

Therapeutics Pipeline

Targeting DUX4 Expression

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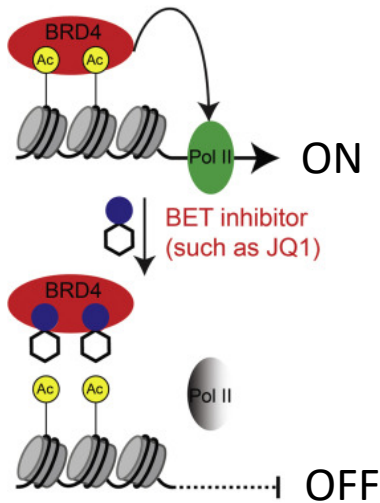
Saint Louis University

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- Small molecule screening: BET inhibitors, others
- Understanding therapeutic potential: human FSHD xenografts

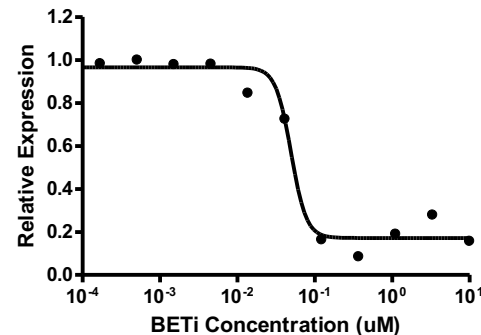
BET inhibitors block DUX4 expression

Bromodomain and Extra-Terminal (BET) Family



Cell Rep. 2016, 11, 2829–2837.

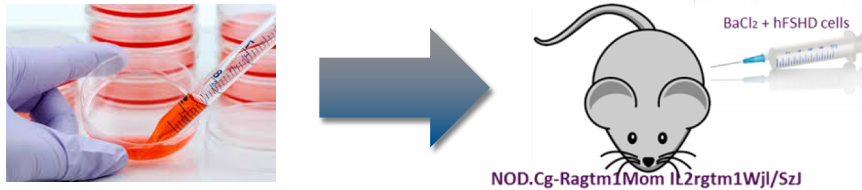
- Four BET family genes: BRD2, BRD3, BRD4, BRDT
- BET proteins activate gene transcription (turn on genes)
- BET proteins bind to D4Z4 repeats/DUX4 gene
- BET inhibitors (BETi) block DUX4 expression in differentiating FSHD muscle cells in culture



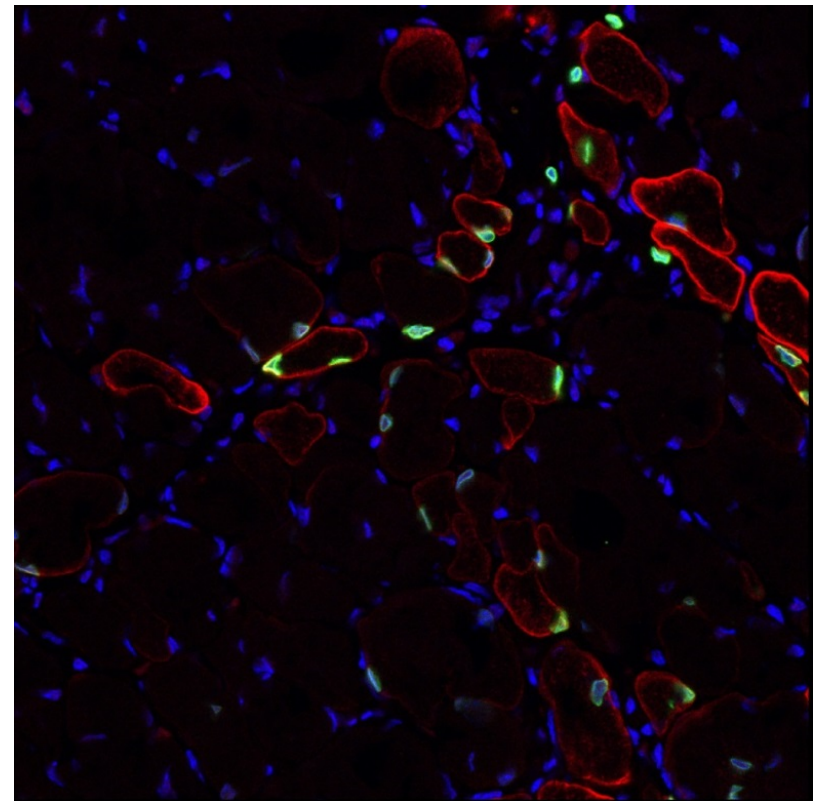
➤ We are optimizing novel BETi to suppress DUX4 in FSHD muscle cells

Xenograft model of FSHD

Human epigenetic regulation of DUX4 in a mouse

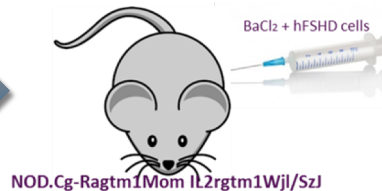
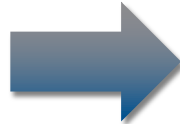


- Human FSHD myoblasts contribute to regenerating myofibers
- Human spectrin staining (red) outlines mature myofibers



Xenograft model of FSHD

Human epigenetic regulation of DUX4 in a mouse



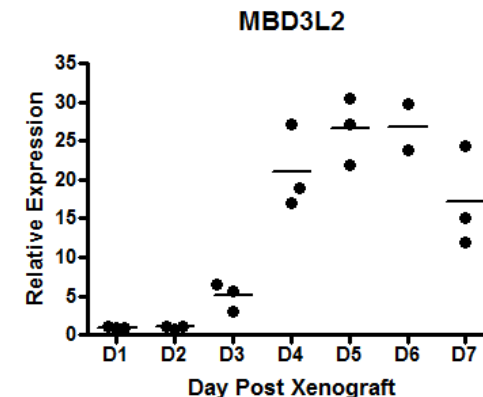
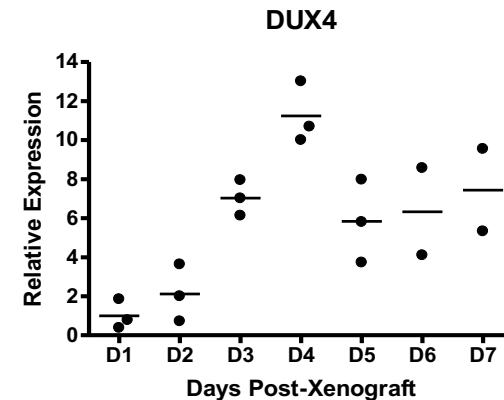
+/- Drug



Outcomes:

- gene expression
- muscle health

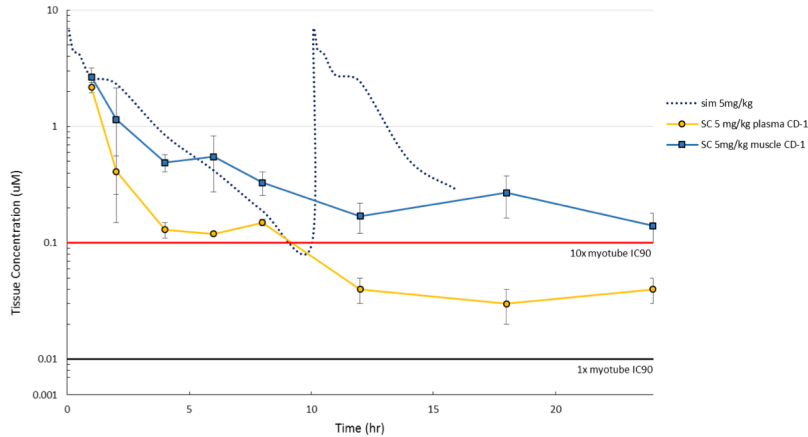
- Maintains human FSHD genetic arrangement and DUX4 epigenetic regulation
- DUX4 and DUX4 target genes expressed as muscle cells differentiate in vivo
- Pharmacology model to test modulation of DUX4 expression in muscle



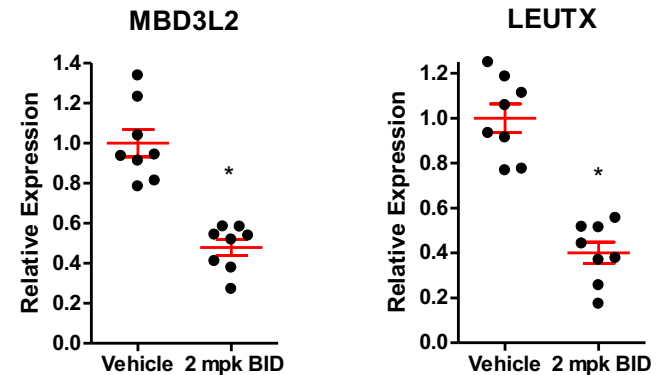
Xenograft model of FSHD

Enabling Drug Discovery – BET inhibitor proof of concept

Pharmacokinetics: drug exposure in muscle

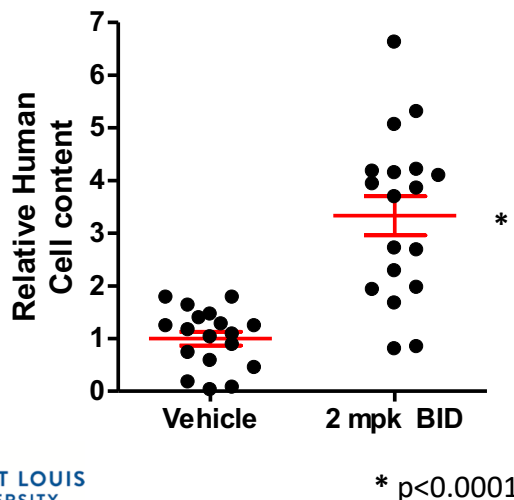


Pharmacodynamics: suppression of DUX4

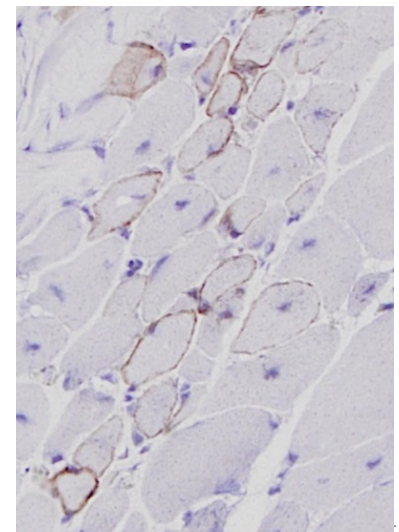
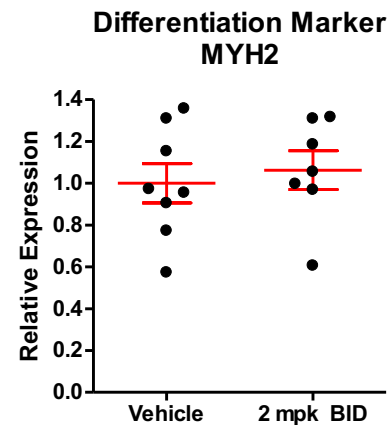


* p<0.01

Pharmacodynamics: human FSHD cell survival



Safety: human cell differentiation and engraftment



BET inhibitors and other mechanisms for FSHD

Current Progress

- BET inhibitors suppress the expression of DUX4 in FSHD muscle cells
- Xenograft model utilized to measure DUX4 expression in vivo (mice), including FSHD cell survival and muscle differentiation: therapeutic potential of BET inhibitors
- Characterizing additional mechanisms (identified from compound screening) in xenograft model
- Evaluating both repurposing candidates and novel compounds for therapeutic development

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