to oncology, there may be logistical advantages for hybrid PET/MRI over sequential scanning in drug trials in neurodegenerative conditions such as Alzheimer's disease. Routine MRI scans for safety assessment and to assess cortical atrophy match well to amyloid-PET to assess drug effect on its target. However the most compelling application of PET/MRI is to study dynamic processes that are too fast to be recorded in sequential scans. In drug development, the best example of this is the early phase evaluation of brain-penetrant small molecules. Often, target engagement is confirmed by dynamic PET scanning of the uptake of a tracer designed to compete with the candidate therapeutic drug. Scans are performed in the absence and presence of various concentrations of the therapeutic to assess neuroreceptor occupancy. Pharmacological MRI (Ph-MRI) is emerging as a useful tool to measure the regional hemodynamic effects novel CNS drugs. Such PET and MRI information is naturally complementary in fully assessing the drug. For practical (effects are often dynamic with fast washout) and safety (one may not be able to give multiple administrations of the test drugs) reasons this combined information may only be obtained by simultaneous PET/MRI. Other areas where hybrid PET/MRI may prove beneficial include trials evaluating new drugs for atherosclerosis, myocardial ischemia, Crohn's disease and potentially stroke. In general, hybrid imaging will be important to allow accurate co-localization of metabolic/molecular and functional/anatomical indicators of disease, which are critical for differentiating tissues that are viable (treatable) from non-viable (necrotic, fibrotic, etc).