ABSTRACT. RyR1 myopathies are a severe class of monogenic muscle diseases arising from rare mutations in the skeletal muscle calcium release channel *RYR1*. The majority of RyR1 myopathies are autosomal dominant, where a single copy of the mutant allele adversely impacts the function of the tetrameric RyR1 channel. Mutations that make the RyR1 channel "leaky" to calcium cause Malignant Hyperthermia (MH), a serious condition where individuals are at risk of life-threatening hypermetabolic responses to heat and inhalation anesthetics. Conversely, "permeation defective" mutations can also cause a very severe myopathy known as Central Core Disease (CCD). There are currently no corrective treatments for any form of RyR1 myopathy. In this proposal we will design Adeno-Associated Viral (AAV) vectors for the delivery of the Clustered Regularly Interspaced Palindromic Repeats (CRISPR)/Cas9 genome editing system to skeletal muscle. We will determine if CRISPR/Cas9 can be used to selectively disrupt the disease-causing allele(s) and promote removal of the mutant RyR1 subunit. Specifically, we will identify the optimal guide RNA sequences for selective removal of mutant *Ryr1* alleles (Y524S and I4895T) in cells (Aim 1), and test the efficiency and specificity of *in vivo* genome editing with AAV in skeletal muscle in vivo (Aim 2).

RYR1 RESEARCH PRIORITY AREA: *D)* Utilization of CRISPR/Cas9 as a therapeutic strategy for RYR1-myopathy and related diseases.