Institution: Newcastle University

Unit of Assessment: UoA4

Title of case study:
e-Therapeutics: a University spin-out company that uses a new approach to discover medicines

1. Summary of the impact

Professor Malcolm Young and colleagues at Newcastle University developed new mathematical and computational tools with which they could analyse large amounts of data on connections in the brain and produce models of how the brain is organised. Young realised that those research tools could also be used to analyse networks of proteins involved in disease processes and predict their susceptibility to drugs and in 2003 he set up the medicines discovery company e-Therapeutics to exploit the technology. The company listed on the AIM of the London Stock Exchange in November 2007 and in May 2013 became the eighth largest company in the biotechnology/pharmaceutical sector listed on the index, with a market capitalisation of over £90 million.

2. Underpinning research

Key Newcastle University researchers
(Where people left/joined the university in the period 1993-2013, years are given in brackets)

- Professor Malcolm Young, Professor of Psychology (1994–2002), and subsequently Pro-Vice Chancellor (2002–2009).
- Dr Peter Andras, Research Associate (2000–2001), Lecturer (2001–2005), and subsequently Reader in Complex Systems in the School of Computing Science.

Background
For decades, neuroanatomists have used tracer chemicals to highlight the neural connections between different areas of the brain. By examining the origin and termination of neurons in the different layers of the brain cortex, they have also been able to make general inferences about the relationship of different areas to each other.

The organisation of the mammalian brain cortex
In 1999, Young and his group published a paper describing new mathematical and computational tools that the researchers had used to explore the organisation of a neural network in the cat brain. Analysis of data covering about 1500 neural connections showed that the whole network was in fact arranged into four distinct systems (the visual, auditory, somatosensory/motor systems, and a fourth higher processing system) (R1). In another study, the researchers used similar methods to model the organisation of the macaque cortex, developing a scheme that represented both the degree of connectivity between different areas and the hierarchical ordering of them (R2).

To test their theoretical models of brain organisation, the researchers needed functional data derived from experiments that they could then compare with their expectations from the model. In collaboration with Professor Rolf Kotter at the Vogt Brain Research Institute in Germany, Young and colleagues used connection data to develop an organisational model of the macaque cortex and then used a set of functional data (on the spread of brain activity after pharmacological manipulation of the cortex) to build a separate database that contained information about the relationships between the different cortical areas. When the two representations of the cortex were compared, the researchers found them to be similar in many respects, establishing the significance of the connectivity analysis (R3).

The structural properties of brain networks
Complex networks, whether biological or artificial, can be classified on the basis of their structure (one important aspect, for example, is the pattern of distribution of connections between nodes). A network's structure is important as it can influence the robustness of the underlying system. In

collaboration with Andras in the School of Computing Science, Young developed computer models of cortical networks and probed their structure by removing nodes and connections and then simulating the effects. The researchers found that cortical networks closely resembled a particular network type – scale-free – and were characterised by the presence of highly connected nodes and bottleneck connections (R4). They speculated that this might partly explain the conditional robustness of brain systems (such as the variable effects of lesions made in the cortex on brain function) and relate to how brain networks develop.

The networks that control processes in health and disease are also scale-free networks, most of whose nodes can be bypassed but with a few nodes that receive many connections and make the whole network vulnerable when they are disrupted. Thus, by applying the network analysis used in brain connectivity it was possible to identify the key nodes in disease processes and provide a new route to drug discovery.

3. References to the research

(Newcastle researchers in bold. Citation count from Scopus, July 2013)

R1. **Scannell JW, Burns GA, Hilgetag CC**, O'Neil MA, **Young MP** (1999). The connectional organization of the cortico-thalamic system of the cat. *Cerebral Cortex* 9(3):277–99. DOI: 10.1093/cercor/9.3.277. **178 citations.**

R2. Hilgetag CC, **O'Neill MA**, **Young MP** (2000). Hierarchical organization of macaque and cat cortical sensory systems explored with a novel network processor. *Philosophical Transactions of the Royal Society B: Biological Sciences* 355(1393):71–89. DOI: 10.1098/rstb.2000.0550. **60 citations.**

R3. Stephan KE, **Hilgetag CC**, Burns GA, **O'Neill MA, Young MP**, Kotter R (2000). Computational analysis of functional connectivity between areas of primate cerebral cortex. *Philosophical Transactions of the Royal Society B: Biological Sciences* 355(1393):111–126. DOI: 10.1098/rstb.2000.0552. **129 citations.**

R4. **Kaiser M, Martin R, Andras P, Young MP** (2007). Simulation of robustness against lesions of cortical networks. *European Journal of Neuroscience* 25(10):3185–92. DOI: 10.1111/j.1460-9568.2007.05574.x. **76 citations.**

Select research grants

- Royal Society. 1992–7. £145 000. *Structure and function in primate cerebral cortex.* (Young was employed at Newcastle University from October 1994).
- Wellcome Trust. 1993–6. £57 000. *Interactions between cortical and subcortical structures in the mammalian brain.*
- Wellcome Trust. 1996–9. £54 000. *Mathematical approaches to the analysis of connectivity in the mammalian brain.*
- Wellcome Trust, Biomedical research collaboration grant for links with the Vogt Institute. 1997–2000. £17 000. *Neuroinformatics: integrating connection and activation data.*

4. Details of the impact

How research on brain networks led to a new approach to discovery of medicines

In the course of their research at Newcastle University, Young and Andras gained insights into how neural connection data could be transformed into models of the structure and organisation of neural networks. In later work, they showed that such models were capable of simulating certain features of the brain systems they described, including the vulnerability of brain functions to specific lesions in the neural network (which have been extensively described by experimental neuroscientists over the years). The intuitive leap made by Young was that the same techniques he used to transform neural connection data into representations of neural networks could be used to transform protein interaction data (of which there is much in the literature) into representations of the protein networks that underpin basic cellular processes, including those associated with disease. Thus by probing the network underpinning a disease process, one should be able to

identify a set of network points (proteins) which when targeted will disrupt the functioning of that network and thereby treat disease. The approach is set out in the first patent: *Method and apparatus for identifying components of a network having high importance for network integrity* (Ev a).

e-Therapeutics

In 2003 Malcolm Young founded e-Therapeutics (Ev b), a medicines discovery company spun out from his research at Newcastle University. The company's new and unique approach, which involves network pharmacology, is protected by six patents that contain more than 200 separate claims of invention and granted in Europe and the USA (Ev a).

A key feature of the company's method is that it identifies the crucial few proteins that must be targeted to disrupt the disease process; it therefore follows that a drug candidate which interacts selectively with those target proteins must be identified. The company initially sought candidates from among known molecules, using its approach to identify those suitable for 'repositioning' into the disease in question. Such molecules often have safety data that can support rapid progress into clinical trials and typically have well-characterised interactions with human proteins. Previously undeveloped compounds are more likely, however, to garner the strongest forms of intellectual property protection, so the company's drug discovery programme is now mainly focused on identifying novel molecules.

Industry analysts have commented favourably on this new way of finding medicines. The productivity of research and development spending by the pharmaceutical industry has fallen dramatically over recent decades, and it may be that the existing method of reductionist drug discovery – identifying one 'target' protein and then finding a drug that binds to it – is not suitable for treating complex diseases such as depression and cancer. In September 2011, the Wall Street Journal published an article titled *Drugs that are as smart as our diseases* in which the limitations of the old approaches to drug discovery and the merits of e-Therapeutics' implementation of network pharmacology are described (Ev c).

Drugs in clinical trials

Two drugs, both repositioned, are currently being evaluated in clinical trials. The company's anti-cancer drug candidate, ETS2101, is in phase I clinical trials in the US and UK. ETS2101 is dexanabinol, a compound that was thought to have a neuroprotective function after brain injury, but that was shown in a phase III trial to be safe but ineffective for this indication (Maas et al.,Lancet Neurology 2006. PMID:1636102). Network modelling predicted an anti-apoptotic action. One trial involves patients with primary or secondary brain cancer (started June 2012; key data on safety and dosing expected Q4 2013) and the other involves patients with solid tumours (started September 2012; key data expected Q1 2014). By May 2013, a total of 17 patients had been treated in the two phase I trials. No patient had experienced serious adverse events related to treatment (although one patient experienced severe fatigue after dosing and continued on a lower dose). One patient with oesophageal cancer had experienced an objective anti-tumour response (Ev d and Ev j).

The second drug candidate, ETS6103, is a generic drug with an established safety profile. Trials of ETS6103 for an anti-depressant indication are more advanced. A controlled phase IIa trial of the drug, which ended in January 2009, demonstrated encouraging results when the drug was compared with a marketed tricyclic anti-depressant (Ev e). A larger phase IIb trial is expected to start shortly (Ev f). A third drug is currently in pre-clinical development, which shows strong *in vitro* activity against *C.difficile*, a major cause of hospital acquired infections (Ev f).

The company

e-Therapeutics has grown substantially since it was founded in 2003. It was listed on the Alternative Investment Market (AIM) of the London Stock Exchange in November 2007, and with a market capitalisation of £37.3 million at flotation it has become a significant presence in the UK marketplace with a current (26/06/2013) valuation of £92.7 million (Ev g). In May 2013, e-Therapeutics became the eighth largest company by market capitalisation in the pharmaceutical / biotechnology sector on the AIM (Ev h).

In the context of UK university spin-outs, e-Therapeutics ranks favourably. The 2010/11 UK Higher Education Business Community and Interaction Survey showed there were just over 1000 active spin-outs in which HEIs had equity stakes that year and the average external investment was of the order of £0.7 million per company (Ev i). In contrast, e-Therapeutics raised £18 million in February 2011 and another £40 million in February/March 2013 via share issues (Ev j). The major investors are currently Invesco (49.8% share) and Aviva (16.2% share) (Ev a and Ev j).

e-Therapeutics employs 20 skilled people across two sites in the UK; the Network Pharmacology Centre in Oxfordshire (opened in February 2012) and the company's facility in Newcastle. Since 2008, research and development spending has totalled more than £11.3 million, and the money raised from recent share issues is expected to sustain employment and high levels of research spending through 2017 (Ev j).

5. Sources to corroborate the impact

Ev a. Patents assigned to e-Therapeutics: EP1968237, EP2028792, EP2157734, EP2154824; US8301391, US7768942, US7990878. Search at www.google.com/patents

Ev b. e-Therapeutics website: http://www.etherapeutics.co.uk. Investor information: http://www.etherapeutics.co.uk/Information/investor-relations.html

Ev c. Wall Street Journal (September 2011): Drugs that are as smart as our diseases. http://online.wsj.com/article/SB10001424053111904265504576567070931547618.html

Ev d. Company update on progress of ETS2101 cancer trials. http://www.etherapeutics.co.uk/userfiles/file/ets2101_trials_update_dec_2012_final_181212.pdf

Ev e. Company-reported results of the completed phase IIa trial of ETS6103. http://www.etherapeutics.co.uk/userfiles/file/e-Therapeutics%20antidepressant%20trial%20announcement_FINAL.pdf

Ev f. Company plan for phase IIb trial of ETS6103 and information on the C.difficile programme. http://www.etherapeutics.co.uk/index.php?option=com_content&view=article&id=3&Itemid=5

Ev g. London Stock Exchange: financial information on e-Therapeutics http://www.londonstockexchange.com/exchange/prices-and-markets/stocks/summary/company-summary.html?fourWayKey=GB00B2823H99GBGBXAIM

Ev h. London Stock Exchange: AIM index statistics (May 2013). http://www.londonstockexchange.com/statistics/historic/aim/may-2013.xls

Ev i. HEFCE HE-BCI (2010-11). Section B UK sector figures for spin-off and start-up activity. Table 4d. http://www.hefce.ac.uk/media/hefce/content/pubs/2013/201311/Annex%20A%20Summary%20data%20-%20UK.xls

Ev j. Corroborating source: Chief Financial Officer, e-Therapeutics.