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CDC7 inhibitors for ALS and FTD therapy

Ana Martínez

Content

Traslational Medicinal and Biological Chemistry Laboratory (827411, Group qualification: **A -** Outstanding)

Tenured researcher team:

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Dra. Carmen Gil, IC

Dra. Nuria Campillo, CT

Tenured technical support:

Eva Pérez Cuevas (PhD, biology) (since 1.10.2019)

Investigadores en formación:

Pre-Doc:

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Vanesa Nozal (FPU 16/04466)

Inés Maestro (MSC-ITN)

Marcos Morales (FPU 18/03493)

Rocío Benítez (hired)

JAE Intro:

Elena Caballero

Enrique Madruga

Practices

Santiago Barber

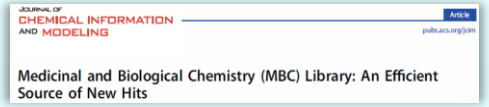
Ricardo Moreno (ERASMUS)

Investigadores Jr:

Alfonso García-Rubia (hired) (PhD, chemistry)

Javier Garcia-Carceles (hired) (PhD, chemistry)

Tiziana Ginex (hired) (PhD, molecular modelling)



J. Chem. Inf. Model. 2017, 57:2143

ANKAR PHARMA
PASSION FOR HEALING

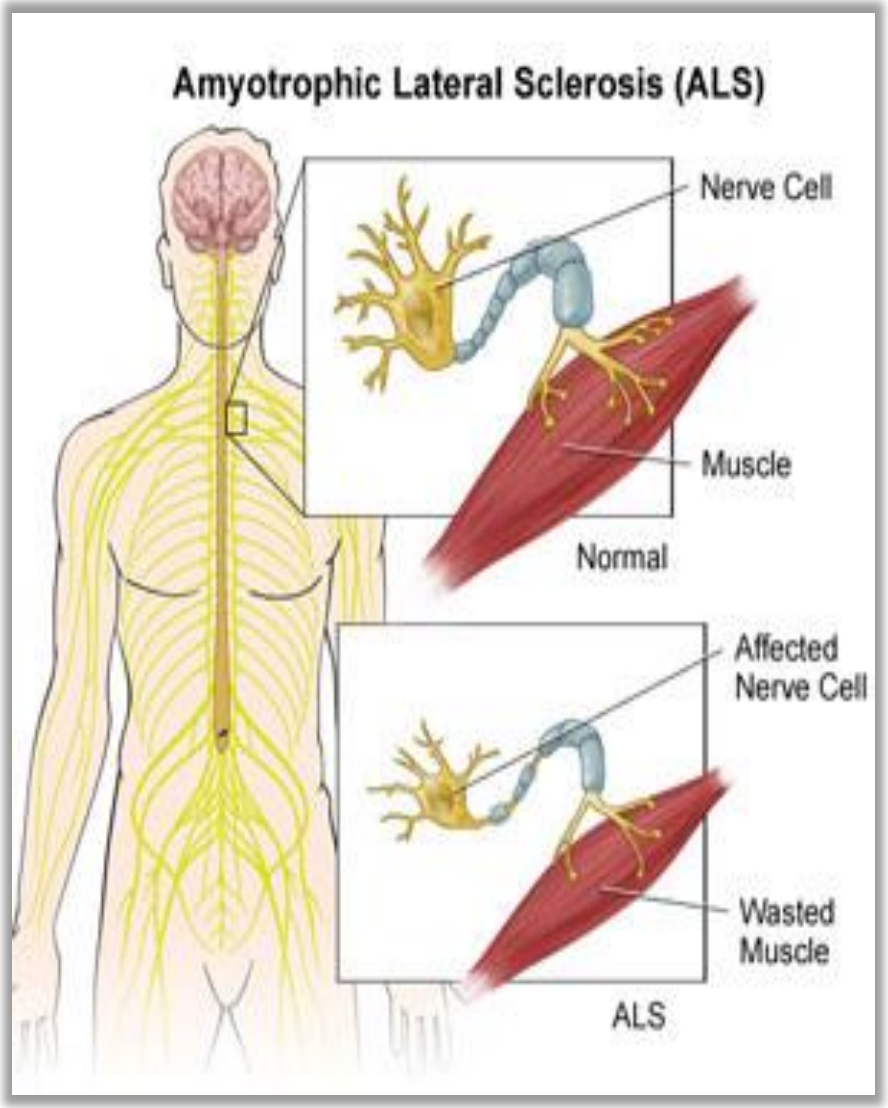
Altenea® biotech

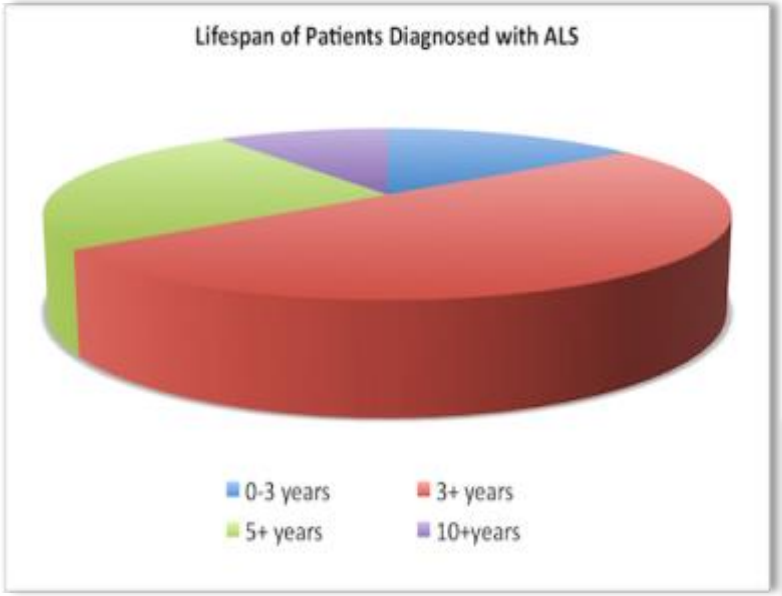
eu::openscreen

Drug discovery for neurodegenerative diseases

Drug discovery for infectious diseases

Chemoinformatics applied to drug discovery





ALS: **rare disease** (800,000 patients) responsible for two deaths per 100,000 people per year.

No cure exists

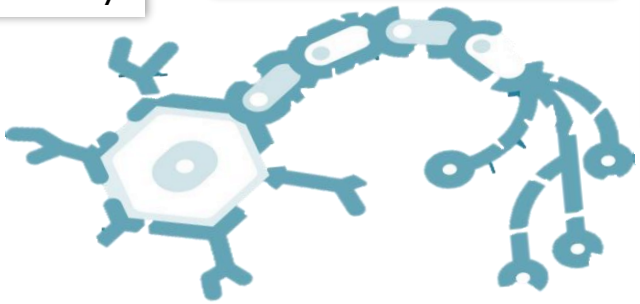
Only palliative therapies

b) Innovative mechanisms of action

Excitotoxicity

Oxidative stress

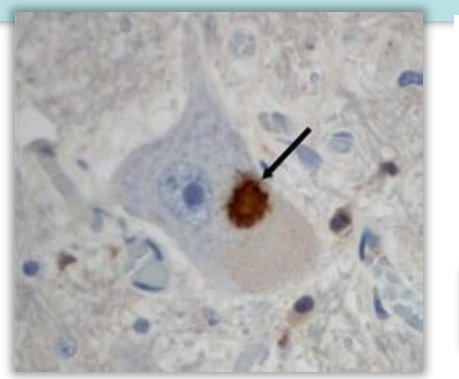
Microglia activation



Protein aggregation

TDP-43

97% patients

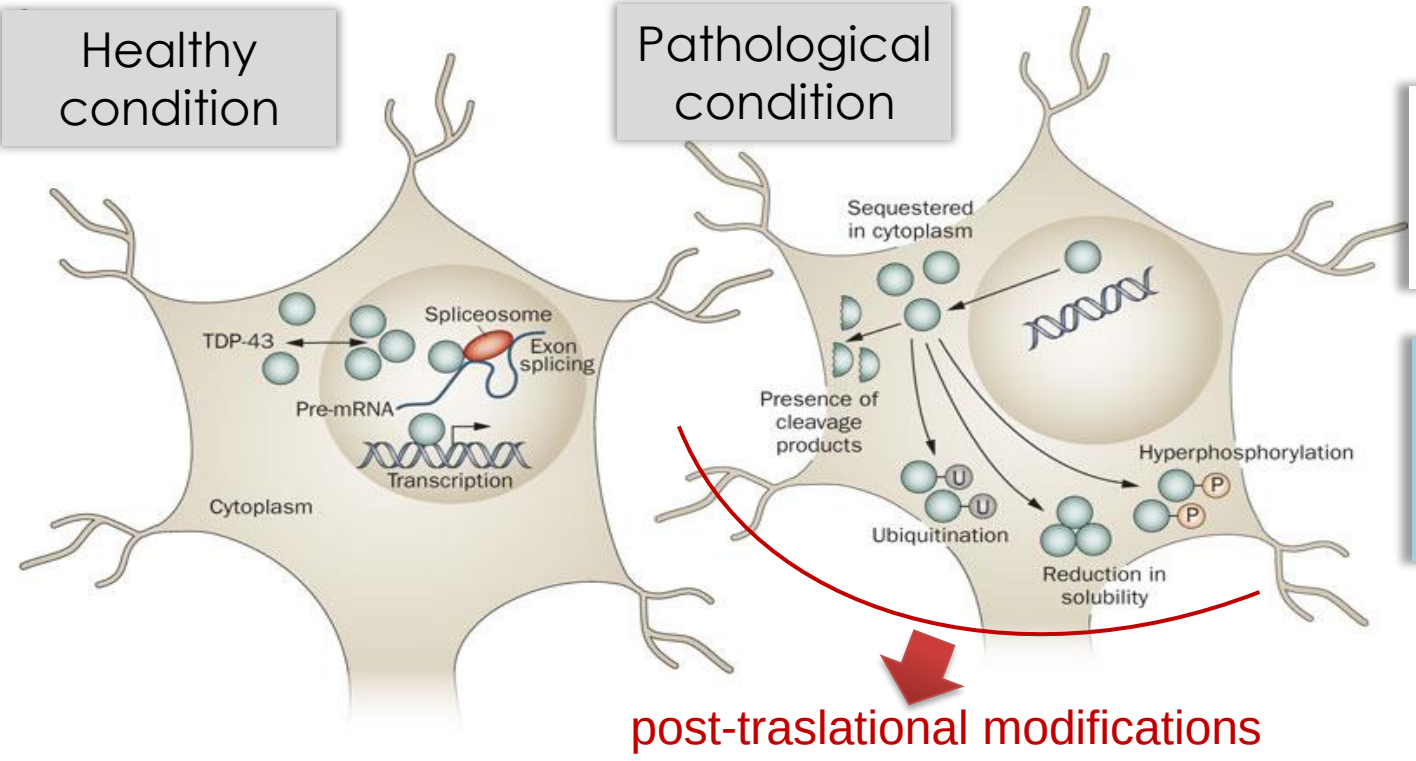


TDP-43 aggregates are present both in **sporadic and familial** ALS

ALS is a TDP-43-pathy

Healthy condition

Pathological condition



post-traslational modifications

Transactive response **D**NA binding **p**rotein **43** kDa is a nuclear protein with multiple functions in transcriptional repression

Working hypothesis:
recovery TDP-43 homeostasis with small molecules

c) Differential features facing the market

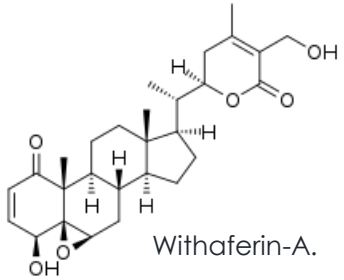
COMPETITORS TARGETING TDP-43's AGGREGATION & CLEARANCE

#	Drug Name	Company Name	Development Stage	Molecule Type	Mechanisms of Action	PoS[1]
1	Arimoclomol citrate	**Orphazyme A/S**	**Phase III**	Small Molecule	Chaperone Activator Heat Shock Protein 70 Activator	**0.34**
2	Sirolimus	**Pfizer Inc**	**Phase II**	Small Molecule	Serine/Threonine Protein Kinase mTOR Inhibitor	**0.17**
3	GDC-0134	**Genentech Inc**	**Phase I**	Small Molecule	Mitogen Activated Protein Kinase Kinase Kinase 12 Inhibitor	**0.13**
4	Bosutinib	**Pfizer Inc**	**Phase I**	Small Molecule	Bcr-Abl Tyrosine Kinase Inhibitor Tyrosine Protein Kinase CSK Inhibitor Tyrosine Protein Kinase HCK Inhibitor Tyrosine Protein Kinase Lyn Inhibitor	**0.13**
5	BIIB-100	**Biogen Inc**	**Phase I**	Small Molecule	Exportin 1 Inhibitor	**0.13**
6	Small Molecules to Inhibit ASK1	**Kyowa Kirin Co Ltd**	**Preclinical**	Small Molecule	Mitogen Activated Protein Kinase Kinase Kinase 5 Inhibitor	**0.09**
7	SNR-1611	**Genuv Inc**	**Preclinical**	N/A	Dual Specificity Mitogen Activated Protein Kinase 1 Inhibitor Dual Specificity Mitogen Activated Protein Kinase 2 Inhibitor	**0.09**
8	Small Molecules to Activate HSF-1	**Chaperone Therapeutics Inc**	**Preclinical**	Small Molecule	Heat Shock Factor Protein 1 Activator	**0.09**
9	Antibodies to Inhibit TARDBP	**ImStar Therapeutics Inc**	**Preclinical**	Antibody	TAR DNA Binding Protein 43 Inhibitor	**0.09**
10	IMS-088	**ImStar Therapeutics Inc**	**Preclinical**	Small Molecule	TAR DNA Binding Protein 43 Inhibitor	**0.09**
11	Monoclonal Antibodies to Inhibit TDP43	**ProMIS Neurosciences Inc**	**Preclinical**	Monoclonal Antibody	TAR DNA Binding Protein 43 Inhibitor	**0.09**
12	NI-205	**Biogen Inc**	**Preclinical**	Monoclonal Antibody	TAR DNA Binding Protein 43 Inhibitor	**0.09**
13	Small Molecules to Inhibit TDP43	**Biohaven Pharmaceutical Holding Company Ltd**	**Preclinical**	Small Molecule	TAR DNA Binding Protein 43 Inhibitor	**0.09**
14	Small Molecules to Inhibit TDP43	**Aquinnah Pharmaceuticals Inc**	**Preclinical**	Small Molecule	TAR DNA Binding Protein 43 Inhibitor	**0.09**
15	Cyclosporine	**Maas Biolab**	**Preclinical**	Small Molecule	Calcineurin Inhibitor	**0.09**
16	CT-526	**Cogentis Therapeutics Inc**	**Preclinical**	Small Molecule	Cyclin Dependent Like Kinase 5 Inhibitor	**0.09**
17	A-007	**MeiraGTx Holdings Plc**	**Preclinical**	Small Molecule	Regulator Of Nonsense Transcripts 1 Activator	**0.09**
					Total	**1.98**

c) Differential features facing the market

IMSTAR THERAPEUTICS

IMS-088
Small molecule, **targets NF-kB** and is **based on Withaferin-A.** When given orally in animal studies, IMS-088 significantly **reduced TDP-43 aggregation**, reduced microglial activation, rescued neuronal protein transcription, restored motor and cognitive performance in a spectrum of functional models of ALS and frontotemporal dementia. The drug is currently poised for IND-enabling studies and human clinical testing.



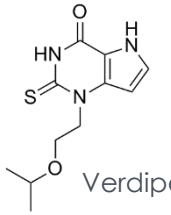
Withaferin-A.

Aquinnah

We are currently conducting animal trials. Human trials are scheduled to begin in the next 2-3 years.
Eliminate stress granules

biohaven pharmaceuticals

Brain-penetrant, irreversible myeloper-oxidase (MPO) enzyme inhibitor. Reduce microglial activation and neuroinflamation



Verdiperstat

CDC7 inhibitor

New small molecule

Easy synthesis

Innovative mechanism of action

Recovery TDP-43 function without eliminating the protein

Druggable target

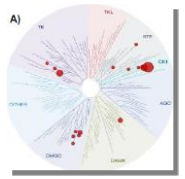
2. The Product

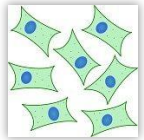
d) Current status of development

In vitro PoC

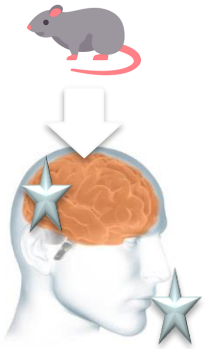
In vivo PK

In vivo PoC

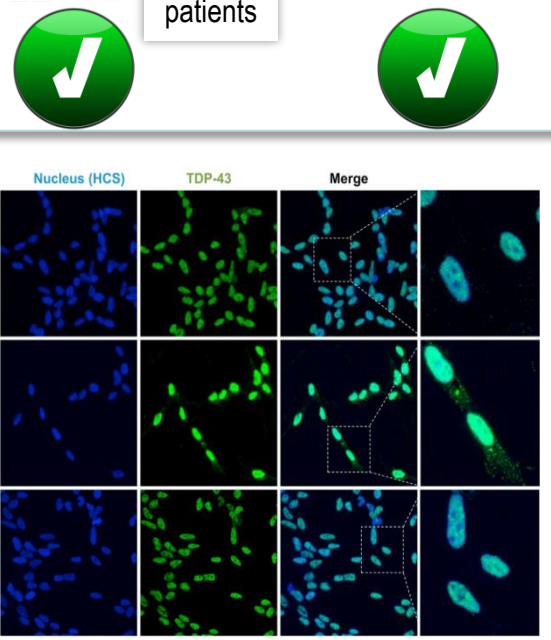


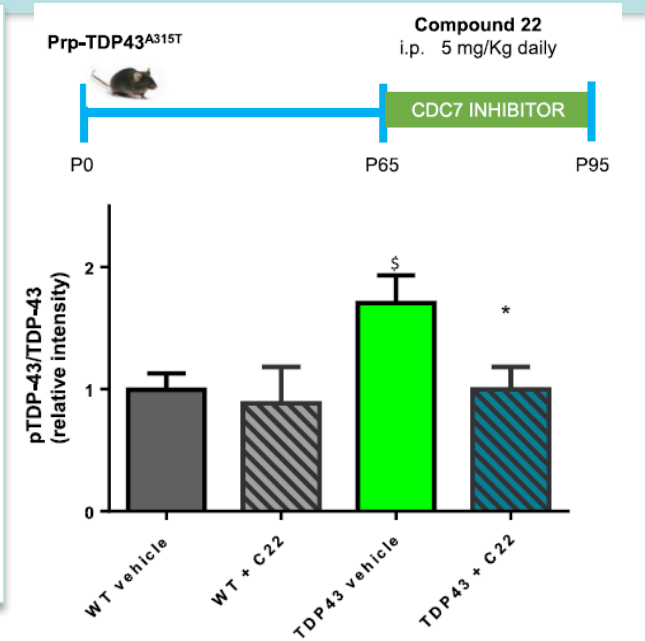


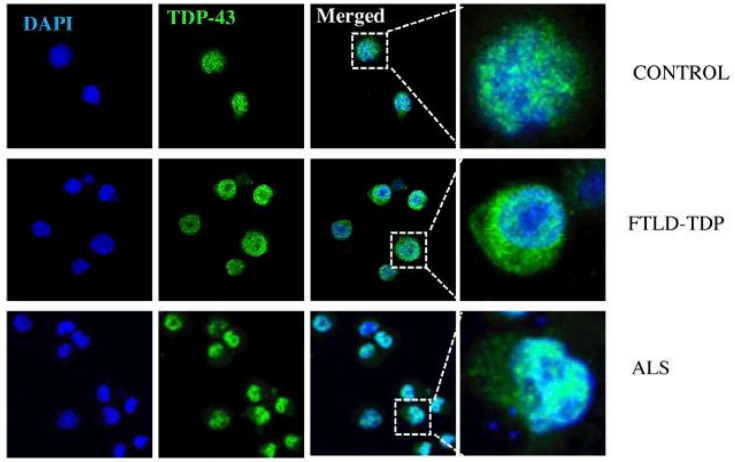
ALS And FTD patients

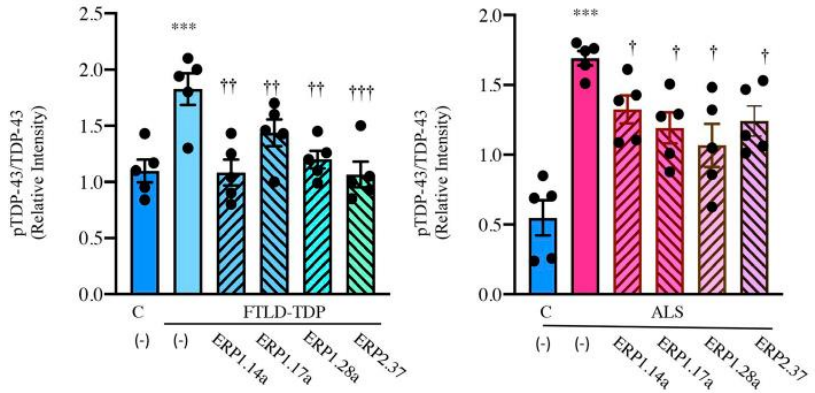


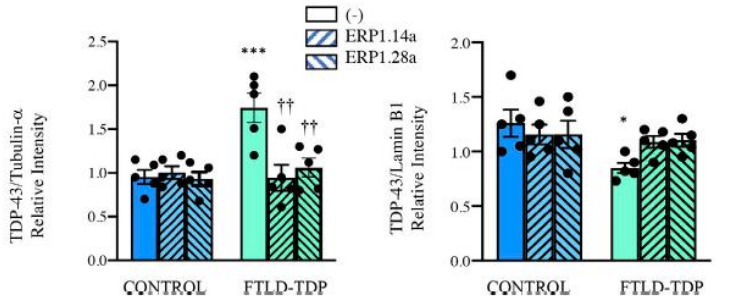
Tg-TDP43

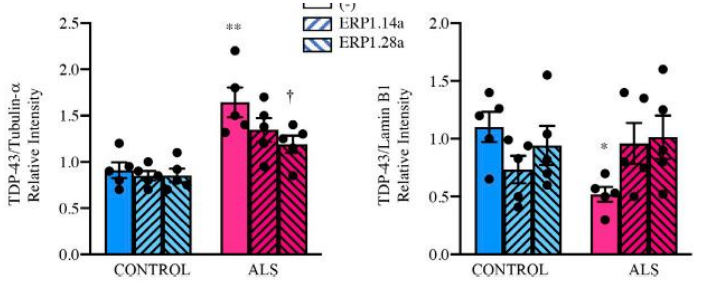












Eur J Med Chem. 2021; 210:112968.
J Neurochem. 2021 Feb;156(3):379-390

CDC7-INHIBITING PURINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF NEUROLOGICAL CONDITIONS

WO2020058558

Priority 9 2018

ES2749743 (B2)

CDC-7-INHIBITOR COMPOUNDS AND USE THEREOF FOR THE TREATMENT OF NEUROLOGICAL CONDITIONS

WO2018172587

Priority 3 2017

AU2018240527 (A1)

EP3604310 (A1)

US2020093828 (A1)

ES2686909 (B1)

3. Partnering Opportunities

Research partner for further development

Public-private cooperation

Opportunities for Patent licencing