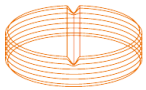
XI Encuentro de Cooperación Farma-Biotech

New epigenetic agents: therapeutic approach in cancer

cima
CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

Madrid, 2 de julio de 2014

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD



MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

Outline

- **Institution: CIMA**
- **Project**
- **Partnering Opportunities**

CIMA

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

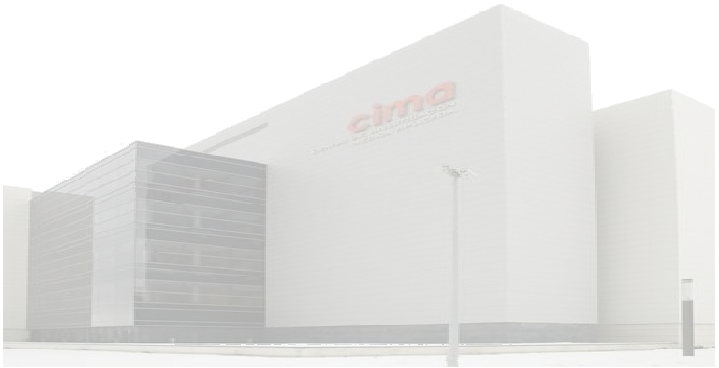
CUN

Medical Center

- **Target Rich**
  - BioBank
  - Patient Data

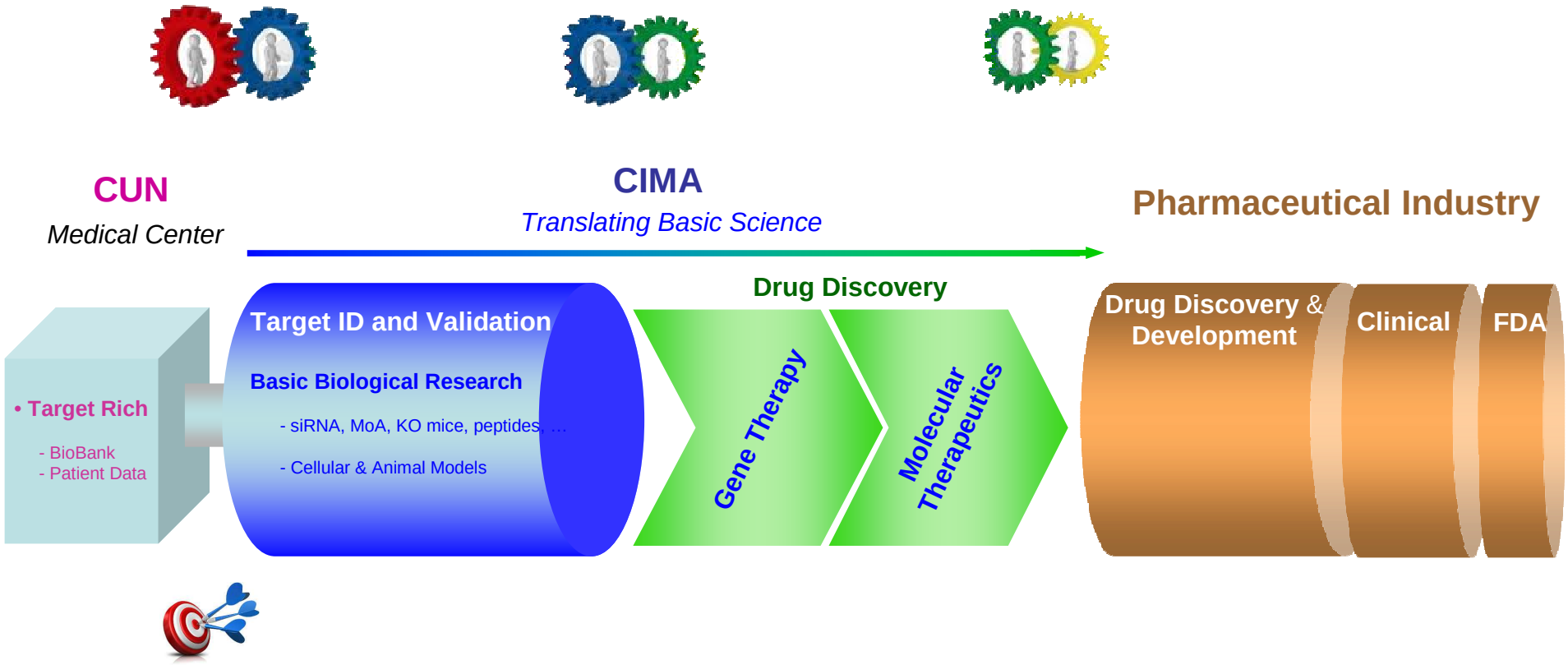
CIMA

Translating Basic Science



Pharmaceutical Industry

CIMA. De-risking Drug Discovery Process



• 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/and *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

From Bed to Bench and Back

CUN

Medical Center

CIMA

Translating Basic Science

Pharmaceutical Industry

Drug Discovery

- **Target Rich**
  - BioBank
  - Patient Data

Target ID and Validation

Basic Biological Research

- siRNA, MoA, KO mice, peptides …
- Cellular & Animal Models

Gene Therapy

Molecular Therapeutics

Goal: Partnering Licensing

Drug Discovery & Development | **Clinical** | **FDA**

- Expected Deliverables:

  i.- **Novel Target / MoA**

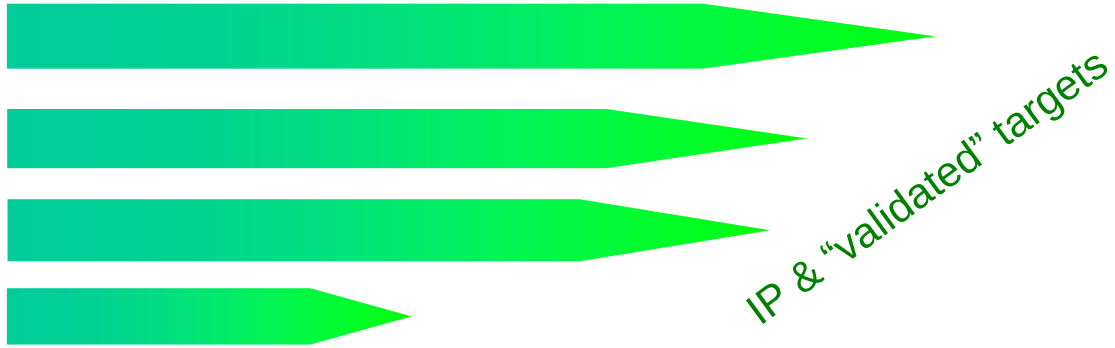
  ii.- In-vitro & **In-vivo PoC** with "drug-like" molecules or biologics: **Efficacy & Safety** → Advanced **Lead(s)**

  iii.- Lead(s) with **proprietary IP** *(Availability for further development)*

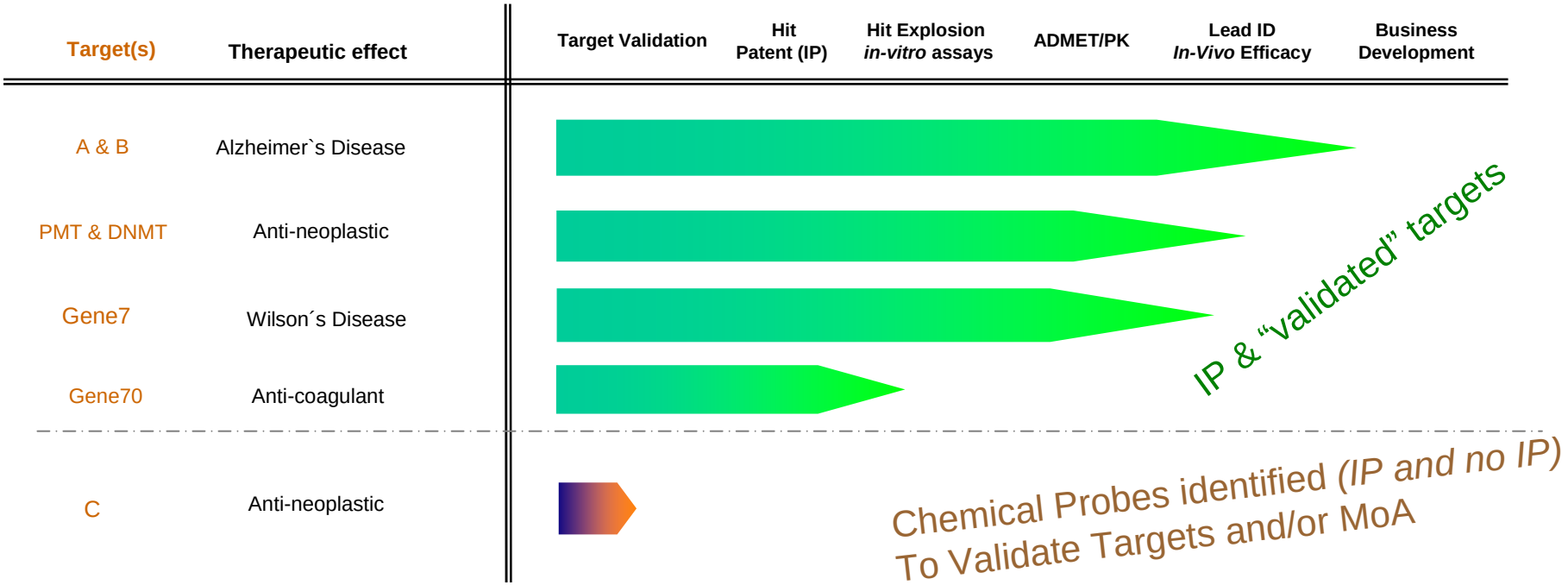
  iv.- **"Know-how"**

Projects Overview

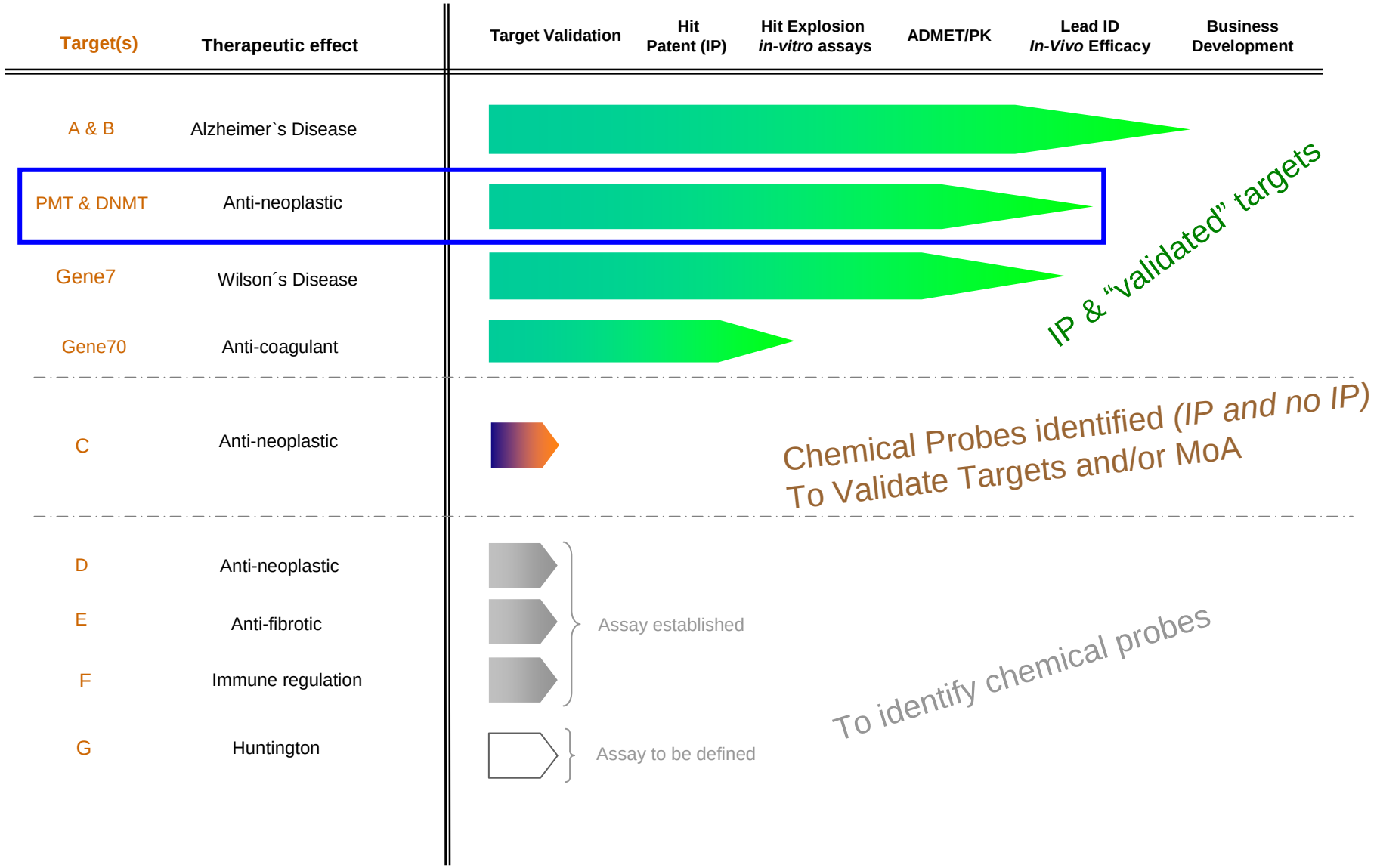
Target(s)	Therapeutic effect
A & B	Alzheimer`s Disease
PMT & DNMT	Anti-neoplastic
Gene7	Wilson´s Disease
Gene70	Anti-coagulant



Projects Overview



Projects Overview



Outline

- Institution: CIMA
- **Project**
- Partnering Opportunities

Targeting Epigenetics: **Cancer**

Aim

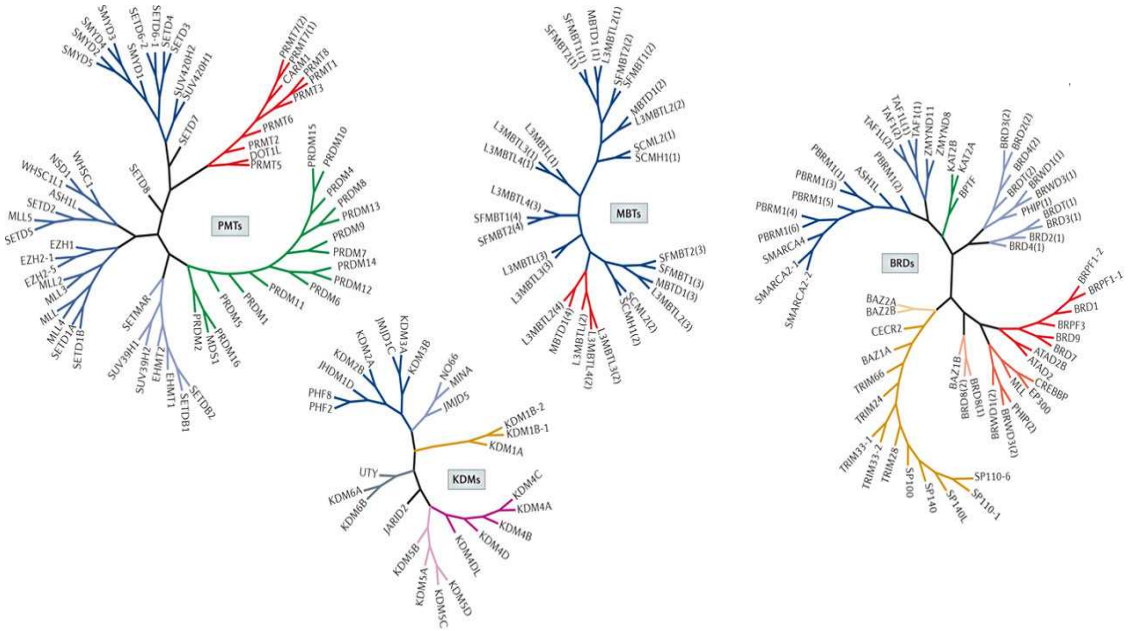
Effective therapeutic agents targeting a novel epigenetic MoA: *Unmet needs in cancer*

Approach

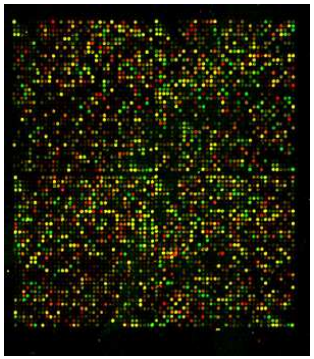
1. Target identification strategies: siRNAs, functional and expression studies ✓
2. Targets validation ✓
3. Hit ID (proprietary chemical series, IP). ✓
4. Hit Explosion and Lead(s) ID, acceptable PK, *in-vivo* PoC ✓
5. Lead Optimization ***On-going***

Target Identification

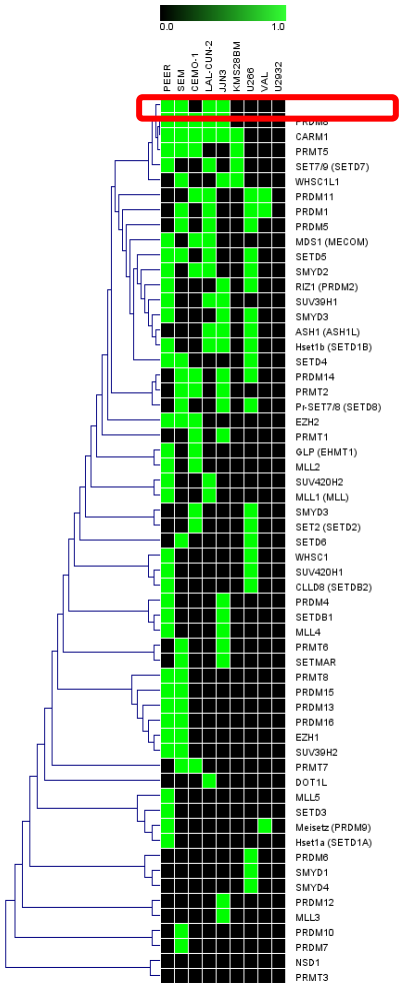
- **Use of siRNAs**



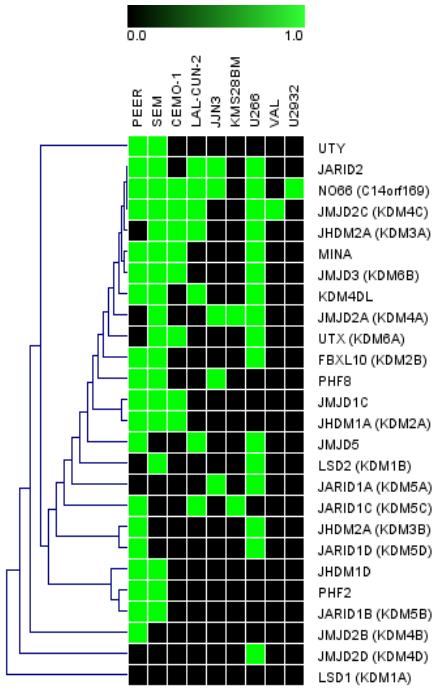
- **Expression studies: RNA-seq, ChIP on Chip**



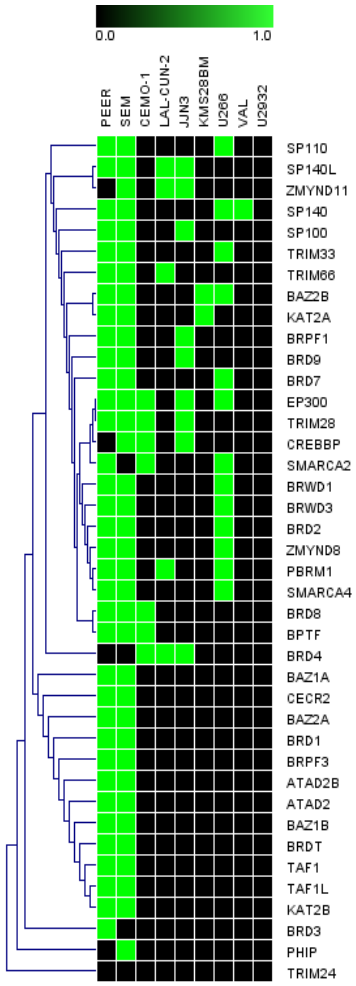
Target Identification. ***Hematologic disorders***



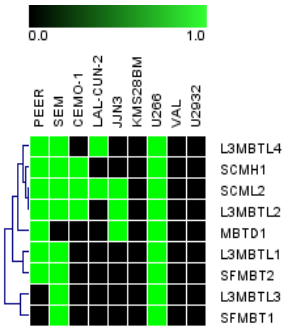
PMTs: Target1
Target2
Target3



KDMs: Target4
Target5



BRDs: Target6

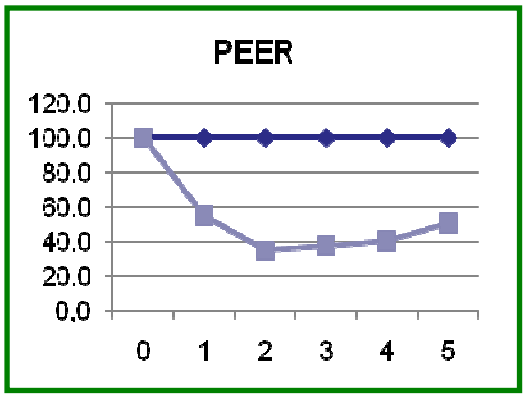


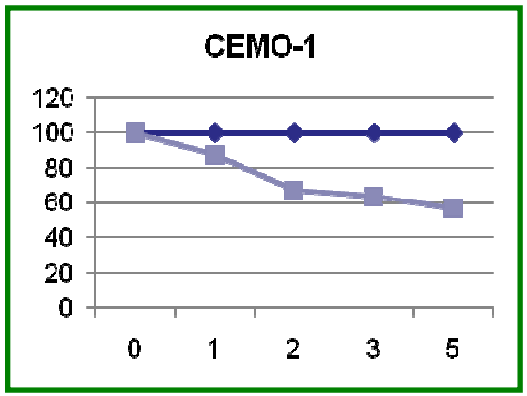
MBTs: Target7
Target8

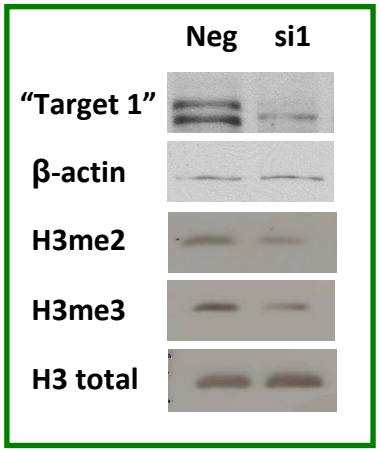
Target ID & Validation. ***Hematologic disorders***

- **"Target1"** is a mammalian histone methyltransferase that contributes to the epigenetic *silencing* of tumor suppressor *genes*.

- **"Target 1" inhibition with siRNA in ALL cell lines**

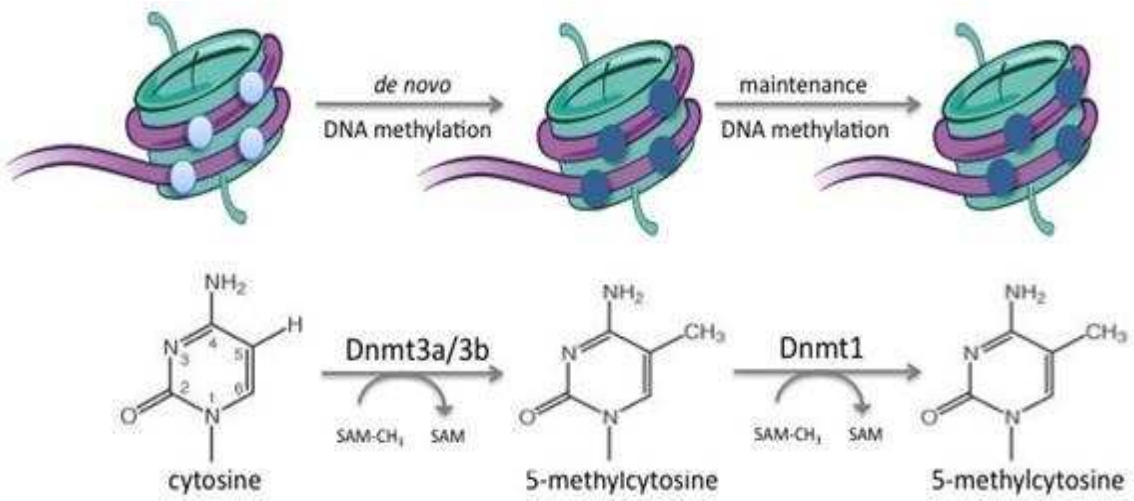






Target ID & Validation. ***Hematologic disorders***

- **DNMTs** *(DNA methyl transferases)*



- **State of the art:**

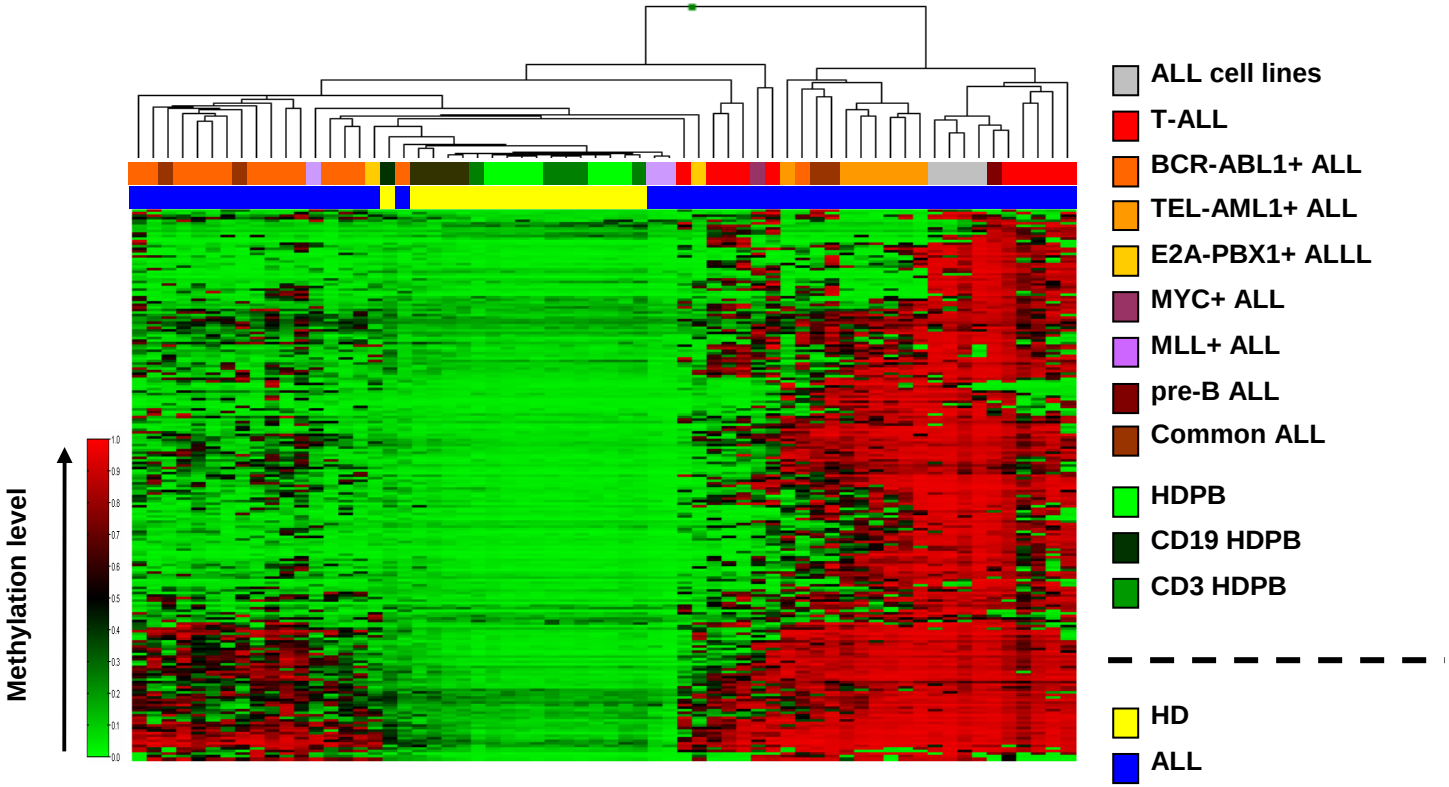
- Azacitidine
- Decitabine

} **Marketed →** irreversible covalent complex with DNMT1
where DNA hypomethylation is observed at 300nM & 30nM respectively

- SGI-110 **Phase 2 →** irreversible covalent complex with DNMT1

Target ID & Validation. ***Hematologic disorders***

- **DNMTs** *(DNA methyl transferases)*



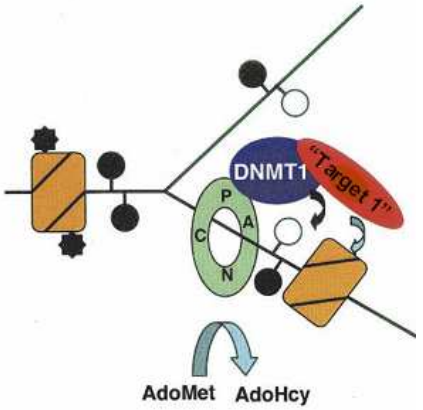
Agirre X, Vilas-Zornoza A. PLoS ONE 2011

Biological Chemistry: Hit ID

- **Aim:**

  i.- First-in-class dual and *reversible* inhibitors: molecules targeting "**Target1**" & **DNMTs**

  ii.- Novel chemical series with proprietary IP



- **Approach:**

  - Knowledge-based
  - Structure-based

  } ***de-novo* design**

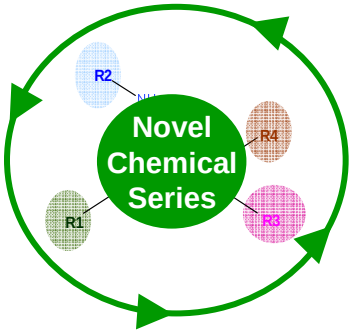
- **Achievement:**

  ✓ • Synthesis

  ✓ • IP – *patent filed in June 2014*

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,

SAR

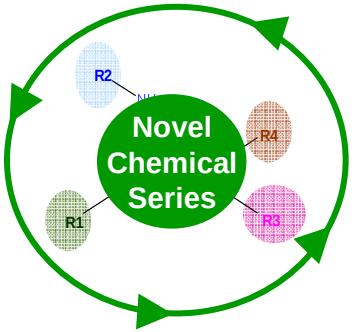
i.- Design
ii.- Synthesis
iii.- *In-vitro* binding assays (vs “Target 1” & DNMT1) *(initial decision point)*
iv.- *In-vitro* cellular assay (MTS)
v.- *In-vitro* functional assay (cellular, epigenetic marks)

SPR

vi.- Toxicity (THLE-2 & PBMC) *(decision point)*
vii.- ADME profiling
viii.- Pharmacokinetics *(decision point)*
ix.- *In-vivo* efficacy model(s)

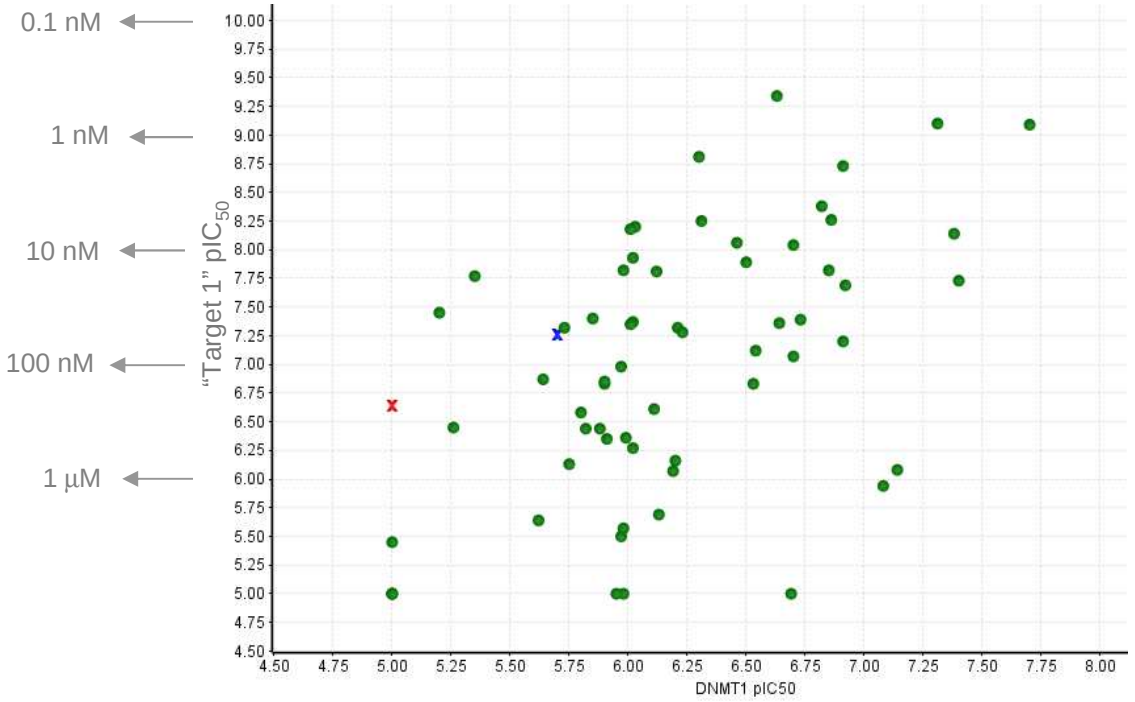
Lead ID: Biochemical Profiling

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



  - 71 compounds synthesized

  - **Biochemical assay** *vs* **"Target 1" & DNMT1**



References:

Compound 1

Compound 2

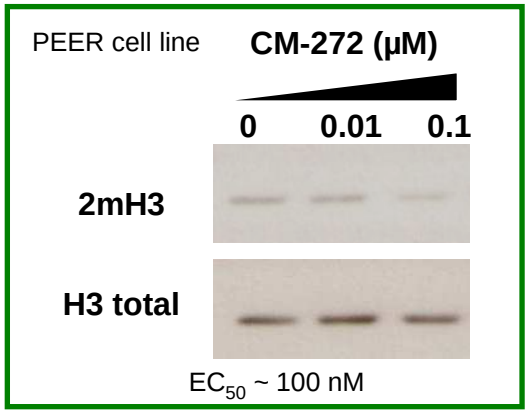
Proprietary Molecules

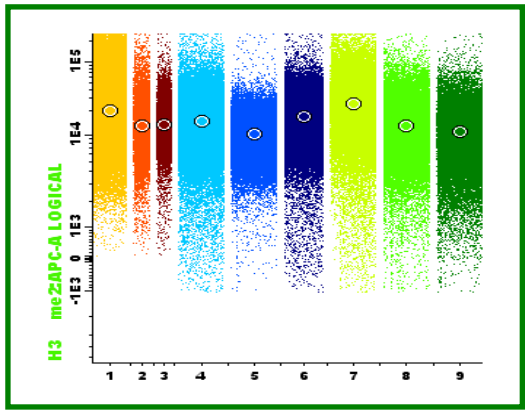
Lead ID: Functional profiling

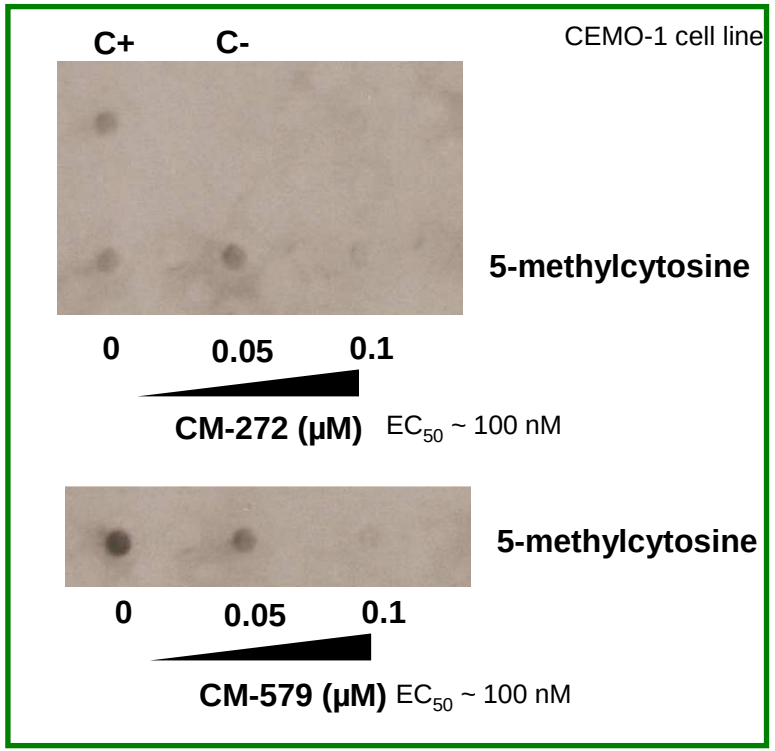
• Selected, from our proprietary chemical series, as pharmacological tool compounds: **CM-272** & **CM-579**

"Target 1"	IC_{50} (nM)	9	7
DNMT1	IC_{50} (nM)	347	42
DNMT3A	IC_{50} (nM)	85	92
DNMT3B	IC_{50} (nM)	256	974

• **Epigenetic marks,** *in-vitro* cellular

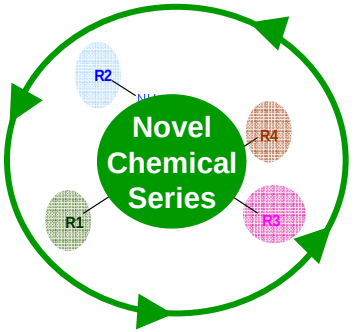






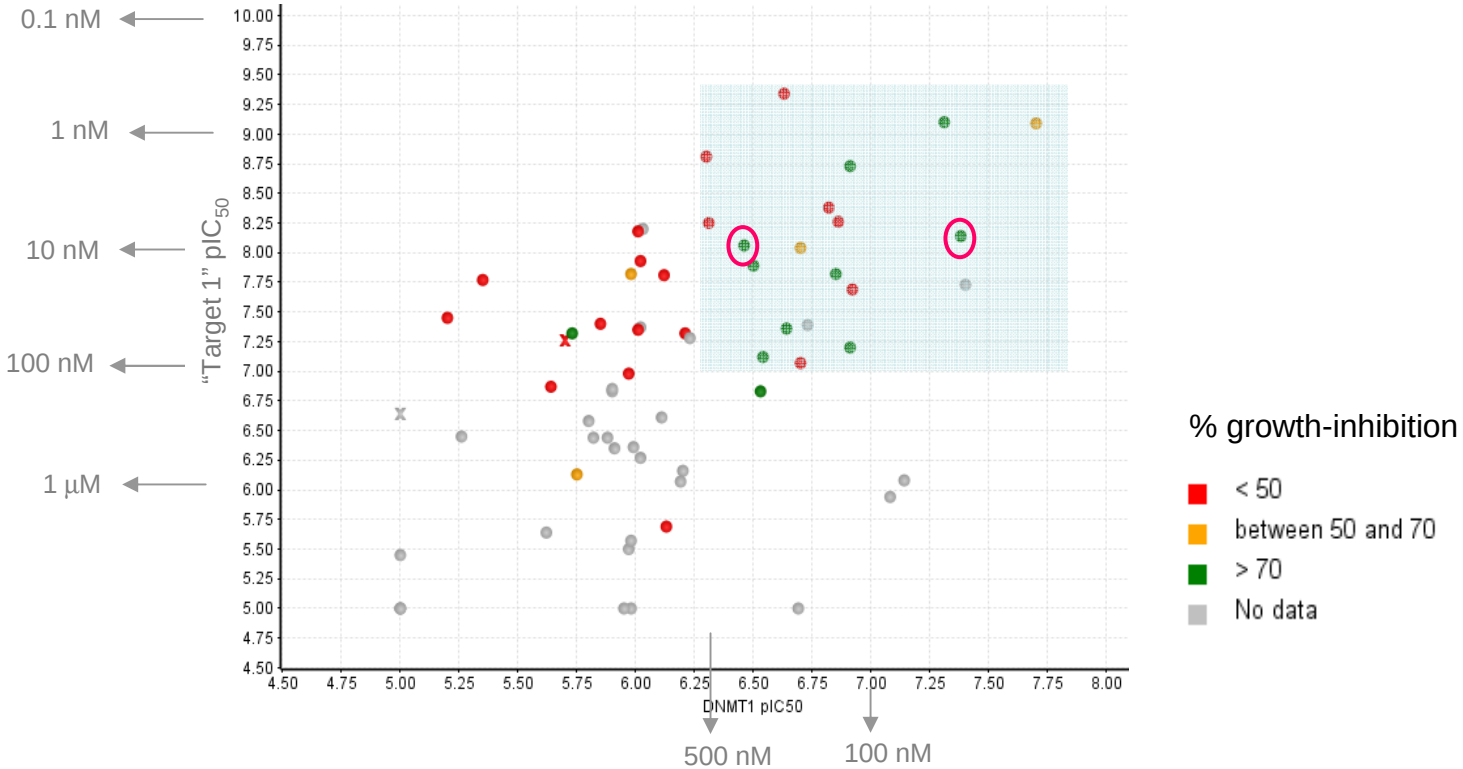
Lead ID: Cell proliferation

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



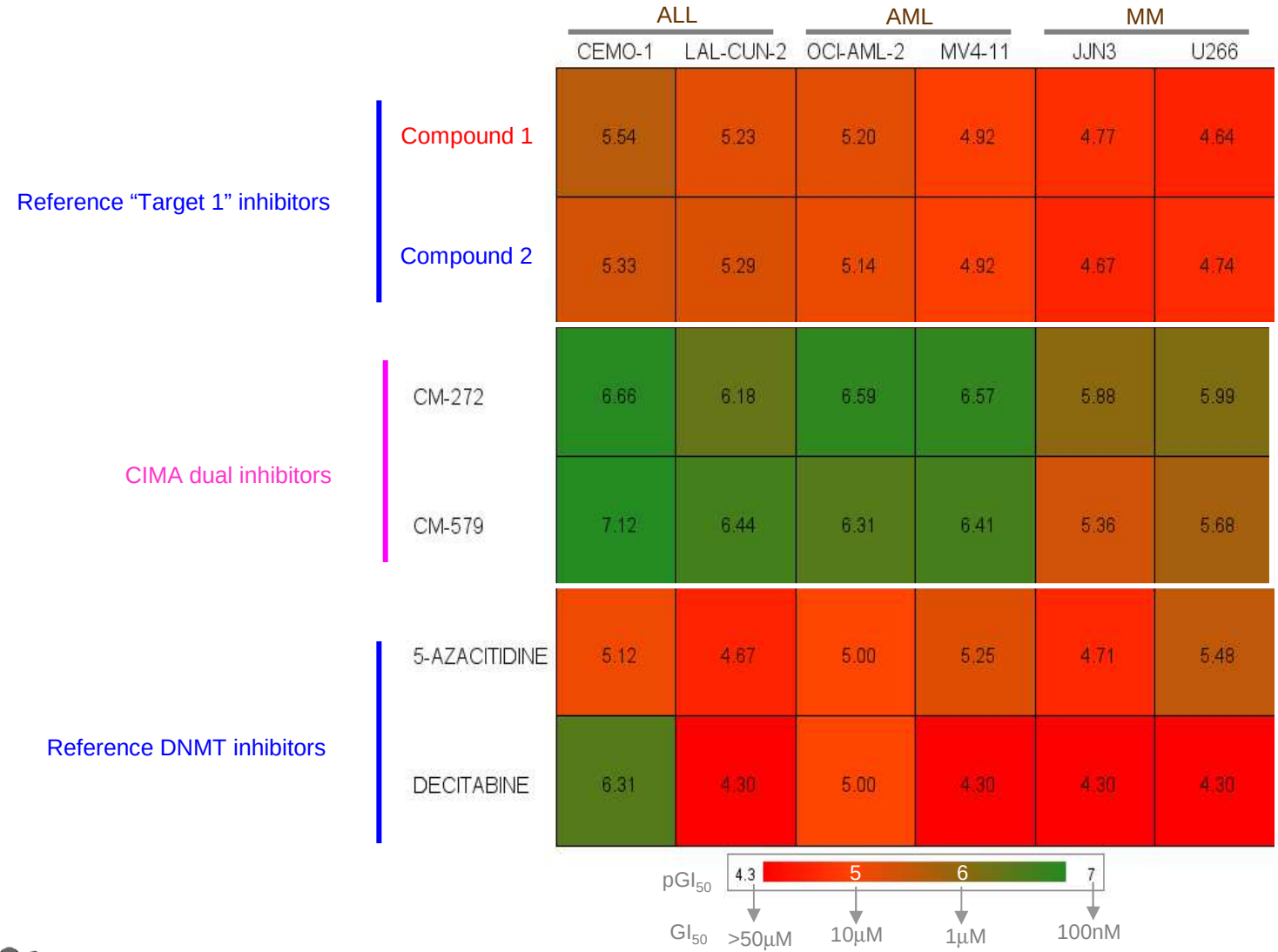
  - 71 compounds synthesized

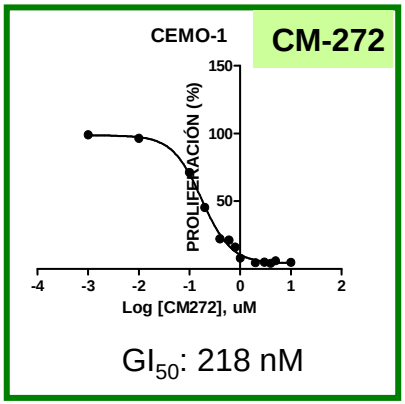
  - **Biochemical assay** *vs* **"Target 1" & DNMT1;** colour-coded by cellular activity *vs* CEMO-1 (ALL) @ 1µM



Comparison: Proprietary Lead Molecules *vs* References

- **Heat-map,** *proliferation (GI_{50})*





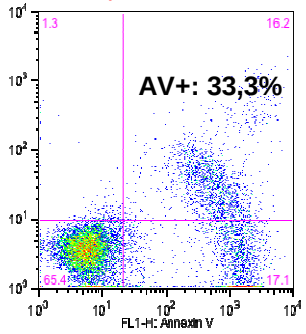
Comparison: Proprietary Lead Molecules *vs* References

- **Apoptosis,** *MV4-11 cell line*

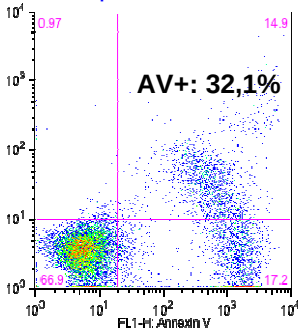
AML (Myeomonocytic)

Reference “Target 1” inhibitors

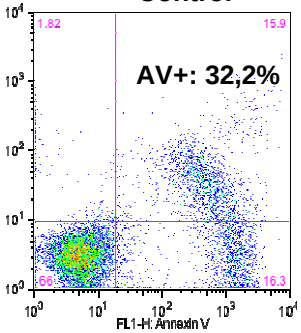
Compound 1 **385nM**



Compound 2 **385nM**

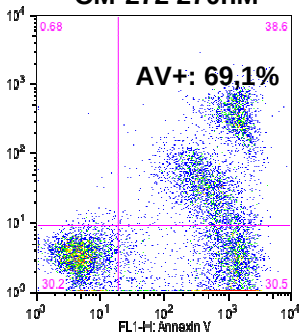


Control

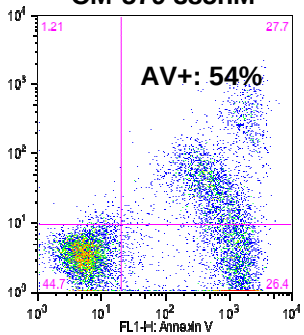


CIMA dual inhibitors

CM-272 270nM *

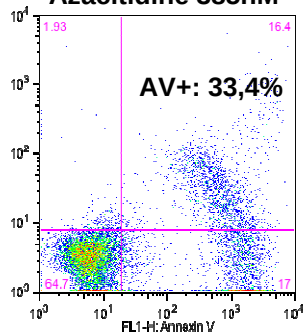


CM-579 385nM *

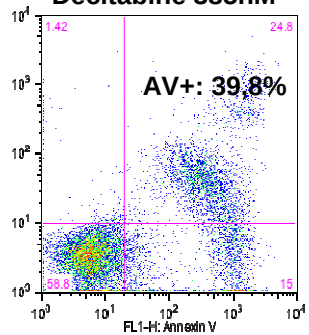


Reference DNMT inhibitors

Azacitidine 385nM



Decitabine 385nM

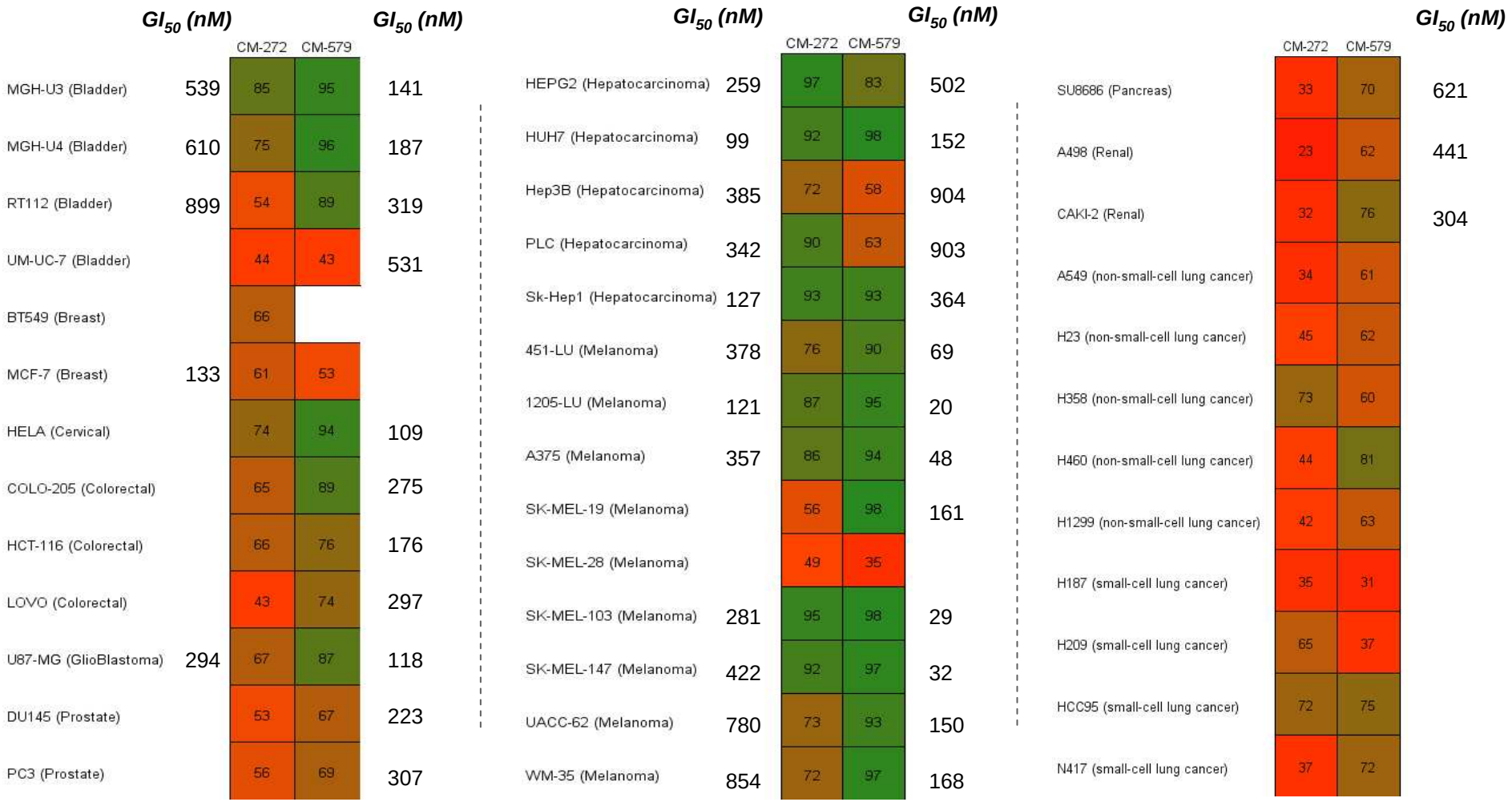


*GI_{50}

cima
Targeting Epigenetics

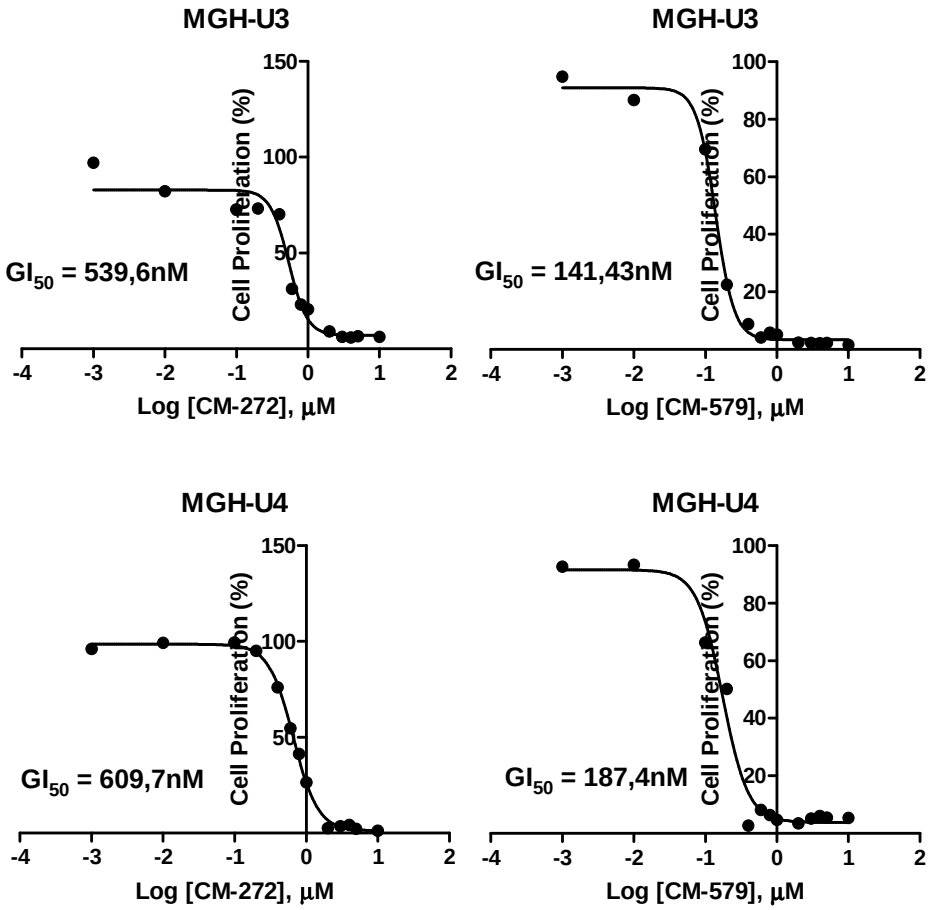
Lead ID. Cell lines panel

- **Selected compounds, CM-272 & CM-579, @ 1μM *vs* 40 cell lines (Solid Tumors)**

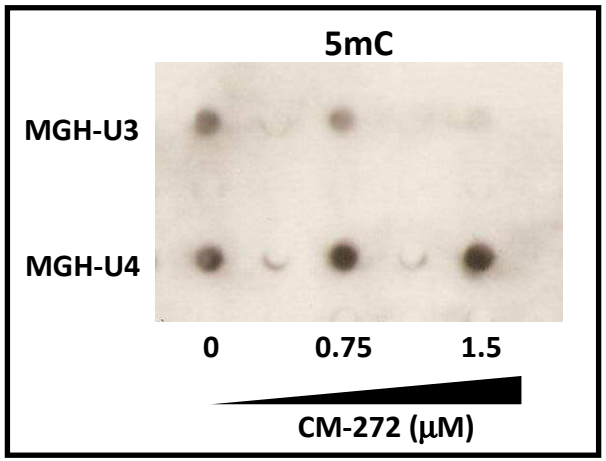


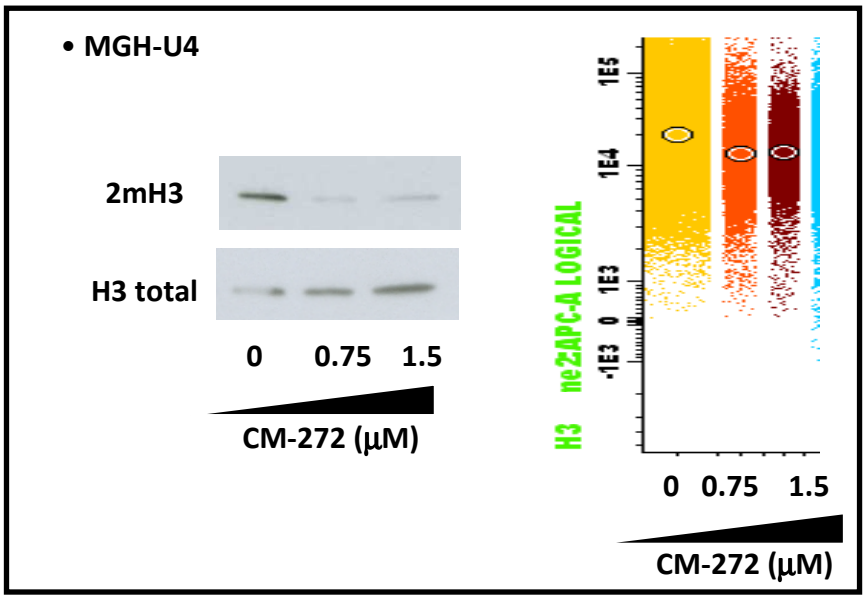
Lead ID. Impact on bladder cancer

- **Proliferation**



- **Epigenetic marks**





Lead ID. ADME profiling

- Selected, from our proprietary chemical series, as pharmacological tool compounds: **CM-272** & **CM-579**

- ***In-Vitro* ADME & Off-target selectivity profiling**

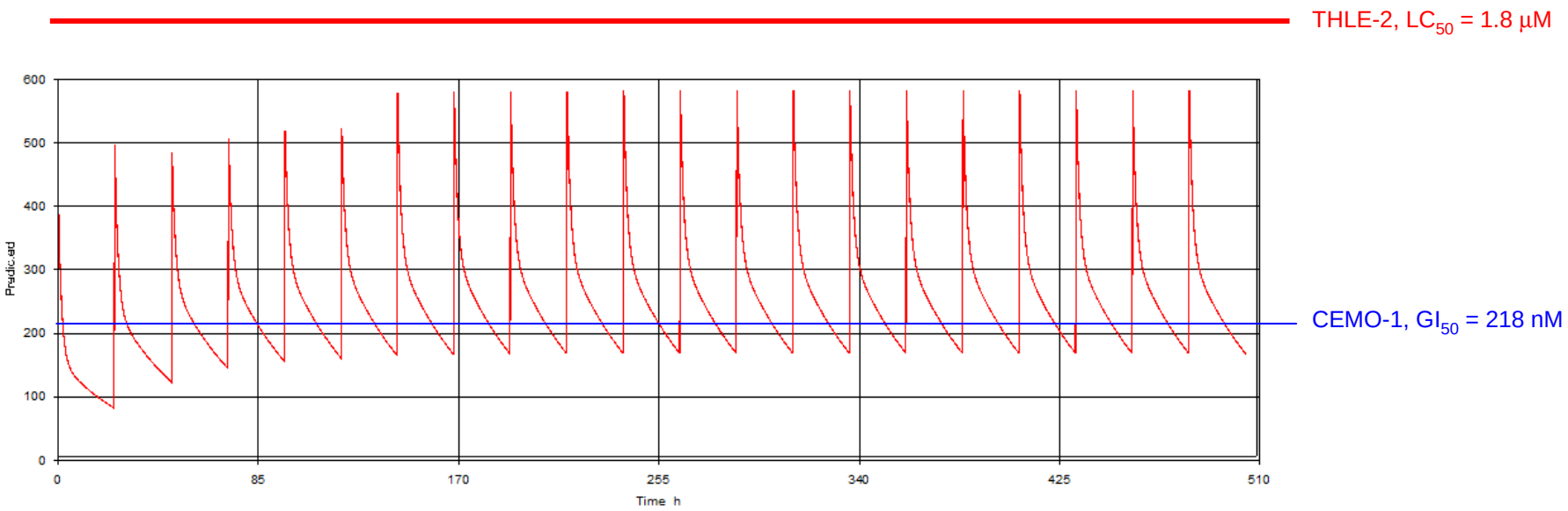
		• CM-272	• CM-579
ADME	P450s: 1A2, 2C19, 2C9, 2D6, 3A4 (<50% @ 10µM)	✓	✓
	Plasma Protein Binding (% unbound)	24.4(H), 25.0(M)	14.7 (H), 4.6(M)
	Solubility (>100 µg/mL) @ pH=7.4	✓	✓
	PAMPA (Pe 10^{-6} in nm/s)	0.16 (Low)	0.01 (Low)
	Liver Microsomal Stability ($t_{1/2}$ estimation) *in minutes*	>145(H), 35.2 (M)	133 (H), 10.4 (M)
CV safety	hERG binding (IC_{50} >100 µM)	✓	✓
	Patch Clamp (IC_{50} >50 µM)	*on-going*	*on-going*
Toxicity	PBMC (LC_{50}, µM)	9.8	>100
	THLE (LC_{50}, µM)	1.8	1.3
Off Target	37 additional epigenetic targets (<50% inhibition @ 10µM)	34	✓
PK	Mice (i.v.); e.g. V_{ss}, $t_{1/2}$ & C_{max} @ 2.5 mg/Kg	0.7 (L), 24 (h) & 406 (nM)	*on-going*

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

• Selected, from our proprietary chemical series, as pharmacological tool compound for *in-vivo* PoC: **CM-272**

• **Pharmacokinetic study & Therapeutic window**

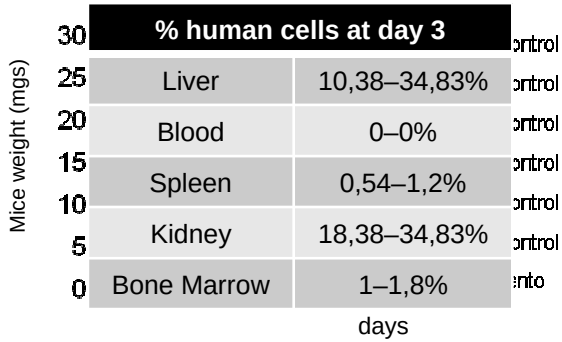
- Based on PK parameters, *based on i.v. and i.p administration*, simulations of CM-272 plasmatic concentrations

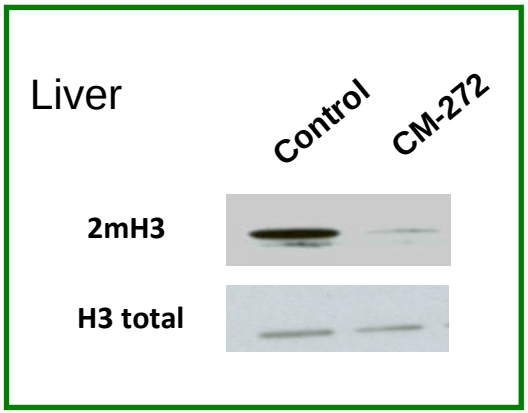


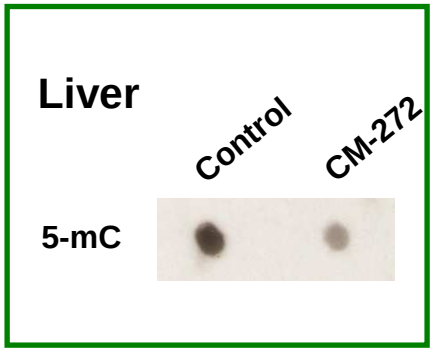
Predicted CM-272 plasmatic concentration (nM) evolution vs time after **i.v. (2.5mg/kg)** administration every **24 h during 3 weeks**.

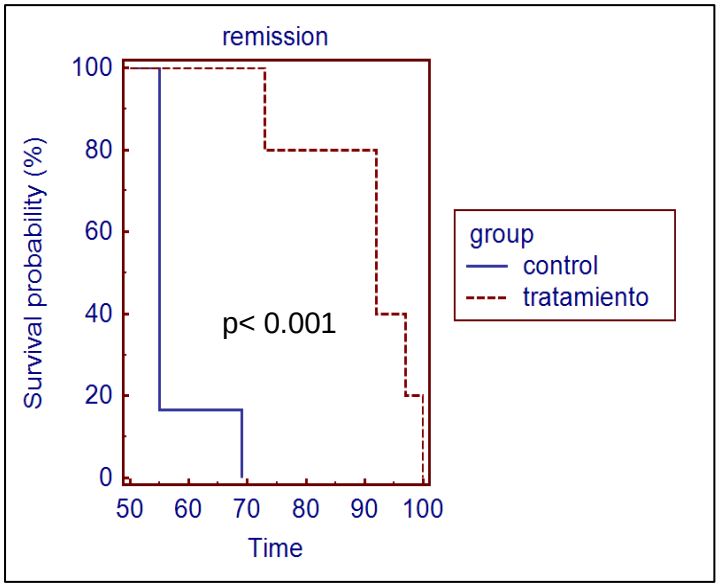
Lead ID. *In-Vivo* Proof-of-Concept (PoC)

• Selected, from our proprietary chemical series, as pharmacological tool compound for *in-vivo* PoC: **CM-272**



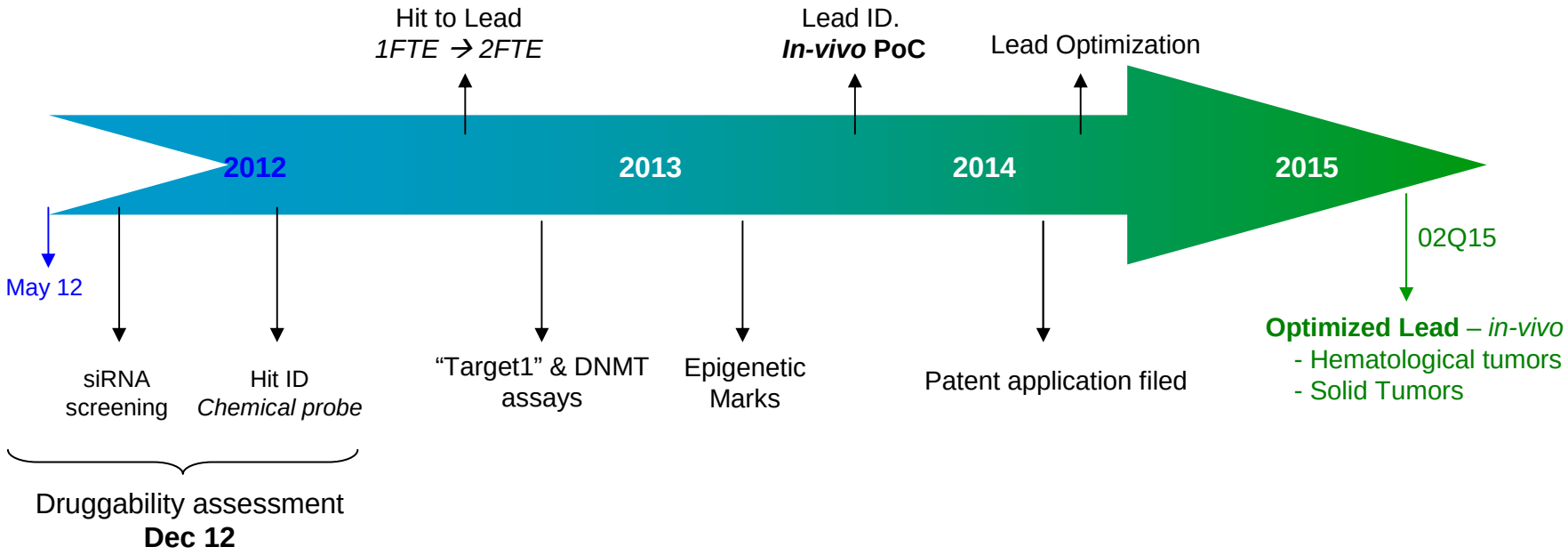






Timeline & Next Steps: *Lead Optimization*

- **Timeline**



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

  i.- Improving cell permeability

  ii.- Pharmacokinetics (oral admin)

  iii.- Increasing therapeutic window

Outline

- **Institution: CIMA**
- **Project**
- **Partnering Opportunities**

Partnering Opportunities

- **Value Proposition**

  - Novel Mode of Action: “Target 1” & DNMTs

    a) Their corresponding functional epigenetic marks overexpressed in several cancer cell lines
    b) This dual inhibition leads to synergistic effect in epigenetic mechanistic pathway.

  - First-in-class dual and reversible inhibitors targetting “Target1” and DNMTs

  - Proprietary chemical series; *patent filed in June 2014*

  - Pairwise comparison using FDA approved irreversible DNMT inhibitors and “Target 1” reference inhibitors *vs* our dual inhibitors clearly highlights higher efficacy in cell proliferation and apoptosis.

  - Identified lead compound for *in-vivo* Proof of Concept:

    a) Remarkable overall survivial, *no toxicity issue*
    b) Epigenetic marks as biomarkers for efficacy assessment

Partnering Opportunities

- **Partnering**

Two scenarios are initially envisioned:

1.- Product license (IP)

2- Stepwise research investment & first option (right of first refusal)

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Thank you !