Institution: The Open University

Unit of Assessment: A3, Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: Economic impact of development of neural tissue models

1. Summary of the impact

Researchers at the Biomedical Research Network (BRN) at The Open University (OU) have developed two novel technologies:

- Engineered neural tissues that model the central nervous system (CNS)
- A brain endothelial cell line to model the human blood–brain barrier for drug delivery studies.

These patented technologies have been adopted by industrial partners, who have either invested in their further development and the automation of the production process to generate neural tissue model kits or have adopted the technology for their own use following licence transfer and/or temporary industrial contracts.

2. Underpinning research

Neurological and mental health conditions represent a sizeable societal burden that impacts on the quality of life and well-being of individuals affected by them and their carers. These health issues have created an economic drive for the development of CNS therapeutics that industry is attempting to meet; the technologies developed at the OU have helped make this process more efficient and cost-effective.

Nervous system tissue engineering Since his appointment in 2004, nervous system tissue engineering research by **Phillips** led to the development of technology to control the three-dimensional (3D) alignment of neural cells within hydrogels. Complex three-dimensional *in vitro* models have been developed for use by industry to test CNS-active drugs as it closely mimics the *in vivo* cellular architecture. The culture model involves cells being seeded within protein matrices (typically collagen gels), tethered such that the endogenous forces produced by the cells generate an axis of tension to which the cells align, forming a 3D construct of highly aligned cells and matrix that can support and guide neuronal regeneration. This 'Self-Aligning Tissue Growth Guide' was patented in 2004 and further developed to provide implantable conduits for nervous system repair [3.1, 3.2]. The Phillips group has used tissue-engineered culture models to research the sensitivity of peripheral nervous system cells to cancer therapy [3.3], and to explore the effect of astrocyte alignment on neuronal regeneration [3.1].

Brain endothelial cell line Drugs targeted to the central nervous system form a minority within those commercially available due, in part, to the presence of the blood–brain barrier. Therefore development of *in vitro* models of the human blood–brain barrier, is not only a means to reduce animal use in medical research but also provides a tool for pharmaceutical companies to test human central nervous system penetrability of candidate drugs.

The **Male** and **Romero** group have extensive experience in isolating human brain endothelial cells (the cells that form the blood–brain barrier) and between 2003 and 2005, they collaborated with groups in Paris (Dr P.O. Couraud, INSERM) and New York (Dr B. Weksler, Cornell University) with experience in immortalising techniques, to produce an easy-to-grow immortalised human brain endothelial cell line that closely mimics the *in vivo* blood–brain barrier [3.4].

This cell line has been patented and distributed freely to more than 160 research groups worldwide to investigate pathogenic mechanisms of diverse neurological conditions such as Alzheimer's disease, multiple sclerosis and infections (for a review on research applications, see 3.5). This research has attracted funds from diverse charity-based and Research Council bodies (e.g. BBSRC, The DANA Foundation, the Multiple Sclerosis Society) to investigate inflammation at the

blood–brain barrier and from industry (MedImmune, Midatech Ltd.) to develop drug delivery strategies to the central nervous system.

Combination of both technologies Within the past 2 years, Phillips, Male and Romero have combined both technologies to develop a 3D model of the human blood-brain barrier with human CNS constructs. This has been used to investigate gold nanoparticles as delivery agents for CNS drugs [3.6].

3. References to the research

Peer-reviewed journals

1. East, E., de Oliveira, D.B., Golding, J.P. and Phillips, J.B. (2010) 'Alignment of astrocytes increases neuronal growth in three-dimensional collagen gels and is maintained following plastic compression to form a spinal cord repair conduit', *Tissue Engineering Part A*, vol. 16, no. 10, pp. 3173–83.
2. Phillips, J.B., Bunting, S.C., Hall, S.M. and Brown, R.A. (2005) 'Neural tissue engineering: a self-organizing collagen guidance conduit', *Tissue Engineering*, vol. 11, nos. 9-10, pp. 1611–17.
3. Wright, K.E., Liniker, E., Loizidou, M., Moore, C., MacRobert, A.J. and Phillips, J.B. (2009) 'Peripheral neural cell sensitivity to mTHPC-mediated photodynamic therapy in a 3D *in vitro* model', *British Journal of Cancer*, vol. 101, no. 4, pp. 658–65.
4. Weksler, B.B., Subileau, E.A., Perrière, N., Charneau, P., Holloway, K., Leveque, M., Tricoire-Leignel, H., Nicotra, A., Bourdoulous, S., Turowski, P., Male, D.K., Roux, F., Greenwood, J., Romero, I.A. and Couraud, P.O. (2005) 'Blood–brain barrier-specific properties of a human adult brain endothelial cell line', *FASEB Journal*, vol. 19, no. 13, pp. 1872–4.
5. Weksler, B., Romero, I.A. and Couraud, P.O. (2013) 'The hCMEC/D3 cell line as a model of the human blood brain barrier', *Fluids and Barriers of the CNS*, vol. 10, no. 16 [online] http://www.fluidsbarrierscns.com/.
6. Gromnicova, R., Davies, H.A., Sreekanthreddy, P., Romero, I.A., Lund, T., Roitt, I.M., Phillips, J.B. and Male, D.K. (2013) Glucose-coated gold nanoparticles transfer across human brain endothelium and enter astrocytes in vitro. PLOS ONE, in press (accepted on 18/10/2013, the output can be supplied by the OU on request).

Grants

2013-2016. BBSRC. Role of microRNAs in ageing at the blood-brain barrier. £386,000. Romero (PI), Saffrey (OU); Wharton, Heath (Sheffield)

2013-2016. MedImmune. Development of a drug delivery system to the CNS using brain endothelial-specific non-antibody binding domains as transport carriers. £75,000. Romero (PI)

2012-2013. Midatech Ltd. Nanoparticles for gene delivery across the blood brain barrier. £45,000. Male (PI)

2011-2014. Multiple Sclerosis Society of Great Britain and Northern Ireland. MicroRNAs in the cerebral vasculature and multiple sclerosis. £205,122. Romero (PI), Hirst, Male (OU), Sharrack (Sheffield), Baker, Michael (QMUL)

2011-2014. TAP Biosystems. Development of novel, robust 3D CNS tissue models for neurobiological studies and drug discovery. £58,100. Phillips (PI) and Loughlin (OU).

2009. Multiple Sclerosis Society of Great Britain and Northern Ireland. Expression profile of microRNAs by human brain endothelium in neuroinflammation: implications for blood-brain

barrier breakdown in multiple sclerosis. £25,677. Romero (PI), Male, Hirst (OU) and Sharrack (Sheffield).

2008-2011. The Migraine Trust The response of human brain endothelium and astrocytes to vasoactive mediators. £70,000. Male (PI)

2007-2011. The Wellcome Trust. Modelling and overcoming the biological interfaces that prevent nerve generation. £188,124. Phillips (PI) and Golding (OU).

2006-2009. DANA Foundation. Determining the transcriptional environment that suppresses expression of tight junctional proteins at the blood-brain barrier in neuroinflammation. $200,000. Romero (PI) and Male (OU)

4. Details of the impact

The impact of our research into development of neural tissue models involves the adoption of the technologies established by OU researchers (in international and/or national consortia) by pharmaceutical and biotechnology companies. Both technologies addressed specific needs within the industrial sector, targeted at improving CNS *in vitro* models. Adoption of these technologies has benefited industrial partners by leading to changes in their practice including the use of the technology for testing CNS drug candidates and the novel application of commercial products already developed by the company. The technologies developed at the OU have thus helped make industrial practices more efficient and cost-effective and opened up new applications for product placement.

The impact of our research has been global. Both technologies have been adopted by many UK-based and international pharmaceutical and biotechnology companies in Europe, the USA and Japan (see list below). As a result of our established international patents, we hold licensing agreements with companies who can use the models in the drug development process (i.e. drug toxicity, drug delivery, etc.) and can apply the technology within their products. This commercialisation has established sustained streams of royalty income for The Open University. It has also led to joint research activities and publications with industry and a grant of £70K from MedImmune to sponsor an industry–academia co-supervised studentship at the OU.

An '*in vitro* human blood–brain barrier model' patent, managed by INSERM, and for which the OU has an active revenue share agreement in place (33% of the received licences fees), has generated >£150,000 of royalty income since 2008 through licences and/or agreements with the following companies: Abbott GmBh, Amgen, Dainippon Sumitomo Pharma, GSK, Hoffman La Roche, MedImmune, Novartis, Pfizer Japan and Sanofi-Aventis. After recovering investment for the patent prosecution, the licence income received by the OU from this patent has been £53,628 to date.

In the context of the nervous tissue engineering model, a member of Phillips's team received a prestigious 1st prize for part of their work, at the Tissue Engineering and Regenerative Medicine International Society (TERMIS) World Congress 2012, an academic conference where clinicians and scientists from academia and industry interact. The group is now working with leading regenerative medicine companies (e.g. TAP Biosystems) to develop a therapeutic product.

Following a keynote talk by Phillips, 'Tissue engineering: a new dimension to animal replacement', at the NC3Rs/BBSRC Symposium (April 2009) for researchers in academia and industry, the group was approached by The Automation Partnership (now TAP Biosystems) with a view to developing a commercially engineered CNS culture model for the research and development community. This led to a collaborative project between the OU and TAP to explore options for exploiting the Phillips group's technology as a way to adapt TAP's commercially available 3D system, termed RAFT, for CNS use.

As a result of this collaboration, in 2011 TAP invested in a three-year project based at the OU to generate and manufacture advanced 3D CNS tissue models. This provides a clear example of impact – the technology was originally developed in the academic group and has been adopted by TAP, who are a leading supplier of cell culture technology with global reach.

The economic impact of this technology on industry is manifested by the recent addition in 2011 of the alignment technology to TAP's RAFT system, which is a significant new product option for the company. A more immediate impact as a result of the OU/TAP collaboration has already been made by applying the current RAFT system to CNS research, as evidenced by press releases, application notes, a joint TAP/OU webinar (November 2012) and a number of joint conference presentations.

Combining both technologies to create CNS/endothelial cell constructs has attracted a great deal of interest from international companies. For example, an application note used to launch TAP's new RAFT insert product, which combines endothelial barrier systems with 3D CNS models, has already been released. In addition, the supporting data for a patent application in February 2013 on their nanoparticle-based delivery system for CNS-active drugs by Midatech Ltd, is based on studies carried out at the OU combining both technologies.

5. Sources to corroborate the impact

Patents

Phillips, J.B. and Brown, R.A. (2004) Self-aligning tissue growth guide WO2004087231 (EU, USA, Japan, Canada, Australia) assigned to The Open University.

Couraud, P.O., Romero, I.A. and Weksler, B.B. Human blood–brain barrier model. INSERM (France) and Cornell University (USA). Patent no. WO/2006/056879. Pub date: 01.06.2006.

Midatech Limited. Nanoparticle Delivery Compositions. UK Patent Application no. 1302427.8.

Contacts who can corroborate claims of contribution, benefit and impact

Deputy Director Intellectual Property, European Patent Attorney, INSERM Transfert
Associate Director, ADPE, MedImmune
Chief Scientific Officer, TAP Biosystems
Chief Scientific Officer and Chairman, Midatech Limited

Prize based upon external assessment of this research and its impact

TERMIS World Congress 2012:
http://www.jamesphillips.org/news/nerve-repair-research-wins-international-prize

Public engagement and media coverage:

OU Press release: TERMIS prize http://www3.open.ac.uk/media/fullstory.aspx?id=24289

TAP Biosystems press release on their website:
http://www.tapbiosystems.com/tap/news/pages/curr_news.asp?id=AAAAD041-9A22-4A2D-AB59-5427B38690FF

OU-TAP joint Press release: http://www3.open.ac.uk/media/fullstory.aspx?id=23419

RAFT Webinar, 8 November 2012:
http://www.tapbiosystems.com/tap/news/pages/curr_news.asp?id=CB005951-367B-4FE9-8A7E-AC9952099D4F

Combination of technologies developed by the OU:
http://www.tapbiosystems.com/tap/news/pages/curr_news.asp?id=A6B079E5-9D1E-4A43-8E09-8F7EEE9F59E6