Future treatment options for Parkinsonism: Stem cell therapy

Cindy Towns
Dunedin School of Medicine

Abstract
Parkinson's disease (PD) and multiple systems atrophy (MSA) are neurodegenerative disorders with distinct clinical and pathological features. Both disorders are severely debilitating and although sufferers may respond to dopamine agonists in the short term, there is currently no effective long-term treatment option. Embryonic stem (ES) cells have attracted much hype and optimism with regard to neurodegenerative diseases. ES cells are regarded as having the potential to overcome the material shortages and technical difficulties that have hindered fetal neural transplants. However, the interactions between ES cells and their microenvironment are complex and further research is required in order to accurately and consistently control proliferation and differentiation. Ethical issues will also need to be considered before ES cells make the transition from the laboratory to mainstream medical practice.

Parkinson's Disease (PD) was first described by James Parkinson in 1817 and is characterised by bradykinesia, resting tremor, cogwheel rigidity and postural reflex impairment.[1] Degeneration of the dopamine-containing neurons and deposition of Lewy bodies in the substantia nigra are the most obvious pathological features of PD although damage may also occur in the cortex, brainstem, cranial nerve nuclei and the autonomic nervous system. Multiple systems atrophy (MSA), by comparison, is a neurodegenerative syndrome in which Parkinsonism is associated with signs of more extensive neurological damage.

Extrapyramidal signs in MSA are similar to those appearing in PD, for example, bradykinesia, rigidity and postural instability, but cerebellar dysfunction and autonomic signs may also be present; a result of neuronal loss and damage in multiple neurological structures. Cerebellar signs include ataxia of speech, ataxia of limb movement, and difficulties with gait whilst autonomic insufficiency can result in orthostatic hypotension, urinary retention or incontinence, constipation and sweating.[2] The terms striato-nigral degeneration, Shy-Drager syndrome and olivo-pontocerebellar atrophy refer to various manifestations of MSA although such disorders may be referred to by the more general term "Parkinsonism plus".[3]

In PD, the clinical triad of akinesia, rigidity and tremor reflects damage to the substantia nigra and responds to treatment with levodopa (L-Dopa), a precursor to dopamine. However, despite often marked initial improvements, response to L-dopa diminishes over time. In patients treated for over five years, greater than 50% will develop instability of their motor response.[4] Administration of L-dopa may also provide MSA sufferers some relief from bradykinesia, rigidity and tremor but the response is usually small and not well sustained.[2] This lack of response to L-dopa assists in distinguishing MSA from PD, particularly in the early stages.

Thus PD and other Parkinsonism syndromes are characterised not only by their distinctive clinical and pathological features, but also by their continual progression. Although pharmacological treatment offers amelioration of motor deficits, effects decline within five to ten years. The debilitating nature of these diseases and the lack of long-term treatment options have prompted patients, their families and physicians to look beyond traditional therapies. To many of these people, the successful derivation of human embryonic stem (ES) cells represents the future miracle cure for PD and other neurodegenerative conditions.

ES cells have gained unprecedented attention both in the scientific and general media. Predicted to have a greater impact on health care than the advent of anaesthesia or the development of antibiotics[5] and hailed as the next revolution for medicine, ES cells have been described as the future of molecular biology and the

biggest development since recombinant DNA.[6] Many believe that stem cells will create a whole new genre of medical therapies.[7]

The two unique properties of ES cells are pluripotency and immortality. Pluripotency refers to the ability of stem cells to form cells from all three germ layers: ectoderm, endoderm and mesoderm. In essence, it denotes a capacity to form all cell types within the human body. Immortality refers to the ability of stem cells to self-renew; to divide for an indefinite and potentially infinite period of time. It is these properties that render these cells of particular interest to PD sufferers and their families. ES cells have the capacity to differentiate into neural stem cells, and subsequent neuronal subtypes, that deteriorate during the course of this disease.

Neural stem cell transplantation is receiving considerable attention with regard to neurodegenerative disorders due, partly, to the success with fetal neural transplants. Fetal dopamine cell transplants have been used in treating PD for many years. Positron emission topography used to image the brain following surgery with L-dopa producing neurons (derived from fetal material) has demonstrated that transplants are still alive, producing dopamine and providing therapeutic benefit, ten years after replacement.[8]

Although fetal neural transplantation has demonstrated success in Parkinson's disease, efforts are constrained for at least two reasons. First, deriving material from aborted fetuses is difficult and the tissue itself is in short supply. It takes six fetuses to provide enough material for one graft, as 90-95% of neurons die shortly after grafting.[9] Secondly, the low efficiency of producing dopamine neurons from fetal, neonatal and adult stem cells has limited the therapeutic benefit of transplants for Parkinson's disease.[10] Freed notes that an unlimited supply of dopamine cells produced in culture would solve both the accessibility and mortality problems in these cells.[11] ES cells could be used to produce a potentially infinite supply of neural stem cells in culture that could then be used to produce the dopamine-producing neurons that are deficient in PD. This would render the shortages in fetal material and the effects of early apoptosis inconsequential.

Initial results provide some encouragement toward eventual clinical goals of symptom alleviation. For example, Connor et al note that embryonic cells have shown potential in restoring neurochemical and behavioural problems in animal models of degenerative disease.[12] ES cells have generated dopamine-producing neurons that function in an animal model of PD[13] and there is also an unpublished report of an autologous transplant of neural stem cells alleviating symptoms in a human PD sufferer.[14] Other recent work has illustrated that stem cells implanted into the brains of rats and mice can grow into L-dopa producing neurons. This work suggests that all of the instruction mechanisms necessary for maturation are present in the adult brain.[15]

Of particular interest is the work by Gökhan and Mehler, who cite an increasing body of evidence suggesting that neurodegenerative disorders may represent fundamental disorders of neural development.[16] These may result from pathogenic mutations in the neurodisease-related genes, which then have delayed neuropathologic consequences. According to these authors, ES cells represent an essential experimental tool for strategies aimed at intervening prior to irreversible neural injury. Specifically, the study of ES cell lines, and their *in vitro* and *in vivo* development, will provide insights into gene-environment interactions and critical periods in neurogenesis. Regenerative strategies can then be used to target vulnerable neural precursor populations during the 'presymptomatic' stages of disease.

Early promising signs need to be accompanied by care in interpreting experimental data. Collier and Kordower state that animal studies show advanced age and a long history of dopamine depletion have a negative influence on behavioural efficacy and anatomic features of dopamine neuron transplants.[17] They suggest that some early animal models do not accurately reflect PD as they are based on grafts into young adult rats within only one to two months of experimentally-induced dopaminergic denervation of the striatum. A 2001 trial further indicates the importance of age and history of neural degeneration.[18] The double-blind, placebo-controlled surgical trial demonstrated that 85% of patients under the age of 60 had surviving grafts and a reduction in their symptoms, but that similar benefits were not displayed in older patients.

Freed (2002) states that it is too early to say whether ES cells will provide an infinite and safe supply of dopamine neurons.[11] This author explains that much work remains to be done with regard to optimising conditions for accurate differentiation, proliferation and transplantation. He also notes that although ES cells are opening "an exciting era in human therapies", success will also depend upon eliminating the threat of uncontrolled proliferation. This risk is inherent to undifferentiated, self-renewing stem cells and one that will require extensive testing if stem cells are to enter mainstream medical practice.

Although it can be stated that stem cell therapy provides some hope for PD, it remains questionable as to whether sufferers of other Parkinsonism-type disorders, such as MSA, will benefit. MSA patients do not show the marked response to L-Dopa, or other dopamine agonists, that characterises the early stages of PD. It is, therefore, unlikely that such patients will benefit from the replacement of dopamine-producing cells that current stem cell research focuses on. Although transplants may ameliorate some of the motor symptoms associated with MSA, greater success may rely on the transplanted cells homing to other sites of neuronal loss, for example, the putamen, globus pallidus, caudate

and subthalamic nuclei and differentiating into the required cell type. Such activity would rely heavily on cues within the host environment. Unfortunately, much work remains to be done in accurately delineating the components of this "stem cell niche" and its effects on stem cell survival and differentiation.

It is necessary to acknowledge the controversy that surrounds ES cell research as the successful isolation and culturing of these cells has opened a Pandora's box of ethical dilemmas. Dissenters to the research argue that medicine is being advanced by means of sacrificing human life. Central to these heated debates is the fact that ES cells are being derived from human embryos. Specifically, they must be derived from a blastocyst, which develops approximately five to seven days post-fertilisation and, therefore, represents the very early embryo. ES cells are derived from the 'inner cell mass' of the blastocyst, and the process of acquisition necessitates its destruction; hence, there is a moral and ethical debate surrounding this research. It is not my intention to elaborate on the moral status of the human embryo and resulting societal divisions, but readers should be aware that the field is fraught with ethical issues. This is of particular relevance to ES cell research undertaken in countries such as the US and Germany, where ethical concerns have played a significant role in research guidelines.

In summary, there is therapeutic potential for ES cells and their derived sublineages in the treatment of Parkinson's disease. Accurate and safe cellular differentiation is a fundamental prerequisite to mainstream clinical application. Research currently relies heavily on animal models and hence success, as measured by human clinical trials, is likely to be long term rather than short term. The potential of similar transplants for treating MSA remains more questionable due to a lack of response to dopamine agonists in these patients.

Acknowledgements

The author wishes to thank the University of Otago, Department of Anatomy and Structural Biology and the University of Otago, Faculty of Medicine for their contribution to the course of study.

Cindy Towns is an MBChB/PhD student entering her fifth year at the Dunedin School of Medicine. Her thesis considers the ethical issues relating to embryonic stem cell research. She is the co-author of a paper on stem cells and embryos recently accepted by *The Journal of Medical Ethics*. This paper was written originally as a Case Appreciation.

References

1. Goldman S, Tanner C. Etiology of Parkinson's Disease. *Parkinson's disease and movement disorders* 3rd ed. (ed. Jankovic J, Tolosa E) Baltimore, MD: Williams & Wilkins, 1998, 133-58.
2. Gilman S. Multiple System Atrophy. *Parkinson's disease and movement disorders* 3rd ed. (ed. Jankovic J, Tolosa E) Baltimore, MD: Williams & Wilkins, 1998, 245-62.
3. Kumar R, Clarke D. *Clinical Medicine* 4th ed. London: Saunders, 1998, 1047-9.
4. Poewe W, Wenning G. Levodopa in Parkinson's Disease: Mechanisms of Action and Pathophysiology of Late Failure. *Parkinson's disease and movement disorders* 3rd ed. (ed. Jankovic J, Tolosa E) Baltimore, MD: Williams & Wilkins, 1998, 177-90.
5. Okarma TB. Human primordial stem cells. *Hastings Cent Rep* 1999; 29: 30.
6. Butler, D. Breakthrough stirs US embryo debate. *Nature* 1998;396: 104.
7. Committee on the Biological and Biomedical Applications of Stem Cell Research. *Stem cells and the future of regenerative medicine*. Washington DC: National Academy Press, 2002.
8. Piccini P, Brooks DJ, Bjorkland A, Gunn RN, Grasby PM, Rimddi D et al. Dopamine release from nigral transplants visualized in vivo in a Parkinson's patient. *Nat Neurosci* 1999; 2: 1137-40.
9. Barinaga M. Fetal neuron grafts pave the way for stem cell therapies. *Science* 2000; 287: 1421-2.
10. Hawley RG, Sobieski DA. Somatic stem cell plasticity: to be or not to be. *Stem Cells* 2002;20: 195-7.
11. Freed CR. Will embryonic stem cells be a useful source of dopamine neurons for transplant into patients with Parkinson's disease? *Proceedings of the National Academy of Sciences of the United States of America* 2002; 99: 1755-7.
12. Connor B, van Roon-Mom WM, Curtis MA, Dragunow M, Faull RL. Stem cells and neurodegenerative diseases. *NZMJ* 2001;114: 477-9.
13. Kim JH, Auerbach JM, Rodriguez-Gomez JA, Velasco I, Gavin D, Lumelsky N et al. Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature* 2002; 20: 20.
14. Stewart J. Breakthrough in fight against Parkinson's. ABC news online. 2002 http://www.abc/net.au/am/s527709/htm
15. Strauss E. AAAS meeting. Stem cells make brain cells. *Science* 2001; 291: 1689-90.
16. Gokhan S, Mehler MF. Basic and clinical neuroscience applications of embryonic stem cells. *Anat Rec* 2001;265: 142-56.
17. Collier T, Kordower J. Neurotransplantation for the treatment of Parkinson's Disease: Present-day optimism and future challenges. *Parkinson's disease and movement disorders* 3rd ed. (ed. Jankovic J and Tolosa E) Baltimore, MD: Williams & Wilkins, 1998, 1065-84.
18. Freed CR, Greene PE, Breeze RE, Tsai WY, DuMouchel W, Kao R et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med* 2001;344: 710-19.