Institution: University College London

Unit of Assessment: 3B - Allied Health Professions, Dentistry, Nursing and Pharmacy: Pharmacy

Title of case study: Development of the spin-out company PolyTherics, a major provider of conjugate therapy and protein modification technology to the pharmaceutical and biotechnology industries.

1. Summary of the impact

Protein modification represents a highly significant and growing source of new products for the biopharmaceuticals market. This case study outlines the development of PolyTherics, a highly successful spin-out company from the UCL School of Pharmacy, and the impact that their enabling technology has had on the pharmaceutical and biotechnology industries. The company was developed as a direct result of new conjugate technology developed by Professor Steve Brocchini and coworkers at the School. The company moved to independent premises in 2006 and now manages a portfolio of over 100 granted and pending patents. Several licensing agreements are in place, including with Celtic Pharma Holdings for haemophilia treatments and Nuron for a multiple sclerosis treatment based on PEGylation conjugation technology. Revenue is expected to be £8m in 2013. The impact of Polytherics is therefore as a significant and effective technology provider to the pharmaceutical and biotechnology industries.

2. Underpinning research

Conjugate technology is an approach to medicines development whereby a bioactive molecule (typically a protein such as a cytokine, an antibody or a low molecular weight drug) is synthetically altered so as to incorporate a second molecule (typically a polymer such as poly(ethylene glycol) (PEG)) which significantly improves the pharmacokinetics or stability of the bioactive agent. Initial research in this area at the School of Pharmacy formed the basis of spin-out company Polytherics, with further underpinning research and the development of the patent portfolio continuing in close collaboration between Polytherics and the School over the following years, in parallel with the development of the company.

PolyTherics was founded in 2001 by Steve Brocchini from the School of Pharmacy and Sunil Shaunak, a clinician then based at the Hammersmith Hospital and who is currently Professor of Infectious Diseases at Imperial College London. Anthony Godwin, who was a PhD student supervised by Brocchini at the School of Pharmacy, was also a co-founder and remains with the company as VP of Chemistry. The contribution of the School lay in the management of IP and the development of the conjugation, synthetic, purification, characterisation and modelling technologies, with the animal testing and *in vitro* work being conducted at the aforementioned partner institutions. Initially, the research strategy was based on a portfolio of work derived from the development of polyvalent medicines **[1]**, although this aspect of the portfolio is now being developed by a separate spin-out company. In brief, this work examined systems such as anionic dendrimers (hyperbranched macromolecules that can be chemically synthesised to have precise structural characteristics). Water-soluble conjugates of these molecules with D(+)-glucosamine and D(+)-glucosamine 6-sulfate were found to have significant immunomodulatory and anti-angiogenic properties respectively, with highly encouraging results found for the prevention of scar tissue formation after glaucoma surgery using a rabbit model.

However, around this time the group also identified a significant limitation within the protein conjugate therapy field, namely the need to site-specifically modify proteins efficiently to provide homogeneous products. Prior to their initial work, it was necessary to re-engineer most proteins to have a free cysteine thiol to achieve site-selective modification. This is usually not scalable because during production a protein will misfold and/or aggregate, hence the re-engineering process would render the system unusable as a clinically viable product. The team hypothesised that if it were possible to exploit the innate reactivity of the two cysteine thiols in a disulphide bond (which would be already present within the protein) then such proteins could be site-specifically

conjugated with the added benefit of increased stability. If achievable, then such a solution would effectively remove a key barrier to commercialise many classes of protein-based therapeutics.

A grant from the BBSRC was obtained in 2004/5 and the associated work was published in 2006 **[2]**. One key insight of this research was that most therapeutic proteins do indeed have accessible disulphides and that the two cysteine thiols from a native disulphide could be used to achieve site-specific conjugation, while maintaining the biological activity of the protein. It was nevertheless surprising that a disulphide in a therapeutic protein such as a cytokine could be modified and the protein still remain active. The views of most experts at the time were that proteins would be expected to lose activity when their cysteine disulphide bonds had been altered in any way. This was therefore a ground-breaking insight and led directly to the patented TheraPEG™ technology **[3]** which enables the disulphide bond approach to be used to attach PEG molecules via a three carbon bridge reagent. Although initial work was focused on the development of "C-3" bridging technologies, a "C-1" re-bridging technology has also been developed, thereby extending the range of opportunity for conjugation **[4]**.

Since this initial work, numerous significant advances have been made and published. In particular, PolyTherics developed new site-specific reagents such as CyPEG™**[5]**, which allow selective binding to thiols on a free cysteine for proteins which have stable folds such as fibronectins. Recent work has led to the development of the HiPEG™ technology to allow conjugation to two histidines close together **[6]**. This new HiPEG™ technology is 'site-selective' rather than just 'site-specific' as it allows the conjugation site to be engineered at an optimal position on the protein. Histidines are easier to engineer into proteins than non-native amino acids, which have been the best way to achieve site-selective conjugation. Histidines are also easier than cysteines to engineer into proteins that already have existing native disulphide bonds. In parallel, the team has ensure the technology was described in detail to the academic community **[7]** and they developed a computational approach whereby public protein databases and molecular modelling programs may be used to select a protein rationally and to identify the optimum disulphide bond for experimental studies. This approach allows identification of accessible disulphide bridges in merely two hours, which can be of significant use for more complex proteins with multiple disulfide bonds **[8]**.

The company was therefore founded on the development of novel conjugation technologies and continues to innovate based on these early approaches. Much of PolyTherics' ongoing commercial activity is underpinned by the PEGylation (e.g. TheraPEG™) technologies outlined here to optimise protein pharmacokinetics and recently developed reagents (ThioBridge™) now being used to develop antibody drug conjugates (ADCs).

3. References to the research

[1] Shaunak S, Thomas S, Gianasi E, Godwin A, Jones E, Teo I, Mireskandari K, Luthert P, Duncan R, Patterson S, Khaw P, Brocchini S. Polyvalent dendrimer glucosamine conjugates prevent scar tissue formation. Nat Biotechnol. 2004 Aug;22(8):977-84. http://doi.org/c3jsmz

[2] Shaunak S, Godwin A, Choi JW, Balan S, Pedone E, Vijayarangam D, Heidelberger S, Teo I, Zloh M, Brocchini S. Site-specific PEGylation of native disulfide bonds in therapeutic proteins. Nat Chem Biol. 2006 Jun;2(6):312-3. http://dx.doi.org/10.1038/nchembio786

[3] Godwin A, Pedone E, Choi J, Shuanak S, Brocchini S. Conjugated biological molecules and their preparation. WO/2005/007197 (54 pp). EP 1648518, 2133099, 2253330 and 2277550; US 7595292 and 7939630. Also granted in China and India. Several additional patents have subsequently been filed by PolyTherics based on this initial patent. http://www.google.com/patents/WO2005007197A2

[4] Godwin A, Brocchini S. Conjugated proteins and peptides. WO/2010/100430 (36 pp). https://www.google.com/patents/WO2010100430A1

[5] Godwin A. Novel reagents and method for conjugating biological molecules. WO/2010/010324 (70 pp). https://www.google.com/patents/WO2010010324A1

[6] Cong Y, Pawlisz E, Bryant P, Balan S, Laurine E, Tommasi R, Singh R, Dubey S, Peciak K, Bird M, Sivasankar A, Swierkosz J, Muroni M, Heidelberger S, Farys M, Khayrzad F, Edwards J, Badescu G, Hodgson I, Heise C, Somavarapu S, Liddell J, Powell K, Zloh M, Choi JW, Godwin A, Brocchini S. Site-specific PEGylation at histidine tags. Bioconjug Chem. 2012 Feb 15;23(2):248-63. http://dx.doi.org/10.1021/bc200530x

[7] Brocchini S, Balan S, Godwin A, Choi JW, Zloh M, Shaunak S. PEGylation of native disulfide bonds in proteins. Nat Protoc. 2006;1(5):2241-52. http://dx.doi.org/10.1038/nprot.2006.346

[8] Zloh M, Shaunak S, Balan S, Brocchini S. Identification and insertion of 3-carbon bridges in protein disulfide bonds: a computational approach. Nat Protoc. 2007;2(5):1070-83. http://dx.doi.org/10.1038/nprot.2007.119

4. Details of the impact

Polytherics was founded in 2001 with funding from the Wellcome Trust Catalyst Biomedica, the Bloomsbury Bioseed Fund (of which the School was a shareholder) and Imperial Innovations **[a]**. PolyTherics moved in 2006 to the London Biotechnology Innovation Centre. The company currently employs about 80 staff at three sites: London, Cambridge (following acquisition of Antitope) and Coventry (following acquisition of Warwick Effect Polymers). It manages a patent portfolio of over 100 granted and pending patents. Annual revenue has grown to over £8m for the combined businesses for the 2013 calendar year. Brocchini is now a consultant to the company, having stepped down from the board to address new projects and commitments, but remains very closely aligned to the development of the patent and licencing portfolio.

The impact of the company has been on the pharmaceutical and biotech industries as a result of the development of technologies which overcome significant technical and clinical challenges that are needed to develop new biopharmaceutical medicines. It is also worth noting that Brocchini is a key member of the EPSRC Centre for Innovative Engineering in Macromolecular Therapies, based at UCL which was set up to provide practical solutions to the issues associated with the commercial production of macromolecular medicines such as conjugate therapies. The impact of Polytherics has been derived through the new technologies based on academic research (e.g. TheraPEG™, CyPEG, HiPEG, ThioBridge) **[b]**. These technologies have additionally been combined with those obtained through the purchases of Warwick Effect Polymers in 2012 **[c]** and Antitope in 2013 **[d]**.

The net effect is an innovative and growing company that is demonstrating significant impact via the licensing of new technologies to the pharmaceutical industry. This is corroborated by the development of associated products into clinical trials. While exemplar projects are specified here, PolyTherics and its affiliate companies have collaborative agreements and/or relationships with approximately 40 pharmaceutical and biotech companies. The conjugation technologies are being used commercially to (i) increase protein circulation half-life (TheraPEG™, CyPEG™, HiPEG™), (ii) develop ADCs (ThioBridge™) and other protein-drug conjugates and (iii) to develop new product formats (e.g. bispecific antibodies). Other technologies within the subsidiary company Antitope are focused on protein de-immunisation and protein engineering which is being used to produce better conjugates and modified protein-therapeutics. These technologies are being merged to provide new platforms to innovate in the development of new biopharmaceuticals.

Examples are given here of projects whereby the PolyTherics' TheraPEG™ technology is being used to develop products with partner companies, inevitably representing considerable investment by those organisations. Programs in development utilising TheraPEG technology include:

- Licence agreement for a long-acting interferon β for the treatment of relapsing-remitting multiple sclerosis with Nuron Biotech Inc (US), with a view to reducing dosing frequency for interferon β-1b products from every two days to potentially fortnightly injections **[e]**.
- Licence agreement with Celtic Pharma Holdings for long-acting forms of blood-clotting factors VIIA, VIII and IX for the treatment of haemophilia A & B. These products have the potential to be administered via subcutaneous rather than intravenous injection, thus providing a viable option for self-administered prophylactic therapy **[f]**.

In addition, the ThioBridge antibody-drug conjugate technology is being developed in a research collaboration with several partners including the following:
[Text removed for publication]

- Spirogen (another UCL spin-out company) and Polytherics are collaborating to conjugate Spirogen's pyrrolobenzodiazepine (PBD) cytotoxic agents to antibodies and antibody fragments **[g]**.
- PolyTherics is working with Biotecnol to attach cytotoxic payloads to Tribodies (multi-specific antibody products generated via heterodimerisation of Fab fragments) for the development of targeted cancer therapies **[h]**.

With the successful development of the TheraPEG™, HiPEG™, CyPEG™ and ThioBridge™ technologies and their commercialisation, PolyTherics is now leveraging this success by integrating other services and technologies into its offering. PolyTherics position as a leading UK life sciences company has been pursued through the acquisition of University of Warwick spin-out company **[c]**, Warwick Effect Polymers (where Brocchini's expertise with polymer technologies has enabled the further development and utilisation of their technologies) and in July 2013 the acquisition of Antitope **[d]**, the leading provider in the field of assessment of immunogenicity potential for protein and antibody therapeutics and protein re-engineering in an agreement that was secured with further investment of £13.5m, with a substantial investment from Invesco.

Polytherics continues to benefit from the close connections with UCL School of Pharmacy and the venture capital arm of Imperial Innovations. The company now has a valuation of [text removed for publication], a clear indication that it is a major provider of expertise and technology relating to conjugate therapies and protein modification approaches to the pharmaceutical and biotechnology industries.

5. Sources to corroborate the impact

[a] Details about the spin-out from SoP can be corroborated by the appropriate Business Manager at UCLB. Contact details provided.

[b] PolyTherics website: www.polytherics.com. See in particular the Jan 2013 company fact sheet: http://www.polytherics.com/uploads/default/files/polytherics-corporate-fact-sheet-final-14jan13.pdf. Details about PolyTherics can be corroborated by the CEO. Contact details provided.

[c] http://polytherics.com/index.php/news/2012/01/polytherics-acquires-warwick-effect-polymers-and-expands-technology-portfolio-to-enable-the-development-of-better-biopharmaceuticals

[d] 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

[e] http://eon.businesswire.com/news/eon/20110526006915/en/Nuron-Biotech/multiple-sclerosis/relapse-remitting-multiple-sclerosis

[f] http://www.polytherics.com/index.php/news/2013/03/therapeg-factor-viii-milestone-received-from-celtic-pharma

[g] http://www.businesswire.com/news/home/20120402005786/en/PolyTherics-Spirogen-Announce-Research-Collaboration-Develop-Antibody-Drug

[h] http://www.biotecnol.com/news/biotecnol-and-polytherics-enter-into-a-research-collaboration-for-the-development-of-tribody-antibody-drug-conjugates/#.UhNsllv1Bcw