Institution: Glasgow Caledonian University

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

Title of case study: Biopta: Delivering Drug Testing in Human Tissues to Big Pharma

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

Biopta is a profitable, award-winning company spin-out from Glasgow Caledonian University (GCU). Established in 2002, to deliver commercial products and services developed by university employees, it employs 19 staff across its Glasgow and Beltsville (Maryland USA) offices. It specialises in the provision of instruments and services monitoring drug effects in ethically donated, healthy and diseased human tissue, and counts eight of the top 10 major pharmaceutical companies as clients. To date, Biopta has provided early stage testing on more than 400 new drugs, designed to treat conditions such as high blood pressure, asthma and irritable bowel syndrome, determining their efficacy and potential side effects.

2. Underpinning research (indicative maximum 500 words)

Working within GCU's Department of Biological Sciences (1996 to 2004), Professor Chris Hillier (Reader during period of research, left GCU 30-10-11) and Dr David Bunton (Lecturer during period of research, left GCU 01-01-08) investigated the structural and functional aspects of healthy human arteries and veins, and the same tissues from a wide variety of patients with vascular dysfunction[1-6] [grants (G) 1-5]. These ground-breaking studies emphasised the absolute importance of using human tissues in research[1-5]. It is clear from the failure of numerous Phase II and III clinical trials, that animal models cannot reliably predict drug effects in humans. Equally, it is evident that short-lived animal models[6] cannot successfully phenocopy the complex, progressive changes occurring in human arteries during aging, chronic heart failure, and critical limb ischaemia.

Supported by funding (British Heart Foundation, Chest Heart and Stroke, Scotland, and Scottish Enterprise [G1-5]) Hillier led and contributed to studies in human tissues[1-5]. This involved characterising alpha1-adrenoceptor subtypes in human subcutaneous resistance arteries, alterations in the morphology and reactivity of these tissues induced by critical limb ischaemia (CLI) and chronic heart failure, and differential responses in human subcutaneous and skeletal muscle vascular beds in CLI, most notably hypersensitivity to catecholamine-induced contractions. Research also investigated the impact of angiotensin II, urotensin II and endothelium-derived hyperpolarizing factors in human subcutaneous resistance arteries, and utilised confocal microscopy to image vascular remodelling[1-5]. Further, Bunton characterised the mechanisms by which bradykinin and 5-hydroxytryptamine regulate relaxation, and constriction, in bovine pulmonary supernumerary arteries[6].

Together, Bunton and Hillier combined optical technology, molecular pharmacology and software engineering, to produce an integrated tool for drug delivery and analysis. Based on this highly original research, GCU received Scottish Enterprise Proof-of-Concept funding (£122K; G3) to develop a prototype testing instrument, and provided a commercialisation sabbatical (£11,000) to Hillier and Bunton. Biopta Ltd. was founded in 2002 and work began on a commercial prototype of 'PERF-EXION™' software and PM-1 instrument, supported by a Scottish Government SMART award (£75K; 2001). Furthermore, Bunton led on the development of their automated perfusion myograph, which can detect external and internal dimensions of tubular biological structures, allowing intra- and extra-luminal infusion of novel drugs to determine effects on constriction, relaxation of vascular tone, and the measurement of vascular permeability.

Glasgow Caledonian University has continued to work in vascular research, supported by funding (>£350K; 2008-2013) from the British Heart Foundation, Heart Research UK, and a BBSRC/CASE award with Biopta. This GCU/Biopta studentship (2010-2013), which involved a collaboration between GCU and both UK and USA Biopta sites, continued the theme of researching responses in human tissue, investigating the role of the slow delayed rectifier potassium channel in the human heart. This study clearly revealed species (human *versus* rodent) differences in the mechanisms of ventricular arrhythmias, creating a novel model to test pro-and anti-arrhythmic properties of new pharmacological entities to treat this potentially fatal cardiovascular condition.

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

1. Coats, P, Johnston, F., MacDonald, J., McMurray, J.J. and Hillier, C. (2001) Endothelium-derived hyperpolarizing factors: identification and mechanisms of action in human subcutaneous resistance arteries. Circulation 103: 1702-1708. http://circ.ahajournals.org/content/103/12/1702.long

2. Hillier, C., Berry, C., Petrie, M.C., O'Dwyer, P.J., Hamilton, C., Brown, A. and McMurray, J. (2001) Effects of urotensin II in human arteries and veins of varying calibre. Circulation 103: 1378-1381. http://circ.ahajournals.oprg/content/103/10/1378.long

3. Jarajapu, Y.P., Coats, P., McGrath, J.C., MacDonald, A. and Hillier, C. (2001) Increased alpha(1) and alpha(2)-adrenoceptor-mediated contractile responses of human skeletal muscle resistance arteries in chronic limb ischaemia. Cardiovasc. Res. 49: 218-225. http://cardiovascres.oxfordjournals.org/content/49/1/218.long

4. Coats, P., Johnston, F., MacDonald, J, McMurray, J J and Hillier, C. (2001) Signalling mechanisms underlying the myogenic response in human subcutaneous resistance arteries. Cardiovasc. Res. 49: 828-837. http://cardiovascres.oxfordjournals.org/content/49/4/828.long

5. Hillier, C., Cowburn, P.J., Morton, J.J., Dargie, H.J., Cleland, J.G., McMurray, J.J. and McGrath, J.C. (1999) Structural and functional assessment of small arteries in patients with chronic heart failure. Clinical Science 97: 671-679. http://www.clinsci.org/cs/097/0671/cs0970671.htm.

6. Tracey, A., Bunton, D, Irvine, J., MacDonald, A. and Shaw, A. (2002) Relaxation to bradykinin in bovine pulmonary supernumerary arteries can be mediated by both a nitric oxide-dependent and –independent mechanism. Br. J. Pharmacol.137: 538-544. http://onlinelibrary.wiley.com/doi/10.1037/sj.bjp.0704890/full

Key Grants

1. Hillier C. Relaxin - A novel hormone with therapeutic possibilities in heart failure; British Heart Foundation; 2001-2003, £90,000.
2. Hillier C. Intimal hyperplasia in human large arteries; British Heart Foundation; 2002-2004, £48,000
3. Hillier C and Bunton D. Proof-of-concept award for development of PERF-EXION, a non-imaging technology; Scottish Enterprise; 2001-2002, £122,500.
4. Hillier C. Mechanisms of interaction between adrenomedullin and endothelin; Chest, Heart and Stroke Scotland; 2001-2002, £26,363.
5. Hillier C. Scottish Enterprise and the Royal Society of Edinburgh Enterprise Fellowship in Biotechnology; 2001-2002, £32,000.

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

In August 2002, Biopta was spun out from GCU as a life sciences company specialising in the provision of instruments and services to measure the effect of novel drug candidates in human

tissue samples. Biopta continues to grow at an annual average rate of 25%; as a profitable business it is self-funding and employs a total of 19 staff at its Glasgow Headquarters, and its USA subsidiary company. As a shareholder, GCU receives quarterly board reports from Biopta. Biopta counts eight out of the top 10 major pharmaceutical companies as its clients, achieving more than 70% of its service revenues out with the UK.

With an intellectual property portfolio and fee for service model, Biopta has leveraged funding from Scottish Enterprise (Proof of Concept and SMART awards) (sources [S] 1, 2), to develop innovative drug delivery and analysis prototypes. The project was identified as one of the eight most innovative technologies in Scotland at the Edinburgh International Science Festival (2000), and won a regional John Logie Baird Award for Innovation (2001). An initial tranche of investment funding (£575K; Braveheart Ventures, Scottish Co-investment Fund, LINC Scotland and a Scottish Executive SPUR grant) was followed by a further round of funding in 2008 (£900K; Braveheart, Scottish Enterprise's (SE) Scottish Co-Investment Fund and TRI Cap. Biopta won the Glasgow Business Award for International Business (2008) in recognition of overseas business. A further round of funding was closed in 2010, bringing the total investment in Biopta to >1.74 million [S1].

The details of Biopta's research data are commercially sensitive and owned by companies sponsoring this research. However, it is clear that the PERF-EXION software and PM-1 drug delivery instrument forms one of Biopta's key lines of business and has established Biopta as a world leader in the use of fresh human tissues to better predict drug activity prior to clinical trials. As part of Biopta's research services, these tools have been used to assess over 50 new drug candidates for safety and efficacy in blood vessels, generating valuable information for pharmaceutical companies developing drugs that may impact on the cardiovascular system [S2, S4]. Furthermore, Biopta is the first Contract Research Organisation worldwide to focus on the use of ethically-donated living human tissues in the development of new drugs. This profitable company has delivered projects to 75 pharmaceutical and biotechnology companies and has investigated over 400 potential new drugs for their preclinical safety and efficacy [S2, S4].

Biopta's radical approach, using human tissues to develop new drugs, is viewed as a major step forward in the creation of safe, effective medicines. Biopta's human tests are considered to be more reliable than many of the animal models that continue to dominate the drug testing process, because of its ability to study disease tissues from a range of patient groups. Biopta is pioneering in this regard, publishing influential articles (Hillier and Bunton (2007) *Functional human tissue assays* Drug Discov Today 12: 382-388; Hillier and Bunton (2009) *Could fresh human tissues play a key role in drug development?* Altern Lab Anim. 38: Supp 1:5-10). Biopta has also contributed to policy debate in Archibald *et al* (2011) (*Safety of medicine and the use of animals in research* (2011) Lancet 378(9802)) and the House of Lords (2009) and House of Commons (2010) [S3] in order to raise awareness of the need for a coordinated effort to make tissues generated during surgery (many of which are incinerated) more available to researchers for the benefit of pharmaceutical development.

The economic value of this technology and testing is evidenced by the jobs (19) created and retained by Biopta over a ten-year period. Further, the excellent staff development and training within Biopta has enriched the skills and knowledge base of the wider Scottish labour force as scientists move between companies. For example, former employees of Biopta have progressed to Executive Director positions at other SMEs in Scotland (Arrayjet Ltd and Fios Genomics). As part of its expansion into the North American market Biopta Ltd has created a wholly-owned subsidiary company, Biopta Inc. based in Beltsville, Maryland, USA, which employs two full-time scientists and one part-time scientist.

The scientific and societal (e.g. patients, healthcare) benefits of Biopta's research activities have been justified and verified by approval of the company as an ethically-approved UK Research

Tissue Bank (Approval number 07/S0704/45+5 (12/WS/0069)). The importance of Biopta's work is emphasised by the contribution of its data to the regulatory approval of drugs for clinical trials or marketing authorisation, which requires membership of the UK Department of Health's Good Laboratory Practice (GLP) programme. Biopta's established expertise in functional human tissue studies and focus on translational science means it has become a partner in the new £20 million Stratified Medicine Scotland Innovation Centre (SMS-IC) at the new South Glasgow Hospitals Campus, which involves a consortium of universities, NHS Scotland and industry partners.

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

1. Representatives of investors in Biopta can be contacted to verify the progress of the company (Portfolio Manager, Braveheart Investment Group) and the economic impact of its research (Scottish Enterprise, Account Manager for Biopta Ltd).

2. Testimonials as to the effectiveness of the approach adopted by Biopta have been provided by UK, European and Canadian Biotechnology companies.
Senior Vice President and Chief Medical Officer, Proteon Therapeutics: "*Biopta has provided Proteon with high quality data in human tissue to guide dose selection for human clinical trials. The information has been extremely valuable in demonstrating the potential benefit of PRT-201 in patients needing hemodialysis access or treatment of peripheral arterial disease. The information has and will continue to be an important part of our nonclinical data for regulatory submissions."*

Chief executive of Braveheart, said: *"Biopta is now recognised as an established brand in human tissue testing and we are pleased to support the company in its continued development."*

Head of Scottish Enterprise's Co-Investment Fund said: *"The Scottish life sciences sector continues to attract significant investment through innovative young companies such as Biopta. We are pleased to continue our support for Biopta through our equity investment funds and account management support."*

Chairman of TRI Cap, added: "*Our members first invested in Biopta in 2008 and we are pleased to continue that association as the company expands its range of activities*."
http://www.tricapital.co.uk/content/news/BIOPTANEWSRELEASEOCT2010.php

3. http://www.safermedicines.org/pdfs/human_tissues_abstracts.pdf (House of Lords)
http://www.publications.parliament.uk/pa/cm201011/cmhansrd/cm100623/halltext/100623h0001.html (House of Commons)

4.Publications by clients of Biopta, which reflect the contribution of Biopta's services and products, include:

Neuraxon Inc., Toronto, Canada. Discovery of N-(3(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-6-yl) thiopene-2-carboximidamideas a Selective Inhibitor of Human Neuronal Nitric Oxide Synthase (nNOS) for the Treatment of Pain. *Journal of Medicinal Chemistry* 20: 7408:7416 (2011). Annedi S.C., Maddaford S.P., Mladenova G., Ramnauth J., Rakhit S., Andrews J.S., Lee D.K.H., Zhang D., Porreca F., Bunton D.C., Christie L.

Theravance Inc., California. The inability of tegaserod to affect platelet aggregationand coronary artery tone at supratherapeutic concentrations. *Naunyn-Schmiedeberg's Arch Pharmacol* 385:103–109 (2012).Higgins D. L., Ero M. P., Loeb M., Kersey K., Hopkins A., Beattie D. T.