Final report for The Butterfly AVM Charity

THE ROYAL FREE LONDON AND UNIVERSITY COLLEGE LONDON ARTERIOVENOUS MALFORMATION RESEARCH PROGRAMME: VASCULAR BIOLOGY WORK

BACKGROUND

Arteriovenous malformations (AVMs) are rare vascular lesions caused by abnormal connections between arteries and veins. AVMs affect all age groups and can occur anywhere in the body with over half of the cases involving the head and neck. Patients with AVMs suffer from various symptoms, including disfiguration, pain, life-threatening bleeding, and organ failure. Clinical diagnosis, monitoring, and management of patients with AVMs remains suboptimal. This is due to our very poor understanding of the disease mechanism. However, with generous funding from the Butterfly AVM charity, we have made great strides!

RECENT FINDINGS

We have identified bone morphogenetic protein 9 (BMP9) as a potential serum biomarker that could be utilised in the diagnosis of AVMs, differentiating them from other vascular malformations (including venous and lymphatic). As shown in **Figure 1**, we found markedly lower levels of BMP9 in the blood of patients with AVMs (high-flow VMs) compared to healthy subjects and patients with low-flow VMs (venous and lymphatic VMs). BMP9 is known to maintain endothelial cells in a quiescent (calm) state. However, in AVMs, we believe that the reduced BMP9 levels lead to the activation of endothelial cells, resulting in increased leakiness, proliferation and vessel sprouting. Therefore, not only has BMP9 revealed itself to be a useful diagnostic biomarker but its reduced levels have provided insight into the disease mechanisms of AVMs.

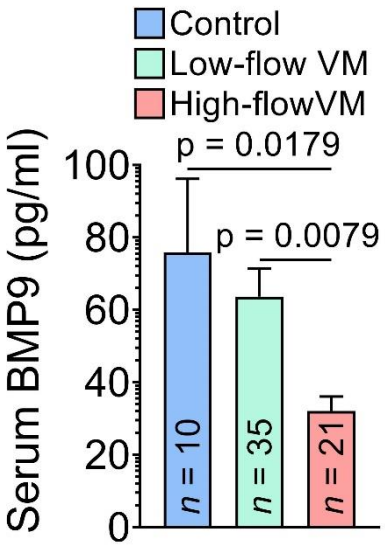

Figure 1: Serum BMP9 levels are markedly lower in patients with high-flow VMs (AVMs).

Secondly, we have identified epigenetic changes in endothelial cells derived from VM lesions that underlie their activated state (**Figure 2**). These changes can be attenuated using small-molecule inhibitors to normalise the endothelium and potentially reduce the pathological sprouting and inflammation that are seen in AVM lesions.

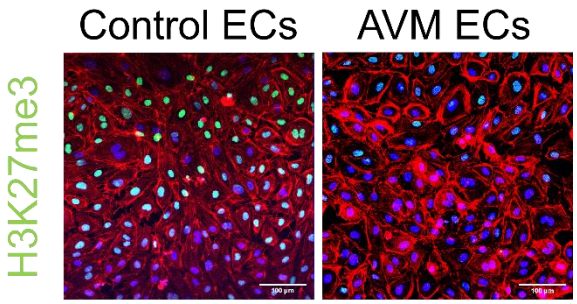

Figure 2: Epigenetic H3K27 demethylation is enhanced in AVM ECs.

SUMMARY

We are excited about these two potentially important recent findings from our research: BMP9 may have potential as a biomarker for AVM both of value in diagnosis and monitoring of successful treatment whilst targeting specific gene expression changes that cause increased endothelial cell activity may be useful in the treatment of AVMs.

OTHER NEWS AND UPDATES

Our group had a strong presence at the Basic Vascular Science meeting in Leiden, the Netherlands in October 2022 with Dr Abu-Hanna presenting a poster on diagnostic biomarkers for vascular malformations and Mr Calver Pang presenting a poster on histopathological analysis of vascular anomalies. Work in both these areas are now being submitted for publication.

Our MSc student, Omar Hamza, has successfully completed his project on thromboinflammation in vascular malformations, receiving a high Merit. We congratulate Omar on his achievement and wish him the best of luck with his future endeavours.

We have submitted an application to Medical Research Council (MRC) to hopefully obtain further funding for research into the pathogenesis and treatment of vascular malformations.

Finally, Dr Jeries Abu-Hanna has recently left the group and joined the University of Oxford as a postdoctoral researcher to investigate the role of the endothelium in regulating bleeding and clotting in patients with traumatic injuries. We thank him for all his hard work and enthusiasm and wish him the very best. He remains active in our AVM research programme and we hope he will return with new ideas and skills to take AVM research further in the near future.

We highly appreciate the Butterfly AVM Charity's support without which we could not have started this research programme.