Hemorrhage Control by Delivering Tranexamic Acid and Thrombin into Wounds with CounterFlow

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Important Required Disclosures

I am a co-founder, director and shareholder in:

NanoVation Therapeutics, Inc.

- Provides lipids and LNP for partner companies

SeraGene Therapeutics, Inc.

- RNA therapies for blood disorders

CoMotion Drug Delivery Systems, Inc.

- Device engineering for controlling traumatic hemorrhage

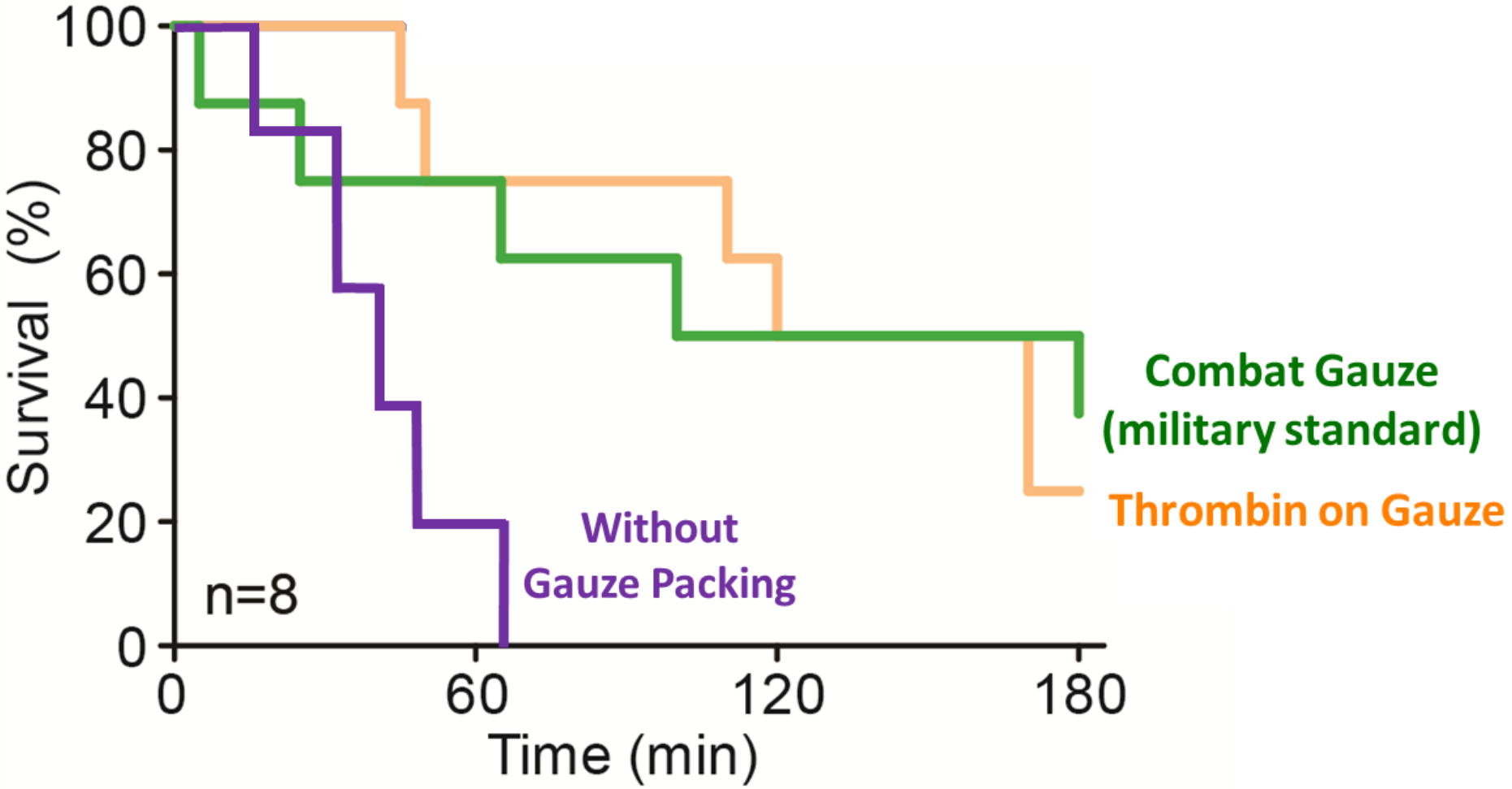
Consulting and/or Contract research :

- **Moderna**
- **CSL Behring**
- **Alnylam**
- **Bayer**
- **Acuitas**
- **Novo Nordisk**

Bleeding... It's a problem.

Problem Hemorrhage without compression = hemorrhage

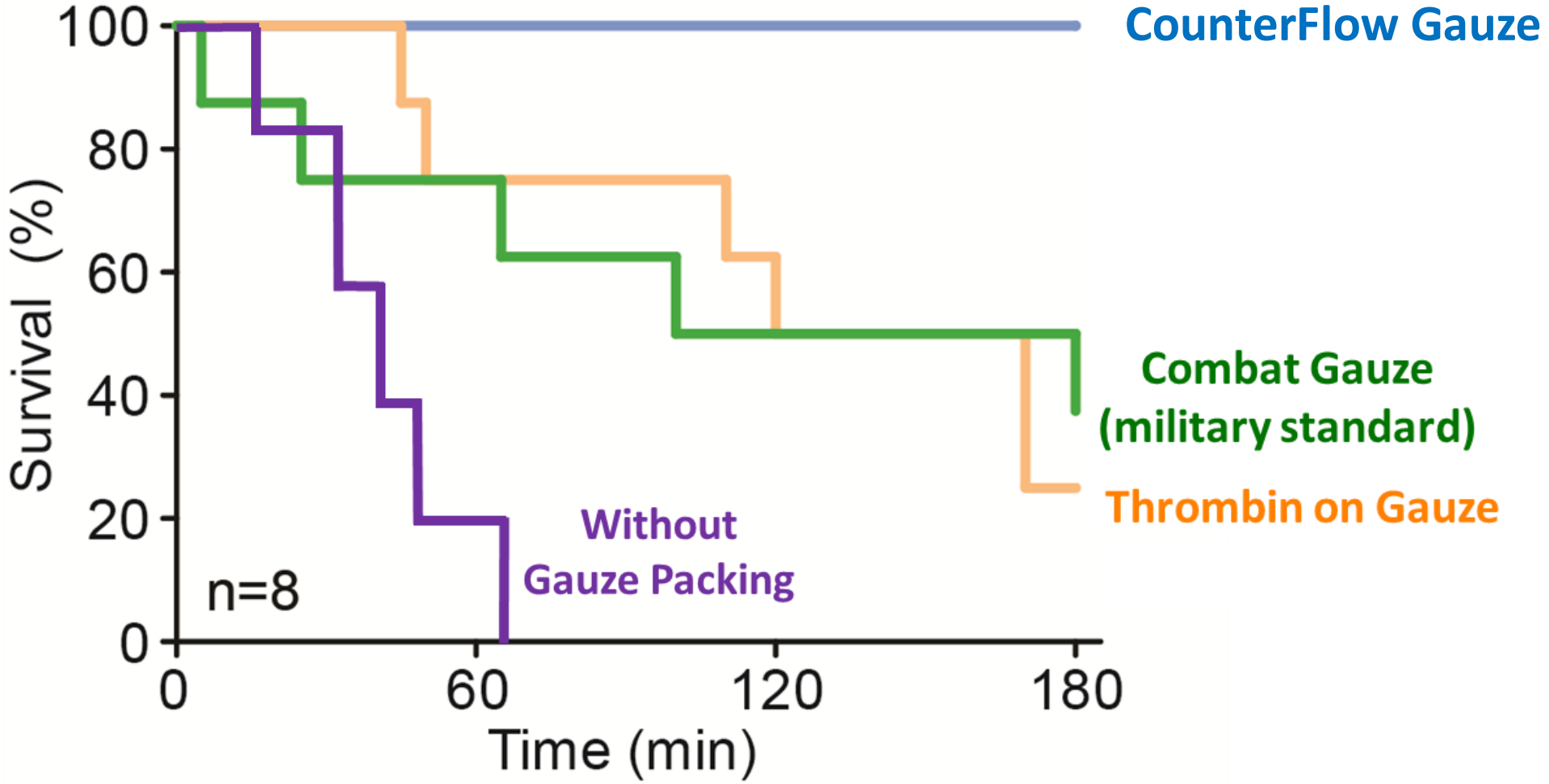
Without manual compression, current topical hemostatics can fail.



Baylis, Cau, others, White, Beckett, Kastrup *Science Advances* **(2015)**, *Shock* **(2016)**, *J Thrombosis Haemostasis* **(2019)**

A Gauze Coated with "CounterFlow" Powder can Stop External Hemorrhage, Even Without Compression

Survival rate reached 100% at 3-hour with CounterFlow coated Gauze.



Baylis, Cau, others, White, Beckett, Kastrup *Science Advances* **(2015)**, *Shock* **(2016)**, *J Thrombosis Haemostasis* **(2019)**

CounterFlow Safely Delivers Tranexamic Acid and Thrombin

Gauze Delivers:

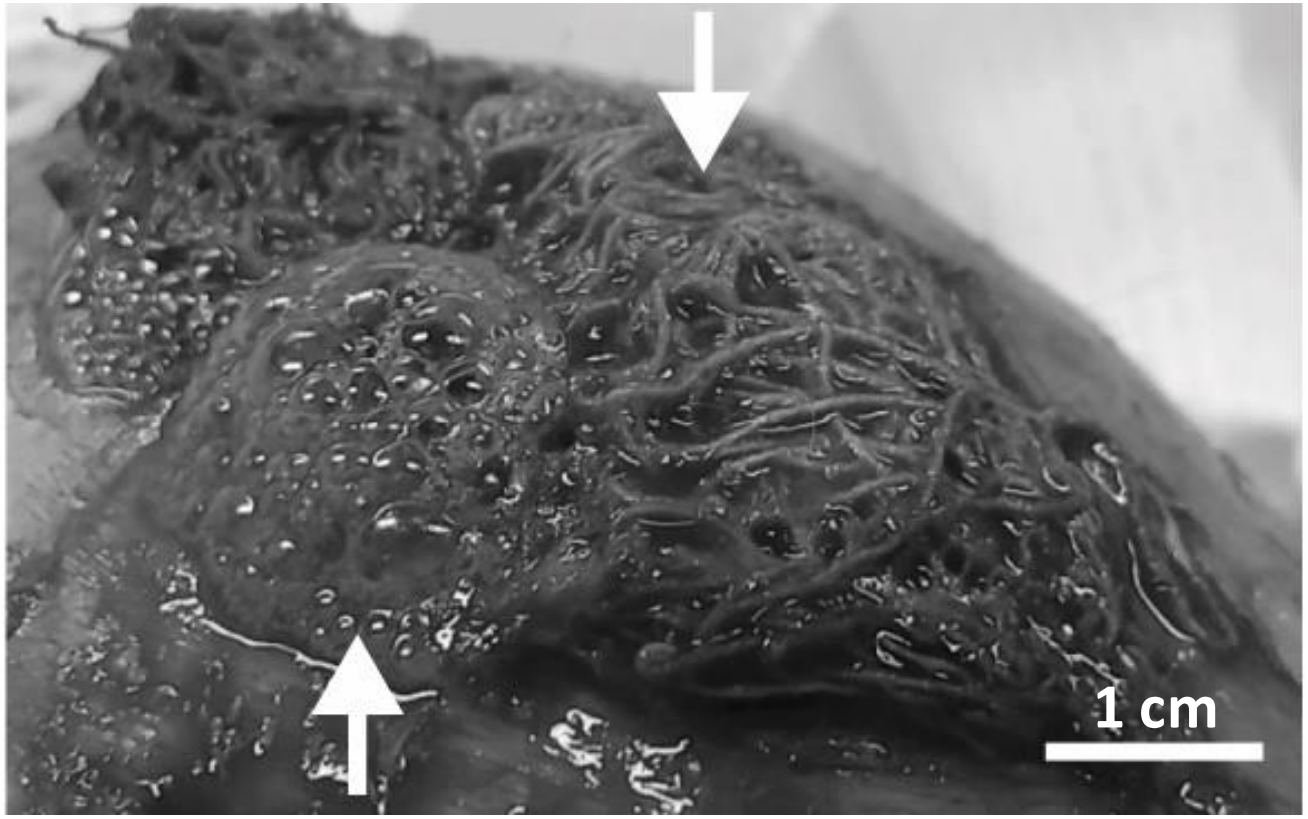
- Systemic TXA
- Ca^{2+}
- Pressure from CO_2
- Thrombin

CounterFlow Components are Safe:

$CaCO_3$ and CO_2

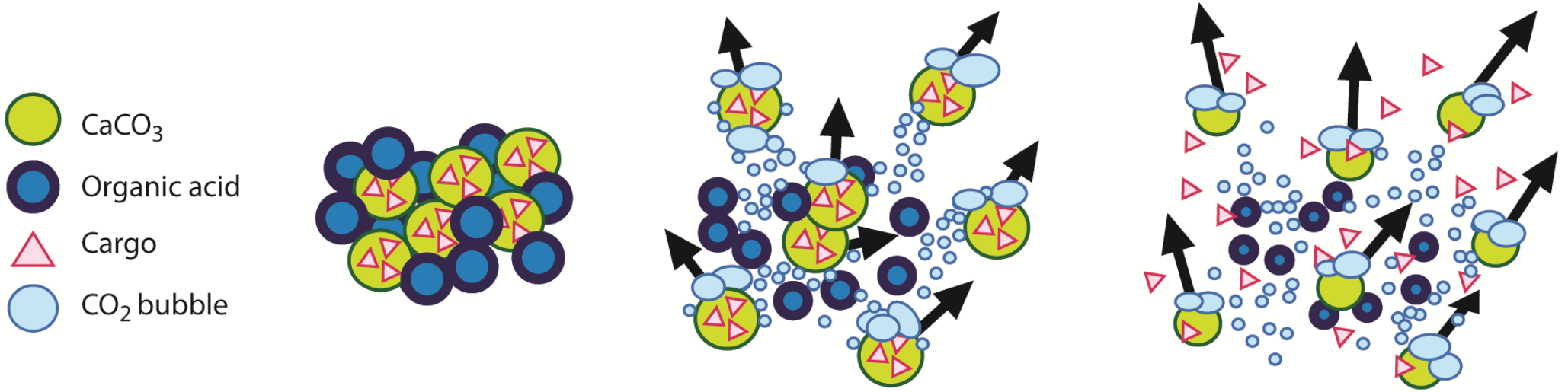
- Bioabsorbable and soluble in blood, wounds and vessels

CounterFlow Gauze



Bubbles escaping wound

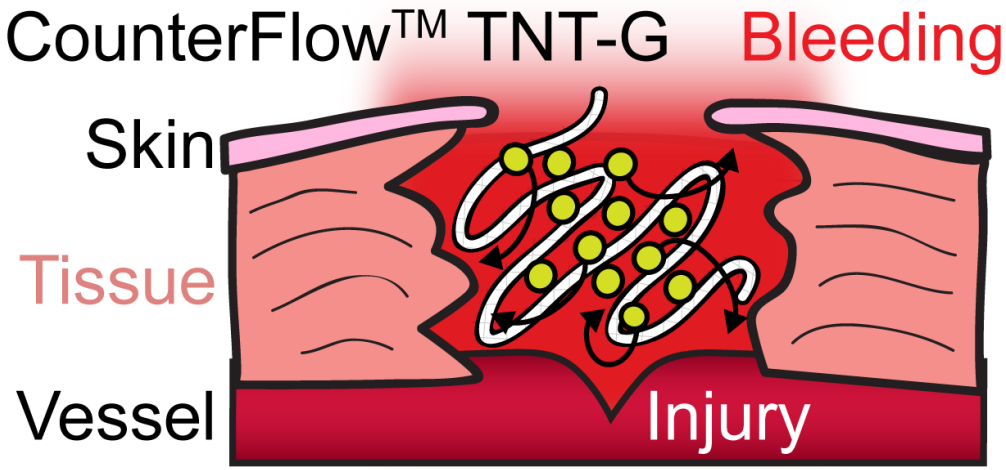
CounterFlow Uses Self-Propelling Carbonate Particles To Deliver Thrombin and TXA



$$CaCO_{3(s)} + 2H^+_{(aq)} \longrightarrow Ca^{2+}_{(aq)} + CO_{2(g)} + H_2O_{(l)}$$

Tranexamic acid (TXA)

TXA is an antifibrinolytic drug, a "clot stabilizer"



Baylis, others, White, Kastrup *Science Advances* ***(2015)***

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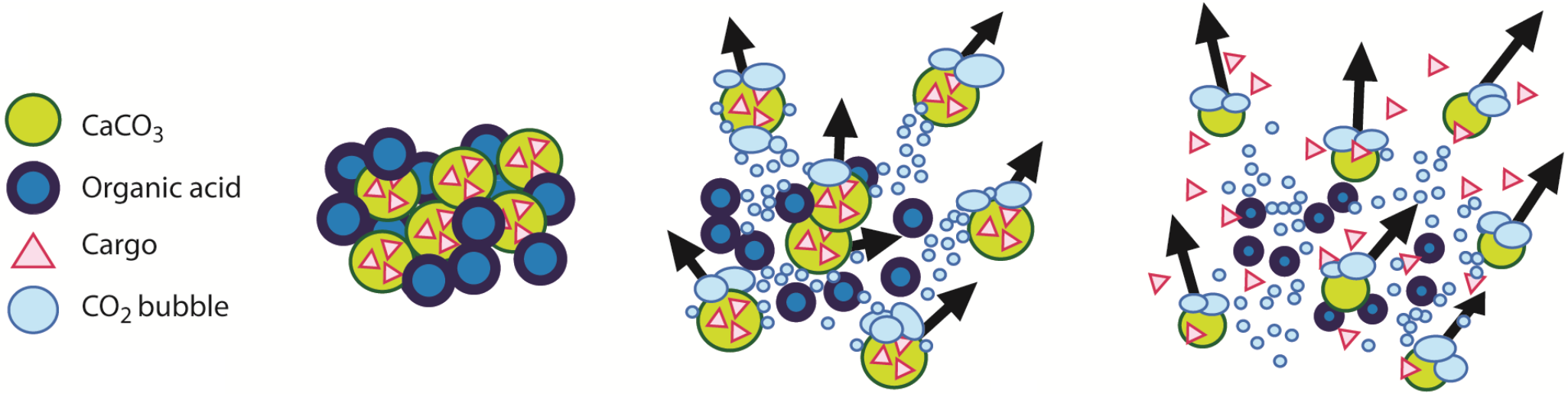

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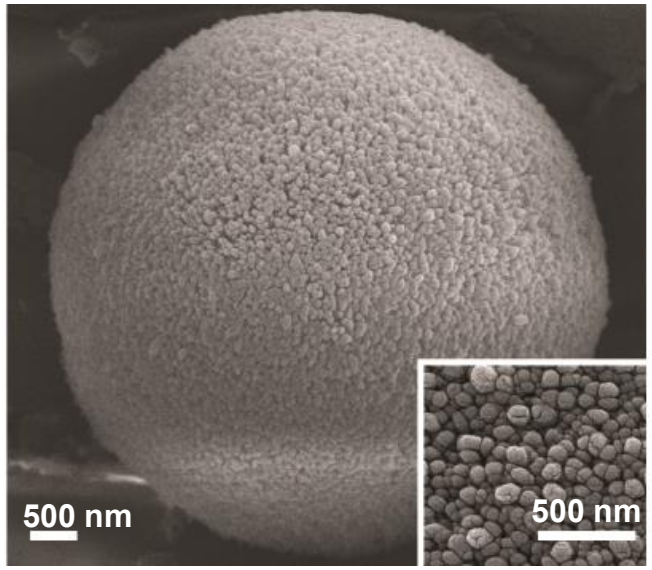
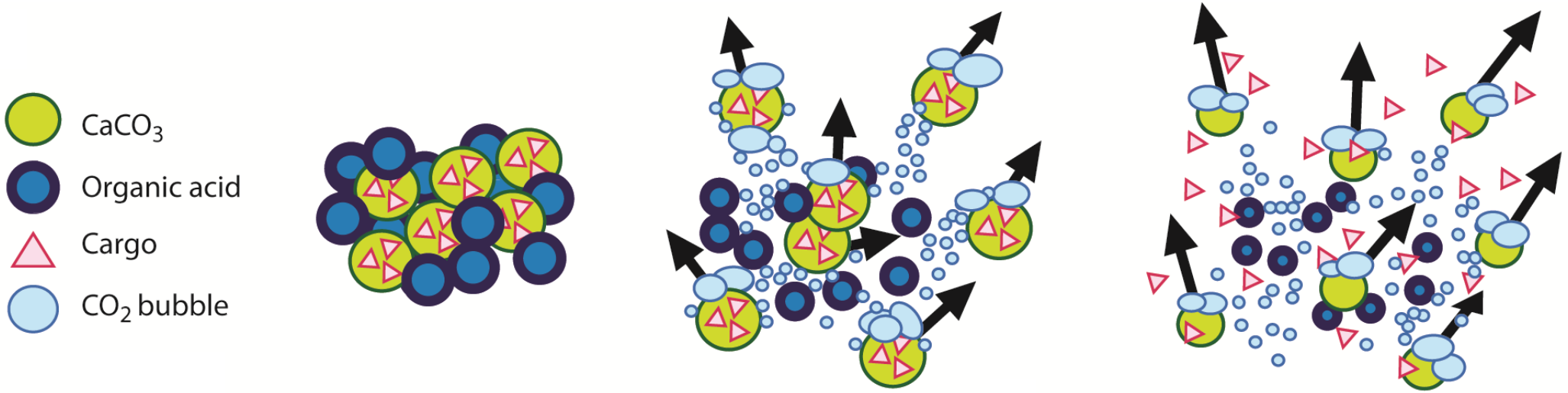


Baylis, others, White, Kastrup *Science Advances* ***(2015)***

A Wound-Penetrating Technology: Self-Propelling Particles (CounterFlow)



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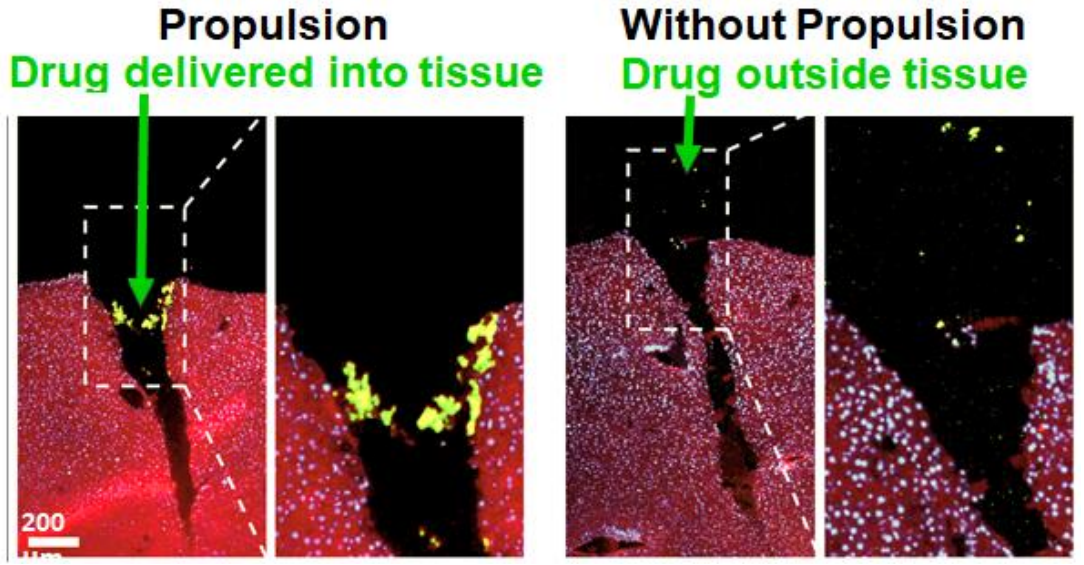
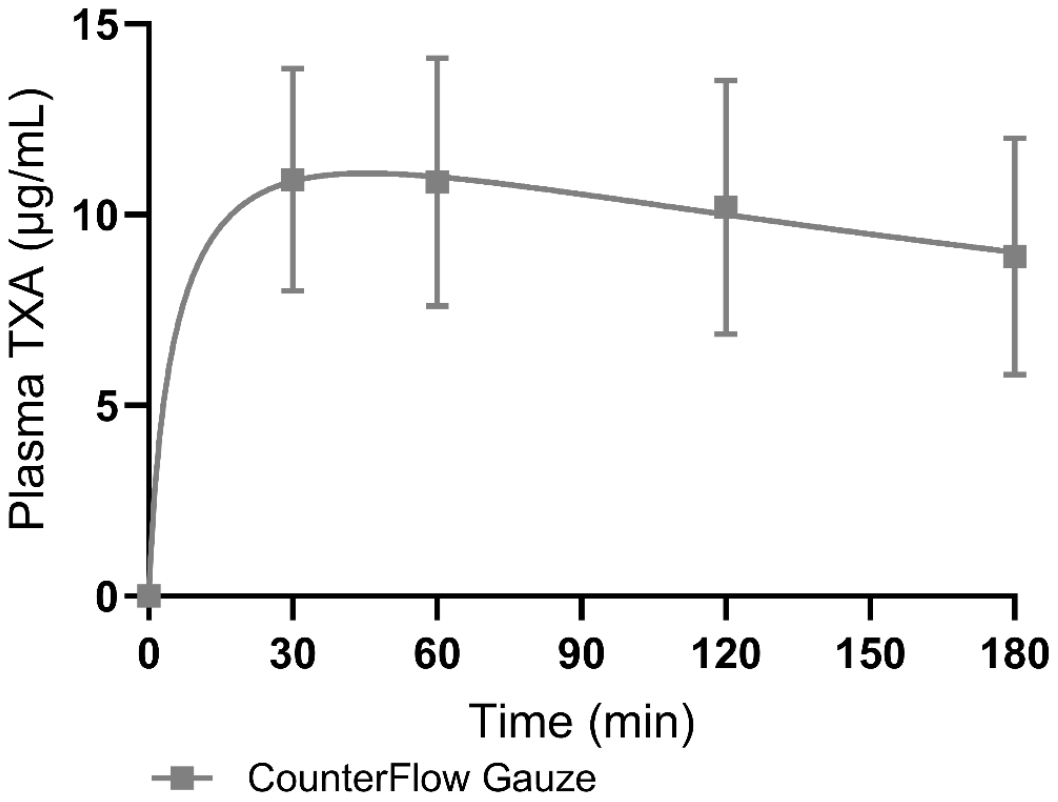


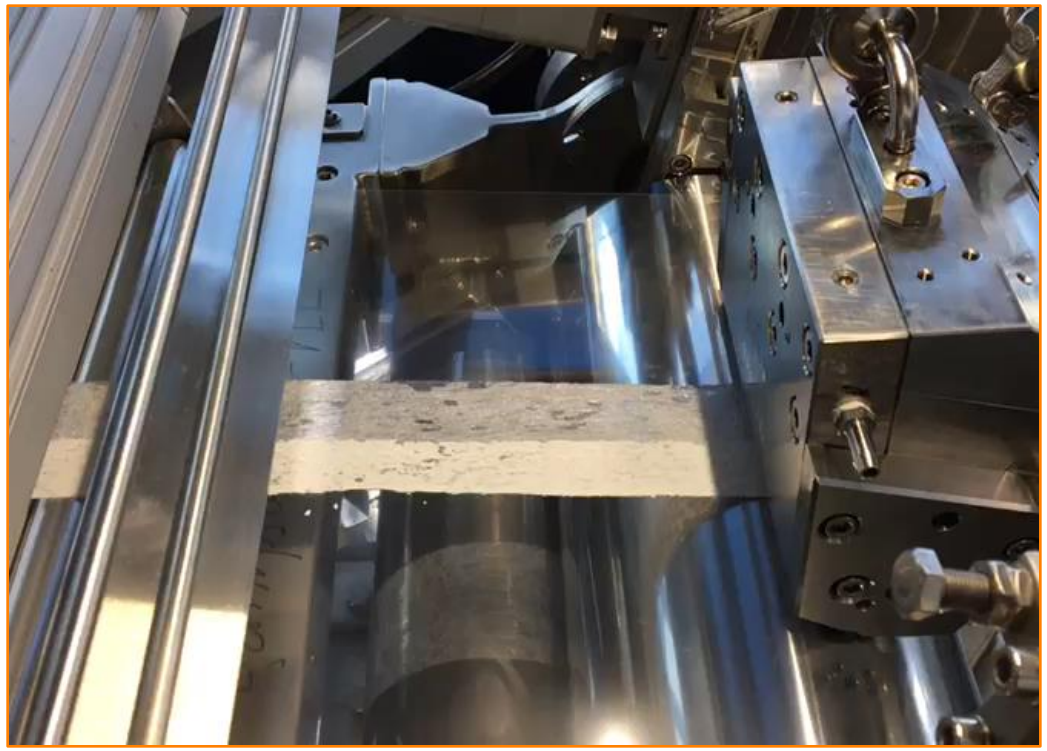
Baylis, others, White, Kastrup *Science Advances* **(2015)**

TXA from gauze is absorbed systemically following medic packing in junctional wounds, reaching inhibitory levels



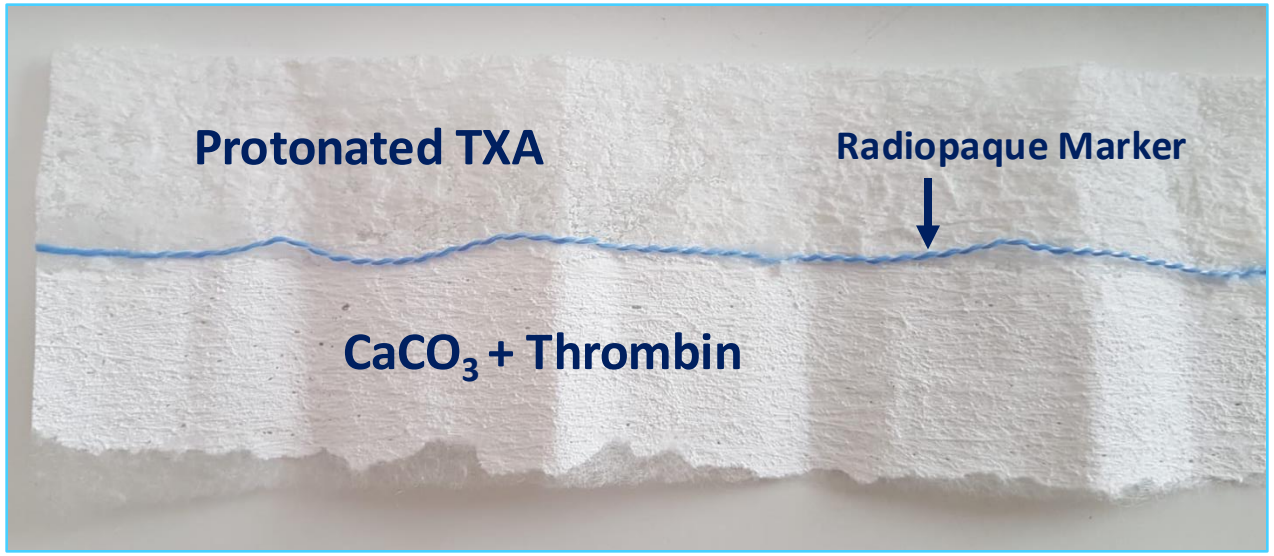
- Sustained TXA plasma concentration of ~10 µg/mL after CounterFlow-Gauze, which is in the therapeutic window.
- This delivery mechanism is well-suited to use in cold environments and/or without vascular access.

CounterFlow Gauze is Being Scaled Up



Roll to roll production of CounterFlow Gauze

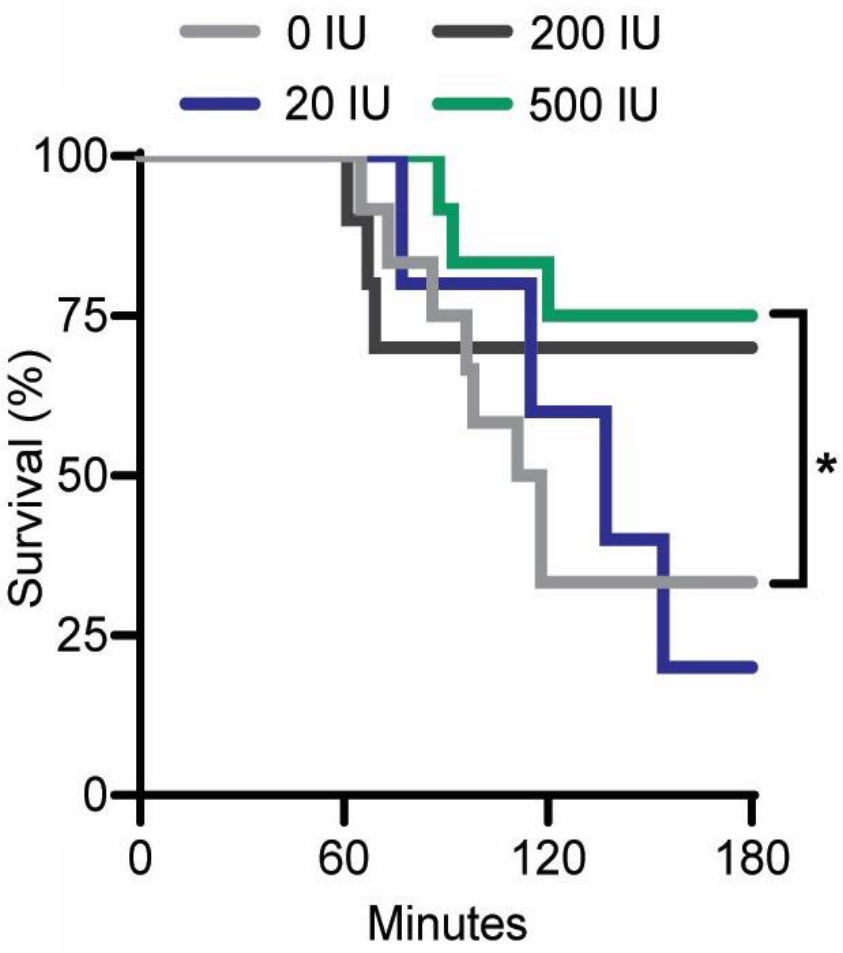
CounterFlow Gauze Design

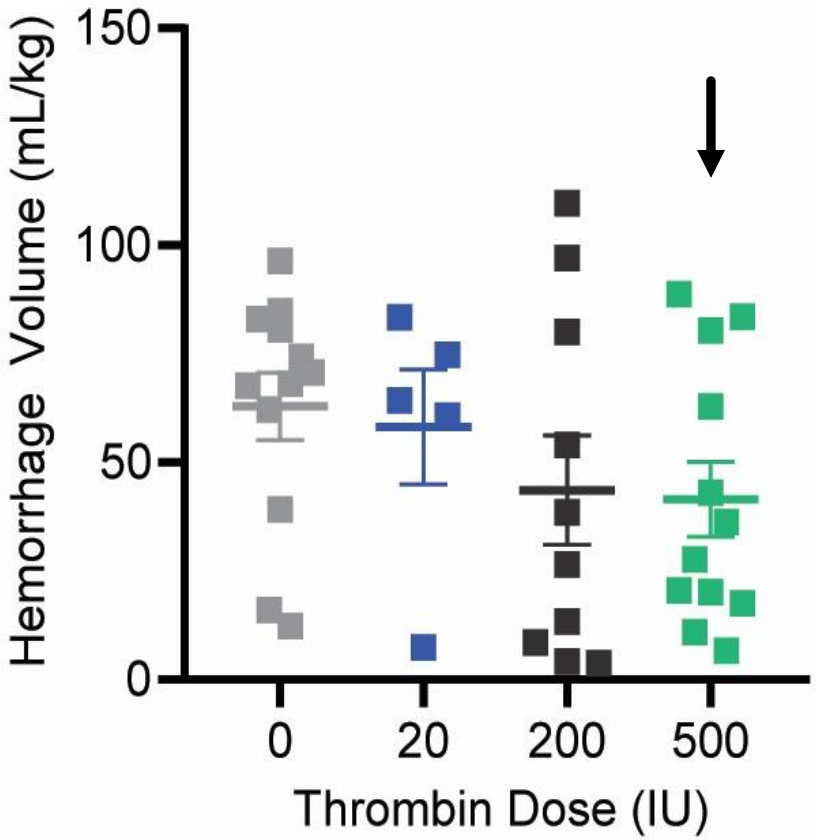


Ali-Mohamad, Cau, Baylis, others, White, Beckett, Kastrup, *Military Medicine* **(2023)**

Thrombin dose on CounterFlow Gauze is optimized

Swine model of femoral artery hemorrhage W/O manual compression (n= 6-12)

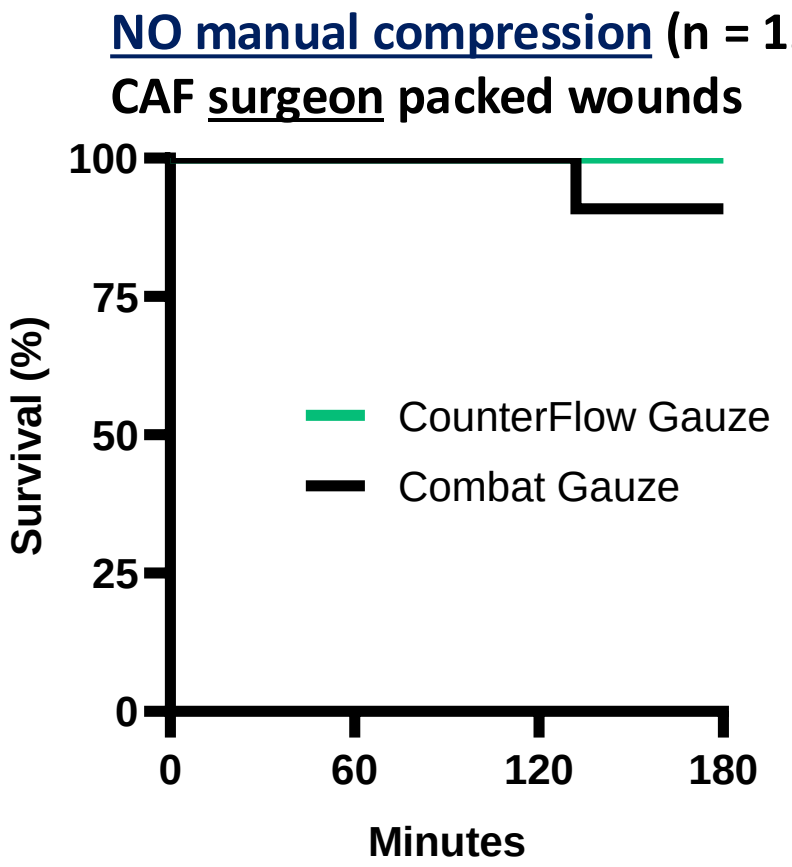


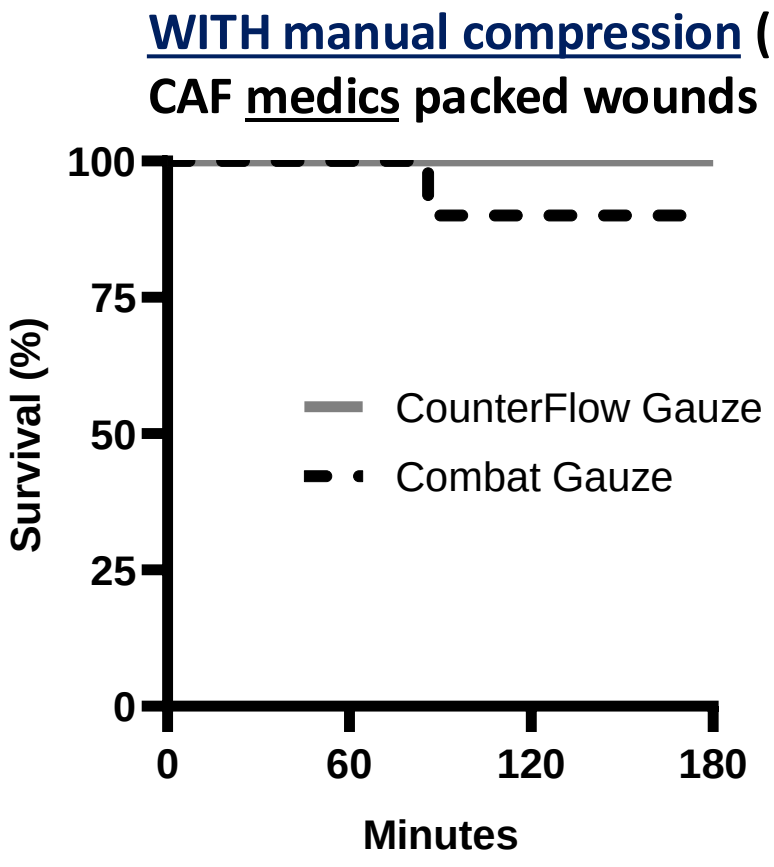


Ali-Mohamad, Cau, Baylis, others, White, Beckett, Kastrup, *Military Medicine* **(2023)**

Refined CounterFlow-Gauze prevents death from junctional hemorrhage, and can be used similarly to Combat Gauze

Two separate experiments using a swine model of 4.0 mm femoral arteriotomy





Ali-Mohamad, Cau, Baylis, others, White, Beckett, Kastrup, *Military Medicine* **(2023)**

Canadian Armed Forces (CAF) Medics like CounterFlow-Gauze

End User Product Comparison Survey – ranking 1-5

	CounterFlow-Gauze (mean ± SEM)	Combat Gauze (mean ± SEM)	P value
The product was easy to handle.	4.8 ± 0.1	4.4 ± 0.2	0.522
The product was easy to pack.	4.9 ± 0.1	4.4 ± 0.3	0.522
The product was effective in controlling bleeds.	4.3 ± 0.3	3.0 ± 0.4	0.088
I am comfortable using this product to treat a casualty.	4.6 ± 0.2	3.6 ± 0.3	**0.039**
My overall sentiment towards this product.	**4.7 ± 0.2**	**3.8 ± 0.3**	0.088

Common narrative themes:

- **CounterFlow-Gauze feels very effective and stops bleeds promptly**
- **Less effort was needed to control bleeds when using CounterFlow**
- **Bubbling and discolouration of blood was reassuring that the gauze was effective.**
- **"I would choose [CounterFlow] in an operational setting every time"**

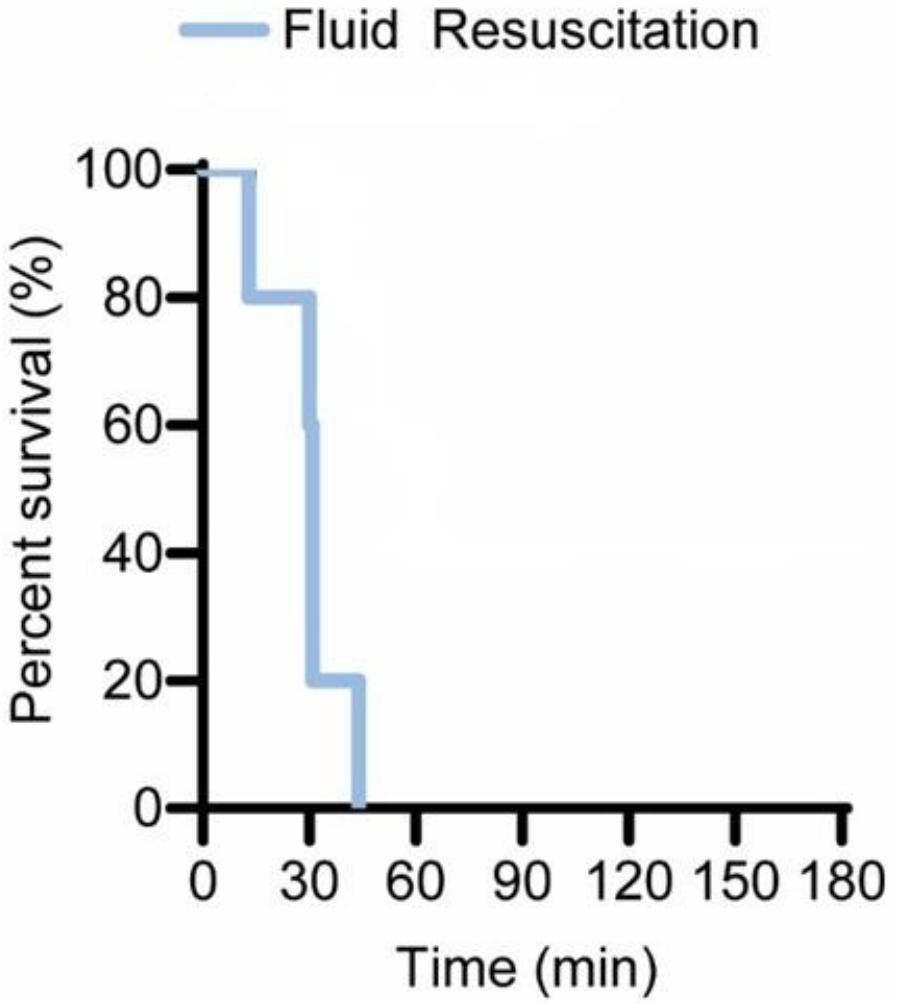
Common suggestions for improvement:

- **Packaging improvements (visual indicators or multiple small tears for opening)**
- **Increased length/material of gauze**

  (tested prototype was only 1.2 m long)

Ali-Mohamad, Singh, others, Tenn, Beckett, Kastrup (unpublished).

Can CounterFlow Powder be used in Non-Compressible Truncal Hemorrhage?



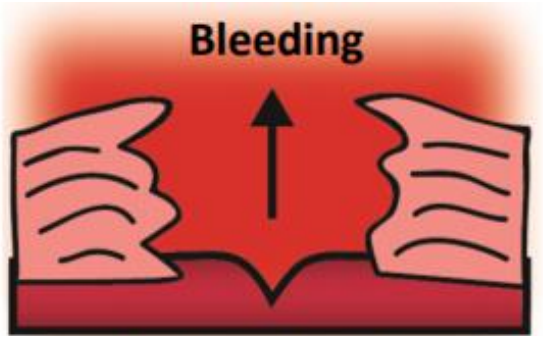
Cau, Ali-Mohamad, Yeh, Baylis, others, Rezende-Neto, Semple, Beckett, Kastrup.
Journal of Trauma and Acute Care Surgery **(2022)**

Intra-Abdominal Hemorrhage is a Major Cause of Death
New Technology is Needed to Decrease Mortality

Applied hemostatics cannot reach the bleeding site within the torso at high enough local concentrations [1-4]

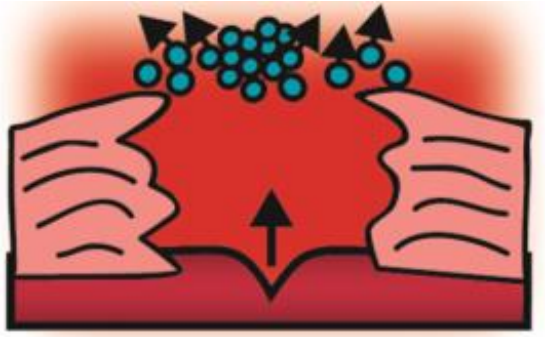
Delivery systems do not exist for transporting hemostatics:

- against high flow rates and through pooled blood – agents flushed out
- into difficult to reach anatomical areas



Internal injury

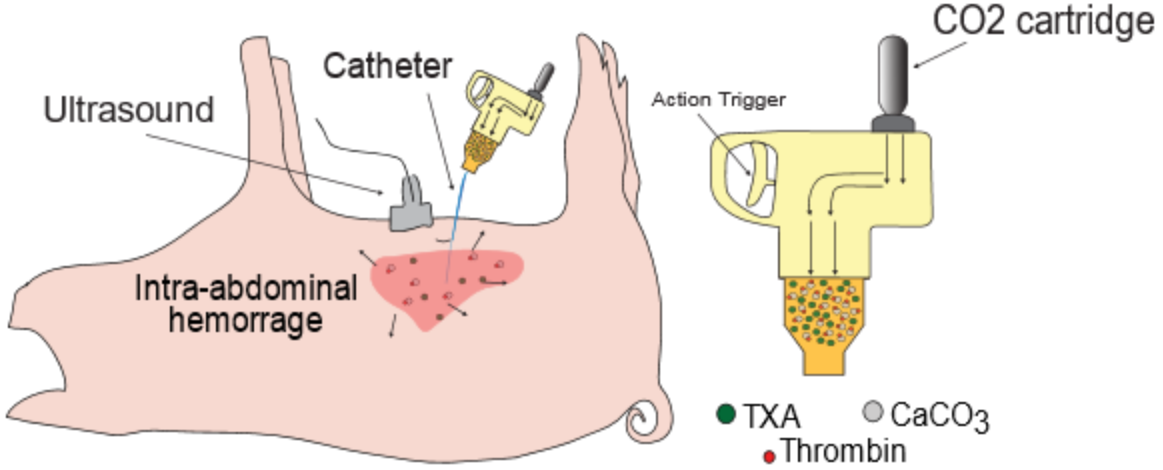
Agents not delivered

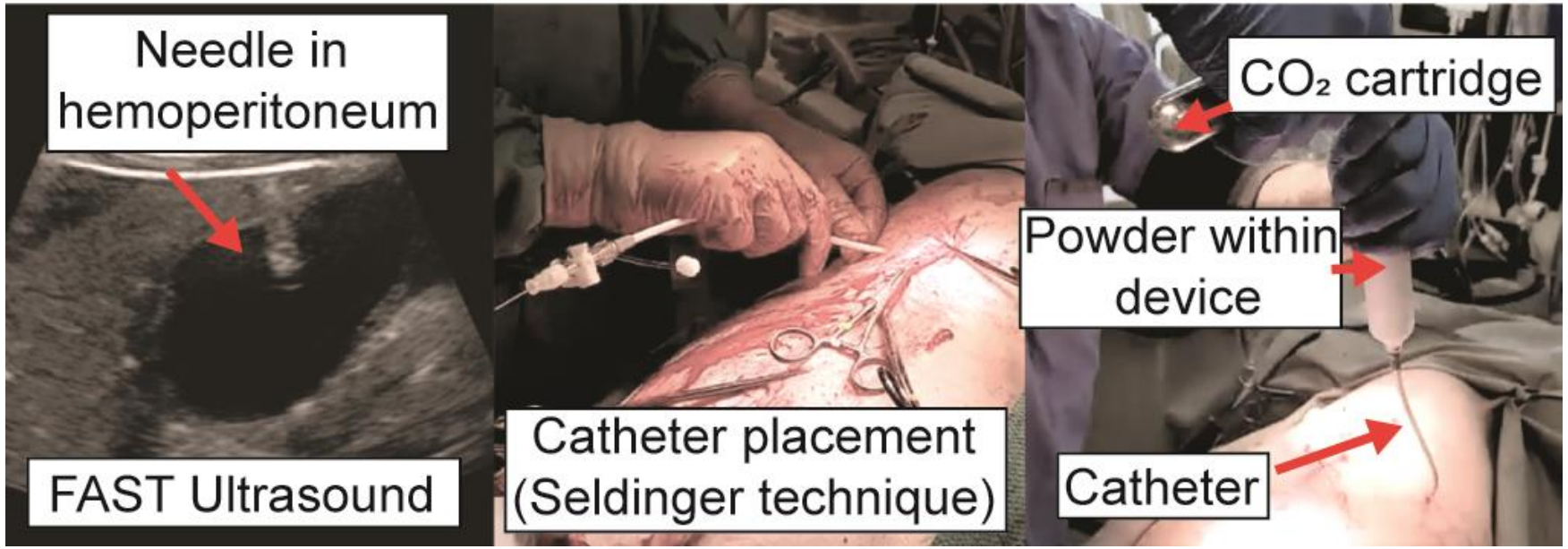


Baylis, Chan, Kastrup, *Thrombosis Research* (2016)

1 Kheirabadi B and Klemcke HS *"Combat Casualty Care in Ground Based Tactical Situations: Trauma Technology and Emergency Medical Procedures"* **(2004)**
2 *DARPA Wound Stasis Research Program* **(2010)**
3 Mueller et al. *J Trauma Acute Care Surg* **(2012)** **4** Gordy SD and Rhee P**,** *Expert Review of Medical Devices* **(2011)**

CounterFlow Powder can be Delivered with Percutaneous Access For Non-Compressible Truncal Hemorrhage (NCTH)

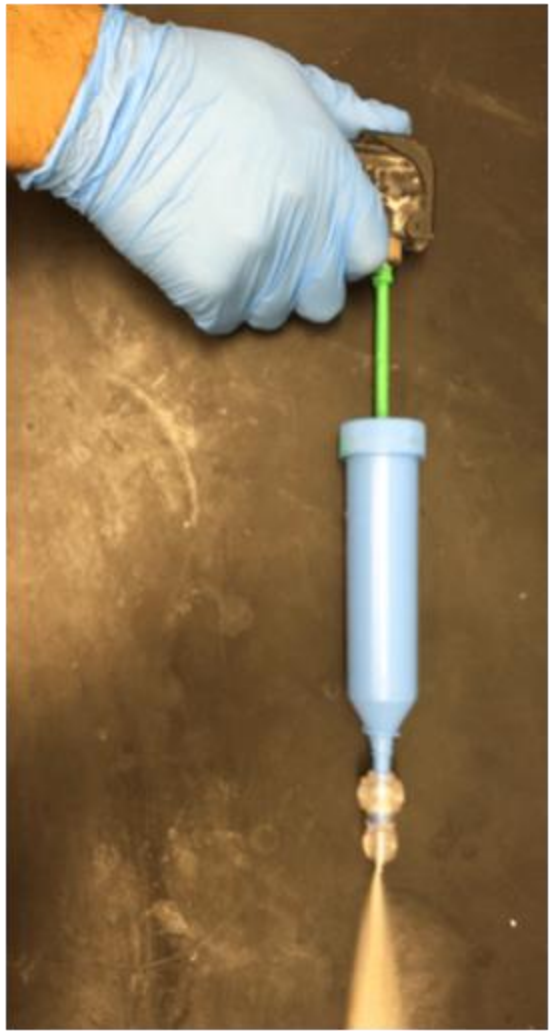




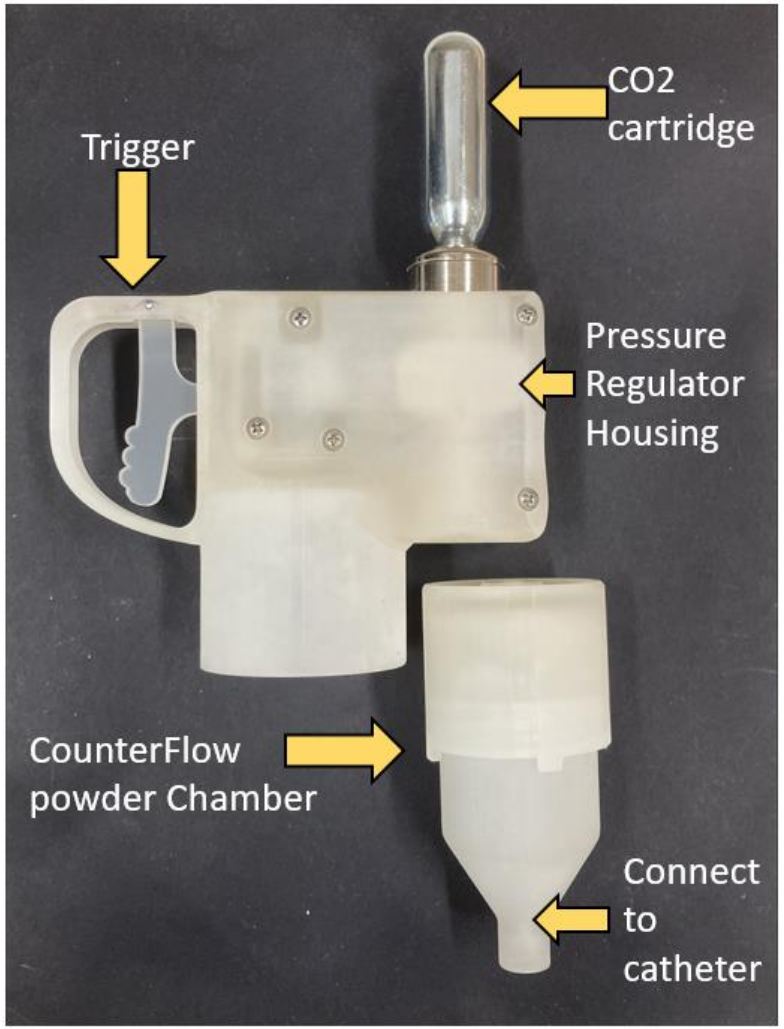
Cau, Ali-Mohamad, Baylis, Khavari, Peng, others, Rezende-Neto, Semple, Beckett, Kastrup *Injury* **(2021)**

A Modular Device was Engineered to Deliver CounterFlow Powder Within Minutes

Device Prototype 1



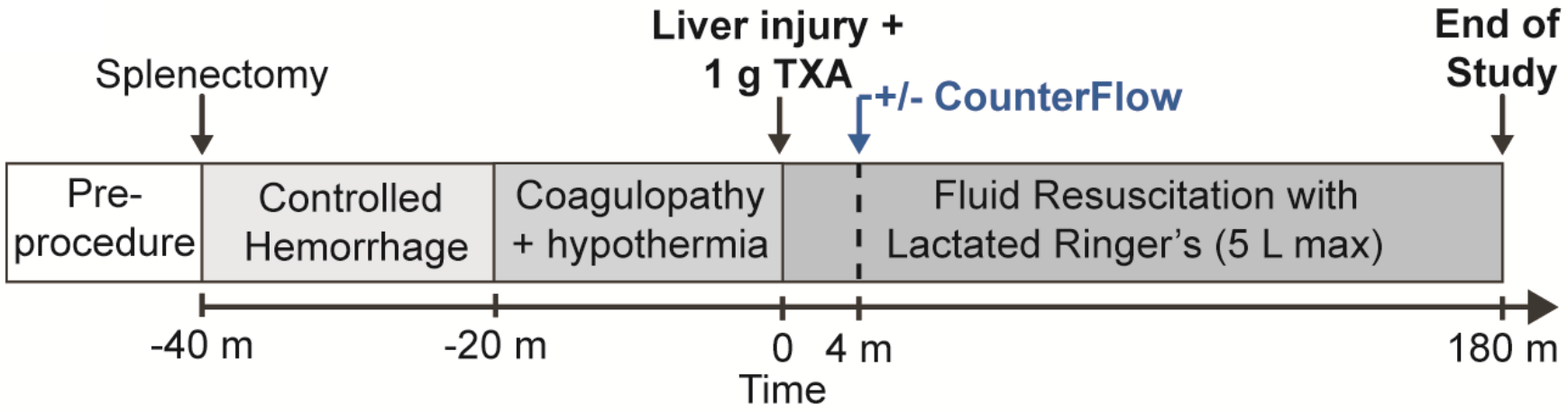
Device Prototype 2

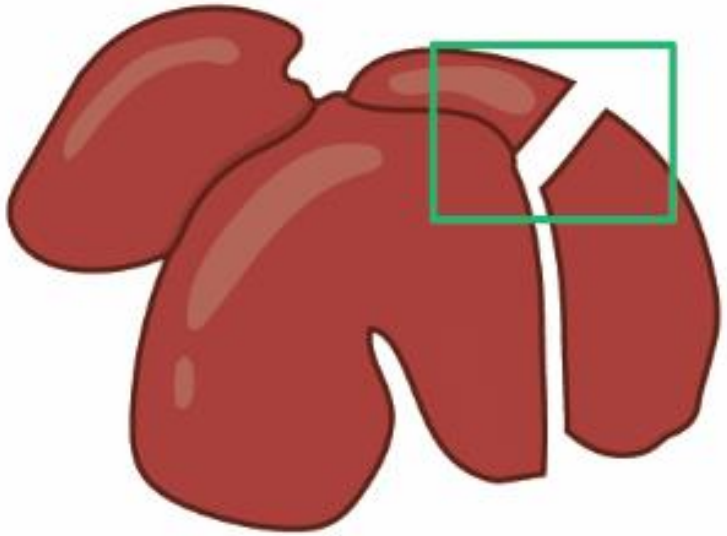


Device Features

- **Modular design for easier parts replacement and trouble-shooting.**
- **Safer to use with updated pressure regulator.**
- **Easier to use with detachable powder chamber.**
- **Uses Veress needle for quicker and easier access into intra-abdominal cavity.**

Efficacy and safety of CounterFlow tested in multiple swine models of severe NCTH

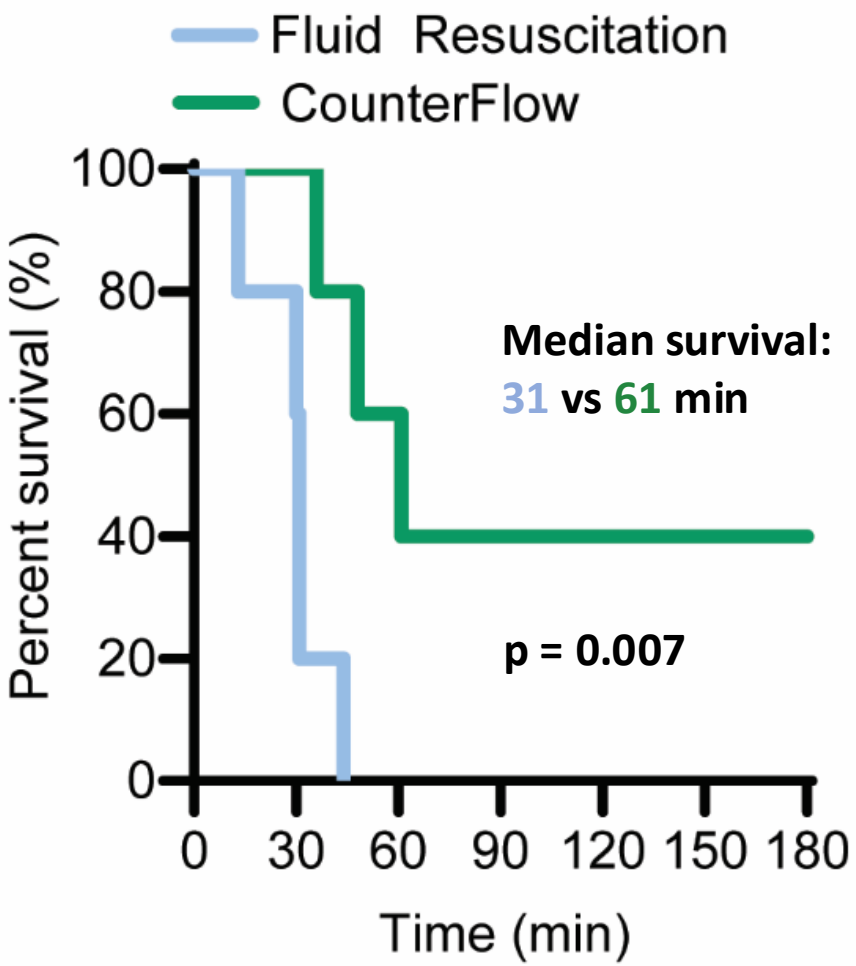




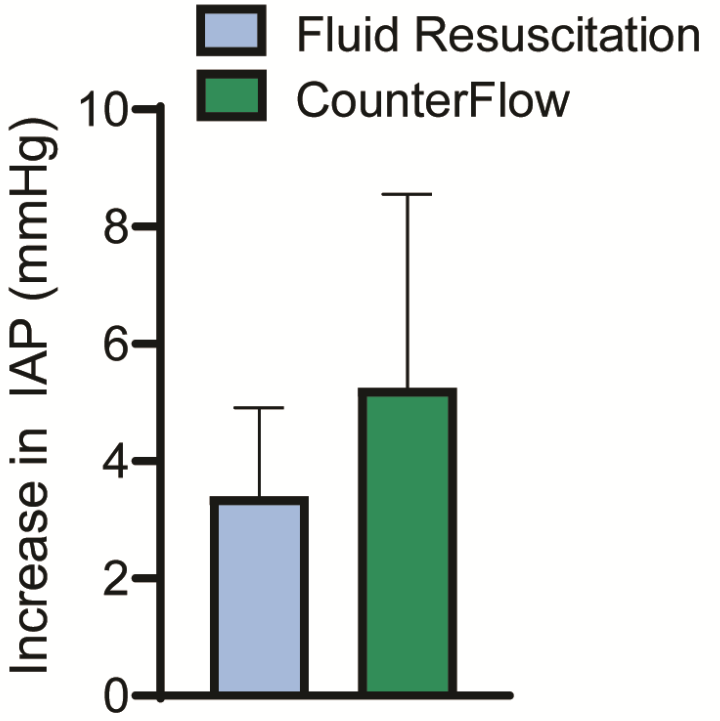
Left <u>lateral</u> lobe transection (~70 % of total lobe)

Cau, Ali-Mohamad, Yeh, Baylis, others, Rezende-Neto, Semple, <u>Beckett</u>, <u>Kastrup</u>.
Journal of Trauma and Acute Care Surgery **(2022)**

CounterFlow Powder for Noncompressible Abdominal Hemorrhage

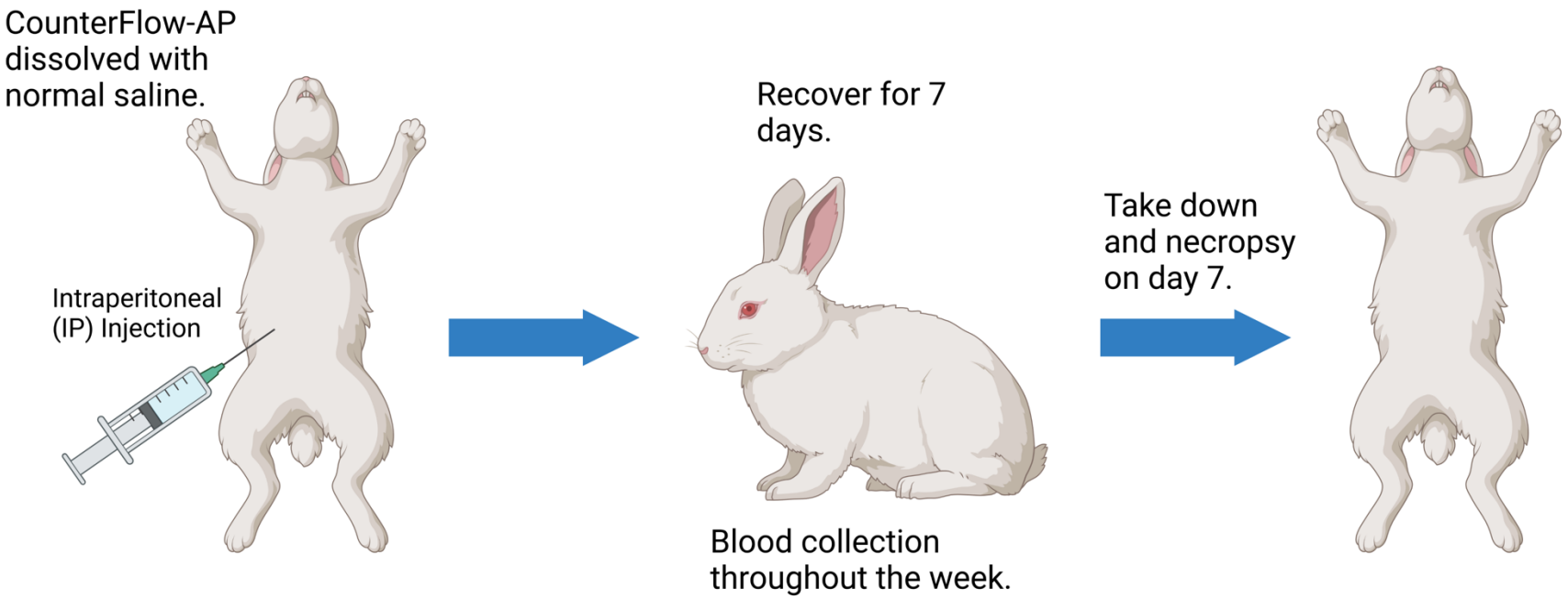


Safe increase in Intra-abdominal pressure (IAP)



Cau, Ali-Mohamad, Yeh, Baylis, others, Rezende-Neto, Semple, Beckett, Kastrup.
Journal of Trauma and Acute Care Surgery **(2022)**

CounterFlow with Thrombin and TXA Does Not Show Major Adverse Effect with High Doses in Rabbit

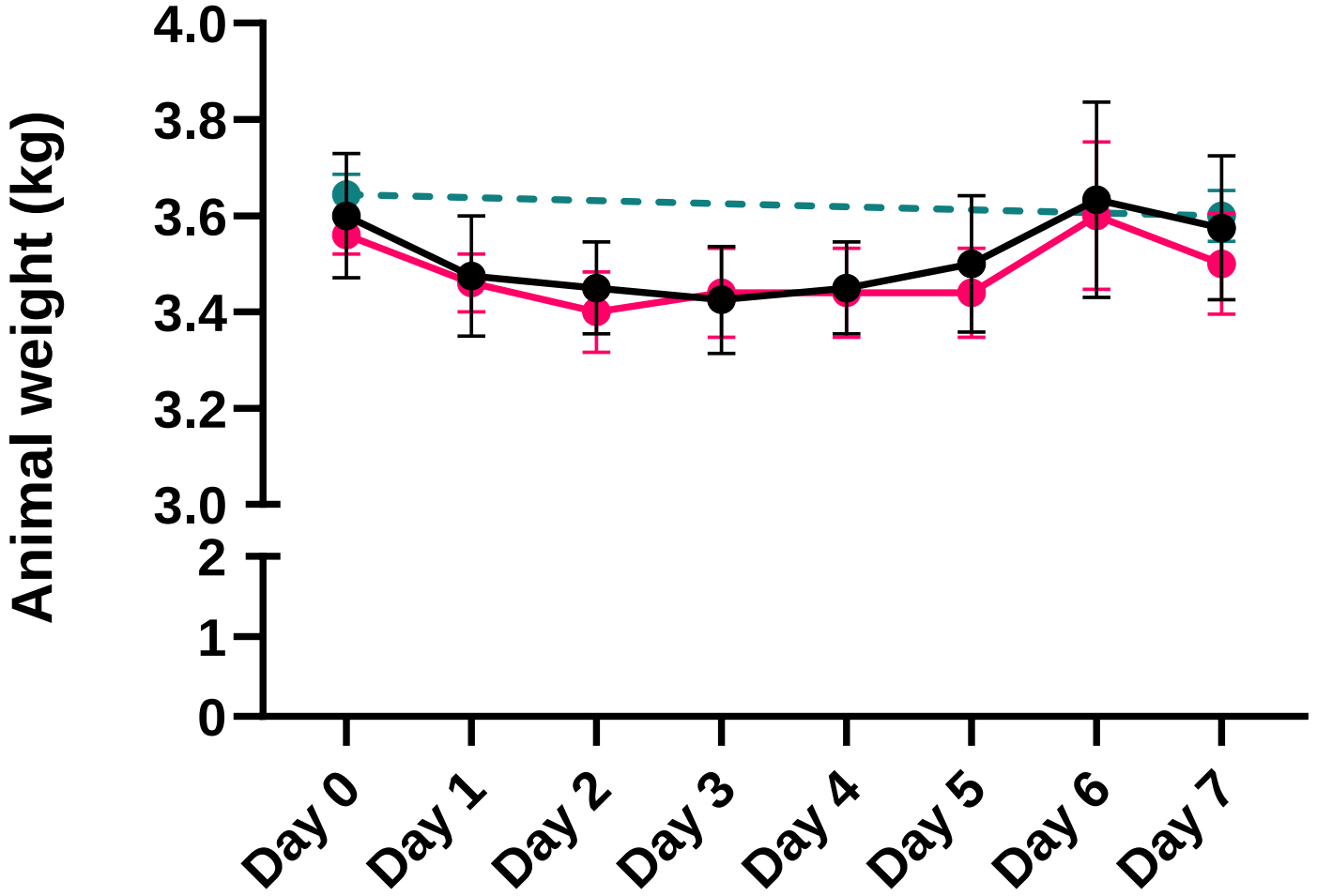


- Five different doses of CounterFlow-AP were tested in rabbit with IP injection:
  - 0, 0.25, 0.5, 1, 1.5 g/kg
  - Highest dose (1.5 g/kg) is human equivalent dose of using 40 g in human.

- CounterFlow powder (g) used in this experiment was loaded with Thrombin (IU)

Created with BioRender.com

High Doses of CounterFlow-AP with Thrombin Does Not Adversely Affect Rabbit Weight



1.0 g/kg

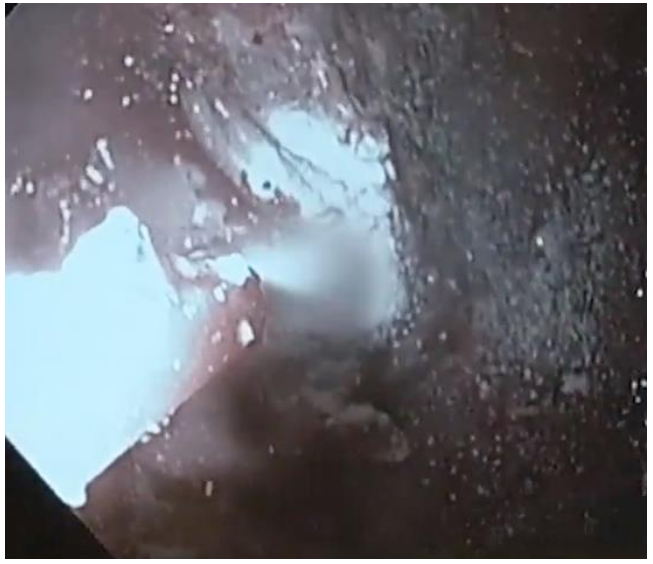
1.5 g/kg

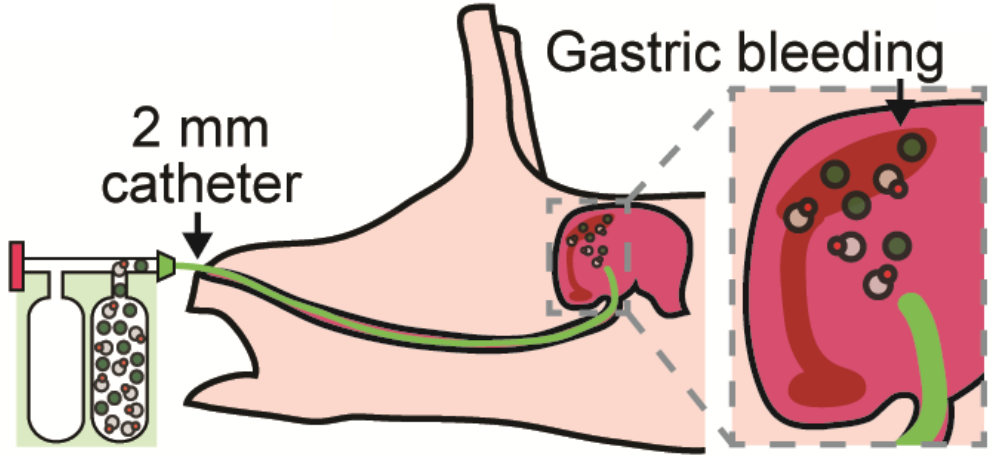
Lower Dose

- Green dash line indicate the rabbits that received lower dose of CounterFlow-AP (0-0.5 g/kg).

- CounterFlow powder (g) used in this experiment are loaded with Thrombin (IU)

CounterFlow Powder Halts Severe Upper Gastrointestinal Bleeding



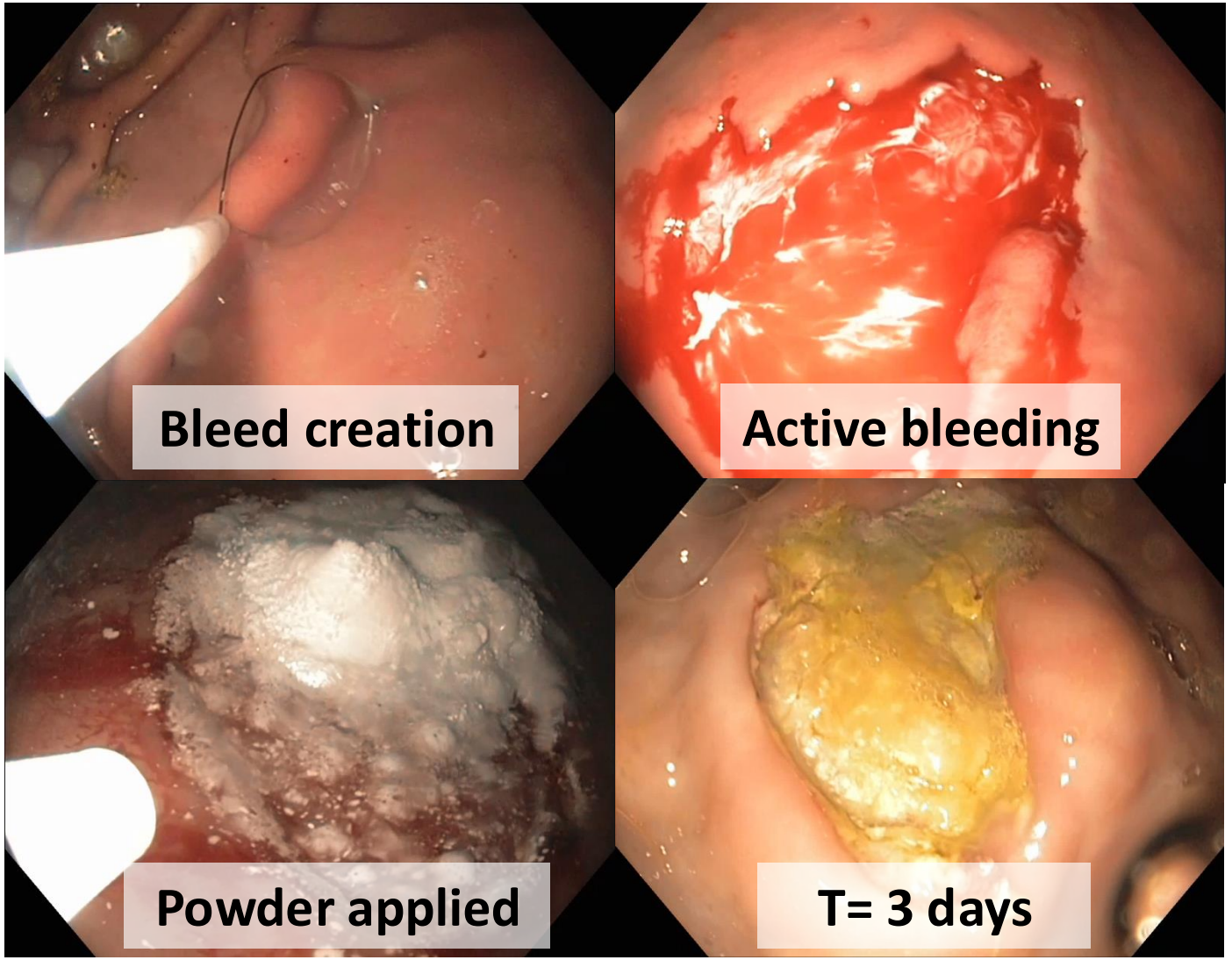


12 vessels injured in total of 5 pigs

Time to hemostasis (min)	Mass Particles delivered (g)
4.3 +/- 0.9	2.4 +/- 0.6

Ali-Mohamad, Cau, Baylis, Semple, Beckett, Donnellan, Kastrup, *Endoscopy International Open* **(2021)**

CounterFlow Powder Halts Severe Upper Gastrointestinal Bleeding



Ali-Mohamad, Cau, Baylis, Semple, Beckett, Donnellan, Kastrup, *Gastrointestinal Endoscopy* **(2023)**

Conclusions

- **CounterFlow enhances the delivery of hemostatics in wounds, even without added manual compression**

- **Administered as a gauze for non-compressible junctional hemorrhage:**

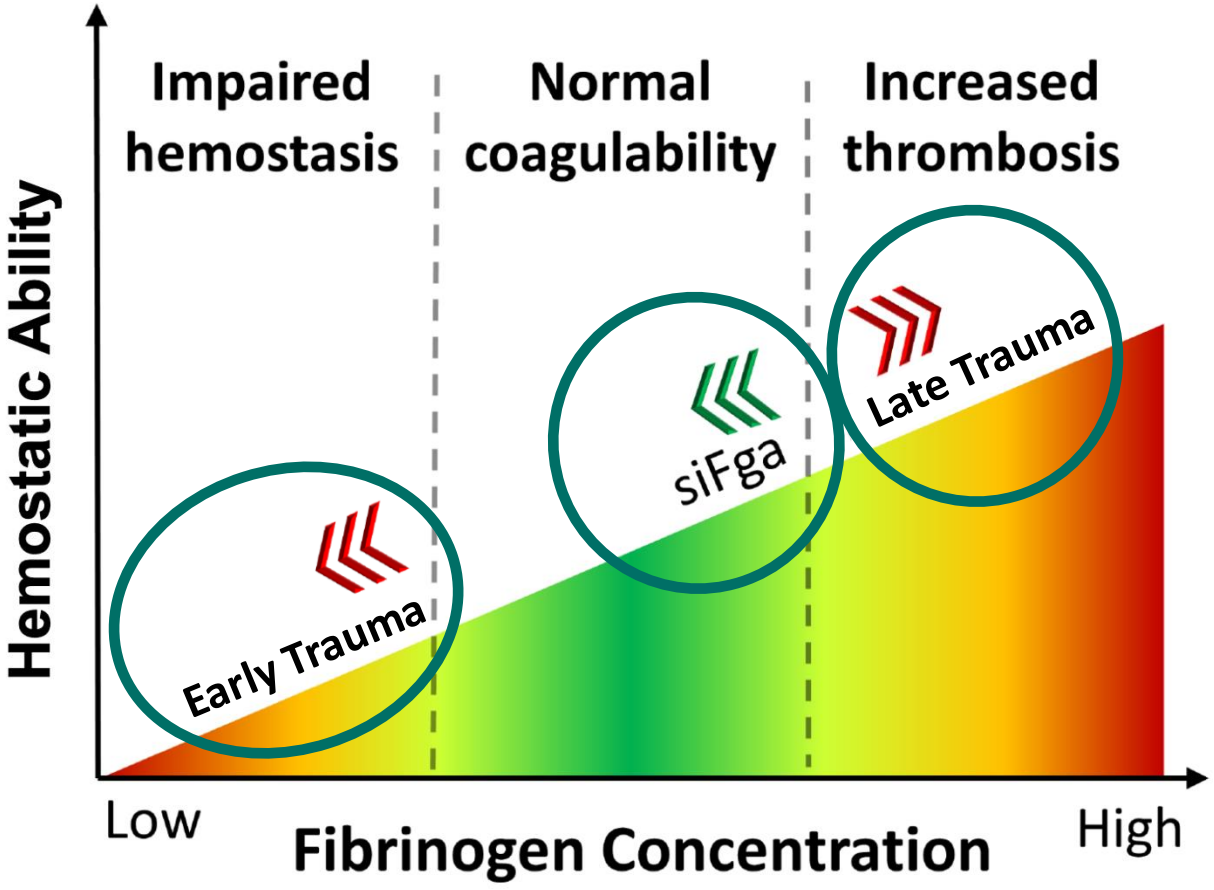
  Able to deliver TXA without IV or autoinjector

- **Ruggedized design with defined packaging which can be manufactured roll-to-roll using automated methods with sterilization**

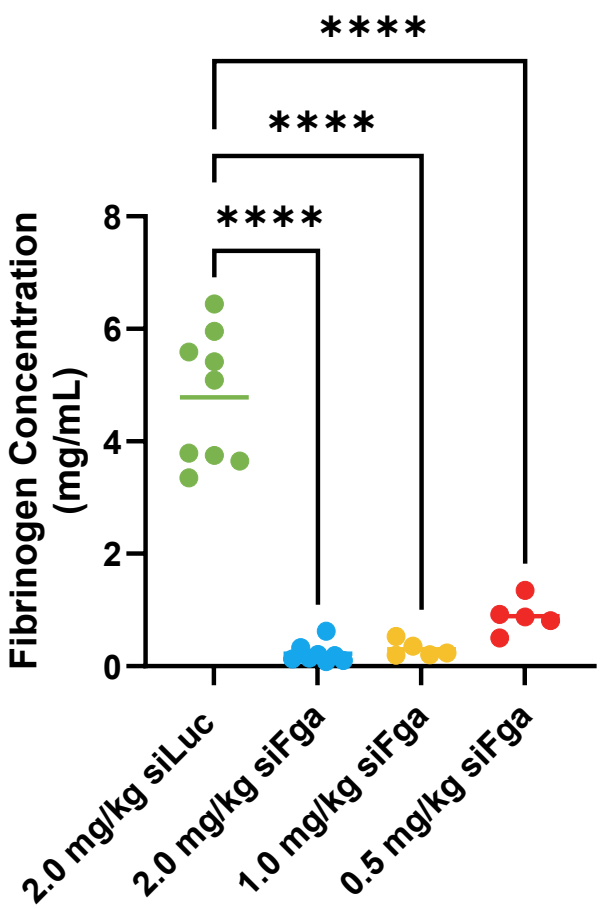
- **Administered as a powder percutaneously without surgical techniques for NCTH and upper GI bleeds**

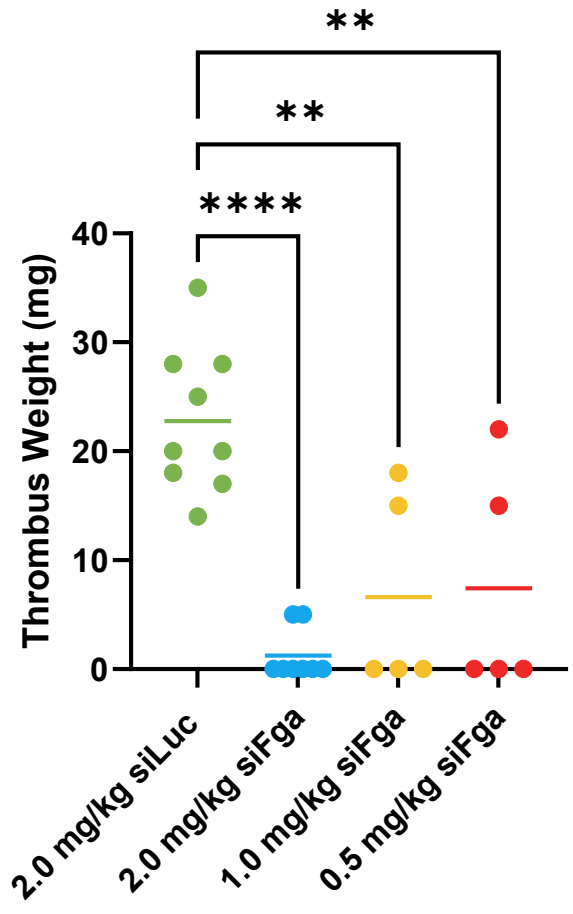
BONUS SLIDE! A "vaccine" to safely prevent thromboinflammation

siRNA knockdown of excess fibrinogen (siFga)



Mice and Pigs: Prevents post-trauma thrombosis without bleeding





Juang, many others, Cap, Flick, Kastrup *Science* **(2021)**, *Blood* **(2022, 2022)**, *JTH* **(2022)**, JTACS **(2024)**

Collaborators (this work):

- **Andrew Beckett** (U. Toronto/Canadian Armed Forces)
- **Hugh Semple, Catherine Tenn** (Defence Research and Development Canada)
- **Joao Rezende-Neto** (U. Toronto)
- **Nathan White** (U. Washington)
- **Fergal Donnellan** (Vancouver. Gen. Hosp.)
- **Dana Grecov** (UBC)
- **Lindsay Machan** (Vancouver Gen. Hosp.)
- **Andrew Cap, Adam Meledeo, Zachary Booms** (USAISR)

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