Institution: Swansea University
Unit of Assessment: 15 - General Engineering
Title of case study: Use of new diagnostic medical technology to improve detection of abnormal blood clotting: the health and economic benefits.
1. Summary of the impact

Research based on haemorheological technology has led to the invention, trialling, adoption and commercialisation of technology for the early detection of abnormal blood clots. The development of this technology was stimulated by an unmet clinical need for improved detection of abnormal clotting responses to therapy or disease. The research has delivered significant health, economic and public engagement impacts, including:

- a new diagnostic technology developed and trialled with patients at NHS Hospitals, with a dedicated NHS hospital-based unit established for this purpose;
- two new companies created based on IP related to this invention; a third company has relocated to exploit it; jobs have been created and investment has been secured; new products have been developed and sold; and licensing revenues generated;
- the work has been adopted as an exemplar of '*Excellence with Impact*' by RCUK; exhibited at the Science Museum London and Smithsonian Washington; and included in TV documentaries broadcast on Channel 4 and the Smithsonian Channel, USA.

2. Underpinning research

The underpinning research is the development of rheometric techniques for the characterisation of gel microstructure and complex fluids, undertaken by **Prof PR Williams** (1990-date). Initial research published in 1994 established a basis for exploiting the viscoelastic dispersion of shear waves [R1] and was supported by an EPSRC Advanced Fellowship (PR Williams, 1990-1995; 1995-98). These findings were further developed to characterise soft-solids under EPSRC grants [G3 and G4], and viscoelastic fluids and industrial process materials (with Unilever, Nestle, Proctor & Gamble). The research was used as a basis for developing a new haemorheological technique for the detection of incipient clot formation in blood [R2; **Dr M Lawrence** and **RL Dr Williams** PDRA, 2007-2009] and led to PR Williams receiving the British Society of Rheology's *Annual Award* (1997), This involved, *inter alia*, the optimisation of rheometric wavegroups suitable for measurements of the complex shear modulus of small (<0.2 ml) samples of whole blood.

Further theoretical and technical development underpinning these techniques was carried out under an EPSRC *Portfolio Partnership* Award, reserved by EPSRC for groups it considers "World-leading" [G2, PI PR Williams). The flexibility of resource deployment afforded by the award allowed a strategic approach to haemorheological work, a prerequisite being the establishment of the NHS-EPSRC Clinical Haemorheology Laboratory in 2005 with **Prof PA Evans** (College of Medicine, 2003-present) and **Dr K Hawkins** (College of Engineering, PDRA, 2003-2006; College of Medicine Lecturer 2006-present). This was the first such laboratory of its kind. Work conducted in it led to the discovery that the fractal microstructure of incipient clots provides significant new biomarkers for clotting [R2] in therapeutically modified (heparinised) blood. This work was published in *Blood* – the leading journal in the field [R3].

The potential for developing a point-of-care version of the technique based on haemorheometry with automated gel point location and its application in the investigation of therapeutically modified blood was addressed under PR Williams' Royal Society *Brian Mercer* Award (2007) [R4; **Dr MS Barrow** and **Dr MR Brown**, PDRAs, College of Engineering 2003-2009]. Related work involved the development of new rheometrical protocols specifically for strain sensitive gelling systems, including blood [R5, **D Curtis** and **M Davies**, PhD students, 2006-2009]. This work was underpinned by molecular dynamics simulation studies of fractal cluster growth based on a new mechanism termed activation-limited cluster-cluster aggregation [R6]. That work is being further exploited in studies of gel microstructural development in collagen gels [G5, 2010-2013].

Further enhancement of instrument sensitivity was initiated under an EPSRC Grand Challenge award [G1; PR Williams (PI), MS Barrow 2009-2012] for screening and anticoagulant therapy monitoring. Commercialisation of the clotting diagnostic is being accelerated under a Royal Academy of Engineering Enterprise Fellowship award to PR Williams (2012-2013).

3. References to the research

The following international journals are ISI listed and are the leading journals in the fields they represent. R3, R5 and R6 are those which best represent the quality of the underpinning research.

R1. **PR Williams, DJA Williams**. The influence of wave dispersion characteristics on the determination of mechanical relaxation spectra. Journal of Rheology 38 (1994) 1211-1226.

R2. **PA Evans, K Hawkins, M Lawrence, PR Williams & RL Williams**. Studies of whole blood coagulation by oscillatory shear, thromboelastography and free oscillation rheometry. Clinical Hemorheology and Microcirculation, 38 (2008) 267-277

R3. **PA Evans, KM Hawkins**, RHK Morris, N Thirumalai, R Munro, L Wakeman, **MJ Lawrence, PR Williams**. Gel Point and fractal microstructure of incipient blood clots are significant new markers of haemostasis for healthy and anticoagulated blood. Blood 116:17 (2010) 3341-3346

R4. **PA Evans, KM Hawkins**, RHK Morris, N Thirumalai, R Munro, L Wakeman, **MJ Lawrence**, A Beddel, **PR Williams, MR Brown, MS Barrow**. Fractal analysis of viscoelastic data with automated Gel Point location and it's application in the investigation of therapeutically modified blood coagulation. Rheologica Acta 49:19 (2010) 901-908

R5. **KM Hawkins, PA Evans, MJ Lawrence, D Curtis, M Davies, PR Williams**. Development of rheometry for strain sensitive gelling systems and its application in a study of fibrin-thrombin gel formation. Rheologica Acta 49:19 (2010) 891-900

R6. **DJ Curtis, MR Brown, K Hawkins, PA Evans, MJ Lawrence, P Rees, PR Williams**. Rheometrical and molecular dynamics simulation studies of incipient clot formation in fibrin-thrombin gels: an activation limited aggregation approach. J. Non-Newtonian Fluid Mechanics 166:16 (2011) 932-938

Note: non-SU co-authors on the above are NHS-based staff collaborators in the research with the exception of RHK Morris (UWIC) who contributed to statistical analysis of data.

Related RCUK grants

G1 EPSRC EP/G061882/1, Grand Challenge Nanotechnology for Healthcare: *Point of care nanotechnology for early blood clot detection and characterisation in disease screening, theranostic and self monitoring applications*. £906,522; 2009-12, PI Professor PR Williams.

G2 EPSRC EP/C513037/1, Portfolio Partnership in *Complex Fluids and Complex Flows*, £3.1M; 2004-09, PI Professor PR Williams. (One of the 5 Co-Investigators was based at Cardiff University, all others at SU. All work referred to herein relating to this grant conducted by PR Williams).

G3 EPSRC GR/S64431/01, *Complex Fluids And Complex Flows - From Physics To Processes,* £437,072, 2004-09, PI Professor PR Williams.

G4 EPSRC GR/S10438/01, *High speed and ultra-high speed microphotographic studies of meso-scale rheological and cavitation phenomena in a modified Atomic Force Microscope*. £317,009, 2003-07, PI Professor PR Williams

G5 EPSRC EP/H045848/1, *Probing the mechanical control of stem cell fate through the development of novel, non-invasive imaging technologies.* £1,545,307, 2010-2013
This award is shared with Cardiff University. The rheological work referred to in this Case Study which relates to this grant is conducted at SU and is led by Prof PR Williams with co-

Investigators Dr KM Hawkins (College of Medicine) and Dr C Wright (College of Engineering).

Awards cited

- 1997 British Society of Rheology *Annual Award* (to PR Williams)
- 2007 Royal Society *Brian Mercer* Award (to PR Williams)
- 2012 Royal Academy of Engineering, *Engineering Enterprise Fellowship* (to PR Williams)

4. Details of the impact

The underpinning research has delivered clear, international health, economic and societal impacts, as described below.

Health impact is evidenced through the development of a new test based on a haemorheological diagnostic medical technology arising from the rheological research described above. The test exploits the discovery of a new functional biomarker for abnormal clot structure formation in blood (R3). Clotting abnormalities are inter alia responsible for some 25,000 preventable deaths annually *inside* UK hospitals (from 60,000 total) and ~1 million NHS outpatients require monitoring of anticoagulant therapy. Correlation of existing standard tests to clinical outcome has been unsatisfactory, with uncertain benefits. The new test provides clinicians with **the earliest possible indication of altered clot structure** due to therapeutically or pathologically modified clotting. No previous diagnostic has been able to detect *incipient* clot formation. It allows clot detection several minutes in advance of any other test, providing clinicians with an improved ability to monitor the progression of disorders and responses to treatment.

Conventional tests provide information which can lag significantly on changes in patient state. The World Health Organisation has highlighted the need for improved tests and NICE guidelines (2010) require all 1.3m annual UK hospital admissions to be screened for clotting abnormalities. NHS-based trials on patients undergoing oral anticoagulation (by warfarin) due to venous thromboembolic disease reveal that **the new test is the only diagnostic presently capable of detecting abnormal clots** in patients who appear fully anticoagulated when tested by the current standard INR haematological assay.

This new test's capability is the basis for the creation (in 2010) of a wholly new NHS hospital-based unit employing 10 staff in fully equipped haemorheological laboratories. This £1.5m NISCHR (Welsh Government)-funded unit is responsible for evaluation and validation of the test in NHS operating theatres, treatment rooms and patient wards.

> "*The new haemorheological clotting test developed at Swansea University is the key, principal technology underpinning our NHS based clinical evaluation of patients involving therapeutic intervention in care pathways including stroke and sepsis*."
> Director, NISCHR HBRU, ABMU NHS Hospital Morriston Swansea

The test has been used to target care pathways involving over 900 NHS patients at 2 hospital sites to date (covering stroke, sepsis, diabetes, COPD and cancer patients, and warfarinised clinic outpatients). The test has also been adopted internationally (the Schools of Medicine at University of Pennsylvania, Philadelphia, are using the test in pre-clinical studies of heparin-induced thrombocytopaenia).

Economic impact is evident in the technique's use by a medical device company (Haemair Ltd), which led to an IChemE Industry Award for Innovation and Excellence in 2008.

> "*Swansea's haemorheology technology has been a key underpinning and enabling technology in the development, testing, trialling and sale of our products. Our need to exploit it was a principal driver in the company's decision to locate, recruit and operate at Swansea University and it is a vital part of our ability to attract ongoing investment*".
> Operations Manager, Haemair Ltd.

Commercialisation of the research began in 2005 with the establishment of an IPR portfolio which has since resulted in:

(i) the relocation of one company (Haemair Ltd) to Swansea University, leading to
(ii) the introduction and sales (ca. £100,000 in 2011) of two wholly new, previously unavailable commercial medical device technology products and
(iii) the payment of license revenues to Swansea University (estimated value >£100,000, source Department of Research & Innovation (DRI), Swansea University); and
(iv) the establishment of two further Swansea spin-out companies (Haemometrics Ltd and Haemaflow Ltd) which exploit the technology.

To date, 17 highly skilled jobs have resulted directly from this activity. The total value of this work with Haemair to date is **in excess of £700,000** (DRI). Cash investment of **over £2m** (to January 2012) has been raised from private and commercial sources in addition to £400,000 company-derived grant income to Swansea University. A Royal Academy of Engineering awarded to PR Williams in 2012 provided £85,000 for commercial development and IP costs associated with the test. **Patents relating to the test have been awarded** for the UK, Europe, Australia and Canada.

Societal impact has been delivered through public engagement activities that have raised the profile of engineering research, its commercial development and healthcare applications. The research has been selected by RCUK as an **'*Excellence with Impact*' Case Exemplar**, which highlights research based on fostering partnerships with business and industry to achieve economic and societal impact. It also features in Exhibitions in 2013 at the **Smithsonian (Washington) and the Science Museum,** London (with 5,208 visitors to this exhibit 19-21 February 2013). The research has also featured in two television documentaries on medical device technology. The first *How to Build a Bionic Man,* was broadcast on Channel 4 (9pm, 07/02/13) and attracted **an audience of 1.23 million viewers** (Source: BARB). The second will be broadcast in 2013 on the Smithsonian Channel, USA.

5. Sources to corroborate the impact

Health Impacts and Underpinning Research (Sections 2 and 5)

1. Director of Operations, National Institute for Social Care and Health Research (NISCHR)
2. Assistant Manager, Research Programmes, The Royal Academy of Engineering
3. Awards Scheme Manager The Royal Society
4. Programme Director (i4i), NIHR National Institute for Health Research
5. Director, Haemostasis Biomedical Research Unit, Morriston Hospital, ABMU Health Board

Commercial (Section 5, Economic Impacts)

6. Operations Manager, Haemair Ltd, Haemaflow Ltd
7. Director, Department of Research and Innovation (DRI), Swansea University
8. Press and Communications Manager, RCUK

Other

9. Assistant Content Developer, Contemporary Science, Science Museum
10. RCUK Excellence with Impact: www.rcuk.ac.uk/media/brief/impactcase
11. Broadcasters' Audience Research Board (BARB): www.barb.co.uk/viewing/weekly-top-30?_s=5&period[]=201302060110