Institution: University of Strathclyde

Unit of Assessment: 3

Title of case study: Economic benefit and competitive advantage from commercial adoption of an innovative non-invasive delivery method for drugs and vaccines

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

Research into non-ionic surfactant vesicles (NIV) led to the development of an innovative platform system for delivery of vaccines and drugs, either through oral administration or inhalation. The technology was licensed to a US company, VBI Vaccines in 2008 and led to product development in that company. The adoption of the technology supported the creation of 35 FTE jobs in US/Canada and attracted 50% of the licensor company's Series A VC investment (approximately $18M). It was also adopted by Morvus Technology Ltd. (2010). The University collaborated with Biovaxpahrma Ltd to create a new biotechnology spin out Inhalosome-C, which was awarded a £196k TSB grant in December 2012. The technology is currently being used in commercial R&D in two further companies, Aptuit Ltd and Philips Respiratory Drug Delivery.

2. Underpinning research (indicative maximum 500 words)

Context

Non-ionic surfactant vesicles (NIV) have a synthetic bi-layer that mimics naturally derived cell membranes. These make them chemically stable in a biological environment, with very low toxicity. The Strathclyde research into NIV as a system for drug delivery led to a non-invasive delivery, directly to the site of therapeutic need. This method negates the need for injections removes cold chain storage and enables lower doses of drug to be used therapeutically, increasing treatment options and reducing manufacturing costs, all of which are desirable attributes by both consumers and the pharmaceutical industry. Delivery systems have been used to improve drug treatment and vaccination as they can target the incorporated therapeutic to the site of action and protect it from degradation. This ensures that sufficient quantities of the therapeutic are present to kill the pathogen (with respect to drug) or to elicit the appropriate immune response (with respect to vaccine). A successful delivery system must give high entrapment values for the relevant therapeutic, favourably modify its *in vivo* pharmacokinetics, allow treatment by different routes of administration, and have the potential to be adapted so that it can be used with a range of therapeutics. This is challenging as the delivery system must incorporate therapeutics with different physiochemical properties, be non-toxic, be stable on storage and have a simple manufacture method to make it economically viable as a product.

Key findings: The core technology, non-ionic surfactant vesicles, has led to two parallel streams of research for two administration routes (oral and inhalation) using two therapeutic agents (vaccines and drugs respectively). The purpose of the core technology was to produce a delivery system that not only resulted in improved therapeutic efficacy but allowed treatment by a non-invasive route and could be manufactured on a commercial scale. We originally demonstrated that NIV could be used to improve the delivery of a number of antileishmanial drugs and identified the optimal NIV formulation for the delivery of sodium stibogluconate (SSG) in a World Health Organisation funded project [References 1 and 3]. We demonstrated that this formulation was effective against *Leishmania donovani*, a major parasitic disease that causes significant mortality in endemic countries, could be manufactured using a method suitable for large-scale production, and pre-clinical toxicology studies in rats showed that it was safe. We also demonstrated that the SSG-NIV formulation was more effective in dogs than conventional treatment with SSG solution, an important finding as the dog can act as the reservoir host for *Leishmania* and canine leishmaniasis is a significant veterinary health problem. We then extended our studies to demonstrate that NIV could be used for the oral delivery of proteins for vaccination and that vaccination using this formulation was not only more effective that similar vaccination with protein solution as it not only induced higher antibody titres, it also induced a cell-mediated immune responses. Inclusion of bile salts into the formulation helped to protect the incorporated protein from degradation in the gastro-intestinal tract [References 2, 4 and 5]. We named this type of formulation 'Bilosome' to give it its own identity and showed that lyophilisation of Bilosomes removed the requirement for cold storage. The high efficacy of Bilosomes was demonstrated in a ferret model (gold standard for influenza) where oral immunisation induced higher antibody responses and reduced the time of infection

compared with a commercially available injectable vaccine. The Bilosome technology was licensed to Variation Biotechnologies Inc. and more recently we have identified a new method of manufacture that is more environmentally friendly and significantly reduces the time of manufacture (new patent filing). NIV can be used to deliver drugs by inhalation, resulting lung levels compared to administration by the intravenous route [Reference 6]. We have named this type of formulation 'Inhalosome' to give it its own identity and shown in a murine model of lung cancer that treatment with Inhalosome formulations of cisplatin or gemcitabine is more effective than similar treatment of drug solution by the pulmonary route. We have also shown that an amphotericin B Inhalosome formulation is more effective than amphotericin B solution in a rodent model of aspergillosis.

Key researchers and positions at University of Strathclyde: Research was carried out between 1995 and 2012 by academic staff in the School of Pharmacy and Biomedical Sciences - Dr K. C. Carter (Post-doctoral Research Fellow, Royal Society Research Fellow, Lecturer, Senior Lecturer); Dr V.A. Ferro (Post-doctoral Research Fellow, Senior Research Fellow, Lecturer), Dr A.B. Mullen (PhD student, Lecturer, Professor), Prof James Alexander (Senior Lecturer, Reader, Professor).

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

1. Williams DM, Carter KC, Baillie AJ. Visceral leishmaniasis in the BALB/c mouse: a comparison of the *in vivo* activity of five non-ionic surfactant vesicle preparations of sodium stibogluconate. J Drug Target. 1995 3(1):1-7.
2. Conacher M, Alexander J, Brewer JM. Oral immunisation with peptide and protein antigens by formulation in lipid vesicles incorporating bile salts (bilosomes). Vaccine. 2001 19(20-22):2965-74.
3. Carter KC, Mullen AB, Sundar S, Kenney RT. Efficacies of vesicular and free sodium stibogluconate formulations against clinical isolates of *Leishmania donovani.* Antimicrob. Agents Chemother. 2001 45(12):3555-9.
4. Mann JF, Shakir E, Carter KC, Mullen AB, Alexander J, Ferro VA. Lipid vesicle size of an oral influenza vaccine delivery vehicle influences the Th1/Th2 bias in the immune response and protection against infection. 2009. Vaccine, 27(27):3643-9
5. Bennett E, Mullen AB, Ferro VA Translational modifications to improve vaccine efficacy in an oral influenza vaccine. 2009. Methods 49(4):322-7
6. Alsaadi M, Italia JL, Mullen AB, Ravi Kumar MN, Candlish AA, Williams RA, Shaw CD, Al Gawhari F, Coombs GH, Wiese M, Thomson AH, Puig-Sellart M, Wallace J, Sharp A, Wheeler L, Warn P, Carter KC. The efficacy of aerosol treatment with non-ionic surfactant vesicles containing amphotericin B in rodent models of leishmaniasis and pulmonary aspergillosis infection. J Control Release. 2012 160(3):685-91.

Other evidence for quality of research

All references have undergone rigorous peer-review process prior to publication.

A portfolio of external funding from a variety of sources has supported the research. This includes total funding from the following:

World Health Organisation	1993-1998	$177,556
Scottish Enterprise/Proof of Concept:	2002-2010	£523, 523
NIH funding:	2008-2013	$4,280,909, SIPBS allocation: £350,000
Commercial sources	2007-2013	£137, 868

Examples of grant funding include

- Application of an oral delivery technology to the development of a near-to-market influenza vaccine, based on NISV technology, 2005-2006, Synergy Fund, (£150, 000), VA Ferro, J Alexander, KC Carter, AB Mullen
- Development of an oral vaccine, 2002-2004, Scottish Enterprise Proof of Concept Fund Round 3, (£162, 000), WH Stimson, J Alexander, KC Carter, VA Ferro
- Demonstration of a platform enabling delivery system for non invasive drug delivery to the lungs, 2008-2009 Scottish Enterprise Proof of Concept (£100,500) Carter, K.C., Ferro V. A., Mullen A B.,

Patents awarded or applied for:

- Vesicle Formulation. PCT/GB95/01859 Priority date 10/8/94 UK, Europe, EP0774958; USA, 5,869,091; pending in Japan, JP10504034)
- Pulmonary drug delivery published by the USPTO on 31st December 2009 under publication number US-2009-0324743-A1
- Patent Number US20110177163 Compositions and methods for treating hepatitis A - 21st July 2011
- Patent Number US 20110097418 Compositions and methods for treating influenza 28th April 2011
- Patent Number US-20120177683 Methods for preparing vesicles and formulations produced therefrom. 12th July 2012
- Patent Number US 20120156240 Methods for preparing vesicles and formulations produced therefrom 21st June 2012

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

Process from Research to Impact

The underpinning research led to two non-invasive drug delivery methods with commercial potential. The development of an effective oral delivery system for vaccines, Bilosomes, and the development of an inhalation formulation technology for delivery of drug, Inhalosomes. The inhalosome technology initially encapsulated Cisplatin for the treatment of non-small cell lung cancer, but has potential for application to all lung cancers and other respiratory diseases. Several commercial collaborations then developed involving the Research and Knowledge Exchange Service at the University of Strathclyde, leading to the following types of impact.

Commercial adoption of new technology: VBI Vaccines is a company dedicated to the innovative formulation, development and delivery of safe and effective vaccines. Their approach to vaccine development addresses significant market opportunities, and aims to fulfil critical unmet medical needs. Through a recent strategic acquisition, VBI has expanded its pipeline of thermostable vaccine programs and is also developing its own Lipid Particle based vaccines (Source A). VBI licensed the patented Bilosome technology from Strathclyde University in July 2008, and benefitted from access to the Bilosome patent. Technology transfer assistance from the Strathclyde research team has allowed VBI to further develop the Bilosome technology and they have filed further patents in related areas between 2008 and 2013. The Vice President Operations of VBI has confirmed that "*After acquiring the Bilosome technology from the University of Strathclyde in 2007 VBI has made great efforts in attempting to formulate and manufacture various antigens into effective vaccine candidates. Three of the key antigens focused on within VBI's bilosome projects were Hepatitis A, shigella and Influenza. The experiments conducted between 2008 and 2012 helped to build a knowledge base on the technology's advantages and disadvantages as an effective drug delivery platform. The existing bilosome technology was effective in its ability to induce an immunogenic response with the appropriate antigen however its manufacturing method in Chloroform was viewed as not viable for manufacturing at a commercial scale. As a consequence and based on feedback from Strathclyde scientists, VBI began evaluation of alternate manufacturing processes*." (Source B).

Following the signing of the licence agreement in 2008 VBI Vaccines achieved a Series A funding of $36M and accredit 50% of that to access to the NIV technology. This funding allowed them to employ between 35 and 40 skilled scientists in two locations in North America, working on NIV related activities (Source A).

Morvus Technology Limited is a pharmaceutical company specialising in the discovery and commercialisation of novel drugs for the oncology market (Source C). The company has the capability to generate revenue by out-licensing a number of early-stage products whilst simultaneously progressing selected candidates through clinical development and into patient trials. Morvus collaborated with the researchers at Strathclyde to understand how NIV technology could improve the solubility of certain small molecule compounds and therefore make them viable drug candidates. Success has meant that they are now looking to partner and license their IP for further development.

The Chief Executive Officer of Morvus has confirmed that "*In 2010-2012 Morvus Technology Ltd*

used the research findings of Dr K. C. Carter, Dr V. Ferro and Professor A. Mullen to help develop a formulation of their in-house drug for delivery using Inhalosomes as a treatment for lung cancer. This has involved knowledge transfer from the University to establish processes and protocols. The Strathclyde 'inhalosome' method offers significant advantages over other available delivery systems as it permits us to target (Cisplatin or drug) directly to the lung - reducing the need for intravenous delivery with associated disadvantages (discomfort to patient/side effects). The application of this technology is affecting our business plans as we anticipate it will give us competitive advantage over other pharmaceutical companies in this area." (Source D)

Investment in research and development: The University of Strathclyde has collaborated with Biovaxpahrma Ltd to create a new biotechnology spin out Inhalosome-C, which was awarded a £196k TSB grant in December 2012 to develop the NIV/cisplatin combination for inhalation delivery in lung cancer. In collaboration with Respironics Respiratory Drug Delivery Inc. a subsidiary of Philips Healthcare, the researchers are also investigating how nebulisers can be used to improve pulmonary delivery. This project is in the early stages and the Business Development Manager of Philips Respironics Drug Delivery confirms that "*Since this project commenced in July 2013 there has been a useful exchange of information. In particular, Philips Respiratory Drug Delivery (RDD) has used your research findings…to assess the Inhalosome technology in drug delivery. This has helped RDD develop processes and protocols for the in-vivo and in-vitro delivery of the NIV platform with our I-neb aerosol drug delivery device."* (Source E)

Inhalosome technology has been the subject of a technology transfer project with Aptuit Ltd, a pharmaceutical services company that delivers early to mid-phase drug development solutions. This has enabled the technology to move to proof of manufacture through the creation of suitable processes and protocols related to the manufacture of Inhalosomes encapsulating the chemotherapy drug Cisplatin. They have a successful division working on Inhaled Dosage form and formulation (Source F) and this experience of working with the University of Strathclyde Inhalosome project fits well within their expertise and areas of scientific interest. The Director of Development at Aptuit confirms that "*From February 2013 Aptuit has used the research findings of Dr K. C. Carter, Dr V .Ferro and Professor A. Mullen to successfully establish a manufacturing process for Inhalosomes as a step towards scale-up for commercial production*" (Source G).

Improved drug manufacture and delivery: The new inhalation formulation technology (inhalosomes) permits delivery of small molecule therapeutics, initially encapsulating Cisplatin for the treatment of non-small cell lung cancer, but with potential for other therapeutics for lung cancers and other respiratory diseases. The development of an oral vaccine allows for absorption of the pharmaceutically active ingredients into the blood stream from contact with the mucous membranes of the gastrointestinal tract, providing greater effectiveness of the vaccine. A further beneficial impact is the "green synthesis" of the vaccine removing the need for the use of chloroform in its preparation. The new manufacturing process with inclusion of novel lipids has been tested with Encap Drug Delivery Ltd, Livingstone and has reduced the time of manufacture. In addition both delivery systems allow the therapeutic to be given by a non-invasive method, reducing the need for trained staff (which is a requirement for intravenous delivery). This will reduce healthcare costs and increase patient compliance, particularly with those who are reluctant to take injectable medication.

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

A. http://www.vbivaccines.com/pdfs/VBI-Fact-Sheet.pdf
B. Statement via email from Vice President, Operations VBI Vaccines
C http://www.morvus.com/index.htm - Morvus Techology Ltd website
D. Statement from Chief Executive Officer Morvus Technology Ltd
E. Statement from Business Development Manager, Respironics Respiratory Drug Delivery, Philips Healthcare
F Aptuit website http://www.aptuit.com/Services/Inhaled-Dosage-Form-Development-and-Manufacture.aspx
G. Statement from the Director of Development, Aptuit Ltd.