Institution: University of Oxford

Unit of Assessment: UOA5

Title of case study:

Everest Biotech Ltd: providing high quality reagents for research

1. Summary of the impact

Professor Neil Barclay and Dr Nick Hutchings established Everest Biotech Ltd in 2000 in response to the increasing demand for high quality antibodies within the research community. This successful spin-out company has since become a major power in antibody research and production, a position reflected by its portfolio of more than 6,000 antibodies recognising human, mouse and rat proteins, and the generation of 60 new antibodies each month. With offices in the UK and Nepal, Everest Biotech Ltd also benefits one of the poorest communities in the world by providing additional income to hundreds of farmers in the Nepalese foothills.

2. Underpinning research

Modern research continues to identify increasing numbers of proteins and the ability to study these molecules at the single cell level is crucial in order to identify and understand their functional roles. Cell surface proteins play important roles in communicating between a cell and its environment, and are thus involved in fundamental cellular processes such as signalling and molecular recognition. Structural analysis of these proteins is complicated because many are embedded in the cell membrane. The study of cell surface proteins therefore required the development of methods to express soluble forms of the proteins in mammalian cells; these soluble forms had to be correctly folded and glycosylated. In 1993, Professor Neil Barclay in the MRC Cellular Immunology Unit at the Dunn School of Pathology pioneered an approach to achieve this goal whilst investigating the biochemical nature of proteins on the cell surface of leukocytes and their role in immune regulation[1,2]. The approach was based on the expression of recombinant chimeric proteins that were secreted from cells. Because the secreted proteins could be detected with antibodies that recognised the known 'carrier' portion of the chimera, the new technology enabled rapid advances in our understanding of receptor–ligand interactions and accelerated the X-ray crystallography of immune receptor molecules[3].

The Barclay group subsequently applied proteomics approaches to screen all proteins involved in functions on the cell surface, rather than concentrating on selected proteins. Using mass spectrometry techniques they identified the many proteins involved in transmitting signals from the cell surface into the cell. This advance meant that higher-throughput technologies were needed for subsequent functional analyses. To this end, the group has remained at the forefront of developing assays for studying protein interactions, including protein microarrays and high-throughput screening for ligands using microarrays[4,5].

In 2000, Barclay realised that, given many of the chimeric proteins were also powerful immunogens, this provided the opportunity to generate antibodies against large numbers of correctly folded soluble proteins. This opportunity was commercialised in the University spin-out company Everest Technology. Ongoing research in Oxford supports the company and maintains its focus on high quality reagents against proteins that may be a focus of future interest. This forward thinking facilitates the fast and efficient study of new proteins as and when they are identified. For example, Everest's antibodies to FOXP3 protein were available when FOXP3 became of central importance because of its role in immunoregulation[6].

3. References to the research

1. Brown MH, Barclay AN. (1994) Expression of immunoglobulin and scavenger receptor

superfamily domains as chimeric proteins with domains 3 and 4 of CD4 for ligand analysis. Protein Eng. 7: 515-521. doi: 10.1093/protein/7.4.515 ***Describes the general approach to expressing chimeric proteins in the immunoglobulin superfamily of cell surface proteins.***

2. Barclay AN. (2001) Biochemical analysis of the lymphocyte cell surface--from alloantisera to the role of membrane proteins. Immunol Rev. 184: 69-81. doi: 10.1034/j.1600-065x.2001.1840107.x ***Describes the history of the Oxford group's approach to develop antibodies to cell surface receptors on immune cells.***

3. Brady RL, Dodson EJ, Dodson GG, Lange G, Davis SJ, Williams AF, Barclay AN. (1993) Crystal structure of domains 3 and 4 of rat CD4: relation to the NH2-terminal domains. Science 260: 979-83. doi: 10.1126/science.8493535 ***An example of using the Oxford protein expression systems to study protein structure.***

4. Letarte M, Voulgaraki D, Hatherley D, Foster-Cuevas M, Saunders NJ, Barclay AN. (2005) Analysis of leukocyte membrane protein interactions using protein microarrays. BMC Biochem. 6: 2. doi: 10.1186/1471-2091-6-2 ***The development of microarray technology to study protein interactions.***

5. Jiang L, Barclay AN. (2010) Identification of leucocyte surface protein interactions by high-throughput screening with multivalent reagents. Immunology 129: 55-61. doi: 10.1111/j.1365-2567.2009.03153.x ***The development of high-throughput screens for ligands.***

6. Everest BIOTECH. Goat Anti-FOXP3/Scurfin (Mouse) Antibody (EB06376). Available from http://everestbiotech.com/product/goat-anti-foxp3-scurfin-antibody/ ***Webpage of the Everest Biotech Ltd goat FOXP3 antibody describing the reagent and listing references from where it has been used to study FOXP3 expression.***

Funding for research: Since 1999, funding of around around £6.3M has been obtained from the MRC, Wellcome Trust, Arthritis Research Council and Smith Kline Beecham.

4. Details of the impact

By the end of the 1990s, the Human Genome Project and associated large-scale projects were fuelling the expanding worldwide demand for antibodies that recognised relevant target proteins. The development of extensive new methodology for the production and characterisation of conformationally accurate mammalian proteins, which had evolved during work on the role of leukocyte cell membranes in immunity, placed Barclay's group in an ideal situation to establish a pipeline for the large-scale production of high quality and reliable polyclonal antibodies. This commercial opportunity was exploited and has had wide-reaching impacts.

Professor Neil Barclay and Dr Nick Hutchings, assisted by Mr Ravindra Sapkota and Dr Raju Adhikari (Nepalese graduates from the Department of Biochemistry at the University of Oxford), developed a business plan to produce polyclonal antibodies on a high-throughput basis utilising the combination of competitive production facilities and locally-farmed goats in Nepal. A Business Angel provided £350,000 and the spin-out company Everest Biotech Ltd[7] and its Nepalese subsidiary Everest Biotech Pvt. Ltd, were successfully launched in 2000. Hutchings became the Chief Executive of Everest Biotech Ltd and the Chairman of Everest Biotech Pvt. Ltd in 2001. Antibodies went on sale in 2002 through a variety of companies including Abcam and Serotec. More than 6,000 products have now been produced and marketed with approximately 60 more antibodies being produced every month. Everest Biotech Ltd also works in collaboration with researchers to produce custom made antibodies for individual research projects and more than 200 custom antibodies have been made in this way. Importantly, the company also provides technical support to its customers. In 2005, Everest Biotech Ltd began selling antibodies under its own brand name to customers in the USA, an event that was facilitated by outsourcing with

LifeScience Logistics[8]. Sales grew steadily without further external investment to reach £0.49M in the year to 31st May 2008[9].

Since 2008, Everest Biotech Ltd has become an important commercial company, not only making a significant contribution to scientific and medical communities, but also benefiting the small Nepalese community it sustains through agricultural support and employment. The success of Everest Biotech also led Barclay and Hutchings to establish the company Absolute Antibody in 2012, to provide monoclonal antibodies made by recombinant DNA technology to the scientific and medical communities[10].

Commercial engagement

Everest Biotech Ltd has up to five full-time staff in the UK involved in product design and distribution with Hutchings as Chief Executive, and 25 Nepalese employed full-time in the antibody production facility at Everest Biotech Pvt. Ltd. The Nepalese subsidiary has been described as one of the ten key institutional stakeholders in the medical biotechnology sector in Nepal[11]. Everest Biotech has been a major supplier to Abcam Ltd, one of the most successful UK companies selling antibodies, and recently began supplying antibodies to Sigma-Aldrich. Everest Biotech antibodies are now distributed throughout the world under the Everest brand via companies such as Abcore (USA), Sanbio (Netherlands), Funakoshi (Japan) and Sapphire Bioscience (Australia and New Zealand)[12]. This commercial success has also enabled Everest Biotech to open a branch in California[13].

Everest Biotech is now a profitable company with approximately 75% of its products being exported. Since 2008, over £7.5 million of Everest Biotech antibodies have been sold worldwide and turnover in the year to 31 May 2012 exceeded £1 million[9]. An important role of Everest Biotech Pvt. Ltd is as an export industry, bringing in approximately £250,000 per annum to Nepal, an economy that is greatly unbalanced towards the import of goods[14].

Community engagement (social, cultural and economic impact)

As the only biotech company in Nepal providing employment within the poorer rural communities, Everest Biotech Pvt. Ltd has had an important social and economic impact on the lives of many Nepalese workers and farmers. Everest Biotech Ltd uses several hundred goats per year purchased from local breeders to make its antibodies. These goats are then distributed to approximately 100 individual farmers in the villages around Kathmandu who are paid a premium for looking after them, a situation akin to the establishment of a large number of small animal facilities. One very important aspect of this support has been that owing to the farmers' increased income, many children now attend school in these villages rather than remain at home to help with farm work. The company also promotes animal welfare at the village level by providing veterinary care and vaccines for all goats in the community, including those owned by the farmers as well as those being used for antibody production[14].

The employment of 25 Nepalese staff at Everest Biotech Pvt. Ltd in Kathmandu further promotes the local economy. Many of the staff, after obtaining excellent training within an industrial setting, progress on to obtain higher qualifications either in Nepal or overseas. Additionally, the company provides expertise to the life science community of Nepalese universities[14]. Furthermore, Everest Biotech Ltd is the major benefactor to a number of good causes in Nepal such as The Esther Benjamins Trust[15], which is a UK based charity supporting the rescue of trafficked children in Nepal.

5. Sources to corroborate the impact

7. Everest Biotech: Creating Novel Antibodies. Available from: http://everestbiotech.com/ ***The website of Everest Biotech Ltd. detailing its contact details in the UK and USA, products and services.***

8. NGP. Available from: http://www.ngpharma.com/article/Everest-Biotechs-Distribution-Challenge-Met-by-LifeScience-Logistics/ ***Website describing the linking up of Everest***

Biotech with LifeScience Logistics in 2005. This step enabled customers in the USA to receive Everest antibodies with a next day delivery.

9. Sales can be confirmed by the Chief Executive, Everest Biotech Ltd.

10. Absolute Antibody. Available from http://absoluteantibody.com/ ***The website of a privately funded start-up company based in Oxfordshire to produce specific monoclonal antibodies for the research and diagnostics markets. Professor Neil Barclay is the Chairman and Dr Nick Hutchings is Head of the Management Team.***

11. Nepal Academy of Science and Technology (NAST) and Ministry of Environment, Science, Technology (MoEST). National State-of-the-Art Report on Biotechnology for Nepal. Nepal: Government of Nepal, Dec 2008. Available from http://www.nast.org.np/alluploads/National-State-of-the-Art-Report.pdf ***National State-of-the Art report on Biotechnology for Nepal in 2008, describing Everest Biotech Pvt. Ltd as a key stakeholder biotechnological institution of Nepal.***

12. Sapphire Bioscience. Available from http://www.sapphirebioscience.com/supplier.jsp?id=83 ***Example of a distributor for Everest Biotech in Australia.***

13. The Pharmaceutical Directory for 381000 Global Buyers. Available from http://www.jazdlifesciences.com/pharmatech/company/Everest-biotech.htm?supplierId=30021651 ***Website introducing Everest Biotech in Ramona California.***

14. Details of the impact in Nepal can be confirmed by the former CEO of Everest Biotech Pvt. Ltd in Nepal, responsible for setting up the Nepalese operation and currently a director of this subsidiary. Email evidence is held on file.

15. Details of the donation made by Everest Biotech to the Esther Benjamins Trust can be corroborated by contacting the Fundraising Manager at the Trust.