S5: Novel mechanisms regulating blood cell rheology

S5-1 Interaction of mesenchymal stem cells with platelets: aid to targeting to tissue or thrombotic risk?

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Mesenchymal stem cells (MSC) may be used therapeutically via injection into the blood, where their adhesive properties and interactions with other blood cells will influence ability to target disease. For therapy, MSC are most commonly derived from human bone marrow (BMMSC) or umbilical cord (UCMSC). When we mixed MSC with human or mouse blood in vitro, UCMSC caused a marked drop in platelet count, but BMMSC did not. When mixed with platelet-rich plasma, UCMSC caused platelet aggregation, but BMMSC did not. We next injected UCMSC into the tail veins of mice and found that platelet count decreased in the period 4-24h, and then recovered. Injection of BMMSC had no effect on circulating count. Comparing the surfaces of the MSC, we found podoplanin (a ligand which can activate platelets through its receptor CLEC-2) expressed highly on most isolates of UCMSC but not on BMMSC. Soluble CLEC-2 could inhibit platelet aggregation induced by UCMSC, while those isolates of UCMSC that lacked podoplanin failed to aggregate platelets. Platelets from mice lacking expression of CLEC-2 were not aggregated by podoplanin-positive UCMSC. When UCMSC were infused into these CLEC-2 deficient mice, there were variable responses with some mice experiencing reduction in platelet count and others not. This may reflect imperfect reduction of platelet CLEC2 in the Cre-Lox strains crossed to obtain conditional knockout, or existence of additional pathways for podoplanin to exert effects. Thus, the origins of MSC and their expression of PDPN may have impact on their behaviour in the blood. During therapy, interactions with platelets could be thrombotic, but there is also evidence that interaction with platelets can assist targeting to damaged tissue.

S5-2 Malaria and babesiosis: same rheopathobiology but different molecular mechanisms

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The pathogenesis of falciparum malaria and bovine babesiosis are remarkably similar. In both, parasite-infected red blood cells (RBCs) accumulate in the microvasculature causing vaso-occlusive clinical syndromes. Whilst the cellular and molecular mechanisms underpinning the pathogenesis of malaria have been intensely scrutinised, babesiosis has been relatively ignored; despite the fact that babesia parasites offer considerable experimental advantages to relate the function of specific parasite genes to pathological sequelae. We characterised the rheological properties of bovine RBCs infected by B. bovis (BbRBCs) and compared them with human RBCs infected with P. falciparum (PfRBCs). Like PfRBCs,

flowing BbRBCs adhere to vascular endothelial cells and form stable interactions that correlate with microvascular sequestration. Intriguingly however, high resolution imaging of BbRBCs revealed structures on their surface (that mediate adhesion) that were morphologically very different to the knob-like structures on the surface of PfRBCs that mediate their adhesion. Using multiple approaches, we have now identified numerous novel proteins at the membrane skeleton of BbRBCs which we believe will be directly involved in the formation of these unique 'ridge-like' structures and hence in pathogenesis and virulence. Linking these novel proteins with physiologically-relevant functions in BbRBCs may also identify future therapeutic strategies to combat both babesia and malaria infections.

S5-3 Form and function: erythrocyte responses to supra-physiological shears and circulatory support

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Mechanical circulatory support is essential for advanced cardiothoracic interventions; these circuits effectively perform the work of the heart and lungs during surgery. Previous generations of these circuits induced haemolysis and platelet damage, although "blood trauma" is now less common in well-functioning mechanical circulatory support. Nevertheless, close inspection of the secondary complications following chronic exposure to mechanical circulatory support indicates that microcirculatory dysfunction may be common and causal. Haemorheological assessment is now providing accumulating evidence that blood trauma should not be simply defined as overt cell destruction, but rather, include "sublethal" changes to the cells' properties and function. At the macro-level, for example, blood viscosity may decrease during surgeries that require rotary blood pumps – a potential indication of haemolysis. On the other hand, high-shear blood viscosity may increase in the absence of haemolysis, highlighting that structural changes to the erythrocyte are likely. Micro-rheological assessments may thus prove to extend our understanding of blood responses to mechanical circulatory support, and several teams have now confirmed that cellular deformability and aggregability of erythrocytes may be negatively impacted by shears previously thought to not induce blood trauma. Whether the altered function and physical properties of erythrocytes is permanent, or simply transient, following exposure to high shears is an important topic of current investigation. Moreover, how blood cells behave under physiological flow conditions following sublethal trauma is topical for exploring clinical outcomes. It appears that sublethal trauma may still be common in mechanical circulatory support, and likely involves both physical and biochemical mediation.

S5-4 Blood rheology, arterial stiffness, and clinical complications in diabetic patients with and without sickle-cell trait.

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Rates of Type 2 diabetes (T2D) are rapidly increasing in sub-Saharan Africa, a region where sickle-cell trait (SCT) is prevalent. T2D is characterized by vascular dysfunction and an increased risk of vascular complications. Although SCT has historically been considered to be a benign condition, recent research has revealed that vascular function is more severely impaired in patients with both T2D and SCT than in those with T2D only. However, the consequences of this exaggerated vascular dysfunction have yet to be fully elucidated. Therefore, the primary objective of this study was to determine whether patients with both SCT and T2D are more likely to suffer from vascular complications than those with T2D only. The present study, conducted in 176 Senegalese individuals, compared blood viscosity, Advanced Glycation End-products (AGEs), arterial stiffness and rates of vascular complications in control subjects (CONT), subjects with T2D or SCT and subjects with both T2D and SCT (T2D-SCT).

Blood viscosity was higher in the SCT, T2D and SCT-T2D groups compared to the CONT group, and was higher in the SCT-T2D group than in all of the other groups. AGEs were elevated in the T2D and T2D-SCT groups compared to the CONT group. Carotid-femoral pulse wave velocity measurements revealed increased arterial stiffness in the SCT-T2D group compared to all other groups. Rates of hypertension, retinopathy and renal insufficiency were higher in the SCT-T2D group than in the other three groups.

We observed a higher prevalence of vascular complications, increased blood viscosity and elevated arterial stiffness in individuals with both T2D and SCT, compared to those with T2D only. Our results suggest that SCT could increase the risk of developing vascular complications in individuals with T2D.

S5-5 The importance of hemorheology in the design of continuous flow left ventricular assist devices

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Heart failure remains an epidemic of the 21st century; more than 38 million individuals are affected Worldwide and 500,000 new cases are diagnosed annually. An increasing number of patients with end stage disease (Stage D) are supported with a continuous flow left ventricular assist device (LVAD) as the number of hearts available for transplantation is limited. Better understanding and computer modeling of fluid dynamics over the past decades revolutionized axial flow and centrifugal LVAD design, including the development of smaller and increasingly hemocompatible pumps capable of providing circulatory support up to 10 liters

per minute. The mechanically suspended or magnetically levitated impeller rotates at high speeds (2,300 RPM – 12,000 RPM) exposing the blood to extreme shear forces often leading to hemolysis, pump thrombosis and embolic complications. The importance of various hemorheological factors in the design of contemporary LVAD devices and their clinical relevance will be reviewed in this presentation.