SECTION III. ABSTRACT

Patients born with mutations in the ryanodine receptor (RyR1), a skeletal muscle calcium channel, suffer from muscle dysfunction associated with significant morbidity. Approximately 300 mutations in the skeletal muscle ryanodine receptor calcium (Ca^{2+}) release channel (RyR1) are responsible for autosomal dominant and recessive myopathies (RyR1-RM) and susceptibility to malignant hyperthermia (MH) [1]. Patients suffer from neonatal hypotonia, poor feeding, and respiratory involvement [2] or minimal or no disability [3]. Proposed pathophysiologic mechanisms include RyR1 Ca^{2+} leak [4], altered sensitivity of RyR1 to activation and/or inactivation by Ca^{2} [5], reduced RyR1 expression [6], and uncoupling of excitation from contraction [6]. Solving of a 4.8 Å cryo-EM structure of RyR1 [7] creates new opportunities to study structure-function relationships. Our hypothesis is that the functional effects of RyR1 mutations can be predicted based on spatial localization with functionally characterized mutations and known functional domains. Ca^{2+} leak through RyR1 may affect gene expression, protease activity, and redox homeostasis and has been linked to Duchenne muscular dystrophy [8], sarcoglycanopathies [9], and sarcopenia [10]. In these conditions, secondary, post-translational modification of RyR1 including nitrosylation, oxidation, and depletion of calastabin1 (FKBP12) cause pathologic Ca^{2+} leak contributing to myopathy. Stabilizing RyR1 with Rycals (e.g. S107) reduces Ca^{2+} leak and improves muscle function in mice. MH and RyR1-RM are caused by mutations in RyR1 causing dysregulation of Ca^{2+} homeostasis via increased SR Ca^{2+} leak. [11-14]. Rycals stabilize leaky RyR1 [9, 10, 15, 16]. The proposed research aims to improve understanding of how mutations in RyR1 cause channel dysfunction and clinical disease. We will develop a public structure-function database of all disease causing RyR1 mutations that will be used by all interested investigators to study RyR1 mutations. Structure-function predictions can then be validated *in-vitro* using recombinant mutant RyR1 and *ex-vivo* using RyR1 isolated from skeletal muscle biopsies from patients with RyR1-RM. These data will help guide the clinical management of patients with RyR1-RM and the development of novel therapies for RyR1-RM and predict which patients may respond to Rycal therapy.