Institution: University of Oxford		
Unit of Assessment: 5 - Biological Sciences		
Title of case study: Oxford Biomedica: viral vectors for effective gene therapy		
Period when the underpinning research was undertaken: 2000-2001		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Susan Kingsman	Professor	Oct 1979 - Sep 2003
Alan Kingsman	Professor	Oct 1979 - Sep 2003
Period when the claimed impact occurred: Aug 2013 - Oct 2020		
Is this case study continued from a case study submitted in 2014? Y		

1. Summary of the impact

Oxford Biomedica is an established company in the field of gene and cell therapy, founded in 1995 by Professors Alan and Sue Kingsman based on their research in the Department of Biochemistry at the University of Oxford. Subsequent research by the Kingsman group was essential for the development, efficacy, and safety of the company's current lentiviral vector technology. The technology has been licensed to major pharmaceutical companies, who have achieved commercial and clinical success with gene and cell therapy products in several diseases. Notably, the Oxford Biomedica vector is used in the first approved chimeric antigen receptor (CAR) T cell therapy, which was approved and given breakthrough designation by the US Food and Drug Administration (FDA) in 2018 and has achieved remission in approximately 80% of cancer patients who had failed to respond to all other treatment options. This treatment has been used in more than 1,800 patients and approved in at least 25 countries. The success of their vector technology has yielded increased revenue and expansion for Oxford Biomedica.

2. Underpinning research

Background on Oxford Biomedica

The Retrovirus Molecular Biology Group in the Department of Biochemistry at the University of Oxford was led by Professors Alan and Sue Kingsman. The group focused on the use of viruses as vectors for gene-based therapies, for safely and effectively transferring genes into human cells. Their early work showed how to engineer vectors to produce high titre viral stocks (essential for scalable clinical development), how to control the production of viral coat proteins, and how all of the genes that make the virus pathogenic could be eliminated without affecting the ability of the virus to enter cells. They showed proof-of-principle for translating lentiviral gene therapy into clinical application. This work led to the founding of Oxford Biomedica in 1995, to develop the viral vector technology for gene therapy. The Oxford Biomedica vector technology is based on two lentiviruses from the retrovirus family: HIV-1 and EIAV. Work in the Kingsman laboratory continued to make essential contributions to optimisation of the vector platform being developed for clinical applications by Oxford Biomedica.

Discoveries to improve vector safety and efficacy

Research in the Kingsman laboratory in the Department of Biochemistry led to two major advances in lentivirus technology in 2000 and 2001, to address the key safety challenge of preventing the generation of infectious and dangerous virus able to replicate in a patient.

Codon optimisation: Most amino acids are specified by more than one codon in the genetic code, but the genomes of different organisms have biases in which codons are used more frequently, and codon usage alters the efficiency of gene expression. The HIV-1 genome has an extreme codon bias favouring AU-rich sequences, which is very different from that of the human genome. Efficient HIV-1 protein expression — desirable for its use as a vector — normally requires the accessory factor Rev. The Kingsman group optimised the codons in viral genes (*gag* and *pol*),

which allowed viral vectors to be made in the absence of Rev, and resulted in a 10-fold increase in protein production and no decrease in viral titre [1]. Removal of the requirement for the Rev accessory protein lifted a limitation on the development of HIV-based vectors. The codon-optimized *gag-pol* gene also provided another essential clinical safety feature in that there is no homology with natural HIV-1 or HIV-2 strains, eliminating the possibility of homologous recombination [1].

Split introns and polyadenylation signals: Inclusion of introns in expression vectors had been shown to increase gene expression in eukaryotic cells, but inclusion of introns in retroviral vectors had been problematic. In 2000, the Kingsman group, collaborating with Oxford Biomedica, developed a novel method for efficient intron inclusion that exploits the viral reverse transcription cycle and results in expressed transcripts containing a synthetic splice donor site and a downstream consensus splice acceptor site [2]. Their new vector showed enhanced expression levels and significantly improved safety over the vectors from which it was derived, as the transcripts lack a viral packaging signal [2].

The efficiency of gene expression is also influenced by polyadenylation signals, which alter the processing of transcripts. In 2001, the Kingsman group, collaborating with Oxford Biomedica, discovered that inclusion of intron-disrupted polyadenylation signals in retroviral vectors led to significant improvements in gene expression levels and reduced risk of vector mobilisation within transduced cells (i.e. decreasing the risk of virus spread) [3]. Inclusion of intron-disrupted polyadenylation signals is relatively simple and can confer these advantages to any retroviral expression vector.

These studies at the Department of Biochemistry thus created essential tools and knowledge for a novel class of retroviral expression vector with improved vector performance and safety.

3. References to the research (University of Oxford employees in bold; students underlined)

1. Kotsopoulou E, Kim VN, **Kingsman AJ, Kingsman SM**, Mitrophanous KA (2000). A Rev-independent human immunodeficiency virus type 1 (HIV-1)-based vector that exploits a codon-optimized HIV-1 gag-pol gene. *Journal of Virology* 74(10):4839-52. DOI:10.1128/jvi.74.10.4839-4852.2000 284 citations (Google Scholar, 07-2020)
2. Ismail SI, **Kingsman SM, Kingsman AJ**, Uden M (2000). Split-intron retroviral vectors: enhanced expression with improved safety. *Journal of Virology* 74(5):2365-71. DOI:10.1128/jvi.74.5.2365-2371.2000 28 citations (Google Scholar, 07-2020)
3. Ismail SI, Rohll JB, **Kingsman SM, Kingsman AJ**, Uden M (2001). Use of intron-disrupted polyadenylation sites to enhance expression and safety of retroviral vectors. *Journal of Virology* 75(1):199-204. DOI:10.1128/JVI.75.1.199-204.2001

4. Details of the impact

A vector platform for gene and cell therapy

The use of viral vectors to introduce new genes into cells is a technology with wide application in biomedical research and disease treatments. Oxford Biomedica is a pioneer in the field of gene-based therapy and the production of gene therapy products and was the first company to test lentiviral therapy in humans. The REF2014 Impact Case Study on Oxford Biomedica described how University of Oxford research contributed to impacts up to July 2013 on the early growth of the company and initial development of clinical applications of lentiviral gene therapy, specifically clinical trials for Parkinson's disease and eye disorders. Here we describe the contribution of University of Oxford research (since Jan 2000) to impacts between Aug 2013 and Oct 2020, which includes major new applications and breakthrough clinical approvals, including for blood cancers, haemophilia, immunodeficiency, and a more effective strategy for Parkinson's disease, as well as substantial commercial benefits.

Oxford Biomedica's lentivirus technology (LentiVector®) has proven to be a safe and flexible method of delivering gene-based therapies. It can deliver the therapeutic gene of choice to the relevant cell population without provoking a destructive immune response. For long-term expression, the expression cassette integrates into the host DNA without triggering changes in the expression of host genes that might lead to cancer. The gene can also be appropriately controlled to allow permanent expression of the desired proteins and thus long-term clinical benefit. Much of

Oxford Biomedica's clinical work is through partnership with pharmaceutical companies, utilising the vector technology to address specific clinical challenges.

Oxford Biomedica's LentiVector® platform is based on lentiviral vector technology research by the Retrovirus Molecular Biology Group at the University of Oxford. Specifically, the research from the Kingsman group in 2000 and 2001 is essential to the platform and products. According to the Chief Scientific Officer of Oxford Biomedica in 2020, the company's "*current success and its product portfolio has been materially contributed to by research carried out by the company and Oxford University*" [A], citing University of Oxford research [2, 3]. For example, the CSO stated: "*out of over 23 product development programmes…14 depend on the codon optimization technology developed through the work of the Department of Biochemistry*" [1], and these "*include leading gene and cell therapy product development programmes*" [A]. The CSO confirmed "*these technological developments have led to many of the deals [Oxford Biomedica] has made, including with Novartis, Bristol Myers Squibb, Orchard Therapeutics, Sanofi, Boehringer Ingelheim and Santen*" [A].

Cell therapy for advanced cancer

Kymriah (Tisagenlecleucel) is the most clinically advanced therapy based on the Oxford Biomedica LentiVector® platform. This CAR T cell therapy was developed by Novartis in partnership with Oxford Biomedica, with Oxford Biomedica as the sole manufacturer of the lentiviral vector used in Kymriah (agreement signed in July 2017 and extended in Dec 2019) [F, Bi]. In CAR T cell therapy, a patient's own T cells are specifically reprogrammed to recognise and attack their cancer cells. In August 2017, Kymriah was the first CAR T cell cancer therapy to be approved by the US FDA – the first gene-based therapy to be made available in the US – and was given breakthrough designation [C]. In August 2018 it was granted marketing authorisation in the European Union [D]. By the end of 2019 there were more than 200 treatment centres using Kymriah in at least 25 countries, including UK, Japan, Australia, and Canada [A, E].

Revenue and growth for Novartis and Oxford Biomedica: Oxford Biomedica received an upfront payment of USD10,000,000 in 2017 [F], and an agreed minimum of USD75,000,000 over 5 years in manufacturing revenues, as well as royalties [Bi]. For Novartis, net sales of Kymriah were USD278,000,000 in 2019 [E]. Novartis also holds a portfolio of more than 30 patents associated with Kymriah, and in 2019 Novartis increased manufacturing capacity in Switzerland and France in response to strong global demand for this treatment [E].

Transformative treatment for patients with relapsed or refractory blood cancers: Kymriah is approved to treat patients up to 25 years old with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia (ALL), or adults with r/r diffuse large B-cell lymphoma (DLBCL). Since 2018, Novartis has also initiated 6 trials for new or expanded indications [E]. For example, in April 2020, the FDA granted Regenerative Medicine Advanced Therapy designation to Kymriah for patients with r/r follicular lymphoma [A].

B-cell ALL is the most common cancer in children. In the pivotal trial for Kymriah (study started April 2015; published Feb 2018), approximately 83% of the 63 treated children and young adults had their cancers go into remission within 3 months, transforming their chance of survival [F]. As of Dec 2019, Novartis had provided CAR T therapies to at least 1,800 patients with leukaemia or lymphoma [G]: in each case, the cells are personalised for the patient using the University of Oxford-derived lentiviral technology. The patients receiving CAR T have poor prognosis and other treatments have failed. For example, in the UK, the National Institute for Health and Care Excellence (NICE) recommends its use for DLCBL within the Cancer Drugs Fund after failure of two or more systemic therapies, as there is no standard treatment for r/r DLBCL [H].

Evaluation of Kymriah in the real-world setting (i.e. post-trial clinical practice) has shown similar safety and efficacy compared to the pivotal trials that led to regulatory approval. Specifically, for ALL, in the trial the treatment achieved 80% remission in patients for whom all other treatments had failed, and in the real-world setting the best overall response rate (complete response, CR) was 88% (95% CI 80%-94%) [Ii]. In the real-world setting for DLBCL, the overall response rate (ORR) was 59.6% (28 of 47 patients) including 38.3% (18 patients) achieving a CR [Iii].

In 2018, the lead clinician on the Kymriah trial at the Children's Hospital of Philadelphia, USA, stated

> "*Before this personalized, cellular gene therapy, the patients…had about a ten percent chance of surviving…Hundreds of patients later, we're able to say those children who safely achieve durable remissions have a good chance of long-term disease control, and our hope is this is the last treatment they ever need*" [Ji].

The first child treated with this CAR T therapy remains cancer free after 8 years [Jii]. Thus, Kymriah provides transformative, life-saving benefit to a high proportion of treated adults and children for whom there was previously no treatment option.

Expanding CAR T therapies: Oxford Biomedica's vector system is recognised as a platform for CAR T therapy that is being harnessed for a wider range of diseases. In March 2020, Oxford Biomedica signed a new license and 5-year supply deal with Juno Therapeutics (Bristol Myers Squibb) to produce a CAR T therapy for undisclosed cancers, providing Oxford Biomedica with an up-front payment of USD10,000,000. This deal agreed that up to USD217,000,000 would be paid to Oxford Biomedica in milestones [Bii].

Gene therapy successes for pharmaceutical companies and benefits to patients lacking treatment options

Oxford Biomedica's lentiviral vector technology is also the basis for gene therapy product development programmes for several debilitating or life-threatening diseases. These products have yielded commercial benefits for Oxford Biomedica and their partner companies, with benefits to patients within clinical trials.

Parkinson's disease: Stemming from the University of Oxford-derived technological developments, since 2018 Oxford Biomedica is in partnership with Axovant Gene Therapies [A], to develop lentiviral-based gene therapy treatment for Parkinson's disease (AXO-Lenti-PD). Parkinson's disease affects an estimated 10,000,000 people globally. In 2019, the ongoing phase II trial yielded promising 3-month data from the first cohort, triggering progression to the second cohort and a USD15,000,000 milestone payment to Oxford Biomedica [Bi]. AXO-Lenti-PD is the most advanced of Axovant's products, thus contributing substantially to the company's closing public offering of USD74,700,000 in Feb 2020 [K]. In January 2020, 12-month data —considered an important timeframe for assessment of therapeutic response and durability of gene therapy— from the first patient cohort (30 patients) demonstrated 37% improvement in motor function [Bii].

Haemophilia: Haemophilia represents the largest world market for rare diseases, affecting approximately 400,000 people worldwide. In 2018, Oxford Biomedica agreed a partnership with Bioverativ, a Sanofi company, to license the LentiVector® technology to treat haemophilia with gene therapy. Oxford Biomedica received an initial payment of USD5,000,000, to be followed by milestone payments of more than USD100,000,000 [F].

Severe combined immunodeficiency: In 2018, Oxford Biomedica formed an alliance with Orchard Therapeutics for the development of *ex vivo* gene therapy, using LentiVector®, for indications including the life-threatening severe combined immunodeficiency disease ADA-SCID [Bi], which affects between 1 in 200,000 and 1 in 1,000,000 newborns. In 2019, 2-year follow-up results from 20 ADA-SCID paediatric patients treated with the LentiVector-based product OTL-101 showed an impressive 100% overall survival (OS) and 100% event free survival (EvFS), compared to 88% OS and 56% EvFS for an historical control cohort of 26 patients who underwent haematopoietic stem cell transplant [L].

Inherited retinal disease: In their first collaboration in Japan, in June 2019 Oxford Biomedica partnered with Santen to develop gene therapy for inherited retinal diseases, with undisclosed milestone payments and royalties on sales to Oxford Biomedica [Bi]. These diseases cause vision loss or blindness, often in children and young adults. The use of the University of Oxford-derived lentiviral vector system was essential for this application, as lentiviral vectors can deliver large genes to the eye, which is challenging with other vector systems.

Commercial success and expansion of Oxford Biomedica

Oxford Biomedica's product development based on the University of Oxford research has contributed substantially to the company's expansion and commercial success [A]. It maintains a

portfolio of over 60 patent families and employs more than 600 people across 6 sites, of whom more than 120 have a PhD (Oct 2020) [A, Bi Bii]. Oxford Biomedica has expanded to have a footprint of approximately 21,000m^2, including a new approximately 3,000m^2 research laboratory for LentiVector® platform innovation and an approximately 8,000m^2 facility for clinical manufacturing in Oxfordshire, both in use from 2019 [Bi]. In 2020, Oxford Biomedica agreed with AstraZeneca to produce their COVID-19 vaccine at this manufacturing facility. In 2019, the Oxford Biomedica generated revenues of GBP64,100,000 (an increase from GBP37,600,000 in 2017) [Bi]. The company is in the FTSE 250 Index with a valuation of approximately GBP700,000,000 (10-2020) [A].

5. Sources to corroborate the impact

A. Letter from Oxford Biomedica Chief Scientific Officer, Oct 2020, confirming importance of cited University of Oxford research to product development and commercial activities.

B. Oxford Biomedica (i) Annual Report 2019, (ii) Interim Report 2020 (1 Jan – 30 June), containing details of company revenues, commercial, clinical and scientific activities. https://www.oxb.com/financial-reports/2019; https://www.oxb.com/financial-reports/2020

C. US Food and Drug Administration news release announcing of approval of Kymriah, 30 August 2017. https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states

D. European Medicines Agency information on Kymriah (tisagenlecleucel), including date of marketing authorisation 22 August 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/kymriah

E. Novartis Annual Report 2019, providing details of sales, manufacturing and treatment centres for Kymriah (p70) and new trials (p39). https://www.novartis.com/news/media-library/novartis-annual-report-2019

F. Oxford Biomedica Annual Report 2017, including statement of payment from Novartis (p26), summary of Kymriah trial results (p11). https://www.oxb.com/financial-reports/2017

G. News report by BioPharmaDive, 11 Dec 2019, stating that Novartis has provided CAR-T cell therapies to approximately 1,800 patients with blood cancer. https://www.biopharmadive.com/news/novartis-kymriah-car-t-manufacturing-difficulties-cell-viability/568830/

H. NICE Guidance TA567 for use of Kymriah for DLCBL, 13 Mar 2020; recommendation 1.1 stating use in adults after 2 or more systemic therapies. https://www.nice.org.uk/guidance/ta567

I. Published abstracts from American Society of Hematology meeting, 13 Nov 2019: i) S. Grupp *et al*. DOI: 10.1182/blood-2019-129279, describing real-world experience of using Kymriah for ALL; ii) S. Jaglowski *et al*. DOI: 10.1182/blood-2019-130983 describing real-world experience of using Kymriah for DLBCL.

J. News reports stating benefits to children treated with Kymriah: i) Children's Hospital of Philadelphia press release quoting lead clinician on Kymriah trial, 4 Dec 2018; https://www.eurekalert.org/pub_releases/2018-12/chop-ipr120418.php
ii) Cancer Research Institute online feature about first child treated with Kymriah, updated May 2019. https://www.cancerresearch.org/immunotherapy/stories/patients/emily-whitehead

K. Axovant press release, stating closing of public offering, 24 Feb 2020 http://investors.axovant.com/node/8816/pdf

L. Orchard Therapeutics press release, stating 2-year follow-up data from trial of OTL-101 for ADA-SCID, 22 Feb 2019. https://ir.orchard-tx.com/node/6676/pdf