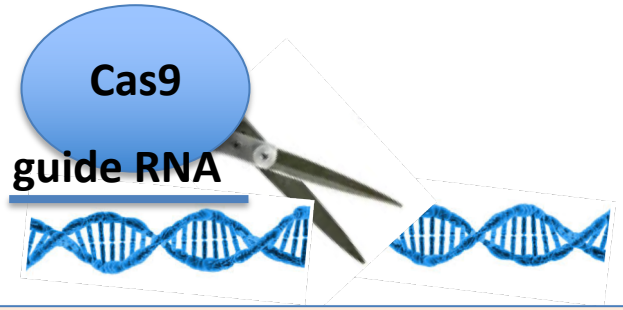
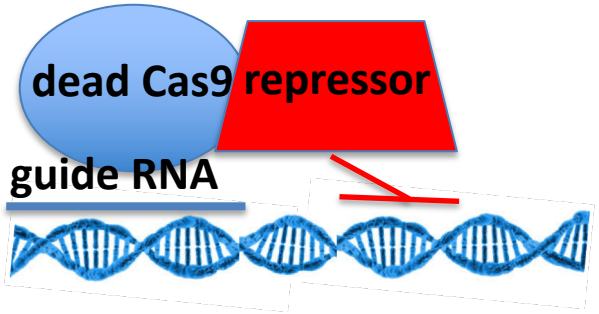
Can we use CRISPR technology as a therapeutic approach for FSHD?

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



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

CRISPR inhibition:
guide RNA recruits "dead" Cas9 protein
fused to a repressor protein
to a specific location 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?**

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A Voice for FSHD
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FSH SOCIETY
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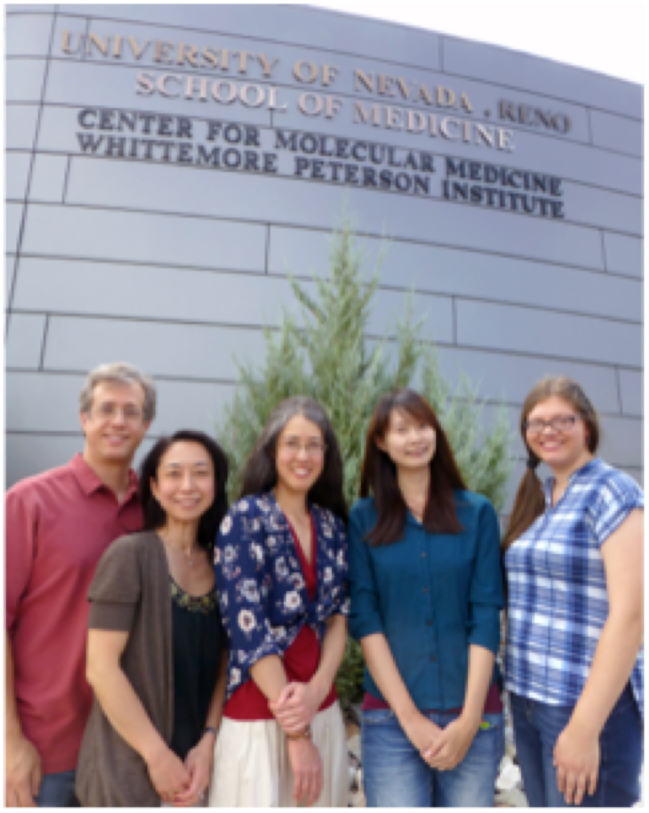

AFM
Association Française contre les Myopathies

NIAMS
National Institute of Arthritis and Musculoskeletal and Skin Diseases

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