Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

BioAnaLab Limited: a contract analytical laboratory

1. Summary of the impact

BioAnaLab's mission is to advance innovative biopharmaceuticals, such as therapeutic antibodies for cancer treatment, into the clinic. From 1995, the University of Oxford pioneered methodology essential for validating top quality therapeutic antibodies and monitoring their activity in patients. This expertise led to the establishment in 2002 of BioAnaLab, a successful Isis Innovation spin-out company. By 2009 BioAnaLab employed 50 staff providing analytical services to approximately 100 pharmaceutical and biotechnology companies worldwide and had annual sales exceeding £3.13 million. BioAnaLab was subsequently acquired in 2009 by Millipore Corporation to become an integral part of Merck/Millipore's global drug discovery unit.

2. Underpinning research

Biopharmaceuticals, which include therapeutic monoclonal antibodies, vaccines and hormones, offer exciting new options for the effective treatment of a wide range of diseases. There is an increasing demand for their production and use, to permit specific and effective treatment of diseases such as cancer and autoimmune disease. Not only do they possess significantly higher potency and greater specificity than the small molecule pharmaceutical drugs used in many current therapies, they can also be manufactured to provide personalised treatment for patients.

The Therapeutic Antibody Centre (TAC) was established in 1995, by Professors Herman Waldmann and Geoff Hale of the Dunn School of Pathology at the University of Oxford. The aim of TAC was to become a leading academic Good Manufacturing Practice (GMP) facility for the production of therapeutic monoclonal antibodies worldwide. The Oxford researchers pioneered methods to measure the levels of these antibodies in patients during treatment, as well as to evaluate the patient's own antibody response to the therapeutic agent[1-4]. Such information was essential to ascertain the safety and efficacy of the therapy.

Two pieces of research applied to the production of the therapeutic antibody alemtuzumab were key to the founding of the company, enabling it to develop core services that could be offered to other users. First was the development of an accurate sandwich enzyme-linked immunoassay assay (ELISA) to measure the level of a patient's own immune response against a therapeutic antibody[1]. Second was the development of a reliable flow cytometric assay to measure the concentration of the therapeutic antibody present in patient's serum[2]. These innovations were achieved through research carried out at TAC between 1996 and 1999. The research overcame technical issues, provided proof of principle, and led to bioassays with high sensitivity and robustness that could become industry standards.

The essential step leading to the formation of BioAnaLab in 2002 was the rigorous validation of these two assays according to guidelines that were just being developed in the industry, and their application to the measurement of blood samples from a number of different clinical trials.

3. References to the research

1. Rebello P, Hale G, Friend P, Cobbold SP, Waldmann H. (1999) Anti-globulin responses to rat and humanised CAMPATH-1 monoclonal antibodies used to treat transplant rejection. Transplantation 68: 1417-1420. Available from http://www.ncbi.nlm.nih.gov/pubmed/10573085 ***Paper describing the development and use of the ELISA assay for alemtuzumab (CAMPATH).***

2. Rebello P, Hale G. (2002) Pharmacokinetics of CAMPATH-1H: assay development and validation. J Immunol Methods 260: 285-302. doi: 10.1016/S0022-1759(01)00556-7 ***Describes use of flow cytometry assay for the measurement of the therapeutic antibody CAMPATH-1H (alemtuzumab) in patients.***

3. Hale G, Rebello P, Brettman L, Fegan C, Kennedy B, Kimby E, Leach M, Lundin J, Mellstedt H, Moreton P, Rawstron A, Waldmann H, Osterborg A, Hillmen P. (2004) Blood concentrations of alemtuzumab and antiglobulin responses in patients with chronic lymphocytic leukaemia following intravenous or subcutaneous routes of administration. Blood 104: 948-955. doi: 10.1182/blood-2004-02-0593 ***Measurements of the pharmacokinetics of alemtuzumab and the presence of autoantibodies against it in two clinical trials where alemtuzumab was administered either subcutaneously or intravenously.***

4. Keymeulen B, Vandemeulebroucke E, Ziegler A, Mathieu C, Kaufman L, Hale G, Gorus F, Goldman M, Walter M, Candon S, Schandene L, Crenier L, De Block C, Seigneurin JM, De Pauw P, Pierard D, Weets I, Rebello P, Bird P, Berrie E, Frewin M, Waldmann H, Bach JF, Pipeleers D, Chatenoud L. (2005) Insulin needs after CD3-antibody therapy in new-onset type I diabetes. N Engl J Med 352: 2598-2608. doi: 10.1056/NEJMoa043980 ***Use of the assays in an international phase II study providing evidence to show a clinical benefit of the use of a therapeutic antibody to CD3 in type I diabetes.***

Funding for research: Grants totalling in excess of £5.5M between 1995-2004 were received from the Medical Research Council, LeukoSite Inc. and Millennium Pharmaceuticals Inc. Of this, £200,000 received from Millennium Pharmaceuticals Inc. was especially relevant to the establishment of BioAnaLab.

4. Details of the impact

In 2002, the expertise and methods developed by Professor Hale, Dr Steve Cobbold and Mrs Peppy Rebello were used to form the Isis Innovation spin-out company BioAnaLab. The company was founded with approximately £1M of equity investment from business angels and venture capital funds. The success of this launch was demonstrated when BioAnaLab was awarded the 'Best New Laboratory Start-Up UK' at the Laboratory News Industry Awards event in 2002. BioAnaLab went on to achieve full membership of the UK Good Laboratory Practice (GLP) Compliance Programme in 2006[5], and subsequently to receive Good Manufacturing Practice (GMP) accreditation from the Medicines and Healthcare products Regulatory Agency (MHRA) in 2008[5]. Professor Hale was appointed as Chief Executive Officer in 2005.

The assessment of any new biopharmaceutical drug must include an accurate correlation of its biological activity and levels *in vivo*. Minimum therapeutic levels of the drug must be determined; and it is important that antibody responses produced by the patient to the drug (which may neutralise its effect) are kept to a minimum. These data are essential to maximise the effectiveness of the treatment whilst minimising any associated hazardous side effects[6]. This is the area in which BioAnaLab has proved itself to be indispensable, in developing the safety and efficacy of biopharmaceutical drugs and vaccines[6-10]. BioAnaLab has provided a broad range of services, including measurements of the pharmacokinetics, toxicity and biological potency of biopharmaceuticals such as antibodies, vaccines, growth factors and hormones. Its first contract was with Ilex, a US Biotech company marketing therapeutic antibodies. The outstanding success of the company was demonstrated by its financial growth: its sales grew from £65,038 in 2002 to more than £2.2M in 2008 and £3.12M in 2009, 75% of which was earned from abroad.

The success of BioAnaLab with its strong pipeline of orders resulted in its acquisition by Millipore Corporation for £7.7M in 2009. The teaming up of the resources of BioAnaLab with Millipore Corporation[11], which is a leader in the provision of cutting edge technologies and services to research and biopharmaceutical communities, resulted in the establishment of Millipore's BioPharma Services at Milton Park, Oxfordshire, UK. BioPharma Services was the first global

contract research organisation (CRO) in the world dedicated exclusively to large molecule bioanalytical work[12]. The subsequent merging of Millipore and Merck KGaA in 2010 resulted in the launch of EMD Millipore, and has extended the reach of the company in the Life Sciences sector[13, 14]. Professor Hale continued as the Managing Director and Director of BioPharma services in the Europe Division until 2010 and now serves as a consultant, whilst retaining professorial status at Oxford University.

The technology and expertise developed and used by BioAnaLab continues to exert a major impact on the translational advancement of drugs from 'laboratory bench' to the patient. By 2009, BioAnaLab had already collaborated on the clinical development of approximately 120 new biological drugs. The company also developed innovative solutions to analytical problems and participated in international clinical trials, workshops and conferences[6–10].

Within the REF2014 period, the company played an important role in the career development of several talented Oxford graduates. By 2009, BioAnaLab employed 50 staff providing analytical services to the pharmaceutical industry and was the first employer for 39 members of staff, mostly new graduates, but also including some students on paid work experience. These young people entered a training programme that provided the practical skills and understanding to follow a career in the pharmaceutical industry. At the time of this report, and to the best of our knowledge, all of them continue in employment with promotion of the majority to more senior positions.

5. Sources to corroborate the impact

The primary sources describing the financial, personnel and clinical impacts remain confidential from 2009 due to the commercial nature of the business and the acquisition by Millipore Corporation and Merck KGaA.

5. Isis Innovation. BioAnaLab achieves full membership of the UK Good Laboratory Practice Compliance Programme. Available from http://www.isis-innovation.com/news/news/bioanalab-jan06.htm ***Press release describing BioAnaLab achieving full membership of the UK GLP compliance Programme.***

6. Chapman K, Pullen N, Coney L, Dempster M, Andrews, L, Bajramovic J, Baldrick P, Buckley L, Jacobs A, Hale G, Green C, Ragan I, Robinson V. (2009) Preclinical development of monoclonal antibodies: considerations for the use of non-human primates. mAbs 1: 505-516. Available from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2759500/ ***Describes the safety issues of therapeutic antibodies.***

7. Angiolillo AL, Yu AL, Reaman G, Ingle AM, Secola R, Adamson PC. (2009) A phase II study of Campath-1H in children with relapsed or refractory acute lymphoblastic leukaemia: a Children's Oncology Group report. Pediatric Blood & Cancer 53: 978-983. doi: 10.1002/pbc.22209 ***BioAnaLab measured the levels of anti-Campath-1H antibodies during the clinical trial.***

8. Bakker ABH, Python C, Kissling CJ, Pandya P, Marissen WE, Brink MF, Lagerwerf F, Worst S, van Corven E, Kostense S, Hartmann K, Weverling GJ, et al. (2008) First administration to humans of a monoclonal antibody cocktail against rabies: Safety, tolerability, and neutralising activity. Vaccine 26: 5922-5927. doi: 10.1016/j.vaccine.2008.08.050 ***Measurement by BioAnaLab Ltd. of anti-human antibodies in subjects.***

9. Somerfield J, Hill-Cawthorne, GA, Lin A, Zandi MS, McCarthy C, Jones JL, Willcox M, Shaw D, Thompson SAJ, Compston AS, Hale G, Waldmann H, Coles AJ. (2010) A novel strategy to reduce the immunogenicity of biological therapies. Journal of Immunology 185: 763-768. doi: 10.4049/jimmunol.1000422 ***BioAnaLab Ltd. measured levels of alemtuzumab binding antibodies in patients.***

10. Hale G, Rebello P, Al Bakir I, Bolam E, Wiczling P, Jusko WJ, Vandemeulebroucke E, Keymeulen B, Mathieu C, Ziegler AG, Chatenoud L, Waldmann H. (2010) Pharmacokinetics

and antibody responses to the CD3 antibody otelixizumab used in the treatment of type 1 diabetes. J Clin Pharmacol 50: 1238-1248. doi: 10.1177/0091270009356299 ***BioAnaLab produced information on the pharmacokinetics and immunogenicity of the anti-CD3 antibody to optimise the treatment of type 1 diabetes.***

11. Isis Innovation. Millipore Acquires Isis Spin-out BioAnaLab. Available from http://www.isis-innovation.com/news/news/milliporeacquired.html ***Isis Innovation website describing the acquisition of BioAnaLab by Millipore Corporation.***

12. Merck Millipore. Millipore's Biopharma services and BioAnaLab: The rules have changed; available from http://www.millipore.com/techpublications/tech1/pf0048en00 ***Website with the first mention of the acquisition of BioAnaLab with Millipore Corporation resulting in a CRO.***

13. Merck Millipore. News Release. Merck KGaA, Darmstadt, Germany Completes Millipore Acquisition and Launches New EMD Millipore Division (Merck Millipore Division outside U.S. and Canada). Available from http://www.millipore.com/press/pr3/pressrelease_071510 ***Merck website announcing Millipore acquisition.***

14. Merck Millipore. Quarterly Financial Report Q1 2012. Available from http://www.millipore.com/press/pr3/press_release05192010 ***Website providing financial details for Merck Millipore for the first quarters of 2011 & 2012.***