Novel ScFv antibody binding a unique epitope in Von Willebrand Factor (VWF) reducing platelet hyper-aggregation under pathological shear conditions. Potential to be a powerful anti-thrombotic agent with reduced adverse effects such as bleeding, commonly associated with clinically approved agents.

- Anti-thrombotic action with reduced bleeding risk
- Targets blood clotting in areas of high shear only and does not interfere with normal haemostasis.
- Targets a newly identified biomechanical axis of platelet aggregation

THE CHALLENGE

Bleeding complications remain a major limitation of current antiplatelet therapy and prevent the use of higher, more effective doses. As a result, the efficacy of antiplatelet drugs in preventing acute thrombotic events, although proven, has remained disappointingly low and highly variable in the individual patient. Despite primary and secondary prevention, thrombotic and embolic events such as myocardial infarction and stroke, remain leading causes of mortality and morbidity worldwide.

In the last decade, it has become clear that the magnitude of thrombosis is not solely determined by the thrombogenic state of the blood and the vessel wall, but also by the complex blood flow conditions at the site of clot formation. Arterial thrombosis distinguishes itself from normal haemostasis by the formation of large platelet thrombi that restrict the lumen of a vessel and locally dramatically increase the shear stress acting on blood components.

The Monash research team has previously made the seminal finding that rapid changes in shear, known as shear stress gradients, are strongly pro-thrombotic compared to constant shear stress, through increased activation of plasma von Willebrand Factor (VWF), the only plasma protein capable of arresting platelets at the vessel wall under high blood flow conditions.

As such, shear stress gradients are thought to be directly linked to thrombotic events.

THE TECHNOLOGY

The Monash University research team led by A/Prof Christoph Hagemeyer have identified shear-sensitive epitopes in Von Willebrand Factor responsible for binding to the platelet counter receptor, which may be targeted to block platelet hyper-aggregation caused by shear stress gradients.

The research team now has developed ScFv antibodies targeting a shear gradient-sensitive epitope in the vWF domain, and demonstrated that these antibodies can attenuate hyper aggregation of platelets under shear stress gradients, but do not affect platelet aggregation under normal constant shear conditions.

THE OPPORTUNITY

Monash is currently pursuing further antibody development, antibody binding co-crystallisation studies and will be progressing towards in vivo preclinical studies.

Monash now seeks a commercial partner to develop and translate this opportunity through further preclinical and clinical development.

References


Figure 1: Visualisation (A) and quantification (B) of platelet aggregate growth at sites of shear stress gradients or at constant shear in the presence of scFv-VWF (5 µg ml⁻¹), control scFv or the GPIb inhibitor, OS1 (0.1 µg ml⁻¹). Note the inhibitory effect of scFv-VWF at shear stress gradients (right panel) but not under constant shear. Data represented as mean ± SEM; n=3-5; * p<0.05

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