All-in-One Genome Editing Therapy for the Treatment of Duchenne Muscular Dystrophy

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Duchenne Muscular Dystrophy (DMD) is a deadly genetically caused disease. Palliative measures (respiratory support, enteral and parenteral nutrition), anti-inflammatory drugs (steroids), and heart failure medication represent the standard-of-care, but do not prevent loss of ambulation and death of DMD patients at a young age. Novel therapeutic approaches, including antisense oligonucleotide-mediated exon skipping, read-through therapeutics and gene supplementation show limited effectiveness. Genome editing is emerging as a new treatment option to convert deadly DMD into a milder or even asymptomatic condition. In a collaborative project, we aim to establish a nonclinical pipeline for patient/exon-tailored genome editing by All-in-One delivery of small CRISPR/Cas9 to skeletal and heart muscle using optimized adeno-associated virus (AAV) vector-mediated transduction. Preliminary experiments demonstrated that CRISPR/Cas9-mediated genome editing can indeed lead to improvement of contractile function. Aligned with obtained regulatory advice, we will advance our most promising genome editing therapy candidate through a nonclinical pipeline of investigations, which includes (1) advanced patient-specific in vitro potency assays, (2) genome safety studies by whole genome sequencing, and (3) pivotal animal studies in non-human primates. AAV-capsid engineering will be explored to enhance muscle delivery, reduce off-target liabilities, and attenuate immunotoxicity. Our strategy will serve as the basis for the conversion of a patient-tailored (n=1) to an off-the-shelf exon-tailored (n>1) therapy, adaptable to most DMD-causing deletions/mutations.