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SLA: le ultime sperimentazioni

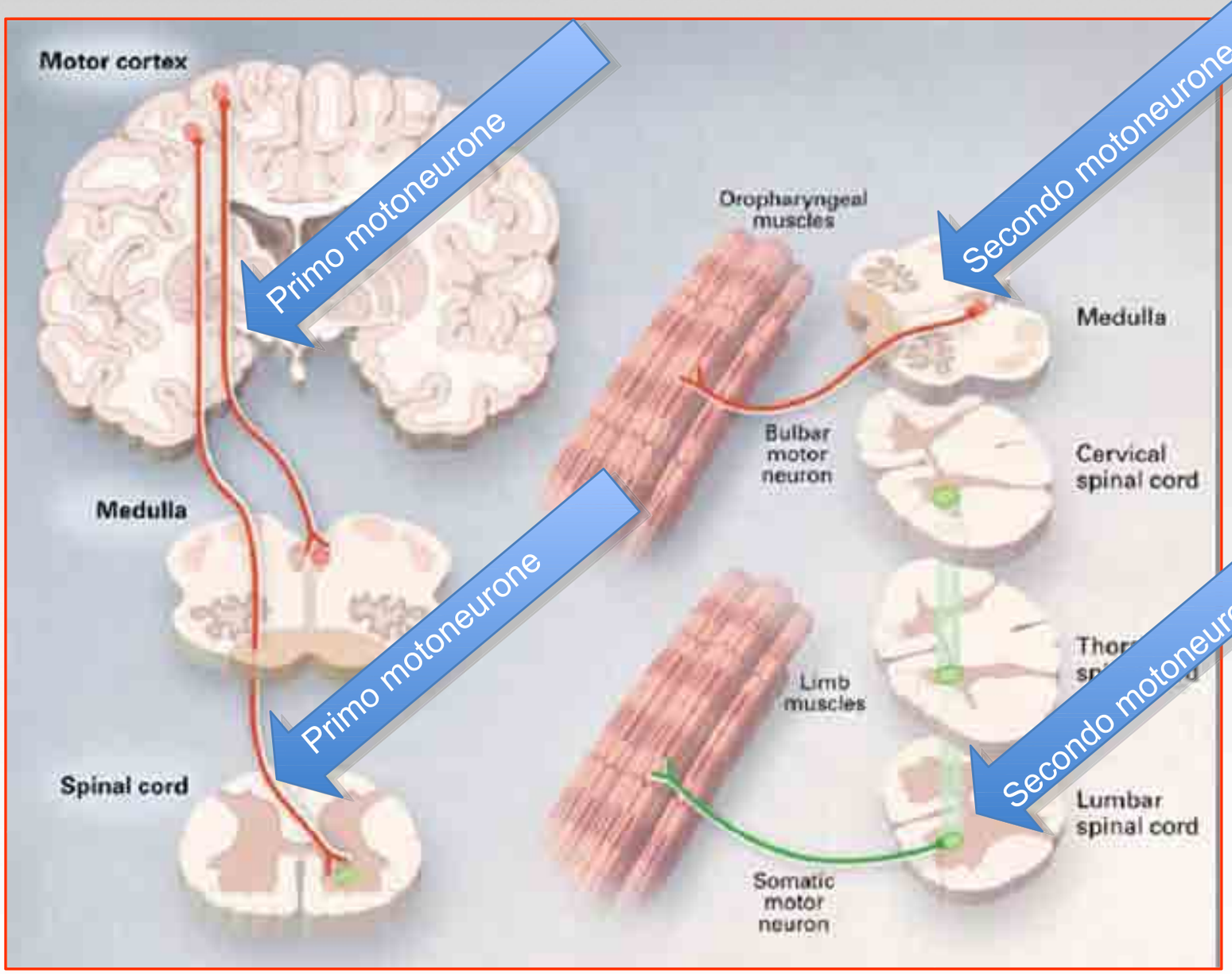
Christian Lunetta

Angri
08 luglio 2013

Una visione d'insieme

Malattia degenerativa del primo e secondo motoneurone

Lou Gehrig (1903-1941)



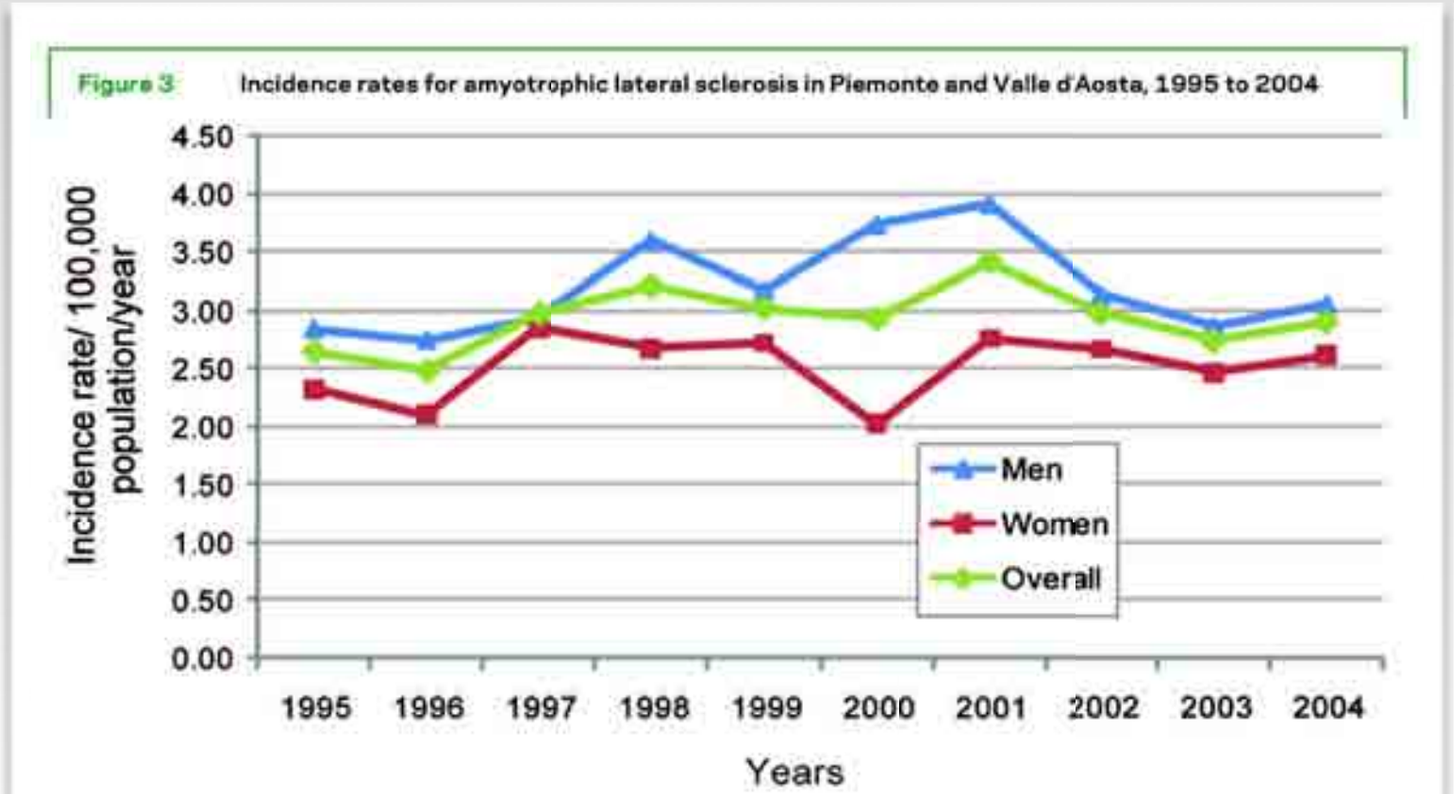
CENTRO CLINICO NEMO

Sistema Sanitario Regione Lombardia

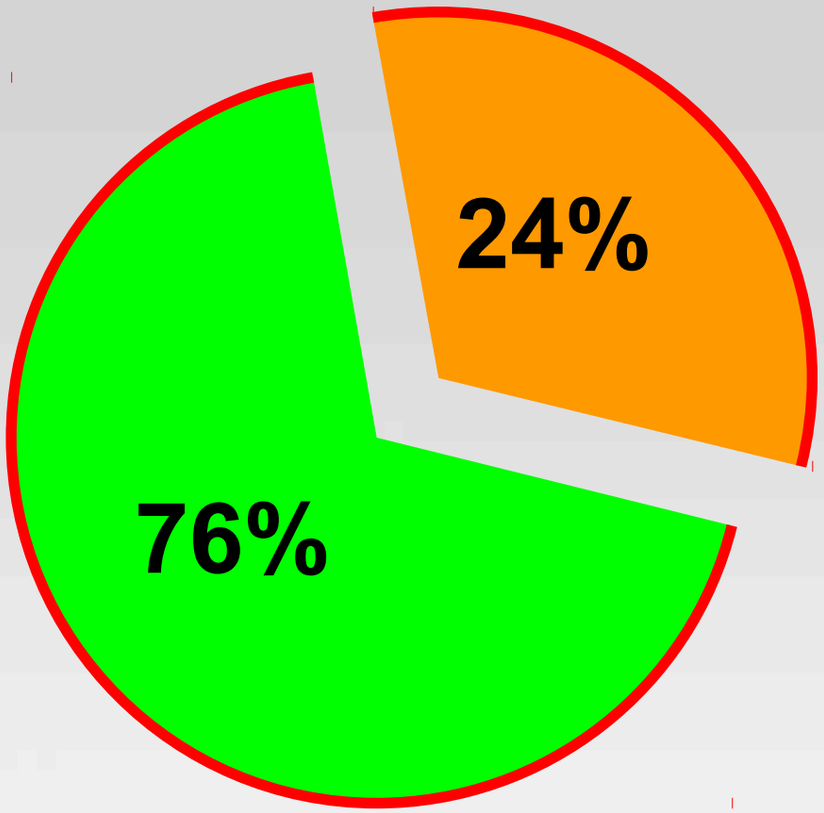
aisla ONLUS
ASSOCIAZIONE ITALIANA SCLEROSI LATERALE AMIOTROFICA

Epidemiologia della SLA

- **Incidenza della forma sporadica**: 1.5 - 2.7/100.000/anno in Europa e Nord America [*Worms, 2001*]
- **Prevalenza**: 2.7 - 7.8/100,000/anno nel mondo occidentale [*Worms, 2001; Chiò et al., 2009*]



Modalità di presentazione



Bulbare → disfagia, disartria, lingua atrofica

Spinale → ipostenia, atrofia del cingolo, mano atrofica, piede cadente

Esordio “diaframmatico” (raro) → insufficienza respiratoria acuta o subacuta

Esordio “generalizzato” (raro)

Esordio “demenza"

JNNP Online First, published on March 14, 2011 as 10.1136/jnnp.2010.235952

Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study

Adriano Chiò,[1,2] Andrea Calvo,[1] Cristina Moglia,[1] Letizia Mazzini,[3] Gabriele Mora,[4] PARALS study group*

► Additional tables are published online only. To view these files please visit the journal online (http://jnnp.bmj.com).

[1]ALS Centre, Department of Neuroscience, University of Torino, AOU San Giovanni Battista, Torino, Italy [2]Neuroscience Institute of Torino (NIT), Torino, Italy; [3]ALS Centre, Department of Neurology, University of Eastern Piedmont 'Amedeo Avogadro', Novara, Italy [4]ALS Centre, Department of Neurological Rehabilitation, Fondazione Salvatore Maugeri, IRCCS, Scientific Institute of Milano, Italy

Correspondence to
Professor A Chiò, Department of Neuroscience, University of Torino, AOU San Giovanni Battista, Via Cherasco 15, 10126 Torino, Italy; achio@usa.net

*For author footnote see end of the article.

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ABSTRACT

Background Different amyotrophic lateral sclerosis (ALS) phenotypes have been recognised, marked by a varying involvement of spinal and bulbar upper and lower motor neurons. However, the differential characteristics of these phenotypes are still largely unknown.

Objective To define the epidemiology and outcome of ALS phenotypes in a population based setting.

Methods All ALS cases incident in two Italian regions were prospectively collected from 1995 to 2004 in an epidemiological register. Cases were classified according to established ALS phenotypes: classic, bulbar, flail arm, flail leg, pyramidal, respiratory, pure lower motor neuron (PLMN) and pure upper motor neuron (PUMN).

Results ALS phenotype were determined in 1332 out of 1351 incident patients (98.6%). Classic and bulbar phenotypes had similar mean annual incidence rates. Gender specific incidence rates showed a male preponderance in respiratory, flail arm, classic and PLMN phenotypes; in all other phenotypes, men and women had similar incidence rates. Age at onset was significantly lower in pyramidal, PLMN and PUMN phenotypes and higher in the bulbar phenotype. The best outcomes were observed in PUMN, pyramidal, PLMN and flail arm phenotypes and the worst in respiratory and bulbar phenotypes.

Conclusions Our epidemiological findings suggest that ALS phenotypes carry distinctive and easily distinguishable clinical and prognostic characteristics, strongly related to a complex interplay between gender and age. The categorisation of ALS patients according to more homogenous clinical groups is relevant in identifying biological markers for ALS and should be considered for the design of clinical trials.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of adult life characterised by the progressive involvement of lower and upper motor neurons at the bulbar and spinal level. In 5–10% of patients, a positive family history for ALS can be detected. However, in most patients the cause of ALS remains unknown. It is a generally accepted notion that the clinical spectrum of ALS includes different phenotypes marked by a varying involvement of spinal and bulbar upper and lower motor neurons.[1 2] Accordingly, eight distinctive clinical phenotypes are recognised in the literature: classic, bulbar, flail arm, flail leg, pyramidal, respiratory, pure lower motor neuron (PLMN) and pure upper motor neuron (PUMN).[3–9]

A discussion has recently arisen concerning the possibility that different ALS presentations have different aetiologies or underlying factors—whether genetic, environmental or both—that modify the phenotype.[10] However, to present, no studies have been carried out to assess and compare all ALS phenotypes using an epidemiological approach.

The aim of this study was to evaluate the clinical characteristics and outcome of different ALS phenotypes in a large population based setting.

METHODS

The Piemonte and Valle d'Aosta Register for ALS (PARALS) is a prospective register collecting all cases of ALS in the Piemonte and Valle d'Aosta regions of Italy (total population at the 2001 national census 4 332 842; total area 28 692 km^2). The register was established in 1995 and is still in operation. Epidemiological data regarding the 1995–2004 period have recently been published.[11]

Case collection

The main sources of cases were the neurology departments of the two regions. Investigators used an ad hoc questionnaire to collect patient demographic data, disease history, neurological and laboratory findings, and treatments. Diagnostic EMG examination was performed in all patients according to standard procedures. The secondary sources for case collection were: the Piemonte and Valle d'Aosta Central Regional Archives; and the mortality coding from the Italian Bureau of Statistics. Clinical records of cases found through secondary sources were obtained, and relevant clinical information for each case was analysed in order to verify if the patient met the eligibility criteria; all living patients were contacted by phone and visited by one of the neurologists involved in the study.

Diagnostic criteria

The diagnosis of ALS was based on the original El Escorial diagnostic criteria[12] although from 2000, cases were also classified according to the El Escorial revised criteria.[13] Patients with PUMN[4 5] and PLMN[6] were prospectively included in the register; they were not considered in the original epidemiological paper[11] but are included in this study. A clinical follow-up of each patient was performed at regular intervals (2–4 months). A standard form was used for collecting clinical information at each follow-up visit. The presence of frontotemporal dementia (FTD) was determined using an internally generated questionnaire administered to caregivers during the follow-up visits and was based on Neary's criteria.[14 15]

Modalità di presentazione

1. **Classic (Charcot's) phenotype**
2. **Bulbar phenotype**
3. **Flail arm phenotype**
4. **Flail leg phenotype**
5. **Pyramidal phenotype (predominant upper motor neuron ALS)**
6. **Respiratory phenotype**
7. **Pure lower motor neuron**
8. **Pure upper motor neuron**

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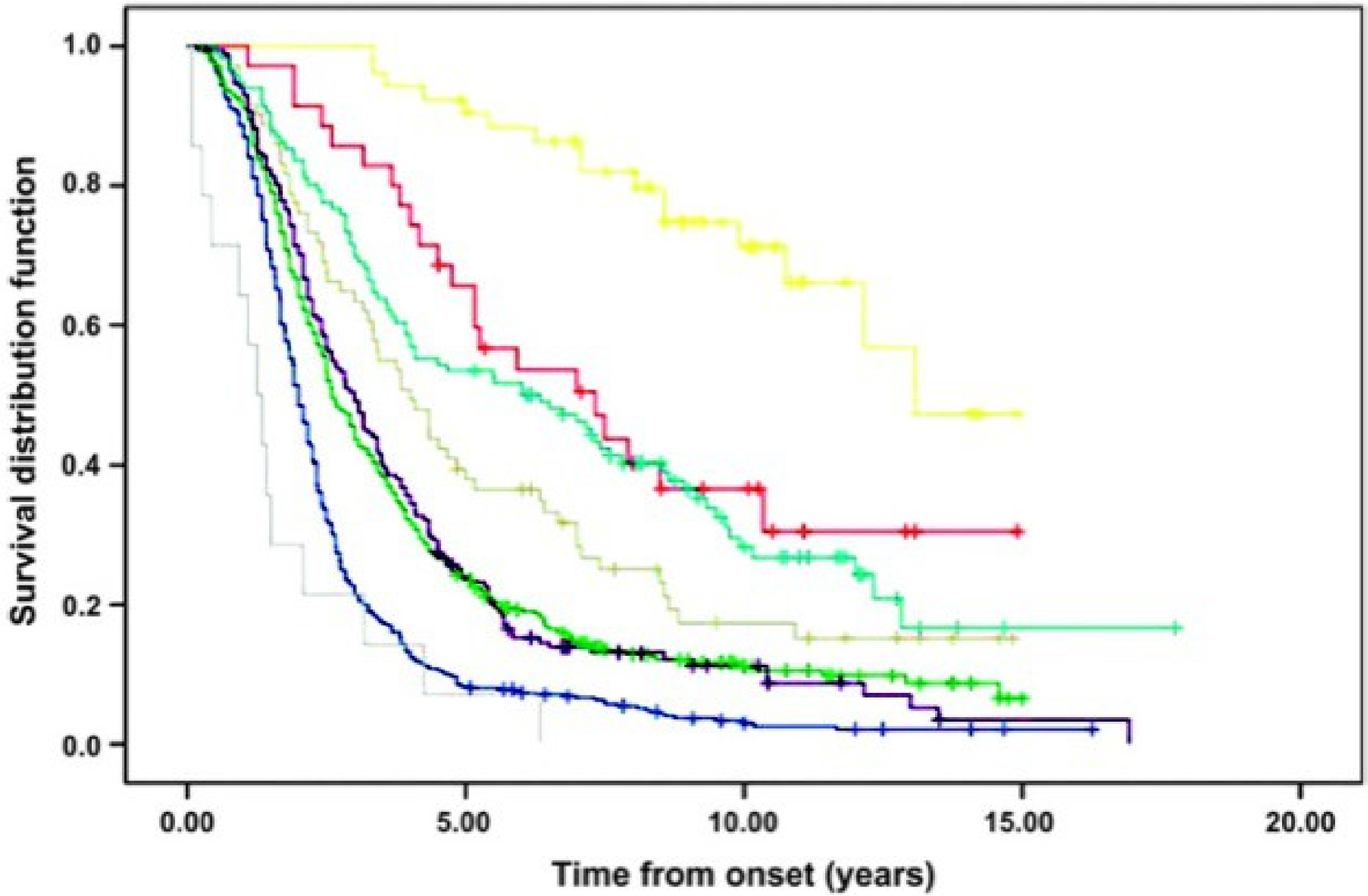
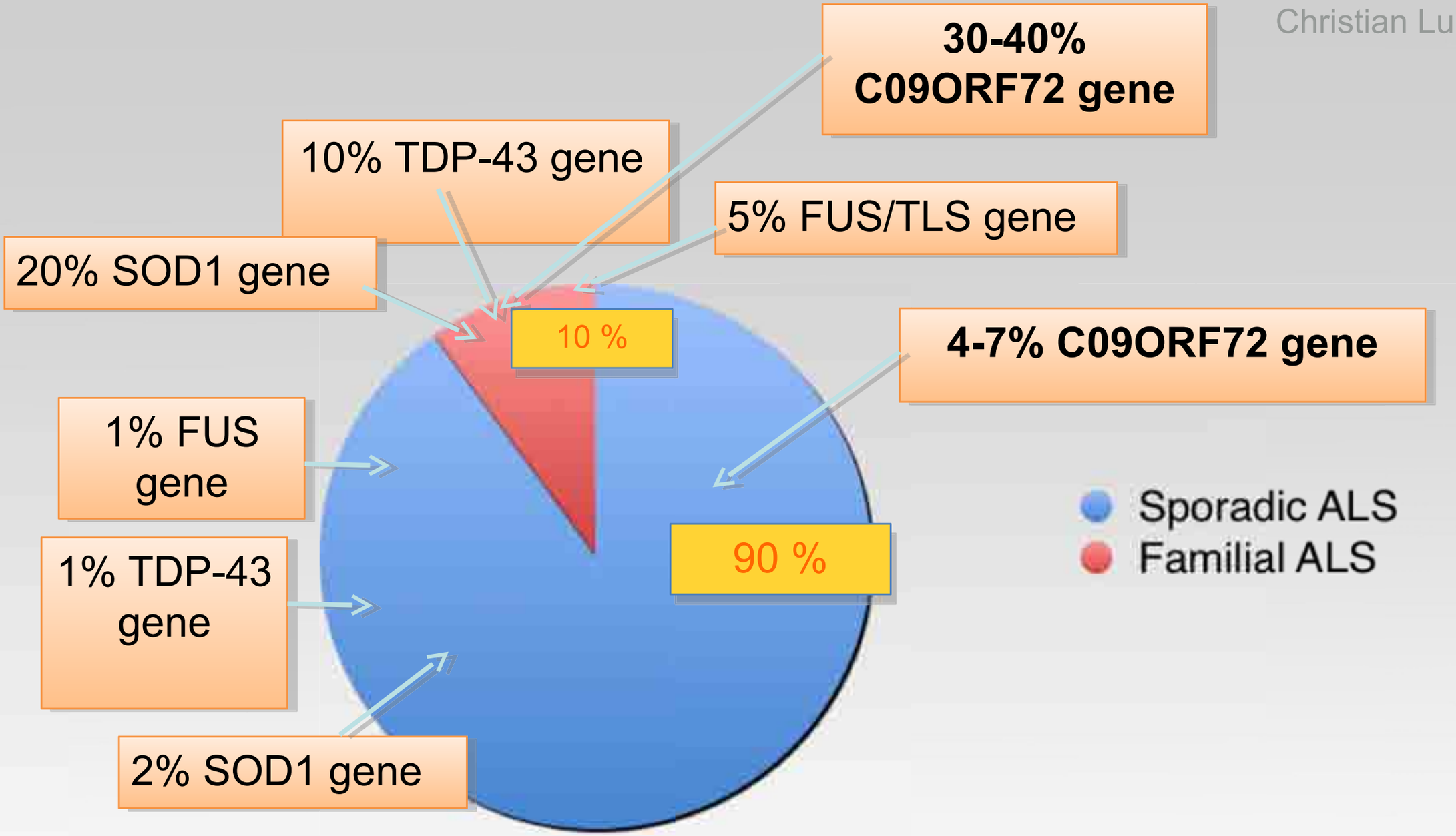
Figure 3 Tracheostomy free survival, according to amyotrophic lateral sclerosis (ALS) phenotype. Yellow, PUMN; red, PLMN; light blue, pyramidal ALS; grey, flail arm; violet, classic ALS; green, flail leg; blue, bulbar; cyan, respiratory. Crosses are censored patients. PLMN, pure lower motor neuron phenotype; PUMN, pure upper motor neuron phenotype.





90% autosomal dominant pattern of inheritance

10% autosomal recessive pattern of inheritance

Ipotesi etiopatogenetiche

Fattori genetici

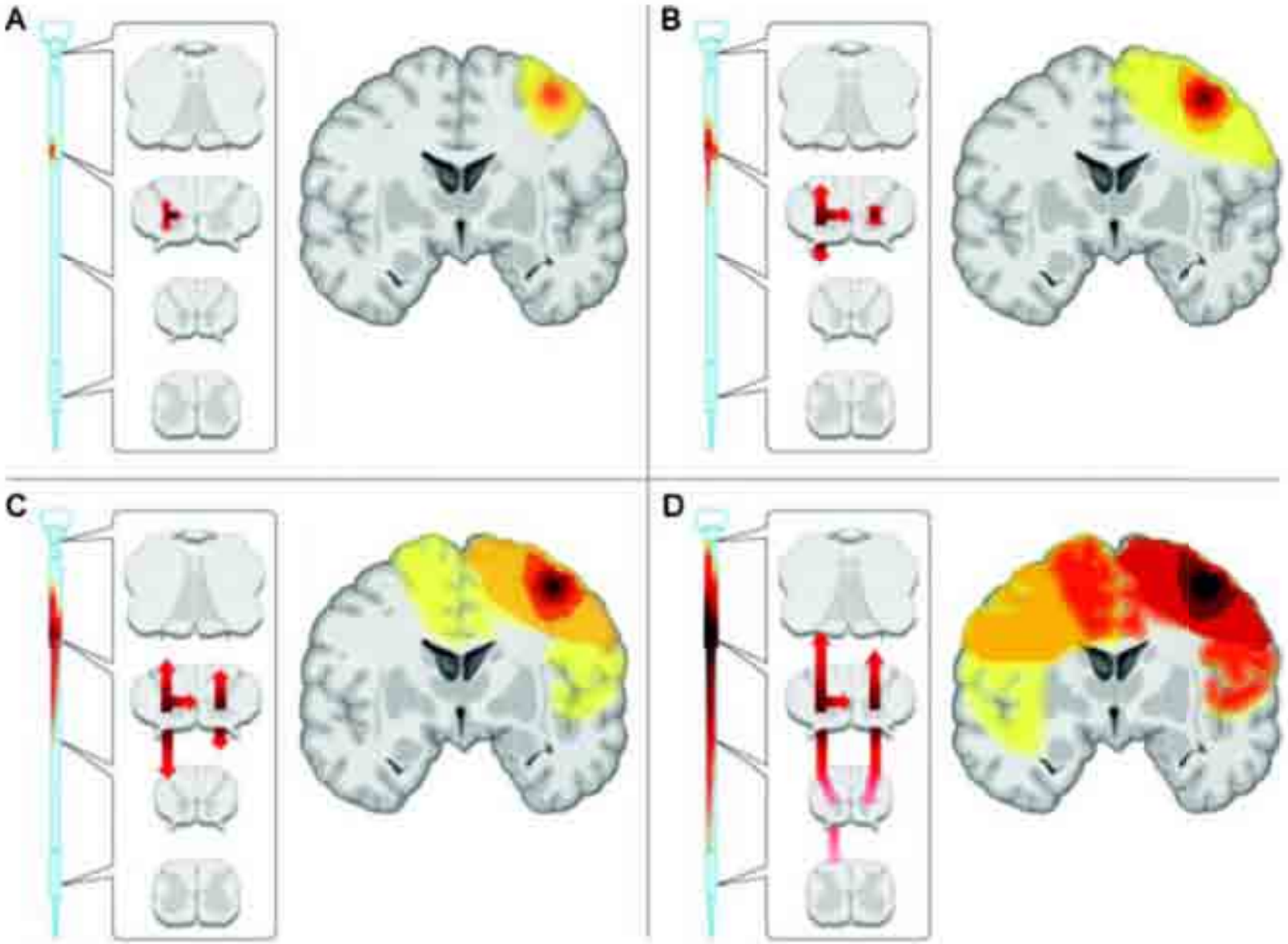
Fattori ambientali

La malattia è genetica
il ruolo dell'ambiente
è nullo
(SLA familiare)

La malattia è dovuta a
fattori neurotossici
presenti nell'ambiente
(ALS-PDC di Guam)

La malattia è determinata dall'azione
integrata di fattori genetici e ambientali
(non necessariamente neurotossici)
(SLA sporadica)

Figure **An idealized model of the natural history of amyotrophic lateral sclerosis (ALS) based upon focality and contiguous spread**



(A) Onset: At clinical onset, degeneration involves upper motor neurons (UMNs) and lower motor neurons (LMNs) that innervate the same peripheral body region; the site of onset, ratio of UMN to LMN involvement, and rate of progression are each highly variable but independent of each other. (B) Early spread: As the disease process spreads neuroanatomically through UMN and LMN levels, clinical manifestations become complex due to differences ("incongruity") between somatotopic anatomy and anatomic distances of the 2 levels. (C) Continued outward spread: For LMN, the ALS disease process continues to spread rostral-caudal (severity ipsilateral > contralateral) and must pass through the long thoracic region and thus appears to be mostly at one level. Degeneration may have preferential caudal spread ("directionality") as discussed in the text. For UMN, however, the ALS disease process continues to spread medial-lateral and more quickly begins to appear as diffuse. (D) Advanced spread: Ultimately, degeneration appears to be diffuse and symmetric through temporal-spatial summation within and between UMN and LMN levels, the natural history of which has depended upon the features established at onset.

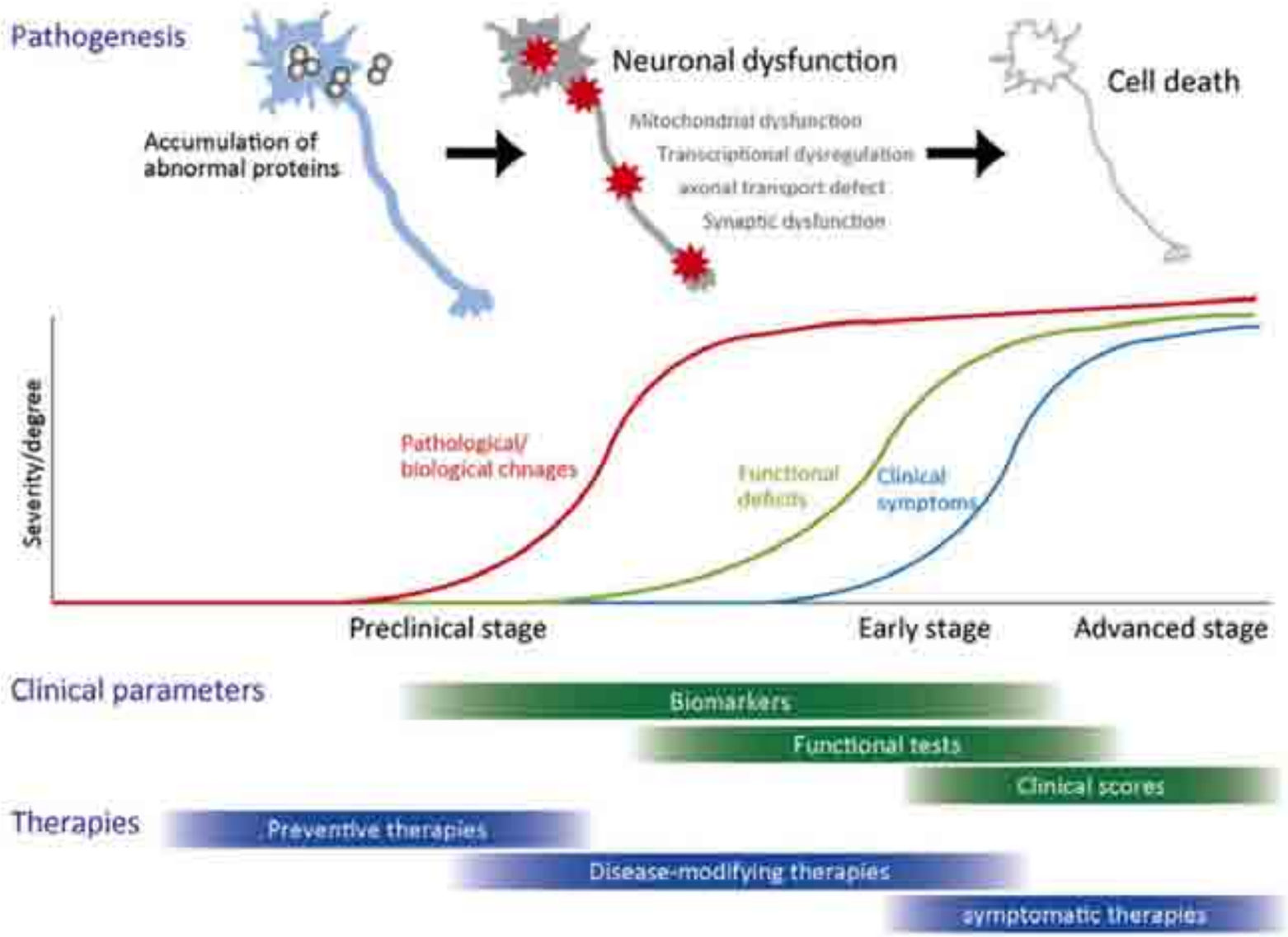


Figure 2 Time course of neurodegeneration and related parameters. Accumulation of abnormal proteins instigates a variety of molecular changes that precede neurophysiological dysfunctions and eventual manifestation of clinical symptoms. Appropriate markers and measures are required for detecting pre-symptomatic neurological and biological changes in patients with neurodegenerative diseases. Katsuno *et al*. Molecular genetics and biomarkers of polyglutamine diseases. *Current Mol Med* 2008;**8**:221–34.

LA RICERCA e LA SPERIMENTAZIONE

CENTRO CLINICO Nemo

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Emerging targets and treatments in amyotrophic lateral sclerosis

Lorne Zinman, Merit Cudkowicz

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease that is currently untreatable. Many compounds have been tested in laboratory-based models and in patients with ALS, but so far only one drug, riluzole, has shown efficacy, yet it only slightly slows disease progression. Several new insights into the causes of motor neuron death have led to the identification of some important novel targets for intervention. At no time have studies involved such a wide range of innovations and such advanced technologies. Many promising studies are underway to test potential targets that will hopefully translate into meaningful therapeutics for patients with ALS.

Sunnybrook Health Sciences Centre, Toronto, ON, Canada
Neurology Clinical Trials Unit, Massachusetts General Hospital, Charlestown, MA,

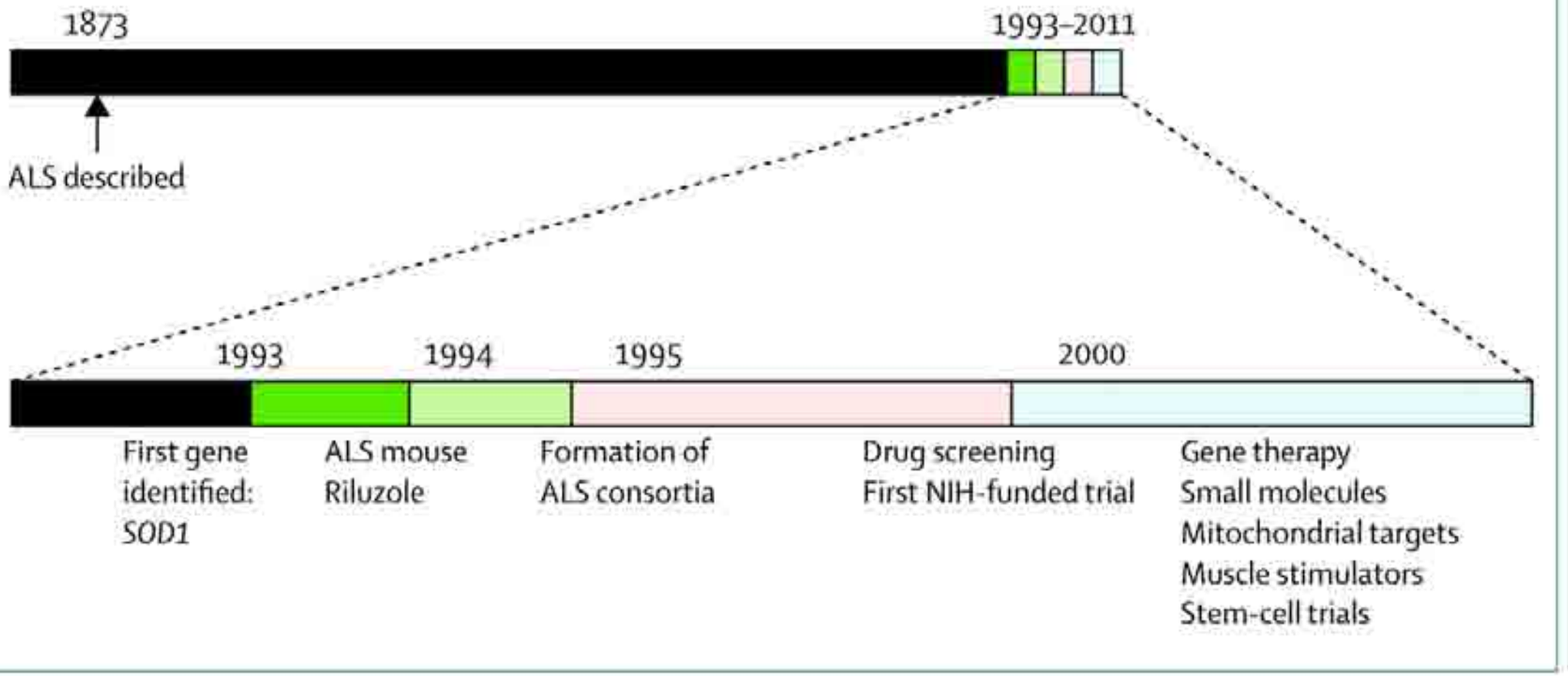

Figure 1: **The increasing pace of advances in ALS**
ALS=amyotrophic lateral sclerosis. NIH=National Institutes of Health.

"Ogni individuo ha diritto alla vita, alla libertà e alla sicurezza della propria persona".

Dichiarazione Universale dei Diritti Umani, art. 3 (1948)

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***Table 1** Evaluation criteria for potential neuroprotective agents in ALS*[®]

Criteria	Operational definition
Scientific rationale	Consistency of preclinical data; credible mechanism relevant to ALS although mechanism may be unknown in many cases
Safety and tolerability	Safe and tolerable in humans in the dose and route of administration needed for the proposed effect. Further safety data may be required before use in ALS
Efficacy in relevant animal	Efficacy in rodent model of ALS or other relevant models of disease
Indication of benefit in human clinical studies	Evidence from previous trials that is suggestive of a neuroprotective effect or epidemiologic data fulfilling criteria for causal inference

Emerging targets and treatments in amyotrophic lateral sclerosis

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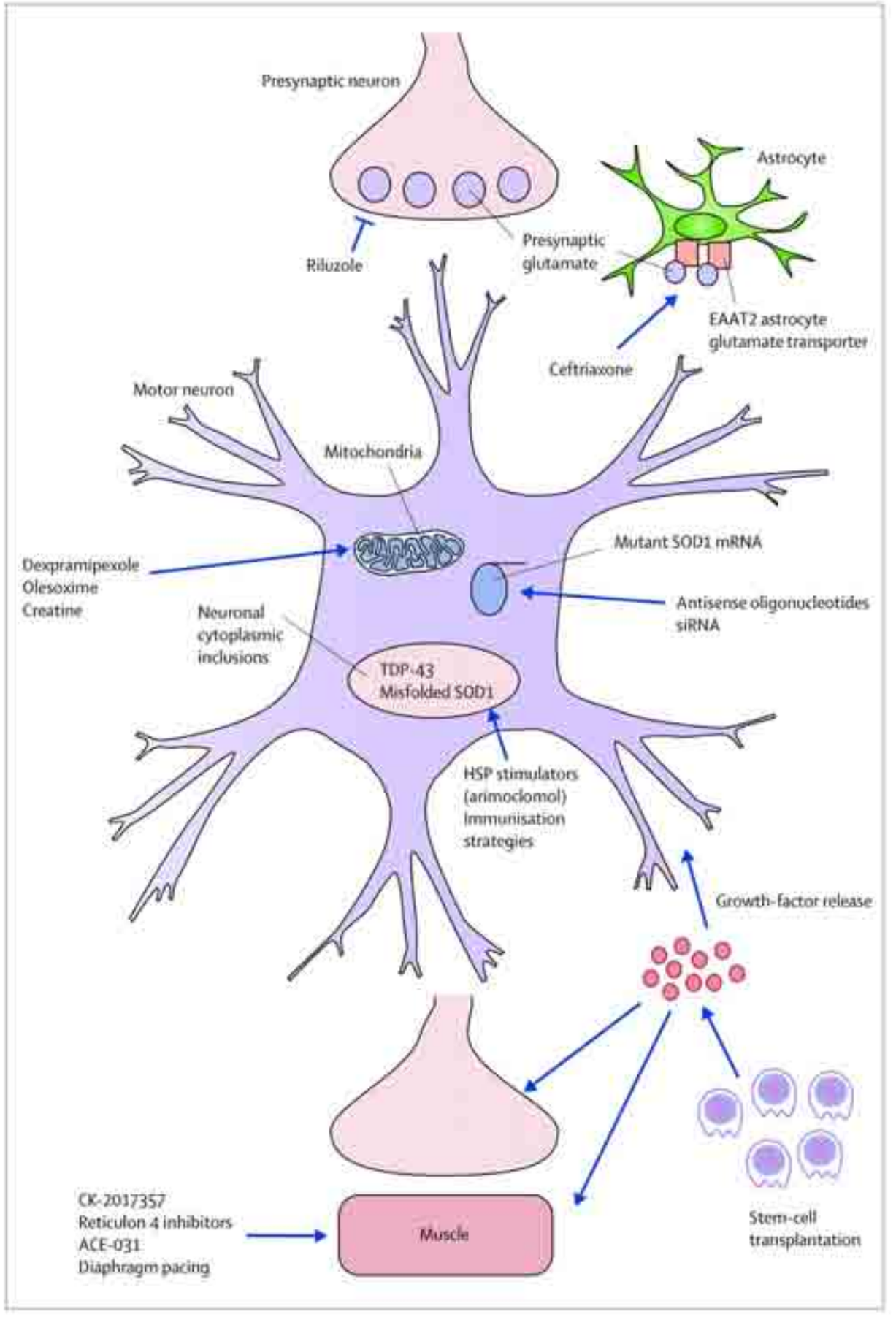


Figure 2: **Novel therapeutic targets in ALS**

Emerging targets
sclerosis

Liana Zinman, Merit Cudkowicz

Amyotrophic lateral sclerosis (AL
compounds have been tested in hi
has shown efficacy, yet it only sligh
death have led to the identification
such a wide range of innovations
potential targets that will hopefully

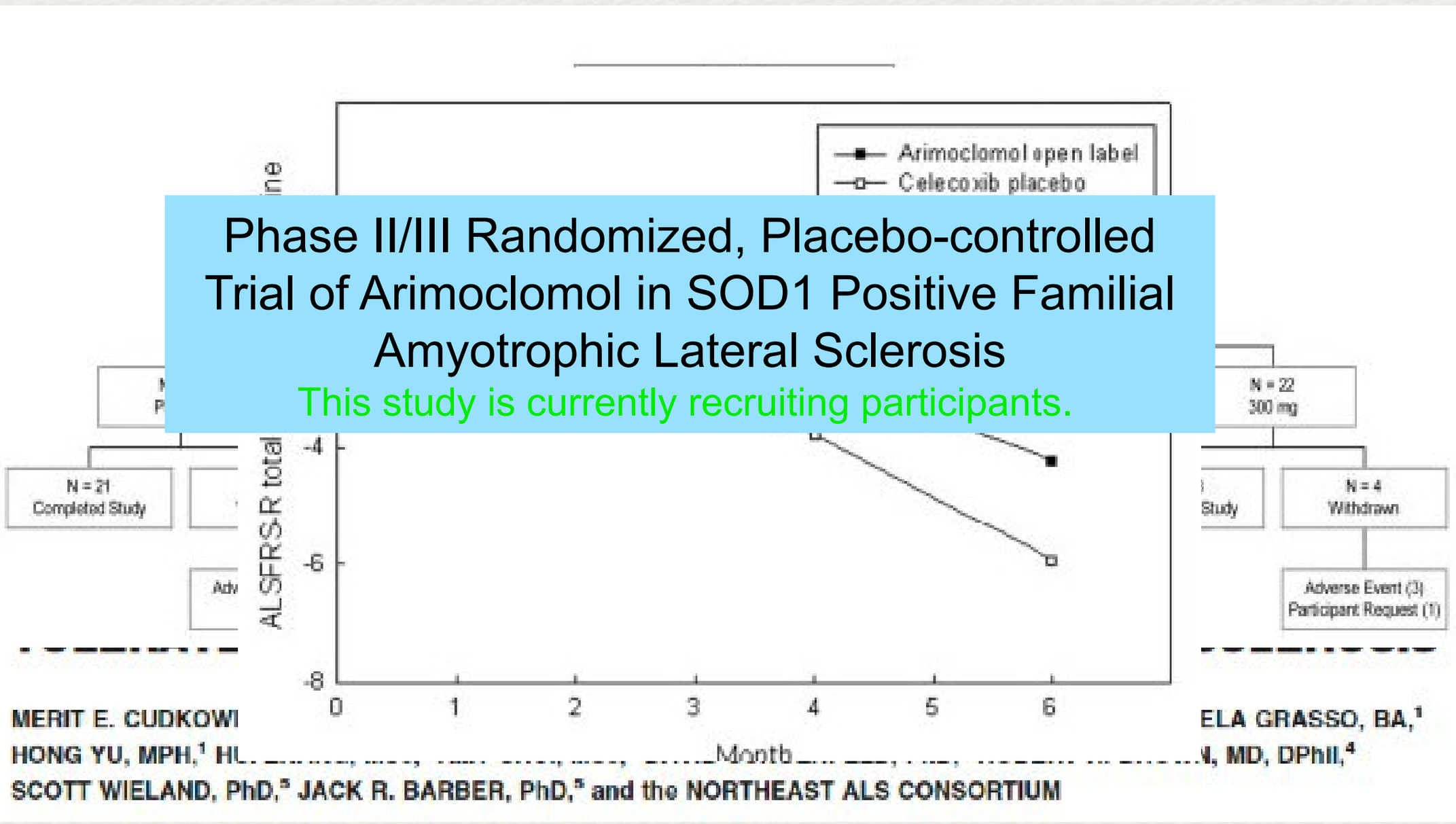
	Proposed mechanism	Stage of development	Preliminary results and comments
Glutamate targets			
Ceftriaxone[7]	Decreases synaptic glutamate	Phase 3 study	Criteria for tolerability met; study in stage 3 and more than two-thirds of patients recruited
Protein misfolding			
Arimoclomol[8]	Amplifies HSP gene expression	Phase 2/3 study in FALS	Human placebo-controlled study showed safety and CSF penetration[9]
Immunisation	Removes misfolded SOD1	Preclinical studies	Promising preclinical data in SOD1 transgenic mouse model[10–12]
RNA targets			
Antisense *SOD1* oligonucleotides (ISIS 333611)[13]	Lowers concentrations of mutant SOD1	Phase 1 study in FALS	Concentrations of mutant messenger RNA reduced with antisense oligonucleotides and small inhibitory RNA molecules, leading to slowed disease progression in the mutant *SOD1* transgenic mouse model[10–12]
Mitochondrial targets			
Olesoxime (TRO19622)[14]	Mitochondrial pore modulation	Phase2/3 study	Preclinical studies showed in-vitro and in-vivo efficacy[14]
Dexpramipexole[15]	Increases mitochondrial function	Phase 3 study	Phase 2 study of 102 patients with ALS showed safety and tolerability, and motor decline lessened and survival improved in a dose-response manner
Growth factors			
VEGF (sNN0029)[16]	Angiogenesis and neuroprotection	Phase 1/2 study of intracerebroventricular administration	Preclinical animal data showed efficacy[17,18]
Stem-cell therapy			
Bone marrow or embryonic stem cells into CNS[19–22]	Neuroprotection	Phase 1 study	For both strategies, additional preclinical and safety data required Optimum cell-type, dose, cofactor requirements, and location of transplantation unknown
iPS cells in SC	Neuroprotection	Phase 1 study pending	
Muscle targets			
Diaphragm pacing[23]	Diaphragm contraction	Phase 1 study	Safety and efficacy reported[24] FDA approval for humanitarian designation exemption pending
Skeletal muscle troponin activator (CK-2017357)[25]	Increases muscle force	Phase 2 study completed	Fatigue, strength, and pulmonary function improved in a dose-response manner[26]
GDF-8 (myostatin) inhibitor (ACE-031)[27]	Promotes muscle growth	Phase 1 study in postmenopausal women	Future studies in ALS expected
Reticulon 4 (Nogo-A) inhibitor (GSK1223249)[28]	Promotes neurite growth	Phase 1 study	Study to be completed in 2011

ALS=amyotrophic lateral sclerosis. HSP=heat shock protein. FALS=familial ALS. VEGF=vascular endothelial growth factor. iPS=induced pluripotent stem. SC=spinal cord. FDA=US Food and Drug Administration.

***Table 1*: Summary of ALS therapeutic targets being tested in clinical trials**

Phase II/III Randomized, Placebo-controlled Trial of Arimoclomol in SOD1 Positive Familial Amyotrophic Lateral Sclerosis

This study is currently recruiting participants.



MERIT E. CUDKOWI ELA GRASSO, BA,[1]
HONG YU, MPH,[1] HL ..., MD, DPhil,[4]
SCOTT WIELAND, PhD,[5] JACK R. BARBER, PhD,[5] and the NORTHEAST ALS CONSORTIUM

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An antisense oligonucleotide against *SOD1* delivered intrathecally for patients with *SOD1* familial amyotrophic lateral sclerosis: a phase 1, randomised, first-in-man study

Timothy M Miller, Alan Pestronk, William David, Jeffrey Rothstein, Erickt Simpson, Stanley H Appel, Patricia L Andres, Katy Mahoney, Peggy Allred, Katie Alexander, Lyle W Ostrow, David Schoenfeld, Eric A Macklin, Daniel A Norris, Georgios Manousakis, Matthew Crisp, Richard Smith, C Frank Bennett, Kathie M Bishop, Merit E Cudkowicz

Summary

Background Mutations in SOD1 cause 13% of familial amyotrophic lateral sclerosis. In the SOD1 Gly93Ala rat model of amyotrophic lateral sclerosis, the antisense oligonucleotide ISIS 333611 delivered to CSF decreased *SOD1* mRNA and protein concentrations in spinal cord tissue and prolonged survival. We aimed to assess the safety, tolerability, and pharmacokinetics of ISIS 333611 after intrathecal administration in patients with *SOD1*-related familial amyotrophic lateral sclerosis.

Methods In this randomised, placebo-controlled, phase 1 trial, we delivered ISIS 333611 by intrathecal infusion using an external pump over 11·5 h at increasing doses (0·15 mg, 0·50 mg, 1·50 mg, 3·00 mg) to four cohorts of eight patients with *SOD1*-positive amyotrophic lateral sclerosis (six patients assigned to ISIS 333611, two to placebo in each cohort). We did the randomisation with a web-based system, assigning patients in blocks of four. Patients and investigators were masked to treatment assignment. Participants were allowed to re-enrol in subsequent cohorts. Our primary objective was to assess the safety and tolerability of ISIS 333611. Assessments were done during infusion and over 28 days after infusion. This study was registered with Clinicaltrials.gov, number NCT01041222.

Findings Seven of eight (88%) patients in the placebo group versus 20 of 24 (83%) in the ISIS 333611 group had adverse events. The most common events were post-lumbar puncture syndrome (3/8 [38%] *vs* 8/24 [33%]), back pain (4/8 [50%] *vs* 4/24 [17%]), and nausea (0/8 [0%] *vs* 3/24 [13%]). We recorded no dose-limiting toxic effects or any safety or tolerability concerns related to ISIS 333611. No serious adverse events occurred in patients given ISIS 333611. Re-enrolment and re-treatment were also well tolerated.

Interpretation This trial is the first clinical study of intrathecal delivery of an antisense oligonucleotide. ISIS 333611 was well tolerated when administered as an intrathecal infusion. Antisense oligonucleotides delivered to the CNS might be a feasible treatment for neurological disorders.

Funding The ALS Association, Muscular Dystrophy Association, Isis Pharmaceuticals.

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See Comment page 416

Washington University School of Medicine, St Louis, MO, USA (T M Miller MD, Prof A Pestronk MD, G Manousakis MD, M Crisp BSc); Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA (W David MD, P L Andres MS, K Mahoney BA, P Allred DNP, Prof D Schoenfeld PhD, E A Macklin PhD, Prof M E Cudkowicz MD); Johns Hopkins University School of Medicine, Baltimore, MD, USA (Prof J Rothstein MD, L W Ostrow MD); Methodist Neurological Institute, Houston, TX, USA (E Simpson MD, Prof S H Appel MD); Center for Neurologic Study, La Jolla, CA, USA (R Smith MD); and Isis Pharmaceuticals, Carlsbad, CA, USA (K Alexander BA, D A Norris PhD, C F Bennett PhD, K M Bishop PhD)

Correspondence to:
Dr Timothy M Miller, Washington University, 315 Bernard Building, Box 8111, 660 S Euclid, St Louis, MO 63110, USA
millert@neuro.wustl.edu

Introduction

Our knowledge of the genetic basis of many neurodegenerative diseases has progressed greatly in the past 20 years. Causative mutations have been identified for Huntington's disease, spinal muscular atrophy, spinal and bulbar muscular atrophy, Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.[1] The challenge now is to turn this knowledge into effective treatments. For dominantly inherited disorders in which a mutant protein becomes toxic, reducing the concentration of the protein is a potential approach and antisense oligonucleotides are one means of doing so.[2] Antisense oligonucleotides are short, synthetic nucleic acids that have been chemically modified to increase their stability in biological fluids and their potency in binding their mRNA target. One mechanism by which antisense oligonucleotides function is by binding to a specific target mRNA through Watson-Crick base-pairing and causing degradation of the mRNA by activation of the nuclear enzyme RNase H.[3] Because antisense oligonucleotides do not cross the blood-brain barrier,[4] they must be delivered directly to the CNS to treat neurodegenerative diseases. One possible approach is to administer them intrathecally into the CSF, which results in widespread delivery to the CNS.[4,5]

Genetic changes in more than ten genes are known to cause familial amyotrophic lateral sclerosis, an adult-onset neurodegenerative disease characterised by loss or dysfunction of both upper and lower motor neuron pathways[6] and in some cases dementia. Mutations in *SOD1* account for roughly 2% of all cases of amyotrophic lateral sclerosis. Although such mutations were identified almost 20 years ago, no treatments exist that substantially slow either the sporadic or *SOD1*-linked forms of amyotrophic lateral sclerosis. Different *SOD1* mutations are associated with different ages of onset and rates of progression, and nearly all are inherited dominantly.[6] The toxicity of *SOD1* is the result of a gain of toxic function rather than a loss of enzymatic function; thus, reducing concentrations of the mutant protein

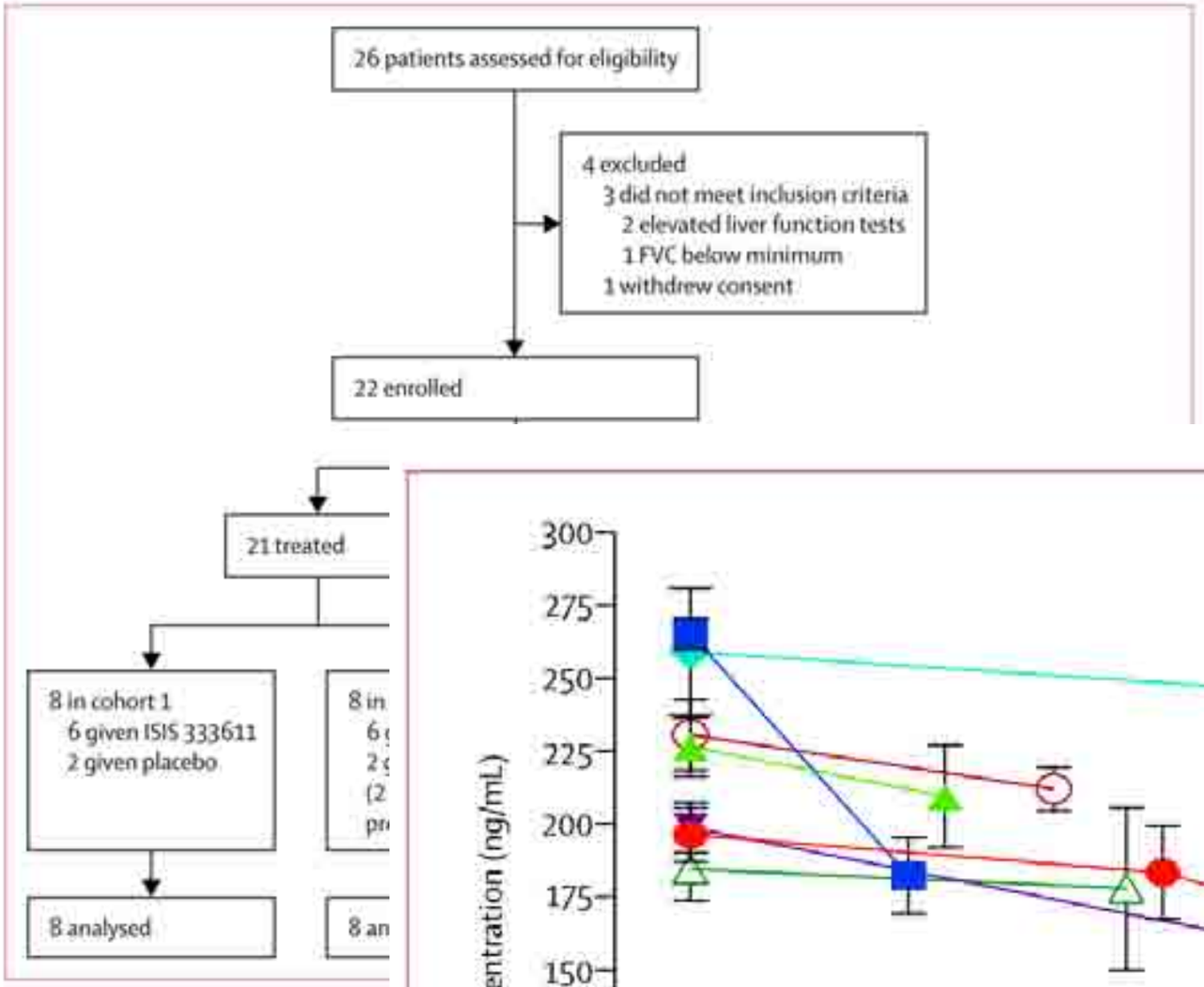


Figure 1: **Trial profile**
FVC=forced vital capacity. *Not treate

	Sex	Age (years)	Family history of amyotrophic lateral sclerosis	SOD1 mutation	Age at onset (years)	Site of onset
1	Female	49	Yes	Glu49Lys	47	Limb
2	Male	59	Yes	Ala4Val	59	Limb
3	Female	36	Yes	Gly37Arg	23	Limb
4	Male	41	Yes	Ala4Thr	41	Limb
5	Male	47	Yes	Leu38Val	45	Limb
6	Male	51	Yes	Ile113Thr	47	Limb
7	Female	50	Yes	Ala4Val	50	Limb
					58	Limb
					63	Limb
					51	Limb
					45	Limb
					48	Limb
					42	Limb
					43	Limb
					45	Limb
					46	Bulbar
					22	Limb
					55	Limb
					43	Limb
					37	Limb
					45	Limb

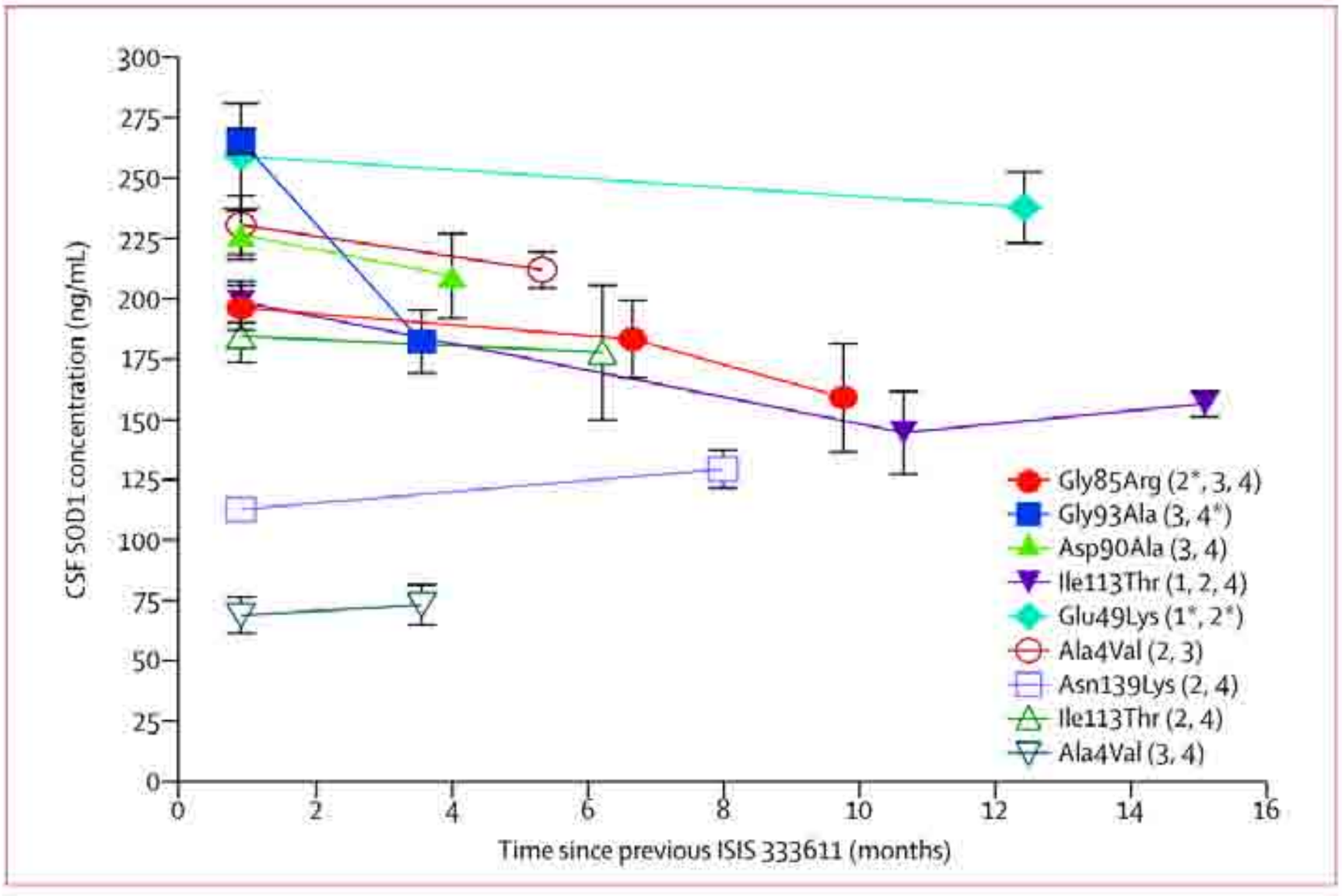


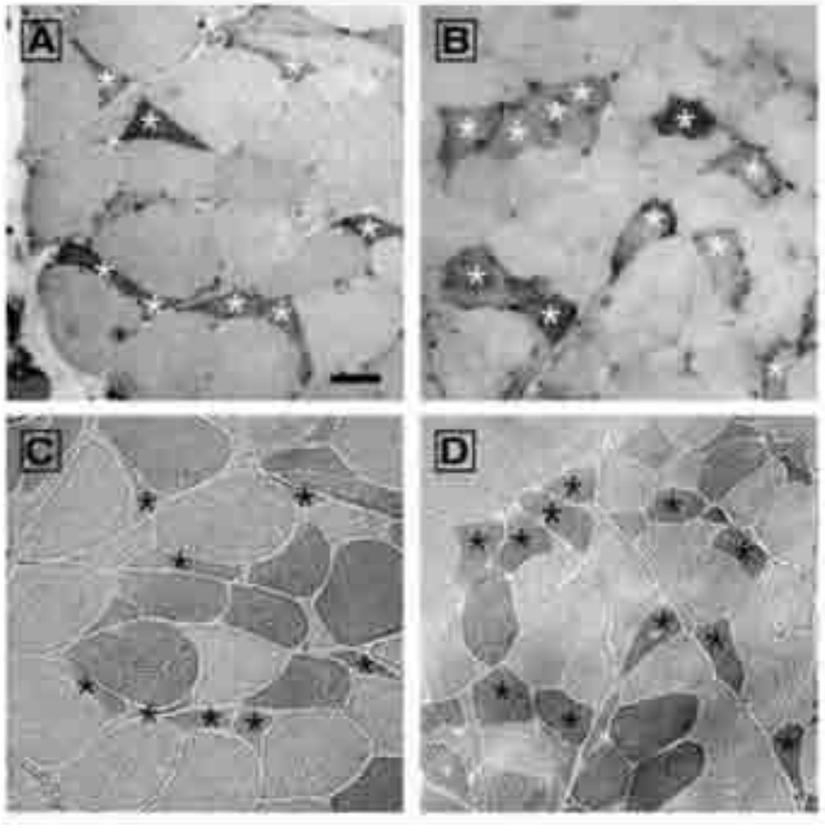
Figure 3: **SOD1 protein concentrations in CSF of patients enrolled in more than one cohort**
Measured by ELISA. SOD1 mutation and cohort number are shown for each patient. *Placebo group for that cohort.

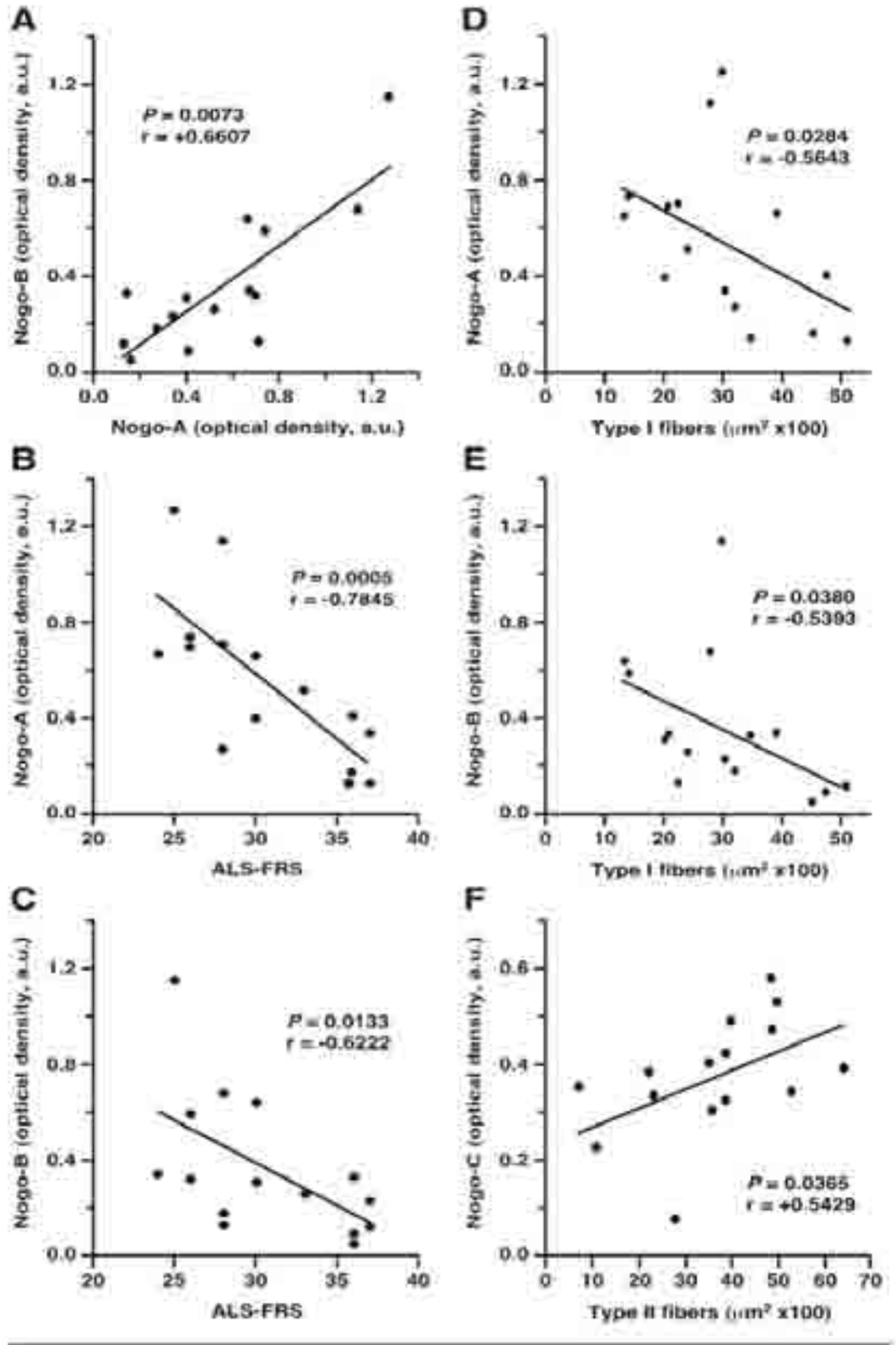
Nogo Expression in Muscle Correlates with Amyotrophic Lateral Sclerosis Severity

Natasa Jokic, MSc,[1] Jose-Luis Gonzalez de Aguilar, PhD,[1] Pierre-François Pradat, MD, PhD,[2] Luc Dupuis, PhD,[1] Andoni Echaniz-Laguna, MD,[1,3] André Muller, MD, PhD,[1,4] Odile Dubourg, MD, PhD,[5] Danielle Seilhean, MD, PhD,[5] Jean-Jacques Hauw, MD, PhD,[5] Jean-Philippe Loeffler, PhD,[1] and Vincent Meininger, MD, PhD[2]

Nogo, a protein inhibiting axonal regeneration, exhibits a characteristic isoform-specific pattern of expression in skeletal muscle of transgenic mice and patients with amyotrophic lateral sclerosis. Here, the increased levels of Nogo-A or Nogo-B in muscle biopsies of 15 amyotrophic lateral sclerosis patients significantly correlated with the severity of clinical disability and with the degree of muscle fiber atrophy. Nogo-A immunoreactivity was observed selectively in atrophic slow-twitch type I fibers. These results suggest that Nogo expression in muscle is a marker of amyotrophic lateral sclerosis severity.

Ann Neurol 2005;57:553–556





Study of Ozanezumab (GSK1223249) Versus Placebo in the Treatment of Amyotrophic Lateral Sclerosis

This study is currently recruiting participants.

Verified June 2013 by GlaxoSmithKline

Sponsor:
GlaxoSmithKline

Information provided by (Responsible Party):
GlaxoSmithKline

ClinicalTrials.gov Identifier:
NCT01753076

First received: December 17, 2012
Last updated: June 27, 2013
Last verified: June 2013
History of Changes

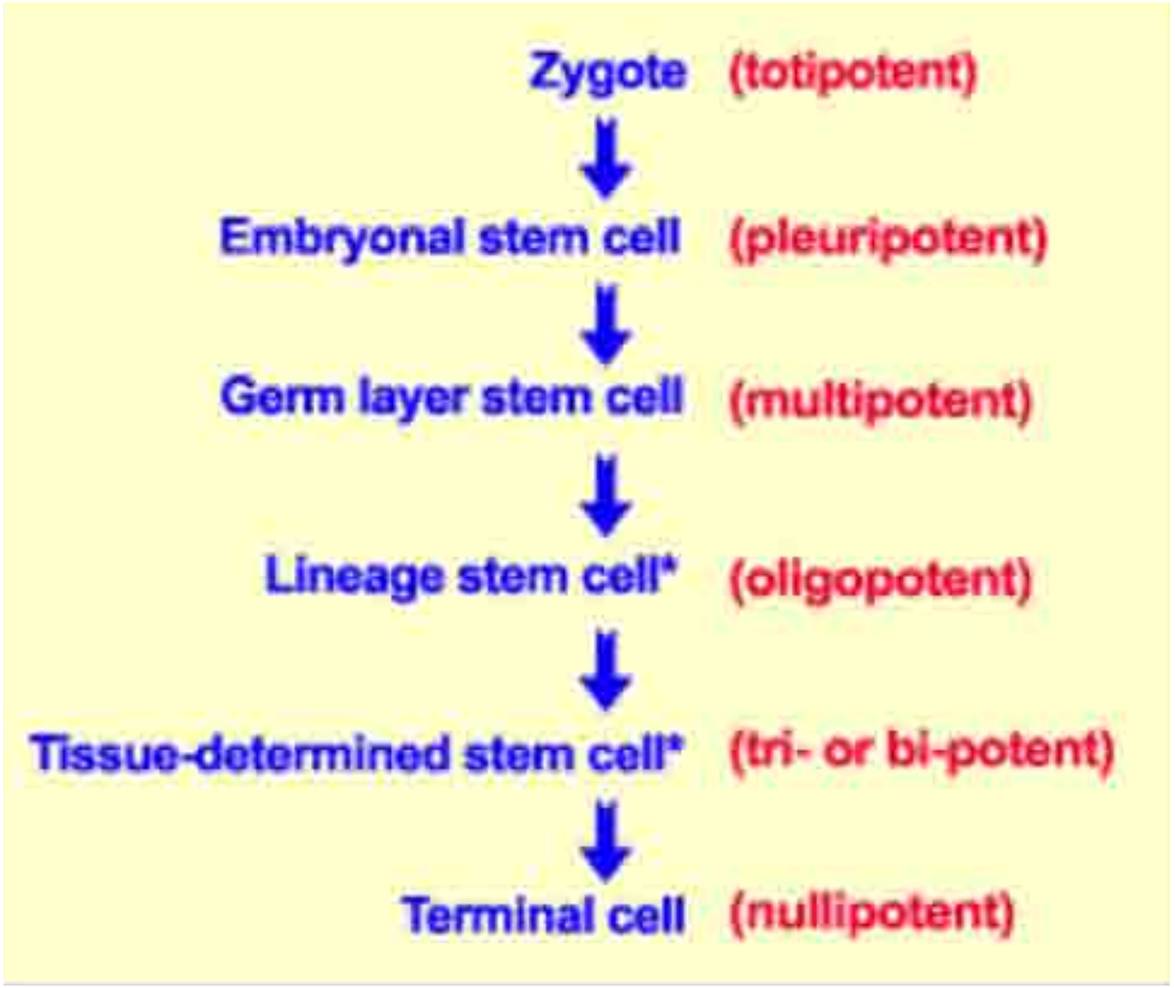
Purpose

This is a 48-week, randomised, multi-centre, double-blind, placebo-controlled, parallel group investigation of the efficacy and safety of intravenous (IV) **ozanezumab** (GSK1223249) compared to placebo in subjects with Amyotrophic Lateral Sclerosis (ALS). Following a screening period of up to four weeks, eligible subjects will be randomised (1:1) to receive IV placebo or 15 milligram (mg)/ kilogram (kg) IV **ozanezumab** every 2 weeks for a

Cellule staminali

Stem cells are unspecialized cells that have two defining properties:
1.the ability to differentiate into other cells
2.the ability to self-regenerate.

The ability to differentiate is the potential to develop into other cell types.
A **totipotent stem cell** (e.g. fertilized egg) can develop into all cell types including the embryonic membranes.
A **pleuripotent stem cell** can develop into cells from all three germinal layers (e.g cells from the inner cell mass).
Other cells can be **oligopotent**, **bipotent** or **unipotent** depending on their ability to develop into few, two or one other cell type(s).

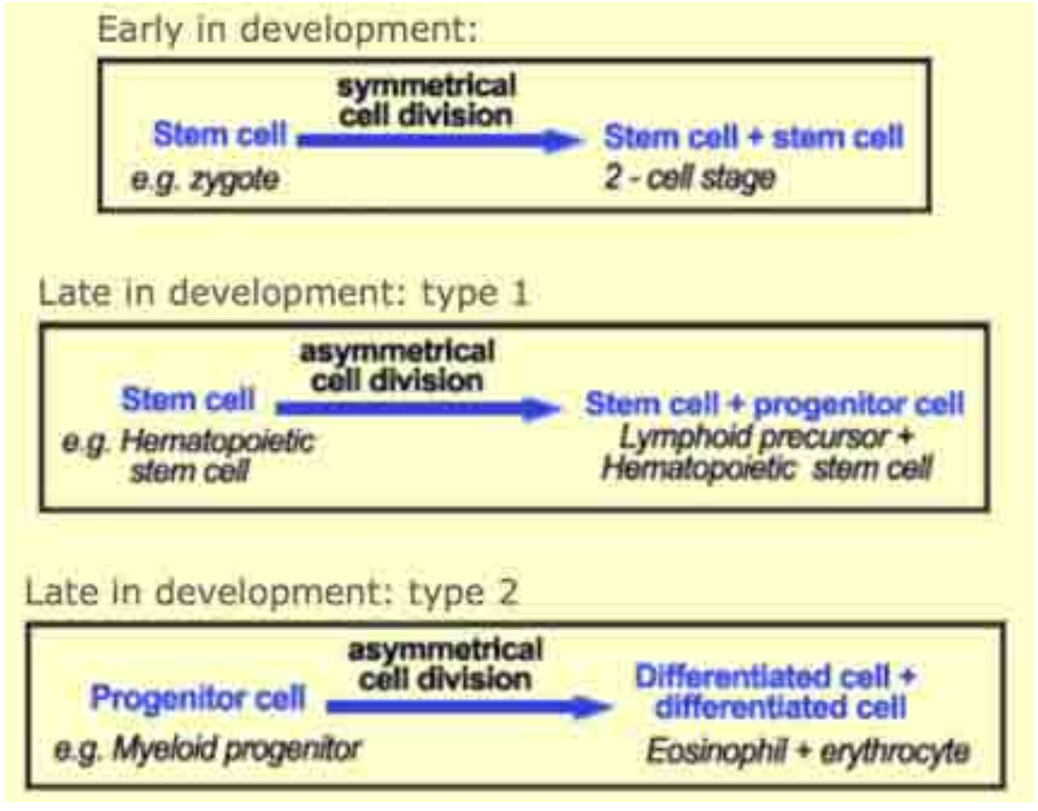


Sell, S. (2004) Stem cells. Stem Cell Handbook ed. by Sell, S. 1-18

Mesenchymal progenitor cell

Stem cells are unspecialized cells that have two defining properties:
1.the ability to differentiate into other cells
2.the ability to self-regenerate.

Self-regeneration is the ability of stem cells to divide and produce more stem cells. During early development, the cell division is symmetrical i.e. each cell divides to gives rise to daughter cells each with the same potential. Later in development, the cell divides asymmetrically with one of the daughter cells produced also a stem cell and the other a more differentiated cell.



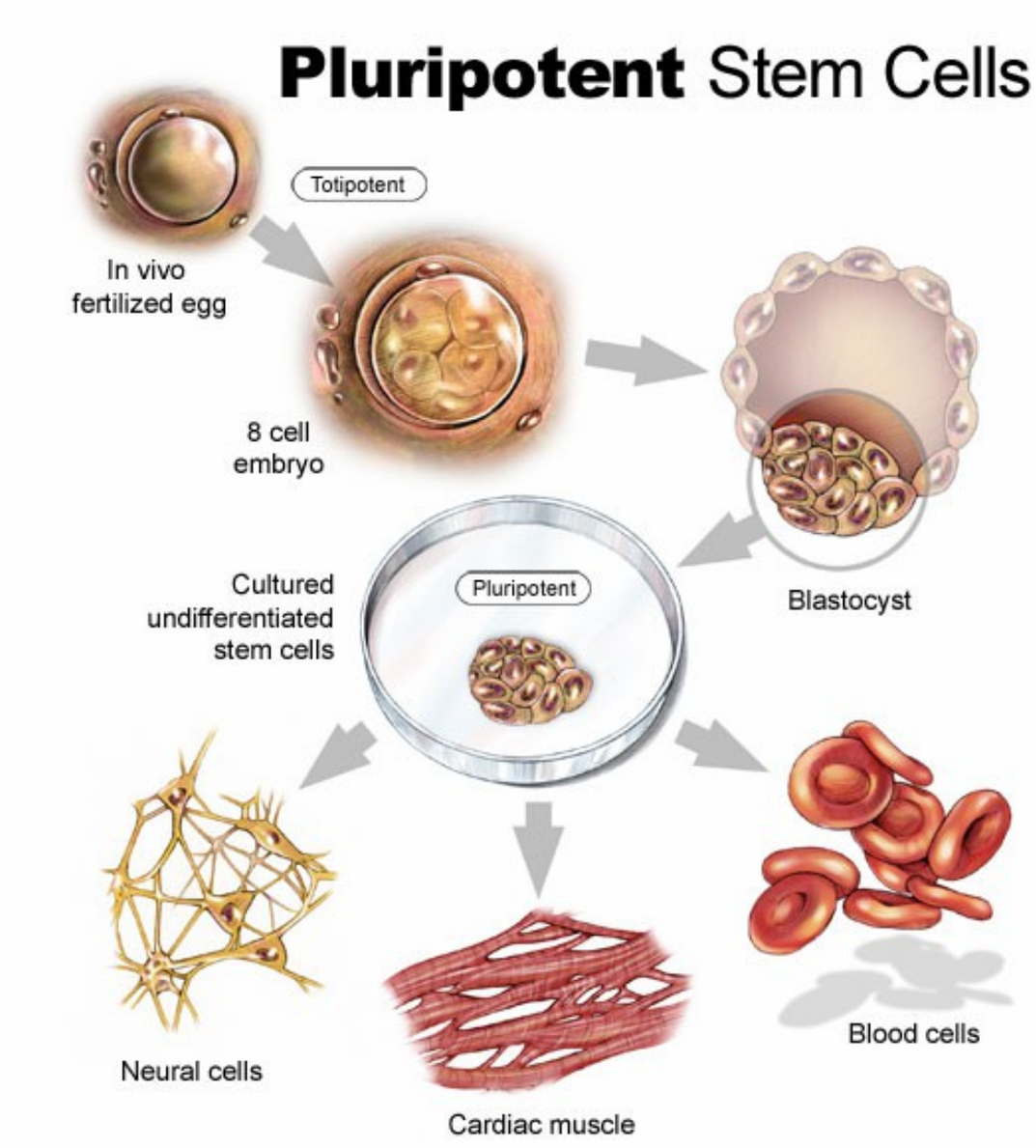
Lindblad, W.J. (2004) Stem cells in Dermal Wound Healing. Stem Cell Handbook ed. by Sell, S. 101-105.

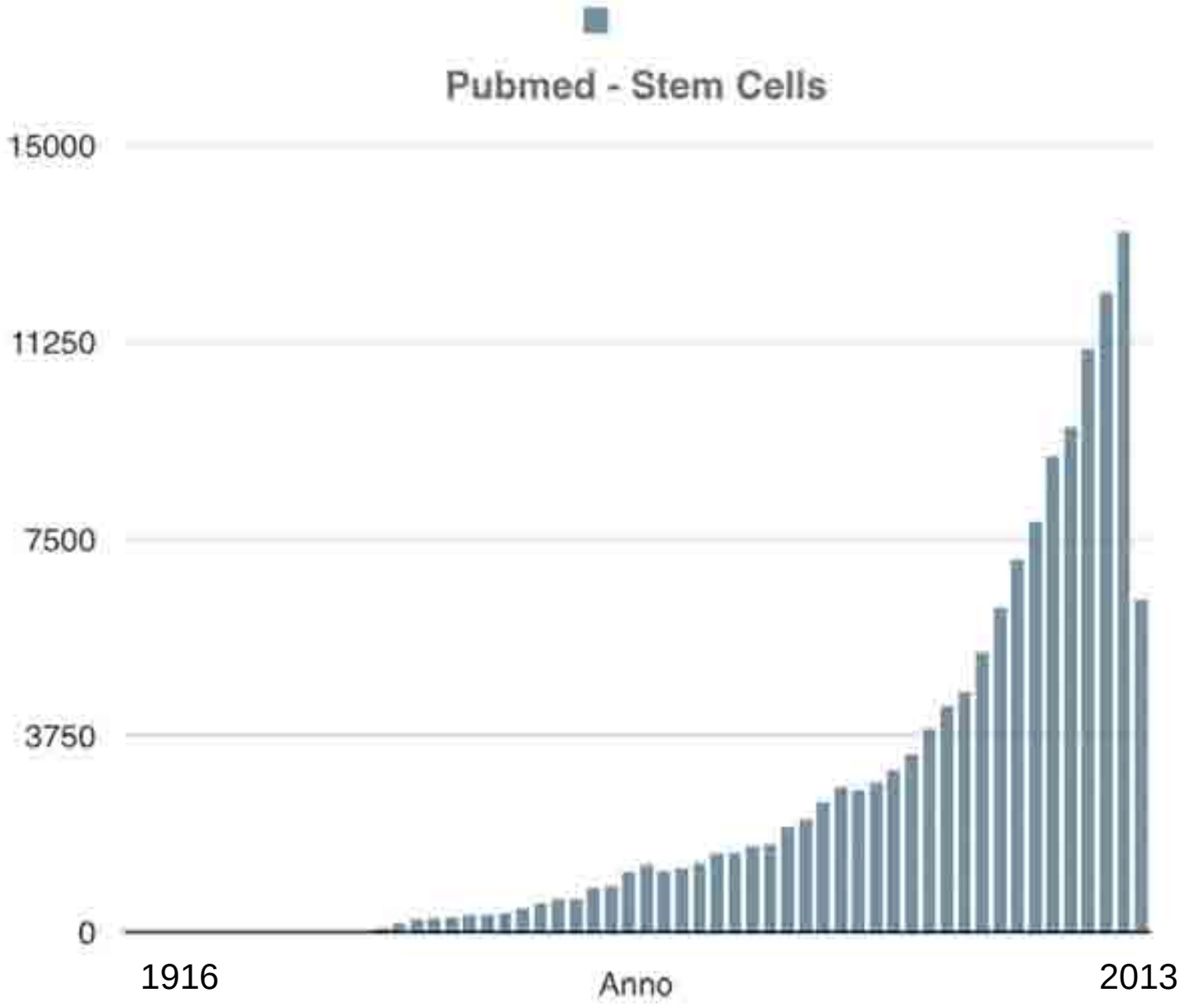
McCulloch, E.A. (2004) Normal and Leukemic Hematopietic Stem cells and Lineages. Stem Cell Handbook ed. by Sell, S. 119-131.

Stem cells have the remarkable potential to develop into many different cell types in the body **during early life** and **growth**.

In addition, in many tissues they serve as a sort of **internal repair system**, dividing essentially without limit to replenish other cells as long as the person or animal is still alive

In some organs, such as the **gut** and **bone marrow**, stem cells regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the **pancreas** and the **heart**, stem cells only divide under special conditions.





1981: Scientists discovered ways to derive embryonic stem cells from early mouse embryos.
1998: method to derive stem cells from human embryos and grow the cells in the laboratory (as called human embryonic stem cells).
2006: researchers made another breakthrough by identifying conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state (as called induced pluripotent stem cells or iPSCs)

Stem cells in ALS

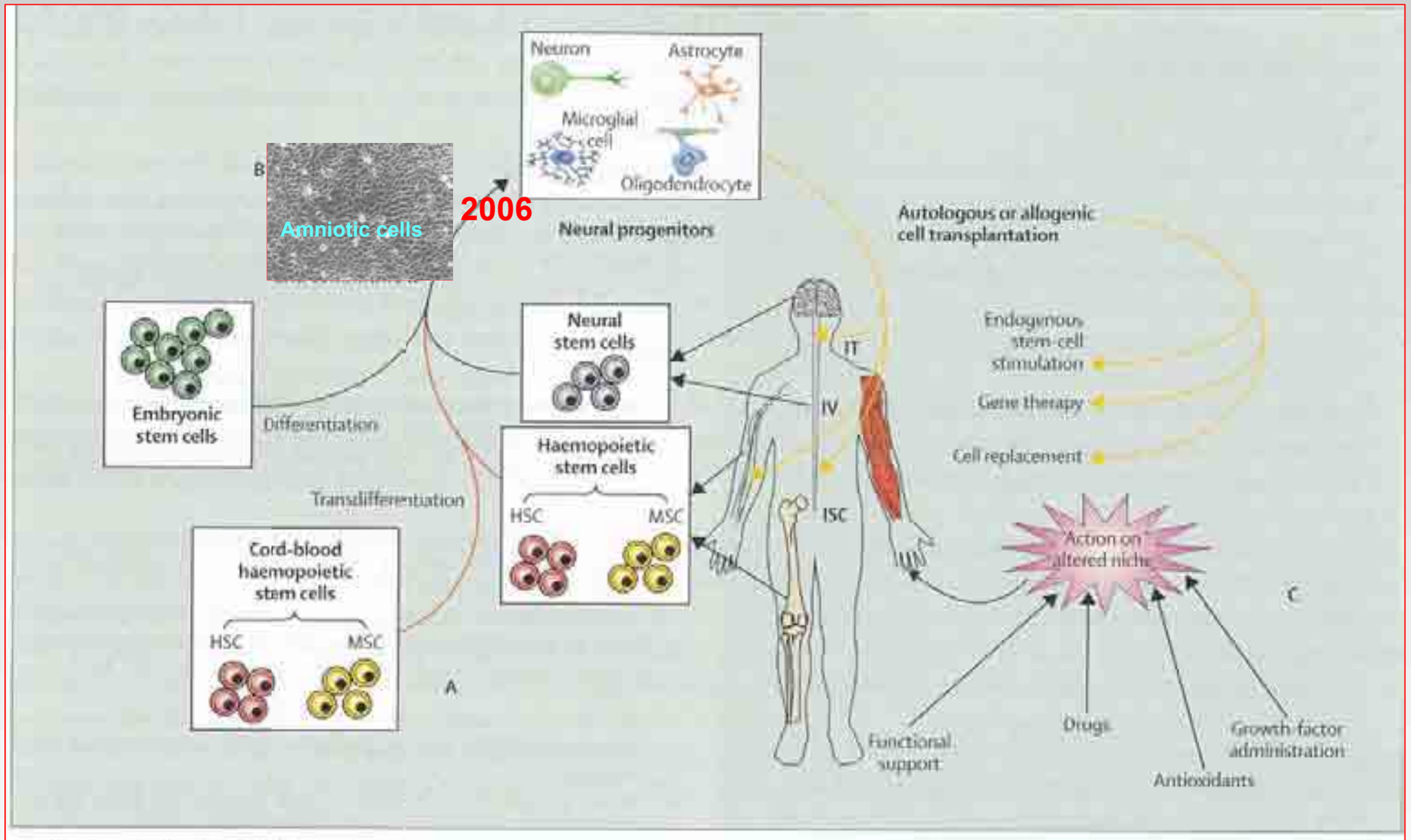


Figure: **Stem-cell therapy in ALS**
Effective stem-cell therapy in ALS requires complex strategy with several molecular and cellular techniques. In-primis donor-cell source (autologous vs allogeneic) and stem-cell choice (neuronal vs non-neural) should be carefully evaluated (A), and stem cells maintained and amplified in vitro without altering their properties (B). Before transplantation, stem cells have to be transdifferentiated (if non-neural) and committed towards neural phenotypes, and eventually genetically modified for release of trophic factors. Permissive niche (combining drugs, artificial extramatrix proteins, antioxidants, stimulation of endogenous stem cells, infusion of trophic factors) will increase graft survival and integration into damaged tissues of host (C). (Re)injection site or route and patient's selection will influence post-transplantation recovery. HSC=haemopoietic stem cells, MSC=mesenchymal stem cells, IV=intravenous, IT=intrathecal, ISC=intraspinal cord.

Silani et al., Lancet, 2004

Allogeneic or Autologous transplantation

PRO

Allogeneic transplantation using donor stem cells has a seemingly better potential for neuronal repair, as in such a setting the transplanted stem cells **do not carry the putative genetic defects** which may be involved in the pathogenesis of the disease to be treated. In addition, they may actually provide the vehicles **for transfer of normal genes in genetic syndromes**. Aside from small studies on hematopoietic stem cells, there are very limited clinical data on allogeneic stem cell transplantation in the literature. In a pioneering study [48], infusion of allogeneic MSC in patients with Hurler syndrome (mucopolysaccharidosis type-IH) or metachromatic leukodystrophy did not reveal any toxic effects and, despite no apparent clinical change, appeared to improve nerve conduction velocities.

CONS

The obvious disadvantage of such an allogeneic approach is the **risk of rejection of the transplanted stem cells** and the possible **need for additional chemotherapy/immunosuppression** to improve long-term cell viability. This problem seems to be less prominent in the case of embryonic stem cells since these cells may be immune-privileged at a signi f cant degree.

The vast majority of the available clinical data comes from trials with autologous stem cells.

Replacing lost neurons or glial cells by transplantation of stem cell–derived cells

Inducing endogenous SCs in the adult CNS to form new neurons and glial cells

Stem cell–based approaches to restore function in neurodegenerative disease

Using stem cells and their derivatives to release therapeutic molecules that are neuroprotective or modulate inflammation

Review series

Stem cells in human neurodegenerative disorders — time for clinical translation?

Olle Lindvall[1,2] and Zaal Kokaia[2,3]

[1]Laboratory of Neurogenesis and Cell Therapy, Wallenberg Neuroscience Center, University Hospital, Lund, Sweden.
[2]Lund Stem Cell Center, Lund, Sweden. [3]Laboratory of Neural Stem Cell Biology and Therapy, University Hospital, Lund, Sweden.

Stem cell–based approaches have received much hype as potential treatments for neurodegenerative disorders. Indeed, transplantation of stem cells or their derivatives in animal models of neurodegenerative diseases can improve function by replacing the lost neurons and glial cells and by mediating remyelination, trophic actions, and modulation of inflammation. Endogenous neural stem cells are also potential therapeutic targets because they produce neurons and glial cells in response to injury and could be affected by the degenerative process. As we discuss here, however, significant hurdles remain before these findings can be responsibly translated to novel therapies. In particular, we need to better understand the mechanisms of action of stem cells after transplantation and learn how to control stem cell proliferation, survival, migration, and differentiation in the pathological environment.

Stem cells in human neurodegenerative disorders — time for clinical translation?

Olle Lindvall[1,2] and Zaal Kokaia[2,3]

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[2]Lund Stem Cell Center, Lund, Sweden. [3]Laboratory of Neural Stem Cell Biology and Therapy, University Hospital, Lund, Sweden.

four main issues

First, it is necessary to def ne what is required for the stem cell–based approach to be clinically competitive and what risks to the patient are acceptable.

Second, disease pathology has to determine which cells should be generated from stem cells; for cell replacement therapy, different cells will be needed for different diseases. **Disease pathology may also affect the cells derived from the transplanted cells,** as has been observed in intrastriatal grafts of embryonic mes- encephalic tissue more than a decade after they were implanted in PD patients

Third, prior to clinical application, it must be **demonstrated in animal models** that the stem cell–based approach induces substantial improvement of functional def cits that resemble the debilitating symptoms in patients.

Last, it is important **to determine the biological mechanism** underlying the observed effects of a stem cell–based treatment in an animal model.

Healthy transplanted cells cross talk with the surroundings may be compromised by the abnormal cellular RNA metabolism, able to trigger MN degeneration, thus impeding any therapeutic outcomes related to Stem Cells.

In this case, no SC strategy could maintain positive therapeutic outcomes in the long term, without a supportive treatment able to prevent the spread of the disease

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Study	Phase	Number of Pts	Stem Cell Type	Conclusion
Karussis D et al. **Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis.** *Arch Neurol* 2010	I/II	19	autologous mesenchymal stem cells (intrathecal and intravenous administration)	Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects.
Mazzini L et al. **Mesenchymal stem cell transplantation in amyotrophic lateral sclerosis: A Phase I clinical trial.** *Exp Neurol* 2010	I	10	autologous MSC isolated from bone marrow (implanted into the dorsal spinal cord)	MSC transplantation into the spinal cord of ALS patients is safe and that MSCs might have a clinical use for future ALS cell based clinical trials
Martinez HR et al. **Stem-cell transplantation into the frontal motor cortex in amyotrophic lateral sclerosis patients.** *Cytotherapy* 2009	I/II	10	autologous transplantation of CD133(+) stem cells (implanted in motor cortexes)	The autologous transplantation of CD133(+) stem cells into the frontal motor cortex is as afe and well-tolerated procedure in ALS patients. The survival of treated patients was statistically higher (P=0.01) than untreated control patients
Deda H. **Treatment of amyotrophic lateral sclerosis patients by autologous bone marrow-derived hematopoietic stem cell transplantation: a 1-year follow-up.** *Cytotherapy* 2009	I	13	bone marrow (BM)-derived hematopoietic progenitor stem cells (intraspinal infusion)	During the follow-up of 1 year after stem cell implantation, nine patients became much better compared with their pre-operative status, confirmed ENMG. Three patients died 1.5, 2 and 9 months, respectively, after stem cell therapy as a result of lung infection and myocardial infarction.
Appel SH et al. **Hematopoietic stemcell transplantation in patients with sporadic amyotrophic lateral sclerosis.** *Neurology* 2009	I/II	6	Allogeneic hematopoietic stem cell transplantation (peripheral blood infusion)	Hematopoietic stem cells can enter the human CNS, primarily at sites of motoneuron pathology and engraft as immunomodulatory cells. Although unmodified hematopoietic stem cells did not benefit
Mazzini L et al. **Stem cell treatment in Amyotrophic Lateral Sclerosis.** *J Neurol Sci* 2008	I	9	autologous MSC isolated from bone marrow (implanted into the dorsal spinal cord)	Four patients show as gnificant slowing down of the linear decline of the forced vital capacity and of the ALS-FRS score. Intraspinal injection of MSCs is safe also in the long term
Mazzini L et al. **Autologous mesenchymal stem cells: clinical applications in amyotrophic lateral sclerosis.** *Neurol Res* 2006	I	9	autologous bone marrow mononuclear cells (**intraspinal infusion**)	direct injection of autologous expanded MSCs into the spinal cord of ALS patients is safe, with no significant acute or late toxicity, and well tolerated
Mazzini L et al. **Stem cell therapy in amyotrophic lateral sclerosis: a methodological approach in humans.** *Amyotroph Lateral Scler Other Motor Neuron Disord* 2003		9	autologous bone marrow mononuclear cells (**intraspinal infusion**)	the procedures of ex vivo expansion of autologous mesenchymal stem cells and of transplantation into the spinal cord of humans are safe and well tolerated by ALS patients.

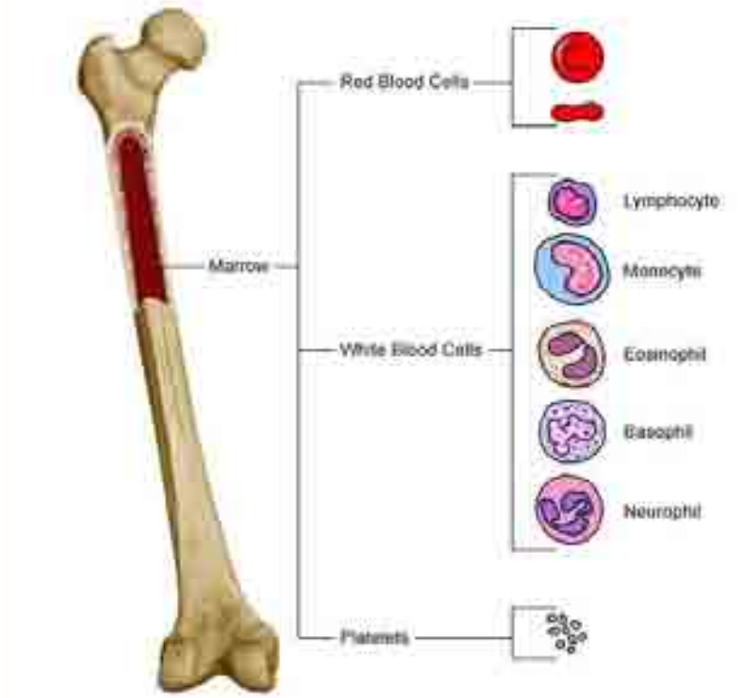
Study	Phase	Number of Pts	Stem Cell Type	Conclusion
Riley J et al. **Intraspinal stem cell transplantation in ALS**.. *Neurosurgery.* **2012**	I	12	neural stem cell-based treatment from a fetal spinal cord (intraspinal infusion)	the procedural of unilateral and bilateral intraspinal lumbar microinjection was safety
Moviglia GA et l. **Feasibility, safety, and preliminary proof of principles of autologous neural stem cell treatment combined with T-cell vaccination for ALS patients**. *Cell Transplant.* **2012**	I	7	autologous neural stem cell treatment	TCV in conjunction with an autologous neural stem cell treatment might be a feasible, minimally invasive, safe, and effective approach to obtain enduring therapeutic effects in ALS patients.
Blanquer M et al. **Neurotrophic bone marrow cellular nests prevent spinal motoneuron degeneration in amyotrophic lateral sclerosis patients: a pilot safety study**. *Stem Cells.* **2012**	I	11	autologous bone marrow mononuclear cells (intraspinal infusion)	This clinical trial confirms not only the safety of intraspinal infusion of autologous BMNC in ALS patients but also provides evidence strongly suggesting their neurotrophic activity
Glass JD et al. **Lumbar intraspinal injection of neural stem cells in patients with amyotrophic lateral sclerosis: results of a phase I trial in 12 patients**. *Stem Cells.* **2012**	I	12	neural stem cell-based treatment from a fetal spinal cord **(intraspinal infusion)**	These results allow us to report success in achieving the phase I goal of demonstrating safety of this therapeutic approach.
Mazzini L et al. **Mesenchymal stromal cell transplantation in amyotrophic lateral sclerosis: a long-term safety study.** *Cytotherapy.* **2012**	I	19	autologous MSC isolated from bone marrow (implanted into the dorsal spinal cord)	safety of MSC transplantation in the central nervous system during a follow-up of nearly 9 years
Prabhakar S. **Autologous bone marrow-derived stem cells in amyotrophic lateral sclerosis: a pilot study.** *Neurol India.* **2012**	I	10	autologous bone marrow-derived stem cells (intrathecal administration)	Autologous bone marrow-derived stem cell therapy is safe and feasible in patients of ALS. Short-term follow-up of ALSFRS-R scores suggests a trend towards stabilization of disease.
Baek W. **Stem cell transplantation into the intraventricular space via an Ommaya reservoir in a patient with amyotrophic lateral sclerosis**. J Neurosurg Sci. 2012	I	1	autologous mesenchymal stromal cells **(intraventricular injection)**	the procedure is safe and viable.
Blanquer M et al. **Bone marrow stem cell transplantation in amyotrophic lateral sclerosis.** *Methods Find Exp Clin Pharmacol.* **2010**	I/II	patients with bulbar onset	autologous bone marrow mononuclear cells **(intraspinal infusion)**	the procedure is safe and viable.

ORIGINAL ARTICLE
Year : 2012 | Volume : 60 | Issue : 5 | Page : 465-469

Autologous bone marrow-derived stem cells in amyotrophic lateral sclerosis: A pilot study

Sudesh Prabhakar[1], Neelam Marwaha[2], Vivek Lal[1], Ratti R Sharma[2], Roopa Rajan[1], Niranjan Khandelwal[3]
[1] Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[2] Department of Transfusion Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India
[3] Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh, India

intrathecal infusion



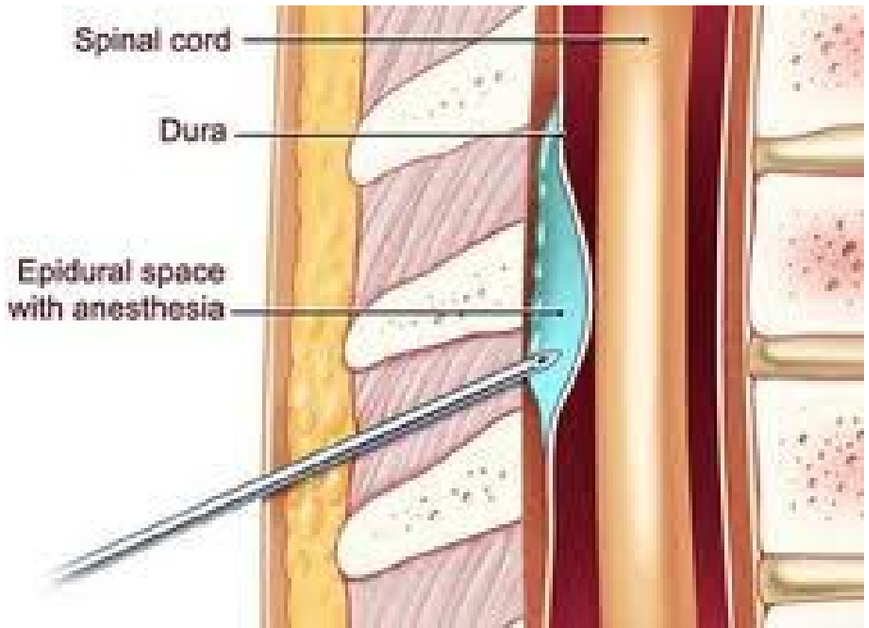


Table 1: Baseline characteristics of patients receiving intrathecal autologous bone marrow-derived stem cells

Variable	
Age (years)	49.1 (± 15.3)
Female (n)	7
Clinically definite ALS (n)	6
Bulbar onset ALS (n)	3
Median duration of illness (months)	16 (range: 3- 48)
ALSFRS-R composite score	32.2 (± 10.6)

Table 2: Bone marrow volumes and cytological characteristics

Parameter	Mean value (SD)
Bone marrow aspirate volume (ml)	103 (± 12.8)
Mononuclear cell concentrate volume (ml)	4.7 (± 1.6)
Mononuclear cell count (n)	1.81×10^8 ($\pm 0.92 \times 10^8$)
Viability (%)	91.4 (± 2.6)
CD34+ cell count (n)	3.44×10^6 ($\pm 1.58 \times 10^6$)

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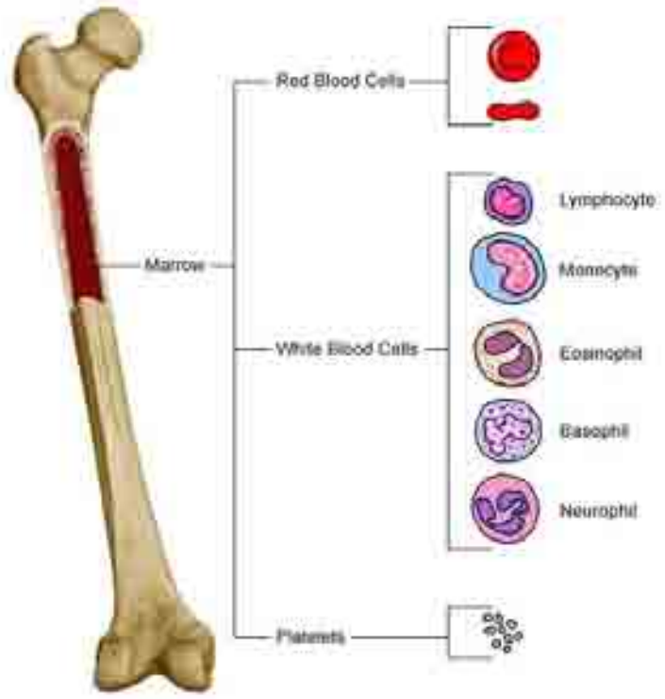


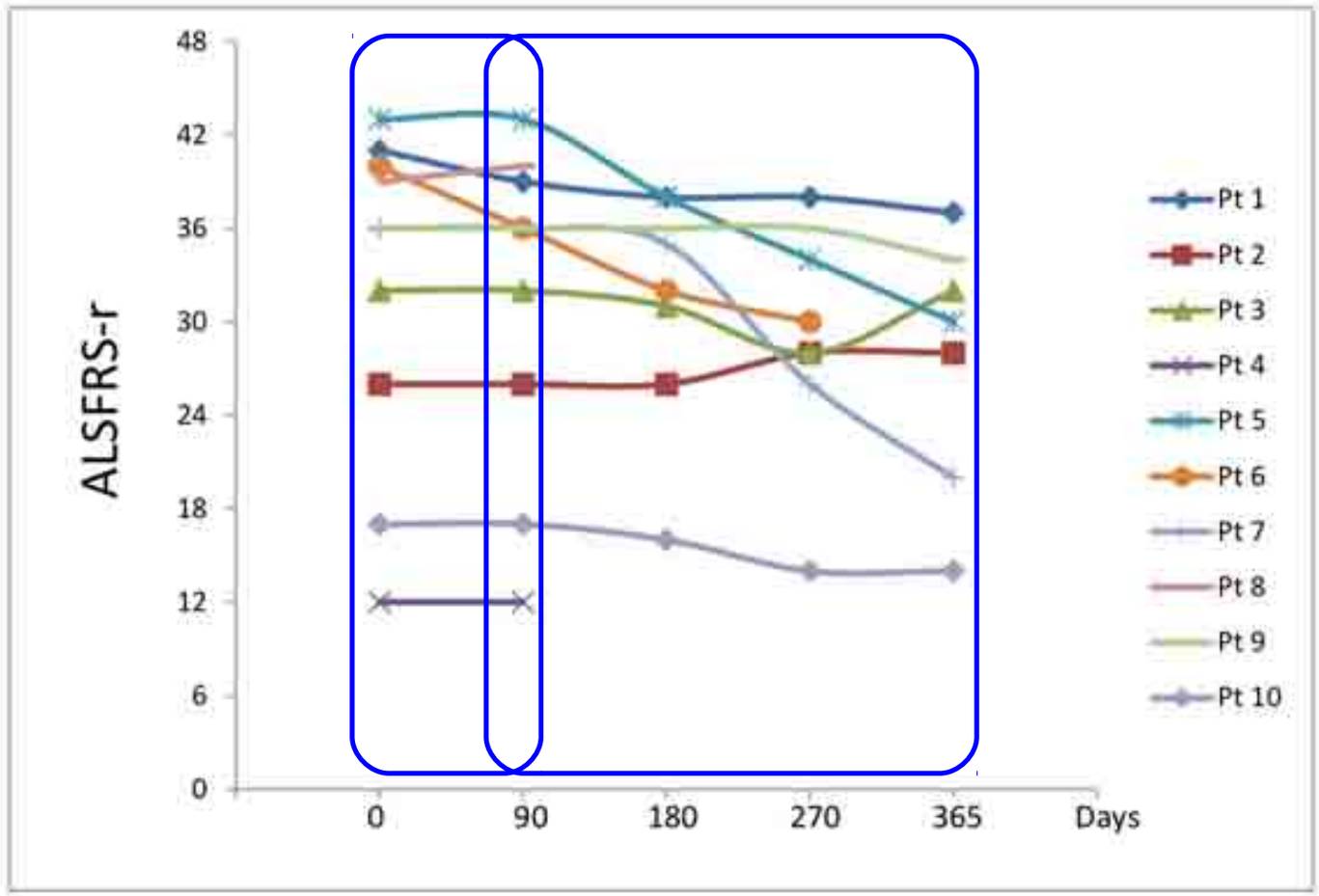


Table 4: Composite ALSFRS-R scores at follow-up compared to baseline

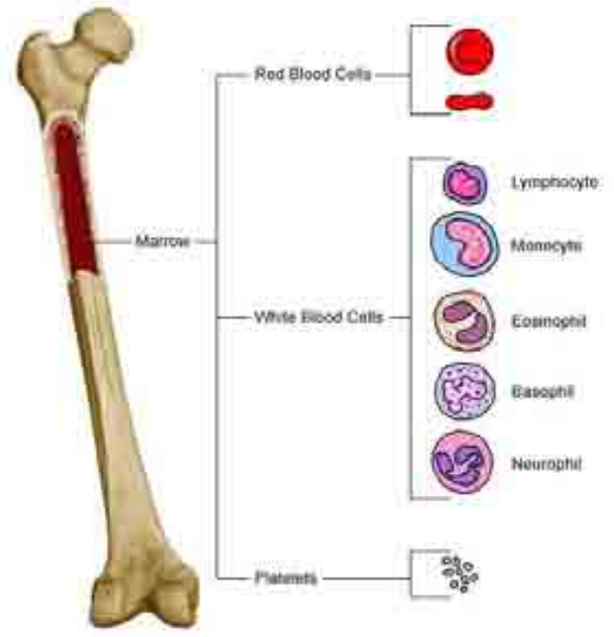
Follow-up duration	Number of patients	Mean difference from baseline	95% Confidence Interval	*P* value
Day 90	10	0.50	-0.53-1.53	0.299
Day 180	8	2.38	0.01-4.74	0.049
Day 270	8	4.62	0.78-8.46	0.025
Day 365	7	5.14	-1.09-11.38	0.090

STEM CELLS
TRANSLATIONAL AND CLINICAL RESEARCH

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

MIGUEL BLANQUER,[a] JOSE M. MORALEDA,[a] FRANCISCA INIESTA,[a] JOAQUÍN GÓMEZ-ESPUCH,[a,b] JOSÉ MECA-LALLANA,[c] RAMÓN VILLAVERDE,[b] MIGUEL ÁNGEL PÉREZ-ESPEJO,[d] FRANCISCO JOSÉ RUIZ-LÓPEZ,[e] JOSÉ MARÍA GARCÍA SANTOS,[f] PATRICIA BLEDA,[a] VIRGINIA IZURA,[g] MARÍA SÁEZ,[g] PEDRO DE MINGO,[g] LAURA VIVANCOS,[h] RAFAEL CARLES,[h] JUDITH JIMÉNEZ,[h] JOAQUÍN HERNÁNDEZ,[i] JULIA GUARDIOLA,[e] SILVIA TORRES DEL RIO,[f] CARMEN ANTÚNEZ,[b] PEDRO DE LA ROSA,[d] MARIA JULIANA MAJADO,[a] ANDRÉS SÁNCHEZ-SALINAS,[a] JAVIER LÓPEZ,[j] JUAN FRANCISCO MARTÍNEZ-LAGE,[d] SALVADOR MARTÍNEZ[k]

[a]Hematopoietic Progenitors Transplant and Cell Therapy Unit, [c]Neurology, [d]Neurosurgery, [e]Neumology, [g]Neurophysiology, [h]Neuropsychology, and [i]Anesthesiology, Hospital Virgen de la Arrixaca, Universidad de Murcia, Murcia, Spain; [b]Neurology and [f]Radiology, Hospital Morales Meseguer, Universidad de Murcia, Murcia, Spain; [j]Statistical Analysis, Fundación para la Formación e Investigación Sanitarias de la Región de Murcia, Hospital Universitario Virgen de la Arrixaca, Murcia, Spain; [k]Instituto de Neurociencias, UMH-CSIC, Alicante, Spain



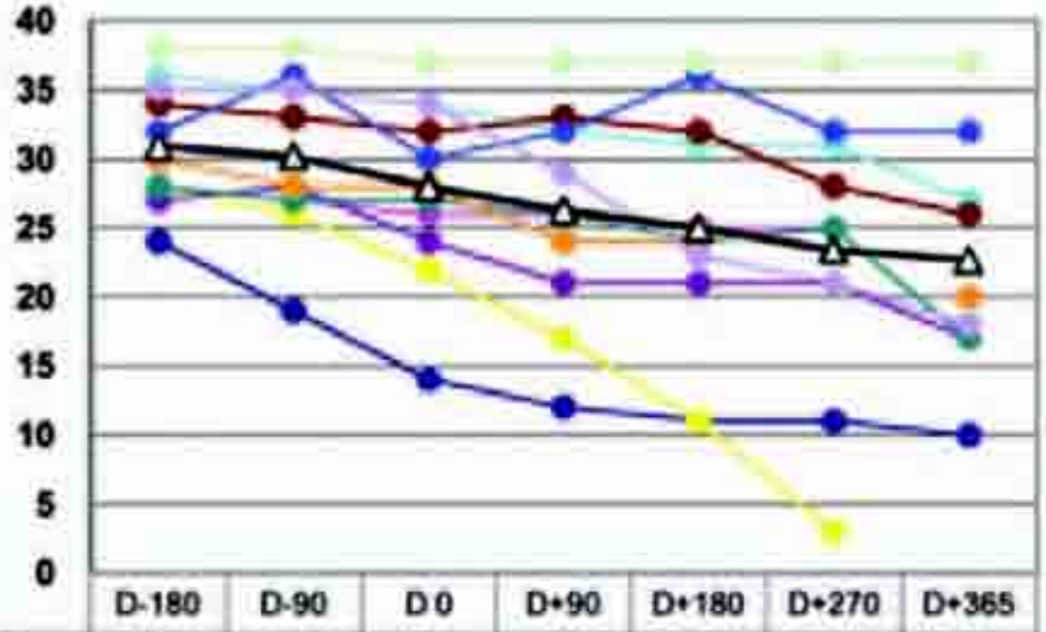
Key Words. Amyotrophic lateral sclerosis • Bone marrow • Adult stem cells • Somatic cell therapy • Stem cell transplantation • Clinical trials

Table 1. Demographics and baseline characteristics

Patient no.	Sex	Age	TTI (months)	FVC (%)	ALS-FRS	Norris	MRC	ALS treatment
1	F	46	20	113	24	54	45	R, E, C, L, B, T
2	M	61	21	104	28	74	37	E, C, L
3	F	54	16	94	28	69	38	R, T
4	F	43	40	105	36	87	47	R
5	M	45	38	79	27	74	42	R, E
6	M	31	33	104	34	79	46	R, E, C, B
7	F	49	29	115	28	71	35	R
8	F	50	23	99	30	70	46	R, E
9	F	52	24	121	32	81	50	R, E, B
10	M	43	14	120	35	83	50	R, L
11	M	41	15	116	38	95	54	R
Median		46	21	105	30	74	46	

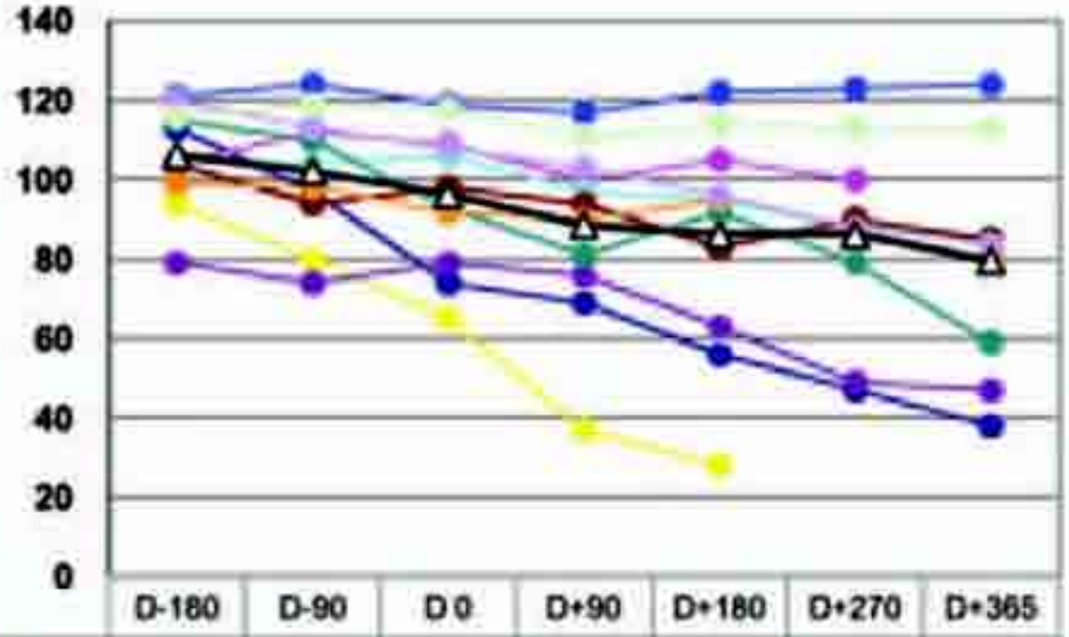
Abbreviations: ALS-FRS, amyotrophic lateral sclerosis functional rating scale; B, baclofen; C, creatine; E, vitamin E; FVC, forced vital capacity; L, lithium carbonate; MRC, medical research council scale for assessment of muscle power; R, rilutek; T, tizanidine; TTI, time from diagnosis to infusion.

ALS-FRS



	D-180	D-90	D 0	D+90	D+180	D+270	D+365
1	24	19	14	12	11	11	10
2	28	27	26	26	25	25	
3	28	26	22	17	11	3	
4	36	35	34	32	31	31	27
5	27	28	24	21	21	21	17
6	34	33	32	33	32	28	26
7	28	27	27	26	24	25	17
8	30	28	28	24	24		20
9	32	36	30	32	36	32	32
10	35	35	34	29	23	21	18
11	38	38	37	37	37	37	37
Mean	31	30	28	26	25	23	23
SD	4	6	7	7	9	10	8

FVC (%)



	D-180	D-90	D 0	D+90	D+180	D+270	D+365
1	113	97	74	69	56	47	38
2	104	112	109	100	105	100	
3	94	80	65	37	28		
4	105	104	106	97	95	88	86
5	79	74	79	76	63	49	47
6	104	94	98	94	83	90	85
7	115	110	93	81	92	79	59
8	99	98	92	90	95		81
9	121	124	119	117	122	123	124
10	120	113	108	103	96	88	84
11	116	119	118	111	114	113	113
Mean	106	102	96	89	86	86	80
SD	13	16	18	22	27	26	28

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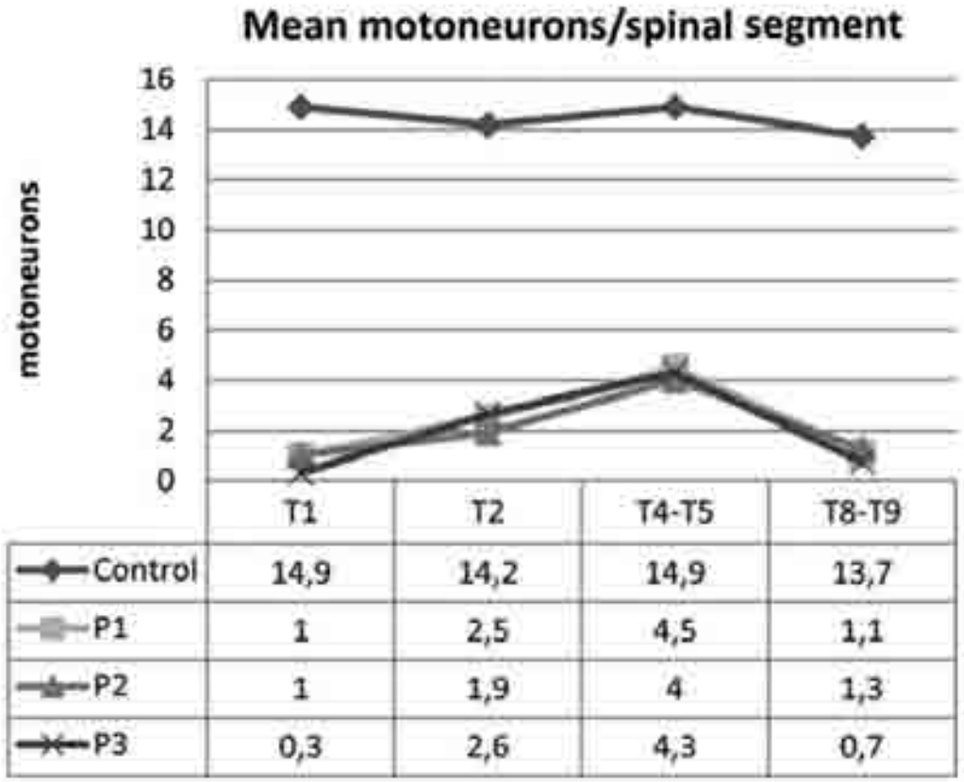
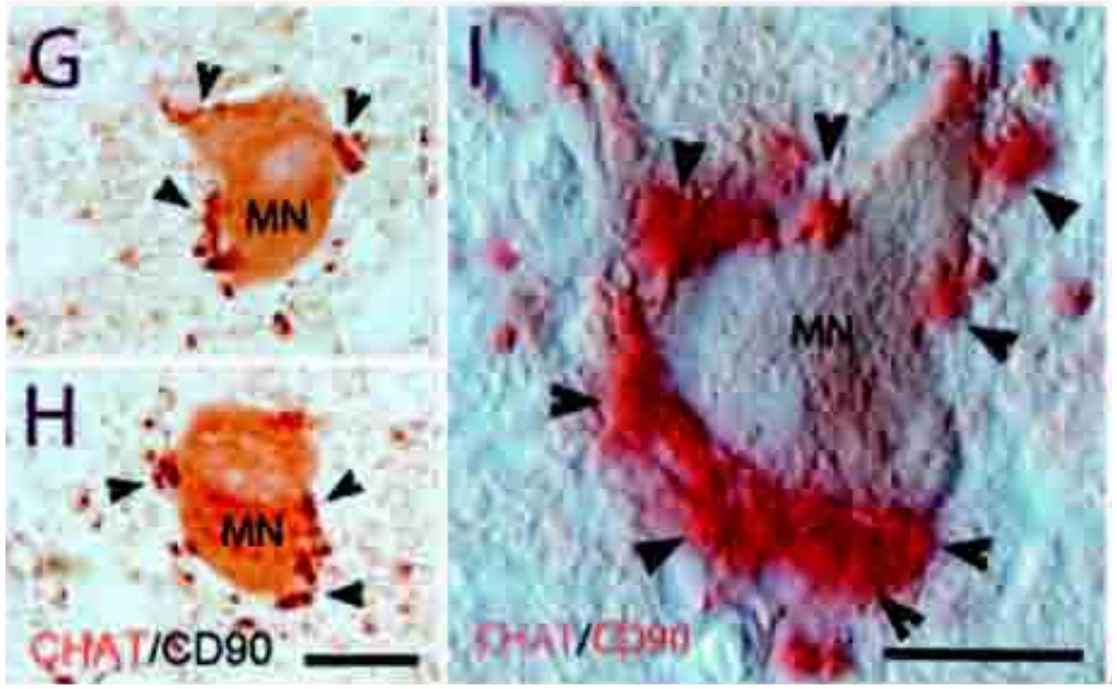
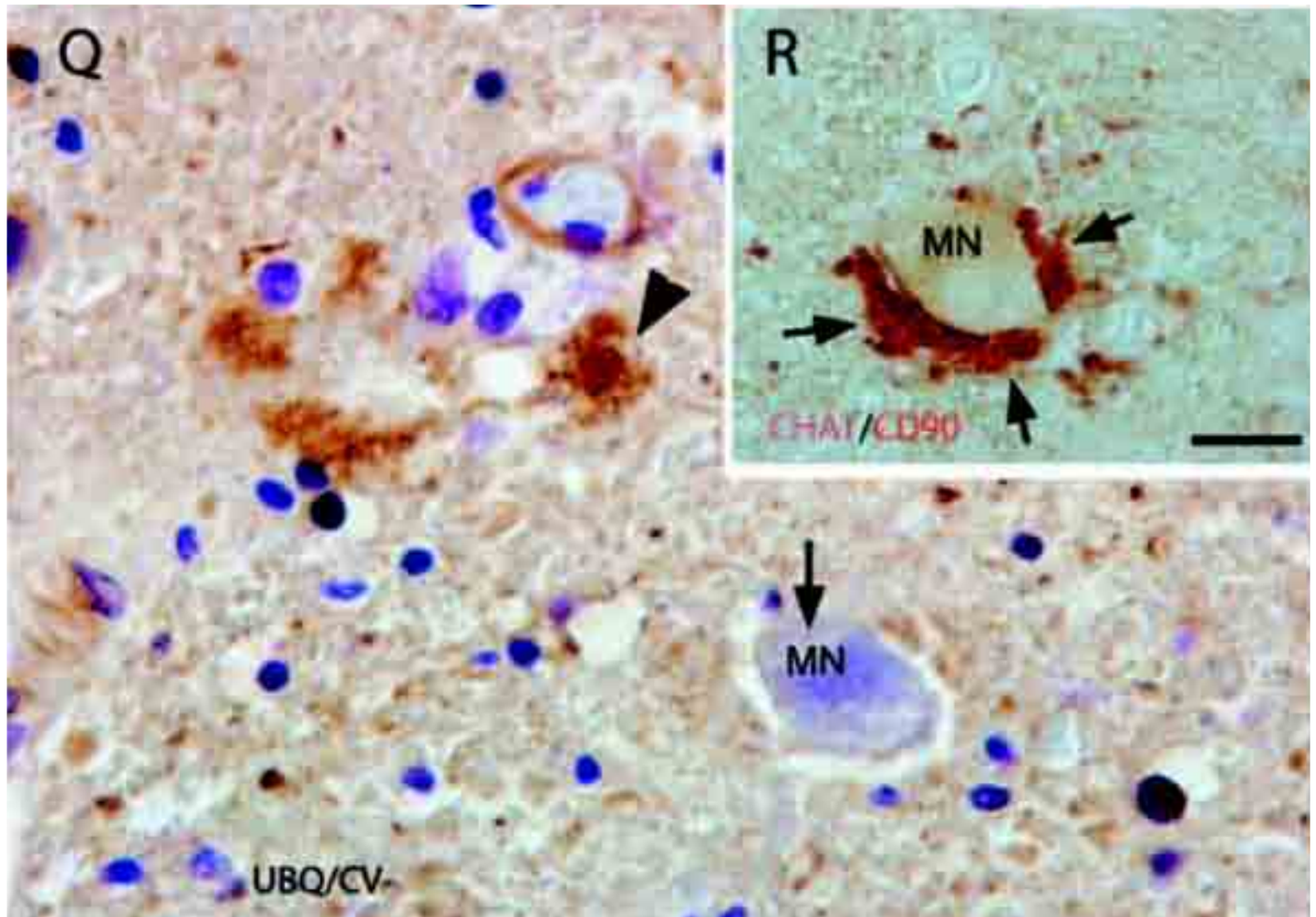


	T1	T2	T4-T5	T8-T9
Control	14,9	14,2	14,9	13,7
P1	1	2,5	4,5	1,1
P2	1	1,9	4	1,3
P3	0,3	2,6	4,3	0,7

Figure 5. Mean motoneurons per spinal segment. The mean number of motoneurons, although inferior to that of a control spinal cord, increased progressively from the distal segments of the spinal cord of the patients to the infused T_4-T_5 level, where the highest number of conserved motoneurons was observed.





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]

[1] Department of Neurology, Emory University School of Medicine, Atlanta, GA 30322 USA; [2] Department of Neurosurgery, Emory University School of Medicine, Atlanta, GA 30322 USA; [3] Neuralstem, Inc., Rockville, MD USA; [4] Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA USA; [5] Department of Neurology, Univers...

Key words. Amyotrophic Lateral Sclerosis • motor neuron disease • stem cells • spinal cord • clinical trial

Table 1: Inclusion Criteria.

Table 2: Patient groups

Figure 1. Quantitative evaluation of disease progression: Left column patients 1-6, right patients 7-12. Note that there was no precipitous decline in function after surgery for any Patients 1, 2, and 4 do not show FVC scores because they were on mechanical ventilation. P and 5 did not have measurable HHD scores at any point. Note that patient 11 (dotted line) apparent improvement in ALSFRS-R and HHD. HHD is shown as the composite "megascore" for lower extremities, normalized to the percent of the score at baseline. X-axis is days pre or post surgery (day of surgery = day 0).

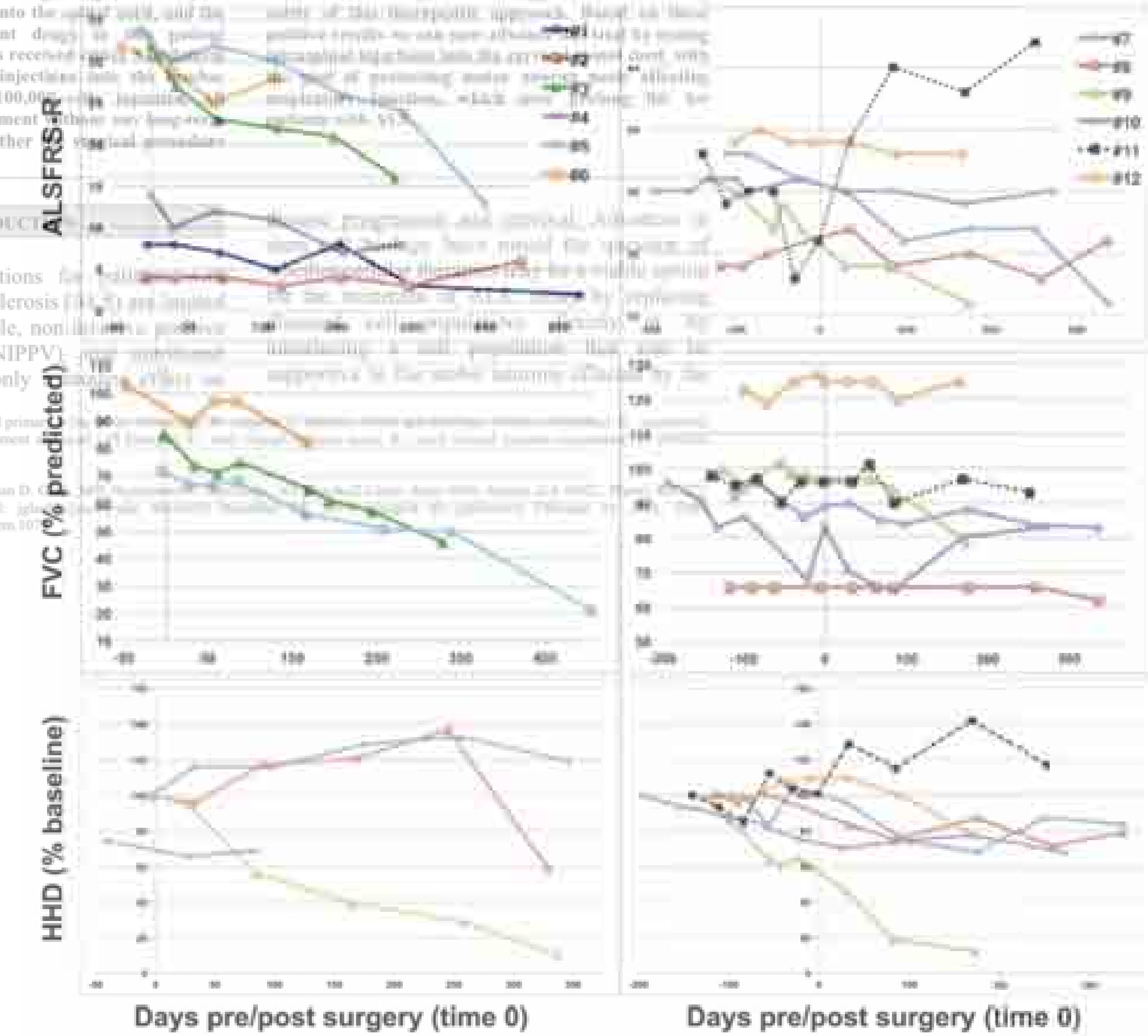


Figure 2. Disease progression as measured using EIM. Average 50 kHz phase for the 6 muscle studied (bilateral quadriceps, tibialis anterior, and medial gastrocnemius) in all 12 subjects. The line represent linear fits of the data. Note again the consistent improvement in EIM score for patient 1 after surgery (dotted line).

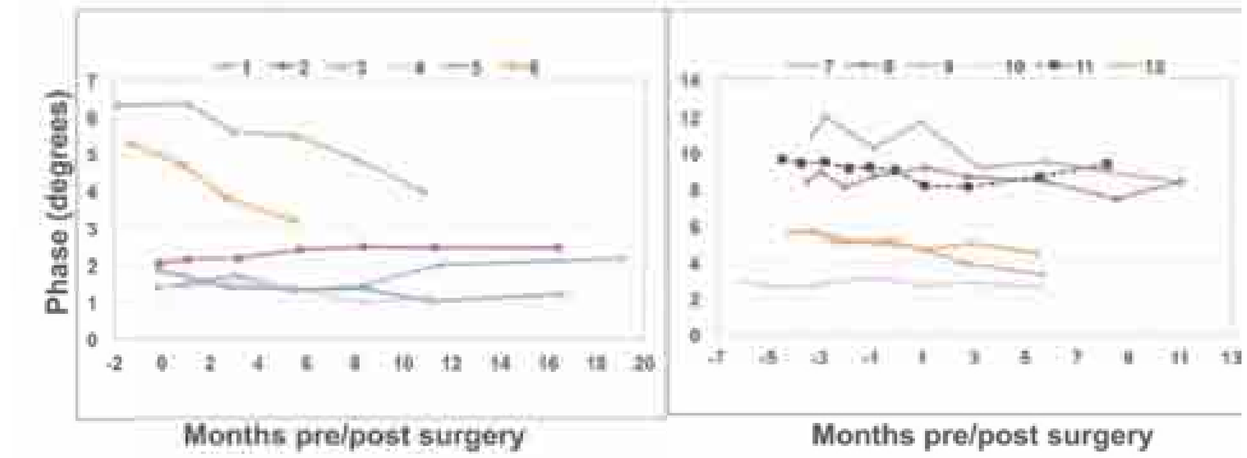


Table 4: Serious Adverse Events (SAE)

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

in Italia?

Il Progetto sostenuto

Trattamento della Sclerosi Laterale Amiotrofica con Ciclofosfamide, sostenuto da Trapianto Autologo di Cellule Staminali Ematopoietiche.

Lo studio avrà come centro coordinatore il Dipartimento di Neuroscienze, Oftalmologia e Genetica dell'Università degli studi di Genova e come centro promotore il Centro Clinico NEMO di Milano

Attualmente stiamo effettuando solo il reclutamento dei pazienti del I gruppo .

Il primo gruppo (**Gruppo A**) includerà pazienti che non sono in grado di deambulare. I pazienti appartenenti a questo gruppo devono avere una spirometria con un valore di Capacità Vitale Forzata >60% del predetto oppure essere portatori di tracheotomia da almeno 3 mesi ed essere comunque in grado di respirare anche autonomamente per lunghi periodi al fine di consentire l'esecuzione della Risonanza Magnetica Nucleare.

Growth Factors, June 2009; 27(3): 133–140

informa
healthcare

Stem cells: comprehensive treatments for amyotrophic lateral sclerosis in conjunction with growth factor delivery

J. SIMON LUNN[1], MICHAEL P. HEFFERAN[2], MARTIN MARSALA[2], & EVA L. FELDMAN[1]

[1]*Department of Neurology, University of Michigan, Ann Arbor, MI 48109-2200, USA, and* [2]*Anesthesiology Research Laboratory, University of California, San Diego, CA 92182, USA*

(*Received 22 August 2008; revised form 29 January 2009; accepted 12 February 2009*)

Abstract

Amyotrophic lateral sclerosis (ALS) is characterized by loss of both upper and lower motor neurons. ALS progression is complex and likely due to cellular dysfunction at multiple levels, including mitochondrial dysfunction, glutamate excitotoxicity, oxidative stress, axonal dysfunction, reactive astrocytosis, and mutant superoxide dismutase expression, therefore, treatment must provide neuronal protection from multiple insults. A significant amount of ALS research focuses on growth factor-based therapies. Growth factors including insulin-like growth factor-I, vascular endothelial growth factor, brain-derived neurotrophic factor, and glial-derived neurotrophic factor exhibit robust neuroprotective effects on motor neurons in ALS models. Issues concerning growth factor delivery, stability and unwanted side effects slow the transfer of these treatments to human ALS patients. Stem cells represent a new therapeutic approach offering both cellular replacement and trophic support for the existing population. Combination therapy consisting of stem cells expressing beneficial growth factors may provide a comprehensive treatment for ALS.

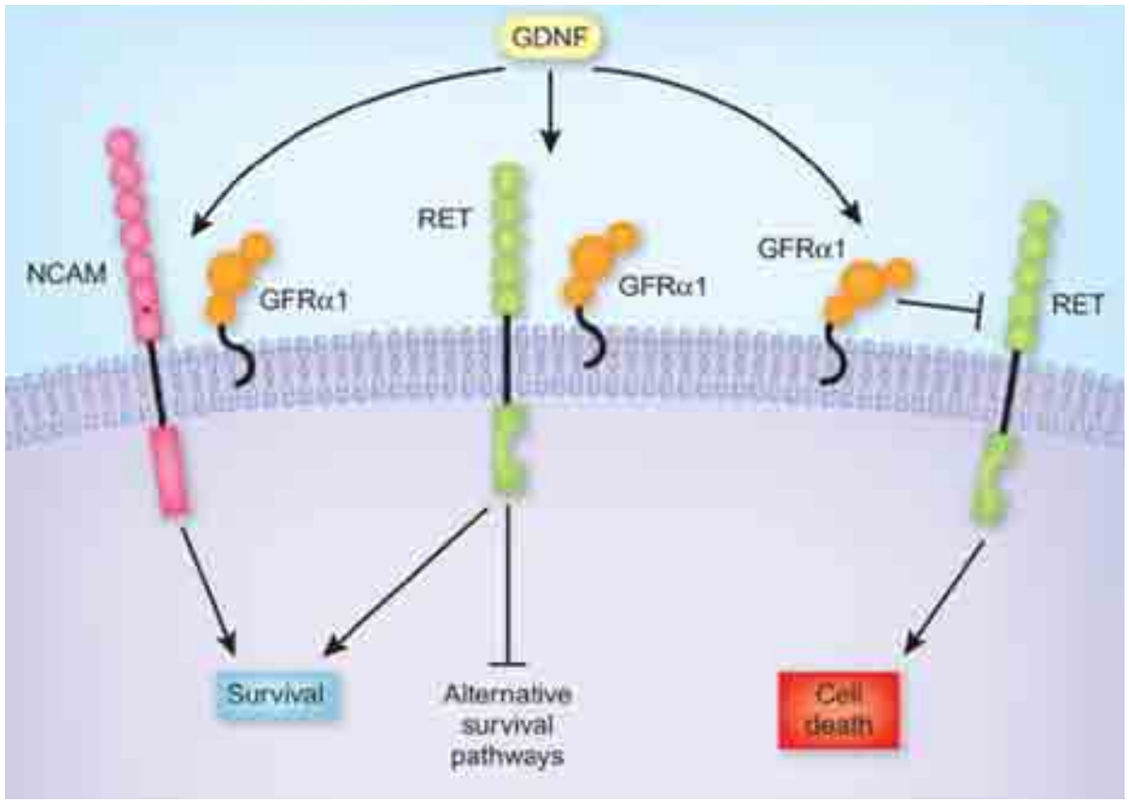
Keywords: *Amyotrophic lateral sclerosis, growth factors, stem cells, gene therapy*

2008

Mesenchymal Stem Cells as Trojan Horses for GDNF Delivery in ALS

Brian K Kaspar[1]

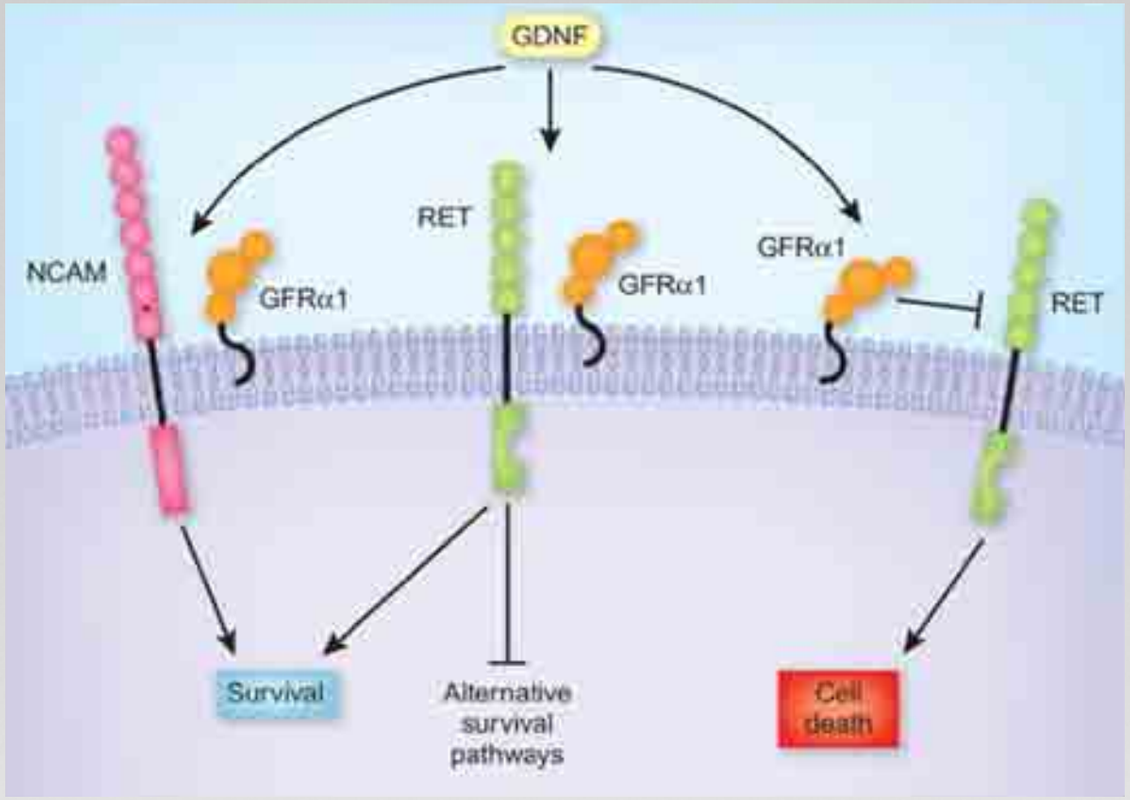
doi:10.1038/mt.2008.216



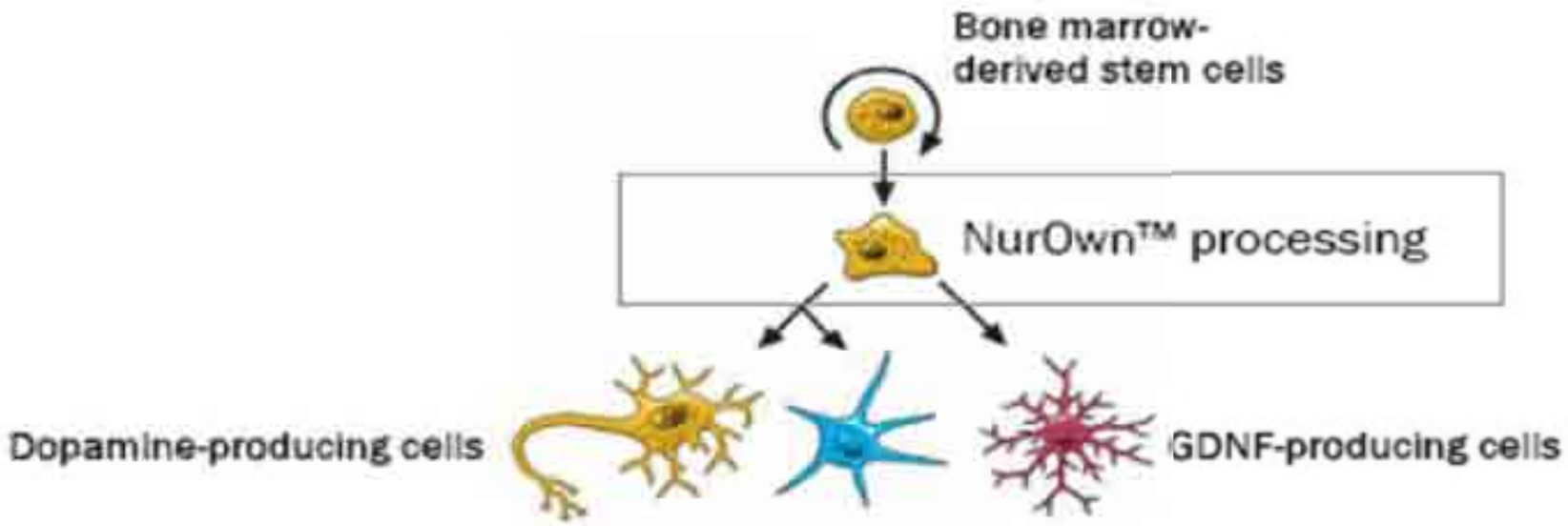
GDNF are effective in:

- sparing motor neuron death
- increase survival in a very rapidly progressing animal model of ALS
- increase in life span of several weeks to a month.

Several studies have demonstrated that GDNF seems to inf uence primarily disease onset and not progression, making it a **diff cult therapeutic candidate for individuals with more advanced ALS**



The NurOwn™ Process



ALSTDI
ALS Therapy Development Institute

Autologous Cultured Mesenchymal Bone Marrow Stromal Cells Secreting Neurotrophic Factors (MSC-NTF), in Patients With Amyotrophic Lateral Sclerosis (ALS)

Quick Info:

Status:
Currently Recruiting

Estimated Enrollment:
12

Phase:
IIA

Treatment Type:
Intramuscular or intraspinal

Trial Type:
Open Label

Sponsor:
Hadassah Medical Organization

Primary Investigator:
Dimitrios Karusis, MD, PhD

Contact Information:
+972-2-6776939
karus@cc.huji.ac.il

Enrollment Criteria:

Breathing Ability — N/A
Percent lung function (FVC) or (SVC)

Months Since Onset — <24
Number of months since first symptoms of ALS

Non-Invasive Ventilation (NIV) — Unknown
Can PALS use a BiPAP in the trial?

Diaphragm Pacer (DPS) — Unknown
Can PALS use a DPS in the trial?

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March 21, 2013

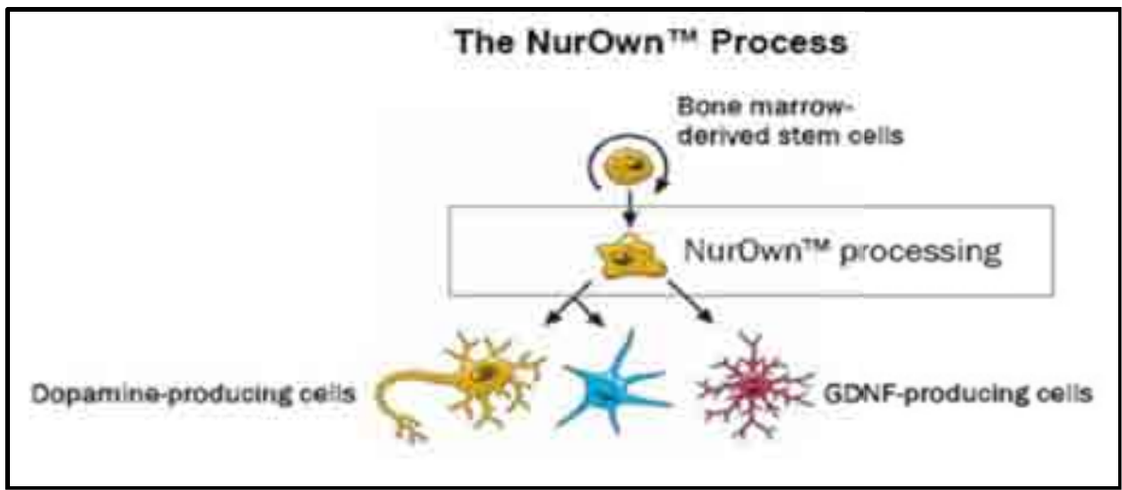
RESULTS OF NUROWN™ CLINICAL TRIAL SUGGEST EFFICACY IN ALS PATIENTS

Data Indicate Initial Clinical Benefit in Overall Clinical and Respiratory Function

New York, NY and Petach Tikvah, Israel – March 21, 2013 – BrainStorm Cell Therapeutics (OTCQB: BCLI), a leading developer of adult stem cell technologies for neurodegenerative diseases, today reported some of the final results from a clinical study evaluating the company's NurOwn™ technology in 12 ALS patients. NurOwn is a proprietary, first-of-its-kind technology for the propagation and differentiation of autologous Mesenchymal Stem Cells (MSCs) into NeuroTrophic Factor (NTF)-secreting cells. The data were presented yesterday, Wednesday, March 20, 2013 during the 65th Annual Meeting of the American Academy of Neurology (AAN) in San Diego, California.

Rasheda Ali's visit to BrainStorm's cleanroom at Hadassah Medical Center, August 2012

An oral and poster presentation were made in the Emerging Science Session by Principal Investigator Dimitrios Karussis, M.D., Ph.D., entitled, "Analysis of 12 Patients with Amyotrophic Lateral Sclerosis (ALS) Treated with Autologous Differentiated Mesenchymal Stem Cells: a Phase I/II Clinical Trial." Karussis reported a significantly slower decline in overall clinical and respiratory function, as measured by the ALS Functional Rating Score (ALSFRS-R) and Forced Vital Capacity (FVC) score respectively, in the six patients that received an intrathecal (IT) injection of the cells in the six months following treatment, as compared to the three months preceding treatment. The study concluded that in addition to establishing the safety of the treatment protocol, initial indications of clinical benefit were observed, which require further confirmation in additional trials. The company is currently conducting a Phase IIa dose-escalating trial pursuant to recent acceleration by the Israeli Ministry of Health.



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Virginia B Mattis, Cliv

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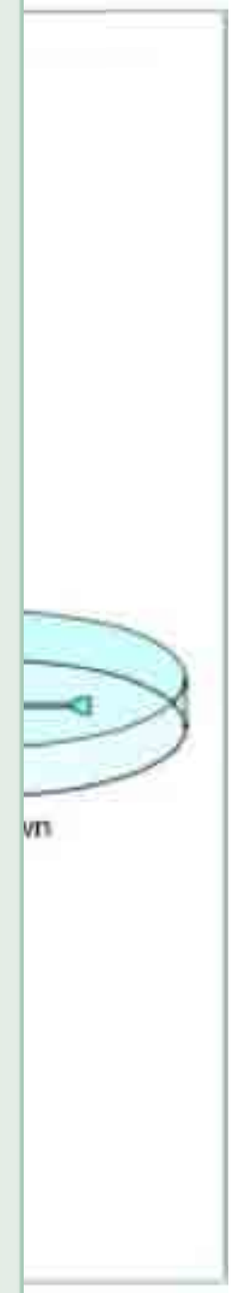

Figure 2: Met

	Associated genes		iPS cells generated
	Leading to disease	Increasing susceptibility	
Neurodevelopmental disorders			
Single-gene mutation			
Angelman's syndrome	*UBE3A*	..	No
Rett's syndrome	*CDKL5, MECP2*	..	Yes[44]
Nucleotide repeat disorder			
Fragile X syndrome	*FRAXA*	..	Yes[45]
Chromosomal abnormalities			
Down's syndrome	Trisomy 21	..	Yes[14]
Prader-Willi syndrome	Paternal 15q11-13	..	Yes[46]
Cri du chat syndrome	5p15	..	No
Autism	..	*NLGN3, NHE9, SLC9A9, CNTNAP2, PCDH10, SCN7A, BZRAP1, MDGA2*	No
Neurodegenerative disorders			
Single-gene mutation			
Spinal muscular atrophy	*SMN1*	..	Yes[13]
Batten's disease	*CLN3*	..	No
Familial dysautonomia	*IKBKAP*	..	Yes[47]
Ataxias	*SPTBN2, TTBK2, PP2R2B, PP2R2B, PRKCG, ITPR1, PDYN, FGF14*	..	No
Nucleotide repeat disorder			No
Huntington's disease	*HTT*	..	Yes[14,48]
Spinocerebellar ataxia	*ATXN1, ATXN2, ATXN3, ATXN10, CACNA1A*	..	No
Friedreich's ataxia	*USP9X*	..	Yes[49]
Multigene or unknown origin			
ALS	*SOD1, VCP, ALS2, TARDBP* (also known as *TDP43*)	*DPP6, ITPR2*	Yes[24]
Retinal degeneration or disease	*CLRN1, USH1C, USH1G, USH2A, FZD4, LRP5, NDP, BEST1, PRPH2, VCAN*	*CDH23, GPR98, MYO7A, PCDH15, MT-ATP6*	No
Parkinson's disease	*PRKN, SNCA, LRRK2, PARK7, PINK1,*	*GBA, SNCAIP, UCHL1*	Yes[14,50,51]
Alzheimer's disease	*PSEN1, PSEN2, APP*	*APOE, CR1, CLU, GSTO1, IDE*	No
Stroke	..	*PDE4D, ALOX5AP, SORBS1, FGG, FGA, LDL-PLA2*	No
Charcot–Marie–Tooth disease	*BSCL2, DNM2, EGR2, FGD4, FIG4, GARS, GDAP1, GJB1, HSPB1, HSPB8, KIF1B, LITAF, LMNA, MFN2, MPZ, MTMR2, NDRG1, NEFL, PMP22, PRPS1, PRX, RAB7A, SBF2, SH3TC2, YARS*	..	No

iPS=induced pluripotent stem. ALS=amyotrophic lateral sclerosis.

Table 2: **Neurodevelopmental and neurodegenerative diseases potentially suitable for modelling with iPS cells**

Induced pluripotent stem cells: a new revolution for clinical neurology?

Virginia B Mattis, Clive N Svendsen

iPS cells are biologically indistinguishable from embryonic stem (ES) cells. Human iPS cells, like ES cells, can differentiate into a variety of cell types and may therefore be another cell source for regenerative medicine.

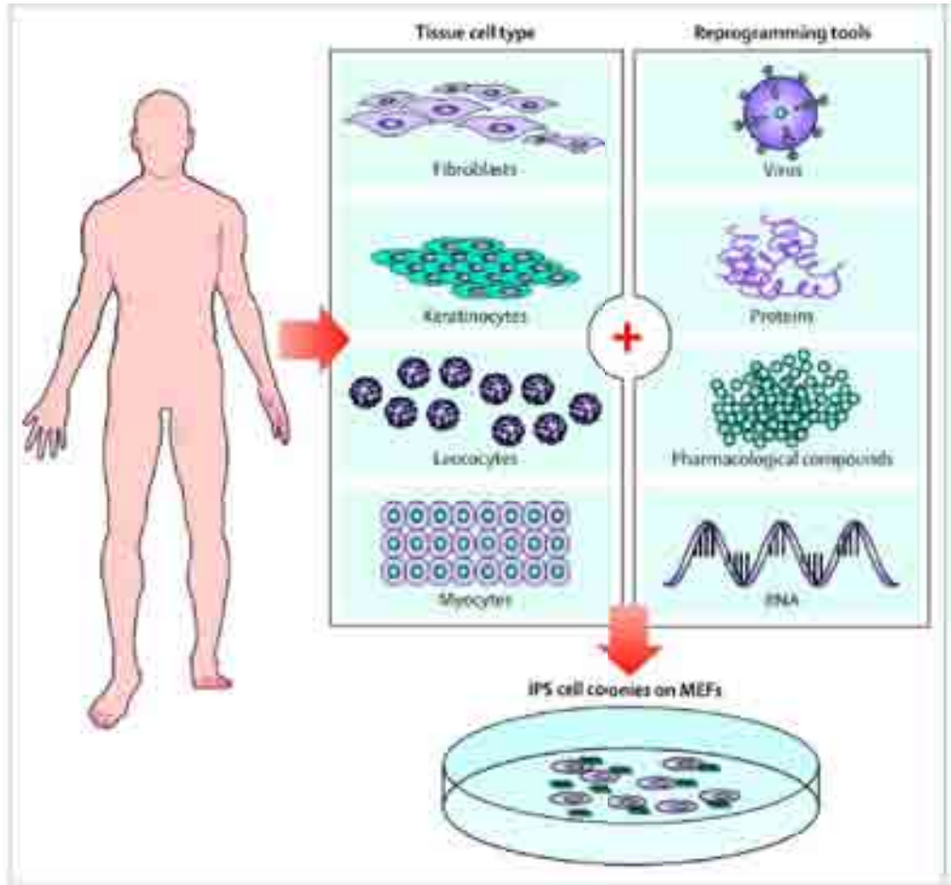

Figure 1: Generation of IPS cells

J Cell Mol Med. 2013 May 26. doi: 10.1111/jcmm.12062. [Epub ahead of print]

2. # The tumourigenicity of iPS cells and their differentiated derivates.

Liu Z, Tang Y, Lü S, Zhou J, Du Z, Duan C, Li Z, Wang C.

Department of Advanced Interdisciplinary Studies, Institute of Basic Medical Sciences and Tissue Engineering Research Center, Academy of Military Medical Sciences, Beijing, China.

Abstract

Induced pluripotent stem cell (iPSC) provides a promising seeding cell for regenerative medicine. However, iPSC has the potential to form teratomas after transplantation. Therefore, it is necessary to evaluate the tumorigenic risks of iPSC and all its differentiated derivates prior to use in a clinical setting. Here, murine iPSCs were transduced with dual reporter gene consisting of monomeric red fluorescent protein (mRFP) and firefly luciferase (Fluc). Undifferentiated iPSCs, iPSC derivates from induced differentiation (iPSC-derivates), iPSC-derivated cardiomyocyte (iPSC-CMs) were subcutaneously injected into the back of nude mice. Non-invasive bioluminescence imaging (BLI) was longitudinally performed at day 1, 7, 14 and 28 after transplantation to track the survival and proliferation of transplanted cells. At day 28, mice were killed and grafts were explanted to detect teratoma formation. The results demonstrated that transplanted iPSCs, iPSC-derivates and iPSC-CMs survived in receipts. Both iPSCs and iPSC-derivates proliferated dramatically after transplantation, while only slight increase in BLI signals was observed in iPSC-CM transplanted mice. At day 28, teratomas were detected in both iPSCs and iPSC-derivates transplanted mice, but not in iPSC-CM transplanted ones. In vitro study showed the long-term existence of pluripotent cells during iPSC differentiation. Furthermore, when these cells were passaged in feeder layers as undifferentiated iPSCs, they would recover iPSC-like colonies, indicating the cause for differentiated iPSC's tumourigenicity. Our study indicates that exclusion of tumorigenic cells by screening in addition to lineage-specific differentiation is necessary prior to therapeutic use of iPSCs.

STEM CELLS

Drug Screening for ALS Using Patient-Specific Induced Pluripotent Stem Cells

Naohiro Egawa,[1,2]* Shiho Kitaoka,[1,2]* Kayoko Tsukita,[1,2] Motoko Naitoh,[3] Kazutoshi Takahashi,[1] Takuya Yamamoto,[1,4] Fumihiko Adachi,[1] Takayuki Kondo,[1,5] Keisuke Okita,[1] Isao Asaka,[1] Takashi Aoi,[1] Akira Watanabe,[1,4] Yasuhiro Yamada,[1,4] Asuka Morizane,[1,6] Jun Takahashi,[1,6] Takashi Ayaki,[5] Hidefumi Ito,[5] Katsuhiro Yoshikawa,[3] Satoko Yamawaki,[3] Shigehiko Suzuki,[3] Dai Watanabe,[7] Hiroyuki Hioki,[8] Takeshi Kaneko,[8] Kouki Makioka,[9] Koichi Okamoto,[9] Hiroshi Takuma,[10] Akira Tamaoka,[10] Kazuko Hasegawa,[11] Takashi Nonaka,[12] Masato Hasegawa,[12] Akihiro Kawata,[13] Minoru Yoshida,[14] Tatsutoshi Nakahata,[1] Ryosuke Takahashi,[5] Maria C. N. Marchetto,[15] Fred H. Gage,[15] Shinya Yamanaka,[1,4,16] Haruhisa Inoue[1,2,16†]

Amyotrophic lateral sclerosis (ALS) is a late-onset, fatal disorder in which the motor neurons degenerate. The discovery of new drugs for treating ALS has been hampered by a lack of access to motor neurons from ALS patients and appropriate disease models. We generate motor neurons from induced pluripotent stem cells (iPSCs) from familial ALS patients, who carry mutations in Tar DNA binding protein-43 (TDP-43). ALS patient–specific iPSC–derived motor neurons formed cytosolic aggregates similar to those seen in postmortem tissue from ALS patients and exhibited shorter neurites as seen in a zebrafish model of ALS. The ALS motor neurons were characterized by increased mutant TDP-43 protein in a detergent-insoluble form bound to a spliceosomal factor SNRPB2. Expression array analyses detected small increases in the expression of genes involved in RNA metabolism and decreases in the expression of genes encoding cytoskeletal proteins. We examined four chemical compounds and found that a histone acetyltransferase inhibitor called anacardic acid rescued the abnormal ALS motor neuron phenotype. These findings suggest that motor neurons generated from ALS patient–derived iPSCs may provide a useful tool for elucidating ALS disease pathogenesis and for screening drug candidates.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by a loss of upper and lower motor neurons that typically develops in the fifth or sixth decade of life, with a survival of less than 5 years and a prevalence of 2 in 100,000 (*1*, *2*). The histopathological hallmarks of this fatal disease include cytosolic aggregates in the motor neurons of most ALS patients with the sporadic form of the disease. These aggregates are composed of Tar DNA binding protein-43 (TDP-43) (*3*–*5*), a 414–amino acid nuclear mRNA binding protein containing two RNA recognition motifs. Genetic analysis has identified more than 30 mutations in the *TDP-43* gene in both familial and sporadic ALS cases (*6*). ALS-associated abnormalities have been reported in patient samples and cellular and animal models (*6*–*10*), and several compounds have been identified as abrogating the disease phenotype in an ALS mouse model. However, when these compounds were tested in ALS patients, no clinical improvements were observed (*11*).

Induced pluripotent stem cells (iPSCs) have been generated from ALS patients and differentiated into motor neurons (*12*, *13*), but it is not yet clear whether the abnormal cellular and molecular phenotypes of ALS can be recapitulated in vitro. A lack of access to human motor neurons and appropriate disease models has hampered efforts to test new drug candidates for ALS. Here, we generated human motor neurons from iPSCs derived from familial ALS patients carrying *TDP-43* mutations and used them to identify a compound that rescued the ALS-associated phenotype.

RESULTS

Spinal motor neurons were generated from iPSCs derived from dermal fibroblasts from patients with familial ALS or from control individuals by means of retroviral or episomal vectors. Seven control human iPSC lines were derived from five unrelated individuals without mutations in the *TDP-43* gene, and nine ALS iPSC lines were generated from three ALS patients with mutations in *TDP-43* (*14*, *15*) (Fig. 1A, fig. S1A, and table S1). ALS patients A21, A34, and ND32947 were heterozygous for the Q343R, M337V, and G298S mutations in *TDP-43*, respectively. Neural populations including motor neurons derived from the ALS patient iPSCs retained these *TDP-43* mutations (Fig. 1B).

[1]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto 606-8507, Japan. [2]Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency, Tokyo 102-0075, Japan. [3]Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan. [4]Institute for Integrated Cell-Material Sciences, Kyoto University, Kyoto 606-8501, Japan. [5]Department of Neurology, Graduate School of Medicine, Kyoto University, Kyoto 606-8507, Japan. [6]Department of Biological Repair, Institute for Frontier Medical Sciences, Kyoto University, Kyoto 606-8507, Japan. [7]Department of Biological Sciences, Graduate School of Medicine and Department of Molecular and System Biology, Graduate School of Biostudies, Kyoto University, Kyoto 606-8501, Japan. [8]Department of Morphological Brain Science, Graduate School of Medicine, Kyoto University, Kyoto 606-8501, Japan. [9]Department of Neurology, Osumi University Graduate School of Medicine, Mashiki 571-0011, Japan. [10]Department of Neurology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba 305-8575, Japan. [11]Department of Neurology, Sagamihara Hospital, Sagamihara 252-0392, Japan. [12]Department of Neuropathology and Cell Biology, Tokyo Metropolitan Institute of Medical Science, Tokyo 156-8506, Japan. [13]Department of Hematology, Tokyo Metropolitan Neurological Hospital, Tokyo 183-0042, Japan. [14]Chemical Genetics Laboratory, Molecular Ligand Biology Research Team, Chemical Genomics Research Group, RIKEN Advanced Science Institute, Wako, Saitama 351-0198, Japan. [15]The Salk Institute for Biological Studies, La Jolla, CA 92037, USA. [16]Yamanaka iPS Cell Special Project, Japan Science and Technology Agency, Kawaguchi 332-0012, Japan.
*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: haruhisa@cira.kyoto-u.ac.jp

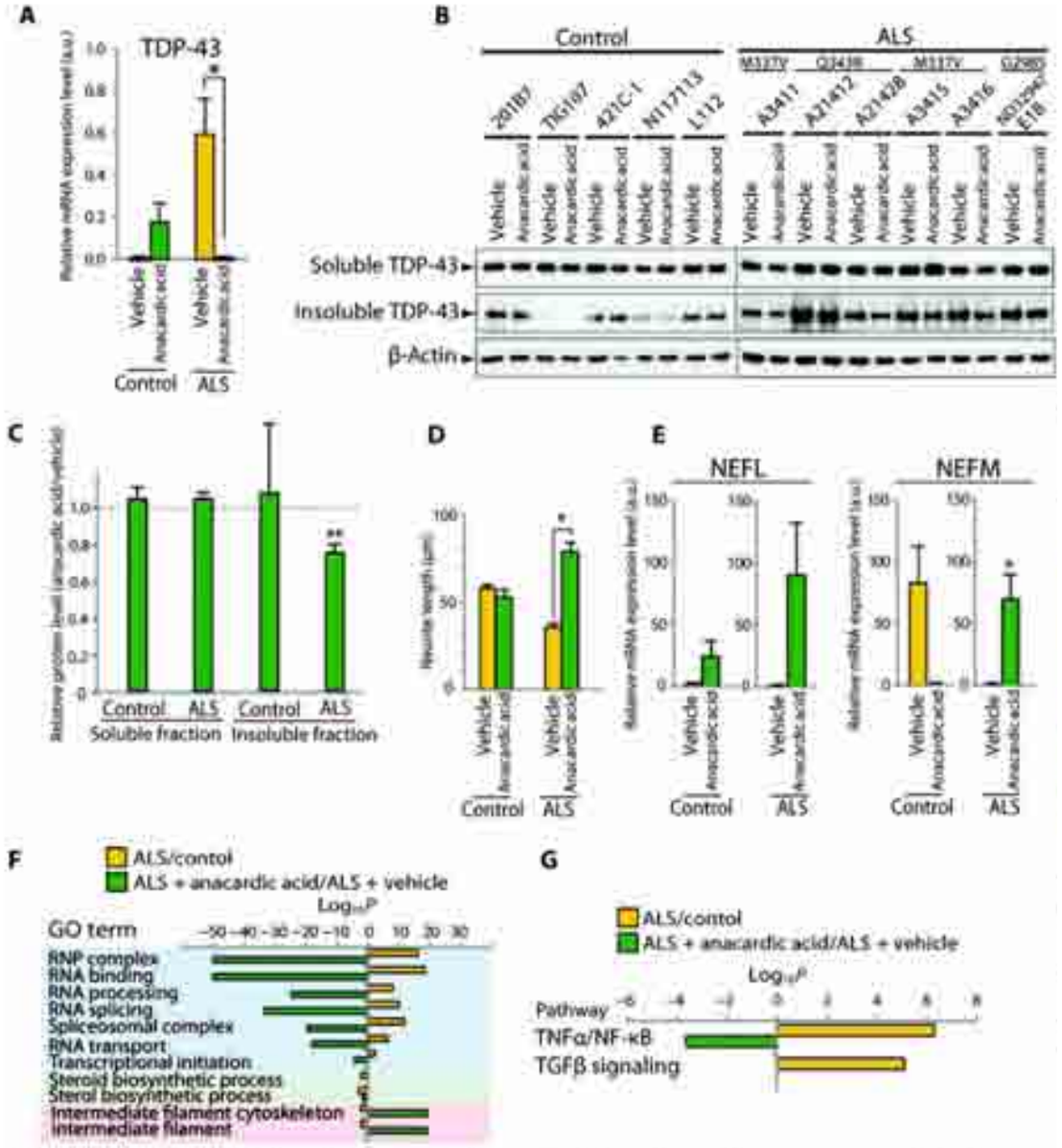

Fig. 4. Anacardic acid–induced phenotypic changes in ALS and control motor neurons. (**A**) qPCR confirmed that 5 μ*M* anacardic acid treatment for 16 hours down-regulated TDP-43 mRNA expression in purified ALS iPSC–derived motor neurons. $P = 0.047$ by two-way ANOVA. Error bars are SEM. (**B**) After treatment with vehicle or 5 μ*M* anacardic acid for 48 hours, cells were lysed, separated into soluble and insoluble fractions, and immunoblotted with TDP-43. (**C**) Quantification of protein band densities after immunoblotting. The dotted line indicates the baseline (vehicle only) of relative protein levels (anacardic acid/vehicle). $P = 8.2 \times 10^{-3}$ by *t* test. Error bars are SEM. (**D**) Neurite length of purified motor neurons was measured 16 hours after treatment with vehicle or 5 μ*M* anacardic acid. $P = 0.014$ by two-way ANOVA. Error bars are SEM. (**E**) qPCR revealed that anacardic acid treatment up-regulated expression of NEFM mRNA in ALS iPSC–derived motor neurons. $P = 0.032$ by *t* test. Error bars are SEM. (**F** and **G**) After purified motor neurons were treated for 16 hours with vehicle or 5 μM anacardic acid, cells were lysed and analyzed by expression array profiling. (Yellow bars) *P* value for significant changes in expression of genes and signaling pathways in ALS versus control iPSC–derived motor neurons was expressed on a logarithmic scale. (Green bars) *P* value for GO terms and signaling pathways of anacardic acid–treated ALS motor neurons compared to vehicle-treated ALS motor neurons was expressed on a logarithmic scale. *$P < 0.05$, **$P <$

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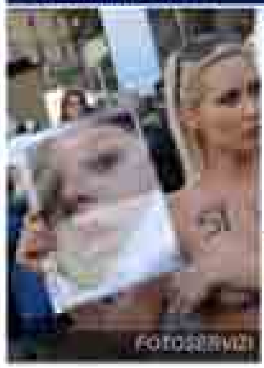
26 March 2013



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NATURE | NEWS

Stem-cell ruling riles researchers

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

Alison Abbott

26 March 2013

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

del 28 Maggio 2013

Il Sole 24 ORE Sanità
MILANO/ITALIA

estratto da pag. 1, 2, 3

Staminali, dubbi e misteri

La prima legge della XVII legislatura, quella su staminali e Opg, ha messo a dura prova Parlamento e ministro della Salute, fino a un compromesso tra pressione mediatica, sentenze e opposizione della comunità scientifica.

SERVIZI E TESTO A PAG. 2-4

«Sì» del Senato alla conversione del Dl Balduzzi: passa il compromesso deciso alla Camera

Staminali, il decreto è legge

Il metodo Stamina equiparato a un farmaco: 3 milioni per la sperimentazione

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aisla ONLUS
ASSOCIAZIONE ITALIANA SCLEROSI LATERALE AMIOTROFICA

6. Perchè la comunità scientifica mondiale non concorda sul Metodo Vannoni?

Per agire secondo le regole il metodo Vannoni deve essere "mostrato": si deve dire quali cellule vengono impiegate, quante ne sono state isolate, quante volte è stato ripetuto l'esperimento.

E dimostrare che ogni volta che le cellule vengono trattate nel modo "truce" enunciato da Vannoni, cioè esponendole ad alcol, non solo sopravvivono ma si trasformano anche in neuroni.

Noi sappiamo che tutto ciò non accade: gli stessi uff ci brevetti americani hanno affermato che nell'intero procedimento procedimento
Stamina non c'è nulla di simile a un neurone o a un metodo scientif co. Quest'ultimo, perché sia tale, deve essere stato replicato almeno 20 volte con gli stessi risultati, trascritti nero su bianco in una relazione dettagliata.
Il metodo Stamina è privo di questi requisiti. Ma se Vannoni ha da qualche parte la documentazione opportuna e per qualche motivo non l'ha mai presentate, ora la legge gli dà la possibilità di mostrare le carte

Elena Cattaneo
direttore del centro UniStem dell'Università di Milano

Available online at www.sciencedirect.com

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Neuromuscular Disorders 22 (2012) 1032–1034

www.elsevier.com/locate/nmd

Letters to the Editor

Ultrasonography of MADSAM neuropathy: Focal nerve enlargements at sites of existing and resolved conduction blocks

I read with great interest the article by Scheidl et al. [1] focused on the ultrasonography findings of the acquired demyelinating sensory and motor neuropathy (MADSAM). The authors depicted for the first time in the literature, that focal nerve enlargements can be detected by ultrasound in MADSAM, at sites of previous conduction blocks, well after complete clinical and electrophysiological resolution. This observation highlights in my opinion two important aspects in the clinical course of the disease. On one side, it shows that ultrasonographic morphological changes may outlast functional recovery in such demyelinating neuropathies. On the other side, this study highlights the fact that although the clinical course of the disease is expected to be predominantly in the upper extremities, morphological changes to the nerves of the lower extremities can be detected by ultrasound prior to clinical and electrophysiological affection.

A similar sonographical observation has been done only in the case of multifocal motor neuropathy (MMN) by Beekman et al. [2]. They reported in a study of 21 patients, that a sonographic enlargement could be found not only in nerve segments without conduction abnormalities indicating demyelination, but also in nerves with normal conduction.

In our neurophysiologic and ultrasound lab we recently started to perform ultrasound in patients affected from immune-mediated neuropathies. Experiencing a case of a MADSAM neuropathy with disease course over 2 years, we detected sonographically a hypertrophy of the median and ulnar nerve in the forearm on both sides, but no pathological findings could be detected in the lower extremities. The site where the hypertrophy was detected in ultrasound correlated with the site of conduction block in the electrophysiological studies.

Considering the study from Scheidl et al. and our findings we would like to draw attention to the usefulness of ultrasonography for detecting and diagnosing segmental lesions of the peripheral nerves in MADSAM and other immune-mediated neuropathies. These findings indicate that the disease process in MADSAM is more widespread than expected on the basis of clinical and electrophysiologic abnormalities. In our case though, we could not detect any pathological abnormalities in the lower extremities, so the time course of the disease may play an important role for the detection of these changes. Unfortunately there are no histologic studies of nerves in MADSAM without electrophysiologic abnormalities that could confirm these ultrasound findings. These ultrasound observations could help though to understand the underlying mechanisms of nerve damage and facilitate the development of more effective treatments.

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Antonios Kerasnoudis
Dept. of Neurology, Ruhr University, St. Josef-Hospital, Gudrunstr. 56, 44791 Bochum, Germany
Tel.: +00491766292323 5; fax: +49 2345093024.
E-mail address: antonis.kerasnoudis@gmail.com

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Stem cells in severe infantile spinal muscular atrophy (SMA1)

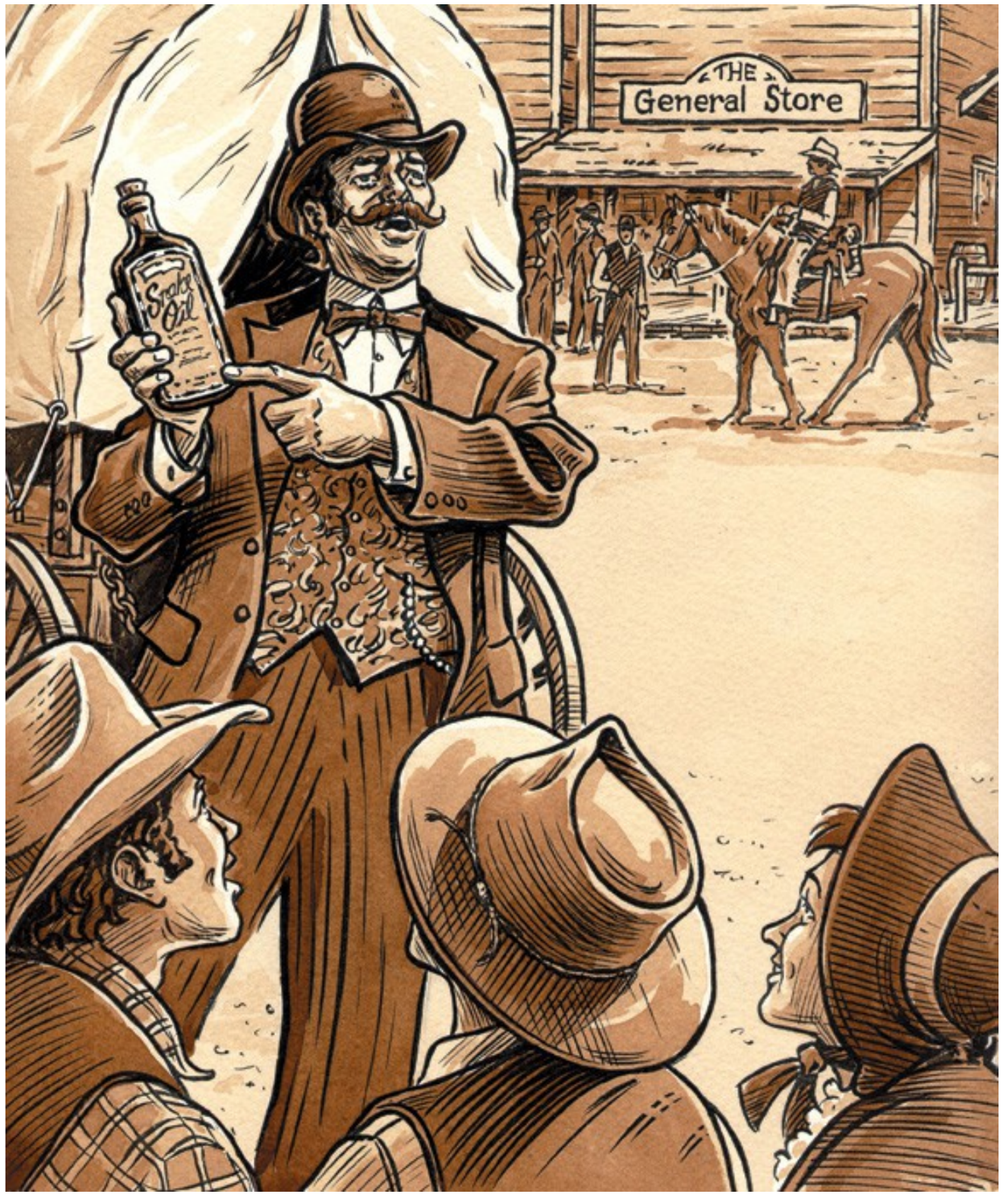
Dear Sir,

We would like to share our recent experience on the use of intrathecal mesenchymal stem cells in children with type I spinal muscular atrophy (SMA) as we believe it raises several issues of concern.

Human mesenchymal stem cells (hMSCs) are known to secrete a variety of cytokines and growth factors that show both paracrine and autocrine activities for damaged tissues, including nervous cells. The paracrine effects are distinct from the classical model of direct differentiation of stem cells into the tissue to be regenerated, and are supposed to have a possible pivotal role in various forms of nervous cells damage [1].

Their therapeutic role has been recently proposed in some human and animal models of second motoneuron

One of the f ve patients who entered the study, enrolled at the age of 13 months, **died from respiratory failure at the age of 18 months, 1 month after the second injection**. The family of another patient asked to stop the treatment after the 5th injection, at 8 months of age, and the child **died at the age of 12 months of respiratory failure**. The other three patients completed the 6 month treatment course. During this period in all three there was the need to initiate sup- portive therapy with nutritional and respiratory aids. **In all three patients there was a progressive decline of motor function** as demonstrated by the reduction of the CHOP Intend scale total score and no clinical evidence of any improvement.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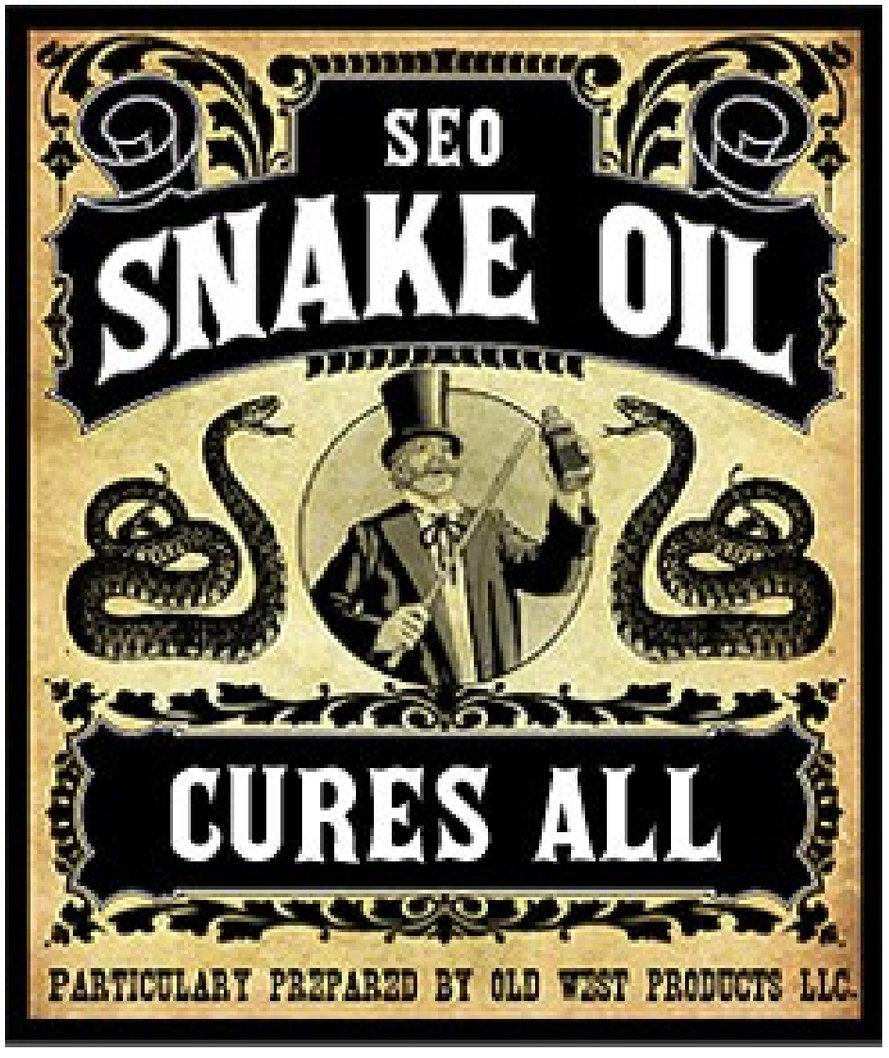
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Darren Lau,[1] Ut
[1]Department of P
[2]Health Law Instit
University of Albe
*Correspondence
DOI 10.1016/j.ste

Table 1. Nature of Therapies Offered across Surveyed Websites

Stem Cell Type	Frequency	%
Adult, autologous	9	47
Fetal	6	32
Cord blood	4	21
Embryonic	2	11
Adult, allogeneic	2	11
Adjuncts	0	0
Unspecified	0	0
Stem Cell Source	**Frequency**	**%**
Bone marrow	7	37
Blood or marrow donors	5	26
Peripheral blood	5	26
Fetuses	4	21
Fat	2	11
Unspecified	2	11
Other	3	16
Transplantation Procedure	**Frequency**	**%**
Intrathecal, into the CSF	6	32
Intravenous	6	32
Subcutaneous or intramuscular	4	21
Surgical transplantation	4	21
Catheterization of deep body vessels	3	16
By mouth	1	5
Topical	1	5

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REVIEW

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Douglas Sipp

Research Unit for Scien
Kobe 650-0047, Japan

Table 1 Companies marketing stem cell treatments for amyotrophic lateral sclerosis (ALS)*

Name	Location	Cell type used	Delivery method	Cost
Beike Biotechnology	China	Allogeneic umbilical cord blood-derived stem cells (Beike also uses umbilical cord- and autologous bone marrow-derived stem cells)	Multiple (IV, lumbar puncture)	$26 300 USD for initial six injections
Chaitanya Stem Cell Therapy Center	India	Autologous bone marrow; Fetal stem cells	Intrathecal/intralesional injection	$6 000–$12 000 (bone marrow); $16 000 (fetal)
EmCell	Russia	Fetal stem cells	Not listed	Not listed
Integra Medical Center	Mexico	Placenta stem cells	Implantation in "different areas according to the patient's condition"; often in combination with acupuncture	Not listed
Nova Cells Institute	Mexico	Autologous bone marrow-derived stem cells	Not listed	Not listed
Stem Cell Rejuvenation Center	USA	Adipose-derived stem cells	Multiple (IV, in situ, IM, intranasal)	$8 750 USD
Stem Cells 21	Thailand	Adipose-derived stem cells	IV/IM injection	$18 000 USD
StemProCell	USA	Adipose-derived stem cells (processed using Adistem system)	Not listed	Not listed
Tissü	Seychelles	Mesenchymal stem cells	IV injection	Not listed
Wu Stem Cells Medical Center	China	Neural stem cells	Multiple (lumbar puncture, intracerebral injection)	Not listed
XCell-Center	Germany	Autologous bone marrow-derived cells	IV injection co-administered with mannitol	7 995 euros (adult); 9 000 euros (child)

* All data are taken from website and patient information resources published by the companies listed. All data reflect claims made as of March 13, 2011. Website data are archived using SiteSucker software ver 2.3.2. Abbreviations: IV = intravenous; IM = intramuscular.

- The marketing of untested and under-regulated stem cell products has developed into a global industry involving hundreds of companies
- Private clinics and physicians around the world claim to use stem cells of various types to treat an extraordinarily broad range of medical and quality of life indications
- Such stem cell clinics operate in regulatory gaps, or even in direct violation of local laws and guidelines; many are based in advanced economies
- Bringing this industry under responsible oversight will require concerted efforts on the part of regulatory authorities, medical and scientif c organizations, as well as education and engagement of patient groups

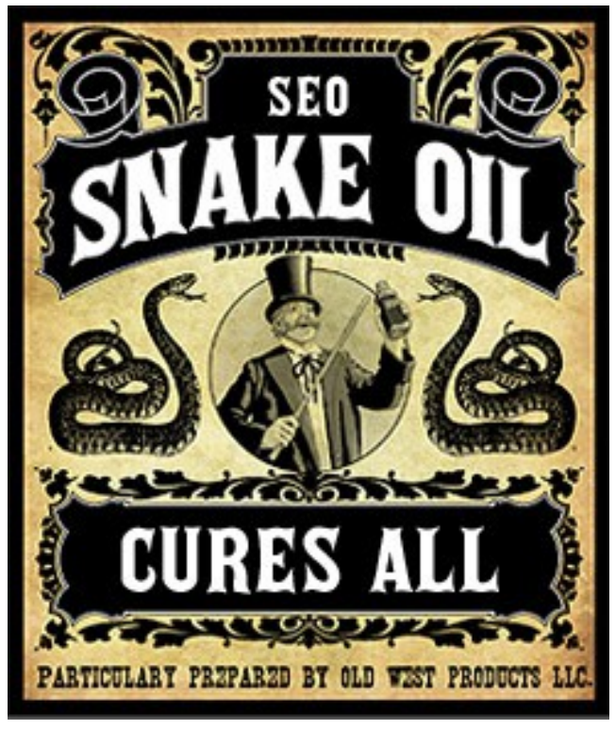
Cytotherapy. 2010

Cellular transplants in amyotrophic lateral sclerosis patients: an observational study.

Gamez J, et al.

Neurology Department, Hospital Universitari Vall d'Hebron, Autonomous University of Barcelona, Barcelona, Spain. 12784jgc@comb.es

BACKGROUND AIMS: Cytotherapy is a promising option for neurodegenerative disease treatment. Because of the fatal prognosis and imperative need for effective treatment, amyotrophic lateral sclerosis (ALS) patients request this therapy before its effectiveness has been verif ed. The increase in clinics offering cytotherapies but providing little scientif c information has prompted considerable medical tourism. We present an observational study of Spanish ALS patients receiving cytotherapy, analyzing the experiences arising from the treatment (TX) and considering two progression markers, FVC and ALSFRS-R.
METHODS: **Twelve ALS patients with a mean age of 48.6 years (SD 12.8) received cytotherapy 26.9 months (SD 15.8) after clinical onset.** ALSFRS-R and FVC at TX were 32.3 (SD 6.8) and 63.4% (SD 15.3), respectively. TX involved transplants of olfactory ensheathing cells in three patients, and autologous mesenchymal stromal cells in the remainder.
RESULTS: One patient died 33 months post-TX after surviving for 49 months. Five required mechanical non-invasive home ventilation 7.4 months post-TX. Two required invasive ventilation 13 months post-TX. Five patients needed gastrostomy feeding 23.3 months post-TX. Survival between clinical onset and the study end date was 50 months (SD 17.2). No signif cant adverse events or changes in the decline of FVC and ALSFRS-R compared with the disease's natural history were observed.
CONCLUSIONS: Our observations suggest that these therapies do not halt the course of the disease. Cytotherapy cannot yet be considered a curative treatment for ALS.



Grazie per l'attenzione