BRITISH SOCIETY FOR HAEMOSTASIS AND THROMBOSIS

Annual Scientific Meeting 2023

Novel therapeutics & emerging technology in haemostasis & thrombosis

Wednesday 25 – Friday 27 January

Edgbaston Park Hotel & Conference Centre, Birmingham

Plenary speaker summaries + biogs

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Plenary speaker summary and biography

Recent advances in haemophilia treatment

Professor Pratima Chowdary
London

Haemophilia therapeutic area is entering a golden phase, and for the first time, there is an active discussion about the right treatment for the right patient. We are now able to exercise a choice between reversible therapies, conventional and new and irreversible gene therapy. Clinician and patient education have become critical in negotiating the choice and challenges posed by different therapies, and active discussion is vital to excellent patient outcomes. The presentation will cover the most recent advances in the context of existing therapies.

Professor Pratima Chowdary
MD, FRCPath
Consultant Haematologist
Royal Free London NHS Foundation Trust
Katharine Dormandy Haemophilia and Thrombosis Centre
London, UK

Pratima Chowdary is Professor of Haemophilia and Haemostasis at University College London and Haemophilia Centre Director at the Katharine Dormandy Haemophilia & Thrombosis Centre at the Royal Free Hospital in London, UK.

She is also Chair of the UK Haemophilia Centre Doctors Organisation, co-director of the UK National Haemophilia Database. Her research interests lie in developing strategies for improving personalized management of haemophilia and clinical outcomes. Dr Chowdary has served as the chief investigator for a number of academic and commercial clinical trials, including gene therapy and other novel treatments for severe haemophilia.

Plenary speaker summary and biography

Microlyse – busting clots by targeting VWF

Dr Coen Maas
Utrecht, The Netherlands

Von Willebrand Factor (VWF) is a critical player in the pathogenesis of thrombotic thrombocytopenic purpura (TTP). This rare disease causes life-threatening attacks of disseminated microvascular thrombosis. In this condition, autoantibodies against ADAMTS13 limit its capacity to act as an enzymatic regulator of VWF thrombogenicity. The resulting microthrombi are poor in fibrin and rich in platelets. Previous studies by us and others pointed out that the fibrinolytic enzyme plasmin has the ability to cleave VWF, after which we found evidence for plasminogen activation in TTP patients during attacks and found that modulation of endogenous plasminogen activation influenced disease severity in preclinical disease models for TTP. We subsequently designed a fusion protein called Microlyse consisting of a high-affinity VhH targeting the CT/CK domain of VWF and the protease domain of uPA, for localized plasminogen activation on these microthrombi. This strategy leads to rapid plasmin-dependent destruction of platelet-VWF complexes *in vitro*, under flow and in a preclinical TTP disease model *in vivo*. We subsequently reasoned that this strategy may prove useful beyond TTP. In acute ischemic stroke (AIS), the clinical efficacy of rh-tPA (survival without disability) is estimated to be less than 35%. One possible explanation is "tPA-resistance": differences in thrombus architecture influence the susceptibility to this fibrin-dependent thrombolytic agent. We compared rh-tPA with Microlyse in two AIS mouse models. In a fibrin-rich AIS model, both rh-tPA and Microlyse increased cortical reperfusion and reduced cerebral lesion volume. In contrast, in a platelet-rich AIS model, only Microlyse reduced cerebral lesion volumes. Together, these findings support broad applicability of Microlyse in a variety of thrombotic conditions.

Dr Coen Maas
PhD
Associate professor
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CDL Research
Utrecht, The Netherlands

Coen Maas is Associate professor of immunothrombosis at the University Medical Center Utrecht, the Netherlands. His research bridges the fields of cardiovascular research and clinical immunology (~100 publications). This work leads from deep fundamental mechanistic studies to the development of therapeutic proteins and biomarker assays. He founded the biotech spinout companies SERPINx BV and TargED Biopharmaceuticals with patents on anti-inflammatory protease inhibitors and therapeutic agents against microvascular thrombosis.

Plenary speaker summary and biography

Low VWF – a bleeding disorder of unknown cause

Professor James O'Donnell
Dublin, Ireland

von Willebrand disease (VWD) represents the commonest inherited bleeding disorder. The majority of VWD cases are characterized by partial quantitative reductions in plasma von Willebrand factor (VWF) levels. Management of patients with mild to moderate VWF reductions in the range 30-50 IU/dL poses a common clvinical challenge. Some of these Low VWF patients present with significant bleeding problems. In particular, heavy menstrual bleeding and postpartum hemorrhage can cause significant morbidity. Conversely however, many individuals with mild plasma VWF:Ag reductions do not have any bleeding sequelae. In contrast to type 1 VWD, most patients with Low VWF do not have detectable pathogenic VWF sequence variants, and bleeding phenotype correlates poorly with residual VWF levels. These observations suggest that Low VWF is a complex disorder caused by variants in other genes beyond VWF. With respect to Low VWF pathobiology, recent studies have shown that reduced VWF biosynthesis within endothelial cells likely plays a key role. However, pathological enhanced VWF clearance from plasma has also been described in approximately 20% of Low VWF cases. For Low VWF patients who require haemostatic treatment prior to elective procedures, tranexamic acid and desmopressin have both been shown to be efficacious. In this manuscript, we review the current state of the art regarding Low VWF. In addition, we consider how Low VWF represents an entity that appears to fall between type 1 VWD on the one hand, and Bleeding Disorders of Unknown Cause on the other.

Professor James O'Donnell
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President, Haematology Association of Ireland

Professor O'Donnell received his medical degree from Trinity College Dublin. He completed haematology training in the Hammersmith and Royal Free Hospitals in London. He is a Fellow of both the Royal College of Physicians of Ireland, and the Royal College of Pathologists (UK). Prof O'Donnell is currently Professor of Vascular Biology in the Royal College of Surgeons in Ireland; Director of the Irish Centre for Vascular Biology; and a Consultant Haematologist in the National Coagulation Centre in Dublin. The Haemostasis Research laboratory led by Prof. O'Donnell has focussed on biochemistry relating to clinical bleeding and thrombosis. He has published more than 200 publications in high impact journals and received > €12M in peer-reviewed grant funding awards.

Plenary speaker summary and biography

Venous thromboembolism in cancer patients

Professor Ingrid Pabinger-Fasching
Vienna, Austria

Venous thromboembolism (VTE) is a frequent complication in cancer patients, either even before diagnosis of cancer or during the course of disease. Incidence rates vary, depending on cancer type, histological grade and stage of disease. Cancer types with the highest risk of VTE are pancreatic cancer, gastric cancer and brain cancer. Also, patient-related aspects and specific anti-cancer treatments, such as Platin-based chemotherapy or immune checkpoint inhibitors can increase the risk of VTE.

With models that include cancer-specific characteristics and biomarkers, an individual's risk of VTE during the course of disease can be predicted to a certain extent. In patients with a high risk, thromboprophylaxis either with low molecular weight heparin or with a direct oral anticoagulants has to be considered.

When patients develop a deep-vein thrombosis or pulmonary embolism, anticoagulant treatment has to be initiated. Recent interventional trials show that direct oral anticoagulants are effective and in most patients also safe with regard to bleeding. Patient with gastro-intestinal cancer have a higher risk of bleeding, so they need specific attention with regard to the choice of anticoagulant.

In conclusion, it is now possible to effectively prevent and treat VTE in cancer patients.

Professor Ingrid Pabinger-Fasching
MD
Retired Professor of Haemostaseology
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Ingrid Pabinger's scientific fields of expertise encompass hereditary and acquired bleeding disorders, including hemophilia, and thrombotic disorders. She has published more than 490 papers in peer-reviewed journals. She worked as Section or Associated Editor for several scientific journals, e.g. *Haematologica*, the *Journal of Thrombosis and Haemostasis*, *Thrombosis and Haemostasis* and *Thrombosis Research.*

Professor Pabinger has acted as principal investigator of numerous clinical studies in bleeding and thrombotic disorders as well as immune thrombocytopenia. She has been involved in several international scientific societies, including the Board of the German, Austrian and Swiss Society of Thrombosis and Haemostasis (GTH, chair) and the European Hematology Association (EHA), and committees of the American Society of Hematology (ASH). For the period 2016-2018 she was President of the International Society of Thrombosis and Hemostasis (ISTH) and from 2021 until 2023 she is Chair of the European Thrombosis and Haemostasis Alliance (ETHA). In 2022 she received the Esteemed Career award from ISTH.

Plenary speaker summary and biography

Platelet receptor clustering and signalling

Dr Natalie Poulter
Birmingham, UK

Background: Collagen-induced platelet activation is predominantly mediated by the receptor GPVI. Ligand engagement of GPVI triggers a Src-family kinase and Syk-dependent signalling cascade, resulting in formation of a LAT-based signalosome, activation of phospholipase Cγ2, intracellular calcium increase, integrin activation and platelet activation. GPVI has been shown to form dimers and higher oligomers upon activation, thereby increasing the avidity for collagen and enhancing signalling. Furthermore, GPVI can be cleaved by the metalloproteinase ADAM10, thus limiting platelet activation.

Methods: We have used a combination of advanced microscopy techniques, novel GPVI probes and Western blotting to investigate the clustering and signalling of GPVI in both spread platelets and platelets adhering and forming a thrombus under flow.

Results: In spread platelets GPVI forms large, stable clusters along collagen fibres. These clusters are signalling hot spots, colocalising with activated Syk and LAT, and are protected from shedding by ADAM10. Using a novel fluorescently labelled nanobody (Nb28) against GPVI, we have visualised these macroclusters of GPVI in platelets adhering to collagen under flow. Using different collagen-based peptides with varying platelet activation potentials, we have demonstrated a link between GPVI cluster size and platelet activation in the thrombus, measured by phosphatidylserine exposure. Nbs which block the interaction of collagen with GPVI prevent the clustering and downstream signalling of the receptor, as well as thrombus formation, providing further evidence of the importance of clustering.

Conclusion: Clustering of GPVI protects the receptor from shedding and permits sustained signalling to occur, resulting in full thrombus formation and platelet activation on highly GPVI-dependent collagen surfaces.

Dr Natalie Poulter
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Dr Natalie Poulter is an Assistant Professor in the Birmingham Platelet Group, University of Birmingham. She has an interest in platelet cell biology, with a particular focus on using advanced microscopy techniques to understand platelet activation via receptor clustering and signalling.

Plenary speaker summary and biography

New links between immunity and blood coagulation

Dr Roger Preston
Dublin, Ireland

Individuals with chronic inflammatory disease or haematological malignancies have an increased risk of venous thrombosis, although the molecular basis for this phenomenon remains poorly understood. This presentation will describe mechanisms by which inflammation impacts blood clotting, the endothelium and the innate immune system to promote thrombosis. In addition, the presentation will discuss how inflammatory events can induce long-term phenotypic changes in immune cells that lead to hypercoagulability.

Dr Roger Preston
PhD
Senior Lecturer
Royal College of Surgeons in Ireland
Irish Centre for Vascular Biology
Dublin
Ireland

Roger Preston is a Senior Lecturer at the Royal College of Surgeons in Ireland (RCSI) and Scientific Director of the Irish Centre for Vascular Biology based at RCSI. His lab studies blood coagulation and cell signalling in the context of inflammatory disease. He is an Associate Editor of 'Journal of Thrombosis and Haemostasis' and also serves on the Editorial Board of 'Seminars in Thrombosis and Haemostasis'.