Our group studies the post-translational modification of Huntingtin (HTT), the protein mutated by polyglutamine (polyQ) expansion in the neurodegenerative disorder Huntington’s Disease (HD). We were the first to report that the normal function of HTT appears to include serving as a scaffold for selective autophagy, and suggest that this function may be regulated by HTT phosphorylation by the kinase IKKβ [1, 2]. We found that HTT is directly phosphorylated on serine (S) 13 by IKKβ increasing S16 phosphorylation and regulating degradation of HTT by the lysosome in cells [3]. HTT polyQ expansion reduces levels of this S13/S16 phosphorylation, while mimicking this phosphorylation in the context of full length mutant HTT in mice blocks HD pathogenesis [4]. We are currently investigating whether IKKβ is protective in vivo early in HD progression through phosphorylation of HTT to potentially activate HTT’s autophagic scaffold function thereby increasing HTT clearance. We are also evaluating the effect of IKKβ in the regulation of autophagy gene expression in wt and HD mice. These studies are designed to support therapeutic intervention for HD by gaining a detailed understanding of the pathways which modulate normal and pathogenic HTT function and levels, and the ways in which effectively correcting HTT dysfunction may lead to improved therapeutic outcome.