Institution: **University of Sheffield**

Unit of Assessment**: 5 - Biological Sciences**

Title of case study: **The Development of Stem Cells for Regenerative Medicine**

1. Summary of the impact

Research on stem cells has led to an explosion of interest in the field of regenerative medicine, with the potential for new clinical interventions and treatments. Pioneering research in Sheffield led to the founding of a spin-out company, Axordia, in 2001, focussed on the applications of human embryonic stem cells (hESC) in medicine. Several hESC lines (including SHEF-1) were generated in Sheffield by Axordia, which was sold to Intercytex in 2008 for £1.68M. These Sheffield-derived hESC lines were then sold on to a major pharmaceutical company, Pfizer, for £0.75M in 2009. As a result, a clinical grade derivative of SHEF-1 has been developed and approved for clinical trials for treating age-related macular degeneration (AMD). In addition, Sheffield research has led to the licensing and sales of key hESC marker antibodies for stem-cell quality control. Finally, Sheffield researchers have informed emerging regulatory guidelines about the safety of hESC regenerative medicine applications by authoring reports and providing evidence to a Parliamentary committee. The case study has significant impact on commerce, health and welfare and public policy.

2. Underpinning research

Embryonal carcinoma (EC) cells, the malignant counterparts of human embryonic stem cells (hESC), were the only available pluripotent human stem cells until hESC were first reported in 1998. Professor Peter Andrews, Co-Director of the Centre for Stem Cell Biology at the University of Sheffield, pioneered human EC cell research and was the first to work with hESC in the UK, with lines acquired from Dr James Thomson in 1999. Andrews co-founded the spin-out company Axordia Ltd In 2001, which derived a unique portfolio of hESC lines, including the SHEF lines. In addition, Andrews characterized several monoclonal antibodies that are used to identify both EC cells [**R1**] and hESC [**R2**], and he studied their differentiation into neural cell types [**R3**]. Continuing this line of work, in collaboration with Peter Coffey, (initially in Sheffield, and later at University College London), he demonstrated that neural cells derived from hESC would integrate well when transplanted to the eyes of newborn rats, and that among these cells retinal pigment epithelial (RPE) cells could be derived [**R4**]. This research underpins the impact on clinical application of hESC for age-related macular degeneration (AMD), which is the most common cause of vision loss in those aged over 50.

In collaboration with Paul Kemp from Intercytex Ltd, Andrews studied the reprogramming of somatic cells by fusion with EC and hESC as a potential route to obtaining pluripotent stem cells (Patents PCT/GB00/00582 and PCT/GB00/00576 inventors Andrews and Kemp, filed 1999). As a result of his standing in the stem cell research community, Andrews was asked in 2004 by the International Stem Cell Forum (ISCF) (www.stem-cell-forum.net/), a consortium of healthcare funding agencies from 13 countries, to lead the International Stem Cell Initiative (ISCI). This represented a group of ESC researchers aiming to compare the different isolates of hESC from around the world, especially seeking a consensus about surface antigen and gene expression markers that can be used to identify undifferentiated hESC. This consortium described a surface antigen and gene expression signature characteristic of hESC [**R5**]**.** The antigens highlighted by the ISCI study included several (SSEA3, SSEA4, TRA-1-60, TRA-1-81) characterized by Andrews. The consortium also incorporated a collaboration with ABI Inc to design a low-density qPCR array to assay the expression of 96 genes by putative hESC. This research underpins the commercial

use of these markers in the quality control of hESC.

Finally, in another study Andrews showed for the first time that, on long-term culture, hESC may acquire non-random genetic changes that could compromise safety in regenerative medicine applications [**R6**], a result confirmed in further studies of the ISCI led by Andrews. As a result of these data, and his long-term leadership in the field, Andrews was invited to contribute to a UK Parliamentary Committee on regenerative medicine in 2012, underpinning impact on policy.

3. References to the research

R1 Andrews PW et al. (1996). Comparative analysis of cell surface antigens expressed by cell lines derived from human germ cell tumours. *Int. J. Cancer* 66: 806-816.

R2 Draper JS, Pigott C, Thomson JA, Andrews PW (2002). Surface antigens of human embryonic stem cells: changes upon differentiation in culture. *J. Anat*. 200: 249-258. doi: 10.1046/j.1469-7580.2002.00030.x

R3 Przyborski SA, Morton IE, Wood A, Andrews PW (2000) Developmental Regulation of Neurogenesis in the Pluripotent Human Embryonal Carcinoma Cell Line NTERA-2. *Eur. J. Neurosci*. 12: 3521-3528. doi: 10.1046/j.1460-9568.2000.00230.x

R4 Vugler A, Carr AJ, Lawrence J, Chen LL, Burrell K, Wright A, Lundh P, Semo M, Ahmado A, Gias C, da Cruz L, Moore H, Andrews P, Walsh J, Coffey P (2008) Elucidating the phenomenon of HESC-derived RPE: anatomy of cell genesis, expansion and retinal transplantation. *Exp. Neurol*. 214: 347-361. doi: 10.1016/j.expneurol.2008.09.007

R5 The International Stem Cell Initiative (Corresponding Author, PW Andrews) (2007) Characterization of human embryonic stem cell lines by the International Stem Cell Initiative. *Nature Biotech.* 25:803-816. doi: 10.1038/nbt1318

R6 Draper JS, Smith K, Gokhale P, Moore HD, Maltby E, Johnson J, Meisner L, Zwaka TP, Thomson JA, Andrews PW (2004) Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells. *Nature Biotech*. 22: 53-54. doi: 10.1038/nbt922

4. Details of the impact

Commercial investment Enabling the Development of Regenerative Medicine

a) Commercial development of pluripotent stem cells for regenerative medicine

To exploit the opportunities created by the first derivation of hESC, Axordia Ltd was founded as a spin-out company of the University of Sheffield in 2001 with Professors Andrews and Moore (also of Sheffield) as founding directors [**S1**]. The initial investment in Axordia from the White Rose Technology Seedcorn Fund (a £9M scheme funded by contributions from the then Regional Development Agency, the then DTI and the White Rose universities) was secured based upon the strength of the underlying research programmes of the founding scientists (Press Release [**S2**]). The patent applications relating to reprogramming somatic cells (that had been filed by Andrews and Kemp in 1999) were assigned to Intercytex Ltd, another early stage biotech company working towards regenerative medicine (who later purchased Axordia). Acquisition of these patents from Sheffield in exchange for founder shares contributed to Intercytex obtaining its initial investment of £1.4 million. Andrews served as an Executive Director of Axordia and was a member of the Scientific Advisory Board of Intercytex. His research underpinned the patents on hESC and his board membership contributed to assuring investors of the potential of Axordia and Intercytex. In 2006, Axordia secured additional investment of £420,000 from BioFusion Ltd [**S3**]. In particular, collaborative work with Coffey after his move from Sheffield to UCL on the production of RPE cells from hESC allowed Axordia to enter negotiations with UCL to provide cells for future clinical trials for AMD. Pfizer and Coffey have received approval from the MRHA to carry out clinical trials for AMD using RPE cells derived from SHEF-1 (letter from Paul Whiting, Pfizer Neusentis [**S4**]).

The potential opportunities in Regenerative Medicine, exemplified by the possibility of treating AMD with hESC-derived RPE cells, encouraged Pfizer to establish a new unit and wholly owned subsidiary, Neusentis (evidenced by letter from Pfizer Neusentis [**S4**]). Eventually, Intercytex purchased Axordia for shares valued at £1.68M in 2008 (Intercytex Press Release [**S5**]). In 2009 Intercytex sold Axordia cell lines, including SHEF-1, to Pfizer for $750,000 (Pfizer Press Release [**S6**]). Currently, Pfizer are supporting the clinical trials for AMD using cells derived from a clinical grade SHEF-1 hESC line isolated at Sheffield under contract to Pfizer. As stated in the letter from Pfizer Neusentis:

> "*The hESC line we are using is SHEF1. This was first shown by Professor Andrews (in collaboration with Professor Coffey at the Institute of Ophthalmology) to be capable of differentiating into RPE. Clearly this was critical information to enable the subsequent focus on SHEF-1 as opposed to other hESC lines*."

Thus, this work has had a significant direct commercial impact of several million pounds (purchase of Axordia hESC lines by Intercytex and Pfizer, development of Neusentis, and Pfizer contract work at Sheffield), has influenced commercial decisions of a major pharmaceutical company, and has influenced the emerging field of novel health outcomes via the generation of clinical grade stem cells that will be used in human trials.

b) Commercial development of markers for quality control of hESC

A requirement anticipated for the approval of hESC based regenerative medicine applications is a demonstration, using multiple approaches, that preparations of differentiated cells for transplantation are not contaminated with persisting undifferentiated stem cells. One approach is a demonstration that such preparations do not contain cells expressing specific surface antigens (such as TRA-1-60) defined by the research of Andrews. As stated in the letter from Pfizer Neusentis, [**S4**]:

> "*Professor Andrews' research showed that a cell surface marker known as Tra-1-60 identifies pluripotent stem cells such as hESC. This observation has proven very useful for our cell therapy programme as using an antibody to Tra-1-60 enables us to identify any contaminating hESC in preparations of RPE cells. This purity assay is critical to ensure safety of the therapeutic product, and was a requirement of the UK regulatory agency, the MHRA*"

Following commercial agreement with Andrews, the markers (SSEA3, SSEA4, TRA-1-60, TRA-1-81) for determining stem cell state are now sold under licence from the Wistar Institute (a US biomedical centre) by at least 17 companies, including Life Technologies, who acknowledge the work of the ISCI consortium led by Andrews [**S7**]. The value of these products is commercially sensitive but Andrews has received licence revenue from Wistar [**S8**].

Regulation of the Clinical Use of Stem Cells

The use of stem cells in regenerative medicine is an emerging field in which the regulatory authorities are still developing guidelines. Andrews has contributed to this policy debate by:

a) Informing government policy

Andrews was invited to advise government on hESC research, as an expert witness to the House of Lords Science and Technology regenerative medicine inquiry in 2013 (House of Lords Report [**S9**]).

b) Safety and regulatory approval

Andrews' research led to the recognition by regulatory authorities that genetic change can occur in hESC and that this must be taken into account in safety assessments of hESC-based regenerative medicine. This requirement relates directly to the research performed by Andrews. For example, documentation about the absence of such genetic changes (e.g., gains of chromosomes 17 or 12) was required before the UK government agency, the Medicines and Healthcare products Regulatory Agency (MHRA), provided approval for the planned UCL/Pfizer AMD clinical trial (see letter from Pfizer Neusentis, [**S4**]).

The development of regenerative medicine, particularly based upon hESC, is a national priority of the UK government and research councils. It is recognized that this development requires active commercial investment, which must be underpinned by the strength of the UK research and regulatory environment. Prof Andrews' activities have had considerable impact in the development of policy and in the commercialisation and testing of hESC lines for research and clinical use.

5. Sources to corroborate the impact

S1 Information on Axordia Ltd available at Bioity.com www.bionity.com/en/companies/12384/axordia-ltd.html

S2 **White Rose Technology Seedcorn Fund Press Release. 12 November 2001** '*White Rose investment sees Axordia at cutting edge of stem cell research*'. Provides evidence of the initial investment of £250,000 in Axordia as start-up company 'to extend their leading stem cell research and to develop therapeutic treatments for a range of debilitating diseases'. Available at www.kazwoz.nildram.co.uk/whiterose/new/axordiapress.html

S3 **BioFusion Press Release, 20 January 2006** '*Funding to further advance Axordia's stem cell programmes'*. Provides evidence of further capital investment of £420,000 in Axordia. Available at: www.fusionip.co.uk/wp-content/uploads/2013/09/axordia_financing_release.pdf

S4 **Letter from Professor Paul Whiting, Executive Director Pfizer Regenerative Medicine, Cambridge UK**: provides evidence of the commercial choices made by Pfizer in the choice of SHEF-1 line for clinical trials, the role played by Peter Andrews in their development, and the use of Andrew's markers as part of regulatory requirement by Medicines and Healthcare products Regulatory Agency (MHRA). Cited in text above and available on request.

S5 **Intercytex Purchase of Axordia for £1.68M in 2008**. Evidence of commercial impact of Axordia within REF period. Details available from Bloomberg and Interactive Investor websites at: www.bloomberg.com/apps/news?pid=newsarchive&sid=axLHnX5kJX3g www.iii.co.uk/investment/detail?code=cotn:FIP.L&display=news&it=le&period=2008

S6 **Press releases on Pfizer's collaborative and licensing agreement with Intercytex and its purchase of Intercytex assets in 2009.** Available from: www.evaluategroup.com/Universal/View.aspx?type=Story&id=183892 www.uclb.com/news-and-events/news-post/pfizer-secures-assets-from-intercytex-to-support-ucl-collaborative-research-project

S7 Details of commercial use of antibody markers developed by the Sheffield group in the TaqMan® Array Human Stem Cell Pluripotency Panel marketed by Life Technologies www.lifetechnologies.com/order/catalog/product/4385344

S8 **Commercial licensing agreement** between The Wistar Institute and Andrews. Confidential document relating to the commercial value of the antibody markers developed in Sheffield. Available on request.

S9 **Regenerative Medicine Policy Document:** Andrews gave oral evidence to the House of Lords Science and Technology Committee in Oct/Nov 2012. His evidence is cited in House of Lords Science and Technology Committee Report on Regenerative Medicine, July 2013, available at www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/23.pdf