Angiogenesis is regulated by complex interplay of a number of angiogenic growth factors, including members of the TGFbeta family. Endoglin and ALK1 are endothelial receptors of this family and regulate endothelial cell proliferation, migration and apoptosis. Patients with mutations in Endoglin or ALK1 suffer localised vascular abnormalities leading to large arteriovenous malformations (AVMs) in major organs such as the brain or lung, as well as to smaller telangiectases, which may bleed extensive-ly and give rise to the name of this genetic disorder, hereditary haemorrhagic telangiectasia (HHT).

To investigate the abnormalities that occur during HHT, we used an endothelial specific and tamoxifen-activated Cre line (Cdh5-Cre$^{ERT2}$) to allow endothelial cell-specific inactivation of floxed Endoglin or floxed Alk1 genes during development of the neonatal retinal plexus, a well established model of angiogenesis.

Endothelial specific loss of Endoglin or Alk1 leads to abnormal AVMs showing increased endothelial cell proliferation, and venous identity. Alk1 deficiency caused neonatal lethality within 48 hours, whereas Endoglin deficient mice remain viable. Differences in vascular plexus remodelling, branching and artery/venous identity between the two models, indicated that the pathogenetic mechanisms underlying the development of AVMs in HHT1 (endoglin deficient) and HHT2 (ALK1 deficient) might be different. Preliminary analysis of anomalous molecular responses downstream implicates defects in both canonical and non-canonical TGFbeta signalling pathways in HHT pathogenesis.