Institution: King's College London

Unit of Assessment: UoA4 - Psychology, Psychiatry & Neuroscience

Title of case study: 15: Opening up the opportunities for stem cell therapies for neurodegenerative diseases

1. Summary of the impact

Neural stem cells offer enormous therapeutic potential for stroke but they require regulatory approval. Researchers at King's College London (KCL) devised a technology to immortalise stem cells, generated clinical-grade neural stem cell lines and demonstrated efficacy in an animal model of stroke. KCL research underpins the first approvals in the UK for a therapeutic stem cell product. This led to an industry-sponsored clinical trial of a stem cell therapeutic that has demonstrated vital improvement in all the first five stroke patients treated. KCL research has made a significant impact by considerably reducing the timetable for delivering potential therapies which will affect the life sciences industry and the process now in place acts as a model for other technology developments in this area.

2. Underpinning research

At any one time around 900,000 people in the UK are living with the effects of a stroke, which can include considerable disability. Neural stem cells show great promise as therapeutics for neurodegenerative disease, but this requires stable, clinical-grade neural stem cell lines with demonstrable efficacy. Research conducted at the Institute of Psychiatry, King's College London (KCL) sought to develop a stem cell therapy for neurodegenerative disorders. This work was initiated by Prof Jeffrey Gray (1983-1999, Chair of Psychology), Dr Helen Hodges (1985-2004, Reader in Psychology) and Dr John Sinden (1984-1998, Reader in Neurobiology of Behaviour) and continued by Prof Jack Price (1998-present, Head of the Centre for the Cellular Basis of Behaviour), Dr Mike Modo (2001-2011, Lecturer) and Dr Sandrine Thuret (2006-present, Research Fellow). This was in collaboration with ReNeuron Ltd, a KCL spin-out company founded by KCL researchers in 1998 and initially based on site. A collaborative relationship has continued ever since, with the company now operating from an outside base.

Generating a stable and robust cell line for safe therapeutic use

KCL research initially addressed the question of whether human neural stem cells could be generated that would be sufficiently stable and robust for clinical development. While many sources of these cells have been identified under research conditions, none had met the standards of purity and sterility required of a biological therapeutic set by the Medicines and Healthcare products Regulatory Agency and the Human Tissue Authority. In a pivotal KCL publication in 1999, researchers demonstrated that transplantation of immortalised rodent neural stem cells led to the integration and development of regionally appropriate neurons and astrocytes, which brought about functional improvement following brain damage in both rodents and primates (1).

The challenge following these studies was to develop human stem cells that would be therapeutic and safe in patients and also meet regulatory standards. Cells in culture tend to be unstable: they lose chromosomes and begin to differentiate, losing their ability to rebuild brain tissue. Over the next 7 years, in collaboration with colleagues at ReNeuron, KCL researchers discovered a new method of making neural stem cells through a process named "conditional immortalisation," which allows the generation of millions of identical and stable stem cells.

A clinical grade human cell line is patented and efficacy is shown

The technology led to the patenting of CTX0E03, the first and only such line of clinical grade human cells to emerge from UK stem cell research. CTX0E03 was derived from human somatic stem cells following genetic modification with a conditional immortalising gene, c-mycER(TAM). This transgene generates a fusion protein that stimulates cell proliferation in the presence of the drug 4-hydroxy-tamoxifen (4-OHT). The cell line is clonal, expands rapidly in culture and has a normal human karyotype (46 XY). In the absence of growth factors and 4-OHT the cells undergo growth arrest and differentiate into neurons and astrocytes. In order for stem cells to be incorporated into a clinical trial they must also demonstrate efficacy in a validated animal model of neurodegenerative disease. KCL research demonstrated that CTX0E03 does indeed bring about functional recovery when engrafted into a rat model of ischaemic stroke. Appropriate cell migration and survival was accomplished 6-12 weeks post-grafting with no evidence of undesirable effects

e.g. significant cell proliferation accompanying (2).

These findings were followed up in 2012 with studies that enabled clinical trials to commence. KCL research provided pivotal data of efficacy and dose relationships, whereby intraparenchymal implant of 450,000 human neural stem cells in a rat model of stroke were shown to improve sensorimotor dysfunctions and motor deficits over 3 months (3). KCL research also provided evidence for the mode-of-action of the cells indicating that engrafted stem cells induce endogenous brain repair mechanisms (4).

3. References to the research

1. Virley D, Ridley RM, Sinden JD, Kershaw TR, Harland S, Rashid T, French S, Sowinski P, Gray JA, Lantos PL, Hodges H. Primary CA1 and conditionally immortal MHP36 cell grafts restore conditional discrimination learning and recall in marmosets after excitotoxic lesions of the hippocampal CA1 field. Brain 1999;122(Pt 12):2321-35. Doi: 10.1093/brain/122.12.2321 (44 Scopus citations)
2. Pollock, K; Stroemer, P; Patel, S; Stevanato, L; Hope, A; Miljan, E; Dong, Z; Hodges, H; Price, J; Sinden, J D. A conditionally immortal clonal stem cell line from human cortical neuroepithelium for the treatment of ischemic stroke. Exp Neurol 2006;199(1):143–55. Doi:10.1016/j.expneurol.2005.12.011 (100 Scopus citations)
3. Smith EJ, Stroemer RP, Gorenkova N, Nakajima M, Crum WR, Tang E, Stevanato L, Sinden JD, Modo M. Implantation site and lesion topology determine efficacy of a human neural stem cell line in a rat model of chronic stroke. Stem Cells 2012;30(4):785–96. Doi: 10.1002/stem.1024 (11 Scopus citations)
4. Hassani Z, O'Reilly J, Pearse Y, Stroemer P, Tang E, Sinden J, Price J, Thuret S. Human neural progenitor cell engraftment increases neurogenesis and microglial recruitment in the brain of rats with stroke. PLoS ONE. 2012;7(11):e50444. Doi: 10.1371/journal.pone.0050444 (1 Scopus citations)

Grants

- 2000-4. £129,290. European Commission Framework V RTD Action. *Neural Stem Cells and stem cell-based therapies*. Grant Holders: A Giangrande (co-ordinator), T Edlund, D Henrique, J Price, B Richardson, G Technau, A Vescovi
- 2004-7. £199,073. BBSRC. *Is translational control a mechanism for controlling neural stem cell differentiation?* Grant Holders: J Price, S Williams
- 2004-6. £125,654. European Commission Fr. V. *Genetic Mechanisms that determine neuronal progenitor identity in the ventral spinal cord.* Grant Holders: S Malas, J Briscoe, J Ericson, F Guillemot, E Martí, P Legrain, J Price
- 2004-7. £332,074. BBSRC Project Grant. *The relevance of embryonic positional specification to neural stem cell differentiation.* Grant Holders: B Williams, J Price
- 2004-12. £963,356. Charles Wolfson Charitable Trust. *Stem Cell Research into Neurodegenerative Disease*. Grant Holder: J Price
- 2005-8. €458,342. European Commission Framework 6. *From Stem Cell Technology to Functional Restoration after Spinal Cord Injury.* Grant Holders: A Privat, J Schoenen, E Sykova, J Mallet, M Gaviria, A Sirven, G Brook, M Gimenez y Ribotta, J Price
- 2006-9. £260,617. BBSRC Project Grant. *Controlling in vivo cell behaviour of stem cells by transplantation on engineered substrates.* Grant Holders: M Modo, J Price, K Shakesheff
- 2006-9. $315,138. NIBIB (NIH) QUANTUM Grant. *Neurovascular Regeneration.* Grant Holders: K Hirschi, M Dickenson, T Zwaka, J Wild, M Brenner, J Price, R Lovell-Badge, C ffrench-Constant

4. Details of the impact

Prior to KCL research, in collaboration with ReNeuron, regulatory approval had not been reached for any stem cell product in the treatment of a neurodegenerative disorder. This is despite the UK being often cited by Government bodies as having a strategic advantage in stem cell research and despite considerable funds being committed to UK stem cell research. KCL research led to regulatory approval, made significant impact on the life science industry and has led to improved outcomes in the treatment of stroke.

Regulatory approval for first UK stem cell therapy trial for neurodegeneration

KCL's pre-publication research provided the core of the regulatory submission for the first stem cell therapy trial. Approval is given by the Medicines and Healthcare products Regulatory Agency (MHRA) who consult an expert committee followed by interim approval. Full approval is only given once the application has been approved ethically by the Gene Therapy Advisory Committee (GTAC). No clinical trial on humans can begin without these approvals. In 2009, Prof Jack Price presented at the MHRA Expert Advisory Group as part of the process of acquiring the preliminary MHRA approval. The evidence presented included the technology underpinning the stem cell production process and the efficacy and safety data (Pollock et al. 2006) (1a). GTAC requested further research on safety and efficacy and these new data (Smith et al. 2012; Hassani et al. 2012) were presented at GTAC meetings in April (1b) and July 2009 (1c), as evidenced by the minutes of those meetings and the GTAC Annual Report (1d). These presentations led directly to the first approvals for a stem cell therapy trial in neurodegeneration in the UK, a major breakthrough for regenerative medicine. The research that led to the approvals also secured the future of the KCL spin-out company ReNeuron (1e) as an SME (1f), which holds the patents for the cell line (1g,h). Of further impact is that the process of meeting the regulatory standard developed during these presentations and meetings now acts as a model for other technology developments in this area.

First industry sponsored trial in stroke shows improvements in patients

Following these approvals, the stem cell line CTX0E03 became the first, and so far only, fully regulated neural stem cell line (named ReN001) for disabled stroke patients to reach a clinical trial in the world. The ReNeuron sponsored PISCES (Pilot Investigation of Stem Cells in Stroke) trial, which began in November 2010 in Glasgow, involves injecting 2, 5, 10 or 20 million ReN001 cells into the brains of 12 stroke patients (three at each dose) with moderate to severe functional neurological impairments following an ischaemic stroke 6-60 months previously. This is carried out using MRI brain imaging to guide the injection to the areas neighbouring the stroke damage (2a).

At this stage, the primary aim was to test the safety and tolerability of the treatment, and indeed, there were no cell-related or immunological adverse events reported in any of the patients. Additionally though, the majority of the nine patients who had received treatment by January 2013, some of whom had had considerable disability, showed reductions in neurological impairment and spasticity compared with their pre-treatment baseline performance. Improvements were sustained, and in some cases increased, in the first five patients treated in 2010-2011 who have been followed-up for a year. Functional MRI data indicated improved signalling in parts of the cortex related to movement (2b,c). These are vital improvements which herald faster recovery pathways for stroke victims reducing the disability and care burden and improving quality of life. These promising results have led to the approval of the next set of larger studies (2d).

Government and public dissemination

With their expertise in regenerative medicine research, representatives from both KCL and ReNeuron recently provided evidence to the Government's Science and Technology Committee whose aim was to "pinpoint the UK's strengths in regenerative medicine, identify barriers to translation and commercialisation and recommend solutions." The findings of the committee were presented in their First Report in June 2013, which concluded that "Regenerative medicine has the potential to save lives and to help support the UK economy … accordingly, we recommend that the Government appoint the chair of the independent regenerative medicine delivery expert working group as the UK's regenerative medicine champion (with) a budget and support from a Government office (3a).

The results of ReNeuron's first trial have been widely highlighted in the media, including in reports from the BBC (3b), Channel 4 (3c) and Scottish Television (3d), which feature one of the patients in the trial who reported improvements in balance and mobility and activities of daily living such as being able to tie his shoelaces and play the piano. Overseas, in the USA ReNeuron was highlighted by the Alliance for Regenerative Medicine (ARM) in their 2012 'Biotech Showcase.' ARM is a Washington, DC-based global advocacy organisation that promotes initiatives to accelerate the development of safe and effective regenerative medicine technologies and works to increase public understanding of the field and its potential to transform human healthcare (3e,f).

5. Sources to corroborate the impact

1. **Regulatory approvals**
   a) GTAC Meeting 11th February 2009: http://webarchive.nationalarchives.gov.uk/20120104125945/http://dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_099131.pdf
   b) GTAC Meeting 29th April 2009: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_103400.pdf
   c) GTAC Meeting 8th July 2009: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_107761.pdf
   d) GTAC 16th Annual Report (see pages 11-12): http://webarchive.nationalarchives.gov.uk/20120104125945/http://dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_129676.pdf
   e) ReNeuron Ltd: http://www.reneuron.com/
   f) ReNeuron Lit Financial Report 2009: http://www.reneuron.com/images/stories/Financial%20Reports/Annual%20Report%2031%20March%202009%20-%20Group%20PLC%20(7mb).pdf
   g) Patent: Methods of treating stroke through administration of ctx0e03 cells. Sanberg P, Sinden J, ReNeuron Limited. Publication date: Feb.21.2013. http://www.google.com/patents/US20130045189
   h) Patent: Cell lines. US 7416888 B2. Pollock K, Sinden J, Stroemer P. ReNeuron Limited. Publication date: Aug.26.2008. http://www.google.com/patents/US7416888. Cites Virley et al. 2009

2. First industry sponsored trial in stroke
   a) PISCES Trial: http://www.clinicaltrials.gov/ct2/show/NCT01151124?term=CTX0E03&rank=1
   b) Abstract 495. Pilot Investigation of Stem Cells in Stroke [PISCES]. A Phase I Trial of CTX0E03 Human Neural Stem Cells. Kalladka D, et al. 22nd European Stroke Conference. 28-31 May 2013. London. http://www.esc-archive.eu/22ESC_London_2013/pubData/source/ESC%20London%202013.pdf
   c) ReNeuron Press Release (28 May 2013): http://www.reneuron.com/press-release/interim-data-from-clinical-trial-of-reneuron-s-stem-cell-therapy-for-stroke-to-be-presented-at-leading-stroke-conference-longer-term-data-continue-to-show-good-safety-profile-and-evidence-of-sustained-reductions-in-neurologica
   d) ReNeuron Press Release (11 Sept 2012): http://www.reneuron.com/press-release/reneuron-files-two-new-clinical-trial-applications-ahead-of-plan-in-stroke-and-critical-limb-ischaemia-as-its-stem-cell-programmes-advance

3. Government and public dissemination
   a) Science and Technology Committee Report on Regenerative Medicine in the UK (26 June 2013): http://www.publications.parliament.uk/pa/ld201314/ldselect/ldsctech/23/2302.htm
   b) BBC News - Stroke patients see signs of recovery in stem-cell trial (27 May2013): http://www.bbc.co.uk/news/health-22646103
   c) Channel 4 News - New stem cell hope for stroke patients (27 May 2013) http://www.channel4.com/news/new-stem-cell-hope-for-stroke-patients
   d) STV News - Stroke victims show signs of recovery following stem cell therapy (27 May 2013) http://news.stv.tv/west-central/226967-stroke-victims-show-signs-of-recovery-following-stem-cell-therapy/
   e) Alliance for Regenerative Medicine: http://alliancerm.org/
   f) ARM Biotech Showcase: http://www.youtube.com/watch?v=KDpVsFlxIic