Institution: University of Nottingham

Unit of Assessment: 5 - School of Life Sciences

Title of case study:

Validating serotonin receptor targets for pharmaceutical drug discovery

1. Summary of the impact

Research by Professor Kevin Fone in the Neuroscience group has established and characterised rodent models of CNS disorders that have been instrumental in validating several 5-hydroxytryptamine (5-HT) receptors as therapeutic drug targets to treat learning and memory dysfunction in humans. Specifically, animal studies to validate the 5-HT_6 receptor for cognitive impairment in Alzheimer's disease (AD), depression and schizophrenia have resulted in R&D investment in drug discovery programmes by several global pharmaceutical companies. Consequent advances in healthcare benefits (current and potential) are also summarised.

2. Underpinning research

Adoption of a novel target for drug discovery by the pharmaceutical industry requires validation of the target's functional role in a particular disorder, tested in a well characterised animal model by using selective compounds or antibodies to block the function of the target protein, or genetic knock-out or knock-down techniques to remove or reduce expression of the protein. Definitive establishment of the role of the target in the disease thus underpins significant pharmaceutical investment to develop new drugs for that disorder.

Members of the Neuroscience research group, led by Professor Kevin Fone and supported by over £2 million of grant[7-9] and industrial funding[10-15] over the past 8 years, have developed an integrated whole animal behavioural, imaging and neurochemical analysis approach to investigate the neurobiological basis of common CNS disorders including: cognitive dysfunction (e.g. in dementia, depression, and schizophrenia), Attention Deficit Hyperactivity Disorder (ADHD) and anxiety.

This combined approach has demonstrated receptor localisation (by producing highly selective antibodies for immunohistochemistry) and functions (using selective ligands through pharmaceutical collaborations) of several 5-HT receptors (e.g. 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, 5-HT_7) in these disorders, validating them as potential targets for drug discovery.

5-HT_6 receptor validation:

Studies by Fone and colleagues in 1999 and 2001, in collaboration with F. Hoffman-La Roche, Switzerland, pioneered the use of antisense oligonucleotides to reduce the expression of the 5-HT_6 receptor, and selective 5-HT_6 antagonists to block its function, which enhanced cholinergic activity and improved learning and memory in the rat Morris water maze[1,2]. Although the rat and human 5-HT_6 receptors had been cloned and sequenced previously in 1993 and 1996 respectively, research by the Fone group demonstrated for the first time that reduced 5-HT_6 expression enhanced memory retention[2], linking receptor function to cognition. This observation provided the key validation in an animal model that the 5-HT_6 receptor was a therapeutic target for drug development to enhance memory. A subsequent study in 2004, using a novel object discrimination task, showed that 5-HT_6 antagonists prevented time-dependent natural memory loss[3], and enhanced the process of consolidation through modification of glutamate function, confirming the receptor as a therapeutic target to aid learning and memory retention in dementia. Further studies by Fone and others from 2007-2008 on perturbations of serotonergic neurotransmission and their effects on social recognition memory in isolation reared rats[4], established a potential role for 5-HT_6 antagonists to treat cognitive deficits associated with schizophrenia. Following industrial development of selective high affinity 5-HT_6 receptor agonists, in 2011 the Fone group demonstrated, in collaboration with Laboratorios Dr Esteve, that these compounds also paradoxically enhance learning and memory by alteration of cholinergic and glutamatergic function, offering further novel therapeutic strategies[5]. Most recently in 2012, in collaboration with Servier, the group identified that the 5-HT_6 receptor couples with a novel, non-G-protein mediated signalling pathway (mTOR), which is overactive in rodent models of schizophrenia, and reduced by 5-HT_6

antagonists, resulting in reversal of learning and memory deficits[6] – thus providing evidence for the potential cognitive therapeutic mechanism for the 5-HT_6 receptor antagonist drug class.

3. References to the research

Publications (University of Nottingham authors in bold, key author underlined)

1. **Bentley JC**, Bourson A, Boess FG, **Fone KC**, **Marsden CA**, Petit N, Sleight AJ (1999) Investigation of stretching behaviour induced by the selective 5-HT_6 receptor antagonist, Ro 04-6790, in rats. British Journal of Pharmacology 126:1537-1542. doi: 10.1038/sj.bjp.0702445
2. **Woolley ML**; **Bentley JC**; Sleight AJ; **Marsden CA**; **Fone, KC** (2001). A role for 5-HT_6 receptors in retention of spatial learning in the Morris water maze. Neuropharmacology 41: 210-219. doi: 10.1016/S0028-3908(01)00056-9
3. **King MV**, Sleight AJ, **Woolley ML, Topham IA**, **Marsden CA**, **Fone KCF** (2004) 5-HT_6 receptor antagonists reverse delay-dependent deficits in novel object discrimination by enhancing consolidation—an effect sensitive to NMDA receptor antagonism. Neuropharmacology 47: 195–204. doi: 10.1016/j.neuropharm.2004.03.012
4. **King MV, Marsden CA, Fone KCF** (2008) A role for the 5-HT_{1A}, 5-HT_4 and 5-HT_6 receptors in learning and memory. Trends in Pharmacological Sciences 29: 482-492. doi: 10.1016/j.tips.2008.07.001
5. **Kendall I, Slotten HA,** Codony X, Burguerio PJ, Pauwels PJ, Vela JM, **Fone KC** (2011) E-6801, a 5-HT_6 receptor agonist, improves recognition memory by combined modulation of cholinergic and glutamatergic neurotransmission in the rat. Psychopharmacology 213: 413-420. doi: 10.1007/s00213-010-1854-3
6. Meffre J, Chaumont-Dubel S, Mannoury la Cour C, Loiseau F, **Watson D**, Dekeyene A, Seveno M, Rivet J-M, Gaven F, Herve D, **Fone KCF**, Bockaert J, Millan MJ, Marin P (2012) mTOR recruitment by 5-HT_6 receptors as a potential mechanism for cognitive deficits of schizophrenia. EMBO Molecular Medicine 4, 1043-1056. doi: 10.1002/emmm.201201410

Funding and Collaborations

7. BBSRC: **CM Bradshaw**, **E Szabadi**, (UoN Medical School) and **KCF Fone**; 2006-2009: £433,346.
8. EU Commission: **CA Marsden**, **DA Kendall**, **KCF Fone** and **T Sharp**; 6th Framework Program; 2007-2010; £316,286.
9. Wellcome Trust: **PM Moran** (Psychology), **KCF Fone**, **HJ Cassaday** (Psychology), JL Waddington (Royal College of Surgeons, Ireland); 2008-2011; £219,547.
10. Predix Pharmaceuticals/Epix Pharmaceuticals: **KCF Fone**; 2005-2007; £148K.
11. Institute Recherches Internationales Servier: **CA Marsden** and **KCF Fone**; 2007-2009; £290,458; **KCF Fone** and **CA Marsden**; 2009-2011; £333,255.
12. Laboratorios Dr Esteve: **KCF Fone**; 2008-2009; £126,618.
13. Proximagen Ltd: **KCF Fone** and **MV King**; 2010-2011: £25,780.
14. Shire Pharmaceuticals Development Ltd: **KCF Fone**; 2012; £30,195. **KCF Fone** and **MV King**; 2012; £75,334.
15. F.Hoffmann-La Roche Ltd: **KCF Fone**; 2009-2012; £74,580.

4. Details of the impact

Impact 1: Pharmaceutical Industry Drug Development

A good indicator of the importance of a particular validated receptor target to the pharmaceutical industry is the number of patents filed to protect compounds in development. To date, in excess of 800 Patent Co-operation Treaty (PCT) patents surrounding the use of 5-HT_6 receptor ligands to treat cognitive impairments (e.g. in dementia and schizophrenia) have been published worldwide from 2002 onwards[A] (subsequent to the underpinning research). Searching within these patents,

99 (12%) include direct citations to research by the Fone group that validated the 5-HT_6 receptor as a drug target[1,2,3,A]. A number of pharmaceutical companies contributed these filings, most notably F.Hoffmann-La Roche, Glaxo-SmithKline, Esteve, Servier and Epix Pharmaceuticals, all of whom the Fone group collaborated with. It has been confirmed by three of these companies that their confidence in the 5-HT_6 receptor as a valid drug discovery target, leading to patent filings and subsequent R&D investment, are dependent (at least in part) upon the underpinning research by the Fone group[B,C,D]. Specifically, Esteve stated that "*the research of the Nottingham group and [Fone's] contribution were critical to the success of the project*"[B], and for Servier "*proved crucial in internal deliberations to establish and pursue a broad based R&D programme*"[C]. GSK conclusively stated: "*a significant in-house research programme, representing several millions of pounds investment, continued for approximately a decade, culminating in the identification and progression of SB-742457 into Phase II clinical studies in Alzheimer's disease*"[D]. Several other pharmaceutical companies also progressed 5-HT_6 antagonists into clinical development on the groundswell of confidence in this target to address cognitive deficits associated with AD and dementia[E], (e.g. Phase I: Proximagen [BVT.74316], Roche/Biotie Therapies [SYN-120], Abbott [ABT-354], AviNeuro [AVN-322]; Phase II: Pfizer [PF-5212377], Lundbeck [Lu AE58054]).

The extended 10 year+ timeframe of drug development makes it difficult to assess impact on the pharmaceutical industry within the 5-6 year window since the beginning of 2008. However, it is possible to estimate the investment by pharma companies in a specific drug development target from the industry-recognised costs and timeframes of the different phases of drug development (e.g. Morgan S et al. 2011. Health Policy 100: 4-17). Thus, for Proximagen alone, completing preclinical development and Phase I for their 5-HT_6 antagonist indicates an R&D investment of around £50 million, which is reflected in the sale of the business to Upsher-Smith for £357 million in 2012[E].

Impact 2: Healthcare Costs and Benefits

Although compounds acting at the 5-HT_6 receptor have progressed into Phase II clinical trials, and therefore are likely to have already brought drug benefit to restricted numbers of patients, none has yet received Regulatory approval for human therapy, so the full global healthcare and societal benefits are yet to be fully realised. However, to indicate the potential return on pharma R&D investment in the context of heath care costs and benefits: it was estimated in 2010 that there were 35.6 million people worldwide affected by dementia (including AD), with this figure set to rise to 65 million by 2030[F]. The global market for AD treatments was $4.1billion in 2008, with the expectation that this would rise to $10.4 billion in 2018 as the population ages[F]. If the formal and informal costs of patient care are added to the therapeutic costs, the global economic impact of dementia was estimated to be a staggering $604 billion in 2010[F]. Although drugs targeting 5-HT_6 receptors will only comprise part of the dementia/AD therapeutic arsenal (currently there are around 70 dementia/AD drugs in development[B], of which drugs targeting 5-HT_6 constitute about 10%), and will therefore only address part of this global therapeutic and health care cost, nevertheless the benefits they will bring to patients and their carers is enormous.

Impact 3: Advisory Expertise provided to the Pharma Industry

Professor Fone has also had a direct impact on Pharmaceutical R&D strategy by serving as an industrial consultant (e.g. Consultant adviser for 5-HT_6 cognitive research programmes around E-6801 for Laboratorios Dr Esteve S.A.; around Ro 04-6790 for F. Hoffman-La Roche; and around SB-271,046 for GSK).

5. Sources to corroborate the impact

A. Patent search performed on 16th October 2012 at http://patentscope.wipo.int using terms:
EN_ALLTXT:((5HT6 or "5-HT6") and (cognit* or dementia))
EN_ALLTXT:((5HT6 or "5-HT6") and (cognit* or dementia) and (Woolley or Bentley or Fone or "Neuropharmacology 41"))

B. Corroborative statement from former 5-HT_6 Project Leader, Laboratorios Dr Esteve

C. Corroborative statement from Director of Experimental Sciences, CNS, Servier

D. Corroborative statement from former VP Biology, Psychiatry Centre of Excellence, GSK; http://www.gsk.com/content/dam/gsk/globals/documents/pdf/GSK%202013%20Pipeline.pdf

E. Other companies developing 5-HT6 antagonists:
http://www.alzforum.org/new/detail.asp?id=3169
Proximagen: http://www.proximagen.com/docs/ProximagenUpdate%20-%20Edison.pdf
Abbott: http://clinicaltrials.gov/ct2/show/NCT01908010
Lundbeck: http://clinicaltrials.gov/ct2/show/NCT01019421
BioTie: http://www.biotie.com/en/product_and_development/development_pipeline/syn120
Pfizer: http://clinicaltrials.gov/ct2/show/NCT01712074
AviNeuro: http://www.avineuro.com/pipeline/

F. http://www.alz.co.uk/research/files/WorldAlzheimerReport2010ExecutiveSummary.pdf

Corroborative documents and copies of webpages are held on file and are available on request.