A seminar on:
Astrocyte signaling regulates oligodendrocyte regeneration and remyelination in the CNS

Reactive astrogliosis is the cellular and biochemical transformation of astrocytes in response to brain injury, and significantly impacts – both positively and negatively – neural regeneration. Reactive astrogliosis was once thought to be an all-or-nothing transformation, but emerging evidence suggests that reactive astrocytes (RAs) are highly dynamic and tailor their transcriptional response to the type of injury and the region in which it occurs. This response includes production of growth factors, cytokines, and other intercellular signaling molecules that influence the ability of progenitor cell populations to repair damaged tissue. Therefore, it is essential to understand how specific signals produced by RAs impact neural regeneration, so that we can develop targeted approaches to enhance the beneficial aspects of the astrocyte response while preventing the deleterious ones.

Multiple Sclerosis is a disease characterized by oligodendrocyte (OL) death, focal demyelinated central nervous system (CNS) lesions and extensive RA scar formation. In response to demyelination, oligodendrocyte progenitor cells (OPCs) can replace lost OLs by maturing into new myelin-producing cells in a process called remyelination. However, stalled OPC differentiation is frequently found in patients with progressive MS, possibly due to the aberrant expression of signals within the demyelinated lesions. These signals could derive - in part - from permanent astrocytic scars that are common in MS brain tissue.

Our lab has identified a secreted intercellular signaling molecule, called endothelin-1 (ET-1), which is expressed at high levels by RAs in MS lesions and limits repair by delaying oligodendrocyte progenitor cell (OPC) maturation. While ET-1 has been well characterized for its role as a secreted signaling peptide in the cardiovascular system, its role in the normal and pathological brain is not well defined. I will discuss our recent gain- and loss-of-function studies that demonstrate that ET-1 acts as an astrocyte-OPC signal that inhibits OL maturation and remyelination after demyelination. I will also describe pharmacological and genetic evidence in vivo demonstrating that RAs are key intermediary cells that modulate OPC differentiation in response to demyelinating injury through a specific ET-1 receptor subtype. Our results reveal that targeting specific pathways in RAs following injury represents a promising therapeutic target in diseases with extensive reactive astrogliosis, including MS.