Institution: University of Brighton
Unit of Assessment: A3 Allied Health Professions, Dentistry, Nursing and Pharmacy
Title of case study: Stimulating medical device innovation in a SME **ICS [1]**

1. Summary of the impact

A sustained joint research partnership with Biocompatibles UK Ltd has stimulated innovation underpinning the company's product development pipeline. Products include a family of soft contact lenses, enhanced medical device coatings, and novel treatments for liver cancer. Innovative enhancements, such as the unique non-biofouling nature of the company's ocular and cardiovascular devices and the practical utility of its drug eluting therapies for targeting liver malignancies, have delivered improved clinical performance and differentiated these products from those of competitors in the same markets. The company's continuing success in developing innovative medical technology products was recognised by the sale of Biocompatibles UK for £177m in 2011.

2. Underpinning research

The research partnership between University of Brighton (UoB) and Biocompatibles UK (BUK) was originally established in the early 1990s through an MRC/SERC/DTI/DOH Medical Implants LINK Programme to support the synthesis, characterisation, evaluation and development of novel phosphorylcholine (PC) polymer materials for medical device applications in the ophthalmic field. This fuelled the development of PC coatings and bulk materials for a wide range of medical device applications, including the development of novel contact lens and intraocular lens materials and provided a range of clinically reflective assays for assessing the ocular compatibility of novel biomaterials [references 3.1, 3.2], which were ultimately translated from the University of Brighton to the company through a Teaching Company Scheme. These assays offered more clinically relevant approaches of assessing ocular biocompatibility *in vitro* than those that were required at the time by regulatory authorities and helped to demonstrate the advantages of the PC materials.

The joint research extended into the evaluation of biocompatible coatings based upon sulfo- and phosphobetaines, physi-sorbed and cross-linkable systems, blends and systems modified with cationic charge through internal company investment. This work enabled the university to jointly demonstrate advantages for PC coatings over conventional hydrogel coating systems, extending beyond ocular biomaterials into other areas, including blood-contacting devices such as extracorporeal circuits, coronary guidewires, catheters, stents and a variety of urological devices [3.3].

Focus within BUK switched to the development of drug eluting stents and through the collaboration with Professor Steve Armes of the Chemistry Department at the University of Sussex, UoB researchers also collectively sought to develop further drug delivery applications for new PC polymers. This involved exploring novel architectures provided by controlled radical polymerisation and the self-assembled structures that these materials could generate, including the first reports of thermo-responsive PC polymer gels and pH-responsive PC nanoparticulate systems [3.4]. The success of this partnership was recognised with the accolade of the Sussex Business Award 2002 for 'Best Industry-University Collaboration'.

In 2002, BUK sold both its contact lens and cardiovascular divisions and started a new business in the field of embolotherapy, with a view to develop novel drug-eluting bead (DEB) systems for the treatment of liver cancer. UoB was intrinsically involved in the characterisation of these novel systems, supported by a number of EPSRC/BBSRC CASE studentships and industrially funded PhD projects, the majority of which were based within the company's laboratories. This has extended our knowledge of the DEB technology, particularly its drug loading and release properties [3.5, 3.6]. Further work has extended into DEBs based on alginate biopolymers as a degradable embolic agent and currently the research partnership is focused on development of novel cell-based assays for the evaluation of drug combinations in both normoxic and hypoxic conditions and the development of a novel hypoxia-responsive DEB system.

Key researchers:

Stephen Denyer:	Professor of Pharmaceutical and Applied Microbiology (Jan 1991–Oct 2003).
Richard Faragher:	Research Fellow (Jan 1994–Aug 2000), Senior Research Fellow (Sept 2000–Mar 2003), Principal Research Fellow (Apr 2003–July 2009) Professor of Biogerentology (Aug 2009–to date).
Paul Gard:	Lecturer (Sept 1983–Aug 1988), Senior Lecturer (Sept 1988–Nov 2001), Principal Lecturer (Dec 2001–Mar 2009), Reader (Mar 2009–Sept 2013), Professor of Experimental Therapeutics (Oct 2013–to date).
Geoffrey Hanlon:	Research Assistant (Jan 1976–Dec 1978), Lecturer (Jan 1979–Aug 1982), Senior Lecturer (Sept 1982–Aug 1992), Principal Lecturer (Sept 1992–Nov 1999), Reader (Nov 1999–Dec 2003), Professor of Pharmaceutical Microbiology (Dec 2003–Sep 2012).
Andrew Lloyd:	Research Assistant (Sept 1986–Aug 1989), Lecturer (Sept 1989–Aug 1993), Senior Lecturer (Sept 1993–Aug 1998), Reader (Sept 1998–June 2000), Professor of Biomedical Materials (June 2000–to date), Dean (Aug 2003–to date).
Wendy MacFarlane:	Reader (Oct 2006–to date).
Sergey Mikhalovsky:	Research Fellow (Apr 1994–Sept 1996), Lecturer (Oct 1996–Aug 1997), Senior Lecturer (Sept 1997–Feb 2001), Principal Lecturer (Mar 2001–May 2001), Reader (May 2001–June 2003), Professor of Materials Chemistry (June 2003–to date).
Susanna Rose:	Research Officer (Jan 2002–Aug 2002), Research Fellow (Jan 2002–Nov 2007).
Gary Phillips:	Research Assistant (Dec 1990–May 1994), Research Assistant (Jan 1995–Dec 1995), Research Officer (Dec 1995–Dec 1996), Research Fellow (Jan 1997–Feb 2002), Senior Research Fellow (Mar 2002–July 2006), Principal Research Fellow (Aug 2006–to date). Deputy Director of Postgraduate Studies - Science & Engineering (Nov 2011–July 2013).
Jonathan Salvage:	Research Officer (June 2004–July 2009), Research Fellow (Aug 2009–to date).

3. References to the research

Optimisation of ophthalmic lens material:

[3.1] LLOYD, A.W., FARAGHER, R.G.A., WASSALL, M., RHYS-WILLIAMS, W., WONG, L., HUGHES, J.E. and HANLON, G.W., (2000) Assessing the in vitro cell-based ocular compatibility of contact lens materials. *Contact Lens & Anterior Eye*, 23, pp.119–123. DOI: 10.1016/S1367-0484(00)80004-1 [Quality validation: leading peer-reviewed journal]

[3.2] LLOYD, A.W., DROPCOVA, S., FARAGHER, G.A., GARD, P.R., HANLON, G.W., MIKHALOVSKY, S.V., OLLIFF, C.J. and DENYER, S.P. (1999) The development of in vitro biocompatibility tests for the evaluation of intraocular biomaterials. *Journal of Materials Science–Materials in Medicine.* 10, pp.621–627. DOI: 10.1023/A:1008935707910 [Quality validation: leading peer-reviewed journal].

Biocompatible coatings for medical device use:

[3.3] GOREISH, H.H., LEWIS, A.L., ROSE, S. and LLOYD, A.W. (2003) The effect of phosphorylcholine-coated materials on the inflammatory response and fibrous capsule formation: in-vitro and in-vivo observations. *Journal of Biomedical Materials Research Part A,* 68A, pp.1–9. DOI: 10.1002/jbm.a.10141 [Quality validation: leading peer-reviewed journal].

Self-assembled drug delivery systems:

[3.4] SALVAGE, J.P., ROSE, S.F., PHILLIPS, G.J., HANLON, G.W., LLOYD, A.W., MA, I.Y, ARMES, S.P., BILLINGHAM, N.C, and LEWIS, A.L. (2005) Novel biocompatible phosphorylcholine-based self-assembled nanoparticles for drug delivery. *Journal of Controlled Release,* 104,

pp.259–270. DOI: 10.1016/j.jcornel.2005.02.003 [Quality validation: leading peer-reviewed journal].

Drug eluting embolisation materials:

[3.5] LEWIS, A. L., GONZALEZ, M. V., LEPPARD, S. W., BROWN, J.E., STRATFORD, P.W., PHILLIPS, G.J. and LLOYD, A.W. (2007) Doxorubicin eluting beads-1: effects of drug loading on bead characteristics and drug distribution. *Journal of Materials Science–Materials in Medicine,* 18, pp.1691–1699. DOI: 10.1007/s10856-007-3068-8 [Quality validation: leading peer-reviewed journal]

[3.6] LEWIS, A.L., GONZALEZ, M.V., LLOYD, A.W., HALL, B., TANG, Y., WILLIS, S.L., LEPPARD, S.W., WOLFENDEN, L.C., PALMER, R.R. and STRATFORD, P.W. (2006) DC Bead™: in-vitro characterisation of a drug delivery device for transarterial chemoembolization. *Journal of Vascular and Interventional Radiology,* 17(2), pp.335–342. DOI:10.1097/01.RVI.0000195323.46152.B3 [Quality validation: 112 cites].

Peer-reviewed research grants:

Medical Implants LINK Programme 'Biomimetic Polymers to Improve the Ocular Compatibility of Intraocular Lenses' MRC/SERC/DTI/DOH (1993–1997). Total funding: £904k.

Medical Implants LINK Programme 'Advanced Glaucoma Filtration Implant Device' MRC/SERC/DTI/DOH (1995–1997). Total funding: £360k.

'Synthesis and characterisation of novel betaine-based copolymers for high performance biocompatible coatings' BBSRC Project Grant (1999–2002). Total funding: £220k.

4. Details of the impact

The impact of the research has been in supporting the cyclical innovation within an SME through joint research and development programmes. The integrated partnership has: (a) involved the placement of university researcher(s) within the company (as part of Knowledge Transfer Partnerships and EPSRC/BBSRC CASE Studentships) to work alongside company employees, and; (b) allowed company employees to register for higher degrees and to work alongside university academics and researchers within the university. Innovation oversight has been managed by LLOYD (UoB) and Professor Lewis (BUK) and further informed through LLOYD's membership of the company's Scientific Advisory Board from 2003 to 2008 and appointment as an ongoing scientific consultant to the company. The joint advancement of knowledge through the partnership has stimulated and supported innovation within the company, leading to on-going marketing benefits for existing products, new material applications, new products and patents, as illustrated below.

Product performance data: The development and marketing of the Proclear® family of soft contact lenses by the EyeCare Division of Biocompatibles UK Ltd. The Proclear® family of lenses was launched and was able to establish a niche in the monthly disposable segment, supported by strong scientific data generated through the collaboration with UoB that demonstrated significantly less bio-fouling with proteins and bacteria, leading ultimately to a more comfortable contact lens – using assays that were originally developed to support material optimisation for a novel intraocular lens and glaucoma filtration device. These assays became standard in-house test methods for the company (source 5.2). The data produced by UoB researchers underpinned the submission to the U.S. FDA for the claim: 'may provide improved comfort for contact lens wearers who experience mild discomfort or symptoms relating to dryness during lens wear'. This is the only contact lens worldwide cleared for this claim. This contact lens business was sold in 2002 to the Cooper Group for ~£70m and was then the 6th largest contact lens business. In 2011, net sales of CooperVision's PC Technology products represented 28% of CooperVision's soft lens net sales of £650m and with forecast sales of >$1.3bn in 2013, the Proclear sales are now worth circa. $300m per annum (5.1, 5.2, 5.3).

New material applications: Early work by the company had identified the potential use of PC-materials in blood contacting and protein biofouling applications. The early observations made through the joint research programme into the propensity of these coatings to reduce cellular adhesion and activation increased the scope of the PC-coating applications. The optimisation of the biological performance of PC coatings through the research undertaken by UoB contributed to the broader regulatory approval of PC-coated medical devices for clinical use and assisted in

the development of the BiodivYsio® family of coronary stents and the Yellowstar® family of urological catheters and stents. The coating technology was licensed to Vertellus Specialities UK Ltd, which has continued to exploit the PC technology in a wide range of medical device applications based on the data originally generated by UoB and BUK. The research publications derived from this work still form part of the company's marketing data and the data is used by Vertellus to inform development programmes with companies around the world (5.2, 5.4).

New products: (i) Celluminate®, a fluorescent cell-tracker system, developed and marketed by BUK from 2008 until 2011, is based on the research funded by BBSRC into novel bioresponsive self-assembling PC polymers. (ii) DC Bead® Technology – a novel combination product for the treatment of liver cancer, was developed initially as a bland embolic device intended for the purpose of embolising the blood vessels of a variety of hypervascularised tumours (e.g. uterine fibroids) and arteriovenous malformations in-licensed by BUK. The DC Bead® drug-eluting bead technology arose as a consequence of the company's experience in drug eluting devices and interventional procedures. A series of joint research programmes funded by BUK, EPSRC and the Royal Commission for the Exhibition of 1851 broadened the potential of this technology and provided much of the scientific underpinning that supports the product in market. It has been evaluated in clinical trials worldwide and is rapidly becoming recognised as the gold-standard treatment for intermediate primary liver cancer. The product is now available globally in over 600 hospitals in 50 different countries and there have been over 100,000 reported procedures. The value of this business was recognised in early 2011 when BTG Limited successfully acquired Biocompatibles for £177m (5.5 and 5.6).

Patents: (i) LEWIS, A.L., ARMES, S.P., LLOYD, A.W. and SALVAGE, J.P. (2002) Drug Carriers comprising amphipathic block copolymers US2012157550. (ii) LEWIS, A.L., FORSTER, R.E.J., GONZALES-FAJARDO, V.M., TANG, Y., LLOYD, A.W. and PHILLIPS, G.J. (2007) Delivery of Drug Combinations US2011229572 (iii) ASHRAFI, K., LEWIS, A.L., HEAYSMAN, C., LLOYD, A. and PHILLIPS, G. (2011) Drug Delivery Systems WO2012101455.

5. Sources to corroborate the impact

5.1 Testimonial available from Director of Research & Development, Biocompatibles UK Ltd. This testimonial confirms the partnership with UoB and the effect of cyclical innovation within the company.

5.2 Testimonial available from Business Director, Vertellus Biomaterials Ltd that confirms the effect on product performance, innovation and the use of the data in marketing materials and development programmes.

5.3 Cooper Companies' financial statements, 'The Cooper Companies, Inc and Subsidiaries – Valuation and Qualifying Accounts.' Three Years Ended October 31, 2011. Available at: http://www.sec.gov/Archives/edgar/data/711404/000119312511343993/d238160d10k.htm#tx238160_20) http://investor.coopercos.com/common/download/download.cfm?companyid=COO&fileid=364552&filekey=31AB9841-EE51-490B-9F9F-9E830FB1432C&filename=COO_2013.pdf [Accessed: 8 November 2013] This confirms the sales data included in the case study.

5.4 'Vertellus Biomaterials – Biocompatible Coating Material'. Marketing data available at: http://www.medicaldevice-network.com/contractors/biotechnology/vertellus-bio; http://www.pcbiomaterials.com/ [Accessed: 8 November 2013]

5.5 'Celluminate® intracellular delivery system' product release. 08/27/2009. Available at: http://www.rdmag.com/product-releases/2009/08/celluminate-intracellular-delivery-system [Accessed: 8 November 2013].

5.6 'Biocompatibles UK Ltd Wins The 2011 Prince Philip Award for Plastics in the Service of Mankind for DC Bead®' 24 Oct 2012. Available at: http://www.iom3.org/news/biocompatibles-uk-ltd-wins-2011-prince-philip-award-plastics-service-mankind-dc-bead. [Accessed: 8 November 2013]. This confirms that the product is now available globally in over 600 hospitals with over 100,000 reported procedures and that this product was acquired by the BTG Group for £177m in 2011.