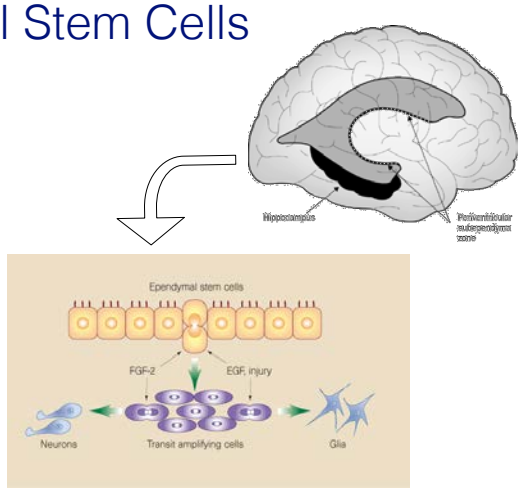
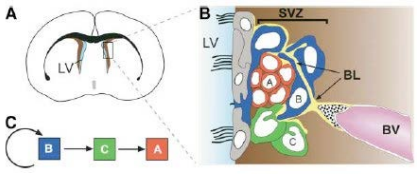
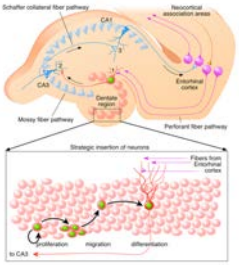
Neural Stem Cells



The neurogenic niche



Restriction of neurogenesis to the hippocampus and subventricular zone is related to local microenvironment: astrocytes in the neurogenic zones secrete factors and cytokines that promote expansion and neural differentiation whereas astrocytes in non-neurogenesis regions of the brain secrete inhibitory factors



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Retrospective Birth Dating of Cells in Humans

Kirsty L. Spalding,* Ratan D. Bhardwaj,* Bruce A. Buchholz,† Henrik Druid,* and Jonas Frisén*‡
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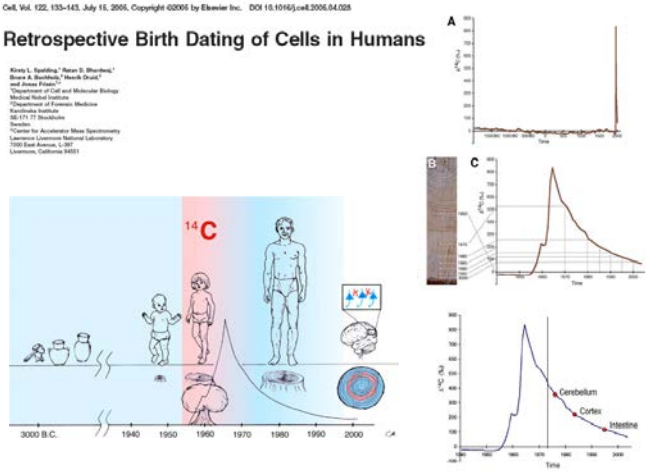
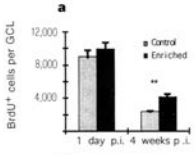
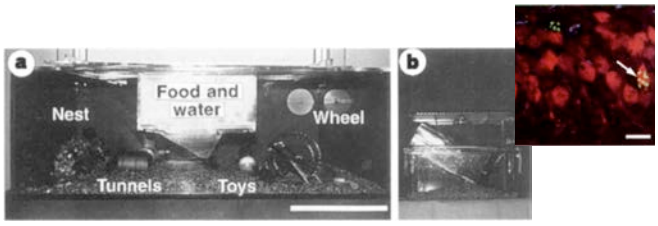


Neurogenesis and temporal associations in long-term human memory

More hippocampal neurons in adult mice living in an enriched environment

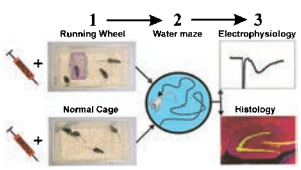
Gerd Kempermann, H. Georg Kuhn & Fred H. Gage





Running enhances neurogenesis, learning, and long-term potentiation in mice

Henriette van Praag*†, Brian R. Christie†‡, Terrence J. Sejnowski‡§, and Fred H. Gage*¶



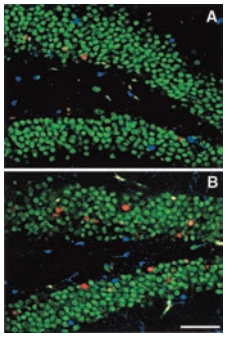


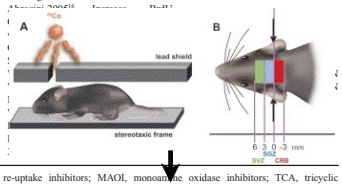
Fig. 4. Confocal images of BrdU-positive cells in control (A) and runner coronal sections (B). Sections were immunofluorescent triple-labeled for BrdU (red), NeuN, indicating neuronal phenotype (green), and S100β, selective for glial phenotype (blue). (Scale bar indicates 50 μm.)

Many antidepressants increase hippocampal neurogenesis

Table 1 Effects of psychotropics and electroconvulsive shock on neural precursor proliferation (prolif.) in neurogenic regions of the brain

Compounds	Model	Study	Hippocampus		Subventricular zone	
			Prolif.	Neurogenesis	Prolif.	Neurogenesis
Fluoxetine SSRI	Sprague-Dawley adult rat 28 days *in vivo*	Malberg 2000[15]	Increase	75% NeuN		
Reboxetine NRI	Sprague-Dawley adult rat 28 days *in vivo*	Malberg 2000[15]	Increase	75% NeuN		
Electroconvulsive shock	Sprague-Dawley adult rat 28 days *in vivo*	Malberg 2000[15]	Increase	75% NeuN		
Tranylcypromine MAOI	Sprague-Dawley adult rat 28 days *in vivo*	Malberg 2000[15]	Increase	75% NeuN		
Morphine μ receptor agonist	Sprague-Dawley adult rat 28 days *in vivo*	Malberg 2000[15]	Decrease			
Thyroxine	Adult rat	[illegible]	[illegible]			
Tianeptine TCA	Adult male tree shrews 28 days *in vivo*					
Exercise (voluntary running)	Adult mice					
Lithium	Sprague-Dawley adult rat 28 days *in vivo*					
Fluoxetine	Adult mouse 28 days *in vivo*					
Olanzapine	Adult Wistar 21 days *in vivo*					
Risperidone	Adult Wistar 21 days *in vivo*					
Haloperidol	Sprague-Dawley adult rat 28 days *in vivo*					
	Adult Wistar 21 days *in vivo*					
	Adult rat 28 days *in vivo*					
Clozapine	Adult rat 28 days *in vivo*					
Quetiapine	Adult rat acute *in vivo*					

SSRI, Selective serotonin re-uptake inhibitors; NRI, noradrenaline re-uptake inhibitors; MAOI, monoamine oxidase inhibitors; TCA, tricyclic antidepressants; BrdU, bromodeoxyuridine; NeuN, neuronal nuclei.



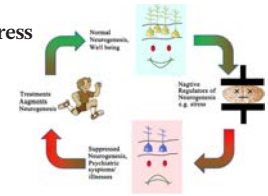
Novelty-suppressed feeding test:
time required for a mouse to eat in a novel environment after fasting (anxiety, anti-depressant)

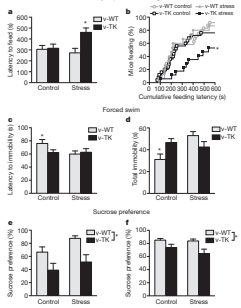
Adult hippocampal neurogenesis buffers stress responses and depressive behaviour

Jason S. Snyder[1], Amélie Soumier[1], Michelle Brewer[1], James Pickel[2] & Heather A. Cameron[1]

460 | NATURE | VOL 476 | 25 AUGUST 2011

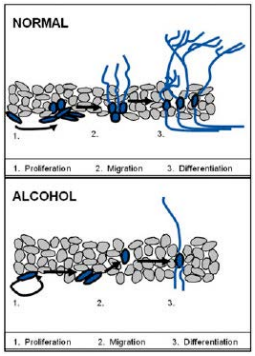
Glucocorticoids are released in response to stressful experiences and serve many beneficial homeostatic functions. However, dysregulation of glucocorticoids is associated with cognitive impairments and depressive illness[1,2]. In the hippocampus, a brain region densely populated with receptors for stress hormones, stress and glucocorticoids strongly inhibit adult neurogenesis[3]. Decreased neurogenesis has been implicated in the pathogenesis of anxiety and depression, but direct evidence for this role is lacking[4,5]. Here we show that adult-born hippocampal neurons are required for normal expression of the endocrine and behavioural components of the stress response. Using either transgenic or radiation methods to inhibit adult neurogenesis specifically, we find that glucocorticoid levels are slower to recover after moderate stress and are less suppressed by dexamethasone in neurogenesis-deficient mice than intact mice, consistent with a role for the hippocampus in regulation of the hypothalamic–pituitary–adrenal (HPA) axis[6,7]. Relative to controls, neurogenesis-deficient mice also showed increased food avoidance in a novel environment after acute stress, increased behavioural despair in the forced swim test, and decreased sucrose preference, a measure of anhedonia. These findings identify a small subset of neurons within the dentate gyrus that are critical for hippocampal negative control of the HPA axis and support a direct role for adult neurogenesis in depressive illness.

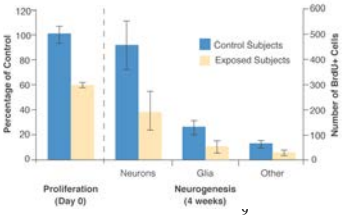




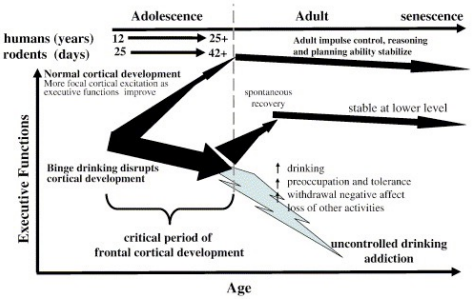
Mice lacking neurogenesis show increased anxiety/depression- like behaviours

Alcohol disrupts neurogenesis in the adult brain

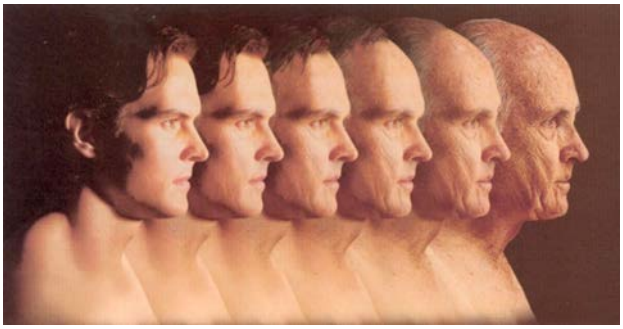




Adolescent alcohol abuse disrupts frontal cortical development and maturation of executive function



When neurogenesis encounters aging and disease



A reduction in neurogenesis underlies aging-related cognitive deficits and impairments in disorders such as Alzheimer's disease (AD).

Sleep deprivation/fragmentation inhibits neurogenesis

Sleep deprivation inhibits adult neurogenesi hippocampus by elevating glucocorticoids

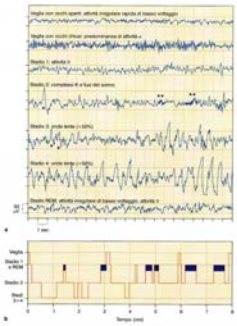
Christian Mirescu, Jennifer D. Peters, Liron Noiman, and Elizabeth Gould*

PNAS | December 12, 2006 | vol. 103 | no. 50 | 19171

Neuroscience 148 (2007) 325–333

HIPPOCAMPAL NEUROGENESIS IS REDUCED BY SLEEP FRAGMENTATION IN THE ADULT RAT

Ł. GUZMAN-MARIN,[a,b] T. BASHIR,[a] N. SUNTSOVA,[a,b,d]
Ł. SZYMUSIAK[a,c] AND D. McGINTY[a,b]*



Neuroscience Letters 515 (2012) 177–180

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journal homepage: www.elsevier.com/locate/neulet

Direction-dependent effects of chronic "jet-lag" on hippocampal neurogenesis

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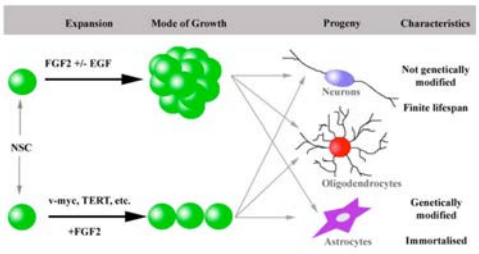
Doublecortin
Phase delay
Phase advance

ABSTRACT

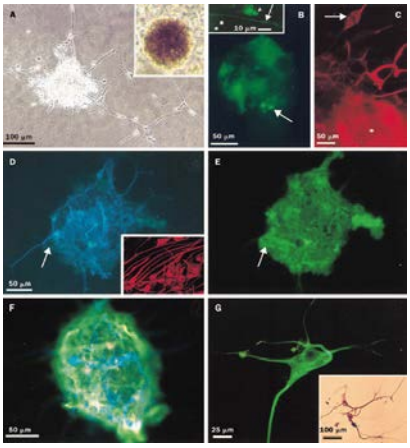
Disruptions in circadian rhythms, as seen in human shift workers, are often associated with many health consequences including impairments in cognitive functions. However, the mechanisms underlying these affects are not well understood. The objective of the present study is to explore the effects of circadian disruption on hippocampal neurogenesis, which has been implicated in learning and memory and could serve as a potential pathway mediating the cognitive consequences associated with rhythm disruption. Circadian rhythm disruptions were introduced using a weekly 6 h phase shifting paradigm, in which male Wistar rats were subjected to either 6 h phase advances (i.e. traveling eastbound from New York to Paris) or 6 h phase delays (i.e. traveling westbound from Paris to New York) in their light/dark schedule every week. The effects of chronic phase shifts on hippocampal neurogenesis were assessed using doublecortin (DCX), a microtubule binding protein expressed in immature neurons. The results revealed that chronic disruption in circadian rhythms inhibits hippocampal neurogenesis, and the degree of reduction in neurogenesis depends upon the direction and duration of the shifts. In two cohorts of animals that experienced phase shifts for either 4 or 8 weeks, a greater decrease in neurogenesis was observed when the phase was advanced versus delayed in both groups. The direction-dependent effect mirrors the findings on clock gene expression in the SCN, suggesting a causal link between the reduction in hippocampal neurogenesis and a disrupted SCN circadian clock.

NSCs can be maintained in culture for expansion:

1. As free-floating, clonally-derived neurospheres, grown in the presence of EGF and/or FGF-2
2. As adherent, immortalized NSC lines, tipically carrying an oncogene to facilitate continued proliferation, again growing in the presence of FGF2 (and/or EGF)



Human neurospheres

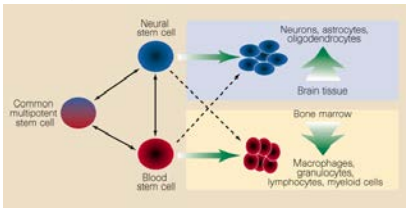


A neurosphere is a tissue-culture-generated clone of cells in different states of differentiation, all arising from a single multipotent stem/progenitor cell

A. Neurosphere on laminin (inset: semi-solid media)
B. α-nestin
C. α-vimentin
D. α-GFAP
E. α-βIII tubulin
F. α-GFAP + α-βIII tubulin
G. De novo generated neuron (α-β III tubulin and peroxidase)

Evidences of NSC plasticity

- Bjornson CRR, Rietze RL, Reynolds BA, Magli MC, Vescovi AL. Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells in vivo. Science 1999; 283: 534-37



- Clarke DL, Johansson CB, Wilbertz J, et al. Generalized potential of adult neural stem cells. Science 2000; 288: 1660-63

Turning Blood into Brain: Cells Bearing Neuronal Antigens Generated in Vivo from Bone Marrow

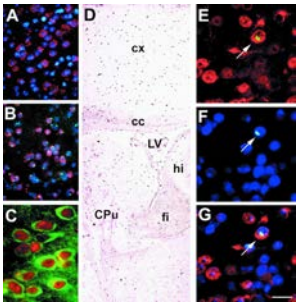
Éva Mezey,[1*] Karen J. Chandross,[2] Gyöngyi Harta,[1] Richard A. Maki,[3,4] Scott R. McKercher[3]

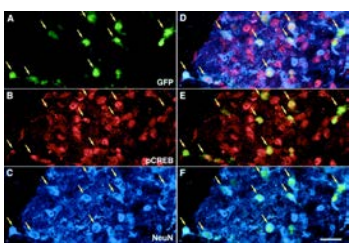
Bone marrow stem cells give rise to a variety of hematopoietic lineages and repopulate the blood throughout adult life. We show that, in a strain of mice incapable of developing cells of the myeloid and lymphoid lineages, transplanted adult bone marrow cells migrated into the brain and differentiated into cells that expressed neuron-specific antigens. These findings raise the possibility that bone marrow–derived cells may provide an alternative source of neurons in patients with neurodegenerative diseases or central nervous system injury.

From Marrow to Brain: Expression of Neuronal Phenotypes in Adult Mice

Timothy R. Brazelton, Fabio M. V. Rossi, Gilmor I. Keshet, Helen M. Blau*

After intravascular delivery of genetically marked adult mouse bone marrow into lethally irradiated normal adult hosts, donor-derived cells expressing neuronal proteins (neuronal phenotypes) developed in the central nervous system. Flow cytometry revealed a population of donor-derived cells in the brain with characteristics distinct from bone marrow. Confocal microscopy of individual cells showed that hundreds of marrow-derived cells in brain sections expressed gene products typical of neurons [NeuN, 200-kilodalton neurofilament, and class III β-tubulin] and were able to activate the transcription factor cAMP response element–binding protein (CREB). The generation of neuronal phenotypes in the adult brain 1 to 6 months after an adult bone marrow transplant demonstrates a remarkable plasticity of adult tissues with potential clinical applications.

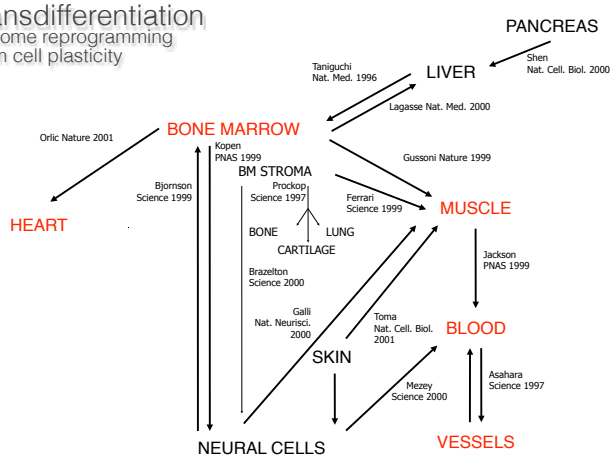




Only phenotypic markers, no functional data!

Transdifferentiation

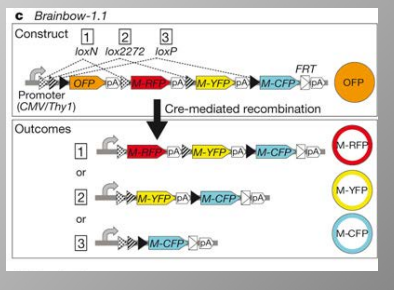
Genome reprogramming
Stem cell plasticity

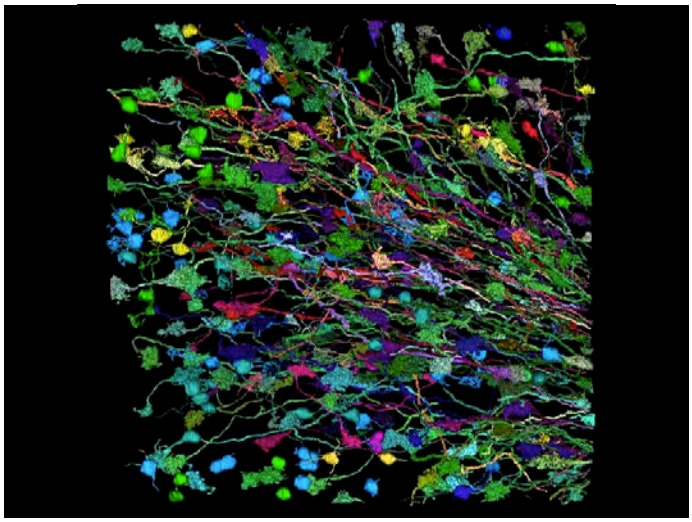


"Having cells go where they're supposed to go, connect up and become functional…is a bigger problem in the nervous system than anywhere else"

Mark Mattson, NINDS, Bethesda

Brainbow mice





Cell therapy for Parkinson's Disease

early proof of principle from human mesencephalic tissue from aborted fetuses

1980 Transplantation of dopamine-producing cells from patient's own adrenal glands

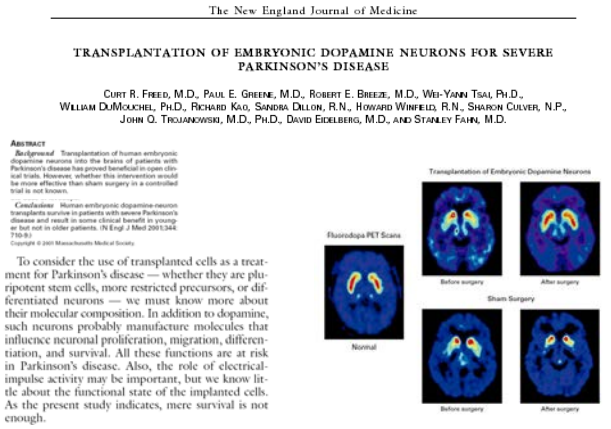
1982 Dopaminergic fetal neurons can survive in the eye anterior chamber
Transplantation of fetal tissue into the damaged area of the brains in rats and monkeys models of Parkinson's Disease (MPTP)

1985 Fetal tissue (7-9 weeks) transplantation in humans

1995 NIH funding for two double blind, placebo control clinical trials of fetal tissue transplantation

Studies in patients with PD after intrastriatal transplantation of human fetal mesencephalic tissue (7-9 weeks), rich in post-mitotic dopaminergic neurons, have provided proof of principle that neuronal replacement can work in the human brain

- The grafted neurons survive and reinnervate the striatum for as long as 10 years, despite an ongoing disease process that destroys the patient's own dopaminergic neurons *(Kordower et al., NEJM 1995; Piccini et al., Nat Neurosci, 1999)*
- The grafts are able to normalize striatal dopamine release and to reverse akinesia, thus becoming functionally integrated into neuronal circuitries *(Piccini at al., Ann Neurol, 2000)*
- Several open-label trials have reported clinical benefit, and some patients have been able to withdraw from L-dopa treatment for several years *(Pongar at al., Brain Res Bull, 2003)*
- Two recent sham surgery-controlled trials showed only modest improvement *(Freed et al, NEJM 2001; Olanow et al., Ann Neurol, 2003)*



The New England Journal of Medicine

TRANSPLANTATION OF EMBRYONIC DOPAMINE NEURONS FOR SEVERE PARKINSON'S DISEASE

Curt R. Freed, M.D., Paul E. Greene, M.D., Robert E. Breeze, M.D., Wei-Yann Tsai, Ph.D., William DuMouchel, Ph.D., Richard Kao, Sandra Dillon, R.N., Howard Winfield, R.N., Sharon Culver, N.P., John Q. Trojanowski, M.D., Ph.D., David Eidelberg, M.D., and Stanley Fahn, M.D.

Abstract

Background Transplantation of human embryonic dopamine neurons into the brains of patients with Parkinson's disease has proved beneficial in open clinical trials. However, whether this intervention would be more effective than sham surgery in a controlled trial is not known.

Conclusions Human embryonic dopamine-neuron transplants survive in patients with severe Parkinson's disease and result in some clinical benefit in younger but not in older patients. (N Engl J Med 2001;344:710-9.)

Copyright © 2001 Massachusetts Medical Society.

To consider the use of transplanted cells as a treatment for Parkinson's disease — whether they are pluripotent stem cells, more restricted precursors, or differentiated neurons — we must know more about their molecular composition. In addition to dopamine, such neurons probably manufacture molecules that influence neuronal proliferation, migration, differentiation, and survival. All these functions are at risk in Parkinson's disease. Also, the role of electrical-impulse activity may be important, but we know little about the functional state of the implanted cells. As the present study indicates, mere survival is not enough.

Transplantation of Embryonic Dopamine Neurons

Fluorodopa PET Scans

Before surgery

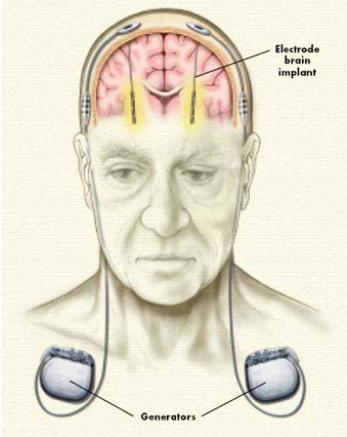
After surgery

Sham Surgery

Normal

No clinical improvement
Dyskinesia (aberrant reinnervation? inflammation? contaminants?)

No new trials have been performed in PD patients in the last few years, as cell transplantation has turned out to be less effective than deep brain stimulation



To date, thousands of patients with Parkinson's disease have been treated with deep brain stimulation. The electricity-based technique requires the insertion of one or two pager-sized generators under the skin, usually near the collar bone. The generator emits tiny electrical pulses that pass along wires, also under the skin, through electrodes implanted in select areas of the brain. Some patients experience a tingling sensation, but typically the stimulation pulses go unnoticed.

Long-term clinical outcomes after fetal cell transplantation in parkinson disease: implications for the future of cell therapy

JAMA Neurology

Long-term Clinical Outcome of Fetal Cell Transplantation for Parkinson Disease: Two Case Reports

Zinovia Kefalopoulou, MD, PhD; Marios Politis, MD, PhD; Paola Piccini, MD, PhD, FRCP; Niccolo Mencacci, MD; Kailash Bhatia, MD, PhD; Marjan Jahanshahi, PhD; Håkan Widner, MD, PhD; Stig Rehnrona, MD, PhD; Patrik Brundin, MD, PhD; Anders Björklund, PhD; Olle Lindvall, MD, PhD; Patricia Limousin, MD, PhD; Niall Quinn, MD; Thomas Foltynie, MRCP, PhD

Importance: Recent advances in stem cell technologies have rekindled an interest in the use of cell replacement strategies for patients with Parkinson disease. This study reports the very long-term clinical outcomes of fetal cell transplantation in 2 patients with Parkinson disease. Such long-term follow-up data can usefully inform on the potential efficacy of this approach, as well as the design of trials for its further evaluation.

Observations: Two patients received intrastriatal grafts of human fetal ventral mesencephalic tissue, rich in dopaminergic neuroblasts, as restorative treatment for their Parkinson disease. To evaluate the very long-term efficacy of the grafts, clinical assessments were performed 18 and 15 years posttransplantation. Motor improvements gained gradually over the first postoperative years were sustained up to 18 years posttransplantation, while both patients have discontinued, and remained free of any, pharmacological dopaminergic therapy.

Conclusions and Relevance: The results from these 2 cases indicate that dopaminergic cell transplantation can offer very long-term symptomatic relief in patients with Parkinson disease and provide proof-of-concept support for future clinical trials using fetal or stem cell therapies.

JAMA Neurol. doi:10.1001/jamaneurol.2013.4749

JAMA. 2014;311(6):617-618. doi:10.1001/jama.2013.285516.

TRANSEURO is a European research consortium with the principal objective to develop an efficacious and safe treatment methodology for Parkinson's disease suffering patients using fetal cell based treatments. The consortium has gathered international experts including leading clinicians, scientists, industrial partners, ethicists and patients' representatives who have joined forces in a new round of experimental work and cell therapy trials in Parkinson's Disease.

The principal goals of Transeuro are:

To show that the consistency and efficacy of dopaminergic cell replacement in Parkinson's disease can be improved by careful attention to tissue preparation and delivery, patient selection and immunosuppressive treatment

To show that dopaminergic cell replacement can be clinically efficacious in the absence of any troublesome off-state dyskinesias in clinical trials of fetal ventral mesencephalic transplants in patients with mild Parkinson's disease

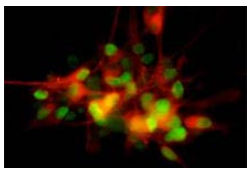
To develop a protocol that can serve as a template for all future clinical trials in the cell therapy field including stem cell-based therapies and the ethical implications and ramifications of such work.

Clinical Progress

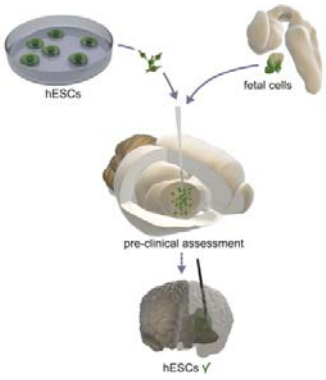
Cell Stem Cell

Human ESC-Derived Dopamine Neurons Show Similar Preclinical Efficacy and Potency to Fetal Neurons when Grafted in a Rat Model of Parkinson's Disease

Cell Stem Cell *15*, 653–665, November 6, 2014 ©2014



Dopamine-producing nerve cells (labelled red and green) made from iPS cells created from a Parkinson's patient



Stem Cell Reports

Article

OPEN ACCESS

Human Clinical-Grade Parthenogenetic ESC-Derived Dopaminergic Neurons Recover Locomotive Defects of Nonhuman Primate Models of Parkinson's Disease

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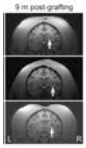
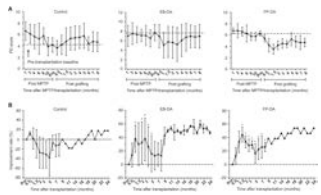
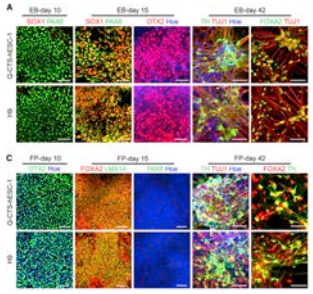
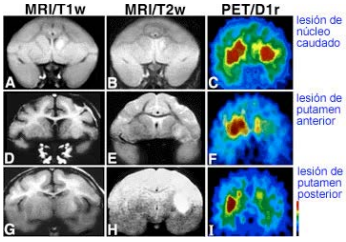






Huntington's disease

- chorea and progressive dementia
- mutations in the huntingtin gene
- the defective protein forms large clumps that gradually destroy the medium spiny projection neurons in the striatum



- Intrastriatal grafts of fetal striatal tissue containing projection neurons re-establish connections with the globus pallidus and receive inputs from host cerebral cortex, reversing motor and cognitive deficits in rats and monkeys.

- Clinical trial with intrastriatal transplantation of human fetal striatal tissue showed that grafts survived, contained striatal projection neurons and interneurons, and received afferents from the patient's brain. The extent of clinical benefit is unclear.

Cell therapy for Huntington's disease

Transplanted fetal striatum in Huntington's disease: Phenotypic development and lack of pathology

Thomas B. Freeman[a,b,c,d,e], Francesca Cicchetti[d,f], Robert A. Hauser[b,c,g], Terrence W. Deacon[c], Xiao-Jiang Li[h], Steven M. Hersch[i], G. Michael Nauert[i], Paul R. Sanberg[a,b,c], Jeffrey H. Kordower[e], Samuel Saporta[a,c,j], and Ole Isacson[a,d]

and macrophages. Notably, neuronal protein aggregates of mutated huntingtin, which is typical HD neuropathology, were not found within the transplanted fetal tissue. Thus, although there is a genetically predetermined process causing neuronal death within the HD striatum, implanted fetal neural cells lacking the mutant HD gene may be able to replace damaged host neurons and reconstitute damaged neuronal connections. This study demonstrates that grafts derived from human fetal striatal tissue can survive, develop, and are unaffected by the disease process, at least for 18 months, after transplantation into a patient with HD.

10 patients
10 fetuses per patient
1 autoptic report

THE LANCET • Vol 356 • December 9, 2000

Early report

Motor and cognitive improvements in patients with Huntington's disease after neural transplantation

Anne-Catherine Bachoud-Lévi, Philippe Rémy, Jean-Paul Nguyen, Pierre Brugières, Jean-Pascal Lefaucheur, Catherine Bourdet, Sophie Baudic, Véronique Gaura, Patrick Maison, Bassam Haddad, Marie-Françoise Boissé, Thierry Grandoulgin, Roland Jény, Paolo Bartolomeo, Gianfranco Dalla Barba, Jean-Denis Degos, Fabrice Lisovoski, Anne-Marie Ergis, Edwige Pailhous, Pierre Cesaro, Philippe Hantraye, Marc Peschanski

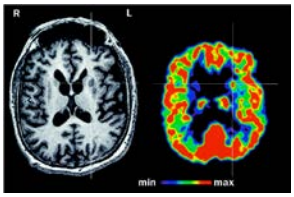


TABLE 1. *Clinical Trials of Cell Transplants in Huntington's Disease*

Study	*n*	Donor Tissue/Side *n*	Weeks	Dissect	Implant Tracks	Immune Treatment	Safety	Efficacy	Imaging	Anatomy
Cuba and Czech	4	2–3	?	VM or WGE	2–3 ? [B]	CyA	No pathological or immunological response[135]	Not yet possible to determine	MRI-guided stereotaxy; no reported follow-up	
Mexico City	2	1	E12–13	WGE	CN cavity	CyA + Pred	No surgical incidents or subsequent SEs[136]	Slow progression of disease	Not reported	
Los Angeles	14	5–8	E8–10	LGE	1 CN + 4 Pu [B]	Not reported	Safe, no serious SEs[74]	Benefit motor,[75] limited neuropsych tests[76]	MRI MRS[78] and FDG PET[75]	
Boston	12	35–38	Porcine	LGE	2 CN + 4 Pu [U]	CyA or anti-MHC	Safe, no serious SEs[80]	No change over 12 months[80]	Not reported	
Tampa	7	2–8	E8–9	LLGE	poPu [B]	CyA 6 months	1 death, 3 subdural hematomas[45]	Modest (NS) changes in motor tests at 12 months[45]	MRI and PET	2 postmortem cases with good survival[84]
Créteil	5	2–4	E7.5-9	WGE	2 CN + 3 Pu [B]	CyA 1 year	Procedure safe[60]	Motor and electrophysiol improvements[81] continue over 4 years	MRI and FDG PET; graft survival in 3 functional cases[82]	
London	2						Mild psychiatric SEs Possible psychiatric SE in one patient	Improvement in chorea in 1 of 2 patients	MRI and D_2R PET; survival in PET	
NEST-UK	4	2–3	E8–12	WGE	2 CN + 4 Pu [U]	Triple	Only SEs related to immunosuppression[45]	Safety only, efficacy not reported	MRI; graft survival	

[B] = bilateral implants; CN = caudate nucleus; CyA = cyclosporin A; E = weeks of embryonic age; LLGE = lateral aspect of the lateral ganglionic eminence; Pred = prednisolone; poPU = postcommissural putamen; Pu = putamen; SEs = side effects; Triple = combined cyclosporin A, prednisolone, and azothiaprine; WGE = whole ganglionic eminence; [U] = unilateral implants; VM = ventral mesencephalon.

- A European trial on more than 100 patients is currently ongoing

No clinical benefit in MIG-HD trial

Research Article

Human Fetal Cell Therapy in Huntington's Disease: A Randomized, Multicenter, Phase II Trial

Anne-Catherine Bachoud-Lévi ... See all authors

First published: 15 July 2020 | https://doi.org/10.1002/mds.28201 | Citations: 6

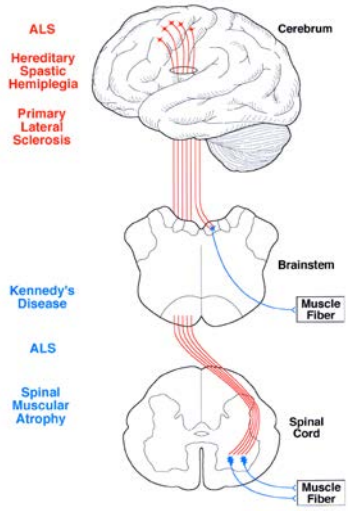
Members of the Multicentric Intracerebral Grafting in Huntington's Disease Group are listed in the Appendix.

Relevant conflicts of interests/financial disclosures:: Nothing to report.
Funding agency:: AOM00139 and AOM04021 Direction de la Recherche Clinique (Assistance Publique–Hôpitaux de Paris) and Association Française contre les Myopathies.

SC4HD consortium

Motoneuron diseases

involve lesions in one or both components of a two-neuron pathway



Amyotrophic lateral sclerosis
(Lou Gehrig's disease)

- Lower and upper motor degeneration
- Onset at 40-50 years
- Respiratory failure within 2-5 years
- Deterioration can be slowed by riluzole (glutamate-blocking drug) and antioxidant vitamins - but modest/no improvement
- 10% genetic forms: earlier onset, Lewy body inclusions and spinocerebellar degeneration

NeuralStem has received FDA approval for a clinical trial in which 12 patients with ALS will be treated by injection of human fetal-derived NSCs into the lumbar region of the spinal cord, where it is hoped they will exert a neuroprotective effect.

Eligibility Criteria:

1) Confirmed diagnosis of ALS by a neurologist

2) Has tracheostomy and is ventilator dependent for greater than 3 months OR a vital capacity greater than 60% predicted value

3) Unable to walk due to ALS

4) Lack of complicating medical conditions

5) Live in geographic proximity to Emory University Hospital

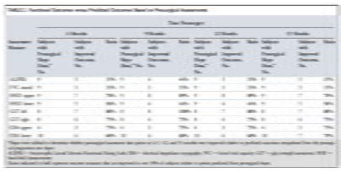
6) Ability to communicate vocally or with low-tech tools (writing or letter board)

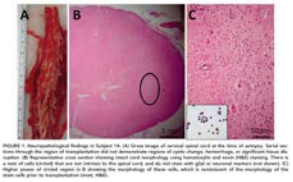
7) A willing and able caregiver who is committed to the study.

NEURALSTEM INC.

Intraspinal Neural Stem Cell Transplantation in Amyotrophic Lateral Sclerosis: Phase 1 Trial Outcomes

Eva L. Feldman, MD, PhD,[1] Nicholas M. Boulis, MD, PhD,[2] Junguk Hur, PhD,[1] Karl Johe, PhD,[3] Seward B. Rutkove, MD,[4] Thais Federici, PhD,[2] Meraida Polak, RN,[1] Jane Bordeau, RN,[1] Stacey A. Sakowski, PhD,[1] and Jonathan D. Glass, MD[1]





STEM CELLS 2012;30:1144–1151 www.StemCells.com

STEM CELLS
REGENERATIVE MEDICINE

Lumbar Intraspinal Injection of Neural Stem Cells in Patients with Amyotrophic Lateral Sclerosis: Results of a Phase I Trial in 12 Patients

JONATHAN D. GLASS,[a] NICHOLAS M. BOULIS,[b] KARL JOHE,[c] SEWARD B. RUTKOVE,[d] THAIS FEDERICI,[b] MERAIDA POLAK,[a] CRYSTAL KELLY,[a] EVA L. FELDMAN[a]

ABSTRACT

Advances in stem cell biology have generated intense interest in the prospect of transplanting stem cells into the nervous system for the treatment of neurodegenerative diseases. Here, we report the results of an ongoing phase I trial of intraspinal injections of fetal-derived neural stems cells in patients with amyotrophic lateral sclerosis (ALS). This is a first-in-human clinical trial with the goal of assessing the safety and tolerability of the surgical procedure, the introduction of stem cells into the spinal cord, and the use of immunosuppressant drugs in this patient population. Twelve patients received either five unilateral or five bilateral (10 total) injections into the lumbar spinal cord at a dose of 100,000 cells per injection. All patients tolerated the treatment without any long-term complications related to either the surgical procedure or the implantation of stem cells. Clinical assessments ranging from 6 to 18 months after transplantation demonstrated no evidence of acceleration of disease progression due to the intervention. One patient has shown improvement in his clinical status, although these data must be interpreted with caution since this trial was neither designed nor powered to measure treatment efficacy. These results allow us to report success in achieving the phase I goal of demonstrating safety of this therapeutic approach. Based on these positive results, we can now advance this trial by testing intraspinal injections into the cervical spinal cord, with the goal of protecting motor neuron pools affecting respiratory function, which may prolong life for patients with ALS. STEM CELLS *2012;30:1144–1151*

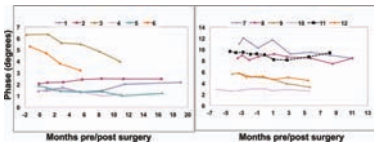
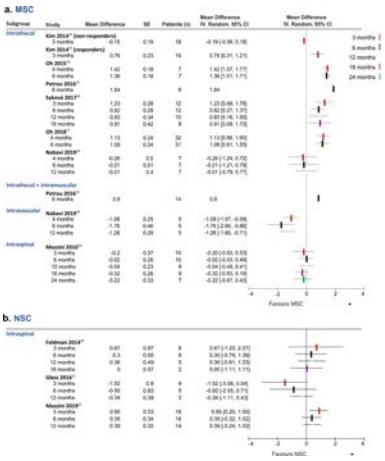


Figure 2. Disease progression as measured using electrical impedance myography (EIM). Average 50 kHz phase for the six muscles studied (bilateral quadriceps, tibialis anterior, and medial gastrocnemius) in all 12 subjects. The lines represent linear fits of the data. Note again the consistent improvement in EIM score for patient 11 after surgery (dotted line).

Meta-analysis Clinical score



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volume 6, Article number: 20 (2021)

Multiple Sclerosis

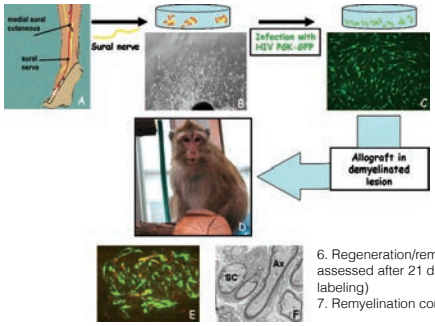
Problems for a cell therapy approach:

- It is both an autoimmune and a neurological disorders: “adding cells may be adding fuel to the fire”
- The damage sometimes extends beyond the myelin sheets to the underlying neurons

Autologous Schwann cell transplantation

Remyelination of the Central Nervous System: A Valuable Contribution from the Periphery

1. Donors: adult macaques, 7-10 years old
2. Biopsy of sural nerve to purify and expand SCs



3. SC labeling
4. Acute demyelination induced by stereotactic injection of LPC (lysophosphatidylcholine) in the donor cortico-spinal tract
5. Grafting after 48h

6. Regeneration/remyelination assessed after 21 days (GFP/PO labeling)
7. Remyelination confirmed by EM

The Journal of Neuroscience, February 1, 2001, 21(3):944–950

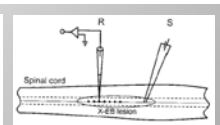
Transplantation of Cryopreserved Adult Human Schwann Cells Enhances Axonal Conduction in Demyelinated Spinal Cord

Ikuhide Kohama, Karen L. Lankford, Jana Preiningerova, Fletcher A. White, Timothy L. Vollmer and Jeffery D. Kocsis

Department of Neurology, Yale University School of Medicine, New Haven, Connecticut 06510, and Paralyzed Veterans of America/Eastern Paralyzed Veterans Association, Neuroscience Research Center and Rehabilitation Research Center, Veterans Affairs Medical Center, West Haven, Connecticut 06516

Schwann cells derived from human sural nerve may provide a valuable source of tissue for a cell-based therapy in multiple sclerosis. However, it is essential to show that transplanted human Schwann cells can remyelinate axons in adult CNS and improve axonal conduction. Sections of sural nerve were removed from amputated legs of patients with cancer, trauma or diabetes, and Schwann cells were isolated and cryopreserved. Suspensions of reconstituted cells were transplanted into the X-irradiation/withdrium bromide lesioned dorsal columns of immunosuppressed Wistar rat. After 3–5 weeks of extensive remyelination, a typical Schwann cell pattern was observed in the lesion zone. Many cells in the lesion were immunopositive for an anti-human nuclei monoclonal antibody. The dorsal columns were removed and maintained in an *in vitro* recording chamber; the conduction properties were studied using field potential and intra-axonal recording techniques. The transplanted dorsal columns displayed improved conduction velocity and frequency-response properties, and action potentials conducted over a greater distance into the lesion, suggesting that conduction block was overcome. These data support the conclusion that transplantation of human Schwann cells results in functional remyelination of a dorsal column lesion.

Key words: cell transplantation; human Schwann cells; demyelination; restoration of conduction; xenotransplantation; multiple sclerosis



Jeffrey Kocsis at Yale University has conducted a clinical trial with five MS patients to test the safety of injecting the patient’s own Schwann cells directly into brain lesions: no publications

Stem cell therapy for CNS diseases: where do we stand?

UNA DONNA MORTA A BANGKOK

Prima vittima per il turismo delle staminali

Affetta da una patologia renale, s’era fatta convincere da un annuncio sul web: fatali le iniezioni di cellule

«Diffidare assolutamente di chi promette vaghe e generici trattamenti con le cellule staminali per qualsiasi tipo di malattia, di chi non ha pubblicato sui riviste scientifiche importanti ma magari ha scritto libri autofinanziati e informarsi e vedere bene con i clinici cosa sono alcuni dei consigli che Giulio Cossu, direttore della divisione di Medicina rigenerativa del San Raffaele di Milano, dà a chi pensa di andare all’estero per ricevere cure con cellule staminali.

Un avvertimento lanciato tante volte e che suona più che mai attuale dopo il caso della donna inglese, morta in seguito ad alcune iniezioni di cellule staminali in Thailandia per curare una malattia renale, così come riportato oggi dal *New Scientist*. Secondo l’analisi *post mortem* riportata sul *Journal of the American society of nephrology*, si erano formati strani noduli sul rene, il fegato e la ghiandola surrenale, quasi sicuramente provocati dalla terapia di staminali.

Da sempre esperti e ricercatori sono impegnati contro il fenomeno del turismo da staminali. Tanto che nel 2008 la Società Internazionale per la Ricerca sulle Cellule Staminali (Isscr) ha emanato delle linee guida per mettere ordine in questo campo. «Sono linee guida importanti perché le regole che i Paesi occidentali si impongono in questo tipo di ricerche non sempre sono osservate in Paesi emergenti, come Cina, India o Corea», commenta Michele De Luca, uno degli autori italiani delle linee guida. Impegnato su questo fronte è anche Gianvito Martino, direttore della Divisione di Neuroscienze dell’Istituto San Raffaele di Milano. «Sono centinaia i pazienti italiani che ogni anno intraprendono questi viaggi, attratti dalle promesse di una cura, e che, nella migliore delle ipotesi, tornano così come sono partiti, ma con le tasche alleggerite. Al contrario, cominciano a essere frequenti i casi di infezioni e di tumori».

Queste cliniche delle cellule staminali si trovano in vari Paesi del mondo, dalla Cina alla Thailandia, dalla Repubblica Dominicana a Manila, a Barbados. «Assicurano l’efficacia della terapie nel 40-50% dei casi - aggiunge il neurologo - e curano ogni tipo di problema, dalla calvizie all’Alzheimer, non solo la Sclerosi Multipla, ma non dicono nulla circa il tipo e la qualità delle staminali che utilizzano. Pantano sull’effetto placebo per indicare i pochissimi trasposi tivi, ma alla fine non si sa che cosa fa che cosa». Martino pensa che in molti casi si arrivi anche a infondere acqua invece che staminali, oppure cortisone, che dà qualche giorno di sollievo e alimenta l’illusione. Preventare falsi miraggi e drammatici viaggi della speranza di chi insegue cure miracolose e custodissime, pubblicizzate online da cliniche con pochi scrupoli, da oggi è anche un sito (*www.cosasonolestaminecelle.org*).

Amyotroph Lateral Scler. 2010 May 3;11(3):328-30.

No benefits from experimental treatment with olfactory ensheathing cells in patients with ALS.

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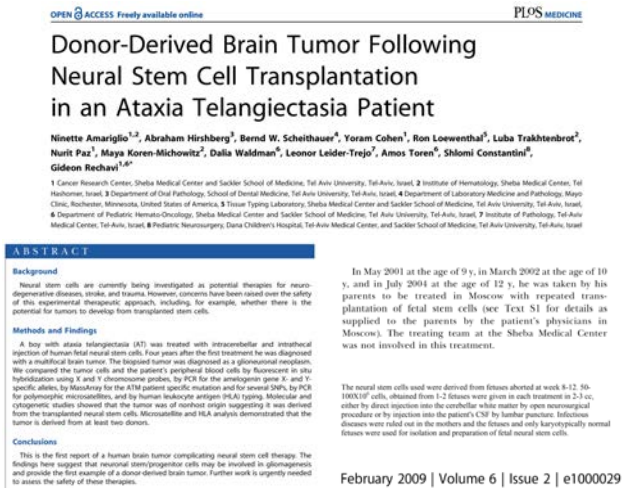
Abstract

Cell based therapies may be promising options for treating ALS. These therapies aim at neuronal replacement or they may prevent dysfunctional motor neurons from dying. **Conflicting results on transplantation of olfactory ensheathing cells (OECs) in ALS mouse models indicate that this technique is not yet ready to progress to clinical trials. A Chinese group has nevertheless treated ALS patients with OECs.** We carried out a prospective study of seven patients who underwent OEC treatment in China, following them from four months before departure until one year after treatment. Muscle strength, level of daily functioning and respiratory capacity were measured at regular intervals. **Three patients reported subjective positive effects directly after treatment. No individual objective improvement was measured, and outcome measures gradually declined in all patients. Two patients had severe side-effects. Based on our findings in these ALS patients who underwent experimental OEC treatment, we conclude that there are no indications that this treatment is beneficial.**



OPEN ACCESS Freely available online PLoS MEDICINE

Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient

Ninette Amariglio[1,2], Abraham Hirshberg[3], Bernd W. Scheithauer[4], Yoram Cohen[1], Ron Loewenthal[5], Luba Trakhtenbrot[2], Nurit Paz[1], Maya Koren-Michowitz[2], Dalia Waldman[6], Leonor Leider-Trejo[7], Amos Toren[6], Shlomi Constantini[8], Gideon Rechavi[1,6]*

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ABSTRACT

Background

Neural stem cells are currently being investigated as potential therapies for neurodegenerative diseases, stroke, and trauma. However, concerns have been raised over the safety of this experimental therapeutic approach, including, for example, whether there is the potential for tumors to develop from transplanted stem cells.

Methods and Findings

A boy with ataxia telangiectasia (AT) was treated with intracerebellar and intrathecal injection of human fetal neural stem cells. Four years after the first treatment he was diagnosed with a multifocal brain tumor. The biopsied tumor was diagnosed as a glioneuronal neoplasm. We compared the tumor cells and the patient's peripheral blood cells by fluorescent in situ hybridization using X and Y chromosome probes, by PCR for the amelogenin gene X- and Y-specific alleles, by MassArray for the ATM patient specific mutation and for several SNPs, by PCR for polymorphic microsatellites, and by human leukocyte antigen (HLA) typing. Molecular and cytogenetic studies showed that the tumor was of nonhost origin suggesting it was derived from the transplanted neural stem cells. Microsatellite and HLA analysis demonstrated that the tumor is derived from at least two donors.

Conclusions

This is the first report of a human brain tumor complicating neural stem cell therapy. The findings here suggest that neuronal stem/progenitor cells may be involved in gliomagenesis and provide the first example of a donor-derived brain tumor. Further work is urgently needed to assess the safety of these therapies.

In May 2001 at the age of 9 y, in March 2002 at the age of 10 y, and in July 2004 at the age of 12 y, he was taken by his parents to be treated in Moscow with repeated transplantation of fetal stem cells (see Text S1 for details as supplied to the parents by the patient's physicians in Moscow). The treating team at the Sheba Medical Center was not involved in this treatment.

The neural stem cells used were derived from fetuses aborted at week 8-12. 50-100X10[6] cells, obtained from 1-2 fetuses were given in each treatment in 2-3 cc, either by direct injection into the cerebellar white matter by open neurosurgical procedure or by injection into the patient's CSF by lumbar puncture. Infectious diseases were ruled out in the mothers and the fetuses and only karyotypically normal fetuses were used for isolation and preparation of fetal neural stem cells.

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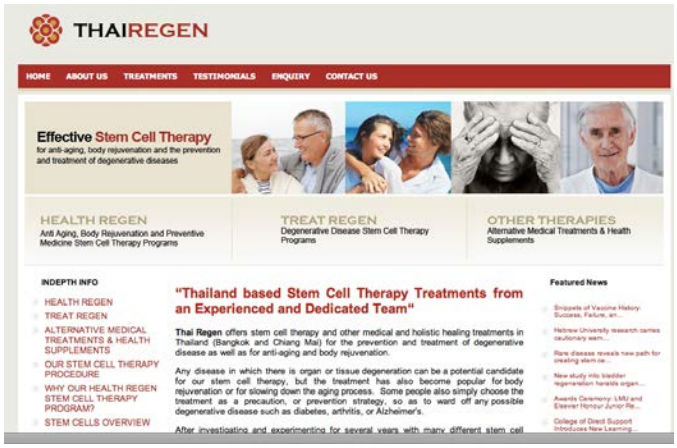

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Thai Regen offers stem cell therapy and other medical and holistic healing treatments in Thailand (Bangkok and Chiang Mai) for the prevention and treatment of degenerative disease as well as for anti-aging and body rejuvenation.

Any disease in which there is organ or tissue degeneration can be a potential candidate for our stem cell therapy, but the treatment has also become popular for body rejuvenation or for slowing down the aging process. Some people also simply choose the treatment as a precaution, or prevention strategy, so as to ward off any possible degenerative disease such as diabetes, arthritis, or Alzheimer's.

After investigating and experimenting for several years with many different stem cell

Featured News

CLINIC CRYOBANK SCIENCE NEWS COOPERATION CONTACTS

Departments Clinic today TREATMENT From the history of cellular therapy Questions and answers

RU EN HU BL RO AR

List of diseases and syndromes, in case of which the efficiency of treatment by means of stem cells is clinically proved
- Diabetes mellitus
- Crohn's disease
- Cirrhoses
- Pancreatonecrosis post-operational
- Critical lower limb ischemia
- Alzheimer's disease
- Disseminated sclerosis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Arthrosis deformans
- Insult
- Myocardiodystrophy

Alzheimer's disease

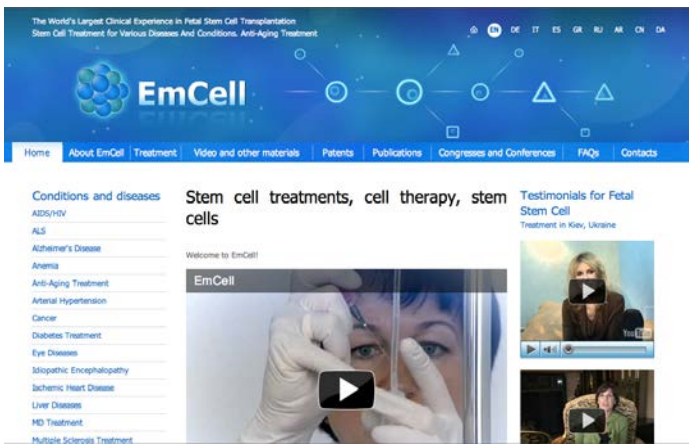
Alzheimer's disease (AD) or senile dementia is the most severe form of weakness of mind (dementia).

Until recently AD is considered to be unremediable (incurable) terminal form of degenerative disease, which was described for the first time by German psychiatrist and neuropathologist Alois Alzheimer in 1906. This disease is considered to be typical for people at the age after 65, but in recent years AD can be met more often at more younger age. In 2006 the number of sick with AD reached 26,6 millions people. It is forecasted that till 2050 this number will increase in 4 times.

The earliest manifestation of AD is incorrectly evaluated as age-related or related to chronic stress hypomnesia, especially for yesterday. During this period doctor can diagnose AD by means of special tests and method of brains computer scanning. In the period of disease progressing there can develop estrangement, restraint, apathy, sometimes aggression, speech disturbance, loss of long-term memory, less mobility. Patient ceases to communicate, doesn't talk, and doesn't respond to surrounding people. Physiological functions are violated progressively, after that death comes. Average duration of life after establishing diagnosis does not exceed 7 years.

The causes of AD progression have not defined till the end. There exist three main theories of AD development. The oldest one – cholinergic theory, according to which AD is the result of violation of fusion of acetylcholine neurotransmitter. According to amyloid theory the cause of AD is concentration of amyloid-beta protein in brain, and it destroys neurons. Tau- hypothesis consists in the fact that abnormal (hyperphosphorilated) tau-protein launches cascade of disease as a result of violation of neurofibril function in neuron body with disintegration or collapse of microtubular transport system of neuron.

It is important that AD is characterized by **decrease of neuron number** and synapsis in cortex and central subcortical zone. In other words, colossal atrophy of information perception zone, affecting the most important zones of brain.



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Stem cell treatments, cell therapy, stem cells

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Treatment Available Today

Brian - Stroke
Brian's Dad - "Brian suffered a series of debilitating strokes, which left him in a comatose state, severely brain damaged... Sixty days following his first stem cell treatment, miraculously Brian began to speak."

Hannah - Epilepsy
Hannah's mother - "The prognosis for Hannah was grim. We were completely numb... After the stem cell treatment, Hannah woke up. She got her health and quality of life back."

Lisa - Multiple Sclerosis
"Having unsuccessfully tried everything I could find to help me, I was on the verge of giving up any hope of recovery...Today, after the stem cell treatment I feel great. And more important than how I feel, is the look in my husband Andy's eyes."

The Telegraph

Costa Rica cracks down on controversial stem cell treatments

Costa Rica is cracking down on an unauthorised stem cell clinic that has attracted hundreds of foreigners seeking relief from degenerative diseases and serious injuries.

Better known for its idyllic tropical beaches and lush cloud forests, Costa Rica's many hospitals and clinics have made medical tourism one of the fastest growing segments of its tourism sector, the motor of its economy.

They lure tens of thousands of foreigners seeking surgery, dental work, cancer treatment, cosmetic surgery, and dozens of other procedures at a fraction of their cost in the United States.

Until this week, one of those draws was stem cell treatment, using master cells gleaned from umbilical cords, fat and elsewhere.

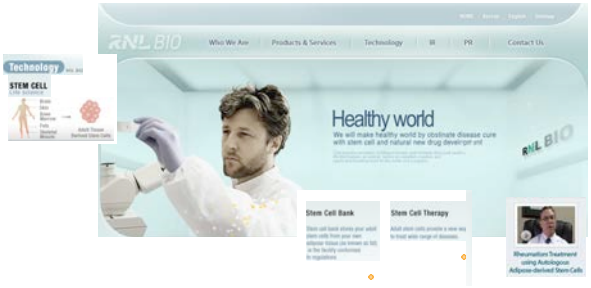
The health ministry last month ordered the country's largest stem cell clinic to stop offering treatments, arguing there is no evidence that the treatments work or are safe.

Stem Cell Tourism

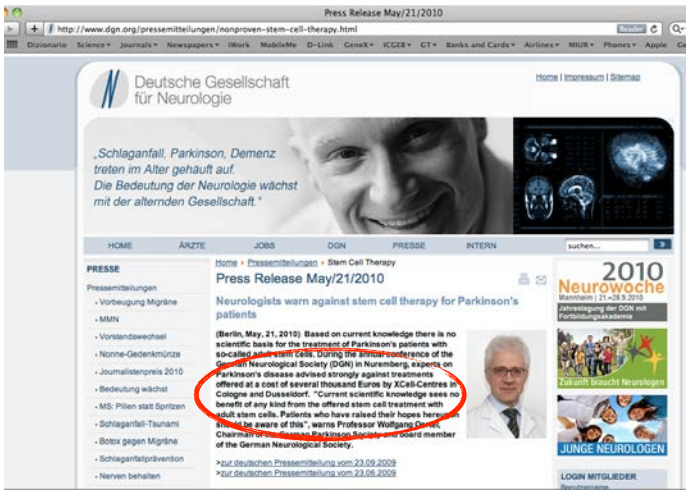
NewScientist

First case of alleged stem-cell fraud enters US courts

Six residents of Los Angeles, California, are suing South Korean company RNL Bio and associates in a Californian court for alleged fraud. They claim the company convinced them to travel to clinics in South Korea, China or Mexico to donate fat tissue and have stem cells from it re-administered to cure diseases and even reverse ageing.



New Scientist, 13 July 2012



The Telegraph

Europe's largest stem cell clinic shut down after death of baby

Europe's largest stem cell clinic, which is at the centre of a scandal over the death of a baby given an injection into the brain, has been shut down.

XCell had exploited a loophole in German law allowing it to charge for experimental procedures

Eurovision Song Contest

IL PICCOLO

STAMINALI
Trapianto positivo al Burlo su bambina con atrofia spinale

Si è trattato del primo caso di terapia con cellule staminali intratecali effettuato in Italia e il primo in Europa in una malattia come questa. Dopo l'intervento effettuato al Burlo di Trieste si aprono prospettive di salvezza per molti bambini affetti da malattie genetiche che colpiscono il sistema nervoso

L'ospedale Burlo

TRIESTE. Una bambina di sei mesi, affetta da atrofia muscolare spinale, completamente paralizzata e con una breve aspettativa di vita è stata sottoposta a terapia con cellule staminali, al Burlo di Trieste, e i sanitari oggi hanno reso noto che le sue condizioni "sono chiaramente migliorate.

"L'operazione - ha reso noto il Burlo - è stata resa possibile grazie alle decisioni del giudice del Tribunale Civile di Venezia e utilizzando il protocollo medico della Stamina Foundation Onlus con cellule prodotte dal Laboratorio Verri di Monza".

Si è trattato del primo caso di terapia con cellule staminali intratecali effettuato in Italia e il primo in Europa in una malattia come questa. Si aprono così prospettive di salvezza per molti bambini affetti da malattie genetiche che colpiscono il sistema nervoso.

Michele De Luca

Centro di Medicina Rigenerativa "Stefano Ferrari" - UNIMORE