Jean Hanson Keynote Lecture

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Muscle making and muscle breaking: from developmental mechanisms to therapeutics for muscle disease

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We seek to delineate the mechanisms that govern development, disease and regeneration of skeletal muscle and the heart and to build upon this knowledge to restore muscle function during disease and aging. Recently, we have advanced new gene editing strategies for the correction of genetic disorders of muscle, such as Duchenne muscular dystrophy (DMD) and various cardiomyopathies. We refer to this approach as myoediting. We have optimized myoediting for the correction of mutations associated with DMD and various cardiomyopathies in skeletal and cardiac muscle cells derived from induced pluripotent stem cells (iPSCs) generated from blood samples of affected patients. In a complementary approach, we have established mouse models of these genetic disorders as a platform for therapeutic optimization of myoediting strategies. Single-cut CRISPR editing, together with base and prime editing, has allowed the restoration of skeletal and cardiac muscle function in these animal models of muscle disease. Combining single cell RNA sequencing technologies with gene editing has also provided insights into gene correction strategies at single nuclear resolution and has revealed intercellular cross-talk among muscle and nonmuscle cells that underlies muscle pathogenesis. Opportunities and challenges in the path toward permanent correction of disease-causing mutations through the normalization of muscle gene expression by myo editing will be discussed.