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CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

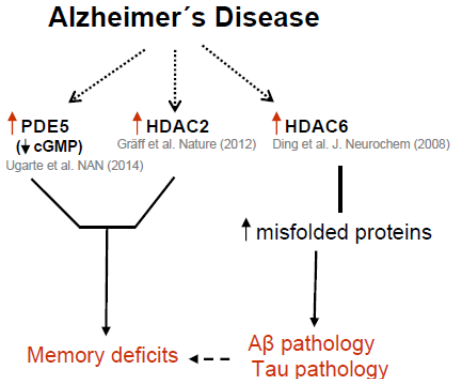
Alzheimer's Disease treatment:
a novel approach

- **Alzheimer's disease (AD)** is particularly devastating since there is no cure, no way to prevent it and no proven way to slow its progression.
- Currently, approximately **18 million people** worldwide are afflicted with this disease and it is projected to reach over **30 million** by 2025.
- **Novel strategy** for symptomatic & disease-modifying treatment of Alzheimer's disease hitting two independent but synergistic pathways: epigenetic (HDAC) and non-epigenetic (PDE5, over-expressed in the brain of AD patients)[1].
- Novel **proprietary compounds, first-in class dual inhibitors (HDAC and PDE5)**[2] show safety and efficacy in reversing AD phenotype using transgenic mice (APP/PS1, Tg2576)[3].

There is an imperative need to explore new therapeutic targets in Alzheimer's disease

Hypothesis: Targets proposal

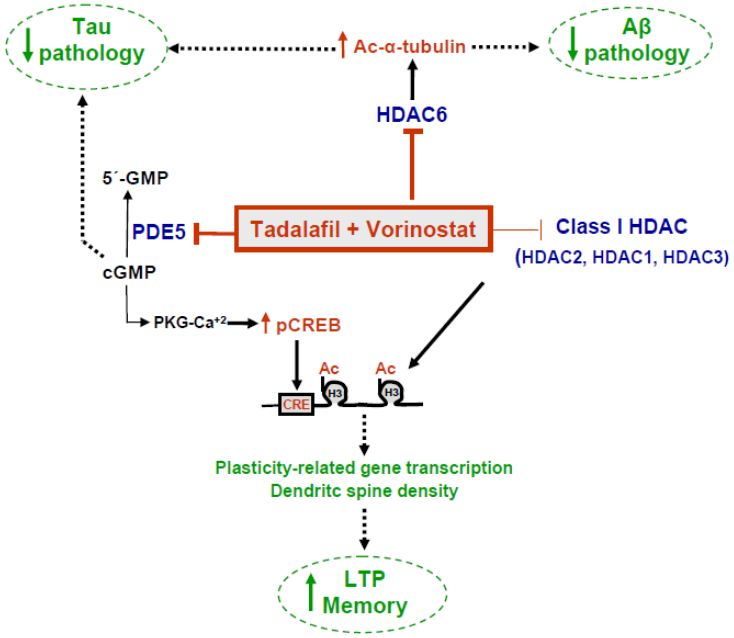
- ✓ By repressing gene transcription, HDAC2 plays a relevant role in memory function whereas HDAC6 is involved in axonal transport and protein aggregation.
- ✓ HDAC2 and HDAC6 are over-expressed in post-mortem brains of AD patients[4,5].
- ✓ PDE5 is over-expressed in post-mortem brains of AD patients, and levels of its substrate cGMP are reduced in CSF from AD patients[1].



Simultaneous inhibition of several targets is a strategy to attain synergistic efficacy and to improve safety profile

Hypothesis validation (proof of concept)

- ✓ Simultaneous inhibition of HDAC and PDE5 with reference compounds leads to a synergistic effect in AD models[6]



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CM-414 is a lead compound of a first-in-class chemical series that simultaneously inhibits class I HDAC, HDAC6 and PDE5[3]

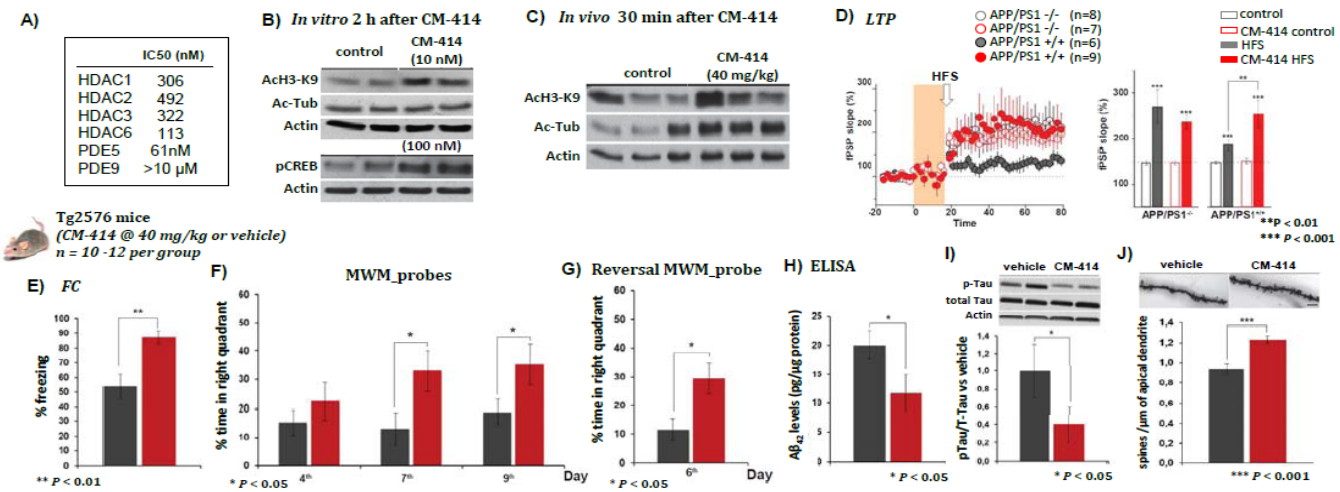
Product profile

- ✓ CM-414 has strong HDAC6 and PDE5 activity (IC_{50} values < 100 nM) (A).
- ✓ CM-414 has a **moderate** class I activity (IC_{50} 300-400 nM) **to minimize potential toxicity** associated to HDAC class I inhibition (A).
- ✓ CM-414 shows **functional effect** in neuronal culture, 10 nM for AcH3 and 100 nM for pCREB (B).
- ✓ CM-414 shows adequate ADME and pharmacokinetic profiles. The **half-life** (2.8 h) is optimal to trigger gene transcription avoiding sustained targets inhibitions.
- ✓ CM-414 **crosses BBB**, at a safe dose for chronic treatment, and shows *in vivo* functional response (histone acetylation and CREB phosphorylation) at brain level (C).
- ✓ CM-414 has an adequate therapeutic window, >2.7 log units.

CM-414 shows a sustained efficacy in AD animal models suggesting a disease modifying mechanism[3]

Preclinical assays

- ✓ CM-414 rescues impairment of Long-Term Potentiation (LTP) in APP/PS1 hippocampal slices (D)
- ✓ CM-414 (3-weeks of treatment) restores memory deficits in aged-AD Tg2576 mice (E, F)
- ✓ The **memory recovery** induced by CM-414 was maintained after a washout period of **4 weeks** in aged Tg2576 mice (G)
- ✓ Analysis of AD pathological marks in treated Tg2576 mice showed **significant decrease in amyloid and Tau pathology** (I).
- ✓ CM-414 treatment **reverts spine density loss** in the hippocampus of Tg2576 mice (J).



Intellectual Property	Strong IP position: WO2014131855, WO2016020307 and WO2016030345 (4 different chemical series)
Papers	[1]Ugarte A. et al. Neuropathol Appl Neurobiol. **2015**, *41,* 471; [2]Rabal et al., J Med Chem 2016 59: 8967-9004 [3]Cuadrado-Tejedor M., et al. Neuropsychopharmacology 2017 42: 524-539 [4]Gräff et al.Nature **2012**, 483 (7388); Ding et al. J. Neurochem **2008,** 106 (5); [6]Cuadrado-Tejedor M., et al. Clin Epigenetics. **2015**, 7:108.

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