Institution:
University of Cambridge

Unit of Assessment:
UoA6

Title of case study:
Cell therapies for spinal cord injury

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

Between 2008 and 2011 researchers at the Department of Veterinary Medicine (DVM) undertook the first randomized double-blinded clinical trial of a cell therapy for spinal cord injury (SCI). The trial involved transplantation of autologous olfactory ensheathing cells into domestic dogs with chronic pelvic limb paraplegia as a consequence of clinical SCI. The results indicated a significant improvement in locomotor function. This study has had a major impact on 1) the public awareness of the use of veterinary disease in biomedical research, 2) public awareness of SCI and approaches to its treatment, and 3) current programmes, both veterinary and human, for SCI treatment.

2. Underpinning research (indicative maximum 500 words)

This case study has emerged from work started in DVM by Prof Robin Franklin (employed since Oct 1991, Professor of Neuroscience since 2005) and Prof Nick Jeffery (employed between Jan 2000 and Oct 2010, Professor of Veterinary Medicine from 2006). The profound and often permanent loss of function that accompanies traumatic injury to the spinal cord results in large part because of the failure of regeneration of damaged axons. Axons fail to regenerate mainly because they are prevented from doing so by the cells that accumulate at the injury site. A long-standing experimental approach to promote recovery is to transplant into the injury site cells that encourage axon regeneration. Although many cell types have been transplanted in experimental models of SCI, there is a generally accepted view that olfactory ensheathing cells (OECs), a population of cells found only in the peripheral olfactory system where axon growth occurs continually as a normal physiological process, are the most promising. However, nearly all previous studies have been undertaken using experimental injury in laboratory animals, where the tight control of variables and the often slight functional improvement does not necessarily accurately predict how such an approach will translate into clinical trials in larger species, especially humans. Profs Franklin and Jeffery proposed using domestic dogs, where impact injury to the spinal cord is relatively common due to disc extrusions and accidents, as a suitable translational model. This model address both the issue of 'scaling up' from rodents to humans and the more challenging issue of whether the intervention was clinically effective, since SCI in domestic dogs is naturally occurring and not experimental. The partnership between Franklin and Jeffery made the DVM uniquely placed to undertake this study. Franklin is a pioneer of OEC transplantation (both rodent and human) and the basis of their regenerative function, while Jeffery, a veterinary neurologist, has a long-standing interest in clinical canine SCI.

Following on from the experimental work in the Franklin laboratory of rodent (started in 1996 and continued to the present) and human (2000) OECs it was established that adult dog OECs can be readily grown in tissue culture [1]. It was subsequently established that these could be harvested and grown from the dog frontal sinus with minimal trauma [2]. In parallel, techniques were developed for the digitalisation, quantification and detailed analysis of canine gait using infrared cameras – an essential element of the outcome measures by which the efficacy of cell transplants could be assessed [3, 4]. An initial Phase 1 trial by Franklin and Jeffery, funded by the International Spinal Research Trust, established that transplantation of autologous OECs, expanded ex vivo, into clinical (i.e. non-experimental) SCI was a safe procedure with no serious adverse consequences [5]. This then led to the MRC supporting a Phase 2 clinical trial led by Franklin and Jeffery, the first veterinary clinical trial supported by the MRC, in which the efficacy of autologous OEC transplantation was assessed in a range of outcome measures of both locomotor and autonomic function [6]. Twenty dogs with severe stable SCI (equivalent to ASIA grade A human patients) were transplanted with OECs and compared over a six-month period with 10 similarly affected dogs transplanted with cell transport medium alone. Recipients of cell transplants gained significantly better fore–hind coordination than those dogs receiving cell transport medium alone. Thus, intraspinal OEC transplantation improves communication across the damaged region of the injured spinal cord, even in chronically injured individuals.

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

a. Selected references (authors who are or were members of DVM in bold)

1. **Smith PM**, **Lakatos A**, Barnett SC, **Jeffery ND**, **Franklin RJM**: Cryopreserved cells isolated from the adult canine olfactory bulb are capable of extensive remyelination following transplantation into the adult rat CNS. *Exp Neurol* 2002, 176:402-406.
2. **Skinner APC**, **Pachnicke S**, **Lakatos A**, **Franklin RJM**, **Jeffery ND**: Nasal and frontal sinus mucosa of the adult dog contain numerous olfactory sensory neurons and ensheathing glia. *Res Vet Sci* 2005, 78(1):9-15.
3. **Hamilton L, Franklin RJM**, **Jeffery ND**: Development of a universal measure of quadrupedal forelimb-hindlimb coordination using digital motion capture and computerised analysis. *BMC Neurosci* 2007, 8:77.
4. **Hamilton L, Franklin RJM**, **Jeffery ND**: Quantification of deficits in lateral paw positioning after spinal cord injury in dogs. *BMC Vet Res* 2008, 4:47.
5. **Jeffery ND**, **Lakatos A**, **Franklin RJM**: Autologous olfactory glial cell transplantation is reliable and safe in naturally occurring canine spinal cord injury. *Journal of Neurotrauma* 2005, 22:1282-1293.
6. **Granger N**, **Blamires H**, **Franklin RJM**, **Jeffery ND**: Autologous olfactory mucosal cell transplants in clinical spinal cord injury: a randomized double-blinded trial in a canine translational model. *Brain* 2012, 135(Pt 11):3227-3237.

b. Selected research grant support

"The functional effects of olfactory ensheathing cell transplantation on severe clinical spinal cord injury in dogs" **Medical Research Council** RGP0015 01/04/08-31/03/2011, *£469,523.* (Jeffery/Franklin PIs)

"Olfactory mucosa – an- accessible source of neural stem cells?" **Medical Research Council.** Strategic grant (67395). 01/10/04-31/9/07. *£304,184*. (Franklin PI)

"Canine models of spinal cord injury: characterising and establishing the regeneration potential of canine olfactory ensheathing cells" **International Spinal Research Trust.** Network Grant (NET003) 2003-2006. *£184,765*. (Jeffery/Franklin PIs)

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

The impact of SCI on society is enormous. In the UK a person is paralysed every 8 hours and there are around 1200 people paralysed from a SCI every year. There are currently thought to be approximately 50,000 people in the UK living with paralysis.

It has been estimated by the charity Spinal Research that the current annual cost of caring for people paralysed by SCI in the UK alone is more than £1 billion. 21% of people discharged from SCI Centres go into nursing homes, hospitals or other institutionalised settings rather than their own homes. The support group Apparelyzed estimates that 20% of patients leave SCI Centres clinically depressed. There have been no effective treatments for SCI to date. This work has driven a significant increase in public awareness, in part due to its mention in Melanie Reid's weekly column ('Spinal Column') in The Times (Ref 2).

The programme of work described here led to the first demonstration that cell therapies are beneficial in clinical SCI. The impact of this has been several-fold: our work, published in 2012, has 1) provided a novel and effective therapy for canine SCI, 2) validated canine SCI as a clinically relevant translational model of human SCI, and more generally achieved the important objective of validating the use of veterinary disease models in human medical research, and 3) provided justification for proceeding with clinical trials in humans (for example, these are already planned in the UK on the basis of this work with support from Wings for Life.

The publication of the clinical trial in the leading neurology journal *Brain* in November 2012 triggered an avalanche of media coverage around the world (Ref 1). For example, in the UK the story was covered on the Radio 4 Today programme, Radio 5 morning programme, and the BBC, ITV, Channel 4 and Channel 5 main news programmes. The story was covered in all the main daily

newspapers. Requests for interviews were received (and in many cases provided) from France, Germany, Australia, Finland, Brazil and other countries.
Public awareness of the study has been raised further via the University's own website of research highlights and "You tube" video which have received 8,489 and 72,784 views to date, respectively (Refs 4a and 4b).

This level of coverage raised the profile of veterinary medicine in translational research as well as the profile of SCI and has stimulated both practicing veterinarians and owners of dogs with SCI, as well as clinicians dealing with human SCI around the world, to enquire how this work can be made available and how it is advancing (enquiries that continue to be made). We are aware of a similar programme under way at the University of Tokyo Veterinary School.

The study had impact at HM Government level, featuring as the example of UK-based achievements in regenerative medicine in a keynote Eight Great Technologies speech (Ref 3) by Rt Hon David Willetts MP, Minister of State for Universities and Science, Department for Business, Innovation and Skills (Speech 24/01/13).

5. Sources to corroborate the impact (indicative maximum of 10 references)
Organisations who can corroborate impact:

1. Examples of television coverage of publication of clinical trial:

Channel 4; http://www.channel4.com/news/paralysed-dog-breakthrough-offers-hope-for-humans

ABC; http://abcnews.go.com/Health/nose-cells-paralyzed-dogs-walk/story?id=17763218#.UKtB66JKRM0

ITV Anglia; http://www.itv.com/news/anglia/story/2012-11-19/paralysed-dog-walks-again/

CNN; http://edition.cnn.com/video/?hpt=hp_c3#/video/bestoftv/2012/11/20/sproj-paralyzed-dogs-walk-again-max-foster-pkg.cnn

ITN ; http://www.itn.co.uk/UK/61951/paralysed-dog-walks-after-pioneering-research

BBC News; http://www.bbc.co.uk/news/health-20390966

2. Example of newspaper coverage

The Times – Melanie Reid 'Spinal Column' -
http://www.thetimes.co.uk/tto/health/article3605415.ece

3. Rt Hon David Willetts, MP, speech

https://www.gov.uk/government/speeches/eight-great-technologies
http://www.policyexchange.org.uk/images/publications/eight%20great%20technologies.pdf

4a. University website

8,489 views on www.cam.ac.uk/research
http://www.cam.ac.uk/research/news/first-randomised-controlled-trial-to-show-spinal-cord-regeneration-in-dogs

4b. University YouTube channel

72,784 views on YouTube - http://www.youtube.com/watch?v=YLnegrzbBBk