

Gene Therapy in Mouse Models of Spinal Muscular Atrophy: Using SMN Gene Replacement to Address Biological Questions

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ABSTRACT

Spinal Muscular Atrophy (SMA), an autosomal recessive neuromuscular disorder, is the leading genetic cause of infant mortality. SMA is caused by the functional, homozygous loss of the *Survival Motor Neuron-1* (SMN1) gene which encodes for the ubiquitously expressed Survival Motor Neuron (SMN) protein.

Here we utilize SMA mouse models to demonstrate that self-complementary Adeno-associated virus encoding SMN1 (scAAV-SMN) is a promising therapeutic for the treatment of SMA. We show that pre-symptomatic, ubiquitous restoration of SMN via scAAV is able to dramatically improve the SMA phenotype extending lifespan from ~14 to 200+ days. We show that direct delivery of scAAV-SMN into the central nervous system is able to more robustly rescue the phenotype of a mouse model of SMA compared to systemic, intravascular delivery. After determining the most efficacious route of injection, we seek to determine the therapeutic window and investigate the effectiveness of viral delivery after the onset of disease symptoms. We report that early, pre-symptomatic scAAV-SMN delivery produces a better phenotypic rescue than treatment after the onset of symptoms, emphasizing the need for early therapeutic intervention. We assess the need for SMN in a specific cell population, upper cortical motor neurons, reporting that restoration of SMN to solely to these cells is not sufficient to modify the SMA phenotype. Lastly, we use the scAAV vector to delivery mutant forms of SMN and other genes which may be able to modify the SMA phenotype. In this experiment, we identify several modifying genes which are able to improve the phenotype of an intermediate mouse model. Collectively, these studies help to provide insight into the use of scAAV-SMN as a therapeutic and help to address clinically relevant questions about the temporal and spatial requirements of SMN protein during disease progression.