Institution: University of Dundee

Unit of Assessment: 5: Biological Sciences

Title of case study: The impact of protein phosphorylation and kinase profiling research at the University of Dundee on identifying drug targets and accelerating product development in the pharmaceutical industry.

1. Summary of the impact (indicative maximum 100 words)

Kinases, the enzymes that catalyse phosphorylation events, have been implicated in hundreds of different diseases, and hold rich promise for drug development. In 1998, The University of Dundee developed the first systematic assay to analyse the selectivity of protein kinase inhibitors, termed 'kinase profiling'. This technology has been crucial for the development of new therapeutic drugs targeting protein kinases. In order to promote drug discovery in the area of kinases, the Division of Signal Transduction Therapy (DSTT) was formed and provides a unique collaboration between the University and six of the world's leading pharmaceutical companies.

2. Underpinning research (indicative maximum 500 words)

Reversible protein phosphorylation constitutes a key process in cell regulation and controls almost all aspects of cell function. It is misregulated in many human diseases. **Prof Sir Philip Cohen FRS** (Director of the MRC Protein Phosphorylation Unit from 1990 to 2012),and researchers based at the University of Dundee have played a major role in validating drug targets and helping to accelerate drug development.

In 1994, a kinase cascade activated in response to osmotic or chemical stress, called the p38 Mitogen Activated Protein Kinase (MAP kinase) pathway, was discovered in a collaboration between Philip Cohen's group at the University of Dundee and Tim Hunt's group in London (1). Following this discovery, Prof Cohen was asked to serve on an advisory board for SmithKline Beecham where data was presented on a novel class of drug to treat rheumatoid arthritis, targeting the same p38 MAP kinase. This triggered a programme of work In Dundee investigating the specificity of kinase modulation. Prof Cohen's lab established that the compound, SB203590, was a relatively specific inhibitor of p38, resulting in the publication of a paper describing the first systematic profiling of inhibitors against a panel of different protein kinases (2). A later collaboration with Parke Davis Pharmaceuticals led to an understanding of how the first specific inhibitor of the p44/p42 MAP Kinase pathway, PD098059, prevented the activation of MAP Kinase Kinase (also known as MEK1) by the protein kinase Raf (3). This paper, authored by **Prof Dario Alessi FRS** (a postdoctoral fellow then Programme Leader at the MRC Protein Phosphorylation Unit) was the UK's most highly cited research paper in the field of Biology and Biochemistry from 1993-2003 and was the first description of an allosteric inhibitor of a protein kinase (3).

From this work it was apparent that analysis of the selectivity of protein kinase inhibitors by "kinase profiling" could greatly speed up the development of protein kinase inhibitors with therapeutic potential. As a result in 1998, Prof Cohen and **Prof Pete Downes OBE FRSE FMedSci** (Professor of Biochemistry in the College of Life Sciences from 1989 to 2009) established the Division of Signal Transduction Therapy (DSTT) to provide a means for collaboration between scientists in the College of Life Sciences at the University of Dundee and leading pharmaceutical companies. Using kinase profiling technology, Prof Cohen's laboratory published a systematic analysis of many commercially available kinase inhibitors (4). This highly cited publication has been invaluable to the commercial and academic life sciences communities. Subsequent follow up papers have extended and developed the original assay (5,6). Further examples of how this research has promoted the development of kinase inhibitors include characterisation of inhibitors to p90 RSK, mTOR, p70 ribosomal S6 kinase and PKB/Akt by researchers at the College of Life Sciences in Dundee. In 2008, Prof Cohen was awarded £1 million by the MRC to create the UK's National Centre for Protein Kinase Profiling (now the International Centre for Protein Kinase Profiling) that provides kinase profiling services to commercial and academic clients.

3. References to the research (indicative maximum of six references)

Publications:

1. Rouse, J., **Cohen, P.**, Trigon, S., Morange, M., Alonso-Llamazares, A., Zamanillo, D., Hunt, T., Nebreda, A.R. (1994) A novel kinase cascade triggered by stress and heat shock that stimulates MAPKAP kinase-2 and phosphorylation of the small heat shock proteins. Cell *78*, 1027-1037. (doi:10.1016/0092-8674(94)90277-1) (Citations 1259, Scopus Nov 2013)

2. Cuenda, A., Rouse, J., Doza, Y.N., Meier, R., **Cohen, P.**, Gallagher, T.F., Young, P.R., Lee, J.C. (1995) SB 203590 is a specific inhibitor of a MAP kinase homologue which is stimulated by cellular stress and interleukin-1. FEBS Lett. *364*, 229-233. (doi: 10.1016/0014-5793(95)00357-F) (Citations 1704, Scopus Nov 2013) ***Collaborating company: SmithKline Beecham Pharmaceuticals***

3. **Alessi, D.R.**, Cuenda, A., **Cohen, P.**, Dudley, D.T., and Saltiel, A.R. (1995) PD 098059 is a specific inhibitor of the activation of mitogen-activated protein kinase kinase in vitro and in vivo. J. Biol. Chem., *270*, 27489-27494. (doi: 10.1074/jbc.270.46.27489) (Citations 2794, Scopus Nov 2013). ***Collaborating company: Pfizer Global Research and Development***

4. Davies, S.P., Reddy, H., Caivano, M., and **Cohen, P.** (2000) Specificity and mechanism of action of some commonly used protein kinase inhibitors. Biochem J. *351*, 95-105. (doi:10.1042/0264-6021:3510095) (Citations 3062, Scopus Nov 2013)

5. Bain, J., McLauchlan, H., Elliott, M., and **Cohen, P.** (2003) The specificities of protein kinase inhibitors: an update. Biochem J. *371*, 199-204. (doi: 10.1042/BJ20021535) (Citations 886, Scopus Oct 2013)

6. Bain, J., Plater, L., Elliott, M., Shpiro, N., Hastie, C.J., McLauchlan, H., Klevernic, I., Arthur, J.S.C., **Alessi, D.R.**, and **Cohen, P.** (2007) The selectivity of protein kinase inhibitors: a further update. Biochem J. *408*, 297-315. (doi: 10.1042/BJ20070797) (Citations 977, Scopus Nov 2013)

4. Details of the impact (indicative maximum 750 words)

Beneficiaries:

(a) The pharmaceutical and biotech industries.
(b) Patients, for multiple indications but particularly cancer.

Benefits and impacts:

(a) The demonstration of selective protein kinase inhibition and the invention of 'kinase profiling', profoundly influencing the direction of the Pharma industry.
(b) The establishment of a paradigm for pre-competitive collaboration and knowledge-transfer between the University and multiple Pharma partners.
(c) Direct contribution to the discovery of the GSK melanoma drug Tafinlar™
(d) Inward investment and company growth in the local Dundee Biotech cluster.

Impacts:

Selective kinase inhibition and 'kinase profiling'

Demonstration by the University of Dundee in 1994 that kinase inhibitors could exhibit relatively high degrees of specificity was crucial for convincing Pharma that drugs could be designed against specific protein kinases to regulate cellular responses. Moreover, the publication of methods to determine the selectivity of protein kinases using "kinase profiling" has been of enormous benefit to the industry. Since 1998 there has been an exponential increase in kinase profiling and protein kinases have become the most studied class of drug target (30% of drug discovery programs are directed towards protein kinases (1)). Further, work by the University of Dundee on the effect of

specific kinase inhibition, together with the research by Nick Lydon (a Dundee alumnus) and colleagues demonstrating that Gleevec (which inhibits kinases Abl and cKit) could successfully treat specific forms of leukaemia, was the tipping point that convinced the pharmaceutical industry that kinases were good therapeutic targets (2).

Kinase-focused drugs are under investigation for a wide range of cancers and inflammatory diseases. Since 2001, 23 new drugs that target kinases have been approved for clinical use (19 for cancer (3)) and in 2013 over 50 protein kinase inhibitors are undergoing Phase III clinical trials (4). None of these drugs could have been developed without kinase profiling. The fundamental importance of kinase profiling is also highlighted by the uptake of this technology by numerous life-sciences companies, including Invitrogen, Merck, GE Healthcare, Perkin Elmer and Promega.

A paradigm for industry-academic collaboration and knowledge-exchange

The Division of Signal Transduction Therapy (DSTT) is one of the largest and longest ever collaborations between the pharma industry and an academic institute. Since 2008, it has carried out work with 72 academic institutions and 36 commercial companies worldwide. Currently supported by six of the world's leading pharmaceutical companies (AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck-Serono, Pfizer and Janssen Pharmaceutica NV), the DSTT is widely cited as a model of effective interaction between a university and the commercial sector (5). Companies involved in the consortium invested £10.8 million in 2008 and funding was renewed again in 2012 with an award of £14.4 million. Since its launch in 1998, a changing roster of companies has invested over £50 million into the effort (6). The DSTT has delivered pilot amounts of kinases and phosphatases to establish assays on 1987 occasions. In addition, 1059 antibodies and 1080 DNA constructs have been delivered to the Pharma companies (7). The DSTT also makes 236 separate kinase reagents (protein and lipid kinases and mutants) and 81 substrate proteins available to its partners on request and generates 150 new antibodies and 5000 new DNA constructs per annum. It provides the companies with detailed information about the selectivity of thousands of their compounds (an average of 705,500 data points per year) (7). The level of investment and commitment the pharmaceutical companies have made to this consortium through recurrent funding provides the evidence for the impact that this novel arrangement with industry delivers. Furthermore, the diversification by the MRC Unit and the DSTT into protein ubiquitylation is of considerable interest to the Pharma partners.

Contribution to the discovery of melanoma drug Tafinlar™

The DSTT and the technique of kinase profiling has contributed significantly to the development and launch of new drugs by the Pharma industry. As a specific example, the technology developed by the DSTT to manufacture and assay the BRAF enzyme played a major role in underpinning the drug development programme by GlaxoSmithKline to develop Tafinlar™ (dabrafenib) as an oral treatment for melanoma (8). In 2013, Tafinlar™ was authorized for use in the EU (9).

Inward investment and company growth in the local Biotech cluster.

Kinase profiling and reagent production have directly stimulated of the local Dundee economy: in the mid-1990s, the MRC Protein Phosphorylation Unit generated cell signaling reagents which US-based biotechnology company Upstate Biotechnology Inc sold to academia and pharmaceutical companies. In 1998, Upstate established a new European division in the Technology Park in Dundee. This venture was very successful (employing more than 100 people in 2013) and contributed to the acquisition of Upstate by Serologicals Corp in 2004 for $205 million, which later became a subsidiary of Millipore Corp and is now currently Merck KGaA. Royalties accruing to Dundee University from this arrangement amount to £4.2 million, with £870,000 accruing during the assessment period (10).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Netterwald, J. (2007) Who likes kinases? Drug Discovery & Development magazine. *10*, 18-22. http://www.dddmag.com/articles/2007/12/who-likes-kinases
2. Lydon, N. (2009) Attacking cancer at its foundation. Nat Med.*15*, 1153-1157 (doi: 10.1038/nm1009-1153)
3. Cohen, P., and Alessi D.R. (2013) Kinase Drug Discovery − What's Next in the Field? ACS Chemical Biology *8*, 96-104. (doi: 10.1021/cb300610s).
4. Clinical Trials.Gov http://www.clinicaltrials.gov
5. http://www.mrc.ac.uk/Newspublications/News/MRC008647
6. http://www.pharmatimes.com/Article/12-05-17/New_pharma_funding_for_Dundee_s_Division_of_Signal_Transduction_Therapy.aspx
7. Confirmation of the number and value of reagents can be obtained from the Operations Manager, Division of Signal Transduction Therapy, College of Life Sciences, the University of Dundee.
8. External corroboration can be obtained from the Head of Academic Liaison, GlaxoSmithKline.
9. Announcement of marketing authorization of Tafinlar™ by GSK: http://www.gsk.com/media/press-releases/2013/gsk-receives-marketing-authorisation-from-the-european-commissio0.html
10. Confirmation of the value of royalties from this arrangement can be obtained from Research Innovation Services, The University of Dundee.