



# integrando la Innovación

X Congreso Nacional de  
**ALZHEIMER**  
GIJÓN. 8, 9, 10 y 11 /NOV/ 2023

## Luchar contra la neuroinflamación como estrategia terapéutica en la enfermedad de Alzheimer

Dra. Mercè Pallàs Lliberia

Departament de Farmacologia, Toxicologia i Química  
Terapèutica

Facultat de Farmàcia. Institut de Neurociències  
Universitat de Barcelona



UNIVERSITAT DE  
BARCELONA



Institut de Neurociències  
UNIVERSITAT DE BARCELONA



MCP | Medicinal  
Chemistry &  
Pharmacology



EXCELENCIA  
MARÍA  
DE MAEZTU

ciber | NED

CENTRO DE INVESTIGACIÓN  
BIOMÉDICA EN RED  
Enfermedades Neurodegenerativas



MINISTERIO  
DE CIENCIA  
E INNOVACIÓN



Financiado por  
la Unión Europea  
NextGenerationEU



Plan de Recuperación,  
Transformación y  
Resiliencia



AGENCIA  
ESTATAL DE  
INVESTIGACIÓN



**Inhibidores de AChE**  
Donepezilo  
Galantamina  
Rivastigmina



**Ninguno de los tratamientos disponibles curan ni frenan la progresión de la enfermedad**

**Antagonistas del receptor NMDA**  
Memantina



**Tratamiento dual**  
Inhibidores de AChE +  
Memantina



**Anticuerpos monoclonales**  
Anti-A $\beta$

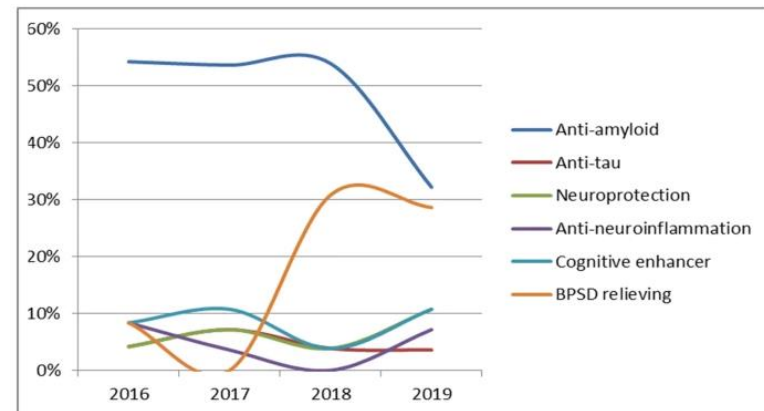
Review | [Open Access](#) | [Published: 06 January 2020](#)

## Clinical trials of new drugs for Alzheimer disease

[Li-Kai Huang](#), [Shu-Ping Chao](#) & [Chaur-Jong Hu](#)

[Journal of Biomedical Science](#) **27**, Article number: 18 (2020) | [Cite this article](#)

**49k** Accesses | **210** Citations & **280** Altmetric | [Metrics](#)



**% de ensayos clínicos en fase 3 por la MA**



integrando la Innovación

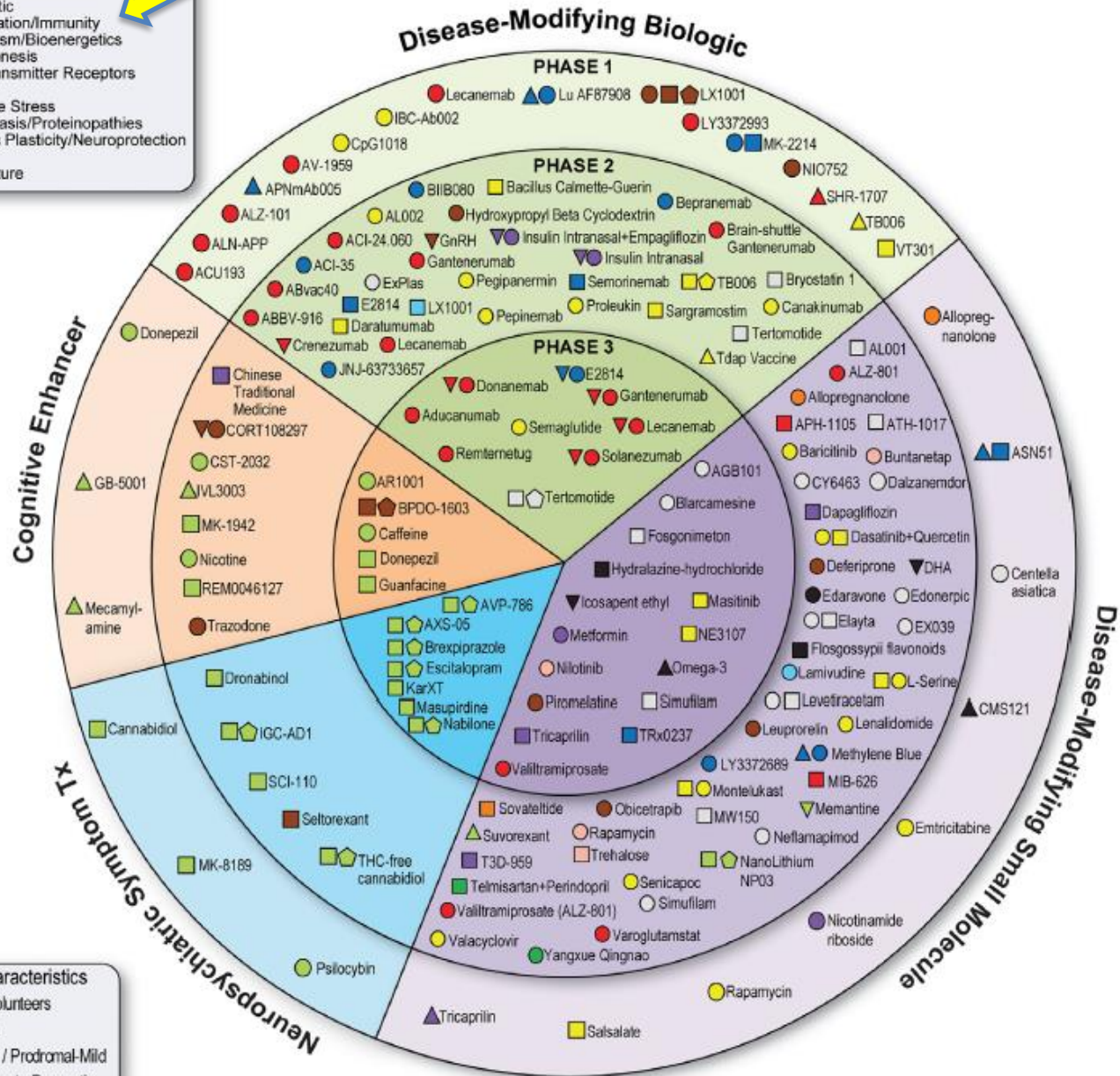
# 2023 Alzheimer's Drug Development Pipeline

**Target Class**

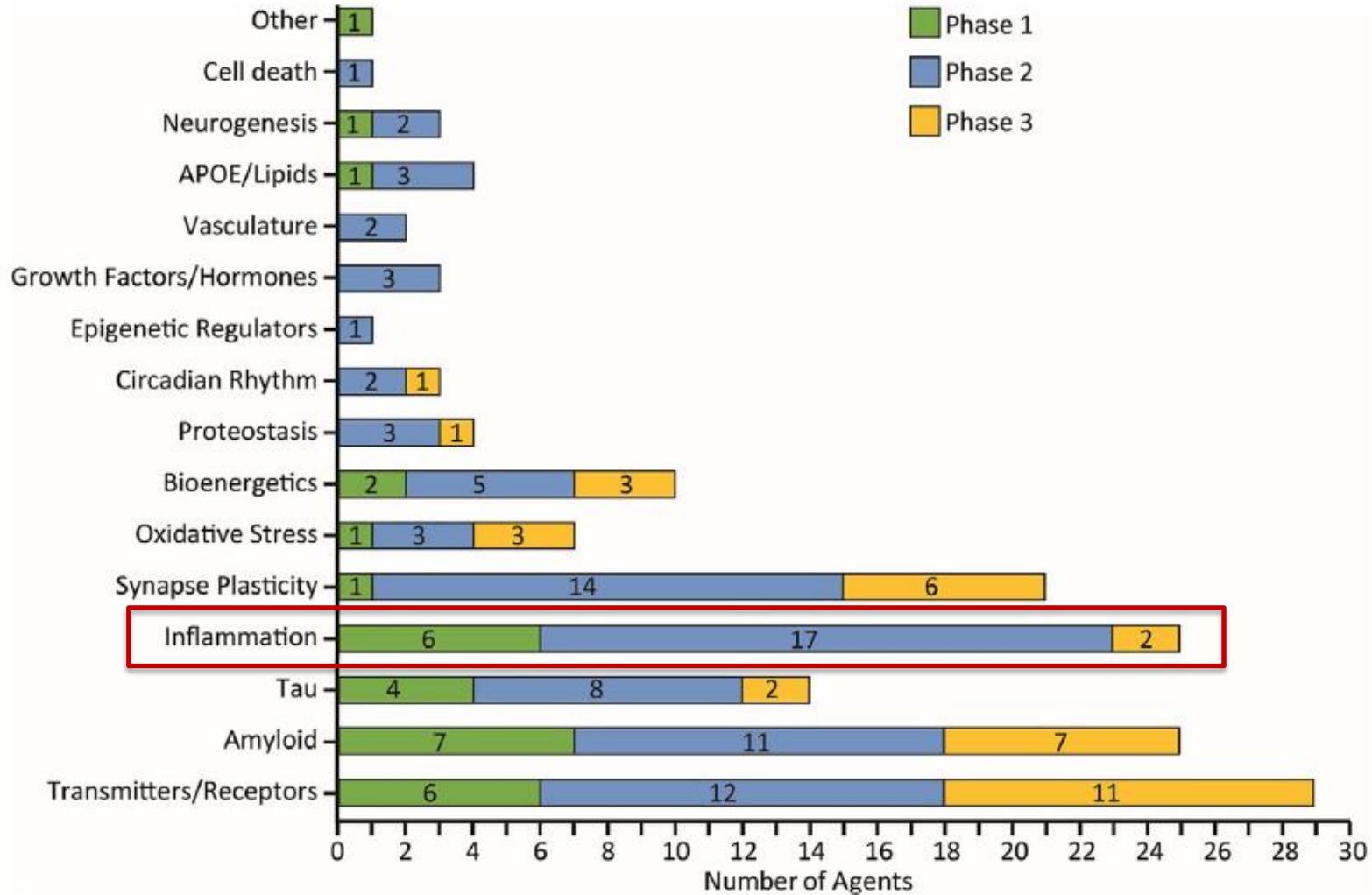
- Amyloid
- Epigenetic
- Inflammation/Immunity
- Metabolism/Bioenergetics
- Neurogenesis
- Neurotransmitter Receptors
- Other
- Oxidative Stress
- Proteostasis/Proteinopathies
- Synaptic Plasticity/Neuroprotection
- Tau
- Vasculature

**Subject Characteristics**

- ▲ Healthy Volunteers
- ▼ Preclinical
- Prodromal / Prodromal-Mild
- Mild-Moderate Dementia
- ◆ Severe Dementia



Cummings et al., Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement* (N Y). 2023 May 25;9(2):e12385.

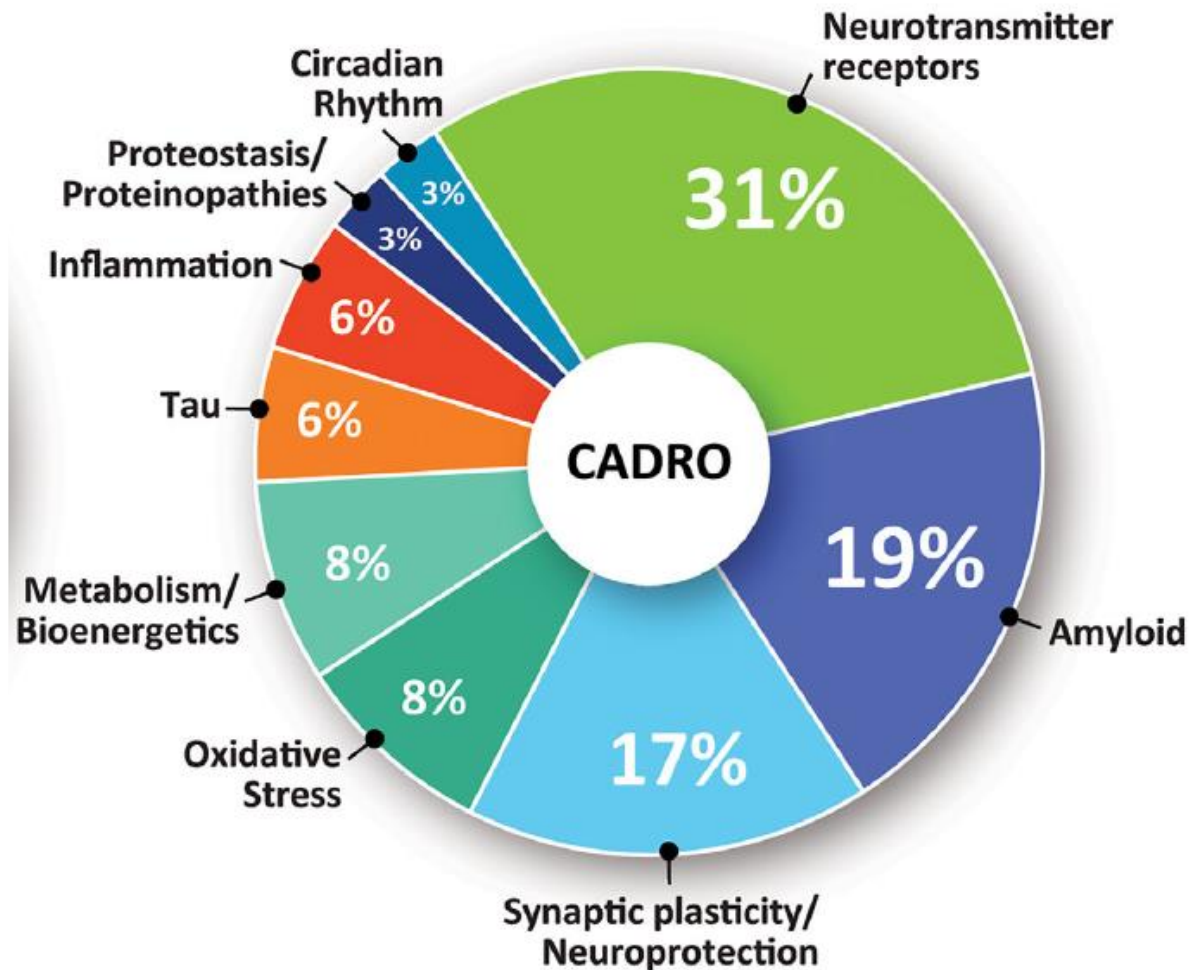


- **Masitinib**

Tyrosine kinase inhibitor exhibits neuroprotection via inhibition of mast cell and microglia/macrophage activity

- **NE3107**

Beta-androstenetriol with anti-inflammatory and insulin signaling effects via ERK 1 and 2



# ETAPAS DEL PROCESO DE DESCUBRIMIENTO Y DESARROLLO DE FÁRMACOS

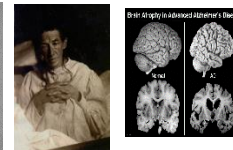
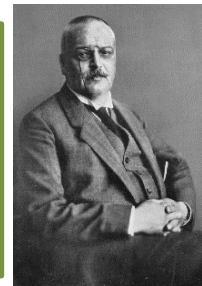


## IDENTIFICACIÓN DE LA DIANA

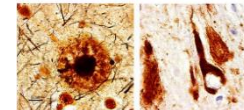


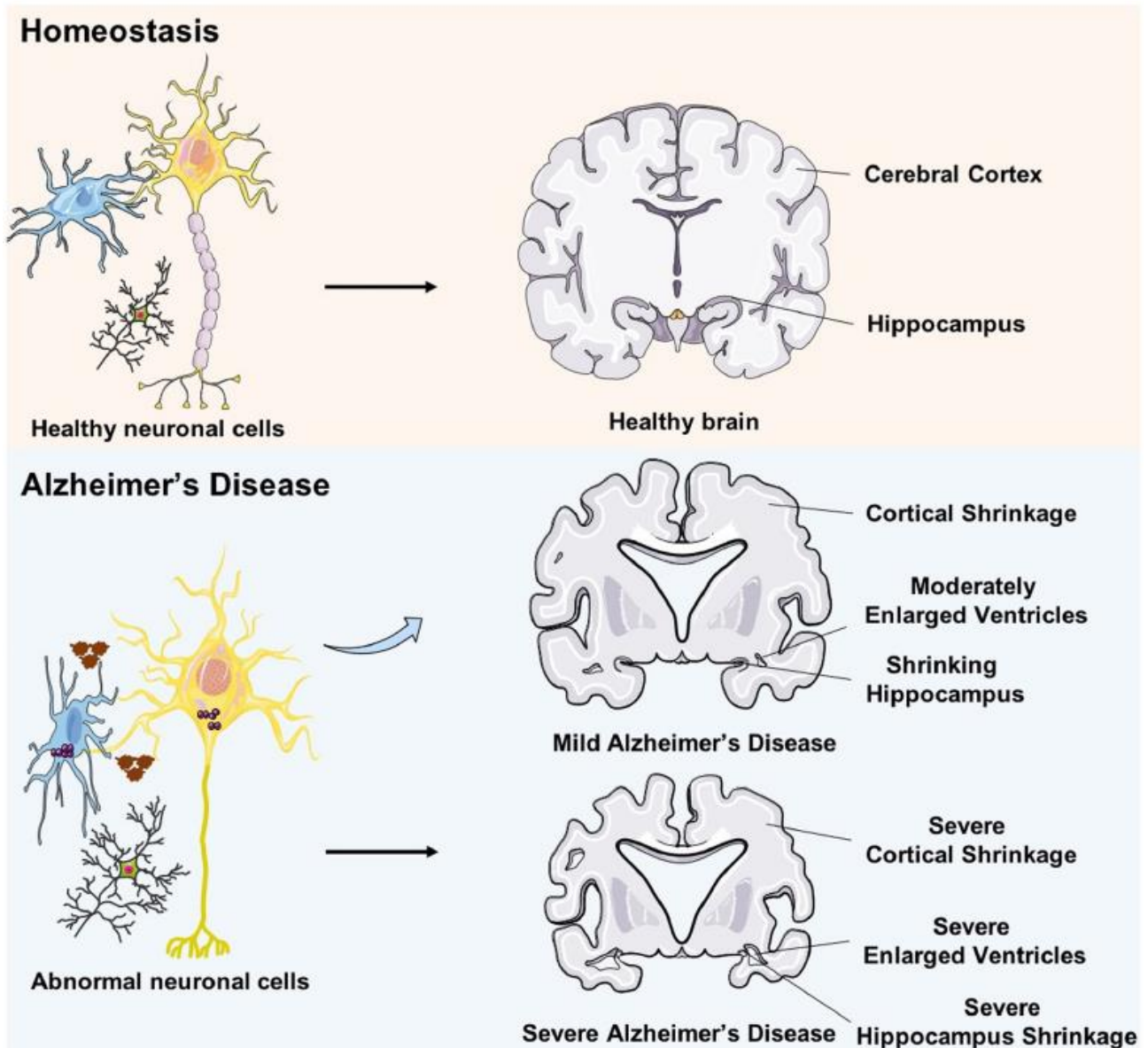
- Target Discovery
- Target Deconvolution

PRIMER PASO  
Comprender la enfermedad:  
Alzheimer



Plaques Neurofibrillary Tangles

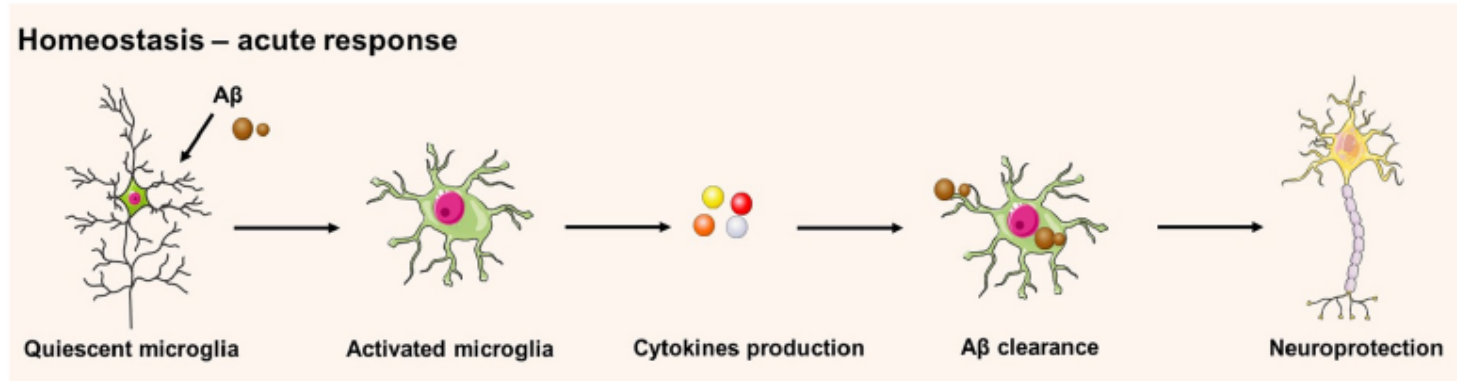






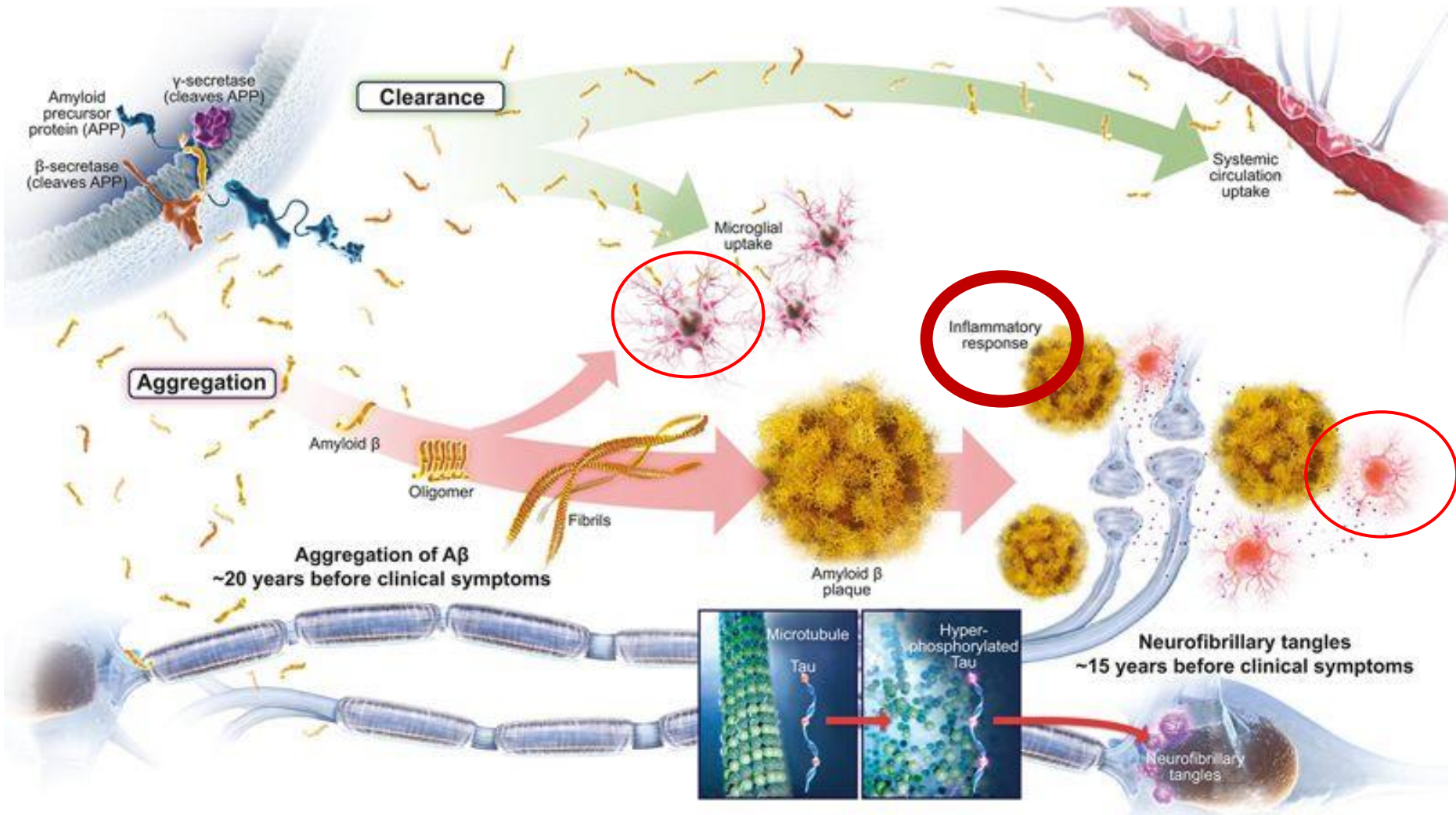
# FISIOPATOLOGÍA DE LA ENFERMEDAD DE ALZHEIMER

## Neuroinflamación



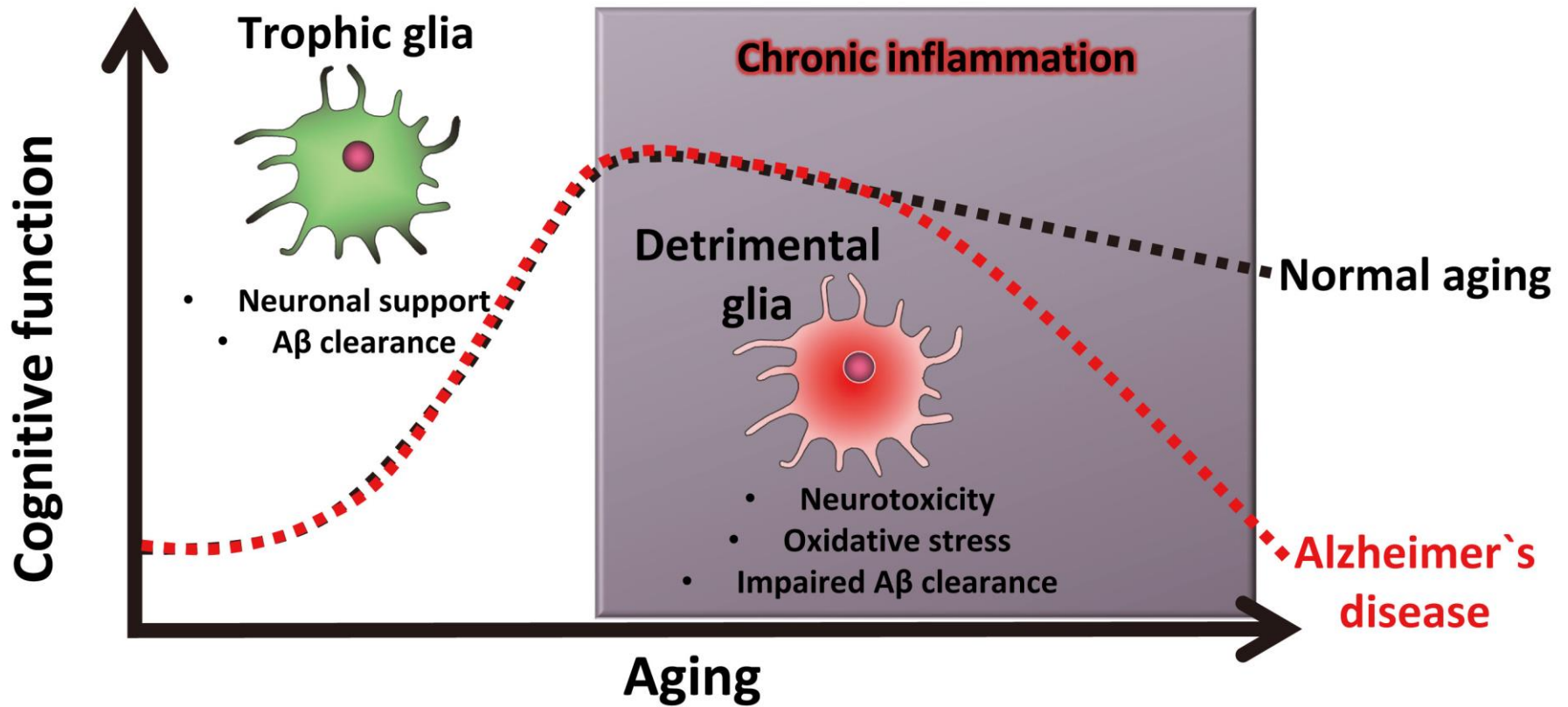
# FISIOPATOLOGÍA DE LA ENFERMEDAD DE ALZHEIMER

## Neuroinflamación



# FISIOPATOLOGÍA DE LA ENFERMEDAD DE ALZHEIMER

## Neuroinflamación



## **IDENTIFICACIÓN DE LA DIANA**



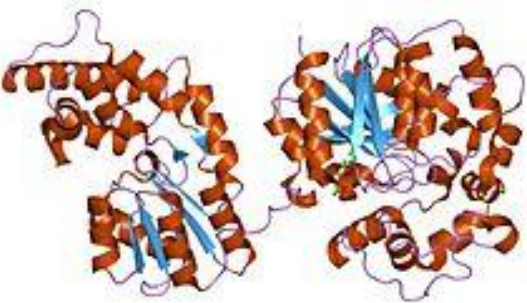
**Conocer la patología  
Identificación y  
validación de la diana**

**SEGUNDO PASO**  
Identificación de la diana

## IDENTIFICACIÓN DE LA DIANA



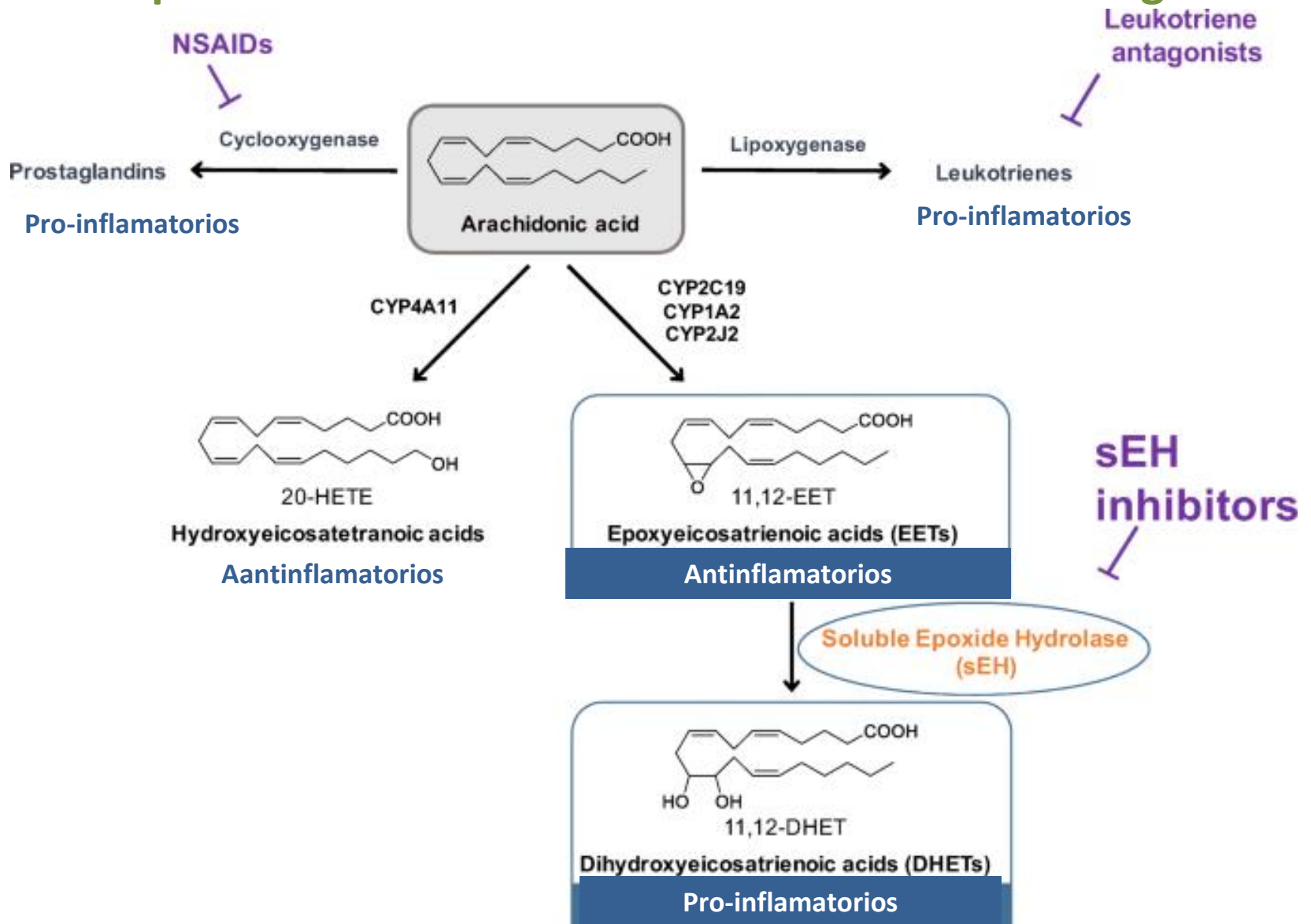
Conocer la patología  
Identificación y  
validación de la diana



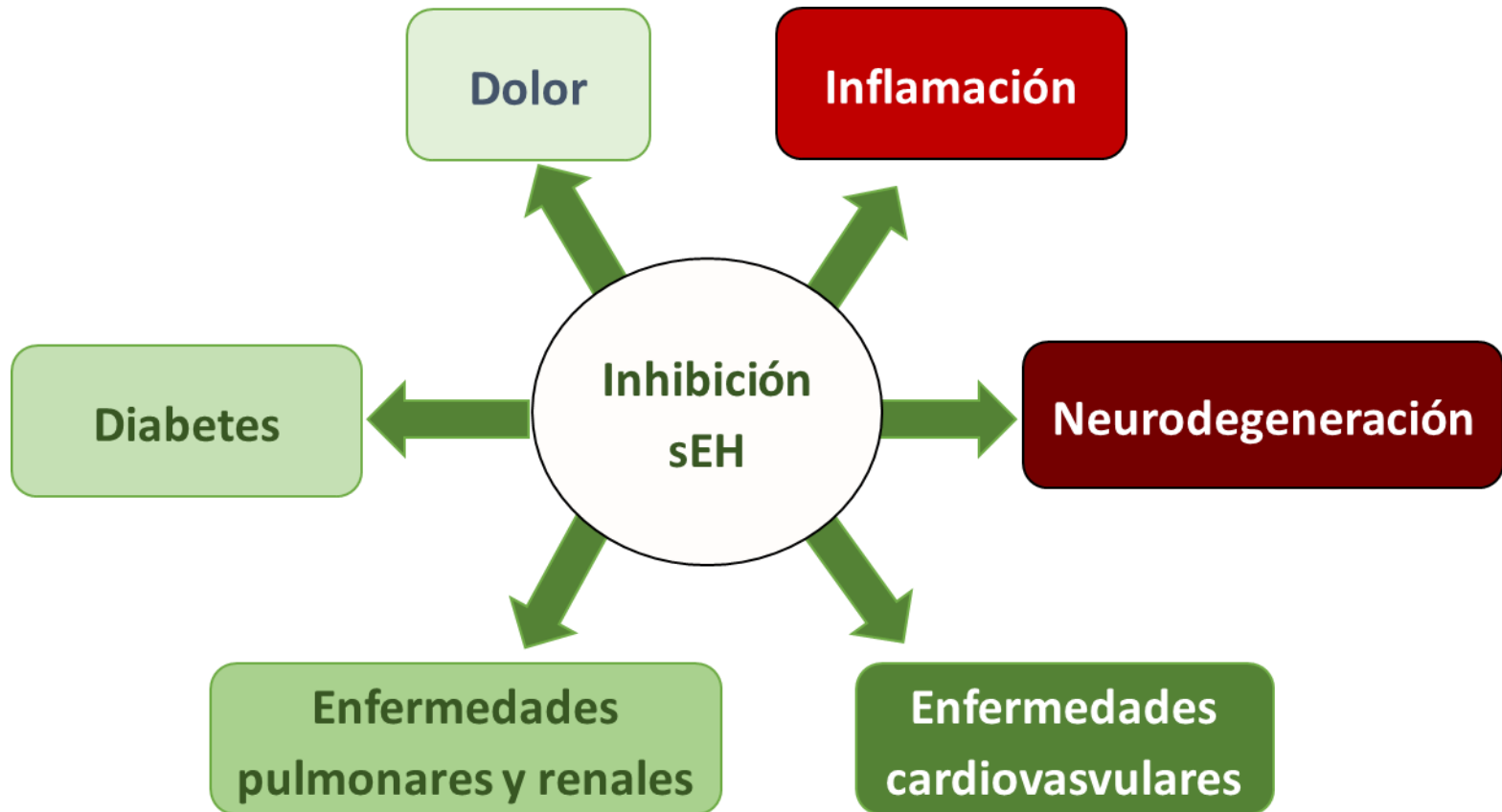
SEGUNDO PASO  
Identificación de una (nueva) diana

sEH como diana farmacológica

# Epóxido hidrolasa soluble como diana farmacológica



## Epóxido hidrolasa soluble como diana farmacológica





# sEH como diana farmacológica: primeras evidencias

Wu et al. *Journal of Biomedical Science* (2015) 22:94  
DOI 10.1186/s12929-015-0202-7

科技部 Ministry of Science and Technology

The cost of publication in *Journal of Biomedical Science* is borne by the Ministry of Science and Technology, Taiwan.



JOURNAL OF  
BIOMEDICAL SCIENCE

RESEARCH

Open Access



## Soluble epoxide hydrolase inhibitor enhances synaptic neurotransmission and plasticity in mouse prefrontal cortex

Han-Fang Wu<sup>1</sup>, Hsin-Ju Yen<sup>1</sup>, Chi-Chen Huang<sup>2,3</sup>, Yi-Chao Lee<sup>2,3</sup>, Su-Zhen Wu<sup>4</sup>, Tzong-Shyuan Lee<sup>1,5</sup> and Hui-Ching Lin<sup>1,2,5\*</sup>

Published: 08 June 2018

The Journals of  
GERONTOLOGY® SERIES a

ACCEPTED MANUSCRIPT

## Obesity in Aging Exacerbates Neuroinflammation, Dysregulating Synaptic Function-related Genes and Altering Eicosanoid Synthesis in the Mouse Hippocampus: Potential Role in Impaired Synaptic Plasticity and Cognitive Decline

Marta Noa Valcarcel-Ares, Ph.D, Zsuzsanna Tucsek, Ph.D, Tamas Kiss, MD, Cory B Giles, Ph.D, Stefano Tarantini, Ph.D, Andriy Yabluchanskiy, M.D., Ph.D, Priya Balasubramanian, Ph.D, Tripti Gautam, M.S, Veronica Galvan, Ph.D, Praveen Ballabh, M.D Arlan Richardson, Ph.D, Willard M Freeman, Ph.D, Jonathan D Wren, Ph.D, Ferenc Deak, M.D., Ph.D, Zoltan Ungvari, M.D., Ph.D, Anna Csiszar, M.D., Ph.D ✉

*Am J Physiol Heart Circ Physiol* 306: H475–H484, 2014.  
First published November 27, 2013; doi:10.1152/ajpheart.00001.2013.

CALL FOR PAPERS | *Mitochondria in Cardiovascular Physiology and Disease*

## Epoxyeicosatrienoic acids pretreatment improves amyloid $\beta$ -induced mitochondrial dysfunction in cultured rat hippocampal astrocytes

Pallabi Sarkar,<sup>1</sup> Ivan Zaja,<sup>2</sup> Martin Bienengraeber,<sup>2</sup> Kevin R. Rarick,<sup>1</sup> Maia Terashvili,<sup>1</sup> Scott Canfield,<sup>1</sup> John R. Falck,<sup>3</sup> and David R. Harder<sup>1</sup>

<sup>1</sup>Department of Physiology, Cardiovascular Center, Medical College of Wisconsin, Milwaukee, Wisconsin; <sup>2</sup>Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, Wisconsin; and <sup>3</sup>Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, Texas



Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators

journal homepage: [www.elsevier.com/locate/prostaglandins](http://www.elsevier.com/locate/prostaglandins)



Prostaglandins and Other Lipid Mediators 136 (2018) 84–89

## An inhibitor of soluble epoxide hydrolase ameliorates diabetes-induced learning and memory impairment in rats

Nathani Minaz<sup>a</sup>, Rema Razdan<sup>a</sup>, Bruce D. Hammock<sup>b</sup>, Sumanta Kumar Goswami<sup>c,\*</sup>

<sup>a</sup> Department of Pharmacology, Al-Ameen College of Pharmacy, Bangalore, Karnataka, India

<sup>b</sup> Department of Entomology and Nematology, and Comprehensive Cancer Center, University of California, Davis, CA, USA

<sup>c</sup> Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA, USA



# Soluble epoxide hydrolase plays a key role in the pathogenesis of Parkinson's disease

Qian Ren<sup>a</sup>, Min Ma<sup>a</sup>, Jun Yang<sup>b,c</sup>, Risa Nonaka<sup>d,e,1</sup>, Akihiro Yamaguchi<sup>e</sup>, Kei-ichi Ishikawa<sup>d,e</sup>, Kenta Kobayashi<sup>f</sup>, Shigeo Murayama<sup>g</sup>, Sung Hee Hwang<sup>b,c</sup>, Shinji Saiki<sup>d</sup>, Wado Akamatsu<sup>e</sup>, Nobutaka Hattori<sup>d</sup>, Bruce D. Hammock<sup>b,c,2</sup>, and Kenji Hashimoto<sup>a,2</sup>

<sup>a</sup>Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, 260-8670 Chiba, Japan; <sup>b</sup>Department of Entomology and Nematology, University of California, Davis, CA 95616; <sup>c</sup>UC Davis Comprehensive Cancer Center, University of California, Davis, CA 95616; <sup>d</sup>Department of Neurology, Juntendo University School of Medicine, 113-8431 Tokyo, Japan; <sup>e</sup>Center for Genomic and Regenerative Medicine, Juntendo University School of Medicine, 113-8431 Tokyo, Japan; <sup>f</sup>Section of Viral Vector Development, National Institute of Physiological Sciences, 444-8585 Okazaki, Japan; and <sup>g</sup>Department of Neurology and Neuropathology (Brain Bank for Aging Research), Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, 173-0015 Tokyo, Japan

Contributed by Bruce D. Hammock. April 16, 2018 (sent for review February 16, 2018; reviewed by Cesar Borlongan and Anumantha G. Kanthasamy)

6322–6324 | PNAS | June 19, 2018 | vol. 115 | no. 25

Neurotherapeutics (2020) 17:1825–1835  
<https://doi.org/10.1007/s13311-020-00854-1>

ORIGINAL ARTICLE



## Pharmacological Inhibition of Soluble Epoxide Hydrolase as a New Therapy for Alzheimer's Disease

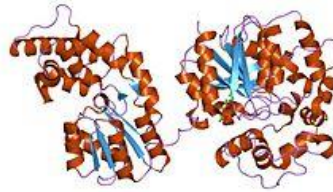
Christian Griñán-Ferré<sup>1</sup> • Sandra Codony<sup>2</sup> • Eugènia Pujol<sup>2</sup> • Jun Yang<sup>3</sup> • Rosana Leiva<sup>2</sup> • Carmen Escolano<sup>2</sup> • Dolors Puigoriol-Illamola<sup>1</sup> • Júlia Companys-Alemaný<sup>1</sup> • Rubén Corpas<sup>4,5</sup> • Coral Sanfeliu<sup>4,5</sup> • Belen Pérez<sup>6</sup> • M. Isabel Loza<sup>7</sup> • José Brea<sup>7</sup> • Christophe Morisseau<sup>3</sup> • Bruce D. Hammock<sup>3</sup> • Santiago Vázquez<sup>2</sup> • Mercè Pallàs<sup>1</sup> • Carles Galdeano<sup>8</sup>

## IDENTIFICACIÓN DE LA DIANA



**Conocer la patología  
Identificación y  
validación de la diana**

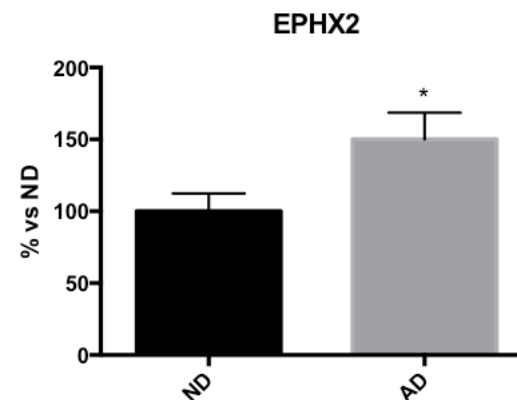
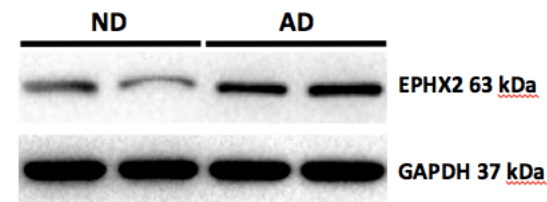
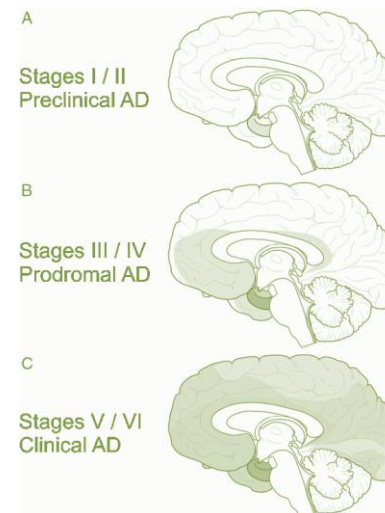
## sEH como diana farmacológica



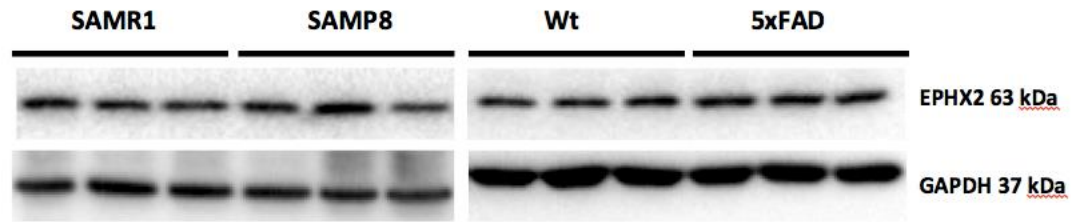
Es el proceso se vincula una diana molecular con una acción farmacológica que conduce a una respuesta terapéutica en una enfermedad. Es obligatorio demostrar que:

- 1.-La diana se expresa en las células/tejidos relevantes para la enfermedad,**
- 2.-Puede ser modulada directamente por un fármaco o molécula similar a un fármaco con una potencia adecuada en el ensayo bioquímico, y
- 3.-La modulación de diana en modelos celulares y/o animales mejora el fenotipo de la enfermedad

GENDE R	AGE	POSTMORTEM DELAY	DIAGNOSIS
Male	85	5h 45min	Control
Male	78	2h 15min	Control
Male	79	7h	Control
Male	93	7h 20min	AD BRAAK STAGE V/C
Female	82	1h 45min	AD BRAAK STAGE V/B
Female	72	9h 30min	AD BRAAK STAGE V/B
Female	75	4h 15min	AD BRAAK STAGE V/B



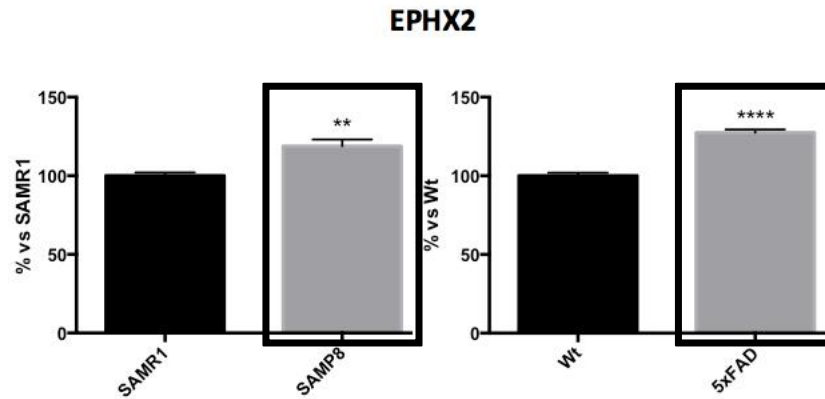
N = 3-4. \*p < 0,05 vs. Non-demented



♂ SAMP8



Modelo de ratón de deterioro cognitivo relacionados con la edad



♂ 5XFAD

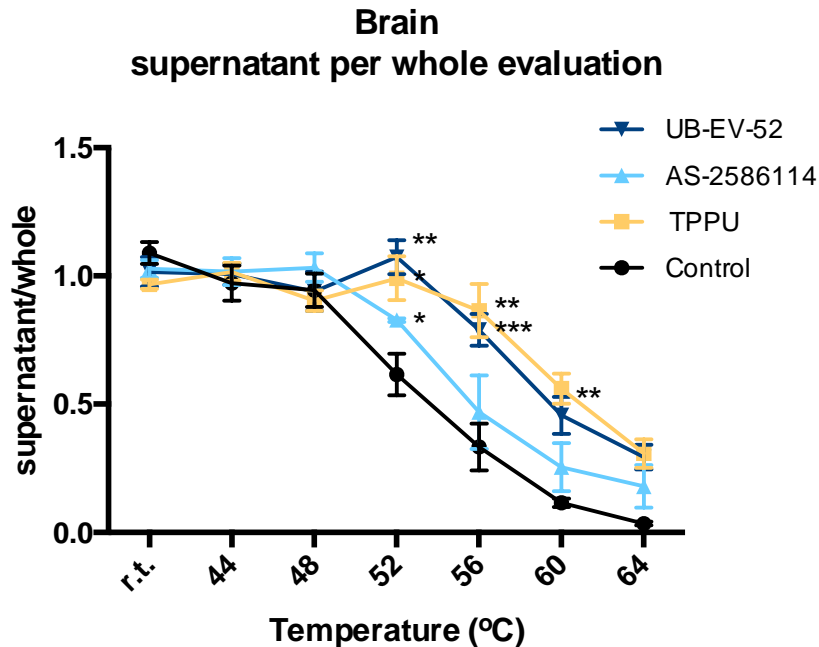
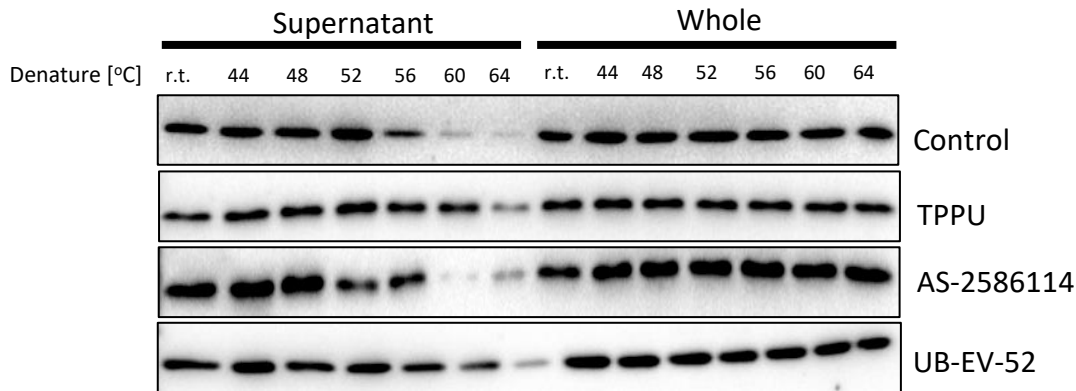


Ratón transgénico modelo de AD

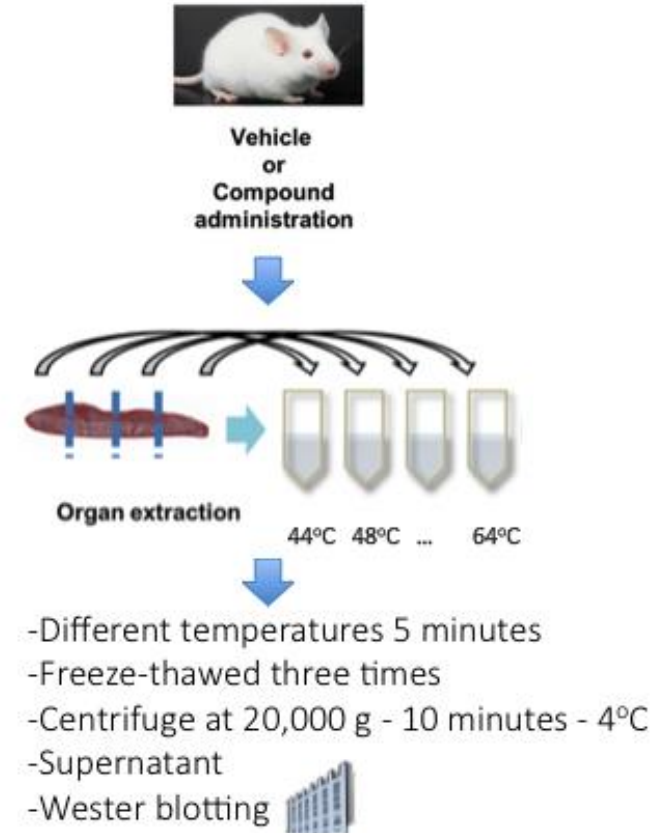
N = 12-14. \*\*p<0,01 vs. SAMR1

N = 12-14. \*\*\*\*p<0,001 vs. Wt

# sEH validation: In vivo Brain CETSA evaluation



## Experimental procedures for *in vivo* CETSA



Confirm Target Engagement  
of our selected compound UB-EV-52

N= 3 for each compound. \*p<0.05 vs. RT  
\*\*p<0,01 vs. RT; \*\*\*p<0,001 vs. RT

# sEH como diana farmacológica

## IDENTIFICACIÓN DE LA DIANA



- Conocer la patología
- Identificación y validación de la diana

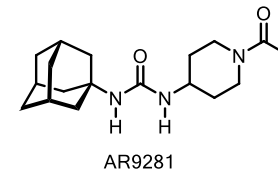


## IDENTIFICACIÓN DEL NUEVO COMPUESTO Y OPTIMIZACIÓN

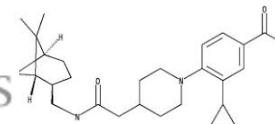


- Nueva síntesis
- Compuestos ya existentes

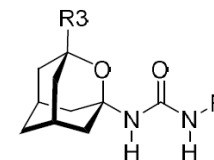
**UC DAVIS**  
UNIVERSITY OF CALIFORNIA



**astellas**



 **UNIVERSITAT DE  
BARCELONA**



2.-Puede ser modulada directamente por un fármaco o molécula similar a un fármaco con potencia adecuada en ensayo bioquímico

# sEH como diana farmacológica

## IDENTIFICACIÓN DE LA DIANA

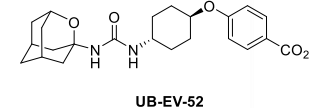
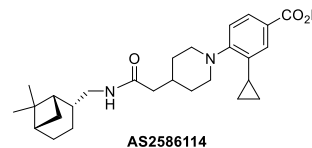
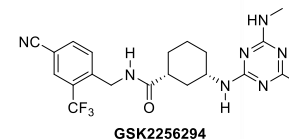
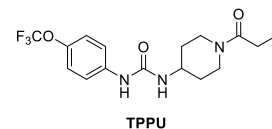


**Conocer la patología  
Identificación y  
validación de la diana**

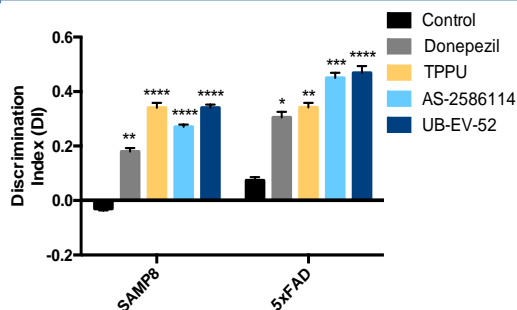
## IDENTIFICACIÓN DEL NUEVO COMPUESTO Y OPTIMIZACIÓN



**Nueva síntesis  
Compuestos ya  
existentes**



3.-La modulación de diana en modelos celulares y/o animales mejora el fenotipo de la enfermedad



Neurotherapeutics (2020) 17:1825–1835  
<https://doi.org/10.1007/s13311-020-00854-1>

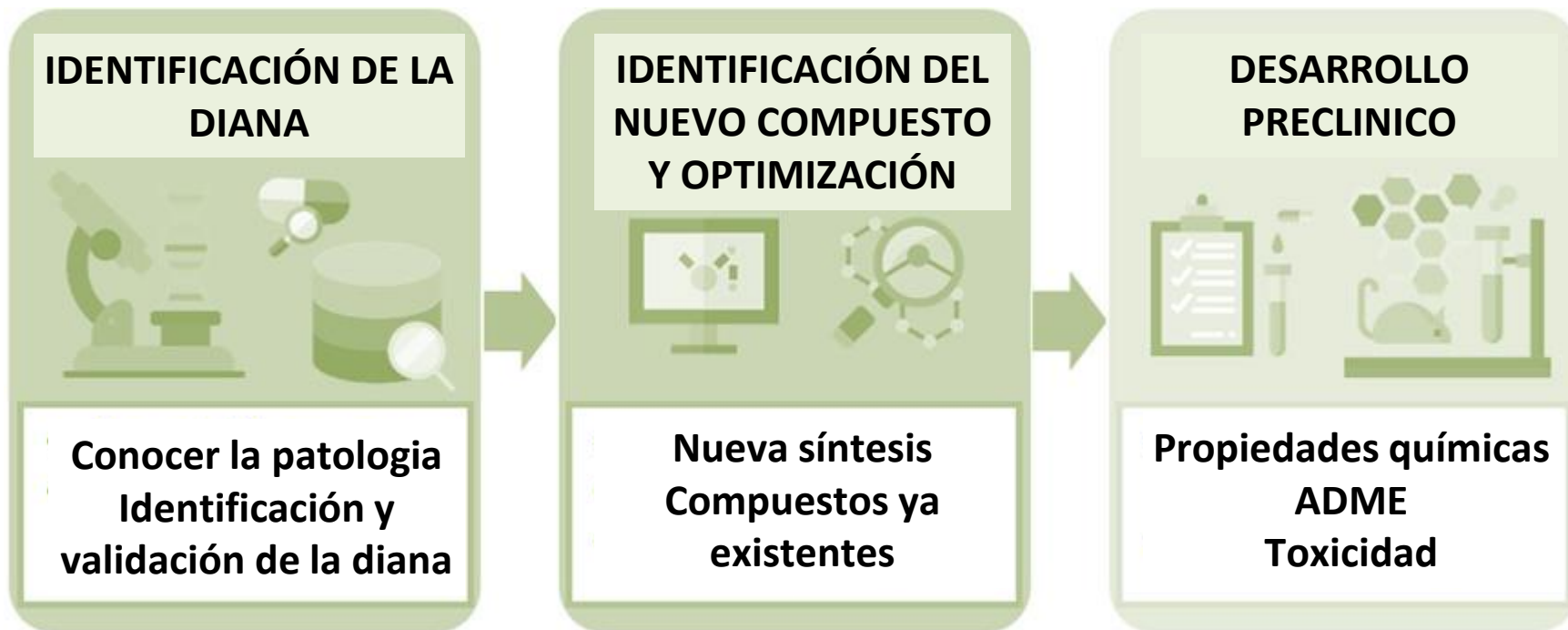
ORIGINAL ARTICLE



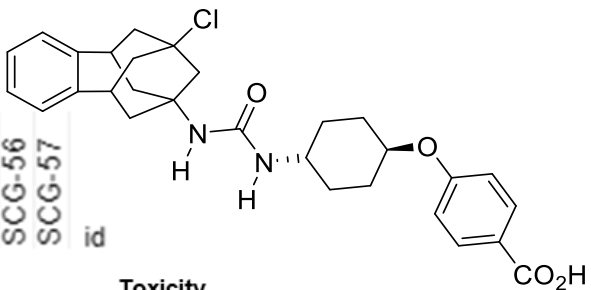
## Pharmacological Inhibition of Soluble Epoxide Hydrolase as a New Therapy for Alzheimer's Disease

Christian Griñán-Ferré<sup>1</sup> · Sandra Codony<sup>2</sup> · Eugènia Pujol<sup>2</sup> · Jun Yang<sup>3</sup> · Rosana Leiva<sup>2</sup> · Carmen Escolano<sup>2</sup> · Dolors Puigoriol-Illamola<sup>1</sup> · Júlia Companys-Alemany<sup>1</sup> · Rubén Corpas<sup>4,5</sup> · Coral Sanfeliu<sup>4,5</sup> · Belen Pérez<sup>6</sup> · M. Isabel Loza<sup>7</sup> · José Brea<sup>7</sup> · Christophe Morisseau<sup>3</sup> · Bruce D. Hammock<sup>3</sup> · Santiago Vázquez<sup>2</sup> · Mercè Pallàs<sup>1</sup> · Carles Galdeano<sup>8</sup>

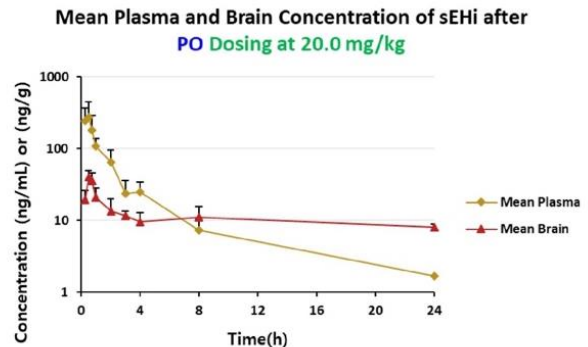
# sEH como diana farmacológica



id	Ctrl	AbO	SCG-50	SCG-51	SCG-55	SCG-54	BJ-02	SCG-60	BJ-05	BJ-01	BJ-06	JML-75	JML-101	JML-99	SCG-59	BJ-03	SCG-56	SCG-57	
			*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*
			*	*	*	*	*	*		*	*	*	*	*	*	*	*	*	*
			*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
			*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
			*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*

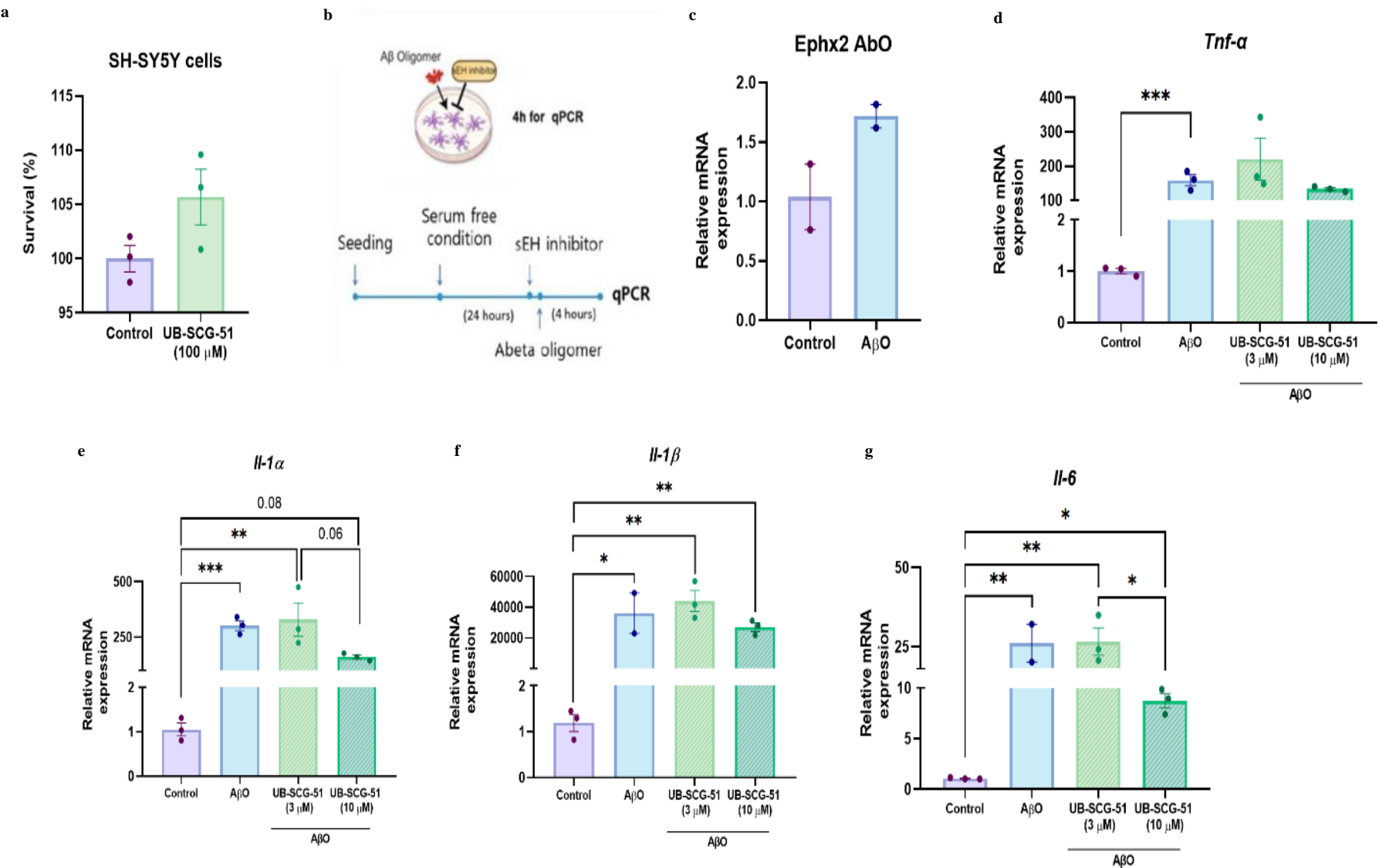


**Toxicity**  
 iNOS/COX2 in microglia  
 Reactive microglia  
 BBB penetration  
 Reactive astrocyte





# Prevención de la neuroinflamación inducida por beta-amiloide in vitro

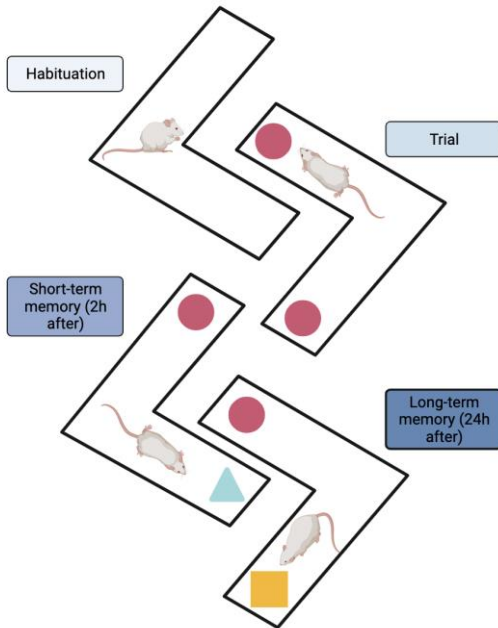
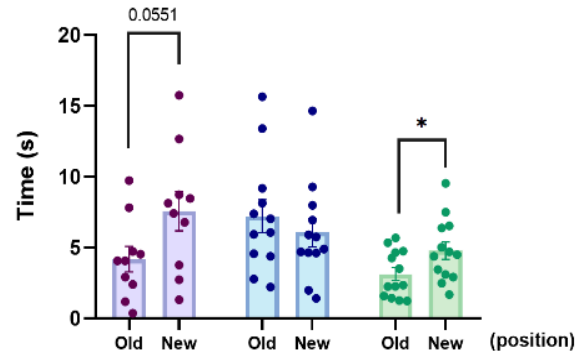


# Prevención de la pérdida cognitiva con el tratamiento de un inhibidor de la sEH

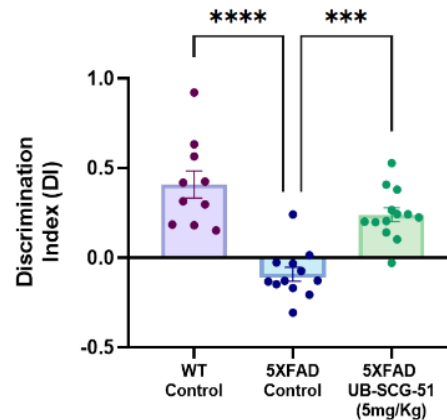


Ratón transgénico  
modelo de AD  
5XFAD

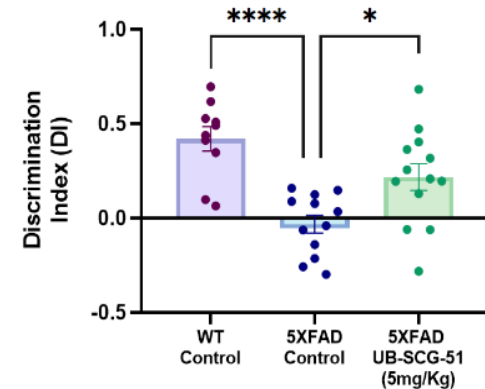
## Memoria espacial



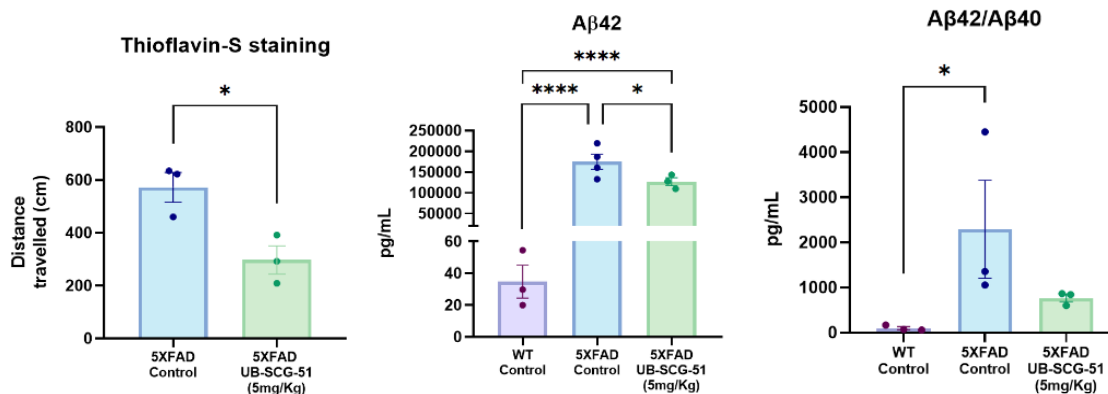
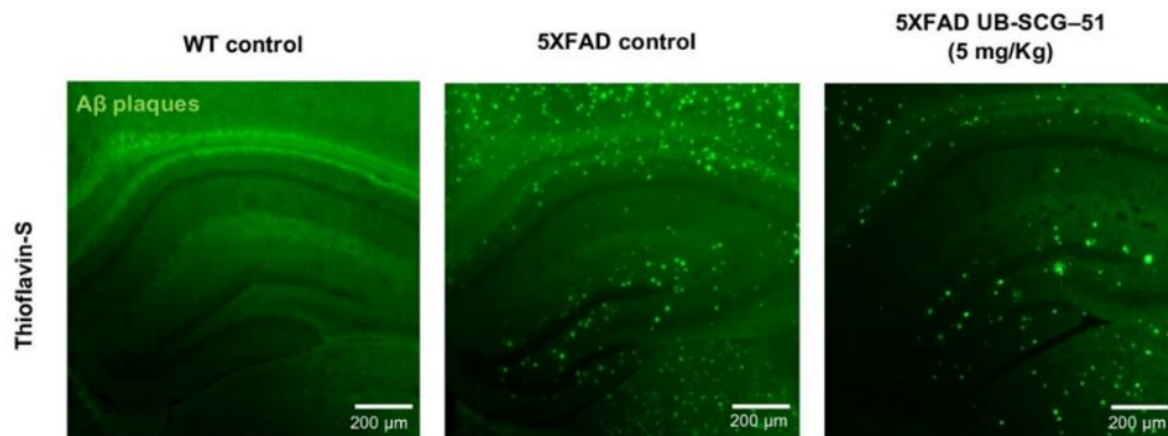
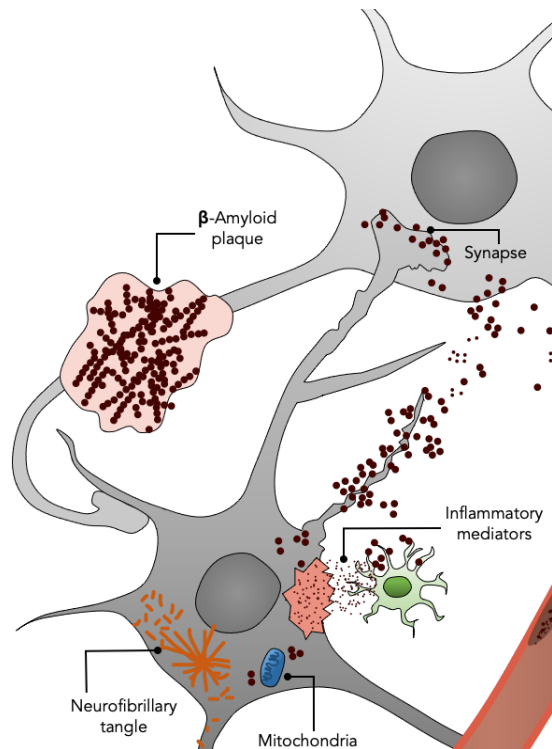
## Memoria a corto plazo



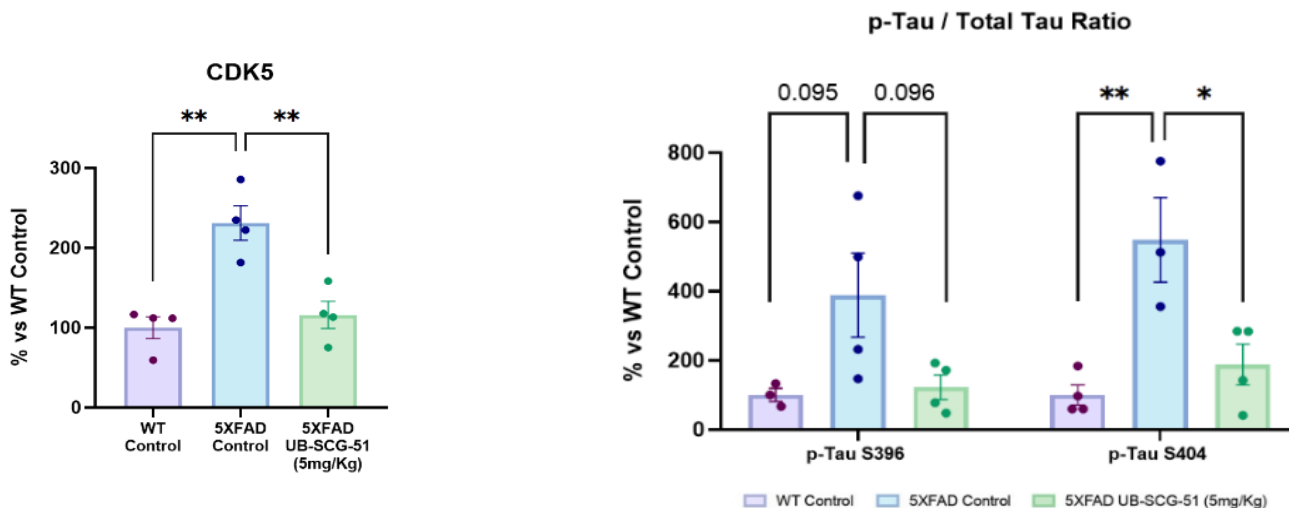
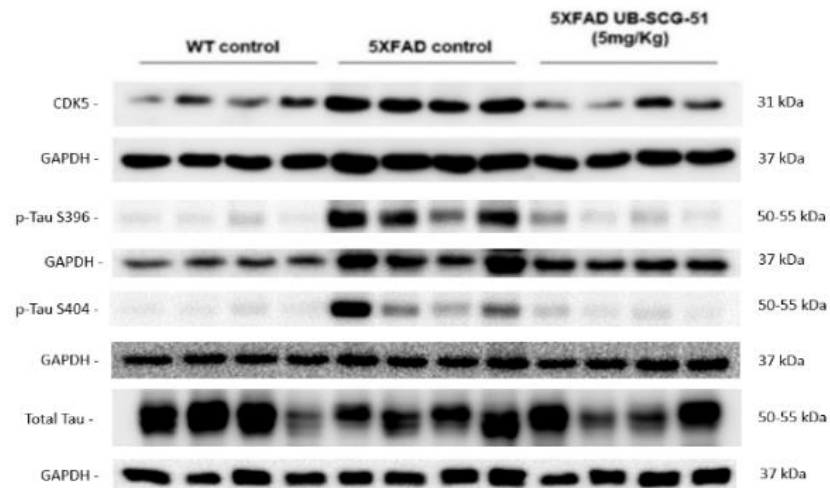
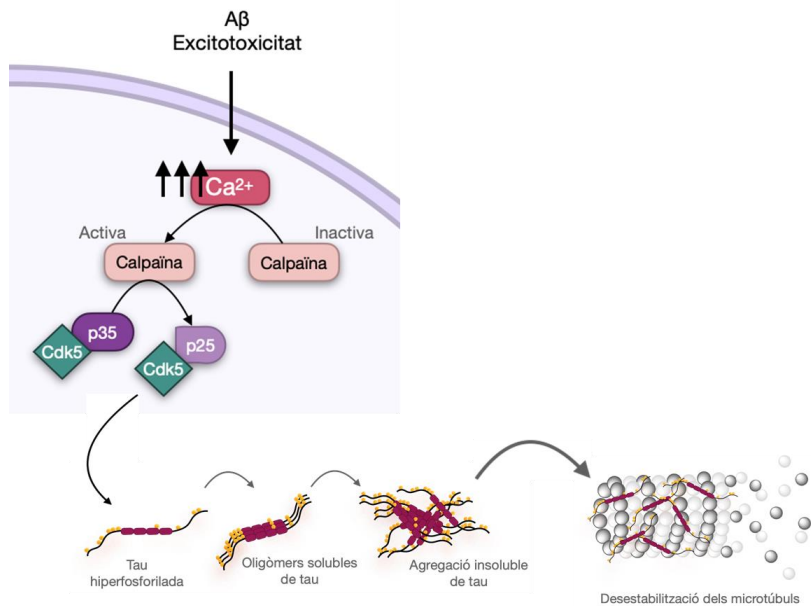
## Memoria a largo plazo



# Reducción del número de placas y de la acumulación de beta amiloide en cerebro con el tratamiento de un inhibidor de la sEH

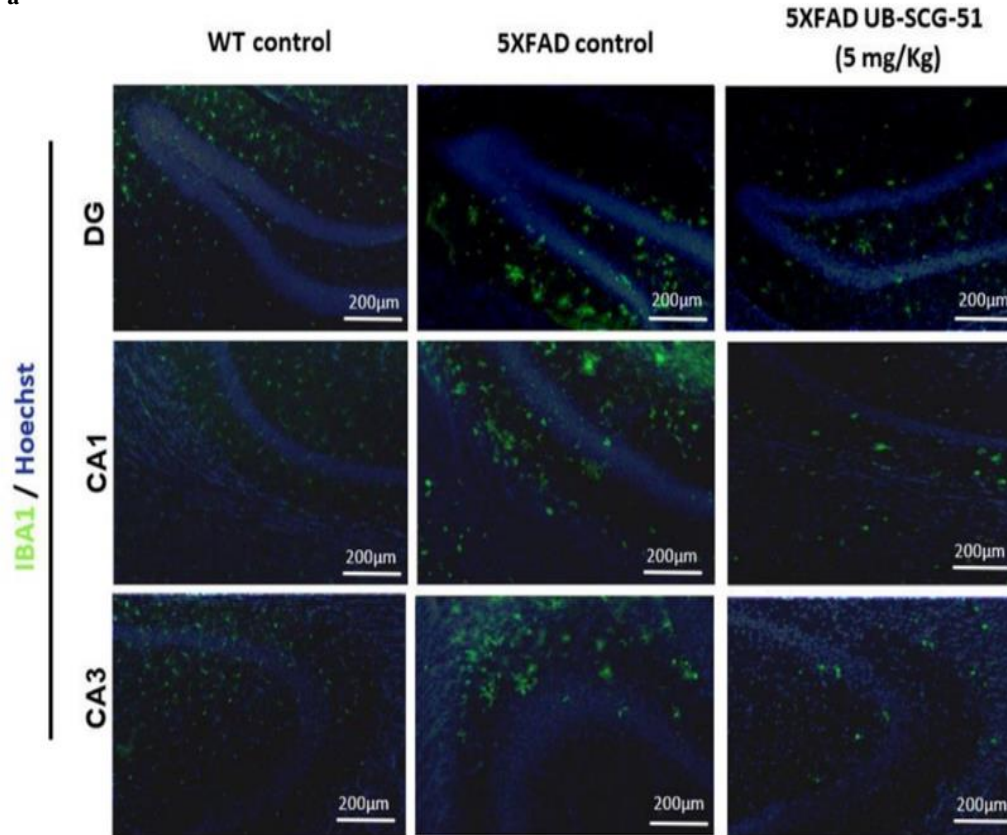


# Reducción de la hiperfosforilación de tau en cerebro con el tratamiento de un inhibidor de la sEH

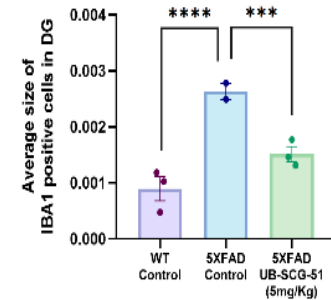


# Reducción de microgliosis en cerebro con el tratamiento de un inhibidor de la sEH

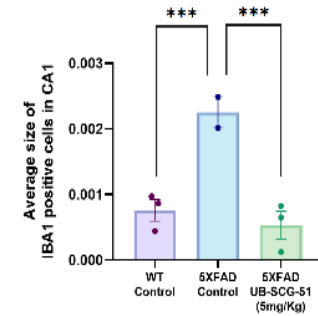
a



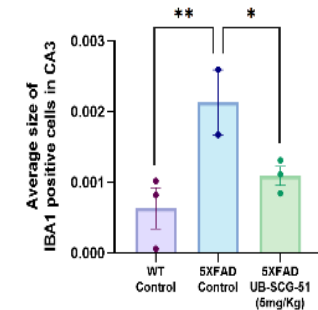
b



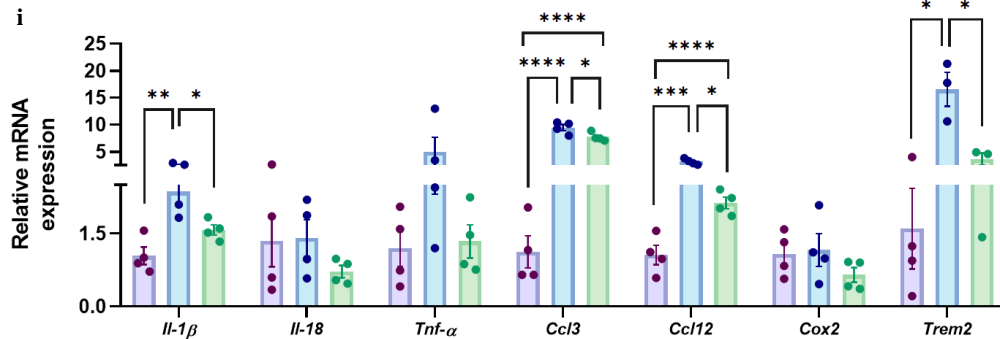
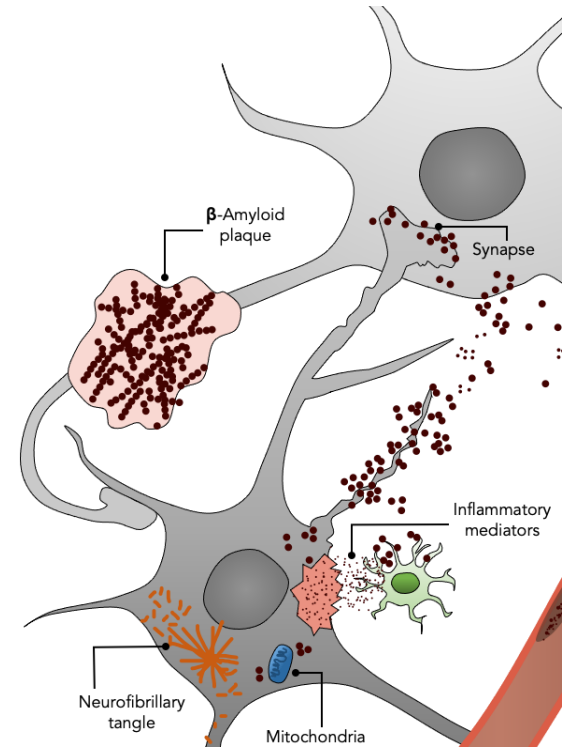
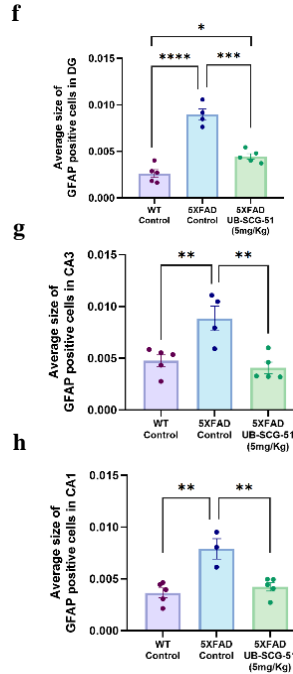
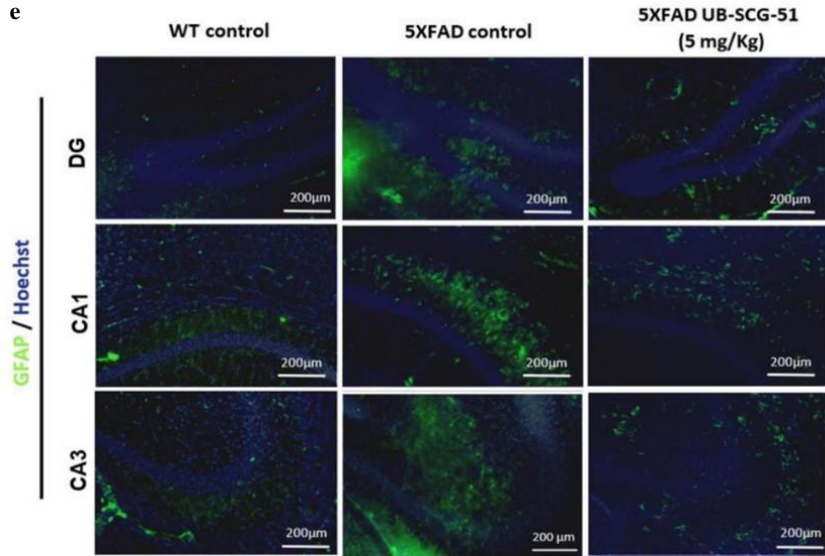
c



d



# Reducción de astrogliosis en cerebro con el tratamiento de un inhibidor de la sEH



# Oportunidad de tratamiento de la enfermedad con un inhibidor de la sEH

## IDENTIFICACIÓN DE LA DIANA



Conocer la patología  
Identificación y validación de la diana

## IDENTIFICACIÓN DEL NUEVO COMPUESTO Y OPTIMIZACIÓN

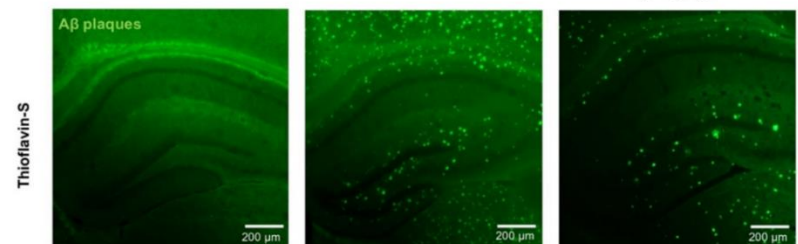
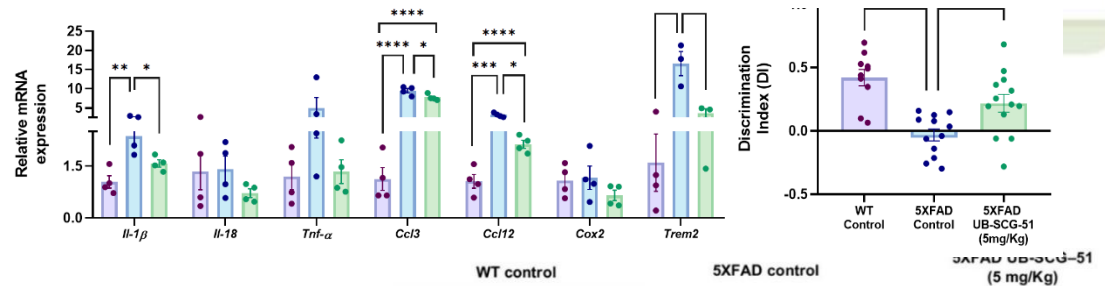
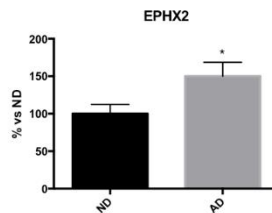
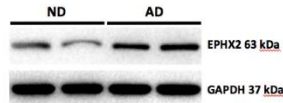
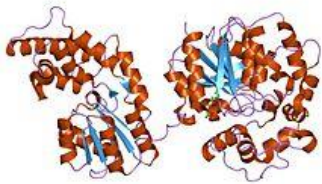


Nueva síntesis  
Compuestos ya existentes

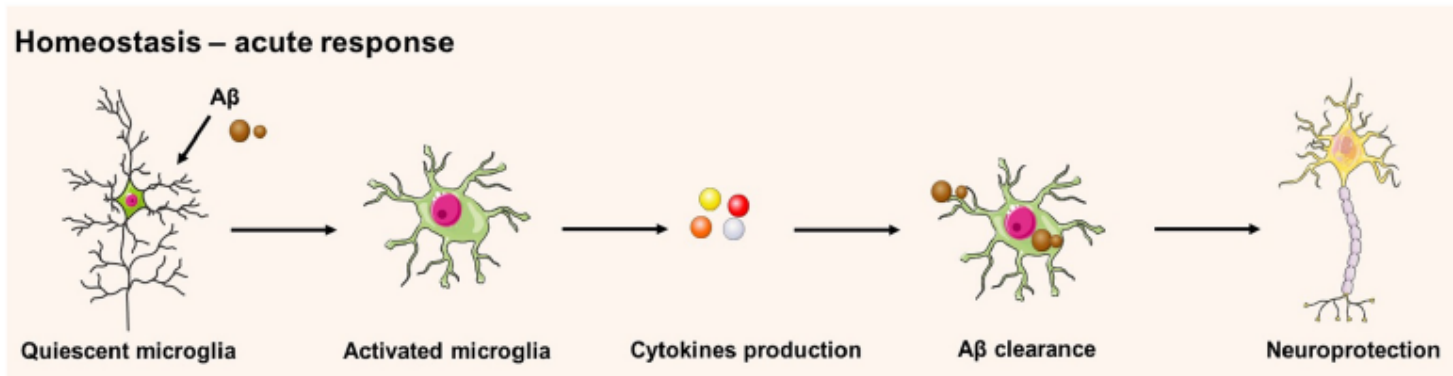
## DESARROLLO PRECLINICO



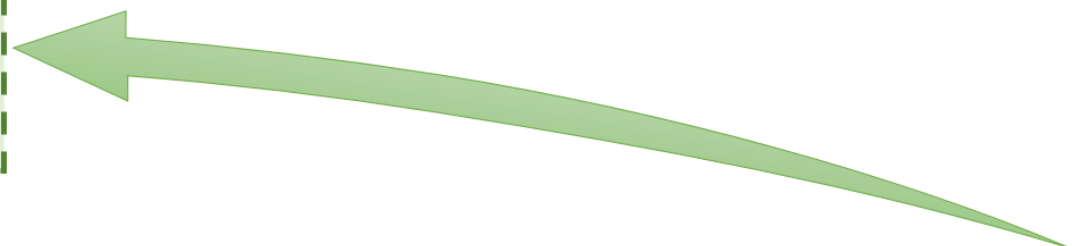
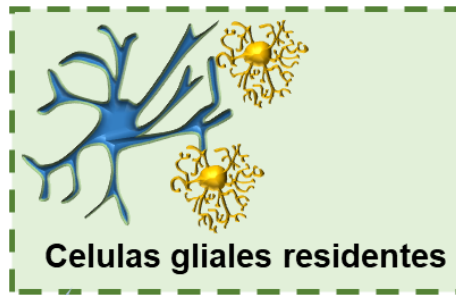
Propiedades químicas  
ADME  
Toxicidad



# Recuperar la función homeostática de la glia







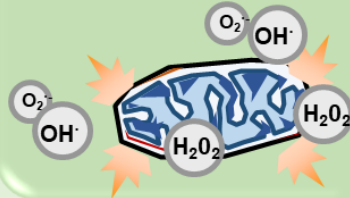
### Neuroinflamación



Expresión y liberación de citocinas



### Estrés Oxidativo



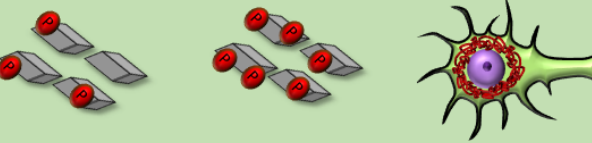
### Estrés de Reticulo



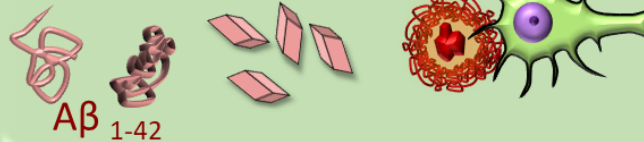
Inhibidores sEH



### Hiperfosforilación Tau



### Placas de amilode



### Enfermedad de Alzheimer



integrando la  
Innovación



GRÀCIES!!!

Dr Mercè Pallàs  
Dr Christian Griñán-Ferré  
Dr Ana Guerrero

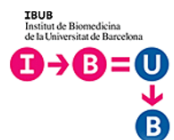
Aina Bellver  
Júlia Jarne  
Alba Irisarri  
Teresa Taboada



## Medicinal Chemistry and Pharmacology of Neurodegenerative Diseases



Dra Carmen Escolano  
Dr. Diego Muñoz-Torrero  
Dr Santi Vázquez



2021SGR106



PID2022-138079OB-I00

Webpage:

