EHA Perspectives on Non-malignant Hematology

Highlights from EHA2025 Congress held in Milan, Italy
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European Hematology Association

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Welcome

On behalf of the European Hematology Association (EHA), we are delighted to present one of the two EHA2025 Scientific Congress Reports, titled “EHA Perspectives on Non-malignant Hematology.”

These two Scientific Congress Reports have been developed as an initiative to provide our community with a concise overview of the most important works showcased at EHA2025. The new editions serve as an essential summary of scientific information and breaking news on the latest technological advancements in the field, relevant to clinicians, researchers, healthcare professionals, regulators, nurses, patients, payers, pharmaceutical representatives, and all stakeholders in hematology. Having introduced a new scientific content and formats at the EHA2025 Congress, the reports underscores the significance of the latest developments in the various fields of hematology.

This specific report focuses on non-malignant hematology including bone marrow failures, sickle cell diseases and other hemoglobinopathies, iron homeostasis and erythropoiesis, pathophysiology of hematopoietic stem cells, recent advances in the treatment of platelets disorders, as well as innovative developments in thrombotic and bleeding conditions, which are already driving advancements in clinical practice and patient care. Whether you attended the Annual Congress or not, and whether you are an EHA member or not, this is an important overview that you cannot afford to miss!

Martin Dreyling
EHA2025 Scientific Program Committee Chair

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- Dr. **Immacolata Andolfo**
  Assistant Professor of Medical Genetics/Department of Molecular Medicine & Medical Biotechnologies at the University of Naples
  Naples, Italy

- Dr. **Shahram Kordasti**
  Associate Professor and Group Leader in Applied Cancer Immunopathology at King’s College London
  London, England

- Dr. **Elisa Laurenti**
  Professor at the Cambridge Stem Cell Institute at the University of Cambridge
  Cambridge, England

- Dr. **Karina Meijer**
  Professor and Head of the Division of Hemostasis and Thrombosis at the University Medical Clinic, University of Groningen
  Groningen, Netherlands

- Dr. **Mirjana Mitrovic**
  Assistant Professor and Hematologist at the Clinic of Hematology, University Clinical Center of Serbia, University of Belgrade
  Belgrade, Serbia

- Dr. **Eduard van Beers**
  Associate Professor Hematology, Center for Benign Hematology, Thrombosis and Hemostasis, Van Creveldkliniek , University Medical Center Utrecht
  Utrecht, Netherlands

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Disclaimer

Expert videos

This scientific congress report was developed in collaboration with top experts in malignant hematology. While in Milan, some of the experts shared their personal highlights of the topics presented. Their videos can be viewed by clicking on the thumbnail at the beginning of the respective sections of the report.

More from EHA

This scientific congress report not only highlights the top contributions to hematology within the topics listed above, but as of this year also highlights other EHA activities and assets related to these topics. At the end of each section, you will find icons which are linked to the related elements. Here is a list of the icons and what they represent:


Meeting


Education

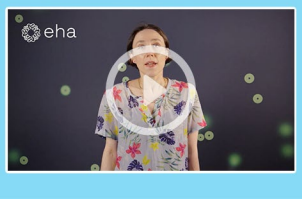

Paper/Guideline


Podcast


Activity

01

HSCs and their niche, from physiology to pathology



Dr. Elisa Laurenti shares her highlights on HSCs from EHA2025

Hematopoietic stem cells (HSCs) play a crucial role in the continuous replenishment of blood cells, occupying the top position in the hierarchy of hematopoietic cells. HSCs are defined by their potential to self-renew and differentiate into multiple cell types, producing all mature blood lineages in the bone marrow (BM). HSCs function through a hierarchy of intermediate progenitors, providing one replenishment pathway for each lineage.

The BM microenvironment, or niche, regulates HSC maintenance and differentiation by supplying essential components for self-renewal and ongoing hematopoiesis.

Fate mapping to identify lineage-restricted HSC pathways

In addition to previously identified myeloid- and lymphoid-biased HSCs, the full extent and the interplay of other lineage-biased restricted HSCs remain to be characterized.

Using single-cell transplantation, researchers have found that mouse HSCs have a limited range of lineage restriction patterns, with platelet-restricted (P-restricted) being the only single lineage-restricted HSCs they identified.[1] On the other hand, HSCs restricted to platelet-erythroid-myeloid (PEM) and PEM plus B-cell (PEMB) restricted lineages were common in young mice. No other patterns of lineage restriction or bias were observed in mouse HSCs.

Von Willebrand factor (Vwf)- positive P-HSCs and Vwf-negative multi-HSCs were not hierarchically

related and utilized alternative progenitor pathways for platelet replenishment and replenished phenotypically and molecularly distinct megakaryocyte progenitors. Platelet production through the P-restricted pathway was transiently enhanced upon acute progenitor depletion (chemotherapy) and aging.

For human HSCs, clonal hematopoiesis (CH) driver mutations were used to perform clonal HSC lineage fate mapping. PEM- and PEMB-HSCs were the only lineage-restricted HSCs observed. PEM- and PEMB-HSCs were hierarchically replenished from multilineage PEMB and T-cell (PEMBT) HSCs. PEM- and PEMBT-HSCs expanded upon aging but emerged at a young age.

Retrospective and prospective analyses revealed that human HSC clonal lineage replenishment patterns remained stable over time and following transplantation, suggesting that they were intrinsically programmed.

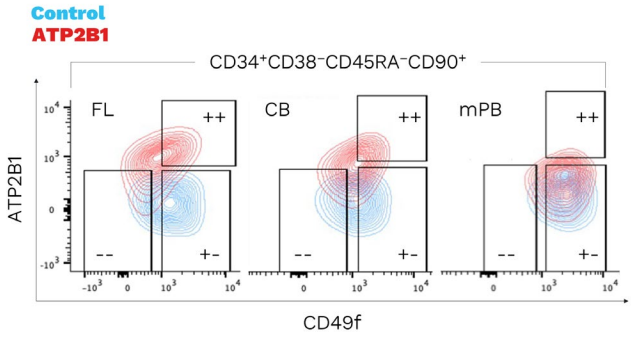
Markers of long-term human HSCs

Long-term hematopoietic stem cells (LT-HSCs) maintain lifelong hematopoiesis while preserving the stem cell compartment through self-renewal. The expression of canonical HSC markers, such as CD49f (integrin α6) and CD90, is most commonly used to resolve hematopoietic stem-enriched cells into short-term HSC and LT-HSC in humans. However, immunophenotypic markers to precisely purify LT-HSC from transiently repopulating short-lived progenitors, which are conserved throughout the lifespan, are still limited.

ATP2B1, a calcium-transporting ATPase, is a novel cell surface marker that is heterogeneously expressed by CD49f+ LT-HSCs across ontogeny, from fetal liver, neonatal cord blood, and adult mobilized peripheral blood sources.[2] ATP2B1 expression further separates CD49f+ HSC – the current gold-standard purification method – into two populations, with CD49f+ATP2B1+ LT-HSC

exhibiting superior long-term repopulation and self-renewal capacities *in vivo* compared to CD49f+ATP2B1– LT-HSC.

Representative flow cytometric plots of ATP2B1+/– and CD49f+/– cells within human HSC in fetal liver (FL), neonatal cord blood (CB) and mobilized peripheral blood (mPB)



Precision epitope editing in HSC

BM conditioning is typically required before HSC transplantation (HSCT); however, traditional approaches are highly genotoxic. Non-genotoxic BM conditioning using targeted immunotherapy has the potential to minimize adverse events in transplant patients.
Epitope editing is a precise genetic manipulation that introduces a single-nucleotide mutation, chosen to render HSCs and progenitor cells (HSPCs) invisible to immunotherapy. This technique can enable non-genotoxic conditioning and *in vivo* selection of HSPCs wherein the target epitope is removed without gene knock-out.
cKIT/CD117 – a well-established stem cell antigen – was analyzed with epitope mapping, which identified *KIT H378R* as a mutation that could abrogate the binding of the therapeutic antibody Fab-79D.[3] Validation confirmed that *KIT H378R*, installed via adenine base editing, maintained ligand binding and intracellular signaling.[1]
In vivo experiments revealed that KIT epitope-edited hematopoiesis, achieved through Fab-79D selection, preserved HSPC repopulation and multilineage differentiation capacity. Epitope editing could be combined with *BCL11A* therapeutic genome editing to co-select multiplex gene-engineered cells *in vivo* and induce fetal hemoglobin (HbF).
As separate clinical indications may require different potencies in antibody pharmacological actions, an anti-KIT SR-1 clone – an SCF-blocking monoclonal antibody (mAb) with 25 times the potency of FAD-79D – was also validated. When prime edited, it enabled non-genotoxic conditioning for hematopoietic replacement.
Epitope editing may eliminate limitations associated with mAb pharmacokinetics, enabling innovative HSC transplant strategies.

BM niche under stress conditions

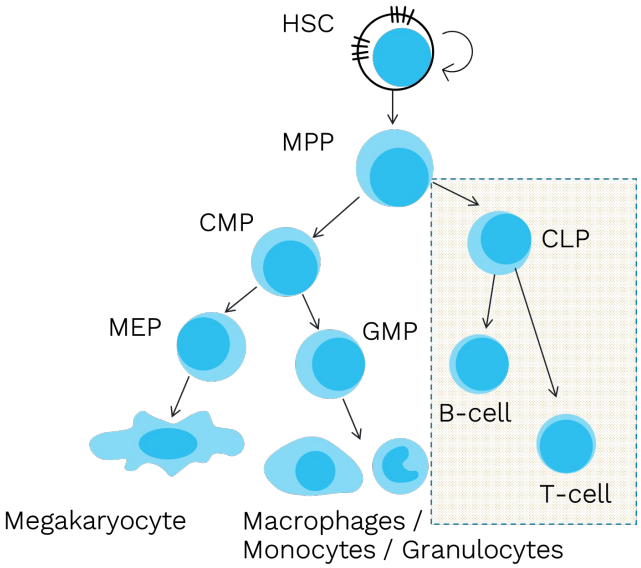
The BM microenvironment provides a structural framework to HSCs through the dense nature of stromal cell networks. Various immune and stromal cells shape the BM microenvironment, interacting with HSCs and regulating their state, while non-cellular substances such as growth factors, cytokines, and extracellular matrix (ECM) provide essential nutrients and signals for HSC growth and maintenance.
The non-hematopoietic stromal framework of BM consists of sinusoidal endothelial cells (SECs) and arterial endothelial cells, as well as the mesenchymal stromal cell (MSC) compartment – especially CXCL12-abundant LepR+ reticular cells (CARc), which play an active role in regulating hematopoiesis.[4] The organization and interaction between the SEC and CARc networks are highly conserved throughout the BM.
In mice, these stromal networks are highly resilient to injury, with complete rebuilding of a structurally normal network topology achieved after severe myeloablative destruction, through a self-organizing, regenerative process. The regeneration of a homeostatic CARc population activates stress repair pathways, particularly mTORC1 signaling, and causes long-term transcriptomic sequelae in the BM stroma, which are linked to alterations in ECM production and cellular senescence.
BM endothelial cells (ECs) play a crucial role in hematopoietic regulation, as demonstrated among others, in disease models such as Fanconi Anemia; however, the molecular drivers of dysfunctional ECs remain poorly understood. TGF-ß1 regulates hematopoiesis in various cell types, and its inhibition was tested to see if it could enhance hematopoiesis in dysfunctional EC models.[5]
TGF-β1 overexpression impaired BM EC functions *in vitro*, including migration and tube formation, while increasing apoptosis and levels of reactive oxygen species (ROS); these impairments could be restored by silencing TGF-β pathway genes. In a mouse model, AAV-mediated overexpression of a constitutively active TGF-β receptor (TGF-βRI) in BM EC resulted in impaired BM EC function and aggravated hematopoietic injury. Multi-omics studies have clarified that sustained activation of TGF-β1 drives BM ECs toward a maladaptive repair process, likely due to dysregulated crosstalk between the VEGF and Notch pathways, resulting in the activation of p38α.
To validate the clinical relevance of these findings, TGF-β1 was inhibited *in vitro* in samples from patients with poor graft function (PGF), as part of a prospective study involving matched patients with good graft function post-HSCT and healthy donors. TGF-β1 inhibition restored the function of BM ECs in the PGF patient samples.
Initial data from a prospective clinical trial evaluating luspatercept – a TGF-β ligand trap – in

patients with anemia following HSCT were promising, with enhanced recovery of multilineage hematopoiesis.

RANK ligand (RANKL) is a cytokine secreted by osteoblasts and osteocytes that binds to RANK on the membrane of osteoclast progenitors, resulting in bone resorption by mature osteoclasts. Mutations in RANKL lead to osteoclast-poor osteoporosis, defining its role in maintaining bone homeostasis and efficient hematopoiesis. RANKL can also regulate the differentiation of stromal stem cells (SSCs) along the osteochondrogenic lineage. Since SSCs are important factors in the HSC niche, the effect of knocking out the RANKL gene on the ability of BM SSCs to support HSCs was tested.[6]

Stem and progenitor cells extracted from the BM of RANKL-KO mice showed loss of quiescence and premature myeloid differentiation. The proportion of common lymphoid progenitors was decreased, along with their ability to differentiate into B cells. These defects were BM-specific and not observed in fetal liver or spleen of RANKL knockout (RANKL-KO) mice. BM reconstitution assays in wild-type recipients with RANKL-KO BM transplanted cells showed that the hematopoietic defects were due to a defective microenvironment in RANKL-KO mice, not to a cell-autonomous defect. Gene-expression studies confirmed alterations in expression of SSC genes related to HSC support, with defects in lineage priming as early as the HSC stage. The findings indicate that sustained inhibition of RANKL signaling in the BM microenvironment could influence the overall balance of BM homeostasis.

Overview of stages of hematopoiesis and the affected progenitor and mature cells in RANKL KO mice (dashed area)



CH and Alzheimer's disease

Mutations in the genes *Dnmt3a* and *Tet2* are positively selected in HSCs, resulting in clonal hematopoiesis (CH). Interestingly, clonal hematopoiesis of indeterminate potential (CHIP) was previously linked to a reduced risk of Alzheimer's disease (AD) and validated in a large cohort from the UK Biobank.[7]

Correlation between CH and AD was tested by transplanting *Dnmt3a* or *Tet2* loss-of-function (LoF) BM in 6-to-8-week-old AD-prone mice (5xFAD). The mice were injected with 8 cycles of lipopolysaccharide (LPS) administered weekly, 8 weeks after transplantation.

In this AD-prone mouse transplantation model, mice with *Tet2* LoF had reduced risk of late-onset AD, but mice with *Dnmt3A* LoF did not. *Tet2* LoF promoted CCR2-mediated central nervous system infiltration of non-classical monocytes and M1-macrophages via enhanced chemokine signaling. *Tet2* LoF myeloid cells and microglia-like cells demonstrated enhanced β-amyloid clearance, thus potentially reducing the features of AD.

Anemia in space

Testing astronauts' blood has revealed that space travel causes changes in gene expression related to fundamental pathways, including those involved in insulin and estrogen signaling.

Astronauts are healthy adults, but in space, they often develop a form of anemia, characterized by elevated HbF. The expression of hemoglobin at various stages of erythropoiesis at different times in space has been investigated using a unique suite of multiomics.[8]

Findings reveal significant variations in globin gene expression, corresponding to distinct spatiotemporal characteristics of the samples. Due to the limited number of astronauts and the small volume of blood samples, a new protocol has been developed to enrich erythroid cell lineages. Future findings may shed light on the phenomenon of hemoglobin gene switching observed in hemoglobinopathies, such as sickle cell disease and beta-thalassemia.

In conclusion, new research presented at EHA2025 has advanced our understanding of HSC regulation within niches during both normal and stress conditions, with implications for therapies targeting aging and malignant niches

More from EHA

Are stem cells the focus of your research? Join the EHA SWG Journal Club for engaging discussions about scientific findings in this field. Explore the secrets of hematopoiesis with this HemaSphere podcast dedicated to the mechanisms of thrombopoiesis.

Stem Cells Journal Club

Unraveling the secrets of thrombopoiesis

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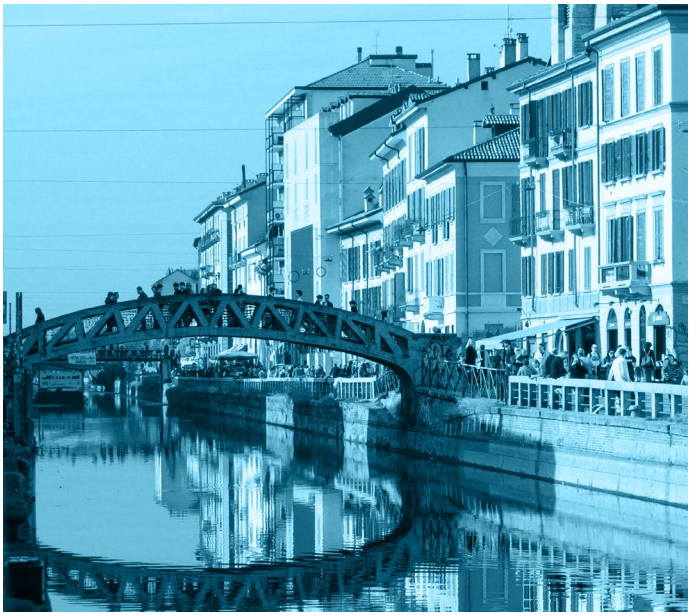
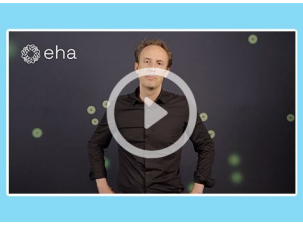
02

The global burden of SCD: How to combine universal access with the latest genetic treatments?



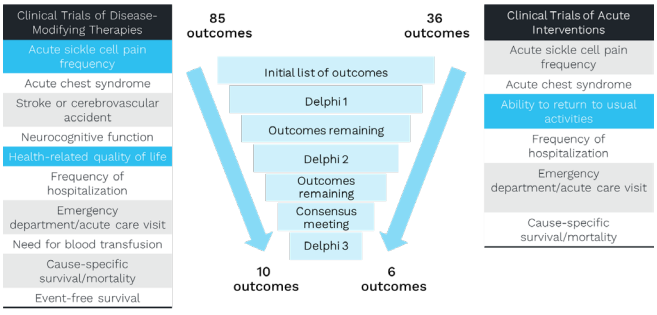


Dr. Eduard van Beers shares his highlights on SCD from EHA2025

Challenges of endpoint selection and patient inclusion in SCD trials

Sickle cell disease (SCD) has a complex pathophysiology, but this intricacy offers multiple therapeutic targets. Yet, of those disease-modifying agents that have reached the market, 50% have subsequently been withdrawn. A presentation at EHA2025 raised the question of whether this is due to a lack of efficacy or suboptimal endpoint selection in clinical trials.[1] Vaso-occlusive crisis is the most common primary endpoint, but subjective factors strongly influence it, and as such, it is difficult to define consistently. Anemia and hemolysis have been suggested as clinically relevant surrogate endpoints, but these are also highly variable. Other biological or radiological endpoints may prove valid proxies for exploring pathophysiological hypotheses, but they may not translate into clinical benefits. To address this, a multi-stakeholder consensus has developed two core outcome sets in SCD – one for trials of disease-modifying therapies, and one for acute interventions.[2] Both sets include clinical outcomes as well as measures related to functioning, quality of life (QoL), resource utilization, and survival. In the future, endpoint selection should consider a range of factors, including diversity, variability, genotype, environment, healthcare costs, and safety. The following talk considered the challenges of diversity and patient enrolment in SCD trials.[3] Key issues include diverse patient characteristics and inequalities in diagnosis and access, as well as socioeconomic determinants of health and the transition from pediatric to adult care. There can be a lack of awareness about SCD trials, and low patient motivation to enroll. However, actionable targets to address these issues include early patient engagement, recruitment, and retention, as well as the use of digital health technology. In addition to aligning with regulatory bodies and stakeholders, trial design should also acknowledge inequities and the diversity that impacts disease phenotype and management.

Results from a multi-stakeholder consensus on core outcomes for SCD clinical trials



Reliable PoC screening tests for SCD

Newborn screening for SCD is recommended, since early diagnosis decreases morbidity and mortality. This is routine in developed countries, but in Sub-Saharan Africa, only 50% of newborns are tested, mainly in large urban centers, and often only within PoC pilot projects, since testing requires trained healthcare professionals (HCPs), laboratory facilities, and funds. To address this, reliable point-of-care (PoC) tests are crucial where laboratories are limited, enabling accurate and rapid results without the need for a medical expert.[4] Three innovative SCD PoC tests have been examined under real-life conditions in Europe, Asia, and Africa; all were comparable in terms of

sensitivity and specificity, and took only 10 minutes and approximately $2 to administer. There is a need for screening to be linked to comprehensive care, and for positive tests to be confirmed, but in general, PoC options for SCD look robust and user-friendly.

The process from pediatric to adult care for SCD

Today, with the advent of effective treatments, many people with SCD survive childhood – and there is demand for care tailored to adolescents and young adults.[5] Healthcare systems are often divided into pediatric and adult care, which creates challenges around transition. With the move into adult care, the responsibility for management tends to shift from the parent or caregiver to the patient. This responsibility can come at a difficult time, since adolescence involves considerable physical and sociopsychological growth and change. The transition of SCD patients from pediatric to adult care requires better support and planning, with gradual preparation, clear communication, and emotional support. A new consensus recommends a successful transfer of care is defined as two visits with a comprehensive adult program in the first year – in person or via telemedicine, and successful integration into adult care be defined as completion of 50% of scheduled annual outpatient visits in the 5 years after transfer.[6]

Understanding hydroxyurea metabolism could improve SCD treatment

A poster shared at EHA2025 focused on work to detect hydroxyurea metabolites and analyze associations with laboratory indices and clinical implications. European homozygous hemoglobin S patients with or without a prescription for hydroxyurea were grouped by age (under or over 10 years), and dried blood spots from patients and healthy controls were analyzed using untargeted metabolomics. Results showed low or non-detectable metabolites in 20% of the under-10s with a prescription compared to 39% of the older group, possibly due to increased hyperfiltration in younger patients. Low percentage of detectable hydroxyurea metabolites might also be explained by non-compliance or increased metabolism. Relative high levels of hydroxyurea were associated with increased HbF, mean corpuscular volume, albumin to creatinine ratio, and decreased estimated glomerular filtration rate; these data support an already described link between kidney function and hydroxyurea metabolism.[9,10] Hydroxyurea metabolism and metabolite half-life – as well as therapy timing, adherence, and pharmacokinetics – might influence detection of metabolite levels. A better understanding of the metabolism could contribute to optimized SCD treatment.

The hydroxyurea program in Western Kenya as an example for community-driven innovation in SCD care

Sustainable progress in SCD care requires further attention. Closing the care gaps depends not only on medical advances, but also shared responsibility among patients, community, HCPs, governments, and partners.[11] An example of this is Western Kenya, which has introduced a community-led, collaborative model to improve outcomes within existing resource constrains. The AMPATH SCD program currently covers 24 million people and is built on the three pillars of care, education, and research. A key outcome is the introduction of hydroxyurea through an initial free drug access program, and establishment of dedicated clinics offering guidance-based care, including prophylaxis and monitoring. A Revolving Fund Pharmacy model has also been developed to ensure sustainable drug availability – reducing reliance on external funding by reinvesting local pharmacy revenue. These initiatives show that SCD care can be improved through community engagement, stakeholder collaboration, and local system coordination.

Gene therapy versus HSCT for SCD

Survival rates in SCD are concerning, with 81% of patients not reaching the age of 50. A cure would reduce fear and allow patients to plan for their futures. Two potentially curative treatments are hematopoietic stem cell transplant (HSCT) – which is already well established – and the emerging option of gene therapy. A thematic debate held at EHA2025 pitted these two options head-to-head.[7,8] Dr. Mariane de Montalembert argued in favor of gene therapy, citing advantages such as the evidence of good results from the first gene therapy protocols, and the rapid progress seen in the field. Compared to HSCT, gene therapy requires fewer cycles for mobilization, and has a short recovery from aplasia as well as induction of high levels of fetal hemoglobin (HbF). Safety profiles appear consistent with the risks of autologous HSCT. Ultimately, gene therapy offers patients the hope of a complete cure. In reply, Dr. Erfun Nur postulated that HSCT is effective, widely available, and affordable – with a low risk of graft-versus-host disease (GvHD). It delivers good outcomes in children, with overall survival (OS) in excess of 95%, and event-free survival of 92% – but HSCT works at all ages, and is available for almost every patient.

However, both approaches have their challenges. For gene therapy, mobilization is not possible in some patients, and the fitness of autologous hematopoietic stem and progenitor cells is potentially impaired. Additionally, there are concerns about myeloid malignancies, off-target effects, and long-term safety. Gene therapy is available in only a few specialized centers, and at much higher costs than autologous graft. Challenges for HSCT include the low probability of finding a donor, and the increased risk of graft rejections with haplo-identical HSCT. From a patient perspective, therapy is complicated and demanding, and for some people QoL does not rise as expected after transplantation.

New real-world data for HSCT in SCD

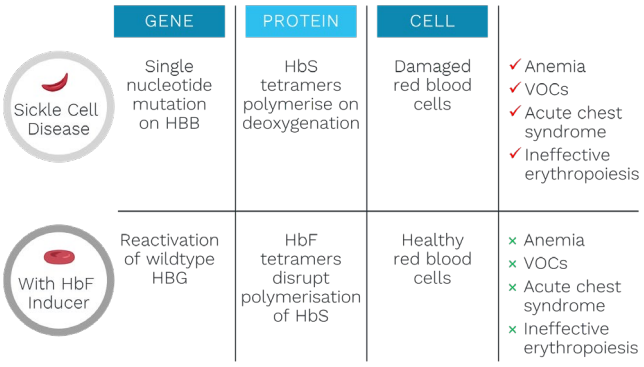
Haploidentical HSCT is an established curative treatment for adults with SCD who lack an human leukocyte antigen identical donor.[12] Data were presented from a retrospective multi-center cohort study examining whether using peripheral blood stem cells (PBSC) alone or in combination with bone marrow (BM) stem cells could improve event-free survival without significantly increasing GvHD risk, as compared to receiving BM alone. Out of 41 patients, 26 received BM, and 15 received PBSC. There were 3 deaths and 1 graft failure in BM, and none in PBSC, with estimated 1-year event-free survival of 100% in the PBSC group – compared to 85% for BM. No increased incidence of acute or chronic GvHD was observed with PBSC compared to BM, and there was significantly faster neutrophil recovery. The authors concluded that PBSC is less invasive and viable stem cell source for haplo-HSCT in SCD.

Another abstract looked at SCD-related ocular complications, using data from a prospective observational study to investigate whether HSCT can halt the progression of pre-existing sickle cell retinopathy (SCR) and maculopathy (SCM), and prevent the development of new ophthalmic complications.[13] Overall, 89 SCD patients were included – 32 undergoing HSCT, and 57 controls. Ophthalmic assessments were made before and at least 1 year after transplant. Results showed the progression rate of retinopathy and macular thinning were significantly lower in the HSCT cohort. Cases of vitreous hemorrhage, retinal detachment, and laser treatment were more frequent in control patients. The authors concluded that nonmyeloablative HSCT diminishes the progression rate of SCR and SCM in adults with SCD.

HbF induction can resolve SCD symptoms

The expression of fetal γ-globin and the subsequent formation of HbF tetramers can largely compensate for most complications associated with SCD – with even small increases in HbF linked to significant improvements in patient outcomes. Currently approved HbF inducers include hydroxyurea and CRISPR-based gene therapy. But there remains an unmet need for a safe and specific inducer that can reach transformative HbF levels for the majority of patients. A novel small activating RNA (saRNA) has been developed to specifically increase γ-globin expression to therapeutically relevant levels *in vivo*. MT011391 has demonstrated induction of pan-cellular, dose-dependent γ-globin RNA and protein in a primary erythroid-derived progenitor cell model using BM-derived CD34 cells from healthy human donors, where it achieved γ-globin upregulation in both hydroxyurea-responsive and non-responsive donor cells, and induced 62% HbF induction. Pharmacodynamic activity has also been observed in a non-human primate model, with efficient liposomal delivery.[14] With once-monthly intravenous dosing, protective levels of HbF are stimulated, and this candidate is now advancing into investigational new drug studies.

<u>HbF induction corrects the SCD phenotype by disrupting polymerization of HbS</u>



In conclusion, the EHA2025 congress showcased a strong presence of SCD through abstracts and dedicated sessions. Discussions about gene therapy and hydroxyurea emphasized that while gene therapy offers promising opportunities for some patients, optimizing existing treatments remains crucial for most. This optimization includes adjusting hydroxyurea dosing strategies based on patient adherence, metabolism, care transitions, and newborn screening. Furthermore, advancing the SCD treatment landscape involves improving clinical outcome assessments, increasing patient engagement, and enhancing recruitment and retention in clinical trials.

More from EHA

Listen to SCD patients' perspective on the EHA podcast series and focus on challenges in SCD drug development and access in this HemaSphere editorial. In addition, if you are a researcher working on sickle cell disease, check out the EHA Topic in Focus Research Grant opportunities: last call for applications opened on June 9, 2025.

SCD: What Physicians Can Learn From Patients And Carriers

HemaSphere What's wrong with drug development for sickle cell disease?

Topic in focus Research Grants

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03

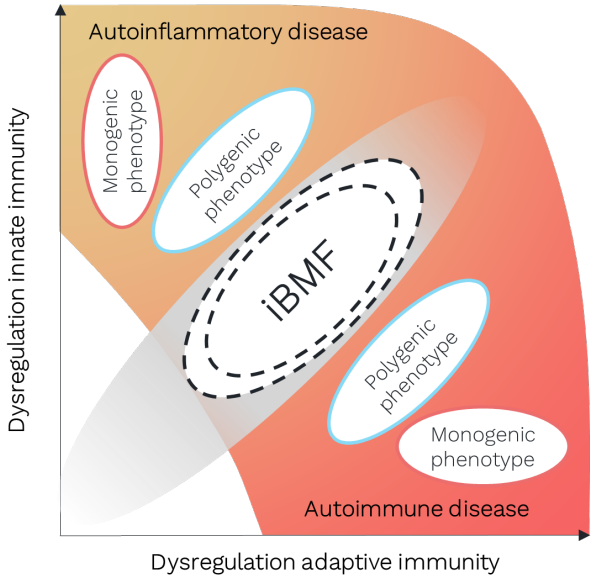
Novel insights into BM failure syndromes pathophysiology and immune treatment

Dr. Shahram Kordasti shares his highlights on BM failure syndromes from EHA2025

Immune bone marrow failure (iBMF) syndromes

iBMF syndromes are a heterogeneous group of disorders characterized by a complex interplay of genetic predisposition, autoinflammation, and autoimmunity.[1] While aplastic anemia (AA) is a well-established example, hypoplastic myelodysplastic syndrome (MDS-h) is also considered part of the iBMF spectrum. MDS-h demonstrates a distinct clinical course, with a unique survival pattern and progression trajectory more closely resembling AA than typical MDS.[2]

IBMF across the auto-inflammatory and autoimmune disease continuum



Treg-based strategies for iBMF

Regulatory T cells (Tregs) can potentially be utilized as a therapeutic strategy to modulate the immune response in iBMF syndromes. Tregs play an important role in restoring immune balance and homeostasis; however, not all Tregs have the same effectiveness. Tregs can be classified into two populations (TregA and TregB) based on their expression of eight markers, including Fas (CD95).[3] In AA, the levels of Tregs are low due to Fas ligand (FasL)-mediated apoptosis. Expanding Tregs has shown feasibility, safety, persistence, and potential efficacy in AA and other conditions, according to Phase I trial data. The ratio of TregB cells to CD8+ T cells significantly increased post-immunosuppressive therapy in patients with AA, suggesting that the quality and phenotype of Tregs are more important than quantity. Novel approaches, such as Fas knockdown and targeted trafficking to the bone marrow (BM), may improve the durability and functionality of Tregs.[2]

Targeting the JAK-STAT pathway in AA

The JAK-STAT signaling pathway is essential for immune function, hematopoiesis, and cellular proliferation, playing a central role in cytokine and growth hormone signaling. Dysregulation of this pathway has been implicated in various human diseases. Inhibition of the JAK-STAT pathway can be achieved through antibody-based blockade of the receptor, JAK inhibitors, or STAT inhibitors. In AA, cytotoxic T cells mediate an immune attack on bone marrow stem cells, primarily via type 1 cytokines such as interferon-γ and TNF-α. While Fas-mediated apoptosis of hematopoietic stem and progenitor cells appears to be the dominant mechanism, recent evidence also implicates the JAK-STAT and MAPK signaling pathways.

Ruxolitinib, one of four JAK2-specific drugs currently approved for use in myeloproliferative

neoplasms, demonstrated a reduction in BM hypoplasia and improved peripheral blood cytopenia in an iBMF murine model. It also mitigated Fas-mediated apoptotic destruction of target hematopoietic cells and led to improved overall survival. Additionally, analysis using a targeted inflammatory cytokine panel revealed that ruxolitinib-treated mice exhibited a marked reduction in IFN-γ and TNF-α levels.[4]

As JAK2 plays a critical role in normal hematopoietic signaling of growth hormones, its inhibition can impair erythropoiesis and megakaryopoiesis, often resulting in adverse events such as anemia and thrombocytopenia, which may be dose-limiting in clinical practice.

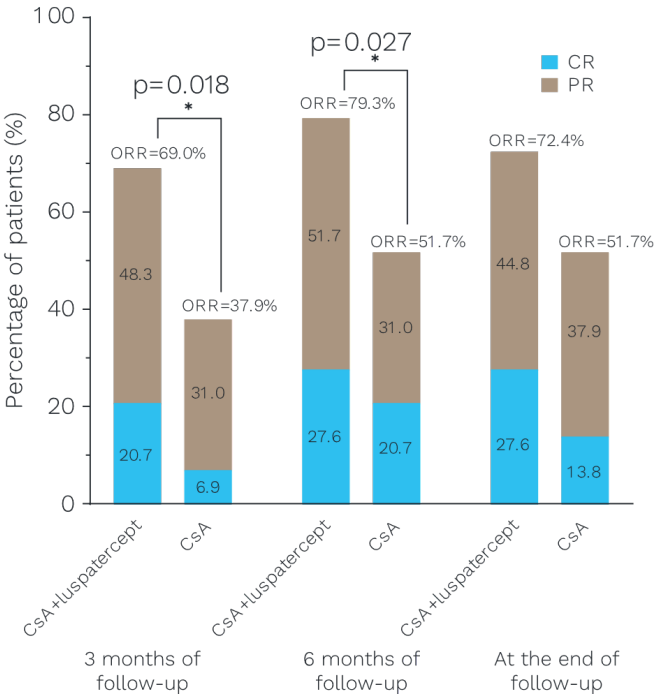
An ongoing trial is evaluating ruxolitinib in patients with relapsed or refractory severe aplastic anemia myelodysplastic anemia, pure red cell aplasia, large granular lymphocyte leukemia, and hMDS, with weekly dose escalation up to 20 mg twice daily and careful monitoring of hematologic toxicity.

Given the hematologic risks, alternative non-selective JAK inhibitors like momelotinib, which may have a more favorable toxicity profile, are also being considered.[5]

Cyclosporin (CsA) and luspatercept for non-severe aplastic anemia (NSAA)

Despite a 50-70% response rate with immunosuppressive therapy, patients with NSAA often achieve only partial hematologic responses or show no erythroid improvement. Luspatercept, which promotes late-stage erythroid maturation by inhibiting TGF-β superfamily ligands, was evaluated in a single-center, prospective, open-label, randomized study (NCT05399732) comparing luspatercept plus cyclosporine A (CsA) to CsA alone in newly diagnosed, transfusion-independent NSAA. The primary endpoint was the 6-month overall response rate (ORR), with secondary endpoints including hemoglobin response (HR), safety, and predictors of response. Patients receiving CsA + luspatercept had significantly higher ORRs at 3 and 6 months compared to CsA alone. HR rates were also significantly higher at these time points, although the difference was not maintained at the end of follow-up. Additionally, the time to overall response was shorter with CsA + luspatercept, and subgroup analysis indicated that older patients derived greater benefit from the combination therapy. The AE rate was 34.5% in the combination group compared to 24.1% in the monotherapy group, with no statistically significant difference (*P*=0.387), and most of the AEs were mild.[6]

ORR for CsA + luspatercept and CsA



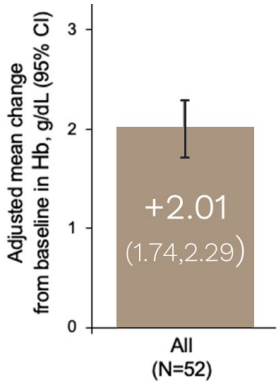
Oral iptacopan monotherapy in paroxysmal nocturnal hemoglobinuria (PNH)

In PNH, impaired complement regulation caused by deficiencies in CD55 and CD59 leads to intravascular hemolysis (IVH).[7] While anti-C5 therapy helps reduce IVH, it can result in red blood cell (RBC) opsonization and the development of extravascular hemolysis (EVH). Patients with PNH who achieve hemoglobin (Hb) levels ≥10 g/dL with anti-C5 therapy may still experience ongoing EVH and face a significant quality-of-life burden. Iptacopan, an oral agent targeting factor B, selectively inhibits the alternative pathway C3 convertase and provides comprehensive control of hemolysis. The APPULSE-PNH study evaluated oral iptacopan monotherapy in anti-C5-treated patients with hemoglobin ≥10 g/dL who continued to have EVH, persistent anemia, and required regular hospital visits for intravenous anti-C5 infusions.

Oral iptacopan monotherapy led to Hb improvements to near-normal levels by providing comprehensive control of hemolysis. The primary endpoint was the adjusted mean change in Hb from baseline between Days 126 and 168, based on the average of four visits. Iptacopan demonstrated non-inferiority (*P*<0.0001) and superiority (*P*<0.0001) compared to anti-C5 therapy, with a mean Hb increase of +2.01 g/dL (95% CI: 1.74, 2.29). Most patients (92.7%; 95% CI: 84.6, 98.1) achieved Hb ≥12 g/dL, and all remained transfusion-free. C3 deposition on PNH red blood cells, a marker of EVH, was reduced to negligible

levels by Week 16. Patients also reported improvements in fatigue and treatment satisfaction. Iptacopan was well-tolerated, with no new safety concerns and no patients experiencing a major adverse vascular event. Treatment-emergent adverse events (TEAEs) occurred in 42.3% of patients (22/52) in the infections and infestations system organ class.[8]

Adjusted mean change from baseline in Hb between Day 126 and 168



Management of late-onset telomere biology disorders (TBDs)

In somatic cells, telomeres shorten with age, with the most significant attrition occurring in the first two decades of life. Telomerase restores telomere length in certain cells, such as germ and stem cells. However, disruption in various factors can lead to telomerase deficiency and altered telomere structure, resulting in accelerated shortening and early cell senescence.[9] TBDs arise from these defects and are associated with a range of life-threatening clinical features, including bone marrow failure. While young patients are now surviving longer, new disease manifestations, such as severe gastrointestinal bleeding, are being identified later in life. Given the broad spectrum of clinical presentations, comprehensive evaluation and subspecialty care are essential. Some patients may not present until adolescence or early adulthood.[10]

Arriving at the correct diagnosis for TBDS can be challenging, as lymphocyte telomere length below the 1st percentile alone is not diagnostic. Pulmonary fibrosis (PF) is the most prevalent TBD, with 30–35% of individuals with familial idiopathic PF found to have an underlying TBD. Additionally, about 30% of young people with TBD exhibit clonal hematopoiesis with genetic variants distinct from those typically seen in normal aging.[11,12] Screening for late-onset TBD involves a thorough physical exam to identify mucocutaneous features and premature graying, a detailed medical history to assess for esophageal stenosis or webs and epiphora, and a complete blood count with bone marrow examination, including a hematologic somatic mutation panel. Lifelong cancer surveillance is necessary for these patients.

This year's EHA congress provided new insights into the pathophysiology and future therapies for iBMFs, with a focus on mechanisms that target the underlying immune dysregulation. It also highlighted strategies for managing acquired rare inherited BMF syndromes such as TBD, including screening approaches, proposed pathophysiological pathways, and the potential of gene therapy to transform care.

More from EHA

Do you want to refresh your knowledge and test your clinical skills in BM failure syndromes? Grab your phone and go through our two engaging and interactive QR clinical cases. No need to go back to your computer to listen to our EHA Unplugged podcast episode focused on precise genetic-based diagnosis in true acquired and constitutional BM failure disorders.

QR Case 17 – Chromosome Instability Syndromes (Mykhailo)

QR Case 15 - Aplastic Anemia (Rolf)

Precision Medicine in Inherited Bone Marrow Failure Syndromes

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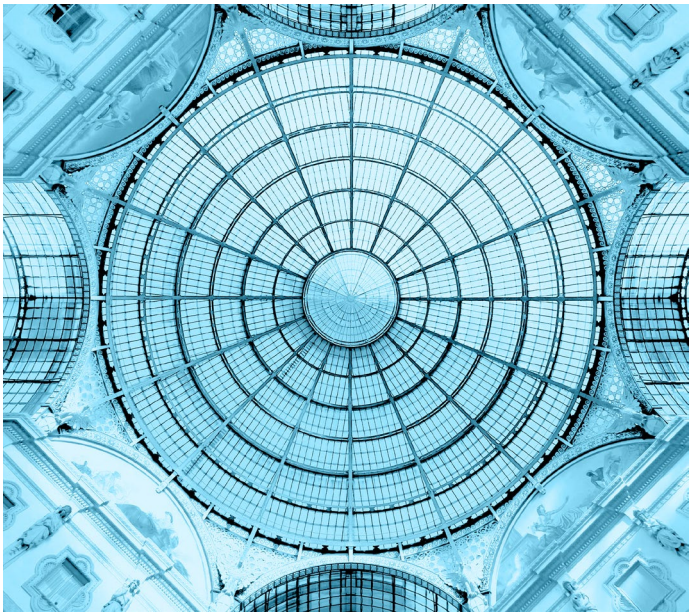
04

New treatment modalities for platelet disorders



Targeted therapies in immune thrombocytopenia (ITP)

ITP is a hematological autoimmune disease characterized by a decreased platelet count in the blood (<100 × 10^9/L).[1]

Thrombopoietin receptor agonists (TPO-RAs)

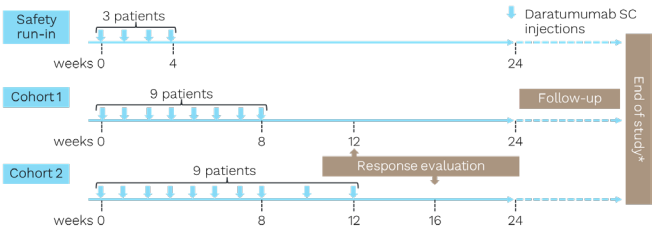
In patients with immune thrombocytopenia (ITP), thrombopoietin (TPO) levels are normal or only slightly elevated, despite a low platelet count. This is due to increased platelet clearance, even when thrombopoiesis remains normal. Native TPO binds to the extracellular domain of the TPO receptor. TPO-RAs mimic native TPO by binding either to the extracellular domain (e.g., romiplostim) or the transmembrane region (e.g., eltrombopag and avatrombopag) of TPO-R.[2] Approximately 58% of patients treated with eltrombopag or romiplostim achieve a good platelet response; however, up to 42% still require alternative therapies.[3]

The c-MPL receptor is the primary target of both endogenous TPO and synthetic agonists. Normal receptor function requires proper surface expression and signal transduction via the JAK2/STAT3 pathway, which is negatively regulated by SOCS proteins.[4] Excessive c-MPL internalization may contribute to TPO-RA resistance by reducing the number of surface receptors available.[5]

siRNA knockdown experiments identified AP2 and GAK, as promoters of c-MPL internalization. Baricitinib, a GAK inhibitor, was shown to inhibit c-MPL internalization and restore JAK2/STAT3 signaling by significantly downregulating SOCS1 expression at the transcriptional level. In mouse models of ITP, treatment with baricitinib led to increased peripheral blood platelet counts. Baricitinib also downregulated abnormally elevated SOCS1 protein levels in the bone marrow and enhanced phosphorylation of JAK2 and STAT3.

These findings suggest that baricitinib corrects AP2-NAK-mediated c-MPL endocytic dysregulation to restore megakaryocyte TPO-RA sensitivity in ITP.[5]

Platelet count in baricitinib-treated ITP mice



Overview of B-cell-targeted therapies

The latest developments in B-cell–targeting therapies for ITP were presented at EHA2025.

The anti-CD20 monoclonal antibody rituximab achieves response rates ranging from 30–50% in patients with ITP. It is generally well-tolerated and shows better outcomes when administered within the first year of disease, particularly in female patients. While relapses are common, most patients respond to re-treatment.[3]

Fostamatinib, a spleen tyrosine kinase inhibitor, targets macrophage-mediated platelet destruction. In patients with multi-refractory ITP, clinical trials have shown an overall response rate of 43% and a stable response rate of 18%. Real-world data suggest higher response rates, especially when fostamatinib is used earlier in the disease course or in combination with TPO-RAs.

Rilzabrutinib, a Bruton's tyrosine kinase inhibitor, inhibits B cell proliferation and macrophage-mediated platelet clearance. Phase 2 trials reported response rates of 30–40%, along with notable improvements in fatigue and quality of life.[3]

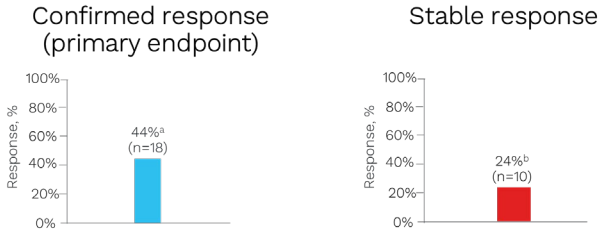
LUNA is a Phase 3 study investigating the safety and efficacy of rilzabrutinib in adult and adolescent patients with persistent or chronic primary ITP (NCT04562766). Long-term extension (LTE) data, presented at EHA2025, showed that complete response was achieved in 54% of patients. Rilzabrutinib treatment further improved physical fatigue and improved bleeding scores during the LTE. All treatment-related adverse events were grade 1 or 2. The most commonly reported adverse events were nausea (7%), diarrhea (4%), and upper abdominal pain (2%), with all other events occurring in only one patient each.[6]

Novel B-cell-targeting agents currently under investigation include those targeting CD38 and BAFF-R, with promising results for both approaches presented at EHA2025.[3]

DART is an open-label, multicenter, Phase 2 investigator-initiated study evaluating the safety and efficacy of daratumumab, a CD38-targeting mAb, in adult patients with primary ITP, conducted with a safety run-in followed by two cohorts (NCT04703621). The primary efficacy endpoint, defined as two consecutive platelet counts >50 × 10^9/L measured more than 24 hours apart, was achieved in 48% of the overall population, with 44% response rates observed in both Cohort 1 and Cohort 2. Although rapid responses were seen, they diminished over time, with sustained response rates of 38% overall, 44% in Cohort 1, and 33% in Cohort 2. The primary safety endpoint was the incidence and severity of treatment-emergent adverse events (TEAEs) of grade ≥2. Grade 2 infections occurred in 4.7% of patients, while grade 2 diarrhea, considered treatment-related, occurred in 9.5%. Infections were the most frequently reported TEAE, occurring in 38% of patients.[7]

Ianalumab, an investigational, fully human mAb targeting B-cell activating factor receptor (BAFF-R). VAYHIT3 is a Phase 2 study evaluating the efficacy and safety of a short course of intravenous ianalumab in heavily pretreated patients with primary ITP (NCT05885555). Preliminary results showed that 44% of patients achieved a confirmed platelet response, with a median time to response of 6 weeks. Additionally, 24% of patients demonstrated a stable response, with 56% (10/18) of responders maintaining platelet counts at week 25, including 9 who achieved a complete response. Ianalumab was generally well tolerated, with most adverse events reported as unrelated to the study drug. No treatment discontinuations occurred due to adverse events. Infusion-related reactions and infections were mostly grade 1 or 2, with only a single grade 3 infection reported.[8]

Confirmed response and stable response



The response rates to B-cell–directed therapies (30–50%) raise questions about treatment timing, the need for broader B/plasma cell depletion, or alternative immune pathways driving platelet destruction.[3]

Potential for targeting cytotoxic T-cells in patients with refractory ITP

In ITP, rituximab non-responders exhibit a distinct immune profile, which includes an increase in terminally differentiated effector memory $CD8^+$ T cells re-expressing CD45RA (TEMRA) that are highly cytotoxic and senescent. These cytotoxic $CD8^+$ T cells contribute to platelet destruction. Deep sequencing of the T-cell receptor (TCR) revealed reduced T-cell diversity, alongside clonal expansions in refractory cases. Notably, T-cell diversity appears to track with platelet counts in chronic ITP, where expanded individual T-cell clones are associated with lower diversity and declining platelet levels. Paired TCR and gene expression profiling confirmed that these expanded $CD8^+$ T cells are predominantly enriched in the TEMRA subset. This suggests a potential for targeting cytotoxic T-cells in patients with refractory ITP.[3]

TCR diversity and clonal expansion

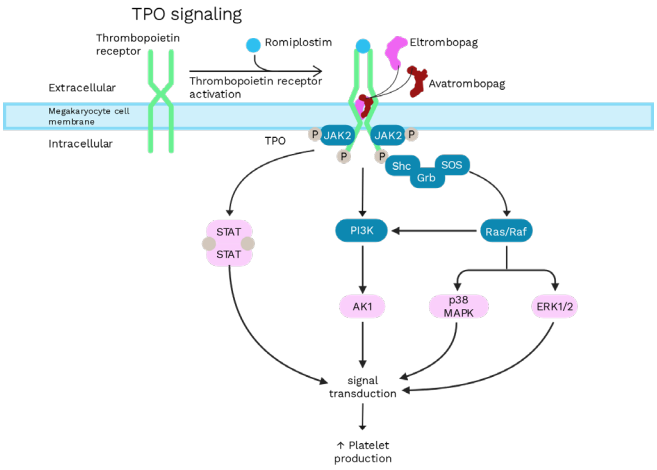


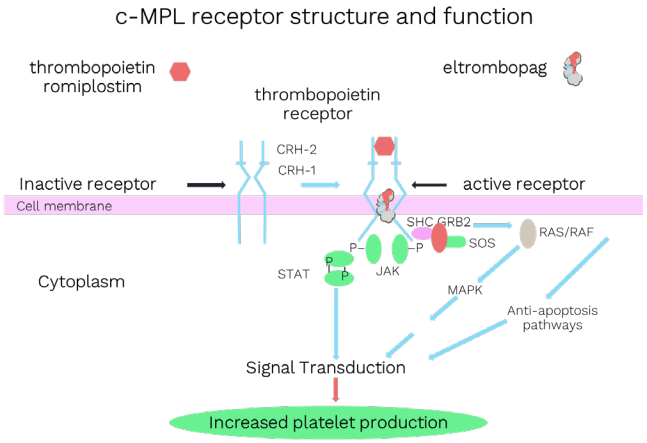
Image created with BioRender.com

T-cell–targeted therapies, including mycophenolate mofetil (MMF), azathioprine, cyclophosphamide, and cyclosporin, demonstrate response rates of 30–50% in ITP, though they are often poorly tolerated. Interestingly, $CD8^+$ TEMRA cells are reduced in patients who respond to

eltrombopag. Eltrombopag has been shown to exert anti-proliferative effects on leukemic cells and inhibit the proliferation of $CD8^+$ T cells. In a small cohort of patients with refractory ITP, combination therapy with eltrombopag and MMF yielded a higher response rate of 72%, suggesting potential dual activity and synergistic effects.[3]

Patients with GPIb/IX antibodies may have lower platelet counts, poorer response to conventional treatments, and a higher likelihood of progressing to refractory or relapsed ITP. Studies have shown that regulatory T (Treg) cells can be leveraged to modulate the immune microenvironment and treat autoimmune disease. Building on this, engineered chimeric antigen receptor (CAR)-Treg cells are hypothesized to provide comprehensive immune regulation by suppressing B cell antibody secretion, effector T cell proliferation, and antigen-presenting cell activity.

Targeted modulation of the immune microenvironment



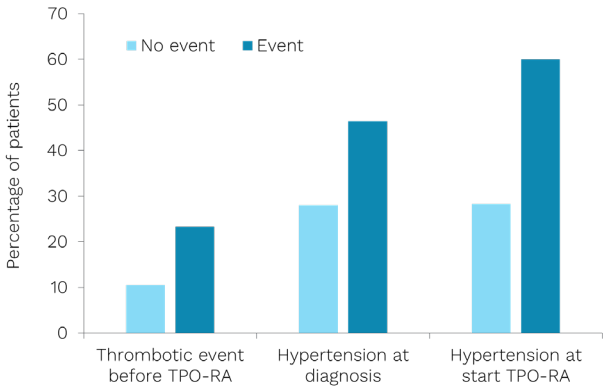
To explore this concept, a GPIbα-targeting chimeric autoantibody receptor (CAAR) was designed with an extracellular ligand-binding domain containing autoantigens. Human naïve Treg cells were isolated via flow cytometry and transduced with the CAAR construct using lentiviral vectors. Inhibitory functional assays confirmed that GPIbα CAAR-Treg cells exhibited selective antigen-specific activation *in vitro* and demonstrated both specific and non-specific suppressive effects. Furthermore, these cells effectively inhibited the cytotoxic activity of CAAR-effector T cells against anti-GPIbα hybridoma cells in a hematopoietic hybridoma model, supporting their potential as a novel therapeutic strategy in ITP.[9]

Predictors of thrombotic adverse events in patients receiving TPO-RA

Immune thrombocytopenia (ITP) is a complex autoimmune disorder that leads to bleeding but can paradoxically also lead to thrombosis, making the management of the disorder challenging. Secondary ITP and use of thrombopoietin receptor agonists (TPO-RA) are the strongest independent predictors of thrombosis. At EHA2025, data were shared from the Vertex 3 study.[10]

This aimed to evaluate the incidence, characteristics, and risk factors for thrombotic adverse events in ITP patients receiving TPO-RA, providing insights into potential predictors and strategies to optimize safety. A total of 417 TPO-RA treatment courses were analyzed, including 267 first, 113 second, and 37 third courses. Results per 100 TPO-RA courses found a thrombotic event rate of 8.2% in the first course, and 7.3% in the second or third course. Key predictors of thrombosis under treatment were a previous thrombotic event, hypertension at diagnosis, and hypertension at the start of therapy. Other predictors included highest platelet count and platelet count at 6 months on TPO-RA, as well as having a fast response to TPO-RA. Most cases resolved, and 44% of patients who discontinued treatment later resumed TPO-RA therapy. The authors conclude that these findings emphasize the need for careful monitoring and risk stratification in people receiving TPO-RA, but note that further studies are warranted to optimize thrombotic risk management in this patient population.

Patient characteristics with significant differences regarding the occurrence of thrombotic events during TPO treatment



In summary, EHA2025 highlighted significant advances in emerging treatment modalities for ITP, targeting multiple components of its complex pathogenesis.

Genetic screening of pathogenic variants in inherited platelet disorders

To date, pathogenic variants associated with inherited platelet disorders have been identified in 68 genes. More genes have been linked to thrombocytopenia with associated dysfunction than to isolated platelet dysfunction. In clinical practice, the genetic diagnosis of these disorders is typically performed using gene panels and targeted sequencing methods. According to

guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, genetic variants are classified into five categories: pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, or benign.[11]

A significant effort is underway to reclassify VUS, which can be redefined through familial segregation studies, detailed phenotyping, functional assays, and protein modeling.[12]
Computer-assisted tools, such as Franklin, are increasingly used for variant classification. Franklin integrates a suite of prediction software tools, including dbscSNV, Splice AI, Primate AI, FATHMM, AlphaMissense, and Revel, to generate aggregated predictions of variant pathogenicity. However, no single tool is sufficient on its own; predictions must be corroborated with phenotype data and cross-referenced with existing databases like ClinVar to confirm whether a variant has been previously described in other patients.[13]

More from EHA

Interested in thrombocytopenia? Listen to this podcast focused on EHA Guideline on antithrombotic treatment in thrombocytopenic patients or explore the Guidelines themselves. Detangle the intricacies of vWF and platelets interactions following our dedicated EHA Campus course. And don't forget to check out the upcoming EHA SWG meeting on Bleeding and Platelets Disorders, taking place in April 2026.

HemaSphere: EHA Guidelines on Management of Antithrombotic Treatments in Thrombocytopenic Patients With Cancer

Management of Antithrombotic Treatments in Thrombocytopenic Patients With Cancer

Course: The interactions of vWF with platelet glycoprotein Iba

EHA SWG meeting on Bleeding and Platelets disorders

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05

Iron homeostasis and erythropoiesis

Iron plays a crucial role in essential physiological processes such as oxygen transport, energy production, and cell proliferation. The interplay of proteins responsible for iron import, storage, and export balances iron homeostasis. Systemic iron levels are primarily regulated by the hepcidin–ferroportin (FPN) axis involved in recycling of iron from red blood cell (RBC) breakdown.

Dysregulation of iron homeostasis in anemia of inflammation

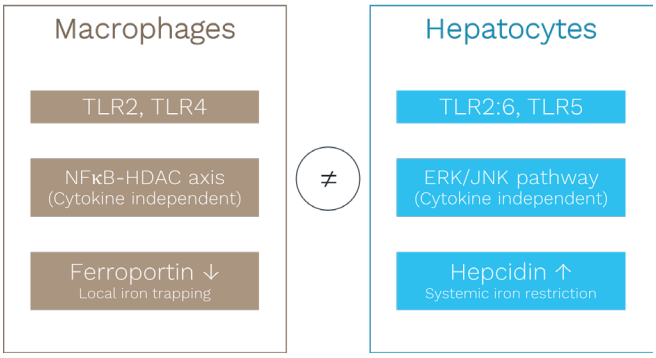
During infections or inflammation, immune cells detect pathogens or damaged components, releasing pro-inflammatory cytokines that activate hepcidin, the master regulator of systemic iron flow produced by hepatocytes. Hepcidin blocks iron absorption in the gut and iron release from macrophages by degrading FPN, the iron exporter.[1,2] This creates abnormally low levels of iron in the blood (hypoferremia) and since RBC production depends heavily on iron, prolonged restriction leads to anemia of inflammation.
Macrophages and hepatocytes are involved in the systemic iron regulation, as well as the local iron release to neighboring cells for their selective needs, such as in follicular development and wound healing. Iron retention in macrophages is a key factor causing hypoferremia, which impairs erythroid cell development, whereas hepatocytes play a crucial role in iron storage. Toll-like receptor (TLR) activation serves as the initial trigger, decreasing FPN transcription in macrophages and creating local iron restriction, as well as increasing hepcidin, which blocks the iron export systemically and creates comprehensive iron restriction in hepatocytes. But the exact mechanism of iron sequestration and the molecular mechanism with which TLRs control these pathways is still unclear.

TLRs coordinate a dual response resulting in hypoferremia

Previous studies have shown that TLR ligands reduce FPN transcription in macrophages, with similar transcriptional repression observed in patients with anemia of inflammation. Pharmacological and RNA interference screens have shown that during an infection, pathogen- and disease-associate molecular patterns (PAMPs/DAMPS) activated TLRs – specifically TLR2 and TLR4 – and promote NFκB signaling in macrophages, resulting in the decreased expression of *FPN*. NFκB then recruit histone deacetylase (HDAC) 1 and 3 to the antioxidant response element (ARE) of *FPN*, resulting in repression of *FPN*. NFκB and HDAC inhibitors, as well as NRF2 activators, may potentially attenuate inflammation-mediated repression of *FPN* transcription in macrophages.
Although it is known that hepcidin responds to cytokines released by immune cells, especially interleukin (IL)-6 and IL-1b, the role of hepatocytes – which also express TLRs and can mount downstream antimicrobial responses – remains unclear. By stimulating primary hepatocytes with a panel of TLR ligands, it was observed that some TLRs in hepatocytes, specifically TLR2/6 and TLR5, mount an inflammatory response by FSL1-mediated upregulation of hepcidin. Hepatocytes upregulate hepcidin in response to pathogens, in a TLR2- and TLR6-dependent manner, which appears to be a cytokine-independent pathway. TLR activation with pathogens drives hepcidin upregulation through ERK and JNK signaling pathways.
These findings of parallel mechanisms challenged the prevailing notion of how inflammatory hypoferremia is caused and questioned the critical role of hepcidin in anemia of inflammation. This cell-type specificity also revealed a therapeutic challenge, where effective treatments

may need to target multiple pathways simultaneously.

Overview of the parallel mechanism of hypoferremia in macrophages and hepatocytes upon infection/inflammation



Iron release from macrophages

BM-resident macrophages represent readily available sources of iron for developing cells of the hematopoietic system. The impact of iron retention in macrophages on BM hematopoietic stem and progenitor cells was tested in mice with targeted conditional knockout of *Fpn* in the myeloid lineage, characterized by higher red blood counts with lower hematocrit and hemoglobin levels.[3]

Long-term iron retention was detrimental to BM macrophages and their function, with local and systemic compensatory mechanisms being put in place (increased transferrin receptor (TfR1) expression, extramedullary hematopoiesis, and an erythropoietin-dependent increase in erythroferrone). However, these compensatory mechanisms were insufficient to restore iron homeostasis. These findings suggest that iron trapping in macrophages leads to multiple defects in the hematopoietic system and that FPN-mediated iron release from macrophages is essential for preventing age-associated anemia.

Iron overload in the BM niche

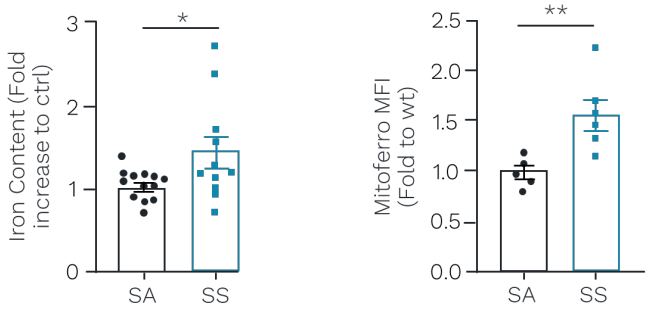
Hematopoietic stem cell (HSC) function is regulated by signals from the BM microenvironment, or niche, which modulate hematopoiesis. Regulation within the niche involves several cell populations, such as mesenchymal stromal cells (MSCs), that interact with HSCs and secrete growth factors and cytokines. Physical cues and biochemical factors – including iron, reactive oxygen species (ROS), and inflammatory cytokines – also influence HSC behavior. Preclinical data from sickle cell disease (SCD) mouse models show that elevated levels of iron and ROS may disrupt multiple BM niche components, including MSCs and endothelial cells. The presented talk aimed to understand whether HSC defects in SCD are dependent on the BM niche and the molecular and cellular players involved.[4]

HSCs showed increased myeloid differentiation in an SCD mouse model, resulting in the expansion of myeloid progenitors, which led to a rise in terminally differentiated myeloid cells and a reduction of RBCs, at the expense of the lymphoid lineages. Long-term SCD HSCs exhibited a modest decline in self-renewal capacity, with enhanced myeloid regeneration and decreased B-cell output. In SCD HSCs, there was evidence of intracellular iron overload and increased mitochondrial iron accumulation, along with a trend towards elevated mitochondrial ROS and a metabolic shift favoring glycolysis.

MSCs isolated from pediatric SCD patients exhibited delayed proliferation and premature exhaustion, which was associated with increased mitochondrial oxidative stress and DNA damage. SCD-derived MSCs were less efficient than those from healthy donors in maintaining primitive HSPCs and instead promoted differentiation toward the erythroid lineage.

Therefore, iron and ROS can affect HSCs both directly and indirectly by acting on MSCs, which in turn fail to preserve HSCs. Targeting iron overload and correcting the defective stromal niche may enhance HSC during ex vivo engineering, as well as the recipient's BM niche before and after transplantation, whether it's autologous or allogeneic.

Intracellular and mitochondrial iron (Fe2+) content



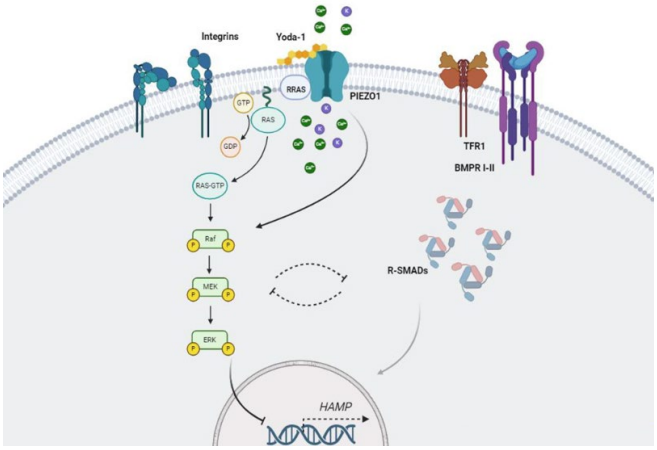
From stress to ineffective erythropoiesis

Human erythropoiesis is a complex process leading to the production of erythrocytes at a constant rate. The disruption of steady-state erythropoiesis leads to impaired erythrocyte production.

Stress erythropoiesis generates a wave of new erythrocytes to restore homeostasis, relying on the rapid proliferation of immature progenitor cells. Genetic or environmental factors can disrupt the process of stress erythropoiesis, leading to an expansion of erythroid precursors without proper maturation and differentiation.

Dysfunctional metabolism is a key contributor to both common and rare erythrocyte disorders.
Congenital dyserythropoietic anemia (CDA) is a rare group of inherited blood disorders in which RBCs do not develop properly, resulting in anemia. Approximately 5% of suspected CDAs show pathogenic variants in *PIEZO1*, the causative gene of dehydrated hereditary stomatocytosis (DHS).[5] PIEZO1-related anemias showed differentially expressed metabolites related to redox metabolism, lipid synthesis, and glycolysis. Analyzing transcriptomic, proteomic, and metabolomic changes in erythroid cells during differentiation and in mature RBCs has unveiled common deregulated pathways across seemingly unrelated disorders. An improved understanding of erythropoiesis has significant implications for the development of future therapeutic interventions.
PIEZO1 is an ion channel protein that responds to mechanical stimuli. PIEZO1-gain-of-function (GoF) mutations disrupt iron homeostasis via hepcidin suppression in DHS patients. RAS/MAPK and PI3K/AKT/mTOR pathways are both dysregulated in hepatocytes with PIEZO1-GoF alterations. mTOR could represent an additional player in the crosstalk between PIEZO1 signaling and iron homeostasis, making it a potential pharmacological target.
From 401 PI3K/AKT/mTOR-targeting compounds, 12 drugs that restored HAMP expression in PIEZO1-GoF cells were identified.[6] Two lead candidates show promising results in rescuing both iron and metabolic markers in primary murine hepatocytes and will be tested further as potential targeted therapies for DHS.

PIEZO1-mediated suppression of Hepcidin (HAMP) via the mTOR pathway



In conclusion, hemoglobin production in erythroblasts demands significant iron levels, highlighting the necessity of regulating iron availability during erythropoiesis. This year's EHA has provided a more robust mechanistic understanding of how iron availability is regulated by erythropoiesis. Common deregulated pathways are observed across seemingly unrelated disorders, with the mTOR pathway playing a role in regulating PIEZO1-mediated iron overload.

More from EHA

Discover the comprehensive EHA Campus Program on Iron Deficiency Management in different clinical settings, featuring diagnostic algorithms, clinical cases, and podcasts. Listen to the latest insights on pyruvate kinase activators in rare hematological diseases on the EHA Unplugged podcast.

EHA Diagnosing And Treating Iron Deficiency Program

Precision Medicine in Rare Hematological Diseases: Pyruvate Kinase Activators

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06

Innovative developments in thrombotic and bleeding conditions

Dr. Karina Meijer shares her highlights on thrombotic & bleeding conditions from EHA2025

This year's EHA highlighted a range of innovative developments in thrombotic and bleeding conditions, spanning novel therapeutics, targeted pathways, and precision medicine approaches that are shaping the future of care.

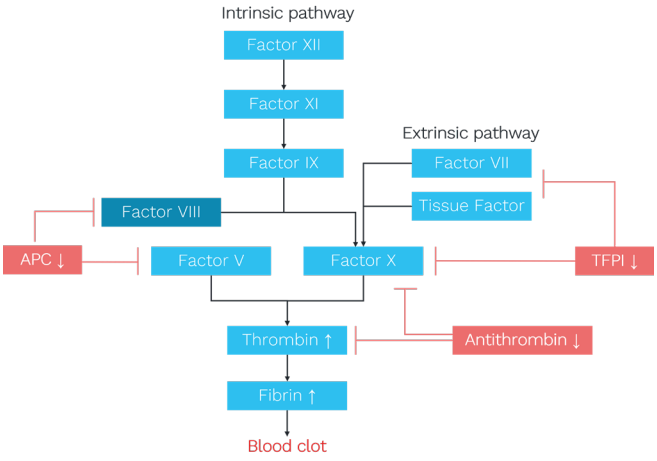
Rebalancing the coagulation cascade by restoring thrombin generation

Hemophilia A and B are inherited clotting factor deficiency, affecting Factor VIII (hemophilia A) or Factor IX (hemophilia B), that result from alterations in the coagulation cascade. Thrombin (Factor IIa) is a central enzyme in the coagulation cascade that converts fibrinogen to fibrin, which is essential for blood clot formation. Novel non-replacement therapies, aimed at reducing bleeding by rebalancing the coagulation system, increase thrombin generation, which helps form clots and prevents excessive bleeding in severe hemophilia, ultimately improving hemostasis and minimizing the disease's impact.[1] Two main approaches have been utilized to rebalance the coagulation system. First, to target the natural anticoagulants, such as antithrombin, activated protein C, and tissue factor pathway inhibitor (TFPI). And second by mimicking clotting factors using agents like FVIII-activity mimicking agent, Mim8, and emicizumab. These therapies can

enhance treatment adherence and quality of life for hemophilia patients due to their infrequent dosing, convenient administration, and the absence of the need for regular monitoring.

However, a limitation of these therapies may include an increased risk of thromboembolic events.

<u>Restoring thrombin generation in the coagulation cascade for hemophilia treatment</u>



Knockdown of hepatic plasminogen production by siRNA

Plasminogen is primarily produced in the liver and enzymatically degrades blood clots. This suggests that lowering hepatic plasminogen in bleeding disorders could be a safe alternative to conventional anti-fibrinolytic therapy. To explore this, the risk of thrombosis in patients with low plasma plasminogen was assessed using UK Biobank data, looking for associations between normalized plasminogen protein levels and thrombotic risk, with logistic regression adjusted for age and sex.[2] Mouse injury models were also used to assess thrombus formation. Interestingly, the findings showed that plasma plasminogen protein levels do not associate with a diagnosis of thrombosis. In the mouse model, over 99%

knockdown of hepatic plasminogen using a liver-directed small interfering RNA (siRNA) was not associated with thrombus formation. These results suggest that hepatic targeting of plasminogen with RNAi is unlikely to confer thrombotic risk and support clinical development of ALN-6400 – an investigational therapeutic for the treatment of bleeding disorders.[3]

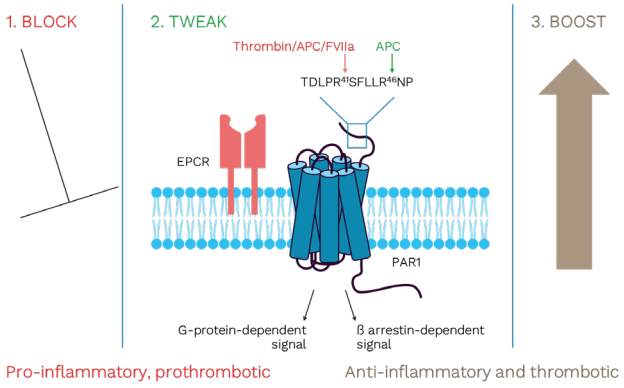
Innovations in hemophilia therapy

Factor replacement challenges include the need for venous access, short half-life, and immunogenicity. New strategies include extended half-life Factor products, antibodies, and gene therapy. Extending the half-life can be achieved by introducing mutations and peptide fusions to lower the elimination rate.[4] Bispecific antibodies such as emicizumab bind to FIXa and FX to mimic FVIIIa function, and subcutaneous weekly administration achieves stable plasma levels with no immunogenicity.[5] Other options include FVIIIa mimetics in clinical development, which can be administered orally with an absorption enhancer.[6] Rebalancing of the coagulation cascade can also alleviate severe hemophilia by increasing thrombotic activity,[1,7] and binding aptamers and nanobodies protect von Willebrand factor from degradation. Finally, gene therapy options include AAV or lentiviral vectors, and aim to provide patients with missing Factors.[8,9]

Coagulation proteases: New therapeutic targets beyond clotting

Coagulation proteases act beyond coagulation via protease-activated receptors (PAR), enabling cellular responses to vascular injury and inflammation, and eliciting diverse cellular outcomes in many tissues. PAR signaling is driven by receptor cleavage site, intracellular effectors, and plasma co-factors. This knowledge could be used to harness the power of coagulation protease signaling to exert therapeutic benefits.[10] For example, blocking unwanted PAR signaling with vorapaxar – a PAR1 antagonist – reduces cardiovascular events but increases bleeding. In contrast, small tweaks of PAR signaling with parmodulins allow inhibition of coagulation and platelet activation while preserving endothelial cytoprotection. Boosting PAR with engineered activated protein C analogs shows promise in stroke, cerebral malaria, and inflammatory bowel disease. Ultimately, decoupling and selectively enhancing the signaling properties of coagulation proteases has many potential therapeutic applications to treat thromboinflammatory and vascular diseases.

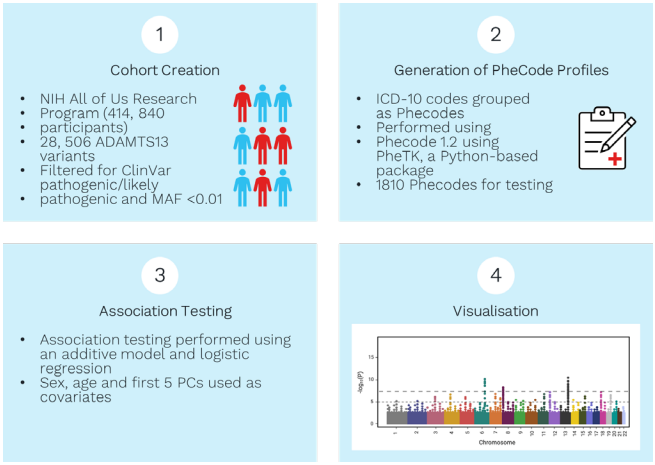
Manipulation of PAR signaling for therapeutic benefit



PheWAS give insight into the effect of *ADAMTS13* mutations

Congenital thrombotic thrombocytopenic purpura occurs due to inherited biallelic mutations in *ADAMTS13* on chromosome 9. Over 300 variants have been identified in patients – but there are more than 20,000 variants in population databases. An abstract presented at EHA2025 described how a phenome-wide association study (PheWAS) has been used to identify phenotypes associated with genetic variation in *ADAMTS13*.[11] A PheWAS is a hypothesis-generating methodology – with testing performed across all phenotypes without a prior hypothesis. The study included 414,840 participants from the All of Us Research Program, and analysis focused on the intronic variant rs28446901 – which has previously been linked to thrombotic diseases. Variant-based PheWAS of rs28446901 revealed associations with increased risk of venous embolism, deep vein thrombosis, and pulmonary embolism. Replication in the UK Biobank showed most significant association with phlebitis, thrombophlebitis, and pulmonary embolism. In sub-analyses the association remained consistent in both hetero- and homozygous individuals, suggesting a dominant negative effect on thromboembolic disease risk. There was also an unexpected association with peripheral angiopathy and osteomyelitis, highlighting the importance of *ADAMTS13* testing. Further functional studies are needed to explore this variant and consider its functional consequences.

PheWAS methods to explore phenotypes associated with genetic variation in ADAMTS13



Microfluidic testing using the Maastricht FlowChamber in BDUC

Of all patients with a clinically relevant bleeding tendency, 40–70% show no abnormalities in laboratory tests – a so-called bleeding disorder of unknown cause (BDUC). Standard tests such as prothrombin time or clotting factor analysis are static and use citrated plasma. An abstract presented at EHA2025 described the Maastricht FlowChamber, which better represents the *in vivo* environment by using whole blood and shear rates, and coating with collagen or tissue factor.[12] The study aimed to investigate the ability of this microfluidic assay to identify the underlying pathophysiology. In total, 48 BDUC patients underwent testing, with 49 healthy volunteers as a reference group. Results showed 54% of BDUC patients had one or more abnormalities, mostly on the collagen I spot. The authors concluded that these patients have shear-dependent primary hemostasis defects.

More from EHA

Mark your calendar for the EHA SWG meeting on Bleeding and Platelet Disorders in April 2026. Review the scientific program and reserve your spot now. Discover gene therapy's potential to liberate hemophilia patients from traditional coagulation factor replacement on our EHA Unplugged podcast.

EHA SWG meeting on Bleeding and Platelets disorders

Gene Therapy for Hemophilia

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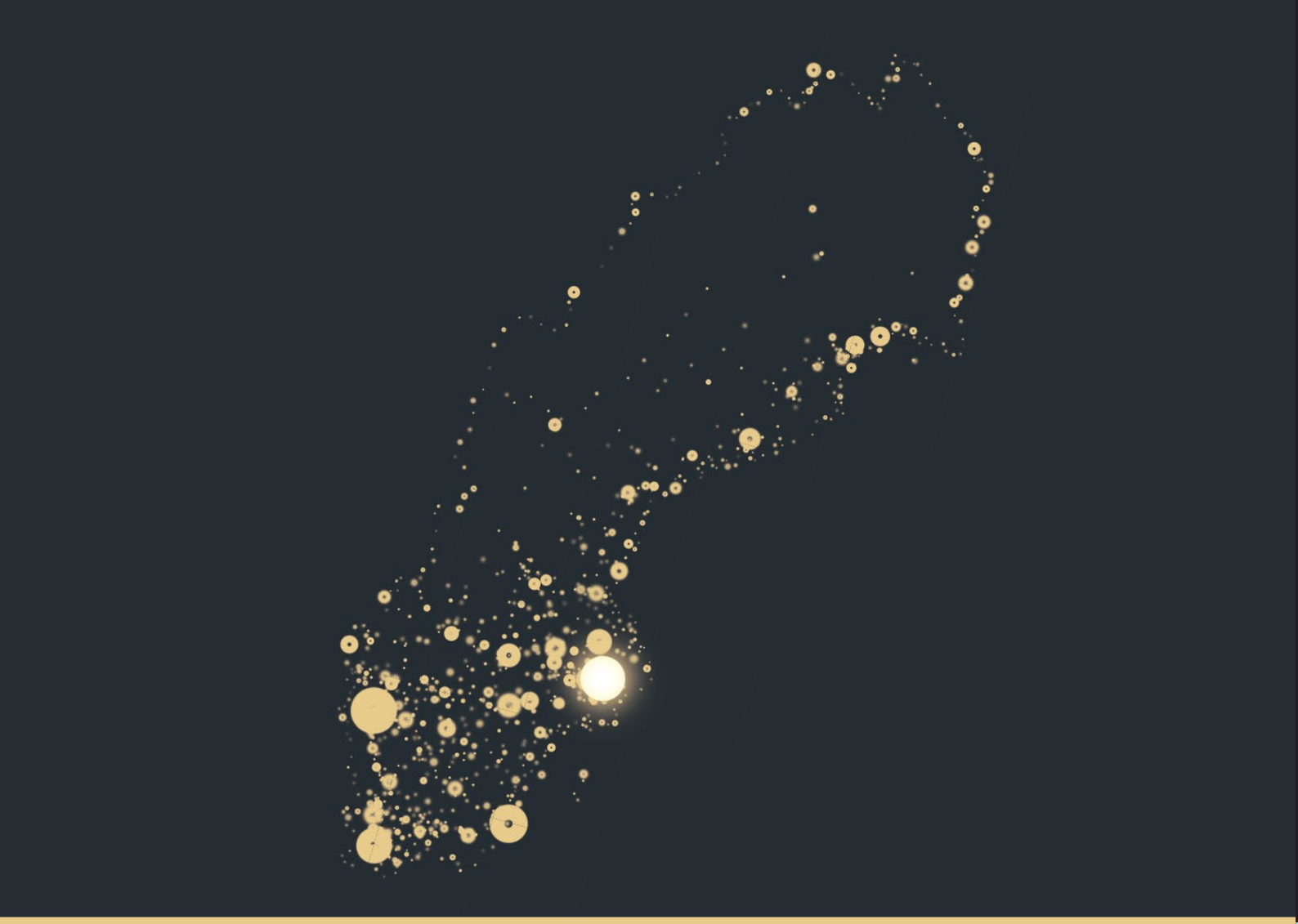

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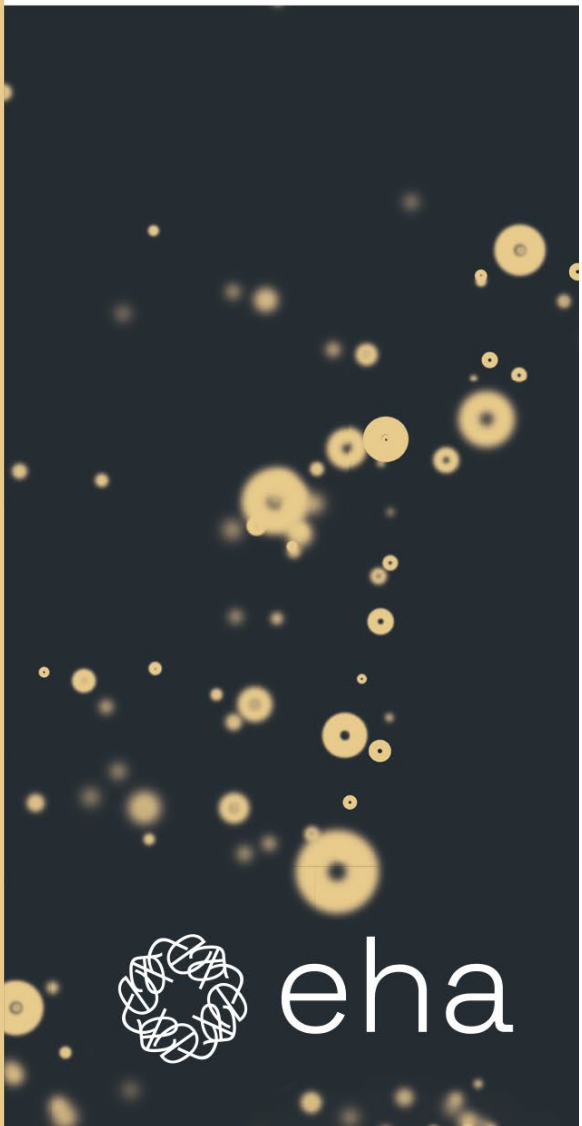

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