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Leiden  
The Netherlands

## Elucidating DUX4-mediated molecular mechanisms underlying FSHD pathophysiology using multiomics approaches

Zheng, D.

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Stellingen behorend bij het proefschrift getiteld

**Elucidating DUX4-mediated molecular mechanisms underlying FSHD pathophysiology using multi-omics approaches**

1. DUX4 induces transcriptional heterogeneity within multinucleated myotubes by activating distinct early embryonic-like gene programs in nuclear subpopulations (this thesis).
2. Single-myofiber RNA-sequencing reveals that DUX4 activation occurs in a small subset of myofibers, highlighting focal pathogenicity as a defining molecular feature of FSHD (this thesis).
3. Three-dimensional tissue-engineered skeletal muscles (3D-TESMs) provide a more physiologically relevant model for FSHD than conventional 2D cultures, and uncover limitations of current drug candidates (this thesis).
4. DUX4 drives similar gene-level programs but produces distinct isoform-level outcomes across cellular contexts (this thesis).
5. Increasing resolution across spatial, molecular and temporal dimensions of single-cell omics is transforming our understanding of cellular heterogeneity (Baysoy et al., 2023).
6. Repetitive elements are not merely genomic parasites but function as regulatory modules contributing to cell-type-specific and disease-specific transcriptional complexity (Chuong et al., 2017).
7. Long-read sequencing is indispensable for accurate annotation of disease transcriptomes, as isoform-level regulation proves increasingly functional (Monzó et al., 2025).
8. Faithful disease modeling requires not only the right genetic background but also the right structural and physiological context (Rowe et al., 2020).
9. Biological insight emerges from the iterative interplay between reductionist experimentation and integrative analysis, not from either approach alone (Ahn et al., 2006).

10. Scientific progress depends as much on technological innovation as on conceptual imagination; without the former, the latter remains untestable (Brenner, S., 'Biology in the 1980s', speech at Friedrich Miescher Institute Basel, 1980).
11. The growing integration of computational and experimental biology blurs traditional disciplinary boundaries, calling for a new definition of scientific expertise (Shani et al., 2024).
12. 世之奇伟、瑰怪，非常之观，常在险远。“*The marvelous and extraordinary are often found in the remote and the perilous.*” — Wang Anshi, You Bao Chan Shan Ji (1054). Scientific progress is limited not by the complexity of nature, but by our willingness to pursue the inaccessible.