RESVERLOGIX

TSX: RVX

Apabetalone, a Clinical-stage Cardiovascular Disease Drug, Inhibits DUX4 Expression in FSHD Cells

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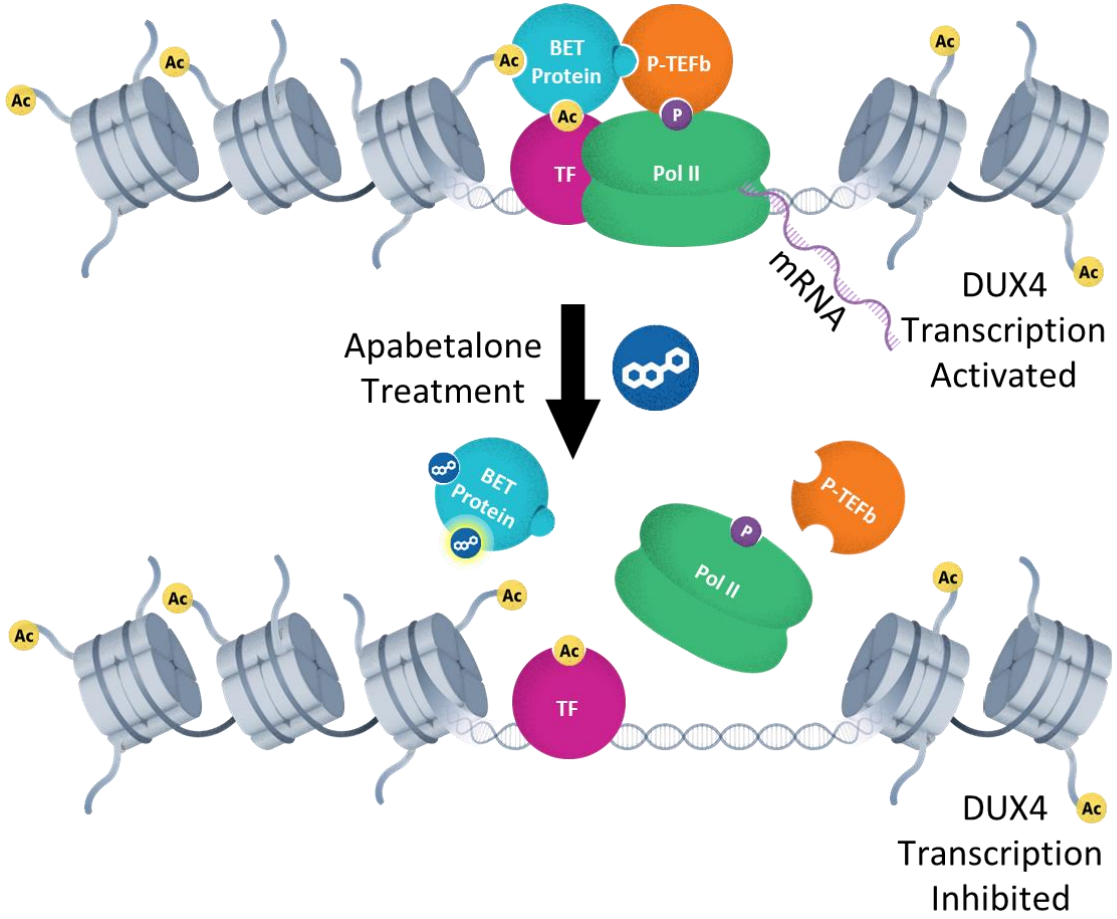
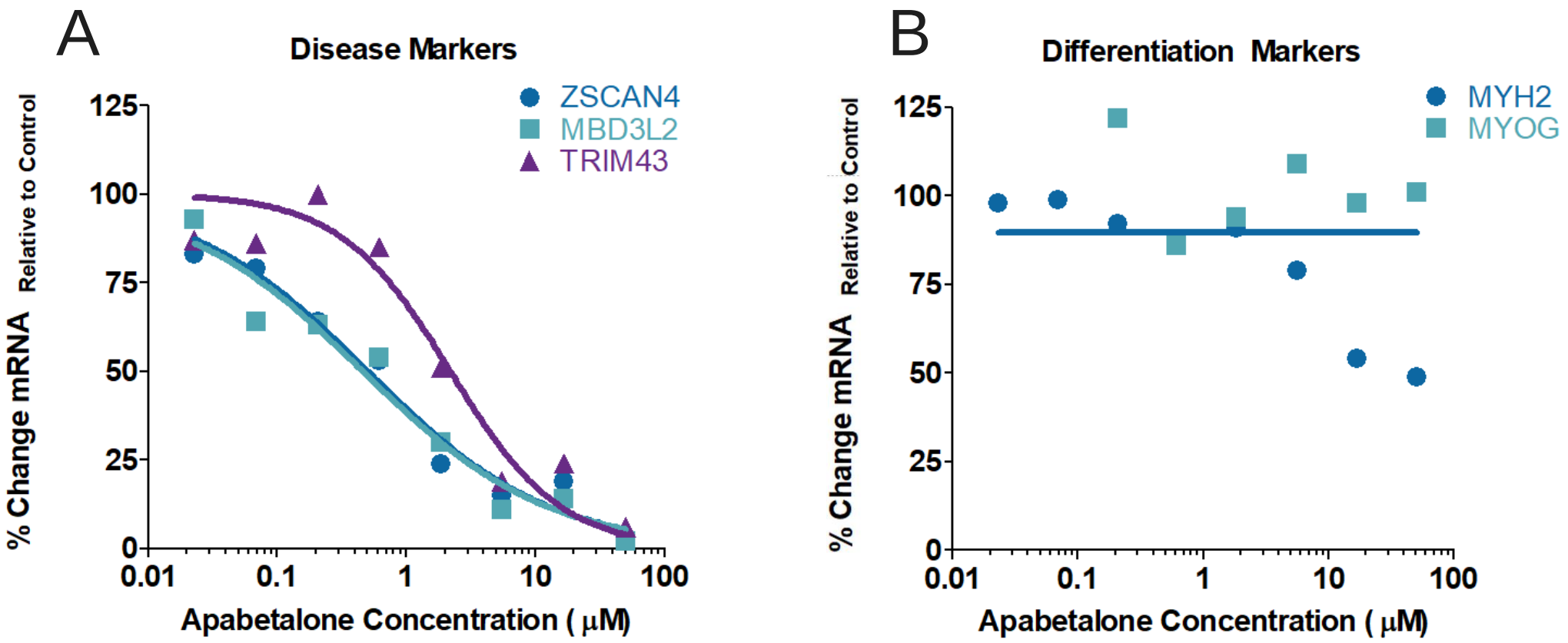
Introduction

- Apabetalone is a clinical stage BET inhibitor for cardiovascular disease
  - With a demonstrated clinical safety profile
- Apabetalone inhibits DUX4 transcription through an epigenetic mechanism
- Here we show apabetalone reverses DUX4-mediated gene expression
  - Without significantly impacting muscle cell differentiation or viability



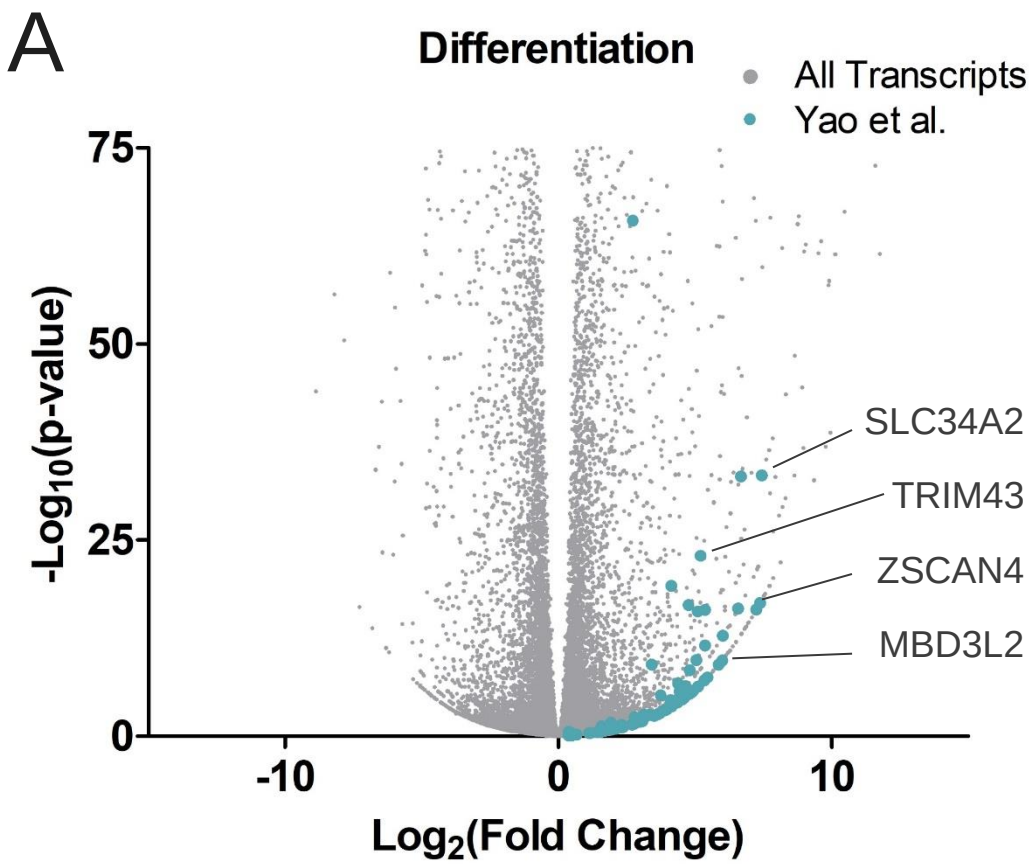
Apabetalone Inhibits FSHD Disease Makers in Primary Myotubes

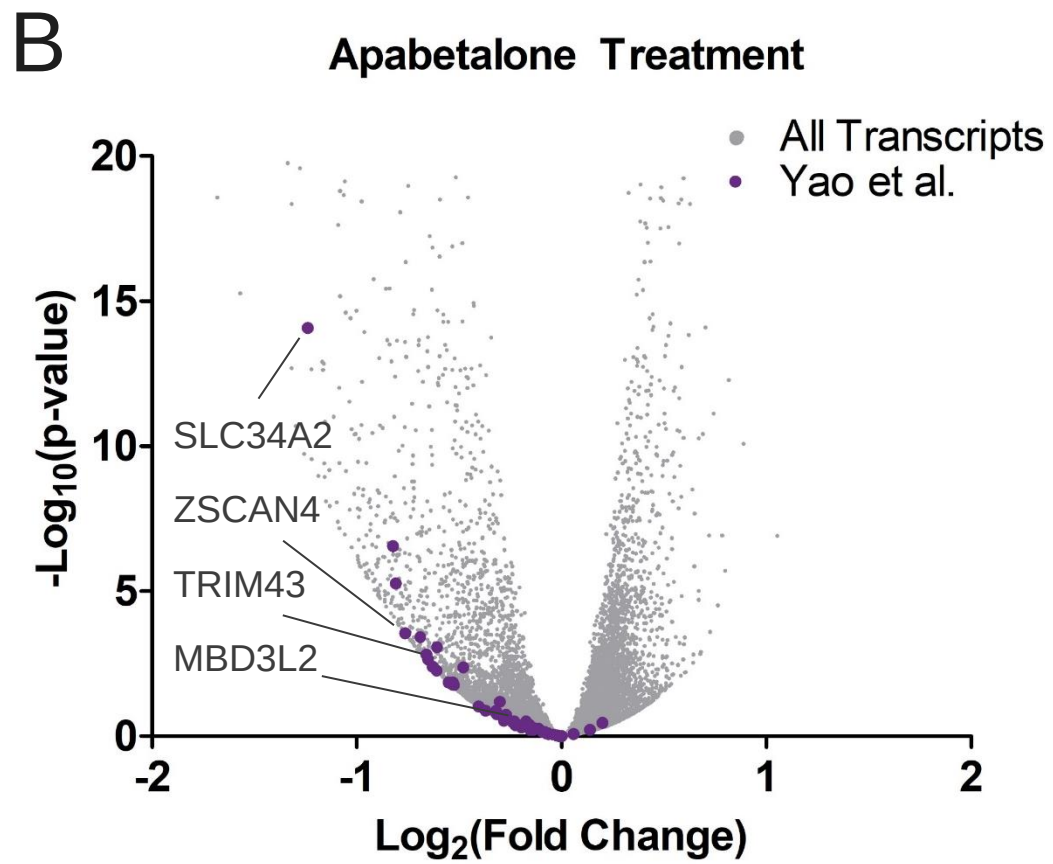
Apabetalone treatment effectively inhibits FSHD disease markers (A), without significantly affecting markers of muscle cell differentiation (B)



Apabetalone Counters DUX4 Activation During Differentiation

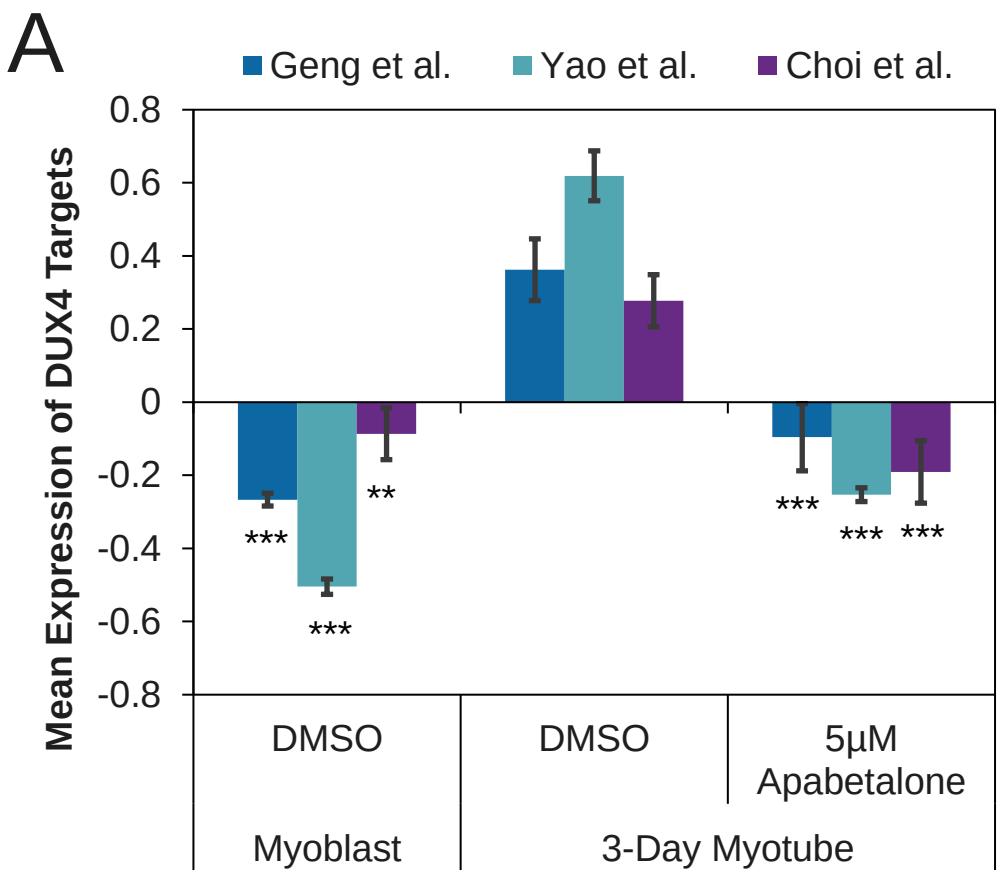
DUX4 activation during differentiation (3 day) increased expression of known DUX4 targets (A). Apabetalone treatment (5µM for 24h) significantly reduced expression of nearly all DUX4 targets in differentiated myotubes (B)

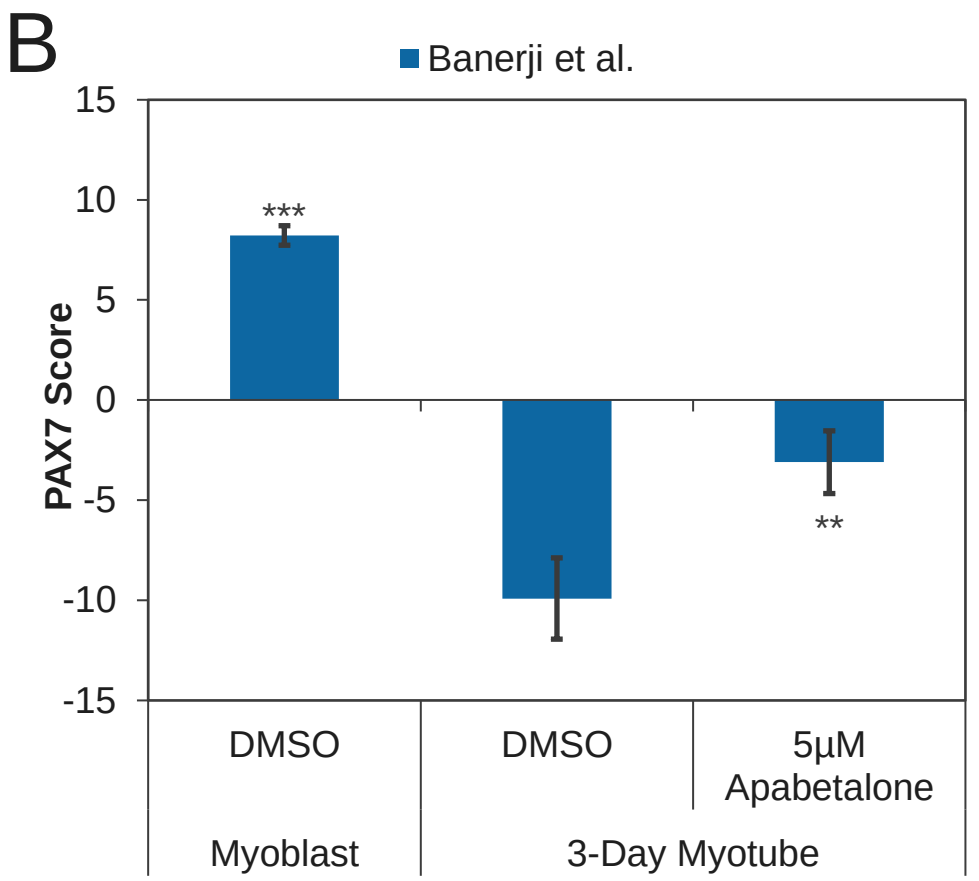




Apabetalone Reduces DUX4 Signature and Rescues PAX7 Activity

Apabetalone treatment (5μM for 24h) lowers the mean expression of DUX4 signature genes (A) and partially rescues PAX7 activity (B), which is a critical signal of muscle cell function





Conclusions

- Misexpression of DUX4 drives pathogenesis in FSHD
- Apabetalone inhibits the expression of DUX4 in FSHD muscle cells
- Mean expression of DUX4 target genes was significantly reduced with apabetalone treatment
- PAX7 activity, as well as CNTF and ERK/MAPK signaling, all important for muscle function, were rescued by apabetalone treatment
- Cell viability and apoptosis were not significantly impacted by apabetalone treatment
- These findings reinforce apabetalone’s safety and provide a strong rationale for clinical study of its potential benefits in FSHD