Institution: Sheffield Hallam University

Unit of Assessment: 5 Biological Sciences

Title of case study: Biologically Functionalised Sol-gel Coatings

1. Summary of the impact

Interdisciplinary work by microbiologist **Smith TJ** and materials science collaborators has led to (**i**) the development of novel environmentally friendly coatings for anti-corrosion and anti-biofouling applications that have attracted attention across diverse industries; (**ii**) the development of a platform technology that includes an antimicrobial coating currently under investigation for use on orthopaedic prostheses and (**iii**) associated work quantifying elution of antibiotics from orthopaedic cement in clinical use. The research has been disseminated via journal publications and patents have been obtained. Impact is evidenced by commercial interest, which has led to collaborative field trials under an EPSRC follow-on fund grant and contract research and consultancy funded by industry and the NHS.

2. Underpinning research

Smith TJ was appointed by Sheffield Hallam University (SHU) in 2001 as Senior Lecturer in Microbiology (Professor of Microbiology, 2011–present). His expertise in bacterial monooxygenases (e.g. reference 1) underpinned a successful Biotechnology and Biological Research Council (BBSRC) New Investigator grant in 2002 (grant 1). His research track record includes applied microbiology, enzymology and characterisation of bacterial endospores (grants 2-4). In 2005, **Smith TJ** was funded by SHU's Promising Researcher Fellowship Scheme (£49,964) to undertake full time research. During this period, **Smith TJ** and Akid (Materials and Engineering Research Institute at SHU 1999-2012, University of Manchester since March 2012) initiated a collaboration combining Smith's expertise in microbiology with Akid's expertise in materials science to develop functionalised coatings with wide ranging potential applications. The original coating concept, supported by a "Yorkshire Concept" grant from the Regional Development Agency (grant 5), combined a robust sol-gel coating with immobilised bacterial endospores to produce a biological anti-corrosion coating. We demonstrated that the coating was effective against corrosion of aluminium alloy in the laboratory and during a six-month field trial in the estuarine environment at the Thames Barrier, conducted in collaboration with the Environment Agency (reference 2).

Use of immobilised bacteria is superior to other functionalised coatings in that bacterial growth has the capacity to replenish the active agent, and the sol-gel coating offers a physically more robust matrix for long-term immobilisation than softer hydrogels. **Smith TJ's** insight as a microbiologist enabled a critical improvement, which involved immobilising the bacteria in the form of endospores, the most resistant life-form known, which can withstand the harsh conditions imposed during coating curing. **Smith TJ** performed all microbiology laboratory work leading to reference 2.

Further development of the functionalised sol-gel coating led to coatings with anti-fouling activities that resist colonisation by barnacles and other fouling organisms in the marine environment (grant 6). The team subsequently obtained an Engineering and Physical Sciences Research Council (EPSRC) Follow-on Fund grant to drive the technology towards market and to establish commercial collaborations (grant 7); this has included a collaboration, incorporating field trials, with International Paint.

Seed-corn funding to **Smith TJ** via an EPSRC Bridging the Gap grant (EP/H000275) held by SHU in addition to a Regional Development Agency Fellowship to collaborator Akid (whilst still at SHU) enabled **Smith TJ** to produce a derivative coating containing antibiotics, for use as controlled-release antimicrobial coatings in orthopaedic surgery. The release kinetics indicated that the coating would give protection during the critical perioperative period when pathogenic microorganisms can enter the surgical wound. These encouraging results led to a Medical Research Council (MRC) Development Pathway Funding Scheme grant (grant 8), with microbiology and coating development being conducted in the Biomedical Research Centre at SHU under **Smith TJ's** supervision and *in vivo* trials in rat models by collaborator Hatton at the University of Sheffield. At the time of writing (10/2013), coatings had been reformulated to

optimise adhesion and release kinetics and are currently under test in the animal model.

The novel coating technologies have been patented by SHU (Patents 1, 2) with **Smith TJ's** lead position in the field having been further consolidated by a recent comprehensive review article (reference 3). Our work toward antimicrobial coatings for orthopaedic surgery led local orthopaedic surgeons and consultant microbiologists to become aware of **Smith's** group's expertise and led to a study characterising elution kinetics of antibiotics from orthopaedic cement (reference 4) that was required in order to inform clinical practice in orthopaedic surgery. This, in turn, has resulted in contract research funded by industry and the NHS and associated knowledge transfer relating to the incorporation of antibiotics into orthopaedic cement, as detailed in section 4 below.

3. References to the research (citations from Scopus 25/10/2013)

1. Borodina, E., Nichol, T., Dumont, M. G., **Smith, TJ** and Murrell, J. C. 2007. Mutagenesis of the "leucine gate" to explore the basis of catalytic versatility in soluble methane monooxygenase. Appl. Environ. Microbiol. **73,** 6460-6467. DOI 10.1128/AEM.00823-07 (**9 citations**, underpinned successful application for BBSRC grant – grant no. 3 below).
2. Akid, R., Wang, H., **Smith, TJ**, Greenfield, D. and Earthman, J. C. 2008. Biological functionalisation of a sol gel coating for the mitigation of Microbial Induced Corrosion (MIC). Adv. Functional Mat. **18,** 203-211. **(9 citations)** DOI 10.1002/adfm.200600493.
3. Gittens, JE, **Smith TJ**, Suleiman R and Akid R 2013. Current and emerging environmentally-friendly systems for fouling control in the marine environment accepted for publication in Biotechnology Advances. DOI 10.1016/j.biotechadv.2013.09.002.
4. Dodds, S., **Smith, TJ**, Akid, R., Stephenson, J., Nichol, T., Banerjee, R.D., Stockley, I. and Townsend, R. 2012. Contrasting effects of physical wear on elution of two antibiotics from orthopedic cement. Antimicrob. Ag. Chemoter. 56, 1471-1475. DOI 10.1128/AAC.01588-10.

Patents

1. Wang H, **Smith T** and Akid R. 2008. Sol Gel Biocote 1, EP08788766.7. Biological functionalisation of a sol gel coating for the mitigation of biofouling microbial induced corrosion.
2. **Smith T**, Wang H, Gittens J, Akid R. 2012. Sol Gel Biocote 2. GB1221703A.
3. Wang H, Akid R and **Smith T.** 2007. WO 2010/023483. Sol Gel Antibiotic. EP2328627A & US13/060859.

Research grants:

(Amounts of funding on collaborative grants are the amounts received by Sheffield Hallam University. **Smith TJ** is PI unless stated otherwise).

1. 2004 – 2007 BBSRC *'Laboratory evolution of alkene monooxygenase for improved chiral synthesis*' E20252 £182,933).
2. 2005 – 2007 BBSRC '*Exploring the catalytic versatility of soluble methane monooxygenase*' BB/C00399X/1, £108,241 in collaboration with University of Warwick
3. 2008 - 2011 BBSRC. *Novel monooxygenase biocatalysts from the environment and the laboratory*. BB/F01449X/1 £293,905 in collaboration with University of Warwick
4. 2010-2013 Healthcare Infection Society. (£76,620) Molecular microbial ecology of hospital ward environments: a new tool to understand the role of the environment in hospital acquired infections.
5. 2005-2006 Yorkshire Concept '*Biocoat: A novel coating application which combines bio technology with traditional sol gel coatings as a means of resisting corrosion*', £40,000
6. 2009-2011 Akid and **TJ Smith** EPSRC, 20 07-10, EP/F008643/1, £355,000. '*Development of a functional sol gel coating system via encapsulation of microorganisms*'
7. 2011 -2012 Akid, **TJ Smith**, Wang, EPSRC (Follow-on Fund), EP/I028471/1, £ 130,394. '*Probiotic, biocide-free antifouling coatings based upon sol-gel encapsulated micro-organisms*'
8. 2012 -2014 (MRC DPFS grant, MR/J014656/1), 2013-5, £170,311. **TJ Smith Co-I**, '*Controlled release therapeutic coatings for orthopaedic devices based upon novel sol-gel formulations*' in collaboration with Universities of Manchester and Sheffield.

4. Details of the impact

Biologically functionalised coatings for mitigation of corrosion and biofouling

Our biologically functionalised coatings technology has been recognised as a promising and potentially transformative technology, with diverse applications in medicine and engineering; this has occurred, through the initial publication in Advanced Functional Materials (reference 2), together with national and international presentations made by **Smith TJ** and collaborator Akid. Presentations on the anti-corrosion and anti-fouling technology delivered to audiences with substantial commercial representation have included: an oral presentation at *"Advances in Corrosion Protection by Organic Coatings*" (Cambridge, 2009) (source 6) that was also reported as a paper in ECS transactions, student poster prizes and associated publicity from conferences at the Materials Knowledge Transfer Network (London, 2009) (source 7) and Royal Institute of Structural Engineers (London, 2010) and invited joint oral presentations by **Smith TJ** and Akid at two meetings at The Institute of Materials, Minerals and Mining (*Industrial uses of bacteria* and *Cleaning up antifouling*, both held in London during 2010) (source 8). In addition, the favourable outcome from the Yorkshire Concept funded project in showing the feasibility of the anticorrosion coating in the marine environment, which was publicised via the funder's website (source 9) and reference 2, led to enquiries from at least 10 companies during the period 2009-13. Interested companies in the anti-corrosion and antifouling coatings industry included: International Paint, (a subsidiary of AkzoNobel N.V., the world's largest coatings manufacturer), which worked with us under the EPSRC Follow on Fund grant (2011-12) (grant 7) providing access to its field test facilities (source 1). Given the magnitude of microbial induced corrosion and biofouling problems, especially in the marine engineering sector as well as other industries (including transport infrastructure, power industry, etc.), there is an acute need for non-polluting new coating technology to be developed further. Together with the need to move away from established biocide-based technologies, due to increasingly stringent environmental legislation, this issue has advanced commercial interest in the coating. Identified beneficiaries include the shipping industry, off-shore power generation companies with structures in the marine environment, as well as diverse sectors where the corrosion and fouling of materials in the environment is a threat (source 2).

Coatings and antibiotics in orthopaedic surgery

Presentations relating to the medical applications of antimicrobial coatings have included the International Conference on Antimicrobials Research (oral presentation, Valladolid, Spain, 2010) and the Federation of Infection Societies (poster, Manchester, 2011), both with substantial representation from industry and clinical medicine, and also national meetings for microbiologists, surgeons and device manufacturers with interests in treating orthopaedic infections held in Sheffield in 2011 and 2012. Following these events, a number of medical device manufacturers have held meetings with us, under 'confidentiality agreements', on their interest in the antibiotic sol-gel coating for orthopaedic devices. These manufacturers include De Puy Orthopaedics (2008), an international device manufacturer part of the Johnson and Johnson Group, and Biomet UK, an advanced engineering and manufacturing technology orthopaedic joint replacement company, Bridgend, Wales. Our funding from MRC precludes any exclusive relationship with commercial partners. However, we plan to seek a commercial partner on completion of the current MRC-funded (grant 8).

Collaboration with NHS consultant orthopaedic surgeons at the Sheffield Teaching Hospitals NHS Foundation Trust (STH NHS FT) (source 3) on the use of the antimicrobial coatings resulted in further applications of the coating technology in relation to infection control following joint replacement operations. In addition, our discussions with orthopaedic consultants and the work reported in reference 4 have led to industry- and NHS-funded contract research to provide information about the suitability of new antibiotics for incorporation into orthopaedic cement to inform clinical practice and to help combat increasing antibiotic resistance in the clinical arena. The Sheffield Teaching Hospital Research and Development Fund supported **Smith TJ** in delivering two projects in 2012: on 'Clinical use and underlying elution characteristics of combined gentamicin and daptomicin in orthopaedic cement' (value £2,800); and 'Quantifying elution of antibiotics vancomycin and gentamicin from orthopaedic cement samples; physical strength testing

of samples' (value £3,000). These projects were funded to address specific needs for knowledge to inform clinical practice in orthopaedic surgery. Information about the activity and elution of the antibiotics from cement was required by surgeons and clinical microbiologists to determine which antibiotics could be used in orthopaedic cement in difficult-to-treat cases of revision surgery. Source 3, a nationally recognised senior consultant orthopaedic surgeon, has commented on this work: "*Collaborative research with the BMRC at Sheffield Hallam University evaluating the elution properties of different antibiotics from acrylic bone cements has made a significant impact in the management of difficult periprosthetic joint infections*." Results have been communicated to clinicians in the STH NHS FT and will be submitted to peer reviewed journals shortly. Through collaboration with clinicians, **Smith TJ** secured an introduction to Heraeus (source 4), a manufacturer of orthopeadic bone cement; this led to **Smith TJ** advising the company on measurement of elution rates of antibiotics from bone cement and to our performing laboratory tests to characterise the elution of antibiotics from their products. Work this the pharmaceutical manufacturer Eumedica included supply of the antibiotic temocillin, which together with funding via a 'student into work' grant (£2000) June-August 2012 (from the Society for Applied Microbiology) allowed us to establish that temocillin remained active after curing of bone cement and eluted on a timescale that suggests it would be appropriate for use in surgery. Funding for a larger project was provided by Pfizer PLC via an Anti-Infectives Research Foundation grant (2010-11; £46,750) to **Smith TJ** and Akid in MERI at SHU; this project investigated the elution of antibiotics linezolid and tigecycline to assess their suitability for use in orthopaedic cement (source 5).

Further to this, we have engaged in knowledge transfer with the orthopaedic department of STH NHS FT by training three orthopaedic registrars (junior clinicians in orthopaedic surgery) in methodology and theory relating to measurement of antibiotic elution from orthopaedic cement.

5. Sources to corroborate the impact

Source 1. Principal Research Technologist, International Paint Ltd Gateshead.

Source 2. Principal Scientist in physical sciences group on corrosion and erosion related issues, Defence Science and Technology Laboratory, Wiltshire.

Source 3. Consultant orthopaedic surgeon, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield.

Source 4. Area Manager, Heraeus Medical Division, Newbury.

Source 5. Investigator Initiated Research Manager, Pfizer PLC, Surrey.

Source 6. Advances in Corrosion Protection by Organic Coatings: Christ's College, Cambridge 13th-17th September 2009 - 30 minute presentation and conference paper (Gittens J. E., Wang, H., **Smith TJ,** Akid, R. and Greenfield, D. (2009). Biotic sol-gel coating for the inhibition of corrosion in seawater. *ECS transactions*, **24** (1), 211-229).

Source 7. Materials for a Safer World - Materials KTN Annual Meeting 23/04/2009, Church House Conference Centre, London. Overall winner for poster competition, 'A Novel Biocide-free Approach to the Prevention of Corrosion and Marine Biofouling'.
https://connect.innovateuk.org/documents/2998699/3675992/Focus+Magazine+Issue+12.pdf/9d330c8b-85d5-4446-b8b3-eab5d53661be

Source 8. Marine Corrosion Forum, Technical Presentations at the July 2010 Meeting http://www.marinecorrosionforum.org/tpjul10.htm

Source 9. http://www.yorkshireconcept.org/downloads/Case%20Studies/CP5274%20-%20YC_A0%20Poster_Ref%2006_Mitigation_Sheffield_V3.pdf