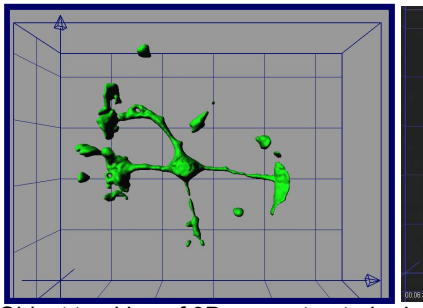
Neuroinflammation controls microglial expression of cell surface receptors



Object tracking of 3D-reconstructed primary microglia (left) allows studying of microglial process and cell body motility. Some of the measured parameters include object displacement and instantaneous velocity independent of vector displacement. The red “tracks” in the image on the right show changes in process position over time.

Work over the past decade has lead to an increased appreciation of the role of neuroinflammation in many neurodegenerative diseases. Activated microglia in injured and dying tissue are now thought to actively exacerbate the injury. While it is well-known that resting microglia are attracted towards ATP released from dying neurons, we have recently discovered that microglia that are "activated" in the context of neuroinflammation migrate away from ATP *in vitro* and *in vivo*. This is accompanied by a reversal of ATP-induced microglial process extension to process retraction. These effects are mediated through ATP breakdown to adenosine and activation of adenosine A2A receptors, which are selectively upregulated in activated microglia. This differential receptor expression in resting and activated microglia suggests that modulation of cell surface receptor signaling might provide a therapeutic target that could minimize some of the harmful actions of microglia in situations of chronic neuroinflammation. We employ various imaging modalities, biochemical assays and pharmacologic interventions to study the contribution of microglial receptors (such as A2A, PAR1) to the control of microglial functions, including proliferation, motility, phagocytosis, and cytokine secretion. We study activated microglia at the level of isolated primary cells, brain slices and in live animals to understand their role in neurodegeneration. Our long term goal is to identify cell surface receptors that could serve as new targets for the development of compounds that minimize the contribution of microglia to neurodegeneration.