essential for correct fibre-type specification and emergent stem cell function. These data plug a significant gap in the natural history of muscular dystrophy and will be invaluable in establishing an earlier diagnosis for DMD/LGMD and in designing earlier treatment protocols, leading to better clinical outcome for these patients.

**P29**
Preventing dystroglycan phosphorylation as a route to therapy in DMD
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Dystroglycan is a central component of the dystrophin glycoprotein complex (DGC) of striated muscle, mediating essential connections between the extracellular matrix and the actin cytoskeleton of muscles. No muscle disease involving mutations in dystroglycan itself have so far been described, however mutations in genes that post-translationally modify dystroglycan give rise to a class of diseases known as the dystroglycanopathies. All dystroglycanopathies currently characterised arise from proteins involved in the glycosylation of α-dystroglycan, a post-translational modification that is essential for dystroglycan function in binding to laminin in the ECM. However b-dystroglycan is also post-translationally modified, by glycosylation and by phosphorylation. In vitro analyses have demonstrated that phosphorylation of b-dystroglycan on tyrosine targets b-dystroglycan for degradation and this could be part of the mechanism that underlies loss of dystroglycan and the whole DGC in conditions such as DMD. Restoration of dystroglycan in DMD could prevent loss of DGC components and allow other compensatory proteins such as utrophin and plectin to bind to and stabilise the complex, thus ameliorating the DMD phenotype. We are using dystroglycan-null zebrafish and a new knock-in dystroglycan mutant in mouse to test the restorative effect of preventing dystroglycan phosphorylation on a key regulatory tyrosine. The homozygote dystroglycan knock-in mice are phenotypically normal with no obvious signs of muscle pathology. The knock-in has been crossed with mdx and analyses are in progress to determine any affect on pathology.

**P30**
The integrin effectors talin 1 and 2 are essential for skeletal muscle development and integrity
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Integrins are essential for development and maintenance of skeletal muscle. Mutations in α7-integrin cause congenital myopathy in humans, and integrin ablation causes muscular dystrophy and defects in myofibre development in mice. Talin 1 and talin 2 mediate a connection between integrins, actin and signaling proteins, and in muscle, they concentrate at the myotendinous junction (MTJ). We have used genetically modified mice to identify the specific functions of the talin genes in muscle development. Ablation of either talin 1 or talin 2 leads to a myopathy characterized by the detachment of myofilaments from the sarcolemma at the MTJ. Defects are more pronounced in talin 2-null mice, which present with centrally nucleated fibers, and appear not to be caused by an increase in sarcolemmal damage as observed for example in mdx mice. Interestingly, the phenotype of talin2-null mice resembles that of α7-integrin-null mice, which also present centrally nucleated fibres with only a moderate increase in serum creatine kinase. Ablation of both talin isoforms causes severe developmental defects, with impaired myoblast fusion and myofibrillogenesis. Together, the data reveal an essential function for talin 1 and talin 2 in muscle development and integrity. The similarity of the phenotype of talin 2- and α7-integrin-null mice suggests that mutations in talin 2 could lead to a congenital myopathy similar to that caused by α7-integrin mutations, and suggests that this gene should be considered as a candidate in patients without an identified genetic defect.

**P31**
Myofibrillar myopathy caused by a mutation in the mouse Myh4 gene
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Ariel is a mouse mutant selected from a cohort of ENU mutagenized mice owing to the onset of hind-limb paralysis at post-natal day 12 in homozygotes. Histopathology showed the presence of large protein aggregates and myofibrillar degeneration in skeletal muscle. The mutation, identified by positional cloning, causes a L349G change within the motor domain of MYH4 (MyHC IIb), the most abundant skeletal muscle myosin in the adult. Biochemical analysis of the aggregates indicated the presence of proteins found to be mutated in myofibrillar myopathies (Filamin, ZASP and A/B-Crystallin) and ultrastructural analysis showed predominantly disorganized filamentous material. Transfections in vitro using GFP tagged versions of the proteins, showed that over-expression of MYH4(L349G) in a non-sarcomeric cell line produced twice as many cells with intracellular aggregates compared to MYH4, suggesting that the pathogenic mechanism involves a change in the folding of the motor domain. In fully differentiated myotubes, overexpressed MYH4 is incorporated into the A-band effectively, but MYH4349G forms aggregates. Intriguingly, the purely recessive nature of the mutation indicates that dimers of wild type and mutant MYH4 assemble into thick filaments and that this is sufficient to prevent the onset of molecular pathogenesis. This mouse model represents a useful resource to elucidate the mechanisms of myofibrillar degeneration and to study the prevention of protein aggregates formation.

**P32**
Investigating novel mutant mouse models of motor neuron disease
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Mutations in Tar DNA binding protein (TDP-43) have been identified as causes of both sporadic and familial motor neuron disease. TDP-43 is a ubiquitous, multi-domain and multifunctional nuclear protein and is crucially involved in gene expression, development and RNA metabolism. It remains unclear as to why mutations in the protein selectively cause motor neuron death. However since it has been identified as a cause of motor neuron disease, interest has heightened as to whether aberrant RNA metabolism could lead to selective motor neurone degeneration. We have access to two lines of mutant TDP-43 mice (K160R, Q101STOP), produced by ethynilnorsourea (ENU) mutagenesis. We will initially investigate these mice with a combination of in vitro and in vivo techniques. Firstly, embryonic motor neuron cultures will be prepared and stress granule formation will be assessed. Stress granules are discrete cytoplasmic granules, containing untranslated mRNAs, dynamically formed following cellular insult as an anti-apoptotic mechanism. We will determine whether the TDP-43 mutations affect stress granule formation and cell viability. Secondly, muscle strength and number of functional motor units of the Tibialis Anterior and Extensor Digitalis Longum will be assessed in anaesthetised adult animals to determine whether the TDP-43 mutations cause motor neuron degeneration and muscle wasting.