Preclinical therapy development in FSHD: evaluation of pathophysiological aspects and therapeutic intervention in FSHD mouse models

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Stellingen behorende bij het proefschrift getiteld

Preclinical therapy development in FSHD

Evaluation of pathophysiological aspects and therapeutic intervention in FSHD mouse models

1. DNMT3B has a role in silencing the D4Z4 repeat array, however its role in the regulation of DUX4 is more modest compared to SMCHD1 (this thesis).
2. ACTA1-MCM;FLExD mice that are not exposed to tamoxifen show phenotypes that are more similar to individuals with FSHD compared to induced ACTA1-MCM;FLExD mice (this thesis).
3. Although the DUX4-targeting ASO was effective in reducing DUX4 and DUX4-induced gene expression in skeletal muscle, optimizations are needed as the skeletal muscle functionality barely improved (this thesis).
4. There is no perfect mouse model that completely recapitulates the genetics, epigenetics, and phenotypes as found in individuals with FSHD, however the individual mouse models described in this thesis each have their own merit for FSHD research and therapy development (this thesis).
5. One of the toxic consequences of DUX4 activation is the dysregulation of immune system components. Greco et al. Clin Genet (2020).
6. In some somatic tissues, DUX4 might have a physiological role in regulating apoptosis. Mocciaro et al. Cells (2021).
7. As FSHD is a gain-of-function disease, the DUX4 transcript is an excellent target for a knockdown approach using RNA therapies as targeting DUX4 directly would most likely result in more clinical benefit then targeting one of its toxic downstream effects. Himeda et al. J Pers Med (2022).
8. The relatively slow disease progression, patient heterogeneity, and lack of sensitive biomarkers makes it challenging to demonstrate efficacy of new treatments in clinical trials for FSHD. Ghasemi et al. Cells (2022).
9. Science would benefit if universities would offer employees long-term prospects instead of continuously hiring new (PhD) researchers and letting them go when their non-fixed contract ends.
10. All publications from academic researchers should be published in open access journals to promote accessibility.