Confidential
Personal Statement

My laboratory is focused on understanding the pathogenic mechanism of Huntington’s disease (HD). HD is a dominantly inherited neurodegenerative disorder that affects approximately 1 in 10,000 people in the United States. In the most common form of the disease, onset of involuntary movements, cognitive deficits, and dementia occurs between the ages of 30 and 50. There is no known effective therapy, and disease progression over a 10-20 year period ends inevitably in death. HD belongs to a class of neurodegenerative diseases that include the spinocerebellar ataxias (1, 2, 3, 6, 7, 17), Jentatorubral and pallidoluyarian atrophy (DRPLA), and spinal and bulbar muscular atrophy (SBMA or Kennedy’s disease). All of these diseases are caused by the expansion of an unstable stretch of CAG triple repeats (encoding polyglutamine stretches) within each disease gene. Although neuronal loss is selective and specific for each of the polyglutamine disorders, the inverse correlation of time of onset with triplet repeat length, the relatively slow progression of these diseases, and the appearance of both nuclear and cytoplasmic aggregates within brain neurons, suggests a common pathological mechanism.

Although the gene mutation responsible for HD was discovered over a decade ago, many basic questions regarding the mechanism of pathogenesis remain unanswered. What determines the specificity of neuronal death in HD? What is the relationship of the normal function of the protein encoded by the HD gene, huntingtin, with the postulated gain-of-function (dominant nature) conferred by the mutation? Does a dominant-negative mechanism (resulting in loss of normal huntingtin function) contribute to disease phenotypes in the brain? My laboratory’s current research is aimed at answering these questions using the mouse as a model system.

Erin Clabough, my most senior graduate student, has been studying the function of the normal stretch of polyglutamine within the mouse huntingtin gene. She has developed a mouse model that expresses a version of huntingtin lacking precisely the polyglutamine stretch (ΔQ-huntingtin). Although this project was designed initially as a means to understand the role of different huntingtin protein domains in normal huntingtin function, the phenotypes of Erin’s ΔQ mice have provided some intriguing leads into a potential therapy for HD. Mice expressing two copies of the huntingtin gene lacking the polyglutamine stretch exhibit improved motor coordination relative to wild-type controls. Interestingly, ΔQ-huntingtin fibroblasts have a higher concentration of ATP than do the corresponding controls. We have interpreted this data to suggest that the polyglutamine stretch modulates a normal function for huntingtin in regulating cellular energy metabolism. A manuscript describing this phenotype is being prepared for submission this fall. Interestingly, when the ΔQ mutation is crossed with our HD knock-in mouse model expressing an allele of huntingtin with a stretch of 140 glutamines (140Q, a polyglutamine length that causes early-onset HD in humans), ΔQ-huntingtin is able to alleviate behavioral and motor phenotypes exhibited in a mouse expressing one copy of 140Q-huntingtin gene. Rescue of our model HD phenotypes is seen in both a motor coordination test (rotorod), and in a spatial learning task. Erin will present these results at the 2005 Society for Neuroscience Meeting in November, and a manuscript describing this work is in preparation, also for submission this fall. Future work will focus on developing ΔQ-huntingtin as a potential therapy by first determining if our mouse models can also rescue phenotypes in HD mouse models expressing elevated levels of mutant huntingtin, and second, by developing our own transgenic mouse model expressing an elevated level of ΔQ-huntingtin. Characterization of these models should provide a proof of principle to determine the feasibility of developing a gene therapy viral vector expressing ΔQ-huntingtin for preclinical trials in HD mouse models.
My second-year graduate student, Michelle Neveklovska, is developing a mouse model system, in collaboration with Dr. Jim Mandell in the Department of Neuropathology, to study the function of huntingtin in glial cells. Although most HD research has focused on the neuron, glial cells play an important support role in the adult brain. Based on our earlier observations that huntingtin plays a similar support role in extraembryonic tissues during mouse development, we hypothesize that loss of a huntingtin support function in glia (via a dominant-negative loss-of-function mechanism) could contribute to HD pathogenesis. Using an inducible conditional knock-out system that is targeted to glial cells, Michelle is now at the stage of characterizing the efficiency of huntingtin-loss in the glia of her model mice. Eventually, her conditional glial cell knock-out model mice will also be crossed with our HD model knock-in mice in order to assess the consequence of eliminating huntingtin expression in glial cells on the HD mutant phenotype.

In parallel with the projects of my graduate students, my technician, Nima Ghitani, is studying the phenotype of mice that lack huntingtin expression throughout the central nervous system. This project extends our earlier work performed with forebrain-specific loss of function mouse mutants, and is aimed at comparing loss-of-function phenotypes with the phenotypes observed in our knock-in HD mouse model. Neuronal degeneration in the thalamus and hypothalamus is emerging as a common feature of both kinds of models. Interestingly, although the striatum is affected most in HD patients, degeneration in both the thalamus and hypothalamus is also observed consistently.

My laboratory has also developed recently mouse models expressing epitope tags at the amino-terminus of both normal and mutant huntingtin. A former technician, Jessica Blackburn (now a graduate student at Dartmouth), assisted in the development of these mice (first reported at a triplet repeat disease meeting sponsored by the Hereditary Disease Foundation in 2004), and a 2005 Summer Research Internship Program student, Jasmine Pettiford, has performed experiments with these mice aimed at the characterization of potential interactions occurring between normal and mutant huntingtin. Although my main interest in these models is to determine if mutant huntingtin can exert a dominant negative effect on normal huntingtin via abnormal sequestration via the polyglutamine stretch, the models can also be used to explore alternative hypotheses in HD pathogenesis, such as the role of huntingtin proteolytic processing. Recently, we initiated a collaboration with Dr. Marian DiFiglia at the Massachusetts General Hospital in order to characterize amino-terminal proteolytic products of epitope-tagged huntingtin in our new mouse models.

My collaborations with Drs. Jeff Corwin and Heidi Scrable in the Department of Neuroscience are also ongoing. Both of these projects utilize embryonic stem cell technology as a tool to (1) develop a method of in vitro differentiation of stem cells into functional sensory hair cells (Dr. Corwin, PI), and (2) develop the lac operon conditional expression system as a tool to regulate endogenous gene expression in the mouse, and in a separate project, explore p53 function in HD (Dr. Scrable, PI). These projects are exciting, enjoyable, and I believe their development was a testimony to the collaborative research culture that is fostered at the University of Virginia. Finally, I wish to express gratitude to all the other members of the medical and research community at the University of Virginia that are dedicated to treating and understanding the causes of neurodegenerative disease— they have created an environment here that is collegial, supportive, and stimulating. Ultimately, my goal is to develop an effective therapy for HD. To accomplish this goal will require a lot of hard work, and a little luck, but with the help of my colleagues here at the University of Virginia, the process is bound to be a fascinating and rewarding journey.