Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study:
Developing unique conjugation (PEGylation) technology and commercial spinout through PolyTherics Ltd.

1. Summary of the impact (indicative maximum 100 words)

A novel conjugation technology has been developed to enable site-specific attachment of polyethylene glycol (PEG) to proteins to extend the in vivo half-life of biopharmaceuticals. The technology has been commercialised by an Imperial College spin-out company, PolyTherics Limited. In 2013, the merger of PolyTherics with Antitope Limited, enhanced the company's biopharmaceutical technology development offering. PolyTherics issued new shares to the value of £13.5 million to investors and Antitope shareholders in connection with the merger.

The company has enabled the development of novel forms of interferon β (for the treatment of multiple sclerosis) and blood factors VIIA, VIII and IX (for the treatment of haemophilia A and B) utilising original Imperial TheraPEG™ technology. This is achieved through licences granted by PolyTherics to Nuron Biotech and Celtic Pharma Holdings who are in early pre-clinical development. PolyTherics has further developed the conjugation technology (ThioBridge™) for its application in the creation of stable, homogeneous antibody-drug conjugates for the targeted cancer therapy.

Polytherics has impacted the UK economy generating intellectual capital, capital investment, new employment and novel compounds to treat disease.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Sunil Shaunak, Professor of Infectious Diseases (1991-present)

PEGylation is a clinically proven strategy for increasing the therapeutic efficacy of protein-based medicines. PEGylation is the process of covalent attachment of polyethylene glycol (PEG) polymer chains to another molecule, normally a drug or therapeutic protein. The application of this technology is best illustrated in the development of PEGylated interferon-α which is used to treat and cure Hepatitis C infection. However, before the Imperial work, earlier technologies for PEGylation produced very heterogeneous products based on conjugation to ε-amino groups of lysines, with multiple isomers produced with varying activity and pharmacokinetic profiles and introducing significant complexity into the production and analytical processes.

In 2004-2005, Professor Shaunak, in collaboration with Professor Brocchini (London School of Pharmacy), developed a novel approach to site-specific PEGylation based on equilibrium transfer alkylation crosslinking through the reduction of protein di-sulphide bonds (1). Specifically, this approach exploits thiol selective chemistry via a multi-step reaction pathway that leads from controlled reduction of accessible disulphide bonds of proteins, through two-step Michael additions using α-β-unsaturated-β'-mono-sulfone functionalized PEG reagents, to introduce a three-carbon bridge into the former disulphide bond with PEG covalently attached to the three carbon bridge.

This technology ensures that that only one PEG molecule is conjugated at each disulphide bond. The research was published in academic journals (2-5) and has led to the PEGylation reagents (TheraPEG™). TheraPEG™ technology was developed and commercialised through collaborations between Imperial and PolyTherics Ltd (2003-2005). It enabled the therapeutic efficacy of protein-based medicines to be significantly improved. The conjugation process and the resulting products becoming the subject of granted patents in Europe, US, India, China, Japan, South Korea and Australia (2005-2009).

Initial Imperial research focused on the application of TheraPEG™ technology to interferon α as a potential alternative to other pegylated interferon α products for the treatment of Hepatitis C infection. Further research studies conducted by PolyTherics with a range of different proteins and peptides under commercial contracts. TheraPEG™ technology enabled enzymes and antibody fragments to be site-specifically PEGylated using a native and accessible disulphide bond without destroying the molecules' tertiary structure or abolishing its biological activity.

3. References to the research (indicative maximum of six references)

(1) Core technology patent - awarded: A. Godwin, E. Pedone, J. Choi, S. Brocchini, S. Shaunak. Conjugated biological molecules and their preparation. World - WO2005/007197A3(2005); US - US7595292B2(2009) - awarded; Europe - EP04743335(2009) - awarded.

(2) Shaunak, S., Godwin, A., Choi, J., Balan, S., Pedone, E., Vijayarangam, D., Heidelberger, S., Teo, I., Zloh, M., Brocchini, S. (2006). Site-specific PEGylation of native disulfide bonds in therapeutic proteins. *Nat. Chem. Biol*, 2, 312-313. DOI. Times cited: 87 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 12.94

(3) Brocchini, S., Balan, S., Godwin, A., Choi, J.W., Zloh, M., Shaunak, S. (2006). PEGylation of native disulfide bonds in proteins. *Nat Protocols*, 1 (5), 2241-2252. DOI. Times cited: 29 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 7.96

(4) Balan, S., Choi, J., Godwin, A., Teo, I., Laborde, C., Heidelberger, S., Zloh, M., Brocchini, S., Shaunak, S. (2007). Site-specific PEGylation of protein disulfide bonds using a three-carbon bridge. *Bioconjug Chem*. 18 (1) (2007) 61–76. DOI. Times cited: 57 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 4.58

(5) Zloh, M., Shaunak, S., Balan, S., Brocchini, S. (2007). Identification and insertion of 3-carbon bridges in protein disulfide bonds: a computational approach. *Nature Protocols*, 2, 1070-1083. DOI. Times cited: 10 (as at 7th November 2013 on ISI Web of Science). Journal Impact Factor: 7.96

Patents:

- Conjugated biological molecules and their preparation. Godwin, A.R., Pedone, E., Choi, J.W., Shaunak, S., Brocchini, S.J. World Patent WO 2005/007197A3.
- European Patent: EP 04743335 (2009) – granted.
- US Patent: US 10564340 (2009) – granted.

Key funding:

- Wellcome Trust (2002-2006; £500,000), Principal Investigator (PI), S. Shaunak, The design, synthesis and testing of novel polymer therapeutics.
- Bloomsbury Bioseed University Challenge Fund (2002-2006; £250,000), PI S. Shaunak, The design, synthesis and testing of novel polymer therapeutics.
- Department of Trade and Industry (2004-2007; £160,706), PI S. Shaunak, Rapid development of protein-based medicines using a precise conjugation technology.
- Biotechnology and Biological Sciences Research Council (2006-2008; £280,932), PI S. Shaunak, Disulfide bridging protein conjugation.

4. Details of the impact (indicative maximum 750 words)

Impacts include: commercial
Main beneficiaries include: industry

PolyTherics was established as a joint spin-out company of Imperial College and London School of Pharmacy. By 2013, following four successful rounds (2007, 2010, 2011 and 2013) of venture capital funding, PolyTherics had raised over £20 million of funding (£2.5 million raised prior to 2008). This established PolyTherics as one of London's leading life sciences companies, with

revenues of £3.2 million in 2012 [1], and licence agreements (detailed below & [4-6]) with the potential to deliver significant milestone and royalty payments from exploitation of the Imperial conjugation technology (TheraPEG™) developed by Professor Shaunak as applied to novel protein therapeutics.

PolyTherics has 45 highly skilled employees commercially exploiting and developing the TheraPEG™ technology based at the London Bioscience Innovation Centre and at its site on the University of Warwick Science Park [2]. The company has recruited a strong management team, experienced in the pharmaceutical and biotech industries, led by John Burt who has strong links to Imperial. PolyTherics has been successful at commercialising the technology developed at Imperial through commercial licence agreements with Nuron Biotech (TheraPEG interferon β) [3] and Celtic Pharma [4] and Pro Bono Bio (TheraPEG FVIIA, FVIII & FIX) [5].

In July 2013 PolyTherics announced its merger with Antitope Limited, the leading provider of antibody engineering and immunogenicity screening services [6]. The expanded offering will provide the PolyTherics group with a broad technology platform for growth and a solid financial base with sustainable revenue streams over the short-, medium- and longer-term. The enlarged company will deliver a more extensive suite of services and technologies for the development of better biopharmaceuticals. PolyTherics issued new shares to a value of £13.5 million to fund the merger and provide working capital. Imperial Innovations led the investment and brought in new investor Invesco Perpetual with further funds provided by Mercia Fund Management and Advantage Enterprise & Innovation Fund.

The successful merger and development of Polytherics demonstrated the strength of the company founded on Imperial technology. The company has impacted the UK economy generating intellectual capital, capital investment, new employment and novel compounds to treat disease.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Polytherics raised $3.5 million in venture capital. http://www.pehub.com/118098/beringea-imperial-innovation-capital-fund-back-Polytherics/. Archived on 7th November 2013.

[2] Company employee information: http://www.Polytherics.com/index.php/about-us/management Archived on 7th November 2013.

[3] Nuron Biotech and interferon-β. http://Polytherics.com/index.php/news/2011/12/nuron-exercises-option-for-a-licence-to-Polytherics-therapeg-technology-to-develop-a-long-acting-human-interferon-beta-1b. Archived on 7th November 2013.

[4] Milestone payment from Celtic Pharma Ltd in 2013. http://Polytherics.com/index.php/news/2013/03/therapeg-factor-viii-milestone-received-from-celtic-pharma. Archived on 7th November 2013.

[5] Pro Bono Ltd and haemophilia A treatment. http://Polytherics.com/index.php/news/2012/09/pro-bono-bio-exercises-option-and-obtains-exclusive-licence-from-Polytherics-to-therapeg-technology-for-the-development-of-a-long-acting-factor-viii-as-a-potential-treatment-for-haemophilia-a. Archived on 7th November 2013.

[6] Merger of PolyTherics and Antitope July 2013 http://www.polytherics.com/index.php/news/2013/07/polytherics-and-antitope-combine-to-create-leading-provider-of-solutions-to-enable-the-development-of-better-biopharmaceuticals. Archived on 7th November 2013.