**Alzheimer’s Disease treatment:**

**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).
- **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).

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.
- PDE5 is over-expressed in post-mortem brains of AD patients, and levels of its substrate cGMP are reduced in CSF from AD patients.

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.

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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 PDE5³

Product profile

- CM-414 has strong HDAC6 and PDE5 activity (IC₅₀ values < 100 nM) (A).
- CM-414 has a moderate class I activity (IC₅₀ 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 mechanism³

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

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<th>Papers</th>
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<tr>
<td>Strong IP position: WO2014131855, WO2016020307 and WO2016030345 (4 different chemical series)</td>
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