Background: A critical limitation of current antiplatelet therapies is their inability to separate a reduction in thrombotic events from an increase in bleeding occurrences. Vaccinia H1-related (VHR) phosphatase is a dual-specific protein phosphatase, the physiological role of which is not known. We used genetic manipulations to generate mice lacking VHR and found that this phosphatase plays a critical role in platelet function and in arterial thrombosis.

Aims: The goal of this project is to investigate the role of VHR in thrombosis and hemostasis, using transgenic mouse model, with a specific focus on deciphering the function of this phosphatase in platelet biology and GPVI signaling pathways.

Methods: VHR deficient mice were generated by homologous recombination. Platelet adhesion, aggregation and secretion assays were performed using VHR deficient and wild type platelets. Intracellular calcium fluxes were studied in fura-2 loaded platelets. Aggregate formation on collagen surface was analyzed under flow conditions. Arterial thrombosis was assessed in a model of pulmonary embolism and upon ferric chloride induced carotid artery injury. Tail bleeding times were measured.

Results: VHR-deficient platelets display impaired collagen-related peptide (CRP) and collagen-induced aggregation and granule secretion compared to platelets from wild-type mice. However, Thrombin- and ADP-induced platelet aggregations were not affected by VHR deficiency. Consistently, aggregate formation and phosphatidylserine exposure of VHR-deficient platelets on collagen under flow was reduced. In addition, VHR-deficient mice were more resistant to collagen- and epinephrine-induced thromboembolism, compared to wild-type mice, and showed impaired thrombus formation upon carotid artery injury. Intriguingly, VHR deficiency did not affect bleeding times compared to wild-type mice. At the molecular levels, we found that VHR deficiency leads to a decrease of Src family kinase activatory phosphorylation upon GPVI triggering with CRP. In addition, convulxin-induced Ca^{2+} flux was greatly reduced (50%) in VHR-deficient platelets compared to wild-type platelets.

Conclusions: All together, our data suggest that VHR plays a selective and essential role in collagen-induced platelet activation and in arterial thrombus formation *in vivo*. Given that VHR-deficient mice remain healthy and do not exhibit any spontaneous phenotype, inhibition of VHR may prove effective as an alternative and safe antiplatelet strategy in the treatment of arterial thrombosis.