3 de julio de 2025

Oxapi-27, a first-in-class epigenetic therapy for CNS disorders

Christian Griñán Ferré

Content

The Institution

Prof. Christian Griñán Ferré

Associate Professor & Principal Investigator of the Neuroepilab

Expertise in **neuroscience**, **epigenetics**, and **drug discovery** for neurodegenerative diseases.

Co-founder of FLAVII THERAPEUTICS

UNIVERSITAT DE BARCELONA

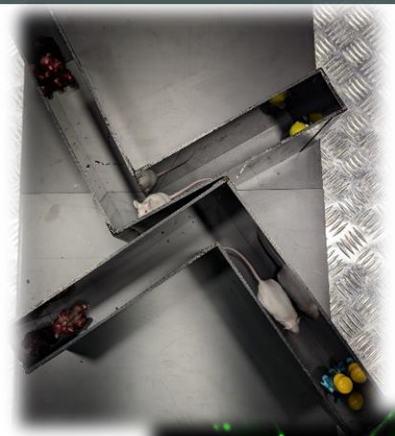
Faculty of Pharmacy and Food Sciences

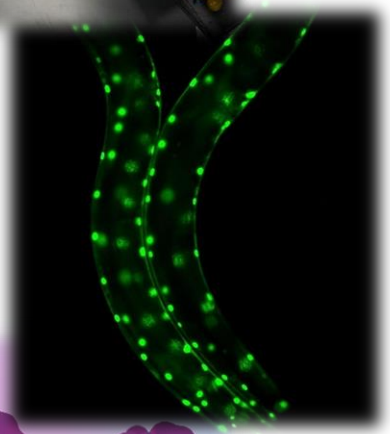
NeuroEpiLab

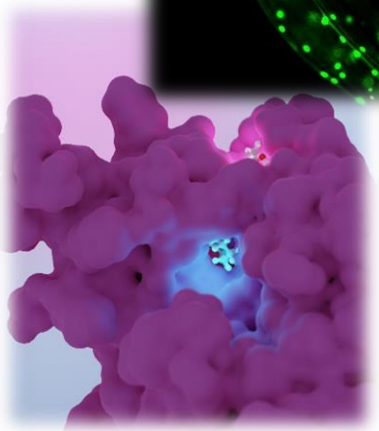
The Neuroepilab focuses on discovering and optimizing novel chemical entities that target epigenetic mechanisms to treat central nervous system (CNS) disorders. The group also investigates how gene expression is regulated by epigenetics and its role in diseases such as Alzheimer's, Parkinson's, and Huntington's.

Research lines

- Neuroepigenetics and Brain Aging
- Development of Epigenetic-Based Drugs
- Neuroinflammation, Oxidative and Mitochondrial Stress
- Innovative Animal Models and Transgenerational Inheritance (C.elegans and mice models)
- Rare Neurodegenerative Diseases
- Pharmacological and Non-Pharmacological Interventions







Oxapi-27, a first-in class epigenetic therapy for CNS disorders

Drug candidates

small molecules

with novel mechanisms of action

for the treatment

Targeting epigenetics

of CNS conditions

Idea conception

UNIVERSITAT DE BARCELONA

PoC development

UNIVERSITAT DE BARCELONA

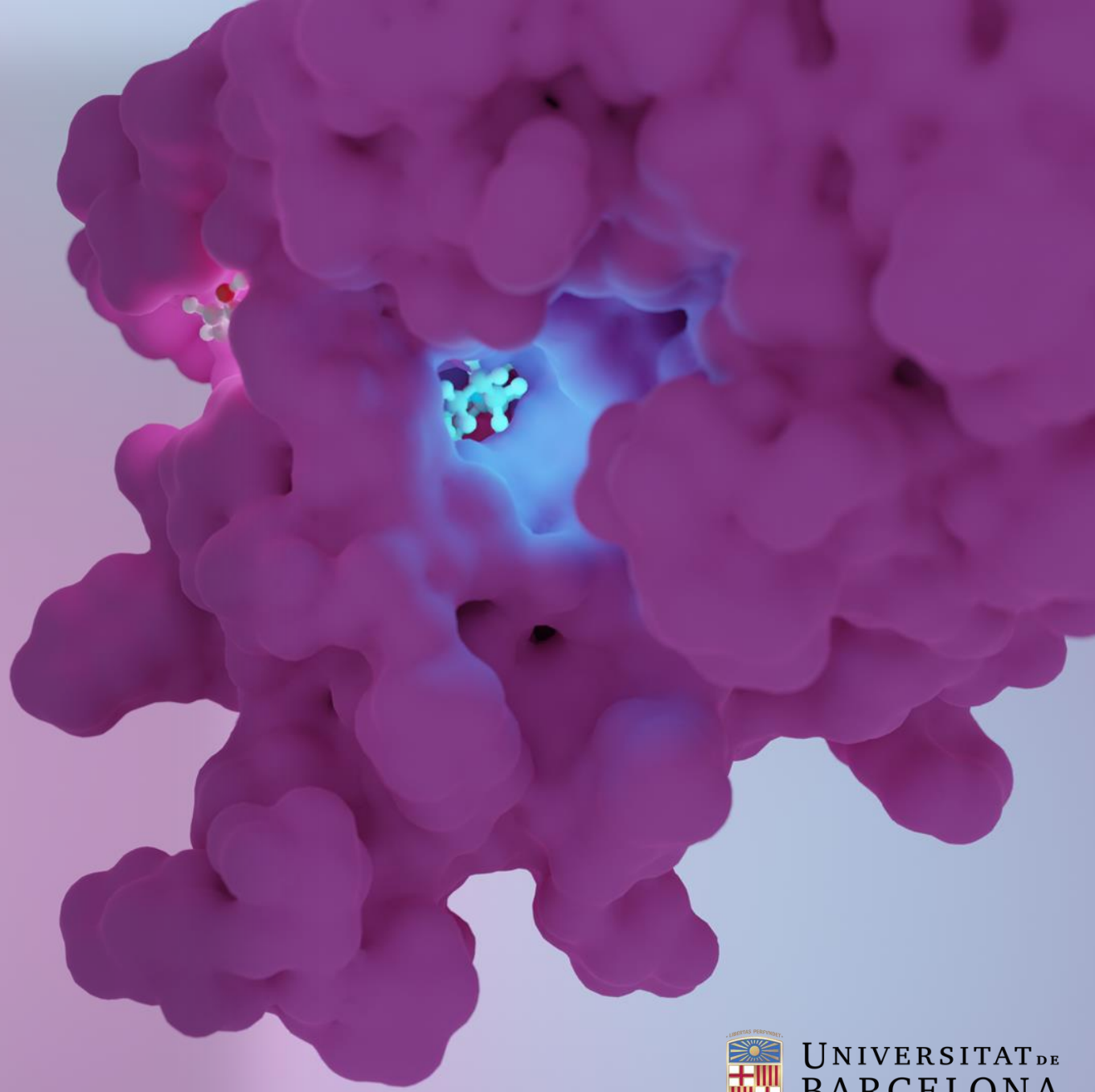
Spin-off creation

FLAVII THERAPEUTICS

FLAVII THERAPEUTICS

Oxapi-27:

A new G9a inhibitor drug for treating CNS conditions



UNIVERSITAT DE BARCELONA

FLAVII THERAPEUTICS Team

UNIVERSITAT DE BARCELONA

Neuropharmacology, neuroepigenetics, neurodegeneration and ageing group

Strong expertise in pharmacology, epigenetics and ageing and neurodegenerative diseases

Christian Griñán Ferré, Prof.

PI and responsible Scientist

Co-founder

Aina Bellver Sanchis, PhD

Post-doctoral researcher

Co-founder

Ariadna Boloix, PhD

Innovation and project manager

Co-founder

Mercè Pallàs, Prof.

Advisor in Pharmacology

Advisory board member

UNIVERSITAT DE BARCELONA

Collaborators & Medicinal Chemistry Advisors

Strong expertise organic and medicinal chemistry

Carmen Escolano, Prof.

Principal Investigator

Santiago Vázquez, Prof.

Principal Investigator

Tech transfer manager

Bosch i Gimpera

UNIVERSITAT DE BARCELONA

Inma Iñiguez

Intellectual property project manager

Business Advisors

Marc Ramis, PhD

CHASINGSCIENCE

Andrés Fernández, PhD

NANOBOTS THERAPEUTICS

Clinical Advisors

Dr. Albert Lladó, PhD

Clínic Barcelona

IDIBAPS

Dr. Alberto Lleó, PhD

SANT PAU Campus Salut Barcelona

Institut de Recerca Sant Pau

Neurodegenerative diseases

1st leading cause of **death** & **disability**

More than **55 million** individuals worldwide

$52 billion in 2024 (CAGR 7%)

Heterogeneous group of **neurological disorders:**

25.000€ is the annual estimated cost/patient

- Alzheimer's disease (AD)
- Huntington's disease (HD)
- Parkinson's disease (PD)

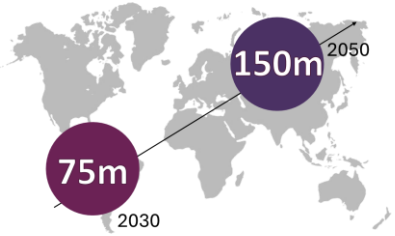
Approved drugs only **alleviate symptoms temporally**

Innovative **therapies** with new **mechanisms of actions** are **required**

In Alzheimer disease

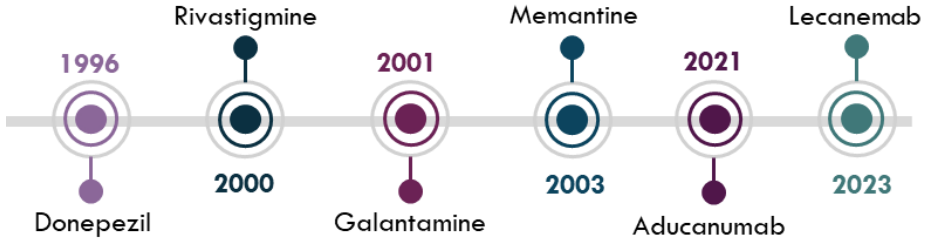
1st form of **dementia**

1/10 people over 65 years have AD



2/3 of AD patients are **women**

~28.000€ is the annual estimated cost/patient in Spain



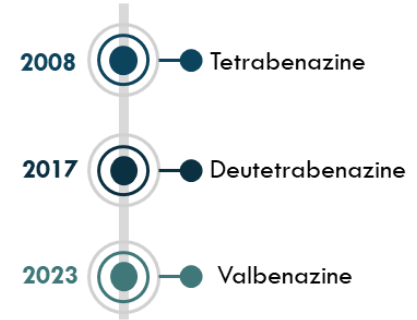
In Huntington disease

Over **60.000** cases in 2024 worldwide

3 cases per 100.000 habitants

~60.000€ is the annual estimated cost/patient

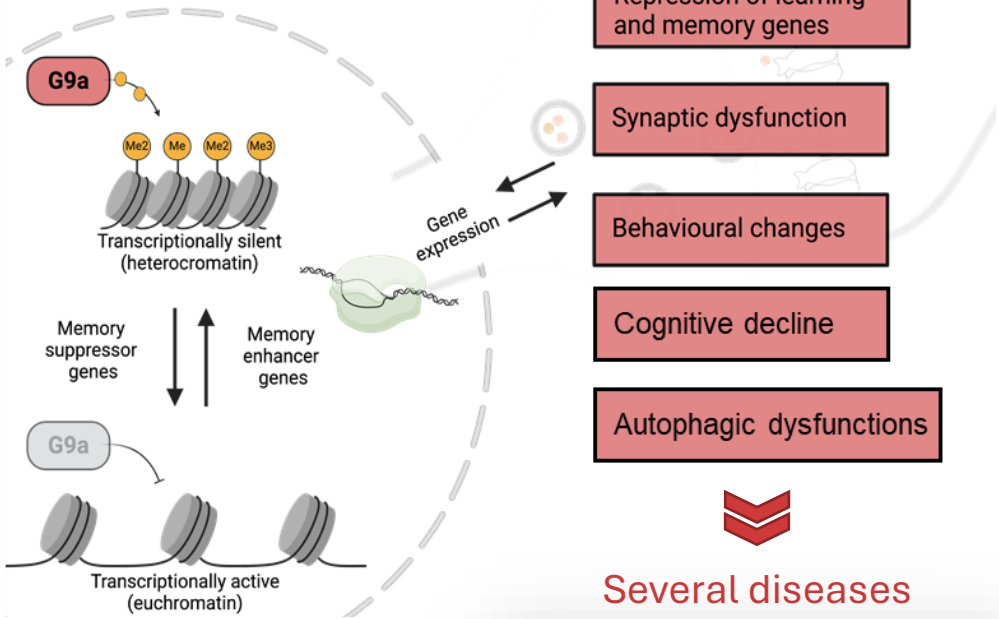
HD is a **rare** disorder with **10** years of **life expectancy** after diagnosis



Innovative MoA

Epigenetic therapies can restore normal gene function, potentially slowing or halting the progression of neurodegenerative diseases

Epigenetic target involved in chromatin reprogramming



- Repression of learning and memory genes
- Synaptic dysfunction
- Behavioural changes
- Cognitive decline
- Autophagic dysfunctions

Several diseases

- Alzheimer's disease (AD)
- Huntington's disease (HD)
- Parkinson's disease (PD)

Epigenetic interest in AD pathology

2010

Altered CpG methylation in sporadic Alzheimer's disease is associated with APP and MAPT dysregulation

Atsushi Iwata[1,2,3,*], Kenichi Nagata[4], Hiroyuki Hatsuta[5], Hiroshi Takuma[6], Miki Bundo[7], Kazuya Iwamoto[3,7], Akira Tamaoka[5], Shigeo Murayama[5], Takaomi Saido[4] and Shoji Tsuji[2]

Human Molecular Genetics, 2014; 23(3):648-656

Aging Cell — Anatomical Society — Open Access

Original Article | Open Access

Epigenetic regulation by G9a/GLP complex ameliorates amyloid-beta 1-42 induced deficits in long-term plasticity and synaptic tagging/capture in hippocampal pyramidal neurons

Mahima Sharma, Tobias Dierkes, Sreedharan Sajikumar

First published: 30 June 2017 | https://doi.org/10.1111/acel.12634 | Citations: 43

2014

EWAS reveal differentiate methylated positions in AD patients

Genome-wide DNA methylation profiling in the superior temporal gyrus reveals epigenetic signatures associated with Alzheimer's disease

Corey T. Watson[1], Panos Roussos[1,2,3], Paras Garg[1], Daniel J. Ho[1], Nidha Azam[1], Pavel L. Katsel[2,4], Vahram Haroutunian[2,3,4] and Andrew J. Sharp[1*]

Genome Med, 2016, 8:5

www.aging-us.com — AGING 2019, Vol. 11, No. 23

Research Paper

Pharmacological inhibition of G9a/GLP restores cognition and reduces oxidative stress, neuroinflammation and β-Amyloid plaques in an early-onset Alzheimer's disease mouse model

Christian Griñán-Ferré[1], Laura Marsal-García[1], Aina Bellver-Sanchis[1], Shukkoor Muhammed Kondengaden[2], Ravi Chakra Turga[3], Santiago Vázquez[4], Mercè Pallàs[1]

Histone acetylome-wide studies, and systematic meta-analysis of miRNAs and lncRNAs

2019

ChemMedChem — An Official Journal of the EFMC — Chemistry Europe

Research Article | Open Access

Structure-Based Virtual Screening and *in vitro* and *in vivo* Analyses Revealed Potent Methyltransferase G9a Inhibitors as Prospective Anti-Alzheimer's Agents

Aina Bellver-Sanchis, Bhanwar Singh Choudhary, Júlia Companys-Alemany, Sukanya, Dr. Pedro A. Ávila-López, Dr. Antón Leandro Martínez Rodríguez ... See all authors

First published: 12 April 2022 | https://doi.org/10.1002/cmdc.202200002 | Citations: 2

2020

Histone methylation-wide association study showed an increase of H3K9me2 and H3K9me3 in AD patients

Aging and Disease — www.aginganddisease.org — Early access date: June 6, 2023 — http://dx.doi.org/10.14336/AD.2023.0424-2

Original Article

G9a Inhibition Promotes Neuroprotection through GMFB Regulation in Alzheimer's Disease

Aina Bellver-Sanchis[1], Qizhi Geng[2], Gemma Navarro[3,4], Pedro A. Ávila-López[5], Júlia Companys-Alemany[1], Laura Marsal-García[6,7], Raquel Larramona-Arcas[8], Lluisa Miró[9], Anna Perez-Bosque[9], Daniel Ortuño-Sahagún[10], Deb Ranjan Banerjee[11], Bhanwar Singh Choudhary[12,13], Francesc X Soriano[8], Coralie Poulard[14,15,16], Mercè Pallàs[1,3], Hai-Ning Du[2], Christian Griñán-Ferré[1,3*]

2025

Oxapi-27 emerges as a potent **therapeutic** agent in **preclinical Alzheimer**'s models

G9a, a histone methyltransferase

- **Overexpressed in AD** patients' brains.
- **Regulates a repressive epigenetic mark the H3K9me2**, found with higher protein levels in AD patients.
- Strong positive **correlation** between **H3K9me2 and Aβ** in AD.

G9a inhibition restores the neuropathological hallmarks of AD.

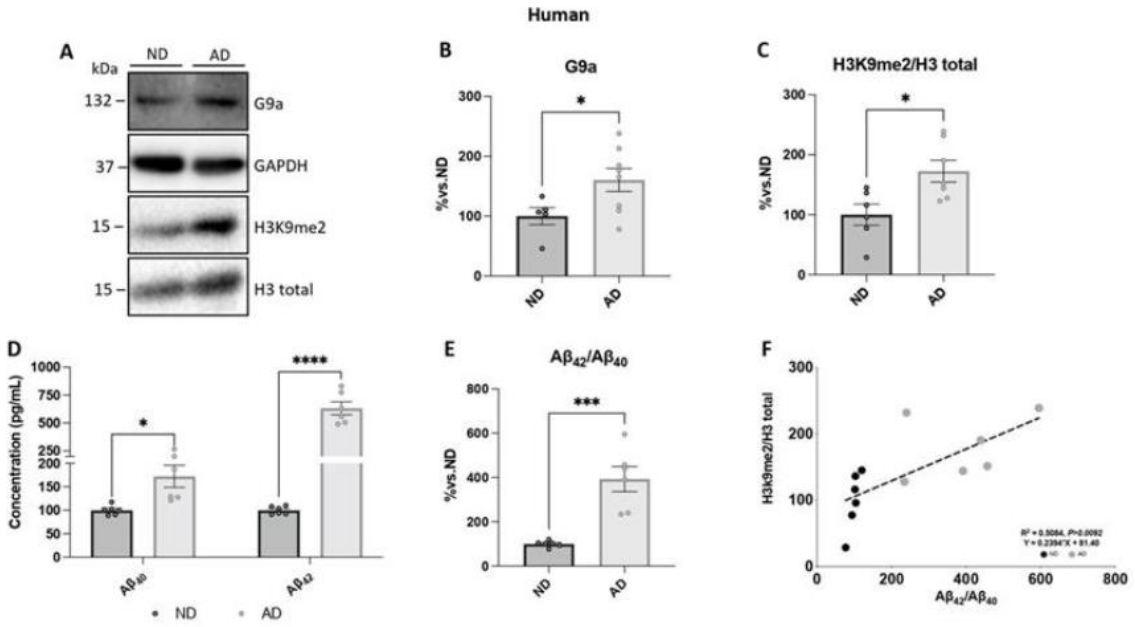
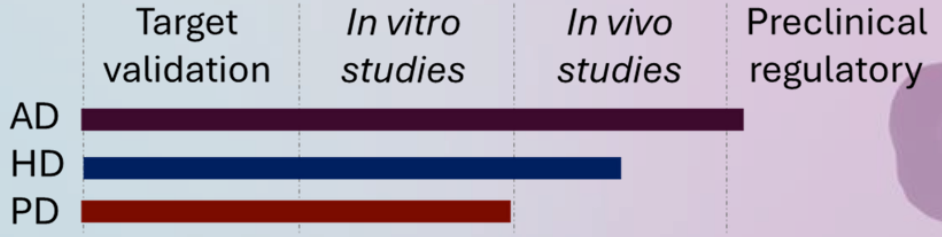


Figure 1. Overexpression of G9a in AD patients' brains and H3K9me2 in both AD patients' and *C. elegans* AD transgenic strains. (A) and **(B)** Representative WB, and quantification of G9a (EHMT2), and **(C)** for histone H3K9me2 in human patients' brains. **(D)** Levels of Aβ40 and Aβ42. **(E)** The ratio of Aβ42/Aβ40 by ELISA in human patients' brains. Values presented are mean ± SEM; (N = 2 groups (ND n = 6, and AD n = 8); Student's t-test; **p*<0.05; ****p*<0.001). **(F)** Correlation between Aβ42/Aβ40 ratio and H3K9me2 (slope = 0.07444). R2 and *p*-values are indicated on graphs. **(G)** Representative gene expression of *set-25* in *C. elegans*.

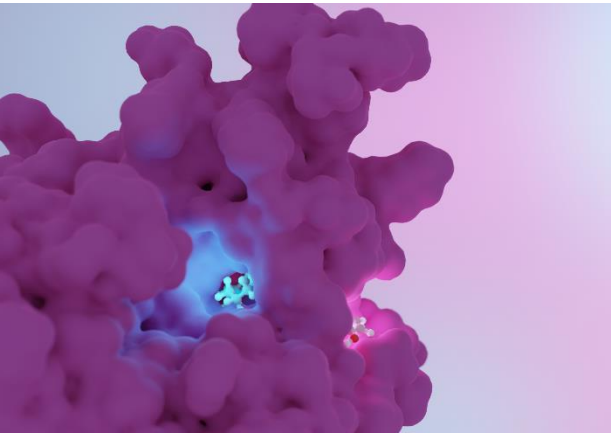
OXAPI-27

A **small molecule** that targets **epigenetics** by **inhibiting G9a**, with potential to **treat Alzheimer's, Huntington's**, and other **CNS diseases.**

- **Novel mechanism of action**
- **SAM-competitive inhibitor**
- **Disease-modifying treatments**
- **Not drug repurposing**



Oxapi-27: innovative MoA



- ☑ **Novel mechanism of action**
- ☑ **SAM-competitive inhibitor**

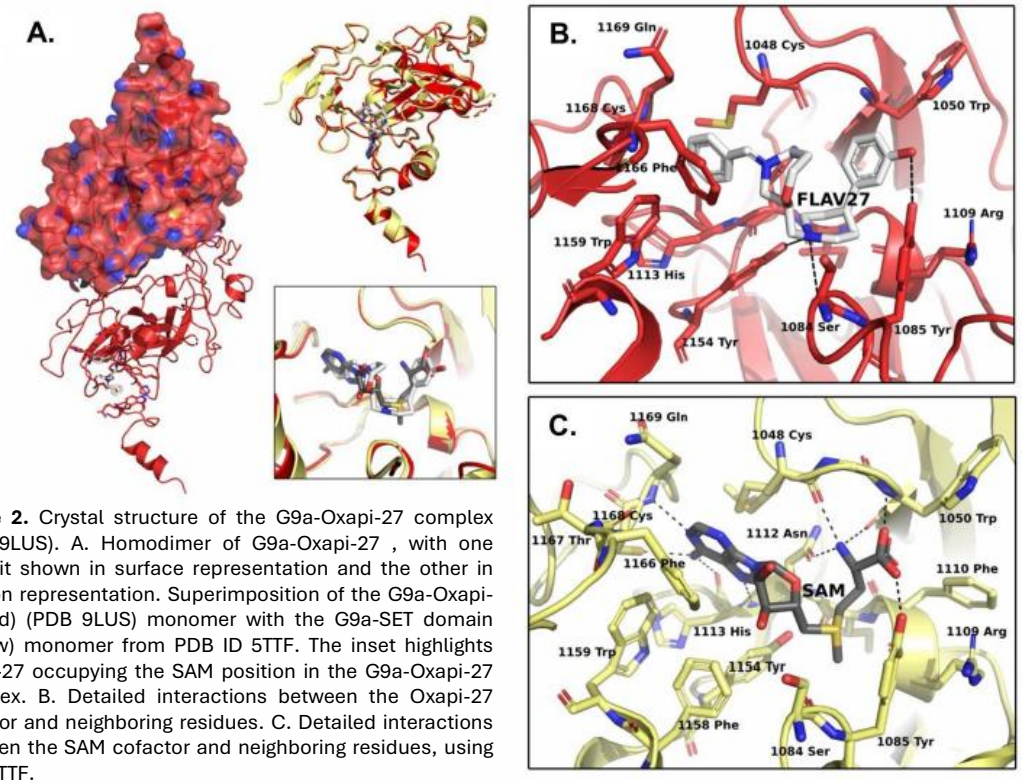


Figure 2. Crystal structure of the G9a-Oxapi-27 complex (PDB 9LUS). A. Homodimer of G9a-Oxapi-27 , with one subunit shown in surface representation and the other in cartoon representation. Superimposition of the G9a-Oxapi-27 (red) (PDB 9LUS) monomer with the G9a-SET domain (Yellow) monomer from PDB ID 5TTF. The inset highlights Oxapi-27 occupying the SAM position in the G9a-Oxapi-27 complex. B. Detailed interactions between the Oxapi-27 inhibitor and neighboring residues. C. Detailed interactions between the SAM cofactor and neighboring residues, using PDB 5TTF.

- **Selective inhibitor** (GLP (3.2% inhibition at 1 μM) vs G9a IC_{50} = 0.6 nM)
- **Oxapi-27** occupies the **SAM (cofactor) binding site**

- **Good solubility**
- High **BBB permeability: ~ 3.8x brain/plasma** concentration ratio
- **Therapeutic dose (5 mg/kg** after oral administration**)**
- **Well tolerated**
- **Wide therapeutic window** (**NOAEL 1g/kg**)
- No toxicity (no MTD observed)

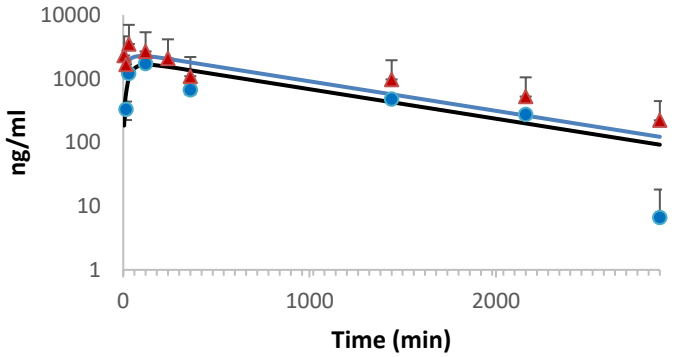
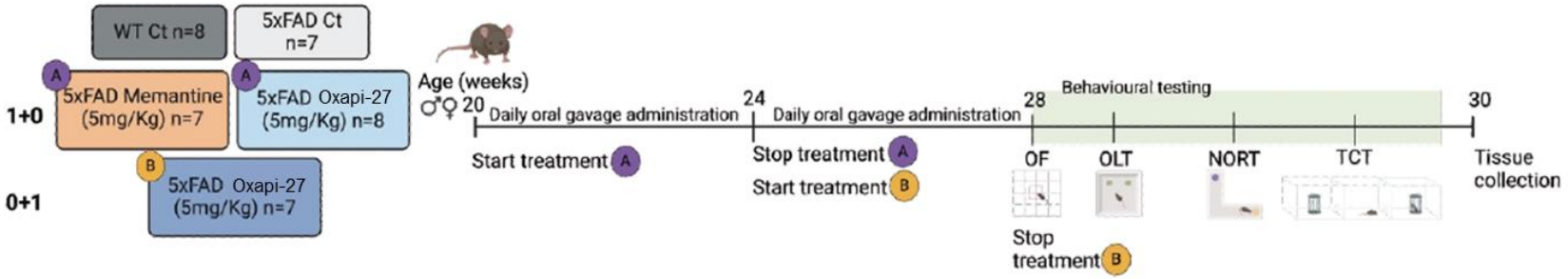
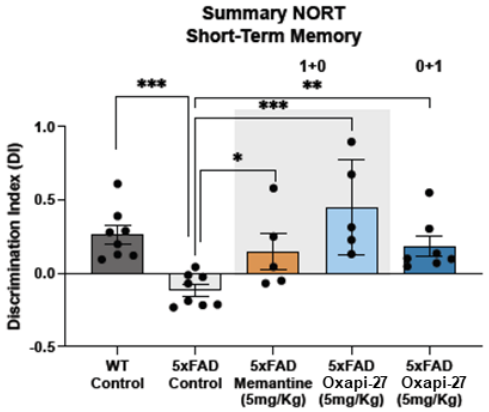


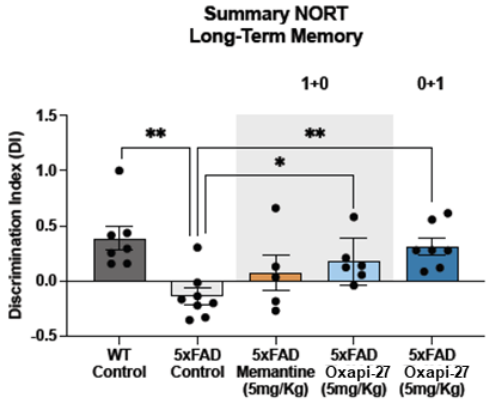
Figure S17. Oxpi-27 plasma concentrations (ng/mL) observed (mean±sd; red triangles) and predicted (blue line) and brain concentrations (ng/mL) observed (blue circles) and predicted (black line) after Oxapi-27 salt oral administration 5mg/kg.

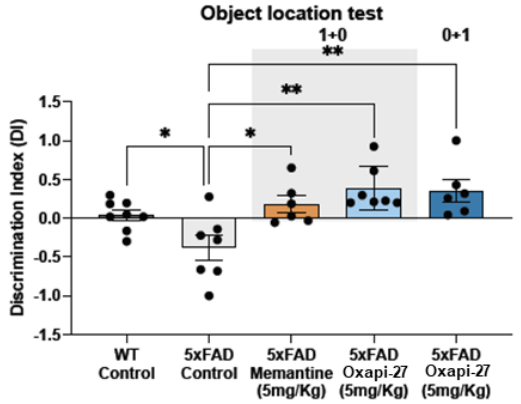
Bellver-Sanchis A et al., *Manuscript accepted*. Angewandte Chemie.

Oxapi-27: PoC in Alzheimer disease









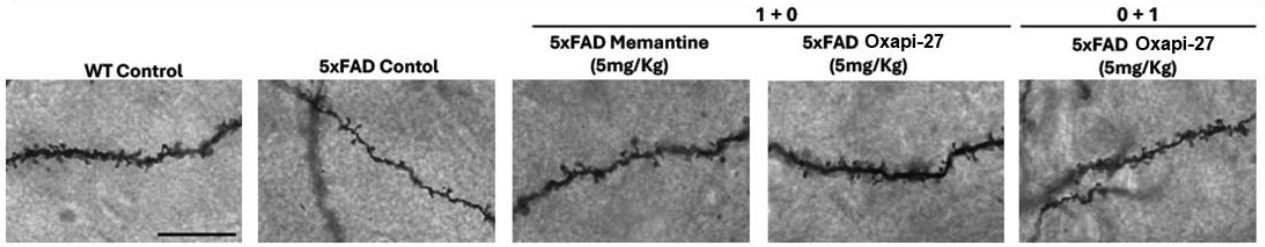
Oxapi-27 acts as a disease-modifying agent

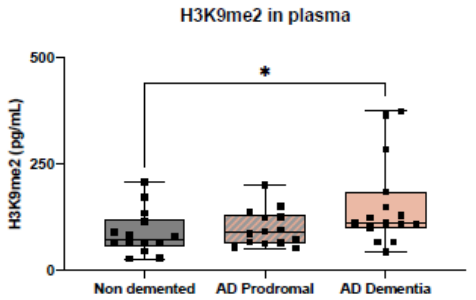
Improved both **short-term and long-term memory.**

Cognitive-enhancing effect.

Oxapi-27 improve neuronal plasticity.

AD patients show alterations in **biomarkers** targeted by **Oxapi-27**





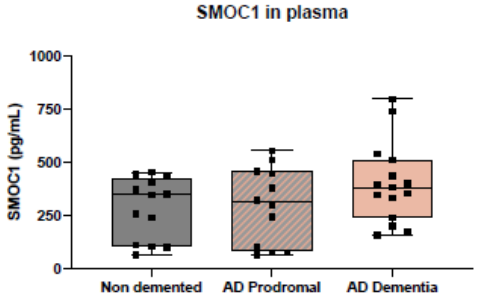
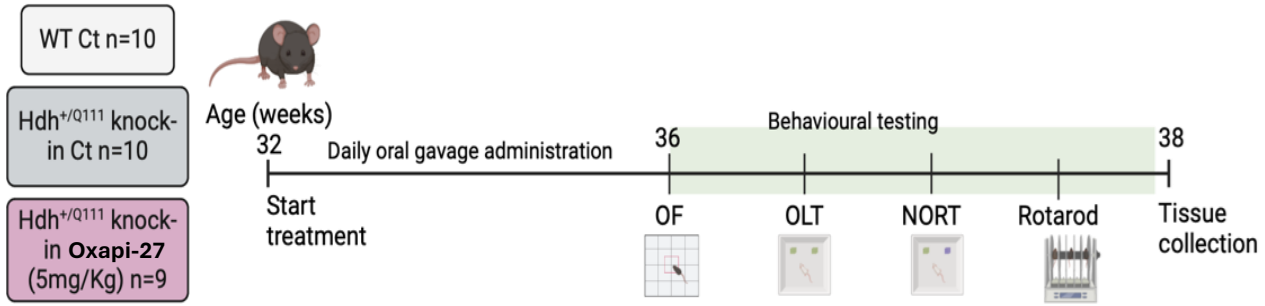
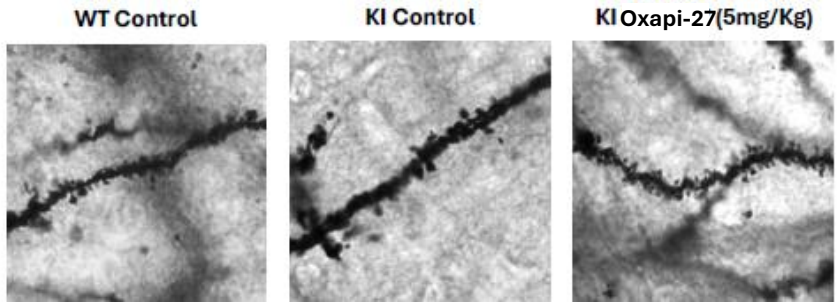


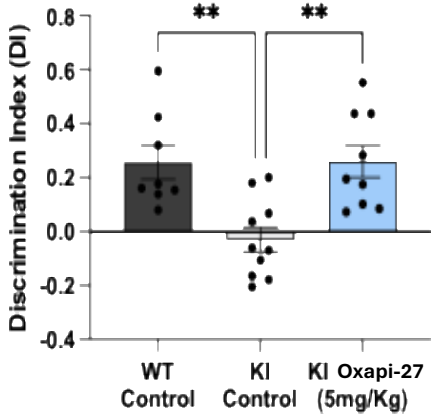
Figure1 . Experimental timeline for drug administration and behavioral test. NORT: Evaluation of the working memory by DI after 2h and 24h. OLT: Evaluation of the spatial memory by DI after changing the location of one object. Representative images of Golgi-stained neurons and the spine density of the different experimental (scale bar = 100 µm). Plasma levels of H3K9me2 and SMOC1 in AD patients.

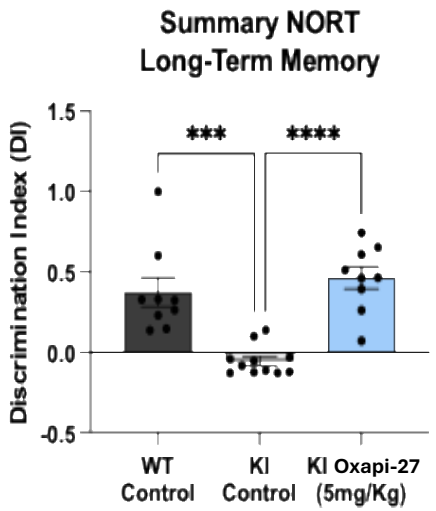
Bellver-Sanchis A et al., *Manuscript under preparation.*

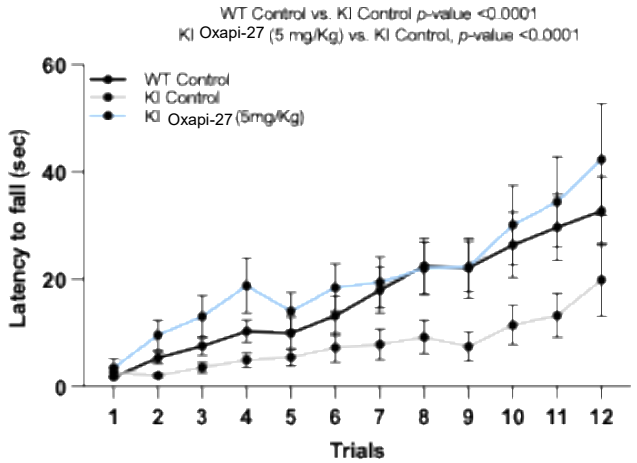
Oxapi-27: PoC in Huntington disease











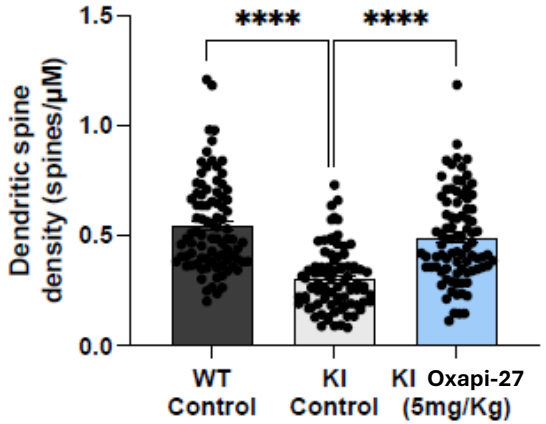


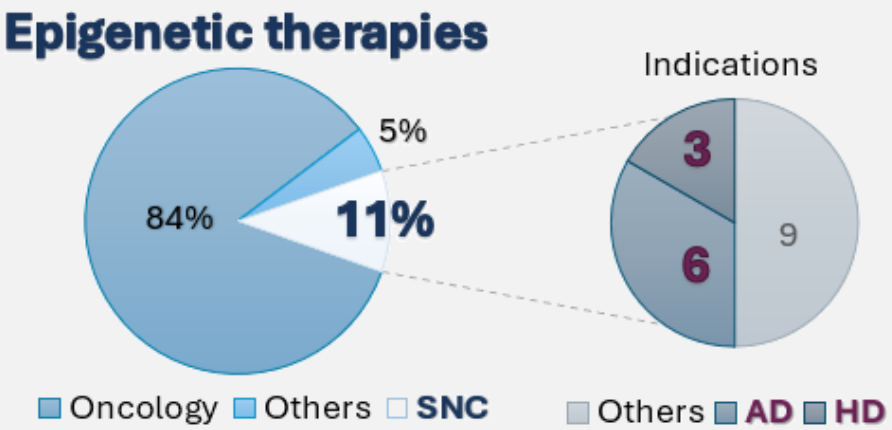
Figure 2. Inhibition of G9a improves exploratory behavior and spatial memory in Hdh+/Q111 mice. Experimental timeline for drug administration and behavioral test. OLT evaluation and NORT evaluation after 24h. Values presented are mean ± SEM. WT Control n = 10, KI Control n = 10, and KI Oxapi-27 (5mg/Kg) n = 10. Statistical analysis: One-Way ANOVA, followed by Dunnet's post-hoc analysis. **p<0.01; ***p<0.001. Latency to fall in the accelerating rotarod task. Values presented are mean ± SEM. WT Control n = 10, KI Control n = 10, and KI Oxapi-27 (5mg/Kg) n = 10. Statistical analysis: One-Way ANOVA, followed by Dunnet's post-hoc analysis. Representative images and quantification of Golgi-stained neurons and the spine density of the different experimental (scale bar = 100 µm). Statistics analysis: One-Way ANOVA, followed by Dunnet's post-hoc analysis. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.

- ✓ **Improved locomotor activity** (reversal of latency to fall)
- ✓ **Improvements on cognition**
- ✓ Improvement in **neuronal plasticity.**

Bellver-Sanchis A et al., *Manuscript under preparation.*

Competitive landscape

None of the epigenetic therapies **approved** were designed for **neurodegenerative diseases**



102 epigenetic drugs | **10 for neurodegenerative diseases**

Epigenetic therapies for treating **CNS** diseases are mainly based on **HDAC inhibitors**

G9a inhibitors

19 in preclinical stages | **1 in clinical trials**

Only 1 for treating **AD in preclinical** development

for **autoimmune disorders**

Oxapi-27 is a **G9ai** designed for **CNS conditions**

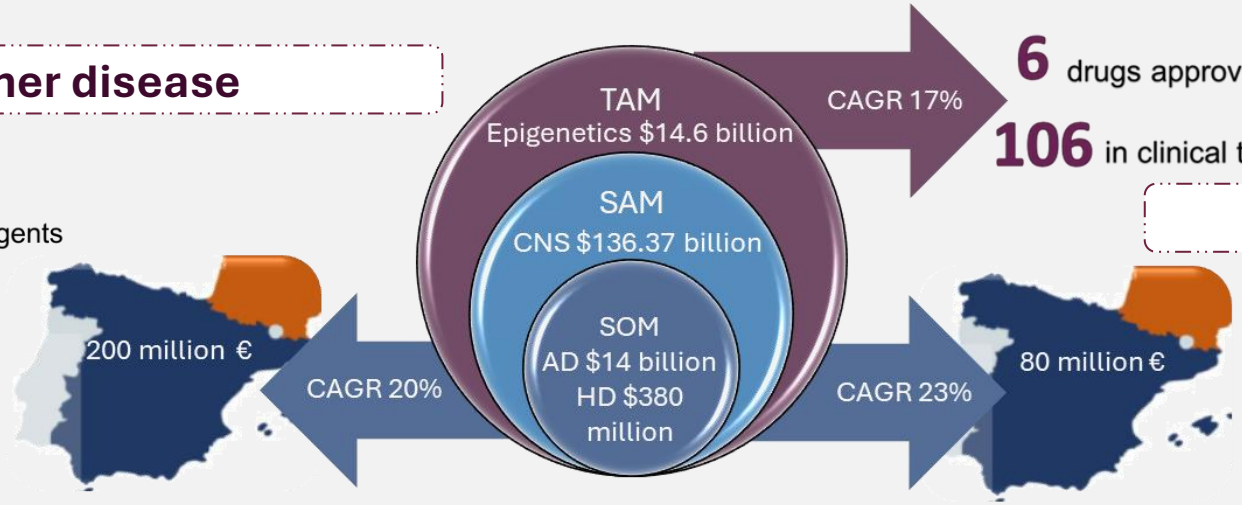
	Other G9a inhibitors	Oxapi-27
Selectivity	● ○ ○ ○ ○	● ● ● ● ●
Safety	● ○ ○ ○ ○	● ● ● ● ●
Efficacy *in vivo*	● ● ○ ○ ○	● ● ● ● ○
BBB permeability	● ○ ○ ○ ○	● ● ● ● ○

Differential features facing the market

In Alzheimer disease

6 Marketed drugs
96 Disease-modifying agents

1.447 clinical trials
891 completed
215 suspended or terminated
121 on going

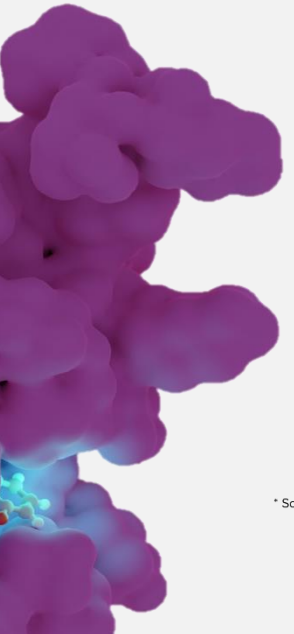


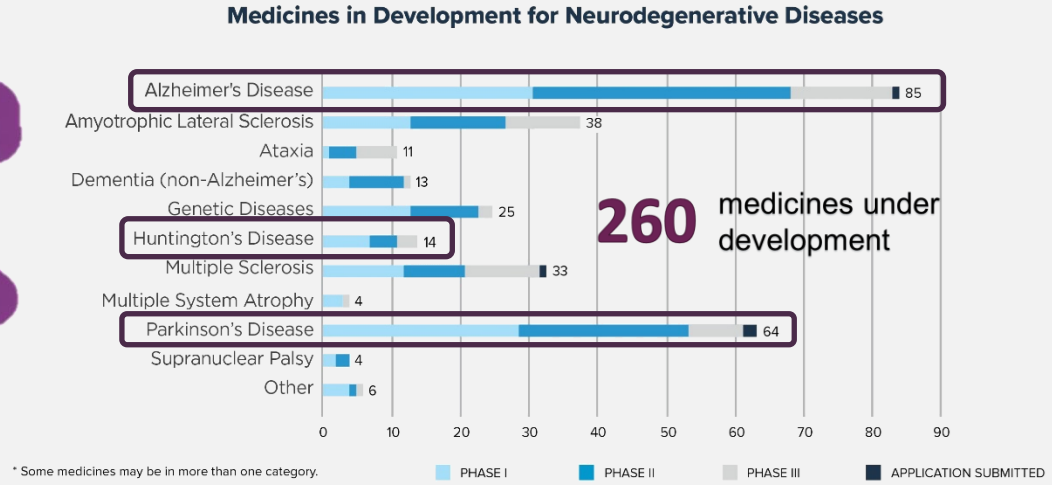
6 drugs approved
106 in clinical trials

In Huntington disease

2 Marketed drugs
7 Disease-modifying agents

277 clinical trials
150 completed
26 suspended or terminated
9 on going





[Discontinued Alzheimer's drug shows surprising long-term promise in genetic form of the disease]

Gantenerumab—an experimental monoclonal antibody discontinued that Roche/Genentech discontinued in 2022, has shown significant effectiveness...

FAILED

[Biogen Abandons Its Controversial Alzheimer's Drug Aduhelm (Published 2024)]

The pharmaceutical company will give up its ownership rights to the drug and stop a clinical trial that had been aimed at confirming whether...

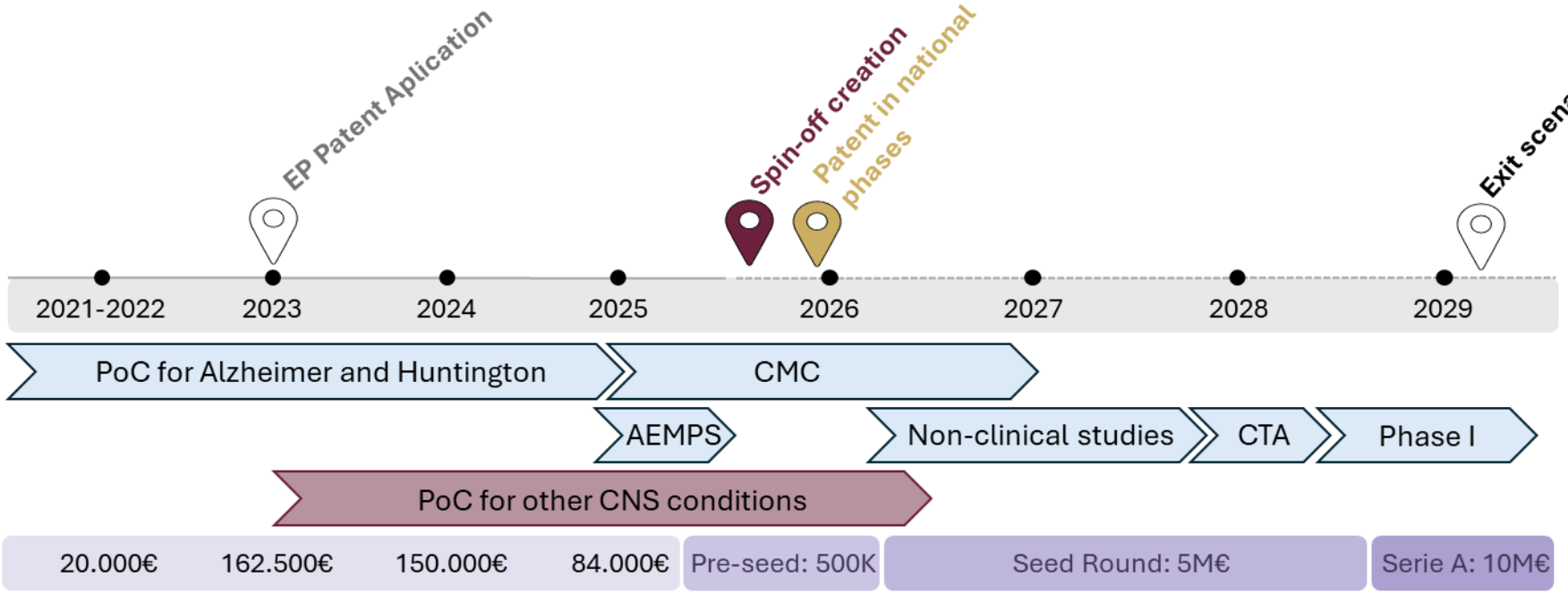
[Sage Therapeutics to end development of key therapy after ...]

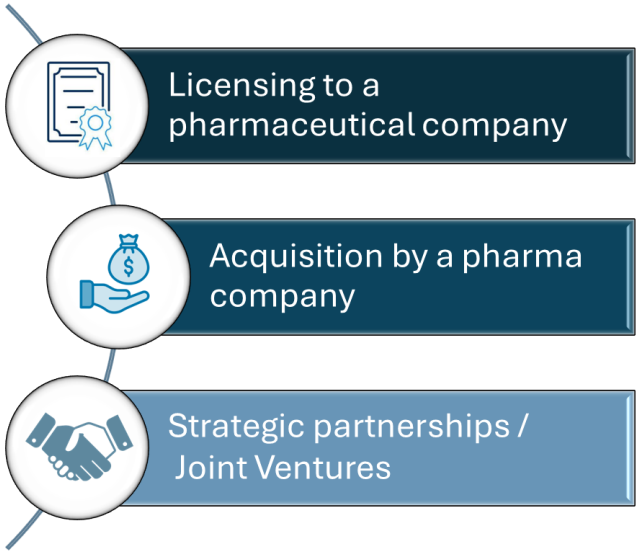
20 de nov. 2024 — Dalzanemdor has **failed** as a **treatment** for cognitive impairment in Alzheimer's, Parkinson's and now Huntington's diseases.

[Novartis Suspends Phase 2 Study of Huntington Disease ...]

25 d'ag. 2022 — **Novartis has temporarily suspended dosing of the phase 2 VIBRANT-HD study** (NCT05111249) evaluating its experimental Huntington disease (HD) drug branaplam.

Future steps





Oxapi-27: IP strategy

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
26 December 2024 (26.12.2024)

WIPO | PCT

(10) International Publication Number
WO 2024/261340 A1

(54) Title: MORPHOLINE AND 1,4-OXAZEPANE COMPOUNDS AND ITS USE IN THERAPY

(57) Abstract: The present invention provides compounds of formula (I), or a salt, solvate or 5 stereoisomer thereof as G9a inhibitors, wherein: R_1 is $CR_xR'_xR_y$; A represents $(CH_2)_m$, wherein m is 0 or 1; Z represents $(CH_2)_n$, wherein n is 2 or 3; R_2 is selected from the group consisting of: (a) an aromatic 5 or 6-membered ring system, wherein the members are selected from the group con sisting of: CR_{z1}, S, N, NH, and O; and (b) an aromatic fused ring system consisting of two rings, wherein one or both rings are aromatic rings, and each one of the aromatic rings have 5 or 6 members selected from the group consisting of CR_{z2}, S, N, NH, and O. The invention also provides uses of the compounds of formula (I) in the treatment of G9a-mediated diseases, as well as pharmaceutical compositions including these compounds. Advantageously, the compounds of the invention are highly potent and selective towards G9a target, among others.

Oxapi-27

Clause 14. The compound as defined in any one of the preceding clauses 1-13 for use in preventing or treating an EHMT2-mediated disorder in a subject in need thereof.

Clause 17. The compound for use of any one of the preceding clauses 14-16 for use in the treatment and/or prevention of a disease selected from the group consisting of Alzheimer's disease, amyotrophic lateral sclerosis, age-related tau astrogliopathy, aortic amyloidosis, argyrophilic grain disease, British familial dementia, cardiac amyloidosis, cerebral amyloid angiopathy, chronic traumatic encephalopathy, corneal dystrophies, corticobasal degeneration, Creutzfeldt-Jakob disease, Danish familial dementia, Down syndrome, familial amyloidosis, familial corneal amyloidosis, fatal insomnia, frontotemporal dementia, Gerstmann-Sträussler-Scheinker disease, globular glial tauopathy, hereditary cerebral hemorrhage with amyloidosis, Huntington's disease, inflammation-associated amyloidosis, kuru, Lewy bodies dementia, Mediterranean fever, Niemann-Pick disease type C, Parkinson's disease, Pick's disease, primary age-related tauopathy, progressive subcortical gliosis, progressive supranuclear palsy systemic amyloidosis, including transthyretin-associated amyloidosis and light-chain amyloidosis, subacute sclerosing panencephalitis and tuberous sclerosis.

International Application nº	PCT/EP2024/067680
Applicant	Universitat de Barcelona
Agent	Hoffmann Eitle, S.L.U
Inventors	Griñán-Ferré C, Pallàs M, Bellver A, Escolano MC, Vázquez S, Barbaraci C

Project starts
2021

Patent priority date
June 22, 2023

Filing date
June 24, 2024

International Publication Date
December 26, 2024

ISR issued
December 26, 2024

Technology transfer agreement
July-September, 2025

National phases
December 23, 2025

Pitfalls & risks to be considered

Animal-to-human translational risk

- ✓ Apply translational and pharmacodynamic **biomarkers**.
- ✓ Include **complementary animal models**.

Off-target effects

- ✓ Perform **epigenomic profiling** (ChIP-seq, ATAC-seq).
- ✓ Optimize **compound selectivity**.

Long-term efficacy or disease-modifying treatment

- ✓ Develop **early-response and progression biomarkers.**
- ✓ Conduct **long-term extension studies.**

Unexpected toxicity

- ✓ Implement **chronic and reversibility toxicity studies**.
- ✓ Use **gradual dose escalation** strategies.

Regulatory and clinical hurdles

- ✓ Engage in **early interactions with regulatory agencies (EMA/FDA)**.

High costs and long recruitment timelines

- ✓ Partner with **consortia or patient foundations** for better cohort access.
- ✓ **Multicenter or decentralized clinical trials** to speed up enrollment.
- ✓ Use **broader inclusion criteria**.

Partnering Opportunities

Pharma companies
Co-development or licensing opportunities

Academic & clinical research centers
Collaboration for preclinical and clinical PoC

Foundations & patient advocacy
Funding, visibility and regulatory support

Public-private partnerships
Co-funding and clinical trials support

Venture capital & business angels
Funding for the spin-off in pre-seed and seed rounds

FLAVII THERAPEUTICS · UNIVERSITAT DE BARCELONA

GeneOnline

Sanofi Acquires Vigil Neuroscience for $470 Million to Advance Neurodegenerative Disease Treatments

Sanofi has finalized an agreement to acquire Vigil Neuroscience for $470 million. This move comes nearly a year after Sanofi made an initial...

PR Newswire

Ionis enters agreement with Roche for two novel RNA-targeted programs for Alzheimer's disease and Huntington's disease

PRNewswire/ -- Ionis Pharmaceuticals, Inc. (Nasdaq: IONS) today announced that it has entered an agreement with Roche for two undisclosed...

Axonis Therapeutics bags $115m for neuromedicine development

Axonis Therapeutics, which specialises in neuromedicines, has announced $115m in Series A financing to advance its therapies.

MJFF awards $6m to Lario Therapeutics for Parkinson's research

The neurological disease is estimated to affect more than ten million people globally. The Michael J. Fox Foundation (MJFF) has awarded $6m...

Navarra Capital

Medibiofarma levanta un millón de euros para potenciar la fase clínica de tres fármacos

Medibiofarma, empresa biofarmacéutica navarra que se dedica a descubrir y desarrollar nuevas terapias para enfermedades de alta necesidad...

*"The moment of **G9a inhibitors for treating CNS conditions** is now, because it overcomes all barriers of medical chemistry."*

FLAVII THERAPEUTICS

UNIVERSITAT DE BARCELONA

Thanks for your attention!

Contact us:

Prof. Christian Griñán Ferré

Principal investigator and associate Professor

Christian.grinan@ub.edu

Faculty of Pharmacy and Food Sciences
University of Barcelona
Av. Joan XXIII, 27-31, building A,
08028 - Barcelona, Catalunya (Spain)