**Institution:** Queen Mary University of London (QMUL)

**Unit of Assessment:** B8 (Chemistry)

**Title of case study:** CS2 – The development of low-cost point of care sensors for the detection of protease enzymes

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

The spin-out company, Degrasense, has developed and protected intellectual property of technology capable of quantifying specific proteolytic enzymes through changes in electrochemical responses (impedance) at electrodes due to the enzymatic degradation of polymer coatings. The company has detected several specific proteases that are relevant to the monitoring and treatment of a number of conditions including: periodontal disease, multiple sclerosis, haemophilia and hypertension. The technology is currently being validated in a clinical trial as a point of care sensor for the detection of active periodontal disease. Point-of-care sensors provide immediate, low-cost test results in non-laboratory settings, offering a more patient-centred approach to healthcare and earlier detection of disease.

**2. Underpinning research** (indicative maximum 500 words)

**Staff leading the underpinning research**

Dr Steffi Krause (School of Engineering and Materials Science) and Professor Michael Watkinson (School of Biological and Chemical Sciences) have been collaborating since 2006 on the development of new, generic, low cost and non-invasive sensor arrays for the specific detection and quantitation of a number of proteolytic enzymes, which are clinically relevant markers for a number of disease states. They have established the spin-out company Degrasense, which owns the underpinning intellectual property and are developing the technology via clinical trials.

Other notable QMUL researchers working with Watkinson and Krause include Dr Jacqueline Stair (BBSRC-funded PDRA, 2008-2009), Dr Xingewi Zheng (IP2IPO Ltd-funded PDRA, 2008-2010) and Dr Joseph Cook (Technology Strategy Board-funded PDRA, 2008-2009).

**Research underpinning the new technology**

The technology is based on the preparation of hydrogel polymers that are cross-linked with short peptide sequences containing amino acid sequences cleaved by the specific proteolytic enzymes being targeted [references 1-4].

Through BBSRC-funded research, Krause, Watkinson and Stair developed new peptide cross-linked dextran hydrogels, which, they demonstrated using a quartz crystal micro-balance, can sense protease cleavage [see publication 1]. The underpinning work involved the preparation of suitably functionalised peptides, which could be used to cross-link dextran to form degradable hydrogel polymers. The key synthetic challenges were to identify both the functional group which could be cross-linked and the nature of the polymeric matrix which would allow degradation by the individual protease in question, at clinically relevant concentrations and within a short time-frame, without non-specific protein binding. Several approaches were investigated including the *in situ* radical polymerisation of peptides and the cross-linking of highly functionalised dendronised polymers. Ultimately it was found that a partially oxidised dextran in combination with amine-functionalised peptides provided suitable substrates which met the technical specification required. Consequently they were able to coat individual electrodes with different polymers so that each electrode is able to detect a specific enzyme. This aspect of the research is central to the technology – without it no point of care device could have been produced.

In a second publication [2], Watkinson, Krause, Zheng and Cook demonstrated the efficacy of this technology in the selective detection of a number of proteases (Human Neutrophil Elastase, Cathepsin-G, and MMP8) that are clinically relevant to periodontal disease. Periodontal disease (periodontitis) is an inflammatory disease that affects the periodontum, the tissues that surround

and support the teeth. If left untreated, chronic periodontitis leads to degradation of bone and ultimately to the loss of teeth. However, progression of the disease is not uniform across infected sites and accurate clinical methods for distinguishing areas where the disease is active, rather than inert, are currently lacking. As a result much unnecessary treatment of periodontal sites that are quiescent occurs. This is both costly and potentially causes additional damage to teeth attachments.

The research, led by Krause and Watkinson [1, 2], clearly established the potential for a new technology, as a point-of-care clinical diagnostic tool of protease activity associated with periodontal disease. The intellectual property underpinning the technology was protected by a European patent [3] and a further patent application has been filed [4].

The potential of this technology led to follow-on funding secured from the BBSRC and the Heptagon fund in 2006. Then with support from the Technology Strategy Board, and in collaboration with a number of key industrial partners, Watkinson and Krause were able to develop the technology to the point where it could be tested in a clinical trial. They have also secured Venture Capital (VC) funding and, most recently, funding from the Barts and the London Charity.

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

**Peer Reviewed Papers**

1. J. Stair, M. Watkinson and S. Krause, “A generic protease sensor material based on the degradation of peptide cross-linked dextran hydrogels”, *Biosensors and Bioelectronics*, 2009, 24, 2113-2118.
2. X. Zheng, J. Cook, S. Yang, S. Krause, M. Watkinson, I. Douglas and A. Rawlinson, “Generic protease detection technology for monitoring periodontal disease”, *Faraday Disc.*, 2011,149, 37-47.

**Patents**

3. S. Krause, D. Kamarun, M. Watkinson and J. Stair, “Sensor coatings for protease detection”, European patent number 07824180.9-1223 PCT/GB2007/003929, granted 10.06.2009 currently at the national phase in the US (WO2008047095(A1)) and the regional phase in Europe (EP2082057(A1)).
4. S. Krause, X. Zheng, and M. Watkinson, A second UK priority application following on from Patent 1 was filed on July 30th 2010 and is entitled “Sensor Coating Layer, Device and Method” (App No. 1012902.1).

**Funding**

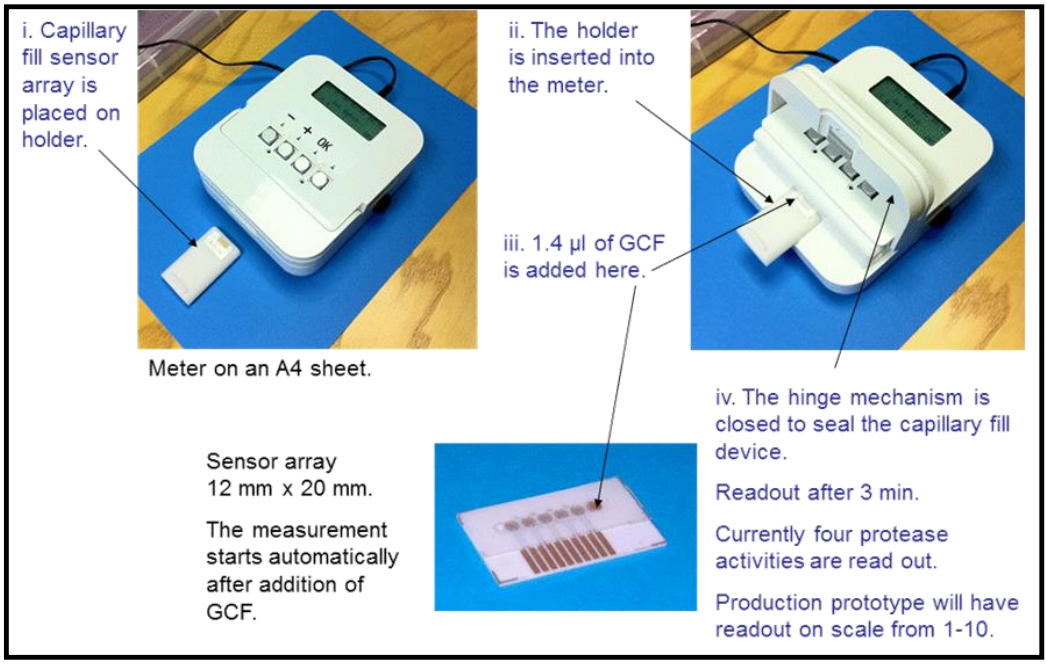
£124,876 to G. Giovannoni (PI), S. Krause (co-I), M. Watkinson (co-I), D. Baker (co-I) and A Nassim (co-I) for a project entitled “MMP-9 detector for inflammation monitoring in autoimmune diseases and solid organ graft rejection” (NSCG1L3R), January 2012-December 2014.
£738,583 EPSRC/DTI Technology Strategy Board to S. Krause (PI) and M. Watkinson (co-I) for a project entitled “Prototype sensor for periodontal disease monitoring” (TP/8/BIO/6/I/Q0020H) April 2008-.December 2011
£18,952 Queen Mary Innovations Ltd to M. Watkinson (PI) and S. Krause (co-I) for a project entitled “Sensor Platform for the Detection of Coagulation Factors” December 2010-March 2011.
£109,710 BBSRC follow-on fund awarded to S. Krause (PI) and M. Watkinson (co-I) for a project entitled "Disposable low cost sensor for periodontal disease", BB/E525877/1 (co-investigator) April 2006-March 2008.
£95,839 Heptagon Fund awarded to S. Krause (PI) for a project entitled "Disposable low cost periodontal disease diagnostic”, (QMUL/AL05), June 2006-May 2008
£48,000 IP2IPO Ltd GRUB funding awarded to Degrasense for a project entitled “Prototype sensor for periodontal disease monitoring” July 2008-June 2009
£12,000 Combined London Colleges University Challenge Partnerships (CLUC) awarded to Degrasense for a project entitled "Disposable low cost periodontal disease diagnostic”, July 2008-June 2009

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

The American Dental Association estimates that there are around 300 million periodontal examinations undertaken in the USA every year, representing ca. 30% of the examinations undertaken world-wide. Based on Watkinson and Krause's research, QMUL's spin-out company Degrasense (established in January 2008) has developed a system with the likely capability to accurately identify periods of active inflammation in relation to periodontal disease that is inexpensive to mass produce. The meter (Figure 1) is a point of care system that is designed to allow rapid, in-house diagnosis of periodontal disease, precluding the need to outsource assays to external laboratories. It has been estimated that the consumables associated with this novel technology, will have a market value of approximately 450m GBP per annum (Oraldent – see below). The technology will improve the targeting of treatment to patients with active periodontitis and ultimately improve clinical outcomes and enhance patient experience.

The device developed by spin-out company Degrasense is shown in Figure 1. Briefly, the meter works by samples of gingival crevicular fluid (GVC) from the gums, being loaded onto the capillary sensor chip, which contains electrodes coated with the QMUL patented technology. This sensor is then loaded into the machine, where protelytic activity of the clinically relevant proteases in the GVC is measured through changes in electrical impedance.

**Figure 1: Meter used to detect protease activity in patients with periodontal disease**




**Companies and charities influenced by the research**

To reach the point of a clinical trial [below, and 1 in section 5] required collaboration with a number of industrial partners. Supported by Technology Strategy Board funding, Watkinson coordinated the industrial partners to develop the technology specifically for the clinical diagnostics market. These partners are:

1. Oraldent (Oraldent: www.oraldent.co.uk) who assessed the size of the potential periodontal market to be 450m GBP per annum in consumables (value of disposable capillary sensor chip).
2. Industrial Design consultancy (IDC: www.idc.uk.com) [2 in section 5] who designed the meter (see Figure 1)
3. AND Technology Research (AND: http://andtr.com) who developed the electronics in the meter [3 in section 5].
4. Gwent Electronic Materials Ltd. (www.gwent.org/gem_index.html) who manufactured the interdigitated electrodes used in the clinical trial [4 in section 5].
5. Barts Charity (www.bartscharity.org.uk) who are currently funding Gwent Electronic Materials to

further refine the electrodes based on insights gained through the clinical trial.

Collectively, these industrial partners contributed over £340k to the project.

**Development of a new clinical diagnostic tool and its application in a clinical trial**

The efficacy of the Degrasense technology is currently being assessed via a clinical trial involving 30 patients suffering from chronic periodonitis. This is an important step on the road to delivery of this diagnostic technology to market. The clinical trials are being undertaken by staff within the School of Clinical Dentistry at the University of Sheffield, in partnership with Sheffield Teaching Hospitals NHS Foundation Trust. The aim of the trial is to assess whether the device can be used to detect active periodontal disease.

The initial 12-month stage of the trial necessitated the appointment of a dental hygienist to collect patient samples. The patients were recruited from a number of sources within the partnering hospital, including the undergraduate periodontology teaching clinic, staff hygienist clinics and consultant clinics. All patients were selected by the clinician in charge [1 in section 5] according to criteria that include; aged 18 or over; a diagnosis of chronic periodontitis but otherwise healthy and; one healthy gingival crevice, one deep bleeding and one deep non-bleeding periodontal pocket.

Data from the first 12 months of the trial have revealed that the interdigitated electrodes produced by Gwent Electronics need further refinement. The company, funded by Barts Charity, are currently modifying the electrodes to increase reliability. All patient samples from the first stage of the trial have been retained for re-testing once these refinements are in place.

**Application of Degrasense technology in other clinical settings**

Krause and Watkinson's technology has already attracted significant interest and investment from multiple industrial partners and its use in a clinical setting has been demonstrated through application in a clinical trial. In addition to increasing the efficacy of diagnostic tools for assessing periodontal disease, the technology has significant potential in a number of other clinical applications where elevated levels of proteolytic enzymes are linked to disease states. Investigations into these applications are ongoing (and are sensitive at this stage) but include: (i) home monitoring of haemophilia; (ii) clinical monitoring of sepsis and trauma; (iii) home monitoring of multiple sclerosis and (iv) the monitoring of arterial ageing and the role of proteinases in hypertension. All of these areas are associated with very significant patient numbers and cost to the NHS. The generic technology that Watkinson and Krause have developed is capable of providing significant improvements in the quality of patient monitoring and consequently also reduction in treatment costs.

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

1. Professor and NHS Consultant, The University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust: the clinician currently undertaking the clinical trial.

2. Programmes Director, AND Technology Research Ltd: this company developed the meter being used in the clinical trial through the TSB project.

3. Project Manager, Industrial Design Consultancy: AND Technology Research Ltd sub-contracted the meter design to Industrial Design Consultancy Ltd.

4. Technical Director, Gwent Electronic Materials: GEM Ltd manufactured the interdigitated electrodes currently being used in the clinical trial in Sheffield and are printing new electrodes coated with the degradable polymer for the ongoing multiple sclerosis study.

5. Director, QED Biosciences: QED provided an independent assessment of the technology for the IP-Group.