Institution: King's College London

Unit of Assessment: UoA5

Title of case study: Establishment of CoCo Therapeutics to take forward new drugs for Alzheimer's disease

1. Summary of the impact

Alzheimer's disease (AD) presents society with one of its biggest challenges, yet despite the investment of billions of dollars there are only two classes of drug approved that have minimal benefit in patients. Scientists at King's College London have implicated dysregulation of retinoid signalling as an early feature of the disease and identified the retinoic acid receptor (RAR) family as an attractive drug target. They have gone on to design and patent protect novel orally available RARα selective agonists and demonstrated that they have the potential to restore many of the deficits reported in AD patients. Advent Venture Partners has provided funds to establish a new UK biotechnology company, CoCo Therapeutics Ltd, in partnership with the Wellcome Trust and KCL, to progress this KCL research into the development of a new treatment for AD.

2. Underpinning research (indicative maximum 500 words)

Alzheimer's disease (AD) affects around 5.3 million people in the US and 420,000 people in the UK, with these numbers predicted to double by 2050. Approved drugs are limited to acetyl-cholinesterase inhibitors and an NMDA antagonist. These provide modest symptomatic benefits for relatively short periods of time. The most recent treatments for AD based on the amyloid cascade hypothesis have failed in the clinic, highlighting the need for new approaches.

Retinoic acid (RA) signalling has a role in the maintenance and regeneration of the adult central nervous system (CNS). It is mediated by retinoid acid receptors (RARs) and retinoid X receptors (RXRs), both of which have three subtypes (α, β and γ) and various isoforms. These receptors are activated by retinoids and control multiple signalling and effector pathways in neurons. Research at King's College London (KCL), led by Prof Jonathan Corcoran (1995-present, Director of the Neuroscience Drug Discovery unit at the Wolfson CARD) has shown that in the adult CNS RARα, as opposed to other RARs, is required for the survival of neurons. This research highlighted how there is a loss of cholinergic activity in cerebral cortex neurons of adult retinoid-deficient rats and that this leads to the deposition of amyloid-β in their brains, as occurs in AD. KCL research has shown the same receptor deficit in human pathology samples of spontaneous cases of AD and that a retinoid signalling defect may be a cause, rather than a consequence, of neurodegeneration (Corcoran J, et al. Eur J Neurosci, 2004). KCL researchers went on to show that RARα signalling has multiple effects on genes known to be involved in AD. For example the pathway up regulates the α-secretase ADAM10, an enzyme involved in processing amyloid precursor protein (APP) into the non amyloidic pathway (Jarvis CI, et al. Eur J Neurosci, 2010). KCL scientists have also shown that the RARα pathway can influence progenitor cell function in the adult brain (Goncalves MB, et al., Dev Biol, 2009) demonstrating a "restorative" function of this pathway.

The RARα signalling pathway also stimulates a neuroprotective pathway in neurons cultured in the presence of the toxic amyloid-β (Aβ) peptides that are found in the brains of AD patients. By feeding Tg2576 mice (which over express a mutated form of human APP leading to human Aβ deposits in their brains) with an RARα agonist, there is a dramatic down regulation of human Aβ and a significant improvement in cognition (Goncalves MB, et al. Eur J Neurosci, 2013). No other target has yet been identified that can carry out these multiple roles in AD and as such there is great therapeutic potential in the use of these orally available agonists for the treatment of AD. With the support of a two independent seeding drug discovery initiative (SDDI) grants from the Wellcome Trust, the KCL team have now developed and patented novel RARα and RARβ selective agonists. The RARα agonists are being further developed by CoCo Therapeutics with the ultimate aim of demonstrating the therapeutic potential of this approach in AD patients.

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

Corcoran J, So P-Lm, Maden M. Disruption of the retinoid signalling pathway causes a deposition of amyloid β in the adult rat brain. Eur J Neurosci 2004;20(4):896-902. Doi: 10.1111/j.1460-

9568.2004.03563.x (76 Scopus citations).

Jarvis CI, Goncalves MB, Clarke E, Dogruel M, Kalindjian SB, Thomas SA, Maden M, Corcoran JPT. Retinoic acid receptor alpha signalling antagonizes both intracellular and extracellular amyloid-β production and prevents neuronal cell death by amyloid-β. Eur J Neurosci 2010;32(8):1246-55. doi: 10.1111/j.1460-9568.2010.07426.x (16 Scopus citations)

Goncalves MB, Clarke E, Hobbs C, Malmqvist T, Deacon R, Jack J, Corcoran JP. Amyloid β inhibits retinoic acid synthesis exacerbating Alzheimer disease pathology which can be attenuated by an retinoic acid receptor α agonist. Eur J Neurosci 2013;37(7):1182-92. Doi: 10.1111/ejn.12142. (1 Scopus citations)

Goncalves MB, Agudo M, Connor S, McMahon S, Minger SL, Maden M, Corcoran JP. Sequential RARbeta and alpha signalling in vivo can induce adult forebrain neural progenitor cells to differentiate into neurons through Shh and FGF signalling pathways. Dev Biol 2009;326(2):305-13. Doi: 10.1016/j.ydbio.2008.11.018 (19 Scopus citations)

Patents

Corcoran J, Maden M. Patent**.** Use of RARα agonists and gene therapy with RALDH-2 to treat neurodegenerative diseases (filed Feb 2001**)** Patent application no: PCT/GB02/0063. Protected with funds from IP2IPO and research support from the Heptagon Seed fund. (Copy available on request)

Grants (drug discovery awards)

Principal applicant Corcoran. Use of RARα agonists for treatment of Alzheimer's disease. Funded by Heptagon Seed funds, **value £92K**. Jan 2006-Dec 2006.

Principal applicant Corcoran Small molecule grant, to delineate structures of retinoids and their utility in Alzheimer's disease models, **Wellcome Trust value £3.1 million over 3 years**. May 2008-June 2012.

Principal applicant Corcoran Identification of retinoic acid receptor β agonists for the treatment of spinal cord injury. **Wellcome Trust** value £3.6 million over 42 months. Jan 2011-July 2014

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

The only licensed drugs for Alzheimer's disease (AD) are acetylcholinesterase inhibitors that enhance central cholinergic neurotransmission by inhibiting the degradation of acetylcholine, or treatment with an NMDA antagonist. Both provide modest symptomatic relief for relatively short periods of time. King's College London (KCL) scientists have developed selective retinoid acid receptorsα (RARα) agonists as a highly innovative new treatment for AD and validated the target using a range of culture and transgenic animal models. Importantly, the RARα agonists have been shown to stimulate numerous beneficial pathways in the diseased brain and as such have the potential to restore function as opposed to simply providing symptomatic relief.

Wellcome Trust and Industry investment in the program

KCL scientist's academic work in the late 1990's led to the hypothesis that RAR signalling would have therapeutic potential in AD and other conditions with patent protection first sought in 2001. In 2008 KCL set up the Drug Discovery Unit based in the Wolfson CARD under the direction of Prof Jonathan Corcoran to bring industry-ethos into an academic environment to translate these academic findings into new treatments for neurodegenerative diseases. Prof Corcoran secured a highly competitive Wellcome Trust Seeding Drug Discovery award to develop orally available brain penetrant selective RARα agonists for AD. The success of this program underpinned a second ongoing Seeding Drug Discovery award to develop selective RARβ agonists.

As part of the RARα program, Prof Corcoran's team created two lead series, a clinical candidate and a number of potential backup compounds (1, 2). This portfolio provided the basis for the Wellcome Trust to seek a commercial partner to take the work forward. Despite a difficult economic climate Advent Venture Partners, one of Europe's most successful venture capital investors in life sciences, provided funding in March 2013 to form a new UK biotechnology company, CoCo Therapeutics Ltd to progress Prof Corcoran's work into Phase IIA clinical trials in man (3-5). To this end, CoCo Therapeutics has recruited highly skilled people such as Project Managers, Medicinal Chemists and Clinicians to develop and commercialise the research generated in the KCL labs.

The underpinning research has several far reaching interrelated impacts. Firstly, a highly innovative new target for AD based on a restorative therapy has been validated in tissue culture and transgenic animal models, and a novel, orally available, clinical candidate drug has been developed. Secondly, the underpinning research has led to the formation of a new UK biotechnology company that will invest considerably in new AD research and provide employment opportunities in the life sciences. Finally, the Wellcome Trust's Seeding Drug Discovery initiative has the aim of encouraging small molecule drug discovery in a variety of settings including academia with a key measure of success being the attraction of follow-on funding from the commercial sector to take the discoveries into clinical trials. The successful formation of CoCo Therapeutics Ltd., as one of the first Seeding Drug Discovery funded projects to be partnered, validates this innovative Wellcome Trust program and is likely to impact positively on this funding model.

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

1) Patent. Corcoran, J et al. Therapeutic Aryl-Amido-Aryl Compounds and Their Use. US 20120149737 A1. Publication date: 14.6.2012: http://www.google.com/patents/US20120149737?cl=fr

2) Corcoran, J et al. Patent, Novel RARβ agonists for treatment of spinal cord injury (Filed 2012).(Copy available KCL)

3) CoCo Therapeutics: http://cocotherapeutics.com/

4) Wellcome Trust Press Release: http://www.wellcome.ac.uk/News/2013/News/WTP051907.htm

5) CoCo Therapeutics Press Release: http://www.drugdiscoverynews.com/index.php?newsarticle=7254

6) Corroboration of Wellcome Trust role is available from the Wellcome Trust's Senior Business Analyst who led on the commercialisation of the project and their Drug Discovery Advisor.