SECTION III. ABSTRACT: The skeletal muscle ryanodine receptor (RyR1) protein is central to muscle function. Mutations in RyR1 are a major cause of congenital myopathies, with as many as 1 in 2000 people likely carrying RyR1 myopathy-linked mutations (Lillis et al., 2012). There is spectrum of RyR1 gene-related disorders including malignant hyperthermia (MH), central core disease (CCD), and multiminicore disease (MmD) (Marty and Faure, 2016) and these conditions can vary in severity from mild muscle fatigue to fatal muscle weakness. Despite the high incidence of these mutations, there is no effective treatment and there is little knowledge of the underlying molecular mechanisms causing the clinical phenotype. Indeed there are few animal models to allow study of the effects of the mutation in adult muscle. There is a considerable body of work defining changes in the function of mutant RyR1 expressed in immature cultured muscle fibers (myotubes) and/or mammalian cell lines. Such studies yield valuable data, but the expression systems lack the significant regulatory modifications and protein associations that develop during maturation in mice and man. Therefore our aim is to use the CRISPR/Cas9 facility in the John Curtin School of Medical Research (JCSMR) at the ANU, to generate a range of mouse models carrying selected RyR1 myopathy-related mutations. With these models we will be able to examine the mutant RyR1 protein expressed in mature muscle fibres and modified following expression in a manner similar to that in patients. These studies will move the field forward towards a closer to understanding the effects of the mutation on the function of RyR1 molecules in humans and move the field towards effective treatment. The mouse models will provide a platform for drug development and other therapeutic strategies to combat the myopathy and will allow such strategies to be tested in the whole animal to better reflect the clinical setting.