Institution: University of Bristol

Unit of Assessment: 1 – Clinical Medicine

Title of case study: New businesses, commercial investment and adoption of new technology result from antigen-specific peptide immunotherapy development.

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

By identifying a novel approach to treat allergy and autoimmune disease the University of Bristol has created a new field of research into antigen-specific peptide immunotherapy. Initial work carried out by Professor David Wraith at the University has since 2008 led to the creation of new businesses, (including the spinout company Apitope), generated 100s of millions of pounds of investment and underpinned both the adoption of new technology and the development of new products by the pharmaceutical industry. The commercial impact of this research into antigen specific immunotherapy is on-going and expanding.

2. Underpinning research (indicative maximum 500 words)

Developed by the University of Bristol, Antigen-Specific Peptide Immunotherapy (ASPI) is a unique approach to treating autoimmune diseases and allergies that selectively targets and effectively neutralises the underlying causes of these conditions. ASPI does not appear to have the damaging side effects of other treatments for these diseases, making it an attractive technology from both a commercial and health perspective.

Autoimmune disease is triggered by our immune system incorrectly perceiving one of the proteins or tissues that compose our bodies as a threat. For example, multiple sclerosis (MS) is primarily caused by immune cells attacking myelin, a group of proteins (MBP, PLP and MOG) that insulate the neurons within our brain and spinal cord. In 1998 Professor David Wraith (Professor of Experimental Pathology, 1995 to present) and Dr Steven Anderton (Research Associate in Pathology and Microbiology 1995 to 2000) presented research carried out at the University of Bristol demonstrating that treatment with select, soluble peptides, derived from myelin, inhibited disease progression in a mouse model of MS.[1] These peptides were identified as being the specific (antigenic) regions of myelin that aberrant immune cells react against.

That same year Professor Wraith also identified that treatment with just one of these peptides was able to protect all the components of myelin from immune attack.[2] This cross-protective effect suggested these peptides could be a powerful therapeutic agent in the treatment of complex, multi-antigen immune disorders.

Further research carried out at the University of Bristol established the key requirements for identifying and designing these therapeutic peptides. In a 2002 paper, Professor Wraith and his team revealed that in order for a peptide to suppress disease it must be 1) able to interact directly with immune cell receptors without any additional processing by the body, 2) in a conformation that mimics the form naturally created by cellular breakdown of the original target protein.[3]

In 2003, working with Dr Anette Sundstedt, a research fellow in his laboratory at the University of Bristol, Professor Wraith discovered that these therapeutic peptides generated a unique population of immune cells within treated mice.[4] Referred to as T-regulatory cells (Tregs) they were able to specifically suppress the immune response against myelin. Of key commercial interest, it was found that this tolerising effect only persisted with succeeding administrations of peptide.[4]

Summarised in a 2005 seminal paper,[5] Professor Wraith's research at the University of Bristol established the medical potential of ASPI, the means to create these therapeutic peptides and the mechanism by which they worked.

In 2008 Apitope, a University of Bristol spinout company founded by Professor Wraith, carried out a study in which six human MS patients were treated with ATX-MS-1467. These preliminary data showed the peptides to be safe and well tolerated with preliminary evidence of efficacy.[6] A further trial in relapsing remitting MS patients (43 subjects) has confirmed that the treatment is safe. Examination of the MRI results demonstrated a significant decrease in the number of contrast-enhancing brain lesions in patients with relapsing multiple sclerosis treated by intradermal injection of ATX-MS-1467 (http://www.apitope.com/News/index.html). These encouraging results have provided the rationale for continuing Phase II trials in MS.

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

[1] Anderton, S.M., Burkhart, C., Liu, G.Y., Metzler B. & Wraith, D.C. Antigen-specific tolerance induction and the immunotherapy of experimental autoimmune disease. *Novartis Foundation Symposium* 215, 120-136 (1998) PMID: 9760575

[2] Anderton, S.M. & Wraith, D.C. Hierarchy in the ability of T cell epitopes to induce peripheral tolerance to antigens from myelin. *European Journal of Immunology*, 28, 1251–1261 (1998) PMID: 9565365

[3] Anderton, S.M., Viner, N.J., Matharu, P., Lowrey, P.A. & Wraith D.C. The influence of a dominant cryptic epitope on autoimmune T cell tolerance. *Nature Immunology* 3, 175-181 (2002) PMID: 11812995

[4] Sundstedt A, O'Neill EJ, Nicolson KS & Wraith DC. Role for IL-10 in suppression mediated by peptide-induced regulatory T cells in vivo. *Journal of Immunology*, 170, 1240–1248 (2003) PMID: 12538682

[5] Larché, M. & Wraith, D.C. Peptide-based therapeutic vaccines for allergic and autoimmune diseases. *Nature Medicine*, 11, pp.S69–S76 (2005) PMID: 15812493

[6] Streeter HB, Pillai S, Scolding NJ & Wraith D.C. ATX-MS1467 a therapeutic peptide vaccine for treatment of multiple sclerosis (Abstract). *Multiple Sclerosis* 14:S185 (2008) DOI:10.1177/1352458508096399

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

Creation of new businesses

Apitope, a University of Bristol spinout company, was established by Professor Wraith in 2002. Apitope develops peptide therapeutics for a range of autoimmune disorders, and currently has five product candidates in its pipeline and employs 26 individuals based in three key sites across the UK and Europe.

Since the University of Bristol's initial research into ASPI was published, a series of patents, start-ups and spin-outs have established themselves, each developing peptide therapeutics for a variety of autoimmune and allergic disorders. Each company listed has made direct reference to Professor Wraith's laboratory at some stage in their initial research and discovery process. Additionally Professor Wraith has collaborated or been in direct communication with the majority of founding researchers listed below.

Circassia was established by Professor Mark Larché who co-authored with Professor Wraith – Circassia is a bio-pharmaceutical company specialising in peptide therapeutics targeted against a range of allergies. Circassia's pipeline currently includes treatments for: cat dander, ragweed, house dust mite, grass, birch and Japanese birch pollen, Alternaria, and dog hair.

ImmuPharma PLC is European pharmaceutical company founded upon Lupuzor, a peptide therapeutic for systemic lupus erythematosus (SLE). ImmuPharma has five drug candidates in development, two platform technologies and approximately 70 patents. ImmuPharma has won several awards including "Best Technology 2009" at the AIM Awards – sponsored by PricewaterhouseCoopers LLP and "Best Medical Research & Development Company – Europe" at the 2012 New Economy's Healthcare awards.[f]

Based in Yavne, Israel Andromeda Biotech is currently in phase III clinical trials for DiaPep277, a peptide therapeutic designed to treat type 1 diabetes.

Industrial investment

Work at Apitope has attracted a high level of investment from industry. In 2008, Apitope received €10 million (~£8.4 million) from an investment consortium based in Belgium for continued research into peptide therapeutics for multiple sclerosis, type 1 diabetes and type A-haemophilia.[a] The following year Apitope entered a licensing agreement worth €154 million (~£130 million) with pharmaceutical industry leader Merck Serono focused on commercialisation of Professor Wraith's ATX-MS-1467 compound.[b] In the Spring of 2013 Apitope received €5.925 million in funding from the European commission for their continued research into therapeutics for Graves' disease [c].

Circassia has successfully completed five fundraising rounds, yielding a total of approximately £105 million.[d] ImmuPharma announced in May 2013 that it has secured a £50 million, five year Equity Financing Facility to fund their late stage Lupuzor compound.[e] In 2010 Teva Pharmaceuticals Ltd invested in Andromeda at a company to money valuation of $170 million (~£111 million). This followed a $13.5 million investment by Teva the previous year.[f]

Adoption of new technology

As a result of its work with Apitope, Merck Serono is continuing investigation into ASPI, initiating its own clinical trial into the efficacy of ATX-MS-1467 as a treatment for multiple sclerosis.[g] Additionally GlaxoSmithKline has joined with Apitope in discovering peptide therapeutics for Graves' disease, an autoimmune condition affecting the thyroid.[c]

The development of new products

A number of candidate products have been created using ASPI, several of which have entered late stage clinical trials. Three of these products are described below:

DNAJP1

Developed through research at Utrecht University, the Netherlands, DNAJP1 is a therapeutic peptide created to treat rheumatoid arthritis. DNAJP1 is currently licensed by the biotechnology company Synthetic Biologics and is undergoing clinical trials to judge its efficacy.[h] Early work on development of DNAJP1, published in 1997, referred to the ASPI approach described by Professor Wraith at the University of Cambridge.[i]

Dirucotide

Derived from myelin basic protein (MBP) and developed by BioMS, a spin-out from the University of Alberta, Canada, Dirucotide is currently under licence by Medwell Capital Corp, and pharmaceutical company Eli Lilly. The therapeutic reached phase III trials in 2009 for the treatment of multiple sclerosis but is currently under review to determine its efficacy.[j] The description of the first clinical trial on Dirucotide, published in 2006, refers back to the original ASPI work from Professor Wraith's laboratory in Cambridge.[k]

Patent US 7858738 B2 Synthetic human peptides and pharmaceutical compositions comprising them for the treatment of systemic lupus erythematosus

A patent was published in 2010 by Yeda Research and Development Co for a pair of therapeutic peptides aimed at treating the auto-immune disease myasthenia gravis. The work preceding this patent directly references Professor Wraith's research carried out at the University of Bristol.[l]

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

[a] Apitope press release 22/10/2008: http://www.apitope.com/Downloads/Archive/221008.pdf
This press release announces the successful completion of a EUR 10M series A financing round for Apitope International NV to develop its ASPI approaches.
[b] Apitope press release 13/01/2009: http://www.apitope.com/Downloads/Archive/130109.pdf
This press release announces the signing of an agreement between Apitope and Merck Serono whereby Apitope is eligible to receive up to €154 million in upfront, development and milestone payments from the development of its ASPI treatment for MS.
[c] EU Commission CORDIS: http://cordis.europa.eu/projects/rcn/110669_en.html
The CORDIS website provides details of the DAVIAD project designed to support development of ASPI treatments for Graves' disease by Apitope International NV and GSK-BIO.
[d] Circassia web page: http://www.circassia.co.uk/company/investors/
This page lists the investors who have provided Circassia with the ~£105 million in funds required to develop ASPI treatments for allergic disorders.
[e] ImmuPharma web page: http://www.immupharma.org/news/2013
This page refers to the £50 million facility allowing ImmuPharma to complete Phase III development of its ASPI approach to the treatment of SLE.
[f] Andromeda Biotech web page: http://www.andromedabio.com/page.php?pageID=67
This page refers to the $170 million investment into the Diapep ASPI treatment for type I diabetes by TEVA pharmaceutical industries Ltd.
[g] Apitope web page: http://www.apitope.com/News/index.html
This press release announces the phase II development the Apitope approach to ASPI for MS by Merck Serono (EMD Serono).
[h] Koffeman, E.C., Genovese, M., Amox, D., Keogh, E., et al. Epitope-specific immunotherapy of rheumatoid arthritis: Clinical responsiveness occurs with immune deviation and relies on the expression of a cluster of molecules associated with T cell tolerance in a double-blind, placebo-controlled, pilot phase II trial. *Arthritis & Rheumatism* 60, 3207-3216 (2009) PMID: 19877047
This paper describes the phase II development of dnaJP1, the ASPI approach for the treatment of rheumatoid arthritis.
[i] Prakken, B.J., *et al.* Peptide-induced nasal tolerance for a mycobacterial heat shock protein 60 T cell epitope in rats suppresses both adjuvant arthritis and nonmicrobially induced experimental arthritis. *Proc Natl Acad Sci U S A* 94, 3284-3289 (1997) PMID: 9096385
This paper refers to the ASPI work of Professor Wraith's laboratory in Cambridge that provided the motivation for development of dnaJP1 for the treatment of rheumatoid arthritis.
[j] Markowitz, C. Dirucotide (MBP8298) for the treatment of multiple sclerosis. *Therapy* 5, 605-612 (2008) DOI: 10.2217/14750708.5.5.605
This paper reviews phase I and II data on Dirucotide, an ASPI for MS.
[k] Warren, K.G., Catz, I., Ferenczi, L.Z. & Krantz, M.J. Intravenous synthetic peptide MBP8298 delayed disease progression in an HLA Class II-defined cohort of patients with progressive multiple sclerosis: results of a 24-month double-blind placebo-controlled clinical trial and 5 years of follow-up treatment. *Eur J Neurol* 13, 887-895 (2006) PMID: 16879301
This paper refers to the ASPI work of Professor Wraith's laboratory in Cambridge that provided support for development of Dirucotide for the treatment of MS.
[l] Ben-David, H., Sela, M. & Mozes, E. Down-regulation of myasthenogenic T cell responses by a dual altered peptide ligand via CD4+CD25+-regulated events leading to apoptosis. *Proc Natl Acad Sci U S A* 102, 2028-2033 (2005) PMID: 15677327
This paper refers to the ASPI work of Professor Wraith's laboratory in Bristol that provided insight into the mechanism of ASPI for the treatment of autoimmune diseases.