Section A

The fields in this section are mandatory.

Institution: Durham University

Unit of Assessment: UoA 5 Biosciences

Title of case study:
New Commercial Strategies for Life Science Research and Product Development

Period when the underpinning research was undertaken:

1st January 2000 to 31st December 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Professor Stefan Przyborski	Professor of Cell Technology	2000 to present
Dr Maria Bokhari	Postdoctoral Research Assistant	2005 - 2008
Dr Ross Carnachan	Postdoctoral Research Assistant	2006 - 2009
Dr Mathilde Roger	Postdoctoral Research Assistant	2015 - 2018
Dr Nicola Fullard	Postdoctoral Research Assistant	2014 - present
Ms/Dr Lydia Costello	PhD student / PDRA	2015 - present
Ms Nicole Darling	PhD student	2016 - present

Period when the claimed impact occurred:

1st August 2013 to 31st July 2020

Is this case study continued from a case study submitted in 2014?

Yes (in part)

Section B

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

Alvetex® technology has been fully commercialised and is recognised as a leading scaffold product in the 3D cell culture market with global sales approaching GBP1,000,000 and widespread strong evidence of adoption in the academic and industrial sectors. This has been made possible through the design of 3D scaffold materials in conjunction with novel cell culture devices and extensive research and product development at Durham University. End-users adopting Alvetex® have recreated native human tissue structure for use in new biological assays, that in turn will enable advances in research, consumer product development, and provide alternatives to using animals.

2. Underpinning research (indicative maximum 500 words)

Work led by Professor Przyborski has focused on the design and application of innovative new approaches to culture cells in the laboratory. This underpinning research performed at Durham University has led to the development of a series of technological advances enabling routine culture of cells in 3D and bioengineering of human tissue equivalents.

It is well recognised that the existing methods to culture mammalian cells *in vitro* on flat surfaces in two-dimensions (2D) results in cells adapting to the planar substrate, changing their architecture and protein expression profile. This in turn alters cell function, limiting the value of such *in vitro* assays, particularly during the development of pharmaceuticals.

Moreover, such cell models are often considered too simplistic and far removed from the complexities of real tissues with multiple cells types interacting within a 3D architecture.

To address this problem, Przyborski engaged in interdisciplinary research to develop a technological solution to culturing cells in 3D. He established a collaboration with materials scientist Professor Cameron (Chemistry, Durham University) that capitalised on an existing methodology known as emulsion templating to produce porous polystyrene materials. Under an EPSRC grant awarded to Professors Przyborski and Cameron (GR/T24043), polystyrene-based scaffold materials were optimised and tailored to provide 3D supports (R1). Further optimisation was required to enable 3D cell culture that resulted in engineering of these materials into thin membranes (R2). Initial testing provided compelling evidence that cell growth, differentiation and function were significantly enhanced in 3D cultures using polystyrene-based scaffolds providing more accurate information on cell behaviour compared with 2D conventional systems (R3). Subsequently, the technology was further refined in terms of scale up for mass production and reproducibility, and specialised devices designed to house the porous membranes (e.g. well inserts) were produced for routine 3D cell culture. This in turn led to the commercialisation of the technology into the product trademarked Alvetex®.

Alvetex® provides a scaffold-based solution for routine 3D cell culture. More recent research has focused on the application of this technology to produce more sophisticated bioengineered 3D models of human tissues, incorporating multiple cell types (R4-6). This has been achieved through extensive research work at Durham University and via partnerships with academic and industrial users of Alvetex®. For example, Procter & Gamble (P&G) has invested heavily (>GBP2,000,000) in various projects using the Alvetex® platform for its skin research programme (R5), including a GBP1,000,000 BBSRC-LINK grant (2013, BB/K019260/1) and GBP361,000 BBSRC-IPA grant (2019, BB/S006710/1)). In addition, multiple BBSRC sponsored projects (>GBP750,000 (e.g. BB/K011405/1; BB/K011413/1; BB/M015653/1) and other commercial partnerships (>GBP250,000) have been awarded to develop new and innovative applications of Alvetex® technology, including research into: (1) human tissue nasal mucosal models (AstraZeneca and Reprocell); (2) 3D neuronal/glial systems (Reprocell); (3) human buccal mucosa; and (4) 3D models of stem cell differentiation to replace the teratoma xenograft assay. Alvetex® technology is also being used to develop methods to reduce and replace the numbers of animals used in research through funding from the NC3Rs (GBP90,000 (NC/N00289X/1); GBP394,000 (NC/S001050/1)) and create models of human skin and gut wall in health and disease (R5-6).

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

R1. Bokhari, M., Carnachan, R.J., **Przyborski, S.A.**, Cameron, N.R. (2007). Emulsion-templated porous polymers as scaffolds for three dimensional cell culture: effect of synthesis parameters on scaffold formation and homogeneity. Journal of Materials Chemistry. 17:4088-4094. DOI: 10.1039/B707499A

R2. Bokhari, M., Carnachan, R.J., Cameron, N.R., **Przyborski, S.A.** (2007). Novel cell culture device enabling three-dimensional cell growth and improved cell function. Biochemical and Biophysical Research Communications, 354:1095-1100. DOI: 10.1016/j.bbrc.2007.01.105

R3. Schutte, M., Fox, B., Baradez, M., Devonshire, A., Minguez, J., Bokhari, M., **Przyborski, S**., Marshall, D. (2011). Rat primary hepatocytes show enhanced performance and sensitivity to acetaminophen during three-dimensional culture on a polystyrene scaffold designed for routine use. Assay and Drug Development Technologies. 9:475-486. DOI: 10.1089/adt.2011.0371

R4. Hill, D.S., Robinson, N.D., Caley, M.P., Chen, M., O'Toole, E.A., Armstrong, J.L., **Przyborski, S.**, Lovat, P.E. (2015). A novel fully humanized 3D skin equivalent to model early melanoma invasion. Molecular Cancer Therapeutics. 14:2665-73. DOI: 10.1158/1535-7163.MCT-15-0394

R5. Roger M, Fullard N, Costello L, Bradbury S, Markiewicz E, O'Reilly S, Darling N, Ritchie P, Määttä A, Karakesisoglou I, Nelson G, von Zglinicki T, Dicolandrea T, Isfort R, Bascom C, **Przyborski S**. (2019). Bioengineering the microanatomy of human skin. Journal of Anatomy. 234:438-55. DOI: 10.1111/joa.12942

R6. Darling, N.J., Mobbs, C.L., Gonzáles-Hau, A.L., Freer, M., **Przyborski, S**. (2020). Bioengineering novel *in vitro* co-culture models that represent the human intestinal mucosa with improved Caco-2 structure and barrier function. Frontiers in Bioengineering and Biotechnology. DOI: 10.3389/fbioe.2020.00992

International interest in this research has led to multiple invited keynote lectures and seminars to disseminate information about these new cell technologies and bioengineered human tissues. Significant peer-reviewed research grants and investments for technology commercialisation (see details above and below) have in part resulted from the publication of this high-quality research. Przyborski awarded the Royal Society of Chemistry, Rita and John Cornforth Medal (2012), in recognition of this research and its commercialisation.

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

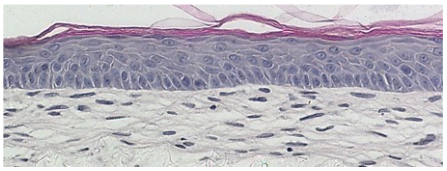
The impact of Przyborski's research is several fold, including: the provision of innovative cell culture products that has transformed the development of new *in vitro* assays and human tissue engineered models to advance research and product development; economic impact through business development (independent company), product sales (ca. GBP1,000,000), and the creation and retention of >35 UK jobs.

By way of background: In 2005 formal commercialisation of the research started with assignment of patent WO200712588 by Durham University to its spinout company, Reinnervate Limited (Registered 04468747); The company raised substantial amounts of funding (>GBP10,000,000) from government grants and private investors (Venture Capitalists, high net-worth individuals, Angel funds) to support product development, intellectual property, and the establishment of independent premises for product development, manufacture and marketing; The concept went through an extensive development and scale-up phase within the Company, resulting in the creation of optimised and proprietary technology for routine 3D cell culture; The product was trademarked Alvetex® and launched in 2011; Reinnervate employed 27 personnel at NetPark Sedgefield County Durham, and 12 at Durham University to support ongoing underpinning research under a commercial collaboration agreement.

In August 2014, Reinnervate was acquired by Reprocell Group (E1), a Japanese Jasdaq-listed company specialising in combining technologies to investigate and supply human tissues. Manufacture and supply of Alvetex® is led by Reprocell Europe within the UK at sites in Sedgefield and Glasgow. Currently, Reprocell Europe employs 25 staff in the UK (E2), linked to an additional ca. 50 employees of Reprocell Group at sites in Japan, USA and India. Alvetex® naturally complements Reprocell's portfolio of products and enables the formation of human tissue models for discovery, drug testing, and safety assessment. Multiple formats of Alvetex® technology such as 12-well, 24-well, 96-well and 384-well culture plates, and 6-well, 12-well, and 24-well inserts, have been introduced to the market to meet the needs of customers along with full online technical support (E3). Reprocell uses multiple distributors

including Fisher Scientific and AMS Bio who are contracted to market its products in different territories around the world (E4). There is also an online store for Alvetex® products via Reprocell's website (E5). Since its launch onto the market, Alvetex® product sales approaching GBP1,000,000 have been achieved (E6), "which is significant for a particular specialised type of cell culture product in a high volume, low cost, consumer product market" (Bunton testimonial, E10), in part reflecting its status as an established scaffold-based technology for 3D cell culture applications.

Product research and development continues through a formal collaboration agreement with Durham University (E7), leading to the creation of new technologies based on the Alvetex® platform. For example, Innovate UK funding has been awarded to Reprocell and Alycomics Ltd, and sub-contracted to Durham University, to design, build and validate a new 96-well insert version of Alvetex® to enable high-throughput analysis of human tissue models (E8). Reprocell also acts as a contract research organisation (CRO), and its Alvetex® products are a critical component in developing novel human bioengineered tissue models and new *in vitro* assays for commercial clients (E8-10). For example, Alvetex® technology has been selected as the preferred platform to construct robust and reproducible models of human skin by Procter & Gamble Cincinnati USA (P&G; Figure). The multi-national corporate has invested heavily (>GBP2,000,000) in various projects using the Alvetex® platform as its preferred option for its skin programme and development of new consumer products (Thompson testimonial, E9). P&G, Reprocell and Durham University have also recently entered a partnership for the full commercialisation of a novel model of human full thickness skin developed on the Alvetex® platform (E9). In addition, multiple BBSRC/industry sponsored projects (>GBP750,000) and other commercial partnerships (>GBP250,000; e.g. AstraZeneca) have been awarded to develop new and innovative applications of Alvetex® technology, including human tissue mucosal models (intestinal, nasal and buccal mucosae), 3D neural systems, and 3D models of stem cell differentiation. Alvetex® technology is also being employed in projects designed to reduce and replace the numbers of animals used in research through funding from the NC3Rs (GBP90,000 (NC/N00289X/1); GBP394,000 (NC/S001050/1)) to create models of the gut wall and ageing skin. The significant impact of the Alvetex® platform is clear, as it has underpinned the development of each of these new and novel human tissue models and is recognised as the "preferred technology" (for example, see Thompson testimonial, E9).



Human full thickness skin equivalent constructed on the Alvetex® platform showing epidermal and dermal layers and prominent stratum corneum (top) reproducing the architecture of native skin tissue.

The ultimate beneficiaries of this impact are the end users who buy and use Alvetex® products, i.e. customers, who are cell biologists and investigators in universities, government labs, hospitals, biotech and the pharmaceutical and consumer product industry (E10). Multiple testimonials illustrate the value and diverse range of applications that Alvetex® has been used for (E8-10). Improving the growth and function of 3D cultured cells and creating novel bioengineered human tissues will ultimately contribute to decreasing R&D costs, reducing animal usage, improving the predictive accuracy during compound development, and advancing basic research. There are now over 70 peer-reviewed scientific publications published by independent customers who have purchased and employed Alvetex® technology (E10). As these testimonials show, there is strong evidence that Alvetex® technology has solved problems and created new opportunities. They demonstrate the ability for researchers to routinely perform 3D cell culture and notably it has transformed the way in which scientists can now more easily bioengineer human tissues based on the Alvetex®

platform. This is strongly evidenced through the adoption of Alvetex® and bioengineered human skin by P&G (E9, E10) but also, for example, breakthroughs by scientists in collaboration with GSK, having purchased Alvetex® and produced novel tissue equivalents of the human airway to study bacterial infections (doi:10.1371/journal.pone.0153985).

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

E1 Company sale - Reprocell acquires Reinnervate:
- Press release (5th August 2014) (link)

E2 Company employees:
- Spreadsheet detailing employees over REF period (confidential)

E3 Product formats and technical support:
- Section of Reprocell website dedicated to Alvetex® products (link)
- Alvetex® promotional flyer (link), catalogue (link), product brochure (link)
- Alvetex® on-line videos (link)
- Alvetex® protocols (link), application notes and whitepapers (link)

E4 Alvetex® Product Distribution:
- Example distributor companies: AMSBio (link); Fisher Scientific (link)

E5 Evidence of availability and sale of Alvetex® products:
- Reprocell Alvetex® online store (link)

E6 Evidence of sales data for Alvetex® products since launch (confidential)

E7 Evidence of continued investment in Alvetex® R&D development:
- Example research collaboration agreement between Reprocell/Durham University

E8 Evidence of commercial collaboration utilizing Alvetex® technology:
Example: Alcyomics/Reprocell
- UKRI funded project for 96-well Alvetex® product and application (£203k) (link)
- Testimonial – Professor Anne Dickinson, CEO Alycomics (26/7/2020)

E9 Example of commercial collaboration utilizing bioengineered tissue model based on Alvetex® platform:
- Commercialisation of novel full thickness human skin equivalent:
  - P&G/Reprocell/Durham University formal agreement and royalty stream;
  - Testimonial – Dr Jim Thompson, Section Head P&G (26/10/2020);
  - Testimonial – Dr David Bunton, CEO Reprocell (24/8/2020).

E10 Evidence of adoption of Alvetex® products:
- Example testimonials from end users and customers (link)
- Testimonial – Dr Jim Thompson, Section Head P&G (26/10/2020)
- Testimonial – Dr David Bunton, CEO Reprocell (24/8/2020)
- Testimonial – Professor Anne Dickinson, CEO Alycomics (26/7/2020)
- Multiple publications by end users of Alvetex® technology (link1) (link2)