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TARGETING FIBRO-ADIPOGENIC PROGENITORS TO TREAT DUCHENNE MUSCULAR DYSTROPHY

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Duchenne Muscular Dystrophy (DMD) is a severe X-linked neuromuscular disorder caused by mutations in the DMD gene, resulting in the absence of dystrophin and progressive muscle degeneration. A hallmark of DMD pathology is the progressive replacement of muscle fibers by fibrotic and adipose tissue, largely driven by the aberrant activation of fibro-adipogenic progenitors (FAPs). Although these mesenchymal stromal cells physiologically support muscle regeneration, in DMD they become dysregulated and contribute to pathological adipogenesis and fibrosis. This project places human biology at its core, leveraging a multi-omic strategy directly on muscle biopsies from DMD patients. By combining single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics, we aim to characterize FAP heterogeneity and identify molecular programs associated with their adipogenic fate. This high-resolution approach has already highlighted Tenascin-C (TNC) as a candidate regulator, enriched in specific FAP DMD subpopulations. In parallel, we will develop a drug-screening platform using human primary FAPs and muscle stem cells derived from DMD patients and healthy controls. Candidate compounds emerging from omics-driven hypotheses, including pathways linked to TNC dysregulation, will be tested in vitro and further validated in vivo using the R-DMDdel52 rat model. By integrating advanced human-centric omics with functional pharmacological assays, this project aims to identify novel therapeutic targets to limit ectopic adipogenesis, improve muscle preservation, and ultimately contribute to disease-modifying strategies for DMD and related muscular disorders.

Keywords: *Duchenne Muscular Dystrophy (DMD), Fibrosis, Adipose tissue replacement, Ectopic adipogenesis, Single-nucleus RNA sequencing (snRNA-seq), Spatial transcriptomics, Tenascin-C (TNC).*