Neurodegenerative diseases, such as Alzheimer’s, ALS, and Parkinson’s, represent significant unmet medical needs. More than 6.5 million individuals in the US suffer from these neurodegenerative diseases, and about 1 in 8 Americans over the age of 65 currently suffer from Alzheimer’s alone. According to the World Health Organization, this accounts for 642,000 years of healthy life lost to disability (YLD) in the USA from Parkinson’s, MS, Alzheimer’s and other dementias. This statistic is projected to rise to approximately 900,000 YLD in 2030. Currently, no therapies exist that are able to slow the course of these diseases. At John Hopkin’s University in 2012, Dual Leucine Zipper Kinase (DLK) was shown to be a neuronally enriched kinase designed to mediate stress-induced cell death. Pharmacological inhibition and genetic deletion of DLK promote survival of retinal ganglion cells in vitro and in vivo rat models. DLK is activated under various extracellular stressors (i.e. ALS, Alzheimer’s, PD, neuron damage) initiating phosphorylation of MKK4/7 to ultimately activate JNK resulting in degeneration of neurons in the CNS. A variety of SAR tactics are explored to design a potent small molecule inhibitor with the right balance of physical and pharmacokinetic properties ideal for both brain penetration and DLK potency. This seminar will focus on how (14) has been discovered and developed from siRNA kinase screening technology and into clinical trials.

References