Institution: University of Aberdeen

Unit of Assessment: 5 - Biological Sciences

Title of case study: Cannabis as a source of medicines: development of the world's first licensed cannabis-based medicine, Sativex®

1. Summary of the impact

Research at the University of Aberdeen has directly contributed to the development of the cannabis-based medicine, Sativex®, which was licensed in the UK in 2010 for relieving neuropathic pain and spasticity of multiple sclerosis (MS), removing the need for patients to self-medicate with illegal, "unregulated" cannabis. The research has both enhanced patient welfare and promoted collaboration with industry. Several other countries have also approved Sativex®. Apart from such direct benefits, the research has also increased understanding of the benefits of cannabis-based medicines among the general public, and the main researcher has advised the Home Office on pertinent legislation. *Therefore the claimed impact here includes benefits to health and welfare guidelines and on the public understanding of science. In addition industry has invested in research and development and a new product has been commercialised.*

2. Underpinning research

Mechoulam, Pertwee and others discovered in the early 1990s the endocannabinoid family of natural substances produced by the body which have actions similar to those of the psychoactive ingredient in cannabis. Since then Pertwee's research, as Professor of Neuropharmacology at the University of Aberdeen, has led him to be a world leader in the study of the pharmacology and therapeutic potential of cannabinoids. Pertwee's research was essential for the development of the drug Sativex® by GW Pharmaceuticals which is used as a medicine in Canada and EU for spasticity and pain in multiple sclerosis.

Pertwee instigated the first survey of cannabis users which revealed its effectiveness to reduce MS spasticity and pain. In the 1980s and early 1990s, numerous reports appeared in the media about claimed benefits of self-medication with cannabis for relieving symptoms of MS, but these reports were not supported by empirical science. This prompted Pertwee, in collaboration with Dr Paul Consroe, University of Arizona and Dr Rik Musty, University of Vermont, to devise a questionnaire sent out in 1995 to known individuals (identified by the Alliance for Cannabis Therapeutics) who self-medicated with cannabis. The replies received indicated that cannabis was regarded as being particularly effective against MS spasticity and pain [1]. The survey results provided impetus for the case for performing large controlled trials with cannabinoids for these MS symptoms.

Pertwee also provided the cannabinoid pharmacological expertise that showed the effectiveness of cannabinoids in animal models of MS. Lorna Layward of the MS Society brought together scientists with cannabinoid expertise (Pertwee) and MS expertise (David Baker, Professor of Neuroimmunology at The Blizard Institute, University of London) to perform the basic research necessary to demonstrate the effectiveness of cannabinoids in treating MS symptoms. Their collaboration in 1998 yielded data showing that cannabinoid receptor agonists can ameliorate spasm, spasticity and tremor in the chronic relapsing experimental allergic encephalomyelitis mouse model of MS. These findings led to a key paper on the scientific rationale for treating MS with cannabinoids [2]. Also, importantly, this paper provided a route to evaluate more selective cannabinoids in the future.

Pertwee's research, as Director of Pharmacology for GW, provided essential pharmacological characterisation of the two major cannabinoid components of the drug Sativex which underpinned its development and helped inform the company's clinical research in development of this drug (review [3] references over 30 of Pertwee's papers in this area). In addition, Pertwee was a major academic contributor to the licencing document produced by GW Pharmaceuticals for Sativex.

In research that will lead to new uses of cannabinoid based drugs, Pertwee's research then led to the discovery both of the first water-soluble cannabinoid (O-1057) (2000), and of a CB1 receptor allosteric site (2005) (in collaboration with the Dutch pharmaceutical company, Organon);

contributed to the first pharmacological characterisation of synthetic cannabinoids widely used as pharmacological tools; and to the discovery of important potential therapeutic applications for phytocannabinoids [4 to 6]. An important result of Pertwee's research has been the demonstration that cannabinoids can be drugs of medical benefit. Prior to this research the therapeutic potential of cannabis was viewed with extreme caution by drug agencies and governments because of adverse media coverage. The reputation of Pertwee's research, demonstrating the protective role of the endogenous cannabinoid system in serious disorders such as MS, has given the cannabinoid research field new respectability. Key to this is Pertwee's research standing, which has been recognized in his status as an ISI Highly Cited Researcher, his major standing on multiple cannabinoid societies and advisory boards and his 2011 award of the Wellcome Gold Medal by the British Pharmacological Society "for outstanding contributions to pharmacology, based mainly on research achievements".

3. References to the research

[1] Consroe P, Musty R, Rein J, Tillery W, Pertwee R (1997). The perceived effects of smoked cannabis on patients with multiple sclerosis. *European Neurology* 38: 44-48. *First survey of the benefits of self-medicating with cannabis claimed by multiple sclerosis patients; the UK part of this survey was made possible by a link that Pertwee had set up with Clare Hodges of the Alliance of Cannabis Therapeutics (ACT UK).*

[2] Baker, D., Pryce, G., Croxford, J.L., Brown, P., Pertwee, R.G., Huffman, J.W. and Layward, L. (2000). Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 404: 84-87. *Paper presenting the first evidence (from experiments with mice performed at University College, London) that cannabis ameliorates multiple sclerosis (MS) in a highly specific manner that involves the activation of cannabinoid receptors; this project was set up by Lorna Layward of the MS Society who brought together scientists with MS expertise (David Baker) and cannabinoid expertise (Pertwee).*

[3] Pertwee R.G. (2008) The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 153:199-215. *This review provides an extensive summary of the science of the plant cannabinoids and references over 30 papers to which Pertwee contributed and which describe cannabinoid pharmacology.*

[4] Thomas, A., Stevenson, L.A., Wease, K.N., Price, M.R., Baillie, G., Ross, R.A. and Pertwee, R.G. (2005). Evidence that the plant cannabinoid Δ^9-tetrahydrocannabivarin is a cannabinoid CB_1 and CB_2 receptor antagonist. *Br. J. Pharmacol. 146: 917-926*. *The discovery in Aberdeen that the plant cannabinoid, Δ^9-tetrahydrocannabivarin (co-discovered by Pertwee in 1970; Nature 228 134-136), is a cannabinoid CB_1 receptor antagonist, has opened up potential therapeutic uses for this compound.*

[5] Bolognini, D., Costa, B., Maione, S., Comelli, F., Marini, P., Di Marzo, V., Parolaro, D., Ross, R.A., Gauson, L.A., Cascio, M.G. and Pertwee, R.G (2010). The plant cannabinoid Δ^9-tetrahydrocannabivarin can decrease signs of inflammation and inflammatory pain in mice. *British Journal of Pharmacology.* 160: 677-687. *Paper providing the first in vitro and in vivo evidence that whereas the plant cannabinoid, Δ^9-tetrahydrocannabivarin, blocks cannabinoid CB_1 receptors, it can activate cannabinoid CB_2 receptor and hence, because of these two actions, has a number of important potential therapeutic uses (e.g. for Parkinson's disease, stroke, chronic liver diseases and cocaine dependence).*

[6] Cascio, M.G., Gauson, L.A. Stevenson, L.A., Ross, R.A. and Pertwee, R.G. (2010). Evidence that the plant cannabinoid cannabigerol is a highly potent α_2-adrenoceptor agonist and moderately potent $5HT_{1A}$ receptor antagonist. *Br. J. Pharmacol*. 159:129-141. *Paper presenting the first evidence that the plant cannabinoid, cannabigerol, is a potent α_2-adrenoceptor agonist and also a 5-HT_{1A} receptor antagonist, findings that prompted collaborative research that has recently shown that cannabigerol acts in vivo to produce α_2-adrenoceptor-mediated signs of pain relief in mice and also amelioration of negative signs of schizophrenia in rats.*

Relevant grant funding:

£6M grant funding awarded to Roger Pertwee since 1992 for work on the pharmacology of cannabinoids. Main funding sources have been the Wellcome Trust, MRC (Cannabinoid Co-

operative Group), BBSRC, US National Institutes of Health and GW Pharmaceuticals.

4. Details of the impact

Patient health and welfare: The study of cannabinoid pharmacology performed by Pertwee and others led to the British company, GW Pharmaceuticals, developing the cannabis-based medicine, Sativex®. Pertwee's research was invaluable as stated by the chairman of GW Pharmaceuticals, Dr Geoffrey Guy, "He has played a pivotal role in cannabinoid science, which has led to GW's development of Sativex®, the world's first cannabis based medicine…" [a]. In 2013 Pertwee received the International Association for Cannabinoid Medicines special award "for his major contributions to the re-introduction of cannabis as a medicine". Sativex® is an oromucosal spray which reduces suffering and increases the quality of life of MS patients and removes any need to self-medicate with cannabis obtained illegally. Internationally, Sativex® has been approved as a treatment for spasticity and pain caused by MS in 20 countries, in eight of which commercialisation has now commenced. GW Pharmaceuticals is awaiting product licences in two further countries (Italy and Ireland) that have recommended approval. Regulatory applications have also been submitted in Switzerland and seven countries in the Middle East. In the US, phase III clinical trials for treatment of pain in cancer patients are underway.

Sativex was licensed in the UK in 2010. Pertwee's earlier input to the House of Lords Select Committee on Science and Technology [b] helped progress the legal issues hitherto slowing the development of cannabis-based medicines and therefore allow its 2010 licensing. One UK Sativex® user who used to self-medicate with cannabis and blogs about the benefits of the new treatment is Sarah Martin [c]. At Pertwee's suggestion (2011), she became UK "Patient Representative" of the International Association for Cannabinoid Medicines.

A colleague of Pertwee's, Dr William Notcutt, Consultant in Anaesthesia and Pain Management at James Paget University Hospital, Norfolk [d], and who treats patients with Sativex, testifies to the significance of Sativex in improving the quality of life of patients and carers:

"Sativex has been shown to have significant effects on symptoms such as spasticity, muscle spasms, sleep disturbance, pain, bladder dysfunction and quality of life for about 50% of patients who are poorly responsive to other therapies. The improvements with Sativex can be substantial for the patient in improving mobility, spasm and spasticity, pain and sleep. For the carers, …any improvement on mobility is a help. 50% of carers/spouses also have a substantial reduction in sleep disturbance."

Collaborations with industry: Pertwee has been Director of Pharmacology for GW Pharmaceuticals since 2002 [a] having previously had formal cannabinoid-related links with other pharmaceutical companies (e.g. Pfizer and Organon). In addition to his own research on cannabinoid pharmacology, Pertwee has established collaborative links with research groups around the world to study the therapeutic properties of cannabinoids. This ongoing partnership between the University of Aberdeen and industry has enabled the discovery and development of other cannabis-based medicines with important new therapeutic applications, such as treating obesity, treating Parkinson's Disease and for suppressing nausea/vomiting in patients undergoing chemotherapy.

Public engagement: The underpinning research and development of Sativex has contributed to the public debate on cannabis [e] and has been discussed by Pertwee at the British Science Association's Festivals of Science, which are organized for the general public. His presentations at these events at Trinity College Dublin in 2005, Aston University, Birmingham, in 2010 and Aberdeen in 2012 attracted audiences of around 100 members of the public.

In addition, Pertwee was a major invited contributor to a Wellcome Witnesses to Twentieth Century Medicine seminar entitled "The Medicalization of Cannabis", which took place in London in March 2009 [e]. The audience was comprised of medical staff, clinicians, pharmaceutical companies and MS patients. He also gave an invited talk on cannabinoids to the general public in London at a Royal Institution event run in association with the University of the Third Age (March 2011). This too attracted an audience of at least 100.

This work contributed to raising awareness and understanding of cannabis as a source of medicines in many media interviews, including BBC Radio 4's science discussion programme *The*

Material World (August 2008); Radio 4's *Today* programme (September 2010, around 7 million listeners); and BBC Breakfast TV (September 2010).

Impacts on policy and legislation: In 2009, Pertwee was requested by the Home Office, on behalf of the Advisory Committee on the Misuse of Drugs, to provide advice about how best to define cannabinoid receptor agonists in a manner that would facilitate future UK cannabis/cannabinoid legislation.

In 2011 Pertwee influenced Canadian healthcare guidelines by assisting in the composition of Health Canada's "Information for Health Care Professionals-Marihuana" document, providing pharmacological information and identifying new potential therapeutic uses for cannabinoids [f].

Cannabinoid patent co-inventor: Pertwee is a named inventor of six GW Pharmaceuticals patents and two University patents. The former are directly linked to the development of new cannabis-based medicines ("beyond" Sativex®) [g].

Therefore the claimed impact as defined by REF is that: the quality of life of individuals has been enhanced and well-being improved. Healthcare guidelines have been influenced by research. Public understanding of the subject has improved. Industry has invested in research and development and a new product has been commercialised.

5. Sources to corroborate the impact

[a] **GW Pharmaceuticals:** summary of Pertwee's GW impact as seen in the following GW web page with a press release about Pertwee relating to his award from the British Pharmacological Society of the 2011 Wellcome Gold Medal "for outstanding contributions to pharmacology, based mainly on research achievements", and with quote from Dr. Geoffrey Guy, see:

http://www.gwpharm.com/GW%20Director%20Wins%20Wellcome%20Medal.aspx
http://www.bps.ac.uk/details/membersPage/836573/Prizes_.html?cat=bps129c64bddf5#Wellcome

[b] **House of Lords Select Committee on Science and Technology:** House of Lords Select Committee on Science and Technology (1998) Cannabis: The Scientific and Medical Evidence: Evidence, HL Paper 151-1. London: The Stationery Office (ISBN 0 10 479298 1); *Pertwee's input (e.g. pp. 64-83 & p. 280) added weight to arguments to allow the development of cannabis-based medicines (see pp. 64-83 & p. 280). For a summary see:* http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/151/15101.htm

[c] **Multiple Sclerosis patient who has greatly benefited from taking Sativex and through Pertwee was a UK "Patient Representative"** (see her Blog):
http://beverlyhillscannabisclub.ning.com/profiles/blog/list?user=2evu6xovyjo82

[d] **Consultant providing support for the efficacy of Sativex for Multiple Sclerosis.** Contact details: James Paget University Hospital, Great Yarmouth, UK.

[e] **Wellcome Witnesses to Twentieth Century Medicine:** Together with many of those who contributed to the "medicalization" of cannabis, Pertwee was a major invited contributor to a Wellcome Witnesses to Twentieth Century Medicine seminar entitled "The Medicalization of Cannabis". This Witness Seminar took place in London in March 2009. A book from this, "The Medicalization of Cannabis" supports Pertwee's impact on the medicalization of cannabis.

http://www.history.qmul.ac.uk/research/modbiomed/wellcome_witnesses/volume40/index.html

[f] **Information for Health Care Professionals-Marihuana document:** http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php

[g] **Patents:** Pertwee is a named inventor on the following cannabinoid patents:
(1) New pharmaceutical formulation comprising cannabidiol and tetrahydrocannabidivarin; (2) Use of tetrahydrocannabinol and/or cannabidiol for the treatment of inflammatory bowel disease; (3) Therapeutic uses of cannabigerol; (4) New use for cannabinoid; (5) Use for cannabinoid; (6) New cannabinoid application; (7) Sulfonamide cannabinoid agonists and antagonists.