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

Emerging Fellows abstracts

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Emerging Fellows abstracts

Pro-thrombotic clot phenotype – potential for novel therapeutic targets and repurposing of agents

Dr Julia Sandrin Gauer
Leeds

Abnormal fibrin clot structure is a common feature of many thrombotic conditions and contributes to a pro-thrombotic phenotype. Therefore, modulating clot structure may contribute to decreased thromboembolic events in high-risk patients. One such high-risk group are patients with diabetes, with deaths related to thrombosis accounting for up to 65% in this patient group. Increasing prevalence of diabetes and obesity highlights the critical need for novel ways to decrease and prevent thrombosis is patients with diabetes.

I demonstrated that the interaction of platelet receptor glycoprotein (GP) VI with fibrin supports thrombosis and that attenuating this interaction has an effect on clot structure. I showed that fibrin-GPVI interaction promotes the development of procoagulant platelets and that inhibition of downstream GPVI-signaling decreased procoagulant platelet number and altered clot structure. Tyrosine kinase (Btk) inhibition also demonstrated a promising effect on decreasing platelet-neutrophil aggregates. More recently, I observed that fiber density and procoagulant platelet number were increased in a hyperglycemic system. I have found that specific polyphenols (plant-derived compounds) decreased procoagulant platelet number, in normal and hyperglycemic conditions, and altered platelet bioenergetics.

In conclusion, I suggest that targeting GPVI-fibrin interaction could decrease thrombosis by ameliorating characteristics of fibrin clot that are commonly associated with a pro-thrombotic phenotype. I also suggest that repurposing of agents, such as tyrosine kinase inhibitors and polyphenols, to attenuate procoagulant platelet response could have important implications in preventative strategies.

Dr Julia Sandrin Gauer
PhD
Mautner BHF Career Development Fellow in Cardiovascular Science
University of Leeds
Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM)
Leeds

Julia obtained her PhD from the University of Leeds in 2017. She then joined the group of Prof. Robert Ariëns on a project investigating the interaction of GPVI with fibrin(ogen), in collaboration with Prof. Steve Watson. In 2021, Julia was awarded an internal Mautner BHF Career Development Fellowship to support the development of her independent research career. Julia's current research focuses on modulating fibrin clot structure and platelet procoagulant response to reduce thrombosis / thromboinflammation in patients with diabetes and cardiovascular disease.

Emerging Fellows abstracts

HaemSTAR: Empowering the next generation of clinical haematology researchers

Dr Pip Nicolson
Birmingham

Haematology Specialty Training, Audit and Research (HaemSTAR) is a UK-wide, registrar-led research network with a focus on classical haematology. It was conceived in 2017 and is supported by the National Institute for Health and Care Research (NIHR) National Specialty Group in Haematology. This talk will summarise its inception, growth, research output and future vision, with a focus on the underserved area of immune thrombocytopenia (ITP), but also incorporating other areas of classical haematology.

Dr Pip Nicolson
MA MB BChir (Cantab) MRCP (UK) FRCPath
Clinical Lecturer in Haematology
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Pip works as a clinical lecturer in the Birmingham Platelet Group and in the department of Haematology at the Queen Elizabeth Hospital, Birmingham. He chairs the UK-wide, registrar-led research network HaemSTAR and was awarded the BSH-NIHR Researcher of the year award in 2019 and the Royal College of Pathologists' Furness Prize in 2021 for his work with this group. He is a drummer and keen cyclist, regularly participating in domestic and international sportives and century rides.

Emerging Fellows abstracts

Endothelial injury in the antiphospholipid syndrome

Dr Charis Pericleous
London

Antiphospholipid syndrome (APS) predisposes patients to vascular dysfunction and recurrent thrombotic events. Endothelial injury is central to APS pathogenesis, yet our understanding of the molecular mechanisms that underpin autoimmune-mediated endothelial injury is limited and robust approaches to monitor and manage vascular dysfunction have not been identified. *In vivo* models for thrombotic APS and *in vitro* models using cultured endothelial cells treated with patient-derived autoantibodies, have demonstrated that antiphospholipid autoantibodies promote a thrombo-inflammatory and oxidative endothelial state by interfering with multiple intracellular signalling mechanisms including Akt, NFκB and p38MAPK. More recently, a role for inflammatory cytokines, particularly Type I interferons, has also been proposed. However, few of these mechanisms have been validated in patients and their identification has not led to implementation of appropriate vasculoprotective agents to mitigate endothelial injury. Our work at Imperial College London provides the first study of blood-derived endothelial colony forming cells (ECFC) from patients with APS as a novel source of patient endothelium, allowing us to confirm previously reported dysregulated biological processes and identify new processes that could be manipulated therapeutically.

Dr Charis Pericleous
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Research Fellow
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Since entering the rheumatology field as a Nuffield Foundation-Oliver Bird PhD student at University College London, Charis' work has focused on improving the management of antiphospholipid syndrome and systemic lupus erythematosus by developing better diagnostic tests and a patented novel therapeutic. For this work, Charis was awarded the annual British Society for Rheumatology Garrod Prize, presented to early career non-clinical scientists for their distinguished contribution to rheumatology research. Charis now leads a research programme at Imperial College London focused on antiphospholipid syndrome and lupus, as well as supporting studies in related autoimmune rheumatic diseases such as vasculitis. Her research aims to provide a molecular understanding of endothelial injury and dysfunction that predisposes patients with rheumatic disease to life-changing vascular events including stroke and heart attacks. Identifying how the endothelium is chronically affected by autoantibodies and other inflammatory mediators will ultimately lead to targeted treatments to redress vascular damage and improve quality of life.

Emerging Fellows abstracts

Evolving Pathophysiological and Clinical Care Considerations in iTTP

Dr Rebecca J Shaw
Liverpool

Thrombotic thrombocytopenic purpura (TTP) is a rare and potentially life-threatening condition which has a mortality of 10-20%. To improve outcomes, a better understanding of the pathophysiology and management in the acute and long-term is needed. This presentation covers both translational research as well as the 'conNeCT study', a UK multi-centre observational study investigating acute and long-term neurological complications of TTP.

Severe deficiency of the VWF-cleaving enzyme, ADAMTS13, leads to accumulation of ultra-large VWF multimers and poor outcomes in TTP are associated with widespread microthrombi and multi-organ dysfunction. Neutrophil extracellular traps (NETs) are released from activated neutrophils, in response to inflammation. NETs trap and kill bacteria, but dysregulated NETosis can induce thrombosis leading to microvascular occlusion and end-organ damage in mice models of sepsis.

We show typical NETs structures were induced when plasma from acute iTTP patients was incubated with normal healthy volunteer neutrophils. NETs formation was compared with paired plasma samples from acute and remission TTP and we observed a significant reduction in the degree of NETs formation from the acute phase of TTP when compared to remission. We also show that moderate-strong NETs formation is associated with severity of neurological injury in acute iTTP, which could possibly be explained by an increased burden of microvascular thrombi in the brain of those most severely affected.

Despite improved management and adjuvant therapies for acute TTP, over recent years, evidence has been emerging of a spectrum of long-term complications. ConNeCT is the 1st multicentre prospective UK study of neurological complications of TTP, following up complications over time from newly diagnosed patients to those diagnosed many years ago.

Dr Rebecca J Shaw
MBChB (Hons)
Haematology Registrar / Senior Clinical Research Fellow
Liverpool University Hospitals NHS Foundation Trust / University of Liverpool
Liverpool, UK

Dr Rebecca Shaw graduated from the University of Birmingham in 2011. Rebecca currently works as a Haematology specialist registrar and senior clinical research fellow with a special interest in TTP in Liverpool. Rebecca is the North-West regional lead and committee member for HaemSTAR and has been actively involved in haemostasis and thrombosis research since commencing her specialist training; she also works closely with patient support groups and pre-hospital services to promote education and training around rare haematological diseases.