

Institution: <b>University of Sheffield</b>
Unit of Assessment: <b>5 - Biological Sciences</b>
Title of case study: <b>Asterion, a Start-Up Company Delivering Third Generation Biopharmaceuticals</b>
<p><b>1. Summary of the impact</b></p> <p>Many drugs require frequent injections, making them both inconvenient and unattractive to patients and increasing the risk of infection. How to make long-acting biopharmaceuticals that retain physiological activity, have limited side effects and which can be administered simply is a major goal for the pharmaceutical industry. Asterion Ltd is a University spin-out company which has developed a new protein technology (ProFuse) for making long-acting biological drugs that can address these industry goals. It has attracted significant investment and developed an extensive portfolio of third generation therapeutic products which has resulted in research and licensing income of £1M. The case study demonstrates significant impact on commerce and collaborations with industry.</p>
<p><b>2. Underpinning research</b></p> <p>Asterion's technologies arose from a collaboration between structural biologist <i>Prof. Peter Artymiuk</i> (this UoA), clinician Prof. Richard Ross, and biochemist Prof. Jon Sayers, all based at University of Sheffield. As Head of Molecular Design, <i>Artymiuk</i> was responsible for the analysis and modelling of the cytokine receptor complexes, and the design of sequences of novel molecular constructs that underpin the company's technological approach.</p> <p><b>Initial Observation &amp; Development of Hypothesis</b></p> <p>Ross and coworkers had previously reported the clinical observation that a single copy of a truncated growth hormone receptor blocked an individual's response to growth hormone (GH). The truncated receptor acted as an inhibitor by binding to active growth hormone at the cell surface but prevented signaling [R1]. In 1999, discussions between <i>Artymiuk</i>, Ross and Sayers led to the proposal to engineer cytokine-receptor fusion proteins for drug improvement. The company Asterion was formed in 2000 to test and exploit these ideas, with the three academics as founding directors. Using structural analyses, <i>Artymiuk</i> created designs for new molecules that would either block or stimulate growth hormone signalling. The resultant patent application (inventors: Ross, <i>Artymiuk</i> &amp; Sayers) [R2] was published in 2001 and ultimately granted in the US in 2008.</p> <p><b>Proof-of-concept</b></p> <p>Work funded by the White Rose Seedcorn Fund (a £9m scheme funded by contributions from the then Regional Development Agency, the then DTI and the White Rose universities) and Asterion enabled the Sheffield group to provide proof-of-concept for this approach. In 2007, Sheffield led an international collaboration with [text removed for publication] pharmaceutical company [text removed for publication] and an analytical group in Germany, which characterized an Asterion-designed protein consisting of growth hormone fused to the extracellular domain of its truncated receptor. In rat studies (conducted and funded by [text removed for publication]) the ligand-receptor fusion had a 300-times reduced clearance as compared to native growth hormone, and a single injection promoted growth for 10 days, far exceeding the growth seen after administration of native growth hormone. The Asterion protein therefore had superior pharmacokinetics and more useful pharmacodynamics compared to natural growth hormone. Such ligand-receptor fusion proteins could be used with much less frequent injections and at lower doses than are currently used for growth hormone and growth hormone antagonists in humans. These ligand-receptor fusions are the basis of the ProFuse technology developed by Asterion. The results for growth hormone fusions were reported in a [text removed for publication] publication in <i>Nature Medicine</i> in</p>

2007 [R3]. This attracted favourable commentaries in *Nature Reviews Drug Discovery* and in *Faculty of 1000 Medicine* [R4].

The Sheffield group has since applied the ProFuse technology to other cytokines including erythropoietin, GCSF, insulin like growth factor, leptin and interferon (United States Patent Applications: 20110275564; 20110182848; 20110152187; 20110092417; and 20100316604, respectively).

### Testing of Immunogenicity

Lack of immunogenicity is crucial if a drug is to be taken into the clinic. The Sheffield group and [text removed for publication] collaborated in conducting research that showed that the Asterion's proteins did not induce significant antibody responses or any detectable pathology [R5], i.e., they showed low immunogenicity. This work was fully funded by [text removed for publication] and was pivotal in [text removed for publication] licensing pay out to Asterion. Further work on Asterion molecules conducted in Sheffield on an R&D contract basis funded by [text removed for publication], has led to the filing of many more patent applications with five now having been granted in the US in the period 2008-present [R6].

### 3. References to the research

- R1** A Short Isoform of the Human Growth Hormone Receptor Functions as a Dominant Negative Inhibitor of the Full-Length Receptor and Generates Large Amounts of Binding Protein (1997) Ross, RJM, Esposito, N, Shen, XY, Von Laue, S., Chew, S. L., Dobson, P. R. M., Postel-Vinay, M.-C. and J. Finidori. *Molecular Endocrinology*, 11, 265-73. doi: [10.1210/me.11.3.265](https://doi.org/10.1210/me.11.3.265)
- R2** Fusion protein comprising growth hormone and growth hormone receptor. Ross, R, **Artymiuk P** and Sayers J. *Granted US Patent No. 7,446,183*, November 2008. Originally published as *PCT/GB01/02645* in 2001.
- R3** A ligand-receptor fusion of growth hormone forms a dimer and is a potent long-acting agonist. (2007) Wilkinson IR, Ferrandis E, **Artymiuk PJ**, Teillot M, Soulard C, Touvy C, Pradhananga SL, Justice S, Wu Z, Leung KC, Strasburger CJ, Sayers JR, Ross RJ. *Nature Medicine*, 13, 1108-1113. doi: 1 doi: [10.1038/nm1610](https://doi.org/10.1038/nm1610)
- R4** Cytokine hormones: Designed to linger Flight, M.H. (2007) *Nat Rev Drug Discov* 6: 783, doi: [10.1038/nrd2430](https://doi.org/10.1038/nrd2430)
- R5** Immunogenicity, toxicology, pharmacokinetics and pharmacodynamics of growth hormone ligand-receptor fusions. Ferrandis E, Pradhananga SL, Touvy C, Kinoshita C, Wilkinson IR, Stafford K, Wu Z, Strasburger CJ, Sayers JR, **Artymiuk PJ**, Ross RJ. (2010) *Clin Sci (Lond)*. 119: 483-491. doi: [10.1042/CS20100241](https://doi.org/10.1042/CS20100241)
- R6 US patents granted on Asterion technology 2008-2013**
- Growth hormone fusion proteins (2013), Ross, R, **Artymiuk P**, Sayers JR  
US Patent 8,470,559
  - Growth hormone fusion proteins (2012), Ross, R, **Artymiuk P**, Sayers JR  
US Patent 8,293,709
  - Modified growth hormone polypeptides (2012) **Artymiuk P**, Ross, R, Sayers JR  
US Patent 8,273,552
  - Modified growth hormone fusion polypeptides (2009) Ross R, Sayers J, **Artymiuk P**  
US Patent 07524649
  - Cytokine polypeptides and antibodies containing a signal sequence for the attachment of a glycosylphosphatidylinositol (2009) Ross R, Sayers J, **Artymiuk P**  
US Patent 07625998
  - Fusion protein comprising growth hormone and growth hormone receptor (2008)  
Ross R, **Artymiuk P**, Sayers J  
US Patent 07446183
  - Fusion protein comprising growth hormone and growth hormone receptor (2008) Ross R, **Artymiuk P**, Sayers J

US Patent 08173782

#### 4. Details of the impact

##### Impact on Commerce and Industrial Collaboration

*Artymiuk*, Ross and Sayers co-founded the spin-out company Asterion Ltd in 2000 using an initial investment of £125,000 from the White Rose Seedcorn Fund (which had been created in 1999 through the Department of Trade and Industry's University Challenge competition) [S1, S2]. The University of Sheffield and the Asterion cofounders filed a patent application on engineered growth hormones and other cytokines commencing in 2000 (inventors: Ross, *Artymiuk* and Sayers), since then over 200 applications have been filed, with a total of 27 granted patents and 23 applications still pending in a number of countries [S3, S4].

The cofounders sought to raise venture capital and collaborative research funding by presenting their proposal to potential investors, including Fusion IP, the University of Sheffield main vehicle for raising commercial IP investment. This has led to total equity/loan funding and investment to Asterion over the REF period in excess of £1M.

In 2003 Asterion signed an R&D deal with [text removed for publication], which ultimately led to licensing milestone payments in 2009. In addition, early in 2008 Asterion entered into a deal with [text removed for publication] that also led to licencing income during the REF period. Details of these partners and their interest in Asterion's products are as follows:

- [text removed for publication], is a global specialty-driven pharmaceutical company with total sales exceeding €1.2 billion in 2012. They licensed the development of long-acting growth hormones patented by Asterion Ltd for clinical development in 2009 [S5], provided R&D funding and funded a number of patents based on Asterion's Profuse technology.
- [text removed for publication], paid license fees to evaluate Asterion's designs in the field of an undisclosed hormone.

Asterion has received licensing income from [text removed for publication] and [text removed for publication] since 2008 exceeding £500,000 [S1]. Asterion research income over the REF period totals £0.96M, with joint R&D contracts and license income from [text removed for publication] since 2004 totalling over £1.7M. Finally, [text removed for publication] have funded applications for over 200 patents in 15 families based on Asterion technologies, with Ross, *Artymiuk* and Sayers as co-inventors.

The research income allowed Asterion to employ train and employ two postdoctoral researchers (Drs. Wilkinson and Padhananga) during the REF period. Their work involved designing, producing and purifying recombinant proteins and testing in bioassays for biological activity. The methodologies developed by Asterion were transferred to [text removed for publication] for scale-up to commercial production and preclinical trials of some of Asterion products. The cost to [text removed for publication] of these studies, and the costs involved in the generation and protection of the associated patents by [text removed for publication], are commercially sensitive but are significant.

The success of Asterion as a University start-up led to a cover story in the 'BBSRC Business' magazine July 2008 ("Sheffield spin-out wins additional investment for novel therapeutic proteins"), and Asterion was one of four new companies highlighted in the BBSRC Annual Report in 2009. Thus the success of Asterion has been used by RCUK to promote the Excellence with Impact agenda, leading to a wider impact on university-based translational research [S6, S7].

**5. Sources to corroborate the impact**

- S1 Documentary evidence of licensing agreements and investments** are available from Company Secretary, Mr Richard Birtles, Asterion Ltd., The Innovation Centre, 217 Portobello, Sheffield, S1 4DP, UK.
- S2 Asterion web-site** (<http://www.asterion.co.uk>)
- S3 Details of patent filings and grants** are available from Asterion Ltd's Patent Attorney, Dr Rob Docherty, Director, Symbiosis IP Limited, Apollo House, Eboracum Way, Heworth Green, YORK YO31 7RE, UK
- S4 All granted US patents** can be accessed via the United States Patent Office web site: <http://patft.uspto.gov/netahtml/PTO/search-bool.html> US Patent numbers: 8,470,559; 8,293,709; 8,273,552; 07524649; 07625998; 07446183 and 08173782.
- S5** [text removed for publication]
- S6 BBSRC Business Magazine**, July 2008, cover and article (page 6) features Asterion's work. <http://www.bbsrc.ac.uk/news/business-magazine/2008/0807-business.aspx>
- S7** <http://www.bbsrc.ac.uk/publications/accounts/bbsrc-annual-08-09.aspx> (**BBSRC "Delivering Excellence with Impact-Annual Reports and Accounts 2008-2009"**). Page 24 highlights BioFusion's investment into Asterion Ltd.