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## Silencing DUX4 Expression in FSHD Cells by CRISPR

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## **Silencing DUX4 Expression in FSHD Cells by CRISPR**

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Facioscapulohumeral Muscular Dystrophy (FSHD) is an autosomal dominant neuromuscular disease affecting 1 in 20,000 to 1 in 15,000 individuals and is characterized by progressive weakness in the facial, scapular, humeral, truncal, and lower extremity muscles (Tawil and Van Der Maarel *Muscle Nerve* 2006). FSHD is associated with the contraction of the D4Z4 microsatellite repeat below a threshold number of repeats (Wijmenga *et al.*, *Nat. Genet.*, 1992), allowing the transcription of the DUX4 gene contained within the last repeat (Snider *et al.*, *PLoS Gen.*, 2010). The disease only develops when DUX4 is expressed from a chromosome with the permissive 4qA allele, which contains a polyadenylation signal (PAS) that stabilizes the DUX4 transcript (Lemmers *et al.*, *Science*, 2010). We are using CRISPR technology to investigate the possibility that disruption of the PAS in cells derived from FSHD patients could prevent expression of the DUX4 protein and restore the cell to a less affected phenotype. We will then take advantage of the high reprogramming efficiency of FSHD cells and generate iPSC from FSHD muscle cells with the repressed DUX4 allele, and determine if they have a similar phenotype to iPSC cells derived from non-affected individuals. Finally, we will use the highly-engraftable iPSC cells in xenograft experiments to determine if the DUX4-silenced iPSCs repopulate injured muscle more efficiently than unaltered FSHD-derived iPSC, and evaluate their potential for use as therapeutics.