AMYOTROPHE LATERALSKLEROSE (ALS)

Neues aus der Forschung

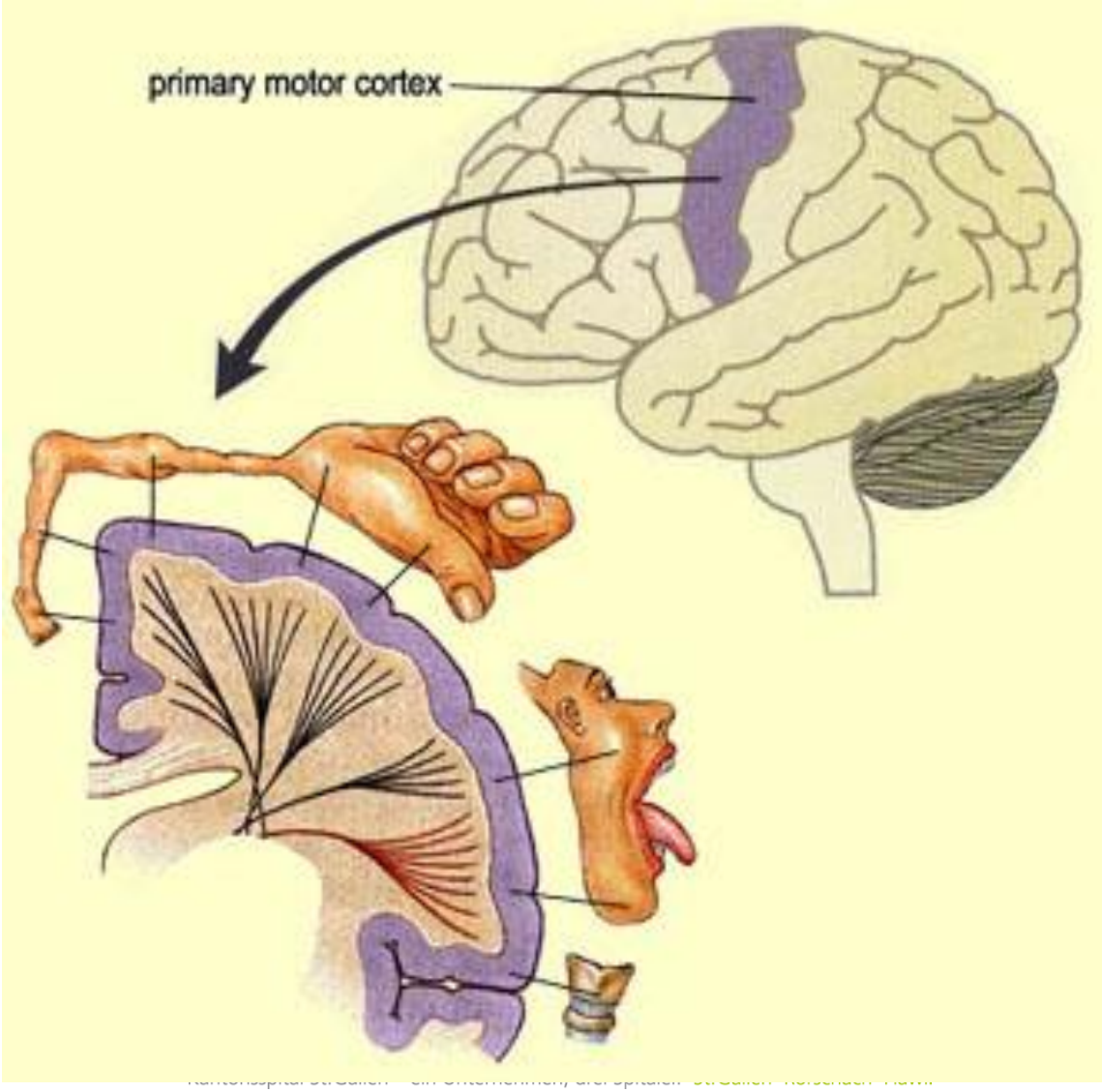
Prof. Dr. Markus Weber

7. ALS Tag 4. November 2016, REHAB Basel

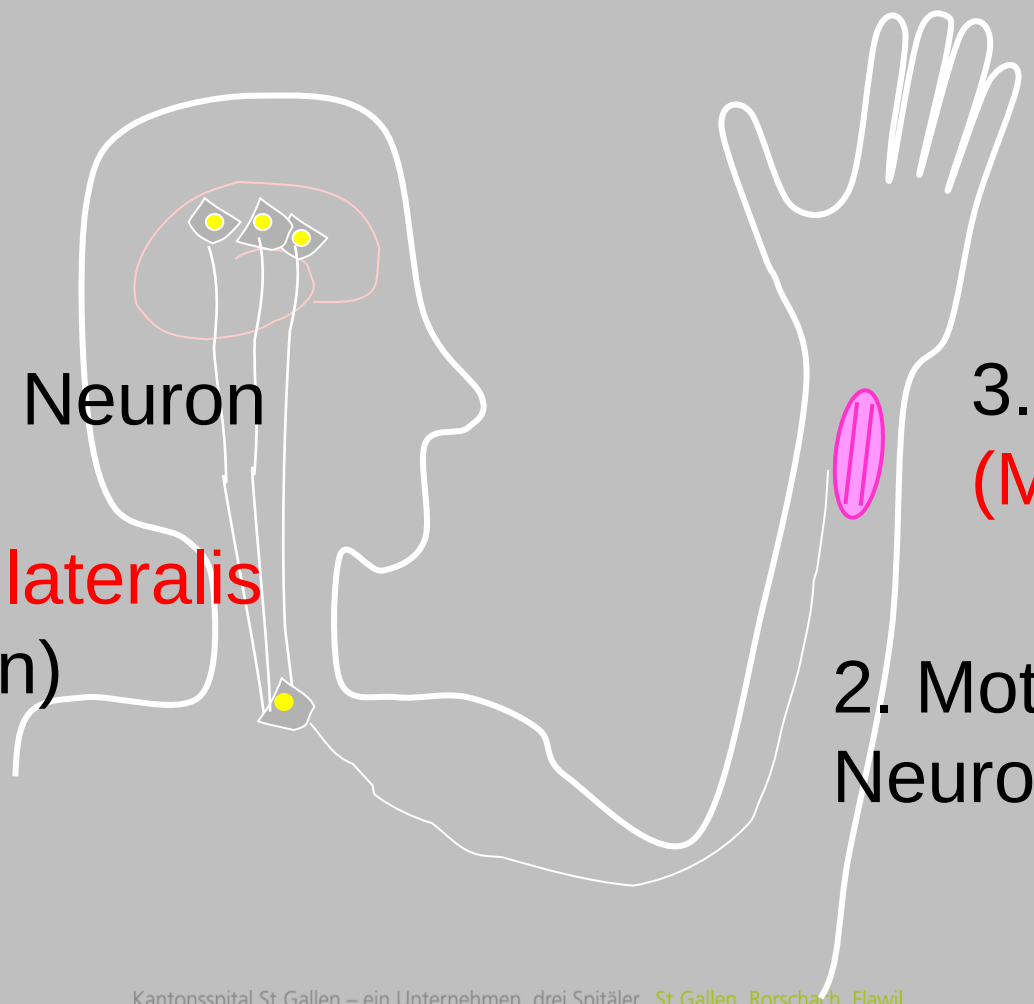
AMYOTROPHE LATERALSKLEROSE (ALS)
-
eine neuromotorische Erkrankung

NEURON=NERVENZELLE
MOTORIK= BEWEGLICHKEIT

Motorische Hirnrinde



DAS MOTORISCHE SYSTEM



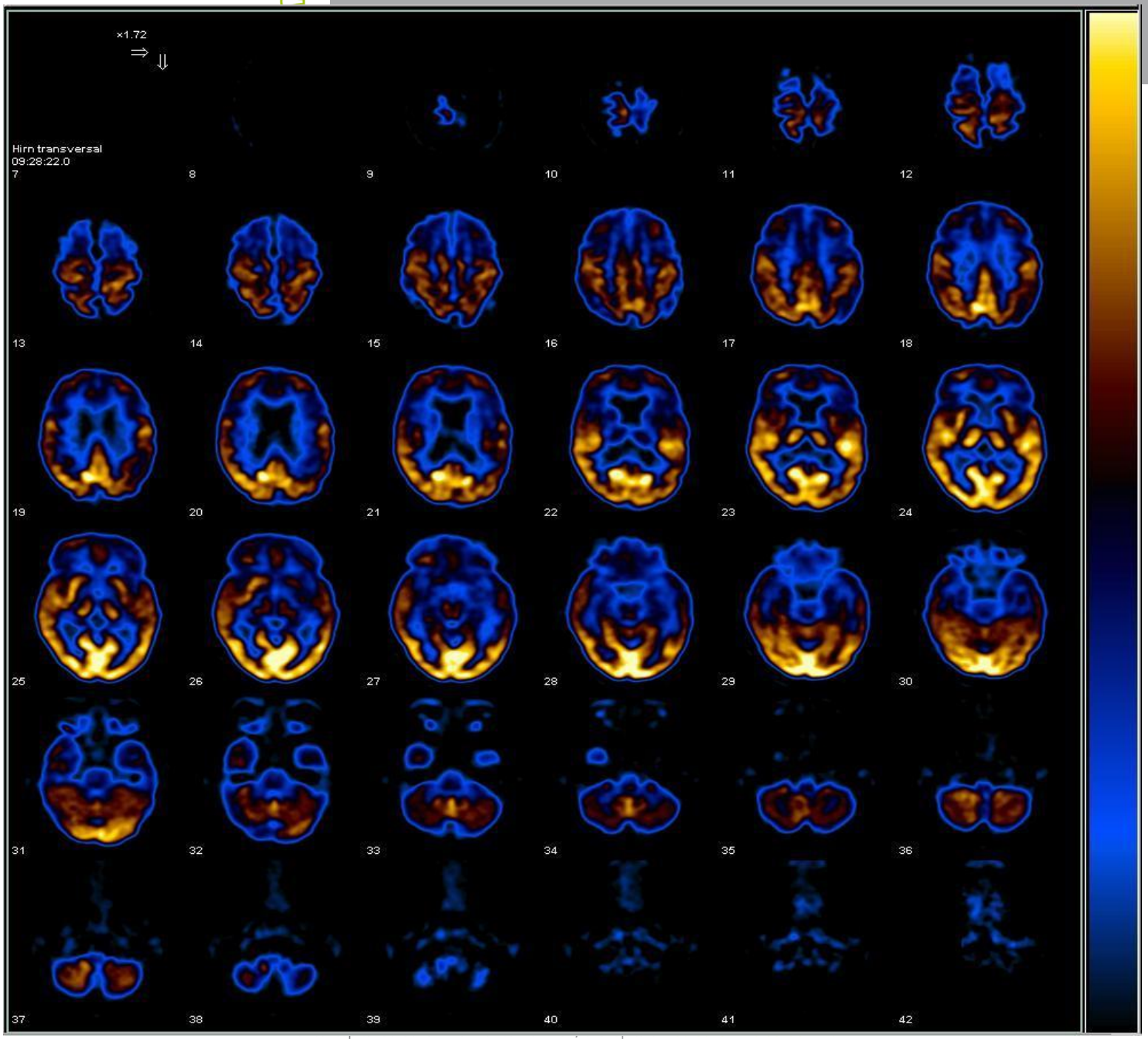
1. Motorisches Neuron (Tractus corticospinalis lateralis Pyramidenbahn)

2. Motorisches Neuron

3. Muskel (Myos)

UNSPEZIFISCHE SYMPTOME

- Gewichtsverlust
- vegetative Symptomatik (Schwitzen, Jucken)
- Kein Aufliegen (Dekubitus)
- Selten Parkinsonsymptome
- Demenz (5%)
- kognitive Störungen (60%)
  - Verlust an Wortgewandtheit
  - Emotionale „Abgestumpftheit“
  - Gestörte Entscheidungsfähigkeit
  - Verlust an Planungsfähigkeit
  - Verlust der Einsichtsfähigkeit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ALS Forschung

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   Brain. 2016 Oct 22. pii: aww250. [Epub ahead of print]
   PMID: 27797809

2. Validity of medico-administrative data related to **amyotrophic lateral sclerosis** in France: A population-based study.
   Vasta R, Boumédiene F, Couratier P, Nicol M, Nicoletti A, Preux PM, Marin B; Fralim Consortium..
   Amyotroph **Lateral** Scler Frontotemporal Degener. 2016 Oct 31:1-8. [Epub ahead of print]
   PMID: 27797285

3. Monitoring peripheral nerve degeneration in ALS by label-free stimulated Raman scattering imaging.
   Tian F, Yang W, Mordes DA, Wang JY, Salameh JS, Mok J, Chew J, Sharma A, Leno-Duran E, Suzuki-Uematsu S, Suzuki N, Han SS, Lu FK, Ji M, Zhang R, Liu Y, Strominger J, Shneider NA, Petrucelli L, Xie XS, Eggan K.
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A Bibliometric Assessment of Global Ice Bucket

Woher kommt ALS?

ALS ist eine komplexe Erkrankung

Neue Gene neue Hoffnung ?

DIE WELT zur Startseite machen

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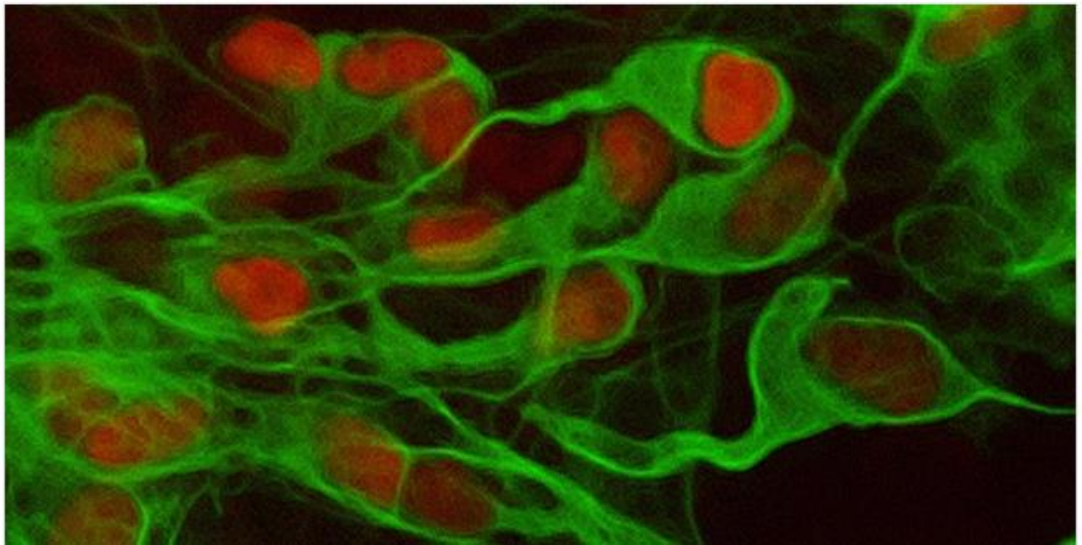
Home > Wissen > Gesundheit > Ursache für Nervenerkrankung ALS gefunden

22.08.11 | **Neurologie**

Ursache für Nervenerkrankung ALS gefunden

Forscher wollen die Ursache für die amyotrophe Lateralsklerose gefunden haben. Das könnte zu wirksameren Medikamenten führen und der Krankheit den Schrecken nehmen.



ARTIKEL EMPFEHLEN

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Kommentare (2) Drucken

ANZEIGE

Mit Geldern der Ice Bucket Challenge

Neues ALS-Gen entdeckt

Mit der Ice Bucket Challenge sammelten Prominente viele Millionen Euro für die Erforschung der Nervenkrankheit ALS. Jetzt berichten Forscher von einem Gen, das bei einigen Betroffen mit der Entstehung zusammenhängt.

Erbsubstanz-Genetik

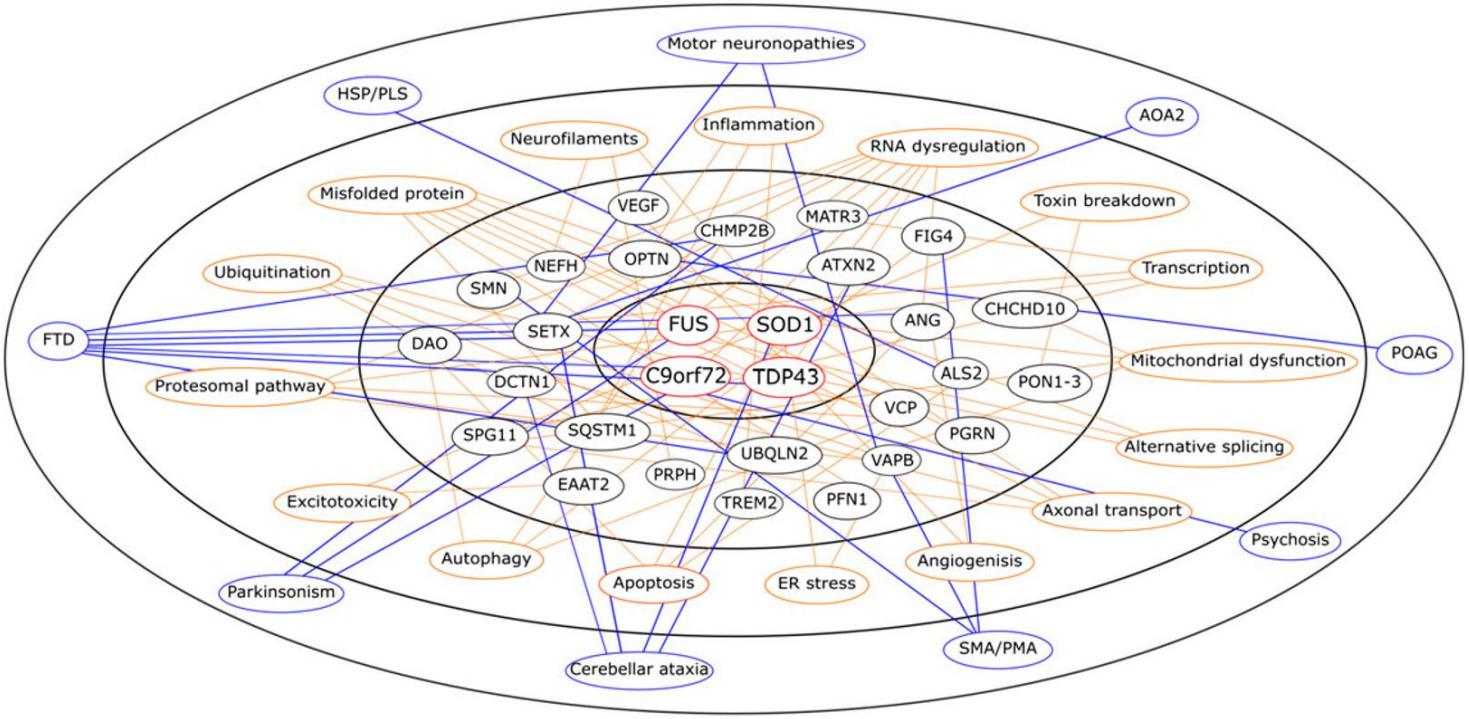

Fig. 2 An illustration of the complexity of ALS pathogenesis. The inner circle includes the associated genes with highest frequency (*C9orf72*, *SOD1*, *TDP-43*/*TARDBP* and *FUS*). The second-order ring includes the large number of genes with a lower frequency of association. The third-order ring includes the possible pathogenic mechanisms that are hypothesized to be associated with these genes. The outer ring includes the other diseases that may be associated with these genes. The complex relationship between genes associated with neurodegeneration, mechanisms of neurodegeneration, and clinical disease phenotypes is apparent. Red = major genes; Black = minor genes; Orange = disease mechanisms; Blue = associated diseases. Mechanistic connections are illustrated by orange lines, and disease associations by blue lines.

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Umwelt

Das et al. N Am J Med Sci. 2012; 4(8): 350–355

n J Med Sci
N Am J Med Sci

Significance level of the risk factors

Risk factors	Total			Male		Female	
	P value	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Occupation							
Farming	0.80416	1.07	(0.62–1.85)	0.99	(0.49–1.99)	0.867	(0.26–2.89)
Industrial	0.90126	1.09	(0.29-4.09)	1.05	(0.28–3.93)	–	–
Mining	0.57198	0.55	(0.09–3.53)	0.51	(0.08–3.34)	–	–
Official/Business	0.95314	0.87	(0.28–2.68)	0.83	(0.26–2.57)	–	–
House Work/Students	0.20675	1.57	(0.79–3.12)	1.52	(0.49–4.70)	1.15	(0.35–3.85)
Living places							
Rural	0.037	1.99	(1.02–3.88)	2.45	(1.18–5.75)	1.04	(1.31–3.48)
Urban	0.063	0.50	(0.26–0.98)	0.40	(0.17–1.74)	0.96	(0.28–3.24)
Toxin exposure							
Insecticides/Pesticides	0.030	1.61	(1.27–1.99)	1.09	(1.27–2.79)	3.51	(1.11–12.25)
Heavy metals (iron)	0.811	1.09	(0.29-4.09)	1.05	(0.27–3.93)	–	–
Solvents/Chemicals	–	–	–	–	–	–	–
Smoking							
Smoking present	0.009	1.88	(1.19–2.96)	2.04	(1.23–3.35)	0.91	(0.22–3.66)
Source of drinking water							
Tube Well	0.249	1.41	(0.79–2.54)	1.25	(0.63–2.48)	1.72	(0.52–5.71)
Well Water	0.859	0.99	(0.46–2.14)	1.05	(0.44–2.25)	0.89	(0.18–4.39)
Ponds	0.253	0.46	(0.13–1.65)	0.83	(0.183–3.79)	0.91	(0.11–6.72)
Corporation supplied water	0.288	1.26	(0.80–2.67)	0.51	(1.51–1.76)	0.47	(0.11–2.18)
Others factors							
Electrical trauma	0.003	6.20	(1.75–21.98)	6.64	(1.512–29.16)	6.15	(0.74–51.05)
Working under electromagnetic field	–	–	–	–	–	–	–

Joint Programme - Neurodegenerative Disease Research
Transnational research proposals 2013

"European research projects for the identification of genetic, epigenetic and environmental risk and protective factors for Neurodegenerative Diseases"

JPND research
EU Joint Programme – Neurodegenerative Disease Research

Proposal Application Form

I. General information

Acronym (10 characters max.): STRENGTH

Project Title: Survival, Trigger and Risk, Epigenetic, eNvironmental and Genetic Targets for motor neuron Health

Project Coordinator: **Ammar Al-Chalabi**

Name	Ammar Al-Chalabi
Institution/Department	King's College London, Department of Clinical Neuroscience
Address	London SE5 8AF
Country	UK
Phone + Fax	+44 20 7848 5187 (P) +44 20 7848 5190 (F)
Email	ammar.al-chalabi@kcl.ac.uk

Total funding applied for: 4,253,547 €

Muskelzentrum/ALS Clinic

Total Funding: To Be Finalised*

Start Date: February, 2014

Duration: 3 years

Coordinator: Ammar Al-Chalabi

T: +44-20784-85187

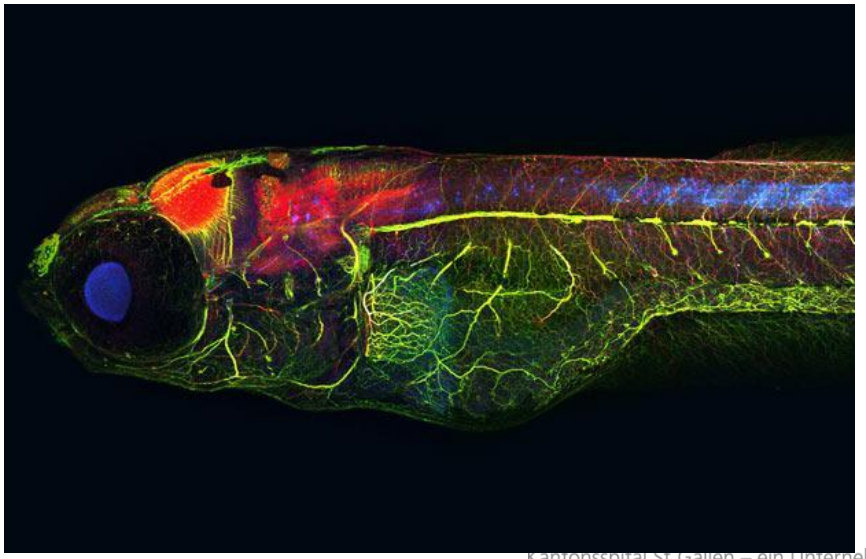
E: ammar.al-chalabi@kcl.ac.uk

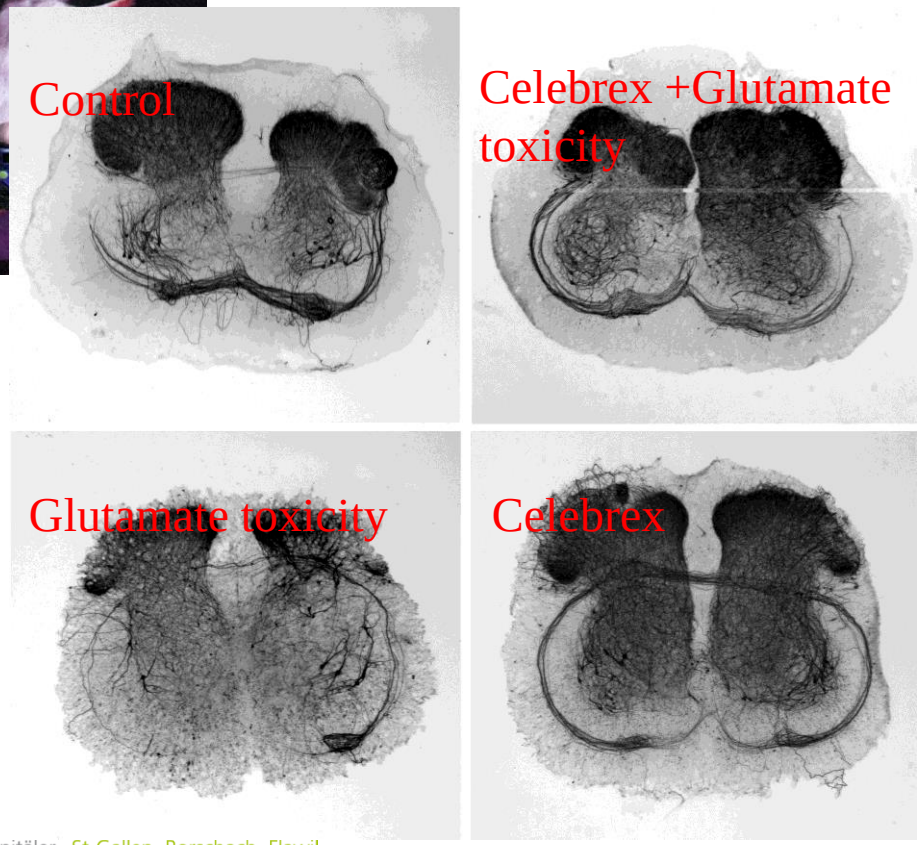
Project Partners:

COORDINATOR I AMMAR AL-CHALABI

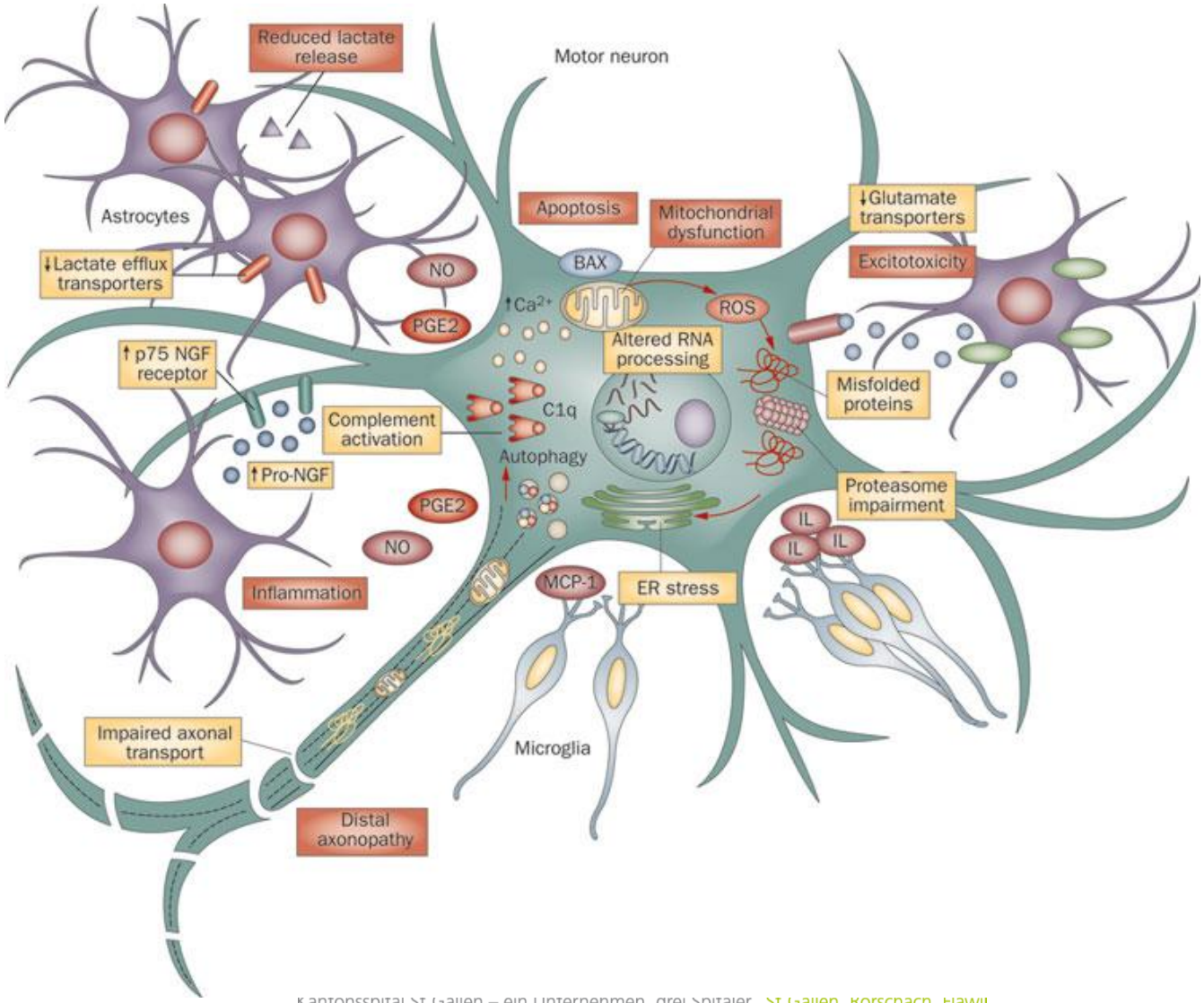
- **Ammar Al-Chalabi**, King's College London, United Kingdom
- **Pamela Shaw**, University of Sheffield, United Kingdom
- **Leonard van den Berg**, University Medical Centre Utrecht, Netherlands
- **Wim Robberecht**, Katholieke Universiteit Leuven, Belgium
- **Adriano Chio**, University of Turin, Italy
- **Vincenzo Silani**, Istituto Auxologico Italiano, Italy
- **Philippe Corcia**, INSERM U930 - Université François Rabelais, France
- **Markus Weber**, Kantonsspital St. Gallen, Switzerland
- **Weimin Ye**, Karolinska Institutet, Sweden
- **Jochen Weishaupt**, University of Ulm, Germany
- **Orla Hardiman**, Trinity College Dublin, Ireland

Krankheitsmodelle zur Erforschung der ALS

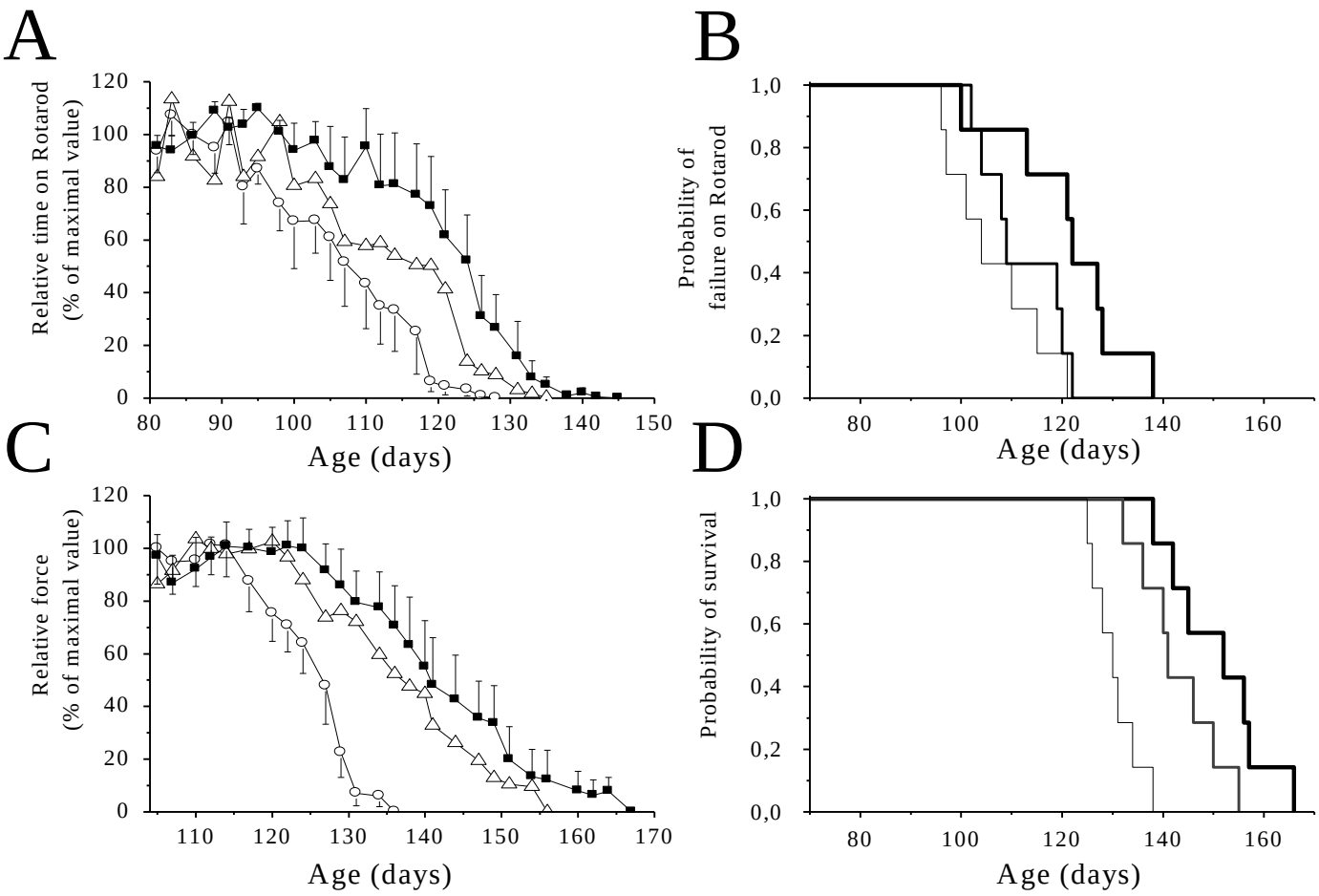




Viele Krankheitsmechanismen



Beispiel Minocyclin ein Antibiotikum



Negative ALS Studien

Su et al. Muscle & Nerve 2014

Table 1. ALS clinical trials.*

Drug	Size†	Year
Acetylcysteine	110	1995[193]
Amantadine / guanidine	20	1981[194]
Arimoclomol	84	2008[195]
β-1a interferon	61	2000[196]
Baclofen	23	1979[197]
BCAA	22	1988[198]
BCAA	126	1993[199]
BCAA / threonine	95	1996[200]
BDNF	1135	1999[201]
BDNF	25	2000[202]
Celecoxib	300	2006[203]
Celecoxib / minocycline	60	2008[204]
CNTF	730	1996[205]
Coenzyme Q10	185	2009[206]
Creatine	175	2003[207]
Creatine	104	2004[208]
Creatine	107	2008[209]
Cyclosporine	74	1988[210]
Dexpramipexole	102	2011[19]
Dexpramipexole	616	2013[18]
Dextromethorphan	14	1993[211]
Dextromethorphan	49	1996[212]
Dextromethorphan	45	1997[213]
Dextromethorphan / quinidine	140	2004[214]
Gabapentin	152	1996[215]
Gabapentin	231	1998[216]
Gabapentin	204	2001[217]
Gangliosides	40	1984[218]
Gangliosides	40	1984[219]
G-CSF	24	2011[220]
Glatiramer	30	2006[221]
Glatiramer	366	2009[222]
Glutathione	32	1998[223]
Growth hormone	40	2012[224]
Guanidine	24	1974[225]
IGF-1	75	1993[226]
IGF-1	266	1997[227]
IGF-1	183	1998[228]
IGF-1	9	2005[229]
IGF-1	330	2008[230]
Indinavir	46	2005[231]
Inosiplex	16	1974[232]
Isoprinosine	25	1971[233]
Lamotrigine	67	1993[234]
Lamotrigine	30	2003[235]
Levamisole	59	1985[236]
Lithium	84	2010[237]
Lithium	133	2012[238]
Lithium	214	2013[239]
L-threonine	23	1992[240]
L-threonine	30	1992[241]
Memantine	63	2010[242]
Methionine / antioxidants	28	2001[243]
Methylcobalamin	24	1998[244]
Minocycline	19	2004a[245]
Minocycline	23	2004b[245]
Minocycline	412	2007[246]
Nimodipine	87	1996[247]
Pentoxifylline	400	2006[248]
Physostigmine	25	1993[249]
Riluzole	155	1994[13]
Riluzole	959	1996[14]
Riluzole	15	1998[250]

TABLE 1. *Continued*

Drug	Size†	Year
Riluzole	168	2002[251]
Selegiline	111	1994[252]
Selegiline	10	1994[253]
Selegiline	133	1998[254]
Talampanel	59	2010[255]
TCH346	553	2007[256]
Thalidomide	37	2008[257]
Thyrotropin	30	1986[258]
Thyrotropin	12	1986[259]
Thyrotropin	41	1986[260]
Thyrotropin	25	1987[261]
Thyrotropin	23	1991[262]
Thyrotropin	36	1992[263]
Tilorone	16	1978[264]
Topiramate	296	2003[265]
Transfer factor	66	1979[266]
Ursodeoxycholic acid	64	2012[267]
Valproic acid	163	2009[268]
Vitamin E	289	2001[269]
Vitamin E	160	2005[270]
Xaliproden	78	2004[271]
Xaliproden	867	2004a[272]
Xaliproden	1210	2004b[272]

BCAA, branched-chain amino acids; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; G-CSF, granulocyte colony-stimulating factor; IGF-1, insulin-like growth factor-1; TCH346, omigapil.

**Modified from Beghi et al.[16] (2011) with permission of the publisher.*

†Total number of patients in study.

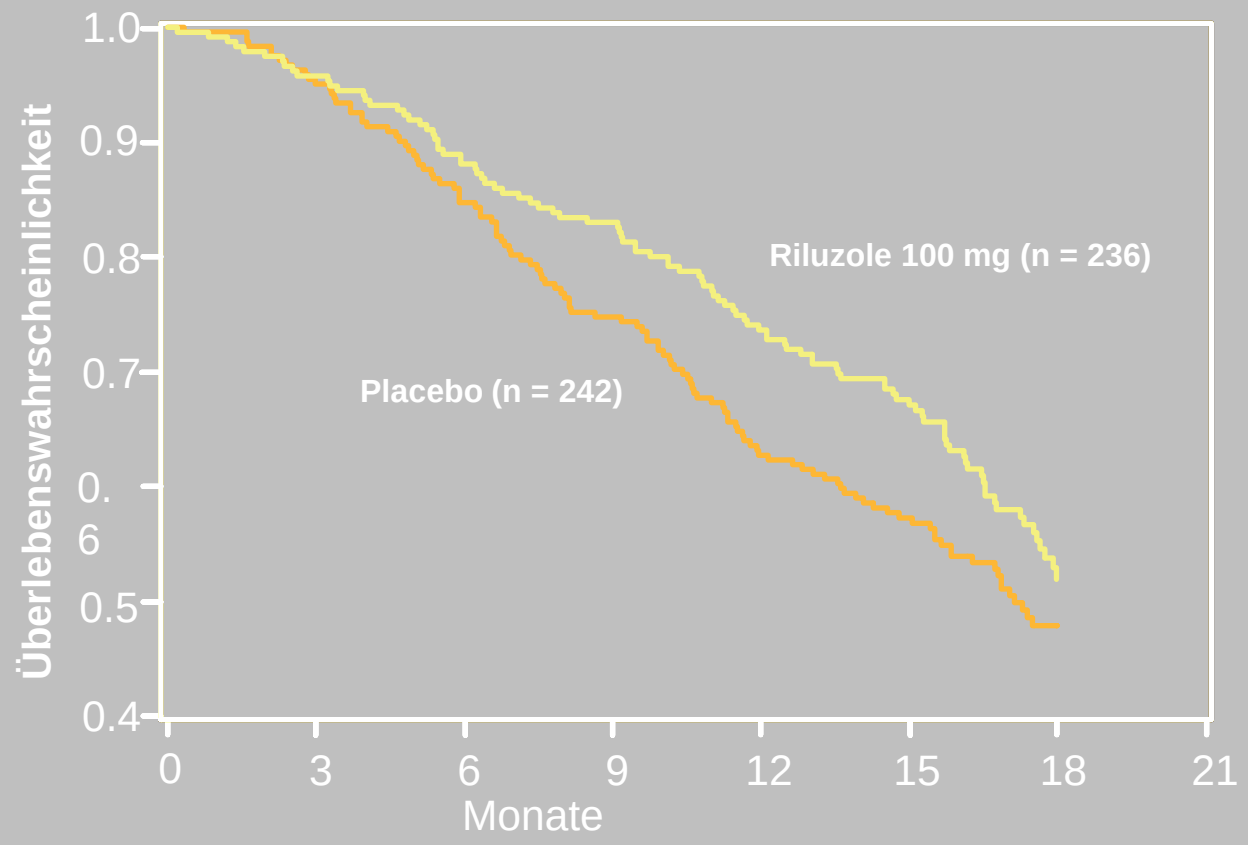
3%. All genes found to be mutated in FALS can also be found to be mutated in SALS, albeit at low frequencies.[38] Even in cases with known genetic etiology, it is unclear how the genetic insult, present in all somatic cells, induces selective vulnerability in motor neurons.[39,40]

An understanding of genes involved in ALS may be essential in developing effective therapeutics. In what follows is a discussion of specific genes linked to ALS. This discussion is not exhaustive, but rather focuses on genes more commonly linked to ALS in epidemiologic studies and also includes rare genetic alterations if they shed light on novel pathways or phenotypes. Genetic mutations that are very rare or those with contributions to ALS that are less well documented are included and referenced in the tables of causative genes (Table 2) or modifiers of disease risk or progression (Table 3), but are not discussed in detail.

Cu/Zn-Superoxide Dismutase (*SOD1*). Modern genetic studies of ALS began with the identification of 11 missense mutations in *SOD1* in 13 distinct FALS families.[21] The discovery was the first to pinpoint a genetic cause for ALS, paving the way for *in vivo* models of FALS that enabled analysis of disease mechanisms[41,42] and large-scale ALS bioinformatics

Wirksamkeit von Rilutek

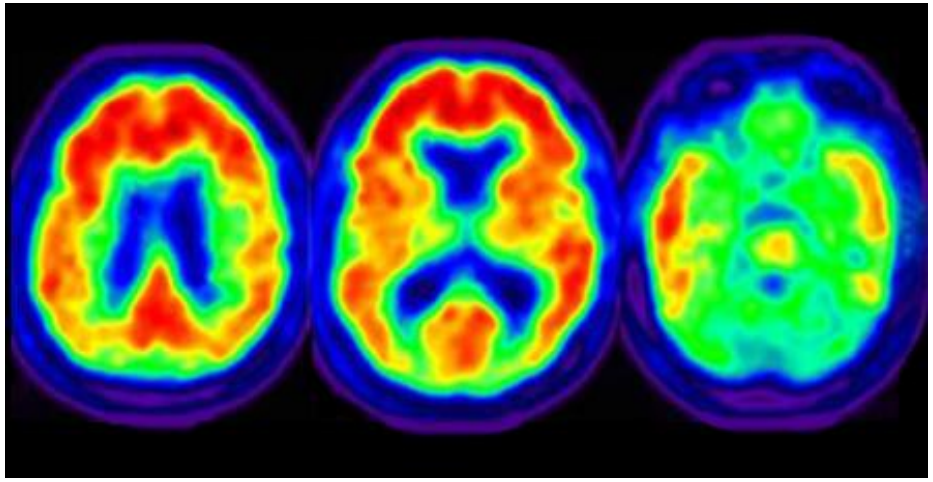
(Lacomblez et al.Lancet 1996)



Was sind die Herausforderung bei der Entwicklung neuer Medikamente ?

- Unklar inwieweit Forschungsergebnisse von Tiermodellen auf Menschen übertragbar sind.
- ALS ist sehr variabel (heterogen)
  - «jeder hat seine eigene Krankheit»
- Es braucht für Studien mehrere hundert Patienten und eine lange Studiendauer
  - Teuer
- Entwicklung von einfachen Messgrössen zum Nachweis von Therapieeffekten (Biomarker) ist prioritär

Biomarker



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

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Methodology Study of Novel Outcome Measures to Assess Progression of ALS

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2016 by *Biogen*

Sponsor:
Biogen

Information provided by (Responsible Party):
Biogen

ClinicalTrials.gov Identifier:
NCT02611674

First received: October 8, 2015
Last updated: September 27, 2016
Last verified: September 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The primary objectives of the study are to estimate and rank-order the longitudinal standardized mean changes over 6 months and over 12 months, for a participants with amyotrophic lateral sclerosis (ALS), in order to identify measures that are more sensitive to disease progression than Amyotrophic Later

Neue Medikamente: Edaravone

Mitsubishi Tanabe Pharma **Press Release**

June 26, 2015

For immediate release:

Mitsubishi Tanabe Pharma Corporation

RADICUT® inj. 30mg and RADICUT® BAG for I.V. Infusion 30mg

Mitsubishi Tanabe Pharma Corporation receives approval for additional indication for Amyotrophic Lateral Sclerosis (ALS) in Japan

Osaka, Japan, June 26, 2015 — Mitsubishi Tanabe Pharma Corporation (President & Representative Director, CEO: Masayuki Mitsuka) announced today that it has received approval of a partial change in manufacturing and marketing approval items related to an additional indication and dosage/usage for Amyotrophic Lateral Sclerosis (ALS) for RADICUT® inj. 30mg and RADICUT® BAG

Edaravone in Tablettenform

Treeway Announces Positive Data from Two Separate Phase I TW001 Clinical Trials

| Print |

Thursday, 10 December 2015 14:00 (UTC + 1)

TREEWAY

Successful dose and confirmatory study solid platform for phase II/III trial in ALS patients

Rotterdam, The Netherlands, December 10, 2015 / B3C newswire / -- Treeway, a biotech company developing therapies against amyotrophic lateral sclerosis (ALS), today announces the completion of two successful phase I trials with their lead compound TW001, a new more patient friendly oral formulation of the Japanese stroke and ALS therapy edaravone. Treeway, founded by two Dutch ALS patients, aims at speeding up ALS research in collaboration with academic and research centers around the globe.

TW001 was tested in both single and multiple dose phase I studies in healthy volunteers and in ALS patients. In the two Phase 1 clinical studies TW001 was shown to be safe and well tolerated and adequate exposure levels with the oral formulation were detected. Based on these trial data, the company is now aiming to start a pivotal phase 2/3 study in 2016. Earlier, Treeway obtained orphan drug designation for edaravone of ALS from both the FDA and EMA.

AB Science

ALS.NET

WHAT IS ALS? ALS RESEARCH ABOUT ALS.NET RESOURCES AFFILIATES

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Masitinib ALS Clinical Trial Interim Report Positive

PREVIOUS
ALS.net to Bring 'ALS Unfiltered' Series to Cities across the Country

0 Tweets 90 Shares

AB Science peeks at Phase 2/3 ALS clinical trial data. Looks positive, but only halfway done with trial.

Biogen

THE ALS RESEARCH FORUM
Discovering a Common Goal, Discovering a Cure

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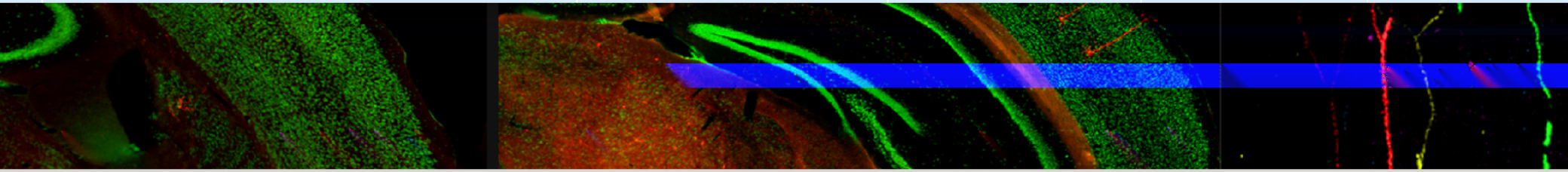

Image credit: Wataka

Biogen and Isis Pharma Launch Clinical Trial of Antisense Drug for SOD1-ALS

December 15, 2015 News in brief Prize4Life Staff

Topics: Clinical Research, Industry R & D

Biogen and Isis Pharmaceuticals have announced the initiation of a phase I/II clinical trial of ISIS-SOD1Rx (BIIB067), an antisense oligonucleotide (ASO) therapy targeting superoxide dismutase (SOD1). ASOs recognize and target specific RNAs for destruction (see Jan 2013 news, Oct 2013 news), ultimately reducing expression of their protein products. ISIS-SOD1Rx is specifically designed to inhibit production of mutant SOD1, which underlies approximately 20% of familial ALS cases and confers toxicity through a gain-of-function mechanism. The ASOs to be tested in this trial are a second generation, more potent version of ASOs previously tested and shown to be safe in phase I trials (see May 2013 news). The current trial will test not only safety, but also treatment effect on SOD1 protein levels in the cerebrospinal fluid, as a measure of drug activity. The study, entitled "Single and Multiple Dose Study of BIIB067 (Isis-SOD1Rx) in Adults With Amyotrophic Lateral Sclerosis (ALS)" will be conducted in two phases, the first of which will enroll both SOD1-ALS patients and patients without SOD1 mutations.

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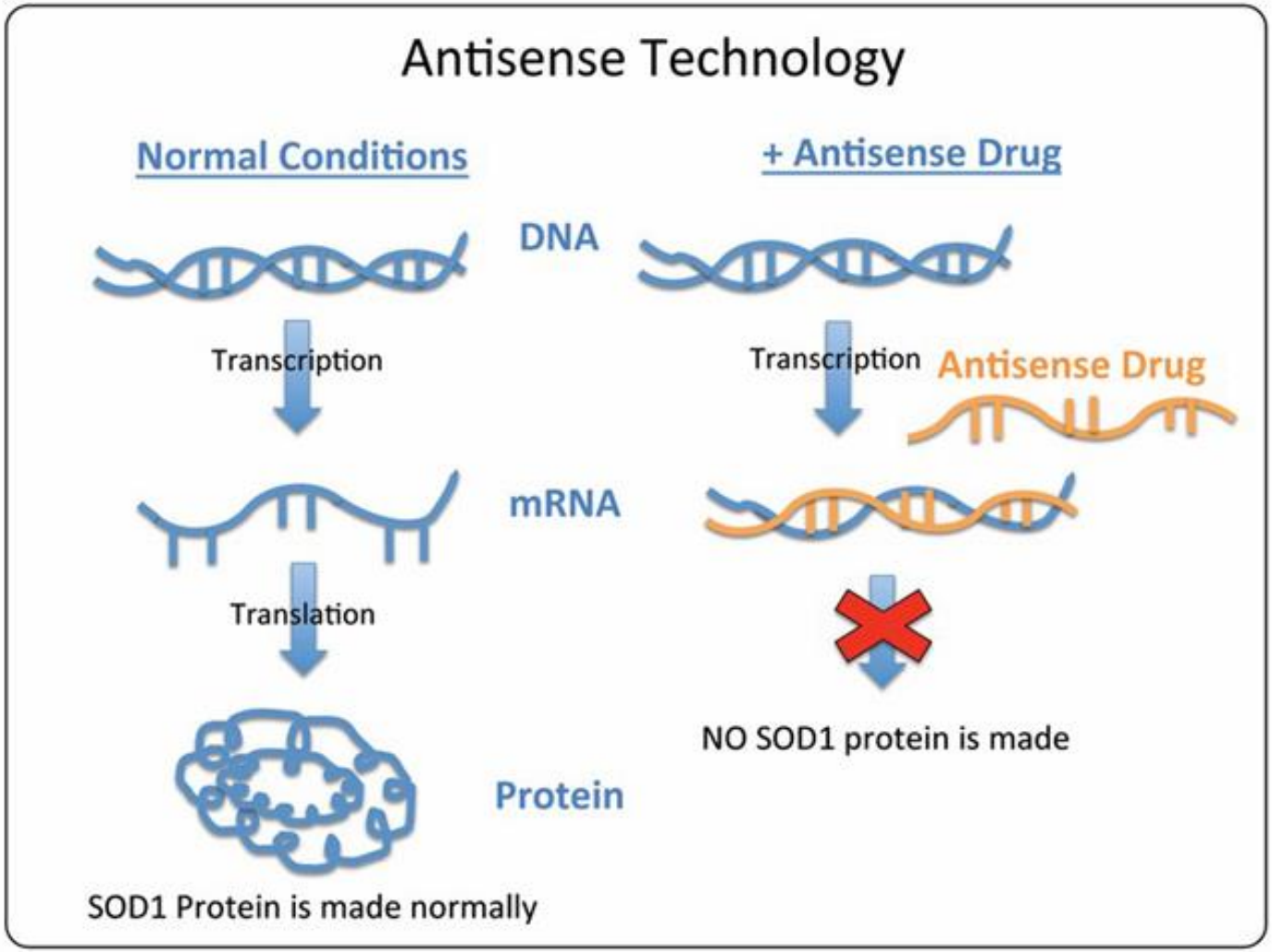
Antisense Technologie



Antisense technology works to eliminate mutated protein by preventing it from being created.

Kantonss
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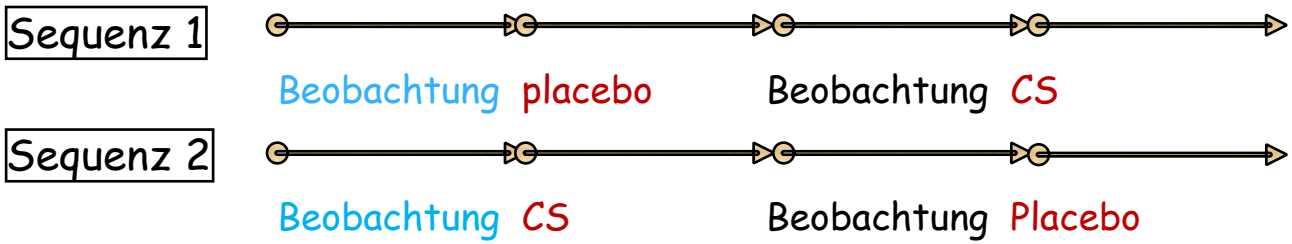
Krampf

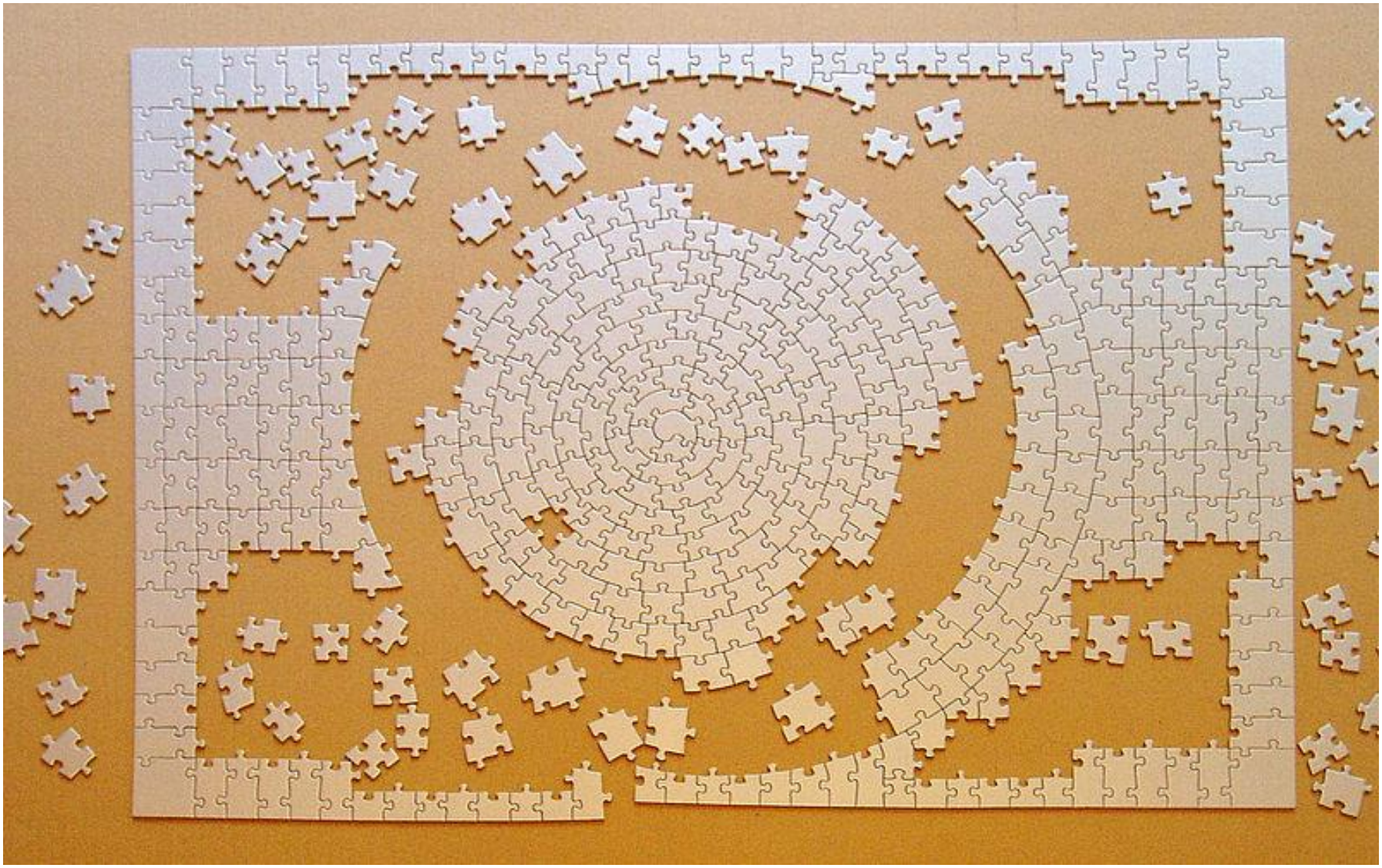
Chinin

- Rinde des Chinarindenbaums
- Seit 17. JH gegen Malaria eingesetzt
- Tonic Water, je nach Hersteller ca. 40-80 mg Chininbase pro Liter Fertiggetränk
- Fiebersenkend, schmerzlindernd, muskelentspannend
- Nebenwirkungen
  - Schwindel, Kopfschmerz, Ohrensausen, Taubheit, Herzrhythmusstörungen

Studiendesign Chininstudie

- Cross-over design
- 8 Wochen, 4 Perioden a 2 Wochen



- Vorteil:
- Nur 24 Patienten notwendig

Muskelzentrum/ALS Clinic