

Our lab develops and uses advanced optical techniques to observe and manipulate in vivo biological systems, with the goal of constructing a microscopic-scale understanding of normal and disease-state physiological processes in the central nervous system. In this talk, I will discuss recent work on unraveling the pathways by which cortical microvascular dysfunction interacts with and exacerbates Alzheimer's disease. Brain blood flow is decreased by ~30% in both human patients and animal models of Alzheimer's disease (AD), but the physiological explanation of this phenomenon remains unclear. Using high-resolution in vivo imaging of blood flow in mouse models of Alzheimer's disease, we have identified plugged capillary segments as a cellular mechanism that contributes to this blood flow decrease. In AD mice, about 2% of capillaries have stalled blood flow due to an adhered leukocyte, while wild type mice have five times fewer stalled capillaries. Because a single stalled capillary decreases blood flow in many downstream branches of the vasculature, having even 2% of capillaries stalled could result in substantially reduced blood flow. When we administered a drug that blocks leukocyte adhesion, we observed a ~60% reduction in the number of stalled capillaries that was accompanied by a ~30% increase in brain blood flow in penetrating arterioles. This brain blood flow increase led to an immediate improvement in cognitive performance of the animals, while a month of treatment led to a decrease in the concentration of some species of amyloid-beta, the protein that aggregates to cause AD, in the brain. Therapies that interfere with capillary plugging could complement existing therapies aimed at reducing amyloid. I will also talk about recent efforts to extend our the capability to study cellular dynamics to the spinal cord, where we have explored the heterogeneity of axon dieback after spinal cord injury and are developing the capability to image neural activity.