Developing a gene therapeutic for *FUS*-ALS

Amyotrophic lateral sclerosis (ALS) is a devastating disease in which patients suffer progressive paralysis due to the loss of motor neurons (MNs). Patients only survive an average of 2-5 years after diagnosis Better therapeutics are urgently needed. Mutations in FUS cause a particularly aggressive form of ALS, with cases as young as 11 years old being reported and most often occur in the nuclear localization signal, leading to mislocalization of FUS protein from the nucleus to the cytoplasm. Thus, *FUS*-ALS could be caused a loss of nuclear FUS function or a toxic gain of function associated with cytoplasmic FUS. Our team as developed an iPSC-based model of ALS, and using this model, this project will develop a gene therapeutic strategy to rescue FUS pathology. First, we will develop a Cas13-based vector to specifically reduce FUS, thereby reducing any toxic function associated with cytoplasmic FUS. In parallel, we will test over-expression of the master chaperone HSC70 as a strategy to reinforce the resilience of motor neurons against cytoplasmic FUS protein. Afterward, the most effective strategy will be developed into an adeno-associated virus (AAV) vector and tested using a mouse FUS-ALS model, which we recently imported. AAV is particularly interesting because it is in clinical use for MN diseases.

Preferred Course of Study/Expertise of Candidate: Cell culture experience, preferably with human pluripotent stem cells. Experience with immunofluorescence, quantitative RT-PCR, and western blot would be helpful.