Institution: University of Reading

Unit of Assessment: 3 Pharmacy

Title of case study: Development of anti-epileptic cannabinoids: from discovery to the clinic

1. Summary of the impact

Epilepsy, a condition that affects ca. 1% of the world's population, has severe clinical consequences; people with epilepsy (PWE) and poorly controlled seizures exhibit nearly an order of magnitude increase in premature death relative to the general population. About one-third of PWE do not benefit from treatment with currently approved medicines. Although historical evidence has suggested that cannabis might be useful in the control of epilepsy, work initiated by Drs Ben Whalley and Gary Stephens at University of Reading revealed that non-psychoactive components of cannabis can control epileptic seizures in animal models. This finding has led to a funded collaboration of ca £1.4M with GW Pharmaceuticals (UK) and Otsuka Pharmaceuticals (Japan) to establish a case for translation of two such components, cannabidiol (CBD) and cannabidavarin (CBDV), to human clinical drug trials. In particular, Reading research has resulted in GW trialling CBD (Phase 2, 50 participants, design stage) for a new indication of epilepsy treatment. A Phase 1 trial for CBDV (20 participants) began in July 2013, with a Phase 2 trial to begin immediately after successful completion of Phase 1. Results from the use of CBD on an open-label basis have shown major quality-of-life improvements for the patients concerned.

2. Underpinning research

Evidence of the effects of cannabis in PWE remains contradictory, with both anticonvulsant and pro-convulsant effects being reported. The psychoactive component of cannabis, Δ^9-THC, causes cognitive decline and can induce seizures *in vivo* in healthy animals. These adverse effects mean that the use of Δ^9-THC itself as an epilepsy treatment remains undesirable.

In 2000, Whalley independently initiated experiments investigating the anti-epileptiform ('anti-epilepsy-like') effects of *non-psychoactive* (i.e. non-Δ^9-THC) constituents of cannabis[1,2]. In 2005, he continued to investigate the effects of isolated components of cannabis in hyperexcitability model systems under an agreement with GW Pharmaceuticals[3], the only company to have successfully developed non-synthetic cannabis-based medicines (e.g. Sativex in 1999) for clinical use. From 2007 onwards, Whalley and Stephens received funding from GW Pharmaceuticals (UK) and their central nervous system drug-discovery partner, Otsuka Pharmaceuticals, to conduct the necessary preclinical research to establish if any plant cannabinoids represented a legitimate candidate for clinical anti-epileptic drug development. This funding, (ca £1.4M to date), has been both continuous and increasing to the present day.

During this time, Whalley and Stephens studied several pure cannabinoids and identified five that exert notable anti-epileptiform effects in isolated acute sections of live rodent brain in which epilepsy-like activity had been induced[4,5,6,7]. Of these five, they showed that two (CBD and CBDV) have significant anticonvulsant effects in several whole-animal models of acute generalised (pentylenetetrazole, maximal electroshock and DBA/2 audiogenic), temporal lobe (pilocarpine), partial (penicillin) and *status epilepticus*-induced spontaneous recurrent seizures[4,5,6,8]. The magnitude of the effects and the doses used were comparable to those of the positive controls used (i.e. clinically-used effective anticonvulsants such as sodium valproate, ethosuximide and phenobarbital) [4,5,6,8]. Moreover, neurotoxicity testing of both CBD and CBDV established that the observed anticonvulsant effects did not arise from sedation or toxicity induced by CBD or CBDV[4,5,6,8] . Furthermore, neither CBD nor CBDV induce any serious adverse effects in these tests in animal models, even at the highest anticonvulsant doses; a finding in direct contrast to all three positive controls (see above) tested at anticonvulsant doses in animal models, which caused notable, diverse and undesirable adverse effects[4,5,6,8]. Whalley and Stephens have also shown that long-term (3 months) CBDV treatment continues to exert anti-epileptic effects without adverse effects upon cognition or motor function in rats. The use of CBD and CBDV for the treatment of epilepsy is covered by several patents owned by GW and Otsuka upon which Whalley and Stephens both appear as named inventors.

Whalley and Stephens have established their expertise in this area during the past ~10 years and their publication track record demonstrates that their expertise was initiated and established independently of the programme's commercial sponsors (Whalley 37 peer-reviewed publications and h-index=9, Stephens 51 peer-reviewed publications and h-index=20). Whalley has also authored the American Herbal Pharmacopeia's monograph on cannabis and epilepsy, demonstrating his established expertise and reputation. The researchers were approached to collaborate in this work on the basis of this established track record in cannabinoid and/or epilepsy research and have dominated this research area during the past 10 years; they are the only group actively and persistently investigating the anti-epileptic potential of individual plant cannabinoids with a clear clinical strategy in place. This research is a fundamental prerequisite for successful translation to the clinic. Dr Whalley joined the University of Reading in 2005 as a Lecturer in Pharmacy Practice and is currently a Senior Lecturer in Pharmacology. Dr Stephens joined the University of Reading in 2005 as Lecturer in Pharmacology and is currently a Reader in Pharmacology.

3. References to the research

All outputs have been published in high quality peer reviewed journals and have been internally assessed as of at least 2* quality.

1. Whalley BJ *et al.* A novel component of cannabis extract potentiates excitatory synaptic transmission in rat olfactory cortex *in vitro*. *Neurosci. Lett.* **365**, 58-63 (2004). [IF=2.1]
2. Wilkinson, JD *et al*. Medicinal Cannabis: is Δ^9-tetrahydrocannabinol necessary for all its effects? *J. Pharm. Pharmacol.* 55: 1687-1694 (2003)
3. Ma Y-L *et al.*The phytocannabinoid Δ^9-tetrahydrocannabivarin modulates inhibitory neurotransmission in the cerebellum. *Brit. J. Pharmacol*. **154**, 204-215 (2008). doi: 10.1038/bjp.2008.57. [IF = 5.1, REF submission]
4. Hill AJ *et al.* Cannabidivarin is anticonvulsant in mouse and rat in vitro and in seizure models *Br. J. Pharmacol.* **167**, 1629-1642 (2012). doi: 10.1111/j.1476-5381.2012.02207.x. [IF = 5.1, REF submission]
5. Jones NA *et al.* Cannabidiol displays anti-epileptiform and anti-seizure properties *in vitro* and *in vivo*. *J. Pharmacol. Exp. Ther.* **332**, 569–577 (2012). doi: 10.1124/jpet.109.159145. [IF=3.9, REF submission]
6. Hill TD *et al.* Cannabidivarin-rich cannabis extracts are anticonvulsant in mouse and rat via a CB1 receptor-independent mechanism. *Br. J. Pharmacol.* (2013) doi: 10.1111/bph.12321. [IF = 5.1, REF submission]
7. Hill, AJ *et al.* Δ^9-tetrahydrocannabivarin suppresses in vitro epileptiform and in vivo seizure activity in adult rat. *Epilepsia* 51(8) 1522-1532 (2010)
8. Jones, NA *et al.* Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures *Seizure* 21(5):344-52.(2012)

4. Details of the impact

Premature mortality is 2-3 times higher in PWE than the general population, rising to 9 times higher in people with uncontrolled or poorly controlled epilepsy. Up to 50% of PWE who gain control of their seizures using current medication (and ~35% do not) will lose this control during the course of their lives as a result of changes in the brain caused by the seizures. All existing anti-epileptic medicines cause notable cognitive, motor and teratogenic adverse effects at therapeutically effective doses. As such, there is a substantial unmet clinical need within the ~50 million PWE worldwide for new, effective and well-tolerated drug treatments. Our extensive preclinical research findings that show CBD and CBDV are well-tolerated and exert significant anti-epileptiform, anti-seizure and anti-epileptic effects in animal models has directly triggered the translation of this research into human clinical trials.

Translation to clinical trials: changes to industrial activities

With only ~1 in 1,000 new drug entities reaching the Phase 1 clinical trial stage, our development of **two** novel anti-epileptic drugs to this point is highly significant. Phase 1 trials alone, which help determine a drug's safe dosage range, pharmacokinetics and safety profile in healthy human volunteers take ~1 year to complete and cost on average >£1 million, and so represent a notable

investment by the pharmaceutical industry on the basis of research conducted by University of Reading academics [a]. In addition to this investment, GW Pharmaceuticals now own patents on which Whalley and Stephens are named as inventors [b].

Phase 1 trials on CBD were originally carried out by GW Pharmaceuticals in the context of treating multiple sclerosis. On the basis of the Reading research with CBD in the context of treating epilepsy, GW Pharmaceuticals has now invested in a Phase 2 clinical trial of CBD for this new indication [c,d] This Phase 2 study, which is currently in its design stage, will include 50 participants and will evaluate the efficacy of the drug in the treatment of epilepsy.

This **change in activity** for GW Pharmaceuticals represents a significant impact which, having been made, commits GW to a substantial financial and organisational commitment.

Similarly, it is on the basis of original research carried out with CBDV at Reading that GW Pharmaceuticals began a Phase 1 trial for CBDV in July 2013 (20 participants) [c,e].

Again, this **change in activity** for GW Pharmaceuticals represents a significant impact; an indication of the commitment of the company to this compound is that a Phase 2 trial will immediately follow upon successful completion of Phase 1.

New drugs with good efficacy in drug-resistant epilepsy will markedly reduce the number of treatment-resistant patients and offer improved tolerability with fewer adverse effects. Taking into account the number of PWE worldwide, a conservative estimate suggests that millions of lives will be affected positively if these new treatments progress onwards to market.

Use in the community: reduction in seizures, benefits to the health of individuals
In addition to our research findings having the necessary significance to justify two separate clinical trials, CBD is also already being used now in the treatment of drug-resistant paediatric epilepsy, where an immediate and highly significant clinical impact has been demonstrated [f]. The prognosis for children with epilepsies of this type is extremely poor; they experience dozens of seizures each day, have cognitive disability before school age, are generally confined to a wheelchair before secondary school age and around 30% die before reaching adulthood. Two children in the US with drug-resistant epilepsy are now receiving CBD on an open-label, named patient basis and this programme has recently been further expanded [d]. Initial results of a survey of a 19 paediatric patients with epilepsy taking CBD have now been published: 13 of 19 children had marked improvements in seizure control with the majority showing an 80% reduction in seizure frequency[f]. The individual impact upon one of the children receiving CBD from GW Pharmaceuticals is powerfully illustrated by a message from received from his mother [g] stating:

"*He had had sixty eight seizures the day before he started CBD. The day he rode the zip line he had just five, each about 10 seconds long. Days later he was down to three and then to one. The day we flew home he had none. So thank you -- for giving my 11 year old the chance to ride the zip line just like any other kid; for making it possible for us to have fun....and for giving our family some badly-needed hope after battling epilepsy for the last seven and a half years"*

Changes in public awareness of, and perceptions of, cannabinoid usage [h]
Our work has now been featured in *The Sunday Telegraph,* on *BBC* local and national television and radio, in *Epilepsy Review Magazine* (a public magazine of the *Epilepsy Society*), as a featured interview with Whalley on *Epilepsy Action Radio* during National Epilepsy Week 2011, *The Washington Post, NBC News* and *Sky News*. The work also attracted >400 attendees to Dr Whalley's public lecture entitled "Cannabis: drug of abuse or medicinal use?*"* at the University of Reading, UK, in October 2008. The work has also generated numerous invited presentations for Drs Whalley and Stephens, including the Comprehensive Epilepsy Centre, Langone School of Medicine and New York University (2013, USA), and the Joint Spanish-Italian Meeting on Cannabinoid Research (SEIC/IRES), Madrid (2012).

In an area where there is a vast amount of purely anecdotal and pseudoscientific information in

circulation, particularly on individual web sites and weblogs, this extensive media coverage has made a significant contribution towards bringing rigorous, peer-reviewed cannabinoid science to the attention of the public.

5. Sources to corroborate the impact

a) **Contracts held by the university funding underpinning research (>£1.4M since 2007)** 01/2012-01/2013 GW Pharmaceuticals (£100,000) Anticonvulsant potential of phytocannabinoids (project expansion) ; 08/2010-07/2013 GW Pharmaceuticals (~£976,722) Anticonvulsant potential of phytocannabinoids (programme extension) ; 08/2009-08/2010 GW Pharmaceuticals (£140,000) Anticonvulsant potential of phytocannabinoids (project expansion) ; 09/2007-2010 GW Pharmaceuticals (£353,000) (†)

b) **Patents owned by GW Pharmaceuticals and on which Whalley and Stephens are named as inventors**: PCT/GB2010/051066 "Use of one or combination of phytocannabinoids in the treatment of epilepsy" (http://bit.ly/1g6wOB1) ; PCT/GB2011/050649 "Use of cannabidivarin in the treatment of epilepsy" (http://bit.ly/1eZb07q) ; PCT/GB2012/050002 "Use of the phytocannabinoid CBD with standard anti-epileptic drugs (SAEDs) in the treatment of epilepsy" (http://bit.ly/1cmhLT7) ; PCT/GB2012/052284 "A pharmaceutical composition comprising the phytocannabinoids cannabidivarin (CBDV) and cannabidiol (CBD)" (http://bit.ly/17rG8uJ)

c) **Confirmation from GW Pharmaceuticals of the origins of the research are available from** the Chairman of GW Pharmaceuticals (*)

d) **Availability of CBD ('Epidiolex') on a named patient basis** http://bit.ly/1a9KCT2

e) **Confirmation of Phase 1 clinical trial** http://www.gwpharm.com/Phase1Epilepsy.aspx

f) **Porter, BE and Jacobson, C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy.** Epilepsy & Behavior. (2013). Advance online article doi:10.1016/j.yebeh.2013.08.037

g) **Internal GW email, containing an account from the mother of the child receiving CBD** (†)

h) **Sample of popular news articles regarding research** Compound in cannabis may help treat epilepsy, researchers say, *Los Angeles Times* (14th Sept 2012, http://tinyurl.com/nezebum); Cannabis anti-convulsant shakes up epilepsy treatment, *New Scientist* (12th Sept 2012, http://tinyurl.com/pcdthnd); Ben Whalley speaks to Canada's biggest talk radio station (*Newstalk 1010*, 06:15 15th Sept 2012); Cannabis could be used to treat epilepsy, *Daily Telegraph* (10th April 2011, http://tinyurl.com/3ltdb8d)

(†) Available upon request
(*) Contact details provided separately as per guidance