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rpth research & practice in thrombosis & haemostasis

ILLUSTRATED REVIEW

Illustrated State-of-the-Art Capsules of the ISTH 2023 Congress

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Abstract

This year's Congress of the International Society of Thrombosis and Haemostasis (ISTH) took place in person in Montréal, Canada, from June 24-28, 2023. The conference, held annually, highlighted cutting-edge advances in basic, translational, population and clinical sciences relevant to the Society. As for all ISTH congresses, we offered a special, congress-specific scientific theme; this year, the special theme was immunothrombosis. Certainly, over the last few years, COVID-19 infection and its related thrombotic and other complications have renewed interest in the concepts of thromboinflammation and immunothrombosis; namely, the relationship between inflammation, infection and clotting. Other main scientific themes of the Congress included Arterial Thromboembolism, Coagulation and Natural Anticoagulants, Diagnostics and Omics, Fibrinolysis and Proteolysis, Hemophilia and Rare Bleeding Disorders, Hemostatic System in Cancer, Inflammation and Immunity, Pediatrics, Platelet Disorders, von Willebrand Disease and Thrombotic Microangiopathies, Platelets and Megakaryocytes, Vascular Biology, Venous Thromboembolism and Women's Health. Among other sessions, the program included 28 State-of-the-Art (SOA) sessions with a total of 84 talks given by internationally recognized leaders in the field. SOA speakers were invited to prepare brief illustrated reviews of their talks that were peer reviewed and are included in this article. These illustrated capsules highlight the major scientific advances with potential to impact clinical practice. Readers are invited to take advantage of the excellent educational resource provided by these illustrated capsules. They are also encouraged to use the image in social media to draw attention to the high quality and impact of the science presented at the Congress.

CONTENTS

Immune attack on platelets

Donald M. Arnold, MD, MSc

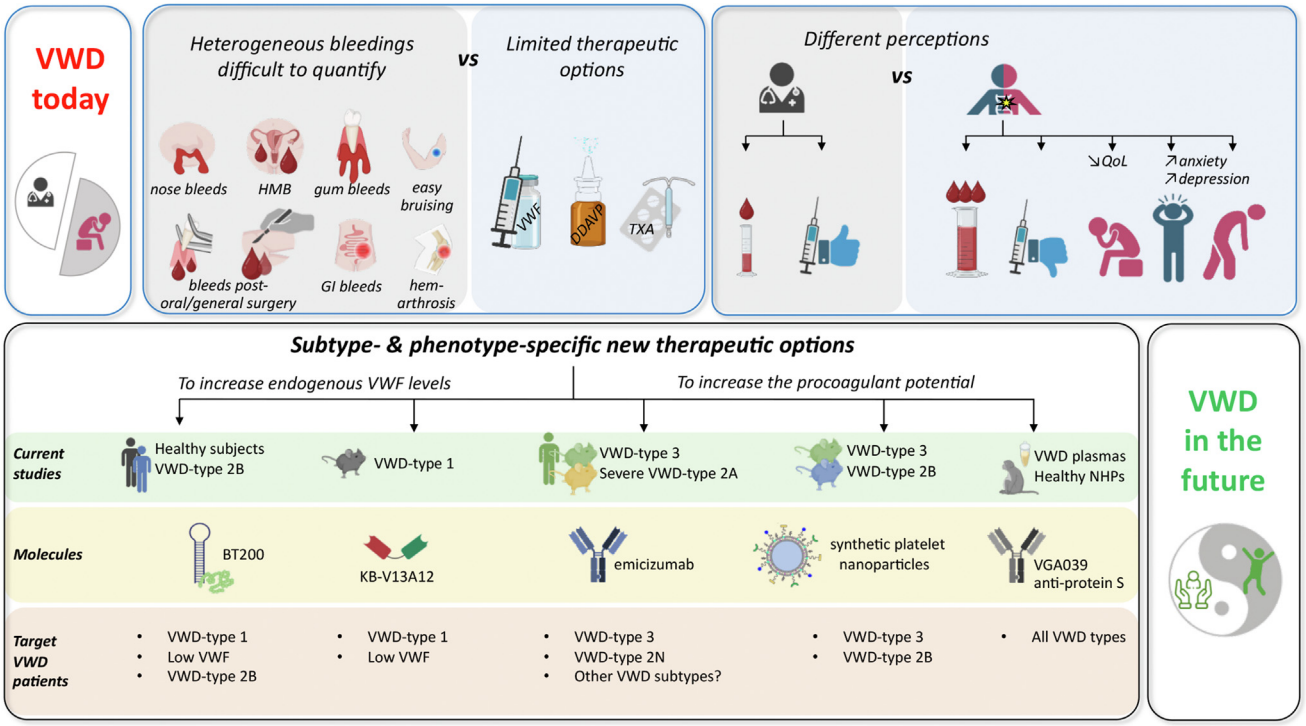
Immune attack on platelets

Reaction	Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)	Vaccine-Associated Immune Thrombocytopenia (VA-ITP)
Described With	Adenoviral vector vaccines (e.g. Johnson and Johnson, AstraZeneca)	Any vaccine (especially Covid-19 and measles, mumps, and rubella vaccines)
Pathophysiology	The vaccine stimulates anti-PF4 antibody production The anti-PF4 antibodies bind to circulating PF4 (which originate from inside platelets) and membrane-bound PF4 on the platelet surface, causing Fc-mediated platelet activation	The vaccine stimulates anti-GPIIbIIIa and anti-GPIbIX antibody production The anti-GPIIbIIIa and anti-GPIbIX antibodies bind to GPIIbIIIa and GPIbIX on the platelet surface, and the antibody-tagged platelets are destroyed in the spleen
Clinical Findings	The platelet activation leads to thrombocytopenia and thrombosis Cerebral venous sinus thrombosis Pulmonary embolism Hepatic vein thrombosis Splenic vein thrombosis Splanchnic vein thrombosis Deep vein thrombosis	The platelet destruction leads to thrombocytopenia and bleeding Intracranial hemorrhage Oral blood blisters Bruising Gastro-intestinal bleeding Genito-urinary bleeding Petechiae/purpura
Incidence Estimate	~1:100,000 with adenoviral vector vaccines	~1:100,000 (or more common) with any vaccine
Management	Non-heparin anticoagulant, IVIG, +/- immune suppressant medications	Corticosteroids, IVIG, thrombopoietin receptor agonists, +/- immune suppressant medications

For references, see Kelton et al. [1] and Arnold and Kelton [2]

Novel therapeutics for VWD

Caterina Casari, PhD

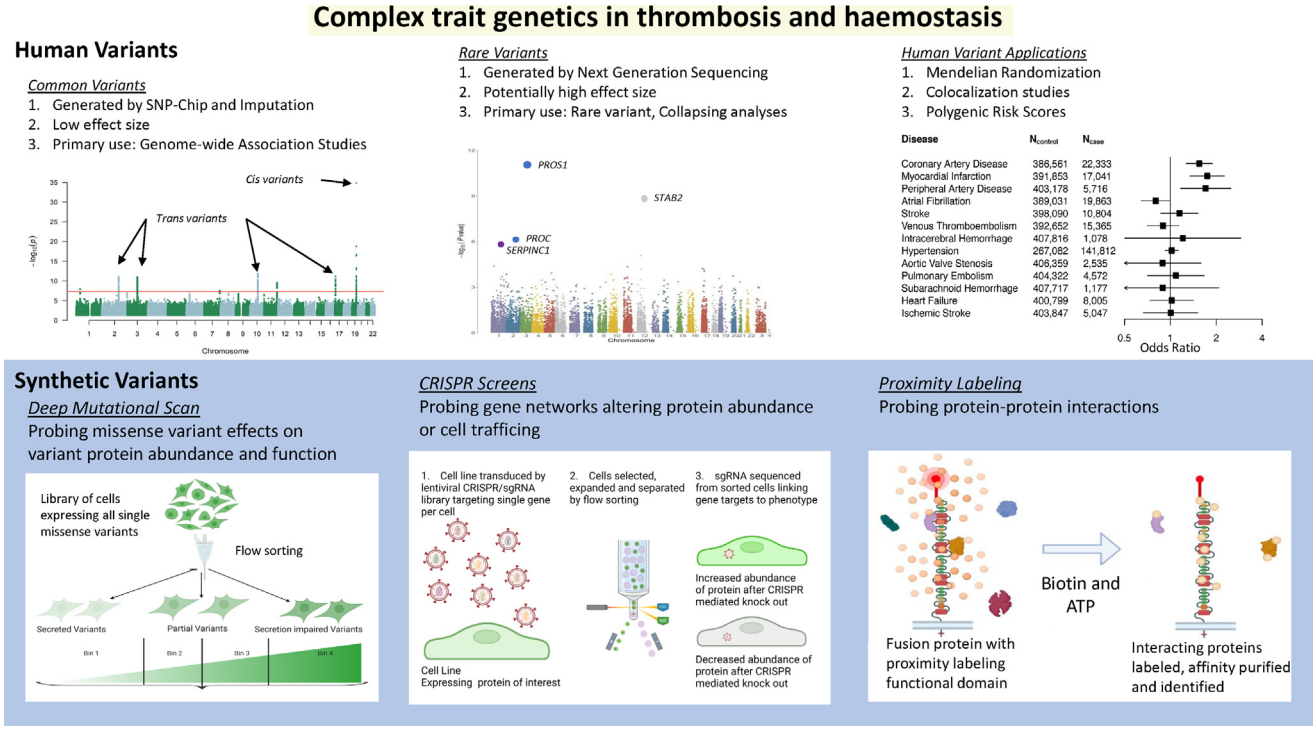


Von Willebrand disease (VWD) is associated with heterogeneous, difficult to quantify bleedings but limited treatment options are currently available. While clinicians generally appreciate that available treatments are quite effective in controlling the bleeding episodes, VWD patients perceive the burden of invasive, mostly on-demand treatments [3]. New therapeutic strategies are under investigation for patients with similar phenotypes, with the hope of better fulfilling their needs. BT200 (rondoraptivon pegol) is a pegylated aptamer inhibiting VWF/GPIbα interaction that increases VWF/FVIII levels and, in thrombocytopenic patients, also rises platelet counts [4]. KB-V13A12 is a bispecific nanobody simultaneously binding albumin and VWF, which corrects haemostasis in a VWD-type 1 mouse model. Emicizumab, has been efficiently used in VWD-type 3 patients [5] and mice, but has no beneficial effects in a VWD-type 2A mouse model. Synthetic platelet nanoparticles that collaborate with endogenous platelets, have been successfully tested in VWD-type 3 and -2B mouse models.

TXA, tranexamic acid; QoL, quality-of-life; HMB, heavy menstrual bleedings; GI, gastrointestinal; NHPs, non-human primates.

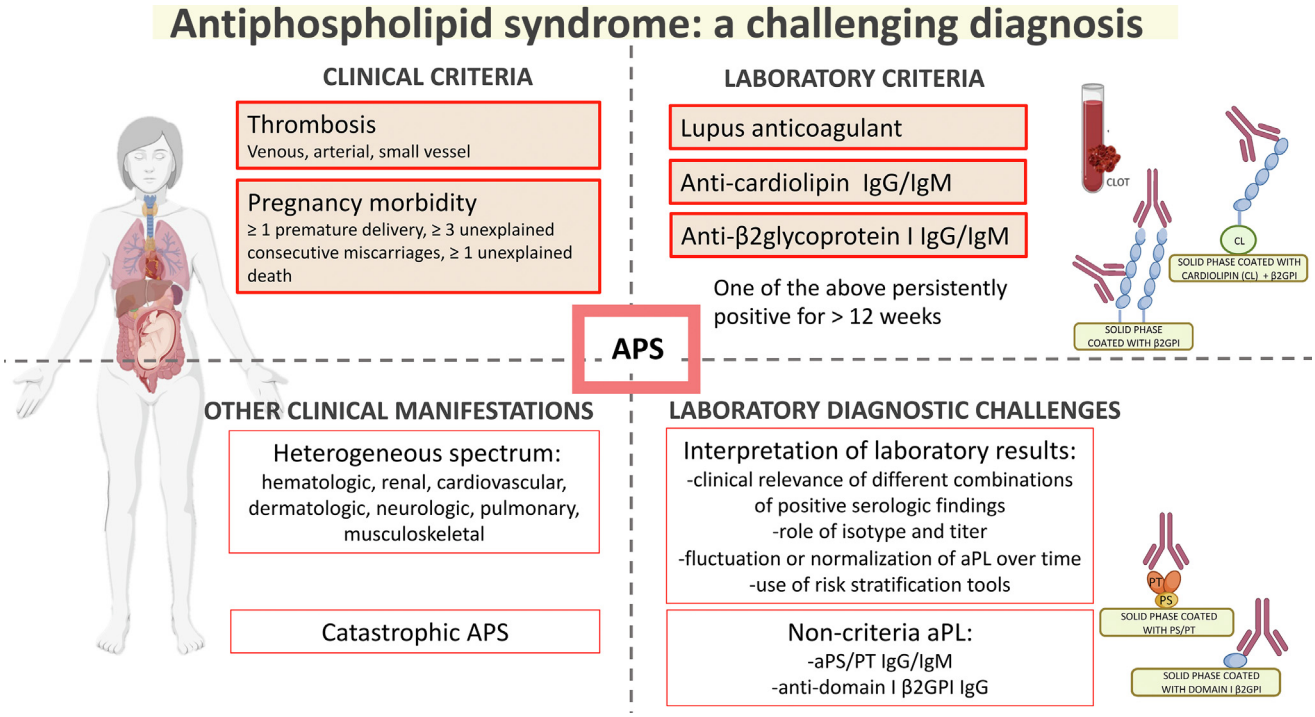
Complex trait genetics in thrombosis and haemostasis

Karl C. Desch, MD



Antiphospholipid syndrome: a challenging diagnosis

Katrien M.J. Devreese



Antiphospholipid syndrome (APS) is an autoimmune disease characterized by thrombosis and/or pregnancy morbidity, in patients persistently positive for antiphospholipid antibodies (aPL). Classification criteria restrict the aPL to lupus anticoagulant (LAC), anti-cardiolipin (CL) (aCL) and anti-beta2-glycoprotein I (β2GPI) antibodies (aβ2GPI) IgG or IgM. However, in clinical practice patients may present with a variety of clinical symptoms, not fulfilling the classification criteria for overt APS, and other aPL may help to diagnose APS.

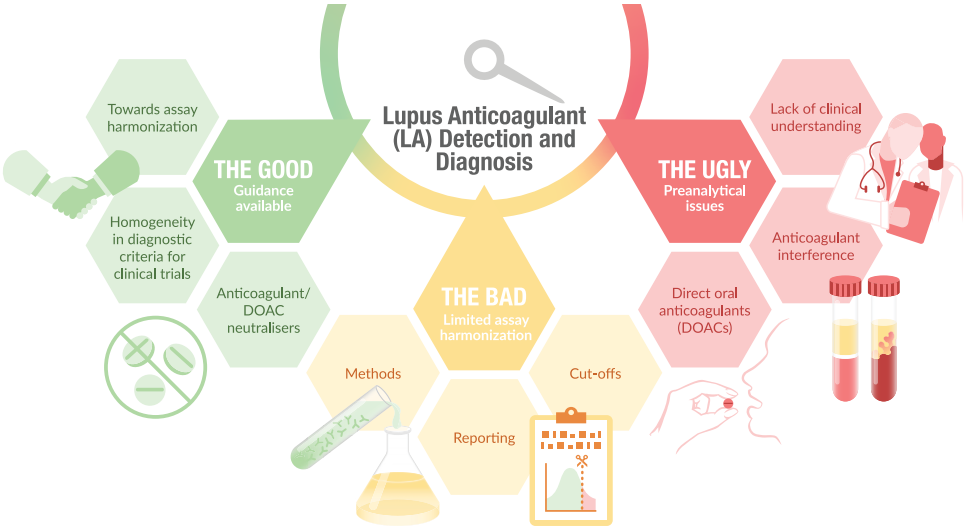
LAC testing remains a complicated procedure using coagulation assays with many pitfalls and interferences. Assays for aCL and aβ2GPI show inter-assay differences. These methodological issues make the laboratory diagnosis of APS challenging, and other aPL tests (antibodies against the domain I of β2GPI and antiphosphatidylserine-prothrombin (aPS/PT) antibodies, as well as antibody profiles and semi-quantitative reporting of titers may help in the laboratory diagnosis of APS.

On both diagnostic sides, clinical and laboratory, APS is heterogeneous and challenging to diagnose.

For references, see Devreese et al. [6,8]; Barbhaiya et al. [7]

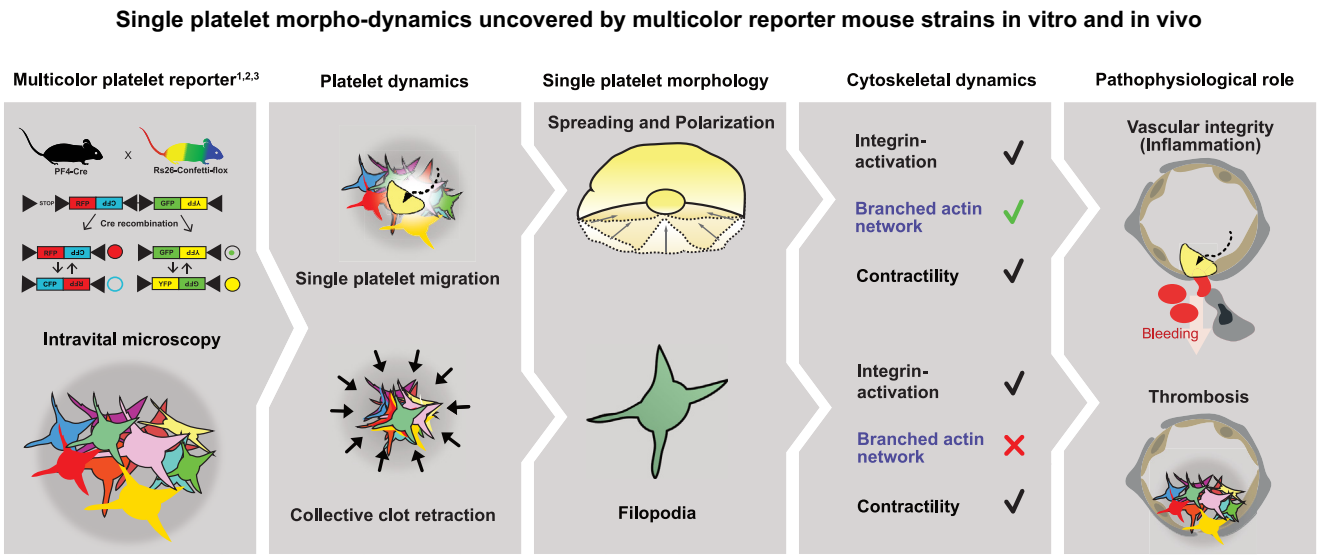
Testing for the lupus anticoagulant (la) over the last decade – are we there yet?

Emmanuel J. Favaloro



Single platelet morpho-dynamics uncovered by multicolor reporter mouse strains in vitro and in vivo

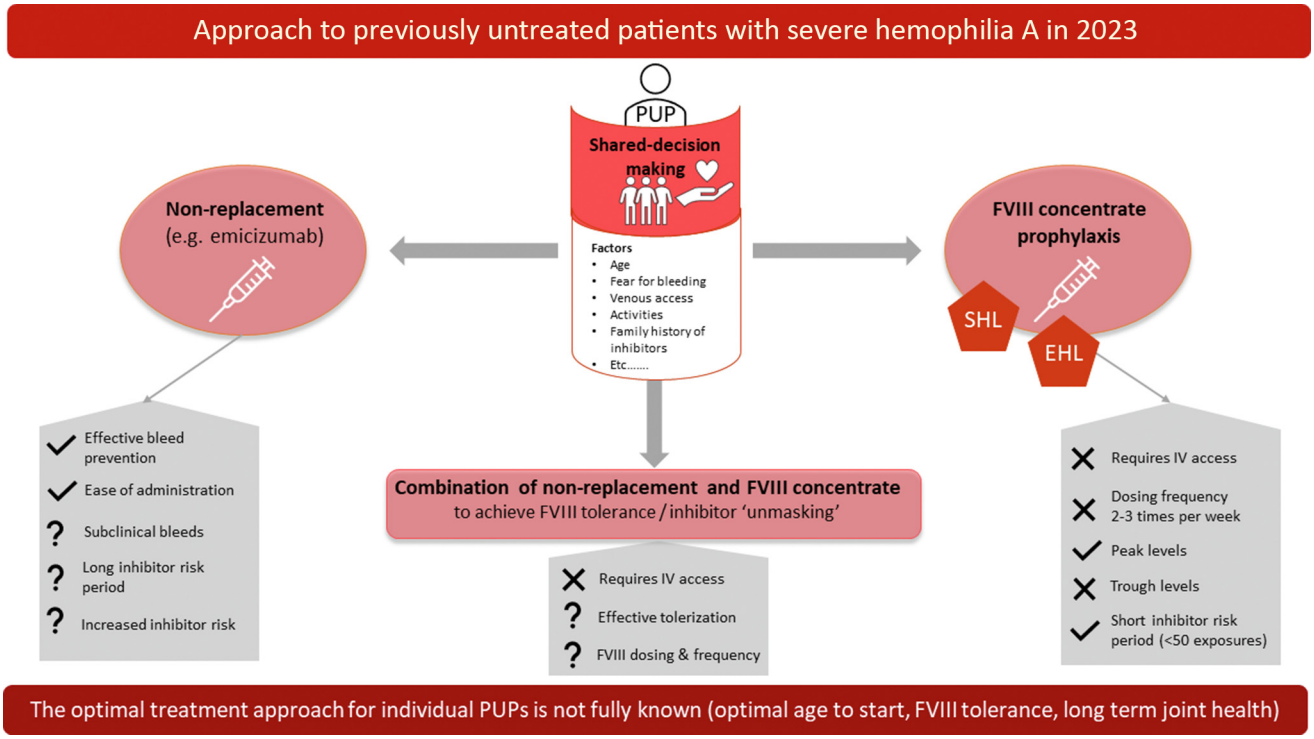
Florian Gaertner, MD, PhD



For references, see Gaertner et al. [9]; Nicolai et al. [10,11]

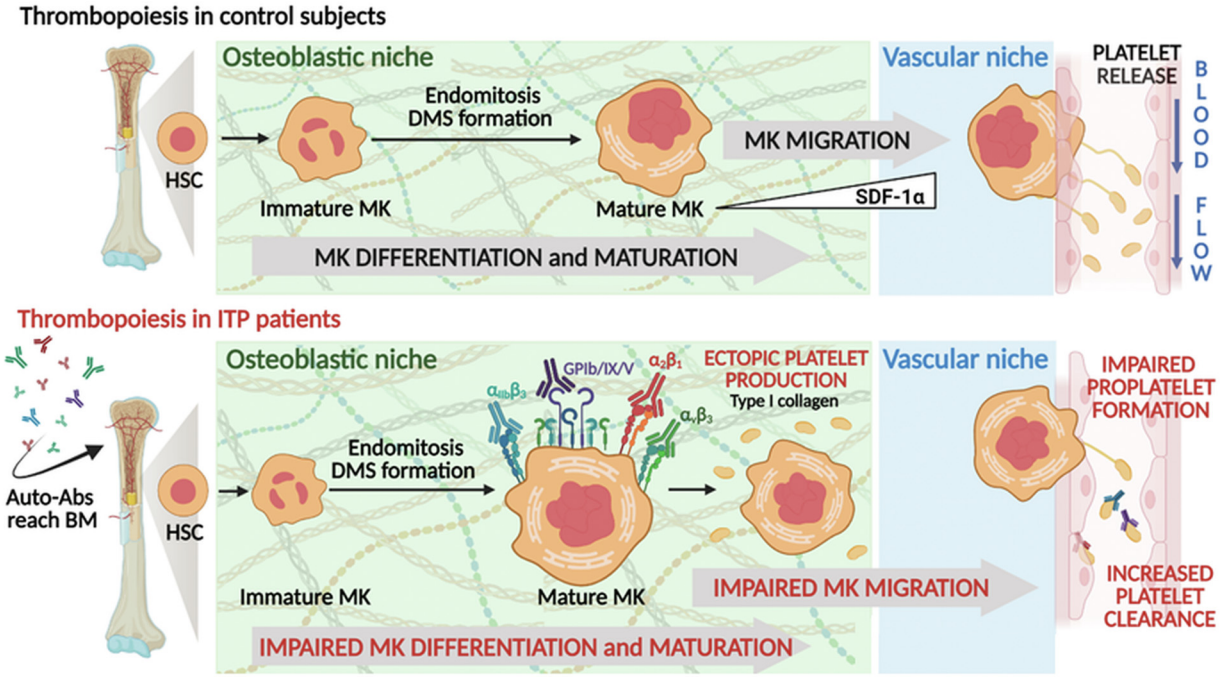
Approach to PUPs in 2023

Samantha C. Gouw



Immune attack on platelets in ITP: the role of megakaryocyte impairment

Prof. Paolo Gresele



Auto-Abs: auto-antibodies; **BM:** bone marrow; **DMS:** demarcation membrane system; **HSC:** hematopoietic stem cell; **MK:** megakaryocyte; **SDF-1α:** stromal cell-derived factor-1α.

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by accelerated platelet turnover due to circulating auto-antibodies (Abs) against platelet and megakaryocyte (MK) surface glycoproteins, such as $\alpha_{IIb}\beta_3$-GPIIb/IIIa, $\alpha_2\beta_1$-GPIa/IIa, GPIb/IX/V, GPIV, GPVI and $\alpha_v\beta_3$.

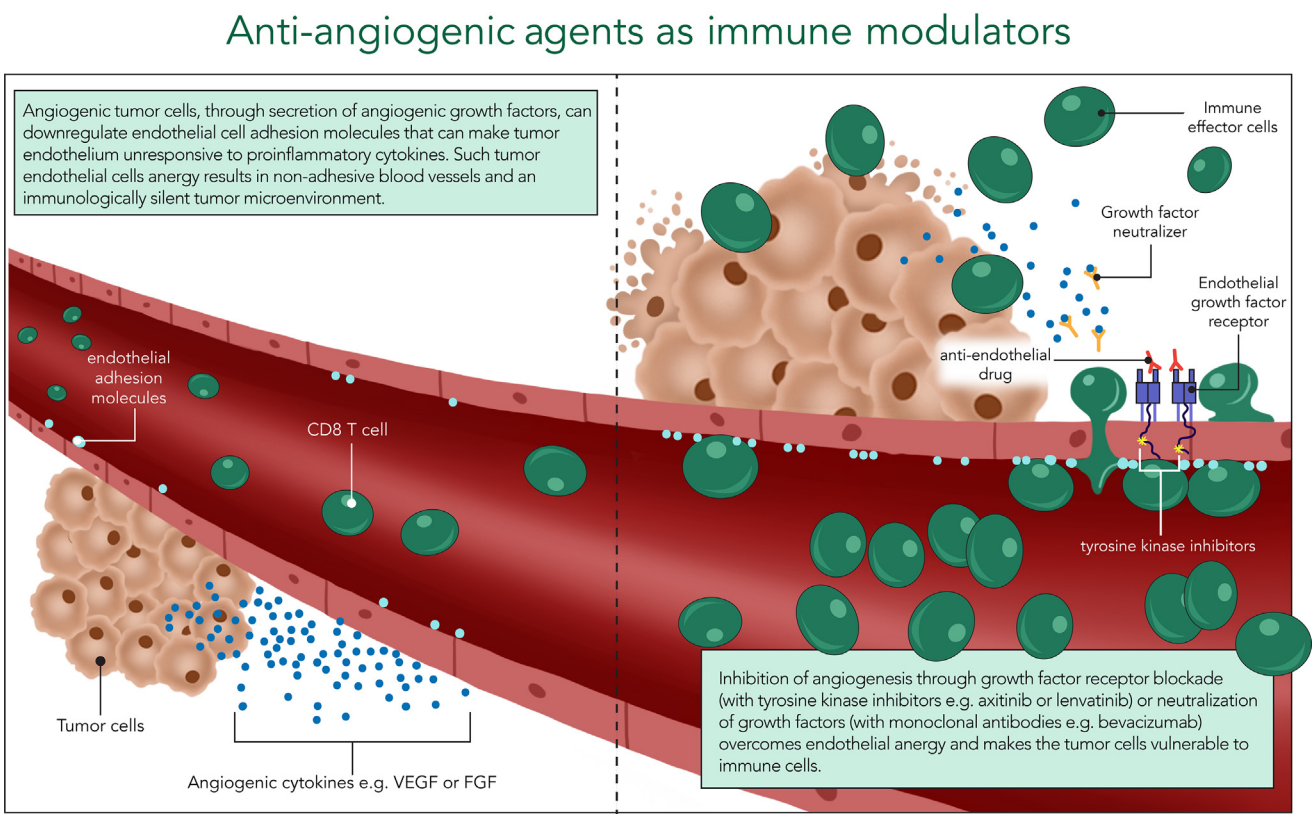
Immunological cells reside and produce Abs in the bone marrow (BM) [12]. Platelet auto-antibodies were detected in the BM of ITP patients [13].

Besides increased clearance of circulating opsonized platelets, platelet auto-antibodies lead to the impairment of many steps of megakaryo/thrombopoiesis, such as MK differentiation and maturation, MK migrationfrom the osteoblastic to the vascular niche, MK adhesion to extracellular matrix proteins, and proplatelet formation, resulting in impaired and ectopic platelet production in the BM and diminished platelet release in the blood stream.

The figure was created with BioRender.com

Anti-angiogenic agents as immune modulators

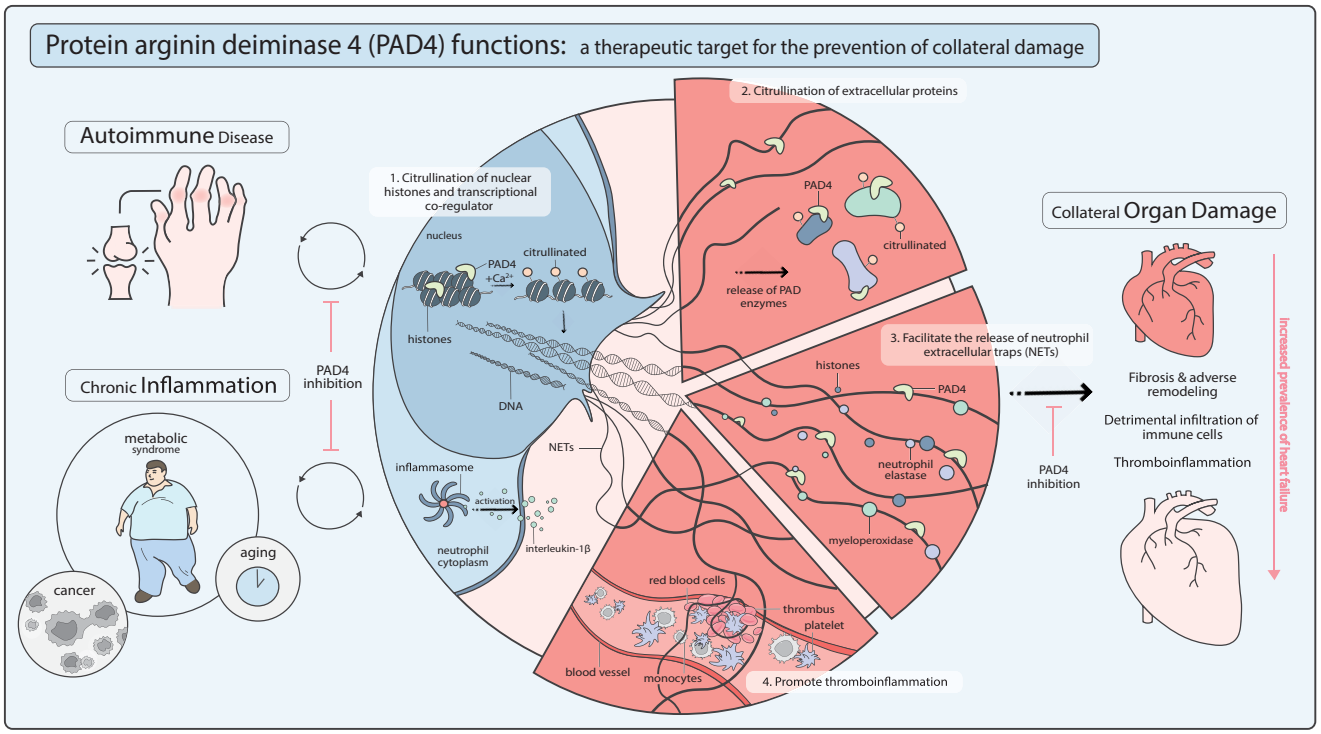
Arjan W. Griffioen



Ongoing angiogenesis, induced by vascular endothelial- and fibroblast growth factors, protects a tumor against leukocyte infiltration through the suppression of endothelial cell (EC) adhesion molecule expression. The main adhesion molecule involved in leukocyte infiltration is intercellular adhesion molecule-1 (ICAM-1). This molecule is both sufficient, as well as required for leukocyte extravasation and is heavily suppressed in the tumor vasculature [14]. Other adhesion molecules such as vascular cell adhesion molecules and E-selectin are also involved. Non-adhesive endothelium, which is the result of tumor endothelial cell anergy, provides the tumor with immune silent conditions, a trait that has been hijacked from embryo development. Inhibition of angiogenesis, by drugs such as bevacizumab, axitinib and Lenvatinib, overcomes endothelial anergy and restores the suppressed expression of ICAMs, VCAMs and selectins in the endothelium and supports anti-tumor immunity [15]. It is becoming evident that the recent FDA approvals for combination therapies of anti-angiogenic agents with immune checkpoint inhibitors [16] are based on the phenomenon of overcoming endothelial cell anergy.

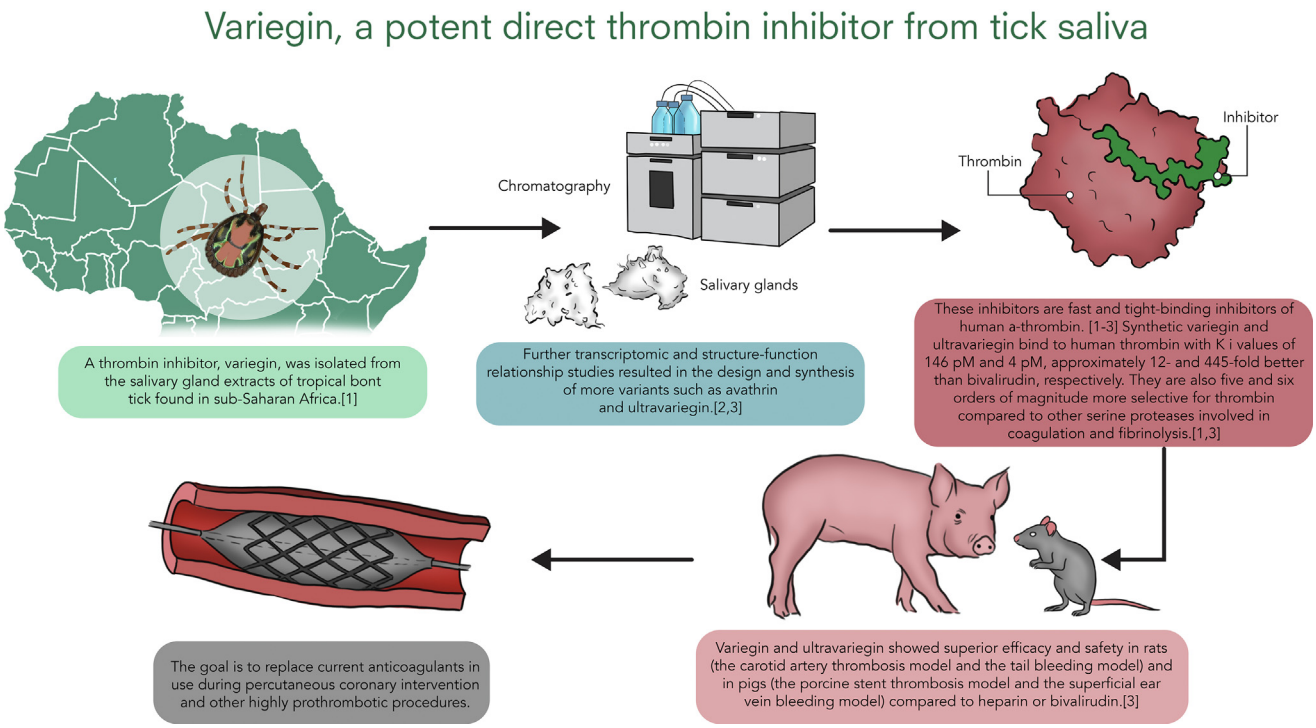
PAD4 inhibition in immunothrombosis

Lukas Heger



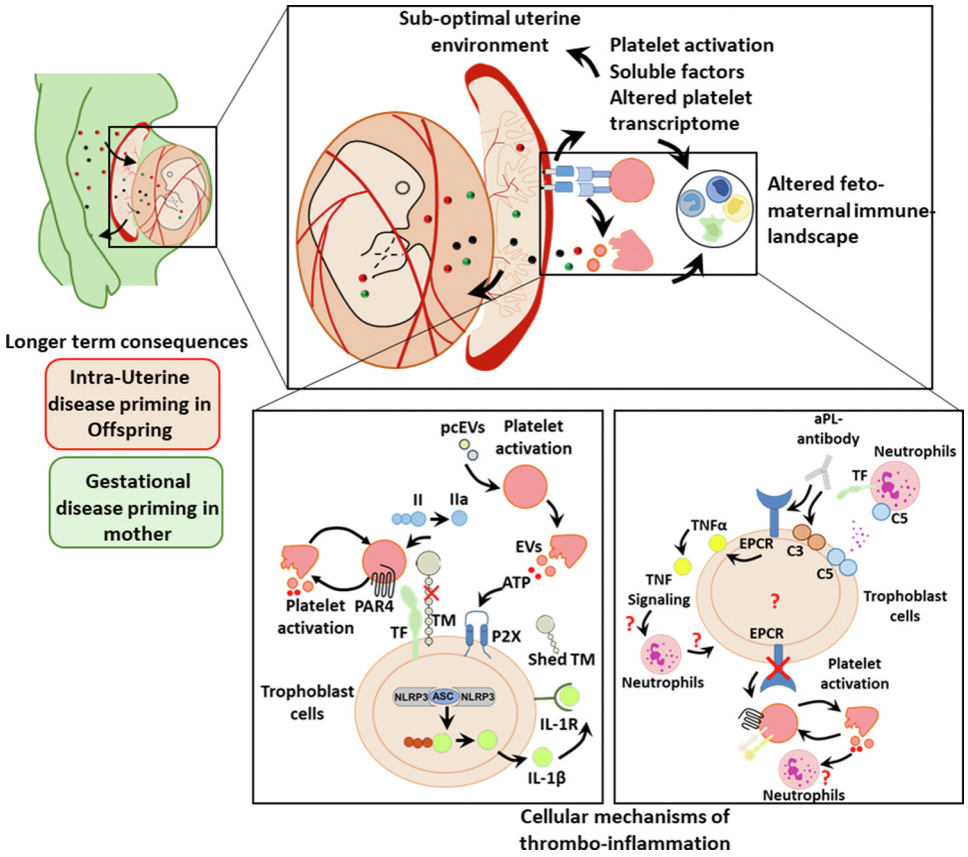
Variegin, a potent direct thrombin inhibitor from tick saliva

R. Manjunatha Kini, PhD



Thrombo-inflammatory mechanisms at the fetal-maternal interface

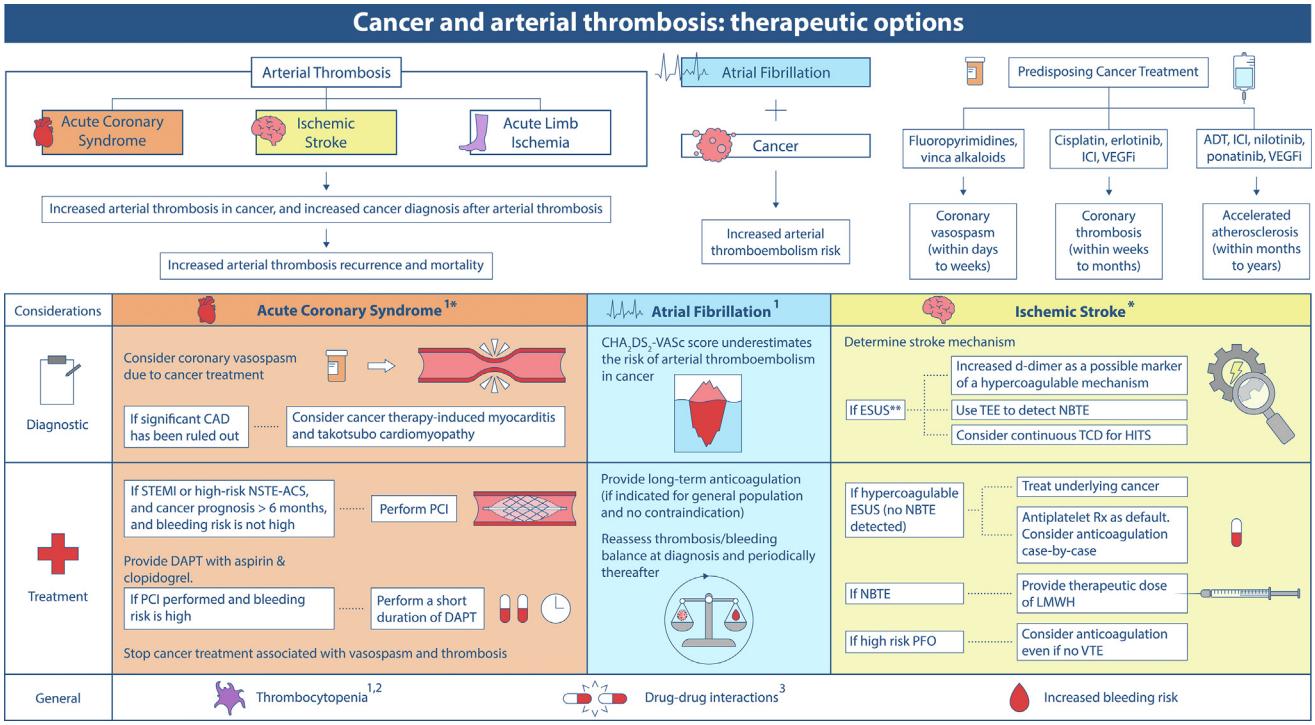
Shrey Kohli



Platelet-mediated inflammatory mechanisms within the placenta contribute to thrombo-inflammatory gestational vascular complications (TIGVCs) such as preeclampsia (PE) and anti-phospholipid (aPL) syndrome. This impairs feto-maternal health during pregnancy, and promote long-term disease priming mechanisms in the mother and the offspring. Pro-coagulant extracellular vesicles (pcEVs) promote platelet activation thereby releasing DAMPs such as ATP which in turn activate the NLRP3 inflammasome and placental sterile inflammation via purinergic receptor (P2X) signaling [17]. This is associated with reduced placental thrombomodulin (TM) expression. TM deficiency results in a tissue-factor (TF) dependent and platelet-mediated embryonic loss in mice. Endothelial protein-C receptor (EPCR) deficiency causes mid-gestational embryonic death via integrin and PAR mediated platelet activation and neutrophil infiltration [18]. On the other hand, EPCR expressing trophoblast promotes aPL antibody mediated signaling and TNF-α release promoting systemic inflammation. Beyond the role of EPCR, aPL antibodies promote complement (C3 & C5) and TF mediated neutrophil infiltration, trophoblast injury and fetal loss [19].

Cancer and arterial thrombosis: therapeutic options

Avi Leader, MD



Acute coronary syndrome (less PCI and less use of potent P2Y12 inhibitors) and atrial fibrillation (~50% don't receive anticoagulation despite an indication) are under-treated in cancer patients. These patients present unique treatment challenges [20,21,22], have an increased bleeding risk, and require management tailored to the cancer setting.

* Address modifiable cardiovascular risk factors

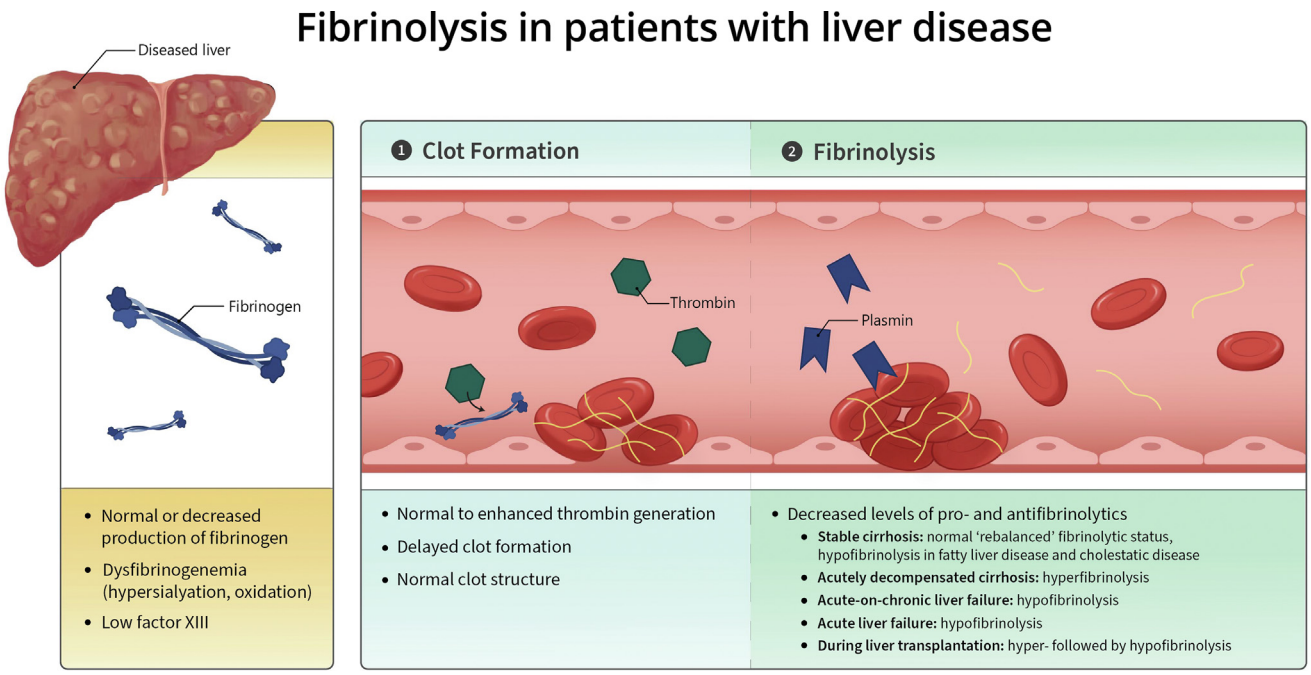
** ESUS defined as a non-lacunar stroke, without a stenotic arterial culprit lesion, and without a known high-risk cardioembolic source

Abbreviations:

ACS, acute coronary syndrome; ADT, androgen deprivation therapy; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; ESUS, embolic stroke of undetermined source; HITS, high-intensity transient signals; ICI, immune checkpoint inhibitor; LMWH, low molecular weight heparin; NBTE, non-bacterial thrombotic endocarditis; NSTE-ACS, non-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PFO, patent foramen ovale; Rx, treatment; STEMI, ST elevation myocardial infarction; TCD, transcranial doppler; TEE, transesophageal echocardiography; VEGFi, vascular endothelial growth factor inhibitor; VTE, venous thromboembolism

Fibrinolysis in patients with liver disease

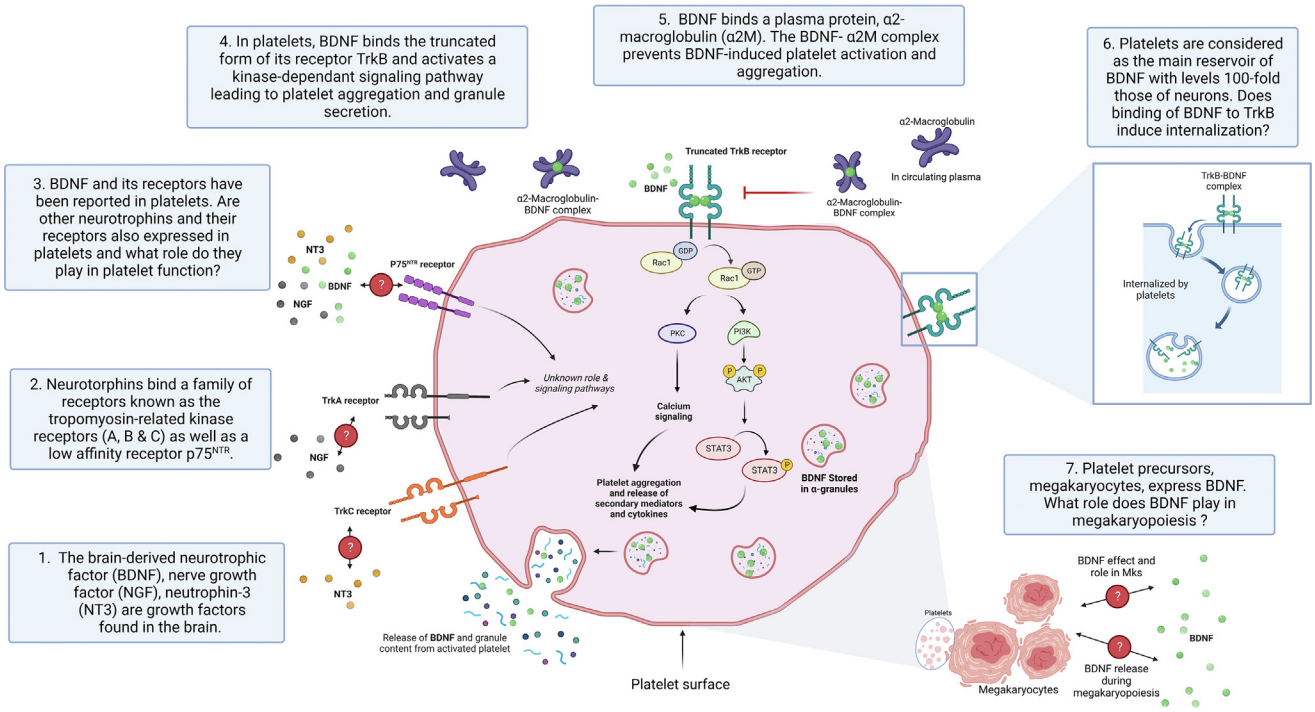
Ton Lisman, PhD



For references, see von Meijenfeldt [23]; Driever [24]

Platelets and neurotrophins

Marie Lordkipanidzé, BPharm, MSc, PhD, FOPQ

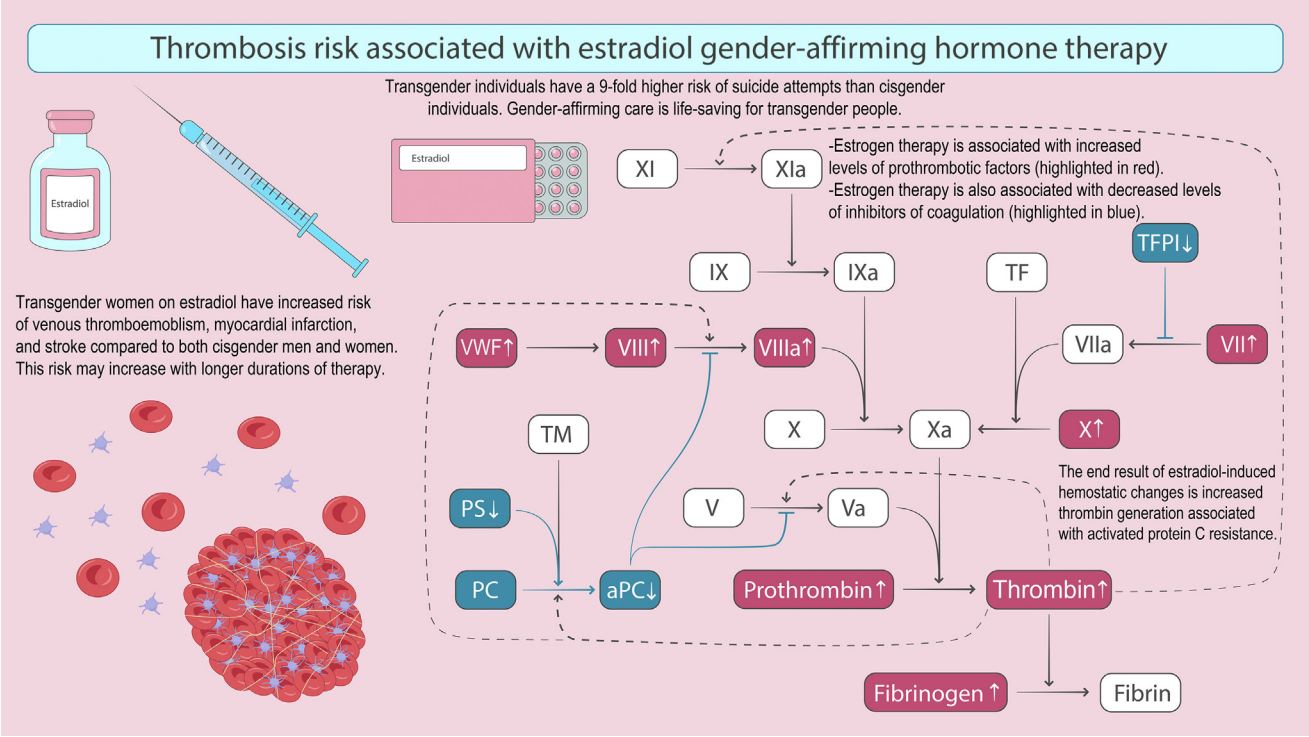


The better characterized neurotrophin in platelet biology is the Brain-Derived Neurotrophic Factor (BDNF), which induces platelet aggregation through binding of its truncated receptor Tropomyosin-related Kinase B (TrkB) on the platelet surface. The regulation of BDNF in the bloodstream is dependent on alpha2-macroglobulin, limiting platelet activation to the site of vascular injury. While it is known that platelets are the main reservoir of BDNF in circulation, the origin of the platelet pool of BDNF remains debated. It appears to be partly inherited from megakaryocytes, and possibly also endocytosed from circulation. Surprisingly, in addition to packaging BDNF into platelets, megakaryocytes release BDNF during megakaryopoeisis, the role of which both in the bone marrow and in circulation remains to be established. Also present on the platelet surface are the other neurotrophin receptors (TrkA, TrkC & $p75^{NTR}$). However, their role and signaling mechanisms remain largely unknown.

For references, see Boukhatem et al. [25]; Fleury et al. [26]; Chacón-Fernández et al. [27]

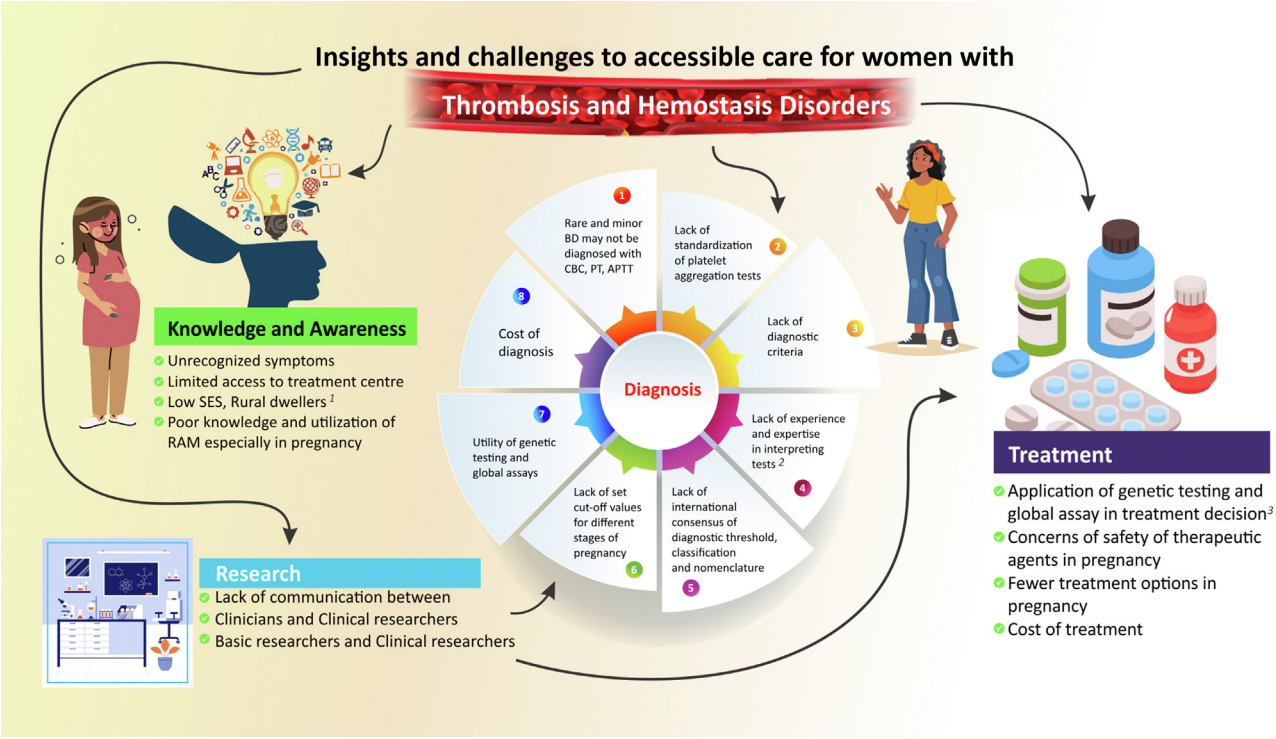
Thrombosis risk associated with transgender care

Eric Mullins, MD



Insights and challenges to accessible care for women with thrombosis and hemostasis disorders

Helen Chioma Okoye; MBBS, MSc, FMCPath, FWACP

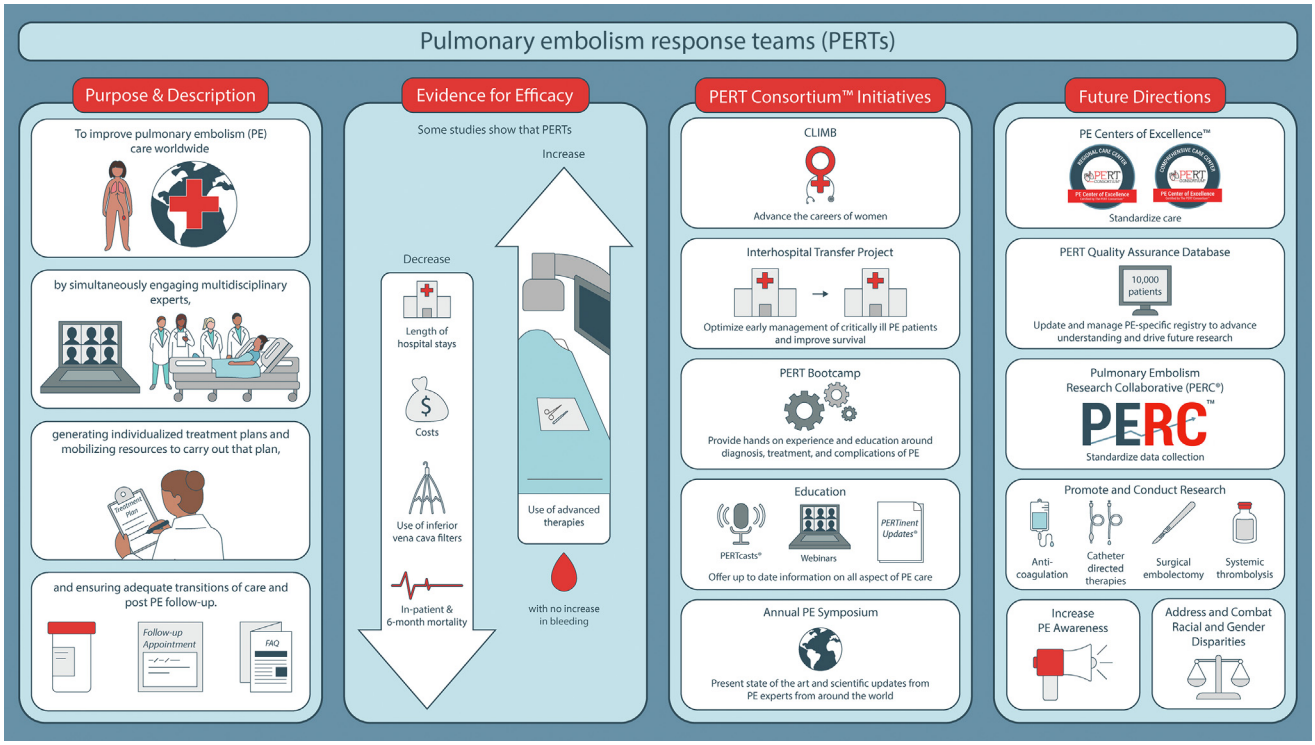


SES – socioeconomic status; RAM – risk assessment model; CBC – complete blood count; APTT – activated partial thromboplastin time test; PT – prothrombin time test

For references, see Arya et al. [28]; Okoye et al. [29]; Murray et al. [30]

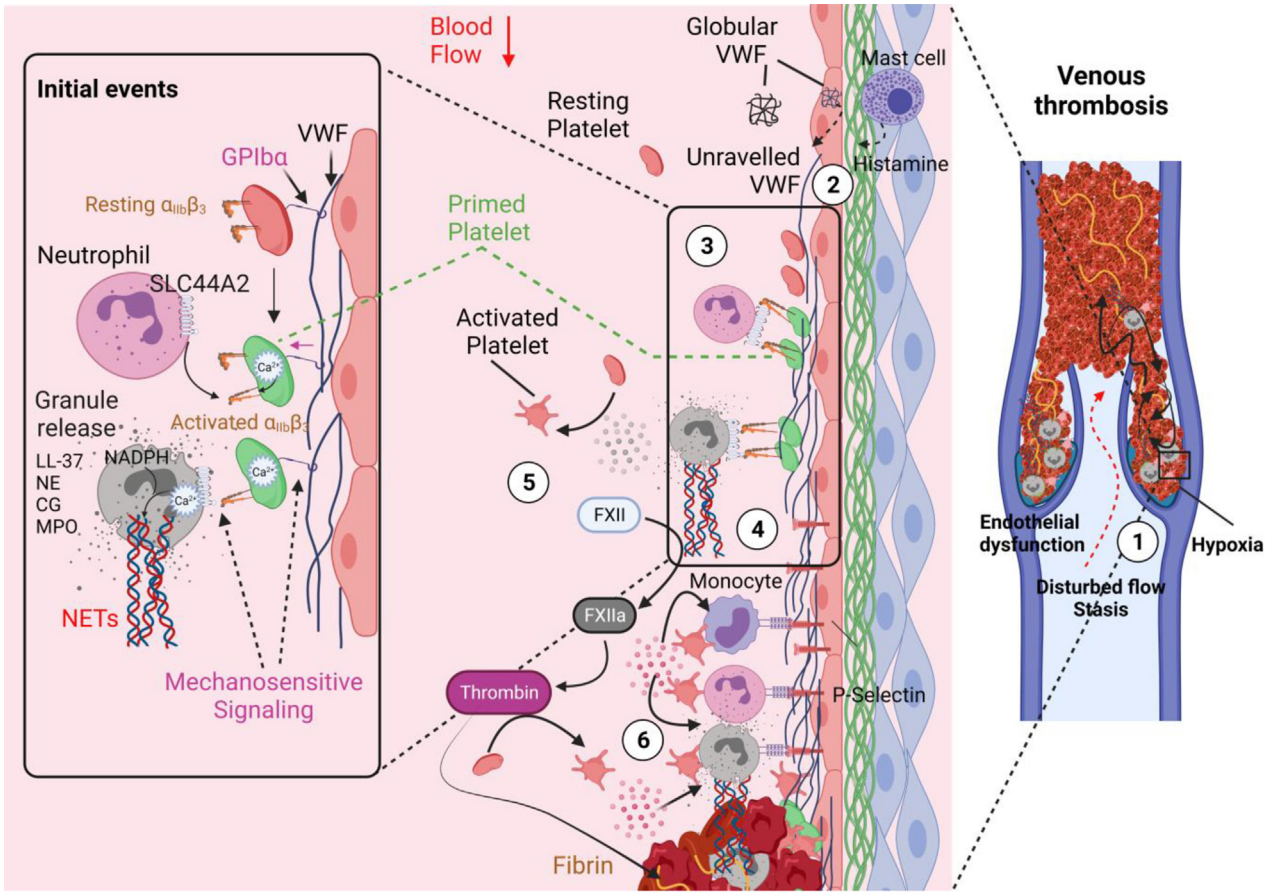
Pulmonary embolism response teams: purpose, evidence for efficacy, and future directions

Rachel P. Rosovsky



Platelet receptors in immunothrombosis

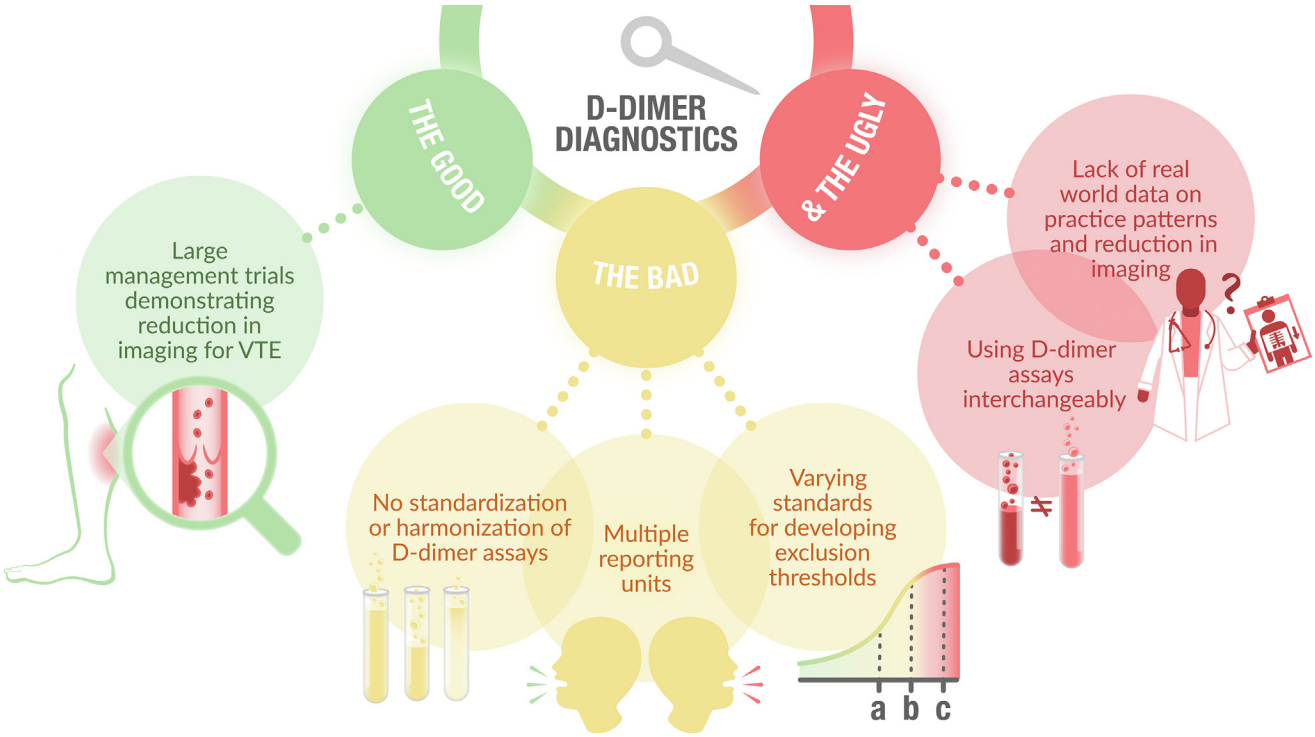
Isabelle I. Salles-Crawley, PhD



1. Venous valve pockets are prone to thrombosis where disturbed flow/stasis creates a pro-thrombotic milieu where hypercoagulability of the blood, hypoxia and endothelial dysfunction trigger thrombus formation which further precipitate this vicious circle.
2. Procoagulant VWF is released from endothelial cells, and under disturbed flow conditions can become unravelled, exposing its A1 domain enabling platelet binding via GPIbα.
3. The VWF-GPIbα interaction under flow induces mechanosensitive signalling leading to Ca^{2+} release from platelet intracellular stores and activation of $\alpha_{IIb}\beta_3$.
4. Neutrophils via SLC44A2 can bind activated $\alpha_{IIb}\beta_3$ on primed platelets and undergo NET formation that is dependent upon shear forces.
5. Activated neutrophils can directly activate platelets through release of granules (e.g. LL-37, neutrophil elastase [NE], capthepsin G [CG], myeloperoxidase [MPO]) or indirectly by generating thrombin via NETs [activation of FXIIa and inhibition of TFPI]
6. Activated platelets can bind to monocytes and neutrophils and further activate them by releasing granule content (e.g. P-selectin, HMGB1, CCL5, CXCL4, CXCL5, serotonin). Monocytes and neutrophils are recruited to the endothelium via PSGL-1 binding to endothelial P-selectin. NETs promote thrombus development and stability which ultimately block the valve and upstream vein causing deep vein thrombosis.

D-dimer diagnostics: can i use any D-dimer assay? bridging the knowledge-to-action gap

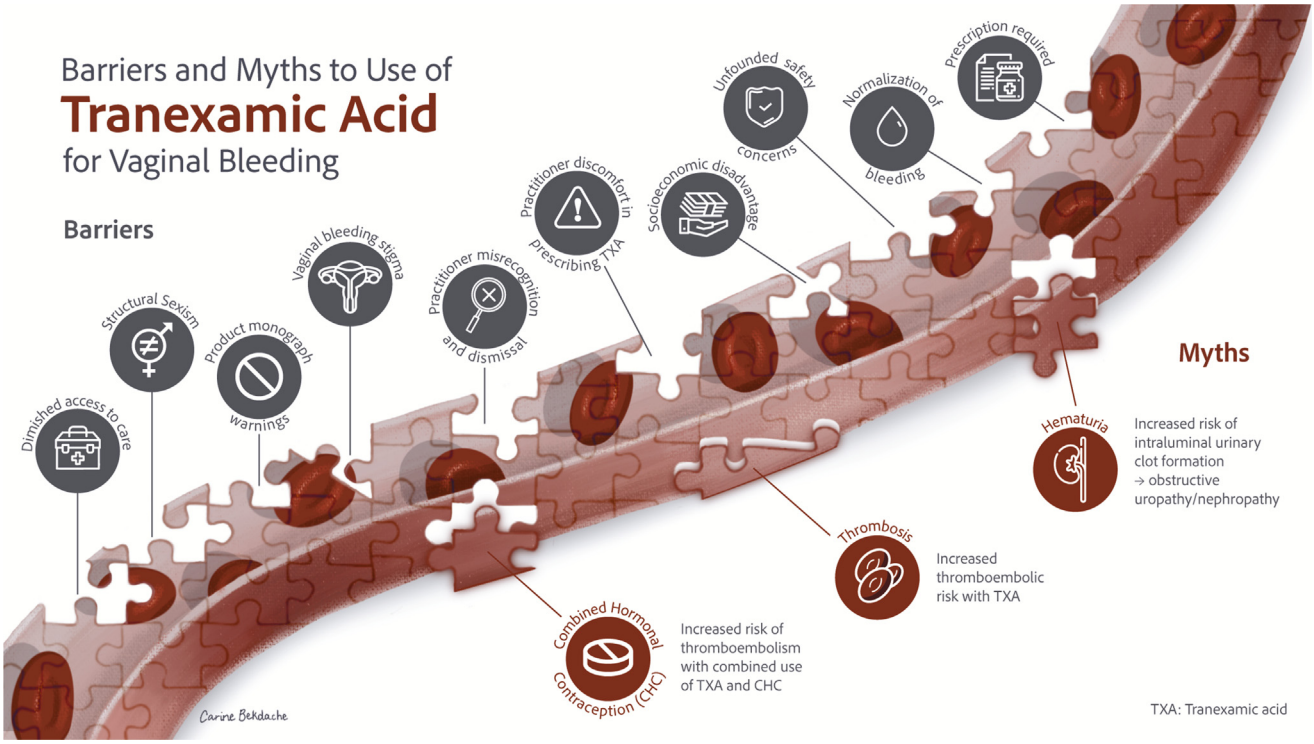
Rita Selby, MBBS, FRCPC, MSc



VTE – venous thromboembolism

Barriers and myths to use of tranexamic acid for vaginal bleeding

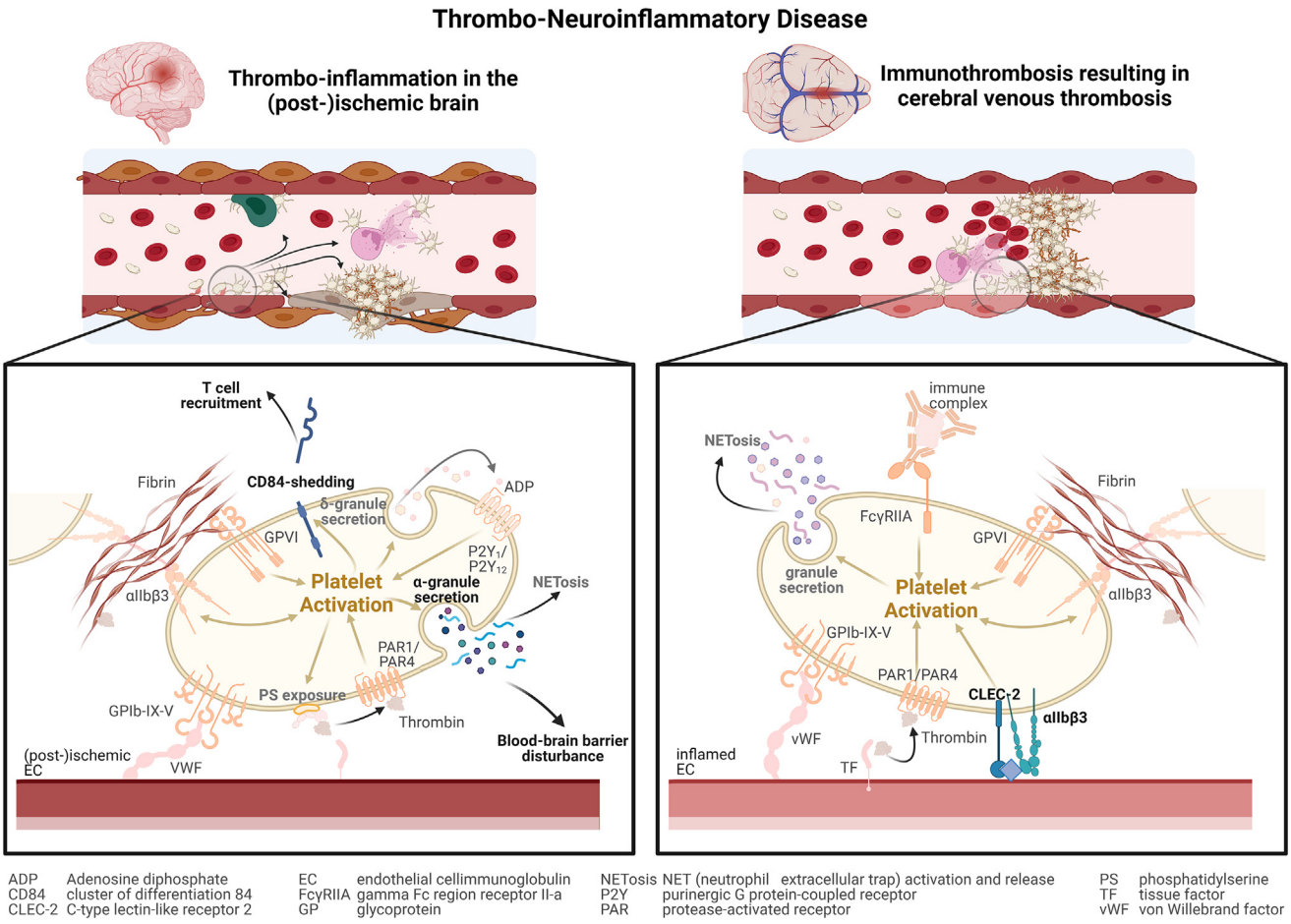
Michelle Sholzberg MDCM, MSc., FRCPC



Heavy vaginal bleeding is the most common symptom experienced by women with bleeding disorders [31]. Tranexamic acid (TXA) is an antifibrinolytic agent that is highly effective in the treatment of heavy vaginal bleeding. Despite its known benefits, there are pervasive myths, individual- and structural-level barriers that preclude its use, interfere with effective patient care and propagate health inequity in women's health. [31,32,33].

Thrombo-neuroinflammatory disease

David Stegner, PhD



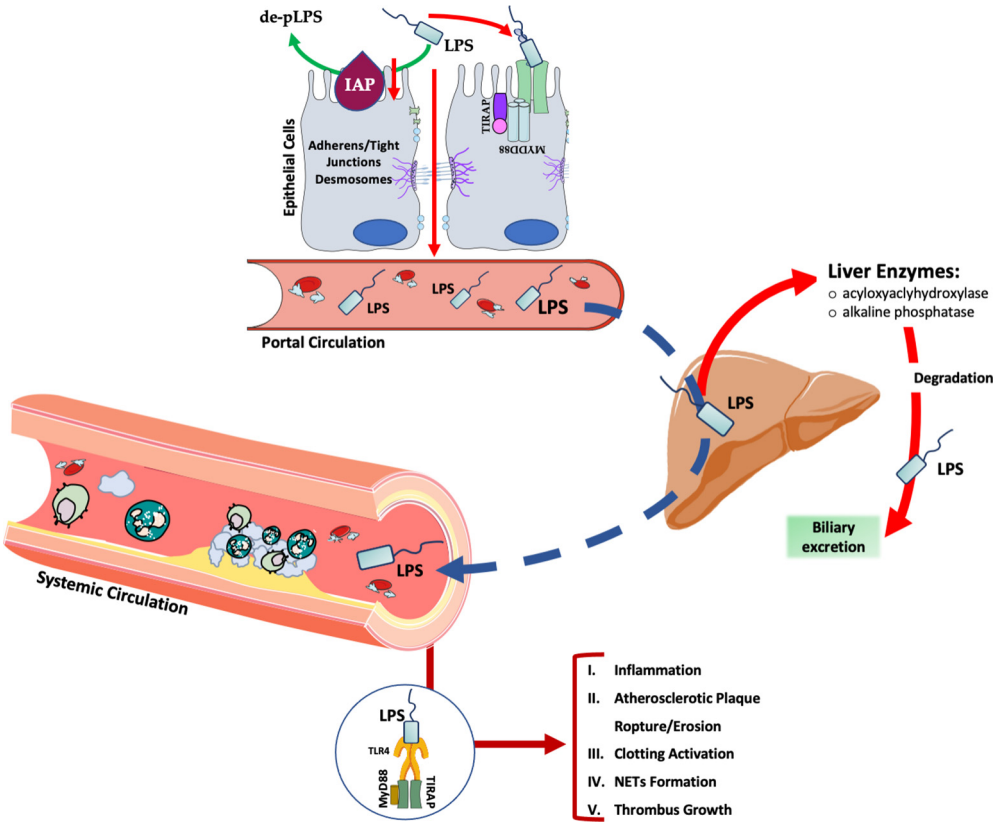
ADP Adenosine diphosphate
CD84 cluster of differentiation 84
CLEC-2 C-type lectin-like receptor 2
EC endothelial cellimmunoglobulin
FcγRIIA gamma Fc region receptor II-a
GP glycoprotein
NETosis NET (neutrophil extracellular trap) activation and release
P2Y purinergic G protein-coupled receptor
PAR protease-activated receptor
PS phosphatidylserine
TF tissue factor
vWF von Willebrand factor

Interactions between platelets, endothelial cells and immune cells contribute to cerebral damage in the context of ischemic stroke and cerebral venous thrombosis (CVT) [34-36]. Following ischemic stroke, platelets become activated at the (post-)ischemic endothelium and procoagulant (promoting plasmatic coagulation and fibrin formation) and secrete their granule content. This contributes to blood brain barrier breakdown and promotes the formation of neutrophil extracellular traps (NETs). Moreover, platelet receptors are shed and soluble CD84 recruits T cells that further aggravate infarct progression. Notably, following recanalization, cerebral thrombosis is no major driver of infarct progression anymore. Instead, proper platelet aggregation is critical to prevent intracerebral hemorrhage in the post-ischemic phase.

In the context of CVT, the situation is different: Here, inflammation triggers overshooting platelet activation resulting in occlusive thrombus formation leading to detrimental CVT. Still, the underlying mechanisms are poorly understood, but platelet (hem)ITAM receptors and αIIbβ3 seem to be crucial.

Gut microbiota and cardiovascular risk

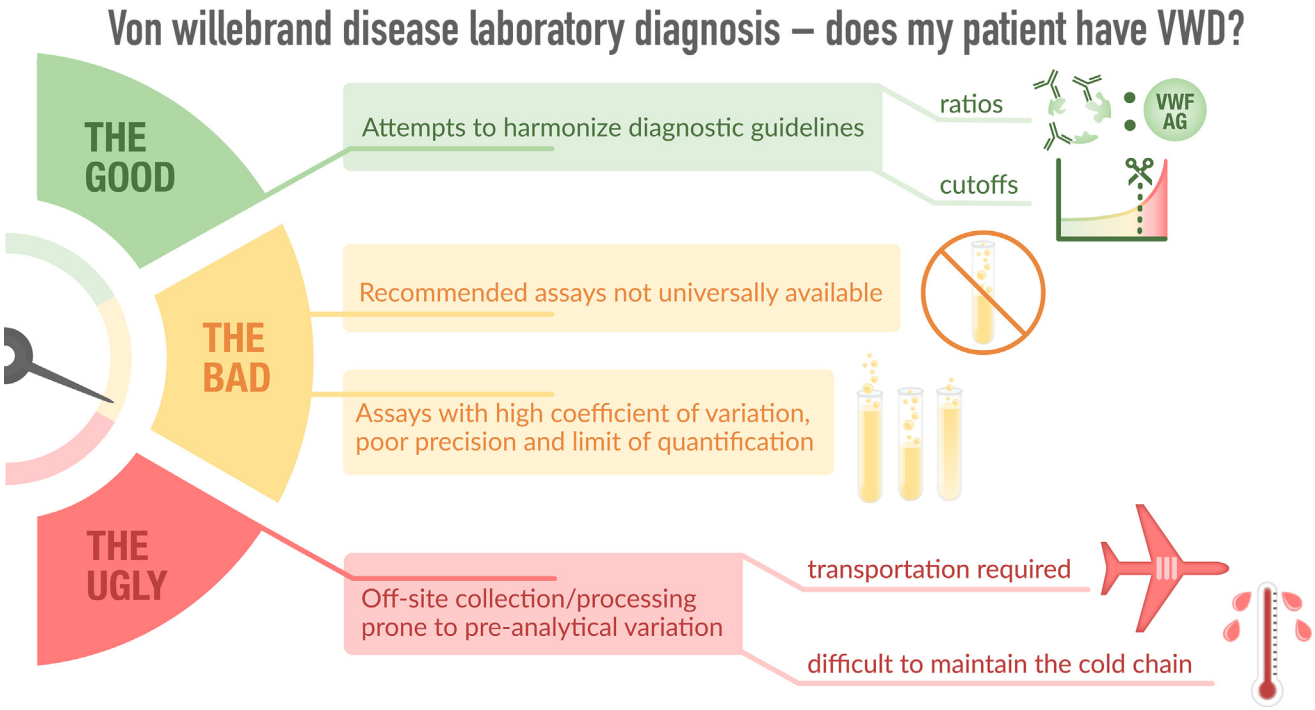
Francesco Violi, MD



Gut dysbiosis may enhance gut permeability to elicit translocation of lipopolysaccharide (LPS) into portal and eventually systemic circulation. Gut as well as liver cells possess an enzymatic armamentarium to catabolize or blunt the toxic effect of LPS. Thus, intestinal cells express the intestinal alkaline phosphatase, that catabolizes LPS, and synthesizes HDL3, that prevents LPS interaction with its receptor toll-like receptor 4 (TLR4); similarly, livers cells express an alkaline phosphatase and hydrolases to catabolize LPS. In case of exaggerated LPS translocation into portal circulation, LPS localizes into liver cells and eventually arterial wall, where it can induce an inflammatory status by interacting with TLR4, leading to non-alcoholic fatty liver disease or favoring atherosclerotic and thrombotic process respectively [37].

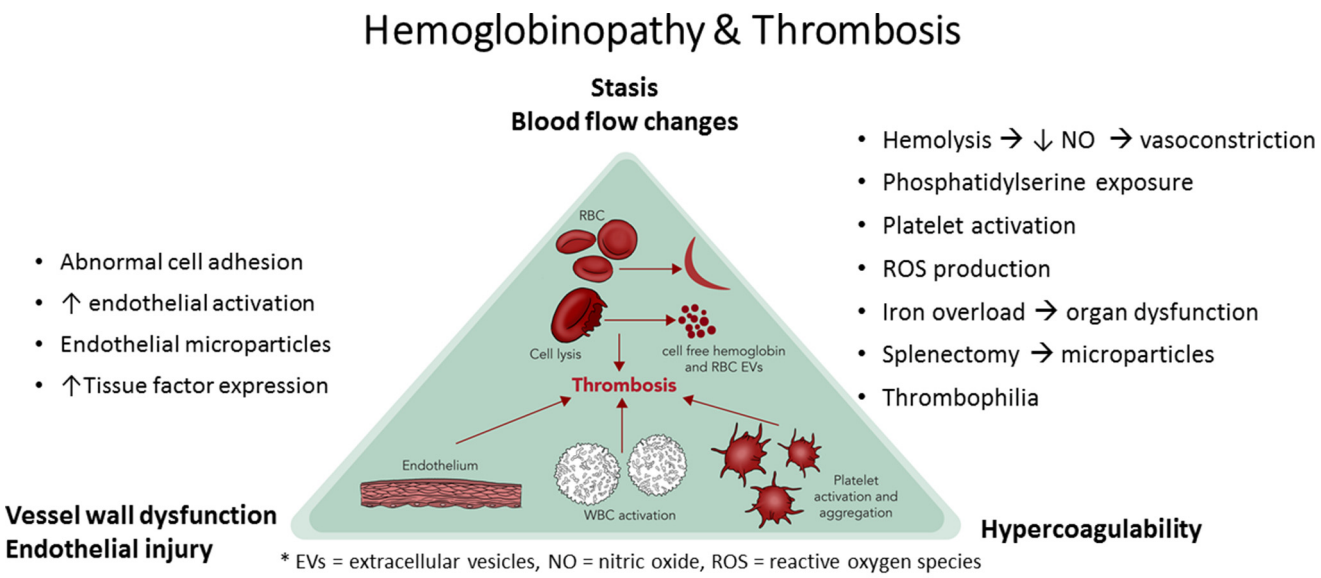
Von willebrand disease laboratory diagnosis – does my patient have VWD?

Angela C. Weyand, MD



Hemoglobinopathy and thrombosis

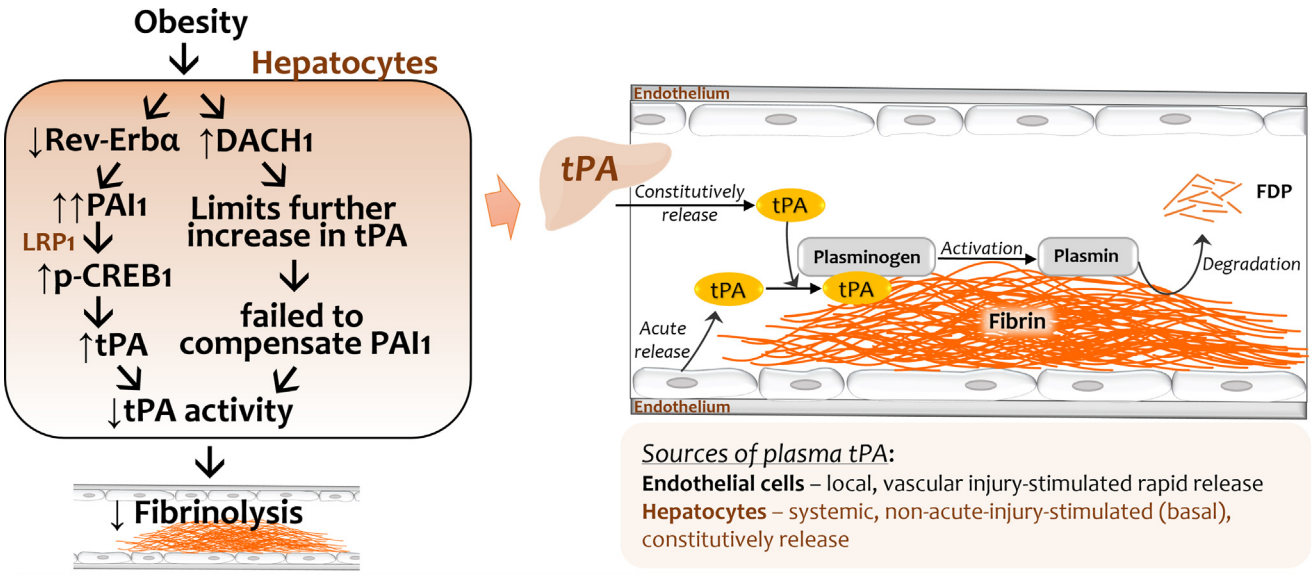
Suzan Williams, BSc, MSc, MD



The activation of the coagulation system in hemoglobinopathy is multifactorial. Hemolysis a triggering factor for thrombosis in both sickle cell disease and thalassemia. Endothelial activation and injury, increased platelet activation, platelet aggregation, vasoconstriction from a dysregulated NO pathway all contribute to thrombotic risk. The increased recognition of thrombotic events in patients with hemoglobinopathy warrant future studies to optimize prevention and treatment.

Fibrinolysis in obesity and dyslipidemia

Ze Zheng, MBBS, PhD



tPA, tissue plasminogen activator
LRP1, LDL receptor related protein 1
DACH1, Dachshund homolog 1
PAI1, plasminogen activator inhibitor
p-CREB1, phosphorylated cAMP responsive element binding protein 1
Rev-Erbα, Reverse strand of Erbα (nuclear receptor subfamiliy 1 group D member 1)
FDP, fibrin degradation product

Obesity increases risks for arterial, venous, and microvascular thrombosis. Hepatocytes synthesize both tissue plasminogen activator (tPA), the serine protease initiating fibrinolysis and the serpin plasminogen activator inhibitor, PAI1 [38,39]. A balance between tPA and PAI1 in plasma is important for breaking down fibrin clot without compromising clotting. The hepatocyte-derived tPA contributes to basal blood tPA concentration, and works in concert with tPA released from endothelium upon vascular injury, thereby initiating fibrinolysis [39]. Lipid-overloaded hepatocytes have reduced transcription co-repressor Rev-Erbα, leading to increased PAI-1, which then stimulates tPA synthesis via a PAI-1-LRP1-PKA-p-CREB1 pathway [40]. This PAI-1-stimulating tPA production mechanism functions as a compensatory pathway to compete with the large increase of PAI-1. However, the small induction of tPA synthesis is limited by its transcription repressor DACH1, which is induced in obese livers. In hepatocytes, where lipids are loaded and incorporated into lipoproteins, this PAI-1-tPA regulatory network influences the degree of impaired fibrinolysis in obesity [40].

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