Institution: University College London

Unit of Assessment: 4 - Psychology, Psychiatry and Neuroscience

Title of case study: The world's first stem cell based transplants: changing the future of organ replacement

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

We were the first to show that human stem cells could be used to create functional organ replacements in patients. These transplants, first performed to save the life of an adult in 2008, and then repeated to save a child in 2010, have changed the way the world views stem cell therapies. We have opened the door to a future where conventional transplantation, with all its technical, toxicity and ethical problems, can be replaced and increased in range by a family of customised organ replacements, populated by cells derived from autologous stem cells. This has altered worldview, changed clinical practice and had key influences on UK policy.

2. Underpinning research (indicative maximum 500 words)

After performing the world's first stem-cell based organ transplant, implanted in Spain in 2008, Professor Martin Birchall moved to UCL as this offered the ideal environment to press forward to clinic with this game-changing technology. Reasons included internationally-leading airway referral centres for children (Great Ormond Street Hospital [GOSH]: Elliott, DeCoppi) and adults (Royal National Throat, Nose and Ear Hospital: Sandhu; University College London Hospitals [UCLH]: Janes), outstanding biomaterials/ nanotechnology science (Seifalian), and the most advanced and productive cell therapy Good Manufacturing Practice (GMP) facility in Europe (UCL-Royal Free, Lowdell). Many scientific questions remained however, about whether the technique could be replicated, verified and lead to beneficial long-term outcomes.

In 2010, based on preclinical work in pigs **[1]**, UCL performed the world's first stem cell based organ (whole trachea) transplant in a child, saving the life of a boy from Northern Ireland. Two years on (Lancet, 2012), he is growing, active and has not needed inpatient care for well over a year (for the first time in his life). This showed for the first time that stem cells could be used to develop organ replacements with long-lasting benefit **[2]**. It further demonstrated the very high scientific importance of the compassionate use of new regenerative medicine technology in a facilitatory regulatory environment such as that in the UK **[3]**.

This success was recognised by the award of £1.2m MRC funding to extend our work into the larynx, a more complex area, but one with far more needy patients. This preclinical work demonstrated the feasibility of this approach and permitted the development of fully GMP-compatible processes that were applied to the treatment of a second child (paper in preparation) in 2012. Meetings with the Medicines and Healthcare Products Regulatory Agency (MHRA) determined the appropriate model for work leading to a Clinical Trials Authorisation (CTA). We gave 16 pigs seeded laryngeal implants. Animal survival to 2 months was 81%. Decellularised scaffolds showed mild inflammatory responses, but, importantly, clear evidence of remodelled cartilage (quite unlike the 'competitor' aortic allografts used in France and the US). In all, endoluminal repair was excellent with glandular and interstitial regrowth. CT scans showed patent airways. Human cells were identifiable at the implant site for four weeks. Thus, we have shown biocompatibility, safety and efficacy in pigs. As part of the same MRC-funded project, we developed Standard Operating Procedures for mesenchymal stem cell (MSC) immunophenotyping (QC/RC), preparation, isolation and ex vivo expansion of mesenchymal stromal cells from haematopoetic progenitor cells prepared from marrow (HPC-M) and seeding of MSC on laryngeal scaffolds.

We found that we were able to substantially accelerate the process of decellularisation by using a variable pressure based method allowing for removal of all nuclear material within the overlaying muscle and cartilage over a seven-day period **[4]**. The technique preserved anatomy, including critically the vocal cords, and biomechanical strength including the structural integrity of the collagen, in a quarter of the time taken by conventional protocols. Again, this method was successfully field-tested in the production of a robust, easily recellularised, tracheal graft for a

second child. After four weeks subcutaneous implantation scaffold prepared in this way proved biocompatible in rats, with no evidence of rejection. Based on observations of scaffolds in these experiments, we hypothesised that decellularised (ECM) scaffolds exert an immunomodulatory (Th1 to Th2 response shift) which is independent of the presence of implanted cells. We then confirmed and measured this paradigm-shifting effect, thus opening up a whole new avenue of potential clinical applications for decellularised technology **[5]**.

We have developed a bioreactor system that comprises a non-disposable central monitoring core connected to disposable bioreactors for individual products. These are customised and disposability facilitates GMP process standards and reduces costs. We generated flexible sheets of mucosa from autologous epithelial progenitor cells for rapid functionalisation of hollow organs as well as GMP transport and storage processes. This clinical experience will be followed by the world's first trial of stem-cell based oesophageal replacement in infants, for which the preliminary work is being supported by a £750,000 peer-reviewed grant from the UK Stem Cell Foundation. UCL will provide a level of insight into the real clinical potential for stem cell/tissue engineering combined technologies with wide implications for the development of hollow organ replacements. We will leverage these trials to develop new pathways for maximising discovery science and health economic benefit from complex regenerative medicine therapies with important generic benefits for medical science.

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

[1] Go T, Jungebluth P, Baiguero S, Asnaghi A, Martorell J, Ostertag H, Mantero S, Birchall M, Bader A, Macchiarini P. Both epithelial cells and mesenchymal stem cell-derived chondrocytes contribute to the survival of tissue-engineered airway transplants in pigs. J Thorac Cardiovasc Surg. 2010 Feb;139(2):437-43. http://dx.doi.org/10.1016/j.jtcvs.2009.10.002

[2] Elliott MJ, De Coppi P, Speggiorin S, Roebuck D, Butler CR, Samuel E, Crowley C, McLaren C, Fierens A, Vondrys D, Cochrane L, Jephson C, Janes S, Beaumont NJ, Cogan T, Bader A, Seifalian AM, Hsuan JJ, Lowdell MW, Birchall MA. Stem-cell-based, tissue engineered tracheal replacement in a child: a 2-year follow-up study. Lancet. 2012 Sep 15;380(9846):994-1000. http://dx.doi.org/10.1016/S0140-6736(12)60737-5

[3] Partington L, Mordan NJ, Mason C, Knowles JC, Kim HW, Lowdell MW, Birchall MA, Wall IB. Lowdell MW, Birchall M, Thrasher AJ. Use of compassionate-case ATMP in preclinical data for clinical trial applications. Lancet. 2012 Jun 23;379(9834):2341. http://doi.org/f2ff94

[4] Partington L, Mordan NJ, Mason C, Knowles JC, Kim HW, Lowdell MW, Birchall MA, Wall IB. Biochemical changes caused by decellularization may compromise mechanical integrity of tracheal scaffolds. Acta Biomater. 2013 Feb;9(2):5251-61. http://doi.org/pcf

[5] Fishman JM, Lowdell MW, Urbani L, Ansari T, Burns AJ, Turmaine M, North J, Sibbons P, Seifalian AM, Wood KJ, Birchall MA, De Coppi P. Immunomodulatory effect of a decellularized skeletal muscle scaffold in a discordant xenotransplantation model. Proc Natl Acad Sci U S A. 2013 Aug 27;110(35):14360-5. http://dx.doi.org/10.1073/pnas.1213228110

Peer-reviewed funding: MRC TSCRC RegenVOX. Stem cell based tissue engineered partial laryngeal replacement: preclinical studies. 2011-13. **£1.2m**; UK Stem Cell Foundation. Cells for Feeding: development of a stem cell based tissue engineered oesophageal replacement for infants with congenital oesophageal agenesis. 2013-16. **£750,000**; MRC DPFS/DCS (Major Awards Committee) RegenVOX. Phase I/IIa Clinical Trial of a stem cell based tissue-engineered laryngeal replacement. 2013-2018. **£2.8m**; Technology Strategy Board. INSPIRE: Phase I/IIa Clinical Trial of a stem cell based tissue-engineered tracheal replacement. 2014-2017. **£2.4m**.

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

With £2.4m MRC/DPFS Major Awards funding and £2m TSB support, we are now implanting 10 laryngeal and 15 tracheal patients with tissue-engineered, stem cell-based implants, the first patients in the world to receive stem-cell based organ replacements within formal clinical trials. We are now also receiving referrals from the United States and Europe for application of our products in difficult-to-treat patients presenting to overseas tertiary referral centres. The principal impact has

been to save the lives and transform the future prospects of the transplanted individuals. However there are also a much broader range of impacts on clinical practice, public policy and the nature of clinical transplantation services globally.

Improved patient outcomes

The child treated in 2010 on compassionate grounds was well, growing, and had not needed medical intervention for 6 months by May 5, 2012 **[see ref 1 above]**. He remains well at 3.5 years post-implantation and a recent biopsy showed normal tracheal epithelium.

We have maximised the use of advantageous aspects of the UK regulatory framework to apply tissue-engineered products for compassionate uses (e.g. both children above, plus a tissue engineered trachea that provided successful palliation and considerable health cost savings in the case of a girl with tracheal cancer at UCLH). Thus, we have also led in the practical understanding of pathways to translation for advanced therapeutic medicinal products (ATMP), recognised by our Lancet editorial (2012).

Our breakthroughs in the application of regenerative medicine to severe airway disorders resulted in a dramatic increase in national and international referrals of these patients to UCLH. In response, Birchall and clinical colleagues Sandhu, George, Janes and Hayward established a world-first complex airway multidisciplinary team in 2009. Since then, more than 200 of the world's most challenging complex airway patients have been assessed by the team with 18 travelling from all corners of the world for treatment. This trend is envisaged to grow considerably as our technologies are tested by clinical trials in the next two years. This activity increases world awareness that these patients, who would otherwise be abandoned to poor quality of life or unpleasant deaths, can be effectively treated, and attracts income to the UK from overseas **[a]**.

Changing the nature of health services

We have fundamentally changed the way that clinicians and NHS managers are thinking about the future of transplantation and healthcare delivery **[b]**. Within range is a new raft of technologies, which can replace or augment the range of transplantation as we presently understand it. Autologous-cell based and other types of Regenmed tissue and organ replacements do not require immunosuppression and offer one-off solutions which could reduce the cost of care of patients with organ failure to a fraction of its present level. Transplant-focused institutions such as Royal Free London NHS Foundation Trust **[c]** and UC Davis Medical Center, California **[d]** are already deciding how to allocate resources to prepare for this future, including new designs of operating theatre suite and near-patient cell and tissue-preparation facilities. Examples of organ replacements in development based on the decellularisation-recellularisation technology which we were the first to translate into man are lung **[e]** and kidney **[f]** replacements. Our success gives these high profile groups confidence to progress.

Impact on UK policy

Our work has substantially informed UK policy on regenerative medicine, with particular respect to autologous products. For example, Birchall advised on the 2012 'roadmap' for UK regenerative medicine research published by four UK Research Councils and the Technology Strategy Board, entitled *A Strategy for UK Regenerative Medicine* **[g]**, which resulted in the release of £100m government funds for regenerative medicine at the translational interface. In addition, he has substantially contributed to a House of Lords briefing on the future impact of tissue-engineered organ replacements **[h]**. We are also approached regularly for advice by both MHRA and EMA. Most recently, UCL's work has been used as exemplar for regenerative medicine as one of the '8 Great Technologies' announced by the Minister for Science and Universities **[i]**

Impact on UK scientific profile

Our work, with Coffey (Moorfields, embryonic stem cells for macular degeneration) represents the most powerful example in the UK, possibly internationally, of the true clinical potential of stem cell treatments. Thus, we are frequently called upon to advise bodies internationally, such as CIRM (e.g. closed CIRM advisory session 2012, which directly resulted in a dedicated call for tissue-engineered product trials **[j]**) and EMA (which has resulted in changes to the regulatory

designation of complex cellularised products).

Impact on the research workforce

For regenerative medicine to achieve its potential as a therapeutic powerhouse for the UK, a skilled, flexible workforce is required. Our multidisciplinary team includes PhD students, postdoctoral scientists and clinical fellows (about 30 at any one time), from a wide range of backgrounds (stem cell and cell biology, engineering, chemistry, business, medicine and surgery). They are all exposed to patterns of highly multidisciplinary working and encouraged to develop their projects by drawing upon the wide panoply of skills around them. We have thus assisted in the development of a highly skilled workforce on whom the future Regenmed-based health and wealth of the UK can build.

Public Understanding of regenerative medicine

Our team regularly engages with the public directly and through the media **[k]**. For example, both Cheltenham and Brighton Science Festivals feature interactive sessions on stem cell transplants based on this work; a recent BBC radio programme focused on the potential healthcare gains to be made from organs built from stem cells, and specifically our recent work developing new larynges; the Lancet produced a video for public education featuring Birchall; the MRC have a major public-facing stem cell education page devoted to our breakthroughs.

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

[a] Patient numbers can be verified by Professor Martin Birchall.

[b] Article in *Science*, April 19, 2013. http://www.sciencemag.org/content/340/6130/266.full.pdf and see: Martinod E, Seguin A, Radu DM, et al; FREnch Group for Airway Transplantation (FREGAT). Airway transplantation: a challenge for regenerative medicine. Eur J Med Res. 2013 Jul 29;18:25. http://dx.doi.org/10.1186/2047-783X-18-25.

[c] Impacts can be corroborated by Chief Executive, Royal Free Hospital.

[d] Impacts can be corroborated by Director, Center for Regenerative Cures, UC Davis.

[e] Ott HC, Clippinger B, Conrad C, Schuetz C, Pomerantseva I, Ikonomou L, Kotton D, Vacanti JP. Regeneration and orthotopic transplantation of a bioartificial lung. Nat Med. 2010 Aug;16(8):927-33. http://dx.doi.org/10.1038/nm.2193

[f] Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med. 2013 May;19(5):646-51. http://dx.doi.org/10.1038/nm.3154

[g] http://www.bbsrc.ac.uk/news/policy/2012/120328-pr-new-strategy-uk-regenerative-medicine.aspx

[h] http://www.parliament.uk/business/committees/committees-a-z/lords-select/science-and-technology-committee/publications/previous-sessions/session-2012-13/regenerative-medicine-evidence

[i] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/249263/regenerative_medicine_infographic.pdf

[j] http://cirmresearch.blogspot.co.uk/2012/01/second-synthetic-trachea-transplant.html

[k] Public and media engagement:

- 2012 Lancet interview: http://www.youtube.com/watch?v=6gdmgmtkMEY
- Cheltenham Science Festival 2013: http://www.cheltenhamfestivals.com/science/whats-on/2013/regenerative-medicine-where-will-we-be-in-50-years/
- BBC Radio Programme Inside Science Episode 'Stem cell transplants', 11th July, 2013. http://www.bbc.co.uk/programmes/p01cnbvt
- MRC web page explaining the wider significance of their funding to Birchall's research programme: http://www.mrc.ac.uk/Achievementsimpact/Profiles/MartinBirchall/index.htm