

004 Oral presentation
Results of a systemic antisense study in Duchenne muscular dystrophy

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The UK MDEX Consortium (<http://www.mdex.org.uk/>) is involved in close collaboration with AVI BioPharma, in clinical trials using antisense oligonucleotides (AOs) to induce exon skipping in boys with DMD. In 2008 we completed a dose-escalation IM study of a morpholino (PMO) AO, AVI-4658, which induces skipping exon 51 in dystrophin mRNA. In February 2009 we initiated a dose escalation study in ambulant DMD boys aged 5–15 years with deletions benefitting from skipping exon 51. This study consists of 12 weekly administrations of AVI-4658 followed by a muscle biopsy to assess dystrophin expression at baseline and 14 weeks. Clinical parameters are followed for 26 weeks, consisting of safety (adverse events, physical examinations, laboratory tests), muscle, pulmonary and cardiac function, and pharmacokinetics at 1st, 6th and 12th doses. A Data Safety Monitoring Board guides dose escalation decisions. Cohorts 1–5 completed 12 weeks of dosing (January 2010), while cohort 6 will complete dosing in March 2010 and clinical observations in June. No drug related SAEs or severe drug related AEs have been reported so far. To date, single doses of 900 mg and cumulative exposure exceeding 10,000 mg have been well tolerated. Exon skipping and dystrophin protein expression in the cohorts analysed so far indicates a dose response in exon skipping and protein expression in the cohorts up to 4.0 mg/kg, with data in the 10.0 and 20.0 mg/kg cohorts available soon. These results suggest that AVI-4658 has the potential to lead to the development of a drug that could play a role in the treatment of DMD.

005 Oral presentation
Acquired inflammatory neuropathy

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The inflammatory peripheral neuropathies are a heterogeneous group of conditions, some of which can be devastating and disabling. This lecture will update participants on the latest developments in common and less common inflammatory neuropathies encountered in practice.

Guillain-Barré syndrome, an acute monophasic post-infectious inflammatory polyradiculoneuropathy is the best understood in terms of pathogenesis. However the prognosis of this condition has not changed for 30 years with the mortality remaining at about 8–10%. New ideas for treatment based on increasing understanding of pathogenic mechanisms are emerging which may improve outcomes in the not too distant future.

Chronic inflammatory demyelinating polyradiculoneuropathy is a relapsing remitting or progressive condition which in most cases responds well to treatment. Intravenous immunoglobulin (IVIG) and steroids remain the backbone of treatment but the healthcare costs and long term side effect profiles are substantial. The ICE trial proved the effectiveness of IVIG in the long term. Future planned studies of rituximab and other long term immunosuppressants may provide curative treatment strategies.

Although no clinician will forget the patient with peripheral nerve vasculitis or POEMS syndrome, these remain 'orphaned' diseases amongst the inflammatory neuropathies. The evidence base for the treatment of peripheral nerve vasculitis is derived from renal and rheumatological medicine but provides good data on safety to support anecdotal regimens for treatment. The diagnosis of POEMS syndrome has become somewhat more straightforward with evidence that VEGF is dramatically raised in the serum and

may mirror disease activity. Aggressive therapeutic management regimens culminating in peripheral blood stem cell transplantation appear to have good outcomes, in the short term at least.

006 Oral presentation
Clinical and molecular aspects of dermatomyositis

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Juvenile dermatomyositis (JDM) is the most common form of idiopathic inflammatory myopathy of childhood. Like adult DM, JDM affects skin and muscle but involves more serious complications such as calcinosis or ulcerative skin disease, than in adults. JDM may also cause serious morbidity through involvement of other organ systems including gut, lung and CNS. At present we do not have prognostic biomarkers with which to predict either response to treatment or development of serious complications. We have developed a system for standardised assessment of muscle biopsy tissue in JDM which is now being validated. Affected muscle tissue from children with JDM taken early in disease may look normal by standard histology but is already immunologically 'abnormal' as evidenced by over expression of MHC Class I and deposition of C5–9 complex. We have demonstrated that juvenile muscle is highly sensitive to MHC Class I protein over expression compared to adult muscle, using a transgenic model of over expression, and that this change induces ER stress. Data on the down stream effects of this insult are under investigation in model systems and patient tissue.

007 Oral presentation
The John Newsom-Davis Lecture: The neuromuscular junction – a wide spectrum of disease mechanisms

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The neuromuscular junction (NMJ) is a relatively simple synapse between nerve and muscle that, being accessible to both circulating substances and to biopsy, has taught us many of the principles on which other synapses work. But in addition it exhibits a wide range of disease mechanisms – autoimmune, toxic and genetic.

John Newsom-Davis studied muscle biopsies initially to look at muscle spindle activity, following on from his work on respiratory physiology with Fred Plum in New York and Tom Sears in London. By happy coincidence, John was also directing the Batten intensive care unit at Queen Square where all the myasthenia gravis (MG) patients were taken after their thymectomies. A recommendation from Tom to Ricardo Miledi in the Biophysics department at UCL led to a collaboration between John and Ricardo that set the scene for all that followed. The autoimmune nature of MG was just being established in the USA, so John, with Tony Pinching and Keith Peters started plasma exchanging the MG patients (this leads to substantial reduction in circulating antibodies). There was a remarkable clinical effect which correlated inversely with the AChR antibody levels – that I had begun to measure – in almost every patient.

The exception was a young man who had had myasthenia since early childhood, and he had no AChR antibodies. John thought that he must have a genetic form of MG, and so we studied muscle biopsies from this and other patients, showing for the first time that congenital/inherited forms of myasthenia were distinct both clinically and, partly, electrophysiologically – leading to much excellent work in this condition by Andrew Engel, David Beeson, Hans Lochmüller and Daniel Hantai.

There were other MG patients, however, who did not have AChR antibodies but DID get better with plasma exchange. Many years later, we showed antibodies to muscle specific kinase (MuSK) in some of these. MuSK antibodies turn out to be interesting both clinically, as the patients have a rather striking phenotype, and functionally as we still don't understand really how the MuSK antibodies cause the NMJ defect.