Institution: University of Aberdeen

Unit of Assessment: 5 - Biological Sciences

Title of case study: Commercialisation of shark antibodies as a platform for biologics drug discovery and development

1. Summary of the impact

Together the University of Aberdeen and Aberdeen city have become a major centre for biologics, the synthesis of medicines from compounds derived from living organisms. Commerce and industry have invested heavily in the process, creating specialist knowledge, jobs and an internationally-recognised network of expertise that promises further growth. This has arisen from ground-breaking research in Aberdeen into the VNAR antibody class that are the smallest binding sites so far identified in the animal kingdom and led to the validation of a new drug discovery platform. Spin-out companies were created (Haptogen Ltd, Cyclogenix Ltd and the pre-commercialisation vehicle Elasmogen) to exploit the emerging technology, which has completed successful efficacy trials in several animal models including late stage pre-clinical models, with trials in humans expected.

The claimed impact is therefore that: spin-outs have been created, highly skilled people have taken up specialist roles in companies; industry and venture money has been invested in patent protected research and development, business has adopted a new technology, award winning industry collaborations have been forged and jobs have been created.

2. Underpinning research

Antibodies are proteins used by the immune system to identify and neutralise foreign objects such as bacteria and viruses. The antibody does this by binding very precisely onto the object to be targeted in a way analogous to a particular key fitting a particular lock. This binding mechanism allows an antibody to tag a microbe or infected cell for attack by other parts of the immune system or to attack it directly itself. Monoclonal antibodies, (mAbs), are so called because they are cloned from the same unique parent cell, which means they all lock onto the same 'key' on the target object. They can thus selectively target a particular disease-causing element, acting as a "magic bullet" against the disease. Animals are used to produce mAbs, for example by fusing cancer cells with the cells making antibodies from specifically immunised mice or rabbits. Humanised versions of mAbs made in this way can be grown in laboratories in unlimited quantities and have become some of the world's bestselling drugs, with worldwide sales of over $40 billion in 2011, with continued rapid growth predicted.

The success of mAbs has encouraged pharmaceutical companies to explore new ways of retaining the disease specificity of mAbs whilst creating them in simpler, cost-effective formats. The University of Aberdeen has taken a leading role in developing this technology. Andy Porter joined Aberdeen in 1991; he is currently Professor of Medical Biotechnology and Director of the Scottish Biologics Facility at the University's Institute of Medical Sciences. Porter's research in this area goes back to the year 2000 and was carried out in collaboration with the University of Maryland in the US. It focused on a type of mAb with an exceptionally small molecular weight, derived from shark antibodies and known as VNAR (variable-domain new antigen receptor). In 2000, Porter and his PhD student Helen Dooley demonstrated for the first time (with publication delayed to protect intellectual property) the generation of monoclonal VNAR using antigen challenge combined with phage display antibody engineering techniques [1]. High affinity, high specificity binders successfully isolated in the process were only 10% the size of a typical human mAb. The team then went on to show, using *in vitro* affinity maturation techniques along with the combinatorial power of synthetic libraries (100 million clones) that this new class of mAb was particularly amenable to antibody engineering and drug discovery technologies. They were also able to demonstrate that the specificity of a VNAR could be altered by genetic engineering from antigen "A" to antigen "B" [2]. The significance of these findings has allowed the team to go on and demonstrate the potential of VNARs as a new class of therapeutic mAb whose structural stability,

ease of production and very small size, allowed them to access sites (e.g. within tumours) or drug targets that are denied to other antibody types. VNARs can also cross the brain-blood barrier (patent filed by Cyclogenix Ltd, 2012) which protects the brain from bacterial infection but also hinders the delivery of many important diagnostic and therapeutic agents, including antibodies, to the brain. VNAR technology is being explored for a range of pharmaceutical applications, including, potentially, treatments for numerous cancers, central nervous system (CNS) diseases (including Parkinson's), degenerative diseases of the eye and rheumatoid arthritis.

In 2006 early IP from this technology was licensed from the University of Aberdeen to the University's spin-out, Haptogen Ltd, a company that was eventually acquired by the US pharmaceutical giants Wyeth and then Pfizer in 2007 and 2009 respectively. In addition, this technology was one of two discovery platforms developed by a new University of Aberdeen spin-out, Cyclogenix Ltd, established in 2008 with first patents filed in 2010. In 2012/13, the University's team in the Scottish Biologics Facility filed new patents on VNAR technology that has led to the creation of a new pre-commercialisation spin-out company called Elasmogen, which is due to begin trading in early 2014. Funding of £1.65 million was raised in 2012 from BBSRC and Scottish Enterprise to support this venture by Professor Porter and Dr Caroline Barelle (Senior Research Fellow and Head of VNAR Discovery).

3. References to the research

[1] Dooley H, Flajnik MF, Porter A.J.R. Selection and characterization of naturally occurring single-domain (IgNAR) antibody fragments from immunized sharks by phage display. Mol Immunol. 40(1):25-33 (2003). *The first time that a monoclonal shark single-domain was successfully isolated. Cited 43 times.*

[2] Shao C-Y, Secombes, C.J., and Porter, A.J.R. (2007). Rapid isolation of IgNAR variable single-domain antibody fragments from a shark synthetic library. Mol Immunol. 44(4):10 (2007). *Demonstrated that in vitro affinity maturation techniques to take a shark antibody that originally recognised hen-egg lysozyme and turn it into an antibody that recognised a different protein leptin.*

[3] Title of Patent Application: ANTIGEN BINDING DOMAINS - Priority Filing Date: 12 August 2001; PCT Filing: PCT/GB2002/03715. Inventors: Helen Dooley, Andrew Porter, Martin Flajnik; Original Assignees: University of Aberdeen, University of Maryland, Baltimore.
A process for the production of an antigen specific antigen binding domain wherein the antigen specific antigen binding domain is derived from a variable region of the immunoglobulin isotype NAR found in a species of Elasmobranchii subclass. National filings grants in several regions.

[4] Title of Patent Application: SINGLE DOMAIN BINDING MOLECULE Filing Date: May 7, 2012; U.S. Provisional Patent Application No. 61/643,407; Inventors: Caroline Barelle, Mischa Müller, Valerie Calabro, Jack Bikker, John Steven Lioudmila Tchistiakova, Oleg Kovalenko, Andrea Olland
Reference: P52896US/NCB/JCS. Fully assigned by Pfizer to University of Aberdeen May 2013. A series of VNAR antibodies that specifically recognise human-serum albumin and extend the half-life of partner proteins in three animal models including late-stage preclinical models.

[5] Title of Patent: SYNTHETIC LIBRARY OF SPECIFIC BINDING MOLECULES: P56943US/ U.S. Provisional Patent Application No. 61/815,043 (23rd April 2013). Single Domain Binding Molecule: International (PCT) Patent Application No. PCT/GB2013/051183 (7th May 2013).
Assigned by Pfizer to University of Aberdeen May 2013 – final author list still under review. A library of over 100 billion synthetic VNAR domains and its use to deliver VNAR binders against a series of potential therapeutic target proteins.

Key funding associated with research: The research was initially funded by a PhD from BBSRC and later a Proof of Concept pre-commercialisation award from Scottish Enterprise. Prof Porter was supported with a Royal Society of Edinburgh Biotechnology Commercialisation Fellowship which was used to establish Haptogen Ltd in 2002. Since 2001 a portfolio of 30+ patents (5 core patents plus divisionals) with over 20 grants in territories globally has been filed by Wyeth, Pfizer,

University of Aberdeen and Cyclogenix Ltd using at their core technology that originated in the University. Funding also included an award winning KTP between Pfizer and Aberdeen University.

4. Details of the impact

Together the University of Aberdeen and the city of Aberdeen have become a major centre for the new technology known as biologics, the synthesis of medical compounds from living organisms. Much of this can be traced to Porter's earlier research on shark antibodies as a new platform for drug discovery, which led industry to adopt the new technology and invest in its research and development. Haptogen, an antibody drug discovery company spun out of the University of Aberdeen by Porter, had a leading role in the early years of this century in the "biologics revolution." In October 2007, in a deal whose figures remain confidential, Haptogen was acquired by Wyeth Inc, at that time the ninth largest pharmaceutical company in the world. Wyeth retained and grew the highly skilled research team in Aberdeen, and the new Wyeth facility, opened by Scotland's First Minister, in March 2009, became the cornerstone of growth in biologic based companies in the city, many of which were established and supported by personnel trained in Haptogen (e.g. NovaBiotics Ltd, Cyclogenix Ltd, Scotia Biologics Ltd,). The world's largest bio-pharmaceutical company, Pfizer plc, took over the Aberdeen facility in late 2009 when it acquired Wyeth, and expanded the Aberdeen facility to 25 research science jobs at its peak in 2010.

The success of this first spin-out has led to a growth in equity investment into Aberdeen spin-outs and continued commercial investment into pharmaceutical research and development. Therefore spin-out businesses and jobs have been created and highly skilled people have taken up specialist roles in companies. For example, Grampian Bio-Partners Ltd (GBP), a life sciences investment specialist, was established by members of some of the former directors of Haptogen in 2008. Staff from Haptogen have successfully spun-out companies in Aberdeen based on protein technologies, new methodologies and skills they had acquired from Haptogen. For example, Duncan McGregor became CEO of Cyclogenix Ltd, which develops novel micro-protein display scaffolds as potential drugs and employs seven staff. Keith Charlton became CEO of Scotia Biologics Ltd, producing therapeutic antibodies and employs ten staff. In addition, Soumya Palliyil and Porter head the Scottish Biologics Facility which deploys a variety of antibody and other protein scaffold platforms to support drug discovery programmes. Porter has also acted as non-executive director of NovaBiotics, since 2009, which have continued to develop strongly in the antifungal drug market leading to the development of the anti-fungal Novexatin®.

The University of Aberdeen's recent pre-spin-out vehicle, Elasmogen, based on Barelle and Porter's unique shark-derived VNAR platform and patent position, is supporting ten full and part-time posts (including commercialisation professionals in the UK) and has raised significant amounts of "investor-ready" investment (e.g. [h]) for what is planned as the next generation of antibody therapeutics. Aberdeen has established a synthetic VNAR antibody library that contains more than 100 billion unique clones. This allows the selection of VNAR leads in a few weeks rather than the months or years it used to take. A key project has been to extend the hitherto short period that some biologic drugs remain active in the human body: a product created using the VNAR library has been shown in trials to extend the half-life of certain drugs in several animal models including late stage pre-clinical models, from a few hours to over a week. It is predicted (from *in vivo* models) to extend a drugs half-life to 20 days in humans. Other programmes include bio-tools for Antibody Drug Conjugate applications, a new type of targeted therapy for cancer and inflammatory diseases.

The medium-term aim is to make Elasmogen an established biologics drug discovery company, developing products both in-house and in collaboration with larger pharmaceutical and bio-pharmaceutical enterprises. The programme of antibody generation via immunisation and the vast antibody library is protected by patent filings (3, 4, 5, [d]). The total patent portfolio for just the University, including divisional and regional grants, now stands at more than 20, with three patent families at its core. New patents from the team were filed in 2012 and 2013.

Porter and Barelle were sponsored by the British Government's Trade and Investment ministry in 2013 to visit Japan and China, where they presented their research to potential commercial partners and at scientific conferences. They presented at Europe's largest bio-partnering and bio-investor gatherings, Bio-Trinity and EPIC Biotech, both London in June 2013. The Aberdeen

team's work around shark antibodies has aroused considerable interest in the media, raising awareness and understanding of this new technology among the general public (see [h] below - all February 2013, reporting new funding for the research).

Claimed impact as defined by REF: spin-outs have been created, highly skilled people have taken up specialist roles in companies, industry and venture money has been invested in patent protected research and development, business has adopted a new technology, award winning industry collaborations have been forged and jobs have been created.

5. Sources to corroborate the impact

[a] *Evidence of successful funding:* http://www.abdn.ac.uk/mediareleases/archive/2002/pr971.hti Scottish Enterprise £190 k. A novel immuno-technology platform (Using shark antibodies to fight disease). Principal Investigator: Professor Andy Porter.

[b] *Evidence of successful licensing of the technology to Haptogen Ltd* : http://www.ft.com/cms/s/0/89083f4a-1add-11dc-8bf0-000b5df10621.html#axzz2HfLZHhAY
A Scottish biotechnology company is pioneering drug discovery techniques using the immune system of sharks after striking a licensing deal with the University of Aberdeen.

[c] *Evidence from selected articles about Haptogen Acquisition by Wyeth plc:*

- http://www.firstwordplus.com/Fws.do?articleid=8118951151594FE9A7581032E52C35A1&src=corp_site
- http://blogs.wsj.com/brussels/2012/01/30/hairy-times-for-llama-based-drug-maker/
- http://www.fiercebiotech.com/story/wyeth-boosts-drug-discovery-with-haptogen-buyout/2007-10-05[d] *Evidence of extensive patent portfolio (recent filings and global grants):* Ablett & Stebbing, (Caparo House 101-103 Baker Street, London W1U 6FQ, GB), Mewburn Ellis LLP patent attorneys (33 Gutter Lane, London EC2V 8AS) and Keltie LLP (Fleet Place House, 2 Fleet Pl, London EC4M 7ET) have been responsible for filing and prosecuting all patents between 2002 – 2012,2012-2013 and 2008-2013 respectively. A portfolio of 30 patents and divisionals has been published, with many of these already granted demonstrating that the novelty, utility and inventive step has been acknowledged by Patent offices. The costs have been borne by University of Aberdeen, Haptogen Ltd the spin-out company, Wyeth plc, Pfizer plc, Cyclogenix Ltd and recent patents by the Elasmogen vehicle and Scottish Biologics Facility.

[e] *Evidence from selected University Websites showing the added value to companies and academics across Scotland as Aberdeen University established a centre for biologics drug discovery:* www.abdn.ac.uk/sbf/

[f] *Evidence from selected Investment Websites showing how money from the acquisition of Haptogen was used to support new Univ Aberdeen spin-outs:* www.grampianbiopartners.com. Letters of support from GBP's Gate Keeper and their London law practise (JAGShawBaker LLP) and an article that describes their investment model are available.

[g] *Evidence from Selected Aberdeen University Company Websites that are part of the next generation of drug discovery companies now in the city:* www.novabiotics.co.uk. This includes a letter of support from the company CEO (Deborah O'Neil) stating how investment by ex-Haptogen employees within Grampian Bio-Partners Ltd has supported this new SME.

[h] *Evidence from various sources covering some of the news of new funding for the Elasmogen team in February 2013*:

- http://www.pharmatimes.com/article/13-02-07/Aberdeen_Uni_researchers_get_%C2%A31_5m_to_fund_shark-based_drugs.aspx
- http://www.bbc.co.uk/news/uk-scotland-north-east-orkney-shetland-21352836
- http://www.prnewswire.com/news-releases/scottish-scientists-lead-this-years-life-science-discoveries-204328231.html