Institution: University of Bristol

Unit of Assessment: 5 – Biological Sciences

Title of case study: Generating commercial impact through industry investment in cancer therapies that target tumour cell metabolism.

1. Summary of the impact

Research conducted at the University of Bristol between 1994 and 2013 has led to major commercial impact through industry investment in cancer therapies that target a family of transporter proteins (MCTs) identified and characterised by Professor Halestrap and his colleagues. Halestrap has worked directly with AstraZeneca, a leading global biopharmaceutical company, to integrate the Bristol-based research into their own research programme to elucidate the mode of action of a group of novel immunosuppressive agents that target MCT1. Subsequent ongoing collaborations have underpinned AstraZeneca's development of these drugs for cancer chemotherapy, with clinical trials of their compound AZD3965 underway, as well as investment in a new cancer drug discovery programme targeting the MCTs.

2. Underpinning research

Since 1994, research at the University of Bristol has focused on identifying the structures and properties of a membrane transporter protein that is critical to glycolysis – a metabolic pathway that is essential to all organisms.

The key Bristol staff contributing to this work are:

Prof Andrew Halestrap - PI, membrane transporters. Appointed lecturer 1975, Reader in Biochemistry (1988-1996) and now Professor of Biochemistry (1996 - present).

Dr Richard Sessions – Scientific Officer and molecular modeller (1990 – present).

Dr David Meredith – Temporary lecturer in Prof Halestrap's laboratory (1998-2001)

Glycolysis, cancer and the role of MCTs

Most cancer cells have an increased reliance on glycolysis for their energy provision. Such metabolism by cancer cells results in the production of lactic acid, which has to be removed in order to maintain the energy supply. Transport of lactic acid out of the cell is mediated by proteins found within the plasma membrane of cells, known as monocarboxylate transporters (MCTs), which facilitate the movement of molecules across the membrane. Halestrap discovered the first MCT in the 1974 and he and his colleagues have been pioneering research into the identity, structure, role and regulation of these proteins ever since.

Identifying the MCT protein family

In 1994, Halestrap and colleagues identified the protein responsible for lactic acid transport in red blood cells (MCT1). This was followed by the identification of three additional MCTs (MCTs 2-4) that are members of the same transporter family (1996-1998) and their functional characterisation by expression in frog eggs (1998-2000). The properties of each of these transporters matched their distinct metabolic roles in the different tissues that expressed them [1]. A key observation made by Professor Halestrap and his colleagues is that the dominant MCT isoform found in most glycolytic cells is MCT4, and through a PhD studentship funded by the UK pharmaceutical company AstraZeneca (AZ), they demonstrated that MCT4 is up-regulated by hypoxia inducible factor 1α (HIF1α) [2]. This is of major significance because the expression of both MCT4 and HIF1α is very high in most aggressive cancers. In the last six

years Professor Halestrap has been working closely with Dr Richard Sessions, a molecular modeller in the School of Biochemistry, on the structure of the MCTs. Such modelling, together with site-directed mutagenesis and transport studies, has led to the development of a likely three-dimensional structure of MCT1 [3]. This provides the basis for an ongoing collaboration with AZ who have developed a group of highly potent MCT1 inhibitors that have been characterised by Professor Halestrap [4], including the identification of the probable binding site in the modelled 3D structure. Current collaborative studies with AZ are directed towards developing equivalent drugs that target MCT4, which is dominantly expressed in many tumours. The modelled structure has allowed Professor Halestrap and his colleagues to identify key differences between MCT1 and MCT4 in the inhibitor binding pocket that can then be exploited by AZ to design novel MCT4 specific inhibitors.

3. References to the research

[1] Halestrap, A.P. and Meredith, D. (2004) 'The SLC16 gene family - from monocarboxylate transporters (MCTs) to aromatic amino acid transporters and beyond', *Pflugers Archiv European Journal of Physiology,* 447:619-628. DOI: 10.1007/s00424-003-1067-2 *(511 citations*)*

[2] Ullah, M.S., Davies, A.J. and Halestrap, A.P. (2006) 'The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1 alpha-dependent mechanism', *The Journal of Biological Chemistry,* 281:9030-9037. DOI:10.1074/jbc.M511397200 (*218 citations)*

[3] Wilson, M.C., Meredith, D., Bunnun, C., Sessions, R.B. and Halestrap, A.P. (2009) 'Studies on the DIDS binding site of monocarboxylate transporter 1 suggest a homology model of the open conformation and a plausible translocation cycle', *The Journal of Biological Chemistry,* 284:20011-20021. DOI: 10.1074/jbc.M109.014217 *(23 citations)*

[4] Ovens, M.J., Davies, A.J., Wilson, M.C., Murray, C.M. and Halestrap, A.P. (2010) 'AR-C155858 is a potent inhibitor of monocarboxylate transporters MCT1 and MCT2 that binds to an intracellular site involving transmembrane helices 7-10', *Biochemical Journal* 425:523-30. DOI: 10.1042/BJ20091515 *(20 citations)*

*All citation values from Google Scholar as of September 6th, 2013.

Grants:

This work has been funded by 9 peer-reviewed grants, 3 PhD students (1 Industrial) and 1 industrial contract, totalling £1.58M. Illustrative grants are listed below.

[5] Halestrap (1994-1997) *Structural and functional studies of the lactate transporter of erythrocytes and other cells*. The Wellcome Trust, £153,968.

[6] Halestrap (1998-2001) *Expression and characterisation of monocarboxylate transporter isoforms*. Wellcome Trust Research Leave Fellowship, £143,000.

[7] Halestrap (1998-2001) *Mechanisms involved in the physiological regulation of mammalian monocarboxylate transporters*. MRC Component Grant, £200,964.

[8] Halestrap (2001-2004) *The role of CD147 and other ancillary proteins in the expression and function of monocarboxylate transporters*. The Wellcome Trust Project Grant, £205,125.

[9] Halestrap (2006-2009) *Monocarboxylate transporters and their ancillary proteins: studies on the molecular basis of their interaction and distinct properties.* The Wellcome Trust Project Grant, £257,700.

4. Details of the impact

Research conducted at Bristol between 1994 and 2013 has led to commercial impact through industry investment in new areas of research and development as well as investment in clinical trials.

AstraZeneca and Cancer Research UK takes MCT1 inhibitor to clinical trial

The global biopharmaceutical company, AstraZeneca, originally discovered MCT inhibitors in a research programme targeted at developing novel immunosuppressive agents. However, the "*extensive and seminal work*" conducted at Bristol, which increased AstraZeneca's understanding of the pharmacology of these agents had a "*major impact on their drug development programme focussed on potent and novel MCT1 inhibitors*" [a]. The research in Bristol has helped AstraZeneca realise their potential as chemotherapeutic agents and this has led to a major drug discovery programme to develop the field, assisted by "*our ongoing collaborations in understanding the pharmacology of these novel inhibitors*" [a]. In 2010, Cancer Research UK and AstraZeneca reached an agreement to take the compound AZD3965, which targets MCT1, into clinical trial [b]. Recruitment for Phase I trials began in February 2013 [c]. AstraZeneca also filed an international patent in 2010 for the novel method of cancer treatment that inhibits lactate transport by MCTs [d].

Research on MCT4 leads to investment in a new drug discovery programme

In addition, Halestrap's work showing MCT4 is up-regulated in response to hypoxia through transcriptional regulation by HIF-1α [2] has had "*particular significance for cancer chemotherapy*" [e]. It has led AstraZeneca to "*initiate a new drug discovery programme directed towards identifying MCT4 specific inhibitors and to extend our collaboration with [Professor Halestrap] to understand this anticancer treatment paradigm*" [a]. Though AstraZeneca's specific investment into this research area is commercially sensitive information, their overall investment into research and development is over US$ 4 billion annually and they have around 15,700 people employed in this sector across 14 centres in 8 countries [a]. In 2012, sales in oncology drugs were valued at US$3,489 million [f, pg 50]. Their investment in the new MCT4 inhibitor drug discovery programme is based on their assessment that "*these inhibitors have the potential to provide a potent therapeutic strategy against aggressive cancers*" [a].

Others in pharmaceutical industry invest in MCT inhibitors

At this point in time, it is not possible to evidence the investment by other pharmaceutical companies in this area of research as it has not yet been released into the public domain. However, in 2012, Pfizer Worldwide Research and Development gave an oral presentation stating that Pfizer is exploring MCT-1 and MCT-4 as "*therapeutic strategies against malignant tumours*" [g]. As well, the National Institutes of Health – the national medical research agency in the U.S. – awarded US$ 3.85 million to Scripps Research Institute Scientists to develop a "*new generation of broad spectrum anti-cancer therapeutics*", which target MCT1 and MCT4 [h].

5. Sources to corroborate the impact

[a] Vice President, Head of Science, AstraZeneca

[b] Cancer Research Technology (September 13, 2010) *Cancer Research UK and AstraZeneca sign deal to trial a first-of-kind cancer drug.* Press Release. <http://www.cancertechnology.com/news/single/cancer_research_uk_and_astrazeneca_sign_deal_to_trial_first-of-kind_ca/> Evidence of industrial investment in taking drug to clinical trial.

[c] Cancer Research UK (2013) *A trial of AZD3965 for advanced cancer.* Website <http://www.cancerresearchuk.org/cancer-help/trials/a-trial-azd3965-for-advanced-cancer>

[d] Critchlow, S.E. and Tate, L. (inventors) "*Use of a MCT1 inhibitor in the treatment of cancers expressing MCT1 over MCT4"*, [patent] International Publication No. WO/2010/089580. 22 Jan 2010. <http://patentscope.wipo.int/search/en/detail.jsf?docId=WO2010089580&recNum=85&docAn=GB2010050096&queryString=PA/astrazeneca&maxRec=2640> The patent illustrates industrial investment in this group of inhibitors.

[e] Schulze, A. and Harris, A. L. (2012) 'How cancer metabolism is tuned for proliferation and vulnerable to disruption', *Nature*, 491(7424):364-373. DOI: 10.1038/nature11706. Independent acknowledgement that the research has had a significant impact on cancer chemotherapy.

[f] AstraZeneca (2012) '*Delivering value through innovation',* AstraZeneca Annual Report and Form 20-F Information 2012. <http://www.astrazeneca-annualreports.com/2012/documents/eng_download_centre/annual_report.pdf> Provides values for AstraZeneca's annual sales for oncology drugs to give context for what this portion of the portfolio is worth to the company.

[g] Unsal-Kacmaz, K., *et al.* (2012) 'MCT4 is an important determinant for the growth of highly glycolytic and aggressive malignancies', *BMC Proceedings*, 6 (Suppl 3):O26. <http://www.biomedcentral.com/content/pdf/1753-6561-6-S3-O26.pdf> Supports claim that Pfizer Worldwide Research and Development is investing in this area of research.

[h] Sauter, E. (March 12, 2012) '*$3.85 Million NIH Grant Funds Development of New Class of Cancer Therapies',* The Scripps Institute News & Views, Vol 12, Issue 9 <http://www.scripps.edu/newsandviews/e_20120312/cancer.html>. Evidence that the United States Government is investing in this area of research.