Institution: University of Bristol

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Health benefits, increased public awareness and changes in national policy result from the successful implantation of the first tissue-engineered trachea, created utilising the patient's own stem cells.

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

In 2008, Professors Martin Birchall and Anthony Hollander (University of Bristol) and a team of scientists and surgeons led from Bristol successfully created and then transplanted the first tissue-engineered trachea (windpipe), using the seriously ill patient's own stem cells. The bioengineered trachea immediately provided the patient with a normally functioning airway, thereby avoiding higher risk surgery or life-long immunosuppression. This sequence of events, which raised public interest and understanding around the world as a result of huge media coverage, acted as proof of concept for this kind of medical intervention. A new clinical technology with far-reaching implications for patients had passed a major test. This development demonstrated the potential of stem cell biology and regenerative medicine to eradicate disease as well as treat symptoms and has already led to the implantation of bioengineered tracheas in at least 14 other patients.

2. Underpinning research (indicative maximum 500 words)

Two strands of research at the University of Bristol were brought together from 2000 onwards, leading up to the tracheal tissue engineering project [1]:

1. Professor Anthony Hollander and Dr Wael Kafienah developed a range of techniques for cartilage engineering on 3D scaffolds,[2], the measurement of the quality of cartilage engineering and finally cartilage engineering using autologous (that is, the patient's own) bone marrow-derived mesenchymal stem cells.[3] These techniques were combined for the potential treatment of cartilage lesions in patients with knee osteoarthritis. However, this approach could readily be adapted to the tissue engineering of cartilage outside the articulating joints and was therefore used as the basis for designing the tracheal cartilage engineering methodology. A key component of this method was the use of Parthyroid Hormone Related Peptide (PTHRP) to prevent the differentiation of the stem cells to hypertrophic chondrocytes that are normally found in the developing growth plates of long bones. This type of chondrocyte has the property of calcifying its extracellular matrix and would pose a problem for hyaline cartilage formation. Calcification within articular or tracheal cartilage is likely to impair its function. The Hollander team hypothesised and then demonstrated that PTHRP could inhibit hypertrophy.[3] PTHRP was therefore used for the tracheal transplantation as part of the pre-conditioning of chondrocytes derived from the patient's stem cells.[1] This body of underpinning research was carried out between 2000 and 2007 and was funded by peer-reviewed grants totalling £1.77m from the European Union, the Arthritis Research Campaign and the Biotechnology and Biological Sciences Research Council.

   Hollander has been Professor of Rheumatology and Tissue Engineering in the School of Cellular and Molecular Medicine at the University of Bristol from September 2000 to the present. Kafienah was a Research Associate in the Department of Clinical Science at North Bristol from February 2001 to January 2006, and subsequently Lecturer in the School of Cellular and Molecular Medicine from February 2006 to the present.

2. Professor Martin Birchall and Professor Mick Bailey (Bristol) have undertaken a programme of research into laryngotrachealeal graft transplantation in pigs.[4,5] This work on upper airway transplantation provided pivotal background information about the need for vascularisation and for the avoidance of immune rejection. This was critical to the subsequent development of the tracheal transplantation methodology. The team's work on culture of airways epithelial cells was also an important part of the tracheal transplantation as the seeding of these cells, derived from an autologous upper airway biopsy, onto the luminal surface was critical to re-establishing the mucosa after transplantation.[6] The laryngotracheal transplantation research was primarily funded by a peer-reviewed, £1.2m Wellcome Trust Clinical Leave Fellowship (2001-2005) awarded to Birchall.

Birchall was Professor of Laryngology at the University of Bristol from April 1995 to December 2003 before taking up a position at UCL. He has been an Honorary Visiting Professor in the School of Clinical Sciences at the University of Bristol from August 2005 to the present. Bailey has been Professor of Comparative Immunology in the School of Veterinary Science from October 1993 to the present.

The study was led by Birchall in Bristol and was dependent on the cell biology skills of the Hollander and Birchall teams to design the cell production methodology and to produce the cells for clinical use. The project was a pan-European collaboration and it was Professor Paolo Macchiarini, Professor of Thoracic Surgery at the Hospital Clinic, Barcelona, Spain, who identified the patient, coordinated the final stages of the tissue engineering and performed the surgery in Barcelona. In Milan, Dr Sarah Mantero developed the bioreactor used to culture the cell-scaffold construct. In Verona, Dr Maria-Theresa Conconi developed the detergent-enzyme method for decellularising cadaver tracheal tissue. Combining these skills and expertise with the stem cell biology, epiltheleal cell culture methods and the laryngotracheal transplant experience in pigs was essential to the project's eventual success.

A patent was filed to protect the use of PTHRP as a method of inhibiting hypertrophy.

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

[1] Macchiarini P, Jungebluth P, Go T, Asnaghi MA, Rees LE, Cogan TA, Dodson A, Martorell J, Bellini S, Parnigotto PP, Dickinson SC, Hollander AP, Mantero S, Conconi MT, Birchall MA 2008 Clinical transplantation of a tissue-engineered airway. Lancet **372**(9655)**:**2023-2030. PMID: 19022496

[2] Kafienah W, Jakob M, Demarteau O, Frazer A, Barker MD, Martin I, Hollander AP 2002 Three-dimensional tissue engineering of hyaline cartilage: comparison of adult nasal and articular chondrocytes. Tissue Engineering **8:**817-826. PMID: 12459060

[3] Kafienah W, Mistry S, Dickinson S, Sims T, Learmonth I, Hollander A 2007 Three-dimensional cartilage tissue engineering using adult stem cells from osteoarthritis patients. Arthritis Rheum. **56:**177-187. PMID: 17195220

[4] Barker E, Macchiarini P, Murison P, Jones A, Haverson K, Bailey M, Birchall M 2005 An ex vivo model for reperfusion of laryngotracheal grafts. Laryngoscope **115**(4)**:**699-702. PMID: 15805884

[5] Birchall M, Idowu B, Murison P, Jones A, Burt R, Ayling S, Stokes C, Pope L, Terenghi G 2004 Laryngeal abductor muscle reinnervation in a pig model. Acta Otolaryngol **124:**839-846. PMID: 15370570

[6] Rees LE, Gunasekaran S, Sipaul F, Birchall MA, Bailey M 2006 The isolation and characterisation of primary human laryngeal epithelial cells. Mol Immunol **43**(6)**:**725-730. PMID: 16360018

Peer-reviewed grants:

Novel bioresorbable scaffolds and culture methods for cartilage tissue engineering
Joint with a consortium of four other European centres
European Framework Five
€6 million across the consortium; £570,000 to Bristol and Sheffield, 2000-2004

Regulation of stem cell differentiation for the tissue engineering of cartilage
Joint with M Billingham, J Holly, M Perry and WZ Kafienah
BBSRC & Smith & Nephew Link grant
£460,000, 2002-2005

A systems approach to tissue-engineering processes and products
(STEPS) EU framework 6
Hollander, and many other EU partners
€23 million (Bristol, £380,000) 2005-2009

The development of a well-vascularised and functional laryngeal transplantation model in the pig
Wellcome Trust
Birchall, Research Leave Fellowship
£1,157,388, 2000-2005

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

A 30-year-old woman was hospitalised in March 2008 with acute shortness of breath due to marked stenosis of the left main bronchus, rendering her unable to carry out simple domestic duties or care for her children. The only conventional option remaining was removal of her left lung, with an attendant risk of complications and a high mortality rate. Based on successful laboratory work previously performed by the team, and given the urgency of the situation, it was proposed that the lower trachea and the left bronchus should be replaced with a bioengineered airway based on the scaffold of a decellularised cadaver human trachea. Stem cells were obtained from the recipient's own bone marrow, grown into a large population in Bristol, and matured into chondrocytes (cartilage cells) using an adapted method originally devised by Professor Anthony Hollander for treating osteoarthritis. The donor trachea was then seeded with chondrocytes on the outside surface. In order to replicate the inside lining of the trachea, epithelial cells, grown in Bristol by Professor Martin Birchall, were seeded onto the luminal surface. Four days after seeding, the graft was used to replace the patient's left main bronchus. The patient remains alive and healthy with no need for immunosuppression or other health care.

4.1 Impact on the patient, Claudia Castillo

Without this intervention, the young mother would either have remained seriously ill with very poor life quality and life-long immune-suppression or, more likely, would have died. Instead, she is alive, not under health care and earning a salary. She commented: "It really is a miracle. The problem has gone... I can go to the park and I can play with my children... I now have a future to look forward to." (source [a])

4.2 Impact on the field of stem cell research and regenerative medicine

4.2.1 This was the first example of a tissue-engineered, three-dimensional organ being created using autologous stem cells and implanted successfully. While the project concerned one patient and a rare disease, it acted as a proof of concept and an exemplar more generally of the possibility of extending this technology to other damaged hollow organs such as the bladder, larynx, intestine and oesophagus. This case also exemplifies the possibility of personalised medicine. While the shape of the implanted organ was provided by a donated cadaveric tracheal segment, the risk of immune rejection was removed by replacement of the donor cells with the patient's own.
The Barcelona hospital that had been treating the patient before the operation has made savings by no longer having to admit Castillo to intensive care twice a week at a cost of £3,000 a day, as it had been doing for the previous three years (source [b]).

4.2.2 It is clear that the use of this technology in similar operations has the potential to generate huge cost savings. Since the original operation a further 14 patients have been transplanted with a bioengineered trachea as discussed in a critical review in "Science" (source [c]). The impact on the wider field of Regenerative Medicine has been summed up by Professor Dame Julia Polak (Imperial College) who has stated to us: "This work has had a truly galvanizing effect on the field, showing that even very serious diseases can be treated using regenerative medicine approaches and I have been excited by this advance both as a scientist and as a transplant recipient."

4.3 Impact on national policy

4.3.1 In April 2012 the UK MRC published a strategic document "A strategy for UK Regenerative Medicine" that formed the basis of subsequent planning for the development of this new branch of medicine. This document refers to "bone marrow stem cells applied to denuded donated trachea for airway replacement" as a key example of a therapy using the patient's own cells (source [d]).

4.3.2 In 2012 the House of Lords Science and Technology Committee published a call for evidence for their enquiry into Regenerative Medicine. In this call it is stated that "Examples of such treatments are the transplantation of a new trachea grown using the patient's own stem cells", directly referring to the tracheal transplant case (source [e]) and Professor Anthony Hollander was called to give evidence to the enquiry (source [f]).

4.4 Impact on the public perception of stem cell biology and regenerative medicine

This case caught the imagination of the public, as reflected in the worldwide coverage in both electronic and print news media. It has been seen as the first fruit to be borne from the investment in stem cell research. It has also shown how regenerative medicine does not just treat symptoms but can remove a disease from the patient's life altogether.

4.4.1 The story received worldwide coverage in newspapers, on television and radio, and on the internet. It was the subject of an article in *The New Scientist* on 19 November 2008 (source [g]), and was picked up across the mainstream media including the BBC (source h) and the *Guardian* (source [i]).

4.4.2 The operation was included in a permanent exhibition entitled "Who am I?" at the Science Museum, forming part of a display demonstrating how new technology, from stem cells to gene therapy, can help to repair damage caused by serious illness, with life-changing results (source [j]). The museum receives almost 3 million visitors each year (source [k]), many of whom will have viewed the exhibit.

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

[a] A statement from Claudia Castillo, the first tissue-engineering trachea transplant patient, corroborating 4.1, is provided by the report at: http://www.dailymail.co.uk/news/article-1088567/World-8217-s-stem-cell-transplant-patient-My-murdered-brother-sick-aunt-professors-pigs-gave-strength-live.html

[b] A report corroborating 4.2.1 is provided in the newspaper article: "Transplant first a giant leap for surgery", *The Guardian*, 19 November 2008 http://www.guardian.co.uk/society/2008/nov/19/stem-cell-transplant-claudio-castillo

[c] A scientific review corroborating 4.2.2 is provided at: Trachea Transplants Test the Limits http://www.sciencemag.org/content/340/6130/266.long

[d] The report referred to as corroborating 4.3.1 is at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008534

[e] The report referred to as corroborating 4.3.2 is at: http://www.parliament.uk/business/committees/committees-a-z/lords-select/science-and-technology-committee/inquiries/parliament-2010/regenerative-medicine/

[f] http://www.parliamentlive.tv/Main/Player.aspx?meetingId=11796

[g] A source corroborating 4.4.1 is at: "Woman receives windpipe built from her stem cells", *The New Scientist*, 19 November 2008. http://www.newscientist.com/article/dn16072-woman-receives-windpipe-built-from-her-stem-cells.html

[h] A source further corroborating 4.4.1 is at: "Windpipe transplant breakthrough", BBC News, 19 November 2008 http://news.bbc.co.uk/1/hi/health/7735696.stm

[i] Another corroboration of 4.4.1 is at: "Transplant first a giant leap for surgery", *The Guardian*, 19 November 2008 http://www.guardian.co.uk/society/2008/nov/19/stem-cell-transplant-claudio-castillo

[j] Corroboration of 4.4.2 is at: "Stem cell breakthrough enters permanent national exhibition", University of Bristol press release http://www.bris.ac.uk/news/2010/7072.html

[k] Further corroboration of 4.4.2 is at: "Visits made in 2012 to visitor attractions in membership with ALVA", Association of leading visitor attractions website http://alva.org.uk/details.cfm?p=423