Institution: The University of Edinburgh

Unit of Assessment: UoA5: Biological Sciences

Title of case study:

06. A portfolio of stem cell culture products is sold globally

1. Summary of the impact

Impact on commerce: Five stem cell culture products derived from UoE research have been brought to a global market since 2009 through the US based company StemCells Inc. StemCells Inc strategically acquired Stem Cell Sciences plc (SCS), with its licensed portfolio of UoE patents, to position themselves as a world leader in cell-based medicine. This enabled them to develop media and reagent tools in order to pursue nearer-term commercial opportunities. These products include the gold standard media for embryonic stem cell culture, iSTEM.

Beneficiaries: Commercial companies and users of the stem cell culture products.

Significance and Reach: iSTEM is the gold standard media used worldwide by researchers for maintaining mouse ES cells in their basal, non-differentiated state. Products are sold worldwide through global life sciences companies.

Attribution: All research was carried out at UoE between 1994 and 2006 (published up to 2008), led by Prof Austin Smith. Collaboration with Prof Philip Cohen, University of Dundee, on one paper (2008).

2. Underpinning research

Stem cells are found in all multicellular organisms and are defined as cells that must either self-renew or differentiate into different cell types at each cell division. Embryonic stem (ES) cells are stem cells derived from an early embryo. They are pluripotent, that is, they can differentiate into any type of cell (with the exception of placental cells) and they can self-renew indefinitely. Identifying the factors governing the self-renewal and pluripotency of stem cells is crucial in the understanding of their regulation. The research by Prof Austin Smith and colleagues at UoE into the regulation of these key mechanisms led to new techniques for selecting undifferentiated stem cells and specific differentiated cell-types and also for growing these cells in culture using completely defined media.

The 1994 PNAS paper [1] investigated the activity of possible regulatory molecules in mammalian embryogenesis. A technique for modifying and reporting chromosomal gene expression was developed that allowed visualisation of putative “stem cell niches” in which raised expression of differentiation-inhibiting activity were localised to the differentiated cells. This work led to the filing of a patent known globally as “The Edinburgh patent” (*Isolation, Selection and Propagation of animal transgenic stem cells* - WO1994024274A1).

In 2003, Ying et al. [2] were the first to show that ES cells could be grown in fully defined media in the absence of serum by adding BMP4, which is a bone morphogenetic protein. This showed that BMP4 acts in conjunction with leukaemia inhibitory factor (LIF) to maintain self-renewal and preserve multi-lineage differentiation. Until 2003 differentiation of ES cells *in vitro* was poorly controlled so their use as a developmental model or as a source of defined cell populations was poor. The research established the technique of neural conversion of ES cells by growing them on a monolayer and removing inductive signals for alternative fates [3]. This technique offered a platform for studying the molecular mechanisms required for neural commitment and for optimising neuronal and glial cell production from pluripotent stem cells. The 2005 PLoS Biology paper [4] followed on from this work showing that epidermal growth factor (EGF) and fibroblast growth factor 2 (FGF-2) are sufficient to for derivation and continuous expansion of pure cultures of neural stem cells by symmetrical expansion.

The 2008 Nature paper [5] was a collaboration with Prof Philip Cohen of Dundee University, led by Smith while at UoE. In it, researchers showed that ES cells could be grown without BMP or LIF if inhibitors of the FGF and GSK-3 signalling pathways are added. Although there is still controversy

on how the molecules work , this was a ground-breaking paper and led to the formulation of the gold standard media, iSTEM, for the derivation, maintenance and propagation of ES cells in the 'ground state' of self-renewal.

Buehr et al. successfully captured rat embryonic stem cells, whose culture had eluded researchers for years, in 2008 [6], paving the way for targeted genetic manipulation in the biomedical model species of choice.

Key people: all UoE on the dates stated. Professor Austin Smith (1990-2006); Professor Ian Chambers (1991-present); Research Fellow Meng Li (1992-2006); PDRAs Qi-Long Ying (1999-2006); Mia Buehr (1994-2008); Luciano Conti (2001- 2002 and 2003-2004); Steven Pollard (2002-2006); Peter Mountford (1991-1993). Work published in 2008 (after Smith moved to Cambridge) was carried out whilst at UoE; patents on this work are held by UoE. Key collaborator on [5]: Philip Cohen, Dundee University.

3. References to the research

1. Mountford P., Zevnik B., Duwel A., Nichols J., Li M., Dani C., Robertson M., Chambers I., Smith A. (1994). Dicistronic targeting constructs: Reporters and modifiers of mammalian gene expression, Proc. Natl. Acad. Sci. USA, **91**, 4303-4307. Doi: 10.1073/pnas.91.10.4303
   256 Scopus citations at 19/09/2013
2. Ying Q.-L., Nichols J., Chambers I., Smith A. (2003). BMP induction of Id proteins suppresses differentiation and sustains embryonic stem cell self-renewal in collaboration with STAT3. Cell, **115,** 281-292. doi: 10.1016/S0092-8674(03)00847-X.
   1014 Scopus citations at 19/09/2013
3. Ying Q.-L., Stavridis M., Griffiths D., Li M., Smith A. Conversion of embryonic stem cells into neuroectodermal precursors in adherent monoculture. (2003) Nature Biotechnology, **21,** 183-186. doi: 10.1038/nbt780.
   630 Scopus citations at 19/09/2013
4. Conti L., Pollard S.M., Gorba T., Reitano E., Toselli M., Biella G., Sun Y., Sanzone S., Ying Q.-L., Cattaneo E., Smith A. (2005). Niche-independent symmetrical self-renewal of a mammalian tissue stem cell. PLoS Biology, **3,** 1594-1606. Doi: 10.1371/journal.pbio.0030283
   260 Scopus citations at 19/09/2013
5. Ying Q-L, Wray J, Nichols J, Batlle-Morera L, Doble B, Woodgett J, Cohen P, Smith A. (2008). The ground state of embryonic stem cell self-renewal. Nature, **453**, 519-523. doi: 10.1038/nature06968.
   688 Scopus citations at 19/09/2013
6. Buehr M, Meek S, Blair K, Yang J, Ure J, Silva J, McLay R, Hall J, Ying QL, Smith A. (2008). Capture of authentic embryonic stem cells from rat blastocysts. Cell, **135,** 1287-98. doi: 10.1016/j.cell.2008.12.007.
   287 Scopus citations at 19/09/2013

4. Details of the impact

Impact on commerce: company purchase and products brought to market with licensed IP

Commercially significant products have been developed directly from UoE research since 2008, including the gold standard medium for stem cell culture.

The 1994 PNAS publication [1] led to the filing of a patent for "*Isolation, Selection and Propagation of Animal Transgenic Stem Cells",* known globally as ***"The Edinburgh patent"***. In the same year, former UoE postdoc [text removed for publication] and others established a company called Stem Cell Sciences (SCS) in Australia. UoE entered into a partnership with SCS through a license agreement enabling them to commercialise the intellectual property that arose from our research in Prof Austin Smith's lab. The 'Edinburgh patent' was included in the license agreement and it helped SCS raise capital from investors. In 2004, SCS moved its headquarters to the UK, strengthening the commercial partnership by basing the company in rented laboratory space within the School of Biological Sciences. Commercially-available stem cell reagents and media were developed by SCS based on UoE research over this period. The company relocated to Cambridge in 2008 and was

subsequently sold to StemCells Inc. (StemCells) for 2.65M shares and approximately $715,000 in cash [a].

As a result of the acquisition, licensing agreements between UoE and SCS (which included six further UoE patents arising from work published by UoE [papers 2-6]) passed to StemCells. This included proprietary cell technologies relating to embryonic stem cells, induced pluripotent stem (iPS) cells, and tissue-derived (adult) stem cells all derived from UoE research. As part of the acquisition, StemCells added 20 employees, based in Cambridge, UK or Australia, to the 55 employees already on their payroll.

StemCells brought the media product, **iSTEM** to market in 2009 [b]. iSTEM was developed from the research published in 2008 [5] and covered by the UoE patent (EP1863904 A1). iSTEM is the gold standard media used worldwide by researchers for maintaining mouse ES cells in their basal, non-differentiated state. It eliminates the requirement for LIF, serum and feeder cells and due to the selective small molecule inhibitors that act on the ERK and GSK-3 pathways the media prevents differentiation and enables ground state self-renewal. Marketed and sold by StemCells, iSTEM retails at £170 per 100mls. It is also sold on licence from StemCells by Millipore, the global life-sciences company.

The product **NDiff 227** (marketed as NDiff N2B27 prior to Oct 2012) is a defined, serum-free medium for the neural differentiation of mouse ES cells in adherent monolayer culture conditions, as described in 2003 [3]. NDiff 227 is sold by StemCells and also distributed and sold through Millipore.[c,d]

GS1-R, the first fully defined serum-free culture media for the ground state maintenance of authentic rat ES cells was launched by StemCells in January 2010 [e]. This was developed from knowledge protected by the UoE patent EP2049654 A2, “Pluripotent cells from rat and other species”, published in 2008 [6].

RHB-A media for neural stem cell culture was invented and sold by SCS and now by StemCells [f]. The development of this product was built on UoE IP which derives from the research published in paper [3].

ESGRO-2i is a defined LIF-containing medium to enhance viability of mouse ES and iPS cells and increased maintenance of pluripotency [g], derived from the work in paper [5] and patent EP1863904 A1. ESGRO-2i was developed and sold by Millipore under licence from StemCells.

Details on revenue and profit to StemCells Inc. arising from this portfolio of products are not available due to commercial confidentiality. We can report with StemCells’ permission that income to the UoE from the combined license portfolio is [text removed for publication] during the REF census period, representing only a fraction of the total commercial sales value from these products.

Patents:

- University of Edinburgh (AG Smith, PS Mountford) (1994), *Isolation, Selection and Propagation of animal transgenic stem cells.* “The Edinburgh patent”. Europe, Israel, Japan, New Zealand, USA. WO1994024274A1.
- University of Edinburgh (AG Smith, Ming, Li) (2008?), *Lineage specific cells and progenitor cells*. Israel and USA. Patent EP1115840 B1
- University of Edinburgh (Ian Chambers, AG Smith) (2003), *Pluripotency determining factors and uses thereof*. Europe, Singapore and USA. Patent EP1698639 A3, WO/2003064463 A3, PCT/GB2003/000366.
- University of Edinburgh (L Conti, S Pollard, QL Ying, AG Smith) (2005), *Control of neural stem cells*. Israel, UK, NZ and Singapore. Patent WO/2005/121318, PCT/GB2005/002289
- University of Edinburgh (QL Ying, AG Smith) (2006), *Culture medium containing kinase inhibitor, and use thereof*. UK, Europe and USA. Patent EP1863904 A1, PCT/GB2006/001064
- University of Edinburgh (QL Ying, AG Smith) (2006), *Pluripotent cells from rat and other species*. UK. EP2049654 A2

5. Sources to corroborate the impact

The Tiny URL(s) provide a link to archived web content, which can be accessed if the original web content is no longer available

a) Sale of SCS and transfer of IP portfolio: http://investor.stemcellsinc.com/phoenix.zhtml?c=86230&p=irol-newsArticle&ID=1261348&highlight or http://tinyurl.com/nc5he2r

b) iSTEM media product info: http://www.stemcellsinc.com/Tools-and-Technologies_SC-Proven-Product-Catalog/Cell-Culture-Products/iSTEM or http://tinyurl.com/q8pl2vj

c) NDiff 227 product info: http://www.stemcellsinc.com/Tools-and-Technologies_SC-Proven-Product-Catalog/NDiff-227 or http://tinyurl.com/ofy4yup

d) Stem Cell Inc licensing product to Millipore: http://www.stemcellsinc.com/Tools-and-Technologies/SC-Proven-Products/Millipore.htm or http://tinyurl.com/nk879mb

e) GS1-R product info: http://www.stemcellsinc.com/CatalogueRetrieve.aspx?ProductID=916995&A=SearchResult&SearchID=3441057&ObjectID=916995&ObjectType=27 or http://tinyurl.com/njn34l7

f) RHB-A product info: http://www.stemcellsinc.com/Tools-and-Technologies_SC-Proven-Product-Catalog/RHB-A or http://tinyurl.com/pnukskz

g) ESGRO-2i product info: http://www.millipore.com/catalogue/item/sf016-200 or http://tinyurl.com/ngewpjp