

eScholarship@UMassChan

Stem cell transplantation for stroke: does it work, and if so, how

Item Type	Journal Article
Authors	Fisher, Marc
Citation	Stroke. 2003 Aug;34(8):2083. Epub 2003 Jul 24. Link to article on publisher's site
DOI	10.1161/01.STR.0000083463.73181.70
Download date	2026-05-15 20:42:44
Link to Item	https://hdl.handle.net/20.500.14038/38815

Stroke

American Stroke
AssociationSM

A Division of American
Heart Association



JOURNAL OF THE AMERICAN HEART ASSOCIATION

Stem Cell Transplantation for Stroke: Does It Work, and If So, How?

Marc Fisher

Stroke 2003;34;2083; originally published online Jul 24, 2003;

DOI: 10.1161/01.STR.0000083463.73181.70

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

Copyright © 2003 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/34/8/2083>

Subscriptions: Information about subscribing to *Stroke* is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Guest Section Editor: Marc Fisher, MD

Cell Therapy: Replacement

Lawrence R. Wechsler, MD; Douglas Kondziolka, MD

Not long ago, the ability of the brain to restore function through regeneration of neural elements was thought to be nonexistent. It is now known that not only does some regenerative capacity exist, but implanted cells can integrate into the host brain, survive, and reverse neurological deficits. Neural stem cells, fetal transplants, immortalized cell lines, and bone marrow stromal cells show promise in experimental models of neurological disease including stroke. Although it is clear that transplanted cells function, the mechanism by which neurological deficits might improve is less certain. Transplanted cells may preserve existing host cells and connections through secretion of trophic factors; establish local connections that enhance synaptic activity; provide a bridge for host axonal regeneration; or actually replace cellular elements. Several observations from animal and human studies of cell therapy support the possibility that transplanted cells exert at least some of their effect through cellular replacement.

In the early stages of brain development, implanting neural stem cells leads to replacement of multiple cellular elements including neurons and glia.¹ Thus, the potential for cell replacement exists, but whether it persists into adulthood is uncertain. Models of Parkinson's disease (PD) provide the most direct support for cell replacement as an important effect of cell therapy. Fetal ventral mesencephalic neurons grafted into the striatum in animal models of PD restore dopamine levels and improve function.² Similar grafts outside the striatum fail to achieve clinical benefit. In humans, such fetal grafts produce clinical benefit³ that accrues gradually rather than immediately, suggesting an accumulation of synaptic connections that eventually results in sufficient dopaminergic transmission to improve neurological deficits. Autopsy findings in patients receiving fetal grafts demonstrate implanted cell survival as well as axon growth and synaptic connections⁴. Additional support comes from positron-emission tomography studies showing a correlation between clinical improvement and increased uptake of

[¹⁸F]fluorodopa in the striatum. This favors the concept that the response to grafting is mediated by direct activity of the transplanted cells replacing the function of the degenerating dopaminergic cells of the host nigro-striatal pathway.

The challenge of cell replacement for treatment of stroke is in some ways similar to that for PD but in other ways is very different. Like PD, the injury is focal but the neuronal loss typically involves many more cell types and neurotransmitters. Neural pathways are more complex, and the likelihood of implanted cells forming appropriately directed connections necessary to restore function seems remote, unless guided by the host brain. Despite the potential pitfalls, treatment of focal ischemia in animals has demonstrated promising results. Fetal cortical grafts placed in adult neocortex following ischemia make connections with host neurons including cortex, thalamus, and subcortical nuclei.⁵ Behavioral improvement occurs in response to these grafts when animals are exposed to an enriched environment. Neuronal cells derived from a human teratocarcinoma cell line (NT2 cells) implanted into the striatum following infarction survive and integrate into the host brain, growing axons and making synaptic connections.⁶ Neurological deficits due to stroke are reversed by implantation.⁷ The clinical benefit occurs only when a critical number of cells are transplanted, ensuring adequate cell survival. The fact that response depends on the number of cells transplanted suggests the benefit may be mediated by cell replacement.

Extrapolating the results of cell implantation in animal models of stroke to humans is problematic, particularly because of the relative lack of adequate primate stroke models. Unlike PD, in which the motor manifestations of striatal lesions mimic the human disease, deficits in animals due to ischemia are more difficult to compare with human stroke. The first human trial of cell therapy for stroke included 12 patients treated with LBS neurons derived from a teratocarcinoma cell line.⁸ This trial was not designed to examine efficacy, but improvement in some patients on the European Stroke Scale scores and NIHSS scores was observed. As in PD, positron-emission tomography studies showed increased metabolic activity in the area of the grafts in several patients 6 and 12 months after implantation.⁹ The results of an autopsy in one patient 18 months after implantation documented survival of transplanted neuronal cells.¹⁰ Taken together, these data support the concept that activity of implanted cells is responsible for clinical changes. Further studies are needed to more precisely determine the role of cell replacement—whether the implanted cells form new neural pathways, make local connections, or work by neurohumoral mechanisms.

The opinions expressed in this editorial are not necessarily those of the editors or of the American Stroke Association.

From the Departments of Neurology (L.R.W.) and Neurological Surgery (D.K.), University of Pittsburgh School of Medicine, Pittsburgh, Pa.

Correspondence to Dr Lawrence R. Wechsler, University of Pittsburgh Medical Center, Stroke Institute, Department of Neurology, C426 PUH, 200 Lothrop St, Pittsburgh, PA 15213. E-mail lwechsler@stroke.upmc.edu (*Stroke*. 2003;34:2081-2082.)

© 2003 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>
DOI: 10.1161/01.STR.0000083461.80316.55

In the end it is likely that multiple mechanisms contribute to the effect of cell transplantation. Trophic factors may be necessary to promote survival and integration of grafted cells. Implanted cells may also induce host responses that both promote function of the graft and directly contribute to neurological recovery. Although the prospect of replacing brain damaged by ischemia appears daunting, initial experience in this field suggests it is not only possible but plausible.

References

1. Yandava BD, Billingham LL, Snyder EY. "Global" cell replacement is feasible via neural stem cell transplantation: evidence from the dysmyelinated shiverer mouse brain. *Proc Natl Acad Sci U S A*. 1999;96:7029–7034.
2. Herman JP, Abrous ND. Dopaminergic neural grafts after fifteen years: results and perspectives. *Prog Neurobiol*. 1994;44:1–35.
3. Olanow CW, Freeman T, Kordower J. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med*. 2001;345:146; discussion 2001;345:147.
4. Kordower JH, Freeman TB, Snow BJ, Vingerhoets FJ, Mufson EJ, Sanberg PR, Hauser RA, Smith DA, Nauert GM, Perl DP, et al. Neuro-pathological evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with Parkinson's disease. *N Engl J Med*. 1995;332:1118–1124.

5. Sorensen JC, Grabowski M, Zimmer J, Johansson BB. Fetal neocortical tissue blocks implanted in brain infarcts of adult rats interconnect with the host brain. *Exp Neurol*. 1996;138:227–235.
6. Kleppner SR, Robinson KA, Trojanowski JQ, Lee VM. Transplanted human neurons derived from a teratocarcinoma cell line (ntera-2) mature, integrate, and survive for over 1 year in the nude mouse brain. *J Comp Neurol*. 1995;357:618–632.
7. Borlongan CV, Tajima Y, Trojanowski JQ, Lee VM, Sanberg PR. Transplantation of cryopreserved human embryonal carcinoma-derived neurons (NT2N cells) promotes functional recovery in ischemic rats. *Exp Neurol*. 1998;149:310–321.
8. Kondziolka D, Wechsler L, Goldstein S, Meltzer C, Thulborn KR, Gebel J, Jannetta P, DeCesare S, Elder EM, McGrogan M, et al. Transplantation of cultured human neuronal cells for patients with stroke. *Neurology*. 2000;55:565–569.
9. Meltzer CC, Kondziolka D, Villemagne VL, Wechsler L, Goldstein S, Thulborn KR, Gebel J, Elder EM, DeCesare S, Jacobs A. Serial [18f] fluorodeoxyglucose positron emission tomography after human neuronal implantation for stroke. *Neurosurgery*. 2001;49:586–591; discussion 2001;49:591–582.
10. Nelson PT, Kondziolka D, Wechsler L, Goldstein S, Gebel J, DeCesare S, Elder EM, Zhang PJ, Jacobs A, McGrogan M, et al. Clonal human (hNT) neuron grafts for stroke therapy: neuropathology in a patient 27 months after implantation. *Am J Pathol*. 2002;160:1201–1206.

KEY WORDS: regeneration ■ stem cells

Stem Cells: Do They Replace or Stimulate?

David Howells, BSc(Hons), PhD

In 2002, more than 6000 articles were published on stem cell biology. Many argued that the importance of these cells lies in their potential to provide transplants for treatment of diseases such as stroke, Parkinson's disease, and spinal cord injury. The fervor is such that human embryos have been cloned, despite substantial ethical concerns, with the justification that "therapeutic cloning" will provide the stem cells needed for widespread transplantation for incurable diseases.

Stem cells prepared from human bone marrow,¹ neuronal progenitor cells from adult rat dentate gyrus,² and embryonic human forebrain³ all engraft successfully within the brain parenchyma and can differentiate into neurons.² Surprisingly these engrafted cells can migrate to join existing neural stem cell migratory pathways,^{1,3} and when the brain is injured, migration is redirected specifically to the site of damage.⁴

After stroke in rodents, stem cells derived from bone marrow induce functional recovery measured by rotarod,

adhesive-removal, and modified neurologic severity score tests when implanted into striatum⁵ or cortex⁶ or after intra-arterial infusion.⁷ Importantly, these improvements were noted when implantation occurred up to 14 days⁷ after stroke, were enhanced by brain-derived neurotrophic factor,⁸ and were achieved when very few implanted cells expressed neural markers⁹ and still retained a relatively undifferentiated morphology.⁶ Importantly, despite marked functional improvements, the infarcts do not get smaller.⁵ This latter observation would appear to exclude the possibility that the stem cells secrete neuroprotective factors that enhance survival of neurons susceptible to infarction.

These observations have led to speculation that increased host plasticity rather than differentiation and integration of new neurons must account for the observed improvements.^{6,9}

The idea of host CNS regenerative responses is not new, but their form and functional significance have remained contentious. At the start of the 20th century, Ramon y Cajal was among the first to study neurite sprouting after brain and spinal injury but decided that these host responses were aborted attempts at reconstruction of severed pathways with little functional significance. This perception changed little until the late 1960s, when Raisman observed that axons in neighboring undamaged pathways could send out additional axonal branches or "collateral sprouts" to reinnervate the septum after it had been denervated.

Interestingly, such observations of host plasticity played a key role in promoting transplantation as a treatment for neurological disease, and today intrastriatal implants of fetal

The opinions expressed in this editorial are not necessarily those of the editors or of the American Stroke Association.

From the University of Melbourne and National Stroke Research Institute, Austin & Repatriation Medical Centre, Melbourne, Australia.

Correspondence to Dr David Howells, University of Melbourne and National Stroke Research Institute, Austin & Repatriation Medical Center, Level 7, Department of Medicine, Heidelberg, Victoria 3084, Australia. E-mail david.howells@unimelb.edu.au

(*Stroke*. 2003;34:2082–2083.)

© 2003 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000083462.47898.DD

dopaminergic neurons are viewed by many as a moderately successful way of alleviating the symptoms of Parkinson's disease. However, as in stem cell transplants for stroke, there is also a body of evidence to suggest that host responses may play a significant role in the functional recovery observed after dopaminergic implants.

Autologous adrenal medullary implants in particular were enthusiastically performed in several countries. However, they have been found to be of only mild benefit in less than half of the transplanted patients, and even in patients who improved, subsequent autopsies consistently demonstrated little or no survival of adrenal grafts. The feature that seemed to best correlate with the clinical improvement in animals and man was the presence of peri-wound host dopaminergic sprouting,¹⁰ which has been shown to be a consequence of surgical injury to the striatum and dependent on neurotrophins and growth factors supplied by activated microglia and macrophages.¹¹

Is enhancement of such host axonal sprouting responsible for stem cell-induced recovery in animal models of stroke?

It would seem prudent to conclude that although stem cell grafts to treat stroke are in their infancy, they do appear to be able to foster functional improvement in animal models of stroke. However, their mechanism of action is far from clear. Perhaps our greatest challenge will be to establish the proportional significance of all mechanisms and fine-tune our treatments to provide the greatest benefit for the victims of stroke.

References

1. Azizi SA, Stokes D, Augelli BJ, DiGirolamo C, Prockop DJ. Engraftment and migration of human bone marrow stromal cells implanted in the

- brains of albino rats: similarities to astrocyte grafts. *Proc Natl Acad Sci U S A*. 1998;95:3908–3913.
2. Gage FH, Coates PW, Palmer TD, Kuhn HG, Fisher LJ, Suhonen JO, Peterson DA, Suhr ST, Ray J. Survival and differentiation of adult neuronal progenitor cells transplanted to the adult brain. *Proc Natl Acad Sci U S A*. 1995;92:11879–11883.
3. Fricker RA, Carpenter MK, Winkler C, Greco C, Gates MA, Bjorklund A. Site-specific migration and neuronal differentiation of human neural progenitor cells after transplantation in the adult rat brain. *J Neurosci*. 1999;19:5990–6005.
4. Veizovic T, Beech JS, Stroemer RP, Watson WP, Hodges H. Resolution of stroke deficits following contralateral grafts of conditionally immortal neuroepithelial stem cells. *Stroke*. 2001;32:1012–1019.
5. Li Y, Chopp M, Chen J, Wang L, Gautam SC, Xu YX, Zhang Z. Intrastriatal transplantation of bone marrow nonhematopoietic cells improves functional recovery after stroke in adult mice. *J Cereb Blood Flow Metab*. 2000;20:1311–1319.
6. Zhao LR, Duan WM, Reyes M, Keene CD, Verfaillie CM, Low WC. Human bone marrow stem cells exhibit neural phenotypes and ameliorate neurological deficits after grafting into the ischemic brain of rats. *Exp Neurol*. 2002;174:11–20.
7. Li Y, Chen J, Wang L, Lu M, Chopp M. Treatment of stroke in rat with intracarotid administration of marrow stromal cells. *Neurology*. 2001;56:1666–1672.
8. Chen J, Li Y, Chopp M. Intracerebral transplantation of bone marrow with BDNF after MCAo in rat. *Neuropharmacology*. 2000;39:711–716.
9. Li Y, Chen J, Chopp M. Adult bone marrow transplantation after stroke in adult rats. *Cell Transplant*. 2001;10:31–40.
10. Kordower JH, Cochran E, Penn RD, Goetz CG. Putative chromaffin cell survival and enhanced host-derived TH-fiber innervation following a functional adrenal medulla autograft for Parkinson's disease. *Ann Neurol*. 1991;29:405–412.
11. Batchelor PE, Porritt MJ, Martinello P, Parish CL, Liberatore GT, Donnan GA, Howells DW. Macrophages and microglia produce local trophic gradients that stimulate axonal sprouting toward but not beyond the wound edge. *Mol Cell Neurosci*. 2002;21:436–453.

KEY WORDS: regeneration ■ stem cells ■ transplantation

Stem Cell Transplantation for Stroke: Does It Work, and If So, How?

Marc Fisher, MD

An increasing number of experiments in animal stroke models demonstrated that a variety of different types of stem cells implanted directly into the central nervous system or delivered systemically beneficially affect functional outcome. In these experiments, stem cells are given days to weeks after stroke onset without affecting infarct size. How the various types of stem cells induce their beneficial effects on functional outcome remains a matter of speculation, but Howells and Wechsler/Kondziolka suggest a

number of intriguing possibilities revolving around direct functional activities of the implanted stem cells versus stimulation of intrinsic host recovery mechanisms. As these authors suggest, it is likely that both effects may occur and different mechanisms may predominate with individual subtypes of stem cells or at different times after stroke onset.

Much further experimental work will be needed to dissect the precise mechanisms of stem cell effects on neurological/functional recovery after stroke. The utility of stem cell treatment for stroke will need to be explored in primate stroke models and then in carefully designed initial and advanced clinical trials. The initial small animal experiments provide reasons for excitement, but as has been learned in other neurological disorders, there are many potential pitfalls. All stroke specialists and stroke patients need to pay close attention to this field as it unfolds with both cautious optimism and healthy skeptical reserve.

From the Department of Neurology, University of Massachusetts Medical School, Worcester, Mass.

Correspondence to Dr Marc Fisher, University of Massachusetts, Department of Neurology, UMASS/Memorial Health Care, 119 Belmont St, Worcester, MA 01606-2982. E-mail fisherm@ummhc.org (*Stroke*. 2003;34:2083.)

© 2003 American Heart Association, Inc.

Stroke is available at <http://www.strokeaha.org>

DOI: 10.1161/01.STR.0000083463.73181.70

KEY WORDS: regeneration ■ stem cells