Institution: Durham University

Unit of Assessment: UoA5

Title of case study: Hair follicle tissues and cells for skin and hair replacement and stem cell research and discovery

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

Fundamental research on developmental biology of skin and skin appendages carried out by Prof Colin Jahoda's group has led to progress in the isolation of specific adult cell populations, understanding of their roles in skin and hair regeneration, and advances towards clinical applications. This has led to the development of new methods to replace human hair follicles, and has been the basis for multi-million dollar research and development projects by companies in the UK, the US and Japan. The Durham research has enabled Intercytex Ltd. to attract £27M in VC funding and £30M in an IPO in 2009, progressing to Phase IIa clinical trials. The US company Aderans Research Institute has spent $100 million in developing this "hair cloning" technology. A Durham University spinout company, ClarinnisBio, was also established in 2009, and has to date attracted ca. £1M in investment and has employed two scientists, in a region of the UK that suffers from relatively high levels of unemployment.

2. Underpinning research (indicative maximum 500 words)

The underlying ideas for the hair replacement work, derived from findings from animal models made by Dr Jahoda and his predecessors over many years, that the hair follicle dermal cells were not only capable of participating in and directing new hair follicle regeneration, but also had the capacity to induce completely new follicles. A major advance came in 1999 when the Jahoda group published a paper in Nature (ref. 1) demonstrating that human hair follicle cells were also capable of inducing new follicles in human skin (HAIR TRANSPLANTATION, PCT/GB2000/004177). This led to an upsurge of interest in "hair cloning" with several commercial companies in particular (including Intercytex in the UK and Aderans in the USA), investigating the concept of multiplying follicle cells in culture and then grafting to create an increased numbers of new hair follicles – so called "hair cloning". In further research we showed that by manipulating cultured hair follicle dermal cells to become three-dimensional spheroids that resemble the native structures in the follicle, many key molecular signatures were restored (ref. 2). This led to greater understanding of the molecular expression underpinning human hair follicle induction, and we have shown that it gives the cells greater potential to make new follicles when grafted. This work is the subject of a joint patent application between Durham and Columbia University, USA (20100303767 - METHODS FOR COMPACT AGGREGATION OF DERMAL CELLS). As a follow on to this idea, with support from the BBSRC, Prof. Jahoda has developed more complex double spheroid organotypic structures in culture. These structures can be created from skin or hair follicle cells, and have the capacity to be used as proto-organs in grafting, either in isolation or as components of larger skin equivalents. This work is the subject of another patent application (WO/2013/014435 - MICRO ORGAN COMPRISING MESENCHYMAL AND EPITHELIAL CELLS). Proof of principle that using cultured hair follicle dermal cells to create 3 dimensional spheres makes it possible to induce entirely new human hair follicles in human skin has been published in PNAS (ref. 3)

In relation to the skin model/skin replacement concept, it has long been recognized that hair follicle epithelial stem cells make an important contribution to skin wounding. Based on direct observations from animal studies and scrutiny of the literature Jahoda proposed that follicle dermal cells might play a parallel in the skin dermis, and published a hypothesis paper outlining this idea (ref. 4). A worldwide patent was granted based on the use of hair follicle dermal sheath cells in wound healing (DERMAL SHEATH TISSUE IN WOUND HEALING, PCT/GB1998/001080).

One focus of the work has been to incorporate hair follicle dermal cells into existing skin equivalent models with the aim of creating more realistic and effective replacement dermal grafts (ref. 5). The other has been the development of new simpler in vitro human skin models (ref. 6) for research purposes and for and drug and molecular testing. A grant has also been obtained during the REF period (from the charity DEBRA) to provide preclinical evidence that the hair follicle dermal cells could be used therapeutically for treating the blistering disease recessive dystrophic epidermolysis bullosa (RDEB).

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

. Reynolds, A.J., Lawrence, C., Cserhalmi-Friedman, P.B., Christiano, A.M. and **Jahoda C.A.B.** (1999) Trans-gender induction of hair follicles. Nature 402, 33-34.
2. Higgins CA, Richardson GD, Ferdinando D, Westgate GE, **Jahoda CA**. (2010) Modelling the hair follicle dermal papilla using spheroid cell cultures. Exp Dermatol. 19(6):546-48.
3. Higgins C.A., Chen J.C., Cerise J.E., **Jahoda C.A.B.*** and Christiano A.M.* Microenvironmental reprogramming by three dimensional culture enables dermal papilla cells to induce de novo human hair-follicle growth. PNAS, e pub. October 2013. (*joint corresponding authors)
4. **Jahoda, C.A.B.** and Reynolds, A.J. (2001) Hair follicle dermal sheath cells – unsung participants in wound healing. Lancet. 358, 1445-1448.
5. Gharzi, A., Reynolds A.J. and **Jahoda, C.A.B**. (2003) Plasticity of hair follicle dermal cells in wound healing and induction. Exp. Dermatol. 12, 126-136.
6. Guo A, **Jahoda CA** (2009) An improved method of human keratinocyte culture from skin explants: cell expansion is linked to markers of activated progenitor cells. Exp Dermatol. 18(8):720-26.

Grants

BBSRC – January 2009, £98,693 Innovative methodologies developing the commercialisation potential of human hair follicle induction.
MRC – October 2011, £454,037, Hair follicle induction by cultured human hair
BRITISH SKIN FOUNDATION – March 2007, £59,969, Hair follicle-derived dermal stem cells.
DEBRA – June 2011, £134,743, Transplantation of Hair Follicle Dermal Cells
DTI (then TSB) – May 2006, £199,708, Process development and scale up of a novel wound healing product using dermal stem cells
RegeNer8 – December 2010, £14,877, Isolation, characterization and scale up culture of new dermal cell subpopulation for wound healing and cell therapies

Esteem

International interest in this research is supported by multiple invitations to present plenary and keynote lectures at international conferences, the most recent being a plenary lecture at the International Hair Research Society meeting in Edinburgh in 2013, and the Norwood lecture at the International Society of Hair Restoration Surgery's (ISHRS) 21st Annual Scientific Meeting in San Francisco, California, USA (October 2013).

Presented with the John Ebling Award for outstanding contribution to hair research.

Invited Professor, Université Joseph Fourier, Grenoble, France.

Winner of the BioNEt Award sponsored by Sanofi-Aventis. Professor Colin Jahoda was awarded this new discretionary award for 2008 for his research work at Durham University. The BioNET

Award recognises excellence in translational research and the pioneering work being carried out in both the private and public sectors throughout the region. BioNEt is the North East of England's leading network for research scientists and is the major platform for sharing ideas and developments in the health, healthcare and life sciences sector.

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

From the hair induction work, the impact has come indirectly from commercial enterprises taking forward the ideas established by the primary research at Durham. In the UK this was exemplified by Intercytex, a company founded in Manchester and relaunched in 2010. This company, listed on the AIM, was the recipient of venture capital funding and a large TSB grant for a robot to culture human hair follicle dermal cells. The Durham research has enabled Intercytex Ltd. to attract £27M in VC funding and £30M in an IPO in 2009. In the USA the company Bosley (now acquired by Aderans) has spent ca. $100 million in developing this “hair cloning” technology (Letter from the Chief Scientific Officer of Aderans Research Institute, Inc.). Both of these companies initiated clinical trials of the process during the REF period. Interestingly the US company has been using a UK company Angel Biotechnology to grow their cells to GMP levels. Numerous other companies and hair transplant clinics worldwide have adopted or tried to adopt variations on the “hair cloning” technique (see supporting letter from the founder of Intercytex).

One of the potential difficulties in using hair follicle cells in a translational context is their relatively low numbers. This was addressed in TSB-sponsored collaboration between Durham University, the NorthEast regional agency CELS, and two industrial companies Avecia and Smith & Nephew. In this project Avecia demonstrated the feasibility of scale-up culturing of human hair follicle dermal cells to numbers sufficient for translational use. The cell processing project carried out in association with Avecia was instrumental/helpful in helping Avecia (now Fujifilm Diosynth Biotechnologies) introduce mammalian cell culture work at their facility, having previously worked exclusively on non-mammalian systems. This includes the building of a new cGMP facility for manufacturing mammalian products, the total investment at the mammalian site being $25M. The company gained know-how and intellectual property (including patents) that now supports their business strategy in this area. This has therefore changed the way in which the company works, and consequently they have improved their working practices (standard operating procedures) and developed new products during the REF period (see supporting letter from the Director of Science and Technology, Fujifilm Diaosynth Biotechnologies).

Recent impact is the creation of ClarinnisBio, a Durham University spinout company. The Company was founded in 2009 by Dr Jahoda, and has raised funding from the TSB, The Three Pillars fund and Regener8 to the value of ca. £2 M. These funds have used to support research and development work, with 2 staff being employed indirectly at Durham University, contracted by the company. This supports the regional agenda of creating and retaining jobs, particularly in new high technology industries, in a region of the UK with relatively high levels of unemployment. This incorporated patents on the use of hair follicle dermal cells from prior work, and has established a new patent portfolio (MICRO ORGAN COMPRISING MESENCHYMAL AND EPITHELIAL CELLS, PCT/GB2012/051759).

5. Sources to corroborate the impact (indicative maximum of 10 references)

Testimonials:

Letter from the founder of Intercytex providing testimony to the importance of the research to the

founding of the company.
Letter from the MD/Vice President of Research and Chief Scientific Officer of Aderans Research Institute, Inc., who has 30 years of expertise in hair follicle biology. He had a 20 year distinguished academic career as a Professor of Pathology and Dermatology at the Yale University School of Medicine and Dr. Stenn spent 10 years as Director of Skin Biology at Johnson & Johnson. He served as a Scientific Advisory Board Member at Follica, Inc. This letter describes the impact that the Jahoda lab research has had on the R and D of skin and hair regeneration by the Aderans company, and on the field in general.

Letter from the Director Science and Technology, Fujifilm Diosynth Biotechnologies. This letter outlines the collaboration between the Jahoda lab and the company for their standard operating procedures for stems cells/cell therapy products and supporting the expansion of mammalian cell culture R and D and cGMP facility at their Billingham site.

Preparation and publication of intellectual property (copies of patents):
WO/2013/014435 - MICRO ORGAN COMPRISING MESENCHYMAL AND EPITHELIAL CELLS. PCT/GB2012/051759
WO/2011/015862 - CELL SUPPORT COMPRISING DERMAL FIBROBLASTS PCT/GB2010/051278
20100303767 - METHODS FOR COMPACT AGGREGATION OF DERMAL CELLS
WO/2001/032840 - HAIR TRANSPLANTATION - PCT/GB2000/004177
WO/1998/048860 - DERMAL SHEATH TISSUE IN WOUND HEALING PCT/GB1998/001080

Creation of a spin out Company:
ClarinnisBio (http://www.cylex-uk.co.uk/company/clarinnisbio-ltd-22394034.html)

Breadth of Interest:
Worldwide interest in “hair cloning” amongst the general public who see it as a future means of treating hair loss - around 3,800,000 results from a Google search on the internet, high profile publicity on BBC and Sky news (October 21-23 2013). Numerous blogs, websites, discussion groups and information from company publicity.