Institution: UCL

Unit of Assessment: 05

Title of case study: A new pharmacological approach for treating ADHD

1. Summary of the impact

Clare Stanford's group has opened up a new line of research for drug treatment of Attention Deficit Hyperactivity Disorder. Based on this work, UCL Business has been awarded an EU patent for the NK1R 'knockout' mouse as an investigative tool and pharmaceutical screen. Cerebricon, a subsidiary of Charles River, has taken an exclusive licence to market this mouse and advertise it on their website. Our studies have also enabled us to identify a new genetic locus in which abnormalities are linked to ADHD in humans, and to identify a new drug candidate for treating ADHD.

2. Underpinning research

The core diagnostic features of Attention Deficit Hyperactivity Disorder (ADHD) are *hyperactivity*, *inattentiveness* and *impulsivity*. All current drug treatments for ADHD augment monoamine transmission in the brain. First-choice treatments are the psychostimulants d-amphetamine and methylphenidate, despite being ineffective in nearly 30% of patients.

Several rat and mouse inbred strains have been used in preclinical studies of ADHD. All express one or more of the abnormalities seen in ADHD, which are relieved by psychostimulants to some extent. However, none matches all key characteristics of ADHD and its treatment.

Our experiments with the substance P-preferring (NK1) receptor knockout (NK1R-/-) mouse, in collaboration with Professor Stephen Hunt (UCL), started in 2004. We aimed to explain why blocking the activation of NK1R has antidepressant effects in humans, as was thought to be the case at the time. In the course of this work, we discovered that NK1R-/- mice have profound abnormalities in monoamine transmission in the brain. As well as an increase in serotonin release, which had been reported already, we found increased noradrenaline release and a striking deficit in dopamine release in the prefrontal cortex. The latter change is inconsistent with an antidepressant profile. We also noted that NK1R-/- mice are *hyperactive* compared with wildtypes **[1]**. This hyperactivity is induced by either genetic mutation (NK1R-/-) or pharmacological antagonism of NK1R and so is a direct consequence of a lack of functional NK1R. Moreover, it was prevented by treatment with d-amphetamine or methylphenidate, as in ADHD **[3]**.

These findings led us to propose that neurochemical and behavioural abnormalities, arising from a lack of functional NK1R, could underlie abnormalities seen in ADHD. This prompted a human genetic study, in collaboration with Professor Hugh Gurling (UCL), which found a strong association between four genetic markers in the *tacr1* gene (the human equivalent of the NK1R gene) and ADHD in a large population sample **[4]**. Since then, polymorphism(s) of the *tacr1* gene have also been found to be associated with bipolar affective disorder, suicidal behaviour and alcoholism, all of which show a high incidence of co-morbidity with ADHD.

In an MRC-funded project (2008-11), we showed that NK1R-/- mice display a higher behavioural *inattentiveness*, *impulsivity*, and *perseveration* (which has been reported in ADHD patients) and that d-amphetamine relieved *perseveration* but not *inattentiveness* or *impulsivity* **[5]**. This pattern of deficits in cognitive performance and their response to amphetamine is consistent with the abnormalities in monoamine transmission in the NK1R-/- mouse, and could explain why some ADHD patients do not respond to psychostimulants.

All these findings strengthen the validity of using NK1R-/- mice to study underlying causes of, and treatments for, ADHD. They also underpin our prediction that drugs that augment activation of NK1R, or its downstream targets, would have beneficial effects in ADHD, particularly in patients

with polymorphism(s) of the *tacr1* gene.

Finally, we have recently uncovered a potential role for nifedipine, a drug already in use as an antianginal and antihypertensive, in the treatment of ADHD, through its effect on L-type calcium channels **[6]**.

3. References to the research

[1] Herpfer I, Hunt SP, Stanford SC. A comparison of neurokinin 1 receptor knock-out (NK1-/-) and wildtype mice: exploratory behaviour and extracellular noradrenaline concentration in the cerebral cortex of anaesthetised subjects. Neuropharmacology. 2005 Apr;48(5):706-19. http://dx.doi.org/10.1016/j.neuropharm.2004.12.016

[2] Fisher AS, Stewart RJ, Yan T, Hunt SP, Stanford SC. Disruption of noradrenergic transmission and the behavioural response to a novel environment in NK1R-/- mice. Eur J Neurosci. 2007 Feb;25(4):1195-204. http://dx.doi.org/10.1111/j.1460-9568.2007.05369.x

[3] Yan TC, Hunt SP, Stanford SC. Behavioural and neurochemical abnormalities in mice lacking functional tachykinin-1 (NK1) receptors: a model of attention deficit hyperactivity disorder. Neuropharmacology. 2009 Dec;57(7-8):627-35. http://dx.doi.org/10.1016/j.neuropharm.2009.08.021

[4] Yan TC, McQuillin A, Thapar A, Asherson P, Hunt SP, Stanford SC, Gurling H. NK1 (TACR1) receptor gene 'knockout' mouse phenotype predicts genetic association with ADHD. J Psychopharmacol. 2010 Jan;24(1):27-38. http://dx.doi.org/10.1177/0269881108100255

[5] Yan TC, Dudley JA, Weir RK, Grabowska EM, Peña-Oliver Y, Ripley TL, Hunt SP, Stephens DN, Stanford SC. Performance deficits of NK1 receptor knockout mice in the 5-choice serial reaction-time task: effects of d-amphetamine, stress and time of day. PLoS One. 2011 Mar 7;6(3):e17586. http://dx.doi.org/10.1371/journal.pone.0017586

[6] Dudley JA, Weir RK, Yan TC, Grabowska EM, Grimmé AJ, Amini S, Stephens DN, Hunt SP, Stanford SC. Antagonism of L-type Ca(v) channels with nifedipine differentially affects performance of wildtype and NK1R-/- mice in the 5-Choice Serial Reaction-Time Task. Neuropharmacology. 2013 Jan;64:329-36. http://dx.doi.org/10.1016/j.neuropharm.2012.06.056

4. Details of the impact

Attention Deficit Hyperactivity Disorder has a worldwide prevalence in children of about 5% and persists in adulthood in 50-60% of cases. ADHD is not a primary learning disorder but its core diagnostic features are deficits in cognitive performance and response control [*'hyperactivity',* '*inattentiveness*' and '*impulsivity*']. These impairments disrupt academic development and can lead to complex social problems in adulthood. The majority of adult patients further experience serious co-morbidity including: perseveration, substance misuse, emotional lability, bipolar disorder, criminality and suicidality, all of which impair the quality of life of the patient and their family and can reduce life-expectancy. An unexplained increased risk of other medical conditions (e.g. obesity, asthma) as well as accidents and social problems leads to ADHD patients costing 2-fold more than the average patient (NICE, 2009). It was predicted that about £78 million would be spent on pharmacotherapy alone for ADHD patients in the UK in 2012 (NICE, 2009). This figure did not take into account the broader economic costs of this illness.

Only three drugs are licensed to treat ADHD in the UK: the psychostimulants *d*-amphetamine & methylphenidate, and the noradrenaline uptake inhibitor atomoxetine. There is widespread unease about long-term use of psychostimulants, and all these treatments can have harmful cardiovascular side-effects and carry a risk of misuse. Furthermore, more than 25% of patients do not respond to any of these treatments. Thus, there is a pressing need for a new approach to pharmacotherapy of ADHD, based on a strong scientific rationale.

New ADHD Animal Model: Commercial Impact

Our research has led to the discovery that disruption of NK1 receptor function causes deficits in cognitive performance and response control similar to those seen in ADHD patients. This research has opened up new directions for investigation of the underlying causes of ADHD as well as the discovery and development of new drug targets. A paper describing some of our recent findings has received more than 2,700 hits since it was published in May 2011. This research has already received MRC funding of more than £600,000 **[a]**.

We were awarded an EU patent in 2010 relating to the use of the NK1R-/- mouse to investigate the underlying neurochemical abnormalities in ADHD and as a screen for putative drug treatments for ADHD **[b]**. We have a US patent application pending **[c]**. A subsidiary of Charles River, Cerebricon (based in Finland), which specializes in validation and marketing of rodent behavioural models, has negotiated an exclusive licence with UCL Business **[d]**. This enables them to market the NK1R-/- for use in research related to the causes and treatment of ADHD and now advertise this on their website. This venture is expected to be highly successful: "*In conjunction with Cerebricon's strategy of increasing our portfolio of pre-clinical models by extending from neurology to psychiatry we are very pleased to have the opportunity to in- license what we believe will prove to be the best and most fully validated mouse model of ADHD for our drug development clientele"* – Dr Yrjanheikki, CEO of Cerebricon **[e]**.

New Genetic Locus for ADHD in Humans: Health Impact

Our research using the NK1R KO mice led us to discover a link between the mutations in the human homologue of the gene, *tacr1*, and ADHD. This discovery is significant to clinical psychiatry at two levels. One is that new treatments targeted at specific individuals, according to the genetic subtype of the disorder that they have inherited, can now be attempted. Secondly, the findings identify a molecular pathophysiology which cuts across traditional diagnostic boundaries and indicates that the use of biomarkers which identify genetic effects acting in sub categories of mental illness will be more powerful and useful than traditional clinical diagnostic categories **[f]**.

Public Engagement

Because of ADHD's often disruptive nature, sufferers can face difficulty in public situations. Increasing public understanding of the disorder is therefore extremely important. Clare Stanford makes regular media appearances to discuss psychopharmacology in general **[g]**, and has written an article on ADHD, which is aimed at the general public and posted on the website (Information for the Public) hosted by the British Association for Psychopharmacology **[h]**.

The development of new treatments for almost all human diseases and disorders requires animal research. However, this can be a contentious issue. Clare Stanford is President of the Laboratory Animal Science Association and has contributed to meetings that aim to increase public understanding of animal research (e.g. meetings for the RSPCA) **[i]**.

5. Sources to corroborate the impact

[a] MRC funding: http://gtr.rcuk.ac.uk/project/2A00138D-E6C5-47B8-8555-C34313F08227

[b] WO2008087419A3 Stanford SC, Gurling HM, Hunt SP: UCL BUSINESS PLC; STANFORD, SUSAN CLARE; GURLING, HUGH; HUNT, STEVEN Patent awarded relating to the use of NK1R-/- mice to screen potential therapeutic treatments for ADHD. http://www.google.com/patents/EP2114130B1

[c] Stanford SC et al. Patent Number 20100169994 [USA] PCT NO: PCT/GB08/00160371 Date: February 15, 2010 The invention relates to the use of a NK1-/- animal as a model for attention deficit hyperactivity disorder and related conditions, to markers for those conditions and to methods of treating such conditions. http://www.google.com/patents/US20100169994

[d] Details can be verified by Business Manager, UCLB. Contact details provided.

[e] Announcement that Cerebricon (a subsidiary of Charles River) has acquired an exclusive licence from UCL Business, which enables them to market the NK1-/- mouse for research of ADHD and its treatment: http://www.uclb.com/news-and-events/news-post/ucl-business-concludes-exclusive-licence-deal-with-cerebricon

[f] Supporting statement from Professor of Molecular Psychiatry, UCL. Available on request.

[g] Stanford has made many media appearances including ITV, Channel 4, Sky TV, Radio 4 and the World Service.

[h] Article on ADHD for the public, written by Stanford for the British Association of Psychopharmacology: http://www.bap.org.uk/publicinformationitem.php?publicinfoID=9.

[i] Stanford talk at RSPCA Lay Members' Forum: http://www.rspca.org.uk/ImageLocator/LocateAsset?asset=document&assetId=1232727973390&mode=prd