Institution: Keele University

Unit of Assessment: B15 General Engineering

Title of case study: Biological and Cell Therapies in Orthopaedics - Autologous Chondrocyte and Mesenchymal Stem Cell Implantation

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

A multidisciplinary team has worked in applied cell engineering implementing cell therapy and biological approaches in clinical practice since 1997. The team has two GMP accredited laboratories in hospital sites and a MHRA manufacturing license for chondrocytes and stromal /stem cells for delivery to patients in orthopaedic clinical trials. The research had impacts on health, economy, public policy and practitioners. Over 400 cartilage patients and over 150,000 knee ligament patients have benefited directly from the research, and associated turnover is over £40,000,000. Team members had influence on government, NICE and professional guidelines.

2. Underpinning research (indicative maximum 500 words)

With ageing and disease, many musculoskeletal tissues lose the ability to regenerate and repair, resulting in impaired function and severe pain. Cartilage deterioration and the development of osteoarthritis form a pervasive and expensive medical problem. According to the OECD, 10% of men and 18% of women over 60 have symptomatic osteoarthritis worldwide. Each year in the OECD, >2.5 million people receive hip replacements and >1.5 million people knee replacements. Increasingly, the health care industry needs low-cost alternatives to treat a growing elderly population susceptible. Finding a safe, effective and enduring solution for millions of people suffering from cartilage deterioration represents an unmet medical need. Developing the clinical science to treat these defects with cell therapy required a multidisciplinary team with underpinning science, clinical and manufacturing disciplines. Whilst our underpinning research has covered many projects and investigations (see grants list in following section), we identify below key scientific advances that have contributed both to this Impact Case Study on Cell Implantation, and also with significant impact in the wider biological and cell therapy field (see section 4).

- *Continual monitoring of patients post-cell implantation –* has led to a better understanding of the science of cartilage repair (Ref 1, 2) and long term clinical efficacy (Ref 2). Key researchers 1997-2013: Prof James B Richardson, Prof Sally Roberts, Dr J-H Kuiper.
- *Biological orthopaedic repair systems* - For cases where concomitant ligament damage or bone loss forms a significant problem in joint repair we have developed novel biological repair systems (composite resorbable Bilok interference screw, hydroxy-apatite Allogran–N bone substitute) with a local company (Biocomposites; Ref 3, 4). Key researchers 1997-2013: Kuiper, Richardson.
- *International Scoring Benchmarks* - Established an international scoring scheme for histology as an outcome measure for cartilage repair (ICRS II; Mainil-Varlet et al 2010 Ref 8) used worldwide as a benchmark for clinical treatments and trials. Other outcome measures, e.g. the Oswestry Arthroscopy Score, have been developed for cartilage repair techniques. Key researchers 1997-2013: Richardson, Roberts.
- *Biomimetic Matrix Analogue* - This technology was patented for application in either the intervertebral disc or intracocular lens in conjunction with Aston and Oxford Universities (WO2009GB01006 200904). The commercial potential of the invention was highlighted as a top three regenerative spinal technologies of the year in the US "Best Spine Technologies of 2009" award (http://ryortho.com/2009/11/the-best-spine-technologies-of-2009/Roberts).
- *Nanotechnology control systems -* Novel patented technology for targeting of stem cells to injury site with controllable activation of differentiation of mesenchymal stem cells into orthopaedic tissues. (Patent portfolio below) A spin-out company MICA Biosystems Ltd (Ref 5) has been formed to market the technology with early stage sales and European funding (section 4). Key researchers: Prof Alicia J El Haj, Prof Jon Dobson. The patented technology won the Welcome Trust Showcase award, Lord Stafford Impact Through Innovation Award, and was shortlisted for the Times Higher Innovation Award.
- *Improved stem cell production systems* – Development of new hypoxic media pre-conditioning system for improved culture of chondrocyte precursors and stem cells in GMP conditions, *HypOxyCool*, has been developed in collaboration with Ruskinn (Contact Greg May, tel 01656776044) as part of EPSRC Centre in Innovative Manufacturing of Regenerative Medicine. The hypoxic media preconditioning unit has been purchased by laboratories in countries throughout Europe, Asia, and the USA. Key researcher: Dr Nicholas R Forsyth.

3. References to the research: Six key publications which underpin this work include:

Richardson JB et al (1999). Repair of human articular cartilage after implantation of autologous chondrocytes. *J. Bone Joint Surg.* **81**(6):1064-8. (Key Paper 1)

Sivan S-S et al. (2008). Collagen turnover in normal and degenerate human intervertebral discs as determined by the racemization of aspartic acid. *J. Biol. Chem.* **283**(14):8796-8801.

Smith HJ et al. (2009). Modification and validation of the Lysholm Knee Scale to assess articular cartilage damage. *Osteo. Cart.* **17**(1):53-8. (Key Paper 2)

Johansson A et al. (2011). A spectroscopic approach to imaging and quantification of cartilage lesions in human knee joints. *Phys Med Biol.* **56**(6):1865-1878.

Gokhale S et al (2005). Variables affecting initial stability of impaction grafting for hip revision. *Clin Orthop Relat Res.* 174-180.

Kanczler J et al. (2010) Controlled Differentiation of Human Bone Marrow Stromal Cells Using Magnetic Nanoparticle Technology. *Tiss. Eng.* **16**(10):3241-50. (Key Paper 3)

These publications are reflected in a patent portfolio of:

El Haj AJ, Dobson JP. Culturing tissue using magnetically generated mechanical stresses. USA Europe, China NZ, Singapore, Korea 2004147015, issued 29/7/2004

El Haj AJ Dobson JP. Generation of cartilage using magnetic particles; US patent 2010/518956 issued 30/12/2010

El Haj AJ Dobson JP - Stem cell targeting using magnetic particles US patent 2010/596594 issued 10/2/2011

Forsyth NR. Methods and apparatuses relating to cell culture media. US Patent 2010184219, issued 22/7/2010

Tighe BJ, Franklin V, Lydon FJ, Roberts S, Urban JPG, Sivan S. Intervertebral disc and intraocular lens. World patent: 2009127844. Issued 22/10/2009.

Richardson, JB. System for measuring stiffness of a fractured bone. World patent: 9535061, Issued 28/12/1995

Research grants underpinning this research:

Awarded To	Title of Grant	Sponsor	Years	Total Award
Richardson	Cartilage Repair by Autologous Chondrocyte Transplantation (ACTIVE).	MRC Multi-centre trial	2004-2016	£759,622
El Haj	BIODESIGN Rational Bioactive Materials Design for Tissue Regeneration	EU VII Framework	2012 - 2016	€ 15,906,812
El Haj	Landscape Award: Tissue Engineering and Regenerative Medicine (E-TERM)	EPSRC	2011 - 2017	£2,884,739
Roberts, Richardson, El Haj	Arthritis Research UK Tissue Engineering Centre	Arthritis Research UK	2011 - 2016	£ 2,490,771
Roberts	Arthritis Research Campaign - Programme Grant	Arthritis Research UK	2010 - 2015	£ 484,207
El Haj, Forsyth Richardson	EPSRC Centre for Innovative Manufacturing in Regenerative Medicine: Enabling the emergence of a new industry in regenerative med (REMEDI+)	EPSRC	2010 - 2015	£ 6,293,766
El Haj	LOLA- Combining stem cell science and tissue engineering to study the development and repair of human skeletal tissue	BBSRC	2009-2014	£ 758,000
El Haj, Forsyth	Hyanji Scaffold- Hyaluronan based injectable material for tissue	EU VII Framework	2009 - 2013	€ 374,400
El Haj	EPSRC Doctoral Training Centre (DTC) in Regenerative Medicine. Joint project with Loughborough and Nottingham Universities. (Loughborough)	EPSRC Life Sciences Interface	2008-2015	£ 6,119,504

Roberts, Kuiper Richardson	Growing a new joint in a Human back (MY JOINT).	EU VI Framework	2007-2012	£ 365,625
El Haj	Marie-Curie Multicentre Training Grant : Shaping the future of a new generation of hybrid human resources for tissue engineering of connective tissues	EU VI Framework	2005-2006	€ 346,436
El Haj	Network of Excellence of Excellence in Tissue Engineering (EXPERTISSUES)	EU VI Framework	2004-2010	£ 276,000
El Haj	Development of a magnetic nanoparticle strategies manipulation and activation of stem cells in vitro	BBSRC	2004-2007	£ 335,435
Richardson	EU Partnership for Autologous Chondrocyte Implantation (EUROCELL)	EU V Framework	2001-2004	€ 272,490
ElHaj /Biocomp-osites Ltd	Biomedical interactions in tissue engineering and tissue engineering in surgical repair (BITES)	EU V Framework	2000 - 2003	€ 2,104,999
MICA Bio-systems Ltd	Magnetic nanoparticles in healthcare (MagNETicFUN)	EU VII Framework	2013-2017	£ 478,000

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

Our research on biological and cell therapy in orthopaedics has had direct impact on health, economics, public policy, practitioners and professional services.

Impacts on health

More than 400 patients had cell therapy in our clinics to treat their cartilage defects (Ref 1). The treatment gave a marked improvement in the condition in most patients, with a beneficial effect sustained for more than eight years (Ref 2). This suggests that cell therapy can delay the progression of osteoarthritis long enough to have a real impact on future health costs (Ref 2).

A further 150,000 patients worldwide have benefited from our research on biological therapies (Ref 3). The composite resorbable interference screw, developed with Biocomposites Ltd (Keele, UK), has benefited over 60,000 patients worldwide through Stryker (Biosteon interference screw), Arthrocare (Bilok interference screw) and Biocomposites (Bilok and Biosteon interference screw). Use of this screw in anterior cruciate ligament reconstruction leads to a measurable improvement in their condition (Ref 4). Finally, over 4000 patients have benefited from our research on bone substitute materials (Ref 3), with Biocomposites Ltd (Keele, UK), distributed as Allogran by Endo Plus and Biocomposites. It gives long-term benefits to patients equivalent to human allograft bone, without the associated infection risks (Ref 4).

Economic impacts

Worldwide sales of 125,000 composite resorbable interference screws (Bilok, Biosteon) are reported with an associated turnover of almost $30,000,000 (Ref 3). In addition, over 4000 units of Allogran have been sold with an associated turnover of £450,000 (Ref 3). Sales from MICA Biosystems are just beginning (£60,000 as of 2013) (Ref 3) with a plan for expansion to worldwide distribution over the next 5 years (MICA MFB)

Impacts on public policy

We contributed to the advice and guidance from the National Institute for Health and Clinical Excellence (NICE) on Autologous Chondrocyte Implantation (ACI). For the present guideline (Ref 5), we contributed evidence, as both a manufacturer, via our GMP-licensed lab, OsCell, and as a commentator in the form of the Robert Jones and Agnes Hunt Orthopaedic Hospital. For the coming guideline (expected in 2014), our GMP laboratory will again contribute evidence (Ref 5).

Our research has put us in a position to contribute to public policy by informing the House of Lords Science and Technology Committee on the UK position on Regenerative Medicine (Ref 6). From October 2012 to February 2013, the House of Lords Committee held evidence sessions, to which members of our team (Roberts and our EPSRC Manufacturing Centre with Loughborough) contributed evidence on behalf of Arthritis Research UK and EPSRC. The report from the House of Lords committee has led to actions from the government on Regenerative Medicine (Ref 6).

Our research has also led to one of our team (Prof. El Haj) to advise to the Focus Group for the

Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA), responsible for assessing the quality, safety and efficacy of advanced-therapy medicinal products (ATMPs) and following scientific developments in the field (Ref 6).

Our impact into policy has contributed on a Global scale with participation (Prof El Haj) in the 2013 Regenerative Medicine World Summit in China, a discussion forum for world leaders in regenerative medicine to debate the barrier to adoption in regenerative medicine (Ref 7).

Impact on practitioners and professional services

Our research on Cell Therapies for Orthopaedics has led to a team member (Prof. Roberts) being on the committee of the International Cartilage Repair Society (ICRS) that has developed the ICRS II Visual Assessment Scale histology scoring system for assessing the quality of human cartilage repair (Ref 8). The scoring system is now part of the ICRS guidelines for the design and conduct of clinical studies in articular cartilage repair (Ref 8) and is currently being used in at least five randomized clinical trials (Ref 9).

Members of the Keele group have been in key positions within International societies, Scientific Advisory Boards and Research council advisory teams in this area: President of the UK Tissue and Cell Engineering Society (2004-9), European Chair for the International Society for Tissue Engineering and Regenerative Medicine (2012-2016), Executive Board of International Cartilage Repair Society (2006-2010), UKRC Stem Cell Advisory Board (2008-2011), Regenerative Medicine Advocacy Group (2009-), Academic Advisory Board of Institute of Physics and Engineering in Medicine (2008-), EPSRC Strategic Advisory Teams in Cross-disciplinary Interface, Healthcare and on the EPSRC Strategic Advisory Network, MRC College of Experts, MRC Developmental Pathway and Clinical Science Funding Panel, BBSRC Bioscience Industry Working Group, Deputy Chair of the BBSRC Bioscience and Biotechnology Panel.

5. Sources to corroborate the impact

Ref 1: Principal Clinical Scientist, OsCell, Oswestry, SY10 &AG, UK.

Ref 2: Bhosale AM et al. (2009). Midterm to Long-Term Longitudinal Outcome of Autologous Chondrocyte Implantation in the Knee Joint A Multilevel Analysis. *Am. J. Sports Med.* 37(1 suppl), 131S-138S. Bhandari M et al. (2012). Clinical and Economic Burden of Revision Knee Arthroplasty. *Clin Med Insights Arthritis Muscoskelet Disord*. 5:89-94.

Ref 3: Managing Director, Biocomposites Ltd, Keele, Staffordshire, ST5 5NL, UK. (http://www.biocomposites.com/). Mr Peter Cunliffe, MICA Biosystems Ltd, 23 Arley Road, Solihull, West Midlands B91 1NJ, UK. Spin-out company, reg 07237355. (http://micabiosystems.com/)

Ref 4: Barber FA & Boothby MH. (2007). Bilok interference screws for anterior cruciate ligament reconstruction: clinical and radiographic outcomes. *Arthroscopy.* 23(5), 476-481. Aulakh TS et al (2009). Long-term clinical outcomes following the use of synthetic hydroxyapatite and bone graft in impaction in revision hip arthroplasty. *Biomaterials,* 30(9), 1732-1738.

Ref 5: National Institute for Health and Clinical Excellence (2005) The use of autologous chondrocyte implantation for the treatment of cartilage defects in knee joints. Review of Technology Appraisal 16. http://guidance.nice.org.uk/TANational Institute for Health and Clinical Excellence (2008) Review proposal of NICE Technology Appraisal guidance no. 89; Autologous chondrocyte implantation (ACI) for the treatment of cartilage injury. Provisional matrix of consultees and commentators http://www.nice.org.uk/guidance/index.jsp?action=download&o=40677.

Ref 6: House of Lords Science and Technology Committee (2013) Regenerative Medicine Report. HL Paper 23.http://www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/2302.htm. Government response to the House of Lords Science and Technology Committee inquiry into regenerative medicine. Cm 8713. http://www.parliament.uk/documents/lords-committees/science-technology/RegenerativeMedicine/GovtresponseRegenMedCm8713.pdf. EMA, Report from CAT-Interested Parties Focus Groups (CAT-IPs FG) on non-clinical development of ATMPs, 23 November 2012.

Ref 7: Xian Papers, World Summit on Regenerative Medicine, Xian, China, 19-21 October 2013

Ref 8: Mainil-Varlet P et al (2010) A new histology scoring system for the assessment of the quality of human cartilage repair: ICRS II. *Am J Sports Med*. 38(5):880-90. Mithoefer K et al (2011). Guidelines for the Design and Conduct of Clinical Studies in Knee Articular Cartilage Repair International Cartilage Repair Society Recommendations Based on Current Scientific Evidence and Standards of Clinical Care. *Cartilage,* 2(2), 100-121.

Ref 9: NIH Trials.gov register: NCT 00414700, 01222559, 01225575, 01221441, 01246635.