Received: 26 April 2024 | Accepted: 26 April 2024

https://doi.org/10.1016/j.rpth.2024.102432

CONFERENCE CAPSULES

# Illustrated State-of-the-Art Capsules of the ISTH 2024 Congress

Chris Ward[1] | Nicola Curry[2] | Magdy El-Ekiaby[3] | Kerstin Jurk[4] | Henri H. Versteeg[5] | Charithani Keragala[6,7] | Tal Burstyn-Cohen[8] | Silvio Antoniak[9] | Yuko Suzuki[10] | Ross I. Baker[11] | Olivier Christophe[12] | Shoshana Revel-Vilk[13,14] | Alice Hart[15] | Carsten Deppermann[16] | Huyen Tran[17] | Nicola Pozzi[18] | Walter H. A. Kahr[19] | Steven P. Grover[20] | Philip Wenzel[21] | Ashley C. Brown[22] | Cécile Oury[23] | Susan M. Shea[24] | James Fredenburgh[25] | Freda H. Passam[26] | James Winearls[27] | Hunter B. Moore[28] | Soumitra Tole[29] | Eileen Merriman[30] | Geoffrey D. Barnes[31] | Z. Leonardo Liu[32] | Michelle Sholzberg[33]

[1]Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia

[2]Oxford University and Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

[3]Shabrawishi Hospital Hematology Unit, Cairo, Egypt

[4]Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany

[5]Leiden University Medical Center, Leiden, the Netherlands

[6]Australian Centre for Blood Diseases, the Central Clinical School, Monash University, Melbourne, Victoria, Australia

[7]Department of Haematology, Monash Health, Clayton, Victoria, Australia

[8]Institute for Biomedical and Oral Research (IBoR), The Hebrew University of Jerusalem, Jerusalem, Israel

[9]UNC Blood Research Center, Department of Pathology and Laboratory Medicine, UNC Lineberger Comprehensive Cancer Center, UNC McAllister Heart Institute, UNC School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[10]Medical Physiology, Hamamatsu University School of Medicine, Hamamatsu, Japan

[11]Perth Blood Institute, Murdoch University, Perth, Western Australia, Australia

[12]Université Paris-Saclay, INSERM, Hémostase Inflammation Thrombose (HITh U1176), Le Kremlin-Bicêtre, France

[13]Pediatric Hematology/Oncology, Shaare Zedek Medical Center, Jerusalem, Israel

[14]School of Medicine, Hebrew University, Jerusalem, Israel

[15]Imperial College London, Imperial College Healthcare NHS Trust, London, United Kingdom

[16]Center for Thrombosis and Hemostasis, University Medical Center Mainz, Mainz, Germany

[17]The Alfred Hospital, Australian Centre for Blood Diseases, Monash University, Melbourne, Victoria, Australia

[18]Saint Louis University, St. Louis, Missouri, USA

[19]Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[20]UNC Blood Research Center, Division of Hematology, Department of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[21]University Medical Center Mainz, Mainz, Germany

[22]Joint Department of Biomedical Engineering at North Carolina State University and the University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

[23]GIGA Research Institute, University of Liège, Liège, Belgium

[24]Trauma and Transfusion Medicine Research Center, Department of Surgery and Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[25]McMaster University, Hamilton, Ontario, Canada

[26]University of Sydney, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia

[27]Gold Coast University Hospital, St Andrews War Memorial Hospital, Monash University, University of Queensland, Brisbane, Queensland, Australia

[28]AdventHealth Transplant Institution at Porter, Denver, Colorado, USA

[29]Children's Hospital, London Health Sciences Center, Western University, London, United Kingdom

[30]North Shore Hospital, Auckland, New Zealand

[31]Frankel Cardiovascular Center, University of Michigan, Ann Arbor, Michigan, USA

[32]Florida State University, Tallahassee, Florida, USA

[33]St Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada

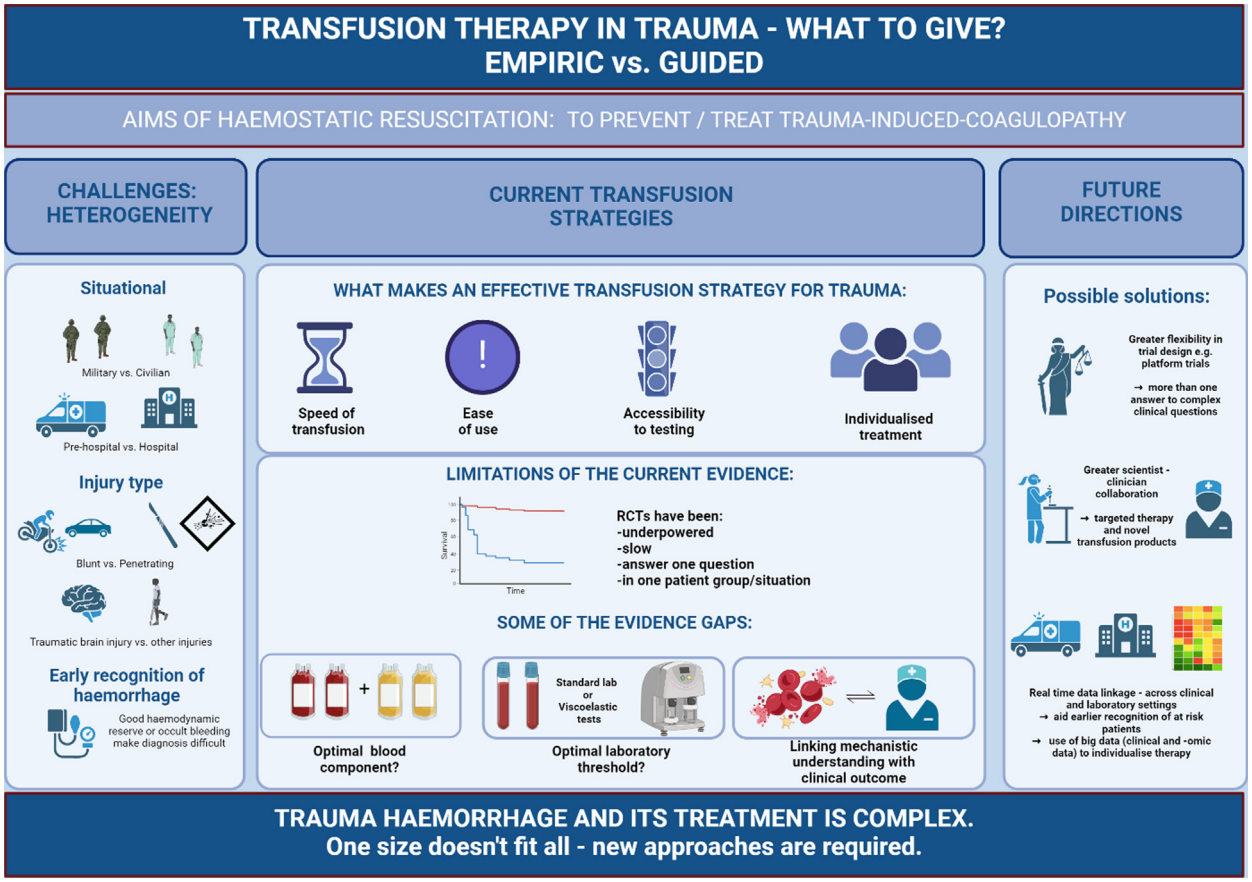
**Handling Editor:** Dr Michael Makris

## Abstract

Here, we present a series of illustrated capsules from the State of the Art (SOA) speakers at the 2024 International Society on Thrombosis and Haemostasis Congress in Bangkok, Thailand. This year's Congress marks the first time that the International Society on Thrombosis and Haemostasis has held its flagship scientific meeting in Southeast Asia and is the first to be organized by an international Planning Committee. The Bangkok program will feature innovative science and clinical updates from around the world, reflecting the diversity and multidisciplinary growth of our field. In these illustrated SOA capsules, you will find an exploration of novel models of thrombosis and bleeding and biomaterial discoveries that can trigger or block coagulation. Thromboinflammation is now understood to drive many disease states, and the SOA speakers cover cellular and coagulation responses to COVID-19 and other infections. The theme of crosstalk between coagulation and inflammation expands with capsules on protein S signaling, complement, and fibrinolytic inhibitors. Novel agents for hemophilia and thrombosis prevention are introduced. Challenging clinical conditions are also covered, such as inherited platelet disorders and antiphospholipid antibody syndrome. The scientific program in Bangkok will also showcase the work of clinicians and scientists from all parts of the world and chronicle real-world challenges. For example, 2 SOA capsules address the diagnosis and management of von Willebrand disease in low-income settings. Take some time to browse through these short illustrated reviews; we're sure that you'll be entertained, educated, and inspired to further explore the world of thrombosis and hemostasis.

# TRANSFUSION THERAPY IN TRAUMA—WHAT TO GIVE? EMPIRIC VS GUIDED

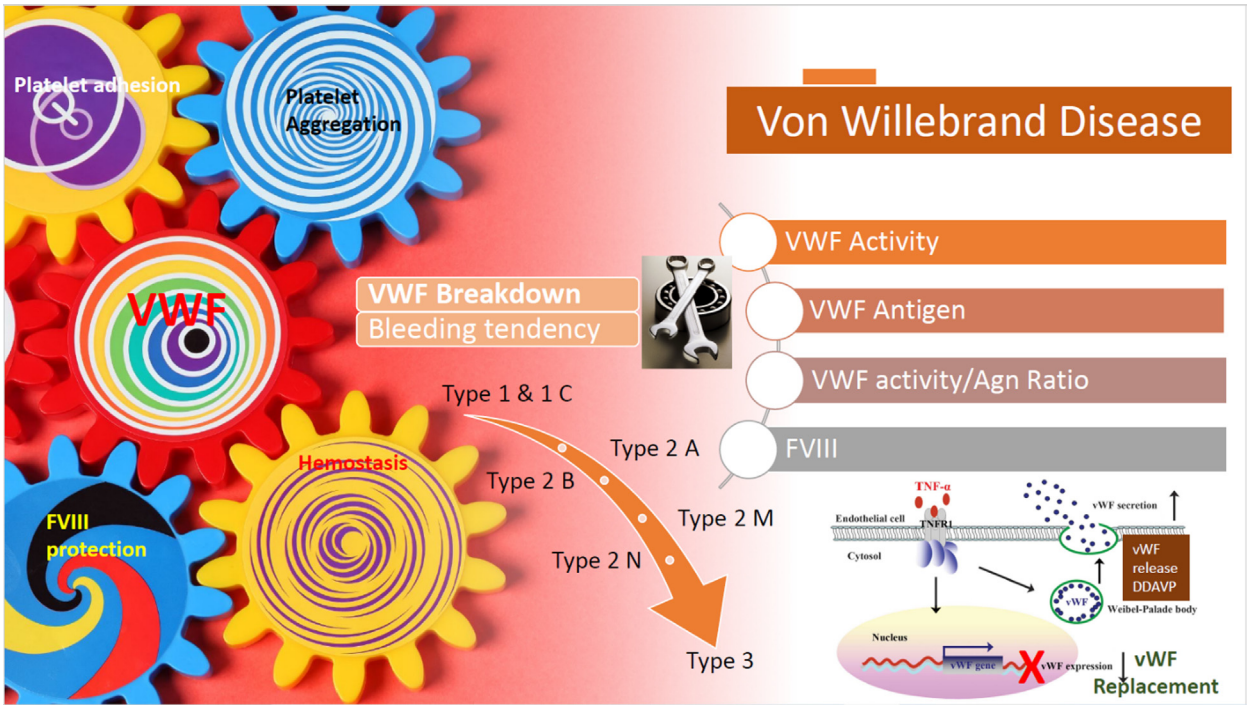
Nicola Curry




Uncontrolled bleeding is the commonest preventable cause of death after traumatic injury [1]. Hemostatic resuscitation forms the basis of transfusion protocols and involves resuscitation with blood components, aiming to treat and/or prevent trauma-induced coagulopathy [2]. Strategies to optimize hemostatic resuscitation include empiric, ratio-based blood component therapy, commonly with red blood cells and fresh frozen plasma in a ratio of 1:1, or guided therapy, using laboratory or viscoelastic hemostatic test results. There are benefits, and limitations, to each of these 2 transfusion strategies, and neither approach has yet been shown to improve outcomes across all patient groups [3]. Questions remain, and future directions for improving transfusion therapy are likely to require novel approaches that have the flexibility to evaluate heterogeneous trauma cohorts. Such approaches may include platform trials, which can also maximize real-time linkage of clinical and laboratory data to both predict patients at greatest risk of bleeding and to direct and individualize transfusion therapies. RCT, randomized controlled trial.

## CHALLENGES WITH VWD MANAGEMENT IN LOWER-INCOME SETTINGS

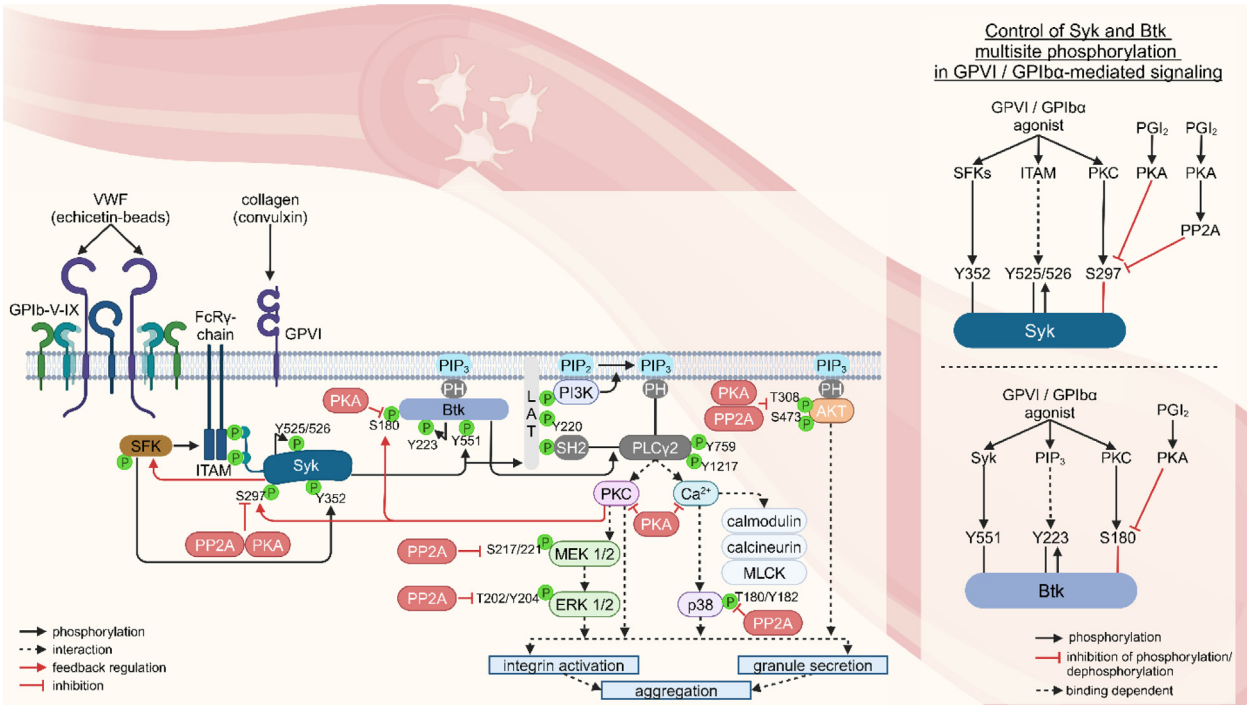
Magdy El-Ekiaby




Von Willebrand factor (VWF) function includes platelet adhesion, platelet agglutination, and factor (F)VIII protection with half-life extension. Quantitative and qualitative defects of VWF lead to different von Willebrand disease (VWD) types and subtypes. Management of VWD includes use of desmopressin (DDAVP) or VWF replacement, largely dependent on VWD type and subtype. Agn, antigen.

# INTERACTIONS OF PLATELET PROTEIN KINASE SIGNALING IN RESPONSE TO ITAM-LINKED RECEPTORS

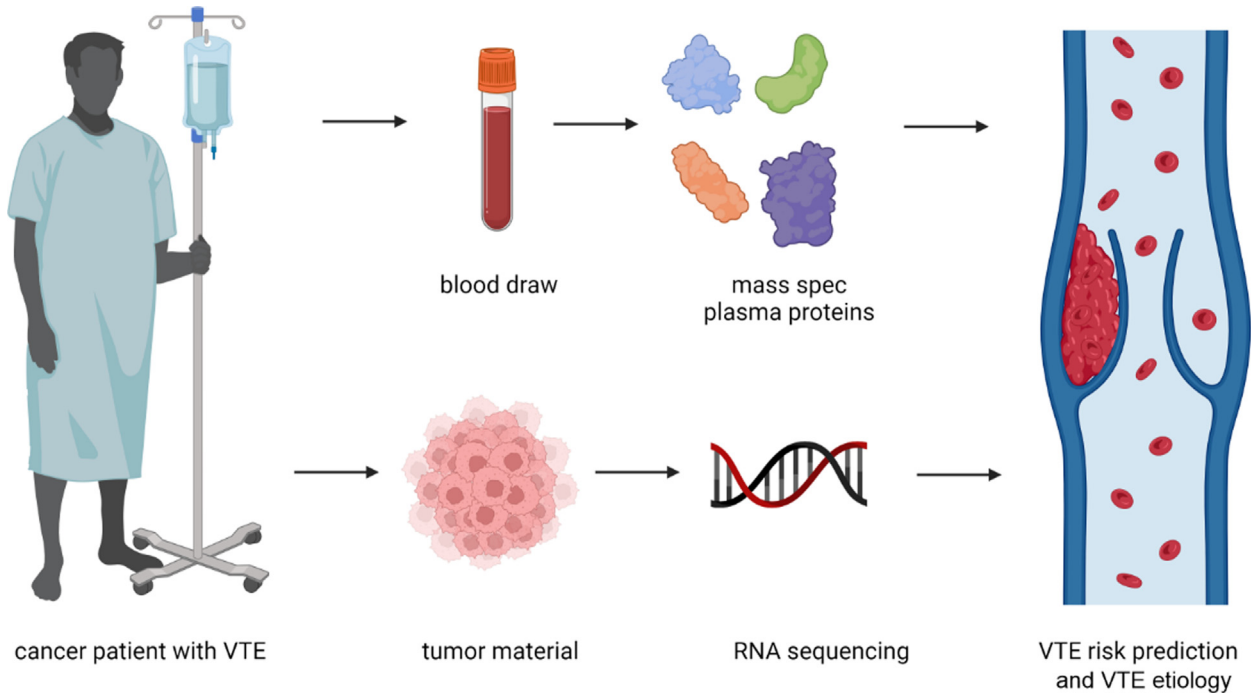
Kerstin Jurk




The immunoreceptor tyrosine-based activation motif (ITAM)–linked receptors glycoprotein (GP) VI and GPIbα (GPIb-V-IX) initiate crucial platelet activation responses. GPVI (eg, collagen and convulxin) and GPIbα (eg, von Willebrand factor [VWF] and echicetin beads) induce tyrosine (Y) phosphorylation/activation of Src family kinases (SFK), ITAM of the Fc-receptor (FcR) γ chain, spleen tyrosine kinase (Syk), Bruton's tyrosine kinase (Btk), linker adaptor for T cells (LAT) with SH domain–dependent recruitment of phospholipase (PL) Cγ2, and then protein kinase C (PKC)–dependent serine (S)/threonine (T) phosphorylation/activation of mitogen-activated protein kinase (MEK) 1/2, extracellular signal-regulated kinase (ERK)1/2 and PKC-independent p38, myosin light chain kinase (MLCK, $Ca^{2+}$-dependent), and protein kinase B (Akt, delayed). Phosphoinositide 3-kinase (PI3K) converses phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate (PIP3), which recruits Btk, PLCγ2, and Akt via their pleckstrin homology (PH) domains. Syk and Btk activation/activity is controlled by multisite phosphorylation. SFK-dependent phosphorylation of Syk Y352 and Syk recruitment to ITAM combined with Y525/526 autophosphorylation results in full Syk activation. SFK/Syk-mediated phosphorylation of Btk Y551 together with Btk recruitment to PIP3 and Y223 autophosphorylation permits full Btk activation. PKC induces Syk S297 and Btk S180 phosphorylation, which is important inhibitory feedback, whereas Syk also inhibits SFK Prostaglandin I2 (PGI2)–stimulated protein kinase A (PKA) reduces PKC responses (eg, Syk S297 and Btk S180 phosphorylation). The protein phosphatase (PP) 2A antagonizes Syk S297 but not Btk S180 phosphorylation. Both PKA and protein phosphatase 2A (PP2A) diminish Akt activation, whereas PP2A antagonizes MEK, extracellular signal-regulated kinase (ERK), and p38 activation. SH2, src homology 2. This figure was created with BioRender.com.

## NOVEL INSIGHTS INTO MECHANISMS OF CANCER-ASSOCIATED THROMBOSIS

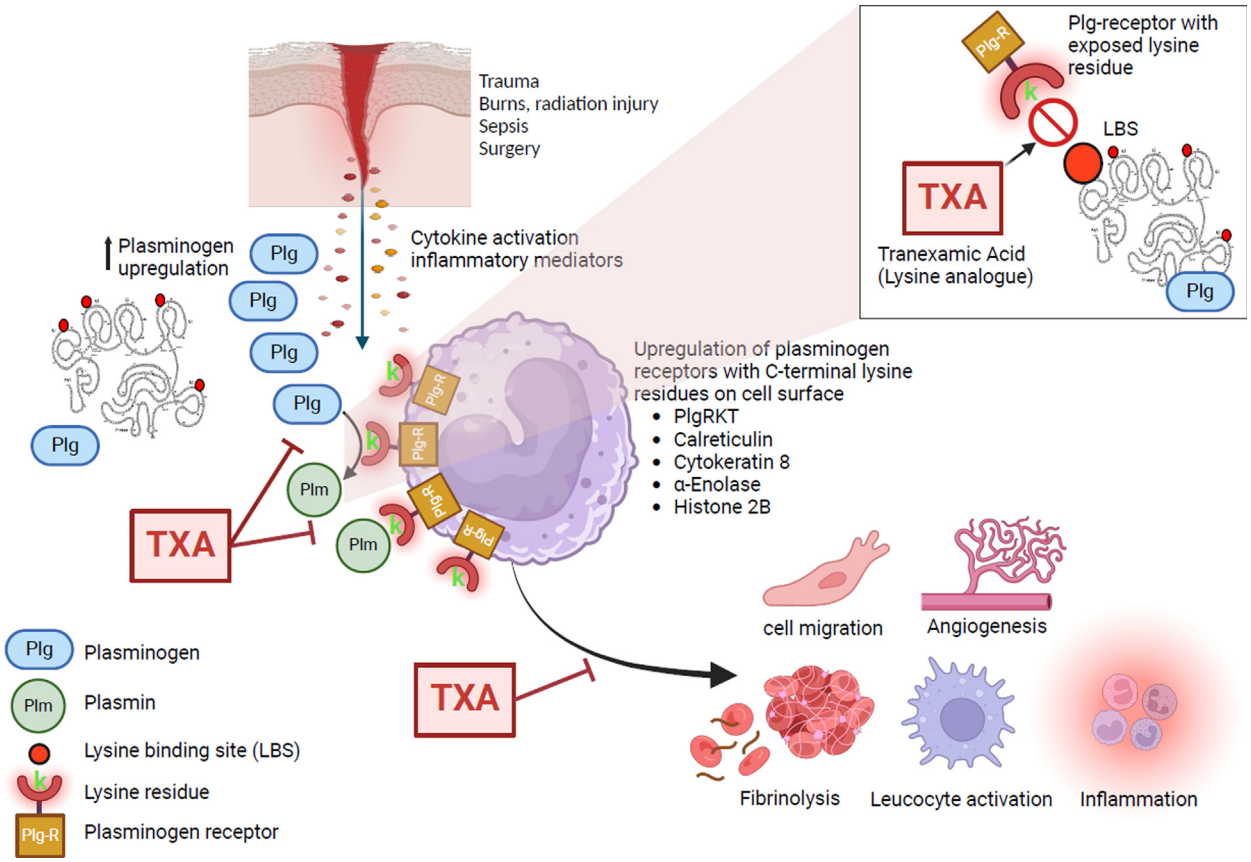
Henri H. Versteeg




Material (blood and/or tumor cells) is collected from cancer patients. Blood-derived plasma can be used to identify plasma proteins associated with venous thromboembolism (VTE), and cancer cells may be interrogated for gene products that are associated with VTE. Finally, estimation models may be made based on these proteins and gene products that predict the risk of VTE in a cancer patient. spec, spectrometry.

## TXA AS A MODULATOR OF INFLAMMATION

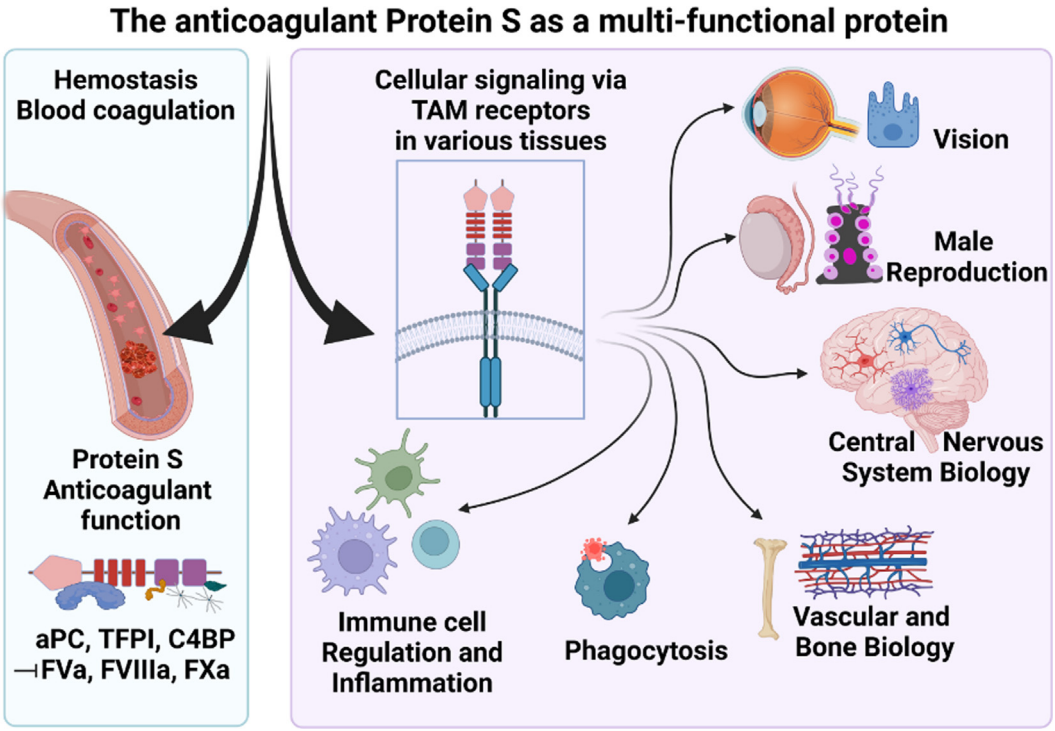
Charithani Keragala




Injury results in the release of cytokines and inflammatory mediators including elements of the plasminogen-activating system. Plasminogen and plasmin can attach to cell surfaces via plasminogen receptors mediating inflammatory and immune effects including leucocyte activation, migration, inflammation, angiogenesis, and of course fibrinolysis. Many of these cell surface plasminogen receptors engage the lysine-binding sites of plasminogen and plasmin via a C-terminal lysine. Tranexamic acid (TXA), a lysine analog, can prevent this lysine interaction with potential modulation of inflammation and innate immune function as well as inhibiting fibrinolysis.

## PROTEIN S AND TAM SIGNALING IN HEALTH AND DISEASE

Tal Burstyn-Cohen

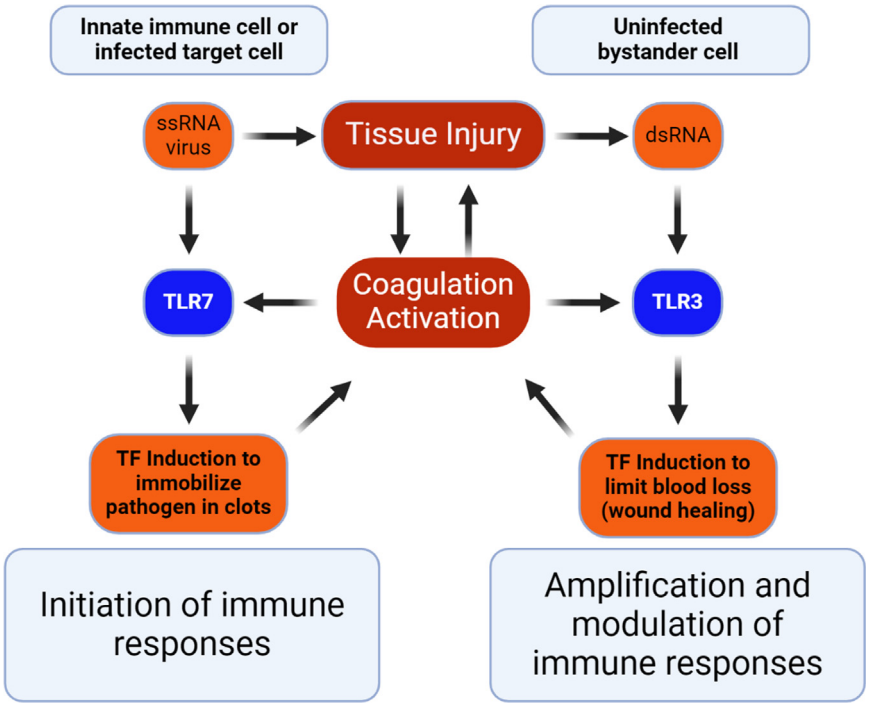



The anticoagulant protein S (PROS1) emerges as a multifunctional protein with key homeostatic roles outside the coagulation cascade. As a potent anticoagulant, PROS1 is a cofactor for activated protein C (aPC), deactivating coagulation factor (F)Va and FVIIIa. PROS1 also directly inactivates FVa, FVIIIa, and FXa. In addition, by binding c4BP and tissue factor pathway inhibitor (TFPI), PROS1 may also regulate these proteins.

As a signaling molecule, PROS1 activates members of the TAM (TYRO3, AXL, and MERTK) receptor tyrosine kinases expressed by many cell types in numerous tissues. In immune cells, PROS1-TAM signaling is anti-inflammatory and promotes phagocytic uptake of apoptotic cells. The development and function of bone, vascular, and neural tissue, as well as phagocytosis by specialized phagocytes, are also regulated by PROS1-TAM signaling. In cancers, PROS1 and TAMs are upregulated, promoting tumor cell aggressiveness. Thus, PROS1 biology has broad implications spanning coagulation and noncoagulation-related systems [4].

## COAGULATION AND PLATELETS IN ANTIVIRAL IMMUNE RESPONSE

Silvio Antoniak



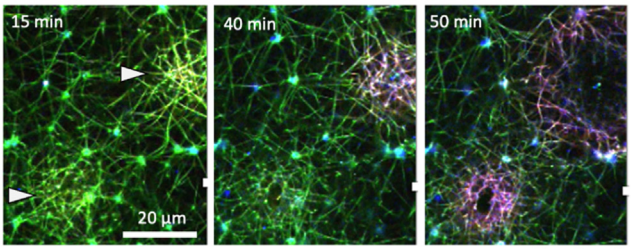

Many pathogenic viruses of public health concern belong to the single-stranded RNA (ssRNA) viruses. The genomes of these viruses are detected by toll-like receptor (TLR) 7. This leads to activation of the immune system and tissue factor (TF) gene induction in infected cells or phagocytic immune cells. Uninfected bystander cells recognize double-stranded RNA (dsRNA), an intermediate of ssRNA virus replication, via TLR3. Together, the increase in TF expression results in activation of the coagulation cascade and platelets. It is thought that the initial TF induction is important to immobilize the pathogen in clots, structurally stabilize the infected tissue, and initiate an effective immune response. Bystander cell–expressed TF is important to further amplify the immune responses, to maintain hemostasis, and to initiate wound-healing processes. Importantly, overactivation of the coagulation cascade and platelets can enhance infection pathology, tissue injury, and thrombosis.

# REAL-TIME IMAGING ANALYSIS OF FIBRINOLYSIS REGULATION

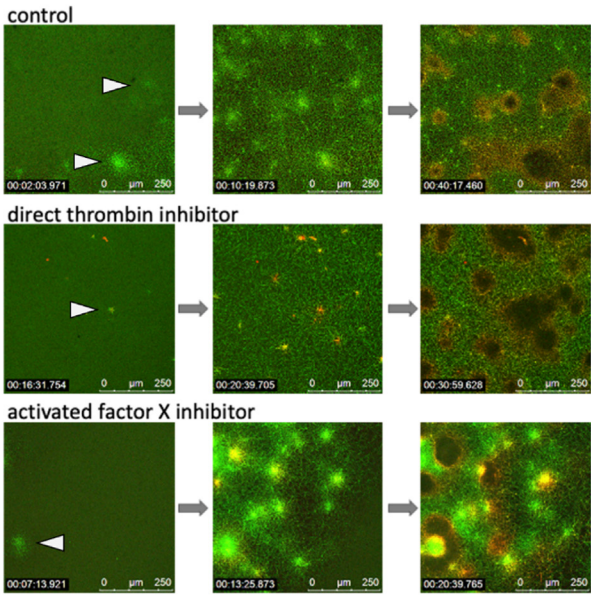
Yuko Suzuki

Spatiotemporal regulation of plasminogen activation and fibrinolysis:

## Real-time imaging analysis of fibrinolysis regulation




fibrin(ogen)
plasmin(ogen)
TAFI (thrombin-activatable fibrinolysis inhibitor)

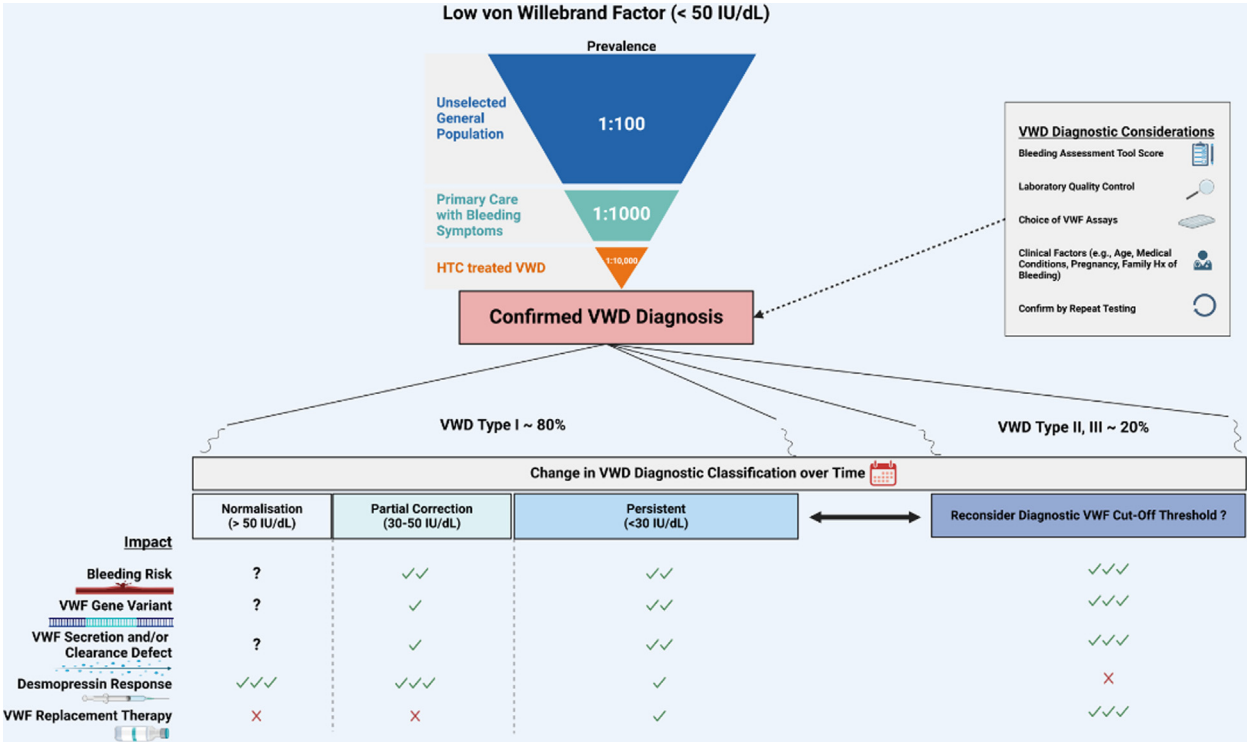



Using human platelet-containing plasma, fibrin clot formation and lysis initiated by tissue factor and tissue-type plasminogen activator were monitored by confocal laser-scanning microscopy.
**Activated platelets** (▻) provided a scaffold for binding coagulation and fibrinolytic factors. Then, they triggered uneven fibrin network formation and the following lysis.

**Upper**: At the lytic edge, accumulation of both plasminogen and TAFI was detected.
**Right**: Direct thrombin inhibitor and activated factor X inhibitor differently modified not only fibrin formation but also plasminogen accumulation and lysis.

# DIAGNOSTIC ASPECTS OF VON WILLEBRAND DISEASE

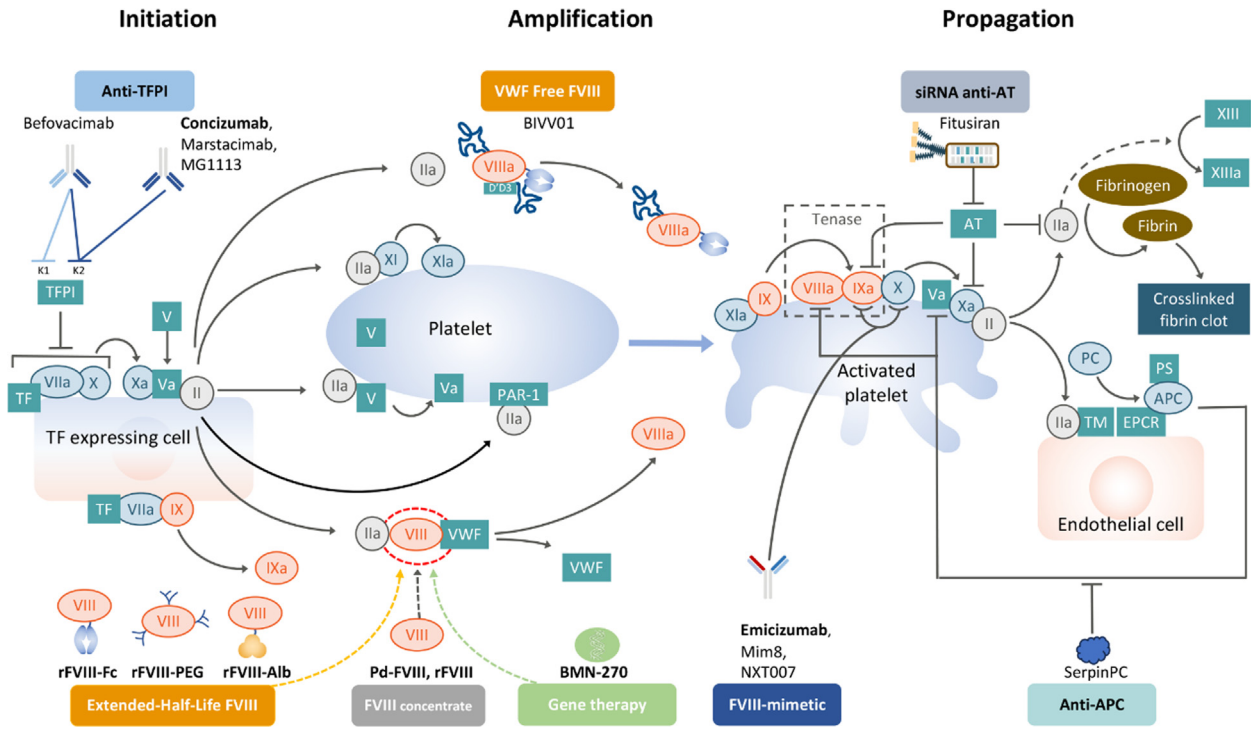
Ross I. Baker




Low von Willebrand factor (VWF; <50 IU/dL) is a frequent finding in the general population, but most do not have a bleeding tendency. Other laboratory and clinical considerations rather than just the VWF level explain the decreasing prevalence of von Willebrand disease (VWD) with increasing expertise [5]. A recent study suggests that type 1 VWD (<30 IU/dL) has distinct subtypes, with around half of the patients either having partial correction (30-50 IU/dL) or normalization (>50 IU/dL) of their VWF level with age over time, while in the other half, there is no change [6]. This finding suggests that low VWF is part of an evolving age-related type 1 VWD phenotype and has important implications for VWD classification, diagnosis, pathogenesis, and treatment. Importantly, regardless of the change in plasma VWF levels, there is no difference in bleeding phenotype, suggesting that there may be another undiscovered process(es) apart from VWF that causes bleeding in these people. HTC, hemophilia treatment center; Hx, history.

## BACKGROUND AND MOA

Olivier Christophe




The mechanism of action of novel treatments for hemophilia A. Bolded are the molecules currently accessible for persons with hemophilia A in certain countries, while those in normal text are undergoing clinical trials.

In recent decades, hemophilia A treatment has advanced significantly, introducing new pharmacologic options. Long-lasting factor (F)VIII products, including von Willebrand factor (VWF)–free FVIII, are now available for replacement therapy via intravenous infusion. Novel non-replacement therapies have also emerged as alternatives, regardless of inhibitors, aiming to restore hemostatic balance by boosting thrombin generation or mimicking FVIII activity. Two main strategies have been explored: inhibiting natural anticoagulants, namely antithrombin (AT), activated protein C (APC), and tissue factor pathway inhibitor (TFPI), and introducing bispecific antibodies. These drugs, with innovative mechanisms and subcutaneous delivery, offer effective bleeding protection, improved adherence, and enhanced quality of life for persons with hemophilia. Liver-directed gene therapy for FVIII is promising, with recent regulatory approvals in some countries opening avenues for its exploration in inhibitor patients.

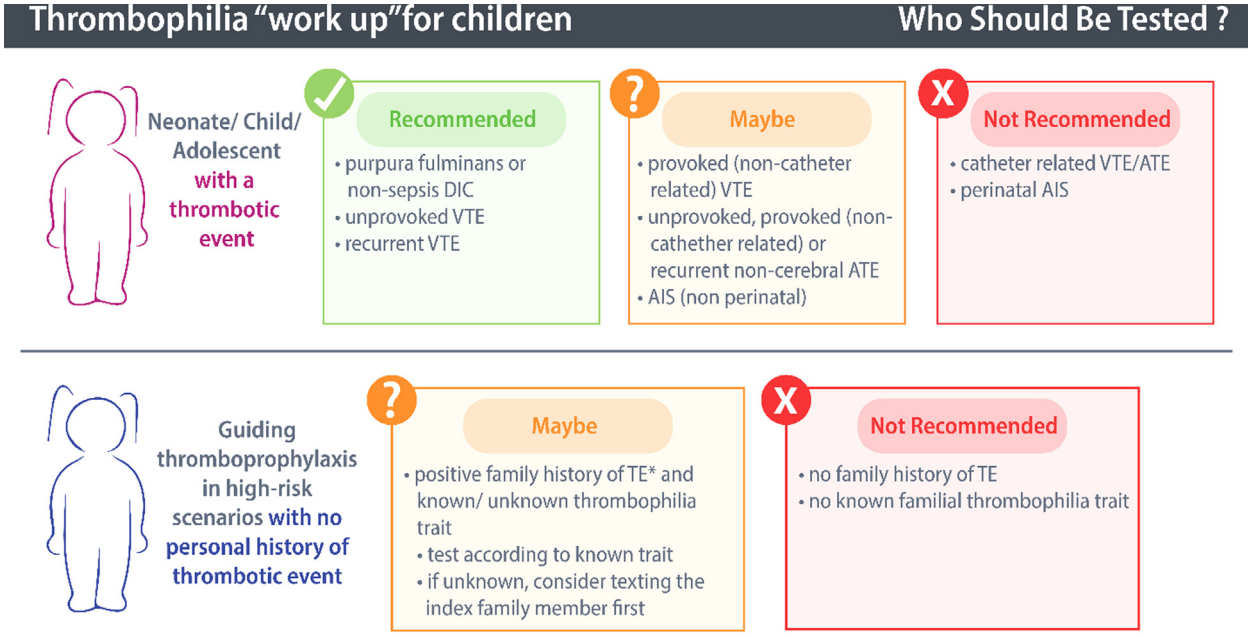
EPCR, endothelial cell protein C receptor; K1, Kringle-1 domain of tissue factor pathway inhibitor; K2, Kringle-2 domain of tissue factor pathway inhibitor; PAR-1, protease-activated receptor 1; PC, protein C; rFVIII, recombinant factor VIII; siRNA, small interfering RNA; TF, tissue factor, TM, thrombomodulin.

⟞ Inhibition.

⟶ Activation.

## DEBATE 1: APPROACH TO THROMBOPHILIA TESTING: FROM NEONATE TO YOUNG ADULT (WESTERN PERSPECTIVE)

**Shoshana Revel-Vilk**

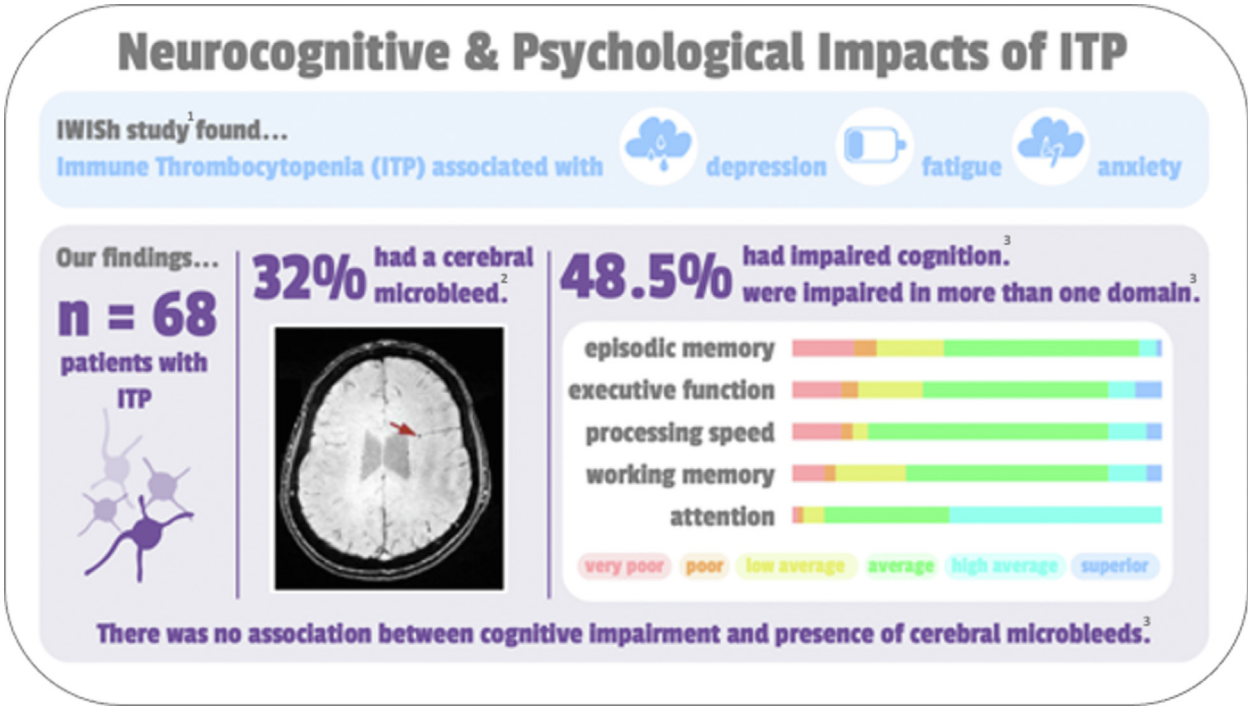



AIS, acute ischemic stroke; ATE, arterial thrombotic events; DIC, disseminated intravascular coagulation; TE, thrombotic event; VTE, venous thrombotic event
* VTE at any age, cardiovascular events at a younger adult age, e.g., <40 years, recurrent miscarriage

Exploring the presence of an underlying hypercoagulable state, often termed a "thrombophilia work-up," may be included in the laboratory assessments for a child experiencing thrombosis. A number of inherited and acquired thrombophilias have been identified; however, the interpretation of thrombophilia test results in individual clinical scenarios may be difficult. The reported prevalence of laboratory thrombophilic risk factors in children with thrombosis varies and mainly reflects differences in study design and the clinical and demographic characteristics of the study populations. The intricate interplay of factors leading to thrombotic events across varied age groups, from neonates to adolescents, complicates the establishment of uniform guidelines for thrombophilia screening. Consequently, the decision to pursue diagnostic testing for thrombophilia in children necessitates a tailored approach, considering the unique aspects of each case. The provided figure outlines specific scenarios where thrombophilia testing is advised, alongside instances where it may not be necessary.

## NEUROCOGNITIVE AND PSYCHOLOGICAL IMPACTS IN ITP PATIENTS

Alice Hart

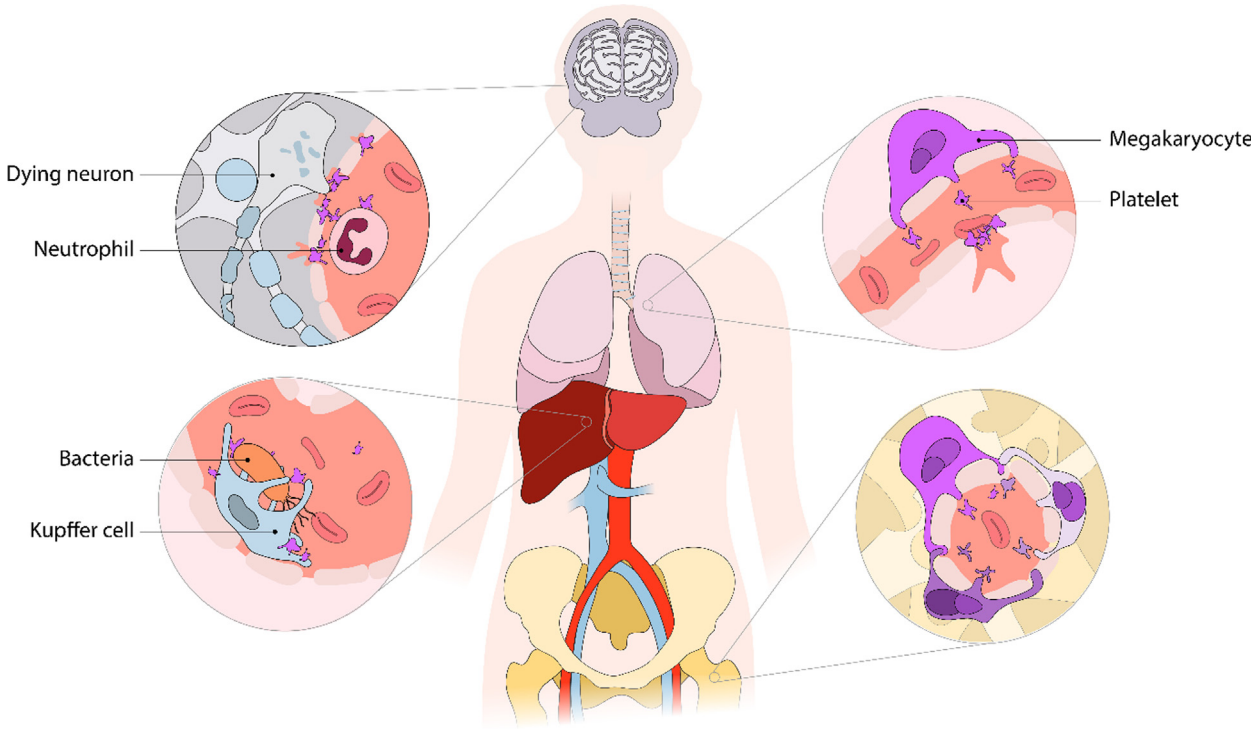



*iWISh*, immune thrombocytopenia World Impact Survey.

We carried out cerebral magnetic resonance imaging and cognitive testing on 68 adults with immune thrombocytopenia (ITP): 32% had a cerebral microbleed, and 48.5% had impaired cognition in 1 or more cognitive domains. There was no statistically significant association between the 2 findings in this cohort. Further study is needed to understand cognitive function in patients with ITP. For references, see Cooper et al. [7], Cooper et al. [8], and Vladescu et al. [9].

## SYSTEMS INTERACTIONS OF HEMOSTASIS

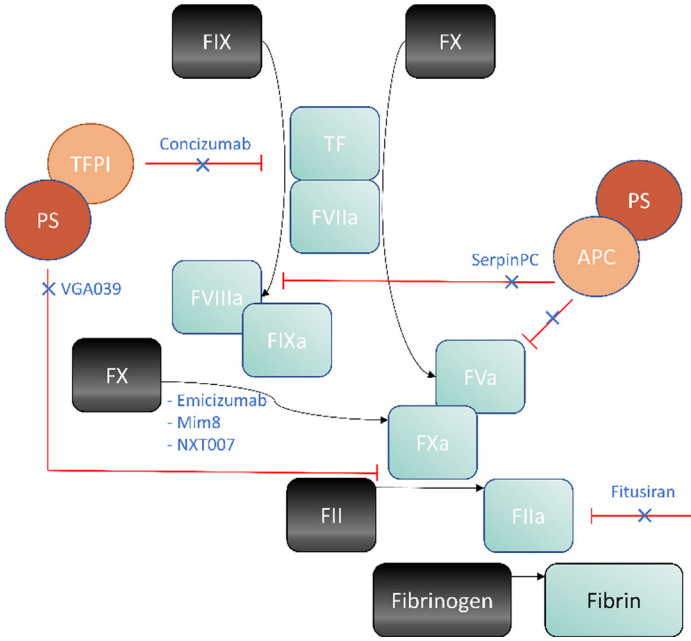
Carsten Deppermann




From platelet production to clearance and from thromboinflammation to maintaining vascular integrity during inflammation, the platelet lifecycle and platelet immune functions span across many different organs. Top left: during thromboinflammation following cerebral ischemia, platelets adhere to the damaged endothelium, become activated, and release their granules. Recruited neutrophils interact with platelets, leading to reciprocal activation. Immune cell infiltration to the brain parenchyma causes further inflammation, release of reactive oxygen species and cytokines, and neuronal cell death. Top right: a specific subpopulation of inflammatory megakaryocytes resides in the lung. Platelets help maintain vascular integrity in the lung during inflammation. Bottom right: the bone marrow is home to the largest, most important population of megakaryocytes generating large quantities of platelets. Specific subpopulations have recently been identified. Bottom left: in the liver, platelets help Kupffer cells eradicate bacteria from the bloodstream. Kupffer cells also clear aged, desialylated platelets at the end of their lifespan.

## CLINICAL EVIDENCE IN ADULTS

### Huyen Tran

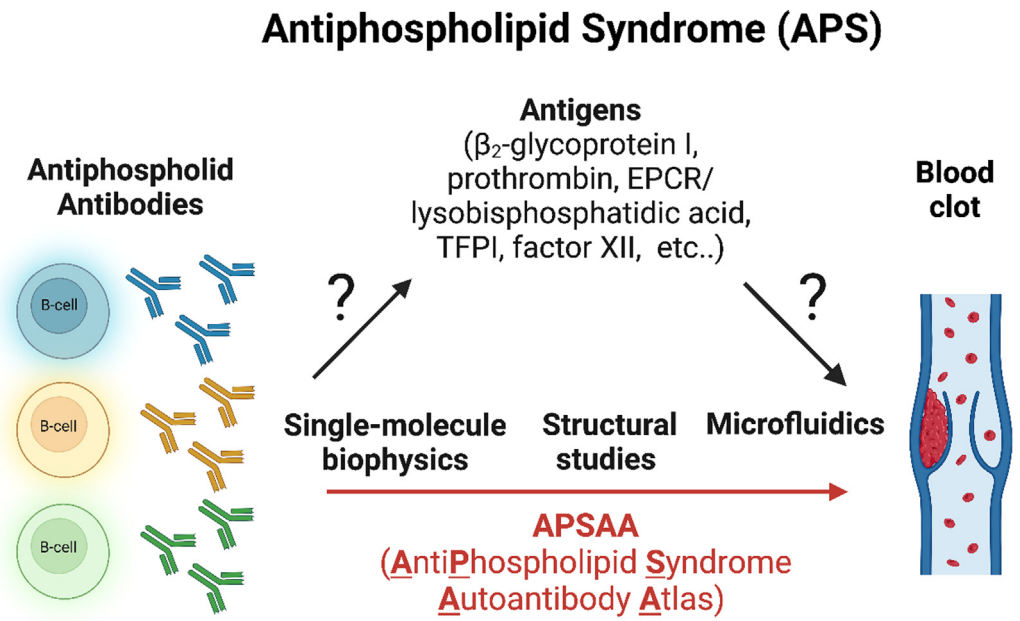



| Mode of action/class | Molecule | Intended Use | Frequent of subcutaneous administration | Clinical development status |
|---|---|---|---|---|
| Factor VIII mimetic | Emicizumab | Haemophilia A with or without FVIII inhibitors | QW, Q2W, Q4W | Approved by many jurisdictions |
| | Mim8 | | QW, Q4W | Phase 3 |
| | NXT007 | | TBD | Phase 2 |
| siRNA knockdown of anti-thrombin | Fitusiran | Haemophilia A or B, with or without inhibitors | Monthly | Phase 3 completed |
| Monoclonal antibody against TFPI | Concizumab | Haemophilia A or B, with or without inhibitors | Daily | Phase 3 completed |
| | Marsticamab | | QW | Phase 3 completed |
| Serine protease inhibitors of APC | SerpinPC | Haemophilia A or B, with or without inhibitors | Q2W | Phase 2 |
| Monoclonal antibody against PS | VGA039 | Haemophilia A or B, with or without inhibitors | TBD | Phase 1 |

Novel targeted therapeutics for hemophilia in varying phases of development. (A) Substitution therapies for factor (F)VIII (emicizumab, Mim8, and NXT007) that restore FXa generation via FIX and FX activation; (B) nonfactor rebalancing therapies that either knock down (small interfering RNA [siRNA] to antithrombin [AT]) or interfere with the function (monoclonal antibodies against activated protein C [APC] or protein S [PS]) of natural anticoagulants to restore hemostasis. QW, once weekly; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TBD, to be established; TF, tissue factor; TPFI, tissue factor pathway inhibitor. *May be adjusted to second monthly (in some).

## BIOPHYSICAL APPROACHES IN UNDERSTANDING THE ANTIPHOSPHOLIPID SYNDROME

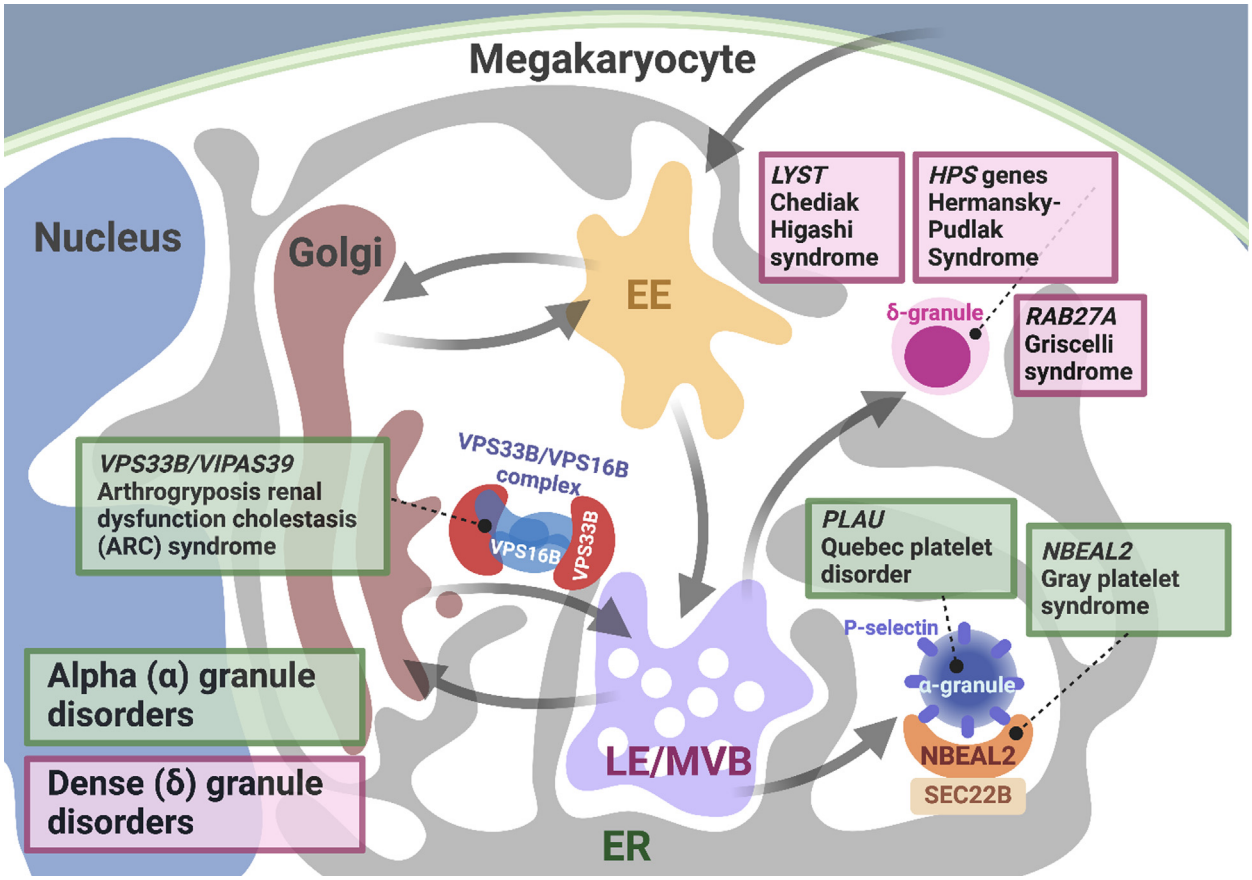
Nicola Pozzi




Antiphospholipid syndrome (APS) is a complex thrombotic disorder characterized by the persistent presence of antiphospholipid antibodies. Several targets of antiphospholipid antibodies have been discovered over the years. Yet how antiphospholipid antibodies interact with their targets to cause thrombosis remains poorly defined. Novel biophysical approaches like those recently utilized to study anti–$\beta_2$-glycoprotein I antibodies [10] and antiprothrombin antibodies [11] are proving extremely useful in filling this knowledge gap. It is anticipated that these new approaches will drive the creation of an Antiphospholipid Syndrome Autoantibody Atlas (APSAA) in which each antiphospholipid antibody is classified according to its biochemical, structural, and functional profile *in vitro* and *ex vivo* in human blood. Creating such an atlas holds great value for basic researchers interested in unraveling the complexity underlying autoimmune responses in APS. It may also provide exciting new opportunities to identify, risk-stratify, and treat APS patients in a more personalized way. EPCR, endothelial cell protein C receptor; TPFI, tissue factor pathway inhibitor.

## INHERITED PLATELET GRANULE DISORDERS—LESSONS FROM PATIENTS

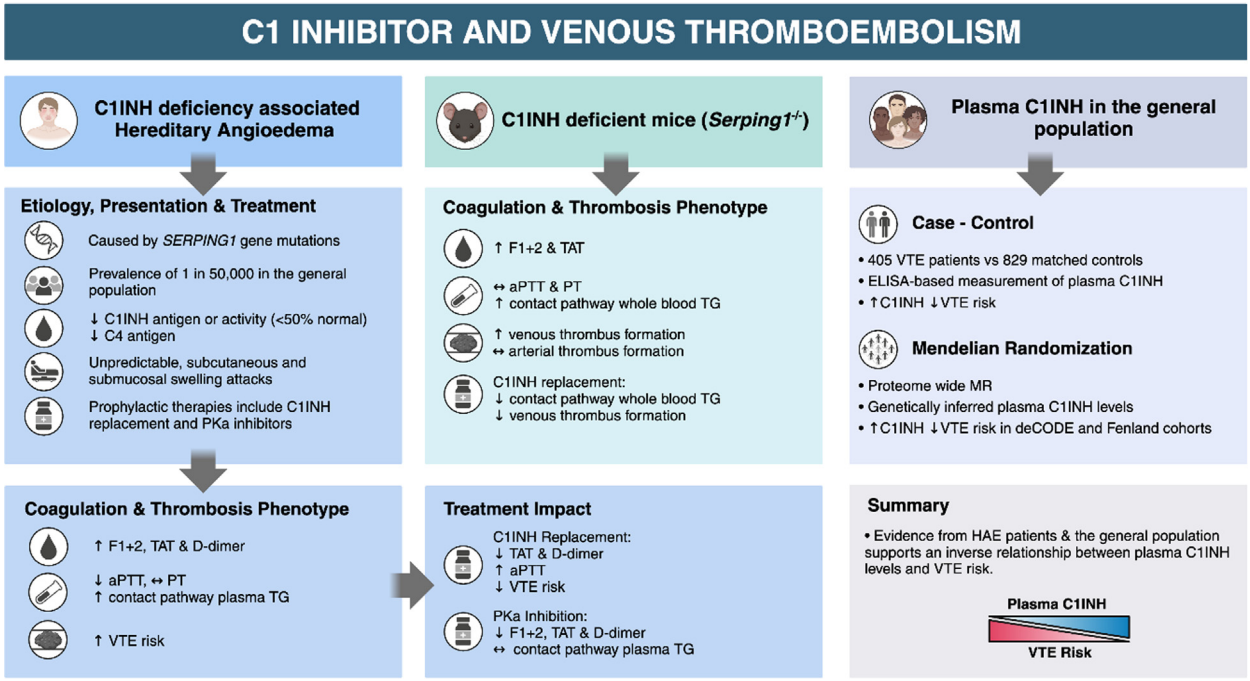
Walter H. A. Kahr




Cellular interactions of megakaryocyte proteins linked to alpha (α, green) or dense (delta, δ, violet) granule formation discovered from studies of inherited platelet disorders. Studies of arthrogryposis-renal dysfunction-cholestasis (ARC) syndrome patients led to the discovery that early α-granule biogenesis requires a bivalent complex containing the Sec1/Munc18 protein VPS33B and VPS16B (VIPAS39) [12], which are thought to act at interfaces involving Golgi, early endosomes (EE) and late endosomes/multivesicular bodies (LE/MVB). Studies of Gray platelet syndrome revealed a key role for NBEAL2 in stabilizing α-granules/precursors via interaction with proteins, including granule surface P-selectin and the endoplasmic reticulum (ER) protein SEC22B [13]. Quebec platelet disorder is caused by the abnormal platelet expression of urokinase (PLAU). Studies of diverse syndromic disorders revealed proteins required for dense granule production, including LYST (Chediak–Higashi syndrome), RAB27A (Griscelli syndrome), and several proteins (AP3B1, AP3D1, BLOC1S3, BLOC1S5, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, and HPS6) acting in complexes associated with Hermansky–Pudlak syndrome [14]. Created with BioRender.com.

## NEW INSIGHTS INTO THE ROLE OF C1 INHIBITOR

Steven P. Grover

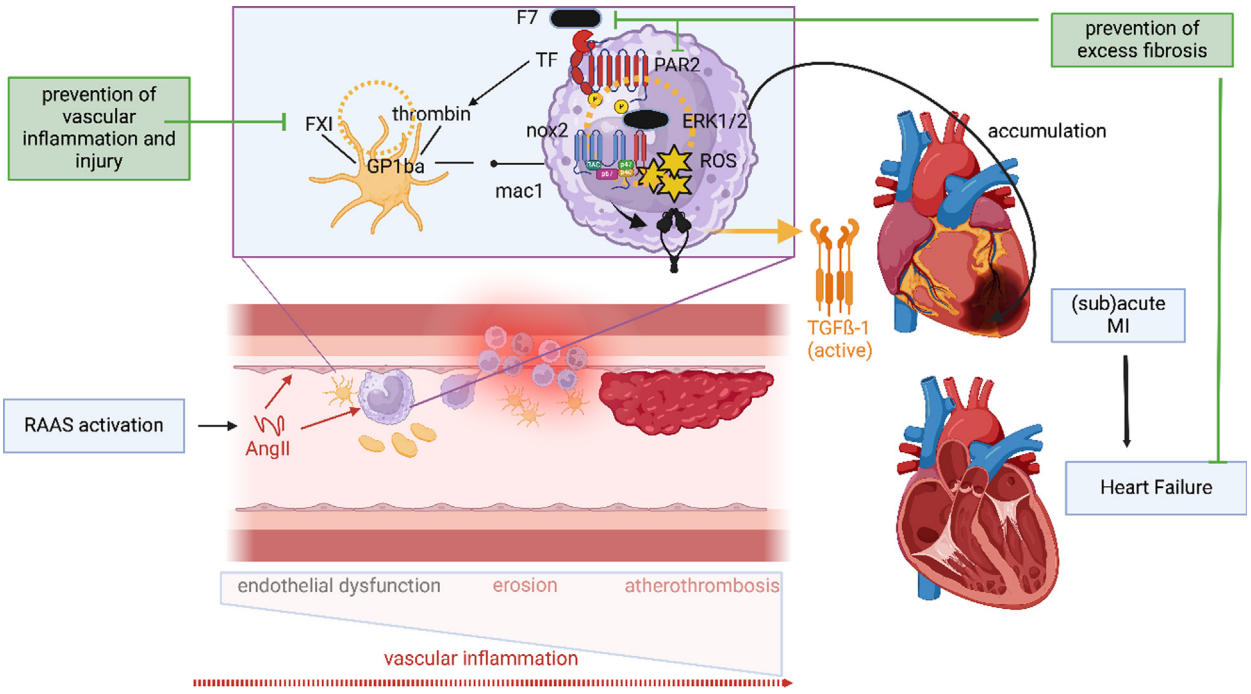



Abbreviations: aPTT, activated partial thromboplastin time; C1INH, C1 inhibitor; F1+2, prothrombin fragment 1+2; HAE, Hereditary Angioedema; MR, Mendelian Randomization; PKa, plasma kallikrein; PT, prothrombin time; TAT, thrombin-antithrombin complexes; TG, thrombin generation; VTE, venous thromboembolism

C1 inhibitor (C1INH) is a multifunctional serine protease inhibitor that functions as the major endogenous negative regulator of components of the complement, coagulation, and kallikrein-kinin systems. Congenital C1INH deficiency results in a rare swelling disorder called hereditary angioedema (HAE). A growing body of literature indicates that HAE is also associated with a procoagulant state and an increased risk of venous thromboembolism (VTE) [15]. Clinical studies have shown that C1INH replacement therapy can ameliorate the procoagulant phenotype associated with HAE. Recent studies with C1INH deficient mice have demonstrated that loss of C1INH is sufficient to enhance activation of coagulation and venous thrombosis [16]. The relevance of C1INH extends beyond HAE into the general population. Individuals in the general population with high plasma levels of C1INH have a reduced risk of VTE [17]. Taken together, these studies indicate that endogenous plasma C1INH plays an important role in limiting venous thrombosis. ELISA, enzyme-linked immunosorbent assay. Image created with BioRender.com.

# NOVEL CONCEPTS IN ATHEROTHROMBOSIS: FROM PLAQUE EROSION TO MYELOID CELL REPROGRAMMING

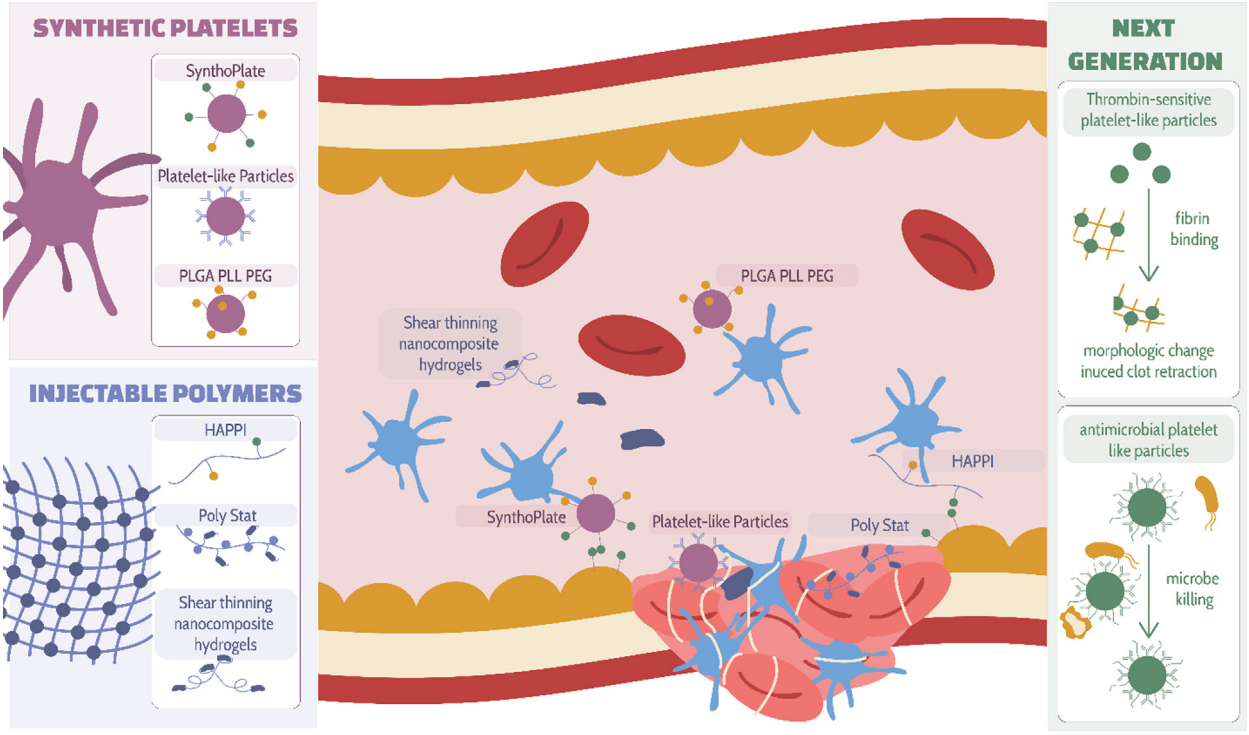
Philip Wenzel




Novel concepts in atherothrombosis: from plaque erosion to myeloid cell reprogramming. RAAS activation is key for understanding the conundrum of atherothrombosis. Prevention of factor (F)XI–thrombin amplification [18] as well as blocking TF/FVII/PAR2-dependent activation of ERK/nox2 complex to attenuate TGFß-1 activation [19] are showcase examples to induce myeloid cell reprogramming (green boxes). These approaches may help to tackle vascular inflammation, endothelial erosion, and excess cardiac fibrosis to avert development of heart failure, the end stage of cardiovascular disease. GP, glycoprotein; MI, myocardial infarction; PAR2, protease-activated receptor 2; TF, tissue factor.

## BIOMATERIALS FOR HEMOSTASIS

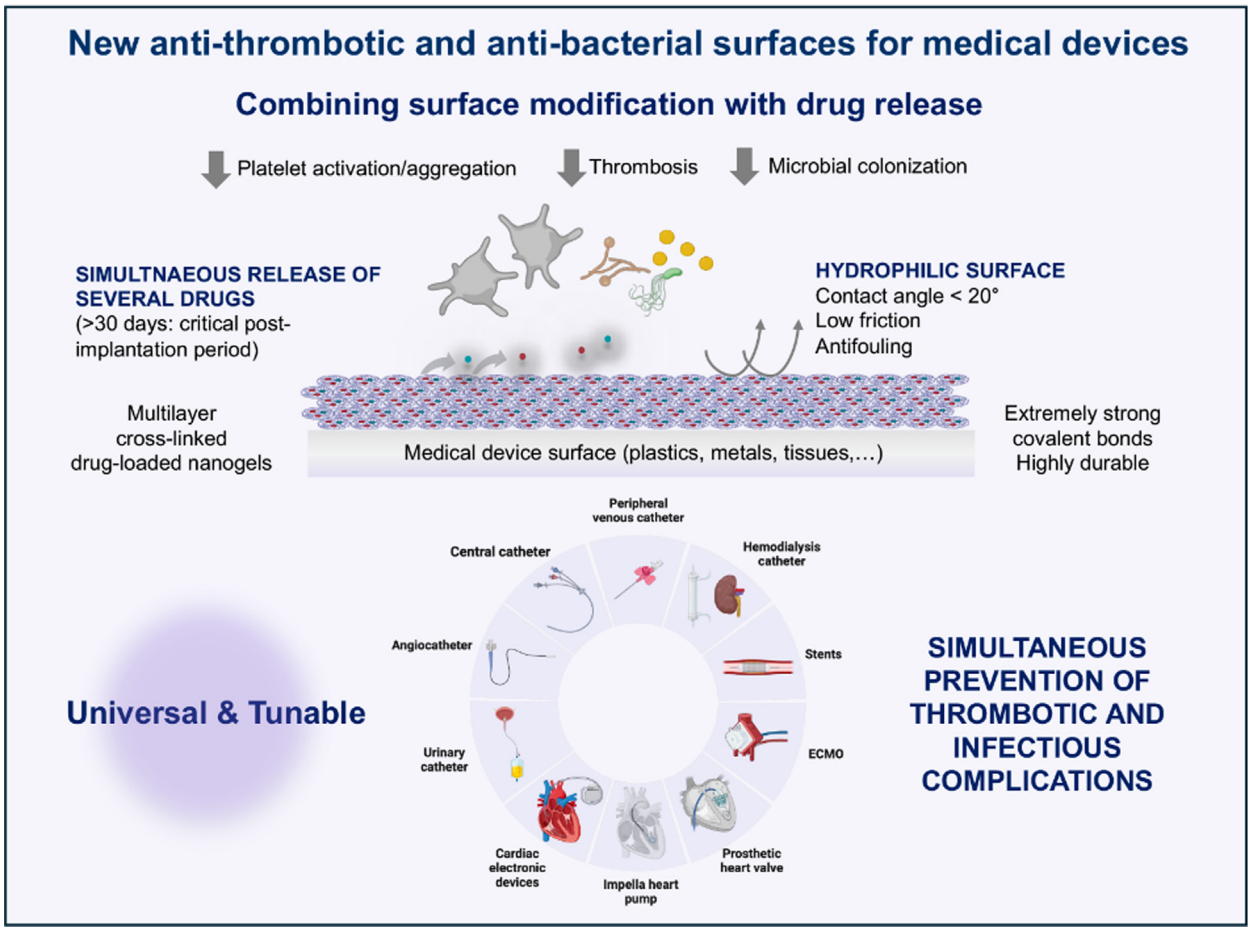
Ashley C. Brown




Innovative biomaterials for hemostasis include injectable nanoparticles and polymers that target bleeding sites without causing off-target thrombosis. Injectable nanoparticle systems include synthetic platelets, such as platelet-like particles and SynthoPlate, that target key components of the coagulation cascade to promote clotting. Nanoparticle systems have included compositions of poly(N-isopropylacrylamide), poly(lactic-co-glycolic) acid (PLGA), poly(L-lysine) (PLL), and polyethylene glycol (PEG). Injectable polymer formulations include PolySTAT, (hemostatic agent via polymer peptide interfusion (HAPPI), and nanocomposite hydrogels. As these technologies are being further advanced, next-generation versions are now being developed that incorporate more advanced biomimetic features such as thrombin generation [20] and wound-sensitive shape change [21]. These types of materials are useful for stopping and controlling bleeding in emergency medicine and surgical applications.

## NEW ANTITHROMBOTIC AND ANTIBACTERIAL SURFACES FOR MEDICAL DEVICES

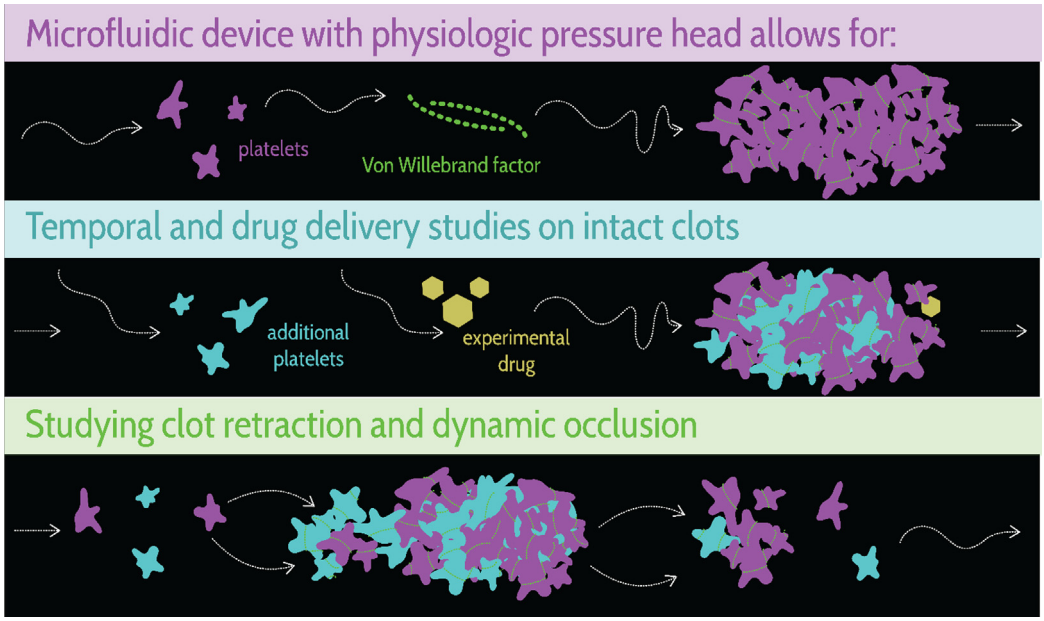
Cécile Oury




Hemocompatibility of blood-contacting medical devices remains a challenge. Infectious complications have dramatic consequences for patients. Since thrombosis and infection are interrelated processes, technologies that could reduce device thrombogenicity will also decrease infection rates. A new and unique coating technology is now available for the simultaneous prevention of thrombotic and infectious complications associated with the usage of medical devices. This technology combines surface modification with drug-eluting properties, and it can be applied to any medical device materials. ECMO, extracorporeal membrane oxygenation.

## MICROFLUIDIC MODELS OF THROMBOSIS

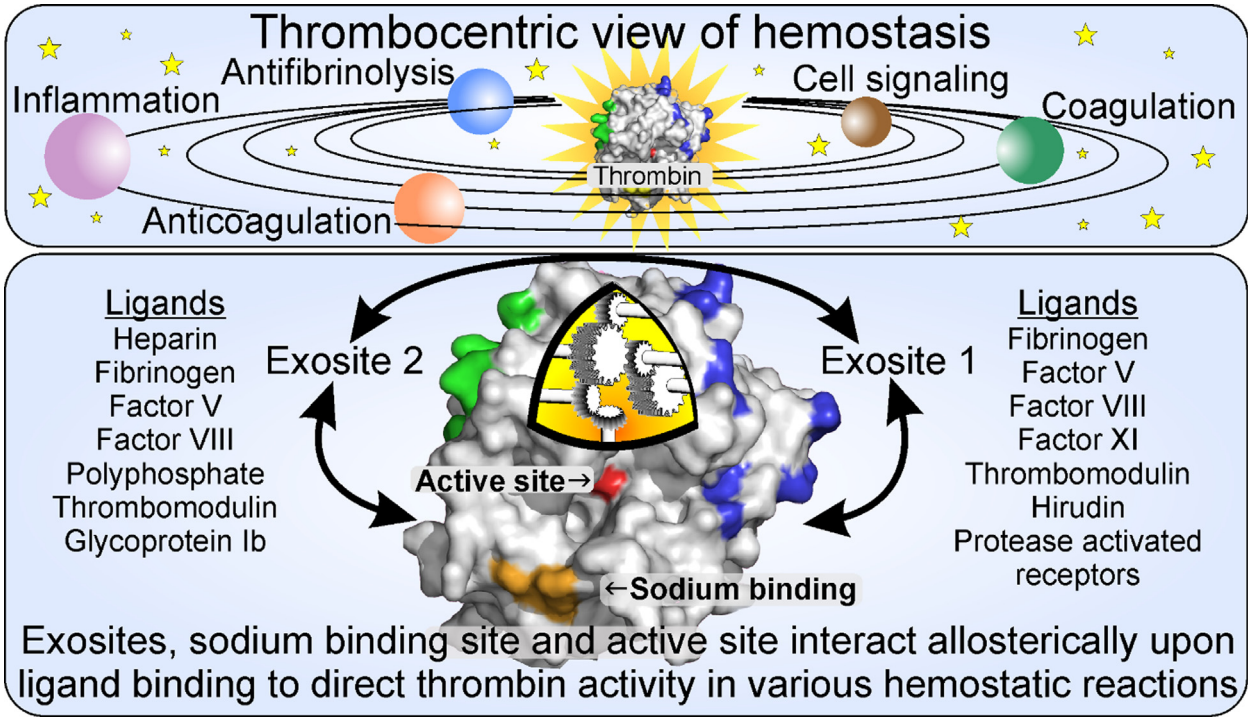
Susan M. Shea




To advance our understanding of mechanisms of thrombosis and identify novel therapeutic approaches, we have developed a microfluidic system that allows for simulation of arterial occlusion. Blood is perfused using a pathophysiologically relevant pressure head achieving arterial shear rates, and thrombus forms on a bioactive region of interest until cessation of flow. After occlusion, clots are allowed to retract for prolonged, clinically relevant periods and undergo retraction and remodeling, and continual occlusion is potentiated by platelet deposition. Immunofluorescent imaging of this process provides novel insights into thrombotic mechanisms. This system also allows for upstream drug delivery without perturbing the occlusive thrombus, recapitulating systemic thrombolytic therapy to assess new therapeutic approaches.

## EXOSITE CROSSTALK IN THROMBIN

James Fredenburgh



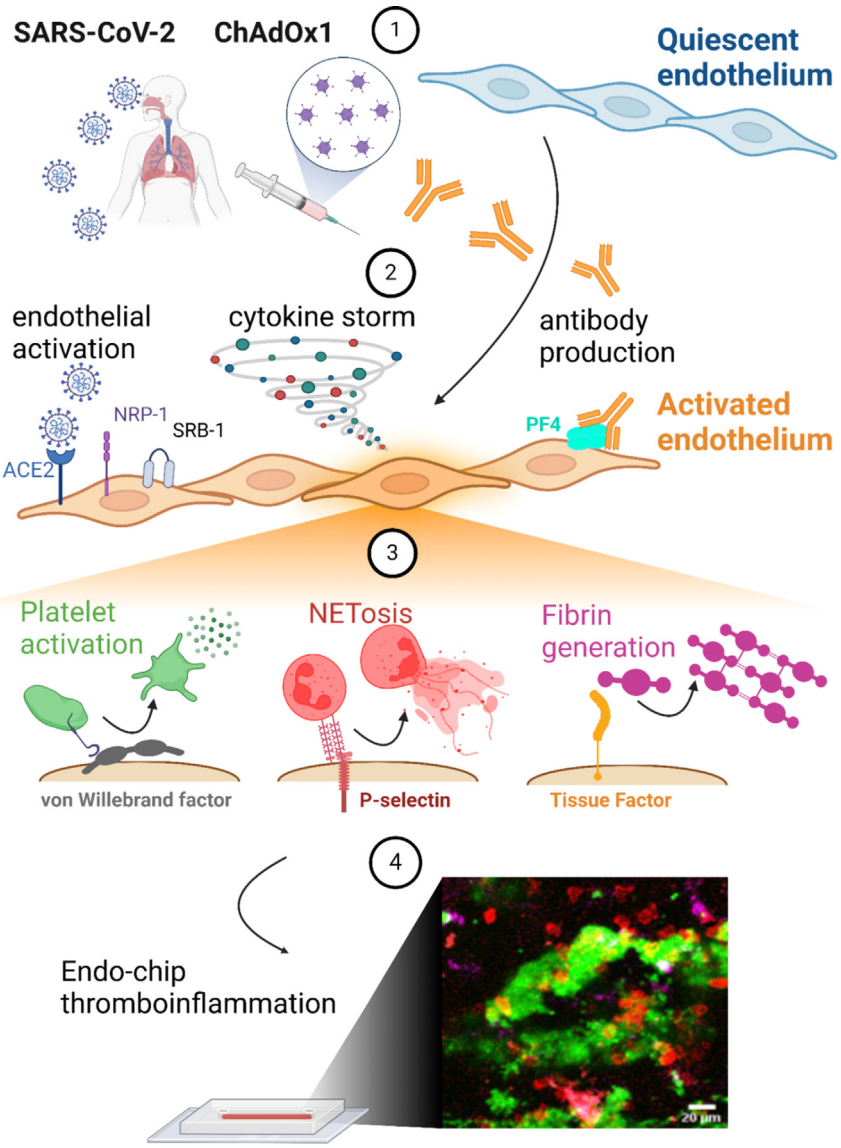

Thrombin is the ultimate product of the coagulation system and is involved in numerous hemostatic processes, including coagulation, anticoagulation, and platelet, endothelial cell, and immune cell activation. Consequently, regulation of thrombin activity is critical to hemostasis.

Thrombin is characterized by 2 positively charged surface domains termed exosites. Exosite 1 guides substrates such as fibrinogen and protease-activated receptors to the active site for cleavage and binds thrombomodulin, which serves as a cofactor in protein C activation. Exosite 2 acts as a binding site for ligands that promote additional interactions, such as heparin, which catalyzes inhibition by antithrombin, and glycoprotein Ibα, which promotes protease-activated receptor activation.

Thrombin also exhibits allosteric regulation as ligand binding at either exosite modulates the active site (arrows). Furthermore, occupation of one exosite can affect the reciprocal exosite. Finally, thrombin possesses a sodium binding site that modulates the function of the exosites and active site. Thus, thrombin is regulated by both intermolecular and intramolecular interactions.

## ENDOTHELIAL THROMBOINFLAMMATORY RESPONSES TO SARS-COV-2 AND CHADOX1 VIRUSES

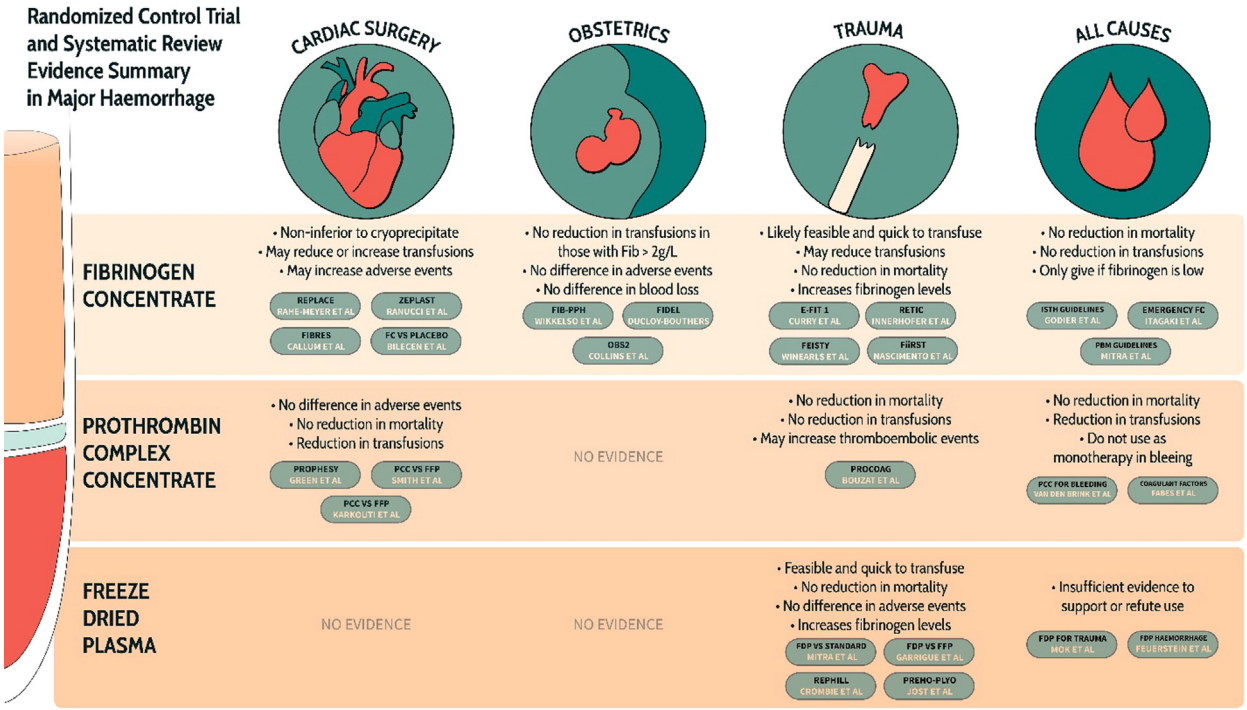
Freda Passam




(1) Endothelial thromboinflammation occurs in patients naturally infected with viruses (ie, SARS-CoV-2) or by immunization (ie, ChAdOx1). (2) SARS-CoV-2 may directly bind to endothelial receptors such as angiotensin-converting enzyme 2 (ACE2), neuropilin 1 (NRP-1), or scavenger receptor class B type 1 (SRB-1), leading to endothelial activation. Endothelial cells are indirectly activated by the production of cytokines from immune cells during viral infection (cytokine storm). ChAdOx1 may induce the production of antibodies against platelet factor 4 (PF4), which bind and activate endothelial cells. (3) Activated endothelial cells secrete von Willebrand factor, which captures platelets; express P-selectin, which traps neutrophils; and express tissue factor, which promotes the production of fibrin. Activated endothelial cells provide a conducive surface for platelet activation, formation of neutrophil extracellular traps (NETosis), and fibrin polymerization. (4) Endothelialized microfluidic devices, such as the Endo-chip, are powerful tools for the measurement and evaluation of novel treatments for vascular thromboinflammation. For references, see Higashikuni et al. [22], Dupuy et al. [23], and Warkentin et al. [24].

# FACTOR CONCENTRATE THERAPY IN MAJOR BLEEDING

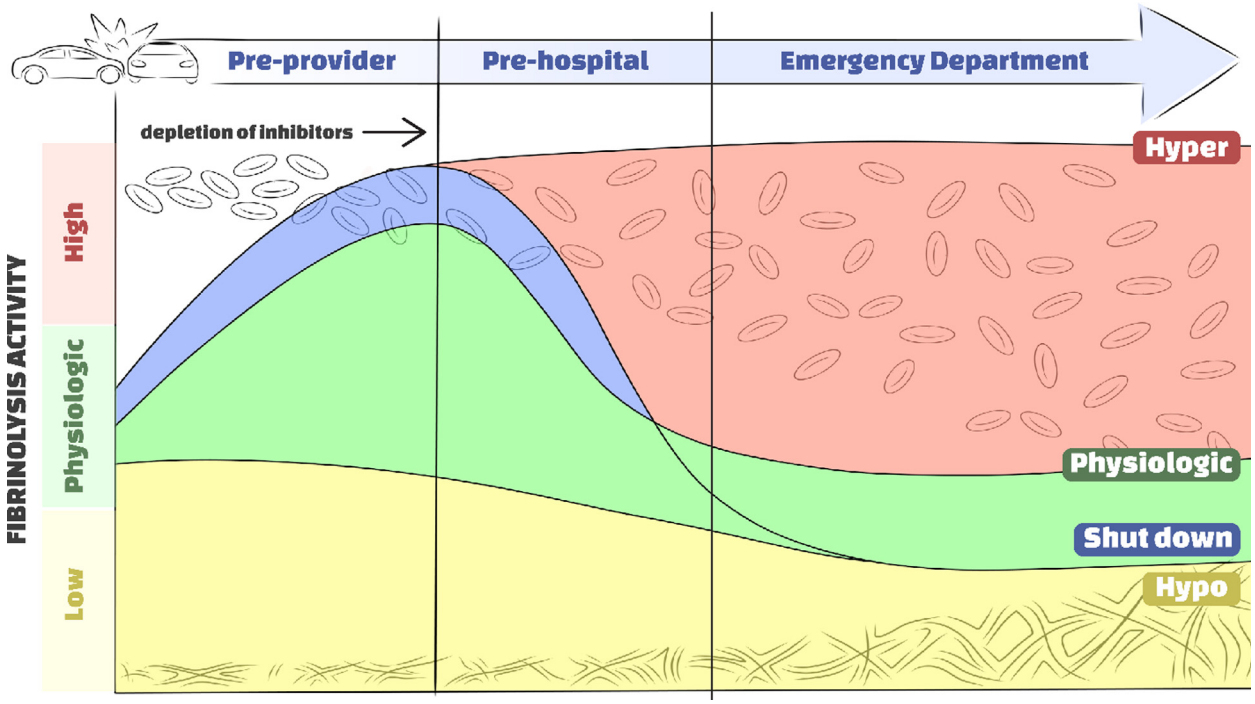
James Winearls




Factor-based resuscitation vs blood component strategy in major hemorrhage stimulates great debate. There are staunch proponents for each, but there remains a paucity of evidence to support one above the other. Nonrandomized studies in various settings report positive outcomes with a factor-based strategy, but these have not been replicated in well-designed randomized control trials [25–27]. In the absence of quality evidence supporting a factor-based strategy, it could be argued that "deconstructing" blood components to factor concentrates is not warranted in the management of major hemorrhage. However, it could also be argued that a factor-based strategy should be utilized when the rapid availability of blood components is not feasible, eg, in the austere clinical environment or when rapid replacement of coagulation factors is required. Large-scale randomized control trials with patient-centered outcomes performed in conjunction with quality mechanistic studies are urgently required to elucidate the optimum strategy for coagulation factor replacement in patients with major hemorrhage.

## USE OF TXA IN THE ACUTE SURGICAL SETTING

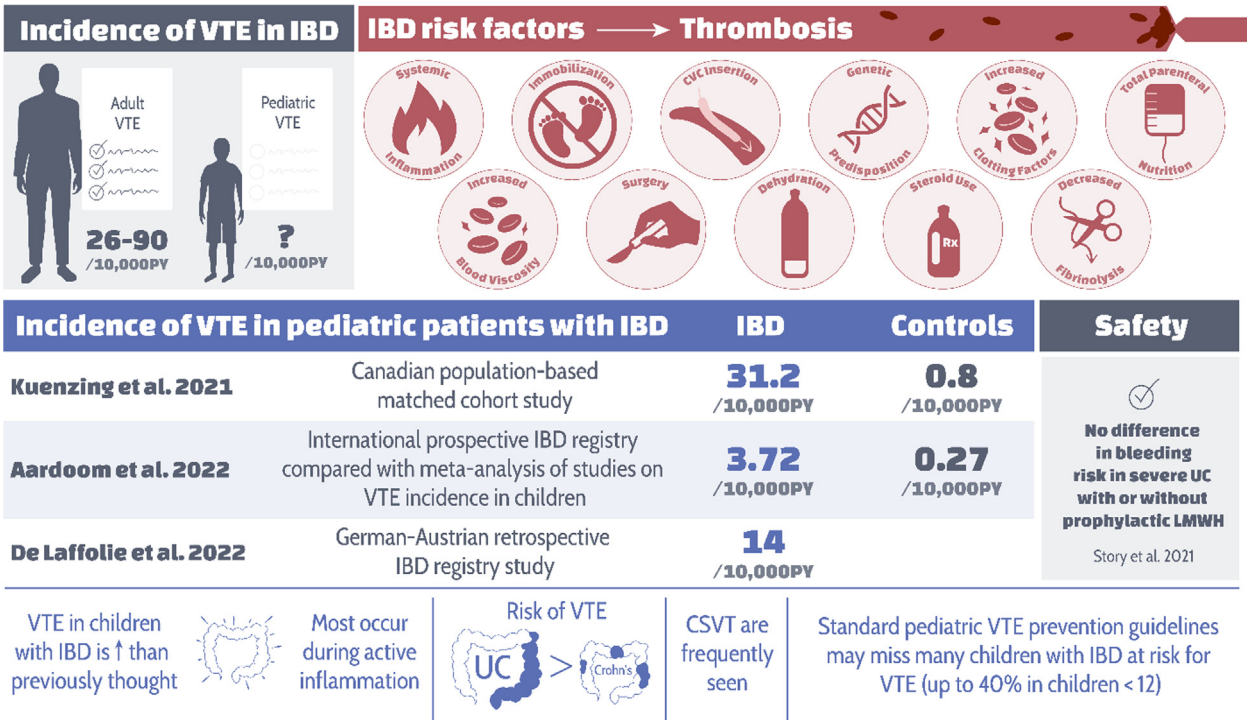
Hunter B. Moore




Trauma has been implicated as a potent stressor driving systemic activation of the fibrinolytic system. However, the degree of fibrinolytic activation and duration are not universal across patients. Trauma can cause sustained high fibrinolytic activity known as hyperfibrinolysis. Other patients may activate and shut down fibrinolytic activity, while others may have a moderate physiological increase in systemic fibrinolytic activity. Alternatively, patients can fail to generate a fibrinolytic response (hypofibrinolysis). Pathology occurs when excessive fibrinolytic leads to depletion of circulating inhibitors, causing unregulated plasmin activity that results in bleeding and downstream inflammatory effects. The use of antifibrinolytics such as tranexamic acid (TXA) in trauma has been demonstrated to decrease mortality in trauma, but the efficacy in improvement in outcomes remains unclear across phenotypes and if any adverse effects occur. The clinical dilemma in stratification of fibrinolytic phenotypes is the time needed for results, which delays delivery of TXA, which is time-critical.

## RISK ASSESSMENT OF ANTICOAGULATION IN INFLAMMATORY BOWEL DISEASE

Soumitra Tole

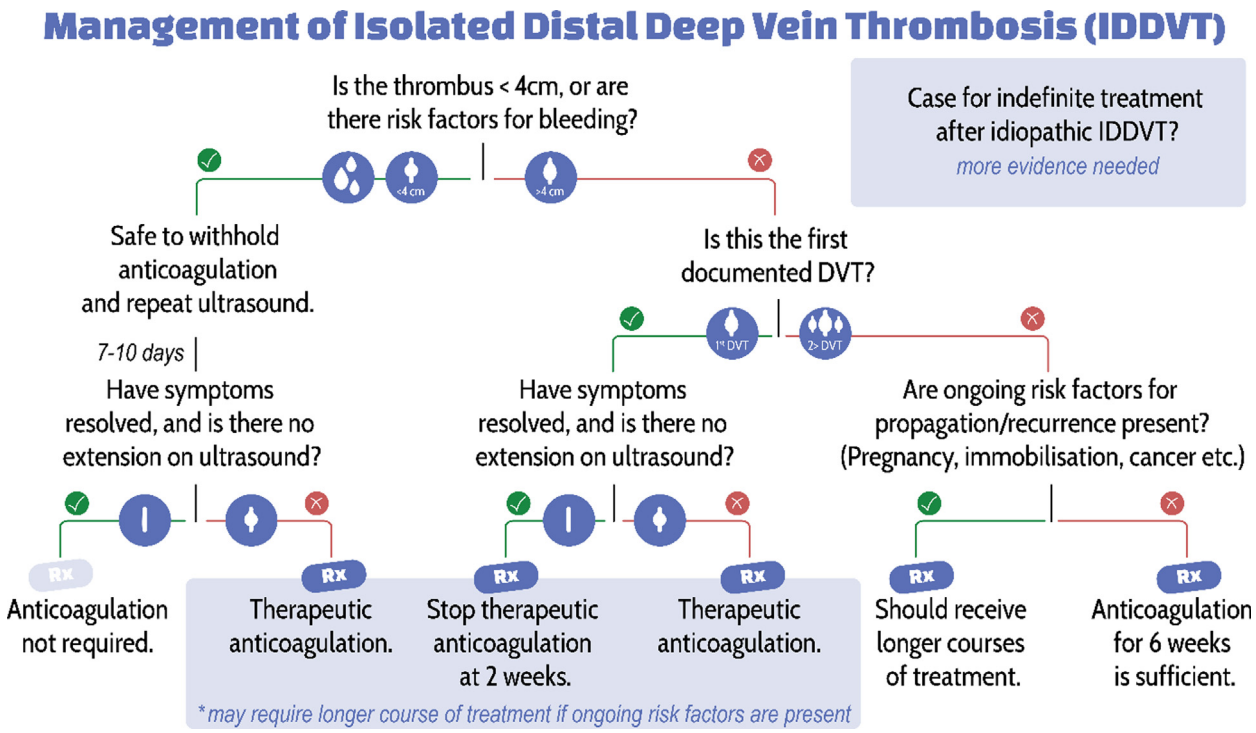



*UC*, ulcerative colitis.

CSVT, cerebral sinus venous thrombosis; CVC, central venous catheter; IBD, inflammatory bowel disease; LMWH, low-molecular-weight heparin; PY, person-years; VTE, venous thromboembolism. For references, see Kuenzig et al. [28], Aardoom et al. [29], and De Laffolie et al. [30], and Story et al. [31].

## DISTAL DVT

Eileen Merriman

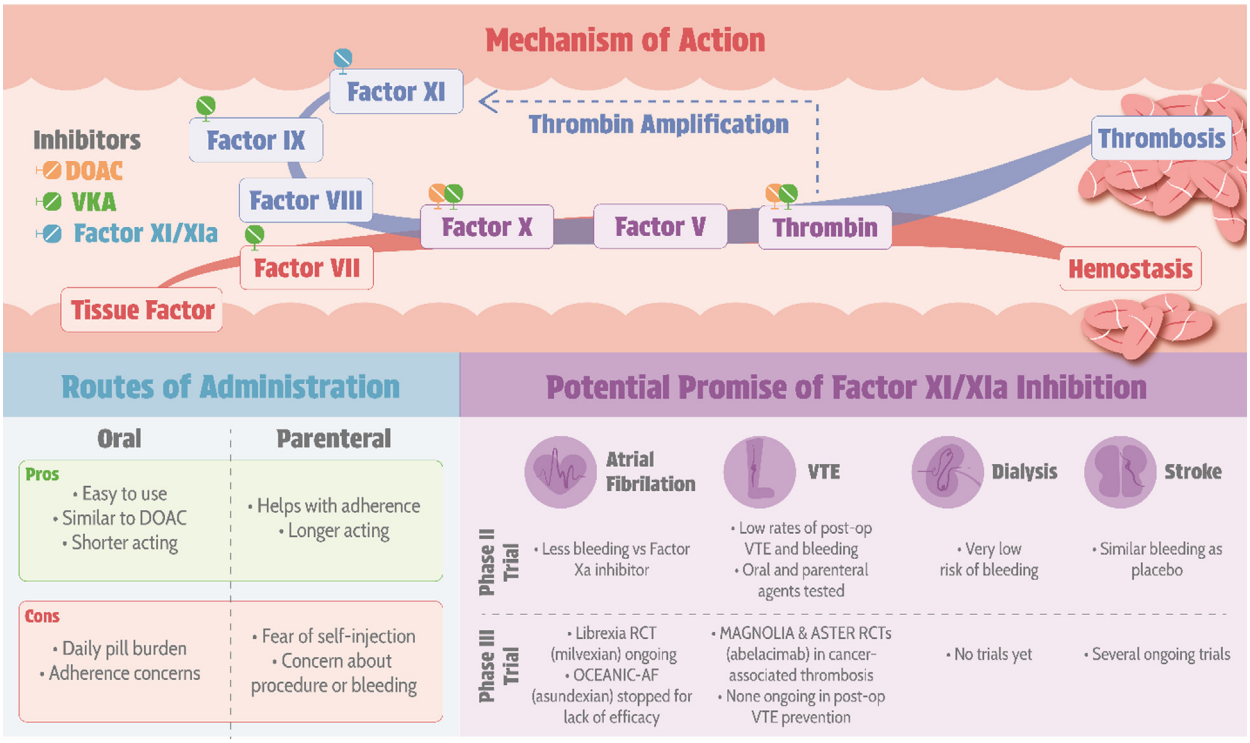



*Rx*, treatment.

The management of isolated distal deep vein thrombosis (IDDVT) is heterogeneous; however, as 90% of IDDVTs will resolve even in the absence of treatment, a simplified management plan can be applied to most. In the absence of ongoing risk factors (eg, malignancy, pregnancy, or immobilization), patients can be treated with 2 to 6 weeks of anticoagulation. For thrombi <4 cm in length or for patients with a high risk for bleeding, anticoagulation can be withheld, although a repeat ultrasound at 7 to 10 days is recommended to exclude propagation. DVT, deep vein thrombosis.

## NEW TARGETS FOR ANTITHROMBOTIC DRUGS

Geoffrey D. Barnes



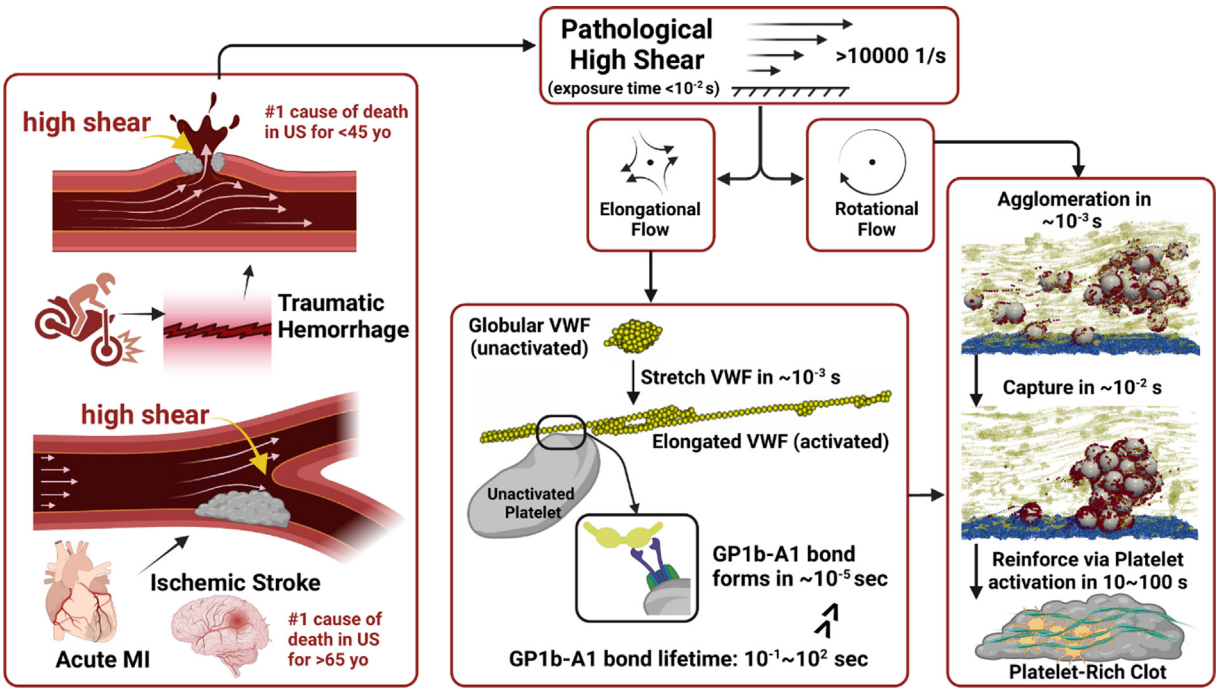

*ASTER*, Effect of Endovascular Contact Aspiration vs Stent Retriever on Revascularization in Patients With Acute Ischemic Stroke and Large Vessel Occlusion; *MAGNOLIA*, A Study Comparing Abelacimab to Dalteparin in the Treatment of Gastrointestinal/Genitourinary Cancer and Associated VTE; *OCEANIC-AF*, A Study to Learn How Well the Study Treatment Asundexian Works and How Safe it is Compared to Apixaban to Prevent Stroke or Systemic Embolism in People With Irregular and Often Rapid Heartbeat (Atrial Fibrillation), and at Risk for Stroke.

Current anticoagulants target either vitamin K–dependent coagulation factors (factor [F]II, FVII, FIX, and FX), FIIa, or FXa. These medications target key mediators of coagulation, therefore inhibiting major hemostatic functions with the goal of decreasing pathogenic thrombosis formation risk. The emerging FXI/XIa inhibitors target FXI, which is located in the intrinsic (or surface contact) pathway. The hypothesis is that by inhibiting the thrombin amplification loop, these emerging drugs will inhibit pathologic thrombosis formation without inhibiting key hemostatic functions, thus decreasing the risk of bleeding.

The emerging FXI/XIa inhibitors are being developed both as oral and parenteral agents. The various routes of administration have certain benefits and drawbacks, including their implications for ease of administration, impact on adherence, and concerns about procedural impact. While several phase II trials have been completed and found to have low rates of bleeding, ongoing phase III trials are currently being conducted on stroke prevention in atrial fibrillation, treatment of cancer-associated venous thromboembolism, and secondary stroke prevention. Completion of the phase III trials is essential to determine if targeting this part of the coagulation system leads to improved clinical efficacy and safety. DOAC, direct oral anticoagulant; post-op, postoperative; VKA, vitamin K antagonist; RCT, randomized control trial; VTE, venous thromboembolism.

# SHEAR-INDUCED PLATELET AGGREGATION: THE HEMODYNAMIC PATHWAY FOR OCCLUSIVE THROMBOSIS AND HEMOSTASIS

Leonardo Liu




Acute myocardial infarction (MI) and ischemic strokes are leading causes of death among the elderly, while traumatic hemorrhage is more common in the younger population. In all cases, high shear rates (>10,000 1/s) trigger shear-induced platelet aggregation, forming occlusive thrombi. High shear comprises elongational and rotational flow components. Elongational flow rapidly stretches von Willebrand factor (VWF), activating it and binding to platelets within 0.1 milliseconds [32]. Glycoprotein (GP) 1b-A1 bonds form within 10 microseconds, much faster than GP1b-A1 bond rupture rate (bond lifetime, 0.1-10 seconds) [33]. Simultaneously, rotational flow agglomerates platelets through VWF in 1 millisecond, leading to mural platelet aggregate formation within 10 milliseconds [34]. This matches short platelet exposure to high shear (~10 milliseconds). Platelet activation (taking 10-100 seconds) reinforces clot stability. Understanding shear-induced platelet aggregation is crucial for developing targeted interventions against thrombus formation, promising improved management of acute MI, ischemic strokes, and traumatic hemorrhage.

## RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

## REFERENCES


[1] World Health Organisation. Global Health Estimates 2016: Death by Cause, Age, Sex, by Country and by Region, 2000-2016. 2018. https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death. [accessed March 29, 2024].

[2] Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, et al. Trauma-induced coagulopathy. *Nat Rev Dis Primers*. 2021;7:30. https://dx.doi.org/10.1038/s41572-021-00264-3

[3] Walsh M, Moore EE, Moore HB, Thomas S, Kwaan HC, Speybroeck J, et al. Whole blood, fixed ratio, or goal-directed blood component therapy for the initial resuscitation of severely hemorrhaging trauma patients: a narrative review. *J Clin Med*. 2021;10:320. https://dx.doi.org/10.3390/jcm10020320

[4] Burstyn-Cohen T, Fresia R. TAM receptors in phagocytosis: beyond the mere internalization of particles. *Immunol Rev*. 2023;319:7–26.

[5] Soucie JM, Miller CH, Byams VR, Payne AB, Abe K, Sidonio RF, et al. Occurrence rates of von Willebrand disease among people receiving care in specialized treatment centres in the United States. *Haemophilia*. 2021;27:445–53.

[6] Atiq F, Blok R, van Kwawegen CB, Doherty D, Lavin M, van der Bom JG, et al. Type 1 VWD classification revisited: novel insights from combined analysis of the LoVIC and WiN studies. *Blood*. 2024;143:1414–24.

[7] Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, et al. Immune thrombocytopenia (ITP) World Impact Survey (IWISh): patient and physician perceptions of diagnosis, signs and symptoms, and treatment. *Am J Hematol*. 2021;96:188–98.

[8] Cooper N, Morrison MA, Vladescu C, Hart AC, Paul D, Malik A, et al. Identification of occult cerebral microbleeds in adults with immune thrombocytopenia. *Blood*. 2020;136:2875–80.

[9] Vladescu C, Hart AC, Paul D, Ademokun C, Teklemichael A, Chivers B, et al. Cognitive impairment in patients with immune thrombocytopenia. *Blood*. 2022;140(Suppl 1):5553–4.

[10] Kumar S, Wulf 2nd J, Basore K, Pozzi N. Structural analyses of $\beta_2$-glycoprotein I: is there a circular conformation? *J Thromb Haemost*. 2023;21:3511–21.

[11] Kumar S, Summers B, Basore K, Pengo V, Flaumenhaft R, Pozzi N. Cryo-EM structure and functional basis of prothrombin recognition by a type-I anti-prothrombin antiphospholipid antibody. *Blood*. Published online February 18, 2024. https://dx.doi.org/10.1182/blood.2023022942

[12] Liu RJ, Al-Molieh Y, Chen SZ, Drobac M, Urban D, Chen CH, et al. The Sec1-Munc18 protein VPS33B forms a uniquely bidirectional complex with VPS16B. *J Biol Chem*. 2023;299:104718. https://dx.doi.org/10.1016/j.jbc.2023.104718

[13] Lo RW, Li L, Leung R, Pluthero FG, Kahr WH. NBEAL2 (neurobeachin-like 2) is required for retention of cargo proteins by alpha-granules during their production by megakaryocytes. *Arterioscler Thromb Vasc Biol*. 2018;38:2435–47.

[14] Bowman SL, Bi-Karchin J, Le L, Marks MS. The road to lysosome-related organelles: insights from Hermansky-Pudlak syndrome and other rare diseases. *Traffic*. 2019;20:404–35.

[15] Grover SP, Sundler Björkman L, Egesten A, Moll S, Mackman N. Hereditary angioedema is associated with an increased risk of venous thromboembolism. *J Thromb Haemost*. 2022;20:2703–6.

[16] Grover SP, Kawano T, Wan J, Tanratana P, Polai Z, Shim YJ, et al. C1 inhibitor deficiency enhances contact pathway-mediated activation of coagulation and venous thrombosis. *Blood*. 2023;141:2390–401.

[17] Grover SP, Snir O, Hindberg K, Englebert TM, Braekkan SK, Morelli VM, et al. High plasma levels of C1-inhibitor are associated with lower risk of future venous thromboembolism. *J Thromb Haemost*. 2023;21:1849–60.

[18] Kossmann S, Lagrange J, Jäckel S, Jurk K, Ehlken M, Schönfelder T, et al. Platelet-localized FXI promotes a vascular coagulation-inflammatory circuit in arterial hypertension. *Sci Transl Med*. 2017;9:eaah4923. https://dx.doi.org/10.1126/scitranslmed.aah4923

[19] Garlapati V, Molitor M, Michna T, Harms GS, Finger S, Jung R, et al. Targeting myeloid cell coagulation signaling blocks MAP kinase/TGF-β1-driven fibrotic remodeling in ischemic heart failure. *J Clin Invest*. 2023;133:e156436. https://dx.doi.org/10.1172/JCI156436

[20] Sekhon UD, Swingle K, Girish A, Luc N, de la Fuente M, Alvikas J, et al. Platelet-mimicking procoagulant nanoparticles augment hemostasis in animal models of bleeding. *Sci Transl Med*. 2022;14:eabb8975. https://dx.doi.org/10.1126/scitranslmed.abb8975

[21] Chee E, Mihalko E, Nellenbach K, Sollinger J, Huang K, Hon M, et al. Wound-triggered shape change microgels for the development of enhanced biomimetic function platelet-like particles. *J Biomed Mater Res A*. 2024;112:613–24.

[22] Higashikuni Y, Liu W, Obana T, Sata M. Pathogenic basis of thromboinflammation and endothelial injury in COVID-19: current findings and therapeutic implications. *Int J Mol Sci*. 2021;22:120812. https://dx.doi.org/10.3390/ijms222112081

[23] Dupuy A, Liu X, Tieng J, Johnston B, Nasser A, Coleman P, et al. Endothelial cell activation enhances thromboinflammation in VITT. *Blood*. 2022;140:1656–7.

[24] Warkentin TE, Baskin-Miller J, Raybould AL, Sheppard JI, Daka M, Nazy I, et al. Adenovirus-associated thrombocytopenia, thrombosis, and VITT-like antibodies. *N Engl J Med*. 2023;389:574–7.

[25] Fabes J, Brunskill SJ, Curry N, Doree C, Stanworth SJ. Pro-coagulant haemostatic factors for the prevention and treatment of bleeding in people without haemophilia. *Cochrane Database Syst Rev*. 2018;12:CD010649. https://dx.doi.org/10.1002/14651858.CD010649.pub2

[26] Godier A, Greinacher A, Faraoni D, Levy JH, Samama CM. Use of factor concentrates for the management of perioperative bleeding: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2018;16:170–4.

[27] Mitra B, Jorgensen M, Reade MC, Keegan A, Holley A, Farmer S, et al. Patient blood management guideline for adults with critical bleeding. *Med J Aust*. 2024;220:211–6.

[28] Kuenzig ME, Bitton A, Carroll MW, Kaplan GG, Otley AR, Singh H, et al. Inflammatory bowel disease increases the risk of venous thromboembolism in children: a population-based matched cohort study. *J Crohns Colitis*. 2021;15:2031–40.

[29] Aardoom MA, Klomberg RCW, Kemos P, Ruemmele FM, , PIBD-VTE Group, van Ommen CHH, et al. The incidence and characteristics of venous thromboembolisms in paediatric-onset inflammatory bowel disease: a prospective international cohort study based on the PIBD-SETQuality Safety Registry. *J Crohns Colitis*. 2022;16:695–707.

[30] De Laffolie J, Ballauff A, Wirth S, Blueml C, Rommel FR, Claßen M, et al. Occurrence of thromboembolism in paediatric patients with inflammatory bowel disease: data from the CEDATA-GPGE Registry. *Front Pediatr*. 2022;10:883183. https://dx.doi.org/10.3389/fped.2022.883183

[31] Liu ZL, Ku DN, Aidun CK. Mechanobiology of shear-induced platelet aggregation leading to occlusive arterial thrombosis: A multiscale in silico analysis. *J Biomechanics*. 2021;120:110349.

[32] Liu ZL, Bresette C, Aidun CK, Ku DN. SIPA in 10 milliseconds: VWF tentacles agglomerate and capture platelets under high shear. *Blood Adv*. 2022;6:2453–65.

[33] Liu ZL, Ku DN, Aidun CK. Mechanobiology of shear-induced platelet aggregation leading to occlusive arterial thrombosis: a multiscale in silico analysis. *J Biomech*. 2021;120:110349. https://dx.doi.org/10.1016/j.jbiomech.2021.110349

[34] Liu Z, Zhu Y, Clausen JR, Lechman JB, Rao RR, Aidun CK. Multiscale method based on coupled lattice-Boltzmann and Langevin-dynamics for direct simulation of nanoscale particle/polymer suspensions in complex flows. *Int J Numer Methods Fluids*. 2019;91:228–46.