Hammersmith Medicines Research

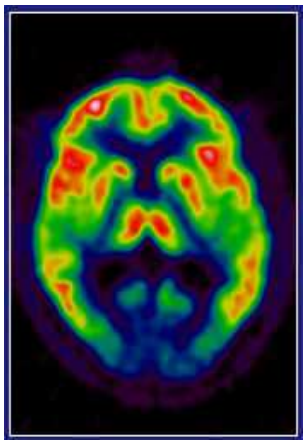
and

Invicro, Hammersmith Hospital

...*working together* on PET studies

Positron emission tomography (PET) is a 3-D imaging technique that can be used to study the distribution, receptor occupancy and pharmacodynamic effects of a radiolabelled ligand (agonist or antagonist) in man. The main uses of PET for drug development are:

- selecting a lead candidate;
- predicting the dose and interval;
- proof-of-principle; and
- predicting disease.



PET uses radionuclides – such as ^{11}C and ^{18}F – that emit positrons and have very short half-lives. On emission, a positron collides with an electron in an atom in the surrounding tissues after travelling only a few tenths of a millimetre. The positron and electron destroy each other, giving off two photons at 180° to each other.

Invicro, on the Hammersmith Hospital site, uses a cyclotron to label the ligand, which is then given to a subject lying in a PET scanner. The photons escape from the body and are detected by the scanner, giving a dynamic, 3-D image that reflects quantitatively the distribution of the radionuclide in the body over time.

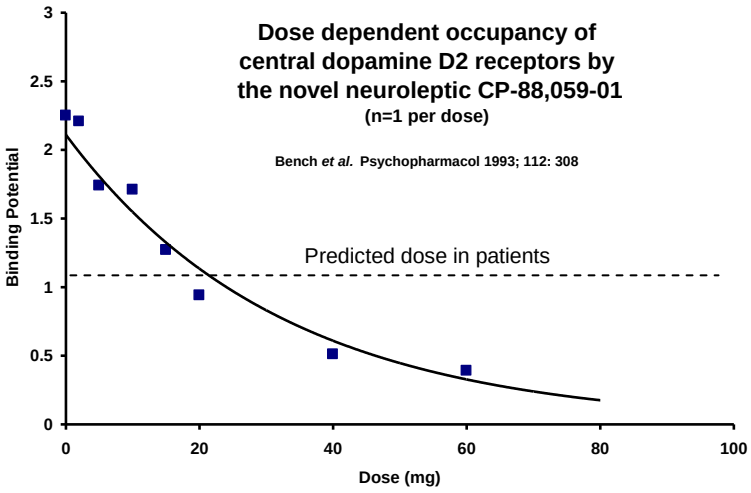
Because the radionuclides have such short half-lives, the cyclotron and PET scanner must be close to each other, and the subject must be given the radioligand soon after it has been made.

Only specialised centres have the resources to do PET studies. HMR has used the imaging facilities on the Hammersmith Hospital site since 1993 to provide a PET service to the pharmaceutical industry.

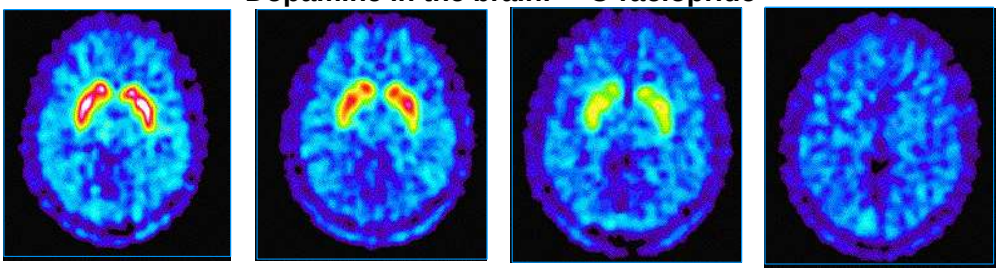
HMR recruits the subjects, does the clinical work and runs the study. Invicro prepares the radioligand, does the PET scans, and analyses and interprets the results. We have done almost 50 studies in healthy subjects or patients, to assess new drugs acting at targets such as dopamine D_2, adenosineA_{2A}, benzodiazepine, MAO, neurotropin, NK_1 and GABA receptors. We have studied medicines to treat conditions such as schizophrenia, Parkinson's, Alzheimer's and depression.

Case study

Using PET, and ^{11}C-raclopride as the ligand, HMR and the imaging centre at Hammersmith Hospital studied two groups of healthy subjects (only eight per group) to predict the dose[1] and dose-interval[2] of a new neuroleptic, CP-88,059-01 (ziprasidone), for trials in patients. Ziprasidone has since been marketed (Geodon®; Pfizer) at the doses (20–40 mg) and dose-interval (twice daily) that we predicted.



Dopamine in the brain: ^{11}C-raclopride



Baseline **increasing dose of ziprasidone**

Some of our references

1. Bench C, Lammertsma A, Dolan R, Grasby P, Warrington S, Gunn K, Cuddigan M, Turton D, Osman S, Frackowiak R. Dose-dependent occupancy of central dopamine D_2 receptors by the novel neuroleptic CP-88,059-01: study using PET and ^{11}C-raclopride. Psychopharmacology 1993; 112: 308–314.
2. Bench C, Lammertsma A, Grasby P, Dolan R, Warrington S, Boyce M, Gunn K, Brannick L, Frackowiak R. The time course of occupancy of striatal dopamine D_2 receptors by the neuroleptic ziprasidone (CP-88,059-01) determined by PET. Psychopharmacology 1996; 124: 141–147.
3. Brooks D *et al*. An open-label, positron emission tomography study to assess adenosine A_{2A} brain receptor occupancy of vipadenant (BIIB014) at steady-state levels in healthy male volunteers. Clinical Neuropharmacology 2010; 33: 55–60.

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