CLINICAL TRIALS FROM MOUSE TO MAN:

PITFALLS OF TRANSLATING PROMISING STUDIES

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CLINICAL TRIALS IN ALS

- Drug Development
- Current approaches to treat ALS
- Why previous trials failed

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HOW ARE NEW DRUGS FOUND?

- Pre-existing knowledge
- The prepared mind
- Serendipity
- Targeted development

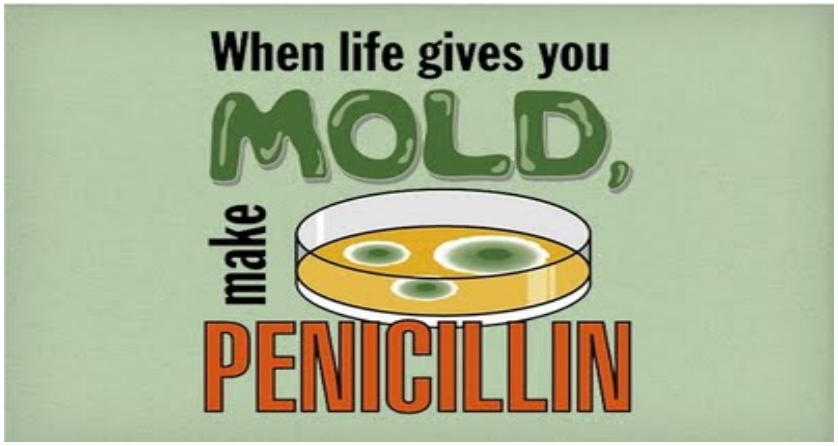
PRE-EXISTING KNOWLEDGE

White Willow.
-Aspirin

Opium

Belladonna,
Atropine /hyoscine

The Prepared Mind



When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer,"

SERENDIPITY

Table 1. Incomplete list of serendipitous discoveries in drug research.

Compound	Accidental Discovery	Ref.
Acetanilide	tested as internal antiseptic (instead of naphthalene)	4,8
Acetylsalicylic acid	irreversible enzyme inhibitor (*vs.* salicylic acid prodrug)	4,8
Aminoglutethimide	breast cancer treatment (instead of antiepileptic)	4
Amphetamine	stimulant (instead of nasal decongestant)	4
Chloral hydrate	prodrug of trichloroethanol (instead of chloroform)	4,8
Chlordiazepoxide	tranquillizer (unexpected chemical rearrangement)	1,4,6-9
Chlorpromazine	neuroleptic (tested to prevent surgical shock)	1,4,7,8
Cinnarizine	cardiovascular (predominant to antihistaminic) activity	4
Cisplatin	cytotoxic effect of electrolysis product	4
Clonidine	antihypertensive (instead of nasal decongestant)	4,6,8
Cromoglycate	antiallergic (accidental formation of chromone dimer)	4
Cyclosporin	immunosuppressant (instead of antifungal agent)	1,4
Dichloroisoprenaline	ß-blockade (instead of bronchodilation)	4
Dicoumarol	fatal cattle poisoning (bleeding) by moldy hay	4,5,8
Diethylstilbestrol	estrogenic impurity of anol (dimerization product)	4
Diphenhydramine	allergy treatment caused prevention of travel sickness	4,5,8
Diphenoxylate	antidiarrhoic (instead of analgesic)	4
Disulfiram	hypersensitivity to alcohol	5,8
Ether	anesthetic activity in inhalation party	1,4,8
Etomidate	anesthetic (instead of chemotherapeutic) activity	4
Griseofulvin	growth inhibition of conifers on certain soils	4
Guanethidine	antihypertensive (instead of antitrypanosomal drug)	4,6
Haloperidol	neuroleptic (instead of analgetic) activity	4,5,8
Heparin	deterioration of lipid coagulant unmasked anticoagulant	4
Imipramine	antidepressant (instead of neuroleptic) activity	1,4,5,8
Iproniazid	antidepressant (instead of tuberculostatic) activity	4,5,8
Isoniazid	tuberculostatic activity of organic intermediate	4,5,8
Levamisole	immunomodulating (instead of antiparasitic) agent	8
Lithium carbonate	antidepressant activity of lithium urate	1,4,7,8
Lysergide (LSD)	hallucinogenic (instead of cardiovascular) activity	4,7,8
Meprobamate	tranquillizer (instead of muscle relaxant)	1,4,7
Merbaphen	diuretic activity (of an antisyphilitic agent)	4,8
Methaqualone	hypnotic (instead of antimalarial activity)	4
Mifepristone	antiprogesterone (instead of glucocorticoid) activity	4
Naftifine	antifungal rearrangement product of CNS drug	4,8
Nalorphine	antagonism instead of respiratory stimulation	4
Nitrogen mustard	cytotoxicity observed after ship bombardment	1,5,8
Nitroglycerin	antianginal activity (headache after inhalation)	4
Nitrous oxide	accidental wounding in laughing gas session	1,4,8
Norethynodrel/Mestranol	estrogenic impurity in the first oral contraceptive	4
Penicillin	antibiotic activity of *Penicillium* infection	1,4,5,8
Pethidine (meperidine)	morphine agonist (instead of spasmolytic)	4,5,8
Phenylbutazone	antiinflammatory activity of solubility enhancer	4,8
Phenolphthalein	laxative (tested as label for cheap wines)	4,8
Praziquantel	antiparasitic agent (instead of antidepressant activity)	8
Prednisone	bacterial oxidation produced highly active analog	4
Propafenone	antiarrhythmic (instead of ß-blocker)	4
Sulphamidochrysoidine	prodrug of sulfanilamide (active only *in vivo*)	1,4,5,8
Sulfonamides, various	diuretic and antidiabetic side effects	4,5,8
Tamoxifen	antiestrogenic activity of *cis*-isomer	4
Urethane	hypnotic activity (instead of alcohol prodrug)	4,8
Valproic acid	anticonvulsant (solubility enhancer for various drugs)	4
Warfarin	low acute toxicity of rat poison in attempted suicide	5,8,10

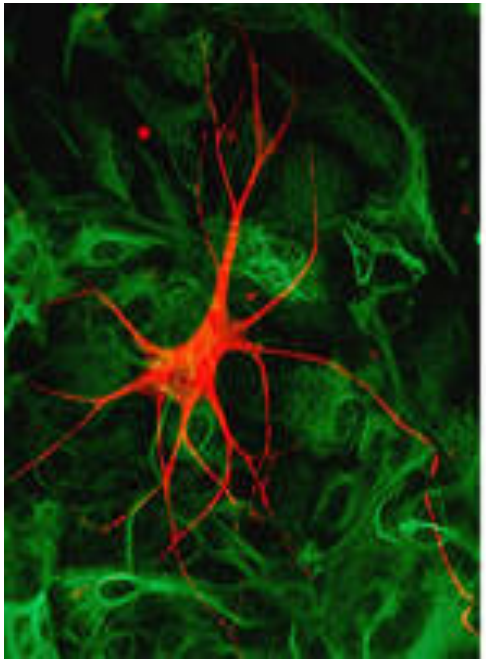
CLINICAL TRIALS IN ALS

- Drug Development
- Current approaches to treat ALS
- Why previous trials failed

PRECLINICAL

LABORATORY BASED DRUG DISCOVERY AND DEVELOPMENT

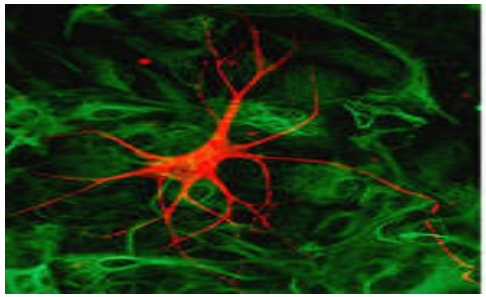
LABORATORY MODELS



Motor neuron cultures

Transgenic SOD1 mice

Zebrafish

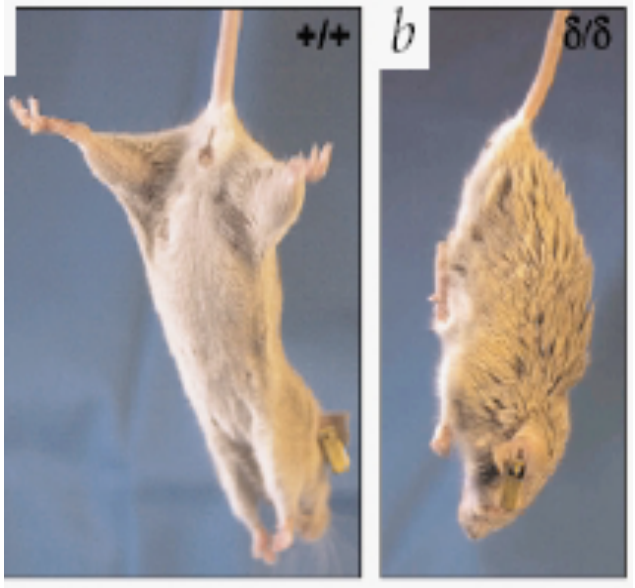


THE ROLE OF THE LABORATORY MODEL

UNDERSTANDING AND MANIPULATION OF PATHWAYS

CHANGING THE COURSE OF THE DISEASE BY TARGETING PATHWAYS

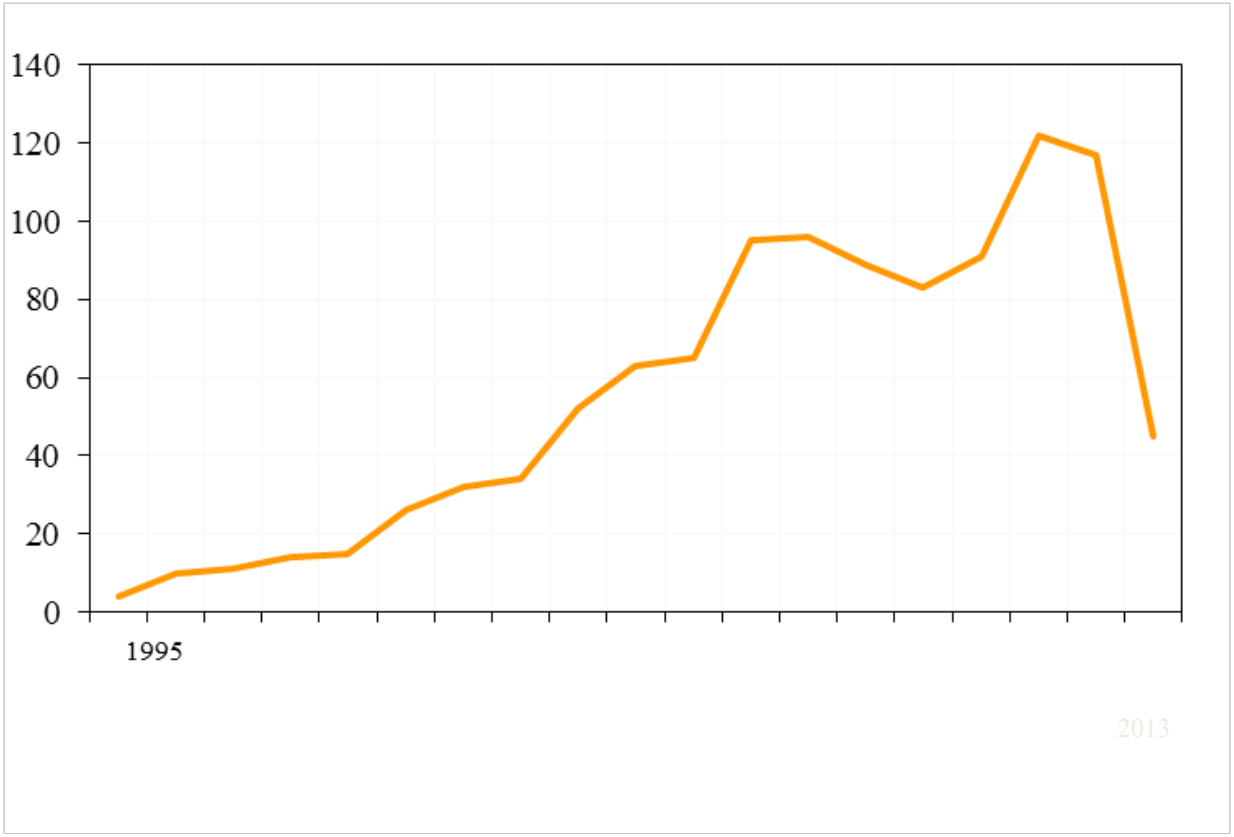
SOD1 TRANSGENIC ANIMAL MODEL



Biology of neurodegeneration

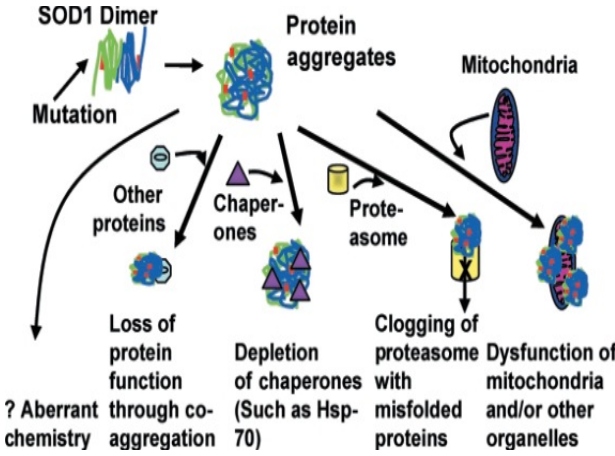
- **Drug efficacy**
- **Drug toxicity**

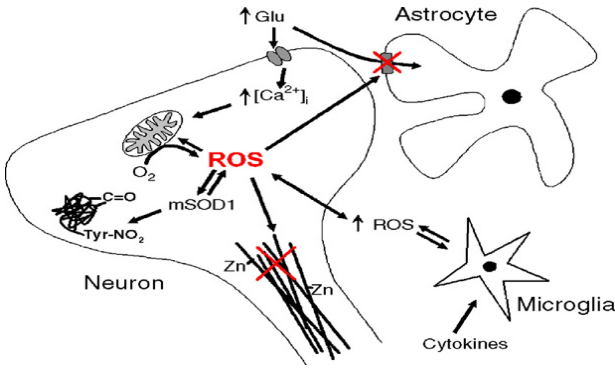
SOD1 Transgenic Mouse (1995-2014)
2060 publications

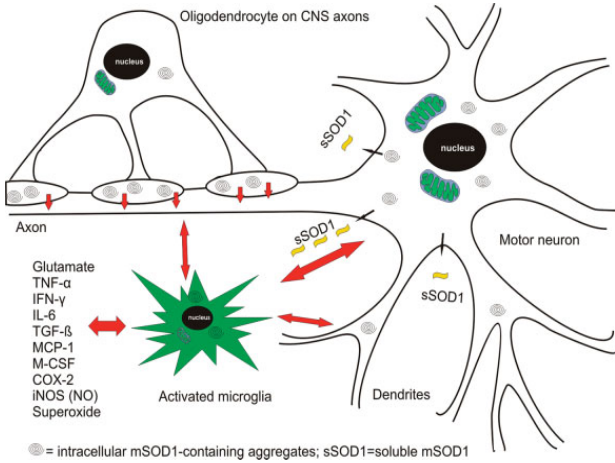


SOD1 ALS in MICE

- Protein misfolding
- Glutamate excitotoxicity
- RNA processing
- Glia cell pathology
- Oxidative stress
- Apoptosis
- Inflammation
- Axonal transport
- Mitochondrial dysfunction
- ???







TARGETS FROM WHICH DRUGS HAVE BEEN DEVELOPED

Glutamate excitotoxicity
RNA processing
Glia cell pathology
Oxidative stress
Apoptosis
Inflammation
Axonal transport
Mitochondrial dysfunction

CLINICAL TRIALS IN MICE

Over 500 Publications

(1995-2014)

PITFALLS OF MOUSE STUDIES

Amyotrophic Lateral Sclerosis. 2008; 9: 4–15

informa
healthcare

REVIEW ARTICLE

Design, power, and interpretation of studies in the standard murine model of ALS

SEAN SCOTT[1], JANICE E. KRANZ[1], JEFF COLE[1], JOHN M. LINCECUM[1], KENNETH THOMPSON[1], NANCY KELLY[1], ALAN BOSTROM[2], JILL THEODOSS[1], BASHAR M. AL-NAKHALA[1], FERNANDO G. VIEIRA[1], JEYANTHI RAMASUBBU[1] & JAMES A. HEYWOOD[1]

[1] *ALS Therapy Development Institute, Cambridge, Massachusetts, and* [2] *Department of Epidemiology and Biostatistics, University of California, San Francisco, USA*

MOUSE TRIALS

- Small numbers of animals
- Same genetic background
- Minimal differences within trial groups
- End points (depend on the model)
  - Survival
  - Rotarod performance & standardized neurological evaluation
  - Weight

OTHER MOUSE PROBLEMS

- Animal models useful but limited…
  - **Anatomy differs**
  - **Genetic background important: “strain effect”**
  - **Gender Differences**
  - **“Copy number” effects**

TRANSLATING FROM BENCH TO BEDSIDE

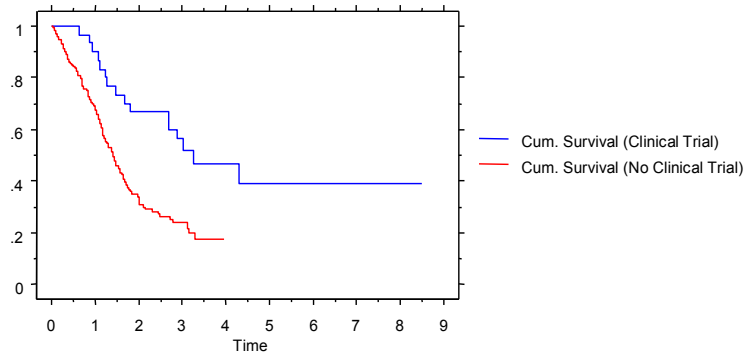
CLINICAL TRIALS IN HUMANS

HOW CAN WE TELL IF A DRUG WORKS?

- Patient stops deteriorating or improves
- Effect can be reproduced in other patients
- Placebo effect can be excluded
- Bias of observers can be excluded

WHY DO WE NEED CLINICAL TRIALS?

- Placebo effect must be excluded
- Bias of observers must be excluded



CLINICAL TRIALS

- **Phase 1 : Safety (Controls- unaffected by disease)**
- **Phase 2 : Proof of Concept (Small numbers with disease)**
- **Phase 3 : Pivotal (Large numbers, *required for regulatory approval*)**
- **Phase 4 : Post marketing**

VERY COSTLY !

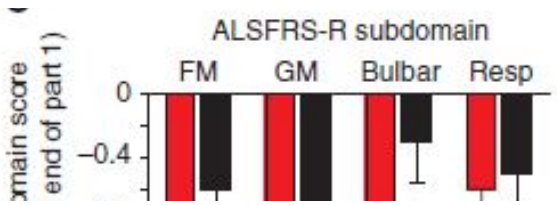
CLINICAL TRIALS IN ALS

- Drug Development
- Current approaches to treat ALS
- Why previous trials failed

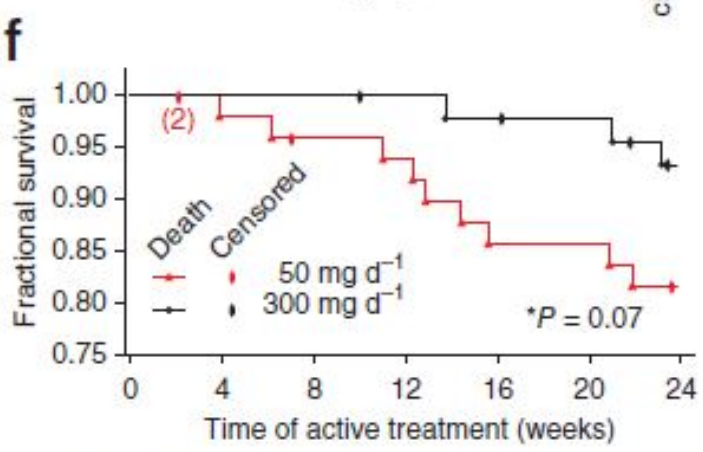
The effects of dexpramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis

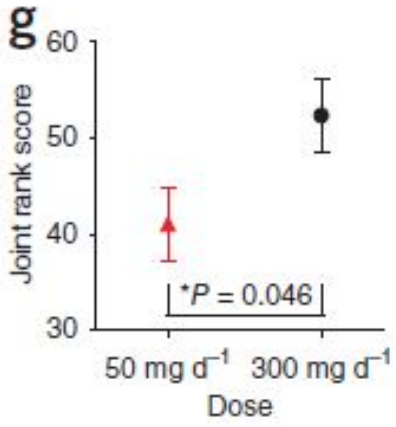
Merit Cudkowicz[1], Michael E Bozik[2], Evan W Ingersoll[2], Robert Miller[3], Hiroshi Mitsumoto[4], Jeremy Shefner[5], Dan H Moore[3], David Schoenfeld[6], James L Mather[2], Donald Archibald[2], Mary Sullivan[2], Craig Amburgey[2], Juliet Moritz[2] & Valentin K Gribkoff[2]

nature medicine



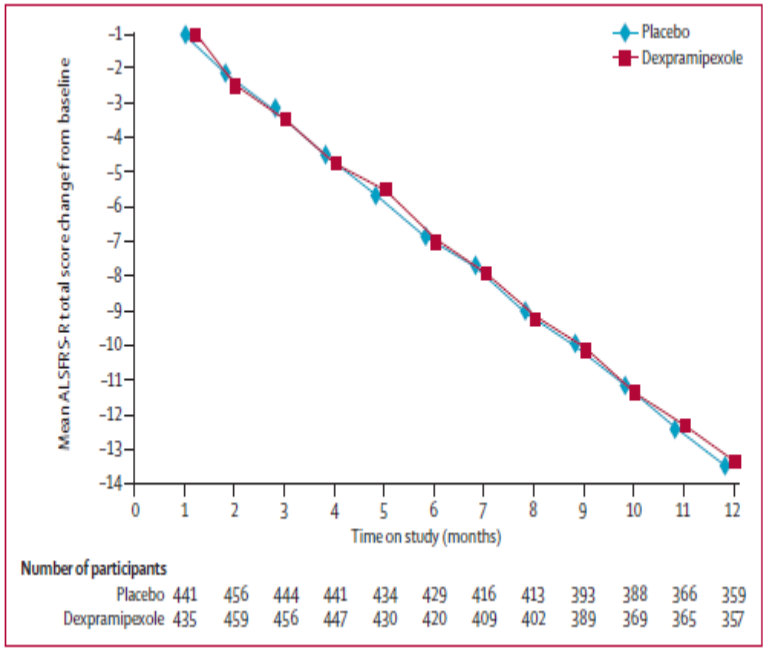
"POSITIVE " PHASE II STUDY





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**



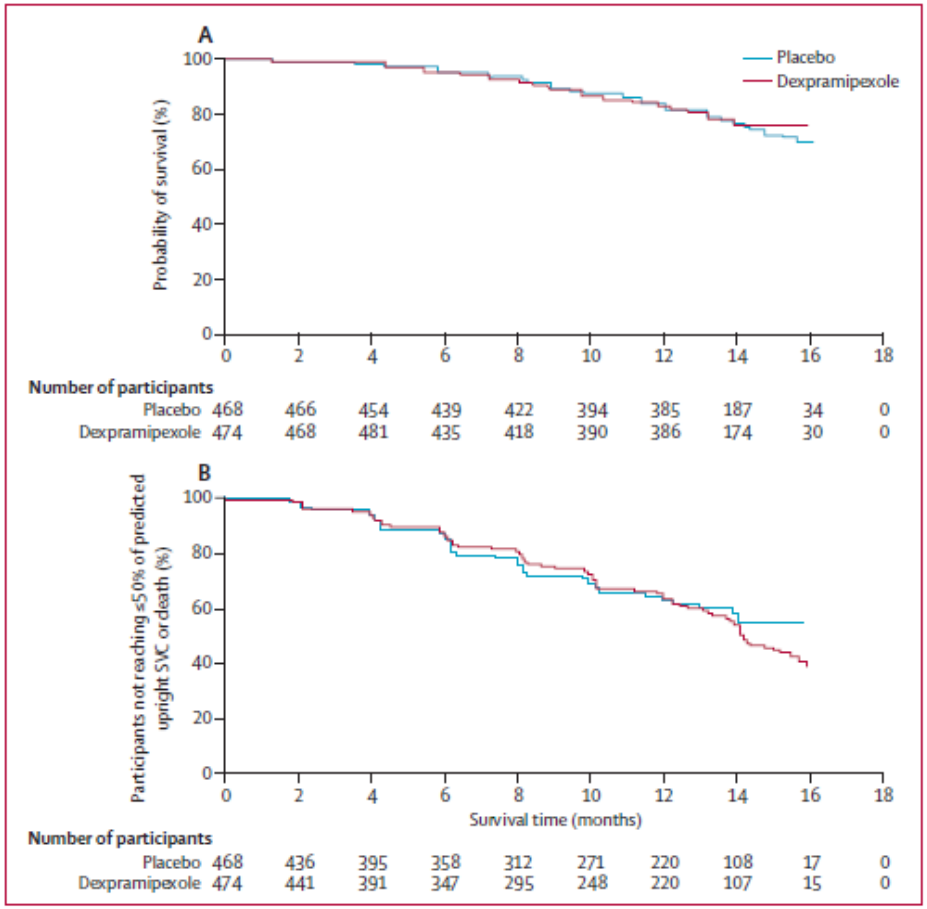


Figure 3: Kaplan-Meier analyses of survival time ≤18 months (A) and time to reach ≤50% slow vital capacity or death (B)

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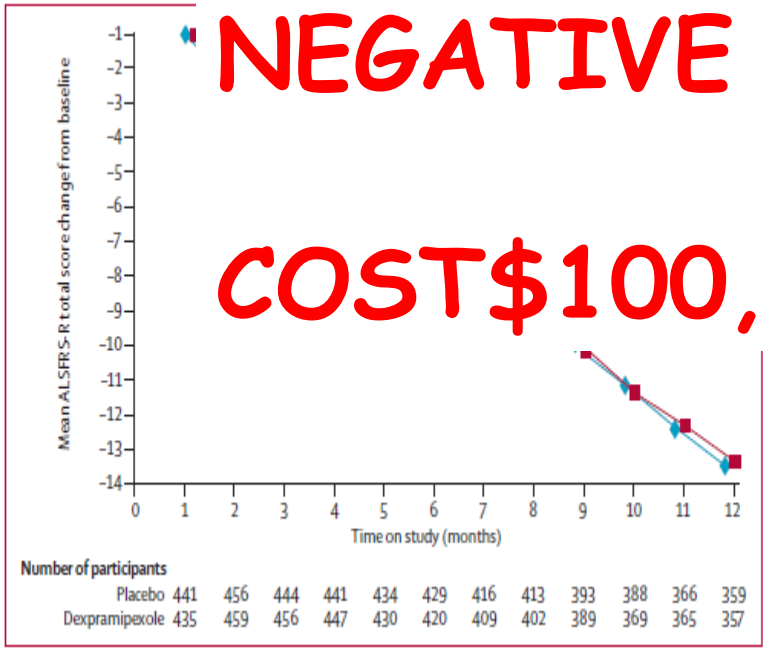
NEGATIVE PHASE 3 STUDY :

COST$100,000,0000



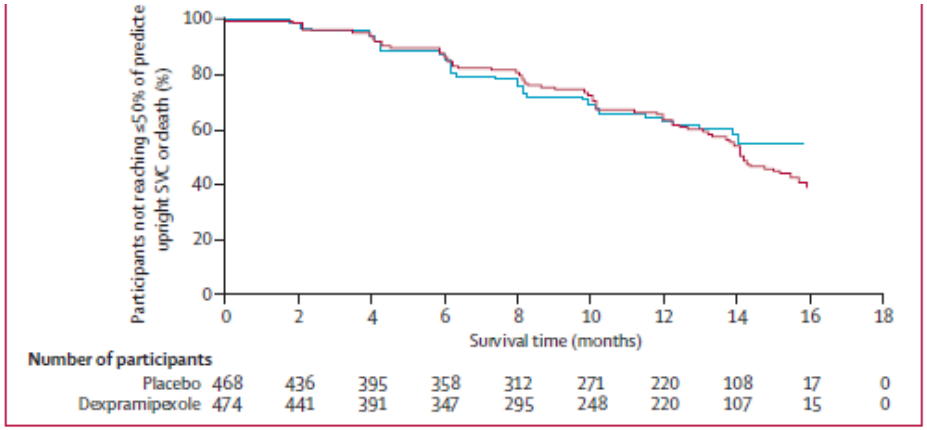


Figure 3: Kaplan-Meier analyses of survival time ≤18 months (A) and time to reach ≤50% slow vital capacity or death (B)

WHY ARE PHASE II TRIALS POSITIVE AND PHASE III TRIALS NEGATIVE?

- Faulty trial design
- Disease heterogeneity
- (Drug doesn’t work)

FAULTY TRIAL DESIGN

- Wrong dose was used
- Drug didn’t get to the right target
- Wrong patient group was used

WHY ARE PHASE II TRIALS POSITIVE AND PHASE III TRIALS NEGATIVE?

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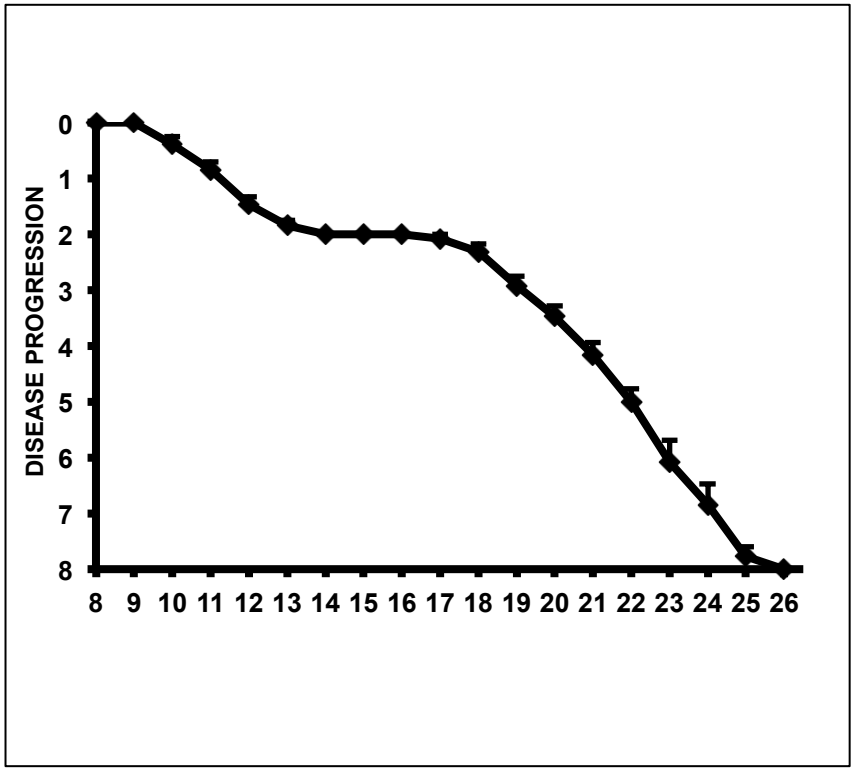
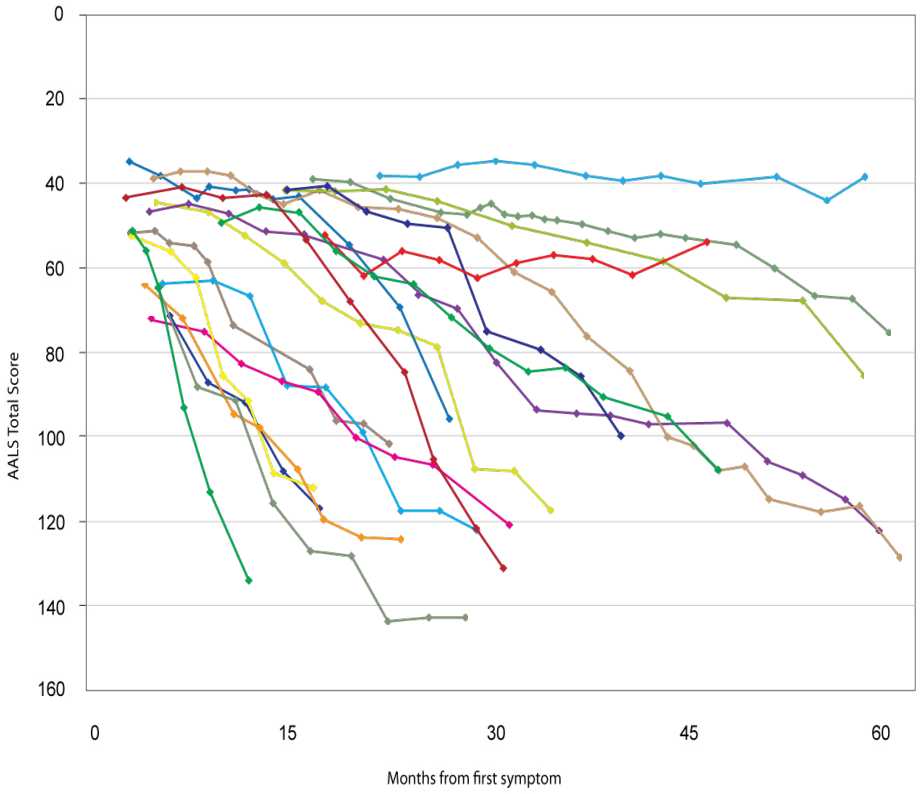
OF MICE AND MEN:
HOMOGENEITY VERSUS HETEROGENEITY OF ALS

ALS mSOD1 Transgenic Mice



Human ALS Patients

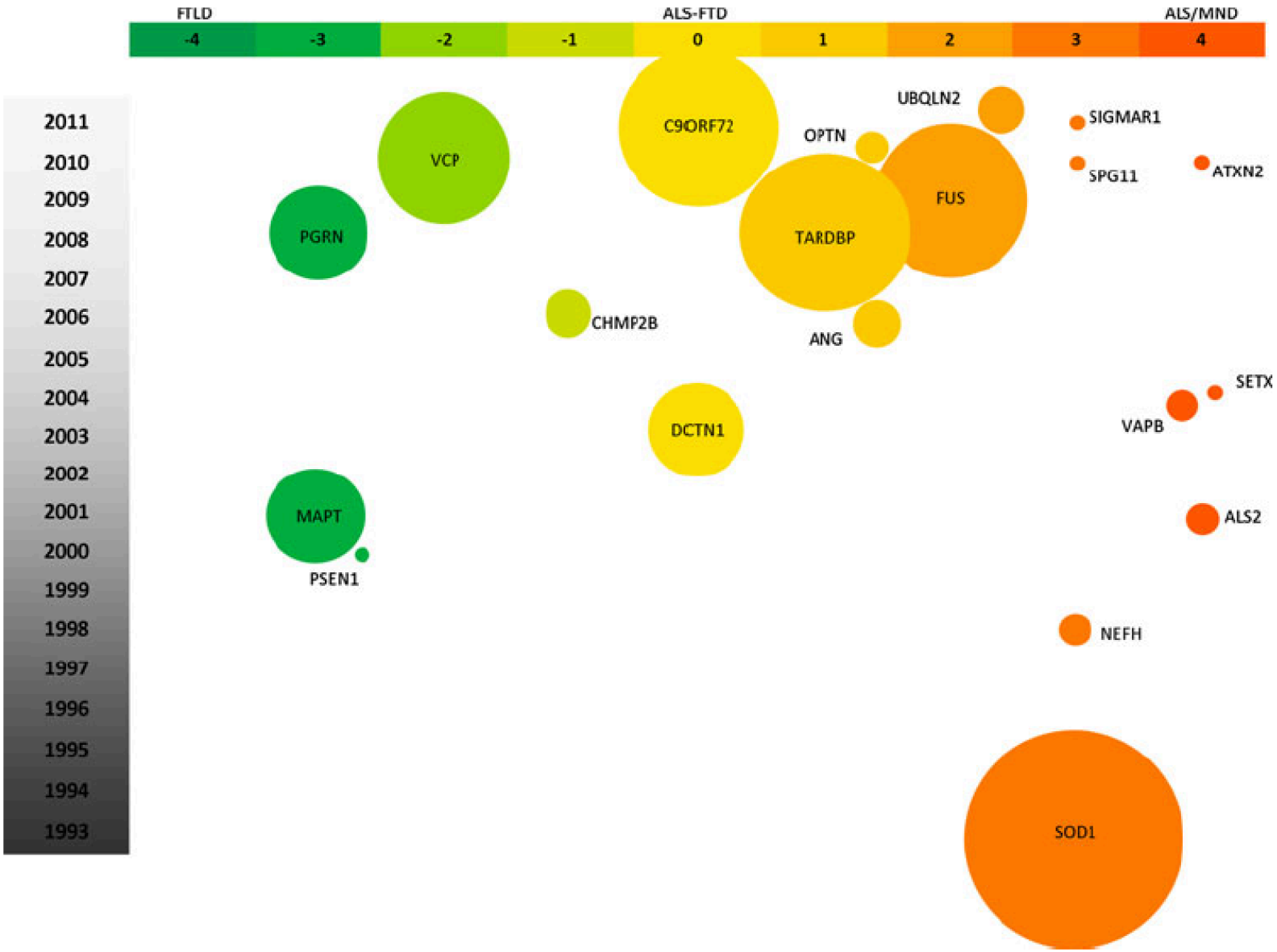


REASONS FOR HETEROGENEITY

Genetics

Other Unknown Factors

ALS genes

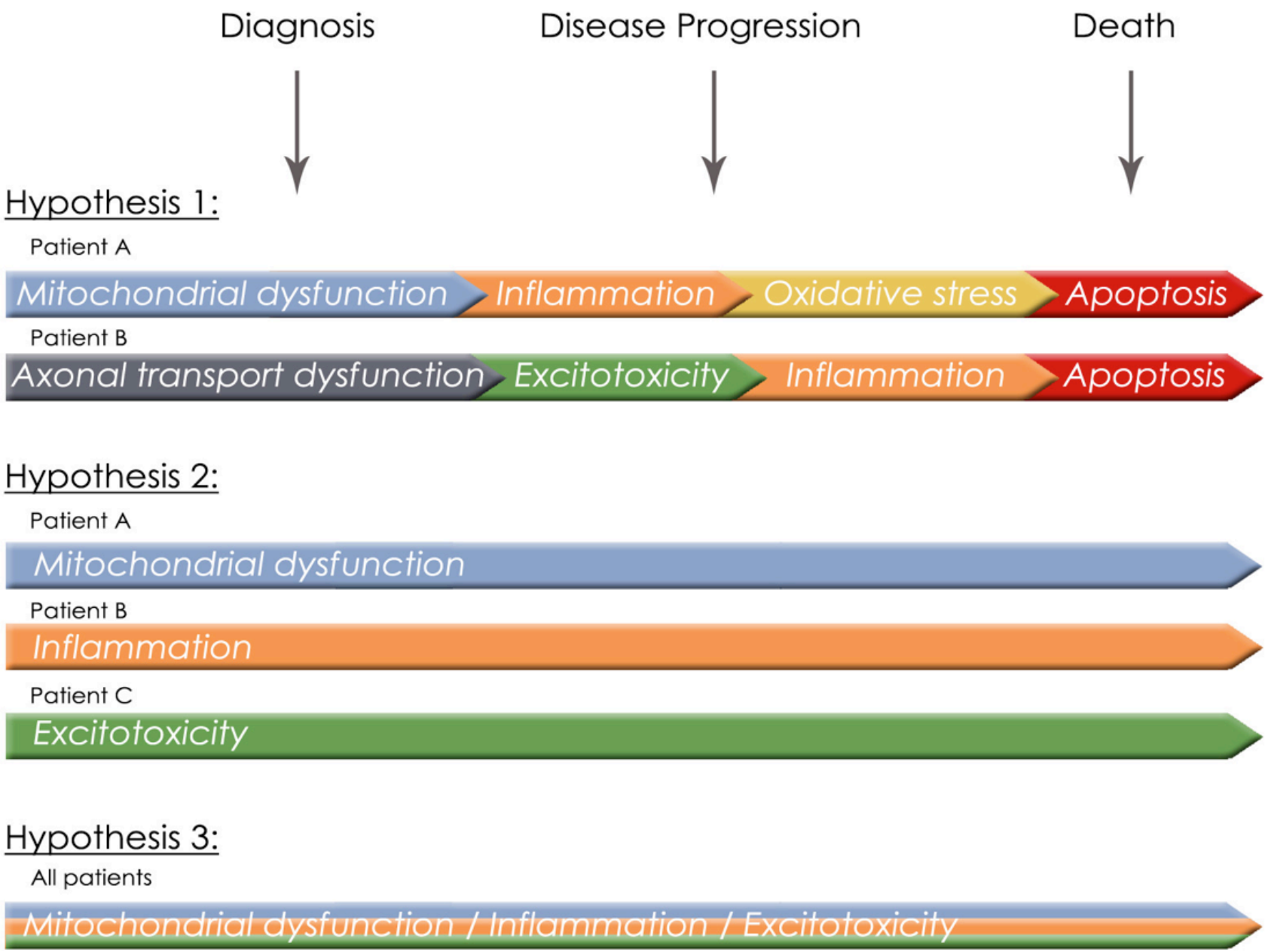

FTLD
ALS-FTD
ALS/MND
-4
-3
-2
-1
0
1
2
3
4
2011
2010
2009
2008
2007
2006
2005
2004
2003
2002
2001
2000
1999
1998
1997
1996
1995
1994
1993
VCP
C9ORF72
UBQLN2
SIGMAR1
OPTN
SPG11
ATXN2
PGRN
FUS
TARDBP
CHMP2B
ANG
SETX
DCTN1
VAPB
MAPT
ALS2
PSEN1
NEFH
SOD1

Frequency of known Genes is Not Uniform Across Populations

	ITALIAN COHORT		IRISH COHORT		
	FALS (n=46)	SALS (n=429)	FALS (n=40)	SALS (n=395)	
FREQUENCY of FALS				**10.1%**	
ANY GENE			50%	1%	
C9orf72	**41%**	1.9%	50%		**9.6%**
SOD1	12.9%	1.4%	0	67%	4.5%
TDP-43	9.1%	1.2%	0	0.4%	
FUS	0.7%	0	0	0.6%	
OPTN	1%	0	0	0	
UNKNOWN	33%	N/A	50%	N/A	

Kenna et al JMG 2013

CAUSES OF DISEASE MAY DIFFER


Diagnosis
Disease Progression
Death
Hypothesis 1:
Patient A
Mitochondrial dysfunction
Inflammation
Oxidative stress
Apoptosis
Patient B
Axonal transport dysfunction
Excitotoxicity
Inflammation
Apoptosis
Hypothesis 2:
Patient A
Mitochondrial dysfunction
Patient B
Inflammation
Patient C
Excitotoxicity
Hypothesis 3:
All patients
Mitochondrial dysfunction / Inflammation / Excitotoxicity

SOLUTIONS

- Drug doesn't work
- Trial design was faulty
- Wrong dose was used
- Drug didn't get to the right target
- Wrong patient group was used

- **More efficient screening, Better drugs ?mutiple actions?**
- **Better trial design**
- **Better pharmacokinetics**
- **Better biomarkers**
- **Better patient groups**

NEW DRUGS & BETTER TRIALS

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PERSONALIZED MEDICINE

Genes

Biomarkers