Institution: University of Leeds		
Unit of Assessment: 12		
Title of case study: Acellular Biological Scaffolds for Tissue Repair and Regeneration		
Period when the underpinning research was undertaken: 2001–2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
John Fisher	Professor	01/08/1993 – date
Sophie Williams	Research Officer, Research Fellow, University Research Fellow, Senior Lecturer, Associate Professor, Professor	01/10/2002 – date
Sotiris A Korossis	Research Assistant/Fellow, EPSRC Advanced Fellow	01/10/2001 – 31/01/2012
Jayanth Katta	Research Fellow	01/01/2008 – 05/12/2008
Abdellatif Abdelgaied	Research Fellow	01/07/2012 – 31/07/2019
Serena Russell	Research Assistant, Wellcome Trust Fellow	01/04/2010 – 30/09/2014
Martin Stanley	Research Assistant, Research Fellow	01/01/2011 – 31/12/2015
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? No		

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

Since 2014, University of Leeds spinout Tissue Regenix has established new manufacturing facilities in Leeds (UK), in Texas (USA), and a Joint Venture Agreement with GTM-V tissue bank Rostock (Germany). Company revenues have grown from zero in 2013 to £11.6M in 2018, together with an increase in the number of people employed from 35 in 2013 to over 100 in 2017. Over this period Tissue Regenix has increased commercial sales of wound care product DermaPure™ in USA and Europe, completed clinical trials of OrthoPureXT™ ligaments, and progressed the development of CardioPure™ dCELL® heart valves. Furthermore, NHS Blood and Transplant have developed, manufactured and successfully translated the dCELL® acellular dermis for chronic wound repair as clinical products supplied within the NHS in the UK.

2. Underpinning research (indicative maximum 500 words)

Original multidisciplinary research on acellular biological scaffolds, led jointly by Professor John **Fisher** in the School of Mechanical Engineering and Professor Eileen Ingham (UoA 5) at the University of Leeds, investigated the creation of tissue specific acellular biological scaffolds that could regenerate with the patient's own autologous cells. **Williams**, and prior to leaving the University, **Korossis**, **Katta**, **Abdelgaied**, **Russell**, and **Stanley**, contributed to the original research as part of **Fisher**'s research group.

The initial discovery, original publications and patent in 2001–2002 [1, 2, 7] defined unique bioprocesses that could remove cells and DNA from animal and human tissue, including cardiovascular tissues, heart valves and dermis, while leaving the collagen and elastin structures (the scaffold) intact. This allowed the form, structure and specific properties of the individual native tissue types to be retained, whilst creating an immunocompatible biological scaffold that

could be repopulated with the patient's own host cells. The engineering researchers worked collaboratively with biologists to develop the decellularisation process and to evaluate and modify the process to optimise the physical properties and biomechanical function of the acellular biological scaffolds to closely match the properties and biomechanical function of the native host tissue that the scaffold was replacing.

This research programme has progressed as a platform technology over the last 18 years to create novel, tissue specific biological scaffolds for regeneration of heart valves, dermis, vascular patches and blood vessels, meniscus, ligaments and tendons, bone and cartilage [1–6]. The distinctiveness of our tissue specific acellular biological scaffolds, which are derived from either animal or human tissue, is that they create a tissue (or site) specific scaffold with the appropriate multiscale architecture, physical properties, structure and function—mimicking that of the target host site tissue. This provides the correct multiscale environment for repopulation by host cells, to deliver the appropriate biological and mechanical stimuli and cues to support site/tissue specific cell differentiation, constructive tissue remodelling, regeneration and repair by natural processes. This site specificity cannot be achieved with synthetic scaffolds or with alternative generic biological scaffolds applied to multiple different sites.

Following successful research and development of thin membrane-like scaffolds, our research progressed to focus on thicker structural soft tissue applications for musculoskeletal repair. New bioprocesses were patented and published to produce acellular biological scaffolds derived from ligament and tendon tissue in 2004 [3], and then subsequently meniscus tissue in 2008 [4, 5].

Many musculoskeletal tissue structures comprise combinations of bone and soft tissue (cartilage, ligaments, tendons). Since 2010 we have further advanced the work to develop, evaluate, patent and publish novel bioprocesses for creating composite hard/soft tissue acellular scaffolds for applications such as bone ligament constructs or osteochondral grafts [6].

The University has continued to support new product development through collaborative research on acellular scaffolds led by **Fisher** and Ingham, with continuous funding from EPSRC from 2003 to the present day (see EPSRC 'Grants on Web'), with additional support from the ERC (Advanced Grant), the Wellcome Trust, and the NIHR.

Recognition to Professor John Fisher:

- CBE for Services to Medical Engineering 2012
- UK Biomaterials Society President's Prize 2013
- European Inventor of the Year Nominee 2018
- IoM^3 Chapman Medal 2019

Recognition to Professor John Fisher's Institute of Medical and Biological Engineering:

- Queen's Anniversary Prize for Higher Education 2011

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

[1] Booth C, Korossis SA, Wilcox HE, Watterson KG, Kearney JN, Fisher J, and 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). https://pubmed.ncbi.nlm.nih.gov/12150290

[2] Korossis S, Booth C, Wilcox HE, Ingham E, Kearney JN, Watterson KG, and 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). https://pubmed.ncbi.nlm.nih.gov/12150291

[3] Ingram JH, Korossis S, Howling G, Fisher J, and 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). https://doi.org/10.1089/ten.2006.0362

[4] Stapleton TW, Ingram J, Katta J, Knight R, Korossis S, Fisher J, and Ingham E. Development and characterization of an acellular porcine medial meniscus for use in tissue engineering. *Tissue Engineering Part A* 14, 505–518 (2008). https://doi.org/10.1089/tea.2007.0233

[5] Abdelgaied A, Stanley M, Galfe M, Berry H, Ingham E, and Fisher J. Comparison of the biomechanical tensile and compressive properties of decellularised and natural porcine meniscus. *Journal of Biomechanics* 48, 1389–1396 (2015). https://doi.org/10.1016/j.jbiomech.2015.02.044

[6] Fermor HL, Russell SL, Williams S, Fisher J, and Ingham E. Development and characterisation of a decellularised bovine osteochondral biomaterial for cartilage repair. *Journal of Materials Science: Materials in Medicine* 26(5), 186 (2015). https://doi.org/10.1007/s10856-015-5517-0

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 all six references.

Underpinning patents licensed by the University and subsequently assigned to Tissue Regenix to enable development of the dCell technology and new products:

[7] Fisher J, Ingham E, and Booth C. Decellularisation of tissue implant material. UK Patent GB2375771A (2001). https://patentscope.wipo.int/search/en/detail.jsf?docId=GB134969187

[8] Ingham E, Fisher J, Stapleton T, and Ingram J. Preparation of Tissue for Meniscal Implantation. International Application Number PCT/GB2007/004349 (2008). Publication number WO 2008/059244 A3. https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2008059244

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

The underpinning research described in Section 2 has been translated through: 1. strategic collaboration with NHS Blood and Transplant (Tissue and Eye Services) (NHSBT); and, 2. through formation of University spin out company Tissue Regenix PLC.

1. Patents were filed by the University, with university academic and research staff named as inventors [7, 8]. NHSBT were granted a licence in 2006 to use the patented processes to generate acellular scaffolds (as human tissue products) for supply into the NHS in the UK. We have collaborated closely with NHSBT to further develop and manufacture acellular human tissue scaffolds for supply into the NHS (2006 to 2020) including acellular dermis for wound care, heart valve grafts and bone tendon bone grafts for ligament regeneration.

2. To commercialise the creation of acellular biological scaffolds derived from animal tissues as class three medical devices, and to develop and commercialise the processing of acellular biological scaffolds derived from human tissue outside of the UK, the University of Leeds spin out company Tissue Regenix was incorporated in 2006. **Fisher** was founding chairman and

Ingham was founding director. The original patent families for the dCELL® technology [7,8] were licensed into the company and first-round investment was secured from IP Group in 2007. Second-round investment was secured in 2008 to support development of the first commercial product. 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 and manufacture of a wider range of commercial products for cardiovascular and musculoskeletal applications.

Tissue Regenix has grown significantly during the REF2021 period, supported by further fund raising and investments to develop and grow the business reported since 2013 [A, B, C, D]. At the end of 2013, revenues from sales had not yet been established [A] but by 2017, Tissue Regenix had achieved sales revenues of £5.2M [B, D] and by 2018, Tissue Regenix had achieved sales revenues of £11.6M with a (proforma) growth of 47% during 2018 [D]. The dCELL® technology product portfolio based on University of Leeds research IP and patents includes the wound care product DermaPure™, launched in the USA in 2014 [A], which achieved £3.4M sales in 2018, together with products SurgiPure™, CardioPure™, and OrthoPure™. Successful clinical trials of the OrthoPure™ ligament repair system have now been completed in Europe. Heart valves (CardioPure™) have been developed and manufactured in Europe. The number of people employed by Tissue Regenix has grown from 35 in 2013 to over 100 in 2017 [B].

Tissue Regenix established new manufacturing facilities in Leeds in 2015 [C]. Responsible for all porcine tissue manufacturing, this facility produces SurgiPure™ (surgical patch for internal soft tissue repair) for export to the US, and also OrthoPure™ (for ligament repair). This facility also acts as the corporate headquarters and research and development hub for future dCELL® applications. In January 2016, Tissue Regenix entered into a Joint Venture Agreement, forming a partnership with the GBM-V tissue bank in Rostock, Germany, granting for the first time a dCELL® human tissue licence (2016) [C]. GBM-V revenues reached £1.8M in 2018 [D]. In August 2017, Tissue Regenix acquired CellRight Technologies® (a US Food & Drug Administration accredited facility in University City, San Antonio) [B], which enabled expansion of DermaPure™ manufacture and sales in the USA [B]. Following this acquisition, it is difficult to attribute commercial growth and impact exclusively to original University of Leeds research and IP, and so reference is not made to the 2019 Annual Report.

NHS Blood and Transplant (Tissue and Eye Services) (NHSBT) have developed, manufactured and successfully translated dCELL® acellular dermis for chronic wound repair (2014 to 2020) and, following completion of our collaborative research, are developing manufacturing processes for acellular bone patellar on grafts for ligament repair (2017 to 2020), based on the underpinning patents licensed from the University of Leeds. Following a successful clinical study (*Wound Repair and Regeneration* 21, 813–822 (2013), https://doi.org/10.1111/wrr.12113), NHSBT now routinely supply dCell® Human Dermis for treatment of chronic wounds. Details of the dCell® Human Dermis product range, case studies and clinical trial results are available on the NHSBT website [E]. The dCell® Human Dermis graft fully integrates into the wound bed replacing the lost dermis.

Overall wider patient and societal benefits: the dCELL® technology portfolio removes DNA and other cellular material from tissue leaving intact an acellular matrix (biological scaffold) that can be colonised by a patient's own cells, creating a positive environment for tissue regeneration. The potential applications of dCELL® are diverse and address critical clinical

needs in wound care, heart valve replacement, and knee repair. Patients receiving acellular scaffolds benefit from improved tissue repair and regeneration and outcomes [F].

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

[A] Tissue Regenix Annual Report for the year ended 31 January 2014. https://s3-eu-west-1.amazonaws.com/tissue-regenix/report-and-accounts-2014.pdf

[B] Tissue Regenix Annual Report for the year ended 31 December 2017. https://s3-eu-west-1.amazonaws.com/tissue-regenix/Tissue-Regenix-AR-2017-webready.pdf

[C] Tissue Regenix Annual Report for the year ended 31 January 2016. https://s3-eu-west-1.amazonaws.com/tissue-regenix/Tissue-Regenix-AR2016-web-ready.pdf

[D] Tissue Regenix Annual Report for the year ended 31 January 2018. https://www.tissueregenix.com/media/2228/tissue-regenix-ar-2018-web-ready.pdf

[E] NHS Blood and Transplant, dCELL® Human Dermis https://www.nhsbt.nhs.uk/tissue-and-eye-services/products/skin/dcell-human-dermis/, accessed 21 January 2021.

[F] da Costa FDA, Etnel JRG, Charitos EI, Sievers HH, Stierle U, Fornazari D, Takkenberg JJM, Bogers AJJC, and Mokhles MM. Decellularised versus standard pulmonary allografts in the Ross procedure: propensity matched analysis. *The Annals of Thoracic Surgery* 105, 1205–1213 (2018). https://doi.org/10.1016/j.athoracsur.2017.09.057