Institution: University of Bristol

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Translating research into novel immunotherapies delivers scientific and economic gains for the pharmaceutical/biotechnology sector in drug discovery.

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

Research into novel immunotherapies has given rise to a novel drug (EtxB), which is now in Phase II clinical trials, and to a profitable contract research company partnering with the pharmaceutical industry to develop their compounds. Trident Pharmaceuticals was formed around patents filed by the University of Bristol, has received investment of *[text removed for publication]*, successfully completed Phase I trials (2011) and is in the midst of Phase IIa trials in humans with inflammatory disease (2013). KWS BioTest arose as a result of the underpinning research and experience gained from developing EtxB, and is now a leading contract research organisation working with pharmaceutical and biotechnology companies developing novel treatments for human disease. KWS has directly contributed to the development of therapies at more than 75 different companies, employs 28 people, has exported *[text removed for publication]* and was 2012 winner of a Biomedical iNet Award for outstanding business achievement.

2. Underpinning research (indicative maximum 500 words)

Research in Infection and Immunology has long been a major strength within Bristol, which was also one of the first Universities in the UK to organise its support for entrepreneurial activities. Neil Williams (appointment at the University of Bristol initially as a Lecturer in 1991, now as a Professor) collaborated with Hirst (then at University of Kent, but subsequently at the University of Bristol 1996-2003) in seeking to understand the unusual ability of a bacterial protein (EtxB) to stimulate mucosal antibodies (Nashar, PNAS 1992; cited 114 times, 6.71/year). This basic immunological finding had little obvious translational value by itself. However, Williams followed these findings up with studies to determine the effects of EtxB on populations of immune cells. He established a range of cellular assays showing that EtxB caused the activation of B lymphocytes, triggered apoptosis in CD8+ T-cells and modulated CD4+ T-cell activation (Nashar, Int Immunol 1996; Immunol 1997). Looking at this range of effects, Williams hypothesised that it may be possible to harness this protein as a novel treatment for human inflammatory diseases.

A combination of cell biology studies and *in vivo* experiments validated the hypothesis, culminating in the ground-breaking discovery that EtxB could completely block the development of disease in the gold standard rodent model of rheumatoid arthritis.[1] The potential to use EtxB as a therapy was patented[12] and a key review foresaw its potential in a range of diseases.[2] Peer-reviewed grant funding directly aimed at determining the therapeutic potential of EtxB and to identify its mechanism of action drove the programme forwards over the following ten years (£2.66m from the MRC, Wellcome Trust, Arthritis Research UK, CRUK and others[7-11]). Further patents were subsequently filed covering the use of EtxB as a treatment for allergic disease[13] and as a modulator for use in a vaccine.[14] Peer-reviewed publications corroborated this potential.[3-6]

Investigations of the potential of EtxB as a novel therapy led the Williams laboratory to establish key translational models of human diseases, including type 1 diabetes (Ola, Immunol 2006), colitis and asthma,[6] and to use state-of-the-art techniques to characterise the effects of EtxB on a range of immune parameters underlying disease pathogenesis in these conditions (Plant EJI, 2003; [5]). The research established that EtxB was able to modulate the activity of T regulatory cells following its delivery. Demonstrating this required the development of a range of assay systems, enabling the activation and differentiation of T-cells to be tracked *in vivo* in rodents, and necessitated their application to diseased animals. These tools were not only critical to uncovering the mechanism of action of EtxB, but also established the Williams laboratory as a centre for the study of immune modulating therapies. The data generated from these endeavours and the resulting reputation of the laboratory provided the springboard for the formation by Williams of KWS BioTest Ltd, which offers these and other models developed following its formation to pharmaceutical and biotechnology companies around the world in support of their drug discovery programmes.

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

Peer reviewed journal publications

30 original articles and 7 refereed reviews since 1992 from the Williams lab relating to the use of EtxB as an immune modulating agent, including:

[1] Williams, N.A., Stasuik, L., Nashar, T.O., Richards, C.M., Lang, A.K., Day, M.J. & Hirst, T.R. (1997). Prevention of autoimmune disease due to lymphocyte modulation by the B-subunit of *Escherichia coli* heat-labile enterotoxin. *Proc Natl Acad Sci U S A*. **94**:5290-5295 *[cited 53 times, 3.31/year]* PMID: 9144230
[2] Williams, N.A., Hirst, T.R. & Nashar, T.O. (1999). Immune modulation by the cholera-like enterotoxins: from adjuvant to immunotherapeutic. *Immunol Today* **20**:95-101 *[cited 172 times, 12.29/year]*. PMID: 10098329
[3] Richards, C.M., Aman, T., Hirst, T.R., Hill, T.J. & Williams, N.A. (2001) Protective mucosal immunity to ocular herpes simplex virus type-1 infection in mice using *Escherichia coli* heat-labile enterotoxin B-subunit as an adjuvant. *J Virol* **75:**1664-1671 PMID: 11160664
[4] Luross, J.A., Heaton, C.P.E., Hirst, T.R., Day, M.J. & Williams, N.A. (2002) *Escherichia coli* heat-labile enterotoxin B-subunit prevents autoimmune arthritis through the induction of regulatory $CD4^+$ T cells. *Arthritis Rheum* **46:**1671-1682 PMID: 12115200
[5] Donaldson DS, Tong KK, Williams NA. (2011) Mucosal administration of the B subunit of E. coli heat-labile enterotoxin promotes the development of Foxp3-expressing regulatory T cells. *Mucosal Immunol* **4**(2):227-238 PMID: 20944556
[6] Donaldson, DS, Apostolaki M, Bone HK, Richards CM, Williams NA.(2013) The Escherichia coli heat-labile enterotoxin B subunit protects from allergic airway disease development by inducing CD4+ regulatory T cells. *Mucosal Immunol* **6**:535-546. PMID: 23032791

Peer reviewed grants

£2.66m peer-reviewed and £1.91m industry funding since 1992 to the Williams laboratory relating to investigations into the use of EtxB as an immune modulating agent, including:

[7] The Wellcome Trust – £280,492 “Receptor mediated effects on molecular and cellular mechanisms in antigen presentation, processing and the generation of immunological memory responses by *Escherichia coli* enterotoxin B-subunits (EtxB)” March 1997-July 2001.
[8] The Medical Research Council – £307,544 “A generic carrier for targeted delivery into both class I and class II processing and presentation pathways” Jun 1999-May 2002.
[9] The Wellcome Trust – £275,917 “Cell signals underlying the immunomodulatory properties of *E. coli* heat-labile enterotoxin” January 1999-December 2002.
[10] The Wellcome Trust – £275,762 “Control of ocular HSV-1 infection using mucosal vaccination strategies which stimulate Th1 or Th2 dominated immune responses” May 2000-April 2003.
[11] Cancer Research Technology (CRUK) – £236,519 EtxB; a novel approach to cancer vaccinations and therapy July 2007-June 2009.

Patents arising, licensed to Trident Pharmaceuticals Inc.

[12] Therapeutic agents and autoimmune diseases; *Priority date*: 5 July 1995 (UK)
Owner: University of Bristol, *PCT Number*: PCT/GB96/01614
Inventors: Williams, N.A., Hirst, T.R. & Nashar, T.O.
Status: Granted Australia, Austria, Belgium, Canada, China, Czech Republic, Denmark, European Patent Convention, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russian Federation, Singapore, Spain, Sweden, Switzerland, United Kingdom, United States

[13] Agent for treating allergic and hypersensitivity condition; *Priority date*: 9 January 1998 (UK)
Owner: University of Bristol, *PCT Number*: PCT/GB99/00070
Inventors: Williams, N.A., Hirst, T.R. & Bienenstock, J.
Status: Granted Australia, Austria, Belgium, Canada, Cyprus, Denmark, European Patent Convention, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Monaco, Netherlands, New Zealand, Portugal, Spain, Sweden, Switzerland, United Kingdom

[14] Vaccination; *Priority date*: 8 May 1998 (UK), *Owner*: University of Bristol
PCT Number: PCT/GB99/01461
Inventors: Williams, N.A. & Hirst, T.R. (Morgan, A.J., Wilson, A.D. & Bird, L.)
Status: Granted Czech Republic, Eurasian Patent Organisation, Israel, Japan, Mexico, US.

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

EtxB is a first in class disease-modifying therapy, with potential utility across a range of human diseases in which there is a unmet need: 125 million people suffer from psoriasis worldwide[a]; approximately 5.5 million people in the UK are being treated for asthma;[b] and rheumatoid arthritis affects approximately 0.5-1.0% of the population.[c] These and other inflammatory diseases are currently treated with chronically administered non-specific drugs, which primarily control damage rather than impacting on the underlying drivers of disease. In contrast, a short course of EtxB can turn off these processes for long periods,[1,4,6] resetting the balance between inflammation and normal physiology.[4,5] This is a novel and exciting new paradigm for treatment.

Williams spun out the EtxB patent portfolio (1999), subsequently rolled into the formation of Trident Pharmaceuticals Inc,[d] established in 2006 to bring EtxB (company code HF1020) through Phase II trials before seeking a large pharmaceutical partner. Williams remains an integral part of the team and KWS (see below) has performed all the preclinical work on EtxB. All 11 substantiating papers cited on the Trident website were published by Williams. Trident generated GMP material (2008-2011) and tested this in formal GLP acute and repeat dose toxicology studies in rodents and primates (completed in 2011). It was found to be safe and in 2011 the MHRA approved a clinical trials application (CTA) for a Phase 1a study in healthy volunteers. Following completion of Phase Ia, in 2013 the MHRA approved a CTA for a Phase II study *[text removed for publication]*. As with all new drugs, the process of getting them to market takes years, but EtxB has already passed many of the major hurdles. Press coverage of its potential impact included articles in international newspapers, television and radio.[e] Other companies including Hunter Immunology are developing approaches to mimic the effects of EtxB using novel peptides that target the same receptor.[f]

The underlying research and the experience gained by Williams of developing EtxB directly gave rise to the formation of KWS BioTest Ltd. Coverage of his work on EtxB established him as a leader in disease efficacy and mechanism of action studies, and repeated requests for work came in from companies wanting to access these models:

- Williams formed KWS BioTest in 2004,[g] with Professor Day (veterinary pathology).
- KWS received £200k of investment from a Government Challenge Fund[h] to employ scientists and commercial management and respond to these requests.
- KWS is now a leading partner for high quality drug discovery and efficacy in Europe, an achievement that was recognised by the award of the 2012 South West Biomedical iNet award for outstanding business achievement.[i] KWS runs validated *in vitro* and *in vivo* models of human disease in inflammation, autoimmunity, pain and infection, all of which are founded on the academic work of the Williams laboratory and other groups within Bristol.

The success of KWS is based on offering in-depth scientific expertise and analysis of the sort that is lacking in large contract research organisations, while providing service and data quality that are lacking from academia (ISO9001 accredited, GLP led). These activities have generated substantial commercial impact directly within KWS and for partner companies, and have contributed to the discovery of new drugs now in clinical trials and development (details of which are confidential).

Since 2004, KWS has carried out experimental studies for more than 75 different companies (39% UK, 44% EU, 12% US, 5% rest-of-the-world; 57% small, 24% medium and 19% large pharma).[j] In the case of small companies, this work has been absolutely critical as they typically lack expertise and facilities to carry out pharmacology testing. In the case of medium and large pharma, partners want the expertise that it can offer, recognising that outsourcing is a more cost-effective and ethical approach to drug discovery.[k]

Dr Sean Mason (Senior Group Leader at UCB) stated "*KWS have provided excellent, high quality scientific support for several projects, covering a range of diverse activities including complex immune cell-based assays and imaging studies, which together with their prompt and detailed feedback has benefited several of our projects*". The ability of KWS to provide *in vivo* efficacy models that are validated with control drugs, and which are run regularly, has a clear 3Rs impact.

Since its formation, KWS has expanded and grown as evidenced by:

- Increased turnover from *[text removed for publication]*.[j].
- Profits have grown from *[text removed for publication]*.
- KWS employs *[text removed for publication]*, and during 2012 contributed *[text removed for publication]* of income to the University of Bristol.
- KWS has become a significant exporter (over *[text removed for publication]* in the last three years).
- Strategic partnership with Quotient Bioresearch facilitating further exports from these companies.

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

[a] National Psoriasis Foundation http://www.psoriasis.org/learn_statistics. *Corroborates the prevalence of psoriasis worldwide.*
[b] Asthma UK http://www.asthma.org.uk/news-centre/facts-for-journalists/. *Corroborates the prevalence and health impact of asthma on the UK population.*
[c] Center for Disease Control (US) http://www.cdc.gov/arthritis/basics/rheumatoid.htm#5. *Corroborates the global prevalence and health impact of arthritis.*
[d] Trident Pharmaceuticals Inc. http://www.tridentpharma.com/index.html. *Main company website for Trident highlighting the current status of the therapy underlining the impact case and demonstrating that this is the sole focus for the company.*
[e] Television and radio**:** *ITN National News* (30 November 1999); *Radio 4 'Science Now'* (January 2000); *Portuguese National Radio* (September 2003); *Dutch National Radio* (Sept 2003); *BBC Radio 5 Live* (September 2003). Print media: *The Daily Mail* (1 December 1999); *New Scientist* (4 December 1999); *The Times* (4 February 2000); *Vogue* (March 2000). *Provide evidence of impact in raising public awareness of the health issues and of potential new approaches to developing therapies for human disease.*
[f] Patent licensed by Hunter Immunology, now Bioxyne. *Evidence that the technology pioneered in Bristol has led other companies to adopt similar approaches (commercial impact and impact amongst peers).*
[g] KWS BioTest http://www.kwsbiotest.co.uk. *Evidence of the current scope of the activities of the spin-out arising from the research and vehicle for the impact.*
[h] Wyvern Investment Fund http://www.wyvernfund.com/. *Evidence that KWS received investment from and remains part of the portfolio of companies within the Wyvern Government Challenge Fund (economic impact).*
[i] Outstanding business award (http://www.inets-sw.co.uk/; Drug discovery Impact 1.pdf). *Evidence of peer recognition of the Economic and Business Impact of KWS BioTest.*
[j] KWS Operating Plan summary 2012 (Confidential document that can be provided for audit purposes). *Evidence of the economic impact of KWS BioTest (CONFIDENTIAL).*
[k] Clark DE (2011) Outsourcing lead optimisation: the eye of the storm. *Drug Discovery Today* 16:147-157. DOI: 10.1016/j.drudis.2010.11.012. *Evidence of the growing business and economic need for the services of KWS Biotest from Biotech and Pharmaceutical Companies.* PMID: 21145413.