Institution: University of Warwick

Unit of Assessment: B8 Chemistry

Title of case study: Warwick Effect Polymers Ltd

1. Summary of the impact

Research at Warwick by Professor David Haddleton's team led to the discovery of a new family of catalysts for living radical polymerisation. A spin-out company, Warwick Effect Polymers Ltd (WEP), was established to develop this research and received a total of £3.77M investment. Supplemented by income from contracts, and operating in purpose-built laboratories on the Warwick Science Park, WEP employed 10–15 people and spent £3.0M over the REF2014 period developing a substantial patent portfolio. WEP's commercial success and intellectual property in polymer therapeutics and nanomedicine led to its acquisition by PolyTherics Ltd in 2012.

2. Underpinning research

A family of pyridine imine and diazabutadiene copper catalysts for living radical polymerization were discovered by Professor David Haddleton and his research team at Warwick [1]. A key design feature of these catalysts is that they stabilise Cu(I) relative to Cu(II) allowing control over the equilibrium position of the key reaction step – radical chain-end formation. The concentration of radicals is thus controlled, preventing termination by radical-radical reaction events, and the result is a so-called living polymerization. In particular the method was unusually successful with methacrylate (as opposed to acrylate) monomers. Funded by the EPSRC [7-9] and others, over 100 papers have been published by Haddleton and group in this area.

This Warwick living radical polymerization catalysis is generally unaffected by the presence of functional groups either in the monomer or the initiator from which the polymer grows. The use of new classes of functionalized initiator was thereby feasible. A range of hydroxy functionalized polymers from standard condensation and ring opening polymerizations were shown to provide useful macro-initiators providing a facile route to AB and ABA block copolymers. These gave new combinations of functional properties in the polymers, such as adhesion, pH sensitivity, thermal response and hydrophobicity/hydrophilicity [2].

Pegylation – the covalent attachment of poly(ethylene glycol) groups to active pharmaceutical ingredients – was a topical strategy in the early 2000s for improvement of drug delivery and pharmacokinetics. Warwick's catalyst technology could provide many new hydrophilic and functional polymer conjugates with highly tuneable properties via living radical polymerization processes. It was further realized that one of the deficiencies of conventional single-site pegylation is that, as the molecular weight of the PEG is increased, clearance from the body becomes a problem. Ranges of new polymers with comb-like architectures and cleavable ester groups were thus developed for this application [3,4,5]. Among the advantages of these new systems are that viscosity is essentially independent of molecular weight (allowing clearance from the body), and that there is a low tendency to crystallise, thus reducing damage to liver, spleen and brain [3,4].

The work was expanded by Haddleton and group to the preparation of synthetic glycopolymers from functional initiators for bioconjugation. The approach used was to add simple sugars to a preformed polymer backbone facilitating the synthesis of the glycopolymers and exploiting the glyco-cluster effect; enhanced binding and lectin (carbohydrate-binding protein) recognition as a result of proximity of a number of sugar units. The majority of this research was conducted with salmon calcitonin – a clinical drug for osteoporosis. This work proved to be a landmark with many research groups and companies now looking at synthetic glycopolymers for a range of glycocode applications; Haddleton's first publication on the subject in 2006 has received >340 citations to date [6].

3. References to the research

Articles

[1] *Atom transfer Radical Polymerisation of MMA by Alkyl Bromide and 2-Pyridinecarbaldehyde Copper(I) Complexes*, D. M. Haddleton, C. B. Jasieczek, M. J. Hannon, A. J. Shooter, *Macromolecules* **1997**, *30*, 2190, DOI: 10.1021/ma961074r.

[2] *Monohydroxyl terminally functionalised polymethyl methacrylate from atom transfer radical polymerisation (ATRP)*, D. M. Haddleton, C. Waterson, P. J. Derrick, C. B. Jasieczek, A. J. Shooter, *Chem. Comm.* **1997**, 683, DOI: 10.1039/A700677B.

[3] *A new approach to bioconjugates for proteins and peptides ("pegylation") utilising living radical polymerization*, F. Lecolley, L. Tao, G. Mantovani, I. Durkin, S. Lautru, D. M. Haddleton, *Chem. Comm.* **2004**, *18*, 2026–2027, DOI: 10.1039/B407712A.

[4] *Alpha-aldehyde Terminally Functional Methacrylic Polymers from Living Radical Polymerization: Application in Protein Conjugation "Pegylation"*, L. Tao, G. Mantovani, F. Lecolley, D. M. Haddleton, *J. Am. Chem. Soc.* **2004**, *126*, 13220–13221, DOI: 10.1021/ja0456454.

[5] *Design and Synthesis of N-Maleimido-Functionalized Hydrophilic Polymers via Copper-Mediated Living Radical Polymerization: A Suitable Alternative to PEGylation Chemistry*. G. Mantovani, F. Lecolley, L. Tao, D. M. Haddleton, J. Clerx, J. J. L. M. Cornelissen, K. Velonia, *J. Am. Chem. Soc.* **2005**, *127*, 2966–2973, DOI: 10.1021/ja0430999.

[6] *Synthesis of Neoglycopolymers by a Combination of "Click Chemistry" and Living Radical Polymerization*. V. Ladmiral, G. Mantovani, G. J. Clarkson, S. Cauet, J. L. Irwin, D. M. Haddleton, *J. Am. Chem. Soc.* **2006**, *128*, 4823–4830, DOI: 10.1021/ja058364k.

Research Council grants

[7] *Living Free Radical Polymerisation*, EPSRC (GR/K04606), Oct 1994 – Sep 1996, £80,612.

[8] *Synthesis and Role in Atom Transfer Chemistry*, EPSRC (GR/K90364), Oct 1996 – Sep 1998, £87,052.

[9] *Atom transfer living free radical polymerisation,* EPSRC (GR/L10314), Oct 1996 – Sep 1998, £88,433.

4. Details of the impact

Polar polymers such as polyesters, polyamides, polycarbonates, acrylates and methacrylates are traditionally used in commodity applications such as in textiles and engineering. The Warwick research was recognized by Haddleton, Warwick Ventures Ltd and investors as having potential to create new high-technology applications in the area of “effect polymers” i.e. polymers as fine rather than bulk chemicals. Therefore the spin-out company Warwick Effect Polymers Limited (WEP) was formed in 2001 with the initial purpose of exploiting the new Warwick living radical polymerization technology with end users. With a DTI SMART award, £5k from 1st prize at a Cambridge Enterprise Launch Pad event and investment from a US business angel [10] the company started trading in 2002. In 2013 WEP is still based in its own laboratories on the University of Warwick Science Park employing 10–15 people on average [11]. The company has also funded over 20 students and research fellows.

The relevant Warwick/Haddleton IP was assigned to WEP, and a pipeline agreement (2002–12) facilitated collaborative work with several companies including Unilever, Courtaulds, ICI, BP, Geltex (Genzyme), Biocompatibles, Syngenta, Elf AtoChem in exploiting the underpinning research. With Unilever, for example, work on ABA triblocks led to patents relating to personal care

products which were subject to large scale customer trials in the US and UK (2002–2006) [12] and this collaboration is ongoing (see below). A director of a VC fund management company and private investor in WEP (2003-2012) notes that the company "had a strong track record of undertaking paid research for large corporations" [13]. During a collaborative project the company caught the attention of a Vice President of a multinational biotechnology company because of its "potential for impact in far-ranging areas" and "belief in the broad potential" of WEP technology [10] and this individual became a director and private investor in WEP. In 2005 the company won the Lord Stafford award for best University spin out in the West Midlands and Haddleton was awarded the RSC Chemistry World Entrepreneur of the year. In 2013 the founder of another VC Fund Management company described WEP as "an exemplar of the high quality research innovations with disruptive global potential." [11]

During the REF2014 period, the focus of the company was the development of the Warwick technology in polymers for therapeutics and nanomedicine [13]; markets that could stand the increased costs of production of precision polymers from living radical polymerization. The pegylation and glycopolymer work described in section 2 became a strategic activity with the aim of improving aspects of protein, peptide and subsequently siRNA (small interfering RNA) therapeutics – classes of biological drug. Building on the collaboratively generated intellectual property, specific protein and peptide therapeutics identified by biotech partners were optimised with the new conjugation and polymerisation technology. WEP's comb polymers (PolyPEG^{TM}) have the advantage of "lower viscosity compared to conventional PEG polymer [that] is utilised to extend the *in vivo* half-life of protein therapeutics by reducing the clearance rate." This advantage "has been demonstrated [in projects throughout the REF2014 period] by WEP's partners within the pharmaceutical industry" [14] and was one of the key drivers for WEP's eventual acquisition (see below).

To support its R&D programme, WEP received £3.77M since 2001 in venture capital funding (angel investors plus national, international and regional venture capital trusts) [15,16] and the company now holds three patent families for targeting polymers; "a very important segment of intellectual property" [10]. As a measure of activity, total expenditure over the REF2014 period was £3.0M spread evenly over that period [15]. Since 2008, WEP has supplemented its capital investment through a portfolio of more than 10 multi-contract projects with major companies. For example, with Unilever, a new technology in protein conjugation of polymers has been developed to protect human hair against damaging treatments [17]. New synthetic glycopolymer technologies, transferred to WEP under the pipeline agreement and developed as GlycoPol^{TM} and ZenoPol^{TM} (trademarked 2009 and 2011 respectively) are being tested by a global pharmaceuticals leader for gene delivery [14, 18].

In 2012 WEP was acquired by PolyTherics Ltd in a substantial (undisclosed) share-for-share deal and is now a wholly owned subsidiary still based at the Warwick Science Park. Polytherics explains that their interest was driven by WEPs patent portfolio and the existence of "a number of programmes with one of the top 5 pharmaceutical companies" [14,19]. The deal "brought together complementary technologies…to extend the pharmacokinetics of biological therapeutics through polymer conjugation" [14]. An industry expert notes, "the continuing evolution of PolyPEG by large pharma companies, and the increased interest in GlycoPol…by some of the same players, continues to validate the strategy" [10]. Products utilising PolyTherics and WEP technologies are "expected to enter clinical development in 2014 and the company will receive milestone payments and royalties from the successful development and commercialisation of these products" [14]. The acquisition has thereby allowed WEP to attain the security required for its long term partner projects in drug delivery and development. The specialist polymer team and laboratory continues with some PolyTherics activities relocating from London to WEP's premises. For the Polytherics group, WEP provides the effect polymers technology and expertise that it was established to create.

In July 2013, following PolyTherics acquisition of WEP and Antitope Ltd, £13.5M further investment was raised from some of WEP's funders (Mercia Fund Management and Advantage Enterprise & Innovation Fund) and Invesco Perpetual. The group now employs more than 80 staff. Revenues of

the combined Polytherics businesses exceeded £8.5M last financial year with WEP "making an increasing contribution to revenues as more significant licence payments are received and as the technology becomes established."[14]

The underpinning research at Warwick by Haddleton and his research team thus led to the establishment of a spin-out company that during the REF2014 period has created a large number of jobs, attracted substantial investment, implemented strategic industry-collaborative projects and developed valuable intellectual property. Acquisition of WEP and its IP portfolio by Polytherics Ltd was accompanied by substantial new investment and forms a key part of the group's nanomedicine strategy.

5. Sources to corroborate the impact

[10] Vice President of a multinational biotech company; statement dated June 27th 2013.

[11] Mercia Fund Management; statement dated 20 June 2013.

[12] Unilever; statement dated 24 June 2013.

[13] Longwall Ventures; statement dated 21 June 2013.

[14] Polytherics Ltd; statement dated 02 Sept 2013.

[15] FAME report, Warwick Effect Polymers Limited, registered number 04182449. Retrieved 24 Sept 2013 (available on request).

[16] Press release: 31 March 2009 (Catapult Venture Managers Limited, Mercia Technology Seed Fund, WEP), *Warwick Effect Polymers raises £2 million in investment* (contains summary of historical investments), web link.

[17] Patent WO2011/134785, *Hair care composition* (Unilever Plc, priority date Apr 28, 2010) https://www.google.com/patents/WO2011134785A3.

[18] Patent WO2011007133, *Polymer modified macromolecules* (WEP Ltd, priority date Jul 13, 2009) https://www.google.com/patents/WO2011007133A3.

[19] Press release: 15 Oct 2012 (Polytherics), *PolyTherics expands collaboration with a top five pharmaceutical company to enhance the clinical properties of biopharmaceuticals using PolyPEG*, web link.