Institution: University of Southampton

Unit of Assessment: 13 Electrical and Electronic Engineering, Metallurgy and Materials

Title of case study: 13-04 Micro-technologies for medical diagnostics

1. Summary of the impact

Pioneering research in miniature *in-vitro* microfluidic diagnostic systems at the University of Southampton has produced major economic impacts by driving new business activities in major multinational corporations. Philips Research Cambridge are investing £5 million p.a. and employing 12 FTEs to develop new Point of Care systems for rapid diagnosis and management of disease based on the research. Patented advances in electronic fluid-handling technologies is driving £3 million R&D investment in Sharp Labs Europe in partnership with Southampton to develop a rapid assay platform for prompt detection of antibiotic-resistant bacterial infections. Health impacts from the research are the provision of new home based diagnostics that provide targeted and early risk identification resulting in improved patient healthcare and reduced costs.

2. Underpinning research

NHS funding is under more pressure than ever before. A 2012 report by the King's Fund showed that reducing the number of overnight stays for over 65's by 2.3 million per year, would allow £462m a year to be reinvested in community and primary care services. However, mechanisms are required that would allow patient care at home, while providing clinicians access to appropriate data and patients with personally relevant and reassuring information about their treatment and condition. Research in Southampton into micro scale systems for fluid handling (known as microfluidic systems) began in 2004, when Prof Morgan was appointed. His fundamental research in microfluidics and techniques for manipulating and analysing particles (electrokinetics) was translated into technologies for miniaturised diagnostic systems. The systems integrate multiple analytical methods, with micro-fluidic technologies and data analysis onto a single platform, termed the Lab-on-a-Chip.

Morgan's early research (grants 1-3) catalysed the development of new miniaturised non-invasive single-cell analysis platforms. Underpinning research included improved understanding of the electrokinetic properties of particles [3.1, 3.2] and the development of new fabrication technologies, integrated cell handling and analysis methods with electronics and signal processing methods [3.3] to enable spectral analysis of single cells in very short time windows. This involved flowing up to 1000 cells per second through a specially designed micro-impedance system.

Capitalising on this work, Southampton worked with Philips (grant 4) to develop a miniature diagnostic system for analysis of cells from small drops (50uL) of blood - the Full Blood Count (FBC). This project focused on the discrimination of the different blood cell types by passing cells through the detection zone of a pair of micro-electrodes, from which the information on cell size and dielectric properties was gathered. This project marked a breakthrough in combining high-speed impedance analysis of cells with innovative microfluidic sample processing [3.4, 3.5], complex electronics and high speed signal processing. Close collaboration with Southampton University Hospital allowed testing on patients. The project also developed a patient-centred information gathering and processing platform implemented on a palm-sized computer – the "Chemoinformer". This symptom-based diagnostic system allows patients undergoing chemotherapy to upload data on daily basis, which is then communicated to the district nurse.

In 2005 Morgan explored electrowetting for fluid control (grant 5). Devices were designed and manufactured to allow trapping and processing of cells using dielectrophoresis in simple, open geometries for generic lab-on-a-chip architectures. Researchers also developed a generic method for combining surface-based electromechanically-mediated microfluidics with "traditional" dielectrophoresis-based cell manipulation. Electric field dispensing and mixing systems were used to disperse and characterise particles such as cells. Researchers showed that it is possible to initiate and control chemical reactions and biological protocols with such a system. This overcame a major bottleneck in miniature diagnostics: the manipulation of nano-litres of liquid under direct electronic control. Southampton then partnered with Sharp Labs Europe (SLE) to build on this early work to develop a complex miniature electronic fluid-handling platform, based on Active Matrix Thin Film Transistor methods, manufactured by Sharp in Japan [3.6]. Since January 2013,

Southampton and Sharp have collaborated with Public Health England (PHE), part of the Department of Health, to develop new bioassays for the platform and develop an analytical system for rapid analysis of viral and bacterial infections (grant 6).

Other key researchers

Nicolas Green (Reader, appointed UoS in 2006); Donna Davies (Professor, School of Medicine); Peter Howarth (Reader, Southampton University Hospital); Judith Holloway (Lecturer, School of Medicine, appointed 2007).

3. References to the research (the best 3 outputs illustrating quality of work are starred)

Papers (**Industrial Collaborators in Bold**):

[3.1] Ramos A, Gonzalez A, Castellanos A, Green N.G. and Morgan H *Pumping of liquids with ac voltages applied to asymmetric pairs of microelectrodes*. Phys Rev E. **67** Article Number: 056302 (2003) 114 citations, IF 2.3

[3.2] Morgan H, Sun T, Holmes D, Gawad, S, Green, NG. *Single cell dielectric spectroscopy* J. Phys D: Appl. Phys. **40** 61-70 (2007) 88 citations; IF 2.55

[3.3] Sun T., Gawad S., Green N.G. and Morgan H*, Single cell impedance spectroscopy using maximum length sequences: theoretical analysis from time domain to frequency domain.* Meas. Sci. Technol. **18** 285902868 (2007), voted best paper in Journal 2007, 24 citations, IF 1.5

*****[3.4] Holmes D, **Pettigrew D., Reccius C., Gwyer J., van Berkel C**, Holloway J., Davies D.E and Morgan H. *Leukocyte Analysis and Differentiation using High Speed Microfluidic Single Cell Impedance Spectroscopy.* Lab on Chip **9** 2881-2889 (2009). 77 citations, IF 6.5

*****[3.5] **van Berkel C, Dean S., Gwyer J.D.,** Green N.G. Holloway J., Hollis V. and Morgan H*., Integrated Systems for Rapid Point of Care (PoC) Blood Cell Analysis. Lab on Chip. **11** 1249-1255 (2011).* 12 citations, *I.F. 6.5*

*****[3.6] **Hadwen B**., Broder G.R. Morganti D., **Jacobs A., Brown C., Hector J.R., Kubotac Y**. and H. Morgan *Programmable large area digital microfluidic array with integrated droplet sensing for bioassays* Lab Chip, 2012, **12**, 3305–3313. Selected as "one of the top 10% articles from all papers" by the editor. 7 citations, IF 6.5. See also http://www.youtube.com/watch?v=WxpQyqoukpc

Key Grants (Morgan PI on all grants):

1. EPSRC "Development of Generic Lab on Chip Systems" GR/M31255/01 £141,976 1999-2002

2. DERA "Flow cytometry on a chip" £156,000 2000-2002

3. EPSRC "Rapid single cell impedance metrology" GR/R28942/01 £179,672 2000-2003

4. EPSRC/TSB Technologies for Health TS/G001405/1 with Philips "Point of Care Blood Cell Analysis" £1,447,000 2009-2012

5. EPSRC "Electromechanically Driven Surface Microfluidics on a Micro-Chip" EP/C512618 £62,152 2005

6. NIHR II-ES-0511-21002 with Sharp and PHE "Rapid detection of infectious agents at point of triage (PoT)". £1,200,440 (2013-2016)

4. Details of the impact

Southampton's research into microfluidic systems has led to both economic and health impacts. The research has been responsible for the creation and expansion of new business activities within two established multinational corporations, Philips and Sharp Corporation, evidenced by substantial investment and new product developments. This has led to the creation of entirely new portable diagnostic and monitoring systems, which are improving the quality of life of patients and will reduce the cost of healthcare.

Economic Impacts: Creation of a new business activity within Philips

Southampton's pioneering research led to an industrial collaboration with Philips in 2006. The encouraging results highlighted the commercial potential for the microfluidic technologies and lab-

on-a-chip to provide low-cost high volume solutions for consumer diagnostics. In 2009, as a direct consequence of their collaboration with Southampton, Philips established a new Biomedical Diagnostics unit at their Cambridge-based research facilities. The lab-on-a-chip technology is now a core part of Philips Home Care Solutions long term strategy and Philips' annual research and development spend in the area around this technology has grown to approximately £5m [5.1]. This unit now employs 12 full-time employees (including one Southampton PhD graduate, Dr Catia Bernabini, who worked for two years in this unit) who collaborate with Southampton in a range of healthcare focused research and development.

Among the tools developed at Southampton with Philips, of particular note is the microfluidic technology for full blood counting. Philips have commercialised the technology and developed a product for the home monitoring of chemotherapy. This product allows the early diagnosis of neutropenia (loss of white blood cells) through analysis of a finger-prick blood sample and sends the results back to the healthcare provider [5.2, 5.3]. The product will be launched commercially in Europe in 2014. A second portable palm-sized device is also being developed into a Philips product. The “chemoinformer” allows patients undergoing chemotherapy to remotely upload data which is then communicated to their nurse on a daily basis. The chemoinformer is being trialled by 18 patients undergoing chemotherapy treatment for small cell lung cancer at Southampton General Hospital. The trial is managed by Dr Christian Ottensmeier [5.4] and is due to finish at the end of 2013.

The importance of the technology and the collaboration with Southampton is evidenced by £250,000 direct industrial research funding from Philips since 2008. In addition, Philips provided £730,355 financial support for the EPSRC/TSB Technologies for Health project “Point of Care Blood Cell Analysis” (TS/G001405/1). The collaboration has led to 5 publications with Philips researchers as co-authors. The IP from a world patent (WO/2010/140127) [5.5] was transferred to Philips at a cost of £12,000 plus royalties and 2 further patents have been filed.

Economic Impacts: Creation of a new business activity within the Sharp Corporation

Southampton’s ground breaking research in electrowetting for fluid control has led to a similar impact on the business activities of the Sharp Corporation. Sharp have collaborated with Southampton to jointly develop a miniature electronic fluid-handling platform now being commercialised for use in bioassays and immunoassays for the rapid analysis of viral and bacterial infections. The collaboration with Southampton led in 2009 to the creation of Sharp’s ‘Health and Energy’ group at its research labs in Oxford. Following Southampton's successful demonstration of bioassays (3.6), this group expanded from six full-time employees (2012) to 10.5 (2013). Since the start of this collaboration, Sharp’s annual research and development spend in this technology has grown to approximately £1.47m with plans to double this to £3m by the end of 2014 [5.6]. A further proposal has been submitted to the board of Sharp Corporation for a total investment of €27m over 6 years for product development and launch. This is a rapidly progressing impact case and the importance of this new business activity to Sharp and the significance of the collaboration with Southampton is evidenced by the numerous on-going joint projects. Morgan was recently awarded a Royal Society Industry Fellowship to work with Sharp Labs Europe from January 2013 to 2017. The collaboration has led to one patent filed with Southampton inventors [5.7].

Health Impacts

The medical technology developed has enhanced the quality of life of patients. The Philips home monitor improves quality of life for cancer patients (particularly the terminally ill) by improving the timing of treatment and providing an early diagnosis of potential complications without the patient leaving their home. Worldwide 9 million people live with cancer and half of them will receive chemotherapy; approximately half of these suffer some degree of neutropenia. Unfortunately, up to 70% of those infected require hospitalisation, and over 40% suffer delay to their chemotherapy. These patients are vulnerable to serious infections that can lead to overwhelming sepsis and death; the morbidity rate from septic neutropenia is up to 10%. Early detection of neutropenia can therefore avoid patient readmission, improve outcome and significantly reduce the cost of healthcare.

Southampton research is also improving the quality of life in developing countries. The technology has been disseminated to medical professionals through events such as the Glycomic Centre's 'Kenya Workshop' (June 25-29, 2012), a conference workshop aimed at Sub-Saharan healthcare practitioners. Morgan oversaw hands-on sessions and visited local health clinics to demonstrate how to use Southampton-developed low-cost diagnostics. Feedback from Thomas Kariuki, Director of the Institute of Primate Research (a Nairobi biomedical facility) testified to the value of the technology: "Through quality diagnosis, public health effort to reduce disease impacts on Kenyans' lives can be realised, as illness means paying for treatment and lost earnings, which impacts on the entire economy." [5.8]

Impact on Society and Culture

Such is the pioneering nature of the lab-on-a-chip technology that the Southampton research has regularly received international news and media attention since 2009. Articles have appeared, among others, in: Science Daily (US science news website, 3m monthly visitors, 29/8/09), *Nursing Times* and 'nursing times.net' (magazine circulation: 12,601; 616,500 unique website users, 25/09/09), CQ News (the Chinese news website, 10 million hits daily, 09/04/10) and *The Huffington Post* (25/06/2012) [5.8].

Summary

This impact case study describes significant industrial investment in new business activities that would not have occurred without the underpinning research in microfluidics carried out at Southampton. These activities are leading to new products for medical diagnostics, providing patient benefits and cost savings.

5. Sources to corroborate the impact

[5.1] Contact for Philips: Principal Scientist, Home Healthcare, Philips Research Cambridge. See www.philips.co.uk/about/company/philipsintheunitedkingdom/healthcare/index.page

[5.2] Podcast on our miniature blood counting system by American Chemical Society - "ACS Podcast", Episode 238 – February 20, 2012, http://web.1.c2.audiovideoweb.com/1c2web3536/ScienceElements_Feb20_2012.mp3

and ACS News Service Weekly PressPac: February 1, 2012 "Handheld device for doing blood tests moves closer to medical use"

[5.3] Viewpoint: Lab Chip, 2009,9, 2875-2876: " Cutting edge: Electronic counting of white blood cells" by Daniel Irimia (http://pubs.rsc.org/en/content/articlelanding/2009/LC/b917138j)

[5.4] Contact for chemoinformer clinical trial: Chair Experimental Cancer Medicine, Southampton General Hospital.

[5.5] Patent: Morgan H. Multi-Frequency Impedance Method and apparatus for discriminating and counting particles expressing a specific marker. WO/2010/140127

[5.6] Contact for Sharp: Research Manager, Sharp Laboratories of Europe Limited,. See www.sle.sharp.co.uk/research/het/

[5.7] Sharp patent filed with Southampton inventors: US filing number: 13/742,564

[5.8] http://www.glycomicscentre.ca/workshops/overview/

http://www.glycomicscentre.ca/wp-content/uploads/2012/07/Diagnostics-opinion-write-up-in-past-tense.pdf

[5.9] http://www.sciencedaily.com/releases/2009/08/090825103225.htm

http://www.nursingtimes.net/whats-new-in-nursing/primary-care/new-device-for-on-the-spot-blood-analysis-in-gp-surgeries/5005576.article

http://english.cqnews.net/stories/201004/t20100409_4250876.htm

http://www.huffingtonpost.co.uk/trevor-davies/mobile-blood-test-unit-wi_b_1625487.html