EXPLORING MODIFIERS OF SPINAL MUSCULAR ATROPHY: THE POWER OF AAV9

Jolill Ross

Dr. Christian Lorson, Thesis Supervisor

ABSTRACT

Spinal Muscular Atrophy (SMA) is the second most common autosomal recessive disorder. The rate of new occurring cases is 1 in 6,000, with a carrier frequency of 1 in 35. SMA is characterized by the loss of Survival Motor Neuron 1 (SMN1) gene, resulting in the degeneration of motor neurons located in the spinal cord, atrophy of muscles, paralysis, and eventually death. We utilize scAAV9, a viral vector, as a tool for introducing heterogeneous genes as a method for delivery. We and others have shown that delivery of full length SMN1 to the “delta 7” SMA mouse model fully rescues the disease. Therefore, we employ scAAV9 to introduce genes that are designed to modify the disease phenotype, such as SMNrp1 and α-synuclein. SMNrp1 is a putative paralogue to SMN, while α-synuclein functions with synaptic vesicle recycling at the pre-synaptic membrane. We hypothesized that SMNrp1 may be able to restore the function of SMN, while α-synuclein may work with SMN to stabilize and protect motor neurons from SMA. Furthermore, we will investigate which domains of SMN are important for its function with scAAV9, by interrogating the ability of phylogenetically diverse SMN proteins to ameliorate the SMA phenotype in mice. These studies will provide insight into the function of SMN as well as provide evidence for potential therapeutics for SMA.