

Basic science research opportunities in thrombosis and hemostasis: Communication from the SSC of the ISTH

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Abstract

Bleeding and thrombosis are major clinical problems with high morbidity and mortality. Treatment modalities for these diseases have improved in recent years, but there are many clinical questions remaining and a need to advance diagnosis, management, and therapeutic options. Basic research plays a fundamental role in understanding normal and disease processes, yet this sector has observed a steady decline in funding prospects thereby hindering support for studies of mechanisms of disease and therapeutic development opportunities. With the financial constraints faced by basic scientists, the ISTH organized a basic science task force (BSTF), comprising Scientific and Standardization Committee subcommittee chairs and co-chairs, to identify research opportunities for basic science in hemostasis and thrombosis. The goal of the BSTF was to develop a set of recommended priorities to build support in the thrombosis and hemostasis community and to inform ISTH basic science programs and policy making. The BSTF identified three principal opportunity areas that were of significant overarching relevance: mechanisms causing bleeding, innate immunity and thrombosis, and venous thrombosis. Within these, five fundamental research areas were highlighted: blood rheology, platelet biogenesis, cellular contributions to thrombosis and hemostasis, structure–function protein analyses, and visualization of hemostasis. This position paper discusses the importance and relevance of these opportunities and research areas, and the rationale for their inclusion. These findings have implications for the future of fundamental research in thrombosis and hemostasis to make transformative scientific discoveries and tackle key clinical questions. This will permit better understanding, prevention, diagnosis, and treatment of hemostatic and thrombotic conditions.

KEYWORDS

hemorrhage, hemostasis, innate immunity, platelet, thrombosis

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1 | INTRODUCTION

The International Society on Thrombosis and Haemostasis (ISTH) is the leading global organization dedicated to the advancement of understanding, prevention, diagnosis, and treatment of conditions related to thrombosis and hemostasis. As part of the recent strategic planning for the Society, ISTH Council leadership created a working group to review the current state of fundamental research into thrombosis and hemostasis. Funding directed toward discovery research in thrombosis and hemostasis has seen a significant reduction in the last 8–10 years. In the same period there has been a steady decline in the number of basic science abstracts submitted to the ISTH congresses (Figure 1). Based on these findings, the Council working group recommended the creation of a basic science roadmap to prioritize areas of research that the Society could support to address the current scientific challenges in the field of thrombosis and hemostasis. As a first step, the ISTH collaborated with the American Heart Association to develop a joint statement focused on venous thromboembolism.¹ The ISTH would then follow up with a roadmap that would incorporate hemorrhagic, thrombotic, and platelet disorders to cover the entire field. The Scientific and Standardization Committee (SSC) of the ISTH was identified as the ideal body to create a new SSC task force to develop the ISTH roadmap. Members of the basic science task force (BSTF) were chosen from the SSC Executive Committee and from leadership in SSC subcommittees with a primary focus on basic science. The BSTF was asked to prioritize the topic areas that would benefit from increased emphasis over the next 3–5 years.

Hemostasis is a vital physiological mechanism that has two distinct but simultaneously occurring functions: (1) to stop the bleeding when disruption of the vessel integrity occurs; this process involves formation of hemostatic plugs comprised of platelets and fibrin; and (2) to maintain blood fluidity within the blood vessel so there is an adequate and constant blood circulation within the body. These two apparently contradictory functions of the coagulation system can only be performed when there is a balance between a constant

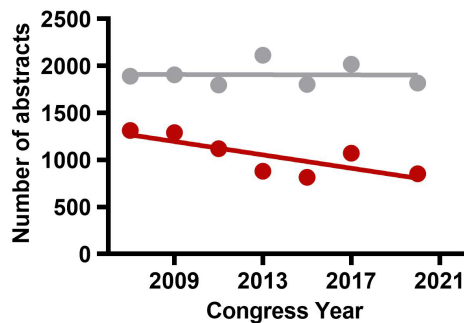


FIGURE 1 Abstract submission to the ISTH Congresses. Linear regression analysis of clinical (gray) and basic abstracts (red) submission to the ISTH congresses from 2007–2020. The data from 2019 (ISTH Melbourne) were considered an outlier and not included due to the lower number of total submission of abstracts (774 basic and 1363 clinical). Source of data: ISTH Headquarters

basal level of coagulation activation and a continuous but low level of anticoagulation. Any pathological deviation of this system can lead to excessive blood clot formation (thrombosis) or to bleeding (hemorrhage).

Thrombosis is one of the most frequent causes of mortality worldwide, as it is the common etiology of ischemic heart diseases, ischemic stroke, and venous thromboembolism (VTE). The development of new antithrombotic therapies and strategies has revolutionized the medical management of patients with thrombosis. However, with the currently available agents there still is an accompanying risk of bleeding complications.

Bleeding complications, arising due to an imbalance in the hemostatic system, also pose a major medical issue. Bleeding can occur in patients with (genetic) coagulation defects, in patients with a normal coagulation system who experience severe postoperative bleeding, in those that undergo surgical procedures known to be associated with major blood loss, and in major trauma. Furthermore, bleeding can be a side effect of anticoagulant therapy. For example, the annual rate of major bleeding when direct acting oral anticoagulants (DOACs) are used in atrial fibrillation patients is between 2% and 3%.² To understand the crucial balance between coagulation and anticoagulation, fundamental research into the field of thrombosis and hemostasis is essential. The current position paper provides insights into areas of basic science in the field of thrombosis and hemostasis that merit attention in the coming years.

2 | METHODS

The BSTF first convened in May 2020 and set to work developing a clear scope for the project. The project scope, agreed in June 2020, was as follows:

To develop a set of recommended priorities for basic science in thrombosis and hemostasis, communicate these priorities to build support in the thrombosis and hemostasis community, and use the priorities to inform ISTH basic science programs and policy.

Of note is the use of the term “priorities” in the initial scope of the project. As the project progressed, BSTF members chose to reframe topics as “opportunity areas,” to communicate that while the opportunities discussed in this article are deemed important by the BSTF, they are not necessarily of higher priority relevant to the many other basic science topics in thrombosis and hemostasis.

The BSTF met via teleconference throughout 2020 and 2021 to discuss potential opportunity areas for inclusion in this project. Opportunity areas were listed comprehensively, and then collaboratively refined and combined where deemed appropriate to develop a complete inventory for scoring and prioritization. The BSTF work was conducted using a modified Delphi process which included a quantitative decision matrix scoring method described below (and within supporting information).

The BSTF members independently identified the top three to five criteria by which candidate basic science opportunity areas would be ranked. These criteria were discussed and refined by the BSTF who then scored the criteria based on importance. Four criteria were determined by which candidate opportunity areas would be assessed to determine their inclusion in this project. The BSTF then agreed on scoring weights for each of the criteria to be used in prioritization of candidate opportunity areas. The final criteria and their scoring weights are shown in [Table 1](#).

Each candidate opportunity area was scored across the defined criteria ([Table 1](#)) by each BSTF member. In the first scoring round, candidate opportunity areas were scored relative to each other, and in the second round, the opportunity areas were scored independently. The BSTF evaluated the score results, and examined overall scores for candidate opportunity areas as well as the scores for individual criteria. Special attention was paid to outlier scores, with discussion to determine the cause behind outliers and determination of their significance. Three of the seventeen opportunity areas identified by the BSTF were deemed to encompass the majority of the other opportunity areas. These three areas, mechanisms causing bleeding, innate immunity and thrombosis, and venous thrombosis, were used to group all the other opportunity areas ([Table 2](#)).

3 | OPPORTUNITY AREAS FOR THROMBOSIS AND HEMOSTASIS FUNDAMENTAL SCIENCE

The 14 opportunity areas identified ([Table 2](#)) were subdivided into clinical and translational themes that relate to five key fundamental research topics including (1) blood rheology-driven vascular effects, (2) platelet production and function, (3) cellular contributions to thrombosis and hemostasis, (4) structure–function of hemostatic proteins, (5) and assessing and visualizing hemostasis ([Figure 2](#)). Below, we outline each of these fundamental research topics, and identify their clinical and translational opportunities and implications for the future of discovery research in thrombosis and hemostasis.

TABLE 1 Criteria by which basic science opportunity areas were ranked by the BSTF

Criteria	Definition	Weight
Originality and innovation	The potential for novel and high-impact research to be conducted in a research priority.	40%
Addresses unmet clinical needs or knowledge gaps	The degree to which a research priority has the potential to drive changes in clinical practice, or address areas of medical knowledge that are currently uncertain or unexplored.	30%
Translational research opportunities	The degree to which a research priority may encourage the development of translational research studies and initiatives.	15%
Research community interest	The level of interest and enthusiasm within the research community regarding new research within a research priority.	15%

Abbreviation: BSTF, basic science task force.

3.1 | Key fundamental research topics

3.1.1 | Blood rheology–driven vascular effects

Hemodynamics play a central role in hemostasis and arterial thrombosis, affecting all aspects of platelet function and coagulation. Thrombus formation is triggered by platelet–platelet and platelet–vessel wall interactions facilitated by blood flow, making rheology an important consideration in (1) platelet receptor function, such as von Willebrand factor (VWF) binding to glycoprotein (GP)Ib–IX–V; (2) thrombus stability, such as the physical removal/embolization of platelet aggregates; (3) the modulation of shear-sensitive receptors, and metalloproteinase function; (4) fibrin deposition and structure; (5) the onset of fibrinolysis; and (6) the delivery of antithrombotic and thrombolytic therapeutics. Clinical evaluation of platelet function and coagulation pathways largely rely on systems that exclude flow and shear stress considerations, and a major opportunity exists to develop new approaches, such as microfluidic devices that include dynamic rheology as a contributing factor.

Parallel plate flow chambers, glass microcapillaries, and microfluidic flow devices are established tools used extensively in hemostasis and thrombosis research, including mechanistic and pharmacological studies, antiplatelet agent screening, and diagnostic developments.^{3,4} These tools allow evaluation of thrombotic events under conditions that mimic the variable hemodynamic conditions found throughout the vasculature and in different (patho-)physiological settings. The next set of challenges will be to fully recapitulate vascular attributes through thrombus formation studies, where thrombin generation is permitted; and through standardized studies of irregular vascular geometries, where contributions from the endothelium, pressure gradients, and deformable basement membrane/matrices are included.

3.1.2 | Platelet production and function

Hematopoiesis generates bone marrow-resident megakaryocytes (MKs) that ensure continuous platelet production of 10^{11} platelets per day to maintain levels of 150 000–400 000 platelets per microliter of blood.⁵ Circulating platelet numbers are tightly regulated and

TABLE 2 Opportunity areas for basic science in thrombosis and hemostasis

Opportunity areas	Mechanisms causing bleeding	Innate immunity and thrombosis	Venous thrombosis
Assessing and visualizing hemostasis	✓	✓	✓
Blood rheology-driven vascular effects	✓		✓
Cancer-associated thrombosis			✓
Cellular contributions to thrombosis and hemostasis	✓	✓	✓
Major hemorrhage	✓		
Obesity-related thrombotic complications		✓	✓
Pathogen-induced effects (e.g., COVID-19, sepsis, etc.)	✓	✓	✓
Platelet production and function	✓		
Rare bleeding diseases	✓		
Rare thrombotic diseases		✓	✓
Safe anticoagulants	✓	✓	✓
Structure-function of hemostatic proteins	✓	✓	✓
Trauma-induced coagulopathy	✓		✓
Universal prohemostatics	✓		✓

Note: Fourteen opportunity areas were identified and subsequently organized into three overarching categories that umbrella many of the various topics.

determined by a host of genetic and molecular factors that control MK maturation and platelet release.⁶ In healthy humans, platelet levels rarely stray from precise numbers, but the mechanisms governing platelet production remain poorly understood. MKs, the platelet precursor cells, originate from pluripotent hematopoietic stem cells (HSCs) through a specialist series of lineage commitment steps, which are regulated by cytokine and growth factor signaling and differential expression of several transcription factors.⁷ MKs undertake a unique series of maturation steps that begin with endomitosis and polyploidization, followed by internal demarcation membrane system development, and finally proplatelet and platelet formation.⁸ A role for turbulent flow in proplatelet release⁹ has been proposed but, along with other pertinent factors, remains to be fully elucidated. This would be important information for programs focused on maximizing efficient platelet production *in vitro* for therapeutic applications, including transfusion.¹⁰

Thrombopoietin (TPO) is a hormone produced in the liver. TPO binds to myeloproliferative leukemia protein (cMPL), present on the surface of HSCs, MKs, and platelets, to regulate the differentiation of HSCs to MK precursor cells and enhance the rate of maturation of MKs, accelerating platelet production. However, the TPO/cMPL interaction is just one facet of the thrombopoiesis pathway.⁷ There are clearly other molecular players that strongly influence platelet production in both steady-state and emergency thrombopoiesis, as demonstrated in cMPL-deficient mice, in which the absence of TPO/cMPL engagement led only to reduced platelet production (by approximately 80%–90%) compared to healthy platelet counts.¹¹

TPO mimetics are approved for use in only limited clinical situations. With these mimetics, increased platelet counts occur in most recipients after months of treatment; however, responses are often

not durable or clinically meaningful.¹² Several studies have identified HSCs with an intrinsic MK bias and propensity to commit directly to the MK lineage, producing MK progenitors, MKs, and platelets bearing the stem cell antigen (Sca)-1 surface marker through this MK-biased pathway.⁸ Performing detailed analyses of this MK-biased pathway and identifying other thrombopoietic pathways remain key focuses of the field. Such analyses could reveal mechanisms of thrombopoiesis regulation that could be targeted by therapeutics treating thrombocytopenia in clinical situations in which bone marrow function is ablated.

3.1.3 | Cellular contributions to thrombosis and hemostasis

Traditionally, non-nucleated platelets have been considered the primary cellular component of thrombosis and hemostasis. Platelets are critical for stopping bleeding at injured vessel sites, but they also play an essential role in the development of arterial thrombosis. Depending on the agonist and environment, platelets are known to react in different ways. The existence of subpopulations of platelets, such as aggregating and procoagulant platelets, has become a subject of intensive research in the last decade.¹³ Future research on the generation and definition of platelet subpopulations and on their potentially distinct (patho)physiological roles in thrombosis, hemostasis, and inflammation is needed to identify novel therapeutic opportunities in the management of bleeding or thrombotic complications.

As our knowledge expands, other blood cells such as leukocytes and red blood cells (RBCs) are increasingly recognized as active

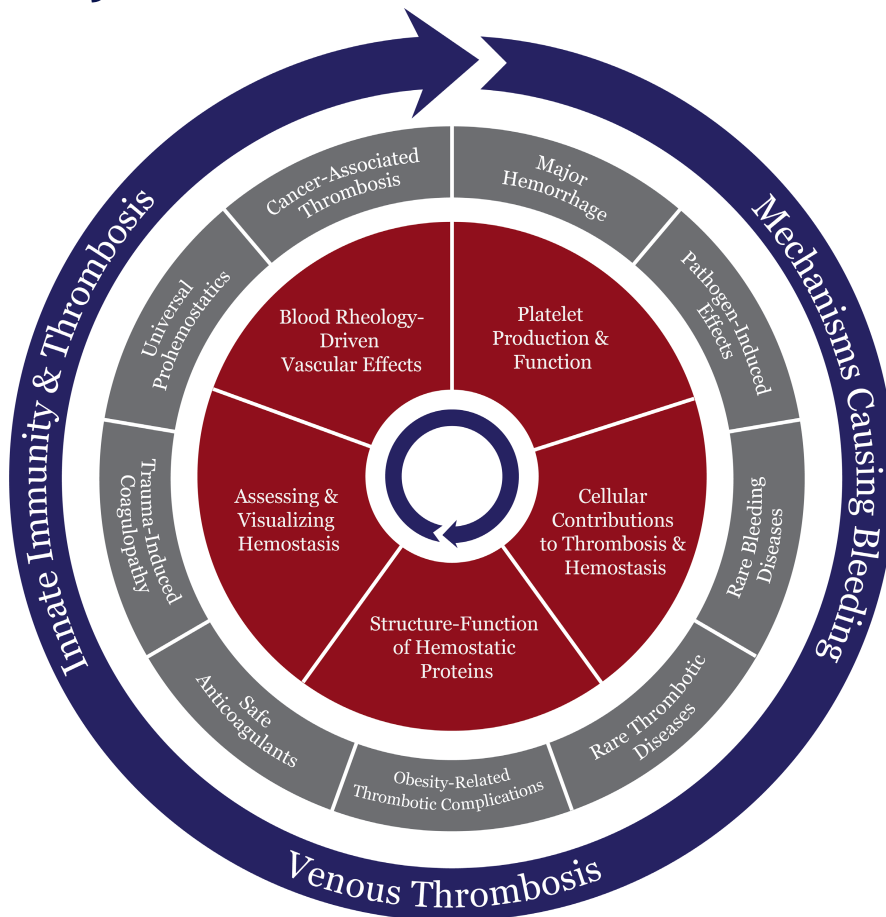


FIGURE 2 Opportunity areas in fundamental science in thrombosis and hemostasis. The 14 opportunity areas identified by the basic science task force were divided in key fundamental research topics (red) that can address the clinical and translational themes (gray) and their relationship with the three overarching categories (blue). The red and blue circles spin to align and address several opportunity areas in the static gray circle. The fundamental research topics are essential to drive new discoveries in clinical and translational research to enhance our understanding, diagnosis, and treatment of thrombotic and hemostatic disorders

contributors to thrombosis, but the underlying mechanisms are incompletely understood. For example, monocytes, macrophages, and neutrophils are known to regulate coagulation by expressing and releasing coagulation and fibrinolytic factors.¹⁴

Animal models of thrombosis have demonstrated a key role of neutrophils, either directly or after binding to platelets, in venous and arterial thrombosis.¹⁵ An important mechanism by which neutrophils can drive thrombus propagation is via the generation of neutrophil extracellular traps (NETs).¹⁶ The mechanisms via which NETs contribute to thrombosis include tissue factor and factor XII (FXII)-mediated initiation of coagulation, adhesion of platelets, recruitment of platelet adhesive proteins such as VWF, recruitment of red blood cells, and inhibition of thrombus breakdown.¹⁷ Continued research is required to further unravel the precise temporal and spatial involvement of leukocytes in different pathophysiological contexts, preferentially using physiologically relevant *in vivo* models of thrombosis. There has been renewed interest in the concept of RBC-mediated cellular effects on thrombosis and hemostasis. RBCs modulate blood clotting through various mechanisms, such as changing the blood flow viscosity and flow dynamics, forming procoagulant microparticles, interacting with platelets and endothelium, expressing adhesive proteins, and forming an impermeable barrier of tightly packed polyhedrocytes after clot contraction.¹⁸ An important consideration in regulation of thrombosis and hemostasis is the interaction of platelets, leukocytes, and RBCs with the endothelium. Indeed,

endothelial cells are also a crucial element of the hemostatic system and their integrity and functionality are critical to maintaining normal hemostasis and preventing thrombosis. Future research should focus on the reciprocal interaction of blood cells with the endothelium and with each other. Better understanding of the fundamental mechanisms of cellular mechanisms that drive thrombosis and hemostasis will lead to the identification of novel potential targets and pharmaceutical interventions for hemostatic and thrombotic disorders, potentially with reduced risks of bleeding. Such knowledge will impact other key areas of development, such as safe anticoagulants, blood rheology-driven vascular effects, and major hemorrhage.

3.1.4 | Structure–function of hemostatic proteins

There are many examples in which the structure–function of proteins has dictated the design and development of therapeutic strategies. Structure–function analysis of proteins can lead to enhanced function of the target or insensitivity to drugs or the human immune system. For example, tenecteplase is a second-generation thrombolytic agent that was developed from alteplase—a first-generation agent that is a recombinant form of tissue-type plasminogen activator (tPA). Protein engineering following structure–function analyses led to the development of tenecteplase, which has improved affinity for fibrin, increased resistance to plasminogen activator inhibitor 1,

and augmented half-life *in vivo* compared to alteplase.¹⁹ In addition, modifications to ADAMTS-13 (A Disintegrin And Metalloprotease with Thrombospondin type 1 motif, 13) render it resistant to autoantibody targeting during thrombotic thrombocytopenic purpura (TTP).²⁰

Determination of protein structures has been instrumental in the characterization of anticoagulant drugs. For example, the structures of thrombin and factor Xa have defined the interaction between the direct oral anticoagulants (DOACs) and their target enzymes via molecular docking of inhibitors into their target substrates.²¹ The antiplatelet drug tirofiban (Aggrastat[®]) is based on the observation that the Arg-Gly-Asp (RGD) triad identified in the parent disintegrin, echistatin (isolated from the venom of the saw-scaled viper), constitutes a specific recognition element for the platelet integrin $\alpha\text{IIb}\beta\text{3}$. Medicinal design of this compound resulted in a peptidomimetic, which had a 3000-fold increase in potency in inhibiting platelet aggregation over its parental compound echistatin.^{22,23} In addition, elucidation of structural changes that occur during activation of coagulation zymogens, factor XI, and prekallikrein, has provided a structural basis for the design of new and potentially safer anticoagulants, which can specifically target zymogen activation to prevent downstream thrombin generation.^{24,25}

3.1.5 | Assessing and visualizing hemostasis

Assessing and visualizing hemostasis represents a fundamental research area in the thrombosis and hemostasis field. The aim is to better understand clot characteristics, including clot formation and degradation processes. This includes examining clot formation at the molecular level, such as assessing associated protein interactions. Evaluation of clot characteristics can also be performed in more complex systems, such as *ex vivo* studies of plasma or whole blood, including all blood cells; *in vitro* models that include endothelial cells and blood flow; investigations using material such as obstructed blood vessels from deceased or living patients; and *in vivo* animal models. Techniques employed to assess and visualize hemostasis are hence extremely diverse. Examples include turbidimetric clot formation and lysis assays performed using plasma^{26,27}; Chandler loop^{28,29} and thromboelastography/rotational thromboelastometry experiments using whole blood³⁰; and microfluidic models that mimic a vessel structure lined with endothelial cells^{4,31-33} which, when combined with confocal microscopy, allow real-time clot formation experiments in whole blood under flow conditions. Of these techniques, recent developments include microfluidic models of various vessel geometries (such as bifurcations) and co-cultures of endothelial cells with vascular smooth muscle cells.^{34,35} In addition, clot characteristics have been assessed in obstructed blood vessels obtained from deceased patients or from patients undergoing surgical procedures. Intravital microscopy in animal models has allowed visualization and assessment of hemostatic plug formation in real-time in living organisms, while monitoring therapy outcomes. Animal models for thrombosis include not only the most common mouse

models, but also various species from zebrafish to non-human primates and a variety of triggers such as ferric chloride, laser injury, or mechanical (stasis).³⁶⁻³⁸

Methods to assess and visualize hemostasis are critical because they link to all opportunity categories and areas identified in this article. These methods can serve as tools to better understand underlying mechanisms in basic research and in translational research, allowing stratification of patients according to certain characteristics and risk factors. Methods to assess and visualize hemostasis will also be instrumental to approach prominent knowledge gaps, such as differences between the physiological process of hemostasis versus the pathological process of thrombosis, or the factors that determine hemostasis and thrombosis in different vascular beds.

3.2 | Overarching clinical and translational opportunity areas

These five fundamental research topics are crucial to our understanding and development of the opportunity areas identified in Table 2. Below, we discuss the overarching opportunity categories that encompass the various clinical and translational themes addressing under-researched areas in thrombosis and hemostasis (Figure 2).

3.2.1 | Mechanisms causing bleeding

Bleeding due to impaired hemostasis and increased antithrombotic activity can have serious consequences; uncontrollable bleeding is often fatal or permanently disabling, and thereby represents a serious medical challenge. Despite advances in identifying targets to potentially improve the efficacies of hemostatic and antithrombotic therapies, evaluation of the safety profile of novel reagents relies on testing of naïve volunteers in clinical trials. This is in part due to a lack of a comprehensive understanding of the mechanisms that cause bleeding in conditions such as trauma-induced coagulopathy, rare bleeding disorders, and major hemorrhage (Figure 2).

The key mechanisms that drive occlusive thrombus formation have largely been elucidated through *in silico*, *in vitro*, *ex vivo*, and *in vivo* models of intravascular thrombus formation in diseased vascular beds under shear flow conditions. Experimental models of bleeding that replicate rheological and vascular conditions found *in vivo* are less common and underdeveloped. The anxiety around assessing safety is largely due to basic scientific and fundamental mechanisms underlying hemostasis remaining undefined. The study of hemostasis *in vitro* will require development of microfluidic models of hemostatic plug formation, termed “bleeding chips,”³⁹ to study the spatial dynamics and cell biology of hemostasis under shear flow and samples with variable platelet counts.³⁹⁻⁴¹ The continued development of techniques such as photolithography to generate relevant vascular bed-specific geometries that can be endothelialized may be used to study pathways that protect against vascular leakage,

to identify targets, and to test agents that enhance the hemostatic function of platelets, endothelial cells, and the coagulation cascade without causing thrombosis.^{4,31,42} Novel *in vivo* models are required to study bleeding observed in vascular beds with high fibrinolytic activity and variable pressure gradients, which are critical in terms of patient safety and health; these new models would complement the current models of hemostatic plug formation in the setting of experimental trauma (such as punctures, tail clippings, and lacerations to the forearm).^{43,44}

A mechanistic understanding of thrombosis has facilitated the development of antithrombotic agents, targeting either platelets or the coagulation cascade, for use in the prevention and treatment of cardiovascular diseases. A fundamental understanding of the physiological interplay between blood cells and coagulation in the context of the hemodynamic microenvironment of vessels and tissues is required to predict bleeding events and to develop novel therapeutics to treat hemorrhage. This knowledge is requisite for predicting how hemostatic homeostasis may be challenged by on- or off-target effects of drugs, changes in blood cell counts, or pathological challenges (including bacteria and viruses).

3.2.2 | Innate immunity and thrombosis

Thrombosis, inflammation, and innate immune responses are closely linked. Various effectors of the hemostatic system are also potent pro-inflammatory mediators, and several innate immune responses promote the formation of a blood clot. Consequently, the terms “thromboinflammation” and “immunothrombosis” have been coined, emphasizing the close relationship between inflammation and thrombosis and the immune system and thrombosis, respectively.²⁶ For example, fibrin can stabilize hemostatic plugs to prevent blood loss after vascular injury, while also forming a physical barrier against invading pathogens. Similarly, both platelets and leukocytes actively bridge thrombotic and inflammatory pathways via common molecular amplification loops.⁴⁵ Although the concept of immunothrombosis indicates that thrombus formation may have a role in immune defense, uncontrolled escalation of the interplay between immune responses, inflammation, and hemostasis can trigger or aggravate typical immunothrombotic or thromboinflammatory complications, such as disseminated intravascular coagulation (DIC) in sepsis and acute thrombotic events in patients with atherosclerosis. Thrombotic complications in COVID-19 are another recent example that has been thrown into the limelight.^{46,47}

Research opportunities in the field of innate immunity and thrombosis include understanding the fundamental role of neutrophils, particularly NETs; the cellular and molecular mechanisms of platelet-leukocyte interactions; and the involvement of the complement system. Generated by neutrophils that release their decondensed chromatin as a network of extracellular fibers, NETs form a scaffold that is an important immune strategy against pathogens and is implicated in thrombosis.^{48,49} Platelets and leukocytes can exert thromboinflammatory effects via direct binding of platelets

to innate immune cells (neutrophils and monocytes/macrophages) or via secretion of cytokines/chemokines.^{45,50} Multiple bidirectional interactions between the complement system and coagulation have been described.⁴⁶ The challenge is now to extract those interactions that occur *in vivo* and are of (patho)-physiological relevance to identify potential therapeutic targets. Increasing our fundamental understanding of the cellular and molecular aspects constituting the link between innate immunity and thrombosis can be complemented via other opportunity areas, including assessing and visualizing hemostasis, the structure–function relationships of hemostatic proteins, and the development of safe anticoagulants (Table 2).

A better understanding of the fundamental mechanisms underlying immunothrombosis will help to identify new antithrombotic drug targets that do not interfere with normal hemostasis or immune response. Such insights could also become relevant for novel translational research lines that focus on new pharmacological antithrombotic approaches, such as pathogen-induced effects (such as COVID-19 and sepsis), obesity-related thrombotic complications, or rare thrombotic diseases.

3.2.3 | Venous thrombosis

Venous thromboembolism is a multifactorial, chronic disorder associated with considerable morbidity and mortality, resulting in a major burden to health care and the economy (Table 2). Every year, there are approximately 10 million cases of VTE worldwide, with approximately 60% of VTE cases manifesting during or after hospitalization.⁵¹ A recent report from the American Heart Association and the ISTH highlights the future research priorities in VTE.¹ VTE increases exponentially with age⁵²⁻⁵⁵ and is dramatically elevated in individuals over 55 years.⁵⁶ VTE is also associated with several disease states, with active cancer accounting for approximately 20% of the overall incidence of VTE.^{57,58} Importantly, cancer is a major cause of death in VTE patients and vice versa. Obesity is associated with a 2- to 5-fold increase in VTE compared to individuals within the normal body mass index range,⁵⁹⁻⁶¹ and similar significant increases in VTE are noted in metabolic syndrome⁶²⁻⁶⁵ and diabetic patients.^{66,67} The relationship between VTE and pathogenic infections has been an area of interest for some years but has jostled to the forefront by way of the COVID-19 pandemic.⁶⁸⁻⁷¹ VTE is now largely considered an immunothrombotic condition that may arise from changes associated with pathogenic infection or during sterile inflammatory states. To manage the burden of VTE in our society, it is imperative that we acquire a solid understanding of pathophysiological mechanisms that underlie this condition.

Elucidating the pathophysiology of VTE has been challenging due to the lack of models and tools available to replicate the complex underlying mechanisms. The German clinician Rudolf Virchow first described three key factors that predispose an individual to VTE, including venous stasis, a hypercoagulable state, and endothelial dysfunction, collectively known as “Virchow’s triad.” Virchow recognized that most diseases are caused by changes at

the cellular level, underscoring the importance of fundamental research in this area. Blood rheology very much determines the fate of a (venous) clot, and the strength of the thrombus. With structure–function research of proteins involved in the thrombotic process, novel targets for treatment may be identified. The involvement of platelets in venous thrombosis has gained traction recently. Similarly, the participation of other cells in the venous thrombotic process has received renewed interest, particularly perturbations in the endothelial layer, interactions between RBCs and the fibrin, and the role of NETs.

A major preclinical approach for understanding the mechanisms underpinning VTE is the development of appropriate models to reflect the various elements of the disease. In the past decade, several advances in animal models and biorheology technology have helped shape our understanding of VTE.⁷²⁻⁷⁵ Use of these models has permitted visualization of initiation, propagation, and stabilization events in deep vein thrombosis (DVT). These models are invaluable tools in exploring the complex etiology of the disease and in identifying novel targets for prevention and treatment of VTE. Combined with our advances in the understanding of cellular contributions to VTE, these models will define novel targets to moderate the hemostatic and inflammatory pathways to negate the burden of VTE on society. Recently, DOACs have proved to be effective in VTE treatment, but it is crucial that we detect the condition at an earlier stage and that we develop safer

anticoagulants, such as those that target the contact pathway for effective management of VTE. Similarly, given the immunothrombotic complications in VTE, therapeutic areas to explore may involve targeting the inflammatory and complement pathways to dampen these pathways *in vivo* and promote more efficient thrombus resolution. To identify novel target areas it is probable that an “omic” approach in large population-based epidemiological studies will be necessary. Inclusion of biological samples in biorepositories integrated with demographics and clinical and laboratory data will help to tease out the key drivers and shared risk factors for VTE in society.

4 | CONCLUDING COMMENTS

Thromboembolic conditions account for one in four deaths worldwide and remain the leading cause of mortality despite increased awareness of the disease and the development of novel treatment and diagnostic options. The rising aging population and the significant burden of metabolic disease and obesity indicate VTE may steadily increase despite our advances. It is apparent that we need to invest significantly in understanding the mechanisms underpinning these processes to decrease the incidence of mortality and disability caused by thrombotic conditions. To tackle this burden, we must employ a holistic approach in which we identify the basic mechanisms

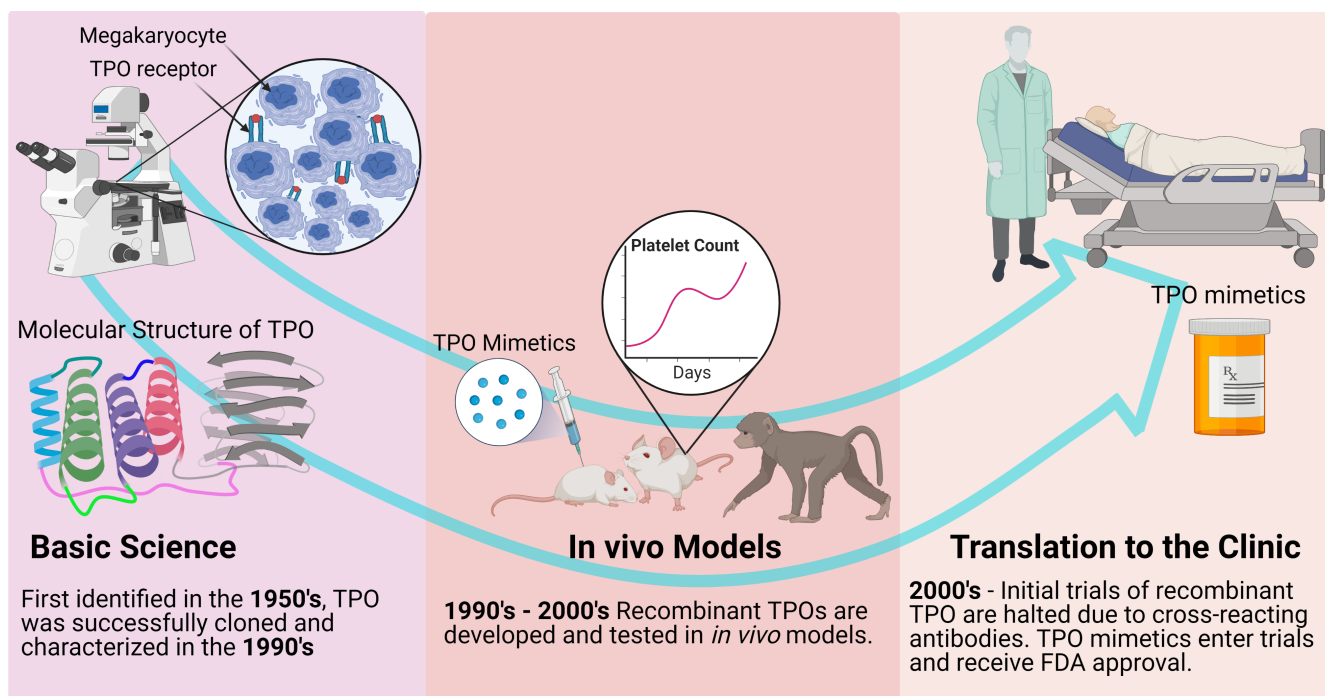


FIGURE 3 An example of a pipeline from discovery research through to a therapeutic with clear clinical outcomes. The existence of a hormone that regulated platelet production was first proposed in 1958,⁷⁸ but was not purified until 1994.⁷⁹ In the intervening years, dedicated discovery research was able to define the cellular pathway by which platelets were produced in the bone marrow by megakaryocytes, with careful cell culture and microscopy, protein purification techniques, and animal models of thrombocytopenia. Decades of work demonstrated that megakaryocytes respond to thrombocytopenia by increasing their number, size, and DNA ploidy, and from this fundamental research platform, the TPO mimetics were created, tested, and released for clinical use. FDA, US Food and Drug Administration; TPO, thrombopoietin

and interactions that drive thromboembolic disease. Similarly, the key drivers of hemostatic dysregulation in bleeding and trauma-induced coagulopathy are poorly understudied and mechanistically undefined. We require the development of novel tools, models, and imaging systems to drive our understanding of these conditions and to develop novel approaches with which to treat patients. This can be achieved by employing a reciprocal “bench to bedside” and “bedside to bench” pipeline (Figure 3), to accelerate our understanding and develop novel therapeutics to treat the myriad hemostatic complications. This was evident during the global COVID-19 pandemic during which scientists and clinicians worldwide rallied to understand the mechanisms promoting the coagulopathy associated with SARS-CoV-2 infection⁷⁶ and to define appropriate treatment options.⁷⁷ It is commendable to see the importance of fundamental science underscored in this crisis and heartening to see colleagues worldwide work together to resolve issues. It will be important to deploy this approach to tackle other important thrombotic and hemorrhagic conditions.

The SSC of the ISTH has played a vital role in evolving our understanding of hemostasis and thrombosis and in defining novel and appropriate models and diagnostic tools. The subcommittees thread together all aspects of hemostasis and thrombosis from fundamental research to translational approaches and clinical issues. However, it is evident in this setting that the funding available to discovery scientists to tackle key scientific questions has significantly dwindled in the past two decades thereby providing major challenges to researchers in the field. This is a call to action to challenge these financial constraints faced by fundamental scientists to foster new discoveries, identify novel targets, and develop sensitive therapeutics. This will promote interplay among all parties to tackle the key clinical and fundamental science questions in our field and improve diagnosis, treatment, and prevention of hemostatic and thrombotic conditions.

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CONFLICTS OF INTEREST

NJM, EEG, OJTM, SFDM, VS, and JCMM declare no conflicts of interest. SW serves as a paid consultant to ISTH.

AUTHOR CONTRIBUTIONS

All authors were members of the ISTH Basic Sciences Task Force and were involved in the identification and grading of the priorities. All authors contributed to the writing of the manuscript and approved the final version. NJM and JCMM edited and revised the manuscript.

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