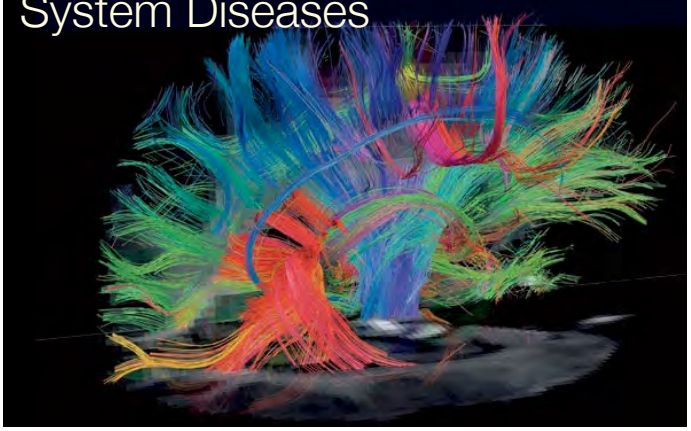
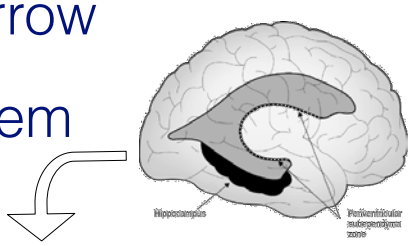
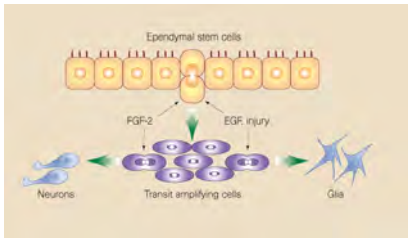
Cell Therapy for Nervous System Diseases

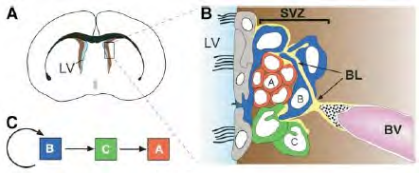


Brain marrow
location of
Neural Stem Cells

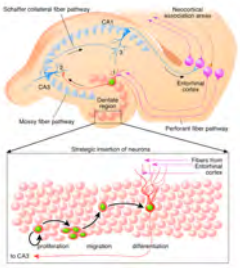


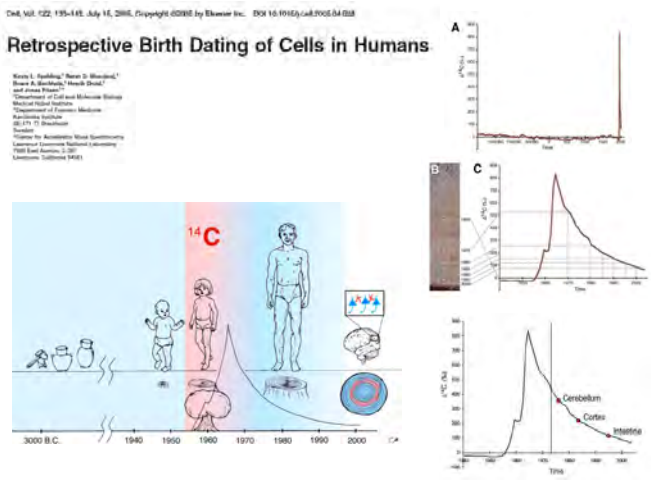


The neurogenic niche



Restriction of neurogenesis to the hippocampus and subventricular zone appears to be related to the 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

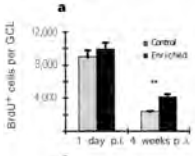


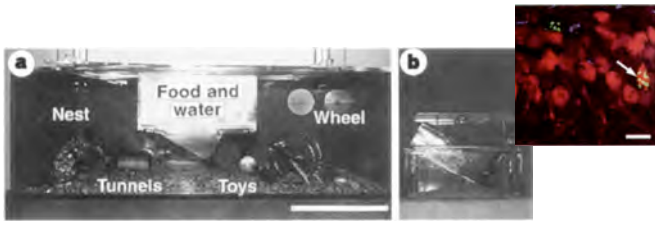


Neurogenesis and temporal associations in long-term human memory

More hippocampal neurons in adult mice living in an enriched environment

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

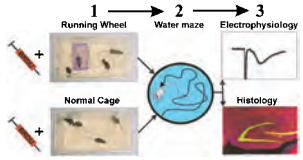




NATURE | VOL 386 | 3 APRIL 1997

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

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



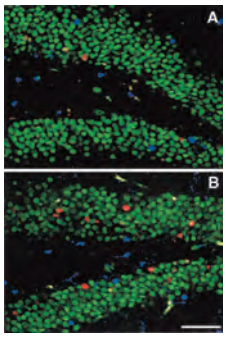


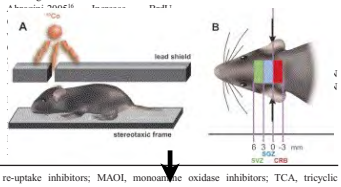
Fig. 4. Confocal images of BrdU-positive cells in control (A) and runner coronal sections (B). Sections were immunofluorescent triple-labeled for BrdU (red), NeuN, indicating neuronal phenotype (green), and S100β, selective for glial phenotype (blue). (Scale bar indicates 50 μm.)

PNAS | November 9, 1999 | vol. 96 | no. 23 | 13429

A wide range of antidepressants share the common feature of increasing 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)

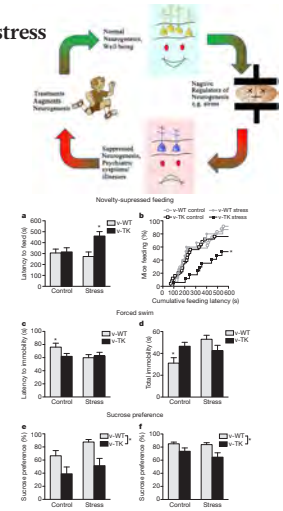
Adult hippocampal neurogenesis buffers stress responses and depressive behaviour

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

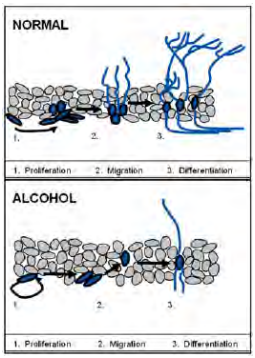
460 | NATURE | VOL 476 | 25 AUGUST 2011

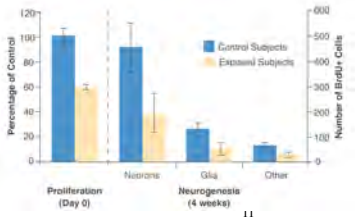
Glucocorticoids are released in response to stressful experiences and serve many beneficial homeostatic functions. However, dysregulation of glucocorticoids is associated with cognitive impairments and depressive illness[1,2]. In the hippocampus, a brain region densely populated with receptors for stress 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





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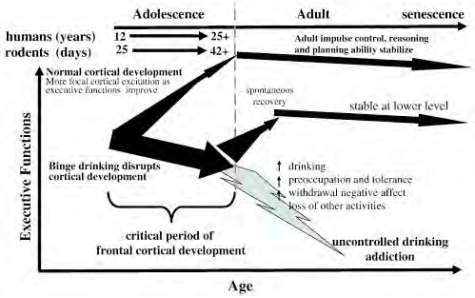
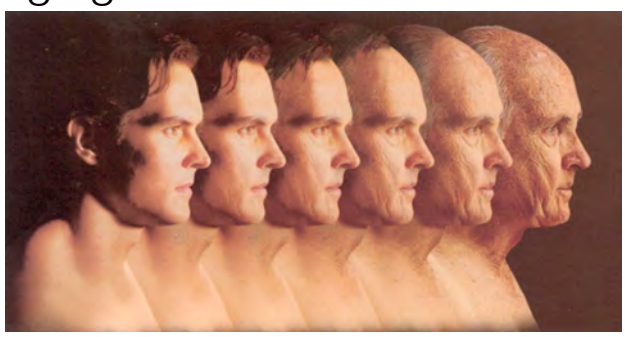
Adolescent alcohol abuse disrupts frontal cortical development and maturation of executive function



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

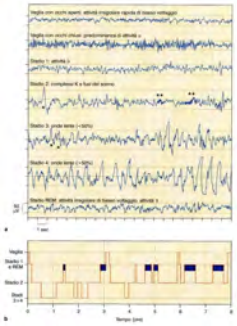
Christian Mirescu, Jennifer D. Peters, Liron Noiman, and Elizabeth Gould*

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

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



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

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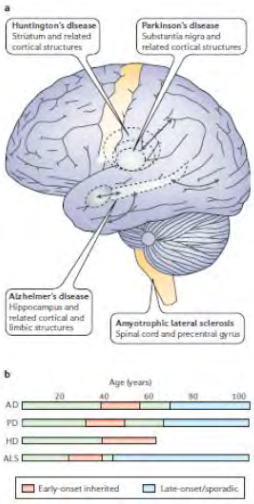
ABSTRACT

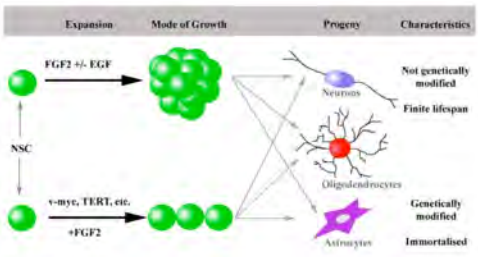
Disruptions in circadian rhythms, as seen in human shift workers, are often associated with many health consequences including impairments in cognitive functions. However, the mechanisms underlying these affects are not well understood. The objective of the present study is to explore the effects of 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.

The who, where and when of neuronal death in age-related neurodegenerative disorders

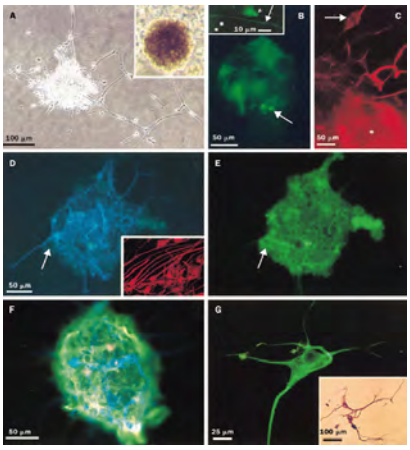


NSCs can be maintained in culture for expansion:

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

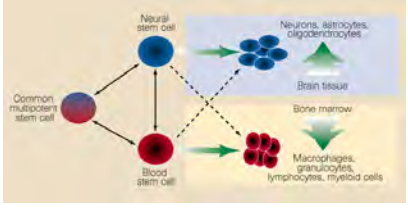


A neurosphere is a tissue-culture-generated clone of cells in different states of differentiation, all presumed to arise from a single multipotent stem/progenitor cell

A. ***Neurosphere on laminin (inset: semi-solid media)***
B. α-*nestin*
C. α-*vimentin*
D. α-*GFAP*
E. α-β*III tubulin*
F. α-*GFAP* + α-β*III 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

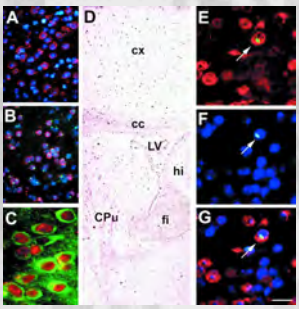
Éva Mezey,[1]* Karen J. Chandross,[2] Gyöngyi Harta,[1] Richard A. Maki,[3,4] Scott R. McKercher[3]

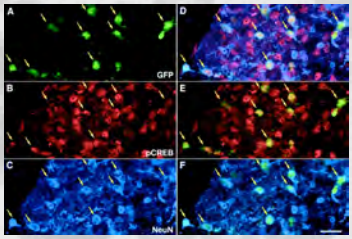
Bone marrow stem cells give rise to a variety of hematopoietic lineages and repopulate the blood throughout adult life. We show that, in a strain of mice incapable of developing cells of the myeloid and lymphoid lineages, transplanted adult bone marrow cells migrated into the brain and differentiated 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.

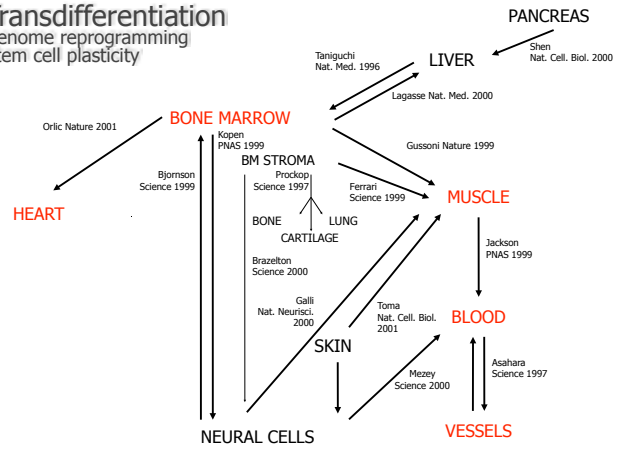




Only phenotypic markers, no functional data!

Transdifferentiation

Genome reprogramming
Stem cell plasticity



Stem cells

Lost in translation

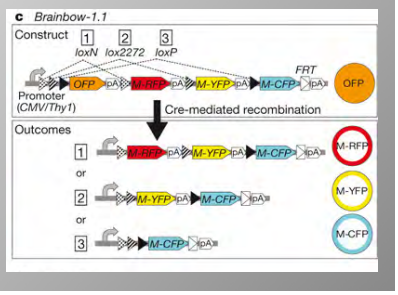
Kenneth R. Chien

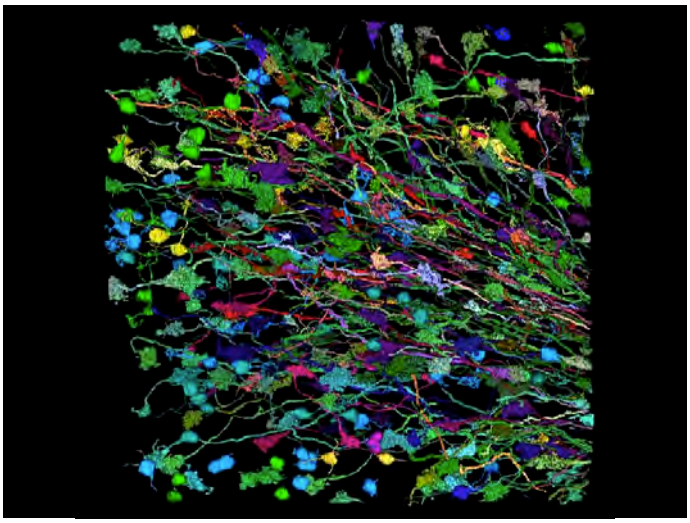
The potential use of stem cells as agents of repair in human disease makes them the subject of high-profile studies. But we should be wary of prematurely pushing laboratory research into clinical practice.

NATURE | doi:10.1038/nature02460 | www.nature.com/nature

"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"

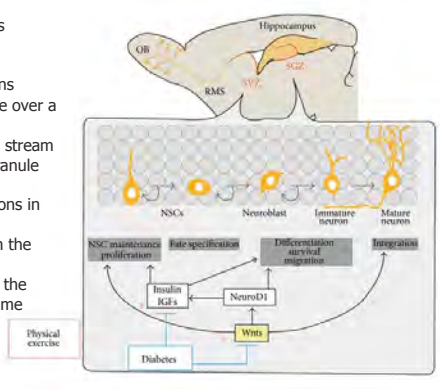
Mark Mattson, NINDS, Bethesda





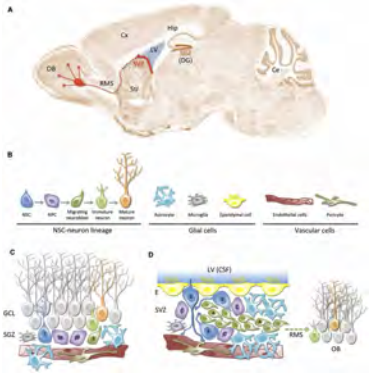
NSC migration in the adult brain

New neurons in these regions originate from a residential population of adult neural precursor cells. Neurons born in the adult **SVZ** migrate over a great distance through the rostral migratory stream (RMS) and become mostly granule interneurons and periglomerular interneurons in the **OB**, whereas neurons born in the adult **SGZ** migrate into the **GC layer** of the dentate gyrus (DG) and become glutamatergic dentate cells in the hippocampus.



The neurogenic niche

Niche constituents that support adult SVZ or SGZ neurogenesis include
- endothelial cells
- ependymal cells
- astrocytes
- microglia
- mature neurons



In contrast to embryonic neurogenesis, one hallmark of adult neurogenesis is its dynamic regulation by neuronal activity at specific stages

The use of genetically modified mice to eliminate adult neurogenesis

Newborn neurons in the adult brain are required for some, but not all hippocampus or olfactory bulb-dependent tasks

Adult **hippocampal neurogenesis** contributes to:

- **spatial-navigation learning**
- **long-term spatial memory** retention
- spatial pattern discrimination
- trace conditioning
- **contextual fear conditioning**
- **clearance** of hippocampal memory traces
- reorganization of memory to extra-hippocampal substrates

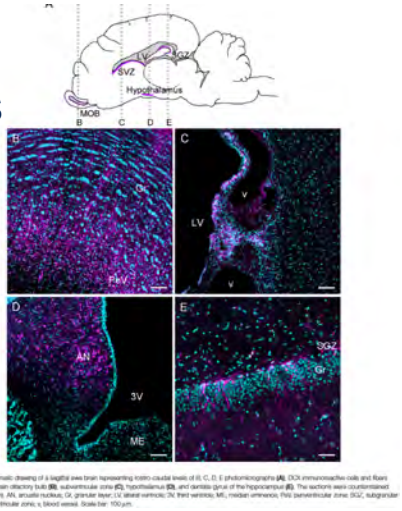
Adult **olfactory bulb neurogenesis** contributes to:

- long-term structural integrity of the olfactory bulb
- **short-term olfactory memory**
- **olfactory fear conditioning**
- **long-term associative olfactory memory** involving active learning
- pheromone-related behaviors, such as **mating** and **social recognition**

Mice versus Sheep to study the functional role of adult neurogenesis

- Sheep development (puberty at 6–8 months) and its **life expectancy (10–12 years)** are rather long in comparison to rodents and differences in life span could influence the rate of neuronal maturation in adulthood.
- Sheep possess a **gyrencephalic brain**, a cortex with a laterally expanded folded pial surface similar to non-human and human primates, and adult neurogenesis could differ from a lissencephalic brain with a smooth cortical surface, like rodents, since major developmental differences exists between both types of brain.
- Sheep is also a **seasonal breeder**, unlike the majority of laboratory rodents, and these seasonal changes are under the control of the hypothalamic region.
- Sheep live under different complexity of **social organization** and in a more natural environment than laboratory rodents.
- Sheep are highly social and develop selective and stable bonds.
- In this species, odors play a key role in individual recognition of conspecifics either in male-female or **mother-young** interactions

DCX labels neuroblasts



Species-specific dynamics

In the OB of **rodents**, the far majority of newborn neurons are observed within 15 days after BrdU injections and are fully mature 15 days later

In the **macaque**, only a very small population of BrdU positive cells is found even at 3 months post-injection in the granular cell layer.

In **sheep**, no variation of BrdU cell density is observed across time except a decrease at 8-month post-injection, suggesting a slow process of apoptosis over this period, in contrast to rodents in which half of the newborn cells die within the first month after birth. Very few **neuroblasts (BrdU+/DCX+ cells)** are found at 1 month after BrdU injections in the granular layer of the sheep MOB. This population **peaks at 3-month and decreases slowly up to 8 months after BrdU injections**. No mature neurons (BrdU+/NeuN+ cells) are observed before 3 months post-injections and the highest proportion of new neurons is found 8 months after BrdU injections. A substantial proportion of immature cells, evidenced by Sox2 labeling, is found both in the periventricular and granular layers, again supporting the hypothesis of the presence of stem cells that could differentiate according to physiological challenges.

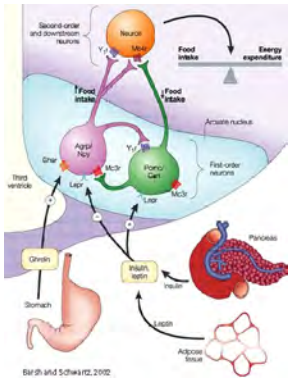
Neuronal maturation takes longer in sheep and macaques compared to rodents

Olphactory neurogenesis and maternal behaviour

In sheep maternal behavior at parturition depends on olfactory attraction toward amniotic fluids that cover the newborn lamb. These cues render the newborn lamb attractive and stimulate its licking by the mother, thus inducing maternal behavior. Moreover, ewes are able to discriminate their own young from an alien lamb by **learning its olfactory signature** within **2 h** after parturition, which is accompanied with neurochemical changes occurring in the MOB.

Decreased cell proliferation occurs in the SVZ, but not in the DG, in ewes that remain with their lambs for the first 2 days after parturition when compared to ewes separated from them, but maturation of the neuroblasts is heightened.
Olfactory experience sculpts newborn neurons with nostril closure decreasing and odor enrichment increasing the arborization complexity of newborn granule cells. In the context of motherhood, olfactory exposure to pups induces changes in structural synaptic plasticity of newly born olfactory neurons.
Although, the functional relevance of the plasticity occurring in the MOB remains to be determined, one can hypothesize that the decrease in the number of neuroblasts would reduce cell competition and consequently increases their maturation, allowing them to be integrated in the neural network involved in learning
Exposure to either own or unfamiliar lambs increases the percentage of neuroblasts activated in the granular layer of the MOB compared to exposure to an unfamiliar ewe, indicating that the preferential activation is not seen for any social odors but is specific to lamb odors.

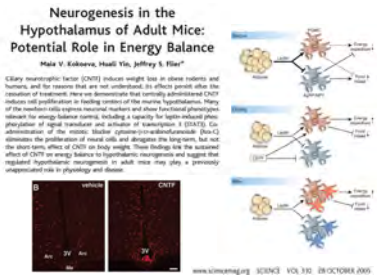
Hypothalamic neurogenesis and food intake



In mice, hypothalamic newborn neurons acquire the identities and the functional phenotypes related to the control of energy homeostasis, including NPY or POMC.

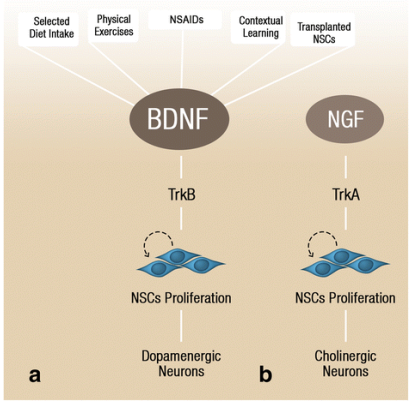
Some of these new neurons are responsive to fasting and leptin.

Diet seems to regulate adult hypothalamic neurogenesis, although the results are equivocal. Opposing effects of high fat diet on neurogenesis and body weight are reported depending on the ages and sexes of the animals tested, as well as the duration of the diet and the targeted hypothalamic area.


Neurogenesis in the Hypothalamus of Adult Mice: Potential Role in Energy Balance

Maia V. Kokoeva, Huaili Yin, Jeffrey S. Flier*

Factors that influence neurogenesis as potential therapy



Commonly, following growth as EBs, cells are specified to adopt a neural progenitor cell (NPC) fate by exposure to retinoic acid (RA) or by maintenance in chemically-defined, minimal medium in the presence of FGF-2, a potent mitogen

Any remaining non-neural pluripotent stem cells could give rise to teratomas upon transplatation, and have been shown to do so in rodents

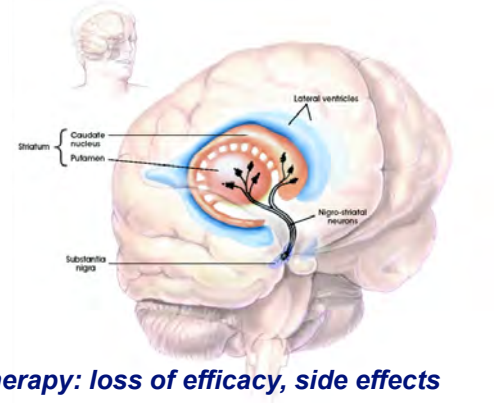
Stem cell type	Source	Pros	Cons
ES cell-derived NSCs	ICM of blastocyst	Pluripotent, unlimited proliferation, stable karyotype	Tumorigenicity, ethical considerations, purification (markers), require neural specification
Embryonic NSCs	Embryonic CNS	Neural lineage-committed, Non-tumorigenic, regionally specified*	Long-term maintenance, ethical considerations,
Adult NSCs	SVZ, SGL of hippocampus	Neural lineage-committed	Long-term maintenance, restricted potential?, limited availability
Non-neural SCs	Bone marrow, skin, umbilical cord, blood etc	No ethical considerations, plentiful/accessible supply, generate autologous cells	Require neural specification, restricted potential?

Lewis X
PNA
Nestin
HAS
Musashi1
Sox1
But none 100% specific

The different regions of the developing brain are patterned by gradients of different secreted and diffusible signaling molecules; the TFs regulated downstream of these molecules then specify positional identity and NPC fate. Mitogens used in vitro, particularly FGF-2, might be responsible for altering NSC gene expression, thus affecting their capacity to generate particular cell types

Neuronal pathways that degenerate in Parkinson's Disease

- tremor
- rigidity
- movement loss



Levodopa therapy: loss of efficacy, side effects

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

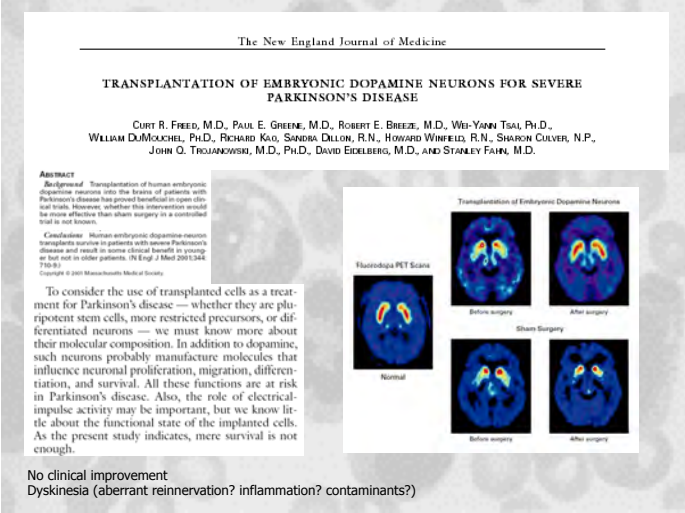
1982 Dopaminergic fetal neurons can survive in the eye anterior chamber
Transplantation of fetal tissue into the damaged area of the brains in rats and monkeys models of Parkinson's Disease (MPTP)

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 et 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.

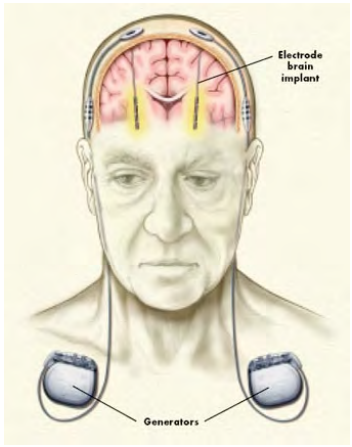
Conclusions Human embryonic dopamine-neuron transplants survive in patients with severe Parkinson's disease and result in some clinical benefit in younger but not in older patients. (N Engl J Med 2001;344:710-9.)

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.

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 Rehnerona, 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.

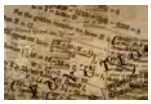
Conclusions and Relevance: The results from these 2 cases indicate that dopaminergic cell transplantation can offer very long-term symptomatic relief in patients with Parkinson disease and provide proof-of-concept support for future clinical trials using fetal or stem cell therapies.

JAMA Neurol. doi:10.1001/jamaneurol.2013.4749

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

TRANSEURO

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.



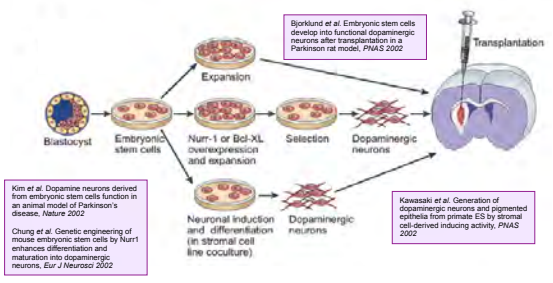
The principal goals of Transeuro are:

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.

Other sources for DA neurons



Bjorklund *et al.* Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. *PNAS 2002*

Kim *et al.* Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature 2002*

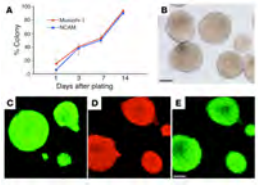
Chung *et al.* Genetic engineering of mouse embryonic stem cells by Nurr1 enhances differentiation and maturation into dopaminergic neurons. *Eur J Neurosci 2002*

Kawasaki *et al.* Generation of dopaminergic neurons and pigmented epithelia from primate ES by stromal cell-derived inducing activity. *PNAS 2002*

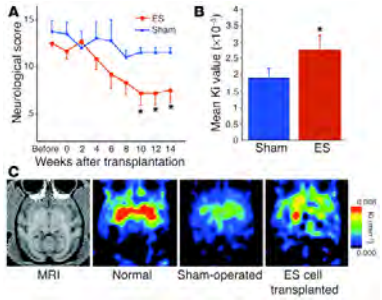
Dopamine neurons can be generated also from human ES cells
However, chromosomal aberrations have been observed in mid-term cultured human ES cells

Dopaminergic neurons generated from monkey embryonic stem cells function in a Parkinson primate model

Yasushi Takagi et al.



Neural progenitors induced from primate ES cells. Spheres were immunoreactive for NCAM (**C**, green), Musashi-1 (**D**, red), and Nestin (**E**, green)

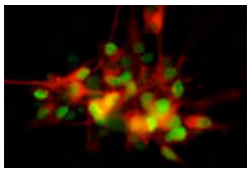


Clinical Progress

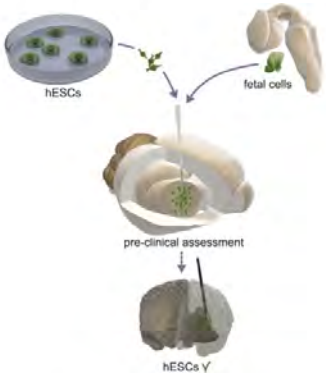
Cell Stem Cell

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

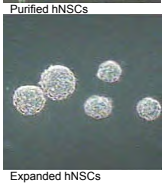


STEMCELLS INC.

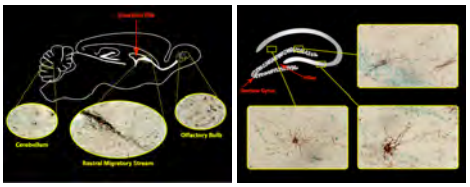
Working in collaboration with StemCells founders Drs. Fred Gage (The Salk Institute) and Irving Weissman (Stanford Medical Center), the team at StemCells, Inc. led by Dr. Nobuko Uchida, has succeeded for the first time in finding markers for human brain stem cells. Using these markers and state of the art cell sorting, we have been able to purify stem cells away from the other cells in the brain tissue. The purified stem cells have been expanded using proprietary cell culture systems and transplanted back into host mouse brains.

The transplanted stem cells engrafted and differentiated into human neurons and glia that intermingled with host brain counterparts. Remarkably, after seven months, the transplanted human cells survived and migrated to specific functional domains of the host brain, with no sign of tumor formation or adverse effects on the recipients.

Purified hNSCs



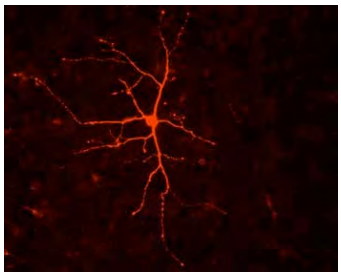
Expanded hNSCs



The dentate gyrus of the hippocampus is a site of continuing neurogenesis in rodents and humans. Various types of mature human neural cells (insets - brown) could be seen in this site of active neuroregeneration.

STEMCELLS INC.

The scientists at StemCells are directly testing the generation of dopaminergic neurons from the cultured neural stem cells. The neural stem cells and the dopaminergic neurons will be tested side by side in preclinical animal models that mimic the cardinal features of Parkinson's disease.



Stem Cell Reports

Article

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ISSCR

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

Yu-Kai Wang,[1,2,3,5] Wan-Wan Zhu,[1,5] Meng-Hua Wu,[1,4,5] Yi-Hui Wu,[1,5] Zheng-Xin Liu,[1] Ling-Min Liang,[1,3,4] Chao Sheng,[1] Jie Hao,[1,2,3] Liu Wang,[1,2,3,4] Wei Li,[1,2,3,4] Qi Zhou,[1,2,3,4,*] and Bao-Yang Hu[1,2,3,4,*]

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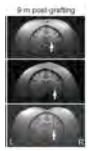
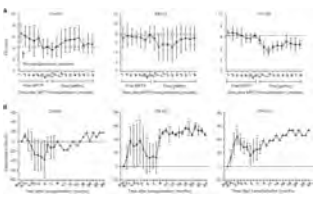
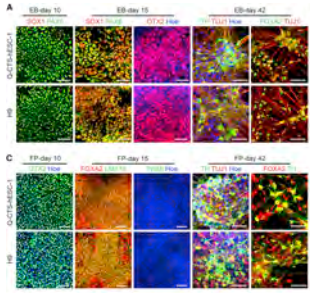
https://doi.org/10.1016/j.stemcr.2018.05.010

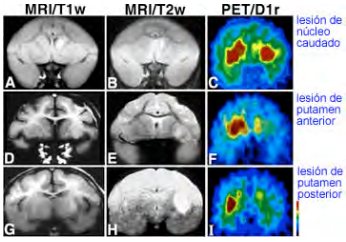






Huntington's disease

- 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

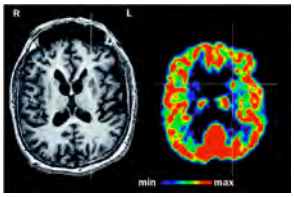


TABLE 1. *Clinical Trials of Cell Transplants in Huntington's Disease*

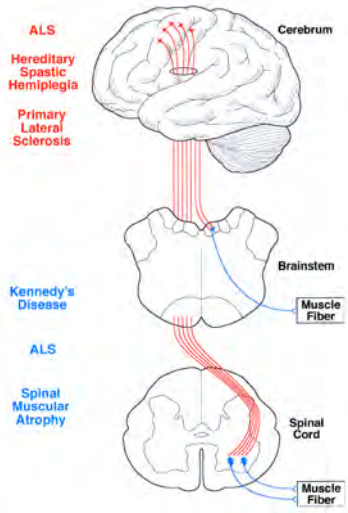
Study	n	Donor Tissue/Side n	Weeks	Dissect	Implant Tracks	Immune Treatment	Safety	Efficacy	Imaging	Anatomy
Cuba and Czech	4	2–3	?	VM or WGE	2–3 ? [B]	CyA	No pathological or immunological response[135]	Not yet possible to determine	MRI-guided stereotaxy; no reported follow-up	
Mexico City	2	1	E12–13	WGE	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	pcPu [B]	CyA 6 months	1 death, 3 subdural hematomas[45]	Modest (NS) changes in motor tests at 12 months[80]	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; pcPU = 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

Motoneuron diseases

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

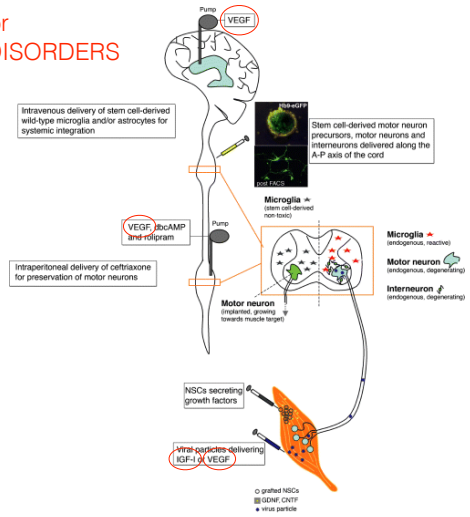


Amyotrophic lateral sclerosis
(Lou Gehrig's disease)

- 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

Novel therapies for MOTONEURON DISORDERS

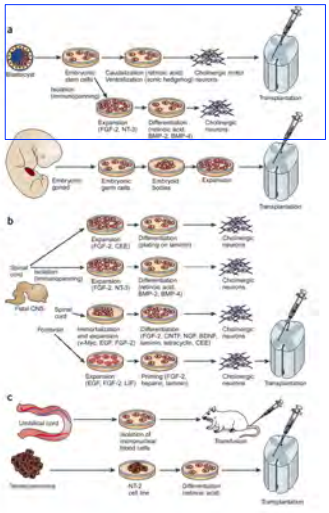
Growth factors hold promise for delaying onset/ progression - no restoration of lost function



Stem cell therapy for amyotrophic lateral sclerosis

In its common form, ALS is characterized by progressive dysfunction and degeneration of motor neurons in cerebral cortex, brain stem and spinal cord. Muscle weakness progresses rapidly and causes death within a few years.

To have long-term value, stem cell therapy must restore function of both upper and lower motor neurons



Directing progenitor cell along specific pathways of neuronal differentiation in a systematic manner has proved difficult, not least because the normal developmental pathways that generate most classes of CNS neurons remain poorly defined.

Cell, Vol. 110, 385–397, August 9, 2002, Copyright ©2002 by Cell Press

Directed Differentiation of Embryonic Stem Cells into Motor Neurons

Hynek Wichterle,[1] Ivo Lieberam,[1] Jeffery A. Porter,[2] and Thomas M. Jessell[1,3]
[1]Howard Hughes Medical Institute
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Columbia University
New York, New York 10032
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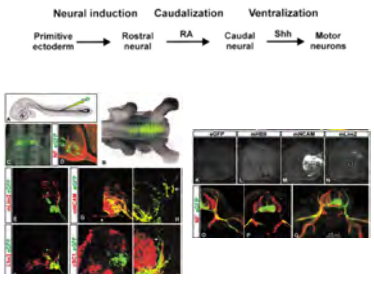
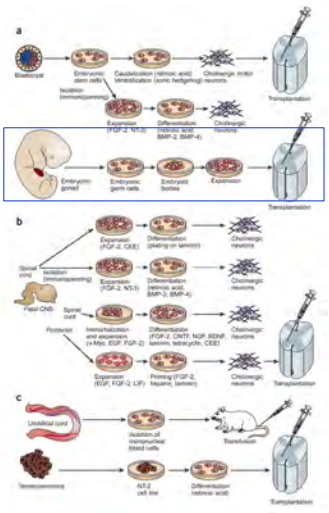
61 South Moulton Street
Cambridge, Massachusetts 02138

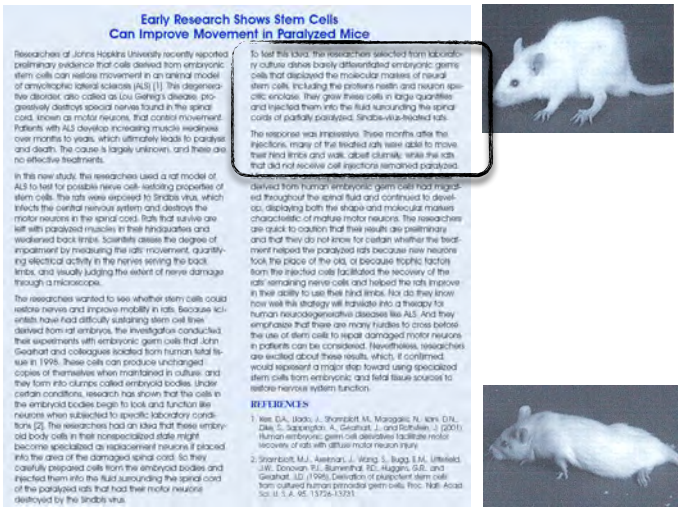
Summary

Inductive signals and transcription factors involved in motor neuron generation have been identified, raising the question of whether these developmental insights can be used to direct stem cells to a motor neuron fate. We show that developmentally relevant signaling factors can induce mouse embryonic stem (ES) cells to differentiate into spinal progenitor cells, and subsequently into motor neurons, through a pathway recapitulating that used in vivo. ES cell-derived motor neurons can populate the embryonic spinal cord, extend axons, and form synapses with target muscles. Thus, inductive signals involved in normal pathways of neurogenesis can direct ES cells to form specific classes of CNS neurons.



Stem cell therapy for amyotrophic lateral sclerosis





Early Research Shows Stem Cells Can Improve Movement in Paralyzed Mice

Researchers at Johns Hopkins University recently reported preliminary evidence that cells derived from embryonic stem cells can restore movement in an animal model of amyotrophic lateral sclerosis (ALS) [1]. This degenerative disorder, also called as Lou Gehrig's disease, progressively destroys special nerves found in the spinal cord, known as motor neurons, that control movement. Patients with ALS develop increasing muscle weakness over months to years, which ultimately leads to paralysis and death. The cause is largely unknown, and there are no effective treatments.

In this new study, the researchers used a rat model of ALS to test for possible nerve cell–restoring properties of stem cells. The rats were exposed to Sindbis virus, which infects the central nervous system and destroys the motor neurons in the spinal cord. Rats that survive are left with paralyzed muscles in their hindquarters and weakened back limbs. Scientists assess the degree of impairment by measuring the rats' movement, quantifying electrical activity in the nerves serving the back limbs, and visually judging the extent of nerve damage through a microscope.

The researchers wanted to see whether stem cells could restore nerves and improve mobility in rats. Because scientists have had difficulty sustaining stem cell lines derived from rat embryos, the investigators conducted their experiments with embryonic germ cells that John Gearhart and colleagues isolated from human fetal tissue in 1998. These cells can produce unchanged copies of themselves when maintained in culture and they form into clumps called embryoid bodies. Under certain conditions, research has shown that the cells in the embryoid bodies begin to look and function like neurons when subjected to specific laboratory conditions [2]. The researchers had an idea that these embryoid body cells in their nonspecialized state might become specialized as replacement neurons if placed into the area of the damaged spinal cord. So they painfully prepared cells from the embryoid bodies and injected them into the fluid surrounding the spinal cord of the paralyzed rats that had their motor neurons destroyed by the Sindbis virus.

To test this idea, the researchers selected from laboratory culture dishes barely differentiated embryonic germ cells that displayed the molecular markers of neural stem cells, including the proteins nestin and neuron-specific enolase. They grew these cells in large quantities and injected them into the fluid surrounding the spinal cords of partially paralyzed, Sindbis-virus–treated rats.

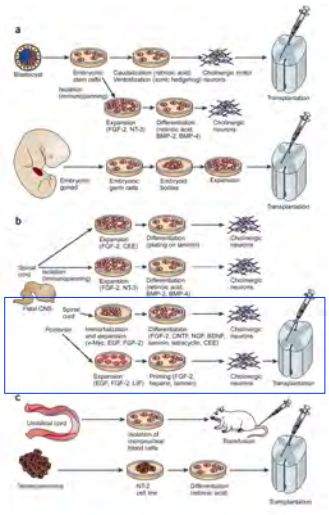
The response was impressive. Three months after the injections, many of the treated rats were able to move their hind limbs and walk, albeit clumsily, while the rats that did not receive cell injections remained paralyzed.

Subsequent examination revealed that the cells derived from human embryonic germ cells had migrated throughout the spinal fluid and continued to develop, displaying both the shape and molecular markers characteristic of mature motor neurons. The researchers are quick to caution that their results are preliminary and that they do not know for certain whether the treatment helped the paralyzed rats because new neurons took the place of the old, or because trophic factors from the injected cells facilitated the recovery of the rats' remaining nerve cells and helped the rats improve in their ability to use their hind limbs. Nor do they know how well this strategy will translate into a therapy for human neurodegenerative diseases like ALS. And they emphasize that there are many hurdles to cross before the use of stem cells to repair damaged motor neurons in patients can be considered. Nevertheless, researchers are excited about these results, which, if confirmed, would represent a major step toward using specialized stem cells from embryonic and fetal tissue sources to restore nervous system function.

REFERENCES

1. Kerr, D.A., Llado, J., Shamblott, M., Maragakis, N., Irani, D.N., Dike, S., Sappington, A., Gearhart, J., and Rothstein, J. (2003). Human embryonic germ cell derivatives facilitate motor recovery of rats with diffuse motor neuron injury.
2. Shamblott, M.J., Axelman, J., Wang, S., Bugg, E.M., Littlefield, J.W., Donovan, P.J., Blumenthal, P.D., Huggins, G.R., and Gearhart, J.D. (1998). Derivation of pluripotent stem cells from cultured human primordial germ cells. Proc. Natl. Acad. Sci. U. S. A. 95, 13726–13731.

Stem cell therapy for amyotrophic lateral sclerosis



The US company 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.

STEM CELLS
REGENERATIVE MEDICINE

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

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[e]

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

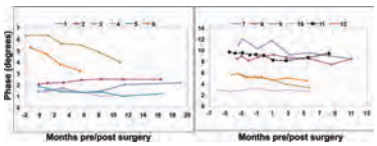


Figure 2. Disease progression as measured using electrical impedance myography (EIM). Average 50 kHz phase for the six muscles studied (bilateral quadriceps, tibialis anterior, and medial gastrocnemius) in all 12 subjects. The lines represent linear fits of the data. Note again the consistent improvement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

NEURALSTEM INC.

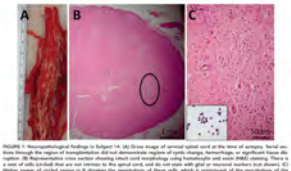
Product status:
U.S.: FDA-approved NSI-566 Phase II trials commenced in September 2013, and concluded final surgeries in July 2014. Phase II concludes after six-month observation period.
Mechanism of Action: Rebuilding neural circuitry
Route of Administration: Direct injections into the spinal cord
- See more at: http://www.neuralstem.com/cell-therapy-for-als#sthash.Tell6aEJ.dpuf

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,[4] and Jonathan D. Glass, MD[1]

ANNALS of Neurology March 2014

The cervical injection procedure was well tolerated and disease progression did not accelerate in any subject, verifying the safety and feasibility of cervical and dual-targeting approaches. Analyses on outcome data revealed preliminary insight into potential windows of stem cell biological activity and identified clinical assessment measures that closely correlate with ALS Functional Rating Scale-Revised scores, a standard assessment for ALS clinical trials.



Multiple Sclerosis

Problems for a cell therapy approach:

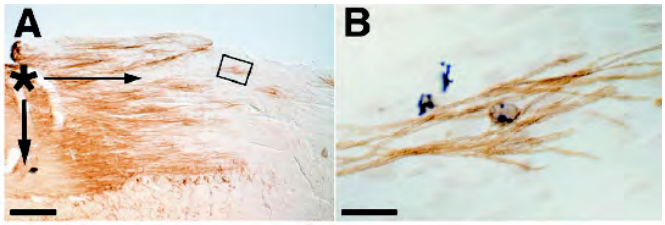
- It is both an autoimmune and a neurological disorders: "adding cells may be adding fuel to the fire"
- The damage sometimes extends beyond the myelin sheets to the underlying neurons

Embryonic Stem Cell–Derived Glial Precursors: A Source of Myelinating Transplants

Oliver Brüstle,[1*] Kimberly N. Jones,[1,2] Randall D. Learish,[3†] Khalad Karram,[1] Khalid Choudhary,[1,2] Otmar D. Wiestler,[1] Ian D. Duncan,[3] Ronald D. G. McKay[2]

Self-renewing, totipotent embryonic stem (ES) cells may provide a virtually unlimited donor source for transplantation. A protocol that permits the in vitro generation of precursors for oligodendrocytes and astrocytes from ES cells was devised. Transplantation in a rat model of a human myelin disease shows that these ES cell–derived precursors interact with host neurons and efficiently myelinate axons in brain and spinal cord. Thus, ES cells can serve as a valuable source of cell type–specific somatic precursors for neural transplantation.

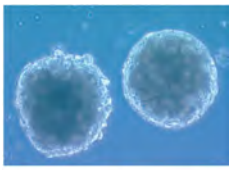
Brown: PLP
Blue: mouse satellite DNA

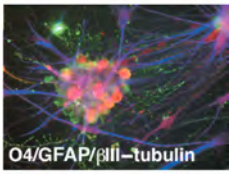


ARTICLES

Identification and isolation of multipotential neural progenitor cells from the subcortical white matter of the adult human brain

White matter biopsy for lobotomy, aneurysm or post-trauma decompression

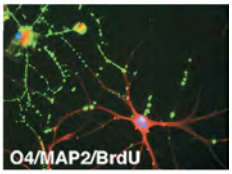




O4 = oligodendrocytes, green

GFAP = astrocytes, blue

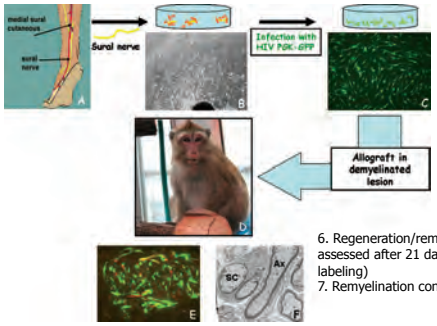
βIII-tubulin, MAP = neurons, red



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

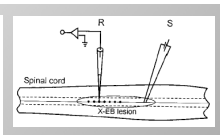


3. SC labeling
4. Acute demyelination induced by stereotactic injection of LPC (lysophosphatidylcholine) in the donor cortico-spinal tract
5. Grafting after 48h
6. Regeneration/remyelination assessed after 21 days (GFP/PO labeling)
7. Remyelination confirmed by EM

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

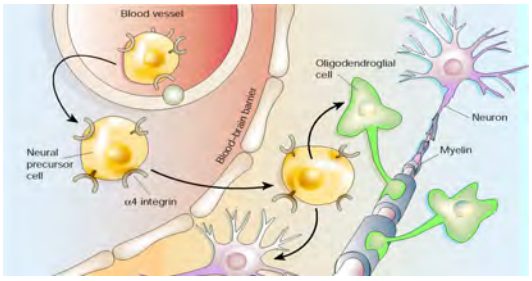


Jeffrey Kocsis at Yale University is currently conducting a clinical trial with five MS patients to test the safety of injecting the patient's own Schwann cells directly into brain lesions

articles

Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis

Stefano Pluchino*, Angelo Quattrini†‡, Elena Brambilla*, Angela Gritti§, Giuliana Salani*, Giorgia Dina†, Rossella Galli§, Ubaldo Del Carro‖, Stefano Amadio‖, Alessandra Bergami*, Roberto Furlan*‡, Giancarlo Comi‖, Angelo L. Vescovi§ & Gianvito Martino*‡



Symptoms improvement even after paralysis onset!
Spontaneous homing appealing for a systemic disease!

Articles

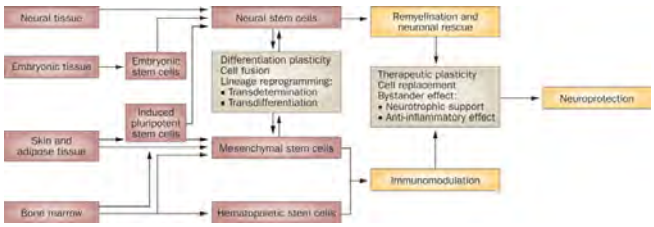
Autologous non-myeloablative haemopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study

21 patients (11 women and 10 men) with relapsing-remitting MS

Autologous non-myeloablative haemopoietic stem cell transplantation

Average follow up time 37 months: 17 of the patients (80 percent) scored better on a standard test used to gauge their vision, muscle strength, motor coordination, and other aspects of neurological function

Stem cell transplantation in multiple sclerosis: current status and future prospects



Nature Reviews Neurology **6**, 247-255 (May 2010)

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 dichiaramente vaghe e generici trattamenti con le cellule staminali per qualsiasi tipo di malattia, di chi non ha pubblicato sulle riviste scientifiche importanti ma magari ha scritto libri autofinanziati e informatisi vedere bene con' è la clinica: ecco 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 rarissima, così come riportato oggi dal *New Scientist*. Secondo l'analisi *post mortem* riportata sul *Journal of the American society of nephrology*, si erano formati tratti nodulari nel rene, il fegato e la ghiandola surrenali, quasi sicuramente provocato dalla terapia di staminali.

Da tempo esperti e ricercatori sono impegnati contro il fenomeno del turismo da staminali. Tanto che nel 2006 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, Indiae Corea», commenta Michele De Luca, uno degli autori italiani delle linee guida. Impegnato su questo fronte è anche Giansito 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, echo, 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. «Assicuriamo l'efficacia della terapia 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. Puntano sull'effetto placebo per indicare i pochissimi casi positivi, 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. Per evitare falsi miraggi e drammatici viaggi della speranza di chi insegue cure miracolose e costosissime, pubblicizzate online da cliniche con pochi scrupoli, da oggi c'è anche un sito (*www.cosertouhatstemcells.org*).

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

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

Piepers S, van den Berg LH.

Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, The Netherlands.
s.piepers-2@umcutrecht.nl

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[8], Shlomi Constantini[9], Gideon Rechavi[1,6]*

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. Notably, 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 Y-chromosome 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 supporting it was derived from the transplanted neural stem cells. Microsatellite and HLA analysis demonstrated that the tumor is derived from at least two donors.

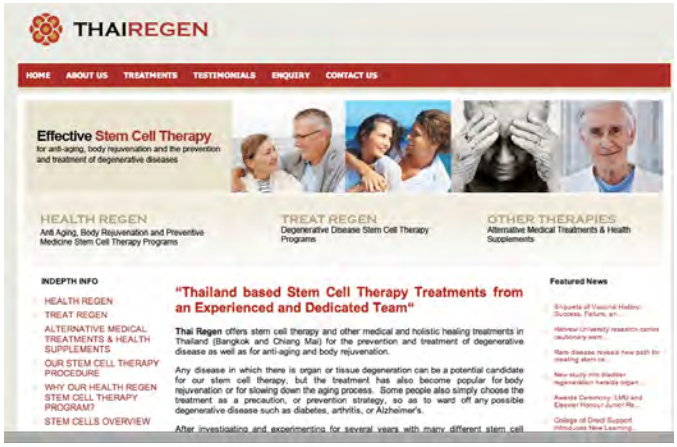
Conclusions

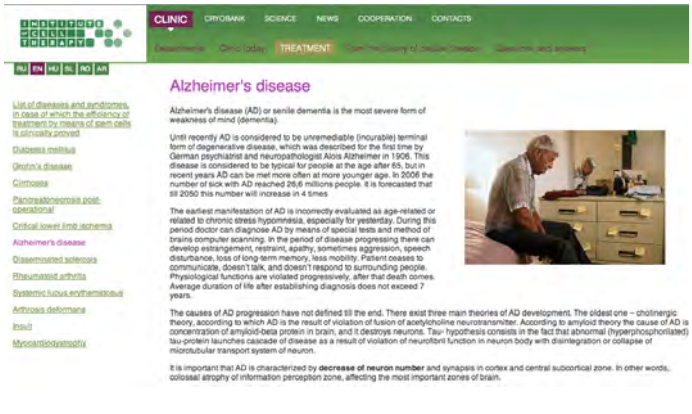
This is the first report of a human brain tumor complicating neural stem cell therapy. The findings here suggest that neuronal stem/progenitor cells may be involved in gliomagenesis and provide the first example of a donor-derived brain tumor. Further work is urgently needed to assess the safety of these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

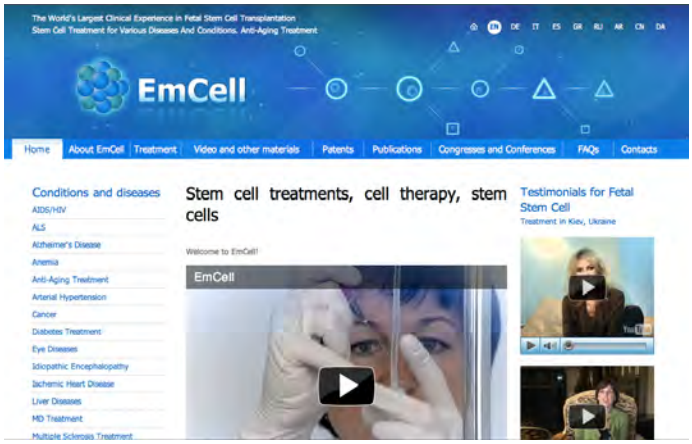
In May 2001 at the age of 9 y, in March 2002 at the age of 10 y, and in July 2004 at the age of 12 y, he was taken by his parents to be treated in Moscow with repeated transplantation of fetal stem cells (see Text S1 for details as supplied to the parents by the patient's physicians in Moscow). The treating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

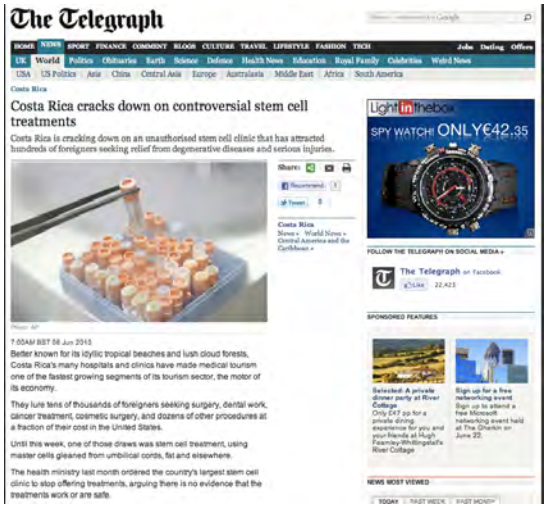
The neural stem cells used were derived from fetuses aborted at week 8-12. 50-100X10^6 cells, obtained from 1-2 fetuses were given in each treatment in 2-3 cc, either by direct injection into the cerebellar white matter by open neurosurgical procedure or by injection into the patient's CSF by lumbar 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.

February 2009 | Volume 6 | Issue 2 | e1000029







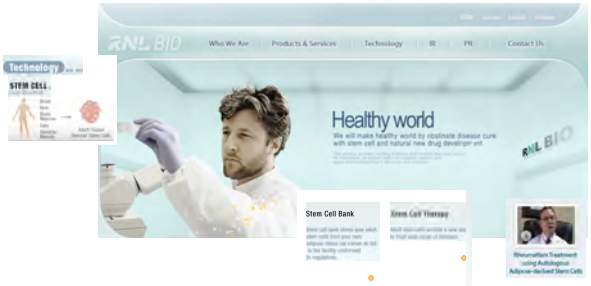


Stem Cell Tourism

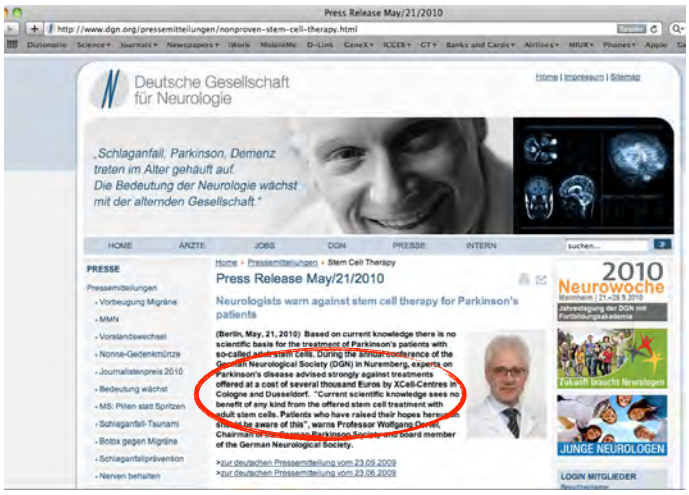
NewScientist

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

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Germany

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

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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.