Project Title:

Preclinical assessment of clinic ready agents for the treatment of muscular dystrophy and spinal muscular atrophy

Project Description:

In Spinal Muscular Atrophy or SMA the motor neuron (the nerve cells which carry impulses from the brain and spinal cord to our muscular system) dies off. SMA is one of the most common inherited causes of infant death with an incidence of 1 in 10,000 live births. Although a gene is usually deleted in SMA, there is a second almost identical gene present in all children with SMA. This gene makes lower levels of the protein which when missing causes SMA; the ability to turn up this second gene to make more of the missing protein has become a goal of ours and a number of other labs. We have identified drugs in use in the clinic today which we have shown turn up this rescue gene in nerve cell culture. We would now like to test the drugs in mice, both normal and mice with SMA, to establish whether what we have observed in the Petri dish holds true in living organisms. We shall establish whether the protein levels are indeed increased in motor neurons as well as monitoring for a reduction in the disease severity seen in the mouse that have been genetically engineered to develop SMA. What is observed in mice frequently is also seen in humans as well; thus if the effect is recapitulated it would suggest that we should move directly to human clinical trials. The advantage of assessing drugs which are in clinical use is that we shall be able take this step quite quickly. Myotonic dystrophy (DM) is one of the most common forms of muscular dystrophy, with estimated incidence of 1 in 8000. An expansion of DMPK gene causes Myotonic dystrophy type 1 (DM1). As is the case with SMA, we have identified drugs which we believe may treat this disorder only in this case the drugs turn down the activity of this gene, making less of the harmful substance known as mRNA. We shall test these drugs in mouse models of myotonic dystrophy to establish whether they suppress the expanded harmful gene.