Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

Oxford BioMedica: effective tools for gene therapy

1. Summary of the impact

Oxford BioMedica is an established company in the rapidly growing field of gene therapy. Founded by Professors Alan and Sue Kingsman from the Department of Biochemistry at the University of Oxford, it develops, commercialises and manufactures safe and effective vectors for use in gene therapy. Its vector system, known as LentiVector®, is based on the Kingsman's research into the biology of a family of retroviruses known as lentiviruses. The company has a portfolio of over 60 patent families, employs over 80 people and has raised almost £150 million since its foundation. Oxford Biomedica's partners include the major pharmaceutical companies Novartis and Sanofi and its vectors are being used in clinical trials to deliver treatments for leukaemia, Parkinson's disease and disorders of the eye.

2. Underpinning research

The Retrovirus Molecular Biology Group in the Department of Biochemistry at the University of Oxford was established by Professors Alan and Sue Kingsman in 1979. Since 1993 its studies have focused on the use of viruses, such as murine leukaemia virus and HIV, as potential vectors for gene-based vaccines. In landmark studies, the group first showed how it was possible to engineer the vector's genetic material to produce high titre viral stocks, and then how to finely control the production of viral coat proteins[1, 2].

The group subsequently went on to address a broader question: what is the minimum number of genes that the HIV retrovirus itself would need to function as a vector? For gene therapy, HIV has the advantage that, unlike adenoviruses or other retroviruses such as murine leukaemia virus, it is able to enter non-dividing cells such as those of the brain and nervous system. The group established that all of the genes that make the virus pathogenic could be eliminated without affecting its ability to enter cells[3]. They also showed that production of the transformed virus was increased by replacing a control element in its sequence. However, realising that the idea of HIV as a therapeutic product might be hard for clinicians and patients to accept, the Oxford scientists began to look for an alternative.

HIV is a lentivirus, so called because it is slow to incubate after entering the host cell. The genus of lentiviruses also includes equine infectious anaemia virus (EIAV), a pathogen that does not cause disease in humans and makes horses only mildly ill. The Retrovirus Molecular Biology Group therefore used the tools it had developed in their studies of HIV to reconstruct a minimal version of the EIAV virus. The group showed that this minimised virus could transduce both dividing and non-dividing cells in culture, and that it could be engineered to express surface (coat) proteins that would target it to different cell populations[4].

In 1995 Professors Alan and Sue Kingsman founded Oxford BioMedica to develop technology based on their patents, including a patent for the construction and use of lentiviral vectors[5]. From 1995 – 2001 the Kingsmans continued to direct research in the Retrovirus Molecular Biology Group and at Oxford BioMedica. Research during this period provided proof-of-principle for the translation of lentiviral gene-therapy into the setting of human disease. A publication by Oxford BioMedica in 2002 (co-authored by the Kingsmans and acknowledging Oxford University) showed that an EIAV lentiviral vector that contained the genes for three enzymes needed to synthesise the neurotransmitter dopamine could produce sustained dopamine production and functional improvement in rats with brain degeneration characteristic of Parkinson's disease[6].

3. References to the research

1. Soneoka Y, Cannon PM, Ramsdale EE, Griffiths JC, Romano G, Kingsman SM, Kingsman AJ. (1995) A transient three-plasmid expression system for the production of high titer retroviral vectors. Nucleic Acids Research 23: 628–33. Available from: http://nar.oxfordjournals.org/content/23/4/628.full.pdf+html ***Describes a new system for the generation of high titre helper-free retroviral stocks at levels 1000 higher than previously possible.***

2. Cannon PM, Kim N, Kingsman SM, Kingsman AJ. (1996) Murine leukemia virus-based Tat-inducible long terminal repeat replacement vectors: A new system for anti-human immunodeficiency virus gene therapy. Journal of Virology 70: 8234–8240. Available from: http://jvi.asm.org/content/70/11/8234 ***Describes how a murine-leukaemia virus-based vector could be used for HIV gene therapy.***

3. Kim VN, Mitrophanous K, Kingsman SM, Kingsman AJ. (1998) Minimal requirement for a lentivirus vector based on human immunodeficiency virus type 1. J Virol 72: 811–816. Available from: http://jvi.asm.org/content/72/1/811.full ***Paper addressing safety concerns over the use of the HIV virus for gene therapy by demonstrating that all viral accessory genes and proteins can be eliminated from the vector without affecting its ability to enter cells.***

4. Mitrophanous KA, Yoon S, Rohll JB, Patil D, Wilkes FJ, Kim VN, et al. (1999) Stable gene transfer to the nervous system using a non-primate lentiviral vector. Gene Ther. 6: 1808–1818. doi: 10.1038/sj.gt.3301023 ***Describes a vector based on EIAV, a virus not dangerous to humans, but which can enter both dividing and non-dividing cells*** **in vitro** ***as effectively as an HIV-based vector.***

5. Kingsman AJ, Kingsman SM. (2001) Lentiviral vectors United States patent 6235522. Available from: https://www.google.com/patents/US6235522?pg=PA2&dq=6235522&hl=en&sa=X&ei=oA3IUaH6KaGe0QXB6oCADg&ved=0CDQQ6AEwAA ***Patent filed in 1997 for retroviral vector particles capable of infecting and transducing non-dividing mammalian target cells, based on lentiviruses such as HIV.***

6. Azzouz M, Martin-Rendon E, Barber RD, Mitrophanous KA, Carter EE, Rohll JB, Kingsman SM, et al. (2002) Multicistronic lentiviral vector-mediated striatal gene transfer of aromatic L-amino acid decarboxylase, tyrosine hydroxylase, and GTP cyclohydrolase I induces sustained transgene expression, dopamine production, and functional improvement in a rat model of Parkinson's disease. Journal of Neuroscience 22: 10302–10312. Available from: http://www.jneurosci.org/content/22/23/10302.full ***Paper from Oxford BioMedica, which acknowledges Oxford University, showing that a dopamine replacement strategy using the EIAV vector provided a successful treatment method in an animal model of Parkinson's disease This result opened up the potential for the use of this vector for gene therapy of late-stage PD patients.***

Funding for research: Research was funded by grants to the University of Oxford in excess of £4.5M during the period 1993 – 2000 from the MRC, Wellcome Trust, Glaxo, BBSRC, European Commission, BBL and Oxford BioMedica.

4. Details of the impact

Arising from the Retrovirus Molecular Biology Group at Oxford University, Oxford BioMedica is a pioneer in the emerging field of gene-therapy and the production of gene therapy products. In addition to the LentiVector® platform products, it has conducted trials of its TroVax® product in cancers of the kidney, colon and prostate. It maintains a broad portfolio of over 60 patent families; it employs over 81 people (December 2012); and it has raised almost £150M since its foundation. This includes £11.6M raised in July 2012 via share pricing and open offer based on the promise of

gene-based medicines for the treatment of cancers, neurodegenerative and ocular diseases. Oxford BioMedica is currently valued at over £30M[7, 8].

The use of viral vectors to transform cells is a technology with very wide application in biomedical research, and one holding promise for clinical application in diseases including cancer and degenerative diseases of the brain. The lentiviral vector technology developed by the Retrovirus Molecular Biology Group and registered by Oxford BioMedica under the brand name LentiVector®, has proven to be an extremely safe and flexible method of delivering gene-based therapies. Oxford BioMedica was launched on the London Stock Exchange in 2001. It continues to apply genetic engineering to tackle difficult diseases, offering real opportunities to large pharmaceutical companies that would not have done this work without the academic lead.

Clinical applications of the Lentiviral® technology are rapidly becoming a reality. A form of gene therapy was granted approval in Europe for the first time in November 2012. Trial results suggest that such therapies will soon play a role in many hard-to-treat conditions. Oxford BioMedica and its LentiVector® technology have established a prominent position in the early development of this therapeutic strategy. The vector can deliver the therapeutic gene or genes of choice to the appropriate cell population without provoking a destructive immune reaction, integrate them into the host DNA without triggering changes in the expression of host genes that might lead to cancer, and enable them to be appropriately controlled to induce permanent expression of the desired proteins.

Oxford BioMedica has also established the safety and therapeutic benefit of its products in clinical applications, with several products in early-to-mid stage clinical trials. In 2008, Oxford BioMedica began a clinical trial of its ProSavin® product, designed to treat patients with Parkinson's disease who are experiencing decreasing benefits from the standard drug therapy. These trails were carried out in partnership with neurologists at the Henri Mondor hospital in Paris, and at Addenbrooke's Hospital in Cambridge. Parkinson's disease is a progressive, incurable, degenerative disease of the brain that causes difficulties with movement, resulting from the death of cells in the substantia nigra that produce the neurotransmitter dopamine. It currently affects over four million people worldwide. Treatment with ProSavin® involves direct injection into the brain of a construct containing the genes encoding three enzymes essential in the production of dopamine. The construct is delivered using the LentiVector® technology. The injection site is the striatum, an area that does not normally produce dopamine, but which is dependent for its function on a supply of dopamine produced in the substantia nigra. To date, 15 patients have received ProSavin®. The objective of the Phase I/II trial was to investigate the safety and efficacy of the product at a range of different doses. It has proven to be extremely safe and well tolerated at all doses. Patients, especially those given the higher doses, have shown significant improvements in motor function up to 12 months after treatment, and their need for the standard L-dopa therapy has either remained stable or been reduced. The company is currently optimising the product for further Phase II trials. Should the results be replicated, ProSavin® could make a substantial contribution to limiting the economic and social costs of this disabling disease[9].

In 2009 Oxford BioMedica set up a partnership with Sanofi to develop products based on the LentiVector® platform for the treatment of eye disorders[10]. RetinoStat®, currently in Phase I clinical trials, is a treatment for 'wet' age-related macular degeneration, a condition that causes severe loss of vision in older people and affects millions of people worldwide. In a single administration, it delivers two genes that prevent the development of new blood vessels in the retina[11]. Further clinical trials are under way of two candidate treatments for less common but equally disabling eye conditions: StarGen™ for Stargardt disease and UshStat® for Usher Syndrome Type 1B. These trials are the first for which FDA approval has been given for direct administration of lentiviral vector-based treatments in the US.

In 2010 the company entered a further collaboration, funded by the Motor Neurone Disease Association, to develop a treatment for amyotrophic lateral sclerosis, MoNuDin®, using the LentiVector® platform.

Since February 2011, Oxford BioMedica has operated its own manufacturing facility, certified by the Medicines and Healthcare Products Regulatory Agency to produce Investigational Medicinal Products. As well as supporting the company's clinical programmes, the facility is available to other partners who wish to develop their own products using this technology under licence. Licencees of the LentiVector® technology include MolMed, an Italian biotechnology company that uses the vector to transform haematopoietic stem cells from partially compatible donors to prevent graft rejection in leukaemia patients, a therapy (called TK) currently in Phase III trials[12]; and Immune Design, an American company working on improved vectors for cancer therapy[13].

In May 2013, Oxford BioMedica announced a contract with Novartis to manufacture clinical-grade, personalised immunotherapies using the LentiVector® technology for trials in the treatment of leukaemia and lymphoma[14]. The contract signed is worth between £2.5M and £4M over 12 months.

5. Sources to corroborate the impact

7. Oxford BioMedica plc. The way we see it: Annual report and accounts 2012. Oxford; 2012. Available from: http://www.oxfordbiomedica.co.uk/uploads/financial-report/2012-oxb-fr-annual-2012.pdf ***Confirms current financial information for Oxford BioMedica.***

8. *Current activity, patents, employee numbers etc. can be confirmed by* Oxford BioMedica plc, Medawar Centre, Robert Robinson Avenue, Oxford Science Park, Oxford OX4 4GA. Tel. 01865-783000; email enquiries@oxfordbiomedica.co.uk

9. Oxford BioMedica plc. ProSavin: An innovative gene-based therapy for Parkinson's disease. 2013. Available from: http://www.oxfordbiomedica.co.uk/uploads/fact-sheet/2013-oxb-fs-prosavin.pdf ***Oxford BioMedica factsheet describing ProSavin® and evidencing its progress through Phase I and II clinical trials.***

10. Isis Innovation Ltd, Ewert House, Ewert Place, Oxford OX2 7SG Tel. (01865) 280830 can corroborate the Sanofi licence details.

11. Binley K, Widdowson PS, Kelleher M, De Belin J, Loader J, Ferrige G, et al. (2012) Safety and biodistribution of an equine infectious anemia virus-based gene therapy, retinostat®, for age-related macular degeneration. Human Gene Therapy 23: 980–991. doi: 10.1089/hum.2012.008 ***Paper describing RetinoStat® and confirming its successful completion of safety trials.***

12. Licence of LentiVector® technology to MolMed. Available from: http://www.oxfordbiomedica.co.uk/our-licensees/ ***Description of TK and confirming its progression to Phase III trials and link to MolMed website.***

13. Partnership details between Oxford Biomedica and Immune Design Corp. Available from: http://www.oxfordbiomedica.co.uk/our-partners/ ***Description of partnership between Oxford Biomedica and Immune Design Corp describing ID-LV, a lentivector therapy for cancer, with link to Immune Design Corp website.***

14. Oxford BioMedica plc. Oxford BioMedica Announces Lentiviral Vector Development and Manufacturing Collaboration. 2013. Available from: http://www.oxfordbiomedica.co.uk/press-releases/oxford-biomedica-announces-lentiviral-vector-development-and-manufacturing-collaboration/ ***Oxford BioMedica press release evidencing the agreement with Novartis to manufacture clinical grade material utilising Oxford BioMedica's LentiVector® gene delivery technology.***