Abstract:
Microangiopathic Thrombocytopenic Purpura (MAT) is a rare but often fatal collection of disorders. The disorder can be categorised by distinct disease states including haemolytic uraemic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and atypical haemolytic uraemic syndrome. Clinical presentations of MAT, however, often represent different but related aetiologies from overlapping syndromes. TTP has an incidence rate of 2-15 cases per million people-years. When left untreated, it has a mortality rate of ~90%; with treatment the mortality rate remains relatively high (~20%). Moreover, TTP patients often suffer a high rate of recurrent relapses. Aetiology, TTP is a result of insufficient cleavage of high molecular weight von Willebrand Factor multimers due to abrogated ADAMTS13 activity. Current diagnosis lacks disease fidelity and temporal resolution, making clinical management difficult. There exists, therefore, a need for a faster and standardised clinical management for TTP. The APMAT project is a retrospective study instigated to fill this information gap. The study aims to collect a total of 150 patient samples from various study centres in the Asia-Pacific (AP) region, with WACTH Murdoch University acting as a repository, co-ordinating and R&D centre. Five key outcomes of APMAT will be: 1. Develop the APMAT research network protocol, 2. Formation of an AP medical advisory panel of APMAT experts for individual clinical advice, 3. Establish a clinical adjudication committee for independent classification of MAT patients, 4. Standardise laboratory testing for ADAMTS13 and any other novel assays in the AP region, 5. Facilitate basic science and translational clinical research into MAT.

Background:

Microangiopathic Thrombocytopenia (MAT)
- Haemolytic Uremic syndrome (HUS): (thrombi is fibrin rich)
- Thrombotic Thrombocytopenia Purpura (TTP): (thrombi is platelet and VWF rich)
- Acquired TTP: ADAMTS13 activity neutralised by auto-antibody
- Thrombotic Thrombocytopenia Purpura (TTP): (thrombi is platelet and VWF rich)

Disease progression independent of ADAMTS13 activity
- ADAMTS13 and von Willebrand Factor (VWF) plays a major role in disease progression

APMAT Network Research Focus

TTP Is a Multifactored Disease:

1. Differential diagnosis between TTP and other thrombotic microangiopathies remains challenging

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<th>Disease</th>
<th>Common symptoms</th>
<th>Differential symptoms</th>
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| Haemolytic uraemic syndrome | Thrombocytopenia, hemolytic anemia with schistocytosis | Thrombotic uraemic microangiopathy (E. coli 0157:H7, Shigella dysenteria)
| HELLP syndrome | Hemolytic anemia, thrombocytopenia | Elevated liver enzymes
| Preeclampsia, eclampsia | Thrombocytopenia, proteinuria | Hypertension
| Disseminated intravascular coagulation | Thrombocytopenia | Markedly increased D-dimer
| Catastrophic antiphospholipid syndrome | Thrombocytopenia | Positive lupus-like anticoagulant antibodies
| Evans syndrome | Hemolytic anemia, thrombocytopenia | Positive Coombs test
| Heparin-induced thrombocytopenia | Thrombocytopenia | Thrombosis mainly in large arteries and veins

2. Two classes of ADAMTS13 autoantibody exist:
- Neutralising
- Non-neutralising

Aims of the study:
1. Develop the APMAT research network protocol
2. Formation of an AP medical advisory panel of APMAT experts for individual clinical advice
3. Establish a clinical adjudication committee for independent online classification of MAT patients

APMAT Network TTP Patient Sample Collection For R&D:

Applications of recombinant ADAMTS13 expressed in KM71H P. pastoris yeast:

1. ADAMTS13 auto-antibody ELISA signature
   - full length and variants
2. Proof of concept: can rADAMTS13 and variants act as a dominant negative? mapping putative dominant negative domain(s)
3. Antigen for monoclonal antibody generation

Patient Recruitment:
- Participant recruitment in the Asia-Pacific region
- The blood sample for genetic analysis and health information are given a unique patient identification number
- At Western Australia Centre for Thrombosis and Haemostasis, the original participant identification number is replaced with a new number
- The link between the original number and the new number is safely stored, and the sample may only be linked back to participants by very few designated people following strict procedures

Genetic research is performed on confidential health information