Institution: Oxford Brookes University

Unit of Assessment: 5 - Biological Sciences

Title of case study: Establishing a Systems Biology approach to drug discovery and therapy design: Physiomics Plc

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

Steered by Professor David Fell of Oxford Brookes University, Physiomics plc, an Oxford-based biotechnology innovation company has, since 2008, firmly established itself as a leading light in systems biology approaches to drug discovery and latterly in therapy design, demonstrable through contracts with three major international pharmaceutical companies. Through its strong advocacy of this approach the sector has invested in and adopted new computational biology processes. As Physiomics has continued to grow, it has expanded its own specialist research team, in many cases recruiting scientists trained within Fell's Brookes-based research group.

2. Underpinning research (indicative maximum 500 words)

For many years, Professor David Fell and colleagues at Oxford Brookes University have been researching computer modelling of biochemistry, primarily metabolism and its regulation of metabolism, but also signal transduction (the signalling from outside the cell to affect what happens within it).

The sequencing of the human genome has transformed biology, but that for the most part, the tools needed to understand and use this information are still at an early stage. This has triggered important developments in bioinformatics, systems biology, and computational biology. In general, the tools for analysing the data (bioinformatics) have progressed faster than the tools for using the predictive power of the data (modelling).

Through various research studies funded by Oxford Brookes University between 1994 and 2001, the Fell laboratory has developed new methods and concepts in the control of metabolism and the analysis of metabolic networks. For example, the study of sites and mechanisms of control in metabolism and signal transduction has a direct relevance to the action of drugs [1-4]. Along with this, the group developed its own software for the modelling and analysis of metabolic networks. One of these programs, SCAMP, was further developed and refined in the late 1990s. It was used as a major tool throughout the investigations described in the subsequent papers from 2001 onwards [3-5]. This later version became the foundation of the Physiomics applications.

Four papers on kinetic modelling of enzyme networks are cited as examples of the underpinning research;

Kashiwaya et al (1994) [1] exemplifies the development of expertise in the analysis of the control of metabolism. Fell and Thomas (PGRA on a SERC research grant) provided the theoretical interpretation to experiments on the control of heart metabolism by insulin carried out by the Veech & Passonneau group.

Brightman & Fell (2000) [2] is based on Frances Brightman's PhD work at Oxford Brookes, modelling the signal transduction pathway for Epidermal Growth Factor, abnormalities of which are common in certain types of tumour. It was one of the first detailed models of this important pathway and has been reused and developed by other researchers.

Chassagnole et al, (2001a) [3] and (2001b) [4] both concern modelling of the pathway of threonine synthesis in the bacterium *Escherischia coli*. The laboratory research on which this paper is based was carried out by Christophe Chassagnole in Prof Mazat's lab at the University of Bordeaux II, and Fell started the construction of a computer simulation during a sabbatical term in 1997 and taught Chassagnole the data fitting and simulation techniques, which then continued collaboratively.

The combination of the research approaches in Fell's group and its application to drug development issues is illustrated by the joint publication with Jackson (2006) [5] which explores the overall effect of a series of drug candidates that have different degrees of specificity for their intended target and other 'off-target' molecules.

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

1. **Y. Kashiwaya, K. Sato, N. Tsuchiya, S. Thomas, D. A. Fell, R. L. Veech, and J. V. Passonneau. (1994) Control of Glucose Utilization in Working Perfused Rat Heart. *J. Biol. Chem*., 269(41), 25502-25514.** http://www.jbc.org/content/269/41/25502.full.pdf+html
   Fell & Thomas (Brookes) provided theoretical insight and interpretation to experimental work carried out by Veech and Passonneau, collaborators from National Institute of Alcohol Abuse and Alcoholism (NIAAA). Y. Kashiwaya, K. Sato, N. Tsuchiya were postdocs in their group.

2. **F. A. Brightman and D. A. Fell (2000) Differential feedback regulation of the MAPK cascade underlies the quantitative differences in EGF and NGF signalling in PC12 cells. *FEBS Lett.,* 482(3), 169-174. DOI: 10.1016/S0014-5793(00)02037-8**
   Brightman – Brookes (research student 1997 to 2001), then Physiomics (2010 to present).
Submitted to RAE2001, Oxford Brookes University, UoA14-Biological Sciences, RA2, DA Fell, Output 4.

3. **C. Chassagnole, D. A. Fell, B. Rais, B. Kudla, and J. P. Mazat (2001a) Control of the threonine-synthesis pathway in Escherichia coli: A theoretical and experimental approach. *Biochem. J.,* 356, 433-444,** http://www.biochemj.org/bj/356/0433/bj3560433.htm
   Chassagnole; Research student (Uni. Bordeaux, 1993-98), then Physiomics staff (2004 to present). Mazat; obtained funding for threonine project and host of Fell's sabbatical (funded by Uni. Bordeaux). Rais & Kudla; Research students in Mazat's research group at Bordeaux who did assorted experimental parts of threonine project.

4. **C. Chassagnole, B. Rais, E. Quentin, D. A. Fell, and J. P. Mazat (2001b) An integrated study of threonine-pathway enzyme kinetics in Escherichia coli. *Biochem. J., 356*:415-423,** http://www.biochemj.org/bj/356/0415/bj3560415.htm
   Quentin also research student in the Mazat lab.

5. **C. Chassagnole, R. C. Jackson, N. Hussain, L. Bashir, C. Derow, J. Savin, & D. A. Fell. (2006) Using a mammalian cell cycle simulation to interpret differential kinase inhibition in anti-tumour pharmaceutical development. *Biosystems, 83(2-3),* 91-97. DOI: 10.1016/j.biosystems.2005.04.007**
   Joint publication with Physiomics and Cyclacel Pharmaceuticals on modelling actions of drug candidates acting on cyclin-dependent kinases, Jackson (Cyclacel); source of experimental data analysed.

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

There are a number of excellent academic groups in the computational biology area, relatively few such groups in industry. Most industrial biologists have limited mathematical skills and training, while most academic bio-mathematicians do not work in collaboration with experimental biologists. Fell's team at Brookes are one of the very few groups attempting to close this gap. Their impact falls into two main areas; through Fell's involvement with Physiomics as Chief Scientific Adviser, they are making powerful modelling tools available to industry; secondly, by training students at Brookes who use modelling tools with systems biology data, they are helping to provide the basis for a more mathematically literate workforce in industrial biology.

In 2001, an independent biotech analyst, John Savin had the idea of using computer modelling of cellular processes to improve the drug development pipeline. He identified Fell's research as exemplifying the concept he had. An investor was found and Physiomics plc was founded independently of Brookes. In the period 2001-2004 Fell was Science Director of Physiomics and from 2005 has been Chief Scientific Adviser attending monthly R & D meetings and Scientific Advisory Boards (3 per year). Both roles have been facilitated through a consultancy agreement with Brookes.

Software for running modelling of biological systems was developed which was used as a demonstration for pharmaceutical companies to try to attract further R&D funding for the systems biology approach to identify targets. Building upon the SCAMP programme, the models of

threonine synthesis and EGF signal transduction described above [2-4] were used to test the Physiomics software.

Physiomics' first major contract was won in 2004 with Bayer Technical Services, and interest from companies undertaking cancer drug development followed, including Cyclacel in Dundee.

Since 2008, Physiomics has secured contracts with major players in the pharmaceutical sector, which demonstrates they have adopted a new systems approach to drug development and therapy design. This can be demonstrated by the numerous contracts which have been reported upon in Physiomics' Annual Reports [a] and Physiomics' News & Events pages [b] and specific press releases including the collaboration with Pharmacometrics Ltd, May 2011 [c] (joint development of DrugCARD database). Building on its work on predicting drug effects on cells, Physiomics has added therapy design to its capabilities, in which the effects of combination drug therapies on tumours are modelled and trialled on the software and the best combination is chosen using the predicted effect. This approach has been demonstrated to be successful in trials funded by Eli Lilly in 2011 [d], in which the results were compared with a trial that used the traditional mouse xenograft model. The software correctly predicted the outcome in 19 out of 21 cases [e]. This indicates huge potential in the reduction in trial costs as the modelling can be run in 4-6 weeks instead of 6 months, and no costs are incurred associated with the animals. This successful trial has resulted in two further contracts with a major global pharmaceutical company, March 2012 [f] and a top-five pharmaceutical company Aug 2012 [g] (names withheld by agreement with the companies). Additional contracts of a therapeutic design focus include:

- ValiRx plc, September 2011 [h]
- Eli Lilly, November 2011 [i]
- Sareum, The Institute of Cancer Research (ICR) and Cancer Research Technology Limited (CRT) joint programme, March 2012 [j]

These contracts demonstrate that the field of systems biology and the modelling approaches pioneered through the work of the Fell research group at Brookes, now form an integral part of the latest approaches to drug discovery and therapeutic design; thus a sector has adopted a new process and technology. Research and Development spending in the three-year period of 2010 to 2012 was £565k, more than double that of the period 2006 to 2008 at £246K. Similarly, the net Share Capital raised in the same periods also more than tripled from £621K to £2.2million [a].

Furthermore, Physiomics has succeeded in its strategic aim of diversifying the applications of its technology beyond drug development and therapeutic design, as demonstrated in the 2010 contract with the Carbon Trust, in collaboration with Green Biologics which involved metabolic modelling of butanol formation in order to optimise its production from waste as a viable fuel source [k].

Brookes has trained a number of the Physiomics staff working on these contracts including Brightman who is still employed at Physiomics. Others who have since moved on include Lubna Bashir, Nazia Hussain, and Cathy Derow (who has returned to Brookes to undertake a PhD). Christophe Cassagnole from the Mazat collaborating lab., joined Physiomics in 2004 and became Chief Operating Officer in 2007 [b].

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

[a] Physiomics Annual Reports 2004 to present. Available from http://www.physiomics-plc.com/investors/reports-prospectus/
[b] Physiomics Plc 'News & Events' http://www.physiomics-plc.com/news-events/
[c] 'New collaboration with Pharmacometrics' http://www.digitallook.com/news/rns/4209197-104396/PYC-New_collaboration_with_Pharmacometrics_Limited_html
[d] 'Virtual Tumour Preclinical - Physiomics Virtual Tumour technology' http://www.physiomics-plc.com/services/schedules-and-combinations/
[e] 'Results Update – Virtual Tumour' 1 April 2011 http://www.physiomics-plc.com/results-update-%E2%80%93-virtual-tumour/

[f] 'New Agreement to advance oncology candidate with global pharma company' 1 March 2012 http://www.physiomics-plc.com/wp-content/uploads/downloads/2012/03/New-Agreement-to-advance-oncology-candidate-with-global-pharma-company-01-03-12.pdf

[g] 'New Agreement to optimise oncology combination with top five pharma company' 10 August 2012 http://www.physiomics-plc.com/wp-content/uploads/downloads/2012/08/New-Agreement-to-optimise-oncology-combination-with-top-five-pharma-company-10-08-12.pdf

[h] "ValiRx to use Physiomics' Virtual Tumour technology to accelerate development of promising prostate cancer drug"http://www.valirx.com/media_files/ValiRx_Plc_-_Physiomics_Collaborative_Agreement.pdf

[i] 'Physiomics shares up 24 pct after new deal with Eli Lilly' Giles Gwinnett, 2 November 2011 http://www.proactiveinvestors.co.uk/companies/news/35090

[j] 'Physiomics to Collaborate with Sareum, the ICR and CRT on Cancer Drug Development Programme' 16 March 2010 http://www.icr.ac.uk/press/press_archive/press_releases_2010/14959.shtml

[k] 'Green Biologics and Physiomics Receive Grant' 16 November 2010 http://www.obn.org.uk/obn_/news_item.php?r=OJK7KR124701