Institution: University of Birmingham

Unit of Assessment: UoA 8 – Chemistry

Title of case study: Continuous Blood Glucose Monitoring for Tight Glycaemic Control

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

GlySure, an Oxfordshire-based company, has developed a continuous blood-glucose monitoring system using an intravascular, optical fluorescence-based sensor to support clinical implementation of Tight Glycaemic Control and Intensive Insulin Therapy. A novel, highly selective chemosensor for glucose developed in the School of Chemistry at the University of Birmingham made a crucial contribution to Glysure's development of this new medical technology. To date, this activity has achieved economic impact, including £9.5 million of venture capital investment in GlySure since 2008 and 30 jobs created at the company, and has demonstrated impact on health through the results of clinical trials of the device in intensive care units. If the company is successful in achieving European and US regulatory approvals for the device, its introduction could improve patient outcomes as studies have shown that tighter control can be valuable in reducing morbidity and mortality amongst intensive care unit (ICU) patients.

2. Underpinning research (indicative maximum 500 words)

The importance of carbohydrate research at Birmingham may be traced back many years (Haworth Nobel Prize 1937). In the modern era, carbohydrate chemistry has continued in the School of Chemistry (SoC) though supramolecular recognition chemistry (James and currently Fossey, appointed 2008) and synthetic chemistry (Cox, appointed 1999).

Professor T. D. James (Royal Society Research Fellow, School of Chemistry, University of Birmingham, Oct 1995 - Aug 2000, now at University of Bath) undertook research in boronic acid-based carbohydrate recognition chemistry at Birmingham (see references listed in section 3). His work uncovered the requirements for high glucose selectivity amongst his saccharide sensors.

Boronic acids reversibly and covalently bind to diols (including sugars); this reversibility is ideal for a continuous sensing ensemble, yet specificity between different sugars is not high. Indeed among common monosaccharides, fructose has the highest binding affinity for simple aryl boronic acids. To engineer a boronic acid construct with non-typical binding affinity (i.e. glucose selective) required the combination of two boronic acid groups into one molecular sensor. Thus, through judicious molecular positioning of two boronic acid groups, a two-point and highly specific binding to glucose is possible.

James' research into saccharide sensors was developed in collaboration with *Beckman Coulter Inc*., who funded a research project led by James at Birmingham on this topic (*Development of Particulate Fluorescent Receptors for Clinical Analyses, Beginning with Glucose*, Sept 1999 to Aug 2000, award value: £59,843). The research led to a patent filed in December 2000 [patent 1, details given below]. James and Arimori (Research Fellow, SoC, University of Birmingham, Jan 2000 - Aug 2000) are recorded as the inventors on this patent. James' research that contributed to this patent was substantially undertaken whilst he was at Birmingham. However, the terms of the contract with *Beckman Coulter* meant that the research outputs directly related to that patent were not published until after he had left the University.

James continued this research after leaving Birmingham to join the University of Bath where he is currently a Professor in the Department of Chemistry. The fundamental discovery of molecularly engineered selectivity in boronic acid sugar recognition in Birmingham by James has been used directly by industrial partners and has inspired subsequent research in Birmingham (Fossey,

Lecturer since October 2008, who worked with James at Bath before joining Birmingham) and at Bath. Recently Fossey, James and collaborators at GlySure have been granted a further patent (patent 2) on the implementation of glucose selective sensors for use in intravascular blood-glucose sensing. This recent work complements the suite of patents (and academic papers) that result from the original research at Birmingham and forms part of the intellectual property foundation of GlySure, who also acquired patent 1 from Beckman Coulter. Two recent papers (5 and 6) use the exact same glucose sensor in the first published "device format".

Patent 1: "Photo-induced electron transfer fluorescent sensor molecules". Inventors: S. Arimori and T. D. James. Applicant: Beckman Coulter Inc., US Patent, Publication & Grant no.: US6387672; Priority date = 4/12/2000; Granted = US (May 2002)

Patent 2: "Indicator system for fibre optic sensor". Inventors: B. C. Crane, T. James, J. Fossey and P. N. Barwell. Applicant: Lightship Medical Ltd. Published under = WO/ 2011/101624, Aug 2011; Priority date = 19/2/2010; Filed in EP(2011704829) AU (2011217066) JP (2012553391)

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

[1] Novel fluorescence sensor for 'small' saccharides, T. D. James, H. Shinmori, S. Shinkai, *Chem. Commun*., **1997**, 71 (29 citations) DOI: 10.1039/A606552J

[2] Exploitation of a novel 'on–off' photoinduced electron-transfer (PET) sensor against conventional 'off–on' PET sensors, H. Kijima, M. Takeuchi, A. Robertson, S. Shinkai, C. Cooper, T. D. James, *Chem. Commun*., **1999**, 2011 (27 citations) DOI: 10.1039/A906825B

[3] Synthesis and evaluation of D-glucosamine-selective fluorescent sensors, C. R. Cooper, T. D. James, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 963 (65 citations) DOI: 10.1039/a909145i

[4] A molecular colour sensor for monosaccharides, C. J. Ward, P. Patel, P. R. Ashton, T. D. James, *Chem. Commun.*, **2000**, 229-230 (57 citations) DOI: 10.1039/A909204H

[5] A bis-boronic acid modified electrode for the sensitive and selective determination of glucose concentrations: H.-C. Wang, H. Zhou, B. Chen, P. M. Mendes, J. S. Fossey, T. D. James, Y.-T. Long, *Analyst,* **2013**, 138, 7146 DOI: 10.1039/c3an01234d

[6] Glucose selective SPR-based bis-boronic acid surface sensor: A. Stephenson-Brown, H.-C. Wang, P. Iqbal, J. A. Preece, Y.-T. Long, J. S. Fossey, T. D. James, P. M. Mendes, *Analyst*, **2013**, 138, 7140 DOI: 10.1039/c3an01233f

(Citations as recorded on Scopus as at 14th October 2013).
References 1, 2 and 3 best indicate the quality of the underpinning research.

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

The fundamental discovery of molecularly engineered selectivity in boronic acid sugar recognition at Birmingham by Prof James has been used by *GlySure*, an Oxfordshire-based company, to provide the novel chemistry for measuring blood glucose in new glucose recognition technology designed for use in hospital intensive care units. Information published on *GlySure*'s website, and also confirmed by the company to the University, proves that this novel chemistry is crucial to the technology that unpins their business.

The impact to July 2013 is evidenced in both commercial and health terms. *GlySure* was founded in 2006 as a new venture to develop the Birmingham invented glucose recognition technology. Since 2008 it has raised £9.5m venture capital investment for this purpose and had 30 employees in June 2013 (increased from 16 in 2012), with the company's activities wholly focused on this device. Positive results of clinical trials, which began in 2010, have been reported by the company. GlySure's focus is now working on achieving regulatory approval in Europe, and the company has reported that it expected to begin CE mark trials in 2013. *GlySure* have reported that the worldwide market opportunity for Tight Glycaemic Control in hospital intensive care units is more than $2billion.

Tight glycaemic control in intensive care units

The value of intensive insulin therapy in reducing mortality and morbidity in patients being treated in intensive care units was identified in a landmark clinical study of more than 1,500 patients in a surgical intensive care unit reported in the *New England Journal of Medicine* in 2001. [source 1] A factor hampering implementation of this approach has been the absence of a practical method of achieving continuous monitoring of patient's glucose levels in an intensive care unit. Clinicians face difficulties in implementing this extent of tight glycaemic control through traditional finger-prick blood samples: taking blood samples in this way is resource-intensive for nursing staff; provides intermittent rather than continuous measurement; patients can be left with sore fingers and hands.

A number of companies, mainly in the US, have tried to find solutions to this issue over the last decade, often trying to apply approaches from the diabetes industry to intensive care purposes, as described in a 2012 article in the medical business press. However, none have been successful in bringing a product to market. *GlySure* is a new entrant to this market, and has used the findings from the Birmingham research as a crucial feature of a novel method designed specifically for intensive case applications. [source 2]

GlySure's monitoring system

The GlySure system comprises two main parts; a monitor and a sterile disposable set (which includes a fibre-optic sensor and integrated calibration module). The sensor interfaces with the patient's pre-existing intravascular line (arterial or venous) without disrupting the clinician's ability to monitor pressure, draw blood or administer medication through those lines. The sensor contains fluorescent indicator chemistry (invented in Birmingham), which produces a signal that is proportional to the glucose concentration in the patient's blood.

The sensor is a sterile single-use device. Its fluorophore-receptor indicator chemistry is patent protected and under exclusive world-wide licence to *GlySure*. The reversible nature of the glucose-fluorophore bond enables monitoring throughout the patient's length of stay with the same sensor. GlySure argue that their technology exceeds the requirements of clinicians, while also significantly reducing time and cost.

Birmingham's contribution to GlySure's system

GlySure were recommended to consider the Birmingham findings by James and subsequently obtained a licence from *Beckman Coulter Inc*. (the original owners of the patent) to utilise them in their product. In 2012, *GlySure* purchased this patent from *Beckman Coulter*, underlining the importance of this to their activity.

Glysure's Chief Technology Officer has confirmed that the Birmingham discovery is making a distinct and material contribution to their product, and that that these findings have enabled them to develop a sensor that is highly selective to glucose in a biological environment [the blood of critically ill patients] that abounds with both exogenous and endogenous potential interferents. This selectivity facilitates the use of a continuous sensor over many hours whilst maintaining its accuracy. [source 3]

The importance of the discovery made at Birmingham to this device is described on the *GlySure* website, which says: *The core to this technology is the fluorescent/receptor glucose indicator chemistry. This chemistry is structured to be selective for glucose and is immobilised into an optical cell that is micro machined into the fibre itself. The selectivity for glucose is imparted by the specifically configured diboronic acid receptor that is covalently linked to the fluorophore and forms*

part of the single molecule indicator chemistry. This fluorophore-receptor indicator chemistry is covered by US patent 6,387,672 B1 which is owned by GlySure. [source 4]

Economic impact

GlySure, which is focused on exploiting the market potential of this innovatory technology, is based in Oxfordshire and by June 2013 had grown to 30 employees. The company has attracted a total of £12.5 million venture capital investment since its formation in 2006, including a £7 million investment in 2012 to be used to complete the necessary clinical trials as part of obtaining regulatory approval for the glucose monitoring system in Europe and the USA. Investors include *Amadeus Capital Partners*, *Delta Partners* and *Morningside Venture*, all of whom have wide experience of backing successful technology enterprises. [source 5] The company has reported that £9.5m of this investment has been achieved since January 2008, a large increase on the £3m achieved in the first two years of operation. [source 3]

In June 2013, *GlySure* announced the appointment of a new executive chairman with extensive experience of the medical diagnostics and devices industry to support its commercialisation programme. [source 6]

Health impact

GlySure have reported on a series of trials of their device, with information on these on their website and presented industry conferences in 2012 and 2013 [source 7]. These reports say that early trials in human serum plasma and whole blood confirmed that the sensor can measure glucose levels effectively and accurately, with this later validated in *in vivo* models. Human trials began in late 2010. [source 8] In January 2012, *GlySure* reported that they had completed initial human trials on over 90 intensive care patients and provided examples from these trials of successful continuous measurement throughout a patient's intensive care treatment of more than 70 hours. [source 9]

The company have informed the University that the trials have shown benefits including reduced patient morbidity, a reduced length of stay in intensive care by around 18 hours and a saving in nursing costs of around $1000 per patient. [source 3]

In March 2013, *Glysure* reported that it expected to begin European CE mark trials later that year (the completion of patient enrolment was confirmed on its website in October 2013) and had obtained ISO 13485 certification of its quality management system, which was an important foundation for these next round of trials. [source 10]

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

[1] G. van den Berghe et al, "Intensive insulin therapy in critically ill patients", *New England Journal of Medicine,* 2001, 345(19), 1359-67

[2] "Tight Glycemic Control: Critical Care's Balancing Act", *In Vivo*, September 2012, pp 44-48

[3] Information provided to the University by Chief Technology Officer, GlySure Ltd, email dated 24th Jan 2013

[4] see: http://www.glysure.com/technology/platform-technology/

[5] GlySure press notice, 9/1/2012, "GlySure Secure £7 million in Series C Financing Round"

[6] PR Newswire 26/6/13, "GlySure appoints William Moffitt as Executive Chairman"

[7[GlySure press notice 20/3/12 and 25/9/12; PR Newswire, 26/3/13

[8] GlySure press notice 5/1/12, "Prototype Clinical Trials"

[9] Clinical trial details: Snapshot of cases from Glysure human clinical trials – January 2012

[10] GlySure press notice 5/3/13, "GlySure Earns ISO 13485 Certification"