PERSPECTIVAS DE NOVOS TRATAMENTOS PARA A ESCLEROSE LATERAL AMIOTRÓFICA

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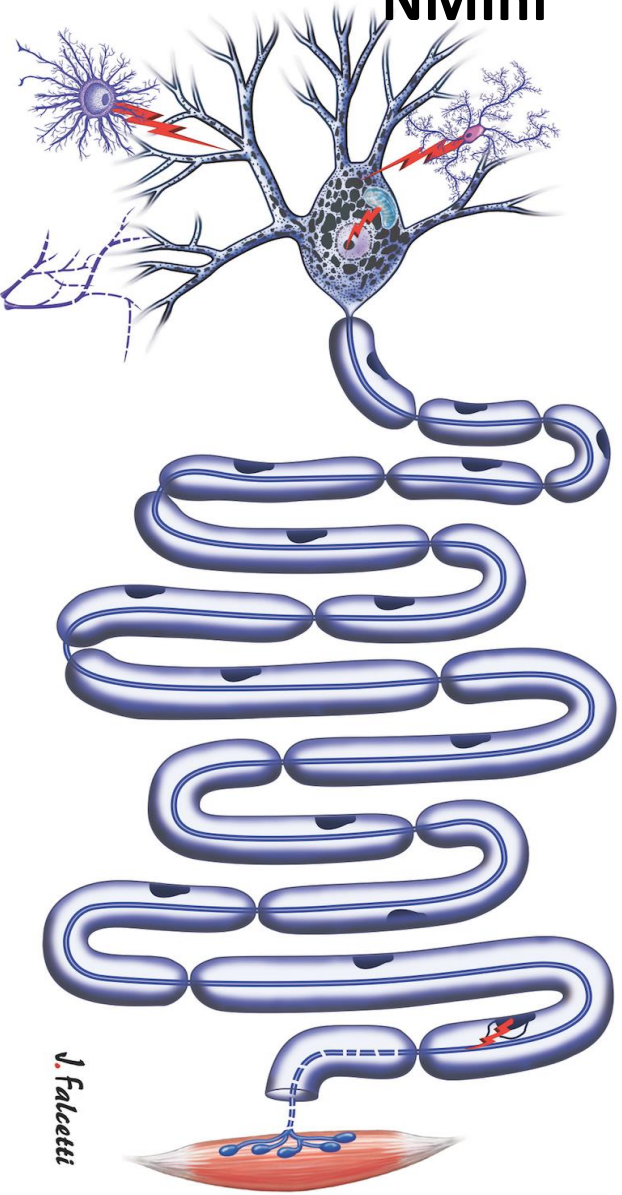
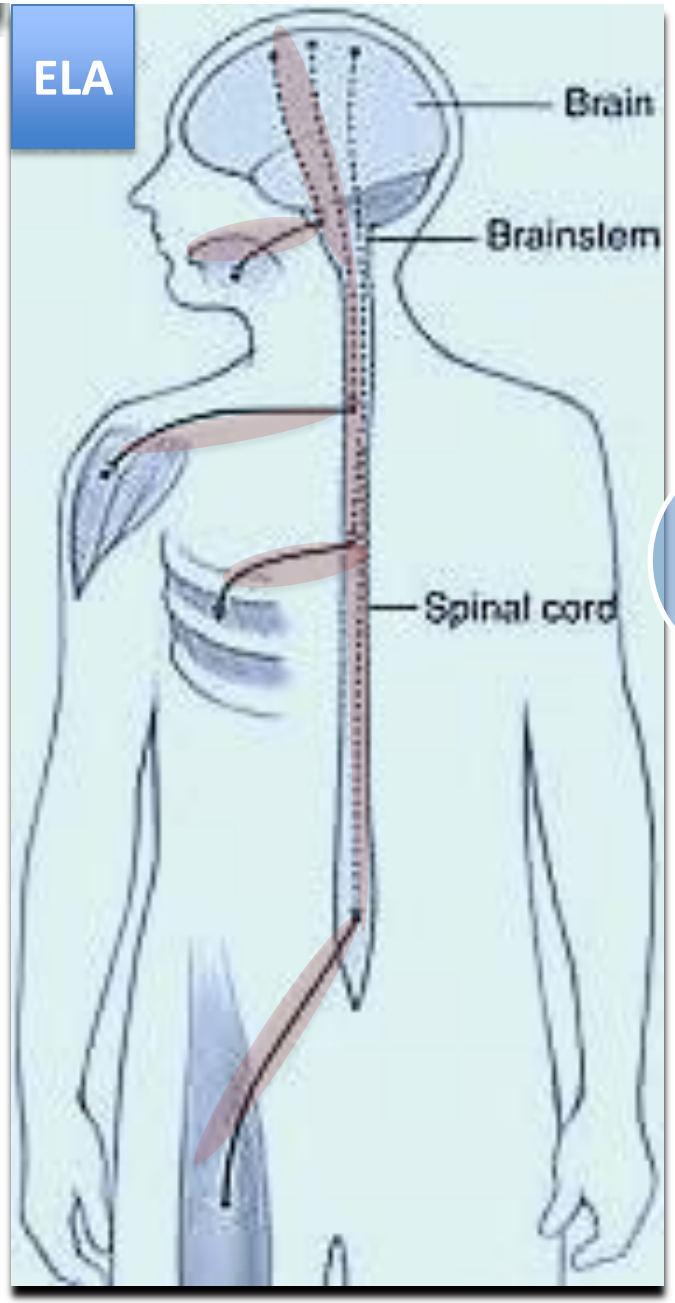
Audiência Pública.
Câmara dos Deputados. Setembro, 2015

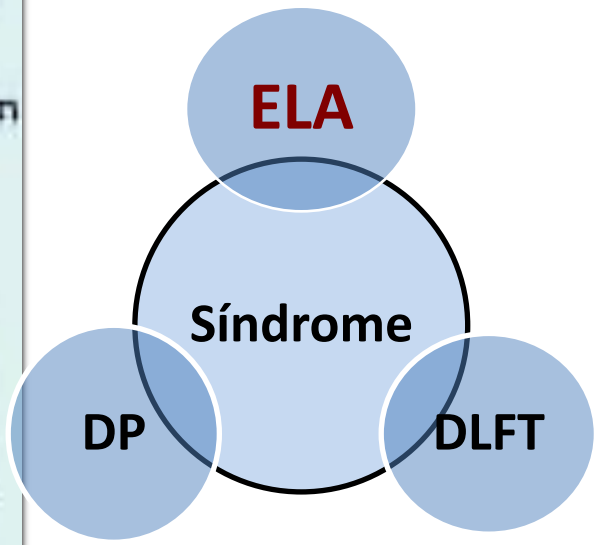
NMSup

NMInf



ELA





PROTEINOPATIA (TDP-43)
C9ORF72

Célula não neuronal?
Processo Inflamatório?
Vias moleculares?

Fraqueza e Atrofia Musculares, hipo/hiper reflexia, fasciculações
Adulto, Progressiva, Morte por falência respiratória

Incidência – (n/ano/100 mil): 2; 4 (>60 anos)
20-30 (ELA Precoce) – Aumentando!!!
Prevalência - 4 - 8 (regionalidade)
Homem: Mulheres - 1,56
- 45 anos (diagnóstico) - HC FMUSP

Formas Clínicas: esporádica (94%) e familiar (6%)
Fatores de Risco: nada comprovado nas formas não hereditárias
Excepcionalidade dos casos das Ilhas do Pacífico Oeste

SOBREVIDA: 2,5 a 5 anos após o diagnóstico

Projeto ELA Brasil (HC FMUSP), após 2010

- **3 casos novos/semana. 600 casos novos**
- **550 pacientes participando de projetos de pesquisa**
- **45 anos (diagnóstico)**

Neurologia Translacional

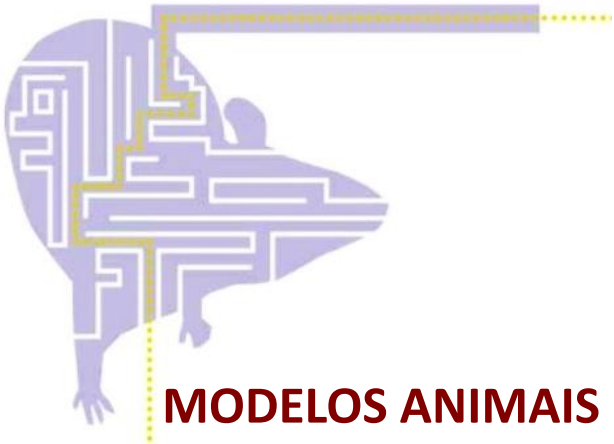
Ensaios Clínicos para ELA
-Drogas (maioria)
-Células (segundo lugar)
-Genética
-Procedimentos/Equipamentos
-Biomarcadores

-Recrutando
-Finalizado
-Finalizado com Resultados
-Ativos, não recrutando
-Retirados

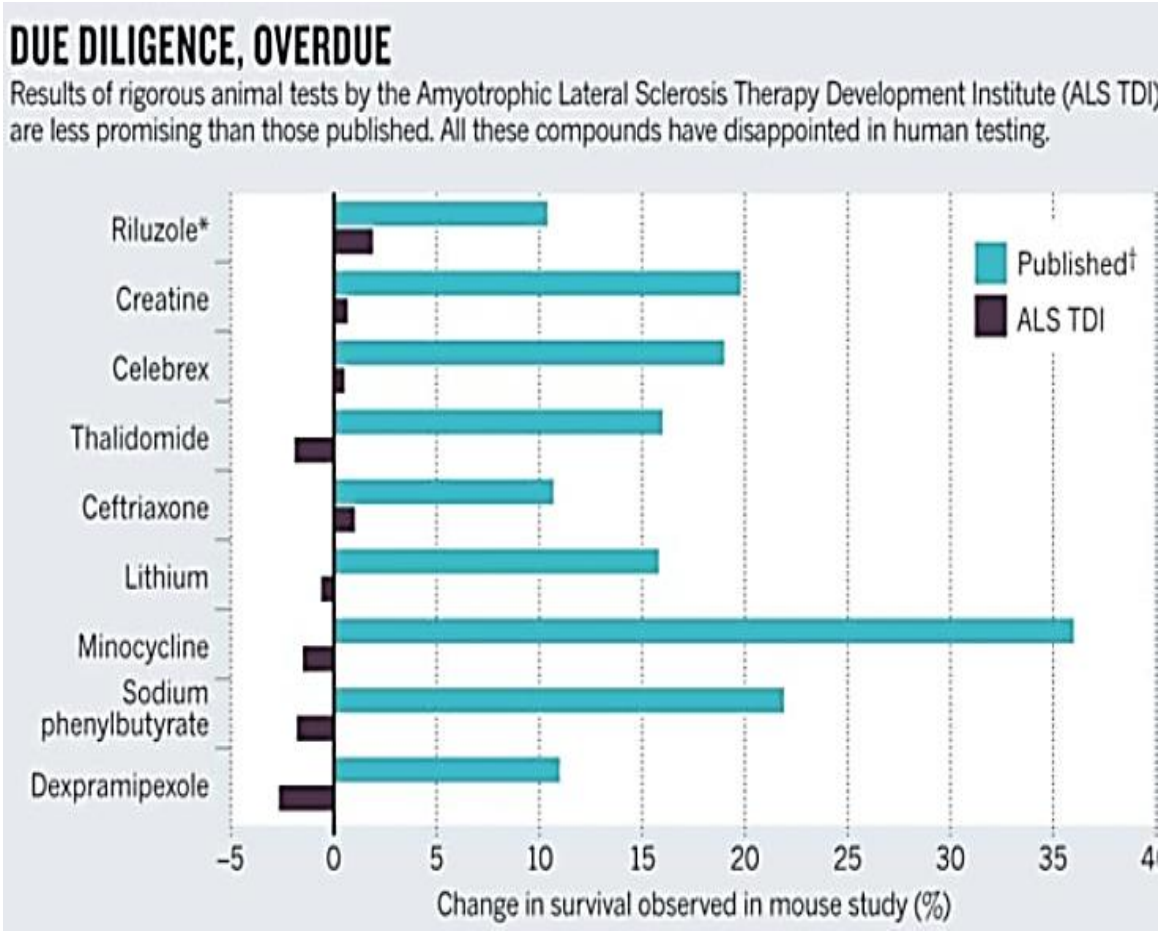
Terapia Celular

- **266 – ELA - 12.4%**
- **1579 – Do. Alzheimer - 0.6%**
- **1415 – Do. Parkinson - 0.8%**

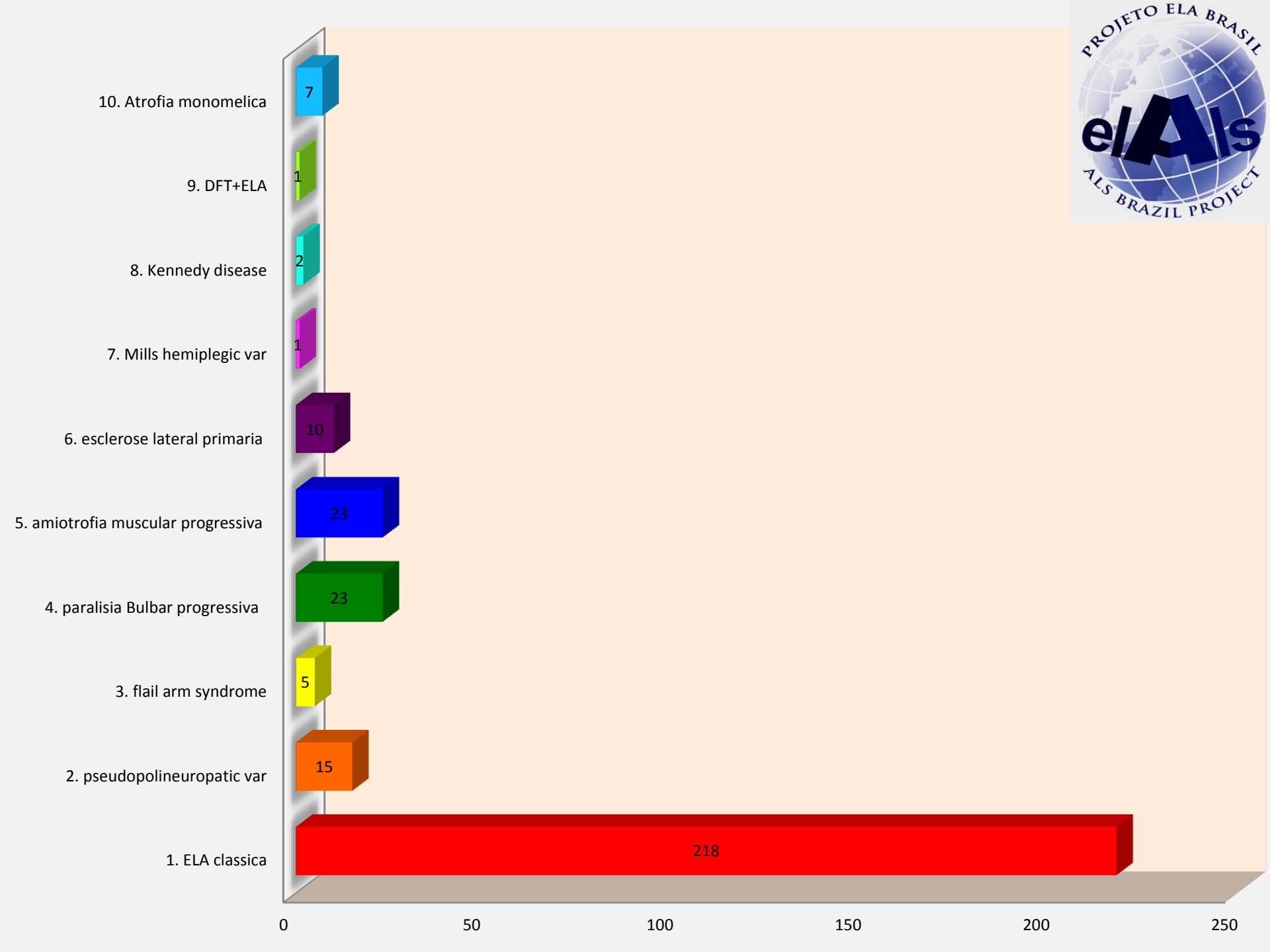
INSUCESSO TRANSLACIONAL DA TERAPÊUTICA NA ELA
Onde está o problema?

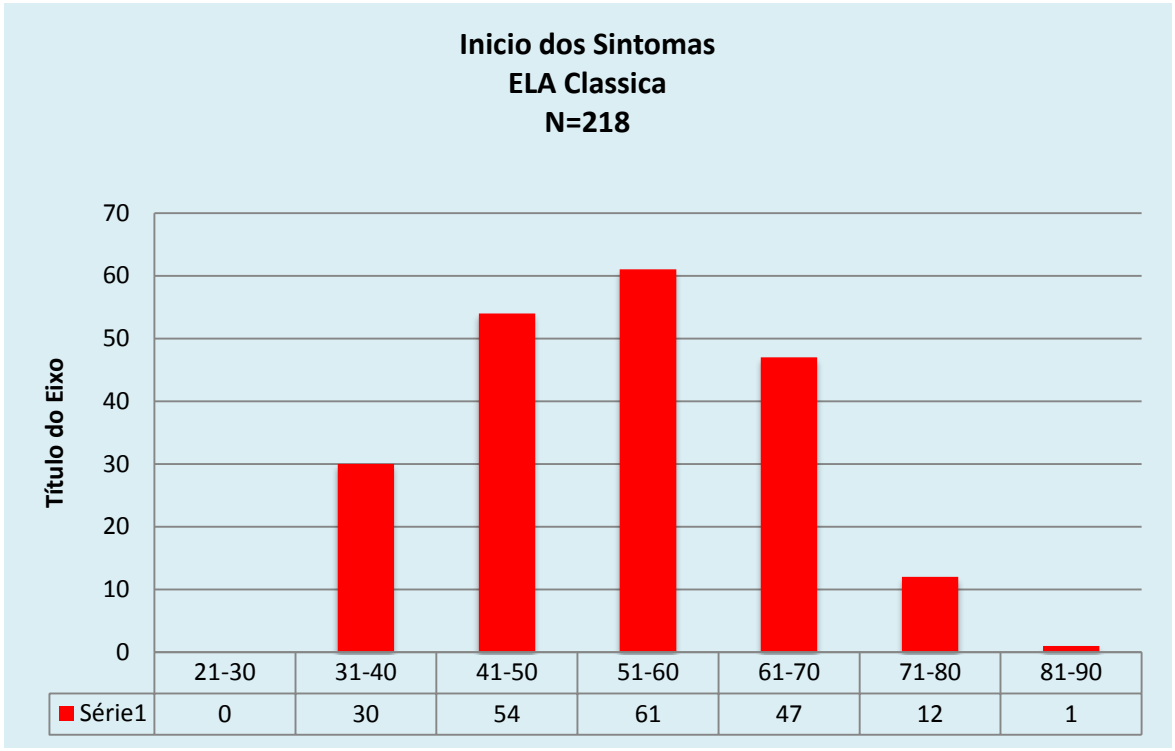


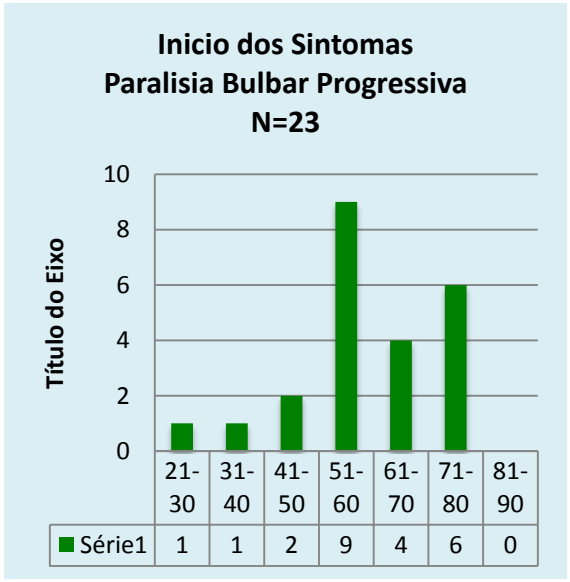
MODELOS ANIMAIS

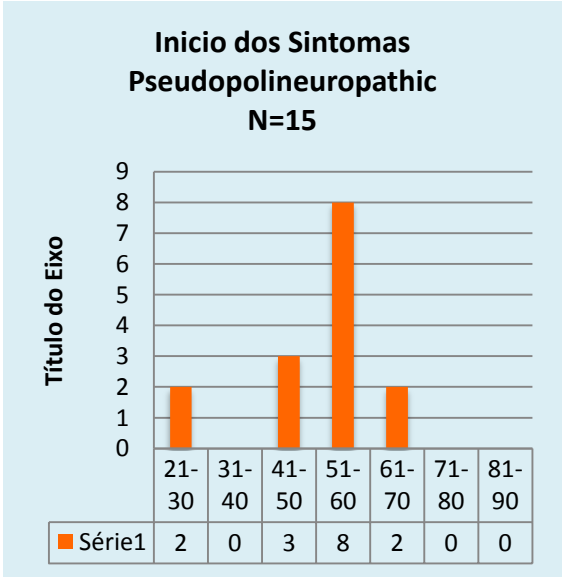


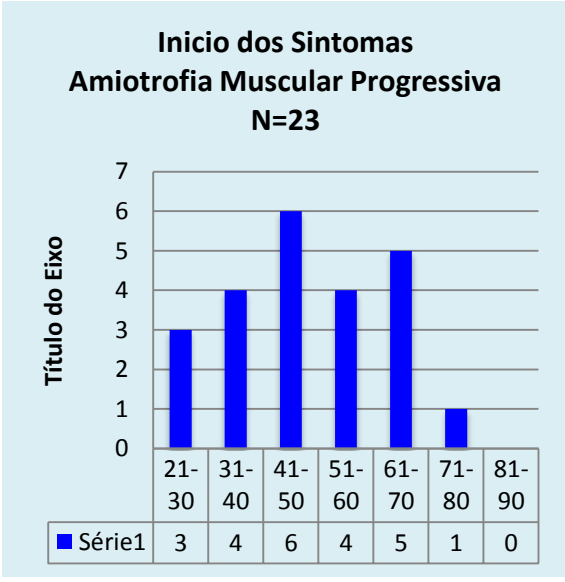
ALS Therapy Development Institute (TDI) in Cambridge, Massachusetts


10. Atrofia monomelica
7
9. DFT+ELA
1
8. Kennedy disease
2
7. Mills hemiplegic var
1
6. esclerose lateral primaria
10
5. amiotrofia muscular progressiva
23
4. paralisia Bulbar progressiva
23
3. flail arm syndrome
5
2. pseudopolineuropatic var
15
1. ELA classica
218
0
50
100
150
200
250
PROJETO ELA BRASIL
elAls
ALS BRAZIL PROJECT

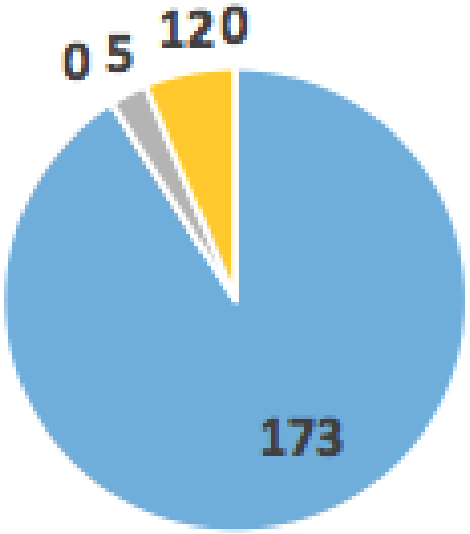

Inicio dos Sintomas
ELA Classica
N=218
Título do Eixo
70
60
50
40
30
20
10
0
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Série1
0
30
54
61
47
12
1


Inicio dos Sintomas
Paralisia Bulbar Progressiva
N=23
Título do Eixo
10
8
6
4
2
0
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Série1
1
1
2
9
4
6
0

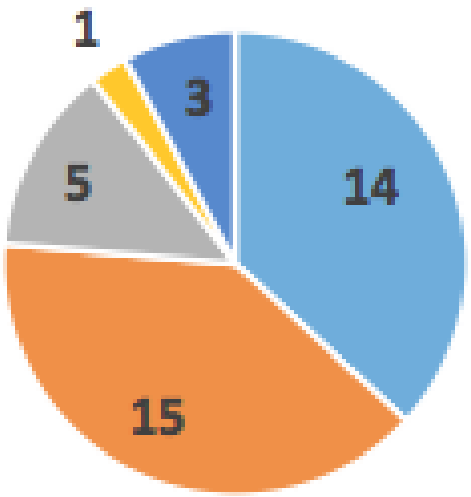

Inicio dos Sintomas
Pseudopolineuropathic
N=15
Título do Eixo
9
8
7
6
5
4
3
2
1
0
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Série1
2
0
3
8
2
0
0


Inicio dos Sintomas
Amiotrofia Muscular Progressiva
N=23
Título do Eixo
7
6
5
4
3
2
1
0
21-30
31-40
41-50
51-60
61-70
71-80
81-90
Série1
3
4
6
4
5
1
0

ELA ESPORÁDICA



ELA FAMILIAL



	Total (228)	Sem mutação	Com mutação encontrada			
			VAPB	C9ORF72	TARDBP	SOD1
LA Esporádica	190	173 91%	0 0%	5 2,6% 5% - 7%	12 6,3% 1% - 0,5%	0 0%
ELA Familiar USA - Europa	38	14 36,8%	15 39,5%	5 13,2% 40% - 40%	1 2,6% 5% - 4%	3 8% 20-20%

BIOMARCADORES
Para a Esclerose Lateral Amiotrófica

-Dignóstico

-Evolução

-Prognóstico

-Moleculares

-Imagem

-Eletrofisiológicos (Outros)

Antiapoptose

Minociclina, Tamoxifeno, Fenilbutirato de Sódio, Pentoxifelina, Cefitreaxone

Antiglutamato

Arimoclonal, Memantina, Telampanel

Antiinflamatório

Copaxone, Nimesulide, Celecoxibe

Terapia Celular

CTDMO, CTMesenquimal, Clone CTFetal

Terapia Gênica

SOD1, C9orf72

	%
Autologous Bone Marrow-derived Stem Cell	30
Autologous Mesenchymal Stem Cell	21
Autologous Mesenchymal Bone Marrow Stromal Cells Secreting NTFs	14
Human Spinal Cord Derived Neural Stem Cell	7
Granulocyte Colony Stimulating Factor (GCSF)	7
Autologous Bone Marrow-derived Stem/Progenitor Cells	3
Umbilical Cord Mesenchymal Stem Cells	3
Hematopoietic Stem Cells in Patients	3
Human Neural Stem Cell	3
Mesenchymal Stem Cell	3
LA-haplo Matched Allogenic Bone Marrow Derived Stem	3
Glycosides(CTG)	3

-Talampanel Teva Pharmaceutical Industries – 559 – Fase 2 Duplo cego- Finaliz– negativo

-SB-509 -Sangamo Biosciences – - Fase 2, Finalizado – preliminar – melhora função muscular

-Thalidomide- Dartmouth-Hitchcock Medical Center- Fase 2, n=24, sem efeito específico, ef colateral
-Tauroursodeoxycholic acid (TUDCA) (antioxidante, derivado de acido biliar) – dimin progressao (54 sem)

-Rasagilina (Parkinson)- University of Ulm, Fase 2, n=250. Excelente resultado preclinico

-Mexiletine p o tto de cãibras musculares. (arrit card, contacao musc, lesao do nervo na NPDiab)
Un California, Fase 4 (i iônicas). Sem outros ef esp
-Arimoclomol in SOD1 ALSf. Phase II/III Randomized, Placebo cont -ongoing, but not recruting
FDA Lifts Ban on Development of Arimoclomol (protetora celular via HSP

-Dexpramipexole – Massachusetts GH) n=943 Knopp Biosciences- fase 3 (Sem benefício)

GM604, Genervon Biopharmaceuti, n=12, (1 ano) – Auto designação de droga órfã . Solicitação aprovacão acelerada no FDA. “Droga do Many many many”. FDA solicitou dados dos ensaios controversos
Tirasemtiv (CK- 2017357)

-MCI-186 – Endaravone Mitsubishi Tanabe Pharma Corporation, n+137, (Progressão Rápida ?)

-Ceftriaxone (cefalosporina de 3ª. G – transp Glu Astroglial) - NEALS Consortium and HIH c 3 coortes
-Ceftriaxone -Massachusetts General Hospital – 513 -Fase 1,2 e 3 (Interrompido)
-Compassionate Use of Ceftriaxone in Patients With Amyotrophic Lateral Sclerosis (ALS) - NCT00718393

-High Dose CoQ10 - Columbia University. Fase 2 , 185, resultados não justificam um fase 3

Gilenya (Fingolimod)

Masitinib inibidores da proteína quinase (PKIs) AB Science

Safety Extension Study of TRO19622 in ALS - Trophos Fr, fase 2 em andamento n=271 Canais mitocond

Ozanezumab (GSK1223249) NOGO-Ainb). Cytokinetics. N=28. fase 2

-Zinco (altas doses)-Phoenix Neurological Associates, LTD – fase 1, 2, n=10. tolerado

Safety and Efficacy of AVP-923 in PBA Patients With ALS or MS (STAR) antcgo MNDA

Tamoxifeno (anticancer) Fase 2a, seguro, eficacia não comprovada
-Creatina-Tamoxifeno – fase 2, n=60, Nazem Atassi, parcial, sugestivo de positivo. Aumentar o n

-*NP001* Neuraltus Pharmaceuticals (macrófagos), fase 2 completada (reultados +), organizando fase 3

-Ketogenic Diet in Amyotrophic Lateral Sclerosis - Johns Hopkins fase 3. 80 (G), 17% (P), 3% (C)

-Plasmid Gene Transfer of Zinc Finger Protein VEGF-A Transcription Activator (SB-509)

-Antisense oligo ISIS 333611. Mass GH. Patients with rapidly progressive forms of ALSf SOD1 gene.

Edaravone

Eliminador de radicais livres, bom anti oxidante como a VitE e ácido ascórbico

2001, Ministério da Saúde aprovou para Infarto Cerebra (IV, 30mg 2x dia por 14 dias)

Relativamente Seguro. Amplamente utilizado no Japão em diversas patologias

Edaravone (MCI-186) , Amyotrophic lateral sclerosis 10 publicações

3 em animais
4 revisões
3 doentes
1 ensaio químico laboratorial

Yoshino H1, Kimura A. Amyotroph Lateral Scler. 2006;7(4):241-5. PubMed NCBI FI= 1,5
Investigation of the therapeutic effects of edaravone, a free radical scavenger, on amyotrophic lateral sclerosis (Phase II study).
N=5, (30 mg) – 3NT no liquor (6 meses)
N=15, (60mg) – Eficácia

Resultado – Diminuição do marcador do estresse oxidativo e contenção da diminuição do escore ALSFRS-R ($p<0.03$)

Abe K, et al., Amyotroph Lateral Scler Frontotemporal Degener. 2014;15(7-8):610-7.

FI = 2,6

Confirmatory double-blind, parallel-group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients.

N= 104 pacebo e N=102 Edaravone. 6 meses de tratamento

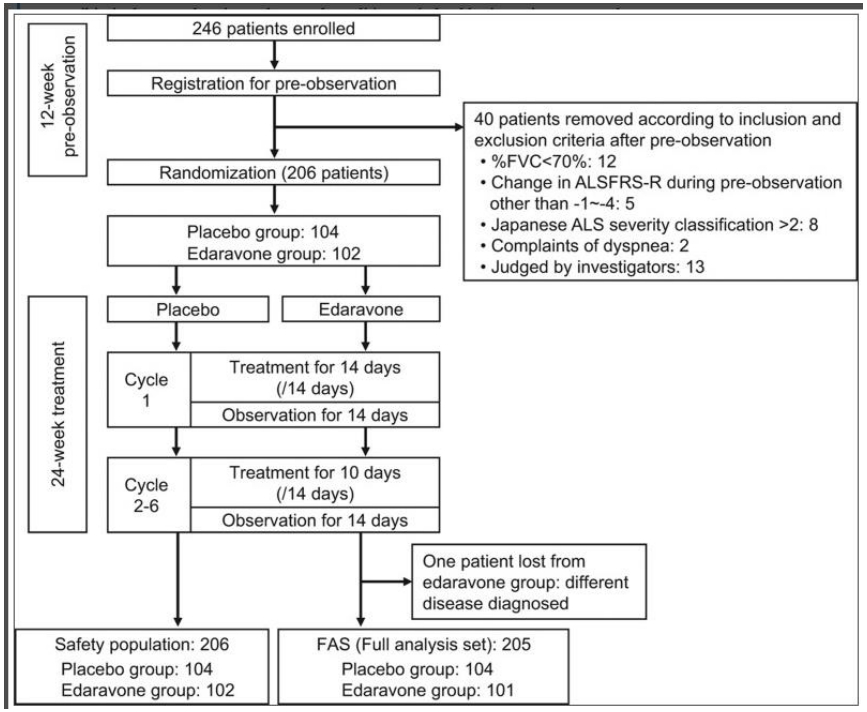
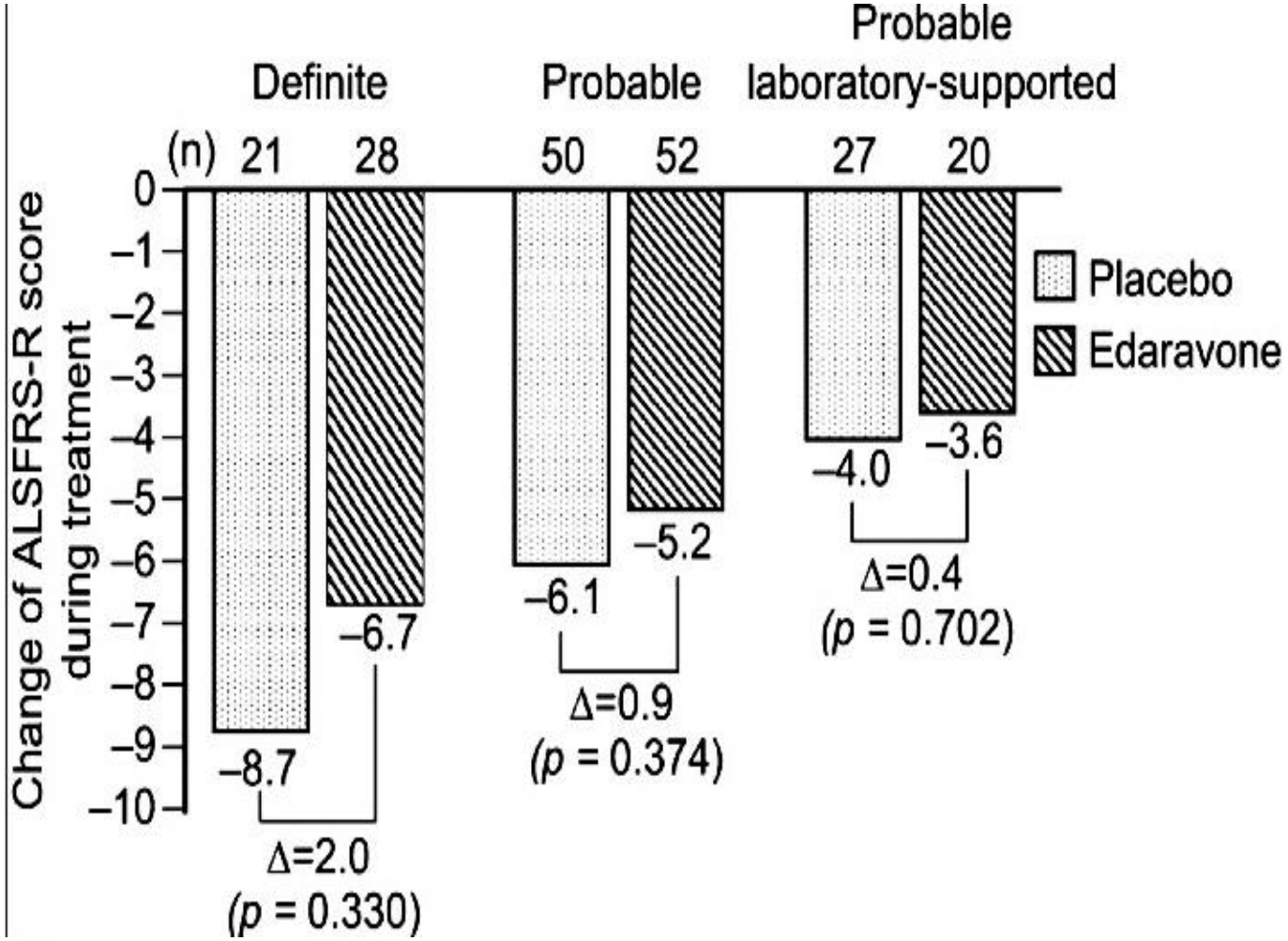


Table III.

Adverse events and serious adverse events.

	AE		SAE					
	Placebo (104)		Edaravone (102)		Placebo (104)		Edaravone (102)	
Treatment	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	***n***	**(%)**
Total	92	(88.5)	91	(89.2)	24	(23.1)	18	(17.6)
Constipation	17	(16.3)	13	(12.7)				
Dysphagia	12	(11.5)	8	(7.8)	11	(10.6)	8	(7.8)
Nasopharyngitis	22	(21.2)	22	(21.6)				
Muscular weakness	9	(8.7)	7	(6.9)	1	(1.0)	1	(1.0)
Contusion	5	(4.8)	12	(11.8)				

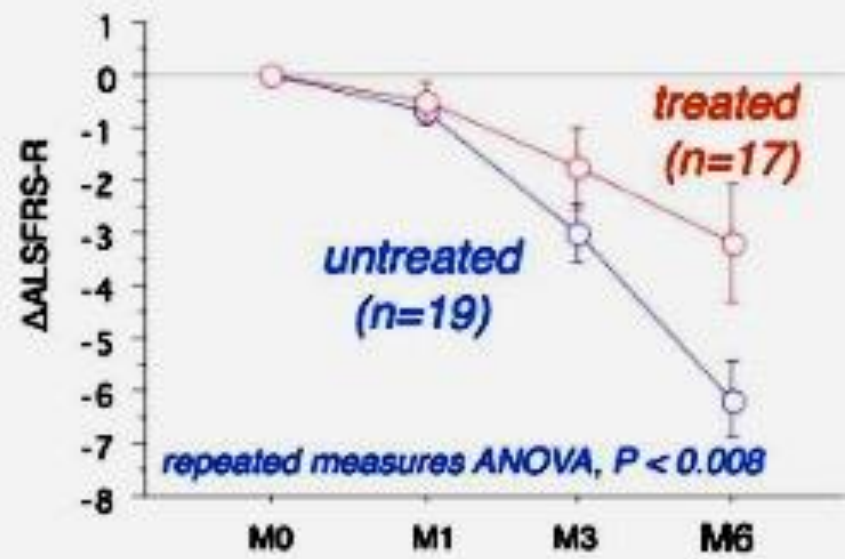
Abe K, et al., 2014;15(7-8):610-7



25% dos Doentes droga e palcebo apresentaram evolução da doença mais lenta q o antecipado

Proposta de desenho de Fase III em pacientes co evolução mais rápida

Nagase M, Yamamoto Y, Miyazaki Y, Yoshino H. Redox Rep. 2015 Jul 20.
[Epub ahead of print] - PubMed NCBI FI= 1,5
Increased oxidative stress in patients with amyotrophic lateral sclerosis and the effect of edaravone administration.



	untreated	treated
M0	41.9 ± 1.4	40.1 ± 1.2
M1	41.2 ± 1.5	39.6 ± 1.4
M3	38.9 ± 1.7	38.4 ± 1.6
M6	35.8 ± 1.6	36.9 ± 2.0

Efeito positivo nas alterações dos marcadoress de Estresse Oxidativo nos pacientes com graus diferentes de evolução

GM604 Phase 2A Randomized Double-blind Placebo Controlled Pilot Trial in ALS

Study Focus:
Study Objectives are: 1. To test the safety and tolerability of GM604 in a population of ALS patients. 2. To test for changes in ALS biomarkers before and after treatment. 3. To determine preliminary effects of injections of GM604 on measures of ALS disease biomarkers and clinical progression.

Disease:
Amyotrophic Lateral Sclerosis (ALS), Sporadic ALS, Familial ALS

Study Category:
Drug Trial

Study Status:
Active, not yet recruiting

Phase:
Phase II

Type:
Interventional Trial
with active agents/drugs & a placebo

Funding Source:
Genervon Biopharmaceuticals, LLC

Study Chair(s)/Principal Investigator(s):
Genervon Biopharmaceuticals, LLC
Hiroshi Mitsumoto, MD (Columbia Medical Center NY)
Merit Cudkowicz, MD (Massachusetts General Hospital)

Clinicaltrials.gov ID:
NCT01854294

NEALS Affiliated?
No

Participant Duration:
12 weeks

# of Subjects:
12

Enrollment Start Date:
07/01/2013

Safety and Efficacy Summary for GM6

Highlights of GM604 safety and efficacy in treating ALS and PD patients where statistical significance or strong trend have been achieved

Normally no one expects statistical significance in data from a small sample size Phase 2A trial. Most trials have a hard time even finding a positive trend. GM6 is so potent that there were multiple endpoints that achieved statistical significance in the ALS phase 2A trial and in the Individual patient Compassionate Use Study, not only in clinical data and results, but also in correlating biomarker data and results.

Safety and Efficacy	Study
1. Safety and tolerability	GM604 is a 6 amino acid endogenous peptide. It is very safe and tolerable as shown in Phase 1 (32 subjects), ALS Phase 2A (12 subjects), PD Phase 2A (6 subjects) and Stroke (28 of 36 subjects, not yet un-blinded) trials. The number of adverse events (AEs) and serious adverse events (SAEs) are comparable to placebo, with no reported drug-related clinically (SEs).
2. Trophic Effect	Axon regeneration in rats with 8 mm gap in severed sciatic nerve, $p<0.001$
3. Tropic Effect	Neurons preferentially projected correctly to motor nerves instead of cutaneous nerve, $p<0.001$
4. Endogenous neuroprotection at fetal development	MNTF expression detected in human placenta peaking at week 9
5. Protection against toxic factors in CSF of CNS diseases patients	The human patient neuron survival percentages (compared to baseline): ALS (175%)
6. Neuroprotection	13 studies with in vitro and in animal models showed GM6 has neuroprotection efficacy in ALS, PD, and stroke models, $p<0.001$
7. PCR Study: GM6 modulates multiple CNS target genes	PCR study of GM6 with SHSY5Y cells (neuroblastoma cells) and microglia showed GM6 modulates (up or down) the expression (by up to two fold or more) of many ALS related genes identified by the scientific community, such as SOD1, TDP-43, FUS, Cystatin-C, tau. and Parkinson Disease related genes such as BDNF.
8. ALS Biomarker: plasma total tau, reduced	ALS Phase 2A, plasma total tau lower than placebo at week 6 ($p=0.0369$)
9. ALS Biomarker: ALS Biomarker: plasma SOD1, reduced	ALS Phase 2A trial, plasma SOD1 percentage change is lower than placebo at week 2, $p=0.0550$
10. ALS Biomarker: plasma TDP-43, reduced	ALS Phase 2A trial, the slope in plasma TDP-43 through week 12 in treated patient group (-3.513 pg/mL/wk) is lower than the placebo patient group (0.493 pg/mL/wk), $p=0.0078$. The mean percentage change in TDP43 of the treated GALS001 patient group was -34% and the mean of percentage change in the placebo patient group was +6% at 12 weeks.
11. ALS Biomarker: plasma TDP-43, reduced in both Phase 2A GM604 treated patients and GALS-C patient	In the GALS-C trial, the plasma TDP43 baseline level was 144.54 pg/ml. This value was as high as those of all the definite ALS patients in the phase 2A trial, who had a mean of 138.88 pg/ml at baseline. The normal range of TDP 43 in plasma is 0-50 pg/ml. At the end of two weeks of treatment (6 doses) the value in the compassionate patient was 92.59 pg/ml and at the end of 12 weeks it was 52.53 pg/ml. The percentage change in TDP43 from baseline in the compassionate patient was thus -63% in 12 weeks.

⚠ The following term was not found in PubMed: gm604.

Pressionando **Senator** Lisa Murkowski e 21 outros

FDA Accelerated Approval of Genervon's GM604 for Use In ALS

Amyotrophic Lateral Sclerosis Statement

FDA U.S. Food and Drug Administration

FDA recognizes the critical unmet medical need for new, effective treatments for amyotrophic lateral sclerosis (ALS). We are committed to working with drug companies and the ALS community to facilitate development and approval of drugs to treat this devastating disease. FDA is prepared to use all expedited development and approval pathways available to us to further this mutual goal.

FDA knows that ALS patients, their families, and others in the ALS community are concerned about the status of Genervon's experimental drug, GM604, for the treatment of ALS. However, FDA is prohibited by law, under usual circumstances, from releasing confidential information about experimental drugs, including GM604.

We call upon Genervon to release all the data from their recently completed trial in order to allow a more informed discussion of the trial findings among ALS stakeholders. Such a release should include the pre-specified clinical outcome measures as assessed by change from baseline observations that were taken just prior to randomization to drug or placebo. Such data provide the strongest basis to assess for drug-related changes in efficacy and safety parameters.

FDA will continue to provide detailed advice and support to Genervon as they pursue further study of GM604 to determine if it is safe and effective to treat ALS. We remain committed to working with the ALS community to find effective treatments for this disease.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Home > Find Studies > Study Record Detail

Phase 3 Study of Dexpramipexole in ALS (EMPOWER)

This study has been completed.

Sponsor:
Knopp Biosciences

Information provided by (Responsible Party):
Knopp Biosciences

ClinicalTrials.gov Identifier:
NCT01281189

First received: January 20, 2011
Last updated: November 24, 2014
Last verified: November 2014
History of Changes

Phase 2 results had been promising

The results are especially disappointing because the drug had shown encouraging results in a phase 2 trial, for which results were announced in November 2011. In that trial, dexpramipexole showed dose-related slowing of functional decline and extension of survival time.

The drug, a molecular mirror image of a drug called *Mirapex*, used to treat Parkinson's disease and restless legs syndrome, had demonstrated neuroprotective properties in laboratory studies. It appeared to improve the function of the *mitochondria*, or cellular energy "factories."

The phase 3 trial — known as *EMPOWER* — enrolled 943 people with ALS at 81 sites in 11 countries and compared dexpramipexole to a placebo. It evaluated trial participants on a rating scale known as the Combined Assessment of Function and Survival (CAFS). In addition to the CAFS, investigators individually evaluated functional decline, survival and respiratory decline.

Bozik et al., 2014. Amyotroph Lateral Scler Frontotemporal Degener.
A post hoc analysis of subgroup outcomes and creatinine in the phase III clinical trial (EMPOWER) of dexpramipexole in ALS.

Neuralstem – NSI 566

Clone de CT Progenitoras Neurais da Medula Espinal de Fetos Humanos

Neuralstem Announces Publication Of Long Term Cell Survival From Phase I NSI-566 ALS Study In The Journal "Annals Of Clinical And Translational Neurology"

Study Concludes NSI-566 Cells Survived for up to 2.5 Years After Transplantation

11/10/2014

Brainstorm Cell Therapeutics – NurOwn™

Células Tronco Mesenquimais secretoras de FNts

Clin Transl Med. 2014 Jul 10;3:21. doi: 10.1186/2001-1326-3-21. eCollection 2014.

Safety of repeated transplantations of neurotrophic factors-secreting human mesenchymal stromal stem cells.

Gothelf Y[1]. Abramov N[1]. Harel A[1]. Offen D[1].

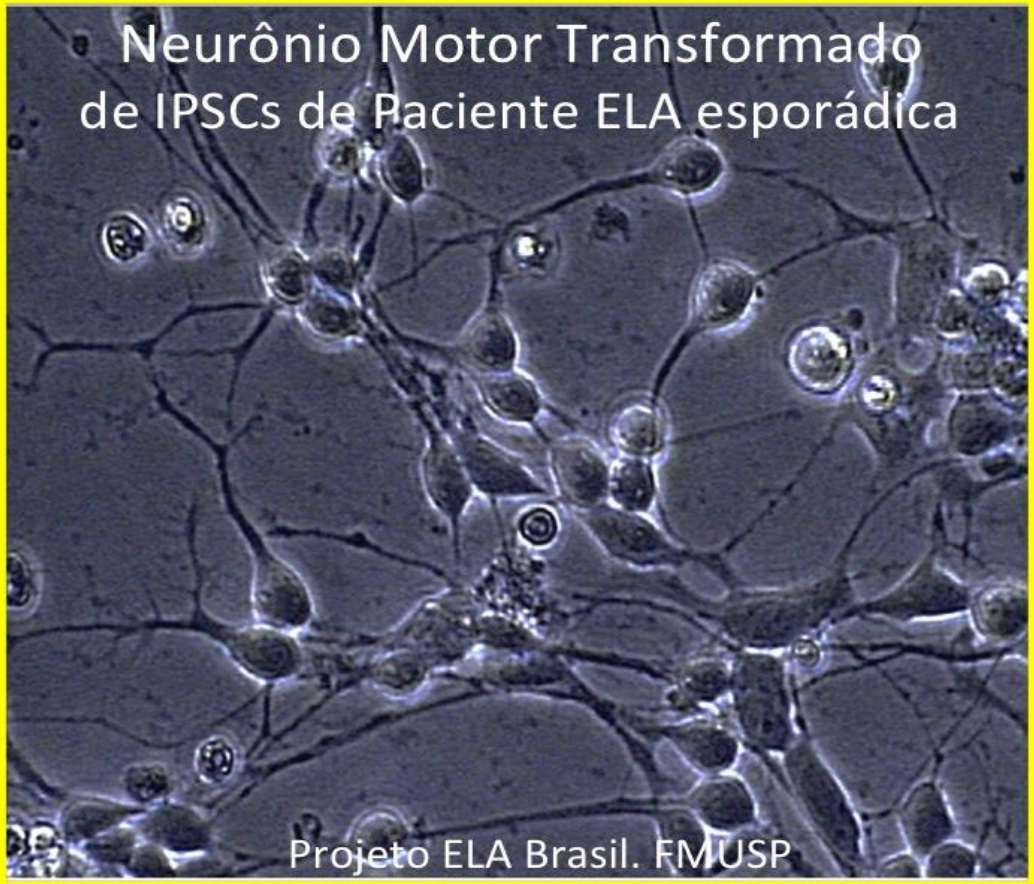
Abstract

BACKGROUND: Therapies based on mesenchymal stem cells (MSC) have been shown to have potential benefit in several clinical studies. We have shown that, using a medium-based approach, MSC can be induced to secrete elevated levels of neurotropic factors, which have been shown to have protective effects in animal models of neurodegenerative diseases. These cells, designated MSC-NTF cells (Neurotrophic factor-secreting MSC, also known as NurOwn™) derived from the patient's own bone marrow, have been recently used for Phase I/II and Phase IIa clinical studies in patients with Amyotrophic Lateral Sclerosis (ALS). In these studies, ALS patients were subjected to a single administration of autologous MSC-NTF cells. The data from these studies indicate that the single administration of MSC-NTF cells is safe and well tolerated. In a recently published case report, it was shown that repeated MSC-NTF injections in an ALS patient treated on a compassionate basis were safe and well tolerated [Muscle Nerve 49:455-457, 2014].

METHODS: In the current study we studied the toxicity and tolerability of three consecutive intramuscular injections (IM) of cryopreserved human MSC-NTF cells in C57BL/B6 mice to investigate the effect of repeated administration of these cells.

RESULTS: Monitoring of clinical signs and immune reactions showed that repeated injections of the cells did not lead to any serious adverse events. Pathology, histology and blood biochemistry parameters tested were found to be within normal ranges with no sign of tumor formation.

CONCLUSIONS: Based on these results we conclude that repeated injections of human MSC-NTF are well tolerated in mice. The results of this study suggest that if the outcomes of additional clinical studies point to the need for repeated treatments, such option can be considered safe.


Neurônio Motor Transformado
de IPSCs de Paciente ELA esporádica
Projeto ELA Brasil. FMUSP

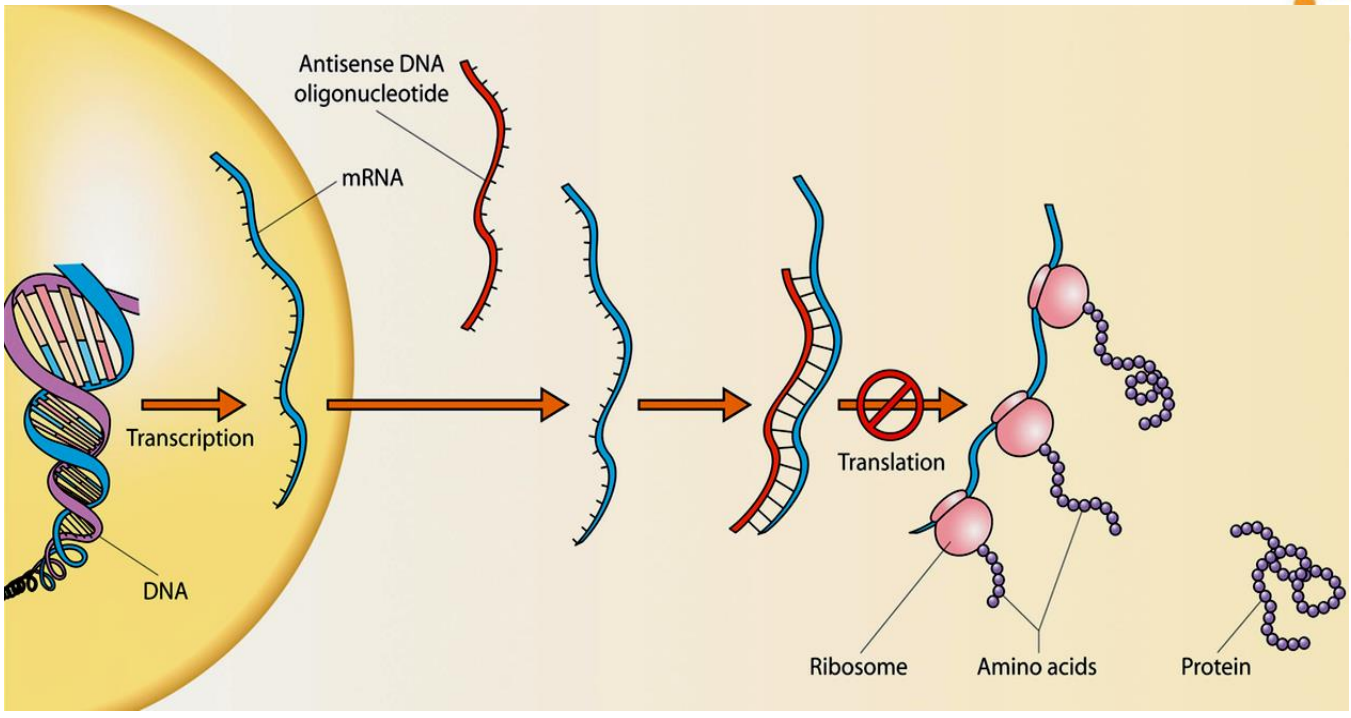

MITOCÔNDRIA
Possível vilão na
ELA esporádica

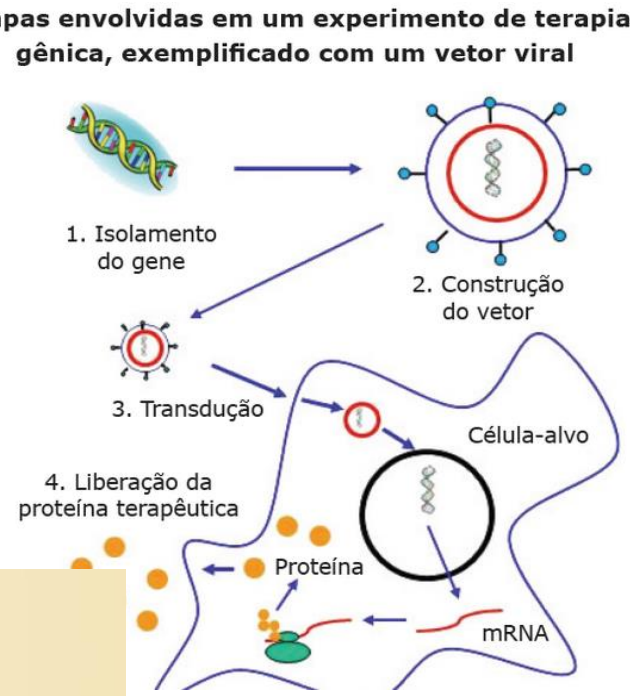
TERAPIA GÊNICA EM ELA

Métodos da terapia gênica
para substituir ou reparar genes

- Substituição do gene anômalo pelo gene normal
- Reparação do gene anômalo
- Regulação do grau de atividade ou inatividade do gene

Oligonucleotídeos Terapêuticos - Antisense





PARECER CFM no. 131/12 após consulta ANVISA

-PROGRAMA DE ACESSO EXPANDIDO

-USO COMPASSIVO
Regulamentado pela Resolução CNS 251/97

-no âmbito da pesquisa

-no âmbito assistencial
CEP local/Conep/Anvisa. Caráter de urgência (*ad referendum*)

-DOAÇÃO PÓS ESTUDOS DE MEDICAMENTOS NOVOS

CONCLUSÕES:

-A CURA DA ELA DEVE SER FUNDAMENTADA NA OBTENÇÃO DE RESULTADOS TRANSLACIONÁVEIS (TERAPÊUTICOS) E NÃO APENAS ACADÊMICO-CIENTÍFICOS

-A ELA É UMA DOENÇA HETEROGÊNEA. A FALTA DE BIOMARCADORES IMPEDE O AVANSO DAS PESQUISAS

NECESSIDADES:

-POLÍTICAS PÚBLICAS PARA O FINACIAMENTO E DESENVOLVIMENTO DA PESQUISA TRANSLACIONAL TERAPÊUTICA NO TERRITÓRIO NACIONAL

-POLÍTICAS PARA A FACILITAÇÃO DA PARTICIPAÇÃO DA INICIATIVA PRIVADA
-FORMAÇÃO DE CENTROS ESPECIALIZADOEM PESQUISA E TRATAMENTO
-POLÍTICA DE ESTÍMULOS AOS ENSAIOS CLÍNICOS

FACILITAÇÃO:

-DO USO COMPASSIVO

-O DIREITO DE TENTAR (Wight to Try)