cima
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.
- Management of AD represents a huge unmet **need**; thus, discovery and development of more effective therapies are critical for worldwide public health and health-care systems.
- **Novel strategy** for symptomatic & disease-modifying treatment of Alzheimer's disease hitting two targets, epigenetic (HDAC) and non-epigenetic (PDE5). Proof of Concept using reference compounds (vorinostat and tadalafil).
  - *In vitro* using primary neuronal cultures: synergistic effect on epigenetic mark (histone acetylation)
  - *Ex vivo*, using hippocampal slices from AD mice (APP/PS1): synergistic effect in long term potentiation (LTP).
  - *In vivo*, using AD mice (Tg2576): behavior studies and AD pathological marks.
- Novel **proprietary compounds, first-in class dual inhibitors (HDAC and PDE5)** show safety and efficacy in reversing AD phenotype using transgenic mice (APP/PS1, Tg2576).

Scope of the problem

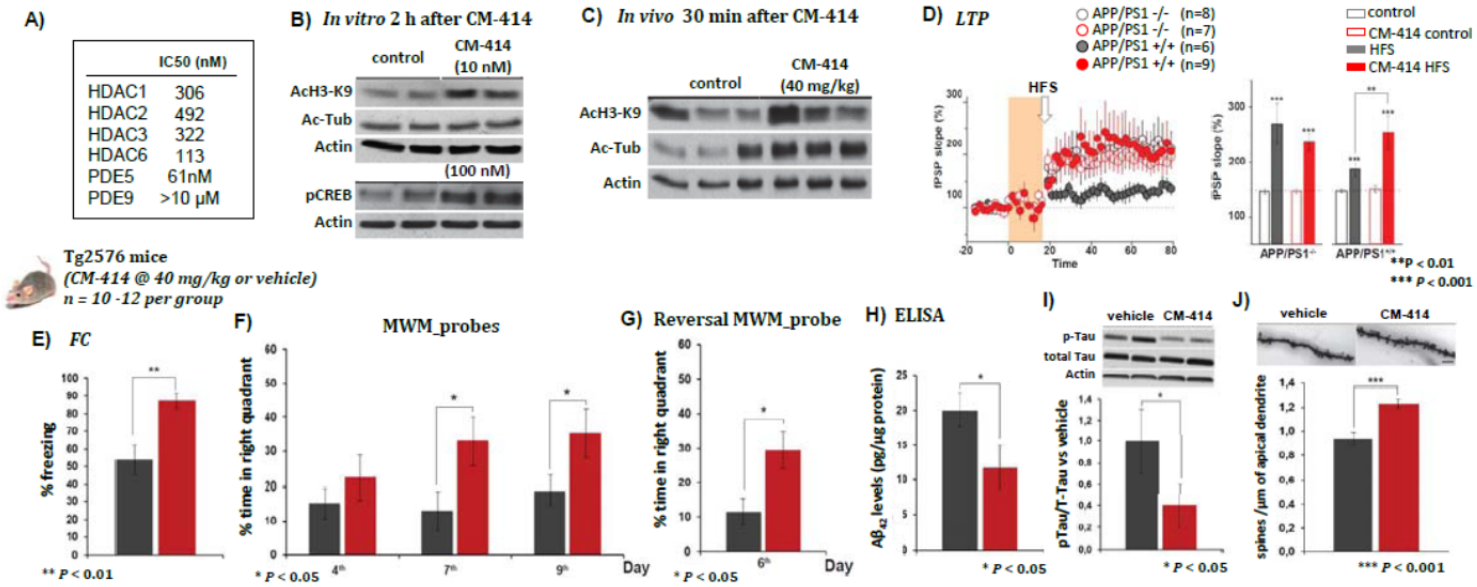
- Currently, approximately 18 million people worldwide are afflicted with this disease and it is projected to reach over 30 million by 2025.
- The current treatment options are only moderately effective. There is an unmet need for therapies that halt of substantially slow disease progression.
- Recent clinical trials of various disease-modifying therapies for AD failed to demonstrate benefit.

Patient need addressed

Substantially slow down the progression of Alzheimer's disease and improve symptoms.

Product Profile

- ✓ Multifactorial optimization process guided to the discovery of the proprietary pharmacological tool compound **CM-414**:
  - Binding affinities, for both targets (A); and, functional effect in neuronal culture, 10nM for AcH3 and 100nM for pCREB (B)
  - Efficacy, according to AD related markers (e.g. C99, pTau, …) in Tg2576 primary cultures, at low nM range
  - Crossing BBB and showing *in vivo* functional response - epigenetic mark- at brain level (hippocampus) (C).
  - Safety window, efficacy *vs* toxicity, >2.5 log units.
- ✓ Effect of CM-414 (200 nM) on slices from APP/PS1 mice showed a restoration of LTP impairment (D)
- ✓ Effect of CM-414 in AD Tg2576 mice, after chronic treatment (3 weeks), showed a <u>restoration of memory deficits</u> in two different behavioral tasks: the Fear Conditioning (C) and the Morris Water Maze (MWM) test (E-F).
- ✓ The memory recovery induced by CM-414 was <u>maintained after a washout period of 4 weeks</u> in aged Tg2576 mice (Reversal MWM test) (G)
- ✓ AD pathological marks analysis, from treated Tg2576 mice, showed significant <u>decrease in amyloid</u> ($A\beta_{42}$) (H) <u>and Tau pathology</u> (I) as well <u>as reversal in deficits in spine density</u> (J).



Intellectual Property

Strong IP position. Three patents filed (WO2014131855 and two unpublished yet) covering four different chemical series.

Contact: Jesús M. Hernández, MD, PhD | Chief Executive Officer | Email: jmhernandez@unav.es; Tel: +34 948 194 700