

# Cellular Therapy for CNS Disorders: A Translational Perspective

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**R**epair of the human central nervous system (CNS) has become a therapeutic goal and is now reaching the clinical translational phase of investigation. Stem cell-based approaches fall under the broader category of regenerative medicine and offer new avenues of clinical research that may fundamentally impact how neurological diseases are treated. Cell-based treatments rely upon the potential for cell transplantation to provide cellular neuroprotection and/or cell replacement. The pathway to develop stem cell therapies for the CNS holds both new challenges and opportunities that involve a spectrum of scientific, ethical, regulatory, translational, and clinical issues. However, the challenges involved with the early stage of stem cell transplantation to treat neurodegenerative disorders are by no means insurmountable. Indeed, the transition from proof-of-concept in animal studies to human clinical trials is already underway for the neural stem cell and other progenitor cells.

This review will highlight the important areas that affect the translation of cell discovery to clinical testing, including the range of target disorders, candidate stem cell technologies, rationale for stem cell therapy, regulatory considerations, and current clinical trial activity. The factors that are likely to impact the future pace of development, commercialization, and clinical success from a corporate and translational perspective will also be briefly described. If basic science emphasizes the theoretical, then translation must focus on the logistical and practical; both of which must be fulfilled in order to successfully introduce a treatment as complex as stem cell therapy to the clinical setting. Concepts that work well at the basic science and animal model level must be adapted and evolved into a format applicable for human safety and efficacy testing.

## CNS Disorders Considered Targets for Stem Cell-Based Therapy

Candidate targets for stem cell therapies span a spectrum of

developmental, degenerative and traumatic neurological conditions in the brain and spinal cord.<sup>1, 2, 3, 4</sup> These diseases or conditions differ in the types and groups of cells involved in the underlying pathology and the clinical manifestations. Consequently, the cells used for therapy will depend upon the affected cell population, and it is possible that the proposed donor cell type could have a therapeutic benefit in more than one indication. Theoretically, neural stem cells have the potential to produce all cell types of the CNS. However, the underlying medical condition may inhibit those cells from maturing into the proper cells needed for functional replacement. Historical interest in reconstituting specific neuronal populations for neurodegenerative conditions such as Parkinson's disease (PD), Huntington's disease, stroke, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease has been based on a cell replacement strategy.<sup>5, 6, 7, 8, 9</sup> For PD, at least two Phase III clinical studies have been conducted with fetal tissue transplants. While the results of these two important investigations demonstrated the safety of allograft transplantation into the CNS, robust efficacy was not observed.<sup>10, 11</sup> For both ethical and clinical reasons, interest has shifted away from fetal tissue transplants to exploring the potential for neural stem cell therapy.<sup>12, 13, 14</sup> The predominant strategy for these neurodegenerative disorders is one that requires the donor cell to terminally differentiate into the correct neuronal subtype with regional specificity, establish correct functional afferent and efferent synaptic connections, and resist the underlying disease process which caused death of the endogenous neurons. As a result, the goal for specific neuronal cell replacement and functional integration is complex, and clinical trials with stem cells testing this approach have yet to be implemented.

Other CNS conditions considered potential targets for stem cell therapy include spinal cord injury and disorders of myelination (such as leukodystrophies, Pelizaeus-Merzbacher disease (PMD), transverse myelitis, multiple sclerosis, and cerebral palsy) secondary to periventricular white matter injury.<sup>15, 16, 17</sup> In these disorders, establishment of donor-derived myelination through transplantation of oligodendrocyte precursors, or stem cells that differentiate into myelinating oligodendrocytes, is the hope.<sup>18</sup> The spectrum of disorders with myelination insults include post-traumatic demyelination in spinal cord injury, hypomyelination in white matter abnormalities associated with premature birth, dysmyelination in select leukodystrophies (i.e., PMD), and finally demyelination lesions in transverse myelitis and multiple sclerosis. From the perspective of a cell therapy approach, the goal of myelination is viewed as less complex than the goal of neuronal replacement, and the ability to

assess myelination by magnetic resonance imaging (MRI) may be a more feasible clinical end-point to measure.<sup>19, 20, 21, 22</sup>

Lysosomal storage diseases (LSDs) are also considered a potential target for stem cell therapy. In this class of diseases the transplantation of donor cells is aimed at producing missing factors or enzymes that would cross-correct the diseased host cells.<sup>23</sup> More specifically, the goal is to achieve migration of transplanted cells throughout the brain parenchyma and then subsequent secretion of appropriate soluble enzymes that will lead to cross-correction of the host cells. Deficient host neurons can then take up the enzymes by receptor-mediated endocytosis, resulting in the normalization of lysosomal function and in the reduction or elimination of abnormal storage of the unprocessed metabolic products. The straightforward requirement for donor cell survival and secretion of a normal gene product creates perhaps the ideal model for initial proof-of-concept of a clinical benefit from neural stem cell transplantation.

Diseases of the retina are also considered appropriate targets for cell therapy, and the principles of both cell protection and replacement strategies are the focus of current research.<sup>24, 25, 26</sup> It is likely that neuroprotection of the retina, rather than photoreceptor replacement, may be the most feasible and achievable goal for stem cell therapy for the eye in the foreseeable future. Further, the eye may offer a better pathway for proof-of-concept for stem cell therapy than the brain or spinal cord. In addition to a large, unmet medical need, the eye offers the practical benefits of a contralateral, unoperated eye, a less complicated route of administration, and a range of objective end-points that could be used to measure a clinical benefit. Cell therapy approaches directly applicable to treating retinal diseases are more fully covered by Sally Temple elsewhere in this report.

## Donor Cell Types for Transplantation

The range of cell and stem cell platforms that may yield potential therapeutic benefit includes embryonic stem cells (ESC), somatic stem cells (which include the neural stem cell), CNS progenitor cells, and cells derived from induced pluripotent stem cells (iPS).<sup>27</sup> Mesenchymal and umbilical cord stem cells are also under investigation for therapeutic potential in the CNS, but are not thought to share the robust properties of survival, migration, and differentiation exhibited by neural stem cells. There are a number of important attributes that any candidate cell for clinical use must display. It must be reliably and consistently isolated from source tissue, easily purified and expanded in order to produce appropriate doses for clinical use, and cryopreservable into a cell bank that will facilitate elective clinical administration to the patient.

Human ESC (hESC) have been used as models to study human development, in gene and drug discovery programs, and perhaps most importantly, as a potentially endless source of specialized neural progenitor cells that may be used for transplantation.<sup>28</sup> However, platforms based on hESC are inevitably linked to the risk of uncontrolled growth and teratoma formation associated with pluripotency. For this reason, continued and extensive research is required to demonstrate safety and effectiveness prior to clinical testing.<sup>29, 30</sup>

Induced pluripotent cells (iPS) have received much attention in recent years as they offer the potential to generate patient-specific

cells for autologous use, presumably avoiding the need for immunosuppression.<sup>31, 32</sup> However, donor cells resulting from iPS technology have years of research ahead before clinical translations, and cells derived from iPS sources have the same risk of tumor formation as cells derived from hESC. Thus far, the horizon for safe clinical testing of iPS remains unclear.

Mesenchymal and umbilical cord blood stem cells have both been purported to be effective in preclinical CNS disease models, but the durability of cell survival, potential for differentiation, and the mechanism of action are different from the neural stem cell.<sup>33</sup> The general applicability of this platform for CNS diseases is less clear than the potential offered by neural stem and progenitor cells.

Neural stem cells are developmentally categorized as somatic stem cells, and may also be referred to as tissue-specific or adult-derived stem cells. The CNS was the first solid organ in which an endogenous stem cell was identified, and human neural stem cells (hNSC) can be isolated from either developing or mature human brain tissue. The hNSC has the combined properties of self-renewal and the ability to differentiate into the three lineages of the CNS: astrocytes, oligodendrocytes, and neurons. hNSC can be isolated by fluorescence-activated cell sorting (FACS), after enzymatic dissociation of the source tissue, and grown in specific growth factor-rich media as free-floating neurospheres. The FACS sorted hNSC can then be expanded in culture, all the while retaining their ability to re-initiate neurosphere formation.<sup>34, 35</sup> Cells obtained in this way have been extensively studied and 1) display a normal karyotype; 2) do not form tumors *in vivo*; 3) do not require pre-differentiation with specific factors; and 4) retain multipotentiality.<sup>36, 37, 38, 39</sup> Neural stem cell platforms are under preclinical investigation for a variety of CNS diseases incorporating both cell replacement and cell protection strategies. The use of neural stem cells as a means for gene therapy has also been proposed,<sup>40, 41</sup> and although the preclinical testing and safety testing required for gene modified stem cells is more strenuous than for non-modified neural stem cells, such an approach could prove useful in certain disease categories.

## Rationale for Stem Cell-Based Approaches to CNS Diseases

Transplantation and engraftment of a donor cell within the diseased CNS may result in several potential benefits to the cellular environment. The classic goal of replacing injured or dysfunctional brain cells with new, healthy cells remains one potential mechanism for cell therapy. This is particularly evident for diseases in which there is loss of specific neuronal populations that, if replaced through transplantation, could result in clinical benefit. However, the requirements for specific neuronal phenotypes to differentiate, integrate and recapitulate complex neurocircuitry, in addition to remaining resistant to the underlying disease process, pose a significant challenge. Neuroprotection is an alternate mechanism of action, and perhaps a more achievable goal, in the early development of CNS cell therapy as the premise in this case is to provide a supportive role to the diseased cell population through production of trophic/growth factors or other cell functions. Neuroprotection in the form of stabilization, rather than replacement of diseased cells, may be applicable to many of the current disease targets and provide a

clinical benefit equally meaningful to cell replacement. The goal of neuroprotection may also represent an incremental approach to demonstrate proof-of-concept for cell therapy, and it is likely that early trials based on this premise will have a higher chance of success given the current understanding of stem cell biology and CNS transplantation.

## Immunology of CNS Transplantation

The ability to achieve prolonged survival of functional CNS allografts will depend on clarifying the factors that contribute to immune-mediated rejection and tolerance.<sup>42, 43</sup> The optimal use of immunosuppression will be advanced as the mechanisms underlying rejection and long-term engraftment are more clearly defined. The prolonged survival of fetal nigral tissue allografts from three different clinical trials for PD was reported in 2008, and the results support the premise that tolerance to transplanted cells is possible because of the relative immuno-privileged characteristic of the CNS.<sup>44, 45, 46</sup> The ability to monitor engraftment through non-invasive methods will also refine the use of immunosuppression and contribute to our understanding of CNS transplant immunology. Informed utilization of immunosuppression will maximize patient safety, promote cellular engraftment, and ultimately allow transplanted cells to achieve a beneficial biological effect for patients.

## Regulatory Aspects of Stem Cell Transplantation

No review of this field would be complete without acknowledging the important influence that the regulatory process imparts on the development of stem cell therapies. Stem cell-based therapies in the U.S. require the regulatory oversight of the U.S. Food and Drug Administration (FDA) for investigational use in humans and ultimately licensing of the product. Equivalent regulatory oversight in Europe is provided by the European Medicines Agency (EMA).

The regulatory process for cellular products is complex and will continue to evolve. Cells that are more than minimally manipulated require a complete regulatory submission and approval before clinical investigation, and most, if not all, stem-cell-based interventions are typically manipulated to a substantial degree by the regulatory agencies. Cells to be studied in human clinical trials are then subject to the statutes described in the Public Health Safety Act, Section 361 (for human cells) and Section 351 (for biologic products). In the U.S., the regulatory process is detailed in the Code of Federal Regulations<sup>47</sup> and in the U.S. FDA Center for Biologics Evaluation and Research.<sup>48</sup> In Europe, cellular therapies are classified as Advanced Therapy Medicinal products (ATMPs) with oversight by EMA via a centralized procedure.<sup>49</sup>

The procurement, processing, expansion and banking process of cells is also held to stringent regulatory requirements. In the U.S., the FDA has established compliance requirements for Current Good Tissue Practice (cGTP) and Current Good Manufacturing Practice (cGMP) to address some of the critical points in source tissue acquisition and subsequent production of the cell intended for transplantation. Both the cGTP and cGMP regulations are designed to prevent the transmission of communicable diseases, and to assure

standard quality assurance across each step in the production process. The compliance requirements for cGTP in the setting of Phase I trials has recently been described in a Guidance for Industry document issued by the FDA in late 2008.<sup>50</sup> The regulatory guidelines have a very practical effect on the feasibility of developing a cell that has demonstrated *in vivo* potential and sufficient expansion to a cell dose amenable for human testing, but must still comply with all of the cGTP and cGMP elements noted above.

The regulatory scope of the FDA covers almost every aspect of stem cell therapeutics, and the governing statutes are derived from the Public Health Safety Act, Sections 351 and 361. The regulatory perspective was further articulated in a Health Policy Report published in the *New England Journal of Medicine* by a former FDA Commissioner.<sup>51</sup> This report emphasized that the safety and efficacy components analyzed by the FDA include the following inquiries: “Does the product pose a risk of infectious or genetic disease transmission?”, “Does the cell product risk contamination or damage to the host tissue?”, “What are the final cell types, purity, and potency?”, and “Will the proposed cell product be safe and offer possible effectiveness when transplanted into the human patient?” Specific safety concerns relative to stem cells focus on potential contamination of immature stem cell populations that can proliferate in an uncontrolled manner forming tumors, as well as transmission of infectious agents or genetic alteration.

Tumorigenicity and karyotype stability studies are required to specifically address the potential for neoplastic transformation of donor cell populations. The former is particularly relevant to cellular interventions using ESC-derived and expanded cells, as establishing the purity of the transplantable cell population and determining the percentage of contaminating undifferentiated ESCs is critical. The interested reader is referred to the presentations of the FDA Cellular, Tissue and Gene Therapy Advisory Meeting of April 2008.<sup>52</sup>

The global regulatory structure for cell-based therapy will become more sophisticated as the biological characteristics of self-renewal, differentiation and cell expansion are further elucidated.<sup>53</sup> It is clear that meeting the regulatory guidelines for clinical translation of stem cell therapies is a factor influencing the pace of development. A balance between regulation of novel therapies, growing interest in investigating the potential clinical utility of stem cell transplantation, and maintaining the necessary safety standards should ultimately facilitate clinical testing for diseases that have no effective therapy.

In addition to established regulatory guidelines, the International Society for Stem Cell Research (ISSCR) has published general guidelines for clinical testing of stem cell interventions.<sup>54</sup> Additional expectations specific to clinical research in spinal cord injury have been published by the International Spinal Cord Society,<sup>55</sup> and general concepts applicable to CNS transplantation have been set forth by the American Society for Neural Transplantation and Repair.<sup>56</sup>

Additionally some organizations have issued position statements regarding the growing activity in stem cell interventions conducted in settings with variable regulatory and ethical oversight. The UK National Stem Cell Network,<sup>57</sup> along with the ISSCR and other medical societies, have issued useful perspectives on the risks involved with patient participation in stem cell “medical tourism.” A recent

publication regarding a patient with ataxia telangiectasia (AT) who underwent multiple cell transplants in Moscow and subsequently developed glioneuronal tumors, serves as a cautionary message.<sup>58</sup>

## Clinical Activity for Stem Cell Transplantation into the CNS

In contrast to the large number of preclinical studies, the actual clinical trial activity to date focused on stem cell therapy for the CNS is perhaps the best measure of progress in the field. Investigations with IND clearance or anticipated FDA authorization best reflect the cell technologies that have managed to navigate the complex pathway toward clinical testing. Recent announcements indicate that important milestones for the field are beginning to emerge. Companies reporting either clinical trial or regulatory activity for brain or spinal cord indications include StemCells, Inc., Geron, ReNeuron, and NeuralStem. Other companies focused on retinal diseases include Advanced Cell Technology (ACT) and Neurotech.

For the treatment of retinal diseases, ACT has announced plans to submit an IND for hESC-derived cells for a study involving Stargardt disease and macular degeneration. Neurotech recently announced the results of two Phase II studies using encapsulated human retinal pigment epithelial cells engineered to secrete ciliary neurotrophic factor as a retinal protective strategy in patients with retinitis pigmentosa and dry age-related macular degeneration.<sup>59</sup>

NeuralStem remains on clinical hold after filing an IND with the FDA for the use of a spinal cord stem cell in a Phase I study for patients with ALS.

ReNeuron has announced filing an IND with the FDA for the use of conditionally immortalized neural stem cells in stroke. The company remains on hold in the U.S., but reported approval by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) in early 2009. However, the company has also disclosed that further approval is now required by the Gene Therapy Advisory Committee (GTAC), which has responsibility for the ethical oversight of clinical trials in the UK involving stem cell therapies.

To date, only three INDs have been authorized by the FDA for stem cell testing in brain or spinal cord indications, with two cleared for StemCells, Inc. and one for Geron. The IND clearance by the FDA for a hESC-based trial for patients with complete spinal cord injury (Geron) is a milestone for the field. However, the recent completion of the first Phase I trial, which tested safety with a neural stem cell platform, marked the true beginning of human translation with stem cell-based therapy for CNS disorders.

Geron announced that its hESC-derived oligodendrocyte progenitor cells (GRNOPC1) IND application received clearance by the FDA in January 2009 for use in a Phase I trial designed to demonstrate safety in patients with complete thoracic spinal cord injury. The multicenter trial will enroll sub-acute patients after injury with the intent to increase cell dose after further FDA approval.<sup>60</sup>

The first IND authorized by the FDA for a neural stem cell approach to a CNS disorder was sponsored by StemCells, Inc. for a Phase I study in infantile and late infantile neuronal ceroid lipofuscinoses (NCL), a fatal lysosomal storage disorder, utilizing the

company's proprietary human central nervous system stem cell (HuCNS-SC®). The Phase I study transplanted six pediatric patients in a dose-escalation design testing total CNS target cell doses of 500 million cells in the low dose cohort and one billion cells in the high dose cohort. The safety profile did not reveal any adverse events considered related to the HuCNS-SC, and all patients tolerated the interventions of surgery, immunosuppression, and HuCNS-SC transplantation into multiple cerebral sites. Evidence of cell engraftment was obtained in the postmortem brain specimen from one subject who expired from the underlying disease eleven months post-transplant. This Phase I study is the first to report human data with a neural stem cell platform, and the demonstration of safety in this trial is expected to enable further clinical development for NCL and other disorders. StemCells, Inc. has also received clearance for a second IND for HuCNS-SC in a Phase I study of patients with PMD, a fatal congenital dysmyelination disorder. The goal of the Phase I PMD study is primarily to demonstrate safety, with a secondary goal of measuring the potential for donor-derived myelination using the neural stem cell.

## Commercialization and Timelines

Continued advances in the development of cell therapy, and ultimately commercialization, will depend on the success of clinical trials and demonstration of proof-of-concept in a human disorder. The impact on CNS diseases could prove significant as cell transplantation may have the potential to alter a disease course based on a single treatment, as opposed to the model of life-long drug therapy. As the incidence of some neurodegenerative diseases increases, the availability of alternative, and potentially more cost-effective, treatment options is critical from a public health perspective. It is hoped that timelines for cell therapy milestones will shorten as clinical activity increases and regulatory bodies continue to establish consistent guidelines for approval.

## Other Factors Likely to Influence the Pace of Development

The pace of development for stem cell-based therapy for the CNS will be influenced by many basic science and clinical elements. Advances in stem cell biology specifically concerning neural stem and progenitor cells will continue to drive progress in the field, particularly with regard to specific desired phenotypes. Animal models of disease that accurately reflect the human condition and permit human cell xenotransplantation will enhance exploration of efficacy. Understanding the immune regulation of the diseased CNS and allograft survival will also contribute to optimizing donor-cell engraftment, particularly because allogeneic transplants are likely to be the type tested for the foreseeable future. The identification of better clinical end-points and validated surrogate markers for neurodegenerative diseases will strengthen clinical trial design and improve the opportunity to measure a biological effect of transplanted cells. Finally, methods to non-invasively track donor cells will allow real-time examination of engraftment and cell behavior post-transplant.

## Conclusion

Continued development of stem cell therapy for the human CNS has the potential to alter how treatment for specific diseases might be approached, and success will require continued and mutual input of scientific, regulatory and clinical experts. The ultimate goal of any therapeutic approach is to reduce human suffering, and stem

cell therapy may prove to be one way to achieve this noble end. Many medical breakthroughs have successfully navigated the translational path from discovery to clinical utility, and, based on the promising preclinical and clinical data to date, there is no reason to believe that stem cell therapy for the CNS will be an exception.



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## References

1. J. E. Le Belle, C. N. Svendsen, *BioDrugs* 2002. 16; 389.
2. I. Singec, R. Jandial, A. Crain, G. Nikkhah, E. Y. Snyder, *Annu Rev Med*, 2007. 58; 313.
3. E. Y. Snyder, G. Q. Daley, M. Goodell, *J Neurosci Res* 76, 157 (Apr 15, 2004).
4. R. Zietlow, E. L. Lane, S. B. Dunnett, A. E. Rosser, *Cell Tissue Res* 331, 301 (Jan, 2008).
5. T. P. Harrower, R. A. Barker, *BioDrugs* 18, 141 (2004).
6. D. H. Park et al., *Med Sci Monit* 15, RA23 (Feb, 2009).
7. D. Kondziolka et al., *J Neurosurg* 103, 38 (Jul, 2005).
8. R. A. Bakay, *J Neurosurg* 103, 6 (Jul, 2005).
9. C. D. Keene et al., *Neurology* 68, 2093 (Jun 12, 2007).
10. C. R. Freed et al., *N Engl J Med* 344, 710 (Mar 8, 2001).
11. C. W. Olanow et al., *Ann Neurol* 54, 403 (Sep, 2003).
12. C. Holden, *Science* 297, 500 (Jul 26, 2002).
13. O. Lindvall, Z. Kokaia, A. Martinez-Serrano, *Nat Med* 10 Suppl, S42 (Jul, 2004).
14. O. Lindvall, Z. Kokaia, *Nature* 441, 1094 (Jun 29, 2006).
15. G. W. J. Hawryluk, J. Rowland, B. K. Kwon, M. G. Fehlings, *Neurosurgical focus* 25, E14 (2008).
16. M. S. Windrem et al., *Cell Stem Cell* 2, 553 (Jun 5, 2008).
17. H. M. Keyoung, S. A. Goldman, *Neurosurg Clin N Am* 18, 93 (Jan, 2007).
18. D. R. Archer, P. A. Cuddon, D. Lipsitz, I. D. Duncan, *Nat Med* 3, 54 (Jan, 1997).
19. B. D. Yandava, L. L. Billingham, E. Y. Snyder, *Proc Natl Acad Sci U S A* 96, 7029 (Jun 8, 1999).
20. C. Radtke, M. Spies, M. Sasaki, P. M. Vogt, J. D. Kocsis, *Int J Dev Neurosci* 25, 149 (May, 2007).
21. C. P. Chen, M. E. Kiel, D. Sadowski, R. D. McKinnon, *Stem Cell Rev* 3, 280 (Dec, 2007).
22. I. D. Duncan, *J Inherit Metab Dis* 28, 357 (2005).
23. E. Y. Snyder, G. Q. Daley, M. Goodell, *J Neurosci Res* 76, 157 (Apr 15, 2004).
24. H. Klassen, B. Reubinoff, *Nat Biotechnol* 26, 187 (Feb, 2008).
25. F. Osakada et al., *Nat Biotechnol* 26, 215 (Feb, 2008).
26. R. Adler, *Adv Exp Med Biol* 613, 3 (2008).
27. G. Kuhn, O. Brustle, U. Martens, A. Wobus, K. Unsicker, *Cell Tissue Res* 331, 1 (Jan, 2008).
28. J. A. Thomson et al., *Science* 282, 1145 (Nov 6, 1998).
29. S. C. Zhang, *J Hematother Stem Cell Res* 12, 625 (Dec, 2003).
30. D. J. Guillaume, S. C. Zhang, *Neurosurg Focus* 24, E3 (2008).
31. G. Amabile, A. Meissner, *Trends Mol Med* 15, 59 (Feb, 2009).
32. C. W. Lederer, N. Santama, *Biotechnol J* 3, 1521 (Dec, 2008).
33. R. Zietlow, E. L. Lane, S. B. Dunnett, A. E. Rosser, *Cell Tissue Res* 331, 301 (Jan, 2008).
34. N. Uchida et al., *Proc Natl Acad Sci U S A* 97, 14720 (Dec 19, 2000).
35. S. Tamaki et al., *J Neurosci Res* 69, 976 (Sep 15, 2002).
36. N. Uchida et al., *Proc Natl Acad Sci U S A* 97, 14720 (Dec 19, 2000).
37. F. H. Gage, *Science* 287, 1433 (Feb 25, 2000).
38. F. H. Gage, I. M. Verma, *Proc Natl Acad Sci U S A* 100 Suppl 1, 11817 (Sep 30, 2003).
39. P. Taupin, *Curr Opin Mol Ther* 8, 156 (Apr, 2006).
40. A. Bjorklund, *J Gene Med* 1, 223 (May-Jun, 1999).
41. E. E. Capowski et al., *J Neurosci Methods* 163, 338 (Jul 30, 2007).
42. R. A. Barker, H. Widner, *NeuroRx* 1, 472 (Oct, 2004).
43. Z. Chen, T. D. Palmer, *Human Molecular Genetics* 17, R84 (2008).

**References** (continued)

44. J. H. Kordower, Y. Chu, R. A. Hauser, T. B. Freeman, C. W. Olanow, *Nat Med* 14, 504 (May, 2008).
45. J. Y. Li et al., *Nat Med* 14, 501 (May, 2008).
46. I. Mendez et al., *Nat Med* 14, 507 (May, 2008).
47. See <<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>>
48. See <<http://www.fda.gov/BiologicsBloodVaccines/default.htm>>
49. See <[http://www.emea.europa.eu/htms/human/advanced\\_therapies/intro.htm](http://www.emea.europa.eu/htms/human/advanced_therapies/intro.htm)>
50. See <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070273.pdf>>
51. D. G. Halme, D. A. Kessler, *N Engl J Med* 355, 1730 (Oct 19, 2006).
52. See <<http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-0471S1andS2-00-index.html>>
53. P. Dupraz-Poiseau, "Implementing the New EU Legislation on Advanced Therapy Medicinal Products" (2009).
54. P. Dupraz-Poiseau, "Implementing the New EU Legislation on Advanced Therapy Medicinal Products" (2009).
55. D. K. Anderson et al., *Spinal Cord* 43, 453 (Aug, 2005).
56. AUTHOR: NEED REFERENCE HERE
57. See <[http://www.uknscn.org/downloads/position\\_statements.html](http://www.uknscn.org/downloads/position_statements.html)>
58. O. Rechavi, Y. Kloog, *Med Hypotheses* 72, 193 (Feb, 2009)
59. Abstract, Association for Research in Vision and Ophthalmology, Annual Meeting (2009).
60. D. Ilic, *Regen Med* 4, 11 (Jan, 2009).