Institution: University of Brighton

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

Title of case study:
Medical device innovation and commercialisation to combat liver disease

Period when the underpinning research was undertaken: 2000 – 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Carol Howell	Principal Research Fellow	2002 – 2017
Ganesh Ingavle	Research Fellow	2013 – 2015/2015 – 2017
Andrew Lloyd	Professor of Biomedical Materials	1986 – to date
Wendy MacFarlane	Reader	2006 – to date
Sergey Mikhalovsky	Professor of Materials Chemistry	1994 – 2018
Gary Phillips	Principal Research Fellow	1995 – 2017
Susan Sandeman	Reader	1999 – to date
Yishan Zheng	Research Fellow	2013 – 2018

Period when the claimed impact occurred: July 2013 – Dec 2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

University of Brighton (UoB) researchers have worked with business to develop two medical device innovations to reduce the global burden of liver disease benefitting patients, providers and private businesses. Pioneering drug-eluting bead therapies (DC Bead® Technology) have been used in 250 hospitals across Europe, North and South America and the Asia-Pacific areas, with approximately 100,000 reported procedures. This technology was the driver behind the acquisition of BTG, an international specialist healthcare company, by Boston Scientific for USD4,200,000,000 in 2019. Additionally, UoB research into adsorbents with tailored internal porosity led to the development of an orally administered device for the treatment of liver disease (Carbalive™). Licensing of the Carbalive™ IP to Yaqrit Ltd attracted GBP25,000,000 investment, enabling the company's expansion, now employing 15 staff.

2. Underpinning research

Researchers at UoB have been tackling the rising burden of liver disease, cirrhosis and liver cancers through the development of medical technologies that can be accurately delivered to the point of need in bead form. In 2018 there were an estimated 841,000 cases of liver cancer diagnosed worldwide and 782,000 deaths. It is one of the most challenging cancers to treat and the second leading cause of global cancer deaths. Furthermore, in developed countries, increasing prevalence of obesity and alcohol consumption in the general population account for the rising incidence of liver cancer and other diseases. Liver cirrhosis results in an estimated 1,000,000 global deaths annually and these rates are rising. In the UK, the British Liver Trust has estimated that the annual cost to the NHS for treatment of liver disease is expected to exceed GBP1,000,000,000. UoB has built capacity around two related strands of research to improve clinical outcomes for these disease groups.

2.1 Development of drug-eluting bead systems

Chemoembolization is an accepted treatment option that eliminates tumours by blocking the blood supply. Drug eluting bead (DEB) systems are designed to improve chemoembolization by targeting the delivery of the drug to the tumour and reducing the systemic exposure, enhancing the efficacy of treatment. UoB built a sustained research partnership with Biocompatibles UK (BUK), and then BTG plc group since the early 1990s, supporting the cyclical development of a number of medical device technology innovations. Since 2002 the research partnership concentrated on the field of embolotherapy through a series of joint research programmes funded by BUK, EPSRC and The Royal Commission for the Exhibition of 1851. This focussed on the optimisation of novel drug-eluting bead (DEB) systems for the treatment of liver cancers. This fundamental understanding led to the

development of new polymer systems and the engineering of physicochemical properties controlling the drug loading and release properties for different chemotherapeutic agents [references 3.1, 3.2]. Since 2014, the core scientific developments centred on innovative radio-opaque drug eluting bead therapies for liver malignancies. The university-business partnership developed novel cell-based assays for the evaluation of drug combinations in clinically reflective biological conditions to provide in vitro assays for product evaluation. This led to the development of a novel hypoxia-responsive DEB system and the commercialisation of the radiopaque chemoembolization bead product [3.3]. This broadened the potential utility of this type of technology and provided much of the scientific underpinning that supports the products in market.

2.2 Development of nanostructured inorganic adsorbents

Current treatment strategies for liver disease have yet to target effectively the role of deteriorating gut barrier function and changing microbiome dynamics in disease progression. Current therapies involve the use of antibiotics with associated problems of antibiotic resistance. UoB researchers were the first to develop a range of nanostructured adsorbents for use in biomedical devices, which have since been adapted as oral adsorbents to treat liver disease. Working with industrial partner MAST Carbon International, UoB developed a series of activated carbon adsorbents with specifically tailored porosity for medical device applications. In EUFP7 and NIHR funded projects [3.7-3.8] UoB showed for the first time that the internal porosity of these adsorbents could be tailored to target both small and large biological toxins including difficult to remove bacterial endotoxin, inflammatory molecules and other metabolic toxins. These toxins build up in life-threatening illnesses such as sepsis, kidney and liver failure and are difficult to remove by means other than adsorption [3.4, 3.5]. The technology was developed through iterative steps to create a scalable synthesis route for bead and monolith forms of the adsorbent, whilst maintaining device porosity and capacity for adsorption of key bacterial and metabolic toxins otherwise poorly removed.

The research linking toxin removal to the creation of specifically tailored porosity underpinned the joint development, with UCL, of this technology in bead form as an orally administered device to treat liver cirrhosis. UoB Innovation Seed Funding supported proof of concept data suggesting that the device targets gut dysbiosis and disrupted gut barrier function; adsorbing inflammatory metabolites and bacterial endotoxin without disrupting bacterial growth kinetics; repressing mechanisms leading to further organ damage and heightened susceptibility to infection in the already immunocompromised liver [3.6]. The research led to a patent assigned to UCL Business Ltd, with co-inventors from UCL and UoB, the award of a Horizon 2020 grant, CARBALIVE [3.9] and licensing of the technology to Yaqrit Ltd for further development under the product trademark name of Carbalive™. Preliminary results of the CARBALIVE study indicated safety and tolerability of the device and therefore positive impact on markers of gut and systemic inflammation.

3. References to the research

[3.1] Lewis, A. L., Gonzalez, M. V., Leppard, S. W., Brown, J. E., Stratford, P. W., Philips, G. J., 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*(9), 1691-1699 https://doi.org/10.1007/s10856-007-3068-8 [Quality validation: leading peer-reviewed journal].

[3.2] Forester, R. E. J., Tang, Y., Bowyer, C., Lloyd, A. W., Macfarlane, W., Phillips, G. J., Lewis, A. L. (2012). Development of a combination drug-eluting bead: towards enhanced efficacy for locoregional tumour therapies. *Anti-Cancer Drugs* 23(4), 355-369 https://doi:10.1097/CAD.0b013e32835006d2 [Quality validation: leading peer-reviewed journal].

[3.3] Hagan, A., Phillips, G. J., Macfarlane, W. M., Lloyd, A. W., Czuczman, P., Lewis, A. L., (2017). Preparation and characterisation of vandetanib-eluting radiopaque beads for locoregional treatment of hepatic malignancies. *European Journal of Pharmaceutical Sciences*, 101, 22-30. https://doi:10.1016/j.ejps.2017.01.033 [Quality validation: leading peer-reviewed journal].

[3.4] Howell, C. A., Sandeman, S. R., Phillips, G., Mikhalovky, S., Tennison, S., Rawlinson, A. P., Kozynchenko, O. P. (2013). Nanoporous activated carbon beads and monolithic

columns as effective hemoadsorbents for inflammatory cytokines. *International Journal of Artificial Organs*, *36*(9), 624-632. https://doi.org/10.5301/ijao.5000231 [Quality validation: leading peer-reviewed journal].
[3.5] Tripisciano, C., Kozynchenko, O. P., Linsberger, I., Phillips, G. J., Howell, C. A., Sandeman, S. R., Tennison, S. R., Mikhalovsky, S. V., Weber, V., Falkenhagen, D. (2011). Activation-dependent adsorption of cytokines and toxins related to liver failure to carbon beads. *Biomacromolecules*, *12*(10), 3733-3740. https://doi.org/10.1021/bm200982g [Quality validation: leading peer-reviewed journal].
[3.6] Macnaughtan, J., Soeda, J., Mouralidarane, A., Sandeman, S. R., Howell, C. A., Mikhalovsky, S., Kozynchenko, S., Tennison, S. R., Davies, N., Oben, J. A., Mookerjee, R. P., Jalan, R. (2012). Gut decontamination using nanoporous carbons reduces portal pressure and prevents liver failure in bile-duct ligated cirrhotic animals by reducing kupffer cell activation. *Journal of Hepatology*. 56(2), S230-231. https://doi:10.1016/S0168-8278(12)60594-7 [Quality validation: leading peer-reviewed journal].

Key research grants

[3.7] Susan Sandeman [PI], EU FP7 Marie Curie Industry-Academia partnerships and pathways (IAPP) project 286366, 2012 – 2016, Adsorbent carbons for the removal of biological toxins (ACROBAT). Total funding: EUR1,449,659. UoB allocation: EUR297,642.
[3.8] Susan Sandeman [PI], National Institute for Health Research i4i project, 2013 – 2015, An adsorbent device to promote toxin removal during haemodialysis (II-LA-1111-20003-ADEPT). Total funding: GBP382,554, UoB allocation: GBP185,539.
[3.9] Susan Sandeman [Co-I], Horizon 2020 Research and Innovation Framework Programme, 2015 – 2021, Clinical evaluation of carbons of controlled porosity as a new therapeutic for the treatment of liver cirrhosis and non-alcoholic fatty liver disease (H2020-PHC-14-634579-CARBALIVE). Total funding: EUR5,913,079. UoB allocation: EUR179,555.

4. Details of the impact

Since the early 2000s UoB researchers have built expertise and delivered innovations to improve outcomes relating to liver disease and liver cancer. Related strands of research developed strategically and incrementally through large-scale, long-standing industry-focused partnerships to improve drug delivery and toxin removal mechanisms for these conditions. Two examples detailed here evidence UoB's distinct approach to impact through embedded partnership working linked to commercialisation and clinical care pathways. This includes: i) the DC Bead® technology, an established cancer treatment product that is now established in the global market, delivering impact for the rapidly growing speciality Interventional Oncology market as well as patients worldwide, and ii) the clinical grade Carbalive™ product, an emergent technology under clinical evaluation for the treatment of advanced liver disease, commercialised through a UCL spin-out, now generating jobs, GBPmulti-million investments and setting a path towards better health outcomes.

4.1 Advancing embolization technologies to target liver cancer

The research partnership between UoB and Biocompatibles UK, and the development of research into DEB technologies, led to joint patents and commercialisation of the DC Bead®, a novel combination product for the treatment of liver cancer [Source 5.1]. The commercialisation process, led by BUK but based on the joint underpinning science, underwent intensive clinical evaluation and was the first product of its type brought to the market for launch in 2005. The DC Bead® has been evaluated in clinical trials worldwide and is now recognised as a gold-standard treatment for intermediate primary liver cancer. The DC Bead® is proven to offer an improved safety profile over conventional procedures, with chemotherapy drugs only delivered to the site of the tumour and not healthy tissues. Studies using these products have shown less leakage of chemotherapy into the systemic circulation than conventional treatments, resulting in reduced side effects. This is set in a context where patients suffering primary and secondary liver cancer may have limited treatment options, or otherwise poor overall prognosis [5.2]. Product sales have increased globally to 850 hospitals (250 in the period), treating patients across Europe, North and South America and the Asia-Pacific areas. There have been 100,000 reported procedures since 2013 [5.3]. In 2016 BTG announced the DC Bead® product was upgraded to a classification of Class III based on its ability to administer medicines and the non-clinical and clinical data supporting

the safe and effective conditions for use. This classification is awarded following rigorous additional evaluations including by the European Commission [5.4].

The later body of collaborative research into innovative radiopaque drug eluting bead therapy has contributed to the development of new vandetanib-eluting radiopaque beads [5.5], which provided the foundation for the vandetanib-eluting bead, developed by BTG plc in collaboration with Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland. Led by UCL's Cancer Institute, in partnership with Biocompatibles UK, the bead has been used in clinical trials by UK clinicians since 2017. The Chair of Radiation Oncology at UCL has confirmed that the radiopaque bead '*offers the advantage of providing visible confirmation of bead location during and after the embolisation procedure, enabling real-time adjustments to optimise patient treatment'*, which is '*helping to develop a liver-directed treatment as a superior alternative to the rather poorly tolerated drug treatments we currently offer patients with this type of cancer*' [5.5]. Following from the success of the DC Bead® the newer radiopaque bead (DC Bead LUMI™) was also awarded a Class III CE Mark classification in 2017. This differs from the other products in the range as it provides real time visible confirmation of the bead's location improving delivery control and analysis post procedure, enabling clinicians to individualize a patient's treatment and evaluate the completeness of tumour treatment, improving patient outcomes [5.6].

Both the DC Bead® and DC Bead LUMI™ continued to be sold by BTG until 2019 with sales data showing the firmly established DC Bead® product as a leader in the market of drug-eluting embolization products, with approximately 70% of the total global market share. Sales of this product provided 15% of BTG's MedTech revenue and 6% of the company's total revenue in 2018 [5.3, 5.7]. In 2019 BTG was sold to Boston Scientific in a USD4,200,000,000 acquisition deal. As a legal requirement within the acquisition process, regulated by the US Federal Trade Commission, Boston Scientific sold their own competing bead products to Varian Medical, in favour of the DC Bead Technology [5.8]. The Vice-President for Research and Development at Boston Scientific confirmed that the DC Bead technologies were the main products that made the sale attractive in the first place as the trade names were long established, trusted and respected and based on a strong body of scientific and clinical evidence and rigorous evaluation processes. These products had long been known as best in class technologies [5.9]. As a result of this acquisition Boston Scientific now has the widest portfolio of products in Interventional Oncology [5.7]. The CEO reported that '*the addition of the BTG Interventional Medicine portfolio reinforces our category leadership strategy and enables us to offer best-in-class technologies, unparalleled clinical evidence and a strengthened commercial infrastructure to support physicians treating some of the most challenging diseases impacting patient health around the world'* [5.8].

4.2 Developing adsorbent technology as a product for oral treatment of liver disease

The second strand of UoB research linking internal, tailored porous structure to the removal of bacterial endotoxins, led to the filing of 2 patents in the period by Mast Carbon International with UoB as co-inventors [5.10]. The first patent *Carbon and its use in blood cleansing applications* was sold to Immutrix Therapeutic Inc with a US patent 9,278,170 granted in 2016. Immutrix have built a manufacturing facility and subsequently developed a blood cleansing device to target inflammatory and immune molecules for a range of medical applications. The second patent, *Shaped nanoporous bodies* was sold to Neoteryx in June 2018 for use within a volumetric blood sampling device. Following generation of proof of concept data for use of the adsorbents as an oral treatment for liver disease using UoB Business Investment seed funding, a patent was filed by UCL Business with UoB named as co-inventors [5.10]. This preparatory research using UoB expertise to develop the adsorbent bead technology for biomedical device applications, supported by patented data, led to the award of a successful Horizon 2020 grant (CARBALIVE, UCL lead project partners) and the first EU multi-centre clinical safety study in patients with liver cirrhosis. The trial included 56 patients from 9 hospitals in UK, France, Italy, Portugal, Spain and Switzerland [5.11]. Results from the Phase 2 trial confirmed the safety and efficacy of the product with patients showing a 90% tolerance rate. Preliminary data showed that measures of gut specific health improved, alongside a wide range of biomarkers of systemic inflammation [5.11].

The IP relating to this product was licensed to a UCL spinout company, Yaqrit Ltd, a clinical stage life sciences company established in 2014, focused on clinical solutions for advanced liver disease. As part of the CARBALIVE project Yaqrit Ltd created a manufacturing facility to supply clinical grade product, now under the trademark name Carbalive™. This is the world's only manufacturing facility capable of making Carbalive™ for oral delivery to humans, resulting in a further planned expansion of the company and a pivotal trial to take the product to the next stage. Yaqrit Ltd is now planning the route to regulatory approvals worldwide [5.12, 5.13]. Yaqrit Ltd employs 15 people and has attracted GBP25,000,000 in investment to develop and supply the product [5.13]. The success of the Carbalive™ technology, which has utilised UoB's cumulative research expertise, shows a clear path towards a reduction in the burden of advanced liver disease. Together with the established DC Bead® brand this shows how teams of UoB researchers apply, position and scale-up their research to meet evolving demands in healthcare worldwide.

5. Sources to corroborate the impact

[5.1] Patents: (i) 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 (ii) Ashrafi, K., Lewis, A. L., Heaysman, C., Lloyd, A. and Phillips, G. (2011) Drug Delivery Systems WO2012101455.
[5.2] NIHR Horizon Scanning Research and Intelligence Centre. Doxorubicin-eluting beads (DC Bead, DC Bead M1 and Radiopaque DC Bead) for hepatocellular carcinoma. November 2015. Doxorubicin-eluting beads (DC Bead, DC Bead M1 and Radiopaque DC Bead) for hepatocellular (nihr.ac.uk) Layout 1 (whichmedicaldevice.com)
[5.3] Testimonial from the former Director of Research & Development at Biocompatibles UK Ltd and BTG Ltd. This confirms sales and performance data. [Available as a PDF].
[5.4] BTG Announces Successful CE Mark Reclassification for DC Bead® to Class III Based on its Ability to Administer Medicines (prnewswire.co.uk) [Accessed 12th January 2021].
[5.5] Reports on first use in patients of new vandetanib-eluting radiopaque beads: https://news.bostonscientific.com/2017-10-09-First-patient-treated-with-microscopic-beads-pre-loaded-with-a-targeted-cancer-drug-and-visible-on-CT-scans [Accessed 12th January 2021].
[5.6] Confirmation of CE classification: BTG wins CE Mark for DC Bead Lumi radiopaque drug-eluting bead | Drug Delivery Business [Accessed 12th January 2021].
[5.7] BTG Annual Reports (2014 – 2018). These reports confirm product and sales data. [Available as a PDF].
[5.8] A series of press articles reporting on the acquisition of BTG by Boston Scientific. These confirm the importance of the bead products as part of the sale: https://www.medtechdive.com/news/boston-scientific-to-offload-beads-clearing-way-for-btg-acquisition/558045/ https://news.bostonscientific.com/2019-08-19-Boston-Scientific-Closes-Acquisition-of-BTG-plc https://www.massdevice.com/report-ftc-clears-boston-scis-4b-purchase-of-btg/ The FTC takes a closer look at Boston's BTG bid | Evaluate [Accessed 12th January 2021].
[5.9] Testimonial from the Vice President for Research and Development at Boston Scientific. This provides details relating to the acquisition of BTG as well as sales and performance data. [Available as a PDF].
[5.10] Patents (i) 'Shaped nanoporous bodies' PCT/GB2016/052154, WO 2017009662 A1, US Patent 10,773,234, 2020 (patent sold to Neoteryx) (ii) 'Carbon and its use in blood cleansing applications', WO 2011/070363 A1, US Patent 9,278,170, 2016 (patent sold to Immutrix Therapeutic Inc) 'Porous carbon particles for use in the treatment or prevention of liver disease' WO 2013136094 A1, US Patent 9,844,568B2.
[5.11] 2018 Clinical trials registry of Carbalive https://ichgcp.net/clinical-trials-registry/NCT03202498 and a press release on the outcomes of the latest efficacy and safety data: https://www.carbalive.eu/press-release [Accessed 12th January 2021].
[5.12] Yaqrit ltd manufacturing facility in development (2017): Yaqrit Carbalive Manufacturing Update April 2017 - YouTube [Accessed on 12th January 2021].
[5.13] Testimonial from the CEO of Yaqrit Ltd confirming UoB's contribution and the details relating to investments and other outcomes [Available as a PDF].