Institution: University of Southampton

Unit of Assessment: 01 Clinical Medicine

Title of case study: 01-02 Therapeutic application of skeletal stem cells for patient benefit

1. Summary of the impact

Seven patients with avascular necrosis of the femoral head and bone cysts have been treated successfully with skeletal stem cell therapy, developed by Southampton researchers, resulting in an improved quality of life. This unique multi-disciplinary approach linking nano-bioengineering and stem cell research could revolutionise treatment for the 4,000 patients requiring surgery each year in the UK and reduce a huge financial burden on the NHS. The work has been granted three patents and the team are in discussions on development of the next generation of orthopaedic implants with industry.

2. Underpinning research

Among the challenges posed by our ageing population is the need for innovative and more cost-effective approaches to skeletal reconstruction. Worldwide, one in three women and one in five men are at risk of an osteoporotic fracture. In the UK, more than 50,000 primary hip replacement operations are performed each year at a cost of £250 million. This is set to rise to 65,000 by 2026, of which 30-50% will require subsequent revision surgery. In a large number of cases bone augmentation will be necessary, and current practice is usually to use donor bone. However, this is costly, dependent on availability and commonly leads to complications including infection and immunological rejection.

Work pioneered by researchers at the University of Southampton's Faculty of Medicine, Health and Life Sciences from 2004 onwards has successfully demonstrated the practicability of using patients' own bone stem cells together with a biocompatible scaffold to create a 'living bone composite', essentially regrowing a patient's own bone. The work took place over seven years with funding from the Biotechnology & Biological Sciences Research Council. It was led by Prof Richard Oreffo (Professor of Musculoskeletal Science since 2004) working with Dr Rahul Tare (Research Fellow from 2004 and Lecturer since 2010) and Douglas Dunlop (Consultant Orthopaedic Surgeon and Honorary Senior Clinical lecturer since 2002).

One project saw the team develop approaches to differentiate skeletal stem cells using template scaffolds manufactured at the University of Nottingham. The work led to the successful use of skeletal stem cells to enhance bone formation in scaffolds containing vascular endothelial growth factor (VEGF) and bone morphogenetic protein2 (BMP-2). In Southampton, in-vitro studies on the ability to modulate skeletal stem cell activity and function led to small animal proof of concept studies and on to application - in defined orthopaedic conditions. These targeted avascular necrosis of the femoral head (the collapse of the ball joint due to interruption of the blood supply) and culminated in patient treatment in 2006 **[3.2]**. Working with Dr Matthew Dalby and Dr Nikolaj Gadegaard at the University of Glasgow, we pioneered strategies to modulate skeletal stem cell function using step changes in the nanotopography of the template scaffolds. We developed techniques to drive skeletal stem cells along the osteogenic lineage **[3.1]**, as well as using discrete nanotopographical cues to maintain skeletal stem cell function **[3.3]**.

Further collaboration with researchers at the University of Glasgow led us to demonstrate modulation of cell adhesion using nanometre-scale shallow pits and grooves. We used discrete nanotopographical cues, in the absence of chemical cues, and demonstrated the ability to drive skeletal stem cells along the osteogenic lineage. Thus, by controlling cell adhesion we were able to induce hard tissue to form directly onto the implant, as opposed to the fibrous capsules which form around the current prosthesis and often lead to the need for revision surgery **[3.4]**. This publication was cited by Nature Materials **[3.1]** as a landmark paper for the last 10 years. In addition, our own studies demonstrated the proliferative and multipotential properties of fetal-derived cells in

comparison with adult-derived cells and their potential application to skeletal tissue regeneration **[3.5]**.

By combining two polymers, chitosan (a protein derived from the shells of crustaceans) and poly(ethylenimine), Southampton researchers have created a biocompatible hydrogel. Crucially, the gel material remained stable under cell-culture conditions and facilitated cell proliferation, yet prevented dedifferentiation of primary human skeletal cells into fibroblasts. The gel is easily made and can stably combine with a variety of biopolymers such as DNA, proteins and peptides **[3.6]**.

3. References to the research

3.1 Dalby MJ, Gadegaard N, Tare R, Andar A, Riehle MO, Herzyk P, Wilkinson CDW, Oreffo ROC. The control of human mesenchymal cell differentiation using nanoscale symmetry and disorder. *Nature Materials* 2007; Dec 6 (12):997-1003

561 Citations; *Nature Materials* October 2012 **cited this paper as one of 20 landmark papers of the last 10 years**.

3.2 Yang X, Tare RS, Partridge KA, Roach HI, Clarke NMP, Howdle SM, Shakesheff KM, and Oreffo ROC. Induction of human osteoprogenitor chemotaxis, proliferation, differentiation, and bone formation by osteoblast stimulating factor-1/pleiotrophin: Osteoinductive biomimetic scaffolds for tissue engineering. *J Bone & Mineral Research* 2003; 18(1); 47-57. **Citations 103**

3.3 McMurray RJ, Gadegaard N, Tsimbouri PM, Burgess KV, McNamara LE, Tare R, Murawski K, Kingham E, Oreffo ROC, Dalby MJ. Nanoscale surfaces for the long-term maintenance of mesenchymal stem cell phenotype and multipotency. *Nature Materials* 2011; 10(8):637-44

3.4 Dalby MJ, McCloy D, Robertson M, Wilkinson CDW, Oreffo ROC. Osteoprogenitor response to defined topographies with nanoscale depths. *Biomaterials* 2006, 27(8); 1306-1315; **Citations 132**

3.5 Mirmalek-Sani SH, Tare RS, Morgan SM, Roach HI, Wilson DI, Hanley NA, Oreffo ROC. Characterization and multipotentiality of human fetal femur-derived cells: implications for skeletal tissue regeneration. *Stem Cells* 2006; 24(4):1042-53

3.6 Khan F, Tare RS, Oreffo ROC, Bradley M. Versatile Biocompatible Polymer Hydrogels: Scaffolds for Cell Growth. *Angew Chem Int Ed* 2009; 48(5):978-82

Selected Grant Support

i. PI Oreffo (with Smith and Nephew) – Collaborative Grant between Smith and Nephew and UoS to develop a stem cell device funded by TSB Industry academia award. We were selected from a PubMed analysis for skeletal stem cells by Smith and Nephew and as a result asked to collaborate on this work, Title: Device for enrichment of skeletal stem cells for orthopaedic applications, Sponsdor:TSB – DTI; Period: Mar 2009 – Feb 2011; Award £400k

ii. Oreffo LEAD PI with Dunlop, Morgan (Southampton) and Shakesheff (Nottingham), Stevens (Imperial), El Haj (Keele), Title: Combining stem cell science and tissue engineering to study the development and repair of human skeletal tissue, Sponsor: BBSRC – LOLA 5 year Programme grant; Period: Sept 2009 - Aug 2014; Award: £4M with £1.64M to Southampton and Oreffo.

4. Details of the impact

The demographic challenges of an ageing population emphasise the need for innovative approaches to skeletal reconstruction to augment and repair tissue lost as a consequence of implant loosening, trauma or degeneration. What is needed is replacement of a patient's damaged skeleton with their own bone using their own bone stem cells. The Southampton team's work has moved the application of skeletal stem cells from bench to clinic through a number of

multidisciplinary approaches. We have transformed understanding of the role of nanotopography in stem cell function and developed protocols for the isolation, enrichment and differentiation of skeletal stem cells from human adult and fetal tissues. The work has exciting potential for patient care and the manufacture of medical components and prosthetics. Accordingly, it has received significant coverage in both the medical and general press.

The work has resulted in the development of strategies to apply human skeletal stem cells for clinical application in areas of unmet need, including in the first instance avascular necrosis and bone cysts. Avascular necrosis can affect people of all ages (male and female), although typically in those aged 30-60 years of age. In the UK about 4,000 people are diagnosed with Avascular Necrosis each year. Since 2008 the Southampton team have successfully used skeletal stem cells to treat seven patients with avascular necrosis of the femoral head and bone cysts, all of whom have shown excellent clinical recovery and improved quality of life. The first patient in 2008 was Carl Millard, who, a year later, was walking normally without pain and in an interview with Sky News in 2009 reported enthusiastically on his state of wellbeing **[5.1]**. This work thus has the potential to reach 4,000 avascular necrosis patients in the UK, and could then reach over 6,000 revision hip fracture patients per year in the UK.

Amidst significant media interest **[5.1, 5.2, 5.3]**, the team have negotiated with industry partners Thermo Fisher Scientific and London-based medical equipment manufacturers Smith and Nephew who are keen to integrate the technology into their own manufacturing processes. Development work began in 2010 in collaboration with Dr Dalby and Dr Gadegaard at the University of Glasgow, following the filing of patents for an Implantable Cartilaginous Tissue Repair Device, July 2009; Polymer Blends, March 2010; and Retention of Stem Cell Phenotype, August 2010 **[5.4]**.

Further recognition came when the team, working with Smith & Nephew, were awarded the prestigious Grand Prix Award at the Engineer Technology and Innovation Awards 2010, in addition to the category for Medical Technology, for a device for the isolation of skeletal stem cells for orthopaedic clinical application. The device provides a prototype with potential to translate into every orthopaedic operating theatre. Jon Excell, editor of *The Engineer* and chairman of the judging panel, said: 'This was a fantastic example of cross-sector collaboration on technology in one of the UK's key emerging technology sectors. It could potentially make an enormous difference to many people's lives.' **[5.5]**. The team's role in taking the use of skeletal stem cells from bench to clinic was also highlighted by UK Trade & Investment in May 2010 **[5.6]** and the step change in stem cell application for hip repair was noted by Dr Chris Watkins, MRC's Translation Theme Leader, who stated "Resilience, repair and replacement is a priority research area in the MRC's strategic plan, 'Research Changes Lives'. This study highlights how a regenerative approach can offer real hope in addressing a significant problem for an ageing population." **[5.7]** and reported in Stem Cells Translational Medicine **[5.8]**.

The team's pioneering work on the role of nanotopography in stem cell function, cited by Nature Materials **[3.1]** as a landmark paper for the last 10 years, was reported in numerous trade publications reaching beyond academia, including Science press **[5.9]**, Stem Cell Net Digest **[5.10]**, and The Engineer **[5.5]**. Extending the reach further, Oreffo et al routinely run a Bone and Joint stand at the University of Southampton's Science Week. The March 2013 event attracted over 3,000 members of the general public and strong press coverage, and the team received good feedback for their stand.

5. Sources to corroborate the impact

5.1 Patient case studies, Sky News, August 2009 http://news.sky.com/home/uk-news/article/15371478 ("Stem cells Op could end hip operations" detailing translational studies using skeletal stem cells for a 39 yr. patient *Mark Venables* - generated significant interest from tabloid and broadsheets. In same story a patient Carl Millard who can now walk normally, without any pain stated "I feel great" and "If this can prevent people having to have a hip replacement, I

think it is wonderful." (all on above www site).

5.2 Media: BBC see: http://news.bbc.co.uk/1/hi/7985142.stm

5.3 Media: Newspaper articles (*Daily Mail - Fiona Macrae 6th April 2009*), Telegraph, London Press Service - see: http://www.dailymail.co.uk/health/article-1168083/Stem-cell-injections-help-heal-fractures-treat-bone-diseases.html.,

http://www.telegraph.co.uk/health/healthnews/6118220/New-stem-cell-treatment-being-used-by-patients-to-avoid-hip-replacements.html

5.4 Patents:

Implantable Cartilaginous Tissue Repair Device, US and European applications published July 2009 and August 2008 respectively: Patent Number US2009171467 (A1)

Polymer Blends, US and European applications filed September 2009: World Patent WO2010023463 (A2)

Retention of Stem Cell Phenotype, US and European applications filed February 2010: Patent Number WO2010094944 (A1)

5.5 Engineer Technology & Innovation Awards for work on a device for the isolation of skeletal stem cells for orthopaedic application http://www.theengineer.co.uk/awards/technology-and-innovation-award-winners-revealed/1006316.article#ixzz1l3OlBvI2

5.6 UK Trade & Investment – 7 May 2010 - Researchers use adult stem cells for bone repairs – http://webarchive.nationalarchives.gov.uk/20100507093704/http://www.ukinvest.gov.uk/South-West/101594/en-CA.html?printable=true

5.7 Using Stem Cells to Mend Damaged Hips -http://insciences.org/article.php?article_id=8554 Published on 18 March 2010, 04:36.

5.8 Science Press: http://stemcellstm.alphamedpress.org/site/misc/News037.xhtml "Stem Cell Finding May End Hip Replacements for Osteonecrosis Sufferers"

5.9 Stem Cell Breakthrough using Nanotopography - In Next Big Future (18 July 2011) carried http://nextbigfuture.com/2011/07/stem-cell-breakthrough-heralds-new-era.html

5.10 "Nanoscale Plastic Easily Solves Laboratory Stem Cell Expansion For Therapeutic Purposes Issue" see http://www.stemcelldigest.net/stemcell/2011/07/nanoscale-plastic-easily-solves-laboratory-stem-cell-expansion-for-therapeutic-purposes-according-to-new-research.html From Stem Cell Net Digest and Interview to Radio Solent July 2011