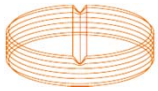
XIV Encuentro de Cooperación Farma-Biotech

CM-352: a new, potent and safe molecule for the prevention and treatment of haemorrhage

cima
CENTER FOR APPLIED MEDICAL RESEARCH
UNIVERSITY OF NAVARRA

Madrid, 17 de noviembre de 2015

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

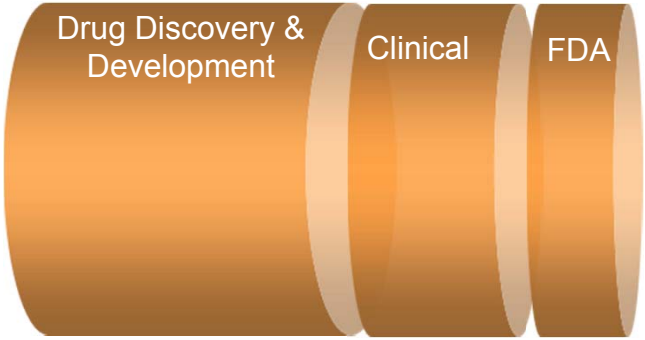
Medical Center

- Target Rich
  - BioBank
  - Patient Data

CIMA

Translating Basic Science

Pharmaceutical Industry



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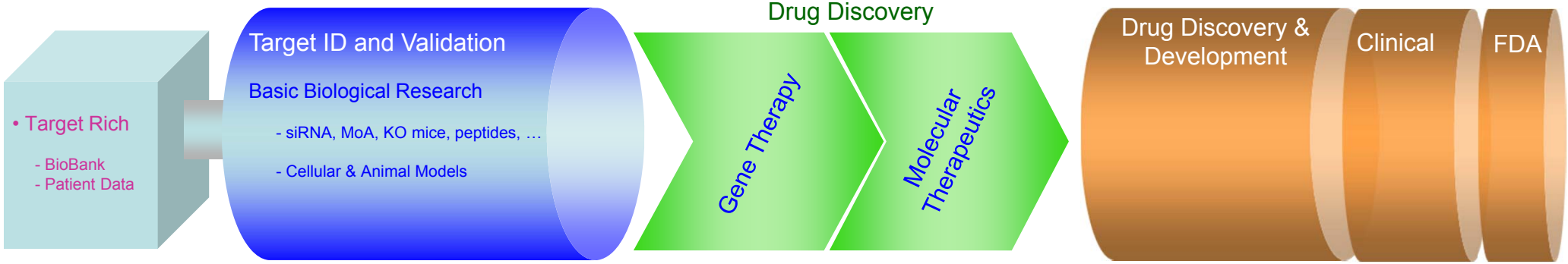


• Translational Medicine

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

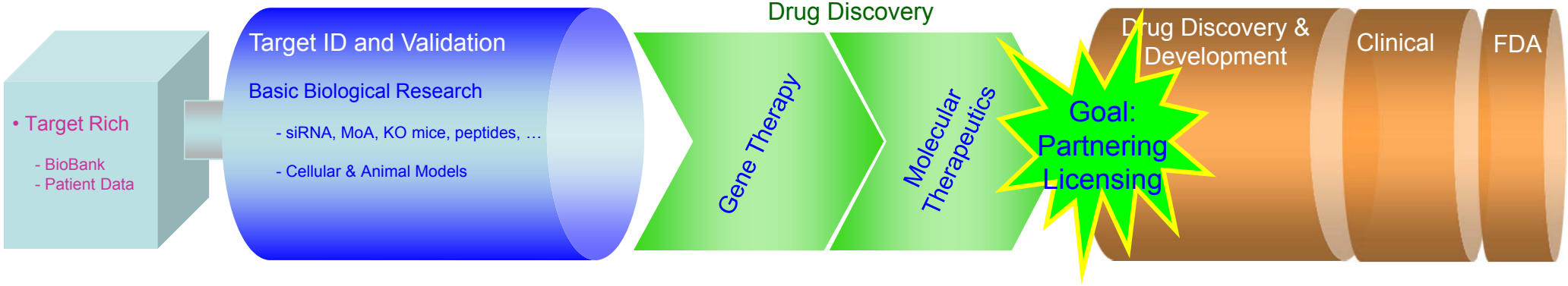
CUN

Medical Center

CIMA

Translating Basic Science

Pharmaceutical Industry



- 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
MMP3 & MMP10	Anti-fibrinolysis
HDAC & PDE5	Alzheimer`s Disease
G9a & DNMT	Anti-neoplastic
Gene7	Wilson´s Disease
Gene70	Anti-coagulant

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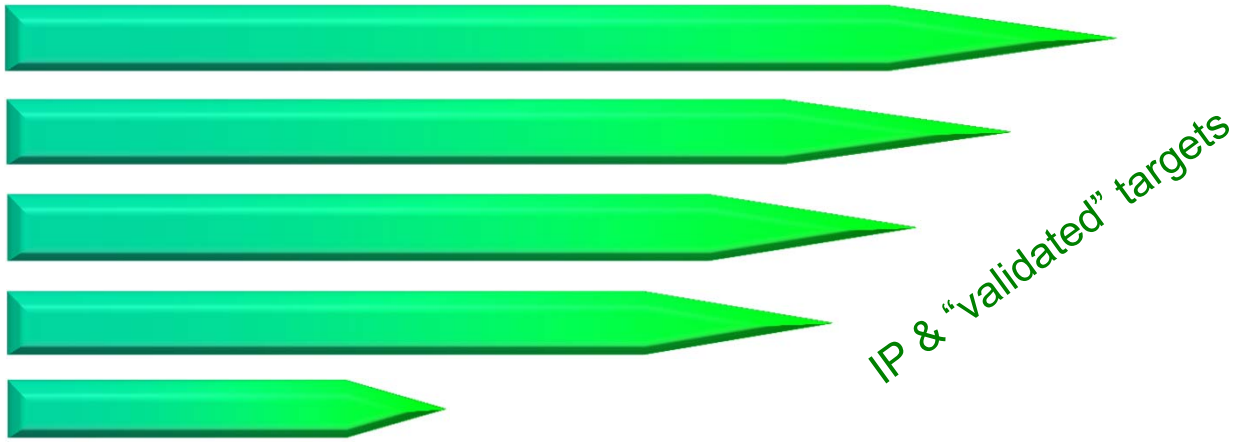

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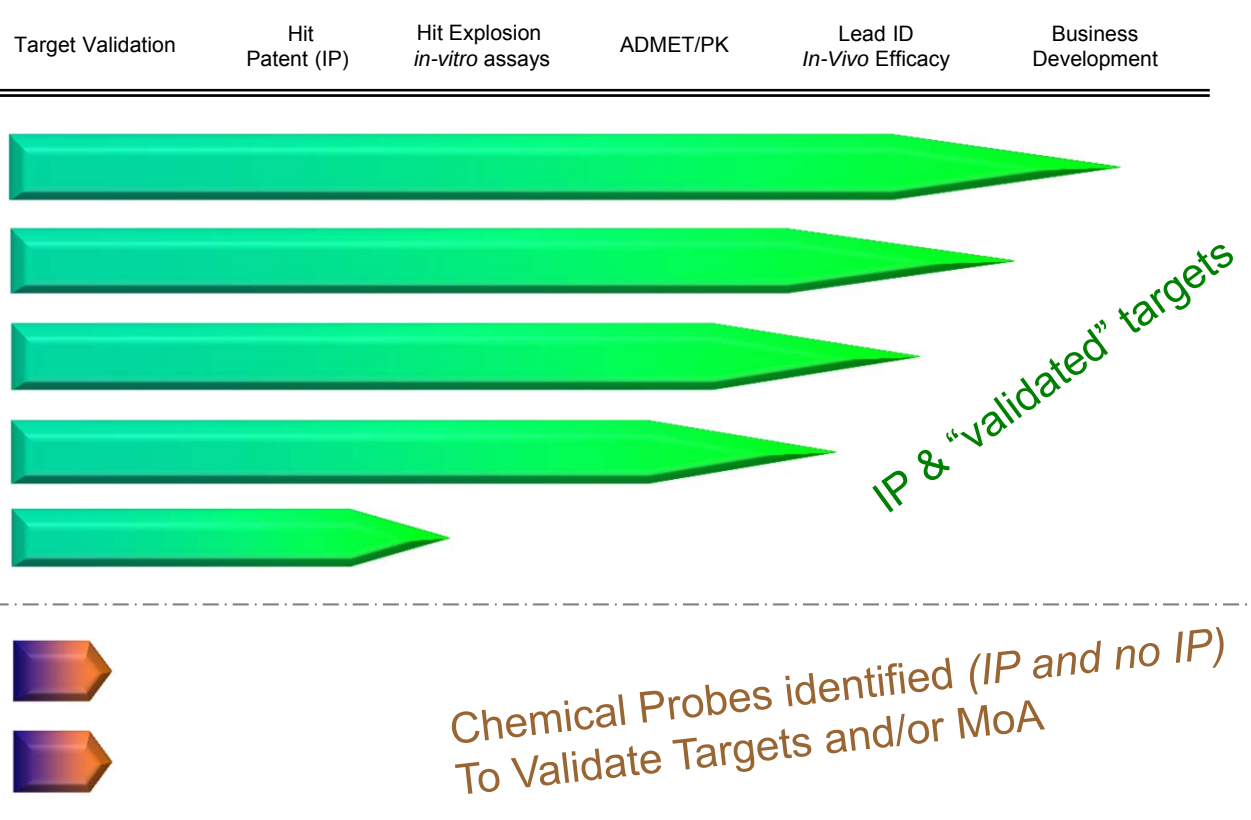
A	Anti-neoplastic
B	Anti-fibrotic



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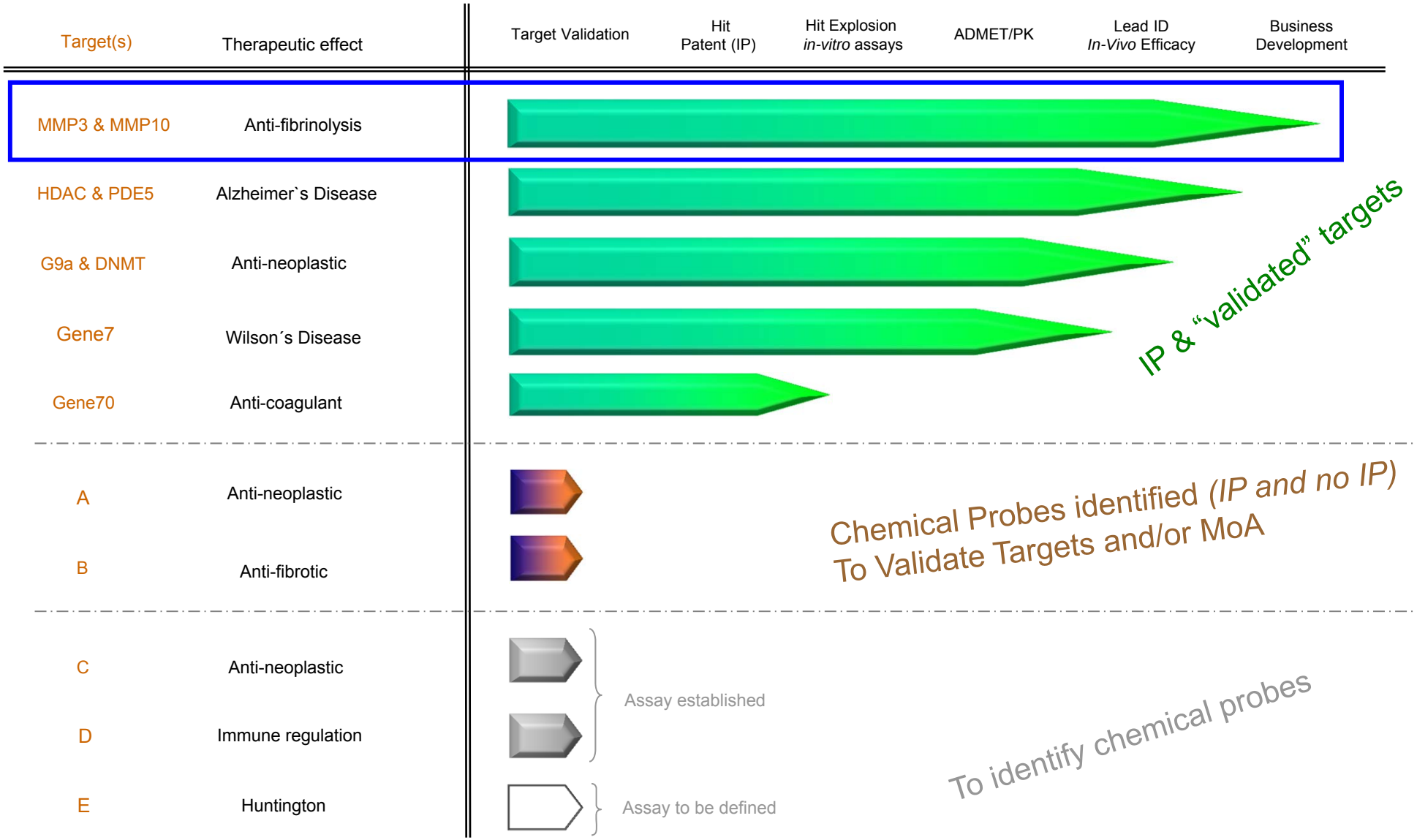

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Antihemorrhagic Agents: Current Standard of Care

HAEMORRHAGE

- Bleeding is a common complication in **surgical** (2.5 to 3.5 % of 100-120 million major surgeries every year in the 7MM) and **trauma patients** (50% deaths occurring within 24 h).

STANDARD OF CARE

- Lysine analogs (indirect inhibitors of fibrinolysis), such as **tranexamic acid** (TXA) reduces surgical bleeding and blood transfusion by about one third.
- **Aprotinin** (direct inhibitor of fibrinolysis) - withdrawn in 2008 due to cardiovascular side effects and increased mortality (BART study). *EMA recommendation (2012), suspension be lifted for a restricted range of indications*

SHORTCOMINGS

- Data suggest that TXA might be less effective than aprotinin in reducing blood loss.
- Allogenic transfusion risk is 23% increased in TXA when compared to Aprotinin.
- TXA side effects include seizures, renal impairment and thromboembolic complications

UNMET NEED

- Medical need for effective and safer agents to manage patients with major bleeding
- Intracraneal hemorrhage (ICH); an important orphan indication

Antihemorrhagic Agents: Novel Approach

AIM

- Effective agents with impact on fibrinolytic function - *no involvement in hemostasis*

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APPROACH

Target ID

- Target identification from array analyses (Affymetrix®) – human cells: **MMP3 & MMP10**

Target Validation

- MMP10 knock-out mice show the desired biological response
- MMP10 *h*MAb shows the desired *in-vitro* functional response
- Pharmacological tool compound identified (dual inhibitor: MMP10 & MMP3); PoC for *in-vivo* validation

Hit ID

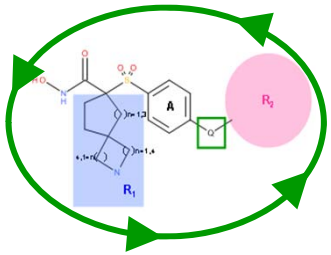
- Knowledge based *de-novo* design, and synthesis

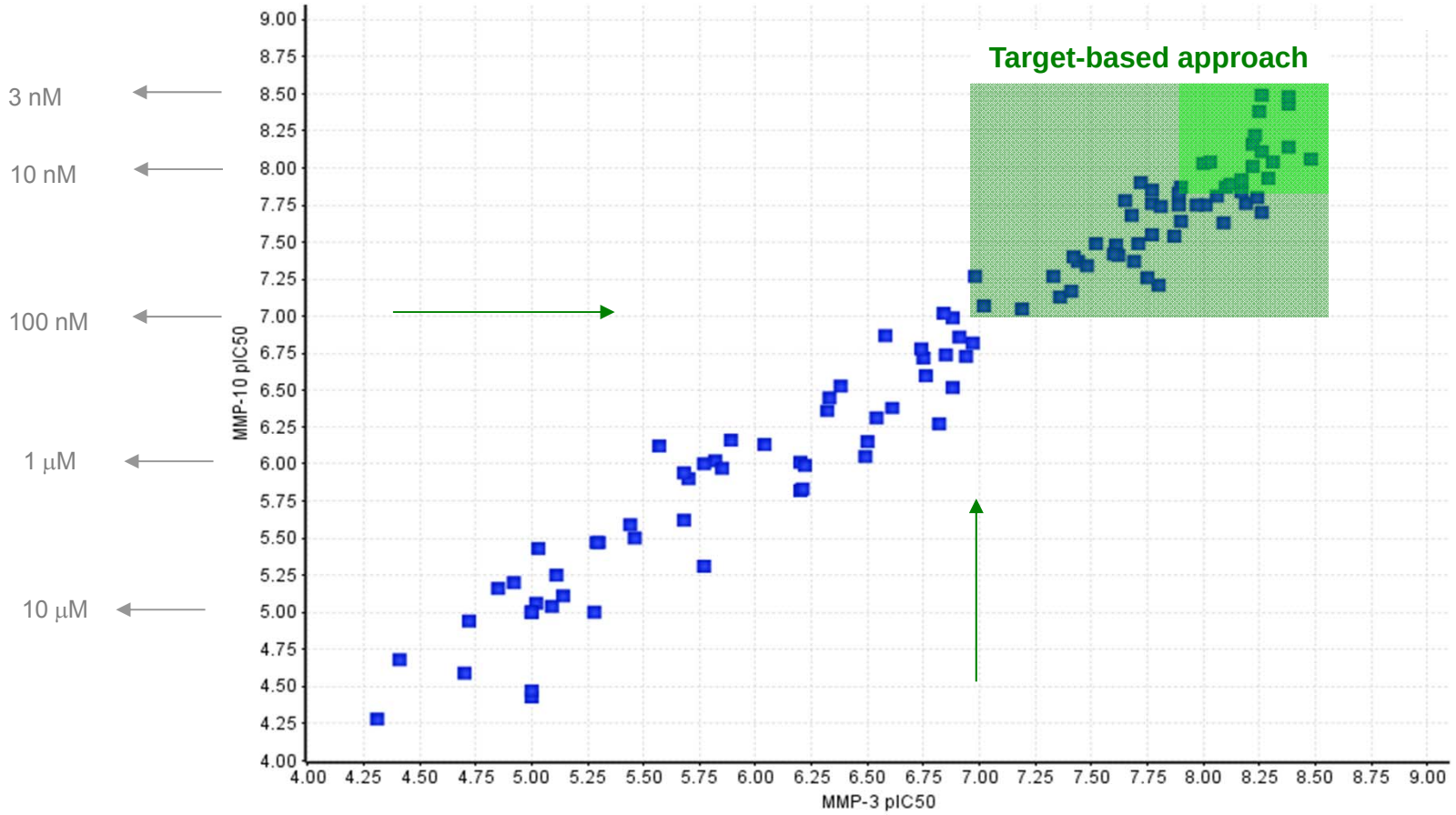
Lead Optimization

- Workflow towards Lead ID
  - Synthesis
  - *In-vitro* binding assay
  - *In-vitro* functional assay; (Thromboelastometry) decision point
  - ADME profiling
  - Toxicology (Anatomophatological study @ 10x efficacious dose)
  - *In-vivo* efficacy model (tail bleeding)

Hit to Lead: *In-vitro* binding assay

- 112 new proprietary compounds synthesized; all diversity points explored
- Biochemical assays *vs* MMP10 & MMP3





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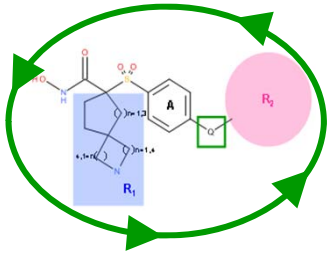
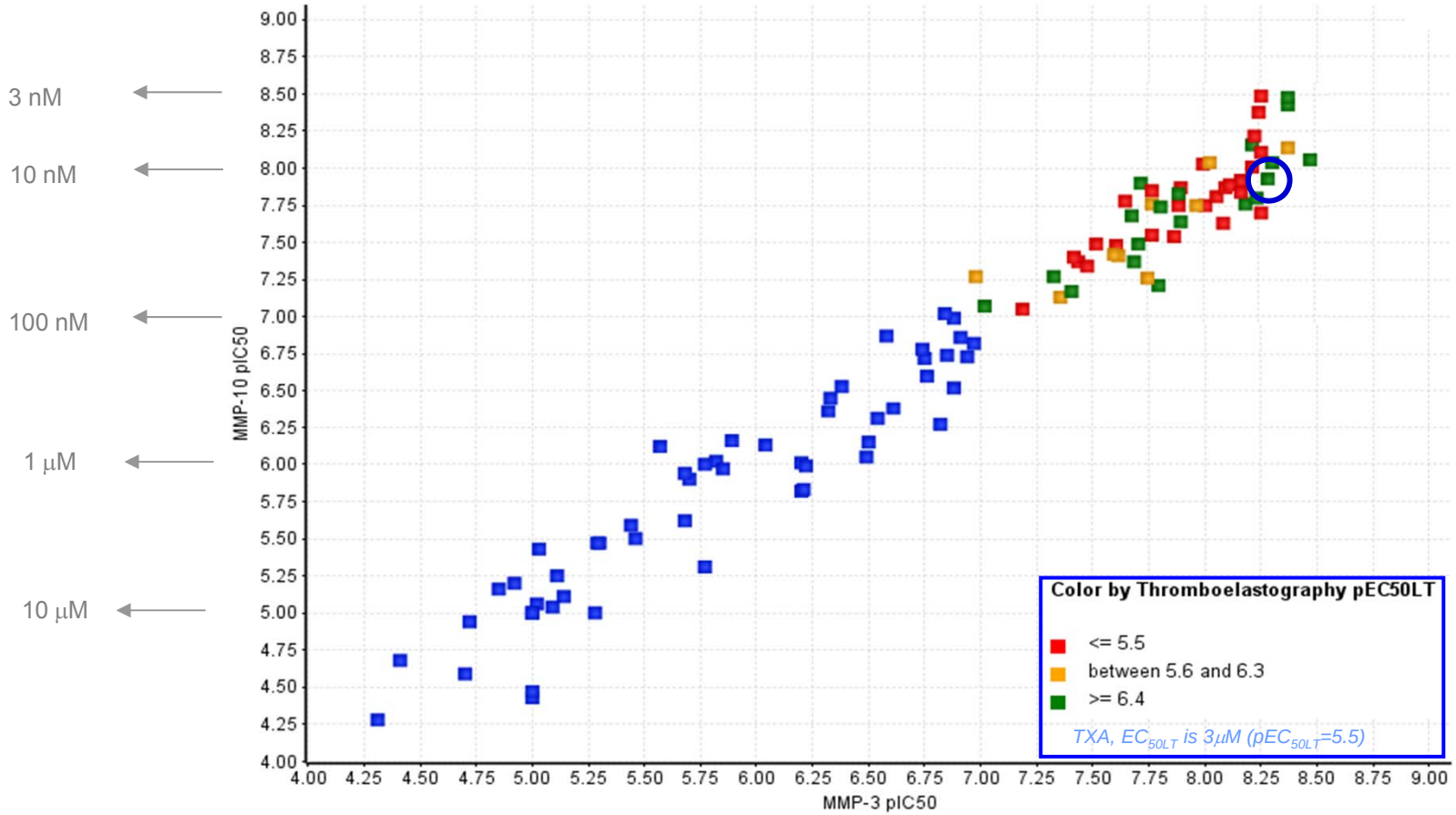
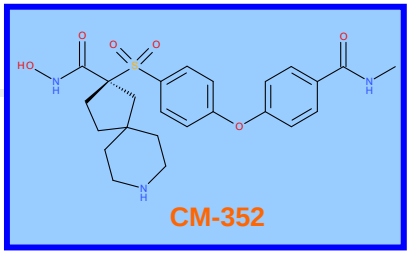
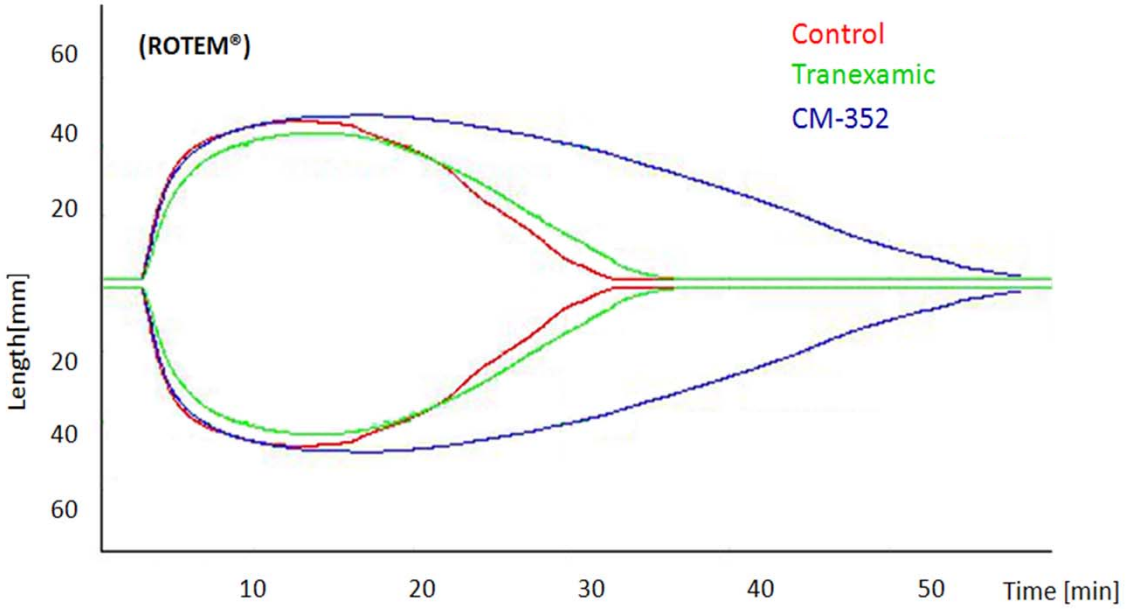




Optimized Lead: CM-352



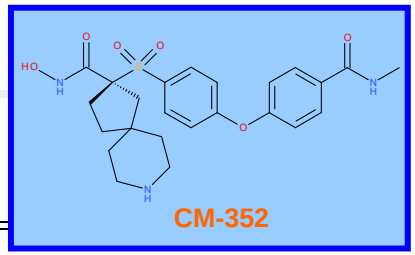
- Multifactorial optimization process led to **CM-352**
- ***In-Vitro* efficacy** model: **Thromboelastometry** *(human whole blood)*



Cmpd	EC_{50LT}
Aprotinin	400 nM
TXA	3 µM
CM352	0.7 nM

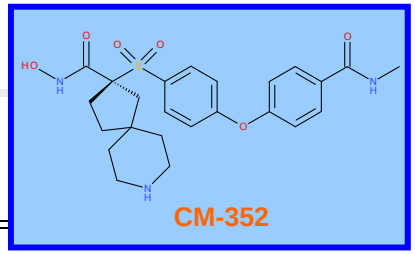
CM-352 is able to reduce by 50% lysis time at sub-nanomolar concentration.

Lead Profiling *(I)*



		• CM-352
Efficacy	Binding affinities (MMP10 & MMP3): Delay in Lysis Time (functional assay in human blood)	IC_{50}: 12nM & 15nM EC_{50}: 0.7nM
ADME	P450s: 1A2, 2C19, 2C9, 2D6, 3A4 (<50% @ 10μM) hPXR (EC_{50} > 100μM)	✓ ✓
	Plasma Protein Binding (% unbound) Solubility (>100 μg/mL)	55(H), 29.1(M), 40.5(R) ✓
	Caco-2 (Pe 10^{-6} in cm/s) & Efflux Ratio Liver Microsomal Stability ($t_{1/2}$ estimation) *in minutes* S9 Stability ($t_{1/2}$ estimation) *in minutes*	0.16 (Low) & 2.6 (PgP-subs) >145(H), >145(M), >145(R) >145(H), >145(M), >145(R)
CV safety	hERG binding (IC_{50} >100 μM) Patch Clamp (IC_{50} >30 μM)	✓ ✓
Toxicity	Mini Ames *(in 2 strains)* THLE & PBMC (LC_{50} > 100μM) Anatomopathological analysis (@ 10 mg/kg) Acute Toxicity	✓ ✓ & ✓ No alteration observed *(lung, brain, kidney & liver)* LD_{50}: 100 mg/Kg
PK	Pharmacokinetics (Vss, $t_{1/2}$ & C_{max}) @ 1 mg/Kg *in mice* (i.v.) Brain tissue/Plasma Ratio @ T_{max} from 1 mg/Kg *in mice* (i.v.)	0.94 (L/Kg), 1.4 (h), 3.3 (μM) 1.1 % *(34 nM)*

Lead Profiling *(II)*



MoA & off-target Selectivity		• CM-352
Isoforms selectivity	Binding affinities *vs 9 additional MMP isoforms* (>50% @ 10μM)	All isoforms (in fact, >70%)
MoA Hemost. & Fibrin.	Fibrinolysis (tPA, uPA, plasmin, PAI1, … @ 10μM)	Inactive*
	Primary Hemostasis (Platelet aggregation @ 10μM)	Inactive*
	Sec. Hemostasis (KLK-1, Factor X, … @ 10μM)	Inactive*
	Additional (Fibrinogen, TAFI, APC, … @ 10μM)	Inactive*
Off-Target	Binding affinities *vs 89 add. targets bearing metal binding sites* (≤ 50% @ 10μM)	✓

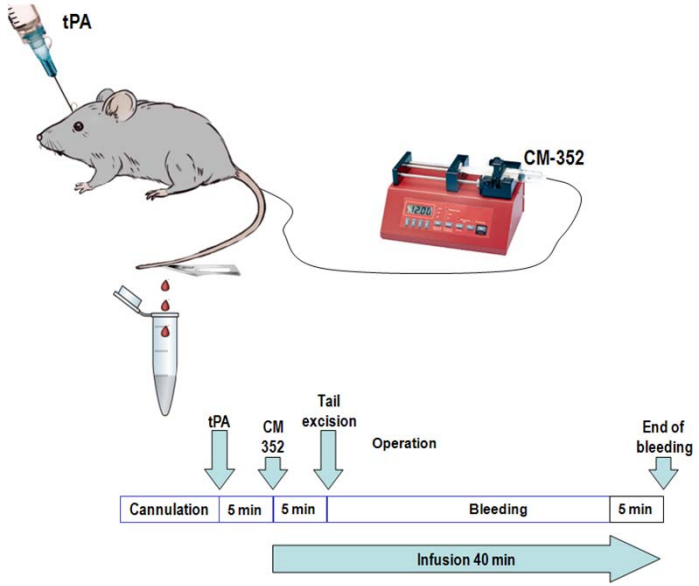
106 targets

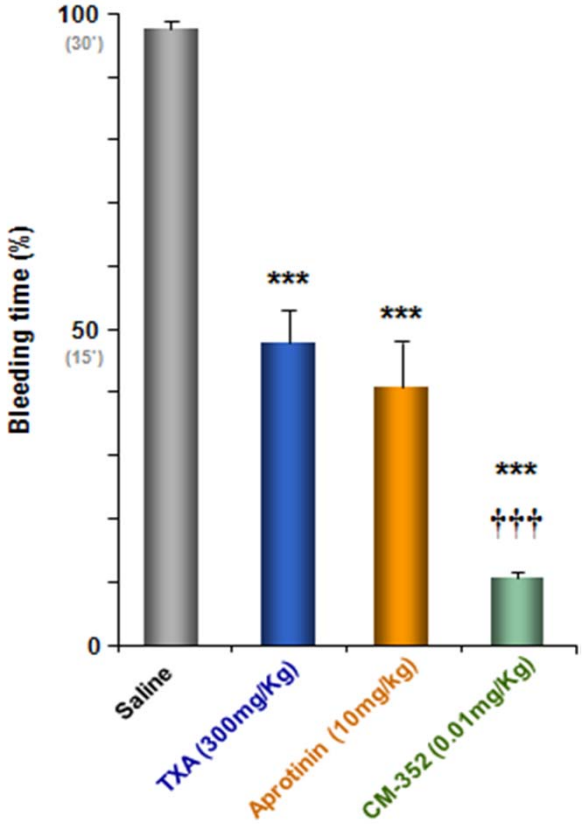
Conclusion: **Effective antifibrinolytic agent; *and, no impact on hemostasis***

**No impact on hemostatic parameters; and, no coagulopathy induction*

Optimized Lead: CM-352

- ***In-Vivo* efficacy** model: **Hyperfibrinolytic Tail Bleeding**



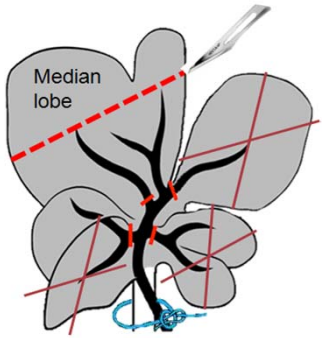


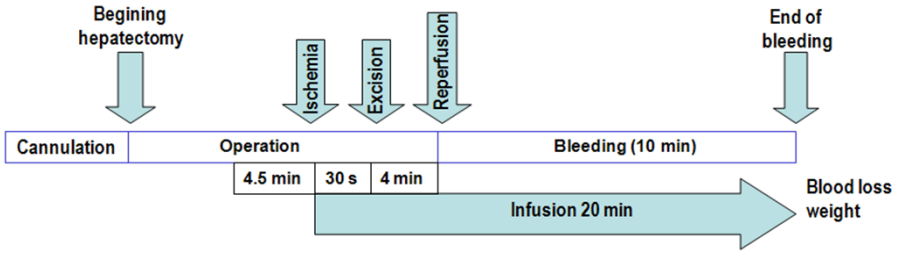
Mean±SME; n≥10 per group; * p< 0.05 & *** p<0.001 vs saline;
††† p<0.001 *vs* TXA

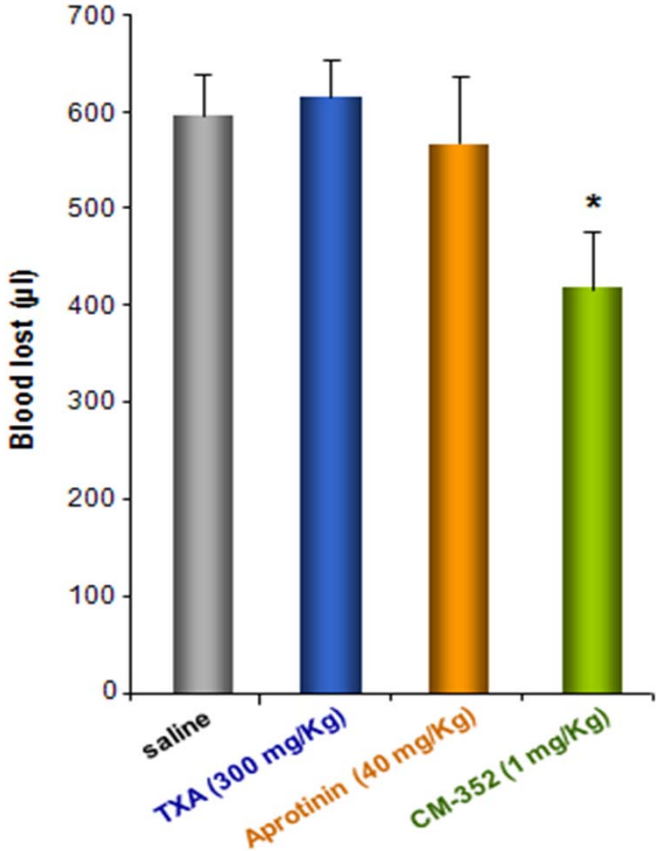
CM-352 reduces bleeding time by >89% at 10µg/kg in hyperfibrinolytic induced conditions

Optimized Lead: CM-352

- ***In-Vivo* efficacy** model: **Hepatectomy Bleeding**





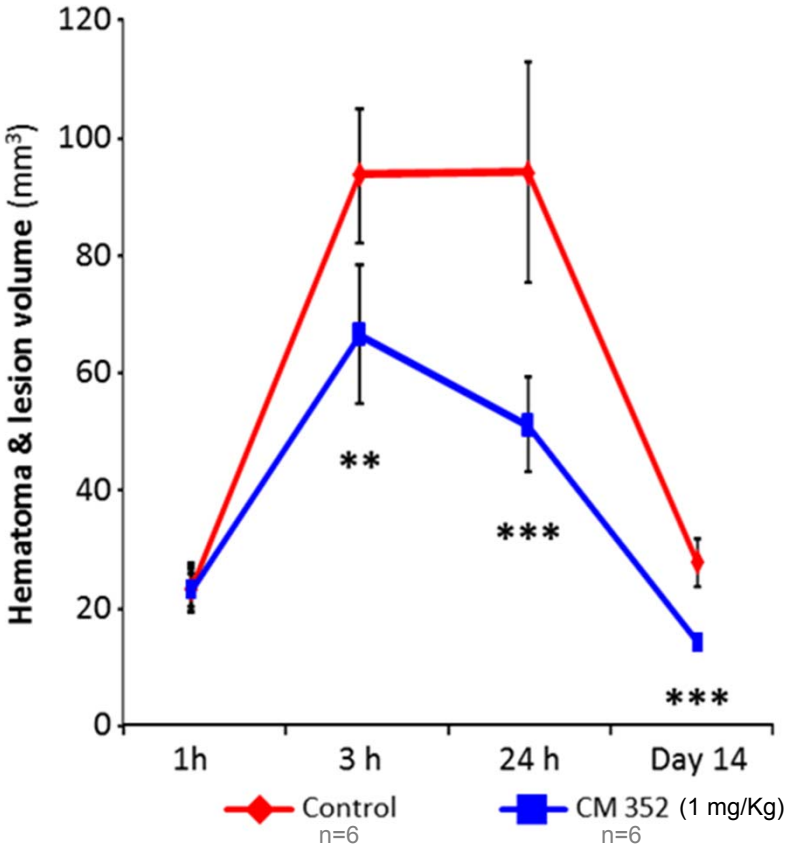


Mean±SME; n≥10 per group; * p< 0.05 vs saline

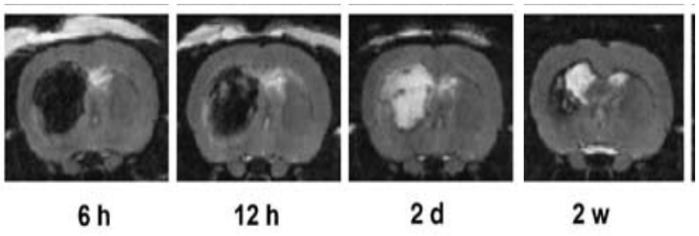
Only **CM-352** is effective at reducing blood loss in an aggressive bleeding model

Optimized Lead: CM-352

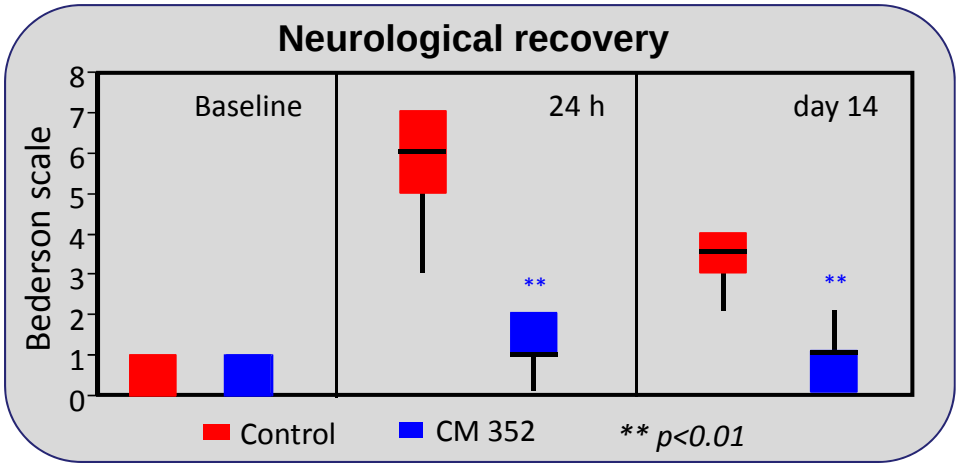
- ***In-Vivo* efficacy** model: **Intracraneal hemorrhage model** – *an important unmet need*



Magnetic Resonance Imaging (MRI)



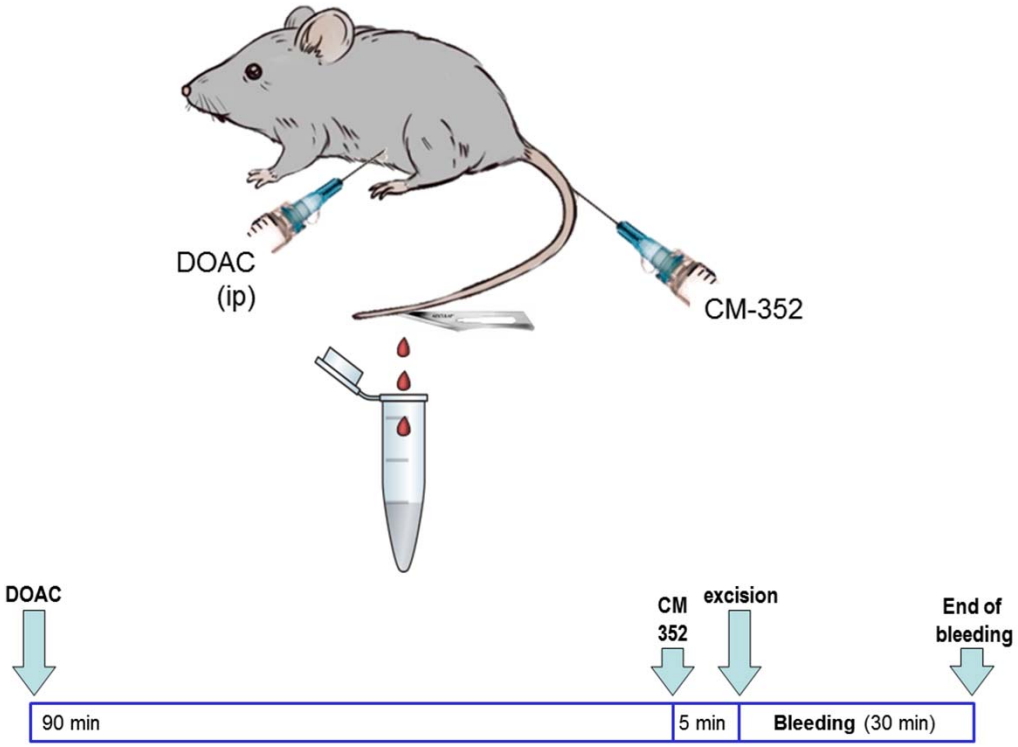
- Hematoma volume:
  - i.- ~30% reduction in 3 hours
  - ii.- ~45% reduction in 24 hours



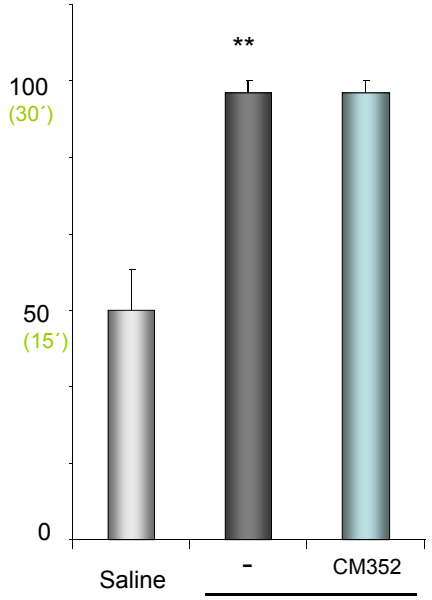
CM-352 is effective at reducing hematoma and lesion volume in intracranial hemorrhage

Optimized Lead: CM-352

- ***In-Vivo* efficacy** model: **Antidote for Rivaroxaban** *(new generation of anticoagulants)*



Where DOAC means new generatino of anticoagulants: Dabigatran and Rivaroxaban



CM-352 @ 1mg/kg

** p<0.01 *vs* saline; ## p<0.01 *vs* Rivaroxaban

CM-352 is effective at reducing bleeding time after Rivaroxaban treatment

Small Molecules as novel antifibrinolytic agents

AIM

- Effective agents with impact on fibrinolytic function - **no involvement in hemostasis**

APPROACH

Target ID

- Target identification from array analyses (Affymetrix®) – human cells: **MMP3 & MMP10**

Target Validation

- MMP10 knock-out mice show the desired biological response
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  - *In-vivo* efficacy model (tail bleeding)

Lead Prioritization

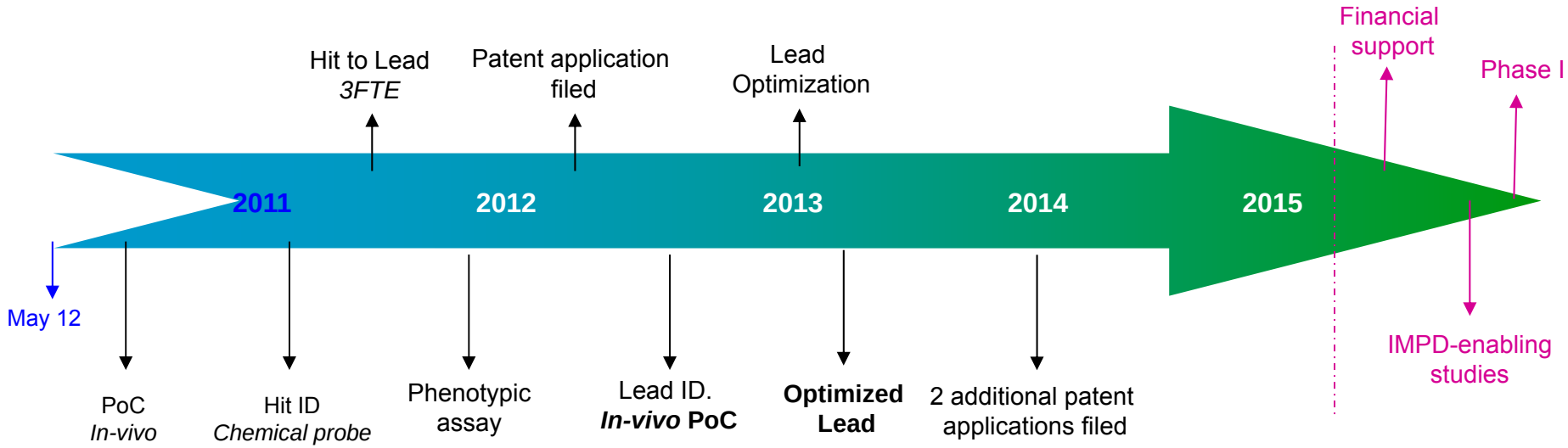
ACHIEVEMENT

- **Proprietary chemical series**, IP –patent applications filed: WO2014012964 & WO2015104343

- **Preclinical Candidate**, **CM-352**, showing optimal profiling:
  - Efficacy (4 *in-vivo* models), ADME, cardiovascular safety, Toxicity, PK, off-target selectivity, ….

Timeline & Next Steps

- **Timeline**



- Critical point is currently ***on-going***, *looking for* **investment** to move to:

  i.- IMPD-enabling studies *(based on EMA feedback)*

  ii.- Phase I

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Value proposition

Efficacy And Safety

- Proprietary small molecules **with *in vivo* proof of concept**; e.g. optimized Lead Compound, **CM-352**:
- ~4 times **more efficacious** at doses up to 30,000 times lower **than TXA**.
- ~4 times **more efficacious** at doses up to 1,000 times lower **than Aprotinin**.
- **Efficacious in aggressive bleeding model** (hepatectomy). Aprotinin and TXA do not stop bleeding.
- Efficacious in ICH model (subarachnoid hemorrhage) → *orphan indication (speeding up the process)*
- Efficacious as antidote for new generation anticoagulant agent (Rivaroxaban; *targeting FXa*)

- Have **no impact on hemostasis**
- **No thrombus formation**
- **Optimal ADME, off-target selectivity and PK profile**; e.g. $t_{1/2}$ is 1.4 hours (optimal for acute treatment)

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Differentiation And Market

- **Novel MoA** and novel **"Markush"** formulas
- Potential to recover **Aprotinin market niche ($600 Million)** – major surgery
- **Life plan** also involves: **first-aid/trauma & ICH** *(orphan indication to speed up the process)*

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  - Target-based approach
  - Phenotypic-based discovery
- Time to IND estimated ~12 to 18 months

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IP

- Novel strategy. **Strong IP position**, 3 patents, available for Worldwide licensing or territory-based
  - 2 patents cover different novel "Markush" formulas (WO2014012964 and WO2015104343)
  - 1 patent claims known MMP inhibitors – *acute treatment* (WO2015107139)

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- **Novel MoA** and novel **"Markush"** formulas
- Potential to recover **Aprotinin market niche ($600 Million)** – major surgery
- **Life plan** also involves: **first-aid/trauma & ICH** *(orphan indication to speed up the process)*

Development

- Project at preclinical stage with follow-on products:
  - Target-based approach
  - Phenotypic-based discovery
- Time to IND estimated ~12 to 18 months

IP

- Novel strategy. **Strong IP position**, 3 patents, available for Worldwide licensing or territory-based
  - 2 patents cover different novel "Markush" formulas (WO2014012964 and WO2015104343)
  - 1 patent claims known MMP inhibitors – *acute treatment* (WO2015107139)

CM-352 first line of therapy to treat blood loss in major surgery, trauma and first-aid as well as ICH

Partnering Opportunities

- **Partnering**

Two scenarios are initially envisioned:

1.- Product license (IP)

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

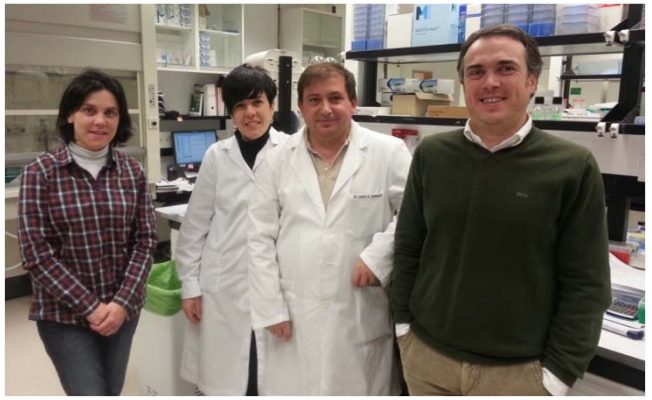
Acknowledgements

Universidad de Navarra

Jesús Hernández, PhD

Atherothrombosis Unit

Small Molecule Discovery Platform



Hospital Clinico Universitario, Santiago de Compostela

- T. Sobrino, PhD
- J. Castillo, PhD

WuXi AppTec

M. Musheng, PhD
W. Wei, PhD
B. Teng, PhD

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

Thank you !!

Atherosclerosis Lab
Jose Antonio Páramo, MD, PhD
japaramo@unav.es

Molecular Therapeutics Program
Julen Oyarzabal, PhD
julenoyarzabal@unav.es