Institution: University of Nottingham

Unit of Assessment: 5 - School of Life Sciences

Title of case study:

Attack from All Sides - Comprehensive Political and Practical Approaches to Reduce Healthcare Acquired Infections

1. Summary of the impact

Professor James and colleagues developed a comprehensive, multi-strand strategy for control of healthcare-associated infections caused by life-threatening bacterial superbugs *Clostridium difficile* (*C.diff*) and methicillin-resistant *Staphylococcus aureus* (MRSA). Founded on research to understand the transmission, virulence and antibiotic resistance of these species, their approach resulted in: (i) increased public awareness of healthcare associated infections; (ii) changed behaviours of the public and healthcare professionals to reduce transmission; (iii) improved national healthcare policies to control infections; and (iv) development of new antibiotic methods to tackle the rapidly-evolving resistance. The outcome is a nationwide decline in reported cases of *C.diff* and MRSA infections in patients since 2008, with consequent economic benefits to the NHS, Government and employers.

2. Underpinning research

The underpinning research comprises a number of complementary programmes conducted within the Centre for Healthcare Associated Infections (CHAI), and more widely in the School of Life Sciences, at the University of Nottingham (UoN).

i) New Colicin and Lysostaphin protein antibiotics

The protein antibiotics programme, led by Professor Richard James, has received in excess of £1.14 million funding[9] from BBSRC and Wellcome Trust for research at UoN from 2000 onwards. It has identified the mechanism of bacterial killing by colicins (protein antibiotics) produced by certain bacteria to kill closely related species[1-3]. This includes formation of ion channel pores in the bacterial membrane, DNA degradation with endonucleases or 16S RNA degradation with ribonucleases. This collaborative research programme with Professors Colin Kleanthous (now at Oxford), Geoff Moore (UEA) and Neil Thomas (Chemistry, UoN) was extended to include lysostaphin, a metalloendopeptidase antibiotic that cleaves protein components of the bacterial cell wall of methicillin-resistant *Staphylococcus aureus* (MRSA)[4,5]. The key insights from this collaborative research are 1) the sophisticated mechanisms adopted by colicins to kill Gram negative bacteria such as *E.coli* and lysostaphin to kill Gram positive bacteria such as *S.aureus* and 2) their potential as novel antibiotics.

ii) Quorum Sensing Inhibitor antibiotics

Research led by Professor Paul Williams at UoN from 1992 onwards, and supported latterly by MRC, BBSRC, Wellcome Trust and others with approximately £3.7 million since 2007[10], has generated an understanding of the process of quorum sensing (QS) in several pathogenic bacterial strains that enables bacteria to co-ordinate their growth, behaviour and virulence. Bacteria release QS molecules into their environment that are sensed by other bacteria as a means to communicate[6]. By sensing the concentration of QS molecules, individual bacteria can estimate the density of the population and alter their gene expression accordingly, co-ordinating changes across the whole population that result in switching from an individual 'planktonic' form to a communal 'biofilm' form. Establishing biofilms leads to immune evasion, antibiotic tolerance and virulence factor production. Interfering with the QS signalling process makes bacteria become less virulent and more vulnerable to antibiotics and/or elimination by the host, thus offering a promising target for the development of novel anti-infective agents, with the advantage of reduced selection pressure for development of resistance due to their lack of bacterial killing. Natural product(s) in garlic show QS inhibitory activity *in vitro* and in animal models. They are now being trialled in patients with Cystic Fibrosis (CF) in which secondary infection and biofilm formation by antibiotic-resistant *Pseudomonas aeruginosa* causes respiratory complications[7].

The overall insight from the combined research at Nottingham is that the increasing prevalence of antibiotic-resistant microbial species highlights the dearth of useful antibiotics to treat superbugs

such as *C.diff* and MRSA in UK hospitals and in the community. This has necessitated development of other measures to control the spread of infections, as well as methods to identify species and antibiotic resistance status so that the current antibiotics are deployed in a more targeted fashion to limit the development of further devastating antibiotic resistance that could lead to us moving fatally from a single treatment option to nil treatment.

3. References to the research

Key publications (UoN authors in bold, key author(s) underlined)

1. **Penfold CN**, Garinot-Schneider C, Hemmings AM, Moore GR, Kleanthous C and **James R** (2000). A 76-residue polypeptide of colicin E9 confers receptor specificity and inhibits the growth of vitamin B_{12}-dependent *Escherichia coli* 113/3 cells. Mol Microbiol 38, 639-649. doi: 10.1046/j.1365-2958.2000.02160.x
2. Pommer AJ, Cal S, Keeble AH, Walker D, Evans SJ, Kühlmann UC, Cooper A, Connolly BA, Hemmings AM, Moore GR, **James R** and Kleanthous C (2001). Mechanism and cleavage specificity of the H-N-H endonuclease colicin E9. J Mol Biol 314, 735-749. doi: 10.1006/jmbi.2001.5189
3. Housden NG, Loftus SR, Moore GR, **James R** and Kleanthous C (2005). Cell entry mechanism of enzymatic bacterial colicins: Porin recruitment and the thermodynamics of receptor binding. Proc Natl Acad Sci USA 102, 13849-13854. doi: 10.1073/pnas.0503567102
4. **Warfield R**, **Bardelang P**, **Saunders H**, **Chan WC**, **Penfold CN**, **James R** and **Thomas NR** (2006). Internally quenched peptides for the study of lysostaphin: an antimicrobial protease that kills *Staphylococcus aureus*. Org Biomol Chem 4, 3626-3638. doi: 10.1039/B607999G
5. Bonsor DA, Hecht O, **Vankemmelbeke MN**, Sharma A, Krachler AM, Housden NG, Lilly KJ, **James R**, Moore GR and Kleanthous C (2009). Allosteric β-propeller signalling in TolB and its manipulation by translocating colicins. EMBO J 28, 2846-2857. doi: 10.1038/emboj.2009.224
6. Jones S, **Yu B**, **Bainton NJ**, Birdsall M, **Bycroft BW**, **Chhabra SR**, Cox AJR, Golby P, Reeves PJ, Stephens S, **Winson MK**, Salmond GPC, **Stewart GSAB** and **Williams P** (1993). The *lux* autoinducer regulates the production of exoenzyme virulence determinants in *Erwinia carotovora* and *Pseudomonas aeruginosa*. EMBO J 12, 2477-2482. PMCID: PMC413484
7. **Randle J**, **Metcalfe J**, **Webb H**, **Luckett JCA**, **Nerlich B**, **Vaughan N**, **Segal J**, and **Hardie KR** (2013). Impact of an educational intervention upon the hand hygiene compliance of children. Journal of Hospital Infection. IF 3.221 (in press). doi: 10.1016/j.jhin.2013.07.013
8. **Smyth AR**, Cifelli PM, **Ortori CA**, **Righetti K**, **Lewis S**, Erskine P, **Holland ED**, Givskov M, **Williams P**, **Cámara M**, **Barrett DA** and **Knox A** (2010). Garlic as an Inhibitor of *Pseudomonas aeruginosa* Quorum Sensing in Cystic Fibrosis—A Pilot Randomized Controlled Trial. Pediatric Pulmonology 45:356–362. doi: 10.1002/ppul.21193

Research Grants

9. **Richard James**: BBSRC: (2000 – 2003), **£203,236;** (2006 – 2009) **£361,846;** Wellcome Trust: (2003 – 2007), **£293,414** (Total value of the Programme grant awarded to RJ, CK and GM, which included this grant, was **£1.07 million**); (2008 – 2011), **£282,742**
10. **Paul Williams**: MRC: (2008) **£929,603**; (2010) **£823,985**; (2010) **£129,904**; BBSRC: (2008) **£638,844**; (2012) **£472,524**; Wellcome Trust: (2009) £**287,073**; others (2006-2009) **£339,408**.

4. Details of the impact

The overarching outcome of the research conducted by Richard James and colleagues is that the development of new antibiotics targeting novel aspects of bacterial biology is difficult, expensive and, even if successful, can only ever be part of an integrated strategy for the prevention and control of HAIs.

Impact 1: Raising Public Awareness and Changing Government Policy

The importance of using the media and other practical means to better inform the public of the scale of the problem posed by HAIs emerged as a strategy to persuade the public and healthcare professions to modify their practices to reduce the spread of infections. This was backed up by lobbying for changes to UK Government policy, to help mitigate the need for new antibiotics. Arguably, greater health and economic benefit has been achieved through changing public awareness and healthcare policies than has been achieved by development of new antibiotics.

Despite the dramatic increase in HAIs caused by antibiotic resistant superbugs such as *C.difficile* and MRSA reaching 8.2% of all hospital admissions in 2006[A], the difficulty of trying to change UK Government policy to control HAIs was revealed in a statement from the Department of Health in 2007, who considered "*talk of a post-antibiotic apocalypse as sensationalist and scaremongering"*. Nevertheless, insights from CHAI research programmes led to development of a strategy of practical and policy measures to prevent and control HAIs, which were proposed by Professor James in the invited article "Battling the bug" for the House of Commons magazine, 'House', in December 2007. The measures proposed were:

- Screening of all hospital admissions for MRSA
- Strong leadership from Trust Chief Executives on the importance of reducing hospital infections
- Provide information to patients about hospital Trust infection and patient isolation policies
- Significant investment in NHS Microbiology laboratories
- Universal MRSA screening to raise concern about the large numbers of patients carrying MRSA into hospital
- Monitor infection rates in individual wards and feedback this information to all staff
- Introduce effective measures to increase staff hand hygiene compliance
- Improve staff training and involvement in improving infection control
- Improve information for patients and visitors concerning infections

A key aim of CHAI was to act as a source of information about infections to journalists and the public. Professor James provided the spinal interview that ran throughout the Panorama investigation (broadcast in April 2008)[B] of the *C.difficile* outbreak at Maidstone & Tunbridge Wells NHS Trust in 2005 to 2006 that resulted in the deaths of approximately 60 patients[C]. He also assisted the production team in their analysis of NHS Trust responses to a number of Freedom of Information Act questions that featured in the broadcast[D]. The average 'reach' of the programme throughout 2007 was around 3.6 million, indicating the size of the viewer audience. Comments from viewers following the broadcast, such as those below transcribed from the BBC News website[E], show the impact that the programme had on public awareness.

"*I was most impressed with this programme. It's about time that we were all made more aware of this awful contagion*". David Knowles, Sutton Coldfield

"*Thanks Panorama for highlighting this issue. Most hospitals have lost their basic nursing care and cleanliness*". Allan Hunt, Blackburn

This was a major factor to bring about changes in government policy to reduce the threat to NHS patients posed by *C.difficile* and MRSA.

The policy of MRSA screening of all patients on admission to hospitals in England began in March 2009 and seven other elements of the strategy were also introduced between 2008 and 2011. The annual report from the Chief Medical Officer (England) for 2011, volume 2 (published in 2013)[F] stated that "*the apocalyptic scenario of widespread antimicrobial resistance … is a threat arguably as important as climate change for the world*", vindicating the policy measures introduced by CHAI.

As a consequence of policy changes, there has been a significant decline in all HAIs from 8.2% in 2006 to 6.4% in 2011[A], with reported cases of *C. difficile* and MRSA infections declining even further. This has brought widespread healthcare benefits to hospital patients, as well as considerable economic benefits to the NHS through reduced in-patients care costs, to Government through increased worker tax revenues and reduced sickness benefit payments, and to employers through reduction of sick-leave. Professor James was awarded the Society for Applied Microbiology Communications award in 2008[G] for his media contributions to raise the profile of the problem of HAIs and antibiotic resistance to the wider public.

Impact 2: Novel Practical Approaches to Promote Public Engagement

Activities to continue to improve public behaviours to reduce the spread of HAIs are ongoing within CHAI. Improving hand hygiene in hospitals and the community has been targeted as the single most effective approach. A member of CHAI, Dr Hardie, has developed a prototype educational toy, the 'GloYo', as a practical aid to teach children good hand hygiene in schools, and for visitors and patients in hospital paediatric departments[7]. Taking a lead from Professor James, media campaigns on television, radio and in newsprint have promoted GloYo as a practical demonstration

to raise public awareness. To date, it has been widely approved by over 1000 children, parents, teachers, hospital visitors and patients, over 75% of whom have improved their hand hygiene after playing with GloYo[H]. A licence agreement for commercial development of the GloYo was agreed between the University and Ravencourt Ltd in 2012, with a view to commercial launch in 2013. Adaptation of GloYo for use with the elderly is also being investigated.

Impact 3: Healthcare Benefits of Novel Antibiotic Approaches

Professor Williams has continued the theme of media involvement to raise public awareness of the need for novel antibiotics, by making TV, radio and webinar broadcasts on the theme of Quorum Sensing[I], most recently with a 'Bang Goes the Theory' episode on BBC1 in 2011 and a 'Frontiers' episode on Radio 4 in 2013. Manipulation of bacterial Quorum Sensing as a means to allow the host immune system to overcome bacterial infections has been tested in an exploratory clinical trial conducted by Professor Williams and colleagues at the University of Nottingham, in collaboration with colleagues in Respiratory and Paediatric Medicine at Nottingham University Hospitals Trust and at the University of Copenhagen[8]. Juveniles and adults with Cystic Fibrosis were treated with garlic capsules containing inhibitors of Quorum Sensing, or placebo. Blood, respiratory and weight parameters were measured to determine if garlic improved patients with lung infections by *Pseudomonas aeruginosa*. The small trial encouragingly indicated beneficial effects on respiratory FEV1, weight gain and clinical scores in the garlic-treated group, suggesting that a larger clinical trial would be worthwhile to evaluate the potential benefit of Quorum Sensing inhibitors in Cystic Fibrosis.

Summary

Thus, a concerted effort by University of Nottingham researchers to control antibiotic resistant superbugs has: 1) introduced new government policies and practical measures to reduce the risk of superbug infection; 2) increased public and professional awareness of the spread of superbug infections; and 3) developed novel antibiotic approaches to treat superbugs; all resulting in a significant decline in healthcare associated infections since 2008.

5. Sources to corroborate the impact

A. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317134304594
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136146912
B. http://news.bbc.co.uk/1/hi/programmes/panorama/7367309.stm
http://news.bbc.co.uk/player/nol/newsid_7370000/newsid_7371100/7371116.stm?bw=bb&mp=wm&news=1&ms3=6&ms_javascript=true&bbcws=2
C. http://news.bbc.co.uk/1/shared/bsp/hi/pdfs/11_10_07maidstone_and_tunbridge_wells_investigation_report_oct_2007.pdf
D. Documents comprising the Panorama questionnaire and NHS Trust responses.
E. Viewer comments on the Panorama programme are available on the BBC News webpage: http://news.bbc.co.uk/1/hi/programmes/panorama/7371379.stm
F. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf
G. Document containing corroborative evidence relating to Professor James and publicity campaigns.
H. Document containing corroborative evidence relating to Dr Hardie and Glo-Yo.
I. Document containing corroborative evidence relating to Professor Williams and Quorum Sensing Inhibitors.

Corroborative documents and copies of webpages are held on file and are available on request.