Determination of the mechanism of disease in myopathies utilizing zebrafish

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We are interested in identifying the genetic causes of muscle disease and the molecular basis for pathology. I will describe the generation and characterisation of zebrafish models for ACTA1 nemaline myopathy and FLNC and BAG3 myofibrillar myopathies that have contributed to our understanding of disease, and highlighted potential therapeutic approaches.

In nemaline myopathy we have identified the subcellular origins of the characteristic protein aggregates, identifying multiple subtypes, explaining conflicting reports in the literature as to their composition, and suggesting multiple factors that contribute to muscle weakness.

In myofibrillar myopathy we have demonstrated that muscle weakness results from protein insufficiency resulting from a toxic gain of function. In contrast to the previously established theory we demonstrate that mutant protein is capable of preserving muscle structure but its sequestration in the cytoplasm limits its sarcomeric function. We examine disruption of the autophagic protein degradation pathway and examine potential approaches to treat myofibrillar myopathy by promoting the autophagic clearance of protein aggregates.