EHA Perspectives on Non-malignant Hematology

Presented at the EHA2025 Congress

Milan, Italy

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Welcome & Objectives

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 format at the EHA2025 Congress, the reports underscore the significance of the latest developments in the various fields of hematology.

Martin Dreyling, EHA2025 Scientific Program Committee Chair

Objectives

The EHA Annual Congress is recognized as the second-largest global event in hematology. Beyond uniting hematology experts from around the world, the EHA Congress serves as a vital platform for disseminating groundbreaking scientific information and developments within the field of hematology. The congress reports are an initiative to give the hematology community a concise overview of the most critical work showcased at EHA2025.

01

Hematopoietic stem cells and their niche, from physiology to pathology

Section 1: Hematopoietic stem cells and their niche, from physiology to pathology

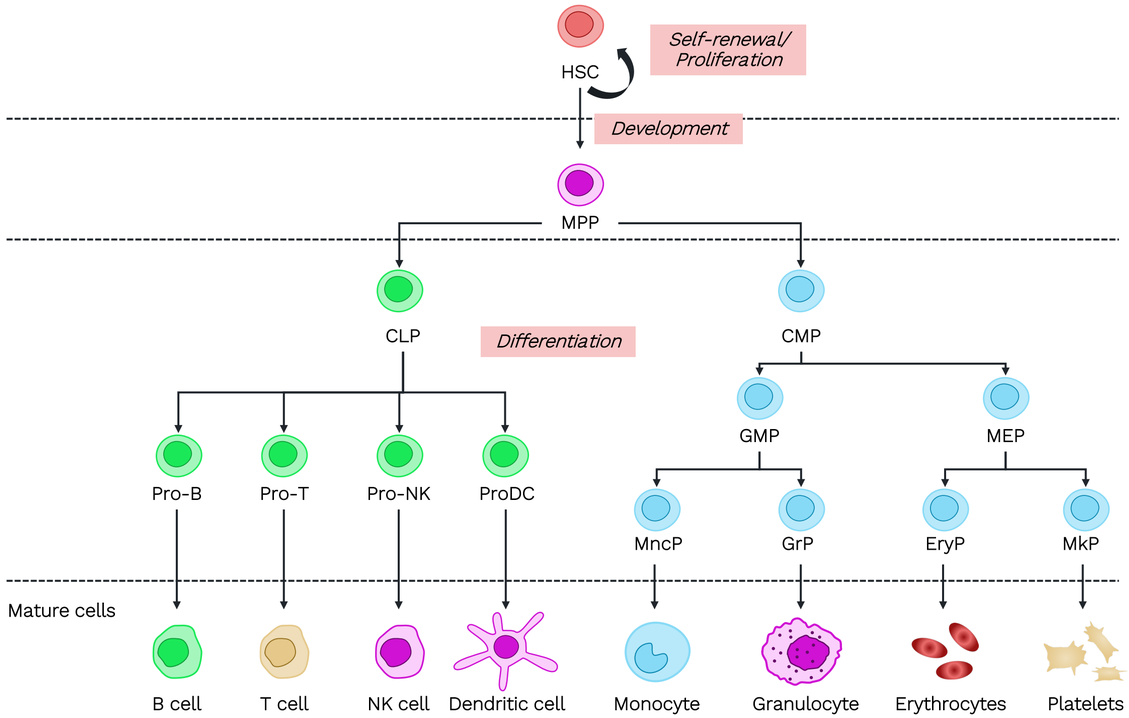
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p202-2	Hematopoietic Stem Cell Heterogeneity: What properties define a stem cell?	Sten Eirik Jacobsen
S270	Discovery of ATP2B1+ CD49F+ human hematopoietic stem cells with superior long-term multilineage reconstitution	Angelica Varesi
S275	Epitope editing enables immune-based selection of multiplex genome engineered stem cells and improved non-genotoxic conditioning	Gabriele Casirati
p272-3	Niche regeneration after injury	César Nombela-Arrieta
S273	TGF-ß1-triggered maladaptive bone marrow endothelium impedes hematopoietic recovery	Zhong-Shi Lyu
S274	Rankl cytokine is a novel supportive signal in the bone marrow hematopoietic niche	Francesca Ficara
p272-2	HSC response to stress during ageing	Katherine King
p296-1	Anemia in space	Joseph Borg

p202-2: Hematopoietic Stem Cell (HSC) regulation in steady state

- HSCs play a crucial role in the continuous replenishment of blood cells, holding the top position in the hierarchy of hematopoietic cells
- HSCs are characterized by their ability to self-renew and their potential to differentiate into multiple cell types and produce all mature blood lineages in the bone marrow (BM)
- HSCs operate through a hierarchy of intermediate progenitors, providing one progenitor replenishment pathway for each lineage
- The microenvironment/niche in BM regulates HSC maintenance and differentiation, providing essential components for self-renewal and ongoing hematopoiesis
- In addition to the previously identified myeloid- and lymphoid-biased HSCs, the full extent and the interplay of other lineage-biased restricted HSCs remain to be characterized

Overview of stages of normal hematopoiesis



CLP, common lymphoid progenitor; CMP, common myeloid progenitor; EryP, erythrocytic progenitor; GMP, granulocyte–macrophage progenitor; GrP, granulocytic progenitor; MEP, megakaryocyte–erythrocyte progenitor; MkP: megakaryocyte progenitor; MncP: monocyte progenitor; NK cells, natural killer cells; Pro-B, progenitor cell-B; Pro-T, progenitor cell-T; Pro-NK, progenitor cell-NK; Pro-DC, dendritic progenitor cell

Image adapted from Kwon M et al. Int. J. Mol. Sci. 2024, 25, 6837.

Jacobsen SE. Hematopoietic Stem Cell Heterogeneity: What properties define a stem cell? Oral presentation p202-2 at EHA2025.

p202-2: Fate mapping in mouse and human HSCs describes novel lineage-restricted pathways

Mouse HSCs

- Using single-cell transplantation, the fate mapping of mouse HSCs revealed a limited repertoire of lineage-restricted HSCs:
  - The only single lineage-restricted HSCs were platelet (P)-restricted
  - PEM- and PEMB-restricted HSCs were common and established in young mice
  - No other HSC lineage restriction (or bias) patterns were observed
- Vwf+ P-HSCs and Vwf- 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

Human HSCs

- CH driver mutations and other mutations were used to perform clonal HSC lineage fate mapping
- PEM- and PEMB-HSCs were the only lineage-restricted HSCs observed (identification of P-HSCs will require other strategies)
- PEM- and PEMB-HSCs were hierarchically replenished from multilineage (PEMBT) HSCs
- PEM- and PEMBT-HSCs expanded upon aging, but emerged already at a young age
- Retrospective and prospective analyses revealed that human HSC clonal lineage replenishment patterns were stable over time and also upon transplantation, suggesting they were intrinsically programmed

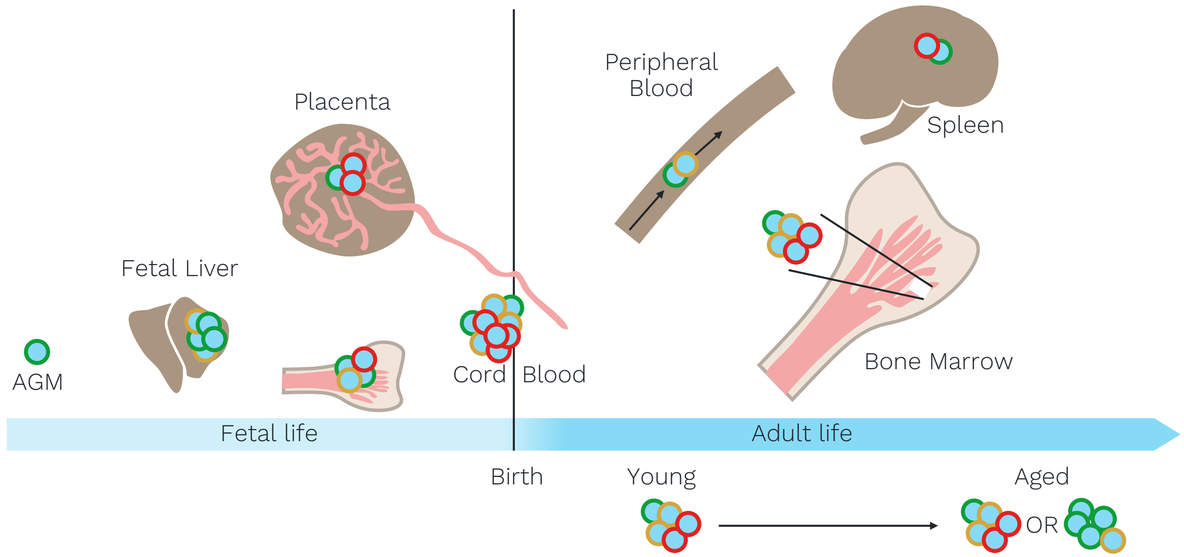
CH, clonal hematopoiesis; HSC, hematopoietic stem cell; Mk, megakaryocytic; P-restricted, platelet-restricted; PEM, platelet-erythroid-myeloid; PEMB, platelet-erythroid-myeloid-B cell; PEMBT, platelet-erythroid-myeloid-B cell-T-cell; Vwf, von Willebrand factor gene

Jacobsen SE. Hematopoietic Stem Cell Heterogeneity: What properties define a stem cell? Oral presentation p202-2 at EHA2025.

S270: Limited markers exist to identify long-term human HSCs, which are conserved throughout the lifespan

- Long-term hematopoietic stem cells (LT-HSC) maintain lifelong hematopoiesis while preserving the stem cell compartment through self-renewal
- 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 are still limited across ontogeny

The composition of the HSPC compartment changes in space and time

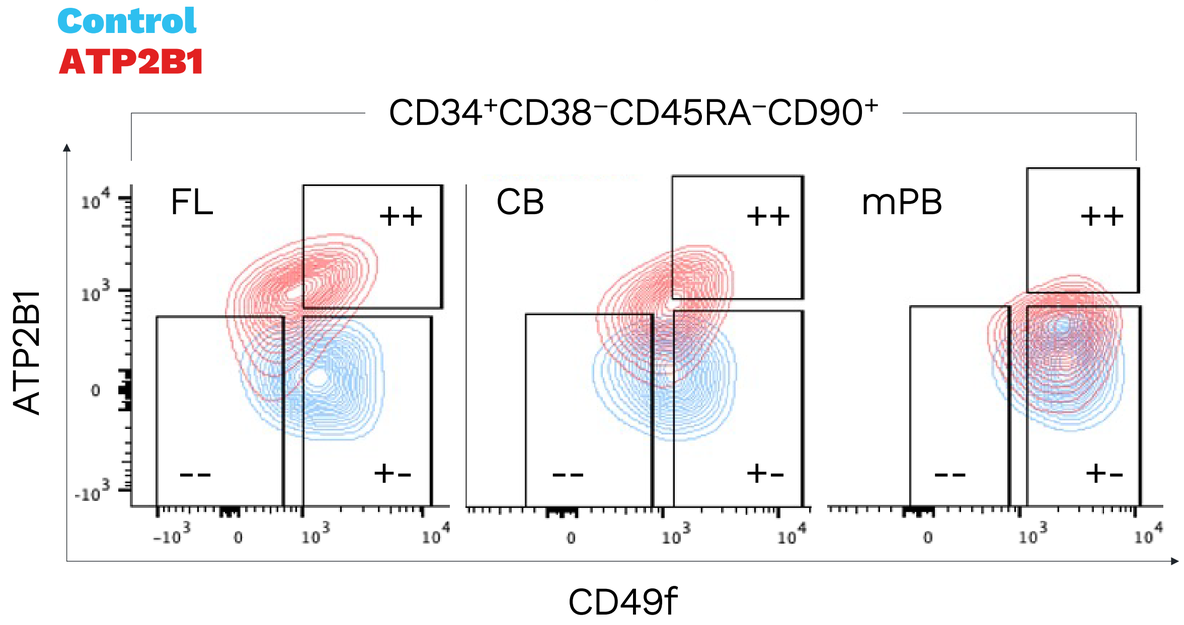


AGM, aorta gonad mesonephros; CD, cluster of differentiation; HSCs, hematopoietic stem cells.
Image adapted from Laurenti E, Göttgens B. *Nature.* 2018;553(7689):418-426.
Varesi A. Discovery of ATP2B1+ CD49F+ human hematopoietic stem cells with superior long-term multilineage reconstitution. Oral abstract S270 at EHA2025.

S270: ATP2B1 marker identified as a new long-term HSC population from across fetal to adult human life

- 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
- ATP2B1 expression further separates CD49f+ HSC, the current gold-standard purification method, into two populations
- CD49f+ATP2B1+ LT-HSC exhibited 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)



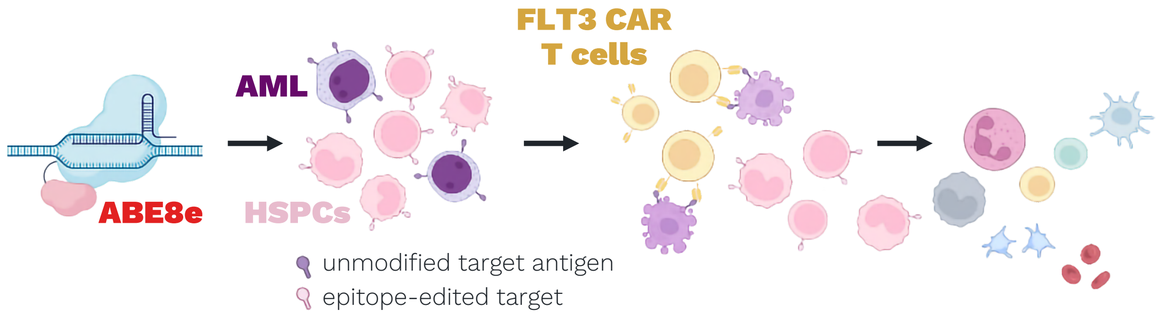
ATP2B1, ATPase plasma membrane Ca2+transporting 1; CD, cluster of differentiation; HSC, hematopoietic stem cell; LT-HSC, long-term hematopoietic stem cell.

Varesi A. Discovery of ATP2B1+ CD49F+ human hematopoietic stem cells with superior long-term multilineage reconstitution. Oral abstract S270 at EHA2025.

S275: Epitope editing enables immune-based selection of engineered stem cells

Steps involved in the epitope-based editing strategy for patients with AML

Epitope base editing	SCT with edited HSPCs	CAR-T cell administration	AML eradication & hematopoietic reconstitution

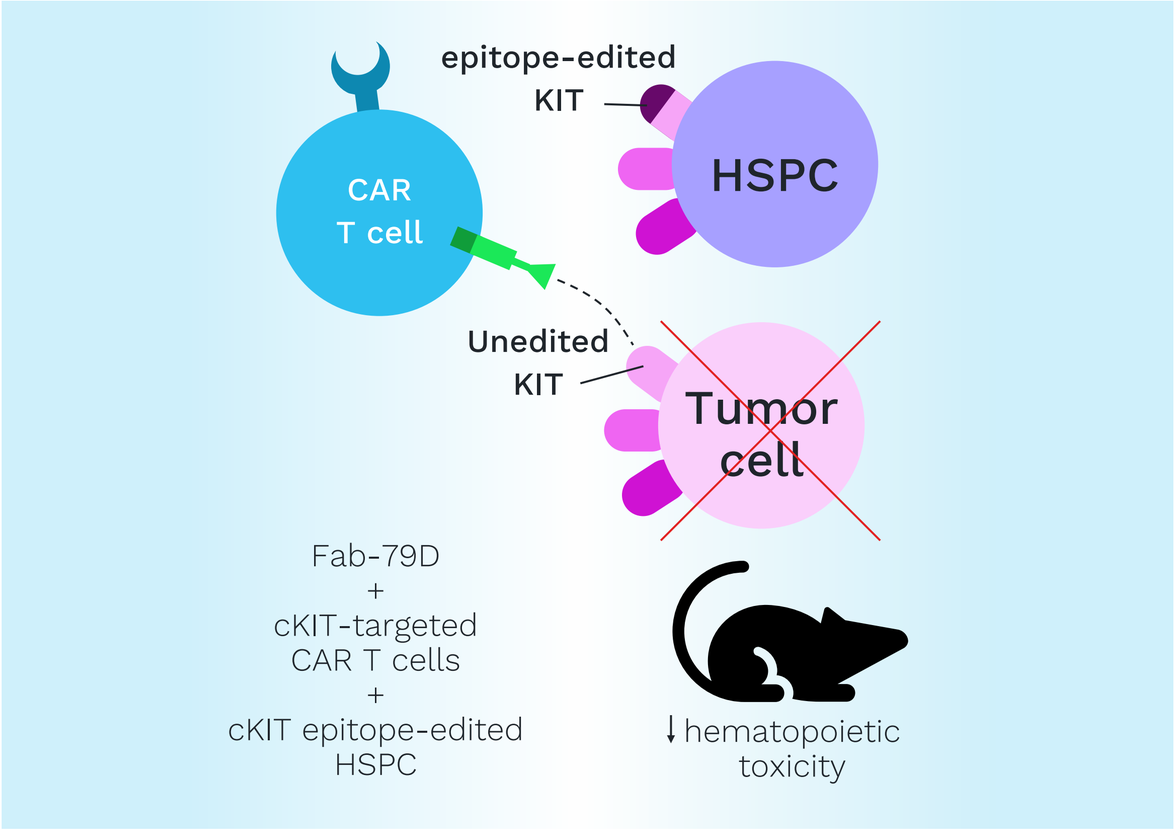


- Bone marrow conditioning is usually needed before HSCT, but traditional approaches are highly genotoxic
- Non-genotoxic conditioning using targeted immunotherapy has the potential to minimize adverse events
- Epitope editing is a precise genetic manipulation that introduces a single-nucleotide mutation, chosen to render HSPCs invisible to the immunotherapy
- Epitope editing can enable non-genotoxic conditioning and *in vivo* selection
- The target epitope is removed without gene knock-out

ABE, adenine base editor; AML, acute myeloid leukemia; CAR-T, chimeric antigen receptor T-cell; HSCT, hematopoietic stem cell transplant; HSPC, hematopoietic stem and progenitor cell; SCT, stem cell transplant.
Image adapted from Casirati G. et al. *Nature.* 2023; 621,404-414
Casirati G. Epitope editing enables immune-based selection of multiplex genome engineered stem cells and improved non-genotoxic conditioning. Oral abstract S275 at EHA2025.

S275: Epitope-editing can enable non-genotoxic conditioning and *in vivo* selection

- 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
- 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 by 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 HbF induction
- As different clinical indications may require different potencies in Ab pharmacological actions, another mAb, anti-KIT SR-1 clone, with 25x the potency of FAD-79D, was validated. When edited by prime editing, it enabled non-genotoxic conditioning for hematopoietic replacement
- Epitope editing may eliminate limitations associated with mAb pharmacokinetics, enabling innovative hematopoietic stem cell transplant strategies



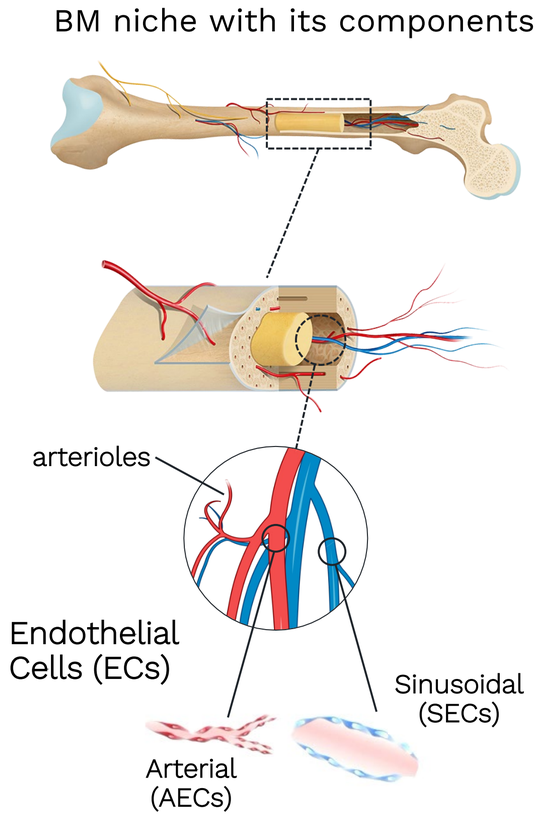
Ab, antibody; CAR, chimeric antigen receptor; ECD, extracellular domain; Fab, fragment antigen binding; HbF, fetal hemoglobin; HSPC, hematopoietic stem and progenitor cell; mAb, monoclonal antibody.

1. Casirati G. et al. Nature 2023; 621,404-414

Casirati G. Epitope editing enables immune-based selection of multiplex genome engineered stem cells and improved non-genotoxic conditioning. Oral abstract S275 at EHA2025.

p272-3: Bone marrow (BM) niche regeneration after injury

- The BM microenvironment provides a structural framework to the 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 like growth factors, cytokines, and extracellular matrix provide essential nutrients and signals for HSC growth and maintenance
- The non-hematopoietic stromal framework of BM consists of sinusoidal endothelial cells and arterial endothelial cells, as well as the mesenchymal stromal cell compartment, especially CXCL12-abundant LepR+ reticular cells , which play an active role in regulating hematopoiesis



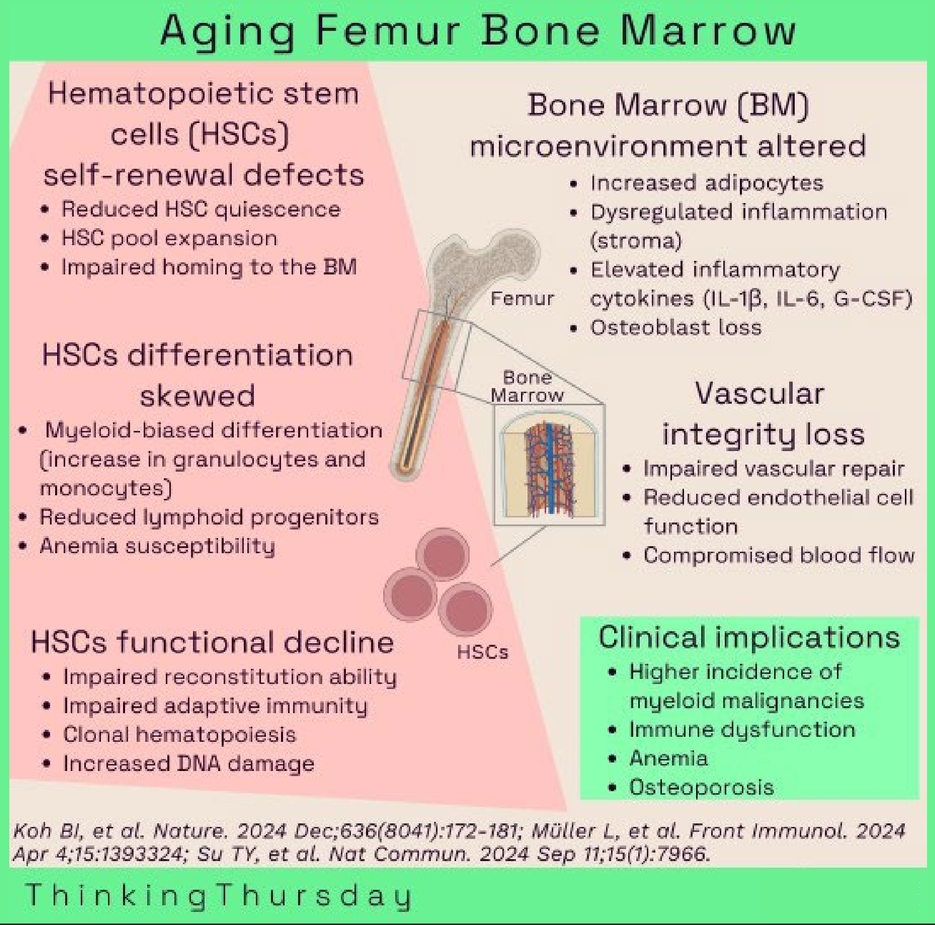
AECs, arterial endothelial cells; BM, bone marrow; CARc, CXCL12 abundant LepR+ reticular cell; CXCL12, CXC motif chemokine 12; ECM, extracellular matrix; HSCs, hematopoietic stem cells; MSC, mesenchymal stromal cells; SECs, sinusoidal endothelial cells

Nombela-Arrieta C. Niche regeneration after injury. Oral presentation p272-3 at EHA2025.

p272-3: Bone marrow (BM) niche regeneration after injury

- The organization and interaction between the SECs and CARc networks are highly conserved throughout the BM
- In mice, these stromal networks are highly resilient to injury, with a 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, especially mTORC1 signaling, and causes long-term transcriptomic sequelae in the BM stroma, linked to alterations in ECM production and cellular senescence

More from EHA #Thinking Thursday

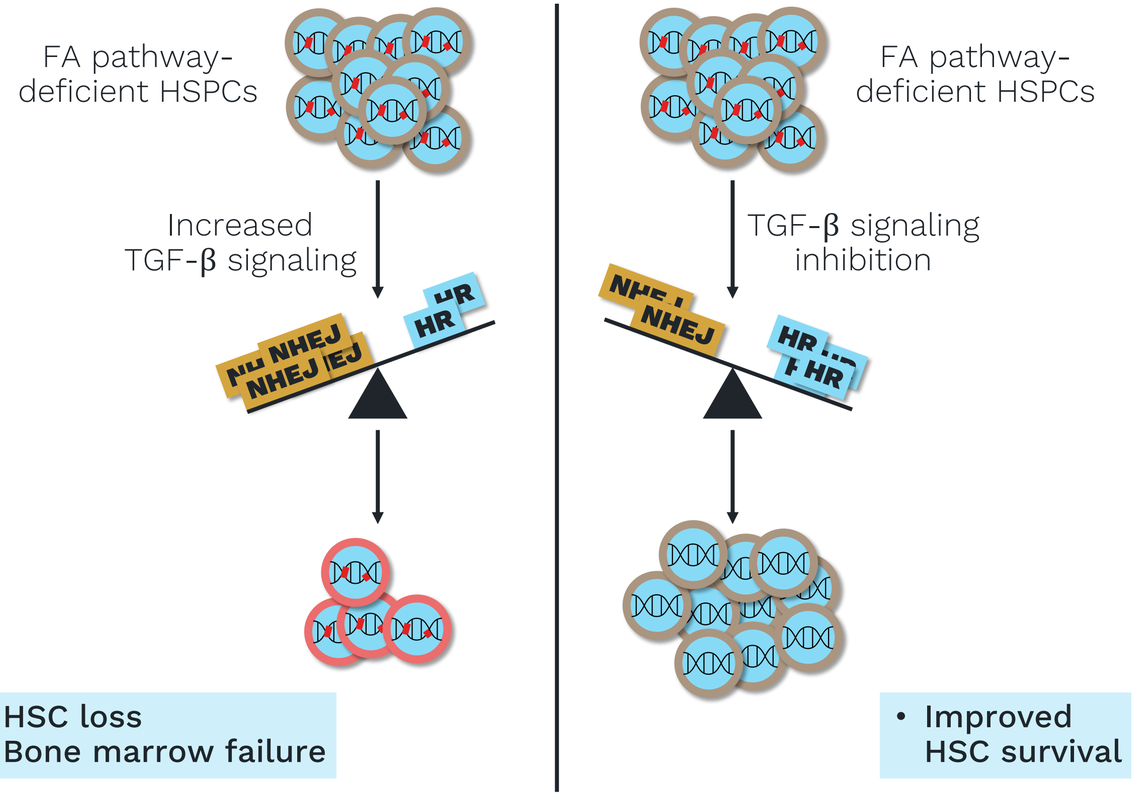


AECs, arterial endothelial cells; BM, bone marrow; CARc, CXCL12 abundant LepR+ reticular cell; CXCL12, CXC motif chemokine 12; ECM, extracellular matrix; HSCs, hem

Nombela-Arrieta C. Niche regeneration after injury. Oral presentation P272-3 at EHA2025.

S273: Role of TGF-β on BM endothelial cells' function

- BM endothelial cells (ECs) form a critical niche for HSC regulation.
- Multiple disease models have previously proven the importance of BM ECs in hematopoietic regulation, for example, in Fanconi Anemia (FA).
- Molecular drivers of dysfunctional ECs remain poorly defined.
- TGF-ß1 has been shown to participate in the regulation of hematopoiesis across diverse cell types.
- The hypothesis that TGF-ß1 inhibition could support hematopoiesis in dysfunctional EC models was tested.



TGF-β inhibition rescues HSC defects and BM failure in Fanconi Anemia

BM, bone marrow; ECs, endothelial cells; HR, homologous recombination; HSC, hematopoietic stem cell; NHEJ, non-homologous end-joining; TGF-β, transforming growth factor-β.
Image adapted from Zhang H et al. Cell Stem Cell. 2016 Mar 24;18(5):668–681
Lyu ZS. TGF-ß1-triggered maladaptive bone marrow endothelium impedes hematopoietic recovery. Oral abstract S273 at EHA2025.

S273: Persistent activation of TGF-β drives maladaptive BM endothelial cells, which can be reversed by inhibiting TGF-β

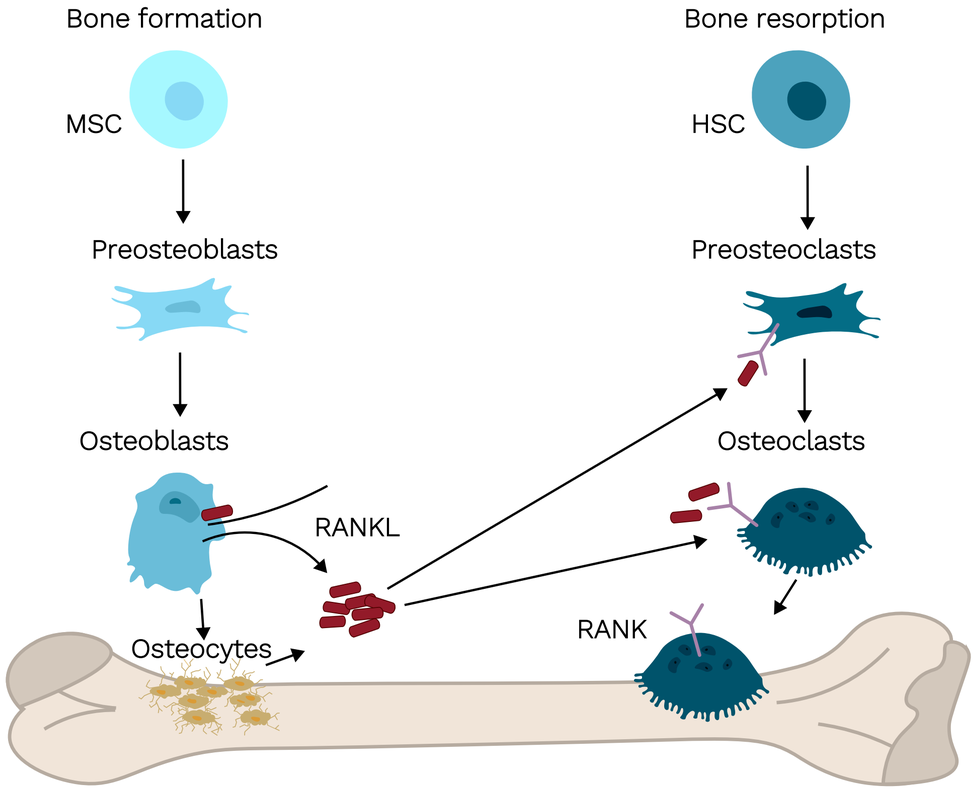
- TGF-β1 overexpression impaired BM EC functions *in vitro,* including migration and tube formation, while increasing apoptosis and ROS levels; these impairments could be restored by silencing TGF-β pathway genes
- In a mouse model, the AAV-mediated overexpression of a constitutively active TGF-β receptor (TGF-βRI) in BM EC resulted in impaired BM EC function and aggravated hematopoietic injury
- Multi-omics studies clarified that sustained activation of TGF-β1 drives BM ECs toward a maladaptive repair process, likely due to dysregulated crosstalk between VEGF/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), resulting in the restoration of the function of BM ECs
- Initial data from a prospective clinical trial evaluating luspatercept, a TGF-β ligand trap, in patients with anemia following HSCT indicated enhanced recovery of multilineage hematopoiesis in these post-HSCT patients

Study design of an ongoing prospective clinical trial of luspatercept, a TGF-β ligand trap.

AAV, adeno-associated virus; ANC, absolute neutrophil count; BM, bone marrow; ECs, endothelial cells; HI-N, hematologic improvement–neutrophil; HI-P, hematologic improvement–platelet; HSCT, hematopoietic stem cell transplant; RBC, red blood cell; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; WBC, white blood cell.
Image adapted from Zhang H et al. *Cell Stem Cell.* 2016;18(5):668–681
Lyu ZS TGF-β1-triggered maladaptive bone marrow endothelium impedes hematopoietic recovery. Oral abstract S273 at EHA2025.

S274: Role of RANKL signaling in osteoblast differentiation

- RANKL, a cytokine, is secreted by osteoblasts and osteocytes and binds to RANK on the membrane of osteoclast progenitors, resulting in bone resorption by mature osteoclasts[1]
- Mutations in the RANKL lead to osteoclast-poor osteoporosis, defining its role in maintaining bone homeostasis and efficient hematopoiesis
- RANKL can also regulate stromal stem cell (SSC) differentiation along the osteochondrogenic lineage[2]
- As SSCs are important HSC niche factors, the presented abstract aimed to test whether knocking out the RANKL gene would affect bone marrow SSCs' ability to support HSC



Role of RANKL/RANK axis on bone homeostasis

HSC, hematopoietic stem cell; MSC, mesenchymal stem cell; RANKL, receptor activator of nuclear factor kappa-B ligand; TNF, tumor necrosis factor.
Image adapted from Ming J et al. Front Oncol. 2020;10:1283

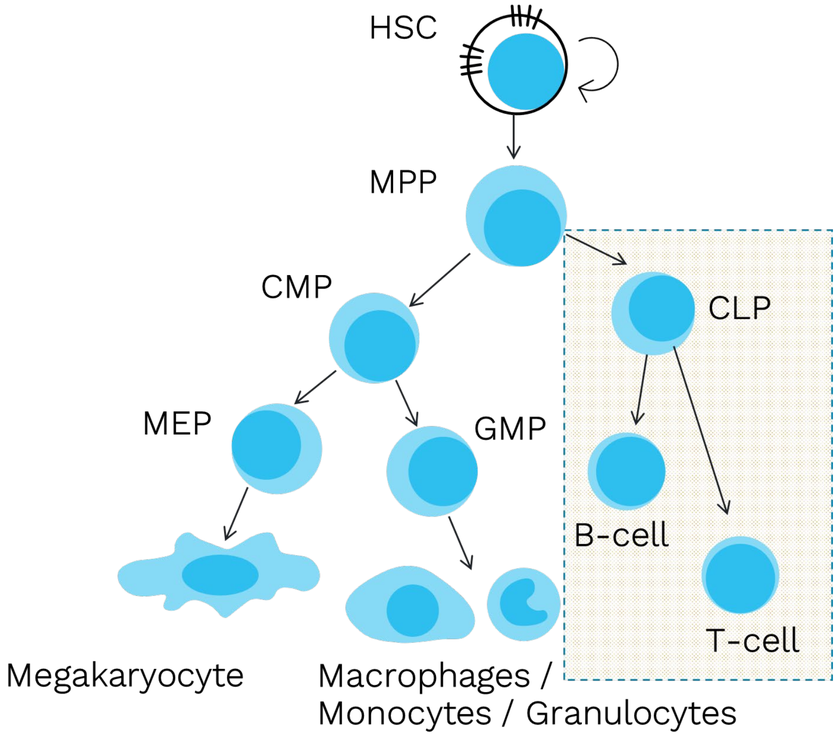
1. Ming J et al. Front Oncol. 2020;10:1283; 2. Sobacchi C et al. Physiology (Bethesda). 2025;40(1):0.

Ficara F. RANKL cytokine is a novel supportive signal in the bone marrow hematopoietic niche. Oral abstract S274 at EHA2025.

S274: RANKL plays a supportive role in the BM hematopoietic niche

- 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 (CLP) 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-KO mice
- BM reconstitution assays in WT 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 indicated 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)

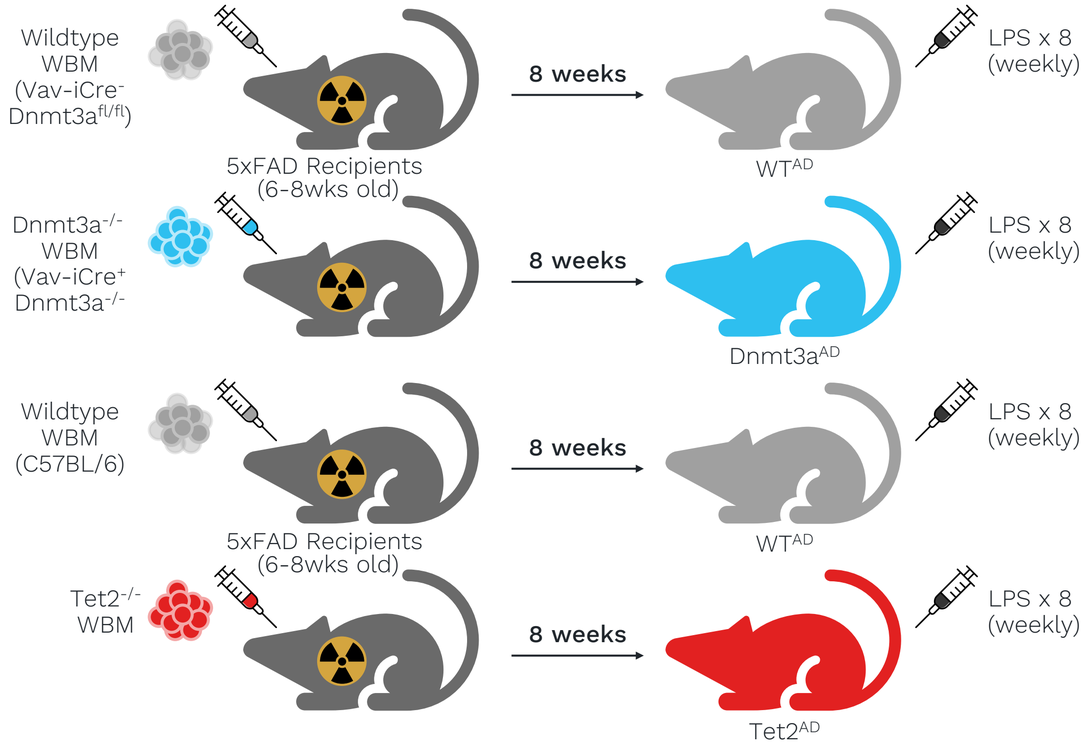


BM, bone marrow: CMP, common myeloid progenitor; GMP, granulocyte-monocyte progenitor; HSC, hematopoietic stem cell; KO, knockout; MEP, megakaryocyte-erythroid progenitor; MPP, multipotent progenitors; RANKL, receptor activator of nuclear factor kappa-B ligand; SSC, stromal stem cell; WT, wildtype.
Ficara F. RANKL cytokine is a novel supportive signal in the bone marrow hematopoietic niche. Oral abstract S274 at EHA2025.

p272-2: Role of *Dnmt3a* and *Tet2* clonal hematopoiesis in Alzheimer's disease pathogenesis

- 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)[1] and validated in a large cohort from the UK Biobank.
- Correlation between CH and AD was tested by transplanting Dnmt3a or Tet2 loss-of-function (LoF) bone marrow in 6-8-week-old AD-prone mice (5xFAD).
  - 8 weeks after transplantation, 8 injections of LPS were administered weekly
- 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 CNS 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.

Schematic representation of the experimental design



CH, clonal hematopoiesis; CNS, central nervous system; Dnmt3A, DNA methyltransferase; FAD, familial Alzheimer's disease; HSCs, hematopoietic stem cells; LoF, loss of function; LPS, lipopolysaccharide; Tet2, ten-eleven translocation 2; WT, wild-type

1. Bouzid et al. Nature Medicine 2023; 29:1662–1670.

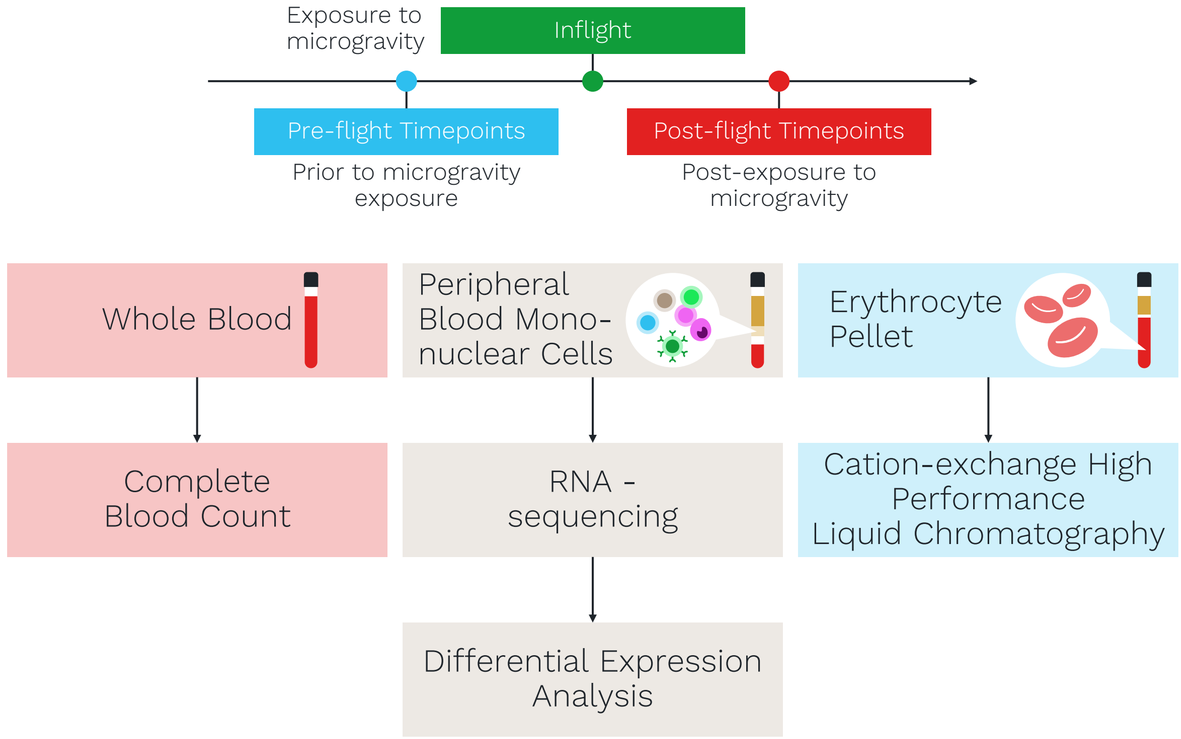
King K. HSC response to stress during ageing. Oral presentation p272-2 at EHA2025.

p296-1: The next frontier: How today's astronauts are helping tomorrow's healthcare for hemoglobinopathies

Cell experiments are done in orbit, but testing astronaut blood is also revealing some interesting findings:

- Space travel causes changes in gene expression related to fundamental pathways, including insulin and estrogen signaling[1]
- Astronauts are healthy adults, but in space, they often develop a form of anemia, with elevated fetal hemoglobin.
- The expression of hemoglobin at various stages of erythropoiesis at different times in space has been investigated using a unique suite of multiomics[2]
  - Findings reveal significant variations in globin gene expression, corresponding to distinct spatiotemporal characteristics of the samples
- Due to the limited number of astronauts and small 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

Schematic representation of the experimental design



BM, bone marrow.
1. Mathyk BA et al. Commun Biol. 2024 Jun 11;7(1):692; 2. Borg J, et al. Nature Communications 2024.15(1):4927.
Borg J. Anemia in space. Oral presentation p296-1 at EHA2025.

Conclusion

- This year’s EHA advanced our understanding of HSC regulation by niches during homeostasis as well as under stress conditions.
- ATP2B1 has been recognized as a novel long-term human hematopoietic stem cell population that spans from fetal development to adulthood.
- Significant progress has been made in understanding the niche cell components and the localization of HSCs under both homeostatic and stressed conditions, with new roles of TGF-β1 and RANKL identified in bone marrow niches that regulate HSC function.
- This new research in the field has implications for the development of therapies to rejuvenate aged HSCs or niches or to disrupt self-reinforcing malignant niches.

RANKL, Receptor activator of nuclear factor kappa-B ligand; TGF-β, transforming growth factor-β.

02

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

Section 2: The global burden of SCD: how to combine universal access with the latest genetic treatments?

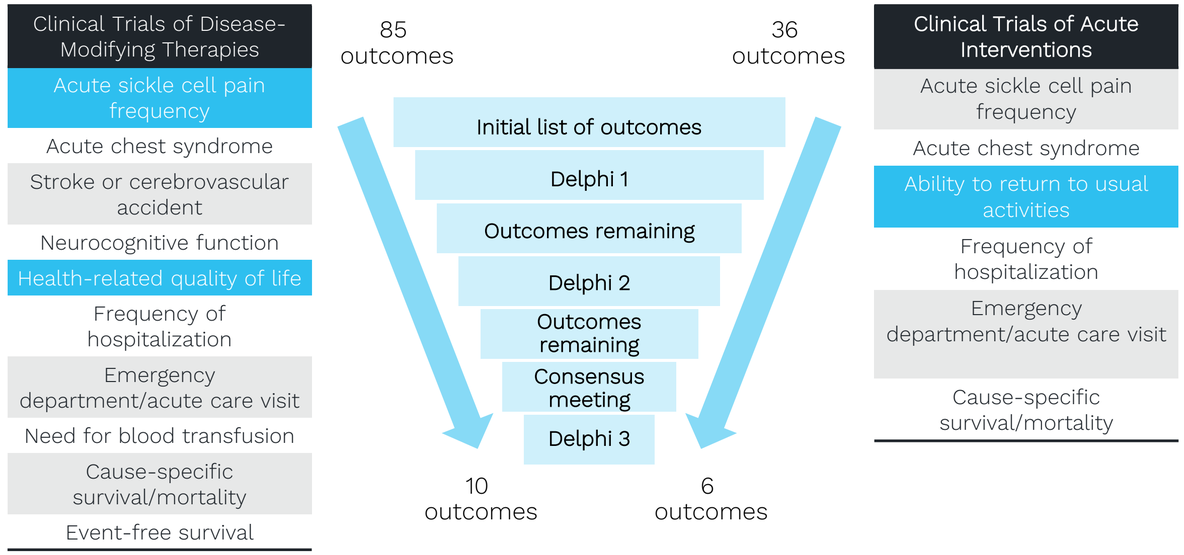
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p128-1	Challenges of endpoints in SCD	Slimane Allali
p128-2	Challenges of diversity and enrolment of patients	Raffaella Colombatti
p268-3	Changing setting, guidelines and perspective in the transition from pediatric to adult care for Sickle Cell Disease	Raffaella Colombatti
p516-1	State-of-the-art on the point-of-care tests for neonatal screening of SCD	Beatrice Gulbis
PF1176	Optimizing hydroxyurea therapy in sickle cell disease: Insights from metabolite detection, treatment response and clinical outcomes	Sigrid van der Veen
p210-4	Community-led hydroxyurea program	Beatrice Jepngetich
p555-1/ p555-2	Gene therapy vs transplant	Mariane de Montalembert & Erfan Nur
S285	Outcomes of peripheral blood stem cells versus bone marrow in adult sickle cell disease patients undergoing haploidentical allogeneic stem cell transplantation	Maud Zwolsman
S288	The impact of allogeneic hematopoietic stem cell transplantation on sickle cell retinopathy and maculopathy: a prospective, observational study	Elisabeth Dovern
S287	Small activating RNA-mediated induction of HBG via liposome delivery for in vivo treatment of sickle cell disease	Bríd Ryan

p128-1 & p128-2: Challenges of endpoint selection in SCD clinical trials

- SCD has a complex pathophysiology, which in turn offers multiple therapeutic targets
- However, only 2 of 4 approved disease-modifying therapies have not been withdrawn from the market again (i.e., HU and L-glutamine) → **lack of efficacy or suboptimal endpoint selection in clinical trials?**
- Typical endpoints in SCD clinical trials are VOC, ACS, anemia, PH, pain, fatigue, reduced QoL and HbF level
- VOC is the primary endpoint in most clinical trials, but is strongly influenced by many factors (a subjective feeling of pain, duration of crisis, triggers linked to environmental factors, …) → difficult to define VOC consistently
- Anemia and hemolysis as surrogate endpoints are clinically relevant but also highly variable
- Other surrogate endpoints (biological/radiological) might help when exploring pathophysiological hypotheses in pilot studies, but may not translate to clinical benefits

- Endpoint selection should consider diversity, variability, genotype, environmental factors, healthcare costs, safety, etc
- Involving patients early is essential for defining meaningful endpoints in SCD trials, as supported by a multi-stakeholder consensus that emphasizes the inclusion of PROs and HRQoL



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

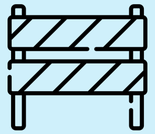
ACS, acute chest syndrome; HbF, fetal hemoglobin; HU, hydroxyurea; HRQoL, health-related quality of life; PH, pulmonary hypertension; PRO, patient-reported outcome; QoL, quality of life; SCD, sickle cell disease; VOC, vaso-occlusive crisis

Figure adapted from Tambor E, et al. *BMC Med Res Methodol*. 2021;21:219.

Allali S. Challenges of endpoints in sickle cell disease. Oral abstract p128-1 at EHA2025.
Colombatti R. Challenges of diversity and enrolment of patients. Oral abstract p128-2 at EHA2025.

p128-1 & p128-2: Current barriers and challenges in SCD and actionable steps to address them

In addition to its complicated pathophysiology, SCD is characterized by extremely diverse patients and health care systems in different parts of the world[1,2]



Current barriers in SCD drug development

- System-level limitations: e.g., systemic inequities, underfunding, poor access to treatments
- Research limitations: e.g., poor trial design, inappropriate endpoints, need for better drug targets
- Pharmaceutical companies: market-driven decisions, rushed market entrance, limited drug access post-approval
- Patient concerns: disappointment with failed treatments, lack of PRO-focused trials, insufficient early patient involvement[3]

Key challenges in SCD clinical trials

- Diverse patient characteristics: e.g., sex, age, genotype, disease burden, clinical variability throughout the lifespan
- Clinical inequalities: e.g., late/missed diagnosis in minority groups, unequal access to treatment options, children underrepresented in clinical trials
- Psychological, social, and demographic inequalities: e.g., emotional burden, transition from pediatric to adult care
- Trial awareness and participation vary, and driving factors for trial participation differ between patients and HCPs

Actionable targets

- Early patient engagement, recruitment, and retention
- Strengthen site networks and research infrastructure[4]
- Use digital health technology
- Align trial design with regulatory guidance and stakeholder collaboration
- Solutions should acknowledge the existing inequities and the diversity that impact disease phenotype and management

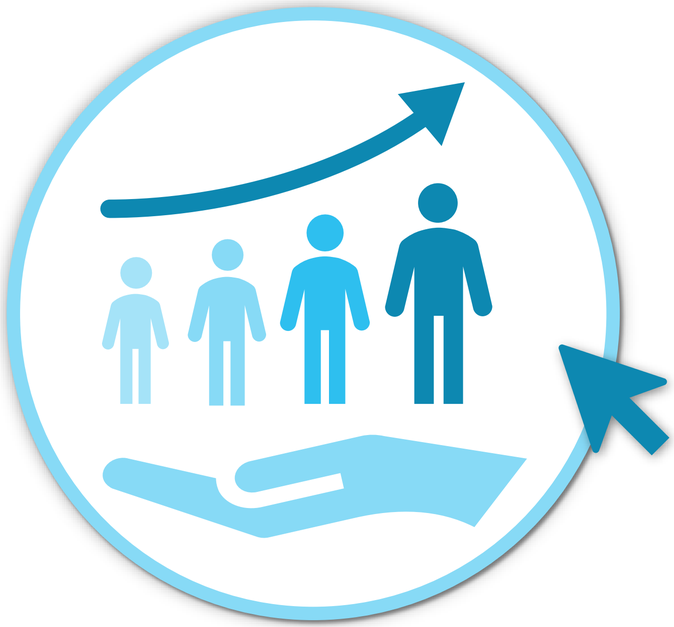
HCP, health-care professional; PRO, patient-reported outcome; SCD, sickle cell disease.

1. Strunk C et al. *Blood Cells Mol Dis*. 2021; 92:102612. 2. Osunkwo I et al. *Am J Hematol*. 2022; 97(8):1055-1064. 3. Brousse V et al. *Hemasphere* 2025; 9(2):e70082. 4. Kelsey MD et al. *Contemp Clin Trials*. 2022; 116:106740.
Allali S. Challenges of endpoints in sickle cell disease. p128-1 at EHA2025.
Colombatti R. Challenges of diversity and enrolment of patients. Oral abstract p128-2 at EHA2025.

p268-3: From pediatric to adult care for SCD – It is a process, not just a transfer!

- Previously, SCD often led to the premature death of affected children. However, with the advent of effective treatments, many now live into adulthood, creating a growing demand for care tailored to adolescents and young adults (AYAs).
- Healthcare systems are often divided into pediatric and adult care, which creates several challenges:
  - Young SCD-patients will face transition from their pediatrician to an adult-oriented provider, which might also involve a change in location/facility, as well as personnel
  - Responsibility for managing the disease also tends to shift from the parent to the patient
  - Adolescence is a phase that involves considerable physical and sociopsychological growth and changes
- The transition of SCD patients from pediatric to adult healthcare requires better support and planning, gradual preparation, consultations, clear communication, and emotional support.[1]

EHA AYA Task Force Survey



SCD, sickle cell disease.

1. Guarino S et al. 2025. *Blood Adv*. 2025015909.

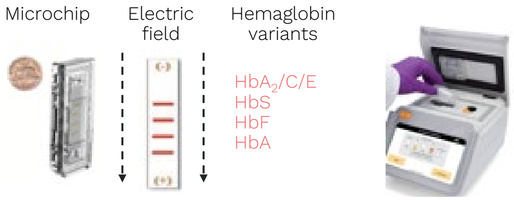
Colombatti R. Changing setting, guidelines and perspective in the transition from pediatric to adult care for Sickle Cell Disease (SCD). Oral presentation p268-3 at EHA2025.

p516-1: Reliable point-of-care (POC) tests for SCD are vital where lab facilities are lacking

- Newborn screening is recommended, as early diagnosis will decrease mortality and morbidity
- Developed countries routinely conduct standard newborn screenings to detect the most common genetic variants
- In contrast, in Sub-Saharan Africa, only about 50% of newborns are tested, mainly in large urban centers, for a limited number of variants, and often only as part of pilot projects
- Traditional testing requires trained HCPs and laboratory facilities, and is costly
- Affordable POC tests that deliver reliable, rapid results without a medical expert present are needed
- Three innovative SCD bedside tests were examined under real-life conditions in several studies within Europe, Asia, and Africa
- The three tests were comparable in respect of sensitivity (94% to 99.9%), specificity (>97.9% to 99.9%), time (10 min), and cost ($2.00 to $2.50)
- Test devices proved to be robust and user-friendly, delivering quick bedside results, which led to immediate clinical decisions

Tests	Genetic variants detected
Lateral Flow Immunoassay (Sicke Scan®)	Hb A, S, C
HemoTypeSCtm	Hb A,S,C
Electrophoresis+AI (Gazelle Hb Variant Test)	Hb A2/C/E -S,F,A

Electrophoresis + AI



Gazelle Hb Variant test

Key limitations

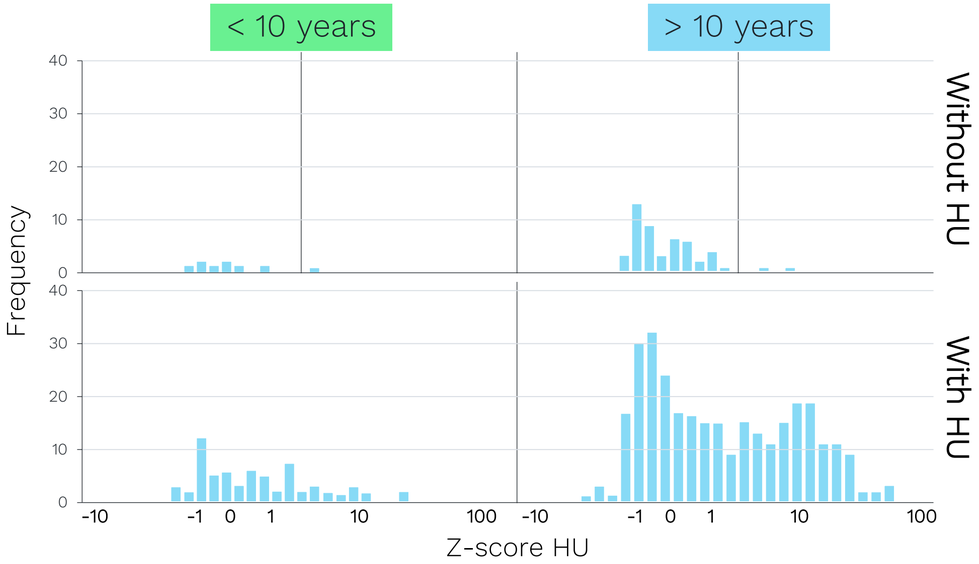
- POC-tests are an option for SCD screening at birth if access to a central lab is limited
- Confirmation tests of positive results are needed
- Screening needs to be linked to comprehensive care
- Need for inclusion of stakeholders, physicians, politicians, but also the affected children's families, to achieve acceptance and sustainability of those programs

AI, artificial intelligence; Hb, Hemoglobin; POC, point of care; SCD, sickle cell disease.

Gulbis B. State of the art point-of-care (POC) tests for neonatal screening of SCD. Oral presentation p516-1 at EHA2025.

PF1176: Understanding hydroxyurea (HU) metabolism could improve SCD treatment

- HU efficacy varies depending on individual drug metabolism, pharmacokinetics, and adherence
- The aims of this study were to detect HU metabolites and analyse associations between HU metabolite levels, laboratory indices, and SCD implications
- A large European cohort of both children and adult HbSS pts with or without HU prescription was grouped by age (<10y or >10y), and dried blood spots of pts and healthy controls were analysed by untargeted metabolomics
- **Results:**
  - HU metabolites were detected in 20% of pts <10y with HU prescription compared to 39% of pts >10y; differences were possibly due to increased hyperfiltration in younger pts or other age differences in HU metabolism
  - In pts with a Z-score <2.5, detected doses of HU might be explained by non-compliance or increased metabolism rates
  - Z-scores >2.5 were associated with increased HbF and MCV, decreased eGFR, and increased ACR; these data supported the already described link between kidney function and HU metabolism[1,2]
  - Acute complication rates (VOE, ACS) were comparable between Z-score groups



HU Z-scores in pts <10y (left) and >10y (right), without HU prescription (top) or with HU prescription (bottom) on a logarithmic scale. Vertical bars are the set cut-off values of a Z-score of 2.5 (CI 99%).

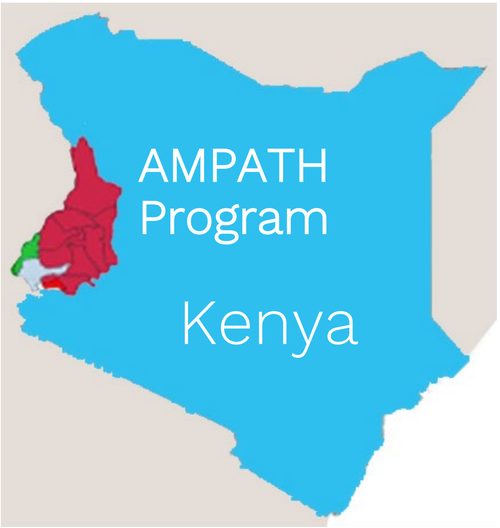
- HU metabolism and metabolite half-life, as well as therapy timing, adherence, and pharmacokinetics, might influence the detection of HU metabolite levels
- Pts with HU detected in their blood showed higher HbF and MCV levels, yet the frequency of crises was similar to those with lower HU levels, indicating a need for further research into compliance, adherence, and outcomes in SCD

ACR, albumin to creatinine ratio; ACS, acute chest syndrome; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbF, fetal hemoglobin; HbSS, homozygous hemoglobin S; HU, hydroxyurea; MCV, mean corpuscular volume; pts, patients; SCD, sickle cell disease; VOE, vaso-occlusive episode; y, years.

1. Pressiat C et al. *Br J Clin Pharmacol* 2021; 87(5):2274-2285. 2. Yan JH et al. *J Clin Pharmacol*. 2005; 45(4):434-445.
Van der Veen S. Optimizing hydroxyurea therapy in sickle cell disease. Insights from metabolite detection, treatment response, and clinical outcomes. Poster abstract PF1176 at EHA2025.

p210-4: The hydroxyurea program in Western Kenya as an example for community-driven innovation in SCD care

- Western Kenya, one of the regions most affected by SCD, introduced a community-led, collaborative model to improve outcomes with existing resource constrains
- The **AMPATH SCD program**, currently covering 24 million people, is built on three pillars: care, education, and research
- Key program outcomes include:
  - Introduction of hydroxyurea in 2012 through an initial free drug access program, reaching >700 patients
  - Establishment of dedicated SCD clinics offering guidance-based care, including prophylaxis and monitoring
  - Implementation of newborn screenings and improved diagnostics
- The **Revolving Fund Pharmacy (RFP) model** was 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



Counties served by the AMPATH program in western Kenya

Sustainable progress in SCD care requires further attention and depends not only on medical components but shared responsibility among patients, community, HCPs, governmental bodies, and committed partners working together to close the care gaps in SCD

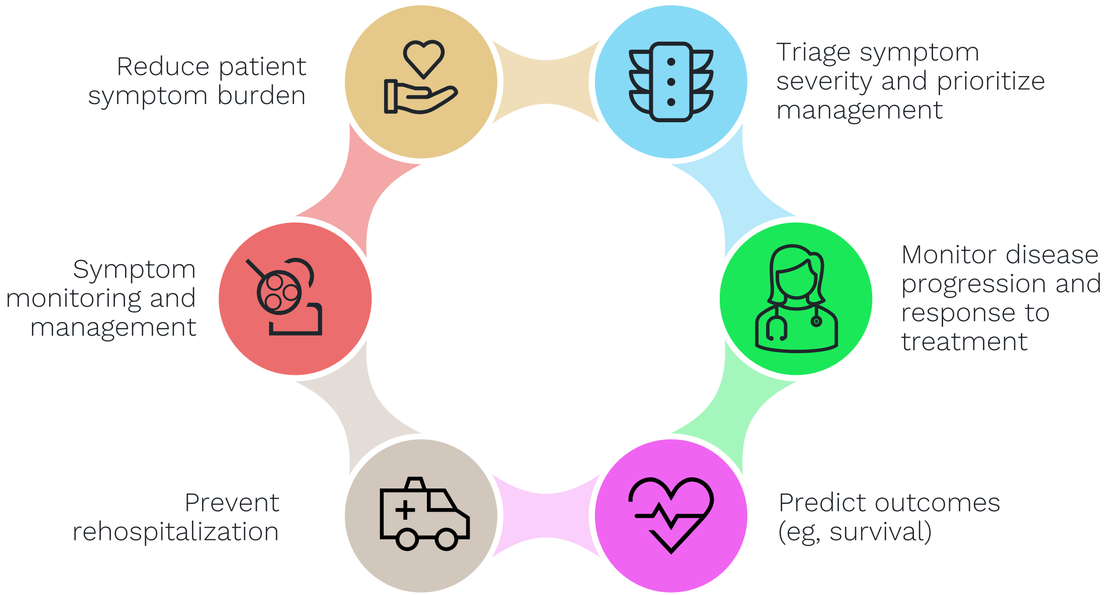
AMPATH, Academic Model Providing Access to Healthcare; SCD, sickle cell disease.

Jepngetich B. Community-led hydroxyurea programme. Oral presentation p210-4 at EHA2025..

p555-1: Gene therapy vs. hematopoietic stem cell transplant for SCD patients – the patient's perspective

- Two potentially curative treatments for sickle cell disease are hematopoietic stem cell transplant (HSCT) and gene therapy. While HSCT is established, gene therapy is still emerging
- Survival rates are concerning, with 81% of patients not reaching age 50
- The disease also carries a substantial burden, causing pain, fatigue, and frequent hospitalizations, which affect both health and social life
- Current treatments have significant limitations: there is no cure, therapy often continues throughout a person's lifespan, and access to care varies by region
- A cure would reduce fear and allow patients to plan for their futures, enabling them to thrive rather than merely survive
- Patients require transparent clinical trial data, patient-centered endpoints, and an emphasis on improving quality of life and long-term sustainability

Importance of patient-reported outcomes in SCD clinical trials

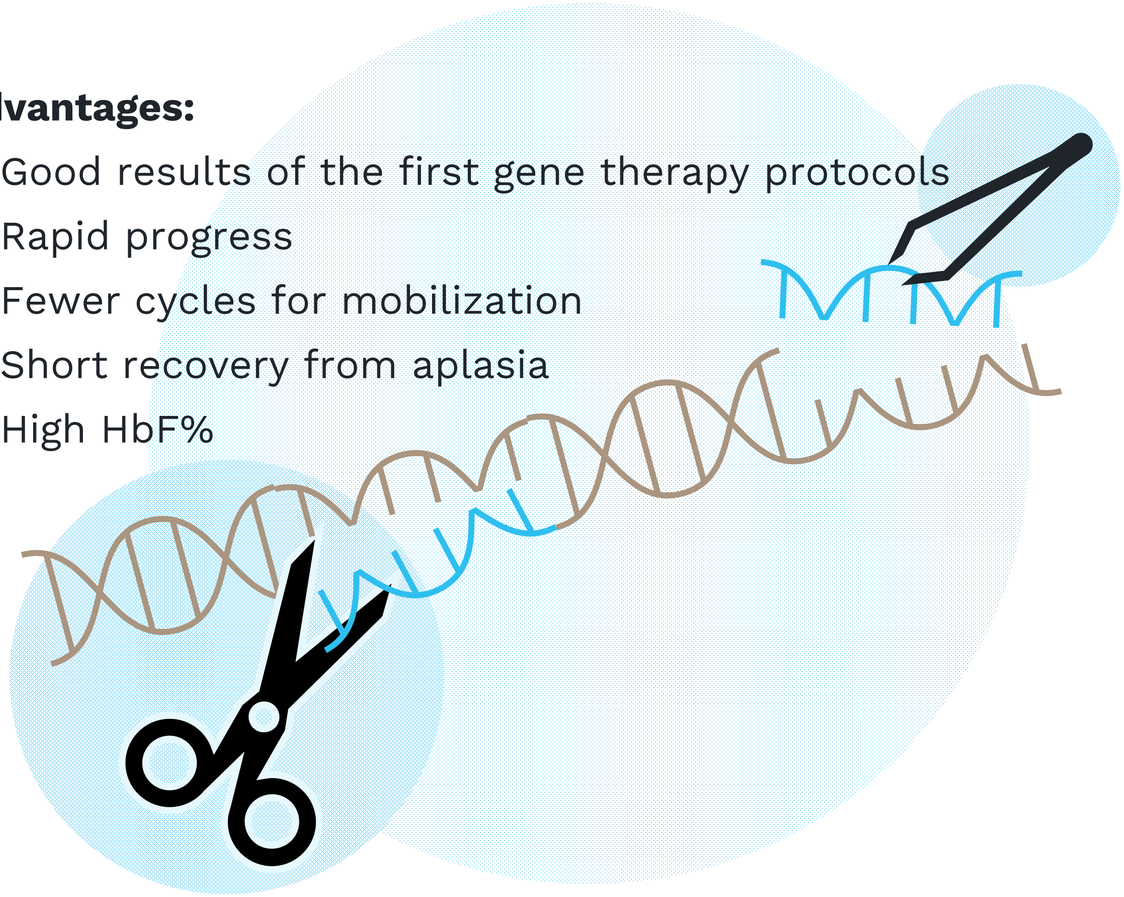


HSCT, hematopoietic stem cell transplantation.
de Montalembert M and Nur E: Thematic debate: Gene Therapy vs hematopoietic stem cell transplant p555-1 at EHA2025

p555-1: Gene therapy is a promising new option in the treatment of SCD, but experience and availability are still restricted

Advantages:

- ✓ Good results of the first gene therapy protocols
- ✓ Rapid progress
- ✓ Fewer cycles for mobilization
- ✓ Short recovery from aplasia
- ✓ High HbF%



Challenges:

- × Mobilization is not possible in some patients
- × Manufacturing induces a significant loss of viable cells
- × Many dropouts
- × The fitness of autologous hematopoietic stem and progenitor cells is probably impaired
- × Specific risks of off-target effects and long-term adverse effects are expected
- × Resting degree of the disease activity
- × Treatment-related mortality
- × Available in even fewer specialized centers, and at much higher costs than allogenic graft

HbF, fetal hemoglobin; SCD, sickle cell disease.

de Montalembert M and Nur E. Thematic debate: Gene Therapy vs hematopoietic stem cell transplant. Oral presentation p555-1 at EHA2025.

p555-2: HSCT is effective, widely available, has a low risk of graft-versus-host disease (GvHD), and is affordable

Advantages:

- ✓ Established therapy for SCD
- ✓ Good results of HLA-identical sibling hematopoietic stem cell transplantations
- ✓ In the absence of HLA-identical donors, haploidentical donors are possible
- ✓ Main challenges largely addressed: nonmyeloablative conditioning developed to avoid toxicity, robust prophylaxis of GvHD
- ✓ Good outcomes in children: OS about 95%, event-free survival 92%

Challenges:

- × Probability of having an HLA-identical sibling as low as 18%; the chance for another donor is only 16%
- × Increased graft rejections with haplo-identical HSCT
- × Therapy is complicated and demanding
- × In some patients, quality of life does not rise as expected after transplantation
- × Older patients still show increased toxicity with myeloablative conditioning

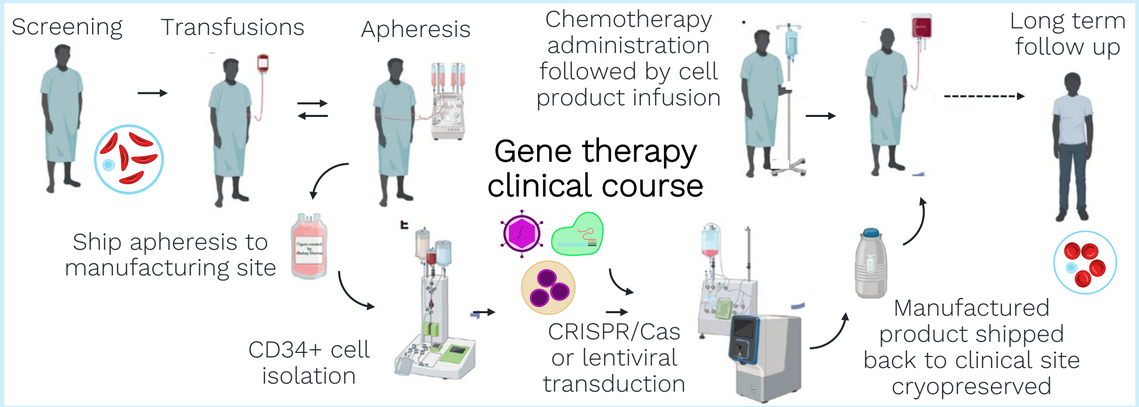


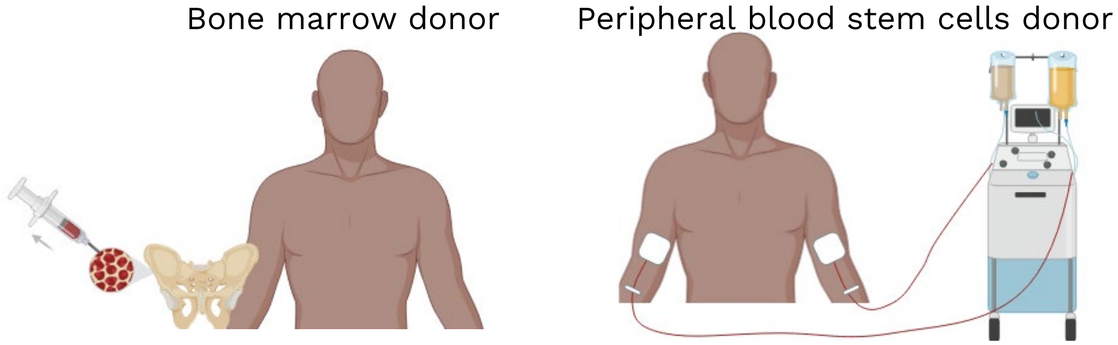
Figure adapted from Sharma A. Blood. 2024;25(144):2693-2705
GvHD, graft versus host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; OS, overall survival; SCD, sickle cell disease.
de Montalembert M and Nur E. Thematic debate: Gene Therapy vs hematopoietic stem cell transplant. Oral presentation p555-2 at EHA2025.

S285: Outcomes of peripheral blood stem cells vs. BM in patients with SCD undergoing haploidentical HSCT

Haploidentical HSCT is an established curative treatment for adults with SCD, who lack an HLA-identical donor, with a low incidence of treatment-related mortality (TRM), graft failure (GF), and graft vs. host disease (GvHD). The current stem cell source is mostly bone marrow (BM), which has low GvHD risk, but includes an invasive procedure as well as the risk of insufficient CD34+ cell yield and GF.

Design: This retrospective multicenter cohort study examined whether the use of PBSCs instead of BM could improve event-free survival (event: GF or death), without significantly increasing the risk of GvHD. Included were cases of haploidentical HSCT at Amsterdam UMC or King Abdulaziz Medical City between 2019 and 2024. Patients were grouped into two arms: one that received BM stem cells only and the other that had PBSC only or BM cells plus PBSC. ATG, thiotepa, fludarabine, cyclophosphamide, TBI, and PTCy were used for conditioning.

Patient characteristics: Out of 41 patients enrolled, 26 received BM, and 15 received PBSC. Included were young adults between 18 and 39, with the PBSC arm being slightly older than the BM arm. The genotype was ≥ 80 HbSS in both arms. The cell yield was higher with PBSC.



Results: The estimated one-year event-free survival rate was higher in the PBSC group (100%) compared to the BM group (85%); 3 deaths and 1 graft failure occurred in the BM group, whereas none occurred in the PBSC group. Median chimerism levels were close to 100% in both groups. No increased incidence of aGvHD or cGvHD was observed with PBSC compared to BM. There was a significantly faster neutrophil recovery in the PBSC group.

Conclusion: PBSC is a viable stem cell source for haplo-HSCT in SCD. Its use is less invasive, with no risk of “rescue” stem cell harvest.

Limitation: The difference in follow-up time warrants validation in a more extended observation period.

aGvHD, acute graft-versus-host disease; ATG, anti-thymocyte globulin; BM, bone marrow; CD, cluster of differentiation; HbSS, homozygous sickle hemoglobin genotype; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; PBSC, peripheral blood stem cell; PTCy, post-transplantation cyclophosphamide; SCD, sickle cell disease; TBI, total body irradiation;.
Image created with BioRender.com
Zwolsman M. Outcomes of peripheral blood stem cells versus bone marrow in adult sickle cell disease patients undergoing haploidentical allogeneic stem cell transplantation. Oral abstract S285 at EHA2025.

S288: Can HSCT reduce retinopathy and maculopathy in SCD patients? Results from a prospective observational study

SCD-related ocular complications comprise maculopathy, non-proliferative, and proliferative retinopathy. Allogenic HSCT is an established curative treatment for adults with SCD and has been shown to improve SCD complications affecting the brain, lungs, spleen, and heart. This prospective observational study is the first to examine the impact of non-myeloablative HSCT on the ocular outcome of adult SCD patients.

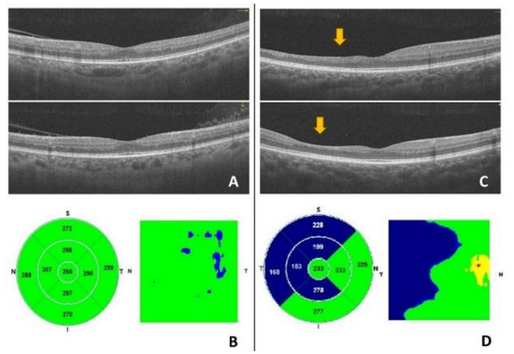
Methods:

- Control group of SCD patients not undergoing HSCT
- Ophthalmic assessment before and at least 1-year post-HSCT using Fundoscopy, SD-OCT, and OCTA-scan
- Linear mixed models and GEE analysis were used to compare ophthalmic outcomes, considering interocular correlation

Patients: HSCT-cohort: N=32, Control: N=57

Median age, sex, and follow-up duration were comparable between groups. Ages ranged from 17 to 66 years, and the prevalent Hb genotype was HbSS (75%). 66% of the patients in the HSCT-cohort and 29% of the control, had been treated with hydroxyurea; numbers for chronic transfusion were 31% and 55%, respectively. The median range of follow-up was 28.5 months (HSCT) and 35 months (control).

Normal macular thickness



Focal macular Tinning, corresponding to blue areas on retinal thickness map

Results: The progression rates of retinopathy and macular thinning (measured with SD-OCT scan) were significantly lower in the HSCT-cohort.

The OCTA scans showed a significant difference in the FAZ perimeter change from baseline to follow-up between the transplant cohort and Hemoglobin SS controls.

Cases of vitreous hemorrhage, retinal detachment, and laser treatment were more frequent in the control cohort.

Conclusion: Nonmyeloablative HSCT diminishes the progression rate of SCR and SCM in adults with SCD.

FAZ, foveal avascular zone; GEE, generalized estimating equations; HSCT, hematopoietic stem cell transplantation; OCTA, optical coherence tomography angiography; SCD, sickle cell disease; SD-OCT, optical coherence tomography; SCR, sickle cell retinopathy; SCM, sickle cell maculopathy.

Dovern:, E. The impact of allogeneic hematopoietic stem cell transplantation on sickle cell retinopathy and maculopathy: a prospective, observational study. Oral abstract S288 at EHA2025.

S287: HbF induction can resolve sickle cell disease symptoms

	GENE	PROTEIN	CELL	
Sickle Cell Disease	Single nucleotide mutation on HBB	HbS tetramers polymerise on deoxygenation	Damaged red blood cells	✓ Anemia ✓ VOCs ✓ Acute chest syndrome ✓ Ineffective erythropoiesis
With HbF Inducer	Reactivation of wildtype HBG	HbF tetramers disrupt polymerisation of HbS	Healthy red blood cells	× Anemia × VOCs × Acute chest syndrome × Ineffective erythropoiesis

HbF induction corrects the SCD phenotype by disrupting polymerization of HbS

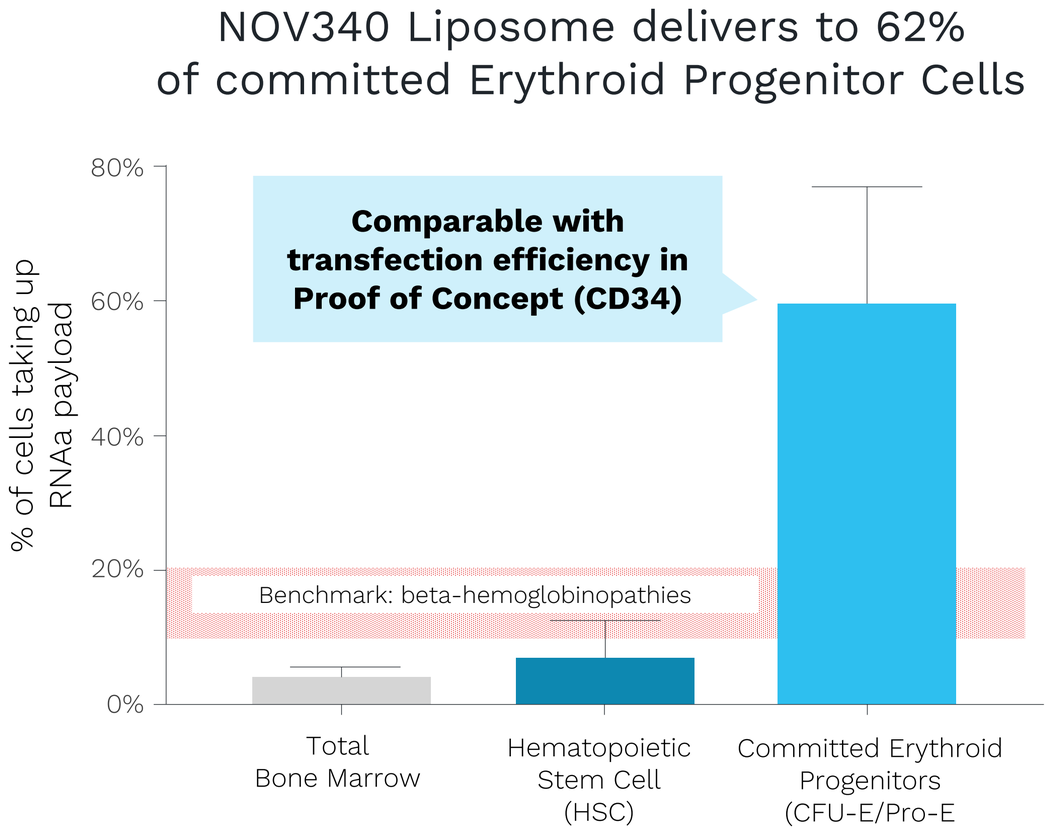
- The expression of fetal γ-globin gene (HBG) and the subsequent formation of HbF tetramers can largely compensate for most complications associated with SCD.
- Even small increases in HbF levels are linked to significant improvements in patient outcomes.
- Currently approved HbF inducers include hydroxyurea and CRISPR-based gene therapy.
- Casgevy® can achieve transformative levels of HbF and nearly eliminate vaso-occlusive crises (VOCs), but it does have some limitations, such as safety risks, lengthy treatment procedure cycles and cost.
- There remains an unmet need for a safe and specific *in vivo* HbF inducer that can reach transformative HbF levels for the majority of SCD patients.
- Small activating RNAs (saRNAs), are short, double-stranded RNA molecules that leverage an evolutionarily conserved mechanism to selectively induce transcription of target genes to therapeutically relevant levels *in vivo*.

CRISPR, clustered regularly interspaced short palindromic repeats; HbF, fetal hemoglobin; SCD, sickle cell disease.

Ryan B. Small activating RNA-mediated induction of HBG via liposome delivery for in vivo treatment of sickle cell disease. Oral abstract S287 at EHA2025.

S287: saRNA-mediated induction of HBG via liposome delivery showed promising results in non-human primates

- A candidate saRNA (MT011391) was identified using a proprietary algorithm (saGE) and screened for HBG mRNA and protein expression in erythroid CD34 cells obtained from healthy donors.
- The candidate saRNA successfully upregulated HBG in both hydroxyurea (HU) responsive and HU non-responsive donor cells, resulting in a 30% induction of HbF in healthy donor cells.
- Additionally, the candidate saRNA achieved an average HbF induction of 62% of total hemoglobin in a pan-cellular manner in erythroid progenitor cells derived from SCD patients.
- The candidate saRNA was encapsulated within NOV340 liposomes (MTL-HBG), which efficiently delivered the saRNA to erythroid progenitor cells and demonstrated pharmacodynamic activity in non-human primates.
- Using a simulated prediction system, MTL-HBG was projected to induce protective thresholds of 20% HbF levels in SCD patients with once-monthly intravenous dosing.
- The next key milestone was planned to advance the candidate saRNA through Investigational New Drug (IND)-enabling studies and into first-in-human clinical trials.



HbF, fetal hemoglobin; HBG, fetal γ-globin gene; HU, hydroxyurea; SCD, sickle cell disease.

Ryan B. Small activating RNA-mediated induction of HBG via liposome delivery for in vivo treatment of sickle cell disease. Oral abstract S287 at EHA2025.

Conclusion

- The EHA2025 congress highlighted key unmet needs in sickle cell disease (SCD) management through dedicated sessions and abstracts.
- Addressing the needs of lower-income countries requires a comprehensive approach that includes reliable point-of-care tests and access to affordable treatments, such as hydroxyurea.
- Discussions about the two potentially curative treatments for SCD - hematopoietic stem cell transplant (HSCT) and gene therapy - highlighted their respective advantages and disadvantages.
- While gene therapy presents promising opportunities for certain patients, optimizing existing treatments is still essential for most. This optimization includes adjusting hydroxyurea dosing strategies based on factors such as 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.
- New data covering a broad range of topics were presented, including:
  - Peripheral blood stem cells as a viable stem cell source for haplo-HSCT in SCD.
  - Nonmyeloablative HSCT diminishes the progression rate of sickle cell-related retinopathy and maculopathy in adults with SCD.
  - Small activating RNA-mediated induction of gamma globin gene via liposome delivery showed promising results in non-human primates.

03

Novel insights into BM failures syndromes pathophysiology and immune treatment

Section 3: Novel insights into BM failures syndromes pathophysiology and immune treatment

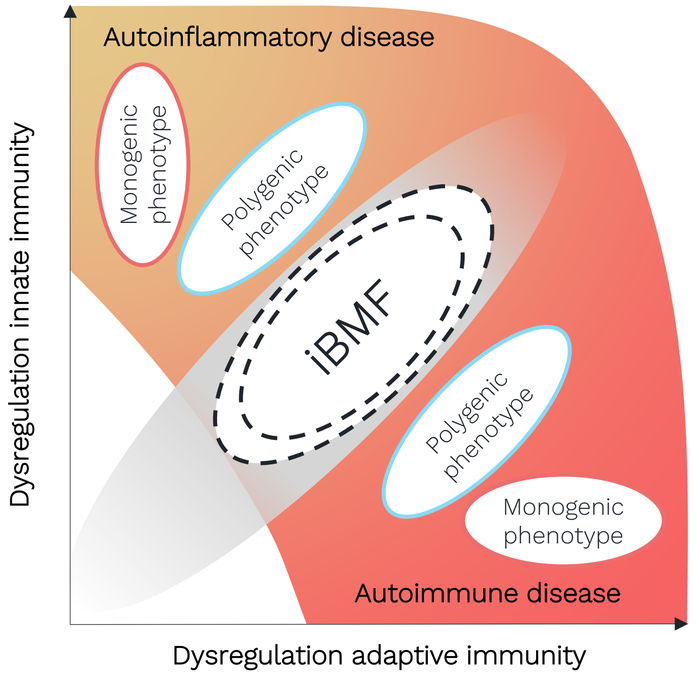
Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p108-1	iBMF: Novel immune cell therapies	Shahram Kordasti
p108-2	iBMF: JAK inhibitors in aplastic anemia	Bhavisha Patel
S184	Efficacy and safety of cyclosporine plus luspatercept versus cyclosporine in newly diagnosed non-transfusion-dependent non-severe aplastic anemia: A prospective randomized trial	Zhuxin Zhang
S183	APPULSE-PNH: Oral iptacopan monotherapy demonstrates clinically meaningful hemoglobin (Hb) increases in patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) and Hb ≥10 g/dl on anti-C5 therapy	Austin Kulasekararaj
p268-1	Management of Late Onset disease and long-term follow-up of patients with telomere biology disorders	Alison Bertuch

p108-1: Immune bone marrow failure (iBMF) syndromes are an under-recognised clinical entity

- iBMF syndromes are a diverse group of diseases characterized by a combination of autoinflammatory and autoimmune features[1]
- AA is an example of an autoimmune-mediated disease, but hypoplastic MDS (MDS-h) also falls under the iBMF umbrella
- This MDS subtype exhibits a distinct survival pattern, a different trajectory of AML progression, and greater similarity to AA than MDS
- A previous history of any autoimmune disease was associated with a 1.7-fold (95% CI, 1.5 to 1.9) increased risk for AML and 2.1-fold (95% CI, 1.7 to 2.6) increased risk for MDS[2]
- iBMF arises from an interplay of genetics, autoinflammation, and autoimmunity

iBMF across the auto-inflammatory and autoimmune disease continuum

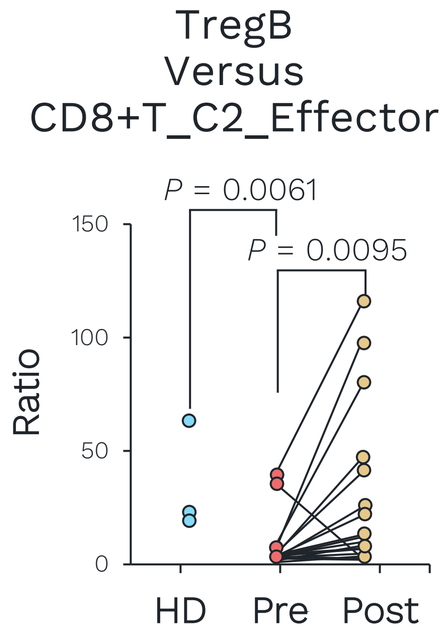


AA, aplastic anemia; AML, acute myeloid leukemia; CI, confidence interval; iBMF, immune bone marrow failure; MDS, myelodysplastic syndromes; MDS-h, hypoplastic myelodysplastic syndromes.
Image adapted from Winter S, et al. *J Clin Oncol*. 2020;38(15):1723-1735.2.
1. Winter S, et al. *J Clin Oncol*. 2020;38(15):1723-1735. 2. Kristinsson SY, et al. *J Clin Oncol.* 2011;29(21):2897-903.
Shahram Kordasti. iBMF: Novel immune cell therapies. Oral presentation p108-1 at EHA2025.

p108-1: Treg-based strategies in iBMF

- 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 8 markers, including Fas (CD95)[1]
- 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 1 trial data
- The ratio of TregB cells to CD8+ T cells significantly increased post-IST, suggesting that the quality and phenotype of Tregs are more important than quantity
- Novel approaches, such as Fas knockdown and targeted trafficking to the BM, may improve the durability and functionality of Tregs
- In the future, therapy for iBMF should be guided by mechanisms that target the underlying immune dysregulation

Ratio of Treg-B abundance versus CD8+ effector T cells in pre- and post-treatment samples of severe AA patients and healthy donors (HD)

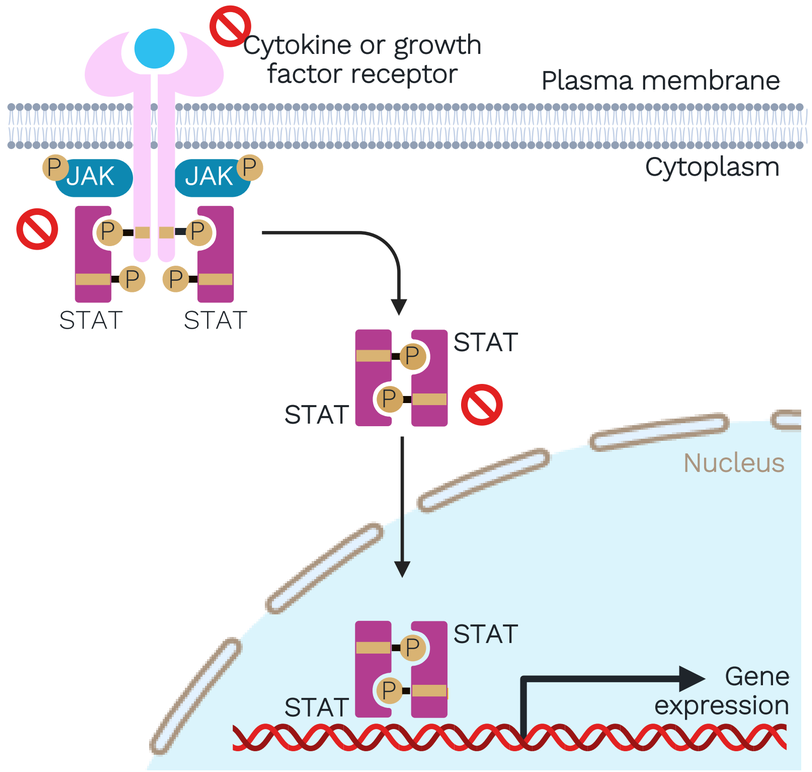


AA, aplastic anemia; BM, bone marrow; CD, cluster of differentiation; iBMF, immune bone marrow failure; IST, immunosuppressive therapy; Treg, regulatory T cell.
Image adapted from Wu Z, et al. *Nature Communications* 2025;16:5048.
1. Kordasti S, et al. *Blood.* 2016;128:1193-1205.
Shahram Kordasti. iBMF: Novel immune cell therapies. Oral presentation p108-1 at EHA2025.

p108-2: The JAK-STAT pathway is a key mediator in aplastic anemia pathogenesis and a potential therapeutic target

- The JAK-STAT signaling pathway is essential for immune function, hematopoiesis and cellular proliferation, and plays a central role in cytokine and growth hormone signaling
- Dysregulation of the JAK-STAT pathway has been implicated in many human diseases, including hematological malignancies
- Inhibition of the JAK-STAT pathway can be achieved in 3 ways:
  - Antibody-based blockade of the receptor
  - JAK inhibitors
  - STAT inhibitors
- In aplastic anemia, cytotoxic T cells mediate an immune attack on bone marrow stem cells, primarily through type 1 cytokines such as interferon-γ and TNF-α
- Fas-mediated apoptosis of hematopoietic stem and progenitor cells (HSPCs) appears to be the dominant mechanism, although recent evidence also implicates the JAK-STAT and MAPK signaling pathways

JAK-STAT pathway with pharmaceutical inhibitor targets

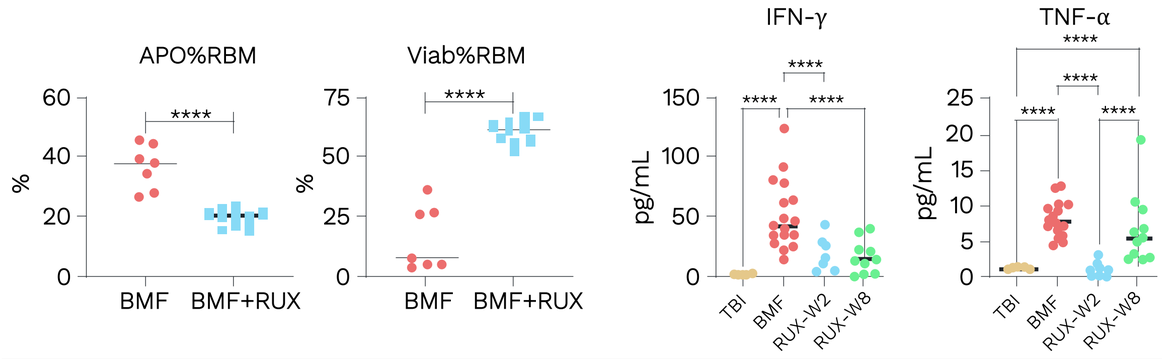


HSPC, hematopoietic stem and progenitor cell; JAK, janus kinase; MAPK, mitogen-activated protein kinase; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor alpha.
Image adapted from Dodington DW, et al. *Trends Endocrinol Metab*. 2018;29(1):55-65 and created with BioRender.com.
Patel B. iBMF: JAK inhibitors in aplastic anemia. Oral presentation p108-2 at EHA2025.

p108-2: Ruxolitinib demonstrated immunomodulatory and hematopoietic benefits in pre-clinical models, supporting its potential as a therapeutic agent in iBMF

- Ruxolitinib, one of four JAK2-specific drugs currently approved for MPN, showed attenuated BM hypoplasia and ameliorated peripheral blood cytopenia in an iBMF murine model[1]
- Ruxolitinib also mitigated Fas-mediated apoptotic destruction of the target hematopoietic cells and improved overall survival[1]
- Using a targeted inflammatory cytokine panel, ruxolitinib-treated mice showed a dramatic reduction in IFN-γ and TNF-α

RUX-treated BMF mice showed reduced BM cell apoptosis and decreased levels of cytokines IFN-γ and TNF-α



- As JAK2 is essential for normal hematopoietic signaling of growth hormones, its inhibition can impair erythropoiesis and megakaryopoiesis, leading to AEs such as anemia and thrombocytopenia, which are often dose-limiting in clinical settings
- Other rare but serious AEs include opportunistic infections, VTE, and major adverse cardiovascular events
- There is an ongoing trial to investigate ruxolitinib in patients with R/R SAA, MAA, PRCA, LGL, and hMDS in the R/R setting. Ruxolitinib is escalated weekly to the maximum dose of 20mg BID with careful weekly hematologic toxicity monitoring
- Other non-selective JAKi, such as momelotinib, with less hematologic toxicity, should be considered
- Future directions include moving effective treatments into upfront settings to enhance response durability and incorporating oral therapies as a bridge to transplantation

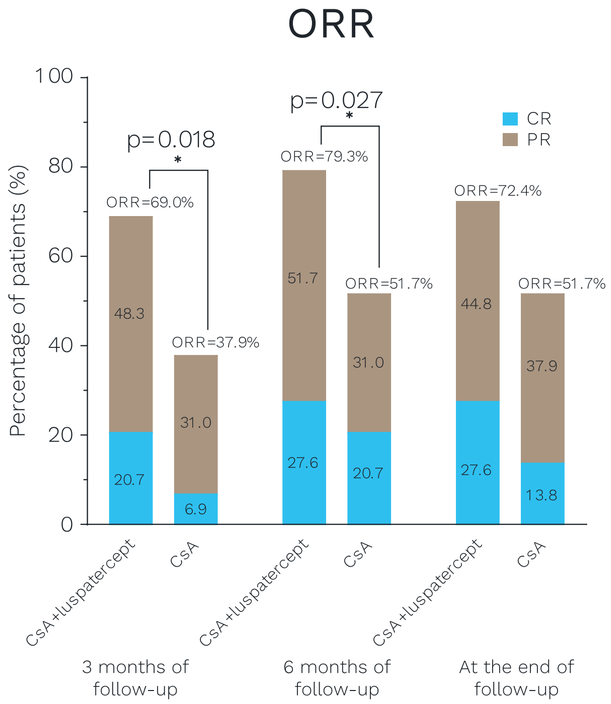
AEs, adverse events; BID, twice daily; BM, bone marrow; BMF, bone marrow failure; hMDS, hypoplastic myelodysplastic syndrome; iBMF, immune bone marrow failure; IFN-γ, interferon gamma; JAK2, Janus kinase 2; JAKi, Janus kinase inhibitor; LGL, large granular lymphocyte leukemia; MAA, moderate aplastic anemia; MPN, myeloproliferative neoplasm; PRCA, pure red cell aplasia; RBM, residual bone marrow; R/R, relapsed/refractory; SAA, severe aplastic anemia; TNF-α, tumor necrosis factor alpha; VTE, venous thromboembolism.

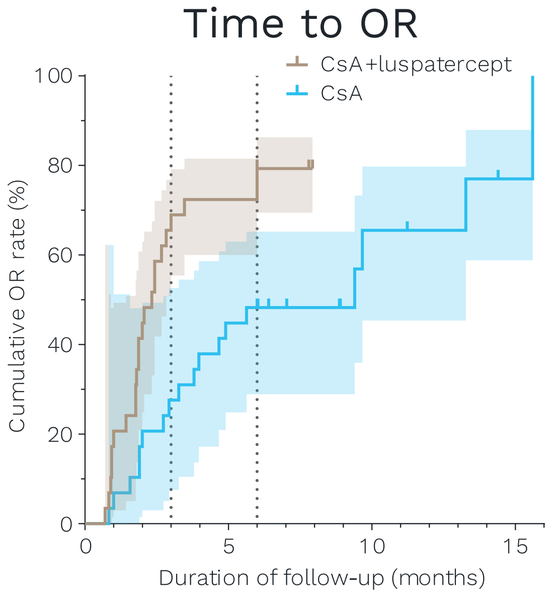
1. Groarke EM, et al. *Blood.* 2023;141(1):72-89.

Patel B. iBMF: JAK inhibitors in aplastic anemia. Oral presentation p108-2 at EHA2025

S184: CsA + luspatercept significantly improved response rates, hemoglobin levels, and time to response compared to CsA alone, and greater benefit was observed in older patients with NSAA

- Despite a response rate of 50–70% for patients treated with immunosuppressive therapy, patients with non-severe aplastic anemia (NSAA) achieve only partial hematologic responses or fail to demonstrate erythroid improvement
- Luspatercept promotes late-stage erythroid maturation by inhibiting TGF-β superfamily ligands
- A single-center, prospective, open-label, randomized study (NCT05399732) evaluated the efficacy and safety of luspatercept plus CsA vs. CsA alone in newly diagnosed transfusion-independent NSAA
- The primary endpoint was 6-month ORR; secondary endpoints included hemoglobin response (HR), safety, and predictors of response
- ORRs were significantly higher in patients treated with CsA + luspatercept vs. CsA alone at 3- and 6-months follow-up
- Hemoglobin response rates were significantly higher in patients treated with CsA + luspatercept vs. CsA alone at 3 and 6 months, but not at the end of follow-up
- The time to OR was lower in the CsA + luspatercept
- Subgroup analysis by age showed the benefit of CsA + luspatercept was more pronounced in older patients



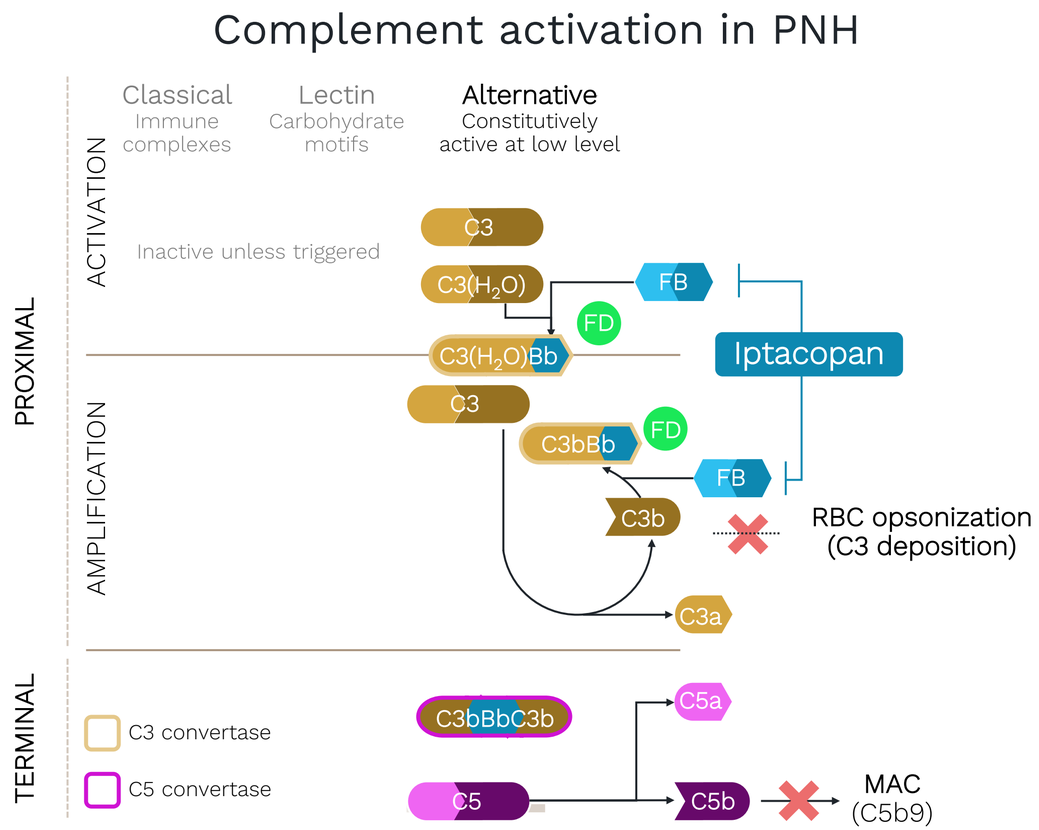


The AE rate was 34.5% in the combination group compared to 24.1% in the monotherapy group, with no statistically significant difference (p = 0.387), and most of the AEs were mild

AE, adverse event; CR, complete response; CsA, cyclosporin A; Hb, hemoglobin; HR, hemoglobin response; NSAA, non-severe aplastic anemia; OR, overall response; ORR, overall response rate; PR, partial response.

Zhang Z. Efficacy and safety of cyclosporine plus luspatercept versus cyclosporine in newly diagnosed non-transfusion-dependent non-severe aplastic anemia: A prospective randomized trial. Oral abstract S184 at EHA2025.

S183: Anti-C5 therapy for PNH can lead to RBC opsonization and the development of extravascular hemolysis (EVH)



- In PNH, impaired complement regulation due to CD55 and CD59 deficiencies results in intravascular hemolysis (IVH)[1]
- Anti-C5 therapy can lead to RBC opsonization and the development of EVH
- Patients with PNH who achieve Hb ≥10 g/dL with anti-C5 therapy may have ongoing EVH and experience a substantial QoL burden
- Iptacopan targets factor B to selectively inhibit the alternative pathway C3 convertase, providing comprehensive control of hemolysis
- The APPULSE-PNH study evaluated oral iptacopan monotherapy in anti–C5–treated patients with hemoglobin ≥10 g/dL who may have ongoing EVH, persistent anemia, and who require regular hospital visits for intravenous anti-C5 infusions

C3, complement component 3; C5, complement component 5; CD, cluster of differentiation; EVH, extravascular hemolysis; FB, factor B; FD, factor D; Hb, hemoglobin; IV, intravenous; IVH, intravascular hemolysis; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria; QoL, quality of life; RBC, red blood cell.

1. Brodsky RA. *Blood.* 2014;124:2804–11.
Kulasekararaj A. APPULSE-PNH: oral iptacopan monotherapy demonstrates clinically meaningful hemoglobin (Hb) increases in patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) and hb≥10 g/dl on anti-C5 therapy. Oral abstract S183 at EHA2025.

S183: Oral iptacopan monotherapy induced Hb improvements to near normal levels by providing comprehensive hemolysis control

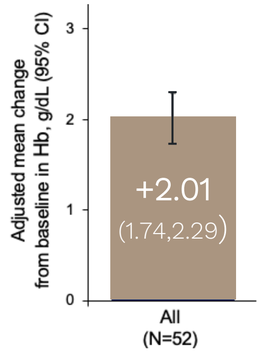
Primary endpoint and statistical analyses

Primary endpoint: adjusted mean change from baseline in Hb using the mean of four visits between Day 126 and 168

Non-inferiority of iptacopan after switch from anti-C5 therapy to be concluded if lower bound of 95% CI >−1 g/dL (**primary objective**)

Superiority of iptacopan after switch from anti-C5 therapy to be concluded if lower bound of 95% CI >0 g/dL (**key secondary objective**)

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



Iptacopan was non-inferior (P<0.0001)‡ and superior (P<0.0001)‡ after switch from anti-C5 therapy

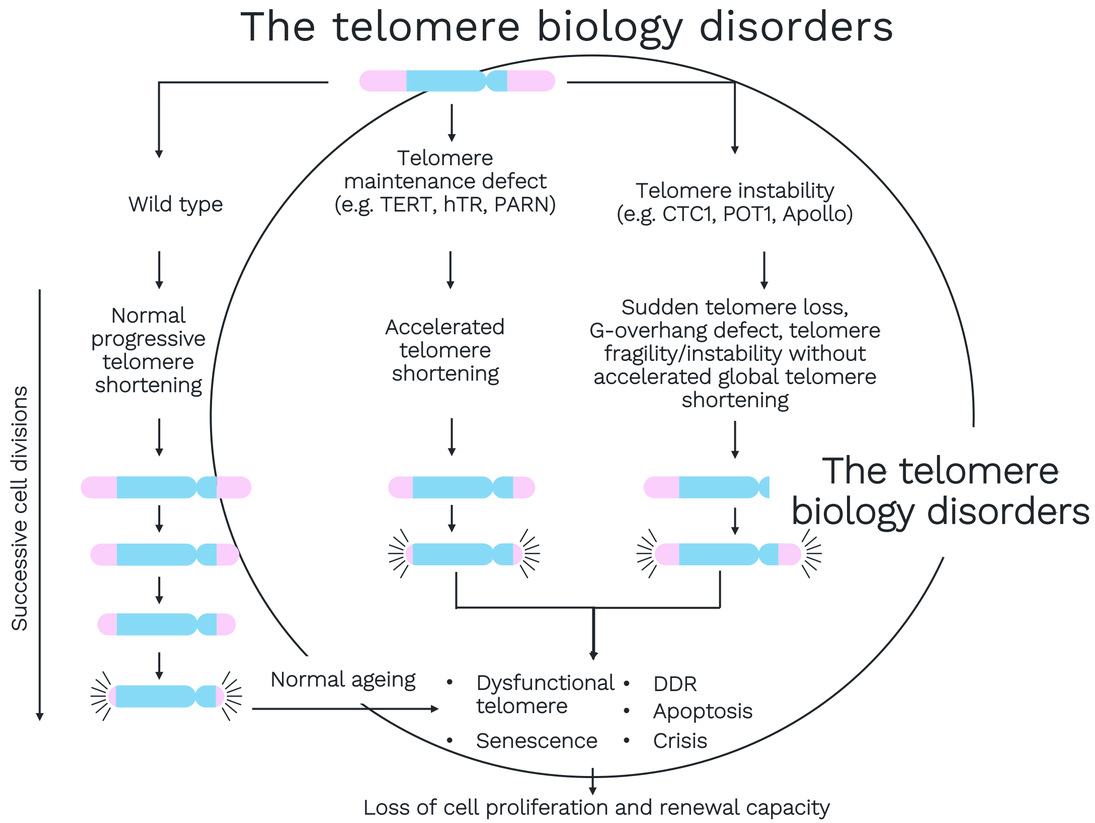
- Most patients (92.7% [95% CI: 84.6, 98.1]) achieved Hb ≥12 g/dL, and all patients remained transfusion-free
- C3 deposition on PNH RBCs, a marker of EVH, was reduced to negligible levels by Week 16
- Patients also reported improvements in fatigue and treatment satisfaction scores
- Iptacopan monotherapy was well-tolerated with no new safety findings
  - No patients experienced a MAVE (secondary efficacy endpoint)
  - 42.3% (22/52) of patients had TEAEs in the infections and infestations system organ class

*Mean baseline Hb: 11.87 (SD 1.32) g/dL; †Analyzed using a a repeated measures model that adjusted for covariates; ‡Assessed using predefined thresholds (lower bound of 95% CI >−1 for inferiority and >0 g/dL for superiority). P values were one-sided and unadjusted.
C3, complement component 3; CI, confidence interval; EVH, extravascular hemolysis; Hb, hemoglobin; MAVE, major adverse vascular event; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell; TEAE, treatment-emergent adverse event.

Kulasekararaj A. APPULSE-PNH: oral iptacopan monotherapy demonstrates clinically meaningful hemoglobin (Hb) increases in patients (pts) with paroxysmal nocturnal hemoglobinuria (PNH) and Hb≥10 g/dl on anti-C5 therapy. Oral abstract S183 at EHA2025.

p268-1: Insights into management of late-onset telomere biology disorders

- In somatic cells, telomeres shorten with age – with the greatest attrition in the first two decades of life
- Telomerase restores length in certain cells – including germ and stem cells
- Disruption in several factors can result in telomerase deficiency and impact telomere structure[1]
- Accelerated shortening may lead to early cell senescence[1]
- TBD are encompassed by these kinds of defects and present with many life-threatening clinical features, including BM failure
- Today, young patients survive better, and new manifestations are being discovered in later life – such as severe GI bleeding
- A broad spectrum of clinical manifestations requires comprehensive evaluation and subspecialty care
- Some patients present late in adolescence and early adulthood



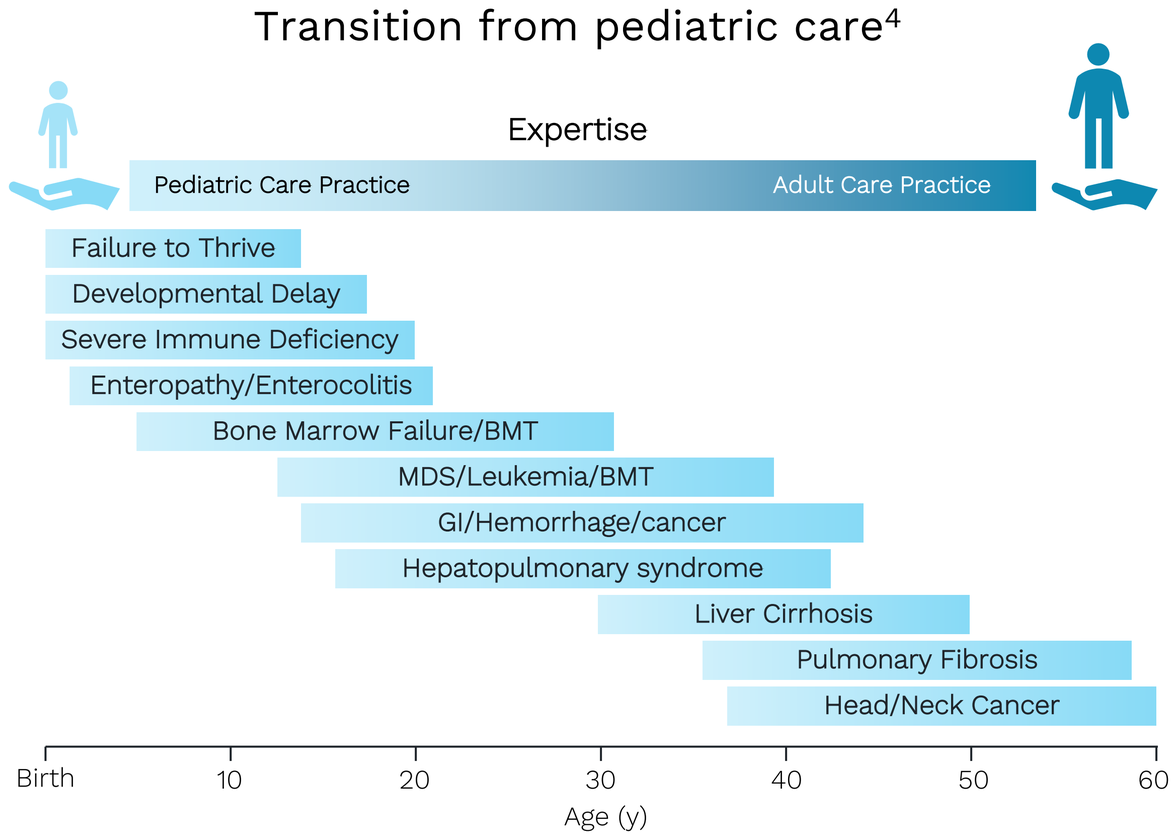
BM, bone marrow; DDR, DNA damage response; GI, gastrointestinal; TBD, telomere biology disorders.

1. Revy P, et al. *Nat Rev Genet.* 2023;24(2):86-108.

Bertuch A. Management of Late Onset disease and long-term follow-up of patients with telomere biology disorders. Oral presentation p268-1 at EHA2025.

p268-1: Insights into management of late-onset telomere biology disorders

- Arriving at the correct TBD diagnosis can be difficult
- Lymphocyte telomere length <1st percentile alone is not diagnostic
- PF is the most prevalent TBD encountered
  - 30–35% of people with familial idiopathic PF have TBD
- 30% of young people with TBD have clonal hematopoiesis with variants that are different from normal aging[1,2]
- Screening approach for late-onset TBD requires:
  - Thorough physical exam for mucocutaneous triad and premature graying
  - Careful history for esophageal stenosis/web, epiphora
  - CBC and BM exam – including a heme somatic mutation panel
- Lifelong cancer surveillance will be needed



AA, aplastic anemia; AML, acute myeloid leukemia; BM, bone marrow; BMF, bone marrow failure; BMT, bone marrow transplant; CBC, complete blood count; GI, gastrointestinal; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; PF, pulmonary fibrosis; TBD, telomere biology disorder.

1. Sande CM, et al. J Clin Invest 2025;135(8):e181659; 2. Gutierrez-Rodrigues F, et al. Blood 2024;144(23):2402-2416; 3. Banaszak LG, et al. Resp Med 2023;220:107464; 4. https://teamtelomere.org/wp-content/uploads/2022/04/Telomere-Biology-Disorders_-Diagnosis-and-Management-Guidelines.pdf.

Bertuch A. Management of Late Onset disease and long-term follow-up of patients with telomere biology disorders. Oral presentation p268-1 at EHA2025.

Conclusion

- BMF syndromes represent a heterogeneous group characterized by various grades of peripheral blood cytopenias with either inherited or acquired pathogenesis.
- This year's EHA offered new insights into the pathophysiology and future therapies for this heterogeneous group of diseases, focusing on mechanisms that target the underlying immune dysregulation.
- Based on promising results from preclinical models, expanded regulatory T-cell expansion and JAK inhibitors were being tested in Phase 1 trials as treatment options for aplastic anemia.
- The combination of TGF-β1 inhibitor luspatercept plus cyclosporine significantly improved response rates and hemoglobin levels in transfusion-dependent non-severe AA patients.
- Monotherapy with oral iptacopan, a Factor B inhibitor of the complement system, induced Hb improvements to near normal levels by providing comprehensive hemolysis control in previously anti-C5-treated PNH patients.
- Insights on managing acquired rare inherited BMF syndromes such as TBD, include screening approaches and the consideration of proposed pathophysiological pathways.

AA, aplastic anemia; BMF, bone marrow failure; DBA, Diamond-Blackfan anemia; PNH, paroxysomal nocturnal hemoglobinuria; TBD, telomere biology disorders.

04

New treatment modalities for platelet disorders

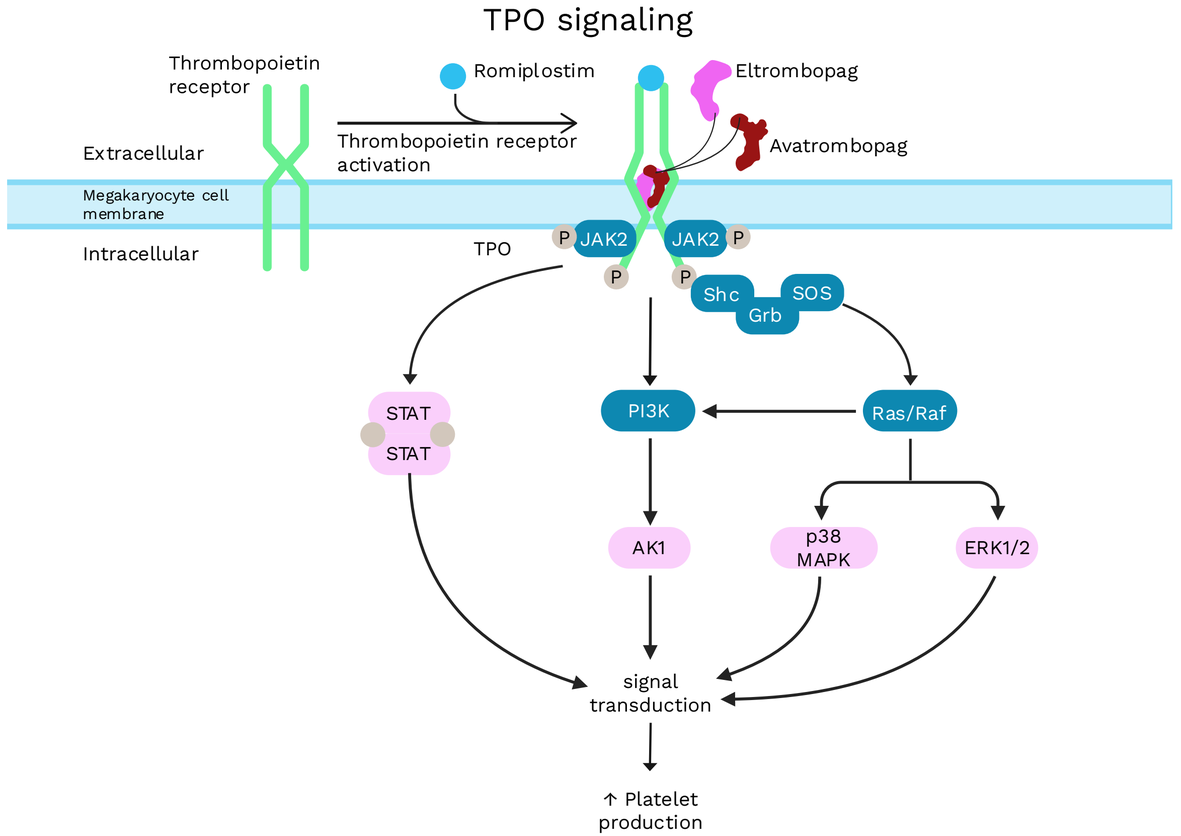
Section 4: New treatment modalities for platelet disorders

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p202-1	From biology to targeted therapies in immune thrombocytopenia	Nichola Cooper
S310	Phase 3 LUNA3 Study: First efficacy/safety report of long-term extension period with rilzabrutinib in adults with persistent/chronic immune thrombocytopenia	Waleed Ghanima
S331	Short-term response and safety of daratumumab treatment in adult immune thrombocytopenia: Results of a Phase 2 study with safety run-in (The DART Study)	Galina Tsykunova
S312	A Phase 2 study of ianalumab in patients with primary immune thrombocytopenia previously treated with at least two lines of therapy (VAYHIT3)	Charlotte Bradbury
S449	Baricitinib corrects AP2-NAK mediated C-MPL endocytic dysregulation to restore megakaryocytes TPO-RA sensitivity in immune thrombocytopenia	Zhuo-Yu An
S318	Targeted suppression of effector T-cells by GPIBα CAAR-TREG cells in refractory/relapsed immune thrombocytopenia	Jinhui Shu
S324	Thrombotic adverse events in patients receiving thrombopoietin receptor agonists: a European multicenter study.	Maria Lozano
p273-2	Genetic screening of pathogenic variants in inherited platelet disorders: where are we?	Kathleen Freson

p202-1: Thrombopoietin receptor agonists provide effective but incomplete platelet response in ITP

- Immune thrombocytopenia (ITP) is a hematological autoimmune disease characterized by a decrease in platelet count in the blood (<100 × 10^9/L), with an incidence of approximately 1 in 10,000 people.
  It is a diagnosis of exclusion and presents with heterogeneous clinical features
- ITP affects the ability to concentrate, schooling, and work, with 50% of patients experiencing fatigue, 48% impaired cognition, and 38% depressive symptoms[1]
- Platelet regulation is impaired in ITP. Whereas TPO levels in patients with ITP are normal or only slightly elevated in the presence of a low platelet count, there is enhanced platelet clearance in the presence of normal thrombopoiesis
- Native TPO binds to the extracellular domain of the TPO receptor (left). After a configuration change, the JAK-STAT pathway is activated. TPO-RAs mimic native TPO by binding to the extracellular domain (romiplostim) or transmembrane region (eltrombopag and avatrombopag) of the TPO receptor[2]
- 58% of patients treated with eltrombopag or romiplostim achieve a good platelet response; however, up to 42% still require alternative treatments



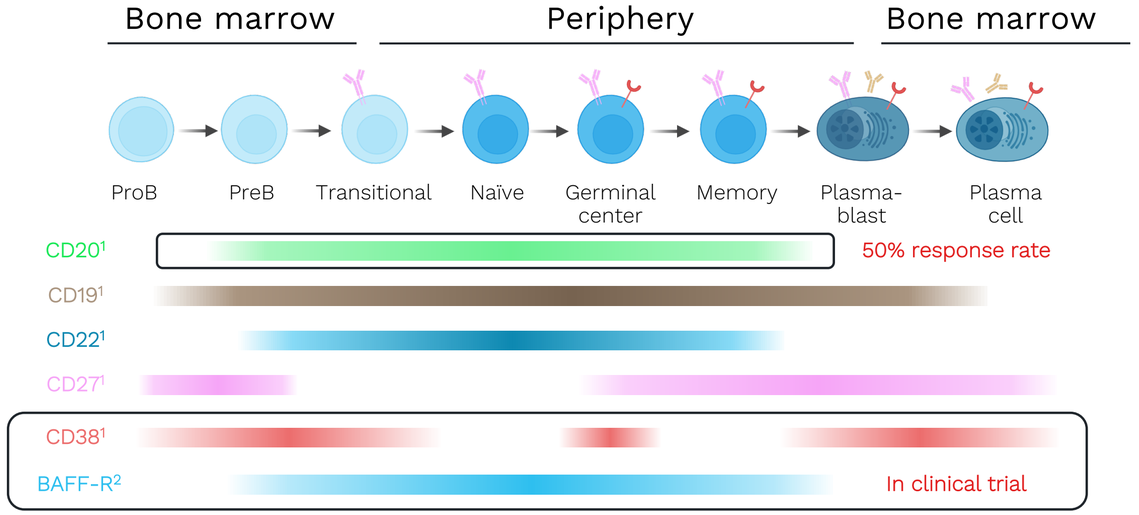
ITP, immune thrombocytopenia; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist.
1. Cooper N, et al. *Am J Hematol.* 2021;96(2):199-207. 2. Provan D, Semple JW. 2022;76:103820. Image adapted from Provan D, Semple JW. 2022;76:103820 and created with BioRender.com.
Cooper N. From biology to targeted therapies in immune thrombocytopenia. Oral presentation p202-1 at EHA2025.

p202-1: B-cell-targeted therapies and beyond in ITP

Rituximab (anti-CD20 mAb):
Response rates range from 30–50%. Rituximab is generally well tolerated, with better outcomes when administered within the first year of ITP and in female patients. Although relapses are common, most patients respond to re-treatment. Anti-platelet antibodies do not predict response, but elevated $CD8^+$ T cells have been observed in non-responders

Fostamatinib (SYK inhibitor):
Targets macrophage-mediated platelet destruction. In patients with multi-refractory ITP, clinical trials demonstrated a 43% overall response rate and an 18% stable response rate. Higher responses have been observed in real-world settings, particularly when used earlier in the disease course or in combination with TPO-RAs

Rilzabrutinib (BTK inhibitor):
Inhibits both B cell proliferation and macrophage-mediated platelet clearance. Phase 2 trials showed 30–40% response rates and notable improvements in fatigue and QoL



Challenges in B-Cell–Targeted Therapy:

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

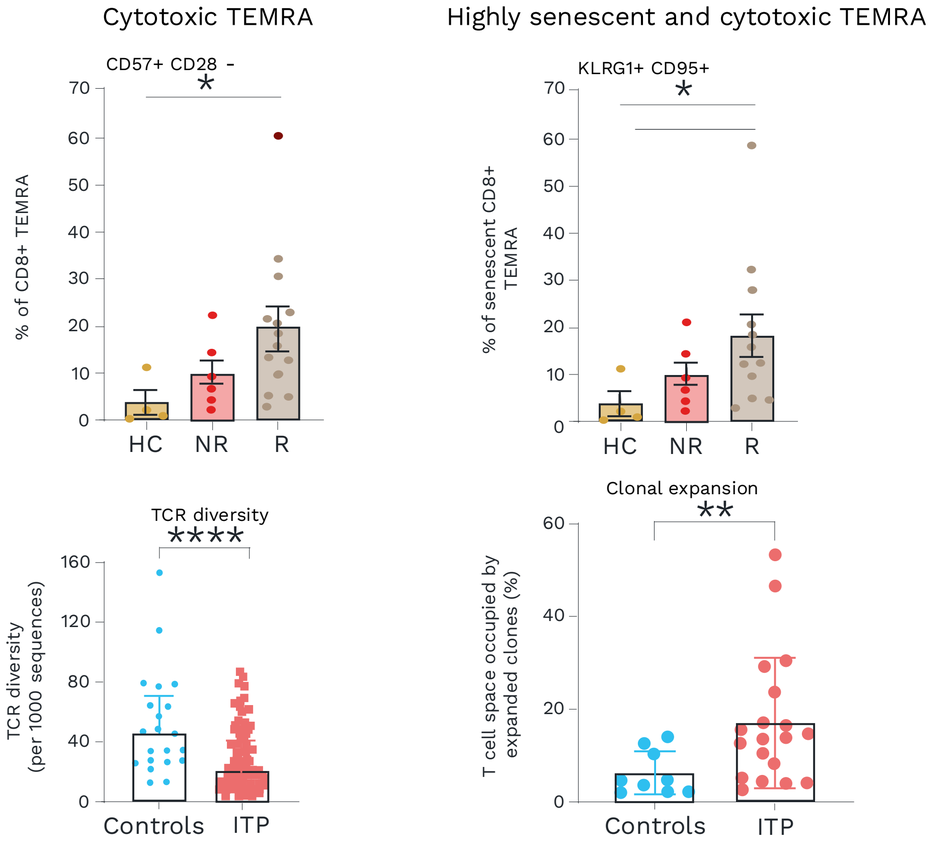
Emerging Therapies in Clinical Trials:

Novel agents targeting CD38 and BAFF-R are under investigation, offering potential for improved disease control in refractory cases

BAFF-R, B-cell activating factor receptor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; ITP, immune thrombocytopenia; mAb, monoclonal antibody; QoL, quality of life; SYK, spleen tyrosine kinase; TPO-RA, thrombopoietin receptor agonist.
Image adapted from Crickx E et al. *Kidney Int.* 2020;97:885–93 and Icreated with BioRender.com.
Cooper N. From biology to targeted therapies in immune thrombocytopenia. Oral presentation p202-1 at EHA2025.

p202-1: Potential for targeting cytotoxic T cells in patients with refractory ITP

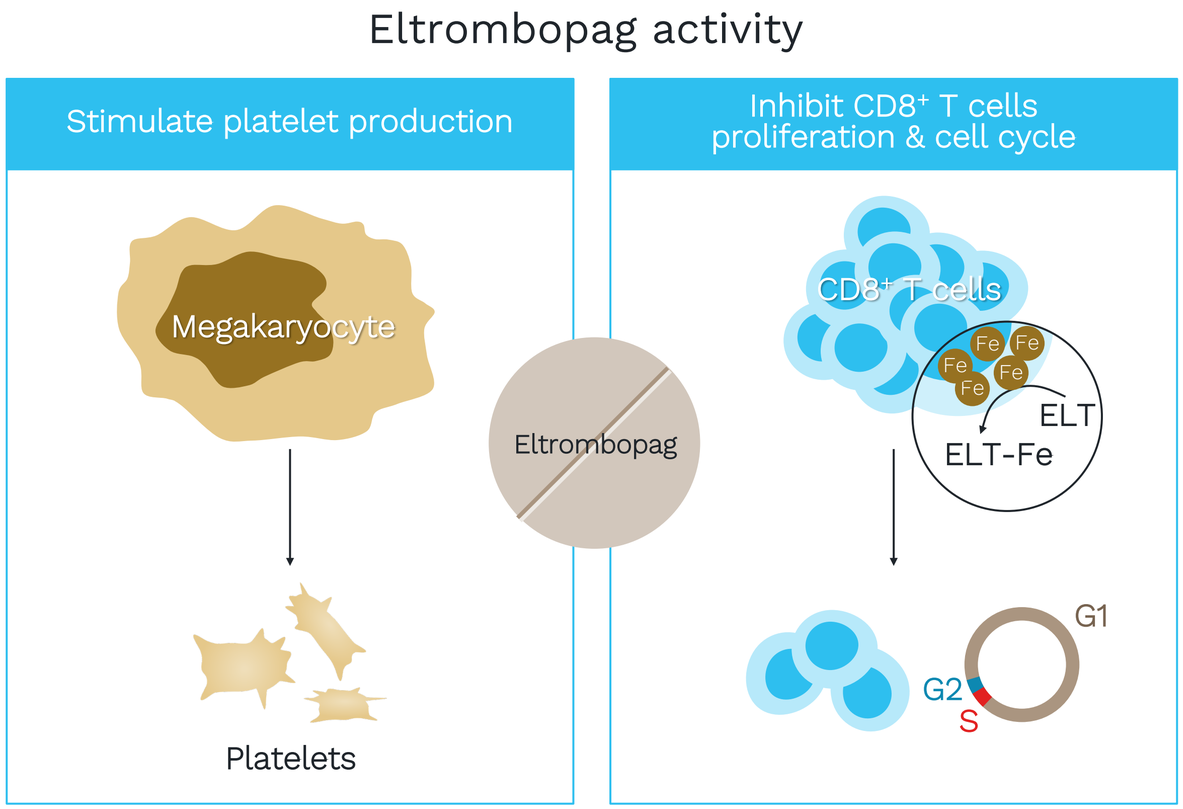
- Rituximab non-responders show a distinct immune profile characterized by increased unswitched and BAFFR⁺ memory B cells, elevated plasma cells, and reduced regulatory B cells, as well as increased activated T cells, cytotoxic TEMRA cells, and activated NK cells
- Patients with refractory ITP have an expanded population of CD8⁺ TEMRA cells that are highly cytotoxic and senescent
- In the context of ITP, cytotoxic CD8⁺ T cells may be clonally expanded to kill platelets
- Deep sequencing of the T cell receptor shows reduced T-cell diversity (the range of antigens the T cell can recognize and respond to) and expanded clones in refractory ITP
- T-cell diversity follows the platelet counts in patients with chronic ITP, and expanded individual T cell clones are associated with reduced diversity and platelet fall counts
- Paired TCR and gene expression profiling showed that the expanded CD8⁺ T cells are enriched in the TEMRA population



BAFFR, B-cell activating factor receptor; CD, cluster of differentiation; HC, healthy control; ITP, immune thrombocytopenia; KLRG1, killer cell lectin-like receptor subfamily G member 1; NK, natural killer; NR, non-responder; R, responder; TCR, T-cell receptor; TEMRA, terminally differentiated effector memory T cell re-expressing CD45RA.

Cooper N. From biology to targeted therapies in immune thrombocytopenia. Oral presentation p202-1 at EHA2025.

p202-1: Eltrombopag demonstrates dual activity and synergistic effects when combined with MMF in patients with ITP



- T-cell–targeted therapies such as MMF, azathioprine, cyclophosphamide, and cyclosporine have response rates of 30–50% and are often poorly tolerated
- CD8+ TEMRA cells are reduced in patients who respond to eltrombopag
- Eltrombopag is a potent iron chelator and shuttler shown to exert anti-proliferative effects on leukemic cells and inhibit proliferating CD8+ T cells
- In a small patient cohort, combining eltrombopag with MMF resulted in higher response rates (72%) in refractory ITP, suggesting dual activity and synergistic effects

CD, cluster of differentiation; ELT, eltrombopag; Fe, iron; ITP, immune thrombocytopenia; MMF, mycophenolate mofetil; TEMRA, terminally differentiated effector memory T cell re-expressing CD45RA.

Cooper N. From biology to targeted therapies in immune thrombocytopenia. Oral presentation p202-1 at EHA2025.

S310: Extended use of rilzabrutinib confers sustained efficacy and a well-tolerated safety profile in adult patients with persistent / chronic primary ITP

- Rilzabrutinib is an oral, covalent, reversible, highly specific BTK inhibitor[1]
- The safety and efficacy of rilzabrutinib were evaluated in the Phase 3, randomized, multicenter LUNA 3 study (NCT04562766) in adult and adolescent patients with persistent or chronic primary ITP
- Complete response was achieved in 54% of patients with primary ITP during the long-term extension (LTE)
- Of 19 patients receiving concomitant TPO-RA with rilzabrutinib, 9 and 4 patients, respectively, had any platelet count >250×10^9/L and >450×10^9/L during the LTE
- Rilzabrutinib treatment during the LTE further improved physical fatigue and improved bleeding scores

LTE Efficacy Endpoints	Patients, n (%)
Complete response (platelet counts ≥100×10^9/L on 2 consecutive visits*)	37/69 (54)
Any platelet count in patients on concomitant TPO-RA	
>250×10^9/L	9/19 (47)
>450×10^9/L	4/19 (21)

*Complete response was platelet counts ≥100×10^9/L on 2 consecutive visits at least 5 days apart and no bleeding or rescue ITP therapy use on or through these visits.

- Of 47 patients receiving concomitant ITP medication during the LTE, 11 (23%) discontinued concomitant medication and remained on rilzabrutinib monotherapy
- All treatment-related AEs were G1 or 2
- Most common treatment-related AEs were nausea (7%), diarrhea (4%), and upper abdominal pain (2%); all others occurred in 1 patient each

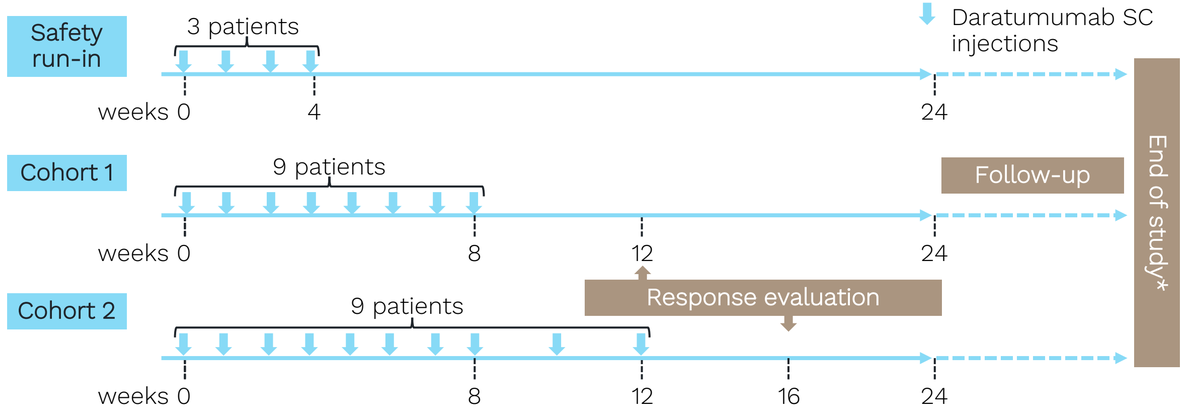
AE, adverse event; BTK, Bruton's tyrosine kinase; G, grade; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

1. Owens TD, et al. *J Med Chem*. 2022;65:5300-5316.
Ghanima W. Phase 3 LUNA3 study: First efficacy/safety report of long-term extension period with rilzabrutinib in adults with persistent/chronic immune thrombocytopenia. Oral abstract S310 at EHA2025.

S331: Subcutaneous daratumumab treatment in primary ITP patients shows promising efficacy with an acceptable safety profile

- Long-lived antibody-producing CD38⁺ plasma cells may contribute to treatment failure in some ITP patients
- Daratumumab is a mAb directed against CD38
- DART is an open-label, Phase 2 multi-center, investigator-initiated study with safety run-in of adult patients with primary ITP
- **Primary efficacy endpoint:** Response defined as 2 consecutive platelet counts >50x10^9/L (measured >24 hours apart), assessed
  at least 4 weeks after the last daratumumab injection (week 12
  for safety run-in and Cohort 1, and week 16 for Cohort 2)
  - The response rate was 48% (n=10) in the overall population, 44% (n=4) in Cohort 1, and 44% (n=4) in Cohort 2
- Rapid responses were observed but diminished over time
  - The sustained response rate was 38% in the overall population, 44% in Cohort 1 and 33% in Cohort 2

- **Primary safety endpoint:** Number and severity of AE ≥2
  - G2 infection occurred in n=1 (4.7%), and G2 diarrhea occurred n=2 (9.5%) and was considered related to daratumumab. Infections (38%) were the most common TEAEs reported



Further studies are needed to validate the findings and identify strategies to enhance and sustain treatment responses.

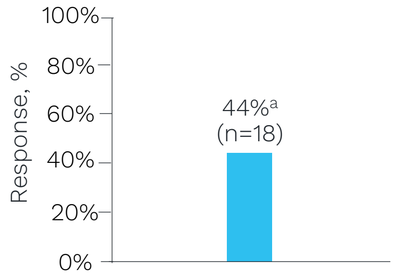
AE, adverse event; CD, cluster of differentiation; G, grade; ITP, immune thrombocytopenia; mAb, monoclonal antibody; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Tsykunova G. Short-term response and safety of daratumumab treatment in adult immune thrombocytopenia: results of a phase 2 study with safety run-in (DART study). Oral abstract S331 at EHA2025.

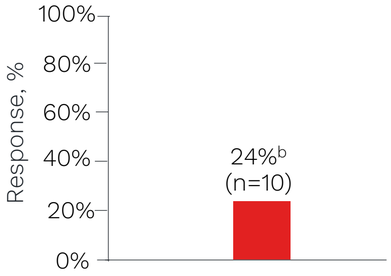
S312: Ianalumab shows promising efficacy and a well-tolerated safety profile in heavily pretreated patients with primary ITP

- Ianalumab is an investigational, fully human, anti–BAFF-R mAb that is thought to deplete pathogenic B cells in blood and tissues and suppress the immune response
- The primary analysis of the Phase 2 VAYHIT3 study (NCT05885555) provides preliminary results on the efficacy (as assessed during the first 25 weeks after treatment start) and tolerability of a short course of ianalumab administered intravenously in heavily pretreated patients with primary ITP:
  - 44% of patients achieved a confirmed response with a median time to confirmed response of 6 weeks
  - 24% of patients achieved a stable response with 10/18 (56%) responders achieving stable response at Week 25, including 9 complete responses*
  - Ianalumab was well-tolerated with most of the adverse events being reported as unrelated to the study drug
  - There were no discontinuations due to AEs. IRRs and infections were of Grade 1 or 2, except one Grade 3 infection

Confirmed response (primary endpoint)



Stable response



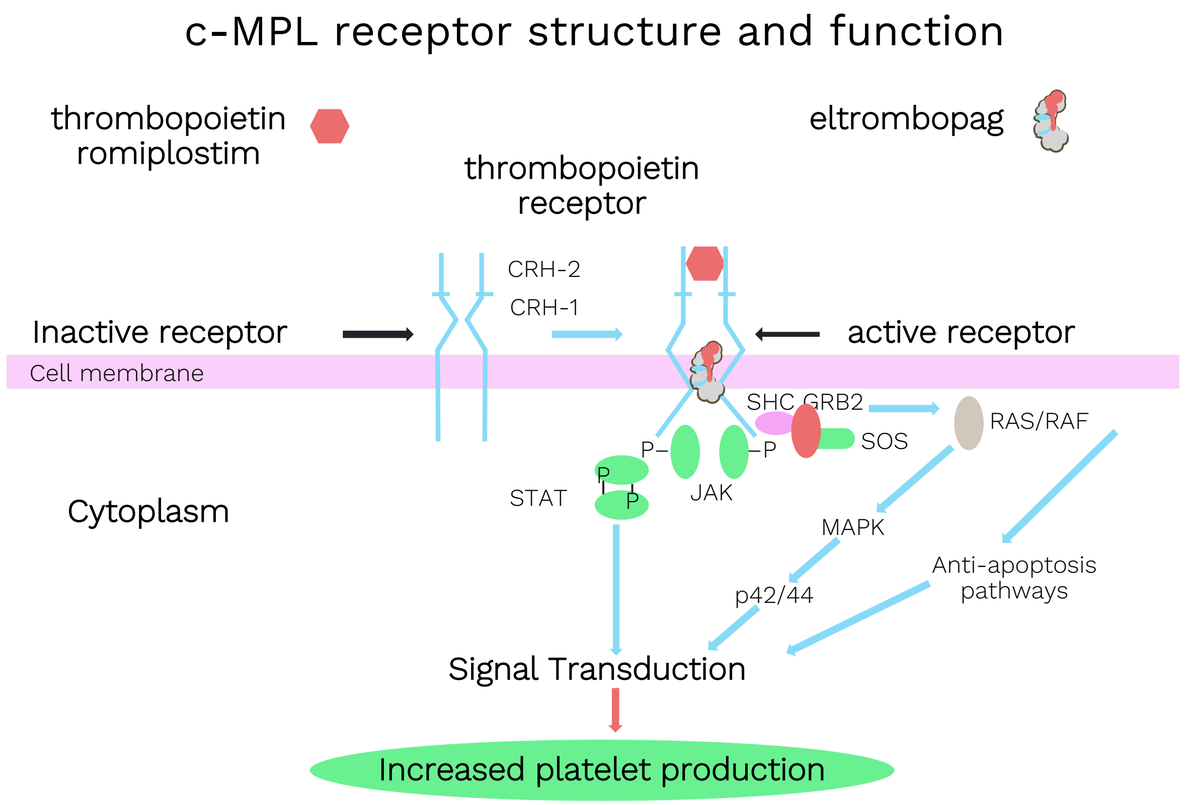
Confirmed response defined as a platelet count of ≥50 G/L at ≥2 consecutive assessments at least 7 days apart between Week 1 and Week 25 with no rescue therapy within ≥4 weeks of platelet count assessment or start of new therapy before confirmed response

Stable Response defined as Platelet count of ≥50 G/L on at least 75% of assessments between Week 19 and Week 25 with no rescue therapy within ≥4 weeks of platelet count assessment or start of new therapy before stable response

*Complete response was defined as a platelet count of ≥100 G/L in the absence of rescue treatment or new ITP treatment. [a]95% Bayesian credibility interval (30, 59); [b]95% confidence interval (12, 40).
AE, adverse event; BAFF-R, B-cell activating factor receptor; IRR, infusion-related reactions; mAb, monoclonal antibody; ITP, immune thrombocytopenia.
Bradbury C. A phase 2 study of ianalumab in patients with primary immune thrombocytopenia previously treated with at least two lines of therapy (VAYHIT3). Oral abstract S312 at EHA2025.

S449: c-MPL internalization may influence TPO-RA responsiveness in ITP

- While TPO-RAs have become standard 2L therapy for ITP, some patients fail to respond or eventually lose response, with the underlying mechanisms remaining poorly understood
- 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[1]
- c-MPL receptor availability is determined by the balance between surface expression and internalization, with the AP2-NAK axis regulating clathrin-mediated endocytosis
- Excessive c-MPL internalization may contribute to TPO-RA resistance by reducing the number of surface receptors available



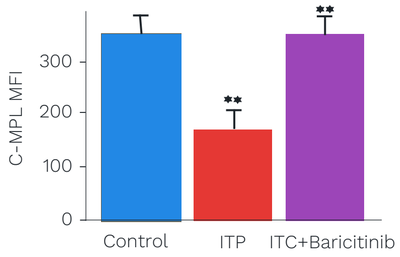
2L, second-line; AP2, adaptor protein complex 2; c-MPL, myeloproliferative leukemia virus oncogene; ITP, immune thrombocytopenia; JAK, Janus kinase; NAK, numb-associated kinase; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TPO-RA, TPO receptor agonist.

1. Garzon AM, Mitchell WB. *Front Pediatr*. 2015;3:70. Image adapted from Garzon AM, Mitchell WB. *Front Pediatr*. 2015;3:70.
An ZY. Baricitinib corrects AP2-NAK mediated c-MPL endocytic dysregulation to restore megakaryocytes TPO-RA sensitivity in immune thrombocytopenia. Oral abstract S449 at EHA2025.

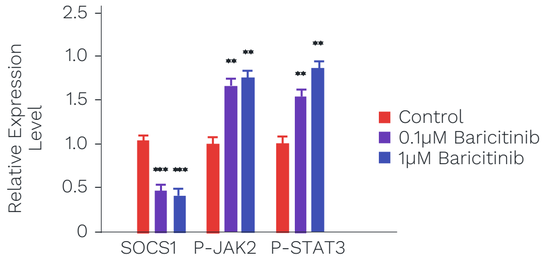
S449: Baricitinib corrects AP2-NAK-mediated c-MPL endocytic dysregulation

- In patients with ITP, c-MPL surface expression was shown to be markedly reduced in megakaryocytes
- siRNA knockdown experiments demonstrated that both AP2 and GAK (a member of the NAK family) promote excessive c-MPL internalization, with GAK playing a critical role in this pathological process
- The GAK inhibitor baricitinib was shown to inhibit c-MPL internalization and restore JAK2/STAT3 signaling by significantly downregulating SOCS1 expression at the transcriptional level
- In ITP mouse models, baricitinib treatment increased peripheral blood platelet counts
- Baricitinib also downregulated the abnormally high SOCS1 protein levels in bone marrow while increasing phosphorylation of JAK2 and STAT3

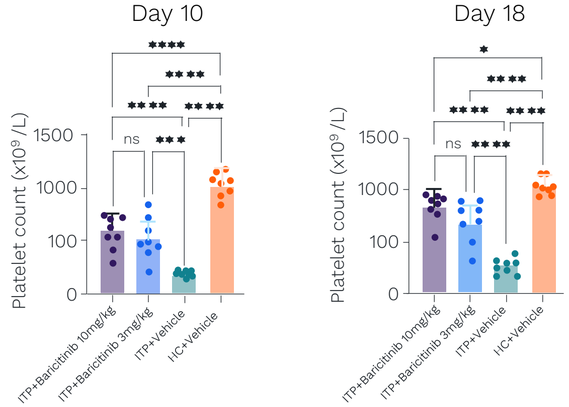
c-MPL internalization



JAK2, STAT3 and SOCS1 expression levels



c-MPL Platelet count in baricitinib-treated ITP mice



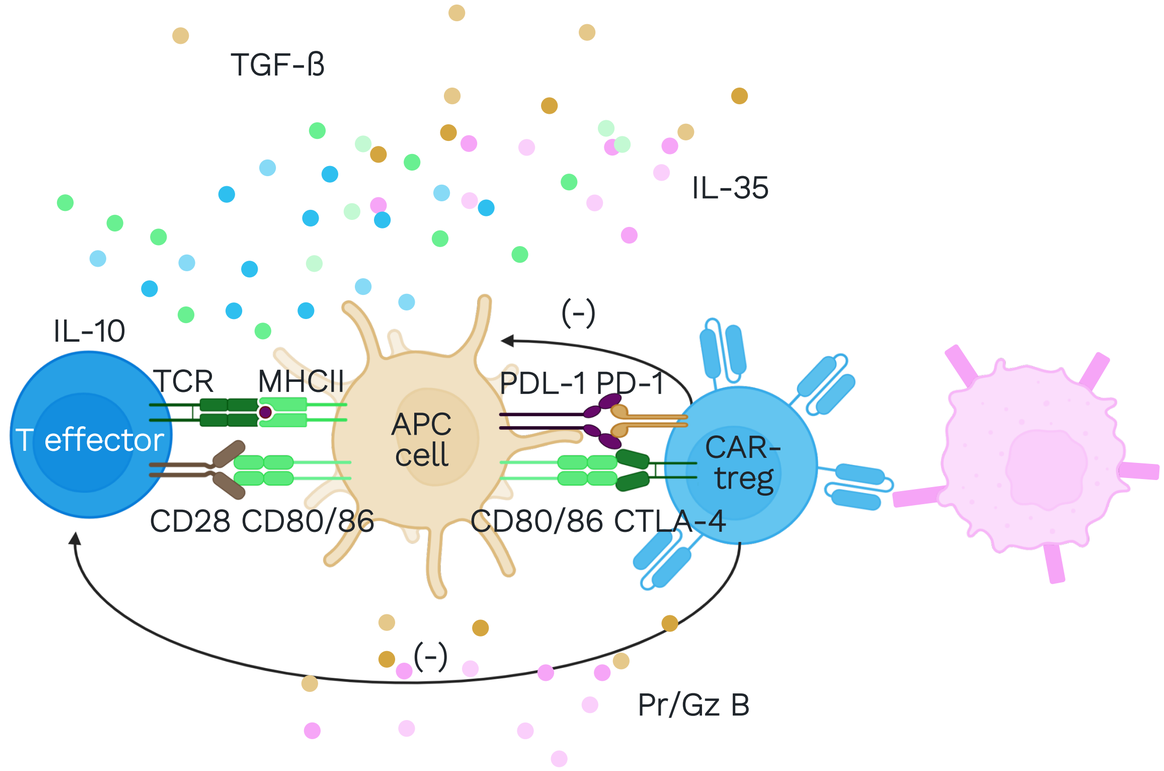
2L, second-line; AP2, adaptor protein complex 2; c-MPL, myeloproliferative leukemia virus oncogene; GAK, cyclin G–associated kinase; ITP, immune thrombocytopenia; JAK, Janus kinase; NAK, Numb-associated kinase; siRNA, small interfering ribonucleic acid; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription.

An ZY. Baricitinib Corrects AP2-NAK Mediated c-MPL Endocytic Dysregulation to Restore Megakaryocytes TPO-RA Sensitivity in Immune Thrombocytopenia. Oral abstract S449 at EHA2025.

S318: GPIbα CAAR-Tregs can effectively suppress antigen-specific T-cell activity in ITP

- ITP is driven by complex immune dysregulation. 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
- Current therapeutic approaches primarily focus on B-cell–mediated pathogenic mechanisms, which rarely achieve complete disease remission
- A subset of patients exhibit overactivation of T cells. In some cases, $CD8^+$ TEMRA cells have been identified as key contributors to thrombocytopenia. There is a lack of effective therapies targeting T-cell–driven mechanisms
- Studies have shown that Treg cells as carriers can effectively treat autoimmune disease by targeted modulation of the immune microenvironment
- **Hypothesis:** Engineered CAR-Tregs can provide comprehensive immune regulation by simultaneously suppressing B cell antibody secretion, effector T cell proliferation, and APC activity within the immune microenvironment

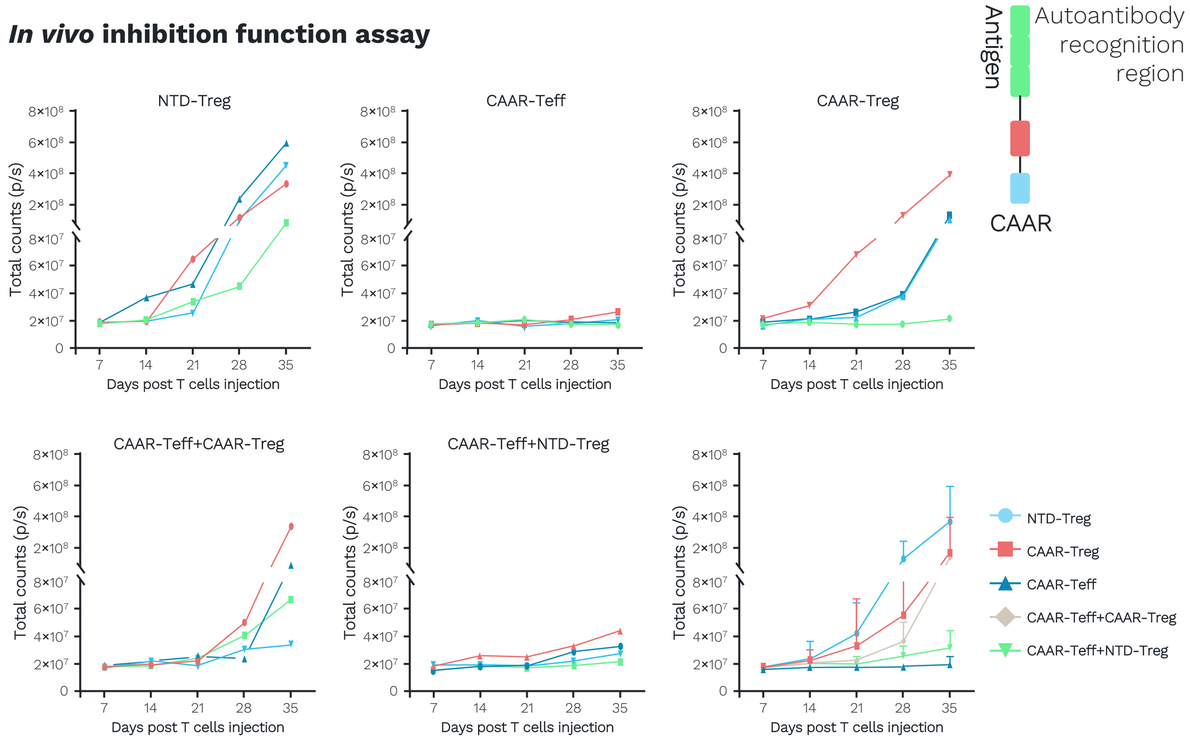
Targeted modulation of the immune microenvironment



AE, adverse events; CAAR, chimeric autoantibody receptor; ITP, Immune thrombocytopenia; TEMRA, terminally differentiated effector memory T cell re-expressing CD45RA..
Image created with BioRender.com.
Shu J., et al. Targeted suppression of effector T cells by GPIbα CAAR-Treg cells in refractory/relapsed immune thrombocytopenia. Oral abstract S318 at EHA2025.

S318: GPIbα CAAR-Tregs can effectively suppress antigen-specific T-cell activity in ITP

- A GPIbα-targeting CAAR was designed with an extracellular ligand-binding domain containing autoantigens – attracting autoreactive B cells and exerting therapeutic effect
- Human naïve Treg cells were sorted using flow cytometry and transduced with the CAAR construct via lentiviral vectors
- Inhibitory functional assay verified the selective antigen-specific activation of GPIbα CAAR-Treg cells *in vitro*, as well as specific and non-specific suppressive effects
- GPIbα CAAR-Treg cells effectively inhibited cytotoxic activity of CAAR-Teff cells against anti-GPIbα hybridoma cells in a hematopoietic hybridoma model



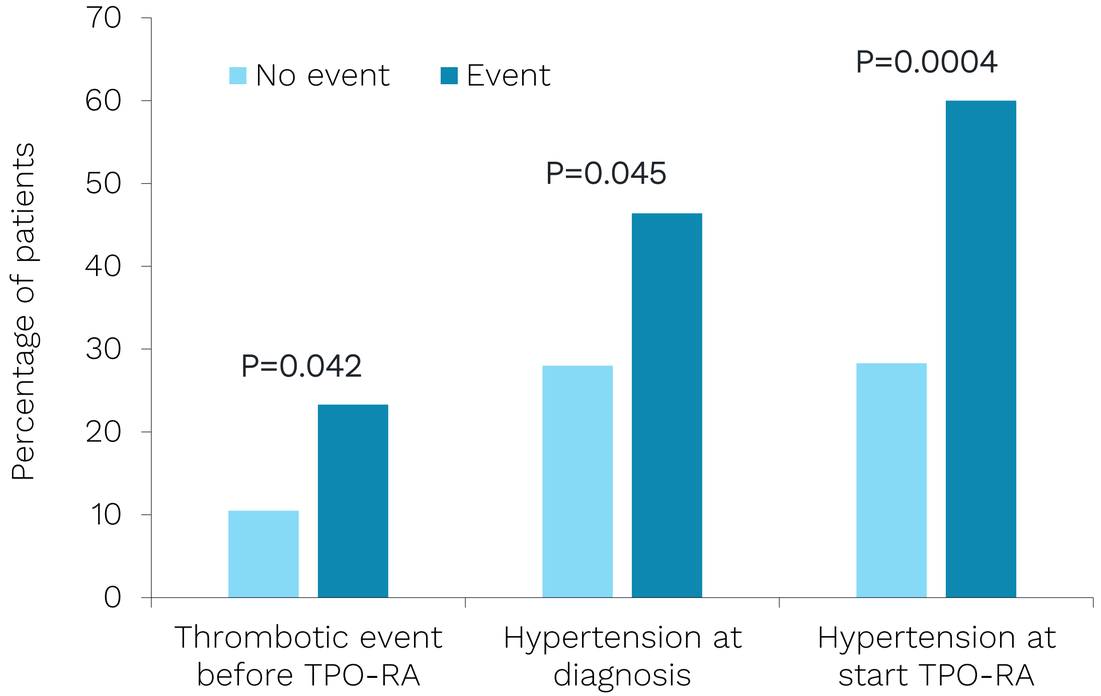
GPIbα CAAR-Tregs can effectively suppress antigen-specific T cell activity, highlighting their potential to restore immune tolerance

CAAR, chimeric autoantibody receptor; GPIbα, glycoprotein Ib alpha; ITP, immune thrombocytopenia; NTD, non-transduced; Teff, effector T cell; Treg, regulatory T cell.

Shu J., et al. Targeted suppression of effector T cells by GPIbα CAAR-Treg cells in refractory/relapsed immune thrombocytopenia. Oral abstract S318 at EHA2025.

S324: Predictors of thrombotic adverse events in patients receiving TPO receptor agonists

- ITP is a complex autoimmune disorder that leads to bleeding but can paradoxically also lead to thrombosis, making the management of the disorder challenging
- TPO-RA use and secondary ITP are the strongest independent predictors of thrombosis
- In the VERTEX 3 study, per 100 TPO-RA courses:
  - 8.2% thrombotic event rate in the first course
  - 7.3% thrombotic event rate in the second/third course
- Key predictors of thrombosis under TPO treatment: previous thrombotic event, hypertension at diagnosis and hypertension at the start of TPO therapy
- Other predictors: Highest platelet count and platelet count at 6 months on TPO-RA, fast response to TPO-RA



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

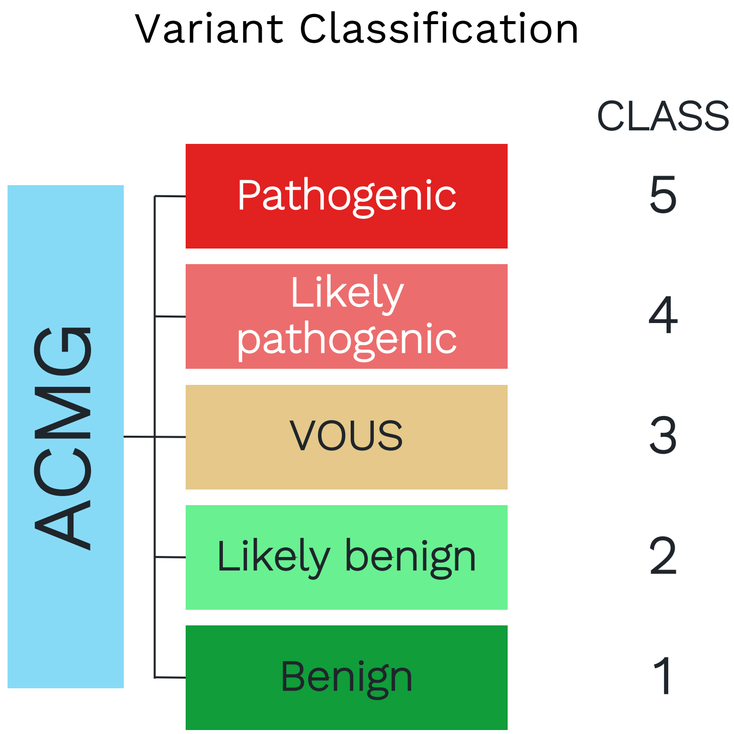
ITP, immune thrombocytopenia; TPO(-RA), thrombopoietin (receptor agonist).

Lozano M, Thrombotic adverse events in patients receiving thrombopoietin receptor agonists: a European multicenter study. Oral abstract S324 at EHA2025.

p273-2: Genetic screening of pathogenic variants in inherited platelet disorders

Genetic Screening

- To date, pathogenic variants associated with inherited platelet disorders have been identified in 68 genes
- More genes have been identified that cause thrombocytopenia (and associated dysfunction) than those that cause isolated platelet dysfunction
- In clinical practice, the genetic diagnosis of inherited platelet disorders is typically performed using gene panels and targeted sequencing
- Guidelines from the ACMG and AMP classify genetic variants as pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign, or benign[1]



ACMG, American College of Medical Genetics and Genomics; AMP, Association for Molecular Pathology; ClinGen, Clinical Genome Resource; VUS, variants of uncertain significance.

1. Richards S, et al. *Genet Med.* 2015;17(5):405-24.

Freson K. Genetic screening of pathogenic variants in inherited platelet disorders: where are we? Oral presentation p273-2 at EHA2025.

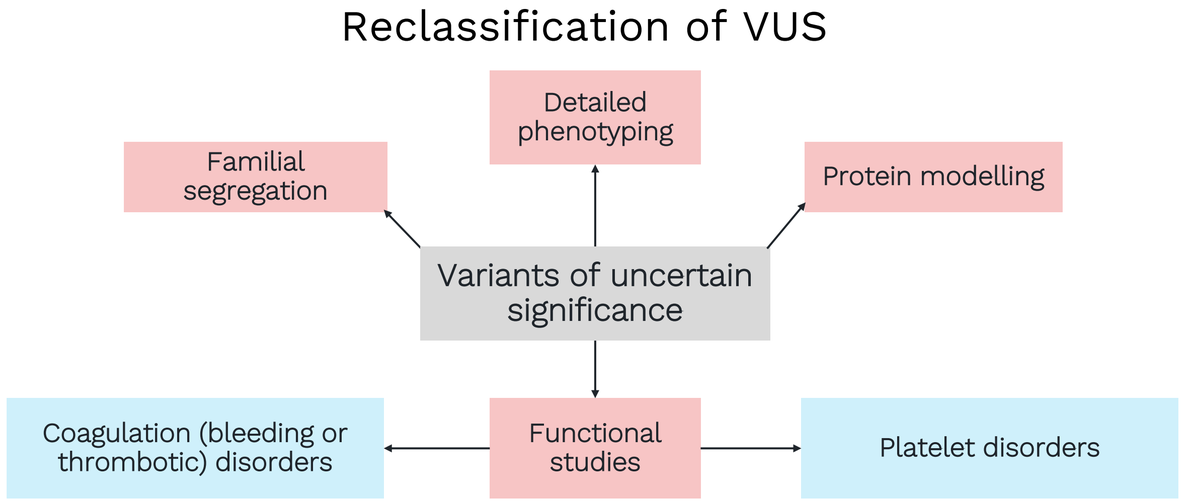
p273-2: Genetic screening of pathogenic variants in inherited platelet disorders is supported by collaborative reclassification efforts

Reclassification of VUS

- A large effort has been made to support variant reclassification
- VUS can be reclassified by familial segregation, detailed phenotyping, functional studies and protein modelling[1]
- The scientific community is encouraged to upload VUS to ClinVar or similar databases, enabling shared knowledge that allows for reclassification if the same variant is identified in patients with comparable phenotype

Computer-assisted variant classification

- Franklin is an example of a variant classification tool
- Franklin uses a number of prediction software tools, including dbscSNV, Splice AI, Primate AI, FATHMM, AlphaMissense, Revel, as well as an aggregated prediction of all the tools to determine whether a variant is likely pathogenic. No one prediction software is sufficient
- Variants are discarded if they don't match the phenotype and cross-referenced with other databases like ClinVar to determine whether the same variant has been described in other patients



When to use gene panel tests in the diagnostic algorithm?

- Inherited thrombocytopenia: No need for platelet function assays, but follow-up molecular tests may support variant classification. Genetic data are crucial for clinical management
- Inherited platelet function disorders: Aggregation/secretion and flow cytometry assays are often required to detect the genetic defect and classify variants

AI, artificial intelligence; AMP, Association for Molecular Pathology; dbscSNV, Database for Splice Site Single Nucleotide Variants; FATHMM, Functional Analysis Through Hidden Markov Models; ISTH, International Society on Thrombosis and Haemostasis; VUS, variant of uncertain significance.

1. Ramanan R, et al. *J Thromb Haemost*. 2025:S1538-7836(25)00277-6.

Freson K. Genetic screening of pathogenic variants in inherited platelet disorders: where are we? Oral presentation p273-2 at EHA2025.

Conclusion

- EHA2025 highlighted significant advances in emerging treatment modalities for ITP, targeting multiple components of its complex pathogenesis.
- Rilzabrutinib (BTKi) demonstrated sustained efficacy and a well-tolerated safety profile in adult patients with persistent or chronic ITP, along with improvements in fatigue and bleeding scores.
- Subcutaneous daratumumab (anti-CD38 mAb) treatment in patients with primary ITP showed promising efficacy and an acceptable safety profile.
- Ianalumab (anti-BAFF-R mAb) demonstrated promising efficacy and a well-tolerated safety profile in heavily pretreated patients with primary ITP.
- c-MPL internalization may influence responsiveness to TPO-RAs. In preclinical models, the GAK inhibitor baricitinib was shown to correct AP2-NAK–mediated endocytic dysregulation.
- Patients with refractory ITP exhibited an expanded population of $CD8^+$ TEMRA cells that were highly cytotoxic and senescent. In a proof-of-concept study, GPIbα CAAR-Treg cells effectively inhibited the cytotoxic activity of CAAR-Teff cells against anti-GPIbα hybridoma cells in a hematopoietic hybridoma model.
- TPO-RA use is associated with a risk of thrombotic events. Data from VERTEX 3 suggest prior thrombotic history and pre-existing or early-onset hypertension are predictive factors for thrombotic events in patients with ITP being treated with TPO-RA.
- Genetic screening of pathogenic variants in inherited platelet disorders is supported by collaborative reclassification.

AP2-NAK, adaptor protein complex 2-associated kinase; BAFF-R, B-cell activating factor receptor; BTKi, Bruton's tyrosine kinase inhibitor; CAAR, chimeric autoantibody receptor; CD, cluster of differentiation; GAK, cyclin G-associated kinase; GPIbα, glycoprotein Ib alpha; ITP, immune thrombocytopenia; mAb, monoclonal antibody; TPO-RA, thrombopoietin receptor agonist; TEMRA, terminally differentiated effector memory T cell re-expressing CD45RA; Treg, regulatory T cell; Teff, effector T cell

05

Iron homeostasis and erythropoiesis

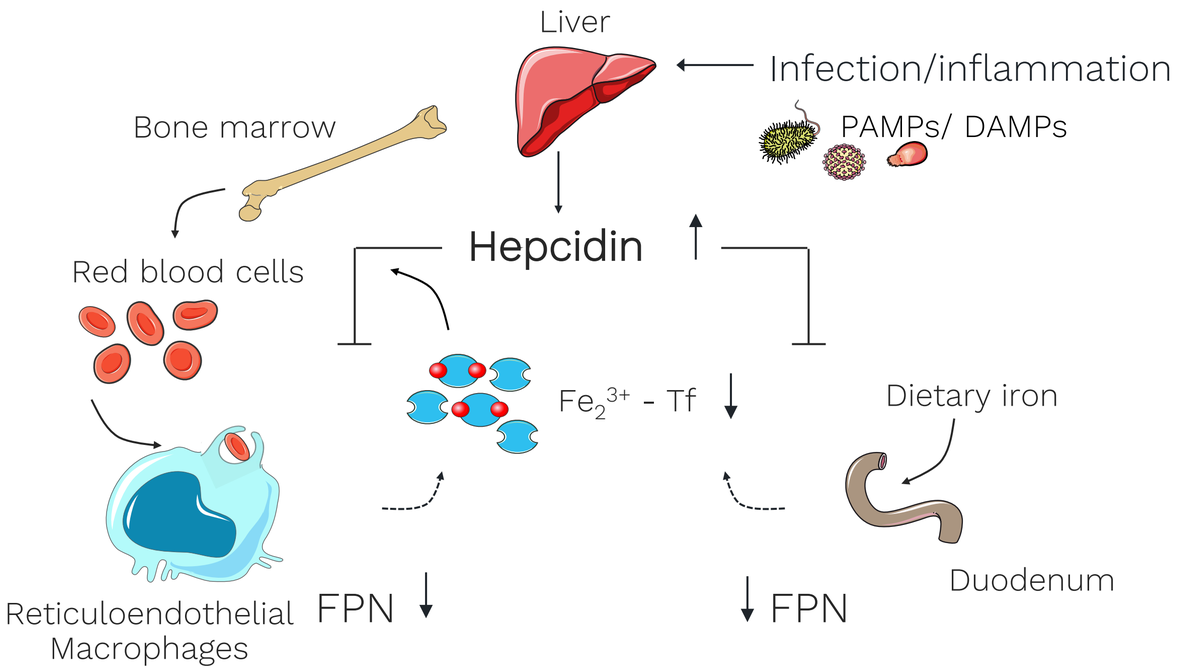
Section 5: Iron homeostasis and erythropoiesis

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
p271-1	Novel mechanisms underlying anemia of inflammation	Martina Muckenthaler
p471-3	Toll-like Receptor Signaling in Anemia of Inflammation	Oriana Marques
S305	Iron trapping in macrophages reshapes the homeostasis of the haematopoietic system	Laura Crisafulli
S294	Intracellular iron overload and defective stromal niche impair hematopoietic stem cells in sickle cell disease	Silvia Sighinolfi
p271-2	Stressed erythropoiesis	Roberta Russo
S306	Targeting the mTOR pathway to regulate PIEZO1-mediated iron overload	Federica Maria Esposito

p471-3: Dysregulation of iron homeostasis in anemia of inflammation

Role of hepcidin and ferroportin in different compartments to maintain iron homeostasis during infection/inflammation

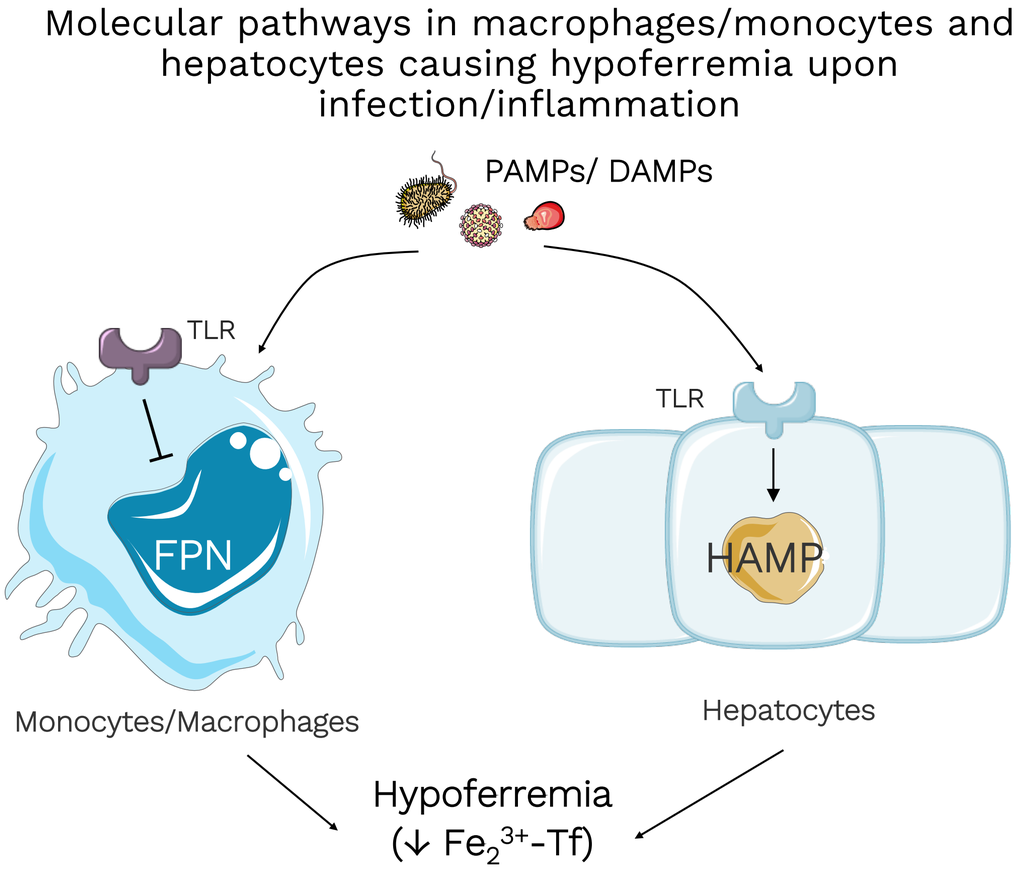


- Iron plays a crucial role in essential physiological processes such as oxygen transport, energy production, and cell proliferation
- Iron homeostasis is balanced by the interplay of proteins responsible for iron import, storage, and export
- Systemic iron levels are primarily regulated by the hepcidin–ferroportin (FPN) axis involved in recycling of iron from RBC breakdown
- During infections or inflammation, immune cells detect pathogens or damaged components, releasing pro-inflammatory cytokines which activate hepcidin, the master regulator of systemic iron flows produced by hepatocytes
- Hepcidin blocks iron absorption in the gut and iron release from macrophages by degrading FPN, the iron exporter
- This creates abnormally low levels of iron in the blood, termed as hypoferremia, and since red blood cell production depends heavily on iron, prolonged restriction leads to anemia of inflammation

DAMPs, damage-associated molecular patterns; FPN, ferroportin; PAMPs, pathogen-associated molecular patterns; Tf, transferrin.

Muckenthaler M. Novel mechanisms underlying anemia of inflammation. Oral presentation P271-1 at EHA2025.
Marques O. Toll-like Receptor Signaling in Anemia of Inflammation: Mechanisms of Iron Sequestration and Therapeutic Opportunities. Oral presentation p471-3 at EHA2025.

p471-3: TLRs coordinate a dual response resulting in hypoferremia

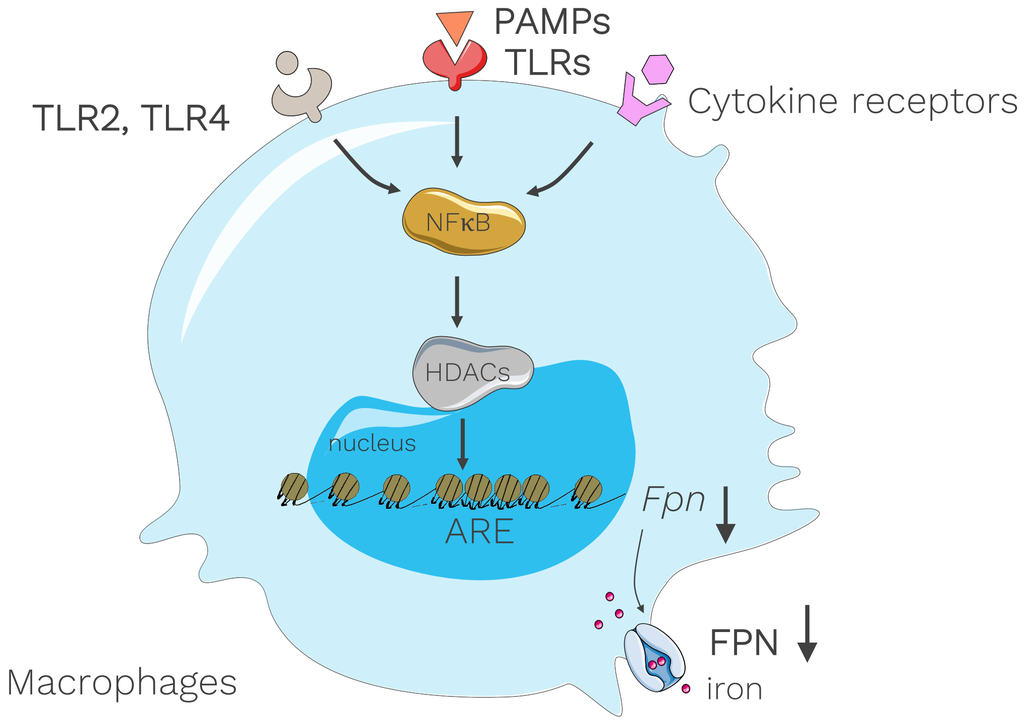


- Macrophages and hepatocytes are involved in the systemic iron regulation, as well as the local iron release to neighboring cells for their selective needs (e.g., in follicular development and wound healing)
- Iron retention in macrophages is a key factor causing hypoferremia, which impairs erythroid cell development, whereas hepatocytes play a crucial role in iron storage
- TLR activation serves as the initial trigger, decreasing FPN transcription in macrophages and creating local iron restriction, as well as increasing hepcidin, blocking the iron export systemically and creating 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

DAMPs, damage-associated molecular patterns; FPN, ferroportin; HAMP, transcriptional activation of hepcidin; PAMPs, pathogen-associated molecular patterns; Tf, transferrin; TLR, toll-like receptor.

Muckenthaler M. Novel mechanisms underlying anemia of inflammation. Oral presentation P271-1 at EHA2025.
Marques O. Toll-like Receptor Signaling in Anemia of Inflammation: Mechanisms of Iron Sequestration and Therapeutic Opportunities. Oral presentation p471-3 at EHA2025.

p271-1 & p471-3: TLR ligands promote Fpn downregulation via the NFκB-NRF2-HDAC axis



Signaling pathway in macrophages responsible for iron retention upon infection/inflammation

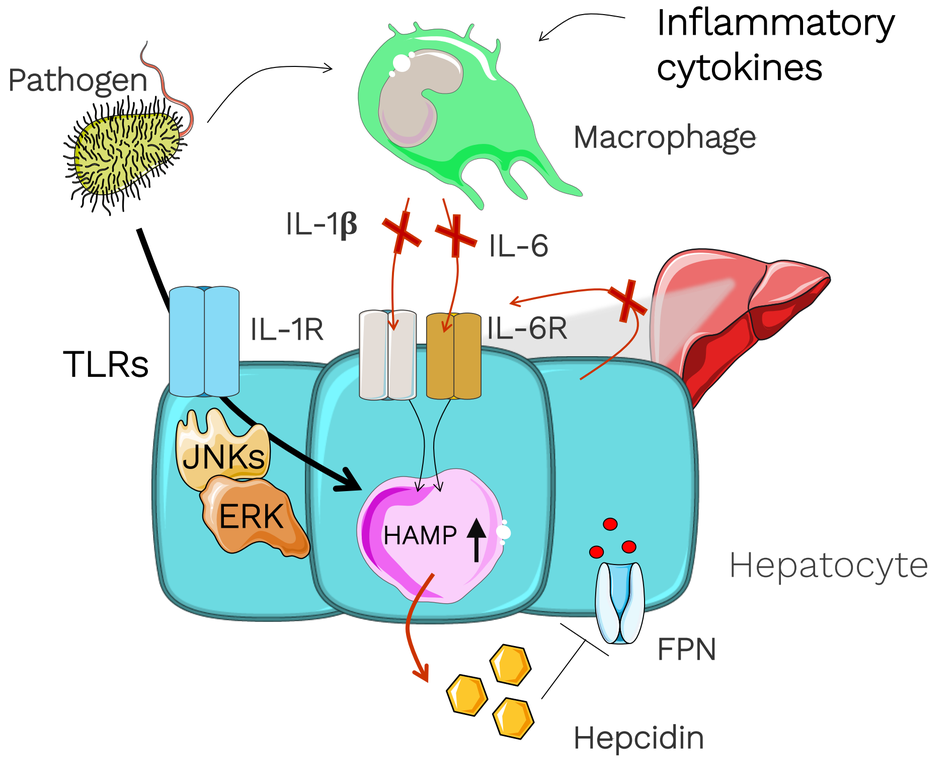
- Previous studies had shown that TLR ligands reduced FPN transcription in macrophages, with similar transcriptional repression being observed in patients with anemia of inflammation
- Pharmacological and RNA interference screens showed that during an infection, PAMPs activate TLRs, specifically TLR2 and TLR4, and promote NFκB signaling in macrophages, resulting in the decrease of Fpn mRNA levels
- NFκB then recruits HDACs 1 and 3 to the ARE of FPN, resulting in the repression of FPN
- Inflammation-mediated repression of FPN transcription in macrophages may potentially be attenuated by NFκB and HDAC inhibitors and NRF2 activators

ARE, antioxidant response element; DAMPs, damage-associated molecular patterns; FPN, ferroportin; HDACs, histone deacetylases; PAMPs, pathogen-associated molecular patterns; Tf, transferrin.

Muckenthaler M. Novel mechanisms underlying anemia of inflammation. Oral presentation p271-1 at EHA2025.
Marques O. Toll-like Receptor Signaling in Anemia of Inflammation: Mechanisms of Iron Sequestration and Therapeutic Opportunities. Oral presentation p471-3 at EHA2025.

p271-1 & p471-3: PAMPs promote *Hamp* upregulation in hepatocytes via the JNK/ERK-MAPK signaling pathway

- Although it is known that hepcidin responds to cytokines released by immune cells, especially IL-6 and IL-1b, the role of hepatocytes, which also express TLRs and can mount downstream antimicrobial responses, was still 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

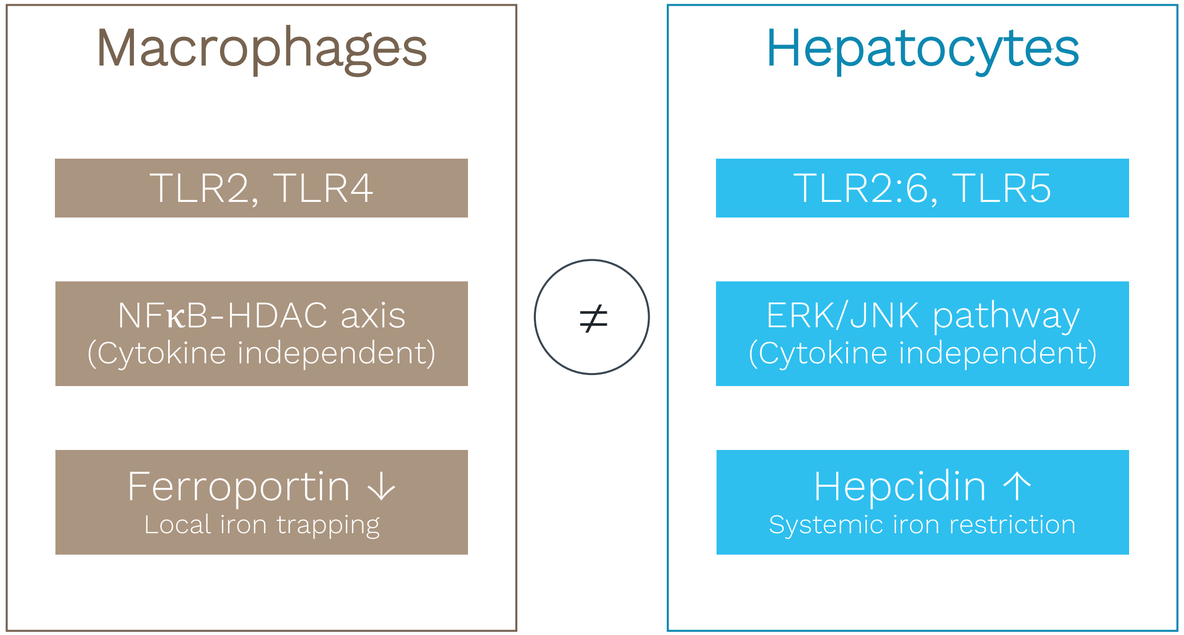


Signaling pathway in hepatocytes responsible for iron retention upon infection/inflammation

DAMPs, damage-associated molecular patterns; FPN, ferroportin; PAMPs, pathogen-associated molecular patterns; Tf, transferrin.

Muckenthaler M. Novel mechanisms underlying anemia of inflammation. Oral presentation p271-1 at EHA2025.
Marques O. Toll-like Receptor Signaling in Anemia of Inflammation: Mechanisms of Iron Sequestration and Therapeutic Opportunities. Oral presentation p471-3 at EHA2025.

p271-1 & p471-3: TLRs activate different intracellular pathways in macrophages and hepatocytes, leading to iron restriction



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

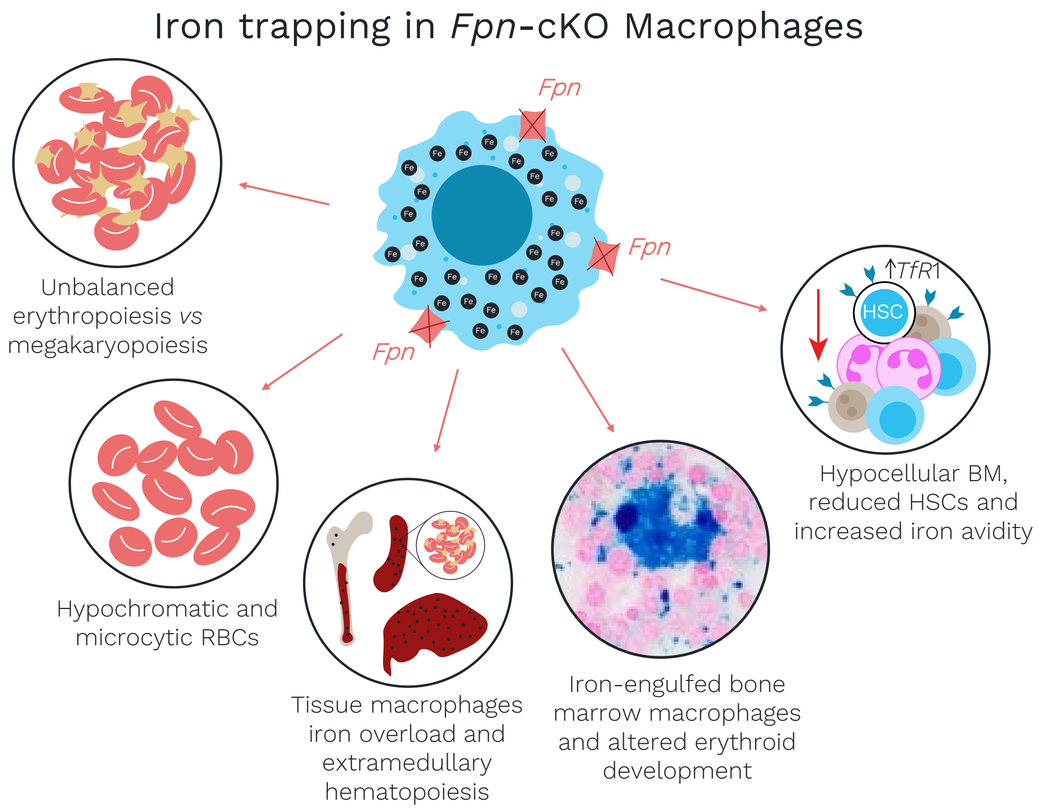
- In macrophages, TLR2 and TLR4 activate the NFκB-HDAC axis to repress ferroportin transcription
- In hepatocytes, TLR2/6 and TLR5 trigger ERK/JNK signaling to drive hepcidin production in a cytokine-independent pathway
- These findings of parallel mechanisms challenged the prevailing notion of how inflammatory hypoferremia is caused and questioned the critical role of hepcidin in the anemia of inflammation
- This cell-type specificity also revealed a therapeutic challenge, where effective treatments may need to target multiple pathways simultaneously

DAMPs, damage-associated molecular patterns; FPN, ferroportin; PAMPs, pathogen-associated molecular patterns; Tf, transferrin.

Muckenthaler M. Novel mechanisms underlying anemia of inflammation. Oral presentation p271-1 at EHA2025.
Marques O. Toll-like Receptor Signaling in Anemia of Inflammation: Mechanisms of Iron Sequestration and Therapeutic Opportunities. Oral presentation p471-3 at EHA2025.

S305: FPN-mediated iron release from macrophages is essential for preventing age-associated anemia

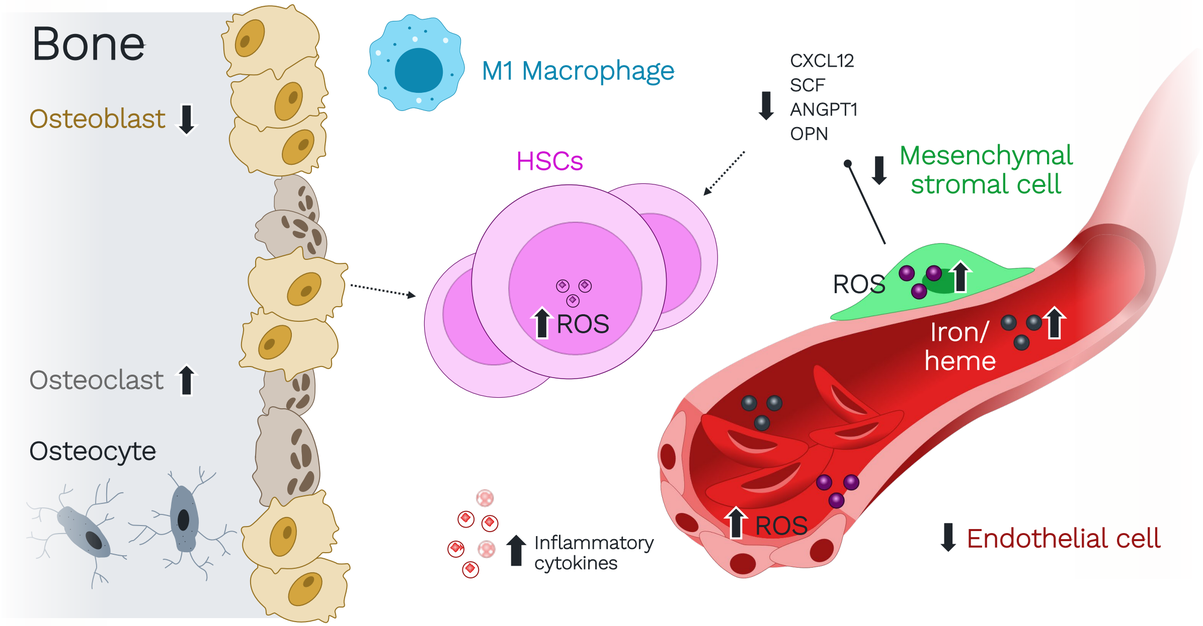
- BM-resident macrophages represent readily available sources of iron for developing cells of the hematopoietic system
- The impact of iron retention in macrophages on BM hematopoietic stem and progenitor cells was tested in mice with targeted deletion of *Fpn* in the myeloid lineage (*Fpn*-cKO), characterized by higher RBC counts with lower hematocrit and hemoglobin levels
- Long-term iron retention was detrimental to BM macrophages and their function
- Local and systemic compensatory mechanisms are put in place (increased TfR1 expression, extramedullary hematopoiesis, EPO-dependent increase of ERFE), but are insufficient to restore iron homeostasis
- The findings suggest that iron trapping in macrophages leads to multiple defects in the hematopoietic system



BM, bone marrow: cKO, conditional knockout; EPO, erythropoietin; ERFE, erythroferrone; FPN, ferroportin; RBC, red blood cell; Tfr1, transferrin receptor.
Crisafulli L. Iron trapping in macrophages reshapes the homeostasis of the haematopoietic system. Oral abstract S305 at EHA2025.

S294: Iron overload and oxidative stress impact the bone marrow niche in sickle cell disease

Schematic representation of the alteration in adult BM niche in β-thalessimia and SCD



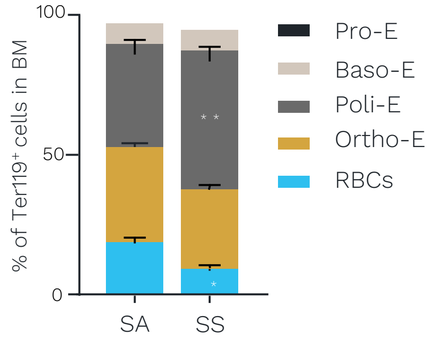
- HSC function is regulated by signals from the BM microenvironment, or niche, which modulate hematopoiesis
- Regulation within the niche involves several cell populations, such as mesenchymal stromal cells (MSCs), that interact with HSCs and secrete growth factors and cytokines
- Physical cues and biochemical factors, including iron, ROS, and inflammatory cytokines, also influence HSC behavior
- Preclinical data from SCD mouse models showed that elevated levels of iron and ROS disrupt multiple BM niche components, including MSCs and endothelial cells[1]
- The presented talk aimed to understand whether HSC defects in SCD are dependent on the BM niche and the molecular and cellular players involved

BM, bone marrow; HSC, hematopoietic stem cell; MSC, mesenchymal stromal cell; ROS, reactive oxygen species; SCD, sickle cell disease.
Figure adapted from Aprile A, et al. *Pharmaceuticals (Basel).* 2022;15(5):592.
Sighinolfi S. Intracellular iron overload and defective stromal niche impair hematopoietic stem cells in Sickle Cell Disease. Oral abstract S294 at EHA2025.

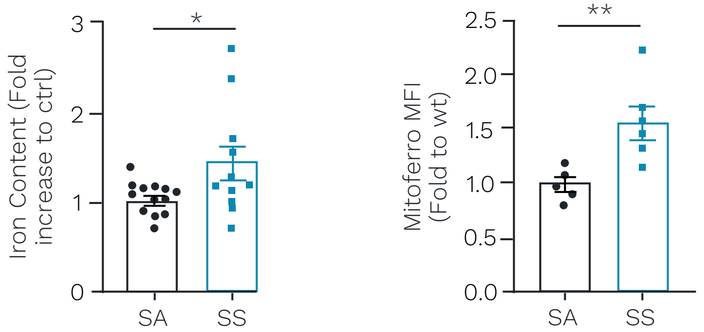
S294: Iron and ROS can affect HSCs both directly and indirectly by acting on MSCs, which in turn fail to preserve HSCs

- HSCs showed increased myeloid differentiation in a 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 demonstrated delayed proliferation and earlier exhaustion, which were 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
- Targeting iron overload and addressing the defective stromal niche may improve
  - HSC during *ex vivo* engineering (autologous transplant)
  - Recipient BM niche pre- and post-transplantation (autologous & allogeneic transplant)

Erythroid subpopulations



Intracellular and mitochondrial iron ($Fe2^{+}$) content

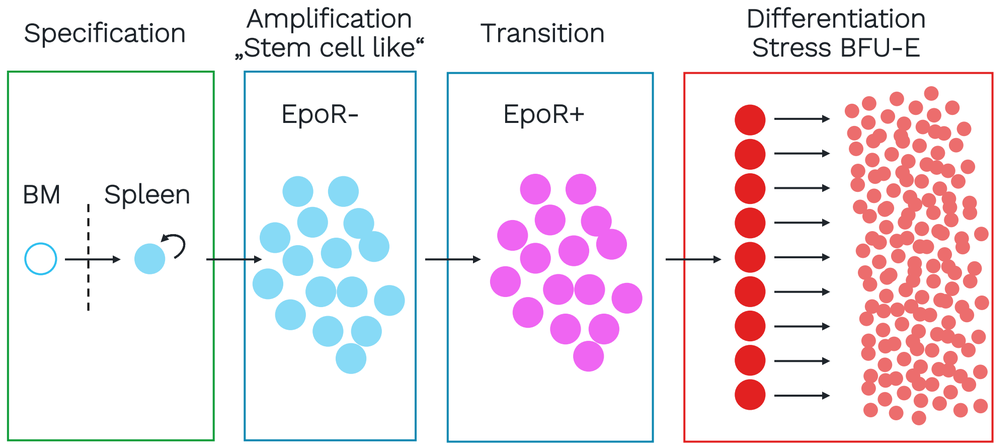


Baso-E, basophilic erythroblasts; BM, bone marrow; HSC, hematopoietic stem cell; HSPC, hematopoietic stem and progenitor cell; MSC, mesenchymal stromal cell; Ortho-E, orthochromatic erythroblasts; Pro-E, proerythroblasts; RBCs, red blood cells; ROS, reactive oxygen species; SA, sickle cell trait; SCD, sickle cell disease; SS, sickle cell disease.

Sighinolfi S. Intracellular iron overload and defective stromal niche impair hematopoietic stem cells in Sickle Cell Disease. Oral abstract S294 at EHA2025.

p271-2: From stress to ineffective erythropoiesis

- Human erythropoiesis is a complex process leading to the production of erythrocytes at a constant rate
- 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



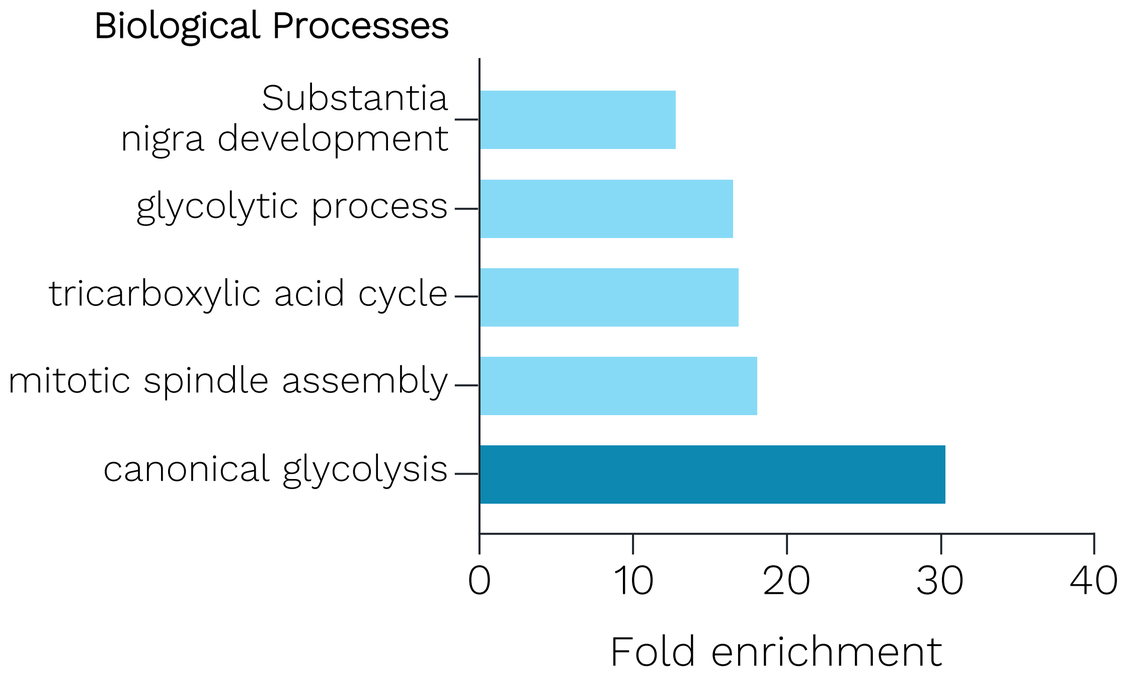
Schematic representation of stress erythropoiesis

BM, bone marrow; EpoR, erythropoietin receptor; BFU-E, burst-forming units erythroid.
Figure adapted from Paulson RF et al. *Cells* 2020, 9(3), 634.
Russo R. Stressed erythropoiesis in hereditary erythrocyte disorders. Oral presentation p271-2 at EHA2025.

p271-2: Improved understanding of erythropoiesis has significant implications for developing future therapeutic interventions

- Congenital dyserythropoietic anemia (CDA) is a rare group of inherited blood disorders in which red blood cells don't develop properly, leading to anemia
- Approximately 5% of suspected CDAs show pathogenic variants in the PIEZO1, the causative gene of dehydrated hereditary stomatocytosis (DHS1)
- PIEZO1-related anemias showed differentially expressed metabolites related to redox metabolism, lipid synthesis, and glycolysis[1]
- Analyzing transcriptomic, proteomic, and metabolomic changes in erythroid cells during differentiation and in mature RBCs has unveiled common deregulated pathways across seemingly unrelated disorders

Gene ontology analysis of the differentially regulated genes in PIEZO1-knock-in cells

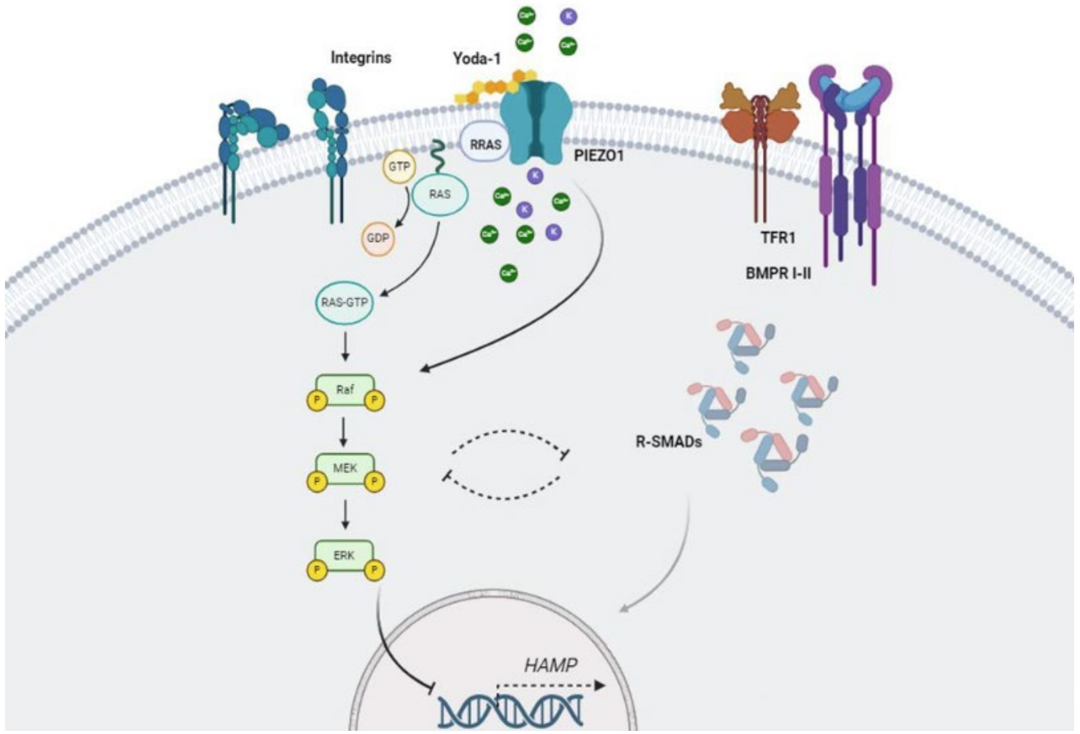


1. Rosato BE, et al. PS2201_EHA2025.
Russo R. Stressed erythropoiesis in hereditary erythrocyte disorders. Oral presentation p271-2 at EHA2025.

S306: mTOR pathway regulates PIEZO1-mediated iron overload

- PIEZO1 is an ion channel protein that responds to mechanical stimuli
- *PIEZO1*-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
- Two lead candidates showed 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



DHS, dehydrated hereditary stomatocytosis; GoF, gain of function.
Esposito FM. Targeting the mTOR pathway to regulate PIEZO1-mediated iron overload. Oral abstract S306 at EHA2025.

Conclusion

- This year’s EHA has provided a more robust mechanistic understanding of how iron availability is regulated by erythropoiesis.
- Hemoglobin production in erythroblasts demands significant iron levels, highlighting the necessity of regulating iron availability during erythropoiesis.
- TLRs were shown to activate different intracellular pathways in macrophages and hepatocytes, leading to iron restriction.
- The release of iron from macrophages mediated by FPN is crucial for preventing anemia that is associated with aging.
- Iron and ROS can both directly and indirectly affect HSCs by acting on MSCs, which in turn fail to preserve HSCs.
- Stress erythropoiesis generates a wave of new erythrocytes to restore homeostasis, relying on the rapid proliferation of immature progenitor cells.
- Common deregulated pathways are observed across seemingly unrelated disorders, with the mTOR pathway playing a role in regulating PIEZO1-mediated iron overload.

FPN, ferroportin; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells; ROS, reactive oxygen species; TLRs, toll-like receptors.

06

Innovative developments in thrombotic and bleeding conditions

Section 6: Innovative developments in thrombotic and bleeding conditions

Overview of selected presentations

Presentation ID	Presentation Title	Presenter
S316	Hepatic plasminogen lowering with RNA interference for the treatment of bleeding disorders is unlikely to pose thrombotic risk based on UK Biobank analyses and mouse models of provoked thrombosis	Rodney Camire
p112-1	Coagulation Factor signaling: Opportunities for novel engineered therapeutics	Roger Preston
S317	Microfluidic testing using the Maastricht FlowChamber in patients with bleeding disorder of unknown cause (BDUC)	Amaury Monard
S323	A phenome-wide association study (PHEWAS) of ADAMTS13 variants yields insight into the effect of ADAMTS13 mutations	Matthew Carter

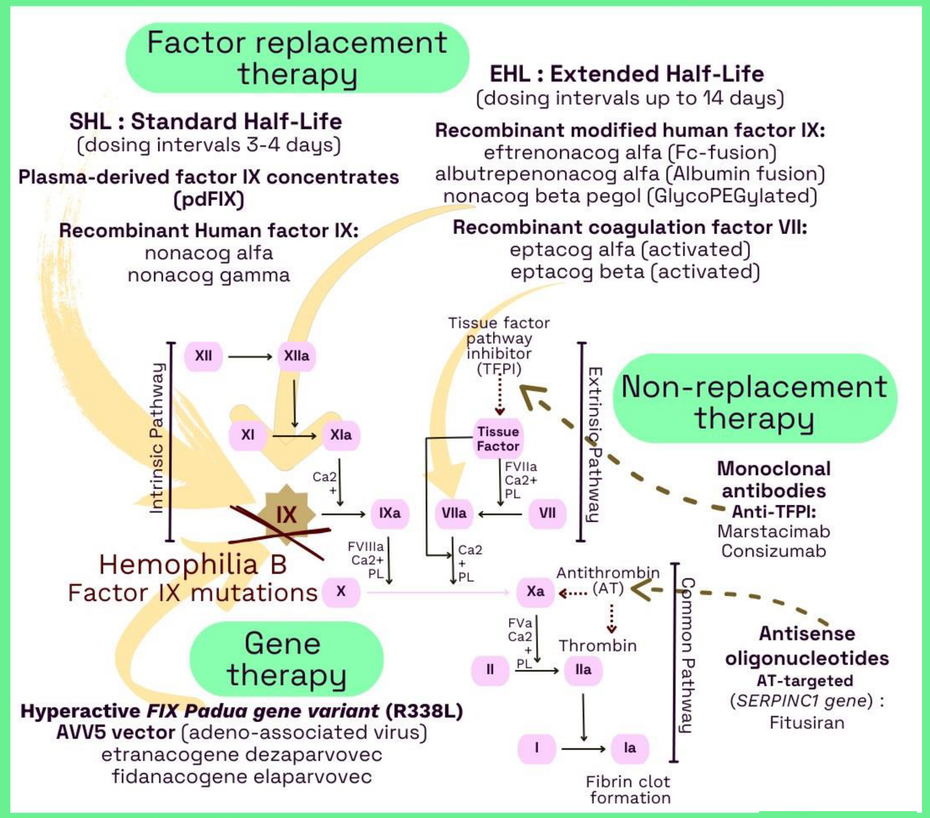
Innovations in hemophilia therapy

Introduction

- Hemophilia is an inherited clotting factor deficiency, affecting FVIII (hemophilia type A, HA) or FIX (HB)
- Patients with mild hemophilia bleed only after trauma, while patients with severe cases suffer from spontaneous bleeds which affect the muscoloskeletal system
- Factor replacement to alleviate symptoms is coupled with pitfalls such as the need for venous access, its short half life and immunogenicity
- Modern hemophilia therapy is expanding from life-saving treatments to helping patients lead normal lives
- Multiple new strategies to improve hemophilia therapy include extended half-life FVIII/FVIX, antibodies that take over the function of FVIII/FIX, and gene therapy

More from EHA #Thinking Thursday

Hemophilia B (Christmas disease) therapies



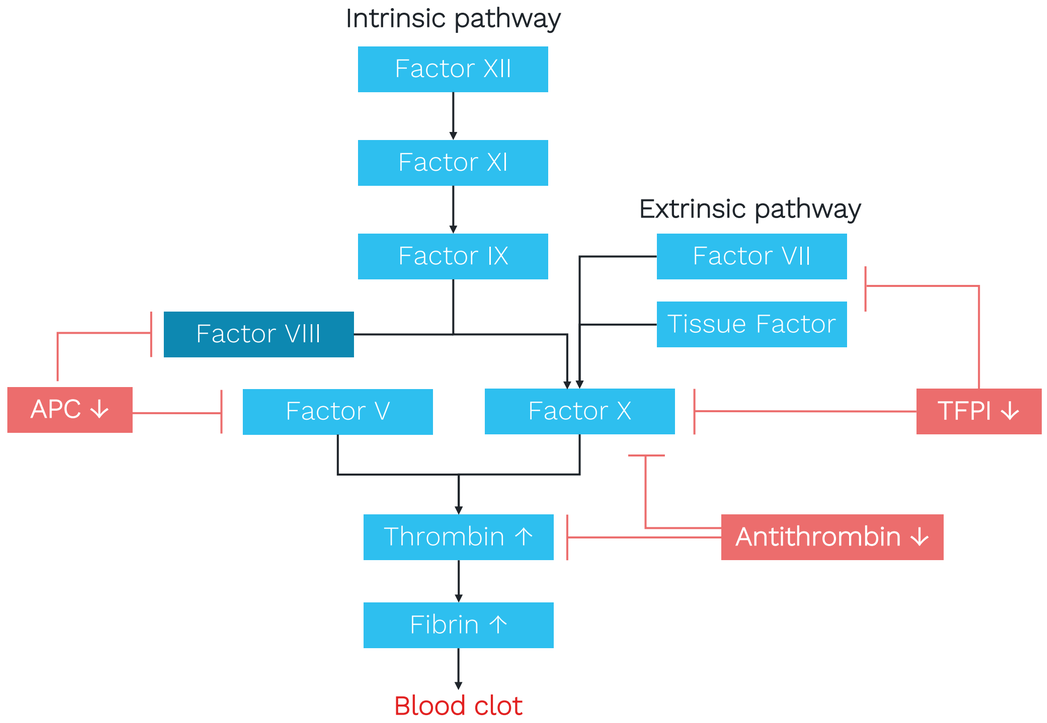
ThinkingThursday

(a)FVIII, (activated) Factor VIII; (a)FIX, (activated) factor IX.

1. Blanchette VS et al., Thromb Haemost. 2014 Nov;12(11):1935-9. 2. Adam MP et al., Hemophilia A (summary) https://www.ncbi.nlm.nih.gov/books/NBK1404/ [accessed 21 June 2025].

Rebalancing the coagulation cascade by restoring thrombin generation for hemophilia

- 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.
- Two main approaches have been utilized to rebalance the coagulation system:
  1. Targeting natural anticoagulants, such as antithrombin, activated protein C, and tissue factor pathway inhibitor (TFPI).
  2. Mimicking clotting factors using agents like FVIII-activity mimicking agent, Mim8, and emicizumab.
- These therapies can enhance treatment adherence and HRQoL 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.



Restoring thrombin generation in the coagulation cascade for hemophilia treatment by targeting the natural anticoagulants (marked in red)

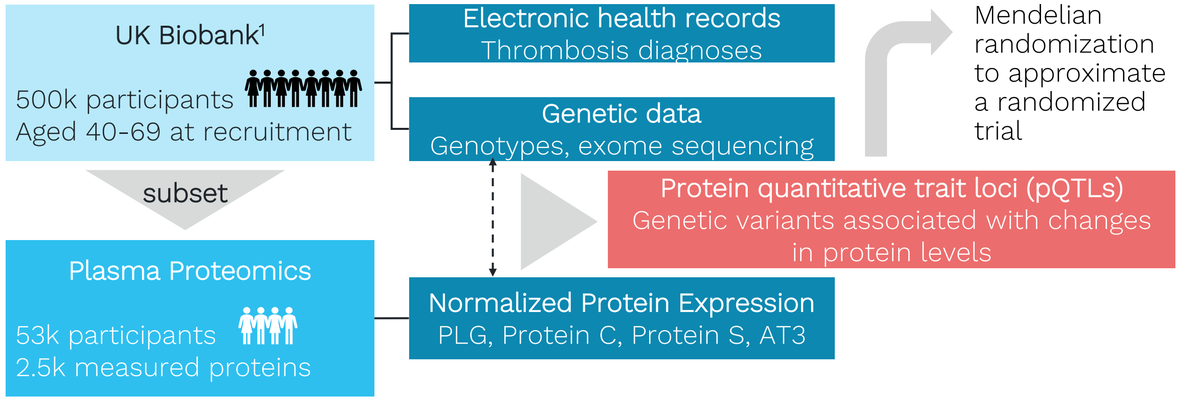
APC, activated Protein C; AT, antithrombin; TFPI, tissue factor pathway inhibitor

1. Gualtierotti R et al. Pharmaceuticals 2022, 15(10), 1183.

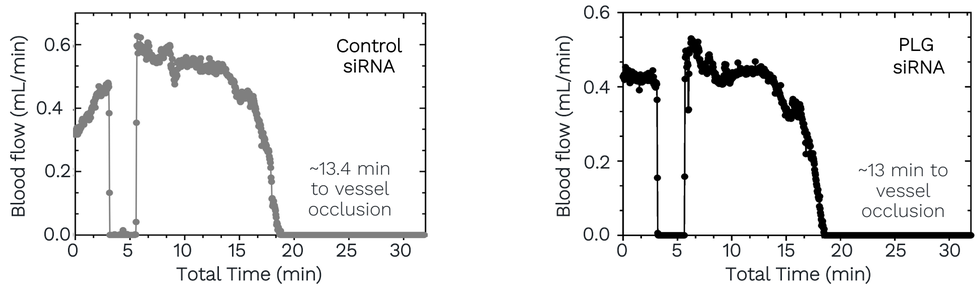
S316: Knockdown of hepatic plasminogen production by siRNA could be a safe treatment of bleeding disorders

- Plasminogen is primarily produced in the liver and enzymatically degrades blood clots; lowering hepatic plasminogen in bleeding disorders could be a safe alternative to conventional anti-fibrinolytic therapy
- The risk of thrombosis in patients with low plasma plasminogen was assessed using available UK Biobank data
  - Interestingly, they found plasma plasminogen protein levels were not correlated with thrombosis
- An *in vivo* study in which the plasminogen siRNA levels of mice were lowered by 99%, there was a comparable time to vessel occlusion between the plasminogen siRNA reduced mice and the control siRNA mice
- Therefore, early evidence suggests lowering plasminogen is safe and further evaluation of role the RNAi therapeutic ALN-6400 in the treatment of bleeding disorders is ongoing (NCT06659640)

Retrospective analysis of plasminogen levels and thrombosis



Vessel occlusion with and without plasminogen knockdown in mice



siRNA, small interfering RNA.

Camire R, Hepatic plasminogen lowering with RNA interference for the treatment of bleeding disorders is unlikely to pose thrombotic risk based on UK biobank analyses and mouse models of provoked thrombosis. Oral presentation S316 at EHA2025

Innovations in hemophilia therapy

Bispecific antibody taking over the function of FVIII

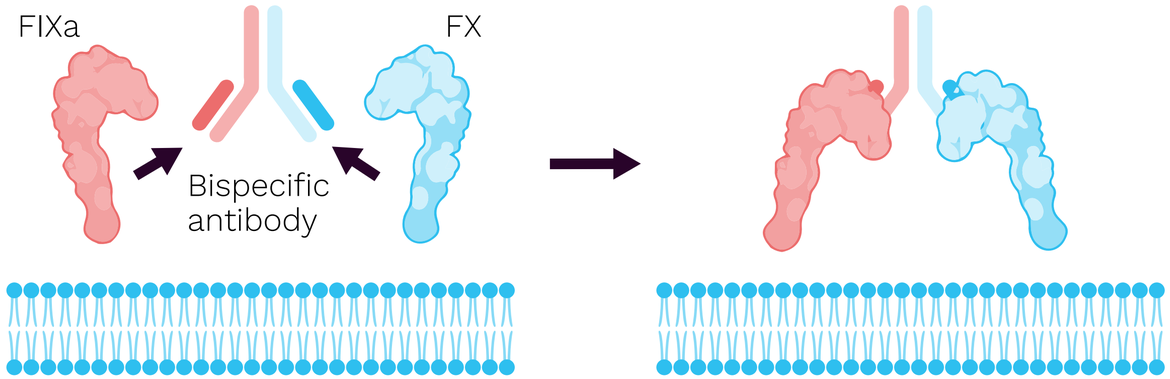


Figure adapted from Sampei et al.[3]

AAV mediated liver transfection[7]	Lentiviral gene therapy with HSCs[8]	CRISPR-mediated gene editing
• Proof of concept successful, but... • Variable expression • AAV is immunogenic • -> does not work in patients with AAV immunity, no redosing	• Transfer of FVIII transgene into patient HSCs • FVIII is then produced by monocytes	• Use of lipid nanoparticles and AAV[9] • Permanent, not episomal integration • Can be redosed if using B-cell transfection[10]

Strategies to improve hemophilia treatment

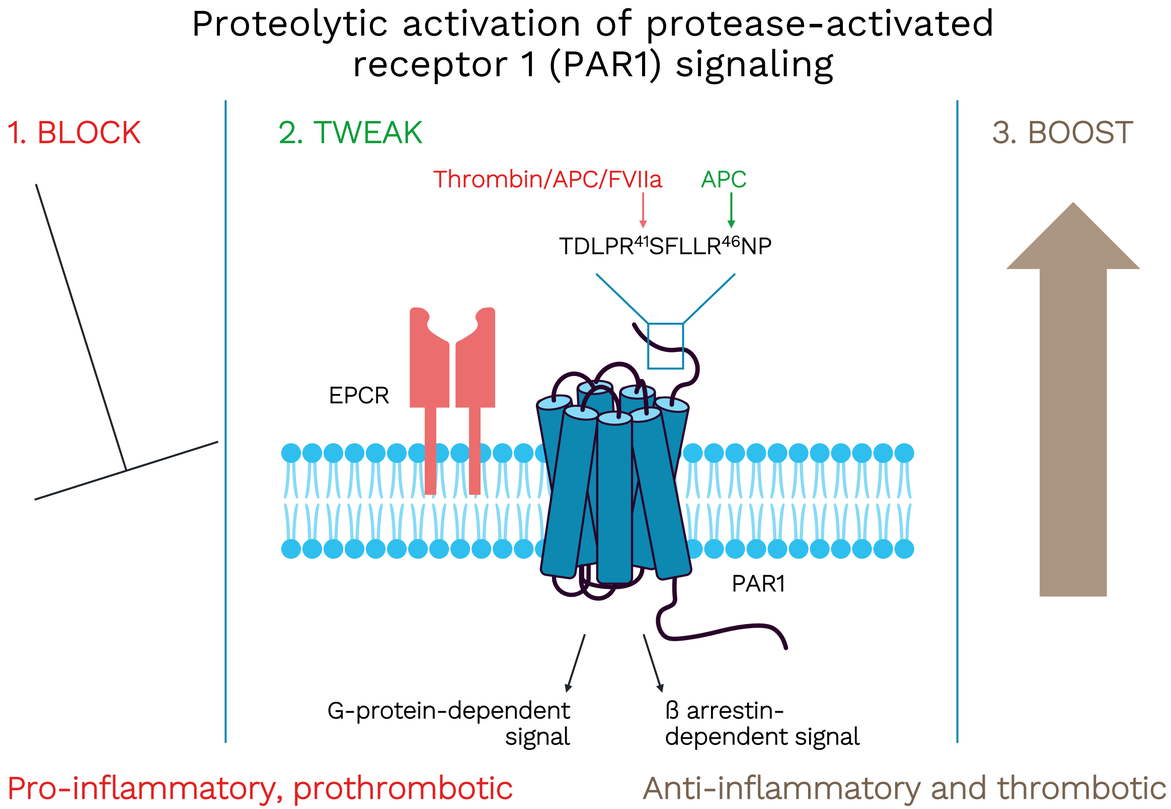
- Extended half-live: Introduction of mutations and peptide fusions to lower the elimination rate[1]
- Bispecific antibodies: Emicizumab binds to FIXa and FX to mimic FVIIIa function
  - subcutaneous weekly administration, stable plasma levels, no immunogenicity[2]
- FVIIIa mimetic Inno8 (in clinical development)[4] can be administered orally with an absorption enhancer (SNAC)
- Rebalancing of the coagulation cascade: Alleviate severe hemophilia by increasing thrombotic activity, e.g. siRNA Fitusiran (antithrombin ↓), TFP inhibitors, Serpin-PC (activated protein C inhibitor)[5,6]
- VWF binding aptamers and nanobodies protect VWF from degradation
- Gene therapy includes AAV[7] or lentiviral[8] and aims to provide patients with missing factors

AAV, adenovirus; (a)FVIII, (activated) Factor VIII; (a)FIX, (activated) factor IX; SNAC, Salcaprozate sodium; TFP, tissue factor pathway; VWF, von Willebrand factor.

1. Chhabra ES et al., Blood. 2020 Apr 23;135(17):1484-1496. 2. Kitazawa A et al., Nat Med. 2012 Oct;18(10):1570-4. 3. Sampei Z et al. , PLoS One. 2013;8(2):e57479. 4. NCT ID: NCT06649630. 5. Boyce & Rangarajan, J Blood Med. 2023 Apr 22:14:317-327. 6. Gualtierotti et al., Pharmaceuticals (Basel). 2022 Sep 23;15(10):1183. 7. Arruda & Doshi, Mediterr J Hematol Infect Dis. 2020 Sep 1;12(1):e2020069. 8. Doering CB et al., Hum Gene Ther. 2018 Oct;29(10):1183-1201. 9. Zhang Z et al., BioDrugs. 2024 Mar 15;38(3):369–385. 10. https://www.clinicaltrials.gov/study/NCT06611436 [accessed 21 June 2025].

p112-1: Coagulation proteases: New therapeutic targets beyond clotting

- **Coagulation proteases** act beyond coagulation by **activating protease-activated receptors (PARs)**, **enabling cellular responses to vascular injury and inflammation**
- PAR signaling is driven by: Receptor cleavage site, Intracellular effectors, Plasma co-factors
- Therapeutic modulation of PAR signaling:
  - **Block:** PAR1 antagonist (Vorapaxar) reduces cardiovascular events but increases bleeding
  - **Tweak:** Parmodulins inhibit coagulation and platelet activation while preserving endothelial cytoprotection
  - **Boost:** Engineered aPC analogs show promise in:
    - **Stroke**: Reduction of tPA-induced neurotoxicity
    - **Cerebral malaria**: Limitation of vascular inflammation and mortality
    - **Inflammatory bowel disease (IBD)**: Suppression of T cell-driven proinflammatory activity
- **Selective targeting of coagulation proteases signaling pathways offers new options to treat thromboinflammatory and vascular diseases**



PAR, protease-activated receptor.
Preston R. Coagulation Factor signaling: Opportunities for novel engineered therapeutics. Oral presentation p112-1 at EHA2025.

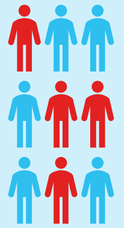
S323: PheWAS gives insight into the effect of *ADAMTS13* mutations in cTTP

- Congenital thrombotic thrombocytopenic purpura (cTTP) occurs due to inherited biallelic mutations in *ADAMTS13* on chromosome 9
  - >300 variants have been identified in patients – but there are >20,000 variants in population databases
- Phenome-wide association study (PheWAS) was used to identify phenotypes associated with genetic variation in ADAMTS13

1

Cohort Creation

- NIH All of Us Research
- Program (414, 840
- participants)
- 28, 506 ADAMTS13 variants
- Filtered for ClinVar pathogenic/likely
- pathogenic and MAF <0.01



2

Generation of PheCode Profiles

- ICD-10 codes grouped as Phecodes
- Performed using
- Phecode 1.2 using PheTK, a Python-based package
- 1810 Phecodes for testing

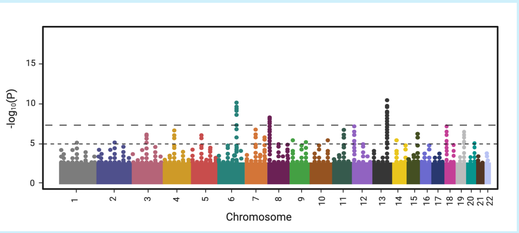
3

Association Testing

- Association testing performed using an additive model and logistic regression
- Sex, age and first 5 PCs used as covariates

4

Visualisation



NIH, National Institute of Health (US).

Carter M. A phenome-wide association study (PHEWAS) of ADAMTS13 variants yields insight into the effect of ADAMTS13 mutations. Oral presentation S323 at EHA2025.

S323: PheWAS gives insight into the effect of *ADAMTS13* mutations in cTTP

- Variant-based PheWAS of rs28446901 revealed associations with increased risk of venous embolism, DVT, and PE
- Association was consistent in sub-analysis in both hetero- and homozygous individuals, though not stronger in homozygotes
- There remains a need to consider the functional consequences of this intronic variant

Variant-led: rs28446901

Chr9-133443675-C-G

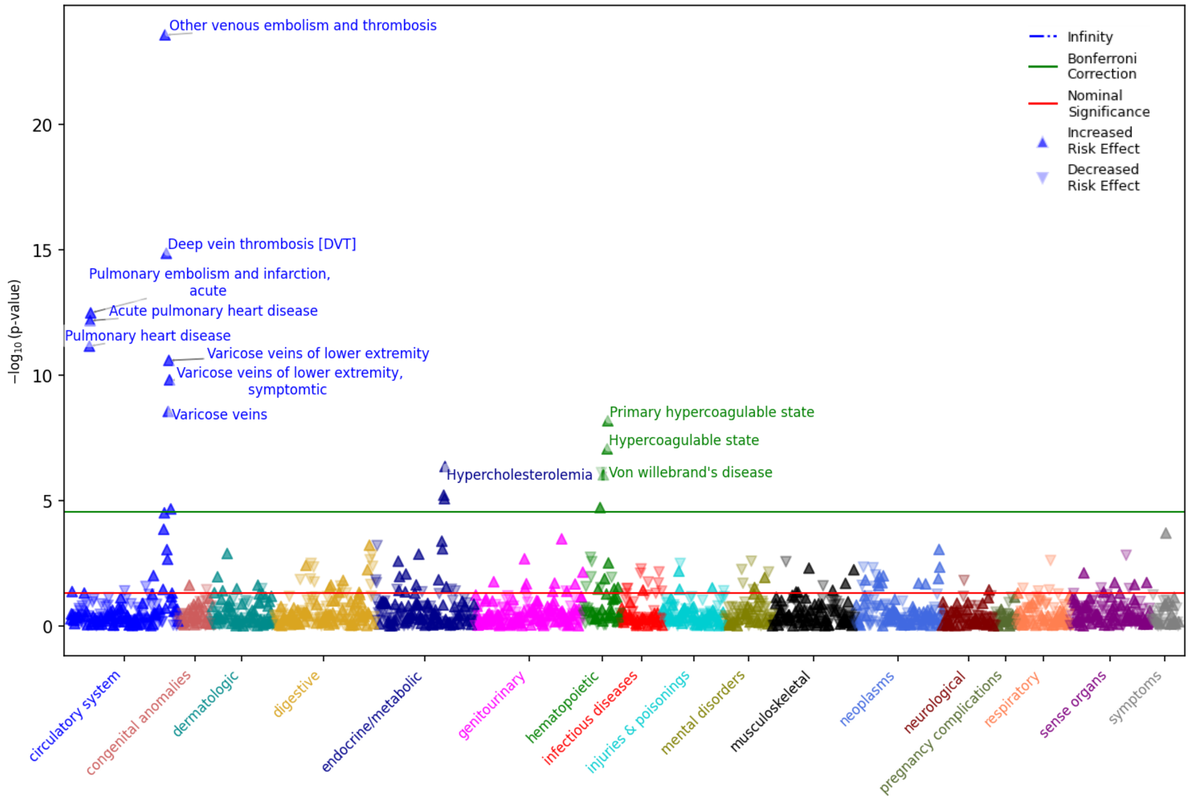
MAF 0.17

Cases: 87,205
Controls: 327,635

Most Significant Phenotypes

Other venous embolism and thrombosis:
-$\log_{10}$p-value = 23.56,
OR 1.22

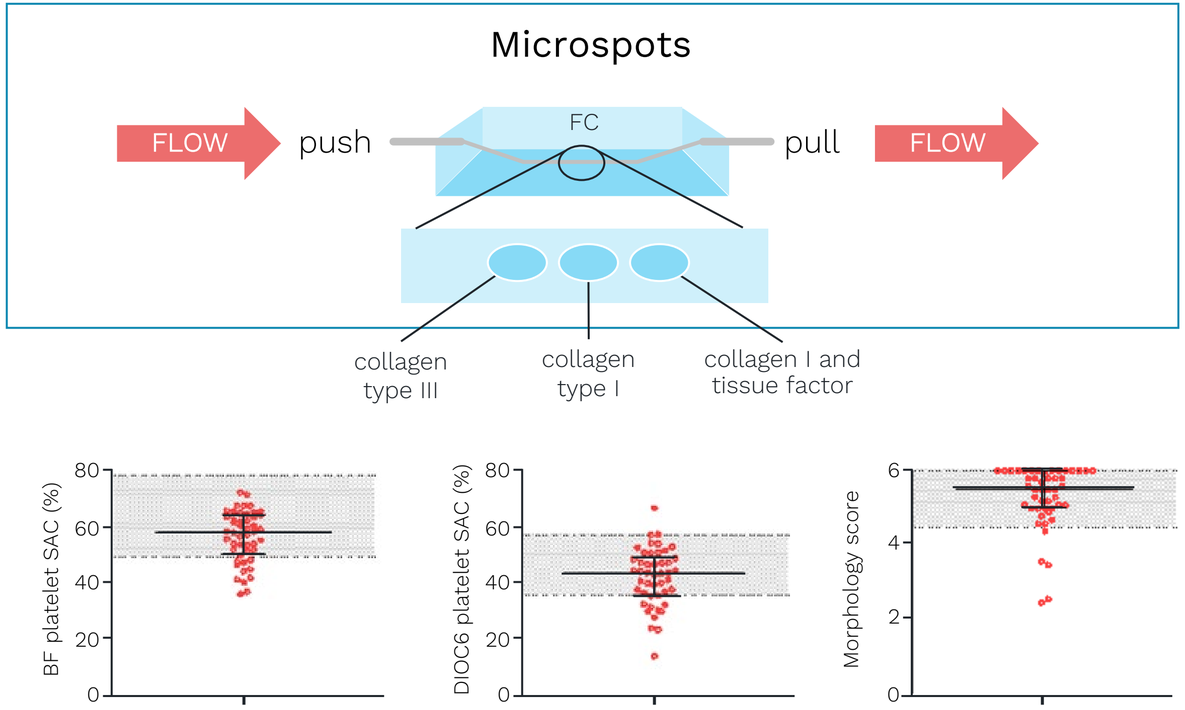
DVT:
-$\log_{10}$p-value = 14.85,
OR = 1.21



cTTP, congenital thrombotic thrombocytopenic purpura; DVT, deep vein thrombosis; PE, pulmonary embolism; PheWAS, phenome-wide association study.
Carter M. A phenome-wide association study (PHEWAS) of ADAMTS13 variants yields insight into the effect of ADAMTS13 mutations. Oral presentation S323 at EHA2025.

S317: Microfluidic testing using the Maastricht FlowChamber in patients with bleeding disorder of unknown cause (BDUC)

- **Introduction:** 40-70% of patients with a clinically relevant bleeding tendency show no abnormalities in laboratory tests (“Bleeding Disorder of Unknown Cause” (BDUC))
- Most standard tests (e.g. prothrombin time, clotting factor analysis, LTA and ATP release test, etc.) are static and plasmatic, using citrated plasma
- **Study design:** Maastricht FlowChamber better represents the *in vivo* environment by using whole blood and shear rates, and coating with collagen or tissue factor
- Patients classified as BDUC were subjected to MF testing, with 49 healthy volonteers as reference group
- **Results** (N=48, 46 female): 26/48 of patients showed one or more abnormalities in Maastricht FlowChamber testing, mostly on the collagen I spot
- **Conclusion:** These patients seem to have sheer-dependent primary hemostasis defects. There is a need for standardization & automation, integration of endothelial cells in the model



The grey areas represent the reference range. Further datapoints that were collected included platelet SAC, fibronogen SAC, PS exposure and P-selectin SAC.

LTA, Light Transmission Aggregometry; PS, phosphatidyl serine; SAC, surface area covering

Monard A, Microfluidic testing using the Maastricht flowchamber in patients with bleeding disorder of unknown cause (BDUC). Oral presentation S317 at EHA2025.

Conclusion

- 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.
- A new strategy for treating hemophilia centers on rebalancing the coagulation cascade by restoring thrombin generation, either by targeting natural anticoagulants or by mimicking the action of clotting factors.
- One example was the plasminogen (PLG) siRNA, which lowers PLG levels by 99% without impairing vessel occlusion, supporting the further evaluation of the RNAi therapeutic ALN-6400 for treating bleeding disorders (NCT06659640).
- Multiple new strategies are being developed to improve hemophilia therapy, including those that extend the half-life of FVIII/FIX, antibodies that substitute for FVIII/FIX function, and gene therapy.
- Selective targeting of coagulation protease signaling pathways, including therapeutic modulation of PAR signaling, offers a promising new strategy to treat thromboinflammatory and vascular diseases.
- PheWAS of genetic variation in *ADAMTS13*, including variant rs28446901, identified associations with increased risk of venous embolism, including DVT and PE, in the context of congenital TTP.
- Microfluidic testing using the Maastricht FlowChamber reveals shear-dependent primary hemostasis abnormalities in a substantial subset of BDUC patients, offering a promising diagnostic tool to uncover functional defects not captured by standard assays.

BDUC, bleeding disorder of unknown cause; DVT, deep vein thrombosis; EHA, European Hematology Association; FIX, factor IX; FVIII, factor VIII; PAR, protease-activated receptor; PE, pulmonary embolism; PheWAS, phenome-wide association study; PLG, plasminogen; RNAi, RNA interference; TPO-RA, thrombopoietin receptor agonist; TTP, thrombotic thrombocytopenic purpura.

07
Appendix

Abbreviations

2L	second-line
AA	aplastic anemia
AAV	adenovirus
Ab	antibody
ABE	adenine base editor
ACMG	American College of Medical Genetics and Genomics
ACR	albumin to creatinine ratio
ACS	acute chest syndrome
AECs	arterial endothelial cells
AEs	adverse events
AGM	aorta gonad mesonephros
aGvHD	acute graft-versus-host disease
AI	artificial intelligence
AML	acute myeloid leukemia
AMP	Association for Molecular Pathology
AMPATH	Academic Model Providing Access to Healthcare
ANC	absolute neutrophil count
AP2	adaptor protein complex 2
APC	activated Protein C
ARE	antioxidant response element
AT	antithrombin
ATG	anti-thymocyte globulin
ATP2B1	ATPase plasma membrane Ca2+transporting 1
BAFFR	B-cell activating factor receptor
Baso-E	basophilic erythroblasts
BFU-E	burst-forming units erythroid
BID	twice daily
BM	bone marrow
BMF	bone marrow failure
BMT	bone marrow transplant
BTK	Bruton's tyrosine kinase
C3	complement component 3
C5	complement component 5
CAAR	chimeric autoantibody receptor
CAR	chimeric antigen receptor
CARc	CXCL12 abundant LepR+ reticular cell
CAR-T	chimeric antigen receptor T-cell
CBC	complete blood count
CD	cluster of differentiation
CH	clonal hematopoiesis
CI	confidence interval
ClinGen	Clinical Genome Resource
CLP	common lymphoid progenitor
CMP	common myeloid progenitor
c-MPL	myeloproliferative leukemia virus oncogene
CNS	central nervous system
CR	complete response
CRISPR	clustered regularly interspaced short palindromic repeats
CsA	cyclosporin A
cTTP	congenital thrombotic thrombocytopenic purpura
CXCL12	CXC motif chemokine 12
DAMPs	damage-associated molecular patterns
DBA	Diamond-Blackfan anemia
dbscSNV	Database for Splice Site Single Nucleotide Variants
DDR	DNA damage response
DHS	dehydrated hereditary stomatocytosis
Dnmt3A	DNA methyltransferase
DVT	deep vein thrombosis
ECD	extracellular domain
ECM	extracellular matrix
ECs	endothelial cells
eGFR	estimated glomerular filtration rate
ELT	eltrombopag
EPO	erythropoietin
EpoR	erythropoietin receptor
ERFE	erythroferrone
EryP	erythrocytic progenitor
EVH	extravascular hemolysis
Fab	fragment antigen binding
(a)FIX	(activated) factor IX
(a)FVIII	(activated) Factor VIII
FAD	familial Alzheimer's disease
FATHMM	Functional Analysis Through Hidden Markov Models
FAZ	foveal avascular zone
FB	factor B
FD	factor D
Fe	iron
FPN	ferroportin
G	grade
GAK	cyclin G–associated kinase
G-CSF	granulocyte colony-stimulating factor
GEE	generalized estimating equations
GI	gastrointestinal
GMP	granulocyte–macrophage progenitor
GoF	gain of function
GPIbα	glycoprotein Ib alpha
GrP	granulocytic progenitor
(a)GvHD	(acute) graft versus host disease
HAMP	transcriptional activation of hepcidin
Hb	hemoglobin
HbF	fetal hemoglobin
HBG	fetal γ-globin gene
HbSS	homozygous sickle hemoglobin genotype
HC	healthy control
HCP	health-care professional
HDACs	histone deacetylases
HI-N	hematologic improvement–neutrophil
HI-P	hematologic improvement–platelet
HLA	human leukocyte antigen
hMDS	hypoplastic myelodysplastic syndrome
HR	hemoglobin response
HRQoL	health-related quality of life
HSCs	hematopoietic stem cells
HSCT	hematopoietic stem cell transplantation
HSP70	heat shock protein 70
HSPC	hematopoietic stem and progenitor cell
HU	hydroxyurea
iBMF	immune bone marrow failure
IFN-γ	interferon gamma
ILD	interstitial lung disease
IRR	infusion-related reactions
IST	immunosuppressive therapy
ISTH	International Society on Thrombosis and Haemostasis
ITP	immune thrombocytopenia
IV	intravenous
IVH	intravascular hemolysis
JAK(i)	Janus kinase (inhibitor)
KLRG1	killer cell lectin-like receptor subfamily G member 1
KO	knockout
LGL	large granular lymphocyte leukemia
LoF	loss of function
LPS	lipopolysaccharide
LTA	Light Transmission Aggregometry
LT-HSC	long-term hematopoietic stem cell
MAA	moderate aplastic anemia
mAb	monoclonal antibody
MAC	membrane attack complex
MAPK	mitogen-activated protein kinase
MAVE	major adverse vascular event
MCV	mean corpuscular volume
MDS	myelodysplastic syndromes
MDS-h	hypoplastic myelodysplastic syndromes

Abbreviations

MEP	megakaryocyte–erythrocyte progenitor
Mk	megakaryocytic
MMF	mycophenolate mofetil
MPN	myeloproliferative neoplasm
MPP	multipotent progenitors
MSC	mesenchymal stromal cell
NAK	numb-associated kinase
NHEJ	non-homologous end-joining
NIH	National Institute of Health (US)
NK	natural killer
NK cells	natural killer cells
NR	non-responder
NSAA	non-severe aplastic anemia
NTD	non-transduced
OCTA	optical coherence tomography angiography
ORR	overall response rate
Ortho-E	orthochromatic erythroblasts
OS	overall survival
PAMPs	pathogen-associated molecular patterns
PAR	protease-activated receptor
PBSC	peripheral blood stem cell
PE	pulmonary embolism
PEM	platelet-erythroid-myeloid
PEMB	platelet-erythroid-myeloid-B cell
PEMBT	platelet-erythroid-myeloid-B cell-T-cell
PF	pulmonary fibrosis
PH	pulmonary hypertension
PheWAS	phenome-wide association study
PNH	paroxysmal nocturnal hemoglobinuria
POC	point of care
PR	partial response
PRCA	pure red cell aplasia
P-restricted	platelet-restricted
PRO	patient-reported outcome
Pro-B	progenitor cell-B
Pro-DC	dendritic progenitor cell
Pro-E	proerythroblasts
Pro-NK	progenitor cell-NK
Pro-T	progenitor cell-T
PS	phosphatidyl serine
PTCy	post-transplantation cyclophosphamide
pts	patients
QoL	quality of life
R	responder
R/R	relapsed/refractory
RANKL	receptor activator of nuclear factor kappa-B ligand
RBCs	red blood cells
RBM	residual bone marrow
ROS	reactive oxygen species
rRNA	ribosomal RNA
SA	sickle cell trait
SAA	severe aplastic anemia
SAC	surface area covering
SC	subcutaneous
SCD	sickle cell disease
SCM	sickle cell maculopathy
SCR	sickle cell retinopathy
SCT	stem cell transplant
SD-OCT	optical coherence tomography
SECs	sinusoidal endothelial cells
siRNA	small interfering ribonucleic acid
SNAC	Salcaprozate sodium
SOCS	suppressor of cytokine signaling
SS	sickle cell disease
SSC	stromal stem cell
STAT	signal transducer and activator of transcription
SYK	spleen tyrosine kinase
TBD	telomere biology disorders
TBI	total body irradiation
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
Teff	effector T cell
TEMRA	terminally differentiated effector memory T cell re-expressing CD45RA
Tet2	ten-eleven translocation 2
Tf	transferrin
TFP	tissue factor pathway
TFPI	tissue factor pathway inhibitor
Tfr1	transferrin receptor
TGF-β	transforming growth factor-β
TLR	toll-like receptor
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
TPO	thrombopoietin
TPO-RA	TPO receptor agonist
Treg	regulatory T cell
VEGF	vascular endothelial growth factor
VOC	vaso-occlusive crisis
VOE	vaso-occlusive episode
VTE	venous thromboembolism
VUS	variant of uncertain significance
VWF	von Willebrand factor
WBC	white blood cell
WT	wildtype
y	years

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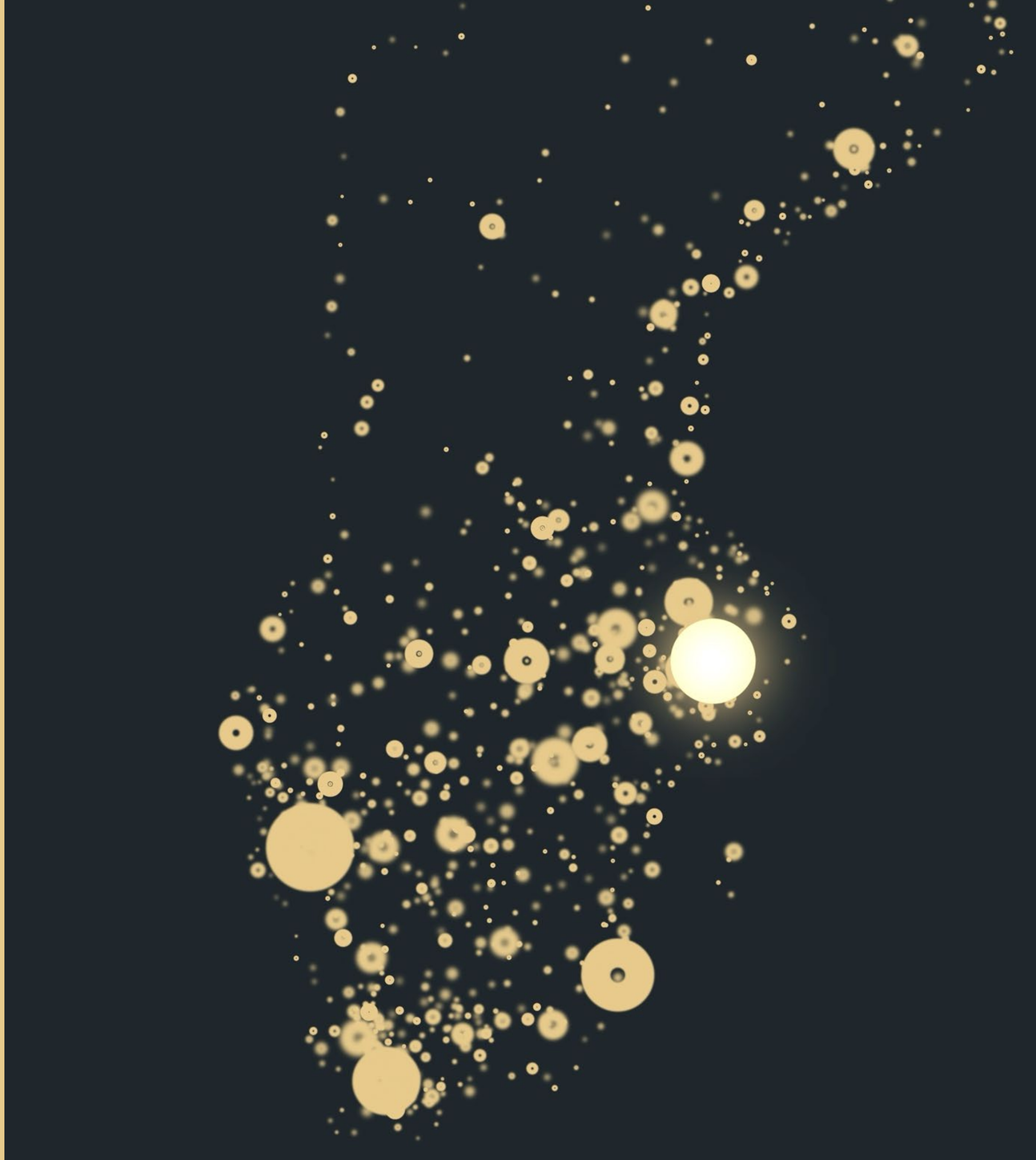

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