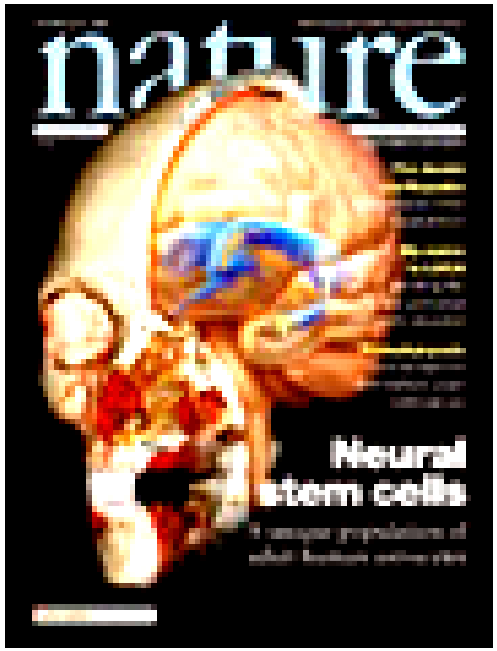
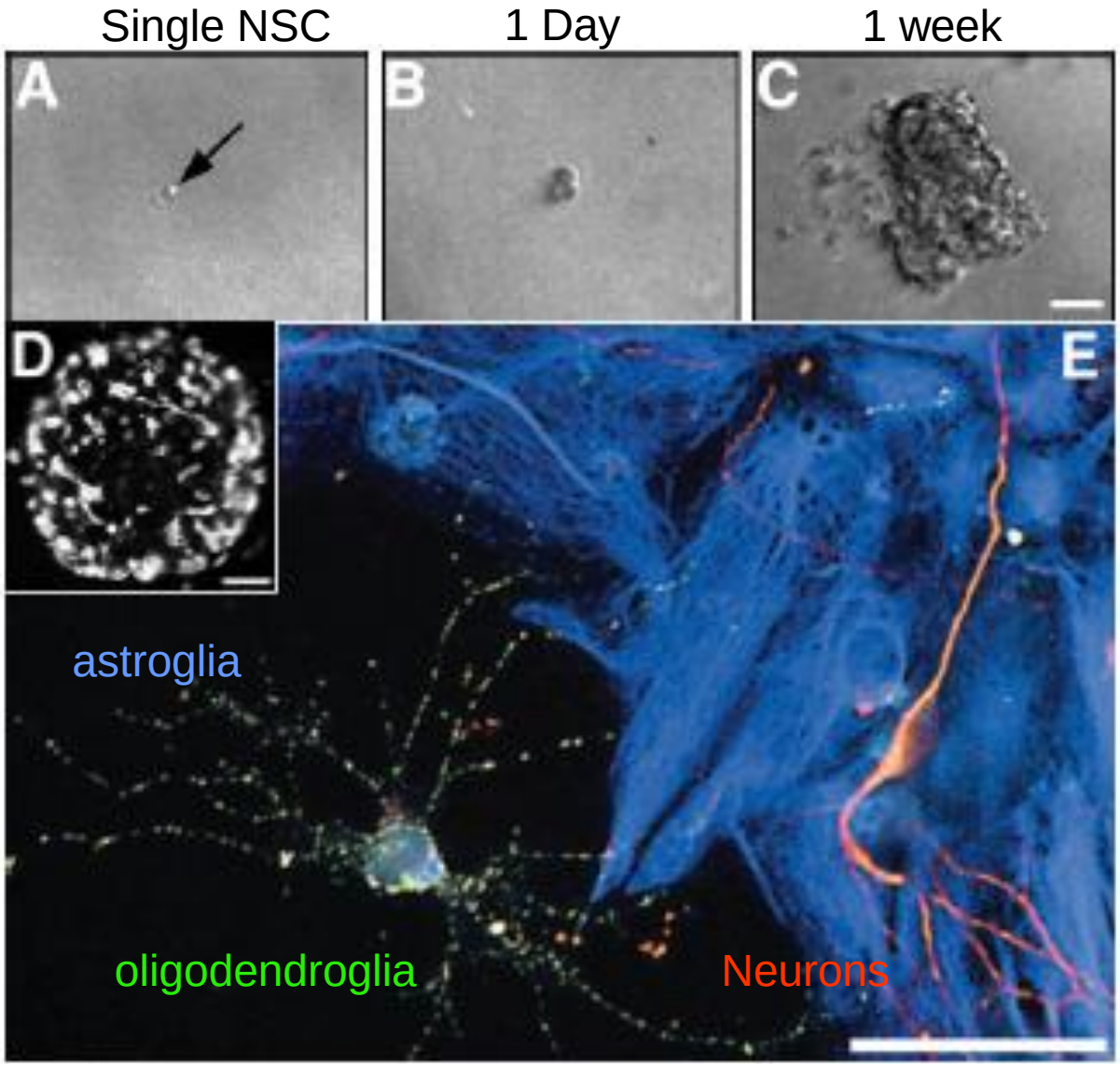
Neural stem cells

1912 discovered in rodent brains, dismissed as artifact



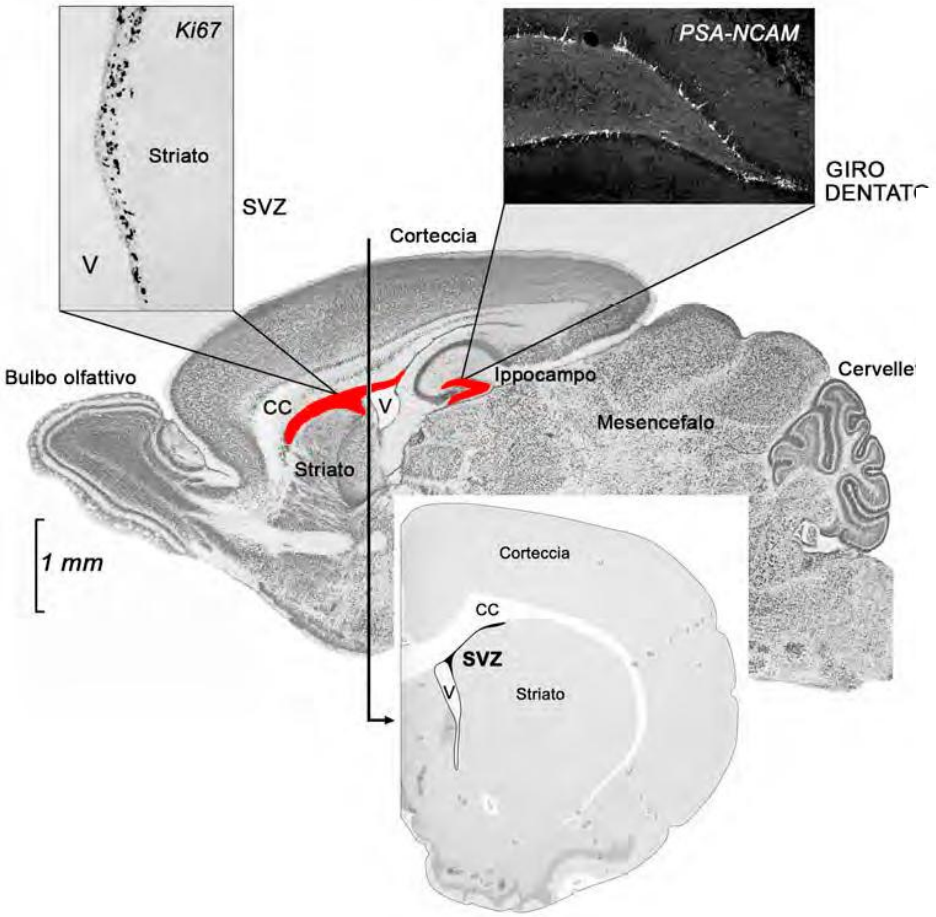
- 1992 multipotent cell in brain of monkey
- 1996-1998 BrdU in brains of cancer patients
- 2001 Neural stem cells in cadavers
- 2006 Neural progenitors from epilepsy surgery

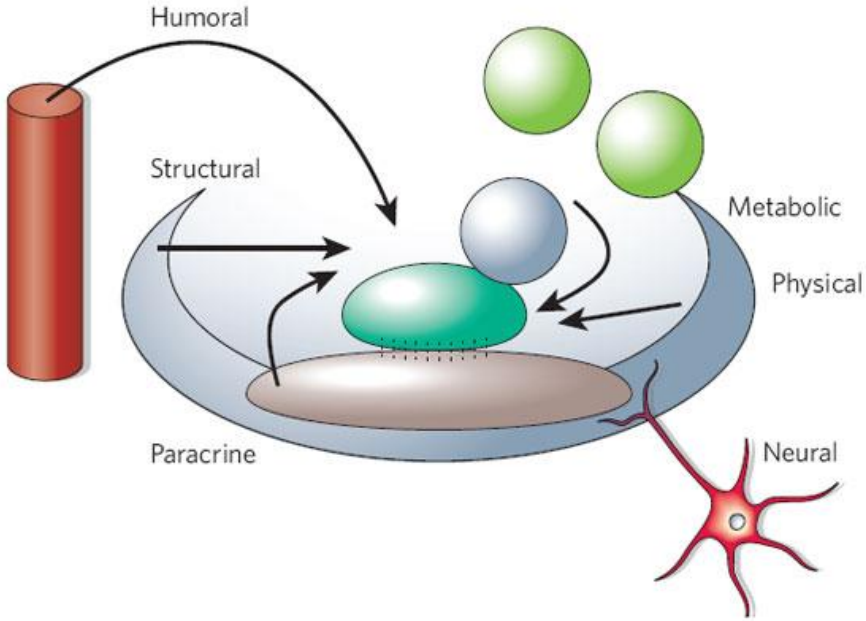


Angelo Vescovi

22 JANUARY 1999 VOL 283 SCIENCE

Neurogenesi e nicchie





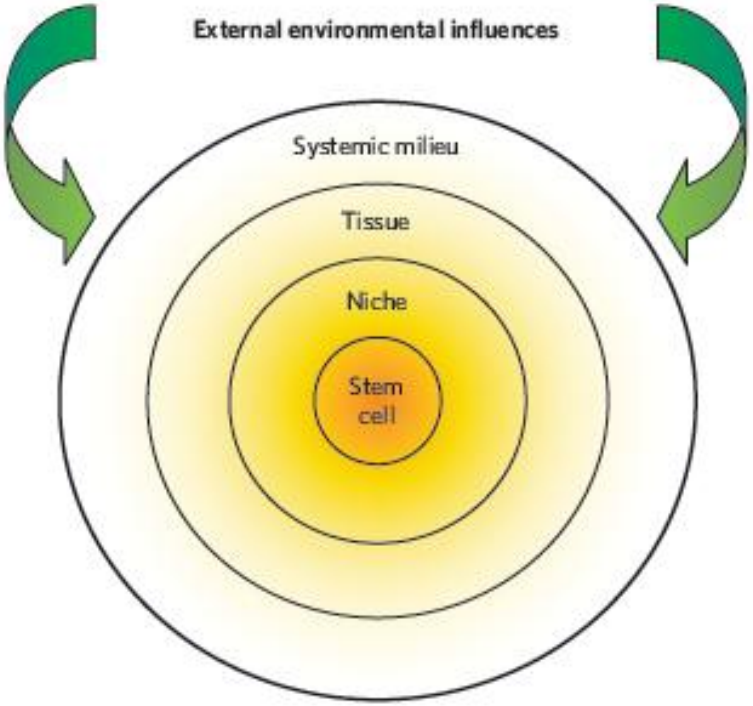
J Pharmacol Sci 115, 425 – 432 (2011)

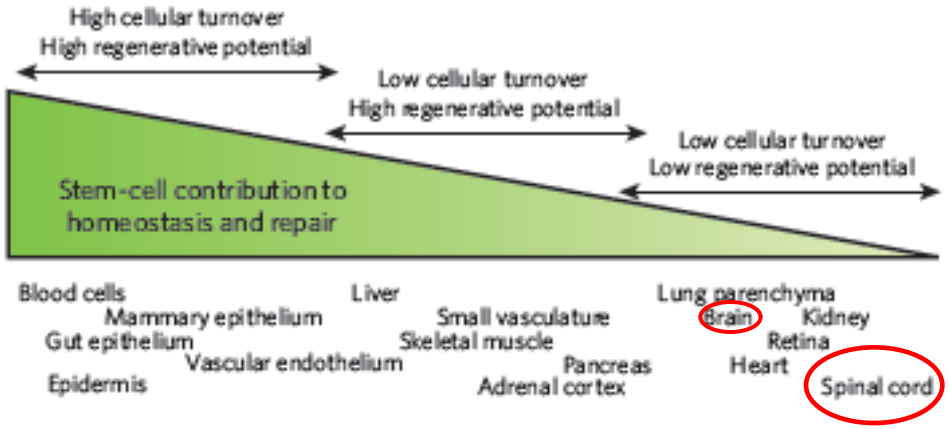
Journal of Pharmacological Sciences

Current Perspective

Adult Neurogenesis Is Regulated by Endogenous Factors Produced During Neurodegeneration

Masanori Yoneyama[1], Tatsuo Shiba[1], Shigeru Hasebe[1], and Kiyokazu Ogita[1,*]





NATURE|Vol 441|29 June 2006

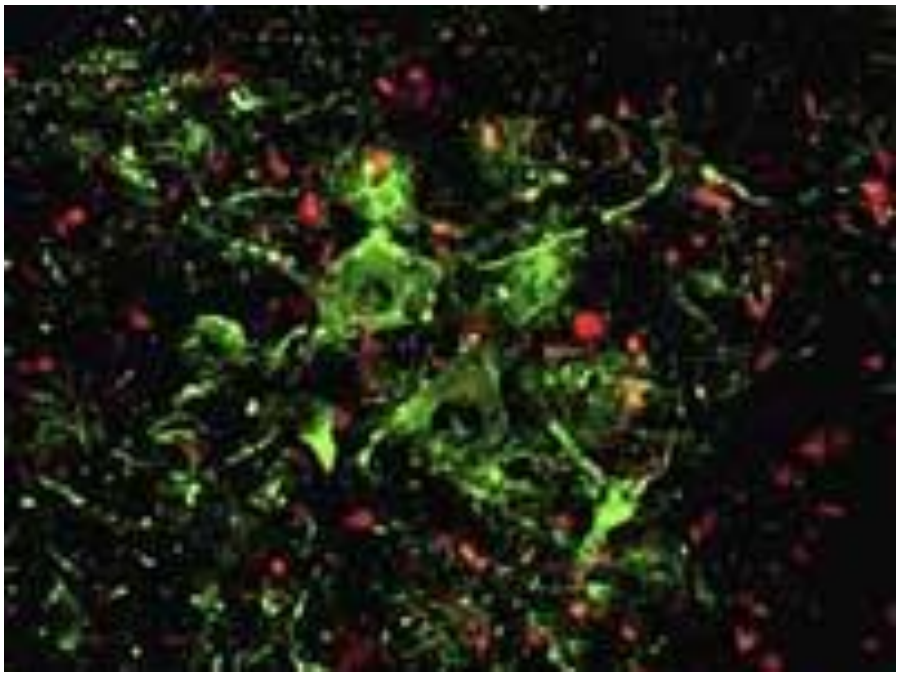
STEM CELLS®

Motor Neuron Degeneration Promotes Neural Progenitor Cell Proliferation, Migration, and Neurogenesis in the Spinal Cords of Amyotrophic Lateral Sclerosis Mice

LIYING CHI,[a] YAN KE,[a] CHUN LUO,[a] BAOLIN LI,[b] DAVID GOZAL,[c] BALARAMAN KALYANARAMAN,[d] RUGAO LIU[a]

[a]Department of Anatomy and Cell Biology, University of North Dakota School of Medicine, Grand Forks, North Dakota; [b]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana; [c]Kosair Children's Hospital Research Institute, Department of Pediatrics, University of Louisville School of Medicine, Louisville, Kentucky; [d]Department of Biophysics, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

STEM CELLS 2006;24:34–43 www.StemCells.com



Human neural stem cells (red) cluster around a motor neuron (green) in the spinal cord of an ALS-afflicted rat (Photo: courtesy Sandra Klein)

THE JOURNAL OF COMPARATIVE NEUROLOGY 497:468–488 (2006)

The Adult Neural Stem and Progenitor Cell Niche is Altered in Amyotrophic Lateral Sclerosis Mouse Brain

ZHIPING LIU[1] AND LEE J. MARTIN[1,2]*

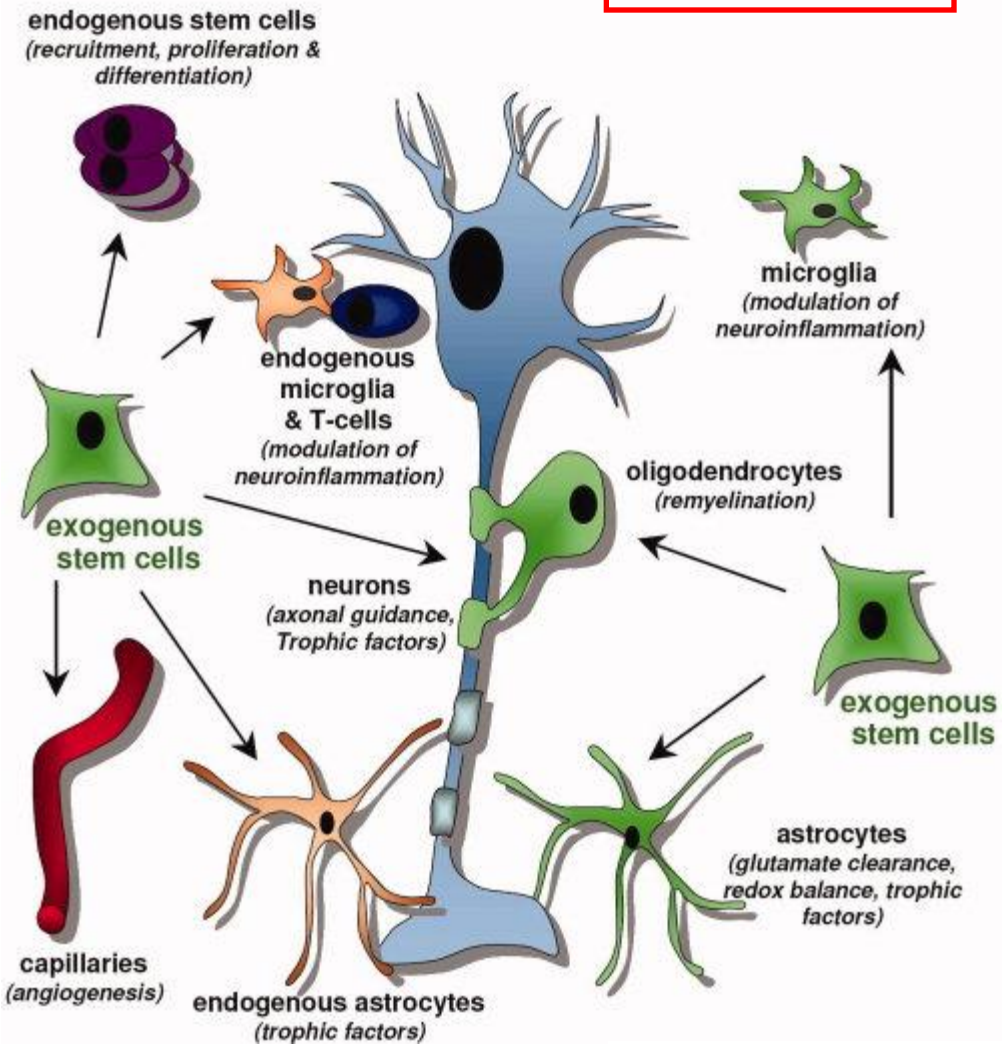
[1]Department of Pathology, Division of Neuropathology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2196

[2]Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2196

Protection of neurons by adult stem cells

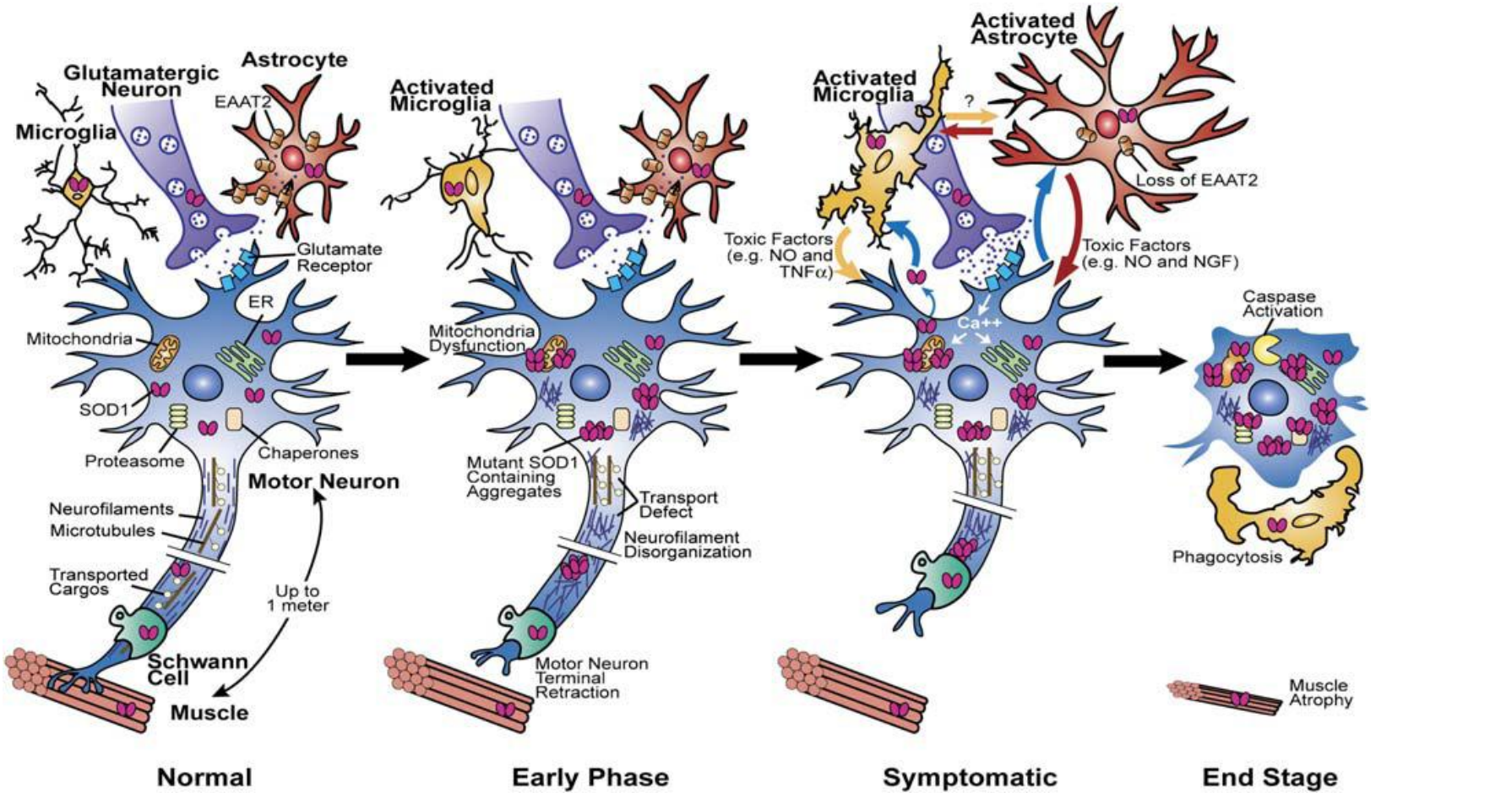
Innate neuroprotective capacities

Generation of glial cells



Journal of Neuroscience Research 87:1509–1521 (2009)

Stem cells therapeutic strategy potentially target several of these putative mechanisms



Cell Stem Cell *10*, 151–155, February 3, 2012

Cell Stem Cell
ISSCR: Committee Forum

Clinical Translation of Stem Cells in Neurodegenerative Disorders

cell replacement, where transplants of cells are given to directly replace those that are lost;
trophic support, where the cells are used to promote survival of affected neurons and endogenous repair of the diseased brain areas;
modulation of inflammation, which may be involved in the disease process.

The transplantation of stem cells for increased neuroprotection through the production of healthy astrocytes and/or the release of neurotrophic molecules, the modification of the inflammatory environment, or the generation of interneurons is a more realistic near-term clinical goal for ALS.

Problemi nella ricerca sulle cellule staminali e rischi nel trasferimento in clinica

- Le cellule staminali e i loro derivati rappresentano un nuovo prodotto
- Sono difficili da controllare (eterogeneità nei risultati) Rischio di tessuti ectopici e tumori
- I modelli animali non sempre rispecchiano la situazione nell'uomo, soprattutto per quanto riguarda la tossicità. Studi in cui si trapiantano cellule umane in animali non possono predire con precisione la risposta immunitaria e biologica nell'uomo
- Le cellule staminali possono sopravvivere per anni nel paziente, o la loro azione essere irreversibile, quindi ci deve essere un attento follow-up

ISSCR

International Society for Stem Cell Research

Guidelines for the Clinical Translation of Stem Cells

December 3, 2008

ISSCR

International Society for Stem Cell Research

Patient Handbook on Stem Cell Therapies

Appendix I of the Guidelines for the Clinical Translation of Stem Cells

December 3, 2008

(7.14.1) As a general principle, a stem cell-based approach must aim at being clinically competitive or superior to existing therapies. If an efficacious therapy already exists, the risks associated with a stem cell-based approach must be low and the stem cell-based approach must offer a pre-clinically demonstrated potential advantage (e.g., better functional outcome; single procedure (cell administration) versus life-long drug therapy with associated side effects; reduction in long-term cost).

(7.14.2) If an efficacious therapy is not available, then the severity of the disease, especially if the disease to be treated is disabling and life threatening, might justify the risks of a stem cell-based experimental intervention in patients. Maximum effort should be made to minimize the risks for all possible adverse events associated with stem cell-based approaches. Care must also be taken with respect to exploitation when enrolling patients with a poor short term prognosis.

http://www.isscr.org/clinical_trans

Francese, tedesco, inglese

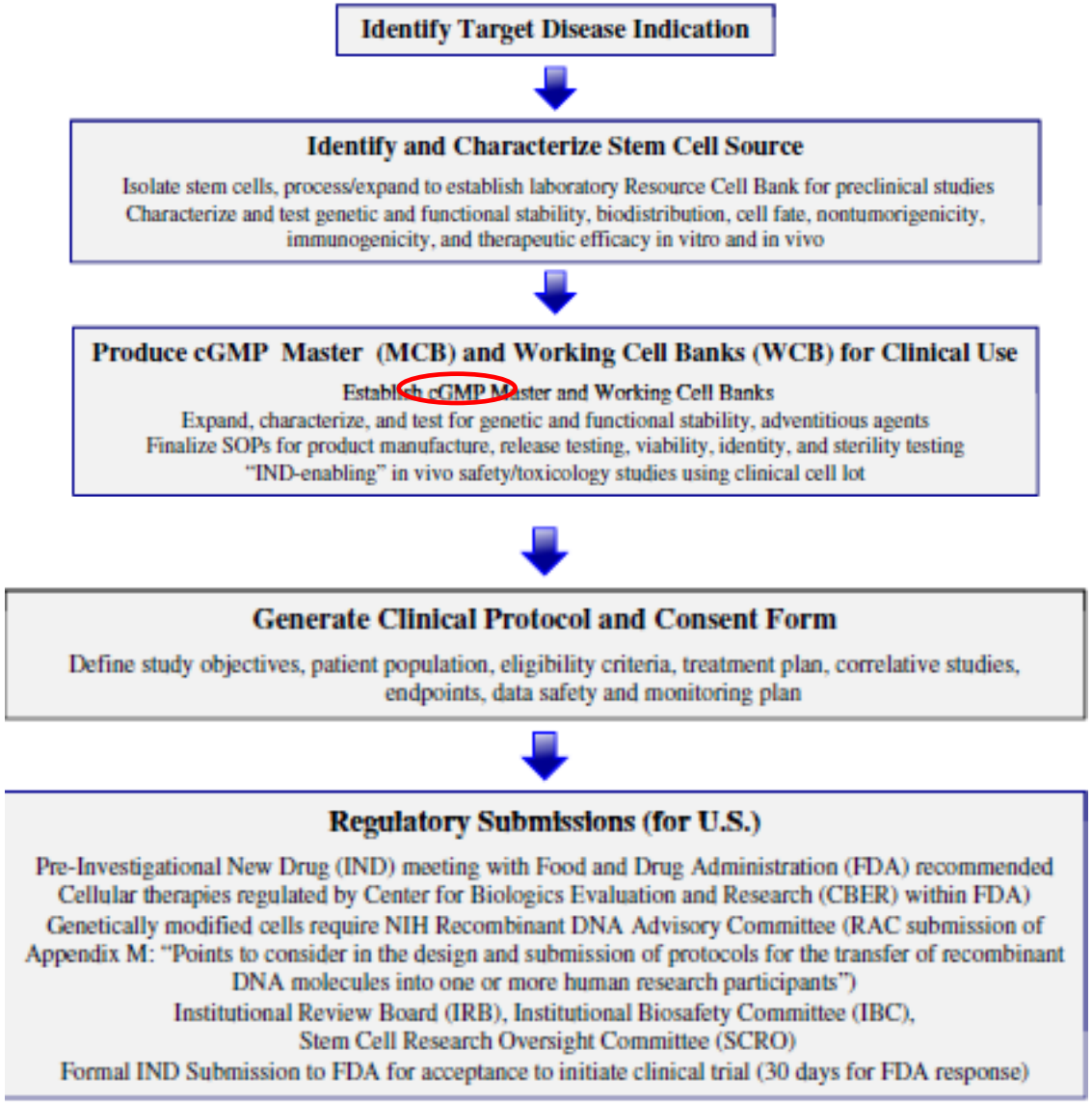


Figure 3. Bench-to-Bedside Translation of Stem Cell Therapies to CNS Clinical Trials
Regulatory information for clinical trials.

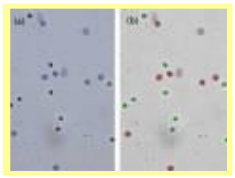
Neuron 70, May 26, 2011

SVILUPPO DI UN PRODOTTO CELLULARE IN CONDIZIONI GMP

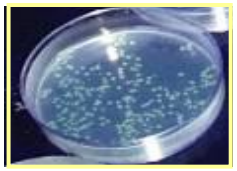
(Good Manufacturing Practices)

- **Regolamento (CE) N. 1394/2007** del Parlamento europeo e del consiglio del 13 novembre 2007 sui medicinali per terapie avanzate recante modifica della direttiva 2001/83/CE e del regolamento (CE) n. 726/2004 (applicabile dal 30 dicembre 2008) riguardante i medicinali per terapie avanzate preparati industrialmente e destinati al commercio negli Stati membri.
- **Linee guida GMP**
  Linee guida EMEA
  Linee guida AIFA-ISS

CONVALIDA DEL PROCESSO DI PRODUZIONE
CONTROLLI DI QUALITÀ PTC

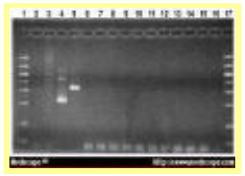


TEST VITALITÀ: MAGGIORE 98%



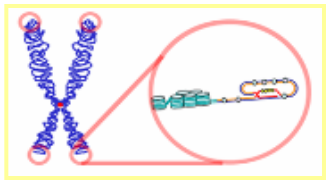
TEST STERILITÀ: NEGATIVO

TEST ENDOTOSSINE BATTERICHE: NEGATIVO

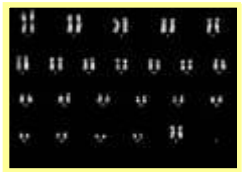


CONTAMINAZIONE DA MICOPLASMA: NEGATIVO

IMMUNOFENOTIPO: CD45-, CD14-,
CD90+, CD105+, CD44+, CD29+, CD106+, CD166+



SENESCENZA CELLULARE: NO ACCORCIAMENTO DEL TELOMERO

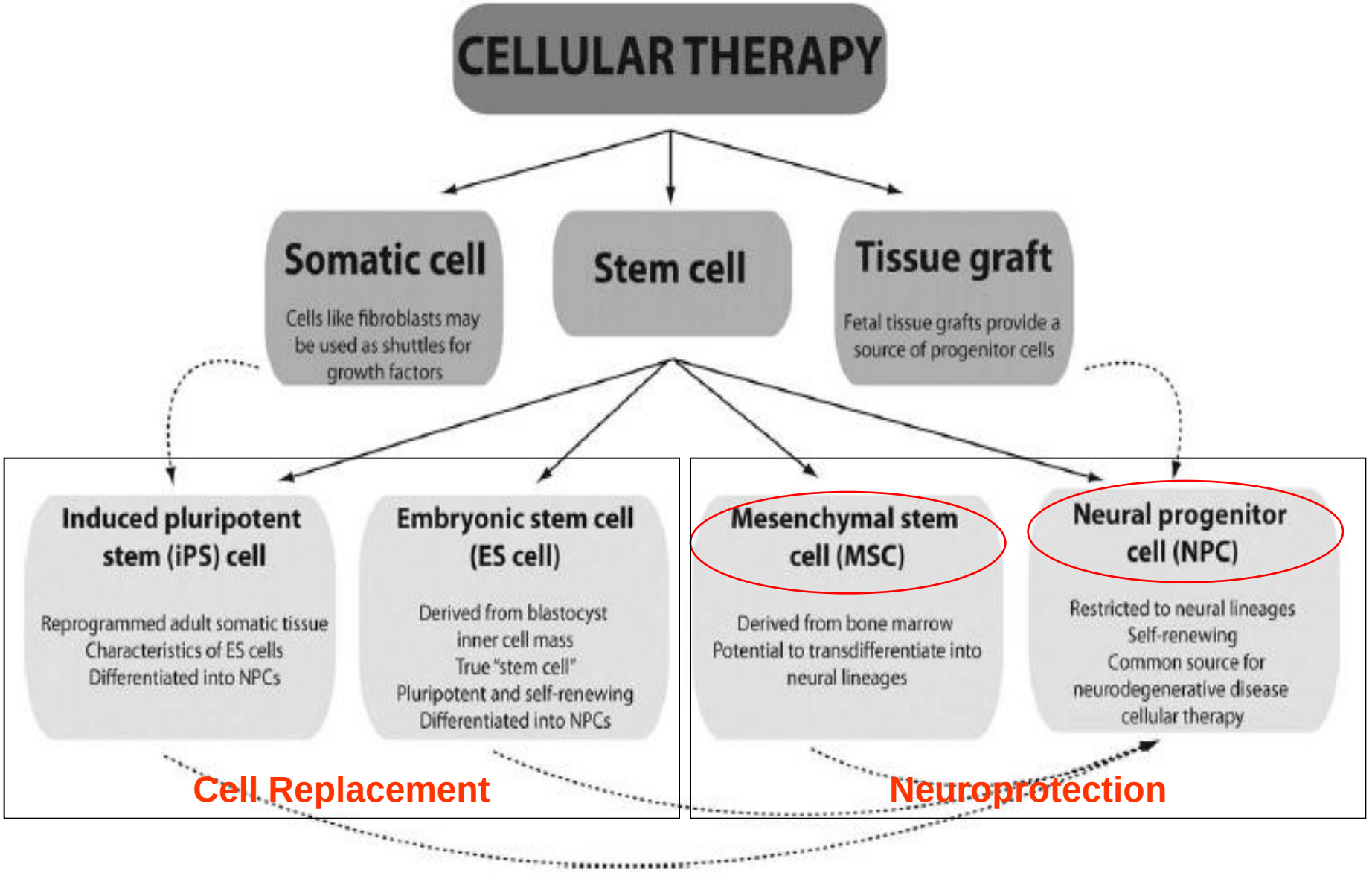


CITOGENETICA: CARIOTIPO NORMALE

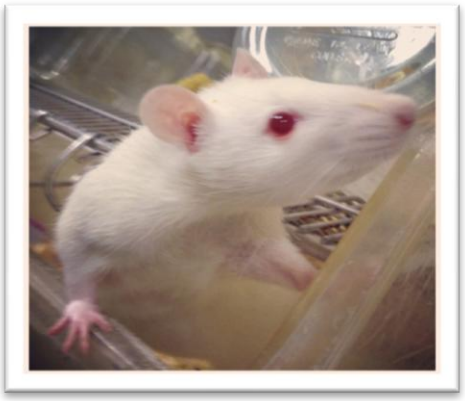
Cell types for transplantation

- Candidates to stem cell therapy in ALS must be able to survive and influence the pathological tissue environment, including inflammatory and immune reactions, and migrate into the sites of diffuse neurodegeneration.

- Moreover, it is fundamental for clinical application that stem cells are safe, and can be easily isolated and expanded.

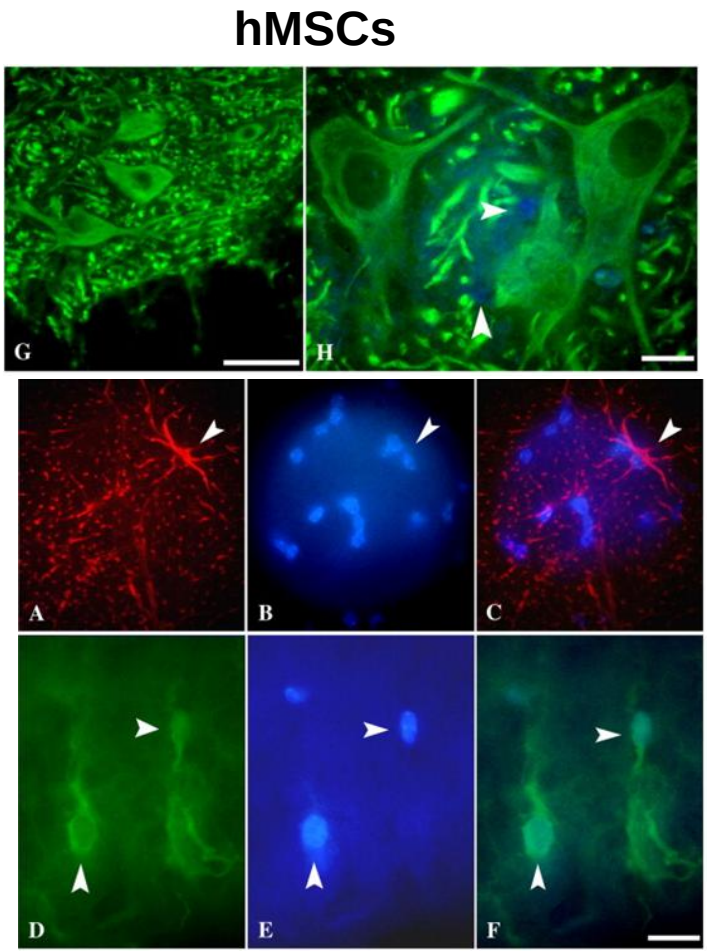


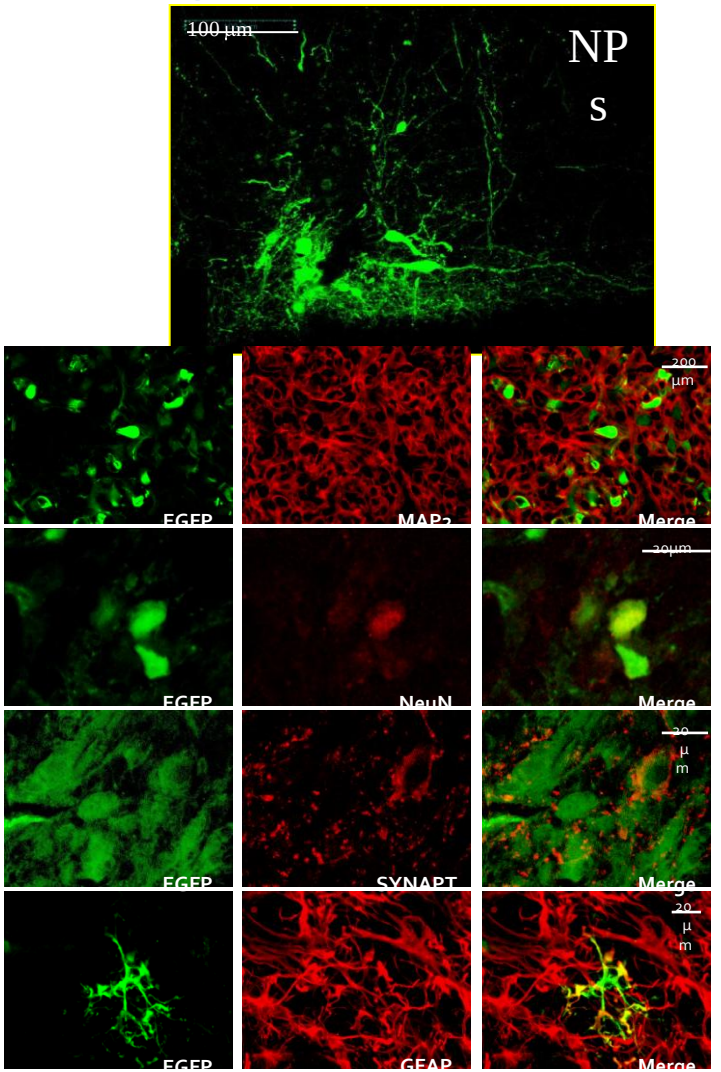
ANN NEUROL 2011;70:353–361



hMSCs and hNSCs Transplantation in SOD1-G93A mice

(Localization, survival and neural markers expression)





Neurobiology of Disease 31 (2008) 395–405

Contents lists available at ScienceDirect

Neurobiology of Disease

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

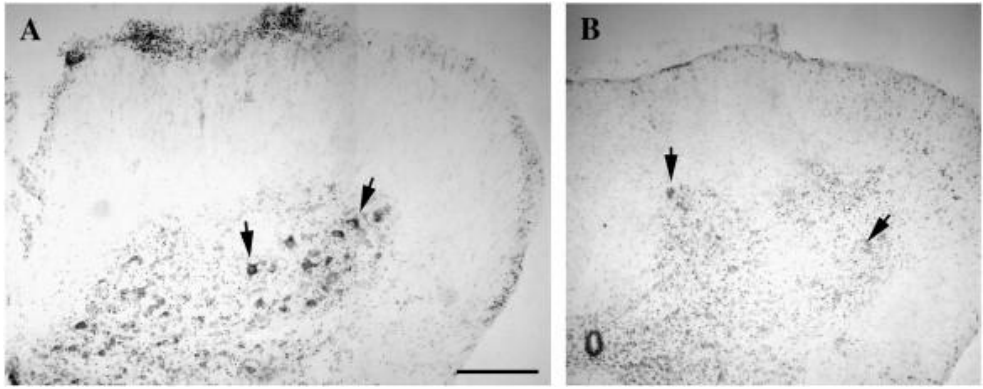
Human mesenchymal stem cell transplantation extends survival, improves motor performance and decreases neuroinflammation in mouse model of amyotrophic lateral sclerosis

A. Vercelli [a,b,*], O.M. Mereuta [a,b], D. Garbossa [a,b], G. Muraca [a,b], K. Mareschi [b], D. Rustichelli [b], I. Ferrero [b], L. Mazzini [c], E. Madon [b], F. Fagioli [b]

Neuroscience Institute, University of Torino

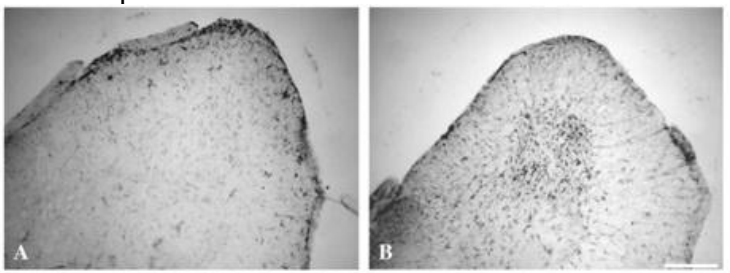
QUANTIFICATION OF LUMBAR MOTOR NEURONS

Transplanted *SOD1*^{G93A} mice	Sham operated *SOD1*^{G93A} mice	
5458 ± 682	3549 ± 607	P<.005



Transplanted Controls

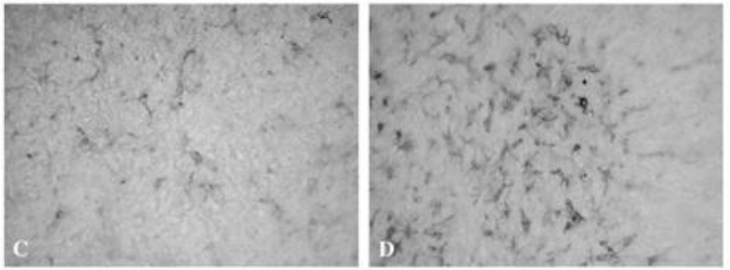
CD11b



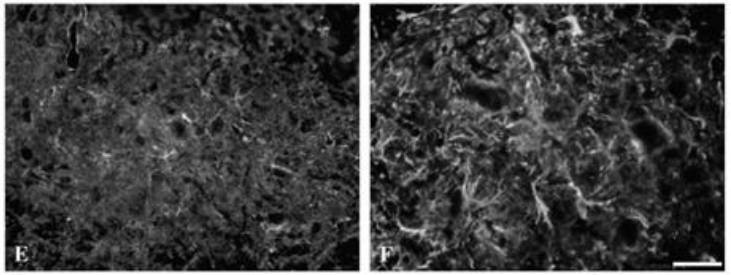
QUANTIFICATION OF MICROGLIA ACTIVATION

	T13	L2	L4
SHAM MICE	28.411	28.485	27.500
TRANSPL MICE	21.647	21.357	20.353

CD11b



GFAP



AND REACTIVE ASTROGLIOSIS

ANOVA p = 0,003286

Allogenic vs autologous stem cells transplantation

Autologous transplantation may obviate the need for immunosuppression and also may facilitate the authorization of clinical studies. However, autologous cells might be more vulnerable to the disease

Table 1. Preclinical transplantation studies of stem cells in animal models of ALS.

Cell source	Disease model	Route of delivery	Number of cells	Proposed therapeutic mechanism	Outcomes	Ref.
Human UCBs (pooled donors)	Presymptomatic, irradiated sod1	Intravenous (retro-ocular)	$34.2 - 35 \times 10^6$	Immunomodulation/ providing non mutant (functional)	Delay in disease onse and increased lifespa	
Human NSCs (GDNF)	Presymptomatic, immunosuppressed SOD1 (G93A) rat	Unilateral lumbar subcutaneous injections, one site	$12 - 18 \times 10^4$	Trophic support	Efficient delivery of GDNF, motor neuron preservation, no improvement in ipsilateral limb use	[55]
Human MSCs (GDNF) from neonatal bone marrow	Presymptomatic, immunosuppressed SOD1 (G93A) rat	Bilateral injection into three skeletal muscle groups	12×10^5	Trophic support	Increased number of neuromuscular connections and motor neuron cell bodies in the spinal cord. Increased overall lifespan by up to 28 days	[92]
Glial-restricted precursors (GRPs)	SOD1 (G93A) rat	Transplantation around cervical spinal cord	9×10^5	GRPs, efficiently differentiated into astrocytes and reduced microgliosis	Extended survival and disease duration, attenuated motor neuron loss and slowed declines in forelimb motor and respiratory physiological functions	[34]
Wild-type rat mesenchymal stem cells (MSCs)	14 weeks transgenic SOD1-Leu126delTT mice	Intrathecal transplantation via the fourth cerebral ventricle	$3 - 4 \times 10^5$	Neuroprotection, modulation of the neural environment	Females, but not males, showed a statistically longer disease duration	[100]
Mouse olfactory ensheathing cells (OECs)	14 weeks transgenic SOD1-Leu126delTT mice	Intrathecal transplantation via the fourth cerebral ventricle	$3 - 4 \times 10^5$	No benefits	No significant differences in clinical evaluation	[101]
Human bone marrow-derived mesodermal stromal cells (hMSCs)	Pre-symptomatic ALS mouse model overexpressing G93A	Intrathecal transplantation (via cisterna magna)	10^5	No benefits	Negative outcome	[100]
Umbilical cord blood cells (hUBCs)	Pre-symptomatic ALS mouse model overexpressing G93A	Intrathecal transplantation (via cisterna magna)	10^5	No benefits	Negative outcome	[100]
Wild-type rats MSCs	Symptomatic hSOD1G93A	Intrathecal delivery (lumbar level)	2×10^6	MSCs substantial infiltration into the ventral horn; massive differentiation into astrocytes; decreased motor neuron loss	In treated rats the first signs of paralysis were detected 14 days later compared with sham animals ; the life expectancy was increased by 16 days	[117]

BMC: Bone marrow cell; GRP: Glial-restricted precursor; h: Human; MSC: Mesenchymal stem cell; MSC (GDNF): MSC engineered to secrete glial cell line-derived neurotrophic factor; NSC: Neural stem cell; NSC(GDNF): NSC genetically modified to release GDNF; SMARD1: Spinal muscular atrophy with respiratory distress type 1; UCB cell: Umbilical cord blood cell.

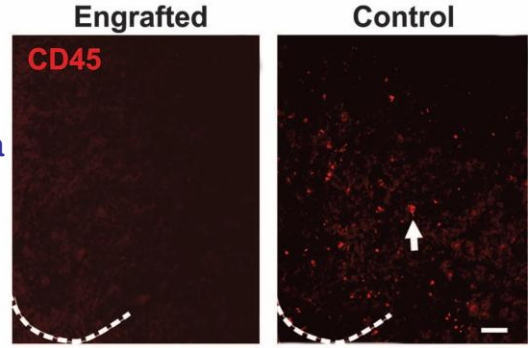
NSC(GDNF): NSC genetically modified to release GDNF; SMARD1: Spinal muscular atrophy with respiratory distress type 1; UCB cell: Umbilical cord blood cell.

STEM CELLS www.ScienceTranslationalMedicine.org 19 December 2012

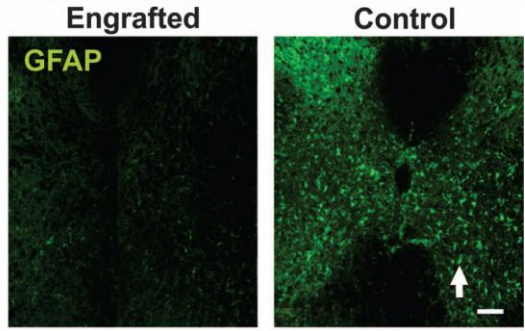
Multimodal Actions of Neural Stem Cells in a Mouse Model of ALS: A Meta-Analysis

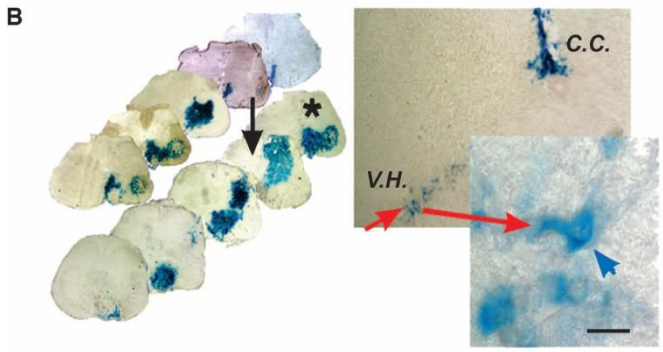
Yang D. Teng,[1,2,3*†] Susanna C. Benn,[4*] Steven N. Kalkanis,[1,4] Jeremy M. Shefner,[5] Renna C. Onario,[1,2,3] Bin Cheng,[6] Mahesh B. Lachyankar,[3] Michael Marconi,[3,7] Jianxue Li,[7] Dou Yu,[1,2] Inbo Han,[1,2] Nicholas J. Maragakis,[8] Jeronia Lládo,[8] Kadir Erkmen,[1,3] D. Eugene Redmond Jr.,[9] Richard L. Sidman,[1,7] Serge Przedborski,[10] Jeffrey D. Rothstein,[8] Robert H. Brown Jr.,[4,11†] Evan Y. Snyder[1,3,7,12†]

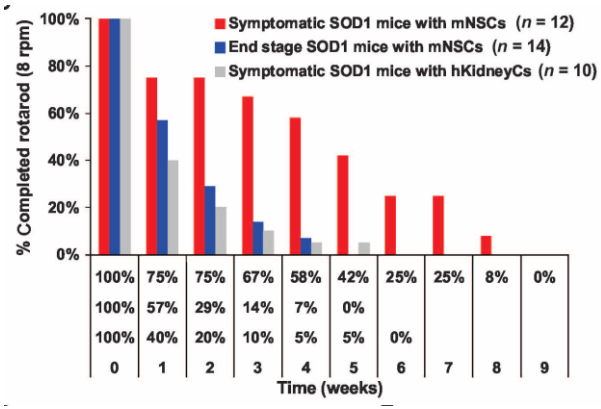
macrophage/microglia infiltration

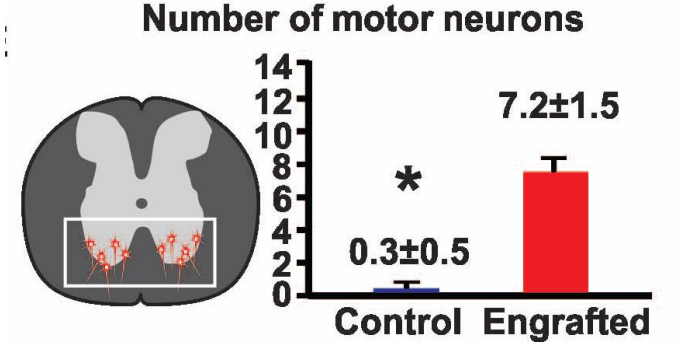


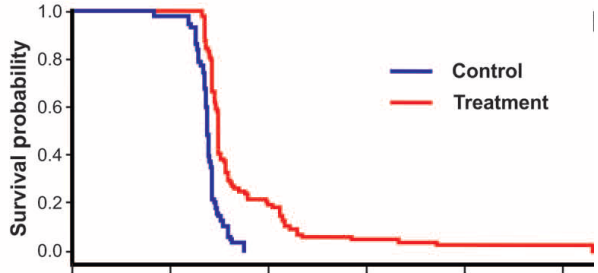
endogenous astrogliosis



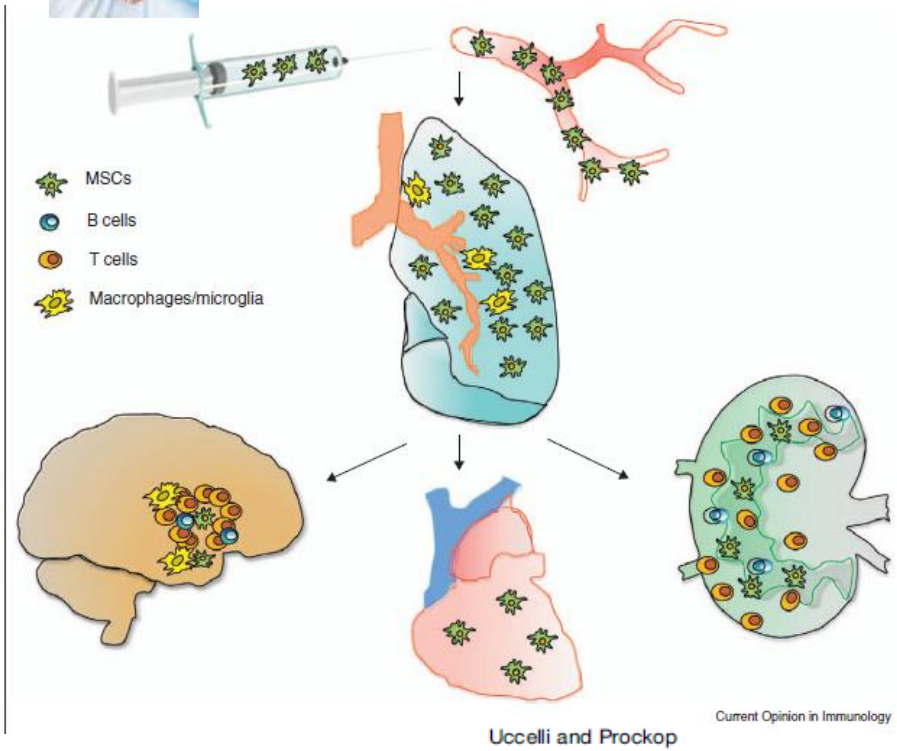




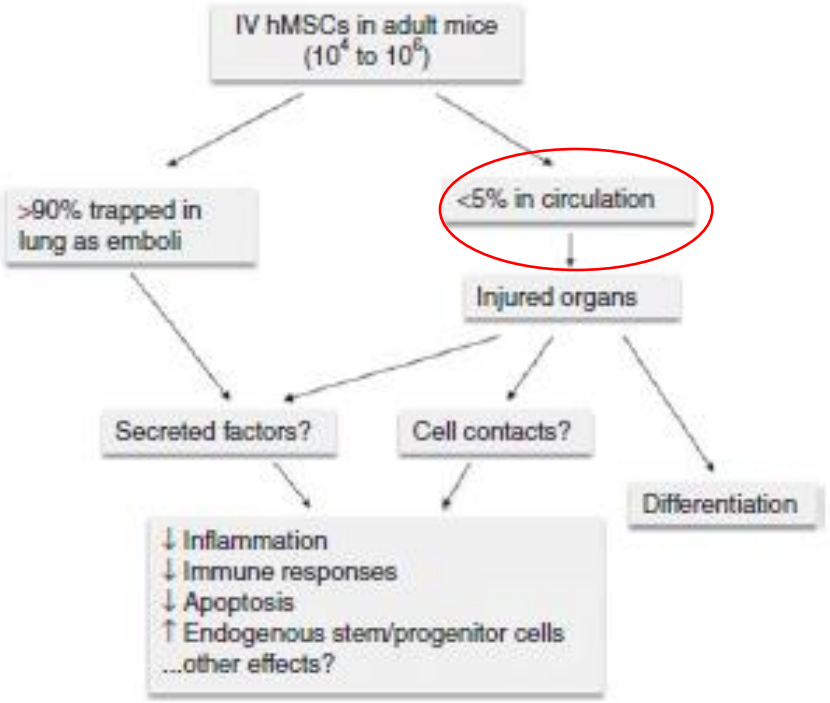




Route of delivery



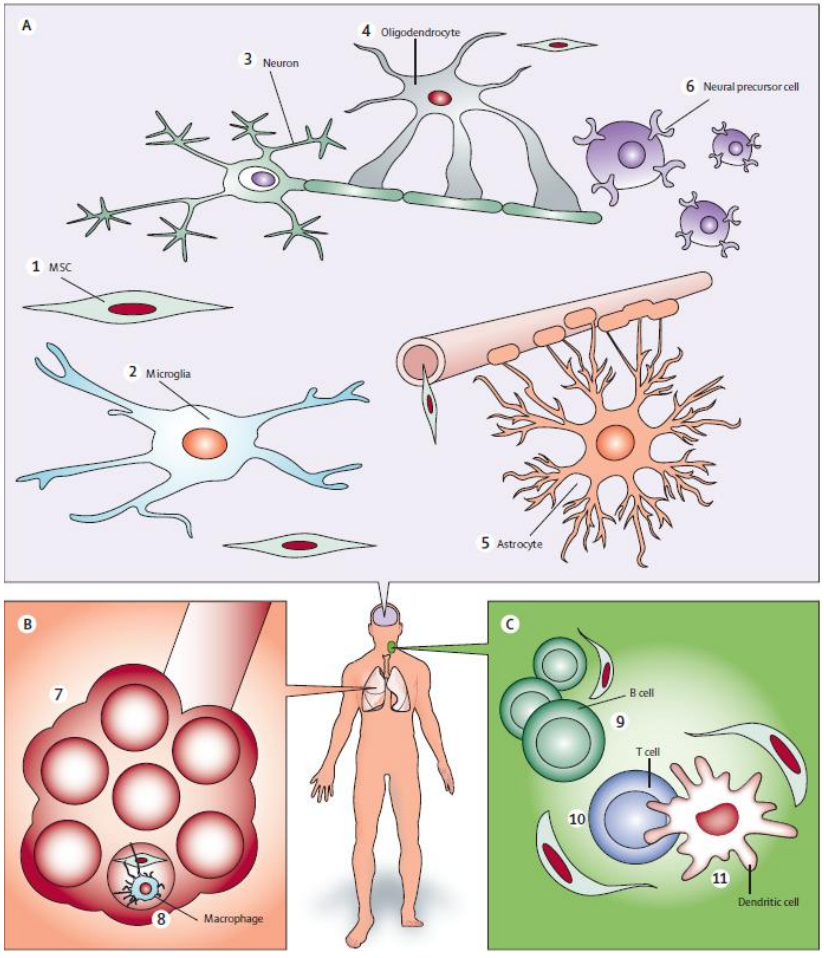
Uccelli and Prockop



Darwin J Prockop[1] *Molecular Therapy* vol. 17 no. 6, 939–946 june 2009

Intravenous Mesenchymal Stem Cells Improve Survival and Motor Function in Experimental Amyotrophic Lateral Sclerosis

Antonio Uccelli,[1,2,3] Marco Milanese,[4] Maria Cristina Principato,[1*] Sara Morando,[1,3] Tiziana Bonifacino,[4] Laura Vergani,[5] Debora Giunti,[1] Adriana Voci,[5] Enrico Carminati,[5] Francesco Giribaldi,[4] Claudia Caponnetto,[1] and Giambattista Bonanno[2,4,6]*



Lancet Neurol 2011; 10: 649-56

Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis

Dimitrios Karussis, MD, PhD; Clementine Karageorgiou, MD; Adi Vaknin-Dembinsky, MD, PhD; Basan Gowda-Kurkalli, PhD; John M. Gomori, MD; Ibrahim Kassis, MSc; Jeff W. M. Bulte, PhD; Panayiota Petrou, MD; Tamir Ben-Hur, MD, PhD; Oded Abramsky, MD, PhD; Shimon Slavin, MD

Table 2. Immunological Effects in Patients With MS and With ALS Undergoing MSC Transplantation Intravenously and Intrathecally[a]

Lymphocyte Subpopulation	Mean (SD) Proportions of Lymphocytes		
	Baseline	4 h After MSC Transplantation	24 h After MSC Transplantation
Patients with MS (n=7)			
$CD4^+CD25^+$	8.4 (6.3)	10.0 (4.5)	12.0 (3.7)
$CD86^+$	93.6 (4.7)	78.7 (14.3)	74.3 (11.0)
$CD40^+$	26.0 (4.0)	13.4 (7.15)	11.5 (8.4)
$HLA\text{-}DR^+$	95.7 (3.8)	81.3 (9.3)	81.0 (8.5)
$CD83^+$	32.4 (4.9)	20.1 (3.4)	19.2 (6.2)
Patients with ALS (n=5)			
$CD4^+CD25^+$	8.3 (2.6)	13.7 (7.2)	16.2 (5.3)
$CD86^+$	74.0 (23.5)	50.0 (18.4)	48.7 (28.3)
$CD40^+$	12.9 (4.1)	5.2 (6.0)	7.0 (6.6)
$HLA\text{-}DR^+$	88.6 (4.2)	68.0 (12.2)	74.3 (9.1)
$CD83^+$	22.4 (2.1)	18.1 (7.1)	17.2 (3.2)

ARCH NEUROL/VOL 67 (NO. 10), OCT 2010

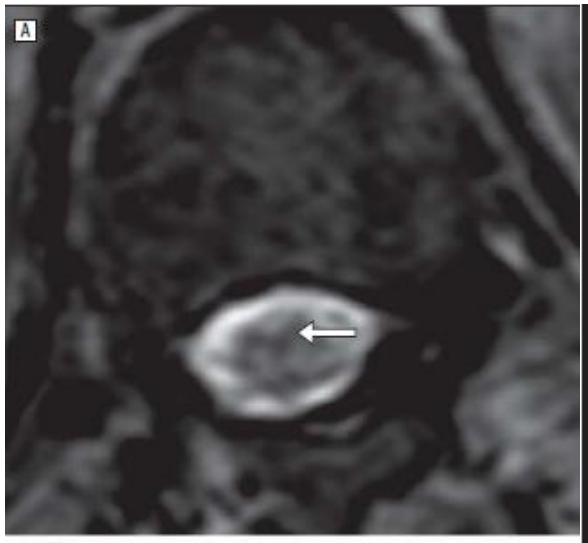
Arch Neurol. 2010;67(10):1187-1194

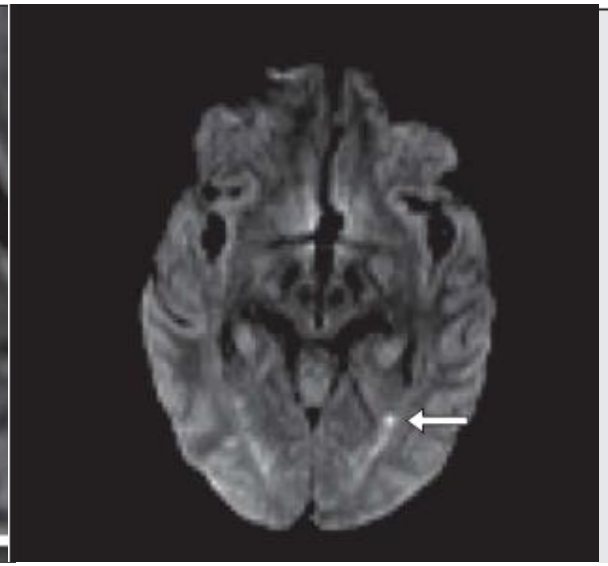
CLINICAL TRIALS

SECTION EDITOR: IRA SHOULSON, MD

Safety and Immunological Effects of Mesenchymal Stem Cell Transplantation in Patients With Multiple Sclerosis and Amyotrophic Lateral Sclerosis

Dimitrios Karussis, MD, PhD; Clementine Karageorgiou, MD; Adi Vaknin-Dembinsky, MD, PhD; Basan Gowda-Kurkalli, PhD; John M. Gomori, MD; Ibrahim Kassis, MSc; Jeff W. M. Bulte, PhD; Panayiota Petrou, MD; Tamir Ben-Hur, MD, PhD; Oded Abramsky, MD, PhD; Shimon Slavin, MD





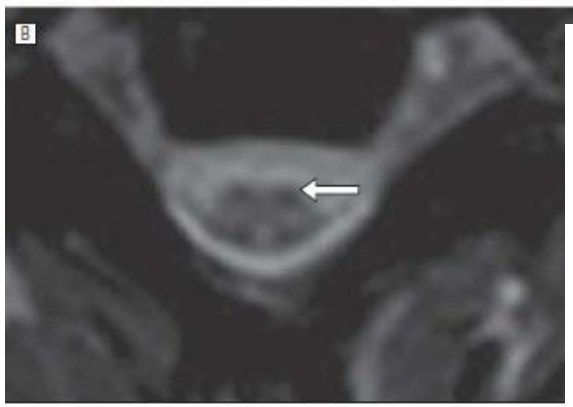
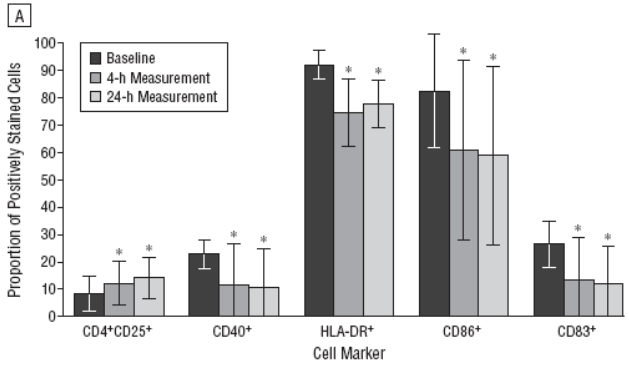


Table 2. Immunological Effects in Patients With MS and With ALS Undergoing MSC Transplantation Intravenously and Intrathecally[a]

Lymphocyte Subpopulation	Mean (SD) Proportions of Lymphocytes		
	Baseline	4 h After MSC Transplantation	24 h After MSC Transplantation
Patients with MS (n=7)			
$CD4^+CD25^+$	8.4 (6.3)	10.0 (4.5)	12.0 (3.7)
$CD86^+$	93.6 (4.7)	78.7 (14.3)	74.3 (11.0)
$CD40^+$	26.0 (4.0)	13.4 (7.15)	11.5 (8.4)
$HLA\text{-}DR^+$	95.7 (3.8)	81.3 (9.3)	81.0 (8.5)
$CD83^+$	32.4 (4.9)	20.1 (3.4)	19.2 (6.2)
Patients with ALS (n=5)			
$CD4^+CD25^+$	8.3 (2.6)	13.7 (7.2)	16.2 (5.3)
$CD86^+$	74.0 (23.5)	50.0 (18.4)	48.7 (28.3)
$CD40^+$	12.9 (4.1)	5.2 (6.0)	7.0 (6.6)
$HLA\text{-}DR^+$	88.6 (4.2)	68.0 (12.2)	74.3 (9.1)
$CD83^+$	22.4 (2.1)	18.1 (7.1)	17.2 (3.2)



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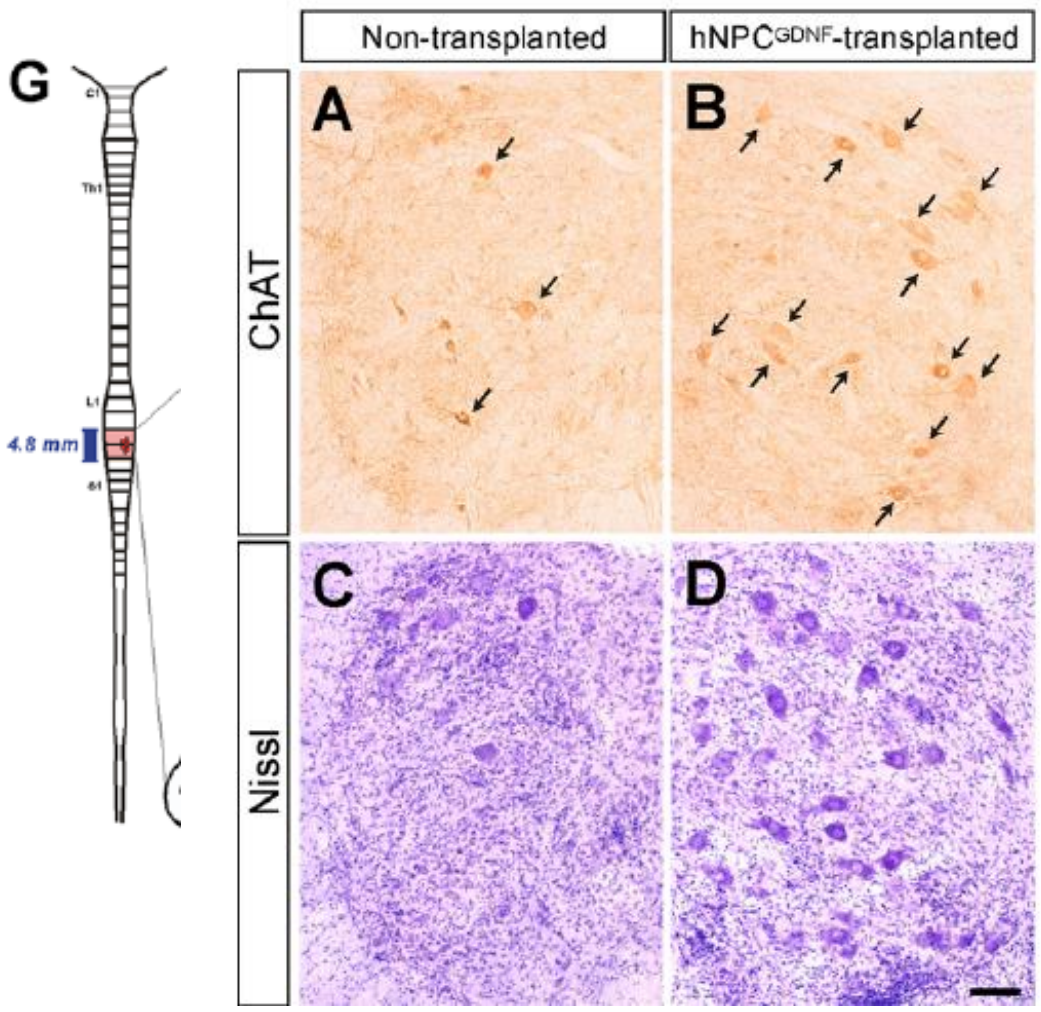
PLoS one

GDNF Secreting Human Neural Progenitor Cells Protect Dying Motor Neurons, but Not Their Projection to Muscle, in a Rat Model of Familial ALS

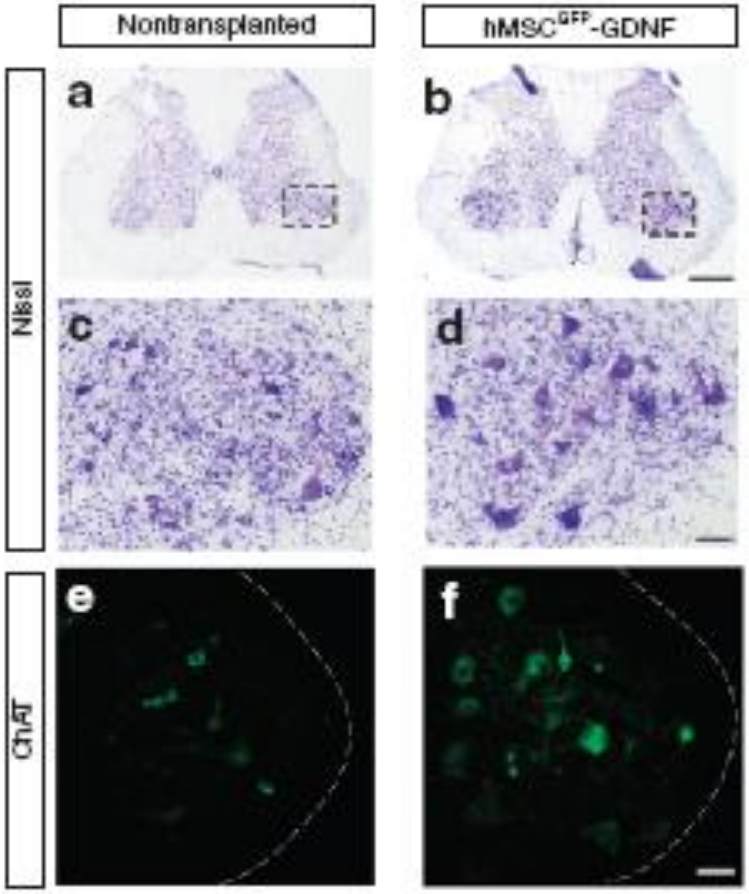
Masatoshi Suzuki[1], Jacalyn McHugh[1], Craig Tork[1], Brandon Shelley[1], Sandra M. Klein[1], Patrick Aebischer[3], Clive N. Svendsen[1,2]*



Direct Muscle Delivery of GDNF With Human Mesenchymal Stem Cells Improves Motor Neuron Survival and Function in a Rat Model of Familial ALS

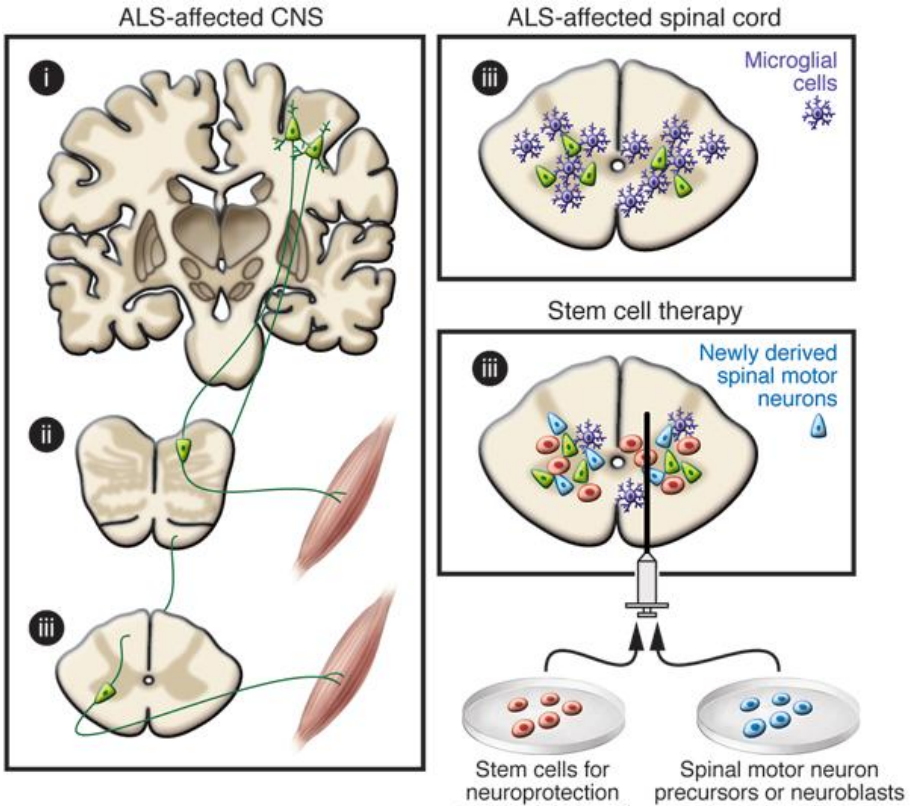
Masatoshi Suzuki[1], Jacalyn McHugh[1], Craig Tork[1], Brandon Shelley[1], Antonio Hayes[1], Ilaria Bellantuono[2], Patrick Aebischer[3] and Clive N Svendsen[1,4,5]

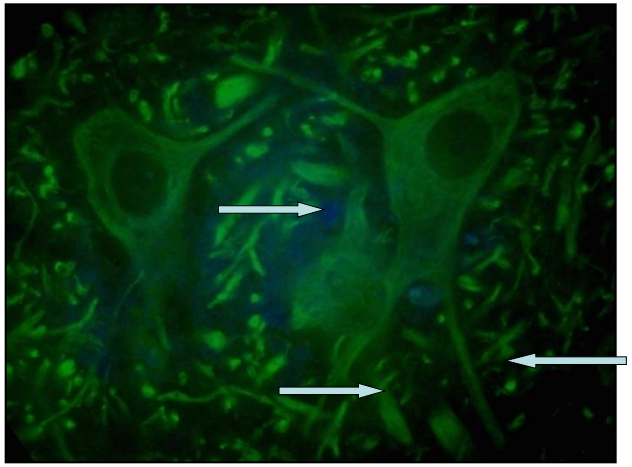
[1]The Waisman Center, University of Wisconsin–Madison, Madison, Wisconsin, USA; [2]Stem Cell Research Group, Royal Manchester Children's Hospital, Manchester, UK; [3]Brain and Mind Institute, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; [4]Department of Anatomy, University of Wisconsin–Madison, Madison, Wisconsin, USA; [5]Department of Neurology, University of Wisconsin–Madison, Madison, Wisconsin, USA



How to get cells where they are needed?

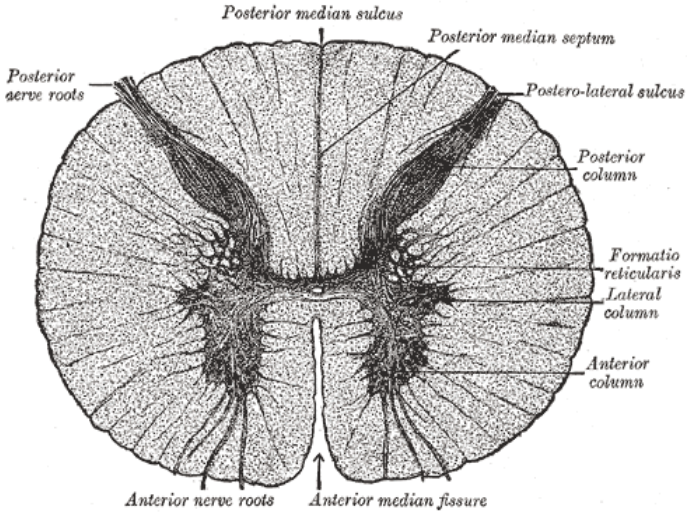
The use of stem cells for therapy requires that they can easily access the target tissue to exert their therapeutic effect as the cells respond to a particular pathological microenvironment.
The proximity of grafted cells favours the diffusion of trophic and immunomodulatory factors to MNs and surrounding glia.



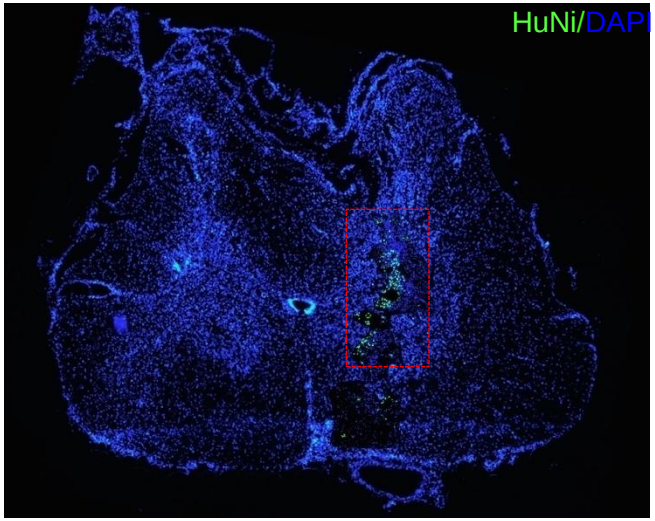


hMSCs and hNSCs
TRAPIANTO IN RATTI SOD1-G93A
Sopravvivenza

A



B

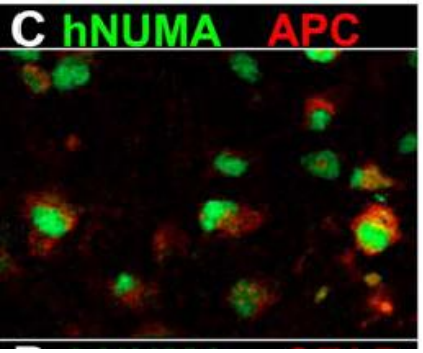


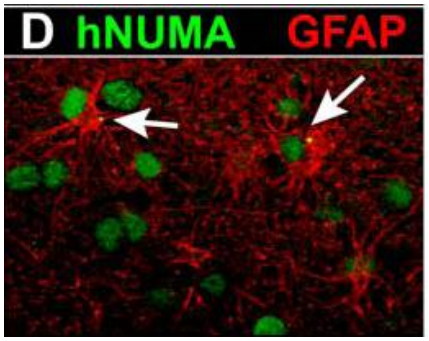
STEM CELLS www.ScienceTranslationalMedicine.org 19 December 2012

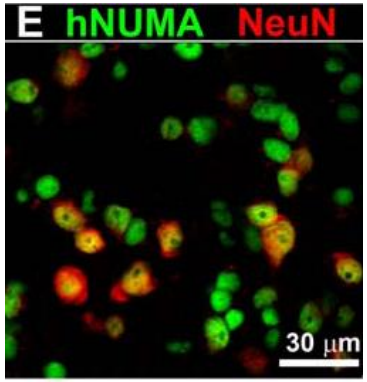
Multimodal Actions of Neural Stem Cells in a Mouse Model of ALS: A Meta-Analysis

Yang D. Teng,[1,2,3*†] Susanna C. Benn,[4*] Steven N. Kalkanis,[1,4] Jeremy M. Shefner,[5] Renna C. Onario,[1,2,3] Bin Cheng,[6] Mahesh B. Lachyankar,[3] Michael Marconi,[3,7] Jianxue Li,[7] Dou Yu,[1,2] Inbo Han,[1,2] Nicholas J. Maragakis,[8] Jeronia Lládo,[8] Kadir Erkmen,[1,3] D. Eugene Redmond Jr.,[9] Richard L. Sidman,[1,7] Serge Przedborski,[10] Jeffrey D. Rothstein,[8] Robert H. Brown Jr.,[4,11†] Evan Y. Snyder[1,3,7,12†]

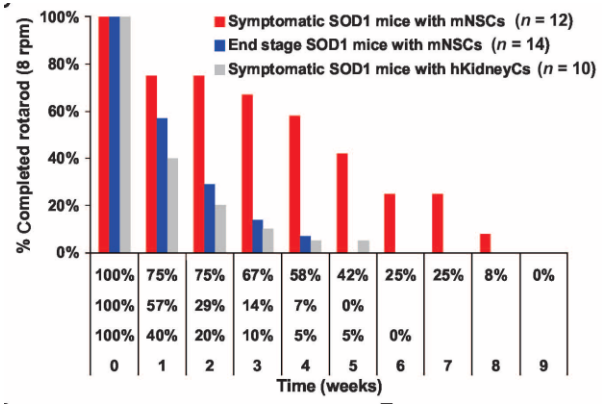
meta-analysis of 11 independent studies performed by a consortium of ALS investigators, we propose that transplanted NSCs (both mouse and human) can slow both the onset and the progression of dinical signs and prolong survival in ALS mice, particularly if regions sustaining vital functions such as respiration are rendered chimeric. The beneficial effects of transplanted NSCs seem to be mediated by a number of actions including their ability to produce trophic factors, preserve neuromuscular function, and reduce astrogliosis and inflammation. We conclude that the widespread, pleiotropic, modulatory actions exerted by transplanted NSCs may represent an accessible therapeutic application of stem cells for treating ALS and other untreatable degenerative diseases.

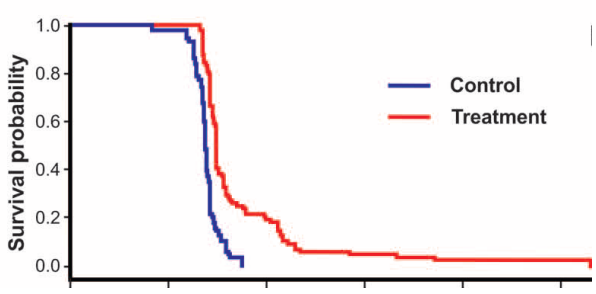






oligodendrocytes astrocytes neuronal phenotype

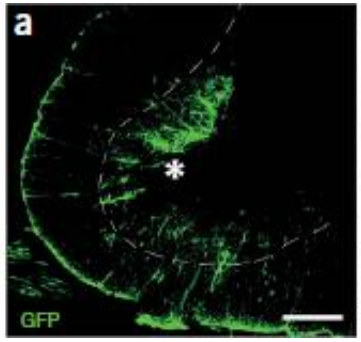


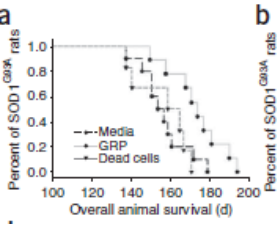


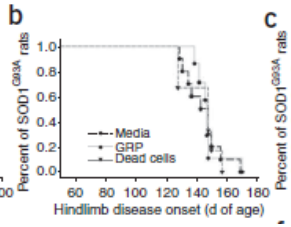
nature neuroscience

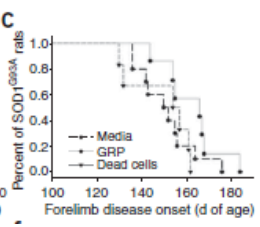
Focal transplantation–based astrocyte replacement is neuroprotective in a model of motor neuron disease

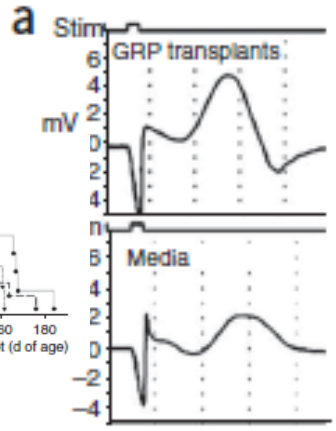
Angelo C Lepore[1], Britta Rauck[1], Christine Dejea[1], Andrea C Pardo[1], Mahendra S Rao[2], Jeffrey D Rothstein[1,3] & Nicholas J Maragakis[1]





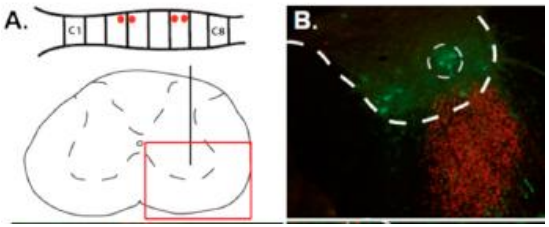


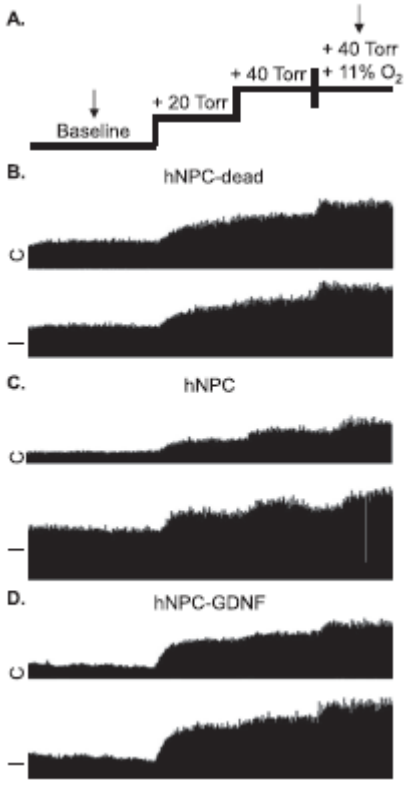




Intermittent Hypoxia and Stem Cell Implants Preserve Breathing Capacity in a Rodent Model of Amyotrophic Lateral Sclerosis

Nicole L. Nichols[1], Genevieve Gowing[2], Irawan Satriotomo[1], Lisa J. Nashold[1], Erica A. Dale[1], Masatoshi Suzuki[1], Pablo Avalos[2], Patrick L. Mulcrone[1], Jacalyn McHugh[2], Clive N. Svendsen[2], and Gordon S. Mitchell[1]





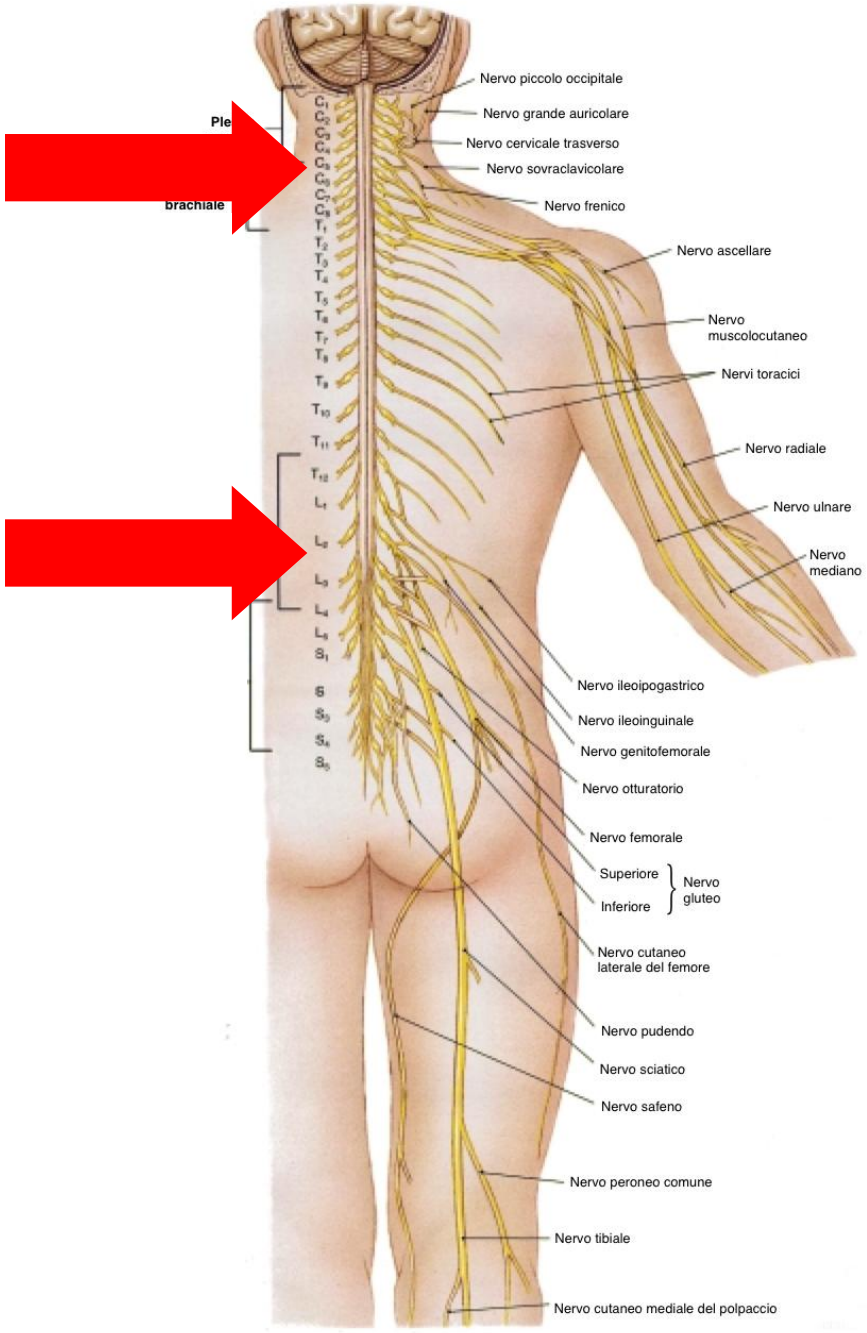
Cervical Transplantation

Upper Limbs

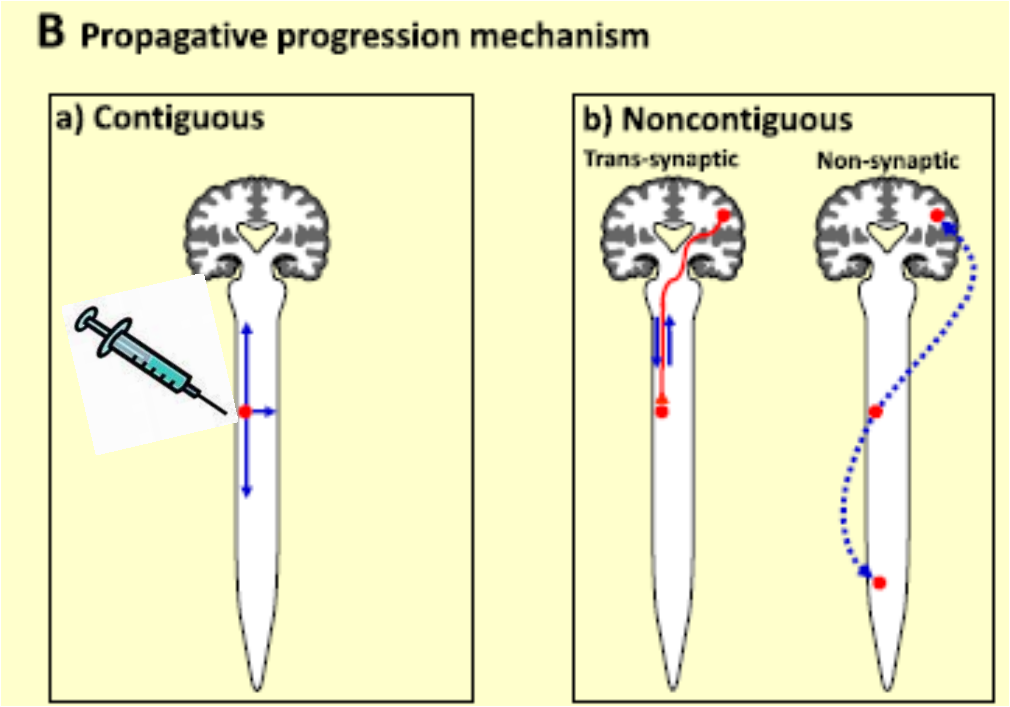
Diaphram

Lumbar Transplantation

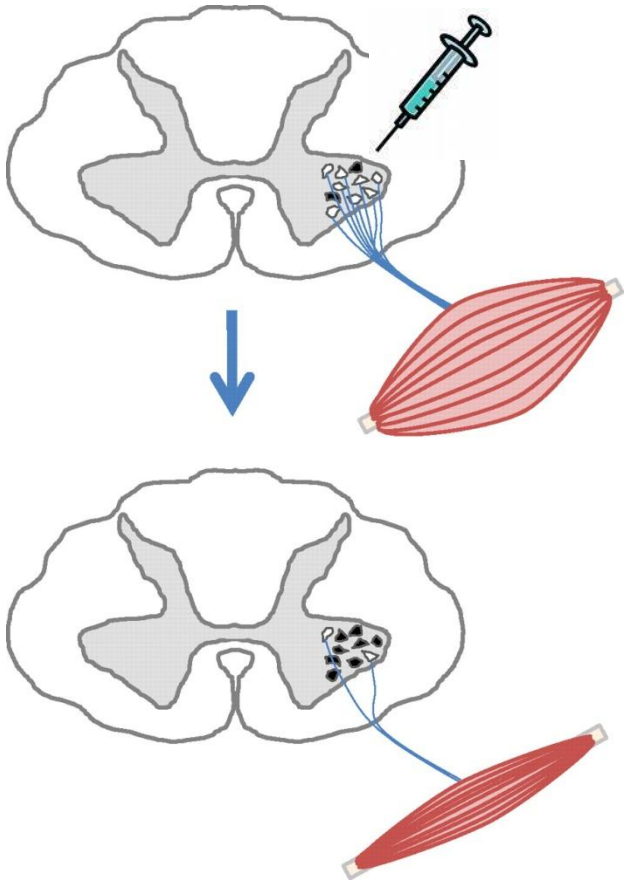
Lower Limbs



Onset and regional spread mechanisms



Local propagation

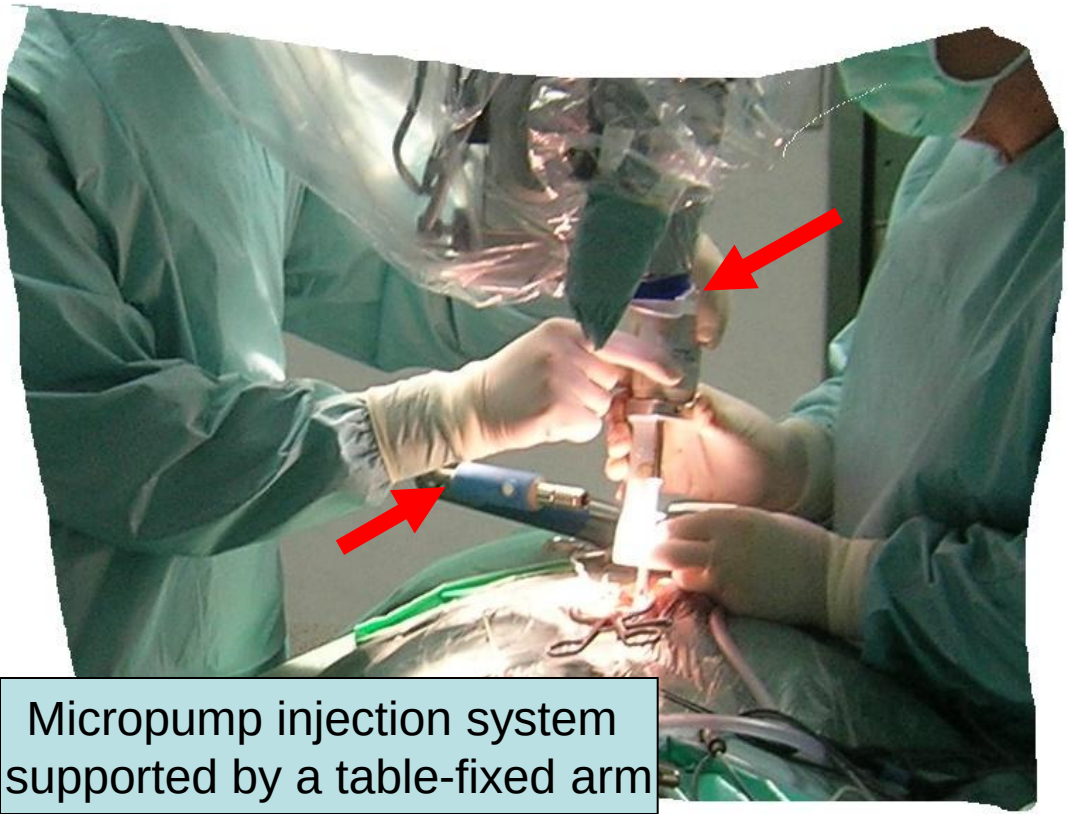


Kanouchi T et al. J Neurol Neurosurg Psychiatry
doi:10.1136/jnnp-2011-301826

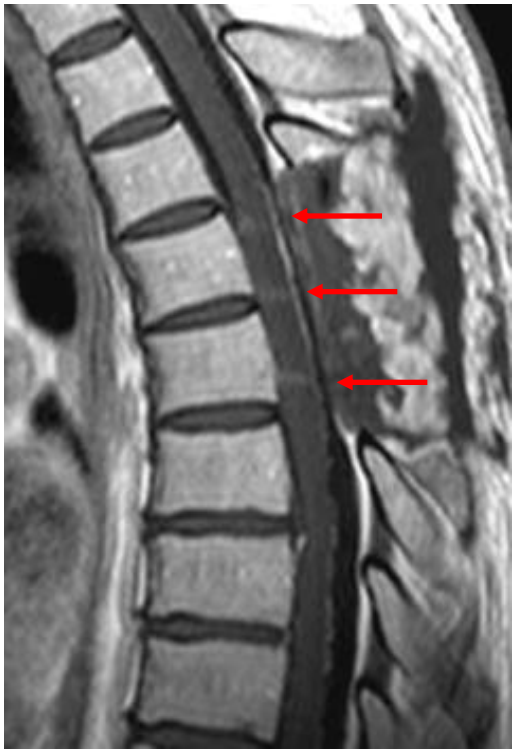
ALS and other motor neuron disorders 2003 4, 158–161
 ISSN 1466-0822

Stem cell therapy in amyotrophic lateral sclerosis: a methodological approach in humans

Letizia Mazzini,[1] Franca Fagioli,[2] Riccardo Boccaletti,[3] Katia Mareschi,[2] Giuseppe Oliveri,[3] Carlo Olivieri,[4] Ilaria Pastore,[6] Roberto Marasso[5] and Enrico Madon[2]



Micropump injection system supported by a table-fixed arm



Experimental Neurology xxx (2009) xxx–xxx

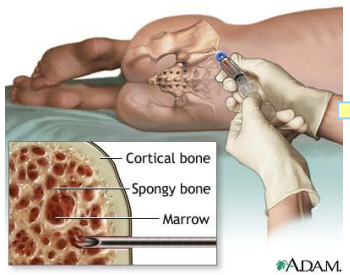
Contents lists available at ScienceDirect

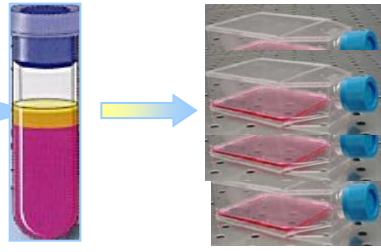
Experimental Neurology

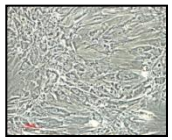
journal homepage: www.elsevier.com/locate/yexnr

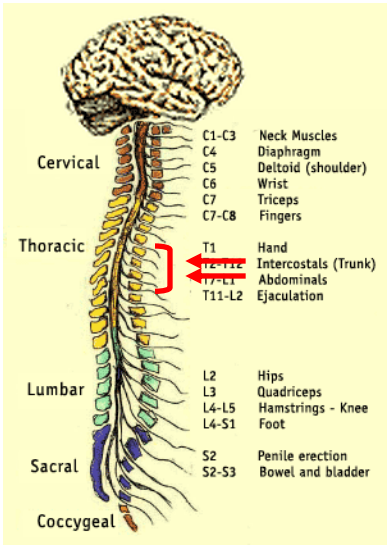
Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: A Phase I clinical trial

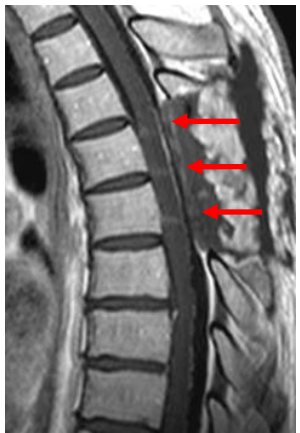
L. Mazzini [a,*], I. Ferrero [b,c], V. Luparello [d], D. Rustichelli [b], M. Gunetti [b], K. Mareschi [b,c], L. Testa [a], A. Stecco [e], R. Tarletti [a], M. Miglioretti [f], E. Fava [a], N. Nasuelli [a], C. Cisari [g], M. Massara [g], R. Vercelli [h], G.D. Oggioni [a], A. Carriero [e], R. Cantello [a], F. Monaco [a], F. Fagioli [b]











Adverse Event	Nb of Patients (%)	Mean Duration (days)
Pain in trunk	13 (68%)	5 ± 2.49 (Range: 1-10)
Sensory light-touch impairment in one LL	10 (52%)	47.7 ± 55 (Range: 6-180)
Tingling sensation in one LL	8 (42%)	107 ± 127 (Range 3-365)
Sensory light-touch impairment in sacral region	3 (21%)	18 ± 10 (Range:7-28)

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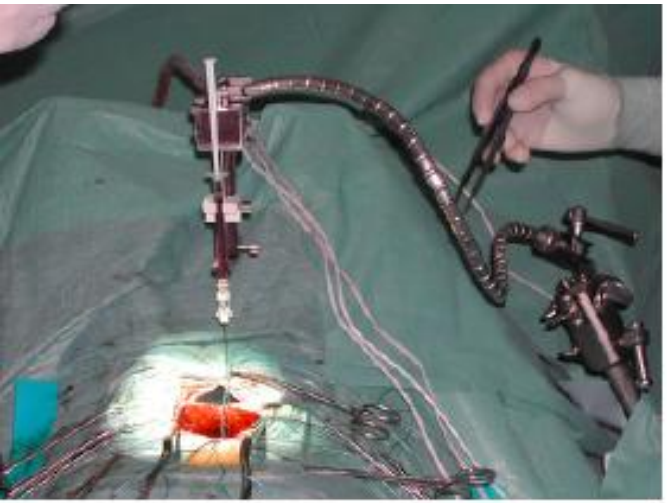
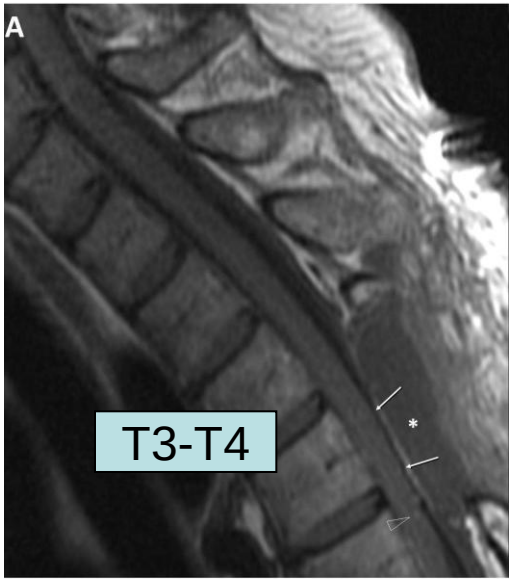
2012 Mar 13. *[Epub ahead of print]*

Neurotrophic Bone Marrow Cellular Nests Prevent Spinal Motoneuron Degeneration in Amyotrophic Lateral Sclerosis Patients: A Pilot Safety Study

Miguel Blanquer Blanquer , Jose M. Moraleda Jiménez , Francisca Iniesta Martínez et al





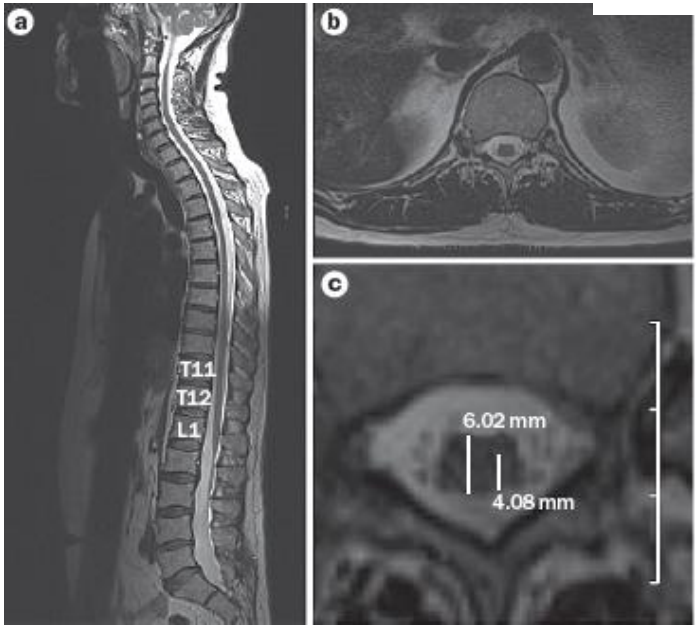
Related non severe adverse events
CONSTIPATION
PAINFUL WOUND
HYPOAESTHESIA
INTERCOSTAL PAIN
PARAESTHESIA
INTRACRANIAL HYPOTENSION
DYSAESTHESIA
HEADACHE
VERTIGO
TRANSPLANT SITE HYPERAESTHESIA
INSOMNIA

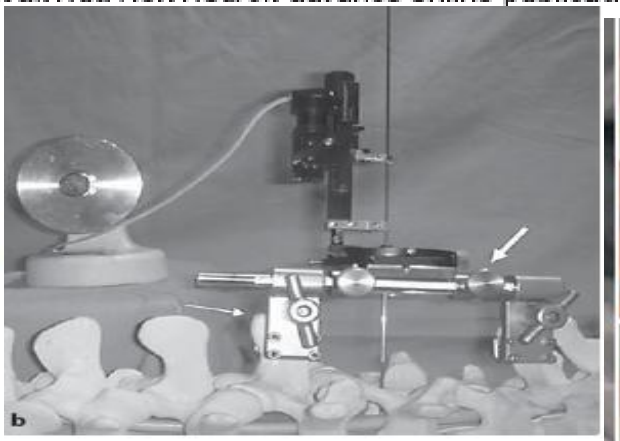
OPINION

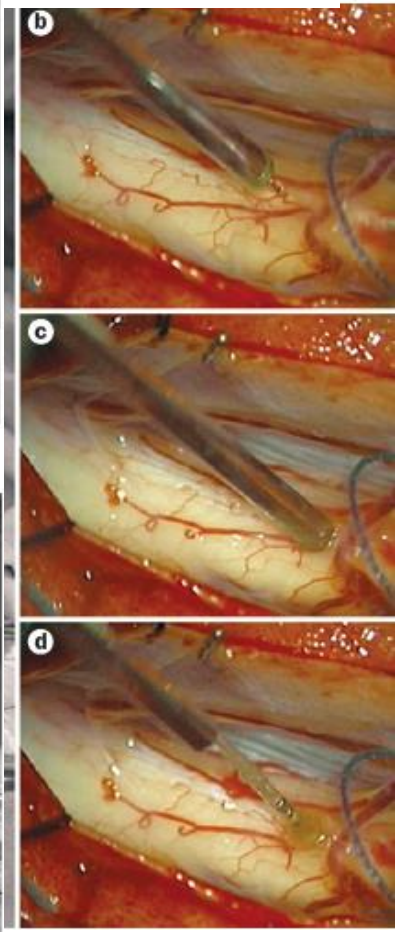
Translational stem cell therapy for amyotrophic lateral sclerosis

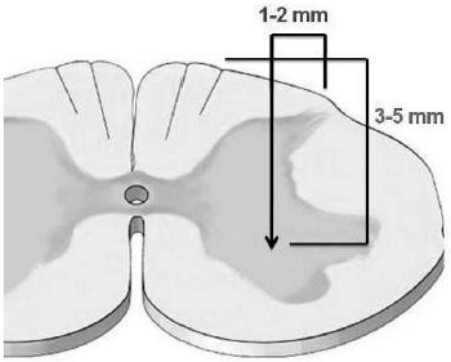
Nicholas M. Boulis, Thais Federici, Jonathan D. Glass, J. Simon Lunn, Stacey A. Sakowski and Eva L. Feldman

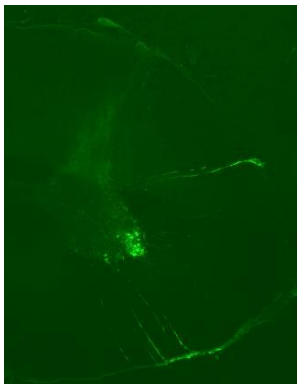
Boulis, N. M. *et al. Nat. Rev. Neurol.* advance online publication 13 December 2011;

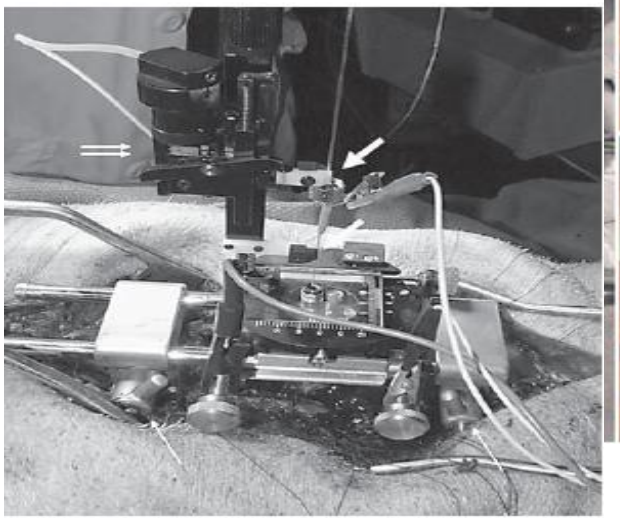












Floating cannula

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2012 Mar 13. *[Epub ahead of print]*

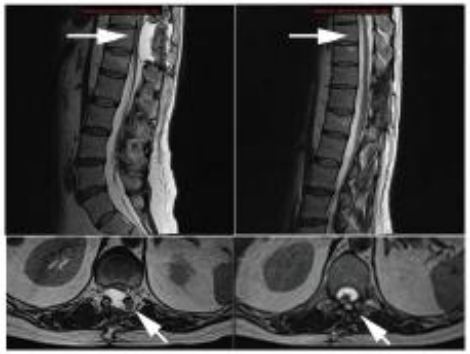
Lumbar Intraspinal Injection of Neural Stem Cells in Patients with ALS: Results of a Phase I Trial in 12 Patients

Jonathan D. Glass, MD[1*], Nicholas M. Boulis, MD, PhD[2], Karl Johe, PhD[3], Seward B. Rutkove, MD[4], Thais Federici, PhD[2], Meraida Polak, RN[1], Crystal Kelly, MA[1], Eva L. Feldman, MD, PhD[5]

Group	Patient numbers	Characteristics	Treatment
A1	1-3	Non-ambulatory, FVC >60% or trach/vent	5 injections, unilateral
A2	4-6	Non-ambulatory, FVC >60% or trach/vent	10 injections, bilateral
B	7-9	Ambulatory, FVC >60%	5 injections, unilateral
C	10-12	Ambulatory, FVC >60%	10 injections, bilateral

Immunosuppression

All patients received an intravenous dose of methylprednisolone (125 mg) immediately prior to surgery, and were treated post-operatively with oral prednisone 60 mg tapering to zero over one month. Two doses of basiliximab (20 mg IV) were given, one during surgery and another on post-operative day 4. Tacrolimus was given in BID oral dosing to maintain a trough level of 4-8 ng/ml, and mycophenolate mofetil was given at 1000 mg orally BID. Tacrolimus and mycophenolate, if tolerated, will be given for the duration of the trial.

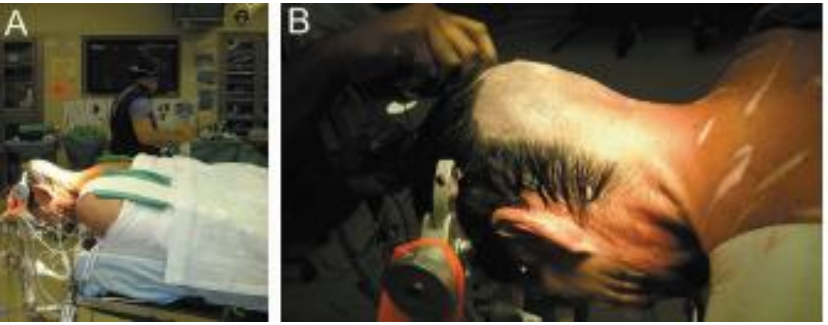


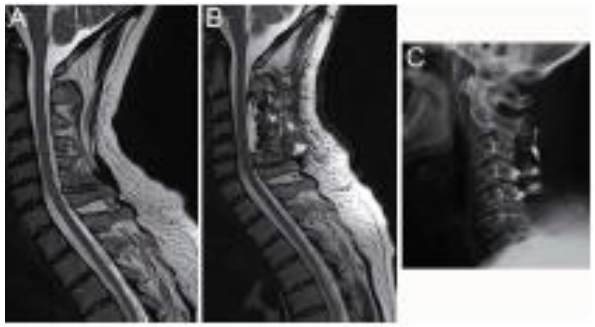
SAE name (related to study)	# of subjects
Transient Encephalopathy	1
Pulmonary Emboli	2
CSF leak	1
Wound dehiscence	1
Bronchitis/ pneumonia	2
Dyspnea	1
Atrial Fibrillation	1
Vomiting	1
Basal cell carcinoma	1

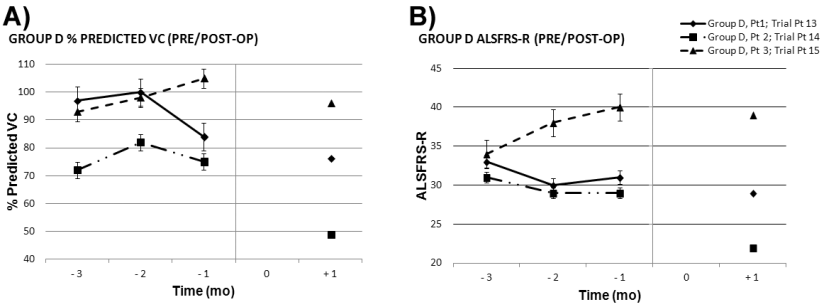
Neurosurgery Publish Ahead of Print
DOI: 10.1227/NEU.0000000000000156

Intraspinal Stem Cell Transplantation in ALS: A Phase I Trial, Cervical Microinjection and Final Surgical Safety Outcomes

Jonathan Riley, MD[1], Jonathan Glass, MD[2], Eva L Feldman, MD PhD[3], Meraida Polak, BSN RN[2], Jane Bordeau, RN[2], Thais Federici, PhD[1], Karl Johe, PhD[4], Nicholas M Boulis, MD[1]







Adverse Event Category	Gp #, Pt #	Severity*	Duration (Days)	Comments
Operative				
Wound Dehiscence	E,3	3	45	• Re-Op 1: superficial wound washout • Re-Op 2: Deep Cx and hardware removal
Non-Operative				
Pain				
Incisional	E,1	2	36	
	E,3	3	64	
	E,2	2	45	
	D,1	3	53	
	D,2	2	10	
	D,3		53	
Muscle Spasm	E,3	2	69	
	E,2	2	45	
	D,1	3	88	• Attributable to progressive kyphosis
Neck Pain	E,3	4	30	
	D,1	2	88	• Attributable to progressive kyphosis
	D,3	2	43	
Headache	E,1	2	1	
	D,2	3	41	
	D,2	2	30	
Cervical Kyphosis	D,1	2	ongoing	
Bowel/Bladder				
Urinary Retention	E,3	1	2	
Constipation	E,1	1	1	
Motor				
No clinical documentation of worsened motor exam from baseline by discharge				
Other				
Grinding in Neck	D,1	2	ongoing	• Attributable to progressive kyphosis
Laryngeal Edema	D,2	4	5	• Req'd re-intubation; Dx Bulbar ALS
Shoulder Pain	D,3	2	14	
Nausea/Vomiting	E,2	1	4	
Hiccups	E,3	2	27	
	E,2	2	13	
Popliteal Vein Thrombosis	E,2	2	50	• Subsequent imaging demonstrated recanalization and clot regression

Experimental Neurology 223 (2010) 229–237

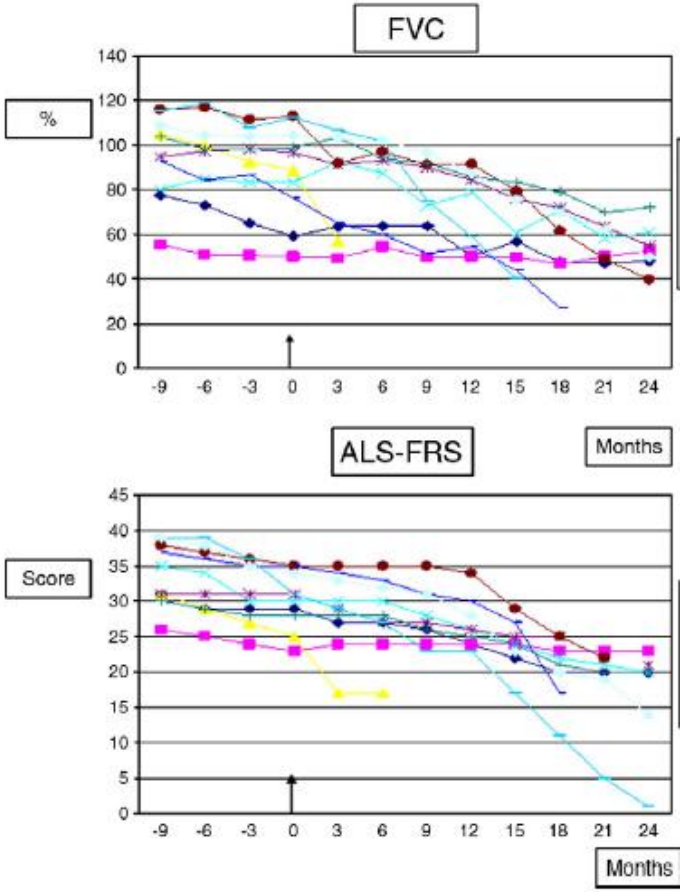
Contents lists available at ScienceDirect

Experimental Neurology

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

Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: A Phase I clinical trial

L. Mazzini [a,*], I. Ferrero [b,c], V. Luparello [d], D. Rustichelli [b], M. Gunetti [b], K. Mareschi [b,c], L. Testa [a], A. Stecco [e], R. Tarletti [a], M. Miglioretti [f], E. Fava [a], N. Nasuelli [a], C. Cisari. [g], M. Massara [g], R. Vercelli [h], G.D. Oggioni [a], A. Carriero [e], R. Cantello [a], F. Monaco [a], F. Fagioli [b]

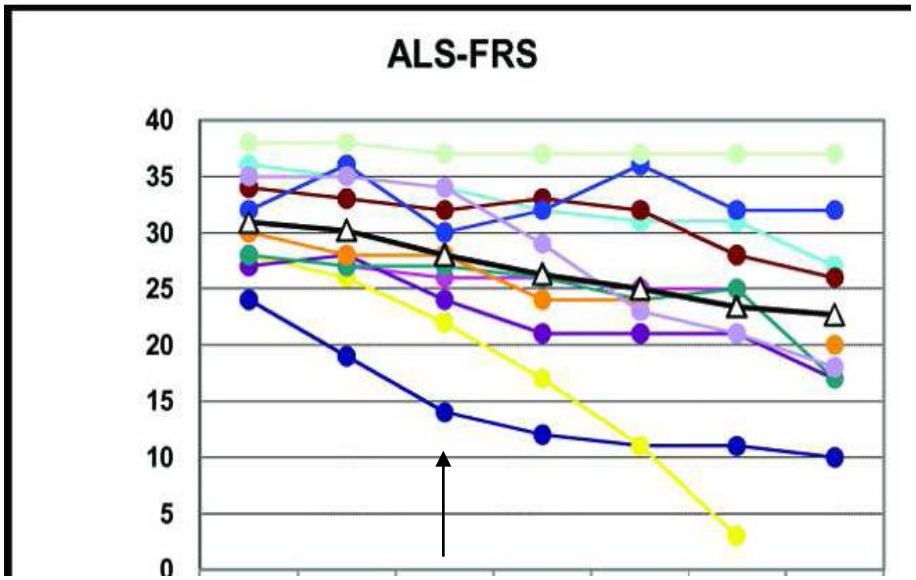


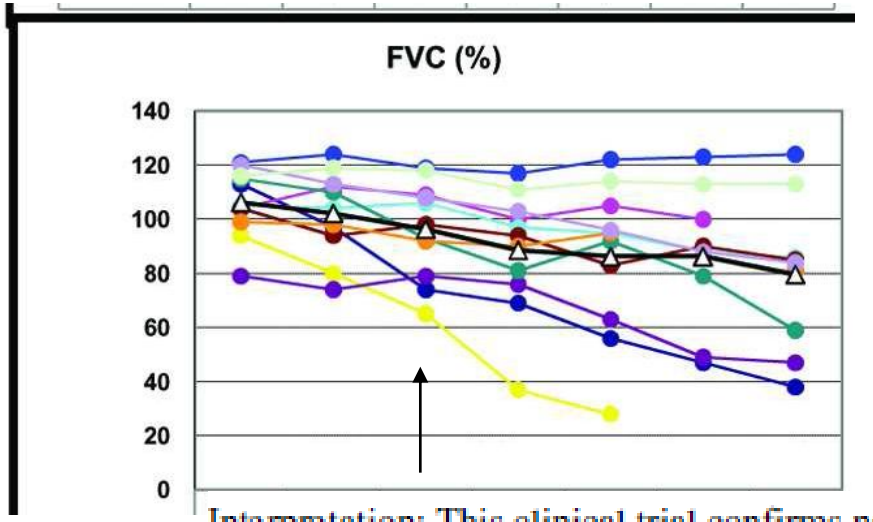
Cytotherapy, 2011; Early Online, 1–5

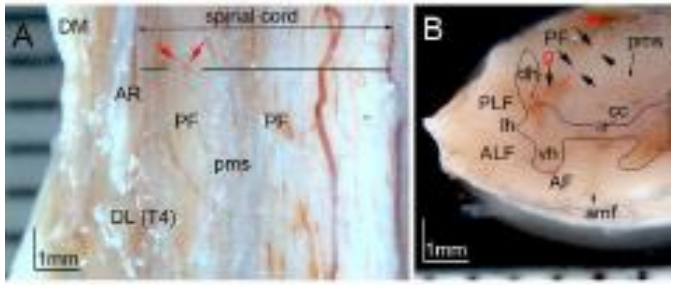
SHORT COMMUNICATION

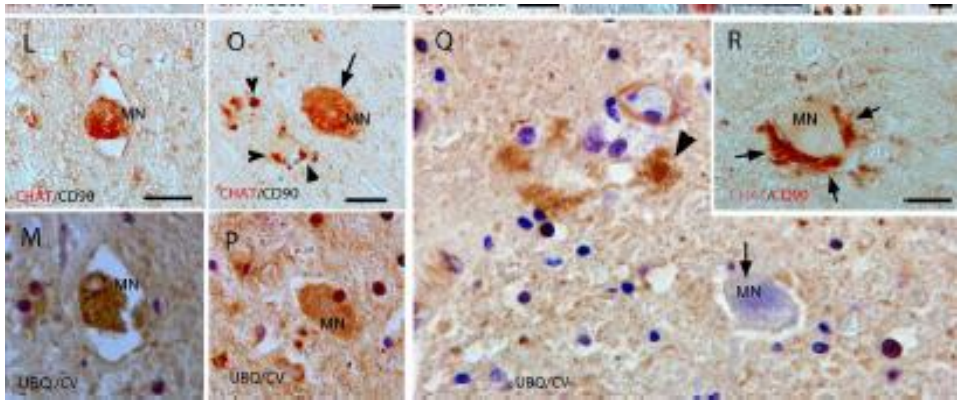
Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study

LETIZIA MAZZINI[1], KATIA MARESCHI[2,3], IVANA FERRERO[2,3], MASSIMO MIGLIORETTI[4], ALESSANDRO STECCO[5], SERENA SERVO[1], ALESSANDRO CARRIERO[5], FRANCESCO MONACO[1] & FRANCA FAGIOLI[2]









T1 T2-T3 T3-T4-T5

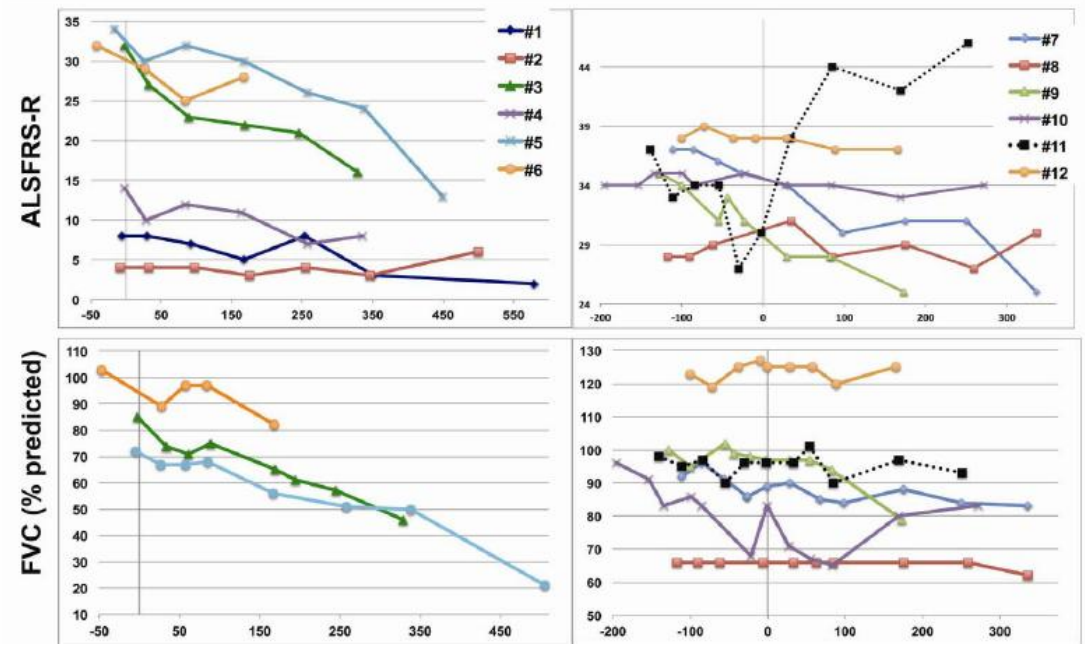
Interpretation: This clinical trial confirms not only the safety of intraspinal infusion of autologous BMNC in ALS patients but also provides evidence of their neurotrophic activity.

STEM CELLS®

REGENERATIVE MEDICINE

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

Jonathan D. Glass, MD[1*], Nicholas M. Boulis, MD, PhD[2], Karl Johe, PhD[3], Seward B. Rutkove, MD[4], Thais Federici, PhD[2], Meraida Polak, RN[1], Crystal Kelly, MA[1], Eva L. Feldman, MD, PhD[5]



patients tolerated the procedure without major surgical complications, and there are no indications to date that the stem cells themselves are either toxic or injurious to the spinal cord. Our quantitative clinical assessments showed no evidence of acceleration of disease following stem cell injections, meeting our stated goal of proving safety for this Phase I trial. We have cautious optimism that a few of the patients may have slowed in their progression of lower extremity weakness, and 1 patient may have improved. Certainly, prolongation of life for patients with ALS will require therapeutic intervention at the level of the cervical spinal motor neurons affecting respiratory function. To reach this ultimate goal we plan to move to injections into the cervical spinal cord, which is the next stage of this Phase I trial.

Stem cells	Study phase	Regulatory Oversight	Route of delivery	Immunosuppressant therapy	Number of cells	Nb of pts tot 107	Patients (inclusion criteria)	Outcome	Refs
Autologous BM MSCs	1	NIH, Ethic Committee	Intraspinal T4-T9	no	Mean $57x10^6$	10	Age 20-75 FVC>50%	Safe also in the long term (9Yrs)	Mazzini et al 2003,2006,2008,2010, 2012
Autologous BM-derived hematopoietic progenitors	Open single arm phase I trial	Clinical Trials Ethics Committee Agencia Medicament os.	Intraspinal (T3-T4)	no	2 mL mononucleated cells	11	Age:33-61 FVC>50% Spinal onset	Safe tolerated (2yrs follow-up)	Blanquer Blanquer et al, 2012
Human spinal cord-derived stem cells (HSSC)	Phase I trial	University Institutional review board	Intraspinal (lumbar spinal cord)	Basiliximab Prednisolone Tacrolimus Mycophenolate	5-10 injections 100,000 cells/ injection	12 + 11	Age >18 yrs ALSFRS-R FVC > 60%	Safe and well tolerated.	Glass et al., 2012,2013
Fetal olfactory ensheathing cells	Controlled pilot study	Chinese Ministry of Health	Bilateral corona radiata	no	$2x10^6$	15	Age: Range: 20-70	Safe ALSFRS score stable in the first 4 months	Huang et al. 2008
Autologous blood purifyed CD133(+)	Single-center pilot trial	Ethic and Research committees of the hospital.	Frontal motor cortex	no	$2,5\text{-}7,5x10^5$	10	Age 38-62 Duration of the disease Range:18-42months	Safe (1 year follow-up). Improvement of survival ALSFRS	Martinez et al., 2009
Autologous BM derived hematopoietic progenitors	Single-center pilot trial	Regional Ethics board Ministry of Health	Intraspinal (C3-C4level) CSF IV	no	$4x10^6$ $15x10^6$ $5x10^6$	13	Age 34-71 Duration Range:2-5yrs Moderate-severe	No complications	Deda et al, 2009
Autologous HSCS	Single-center pilot trial	institutional review board	irradiation; immuno-suppression	Tacrolimus methotrexate	=	6	Age: 35-69 FVC>60% Duration 5-30months	Tolerated. No clinical benefits.	Appel et al., 2008
Autologous BM MSCS	Phase 1/2 open-safety clinical trial	EthicCommittee Registered in the National Institutes of Health database	Intrathecally and intravenously	no	54.710^6 CSF 24.510^6 iv	19	Age 25-65	Feasible and safe . Immediate immunomodulatory effects.	Karussis et al , 2010

Foetal Neural Stem Cells Transplantation in ALS (EudraCT: 2009-014484-39) Lumbar Transplantation

Angelo Vescovi
Milano Bicocca University

Nicholas M, Boulis
Emory University, Atlanta

Agenzia Italiana del Farmaco

AIFA
AREA ISPEZIONI E CERTIFICAZIONI
Ufficio Autorizzazioni Officine

Roma, 26 LUG. 2010

N. AIFA/UAO/92158/P/15.26

Risposta al Foglio del

N.

Alla Società AZIENDA OSPEDALIERA S. MARIA DI TERNI
VIA TRISTANO DI JOANNUCCIO, 1
05100 - TERNI
(TR)

OGGETTO:

Autorizzazione per l'officina farmaceutica AZIENDA OSPEDALIERA S. MARIA DI TERNI sita in TERNI (TR), VIA TRISTANO DI JOANNUCCIO, 1.

Istituto Superiore di Sanità

Relazione sull'ammissibilità alla sperimentazione clinica ai sensi del DPR 439/2001,

del D.lvo 211/2003 e D.lvo 200/2007

Eudract Number	2009-014484-39
Titolo Protocollo	Trapianto intramidollare di cellule staminali neurali umane come terapia putativa per la SLA: proposta di un trial clinico di fase I
Codice Protocollo	NSC
First in Human:	SI
Sponsor:	AZIENDA OSPEDALIERA S. MARIA DI TERNI
Centro clinico coordinatore	**AZIENDA OSPEDALIERA "S. MARIA" - TERNI - TERNI (TR)** disciplina NEUROCHIRURGIA, P.I. PROF. ANGELO LUIGI VESCOVI
Centri partecipanti	**A.O. UNIVERSITARIA MAGGIORE DELLA CARITA' DI NOVARA - NOVARA (NO)** disciplina NEUROLOGIA, P.I. DR.SSA LETIZIA MAZZINI **UNIVERSITA' DEGLI STUDI DI PADOVA - PADOVA (PD)** disciplina NEUROLOGIA, P.I. DR. GIANNI SORARU

Si ritiene pertanto che, in considerazione delle caratteristiche della specifica patologia, il protocollo proposto possa essere autorizzato.
La sperimentazione clinica dovrà essere condotta nel rispetto delle norme di Buona Pratica Clinica (DM 27 Aprile 1992) e successive modifiche (DM 15 luglio 1997 e D.Lvo. 211 del 24 giugno 2003).
Ai sensi del DM 2 marzo 2004, pubblicato nella Gazzetta Ufficiale della Repubblica Italiana, Serie generale n. 97, del 26-4-2004, il proponente dovrà inserire i dati relativi ai pazienti trattati nella banca dati per il monitoraggio della terapia genica e la terapia cellulare somatica
Ai sensi del D.P.R. 439/2001, art. 10, il richiedente dovrà inviare all'Istituto Superiore di Sanità e all'AIFA il rapporto sui risultati al termine della sperimentazione clinica di fase I.

25.03.2011

IL PRESIDENTE
della
Commissione per la valutazione
dell'ammissibilità alla sperimentazione
clinica di fase I

CEAS Comitato Etico Aziende Sanitarie umbria

Prot. N. 28545/11/ACC del 25/08/2011

Al promotore dello studio
Direttore Generale
Dr. Gianni Giovannini
Azienda Ospedaliera di Terni
Via Tristaino di Joannuccio
05100 Terni

Al responsabile dello studio
Vescovi Prof. Angelo
Laboratorio Cellule Staminali, Cell Factory e Biobanca
Azienda Ospedaliera di Terni
V. T. di Joannuccio
05100 Terni

AIFA - Ufficio Sperimentazioni Cliniche
Via della Sierra Nevada, 60
00144 Roma

LORO SEDI

OGGETTO: ***PARERE UNICO del CEAS Umbria***
Codice Studio: ***NSC***
Promotore dello studio: ***Azienda Ospedaliera di Terni***
Registro CEAS N.: ***1815/11***
Codice EudraCT: ***2009-014484-39***

Foetal Neural Stem Cells Transplantation in ALS (EudraCT: 2009-014484-39) Lumbar Transplantation

- Phase I trial, aimed at testing safety and feasibility of intraspinal injection of “clinical grade” (produced following the Good Manufacturing Guidelines in a pharmaceutical grade authorized facility) neural stem cells from natural miscarriages into a cohort of 18 ALS patients using a validated surgical apparatus and injection procedures.

Trapianto intramidollare di cellule staminali neuronali umane come terapia putativa per la SLA: proposta di un trial clinico di fase I
EudraCT: 2009-014484-39

Criteri di Inclusione

Diagnosi di SLA definita in accordo con i criteri rivisti di El Escorial

Età: 20-75 anni

Documentata progressione di malattia negli ultimi 6 mesi

Assenza di patologie concomitanti complicanti il quadro clinico

- **Gruppo 1 (n=6)**

- Deambulazione impossibile
- Capacità Vitale Forzata $\geq$ 60% in posizione assisa.

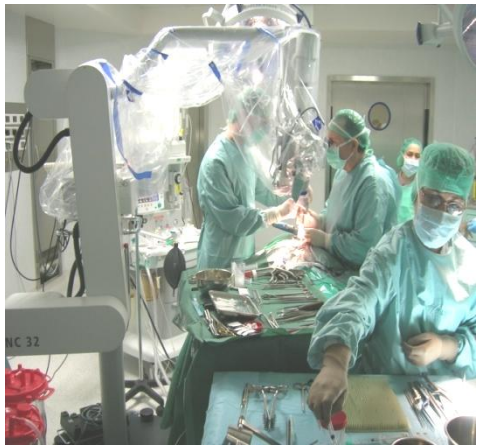
- **Gruppo 2 (n=6)**

- Deambulazione con ausili o assistenza
- Capacità Vitale Forzata $\geq$ 60%; in posizione seduta

- **Gruppo 3 (n=6)**

- Deambulazione autonoma
- Capacità Vitale Forzata $\geq$ 70%; in posizione seduta

Trapianto intramidollare di cellule staminali neuronali umane come terapia putativa per la SLA: proposta di un trial clinico di fase I
EudraCT: 2009-014484-39



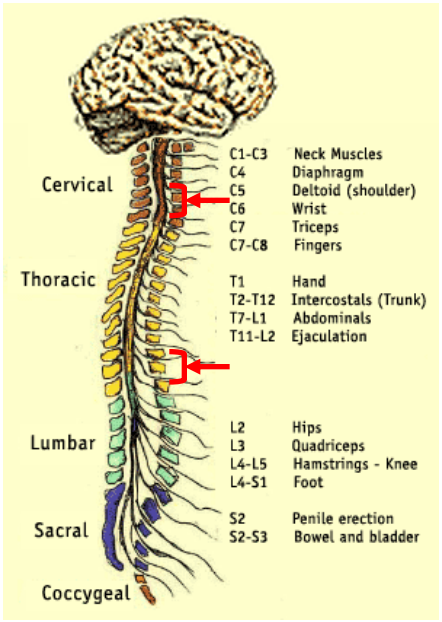
Gruppo 1

(iniezioni D8-D11)

50.000 cellule (15 microlitri) per sito di iniezione

Gruppo 1a:monolaterale

Gruppo 1b: bilaterale



Gruppi 2 e 3

(iniezioni C5-C6)

50.000 cellule (15 microlitri) per sito di iniezione

Gruppo 2a: monolaterale

Gruppo 2b: bilaterale

Gruppo 3a: monolaterale

Gruppo 3b: bilaterale

Impiego delle cellule staminali mesenchimali autologhe in pazienti con sclerosi laterale amiotrofica

Paziente

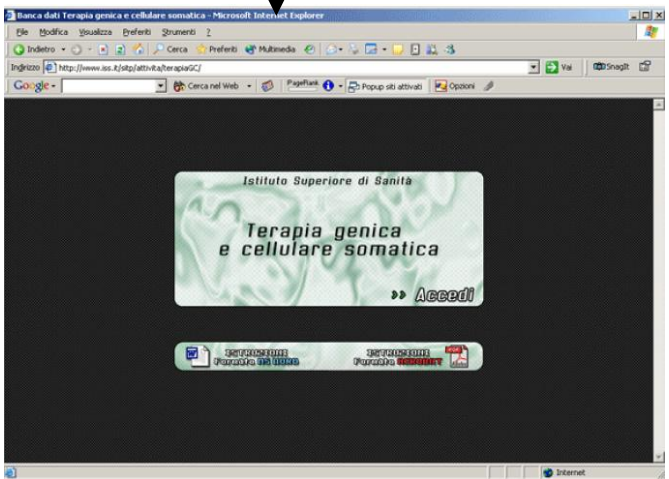
Cod. paziente ISS: **121** Cod. paziente:
Data di nascita: **19/10/1969** Sesso: **F**
Sperimentatore: **Mazzini Letizia (Rif. 102)**
Autorizzazione al trattamento del paziente

Modalità: Parere favorevole ISS		
	Data invio domanda: **02/05/2005**	Data protocollo ISS: **17/05/2005**

Italian National Institute of Health
Approval of the protocol,
Control of the adherence to the protocol
Monitoring of the results

ALS Centre
Recruitment of the patient

Local Ethics Committee
Approval of the protocol
Control of the adherence to the protocol

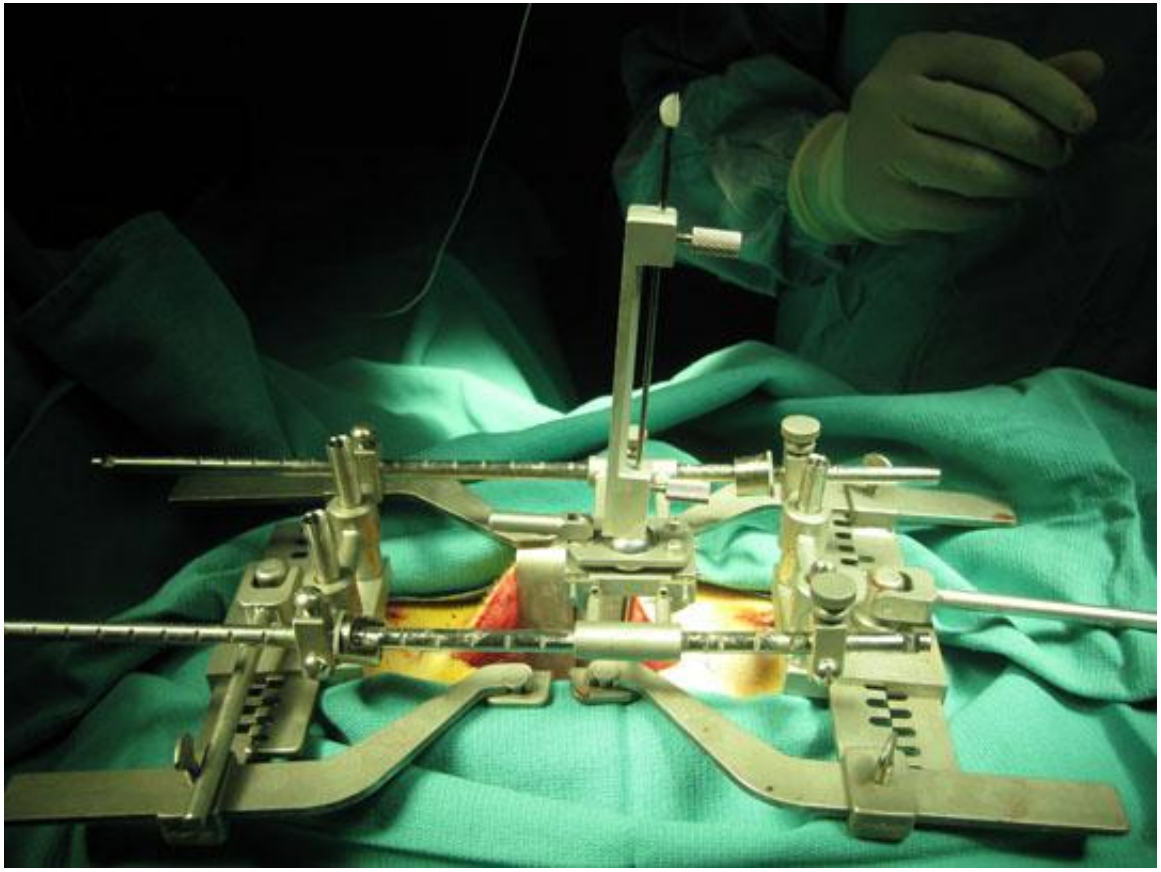


Safety Advisory Board

Control of the adherence to the protocol
Monitoring of the results

Foetal Neural Stem Cells Transplantation in ALS
(EudraCT: 2009-014484-39)
Lumbar Transplantation

Surgery
Device



Immunosuppression

- **Although the brain remains an immunologically privileged site due to the blood–brain barrier, there is evidence that this barrier can be compromised in disease** *(BV. Zlokovic Neuron 57, January 24, 2008)*

- **Studies of cell graft survival demonstrate that immunosuppression increases the survival of graft tissue**
- *(M. Hovakimyan et al. / Annals of Anatomy 194 (2012) 429– 435)*

- **Methyprednisolone** 125 mg IV is administered preoperatively at 2 hours before incision. Patients subsequently receive a 28-day taper with a dose change each week: 60 mg ,40 mg ,20 mg, and 10 mg orally every day.
- **Cefazolin** 1g IV is administered at the time of dural opening. and an equal dose is given immediately after surgery..
- **Tacrolimus** is administered at 0.1 mg/kg orally per day with twice daily dosing beginning on
- postoperative day 1..The drug is titrated to maintain the blood level between 5-10 ng\ml for 6 months and then stopped

Trapianto intramidollare di cellule staminali neurali umane come terapia putativa per la SLA: proposta di un trial clinico di fase I

Responsabile: Prof. Angelo Vescovi

Direttore IRCCS Casa Sollievo della Sofferenza San Giovanni Rotondo

Centri di Reclutamento

Centro Regionale Esperto SLA Novara
(Responsabile drssa Letizia Mazzini)

Ambulatorio Malattie del Motoneuroni Padova
(Responsabile dr Gianni Sorarù)

800 010 010
Tutti i martedì ed i mercoledì dalle 9 alle 13 e dalle 14 alle 17
Alternativamente è possibile inviare una mail al seguente indirizzo:
trialSLA@neurothon.it

Pazienti

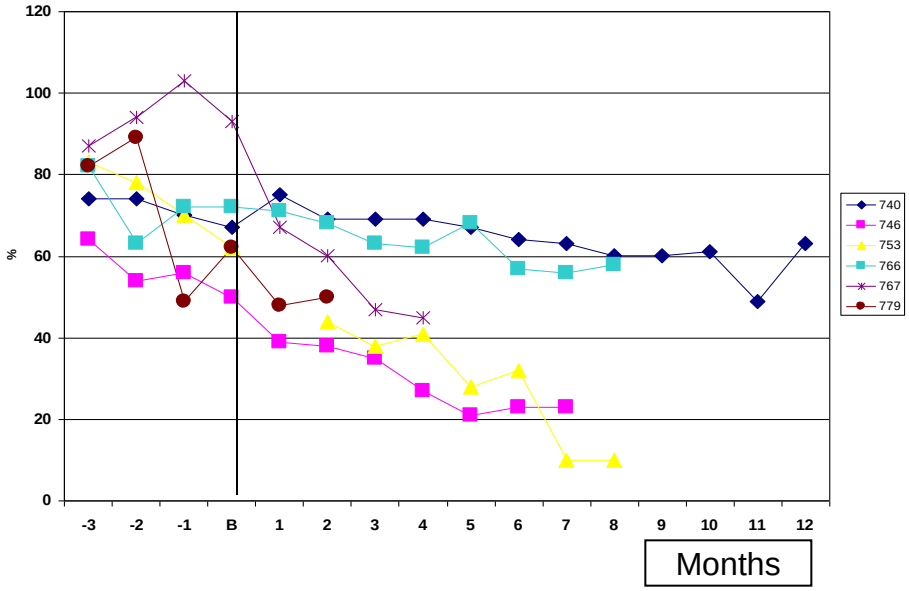
(Trapianto Lombare)

Paziente/Centro	Gruppo	età	sesso	durata malattia(mesi)	Data reclutamento	data intervento	N° mesi follow-up-post
740/Novara	A1	30	M	60	07/03/2012	25/06/2012	15
746/Padova	A1	57	M	68	20/07/2012	31/07/2012	8 †
753/Novara	A1	54	F	16	17/05/2012	24/09/2012	8 †
766/Novara	A2	35	M	72	07/08/2012	05/11/2012	6
767/Padova	A2	67	F	36	29/10/2012	01/02/2013	7
779/Padova	A2	38	M	32	17/12/2012	22/03/2013	6

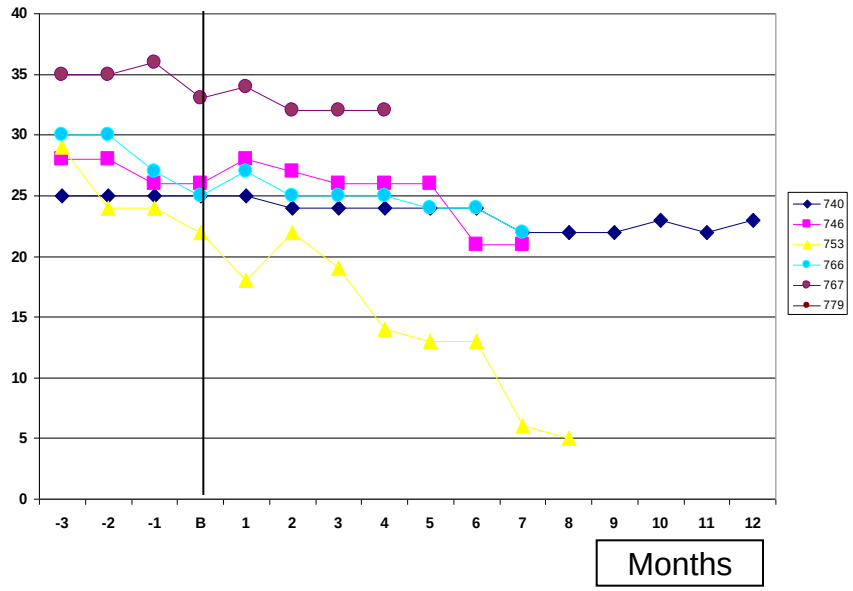
I due pazienti sono deceduti per cause indipendenti dal trapianto come documentato dalle autopsie. Nessuno ha presentato eventi avversi gravi

Foetal Neural Stem Cells Transplantation in ALS
(EudraCT: 2009-014484-39)
Lumbar Transplantation

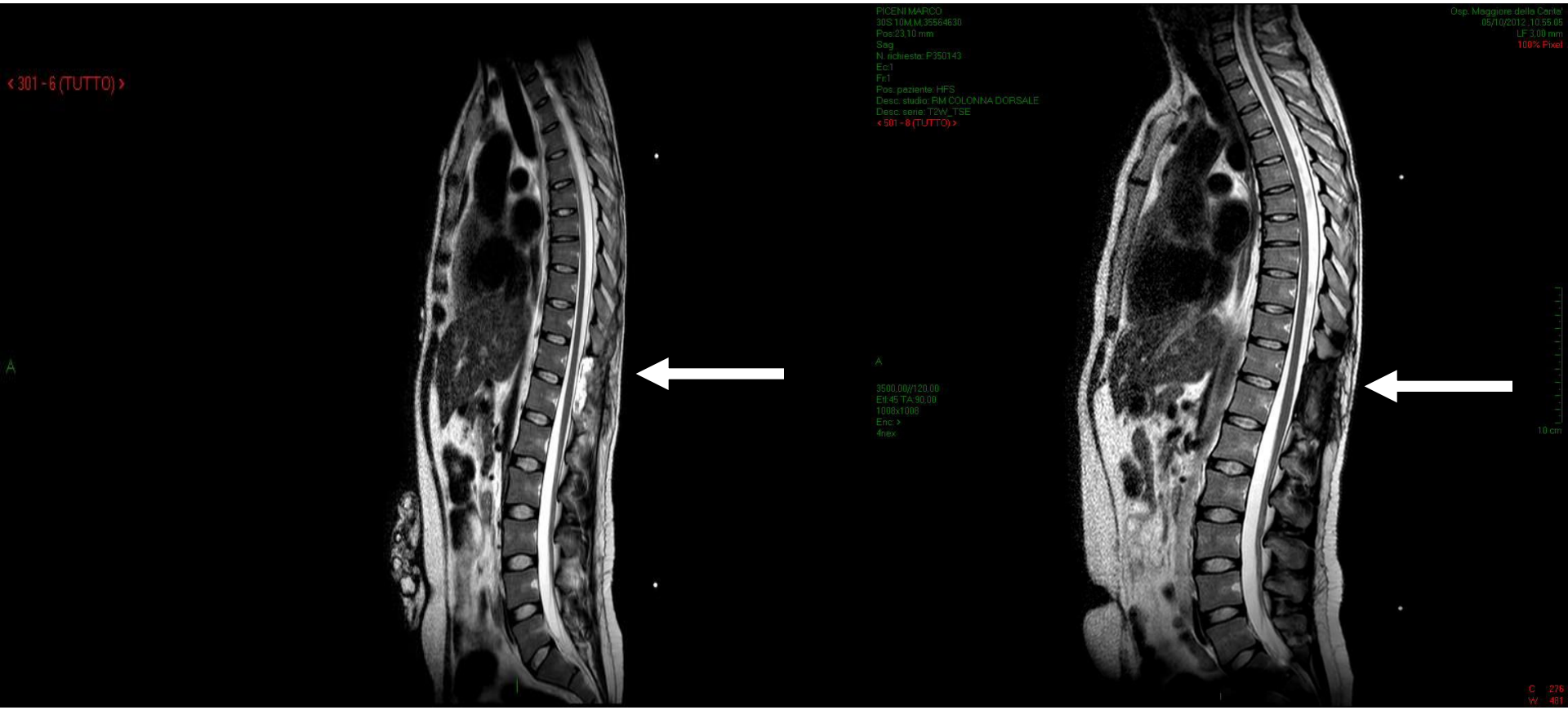
FVC



ALS-FRS



Foetal Neural Stem Cells transplantation in ALS (EudraCT: 2009-014484-39) Lumbar Transplantation



1 month post-surgery

3 months post-surgery

Trapianto intramidollare di cellule staminali neuronali umane come terapia putativa per la SLA: proposta di un trial clinico di fase I
EudraCT: 2009-014484-39

Conclusioni
(I Gruppo)

Il trapianto intramidollare delle cellule staminali neuronali umane a livello lombare è sicuro nel breve e medio termine

RSC/SdG/CT

STDG/P/ 51585

Roma, 17 maggio 2013

Agenzia Italiana del Farmaco

AIFA

Il Direttore Generale

Angelo Luigi Vescovi
Azienda Ospedaliera Santa Maria
Via Tristano da Joannuccio
05100 Terni
vescovia@gmail.com

Sulla base del parere tecnico espresso dall'Istituto Superiore di Sanità, si comunica che lo Studio in oggetto è:

AUTORIZZATO ALLA PROSECUZIONE

SECONDO IL PROTOCOLLO PRECEDENTEMENTE ESAMINATO ED AUTORIZZATO

Sono stati reclutati 4 pazienti. Uno ha terminato i tre mesi di osservazione ed è stato sottoposto a trapianto nel midollo cervicale il 23 settembre scorso senza complicanze chirurgiche. Il prossimo intervento è previsto il 25 ottobre

CNS transplantation

-Motor neuron support:
Stem cells aimed at providing support or modulating inflammation. Cells can also be engineered to release neuroprotective molecules.

-Motor neuron replacement:
iPS or ES cells are required to generate cortical or spinal motor neurons. The challenge is avoiding teratoma and growing axons long distance.

-Combining neuronal support and replacement strategies.

Minimal criteria for a cell based therapy

-Fundamental aspects to be considered prior to proceeding to clinical trial with cell based therapy:
-Safety: cells and transplantation procedure should not cause harm or any deleterious side effects.

-Efficacy: treatment requires demonstration of therapeutic value. Ideally in multiple models, with replication by independant investigators.

Peripheral transplantation

-Grafting MSCs or muscle progenitors expressing growth factors to provide neurotrophic support.

-Grafting stem cells to the blood stream with the hope that they home to areas of damage in the CNS. The challenge will be in the penetration of and survival of cells from the blood in the nervous system.

Autologous transplantation

-Patient specific therapy:
Generation of iPSCs derived from an individual with disease followed by the expansion and differentiation into therapeutically relevant cells.

Drug therapy

-A combination approach:
Treatment with the most promising compounds aimed at thwarting pathological mechanisms associated with disease, promoting neuronal survival or enhancing the function of grafted cells.

From: Gowing and Svendsen, Neurotherapeutics, Sept 9,2011

Amyotrophic Lateral Sclerosis, 2011; 12: 315–317

informa
healthcare

MEETING REPORT

Meeting report of the International Consortium of Stem Cell Networks' Workshop Towards Clinical Trials Using Stem Cells for Amyotrophic Lateral Sclerosis/Motor Neuron Disease

- Stem cells research and application is opening great opportunities in ALS treatment. The scientific community and patients urgently need safety and efficacy to be addressed properly in the framework of rigorous controlled clinical trials.

- Translation, by which we mean advancing scientific discoveries from the laboratory into practical applications for patient benefit, i.e., ‘‘bench to bedside,’’ requires a comprehensive collaborative team approach: research scientists and clinicians must work closely with regulatory agencies, patient advocacy groups, ethic bodies, cell manufacturing facilities, and industry to achieve the quality of studies and necessary funding to ensure success.

BENVEGNÙ/GUAITOLI/CIMAGLIA/JPEG FOTOSERVIZI

A naked woman joined protesters in Rome calling for stem-cell therapy for all incurably ill patients.

REGENERATIVE MEDICINE

Stem-cell ruling riles researchers

Italian health minister's support for a controversial treatment appals the country's scientists.

Smoke and mirrors

Italy's parliament must listen to expert advice before deregulating stem-cell therapies.

Just weeks after the white smoke from the Vatican signalled the election of a new pope, a grimmer pall hangs over the Eternal City — a fog of confusion and misrepresentation about stem-cell therapy. Those who have lit the fire beneath the debate say that they are promoting the translation of stem-cell research into the clinic so that currently incurable diseases can be treated. Nothing could be further from the truth.

Rome 4

Stem Cell Researchers Protest Controversial Treatment

The Stamina Foundation can continue a controversial stem cell treatment in patients with neurodegenerative diseases such as spinal muscular atrophy and Parkinson's, according to a new bill signed by Italian Health Minister Renato Balduzzi on 21 March (and approved by the Council of Ministers). Over

NATURE | NEWS

Italian stem-cell trial based on flawed data

Scientists raise serious concerns about a patent that forms the basis of a controversial stem-cell therapy.

Alison Abbott

02 July 2013

The controversial stem cell therapy has garnered fervent public support, while many scientists decry it as unproven.

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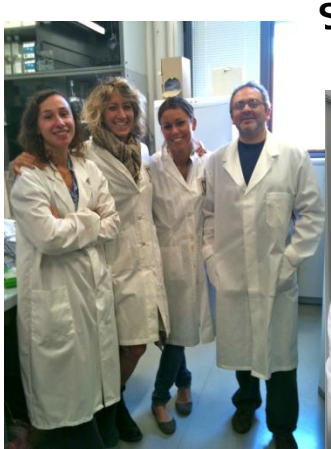

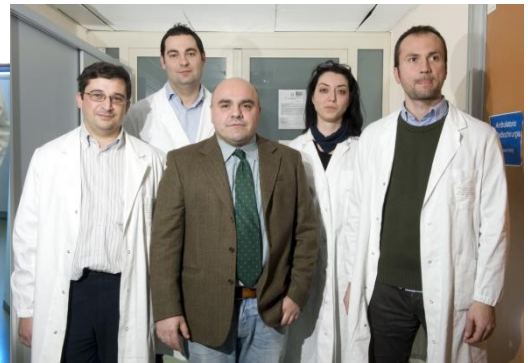

SLA
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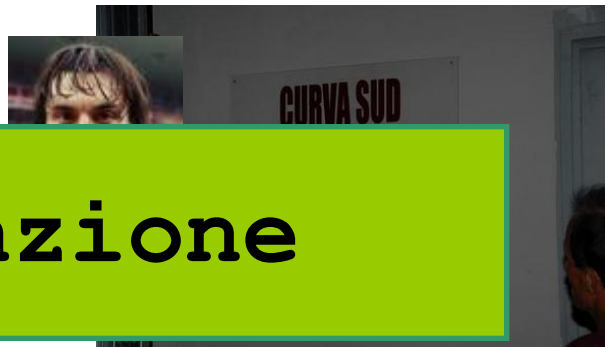
NOVARA



Grazie per l'attenzione