Institution: University of Leeds

Unit of Assessment: 12

Title of case study 1: Development and commercialisation of dCELL® Regenerative Biological Scaffolds for soft tissue repair

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

Novel biological scaffolds that regenerate with the patient's own cells have been researched, and patented and since 2008 developed, taken through successful clinical trials and commercialised. Economic impact within the REF period has been delivered through the University of Leeds spinout company Tissue Regenix plc, which has received £32M private investment, employs 35 people and is AIM listed, with a capital value of £70M. Health impact has been delivered through licensing and development by NHS Blood & Transplant Tissue Services. The biological scaffolds have demonstrated five years' successful clinical use in heart valve replacement and three years' clinical use as a commercial vascular patch.

2. Underpinning research (indicative maximum 500 words)

This case study is underpinned by multidisciplinary research led by Professor J. **Fisher** in this UoA and Professor E. Ingham of UOA 5 at the University of Leeds. **Fisher** led the bioengineering aspects of the research and is Principal Investigator on the grants (i)-(xi) listed in section 3.

Before 2000, soft tissue repair and replacement primarily involved the use of synthetic biomaterials, chemically cross-linked and inert bioprosthetic devices, autograft or allogeneic donor tissues. Although these approaches are still used extensively, they all have limitations.

Research in this area at the University of Leeds started in 2000. The initial aim was to test the hypothesis that it was possible to develop a regenerative biological scaffold, which, upon implantation, would regenerate with the patient's own cells and provide tissue-specific, multi-scale physical architecture. The objective was to develop a scaffold to provide multi-scale biomechanical properties and function at the macroscopic and cellular levels to support physiological function. The scaffolds are designed to transform macro-scale physiological forces to appropriate tissue specific micro-(cellular)-level strains to drive appropriate cell differentiation.

The approach taken was to re-engineer native tissues through the development of biochemical processes that removed the cells, cell fragments and DNA to make them immunologically compatible without compromising the tissue structure and architecture. The unique processes created acellular biological scaffolds that retained the biomechanical function and properties of the native tissue. The novelty of the process was its use of very low concentrations of a detergent (sodium dodecyl sulphate) and proteinase inhibitors in order to protect and maintain the properties of the extracellular tissue matrix, coupled with a complete wash-out of residual chemicals. The multidisciplinary research expertise of the team enabled evaluation of both the biomechanical and biological properties of the resultant regenerative scaffolds.

The initial scientific investigations in 2002 focused on heart valve tissue, which comprises of a complex three-dimensional structure of thin membranes [1, 2]. The research was funded by a local charity (grant i), with clinical collaborators K. Watterson, Cardiac Surgeon at the Leeds Teaching Hospitals Trust, and J. Kearney of NHS Blood & Transplant Tissue Services.

Following the initial proof of scientific principle on heart valves, research was then pursued with the backing of substantial EPSRC funding, including a prestigious Portfolio Partnership Award for work on tissue replacement and regeneration (grant iii). The research focused on cardiovascular and musculoskeletal tissues and involved:

- Investigation of the functional biomechanics in 2005 [3] and recellularisation of scaffolds for heart valve applications
- The development of a bioprocess that allowed the development of the dCELL® vascular patch [4] in 2006
- The development of further bioprocesses and the dCELL® biological scaffolds for ligament and meniscus repair [5, 6] in 2007 and 2008.

The excellence of this research has been recognised by several external awards: **Fisher** and Ingham, ERC Advanced Award (grant xi); **Fisher**, CBE for services to Biomedical Engineering (2011); and the Queen's Anniversary Prize for Higher and Further Education to the University of Leeds, for its contribution to medical engineering.

Research Team
Professor J. **Fisher**, Professor of Mechanical Engineering, 1990-present.
Professor E. Ingham (UoA5), Professor of Medical Immunology, 1990-present.
Fisher and Ingham have been supported by a team of research staff and PhD students.

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

1. Booth C, Korossis SA, Wilcox HE, Watterson KG, Kearney JN, **Fisher** J, Ingham E. Tissue engineering of cardiac valve prostheses I: Development and histological characterisation of an acellular porcine scaffold. Journal of Heart Valve Disease, 11; 457-462 (2002), PubMed ID: 12150290.
2. Korossis S, Booth C, Wilcox HE, Ingham E, Kearney JN, Watterson KG, **Fisher** J. Tissue engineering a cardiac valve prosthesis II: Biomechanical characterisation of decellularised porcine heart valves. Journal of Heart Valve Disease 11; 463-471 (2002), PubMed ID: 12150291.
3. Korossis S, Wilcox HE, Watterson KG, Kearney JN, Ingham E, **Fisher** J. In vitro assessment of the functional performance of the decellularised intact porcine aortic root. The Journal of Heart Valve Disease 14; 408-422 (2005), PubMed ID: 15974537.
4. Mirsadraee S, Wilcox HE, Korossis KA, Kearney JN, Watterson KG, **Fisher** J, Ingham E. Development and characterization of an acellular human pericardial matrix for tissue engineering. Tissue Engineering, 12; 763-773 (2006), DOI:10.1089/ten.2006.12.763.
5. Ingram JH, Korossis S, Howling G, **Fisher** J, Ingham E. The use of ultrasonication to aid recellularization of acellular natural tissue scaffolds for use in anterior cruciate ligament reconstruction. Tissue Engineering, 13; 1561-1572 (2007), DOI: 10.1089/ten.2006.0362.
6. Stapleton TW, Ingram J, Katta J, Knight R, Korossis S, **Fisher** J, Ingham E. Development and characterization of an acellular porcine medial meniscus for use in tissue engineering. Tissue Engineering Part A 14; 505-518 (2008), DOI: 10.1089/tea.2007.0233.

All of the above journals are internationally recognised with rigorous review processes and international editorial boards. The quality of the underpinning research being at least 2* is demonstrated by references 2, 5 and 6.

Underpinning Research Grants (with Fisher as PI)

i) Fisher and Ingham. Children`s Heart Surgery Fund Leeds Tissue engineering heart valves,. 2000- 2003; £248K.
ii) Fisher and Ingham. Ultrasonic modification of soft tissue matrices for enhanced recellularisation EPSRC GR 59489/01; 2002-2003; £90K.
iii) Fisher and Ingham Portfolio Partnership; Tissue Replacement and Regeneration; EPSRC GRS 63892/0; 2003-2008; £2.2M.
iv) Fisher, J. & Ingham, E. Development of small and medium diameter vascular grafts Department of Health [HTD 430]; £421K ,01/10/07-30/09/10
v) Fisher, J., Ingham, E. *et al*. DTC Tissue Engineering & Regeneration. EPSRC; £6M 1/10/08-30/09/2015.
vi) Fisher, J., Ingham, E. *et al.* Functional Tissue replacement and substitution: Platform Grant. EPSRC EPF0438721; £816K, 1/10/08-30/09/13
vii) Fisher, J. NIHR Senior Investigator Award. £60K, 4 years 01/06/08-30/05/12.
viii) Fisher,J., Ingham, E. *et al*. Programme Grant: Biotribology of cartilage and cartilage substitution EPSRC EPG01121721, £5.2M 01/01/09-01/01/14
ix) Fisher, J., Ingham, E. *et al*. Centre of Excellence in Medical Engineering WELMEC, Wellcome Trust and EPSRC, WT088908/z/09/z, £11.2M; five years 01/10/09-30/09/2014
x) Fisher, J., Ingham, E. *et al.* Innovation and Knowledge Centre. Regenerative Therapies and Devices. EPSRC; EP G0324831, EPI0191031, EPJ0176201 £10M, 01/10/09-01/10/14.

xi) Fisher, J., Ingham, E. Re-engineering and regenerating the knee. EU ERC Advanced Investigator Award; €3M (€1.5M to this UoA, ref. 267114); five years 01/04/11-31/03/16.

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

Two strategic research challenges were identified for the research at Leeds in 2000:

- To create regenerative biological scaffolds for cardiovascular tissue repairs such as heart valves and cardiovascular patches;
- To create regenerative biological scaffolds for the repair of thicker, three-dimensional musculoskeletal soft tissue such as ligaments, tendons and menisci.

The unique approach taken at Leeds has generated tissue-specific biological scaffolds and patents for each tissue repair application. This contrasts with previous commercial biological scaffold approaches that developed a single scaffold material with one set of properties and applied it to many different applications. Failure to match site- and tissue-specific properties can result in suboptimal physical performance and regenerative response.

The commercial impact within the REF period has been enabled by protecting the IP generated through the underpinning research in a number of patents. The first patent [A] protected the basic process and demonstrated its application in heart valves and pericardium. The patent was filed prior to publication of the original research [1, 2] and is supported by further research [3]. The second patent [B] protected processes for biological scaffolds for ligament regeneration and is supported by the research at Leeds [5]. The third patent family [C] described biological scaffolds for meniscus regeneration and is supported by the research at Leeds [6]. The patents are owned and sustained by the University of Leeds and have been licensed to Tissue Regenix plc for commercial use and NHS Blood & Transplant Tissue Services for use on allograft tissue within the NHS in the UK [A,B,C].

Economic impact

The University of Leeds spinout company Tissue Regenix was incorporated in 2006. **Fisher** was founding chairman and Ingham was founding director. The corroborating statement [F], together with sources [D] and [E], confirms that the impacts of the underpinning research, the patents and the IP licensed to the company during the REF period has been as follows. The original patent families were licensed into the company and first-round investment was secured from IP Group in early 2007. Second-round investment was secured in 2008 to support development and manufacture of the first commercial product. A full-time chief executive and new company chairman were appointed to lead commercialisation and take the company to the market. Clinical trials were undertaken in 2009 on the first commercial product, the dCELL® Vascular Patch, which was CE marked as a Class III medical device and launched as a commercial product in autumn 2010 [D]. The company was floated on the Alternative Investment Market (AIM) as Tissue Regenix Group (TRG) in 2010 and, in 2012, raised further funds (£25M) to support development of a wider range of commercial products for cardiovascular and musculoskeletal applications. TRG`s market CAP, at a share price of 11p, is £70M (2012 valuation) and it is investing over £32M of private capital in new product development, currently employing 35 people [D,E,F]. The University of Leeds is a shareholder and investor in TRG. **Fisher** and Ingham are shareholders and scientific advisers to the company.

The dCELL® Vascular Patch is now sold throughout Europe [E]. A second commercial product, the dCELL® Meniscal Repair device, is being developed, with clinical trials planned for 2014 [F]. A third commercial product, a biological scaffold for ligament repair, is now in commercial development. The University continues to collaborate with the company and supports commercial development of products through its Innovation and Knowledge Centre in Medical Technologies-Regenerative Therapies and Devices (IKCRTD, grant x).

The University has contributed highly skilled personnel to Tissue Regenix Group, with Leeds PDRA Graindorge employed as chief operating officer and Leeds PDRA Berry, *née* Wilcox, working as the company's chief scientist (co-author on [1,2,3,4]).

Health impact.

Statement [F] confirms that the dCELL® Vascular Patch has completed a successful clinical trial, been CE marked and is bringing benefits to patients undergoing endarterectomies for peripheral vascular disease [6]. Source [G] confirms that clinical studies using the technology have been reported for heart valve replacement by the researcher collaborators in Brazil, with improved outcomes at four years for pulmonary valve replacements.

Statement [H] confirms that NHS Blood & Transplant Tissue Services has licensed the technology for creating biological scaffolds from allogeneic tissues. They are currently undertaking clinical studies on an acellular biological scaffold for dermal repair, with initial results already reported, and are investing in collaborative development projects on cardiac patches, acellular heart valves, acellular vascular grafts and acellular ligaments supported by translation projects through IKCRTD.

5. Sources to corroborate the impact (indicative maximum of 10 references) (Please refer to the extract from the Guidance on Submissions reproduced below and provide contact details separately as necessary)

A. Fisher J, Ingham E, Booth C. Decellularisation of tissue implant material. UK Patent Application GB 2375771 A (2002).
B. Ingham E, Fisher J. Ultrasonic modification of soft tissue matrices. International Patent Application PCT/GB2004/002055, 2004. International publication number WO 2004/103461.
C. Ingham E, Fisher J, Stapleton T, Ingram J. Preparation of tissue for meniscal implantation. Patent Application PCT/GB2007/004349, 2008. International publication number WO 2008/059244 A3.
D. www.tissueregenix.com (accessed December 2012)
E. www.tissueregenix.com/investor-information/share-price (accessed December 2012)
F. Individual written corroboration from Managing Director, Tissue Regenix, on the influence that this UoA's research has had on the development of Tissue Regenix Group.
G. da Costa FDA, Santos LR, Collatusso C, Ingham, E. Thirteen years` experience with the Ross operation. Journal of Heart Valve Disease. **18; 84-94 (2009), PubMed ID: 19301558.**
H. Individual written corroboration from Head of R&D NHS Blood and Transplant Tissue Services on the influence that his UoA's research has had on the development of tissue products for patient use in the NHS.