Can we use CRISPR technology as a therapeutic approach for FSHD?

**Normal CRISPR:**
guide RNA recruits Cas9 protein (cuts DNA) to a specific location in the genome

**CRISPR inhibition:**
guide RNA recruits “dead” Cas9 protein fused to a repressor protein to a specific location in the genome

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**Bad for FSHD!**
Disease locus is one repeat, with hundreds of nearly identical repeats in the genome

**Viable for FSHD**
Other similar repeats in the genome are normally repressed
Stable repression can be inherited by subsequent generations of cells
No permanent modifications to the genome
Proof-of-principle that CRISPR inhibition can reduce pathogenic gene expression in FSHD

In primary FSHD muscle cells:

• CRISPR inhibition returned the FSHD locus to a more normal, repressed state & significantly reduced expression of DUX4 and DUX4 target genes

• CRISPR targeting of the FSHD locus is conceptually possible

Himeda et al. (2016) Molecular Therapy

• Testing CRISPR inhibition *in vivo* (Jones lab FSHD mouse model)
Challenges for CRISPR technology as a therapeutic avenue

General:

• Can we deliver the therapy to all the target cells?
• Will all the target cells be modified?
• What happens if the CRISPR system is recruited to other places in the genome?
• Can CRISPR components stimulate an immune response?
• Will the CRISPR system provide a long-term cure?

FSHD-specific:

• How many muscle fibers need to be corrected?
• Do muscle stem cells need to be corrected?
• How much of a reduction in DUX4 expression will provide functional benefit?
Acknowledgements
Mick Hitchcock, PhD, Endowed Chair in Medical Biochemistry