DIGNA BIOTECH

New antihemorrhagic agents:
a novel antifibrinolytic strategy

- **Hemorrhage** is a leading cause of death and cost associated with blood transfusion.
- There is a **need** for the improvement of current treatments of bleeding associated with **surgery**, **trauma**, **intracerebral hemorrhage** (ICH) or other tissue damages.
- A **novel target** involved in fibrinolysis has been identified.
- **Proprietary novel compounds** to prevent major bleeding have been developed:
  - Small molecule entity (SME).
  - Efficacy: 30,000 times more effective than the currently available therapies.
  - Safety: No thrombus formation and no impact on coagulation.
- **Primary Indication: prophylaxis and acute treatment of bleeding in cardiac surgery.**
- **Life plan** intravenous: cardiac surgery → other major surgeries → trauma and first-aid → ICH
  topical: trauma and first-aid → OTC → veterinary uses

Scope of the problem

- Coronary arteries bypass surgery: 470,000 procedures/year in the 7 Major Markets. Aprotinin withdrawal ($600M market niche) has generated demand and opportunity for new antifibrinolytics that could significantly reduce the number of blood transfusions.
- **Major surgeries**: 100-120 million procedures every year in the 7 Major Markets, 2.5-3.5% with significant blood loss. Tranexamic acid (TXA) is used in 35-45% of surgeries.
- Annual expenditures on blood transfusion: $1.62M-$6.03M per hospital.
- Hemorrhage is responsible for 50% deaths occurring within 24 h of **traumatic injury**.
- **Intracerebral hemorrhage** (ICH; 15% of all strokes), is associated with high mortality (40%) and there is **no proven medical** or surgical **treatment**.

Patient needs addressed

Prophylaxis and treatment of major bleeding in patients undergoing cardiac surgery
Major bleeding (Guidelines ISTH) in trauma and other clinical and surgical settings.

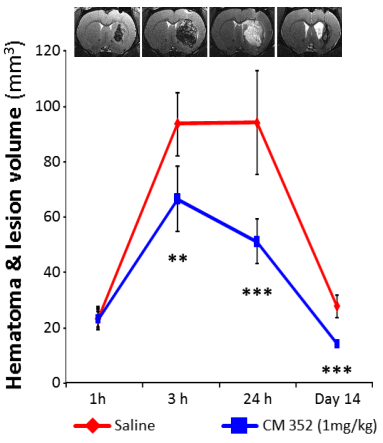
Current Standard of Care & Competitive Landscape

- Antifibrinolytics are the Standard of Care for hemorrhage in surgery and trauma.
- TXA is the only commercially available agent, partially effective at high doses with significant side-effects. Current products in development are restricted to sealants (topical) and clotting factors (plasma derived compounds with higher risk of viral transmissions and thromboembolic complications).

Product Profile

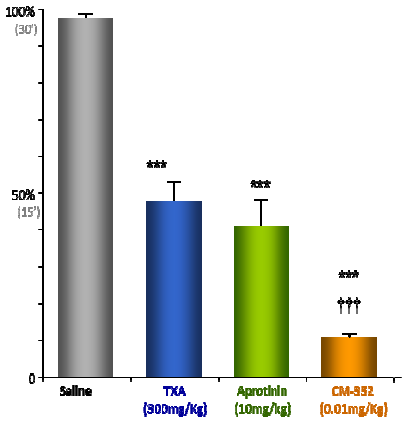
- A new mechanism of action that impacts on fibrinolytic function and not on haemostasis and coagulation.
- Multifactorial process led to optimized compound **CM-352**, safe and efficacious in 3 different *in-vivo* models:
  i.- Intracerebral hemorrhage (ICH). *Figure A*
  ii.- Tail bleeding. *Figure B*
  iii.- Hepatectomy *(severe bleeding)*
- **CM-352:** Optimal profile for acute systemic administration (i.v.) with short half-life, ideal for short term control of bleeding.
- **CM-352,** currently under evaluation by US Department of Defence

A) Intracerebral haemorrhage



Collagenase-induced ICH
Mean±SME; n=6 rats/group
** p<0.01; *** p<0.001 vs saline

B) Tail bleeding model



Mean±SME; n≥10 mice/group
* p< 0.05; *** p<0.001 vs saline
††† p<0.001 *vs* TXA.

Intellectual Property

Strong IP position: 3 patents filed (2012 and 2014) for novel chemical series of proprietary compounds as well as for drug repositioning (licensed to Digna Biotech).
Positive EESR report from EPO examiner, regarding novelty and inventive step.

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