Neuroscience Graduate Program

presents:

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In a Thesis Proposal

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2:00pm in Auditorium K-307 (3-6408)

Human herpesvirus 6 latency gene product alters critical oligodendrocyte precursor cell functions: Implications for demyelinating disease

Repair of central nervous system (CNS) white matter by oligodendrocyte precursor cells (OPCs) is often inefficient in combating continued degeneration and progression of neurological symptoms in demyelinating disease. Although the factors that inhibit successful remyelination have not been fully described, it is understood that the migration and differentiation of OPCs adjacent to white matter lesions is often impaired. Our lab has thus sought to investigate endogenous obstacles to these specific OPC functions. Prompted by the clinical association between demyelinating disease and the presence of human herpesvirus 6A (HHV-6A), we have investigated a link between HHV-6A and OPC function to identify the neurotropic virus as a potential obstacle to remyelination. Although originally believed to be benign in its latent state, preliminary data now suggests that the HHV-6A latency transcript U94A can inhibit migration and differentiation of OPCs *in vitro*. Additional experiments suggest that U94A expression decreases protein levels of the αv integrin subunit, a critical component in signaling cascades mediating OPC migration, differentiation and CNS remyelination. Based on these initial findings, I hypothesize that latent CNS infection with HHV-6A may contribute to the inefficient remyelination phenotype seen in demyelinating disease by altering integrin signaling cascades controlling OPC migration and differentiation. I propose a series of experiments to further characterize the effects of latent HHV-6 infection on αv integrin signaling *in vitro*. I will also develop a murine model of conditional U94A expression in OPCs as a tool to evaluate effects of the U94A gene product on oligodendrocyte maturation and myelin sheath formation following cuprizone-induced demyelination *in vivo*. These experiments aim to test the specific hypotheses that 1) U94A expression alters the dynamics of αv integrin-mediated signaling cascades necessary for efficient OPC migration and differentiation and 2) conditional U94A expression in the oligodendroglial lineage inhibits efficient white matter repair following cuprizone-induced demyelination. Successful completion of these aims will illustrate the mechanism by which the U94A gene product influences critical OPC functions to inhibit successful recovery in patients with demyelinating disease.