Institution: The University of Huddersfield

Unit of Assessment: 8 Chemistry

Title of case study: The Impact of Physical Organic Chemistry Research at Huddersfield

1. Summary of the impact

University of Huddersfield research in physical organic chemistry has delivered economic, industrial and societal benefits. It has led to process improvements in chemical manufacturing, most notably in the optimisation of the synthesis of antisense oligonucleotides and in the use of liquid ammonia as a solvent. It has also led to the development of new inhibitors of bacterial β-lactamases for use as antibacterials. The research team's expertise has been reflected in the success of IPOS (Innovative Physical Organic Solutions), a unit established in 2006 to carry out research in process and other areas of chemistry for the chemical industry. IPOS expanded significantly from 2009 to 2013 and has now collaborated with more than 150 companies, many of them based in Yorkshire/Humberside where regeneration is critically dependent on the success of new, non-traditional, high-technology firms and industries. Through these collaborative projects, IPOS has contributed to the growth and prosperity of both regional and national industry.

2. Underpinning research

The University of Huddersfield's studies in the area of physical organic chemistry have been driven by the ever-growing demand for academic research to meet the needs of industry and, in turn, the people industry serves. Professors M. Page (Dean of School 1989-2004; Deputy VC 2004-2010; Managing Director, IPOS, 2006-present), J. Atherton (2007-present) and A. Laws (1992-present; submitted in UoA 5) have each contributed research outputs describing fundamental research undertaken in collaboration with, and sponsored by, industry. Reflecting the rapid and sustained expansion of activity in this area, Innovative Physical Organic Solutions (IPOS), a research unit offering analytical and chemical process development services to the chemical industry, was established in the Department of Chemistry in 2006. IPOS entered a period of rapid expansion in 2009 with the award of European Regional Development Funding (ERDF) of £3.6M [G1]. Some of the underpinning research described here was carried out in IPOS. The IPOS team has both furthered existing strands of research (e.g. in liquid ammonia) and also initiated a number of new themes (e.g. in catalyst development).

i. Synthetic oligonucleotides for therapy (2001-present)

Small interfering RNA (siRNA) and antisense oligonucleotides have been demonstrated as powerful tools for chemotherapy. There is currently no efficient synthesis of oligonucleotides on an industrial scale. Huddersfield's studies of the mechanisms of the chemical synthesis of oligonucleotides have provided an understanding of the synthetic parameters that can be used to optimise large-scale synthesis. The first part of this work was funded directly by Avecia Biotechnology through PhD studentships for Powles (2001-2004) and Russell (2004-2007) [G2]. Powles' work explored the mechanism of H-phosphonate coupling of oligonucleotides [3.1], while Russell's examined several steps involved in the oligonucleotide synthesis cycle employing phosphoramidite chemistry [3.2]. More recently this work has been taken up by GlaxoSmithKline who have continued to support this research through a CASE award for Scotson [G3].

ii. Providing solutions to antimicrobial resistance (1993-present)

The rise of bacterial resistance to antibiotics has been highlighted in recent years. Huddersfield's work on β-lactams was initiated by Page, who went on to continue research in this area with Laws. The team has published more than 50 papers since 1993 that contribute to understanding how bacteria are able to evade the action of β-lactam antibiotics. The work has focused on demonstrating that β-lactams are not particularly "strained" four-membered rings, a notion facilitating the design of novel alternative antibacterials [3.3]. Through measurement of the intrinsic reactivity of a number of small ring systems including β-lactams, β-sultams and azaphosphetidienes, the work at Huddersfield has facilitated the design of novel alternative enzyme inhibitors of bacterial enzymes [3.4]. Investigations into serine and metallo-β-lactamase enzymes, which are increasingly important causes of bacterial resistance to β-lactam antibiotics,

has raised the possibility of developing novel methods of inhibition [3.5]. The work has been funded through collaboration with pharmaceutical companies (including AstraZeneca and GSK) and engagement in European Networks [G4].

iii. Chemical reactions in liquid ammonia (2007-present)

The use of liquid ammonia as a reaction solvent is advantageous because product isolation and solvent recycling are greatly facilitated, meaning ammonia can be considered an environmentally "green" solvent. Fundamental research in Huddersfield on the use of ammonia as a reaction solvent has revealed the scope of reactions that can be transferred to a liquid ammonia medium, with both catalysed [3.6] and non-catalysed [3.7] reactions showing potential benefits. Supported by funding from Syngenta [G5], current research portfolios include continuous flow processes and biotransformations in liquid ammonia.

3. References to the research (key references starred/bold)

[3.1] M. A. Russell, A. P. Laws, J. H. Atherton and M. I. Page; *The kinetics and mechanism of the acid catalysed detritylation of nucleotides in non-aqueous solution*, (2009), *Org. Biomol. Chem*., **7**, 52–57. DOI: 10.1039/b816235b

[3.2]* N. Powles, J. H. Atherton, and M.I. Page; *Reactive intermediates in the H-phosphonate synthesis of oligonucleotides,* (2012), *Org. Biomol. Chem.,* **10**, 5940-5947. DOI: 10.1039/c2ob07130d

[3.3]* A. P. Laws, and M. I. Page; *The mechanism of catalysis and the inhibition of β-lactamases,* (1998), *Chem. Commum*., **16**, 1609-1617. DOI: 10.1039/a803578d

[3.4] A. P. Laws, and M. I. Page; *The chemical reactivity of β-lactams, β-sultams and β-phospholactams*, (2000), *Tetrahedron* **56**(31), 5631-5638. DOI: 10.1016/S0040-4020(00)00412-9

[3.5] A. Badarau, A. Llinás, A. P. Laws, C. Damblon and M. I. Page; *Inhibitors of metallo-β-lactamase generated from β-lactam antibiotics*, (2005), *Biochemistry*, **45**, 8578-8589. DOI: 10.1155/2008/576297

[3.6]* P. Ji, J. H. Atherton and M. I. Page; *The kinetics and mechanisms of organic reactions in liquid ammonia,* (2010), *Faraday Discuss.*, **145**, 15-25. DOI: 10.1039/b912261n

[3.7] J. H. Atherton, M. I. Page and H. Sun; *Reaction kinetics in liquid ammonia up to 120^{o}C: techniques and some solvolysis and substitution reactions*, (2013), *J. Phys.Org. Chem*., **26,** 1038-1043. DOI: 10.1002/poc.3150

Indicators of the quality of the research: The vast majority of the studies performed by the physical organic chemistry team at Huddersfield, including the bulk of the projects described in the references above, have been in collaboration with international pharmaceutical companies (AstraZeneca, GlaxoSmithKline, Avecia, Syngenta, James Robinson, British Biotech, ICI Pharm., Fisons, PanTherix, Proteus and NPilPharma). Page's contribution to the development of the subject was recognised through the award of the RSC Organic Reaction Mechanisms Prize in 2003.

Grants

[G1] European Regional Development Fund, *Product and process development*, project 903993, £2.3M plus £1.3M matched funding, 2008-2013, PI: Page.

[G2] Avecia direct support for PhD studentships: Powles (01-04) and Russell (04-07), £105,000, 2001-2007, PIs: Page and Laws.

[G3] Scotson BBSRC Case Award with GSK, £114,000, 2012-2016, PI: Laws.

[G4] European Network Funding, *MEBEL – metallo-β-lactamases*, contract no. HPRN-CT-2002-00264, 820,000 Euros, PI: Page.

[G5] Syngenta direct funding, *Liquid ammonia research*, >£125k, 2008-, PIs: Powles and Stirling.

4. Details of the impact

University of Huddersfield studies in the field of physical organic chemistry have led to widespread economic, industrial and societal benefits, in large part through the continued success of IPOS, the formation of which was a direct result of research carried out since the early 1990s. Much of the impact arising from the research described above has been generated directly through the work of IPOS with the chemical industry in the period since 2008.

Although the Innovative Physical Organic Solutions unit (IPOS) was formed in 2006, major expansion has occurred since 2009 with the award of £3.6M of European Regional Development Fund support [G1]. IPOS has moved to new purpose-built laboratories ("Page Laboratory" – 200 m^2); Agilent has added investment of ca. £3M, and the Page Laboratory is now an "Agilent Centre of Excellence". IPOS now consists of five academics (Page and Atherton, with Charsley, Sinnott and Maskill [last three Emeritus/Visiting]). Co-workers include Dr N Powles (Senior Research Fellow, 2006-present), Dr M Stirling (Senior Research Fellow, 2006-present), Dr M Chadha (Quality Manager, 2010-present), and four Research Fellows, six PhD students and four technicians. Atherton, Powles and Stirling have more than 60 years' industry experience between them.

IPOS has become self-financing, with income of £0.6M p.a. Income from consultancy and training for the chemical and related industries in particular has grown significantly, from around £150,000 and £8,000 respectively in 2008/2009 to around £385,000 and £34,000 in 2012/2013. IPOS now provides full-time employment for 11 members of research staff [5.1].

IPOS has so far carried out research projects for more than 150 companies, of which over 70 have been SMEs. The large majority of projects and enquiries are from within the Yorkshire/Humberside region, where regeneration is critically dependent on new, non-traditional, high-technology companies, meaning IPOS's expertise has been vital to economic growth in the area. Around 30 enquiries are now received each month from throughout the UK. Of the many successful projects, one example is their 15-month collaboration on gas-liquid kinetics with ACAL Energy, of Runcorn, which has led to a £15M venture capital investment [SL1].

The Society of Chemical Industry has officially recognised the scale and significance of Page and Atherton's contributions to the industry, most recently through the activities of IPOS. Atherton received an SCI Chemistry for Industry Award in 2013 in recognition of his "contribution to process chemistry", and Page received the same honour in 2011 for work "which provides a potential major benefit to society" [5.2].

Specific areas of work undertaken by the research team before and after the establishment of IPOS have benefited a wide range of stakeholders and end-users, the most notable being the following.

i. Synthetic oligonucleotides for therapy

Huddersfield's work in the area of synthetic oligonucleotides, particularly in terms of improving the economics of the large-scale synthesis of small interfering RNA (siRNA) oligonucleotides, has enhanced industry practice. The findings were first applied by Avecia, which sponsored early research in this field, and later by Pfizer [SL2]. Huddersfield's findings [3.1-3.2] have improved efficiency and delivered cost benefits by highlighting key considerations in the large-scale manufacture of oligonucleotide-based therapeutics particularly with regard to solvent selection and reactant stoichiometries; the large scale synthesis of oligonucleotides traditionally involved considerable volumes of solvents and excessive amounts of expensive and fragile phosphoramidite reagents.

Since 2012 GlaxoSmithKline has supported and drawn on Huddersfield's continuing research in this area as part of the company's efforts to develop a substantial portfolio of oligonucleotide-based therapeutics, many of which are in late-stage clinical trials. GSK has been guided by Huddersfield's

studies in devising the synthesis technologies required for stage 3 trials. GSK's Oligonucleotide Synthesis Group has confirmed: "Your research provides the fundamental chemistry understanding that we need in order to develop robust, scalable and sustainable oligonucleotide manufacturing processes." [SL3] This further underlines the research's contribution to the health of society, as therapeutically important mRNAs are used for treating diseases arising from genetic disorders.

ii. Providing solutions to antimicrobial resistance

Huddersfield's research in the area of antimicrobial resistance (AMR) has also led to improvements in healthcare by helping companies to design new products. The finding that the β-lactam ring is not inherently reactive [3.4] has contributed to a shift towards novel designs of alternative antibacterials and Huddersfield's outputs describing the mechanism by which β-lactamases catalyse the hydrolysis of β-lactams [3.5-3.6] has influenced the development of new therapeutics such as those developed by Basilea Pharmaceutics, of Basel, Switzerland [SL4]. This work has anticipated key elements of the Department for Health's 'UK Five-Year Antimicrobial Resistance Strategy', introduced in 2013, one of the principal strategic aims of which is to improve knowledge and understanding of AMR. Such advances also deliver economic benefits, given that AMR is currently estimated by the European Centre for Disease Prevention and Control to cost €1.5bn in healthcare expenses and lost productivity each year.

iii. Chemical reactions in liquid ammonia

Huddersfield's work on solvolysis reactions, most notably the finding that liquid ammonia can be considered a "green" solvent, has influenced the industrial manufacture of chemicals. The technology has been adopted by Syngenta, which has used it to develop "new route options" and has begun transferring these to the company's laboratories [SL5]. Research in this area has also formed the basis of an IPOS patent application for the conversion of fatty acids to amides [5.3].

5. Sources to corroborate the impact

[5.1] IPOS website http://www.hud.ac.uk/research/researchcentres/ipos/ and list of ERDF outputs, confirm the impact that the physical organic chemistry team has had on the employment of staff at Huddersfield and the economic impact on SMEs in the Yorkshire and Humber Region.

[5.2] http://www.soci.org/News/Awards/Other/Awards-Yorks-RD-Page.aspx

[5.3] H. Sun, J. Atherton and N. Powles, (2013), *Method and apparatus for the conversion of glycerides into amides,* British patent application 1319751.2.

Supporting Letters/Factual Statements:

[SL1] Chief Technology Officer, ACAL Energy Ltd. In receipt of Factual Statement confirming IPOS's contribution to gas/liquid kinetics research, and their crucial part played in securing venture capital.

[SL2] Director, Bio-Manufacturing Sciences Group, Pfizer. In receipt of Factual Statement confirming that Huddersfield's Oligonucleotide work has directed manufacturing practice at Pfizer.

[SL3] GlaxoSmthKline, Oligonucleotide Synthesis Group, API Chemistry and Analysis, UK. In receipt of Factual Statement confirming that Huddersfield's oligonucleotide work has directed process development at GSK.

[SL4] Head of Biology, Basilea Pharmaceuticals. In receipt of Factual Statement confirming that Huddersfield's β-lactam and β-lactamases outputs have been used in directing their R and D.

[SL5] Senior Research Scientist, Syngenta Limited, Jealott's Hill. In receipt of Factual Statement confirming their use of the liquid ammonia technology developed at Huddersfield.