Abstract:
The blood-brain barrier (BBB) maintains a tightly controlled homeostatic environment in the brain that is required for proper neuronal function. The BBB is created by the unique properties of the brain vasculature, including specialized tight junction complexes and reduced transcytosis. Interestingly, these uniquely restrictive properties are not intrinsic to brain vessels, but rather are induced embryonically and actively maintained thereafter by signals from the brain microenvironment. However, what these signals are, which cells produce them, and whether these interactions change throughout life remain poorly understood. To investigate these questions, I turned to zebrafish, which allow me to study and perturb the BBB in vivo. Using a combination of functional tracer leakage assays, confocal and electron microscopy and genetic mutagenesis, I revealed that the zebrafish BBB becomes functionally sealed by 5 days post fertilization (dpf) via the suppression of vesicular trafficking rather than through tight junction function. During these developmental studies, I also identified a novel secreted neuronal signal, Spock1, that specifically and regionally induces barrier properties by controlling the extracellular matrix. And while Spock1 plays a conserved role in inducing BBB properties developmentally in both mouse and zebrafish, adult knock out mice have a completely functional BBB but fish remain leaky, revealing some species-specific differences in the BBB that we are currently exploring in the O'Brown lab.