Institution: Cardiff University

Unit of Assessment: UoA3

Title of case study: Discovery and development of the world's most powerful antiviral agent against shingles

1. Summary of the impact (indicative maximum 100 words)

A new family of antiviral agents, bicyclic nucleoside analogues (BCNAs), discovered in Cardiff University has led to a highly potent anti-VZV (shingles) molecule, FV-100. On a worldwide basis more than two million patients are affected by shingles annually. FV-100 has successfully completed Phase II clinical trials, showing it is safe, potent and effective and with clinical advantages over the current standard of care. FV-100 has received more than $30 million in R&D investment, generating patents and creating highly skilled jobs in the UK and the USA, with the parent company currently valued at $397 million. It will enter registration trials in late 2013.

2. Underpinning research (indicative maximum 500 words)

Discovery of novel antiviral agent

In the mid-1990s, researchers in the medicinal chemistry laboratory at Cardiff University led by Professor Chris McGuigan (Reader 94-96 then Professor of Medicinal Chemistry 1996 - present) discovered an entirely new family of antivirals, the bicyclic nucleoside analogues (BCNAs). The antiviral activities of Cardiff's BCNAs were screened in virology tests performed by Professor Jan Balzarini and his team at the Rega Institute of Katholieke Universiteit Leuven, Belgium.

These two collaborators filed a US and worldwide composition of matter patent in 1997 and first reported their findings on the BCNA family in 1999 [3.1]. The Cardiff/Rega team found the alkyl BCNAs to be potent and selective agents active against the Varicella zoster virus (VZV), the cause of human chickenpox and shingles. This work was unprecedented, the first ever report in either open literature or patents regarding the antiviral action of the BCNAs. Indeed, only the H- and Me-substituted parent compounds had previously been reported at all, and they had been shown to be inactive in a range of biological assays.

The molecules synthesised in McGuigan's BCNA research programme represented completely new chemical entities. The initial 'hit molecule' was about 250-times more powerful *in vitro* than the first-line drugs against VZV, acyclovir and its valyl ester (Valtrex) [3.1].

Improving potency

Subsequent work to generate second generation aryl BCNAs revealed in 2000 that the lead candidate, Cf1743, was the most potent inhibitor of VZV ever reported [3.2]. Cf1743 was roughly 10,000-times more active than acyclovir *in vitro*; with detectable activity in assays at concentrations below 1 nM. This molecule is currently one of the most potent antivirals against any human pathogenic virus.

Cardiff University took the lead to exploit the potent anti-VZV BCNA agents and licensed the patents to Fermavir Pharmaceuticals in August 2005. By 2005 Cardiff had committed over $250K in patent costs on the BCNA family, a sum matched by an upfront payment by Fermavir. Fermavir Pharmaceuticals was a New York based spinout specifically formed to exploit the BCNA family. Fermavir was listed on NASDAQ in October 2005 with a market capitalisation at that time of $24M solely on the basis of the Cardiff/Rega BCNA assets. Working with Fermavir, the Cardiff/Rega team researched and developed FV-100 as a novel orally bioavailable pro-drug of Cf1743 [3.3]. This R&D was highly collaborative with McGuigan (Cardiff) carrying out drug design and synthesis, Balzarini (Rega) performing the antiviral assay and various contract research organisations (sponsored by the commercial partner) undertaking pre-clinical regulatory work. Pre-clinical research and development on FV-100 was completed in 2007, and the agent entered Phase I clinical study in 2008.

Over 56 journal publications have arisen from the Cardiff BCNAs/VZV research from the McGuigan lab (1999-2011). The lead references [3.1] and [3.2] have each been cited over 120 times. Comprehensive reviews were published in 2002 [3.4] and 2009 [3.5]. In addition, 45 patent

international filings have been made at various stages of the work [3.6].

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

[3.1] **McGuigan, C.**, Yarnold, C.J., Jones, G., Velázquez, S., Barucki, H., **Brancale**, **A.**, Andrei, G., Snoeck, R., De Clercq, E. and Balzarini, J. Potent and selective inhibition of varicella-zoster virus (VZV) by nucleoside analogues with an unusual bicyclic base. J. Med. Chem. (1999) 42: 4479-4484. http://dx.doi.org/10.1021/jm990346o

[3.2] **McGuigan, C.**, Barucki, H., Blewett, S., Carangio, A., Erichsen, J.T., Andrei, G., Snoeck, R., De Clercq, E. and Balzarini, J. Highly potent and selective inhibition of varicella-zoster virus by bicyclic furo pyrimidine nucleosides bearing an aryl side chain. J. Med. Chem. (2000) 43: 4993-4997. http://dx.doi.org/10.1021/jm000210m

[3.3] **McGuigan, C.**, Pathirana, R.N., Migliore, M., Adak, R., Luoni, G., **Jones, A.T.**, Diez-Torrubia, A., Camarasa, M-J., Velazquez, S., Henson, G., Verbeken, E., Sienaert, R., Naesens, L., Snoeck, R., Andrei, G. and Balzarini, J. Preclinical development of bicyclic nucleoside analogues as potent and selective inhibitors of varicella zoster virus. J. Antimicrobial Chemotherapy (2007) 60: 1316-1330. http://dx.doi.org/10.1093/jac/dkm376 (cited 30 times)

[3.4] Balzarini, J. and **McGuigan, C**. Bicyclic pyrimidine nucleoside analogues (BCNAs) as highly selective and potent inhibitors of varicella-zoster virus replication. J. Antimicrobial Chemotherapy (2002) 50: 5-9. http://dx.doi.org/10.1093/jac/dkf037

[3.5] Balzarini, J. and **McGuigan, C.** FV-100 as a new approach for the possible treatment of varicella-zoster virus infection. J. Antimicrobial Chemotherapy (2009) 64: 671-73. http://dx.doi.org/10.1093/jac/dkp294

[3.6] **McGuigan C.**, Balzarini J. and Migliore, M. Patent - Anti-viral pyrimidine nucleoside derivatives. WO 2007/129083 (2007).
http://patentscope.wipo.int/search/en/WO2007129083

The research work described above was supported in part by MRC grants (total £157,000, 1996-2003) and by commercial grants from Fermavir (£64,000, 2005-2008) and Inhibitex (part of an overall £1.27 million investment into Cardiff laboratories, 2007-2013) with McGuigan serving as PI on all grants. For example:

- McGuigan, C. (PI and sole investigator). The discovery of new anti-herpetic agents. 2001-2003. MRC. £116K.
- McGuigan, C. (PI and sole investigator). Design, synthesis and evaluation of novel antiviral nucleosides. 2005-2008. Fermavir Research Inc. £63.6K

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

The BCNA anti-VZV (shingles) research of McGuigan has underpinned significant commercial impact during the assessment period with the creation of wealth and highly skilled jobs within the biotechnology sector; overseas industry has invested heavily in this novel technology. Through the development of a potent anti-VZV agent the research is poised to deliver near to market patient benefits; efficacy and safety in patients has been demonstrated.

Although shingles involves a short-term acute phase it frequently has a long and very painful recovery period. This post herpetic neuralgia (PHN) phase will affect ca. 25% of patients who will still have shingles pain 90 days after infection. Indeed, shingles is not ideally treated with the current first-line therapy of acyclovir or its prodrug Valtrex which require high doses to be administered several times daily (e.g. acyclovir 800mg, 5 times daily). The initial clinical data for FV-100 shows it to have superior efficacy for managing PHN which is one of the most significant unmet needs in shingles treatment[5.1]. There are approximately 1 million patients presenting with shingles p.a. in USA/Europe with an estimated pharmaceutical market size ca. $750M p.a.

Clinical development and commercial impact

The discovery of the potent anti-VZV activity of BCNAs by McGuigan along with his laboratory's contributions in the collaborative development of Cf1743 and its counterpart pro-drug FV-100, have

led to the successful progress of a novel first-in-class potent anti-VZV agent through phase I/II human clinical trials.

The effective collaborative research partnership between Cardiff/Rega and Fermavir, and the promising outcomes of FV-100 in pre-clinical studies[5.2] led the US pharmaceutical company Inhibitex Inc. to acquire Fermavir in 2007 [5.3] in a deal worth over $19 million[5.4]. Since FV-100 was Fermavir's only drug candidate asset, this places a direct market valuation on the FV-100 candidate at that time. During the assessment period itself Inhibitex invested research funding (ca. £280K 2008-12) to the McGuigan laboratories to support the FV-100 clinical research programme [5.4]. In 2008 Inhibitex launched phase 1 safety/pharmacokinetic clinical trials in 50 healthy volunteers. This work was followed by a major (ca. $10M) 350-patient double-blind randomised study in shingles patients[5.4]. Two-thirds of patients received FV-100 at two doses. FV-100 was proven to be a safe and effective therapeutic for VZV shingles at about one-tenth of the dose and one-third of the dosing frequency of the current standard of care (Valtrex). At 400mg once a day the incidence of PHN was reduced from 20% (Valtrex, 1g, 3 times a day) to 12%[5.1]. The use of analgesics, including opiates, was also significantly reduced in the FV-100 group. The continued success of FV-100 in Phase I and II clinical studies (including a double-blind randomised study, see above) contributed to the acquisition of Inhibitex by Bristol-Myers Squibb (BMS) [5.4,5.5]. Inhibitex's only other major asset was also designed in Cardiff's laboratories, INX-189, a phase II anti-viral agent against the hepatitis C virus. Based upon the positive outcome of the clinical trials FV-100 was acquired from BMS (2012) for an undisclosed fee by Synergy Pharmaceuticals (New York)[5.6], a NASDAQ listed company (currently valued at $400M) with plans for a FV-100 registration trial for 2014 [5.7].

The development of anti-VZV BCNAs, including Cf1743 and FV-100, has been driven by major financial investment from the commercial pharmaceutical sector, creating wealth (realised through the three acquisition deals related to FV-100 assets, see above) and highly skilled jobs in Cardiff and elsewhere.

The Cardiff research funded by the MRC and Industry has led to the commercial adoption of a new class of anti-VZV agent. Investment has been significant and major multi-$M clinical trials have been undertaken. Industry has been enhanced by this project, and we claim significant commercial impact, and emerging health impact. FV-100 is poised for phase III registration trials and represents the most potent agent currently known versus VZV shingles, but human efficacy is already proven.

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

[5.1] Statement from physician and key opinion leader (University of Alabama at Birmingham and USA Government advisor on in viral disease). Perspective on current VZV (shingles) management and the place of FV-100 as an anti-VZV therapeutic.

[5.2] Contact - CEO, Biovitas, New York and former founder of Fermavir. Corroboration of the effective research partnership between Cardiff/Rega and Fermavir leading to acquisition of Fermavir by Inhibitex Inc., GA, USA.

[5.3] Business Wire Press release: Inhibitex acquisition of Fermavir and recognises the discovery of FV-100 in the Cardiff laboratory of McGuigan.
http://www.businesswire.com/news/home/20070410005529/en/Inhibitex-Signs-Definitive-Agreement-Acquire-FermaVir-Pharmaceuticals

[5.4] Statement from former CEO Fermavir and former Senior VP Research Inhibitex (now retired). Corroboration of FV-100 as the only drug candidate asset in Fermavir at the time of acquisition by Inhibitex (at $19 million) and thus establishing the value of the FV-100 asset at the start of the assessment period. Inhibitex's strategy of continued funding to the McGuigan laboratories to

support the development of FV-100. The positive outcomes of the FV-100 clinical trials.

[5.5] Business Wire Press release: Acquisition of Inhibitex by Bristol-Myers Squibb (BMS) for $2.5 billion with clear mention of FV-100 as one of the two drug candidates in Inhibitex at the time. The other being INX-189, another Cardiff-McGuigan discovered drug.
http://www.businesswire.com/news/home/20120107005030/en/Bristol-Myers-Squibb-Acquire-Inhibitex

[5.6] Synergy Pharmaceuticals Press Release: Acquisition of FV-100 from BMS. The success of FV-100 in Phase II clinical studies and the companies forward plans for the agent.
http://ir.stockpr.com/synergypharma/company-news/detail/93/synergy-pharmaceuticals-acquires-fv-100-shingles-drug-from-bristol-myers-squibb-company

[5.7] Statement from President and CEO Synergy Pharmaceuticals. Corroboration of how the positive outcomes of the FV-100 clinical trials led to the acquisition of FV-100 by Synergy Pharmaceuticals. The incorporation of a new company ContraVir to specifically develop FV-100 and plans for its registration trials in 2014.

All documents, testimony and webpages saved as PDFs are available from the HEI on request.