Institution: University College London

Unit of Assessment: 5 - Biological Sciences

Title of case study: BioVex: UCL spin-out company develops viral cancer therapy to phase III trial and is sold for $1bn

1. Summary of the impact

UCL spin-out company BioVex was launched in 1999 to exploit research undertaken by David Latchman at the UCL Medical Molecular Biology Unit, Department of Biochemistry. (This department is now part of the Department of Structural and Molecular Biology, UCL/Birkbeck and Latchman is now Master of Birkbeck.) Biovex worked to develop inactivated herpes simplex viruses as therapies, and a promising dual-action oncolytic vaccine for solid tumours, OncoVEX^{GM-CSF}, was taken into successful Phase II trials. In 2011 the company was bought out by Amgen for $1 billion – still the largest ever cash sale of a UK biotech – and Amgen has now taken this virus into a Phase III trial with promising initial results.

2. Underpinning research

Gene therapy, or the delivery of therapeutic DNA into human cells, is showing promise in many disease areas, but the problem of how to deliver the DNA into the relevant cells remains difficult. Viruses, which have evolved efficient DNA transport mechanisms, have proved to be effective vectors although often with serious safety concerns. In particular, it is clearly only possible to use pathogenic viruses in this way if they have been attenuated – that is, if their own genetic material has been altered so they are no longer effective pathogens.

David Latchman began work on the adaptation of herpes simplex virus 1 (HSV1) as a vector for gene therapy in 1993. This work was based on an observation (initially by Moira Brown in Glasgow) that this virus, which normally causes cold sores, can be “disabled” by the inactivation of one or more genes so that it only replicates in dividing cells. Latchman initially focused on developing a viral vector for diseases affecting the nervous system, since neurons do not divide. This work was published in a series of papers from 1996 to 2001.

Herpes viruses that lack the protein ICP34.5 are not virulent in the mammalian nervous system. Latchman and his group first showed that viruses in which either this protein alone, or this protein and the virion transactivator protein VMW65, had been inactivated, could deliver genes to cardiac and vascular muscle cells in culture **[1]** and to CNS and peripheral mouse neurons in vivo; they remained latent and expressed a reporter protein in neurons with few side effects **[2]**. These results showed proof of principle for the use of HSV deletion mutants as gene therapy vectors. Later work showed that double mutant viruses lacking two proteins, ICP27 and ICP34.5, could deliver genes to the CNS more efficiently and safely than those lacking ICP34.5 alone **[3]**. Introducing further mutations into the viruses allowed the delivery of multiple genes **[4]** and further manipulation increased the length of time that the genes could be delivered for **[5]**.

In 1999 Latchman and his senior post-doc, Rob Coffin, founded a company initially called NeuroVex to build on these discoveries and develop gene therapies based on inactivated herpes viruses. The company then turned its focus to oncology, based on the principle that these viruses will divide in, and hence lyse, rapidly dividing cancer cells. The company, renamed BioVex, thrived first at UCL and then at laboratories based in Oxford. Scientists there developed an oncolytic inactivated herpes virus vector, OncoVEX^{GM-CSF}, which has a dual action against cancer cells: it divides inside the cells and lyses them, releasing human granulocyte macrophage colony-stimulating factor (GM-CSF) which stimulates the host immune system to attack remaining cancer cells. BioVex took the drug through a successful Phase I clinical trial before moving to the US for the Phase II. In 2011, the company was bought by pharma giant Amgen, and Amgen has now reported very promising results from an initial Phase III trial of this product.

3. References to the research

[1] Coffin RS, Howard MK, Cumming DV, Dollery CM, McEwan J, Yellon DM, Marber MS, MacLean AR, Brown SM, Latchman DS. Gene delivery to the heart in vivo and to cardiac myocytes and vascular smooth muscle cells in vitro using herpes virus vectors. Gene Ther. 1996 Jul;3(7):560-6. http://www.ncbi.nlm.nih.gov/pubmed/8818642 (Copy available)

[2] Coffin RS, MacLean AR, Latchman DS, Brown SM. Gene delivery to the central and peripheral nervous systems of mice using HSV1 ICP34.5 deletion mutant vectors. Gene Ther. 1996 Oct;3(10):886-91. http://www.ncbi.nlm.nih.gov/pubmed/8908502 (Copy available)

[3] Howard MK, Kershaw T, Gibb B, Storey N, MacLean AR, Zeng BY, Tel BC, Jenner P, Brown SM, Woolf CJ, Anderson PN, Coffin RS, Latchman DS. High efficiency gene transfer to the central nervous system of rodents and primates using herpes virus vectors lacking functional ICP27 and ICP34.5. Gene Ther. 1998 Aug;5(8):1137-47. http://www.nature.com/gt/journal/v5/n8/pdf/3300700a.pdf

[4] Palmer JA, Branston RH, Lilley CE, Robinson MJ, Groutsi F, Smith J, Latchman DS, Coffin RS. Development and optimization of herpes simplex virus vectors for multiple long-term gene delivery to the peripheral nervous system. J Virol. 2000 Jun;74(12):5604-18. http://dx.doi.org/10.1128/JVI.74.12.5604-5618.2000

[5] Lilley CE, Groutsi F, Han Z, Palmer JA, Anderson PN, Latchman DS, Coffin RS. Multiple immediate-early gene-deficient herpes simplex virus vectors allowing efficient gene delivery to neurons in culture and widespread gene delivery to the central nervous system in vivo. J Virol. 2001 May;75(9):4343-56. http://dx.doi.org/10.1128/JVI.75.9.4343-4356.2001.

Peer-reviewed funding:

The Wellcome Trust (Ref: 038795). Improved HSV-1 vectors for gene therapy. August 1993 - Jan 1997 (£135,869)

The Parkinson's Disease Society (Ref 3042). (Jointly with Dr P Anderson and Dr S Brown). Gene therapy for Parkinson's disease. October 1993 - September 1996 (£111,801)

Parkinson's Disease Society (Ref MAP 96/27). (Jointly with Prof P Jenner). Safe and efficient gene therapy for Parkinson's Disease. October 1996 - September 1999 (£121,346)

Health and Safety Executive. Interactions of defective herpes simplex virus (HSV) with naturally occurring replication competent HSV: potential for recombination and/or reactivation. February 1997 - March 2000 (£239,151)

4. Details of the impact

The company, initially known as NeuroVex, was spun out from UCL with initial funding from Sir Chris Evans, one of the UK's foremost biotechnology entrepreneurs. It was incorporated as a private company in 1999, initially based at UCL with three employees. Two UK patents were granted to Latchman and Coffin in 2001, one for mutated herpes simplex viruses and their uses (CN1310765) and the other for the cell lines in which these viruses are propagated (CN1321199) **[a]**. Shortly after NeuroVex was founded, it changed focus to the development of HSV as an "oncolytic" virus therapy for solid tumours. At the same time, it entered into an agreement for Wyeth (now part of Pfizer) to continue developing HSV as a vector for delivery to the nervous system **[b]**.

Deleting the HSV protein ICP34.5 produces a virus that will replicate rapidly in rapidly dividing tumour cells but not in normal cells, eventually causing the cancer cells to burst (lyse). The company, renamed BioVex, developed an oncolytic ICP34.5-deleted virus that expressed the granulocyte macrophage colony-stimulating factor (GM-CSF) in infected tumour cells and released

it from those cells when they were lysed so targeting multiple tumours elsewhere. This virus, OncoVEX^{GM-CSF}, must be delivered by injection directly at the site of the tumour, so skin cancers seemed most appropriate for initial clinical tests. A Phase I clinical trial of this virus in thirty UK patients with advanced melanoma or skin metastases from other solid tumours showed it to be safe and well tolerated, and suggested an optimum dose **[c]**.

By the time the Phase I results were released, BioVex employed about 20-25 people, many being highly skilled scientists. Most were based in Oxford, but the company retained its links with UCL; all animal work was carried out there, and they sponsored several PhD studentships at UCL, thus contributing to the training of the next generation of UK researchers. The board, however, took the decision to move to Boston in the US before a Phase II trial, as there were better opportunities for an expanding company there. By 2009, it had grown to 75 employees **[d]**.

An international Phase II trial in 50 patients with melanoma showed that the virus was able to induce both local and site-specific anti-tumour responses **[e]**. These promising results led the giant US biotechnology company Amgen to approach BioVex with a view to a buyout, and the acquisition deal went through in January 2011 **[f]**. Amgen's purchase of BioVex for $1 billion is still the largest sale of a biotech company of UK origin in cash terms. *The Deal* magazine described the buyout as "*likely to be lauded as the industry's best value play of the year*" and its lead product, OncoVEX^{GM-CSF}, as "*potentially revolutionary*" **[g]**. An article on FT.com stated "*The deal represents one of the biggest exits of a venture capital-backed biotechnology company for many years and is a boost for the ailing European venture capital industry which has struggled with a dearth of big success stories*" **[h]**. Just as remarkably, between the launch of the company in 1999 and its purchase by Amgen it had attracted over $130m of venture capital funding from a number of investors, including $70m in Boston in 2009: the second largest venture capital raise by a biotech company in that year **[i]**. In the remaining 10 months of 2011 after the sale, BioVex reported a turnover of £4.6m and an operating profit of £154,000 **[j]**

Amgen has taken OncoVEX^{GM-CSF}, renamed talimogene laherparepvec, into Phase III clinical trials in melanoma **[k]**. A total of 439 patients from 83 study locations in the US, Canada, the UK and South Africa were randomised to receive either the vaccine or the protein GM-CSF. This is the immune stimulant that is released by tumour cells infected with OncoVEX^{GM-CSF} when they are lysed. Large Phase III clinical trials like this one always have a significant economic impact in the regions where they recruit patients, particularly with the creation and/or maintenance of highly skilled jobs in medicine and administration. Full results of the trial are expected to be reported in 2014.

Interim results from this trial presented at a meeting of the American Society of Clinical Oncology (ASCO) in Chicago in June 2013 showed that it had met a primary endpoint of a durable response rate that is statistically longer in the vaccine arm than the GM-CSF (control) arm, and that there were early indications that the vaccine arm will also show an increase in overall survival **[l]**. In an interview with *Forbes* magazine, Amgen's former research chief Roger Perlmutter highlighted research at BioVex and in particular the work of Latchman's colleague and protégé Rob Coffin in developing this promising novel therapy **[m]**.

5. Sources to corroborate the impact

[a] UK Patents held by DS Latchman and RS Coffin http://www.boliven.com/patent/CN1310765

- CN1310765 (A) - Mutant herpes simplex viruses and uses thereof (2001)
- CN1321199 (A) - Cell lines for propagation of mutated herpes viruses (2001)

[b] Agreement between BioVex and Wyeth, for Wyeth to take over investigating HSV delivery to the nervous system: http://www.prnewswire.co.uk/news-releases/biovex-announces-agreement-with-wyeth-pharmaceuticals-154607305.html (2002)

[c] Hu JC, Coffin RS, Davis CJ, Graham NJ, Groves N, Guest PJ, Harrington KJ, James ND, Love

CA, McNeish I, Medley LC, Michael A, Nutting CM, Pandha HS, Shorrock CA, Simpson J, Steiner J, Steven NM, Wright D, Coombes RC. A phase I study of OncoVEXGM-CSF, a second-generation oncolytic herpes simplex virus expressing granulocyte macrophage colony-stimulating factor. Clin Cancer Res. 2006 Nov 15;12(22):6737-47. http://dx.doi.org/10.1158/1078-0432.CCR-06-0759

[d] http://www.xconomy.com/boston/2009/11/10/biovex-nails-down-another-30m-to-finish-pivotal-study-of-cancer-killing-virus/

[e] Kaufman HL, Kim DW, DeRaffele G, Mitcham J, Coffin RS, Kim-Schulze S. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma. Ann Surg Oncol. 2010 Mar;17(3):718-30. http://dx.doi.org/10.1245/s10434-009-0809-6

[f] Amgen to Acquire BioVex, a Privately Held Biotechnology Company Headquartered in Woburn, Mass. Amgen Press Release, 24 Jan 2011. http://www.amgen.com/media/media_pr_detail.jsp?releaseID=1519312

[g] M&A Deals of the Year: Amgen-Biovex (posted 20 January, 2012). Copy available on request.

[h] FT.com article (posted 25 Jan 2011) available from http://www.ucl.ac.uk/advances/files/biovex-exits

[i] Summary on founder investors' site: http://www.excalibur-group.co.uk/portfolio/biovex

[j] BioVex Ltd annual report for the period 5 March 2011 to 31 December 2011, available on request.

[k] ClinicalTrials.gov record for Phase III trial: http://clinicaltrials.gov/show/NCT00769704

[l] Interim results from same Phase III trial: Andtbacka, R.H.I., Collichio, F.A., Amatruda, T. and others. OPTiM: A randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma. J Clin Oncol 31, 2013 (suppl; abstr LBA9008) http://meetinglibrary.asco.org/content/117592-132

[m] Article by Matthew Herper on Forbes.com (19 March 2013) quoting Amgen's former Director of Research, Roger Perlmutter, as saying "Robert Coffin has done a really good job of developing this particular oncolytic virus" … "you can't doubt that the administration of the virus is having an effect". http://www.forbes.com/sites/matthewherper/2013/03/19/modified-cold-sore-virus-shrinks-melanoma-tumors-amgen-says/