

Public Abstract

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

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. In humans, a nearly identical copy gene is present called SMN2. This gene is retained in all SMA patients but is unable to compensate for the loss of SMN1 due to a silent C to T transition at the 5' end of exon 7. This single nucleotide change causes ~90% of the mRNA transcripts generated from SMN2 to be alternatively spliced. The alternatively spliced isoform, lacking exon 7, is termed SMN Δ 7. The SMN Δ 7 transcript encodes an unstable, rapidly degraded protein. Importantly, SMN2 does produce small amounts of full-length SMN protein (~10%) making it a critical disease modifying gene. Low levels of full-length SMN protein result in the development of SMA.

Here we present work demonstrating that SMN1 gene replacement via a viral vector is able to rescue the lifespan of a severe mouse model of SMA. We report the development and assessment of two routes of viral delivery in neonatal mice showing that direct central nervous system delivery is more efficacious than systemic, intravascular delivery. We use two mouse models of SMA to define the therapeutic window of opportunity and investigate the effectiveness of SMN1 gene replacement after the onset of disease symptoms. We conclude that early, pre-symptomatic gene replacement is more effective than treatment administered after disease symptoms are present highlighting the need for early therapeutic intervention. We also identify genes, other than SMN1, which are able to modify the phenotype of an intermediate SMA mouse model, providing insight into potential therapeutic targets. Taken together, these studies 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.