Blood vessel patterning involves iterations of sprout initiation, elongation, anastomosis, lumen formation and stabilization. Endothelial cells concurrently migrate, divide, select dynamic phenotypes and rearrange positions in a coordinated manner to allow organized branching morphogenesis. How exactly the cells orchestrate their behaviour remains poorly understood. Recent work identified a regulatory network of VEGF-VEGFR andDll4/Notch signalling as a key mechanism of pattern generation. We developed clonal mosaic analysis in embryoid body sprouting assays to investigate how differential levels of VEGF receptors impact on formation of endothelial tip and stalk cells in the context of Dll4/Notch signalling. Dynamic imaging illustrated a surprising degree of cell rearrangements and constant competition between cells for the leading tip cell position. Cells with higher levels of the signalling receptor VEGFR2 and lower levels of the decoy receptor VEGFR1 effectively outcompete neighbouring cells thanks to their ability to produce moreDll4. Competition and cooperation via VEGFR levels appears ideally suited to facilitate collective guidance of the nascent sprout towards VEGF-A sources. We further developed an interdisciplinary approach utilising the capabilities of computer simulation in iteration with experimentation to help us advance our understanding of the temporal and spatial control of cell behaviour, and how the timing of cell behaviour and gene regulation might explain the function of the angiogenic branching “pattern generator”.

Systems behaviour insight now provides first predictions for a mechanism of pathological angiogenesis, and possibly for organ specific branching adaptations.