Institution: University of Glasgow
Unit of Assessment: B15: General Engineering
Title of case study: **Lab-on-a-chip technologies deliver diagnostic tools for infection and disease**
1. Summary of the impact

Fifteen years of research in advanced Lab-on-a-Chip technologies at the University of Glasgow has led to three spin-out companies: Mode-Dx, Clyde Biosciences and SAW-Dx. Since 2008 these companies have developed a range of products and services for the diagnostic screening of chronic diseases, for the detection of acute infections and for improving the drug discovery process. The three companies have secured a total of £2.3M in venture funding and secured key strategic collaborations with stakeholders including industry partners and the NHS.

2. Underpinning research

Prof Jonathan Cooper (Lecturer 1991-96, Senior Lecturer 1996-98, Professor 1998-present) leads the Advanced Medical Diagnostics Group in the School of Engineering, and has developed new Lab-on-a-Chip and biosensors technologies, based upon acoustic, optical and electrochemical systems.

Lab-on-a-Chip research in Cooper's group started in 1999, supported by a £3.2M DTI-EPSRC Foresight LINK "Lab on a Chip" programme. The project was co-ordinated by Dr Derek Craston (LGC, now also Government Chemist), and was carried out in collaboration with GlaxoSmithKline (GSK), Unilever and Kodak together with a group of SMEs, including Epigem. Cooper's research has enabled the development of new, advanced microfabrication techniques for on-chip sensing and interconnect technologies for microfludics. Cooper, Dr Igata (Research Assistant (RA) 2000-01) and Dr Arundell (RA 2002) integrated analytical technologies into microfluidic devices using novel fluidic handling strategies for both diagnostic and cell based assays [1].

This work was followed by a Scottish Higher Education Funding Council grant, 'Integrated Diagnostics for Environmental and Analytical Systems'. This supported underpinning research in which Cooper and Dr Johannessen (RA, 2001-04) developed sensors and optimised packaging to create a fully functional ingestible prototype diagnostic device (or pill). This work, when combined with the earlier DTI-EPSRC research, was instrumental in producing a pill-based sensor [2], a concept which led to the formation of Mode-Dx.

In parallel with these activities, the EPSRC supported the Bio-Nanotechnology Interdisciplinary Research Centre (IRC), a collaboration with Professor Ryan (University of Oxford) and Dr Molloy (National Institute for Medical Research) (GR/R45659/01, 2002-09). Here, Cooper led the cellular nanotechnology theme that developed tools for exploring cell-based assays in microfluidic systems. This research, which was carried out in collaboration with Professor Smith (Institute of Cardiovascular and Medical Sciences, University of Glasgow, 1997-present), and Dr Klauke (RA 1999-2009, Research Technologist 2009-11), developed microarrays for electrically stimulating heart cells [3].

Working within a DTI-funded Micro and Nano Technology Programme in 2005-08 with Dr Warrington and Dr Cordingley (GSK), Dr Ryan (Epigem), and Dr Craston (LGC), the University of Glasgow group translated their work into an industrial context and developed high-throughput microfluidic cell-based assays for pharmaceutical testing (relating the new platform to industry-standard assays [4]). Supported by BBSRC (BB/H013369/1) and a Scottish Enterprise Proof-of-Concept Grant (POC/BPT011), Cooper and Smith subsequently implemented these high-throughput technologies as new fluorescence based assay formats to explore cardiotoxic effects of drugs on heart cells. A prototype instrument for optical measurements of action potential and ion flux was developed with Martyn Reynolds at Cairn Research, which resulted in the formation of Clyde Biosciences in 2012 to provide low-cost, early assessment of cardiotoxicity as part of the development process of new medicines.

Most recently, research within the field of acoustics and microfluidics which was underpinned by long-term IRC funding in Proteomic Technologies (BB/C511572) and a Research Landscape Grant (EP/I017887/1) enabled Cooper, Dr Wilson (RA 2005-present) and Dr Reboud (RA 2009-12, Research Fellow 2012-present) to develop frequency dependent phononic structures for shaping ultrasonic fields [5]. This invention is described in WO/2012/114076, whilst methods for manufacturing the technology, developed with Dr Ryan of Epigem under a TSB grant (TSB/61-135, 2010-12), are described in WO/2011/023949. Work within a Scottish Enterprise Proof-of-Concept grant (POC/13-LSM003) permitted the microfluidic research to be translated into a prototype instrument for DNA testing of infectious diseases, and led to the formation of SAW-Dx. Most recently, the technology was validated through the detection of malaria in blood [6], work supported by the Bill and Melinda Gates Foundation (Grant OPP1032927).

3. References to the research

1. Igata, E., Arundell, M, Morgan, H, and Cooper, J.M. (2002); Interconnected Reversible Lab-on-a-Chip Technology. Lab on a Chip, 2, pp. 65-69. ISSN 1473-0197 (doi: 10.1039/b200928p).
2. Johannessen, E.A., Wang, L., Reid, S.W.J., Cumming, D.R.S., and Cooper, J.M. (2006); Implementation of Radiotelemetry in a Lab-in-a-Pill Format, Lab on a Chip, 6, pp. 39-45. ISSN 1473-0197 (doi: 10.1039/b507312j).
3. Klauke, N., Smith, G.L. and Cooper, J.M., (2003); Stimulation of Single Isolated Adult Ventricular Myocytes within a Low Volume using a Planar Microelectrode Array, Biophysical Journal, 85, pp.1766-1774, ISSN 0006-3495, (doi: 10.1016/S0006-3495(03)74606-2).
4. Yin, H., Pattrick, N., Zhang, X.L., Klauke, N., Cordingley, H.C., Haswell, S.J., and Cooper, J.M. (2008); Quantitative Comparison between Microfluidic and Microtiter Plate Formats for Cell-Based Assays, Analytical Chemistry, 80, pp.179-185, ISSN 0003-2700 (doi: 10.1021/ac701958z). *
5. Wilson, R., Reboud, J., Bourquin, Y., Neale, S.L., Zhang, Y. and Cooper, J.M., (2011); Phononic Crystal Structures for Acoustically Driven Microfluidic Manipulations, Lab-on-a-Chip, 11, pp. 323-328 (doi: 10.1039/C0LC00234H). *
6. Reboud, J., Bourquin, Y., Wilson, R., Pall, G.S., Jiwaji, M., Pitt, A.R., Graham, A., Waters, A. and Cooper, J.M. (2012); Shaping Acoustic Fields as a Toolset for Microfluidic Manipulations in Diagnostic Technologies, Proceedings of the National Academy of Sciences, 109, pp. 15162-15167, ISSN 0027-8424, (doi: 10.1073/pnas.1206055109). *

* best indicators of research quality

4. Details of the impact

Cooper's research in medical diagnostics is driven by the demand for new miniaturised formats providing low-cost, disposable point-of-care devices, with applications in near-patient/bathroom environments for screening chronic diseases and diagnosing acute microbial infections. Similarly, the new miniaturised formats of Cooper's work have been applied to the drug discovery process within the pharmaceutical industry through the development of tools that have improved the ease of data acquisition. These tools replace labour-intensive patch-clamp electrophysiological measurements with high-throughput measurements which enable toxicological information on candidate drugs to be obtained earlier in the development cycle. Thus, Cooper's research has generated impact through **three spin-out companies** providing advanced measurement technologies for a range of applications:

Mode-Dx (http://www.modedx.com)**:** Mode Diagnostics (Mode-Dx) was launched in 2008 as a company developing digital homecare diagnostics. It now employs eight staff and in 2009 secured £1.7M of investment from the IP Group, the Scottish Investment Bank and the syndicated investor Kelvin Capital. It received a £72k SMART award in 2011, together with a £23k Innovation Award from Scottish Enterprise in 2011.

Mode-Dx has developed low-cost, easy-to-use electrochemical diagnostic products for the consumer market. Following this successful development work, the company attracted John Brown, formerly Chairman of Axis-Shield, as its Chairman in 2012. The first product, a colorectal cancer diagnostic, called measure® BOWEL HEALTH, Figure 1, detects occult haemoglobin as a proxy for bowel cancer. This product, which is focused on physician-led screening, has been developed under full ISO processes and is now CE-marked, with a full product launch due in 2014. Mode-Dx is also in advanced discussions with a major UK retail pharmacy chain over the placement of this product throughout the UK for over-the-counter home use applications.

Figure 1: ModeDx, Left, measure® BOWEL HEALTH is a hand-held biosensor for measuring faecal occult blood; Right, schematic showing an exploded view of the faecal sampling interface to the biosensor device.

Clyde Biosciences (http://www.clydebiosciences.com): Cardiotoxicity is a major cause of failure of new medicines in the pharmaceutical development process. Clyde Biosciences produces instrumentation, services and biological products for both pharmaceutical companies and contract research organisations to identify these toxic effects earlier in the development process, thereby reducing costs. The technology was configured into a new, high-throughput, low-cost instrument (Figure 2, on left) in collaboration with Cairn Research. This led to Dr Margaret-Ann Craig being awarded the prestigious Royal Academy of Engineering ERA Foundation Entrepreneurship Award (2012) for developing new optical instrumentation, bespoke software (Figure 2, on right) and microsystems technologies for evaluating new drugs. Subsequently seed-funding (£50k in 2012) secured through the University's partnership with IP Group has enabled the successful development of a business model and strategic industrial collaborations, as well as the sale of instruments. The company also received a SMART Award (Project value £137k) in 2013.

Clyde Biosciences has now launched three products: CellOPTIQ (an optical instrument to assess the toxicology of new medicines); XTEND(SR) (for direct measurements of drug-induced changes on cardiac cells); and XTEND (which extends the life of tissue samples). Clyde Biosciences is in the process of selling its first two cell screening systems (total £330k) to Imperial College and INSERM and has developed two partnerships with Astra Zeneca and Johnson & Johnson (both involving contracts for screening of drug candidate libraries).

Figure 2: Clyde Biosciences (left) the CellOPTIQ instrument; (right) proprietary image-analysis software enabling real-time, multiplexed electrophysiological measurements.

SAW-Dx: SAW-Dx is a micro-SME, which uses phononic crystals as 'acoustic holograms' to control the interaction between the ultrasonic fields generated using surface acoustic wave (SAW) devices and the diagnostic sample. Funding from the Scottish Enterprise Proof-of-Concept Fund (2010-12) enabled the technology to be implemented on low-cost disposable chips, coupled into the ultrasonic piezoelectric transducers. A manufacturing technology has been developed with Epigem through a TSB-funded programme (TS/1000097/1, 2010-12). Dr Reboud was awarded the Royal Academy of Engineering ERA Foundation Entrepreneurship Award (2013) to translate the technology into a DNA-based diagnostics technology, leading to seed venture funding from IP Group in 2013. The company was formed in March 2013 and now works on three products.

Firstly, in a development programme with a consultant in Sexual Health & HIV Medicine, NHS Greater Glasgow and Clyde and funded by the NHS, SAW-Dx is developing integrated diagnostics for sexual health. The product uses the company's proprietary technologies for sample preparation and rapid detection, including a new acoustically driven, multiplexed DNA isothermal amplification protocol. The aim is to break the cycle of infection and treatment, by providing rapid diagnosis of a panel of pathogens, enabling the patient to be treated prior to leaving the clinic.

A second product, focussed on food security, has seen SAW-Dx adapt its multiplexed human DNA technologies for sexual health to veterinary applications, with a specific focus on disease diagnosis in cattle and buffalo artificial insemination stations in India. India produces 125bn litres of milk per annum and the 'white revolution' of cow and buffalo milk production underpins its economy. SAW-Dx works on developing these products with the Indian Veterinary Research Institute and the UK Animal Health and Veterinary Laboratory Agency.

Finally, SAW-Dx has also secured a TSB grant (TS/L003392/1), working with MV Diagnostics Ltd and Epigem to develop DNA and protein biomarker tests for tuberculosis (TB), and sees longer-term products based upon developing assays for rapid TB testing.

5. Sources to corroborate the impact

- Statement from and contact details for CEO, Mode-Dx (role of the University in the formation of Mode-Dx)
- Statement from and contact details for CEO, Clyde Biosciences (CB) (on role of the University in the formation of CB)
- IPG (on Venture funder and Shareholder of Mode-Dx, Clyde Biosciences and SAW-Dx) (corroborating the role of IPG as a Venture funder and Shareholder of Mode-Dx, Clyde Biosciences and SAW-Dx)
- Director, Bowel and Cancer Research (on importance of Mode-Dx technology as a home diagnostic test) (contact details provided)
- CEO, Epigem Limited (developing manufacturing technologies and relationship with SAW-Dx)
- Article on Clyde Biosciences (link) (contact details provided)