Institution: Aston University

Unit of Assessment: 3 Allied Professions to Health, Dentistry, Nursing and Pharmacy

Title of case study: Epidiolex as a novel treatment for drug-resistant epilepsy

Period when the underpinning research was undertaken: 2006 to date

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Gavin Woodhall	Lecturer → Professor	2004 to date
Dr Tamara Modebadze	MSc → PhD student	2012-2016
Dr Stuart Greenhill	Senior Lecturer	2019-date

Period when the claimed impact occurred: 2016 to 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

30,000 people are diagnosed with epilepsy every year in the UK. Drug resistance is a major issue, especially in children, and 30-50% of people with epilepsy do not respond to any of the current treatments. Without treatment, seizures lead to a range of problems from cognitive delay to sudden death in epilepsy (SUDEP). Research at Aston (2006-2020) has, with GW Pharma, developed a new treatment, Epidiolex (named Epidyolex in Europe), which radically reduces seizures, transforming the lives of those with resistant syndromes.

Impacts on Public Policy, Health & Wellbeing and Economy are claimed.

2. Underpinning research

Background: 30%-50% of epilepsy sufferers are resistant to current drug treatments and are deemed to have drug-resistant epilepsy, which is defined by the International League Against Epilepsy as **"***failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*". In practice, in syndromes such as Dravet or Lennox-Gastaut, drugs have very little impact at all on seizure activity and have no role at all in preventing debilitating co-morbidities such as depression and cognitive impairment.

Previous approaches to anti-convulsive drug discovery: Over the last 50 years, anti-epileptic drug development has followed a familiar pattern, where novel candidates were screened against relatively unsophisticated models of seizures, such as maximal electroshock (MES) or pentylene tetrazole (PTZ) induction. Typically, to model epilepsy, rodents were shocked via the cornea or given a dose of a proconvulsant drug. These pre-treatments resulted in significant animal mortality, which either went unreported altogether, or else was reported at between 25 and 80% of model animals, prior to any anti-convulsive drug testing. Thus epilepsy research employed a robust seizure phenotype, induced in as-short-as-possible an interval after insult/lesion. Surviving animals, which were *de facto*, the most seizure-resistant, were treated with an anti-convulsant drug candidate whose effect was measured by comparing the number of deaths from seizures in treated, versus untreated animals. Accordingly, many drugs with similar mechanisms of action were identified, which had little difference in efficacy, particularly for human sufferers who were either initially drug-resistant or had become resistant after initially responding to therapy. Shortcomings of previous models of epilepsy were laid bare in a seminal paper: "The neurobiology of temporal lobe epilepsy: too much information and not enough knowledge" (Sloviter, 2005, *C. R. Biol.* **328**, 143-153).

Underpinning Research: Inspired by the problems described by Sloviter, Woodhall *et al* first reported changes in glutamate receptor function in epilepsy in 2006 (**S3.1**). In order to treat devastating, drug-resistant epilepsies, novel drugs were required that act through receptors other than the standard glutamate and GABA receptor pathways. Accordingly, to make such discoveries, there was a pressing need for models of epilepsy that showed greater similarity to human disease, including variability in seizure frequency/intensity and drug-resistance. In 2016, developed with NC3Rs funding and as the culmination of a decade of effort, Woodhall described a method for producing epilepsy in rats that provides a deliberately slow and variable progression towards disease. The **R**educed **I**ntensity **S**tatus **E**pilepticus (RISE) model of epilepsy (**S3.2**) prevents seizures that would result from the gross brain damage caused in other models and has <1% animal mortality.

Research Insights: Resulting from its more subtle phenotype, the RISE model provides seizure-sensitive brains for study. RISE closely recapitulates many features of human temporal lobe epilepsy, including between-subject variation in seizure intensity/duration, little or no brain damage and resistance to common antiepileptic drugs. Accordingly, RISE brains have facilitated study of the processes which underly epilepsy and have demonstrated that glutamate and other receptor changes are in fact widespread in epilepsy (**S3.3**) and complex. In parallel, Woodhall's improvements in brain slice preparations permit visualisation of complex behaviour similar to intact brain (**S3.4**). Finally, Woodhall's enhanced slice preparation techniques have enabled maintenance and recording from resected human brain tissue as a 'gold-standard' with which to compare RISE brains and study epilepsy in a translational manner (**S3.5-3.6**).

3. References to the research

S3.1 Yang, J., **Woodhall, G.L.** & Jones, R.S. (2006). Tonic facilitation of glutamate release by presynaptic NR2B-containing NMDA receptors is increased in the entorhinal cortex of chronically epileptic rats. *J. Neurosci.* **26**, 406-10. https://doi.org/10.1523/JNEUROSCI.4413-05.2006.

S3.2 Modebadze, T., Morgan N.H., Pérès, I.A., Hadid, R.D., Amada, N., Hill C., Williams, C., Stanford, I.M., Morris, C.M., Jones, R.S., Whalley, B.J. & **Woodhall, G.L.** (2016). A low mortality, high morbidity Reduced Intensity Status Epilepticus (RISE) model of epilepsy and epileptogenesis in the rat. *PLoS One* **11**, e0147265. https://doi.org/10.1371/journal.pone.0147265.

S3.3 Needs, H.I., Henley, B.S., Cavallo, D., Gurung, S., Modebadze, T., **Woodhall, G.**, & Henley, J.M. (2019). Changes in excitatory and inhibitory receptor expression and network activity during induction and establishment of epilepsy in the rat Reduced Intensity Status Epilepticus (RISE) model. *Neuropharmacology* **158**, e107728. https://doi.org/10.1016/j.neuropharm.2019.107728.

S3.4 Johnson, N.W., Özkan, M., Burgess, A.P., Prokic, E.J., Wafford, K.A., O'Neill, M.J., Greenhill, S.D., Stanford, I.M., & **Woodhall, G.L.** (2017). Phase-amplitude coupled persistent theta and gamma oscillations in rat primary motor cortex in vitro. *Neuropharmacology* **119**, 141-156. https://doi.org/10.1016/j.neuropharm.2017.04.009.

S3.1 Jones, R.S., da Silva, A.B., Whittaker, R.G., **Woodhall, G.L.** & Cunningham, M.O. (2016). Human brain slices for epilepsy research: Pitfalls, solutions and future challenges. *J. Neurosci. Meth.***15**, 260:221-32. https://doi.org/10.1016/j.jneumeth.2015.09.021.

S3.2 Wright, S.K., Wilson, M.A., Walsh, R., Lo, W.B., Mundil., N., Agrawal, S., Philip, S., Seri, S., Greenhill, S.D., & **Woodhall, G.L.** (2020). Abolishing spontaneous epileptiform activity in human brain tissue through AMPA receptor inhibition. *Ann. Clin. Transl. Neurol.* **7**, 883-890. https://doi.org/10.1002/acn3.51030.

The quality of the research described above is evidenced by **S3.2-S3.6**, published in international, peer-reviewed journals and the competitively-awarded research grant: **NC3Rs G0700639/1, £152,048**, Refinement of a rat epilepsy model (2007-2010) https://www.nc3rs.org.uk/refinement-

rat-epilepsy-model and an industrial PhD studentship granted from GW Pharma to Woodhall of **£115,000** (GWRC000xxx000) and **£42,749** for follow-up experiments.

4. Details of the impact

This case study results from a collaboration involving three key components:

1. The discovery of cannabidiol (CBD) as a potential novel epilepsy treatment (**GW Pharma**)
2. Creation of the RISE rodent model of epilepsy (**Aston, S3.3**)
3. Pioneering the use of living human brain tissue in drug studies (**Aston, S3.6**)

Impact on Public Policy: international, regulatory approval of Epidiolex

During the period when the RISE model was being refined and finalized, Woodhall was approached by GW Pharma, then a UK SME with a novel drug, cannabidiol (CBD), to test in relation to epilepsy. Woodhall and Whalley (Reading, UK) both used RISE to demonstrate the efficacy of CBD in treating epilepsy and showed that it altered the processes underlying the development of the condition. Together, these discoveries explained the mechanism of action (MOA) of cannabidiol (Epidiolex/Epidyolex) and explained why cannabidiol works where other drugs fail (**S5.1**). GW Pharma have now adopted the RISE model such that its use is a mandatory requirement in epilepsy work by all contract or academic research organizations with which GW is involved. Currently, they are now collaborating with Woodhall and New York University Medical Centre to demonstrate the effects of Epidiolex in brain tissue taken from children with drug-resistant epilepsy at Birmingham Children's Hospital.

MOA data forms a key part of any NDA (New Drug Application) for FDA approval (**S5.2**). As a consequence of Woodhall's creation of the RISE model, the MOA of Epidiolex was established by Woodhall and collaborators. This knowledge underpinned the clinical trials of Epidiolex (**S5.3**) and subsequently, the approval of Epidiolex by both the **FDA** and the **EMA** (**S5.4**) for the treatment of three severe epilepsies. Further, following those clinical trials and advice from the Advisory Council on the Misuse of Drugs, Epidiolex was rescheduled (lowered) from a Schedule 2 to a Schedule 5 drug by the UK government (**S5.5**) in order to assist affected families' access.

Impact on Health and Welfare 1: reduction and/or elimination of symptoms in patients with Dravet Syndrome, Lennox-Gastaut syndrome & tuberous sclerosis complex (TSC)

Epidiolex has been prescribed for children with orphan diseases, including Dravet Syndrome (DS) and Lennox-Gastaut syndrome (LG) in the USA (4,700 patients) since December 2018. It is making a significant difference to the lives of children who suffer from these most devastating and life-altering epileptic syndromes. For example, LG patients experienced an average of 40% reduction in seizures and some LG patients have become entirely seizure-free (**S5.3**). Similar results are also seen in Dravet Syndrome trials (**S5.3**), Further, in a large trial for Tuberous Sclerosis Complex (the most severe seizure phenotype) a 50% reduction of seizures was demonstrated (**S5.3**). In addition to the direct benefits on epilepsy, Epidiolex also improves other conditions associated with epilepsy (e.g. memory problems, depression) and reports show consequent improvements in patient quality of life such that memory, anxiety and social interactions are all improved (**S5.6**).

Impact on Health and Welfare 2: reduction of harm to animals used in clinical trials

All UK Research Councils require adherence to the "3Rs" (**R**eplacement, **R**efinement, **R**eduction) as a condition of funding for any use of live animals in bioscience research (**S5.7**). Whilst Replacement is currently impossible, RISE contributes very substantially to Refinement and Reduction ("*Improvements to procedures and husbandry which minimise actual or potential pain, suffering, distress or lasting harm and/or improve animal welfare in situations where the use of animals"* and *"Methods which enable researchers to obtain comparable levels of information from fewer animals*" **S5.7**) respectively. As stated by GW Pharma, "*High mortality directly contravenes the 3Rs*" (**S5.8**). In addition to the more gentle induction of the epilepsy phenotype, RISE very significantly reduces the numbers of animals used, by essentially eliminating the high death rates previously encountered following induction of the epileptic condition (**S3.2**).

Impact on the Economy: GW Pharmaceuticals business growth

Since the FDA approval of Epidiolex by in June 2018, Eplidiolex sales have grown substantially. In

November 2019, GW Pharmaceuticals (of which GW Pharma is a subsidiary) reported Epidiolex sales of $188 million since launch, "*reflecting a total of around 15,000 patients having received Epidiolex prescribed by around 3,000 physicians*" (**S5.8**). By the end of 2019, Epidiolex sales had risen to $296 million for 2019 alone (**S5.9**) and in 2020, full-year (as yet unaudited) sales of Epidiolex have risen to ~$510 million, including ~$144 million in Q4, of which ~$129 million represent US sales and ~$15 million are international ("*ex-US*") sales. Unsurprisingly, GW Pharmaceutical's share price has increased: from a low of $38.46 on 11th March 2016, to $115.41 on 31st December 2020 (**S5.9**). Despite these figures all being quoted in US dollars, GW Pharmaceuticals is a British company, founded in 1998 and based in Cambridge, UK (**S5.10**).

In summary, Woodhall's RISE model "*played a pivotal role in investigations to elucidate the molecular mechanism of action"* [of Epidiolex] (**S5.8**), which in turn, formed a key part of successful regulatory approval. Thus, in addition to the benefits to patient health and animal welfare, GW Pharmaceuticals report total sales in 2020 (all products) of ~$526 million (**S5.9**), meaning that Epidiolex/Epidyolex sales of ~$510 million represent 97% of GW Pharma's total sales for the year.

5. Sources to corroborate the impact

S5.1 Patra, P.H., Barker-Haliski, M., White, H.S., Whalley, B.J., Glyn, S., Sandhu, H., Jones, N., Bazelot, M., Williams, C.M. & McNeish, A.J. (2019). *Epilepsia* **60**, 303–314. https://doi.org/10.1111/epi.14629.

S5.2 https://www.fda.gov/files/about%20fda/published/Determining-the-Established-Pharmacologic-Class-for-Use-in-the-Highlights-of-Prescribing-Information.pdf.

S5.3 Epidiolex Clinical trials - ClinicalTrials.gov Identifiers: Lennox-Gastaut Syndrome (NCT02224560) https://clinicaltrials.gov/ct2/show/results/NCT02224560; Dravet Syndrome (NCT0228698) https://clinicaltrials.gov/ct2/show/NCT02286986?term=GWP42003-P&cond=Dravet+Syndrome&rank=5 and Tuberous Sclerosis Complex (NCT02544763) https://clinicaltrials.gov/ct2/show/NCT02544763 and http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-reports-positive-phase-3-pivotal-trial.

S5.4 FDA and EMA regulatory approvals of Epidiolex/Epidyolex https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms; https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex#authorisation-details-section

S5.5 Rescheduling of Epidyolex from a Schedule 2 to a Schedule 5 drug: Advisory Council on the Misuse of Drugs (ACMD) letter to the Minister of State & Home Office circular 001/2020 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/861607/ACMD_advice_Epidyolex.pdf); https://www.gov.uk/government/publications/circular-0012020-epidyolex-scheduling-si-2020-no-559/circular-0012020-epidyolex-scheduling-si-2020-no-559.

S5.6 Rosenberg, E.C., Louik, J., Conway, E., Devinsky, O., Friedman, D. (2018). Quality of Life of Childhood **Epilepsy** (QOLCE) in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol (CBD). *Epilepsia* **58**, 96-100. https://doi.org/10.1111/epi.13815

S5.7 Responsibility in the use of animals in bioscience research: Expectations of the major research council and charitable funding bodies. https://nc3rs.org.uk/sites/default/files/documents/Guidelines/Responsibility%20in%20the%20use%20of%20animals%20in%20bioscience%20research%202019.pdf

S5.8 Letter from the VP Research, GW Pharma concerning the role of RISE in determining the MOA of Epidiolex/Epidyolex.

S5.9 GW Pharmaceuticals Full Year sales data GW Pharmaceuticals Provides Preliminary Fourth Quarter and Full-Year 2020 Net Product Sales Results and 2021 Program Milestones | GW Pharmaceuticals

S5.10 GW Pharmaceuticals share price data to 31.12.20

https://www.google.com/search?q=gw+pharmaceuticals+share+price&rlz=1C1CHBF_en-GBGB802GB802&oq=GW+pharmaceuticals+share+price&aqs=chrome.0.0l3j0i395l3j0i22i30i395l4.8007j1j7&sourceid=chrome&ie=UTF-8. (downloaded 21.1.21)