Institution: Imperial College London

Unit of Assessment: 04 Psychology, Psychiatry and Neuroscience

Title of case study: Improving Neuroscience Drug Discovery through the Application of Human Molecular Imaging

1. Summary of the impact (indicative maximum 100 words)

Scientists in the MRC Cyclotron Unit within Imperial College pioneered quantitative Molecular Imaging methods for neuroscience drug development that have since been expanded through collaboration between Imperial and GlaxoSmithKline (GSK) scientists. Human Molecular Imaging has had significant commercial impact with adoption by the major pharmaceutical companies to reduce the risks and costs associated with early drug development. This led directly to the selection of the Imperial Hammersmith Hospital site for the world's first clinical imaging centre embedded in a pharmaceutical company. New GSK investment created new and highly skilled UK employment opportunities first at this GSK Clinical Imaging Centre (CIC) and then Imanova, Ltd., a specialised imaging CRO that was "spun out" from the CIC. Outcomes from studies commissioned by GSK in the CIC and later in Imanova have directly influenced GSK clinical development planning, strategy and drug candidate progression. More recently, outcomes from Imanova are influencing clinical development decisions of other pharmaceutical organisations in similar ways.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Paul Matthews, Professor of Clinical Neuroscience (2006- present)
Professor David Brooks, Professor of Neurology (1993-present)
Professor Adriaan Lammertsma, Professor of Medical Physics (1993-1996)
Professor Vin Cunningham, Professor of Imaging (1993-2004)
Professor Terry Jones, Professor of Medical Physics (1993-2001)
Professor Roger Gunn, Professor of Molecular NeuroImaging (1996-present)
Professor Karl Friston, Professor of Neuroscience (1993-1994)

The Medical Research Council Cyclotron Unit (MRC CU, 1955-2011) situated at Hammersmith Hospital, London, enjoyed sustained MRC funding for its continued, pioneering contributions to positron emission tomography (PET) radiochemistry and methodology and became one of the largest and most comprehensive research PET centres in the world (1). It was one of the limited number of centres globally that developed a general [11C] labelling capacity for small molecules generated as part of medicinal chemistry efforts. With the use of appropriate analytical approaches, imaging of such [11C]-labelled molecules could be used to assess their blood brain barrier (BBB) penetration to test whether they can reach pharmacological targets in the brain. This information allows confident decision-making about a major risk to later failure in clinical development of drugs for central nervous system disease. These studies were further enhanced by the development at Imperial of specific radioligands which allowed for the assessment, not simply of BBB penetration, but also of level of drug-target engagement at differing doses and administration regimes through PET occupancy studies (2) (e.g. the first 5HT1A receptor imaging agent, which was later applied to evaluation of GSK163090.

Advances in quantitative image and tracer kinetic analyses by Professors Cunningham, Lammertsma and Gunn with reference tissue approaches enabled quantification of drug-target interactions in the brain without the need to arterial cannulate subjects. This contributes substantially to their feasibility of use in clinical applications. Tissue reference-based image quantitation (3) has become routinely applied in pharmacological studies since then. Professor Friston's pioneering development of Statistical Parametric Mapping techniques during his years at the Hammersmith (4) supports anatomically accurate regional assessment of radioligand signal in the brain, a critical step in accurate signal quantitation for any regionally variable target. These analytical advances have all been combined into a standard molecular imaging analysis workflow that is applied routinely for the analysis of drug development molecular imaging studies across

most centres conducting this work world-wide.

Professor Brooks and his colleagues have been international leaders for the validation of the use of dopaminergic and amyloid molecular imaging agents to support the diagnosis of Parkinson's Disease and Alzheimer's disease, molecular imaging supported tests of efficacy of putative neuroprotective agents in industry and international academic led clinical trials, and rational approaches to clinical management based on them (5, 6). This science has provided a foundation for commercialisation of DaTSCAN™, which is now licenced for differentiating benign tremor from Parkinson's Disease, and for Amyvid™ for detecting beta amyloid, a risk factor for Alzheimer's disease.

Professor Matthews jointly lead imaging investigative medicine research and training at Imperial while directly supporting GlaxoSmithKline's research as founding Head of their Clinical Imaging Centre (CIC). During the period that he led the CIC before its "spin out", Professor Matthews and Professor Gunn, with their teams involving both Imperial and GSK staff, validated several novel tracers (e.g. 5HT4, 5HT6, Histamine H3, GlyT1, PDE10) that were subsequently applied to therapeutics development decision-making in the neurosciences in GSK and, in some cases, in other contexts since.

3. References to the research (indicative maximum of six references)

(1) T Jones and E A Rabiner (2012) The development, past achievements and future directions of brain PET. A. *J Cereb Blood Flow and Metab* 32, 1426-1454. DOI (*Background review*)

(2) Rabiner, E.A., Beaver, J., Makwana, A., Searle, G., Long, C., Nathan, P.J., Newbould, R.D., Howard, J., Miller, S.R., Bush, M.A., Hill, S., Reiley, R., Passchier, J., Gunn, R.N., Matthews, P.M., Bullmore, E.T. (2011). Molecular and functional neuroimaging of human opioid receptor pharmacology. *Molecular Psychiatry*, 16, 785. DOI. Journal Impact Factor: 14.89

(3) Gunn, R.N., Lammertsma, A.A., Hume, S.P., Cunningham, V.J. (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage*, 6 (4), 279-287. DOI. Times cited: 492 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 6.25

(4) Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D., Frackowiak, R.S.J. (1994). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, 2 (4), 189-210. DOI. Times cited: 6929 (as at 7th November 2013). Journal Impact Factor: 6.87

(5) Rinne, J.O., Brooks, D.J., Rossor, M.N., Fox, N.C., Bullock, R., Klunk, W.E., Mathis, C.A., Blennow, K., Barakos, J., Okello, A.A., Rodriguez Martinez de Liano, S., Liu, E., Koller, M., Gregg, K.M., Schenk, D., Black, R., Grundman, M. (2010). 11C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study. *Lancet Neurol*, 9 (4), 363-372. DOI. Times cited: 199 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 23.91

(6) Piccini, P., Brooks, D.J., Björklund, A., Gunn, R.N., Grasby, P.M., Rimoldi, O., Brundin, P., Hagell, P., Rehncrona, S., Widner, H., Lindvall, O. (1999). Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient. *Nat Neurosci*, 2 (12),1137-1140. DOI. Times cited: 386 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 15.25

4. Details of the impact (indicative maximum 750 words)

Impacts include: commercial
Main beneficiaries include: industry

Research undertaken at Imperial's Hammersmith Hospital site in PET radiochemistry and imaging analysis that enabled radiolabelling, quantitative analysis and interpretation of the behaviour of

small molecules in man was a major contributor to making applications of PET imaging to drug development possible. Quantitative *in vivo* assessment in man of whether a putative central nervous system (CNS) drug penetrates the blood brain barrier and interacts with its intended target at the right concentration has been uniquely important for neuroscience drug development because it removes a major risk of failure for molecules progressed. Pharmaceutical companies have extended applications to preclinical studies for early candidate molecule selection, limiting the need to take molecules without likely efficacy into human experiments. The high impact of the approach arises because a single study can provide fundamental "Go/No Go" criteria for an entire development effort. For example, if CNS penetration is needed for target access and a PET study fails to demonstrate significant entry of the radiotagged drug candidate and/or significant engagement of the CNS target, development can be discontinued without further investment, saving costs and time from what would otherwise be a failure in Phase II and limiting exposure of subjects to a molecule that cannot be expected to have any of the desired pharmacological benefit [1]. If target engagement can be assessed, it enables rationale selection of potentially effective doses by defining its relationship to plasma concentration of the drug directly. This, in turn, reduces the range of doses that need to be explored in Phase II studies, limiting exposure of patients to doses without efficacy and trial costs and duration. For example, a single, small Phase I imaging study with the histamine H3 antagonist GSK239512 (using a novel H3 receptor tracer developed by GSK and Imperial scientists in the CIC) confirmed that the compound entered the brain and bound to its target histamine H3 receptor. Unexpectedly, it also demonstrated that the compound had *an order of magnitude* higher affinity (and therefore target occupancy) in man then predicted from preclinical data (ClinicalTrials.gov Identifier: NCT00474513), enabling lower dosing in subsequent Phase II trials that avoided adverse events while achieving the desired pharmacological effect (ClinicalTrials.gov Identifier:NCT01009255 & NCT01772199).

Over 14 CNS assets under commercial development were characterised in humans with biodistribution and target-occupancy studies during the period 2007-2013 at the GSK Clinical Imaging Centre/Imanova in conjunction with Imperial [2]. This work has influenced the global drug development of international pharmaceutical companies such as GSK [2]. The Senior Director and Head, Global Imaging Unit GSK, confirmed that "The quantitative molecular imaging data derived for these assets early in Phase I/II studies has had significant impact on identifying the right molecules and designing later phase studies at the right clinical doses with the inevitable reduction in development timelines and costs…only a few sites in the world have the capabilities to do these. The GSK Imaging Centre and now Imanova with the backup of key Imperial staff … provide a "partner of choice" for GSK…" [2].

Reach has extended beyond GSK and the Imperial site. Other major pharmaceutical companies in the UK and abroad have adopted the methodologies for "in house" or outsourced programmes. They also have been used for quantitative pharmacodynamics outcomes in several Phase II studies, e.g., for bapineuzimab (see reseach reference 5), a beta-amyloid sequestering antibody, and other Alzheimer's disease agents in early evaluation [3], as a pharmacological proof of principle test for a *mu* opioid antagonist in the treatment of addictive disorders (see research reference 2], in evaluation of a novel D3 antagonist and for other neuropsychiatric drug candidates [4].

Direct commercial impact and new job creation came first with a GSK-Imperial partnership to develop the £50M GSK Clinical Imaging Centre on the Hammersmith Hospital site. By 2011 this centre employed over 70 scientists and support staff in development work with Imperial College, leading to an annual direct GSK R&D spend of over £11M in the UK [5]. Work led by Professor Matthews from his joint appointment between Imperial and GSK led the GSK Clinical Imaging Centre in decision-making studies (as noted above, for over 14 molecules in early development) [2]. Additional experimental medicine studies (e.g., pharmacokinetic characterisation of a novel GSK SIRT1 activator [6]) were additionally underpinned by the clinical pharmacology expertise, broader imaging capabilities of the CIC and resources of the Sir John McMichael Centre, which has been supported recently by a £73 million investment from the College, NIHR and the Wellcome Trust. The GSK Clinical Imaging Centre was "spun out" as Imanova in 2011. Imanova continues to employ 70 scientists and staff working on Molecular Imaging studies not just for GSK,

but an even broader range of international Pharma companies involved in CNS drug development. Since its formation, it has secured over £1.5M in commercial revenue from other companies in addition to GSK's continued investments [7]. Imanova Ltd has been identified by the new National Institute for Health Research Dementia Translational Research Collaboration as a UK centre of excellence [8].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Drug Development for CNS disorders:
D. D. Schoepp (2011) Where will new neuroscience therapies come from? N*ature Reviews Drug Discovery*, 10, 715-716. DOI.

[2] Letter from the Head of Global Imaging Unit GlaxoSmithKline detailing impact on drug discovery (available upon request).

[3] Evaluation of a novel Alzheimer's disease agent:
Tzimopoulou, S., Cunningham, V.J., Nichols, T.E., Searle, G., Bird, N.P., Mistry, P., Dixon, I.J., Hallett, W.A., Whitcher, B., Brown, A.P., Zvartau-Hind, M., Lotay, N., Lai, R.Y., Castiglia, M., Jeter, B., Matthews, J.C., Chen, K., Bandy, D., Reiman, E.M., Gold, M., Rabiner, E.A., Matthews, P.M. (2010). A multi-center randomized proof-of-concept clinical trial applying [^{18}F]FDG-PET for evaluation of metabolic therapy with rosiglitazone XR in mild to moderate Alzheimer's disease. *J Alzheimers Dis*, 22 (4), 1241-1256. DOI.

[4] Evaluation of a novel D3 antagonist and other neuropsychiatric drug candidates:
Searle, G., Beaver, J.D., Comley, R.A., Bani, M., Tziortzi, A., Slifstein, M., Mugnaini, M., Griffante, C., Wilson, A.A., Merlo-Pich, E., Houle, S., Gunn, R., Rabiner, E.A., Laruelle, M. (2010). Imaging dopamine D3 receptors in the human brain with positron emission tomography, [11C]PHNO, and a selective D3 receptor antagonist. *Biol Psychiatry*, 68(4):392-399. DOI.

[5] http://cic.gsk.com/downloads/CIC_Information.pdf (archived on 8th November 2013)

[6] Example of pharmacokinetic characterisation:
Libri, V., Brown, A.P., Gambarota, G., Haddad, J., Shields, G.S., Dawes, H., Pinato, D.J., Hoffman, E., Elliot, P.J., Vlasuk, G.P., Jacobson, E., Wilkins, M.R., Matthews, P.M. (2012) A pilot randomized, placebo controlled, double blind phase I trial of the novel SIRT1 activator SRT2104 in elderly volunteers. *PLoS One*, 7 (12): e51395. DOI

[7] Expansion of collaborative base of the Clinical Sciences Centre & Creation and spin out of Imanova Ltd:

- http://www.zenopa.com/news/800497778/GlaxoSmithKline_agrees_new_UK_clinical_imaging_collaboration (archived on 8th November 2013)
- http://www.pmlive.com/pharma_news/mrc_partners_with_academia_to_launch_imaging_research_centre_403411 (archived on 8th November 2013)
- http://www.imanova.co.uk/ (archived on 8th November 2013)
- Letter from Imanova CEO detailing impact on international Pharma companies

[8] The UK government has established the new National Institute for Health Research Dementia Translational Research Collaboration:
http://www.nocri.nihr.ac.uk/research-expertise/dementia-translational-research-collaboration/
Archived on 8th November 2013