



**CASE WESTERN RESERVE
UNIVERSITY**
School of Medicine and
Case School of Engineering

SEN GUPTA LAB
BIO-INSPIRED ENGINEERING for ADVANCED THERAPIES



@JishnuSenGupta

Synthetic and Engineered Platelets for Hemorrhage Control Applications

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Wallace R. Persons Endowed Professor of Engineering

Haima Therapeutics LLC

11000 CEDAR AVE., STE 280
CLEVELAND, OH 44106



Co-founder, Chief Technology Officer, Chair of SAB

Patents:

- US 9107845, US 9636383, US 10426820, US 10434149, US 9107963, US 10716865, US 11439688, US 11648323, are licensed to Haima.
- US 11408844 in negotiation with XaTek.

Acknowledgement

Collaborators



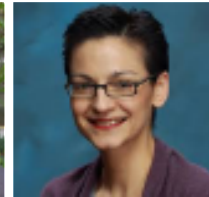
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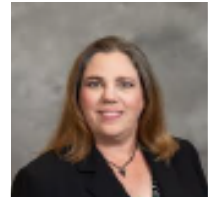
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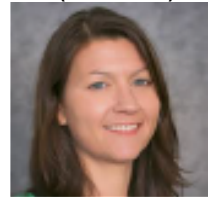
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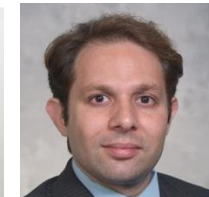
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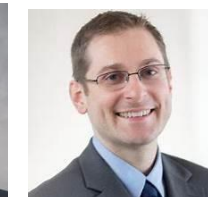
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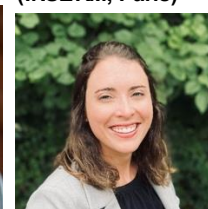
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Dr. Shoffstall
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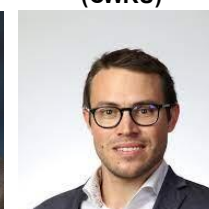
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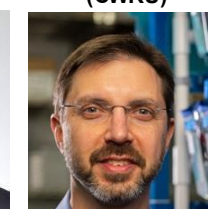
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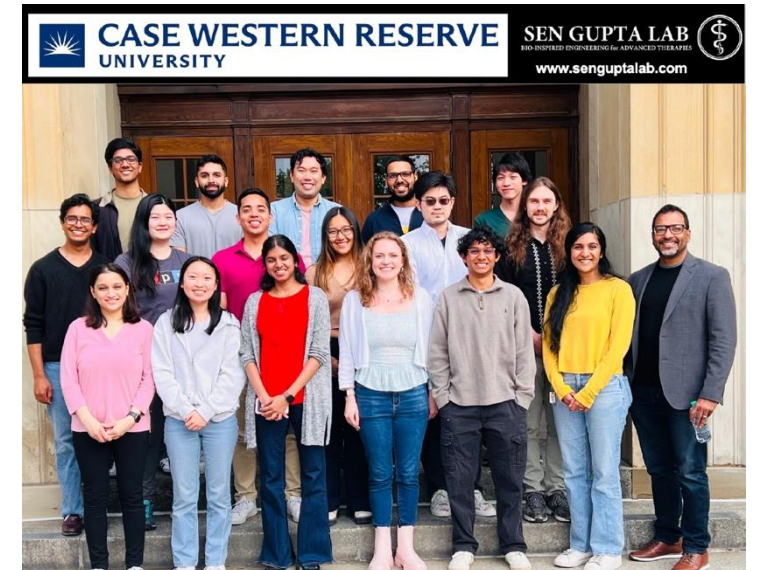


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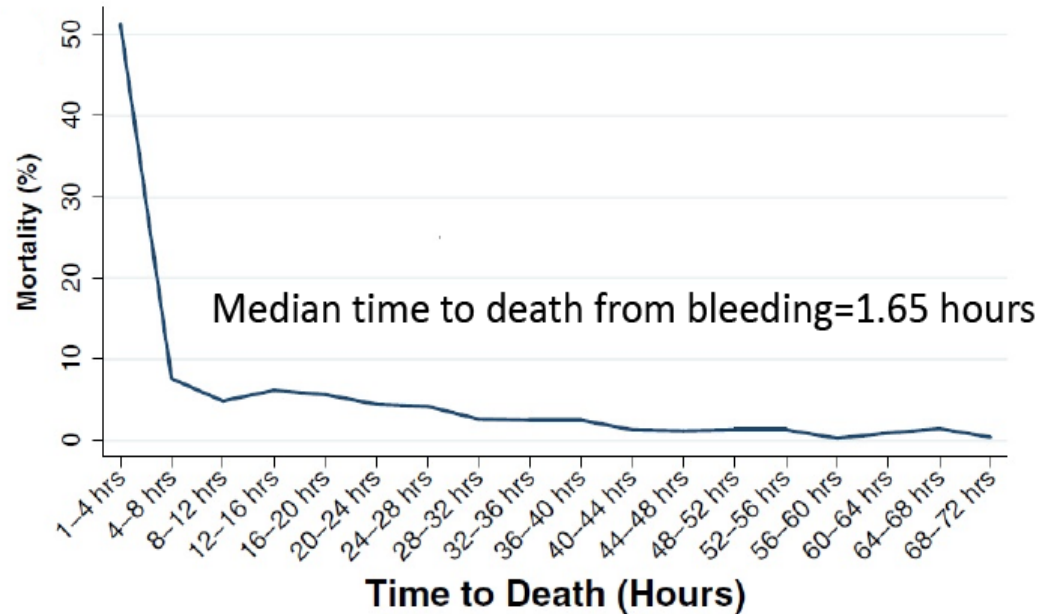
Funding



National Heart, Lung,
and Blood Institute



Platelets help Stop Bleeding → Improve Survival



PROPPR
Pragmatic, Randomized Optimal Platelet and Plasma Ratios

Original Investigation

Transfusion of Plasma, Platelets, and Red Blood Cells in a 1:1:1 vs a 1:1:2 Ratio and Mortality in Patients With Severe Trauma The PROPPR Randomized Clinical Trial

John B. Holcomb, MD; Barbara C. Tilley, PhD; Sarah Baraniuk, PhD; Erin E. Fox, PhD; Charles E. Wade, PhD; Jeanette M. Podbielski, RN; Deborah J. del Junco, PhD; Karen J. Brasel, MD, MPH; Eileen M. Bulger, MD; Rachael A. Callcut, MD, MSPH; Mitchell Jay Cohen, MD; Bryan A. Cotton, MD, MPH; Timothy C. Fabian, MD; Kenji Inaba, MD; Jeffrey D. Kerby, MD, PhD; Peter Muskat, MD; Terence O'Keefe, MBChB, MSPH; Sandro Rizoli, MD, PhD; Bryce R. H. Robinson, MD; Thomas M. Scalea, MD; Martin A. Schreiber, MS; Deborah M. Stein, MD; Jordan A. Weinberg, MD; Jeannie L. Callum, MD; John R. Hess, MD, MPH; Nena Matijevic, PhD; Christopher N. Miller, MD; Jean-Francois Pittet, MD; David B. Hoyt, MD; Gail D. Pearson, MD, ScD; Brian Leroux, PhD; Gerald van Belle, PhD; for the PROPPR Study Group

ANNALS OF SURGERY

Collections ▾ Articles & Issues ▾ Infographics ▾ For Authors ▾ Journal Info ▾

ORIGINAL ARTICLES

Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

Holcomb, John B. MD¹; Wade, Charles E. PhD²; Michalek, Joel E. PhD³; Chisholm, Gary B. PhD⁴; Zarzabal, Lee Ann MS⁵; Schreiber, Martin A. MD⁶; Gonzalez, Ernest A. MD⁷; Pomper, Gregory J. MD⁸; Perkins, Jeremy G. MD⁹; Spinella, Phillip C. MD¹⁰; Williams, Kari L. RN¹¹; Park, Myung S. MD¹²

Author Information

Annals of Surgery 248(3):p 447-458, September 2008. | DOI: 10.1097/SLA.0b013e318185a9ad

REGULAR ARTICLE

blood advances

Check for updates

Loss of GPVI and GPIb α contributes to trauma-induced platelet dysfunction in severely injured patients

Paul Vulliamy,¹ Samantha J. Montague,² Scarlett Gillespie,¹ Melissa V. Chan,¹ Lucy A. Coupland,² Robert K. Andrews,³ Timothy D. Warner,¹ Elizabeth E. Gardiner,² Karim Brohi,¹ and Paul C. Armstrong¹

¹Bizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; ²John Curtin School of Medical Research, Australian Cancer Research Foundation Department of Cancer Biology and Therapeutics, The Australian National University, Canberra, ACT, Australia; and ³Australian Centre for Blood Diseases, Monash University, Melbourne, VIC, Australia

The Journal of Trauma and Acute Care Surgery

Articles & Issues ▾ Collections ▾ Multimedia ▾ CME ▾ For Authors ▾ Journal Info ▾ DEI Resources ▾

ORIGINAL ARTICLE

Increased Platelet:RBC Ratios Are Associated With Improved Survival After Massive Transfusion

Holcomb, John B. MD, FACS; Zarzabal, Lee A. MS; Michalek, Joel E. PhD; Kozar, Rosemary A. MD, PhD; Spinella, Phillip C. MD, FCCM; Perkins, Jeremy G. MD; Matijevic, Nena PhD; Dong, Jing-Fei MD, PhD; Pati, Shiban MD, PhD; Wade, Charles E. PhD the Trauma Outcomes Group

Author Information

The Journal of Trauma: Injury, Infection, and Critical Care 71(2):p S318-S328, August 2011. | DOI: 10.1097/TA.0b013e318227eddb

The Journal of Trauma and Acute Care Surgery

Articles & Issues ▾ Collections ▾ Multimedia ▾ CME ▾ For Authors ▾ Journal Info ▾ DEI Resources ▾

ORIGINAL ARTICLE

A Normal Platelet Count May Not Be Enough: The Impact of Admission Platelet Count on Mortality and Transfusion in Severely Injured Trauma Patients

Brown, Lisa M. MD, MAS; Call, Mariah S. BS; Margaret Knudson, M. MD; Cohen, Mitchell J. MD the Trauma

THE JOURNAL OF AABP

transfusion.org

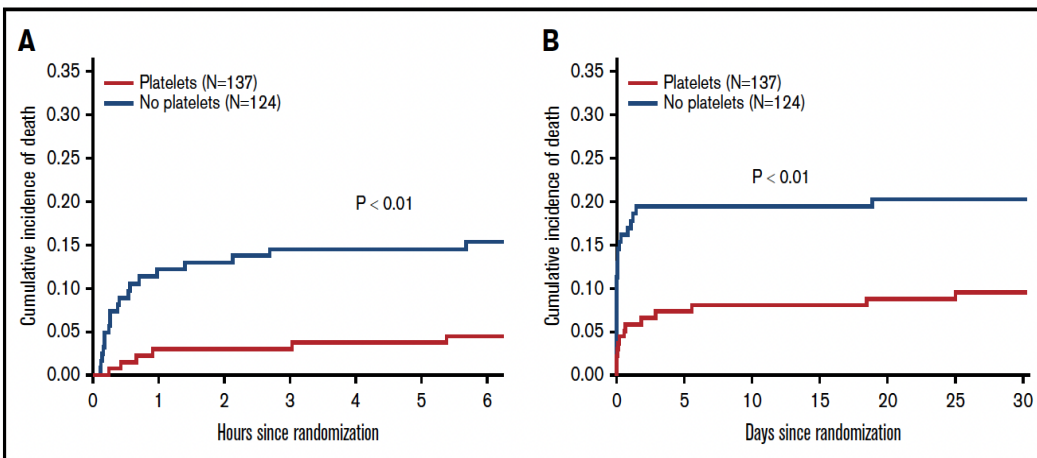
TRANSFUSION

REVIEW | Open Access | CC BY-NC-ND

Platelet dysfunction after trauma: From mechanisms to targeted treatment

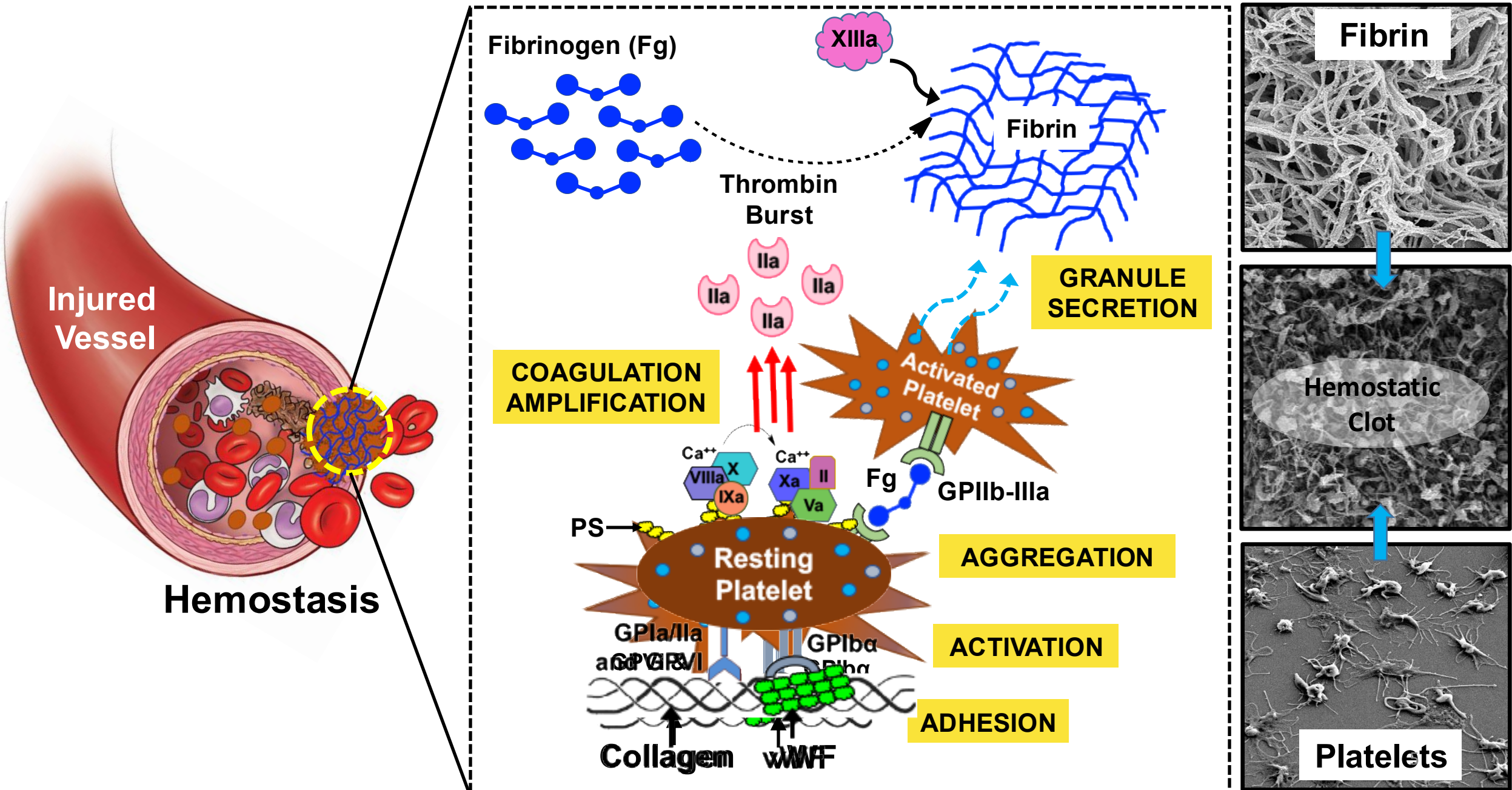
Pieter H. Sloos, Paul Vulliamy, Cornelis van 't Veer, Anirban Sen Gupta, Matthew D. Neal, Karim Brohi, Nicole P. Juffermans, Derek J. B. Kleinveld

First published: 24 June 2022 | <https://doi.org/10.1111/trf.16971> | Citations: 3

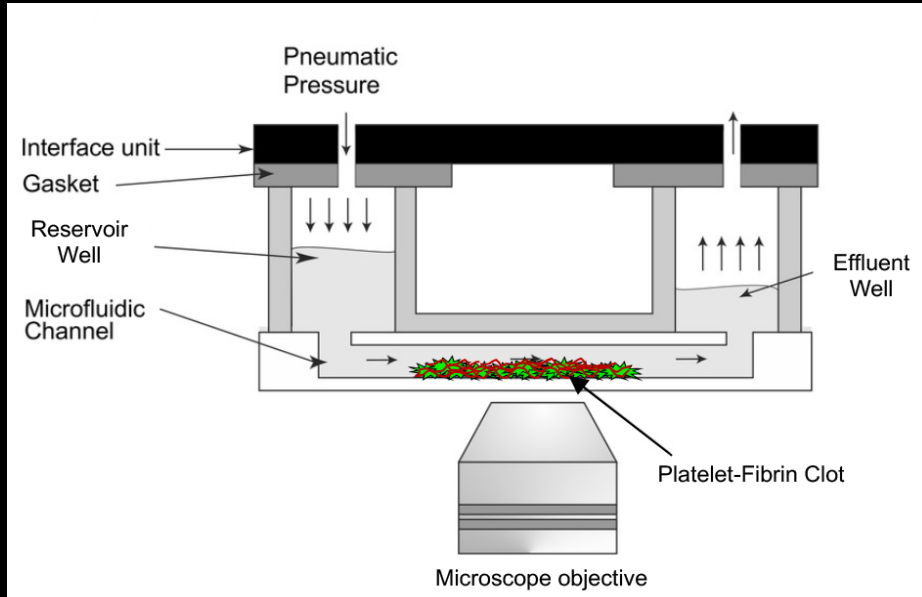


PROPPR Sub-study: Cardenas et al.
Blood Advances, 2018; 2: 1696-1704

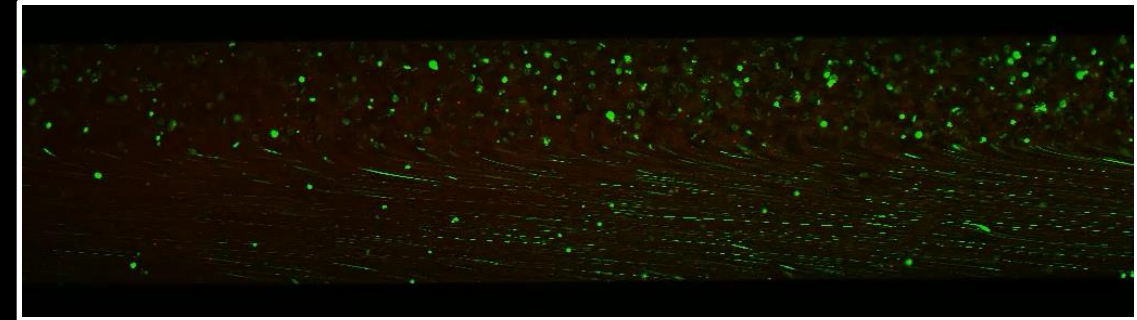
How do Platelets stop Bleeding (Hemostasis) ?



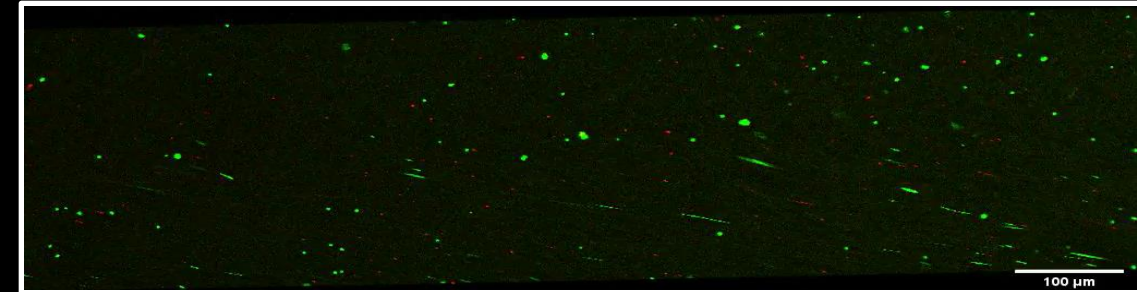
Microfluidic Demonstration of Platelet Effects in Clotting



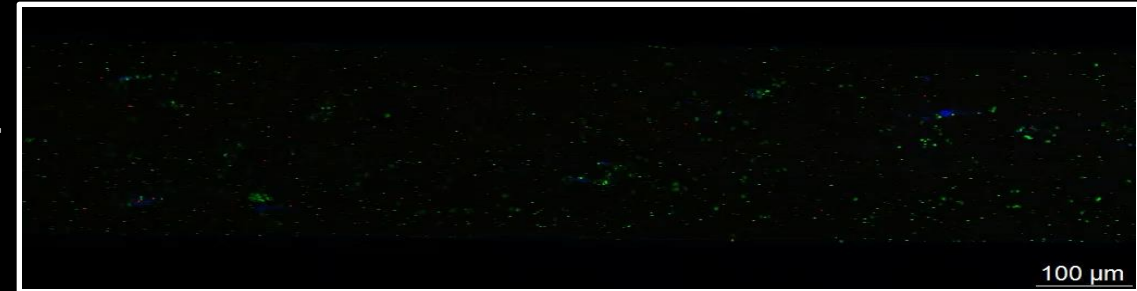
**Whole Blood (WB)
with Healthy Platelet
Count & Function**



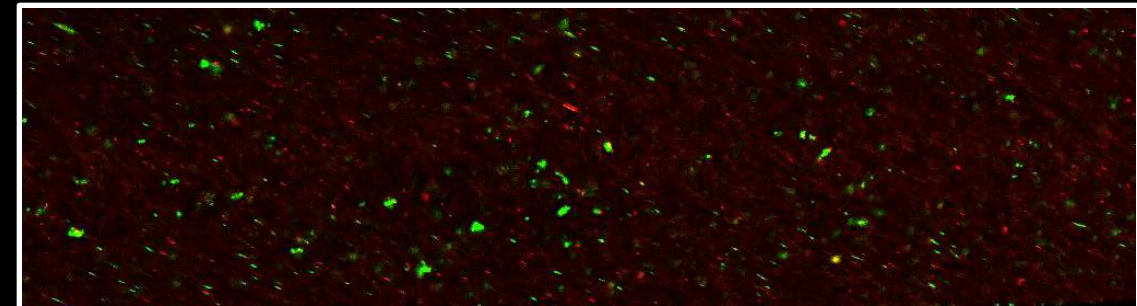
**WB with Reduced
Platelet Count**



**WB containing PS-
inhibited Platelets**



**WB with Inhibition of
Platelet Granule
Secretion**



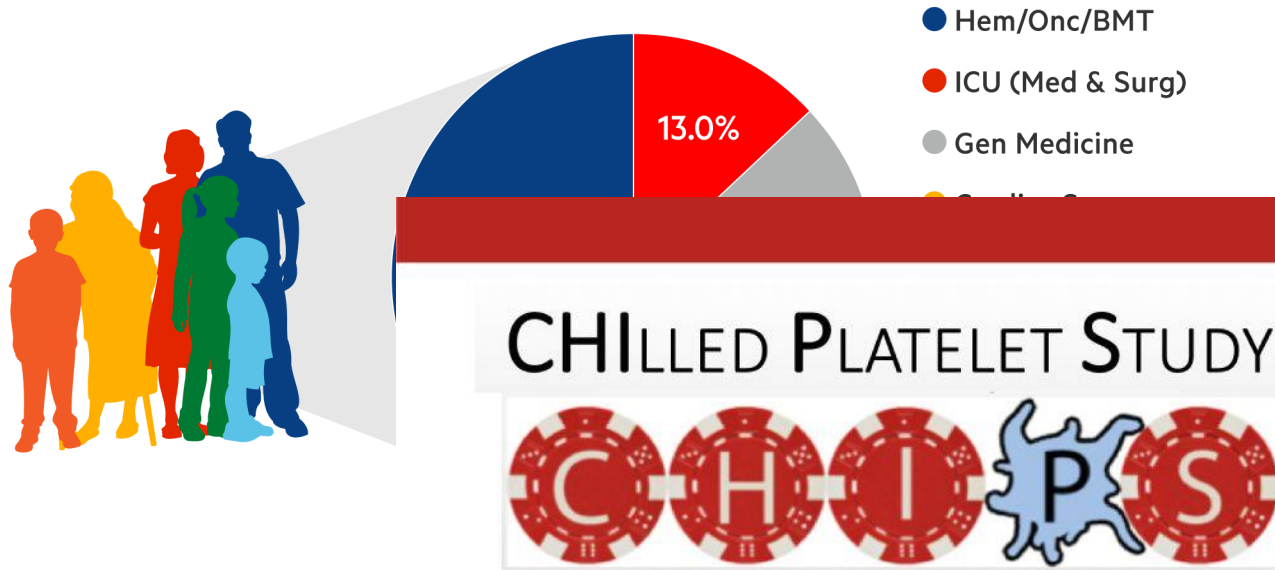
Shear: 5000 sec^{-1}

PLATELET FIBRIN



Platelets are Critical....but Never Sufficiently Available

Platelet Transfusion in the clinic : AABB 2014



Approximately [redacted] are Transfused Daily in the US

- Donor-derived platelets (pooled or apheresis)
- Leukoreduced and pathogen reduced
- Stored at RT (22-24°C) as per FDA guideline
- Shelf-life ~ 5 days
- **Concerns:** Availability, Storage Lesion, Refractoriness, Systemic side-effects

U.S. National Platelet Inventory and Transfusion Practice Survey

August 3, 2021

THE JOURNAL OF AABB

transfusion.org

TRANSFUSION

FUSIC

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W. l

ublish

481

- ~ 80% units in inventory
- ~ 50% report decreased availability



Inventory management, liability

y, Claudia S. Cohn, Richard J. Benjamin, z, Richard R. Gammon

16561 | Citations: 2

COVID-19

Blood Supply Impact



2,700

Blood Drives
Canceled

86,000

Fewer Blood
Donations

As of Monday, March 16



BLOOD SHORTAGE
#GiveNow

RedCrossBlood.org

Work ↔ Life “Convergence”



I/O Blood Loss per time range on right.
Calculated Blood Loss (mL) Hospital Encounter
Total

IV FLUIDS: 1.5L crystalloid

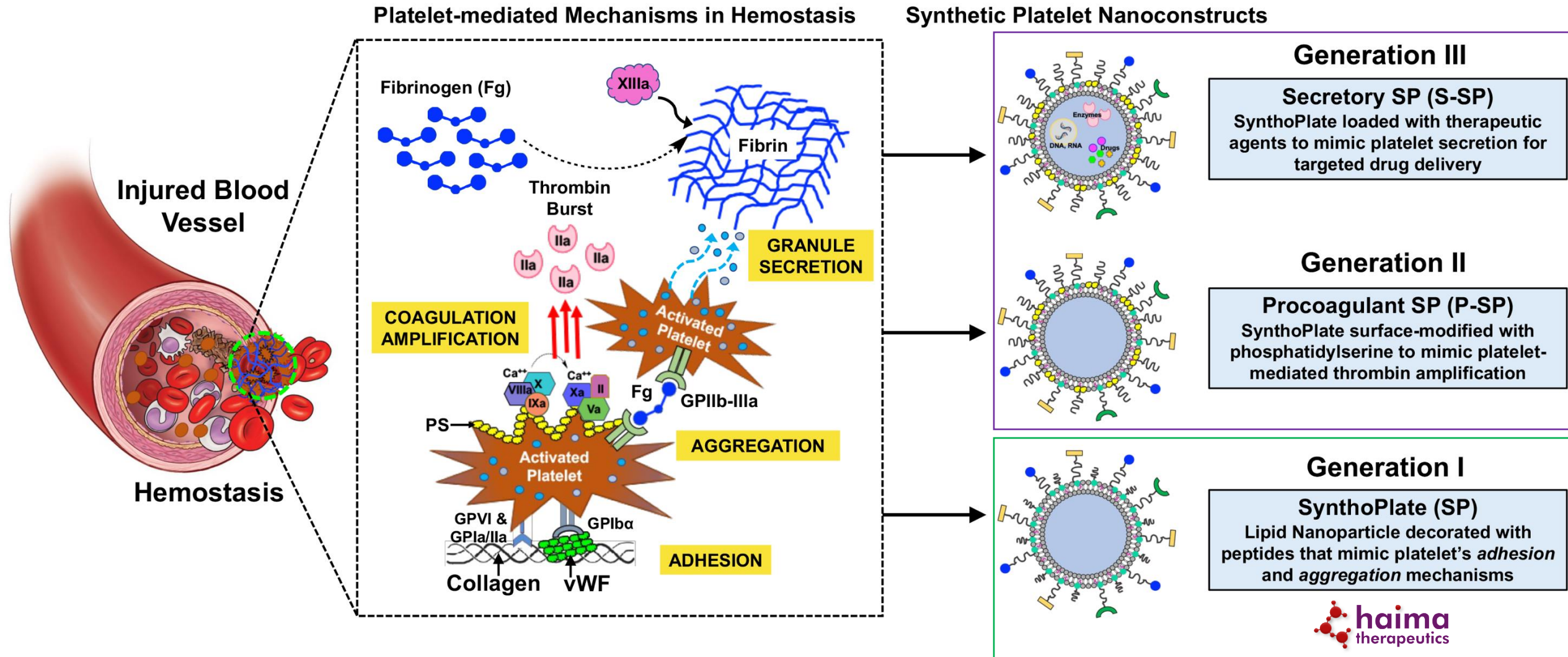
Products received: 2u pRBC, 2u FFP, 1u platelets.

Complications: postpartum hemorrhage QBL 3255

07/15/22 0158 - 07/15/22 0419
3255
3255 cc

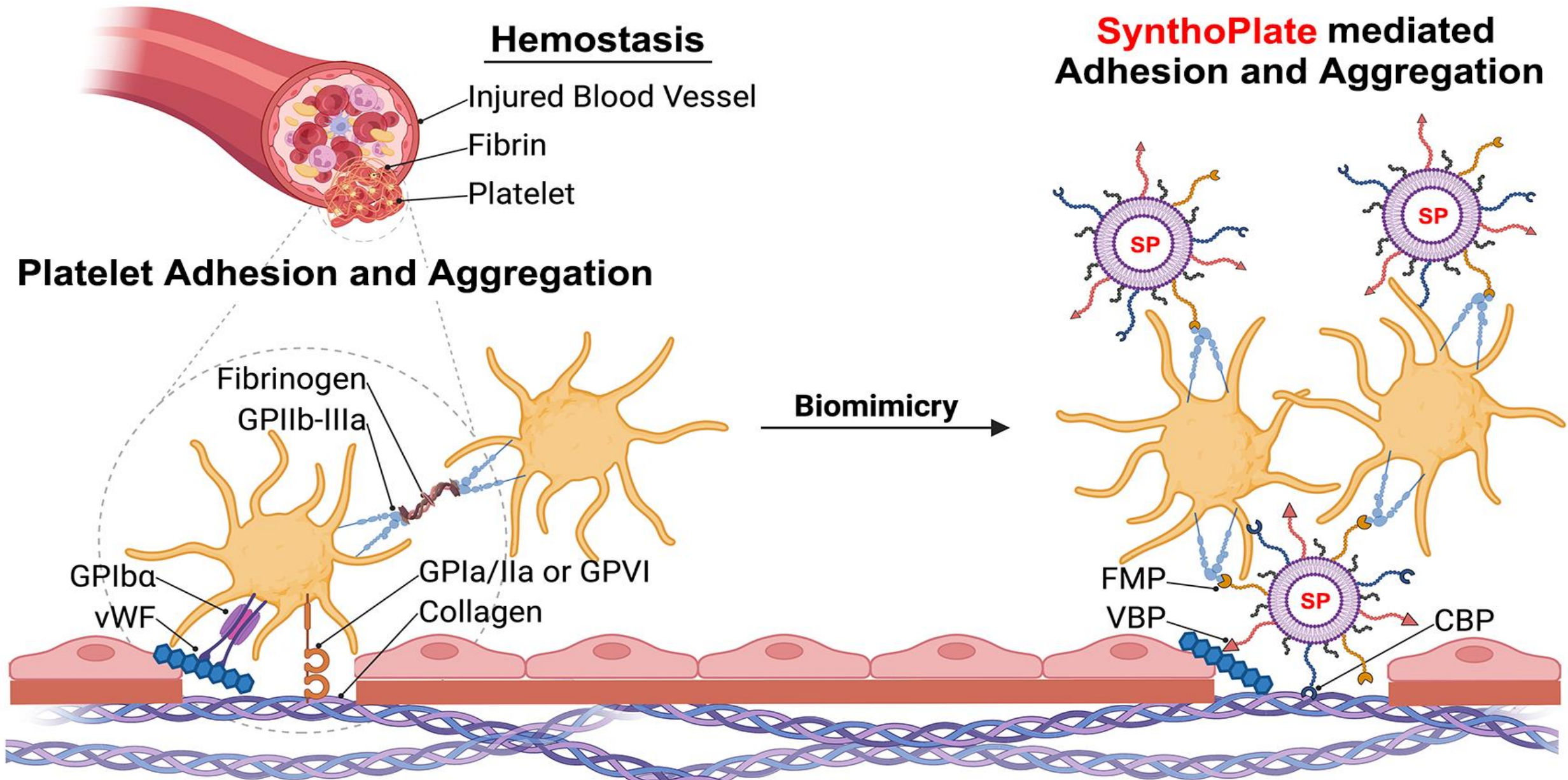


Bio-inspired Synthetic Platelet Design



Fully synthetic; Donor-independent; Scalable; Lyophilizable; Immunosilent; Species-agnostic; Cost-effective

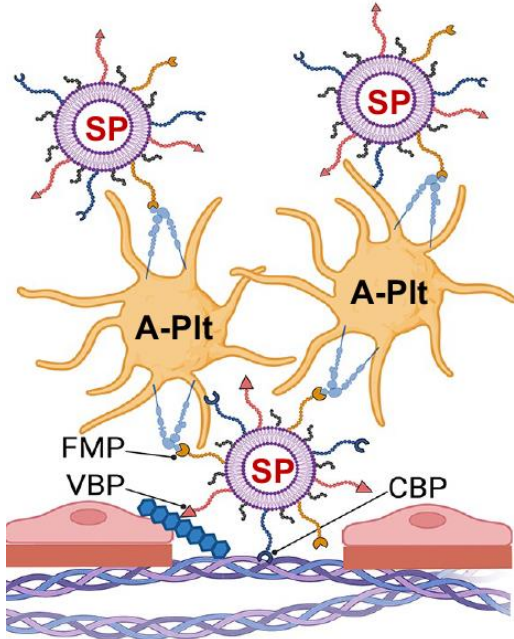
Generation I Synthetic Platelet: SynthoPlate (SP)



CBP: Collagen Binding Peptide; **VBP:** Von Willebrand Factor Binding Peptide; **FMP:** Fibrinogen Mimetic Peptide

SP mimics Platelet Adhesion and Aggregation Properties

SP Mechanism of Action

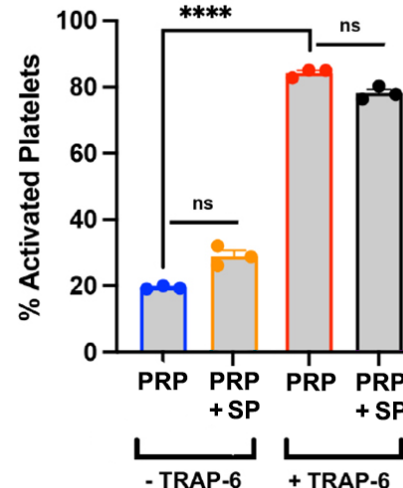


- SP binds to 'VWF + collagen' at kinetics comparable to natural platelets.
- SP does not itself activate resting platelets, nor does it inhibit the activation of platelets.
- SP has enhanced binding to *activated* platelets, improving aggregation.

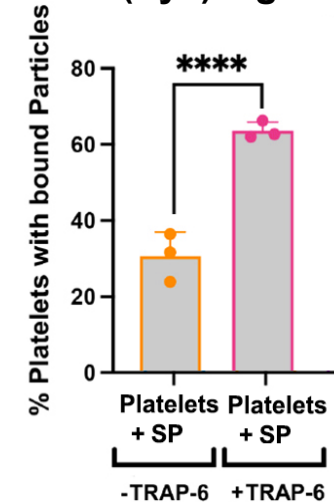
Adhesion to 'VWF + collagen' (Microfluidics)

SP Interaction with platelets (Flow Cytometry)

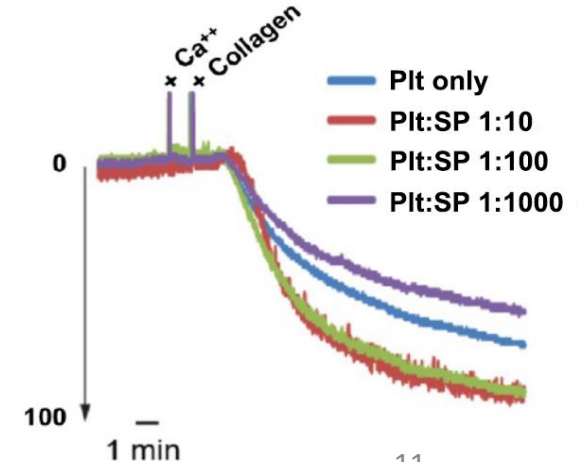
P-selectin (CD 62P) signal



SP (Cy5) signal

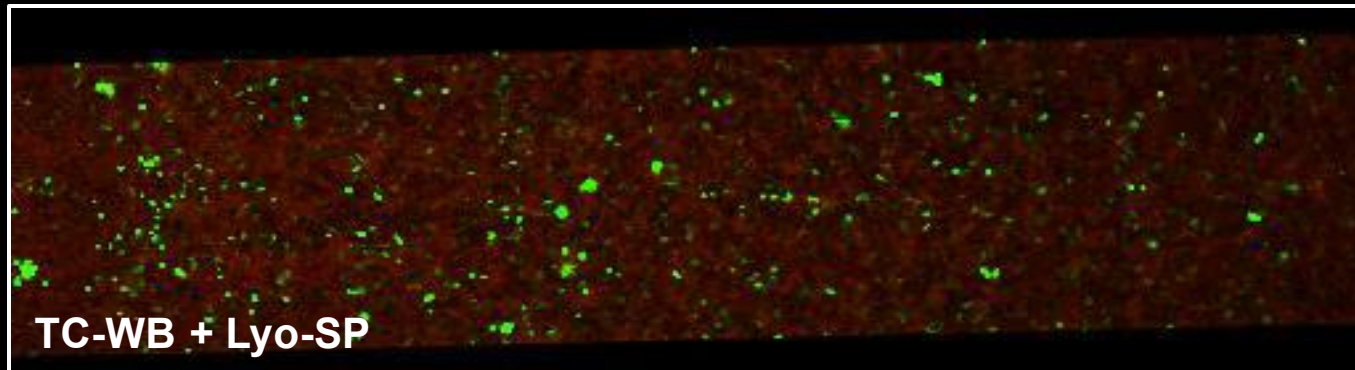
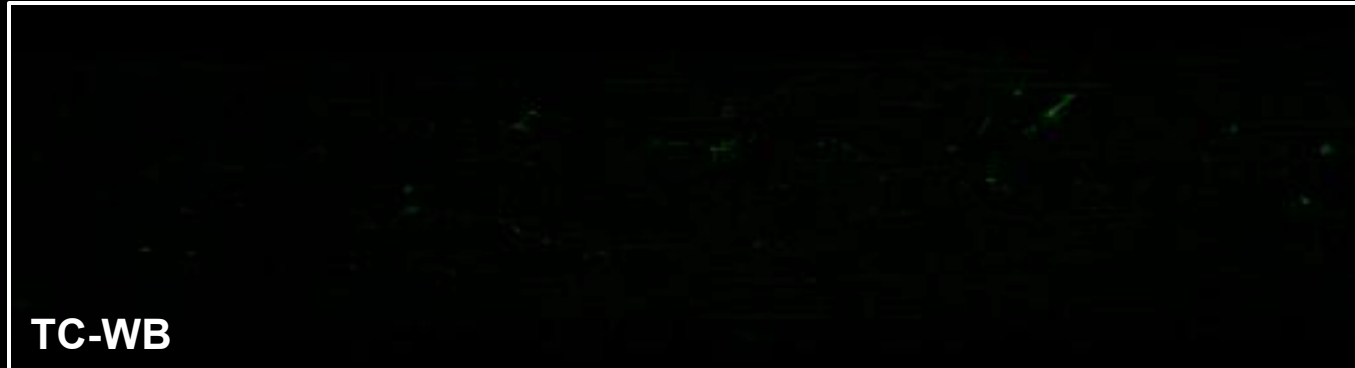
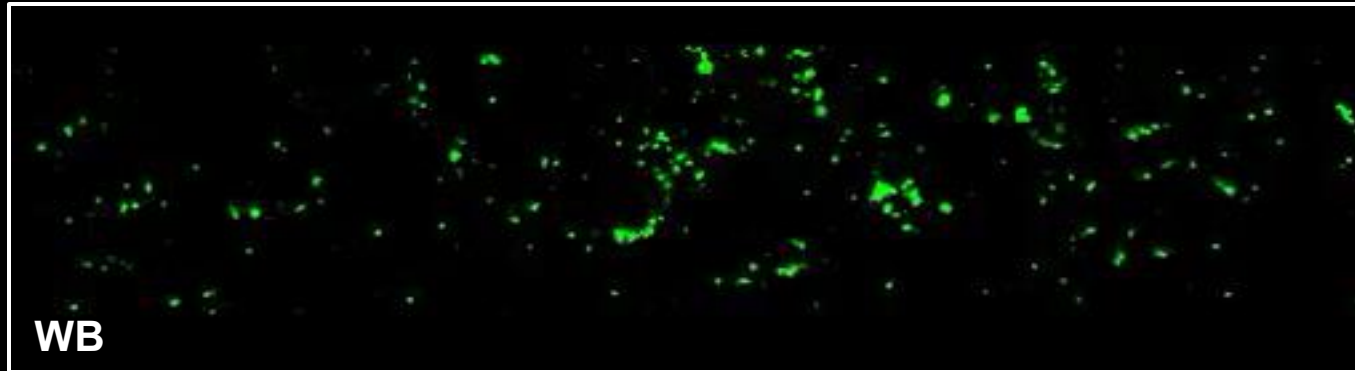


SP Interaction with platelets (Aggregometry)

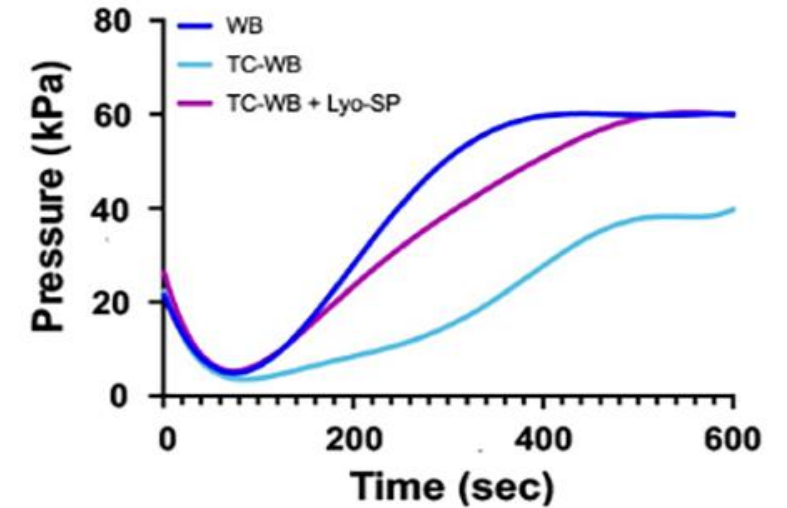


SP Rescues 'Platelet Hemostatic Response' in Whole Blood

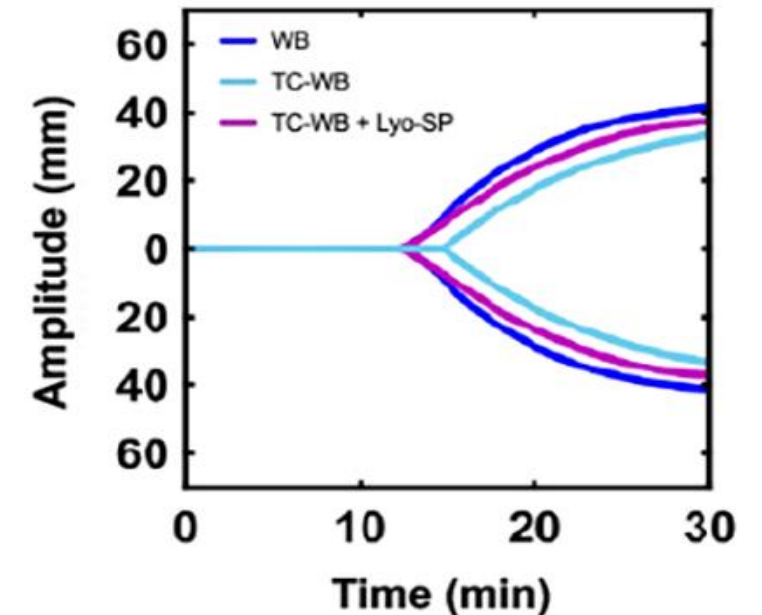
Microfluidics (5000 sec^{-1} shear rate)



T-TAS PL-Chip

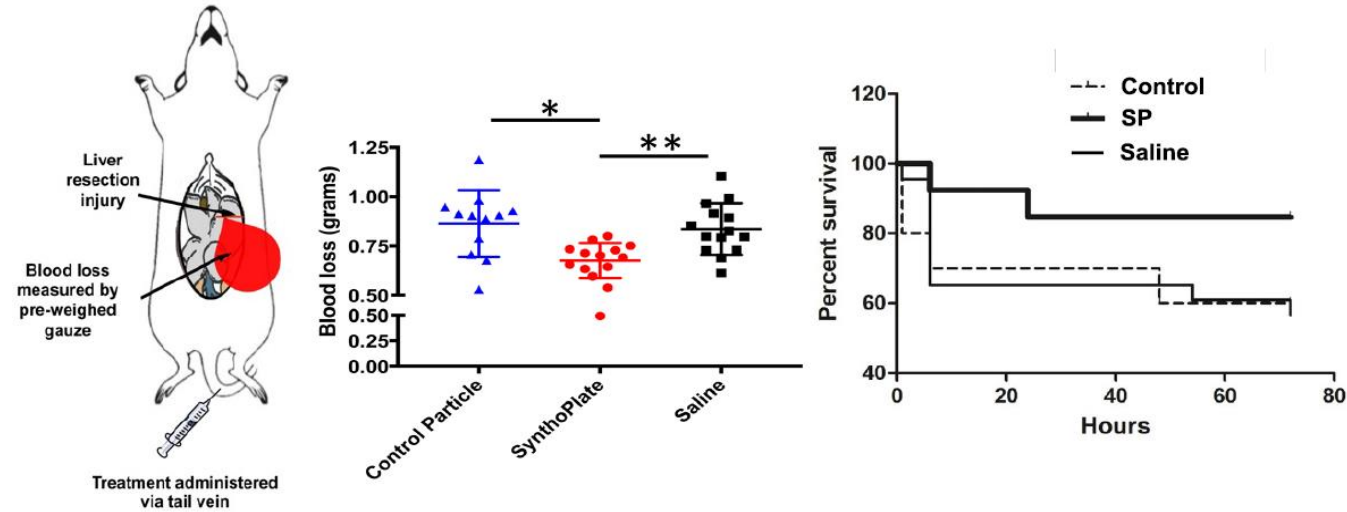


ROTEM

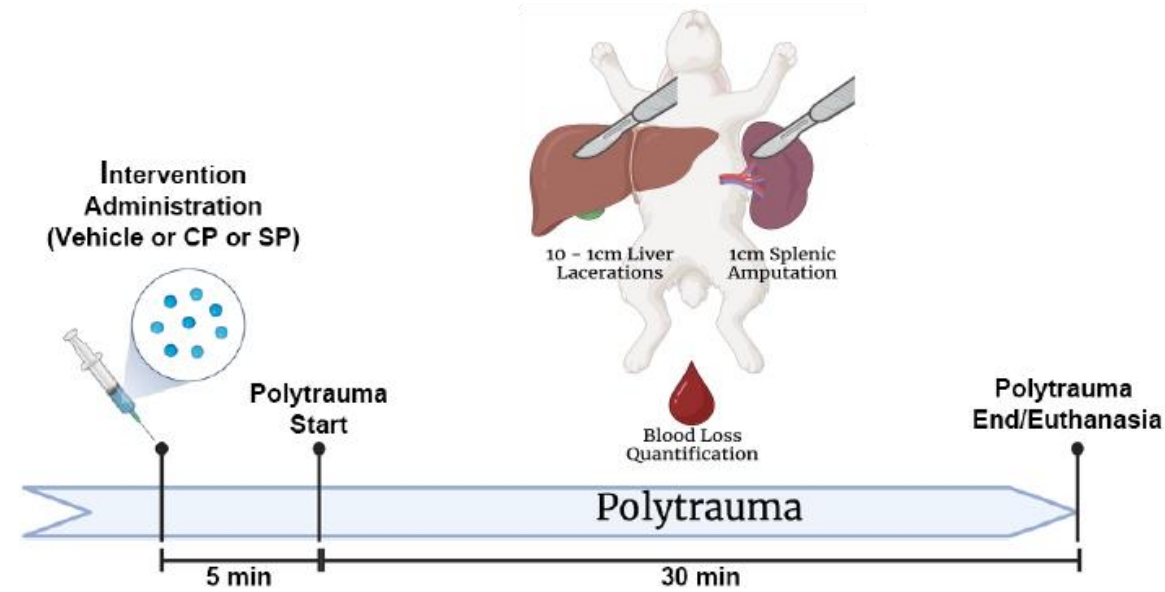


I.V. SP is Highly Effective in Treating Traumatic Hemorrhage

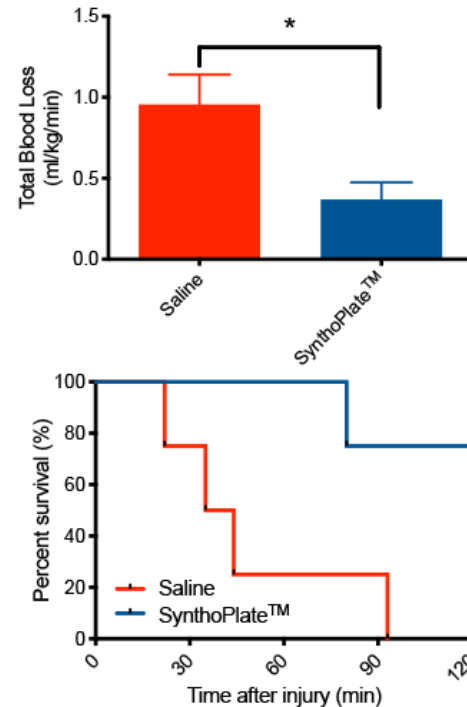
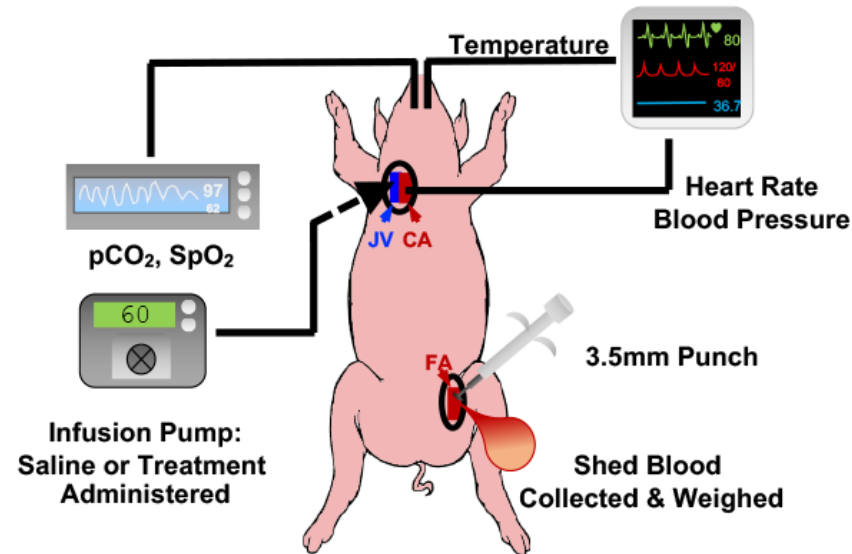
Rat Liver Laceration



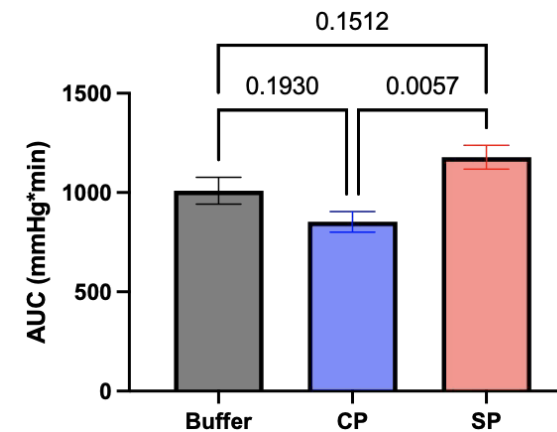
Rabbit Polytrauma Model (Liver + Spleen injury)



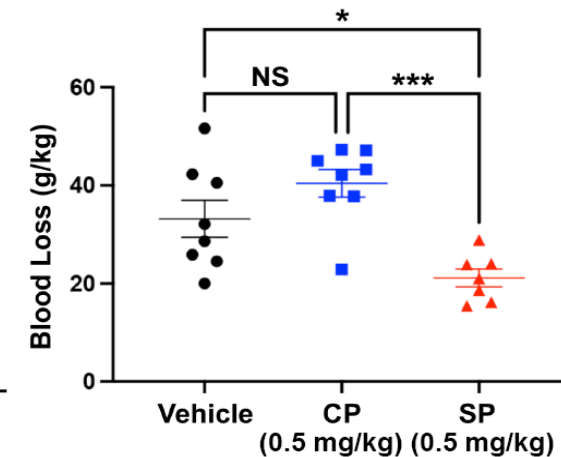
Pig Femoral Artery Transection



Mean Arterial Pressure (MAP)

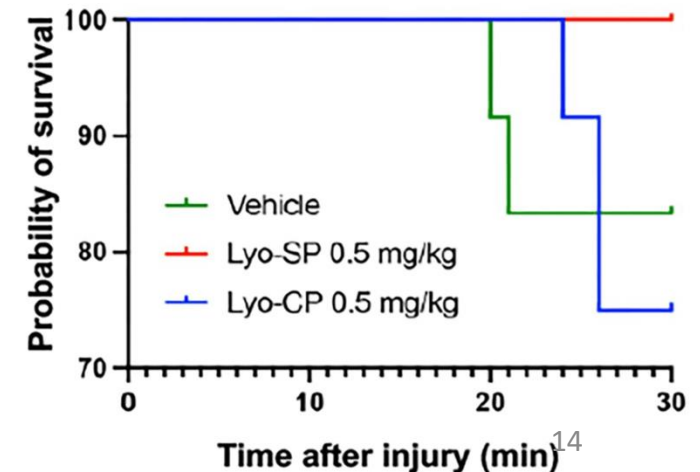
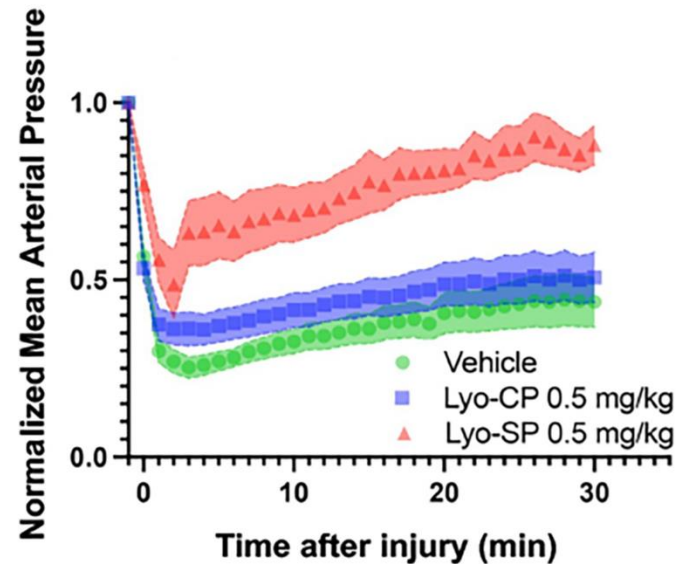
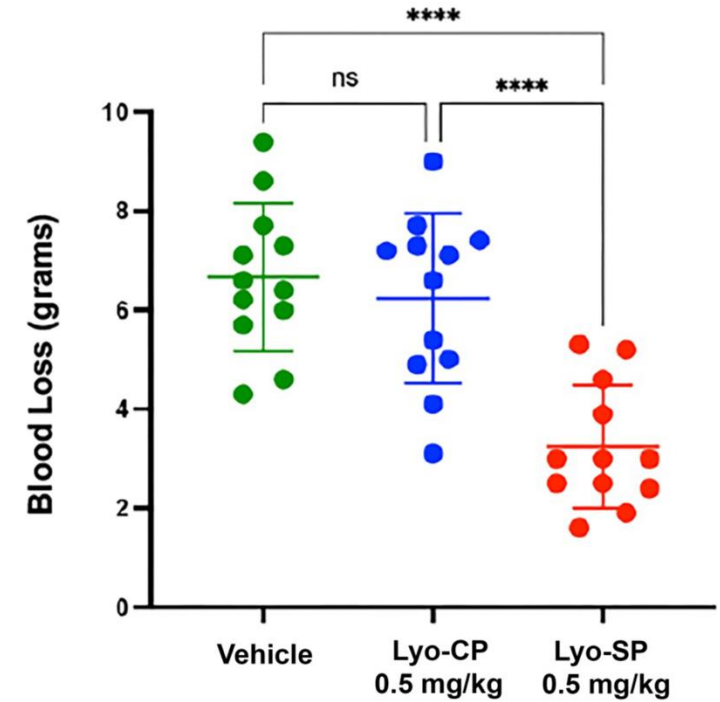
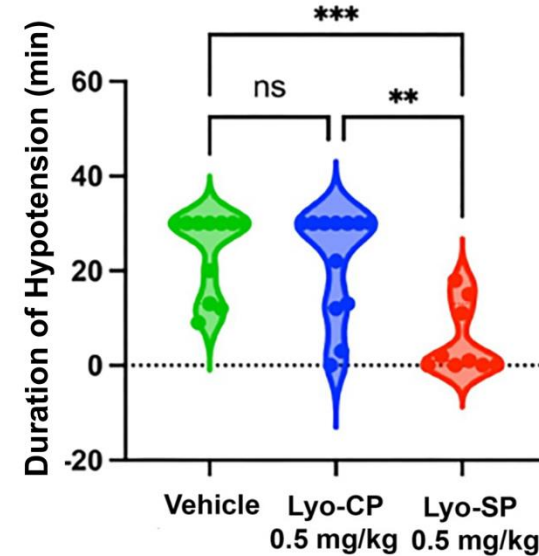
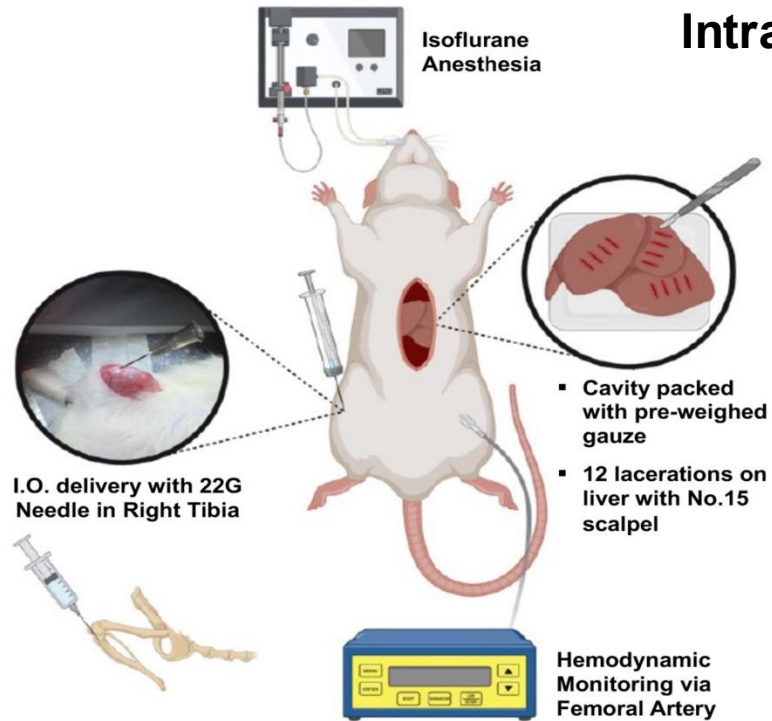


Blood Loss



SP can be Delivered I.O. (Evaluation in Rat Model)

Intraosseous Delivery in Rat Trauma Model

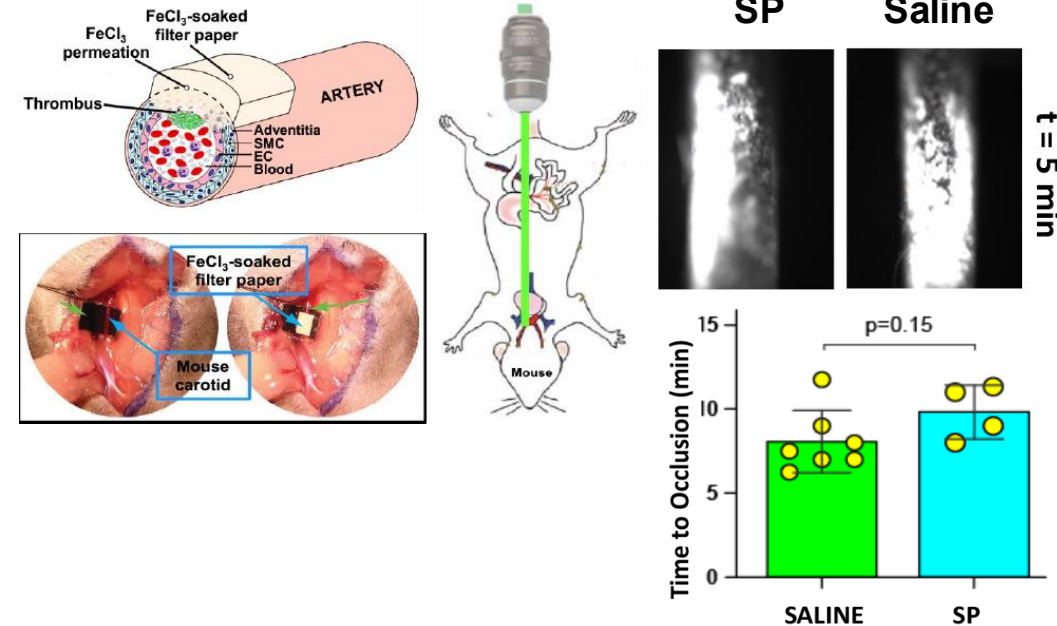


Unpublished

SP Hemostatic Efficacy and Safety in Preclinical Models

Species	Model	SP reduced blood loss by
Mice	Tail Transection in Thrombocytopenia (IV Dose)	73%
Mice	Tail Transection in Type 2B Von Willebrand Disease (IV Dose)	33%
Mice	Tail Transection in vWF Knock-out (IV Dose)	67%
Rats	Liver Laceration (IV Dose)	23%
Rats	Liver Laceration (IO Dose)	43%
Rabbits	Hemodilution + Kidney Incision (IV Dose)	53%
Rabbits	Polytrauma (IV Dose)	48%
Rabbits	Ear Incision in Thrombocytopenia (IV Dose)	34%

Mouse model of FeCl₃-induced thrombosis



Non-GLP Single DRF Tolerability Studies

Species	MTD
Sprague Dawley Rats	Up to 60 mg/kg <i>and</i> 10 mg/min
NZ White Rabbits	Up to 25 mg/kg <i>or</i> 25 mg/min (>250X higher than PAD)
Beagle Dogs	Up to 4 mg/kg <i>and</i> 30 mg/min

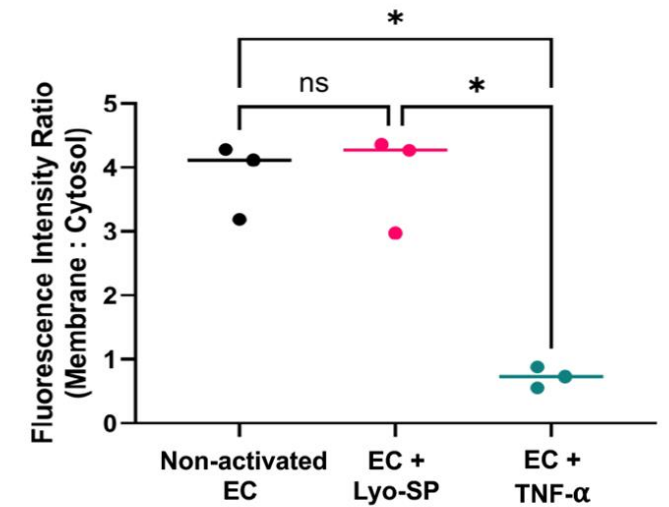
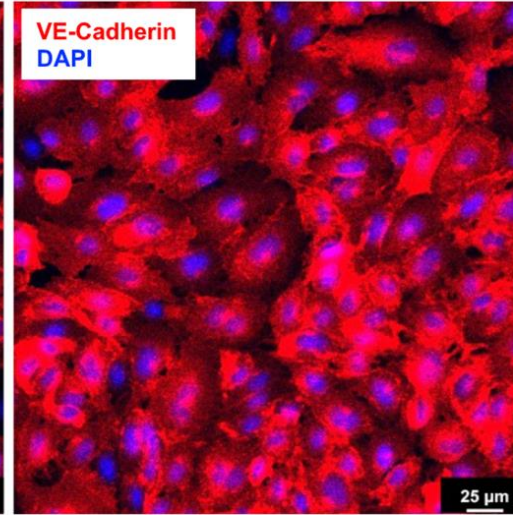
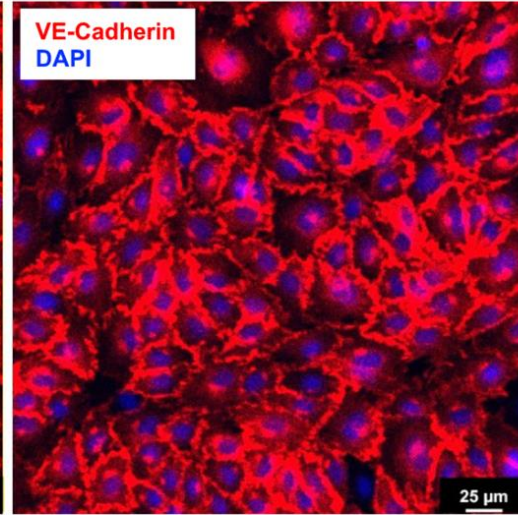
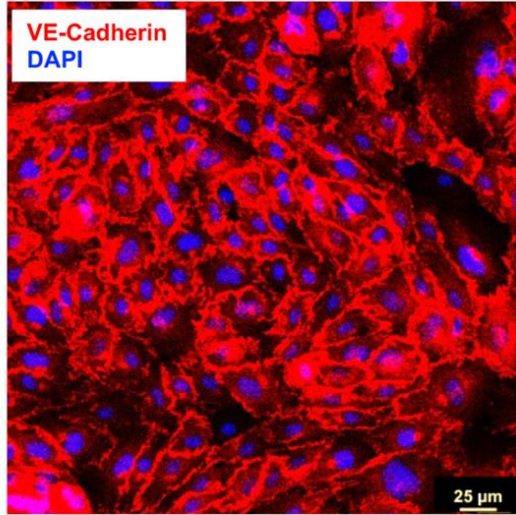
SP does not activate Endothelial Cells

A. Analysis of VE-Cadherin on endothelial cells

Non-activated EC

EC + Lyo-SP

EC + TNF- α

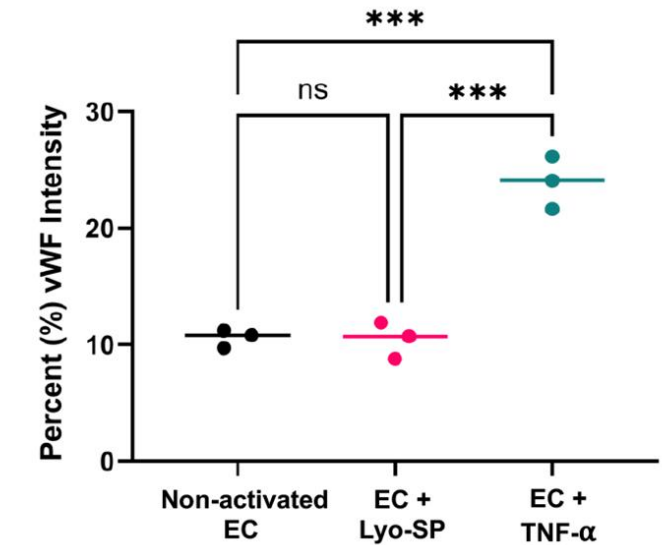
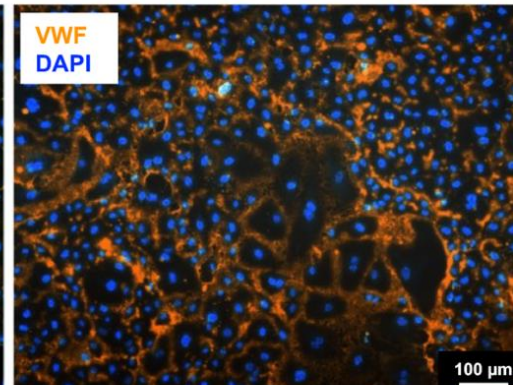
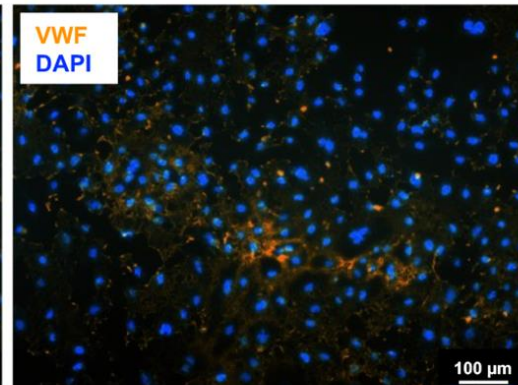
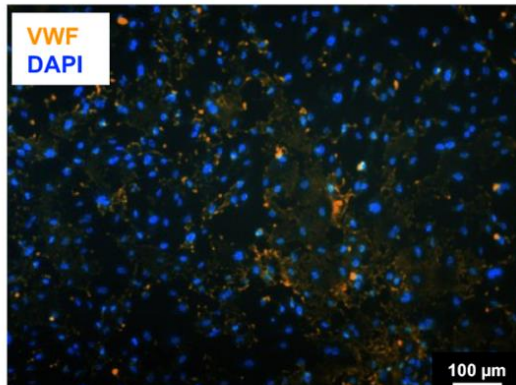


B. Analysis of VWF secretion from endothelial cells

Non-activated EC

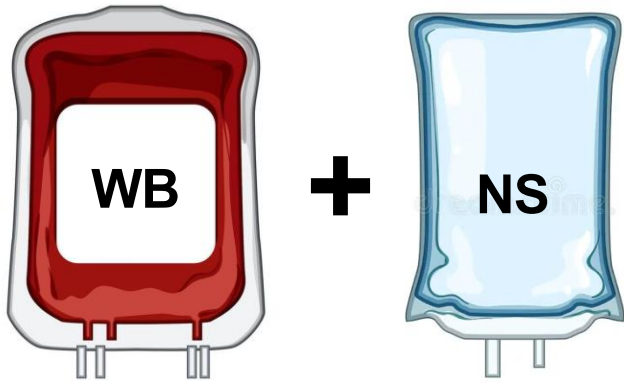
EC + Lyo-SP

EC + TNF- α



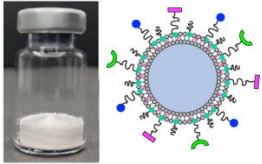
SP as a Hemostatic Force Multiplier in Plasma

Model: Hemodilution (HD 1:1)



Treatments

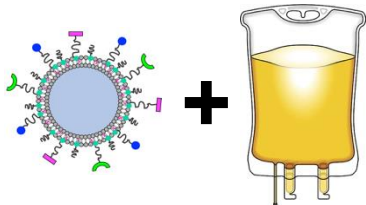
SP



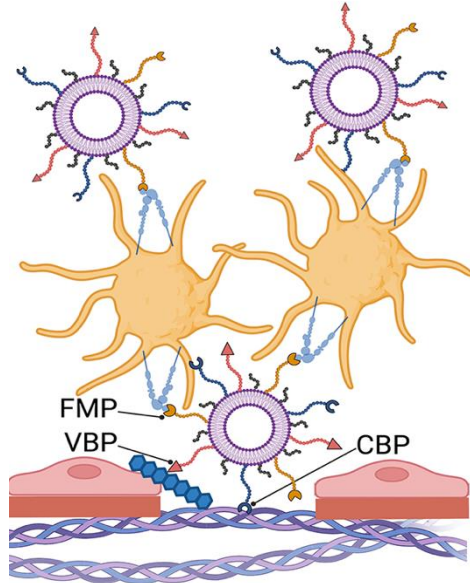
Plasma



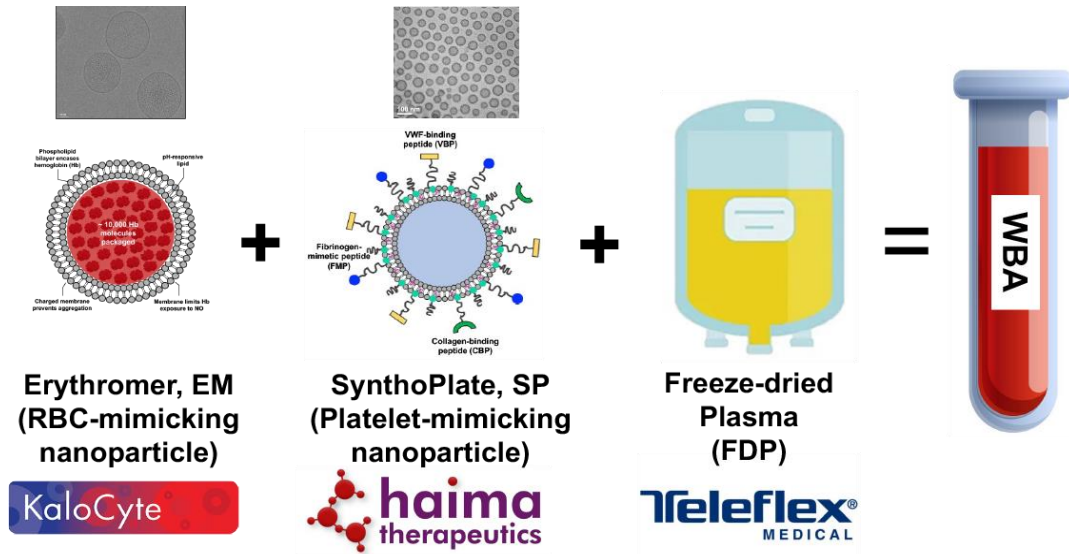
SP +
Plasma



SP as Hemostatic Component in Whole Blood Analog (WBA)

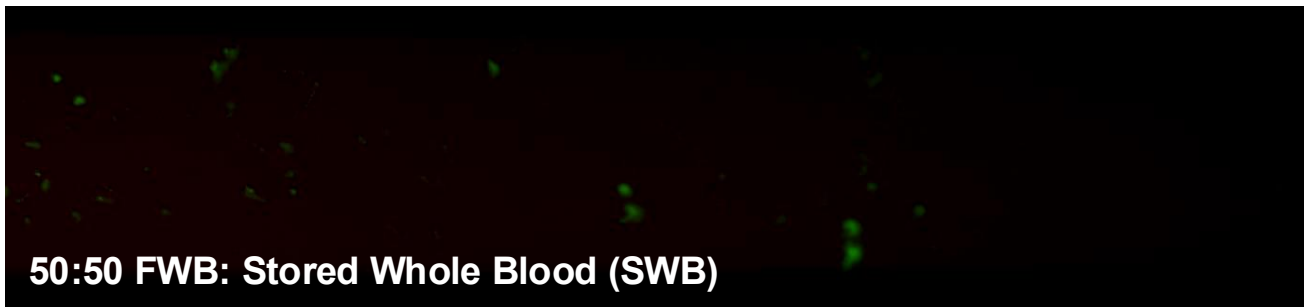
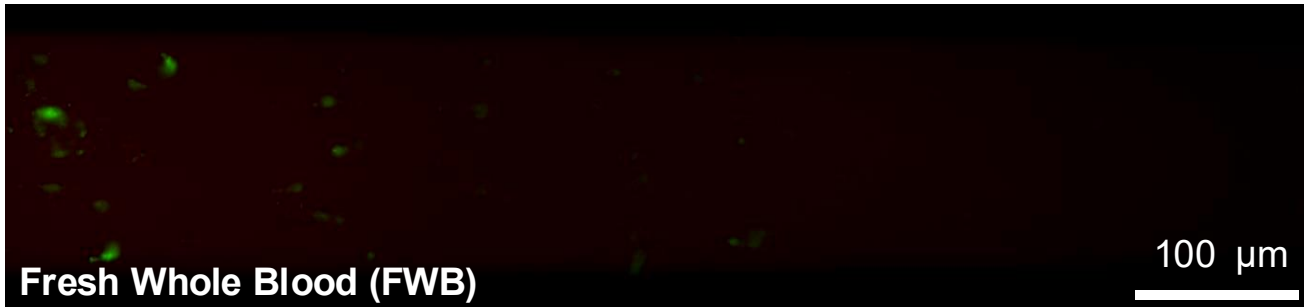


WBA formulation

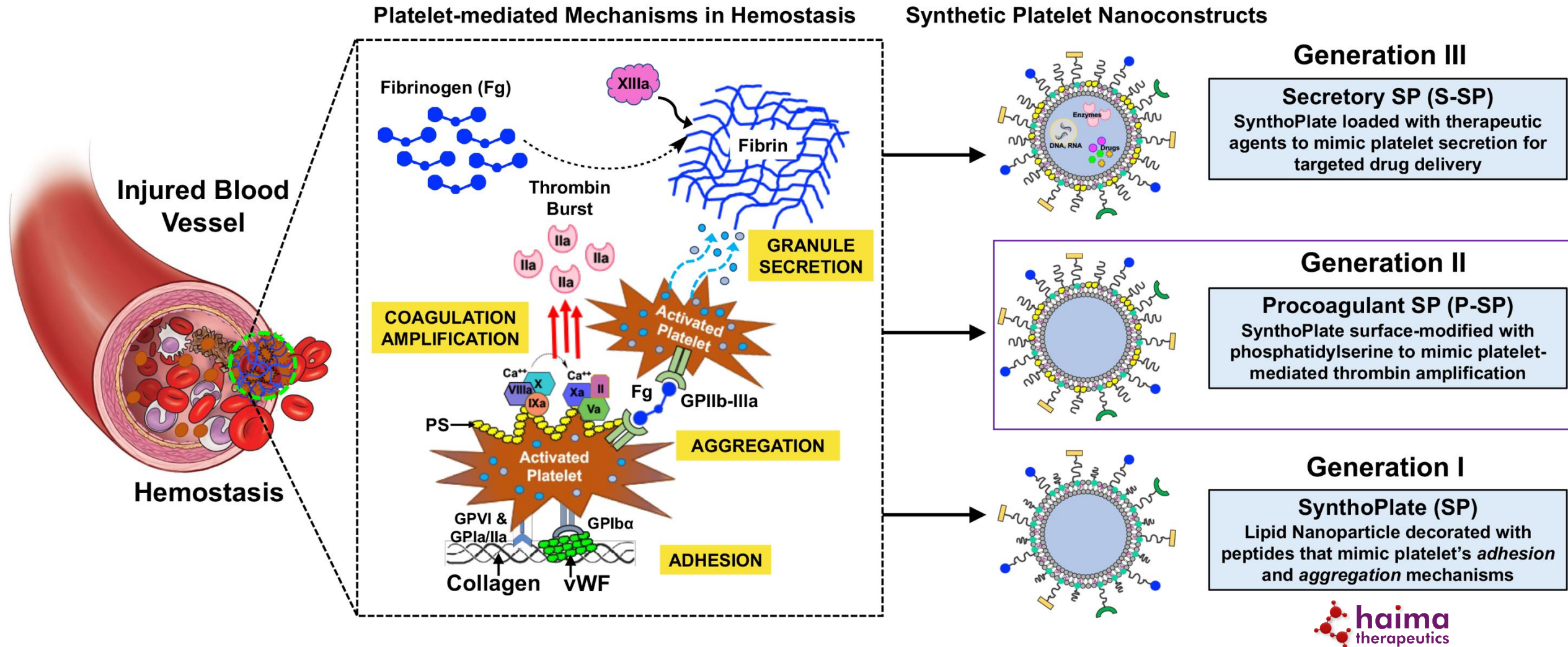


Microfluidics in Human Whole Blood

Platelets Fibrin Overlap



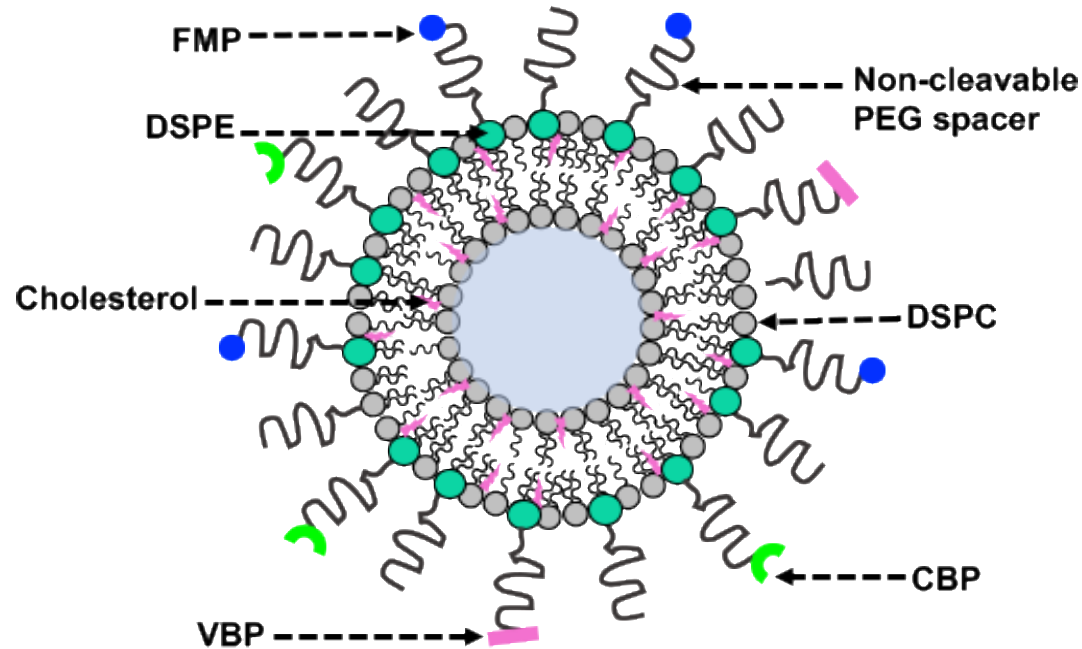
Bio-inspired Synthetic Platelet Design



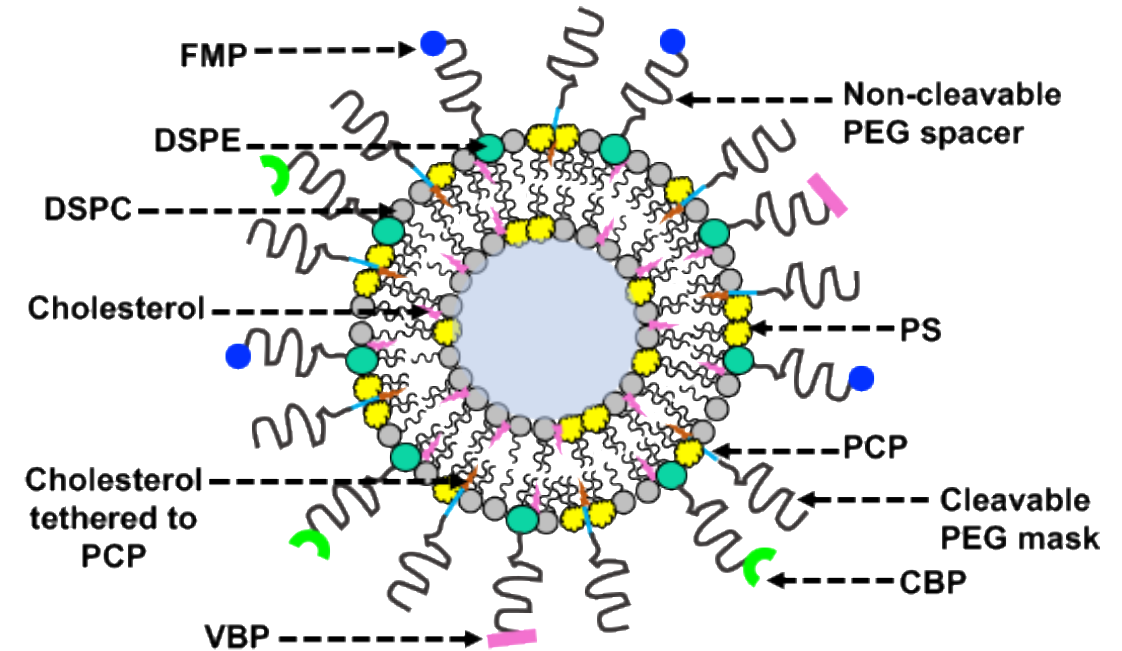
Fully synthetic; Donor-independent; Scalable; Lyophilizable; Immunosilent; Species-agnostic; Cost-effective

Generation II Synthetic Platelet: Procoagulant SP (P-SP)

SynthoPlate (SP)



Procoagulant SynthoPlate (P-SP)

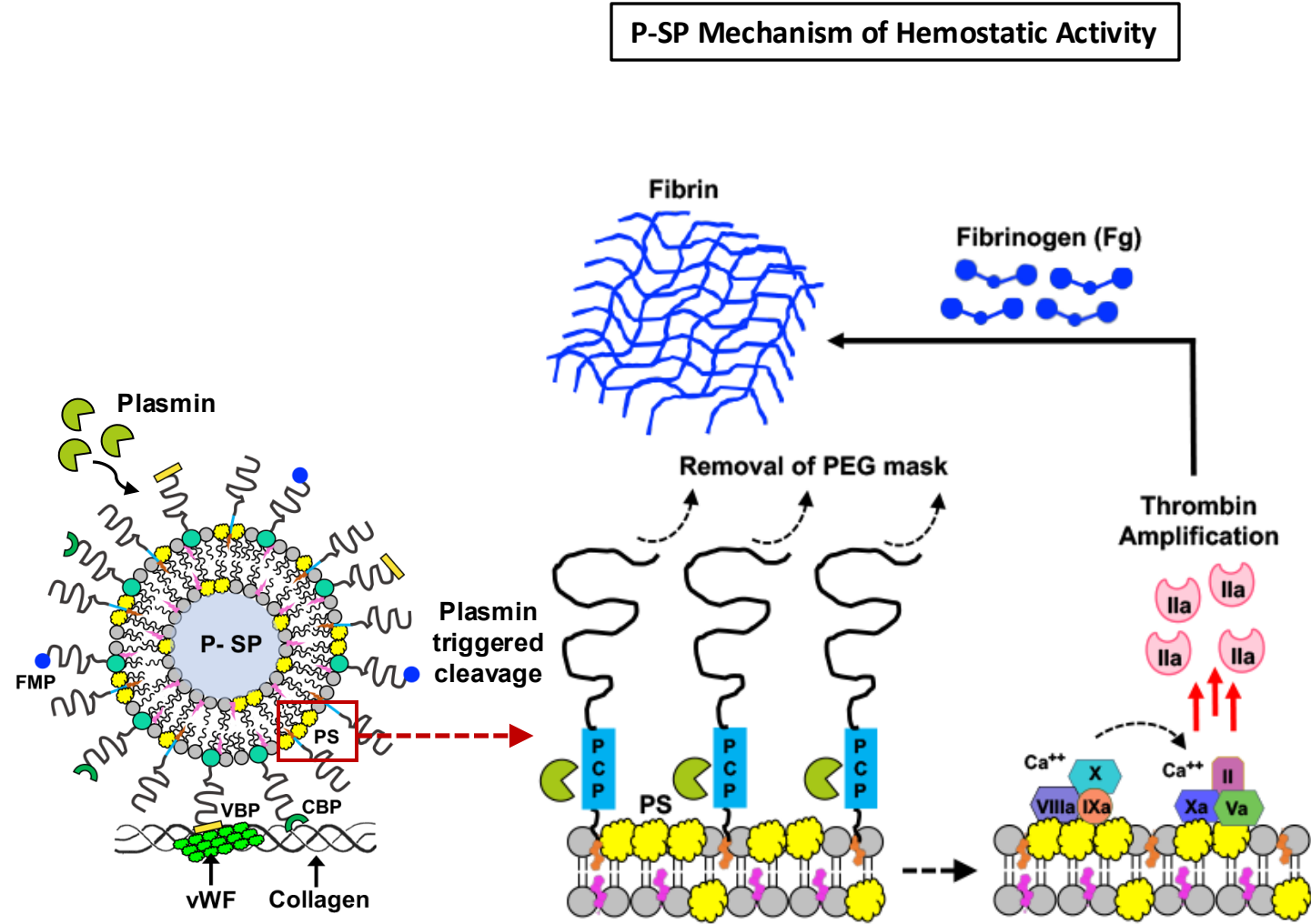
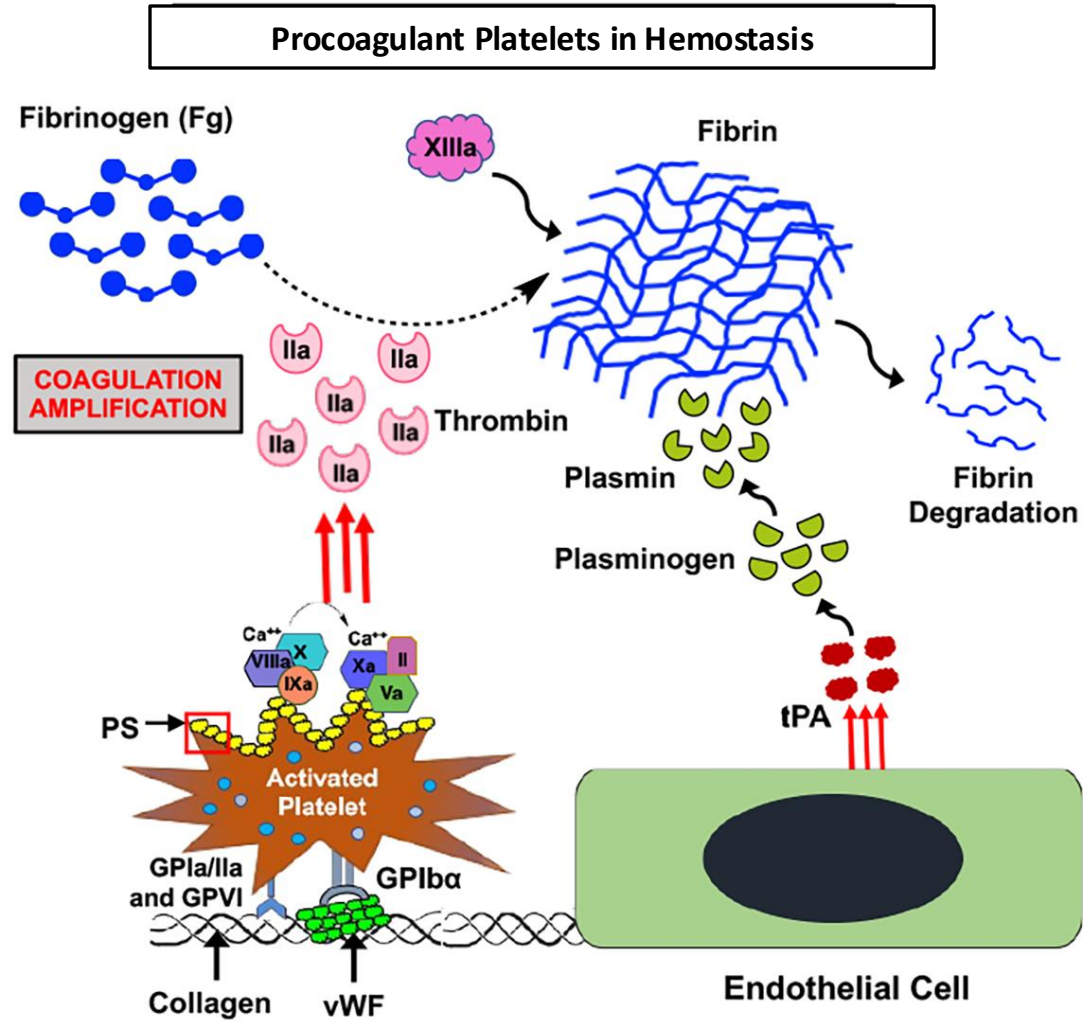


Modery-Pawlowski et al. Biomaterials. 2013
Anselmo et al. ACS Nano 2014
Shukla, Hickman et al. JTH. 2016
Dyer et al. J Acute Trauma. 2018
Hickman et al. Sci Rep. 2018
Srinivasan et al. JTACS 2024



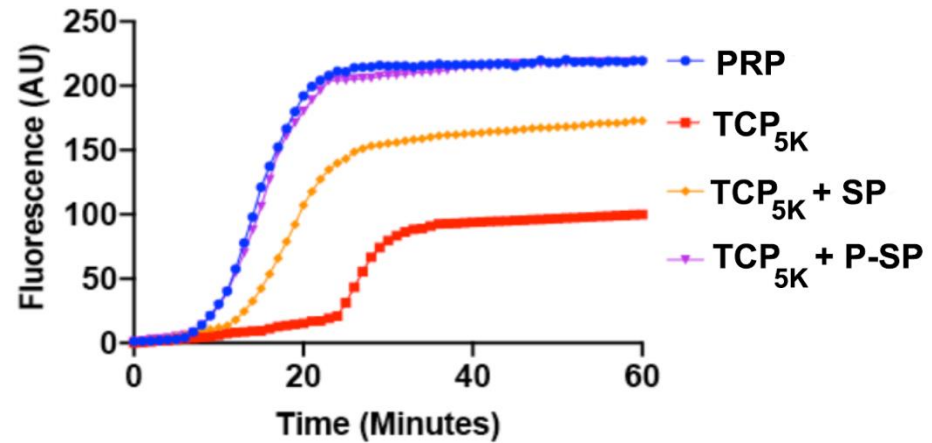
Sekhon et al. 2022, PMC9179936

P-SP Exposes PS triggered by Plasmin to Amplify Thrombin

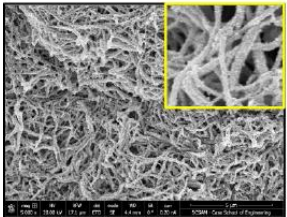


P-SP Can Rescue Coagulation in Platelet Dysfunction Setting

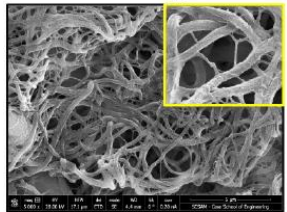
Thrombin Generation Assay



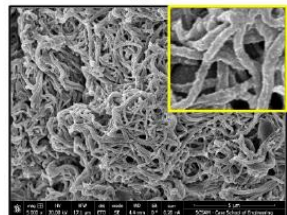
PRP



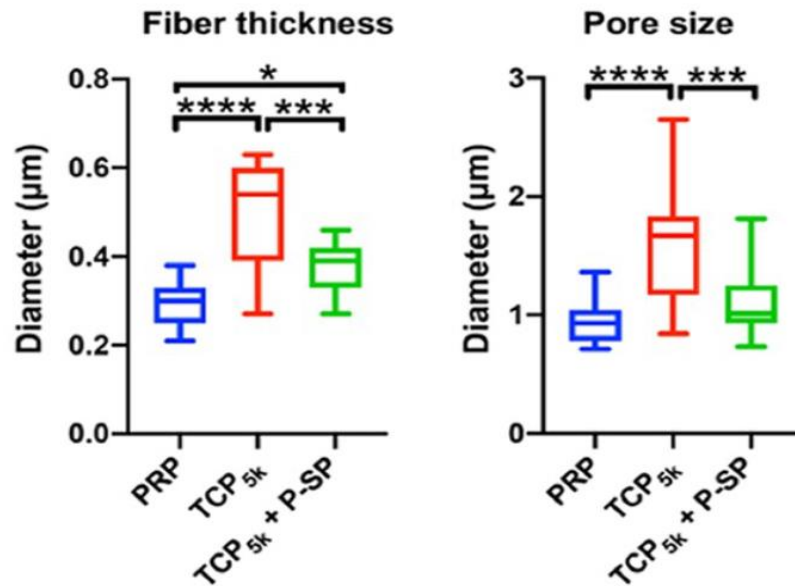
TCP_{5K}



TCP_{5K} + P-SP



Rescue of Fibrin Morphology



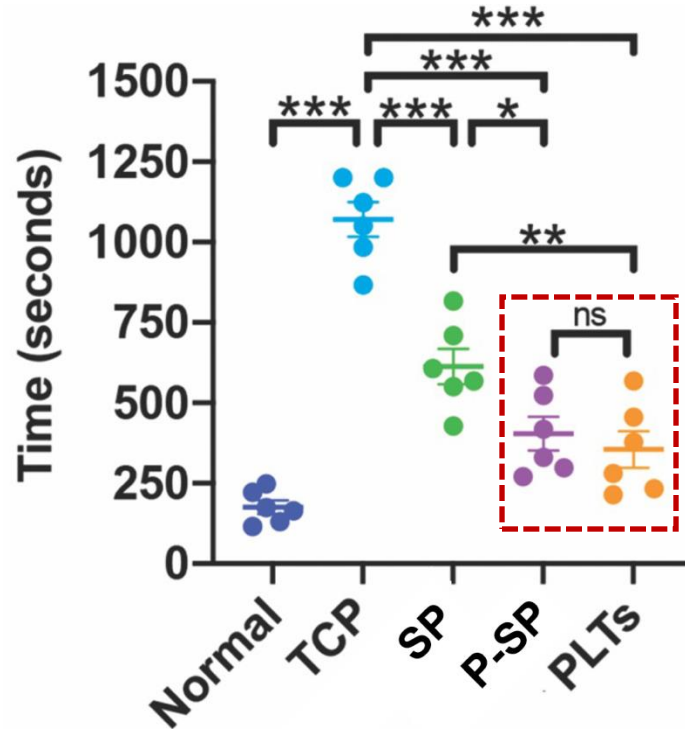
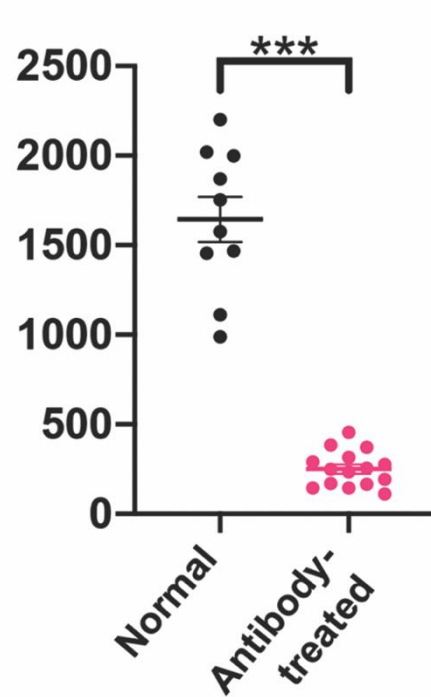
P-SP Reduces Bleeding in Mouse TCP and Rat Trauma Model

Tail-bleed in Thrombocytopenic (TCP) Mouse

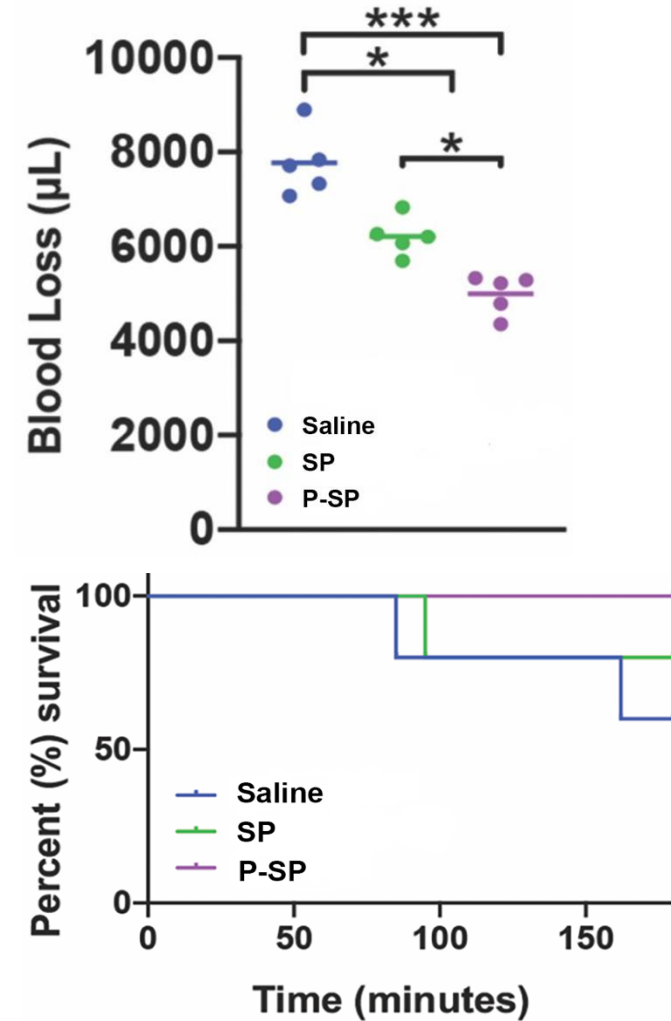
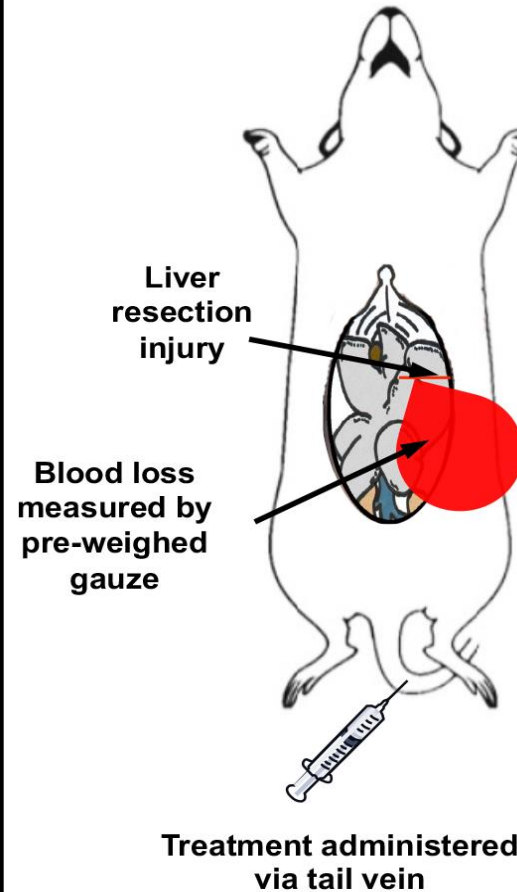


Platelet Count

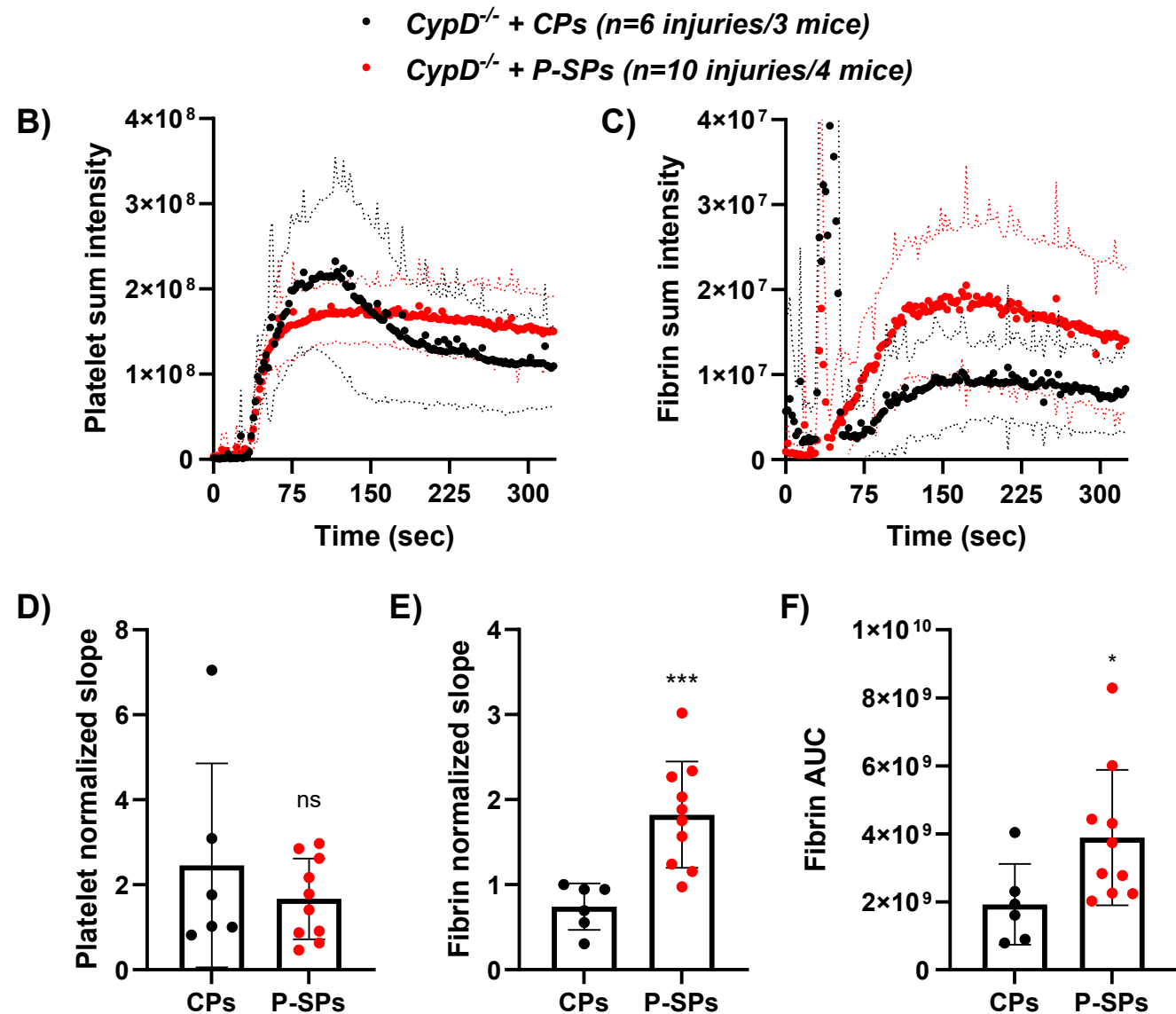
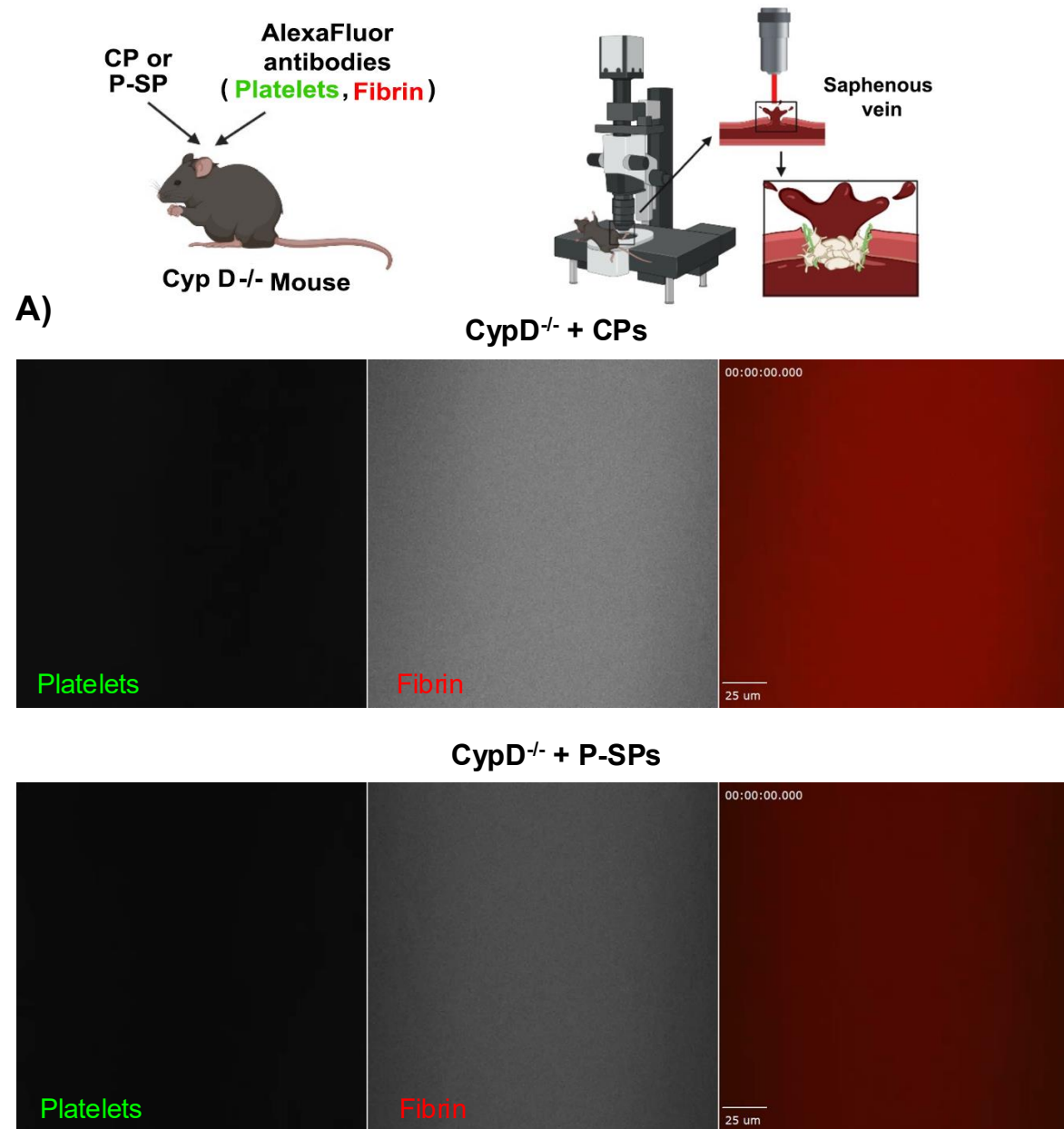
Bleeding Time



Traumatic Liver Laceration in Rats

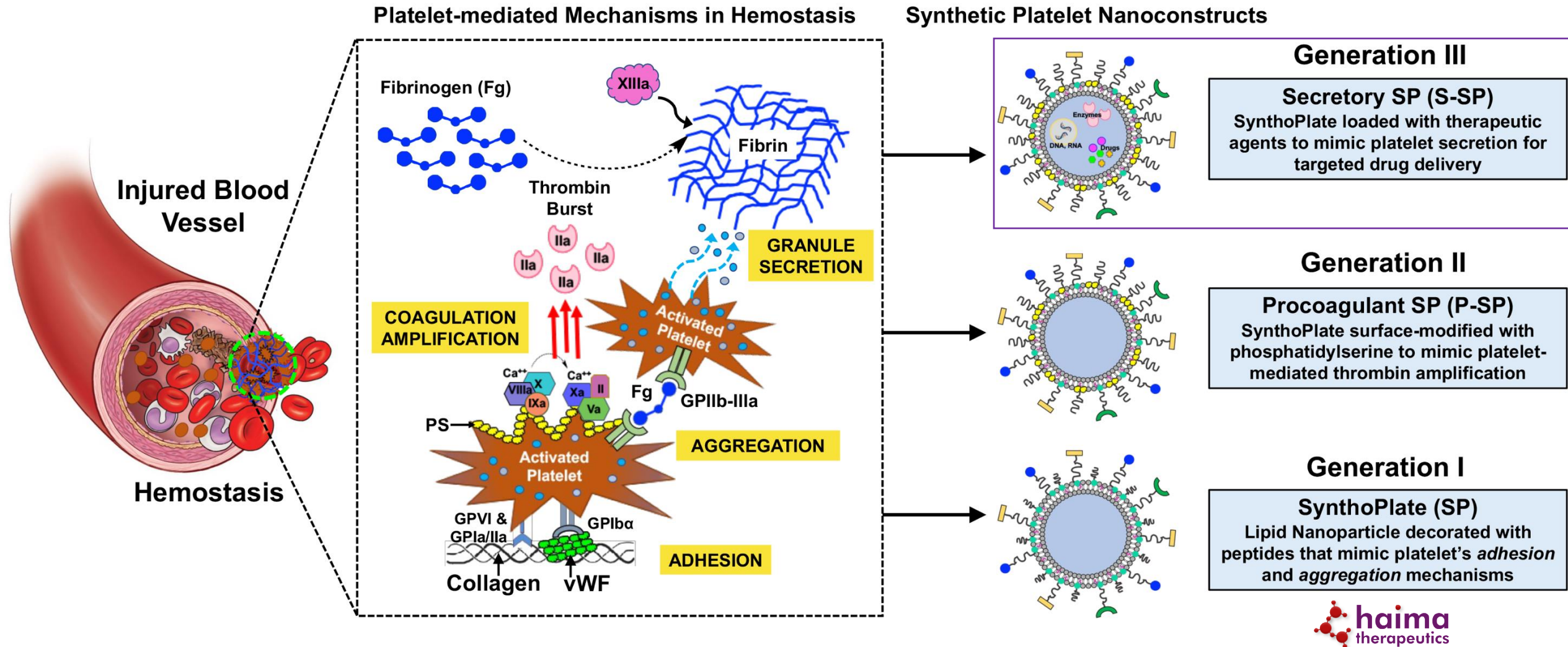


P-SP Rescues 'Fibrin Kinetics' in CypD $-/-$ Mice



■ P-SP rescues hemostatic fibrin in CypD $-/-$ mice

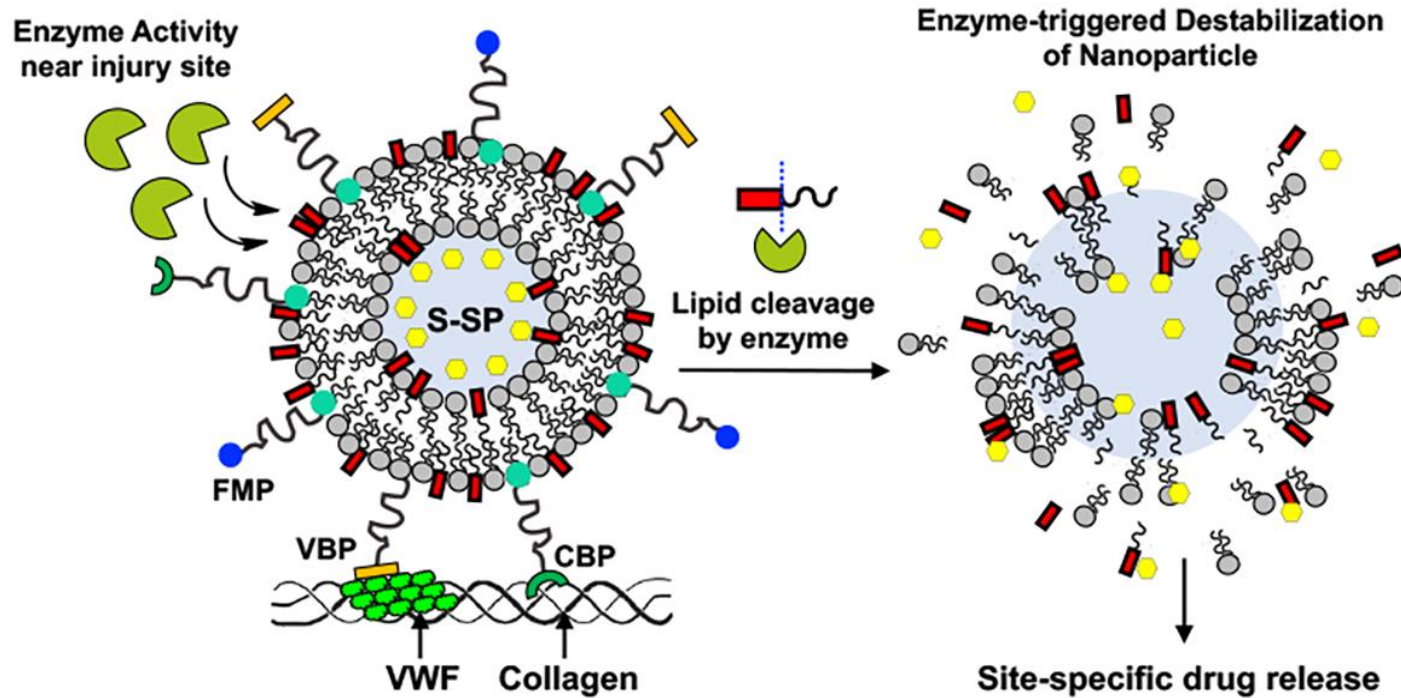
Bio-inspired Synthetic Platelet Design



Fully synthetic; Donor-independent; Scalable; Lyophilizable; Immunosilent; Species-agnostic; Cost-effective

Generation III: Secretory Synthetic Platelet (S-SP)

S-SP Mechanism of Hemostatic Activity

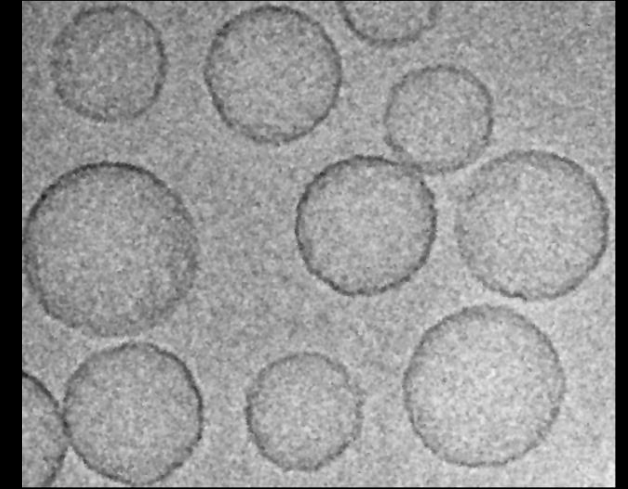


Cargo (⬡) candidates:

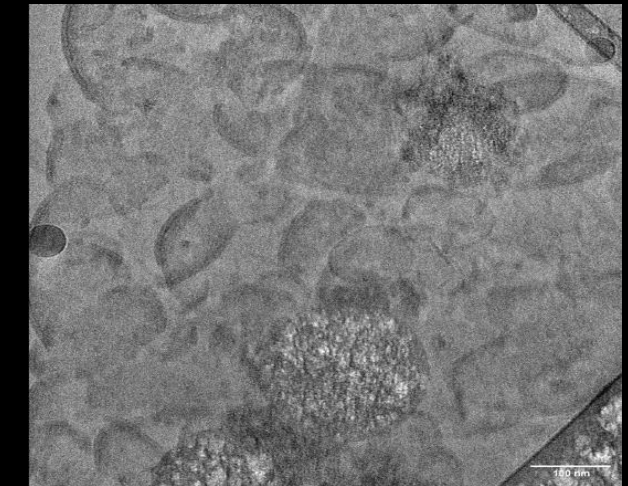
- Tranexamic Acid (TXA)
- Inorganic Polyphosphate (PolyP)
- Thrombin
-can be others.. Including combo

Enzyme trigger (🍷) candidates:

- Phospholipases
- Plasmin
- Thrombin
-can be others.. e.g. MMPs

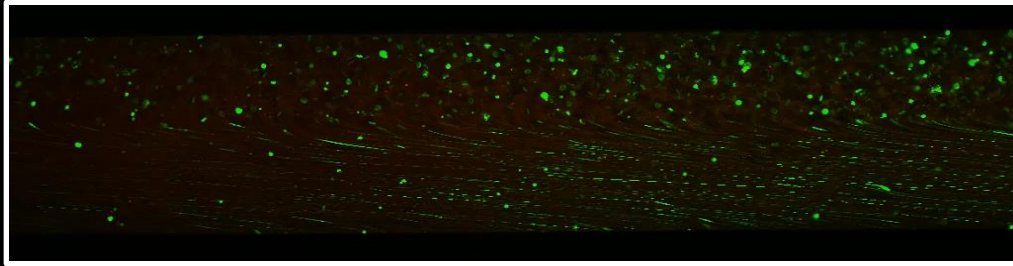


Enzyme-triggered Lipid Cleavage

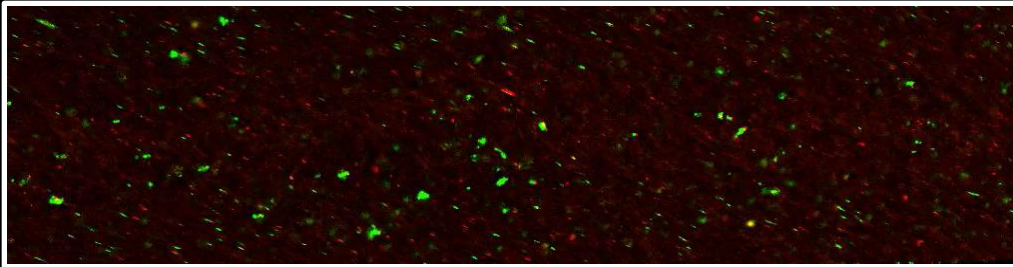


Microfluidics with PolyP-S-SP in Thrombocytopenic Blood

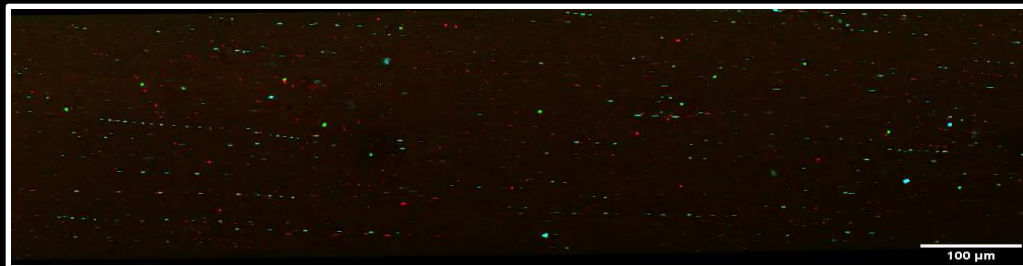
Whole Blood (WB)
with Healthy
Platelet Count



WB with Inhibition
of Platelet Granule
Secretion



Above condition
+ PolyP-S-SP
+ tPA



Shear: 4000 sec⁻¹

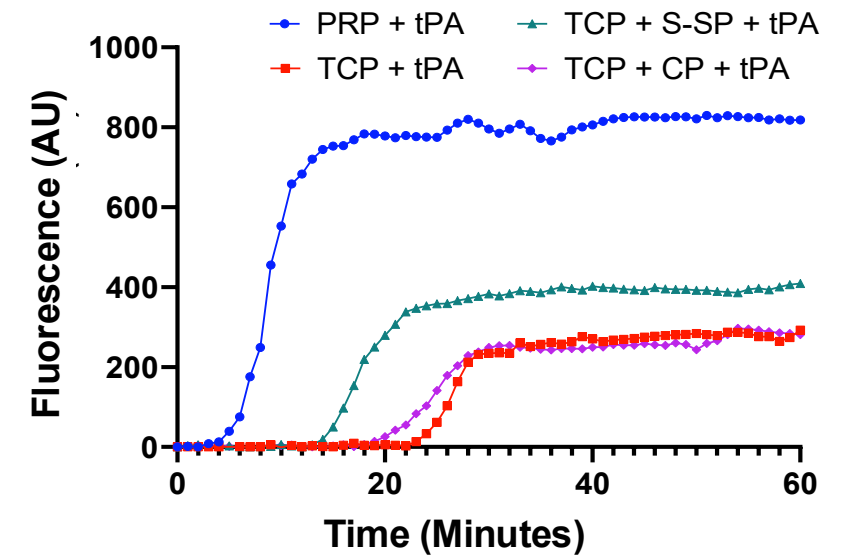
PLATELET

FIBRIN

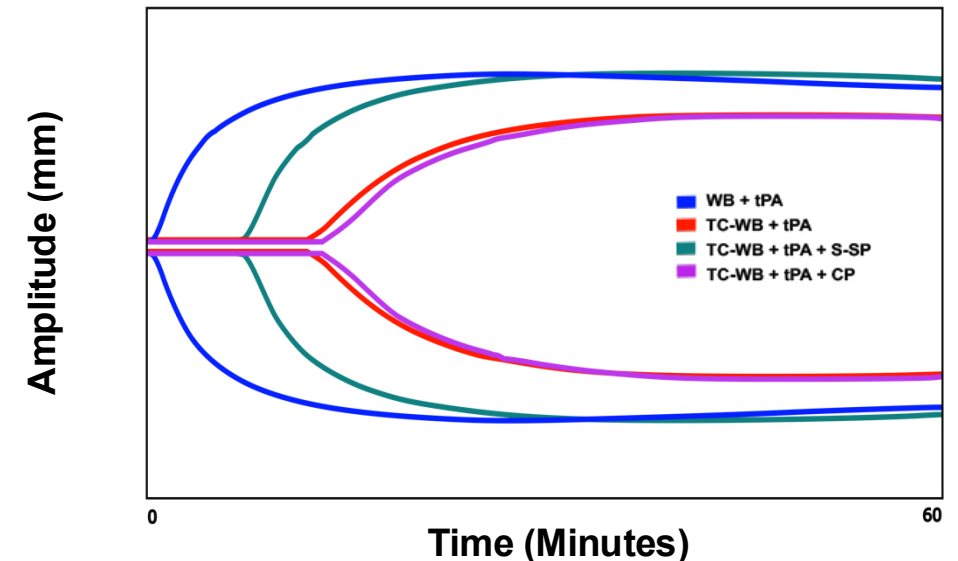
PARTICLES

Unpublished

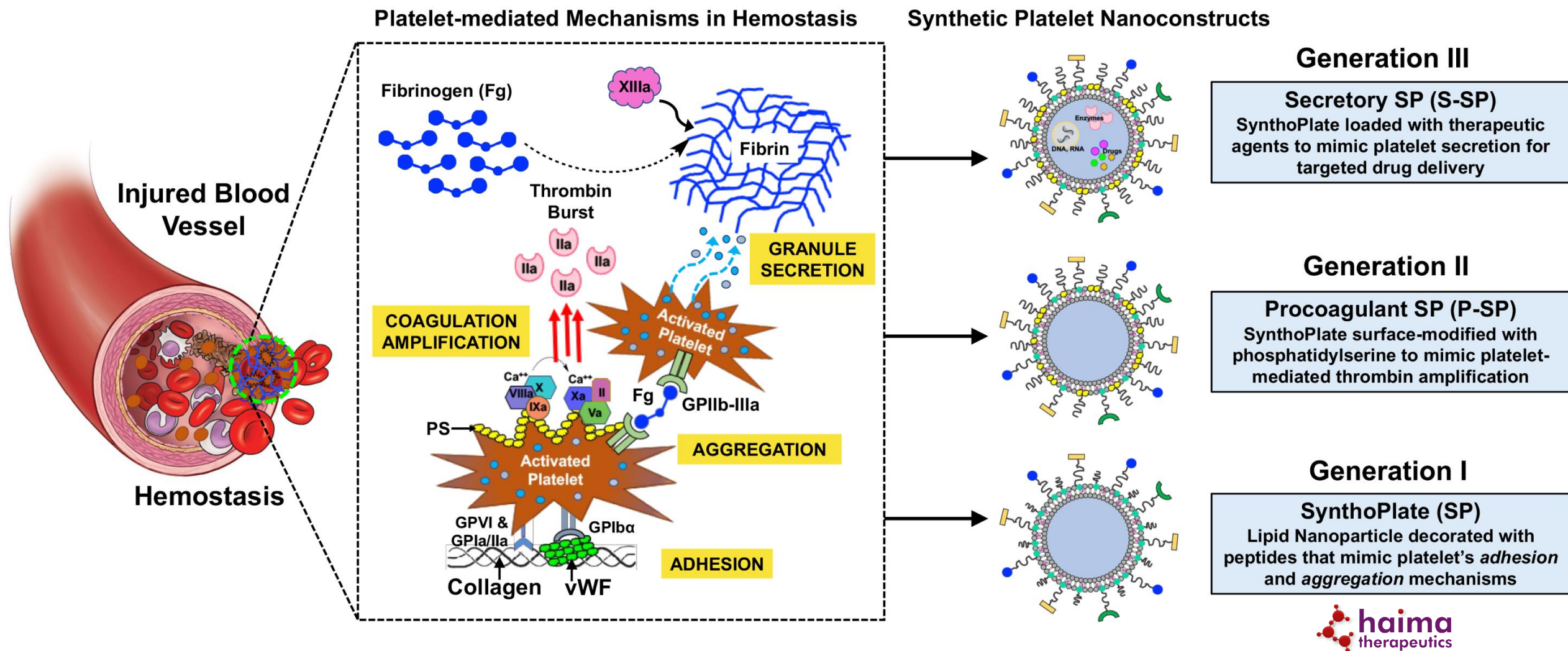
Thrombin Generation Assay



ROTEM Assay

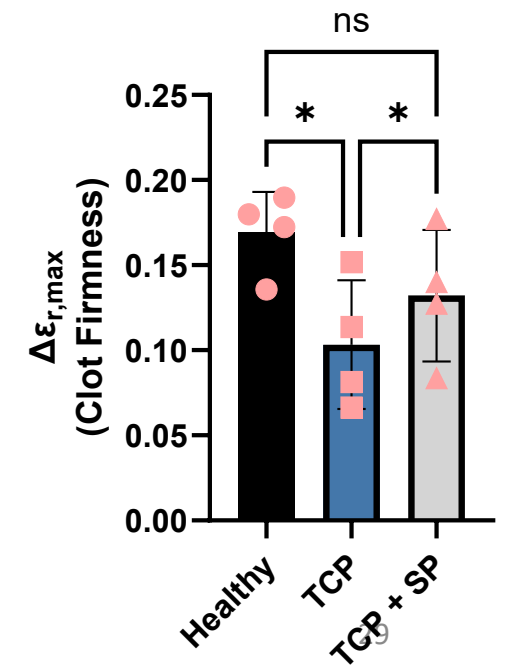
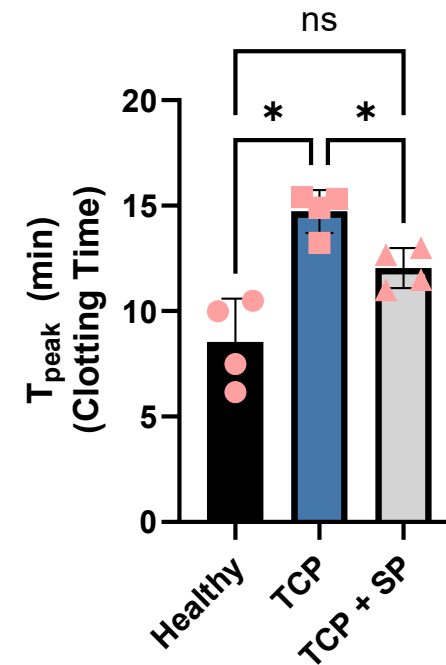
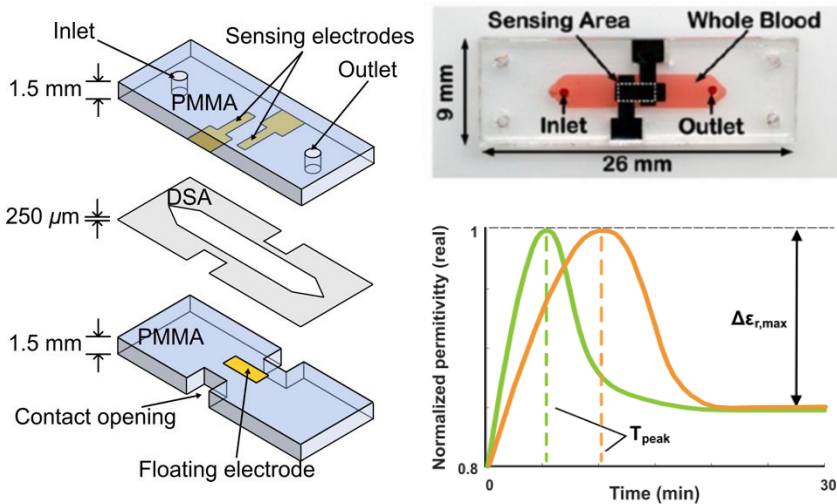
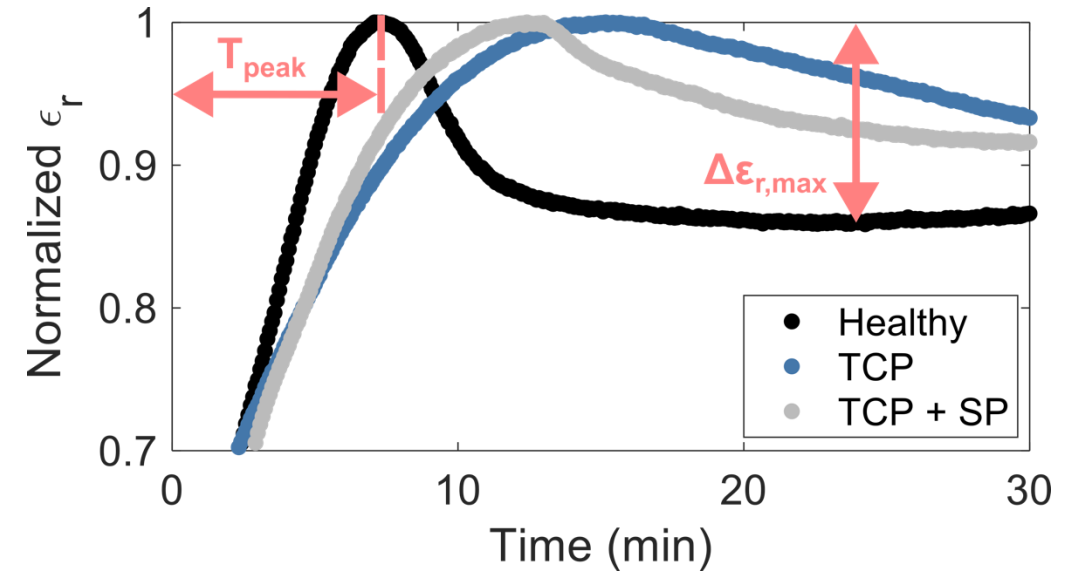
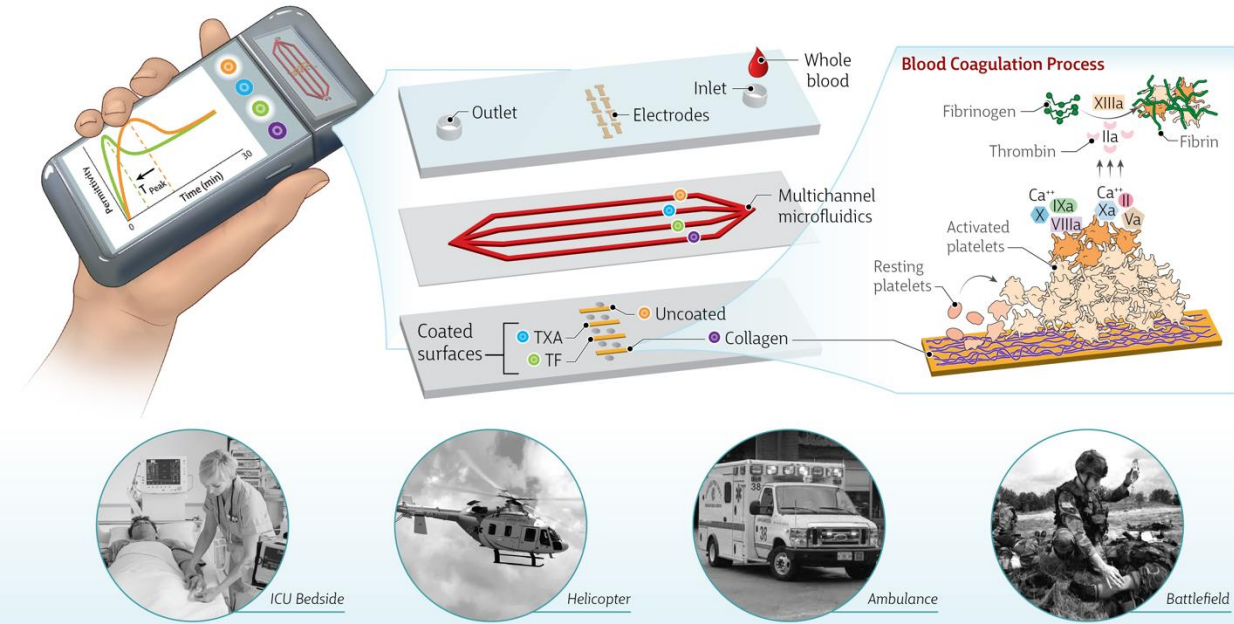


Bio-inspired Synthetic Platelet Design



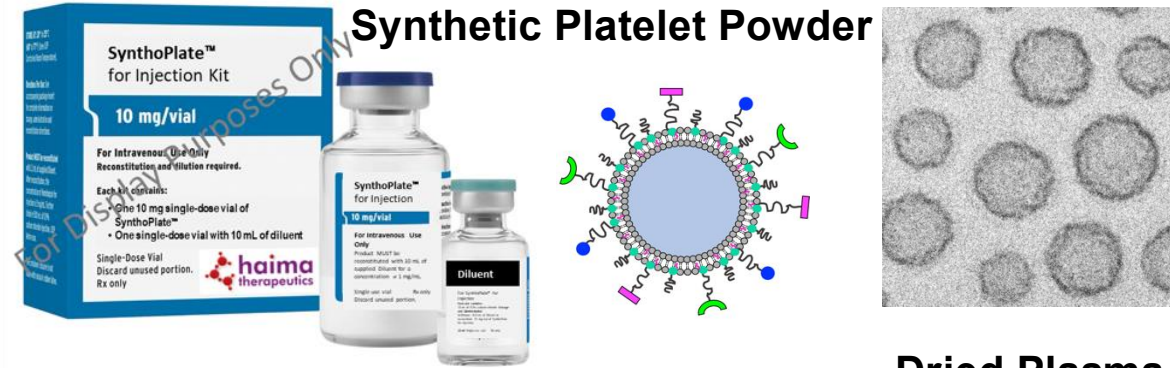
Fully synthetic; Donor-independent; Scalable; Lyophilizable; Immunosilent; Species-agnostic; Cost-effective

Far Forward Diagnostic? → Portable Dielectric Coagulometry



Furiosa links up with Ripley (Force Multiplier)

Synthetic Platelet Powder



Dried Plasma

HBOC Powder



Portable POI Guidance



POI/POC Guided Resuscitation

