CASE SCHOOL OF ENGINEERING
CASE WESTERN RESERVE UNIVERSITY

SEN GUPTA LAB
BIO-INSPIRED ENGINEERING for ADVANCED THERAPIES

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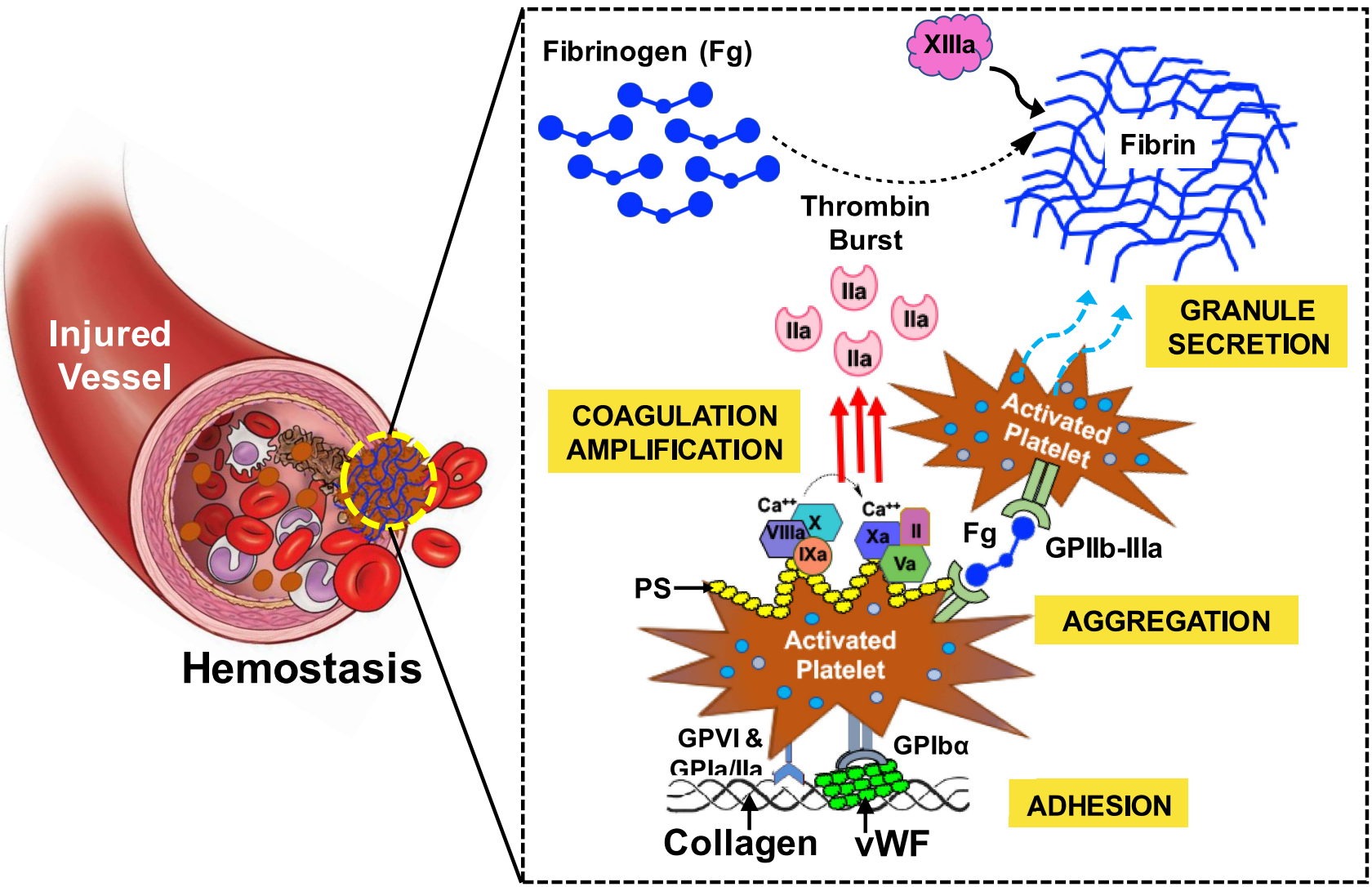
Current Status of Platelet Mimetics in Bleeding Management

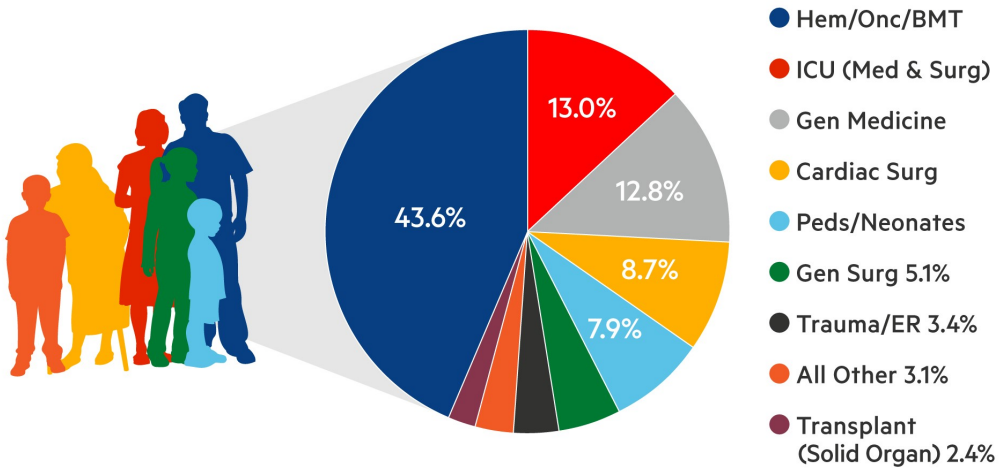
Anirban Sen Gupta, PhD
Leonard Case Jr. Professor of Engineering

Platelets Play Central Role in Hemostasis



Platelet Transfusion to Treat Bleeding Complications

Platelet Transfusion in the clinic : AABB 2014



Approximately 7000 units of Platelets are Transfused Daily in the US

- Donor-derived platelets (pooled or apheresis)
- Leukoreduced and pathogen reduced
- Stored at RT (22-24^{o}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

TRANSFUSION PRACTICE

A survey of US hospitals on platelet inventory management, transfusion practice, and platelet availability

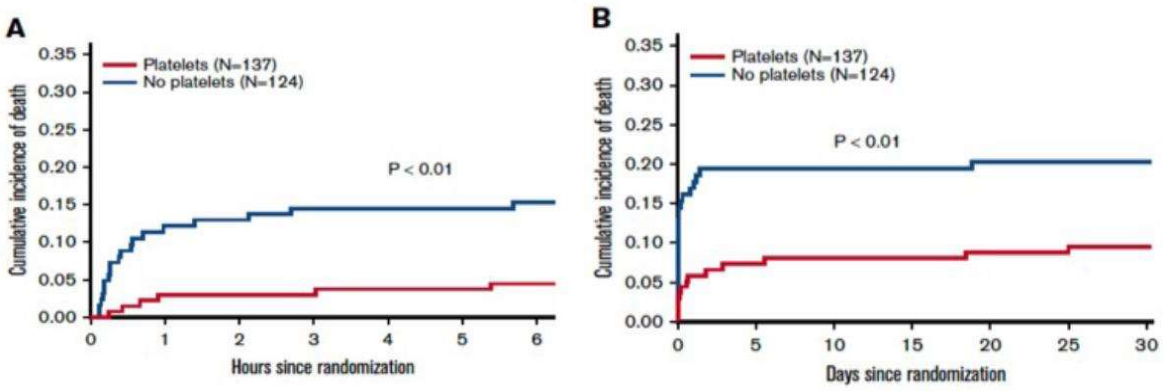
Suchitra Pandey, Geoffrey A. Belanger, Srijana Rajbhandary, Claudia S. Cohn, Richard J. Benjamin, Arthur W. Bracey, Louis M. Katz, Jay E. Menitove, Paul D. Mintz, Richard R. Gammon

First published: 19 July 2021 | https://doi.org/10.1111/trf.16561 | Citations: 2

- 481 hospitals surveyed
- ~ 80% stock ≦ 5 PLT units in inventory
- ~ 50% report decreased availability

Platelet Transfusion to treat Trauma Hemorrhage and TIC

- Current treatment : **Massive Transfusion Protocol (MTP)** → **Platelet**: RBC: Plasma (1:1:1) or whole blood (**WB**) --- in large civilian or military trauma centers
- Robust clinical studies (e.g. **PROMMTT, PROPPR, PAMPer**): established benefit of early platelet transfusion



PROPPR sub-study, Cardenas et al, Blood Adv. 2018

Major Pre-hospital Challenges for Platelet Use:

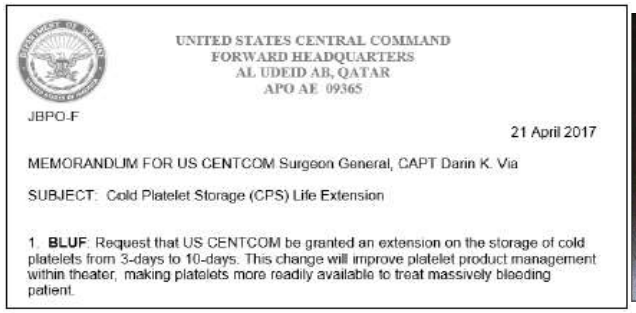
- **Availability:** Essentially zero in civilian first responder and very limited in military setting
- **Portability** and **Storage**: Special requirements of temperature, container, additive solution.
- **Shelf-life:** 5-7 days at RT; High risks of bacterial contamination

CENTRAL QUESTION

Can issues of **Availability**, **Portability**, **Shelf-life** and **Storage** of platelets be improved while **conserving *Hemostatic Function***, to improve transfusion logistics and outcomes in TIC mitigation

Strategies to Improve Platelet Availability and Usage

Cold-stored Platelets



UNITED STATES CENTRAL COMMAND
FORWARD HEADQUARTERS
AL UDEID AB, QATAR
APO AE 09365

JBPO-F

21 April 2017

MEMORANDUM FOR US CENTCOM Surgeon General, CAPT Darin K. Via

SUBJECT: Cold Platelet Storage (CPS) Life Extension

1. **BLUF**: Request that US CENTCOM be granted an extension on the storage of cold platelets from 3-days to 10-days. This change will improve platelet product management within theater, making platelets more readily available to treat massively bleeding patient.

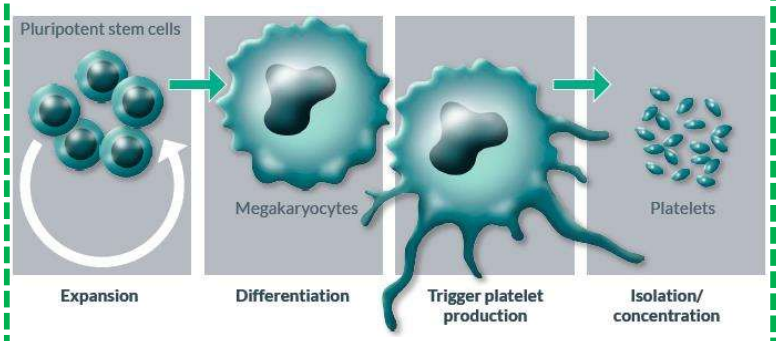
- Cold stored platelets (1-6^{o}C)
- Can potentially increase 'Shelf Life' by reducing bacterial contamination risks

Freeze-dried Platelets

Cellphire Therapeutics, Inc.

- Trehalose-stabilized freeze-dried platelets
- Long shelf-life and high availability

In Vitro Platelet Production

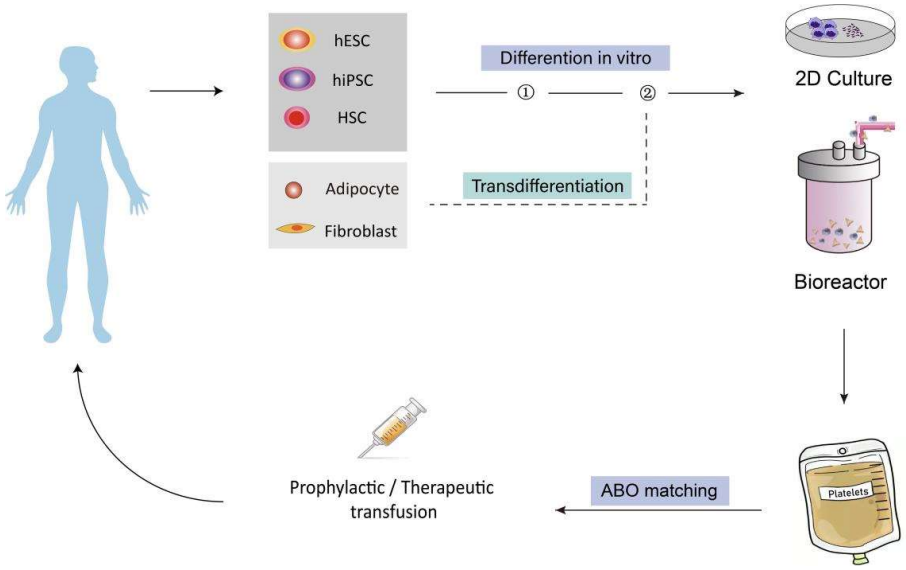


- Bioreactor-based in vitro production of platelets from precursor cells
- Can potentially address 'Platelet Availability' on demand

Synthetic Platelet Surrogate

- Synthetic nanoparticle based technologies that functionally mimic platelet's hemostatic mechanisms while allowing reproducible large-scale manufacture, low volume storage (suspension or freeze-dried), long shelf life, easy portability and on-demand availability

In Vitro Production of *Biologic* Platelets

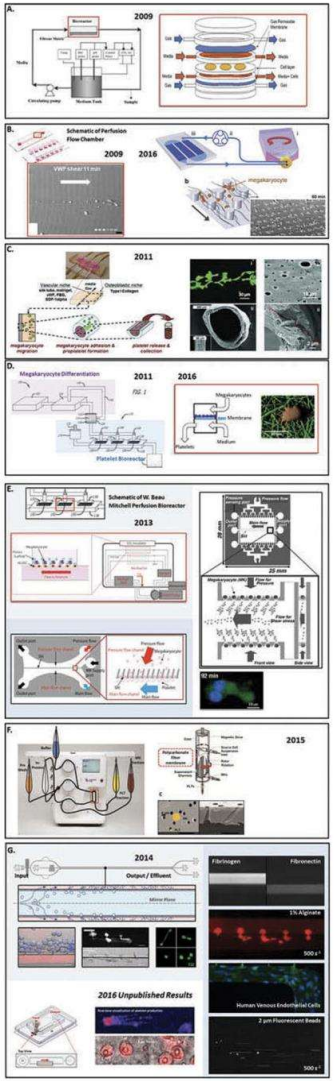


Process analysis of pluripotent stem cell differentiation to megakaryocytes to make platelets applying European GMP

Moyra Lawrence[1,2], Amanda Evans[1,2], Thomas Moreau[1,2,3], Marta Bagnati[4], Matthew Smart[4], Enas Hassan[4], Jahid Hasan[4], Monica Pianella[4], Julie Kerby[4] and Cedric Ghevaert[1,2]✉

NPJ Regen Med 2021, PMC8155004

limiting factors for production. Assuming currently modelled manual production can be increased to 500 doses in year one, the cost of producing a single platelet unit totals £149,571. The



PlateletBio

Italiano

SilkFusior

Balduini

UNIVERSITY OF CAMBRIDGE

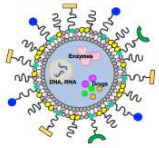
Ghevaert

Center for iPS Cell Research and Application
CiRA Kyoto University

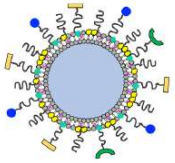
Eto

Synthetic Platelet Mimetics

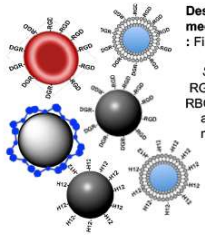
Design inspired by secretory aspects of platelets : Liposomal nanoparticles used for SynthoPlate design are loaded with various therapeutic payloads for clot-targeted and stimuli-triggered release for adjunctive functions



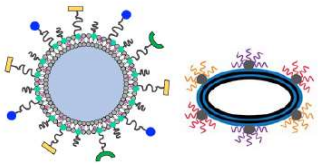
Design that mimics procoagulant mechanism of platelets : Liposomal nanoparticles used for SynthoPlate design are further surface-modified by PS lipid for injury site-targeted PS exposure



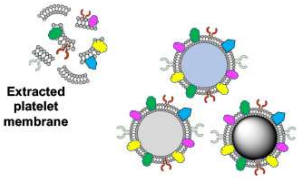
Design that mimics platelet mechanism of clot contraction: Fibrin-binding antibody fragment decorated microgel particles, e.g. *Platelet-like Particles (PLP)*



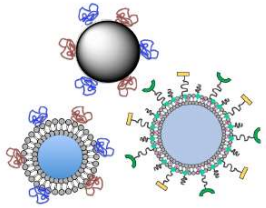
Designs that mimic fibrinogen-mediated platelet 'aggregation' : Fibrinogen-decorated polymeric or albumin particles, e.g. *Synthocyte*, *Fibroplate* etc.; RGD or H-12 peptide decorated RBCs (e.g. *Thromboerythrocyte*), albumin particles, polymeric nanoparticles and liposomal nanoparticles



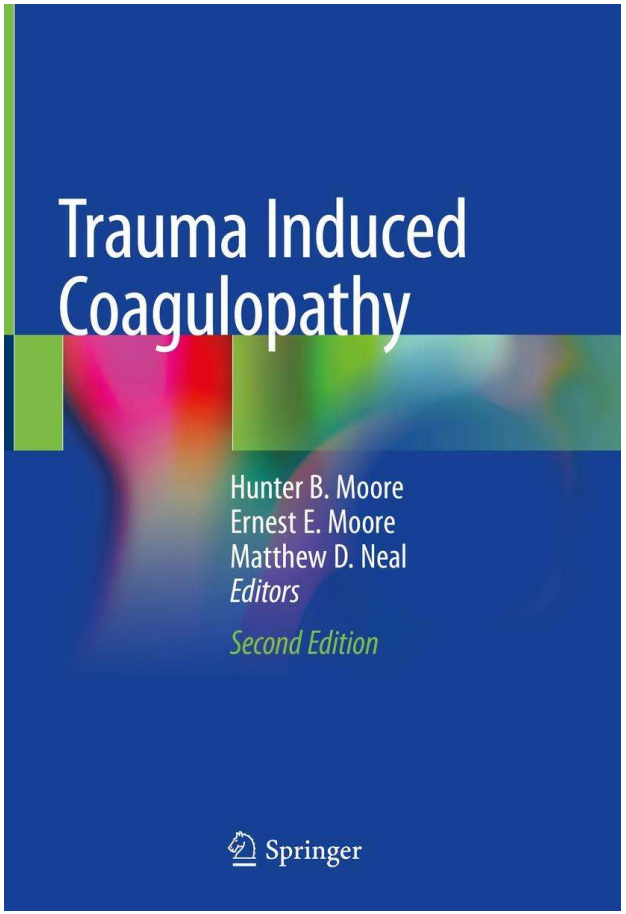
Designs that enable combined mimicry of platelet adhesion and aggregation: Peptide motifs binding to VWF, collagen and GPIIb-IIIa heteromultivalently decorated on liposome or albumin particles, e.g. *SynthoPlate*, *Platelet-like Nanoparticles (PLN)*



Designs that utilize the 'biointerfacing' approach: Membrane components extracted from donor-derived platelets and used to coat synthetic nanoparticles



Designs that mimic platelet 'adhesion' mechanisms: rGPIbα-decorated and rGPIa-IIa-decorated polymeric or albumin or liposomal particles; VBP and CBP peptide-decorated liposomal nanoparticles

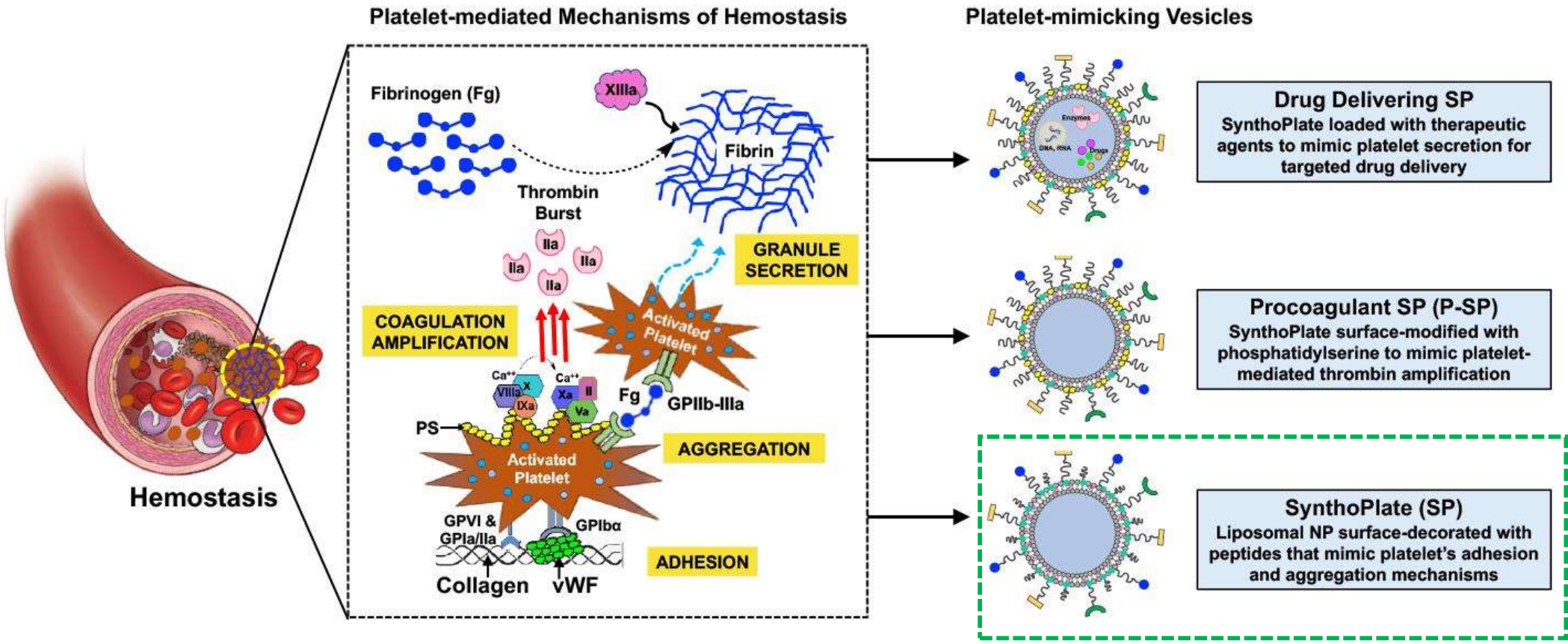


Synthetic Blood Substitutes 43

Anirban Sen Gupta

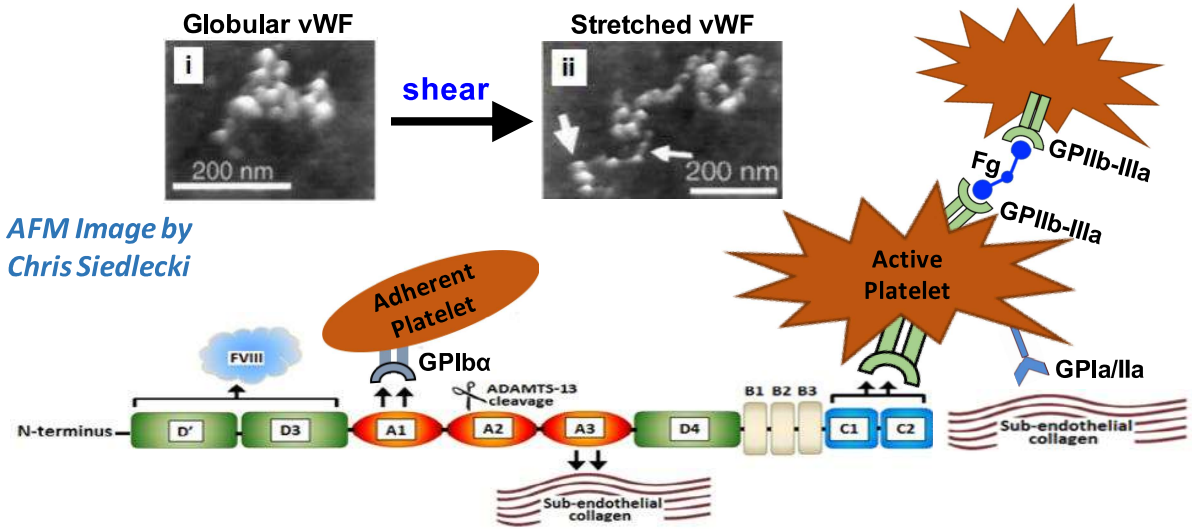
Platelet-inspired Synthetic Hemostats

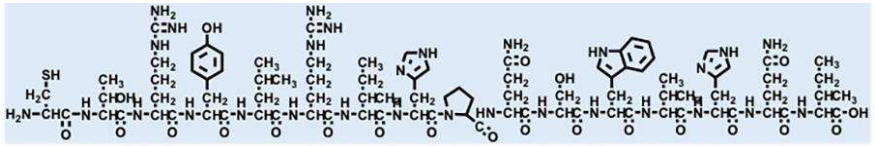
Lipid nanoparticle based designs to modularly mimic hemostatic mechanisms of platelets



Synthetic Platelet (SynthoPlate) Design

vWF Binding Peptide (VBP)

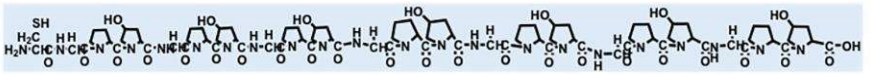




Sequence	IC_{50} (μM)
TRYLRIHPQSWVHQI	9.0

Research in development of FVIII-derived peptide for vWF-anchorage by:
Nogami et al, *Int J Hematol,* 85, 317-2322, 2007.

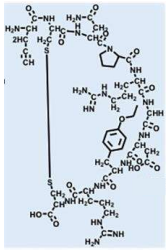
Collagen Binding Peptide (CBP)



Sequence	K_d (μM)
Cys-(Pro-Hyp-Gly)$_7$	~3.0

Research in peptide-based collagen targeting by Mo et al, *Angew Chem Int Ed,* 45, 2267-2270, 2006.

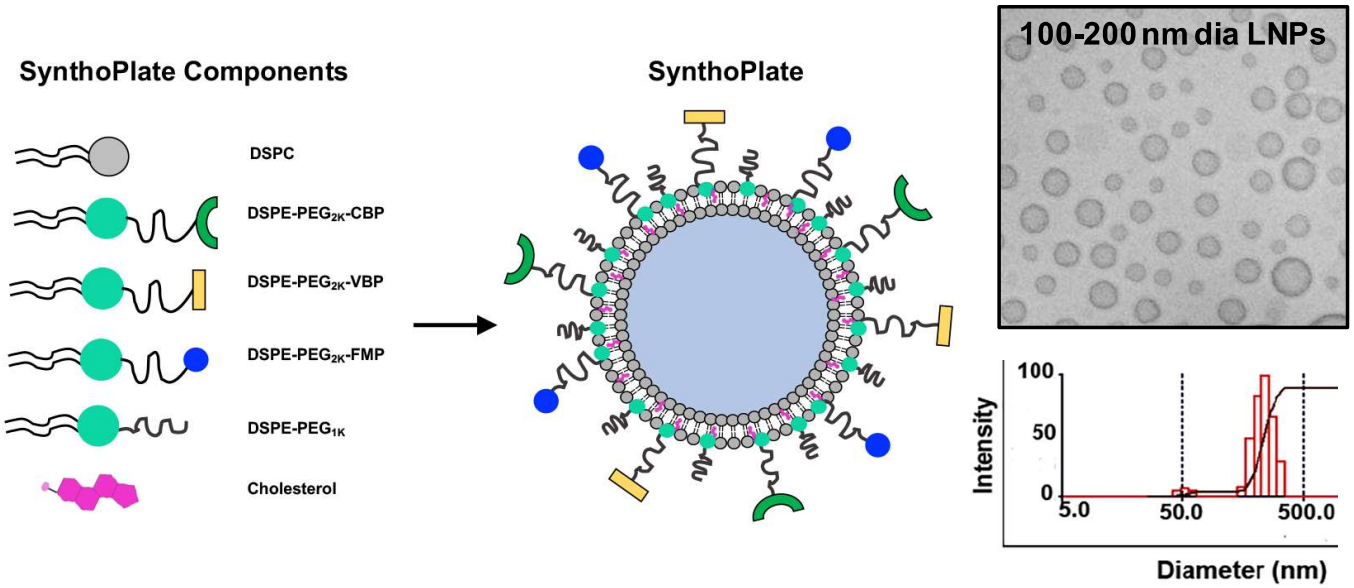
Fibrinogen Mimetic Peptide (FMP)



	IC_{50} (μM)		
Peptide	GPIIb/IIIa	α5β1	αVβ5
Ac-CNPRGD(Y-Oet)RC-NH_2	0.004	10.00	8.40

Research in active platelet GPIIb-IIIa antagonists:
Chen et al, *J Med Chem,* 37, 1-8, 1994

Synthetic Platelet (SynthoPlate) Design



- Made from biocompatible, biodegradable lipids and lipo-peptides
- Main lipid components similar to many FDA approved LNPs (e.g. Doxil®, mRNA vaccines etc.)

CBP: Collagen binding Peptide for Platelet-mimetic Collagen Adhesion

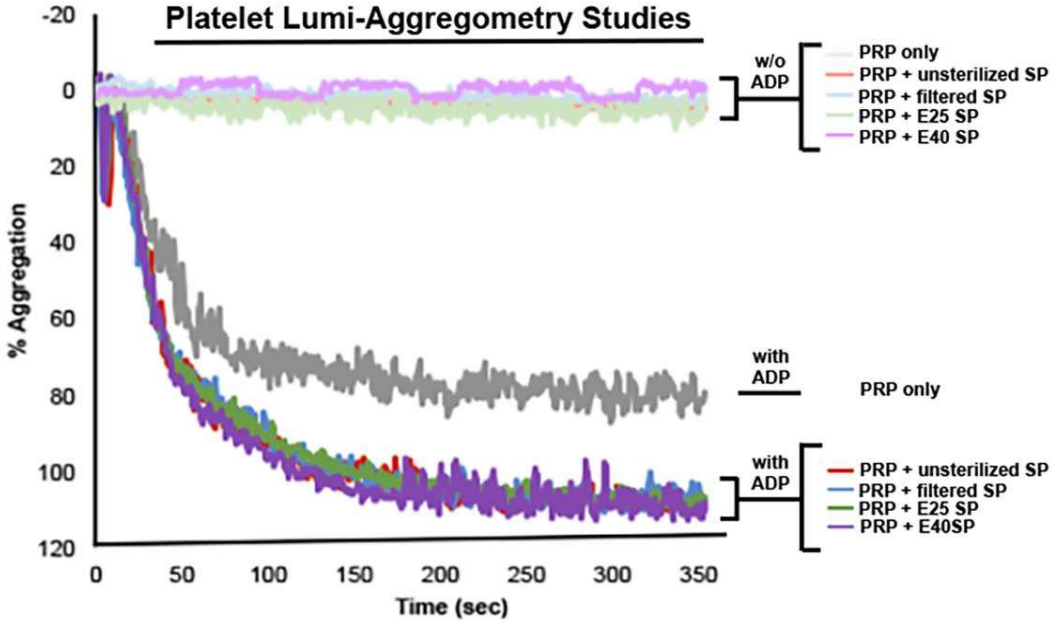
VBP: vWF binding peptide for Platelet-mimetic vWF Adhesion

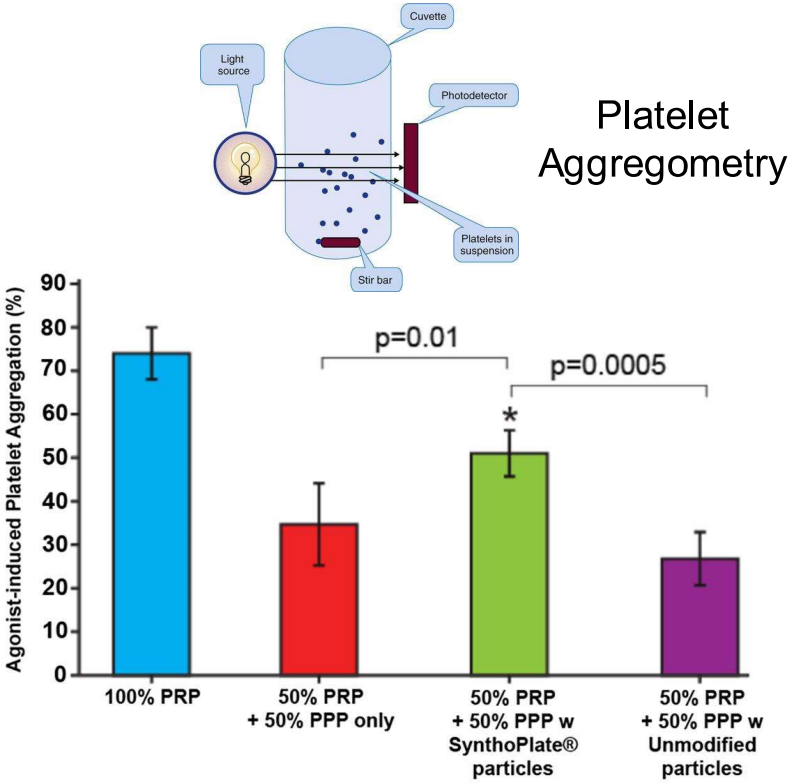
FMP: Fibrinogen mimetic peptide for Platelet-mimetic aggregation

Colloidal sterile suspension of SynthoPlate™

Patents: **US 9107845, US 9636383, US 10426820, US 10434149** licensed to ***Haima Therapeutics***

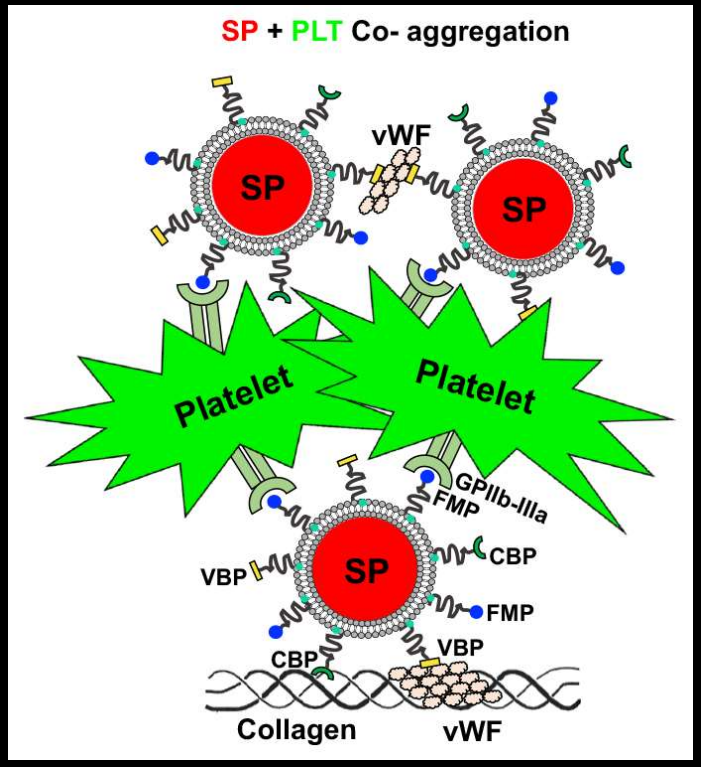
SynthoPlate Enhances Aggregation of Activated Platelets



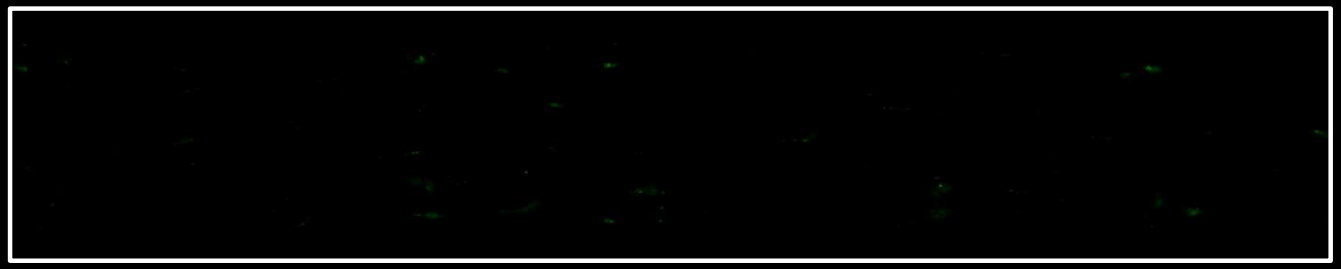


- SynthoPlate particles do not activate or aggregate *resting* platelets (safe towards circulating resting platelets)
- SynthoPlate particles interact specifically with *activated* platelets to enhance overall platelet aggregation
- SynthoPlate effect on active platelet aggregation is not affected by sterilization processes (filtration or E-beam)
- SynthoPlate effect on active platelet aggregation is valid for different platelet agonists (ADP, Collagen, TRAP etc.)

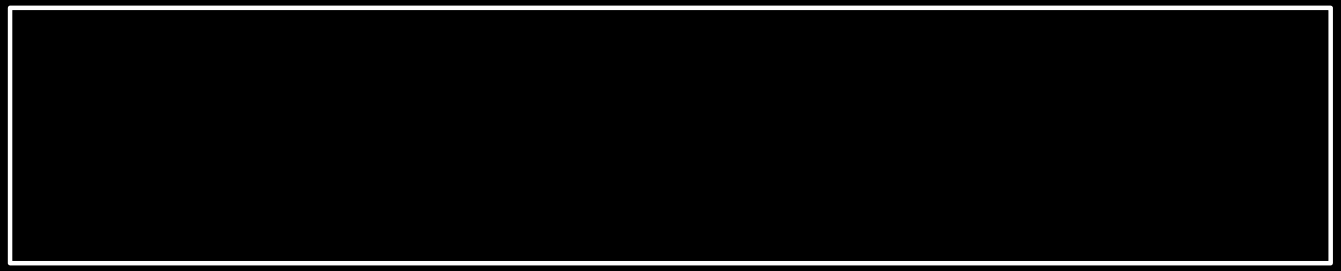
SynthoPlate Rescues ‘Platelet Coverage’ in PPP



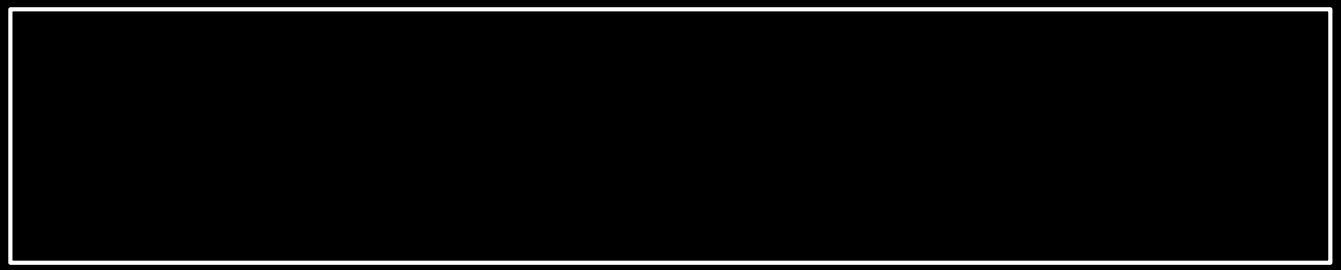
PRP on Collagen + vWF



PPP on Collagen + vWF

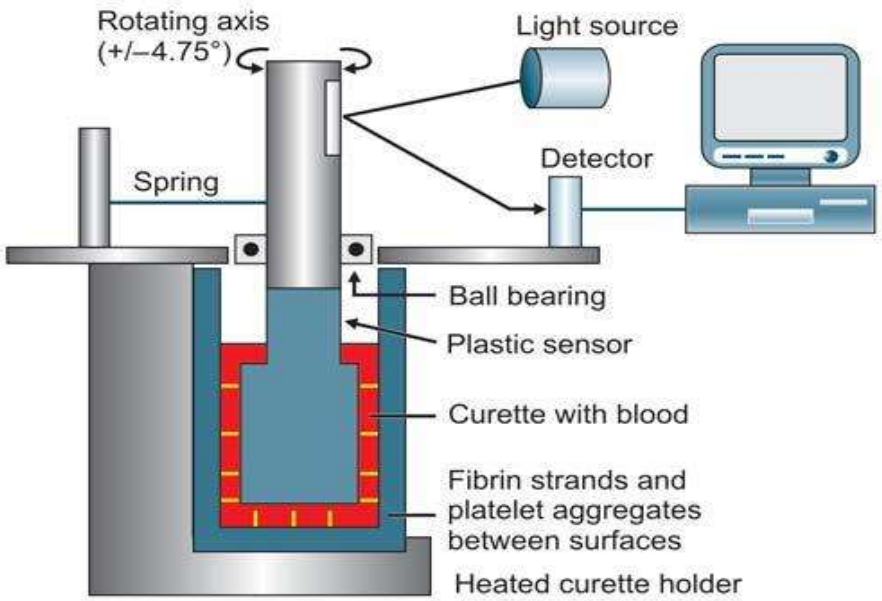


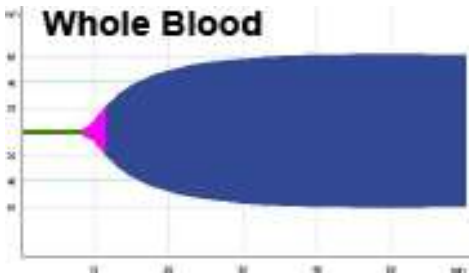
PPP + SP on Collagen + vWF

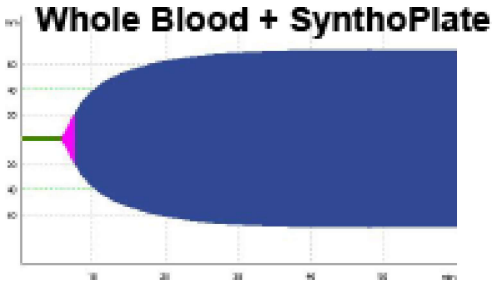


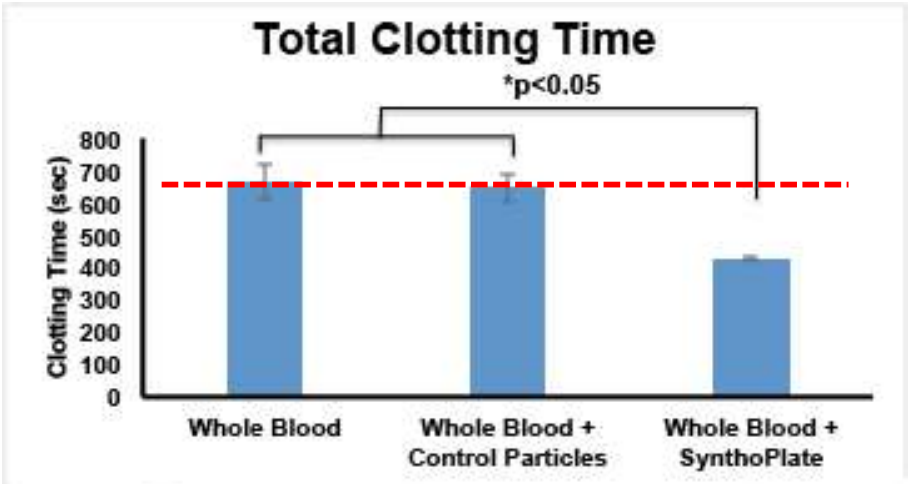
SynthoPlate Enhances Overall Clot Characteristics

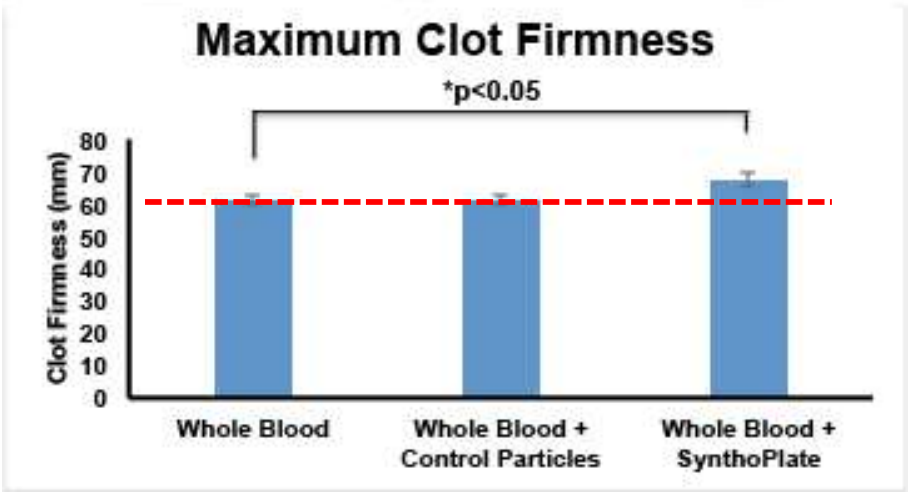
Rotational Thromboelastometry (ROTEM)







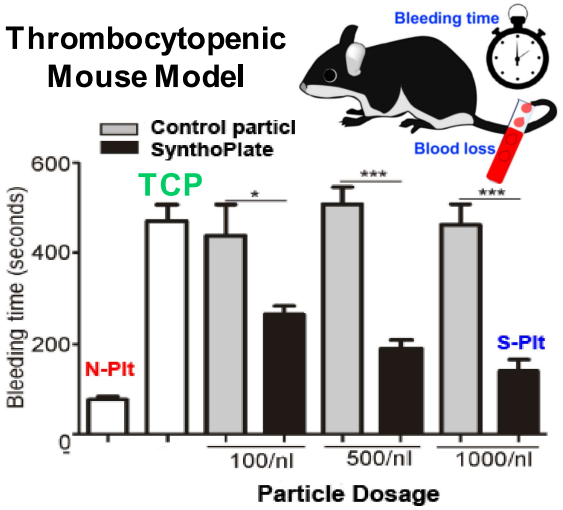




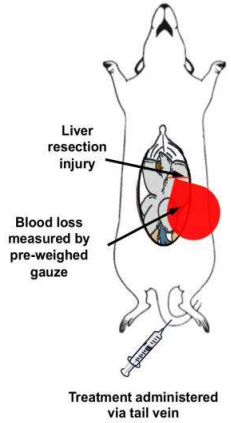
SynthoPlate particles accelerate clot formation and enhance clot firmness

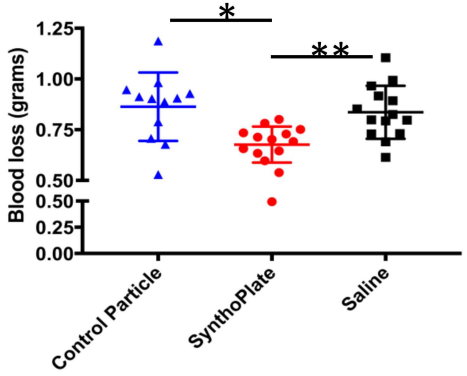
SP Reduces Bleeding in Various Animal Models

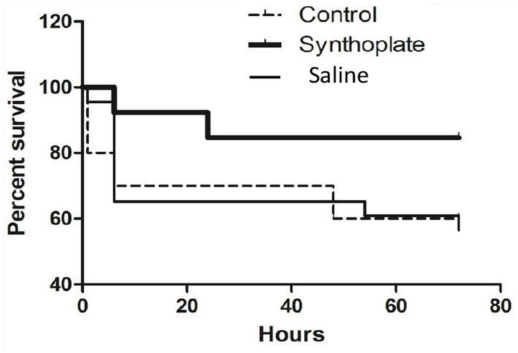
Thrombocytopenic Mouse Model



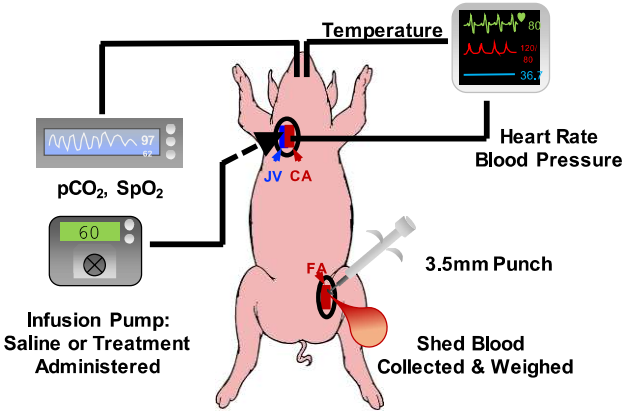
Rodent Liver Laceration

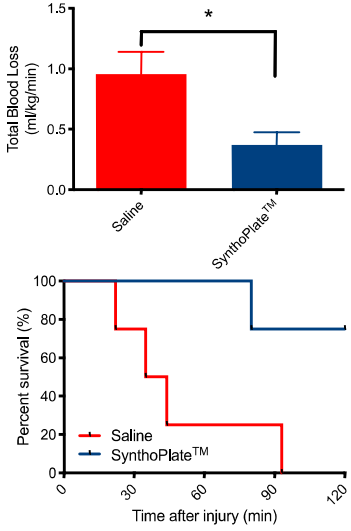




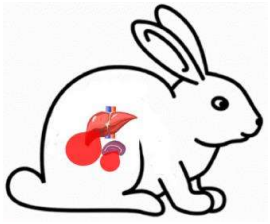


Pig Artery Punch

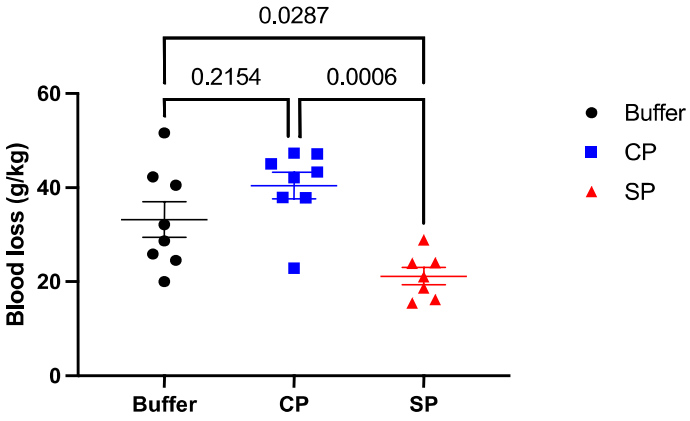




NZW Rabbit 'Liver + Spleen' Laceration



Weight-normalized Blood Loss

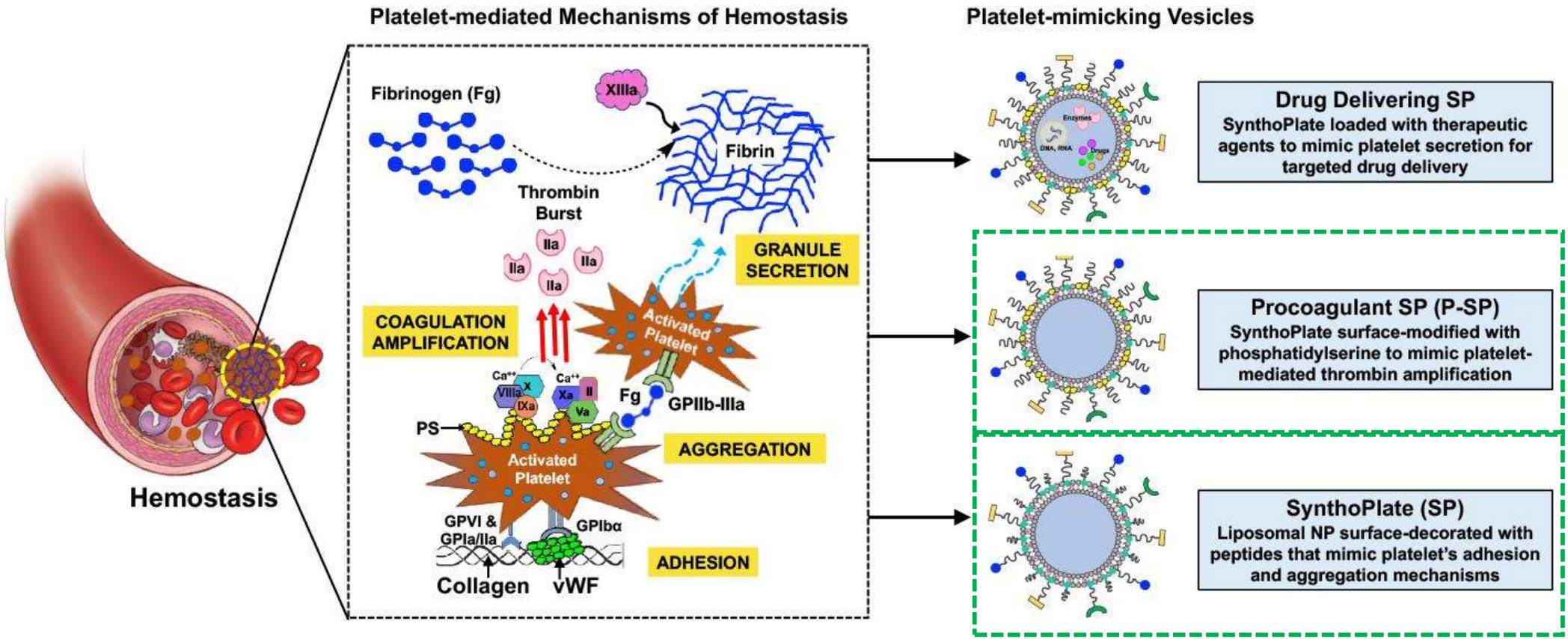


Modery-Pawlowski et al. Biomaterials. 2013
Anselmo et al. ACS Nano 2014

Shukla, Hickman et al. JTH. 2016
Dyer et al. J Acute Trauma. 2018
Hickman et al. Sci Rep. 2018

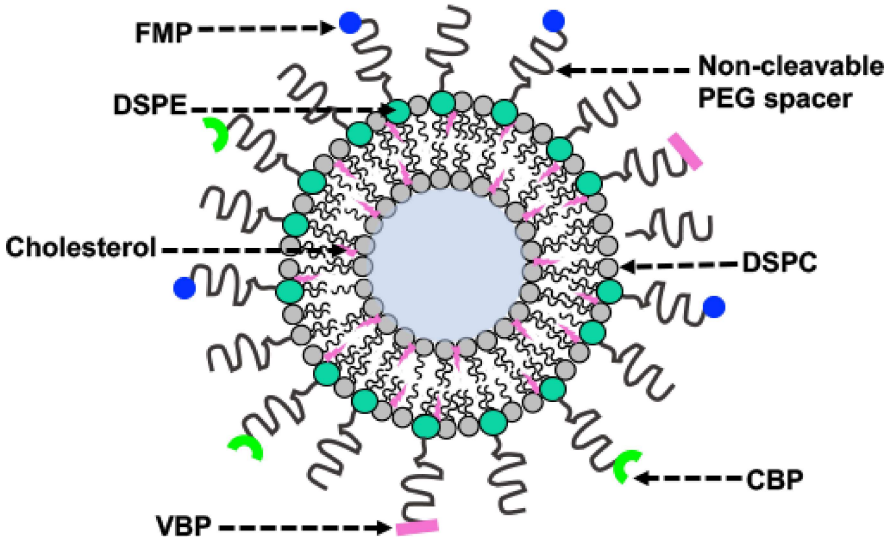
Platelet-inspired Synthetic Hemostats

Lipid nanoparticle based designs to modularly mimic hemostatic mechanisms of platelets

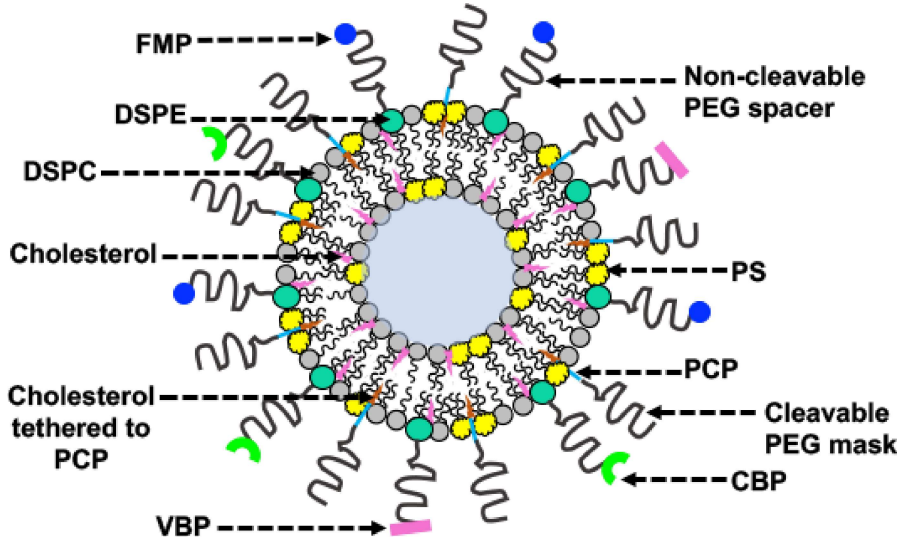


Synthetic Platelet with Pro-coagulant Function (P-SP)

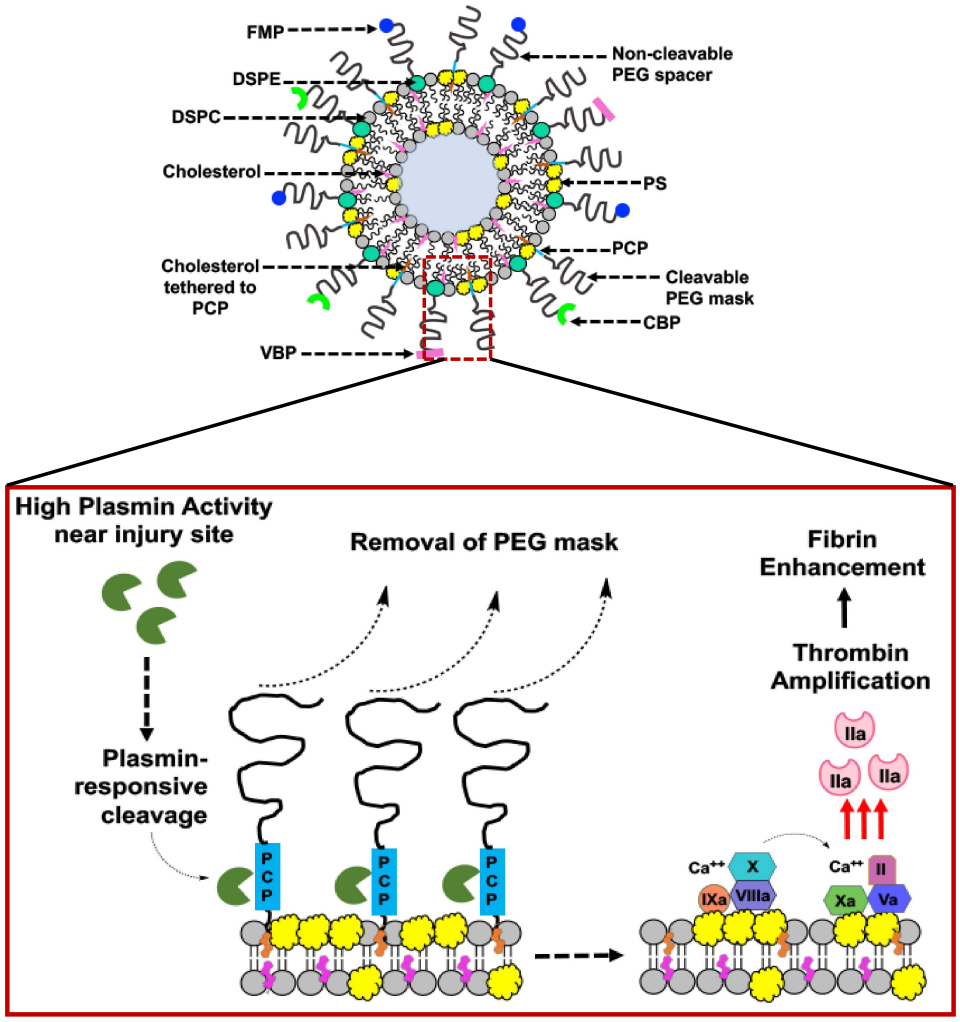
SynthoPlate (SP)



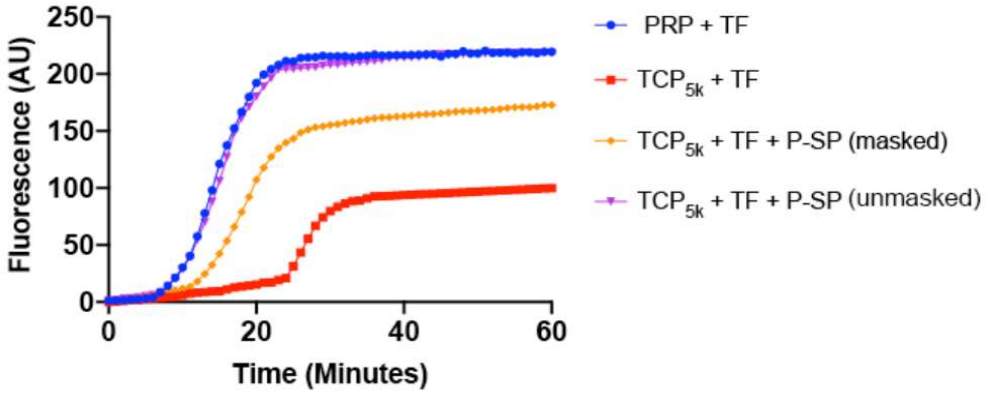
Procoagulant SynthoPlate (P-SP)

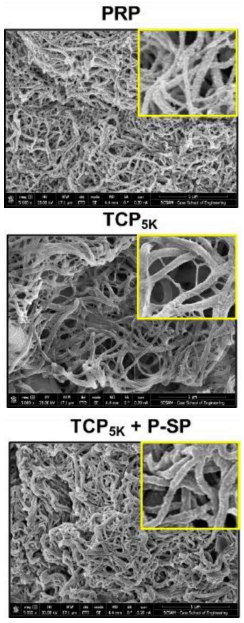


P-SP Exposes PS In Response to Plasmin to Amplify Thrombin

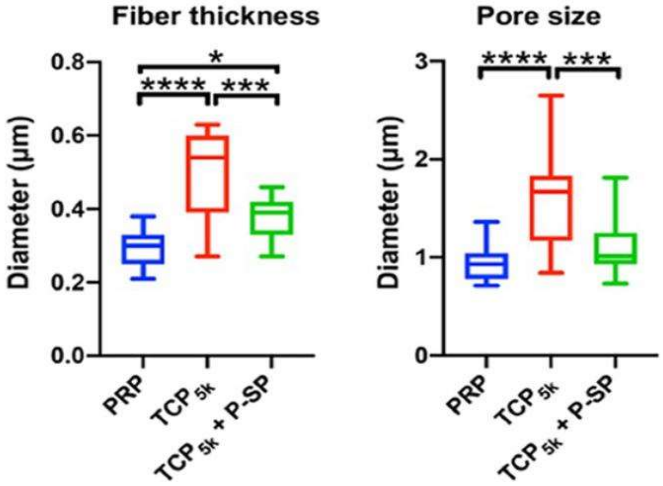


Thrombin Generation Assay





Rescue of Fibrin Morphology



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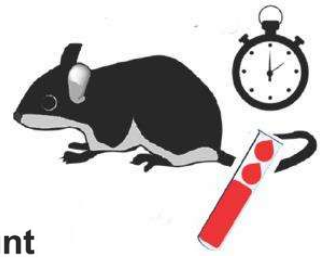
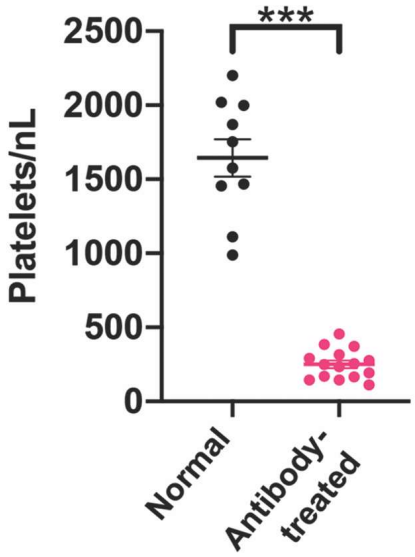
P-SP Reduces Bleeding in Mouse Thrombocytopenia Model and Rat Trauma Hemorrhage Model

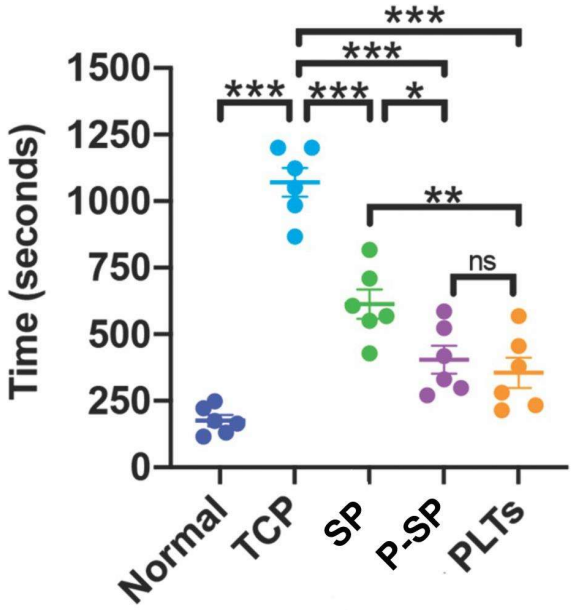
Tail-bleed in Thrombocytopenic (TCP) Mouse



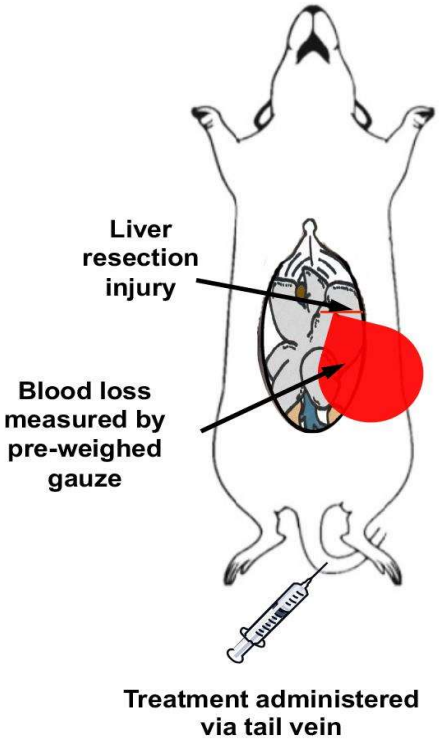
Platelet Count

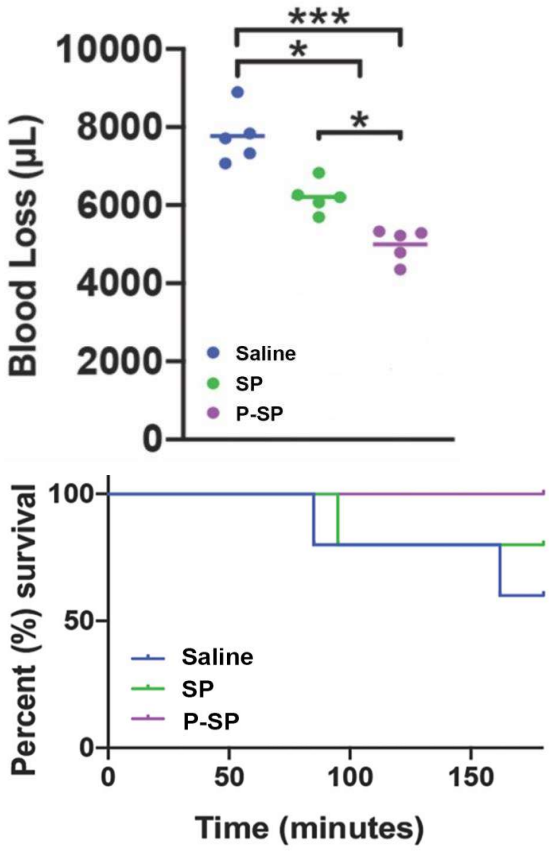


Bleeding Time



Traumatic Liver Laceration in Rats





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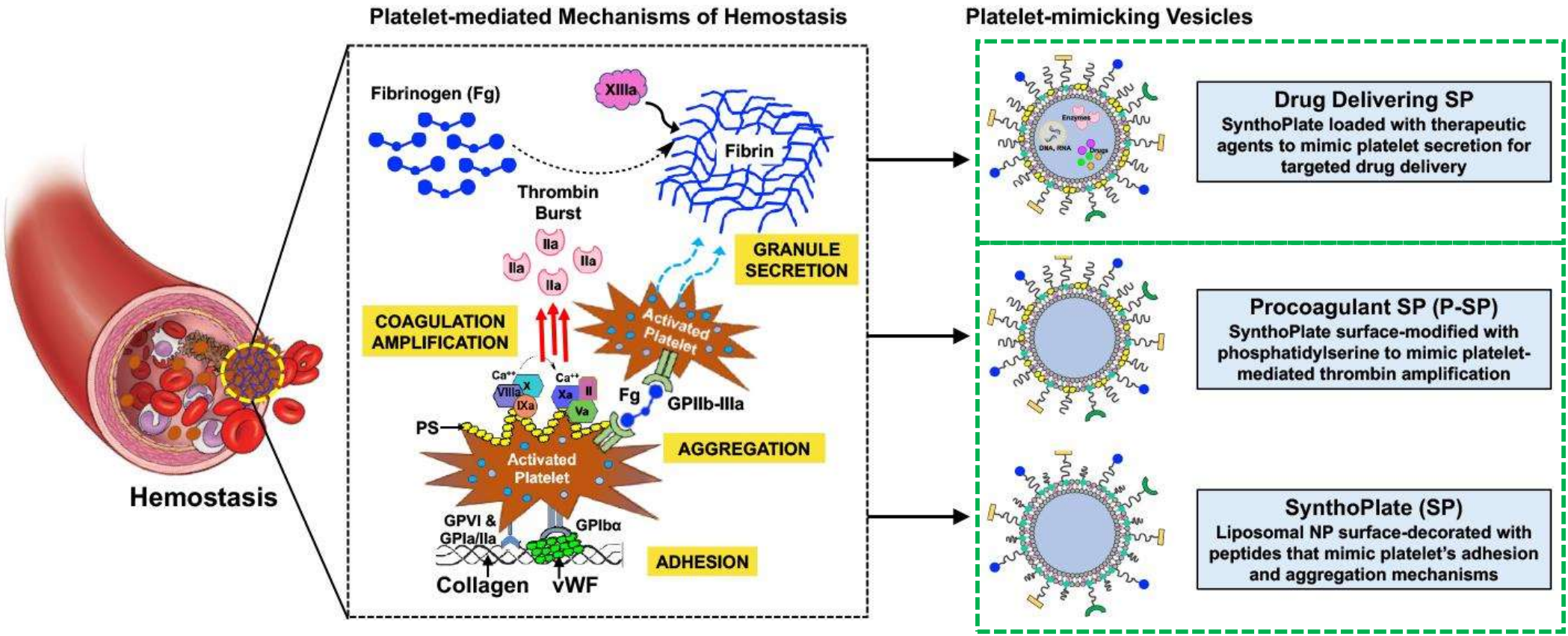
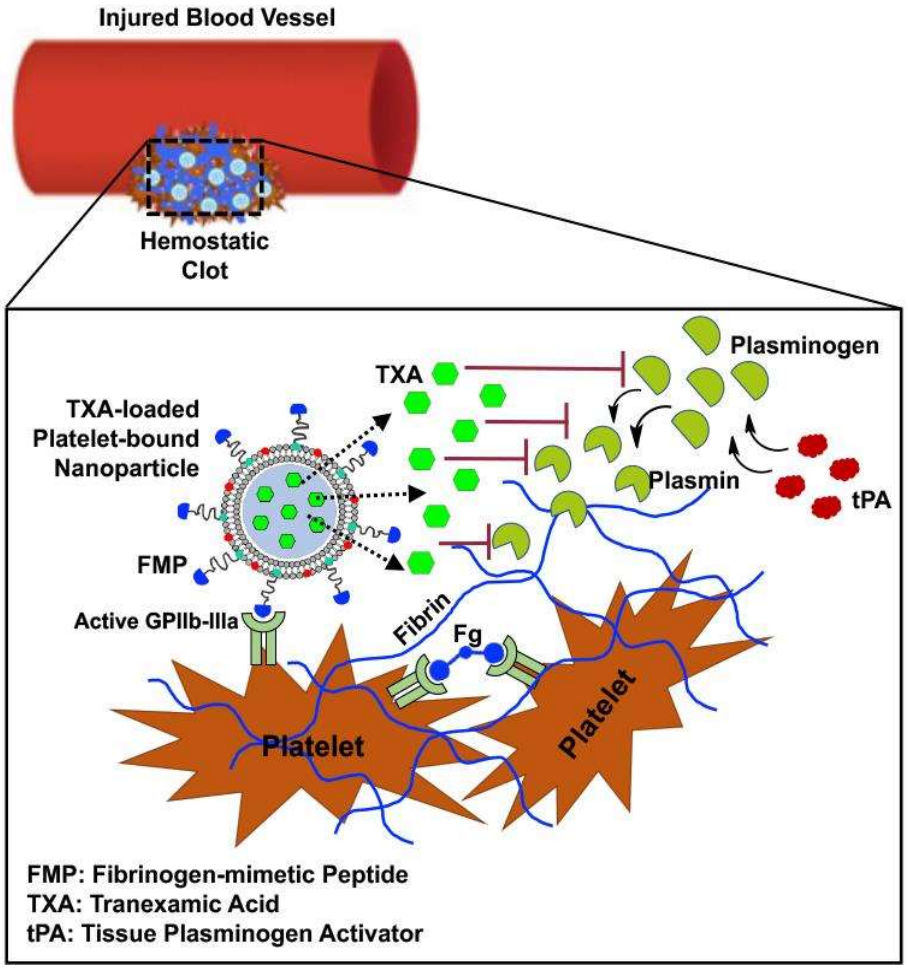
Platelet-inspired Synthetic Hemostats

Lipid nanoparticle based designs to modularly mimic hemostatic mechanisms of platelets

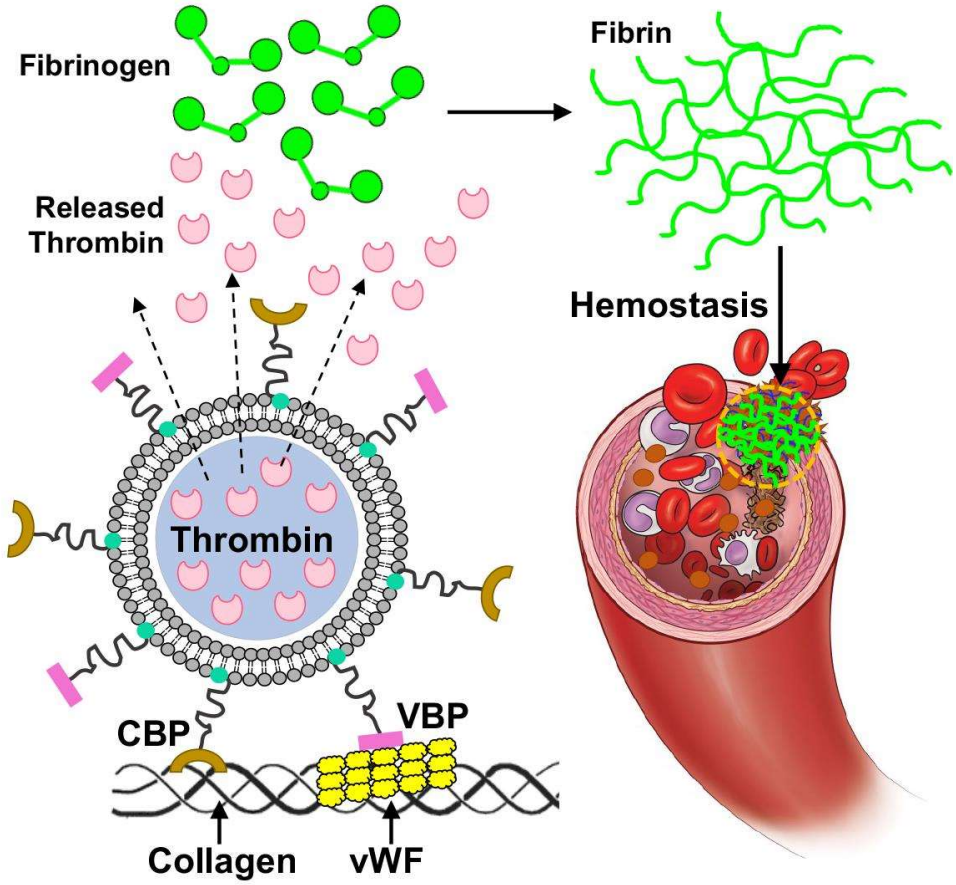


Targeted Delivery of Drugs using Platelet-mimicking Vesicles

Targeted Delivery of TXA to Treat Hyperfirbinolysis

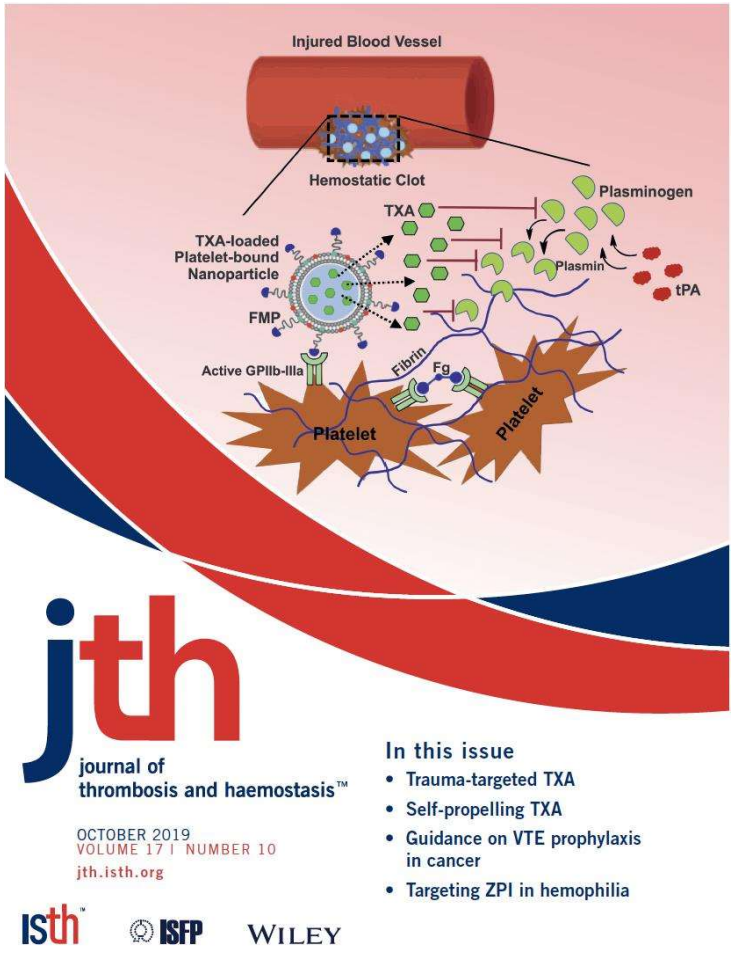


Targeted Delivery of Thrombin to Treat Coagulopathy



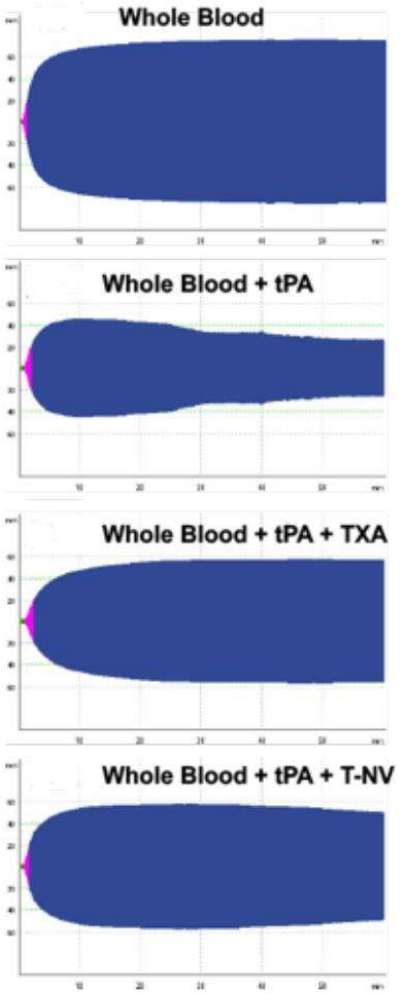
Targeted Delivery of Drugs using Platelet-mimicking Vesicles

Targeted Delivery of TXA to Treat Hyperfirbinolysis

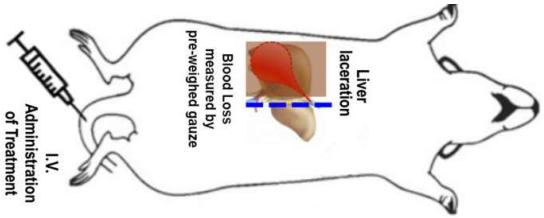


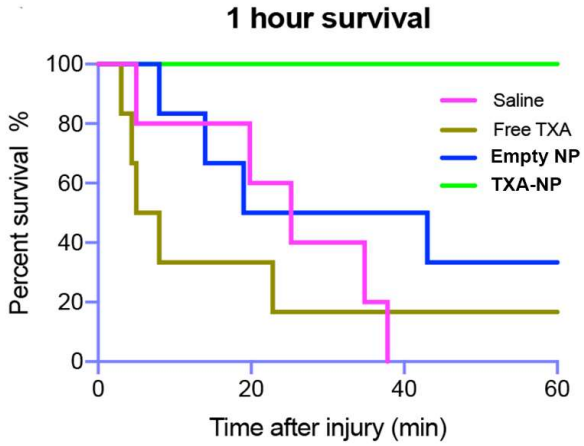
Girish et. al, J Thromb. Haemost. 2019

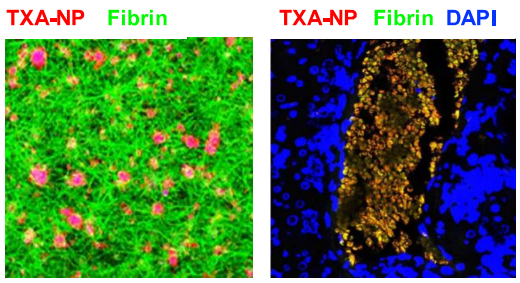
ROTEM



Rat Liver Injury Model

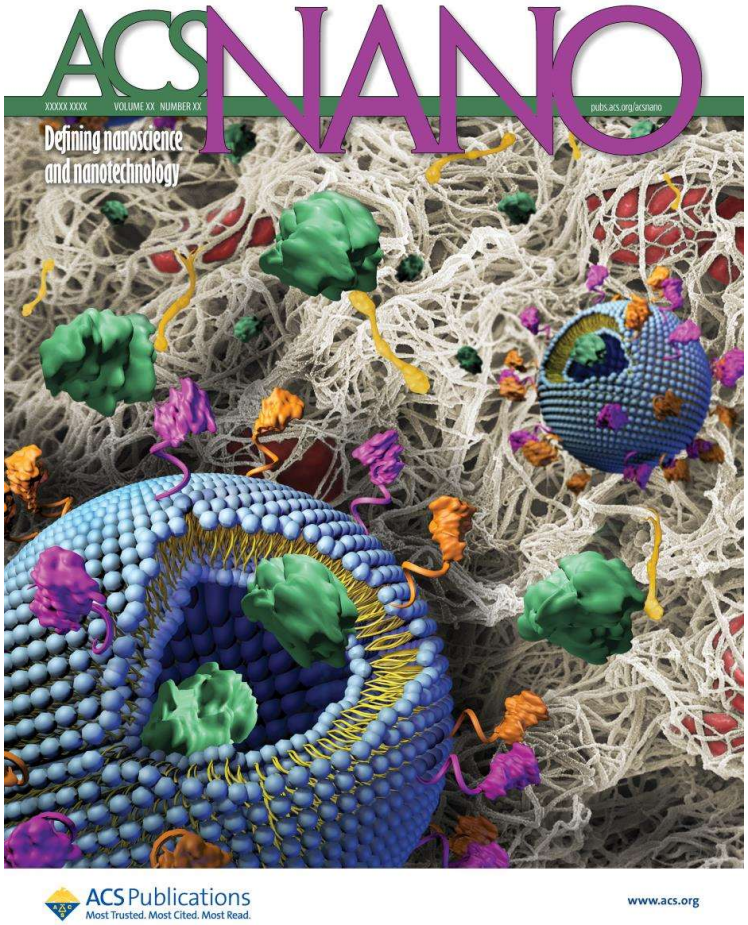




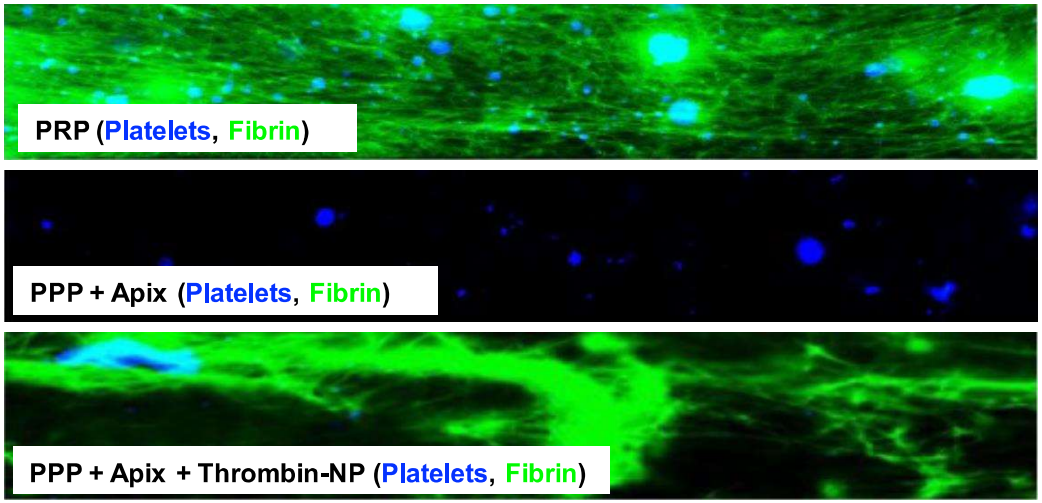


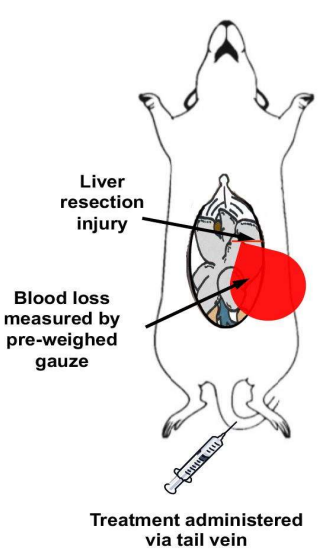
Targeted Delivery of Drugs using Platelet-mimicking Vesicles

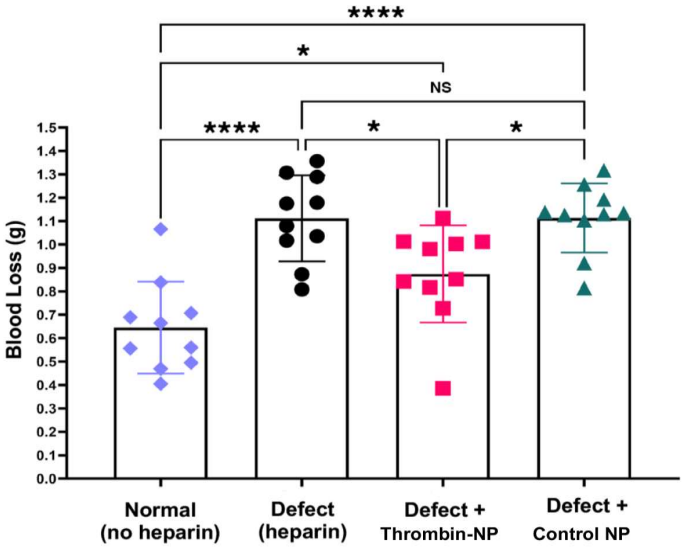
Targeted Delivery of Thrombin to Treat Coagulopathy



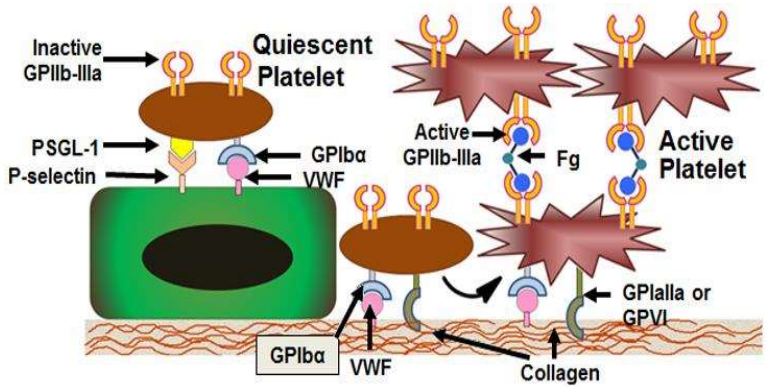
Girish et. al, ACS Nano 2022



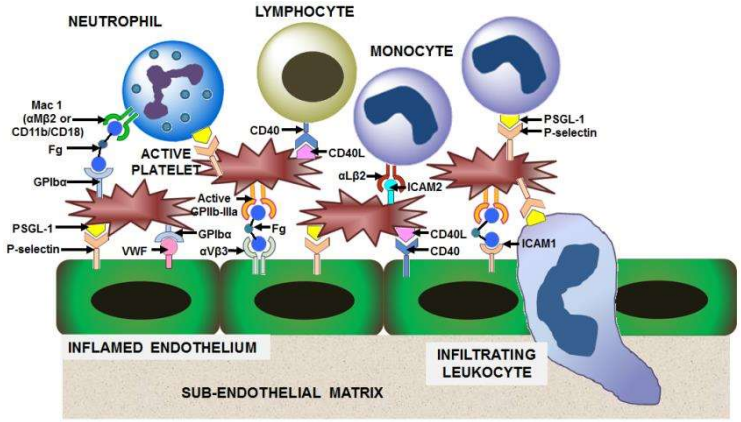




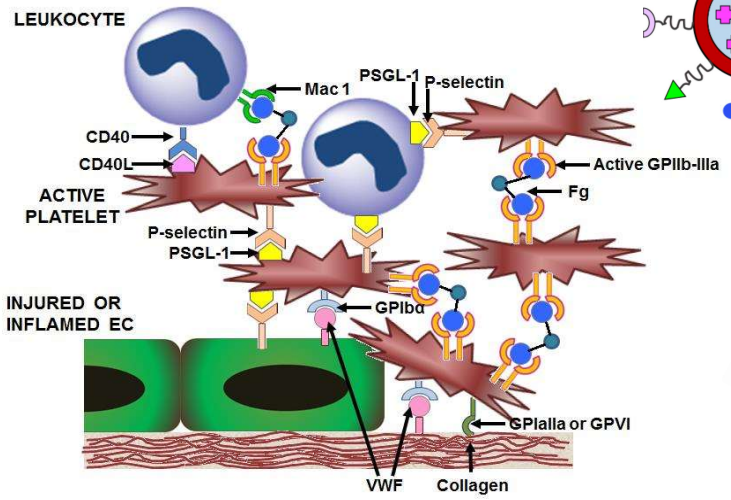
Platelet-inspired Technologies for Biomedical Applications



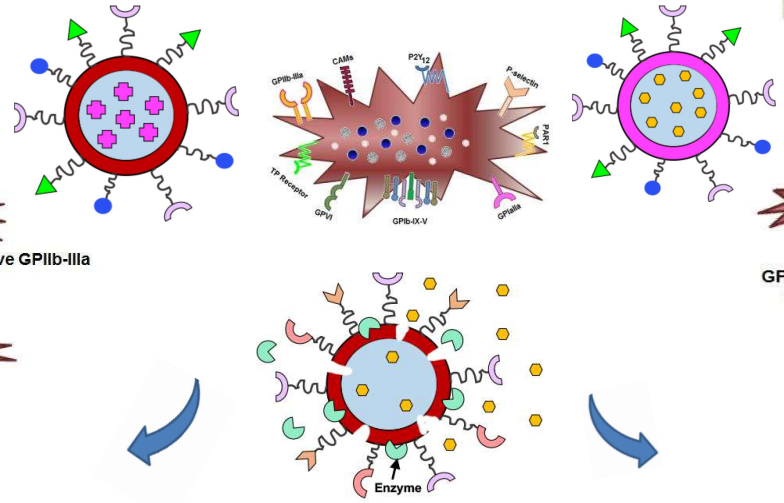
Hemostasis

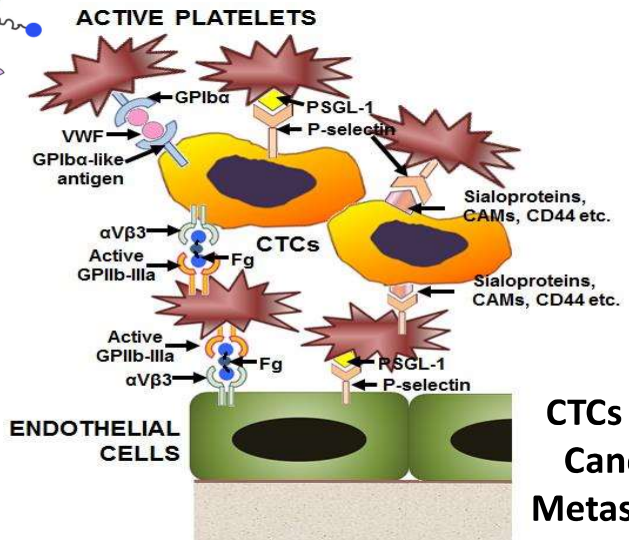


Inflammation and Immune Response



Thrombosis

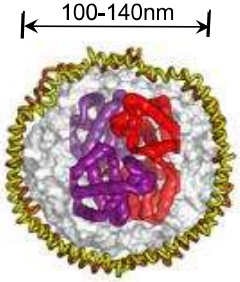




CTCs and Cancer Metastasis

Future: Biosynthetic Mix & Match to Optimize Resuscitation?

Erythromer (RBC mimic)

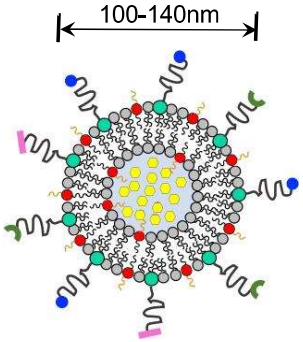


KaloCyte

UNIVERSITY OF MARYLAND 18 56

CBOTH

SynthoPlate and variants (Platelet mimic)



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CASE WESTERN RESERVE UNIVERSITY

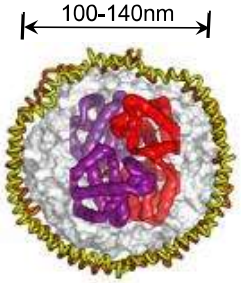
Donor Blood Products

WB RBC FFP aPLT FDP

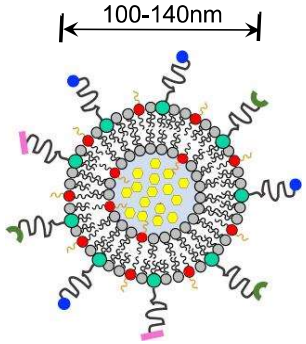
Other Hemostatic Agents (Factors, Drugs)

Biosynthetically Optimized Resuscitative Analogue for TIC

RBC mimic



Platelet mimic



Donor Blood Products

Other Hemostatic Agents (Factors, Drugs)

VERY NICE !!

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Collaborators


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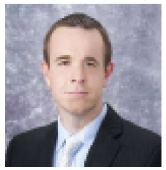
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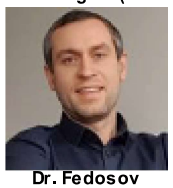
Dr. Sundd (UPMC)


Dr. Neeves (UColorado)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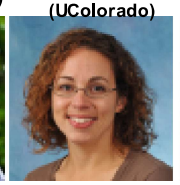
Dr. Smith (UMich)


Dr. Bergmeier (UNC)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BIO-INSPIRED ENGINEERING for ADVANCED THERAPIES

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