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…

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

- Alzheimer Disease
- Parkinson Disease
- Amyotrophic lateral Sclerosis
- Multiple sclerosis
- Stroke
- Myotonic Dystrophy
- Dravet syndrome
- Glioblastome
- Fragil X / Autism
- Schizophrenia
- Retinitis pigmentosa

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

SCIENCE
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

INCREASE COMPETITIVENESS

Chemistry
Pharmacology
Physics
Mathematics
Bioanalysis
Pharmacy
Biology
Medicine

INCREASE COMPETITIVENESS
From the lab to the market

Pharmaceutical Research and Development

- Biological screening
- Pharmacokinetics
- Pharmacodynamics
- Clinical trials (phase I, II, and III)
- Marking approval

.....in the lab .....
Birth of new drug

Preclinical discovery

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<tr>
<th>Years</th>
<th>Study population</th>
<th>Goal</th>
<th>Success Rate</th>
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<tr>
<td></td>
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<td>5000 new</td>
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<td></td>
<td>laboratory and animal studies</td>
<td>To show safety, biological activity and formulation</td>
<td>12-16 years</td>
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<td></td>
<td>IND and/or IMPD</td>
<td>20-100 healthy volunteers</td>
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<td></td>
<td>100-500 volunteers patients</td>
<td>To show safety and dose determination</td>
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<td></td>
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<td>1000-5000 volunteers patients</td>
<td>To show safety and adverse effects first</td>
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Clinical Development

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<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tr>
<td>FDA/EMA</td>
<td>Review/ Approval</td>
<td>Application for market approval</td>
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Translational research

Investment 1.000-1.500 M euros

Only 1 from 5.000 NEW molecules

Academia/Universities
Public Research Centers

Exponential growth in investment

Pharmaceutical and/or Biotechnological industries

Success Rate: 12-16 years

Failure Rate: Only 1 from 5.000 NEW molecules

Academia/Universities → Exponential growth in investment → Pharmaceutical and/or Biotechnological industries
Translational research

The valley of death

From the bench to the patient

B. Mellor, Nature 2008

Translational research

The valley of death

From the bench to the patient
Translational research

From the bench to the patient

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

- Publications
- Patents
- Excellence
- Resilience
- Productivity
- Entrepreneur

Alzheimer’s disease

- Asymptomatic phase
- Mild cognitive impairment
- Alzheimer’s Disease (Mild, Moderated, Severe)

Changes in the brain

Symptoms
Alzheimer’s disease: etiology

- Excitotoxicity
- Inflammation
- Oxidative stress
- Cholinergic system deficits

GSK-3 and AD

- Increased GSK-3 activity
- β-amyloid toxicity
- Microglia activation
- Decreased LTP


C. Hooper et al., J Neurochem. 2008, 104:1433-1439
Work-case: GSK-3 inhibitors


TDZDs: GSK-3 inhibitors

TDZDs are GSK-3 inhibitors

<table>
<thead>
<tr>
<th>TDZD</th>
<th>IC50 (µM)</th>
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<td>TDZD-15</td>
<td>3.3</td>
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<td>TDZD-19</td>
<td>1.6</td>
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<tr>
<td>TDZD-11</td>
<td>10</td>
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<tr>
<td>TDZD-16</td>
<td>2.9</td>
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<tr>
<td>TDZD-34</td>
<td>0.9</td>
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<tr>
<td>TDZD-39</td>
<td>2.5</td>
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<tr>
<td>TDZD-95</td>
<td>5</td>
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<tr>
<td>TDZD-111</td>
<td>3</td>
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<tr>
<td>TDZD-112</td>
<td>1.3</td>
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<td>TDZD-115</td>
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<td>TDZD-117</td>
<td>9.6</td>
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<td>TDZD-118</td>
<td>3</td>
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<td>TDZD-122</td>
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TDZDs: GSK-3 inhibitors


TDZDs do not compete with ATP nor the substrate

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

NP-12 (Tideglusib)
Morris Water Maze

Increase on spatial learning ability and memory


TDZDs: tideglusib

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

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
**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


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**TDZDs: tideglusib**

…..but…..

**Clinical Development**

<table>
<thead>
<tr>
<th>Phase</th>
<th>I</th>
<th>II</th>
<th>III</th>
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<tr>
<td>1.5</td>
<td>2</td>
<td>3.5</td>
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</table>

- >150 Healthy volunteers young and adults
- 3 studies: 30 patients 125 PSP 250 patients
- 1000-5000 volunteers patients

- Tideglusib is safe in man and it can be clinically modulated
- Tideglusib is safe in patients. Efficacy signs
- Efficacy confirmation, monitor of adverse effects and long term treatments

**Success Rate**

1.000 Evaluated new compounds
GSK-3 inhibitors: new avenues

Fragile X Syndrome (Autism)
GSK-3 inhibitors reverse deficits in Long–term potentiation and cognition in Fragile X mice

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

TDZDs: tideglusib

Preclinical discovery

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<tr>
<td>6-8</td>
<td>Laboratory and animal studies</td>
<td>To show safety, biological activity and formulation</td>
<td>5,000 evaluated new compounds</td>
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Phase I Phase II Phase III

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<tr>
<td>FDA/EMA 1.5</td>
<td>Review/Approval</td>
<td>Orphan drug Fast-track</td>
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Tideglusib is safe in patients. Efficacy signs

TDZDs: tideglusib

FDA/EMA

1.5

Review/Approval

Orphan drug

Fast-track

1

Registered drug

Efficacy confirmation; monitor of adverse effects and long term treatments

Clinical Development

IND and/or IMPD

Phase I

Phase II

Phase III

1000-5000 volunteers patients

1000-5000 volunteers patients

1000-5000 volunteers patients

1.5

Review/Approval

Orphan drug

Fast-track
Methodology

Pharmacophore definition and chemical library search
SAR and QSAR studies (lineals, tridimensionals, etc...)
Phenotypic screening of chemical libraries
Drug repurposing

Drug-receptor interaction studies (*in silico*, RMN, X-Ray)
Medicinal chemistry programs directed to optimize drug-receptor interaction
Screening on the target (*in silico*, experimental)
De novo design (fragments)

Structure (tridimensional) known +
unknown -

Drug

Receptor

Work-case

Neurodegenerative diseases: Unknown etiology

Search of innovative drug for Parkinson Disease

Forward chemical genetics

Cells or animals
Phenotypic assay
Molecule identification
Target identification
Phenotype based
Neuroprotection on SH-SY5Y cells treated with 6-OHDPDA. S14 mechanism of action


PDE7 inhibitor for PD therapy

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

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<thead>
<tr>
<th></th>
<th>Ipsilateral</th>
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<tr>
<td>Basal</td>
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<tr>
<td>LPS</td>
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<tr>
<td>LPS+S14</td>
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**6-OHDPDA model:** Decrease dopaminergic cell death in striado

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PDE7 inhibitor for PD therapy

**Target validation by classical genetics methodology (siRNAs)**

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<th>LPS model</th>
<th>6-OHDPA model:</th>
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<tr>
<td>Control</td>
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<tr>
<td>Non-targeting shPDE7+LPS</td>
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<tr>
<td>shPDE7B+LPS</td>
<td>shPDE7B+6OHDA</td>
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**PDE7 inhibitor for PD therapy**

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

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**PDE7 inhibitor for PD therapy**

*In vivo neurogenesis 6-OHDA model*

**S14 increases dopaminergic neurons neurogenesis**


**S14: new drug candidate for PD**

<table>
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<th>Preclinical discovery</th>
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<td>Phase II 2</td>
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5 Compounds in clinical trials

**Clinical Development**

**Clinical Development**

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Methodology

**Emil Fisher**
Chemistry Nobel Prize 1902

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

(a) 
- Activation of CNS-specific T cell
- Recruitment of cells
- Release of toxins
- Activation of microglia
- Myelin phagocyte
- Damage

(b) 
- Activation of immune response
- Recruitment of cells
- Autoreactive T cell
- Macrophage
- Myelin debris
- Apoptosis
- Oligodendrocytes
- Damage
- Neuron

Autoimmune

Neurodegenerative

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
  - Furane derivatives
  - Neuronal Network based drug discovery
  - 5-imino-thiazoles
- Pharmacophoric search on 3D-Compound Data Bases

Experimental IC50 PDE7 (μM)

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| 1.02 | 1.44 | 1.64 | 0.38 | 1.13 | 1.11 | 0.86 | 1.50 | 4.36 | 0.89 | 0.81 | 0.85 | 1.18 | 0.78 | 34.8

Predicted IC50 PDE7 (μM)

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Dual GSK-3/PDE7 inhibitors

5-IMINO TIADIAZOLES

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

Valle Palomo, Daniel I. Perez, Concepcion Perez, Jose A. Morales-Garcia, Ignacio Soteras, Sandra Alonso-Gil, Arantxa Encinas, Ana Castro, Nuria E. Campillo, Ana Perez-Castillo, Carmen Gil and Ana Martinez

Instituto de Química Médica-CSIC, Juan de la Cierva 3, 28006 Madrid, Spain
Instituto de Investigaciones Biomédicas (CSIC-UAM) and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Arturo Soria 4, 28029 Madrid, Spain
**New treatment: VP3.15**

VP3.15 is a dual allosteric inhibitor of GSK-3 and PDE7. It may delicately restore the homeostasis in complex events such as inflammation and neurodegeneration.


---

**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 Theiller virus models and promote the differentiation of OPCs.

*Figure showing the binding sites of cAMP and allosteric inhibitors to PDE7.*

**New treatment: VP3.15**

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

*Graph showing the number of CNPase+*Olig2+ cells/total number Olig2+ cells.

**Immunofluorescence images** to detect the expression of CNPasa and Olig2 on adult OPCs from human cerebral cortex, after 5 days in differentiation medium in the presence of VP3.15 (1 µM). 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 remyelization 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

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 the in vivo remyelization in mice treated with lysophosphatidyl choline (LPC)

Lesioned area to study remyelination in the corpus callosum. B) Brain dissected for being studied
New treatment: VP3.15

Remyelinating activity

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

Traslational research

**Laboratory**

**The valley of death**

**Patients**

*From the bench to the patient*
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.

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

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

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

Acknowledgements

Dr. C. Gil
Dr. N. Campillo
Dr. D.I. Perez
Dr. R. Pérez
Dr. V. Palomo
Dr. M. Redondo
Dr. I. G-Salado
Dr. J. Cumella
Dr. I. Soteras
Dr. S. Petyt
Dr. P. Ceballos

A. Garcia
J. Zaldívar
M. Duarte
V. Sebastian
E. Rojas
M. Bello
C. Fernandez
T. Cantuaria
L. Martínez
A. Espasa
N. De la Cruz

Dr. J. DeFelipe
Dr. C. Guaza
Dr. J.L. Trejo
Dr. A. P-Castillo
Dr. C. Pérez
Dr. S. Conde
Dr. G. Mengod
Dr. J. Avila

Dr. J. DeFelipe
Dr. C. Guaza
Dr. J.L. Trejo

Dr. A. P-Castillo
Dr. C. Pérez
Dr. S. Conde

Dr. J. Avila

Dr. M.I. Loza
Dr. T. Lipina
Dr. J. Woodgett

Dr. E. Carro
Dr. F. J. Luque
Dr. O. Valverde
Dr. MA. Moro

Dr. J. H. Kenny
Dr. J. Woodgett

Dr. H. Eldar-Finkelman
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Dr. F. VanLeuven
¡Muchas gracias!!