Institution: University of Sheffield

Unit of Assessment: 3C – Allied Health Professions: Biomedical science

Title of case study: Commercial impact of a Sheffield Spin-out: Asterion Ltd

1. Summary of the impact

Many drugs require frequent injections, making them inconvenient, unattractive to patients and increasing the risk of infection. Asterion Ltd is a spin-out drug development company specializing in technology designed to reduce the frequency of such injections. It was founded in 2000 by three University of Sheffield academics and has raised equity/loan funding of **£1,055,000** since 2008. Since 2009 Asterion has attracted **licensing income** from two overseas pharmaceutical companies, [text removed for publication], totalling over **£532,959,** clearly demonstrating impact on commerce and collaborations with industry. In addition, since January 2008, Asterion Ltd has **invested £1,269,798** on its research and patent portfolio. Asterion holds 7 US patents granted since 2008; all the named inventors on these patents are University of Sheffield staff. Total research and licensing income for the period was £960,000.

2. Underpinning research

Asterion's technologies developed from collaboration between clinician Professor Richard Ross (1996-current: UOA1), structural biologist Professor Peter Artymiuk (1985-current: UOA5), and biochemist Professor Jon Sayers (1995-current: UOA3), all at the University of Sheffield throughout.

Initial Observation & Development of Hypothesis

Ross led a group that reported the initial 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 signalling **[R1].** Building on this observation, in 1999 Ross held discussions with Artymiuk and Sayers, which led to the design of engineered cytokine-receptor fusion proteins. Using protein engineering techniques, these new molecules were designed to either block or stimulate growth-hormone signalling. The resultant patent application (inventors: Ross, Artymiuk & Sayers) **[R2]** was published in 2001 and ultimately granted in the US in 2008. Artymiuk carried out the structural model-building and Sayers led the protein engineering, production and purification of the new molecules.

Proof-of-concept

Work funded by the White Rose Seedcorn Fund and Asterion enabled the Sheffield research group to provide proof-of-concept for this approach. In 2007, Sheffield led an international collaboration with [text removed for publication] pharma company [text removed for publication] and an analytical group in Germany that characterized an Asterion-designed protein consisting of growth hormone fused to the extracellular domain of its truncated receptor. In rats, the ligand-receptor fusion had a 300-fold 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, as reported in *Nature Medicine* in 2007 **[R3].** The Asterion protein had superior pharmacokinetics and more useful pharmacodynamics compared to natural GH. Thus, it can be expected that such a ligand-receptor fusion protein 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. This work was published in *Nature Medicine* and 6 of the 12 authors (including two of the three first authors and the corresponding author) were at the University of Sheffield. This paper attracted favourable commentaries in *Nature Reviews Drug Discovery* and in

Faculty of 1000 Medicine **[R4]**

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

Lack 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 Asterion's proteins did not induce significant antibody responses or any detectable pathology **[R5],** i.e. they showed low immunogenicity**.** This work was pivotal in [text removed for publication] licensing pay-out to Asterion. Further work funded by Asterion within The University of Sheffield led to filing of many more patent applications, with seven now having been **granted** in the US in the period 2008-present, strengthening Asterion's commercial position:

- 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 glycosylphosphatidylinisitol (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.

3. References to the research

Sheffield authors in **bold**. ***** denotes corresponding author.

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 **Ross, RJM*, Esposito, N, Shen, XY, Von Laue, S,** Chew, SL **Dobson, PRM,** Postel-Vinay, M.-C**.** Finidori J (1997) *Molecular Endocrinology*, 11, 265-73. doi: 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. **Wilkinson** IR**,** Ferrandis E**, Artymiuk PJ,** Teillot M, Soulard C, Touvay C, **Pradhananga SL, Justice S,** Wu Z, Leung KC, Strasburger CJ, **Sayers JR, Ross RJ*** (2007) *Nature Medicine*, 13, 1108-1113. doi: 10.1038/nm1610

R4. Cytokine hormones: Designed to linger. Flight, M.H. (2007) *Nature Reviews Drug Discovery,* 10, 783, doi: 10.1038/nrd2430) and Ho K: F1000Prime doi: 10.3410/f.1091056.544439 F1000Prime.com/1091056#eval544439)

R5. Immunogenicity, toxicology, pharmacokinetics and pharmacodynamics of growth hormone ligand-receptor fusions. Ferrandis E, **Pradhananga SL,** Touvay C, Kinoshita C, **Wilkinson IR,** Stafford K, Wu Z, Strasburger CJ, **Sayers JR, Artymiuk PJ, Ross RJ*** (2010) *Clinical Science* (*London*). 119: 483-491. doi: 10.1042/CS20100241

4. Details of the impact

Impact on Commerce

Asterion Ltd, a University of Sheffield spin-out, generated licensing revenue from two overseas pharmaceutical companies for access to our IP during the census period [**S1, S2, S3**]. The two companies who paid licenses for our technology were:

- [text removed for publication], a global specialty-driven pharmaceutical company with total sales exceeding €1.2 billion in 2012, licensed the development of long-acting growth hormones patented by Asterion Ltd for clinical development in 2009.
- [text removed for publication], paid license fees to evaluate Asterion's designs in the field of an undisclosed hormone in 2009.

Since 2009 Asterion Ltd has received income from licensing agreements of **£532,959**.

During the period 01 Jan 2008–31 July 2013, Asterion Ltd spent £1,295,934 on research and development [**S1**] and funded contract development work during the period at the University of Sheffield, thereby securing employment for two postdoctoral researchers, as well as supporting Asterion's staff. During the current REF census period, this has amounted to 14.5 person years of jobs in the UK.

In the same period, Asterion Ltd attracted equity/loan funding to the value of **£1,055,000** [**S1**]**.**

Asterion Ltd was featured in a cover story in the *BBSRC Business* magazine in July 2008 ("Sheffield spin-out wins additional investment for novel therapeutic proteins"), and one of four new companies highlighted in the BBSRC Annual Report in 2009 [**S4, S5**].

What led to the impact?

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). In total, over 200 applications have been filed since 2000, with a total of 27 granted patents (including 7 US patents **[S6]**), and 23 applications still pending **[S2]**.

Artymiuk, Ross and Sayers co-founded the spin-out Asterion Ltd, in 2000 using an initial investment of £125,000 from the White Rose Technology Seedcorn Fund (which had been created in 1999 through the DTI's University Challenge competition).

The cofounders sought to raise venture capital or collaborative research and development (R&D) funding by presenting their proposal to potential investors including private enterprise, corporate VCs (e.g. Novartis Ventures, 3M, J&J Development Corporation) and to international pharmaceutical companies e.g. GSK, Sanofi, Merck, Pfizer, and Ipsen. These presentations contributed to Asterion signing an R&D deal with [text removed for publication] in 2003, and attracting a second investor (see below). From incorporation to 31 December 2007, Asterion attracted investments of £820,000 plus research and licensing income of £858,110.

Biofusion Ltd (later to become Fusion IP plc) invested £250,000 in Asterion in 2006 **[S1].**

Asterion Ltd and [text removed for publication] entered into a joint R&D deal in the area of growth hormone (2003) **[S3],** which ultimately led to licensing milestone payments in 2009. In early 2008 Asterion entered into a similar deal with [text removed for publication], which also led to licencing income during the period [**S1**]. These developments led to Asterion Ltd receiving a total of £532,959 during the REF census period.

Summary for the REF Census period 01-01-2008 to 31-05-2013 for Asterion Ltd

- Total research income: **£960,118** (including **£532,959 licensing income**)
- Total R&D spend: **£930,286**
- Total investment in IP protection during period: **£339,512**
- Total equity/loan funding attracted into Asterion Ltd: **£1,055,000**

5. Sources to corroborate the impact

S1. Documentary evidence of licensing agreements and investments can be obtained from Company Secretary, Asterion Ltd, The Innovation Centre, 217 Portobello, Sheffield, S1 4DP, UK.

S2. Details of patent filings and grants can be made available from Asterion Ltd's Patent Attorney: Director, Symbiosis IP Limited, Apollo House, Eboracum Way, Heworth Green, York YO31 7RE, UK

S3. [text removed for publication].

S4. **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

S5. 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.

S6. 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.