Advanced modelling of congenital myopathies using human myogenic cells and tissue engineering

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Congenital myopathies represent a group of severe, incurable muscle disorders characterized by early-onset hypotonia and weakness, with limited therapeutic options due to inadequate human disease models. We have developed comprehensive human *in vitro* platforms using induced pluripotent stem cells (iPSCs) and tissue engineering to model these conditions and advance therapeutic development. Our work encompasses X-linked myotubular myopathy (XLMTM) caused by pathogenic *MTM1* variants and RYR1-related myopathies (RYR1-RMs) caused by ryanodine receptor 1 mutations.

For XLMTM, we engineered 3D muscle models using both tissue-derived and iPSC-derived myoblasts, successfully recapitulating key pathological features including hypotrophic myofibers with abnormally positioned organelles, defective nuclear migration and positioning, and contractile and calcium handling dysfunction. Comparative analysis between XLMTM iPSC-derived engineered muscles and isogenic controls validated myofiber hypotrophy findings and revealed that disease onset is associated with early developmental myogenesis events.

Building on this foundation, my main PhD project will focus on developing a RYR1-RM platform through a systematic three-phase approach. Initially, we will generate RYR1-mutant iPSCs from bio-banked patient myoblasts and differentiate them into myogenic progenitors and supporting isogenic motoneurons. Subsequently, we will develop 3D bioengineered skeletal muscle models to validate *in vitro* phenotypic readouts, to be used as therapeutic outcome measures. Once established, this platform will enable proof-of-principle gene therapy studies using adeno-associated vectors to determine optimal delivery conditions and vector dynamics in mutant myofibers.

These integrated platforms establish robust bases for human-specific disease phenotyping, toxicity assessment, and testing of next-generation therapies for congenital myopathies, potentially transforming treatment approaches for these devastating disorders.