Institution: University of Bath

Unit of Assessment:8: Chemistry

Title of case study:
GlySure Ltd: a commercial clinical continuous glucose sensor

1. Summary of the impact

A commercial continuous glucose sensor/monitor that provides real time data has been developed by GlySure, a venture capital funded company founded on the basis of Bath chemistry. The sensor enables Tight Glycaemic Control (TGC) for control of glucose levels in patients in Intensive Care Units (ICUs), reducing severe hypoglycaemia, glycaemic variability and the nursing burden, maximising both patient and economic benefit. This has led to (i) £13.5M investment in the company GlySure Ltd directly for development of the system based on the Bath chemistry and (ii) successful results from full clinical trials of the device, involving more than 200 ICU patients, prior to CE approval and launch in the EU.

2. Underpinning research

The research has been carried out by Professor Tony James, as part of the work by his group in the synthesis of a range of organic compounds for use in sensing applications. James' work maps to the Sensing & Healthcare theme within Bath Chemistry, and is a major component of the CASE (Catalysis and Sensing for our Environment) initiative led by Bath.

The capacity of boronic acid receptors to bind diols effectively in water has made boronic acids the receptor of choice in the James group at the University of Bath, where he has shown that in order to develop saccharide selective receptors systems with two boronic acids must be prepared. Such sensors, pioneered at Bath, consist of three components; a receptor, a support/spacer, and a read-out unit. The unique element of 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.

The James group research has shown that in order to prepare a D-glucose selective fluorescence sensor, two boronic acid units (only through two point binding can saccharide selectivity be engineered), a hexamethylene linker (D-glucose selective spacer) and a fluorophore (read-out) must be included [1, 2]. The sensor used in the current system developed by GlySure Ltd consists of two boronic acids, hexamethylene linker and fluorophore which is then attached to a hydrogel polymer.

The chemistry has been developed over the last decade [3, 4], and has been funded by a combination of research council, direct industry and DTI funding [5]. The specific application in glucose sensing that is relevant to the commercialisation and clinical implementation has been patented (US 7358094) and following the purchase of this patent from Beckman-Coulter by GlySure Ltd, the continued development of the chemistry has focused on the specific requirements of the GlySure sensor system [6].

The development of these technologies has been furthered, into human clinical testing, with GlySure's resources and expertise focused on completion of existing fluorescent intensity based measurement systems using the Bath chemistry. The targeting of this work towards the GlySure sensor has led to Professor James' appointment as Scientific Advisor to GlySure Ltd, emphasising the direct link of the Bath-developed chemistry to the product.

Timeframe

The work relevant to the development of the development of the sensor being used by GlySure Ltd in its devices has been carried out in the timeframe since 2001. The critical step of incorporating established boronic acid sensors into appropriate polymer support matrices and their optimisation and development for operation in the responsive flow environment was carried out initially between 2002 and 2005. This element of the research, crucial to the GlySure technology, resulted in a patent filed in 2003 ("Sensor system for saccharides"; see Section 5), and has been developed subsequently in ongoing research by the James group in Bath [6].

Key Researchers
Professor Tony James (Bath since 2000; synthesis of sensor molecules and support scaffolds; lead academic)
K. A. Frimat (2008-2012; PhD student in James group); S Arimori (2000-2001), S E Flower (20003-2008). N P Barwell (2008-2011); PDRAs in James group

3. References to the research

[1] S. Arimori, M. L. Bell, C. S. Oh, K. A. Frimat and T. D. James, *Chem. Commun.*, **2001**, 1836-1837. *Modular fluorescence sensors for saccharides* [DOI: 10.1039/b105994g]

[2] S. Arimori, M. L. Bell, C. S. Oh, K. A. Frimat and T. D. James (2002), *J. Chem. Soc., Perkin Trans.* **1**, 803-808. *Modular fluorescence sensors for saccharides* [DOI: 10.1039/B108998F]

[3] T. D. James (2007). *Top. Curr. Chem.*, **277**, 107-152. *Saccharide-selective boronic acid based photoinduced electron transfer (PET) fluorescent sensors* [DOI: 10.1007/128_2007_110]

[4] R. Nishiyabu, Y. Kubo, T. D. James, and J. S. Fossey (2011). *Chem. Commun.*, **47**, 1106-1123. *Boronic acid building blocks: Tools for sensing and separation* [DOI: 10.1039/c0cc02920c]

[5] Direct industrial / translation funding
Total of £344k including: EPSRC/DTI, (DT/F00267X/1; with GlySure and Gilden Photonics) 2007-2009 (£247k); Knowledge Transfer Partnership (KTP) (with GlySure) 2010-2011 (£47k); Impact Acceleration Account Award (with GlySure) 2013- (£50k)

[6] S.D. Bull, M.G. Davidson, J.M.H. van den Elsen, J.S. Fossey, A.T.A. Jenkins, Y.B. Jiang, Y. Kubo, F. Marken, K. Sakuyrai, J.Z. Zhao, T.D. James (2013). *Acc. Chem. Res.*, **46**, 312-326. *Exploiting the Reversible Covalent Bonding of Boronic Acids: Recognition, Sensing, and Assembly*. [DOI: 10.1021/ar300130w]

4. Details of the impact

"*[Our] development of medical devices for glucose detection, inward investment in our company and successful clinical trialling of these devices … has relied heavily on the underpinning developments from [Bath] Chemistry research, and on our ongoing interactions in translating [this] into forms appropriate for commercialisation and clinical implementation.*" [A]

Impacts from this work: company, investment, people, new technology, clinical testing

- A spin-out or new business has generated revenue or profits (**GlySure Ltd; £13.5M new investment in REF period** directly attributed to the Bath research [A])
- Highly skilled people having taken up specialist roles that draw on their research (**GlySure staff expansion to 30, largely in technical scientific roles**; including a Senior Chemist at Glysure recruited from Bath)
- A new diagnostic or medical technology has been developed and trialled with patients (**glucose sensor developed; full, successful, clinical trials carried out**)

Clinical Need, GlySure Ltd, and Economic Impact
The development of an invasive fibre optic continuous glucose sensor/monitoring system is in direct response to the clinical need demonstrated by a seminal clinical study in 2001 [B], which showed that continuous intensive administration of insulin (allowing tight glycaemic control) reduced patient mortality by 40% and morbidity by 37-46%, the latter reducing patient length of stay in the Intensive Care Unit (ICU) thus providing economic benefits. GlySure Ltd was founded in 2006 to exploit the Bath-developed research [C], with a 20% equity stake held by the University of Bath. Based in Abingdon, Oxfordshire, it is a venture capital funded company with 30 employees, focused on the development and launch of a continuous real time invasive optical glucose sensor utilizing fluorescent intensity measurements that allows the development of continuous glucose monitoring systems in hospital ICUs. GlySure Ltd was the lead organization in partnership with Bath and Gilden Photonics on a DTI grant, resulting in new IP filings covering long lifetime dendrimer fluorophores and synthesis of an alternative diboronic acid receptor structure

from the Bath research [D]. The automated and continuous dosing and response nature of the GlySure device greatly reduces the nursing workload required to implement tight glycaemic control, and helps to improve compliance.

The GlySure target market includes the medical and surgical ICU units of acute care hospitals. Global admissions in these units alone are approximately 8.6 million per year, representing a market opportunity of approximately $1.5 billion for sensors. Initial investments resulted for GlySure, to develop and build the Bath chemistry into the glucose sensors, which has since been followed, in **January and November 2012,** by further tranches of investment on completion of the initial successful clinical trials [E], **£13.5M of which directly results from the devices developed from the Bath chemistry** [A]. GlySure Ltd has thus established itself as a secure and expanding UK-based company offering highly skilled employment opportunities. GlySure continue to invest in Chemistry developments at Bath and have appointed Professor James as Scientific Advisor: *"Based at the University of Bath, Dr. James is generally accepted as the world's expert in boronic acid fluorophore chemistry. He has played a pivotal role in optimising glucose selective indicator chemistry for continuous measurement in whole blood"* [F].

IP Acquisition and Technology Development

The technology development work has been led from Bath, following the development of the initial chemistry by James; GlySure acquired relevant IP [C] from the more instrument-focused Beckman Coulter and invested direct funding in the James group in Bath to develop the chemistry further towards the function and performance of the appropriate sensor molecules in the required sensing environment [D] Since 2008, through a series of funded industry academic transfer projects [5, above], the chemistry has been incorporated into devices ready for implementation in the clinical environment. To meet the clinical and commercial need, the technology developed by GlySure for ICU applications has required the translation by James of the fluorescent/receptor glucose indicator chemistry developed in Bath into an optimised form for *in situ* sensor operation, immobilised into an optical cell that is micro machined into the fibre. These sensors have advantage over other existing glucose sensor in terms of cost, stability and the ease of the fluorescence measurements, as corroborated by advantages highlighted by Senseonics, a US company in this domain: "The fluorescent glucose chemistry is … not subject to the instabilities intrinsic to current protein based glucose sensors... Consequently, this technology is expected to be inherently more stable and accurate." [G].

Clinical Testing

Since 2008, GlySure have used the Bath-developed chemistry as a fundamental underpinning feature of their sensor device, which is intended to act as the active glucose sensor in clinical settings. The sensors were tested *in vivo* (in pigs) in 2008-2009, and the sensors entered clinical trials in India in 2010. Successful clinical testing has been carried out in the ICU environment and presented at the International Symposium on Intensive Care and Emergency Medicine, attracting more than 2000 physicians, nurses and other healthcare professionals, and the World Federation of Societies of Intensive and Critical Care Medicine [H]. Over two years of human use trials, the GlySure continuous glucose monitoring system has been tested in over 200 intensive care patients to date, in the challenging environment of the ICU. The impressive results from these clinical trials [H-J] show that the GlySure system is capable of monitoring throughout the length of a patient's stay in the ICU.

Scope for Growth

In addition to the ICU device described, the fluorescent lifetime glucose sensor has been incorporated into a development programme to create a small, easy to use continuous glucose sensor for the home diabetic market. This lifetime sensor device would allow expansion of the devices into the home market which is estimated at £1.5 to £2 billion annually.

Key Impacts Summary

2008-2009 – *In vivo* testing of GlySure device, incorporating Bath-developed sensor technology
2010-2011 – Clinical trials, India; more than 150 patients
2012 – Clinical Trial outcomes reported, two rounds capitalisation for Glysure, £13.5M of which results directly from the Bath chemistry

2013 – Clinical trials extended to 200 intensive care patients
2013 – Device enrolled for CE regulatory trial for approval in Europe

5. Sources to corroborate the impact

[A] Letter of evidence of impact, CTO and Director, Glysure Ltd

[B] Van den Berghe et al (2001). New England Journal of Medicine, **345**, 1359-1367. *Intensive insulin therapy in critically ill patients* [DOI: www.nejm.org/doi/full/10.1056/NEJMoa011300]

[C, D] *IP/patents*

[C] M. L. Bell, T. D. James, S. Arimori, *Sensor system for saccharides*, US 7358094 (2008); filed in 2003, with Beckman-Coulter; subsequently acquired by GlySure.
http://worldwide.espacenet.com/publicationDetails/biblio?II=1&ND=3&adjacent=true&locale=en_EP&FT=D&date=20041118&CC=WO&NR=2004099778A1&KC=A1

[D] B. C. Crane, T. D. James, J. S. Fossey, N. P. Barwell, *Indicator System for Fiber Optic Sensor* WO/2011/101624 (2011); for chemistry developed explicitly in Bath for the Glysure sensor applications
http://worldwide.espacenet.com/publicationDetails/biblio?DB=worldwide.espacenet.com&II=7&ND=3&adjacent=true&locale=en_EP&FT=D&date=20130307&CC=US&NR=2013059394A1&KC=A1

[E] *Capitalisation*
Two major rounds of capitalisation in the REF period:

http://www.glysure.com/media-centre/press-releases/new-funding-round/
"GlySure, developer of in-hospital continuous blood glucose monitoring systems, today announced the close of its £7 million Series C financing round" (9 January 2012)

http://www.glysure.com/media-centre/press-releases/series-c-second-closing/
"Glysure Completes Series C Second Closing for a Total of £8.5M" (29 November 2012)

[F] Quotation taken from GlySure Website listing Professor James as Scientific Adviser
http://www.glysure.com/about/directors-advisors/

[G] http://senseonics.com/product/the-sensor

[H-J] *Clinical Trials*
Results presented at ISICEM2012 and WFSICCM clinical conferences, and highlighted by the NIHR (National Institute for Health Research) Horizon Scanning Centre

[H] http://www.glysure.com/clinical-data/icu-pilot-trial/

[I] ISICEM2012: Mulavisala KP, Gopal P, Crane B *et al*. Preliminary ICU experience of a novel intravascular blood glucose sensor. Accuracy of a continuous intravascular glucose monitor in ICU patients. 32nd International Symposium on Intensive Care and Emergency Medicine (ISICEM). March 2012. Poster P175
http://www.glysure.com/media/14997/glysure_poster_isicem_final.pdf

WFSICCM: http://www.glysure.com/media/23434/glysure_poster_durban_2013_updated_v2.pdf

[J] National Institute for Health Research (NIHR) Horizon Scanning Centre, University of Birmingham, May 2013. Glysure intravascular continuous glucose monitoring system for glycaemic control in intensive care
http://www.hsc.nihr.ac.uk/topics/glysure-intravascular-continuous-glucose-monitorin/