

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 independent but synergistic pathways: epigenetic (HDAC) and non-epigenetic (PDE5, over-expressed in the brain of AD patients).¹ Proof of Concept using reference compounds (vorinostat and tadalafil).²
 - *In vitro* using primary neuronal cultures: synergistic effect on epigenetic mark (histone acetylation, AcH3)
 - *Ex vivo*, using hippocampal slices from AD mice (APP/PS1): synergistic effect in long term potentiation (LTP)
 - *In vivo*, using AD mice (Tg2576): restoration of memory function and reduction of AD pathological marks
- Novel **proprietary compounds, first-in class dual inhibitors (HDAC and PDE5)**³ show safety and efficacy in reversing AD phenotype using transgenic mice (APP/PS1, Tg2576)⁴.

Scope of the problem

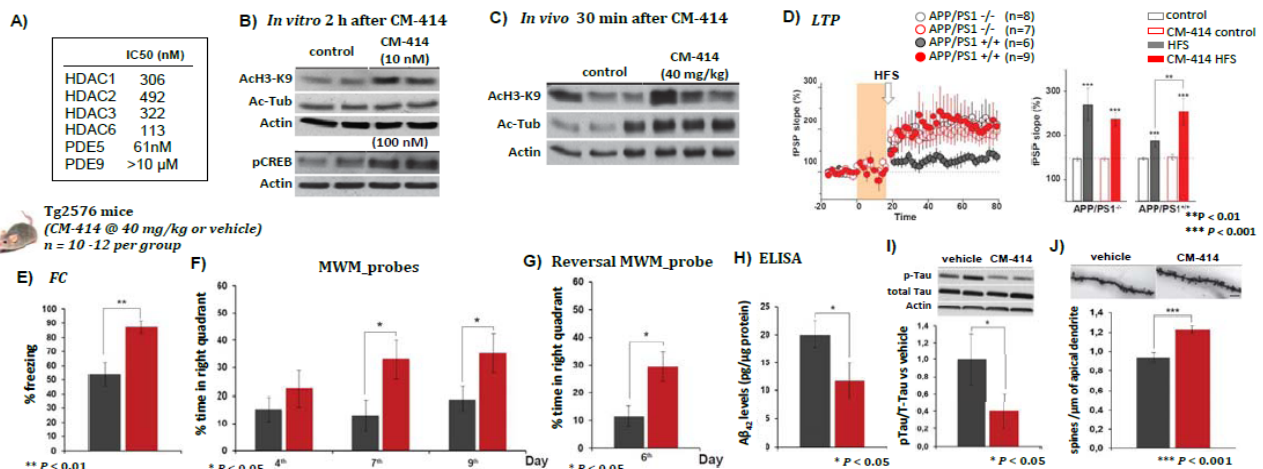
- Currently, approximately 18 million people worldwide are afflicted with this disease and it is projected to reach over 30 million by 2025.
- The current treatment options are only moderately effective; there is an unmet need.
- Recent clinical trials of disease-modifying therapies for AD failed to 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**:
 - Due to the synergistic effect, potent HDAC class I inhibition (related to toxicity effects) is not required to achieve an efficient AcH3. Binding affinities for HDACs and PDEs (A); and, functional effect in neuronal culture, 10nM for AcH3 and 100nM for pCREB (B).
 - Efficacy, according to reduce 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 restoration of memory deficits 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 maintained after a washout period of 4 weeks in aged Tg2576 mice (Reversal MWM test) (G)
- ✓ AD pathological marks analysis, from treated Tg2576 mice, showed significant decrease in amyloid (A β ₄₂) (H) and Tau pathology (through inhibition of GSK3 β) (I) as well as reversal in deficits in spine density (J).



Intellectual Property

Strong IP position: WO2014131855 (US and EP granted), WO2016020307 and WO2016030345

Papers

- ¹Ugarte A. et al. Neuropathol Appl Neurobiol. 2015, 41, 471; ²Cuadrado-Tejedor M., et al. Clin Epigenetics. 2015, 7:108. ³Rabal et al., J Med Chem 2016 59: 8967-9004 ⁴Cuadrado-Tejedor M., et al. Neuropsychopharmacology 2017 42: 524-53