Exploring microglial function in the healthy and diseased brain
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As the resident immune cells of the central nervous system, microglia compose 10% of all cells in the brain. Following infection or neuronal insult, microglia migrate to the site of injury, become activated, and secrete pro-inflammatory molecules, in concert with morphological changes. Microglial activation is thought to account for the prolonged and unresolved inflammation observed following traumatic brain injuries, as well as in neurodegenerative diseases such as Alzheimer's, and to contribute to the disease pathogenesis in ways that impair recovery.

The colony stimulating factor-1 receptor (CSF1R) is a key regulator of myeloid-lineage cells and is only expressed by microglia in the brain. We have recently found that microglia are dependent upon CSF1R signaling for their survival and that we can take advantage of this dependency through administration of CSF1R inhibitors. Dietary treatment with CSF1R antagonists (such as PLX3397, Plexxikon Inc.) results in >90% of brain-wide microglia loss within 7 days, allowing us to explore the role of these cells in both the healthy and diseased brain. We can keep microglia eliminated for as long as we wish, through continued treatment with CSF1R inhibitors.

The importance of microglia in Alzheimer's disease has been highlighted by GWAS, which have identified a number of single nucleotide polymorphisms (SNPs) associated with risk for the development of Alzheimer's disease that are associated with microglia function, including TREM2, CD33, BIN1, and CR1. Thus, understanding the various roles that microglia play in the healthy and Alzheimer’s disease brain are crucial in order to determine how these polymorphisms affect microglial function. Using CSF1R inhibitors we have eliminated microglia from the brains of AD transgenic mice, in order to elucidate the various roles that they play in disease pathogenesis.