Institution: University of Sheffield

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

Title of case study: Commercial 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 developed 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 SHEF1 has been developed and approved for clinical trials for treating Age Related Macular Degeneration (AMD). Finally, Sheffield researchers have informed emerging regulatory guidelines about the safety of hESC regenerative medicine applications by authoring reports for government and research councils.

2. Underpinning research

Professor Harry Moore is Co-Director (University of Sheffield 1992-present), with Professor Peter Andrews (University of Sheffield 1992-present), of the Centre for Stem Cell Biology at the University of Sheffield. Moore's research has laid the foundation for the use of hESC in regenerative medicine by identifying cell surface markers that are a pre-requisite for controlling and directing cell differentiation [**R1**]. This approach has led to some of the first hES cell lines in the UK to be deposited in the newly formed UK Stem Cell Bank [**R2**]. Monoclonal antibodies directed against surface antigens are crucially important for production of well-defined pluripotent cell lines with necessary standards for subsequent clinical use [**R2**]. Funded by the MRC (£1.93M, 2008-2013), the Moore group identified the specific culture conditions for clinical grade (GMP) protocols [**R3**], enabling the development of a novel stem cell defined culture medium that did not rely on serum, which would otherwise present a health risk to patients [**R4**]. They were the first to describe the potential for genetic change in hES cells in culture [**R5**], which raises safety issues if proper assessment is not performed and is of critical importance for Medicines and Healthcare Regulatory Authority (MHRA) approval of clinical trials. Subsequently, they were the first laboratory to be licensed by the Human Tissue Authority for the derivation of clinical grade hES lines for use in patient trials. A collaboration with Professor Peter Coffey (firstly at the University of Sheffield, 1989-2003 and then at UCL, 2003-) and Peter Andrews allowed the first observation that pigmented cells of retinal origin (retinal pigmented epithelium) could develop in culture from hES cells (SHEF-1 cell line). This cell type was then fully characterised [R6] for collaborative development (with Pfizer Ltd, Institute of Ophthalmology) of a novel stem cell therapy for age-related macular degeneration, a debilitating condition affecting 25% of the UK population over the age of 70. Proof-of-concept was demonstrated when 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 [**R6**]. This research underpins the potential clinical application of hESC to treat AMD.

3. References to the research

R1. Draper, J.S, Moore, H.D., Ruban, L.N., Gokhale, P.J., Andrews, P.W. (2004) Culture and characterization of human embryonic stem cells. *Stem Cells Dev*. 13, 325-36 doi: 10.1089/scd.2004.13.325

R2. The International Stem Cell Initiative (Corresponding Author, P.W. Andrews), (2007) Characterization of human embryonic stem cell lines by the International Stem Cell Initiative. *Nature Biotech*. 25:803-816. doi: 10.1038/nbt1318

R3. Hewitt, Z.A., Amps, K.J. and Moore, H.D. (2007) Derivation of GMP raw materials for use in regenerative medicine: hESC –based therapies, progress towards clinical application. *Clin. Pharmacology Ther*. 82: 448-452 doi: 10.1038/sj.clpt.6100321

R4. Furue, M.K., Na, J., Jackson, J.P., Okamoto, T., Jones, M., Baker, D., Hata, R.I., Moore, H.D., Sato, J.D., Andrews, P.W. (2008) Heparin promotes the growth of human embryonic stem cells in a defined serum-free medium. *Proc. Natl. Acad. Sci.* USA **105,** 13409-14 doi: 10.1073/pnas.0806136105

R5. Draper J.S. Smith, K., Gokhale, P.J., Moore, H.D., Maltby, E., Johnson, J., Meisner, L., Zwaka, T.P., Thomson, J.A., Andrews P.W. (2004) Karyotypic evolution of human Embryonic Stem (ES) cells in culture: recurrent gain of chromosomes 17 (17q) and 12. *Nature Biotech.* 22: 53-54. doi: 10.1038/nbt922

R6. 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

4. Details of the impact

Commercial investment enabling the Development of Regenerative Medicine

a) Commercial development of clinical grade stem cells

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. To exploit the opportunities created by the first derivation of hESC, Axordia was founded as a spin-out company of the University of Sheffield by Moore and Andrews in 2001. 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 [**S1**: WRTSF Press Release 2001]. In 2006, Axordia secured additional investment of £420,000 from BioFusion Ltd [**S2:** BioFusion Press Release 2006]. 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 [**S3:** evidenced by letter from Pfizer Neusentis]. Intercytex purchased Axordia for shares valued at £1.6M in 2008 [**S4:** Intercytex Press Release]. In 2009, Intercytex sold Axordia cell lines, including SHEF-1, to Pfizer for $750,000 [**S5:** Pfizer Press Release]. Under contract from Pfizer (£165k) [**S6**], Moore subsequently derived and developed a clinical grade stem cell bank (SHEF1.3), which has been approved by the regulatory authorities (MHRA). This cell bank is being used as starting material in a cell-based patient trial for AMD in 2013, supported by Pfizer to be conducted by Professor Peter Coffey at the Institute of Opthalmology, London (www.thelondonproject.org) [**S7**]. 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, 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.

b) 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. Moore has contributed to the development of these guidelines. He served on the MRC working group on the commercialisation of stem cells (2008-

2011), which reported to both the MRC and government [**S8**]. Moore was also a member of the Human Clinical Stem Cell Forum (2009-2012), which informed the Human Tissue Authority, influencing regulatory procedures. The retinal pigment epithelial cell therapy using SHEF1 hESC has UK Regulatory approval to proceed to a clinical trial [**S3**].

5. Sources to corroborate the impact

S1. **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

S2. **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 http://tinyurl.com/k6w9met

S3. **Letter from Executive Director, Pfizer Regenerative Medicine, Cambridge UK**: Provides evidence of the commercial choices made by Pfizer in the choice and approval of SHEF-1 line for clinical trials and the role played by Harry Moore in their development. Cited in text above and on file.

S4. **Intercytex Purchase of Axordia for £1.68M in 2008**. Evidence of commercial impact of Axordia within REF period. Details available from the Interactive Investor website at http://tinyurl.com/o5z56wa.

S5. **Press release on Pfizer's collaborative and licencing agreement with Intercytex and its purchase of Intercytex assets in 2009**. Available from: www.evaluategroup.com/Universal/View.aspx?type=Story&id=183892

S6. **Pfizer contract** to Moore (cited in text and on file).

S7. **Webpage for Moore's contribution to the London project**.

http://www.thelondonproject.org/AboutUs/?id=394

S8. **MRC report** showing the involvement of Moore in the MRC working group on the commercialisation of stem cells. Available at http://tinyurl.com/p3mj86h Page 13