Novel strategy for symptomatic and disease-modifying treatment of Alzheimer’s Disease
Outline

• Institution: CIMA

• Project

• Partnering Opportunities
The Center for Applied Medical Research (CIMA) is private non-profit biomedical research institution of the University of Navarra, based in Pamplona, Spain.

CIMA carries out high quality scientific work with a strong translational focus.
CIMA. De-risking Drug Discovery Process

CUN
Medical Center

CIMA
Translating Basic Science

Pharmaceutical Industry

Drug Discovery & Development
Clinical
FDA

• Target Rich
  - BioBank
  - Patient Data
**CIMA. De-risking Drug Discovery Process**

**CUN Medical Center**

- **Target ID and Validation**
  - Basic Biological Research
    - siRNA, MoA, KO mice, peptides, ...
    - Cellular & Animal Models

**CIMA Translating Basic Science**

**Drug Discovery**

- Gene Therapy
- Molecular Therapeutics

**Pharmaceutical Industry**

- Drug Discovery & Development
- Clinical
- FDA

**Translational Medicine**
Bidirectional data analysis to identify and/or prioritize clinically relevant molecular targets or pathways.

**Basic Science**
Advanced basic research to decipher MoA underlying clinical evidence.

Implementation of *in-vitro* or *in-vivo* assays for unequivocal assessment: PoC

**Drug Discovery**
Proprietary tool(s), biologics or/and small molecules, for *in-vivo* PoC: efficacy & safety
CIMA. De-risking Drug Discovery Process

- Target ID and Validation
  - Basic Biological Research
    - siRNA, MoA, KO mice, peptides, ...
    - Cellular & Animal Models

- Drug Discovery
  - Gene Therapy
  - Molecular Therapeutics

- Pharmaceutical Industry
  - Drug Discovery & Development
  - Clinical
  - FDA

- Goal: Partnering, Licensing

- Expected Deliverables:
  i. Novel Target / MoA
  ii. In-vitro & In-vivo PoC with “drug-like” molecules or biologics: Efficacy & Safety → Advanced Lead(s)
  iii. Lead(s) with proprietary IP (Availability for further development)
  iv. “Know-how”
# Projects Overview

<table>
<thead>
<tr>
<th>Target(s)</th>
<th>Therapeutic effect</th>
<th>Target Validation</th>
<th>Hit Patent (IP)</th>
<th>Hit Explosion <em>in-vitro</em> assays</th>
<th>ADMET/PK</th>
<th>Lead ID <em>In-Vivo</em> Efficacy</th>
<th>Business Development</th>
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<tr>
<td>A &amp; B</td>
<td>Alzheimer’s Disease</td>
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*IP & “validated” targets*
## Projects Overview

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Chemical Probes identified (*IP and no IP*)
To Validate Targets and/or MoA

IP & “validated” targets
### Projects Overview

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</table>

**Chemical Probes identified** *(IP and no IP)*

To Validate Targets and/or MoA

**IP & “validated” targets**

To identify chemical probes
Outline

• Institution: CIMA

• Project

• Partnering Opportunities
Alzheimer’s Disease

Status

• Currently, approximately 18 million people worldwide.

• At least 11 million Americans expected to have the disease by the middle of the century, boosting the annual costs of health care to more than US$1 trillion.

Incidence

Prevalence


People Age 65 and Over in the U.S. with AD. Using the U.S. Census Bureau Estimates of Population Growth*
Alzheimer’s Disease

Status

- 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. Thus, it is emerging the idea that other pathways not directly linked to Aβ pathology should be explored.
Novel Strategy for the Treatment of AD

Aim

Effective therapeutic agents for the *symptomatic and disease-modifying* treatment of AD
Novel Strategy for the Treatment of AD

Aim

Effective therapeutic agents for the *symptomatic and disease-modifying* treatment of AD

Approach

1. Targets proposal & identification: *Systems Therapeutics* ✓
2. Targets validation ✓
3. Hit ID (proprietary chemical series, IP). ✓
4. Hit Explosion and Lead(s) ID, acceptable PK, *in-vivo PoC* ✓
5. Lead Optimization *On-going*
Targets Proposal

- **HDACs** *(Histone DeACetylases)*

  HDAC2 overexpression impairs memory formation whereas HDAC2 knockout mice exhibit enhanced memory formation
  

- • HDAC2 increases in AD patients


- • HDAC6 increases in AD patients

  Ding et al., J. Neurochem (2008)

  A. Garcia-Osta et al. Neuropsychopharmacology (2009)
• “Target B”

  • “Target B” mRNA expression in hippocampus

 CSF levels of “Target B1” biomarker are significantly associated to cognitive status (MMSE score) and CSF levels of Aβ\(_{1-42}\) in patients with AD, which may confirm its implications in AD.

• CSF levels of “Target B1” biomarker

1 Determined by LC-MS/MS

* p≤0.05, n=83 patients

• SCI, subjective cognitive impairment
• Mild AD, patients with mild Alzheimer’s dementia.

Ugarte et al., (under revision)
Hypothesis Proposal: Systems Therapeutics

• **Aim:** Dual inhibitors targeting “Target B1” & HDACs
  (exploring different selectivity profiles)

- Plasticity-related gene transcription
- Dendritic spine density
- Memory/plasticity
- Tau pathology
- Intracellular transport
  - Cytoskeletal stability
  - Ac-α-tubulin
- Aβ pathology
- iClass IIb (HDAC6)

- Class I HDACs (HDAC2, HDAC1, HDAC3)
- HAT

- pCREB-Ser133
- PKA/PKG-Ca^2+
- pGSK3β-Ser9

- Ding et al., Exp Neurol. (2008)
- Sung et al., Exp Neurol. (2013)
- Govindarajan et al. EMBO (2012)
- Garcia-Barrero et al., (in-press)
Hypothesis Validation

• PoC

✓ iHDAC & i”Target B 1”

SAHA & “Compound B”

*In vitro* (neuronal primary culture)
- WT neurons: AcH3, pCREB
- Tg2576 neurons: AcH3, pCREB, AcTub, C99 and pTau

*In vivo* (AD mouse model: Tg2576 mice)
- Memory function: FC and WM
- Dendritic spine density (Golgi Cox)
- Biochemical determinations: memory and AD-related marks
Hypothesis Validation

• **PoC:** *In vitro* assays in WT-primary neuronal culture

• **AcH3-K9**

![Graphs showing in vitro assays results](image)

### Graph 1:
- X-axis: Compound concentrations (10 nM, 100 nM, 500 nM)
- Y-axis: D.O. (arbitrary units)
- Bars for SAHA and Compound B
- Significant differences indicated by asterisks (*)

### Graph 2:
- X-axis: Compound B concentrations (50, 12.5, 25, 200 nM)
- Y-axis: D.O. (arbitrary units)
- Significant differences indicated by asterisks (*) and triple asterisks (***)

---

*SAHA Compound B***

(nM)(-)

12.5 25 200

(nM)(-)

50 50 50 50

0

1

2

3

4

5

6

7

8

D.O. (arbitrary units)

SAHA Compound B

D.O. (arbitrary units)

SAHA Compound B

XII Encuentro de Cooperación Farma-Biotech
Santiago de Compostela, September 2014
Hypothesis Validation

- **PoC**: *In vivo* studies using Tg2576 AD mouse model

**Animals: (14-16-month)**
- i. WT vehicle (n=7)
- ii. Tg2576 vehicle (n=8)
- iii. Tg2576 “Compound B” 1 mg/Kg (n=7)
- iv. Tg2576 SAHA 12.5 mg/Kg (n=7)
- v. Tg2576 “Compound B” & SAHA (n=8)

**Tg2576 (hAPP<sup>Swe</sup>)**

- Memory impairment
- Synaptic pathology
- Amyloid burden
- Tau pathology
- Neuroinflamation

Mice 14-16 month-old

**Week**

1 2 3 4 5 6 7

**24h**

Sacrifice

Mice 18 month-old

**STOP treatment**

“Compound B”, SAHA, SAHA&“compound B” or vehicle i.p.

**Hippocampus**

Animals: (14-16-month)
Hypothesis Validation

- **PoC: In vivo** studies using Tg2576 AD mouse model

Animals: (14-16-month)

- i. WT vehicle (n=7)
- ii. Tg2576 vehicle (n=8)
- iii. Tg2576 “Compound B” 1 mg/Kg (n=7)
- iv. Tg2576 SAHA 12.5 mg/Kg (n=7)
- v. Tg2576 “Compound B” & SAHA (n=8)

Two-way repeated measures ANOVA followed by Scheffe’s test

- Tg2576 SAHA vs Tg2576 saline ¥¥ (p<0.01)
- Tg2576 SAHA+Cmpd B vs Tg2576 saline *** (p<0.001)
- Tg2576 SAHA+Cmpd B vs Tg2576 Cmpd B 1 mg/kg ### (p<0.001)
- Tg2576 SAHA+Cmpd B vs Tg2576 SAHA $ (p<0.05)
Biological Chemistry: Hit ID

• **Aim:**
  
i.- First-in-class dual inhibitors: molecules targeting “Target B” & HDACs

ii.- Novel chemical series with proprietary IP

• **Approach:**
  
- Knowledge-based
- Structure-based

  \[
  \text{\textbf{de-novo design}}
  \]

• **Achievement:**

  ✓ Hit ID: Synthesis and biochemical evaluation

  ✓ IP – patents filed in 2013 & 2014 (4 different chemical series)
**Medicinal Chemistry: Lead ID**

- **Aim:** From Hit Explosion to Lead ID

- **Approach:**

  a) Synthesis of new compounds to establish Structure Activity/Property Relationships (SAR/SPR)

  b) Workflow,

  i.- Design
  ii.- Synthesis
  iii.- *In-vitro* binding assays (vs “Target Bs” & HDACs) *(initial decision point)*
  iv.- *In-vitro* functional assay (primary neuronal culture, WT & Tg2576):
    - pCREB, AcH3, AcTub, pTau and C99 *(decision point)*
  v.- Toxicity (THLE-2, neuron/glia & PBMC) *(decision point)*
  vi.- ADME profiling
  vii.- Pharmacokinetics: crossing BBB & functional response (pCREB, AcH3) *(decision point)*
  viii.- *In-vivo* efficacy model(s)
Medicinal Chemistry: Lead ID

**Aim:** From Hit Explosion to Lead ID

**Results:**

- Currently, >180 new compounds have been synthesized
- CM-414 was selected as the first lead compound for *in-vivo* studies
- Three additional compounds with different selectivity profiles have been also selected for *in-vivo* studies – corresponding studies are currently *on-going*
# Lead ID. CM-414 profiling

<table>
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<tr>
<th>Efficacy</th>
<th>PK</th>
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<tbody>
<tr>
<td>Binding affinities (HDAC2, HDAC6 &amp; Target B):</td>
<td>Pharmacokinetics (e.g. Vz &amp; $t_{1/2}$) @ 40 mg/Kg in mice (i.p.)</td>
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<tr>
<td>AcH3 (functional assay, WT neurons)</td>
<td>0.5 (L/Kg) and 1.4 % (248 nM)</td>
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<tr>
<td>AcTub (functional assay, WT neurons)</td>
<td>Functional response achieved, Increment in AcH3 and pCREB in hippocampus @ 2 hours</td>
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<tr>
<td>pCREB (functional assay, WT neurons)</td>
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<tr>
<td>APP processing (functional response, Tg2576 neurons)</td>
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</tr>
<tr>
<td>pTau (functional response, Tg2576 neurons)</td>
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<tr>
<td>IC$_{50}$ (nM): 492, 110 &amp; 61</td>
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<tr>
<td>EC$_{max}$ (nM): 10 (190%)</td>
<td>Therapeutic window ~ 3 log units</td>
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<tr>
<td>EC$_{max}$ (nM): 100 (110%)</td>
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<td>EC$_{max}$ (nM): 100 (360%)</td>
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<th>In-Vitro ADME</th>
<th>Toxicity</th>
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<tr>
<td>P450s: 1A2, 2C19, 2C9, 2D6, 3A4 (&lt;50% @ 10mM)</td>
<td>THLE-2 @ 72 hours</td>
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<td>Plasma Protein Binding (% unbound)</td>
<td>Neurons @ 72 hours</td>
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<td>Brain protein binding (% unbound)</td>
<td>PBMC @ 72 hours</td>
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<td>Solubility (at pH=7.4)</td>
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<td>PAMPA (Pe 10$^{-6}$ in nm/s)</td>
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<td>Liver Microsomal Stability (t$_{1/2}$ estimation) in minutes</td>
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<tr>
<td>OK, except 3A4 (75.2%)</td>
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<td>1.8 (H), N.D. (M)</td>
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<tr>
<td>8.4% (M)</td>
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<td>29.8 µg/mL (intermediate)</td>
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<td>0.52 (Low)</td>
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<td>40.1(H), 3.3(M)</td>
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<td>hERG binding</td>
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<td>Patch Clamp</td>
<td>IC$_{50}$: &gt;100 µM</td>
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<td>IC$_{50}$: on-going</td>
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~ Therapeutic window
**Lead ID. In-Vivo Proof-of-Concept (PoC)**

**Animals** utilized in this study: **14-16 month-old**

- WT vehicle (n=12)
- Tg2576 vehicle (n=11)
- Tg2576 SAHA (12.5 mg/Kg) + Compound B (1 mg/Kg) (n=12)
- Tg2576 CM-414 (40 mg/Kg) (n=11)

**In-vivo efficacy (aged-Tg2576 mice)**

Week 1, 2, 3, 4, 5, 6, 7

24h Sacrifice

2.5h FC

3. WM

CM-414, SAHA+Compound B or vehicle i.p.

Reversal_WM

STOP treatment
**Lead ID. In-Vivo Proof-of-Concept (PoC)**

- **Behavior:** Fear Conditioning test after 2 weeks of treatment

One-way ANOVA followed Sheffé test **p<0.01**
**Lead ID. In-Vivo Proof-of-Concept (PoC)**

- **Behavior:** Water-Maze (WM) test after 4 weeks of treatment

![Graph showing Water-Maze (WM) test results](image)

**Hidden Platform**

Two-way repeated measures ANOVA followed Sheffe test

- WT vehicle vs Tg2576 vehicle ### (p<0.001)
- Tg2576 SAHA + Compound B vs Tg2576 vehicle +++ (p<0.001)
- Tg2576 CM-414 vs Tg2576 vehicle *** (p<0.001)
**Lead ID. In-Vivo Proof-of-Concept (PoC)**

- **Behavior:** Water-Maze (WM) test after a washout period of 4 weeks of treatment

The memory recovery induced by CM-414 was maintained after a **washout period** of 4 weeks in aged Tg2576.
Lead ID. *In-Vivo* Proof-of-Concept (PoC)

- **Tau and Amyloid pathology** (*parieto-temporal cortex*)

![Graph showing Eta and Amyloid pathology](image)

- **pTau**
  - Tg2576 vehicle
  - Tg2576 SAHA (12.5 mg/Kg) + Cmpd B (1 mg/Kg)
  - Tg2576 CM-414 (40 mg/Kg)

- **APP**
- **C99**
- **Aβ**

**Statistical Analysis:**
- One-way ANOVA followed Sheffè test; *p* < 0.05

**Key Points:**
- Lead ID:
- In-Vivo Proof-of-Concept (PoC)
-Tau and Amyloid pathology: (parieto-temporal cortex)

**Graph Details:**
- D.O. (fold-change) vs. Treatment Groups
- Bars represent treatment effects with statistical significance indicated:
  - *p* < 0.05
  - **p** < 0.01

**Additional Information:**
- APP
- C99
- Aβ
**Lead ID. In-Vivo Proof-of-Concept (PoC)**

- **Reversal of defects in spine density**

Dendritic spine density

**CA1 pyramidal neurons (hippocampus)**

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**Graphs:**

**Figure 1:**
- **XTG2576 vehicle**
- **Tg2576 SAHA (12.5 mg/kg) + Cmpd B (1 mg/kg)**
- **Tg2576 CM-414 (40 mg/kg)**

**Y-axis:**
- spine/µm of apical dendrite

**X-axis:**
- t-Student test * p<0.05

**One-way ANOVA followed Sheffè test *** p<0.001**
**Lead ID. In-Vitro Proof-of-Concept (PoC)**

- **Functional in-vitro screening by Long-Term Potentiation (LTP) – on-going**

Consequences on synaptic plasticity in APP/PS1 mouse model – *preliminary results*

![Graph showing synaptic plasticity measurement](chart.png)
Lead ID. *In-Vivo* Proof-of-Concept (PoC)

- Gene-expression profiling after a 4-weeks washout period

✓ Gene expression profiling in hippocampus of aged-Tg2576 mice after the washout period using Affymetrix microarray-based gene-expression technology (*Mouse Gene 2.0 ST Array*)

- Saline
- Compound B
- SAHA
- SAHA+Compound B
- CM-414
Lead ID. *In-Vivo* Proof-of-Concept (PoC)

- Gene-expression profiling after a 4-weeks washout period

Physiological System Development and Function

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<th>Name</th>
<th>p-value</th>
<th># Molecules</th>
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<tr>
<td>Behavior</td>
<td>5.39E-04 - 3.45E-02</td>
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</table>

**Fold change vs Tg2576**

**Protein expression**

- Tg2576 vehicle
- Tg2576 SAHA + Cmpd B
- Tg2576 CM-414

EphB2

mRNA expression

Protein expression

one-way ANOVA followed Sheffé test; * p<0.05  ** p<0.01

Nature 469, 47–52 (2011)
**Timeline & Next Steps: Lead Optimization**

- **Timeline**

  - **2012**
    - MoA
    - In-vitro PoC
    - Assessment: 1Q13
  - **2013**
    - Hit ID
    - Chemical probe
    - In-vitro PoC
  - **2014**
    - Hit to Lead
    - 1FTE → 2FTE
    - Lead ID
    - In-vivo PoC
    - Gene expression
  - **2015**
    - Lead Optimization
    - Patent application
    - New patent application
    - Leads, different profiles
    - In-vivo PoC

  - **1Q13**
    - In-Vivo PoC
    - SAHA & “Cmpd B”
  - **2014**
    - Gene expression
  - **2015**
    - 02Q15

- **Lead Optimization** process is *on-going*, mainly focused on:

  - i.- Improving crossing BBB; thus, reducing dose till 10mg/Kg (aim: FIH PoP)
  - ii.- Pharmacokinetics (oral admin; mainly focused on solubility and permeability)

- **ID optimal compound’s target profile.** Balance among HDACs and “Target B”, *impact on gene-expression*
Outline

• Institution: CIMA

• Project

  • Partnering Opportunities
Partnering Opportunities

• Value Proposition

- Novel Mode of Action, a system therapeutics strategy: “Target B” & HDACs
  a) Targets and their corresponding functional marks dysregulated in AD patients.
  b) This dual inhibition leads to synergistic effect in epigenetic mechanistic pathway.

- First-in-class dual inhibitors targetting “Target B” and HDACs

- Proprietary chemical series; patents filed in 2013 & 2014

- Identified lead compound for in-vivo Proof of Concept:
  a) Adequate safety window and PK to perform chronic in-vivo PoC, no toxicity issue
  b) Remarkable efficacy from three perspectives:
    i.- Behavioural models: FC, WM and reversal WM after washout period (4 weeks)
    ii.- Disease modifying markers: Amyloid & Tau pathology
        Reversal in deficits in spine density (and LTP)
    iii.- Over-expression of memory related genes: e.g. EphB2
Partnering Opportunities

• Partnering

Two scenarios are initially envisioned:

1. Product license (IP)
2. Stepwise research investment & first option (right of first refusal)
Acknowledgements

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