THE PLATELET SOCIETY

Edition 2

The Platelet Society: Journal Club

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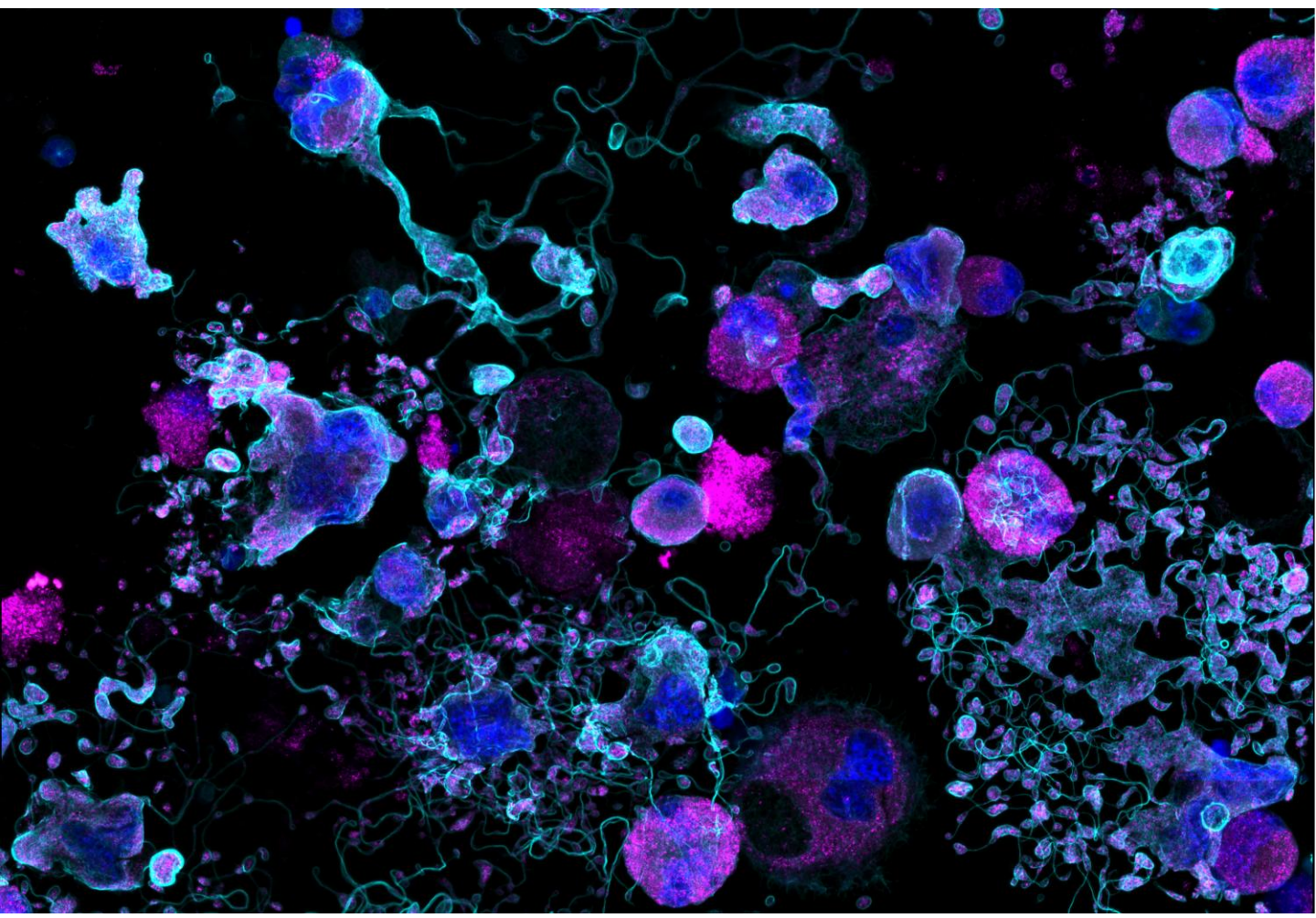

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Supporting Research and Education of Platelet Related Diseases

Papers

Chapter 10 - Platelets and Endothelium

Gasper and Paes; Endothelium and Cardiovascular Diseases (Second Edition), Vascular Biology and Clinical Syndromes, 2026, Pages 125-132.

The second edition of **Endothelium and Cardiovascular Diseases: Vascular Biology and Clinical Syndromes** offers a comprehensive overview of the endothelium's critical role in both cardiovascular and non-cardiovascular diseases. The resource incorporates recent discoveries in cellular, molecular, genetic, and epigenetic mechanisms to provide novel insights that impact pathophysiological understanding and clinical decisions. The book discusses innovations related to cardiovascular and pulmonary medicine, immunity and inflammation, genetics and epigenetics, heart failure, renal disease, familial hypercholesterolemia, diabetes, and hypertension. This work aims to detail the complex biology of the endothelium and its profound implications across systemic health and clinical syndromes.

Layilin inhibits integrin activation, and its loss results in platelet hyperactivation via Rac1 in inflammatory bowel disease

R.A. Mellema et al., Blood, *DOI:*10.1182/blood.2025028477

Layilin, a C-type lectin-like transmembrane protein, functions as an inhibitor of integrin activation on platelets. In this study the authors examined the consequences of Layilin deficiency using inflammatory bowel disease (IBD) models. Genetic or pharmacologic loss of Layilin led to markedly increased platelet activation, adhesion, and aggregation, driven by heightened Rac1-GTPase signalling. Hyperactivated platelets amplified thrombo-inflammatory responses, worsening intestinal inflammation in IBD mice. Restoring Layilin expression or blocking Rac1 normalized platelet behaviour and ameliorated disease severity. These findings identify Layilin as a novel regulator of platelet integrin pathways and suggest targeting the Layilin-Rac1 axis could mitigate platelet-mediated pathology in IBD.

Selection and Optimization Strategy for Rap1-Targeting Single Domain Antibodies as Platelet Activation markers

M. Alessi, Research and Practice in Thrombosis and Haemostasis, *DOI:*10.1016/j.rpth.2025.103294

Rap1, a small GTPase essential for αIIbβ3 integrin activation, is a promising biomarker of platelet activation. The study describes a pipeline to generate single-domain antibodies (VHHs) that specifically bind the active, GTP-loaded form of Rap1. A naïve camelid VHH library was screened by phage display against recombinant Rap1-GTP, followed by competitive ELISA to isolate clones that discriminate active versus inactive Rap1. Lead VHHs were affinity-matured through error-prone PCR and CDR-targeted mutagenesis, yielding nanobodies with sub-nanomolar KD values. The optimized VHHs labelled activated platelets in flow cytometry and microfluidic thrombus assays, demonstrating their utility as sensitive, reagent-light markers for real-time monitoring of platelet activation in vitro and ex vivo.

Platelets in angiogenesis and pulmonary progenitor cell homing under chronic intermittent hypoxia

A.D Şahin et al., Nature, *DOI:* Platelets in angiogenesis and pulmonary progenitor cell homing under chronic intermittent hypoxia | Scientific Reports

This study examines how platelets contribute to angiogenesis and the homing of pulmonary progenitor cells during chronic intermittent hypoxia (CIH), a hallmark of obstructive sleep-apnea. Using a CIH mouse model, the authors show that hypoxia-induced platelet activation leads to selective release of pro-angiogenic mediators (e.g., SDF-1α, VEGF) stored in distinct α-granule subsets, while anti-angiogenic factors are retained, thereby promoting vascular remodelling in the lung microenvironment. Released platelet factors enhance endothelial cell proliferation, tube formation, and the recruitment of bone-marrow-derived progenitor cells to damaged alveolar capillaries, facilitating tissue repair. The findings highlight platelet-driven paracrine signalling as a pivotal mechanism linking intermittent hypoxia to pulmonary angiogenesis and regeneration.

rFVIIIa–platelet Binding Enhances Platelet Procoagulant Activity Independent of Thrombin Generation

A. Strebel et al., Blood VTH, *DOI:*10.1016/j.bvth.2025.100132

The paper demonstrates that recombinant activated factor VIII (rFVIIIa) binds directly to platelet surfaces, markedly increasing platelet pro-coagulant activity without relying on thrombin generation. Using washed-platelet preparations, flow-cytometry, and confocal microscopy, the authors show that rFVIIIa associates with the αIIbβ3 integrin and is rapidly internalized, where it stabilizes phosphatidylserine exposure and augments factor Xa-mediated prothrombinase assembly. In microfluidic flow assays, rFVIIIa-treated platelets form larger, fibrin-rich thrombi under arterial shear, an effect that persists even when thrombin is pharmacologically inhibited. The findings reveal a thrombin-independent, platelet-centric mechanism by which rFVIIIa can boost hemostasis, offering potential therapeutic insight for hemophilia patients with inhibitors.

Papers

An open bone marrow megakaryocyte dataset for automated morphologic studies

Zhuang et al., Scientific Data *DOI:10.1038/s41597-025-06450-2*

In this original research article, Zhuang et al., designed and curated a dataset (termed MK-11) of Wright-Giemsa-stained images of bone marrow smears, with a focus on bone marrow megakaryocytes (MK). The data used was derived from 7204 images of 70 patient samples across a wide range of megakaryocyte associated pathologies. The data set was designed to classify and set a benchmark for future automated megakaryocyte analysis using machine learning with a key focus of defining 11 megakaryocyte subtypes found, including proplatelet forming MKs.

Platelet heterogeneity: variety makes immune and vascular function better

Malloy M., et al. Blood *DOI:10.1182/blood.2025028955*

As part of a new blood review blood series, Malloy et al., discusses platelet heterogeneity. They describe how platelets extend far beyond their classical role in haemostasis, functioning as immune and vascular regulators whose behaviour shifts with context, age, and inflammatory state. Central to this diversity are megakaryocytes, which themselves have been shown to have their own heterogeneity, influenced by spatial characteristics such as tissue origin.

Platelet factor 4 regulates hematopoietic stem cell aging

Zhang, S., et al. Blood *DOI:10.1182/blood.2024027432*

In this original research article, Zhang et al., describe the effects of platelet factor 4 (PF4) within haematopoietic stem cell (HSC) ageing. The authors show that PF4-deficient mice show similar characteristics that are associated with accelerated HSC ageing and that the administration of recombinant PF4 was able to restore old HSCs to more functionally youthful phenotypes. Further mechanistical investigation led to the identification that CXCL3 was responsible for the PF4 signalling.

Inflammatory mediators differentially regulate megakaryopoiesis and thrombopoiesis in myelofibrosis and essential thrombocythemia

Yañuk, D.B., et al. Scientific Reports *DOI:* Inflammatory mediators differentially regulate megakaryopoiesis and thrombopoiesis in myelofibrosis and essential thrombocythemia | Scientific Reports

In this original research article, Yañuk and colleagues describe how inflammatory mediators additional contribute to the development and function of the megakaryocytic lineage in myelofibrosis (MF) and essential thrombocythemia (ET). It is well known that these conditions are driven by clonal mutations in JAK2 , MPL and others, yet the authors show that a pronounced inflammatory state is also responsible for the resulting abnormalities in megakarypoiesis and thrombopoiesis in both pathologies. With this said, the authors suggest perhaps modulation of the cytokines involved may offer novel therapeutic avenues.

Microfluidic Electrochemical Biosensor for the Detection of Platelet Factor 4 Antibody-Mediated Thrombotic Disorders

D. F. Cedillo-Alcantar et al. Advanced Science *DOI:* 10.1002/advs.202513607

This study introduces a microfluidic electrochemical biosensor for the specific and sensitive detection of antibodies associated with Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), a rare, life-threatening disorder characterized by anti-Platelet Factor 4 (PF4) antibodies. The key innovation is using cross-linked PF4 (c-PF4) as a specific antigenic target to differentiate VITT/VITT-like antibodies from those causing Heparin-Induced Thrombocytopenia (HIT). The automated, microfluidic device utilizes gold nanoparticles functionalized with Pb2+ ions (IgG@Pb2+ immunoprobes) and pneumatic microvalves for precise fluid control, requiring only 15µL of serum. Testing 55 serum samples demonstrated significantly higher signals for VITT sera compared to HIT sera, achieving a signal-to-noise ratio of 8.8 after optimization. The authors envision this biosensor complementing existing clinical criteria for timely VITT diagnosis.