PROGETTO VisNova
START LIVING AGAIN

Update nella Clinica e nella Ricerca sulla SLA

Dalla ricerca di base alla sperimentazione clinica

Insieme contro la SLA

Giovedi 3 Ottobre 2013

Letizia Mazzini

Centro Regionale Esperto SLA

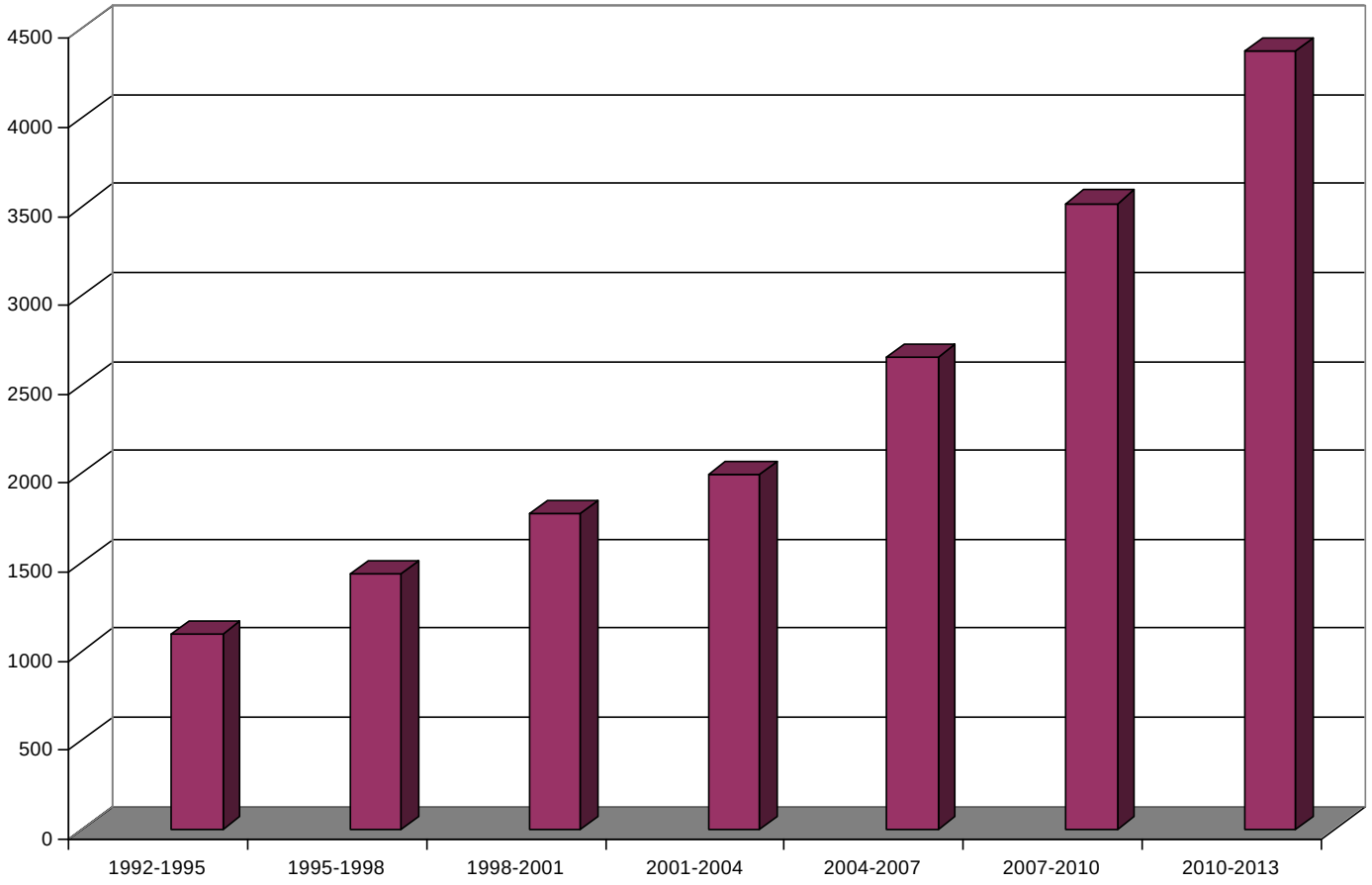
Clinica Neurologica

AOU Maggiore della Carità

Novara

AMEDEO AVOGADRO
università degli studi del piemonte orientale

Pubblicazioni scientifiche recensite PubMed

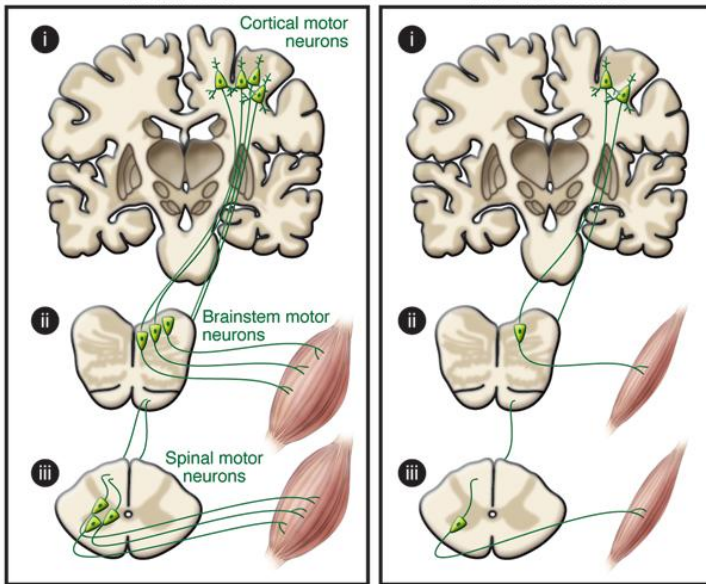


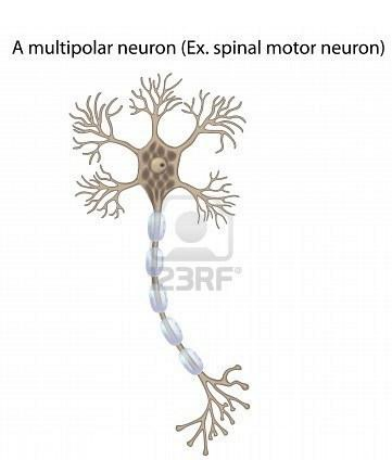
Amyotrophic Lateral Sclerosis

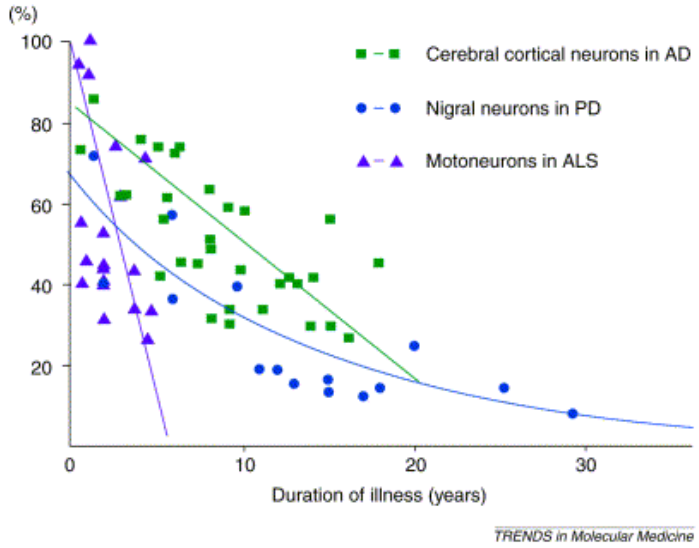
Maladie de Charcot

Motor Neuron Disease

Lou Gehrig's Disease





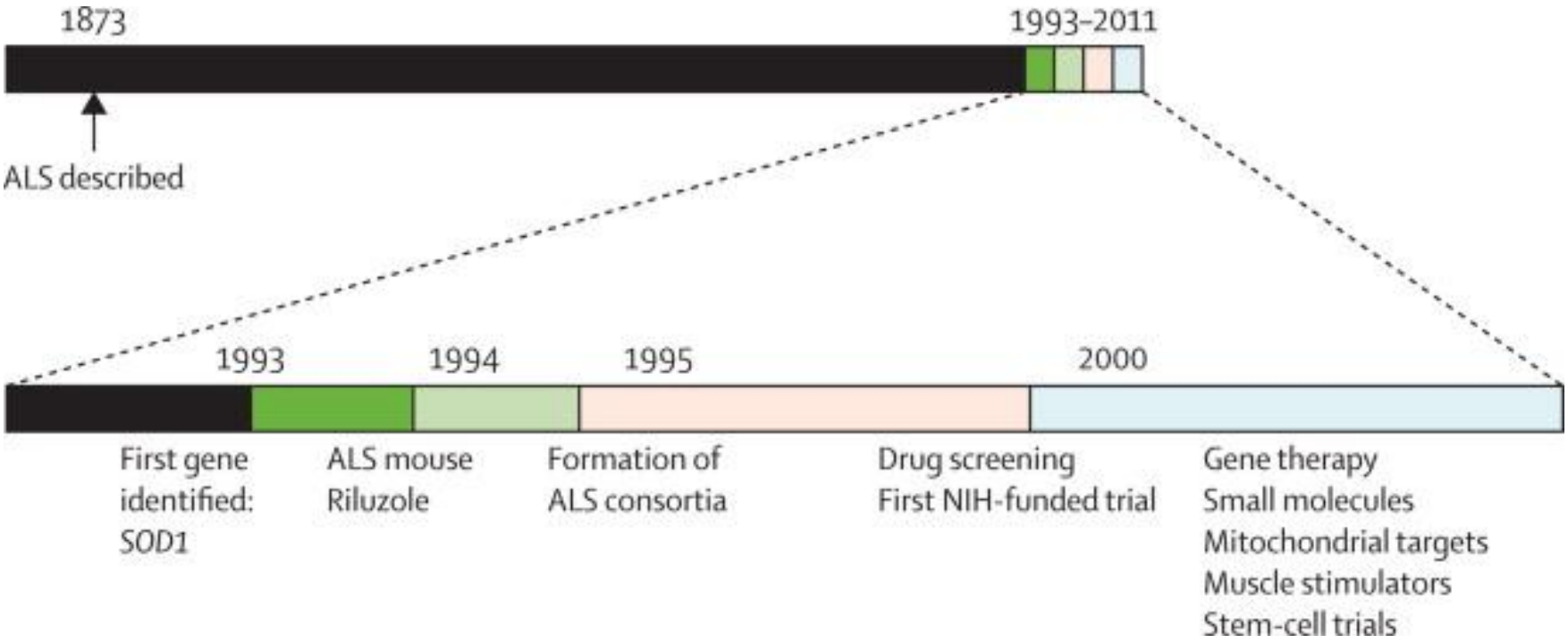


ALS is a rapid and progressive neurodegenerative disease that targets motor neurons in spinal cord, cortex and brain stem.

The selective degeneration of motor neurons manifests as a linear decline in muscular function eventually resulting in paralysis, speech deficits and dysphagia.

(*Rowland LP et al., New Engl J Med, 2001; 344:1688-700).*

Charcot JA Deux cas d'atrophie musculaire progressive avec lesions de la substance grise et des faisceaux antero lateraux de la moelle epiniere. *Arch Physiol Neurol Pathol 1869; 2:744-54*



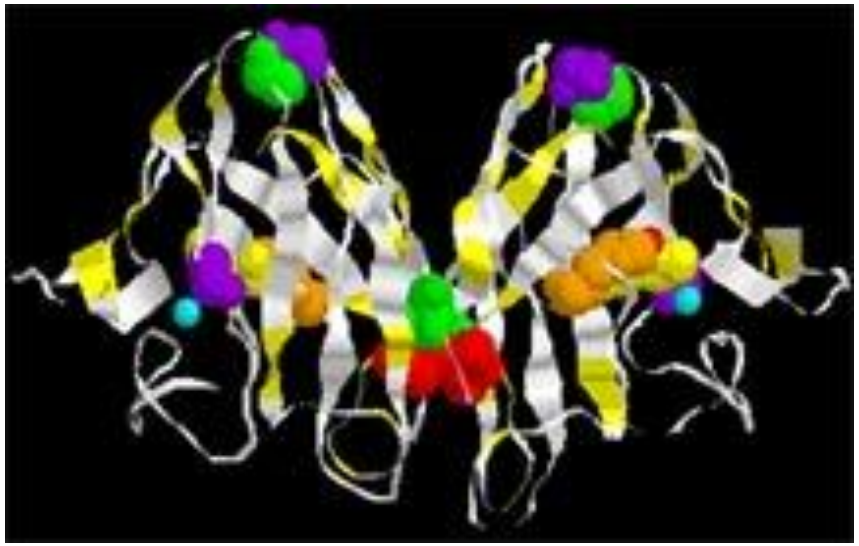
Epidemiologic Investigations of Amyotrophic Lateral Sclerosis: 2. Familial Aggregations Indicative of Dominant Inheritance Part I.
Kurland and Mulder *Neurology*. 1955; 5: 182

5-10% Familial ALS

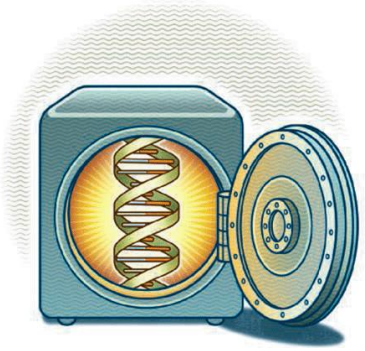
Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis

Daniel R. Rosen*, Teepu Siddique†, David Patterson‡, Denise A. Figlewicz§, Peter Sapp*‖, Afif Hentati†, Deirdre Donaldson‡, Jun Goto§, Jeremiah P. O'Regan*‖, Han-Xiang Deng†, Zohra Rahmani‡, Aldis Krizus§, Diane McKenna-Yasek*, Annarueber Cayabyab†, Sandra M. Gaston*¶, Ralph Berger‡, Rudolph E. Tanzi¶, John J. Halperin**, Brian Herzfeldt†, Raymond Van den Bergh**, Wu-Yen Hung†, Thomas Bird††, Gang Deng†, Donald W. Mulder‡‡, Celestine Smyth†, Nigel G. Laing§§, Edwin Soriano†, Margaret A. Pericak-Vance‖‖, Jonathan Haines¶¶, Guy A. Rouleau§, James S. Gusella¶¶, H. Robert Horvitz‖ & Robert H. Brown Jr*

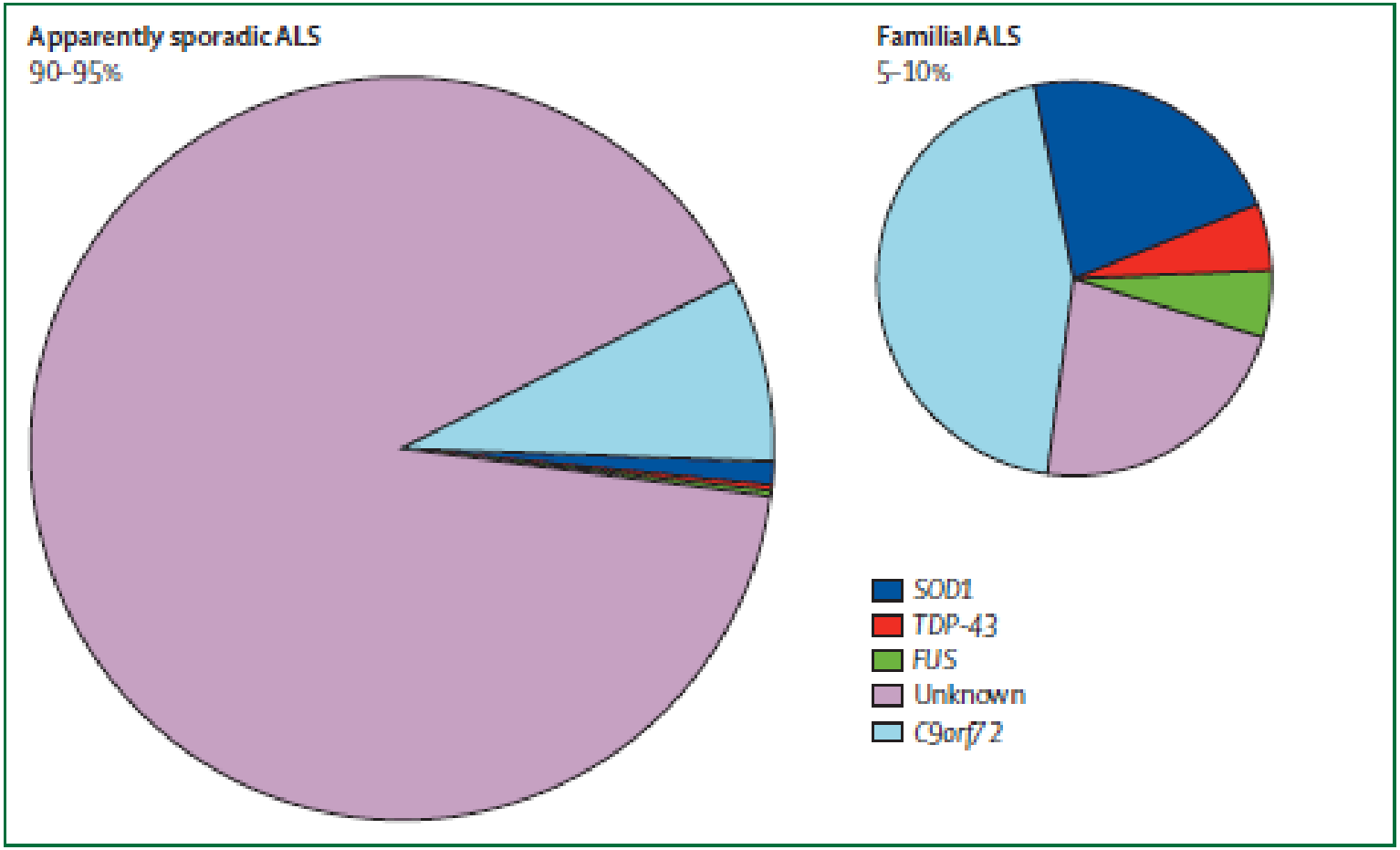
NATURE · VOL 362 · 4 MARCH 1993



Chromosome 21



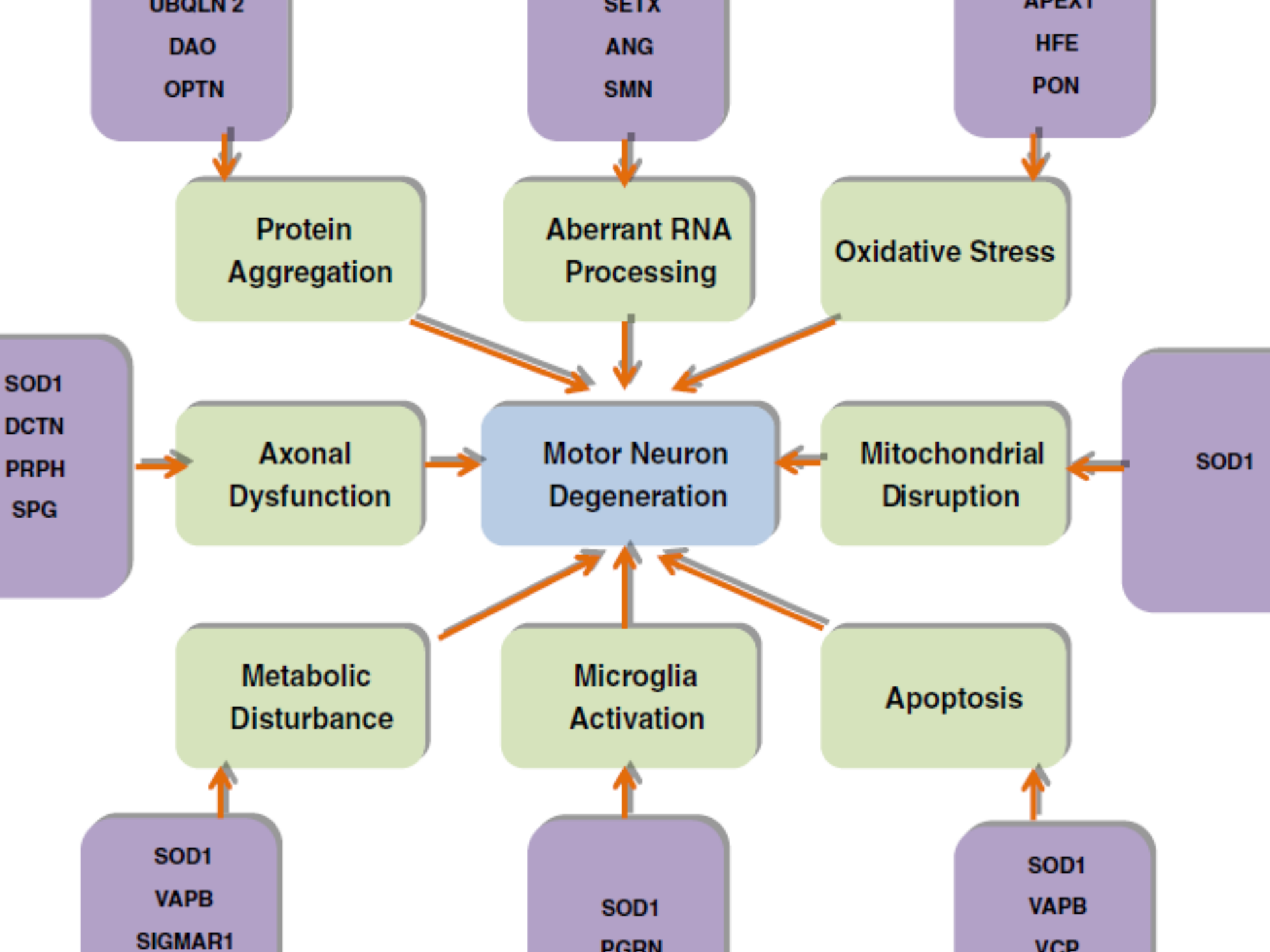
Genetica



Lancet Neurol 2013; 12: 310–22

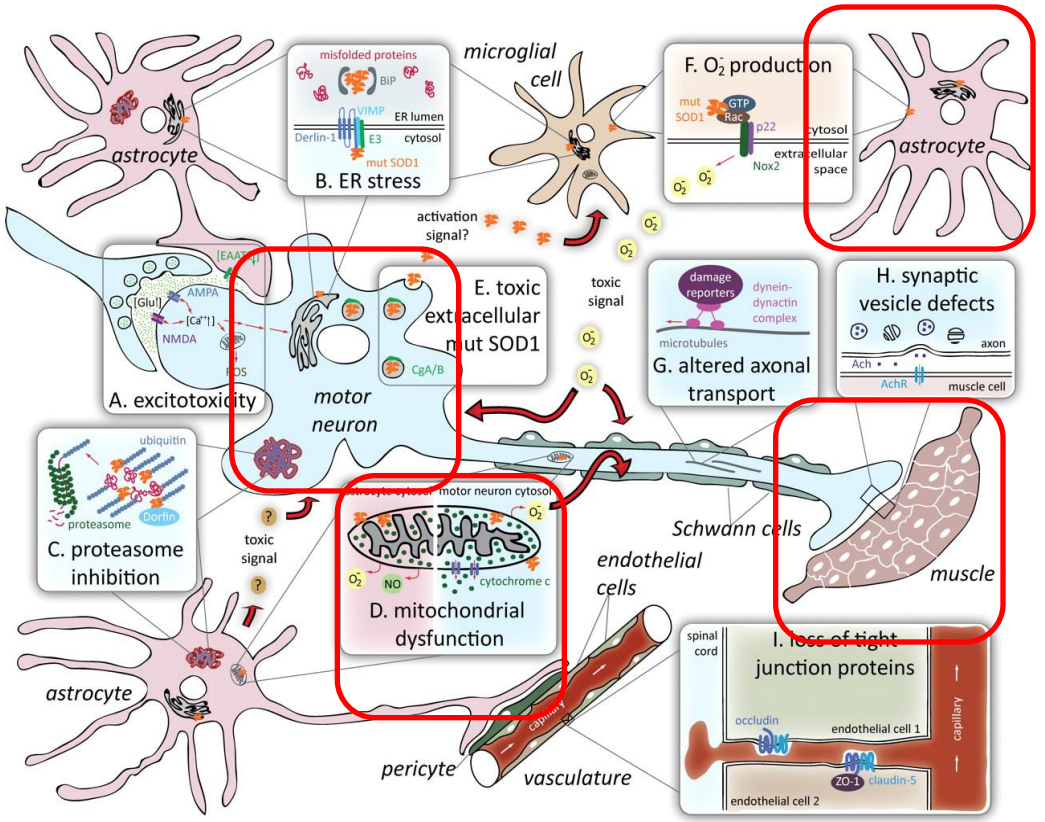
Genetic subtype	Chromosomal locus	Gene	Protein	Onset	Inheritance	Clinical feature	Other diseases caused by the gene
ALS1	21q22.1	SOD1	Cu/Zn SOD-1	Adult	AD/AR	Typical ALS	NA
ALS2	2q33-2q35	Alsin	Alsin	Juv	AR	Slowly progressive, predominantly UMN signs like limb, & facial spasticity	PLS IAHSP
ALS3	18q21	Unknown	Unknown	Adu	AD	Typical ALS with limb onset especially lower limb	NA
ALS4	9q34	SETX	Senataxin	Juv	AD	Slowly progressive, distal hereditary motor neuropathy with pyramidal signs	SCAR 1 and AOA2
ALS5	15q15-21	SPG 11	Spatacsin	Juv	AR	Slowly progressive	HSP
ALS6	16p11.2	FUS	Fused in Sarcoma	Juv/Adu	AD/AR	Typical ALS	NA
ALS8	20q13.3	VAPB	VAPB	Adu	AD	Typical and atypical ALS	SMA
ALS9	14q11.2	ANG	Angiogenin	Adu	AD	Typical ALS, FTD and Parkinsonism	NA
ALS10	1p36.2	TARDBP	DNA-binding protein	Adu	AD	Typical ALS	NA
ALS11	6q21	FIG 4	Phosphoinositide-5phosphatease	Adu	AD	Rapid progressive with prominent corticospinal tract signs	CMT 4 J
ALS12	10p13	OPTN	Optineurin	Adu	AD/AR	Slowly progressive with limb onset and predominant UMN signs	Primary Open Angle Glaucoma
ALS14	9p13.3	VCP	VCP	Adu	AD	Adult onset, with or without FTD	IBMPFD
ALS15/ ALSX	Xp11	UBQLN2	Ubiquilin 2	Adu/Juv	XD	UMN signs proceeding LMN signs	NA
ALS16	9p13.2-21.3	SIGMAR1	SIGMAR1	Juv	AR	Juvenile onset typical ALS	FTD
ALS-FTD1	9q21-22	unknown	unknown	Adu	AD	ALS with FTD	FTD
ALS-FTD2	9p21	C9ORF72	C9ORF72	Adu	AD	ALS with FTD	FTD
NA	2p13	DCTN1	Dynactin	Adu	AD	Distal hereditary motor neuropathy with vocal paresis	NA
Other rare-occurring ALS genes							
ALS3	18q21	Unknown	Unknown	Adu	AD	Typical ALS with limb onset especially lower limb	NA
ALS7	20pter-p13	Unknown	Unknown	Adu	AD/AR	Typical ALS	NA
NA	12q22-23	DAO	DAO	Adu	AD	Typical ALS	NA

Up to date, more than 20-ALS genes have been identified in fALS. These genetic mutations represent different molecular pathways of motor neuron degeneration.


UBQLN 2
DAO
OPTN
SETX
ANG
SMN
APEX1
HFE
PON
Protein Aggregation
Aberrant RNA Processing
Oxidative Stress
SOD1
DCTN
PRPH
SPG
Axonal Dysfunction
Motor Neuron Degeneration
Mitochondrial Disruption
SOD1
Metabolic Disturbance
Microglia Activation
Apoptosis
SOD1
VAPB
SIGMAR1
SOD1
PGRN
SOD1
VAPB
VCP

Gain of function

ure 1. Proposed mechanisms of toxicity in SOD1-mediated ALS



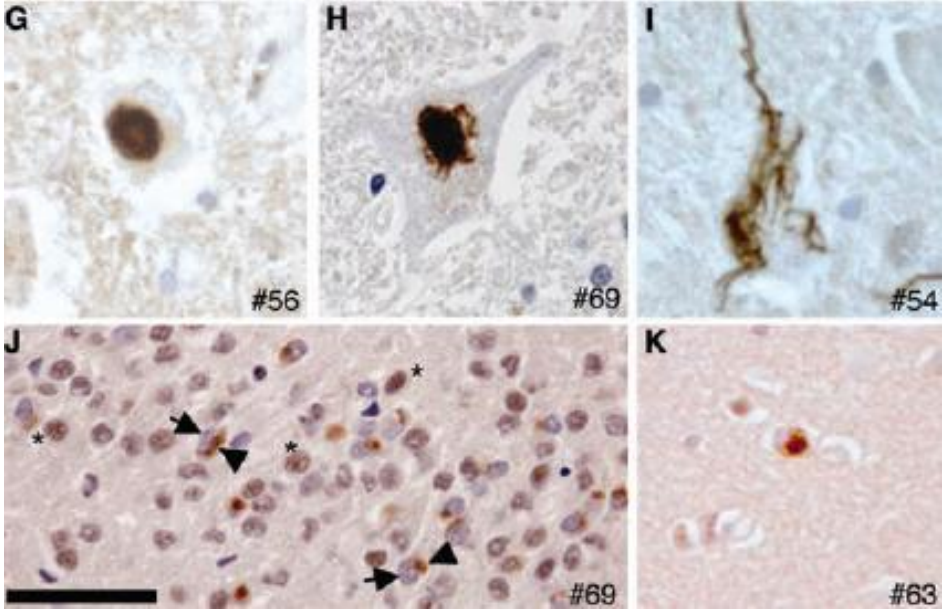
Ilieva et al. J. Cell Biol. 2009:0:jcb.200908164-jcb.200908164

6 OCTOBER 2006 VOL 314 SCIENCE

Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,[1,11*] Deepak M. Sampathu,[1*] Linda K. Kwong,[1*] Adam C. Truax,[1] Matthew C. Micsenyi,[1] Thomas T. Chou,[2] Jennifer Bruce,[1] Theresa Schuck,[1] Murray Grossman,[3,4] Christopher M. Clark,[3,4] Leo F. McCluskey,[3] Bruce L. Miller,[6] Eliezer Masliah,[7] Ian R. Mackenzie,[8] Howard Feldman,[9] Wolfgang Feiden,[10] Hans A. Kretzschmar,[11] John Q. Trojanowski,[1,4,5] Virginia M.-Y. Lee[1,4,5]†

Ubiquitin-positive, tau- and α-synuclein–negative inclusions are hallmarks of frontotemporal lobar degeneration with ubiquitin-positive inclusions and amyotrophic lateral sclerosis. Although the identity of the ubiquitinated protein specific to either disorder was unknown, we showed that TDP-43 is the major disease protein in both disorders. Pathologic TDP-43 was hyperphosphorylated, ubiquitinated, and cleaved to generate C-terminal fragments and was recovered only from affected central nervous system regions, including hippocampus, neocortex, and spinal cord. TDP-43 represents the common pathologic substrate linking these neurodegenerative disorders.



Science
AAAS

TDP-43 Mutations in Familial and Sporadic Amyotrophic Lateral Sclerosis

Jemeen Sreedharan, *et al.*
Science **319**, 1668 (2008);
DOI: 10.1126/science.1154584

September 2008 | Volume 4 | Issue 9 PLoS GENETICS

Novel Mutations in *TARDBP* (TDP-43) in Patients with Familial Amyotrophic Lateral Sclerosis

Nicola J. Rutherford[1], Yong-Jie Zhang[1], Matt Baker[1], Jennifer M. Gass[1], NiCole A. Finch[1], Ya-Fei Xu[1], Heather Stewart[2], Brendan J. Kelley[3], Karen Kuntz[3], Richard J. P. Crook[1], Jemeen Sreedharan[4,5], Caroline Vance[4,5], Eric Sorenson[3], Carol Lippa[6], Eileen H. Bigio[7], Daniel H. Geschwind[8], David S. Knopman[3], Hiroshi Mitsumoto[9], Ronald C. Petersen[3], Neil R. Cashman[10], Mike Hutton[1¤], Christopher E. Shaw[4,5], Kevin B. Boylan[11], Bradley Boeve[3], Neill R. Graff-Radford[11], Zbigniew K. Wszolek[11], Richard J. Caselli[12], Dennis W. Dickson[1], Ian R. Mackenzie[13], Leonard Petrucelli[1], Rosa Rademakers[1*]

OPEN ACCESS Freely available online PLoS GENETICS

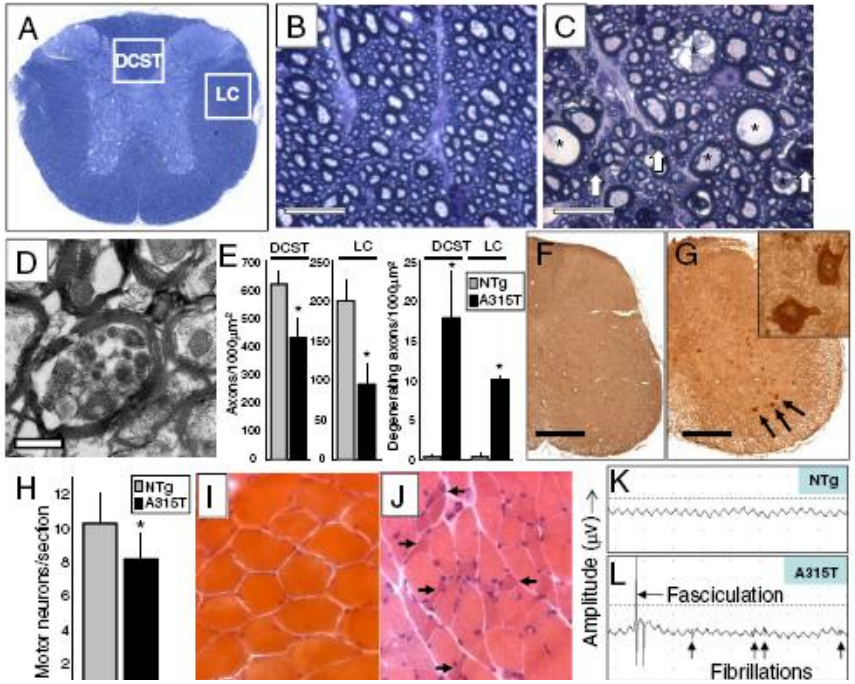
Transgenic Rat Model of Neurodegeneration Caused by Mutation in the *TDP* Gene

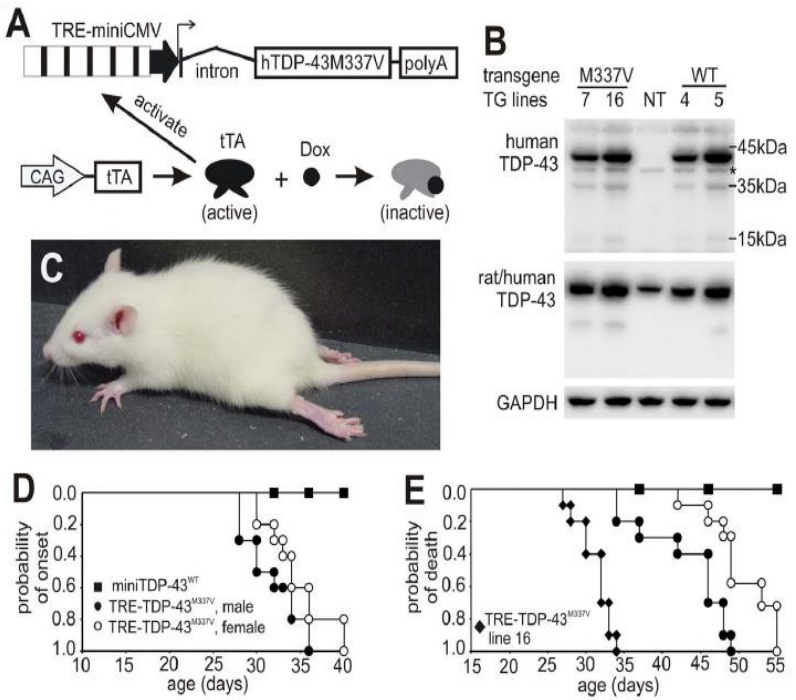
Hongxia Zhou[1☯*], Cao Huang[1☯], Han Chen[2], Dian Wang[1], Carlisle P. Landel[3], Pedro Yuxing Xia[4], Robert Bowser[5], Yong-Jian Liu[6], Xu Gang Xia[1*]

TDP-43 mutant transgenic mice develop features of ALS and frontotemporal lobar degeneration

Iga Wegorzewska[a], Shaughn Bell[a], Nigel J. Cairns[a,b], Timothy M. Miller[a,b], and Robert H. Baloh[a,b,1]

[a]Department of Neurology and [b]Hope Center for Neurological Diseases, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110



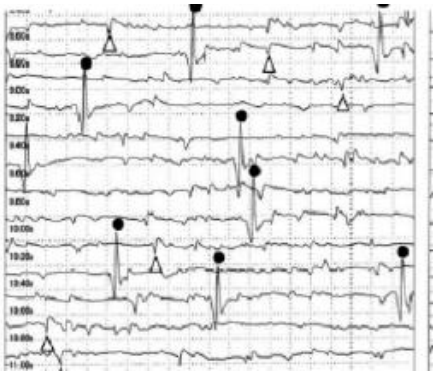


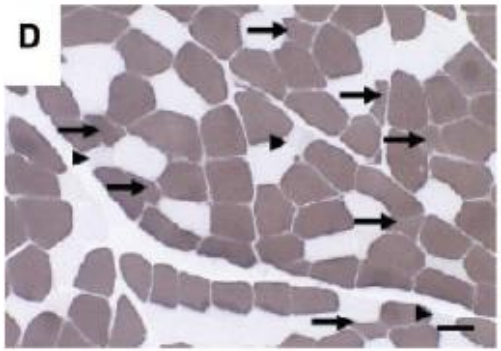
doi:10.1093/brain/awr348 Brain 2012: 135; 833–846 | 833

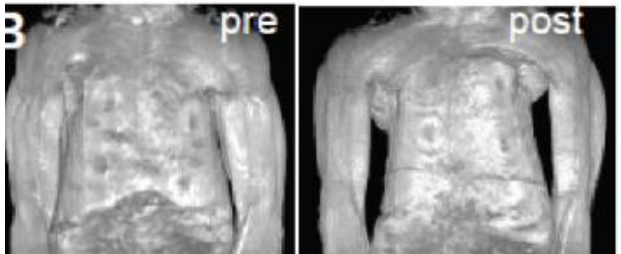
BRAIN
A JOURNAL OF NEUROLOGY

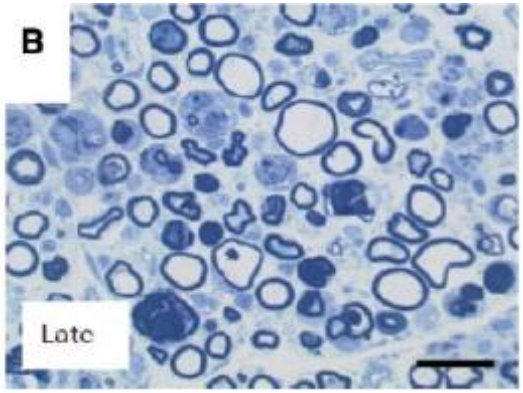
Non-human primate model of amyotrophic lateral sclerosis with cytoplasmic mislocalization of TDP-43

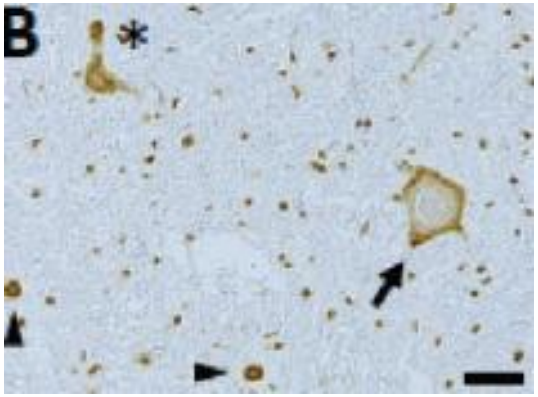
Azusa Uchida,[1] Hiroki Sasaguri,[1] Nobuyuki Kimura,[2] Mio Tajiri,[1] Takuya Ohkubo,[1] Fumiko Ono,[3]











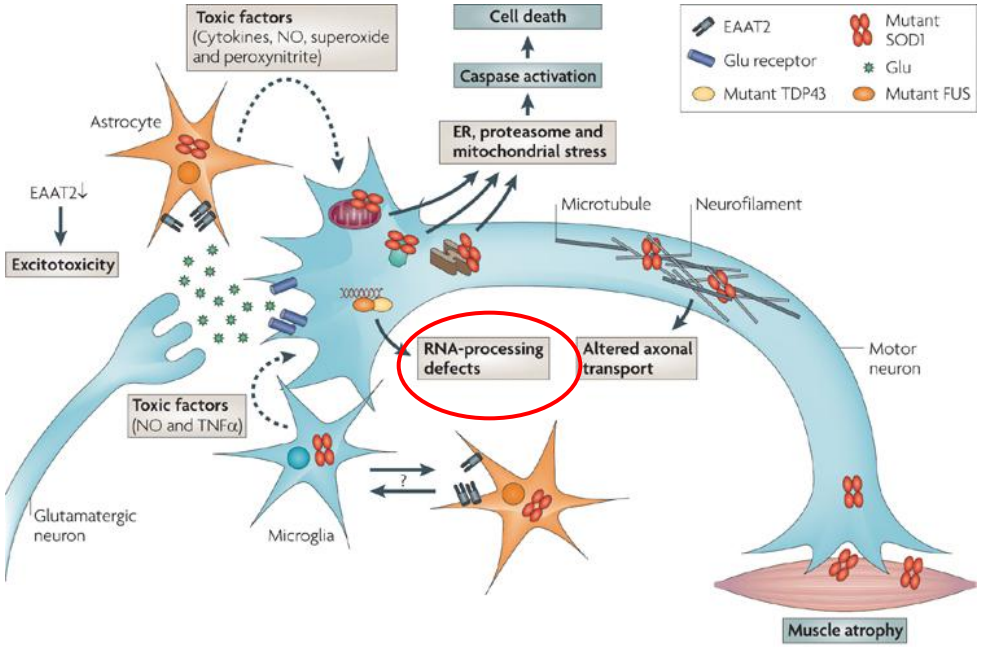
Leading Edge
Minireview

Cell

Rethinking ALS: The FUS about TDP-43

Clotilde Lagier-Tourenne[1] and Don W. Cleveland[1,*]
[1]Ludwig Institute for Cancer Research and Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA 92093-0670, USA
*Correspondence: dcleveland@ucsd.edu
DOI 10.1016/j.cell.2009.03.006

Mutations in TDP-43, a DNA/RNA-binding protein, cause an inherited form of the neurodegenerative disease amyotrophic lateral sclerosis (ALS). Two recent studies (Kwiatkowski et al., 2009; Vance et al., 2009) now report that mutations in FUS/TLS, another DNA/RNA-binding protein, also trigger premature degeneration of motor neurons. TDP-43 and FUS/TLS have striking structural and functional similarities, implicating alterations in RNA processing as a key event in ALS pathogenesis.



Nature Reviews | Genetics

Neuron
Article

Neuron 72, 1–12, October 20, 2011

Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of *C9ORF72* Causes Chromosome 9p-Linked FTD and ALS

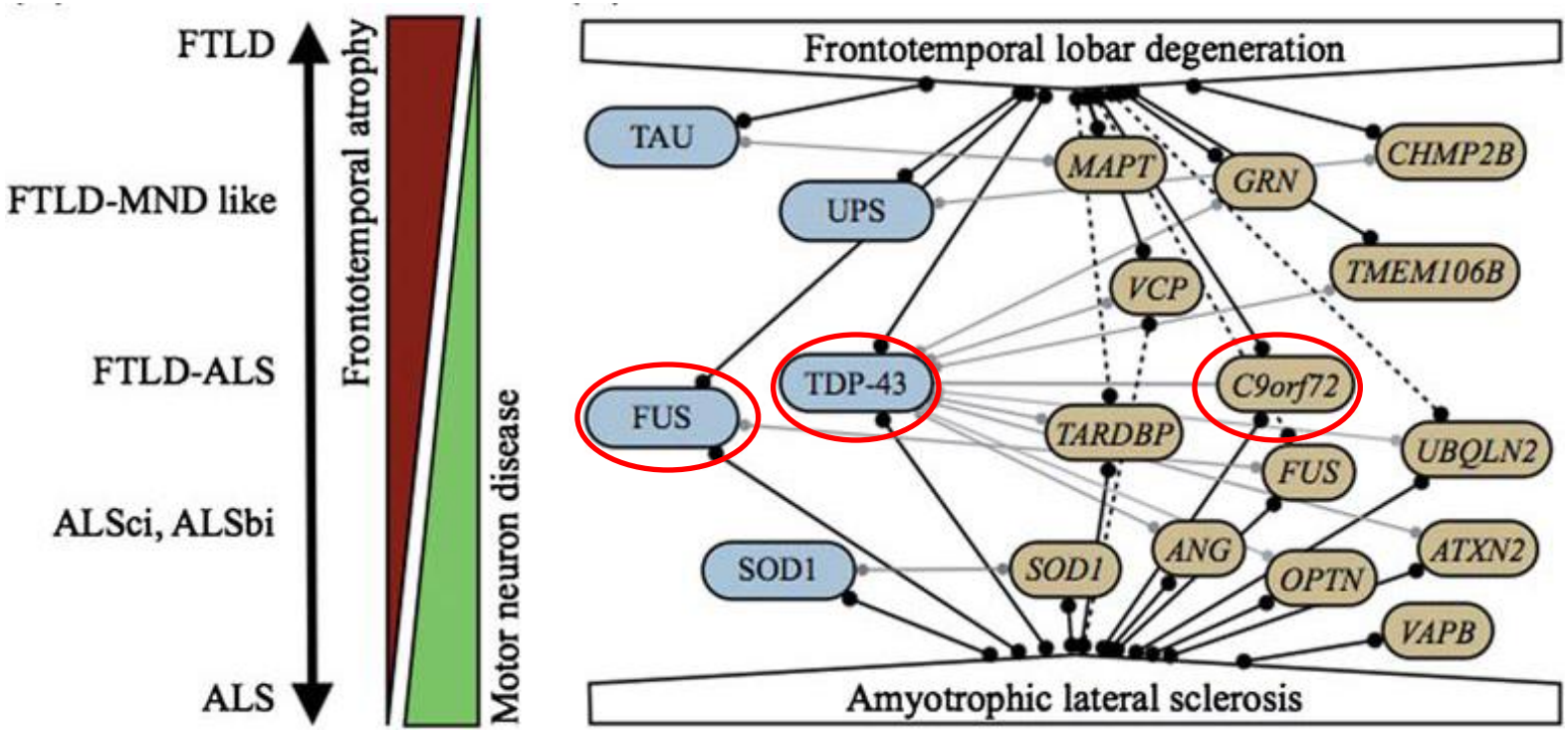
Mariely DeJesus-Hernandez,[1,10] Ian R. Mackenzie,[2,10,*] Bradley F. Boeve,[3] Adam L. Boxer,[4] Matt Baker,[1] Nicola J. Rutherford,[1] Alexandra M. Nicholson,[1] NiCole A. Finch,[1] Heather Flynn,[5] Jennifer Adamson,[1] Naomi Kouri,[1] Aleksandra Wojtas,[1] Pheth Sengdy,[6] Ging-Yuek R. Hsiung,[6] Anna Karydas,[4] William W. Seeley,[4] Keith A. Josephs,[3] Giovanni Coppola,[7] Daniel H. Geschwind,[7] Zbigniew K. Wszolek,[8] Howard Feldman,[6,9] David S. Knopman,[3] Ronald C. Petersen,[3] Bruce L. Miller,[4] Dennis W. Dickson,[1] Kevin B. Boylan,[8] Neill R. Graff-Radford,[8]

Neuron
Article

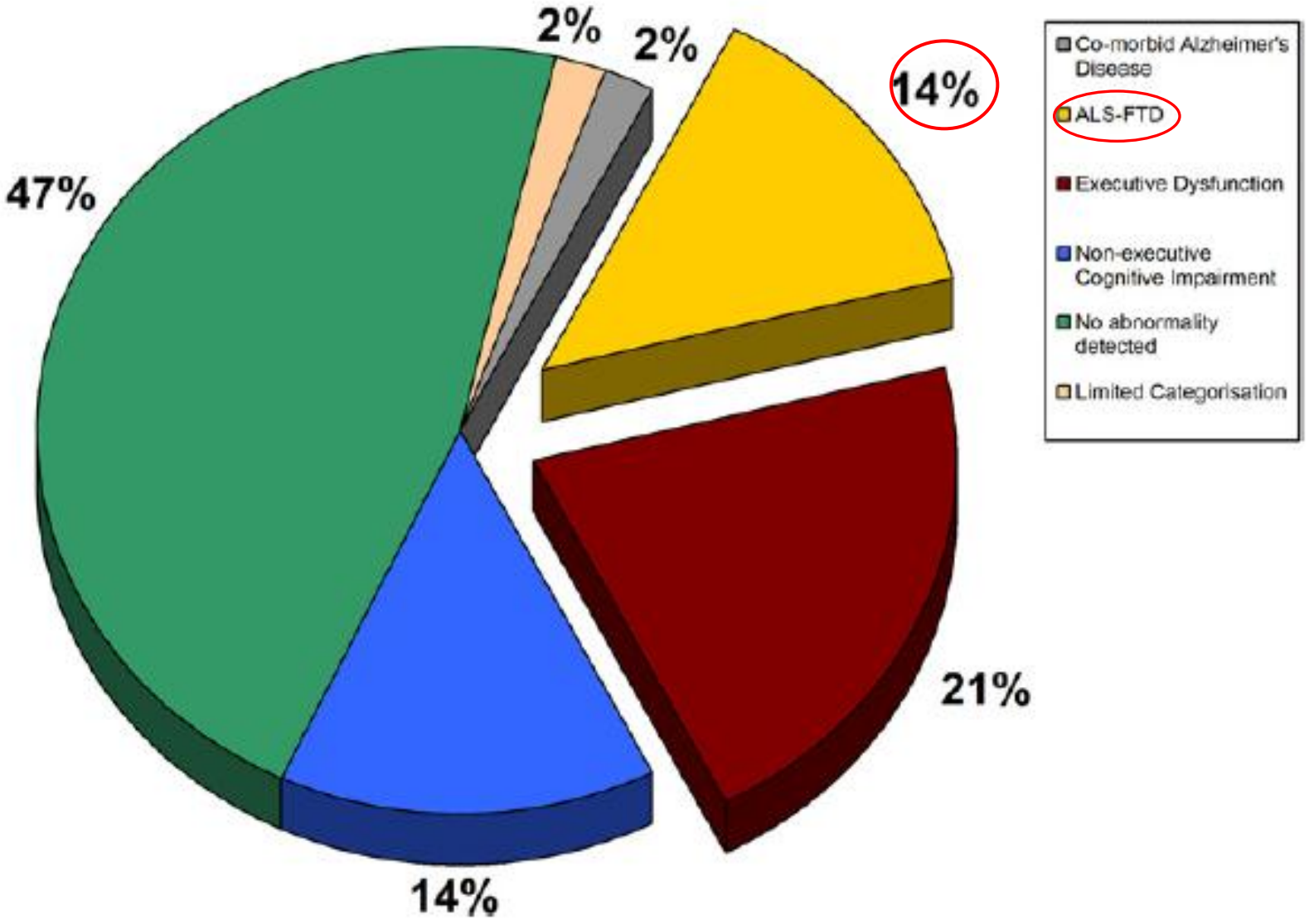
A Hexanucleotide Repeat Expansion in *C9ORF72* Is the Cause of Chromosome 9p21-Linked ALS-FTD

Alan E. Renton,[1,38] Elisa Majounie,[2,38] Adrian Waite,[3,38] Javier Simón-Sánchez,[4,5,38] Sara Rollinson,[6,38] J. Raphael Gibbs,[7,8,38] Jennifer C. Schymick,[1,38] Hannu Laaksovirta,[9,38] John C. van Swieten,[4,5,38] Liisa Myllykangas,[10] Hannu Kalimo,[10] Anders Paetau,[10] Yevgeniya Abramzon,[1] Anne M. Remes,[11] Alice Kaganovich,[12] Sonja W. Scholz,[2,13,14] Jamie Duckworth,[7] Jinhui Ding,[7] Daniel W. Harmer,[15] Dena G. Hernandez,[2,8] Janel O. Johnson,[1,8] Kin Mok,[8] Mina Ryten,[8] Danyah Trabzuni,[8] Rita J. Guerreiro,[8] Richard W. Orrell,[16] James Neal,[17] Alex Murray,[18] Justin Pearson,[3] Iris E. Jansen,[4] David Sondervan,[4] Harro Seelaar,[5] Derek Blake,[3] Kate Young,[6] Nicola Halliwell,[6] Janis Bennion Callister,[6] Greg Toulson,[6] Anna Richardson,[19] Alex Gerhard,[19] Julie Snowden,[19] David Mann,[19] David Neary,[19] Michael A. Nalls,[2] Terhi Peuralinna,[9] Lilja Jansson,[9] Veli-Matti Isoviita,[9] Anna-Lotta Kaivorinne,[11] Maarit Hölttä-Vuori,[20] Elina Ikonen,[20] Raimo Sulkava,[21] Michael Benatar,[22] Joanne Wuu,[23] Adriano Chiò,[24] Gabriella Restagno,[25] Giuseppe Borghero,[26] Mario Sabatelli,[27] The ITALSGEN Consortium,[28] David Heckerman,[29] Ekaterina Rogaeva,[30] Lorne Zinman,[31] Jeffrey D. Rothstein,[14] Michael Sendtner,[32] Carsten Drepper,[32] Evan E. Eichler,[33] Can Alkan,[33] Ziedulla Abdullaev,[34] Svetlana D. Pack,[34] Amalia Dutra,[35] Evgenia Pak,[35] John Hardy,[8] Andrew Singleton,[2] Nigel M. Williams,[3,38] Peter Heutink,[4,38] Stuart Pickering-Brown,[6,38] Huw R. Morris,[3,36,37,38] Pentti J. Tienari,[9,38] and Bryan J. Traynor[1,14,38,*]

FTLD and ALS : two extremes of a clinical continuum.



Annals of Medicine, 2012; Early Online: 1–12



Phukan J, Elamin M, Bede P, *et al*. *J Neurol Neurosurg Psychiatry* (2011). doi:10.1136/jnnp-2011-300188

Proposed criteria for familial amyotrophic lateral sclerosis

Definite FALS	
History:	ALS patient with at least two first- or second-degree relatives with ALS
Genetics:	ALS patient with at least one relative with ALS and gene-positive cosegregation
Probable FALS	
History:	ALS patient with one first- or second-degree relative with ALS
Possible FALS	
History:	ALS patient with a distant relative with ALS (more distant than first- or second-degree)
Genetics:	Sporadic ALS patient with no family history, but positive for a FALS gene
Neurodegeneration:	ALS patient with a family member with confirmed frontotemporal dementia

Amyotrophic Lateral Sclerosis, 2011

doi:10.1093/brain/awr248 Brain 2011: 134; 3454–3457 | 3454

BRAIN
A JOURNAL OF NEUROLOGY

The risk to relatives of patients with sporadic amyotrophic lateral sclerosis

Martha F. Hanby,[1] Kirsten M. Scott,[1] William Scotton,[1] Lokesh Wijesekera,[1] Thomas Mole,[1] Catherine E. Ellis,[1] P. Nigel Leigh,[1,2] Christopher E. Shaw[1] and Ammar Al-Chalabi[1]

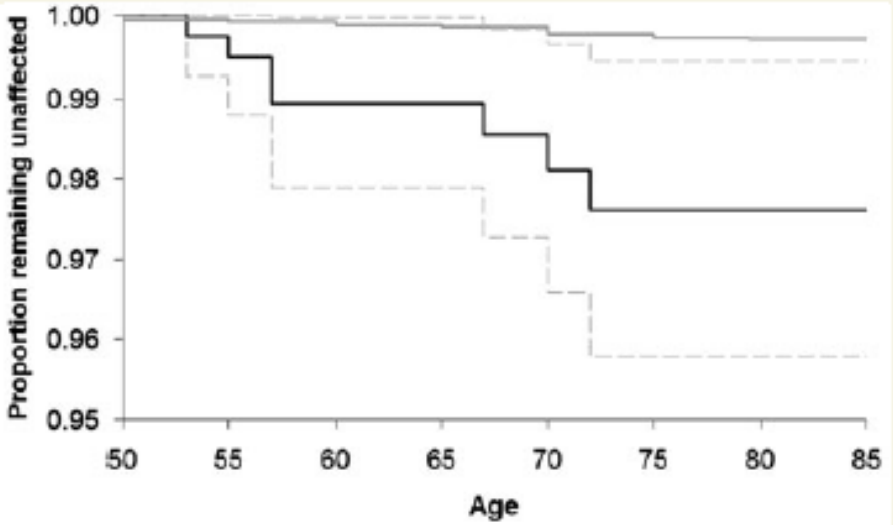


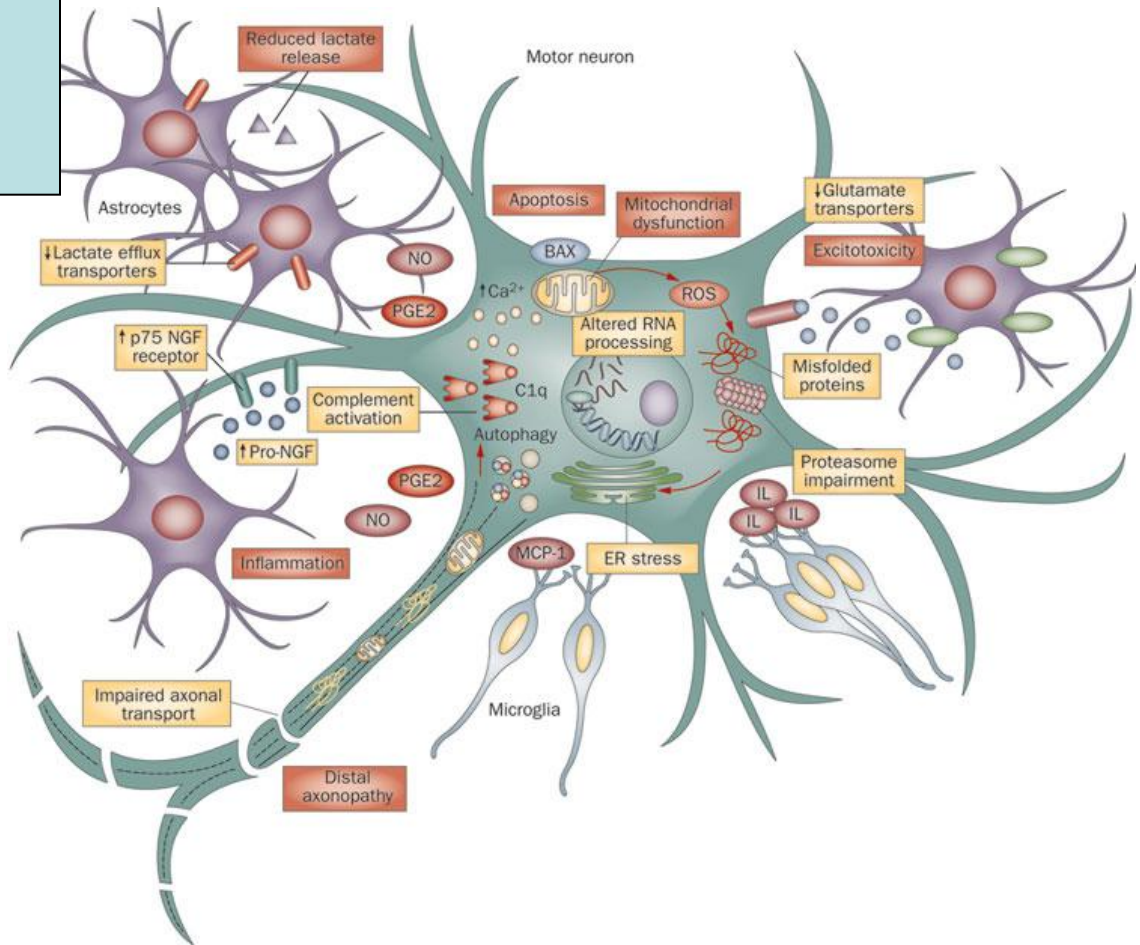
Figure 1 Proportion of siblings remaining unaffected in the clinic population compared with the background population risk. Siblings represented by black line with 95% confidence limits as thinner dashed lines. Risk to local population shown by upper grey line. Note the *Y* axis starts at 0.95, not zero.

Multifactorial Disease

20 GENI

1. RNA processing
2. vesicle trafficking
3. oxidative stress
4. autophagy
5. Unknown function

\+ **Age** \+ ***Environment***



Orphanet Journal of Rare Diseases BioMed Central

Review

Open Access

Amyotrophic lateral sclerosis

Lokesh C Wijesekera† and P Nigel Leigh*†

Appendix 1 - Some exogenous risk factors implicated in sporadic ALS

- Age at menopause (females) [270, 271]
- Dietary factors [272]
- Electrical injury [273]
- Family history of non-ALS neurodegenerative disease (Parkinson's or Alzheimer's disease) [274]
- Geographical residence (rural, suburban or urban) [275]
- Gulf war service (Male veterans) [276-278]
- Maternal age [279], Number of births (in females)& Birth order [81, 279, 280], Loss of child [281]
- Occupation [81, 282]
- Physical activity [283, 284],
- Playing football professionally [285-287]
- Previous poliomyelitis infection [288]
- Race/ethnicity [289]
- Smoking [79-81, 290, 291]
- Toxin exposure (agricultural chemicals, lead) [282, 292]
- Trauma (*e.g.* Head injury) [274, 285, 293]
- Years of education [81]

Amyotrophic Lateral Sclerosis of Guam

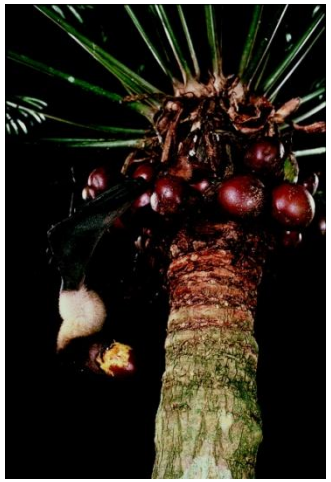
Multifactorial disease

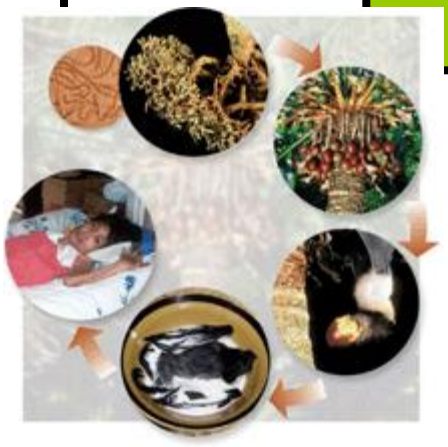
Genetic factors

Maggiore Incidenza (20\100.000)

Environmental Factors

Cycas Circinalis Neurotoxins





Occurrence of amyotrophic lateral sclerosis among Gulf War veterans

R.D. Horner, PhD; K.G. Kamins, PhD; J.R. Feussner, MD, MPH; S.C. Grambow, PhD; J. Hoff-Lindquist, MStat; Y. Harati, MD; H. Mitsumoto, MD, DSci; R. Pascuzzi, MD; P.S. Spencer, PhD; R. Tim, MD; D. Howard, MSPH; T.C. Smith, MS; M.A.K. Ryan, MD, MPH; C.J. Coffman, PhD; and E.J. Kasarskis, MD, PhD

NEUROLOGY 2003;61:742–749

Table 3 Age-adjusted, average, annual 10-year cumulative incidence of ALS among military personnel by self-reported deployment status during the Gulf War

	Self-reported deployment status						
	Deployed, n = 696,118			Nondeployed, n = 1,786,215			
Population	Population	Cases	Rate*	Population	Cases	Rate*	Risk ratio† (95% CL)
Total	696,118	49	0.84 (0.60, 1.07)	1,786,215	58	0.31 (0.23, 0.38)	2.74 (1.87, 4.01)
Unit							
Active duty	587,426	40	0.99 (0.67, 1.31)	1,646,926	53	0.29 (0.21, 0.37)	3.37 (2.21, 5.14)
Reserves/National Guard	108,692	9	0.99 (0.33, 1.65)	139,289	5	0.33 (0.04, 0.61)	3.05 (1.01, 9.16)
Service branch							
Air Force	82,639	14	1.82 (0.86, 2.78)	523,763	18	0.34 (0.18, 0.49)	5.38 (2.67, 10.85)
Army	351,046	20	0.63 (0.35, 0.90)	588,740	21	0.34 (0.19, 0.48)	1.85 (1.00, 3.43)
Marine Corps	103,612	4	0.52 (0.00, 1.04)	146,294	5	0.29 (0.03, 0.55)	1.77 (0.46, 6.76)
Navy	157,969	11	0.83 (0.33, 1.32)	486,559	14	0.28 (0.13, 0.42)	2.99 (1.35, 6.61)

NEUROLOGY 2006;67:771–776

Paraoxonase cluster polymorphisms are associated with sporadic ALS

M. Saeed, MD; N. Siddique, RN, MSN; W.-Y. Hung, PhD; E. Usacheva, PhD; E. Liu, MD; R.L. Sufit, MD; S.L. Heller, MD; J.L. Haines, PhD; M. Pericak-Vance, PhD; and T. Siddique, MD

Toxicology and Applied Pharmacology 157, 227–233 (1999)
Article ID taap.1999.8703, available online at http://www.idealibrary.com on IDEAL®

HIGHLIGHT

Association of Low PON1 Type Q (Type A) Arylesterase Activity with Neurologic Symptom Complexes in Gulf War Veterans

Robert W. Haley,* Scott Billecke,† and Bert N. La Du†

March 2012 | Volume 7 | Issue 3

PLoS one

A High-Density Genome-Wide Association Screen of Sporadic ALS in US Veterans

Lydia Coulter Kwee[1,2,3], Yutao Liu[1,2,3], Carol Haynes[2,3], Jason R. Gibson[1,2,3], Annjanette Stone[4], Steven A. Schichman[4,5], Freya Kamel[6], Lorene M. Nelson[7], Barbara Topol[7], Stephen K. Van Den Eeden[8], Caroline M. Tanner[9], Merit E. Cudkowicz[10], Daniela L. Grasso[10], Robert Lawson[10], Sumitra Muralidhar[11], Eugene Z. Oddone[1,3], Silke Schmidt[1,2,3]*, Michael A. Hauser[1,2,3]*

Our GWAS of US veterans did not identify any genetic associations that reached genome-wide significance ($p<5.0\times10^{-8}$)

Our results underscore the difficulty of identifying and convincingly replicating genetic associations with a rare and genetically heterogeneous disorder such as ALS, and suggest that common SNPs are unlikely to account for a substantial proportion of patients affected by this devastating disorder.

VIEWS & REVIEWS

Smoking may be considered an established risk factor for sporadic ALS

Carmel Armon, MD, MHS

Neurology® 2009;73:1693–1698

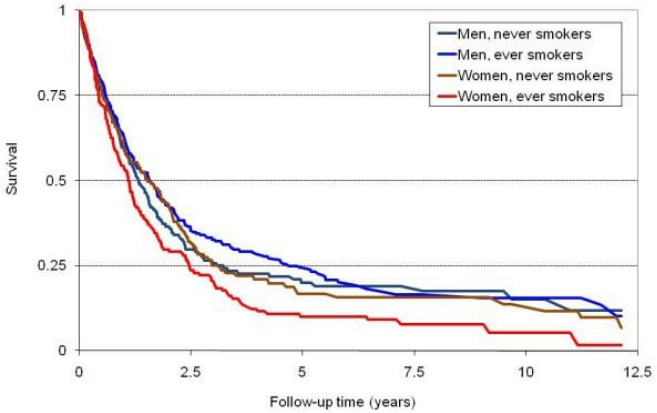
Alonso et al. BMC Neurology 2010, 10:6
http://www.biomedcentral.com/1471-2377/10/6

BMC Neurology

RESEARCH ARTICLE Open Access

Association of smoking with amyotrophic lateral sclerosis risk and survival in men and women: a prospective study

Alvaro Alonso[1,2*], Giancarlo Logroscino[3], Susan S Jick[4], Miguel A Hernán[5,6]



Human Molecular Genetics, 2009, Vol. 18, No. 20 3997–4006
doi:10.1093/hmg/ddp339
Advance Access published on July 23, 2009

Rare missense variants of neuronal nicotinic acetylcholine receptor altering receptor function are associated with sporadic amyotrophic lateral sclerosis

Mario Sabatelli[1,3,*,†], Fabrizio Eusebi[4,6,†], Ammar Al-Chalabi[7], Amelia Conte[1,3], Francesca Madia[1], Marco Luigetti[1], Irene Mancuso[3,2], Cristina Limatola[4,6], Flavia Trettel[4], Fabrizia Sobrero[4], Silvia Di Angelantonio[5], Francesca Grassi[4], Amalia Di Castro[4], Claudia Moriconi[4], Sergio Fucile[4,6], Serena Lattante[2], Giuseppe Marangi[2], Marina Murdolo[2], Daniela Orteschi[2], Alessandra Del Grande[1], Pietro Tonali[1,8], Giovanni Neri[2] and Marcella Zollino[2,†]

Nel 2000→inchiesta antidoping calciatori italiani

doi:10.1093/brain/awh373 *Brain* (2005), **128**, 472–476

Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players

Adriano Chiò,[3] Gianmartino Benzi,[1] Maurizia Dossena,[1] Roberto Mutani[3] and Gabriele Mora[2]

Table 1 *SMRs by age classes*

Age classes	Expected cases	Observed cases	SMR	95% CI
15–49	0.53	4	7.5	2.0–19.2
50–69	0.24	1	4.2	0.1–23.4

Table 4 *SMR by number of years as a professional football player*

Number of years	Expected cases	Observed cases	SMR	95% CI
≤5 years	0.57	2	3.5	0.4–12.7
>5 years	0.20	3	15.2	3.1–44.4

European Journal of Epidemiology (2005) 20: 237–242
DOI 10.1007/s10654-004-6879-7

NEURO-EPIDEMIOLOGY

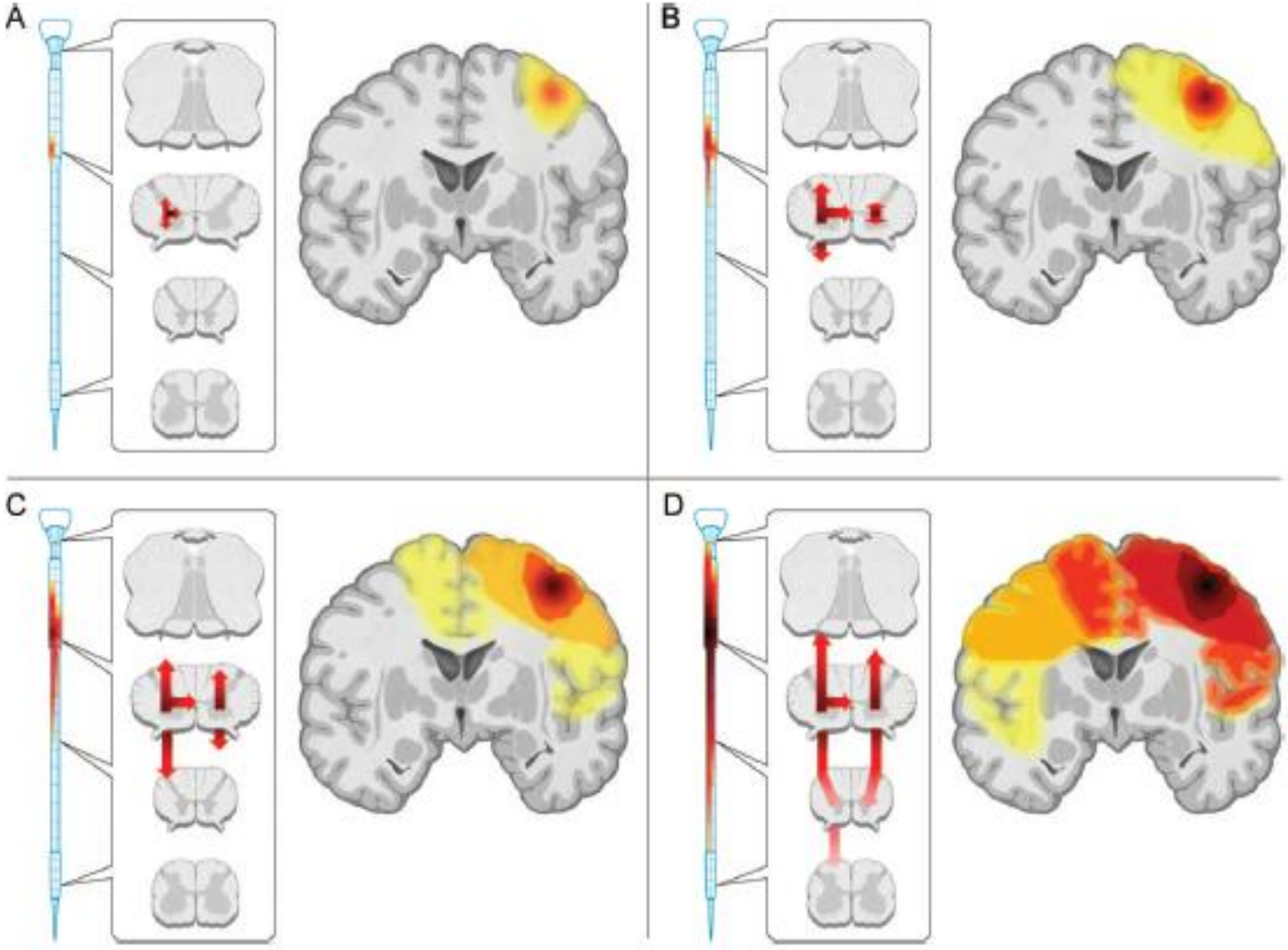
Proportionate mortality of Italian soccer players: Is amyotrophic lateral sclerosis an occupational disease?

Stefano Belli[1] & Nicola Vanacore[2]
[1]*Istituto Superiore di Sanità, Department of Environment and Primary Prevention, Rome, Italy*; [2]*Istituto Superiore di Sanità, National Centre for Epidemiology, Surveillance and Health Promotion, Rome, Italy*

Controversy in ALS—where does the disease begin?

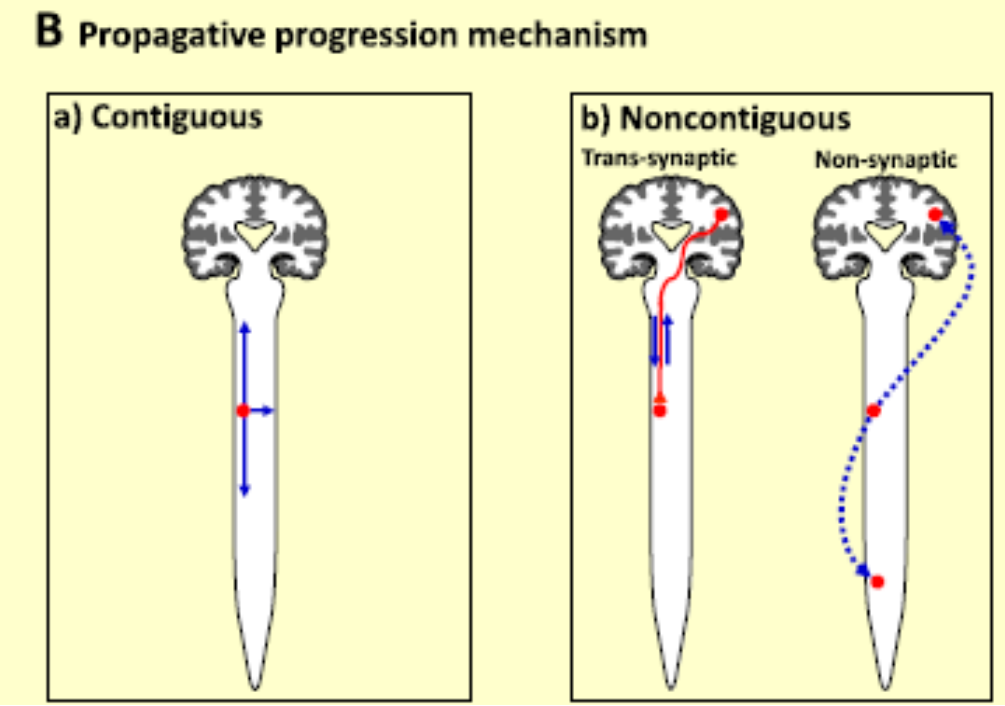
Despite Charcot's initial observation of concomitant UMN and LMN pathological changes in ALS, the question of where ALS begins has not been established.

Resolution of this question might enhance the understanding of the pathophysiology of ALS and has diagnostic and therapeutic importance.

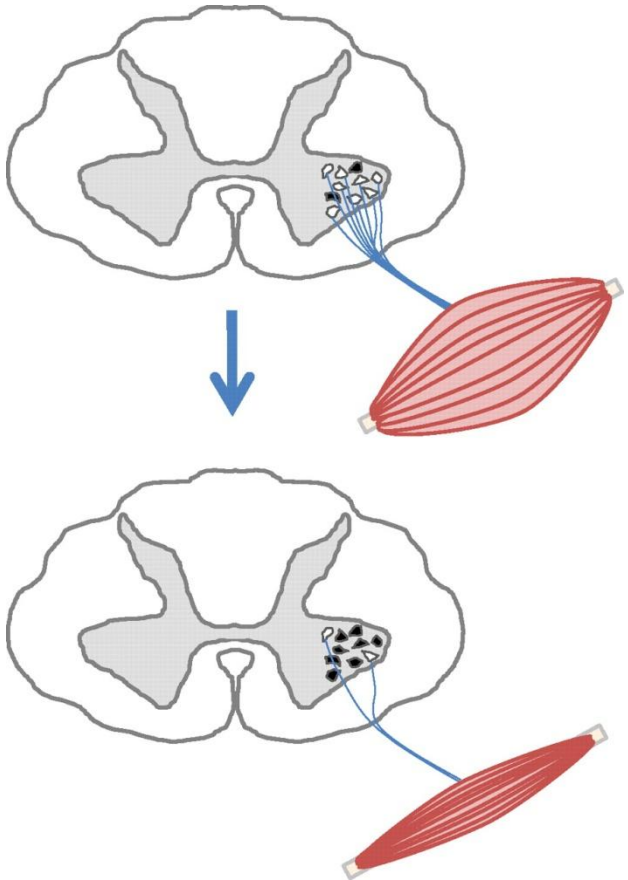


John M. Ravits, MD Neurology 73 September 8, 2009

Onset and regional spread mechanisms



Local propagation

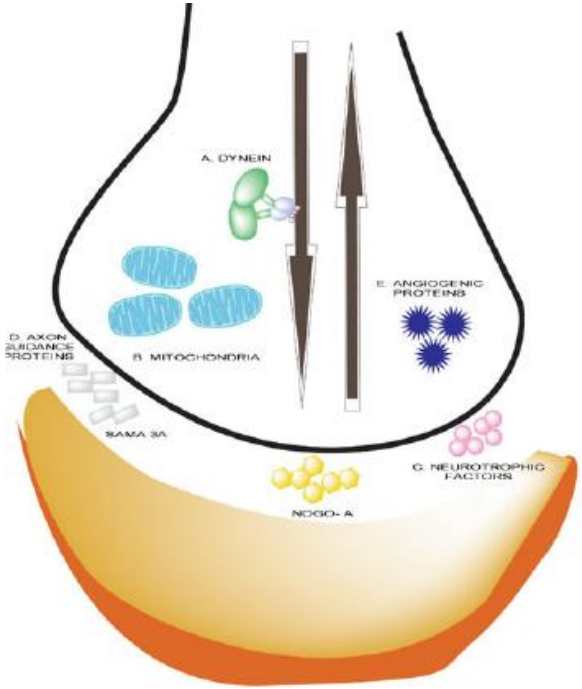


Kanouchi T et al. J Neurol Neurosurg Psychiatry
doi:10.1136/jnnp-2011-301826

J Mol Neurosci (2011) 43:470–477
DOI 10.1007/s12031-010-9467-1

The "Dying-Back" Phenomenon of Motor Neurons in ALS

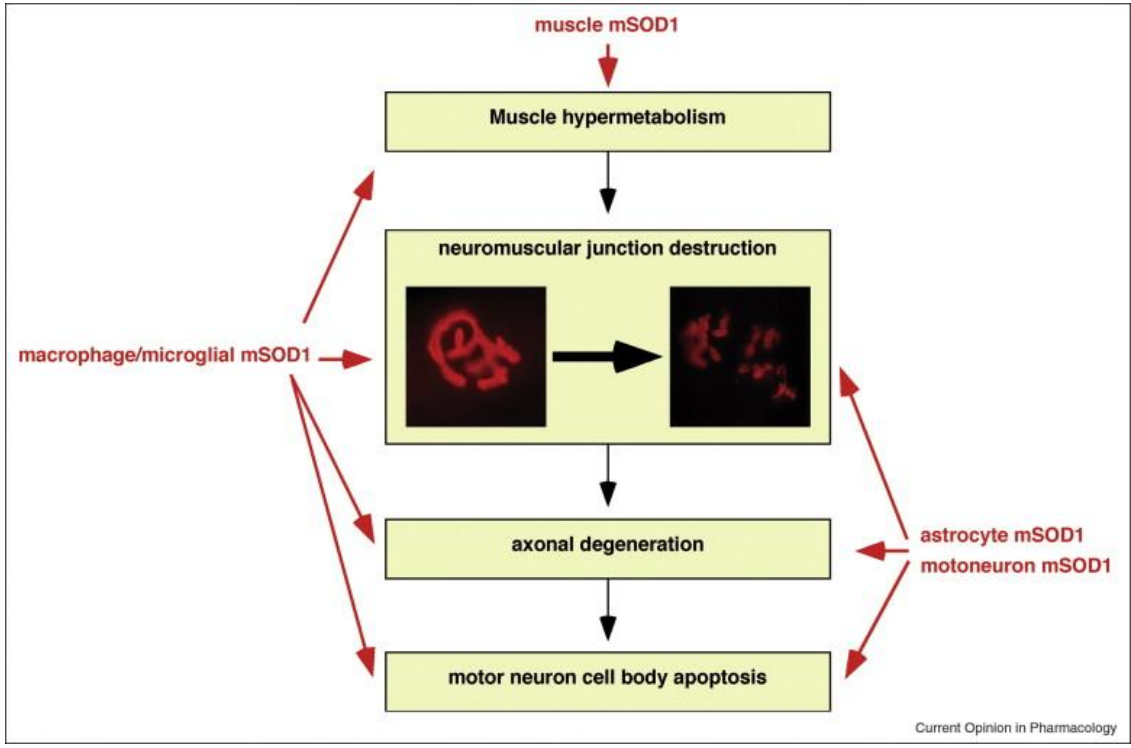
Michal Dadon-Nachum · Eldad Melamed · Daniel Offen



ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Pharmacology

Neuromuscular junction destruction during amyotrophic lateral sclerosis: insights from transgenic models

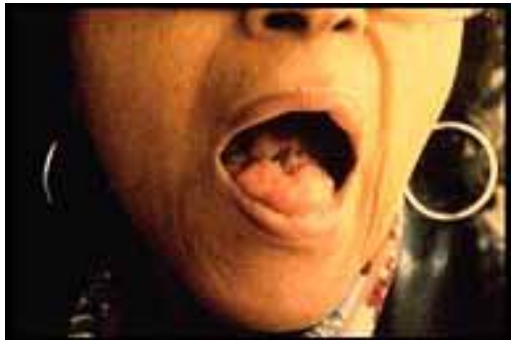
Luc Dupuis[1,2] and Jean-Philippe Loeffler[1,2]

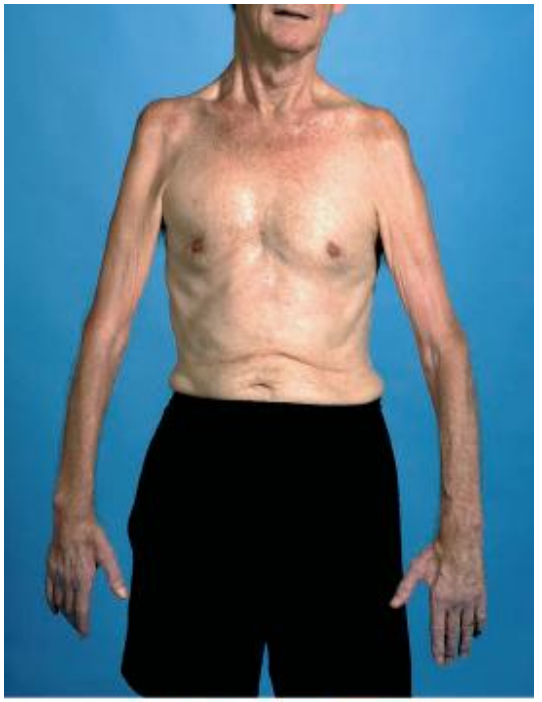


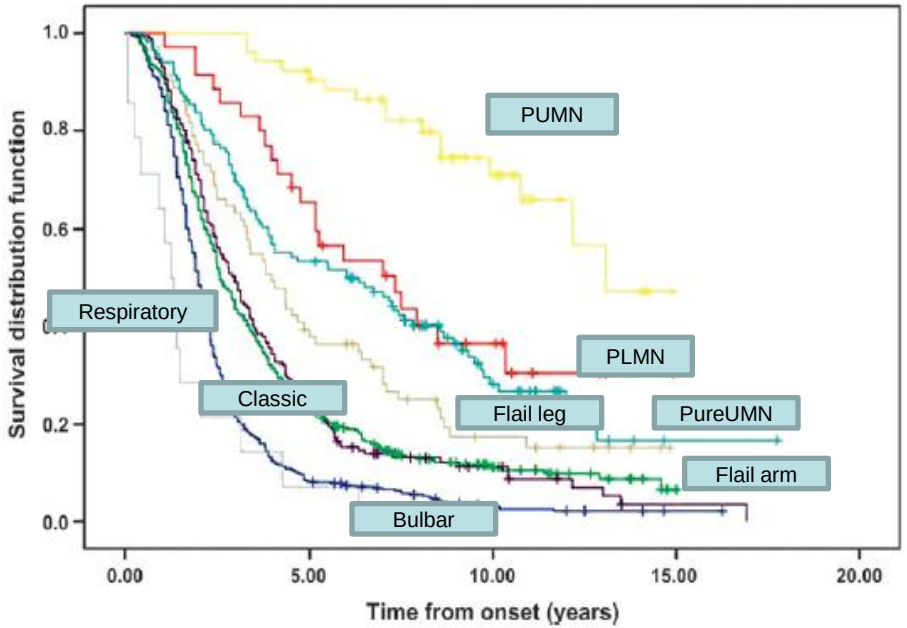
Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study

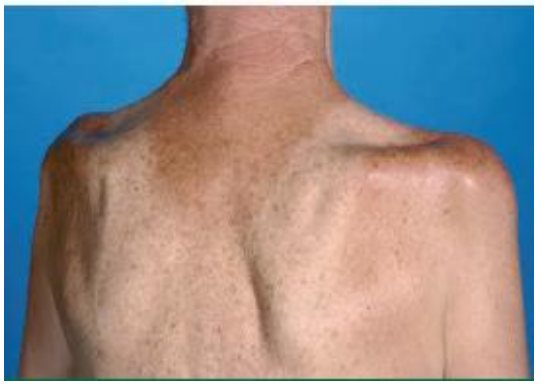
Adriano Chiò,[1,2] Andrea Calvo,[1] Cristina Moglia,[1] Letizia Mazzini,[3] Gabriele Mora,[4]
PARALS study group*

J Neurol Neurosurg Psychiatry (2011).









Biomarkers

Biomarker type	Value	Current benchmarks
Diagnostic	Initiate therapy earlier; Exclude ALS	Neurological history & examination Electromyography (Revised El Escorial/Awaji criteria)[131]
Prognostic	Identify patterns of progression: 1. Improved stratification in therapeutic trials 2. Timely intervention and optimal care e.g. gastrostomy, non-invasive ventilation, cognitive support	Diagnostic latency Neurological evaluation (e.g. clinical phenotypes) Cox modelling of clinical variables[132,133]
Monitoring	Identify ineffective drugs earlier	Revised ALS Functional Rating Score[134] (Electrical impedance myography emergent[102])

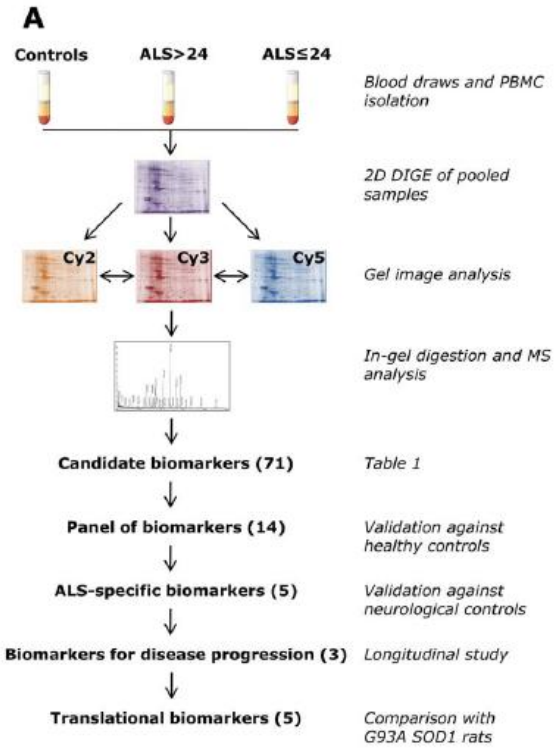
OPEN ACCESS Freely available online

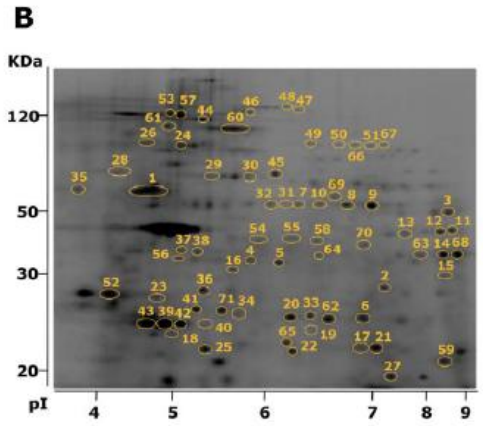
PLoS one

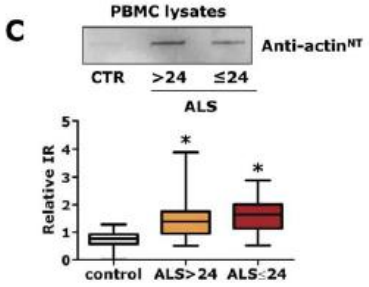
Amyotrophic Lateral Sclerosis Multiprotein Biomarkers in Peripheral Blood Mononuclear Cells

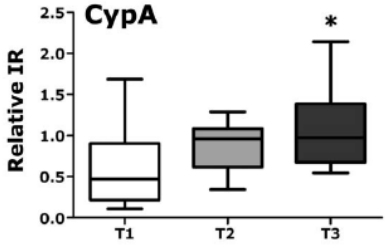
Giovanni Nardo[1,2], Silvia Pozzi[1,2], Mauro Pignataro[1,2], Eliana Lauranzano[1,2], Giorgia Spano[1,3], Silvia Garbelli[4,5], Stefania Mantovani[4,5], Kalliopi Marinou[6], Laura Papetti[6], Marta Monteforte[7], Valter Torri[7], Luca Paris[2], Gianfranco Bazzoni[2], Christian Lunetta[8], Massimo Corbo[8], Gabriele Mora[6], Caterina Bendotti[3], Valentina Bonetto[1,2]*

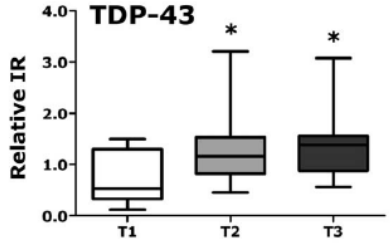
October 2011 | Volume 6 | Issue 10 |

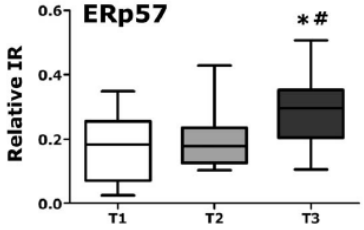












Biomarkers for disease progression (3) *Longitudinal study*

Towards a neuroimaging biomarker for amyotrophic lateral sclerosis

Panel 1: Consensus guidelines on MRI protocol for studies of amyotrophic lateral sclerosis*

Voxel-based morphometry

Essential

- T1 (MP-RAGE or equivalent high-resolution three-dimensional pulse sequence)
- Isotropic voxels (maximum 1 mm^3)

Desirable

- High GM–WM contrast

Diffusion tensor imaging

Essential

- Minimum 12 gradient directions
- Isotropic voxels (maximum 2·5 mm slice thickness)
- T2, FLAIR (to consider other WM pathology such as cerebrovascular disease)
- Minimum b value 800 s/mm^2

Desirable

- Axial acquisition (to maximise brainstem coverage)
- More than one cycle to allow averages to be calculated
- Cervical cord and brain
- Consideration of parallel imaging
- B0 field map

Functional MRI

Essential

- Resting-state sequence (in addition to any task-based measure)
- EPI, isotropic voxels (maximum 3 mm slice thickness)
- Consistent, either eyes open–fixed target, or eyes closed–not asleep for resting-state acquisition

Desirable

- Axial acquisition (to maximise brainstem coverage)
- Pulse-waveform and respiratory-waveform monitoring to allow physiological noise correction
- Task-based protocol for both motor and cognitive functions
- B0 field map

Spectroscopy

Essential

- Standardised methodology
- NAA-based measures within PMC

Desirable

- Myo-inositol, glutamate, and GABA measurements

*For all imaging methods, a minimum scanner field strength of 1·5T is essential, and 3·0T plus a multiple-channel head coil (12-channel to 32-channel) is desirable. MP-RAGE=magnetisation-prepared rapid gradient echo. GM=grey matter. WM=white matter. FLAIR=fluid-attenuated inversion recovery. EPI=echo planar imaging. NAA=N-acetyl aspartate. PMC=primary motor cortex.

The combination of different MRI techniques might improve sensitivity and specificity for ALS, as shown in a study of heterogeneous patients in which the combination of grey-matter voxel-based morphometry and diffusion tensor imaging resulted in 90% for both indices.[3] MRI also allows structure and function

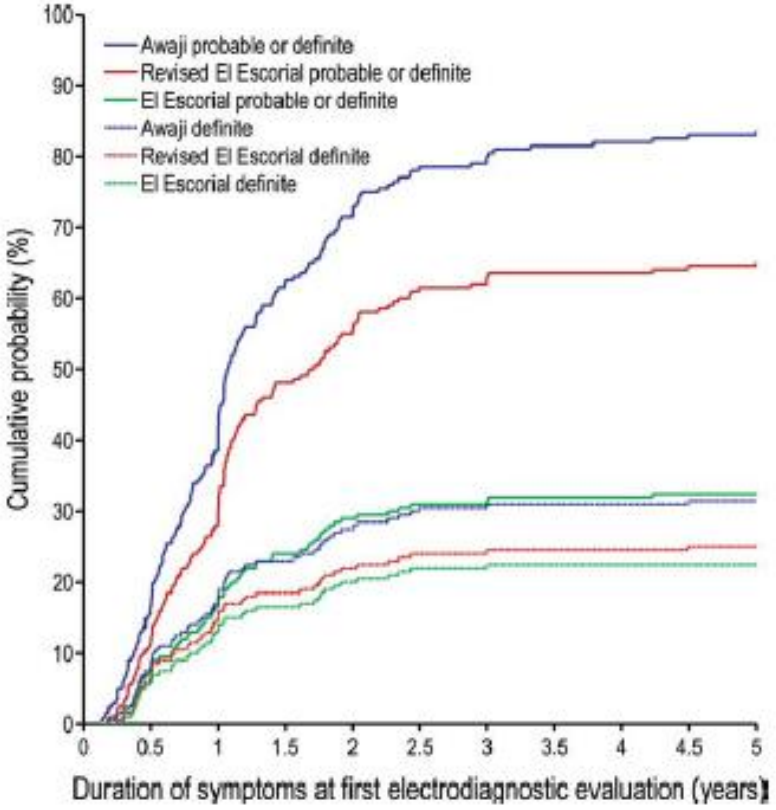
Martin R Turner, Julian Grosskreutz, Jan Kassubek, Sharon Abrahams, Federica Agosta, Michael Benatar, Massimo Filippi, Laura H Goldstein, Martijn van den Heuvel, Sanjay Kalra, Dorothée Lulé, Bahram Mohammadi, for the first Neuroimaging Symosium in ALS (NISALS)

Benefit of the Awaji Diagnostic Algorithm for Amyotrophic Lateral Sclerosis: A Prospective Study

Maarten Schrooten, MD,[1] Charlotte Smetcoren, MD,[1] Wim Robberecht, MD, PhD,[1,2] and Philip Van Damme, MD, PhD[1,2]

TABLE 2: Proportion of Patients Assigned to Each Diagnostic Category at Presentation

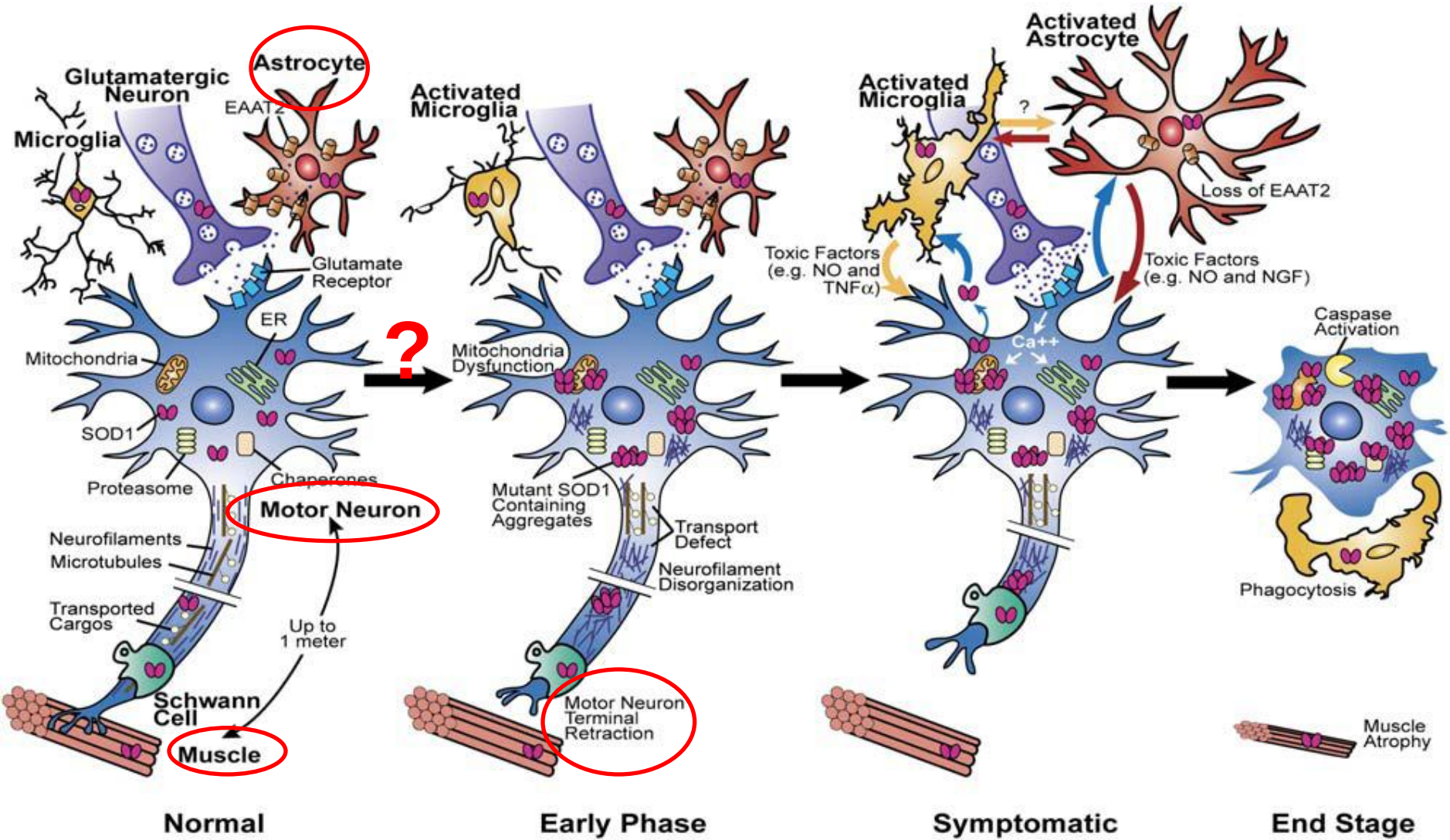
Diagnostic Category	Revised El Escorial (%) (n = 200)	Awaji (%) (n = 200)
Definite	25.0	31.5
Probable	41.0	53.5
Of which Laboratory supported	31.5	—
Possible	24.5	6.5
Nonclassifiable	9.5	8.5



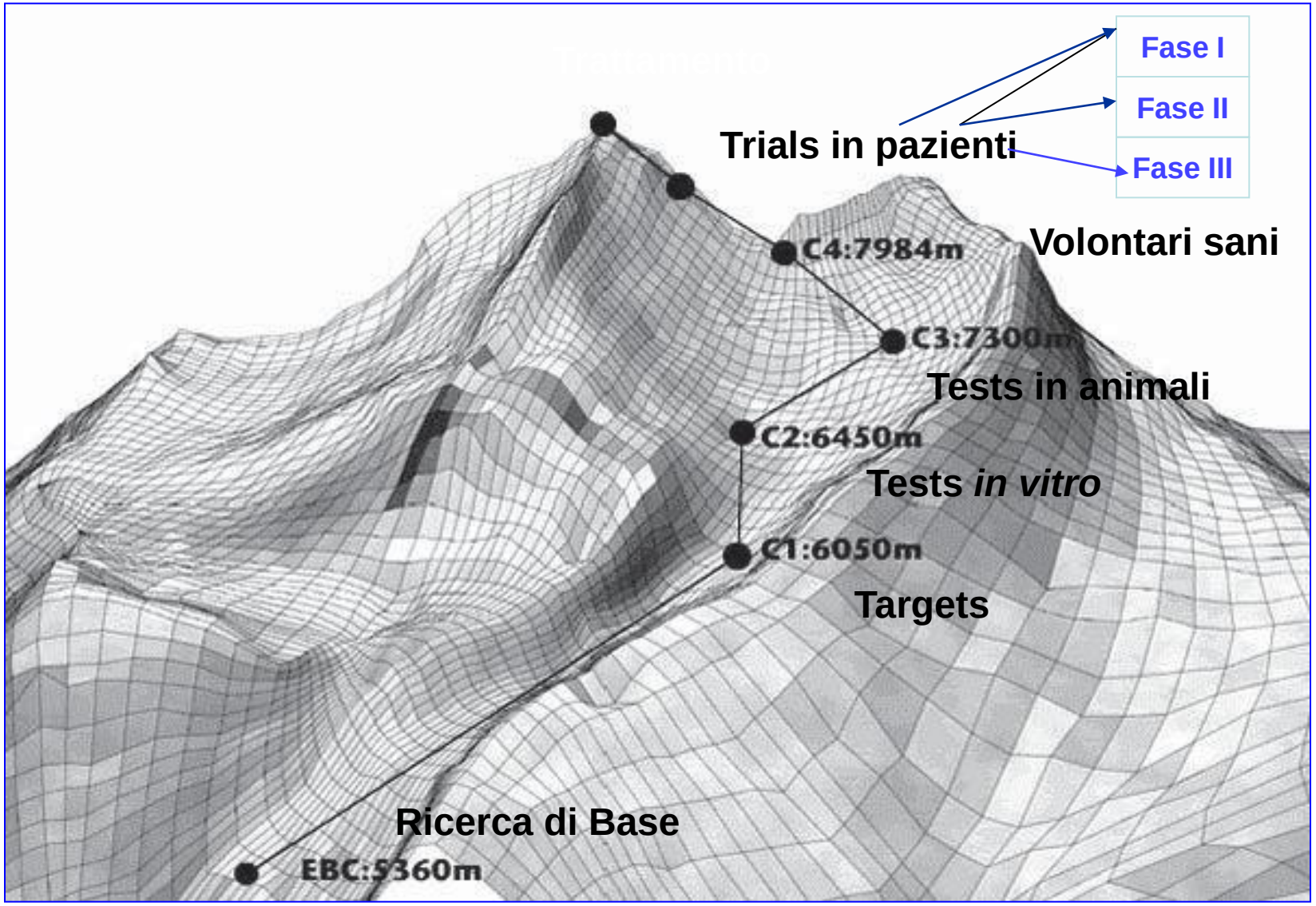
Neuron 52, 39–59, October 5, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.09.018

ALS: A Disease of Motor Neurons and Their Nonneuronal Neighbors

Séverine Boillée,[1] Christine Vande Velde,[1] and Don W. Cleveland[1,*]



Drug Development Phases

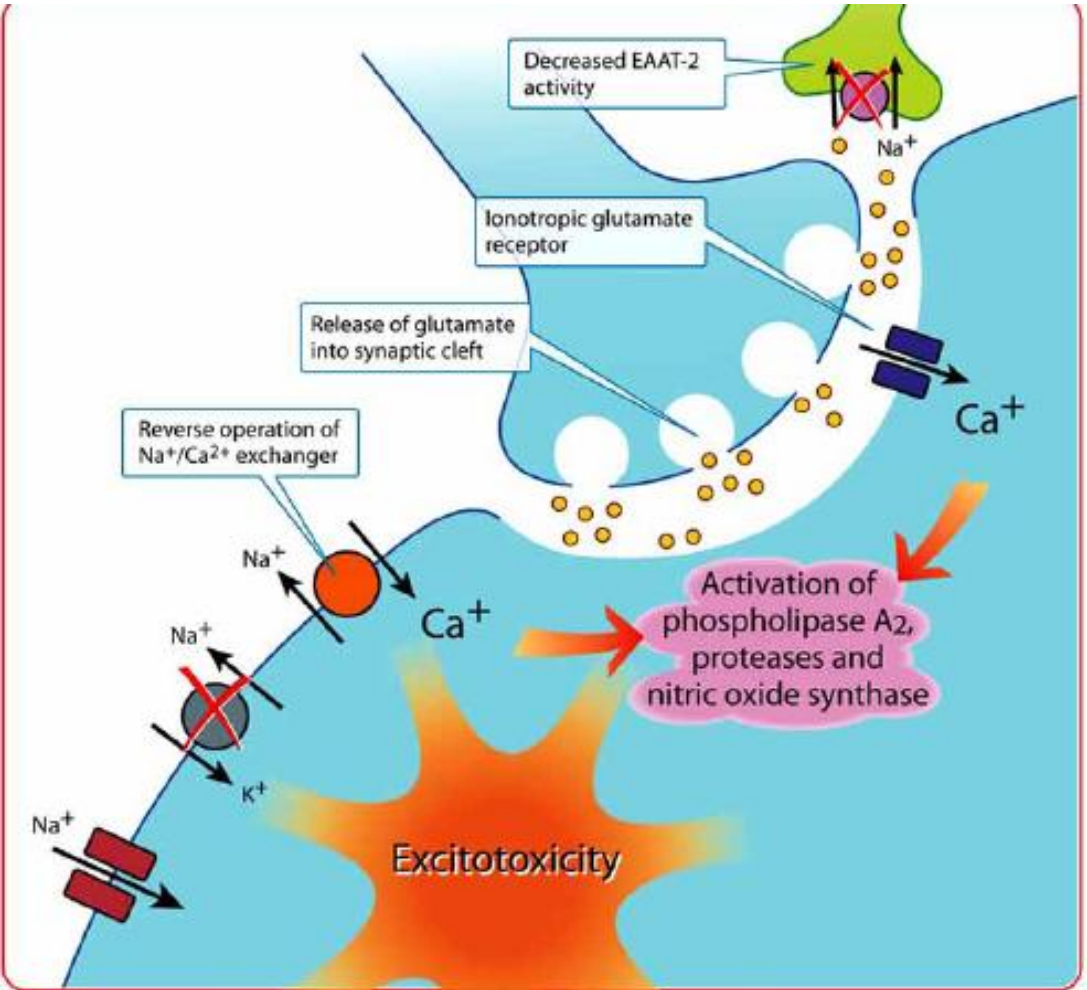


With thanks to Clare Wood-Allum, University of Sheffield

Current Medicinal Chemistry, 2010, *17*, 1942-1959

Riluzole, Neuroprotection and Amyotrophic Lateral Sclerosis

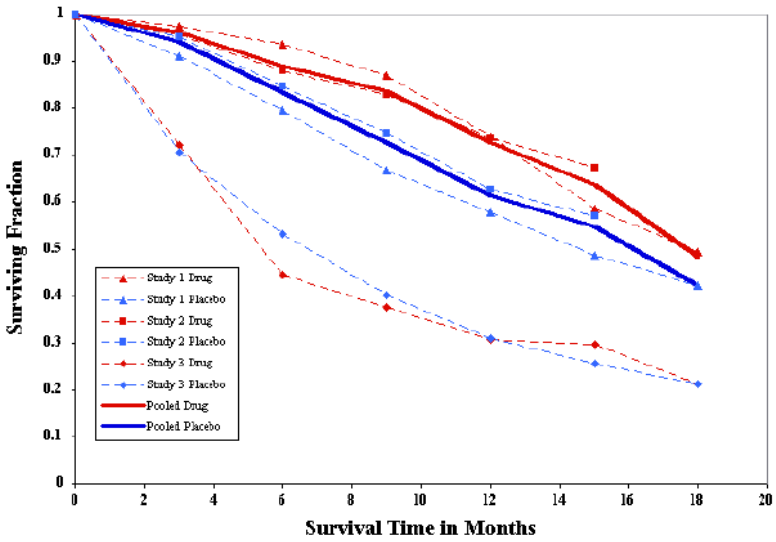
B.C. Cheah[1], S. Vucic[1], A.V. Krishnan[2] and M.C. Kiernan*,[1]



Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) (Review)

Miller RG, Mitchell JD, Lyon M, Moore DH

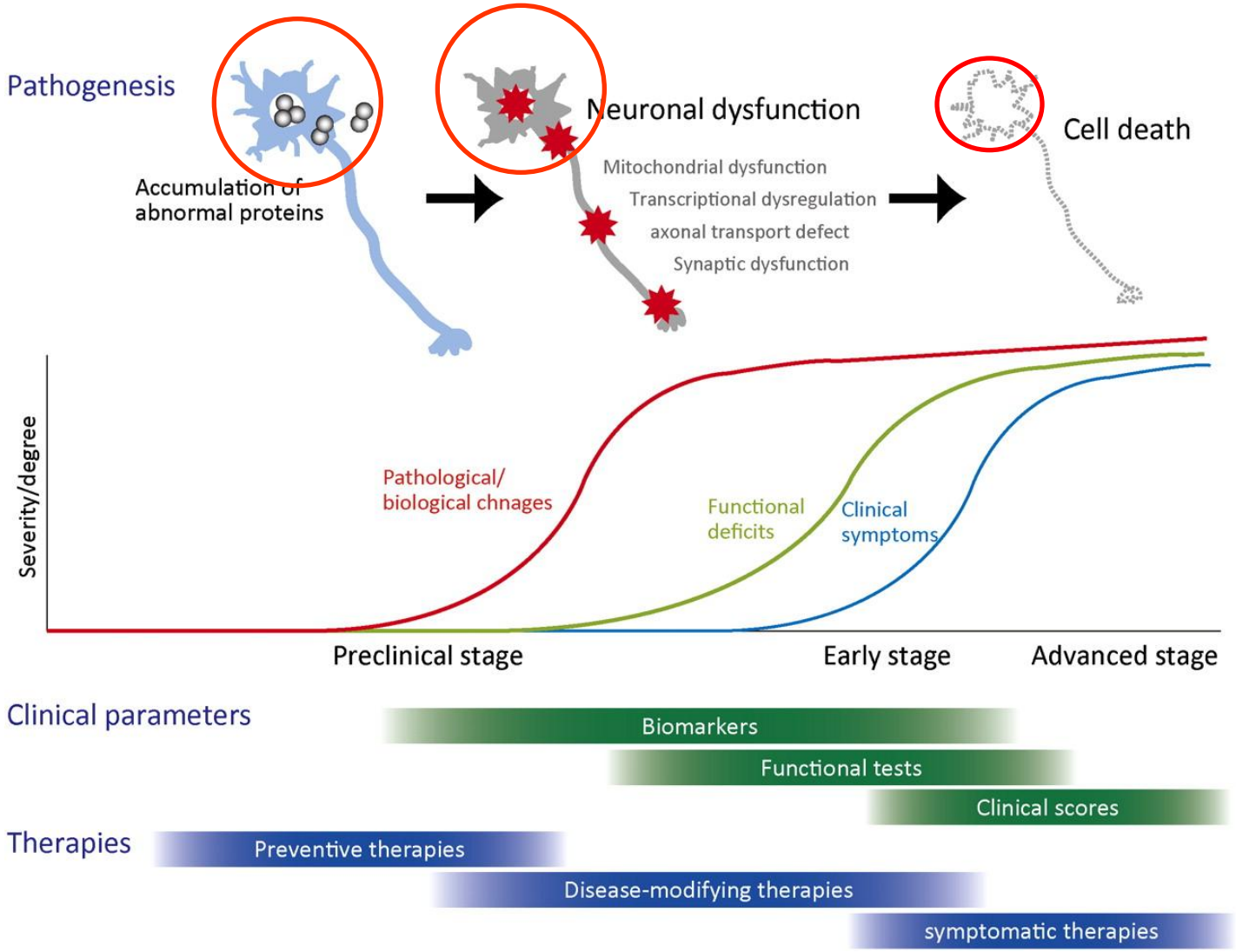
THE COCHRANE COLLABORATION®



Conclusioni dei Revisori

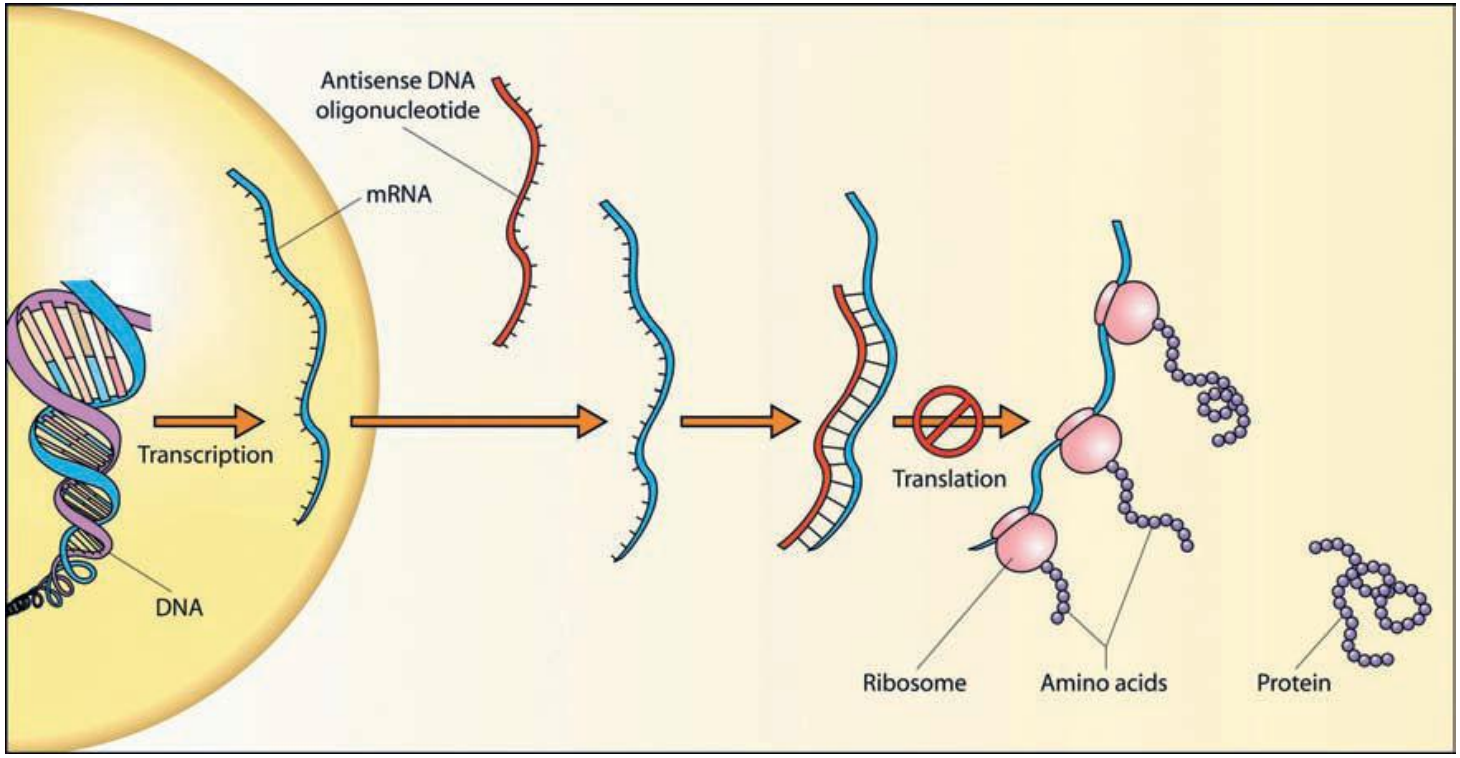
Riluzolo 100 mg/die è ragionevolmente sicuro e probabilmente prolunga la sopravvivenza media di circa 3 mesi nei pazienti con Sclerosi Laterale Amiotrofica

Time course of neurodegeneration and related parameters.



Katsuno M et al. J Neurol Neurosurg Psychiatry 2012;83:329-335

Terapia genica



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

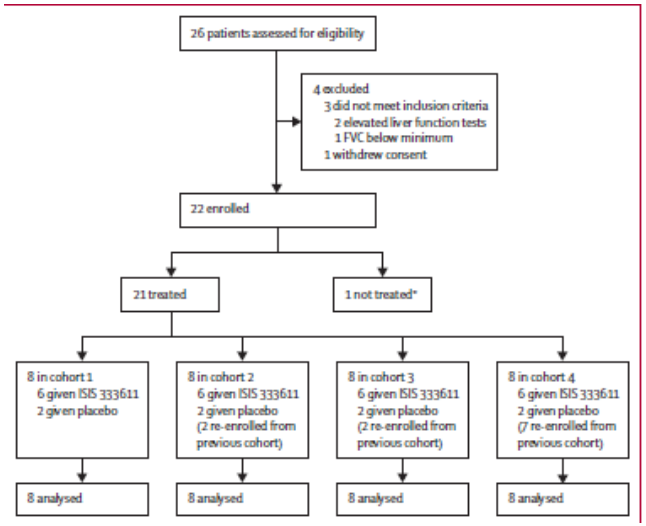
Lancet Neurol 2013; 12: 435–42

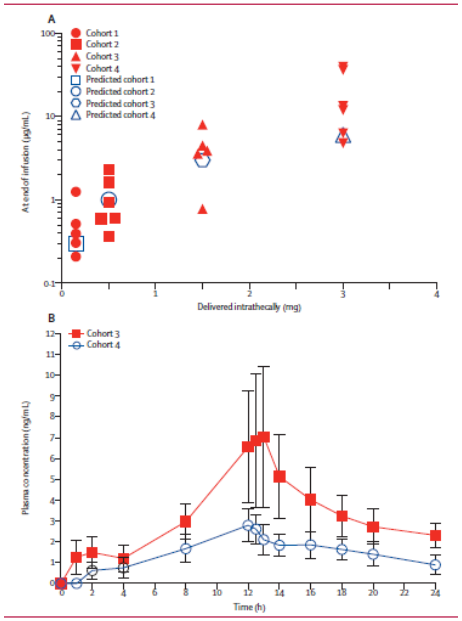
ISIS 333611

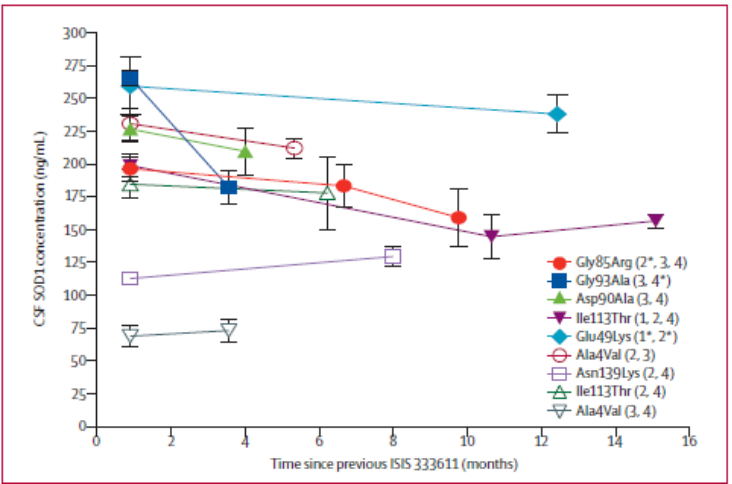
Timothy M Miller, Alan Pestronk, William David, Jeffrey Rothstein, Ericka Simpson, Stanley H Appel, Patricia L Andres, Katy Mahoney, Peggy Allred, Katie Alexander, Lyle W Ostrow, David Schoenfeld, Eric A Macklin, Daniel A Norris, Georgios Manousakis, Matthew Crisp, Richard Smith, C Frank Bennett, Kathie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

	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
8	Female	58	Yes	Ala4Val	58	Limb
9	Male	63	Yes	Gly85Arg	63	Limb
10	Male	52	Yes	Ala4Val	51	Limb
11	Male	48	Yes	Asn139Lys	45	Limb
12	Male	54	Yes	Ile113Thr	48	Limb
13	Male	44	No	Ala89Val	42	Limb
14	Female	56	Yes	Ile113Thr	43	Limb
15	Male	55	Yes	Gly93Ser	45	Limb
16	Male	46	Yes	Ala4Val	46	Bulbar
17	Male	22	Yes	Gly41Ser	22	Limb
18	Male	56	Yes	Asp90Ala	55	Limb
19	Male	51	Yes	Leu8Val	43	Limb
20	Female	38	Yes	Gly93Ala	37	Limb
21	Female	49	Yes	Gln22Leu	45	Limb

Table 1: Demographic and clinical characteristics of each participant



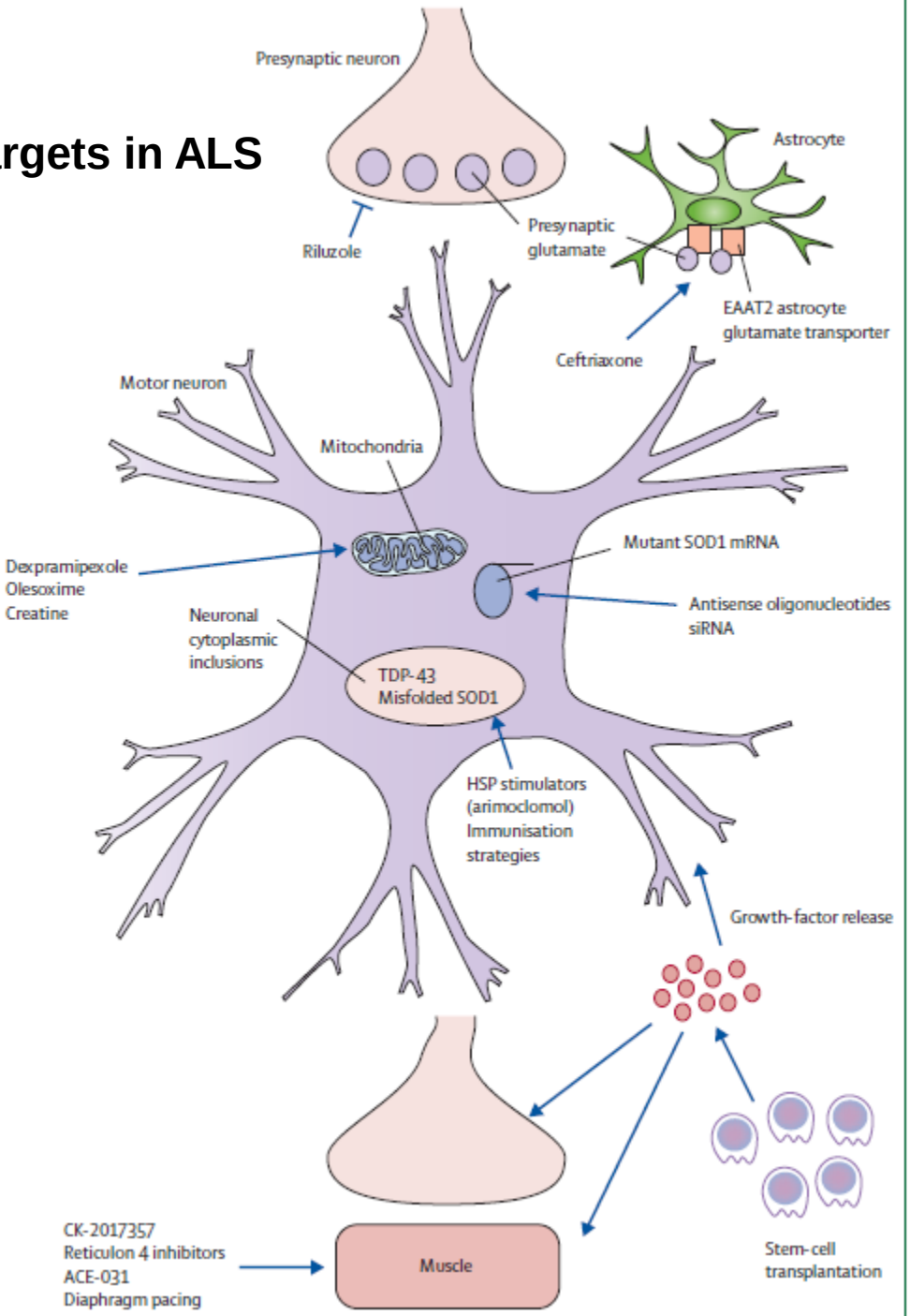




Interpretation

Our study is the first clinical report of delivery of antisense oligonucleotides to the CSF. ISIS 333611 was well tolerated when administered as an intrathecal infusion in patients with SOD1 familial amyotrophic lateral sclerosis. CSF and plasma drug concentrations were consistent with those predicted from preclinical studies. These conclusions are limited by the small doses given and the small numbers of patients studied.

Novel therapeutic targets in ALS



	Trial size	Inclusion	Treatment	Treatment duration	Outcomes	Adverse effects	Reference
CNTF	570	Duration < 3 years, only sporadic case	s.c. 0.5–5 μg/kg/day	6 months	No benefit	Severe. Including death	Miller et al. (1996)
	730	/	s.c. 15–30 μg/kg 3 times/week	9 months	No benefit	Severe, including weight loss	ALS CNTF Treatment Study Group (1996)
BDNF	1135	FVC, ALSFRS	s.c. 25–100 μg/kg/day	9 months	No benefit. Trend in high dose group.	Tolerable, injection site reaction	The BDNF Study Group (Phase III) (1999)
	11	Definite to probable ALS, FVC	Intrathecal, 25–150 μg/day	4–6 weeks	No benefit	No side effects	Kalra et al. (2003)
	13	Definite to probable ALS	Intrathecal, 25–150 μg/day	9 months	No benefit	No side effects	Beck et al. (2005)
IGF-1	266	Duration > 36 month, FVC, AALS score	s.c. 0.05 mg/kg once or twice/day	9 months	Slow decline, better life quality.	No side effects	Lai et al. (1997)
	183	Duration > 36 months, FVC, AALS score	s.c. 0.01 mg/kg/day	9 months	No benefit	Weakness, injection site pain, dyspnea	Borasio et al. (1998)
	9	Duration > 36 months, FVC, Norris scale, in progression, age	Intrathecal, 0.5–3 μg/kg twice a month	40 months	Slow decline of motor functions.	Tolerable, mild skin eruption.	Nagano et al. (2005b)
	330	Definite to probable ALS, FVC, age, MMT	s.c. 0.05 mg/kg/twice a day	2 years	No benefit	Tolerable, hypoglycemia	Sorenson et al. (2008)
G-CSF	39	Definite to probable ALS, FVC	s.c. 5 μg/kg/day for 4 consecutive days (every 3 months)	12 months	No benefit	Tolerable, bone and muscle pain	Nefussy et al. (2009)
	13	Confirmed ALS, FVC	2 μg/kg/day	5 days	Slow decline	Tolerable, mild fever	Zhang et al. (2008)
	10	Confirmed ALS, FVC, nutrition state	s.c. 300 μg/day G-CSF, followed by stem cells transplantation	3 days	Slow decline, better life quality.	Tolerable	Martinez et al. (2009)

Possibili cause di insuccesso terapeutico dei fattori di crescita

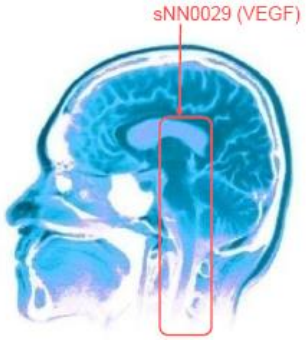
- Inadeguatezza della via di somministrazione (non superano la barriera ematoencefalica)
- Struttura chimica. Si tratta di piccole proteine molto fragili, con una emivita molto breve che per poter esercitare il loro effetto terapeutico devono mantenersi chimicamente intatte.
- L'azione in vivo inoltre potrebbe essere annullata dalla necessità di azione sinergica con altri fattori di crescita.
- Effetti collaterali importanti

sNN0029

A Double-Blind, Randomised, Parallel Group Safety and Tolerability Study of Intracerebroventricular Administration of sNN0029 to Patients With Amyotrophic Lateral Sclerosis, Using an Implanted Catheter and SynchroMed® II Pump

University Hospital Leuven, Department of Neurology

Ongoing phase I/II clinical trial sNN0029



- *Objective:*
  - *Safety and tolerability with efficacy parameters*
- *Drug:*
  - *Three dose levels and placebo (n=28)*
- *Design:*
  - *Part A: Open (done)*
  - *Part B: Blinded, placebo-controlled (o*

BRAIN RESEARCH 1238 (2008) 143–153

available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Motoneuronotrophic factor analog GM6 reduces infarct volume and behavioral deficits following transient ischemia in the mouse

Jin Yu[a], *Hong Zhu*[a], *Dorothy Ko*[b], *Mark S. Kindy*[a,c,d,*]

[a]Department of Neurosciences, Medical University of South Carolina, 173 Ashley Avenue, BSB 403, Charleston, SC 29425, USA
[b]Genervon Biopharmaceuticals, Montebello, CA, USA

GM604 Phase 2A Randomized Double-blind Placebo Controlled Pilot Trial in **Amyotrophic Lateral** Sclerosis (GALS)

ClinicalTrials.gov Identifier
NCT01854294

VOLUME 18 | NUMBER 3 | MARCH 2012

nature medicine

Activation of fast skeletal muscle troponin as a potential therapeutic approach for treating neuromuscular diseases

Alan J Russell[1], James J Hartman[1], Aaron C Hinken[1], Alexander R Muci[1], Raja Kawas[1], Lena Driscoll[1], Guillermo Godinez[1], Kenneth H Lee[1], David Marquez[1], William F Browne IV[1], Michael M Chen[2], David Clarke[1], Scott E Collibee[1], Marc Garard[1], Richard Hansen[1], Zhiheng Jia[1], Pu-Ping Lu[1], Hector Rodriguez[1], Khalil G Saikali[2], Julia Schaletzky[1], Vipin Vijayakumar[1], Daniel L Albertus[3,4], Dennis R Claflin[3,4], David J Morgans[1], Bradley P Morgan[1] & Fady I Malik[1]

Amyotrophic Lateral Sclerosis, 2012; 13: 430–438

Safety, tolerability and pharmacodynamics of a skeletal muscle activator in amyotrophic lateral sclerosis

JEREMY SHEFNER[1], JESSE M. CEDARBAUM[2], MERIT E. CUDKOWICZ[3], NICHOLAS MARAGAKIS[4], JACQUELINE LEE[2], DREW JONES[2], MARY LOU WATSON[1], KATY MAHONEY[3], MICHAEL CHEN[2], KHALIL SAIKALI[2], JOHN MAO[2], ALAN J. RUSSELL[2], RICHARD L. HANSEN[2], FADY MALIK[2], ANDREW A. WOLFF[2] & FOR THE NEALS/CYTOKINETICS STUDY TEAM

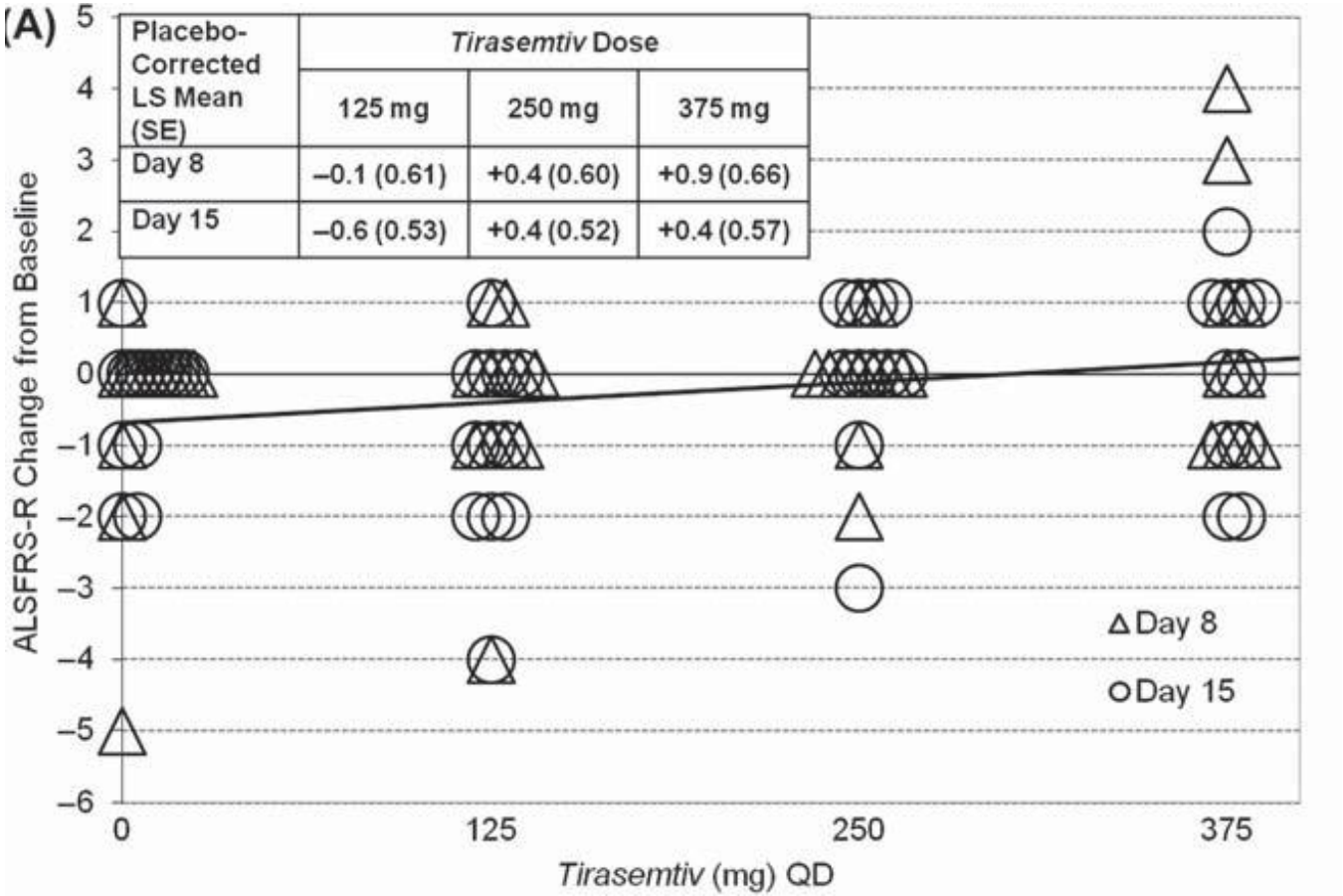
strength. In conclusion, single doses of 250 mg and 500 mg of CK-2017357 were safe and well tolerated by patients with ALS. Measures of endurance appear to be improved in a dose-related fashion, and both patients and investigators perceived a global benefit. Further study of this agent is warranted.

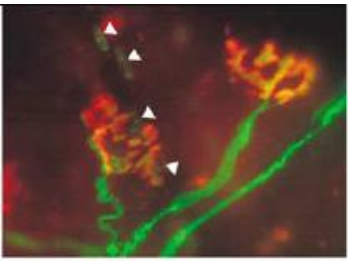
Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013; Early Online: 1–8

ORIGINAL ARTICLE

A study to evaluate safety and tolerability of repeated doses of tirasemtiv in patients with amyotrophic lateral sclerosis

JEREMY M. SHEFNER[1], MARY LOU WATSON[1], LISA MENG[2] & ANDREW A. WOLFF[2]; THE NEALS/CYTOKINETICS STUDY TEAM[3]





The neurite outgrowth inhibitor Nogo-A promotes denervation in an amyotrophic lateral sclerosis model

Natasa Jokic[1,2], Jose-Luis Gonzalez de Aguilar[1,2*], Leda Dimou[3], Shuo Lin[4], Anissa Fergani[1,2], Markus A. Ruegg[4], Martin E. Schwab[3], Luc Dupuis[1,2] & Jean-Philippe Loeffler[1,2+]*

EMBO *reports* VOL 7 | NO 11 | 2006

European Journal of Neuroscience, Vol. 29, pp. 983–996, 2009 doi:10.1111/j.1460-9568.2009.06642.x

BEHAVIORAL NEUROSCIENCE

Anti-Nogo-A antibody treatment promotes recovery of manual dexterity after unilateral cervical lesion in adult primates – re-examination and extension of behavioral data

Patrick Freund,[1,*] Eric Schmidlin,[1,*] Thierry Wannier,[1,2,*] Jocelyne Bloch,[3] Anis Mir,[4] Martin E. Schwab[2] and Eric M. Rouiller[1]

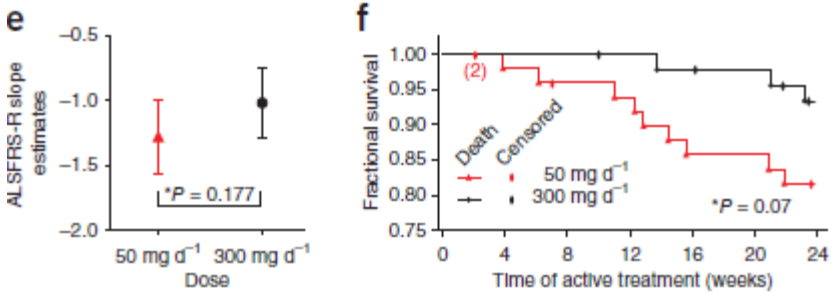
Study of Ozanezumab (GSK1223249) Versus Placebo in the Treatment of Amyotrophic Lateral Sclerosis

ClinicalTrials.gov Identifier:
NCT01753076

VOLUME 17 | NUMBER 12 | DECEMBER 2011 NATURE MEDICINE

The effects of dexpramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis

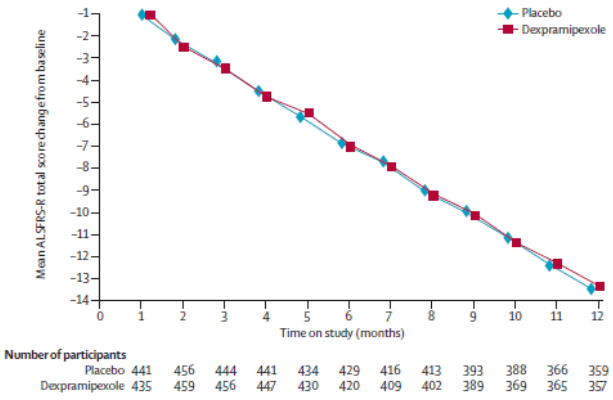
Merit Cudkowicz[1], Michael E Bozik[2], Evan W Ingersoll[2], Robert Miller[3], Hiroshi Mitsumoto[4], Jeremy Shefner[5], Dan H Moore[3], David Schoenfeld[6], James L Mather[2], Donald Archibald[2], Mary Sullivan[2], Craig Amburgey[2], Juliet Moritz[2] & Valentin K Gribkoff[2]

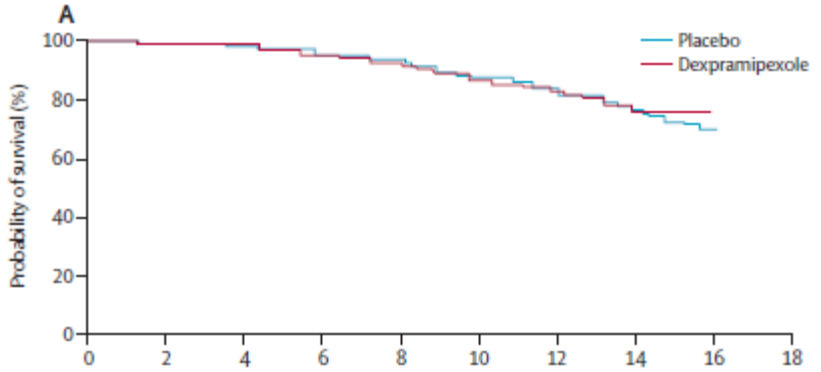


www.thelancet.com/neurology Published online September 23, 2013

Dexpramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): a randomised, double-blind, phase 3 trial

*Merit E Cudkowicz, Leonard H van den Berg, Jeremy M Shefner, Hiroshi Mitsumoto, Jesus S Mora, Albert Ludolph, Orla Hardiman, Michael E Bozik, Evan W Ingersoll, Donald Archibald, Adam L Meyers, Yingwen Dong, Wildon R Farwell, Douglas A Kerr, for the EMPOWER investigators**





EMBO Mol Med (2013) 5, 64–79

Regulatory T-lymphocytes mediate amyotrophic lateral sclerosis progression and survival

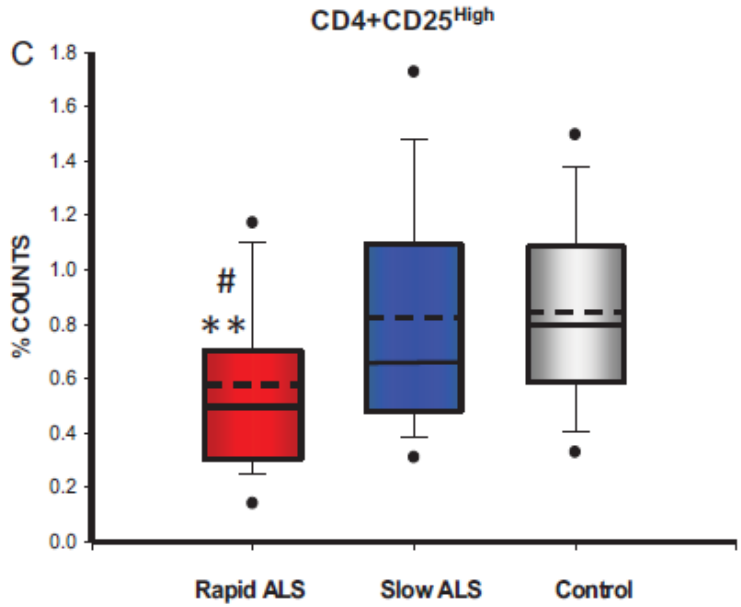
*Jenny S. Henkel[1]**, David R. Beers[1], Shixiang Wen[1], Andreana L. Rivera[2], Karen M. Toennis[1], Joan E. Appel[1], Weihua Zhao[1], Dan H. Moore[3], Suzanne Z. Powell[2], Stanley H. Appel[1]**

Amyotrophic Lateral Sclerosis, 2012; 13(Suppl. 1): 1–188

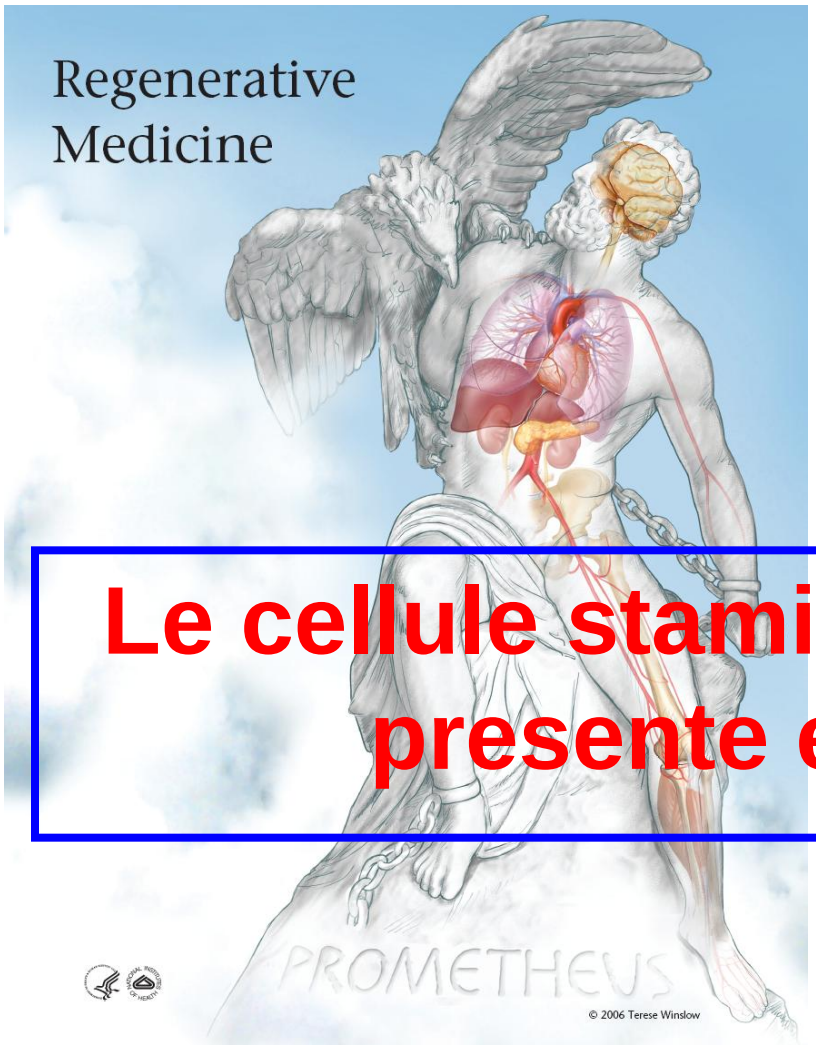
C47 PHASE II SAFETY AND EFFICACY OF NP001: A NOVEL IMMUNE REGULATOR FOR ALS

MILLER RG[1], BLOCK G[2], GOPALAKRISHNAN V[2], McGRATH M[2], STUDY GROUP NP001 PHASE II[2]

[1]*California Pacific Medical Center, San Francisco, CA, USA,*
[2]*Neuraltus Pharmaceuticals, Inc., Palo Alto, CA, USA*



- **The trial results showed that NP001, delivered directly into the blood stream intravenously, was safe and well tolerated, with a modest clinical benefit seen in the high dose group.**
- **Neuraltus are planning a larger Phase III study to test the safety and effectiveness of this treatment in America for the second half of 2013.**



With thousands of people in need of heart transplants, researchers are trying to grow new organs.

HOW TO BUILD A

HEART

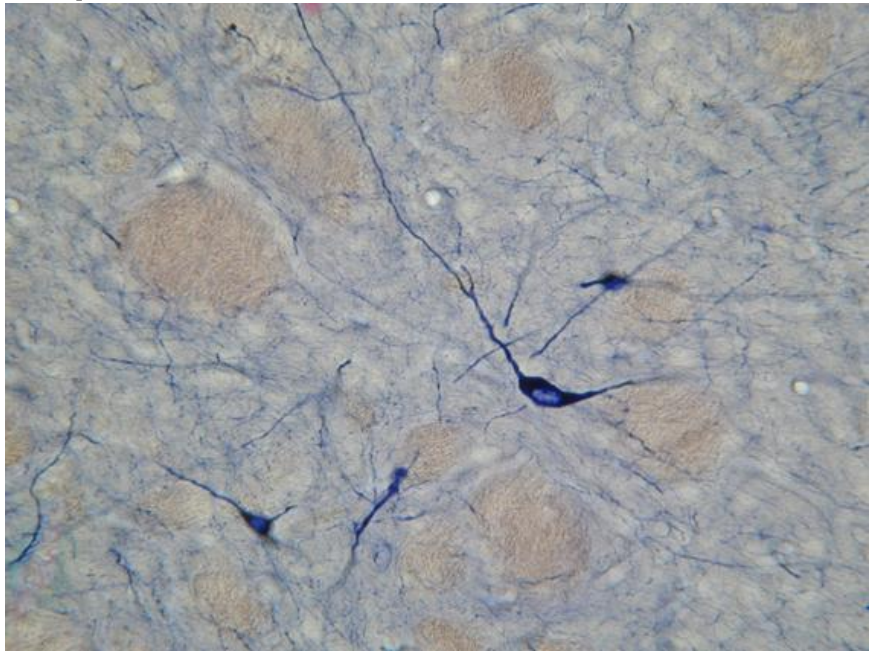
A decellularized human heart awaits rebuilding with an injection of precursor cells.

Le cellule staminali e la SLA: presente e futuro

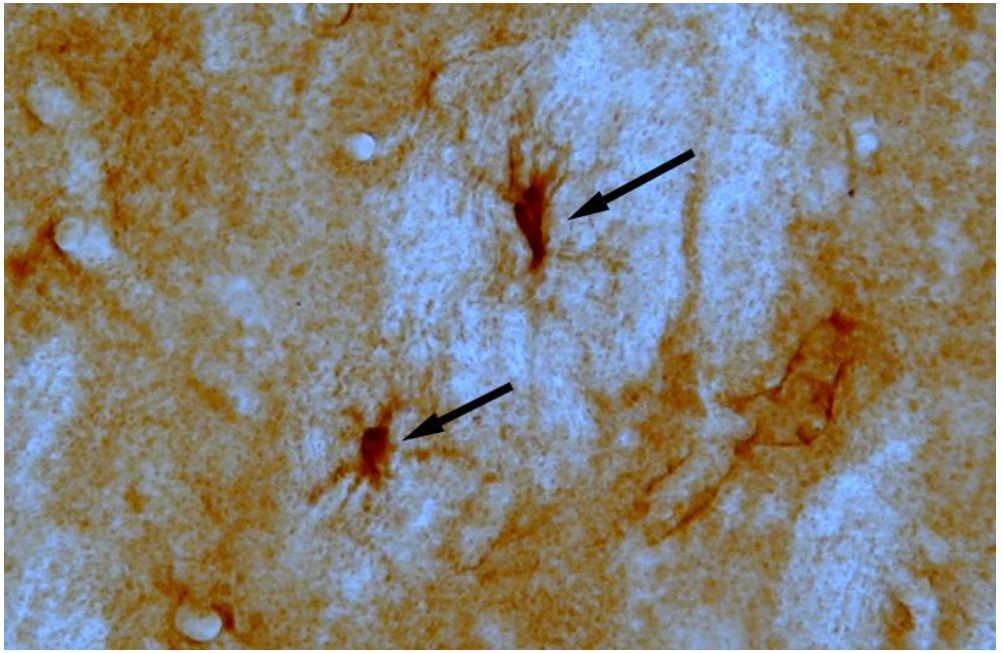
TESSUTO NERVOSO

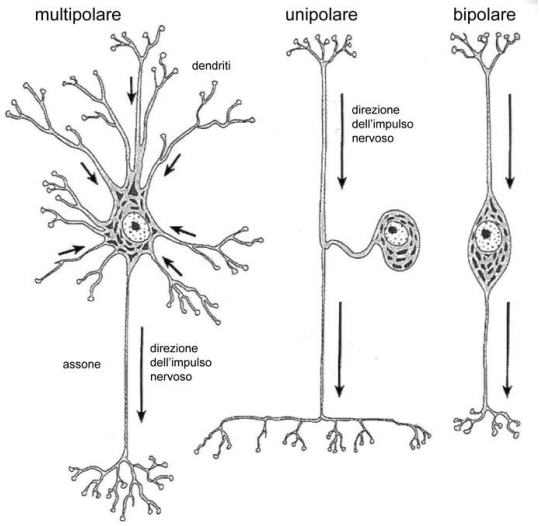
Il tessuto nervoso non contiene matrice extracellulare ed è formato da due tipi di cellule:

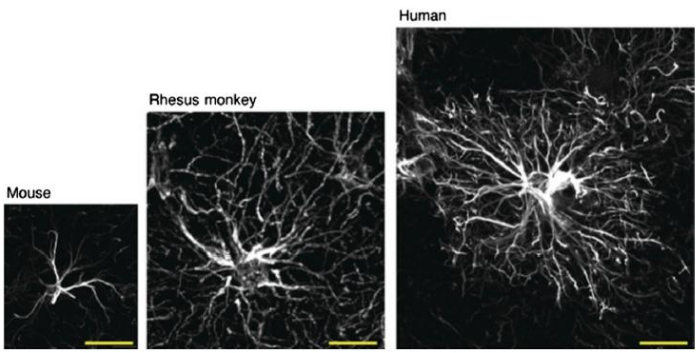
1) cellule nervose o **neuroni**

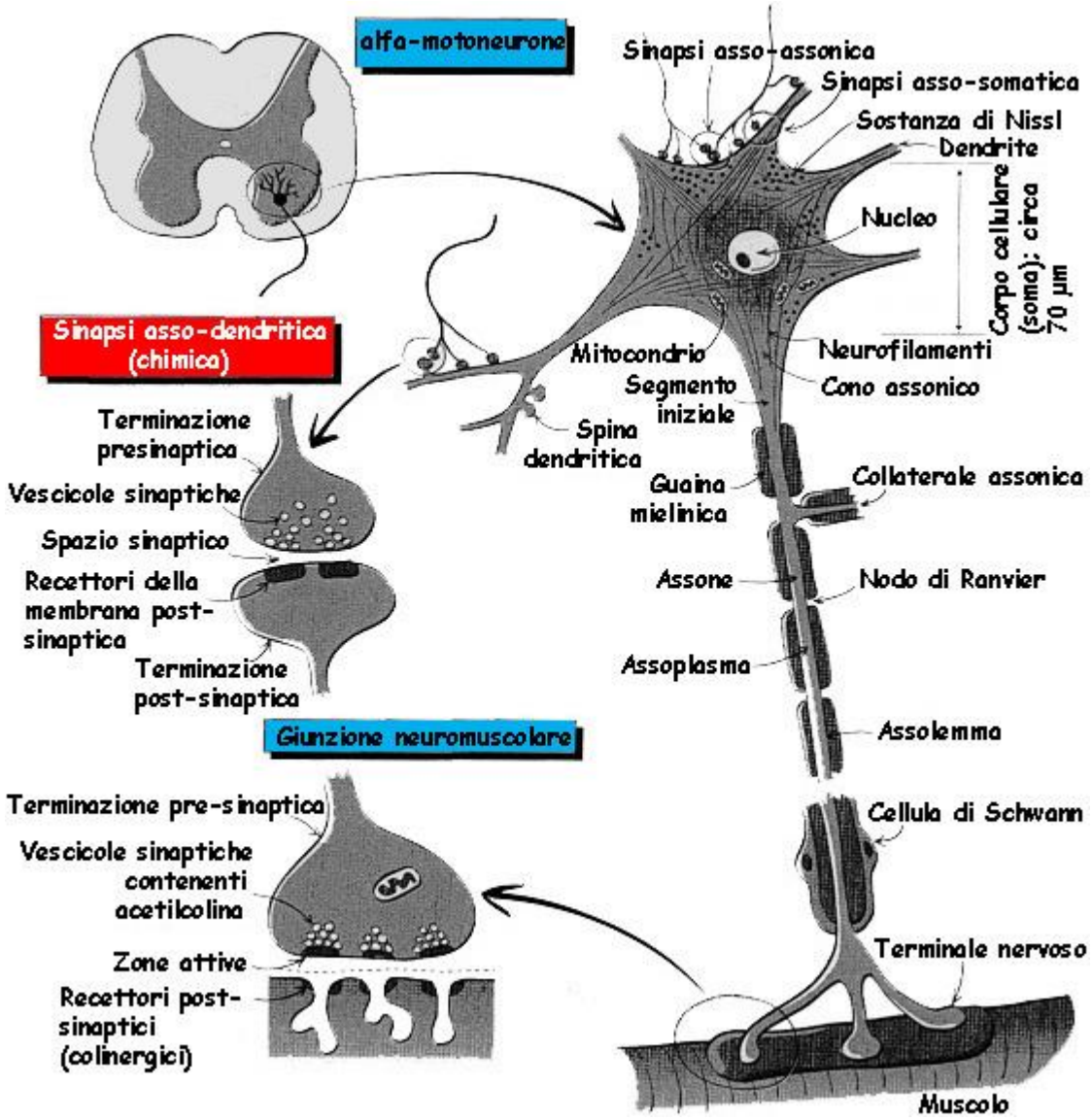


2) cellule **gliali**




multipolare
unipolare
bipolare
dendriti
direzione dell'impulso nervoso
assone
direzione dell'impulso nervoso


Mouse
Rhesus monkey
Human


alfa-motoneurone
Sinapsi asso-assonica
Sinapsi asso-somatica
Sostanza di Nissl
Dendrite
Nucleo
Corpo cellulare (soma): circa 70 µm
Sinapsi asso-dendritica (chimica)
Mitocondrio
Neurofilamenti
Segmento iniziale
Cono assonico
Spina dendritica
Terminazione presinaptica
Vescicole sinaptiche
Spazio sinaptico
Recettori della membrana post-sinaptica
Terminazione post-sinaptica
Guaina mielinica
Collaterale assonica
Assone
Nodo di Ranvier
Assoplasma
Assolemma
Giunzione neuromuscolare
Terminazione pre-sinaptica
Vescicole sinaptiche contenenti acetilcolina
Zone attive
Recettori post-sinaptici (colinergici)
Cellula di Schwann
Terminale nervoso
Muscolo

Cellula Staminale

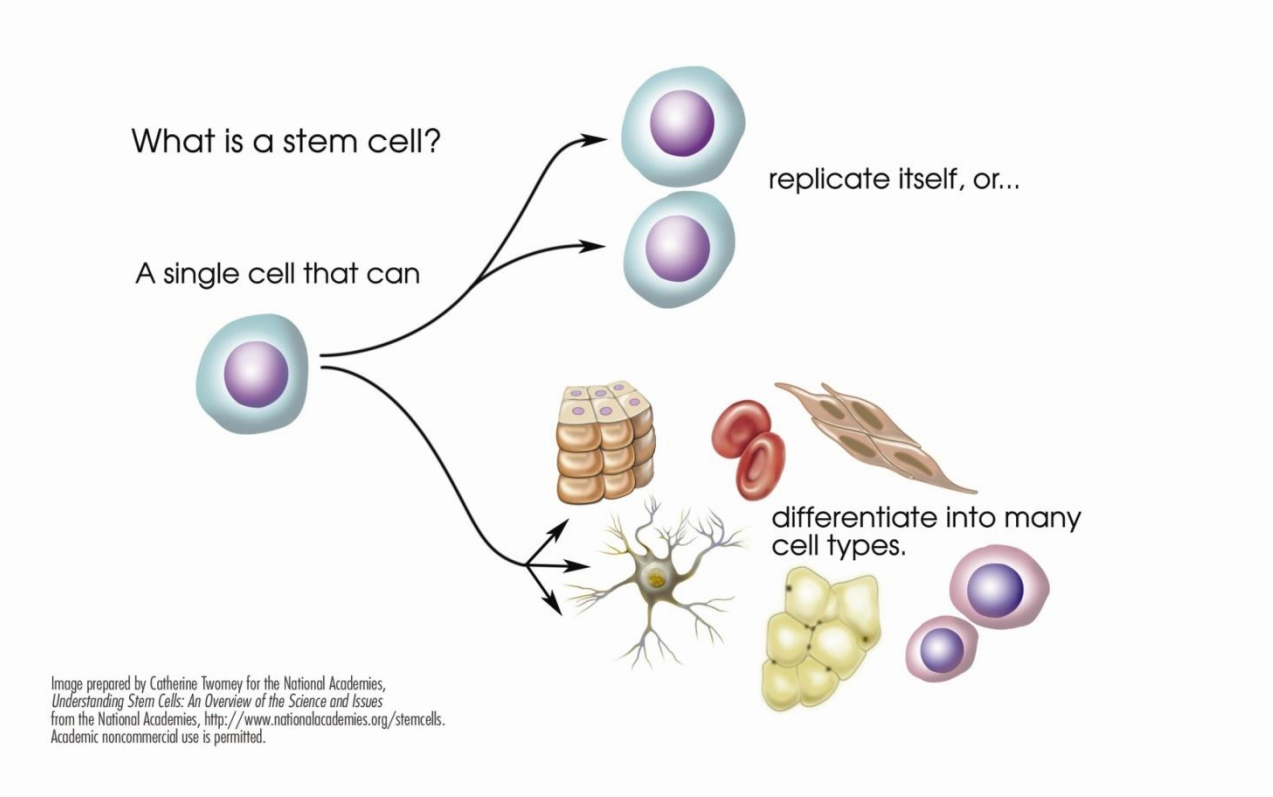
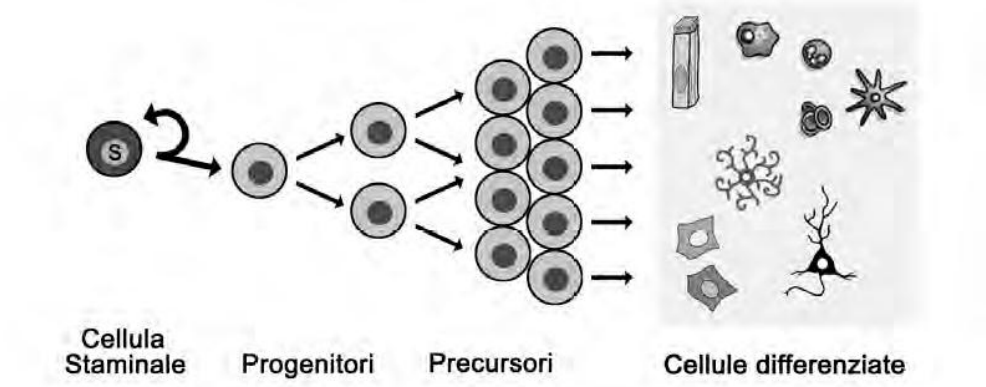
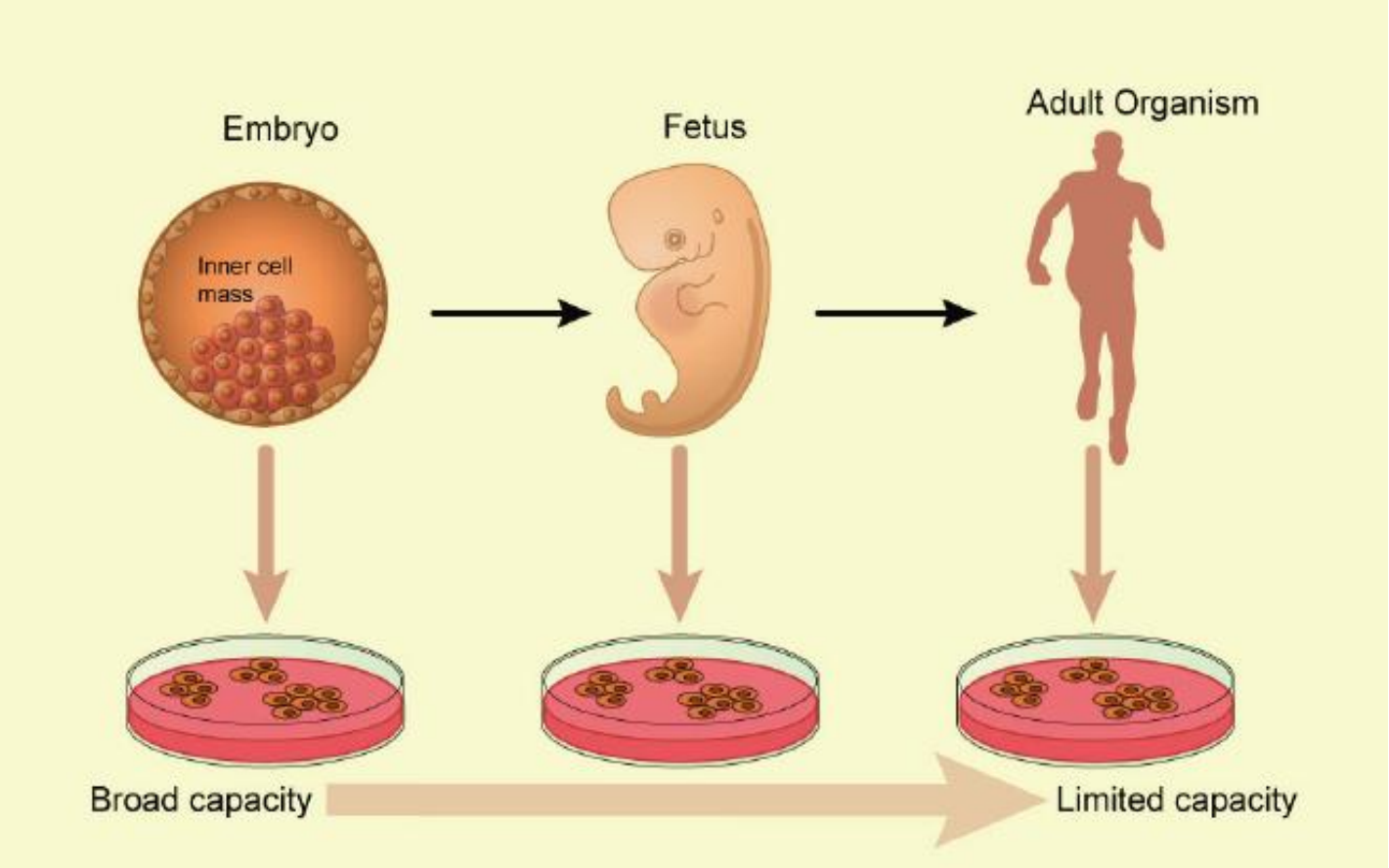


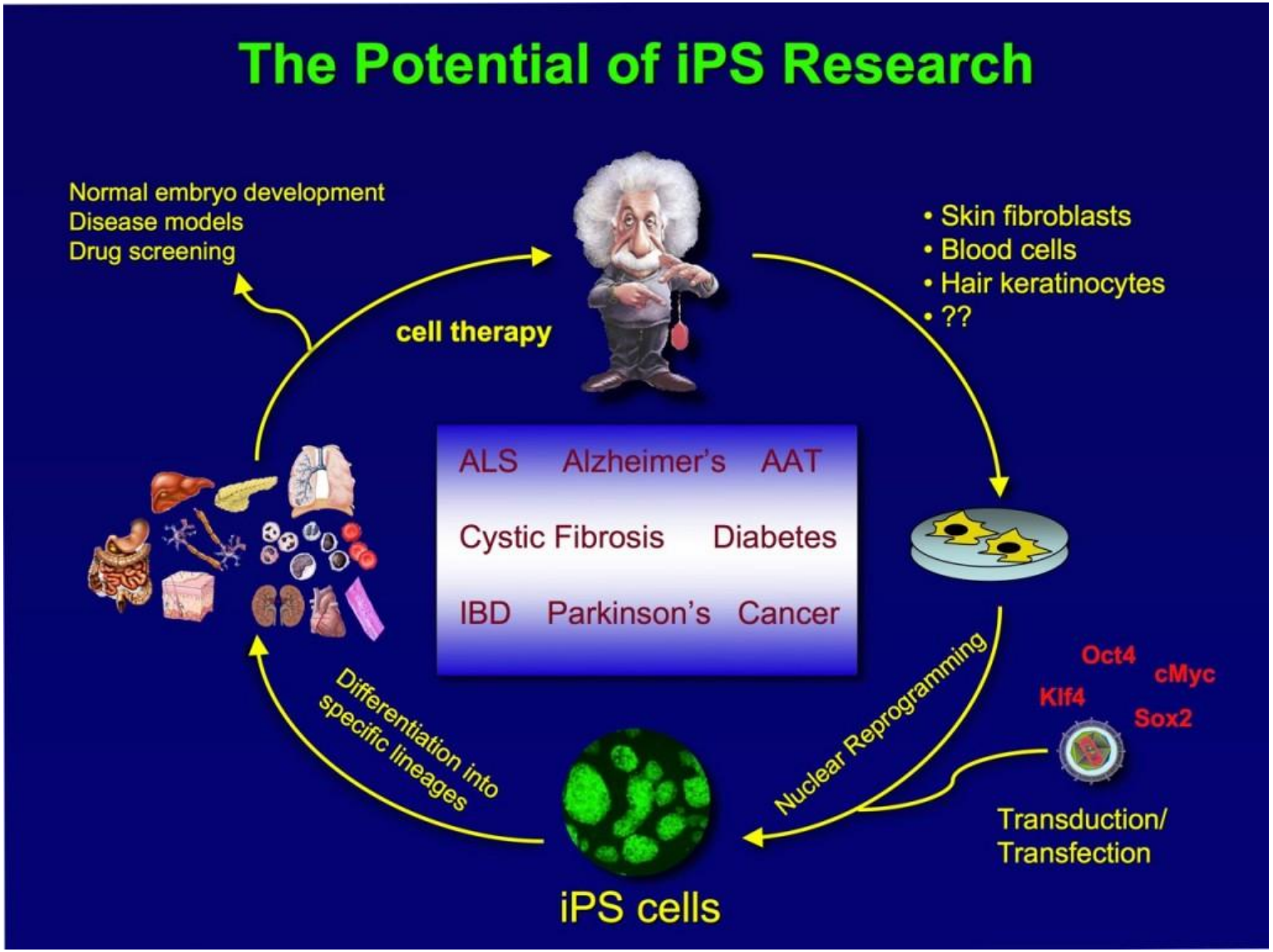
Image prepared by Catherine Twomey for the National Academies,
Understanding Stem Cells: An Overview of the Science and Issues
from the National Academies, http://www.nationalacademies.org/stemcells.
Academic noncommercial use is permitted.



Fonti di cellule staminali



Le cellule staminali sono generalmente classificate come **embrionali e adulte.** Tecnicamente anche le cellule staminali prelevate da tessuti fetali e da cordone ombelicale sono classificate come adulte. Pertanto i ricercatori preferiscono usare il termine **cellule staminali tessutali** per tutte le cellule ad eccezione delle cellule embrionali.


The Potential of iPS Research
Normal embryo development
Disease models
Drug screening
cell therapy
• Skin fibroblasts
• Blood cells
• Hair keratinocytes
• ??
ALS
Alzheimer's
AAT
Cystic Fibrosis
Diabetes
IBD
Parkinson's
Cancer
Differentiation into specific lineages
Nuclear Reprogramming
Oct4
cMyc
Klf4
Sox2
Transduction/
Transfection
iPS cells

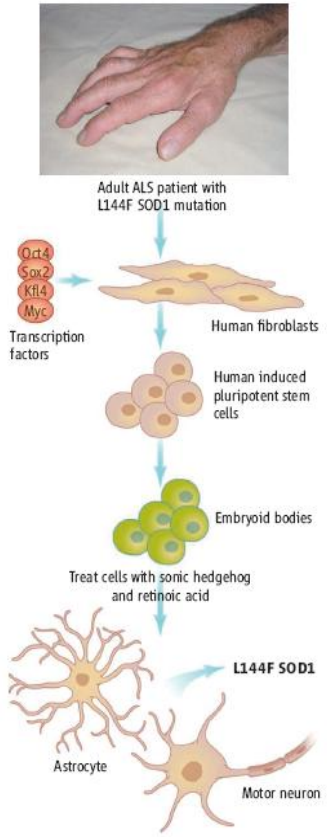
29 AUGUST 2008 VOL 321 SCIENCE www.sciencemag.org

REPORTS

Induced Pluripotent Stem Cells Generated from Patients with ALS Can Be Differentiated into Motor Neurons

John T. Dimos,[1]* Kit T. Rodolfa,[1,2]* Kathy K. Niakan,[1] Laurin M. Weisenthal,[1] Hiroshi Mitsumoto,[3,4] Wendy Chung,[4,5] Gist F. Croft,[4,6] Genevieve Saphier,[1] Rudy Leibel,[5] Robin Goland,[7] Hynek Wichterle,[4,6] Christopher E. Henderson,[4,6] Kevin Eggan[1]†

The generation of pluripotent stem cells from an individual patient would enable the large-scale production of the cell types affected by that patient's disease. These cells could in turn be used for disease modeling, drug discovery, and eventually autologous cell replacement therapies. Although recent studies have demonstrated the reprogramming of human fibroblasts to a pluripotent state, it remains unclear whether these induced pluripotent stem (iPS) cells can be produced directly from elderly patients with chronic disease. We have generated iPS cells from an 82-year-old woman diagnosed with a familial form of amyotrophic lateral sclerosis (ALS). These patient-specific iPS cells possess properties of embryonic stem cells and were successfully directed to differentiate into motor neurons, the cell type destroyed in ALS.



Skin cells generate human neural cells. Fibroblasts from a patient's skin biopsy are transduced with four transcription factors to form pluripotential cells and then embryoid bodies which, after exposure to sonic hedgehog and retinoic acid, generate both motor neurons and astrocytes.

August 2012 | Volume 7 | Issue 8 |

PLOS | ONE

Creation of an Open-Access, Mutation-Defined Fibroblast Resource for Neurological Disease Research

HMG Advance Access published September 17, 2013

Human Molecular Genetics, 2013 **1–13**
doi:10.1093/hmg/ddt425

Minimally invasive transplantation of iPSC-derived ALDHhiSSCloVLA4+ neural stem cells effectively improves the phenotype of an amyotrophic lateral sclerosis model

Monica Nizzardo[†], Chiara Simone[†], Federica Rizzo, Margherita Ruggieri, Sabrina Salani, Giulietta Riboldi, Irene Faravelli, Chiara Zanetta, Nereo Bresolin, Giacomo P. Comi[‡] and Stefania Corti[‡,*]

Dino Ferrari Centre, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Neurology Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy