



# Ciencia y emprendimiento: del laboratorio a la farmacia

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## What is CSIC?

### Consejo Superior de Investigaciones Científicas (Spanish Council for Research)

Main public research organization  
 Staff: > 5.000 tenured scientist  
 Centers/Institutes: >130  
 Eight fields of research: Life sciences  
 Food technology  
 Social Sciences...



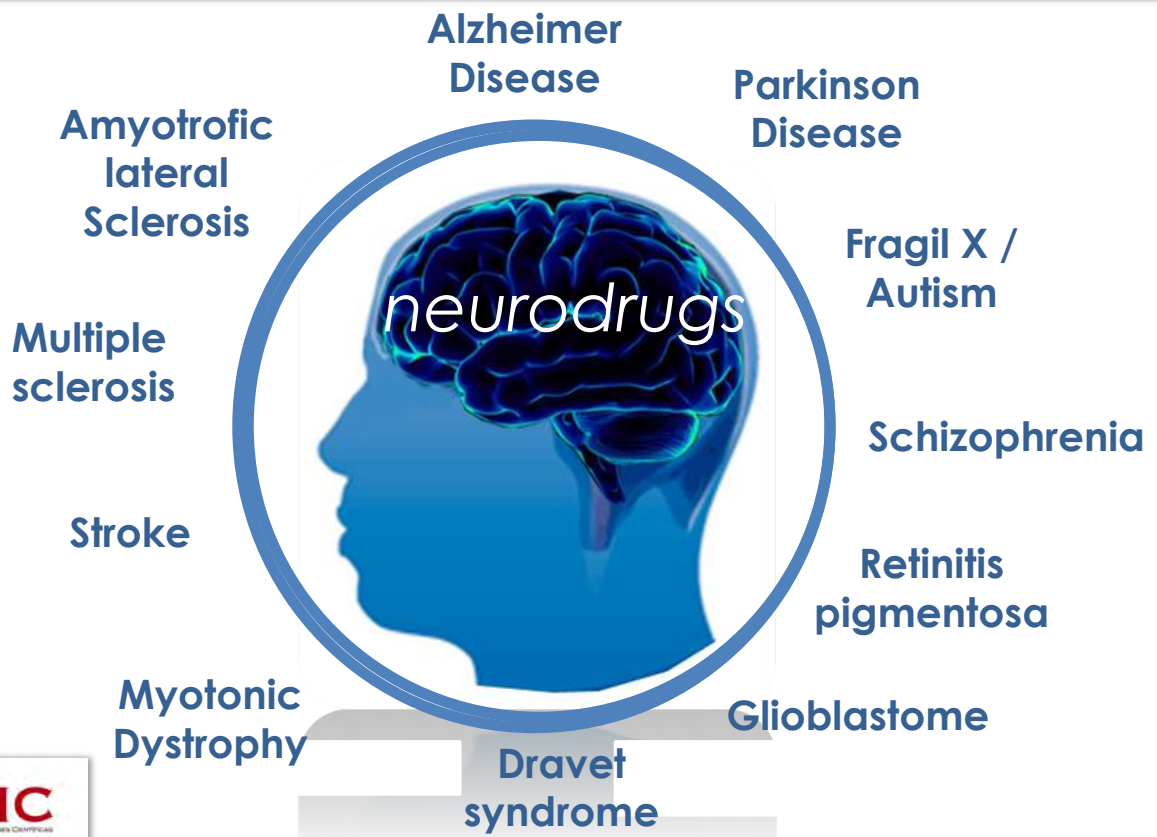
### Centro de Investigaciones Biológicas



### Translational Medicinal & Biological Chemistry Lab.

Design and synthesis of potential new drugs  
 Multidisciplinary medicinal chemistry research  
 Organic chemistry  
 Molecular modeling  
 ADME properties  
 Biological Screening  
 Training of postgraduate students  
 Cooperation with pharmaceutical companies

# Research fields



# Translational research



*From the bench to the society*

# Translational research

## PATIENTS

### WHAT DO THEY NEED?

Accurate diagnostic  
Good drugs  
Quality of life

### WHAT DOES IT PROVIDE?

Molecular knowledge  
New active principles  
Technology

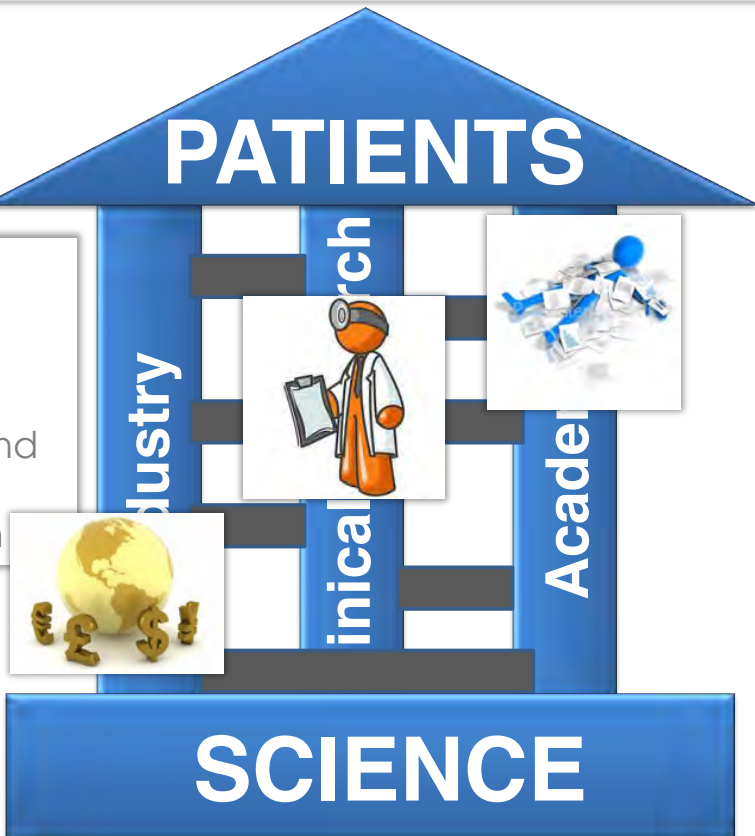
## SCIENCE

# Translational research

## PATIENTS

### Solid social structures:

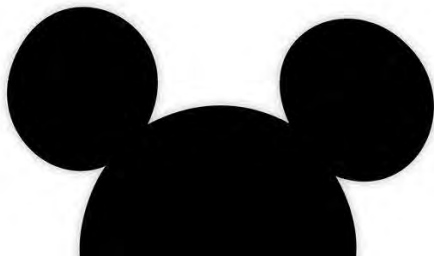
- Health system
- Public and private research



# Translational research

IF YOU CAN  
**DREAM** IT,  
YOU CAN  
**DO** IT.

- WALT DISNEY

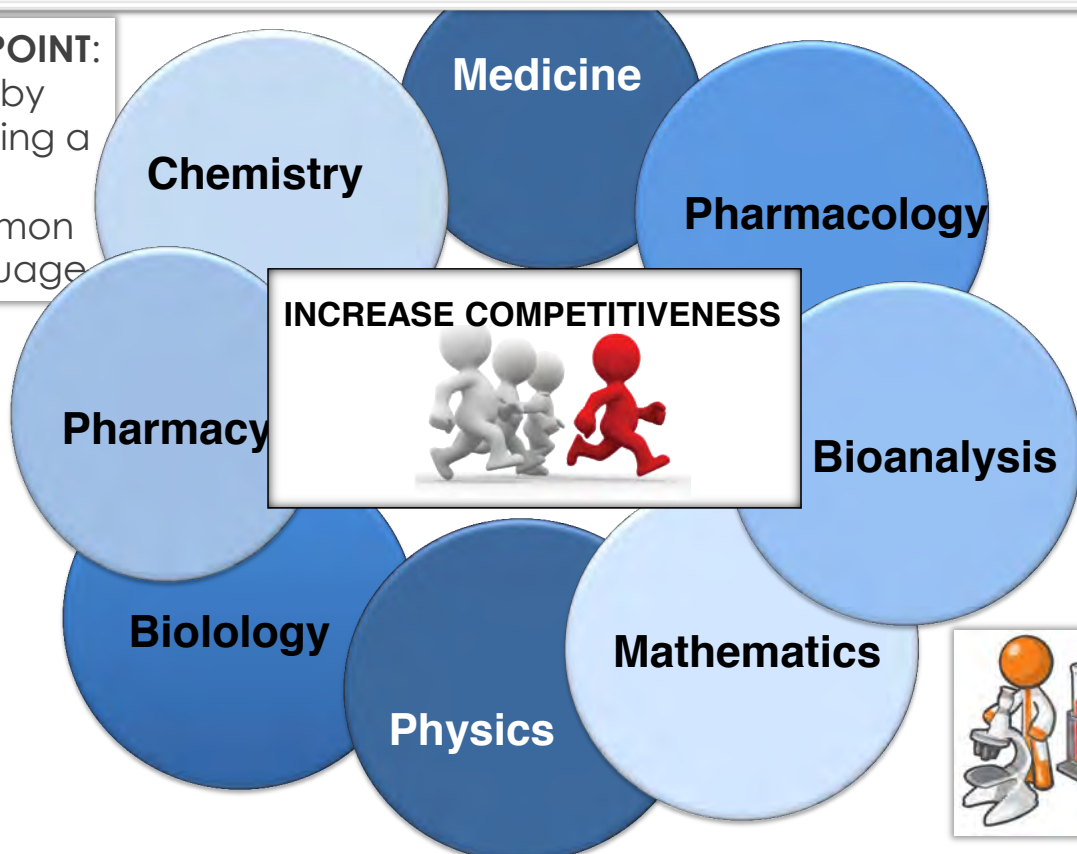


**no**  
negative  
thoughts  
allowed

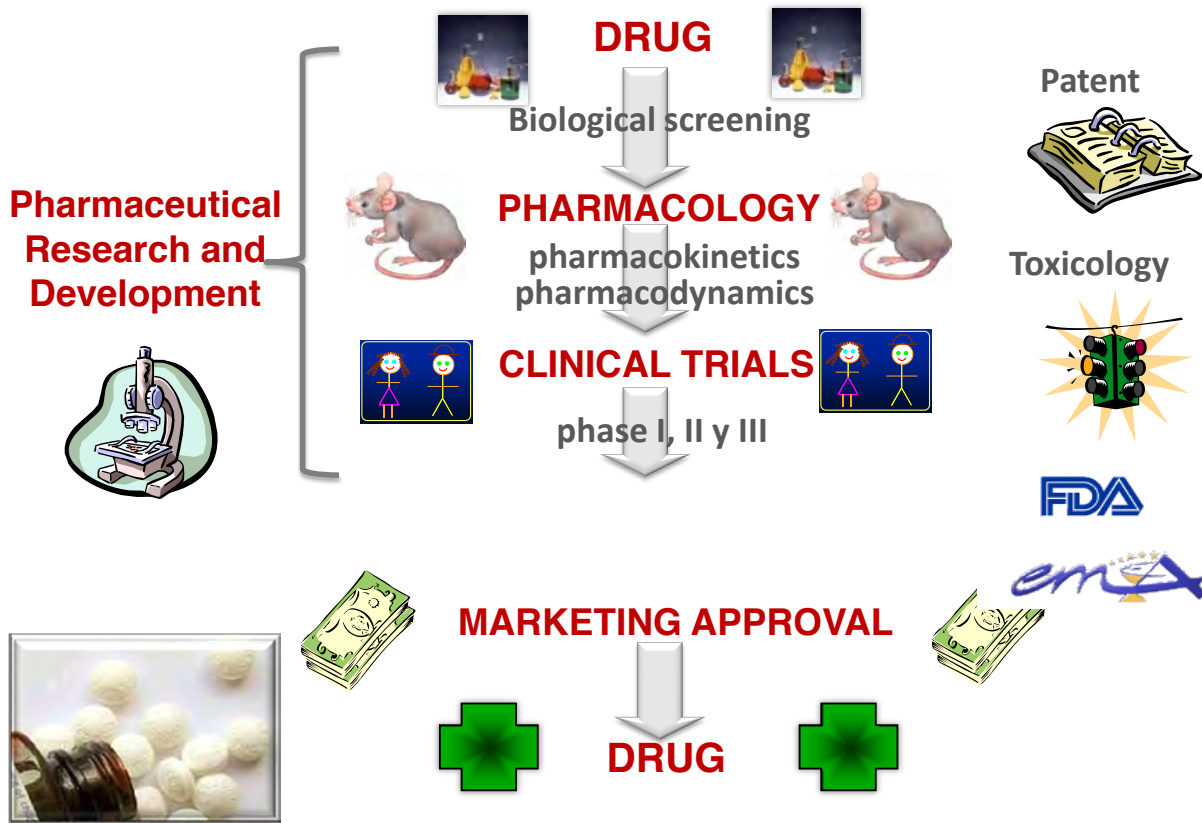


# Transversal research

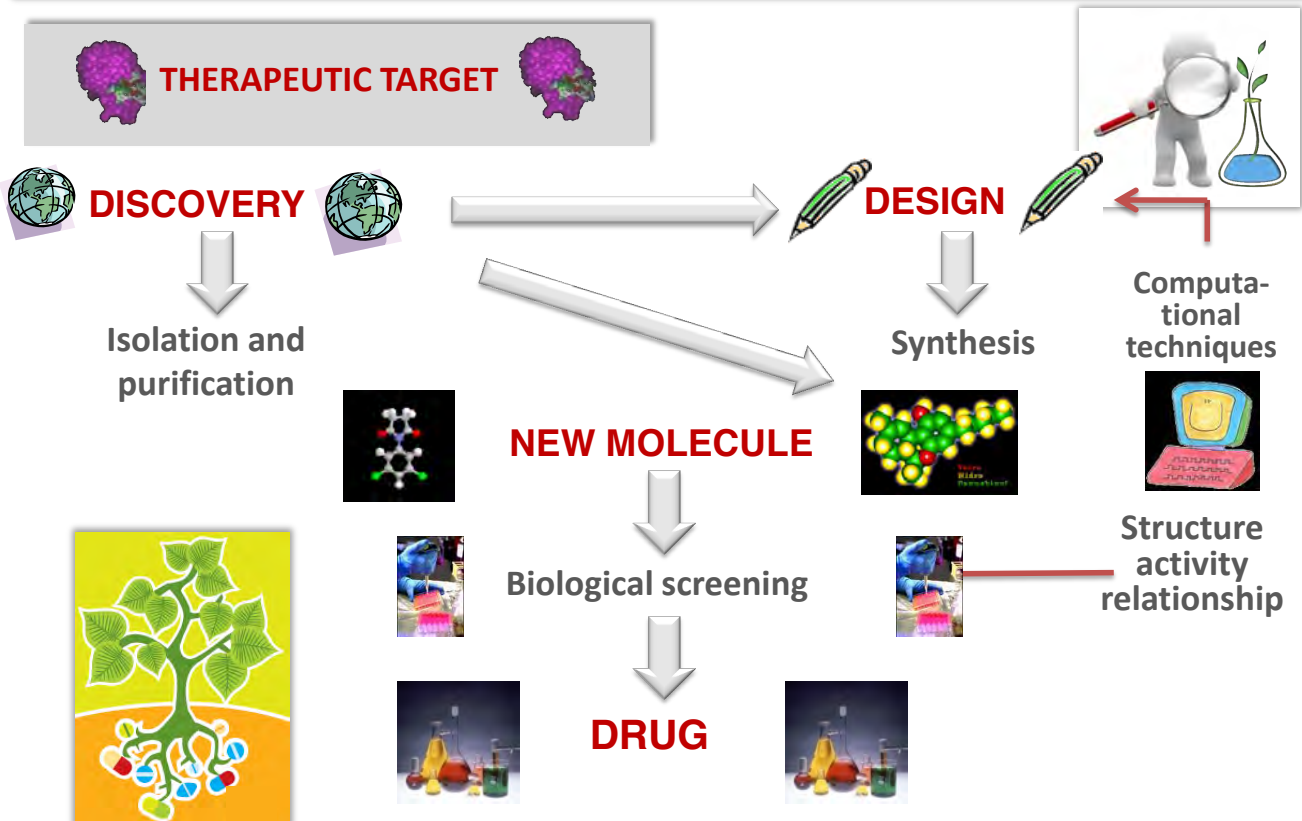
**KEY POINT:**  
Start by  
learning a  
new  
common  
language



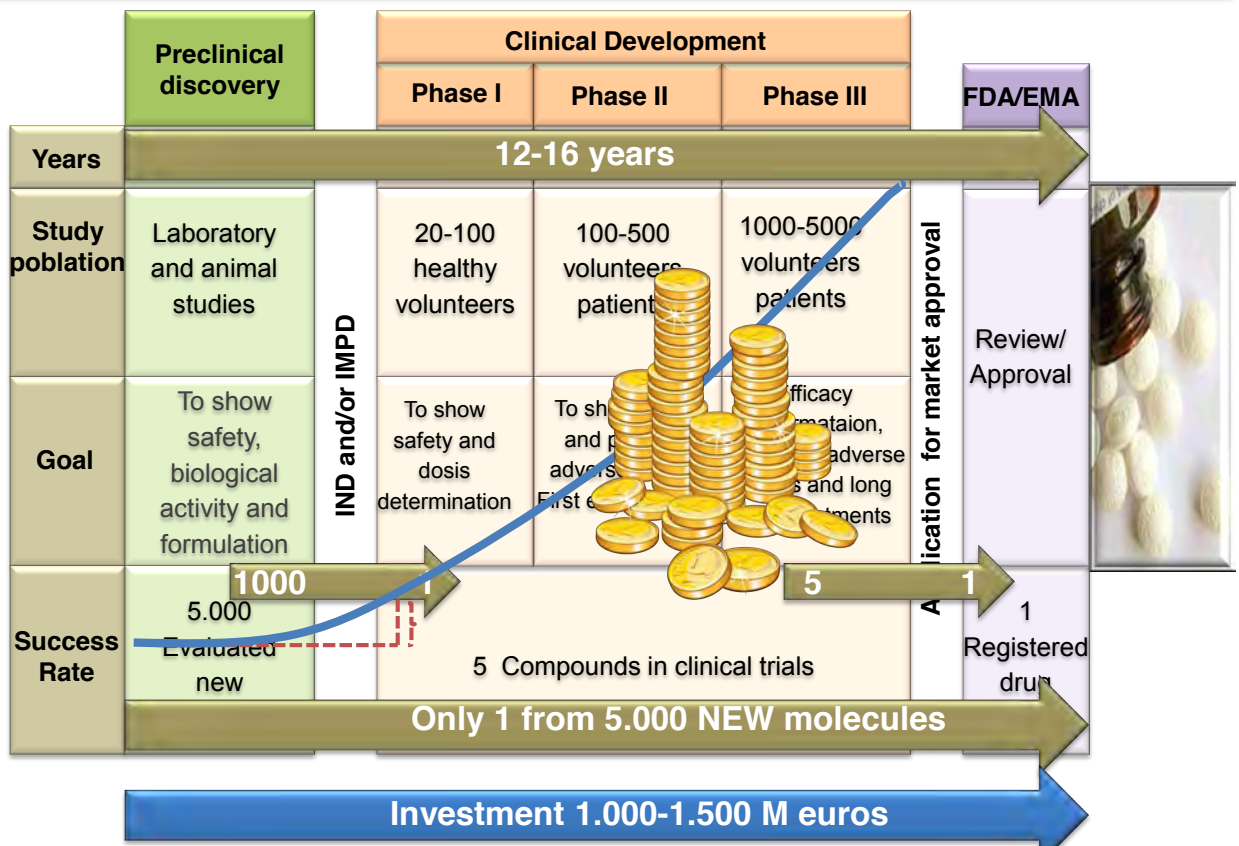
# From the lab to the market



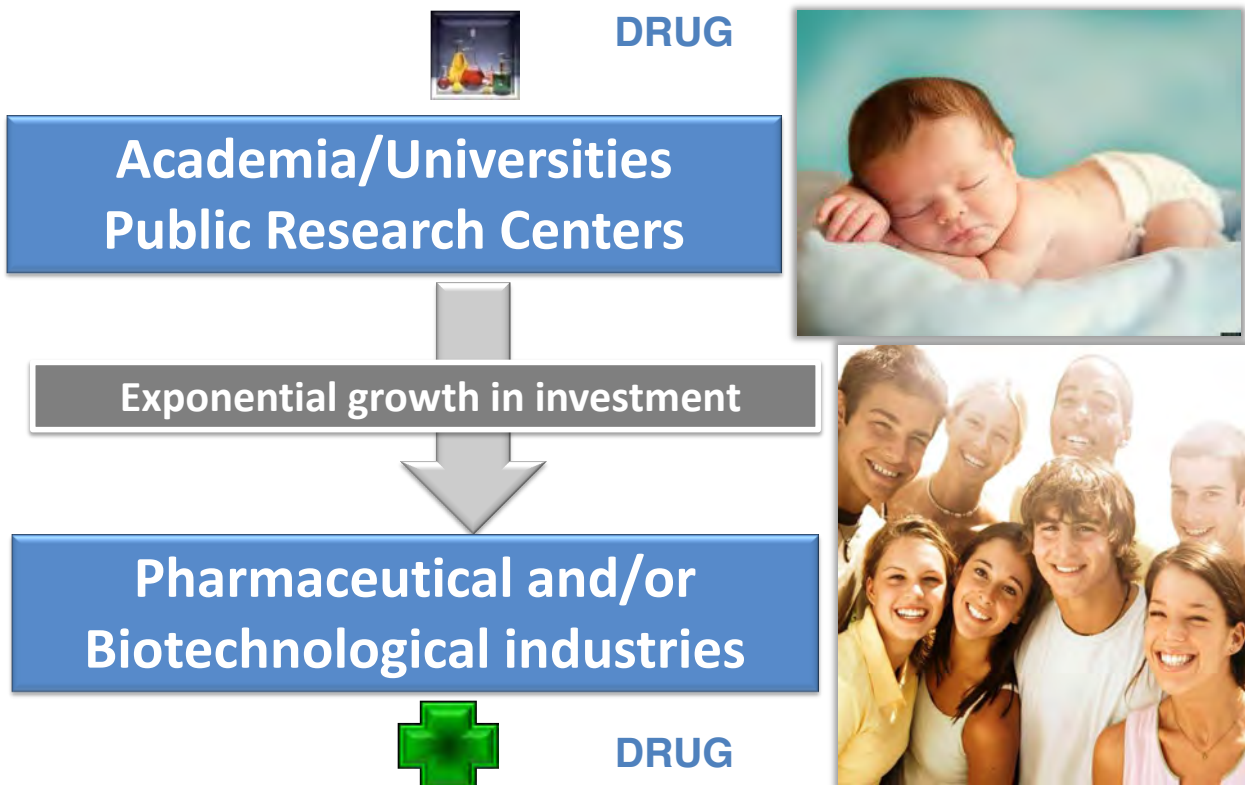
# ....in the lab .....



# Birth of new drug



# Translational research



# Translational research

Laboratory

The valley of death

Patients



B. Mellor, Nature 2008

*From the bench to the patient*

# Translational research

Laboratory

The valley of death

Patients



*From the bench to the patient*

# Translational research



*From the bench to the patient*

# Translational research

## SOME KEY POINTS

### Publications

Sharing the knowledge worldwide

- Impact factor

### Excellence

Quality

### Resilience

Constant

## Paving the way to the market



### Patents

Legal protection document (25 Y)

- Novelty
- Inventive activity

### Productivity

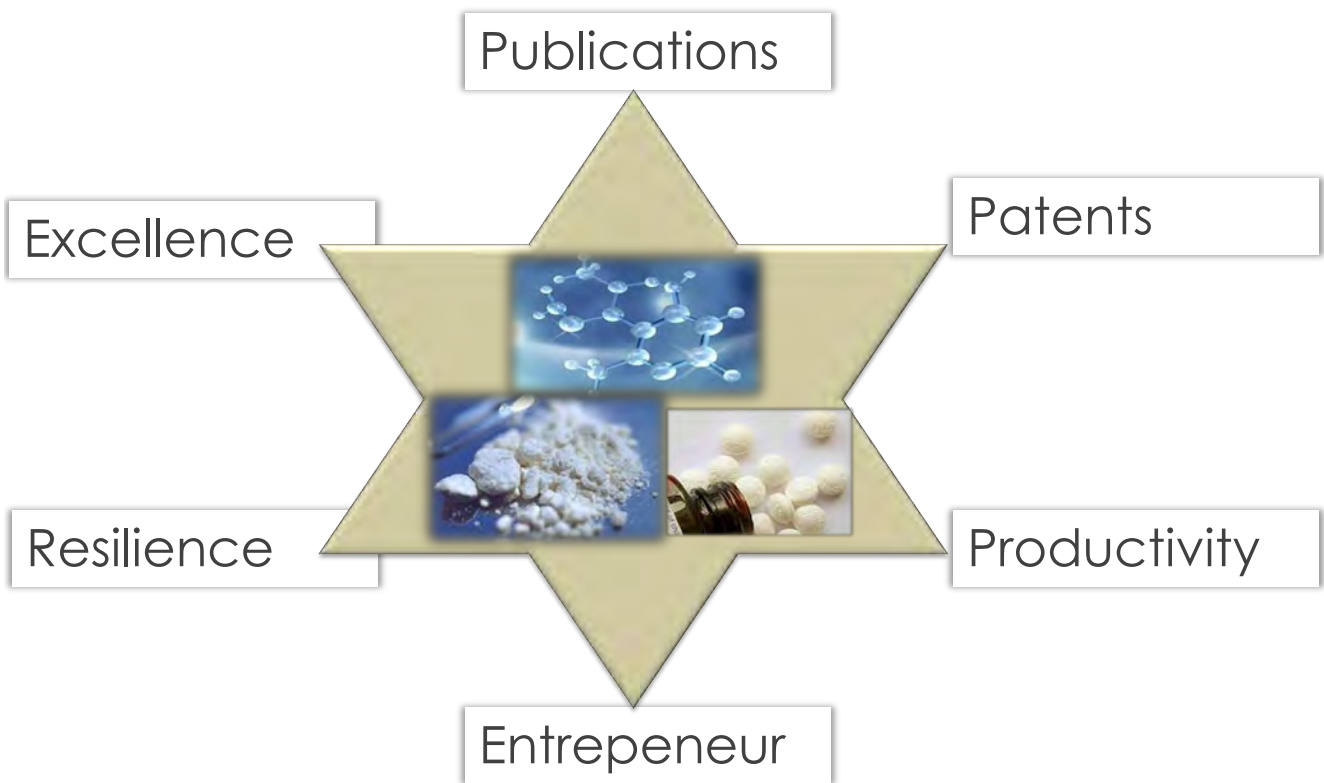
Quantity

### Entrepreneur

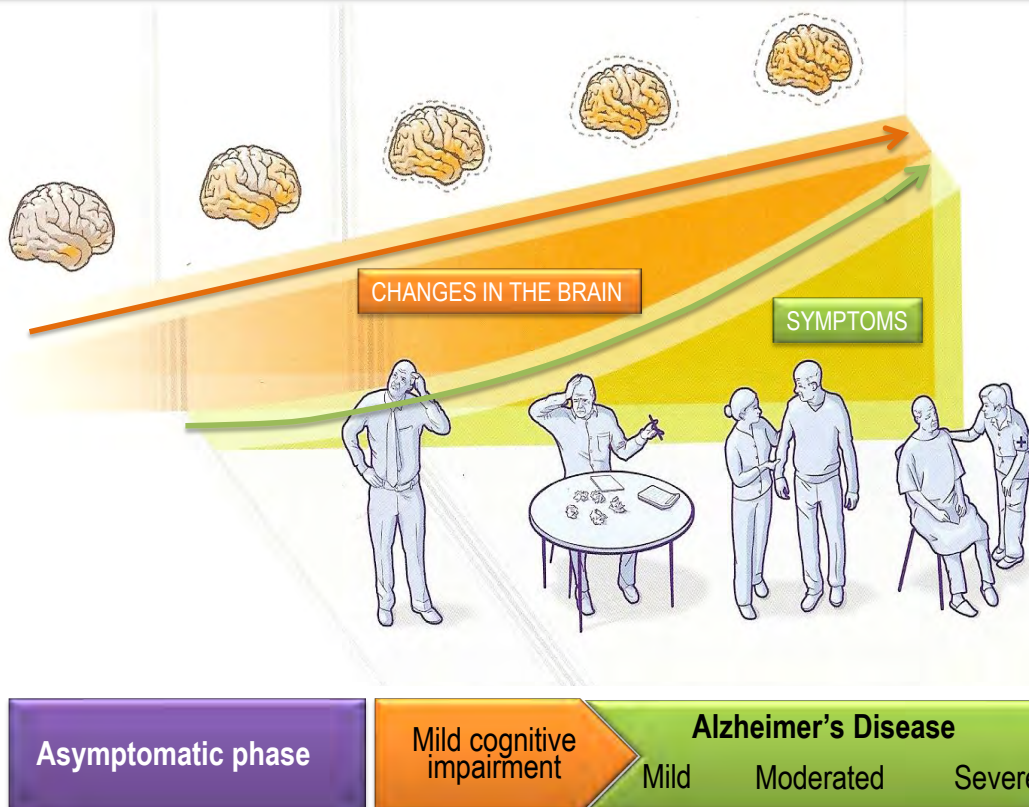
Creative



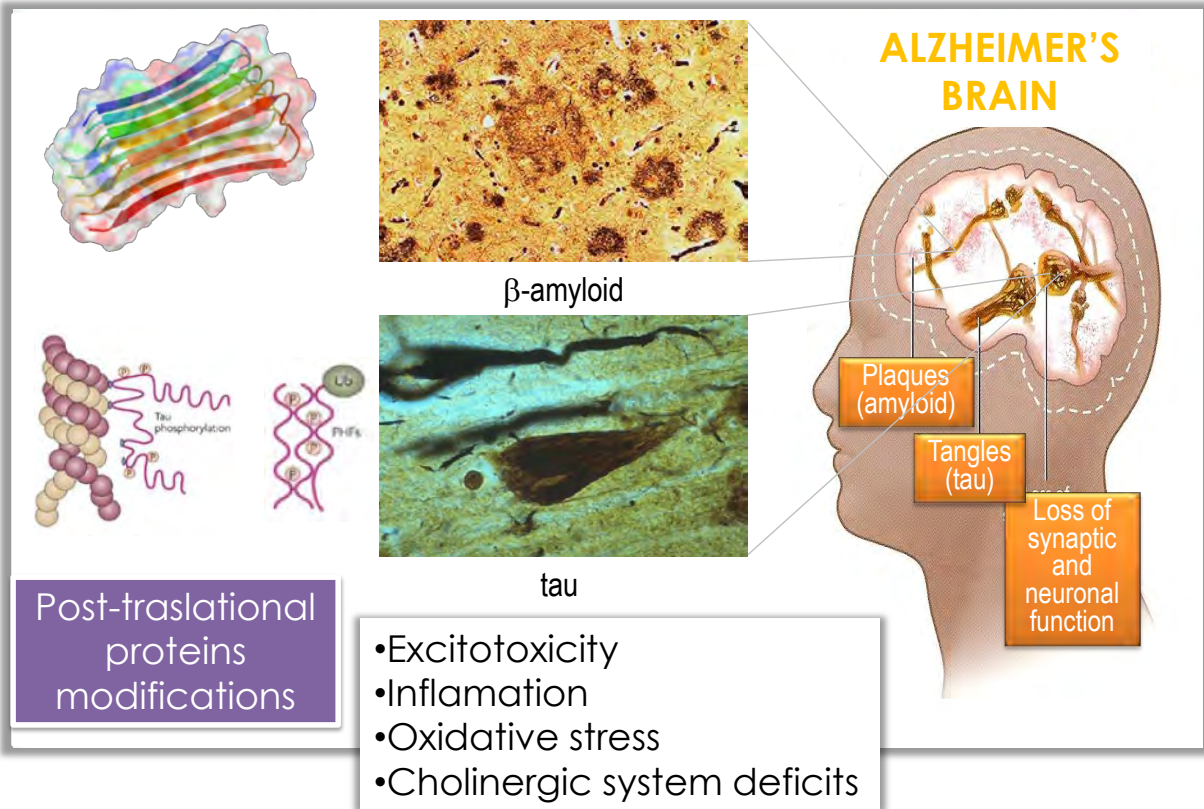
# Translational research



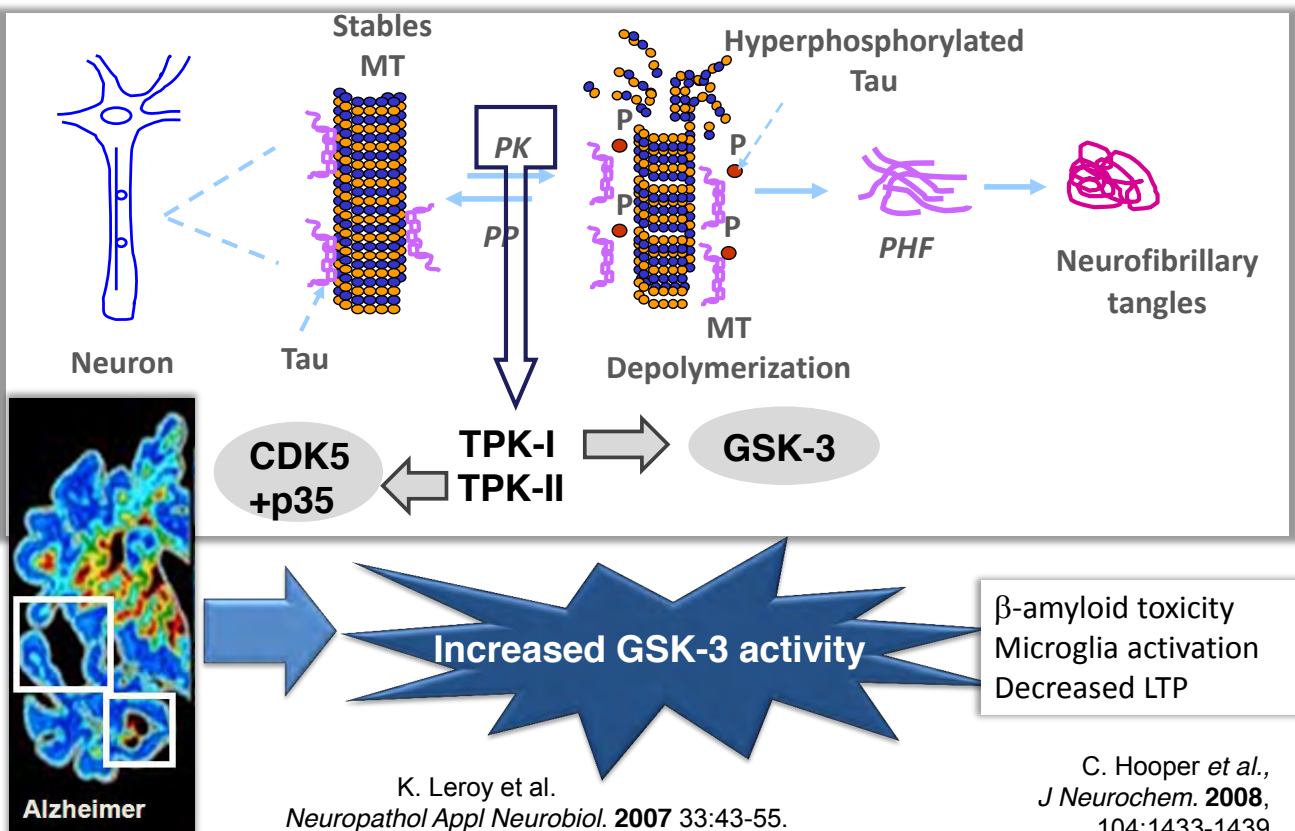
# Alzheimer's disease



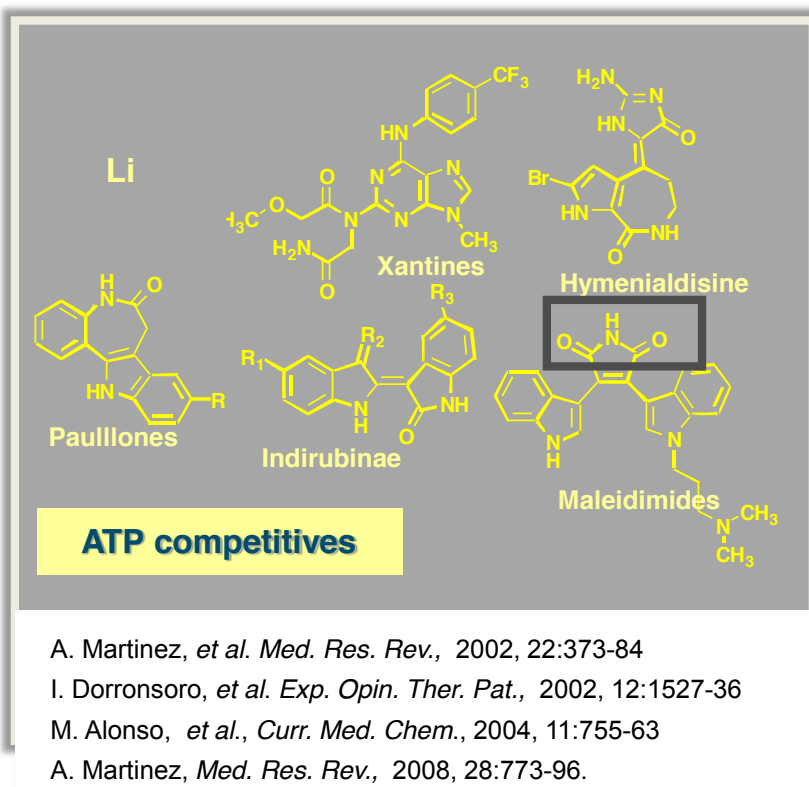
# Alzheimer's disease: etiology



## GSK-3 and AD



# Work-case: GSK-3 inhibitors



**CSIC**  
 Chemical Synthesis of Innovative Compounds

Thiadiazolidindiones  
 TDZD

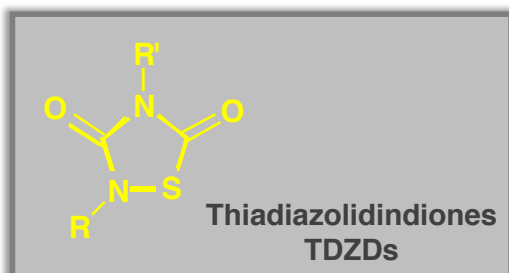
**ATP no-competitives**

WO 01185685

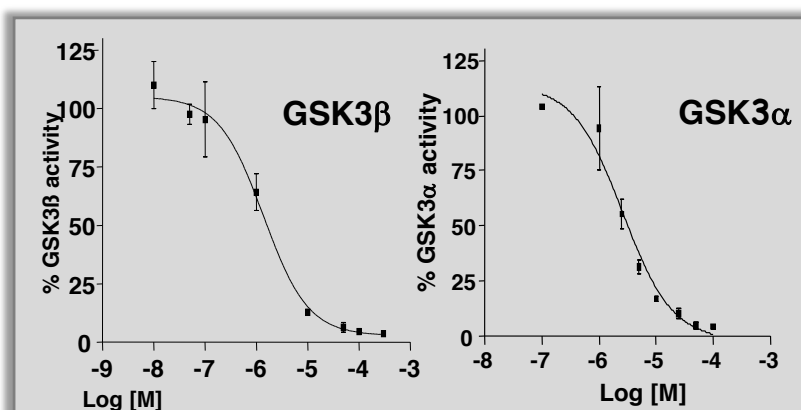
¿Opportunity?  
 ¿Serendipity? ¿Luck?

**noscira**

# TDZDs: GSK-3 inhibitors

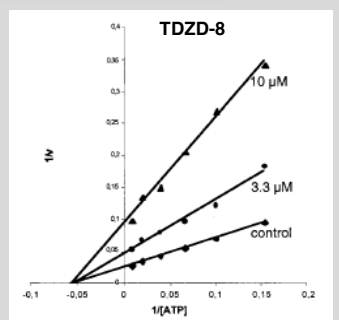
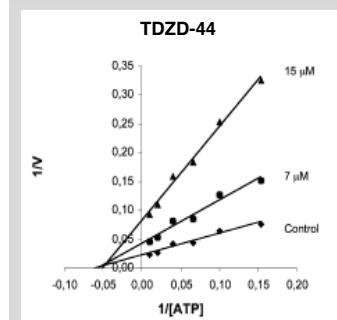
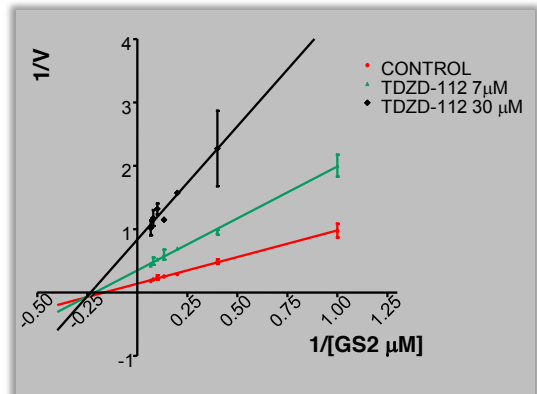
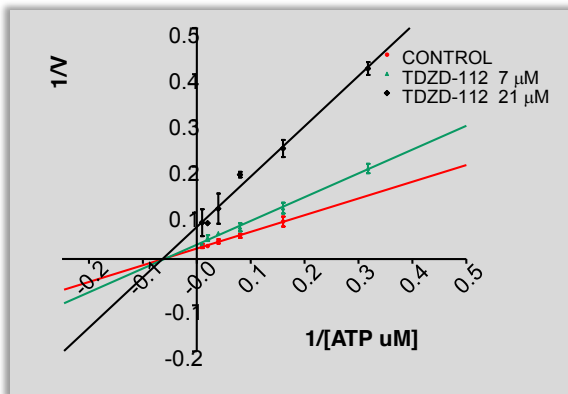


TDZDs are GSK-3 inhibitors

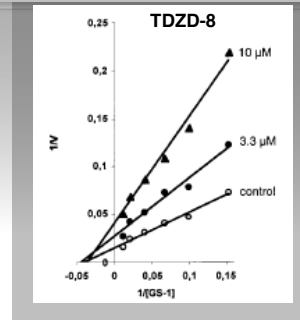


TDZD	IC <sub>50</sub> ( $\mu$ M)
TDZD-15	3.3
TDZD-19	1.6
TDZD-11	10
TDZD-16	2.9
TDZD-34	0.9
TDZD-39	2.5
TDZD-95	5
TDZD-111	3
TDZD-112	1.3
TDZD-115	4
TDZD-117	9.6
TDZD-118	3
TDZD-122	3

# TDZDs: GSK-3 inhibitors

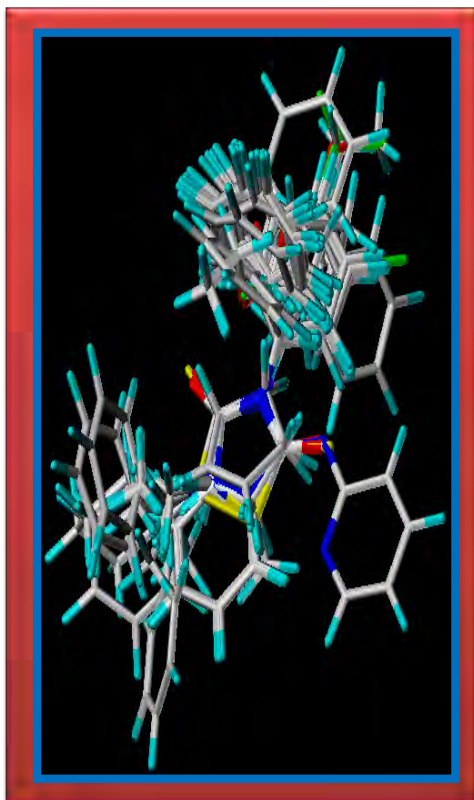


TDZDs do not compete with ATP nor the substrate



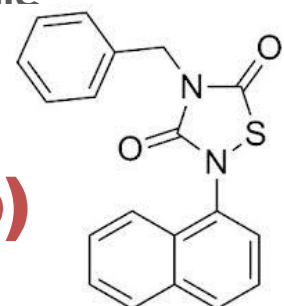
Martinez A et al. *J. Med. Chem.*, 2005, 48:7103-12

# TDZDs: GSK-3 inhibitors



Second generation TDZD's.  
Potent pharmacological action  
and improved  
pharmacokinetic properties  
oral bioavailability  
BBB crossing  
Long half-time life  
safety profile

**NP-12**  
**(Tideglusib)**

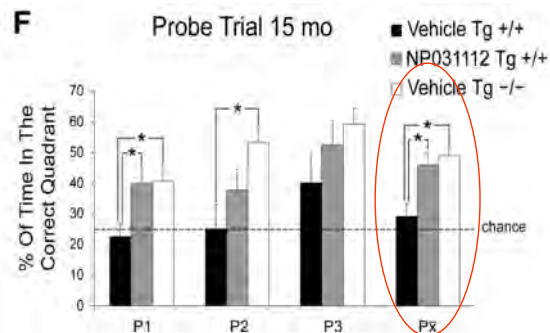
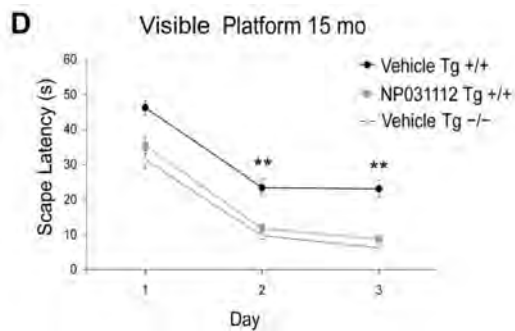
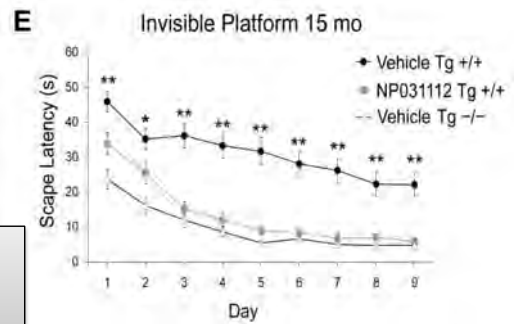


# TDZDs: tideglusib



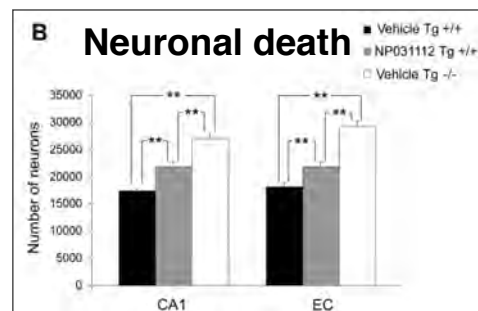
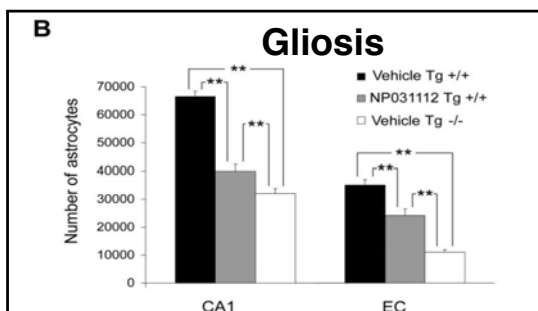
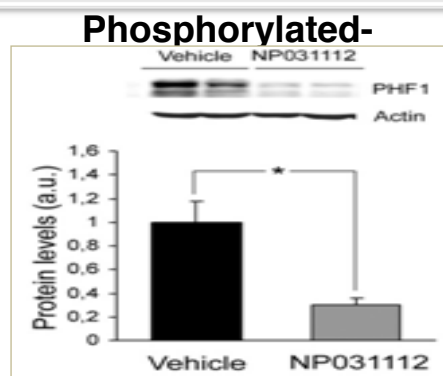
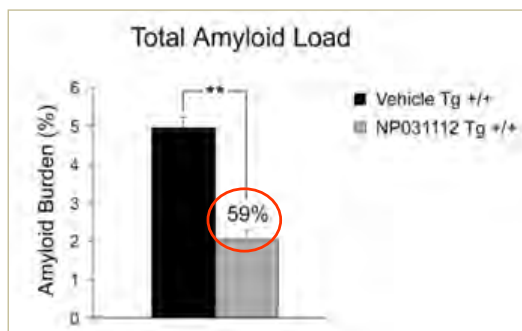
## Morris Water Maze

Increase on spatial learning ability and memory



Serenó L. *et al. Neurobiol Dis.* 2009, 35, 359-67.

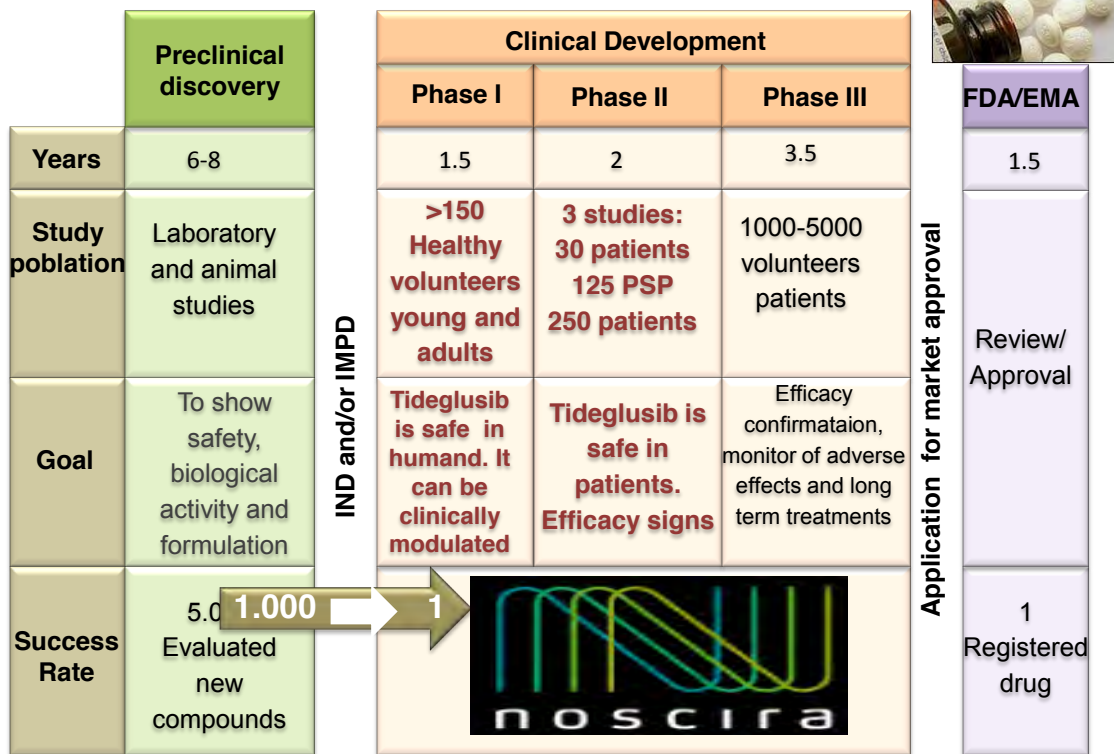
# TDZDs: tideglusib



Chronic oral treatment decreases amyloid load, phosphorylated tau protein, gliosis and neuronal death

Serenó L. *et al. Neurobiol Dis.* 2009, 35, 359-67.

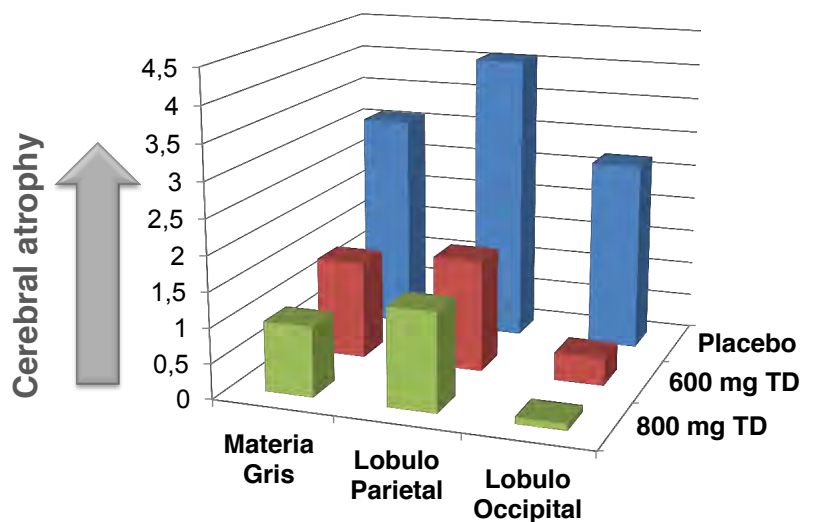
# TDZDs: tideglusib



# TDZDs: tideglusib

## Clinical Phase II TAU Restoration in pSp (TAUROS):

- 125 PSP patients (Golbe's stage: 1-4)
- Daily oral treatment for 12 months (600 and 800 mg)

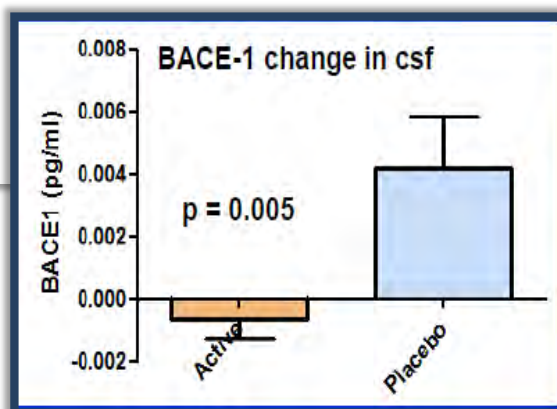
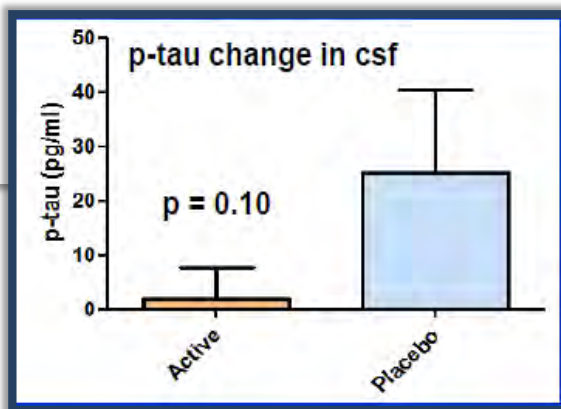


Höglinger GU et al. *Mov Disord.*, 2014, 29:479-87  
 Tolosa E, et al. *Mov Disord.* 2014, 29:470-8

# TDZDs: tideglusib

## Clinical Phase IIb **ARGO**

- 300 AD patients
- Daily oral treatment for 24 weeks (500 and 1.000 mg)

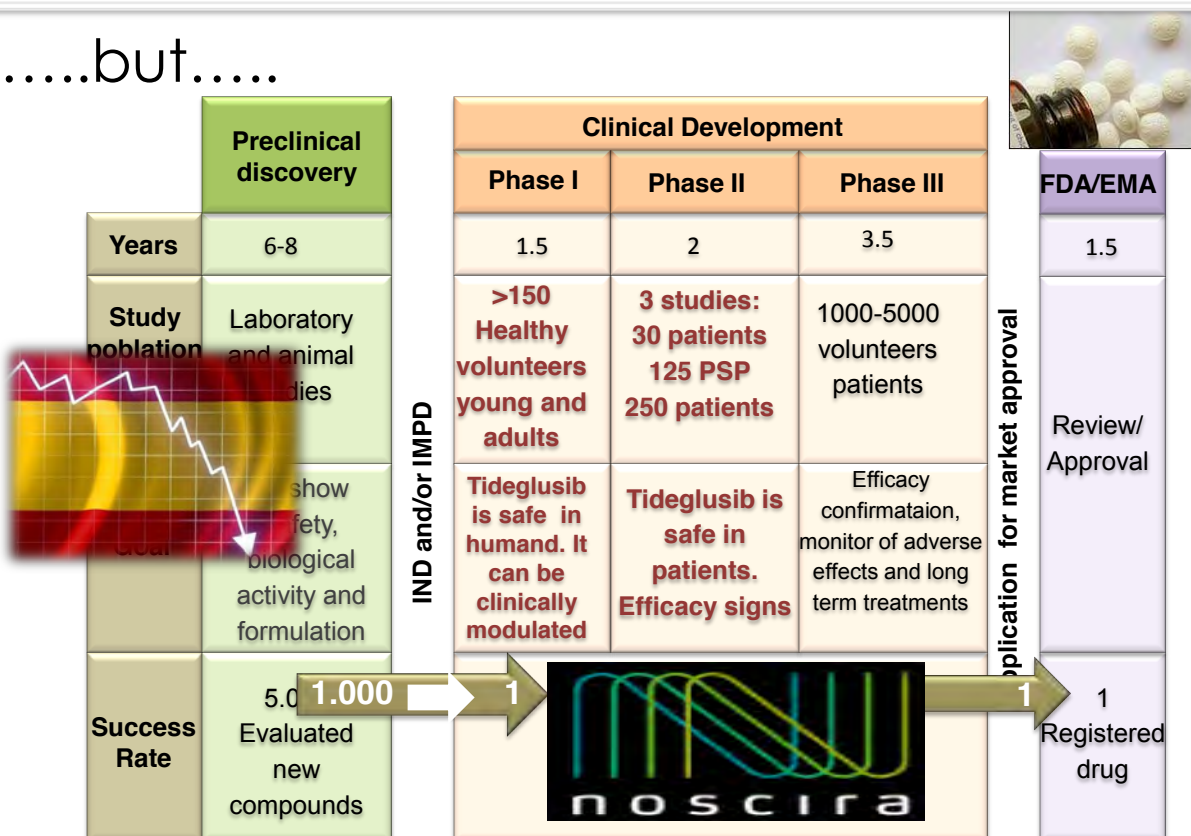


N=15 active and 6 placebo patients

Lovestone S, et al. *J Alzheimers Dis.* 2015, 45:75-88

# TDZDs: tideglusib

.....but.....



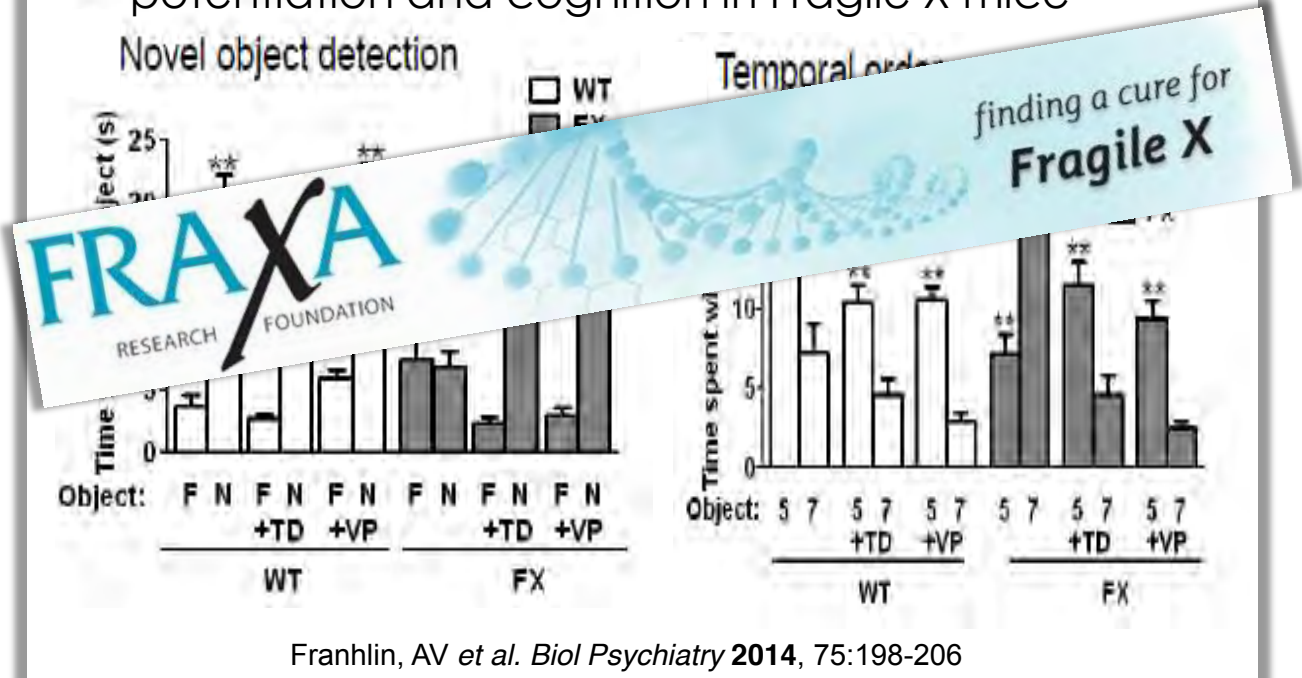
# GSK-3 inhibitors: new avenues

## Fragil X Syndrom (Autism)

GSK-3 inhibitors reverse deficits in Long-term potentiation and cognition in Fragile X mice

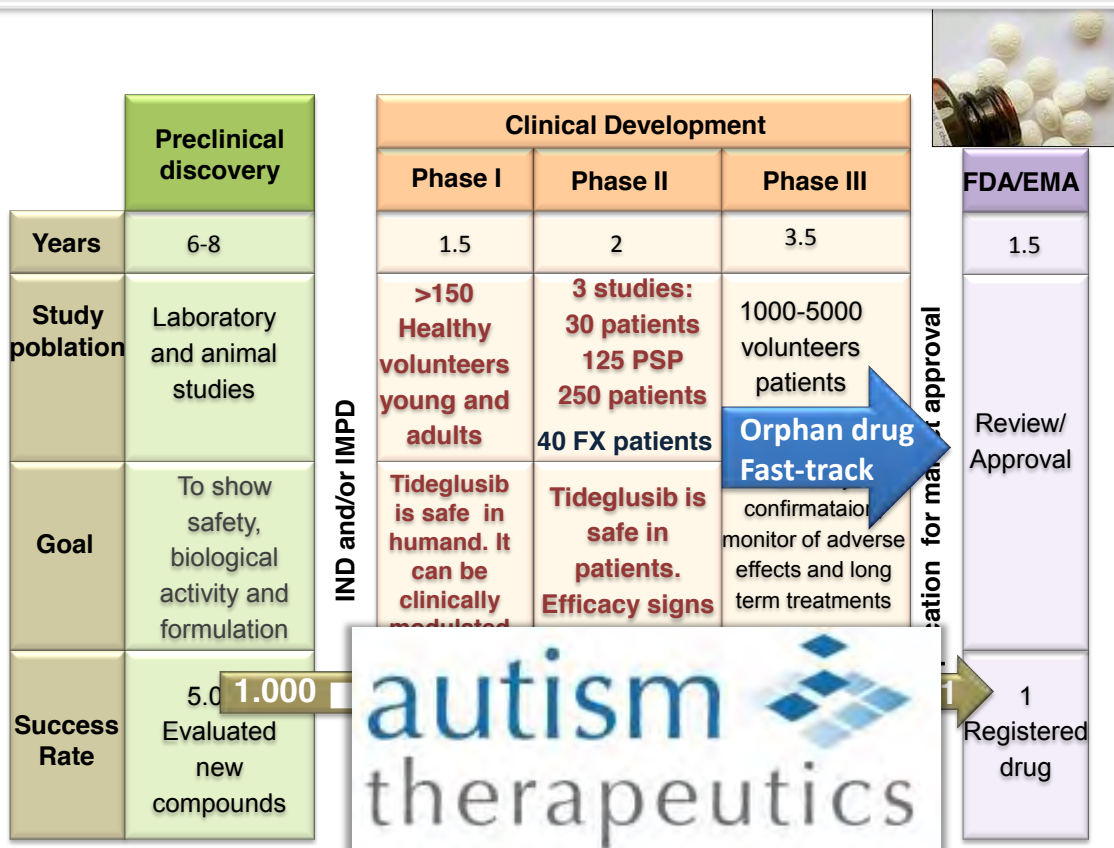
Novel object detection

Temporal order



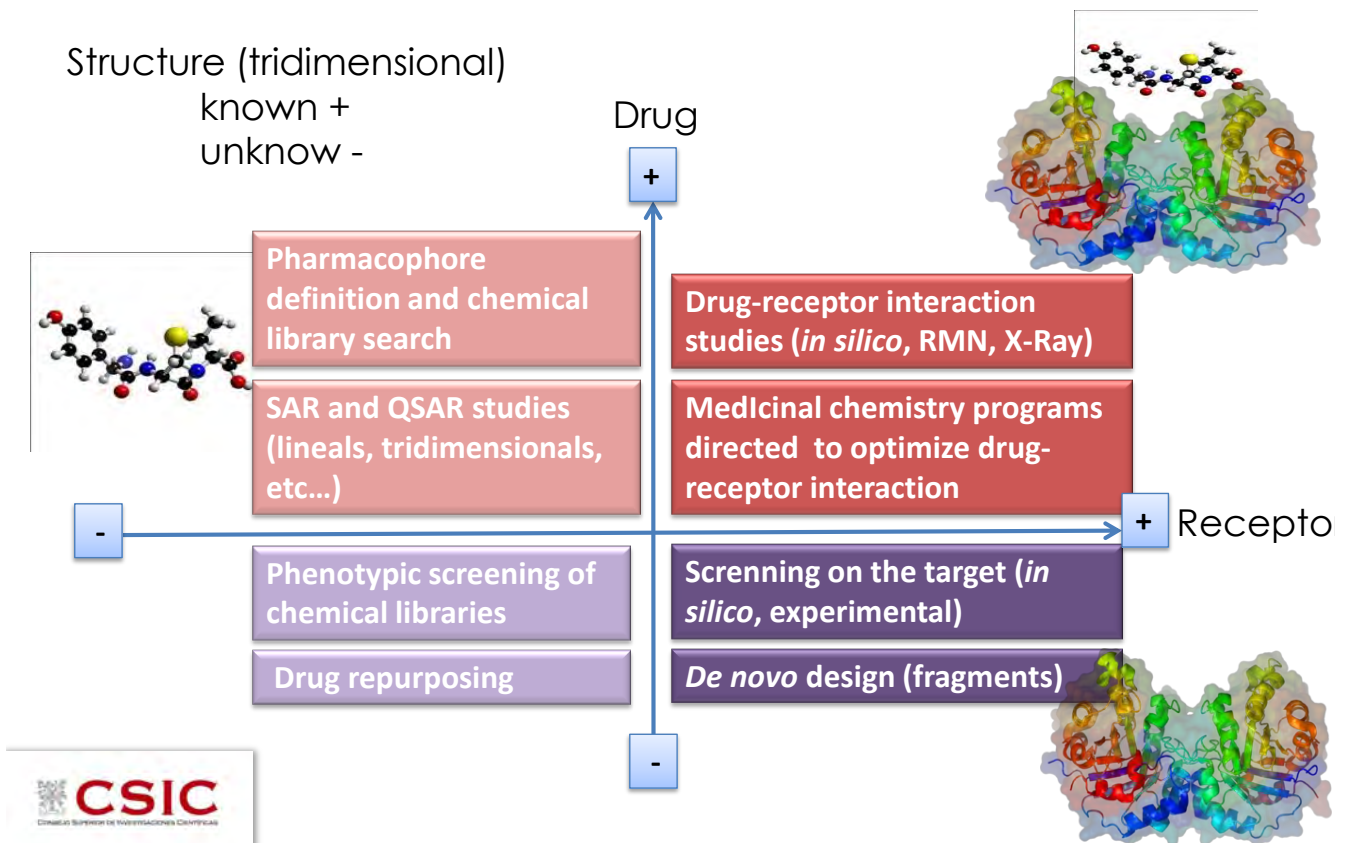
Franhlin, AV et al. *Biol Psychiatry* 2014, 75:198-206

# TDZDs: tideglusib





# Methodology

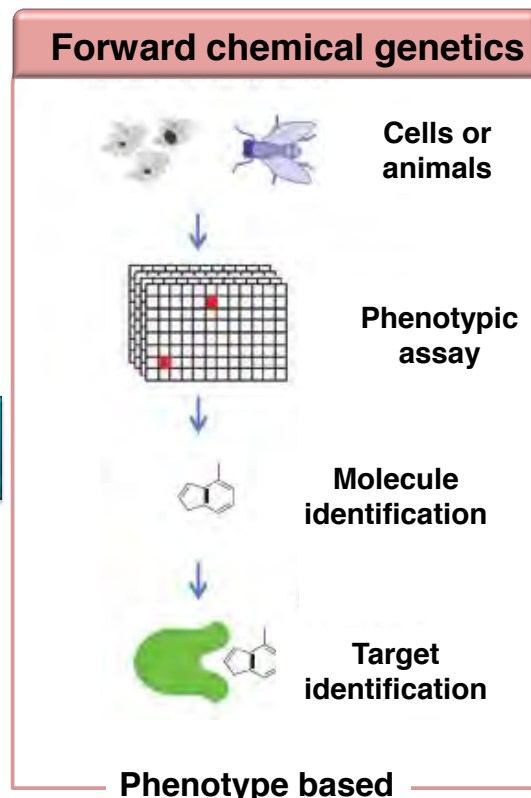


# Work-case

Neurodegenerative diseases: Unknown etiology

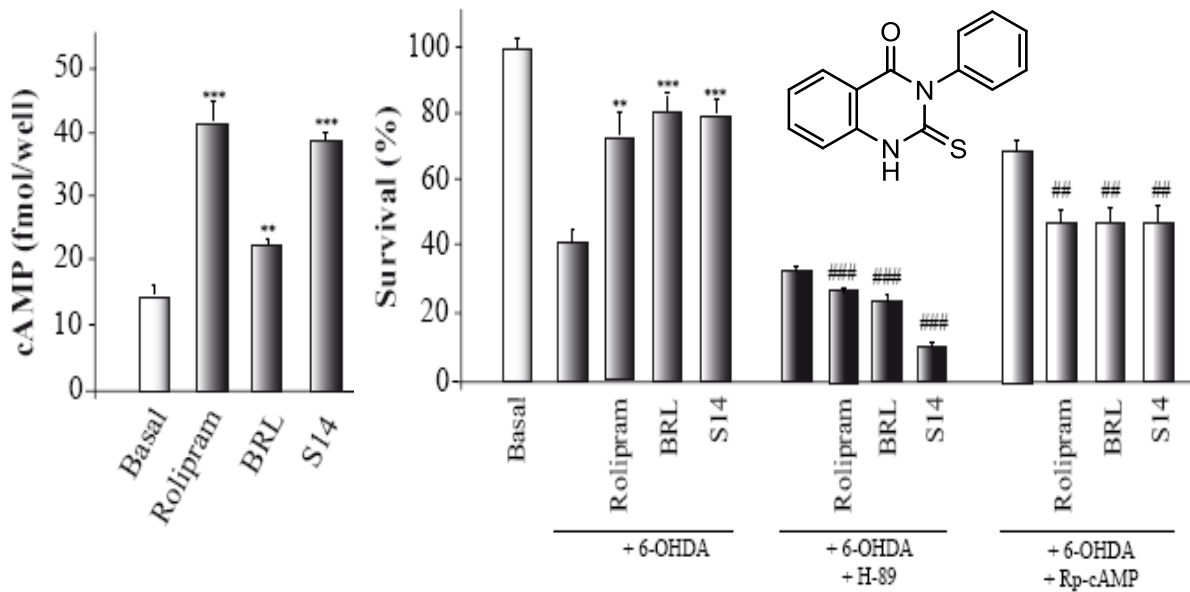


Search of innovative drug for Parkinson Disease



# PDE7 inhibitor for PD therapy

## Neuroprotection on SH-SY5Y cells treated with 6-OHDA. S14 mechanism of action

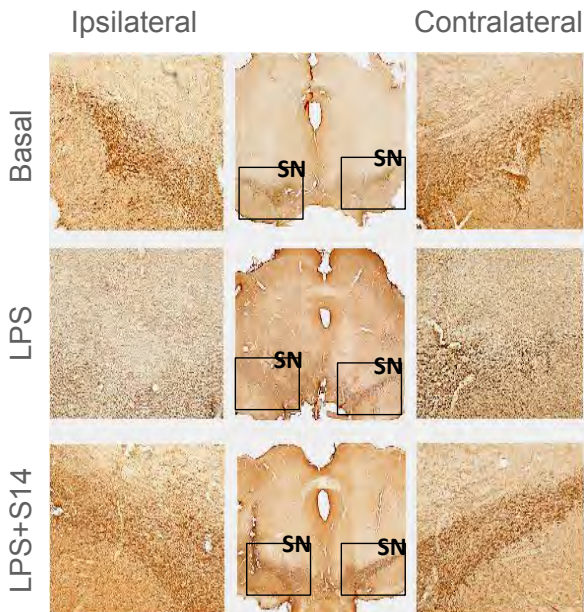


JA Morales, et al. Phosphodiesterase 7 (PDE7) inhibition preserves dopaminergic neurons in cellular and rodent models of Parkinson disease. *PLoS ONE*, 2011; 6(2):e17240.



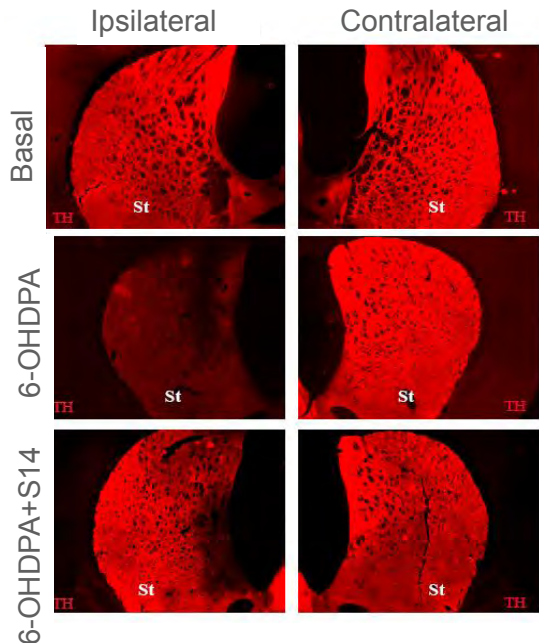
# PDE7 inhibitor for PD therapy

**LPS-model:** Decrease dopaminergic cell death in substantia nigra and inflammation



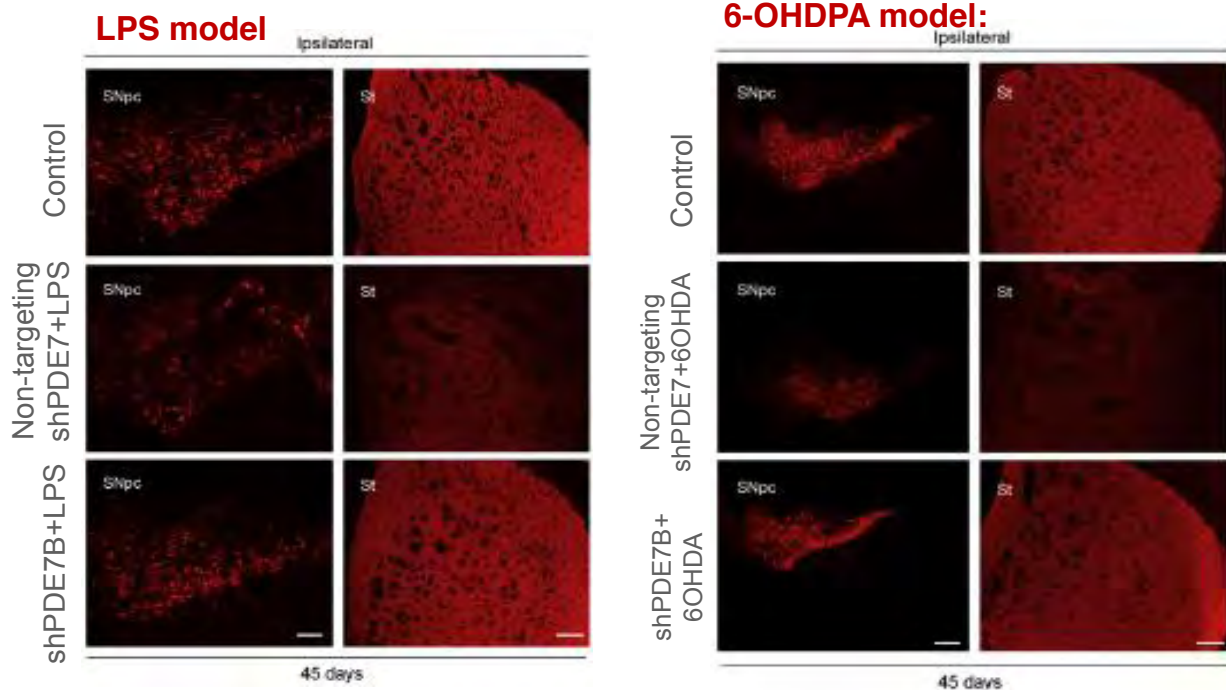
J. Morales-Garcia et al. *PLoS ONE* 2011 6, e17240

**6-OHDA model:** Decrease dopaminergic cell death in striado



# PDE7 inhibitor for PD therapy

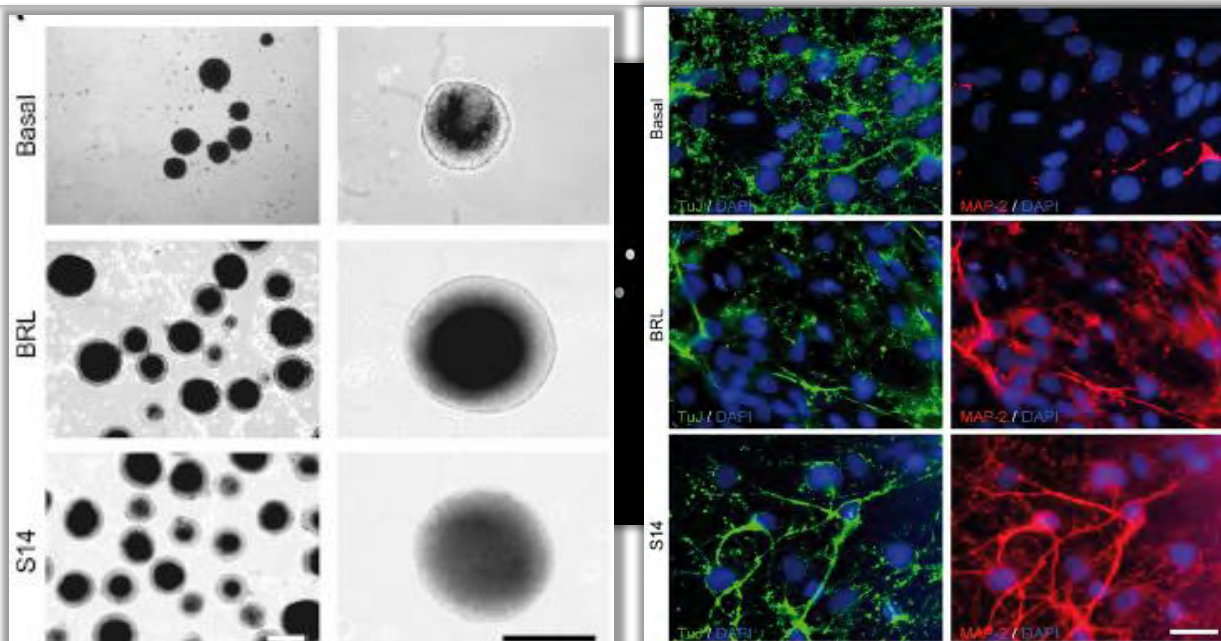
Target validation by classical genetics methodology (siRNAs)



JA Morales, et al. Silencing Phosphodiesterase 7B gene by lentiviral shRNA interference attenuates neurodegeneration and motor deficits in hemiparkinsonian mice. *Neurobiol Aging*, 2015;36:1160-1173.

# PDE7 inhibitor for PD therapy

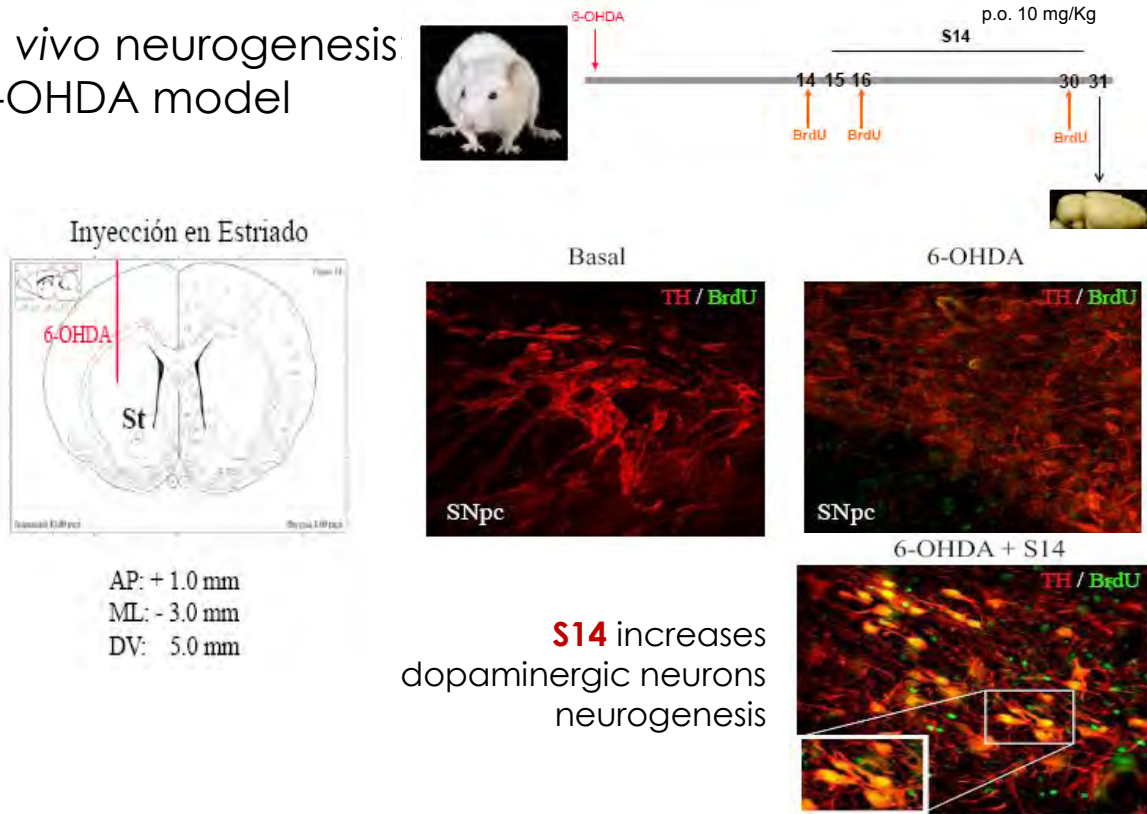
*In vitro* neurogenesis: neurospheres from subventricular zone of adult rat



J. Morales-Garcia et al. Phosphodiesterase 7 inhibition induces dopaminergic neurogenesis in hemiparkinsonian mice. *Stem Cells Trans Med* 2015, 2014-027

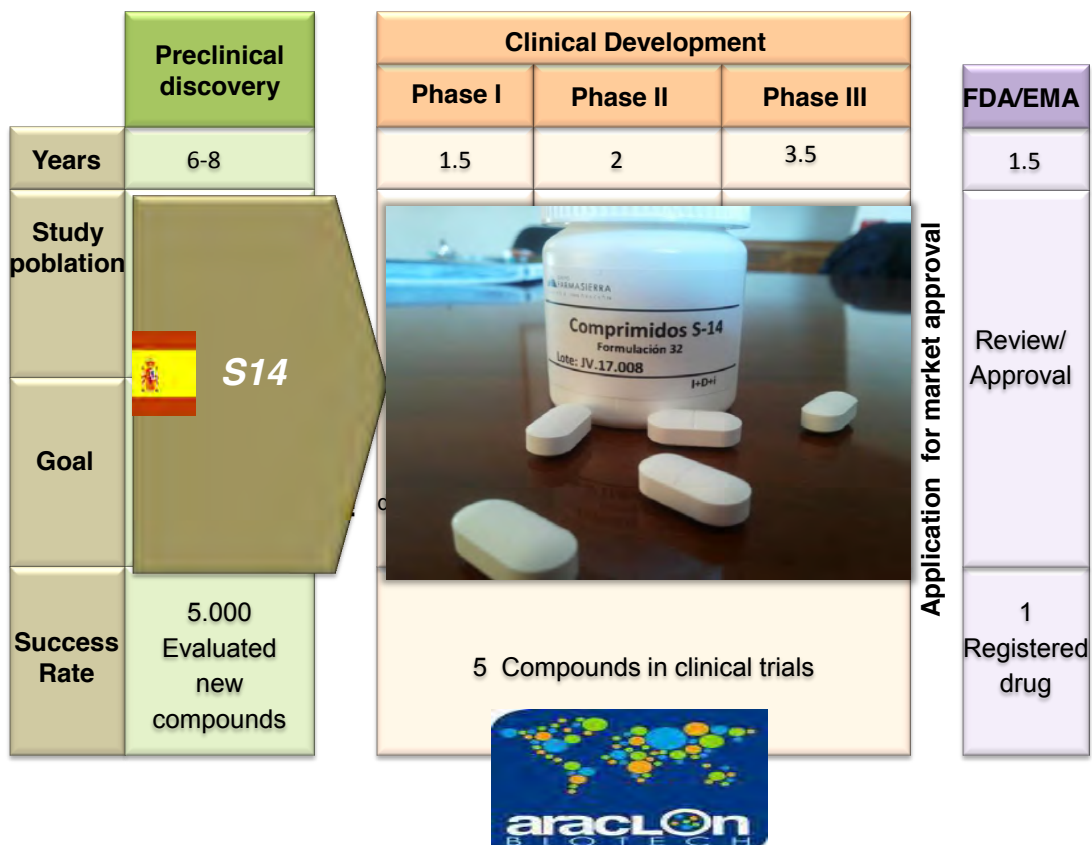
# PDE7 inhibitor for PD therapy

In vivo neurogenesis:  
6-OHDA model



J. Morales-Garcia et al. Phosphodiesterase 7 inhibition induces dopaminergic neurogenesis in hemiparkinsonian mice. *Stem Cells Trans Med* 2015, 2014-027

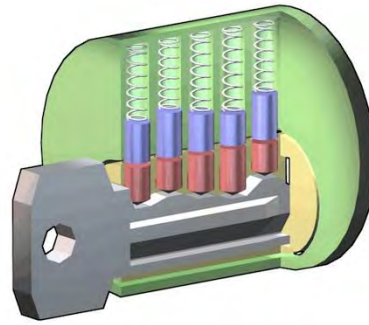
# S14: new drug candidate for PD



# Methodology



**Emil Fisher**  
Chemistry  
Nobel Prize  
1902

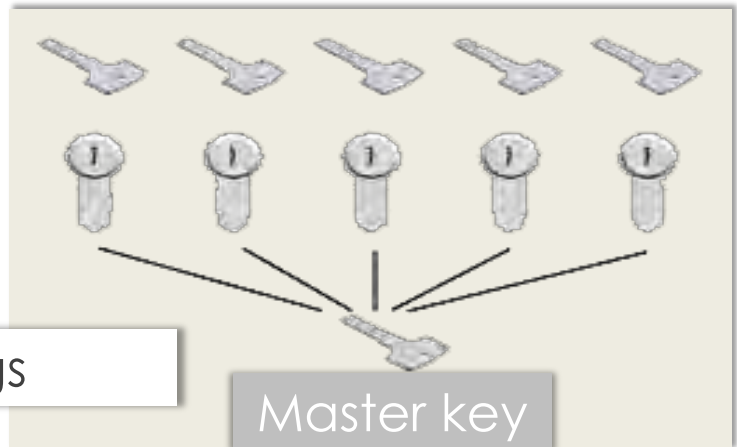


Key and lock  
model

Neurodegenerative  
diseases:

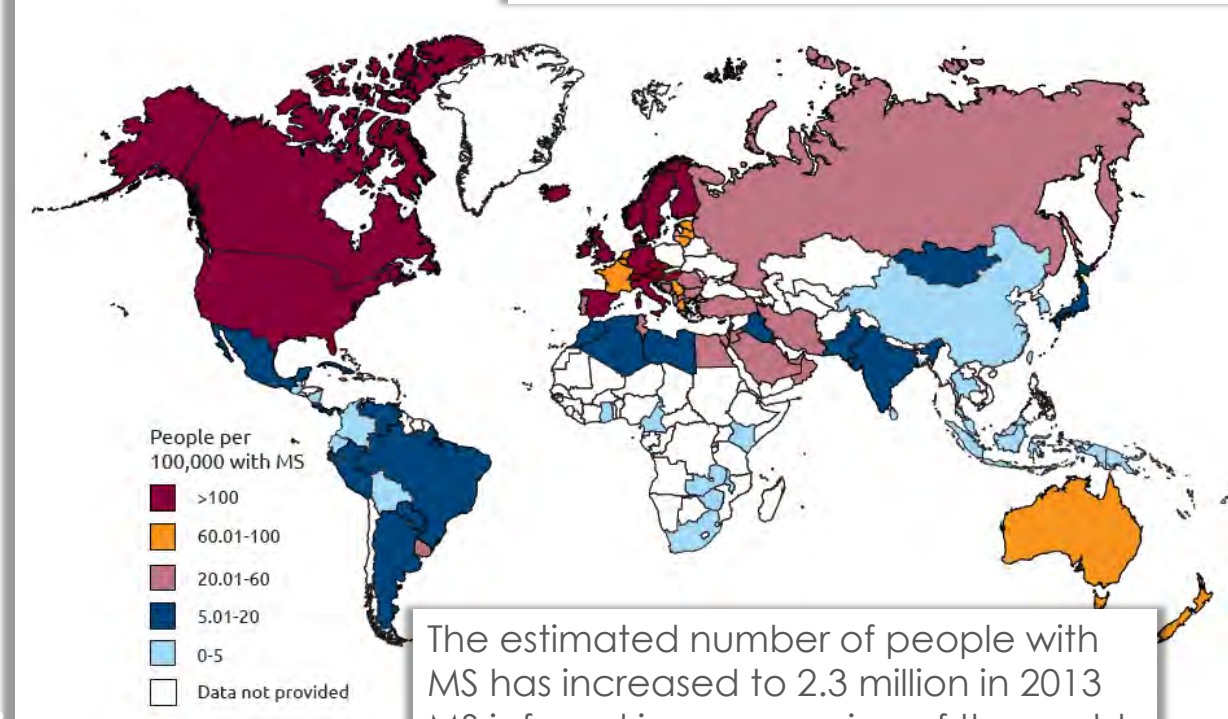
- Complex diseases
- Unknown etiology

Multitarget drugs



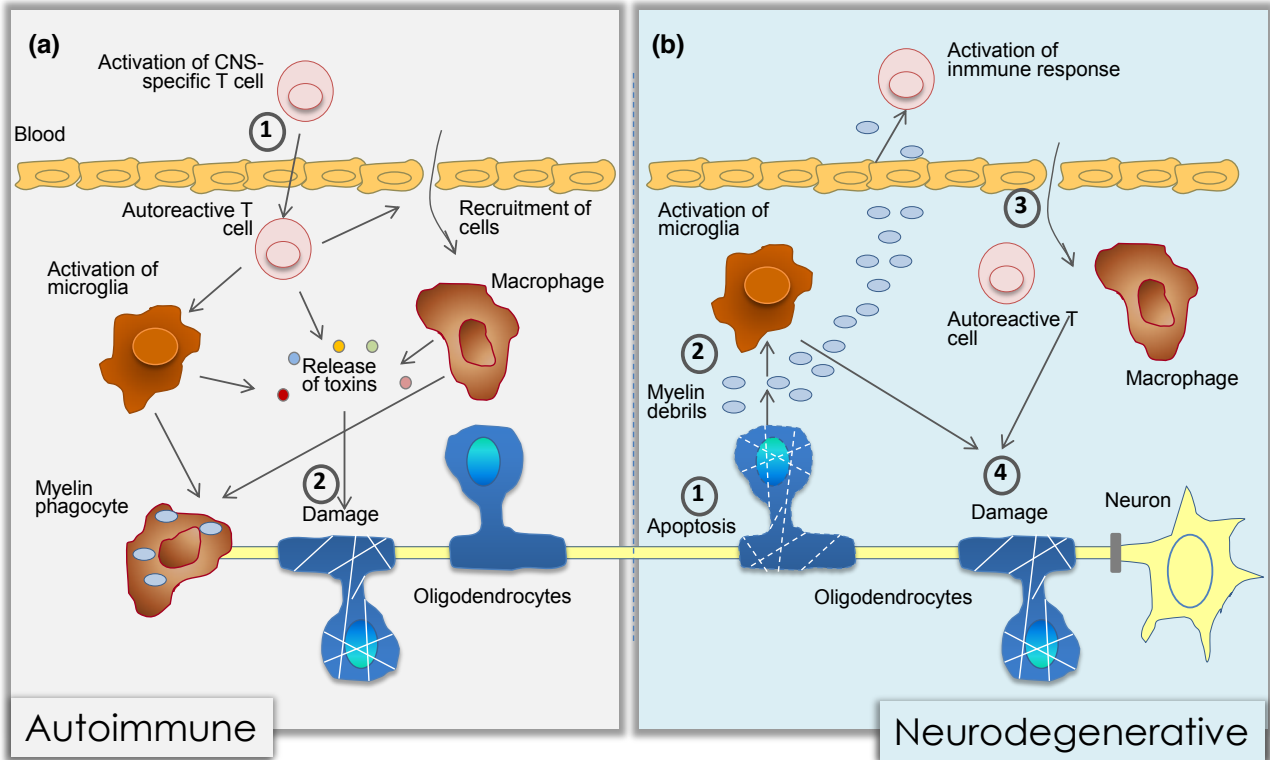
# Multiple Sclerosis

Prevalence by country (2013)



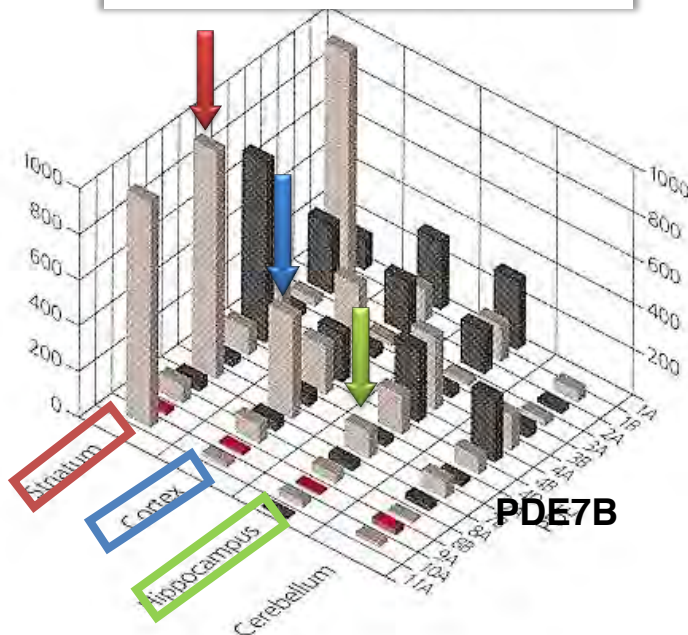
The estimated number of people with MS has increased to 2.3 million in 2013  
MS is found in every region of the world.

# Multiple Sclerosis

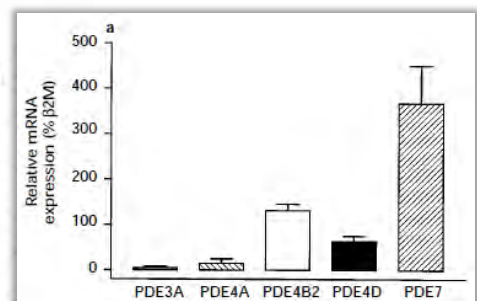


## New therapeutic target

Differential distribution of PDEs in the brain



Differential distribution of PDEs in B cells



F. Gantner et al  
*British J Pharmacol.* **1998**, 123, 1031

C. Gil, et al. PDE7 inhibitors as new drugs for neurological and inflammatory disorders  
*Expert Opin. Ther. Patents* **2008**, 18, 1127.

# PDE7 inhibitors

## Chemical genetic approach

Discover/design chemical probes structurally diverse to study the target cell function (physiological and pathological)

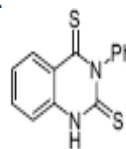
Drug candidates (after drugable profile optimization)

## Medicinal chemistry strategies used:

- Virtual screening using similarity index

quinazolines

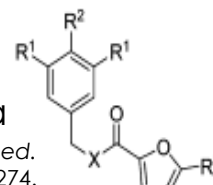
T. castaño, et al  
*ChemMedChem.* **2009**, 4,  
866.



- Pharmacophoric search on 3D-Compound Data Ba

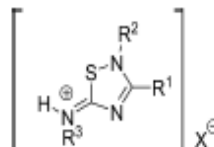
Eurane derivatives

M. Redondo, et al *J. Med.  
Chem.* **2012**, 55, 3274.



- Neuronal Network based drug discover

5-imino-thiazoles



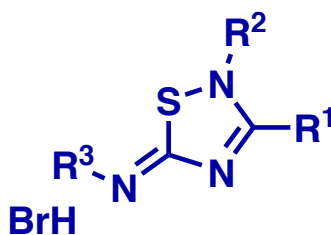
M. Redondo, et al  
*ACS Chem. Neurosci.*  
**2012**, 3, 793.

- Phenotypic cell-based screening

Diaryl-thioethers

# Dual GSK-3/PDE7 inhibitors

## 5-IMINO THIADIAZOLES



Journal of  
**Medicinal  
Chemistry**

Article

pubs.acs.org/jmc

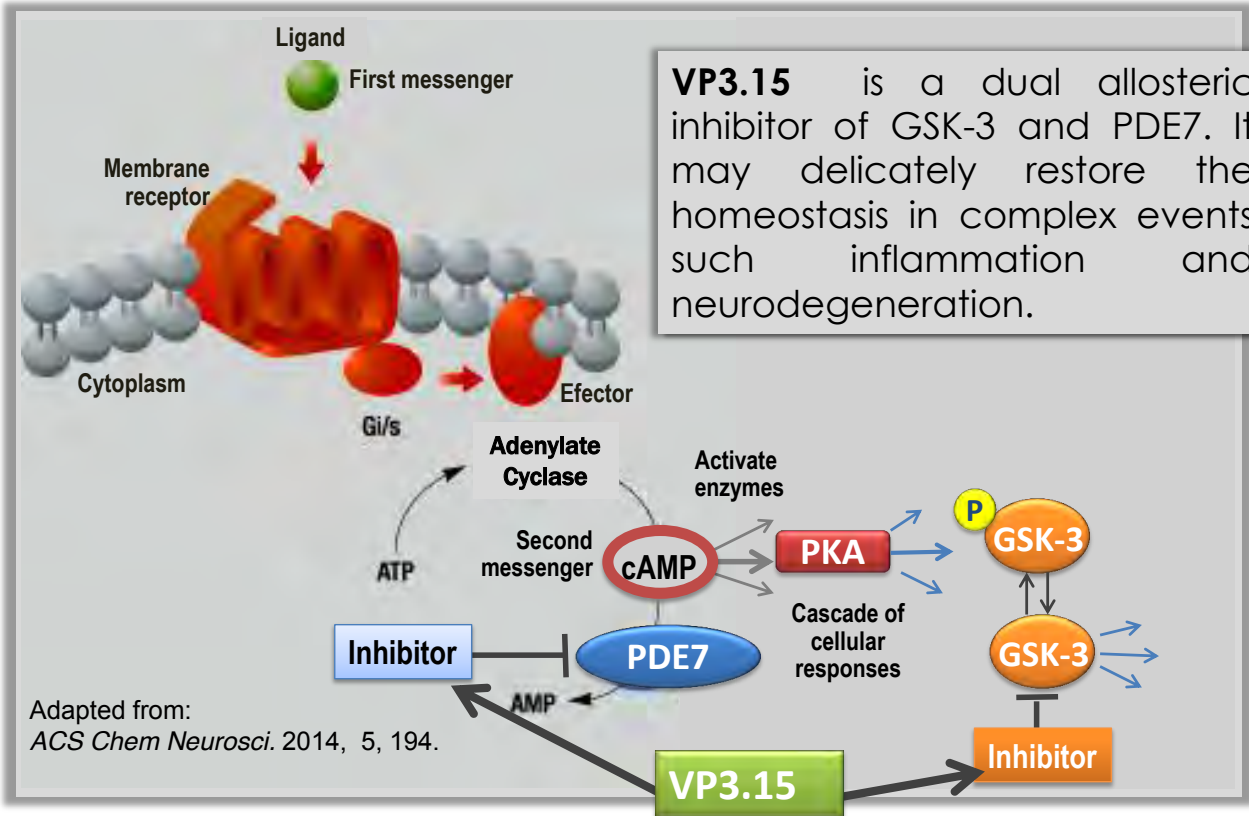
## 5-Imino-1,2,4-Thiadiazoles: First Small Molecules As Substrate Competitive Inhibitors of Glycogen Synthase Kinase 3

Valle Palomo,<sup>†</sup> Daniel I. Perez,<sup>†</sup> Concepcion Perez,<sup>†</sup> Jose A. Morales-Garcia,<sup>‡</sup> Ignacio Soteras,<sup>†</sup> Sandra Alonso-Gil,<sup>‡</sup> Arantxa Encinas,<sup>†</sup> Ana Castro,<sup>†</sup> Nuria E. Campillo,<sup>†</sup> Ana Perez-Castillo,<sup>‡</sup> Carmen Gil,<sup>\*,†</sup> and Ana Martinez<sup>\*,†</sup>

<sup>†</sup>Instituto de Química Médica-CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

<sup>‡</sup>Instituto de Investigaciones Biomédicas (CSIC-UAM) and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Arturo Duperier 4, 28029 Madrid, Spain

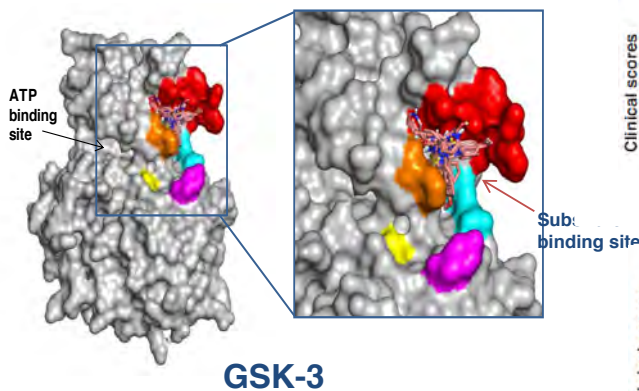
# New treatment: VP3.15



# New treatment: VP3.15

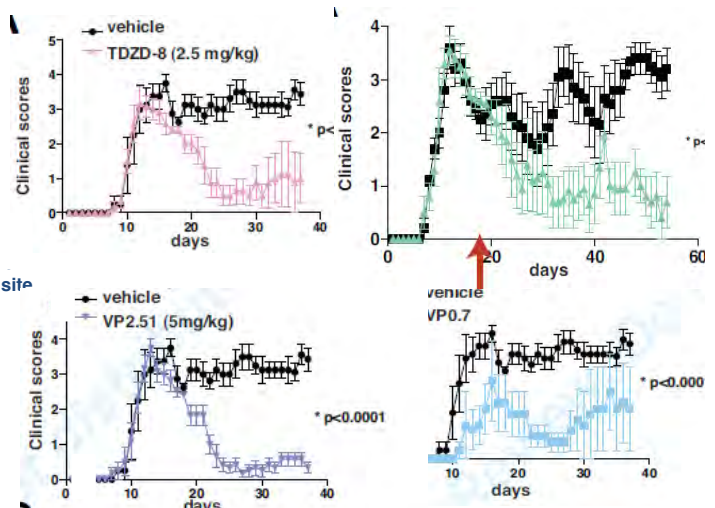
## VP3.15 and GSK-3

- VP3.15 belongs to the iminothiadiazole (ITDZs) family: the first substrate competitive GSK-3 inhibitors reported until now (*J Med Chem.* 2012, 55:1645)



## GSK-3 in MS

- EAE model, administration of GSK-3 inhibitors effectively prevents the disease and almost completely terminates ongoing disease (*J Immunol* 2013; 190:5000-5011).

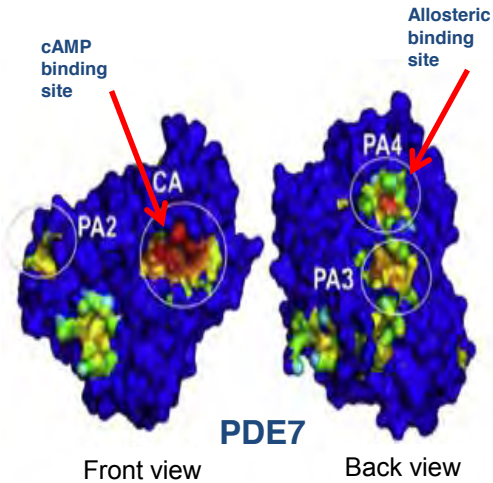




# New treatment: VP3.15

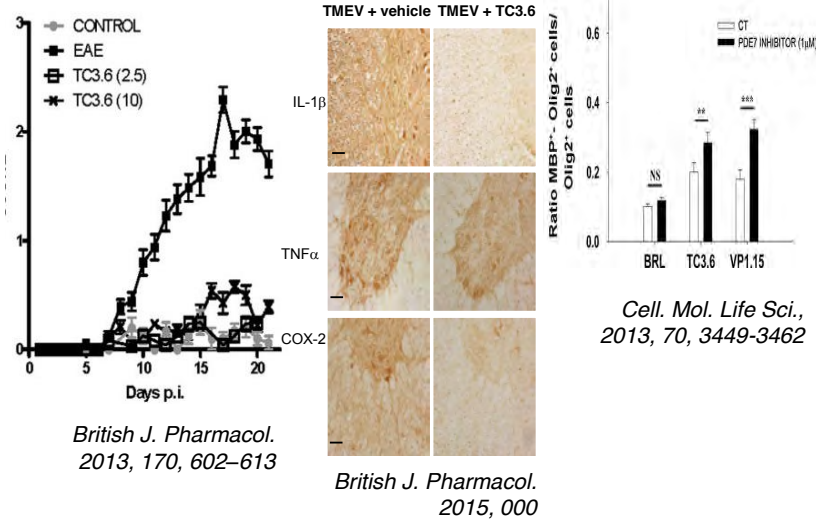
## VP3.15 and PDE7

- VP3.15 is an allosteric inhibitor of PDE7 (*Eur J Med Chem.* 2013, 70:781)



## PDE7 and MS

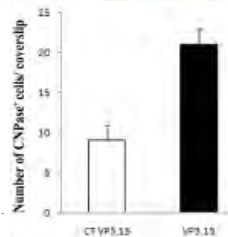
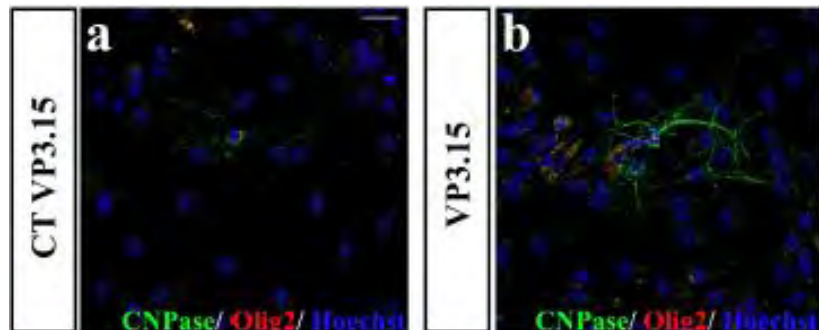
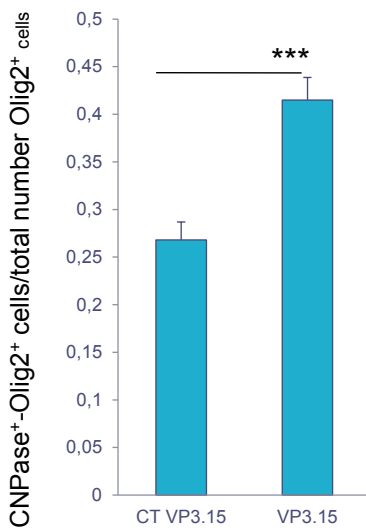
- PDE7 inhibitors produce therapeutic effects *in vitro* and *in vivo* models of MS such EAE and Theiler virus models and promote the differentiation of OPCs.



# New treatment: VP3.15

## Remyelinating activity

- **VP3.15** is able to promote OPC differentiation (from mice and from humans) with great efficacy

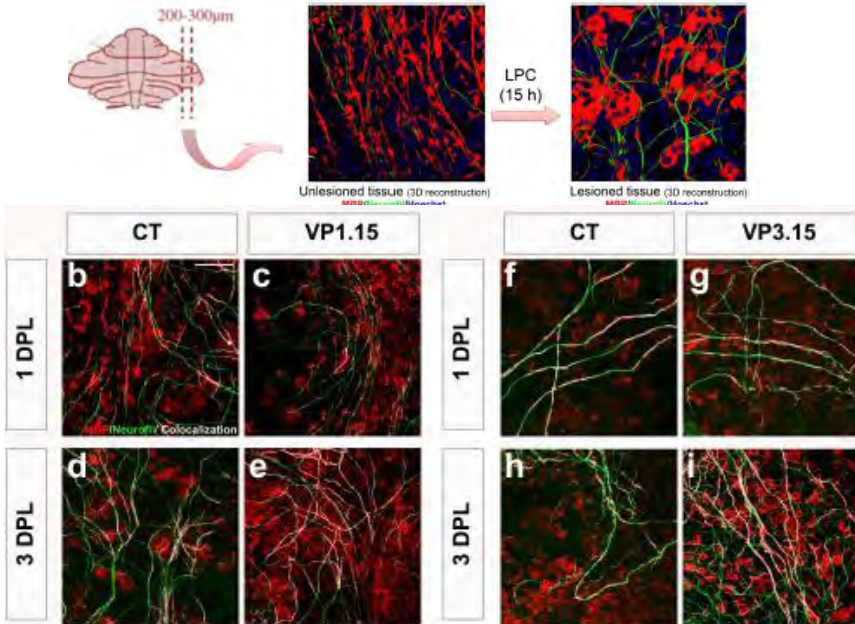


Immunofluorescence images to detect the expression of CNPase and Olig2 on adult OPCs from human cerebral cortex, after 5 days in differentiation medium in the presence of VP3.15 (1  $\mu$ M). The number of differentiated cells was higher than in control conditions

# New treatment: VP3.15

## Remyelinating activity

- **VP3.15** and **VP1.15** increase the *ex vivo* remyelination in cerebellum slices treated with lysophosphatidyl choline (LPC)

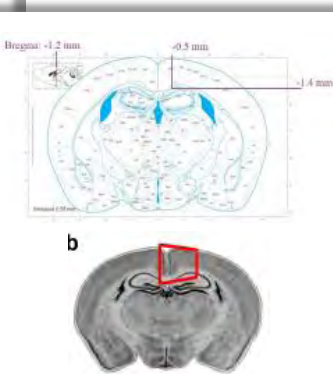


Protocol and images showing a 3D reconstruction of cerebellum slices. Non-lesioned tissue shows most of axons (green) wrapped by oligodendrocytes (red). After induction of demyelination for 16h with LPC, the loss of most of oligodendrocytes was observed. Images show tissue after 1 and 3 days post lesion (DPL) where oligodendrocytes (red) and axons (green) can be observed and the overlapping areas (white) show myelinated fibers after the treatment with 5 mM of VP1.15 and VP3.15

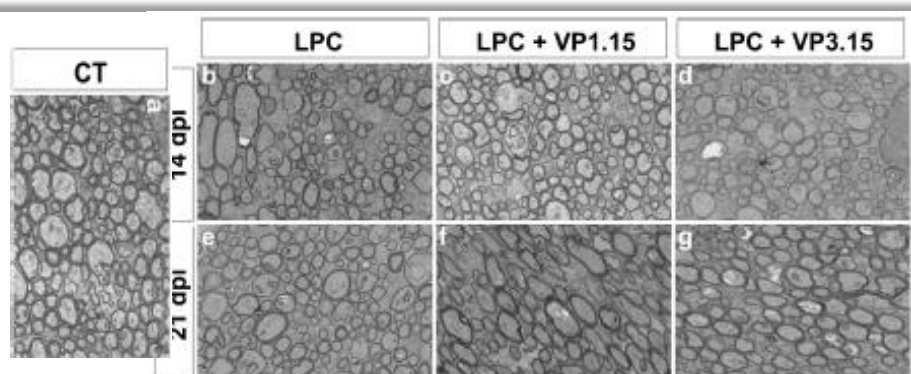
# New treatment: VP3.15

## Remyelinating activity

- **VP3.15** and **VP1.15** increase the *in vivo* remyelination in mice treated with lysophosphatidyl choline (LPC)



Lesioned area to study remyelination in the corpus callosum. B) Brain dissected for being studied

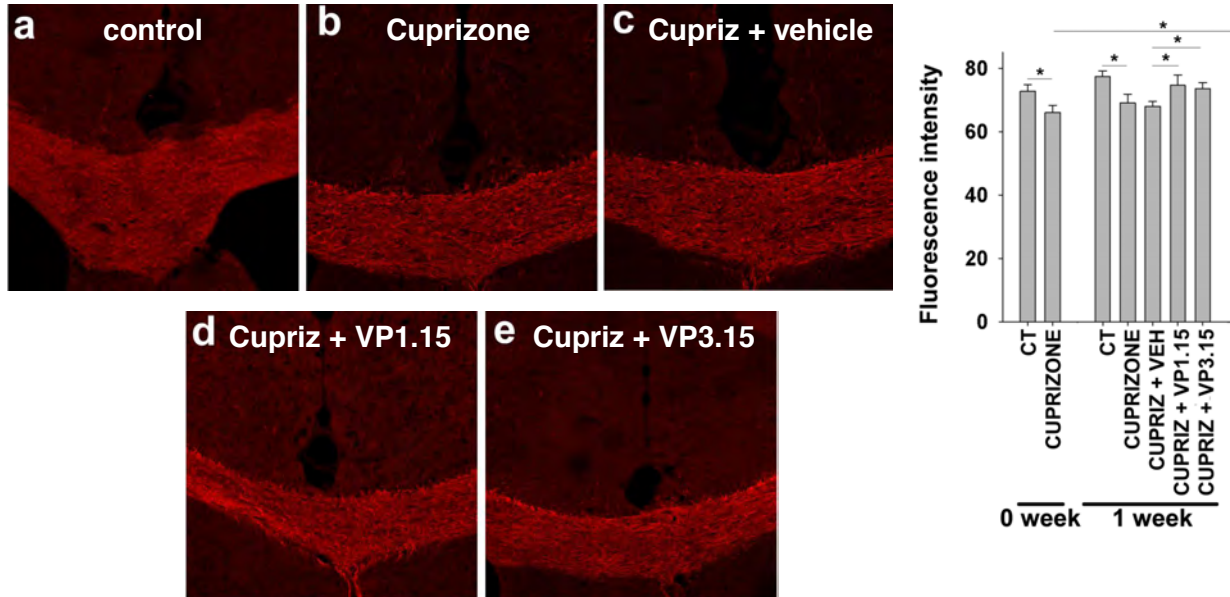


Images of electronic microscopy showing the ultrastructure of the corpus callosum of adult control mice (a) and corpus callosum of mice demyelinated by injection of LPC (b-g) and later intraperitoneally injected with the vehicle (b,e) or VP1.15 (c,f) or VP3.15 (d,g). Mice perfused 14 days post lesion were treated with two injections while mice perfused 21 DPL received one more injection

# New treatment: VP3.15

## Remyelinating activity

- **VP3.15** and **VP1.15** increase *in vivo* remyelination after the treatment with cuprizone



## Traslational research

Laboratory The valley of death Patients

**ANKAR PHARMA**  
PASSION FOR HEALING

B. Mellor, Nature 2008

*From the bench to the patient*

.....looking for a team of investors...



Clinical trials  
Phase 1

2017

(Licence to big  
pharma)



Value  
x 2-10 fold



2015

Financial needs: 2M €  
(tickets from 100.000 €)

2 years

*From the lab. to the bedside (clinical trials)*

## Conclusions



There are strategies and attitudes that allow to pave the way to the market in the drug discovery field

Only multidisciplinary teams are able to translate innovative results to society



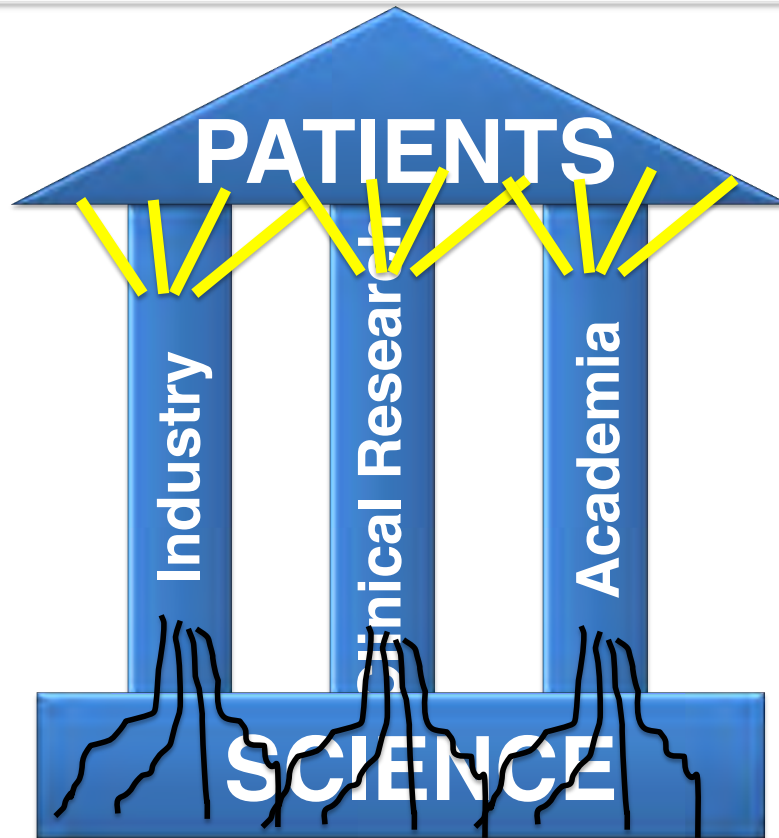
Busca un amigo biólogo  
y..... comparte lo que te  
quede de financiación...¡si  
queda!.



Private-public collaboration is an effective way to have new drugs in the future

Encuentra una empresa que crea en ti.....o....  
¡¡puedes hacerte empresario!!

# Conclusions

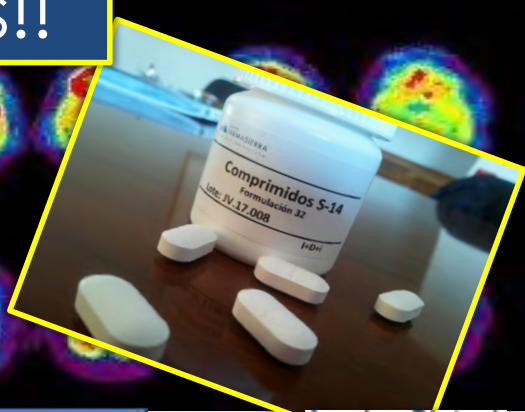


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¡¡Muchas gracias!!



autism  
therapeutics

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Araclon Biotech  
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