Contents

Welcome to the sixth annual meeting of the MRC Centre for Translational Research in Neuromuscular Diseases

UK Neuromuscular Translational Research Conference 2013

Dear Colleagues,

We are delighted that the MRC Centre has been renewed for a further five years from 2013-2018 and to welcome you to Oxford for this sixth annual scientific meeting. We are very pleased that this annual UK Neuromuscular Translational Research Conference continues to be jointly hosted with the Muscular Dystrophy Campaign. In addition, this year we have worked closely with colleagues at the MRC Functional Genomics unit, the MRC Mitochondrial Biology Unit, the Wellcome Trust Centre for Mitochondrial Research and the Centre for Brain Ageing and Vitality to develop the scientific translational research programme. Major themes this year include translational research in mitochondrial diseases, neuromuscular channelopathies, muscular dystrophies and peripheral nerve diseases. Professor Dimitri Kullmann, Editor elect of the journal *Brain,* and channelopathy clinician scientist from the UCL Institute of Neurology, will deliver the second John Newsom Davis lecture.

The mission of the MRC Centre is to translate science into new experimental medicine trials and find treatments for children and adults with serious muscle wasting diseases. Collaborative working and interdisciplinarity represent a fundamental platform for successful translation. The MRC Centre works to bring together clinicians, scientists, patient organisations and patients in order to advance the UK translational research effort. This is a particularly exciting time in the field as a range of scientific discoveries are revealing an increasing number of therapeutic targets.

The MRC Centre continues to work closely with all its partners to support the development of a clinical trials culture and aims to embed an experimental clinical trials network in neuromuscular clinical practice. We will continue to work hard to form effective research and clinical links with as many other UK neuromuscular groups as possible. In the renewed Centre we have developed strong experimental medicine links with, and received important coordinated support from, three NHS NIHR Biomedical Research Centres based at University College London Hospitals, Great Ormond Street and at Newcastle University Hospitals.

The MRC Centre was founded in 2008 as a joint partnership between the UCL Institute of Neurology, Queen Square, the UCL Institute of Child Health and the University of Newcastle upon Tyne. The Centre continues to be closely linked to its partner NHS organisations, University College London Hospitals NHS Foundation Trust, Great Ormond Street Hospital for Children NHS Trust and Newcastle upon Tyne Hospitals NHS Foundation Trust. The Centre has also developed strong links with groups in Oxford and Cambridge which we will develop further in this next phase of the Centre.

Over the next two days this conference aims to showcase a wide range of high quality scientific neuromuscular research from many UK groups, international colleagues and industry partners.

We have received 85 high quality abstracts, and there will be dedicated poster sessions each day as well as guided poster discussions. There will be £500 poster prizes for young investigators. We plan that accepted abstracts will be published in the journal *Neuromuscular Disorders* later this year.

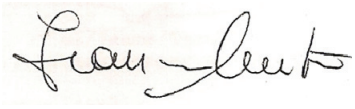
As the Centre Director, I would very much like to thank the joint MRC-MDC meeting scientific planning team: Professors Kate Bushby, Doug Turnbull, Mary Reilly, Francesco Muntoni, Dame Kay E Davies, and Drs Marita Pohlschmidt, David Hilton-Jones and Dave Bennett. I also

especially thank Christine Oldfield and Julia Ambler for all their very hard work in organising this meeting.

Once again this annual meeting has been oversubscribed. We are very encouraged that there continues to be such strong interest in neuromuscular translational research from throughout the UK and beyond.

We sincerely hope that you have a stimulating, useful and entertaining two days in Oxford.

Professor Michael G Hanna
Director
MRC Centre for Neuromuscular Diseases,
UCL Institute of Neurology

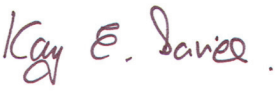


Professor Francesco Muntoni
Co-Director, ICH/GOS
MRC Centre for Neuromuscular Diseases
UCL Institute of Child Health

Professor Mary Reilly
Co-Director
MRC Centre for Neuromuscular Diseases,
UCL Institute of Neurology

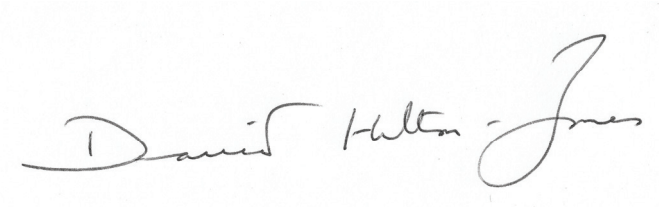
Professor Katie Bushby
Co-Director, Newcastle
MRC Centre for Neuromuscular Diseases,
University of Newcastle upon Tyne

Professor Doug Turnbull
Co-Director
MRC Centre for Neuromuscular Diseases
University of Newcastle upon Tyne



Professor Dame Kay E Davies
Director, MRC Functional Genomics Unit
University of Oxford

Dr Marita Pohlschmidt
Director of Research,
Muscular Dystrophy Campaign



Dr David Hilton-Jones
John Radcliffe Hospital
University of Oxford

Dr David Bennett
University of Oxford

Welcome from Robert Meadowcroft – Chief Executive of the Muscular Dystrophy Campaign

Welcome to the 2013 UK Neuromuscular Translational Research Conference organised in partnership between the MRC Centre for Neuromuscular Diseases and the Muscular Dystrophy Campaign.

This is the sixth time that the Muscular Dystrophy Campaign has been able to support this meeting and we are delighted, once again, that scientists and clinical researchers from across the field of neuromuscular disorders have an opportunity to showcase progress in the field. There is a particular spotlight on how these advances will translate into patient benefit which is what we are all striving so hard to achieve.

The Muscular Dystrophy Campaign has supported research into neuromuscular disorders for over 50 years. During this time our families and supporters have raised more than £50 million to fund cutting-edge science and research, whilst a further £50 million has been invested in care and support for families. Despite the uncertain economic climate the charity is pressing forward and we continue to lead the fight against all forms of muscular dystrophy and related conditions not only in research but through campaigns, advocacy support, information and advice.

The charity continues to successfully campaign for improvements in patient care and support by lobbying the Government and NHS decision makers to ensure patients with neuromuscular disorders can access specialist care. We are particularly pleased to have secured NHS funding for more than 30 Care Advisor posts across the UK – positions, that over the past 20 years, had been solely funded by the Muscular Dystrophy Campaign. As we all recognise, without a well resourced clinical infrastructure, treatments have no route out of the laboratory, so I would like to thank all our clinical colleagues who have worked so hard to help us make the case for a high quality national neuromuscular service.

We are pleased to see impressive progress being made in research and in improving clinical care and this is very much the result of a collaborative effort over many years. I am very pleased that the Muscular Dystrophy Campaign continues to play a positive and influential role on behalf of all patients and families affected by the conditions.

We are very much committed to building on these achievements as well as our research investment into neuromuscular disorders, and will continue to forge strong relationships with scientists and clinical researchers across the globe to ensure that emerging treatments have the best possible chance of leading to patient benefit as quickly as possible. It is a sad and very unwelcome fact that time is often a luxury these patients and families do not have.

I want to thank you for all the hard work that you have put into fighting muscle wasting disease over the last twelve months. I wish you well in your endeavours and hope that you have a very productive and enjoyable conference here in Oxford.

Robert Meadowcroft
Chief Executive, Muscular Dystrophy Campaign

About the MRC Centre for Neuromuscular Diseases

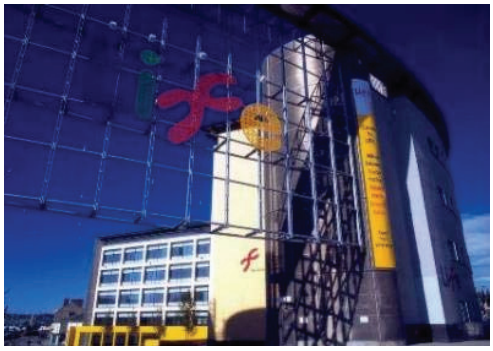
Genetic and acquired neuromuscular diseases represent a major cause of mortality and morbidity in children and adults affecting over 100,000 patients and their families in the UK. There remains an important gap between major science discoveries and patient benefit in these important disorders. The MRC Centre aims to continue to reduce this gap by supporting and promoting multidisciplinary translational research activity in these disabling diseases.

This is a joint Centre between the UCL Institute of Neurology and the UCL Institute of Child Health, London and the University of Newcastle. The Centre is building on long-established UCL-Newcastle research and clinical links. The Centre is forming reciprocal clinical and research links with other major neuromuscular research groups in Oxford and Cambridge and with patient organisations throughout the UK. The Centre works with the very large adult and paediatric neuromuscular disease patient populations cared for at the co-located hospitals: Great Ormond Street NHS Trust, the National Hospital for Neurology and Neurosurgery - Queen Square, UCLH NHS Foundation Trust and Newcastle Upon Tyne Hospitals NHS Foundation Trust.

Our mission continues to be to translate science findings into experimental clinical trials and new treatments for children and adults with disabling neuromuscular diseases. Current world-class science programmes in London and Newcastle attracting in excess of £30m of grant income underpin the activities of the Centre. The Centre continues to develop new cross-cutting collaborations and has capitalised on the recruitment of world-class senior academic personnel to UCL and to the University of Newcastle. We have focused on five key areas which are obstacles to effective translation of basic science findings into patient benefit. These are: experimental clinical trials support, availability of patient tissues and cells, assessing animal models, applying MRI to humans and animals and developing capacity for the future. The Centre is specifically addressing each of these obstacles:

- We are facilitating clinical trials in neuromuscular disease in the UK by forming a single clinical trials support activity drawing on and combining the expertise in London and Newcastle. We are taking advantage of the geography by forming north and south neuromuscular clinical trials centres. We are working together to facilitate clinical trial design, to develop biostatistical support, to develop clinical trial coordination, and to establish patient registries and clinician networks. We are taking advantage of well- established, government funded, collaborative specialist neuromuscular diagnostic services which already exist between London, Oxford and Newcastle (NCG services). The MRC Centre is working closely with TREAT-NMD, the pan-European network of excellence and with the NHS NIHR Biomedical research Centres. In the first phase of the MRC Centre we delivered a step change and well over 2000 patients were entered into natural history studies and clinical trials.

- A shortage of human cell lines and neuromuscular tissues currently hinders basic science efforts and in vitro testing of potential therapies. We have now established a unique UK biobank of human neuromuscular patient tissues and have collected over 2000 human cell lines that have been invaluable for translational research including preclinical therapy evaluation.



- Assessing the validity of animal models of neuromuscular disease and correlating phenotypes with human disease remains an important problem. We have linked clinical and basic scientists, thereby establishing a network and resource for elucidating the validity of mouse models.

- We have developed new outcome measures and biomarkers for NM diseases. We continue to develop new MRI techniques which have started to change the way we assess and monitor neuromuscular disease in patients. We are taking advantage of major new MRI facilities in London and Newcastle to establish cutting edge MRI of nerve and muscle disease in animals and humans.

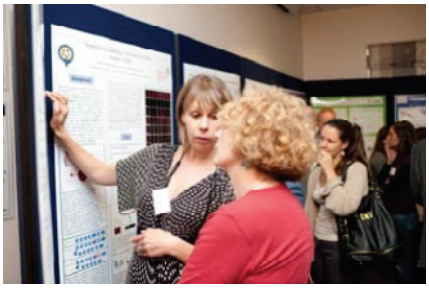
- We recognise the critical importance of training the basic and clinical neuromuscular scientists of the future. The Centre has developed and delivered very susscessful four-year and three year translational neuromuscular disease PhD programmes, and twelve science PhD students have already graduated from this programme. A cadre of 12 new students (from over 150 applicants) have been appointed from 2013. We prioritise the provision of exciting and inspirational translational research environments to continue to train the next generation of basic and clinical neuromuscular scientists, building future capacity in the UK.

By developing these five core areas the Centre will promote translational research and add value to basic science neuromuscular research themes currently active in London, Newcastle and other centres.

About the Muscular Dystrophy Campaign

The **Muscular Dystrophy Campaign** is the leading UK charity focusing on muscular dystrophy and neuromuscular diseases. We have pioneered the search for treatments and cures for 50 years, and are dedicated to improving the lives of all children and adults affected by these conditions.

We fund world-class research to find effective treatments and cures; provide practical and emotional support for individuals and families; campaign to raise awareness and bring about change, award grants towards the cost of specialist equipment, such as powered wheelchairs and provide specialist training and development for health professionals.



Since the Muscular Dystrophy Campaign was founded in 1959 we have supported scientists researching the underlying molecular basis of muscular dystrophies and related neuromuscular conditions. In recent years, these investments have come to fruition and the focus of the research has begun to shift towards the development of therapeutic approaches.

We now need to invest in translational research - this is necessary because we need a speedy bench-to bedside transfer of promising technology. But this involves two-way interaction between the scientists and the clinicians. The basic bench science is important for understanding underlying causes of disease, something that can provide a plethora of potential drug or gene therapy targets.

Equally the observations that clinicians make at the bedside can provide a wealth of new information about a condition focussing the search for the scientist. There are however, many barriers in the meaningful progression of data and observations from the lab to something that ultimately will be life changing for people affected by these devastating conditions, and their families.

The Muscular Dystrophy Campaign aims to speed up this transition by providing support to both scientists and clinicians. We not only fund basic science through to pre-clinical research and where possible clinical trials. We also provide logistic and financial support to create platforms where clinicians and scientists can meet, exchange experiences and discuss ideas.

Research has significantly advanced in recent years and the charity's focus has shifted from funding very basic science to funding translational research, promoting clinical-trial readiness. The charity recognises this shift and we are currently in the process of reviewing our research strategy to address the changing research landscape and to ensure that our funds are invested into areas where they will have the most impact.

In order to give you an overview of the science that we support, we have invited our current grantees to present their work during the poster sessions. We hope these sessions will be of interest to you and will provide you with an update of the recent research advances that the scientists and clinical researchers have made.

Patient Organisations

The MRC Centre and the Muscular Dystrophy Campaign aim to develop strong links with all neuromuscular patient organisations.

UK Neuromuscular Translational Research Conference 2013
Medical Sciences Teaching Centre, Oxford

Thursday 14th – Friday 15th March

PROGRAMME

Day 1 – Thursday 14th March

09:00 – 10.15	**Registration and Coffee**
10:15 – 10:30	Introduction Professor Michael Hanna UCL Institute of Neurology
10:30 – 13:00	**Translational Research in Human Mitochondrial Diseases** **Chairs: Professors Patrick Chinnery (Newcastle University) and Massimo Zeviani (MRC Mitochondrial Biology Unit)**
10:30 – 11:00	Evaluating new therapies in mitochondrial diseases Professor Anu Suomalainen, University of Helsinki, Biomedicum-Helsinki
11:00 – 11:30	Developing new treatments in mitochondrial disease Dr Werner Koopman, Radboud University Medical Centre
11:30 – 12:00	Exercise treatments in mitochondrial myopathies Dr Grainne Gorman, Newcastle University
12:00 – 12:15	Evidence based treatments in mitochondrial diseases - Challenges and pitfalls Professor Patrick Chinnery, Newcastle University
12:15 – 12:30	*NDUFA4* mutations: a new cause of mitochondrial cytochrome *c* oxidase linked neurological disease Rob Pitceathly, UCL Institute of Neurology
12:30 – 12:45	Defective thiolation impairs mitochondrial translation offering a therapy approach in reversible infantile respiratory chain deficiency Veronika Boczonadi, Newcastle University
12:45 – 13:15	**Late breaking abstracts**

12:45 – 13:00	Safety and tolerability of Arimoclomol in patients with sporadic inclusion body myositis: a randomised, double-blind, placebo-controlled, phase IIa proof-of-concept trial Pedro Machado, UCL Institute of Neurology
13:00 – 13.15	The potential of morpholino antisense oligonucleotides for the therapy of spinal muscular atrophy Dr Haiyan Zhou, UCL Institute of Child Health
13:15 - 14:30	**Posters and lunch**
14:30 – 16:30	**Neuromuscular Channelopathies: Bench to Bedside** **Chairs: Professor David Beeson (University of Oxford) and Dr David Hilton-Jones (John Radcliffe Hospital, Oxford)**
14:30 – 15:00	Animal models and new treatments for hypokalemic periodic paralysis Professor Steve Cannon, UT Southwestern Medical Center, Dallas
15:00 – 15:30	Disease mechanisms and MRI monitoring in muscle channelopathies Professor Frank Lehmann-Horn, University of Ulm
15:30 – 16:00	Congenital myasthenia mechanisms and treatments Professor David Beeson, John Radcliffe Hospital, University of Oxford
16:00 – 16:15	A novel mutation in *SCN4A* and its equivalent in *Scn4a* cause periodic paralysis in humans and mice Dr Silvia Corrochano Sanchez, MRC Mammalian Genetics Unit, Oxfordshire
16:15 – 16:30	ALG2 – a new gene that causes congenital myasthenic syndromes Dr Judith Cossins, University of Oxford
16:30 – 17:00	MRC Translational Research Strategy Dr Catherine Elliott, Medical Research Council
17:00 - 17:30	**Posters & tea**
17:30 – 18:30	**John Newsom Davis Lecture:** **Introduced by Dr David Hilton-Jones** Presynaptic channelopathies of the neuromuscular junction and brain Professor Dimitri Kullmann, UCL Institute of Neurology
18:30 – 19:30	**Drinks reception and posters** introduced by Robert Meadowcroft, Muscular Dystrophy Campaign CEO
20:30 - 22:45	**Gala dinner – Balliol College**

Day 2 - Friday 15th March

09:00 – 11:30	**Translational research in peripheral nerve diseases** **Chairs: Professors Mary Reilly (UCL Institute of Neurology) and Dave Bennett (University of Oxford)**
09:00 – 09:30	Pathogenesis and treatment of CMT secondary to MPZ mutations Professor Mike Shy, Carver College of Medicine, University of Iowa
09:30 – 10:00	New insights into the pathogenesis of inflammatory neuropathies Dr Simon Rinaldi, University of Oxford
10:00 – 10:30	Novel insight into painful neuropathic channelopathies Dr Dave Bennett, University of Oxford
10:30 – 11:00	Leprosy neuropathy: Clinical features and treatment Professor Diana Lockwood, London School of Hygiene and Tropical Medicine
11:00 – 11:15	An in-vitro study of distal hereditary motor neuropathy due to homozygous HSJ1 mutations Dr Alex Rossor, UCL Institute of Neurology
11:15 – 11:30	Investigating Riboflavin Transporter Mutations in Brown-Vialetto-Van Laere Syndrome Amelie Pandraud, UCL Institute of Neurology
11:30 - 13:15	**Posters guided tours**
13:15 – 14:00	**Lunch**
14:00 – 17:00	**Muscular Dystrophy** **Chairs: Professors Kay Davies (University of Oxford) and Francesco Muntoni (UCL Institute of Child Health)**
14:00 – 14:30	New understanding of FSHD pathogenesis Professor Silvère M. van der Maarel, Leiden University Medical Centre
14:30 – 15:00	Myotonic dystrophy- is molecular treatment on the horizon? Professor Charles Thornton, University of Rochester Medical Centre
15:00 – 15:30	Muscle stem cells in Duchenne and Emery-Dreifuss muscular dystrophy Professor Peter Zammit King's College London
15:30 – 16:00	Treating DMD using muscle hypertrophy strategies Dr Carl Morris, Rare Disease Unit, Pfizer

16:00 – 16:30 Gene therapy for DMD and OPMD
Professor George Dickson, Royal Holloway, University of London

16:30 – 16:45 Poster prizes and close

Speaker Abstracts

Thursday 14th March 2013

Evaluating new therapies for mitochondrial disorders

Professor Anu Suomalainen
University of Helsinki, Biomedicum-Helsinki, Finland.

Mitochondrial disorders span from neonatal devastating multisystem disorders to neurodegeneration of late adulthood, and can manifest in any organ system. Despite the being a common group of genetic disorders, only palliative treatment can be offered for mitochondrial disease patients. We have created a late-onset mitochondrial myopathy mouse model, which accumulates multiple mtDNA deletions in skeletal muscle and brain. We have shown that the myopathy elicits a molecular response in the muscle that mimics that of starvation. This response is also present in human patients with mitochondrial myopathies. Therefore, we have tested the effect of modified nutrition and nutritional signaling, as well as induction of mitochondrial biogenesis in mice and partially also in patients with mitochondrial myopathies. The results show that nutrition and starvation-associated signaling play an important role in disease pathogenesis and symptoms in mitochondrial myopathy patients, and offer an attractive target for intervention.

Developing new treatments in mitochondrial disease

Dr Werner J.H. Koopman,
Radboud University Medical Centre, Nijmegen, The Netherlands.

Normal cell functioning and survival requires energy in the form of ATP that is generated by a variety of metabolic pathways. Within this metabolism, the mitochondrial oxidative phosphorylation (OXPHOS) system is among the prime producers of ATP. Proper OXPHOS function is also required to sustain many other mitochondrial processes including the exchange of ions and metabolites with the cytosol. In this sense, the OXPHOS system plays a key role in various cellular processes like adaptive thermogenesis, innate immune responses, calcium and redox signalling, and programmed cell death (apoptosis). The OXPHOS system consists of 5 multi-subunit complexes (CI to CV) that contain 92 different structural proteins encoded by the nuclear (nDNA) and mitochondrial DNA (mtDNA). Biogenesis of a functional OXPHOS system further requires the assistance of nDNA-encoded OXPHOS assembly factors (chaperones), of which 35 are currently identified. OXPHOS and mitochondrial dysfunction are not only associated with relatively rare monogenic mitochondrial disorders but also observed during more common pathologic conditions, such as Alzheimer's, Huntington's and Parkinson's disease, cancer, cardiac disease, diabetes, epilepsy, and obesity. In addition, a progressive decline in the expression of mitochondrial genes is observed during normal human aging and mitochondrial function is inhibited by environmental toxins and frequently used drugs. Mutations in OXPHOS structural genes are associated with neurodegenerative diseases including Leigh Syndrome, which is probably the most classical OXPHOS disease during early childhood. My research focuses on gaining a quantitative mechanistic understanding of mitochondrial (patho)physiology at the (sub)cellular level in OXPHOS disorders. To this end, the following research questions are addressed: (i) How are mitochondrial (ultra)structure and metabolic (dys)function connected?) (ii) How does mitochondrial (dys)function affect cellular (dys)function? (iii) How do cells adapt to mitochondrial dysfunction? (iv) How can mitochondrial dysfunction be mitigated? Given the tight integration of mitochondrial and cellular metabolism, the above questions are adressed in living cell systems. To this end, protein-based and chemical fluorescent reporter molecules are introduced in healthy and patient-derived primary cells, as well as established cell lines to allow analysis of mechanistic aspects. (Patho)physiology is then investigated using biochemical and molecular cloning techniques, high-resolution respirometry, state-of-the-art quantitative (sub)cellular life cell microscopy, single-molecule spectroscopy, mathematical modelling, image processing, data mining and machine learning techniques.

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Exercise Treatments in Mitochondrial Myopathies

Dr Grainne Gorman
MRC Centre, Newcastle University

Mitochondrial myopathies are a heterogeneous group of genetic disorders, affecting up to 8,000 adults in the UK, resulting in significant morbidity and disability. The molecular basis of many of the common mitochondrial myopathies has been elucidated over the last decade, yet currently there are no known cures and few effective treatments.
Several independent studies, including work in Newcastle, supported predominantly by the Muscular Dystrophy Campaign, has shown that both resistance and endurance exercise therapy is safe and effective at improving aerobic and oxidative capacity, reversing de-conditioning and improving skeletal muscle strength and health-related quality of life indices in patients with mitochondrial myopathies. Despite this evidence, very few patients are given clear instructions about exercise.
The objective of this presentation is to examine the current evidence of the effects of physical training and to explore the needs and barriers to exercise prescription in patients with mitochondrial myopathies as we endeavour to devise and facilitate the translation of safe and effective therapies into clinical practice, whilst targeting underlying disease mechanisms.

Evidence based treatments in mitochondrial diseases - Challenges and pitfalls

Professor Patrick Chinnery
MRC Centre, Newcastle University

The last two decades have seen major advances in our ability to provide a molecular diagnosis for patients with mitochondrial diseases. This has direct benefits on patient management through an accurate diagnosis and evidence-based genetic and prognostic counselling. However, treatments have not been forthcoming. With over 1500 publications reporting a treatment effect, it is salutary that there have only been 11 randomised controlled clinical trials to date. Although some show promise, the primary end points of these studies were negative.
On a more optimistic note, it is encouraging that advanced understanding of disease mechanisms is opening up new avenues for interventions using both pharmacological and exercise paradigms. In addition, large and medium sized pharmaceutical companies have become interested in the

possibility of developing treatments for mitochondrial diseases. This may have broader relevance for common disorders where mitochondrial mechanisms have been implicated.
Carrying out randomised controlled trials in rare diseases is particularly challenging, in part because patients are scattered over large geographic areas, and also because, even for genetically defined mitochondrial diseases, the phenotype is characteristically diverse and may fluctuate over time. A lack of natural history data makes it difficult to produce robust trial protocols, and as a result, there has been a push towards open labelled studies using biomarkers as measures of disease activity. This approach obviously raises concerns because of the potential bias introduced by investigators and patients, who are both highly motivated to find new treatments. Nonetheless, there are now several examples where international consortia are carrying out natural history studies and are running randomised controlled trials in rare mitochondrial disorders. These studies will set the benchmark for future work in this areana, providing real hope of new treatments in the near future.

NDUFA4 mutations: a new cause of mitochondrial cytochrome _c_ oxidase linked neurological disease
Dr Rob Pitceathly
UCL Institute of Neurology
Please see poster abstracts, no: 30

Defective thiolation impairs mitochondrial translation offering a therapy approach in reversible infantile respiratory chain deficiency
Veronika Boczonadi
Newcastle University
Please see poster abstracts, no: 26

Safety and tolerability of Arimoclomol in patients with sporadic inclusion body myositis: a randomised, double-blind, placebo-controlled, phase IIa proof-of-concept trial
Dr Pedro Machado
UCL Institute of Neurology
Please see poster abstracts, no: 74

The potential of morpholino antisense oligonucleotides for the therapy of spinal muscular atrophy
Dr Haiyan Zhou
UCL Institute of Child Health
Please see poster abstracts, no: 44

Animal Models and a New Treatment for Hypokalemic Periodic Paralysis
Professor Stephen C. Cannon
University of Texas Southwestern Medical Center, Dallas, Texas USA

The clinical hallmark of hypokalemic periodic paralysis (HypoPP) is recurrent episodes of severe weakness in association with low serum K^+ . This dominantly inherited disorder is caused by missense mutations in the voltage-sensor domains of the skeletal muscle sodium channel (NaV1.4) or calcium channel (CaV1.1). Oocyte expression studies of mutant channels have implicated a common pathomechanism, whereby a misfit between the sensor and the channel causes an anomalous inward leakage current at the resting potential. We recently developed knock-in mouse models of HypoPP with the NaV1.4-R669H and CaV1.1-R528H mutations. Mice have a robust HypoPP phenotype with loss of muscle excitability from a glucose + insulin challenge and loss of force with an in vitro low-K^+ challenge. Currents recorded from dissociated fibers had a leakage "gating pore" conductance, approximately 1% of the total resting fiber conductance. This anomalous inward current enhances the susceptibility to paradoxical depolarization of the resting potential in low K^+, which renders the fiber inexcitable. Computational models suggest the chloride gradient has a strong influence on the likelihood of

paradoxical depolarization. Block of a chloride transporter (Na-K-2Cl) with the loop diuretic bumetanide was predicted to stabilize the resting potential. In vitro contraction tests on HypoPP mouse fibers showed that bumetanide prevents the loss of force in a subsequent low-K^+ challenge and can even produce a full recovery of force when applied to fibers already weakened in low K^+.

This work was supported by NIAMS of the National Institutes of Health and by the Muscular Dystrophy Association (USA).

Disease mechanisms and MRI monitoring in muscle channelopathies

Professor Frank Lehmann-Horn, Karin Jurkat-Rott
Neurophysiology, Ulm University, Ulm, Germany

A combination of electrophysiological and molecular genetic studies has resulted in the discovery of certain skeletal muscle disorders caused by pathologically functioning ion channels. The group of thus defined hereditary "muscle channelopathies" comprises congenital myasthenic syndromes, non-dystrophic myotonias, dyskalaemic periodic paralyses, central-core myopathy and multi-minicore myopathy, as well as malignant hyperthermia. Many muscle channelopathies are benign disorders, but muscle hypermetabolism resulting in muscle stiffness and hyperthermia as in an event of malignant hyperthermia can be life-threatening. Also, forms of familial periodic paralysis can be severe when they produce serious dyskalaemia that disturbs cardiac excitation conduction. The hypokalaemia is most pronounced in thyrotoxic periodic paralysis. Some of the periodic paralyses are associated with a progressive permanent weakness. The episodic or chronic weakness usually is caused by a sustained membrane depolarization which results in sodium channel inactivation, rendering the fibres inexcitable. The membrane depolarization is associated with intracellular sodium and water accumulation as shown by 23Na-MRI and by fat-suppressed 1H-MRI in-vivo. The myoplasmic oedema is cytotoxic and should be treated before fatty degeneration takes place. Drugs that repolarize the fibre membrane can restore muscle strength and may prevent progression. Of carbonic anhydrase inhibitors, loop diuretics and aldosterone antagonists (AA), the AA eplerenone seems to have the highest repolarizing power, the parameter considered by us as being most relevant for a beneficial effect.

Congenital myasthenia mechanisms and treatments

Professor David Beeson
Weatherall Institute of Molecular Medicine, Oxford University

Congenital myasthenic syndromes (CMS) are hereditary disorders of neuromuscular transmission characterised by fatigable muscle weakness. The number of cases recognised is increasing with improved diagnosis. To date we have provided a genetic diagnosis for over 425 patients, and identified over 300 different mutations . The underlying genetic defects are diverse involving a series of different genes with a variety of different phenotypes. The type of treatment and its effectiveness depends on the underlying pathogenic mechanism. We aim to define the molecular mechanism for each mutation identified and use this as the basis for a rationaltreatmen strategy for each individual patient. Here, we highlight a series of genes that encode proteins in the initial steps of the N-linked glycosylation pathway in which newly identified mutations cause CMS. We also discuss new paradigms for neuromuscular junction stability that we are using as the basis for optimising patient treatment. The study of these disorders is proving highly informative for understanding the diverse molecular mechanisms that can underlie synaptic dysfunction, and provides an example of how state of the art advances in molecular medicine can be rapidly translated into patient care. In particular, by going from 'bedside to bench and back' we are able to provide personalised medicine that can dramatically benefit patients and their families.

A novel mutation in *SCN4A* and its equivalent in *Scn4a* cause periodic paralysis in humans and mice

Silvia Corrochano Sanchez
MRC Mammalian Genetics Unit, Oxfordshire
Please see poster abstracts, no: 59

ALG2 – a new gene that causes congenital myasthenic syndromes
Judith Cossins, University of Oxford
Please see poster abstracts, no: 72

MRC Translational Research Strategy
Dr Catherine Elliott, Medical Research Council

John Newsom Davis Lecture:
Presynaptic channelopathies of the neuromuscular junction and brain
Professor Dimitri M Kullmann
MRC Centre, UCL Institute of Neurology

The motor nerve terminal is affected in several acquired and inherited disorders of ion channels characterized by muscle weakness, fatigability, stiffness or twitching. These include Lambert-Eaton myasthenic syndrome, acquired neuromyotonia and episodic ataxia type 1. The precise mechanisms of these disorders, and their CNS counterparts, remain poorly understood, in part because of the relative inaccessibility of small nerve terminals for electrophysiological recordings. Several alternative methods have however been developed to study the propagation of action potentials, calcium influx, and triggering of neurotransmitter release from small nerve terminals. Mouse models of the presynaptic channelopathies have also shed light on the fundamental mechanisms of neurotransmitter release. These new approaches are beginning to unravel how autoantibodies and mutations affecting presynaptic potassium and calcium channels cause clinical manifestations.

Friday 15th March 2013

Pathogenesis and treatment of CMT secondary to MPZ mutations
Professor Mike Shy
Carver College of Medicine, University of Iowa

Myelin protein zero (MPZ), a transmembrane glycoprotein of the immunoglobulin supergene family, is the major structural protein in PNS myelin, is expressed exclusively by myelinating Schwann cells, and facilitates compaction of PNS myelin. Human mutations in MPZ give rise to peripheral demyelinating neuropathies, Charcot Marie Tooth disease type 1B (CMT1B). Most patients present with three distinct phenotypes: one with disease onset in infancy, extremely slow nerve conduction studies (NCS), and pathological evidence of abnormal myelin development; a second group with disease onset in the first two decades of life, slow NCS, and pathological evidence of abnormal myelin maintenance; and a third group with disease onset in adulthood, essentially normal NCS and pathological evidence of axonal loss with minimal demyelination. MPZ mutations likely cause neuropathy by multiple disease mechanisms based on the particular mutation. We, and others, have found that some mutations result in the mutant protein being retained in the ER where it activates a Unfolded Protein Response (UPR) that contributes to the neuropathy by altering transcription and the myelinating state of the affected Schwann cells. We have also found that derivatives of curcumin, a component of turmeric, improves the neuropathy and ameliorates the UPR of the R98C knockin mouse model of CMT1B. Whether this response is unique to R98C, and whether the response depends on UPR activation is currently under investigation.

New insights into the pathogenesis of inflammatory neuropathies
Dr Simon Rinaldi
Academic Clinical Lecturer, University of Oxford

For certain inflammatory neuropathies, serological-pathological-clinical associations are well established and consistent. In Miller Fisher syndrome, antibodies directed against the ganglioside GQ1b are detected in 90 to 95% of cases, and have been shown to exert deleterious effects on

the structure and function of the neuromuscular junction. Antibodies against other gangliosides are often found in axonal variants of Guillain-Barré syndrome (GBS). There has been an expansion of knowledge regarding the sites known to be susceptible to anti-ganglioside antibody mediated injury, and also of the pathological end effects which may ensue. Thus in some cases terminal nodes of Ranvier may be more sensitive to injury, and in others antibodies can impair nerve regeneration following injury. It is becoming clear that the nature of the prodromal infecting organism not only influences the subtype of the resultant neuropathy, but also profoundly modulates the nature of the underlying autoimmune response. Nevertheless, in acute inflammatory demyelinating polyradiculoneuropathy (AIDP), the commonest subtype of GBS in the Western world, antibodies are infrequently detected, and the importance of the humoral immune system in this condition has been questioned. Modern combinatorial glycoarray techniques show that antibodies directed against heterodimeric glycolipid complexes are more frequent in these demyelinating subtypes. For some anti-complex antibodies pathogenicity is beginning to be established. Such antibodies have the potential to resolve some of the apparent serological-pathological-clinical inconsistencies which remain in the inflammatory neuropathies. Compared to single ganglioside assays, anti-complex antibodies detected by glycoarray have greater promise as diagnostic and prognostic biomarkers.

Novel insight into painful neuropathic channelopathies

Dr Dave Bennett
University of Oxford

There has been significant progress over the last decade in understanding the molecular basis by which sensory neurons transduce and subsequently transmit noxious (ie. tissue damaging) stimuli giving rise to the sensation of pain. Over this same period we have recognized that mutations in such ion channels (many of which are selectively expressed in sensory neurons) can result in primary neuropathic pain disorders. An excellent example is the voltage gated ion channel Na_V 1.7 encoded by the gene SCN9a. Loss of function mutations in this ion channel result in congenital inability to experience pain and gain of function mutations can cause a number of distinct neuropathic pain disorders including erythromelalgia, paroxysmal extreme pain disorder and small fibre neuropathy. There is a correlation between the impact of mutations on the biophysical properties of the ion channel and the severity of the clinical phenotype. I will also discuss the relationship between other high genetic variants and neuropathic pain disorders including mutations in Na_V 1.8 resulting in small fibre neuropathy and TRPA1 causing familial episodic pain disorder. There is now some tentative evidence that not only are there inherited painful channelopathies but acquired channelopathies due to the generation of autoantibodies to ion channel complexes may result in secondary neuropathic pain disorders.

Leprosy Neuropathy: Clinical Features and Treatment

Professor Diana NJ Lockwood
London School of Hygiene & Tropical Medicine, Hospital for Tropical Diseases

The key messages for neurologists in managing leprosy are:
To think of leprosy as a cause of peripheral neuropathy.
WHO multi-drug therapy is highly effective for treating the infection.
Detecting and treating nerve damage early.
To refer patients with leprosy for management.
The challenge of persistent neural and skin inflammation.

It is important to diagnose leprosy early because then anti-bacterial treatment can be initiated and peripheral nerve damage minimised. Paradoxically it is easier to diagnose leprosy in an endemic country than outside endemic areas. We have a cohort of 145 patients in London, UK who have been diagnosed with leprosy in the last 13 years and have found significant delays in diagnosis. The geographical and ethnic profile of patients reflects migration patterns to the UK, 54% of our patients come from the Indian sub-continent. The period from start of symptoms to diagnosis varies from 1 month to 15 years. Misdiagnoses were common, and there was a high level of nerve damage and reactions. Key pointers for making a diagnosis of leprosy will be

discussed (peripheral trunk nerve damage and glove and stocking neuropath0. Leprosy is essentially a clinical diagnosis, supported by histology.

Current treatments with the WHO multi-drug combinations (Rifampicin, Dapsone and Clofazimine) are highly effective with relapse rates < 1 % year and no evidence of Rifampicin resistance.
The large INFIR cohort study in N India has yielded new data on the presence and detection of nerve damage. 38% of the subjects enrolled had nerve damage at the time of diagnosis. A further 39% developed new nerve damage during the follow up period. Sub-clinical neuropathy was extensive, affecting 20-50% depending on the test used. Changes in temperature were the most sensitive marker of neuropathy. Simple methods of detecting neuropathy need to be done on every patient.

Steroid therapy has been used to treat leprosy associated nerve damage but a recent Cochrane review was only able to include three trials. One trial has suggested that better outcomes are associated with longer treatment periods (20 vs 12 weeks). The outcomes with steroid treatment are disappointing. Other treatments are needed to stop inflammation

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An in-vitro study of distal hereditary motor neuropathy due to homozygous HSJ1 mutations
Dr Alex Rossor
UCL Institute of Neurology
Please see poster abstracts, no: 47

Investigating Riboflavin Transporter Mutations in Brown-Vialetto-Van Laere Syndrome
Amelie Pandraud
UCL Institute of Neurology
Please see poster abstracts no: 48

New understanding of FSHD pathogenesis
Silvère M. van der Maarel, PhD
Professor of Medical Epigenetics, Leiden University Medical Center

Facioscapulohumeral muscular dystrophy (FSHD) is a common form of muscular dystrophy in adults. FSHD is associated with chromatin decondensation of the D4Z4 macrosatellite array on chromosome 4 and expression of the D4Z4-encoded *DUX4* gene in skeletal muscle. DUX4 is a germline transcription factor that is normally suppressed in somatic tissue.
Two equally common variants of chromosome 4 have been identified of which only one is permissive to *DUX4* expression due to the presence of a polymorphic *DUX4* polyadenylation signal. In most patients, somatic derepression of *DUX4* is caused by contraction of the D4Z4 array (FSHD1) on a permissive allele and is inherited as a dominant trait. However, in some patients

D4Z4 chromatin decondensation occurs on normal sized arrays (FSHD2) of both chromosomes 4 and shows a more complex inheritance pattern. We discovered that mutations in the chromatin modifier *SMCHD1* on chromosome 18 segregate with genome-wide D4Z4 CpG hypomethylation in FSHD2 families. FSHD2 patients inherited both mutations in this chromatin modifier and normal-sized D4Z4 arrays permissive for *DUX4* expression. Currently, we have identified >40 mutations in *SMCHD1* explaining approximately 80% of FSHD2. We observed that mutations in *SMCHD1* can also aggravate disease severity in FSHD1 families with borderline D4Z4 repeat sizes.
SMCHD1 is a chromatin modifier involved in establishment and/or maintenance of CpG methylation and binds directly to the D4Z4 repeat. In FSHD2 patients there is reduced binding of SMCHD1 to D4Z4 and knock down of SMCHD1 in normal myoblasts containing a permissive chromosome 4 leads to the activation of *DUX4*.
In conclusion, we identified mutations in an epigenetic modifier of the D4Z4 chromatin structure to cause FSHD2 and to modify clinical severity in FSHD1 suggesting that the disease mechanisms of FSHD1 and FSHD2 converge at the level of D4Z4 chromatin decondensation and somatic *DUX4* expression.

Myotonic dystrophy- is molecular treatment on the horizon?
Professor Charles Thornton
University of Rochester Medical Centre

Recent efforts to develop targeted therapies for myotonic dystrophy are focused on RNA toxicity – the set of transcriptomic changes and other cellular perturbations that are brought about by expression of RNAs that contain expanded CUG or CCUG repeats (in DM1 and DM2, respectively). One of the strategies that is closest to clinical trials is to target these toxic RNAs for rapid degradation using antisense oligonucleotides. This presentation will summarize recent progress in this area. As drug development and optimization is underway, we have a brief opportunity to refine the clinical endpoints, biomarkers, and procedures that are needed for smooth and effective testing of these new therapeutic agents. Results of transcriptome analyses in myotonic dystrophy have identified splicing changes that are specific to the disease, correlated with the extent of neurologic impairment, and completely reversible by experimental treatments in animal models. Efforts to validate these splicing events as biomarkers of disease severity and therapeutic response, and to develop methods for serial analyses of splicing outcomes, will be reviewed.

Muscle Stem cells in Duchenne and Emery-Dreifuss muscular dystrophy
Juergen Scharner[1], Luisa Boldrin[2], Juliet A. Ellis[1,2], Jennifer Morgan[2] and Peter S. Zammit[1]
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Muscular dystrophies are characterised by skeletal muscle weakness and wasting, implying a gradual failure of muscle maintenance and repair: roles attributed to muscle stem (satellite) cells. Although linked by muscle wasting, the underlying genetic causes of muscular dystrophies are very different, ranging from mutations in genes integral to muscle function such as dystrophin, to mutations in ubiquitously-expressed genes encoding nuclear envelope proteins. In conditions such as Duchenne muscular dystrophy (DMD), the pathogenic mutation in *DMD* causes muscle wasting by compromising dystrophin function. Since dystrophin is not present in satellite cells, muscle maintenance and repair is not directly affected. However, chronic muscle wasting produces a degraded micro-environment in dystrophic muscle, which culminates in failure of satellite cell-mediated myofibre repair and regeneration.
Autosomal Emery-Dreifuss muscular dystrophy (EDMD) is caused by mutations in *LMNA,* encoding lamin A/C of the nuclear lamina. These pathogenic *LMNA* mutations instigate muscle disease. *LMNA* is also expressed in muscle satellite cells though, and so mutant forms of lamin A/C could also directly compromise satellite cells. This may combine with excessive use and a hostile environment to further reduce satellite cell performance.

Here I will discuss satellite cell function in mouse models of DMD and EDMD. Transplantation studies show that their regenerative capacity remains intact when removed from the dystrophic environment, indicating that the host environment is critical for efficient satellite cell operation. I will also highlight our recent progress in defining the background for potential exon-skipping therapies for EDMD.

Muscle hypertrophy as a therapeutic strategy for muscular dystrophy

Carl Morris, PhD;
Rare Disease Research Unit, Pfizer Inc.

Loss of muscle mass and function is associated with many muscular diseases and conditions. Currently, there are limited options for stimulation of muscle growth in these diseases that are complicated by severe muscle weakness and frailty. There has been a significant effort directed towards developing strategies to counter the loss of muscle via increasing regeneration / muscle fiber growth or through inhibition of the atrophy process itself. The basic tenet is that maintaining or increasing the muscle cross sectional area equates to increased muscle function. Both anabolic and anti-catabolic approaches are at least theoretically feasible, however the majority of effort has been placed towards stimulating muscle growth. A number of mechanisms have been explored to determine the potential to stimulate muscle growth, including anabolic steroids, growth hormone and IGF-1, and myostatin inhibitors. Each of these approaches has potential issues with the only approved anabolic agents being testosterone and related anabolic steroids. The use of these therapies has been limited due to significant side effects.
Stimulation of the GH/IGF-1/Akt pathway and therapeutic inhibition of myostatin, a member of the TGF-b family and a negative regulator of muscle mass, also hold promise as strategies for the treatment of muscular dystrophy. For both approaches, genetic and preclinical evidence have provided strong evidence of potential benefit, with myostatin inhibition having been tested in patients. Two clinical trials (MYO-029 and ACE-031) have investigated the effects of the myostatin pathway in several muscular dystrophies. Setbacks from these two trials have dampened some of the early enthusiasm, however the pathway still is considered to have significant potential as an anabolic therapy. By using the learnings from previous programs, advances have been in understanding the necessary balance between necessary therapeutic efficacy and safety. Work is ongoing to identify specific candidates to examine this mechanism from diverse approaches, ranging from antibodies to exon skipping to small molecules.
Many issues have been raised regarding the potential effectiveness of anabolic therapies for the treatment of muscular dystrophies, such as possible satellite cell depletion and reduced muscle quality. These are important issues that must be resolved. It is clearly an important and exciting time with many different anabolic therapies being explored to treat muscle frailty conditions and diseases.

Gene therapy for DMD and OPMD

Prof George Dickson
School of Biological Sciences, Royal Holloway - University of London

Muscular dystrophies refer to a group of inherited disorders characterized by progressive muscle weakness, wasting and degeneration. So far, there are no strongly effective treatments but new gene-based therapies are currently being developed with particular advances in using exon skipping and other RNA-based approaches, conventional gene replacement strategies, and cell-based gene therapy. In the case of DMD, putting aside exon skipping therapy, a number of groups are testing gene therapy with adeno-associated virus vectors expressing engineered micro-dystrophins (AAV-MDs). In our hands, highly sequence optimised AAV-MDs are available for use in mouse, dog and ultimately humans, expressed using a strong synthetic promoter specific for skeletal and cardiac muscle cells have been tested in detail in mdx mice, and investigation in the GRMD dog are ongoing. In the case of OPMD, this triplet expansion and nuclear inclusion body disease of muscle is due to mutations which cause a poly-alanine expansion in PABPN1. Here we are developing a gene knockdown/ replacement strategy with highly effective shRNA vectors to knock-down dominant PABPN1 mutants, in conjunction with RNAi-resistant optimised PABPN1 replacement genes. Studies are ongoing in the OPMD mouse using AAV vectors directed ultimately

towards local clinical administration in ricopharyngeal and other affected muscle, or in patient myoblasts using lentiviral vectors for ex-vivo gene-modified autologous cell transplantation.

Poster List

Muscular Dystrophies Preclinical Molecular Therapy Development
Guided Poster Session Leads: Charles Thornton and Francesco Muntoni

1	**U**	**Burki**	Development of an ultrasensitive ELISA method for the determination of phosphorodiamidate morpholino oligonucleotide (PMO) levels in biological samples
2	**V**	**Arechavala**	Optimising novel imaging methods to quantify low levels of dystrophin in Duchenne muscular dystrophy
3	**S**	**Paco Mercader**	Gene expression profiling identifies molecular pathways associated with collagen VI deficiency
4	**C**	**Godfrey**	Longitudinal analysis of dystrophin restoration and serum miRNAs following peptide-PMO mediated exon skipping in a mouse model of DMD
5	**A**	**Ketley**	High content imaging screens using Myotonic Dystrophy cell lines identify small molecules that remove nuclear foci
6	**R**	**Fairclough**	New orally available compounds which modulate utrophin expression for the therapy of Duchenne muscular dystrophy (DMD)
7	**I**	**Zaharieva**	DystromiRs as serum biomarkers for diagnosis and monitoring therapeutic interventions in Duchenne Muscular Dystrophy
8	**C**	**Betts**	Pip6f-PMO successfully restores cardiac function in the exercised mdx mouse
9	**S**	**Hammond**	A new non-base chemical modifier "ZEN" enhances efficacy of splice-switching oligonucleotides
10	**S**	**Winder**	Preventing tyrosine phosphorylation of dystroglycan ameliorates the dystrophic phenotype in models of Duchenne muscular dystrophy
11	**D**	**Wells**	Peptide-PMO induced exon-skipping restores muscle physiology in the mdx mouse.

Databases, Diagnostics and Clinical Practice
Guided Poster Session Leads: Volker Straub and Chris Turner

12	**R**	**Kulshrestha**	Hub and spoke clinical model generating high level of patient satisfaction at the muscle clinic
13	**R**	**Kulshrestha**	An audit of safety of oral bisphosphonates in neuromuscular patients
14	**D**	**Smith**	FSHD 1 and 2 testing – a clinical diagnostic service perspective
15	**S**	**Amin**	Does tuberous sclerosis complex ever involve skeletal muscle? A case for discussion
16	**V**	**Ricotti**	Neuropsychiatric comorbidities in Duchenne Muscular Dystrophy
17	**V**	**Ricotti**	The Northstar Ambulatory Assessment in Duchenne Muscular Dystrophy: Considerations for the design of clinical trials
18	**G**	**Pfeffer**	Titin founder mutation is a common cause of myofibrillar myopathy with early respiratory failure
19	**E**	**Harris**	Deep phenotyping of undiagnosed neuromuscular patients from the North of England
20	**T**	**Whyte**	Finding new genes responsible for congenital myopathies

21	**S**	**Rodger**	Duchenne muscular dystrophy care practices in the UK: results of the CARE-NMD Patient Survey
22	**L**	**Wood**	UK Myotonic Dystrophy Patient Registry: A new tool for clinical research.

Translational Research in Mitochondrial Disease

Guided Poster Session Leads: Massimo Zeviani and Rita Horvath

23	**H**	**Moore**	Progressive cognitive difficulties in adult patients with mitochondrial disease
24	**A**	**Diot**	Screening drugs to identify modulators of mitophagy for treating mitochondrial diseases
25	**L**	**Rochester**	Can discrete gait characteristics serve as a surrogate marker of mitochondrial disease?
26	**V**	**Boczonadi**	Defective thiolation impairs mitochondrial translation offering a therapy approach in reversible infantile respiratory chain deficiency
27	**E**	**Fassone**	Prevalence of subunit mutations in Complex I Deficient Leigh Syndrome revealed by whole exome sequencing
28	**A**	**Pyle**	A novel homozygous mutation in EARS2 causing a fatal multisystem infantile disease
29	**C**	**Fratter**	Molecular genetic diagnosis of mitochondrial DNA depletion syndromes
30	**R**	**Pitceathly**	NDUFA4 mutations: a new cause of mitochondrial cytochrome c oxidase linked neurological disease
31	**R**	**Shahni**	YARS2 mutations associate specifically with Mitochondrial Myopathy, Lactic Acidosis and Sideroblastic Anaemia (MLASA)
32	**J**	**Newman**	Preliminary evaluation of functional outcome measures in mitochondrial disease
33	**Y**	**Wedatilake**	SURF1 deficiency: phenotypes and genotypes
34	**K**	**Jones**	Can high intensity interval training (HIIT) improve functional capacity and clinical symptoms in inflammatory and mitochondrial myopathies?

Translational Research in Glycosylation Disorders

Guided Poster Session Leads: Sue Brown and Katie Bushby

35	**Y**	**Lin**	Missense mutations in β-1,3-N-acetylglucosaminyltransferase 1 (B3GNT1) cause Walker-Warburg syndrome
36	**A**	**Wood**	Investigating differences in the roles of FKRP and fukutin in eye and muscle development
37	**H**	**Booler**	Brain development in a mouse model of muscle-eye-brain disease
38	**J**	**Kim**	Basement membrane deposition during muscle development in the FKRP Deficient Mouse (FKRPKD).
39	**M**	**Fernandez Fuente**	Alterations in α-dystroglycan glycosylation are associated with defects at the neuromuscular junction
40	**E**	**Lacey**	Developing novel Alpha Dystroglycan Antibodies using the Largemyd Mouse
41	**E**	**Stevens**	Flow cytometry analysis for the identification and study of novel dystroglycanopathy variants

42	**G**	**Torabi-Farsani**	Investigating collagen VI biosynthesis and assembly in the context of deficient ALG2; a novel gene identified in a CMS family originally diagnosed with Ullrich's CMD

Translational Research in Peripheral Nerve Disease
Guided Poster Session Leads: Dave Bennett and Mary Reilly

43	**C**	**Burd**	Treatment with Arimoclomol, a co-inducer of the heat shock response, prevents acute mitochondrial damage induced by staurosporin in primary motor neurons
44	**H**	**Zhou**	The Potential of Morpholino Antisense Oligonucleotides for the Therapy of Spinal Muscular Atrophy
45	**E**	**Cottenie**	Using whole-exome sequencing to identify disease-causing genetic variants in inherited neuropathies
46	**A**	**Rossor**	An in-vitro study of distal hereditary motor neuropathy due to homozygous hsj1 mutations
47	**A**	**Pandraud**	Investigating riboflavin transporter mutations in Brown-Vialetto-Van Laere syndrome
48	**M**	**Laura**	Assessment of distal lower limb strength in Charcot-Marie-Tooth disease type 1A
49	**M**	**Laura**	Hereditary sensory neuropathy type 1: a natural history study
50	**T**	**Antoniadi**	Genetic testing for inherited peripheral neuropathies: challenges and opportunities in implementing targeted next generation sequencing as a diagnostic service
51	**C**	**Sinclair**	Diffusion tensor MRI of the sciatic nerve
52	**G**	**Ramdharry**	Exploring the causes of falls and balance impairments in people with neuromuscular diseases
53	**E**	**Cottenie**	Combining Linkage analysis and Exome sequencing in two pedigrees with distal Hereditary Motor Neuropathy
54	**Y**	**Liu**	Hereditary sensory neuropathy and hearing loss caused by DNMT1 mutation
55	**A**	**Gray**	Targeting the endogenous stress response in a mouse model of Spinal Bulbar Muscular Atrophy
56	**P**	**McGoldrick**	An ENU-induced point mutation in mouse Sod1 causes aberrant mitochondrial function and axonal maintenance in primary motor neurons
57	**M**	**Scoto**	Cytoplasmic Dynein Heavy Chain 1 causes congenital lower limbs SMA associated with cortical malformation: a case report
58	**M**	**Scoto**	An unusual double trouble of coexisting distal myopathy and distal motor neuropathy uncovered by exome sequencing

Translational Research in Muscle Channelopathies and Myasthenia Gravis
Guided Poster Session Leads: Steve Cannon and David Beeson

59	**S**	**Corrochano**	A novel mutation in SCN4A and its equivalent in Scn4a cause periodic paralysis in humans and mice
60	**S**	**Huda**	"Seronegative" myasthenia gravis: how useful are cell-based assays
61	**K**	**Zoltowska**	AChR deficiency in GFPT1 congenital myasthenic syndrome
62	**J**	**Cheung**	Rapsyn mutations in congenital myasthenic syndromes
63	**J**	**Spillane**	Effect of LEMS antibodies on synaptic vesicle exocytosis
64	**I**	**Koneczny**	Potential mechanisms in MUSK-Myasthenia Gravis

65	**J**	**Ross**	Integrin-α3 is required for correct skeletal muscle innervation, and integrity of presynaptic specializations at the neuromuscular junction
66	**L**	**Clausen**	Exploring the beneficial effects of β2-adrenoreceptor agonists in Dok-7 CMS
67	**J**	**Ingledew**	Developing model systems to study gfpt1 deficiency
68	**N**	**Amior**	Developing models for the study of Periodic Paralysis
69	**A**	**Gardiner**	Next Generation Sequencing of Ion Channels in Skeletal Muscle Channelopathies
70	**R**	**Mannikko**	Functional characterization of CLCN1 mutations causing Myotonia congenital
71	**S**	**Durran**	A novel Hypokalemic periodic paralysis mutation that causes loss of negative charge in Nav1.4 results in gating pore currents.
72	**J**	**Cossins**	ALG2 – a new gene that causes congenital myasthenic syndromes
73	**F**	**Jaffer**	Next-generation sequencing of ion channel disorders

Translational Research in Inclusion Body Myositis

Guided Poster Session Leads: David Hilton Jones and Michael Hanna

74	**P**	**Machado**	Safety and tolerability of Arimoclomol in patients with sporadic inclusion body myositis: a randomised, double-blind, placebo-controlled, phase IIa proof-of-concept trial
75	**P**	**Fratta**	Alterations in RNA metabolism in sporadic inclusion body myositis
76	**S**	**Brady**	A histopathological assessment of inclusion body myositis
77	**S**	**Brady**	Clinical assessment determines the diagnosis of inclusion body myositis independently of pathological features
78	**S**	**Brady**	Neurogenic inflammation: an explanation for differing responses to immunosuppressive therapy among the inflammatory myopathies
79	**J**	**Morrow**	MRI provides sensitive quantification of disease progression in inclusion body myositis
80	**G**	**Ramdharry**	Evaluating the benefits of community based aerobic training on the physical health and well-being of people with neuromuscular diseases: a pilot study
81	**Q**	**Gang**	Sporadic Inclusion Body Myositis: genetic risk factors and exome sequencing

Muscle Satellite Cells and IPS Cells

Guided Poster Session Leads: Jenny Morgan and Peter Zammit

82	**L**	**Moyle**	Ret affects myoblast proliferation and contributes to Facioscapulohumeral muscular dystrophy (FSHD) pathobiology
83	**J**	**Meng**	Human skeletal muscle-derived AC133+ cells form functional satellite cells after intramuscular transplantation into immunodeficient host mice
84	**F**	**Tedesco**	Patient-specific iPS cell-derived myogenic progenitors for gene and cell therapy of muscular dystrophies and beyond
85	**R**	**Asfahani**	Mouse skeletal muscle-derived CD133+ cells contribute to muscle regeneration in vivo

Poster Abstracts

Muscular Dystrophies Preclinical Molecular Therapy Development

Poster 1
Development of an ultrasensitive ELISA method for the determination of phosphorodiamidate morpholino oligonucleotide (PMO) levels in biological samples

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Antisense oligonucleotide (AON) induced exon skipping is one of the most promising strategies for treating Duchene muscular dystrophy (DMD), with the first generation of AONs advancing to phase 3 clinical trials. Several different chemistries of AONs are available with 2-O-methyl phosphorothioate (2'OMe) and phosphorodiamidate morpholino oligonucleotide (PMO) being the most advanced AONs in development. In addition to determining the efficacy of AON induced dystrophin expression, detecting the levels of AON in blood and tissue is essential for determining the PK/PD relationship.
In comparison with other AON detection methods such as HPLC, LC/MS/MS, an ELISA based approach has demonstrated far greater sensitivity with detection levels in the picomolar range. As a result the ELISA is the method of choice for 2'OMe detection in pre-clinical and clinical development. However, to the best of our knowledge, no such assay has been developed for PMO and therefore a novel PMO ELISA assay is currently being developed in our lab with encouraging results.
The hybridisation-based assay is able to detect PMO levels in buffer with a linear range of detection between 30-1000pM (R^2 = 0.99). More importantly the sensitivity is unaffected in mouse serum, and detection in tissue lysate is currently in progress. The present level of sensitivity should be sufficient for both pre-clinical and clinical analysis. In addition, the assay can be easily adapted for detecting peptide-conjugated PMOs (i.e. PPMOs) which are the next generation of PMO based AONs in pre-clinical development.
Once fully developed, the assay will be essential for validating biodistribution data of radiolabelled PMO/PPMOs from a novel PET-imaging approach, which is also being developed in our lab.

Poster 2
Optimising novel imaging methods to quantify low levels of dystrophin in Duchenne muscular dystrophy

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Precise quantification of dystrophin protein in muscle biopsies taken before and after treatment is crucial to evaluate the biochemical success of therapeutic interventions.
We developed a method[1] to evaluate differences in expression of sarcolemmal proteins that has been used in several clinical trials, mouse and human studies[2-5]. This method uses immunohistological techniques and readily-available analysis software, is sensitive and requires very little sample, but it is labour intensive. Recently, aided by a new spectrin antibody that enabled immunostaining for dystrophin and spectrin on the same section, researchers have been able to automate this technique[6]. However, while the original method collects many data points per muscle section, each corresponding to a muscle fibre, the recent modification involves collecting an average dystrophin intensity of the whole image. As this may exclude some very useful data[7], we are working to combine the co-staining recently proposed with an automated data capture system which collects a higher number of measurements per section. We have developed a macro to be used in conjunction with Image J software and we present here a comparison with previous methods of analysing mouse and human muscle sections.

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Poster 3

Gene expression profiling identifies molecular pathways associated with collagen VI deficiency

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Ullrich Congenital Muscular Dystrophy (UCMD), caused by collagen VI deficiency, is a common cause of congenital muscular dystrophy. The clinical features include hypotonia, delayed motor milestones, proximal muscle weakness, distal joint hyperlaxity and proximal joint contractures within the first years of life. At present, the role of collagen VI in muscle and the mechanism of disease are not fully understood.
To address this we have applied cDNA microarrays to analyse the transcriptome of UCMD muscle and compare it to healthy muscle and other muscular dystrophies. We identified 389 genes which are significantly regulated in UCMD relative to controls. In addition, there were 718 genes differentially expressed between UCMD and dystrophin deficient muscle. In contrast, only 29 genes were altered relative to other forms of congenital muscular dystrophy. Changes in gene expression were confirmed by real-time PCR. The set of regulated genes was analysed by Gene Ontology, KEGG pathways and Ingenuity Pathway analysis to reveal the molecular functions and gene networks associated with collagen VI defects. The most significant regulated pathways were those involved in inflammatory response, regeneration and extracellular matrix remodelling. Moreover, we found that biglycan, an extracellular matrix proteoglycan that binds collagen VI, was markedly reduced from the basal lamina of UCMD patients. We propose that over-expression of biglycan may serve to improve UCMD pathophysiology by restoring the link between the muscle cell surface and the extracellular matrix.
Taken together, our results provide new data about the physiopathology of collagen VI deficiency and point towards novel therapeutic approaches.

Poster 4

Longitudinal analysis of dystrophin restoration and serum miRNAs following peptide-PMO mediated exon skipping in a mouse model of DMD.

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Duchenne muscular dystrophy (DMD) is a progressive and lethal degenerative muscle disorder arising from the absence of dystrophin. The use of oligonucleotides designed to modulate *DMD* pre-mRNA splicing is currently the most promising molecular therapeutic approach to restore dystrophin. We and others have demonstrated that peptide conjugated PMOs can dramatically improve systemic delivery of oligonucleotides and subsequently, body-wide restoration of dystrophin.
In order to better understand the long-term efficacy of these compounds, we have profiled the duration of exon skipping and protein restoration following a single intravenous administration of Pip6a-PMO and Pip6e-PMO into *mdx* mice. Tissue and serum were harvested at various time points following a 12.5mg/kg injection. Both skeletal and cardiac muscle specific exon skipping and protein restoration profiles have been analysed over time.
As serum microRNAs offer potential as biomarkers of disease progression and therapeutic efficacy, we also studied their expression following a single systemic administration of Pip6-PMO. Here were demonstrated that changes in specific serum microRNAs in the *mdx* mouse were partially normalised in response to Pip6-PMO treatment and that this correlated to levels of dystrophin restoration. Interestingly, changes in serum miRNA levels over time suggest a dynamic response to exon skipping therapy and this is being investigated further.
From these data, treatment intervals can be established in order to minimise the frequency of administration yet ensure the therapy remains efficacious throughout. A greater understanding of the dynamic nature of protein restoration and biomarker response will be valuable in the development of appropriate effective therapeutics for DMD.

Poster 5
High content imaging screens using Myotonic Dystrophy cell lines identify small molecules that remove nuclear foci
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We have developed a cell-based assay centred on the identification of nuclear foci in DM cells and have used this as a primary screening assay to identify suitable compounds as possible starting points for a drug development program. A pipeline of assays has been developed to establish the consequences of compound treatment on key aspects of DM pathophysiology. The primary screening assay employs an *in situ* hybridisation protocol on immortalized DM cell lines, with a fluorescently labelled probe against the repeat expansion sequence, analysed via high-content imaging on a scanning plate reader.
Two compounds that reduce and/or remove nuclear foci have been identified, Ro 31-8220 and chromomycin A3. A subset of tertiary assays has assessed the downstream consequences of these compounds on key aspects of DM pathophysiology. These assays allow us to examine the cellular location of the repeat expansion transcript, alternative splicing patterns of specific transcript isoforms (SERCA1 and INSR) and the cellular distribution of MBNL protein, all known to be affected in DM. We show that Ro 31-8220 eliminates nuclear foci, reduces MBNL1 protein in the nucleus and affects SERCA1 alternative splicing, which is MBNL1-dependent. Ro 31-8220 is a PKC inhibitor, previously shown to affect the hyperphosphorylation of CUG-BP1 and ameliorate the cardiac phenotype in a DM1 mouse model (1,2). This data provides a novel and important link between the roles of CUG-BP1 and MBNL1 in the pathophysiology of DM, in addition to new starting points for the development of a treatment for this disease.

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Poster 6

New orally available compounds which modulate utrophin expression for the therapy of Duchenne muscular dystrophy (DMD)

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DMD is a devastating X-linked muscle-wasting disease caused by lack of the cytoskeletal protein dystrophin. There is currently no effective treatment. Through pharmacologically modulating the dystrophin-related protein utrophin, we aim to develop a therapy applicable to all DMD patients by targeting the primary defect and restoring sarcolemmal stability in DMD. In partnership with Summit plc we previously developed SMT C1100; a small molecule utrophin modulator that reduced dystrophic symptoms in the mdx mouse. SMT C1100 entered clinical trials as a potential first-in-class molecule and successfully completed a Phase 1 trial in 2012. This provided crucial proof-of-principle for the strategy we have developed.

We have developed a new drug screening assay based on immortalised myoblasts from the utrophin luciferase knock-in mouse which enables us to screen the utrophin promoter in its genomic context. This better mimics the *in vivo* situation and also enables the identification of compounds which modulate utrophin through regulatory pathways outside of the 8.4 kb promoter fragment that formed the basis of our previous screen. Screening of a filtered subset (7000 molecules) from our 25,000-member compound collection, selected to maximise drug-like properties and the hit rate, has identified new structural classes which increase levels of utrophin. The compounds exhibit favourable solubility, stability, oral absorption and are well tolerated in the mouse. These significantly increase utrophin levels in the mouse screen and importantly, also in human DMD myoblasts. This is a significant step in our drive to identify best-in-class molecules for utrophin modulation in the treatment of DMD.

Poster 7

DystromiRs as serum biomarkers for diagnosis and monitoring therapeutic interventions in Duchenne Muscular Dystrophy

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With the aim of validating the finding that the level of specific miRs in serum correlate with the disease severity, we have quantified miR-1, miR-133a,b, miR-206 and miR-31 in a population of patients affected by Duchenne (DMD), Becker muscular dystrophies (BMD), Ullrich congenital muscular dystrophy (UCMD) and healthy controls. A significant increase in the level of miR-1 and miR-206 was seen in the serum of DMD ($p = 0.01$) and BMD patients ($p=0.008$) compared to healthy controls. Further analysis according to the ambulation status of the DMD patients showed a significant increase of miR-1 in ambulant compared to non-ambulant patients ($p=0.005$).

MiR-1, miR-133a,b, miR-206 and miR-31were also analysed in the serum of DMD patients treated for 12 weeks with morpholino oligomer Eteplirsen (AVI-4658) that induces exon 51 skipping, in order to investigate whether levels of these miRs correlate with the outcome of the therapeutic intervention. We found an increased copy number of dystromiRs in the serum of DMD patients compared to healthy controls, which was statistically significant for all of the studied miRs. No statistical significance was reached when the level of miRs was compared between untreated and treated DMD samples at the time points studied.

The results obtained in our study indicate that dystromiRs have the potential to serve as biomarkers for Duchenne muscular dystrophy, but more studies to clarify the relationship between dystrophin restoration and the modification of their levels following therapeutic intervention (i.e. duration of treatment; levels of dystrophin and optimal timing for sampling) are necessary.

Poster 8

Pip6f-PMO successfully restores cardiac function in the exercised *mdx* mouse

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Duchenne muscular dystrophy (DMD) is a fatal, muscle-wasting disorder caused by mutations and deletions that disrupt the dystrophin reading frame, preventing the production of functional dystrophin protein. Antisense oligonucleotides (AOs) are currently the most promising molecular intervention for DMD and function by modulating dystrophin pre-mRNA splicing, thereby restoring the dystrophin reading frame and generating a truncated, semi-functional dystrophin protein. However, a current shortfall of this approach is the poor systemic AO delivery and inefficient dystrophin correction in affected non-skeletal muscle tissues, particularly the heart. Cell penetrating peptides (CPPs) which may be directly conjugated to the AO can facilitate their delivery to skeletal muscles including to the heart.
In collaboration with the Gait Lab in Cambridge we successfully identified a CPP, Pip5e, which when conjugated to morpholino (PMO) AOs is capable of inducing high levels of exon skipping and dystrophin restoration body wide, including the heart of the DMD mouse model, *mdx*. Further structure-activity studies on derivatives of this peptide have identified superior candidates, Pip6a- and Pip6f-PMO, which display enhanced delivery over Pip5e-PMO. We have now investigated to what extent such peptide conjugated PMOs are capable of restoring cardiac function. Dystrophin-deficient *mdx* mice were subjected to a 3 month exercise-administration regimen concurrently with Pip6f-PMO treatment and cardiac function parameters were assessed using MRI at 6 months of age. Additionally, transcriptional changes in cardiac muscle were assessed to determine to what extent effective cardiac dystrophin restoration resulted in the normalised expression of key cardiac genes which are.

Poster 9

A new non-base chemical modifier "ZEN" enhances efficacy of splice-switching oligonucleotides

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Oligonucleotides used for splice switching therapy are successful due to chemistries which allow high binding affinity toward the pre-mRNA and resistance to nuclease-mediated degradation. Here we describe a new modifier (a napthyl-azo group, or "ZEN") and employ it in splice switching oligonucleotides (SSOs) for the treatment of Duchenne muscular dystrophy. ZEN modifications are placed as insertions between the terminal residues on each end of a phosphorothioate (PS)-backbone 2'OMe RNA antisense oligomer. This modification increases Tm by ~5^{o}C and stabilizes against exonucleases without hampering specificity. A higher Tm value reduces both the number of bases required in the oligonucleotide sequence for specific binding and the concentration required. DMD patients lack dystrophin protein due to mutations that result in out-of-frame transcripts or premature terminal codons. By inducing the skipping of mutant exons, a new splice variant of dystrophin mRNA is made and functional protein generated. In cultured H2K cells from the *mdx* mouse line (which has a stop codon in dystrophin exon 23), a 17mer ZEN-modified 2'OMePS oligo (ZEN oligo) was able to induce significant levels of exon skipping while the same 2'OMePS oligo without ZEN produces no skipping. We compared ZEN-modified 2'OMePS with standard 2'OMePS oligos in the *mdx* model using naked IV administration. No toxicity was detected with the ZEN oligos after high dose bolus injection. As a new chemistry, ZEN is an exciting and important addition to the field of oligonucleotide therapy.

Poster 10

Preventing tyrosine phosphorylation of dystroglycan ameliorates the dystrophic phenotype in models of Duchenne muscular dystrophy.

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Duchenne muscular dystrophy (DMD) is a progressive muscle wasting disease caused by a mutation in the gene encoding the cytoskeletal protein dystrophin, part of the sarcolemmal adhesion complex - the dystrophin glycoprotein complex (DGC). Current therapeutic strategies to treat DMD are centered around correcting the genetic defect such as exon skipping and nonsense codon read-through, or upregulating compensatory genes such as utrophin. Viral and cell therapies are also under investigation.
By studying the fate of the DGC in DMD we can propose that tyrosine phosphorylation of dystroglycan, the key transmembrane laminin receptor, plays a crucial role in the loss of the entire DGC from the sarcolemma. Therefore targeting dystroglycan phosphorylation provides a novel therapeutic avenue for the treatment of DMD.
If we prevent phosphorylation of dystroglycan in *mdx*, a mouse model of DMD, we can ameliorate the dystrophic phenotype. Studies in mouse myoblasts also demonstrate that pharmacological intervention can increase levels of non-phosphorylated dystroglycan. Furthermore by inhibiting tyrosine phosphorylation, ubiquitination or proteasomal degradation pharmacologically we can demonstrate a reduction in dystroglycan phosphorylation and a rescue of the dystrophic phenotype in *sapje* zebrafish, a fish model of DMD.
These studies demonstrate the utility of inhibiting dystroglycan tyrosine phosphorylation as a therapeutic strategy for DMD, particularly as several of the compounds that are effective in myoblasts and zebrafish are in existing clinical use. Obtaining orphan drug status for repurposed drugs could be a rapid and effective route to DMD therapy, either in their own right or as adjuncts to other therapies outlined above.

Poster 11
Peptide-PMO induced exon-skipping restores muscle physiology in the *mdx* mouse.
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Duchenne muscular dystrophy (DMD, a fatal X linked muscle wasting disorder is caused by the absence of dystrophin. Antisense directed exon-skipping has been shown to be a powerful method to induce expression of dystrophin in dystrophic muscle for a range of species including man. Dystrophin expression can be induced in the *mdx* mouse but oligonucleotides targeting exon 23 which removes the premature stop mutation in the murine dystrophin gene. We had previously shown improved resistance to eccentric exercise (10% length change of the active muscle) following intramuscular delivery of a phosphorodiamidate morpholino oligomer (PMO) targeting exon 23 in the *mdx* mouse (Sharp et al., 2011). Little improvement was seen in specific force which is commonly only 60% of wild-type in the *mdx* mouse. We now report similar physiology results following a single intravenous treatment with a peptide-PMO (PPMO). Importantly, repeated intravenous PPMO treatment every two weeks starting at 12 weeks old and continuing for 10 doses, completely prevented the force drop associated with eccentric exercise and significantly improved the specific force, albeit not quite to wild-type levels. Both the acute and chronic dosing results correlated with the increased expression of dystrophin in muscle fibres and decreased levels of TIMP-1 in the serum. These studies show the potential of the PPMO formulation to significantly improve the results of exon-skipping in clinical trials.

Sharp P, Bye-A-Jee H, Wells DJ. (2011) Physiological characterization of muscle strength with variable levels of dystrophin restoration in dystrophic *mdx* mice following local antisense therapy. Mol Ther 19(1):165-71.

Databases, Diagnostics and Clinical Practice

Poster 12
Hub and spoke clinical model generating high level of patient satisfaction at the muscle clinic
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[a]Robert Jones and Agnes Hunt Orthopaedic and District Hospital

Background: Our centre delivers care to paediatric and adult neuromuscular patients based on NHS hub and spoke model. The specialists (physician, pathologist, orthopaedic surgeon, spinal surgeon, physiotherapists, occupational therapist and psychologist) on site constitute the hub and spokes are the

local respiratory, cardiology, endocrine, and general/community paediatric services. Our service is committed to deliver care according to the nationally agreed 'standard of care' for these patients.
Aim: to share the patient's opinion of our service and to gain agreement to move forward in testing of the clinical model.
Methods: information was collected prospectively by paper questionnaire from 101 patients/ carers at each visit.
Results: The patients attending the muscle clinic range from newborn to 90 years and travel 10-200 miles (70% traveling 20-60 miles) distance to attend our service. 80% of patients were satisfied with the pre-visit information and administrative support about flexibility of attending clinic dates. 98% patients experienced enough time during the consultation with the doctor and the therapist. 93% were satisfied by the quality of consultation, explanation of the condition and results. 77% patients felt that the information was useful. The only criticism of the service was the availability of an information leaflet which was given to 20%.
Conclusion: Our experience has generated high level of patient satisfaction supporting hub and spoke model. This supports the team vision to create an integrated, safe, efficient and innovative NHS led muscle service that can thrive in the environment where tertiary hospitals are overburdened with excess work.

Poster 13
An audit of safety of oral bisphosphonates in neuromuscular patients
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[a]Robert Jones and Agnes Hunt Orthopaedic and District Hospital

Background: Bisphosphonates are successfully used to prevent bone fractures and treat bone pain in children with osteoporosis. Current evidence is inadequate to define appropriate bisphosphonate agent, dose, and duration of use in paediatric patients. Our centre is amongst the few in UK to use oral bisphosphonates and our previous experience for 6 patients (ENMC, 2009) has been positive in improvement of bone mineral density (BMD).
Aim: to audit drug safety of oral bisphosphonates for patients with neuromuscular disorders.
Method: Retrospective case note analysis was performed for patients on bisphosphonates. Results: Oral bisphosphonates were used for 11 patients. Average age of starting treatment was 10.4 years (5-14 years). 9 patients had DMD, 1 had Ullrich congenital muscular dystrophy, and 1 had fascioscapular humeral muscular dystrophy. The indication to start bisphosphonate was a combination of low BMD (for hips average: 0.387 gm/cm^2), bone pain and vertebral fracture (4 patients). Oral residronate was used in 10 patients and 1 had aledronic acid. Only 2 patients reported side effects. One patient had back and abdominal pain which resolved spontaneously and another had gastrointestinal upset that resolved with omeprazole. 5 patients experienced fracture while on treatment (3: traumatic long bone; 1: vertebral and 1: traumatic long bone and vertebral).
Conclusion: oral bisphosphonates are well tolerated even in small children and represent a promising therapeutic tool. A number of questions however remain to be answered: precise clinical indication, when to commence treatment, duration of treatment, effective monitoring, oral versus intravenous and early detection of toxic effects.

Poster 14
FSHD 1 and 2 testing – a clinical diagnostic service perspective
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FSHD is the third most common muscular dystrophy, characterized by progressive wasting of upper body muscles. ~95% of cases are associated with contraction of D4Z4 tandem repeat in the subtelomere region of 4q35 (FSHD1, OMIM 158900).
Bristol Genetics Laboratory offers a UKGTN specialist diagnostic FSHD service. First level molecular testing for FSHD1 is by Southern blotting using EcoRI/BlnI/ApoI digests and the probe p13E-11 (to determine chromosome of origin and size contraction); where appropriate the permissive haplotype is confirmed. Patients with an extended deletion of the p13-E11 region (~2%) are identified using the D4Z4 1kb probe.

The remaining ~3% of patients have the clinically indistinguishable FSHD2 (OMIM 158901), with hypomethylation of the D4Z4 repeats and a 'permissive' haplotype at 4q35.
A five year audit of 1190 diagnostic FSHD referrals indicated 37% showed a contraction of the D4Z4 at 4q35. Of the 63% negative cases, 87 patients were referred for extended testing; clinical symptoms assessed using a clinical proforma. 91% showed no deletion of the p13E-11 probe region; for these patients (6.6% of diagnostic referrals) a diagnosis remains on clinical grounds.
Lemmers *et al* (2012) showed 80% of patients with a negative FSHD1 result and D4Z4 hypomethylation have a mutation *SMCHD1* (18p11.23) indicating digenic mode of inheritance for FSHD2; giving a recurrence risk for FSHD2 between 25-50%. Testing for FSHD2 is currently being validated on a cohort of 20 clinically typical patients.
We present an audit of referrals illustrated by interesting cases, highlighting the clinical utility and complexity of FSHD genetic testing.

Lemmers R. et al. Digenic inheritance of an SMCHD1 mutation and an FSHD –permissive D4Z4 allele causes FSHD2 Nat.Genet.(2012) ***44****: 1370-1374*

Poster 15
Does tuberous sclerosis complex ever involve skeletal muscle? A case for discussion
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We report a 4 year old boy with Tuberous Sclerosis Complex (TSC). He suffers from seizures. He has no significant developmental delay. He has cardiac rhabdomyomas but no kidney angiomyolipoma.
He developed right thigh and buttock swelling at 18 months of age [photos]. This was associated with overlying venous distension. He has been unable to weight bear. The swelling has been soft and non-tender, but feels warm. His creatinine kinase was normal.
MRI scan showed uniform enlargement of the muscles of the thigh and buttock with contrast enhancement [MRI images].
Muscle biopsy showed myopathic fibre size variation, but there was no evidence of primary myositis or a dystrophy including normal protein analysis. The associated muscle mass was composed of adipose tissue and collections of blood vessels with abnormal vessel walls. There was no HMB45 immunopositivity [biopsy]. The biopsy was sent for a second opinion. A macrophage-rich infiltrate was noted in the perimysium, raising the possibility of myofasciitis. Steroids were suggested.
He received high dose steroids for 4 weeks with no clinical response.
Skeletal muscle involvement in TSC has not been reported before. However, activation of the mTOR pathway which is seen in TSC has been shown in vivo to cause muscle hypertrophy. If his muscle swelling is TS related, then mTOR inhibitors such as Everolimus or Metformin may be an option.

Poster 16
Neuropsychiatric comorbidities in Duchenne Muscular Dystrophy
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Background
We previously described that 24% of DMD boys present with clinically significant traits of Autistic Spectrum Disorder (ASD) and 35% of DMD boys meet the criteria for ADHD. Other comorbid psychopathologies include internalising (27%) and externalising (15%) behavioural problems. Amongst boys with DMD, IQ is on average ~1 SD below the general population mean, with working memory impairments being especially prominent. Mutations disrupting the shorter C-terminus dystrophin isoforms (Dp260, Dp140, Dp116, Dp71) pose the greatest risk for neurodevelopmental disorder, when compared with mutations at the 5' end of the gene.
Objectives

The objectives of our on-going study are: 1) to describe to what extent neuropsychiatric comorbidities coexist in the same cluster to certain individuals; 2) to describe the bearing that the genotype has on the neuropsychiatric phenotype.

Methods

We recruited 96 DMD boys (68 in GOSH-UK and 28 in Italy), who underwent, standardised neuropsychological assessments including: WISC-IV, 3Di, Conners-3 Questionnaires, and CBCL.

Results

We here describe to what degree these neuropsychiatric comorbidities tended to cluster within particular individuals with DMD. We report associations and correlations observed between learning disability, ASD, ADHD and other neurobehavioural problems. Furthermore we describe the degree of prevalence and the level of severity of these disorders according to the genotype.

Conclusion

Whilst we recognise that neurodevelopmental disorders are highly prevalent in DMD, more in-depth studies, using state-of-the art phenotyping and neurodevelopmental comparison groups, are required to characterise better the neuropsychiatric profile of DMD and how this may differ from classic neuropsychiatric disorders. This will help address the question of whether the high rates of neuropsychiatric diagnoses in DMD reflect true comorbidity; or the presence of a DMD-specific neurodevelopmental syndrome.

Poster 17

The Northstar Ambulatory Assessment in Duchenne Muscular Dystrophy: Considerations for the design of clinical trials

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Background

With the emergence of experimental therapies for Duchenne Muscular Dystrophy, it is crucial to understand the natural history of this disorder to properly design clinical trials.

Objective

The aims of this study are: 1) to assess the motor function decline per year of ambulant DMD boys treated according to the standards of care; 2) to describe the slope of progression up to two years prior to loss of ambulation; 3) to observe the rate of motor function decline in genetic subpopulations of different skippable deletions (by exon 44, 45, 50 51, 53); 4) to describe the natural history of DMD boys below 5 years of age.

Methods

Through the NorthStar Network and database, clinical data systematically collected from 2004-2012 on >400 DMD boys followed-up in 17 UK neuromuscular centres was included in the analysis.
Our study focuses on the NorthStar Ambulatory Assessment (NSAA) as a primary outcome measure.

Results

We previously observed that motor function decline starts around 7 years of age in DMD boys. Irrespective of the glucocorticoids' regimen, here we report the yearly rate of decline of the NSAA total score in boys ≥7 years old. In our database >100 boys became non-ambulant between the age of 6 and 17: we describe their motor function at 12 and 24 months prior to loosing independent ambulation. We report any possible group effect in the subpopulations according to genotype, and finally we describe the rate of motor function improvement prior to 5 years in boys on steroids compared to steroid-naïve.

Conclusion

Our study provides helpful information on the current natural history of DMD in UK. The analysis on motor function decline in different patient sub-population is of help when selecting inclusion criteria in the design for clinical trials.

Acknowledgements

The support of Muscular Dystrophy Campaign for the NorthStar clinical Network (full list of participating centers: http://www.muscular-dystrophy.org/assets/0001/5872/NSCN_collaborating_centres.pdf) is gratefully acknowledged.

Poster 18

Titin founder mutation is a common cause of myofibrillar myopathy with early respiratory failure

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Objective: Titin gene (*TTN)* mutations have been described in 8 families with hereditary myopathy with early respiratory failure (HMERF). Some of the original patients had features resembling myofibrillar myopathy (MFM), arguing that *TTN* mutations could be a much more common cause of inherited muscle disease, especially in presence of early respiratory involvement.
Methods: We studied 127 undiagnosed patients with clinical presentation compatible with MFM. Sanger sequencing for the two previously described *TTN* mutations in HMERF (p.C30071R in the 119th fibronectin-3 (FN3) domain, and p.R32450W in the kinase domain) was performed in all patients. Patients with mutations had detailed review of their clinical records, muscle MRI findings and muscle pathology.
Results: We identified 5 new families with the p.C30071R mutation who were clinically similar to previously reported cases, and muscle pathology demonstrated diagnostic features of MFM. Two further families had novel variants in the 119th FN3 domain (p.P30091L and p.N30145K). No patients were identified with mutations at position p.32450.
Conclusions: Mutations in *TTN* are a cause of MFM, and titinopathy is more common than previously thought. The finding of the p.C30071R mutation in 3.9% of our study population is likely due to a British founder effect. The occurrence of novel FN3 domain variants, although still of uncertain pathogenicity, suggests that other mutations in this domain may cause MFM, and that the disease is likely globally distributed. We suggest that HMERF due to mutations in the *TTN* gene be nosologically classified as MFM-titinopathy.

Poster 19

Deep phenotyping of undiagnosed neuromuscular patients from the North of England

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A recent analysis of neuromuscular patients seen at the Newcastle Muscle Centre, in the north of England, showed that a definite genetic diagnosis is missing in approximately 25% of patients, despite major diagnostic efforts. This study aimed to provide an in-depth phenotypic analysis of undiagnosed neuromuscular patients with the intention of gaining major insight into their clinical features, evaluating the strengths and limitations of our current diagnostic strategy, identifying shared phenotypes on which to base collective diagnostic testing and selection of families/patients that could benefit from the use of new high-throughput diagnostic techniques, such as exomic or genomic sequencing. Following deep phenotyping by analysis of clinical databases and reviewing clinical notes, a hierarchical cluster analysis was performed in order to provide an unbiased interpretation of the data obtained. A correlation of phenotypic features according to the age of disease onset delineated several interesting groups of patients, that could potentially share a common novel genetic cause.

Poster 20

Finding new genes responsible for congenital myopathies

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Congenital myopathies (CMYO) are characterised by muscle weakness and contractures from birth, however the molecular basis of this group of diseases are distinctively different. Defects in the structural components of the sarcomere are often responsible for CMYOs and it is estimated that over 50% of the genes that when mutated lead to such disorders have currently been identified leaving a proportion of patients without a genetic diagnosis. As part of a collaborative study with the Sanger Institute in Cambridge (10KUK project) we have identified by exome sequencing mutations in ECEL1 in one 3 generation consanguineous family affected by a congenital myopathy with distal arthrogryposis and cores, with features resembling King-Denborough syndrome. In this family we found a homozygous non-synonymous change in exon 2; Sanger sequencing of a population of patients with similar phenotypes identified a further affected family with a two nucleotides deletion in exon 15. ECEL1 is a type-2 transmembrane M13 metallopeptidase with unknown substrate, localised to the endoplasmic reticulum and plasma membrane of the central nervous system (CNS) but also expressed in muscle. The ecel1 knock out (KO) mouse model is lethal as pups die at birth from respiratory failure. Knock down (KD) of the gene in zebrafish embryos with the use of morpholino antisense technology induced a muscle phenotype by 24hours of fertilisation with disorganised, reduced number and broken myofibres that coiled up against the myotendenous junction. Embryos had a perturbed swim pattern and curvature of the trunk. Characterisation of the NMJ has not revealed significant changes even though a knock out mouse model demonstrated abolition of the NMJ and subsequent muscle atrophy. Our muscle pathology data in patients and the zebrafish suggest that ECEL1 has a significant role in structural integrity of the myofibres. Further work to identify the substrates for its role is underway.

Poster 21

Duchenne muscular dystrophy care practices in the UK: results of the CARE-NMD Patient Survey

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CARE-NMD conducted the largest ever survey of Duchenne muscular dystrophy (DMD) patients across 7 European countries between September 2011 and April 2012, assessing quality of life and availability of best-practice care. 1,071 valid responses were received, 228 from the UK.
For the UK population, mean age was 13 years; half were non-ambulatory. Age at diagnosis was 4.1 years with a delay from first concerns of 1.14 years. 87% attend a specialist neuromuscular clinic at least annually, the highest of the countries surveyed (43%-87%). However, this figure conceals a disparity between children (91%) and adults (70%), with a similar trend evident internationally. Furthermore, many adults do not receive recommended heart and lung function assessments: 35% have echocardiography less than annually if at all, while 35% report the same for pulmonary tests. International consensus guidelines recommend those aged ≥10 years have annual echocardiography, whilst non-ambulatory patients should have respiratory function assessed at six month intervals. With pulmonary or cardiac failure the leading cause of DMD mortality, this is an area of significant concern. Although UK DMD patients rate their care as better than average, as adults they face difficulties accessing neuromuscular specialists and many do not receive recommended cardiac and pulmonary assessments.

Poster 22

UK Myotonic Dystrophy Patient Registry: A new tool for clinical research.

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The UK Myotonic Dystrophy (DM) Registry is an important tool to facilitate and accelerate clinical research through identification of information and participants. Data is retrieved from patients and care professionals through an innovative and secure online portal. The registry was launched in May 2012 and has been developed in collaboration with the TREAT-NMD Alliance, Myotonic Dystrophy Support Group (MDSG) and the Muscular Dystrophy Campaign (MDC).
The registry uses an internationally agreed data set that includes demographic, clinical and genetic information. There are over 250 people registered from across the country; the majority diagnosed with myotonic dystrophy type 1 (DM1). The age of people registered ranges from 1 to 79 years old, with the greatest numbers between 31 and 50 years old. Fatigue and myotonia are the most commonly reported symptoms with two thirds of registrants reporting both. The majority of people registered are ambulant though a third state that they require some assistance when walking.
Patient registries are invaluable tools in the field of rare diseases. The UK DM registry has the potential not only to accelerate clinical trials but to assist in all areas of research including in the identification of biomarkers, in increasing understanding of phenotype-genotype correlation and in improving standards of care.

Translational Research in Mitochondrial Disease

Poster 23

Progressive cognitive difficulties in adult patients with mitochondrial disease

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Introduction: Mitochondrial diseases are a common group of genetic disorders characterised by heterogeneous clinical features including myopathy, auditory, visual, cardiac, and brain dysfunction. Cognitive features are present in patients with mitochondrial disease, but have not been comprehensively explored. Aims: This study sought to compare estimated premorbid and current levels of general cognitive functioning and examine the cognitive profile of patients with mitochondrial disease. Methods: Forty-nine adult patients harbouring either m.3243A>G or m.8344A>G mtDNA point mutations were recruited. A battery of cognitive tests were used to assess premorbid and current general cognitive

functioning, as well as verbal comprehension, perceptual reasoning, processing speed, memory and executive functions. Patients' baseline data were compared to UK normative data. Results: Patients with mitochondrial disease showed evidence of developmental cognitive problems (Z(49)=-3.06, p=.002), which extended in to adulthood (Z(49)=-6.96, p<.001; 22% >2SD below the norm), showing significant decline (mean change: –8.37 IQ points; t(49)=5.37, p<.001). Patients performed significantly better on Perceptual Reasoning than Processing Speed, equivalent to an average difference of 7 IQ points. Logical memory was impaired in this group compared to the norm (Immediate: Z(49)=-6.29,p<.001, Delayed: Z(49)=-5.62, p<.001), whereas verbal declarative memory was not. Executive dysfunction was also observed. Conclusion: These findings demonstrate widespread cognitive difficulties that can undermine independence and quality of life in patients with mitochondrial disease, and emphasise the need to incorporate cognitive testing into clinical practice, in order to ensure that appropriate care is provided.

Poster 24

Screening drugs to identify modulators of mitophagy for treating mitochondrial diseases.

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Mitochondrial diseases are common, 1/200 individuals carrying mutant mitochondrial DNA (mtDNA), and 1/20,000 carrying mutant OPA1. Patients with mtDNA diseases may have mutant and wild type mtDNA (heteroplasmy), the severity depending on the dose of mutant mtDNA, Symptoms range from isolated presbyacusis, to loss of vision, to catastrophic neurodegeneration, and treatments are ineffective. Given the importance of mitophagy (mitochondrial recycling) in mitochondrial quality control and studies of mitochondrial dynamics suggesting a role for mitophagy in neurodegeneration, we set up a screen to identify compounds able to modulate this process.
Heteroplasmic cells derived from patients bearing the $tRNA^{leu}$ A3243G mutation in their mtDNA. The mutant load, mtDNA copy number, number of autophagosomes and their co-localisation with mitochondria, and the mitochondrial mass are quantified at different time points.
Our first results suggest that we are able to quantitate mitophagy indirectly. These observations correlate with an increase in the level of the LC3-II protein bound to autophagosomal membrane. We are investigating whether this is linked to a decrease in mitochondrial mass concomitant with an increase in autophagic vacuoles, suggesting mitophagy induction.
This will allow us to identify drugs not only for their ability to increase mitophagy but also to inhibit it. This latter case is particularly interesting for a group of patients we identified where mitophagy is excessive in primary cell cultures. Inhibiting mitophagy should ameliorate neurodegeneration in this group. Activators of mitophagy are candidate treatments for mitochondrial diseases in which accumulation of mutant mtDNA underlies disease progression.

Poster 25

Can discrete gait characteristics serve as a surrogate marker of mitochondrial disease?

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Mitochondrial disease is complex and variable making diagnosis and management challenging. Characteristics of gait are sensitive to age and pathology and may be useful surrogate markers. We aimed to describe gait impairments in patients with mitochondrial disease and assess whether gait impairment was associated with disease severity and mutation load. Twenty four patients with genetically confirmed mitochondrial disease (m.3243A>G & m.8344A>G) and 24 controls were recruited. Gait was quantified using an instrumented walkway (GAITRite) over which patients performed 3 x 12 m walks. Discrete gait characteristics were determined according to a predefined model. Compared to controls, patients with mitochondrial disease were globally impaired on all characteristics of gait, however when described by genotype discrete characteristics emerged. Patients with the m.3243A>G mutation who were phenotypically normal, had significantly reduced gait speed, step length and

increased variability in step time and step width compared to controls. Gait characteristics were globally related to disease severity (NMDAS) while mutation load was significantly and selectively associated with discrete gait characteristics (cadence, step width variability and step time asymmetry). Quantification of discrete gait characteristics may provide surrogate markers of mitochondrial disease and enhance clinical measures of disease severity, pathology and efficacy of novel therapies.

Poster 26

Defective thiolation impairs mitochondrial translation offering a therapy approach in reversible infantile respiratory chain deficiency

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Childhood-onset mitochondrial encephalomyopathies are severe, progressive conditions. However reversible infantile respiratory chain deficiency (RIRCD) due to a homoplasmic mt-tRNA^{Glu} mutation and reversible infantile hepatopathy, due to TRMU deficiency, stand out by showing spontaneous recovery and provide the key to treatments of potential broader relevance. Modification of mt-tRNA^{Glu} is a possible functional link between these two conditions, since TRMU is responsible for 2-thiouridylation of mt-tRNA^{Glu}, mt-tRNA^{Lys} and mt-tRNA^{Gln}.
To elucidate the age-dependent, tissue-specific infantile presentation of these diseases, we studied changes in 2-thiouridylation both *in vitro* and *in vivo*. We show that down-regulation of TRMU in RIRCD impairs 2-thiouridylation and exacerbates the effect of the mt-tRNA^{Glu} mutation by triggering a mitochondrial translation defect *in vitro*. Skeletal muscle biopsies of controls and patients of different age were analyzed by high resolution northern blotting to detect the level of 2-thiouridylation. Our results suggest that the rate of 2-thiouridylation in normal human skeletal muscle does not change by age. Interestingly skeletal muscle of two RIRCD patients in the symptomatic phase showed clearly decreased thiolation which improved in parallel with the clinical recovery.
TRMU requires cysteine for its normal function, but the availability of this amino acid in the neonatal period is limited. *In vitro* L-cysteine supplementation improved the activities of complexes I and IV and prevented the decrease of respiratory complexes in TRMU down-regulated RIRCD cells. Our results show that L-cysteine supplementation is a potential treatment for RIRCD which is likely to have broader application for the growing group of mitochondrial translation disorders.

Poster 27

Prevalence of subunit mutations in Complex I Deficient Leigh Syndrome revealed by whole exome sequencing

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Background: Leigh syndrome (LS), a subacute necrotising encephalomyelopathy, is characterised by lactic acidosis and bilateral symmetrical MRI lesions, especially in the basal ganglia and brain stem. Although LS can be associated with any OXPHOS complex defect, complex I deficiency occurs most frequently, accounting for ~30% of cases. LS has been linked to defects in >30 genes to date, including mitochondrial and nuclear genes. Therefore we applied a whole exome Next Generation Sequencing (NGS) approach to investigate a cohort of 14 single-centre cohort paediatric patients with complex I deficient LS.
Methods: Traditional mtDNA sequencing was carried out before seeking for other nuclear defects. As part of a stepwise diagnostic approach, candidate gene and whole exome sequencing (NGS) were employed in the remaining unsolved cases.
Results: A genetic diagnosis was made for all the patients: 7 of them carried mtDNA mutations in (*MT-ND1*, *MT-ND5*, *MT-ND6*), two of which associated with a new clinical phenotype; the remaining patients

carried 4 novel mutations in complex I nuclear encoded subunits (*NDUFV1*, *NDUFV2*, *NDUFS1*, *NDUFS4*) which were identified by NGS.
Conclusions: A stepwise approach including mtDNA and candidate gene sequencing followed by NGS allowed the identification of the genetic defects in all 14 complex I deficient LS patients of our single-centre cohort. All carried mutations in complex I subunits, and none in any of 9 known complex I assembly factors. In conclusion, in order to provide a potentially faster diagnosis for complex I deficient LS patients, the diagnostic process should focus on complex I subunits first.

Poster 28
A novel homozygous mutation in *EARS2* causing a fatal multisystem infantile disease
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Mitochondrial disorders are clinical phenotypes, usually a result of mitochondrial dysfunction, caused by mutations in either mitochondrial DNA (mtDNA) or nuclear-encoded (nDNA) mitochondrial genes. The majority of these gene defects manifest as histological and biochemical abnormalities in affected tissues. Clinical phenotypes are typically early-onset, severe and often fatal. MtDNA-related disorders are well defined and the analysis of mtDNA is standardized. More recently, research focus has shifted to nuclear genes and new mutations have been identified in genes involved in mitochondrial protein synthesis.
We present a patient, the third child of consanguineous Turkish parents with severe infantile multisystem disease, involving the brain and liver. The proband died at 3 months of age of necrotising bronchopneumonia. Biochemical and histochemical analysis of skeletal muscle identified a severe, combined, deficiency of respiratory chain complexes I and IV. Subsequent mtDNA analysis excluded mtDNA depletion, deletions or point mutations in affected tissue. Common nDNA causes of mitochondrial dysfunction, including nuclear encoded mitochondrial elongation factors or ribosomal factors were also excluded. Through a combination of homozygosity mapping and whole exome sequencing we identified a homozygous missense mutation in mitochondrial glutamyl-tRNA synthetase (*EARS2)*. Pathogenicity was confirmed by familial segregation and exclusion in ethnically matched controls
Nuclear-mitochondrial disorders are characterised by disturbed mitochondrial translation and *EARS2* is the newest member of this gene family. We have shown that in addition to central nervous system involvement, some patients develop a progressive and fatal course in infancy and therefore our case widens the clinical spectrum of *EARS2* mutations.

Poster 29
Molecular genetic diagnosis of mitochondrial DNA depletion syndromes
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Mitochondrial DNA (mtDNA) depletion syndromes (MDS) are severe autosomal recessive disorders associated with reduced mtDNA content in affected tissues. Molecular genetic testing for MDS is provided as part of the NCG funded service for rare mitochondrial disorders, of which Oxford is one of three centres. Over the last 5 years the Oxford centre has directly tested muscle and/or liver DNA from 426 patients for mtDNA depletion using real-time PCR. Results were strongly suggestive of mtDNA depletion in 23 patients (copy number <30% of normal), and equivocal (copy number 30-50% of normal) in a further 33 patients. Sequencing of the known causative genes *DGUOK*, *MPV17*, *PEO1*, *POLG*, *RRM2B*, *SUCLA2*, *SUCLG1* and *TK2* identified likely pathogenic mutations in 15 of the 23 patients (65%) with mtDNA depletion: 4 *MPV17*, 3 *POLG*, 3 *DGUOK*, 3 *TK2*, 1 *PEO1* and 1 *RRM2B*. In contrast, mutations were detected in only 2 of the 33 patients (6%) with equivocal (37% and 40%) copy number results, indicating that most equivocal mtDNA copy number results are not due to mtDNA depletion syndrome. In approximately one third of cases with mtDNA depletion, no nuclear genetic diagnosis has been made,

and so current development is focused on translating sequencing of further candidate genes into diagnostic service. Therefore, validation of a next generation sequencing approach to simultaneously sequence the above 8 genes, and an additional 6 genes associated with autosomal disorders of mtDNA maintenance, is in progress using a combination of Agilent HaloPlex and the Illumina MiSeq platform.

Poster 30

***NDUFA4* mutations: a new cause of mitochondrial cytochrome *c* oxidase linked neurological disease**

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The cause of cytochrome *c* oxidase deficiency remains undefined in many cases. A combined homozygosity mapping and whole exome sequencing approach was applied to a large consanguineous pedigree with isolated cytochrome *c* oxidase deficiency linked to a Leigh syndrome neurological phenotype. Unexpectedly, affected individuals harboured homozygous splice donor site mutations (c.42+1G>C, NM_002489.3) in *NDUFA4,* a gene previously assigned to encode a complex I (NADH:ubiquinone oxidoreductase) subunit. Transcriptional studies demonstrated the c.42+1G>C transversion reduces wild-type *NDUFA4* mRNA in addition to producing an aberrant transcript predicted to translate a protein comprising of 14 in-frame followed by 35 out-of-frame amino acids. Both western blot analysis of denaturing gels and immunocytochemistry revealed undetectable steady-state NDUFA4 protein levels indicating that this mutation causes a loss-of-function effect in the homozygous state. Detailed analysis of one and two dimensional blue-native polyacrylamide gels confirmed an NDUFA4/cytochrome *c* oxidase interaction in control muscle. Since cytochrome *c* oxidase was detectable with no abnormal subassemblies in patient muscle, it is likely NDUFA4 is required for activity rather than assembly of the holoenzyme. These observations indicate *NDUFA4* is a new gene important for human cytochrome *c* oxidase function. We suggest the *NDUFA4* is screened in patients with unexplained cytochrome *c* oxidase deficiency.

Poster 31

***YARS2* mutations associate specifically with Mitochondrial Myopathy, Lactic Acidosis and Sideroblastic Anaemia (MLASA)**

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Background: Nuclear-encoded disorders of mitochondrial translation are associated with clinical and genetic heterogeneity. Genetic causes include defects of mitochondrial aminoacyl-tRNA synthetases, and factors required for initiation, elongation and termination of protein synthesis as well as ribosome recycling.

Patient and Methods: The patient presented at 1 year with anaemia which was initially attributed to iron deficiency. Bone marrow aspirate at 5 years revealed ringed sideroblasts but transfusion dependency did not occur until 11 years. Other clinical features included lactic acidosis, extremely poor weight gain, biventricular cardiac hypertrophy and severe myopathy leading to respiratory failure necessitating ventilatory support. Long-range PCR excluded large-scale mitochondrial DNA rearrangements. Clinical similarity to previously reported cases prompted direct sequence analysis of the *YARS2* gene, which encodes the mitochondrial tyrosyl-RNA synthetase.
Results and Discussion: Sequence analysis of *YARS2* revealed homozygosity for a known pathogenic mutation, c.156C>G;p.F52L. Comparison with four previously reported cases demonstrated remarkable clinical homogeneity. First line investigation of MLASA should therefore include direct sequence analysis of *YARS2* and *PUS1* (encoding a tRNA modification factor) rather than muscle biopsy. The reasons for segregation of specific clinical phenotypes with particular aminoacyl tRNA-synthetase defects remain unknown.

Poster 32
Preliminary evaluation of functional outcome measures in mitochondrial disease. Jane Newman, Grad.Dip.Phys[3], Brook Galna, PhD[2], Djordje Jakovljevic, PhD[3], Matthew G Bates, MD[1,], A.M. Schaefer, MRCP[1]; R. McFarland, MRCPCH;[1] Douglass M Turnbull MD, PhD[1], Michael I Trenell, PhD[3], Robert W Taylor, PhD [1],L.Rochester PhD[2], Gráinne S Gorman, MD[1].
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Objectives Mitochondrial diseases are a heterogeneous group of genetic disorders, resulting in significant morbidity and disability. The molecular basis of many of the common mitochondrial disorders has been elucidated over the last decade; yet currently there are no known cures and few effective treatments. This is compounded by the paucity of natural history studies and the lack of uniformity and relevance of outcome measures in therapeutic trials, research and clinical settings, in this patient population. Functional outcome measures have proven reliable measures to monitor natural history and interventions in other neurological conditions. We sought to evaluate the usefulness of validated functional outcome measures for patients with mitochondrial disease.
Methods Twenty-four patients and 12 sedentary controls were recruited to this case control observational study. This included the six minute timed walk (6MTW), 10 meter walk (10MTW), Timed up and Go (TUG) and the 5 times sit to stand (5XSTS). These functional measures were compared to clinical measures of peak exercise capacity, proximal muscle strength and disease burden.
Results All clinical measures used detected significant differences between patients and sedentary controls. Disease severity correlated with TUG($r=0.63$, $p= .02$) and 10MTW($r=0.62$, $p= .001$). Receiver Operating Curve analysis revealed 5XSTS to be the most responsive measure.
Conclusion The 10MTW, 6MTW, TUG and 5XSTS are valid evaluative outcome measures in patients with mitochondrial disease. The 5XSTS can be used to discriminate between mitochondrial and sedentary controls with high accuracy and 10MTW and TUG may serve as useful surrogate markers ofdisease severity.

Poster 33
SURF1 deficiency: phenotypes and genotypes
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Background: SURF1 deficiency is an autosomal recessively inherited mitochondrial disorder, which is the most common cause of cytochrome *c* oxidase (COX, complex IV) deficient Leigh syndrome (LS).

Methods: We identified genotypes in 57 SURF1-deficient patients diagnosed at ten centres in the UK (n=52) and two centres in Australia (n=5). Clinical data were ascertained in 44 patients. Additionally a systematic review of the literature was performed to identify all published SURF1-deficient cases.
Results: In our cohort, most patients (32/44, 73%) presented in infancy (median age 9.5 months) and the most prevalent symptoms were growth failure (95%), hypotonia (93%), poor feeding/vomiting (89%), developmental delay (88%), neurological regression (71%), movement disorder (52%) and ophthalmoplegia (52%). CSF lactate was raised in all patients (mean 4.3 mmol/L, 30/30) and high blood lactate (mean 4.4 mmol/L) was found in 31/38 (81%). Fibroblast COX activity was reduced in 25/25 (100%) although COX histochemistry was normal in 30% of biopsies. A peripheral neuropathy was noted in 13/16 (81%). Neuroimaging demonstrated typical brainstem and/or basal ganglia lesions in 28/33 (85%). Death was frequently due to respiratory failure 28/37 (76%). Kaplan-Meier analysis revealed that SURF1-deficient patients had significantly ($p<0.001$) longer survival compared to *LRPPRC*-associated LS and complex I-deficient LS. Seven patients experienced survival >10 years and 6 of these patients did not experience neurological regression. Six novel *SURF1* mutations were identified.
Conclusion: We demonstrate that SURF1-deficient patients have a homogenous clinical and biochemical phenotype, and the majority of cases can be diagnosed without performing a muscle biopsy.

Poster 34
Can high intensity interval training (HIIT) improve functional capacity and clinical symptoms in inflammatory and mitochondrial myopathies?
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Purpose: To assess the effects of HIIT on functional capacity and clinical symptoms in sporadic Inclusion Body Myositis (sIBM) and mitochondrial myopathies.
Methods: HIIT involved three times per week of short bursts of high intensity cycling followed by active recovery intervals, performed over 16 weeks. Subjects completed a progressive cycle test to assess exercise tolerance (peak work rate and VO_2) before and after the HIIT. Disease burden, muscle strength and electrical activity during voluntary contraction were also assessed and muscle biopsy and DEXA scans were performed to evaluate change in muscle and body composition.
Results: Preliminary results from seven subjects (65±10 years of age) show improved peak exercise VO_2 and a significant increase in peak work capacity following HIIT ($p = 0.036$). For one subject, change in muscle electrical activity during contraction suggested possible denervation following HIIT. However, there was no significant change in peak muscle strength or reported fatigue. There was also no significant change found in bone mineral density following HIIT.
Conclusion: These findings suggest HIIT improved aerobic work capacity in sIBM and mitochondrial myopathies without exacerbating symptoms of fatigue. Further investigations will help to identify the wider safety implications and therapeutic potential of exercise in inflammatory and mitochondrial myopathies.

Translational Research in Glycosylation Disorders

Poster 35
Missense mutations in β-1,3-*N*-acetylglucosaminyltransferase 1 (*B3GNT1*) cause Walker-Warburg syndrome
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Several known or putative glycosyltransferases are required for the synthesis of laminin-binding glycans on alpha-dystroglycan (αDG), including POMT1, POMT2, POMGNT1, LARGE, Fukutin, FKRP, ISPD and GTDC2. Mutations in these glycosyltransferase genes result in defective αDG glycosylation and reduced ligand binding by αDG causing a clinically heterogeneous group of congenital muscular dystrophies, commonly referred to as dystroglycanopathies. The most severe clinical form, Walker-Warburg syndrome (WWS), is characterised by congenital muscular dystrophy and severe neurological and ophthalmological defects. Here, we report two homozygous missense mutations in the β-1,3-*N*acetylglucosaminyltransferase 1 (*B3GNT1*) gene in a family affected with WWS. Functional studies confirmed the pathogenicity of the mutations. First, expression of wildtype but not mutant *B3GNT1* in human prostate cancer (PC3) cells led to increased levels of αDG glycosylation. Second, morpholino knockdown of the zebrafish *b3gnt1* orthologue caused characteristic muscular defects and reduced αDG glycosylation. These functional studies identify an important role for B3GNT1 in the synthesis of the uncharacterised laminin-binding glycan of αDG and implicate *B3GNT1* as a novel causative gene for WWS.

Poster 36
Investigating differences in the roles of FKRP and fukutin in eye and muscle development
MRC Centenary Award Poster
Alasdair J. Wood, Antonia Cumine, Juliane S. Müller, Hanns Lochmüller, Kate Bushby, Steve H. Laval Rita Barresi, Volker Straub.

Deficiencies in fukutin-related protein (FKRP) and fukutin lead to aberrant glycosylation of α-dystroglycan, a key receptor for basement membrane proteins. Appropriate glycosylation of α-dystroglycan is important for interaction with its ligands in the extracellular matrix. There is a broad spectrum of disorders associated with FKRP and fukutin deficiency, ranging from limb-girdle muscular dystrophy to congenital muscular dystrophy syndromes such as Muscle Eye Brain disease and Walker-Warburg syndrome. Here we use zebrafish as a model system to investigate the hypothesis that FKRP and fukutin are required for function of components in the basement membrane of the eye beyond α-dystroglycan. FKRP, fukutin and dystroglycan were knocked down with antisense oligonucleotide morpholinos in wild type fish. Basement membranes in eye and muscle were assessed using high power transmission electron microscopy and immunohistochemically in 3 day post-fertilisation larvae. Muscle fibres in the morphants failed to adhere to the myotendinous junctions as a result of a loss of the α-dystroglycan-laminin interaction at the clearly disrupted vertical myosepta, as determined by whole mount staining. Interestingly there was increased deposition of laminin found in the eye basement membranes of dystroglycan morphants when compared to controls. Since dystroglycan was abolished it is unclear whether this is simply due to disorganisation of laminin or binding to other ligands in retinal cell layers adjacent to the basement membranes. However, reduced laminin expression was found in the eyes of FKRP and fukutin morphants. Overall the data suggests deficiency of FKRP and fukutin could affect additional targets beyond α-dystroglycan within the eye's basement membranes.

Poster 37
Brain development in a mouse model of muscle-eye-brain disease

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The dystroglycanopathies are a clinically heterogenous group of muscular dystrophies, caused by mutations in at least 9 genes, one of which is fukutin-related protein (FKRP). Patients with these mutations demonstrate a wide clinical spectrum of disease, and in the most severe cases, have substantial muscle eye and brain involvement. One of the defining features of this group of diseases is the hypoglycosylation of alpha-dystroglycan, which effectively disrupts the link between the dystrophin-associated glycoprotein complex and the extracellular matrix. This is thought to underpin the basement membrane defects seen in these diseases, and is considered to be central to the disease process. Studies in other mouse models of dystroglycanopathy have shown that the brain initially begins to develop, with defects present from E13.5 (Hu et al., 2007). In this developmental study, we investigate the pathogenesis of brain lesions in the $FKRP^{KD}$ - a mouse model of muscle-eye-brain disease with an 80% knock down in FKRP expression. Previous work from our group has demonstrated that the brain lesions in the $FKRP^{KD}$ are more extensive and substantial than in previous mouse models of dystroglycanopathy investigated.
This study shows that glycosylated alpha dystroglycan is normally present within the neuroepithelium, in addition to at the basement membrane, in wild type mice at E12.5. In the $FKRP^{KD}$, in addition to an absence of IIH6 staining, defects in the pial basement membrane, abnormal neuronal migration and mislocalisation of Cajal Retzius cells are established by this time point.

HU, H., YANG, Y., EADE, A., XIONG, Y. F. & QI, Y. (2007) Breaches of the Pial Basement Membrane and Disappearance of the Glia Limitans During Development Underlie the Cortical Lamination Defect in the Mouse Model of Muscle-Eye-Brain Disease. The Journal of Comparative Neurology, 501, 168-183.

Poster 38
Basement membrane deposition during muscle development in the FKRP Deficient Mouse ($FKRP^{KD}$).

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We previously generated a FKRP deficient mouse ($FKRP^{KD}$) which recapitulates the severe end of the dystroglycanopathy spectrum. In view of the well documented role of α-dystroglycan in basement membrane deposition we sought to determine if secondary myogenesis was altered in the $FKRP^{KD}$ mice. Here we show that glycosylated α-dystroglycan is present from the earliest stages of secondary myotube formation at E15.5 in wild type mice. $FKRP^{KD}$ mice show a mild reduction in laminin α-2 at this time point. However, this reduction is not apparent using an antibody to pan laminin (identifies several laminin chains including β1 and □1 chain). At P0, a marked reduction of laminin α2 was noted in $FKRP^{KD}$ compared to wild type, together with a moderate reduction in the pan laminin. In order to further examine this we have now examined the deposition of laminin α-1, laminin α-4 and laminin γ1 and shown no significant differences between wild type and $FKRP^{KD}$ at either E15.5 or P0. Laminin β1 however, showed a subtle reduction in $FKRP^{KD}$ compared to wild type at E15.5 which became more apparent at P0. In order to determine the effect of these alterations on fibre formation we counted muscle fibres at E15.5 and P0 and showed that neither the number of primary myotubes nor the total number of fibres at P0 was significantly different between $FKRP^{KD}$ and wild type mice. These observations suggest that a alterations in α-dystroglycan glycosylation during myogenesis does not influence fibre formation.

Poster 39
Alterations in α-dystroglycan glycosylation are associated with defects at the neuromuscular junction.

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The defective glycosylation of α-dystroglycan is associated with a group of muscular dystrophies collectively referred to as the dystroglycanopathies. Mouse models for this group of diseases include the LARGEmyd and the FKRP knock down ($FKRP_{KD}$), each of which are characterised by a progressive form of muscular dystrophy. Previous work suggests that impaired neuromuscular transmission contributes to muscle weakness in LARGEmyd mice and that this may be attributed to the effects of LARGE and glycosylated dystroglycan in stabilizing the endplate of the neuromuscular junction (NMJ). Here we show that both hypo and hyperglycosylation of □-dystroglycan lead to fragmentation of the NMJ, as shown after staining with fluorescently labelled □-bungarotoxin. The number of fragments corresponding to each NMJ on both LARGE overexpressing mice and $FKRP_{KD}$ were significantly higher than the controls, without changing the total volume or the surface area of the junction. In wild type controls immunostaining for the presynaptic marker synaptophysin revealed co-localization with the bungarotoxin-stained AChR clusters of the postsynaptic apparatus. However, this was lost in some NMJs of the $FKRP_{KD}$ mice. All axons emerging from the endplates were stained with neurofilament antibodies. No major disruption was observed on the nerve endings from either hypo or hyperglycosylated models.

Poster 40

Developing novel Alpha Dystroglycan Antibodies using the $Large_{myd}$ Mouse

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The dystroglycanopathies are a sub- group of muscular dystrophies with a wide clinical phenotype ranging from the severe Walker Walburg Syndrome to forms of limb girdle muscular dystrophy without structural eye and brain involvement. Central to the disease process is a secondary defect in alpha dystroglycan (αDG) glycosylation which perturbs binding to extracellular matrix ligands such as laminin and perlecan. The current approach for diagnosis is based upon the reactivity of muscle biopsies to IIH6, an anti-αDG IgM and gene sequencing to identify the causative gene. However, IIH6 is unreliable and often gives an inconsistent labelling pattern making initial diagnosis and comparisons between laboratories difficult. Whilst many groups have raised additional polyclonal antibodies these are not available in sufficient quantities for the wider research community. Our project focuses on the generation of novel monoclonal antibodies which will provide a valuable and indefinite resource for future diagnosis and research. We present here our strategy for overcoming the low inherent immunogenicity of αDG by injecting highly purified glycosylated αDG into the 'αDG naïve' $Large_{myd}$ mouse. The muscle of this mouse lacks the laminin binding IIH6 epitope and so by using this model we aim to develop a panel of monoclonal antibodies which can be used to identify fully glycosylated αDG and diseased glycoforms.

Poster 41

Flow cytometry analysis for the identification and study of novel dystroglycanopathy variants.

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Alpha-dystroglycan (α-DG) is a peripheral membrane glycoprotein integral to the dystrophin-glycoprotein-complex. It interacts both with beta-dystroglycan and components of the extracellular matrix (ECM), including the laminins. Reduced α-DG glycosylation characterizes a subset of muscular dystrophies known as the dystroglycanopathies, resulting in lower affinity binding to these ECM components. Techniques such as immunohistochemistry and immunoblotting are used to assess the glycosylation status of α-DG, but the detection of a partial reduction using these techniques is challenging. Flow cytometry enables us to circumvent this problem with its increased sensitivity, complementing the current diagnostic methods. It can also be used to help identify potential dystroglycanopathy cases even if the genetic mutation is not in one of the known causative genes. In this study, flow cytometry helped prove the pathogenicity of dystroglycanopathy variants in GDP-mannose pyrophosphorylase B (*GMPPB*). Firstly, it showed that the fibroblasts from patients with deleterious *GMPPB* variants had characteristically reduced levels of α-DG glycosylation compared to

healthy fibroblast controls. Secondly, transfecting wild-type *GMPPB* constructs into some of these patient fibroblasts as well as supplementing the media with 1mM D-mannose increased the amount of IIH6-reactive glycans, which was detectable and quantifiable in both cases by flow cytometry. This study highlights the use of flow cytometry for diagnostic purposes as well as for the study and therapy of dystroglycanopathy causing genes. The role of mannose supplementation in increasing the glycosylation of α-DG in some *GMPPB* variants warrants further study.

Poster 42

Investigating collagen VI biosynthesis and assembly in the context of deficient *ALG2;* a novel gene identified in a CMS family originally disagnosed with Ullrich's CMD

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CollagenVI related myopathies are associated with mutations in CollagenVIA1, A2 and A3 genes, which are components of extracellular matrix (ECM). Ullrich Congenital Muscular Dystrophy (UCMD) and Bethlem Myopathy (BM) are two examples of CollagenVI myopathies. Several UCMD and BM phenotypes have been reported with no mutation in CollagenVIA genes.

In this study, the role of novel pathogenic variant in the gene Asparagine-linked glycosylation2 (*ALG2)* in non-colVI UCMD was investigated. Combining data from autozygosity analysis and exome sequencing, an indel in the gene *ALG2*, exon1 NM.033087.3:c.283-296delGGGGACTGGCTGCc.283-293insAGTCCCCGGC p.73-76delGDWLinsSPR was found which completely segregated with the disease. *ALG2* encodes the α1, 3-mannosyltransferase which catalyses an essential step in asparagine-linked N-glycosylation of proteins. Considering the role of other N-glycosylation pathway genes in congenital myasthenic syndromes, two patients underwent electromyography repetitive nerve stimulation, suggesting a neuromuscular junction defect despite the clinical presentation of UCMD. In addition, previous research revealed proper post translational modification is essential for secretion of collagens to ECM and their correct assembly(1). Several techniques such as RT-PCR, western blot and immunofluorescence labelling were applied to investigate the role of N-glycosylation pathway in collagenVI secretion. These syndromes form part of the wider spectrum of congenital disorders of glycosylation due to impaired N-linked glycosylation.

Key Word: UCMD, CMS, ALG2.

1. *Sipila, L., et al. Secretion and Assembly of Type IV and VI Collagens Depend on Glycosylation of Hydroxylysines. J. Biol. Chem., 2007.* ***282****(46): p. 33381-33388.*

Translational Research in Peripheral Nerve Disease

Poster 43

Treatment with Arimoclomol, a co-inducer of the heat shock response, prevents acute mitochondrial damage induced by staurosporin in primary motor neurons

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that involves multiple pathomechanisms. Several of these pathomechanisms have been targeted in clinical trials, but almost all have been unsuccessful.

We have previously shown that Arimoclomol, a co-inducer of the endogenous cytoprotective heat shock response (HSR), is neuroprotective both in vitro, in stressed motor neurons, and in vivo, in animal models of ALS. These beneficial effects of arimoclomol are, at least in part, due to the upregulation in heat shock protein expression. However, it is possible that arimoclomol has additional cytoprotective effects that have not been investigated. Here we examined the effects of arimoclomol on intracellular Ca^{2+} and mitochondrial function, since mitochondrial dysfunction and intracellular Ca^{2+}-mediated toxicity, have been implicated in several neurodegenerative diseases including ALS.

Using confocal fluorescent microscopy, we found that treatment of primary motor neurons with arimoclomol prevented the acute loss in mitochondrial membrane potential induced by treatment with staurosporin. Preliminary investigation of the effect of arimoclomol on Ca2+ levels in staurosporin-

stressed cells, suggest that the protective effects of arimoclomol may be mediated by alterations in intracellular Ca^{2+}-responses. This in turn may help motoneurons maintain their membrane potential, thereby limiting subsequent mitochondrial dysfunction and neuronal cell death.
These results identify a novel mechanism of action of arimoclomol, independent of its known ability to up-regulate the HSR, which involves targeting of stress-induced mitochondrial dysfunction. These results suggest that arimoclomol may therefore be of potential therapeutic value in a number of neurodegenerative conditions including ALS, targeting multiple pathological mechanisms.

Poster 44

The potential of morpholino antisense oligonucleotides for the therapy of spinal muscular atrophy

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Morpholino antisense oligonucleotides (PMOs) have been successfully used in Duchenne muscular dystrophy clinical trials, where they have shown an excellent safety profile and encouraging clinical efficacy. PMOs have recently been used to modify the splicing of Survival Motor Neuron gene 2 (*SMN2*) *in* spinal muscular atrophy (SMA) and showed promising efficacy in SMA mouse models. We have developed a 25-mer PMO, PMO25, targeting the intronic splicing silencer in intron 7 of *SMN2*. PMO25 successfully rescued the phenotype of severe type I SMA mice following a single administration by direct intra cerebral ventricular (ICV) delivery or systemic delivery. Specifically, a single ICV injection of PMO25 at 40 µg/g in new born severe SMA mice increased their survival to 298 days, while the untreated type I SMA mice only survive for 10 days; a single systemic delivery of PMO25 at 40 µg/g in new born severe SMA mice also increased the survival beyond 250 days. The successfully treated severe SMA mice weighed more than 80% of normal control mice. No adverse effects were observed in ICV injected or IV injected mice. This is so far the most significant improvement achieved using antisense therapy in SMA mice. Our study suggests that PMO25 should be considered for future clinical applications.

Poster 45

Using whole-exome sequencing to identify disease-causing genetic variants in inherited neuropathies

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Background: Identification of pathogenic mutations causing inherited neuropathies may be challenging, since at least 45 disease-related genes have been reported. More than 85% of the mutations associated with known Mendelian diseases are located in protein-coding exons. Targeted capture and massive parallel sequencing of these genomic regions (whole-exome sequencing) has been recently demonstrated to be an efficient method for the identification of novel mutations and genes in patients with inherited neuropathies.
Objective: To report our preliminary experience with whole-exome sequencing in suspected inherited neuropathies.
Methods: After excluding mutations in inherited neuropathy-related genes according to the phenotype, whole-exome sequencing was performed in 53 individuals from 31 unrelated pedigrees. Enrichment of coding exons and flanking intronic regions was performed with Illumina TruSeq and Agilent SureSelect capture products. Sequencing was performed on HiSeq 1000 and 2000 platforms.
Results: From a total of 31 probands (24 familial cases; 7 sporadic cases), 2 (6%) had a diagnosis of Charcot-Marie-Tooth disease type 1 (CMT1), 6 (19%) had CMT2 or intermediate CMT, 15 (48%) had sensory neuropathy with or without other clinical features, 5 (16%) had a distal hereditary motor neuropathy, and 3 (10%) had a Brown-Vialetto-Van-Laere-like phenotype. A probable or definite pathogenic variant was found in 6 different genes in 6 unrelated probands (5 familial cases; 1 sporadic case).
Conclusion: Our preliminary results suggest a success rate of 19% in the detection of disease-related genes in suspected inherited neuropathies. Analysis of the data is still in process, and we envisage higher success rates.

Poster 46

An in-vitro study of distal hereditary motor neuropathydue to homozygous hsj1 mutations

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During the last decade, mutations in three small heat shock proteins (Hsps) HSPB1, HSPB3 and HSPB8 have been identified as causative of distal hereditary motor neuropathy (dHMN). Hsps are a ubiquitously expressed family of molecular chaperones with versatile functions that include refolding of misfolded proteins. Hsp70, the archetypal ATP-dependent Hsp, binds misfolded proteins with weak affinity. J domain (HSP40) proteins bind to HSP70, thereby increasing its protein binding and refolding capacity. In 2011, an autosomal recessive form of dHMN was described due to homozygous mutations in the Hsp40 gene, HSJ1. We have preliminary evidence that HSJ1 knockout mice develop de novo motor neuron (MN) degeneration. Furthermore, the loss of motor neurons can be rescued by overexpression of the ER specific isoform, HSJ1b but not the cytosolic isoform, HSJ1a implicating ER stress in this form of dHMN. We also examined functional markers of MN function in vitro including axonal transport, and found that the transport of mitochondria in HSJ -/- neurons was normal. HSJ-/- motoneurons therefore display some, but not all of the pathological hallmarks of dHMN.

Poster 47

Investigating riboflavin transporter mutations in Brown-Vialetto-Van Laere syndrome

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Brown-Vialetto-Van Laere (BVVL) syndrome is a rare autosomal recessive neurodegenerative disorder characterised by bilateral sensorineural hearing loss, cranial nerve palsies, respiratory insufficiency, and severe sensorimotor neuropathy with onset in infancy or childhood. Mutations in *SLC52A1*, *SLC52A2*, and *SLC52A3*, encoding riboflavin transporters, cause flavin deficiency. Flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN), the co-enzyme forms of riboflavin, serve as electron acceptors in complexes I and II of the mitochondrial respiratory chain (MRC) and in fatty acid β-oxidation. *SLC52A1*, *SLC52A2*, and *SLC52A3* were sequenced in 71 patients with BVVL-like phenotypes. Levels of Riboflavin/FAD/FMN, MRC enzyme activities, Coenzyme Q_{10} levels, and expression of the endoplasmic reticulum (ER) stress marker BiP were measured in patient fibroblasts. Nine patients were found to have compound heterozygous or homozygous mutations in *SLC52A2.* No mutations were identified in *SLC52A1* and *SLC52A3*. Patient fibroblasts had decreased MRC complexes I and II activities compared to controls as a possible consequence of a deficit in riboflavin, FAD and FMN status. One patient was found to have a decreased CoQ_{10} level. Patients did not have increased levels of the BiP ER stress marker. Mitochondrial dysfunction may play a role in BVVL pathogenesis.

Poster 48

Assessment of distal lower limb strength in Charcot-Marie-Tooth disease type 1A

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Background: Charcot Marie Tooth (CMT) disease type 1A is the commonest form of CMT. The major clinical feature is distal lower limb weakness which impacts on gait. Ankle dorsiflexion and plantarflexion can be assessed by different techniques, some of which have relevance in a clinical setting and some are more used for research purposes. Aims: The aims of this study were to define test-retest reliability of

ankle strength measurement, assess for correlation between measurement techniques and to assess if the techniques have sufficient sensitivity to detect deterioration over 12 months in CMT1A patients. Methods: We assessed ankle dorsiflexion and plantarflexion in 17 CMT1A genetically confirmed patients using manual muscle testing (MRC scale), hand held myometer in an immobilising device, isometric dynamometry and isokinetic dynamometry. All measurements were performed at baseline, one week, 6 months and 12 months. Results: Test retest reliability at one week was good for all measures. There was moderate to strong correlation between the four measurement methods at baseline (rho between 0.61-0.92, all $p<0.01$). Preliminary results did not show significant change in ankle strength over 6 months in 11 patients using any of the four techniques. Conclusion: The four different methods for assessing ankle strength in CMT1A patients show good reliability and moderation correlation between them. However no significant change is demonstrable at 6 months and the 12 month data is awaited.

Poster 49

Hereditary sensory neuropathy type 1: a natural history study

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Hereditary sensory neuropathy type 1 (HSN1) is a predominantly sensory neuropathy due to mutations in *SPTLC1* and *SPTLC2* genes associated with the accumulation of atypical 1-deoxy-sphingolipids (1-dSLs) with probable neurotoxic effect. A recent trial of L-serine in transgenic HSN1 mice showed reduction of the 1-dSLs and improvement in the phenotype. L-serine is therefore an excellent candidate therapy for HSN1, however the lack of natural history studies and outcome measures are major barriers to start a definitive clinical trial. We conducted a natural history study on 31 HSN1 patients to fully characterize the clinical phenotype and to establish correlation of 1-dSLs with disease severity. We have collected 1-year follow-up data on 17 patients to date. Clinical impairment was assessed by the Charcot Marie Tooth Neuropathy score (CMTNS) or CMT examination score (CMTES). Quantitative sensory testing (QST), skin biopsy to assess intraepidermal nerve fibre density and a pain questionnaire were also performed. Baseline CMTNS was 22.8 ± 7.7 (range 7 -35), CMTES was 15.7 ± 6.5 (2-27). Males were more severely affected than females. 1-dSLs were significantly elevated in all patients and correlated with disease severity. QST in 10 patients showed marked abnormalities in thermal thresholds with mechanical detection thresholds more affected than vibration detection thresholds. Longitudinal data to date shows no significant change of CMTNS, CMTES and 1-dSLs over 1 year. These findings show that HSN1 patients have a variable phenotype and 1-dSLs may represent a marker of severity of disease but to date have not shown responsiveness over 12 months.

Poster 50

Genetic testing for inherited peripheral neuropathies: challenges and opportunities in implementing targeted next generation sequencing as a diagnostic service.

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Inherited peripheral neuropathies (IPN) are a heterogeneous group of disorders with a prevalence of 1 in 2,500 and implicating over 50 genes. Bristol Genetics Laboratory currently provides a specialist UK Genetic Testing Network sequencing service for 16 genes. Therefore a significant proportion of patients remains without a genetic diagnosis.

We undertook a project to evaluate the application of targeted capture NGS to the diagnosis of IPN using a cohort of fifteen patients with both known and uncharacterized genetic aetiologies. Consent was

obtained with letters of invitation via clinical genetics. Two different libraries were prepared: a custom 450kb SureSelect capture array was designed encompassing mainly coding regions of 54 genes and a Haloplex assay was also designed for the same regions. Libraries were run on Illumina GAII and MiSeq sequencers for comparison and evaluation of bioinformatics approaches to variant calling and dosage enumeration. Analysis was performed using open-source tools in Linux. Filtered variants were scored using in silico tools and candidate pathogenic variants were confirmed using Sanger sequencing. Candidate pathogenic variants were detected in six of the seven patients with unknown molecular aetiology, a very promising result for the diagnostic yield of this approach.
The quality of data, the extent of genetic variation, the utility of bioinformatics tools and databases in assigning variant status and potential new genotype-phenotype correlations were investigated. The experience of validating a new technology in a clinical context, the approach to downstream analysis and clinically relevant variant findings is discussed.

Poster 51
Diffusion tensor MRI of the sciatic nerve
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Background
Diffusion tensor imaging (DTI) is an MRI technique which is especially suitable for characterising tissues with restricted water mobility such as cerebral white-matter. The similar anisotropic structure of peripheral nerve makes DTI particularly promising for quantifying microstructure in neuropathies. Here we performed a first optimisation of DTI of the sciatic nerve in healthy subjects to quantify fractional anisotropy (FA), a measure of the directional dependence of water diffusion.
Methods
The right thighs of 5 healthy volunteers (mean age 33.0±6.0y) were scanned at 3T with a DTI sequence employing 6 gradient directions, gradient reversal fat suppression and 10 averages. Axial FA maps were generated with a tensor model using the FSL software. Regions of interest drawn on the sciatic nerve and medial quadriceps muscle were used to obtain mean FA values. A single 66y male with Charcot-Marie-Tooth disease 1A (CMT1A) was also imaged.
Results
The mean sciatic nerve FA for the 5 healthy subjects was 0.62±0.04 in contrast to 0.22±0.02 for the surrounding skeletal muscle. This difference permitted clear depiction of the structure and path of the nerve through the thigh. The FA of the sciatic nerve in the single CMT1A patient examined was 0.28.
Discussion
DTI enables clear visualisation and quantification of properties of the sciatic nerve. The suggestion that sciatic FA is reduced in CMT1A provides encouragement for future investigations. These will allow the influence of demyelinating and axonal pathologies on DTI properties to be determined and to assess the value of DTI for detecting focal nerve pathologies.

Poster 52
Exploring the causes of falls and balance impairments in people with neuromuscular diseases
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Falls are commonly reported by people with Charcot-Marie-Tooth disease [1]. In order to successfully manage the problem of falls there needs to be greater understanding of the causes of balance and gait impairment. This study aims to study balance performance and falls frequency in people with neuromuscular disorders, to ascertain the relationship with their clinical presentation.

People with CMT and matched healthy control subjects will be recruited. Kinematic and kinetic analysis of walking and balance will be performed. Static posturography, reactive and proactive balance responses will be measured. In addition, quantitative lower limb muscle testing, sensory measures, functional balance scales and balance confidence will be used to ascertain the predictors of balance impairments. Gait analysis will include a dual task condition to ascertain the impact of cognitive loading on performance. Participants will be screened for vestibular dysfunction and hypermobility syndrome.
All CMT participants will be given a 6 month prospective falls diary. The clinical and motion analysis data will be used to ascertain predictors of falls risk. A sample size of 30 subjects in each group will be recruited. Regression modelling will be used for the statistical analysis.
The results of this study will be used to inform the intervention for a rehabilitation trial to improve balance and manage falls.

[1] G Ramdharry, L Entwistle, A Thornhill, E Dewar, J Marsden, M M Reilly Perception of balance impairments and frequency of falls in people with Charcot Marie Tooth disease (*in submission*)

Poster 53
Combining Linkage analysis and Exome sequencing in two pedigrees with distal Hereditary Motor Neuropathy
Ellen Cottenie[1,2], Sinead Murphy[1,3], Alex Rossor[1], Matilde Laurá[1], Michael G Hanna[1], Mary M Reilly[1], Henry Houlden[1,2]
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Distal hereditary motor neuropathies (dHMN) comprise a heterogeneous group of diseases, characterized by selective loss of motoneurons. Eleven genes have been recognized as the cause for dHMN, however ~80% of genetic causes remain unknown. We present two families with dHMN phenotypes, lacking the common mutations.
The first family consisted of three generations with eleven affected family members out of 23. DNA was available for seven affected and four unaffected members. Exome sequencing of two cousins resulted in 7341 shared non-synonymous variants. After excluding known SNPs with a frequency higher than 2% or a segmental duplication region higher than 0.96, 120 variants remained. Linkage analysis in four affected and three unaffected members narrowed the variants down to 28, located on five linkaged regions.
Our second family had a history of dHMN in four generations and nineteen affected family members out of 42. DNA was available for six affected and one unaffected. Two cousins were sent for exome sequencing, which resulted in 5792 shared non-synonymous variants. Using the same filtering, this was reduced to 196 variants. Linkage analysis in all available members pointed to linkaged regions on two chromosomes, which enabled us to decrease the amount of possible variants to 18.
While segregation analysis, screening dHMN patients, and functional studies still need to be performed to confirm pathogenicity, these pedigrees illustrate how linkage analysis can rule out variants.

Poster 54
Hereditary sensory neuropathy and hearing loss caused by *DNMT1* mutation
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DNA methyltransferase 1(*DNMT1*) plays a crucial role in maintenance of methylation, gene regulation and chromatin stability. Mutations in *DNMT1* have been associated with autosomal dominant hereditary sensory neuropathy with dementia and hearing loss (HSAN IE). In all reported cases, patients presented with sensory neuropathy and sensorineural hearing loss between 20-35 years old and subsequently developed dementia by the fourth decade. Although most cases did not have cerebellar ataxia, subclinical pathological involvement has been reported. *DNMT1* mutations are also responsible for autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN), which is clinically characterised by late-onset narcolepsy-cataplexy, sensorineuronal deafness, cerebellar ataxia and variable dementia. Sensory neuropathy usually develops after the 5th decade. We report a 43-year-old sporadic patient with presumed hereditary sensory neuropathy starting with sensory loss, ulcerations and painless fractures by the age of 30 and progressive hearing loss by the age of 36. On examination, he

had bilateral hearing loss, a tentative gait, reduced pinprick/vibration sensation and decreased reflexes in the lower limbs. There was no weakness. Coordination was normal. Neurophysiology was consistent with an axonal sensory neuropathy. MRI of the brain showed cerebellar atrophy. He had negative genetic testing of several HSAN genes. Whole exome sequencing identified a heterozygous *DNMT1* mutation, p.Tyr495Cys, in *DNMT1* gene. This mutation has been previously reported in patients with HSAN IE. This patient suggests that *DNMT1* mutations can be associated with HSN and deafness without cognitive involvement although this may develop with time as the patient is only 43.

Poster 55

Targeting the endogenous stress response in a mouse model of Spinal Bulbar Muscular Atrophy

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Spinal and bulbar muscular atrophy (SBMA), otherwise known as Kennedy's Disease, is an X-linked, inherited, late onset motor neuron disorder. Molecularly the disease is caused by a polymorphic trinucleotide (CAG) repeat expansion in exon 1 of the androgen receptor (AR) gene, which encodes a polyglutamine (poly-Q) tract in the mature protein. Pathologically, the disease is characterised by selective loss of spinal and bulbar motor neurons with accompanying neuromuscular impairment, leading to significant disability. Disease manifestation is androgen dependant and consequently the clinical phenotype is predominantly restricted to males.

A yeast artificial chromosome (YAC) transgenic mouse model of SBMA with 100 CAG repeats (AR100) in the N terminal of the human androgen receptor gene has been developed (Sopher *et al,* 2004). These mice develop late onset lower motor neuron degeneration and a progressive neuromuscular phenotype, which recapitulates both the pathological and phenotypic characteristics of the human disease.

Using this model of SBMA we have examined the potential of targeting the endogenous cytoprotective heat shock response (HSR) as a therapeutic approach for SBMA. We have previously shown that arimoclomol, a pharmacological co-inducer of the HSR, significantly improves disease phenotype in the SOD1 mouse model of Amyotrophic Lateral Sclerosis, a rapidly progressing motor neuron disease (Kieran *et al*, 2004; Kalmar *et al*, 2009). Arimoclomol is currently in a phase II/III randomized, placebo-controlled clinical trials for ALS. In this study we undertook a preclinical trial of arimoclomol in SBMA, treating the mice from a postsymptomatic stage (12 months) to late stage disease (18 months). Our results show that arimoclomol has significant beneficial effects on the disease phenotype in SBMA mice.

Poster 56

An ENU-induced point mutation in mouse *Sod1* causes aberrant mitochondrial function and axonal maintenance in primary motor neurons

Centenary Award Poster

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Mutations in superoxide dismutase 1 (*SOD1*), a cytoplasmic and mitochondrial enzyme, account for approximately 10% of familial Amyotrophic Lateral Sclerosis (ALS) cases. Mutant SOD1 has been associated with abnormal mitochondrial and neuronal function *in vitro*. However the majority of experimental data regarding the pathological activity of mutant SOD1 has come from transgenic mouse models overexpressing the mutant human protein. We have a mutant mouse created by an ENU mutagenesis project (MRC Harwell, UK) with a single point mutation (D83G) in endogenous mouse *Sod1*,

which is analogous to a pathogenic mutation identified in several ALS families. The mutant protein is expressed in these mice at physiological levels and is not confounded by excessive overexpression. We have observed motor neuron degeneration in these mice and so in order to investigate the underlying cellular pathology, primary embryonic motor neurons were isolated and cultured from *Sod1* D83G mice on embryonic day 13.5 and cultured and neuronal development and mitochondrial function were examined. After 18 hours *in vitro*, we observed significant differences in neurite outgrowth, in particular of axon length, in heterozygotes and homozygotes compared to wildtype motor neurons. Homozygote motor neurons did not survive to 7 days *in vitro*, so mitochondrial membrane potential could only be determined in heterozygote and wildtype motor neurons. The results revealed a significant hyperpolarisation of the mitochondrial membrane potential in heterozygote motor neurons. These results suggest that the D83G mutation in mouse *Sod1* disrupts neuronal development and mitochondrial function, which may contribute to motor neuron dysfunction and degeneration in these mice.
Philip McGoldrick is in receipt of an MRC Centenary Award.

Poster 57

Cytoplasmic Dynein Heavy Chain 1 causes congenital lower limbs SMA associated with cortical malformation: a case report

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A tail domain mutation in Cytoplasmic Dynein Heavy Chain 1 (DYNC1H1) that causes a form of dominantly inherited SMA with early childhood onset of weakness and disproportionate involvement of the legs (SMA-LED) has been reported. Mutations located in other domains of DYNC1H1 have also been described in a family with Charcot-Marie-Tooth disease and in two patients with mental retardation and variable neuronal migration defects but no SMA.
We report a case with congenital SMA-LED caused by a DYNC1H1 mutation associated with CNS involvement.
A ten year old boy presented with congenital arthrogryposis with right dysplastic hip needing surgical correction, followed by motor developmental and speech delay and learning difficulties.
He never walked unaided and at 10 years he uses a self-propelling wheelchair and can mobilise only with assisted devices. CK was normal. NCV was normal while EMG showed chronic denervation especially in lower limbs. Muscle biopsy showed neurogenic changes.
Brain MRI showed bilateral perisylvian polymicrogyria. Sanger sequencing showed a heterozygous missense mutation in the exon 5 of DYNC1H1 (c.791G>A, p.Arg264Gln).
In conclusion we describe for the first time an individual in whom both a severe form of congenital SMA-LED and cortical dysplasia coexisted as a result of a heterozygous mutation in DYNC1H1. This report confirms the importance of DYNC1H1 in both central and peripheral neuronal functions. Further studies are necessary to clarify whether the location and nature of the DYNC1H1 mutations plays a role in the wide phenotypic spectrum that is emerging for this condition.
References:
1. Harms MB et al. Mutations in tail domain of DYNC1H1 cause dominant spinal muscular atrophy. Neurology. 2012 May 29;78(22):1714-20
2. Willemsen MH et al. Mutations in DYNC1H1 cause severe intellectual disability with neuronal migration defects. J Med Genet. 2012 Mar; 49(3):179-83.

Poster 58

An unusual double trouble of coexisting distal myopathy and distal motor neuropathy uncovered by exome sequencing

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Distal muscle weakness and atrophy is the presenting symptom of both distal myopathies and distal motor neuropathies. Differential diagnosis might be complicated by the coexistence of secondary axonal changes in primary distal myopathies, or the identification of unspecific myopathic changes on muscle biopsies in neuropathies.
We report a Caucasian family with at least 2 affected family members presenting with distal weakness and pes cavus in the teens. The index case was referred to us at the age of 14 years, due to Achilles tendon contractures and equinovarus feet deformity; he could not heel walk, had lower leg muscles wasting and, to a lesser extent of the thenar and hypothenar eminence. His muscle power was normal except for ankle plantar and dorsiflexion; deep tendon reflexes were preserved. The electrophysiology was suggestive of a motor neuronopathy. The younger sister presented in her teens with similar problems.
The whole exome analysis in these affected individuals unrevealed two independently co-segregating disease causing mutations: a heterozygous *Myosin Heavy Chain 7* gene mutation (*MYH7*,g.23884965C>T,c.5030G>A, p.R1677H) and a heterozygous mutation in the Berardinelli-Seip Congenital Lypodystrophy type 2 gene (BSCL2, g.62469971T>G, p.N88S), present in each of the affected individuals. Further genetic analysis of other similarly affected family members is in progress.
Our report highlights the power of whole exome sequencing in identifying the whole spectrum of mutations responsible for the phenotype in neuromuscular diseases and suggests that double trouble with overlapping clinical features may be easily missed by more traditional diagnostic approaches.

Translational Research in Muscle Channelopathies and Myasthenia Gravis

Poster 59
A novel mutation in *SCN4A* and its equivalent in *Scn4a* cause periodic paralysis in humans and mice

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Periodic paralysis (PP) is a rare condition characterized by attacks of muscle weakness (paralysis) and/or myotonia. One gene that is mutated in these diseases is the skeletal muscle sodium channel (Nav1.4). We identified *de novo* mutation in a patient with PP, located in the segment S1 of the second domain of the SCN4A gene. The mutation, I588V, is located in a region where no other mutations have been found before, which would help to unravel the functionality of this segment within the channel. Using ENU mutagenesis, we produced and characterized a unique mouse model of PP (named *Draggen*) carrying the exact same novel point mutation in the Scn4a gene that we found in the human patient. This is the first mouse model reported that exhibits all the classical PP symptoms observed in human's patients, including paralysis. We carried out extensive characterization of *Draggen* mice which gave new insights into the disease mechanisms.

Poster 60
"Seronegative" myasthenia gravis: how useful are cell-based assays?

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Acquired myasthenia gravis (MG) is an autoimmune channelopathy that affects approximately 100 patients per million population. The diagnosis is supported by the clinical presentation, neurophysiological examination and antibody status of the patient. Using widely available radioimmunoprecipitation assays, approximately 85% of patients with generalised MG will have antibodies to the AChR, and 0-8% will have antibodies to MuSK, depending on geographical factors. Of the remaining 7-15% some may have antibodies to AChR or MuSK when expressed at high density on HEK cells with antibody binding detected by immunofluorescence (termed "cell-based assays"; Leite et al 2008) and a small number to LRP4 (Low Density Lipoprotein Related Protein-4; Higuchi et al 2011). However, despite clear autoimmune aetiology, a proportion of patients remain 'seronegative' by these tests and confirmation of the diagnosis can be challenging. Added to this, electromyographic testing of the affected muscles in purely ocular MG is not possible.
As a preliminary study, we tested 25 samples negative for AChR and MuSK by radioimmunoprecipitation assays. Seven were positive for AChR and one for MuSK antibodies by the cell-based assays. None of the 25 patients had LRP4 antibodies. These preliminary results confirm the potential of the cell-based assays in helping to improve the diagnosis in seronegative MG patients, and will now be applied to a large series of national and international samples.

Poster 61
AChR deficiency in GFPT1 congenital myasthenic syndrome
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Mutations in a glutamine-fructose-6-phosphate transaminase 1 (GFPT1), which is a key rate-limiting enzyme in the hexosamine biosynthetic pathway which provides building blocks for the glycosylation of proteins and lipids, underlie a congenital myasthenic syndrome (CMS) characterised by a limb-girdle pattern of muscle weakness. It is not readily apparent why mutations in this ubiquitously expressed protein should cause a syndrome with symptoms restricted to muscle. In order to elucidate the pathomechanism of GFPT1 CMS we investigated acetylcholine receptor (AChR) expression in *GFPT1*-mutated human skeletal myotubes and *GFPT1* knock-down TE671 DB40 muscle cell line.
Cultured myotubes derived from two patients with *GFPT1* mutations (Pt1 and Pt2) and *GFPT1* knock-down TE671 DB40 muscle cells showed a significant reduction in cell-surface AChR expression (Pt1 $p<0.0001$; Pt2 $p=0.0097$; TE671 DB40 $p<0.0001$). This decrease, as revealed by western blotting, appeared to be due to the reduced steady-state levels of AChR α, δ, ε, but not β subunits.
The results indicate that the reduced expression of AChR at the motor endplate is likely to be a primary disease mechanism in the *GFPT1* CMS.

Poster 62
Rapsyn mutations in congenital myasthenic syndromes
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RAPSN mutations contribute towards a major subtype of congenital myasthenic syndromes (CMS). At the postsynaptic membrane of the neuromuscular junction, rapsyn interacts directly with acetylcholine receptors (AChR) and is essential for the formation of AChR clusters, structures that are critical for efficient neuromuscular transmission. Mutations in *RAPSN* have an overall effect of causing a deficiency of AChR at patient endplates, possibly through a variety of molecular mechanisms that disrupt rapsyn functions. Rapsyn-CMS is autosomal recessive, with a common mutation, p.N88K, either homozygous or heterozygous in over 90% of patients.
We investigate the pathogenic properties of newly identified *RAPSN* mutations from patients that do not harbour p.N88K. Mutations were introduced into wild type rapsyn cDNA and then subcloned into vector expression plasmids pEGFP-N1 and pBabe-PURO. Mutant rapsyn was then expressed in TE671 cells or introduced into *RAPSN*$^{-/-}$ myoblasts. Expression level of rapsyn variants and co-localisation of rapsyn and AChR were determined in TE671 cells, whereas the effect of the mutations on AChR cluster formation was assessed in differentiated *RAPSN*$^{-/-}$ myotubes. When compared to wild type rapsyn expression, mutations p.V45M, p.N88K, p.R91L and p.A153T impair AChR cluster formation and are thus likely pathogenic, though this occurs through differing molecular mechanisms.

Poster 63
Effect of LEMS antibodies on synaptic vesicle exocytosis
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Lambert Eaton Myasthenic Syndrome (LEMS) is an autoimmune disorder of the neuromuscular junction. LEMS is thought to be caused by antibodies to presynaptic voltage gated calcium channels (VGCCs), which are the major triggers of action potential (AP) - evoked release of neurotransmitters at central and peripheral synapses. Antibodies to P/Q–type VGCCs are detected in 92% of LEMS patients. Passive transfer of LEMS IgG to mice reduces end plate potentials at the neuromuscular junction. However, a direct effect of LEMS IgG on synaptic vesicle exocytosis has not been demonstrated.
We tested the effects of LEMS IgG on synaptic vesicle exocytosis in dissociated hippocampal neuronal cultures. We compared the effects of chronic application (16 hours) of LEMS IgG from three separate patients and three control subjects on AP-evoked vesicular release using fluorescence imaging of the styryl FM dye SynaptoRedC1 (SRC1). Recycling vesicles were labelled with SRC1 using high frequency field stimulation. Subsequent stimulation at 0.5 Hz triggered release of the trapped SRC1 dye from exocytosing vesicles, and the rate of fluorescence loss in individual synaptic boutons was used as a measure of the rate of vesicular exocytosis. The rate of AP - evoked synaptic vesicle exocytosis was significantly decreased in LEMS IgG treated neurones in comparison to neurones treated with control IgG. Our results provide evidence that LEMS IgGs can directly inhibit AP - evoked synaptic vesicle release.

Poster 64
Potential mechanisms in MUSK-Myasthenia Gravis
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MUSK-MG is caused by antibodies to MUSK that lead to neuromuscular transmission defects and muscle weakness. MUSK, a receptor tyrosine kinase, is essential for formation and maintenance of the neuromuscular junction (NMJ). The motor neuron releases agrin, which binds to the post-synaptic protein LRP4. LRP4 then binds to and activates MUSK, leading to the clustering of AChRs via downstream signaling. The pathogenic mechanisms of the MUSK antibodies are unknown, but they interfere with the AChR clustering pathway *in vitro* and are of the IgG4 subclass, which is functionally monovalent and unlike IgG1-3 cannot cross-link a target. We hypothesized that MUSK antibodies might interfere with MUSK-LRP4 interaction. We studied plasmas from 14 MUSK-MG patients, and tested them for their IgG subclass profile by flow cytometry. We purified IgG and produced Fab fragments and quantified their functional effect on AChR clustering in C2C12 myotubes. We purified IgG4 and IgG1-3 subclass from patient plasma. A co-immunoprecipitation assay was developed to study LRP4-MUSK interactions. Both IgG and monovalent Fab fragments from MUSK patients reduced agrin-induced AChR clustering in C2C12. Antibodies from whole plasma, Fab fragments, purified IgG1-3 and purified IgG4 (which was the predominant IgG subclass) from MUSK patients precipitated similar amounts of MUSK, but LRP4-co-precipitation was strongly reduced in all but the purified IgG1-3. We propose that MuSK antibodies of the IgG4 subclass, that bind monovalently like Fab fragments, but not of the divalent IgG1-3 subclasses, block binding between MUSK and LRP4 and lead to impaired downstream signaling cumulating in faulty AChR clustering.

Poster 65
Integrin-α3 is required for correct skeletal muscle innervation, and integrity of presynaptic specializations at the neuromuscular junction.
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Development of the neuromuscular junction (NMJ) is a cooperative process between pre- and postsynaptic elements, and components in the synaptic cleft, such as laminins [1]. Integrin-α3 is an adhesion protein present at the active zones, the sites of neurotransmitter release in the presynaptic terminus of the NMJ [2]. Here it forms a transmembrane link between synaptic laminin-421 and voltage-gated calcium channels, both essential for the correct function of these sites [3]. To determine the roles of integrin-α3 in neuromuscular development, we used the integrin-α3 knockout (α3-KO) mouse [4].
In embryonic diaphragm muscles (E18.5), terminal branching of motoneurons and numbers of NMJs were increased by 3.22-fold ($P<0.01$) and 1.72-fold ($P<0.05$) respectively, in α3-KO compared to wild type controls. Such defects may be due to alterations in either the pre- or postsynaptic sites. Muscle fibres appeared to form normally in α3-KO mice, as did specialisations of the NMJ, as evidenced by localisation of the presynaptic marker SV2, and postsynaptic markers rapsyn and utrophin. However, immunoreactivity of the active zone component bassoon appeared to be reduced in α3-KO, compared to wild type NMJs, suggesting that integrin-α3 is important for the organisation of the presynaptic terminus. These data demonstrate that integrin-α3 is required for the correct innervation patterning in muscle, and assembly and/or maintenance of presynaptic active zones. We postulate that reduced release of the neurotransmitter acetylcholine at active zones leads to increased motoneuron branching in α3-KO muscles. Our data also suggest that mutations in integrin-α3 may cause myasthenic syndromes in humans.

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Poster 66

Exploring the beneficial effects of β2-adrenoreceptor agonists in Dok-7 CMS

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Mutations in *DOK7* cause Congenital Myasthenic Syndromes (CMS), characterised by recessively inherited proximal muscle weakness. *DOK7* encodes the adaptor protein DOK7 which is essential for the development and maintenance of the neuromuscular junction. DOK7 promotes clustering of acetylcholine receptors (AChRs) at high density on the muscle membrane and mutations in *DOK7* such as the common mutation c.1124-27dupTGCC have been shown in cultured cells to significantly reduce AChR clustering. Clinical studies of DOK7 CMS have revealed a beneficial response to β2-adrenoreceptor agonists, such as salbutamol. However, the mechanisms by which salbutamol exerts its effects are poorly understood. We hypothesise that β2-adrenoreceptor agonists act via activation of second messenger systems. cAMP/PKA mediated signalling might increase stabilisation of AChRs on the muscle or feed into the impaired DOK7 signalling pathway to provide a compensatory signal.
The effects of salbutamol application on AChR clustering and the role of the activation of the β2-adrenergic receptor were studied in cell culture models. *DOK7* mutants, including c.1124-27dupTGCC, wild type DOK7 and the β2-adrenergic receptor were overexpressed in C2C12 myoblasts - a mouse muscle cell line capable of differentiation into myotubes.
Results on AChR cluster numbers in response to salbutamol application at different concentrations and time points are reported.

Poster 67
Developing model systems to study gfpt1 deficiency
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Congenital myasthenic syndromes (CMS) are rare hereditary disorders caused by signalling failure at the neuromuscular junction (NMJ). There is a distinct subtype of CMS characterised by a good response to treatment with acetylcholinesterase inhibitors (such as pyridostigmine) and muscle biopsies containing tubular aggregates, not found in other CMS patients. Genetic testing in this cohort has identified mutations in glucosamine-fructose-6-phosphate aminotransferase 1 (GFPT1). GFPT1 is ubiquitously expressed and well conserved among species. As a rate limiting enzyme in the hexosamine biosynthesis pathway, GFPT1 plays an important role in glycosylation. This was unexpected since glycosylation defects had not been previously associated with NMJ disorders. Creating *in vitro* and *in vivo* models with GFPT1 deficiency is an important step to unravel the mechanism of disease at the NMJ in these patients.
The C2C12 mouse myoblast cell line can be differentiated from primary myoblasts into multinucleated myotubes in culture. GFPT1 levels can be reduced *in vitro* by using drug inducible RNA interference system which can be stably transduced into the cells with lentiviral vectors.
The zebrafish (*Danio rerio*) has emerged as an important model of vertebrate disease. Transcription activator-like effector nucleases (TALENs) can edit genes with high efficiency and specificity. TALENs can be used to create a stable germline mutant.
These models will serve as an important resource to compare N- and O- glycosylation of proteins between wild type and GFPT1 deficient cells or tissues, using MALDI and MS/MS data and cell biology/biochemistry.

Poster 68
Developing models for the study of Periodic Paralysis
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Hyperkalaemic Periodic Paralysis is caused by mutations of skeletal voltage gated sodium and calcium channels. The direct effects of these mutations are well characterised, leading to an understanding of the initial disease phenotype (attacks of paralysis). However, many patients develop a progressive untreatable myopathy that may render them wheelchair-bound. The pathophysiological mechanisms that link muscle membrane ion channel dysfunction to myopathy remain obscure. We propose that dysregulation of cellular calcium signalling and downstream effects on mitochondrial biology play a central role. Study of these pathways requires a direct analysis of excitation contraction coupling pathways in functional muscle cells carrying the mutations. Patient muscle biopsies are not available for the study of such diseases and to this end three alternative models are being developed.
1: Myotubes generated from patient and control fibroblasts. The fibroblasts are differentiated into myoblasts by transduction with MyoD. Culture of these cells in low serum medium in a matrigel matrix with addition of Agrin promotes differentiation into myotubes.
2: An immortalised myoblast cell line. A similar differentiation protocol gives rise to myotubes in which mutant sodium channels will be over-expressed.
3: Single fibres dissected from mutant and control mice. The Flexor Digitorum Brevis is removed and single fibres are released.
In each case, dynamic live cell imaging is used to characterise changes in intracellular calcium signalling and mitochondrial function, and respirometry is used to measure changes in oxygen consumption. This will help to determine the impact of mutations on intracellular calcium handling and mitochondrial structure and function.

Poster 69
Next Generation Sequencing of Ion Channels in Skeletal Muscle Channelopathies

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Neurological disorders caused by mutations in voltage-gated ion channels expressed in skeletal muscle are known as skeletal muscle channelopathies. There are two main groups of these, the periodic paralyses and the non-dystrophic myotonias. The phenotypes however often exist in a spectrum, making the genetic cause unclear. Therefore genetic diagnosis of these diseases using traditional Sanger sequencing can be lengthy, expensive and difficult, as various candidate genes must be screened sequentially and a causative mutation may not even be identified, as often only key parts of the genes are screened.
We have used Illumina's next generation technology to address these problems. We have designed and run a panel of genes for the MiSeq containing the exonic regions of the genes associated with these diseases in 69 samples and 26 controls. Patients negative for this panel will then undergo whole-exome sequencing on the HiSeq to search for pathogenic mutations in novel genes.
Through the MiSeq we have identified a number of likely pathogenic mutations, both novel and already described. We have also seen that often the mutation is not in the gene that is most commonly associated with the specific phenotype. We therefore show that with this technology we can quickly and cost-effectively screen patients with suspected channelopathies and should be implemented in a diagnostic setting.

Poster 70
Functional characterization of *CLCN1* mutations causing Myotonia congenita
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Myotonia congenita (MC) is the commonest skeletal muscle ion channelopathy. Studies of an animal model of dominant MC have revealed reduced muscle cell membrane chloride conductance. Mutations in the skeletal muscle voltage-gated chloride channel gene *CLCN1* have since been identified to be the cause of MC in humans. The chloride channel CLC-1 exists as a homodimer with each individual subunit forming a gated pore. Autosomal dominant and recessive forms of MC have been described. Electrophysiological studies have revealed that recessive mutations usually exert their effect by loss-of-function of the mutated subunit, while the mutant subunit in dominant disease has an adverse effect on the function of the co-expressed wild-type (WT) subunit.
We have expressed >50 CLC-1 mutant channels in *Xenopus* oocyte system and measured the currents of homomeric and heterozygous channels. The mutations were found in MC patients with dominant or recessive inheritance, with single or multiple mutations. In homomeric form approximately 1/3 of the mutant channels were non-functional, 1/3 had right-shifted voltage dependence and 1/3 had wild-type-like behaviour. In heterozygous form most of the mutant channels did not exert dominant-negative effects on wild-type subunit function. The correlation of genotype/functional expression/clinical data is discussed.

Poster 71
A novel Hypokalemic periodic paralysis mutation that causes loss of negative charge in $Na_v1.4$ results in gating pore currents.
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Skeletal muscle channelopathies are inherited disorders of muscle excitability due to disruption of the normal functioning of voltage gated ion channels. Hypokalemic periodic paralysis (HypoPP) is one such disorder in which patients experience episodes of flaccid paralysis associated with reduced serum K^+ levels, due to a depolarised and inexcitable muscle membrane. To date causative mutations that give rise to HypoPP have been found in the S4 voltage sensing segments causing neutralisation of arginine residues of either $Ca_v1.1$ (skeletal muscle L-type calcium channel) or $Na_v1.4$ (skeletal muscle voltage gated sodium channel). While these mutations account for ~90% of HypoPP cases, ~10% of cases remain undiagnosed. Expression studies have shown all six $Na_v1.4$ HypoPP mutations tested to date result in an aberrant inward current due to loss of a positively charge arginine residue. We have identified a novel HypoPP mutation in $Na_v1.4$ which is located in an area of the channel outside of the S4

voltage sensor which has not been previously associated with the disorder. Moreover, we found that this mutation causes a gating pore current which is activate at the resting potential. These expression studies prove a change of function from this mutation and support the notion that a common functional deficit, the gating pore current, produces susceptibility to attacks of HypoPP.

Poster 72

ALG2 – a new gene that causes congenital myasthenic syndromes

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Congenital myasthenic syndromes (CMS) are a group of rare inherited conditions in which neuromuscular transmission is impaired, causing fatiguable muscle weakness. We carried out whole genome sequencing to identify the underlying defect in a patient from a consanguineous marriage who had no mutations in any of the genes known to cause CMS. The patient had an inherited limb-girdle phenotype with decrement and jitter on electromyography, and responded well to pyridostigmine. A homozygous variant, c.203T>G (p.Val68Gly), was identified in *ALG2* which co-segregates within the family with an autosomal recessive mode of inheritance. *ALG2* encodes ALG2, an enzyme that catalyses early steps in the N-glycosylation pathway. We show that ALG2 expression is enriched at the neuromuscular junction, indicating an important function at this synapse. There was a marked reduction of ALG2 protein expression in a muscle biopsy from the patient compared with control muscle biopsies. The variant also caused a reduction ~30% of control in expression of recombinant protein when expressed in HEK293 cells. Thus the variant is likely to be pathogenic by reducing expression of the protein. Our data indicate that mutations in genes involved in the N-glycosylation pathway may cause a multi-systems disorder typical of congenital disorders of glycosylation (CDG), or can produce a relatively mild phenotype that is limited to muscle weakness. They confirm an important role for N-glycosylation for correct functioning of the neuromuscular junction. In addition, muscle weakness found in patients with CDG might be improved with the use of acetylcholinesterase inhibitors.

Poster 73

Next-generation sequencing of ion channel disorders

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Ion channel disorders include a range of disorders: episodic ataxia (EA), familial hemiplegic migraine (FHM), pain disorders, epilepsy, movement and skeletal muscle disorders. These are genetically heterogeneous disorders and identification of causative genes has direct translational research and therapeutic implications.

The advances in next-generation sequencing technology has led to the dramatic reduction in the turnaround time and costs involved in DNA sequencing traditionally undertaken using Sanger sequencing often complemented by other laboratory techniques to identify the range of mutations that underlie channelopathies. Using this approach we have developed a targeted screening panel for multiple genes known to cause EA, FHM, paroxysmal kinesiogenic and non-kinesiogenic dyskinesias (PKD and PNKD).

Methodology:

The panel was designed for use with the Illumina platform with amplicons covering the coding regions of: *KCNA1, CACNA1A, CACNB4, SLC1A1, SLC2A3, PNKD, PRRT2 and KCNK18.* Probands with a family history and sporadic cases were analysed. Variants were validated using Sanger sequencing.

Results:
Seventy-nine samples and sixteen controls were screened and a total of 21,619 bp sequenced per sample for 155 amplicons. Post-filtering, ten potentially pathogenic variants were identified, 50% of these in genes not usually tested for the disease (Table 1). Of the controls, ten were identified correctly and six were not and likely due to inadequate coverage or that the mutation type could not identified using this technology.
Conclusions:
Possible pathogenic variants were identified in 13% of the samples and half in genes not routinely screened for the disease thereby widening the genetic spectrum of brain ion channel disorders. Functional work is required to determine the pathogenicity of these variants.

Table 1

Disorder	Gene	Mutation	Sift	Polyphen	Conserved	Is the gene associated with the disorder
EA2	CACNA1A	D302N Het	Deleterious	Probably damaging	Highly	Yes
EA2	CACNA1A	R1352X Het	-	-	-	Yes
EA2	CACNA1A	G1401E Het	Deleterious	Probably damaging	Highly	Yes
PKD	CACNA1A	K1937X Het	-	-	-	No
PKD	KCNA1	S306F Het	Deleterious	Probably damaging	Highly	No
PKD	KCNK18	Y121Lfs*44 Het	-	-	-	No
Complex EA2	SLC2A1	G18R Het	Tolerated	Benign	Moderately	No
EA2	CACNB4	L413Q Het	Tolerated	Probably damaging	Moderately	No
PKD	PRRT2	P138A Het	Tolerated	Benign	Moderately	Yes
PKD	PRRT2	240X Het	-	-	-	Yes

Translational Research in Inclusion Body Myosityis

Poster 74
Safety and tolerability of Arimoclomol in patients with sporadic inclusion body myositis: a randomised, double-blind, placebo-controlled, phase IIa proof-of-concept trial

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Objectives: To evaluate the safety and tolerability of arimoclomol in sporadic inclusion body myositis (sIBM) and to gather exploratory efficacy data of this orally administered amplifier of heat shock protein (HSP) expression in sIBM.
Methods: In this double-blind, placebo-controlled, two-centre, phase IIa study, 24 patients with sIBM were randomised to arimoclomol 100mg TID or placebo (2:1 ratio) over 4 months (as mandated by the FDA), followed by an 8 month follow up period. The primary outcome was adverse event reporting (safety and tolerability). Measures of physical function (IBM functional rating scale (IBMFRS)), muscle strength (manual muscle testing (MMT) and maximum isometric contraction testing (MVICT)) and fat-free mass (dual-energy X-ray absorptiometry (DEXA)) were included as secondary outcome measures.

Results: We enrolled 17 men and 7 women with a mean age of 66.8±7.5 years and mean disease duration of 8.4±4.3 years. The safety and tolerability profiles were similar between the treatment and placebo groups. We detected a trend of slower decline in the IBMFRS and MMT score of the arimoclomol group at 8 months but no differences were seen on the MVICT or DEXA.
Conclusions: Arimoclomol was safe and well tolerated and demonstrated a preliminary signal for potential therapeutic benefit in patients with sIBM. These data support further research of arimoclomol in sIBM.

Poster 75
Alterations in RNA metabolism in sporadic inclusion body myositis.
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Sporadic Inclusion body myositis (sIBM) is the most common acquired muscle disease in adults over the age of 50. Muscle histopathology shows the presence of inflammatory infiltrates and degenerative changes, such as cytoplasmic protein inclusions and rimmed vacuoles. Unlike other inflammatory myopathies, sIBM is unresponsive to immune-suppressive treatments and shows a relentless clinical course with progressive weakening of muscles. The exact pathogenesis of the disease is still poorly understood and both inflammatory and degenerative pathways have been hypothesised to play a role (1).
Recently, the RNA binding protein TDP-43, which is a major component of the neuronal inclusions that characterize fronto-temporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), was shown to be present in s-IBM cytoplasmic inclusions. This finding raises the question whether RNA metabolism is impaired in sIBM and if "degenerative" changes similar to those found in ALS and FTD play a role in this myopathy.
In order to address these hypotheses, we first characterized TDP-43 pathology in sIBM muscle biopsies and confirmed the abnormal TDP-43 localization in sIBM muscle. We then conducted a whole-transcriptome analysis of sIBM muscle biopsies, using polymyositis (PM) and normal muscle as controls. Our results highlight numerous changes in both inflammatory and "degenerative" pathways in sIBM. Further, we identified novel alterations of RNA metabolism and splicing which appear to be specific to sIBM. Finally, we followed-up these findings with immunohistochemistry studies to confirm the alteration of these pathways in sIBM.
In summary our results highlight novel degenerative aspects in the pathogenesis of sIBM and contribute to the investigation of the emerging role for neurodegenerative protein TDP-43 in muscle disease.

Poster 76
A histopathological assessment of inclusion body myositis
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The current Griggs diagnostic criteria for sporadic inclusion body myositis (IBM) are focused on the histopathological findings present on muscle biopsy. However, the classical histopathological features that makes IBM readily recognisable are often absent and therefore lack sensitivity, particularly early in the disease. Better diagnostic markers are required to enable earlier recognition and differentiation of IBM from diseases considered important in the differential diagnosis. Immunohistochemical staining for markers of protein aggregates such as ubiquitin, p62 and TDP-43 have been suggested as diagnostic

markers in IBM. We investigated the diagnostic potential of staining for protein aggregation, mitochondrial changes and inflammation to distinguish IBM. Cases included in this study were clinically and pathologically typical IBM (*n* = 15), clinically typical IBM lacking classical histological features (*n* = 9) and disease controls [protein accumulation myopathies with rimmed vacuoles, (n = 7) and steroid-responsive inflammatory myopathies (n = 11)] were included in the study. We found p62 to be the most common protein identified in aggregates in IBM where it gave a characteristic staining pattern. However, despite being highly specific for IBM p62 aggregates lacked sensitivity. Strong MHC Class I staining, mitochondrial abnormalities and an endomysial lymphocytic infiltrate were consistently present in histopathologically typical IBM and IBM lacking rimmed vacuoles and, therefore, absence of these features strongly suggests an alternative diagnosis. Therefore, we recommend that p62, COX/SDH, MHC Class I and CD8 T-lymphocyte staining are performed in the evaluation of suspected cases of IBM.

Poster 77

Clinical assessment determines the diagnosis of inclusion body myositis independently of pathological features

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The diagnosis of sporadic inclusion body myositis (IBM) currently requires the presence of a number of histopathological findings on muscle biopsy, namely rimmed vacuoles, an inflammatory infiltrate with invasion of non-necrotic muscle fibres (partial invasion) and amyloid or 15-18 nm tubulofilamentous inclusions. However, many patients with clinically typical IBM do not possess these histopathological findings, at least at first presentation. We investigated the clinical and histopathological features at presentation, disease outcomes and prognostic markers of 67 patients with inclusion body myositis seen in a single tertiary centre. At presentation, 51% of patients had the typical clinical features of IBM whereas only 27% fulfilled the current histopathological diagnostic criteria. There were no differences in the clinical features and outcomes between clinically and histopathologically diagnosed patients, but patients lacking the classical histopathological finding of rimmed vacuoles were younger, suggesting that rimmed vacuoles may be a later feature of the disease. These findings have important implications for diagnosis and any future studies or trials in IBM. Adherence to predominantly histopathological diagnostic criteria will exclude large numbers of patients with IBM from studies. Importantly, those excluded from therapeutic trials through absence of histopathological features could be at an earlier stage of the disease and might be more amenable to treatment.

Poster 78

Neurogenic inflammation: an explanation for differing responses to immunosuppressive therapy among the inflammatory myopathies

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Background

Sporadic inclusion body myositis (IBM) is currently classified as an idiopathic inflammatory myopathy (IIM) with polymyositis and dermatomyositis. However, unlike polymyositis and dermatomyositis it is poorly responsive immunosuppressive therapy. In addition to the inflammatory infiltrate, neurogenic features are commonly observed in IBM and cases of focal myositis caused by neurogenic lesions have also been reported - neurogenic myositis. Neurogenic inflammation is an inflammatory reaction mediated by the release of neuropeptides [substance P (SP) and calcitonin gene related peptide (CGRP)] and mast cells and implicated in asthma, arthritis, migraine and brain trauma.

Aims

To determine whether neurogenic inflammation plays a role in the pathogenesis of IBM and neurogenic myositis.

Methods

Cases of IBM (*n* = 27), steroid responsive myositis (*n* = 11), normal control muscle (*n* = 10) and neurogenic myositis (*n* = 1) were selected and sections stained for mast cell tryptase, SP and CGRP.

Results

In IBM and neurogenic myositis there were a significantly greater number of mast cells compared to normal control muscle (p = <0.001) and steroid responsive myopathies (p = <0.001); however, we were unable to demonstrate the presence of SP and CGRP.

Conclusion

Our findings suggest that mast cells and neurogenic inflammation may play a role in the pathogenesis of IBM as well as neurogenic myositis. This could explain the lack of response to immunosuppressive treatment in IBM compared to other IIM. We were unable to demonstrate the presence of neuropeptides, this may be due to the paucity of nerve fibres in muscle biopsies.

Poster 79

MRI provides sensitive quantification of disease progression in inclusion body myositis Centenary Award Poster

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Background: Outcome measures which are sensitive to change are needed for clinical trials in neuromuscular diseases. We aimed to define the standardised response mean (SRM) of MRI quantification of fat infiltration of lower limb muscles over 12 months in patients with inclusion body myositis (IBM).

Methods: We performed lower limb MRI at a 12 month interval in 20 patients with inclusion body myositis and matched healthy volunteers including the 3-point-Dixon fat-water separation method to generate a fat map. Regions of interest were drawn encompassing the full cross-section of 10 thigh and 6 calf muscles bilaterally and mean fat fraction for these regions extracted.

Results: At baseline mean fat fraction of thigh and calf muscles was significantly ($p<0.001$) greater in patients than controls (thigh 29.3±23.2% vs 4.4±2.5%; calf 21.2±23.4% vs 3.4±2.0%). IBM patients (n=8 analysed to date) showed an absolute increase in the fat fraction over 12 months in thigh muscles of 4.1±2.9% (controls 0.6±0.8%) and in calf muscles of 3.6±1.4% (controls -0.0±0.6%). The calculated SRM of 1.4 at thigh level and 2.5 calf level indicates very high responsiveness.

Conclusions: MRI quantification of fatty infiltration of lower limb muscles provides biomarkers of disease progression with very high responsiveness. If used as the primary outcome measure in a 12 month randomised controlled trial in IBM, approximately 44 patients in each arm would be required to allow detection of a 30% reduction of progression with 80% power at $p<0.05$ significance.

Jasper Morrow is in receipt of an MRC Centenary Award.

Poster 80

Evaluating the benefits of community based aerobic training on the physical health and well-being of people with neuromuscular diseases: a pilot study

Amanda Wallace (1), Liz Dewar (1), Annette Sterr (2), Mike Hanna (1), Mary Reilly (1), Karen Butcher (3), Gianluca Baio (4), Mike Trenell (5), Gita Ramdharry (6)

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Here we present the method of a research trial to investigate how aerobic exercise training can help people with two common neuromuscular diseases (NMD): Charcot-Marie-Tooth disease (CMT) and Inclusion Body Myositis (IBM). These diseases cause muscles to become weaker over time which often leads to disability and risk of other disease due to inactivity. Exercise is important to maintain general health but may also help to improve symptoms of NMD. We will therefore study how aerobic training changes fitness levels, muscle strength, walking abilities and general well-being. In addition we will monitor the safety of training, and how practical it is for people to take part in this type of exercise. Motivation, confidence and barriers to exercise will also be explored.

Thirty participants (aged 18 to 75) will be recruited for each condition. Both IBM and CMT will be investigated concurrently with the same methods but will be analysed and reported as separate studies. A crossover design will be used with participants stratified by disease severity score and randomised to exercise or control first.
Participants will train in their local gym using a recumbent exercise bike. Exercising closer to home will be more convenient and also encourage exercise in a community setting after the study finishes. A research physiotherapist will visit twice and participants will be monitored regularly by gym fitness instructors.
Results from the trial will be used to plan further research with the ultimate aim of developing evidence based exercise prescriptions for people with NMD.

Poster 81
Sporadic Inclusion Body Myositis: genetic risk factors and exome sequencing
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Sporadic inclusion body myositis (sIBM) is the most common and untreatable muscle disease among those aged over 50 years with a prevalence of 5-15/1,000,000. Clinically it is characterised by quadriceps and finger flexor weakness. The disease course is slowly progressive with many affected individuals becoming wheelchair dependent 10-15 years after symptom onset. Evidence has suggested that both inflammatory and degenerative mechanisms play important roles in the pathogenesis of sIBM. Although their interaction is still uncertain, it is becoming more likely that the sIBM muscle fibre degeneration leads to the muscle atrophy, indicating that predisposing genetic factors may contribute to sIBM pathogenesis.
We report the analysis of genetic risk factors, including MHC complex, apolipoprotein E, prion gene, β-amyloid precursor protein, C9orf72, Tau and mitochondrial DNA sequence, in a large series of sIBM cases. So far we have not identified any genetic association with sIBM.
Our group based in the International IBM Consortium Genetic Study has already collected 90 sIBM blood DNA samples and 160 British controls. We hypothesize that rare variants are likely to be risk factors for sIBM, and therefore exome analysis is planned on 200 sIBM DNAs from blood and/or muscle and 200 controls to reveal the high risk variants associated with sIBM.

Muscle Satellite Cells and IPS Cells

Poster 82
Ret affects myoblast proliferation and contributes to Facioscapulohumeral muscular dystrophy (FSHD) pathobiology
Louise Moyle, Paul Knopp, Robert Knight and Peter Zammit.
Randall Division, King's College London.
Facioscapulohumeral muscular dystrophy (FSHD) is the third commonest inherited myopathy, linked to deletion of tandem 3.3kb repeats (*D4Z4* units) in chromosome 4q35. Between 1-10 *D4Z4* repeats on a specific chromosomal haplotype leads to expression of the double homeodomain protein DUX4 from the last *D4Z4* unit. Expression of DUX4 inhibits myogenic differentiation and is pro-apoptotic.
To understand the molecular mechanisms of FSHD, we performed a microarray on murine satellite cell (SC)-derived myoblasts expressing DUX4, or its non-apoptotic ortholog DUX4c. The receptor tyrosine kinase c-Ret (rearranged during transfection) was significantly upregulated by DUX4 but not DUX4c, suggesting a potential role in FSHD pathology. We found that Ret is dynamically expressed during SC differentiation and that retroviral-mediated constitutive expression of either Ret9 or Ret51 isoforms increased myoblast proliferation. Neither isoform affected myotube formation or expression of the myogenic regulatory factors Myod, Myf5 and Myogenin. However, siRNA-mediated knockdown of Ret reduced proliferation and Pax7 expression but increased expression of Myogenin in SC-derived myoblasts, suggesting that Ret keeps myoblasts in proliferation. Finally, we used siRNA to block DUX4-mediated Ret signalling and were able to rescue the suppression of myogenic differentiation.

This research suggests that Ret acts to either prevent early myogenic differentiation or maintain SCs in a proliferative state. DUX4-mediated activation of Ret could contribute to the FSHD phenotype, and highlights Ret as a potential drug target for FSHD pathobiology.

Poster 83

Human skeletal muscle-derived AC133+ cells form functional satellite cells after intramuscular transplantation into immunodeficient host mice

Jinhong Meng, Rowan Asfahani, Soyon Chun and Jennifer E. Morgan
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Human skeletal muscle-derived AC133+ (hAC133+) cells are a promising stem cell for treatment of muscular dystrophies such as Duchenne Muscular Dystrophy. hAC133+ cells contribute to extensive muscle regeneration and also give rise to satellite cells following their transplantation into irradiated and cryodamaged tibialis anterior muscles of immunodeficient Rag2-/γ chain-/C5- host mice. Cells of human origin expressing Pax7 were found both underneath the myofibre basal lamina (thus fulfilling the definition of a satellite cell) and outside the basal lamina. In addition, some donor-derived satellite cells expressed the myogenic regulatory factor MyoD, indicating that they were activated. In a second series of experiments, host mouse muscles were injected with donor hAC133+ cells, left to regenerate for 14 weeks, then treated with notexin, which destroys muscle fibres, but spares single cells such as satellite cells. The finding of newly-regenerated muscle fibres of donor origin one week after notexin treatment is evidence that the donor hAC133+ cells had given rise to muscle stem cells that were functional, as they were able to activate in response to injury and contribute to muscle regeneration.

Poster 84

Patient-specific iPS cell-derived myogenic progenitors for gene and cell therapy of muscular dystrophies and beyond

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Mesoangioblasts are stem/progenitor cells derived from skeletal muscle pericytes. They have been shown to ameliorate the dystrophic phenotype of different animal models upon transplantation and this evidence allowed their current clinical translation into a phase I/II clinical trial based upon allogeneic transplantation for Duchenne muscular dystrophy (DMD) children. However, the need to treat all the skeletal muscles of an adult patient challenges mesoangioblast proliferative potency. Moreover, we show

here that patients affected by limb-girdle muscular dystrophy 2D (LGMD2D, characterized by alpha-sarcoglycan deficit) have a reduction of muscle pericytes and hence mesoangioblast could not be derived for cell therapy. Therefore, we reprogrammed LGMD2D fibroblasts or myoblasts to induced pluripotent stem (iPS) cells and developed a protocol for the derivation of mesoangioblast-like cells from them. These cells can be expanded and genetically corrected with a novel lentivector expressing human alpha-sarcoglycan under the transcriptional control of a muscle-specific promoter. Upon xenotransplantation into ad-hoc generated alpha-sarcoglycan-null immunodeficient mice they generated myofibers expressing human alpha-sarcoglycan. Notably, we show morphological and functional amelioration of the dystrophic phenotype upon intra-specific transplantation and extension of this approach to other forms of muscular dystrophy and gene correction (i.e. DMD with a human artificial chromosome containing the entire dystrophin locus). Finally, preliminary evidence of application of this methodology for disease modelling and bioengineering will be discussed. This strategy provides evidence of pre-clinical safety and efficacy of disease-specific iPS cells and paves the way for the use of their differentiated progeny in drug screening and tissue engineering of muscle disorders.

Poster 85

Mouse skeletal muscle-derived CD133+ cells contribute to muscle regeneration in vivo

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Duchenne Muscular Dystrophy (DMD) is an x-linked disease resulting in the degeneration of skeletal muscles due to the lack of dystrophin protein. Stem cell therapy is considered a promising strategy for the treatment of DMD; however, factors such as the type of stem cell, experimental animal models used for pre-clinical testing and the routes of transplantation have a great impact on transplantation efficiency. Human skeletal muscle-derived CD133+ cells have been reported to give rise to a large amount of donor muscle after both intra-muscular and intra-arterial transplantation, thus suggesting them as a promising candidate for future stem cell therapy. Conversely, there have been no reports on the contribution of mouse CD133+ cells to skeletal muscle regeneration. Here, we report that we have been able to isolate CD133+ cells from mouse skeletal muscle by magnetic cell sorting and expand and maintain them *in vitro*. Our preliminary data suggest that these cells are able to express satellite cell markers and differentiate into myotubes in *vitro*. In addition, mouse CD133+ cells gave rise to muscle fibres of donor origin following intra-muscular grafting into tibialis anterior muscles of mdx nude mice.

Current UK Neuromuscular Clinical Trials

MRC Centre CTIMPs Set-up Phase trials

1. TAPP: THERAPEUTIC TRIAL OF POTASSIUM AND ACETAZOLAMIDE IN ANDERSEN-TAWIL SYNDROME
Status: Set-up Phase
Sponsor: University College London (UCL)
Funder: National Institutes of Health (NIH – USA)
PI: Prof Hanna
Recruitment target: 12
Andersen-Tawil Syndrome (ATS) is a rare form of periodic paralysis that is associated with serious heart-rhythm abnormalities. ATS is characterized by a triad of episodic muscle weakness, long-QT syndrome with potentially fatal cardiac dysrhythmias and skeletal developmental anomalies. The underlying cause of this potentially fatal condition is only partly understood and there are no established treatments. Mutations in the KCNJ2 gene encoding Kir2.1, an inward-rectifying potassium channel account for approximately 60% of ATS cases (termed ATS1), the remaining 40% are presumed to have an as yet undetermined gene lesion and are designated ATS2. ATS1 and ATS2 are phenotypically indistinguishable. The treatment of ATS has been largely anecdotal and empirical.
This proposal involves a multi-centre, placebo-controlled 'n of 1' study design of total duration 45 weeks. The expected total enrolment for this multi-centre study is 16 participants. The aim of this study is to determine whether potassium supplements and/or acetazolamide alter the duration of muscle weakness and potentially life-threatening heart rhythm abnormalities in patients with ATS.

For information on the status of recruitment please contact Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

2. A Pilot Study of Valproate Sodium for McArdle Disease
Status: Set-up phase
Sponsor: UCL
Planned start date: 2013
Funder: Muscular Dystrophy campaign
PI: Prof. Ros Quinlivan
Recruitment target: 15
McArdle disease (Glycogen storage disease type V, GSDV) is an inherited metabolic disorder of skeletal muscle. Affected patients are unable to produce lactate during ischaemic exercise [McArdle 1951] because they have a congenital absence of the enzyme muscle glycogen phosphorylase, which is essential for glycogen metabolism [Mommaerts 1959, Schmidt and Mahler 1959]. The condition is caused by homozygous or compound heterozygous mutations in the muscle glycogen phosphorylase gene *(PYGM)* located at chromosome 11q13 [Beynon 2002]. This enzyme deficiency results in the inability to mobilise muscle glycogen stores that are normally required for energy during anaerobic metabolism. In affected people, symptoms of fatigue and cramp occur within minutes of initiating any activity and during strenuous activity such as lifting heavy weights or walking uphill, if the activity is continued despite severe cramping, a contracture occurs which leads to muscle damage (rhabdomyolysis), myoglobinuria and, when severe, acute renal failure.

Currently, there is no satisfactory treatment that can be recommended for the condition [Quinlivan 2008]. Taking glucose prior to exercise may alleviate muscle symptoms by inducing a second 'second wind', but this is not a good strategy for daily living as it may result in significant weight gain [Vissing 2003]. There is limited evidence for subjective benefit from creatine supplementation in five out of nine subjects from a randomised controlled trial [Vorgerd 2002], although this has not been confirmed in the clinic setting.

Although most people with McArdle disease have complete absence of skeletal muscle phosphorylase, there are a small minority of patients who possess splice site mutations that enable production of very small amounts (1-2%) of functional enzyme [Vissing]. These people have a milder phenotype with less severe symptoms, and functional exercise assessments have shown better exercise capacity than typical patients with the condition. Findings from these atypical individuals suggest potential therapeutic agents might only need to produce very small amounts of enzyme for significant functional improvement. Furthermore, finding a therapeutic agent to 'switch on' expression of the foetal isoenzyme may be a potential therapeutic strategy.
Sodium Valproate (Valproic acid) is one of a group of drugs known as histone deacetylase inhibitors (HDACIs) that can affect gene expression by acetylating lysine residues, which in turn has a direct effect on

chromatin [Thiagalingam 2003]. There is some evidence from animal studies to suggest that sodium valproate can 'switch on' the foetal phosphorylase isoenzyme.
A recent clinical trial of the drug in McArdle sheep that were given sodium valproate for three months showed the presence of phosphorylase positive muscle fibres, in the absence of muscle necrosis and/or regeneration [Howell 2010].
The current proposes an open label uncontrolled pilot study to evaluate safety and efficacy of Sodium valproate (slow release) 20mg /kg once daily for six months. 15 subjects, adult male and post menopausal women attending specialist centres for McArdle disease will be recruited across three sites: London, Copenhagen and Dallas.

3. A Double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of BYM338 in patients with Sporadic Inclusion Body Myositis (IBM)
Status: Set-up phase
Sponsor: Novartis
Planned start date: 2013
PI: Michael Hanna
Recruitment target: 5
The purpose of this study is to investigate the pharmacodynamic effect of 30 mg/kg i.v. of BYM338 on muscle volume, strength and physical performance in patients with IBM. There is no effective standard of care for IBM, and the course is progressive. The design of this study addresses the primary objective of determining if BYM338 increases muscle volume and function (strength, physical performance) in patients with IBM, with an initial assessment of PK/PD effect at different dose levels.
Following successful demonstration of proof of preliminary efficacy for BYM338 an additional cohort with treatment groups at dose levels of 1 mg/kg every 4 weeks, 3 mg/kg every 4 weeks and 10 mg/kg every 8 weeks i.v. BYM338 will be investigated to explore the dose-response relationship in this population.
Patients with IBM have increased TGFβ/pSMAD signaling. The underlying hypothesis for this study is that increased signaling will be inhibit by BYM338 and is anticipated to be effective (in terms of primary and secondary efficacy endpoints).
Objectives:
Primary objectives
To evaluate the preliminary efficacy of BYM338 on thigh muscle volume by MRI in terms of change from baseline.
To evaluate the safety and tolerability of bYM338 when administered as single and multiple intravenous (i.v) infusion(s) to patients with IBM
Secondary objectives:
To assess the effect of BYM338 on muscle function by "timed up and go" test in terms of change from baseline
To evaluate the effect of BYM338 on total lean body mass by DXA in patients with IBM in terms of chance from baseline.

4. Eplerenone versus triamterene in CAI non-responsive periodic paralysis (HOP Study)
Status: Set-up phase
Sponsor: UCL
Funder: MDA
Planned start date: 2013
PI: Michael Hanna
Recruitment target: 11
There have been no previous systematic investigations of patients with hypokalemic periodic paralysis who fail to respond or are worsened by carbonic anhydrase inhibitors. The initial impression that only 10-15% of patients fall into this category now appears erroneous (Matthews, Portaro et al. 2011, Neurology).
Approximately 50% of genetically-confirmed patients with periodic paralysis do not derive sufficient benefit to remain on treatment. By pursuing a pilot study of alternative treatments for this subgroup of patients we hope to start addressing what is arguably the greatest need of the community of patients with the periodic paralyses.

Specific Aims

1) To obtain preliminary efficacy data of triamterene and eplerenone in HOP patients unresponsive to or unable to tolerate carbonic anhydrase inhibitors. To achieve these aims, we will perform an 18 week, 2 centres, randomized, double-blind, placebo controlled crossover pilot trial with eplerenone and triamterene versus placebo in CAI non-responsive HOP patients. Patients with clinically well documented HOP who have defined mutations in the Na or Ca channels and who have worsened with, not responded to or not been able to tolarate CAI, will be studied. Following a 4 weeks run in period (phase 1) 22 patients will receive 4 weeks placebo, 4 weeks eplerenone and 4 weeks triamterene in a randomized fashion. Each 4 weeks period will be separated by a 1 week washout period. Improvement in attack rate, severity weighted attack rate, and quality of life will be measured.
2) To select the drug, triamterene or eplerenone, with the optimal efficacy and adverse effect profile for a future larger trial.

5. Bumetanide in HypoPP
Status: Set-up phase
Sponsor: UCL
Funder: TBC
Planned start date: 2013
PI: Michael Hanna
Recruitment target: 12
This is a planned phase II clinical trial, double-blind, randomised, placebo-controlled cross-over, single-site study to investigate the efficacy of bumetanide in patients with hypokalemic periodic paralysis (HypoPP). The objective is to assess the efficacy of bumetanide in reducing severity and duration of acute attacks of weakness in HypoPP patients. Hypokalaemic periodic paralysis is an autosomal dominant muscle channelopathy with onset in the first or second decade, characterized by attacks of reversible flaccid paralysis lasting from several hours to days. These patients may have frequent attacks of weakness interfering with daily activities and work, and are often hospitalized for intravenous potassium treatment causing a significant economic burden. They may also progress to a chronic myopathy especially because there are no optimal treatments available nowadays.
Experimental evidence of the use of bumetanide in a mouse model of HypoPP has provided convincing evidence that it can abort paralytic attacks.
We would expect bumetanide to abort acute attacks of weakness faster and reduce their severity, reducing the likelihood of patients being hospitalized during severe attacks. Bumetanide will add as an adjuvant therapy to potassium intake during an attack.

6. A phase IIb of Arimoclomol in IBM
Status: Set-up phase
Sponsor: UCL
Funder: FDA/Orphazyme (TBC)
Planned start date: 2013
PI: Michael Hanna
Recruitment target: 150
(This is a follow-up of the phase IIa RCT study concluded in 2012)
We are proposing a one year randomized, placebo-controlled Phase II study of arimoclomol in 150 IBM subject. The primary aim is to assess the efficacy and safety of arimoclomol (200 mg TID). The primary efficacy endpoint is the IBMFRS. Secondary efficacy outcomes will include different measures of strength and function: manual muscle testing (MMT), maximum voluntary isometric contraction (MVICT), timed up and go (TUG), timed 10 meter walk test, 6 minute walk test, Purdue pegboard test, grip and pinch test; a general physical function measure: Health Assessment Questionnaire (HAQ- DI); a HRQoL measure using SF36 and MRI acute thigh pathology (oedema), chronic pathology (fat fraction) and muscle volume. Safety laboratory and adverse events will be collected. Our long-term goal is to find an effective treatment for people with IBM.
For further information please contact Dr Pedro Machado at p.machado@ucl.ac.uk

7. FOR-DMD

Full Title: Duchenne muscular dystrophy: double-blind randomized trial to find optimum steroid regimen (FOR-DMD)
Status: Set-up
Sponsor: University of Rochester
Funder: NIH
PI: Prof. Francesco Muntoni
Patients to recruit: 10
This is a multi-centre, double-blind, parallel group, 36-60 month study, comparing three corticosteroid regimens in wide use in DMD:

- daily prednisone (0.75 mg/kg/day)
- intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off)
- daily deflazacort (0.9 mg/kg/day)

Primary study objective: The proposed randomized controlled trial will compare 3 corticosteroid regimens to address the pragmatic hypothesis that daily corticosteroids (prednisone or deflazacort) will be of greater benefit in terms of function and subject/parent satisfaction than intermittent corticosteroids (prednisone).
Secondary study objectives: A second hypothesis is that daily deflazacort will be associated with a better side effect profile than daily prednisone. The study protocol includes standardized regimens for prevention/ treatment of predictable side effects of corticosteroid medication, as well as standards of care for the general management of DMD. The trial directly addresses the current chaos in prescribed treatment schedules; its results will have direct impact on the current and future management of boys with DMD throughout the world by providing the evidence base for rational clinical practice.
The results of the trial will allow the generation of clear and specific evidence-based guidelines for patient treatment.

8. Full Title: A phase III efficacy & safety study of Ataluren (PTC124) in patients with nonsense mutation dystrophinopathy (PTC Phase III)
Status: Set-up
Sponsor: PTC
Funder: PTC
PI: Prof Francesco Muntoni
Patients to recruit: unknown yet – early stages
The primary objective of this study is to determine the ability of ataluren to slow disease progression as assessed by ambulatory decline (decrease in 6MWD) in patients with nonsense mutation dystrophinopathy. Secondary endpoints have been chosen to evaluate changes in skeletal muscle function through assessment of proximal muscle function, as assessed by the time to run/walk 10 meters, time to ascend 4 stairs and time to descend 4 stairs and patient or parent/caregiver perception of physical functioning. Additional secondary endpoints have been selected to enhance understanding of the primary and secondary treatment effects. For example, a beneficial effect in physical function relative to placebo, as assessed by the North Star Ambulatory Assessment (NSAA), would compliment positive changes in ambulation proximal muscle function. Collection of patient and/or parent reported changes in disease status provides an opportunity to expand the implications of a drug effect on the patient's disease symptoms and activities of daily living.

9. Full Title: A phase IIb, open-label study to assess the efficacy, safety, pharmacodynamics and pharmacokinetics of multiple doses of PRO045 in subjects with Duchenne muscular dystrophy (PRO045)
Status: Set-up
Sponsor: Prosensa
Funder: Prosensa
PI: Prof Francesco Muntoni
Patients to recruit: 4-5
Primary objective:To assess the efficacy of PRO045 after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.
Secondary objectives:To assess the safety and tolerability of PRO045 after 48 weeks of treatment in all study subjects with Duchenne muscular dystrophy including subjects from the dose-escalation phase of the study.To determine the pharmacokinetics of PRO045 at different dose levels after subcutaneous administration in subjects with Duchenne muscular dystrophy.

To assess the pharmacokinetics, bioavailability and safety of PRO045 following single intravenous dose administration at different dose levels.
To assess the pharmacodynamics of PRO045 at different dose levels after subcutaneous administration in subjects with Duchenne muscular dystrophy.
To assess trend in efficacy in all subjects with Duchenne Muscular Dystrophy not included in the primary objective after 48 weeks of treatment.

MRC Centre CTIMPs Open Trials

10. Phase II, multicenter, randomized, adaptive, double-blind, placebo controlled Study to assess Safety and Efficacy of Olesoxime (TRO19622) in 3-25 year old Spinal Muscular Atrophy (SMA) patients
Status: Closed to recruitment
Sponsor: TROPHOS
Funder: Association Francaise contre les Myopathies
PIs: Francesco Muntoni, Hanns Lochmuller, Helen Roper
Recruitment target (UK): 30; due for completion by 31st September 2013
The UCL Institute of Child Health and Great Ormond Street Hospital for Children (London), Birmingham Heartlands Hospital, and Newcastle upon Tyne Hospitals Royal Victoria Infirmary have been invited to collaborate in this phase II clinical trial in non-ambulant patients with SMA II and III with a documented homozygous absence of SMN1 exon 7 and/or deletion and mutation on the other allele. This is a multicentre, double-blind, randomized, placebo-controlled study in patients with SMA type 2 or non-ambulant type 3. The study will be conducted in multiple centres across Europe and will be sponsored by Trophos (a biopharmaceutical company based in France) and funded by AFM (Association francaise contre les myopathies). The aim is to assess efficacy, futility, safety and tolerability of a new drug called olesoxime. This is a neuroprotective drug that acts by interacting with protein components of the mitochondrial permeability transition pore (mPTP), preventing the release of apoptotic factors and in turn neuronic death. Olesoxime has displayed an excellent safety profile and has been well tolerated in phase I clinical trials in healthy subjects. For each participant, this phase II study will involve a 4 week screening period followed by a 24 month (104 week) treatment period. Following screening procedures and confirmation of eligibility, subjects will be randomised to receive either olesoxime or placebo in a 2:1 ratio. Olesoxime (or matched placebo) will be taken daily with evening meal as a liquid formulation at a dose of 10mg/kg. 150 subjects in total will be recruited, with a target of 30 patients in the UK. Recruitment is planned to be completed in 6 months. It is possible a dose adjustment may be made once 45 patients across Europe have been received study drug for 3 months based on a review by a designated independent Data Monitoring Committee. The patients to be recruited should be at least 3 years of age but younger than 26 years at the time of enrolment, with the age of onset of symptomsto be at 3 years of age or younger. They should not be taking any medication intended for the treatment of SMA within 30 days prior to being enrolled on the study. Eligible patients can be taking oral salbutamol as long as this has been commenced at least six months prior to enrolment on the study and remains at a stable dose during the study period. Participation in another investigational drug or therapy study within 3 months of enrolment is an exclusion criterion, as well as a hypersensitivity to sesame oil and use of medications that could interfere with olesoxime absorption (including cholesteramine, fibrates, fish-oils, niacin, phytosterols and ezetimibe).
Further information about this study can be obtained from the Clinical Trials Coordinator on 020 7905 2639.

11. HYP HOP: DICHLORPHENAMIDE vs. PLACEBO FOR PERIODIC PARALYSIS
Full Title: Double-blind, placebo-controlled, parallel group, phase III study comparing dichlorphenamide vs. placebo for the treatment of periodic paralysis
Status: Closed to recruitment
Sponsor: University Rochester
Funder: National Institutes of Health (NIH - USA)
PI: Prof. Hanna
Patients recruited:14; target 40
This is a phase III trial into Periodic Paralysis. This proposal involves a multi-centre, double-blind, placebo-controlled parallel group, nine-week studies comparing the effects of dichlorphenamide(DCP) vs. placebo in patients with period paralysis (Hyper, Hypokalemic periodic paralysis). The 9-week studies will investigate

the prevention of attacks of weakness and it will be followed by 1-year extensions without placebo to compare the long term effects of DCP on the course of the diseases and on inter-attack weakness. Approximately 40 participants will be recruited from the United Kingdom. For information on the status of recruitment please contact Dr. James Burge at James.burge@uclh.nhs.uk or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

12. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (GSK Extension Study)
Full Title: An open-label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne Muscular Dystrophy.
Status: Closed to recruitment
Sponsor: GlaxoSmithKline
Funder: GlaxoSmithKline
PIs: Volker Straub, Francesco Muntoni
Patients recruited: 8; target (UK) 8
Description: A Phase III, multicenter, open-label extension, study in male outpatients with Duchenne Muscular Dystrophy (DMD) who have participated in eitherDMD114117 or DMD114044. All subjects will receive 6mg/kg GSK2402968 weekly for a minimum period of two years or an intermittent dosing frequency of 6mg/kgGSK2402968 for a minimum period of two years.
Objective(s)
Primary objective:
• To evaluate the long term safety, tolerability and efficacy of subcutaneous 6mg/kg/weekGSK2402968 in subjects with DMD who have participated in either DMD114117 orDMD114044.
Secondary objectives:
• To evaluate the long-term PK of subcutaneous 6 mg/kg/week GSK2402968 in subjects with DMD who have participated in either DMD114117 or DMD114044.
• To evaluate the long-term impact on health-related quality of life (HRQoL) and functional outcomes of continued treatment with GSK2402968 in subjects with DMD who have participated in either DMD114117 or DMD114044.
• To evaluate DMD disease progression and outcomes (clinical, HRQoL and functional) in subjects who discontinue active treatment during the conduct of study (natural history component).
• To evaluate the long-term safety, efficacy and PK of an intermittent dosing option in those subjects unable to tolerate GSK2402968 6mg/kg/week dosing.
This study aims to enrol approximately 200 subjects. In the primary dosing arm, subjectswill receive GSK2402968 6 mg/kg as subcutaneous injections once a week for a period of 104 weeks. Further information about this study can be obtained from the MRC Centre Clinical Trials Coordinator on 020 7905 2639.

13. The PATH Study
Full title: Randomized, multicenter, double-blind, placebo-controlled, parallel-group phase III study to investigate the efficacy, safety and tolerability of 2 different doses of Igpro20 (subcutaneous immunoglobulin) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) – the Path Study
Status: Open
Sponsor: CSL Behring
Start date: March 2013
PI: Dr Michael Lunn
Patient target: 5
CIDP is an acquired neurological, demyelinating neuropathy with an assumed autoimmune-mediated pathogenesis. Due to its heterogeneous presentation and the limitations in the individual diagnosis procedures (clinical, serologic, and electrophysiological), the diagnosis relies on findings from multiple modalities. The probable autoimmune nature of the condition is most strongly suggested by response to immunotherapies such as intravenous immunoglobulins (IVIGs), plasmapheresis (PE), and corticosteroids. In addition, despite less definitive published evidence of efficacy, corticosteroids are also considered as first-line therapy because of their long history of use.

Apart from IVIGs, there are currently no other medications approved for the treatment of CIDP; however experimental use of azathioprine, mycophenolate mofetil, methotrexate and cyclosporine are common and whilst there are also emerging reports of the use of B Lymphocyte antigen CD20 and anti-complement monoclonal antibody therapies, efficacy has not been established for any of these agents.
This is a prospective, multicenter, randomised, double-blind, placebo-controlled, parallel-group 3-arm study to investigate 2 different doses of SCIG IgPro20 compared to SC (subcutaneous) placebo for maintenance treatment of subjects with CIDP. Subjects on IVIG maintenance therapy experiencing CIDP relapse during an IVIG Withdrawal period will be administered the IVIG IgPro10 (1 loading dose and 3 or 4 maintenance doses every 3 weeks) during an IVIG Re-stabilization Period. Subjects with improved and maintained INCAT score at the last 2 assessments in the IVIG Re-stabilization Period will be randomised to 1 of 2 Igpro20 doses (0.2 or 0.4 g/kg body weight) or placebo during the SC Treatment Period.
IgPro20 is a ready-to-use formulation of human IgG with ≥98% purity for subcutaneous (SC) administration. Igpro20 is approved in the United States of America (US), in the EU, in Switzerland and Canada under the brand name Hizentra® for SC application in primary immune deficiency syndromes and is also under review by other regulatory agencies for use in primary and secondary immunodeficiencies.
IgPro10 is a ready-to-use liquid formulation of polyvalent IgG for intravenous (IV) application approved and marketed in several countries including the European Union (EU) and the US for use in primary immunodeficiency (PID) syndromes and for immune thrombocytopenic purpura (ITP). In the EU, IgPro10 is further approved for other conditions associated with immunodeficiencies resulting in the need for replacement therapy and in Guillian-Barre Syndrome (GBS) where IVIG is thought to have immunomodulatory effects on the peripheral nervous system. For the treatment of GBS and CIDP, a similar mode of action is assumed.
IgPro10 is currently under investigation in a confirmatory phase III study in subjects with CIDP.
Several randomised clinical studies have demonstrated the clinical efficacy and safety of using IVIGs to treat CIDP.
IVIGs requires subjects to visit a clinic or hospital for 1 to 5 days on a regular basis, usually every 2 to 6 weeks. This study is being conducted to provide SCIG as an alternative treatment option for CIDP that allows subject (or their caregiver) to self-administer the product in the home setting.

14. DMD HEART PROTECTION TRIAL
Full-Title: A double-blind randomised multi-centre, placebo-controlled trial of combined ACE-inhibitor and beta-blocker therapy in preventing the development of cardiomyopathy in genetically characterised males with DMD *without* echo-detectable left ventricular dysfunction.
Status: Open to recruitment
Sponsor: Newcastle NHS Foundation
Planned start date: 2011
Funder: British Heart Foundation
PI: Prof. Muntoni
Recruitment target: 70
Patients recruited: 32 (one more year of recruitment to go)
Duchenne muscular dystrophy [DMD] is an X-linked recessively inherited neuromuscular disorder due to a deficiency in the expression of the protein dystrophin on the inner aspect of cell sarcolemma. Its clinical course has traditionally been characterised by progressive weakness of proximal limb-girdle muscles and calf muscle hypertrophy. Duchenne-affected individuals typically lose ambulation and become wheelchair-dependent before the age of 13 and die from cardio-respiratory failure at around the age of 20 years. From the cardiology perspective, some 90% of males with DMD develop a severe, progressive form of cardiomyopathy. Twenty to 30% have evidence of left ventricular impairment on echocardiography by age 10 years. Abnormalities in left ventricular function are evident in an even larger proportion of patients at all ages when more sensitive imaging techniques, such as tissue Doppler, magnetic resonance or metabolic imaging, are deployed. Despite the severity of cardiac involvement in DMD, cardiologists have largely ignored this particular inherited form of cardiomyopathy. This is due to the fact that, because of their inability to exercise, cardiac symptoms only occur terminally in DMD patients when all cardiac reserve has been eroded. Even today in most hospitals, cardio-active drug therapy is only started in patients with DMD when overt heart failure is evident and, even then, is typically deployed tentatively for symptom control,

without any expectation that it can prolong life. The objective of this trial is to determine whether the introduction of ACE inhibitor combined with beta-blocker therapy, before the onset of echo-detectable left ventricular dysfunction, can delay the age of onset and/or slow the rate of progression of cardiomyopathy compared to placebo in males with DMD. This is a double-blind randomised, placebo-controlled Phase III trial of combined ACE inhibitor and beta-blocker therapy (perindopril and bisoprolol) over a minimum of three years and a maximum of five years. 140 participants (70 per arm) are to be enrolled and randomised. For more information about the study please contact the trial coordinator on 020 7905 2639.

15. BIOMARKER STUDIES IN MND/ALS
Full title: Characterisation of a panel of disease biomarkers in peripheral blood from individuals with motor neuron disease
Sponsor: University College London Hospitals NHS Foundation Trust
Start date: May 2009
Funder: Motor Neurone Disease Association
UCL PI: Dr Richard Orrell
Motor neuron disease (MND) is an adult-onset neurodegenerative diseases and one of the commonest neuromuscular disorders. The speed of progression of MND varies among individuals and the condition can develop with different clinical manifestations. Currently, there are no blood tests that could help us to predict the speed of progression of the disease and the likely clinical manifestations (e.g. predominant involvement of speech and swallowing or of the limb muscles). We are testing specific disease biomarkers in the blood. To assess change over time, a blood sample is taken every 3 months. The sample has to be carefully processed as soon as it is taken to preserve the quality of the blood contents. We are studying a range of blood constituents including proteins, DNA and RNA. From some participants we also collect samples of cerebrospinal fluid. If repeated samples are not possible, a single sample of blood for DNA studies is also helpful. We also examine samples from participants without MND/ALS, and individuals with similar but unrelated neuromuscular conditions. Parallel studies of biomarkers in an animal model of ALS are informing our choice of biomarkers. The study is in collaboration with Queen Mary University of London, and other participating centres.

MRC Centre CTIMPs Completed Trials

16. RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF LONG-TERM ASCORBIC ACID TREATMENT IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A Status: Completed.
Sponsor: University College London
Funder: Muscular Dystrophy Campaign (MDC)
PI: Prof. Reilly
Patients recruited: 50 target 50
Charcot-Marie-Tooth disease 1A (CMT1A) is associated with a duplication of the peripheral myelin protein 22 (PMP22) gene. To date there is no pharmacological treatment for CMT1A patients. Treatments and therapy for CMT is restricted to symptomatic treatments such as physiotherapy and surgery for skeletal deformities. Recently, treatment with ascorbic acid (AA) has been shown to be effective for transgenic mice over-expressing PMP22, a model of the human disease. Treated animals had much less severe neuropathy as compared to untreated controls as shown by clinical and histological findings. Some clinical parameters even improved during treatment.
This is a phase III prospective, multi-centre, randomised, double-blind, placebo-controlled study aiming to evaluate the efficacy of AA treatment in CMT1A.
The study is now complete. Fifty participants were enrolled in the UK site at the MRC Centre for Neuromuscular Diseases. Paper published in *Lancet Neurology 2010.*

17. THERAPEUTIC TRIAL OF MEXILETINE IN NON-DYSTROPHIC MYOTONIA
Full Title: A Phase II Randomised, Double-Blind, Placebo controlled, Cross-Over Study to Investigate the Efficacy of Mexiletine in Patients with Non-Dystrophic Myotonia
Status: Completed
Sponsor: University College London (UCL)
Funder: Food and Drug Administration (FDA – USA)

PI: Prof. Hanna
Patients recruited: 14; target 15
The non-dystrophic myotonia (NDM) is a group of rare neuromuscular disorders that causes episodes of muscle stiffness (known as myotonias) and paralysis. Predominantly the muscles of the face, hands and legs are affected. In addition to these episodes a permanent and debilitating muscle weakness can develop. The optimal treatment for these disorders is unknown. Non-dystrophic myotonias are due to abnormalities of ion channels present in skeletal muscle membranes. There is experimental evidence that drugs like mexiletine which block the abnormal function of these ion channels allow the muscle to perform normally. The study aims to test the efficacy of mexiletine in the treatment of the non-dystrophic myotonias. This proposal involves a multi-centre, double-blind, placebo-controlled cross over trial of total duration nine weeks. Fifteen participants have been enrolled in the UK at the MRC Centre.

This work has been completed and outcome data published in *JAMA (*Volume 308, No.13*, pages 1357 - 1365, October 2012).*

18. A PHASE IIb EFFICACY AND SAFETY STUDY OF PTC124 IN SUBJECTS WITH NONSENSE MUTATION-MEDIATED DUCHENNE AND BECKER MUSCULAR DYSTROPHY Status: Completed
Sponsor: PTC Therapeutics
Funder: PTC Therapeutics
PIs: Prof. Muntoni, Prof. Bushby
Patients recruited: 11
Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder affecting young boys. The condition is disabling and life-threatening. A small subset of boys are classified as having Becker muscular dystrophy (BMD), a phenotypically milder form of the dystrophic muscle disease.
In approximately 10 to 15% of boys with DMD and BMD the causative defect is the presence of a nonsense mutation in the dystrophin gene that truncates dystrophin protein production by introducing a premature stop codon into the dystrophin messenger ribonucleic acid (mRNA).
PTC124 is a novel, orally bioavailable, small-molecule drug that promotes ribosomal read-through of mRNA containing a premature stop codon. Through this mechanism of action, PTC124 has the potential to overcome the genetic defect in boys for whom a nonsense mutation causes DMD/BMD.
In vitro studies in cell lines with dystrophin nonsense mutations have shown that PTC124 can restore production of the missing dystrophin gene.
This is an international, multi-centre, randomised, double-blind, placebo-controlled, dose-ranging, efficacy and safety study.
The study primary aim is to evaluate the effect of PTC124 on ambulation as assessed by the distance walked during a 6-minute walk test (6MWT).
The double-blind arm of the study randomised 174 participants worldwide which are to be followed for a period of 12 months. At the completion of the blinded treatment, all compliant participants were eligible to receive open-label PTC124 in a separate extension study.
(Ataluren is now the non-proprietary generic name for PTC124).
This work has been completed.
The preliminary findings from the Ataluren Study 007 did not show significant muscle improvement in the patients who participated in the study. The study was therefore discontinued. An update on this study was presented at the International Congress on Neuromuscular Diseases, Naples, Italy, 17-22 July 2010 by Professor Kate Bushby. Details of this presentation is available on www.ptcbio.com Briefly, analysis showed that, on average, patients treated with low-dose ataluren experienced better outcomes on measures of efficacy than patients treated with high-dose ataluren or placebo - this phenomenon is not unique for ataluren and has been observed with other drugs for other diseases. Further analysis of efficacy data is ongoing.

ANTISENSE OLIGONUCLEOTIDE INDUCED EXON SKIPPING IN DUCHENNE MUSCULAR DYSTROPHY
This initiative is led by the MDEX consortium (The MDEX consortium led by Professor Muntoni, is a multidisciplinary enterprise to promote translational research into muscular dystrophies, and is formed by the clinical groups of Professor Francesco Muntoni (UCL Institute of Child Health) and Professor Kate Bushby and Professor Volker Straub (Newcastle University), and scientists from Imperial College London (Professor

Dominic Wells), UCL Institute of Child Health (Dr Jennifer Morgan), Royal Holloway University of London (Professor George Dickson and Dr Ian Graham), Oxford University (Dr Matthew Wood) and University of Western Australia (Prof Steve Wilton). In addition, the charities Muscular Dystrophy Campaign (MDC), Action Duchenne and Duchenne Family Support Group also participate in the Consortium, www.mdex.org.uk).
The current two trials led by the consortium are mentioned below.

19. RESTORING DYSTROPHIN EXPRESSION IN DUCHENNE MUSCULAR DYSTROPHY: A PHASE I/II CLINICAL TRIAL USING AVI-4658
Status: completed
Sponsor: Imperial College London
Funder: Department of Health (DoH)
PI: Prof. Muntoni
Patients recruited: 8
The primary scope of the trial is to assess efficacy (dystrophin production) and safety of intramuscular administered morpholino oligomer directed against exon 51 (AVI – 4658 PMO).
Antisense therapy with the use of antisense oligomers has the potential to restore effectively the production of dystrophin, the defective protein, in >70% of DMD. This could result in increased life expectancy through improved muscle survival and function. Recent scientific research has demonstrated the potential of this technique to skip mutated dystrophin exons, restore the reading frame and generate functional dystrophin protein. Having demonstrated proof-of-principle in human cell culture and animal model studies, we now intend to determine efficacy and safety of this approach to induce dystrophin exon skipping in children with DMD. This study is aimed at children with Duchenne muscular dystrophy above the age of 10 years with mutations than can be rescued by the skipping of exon 51 [45-50; 47-50; 48-50; 49-50; 50; 52; 52-63].
This work has been completed and outcome data published in the journal *Lancet Neurology (*Volume 8, Issue 10*, Pages 918 - 928, October 2009)*

20. DOSE-RANGING STUDY OF AVI-4658 TO INDUCE DYSTROPHIN EXPRESSION IN SELECTED DUCHENNE MUSCULAR DYSTROPHY (DMD) PATIENTS – (Systemic study)
Status: Completed
Sponsor: AVI Biopharma
Funder: Medical Research Council (MRC) and AVI Biopharma
PI: Prof. Muntoni
Patients recruited: 19
This is a safety study of AVI-4658 (a 30-base phosphorodiamidate Morpholino oligomer [PMO]), to skip exon 51 of the dystrophin gene in relevant subjects with DMD..
This is an open-label, two-centre, dose-ranging comparative clinical study of duration twelve weeks.
The objectives of the study are to assess safety and to select the optimum dose that elicits at least 10% de novo dystrophin-positive fibres and dystrophin in a sentinel muscle group after an intravenous AVI-4658 dosing regimen.
A total of up to 16 subjects (ambulatory paediatric males, aged ≥5 and ≤15 years of age) will be enrolled in this study, consisting of four treatment cohorts and four subjects per cohort. It is expected that there will be four treatment arms ranging from 0.5 mg/kg to 4 mg/kg. All subjects will receive 12 weekly intravenous infusions of AVI-4658.
Precedent studies have demonstrate that AVI-4658 might have therapeutic relevance in managing DMD for boys whose frame-shifted dystrophin gene lesion could be restored after excision of exon 51 if sufficient drug is translocated into the nucleus of the afflicted muscle cell.
This trial was conducted in London and Newcastle.
A total of 19 subject (12 at GOSH and 7 at RVI, Newcastle) were recruited and final data is being analysed for submission to regulatory authorities in Europe and the USA. Outcome data were presented at the World Muscle Society, 12-16 October 2010 in Japan and published.
www.thelancet.com Published online July 25, 2011 DOI:10.1016/SO140-60756-3.

21. ECULIZUMAB FOR MYASTHENIA GRAVIS
Full Title: A Randomised, Double-Blind, Placebo-controlled, Cross-over, Multicenter Study of Eculizumab in Patients with Generalised Myasthenia Gravis (GMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosupressants

Status: Closed
Sponsor/Funder: Alexion Pharmaceuticals, Inc.
PI: Prof. Dimitri Kullmann
This is a randomized, double-blind, placebo-controlled, cross-over, multicenter study to evaluate the safety and efficacy of eculizumab for the treatment of patients with myasthenia gravis. Myasthenia gravis (MG) is an acquired autoimmune syndrome caused by the failure of neuromuscular transmission, which results from the binding of autoantibodies to proteins involved in signaling at the neuromuscular junction (NMJ). These proteins include the nicotinic AChR or, less frequently, a muscle-specific tyrosine kinase (MuSK) involved in AChR clustering.
Current available treatments for myasthenia gravis aim to modulate neuromuscular transmission, to inhibit the production or effects of pathogenic antibodies, or to inhibit inflammatory cytokines. There is currently no specific treatment that corrects the autoimmune defect in MG.
Eculizumab is a humanized murine monoclonal antibody that blocks the activation of complement by selectively binding to C5 and preventing the enzymatic cleavage of C5 to C5a and C5b. The blockade of complement activation at this point in the cascade has been shown to prevent the proinflammatory effects of both C5a and C5b, especially the chemotaxis of inflammatory cells, and MAC (C5b-9)-mediated cell activation and lysis. Since eculizumab effectively inhibits complement, especially MAC formation, it is a potentially effective therapeutic approach for diseases such as MG in which the formation of the MAC and/or the release of C5a leads to localized destruction of the postsynaptic NMJ membrane and play a important role in the disease process.
Patients will receive approximately 22 infusions including 11infusions of eculizumab and 11 infusions of placebo. The estimated duration of a patient's participation is approximately 41 weeks.
Results awaiting publication

22. ARIMOCLOMOL FOR SPORADIC INCLUSION BODY MYOSITIS (IBM)
Full Title: A Randomised, Double-blinded, Placebo-controlled Pilot Study Assessing the Safety and Tolerability of Arimoclomol in Adult Patients with Sporadic Inclusion Body Myositis
Status: Completed
Sponsor: University College London (UCL)
Funder: Arthritis Research UK and Myositis Support Group
PI: Prof. Hanna
Patients recruited: 12; target 12
Sporadic Inclusion Body Myositis (IBM) is the commonest acquired disease of muscle affecting people aged 50 years and over. This is a progressive and debilitating disease with both muscle weakness and wasting, characteristically of the quadriceps and finger flexors. Over time the condition can lead to severe disability, falls and swallowing impairment. Affected muscle tissue demonstrates inflammation and degeneration. Arimoclomol is a new compound which acts by enhancing a normal, inbuilt protective cell reaction to stresses. The products of this response are 'Heat Shock Proteins (HSPs) which counteract processes that end up leading to abnormal protein deposition and to damage mediated by inflammation. This proposal involves a multi-centre, double-blind, placebo-controlled parallel study of total duration twelve weeks. This study proposal aims to assess the safety and tolerability of Arimoclomol (100 mg TDS) as compared with placebo over 4 months of treatment in patients with IBM. Recruitment will take place at the National Hospital for Neurology and Neurosurgery and twelve patients will be enrolled.

23. Investigation of the ability of Otelixizumab to inhibit in vitro antigen-specific T cell responses from Myasthenia Gravis patients
Status: Completed
Sponsor/Funder: GlaxoSmithKline
PI: Prof Kullmann
Patients recruited: 39; target 40
Myasthenia Gravis (MG) is the best understood autoimnune disease (a disease in which the immune system attacks some part of the body). This attack is directed by various parts of the immune system.
There is a continued search for newer drugs that will be of benefit in the treatment of MG. Otelixizumab has been identified as a possible treatment for MG. However before clinical trials can be considered additional information is needed to determine how it interacts with the immune system of patients with MG.

In this study adult patients with MG will be invited to provide blood samples (50 ml) for research purposes. Blood collected from patients will be used for T-cell assay and autoantibody assay development. Patients may be asked to provide a repeat blood sample (additional 50ml) after 46 months following the initial collection to see if T cell activation changes over time. Up to 40 participants will be enrolled in the UK. The study is being sponsored by GlaxoSmithKline group of companies.
For information on recruitment contact Natalie James (natalie.James@uclh.nhs.uk).

24. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (PRO051)
Full Title: A phase II, double-blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy
Status: Completed
Sponsor: GlaxoSmithKline
Funder: GlaxoSmithKline
PIs: Volker Straub, Francesco Muntoni
Patients recruited: 8; target (UK) 8
A multicentre trial with this study drug is recruiting DMD boys in UK at the Great Ormond Street Hospital (GOSH), London and at the Royal Victoria Infirmary, Newcastle. It is a Phase lla, double blind, exploratory, parallel clinical trial to assess the optimal dose of GSK2402968 for safety, tolerability and efficacy, in ambulant patients with DMD. This study is designed to explore efficacy and safety of GSK2402968 given as a continuous regimen and an intermittent regimen over 24 and 48 weeks.
Objective(s)
Primary objective:
• To assess the efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 24 weeks in ambulant subjects with DMD.
Secondary objectives:
• To assess the safety and tolerability of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
• To assess the PK of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
• To assess long term efficacy of 2 different dosing regimens of subcutaneous GSK2402968 administered over 48 weeks in ambulant subjects with DMD.
The study aims to randomise 54 subjects. There will be 2 parallel cohorts. Each cohort will include 16 subjects on GSK2402968 and 8 subjects on matched placebo (2:1 ratio). Further information about this study can be obtained from the MRC Centre Clinical Trials Coordinator on 020 7905 2639.

25. THERAPEUTIC TRIAL OF LITHIUM CARBONATE IN MND/ALS (LiCALS)
Full title: A double-blind, randomised, placebo controlled trial of lithium carbonate in patients with amyotrophic lateral sclerosis.
Status: Completed
Sponsor: University College London Hospitals NHS Foundation Trust
Start date: June 2009
Funder: Motor Neurone Disease Association, and NIHR
UCL PI: Dr Richard Orrell
Patients recruited: 22, target: open-ended
Recent research suggested that lithium carbonate may be effective in lowering the progression of MND/ALS. Lithium may protect motor neurons through a range of mechanisms, including improving the transport of proteins along the motor neuron, improving the transport of mitochondria, and activating cell survival factors. In one study, lithium prolonged survival in a mouse model of MND/ALS. This is a multi-centre UK study, involving 215 patients with MND/ALS, taking lithium or placebo, for 18 months. The trial is designed to assess the safety, efficacy and tolerability of lithium in combination with riluzole as a treatment for MND/ALS. Assessments include survival, symptoms, quality of life, and function. Participants are randomised to take lithium or placebo, the level of lithium in the blood is monitored, and the dose of lithium (and placebo) adjusted as needed. *Results in Press*

26. LiCALS Open Label Extension
Full title: LiCALS open label extension trial of lithium carbonate in amytrophic lateral sclerosis.
Status: Completed
Sponsor: University College London Hospitals NHS Foundation Trust
Start date: March 2011
Funder: Motor Neurone Disease Association, and NIHR
UCL PI: Dr Richard Orrell
Patients recruited: 3 of 8 recruited
This is an open label extension study for those who have completed the randomised double blind trial of lithium carbonate in ALS. The objective is to obtain further evidence of the safety of lithium carbonate in doses achieving levels of 0.4-0.8 mmol/l. *Results in Press*

27. GSK1223249 in MND/ALS (the Nogo-A study)
Full title: A Phase I, multi-centres, randomized, placebo-controlled, double-blind, single and repeat dose escalation of a drug to treat ALS.
Status: Completed
Sponsor: Royal Free Hampstead NHS Trust
Start date: September 2010
Funder: GlaxoSmithKline
UCL PI: Dr Richard Orrell
Patients recruited: 2, target: 2
GSK 1223249 is a new drug developed by GlaxoSmithKline, that targets a protein called Neurite Outgrowth Inhibitor (Nogo-A), which impairs neurone regeneration. There is evidence of increased Nogo-A, which impairs neuron regeneration, in muscle of people with MND/ALS. By blocking the effect of Nogo-A, GSK1223249 may be an effective treatment for the disease. GSK1223249 delays symptom onset and prolongs survival in a mouse model of MND/ALS. The trial will provide safety and tolerability information, together with biomarker and functional information. This may leader to further trials to assess effectiveness. The study includes an infusion of the drug (or placebo), with a muscle biopsy taken before and following the infusion, together with other monitoring assessments. For further information please contact Dr Richard Orrell (r.orrell@ucl.ac.uk). *Results in Press*

Natural History – Longitudinal Studies

Set-up Phase

28. International Guillain-Barre' Syndrome (GBS) Outcome Study - IGOS
Status: set-up
Sponsor: Glasgow University
Funder: Wellcome Trust/GBS Support group
PI: Dr Lunn
Patients target: 10 from the NHNN
Despite partially effective forms of treatment, outcome in patients with Guillain-Barre' syndrome (GBS) has not improved in the last two decades. At present about 10 to 20% of patients remain severely disabled and about 5% die. One explanation for this stagnation is the highly variable clinical course of GBS. Determinants of disease progression and recovery in GBS are still poorly understood. GBS may consist of distinct pathogenic subgroups, in which disease onset and progression is influenced by different types of preceding infections, anti-neural antibodies and genetic polymorphisms. Optimal treatment of individual patients may depend on the pathogenesis and clinical severity.
The international GBS Outcome Study (IGOS) aims to identify clinical and biological determinants of disease progression and recovery in GBS. This information will be used to understand the diversity in clinical presentation and response to treatment of GBS and to develop new prognostic models to predict the clinical course and outcome in individual patients.
IGOS is a prospective observational international multi-centre study including at least 1000 patients with GBS or variants of GBS, including the Miller Fisher syndrome (MFS) and overlap syndromes. The study has a follow-up of one year.
The aim is to obtain a detailed and standardised database on clinic features, treatment, and diagnostic electrophysiology, and collect a biobank with serum samples and DNA at specific visits.
There is an option to collect cerebrospinal fluid (CSF) during routine diagnostic work-up for proteomic studies, and to conduct an extended follow-up of two and three years. Additional studies may be added in the future.
For further details please contact Dr Lunn, Michael.lunn@uclh.nhs.uk

29. LEMS Disease Registry – UK Proposal
Status: set-up
Sponsor: BioMarin Europe Ltd
PI: Hanna
Patients target: 10 from the NHNN
The LEMS registry is a voluntary multi-centre, multinational, observational program for patients with LEMS disease and is intended to track the routine clinical outcomes of patients with LEMS over time.
The purpose of the LEMS registry is to collect additional data on the long term safety and efficacy of Firdapse for patients who have been prescribed Firdapse by their treating physician. The registry will also track the use of treatment for LEMS including drugs other than Firdapse. The data collected by the registry are intended to enable better characterisation of the natural history of LEMS.
As this is an observational (non-interventional) programme no experimental treatments or assessments are involved, it is up to the treating physician to determine the actual frequency of assessments according to the patients' individual need for medical care and routine follow-up.
All patients with a confirmed diagnosis of LEMS is eligible to participate in this programme, confirmation can be by abnormal Electromyogram (EMG) or positive result for Voltage Gated Calcium Channel (VGCC) antibodies, however patients cannot be participating in any other study with Firdapse.

30. Charcot Marie Tooth disease (CMT) Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases (TREAT-NMD) International Database (ID)
Status: Set-up
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Dr Reilly

Patients to be recruited: unlimited
Charcot Marie Tooth Translational Research in Europe for the Assessment and Treatment of Neuromuscular Diseases International Database (CMT-TREAT-NMD-ID) is an observational/registry study. The system will have an international set-up composed of national registries from interested countries around the world. Currently 8 international centers are participating. Its objective is to capture every case of CMT in each participating country, with sufficiently detailed data to identify patients likely to be eligible for a variety of studies.
Inherited peripheral neuropathies are often collectively referred to as Charcot Marie Tooth disease (CMT). These are heterogeneous group of peripheral neuropathies caused by mutations in over 40 different genes. Typically cases of CMT are separable into autosomal dominantly inherited demyelinating (CMT1) or axonal (CMT2), X-linked (CMTX) and autosomal recessive (CMT4) forms. Although most cases of CMT are sensorimotor, predominantly sensory (Hereditary Sensory Neuropathies; HSN) and motor forms (distal Hereditary Motor Neuropathies; dHMN) also exist.
Participants will need to have a diagnosis of Charcot Marie Tooth disease, Hereditary Neuropathy with liability to Pressure Palsies (HNPP), Hereditary Motor Neuropathy (HMN) or Hereditary Sensory Neuropathy (HSN) and also the ability to provide consent.
Data such as diagnosis including genetic testing, family/developmental history, mobility, sensation, optic nerve atrophy and hearing loss will be collected. Patients may also undergo a neurophysiological test.

31. Full Title: Study of clinical and radiological changes in teenagers with Duchenne muscular dystrophy theoretically treatable with exon 53 skipping (Pre-U7)
Status: Set-up
Sponsor: Genethon
Funder: Genethon
PI: Prof Francesco Muntoni
Patients to recruit: 5-8

PreU7-53 is a natural history study. The objective is to monitor the clinical and radiological course of upper limb muscle impairment in patients with DMD, potentially treatable with AAV-mediated exon 53 skipping (ie: deletions exons 10-52, 45-52, 46-52, 47-52, 48-52, 49-52, 50-52, 52 of the dystrophin gene), and to assess serum and urine biomarkers to monitor non-invasively disease progression, and finally to assess the prevalence of immunity against adenoviral vectors in this relevant DMD population.

<u>Open Studies</u>

32. CMT: A NATURAL HISTORY STUDY
Full Title: Charcot-Marie-Tooth Disease and related disorders: A Natural History Study
Status: Open to Recruitment
Sponsor: University College London Hospitals
Funder: National Institutes of Health (NIH – USA)
PI: Dr Reilly/Prof Muntoni
Patients recruited: 422; target (UK) 650
Charcot-Marie-Tooth Disease (CMT) and related disorders (distal hereditary motor neuropathy (dHMN) and hereditary sensory and autonomic neuropathy (HSAN)) are a clinically and genetically heterogenous group of disorders affecting approximately 1 in 2500 people.
People with this condition present with upper and lower limb weakness, wasting and sensory loss as a result of degeneration of the long peripheral nerves supplying the distal muscles. Despite the clinical similarities among patients with CMT the group is genetically heterogeneous. Advances have been made in identifying the genes that cause CMT and the molecular organisation of the peripheral nervous system (PNS) nevertheless the optimal management and treatment of the different variants of this disorder is not known and moreover natural history data is lacking for most forms of inherited neuropathies.
This is a 5 year study that will be conducted by four centres in United States and two centres in the UK (National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital). The aim of the project is to fully characterise the features of different types of CMT and the longitudinal progression of the disease. The data will also be used to establish clinical relevant endpoints for use in therapeutic trials. The identification and genetic characterisation of patients will facilitate the recruitment of participants for future

therapeutic trials. Ultimately the information gained with this study will lead to the improvement in the treatment and management of CMT.
The study is also seeking to establish an appropriate paediatric impairment scoring method for CMT and establish a database for the inherited neuropathies. The study will include both adult and paediatric patients. Evaluations will consist of a neurological history and examination, nerve conduction velocity (NCV) study and in some selected cases skin biopsy.
This is a NIH funded study. At least fifty patients will be enrolled at the National Hospital for Neurology and Great Ormond Street Hospital.
For more information about the study please contact Dr. Matilde Laura at m.laura@ion.ucl.ac.uk.

33. MITOCHONDRIAL DISEASE COHORT
Status: Open to Recruitment
Sponsor: The University of Newcastle Upon Tyne
Funder: MRC
PI: Dr R McFarland, MG Hanna, DM Turnbull
patients recruited 871; target 1000
The current project proposes to develop a cohort of UK patients with mitochondrial diseases. The details are to be stored in a database that will enable clinicians to gain adequate information for future clinical trials. Mitochondrial diseases present a huge challenge to patients and doctors because no effective treatment is available. The extremely diverse phenotypic presentation of mitochondrial disease has previously limited cohort development.
The cohort will comprise symptomatic adults and children, in whom a mitochondrial disease phenotype and (where possible) genotype, have been confirmed. Asymptomatic individuals who have requested genotyping and proved positive will also be included. Genotyping is important because the same mitochondrial phenotype may be caused by several distinct mutations in either the mitochondrial or nuclear genomes. Phenotype will be characterized in all individuals (symptomatic and asymptomatic) on the basis of clinical history, clinical examination and detailed investigation.
Two centres will receive referrals (Newcastle University and University College London Hospitals). The database will physically be stored at Newcastle University and it will have a dedicated, electronic secure server.
The project anticipates collecting details on 1000 patients in total.
For information on the status of recruitment please contact Dr. Robert Pitceathly (London) r.pitceathly@ion.ucl.ac.uk or Julia Maddison@newcastle.ac.uk
J.Neurol Neurosurg Psychiatry 2013 Jan 25: The UK MRC Mitochondrial Disease Patient Cohort Study: Clinical phenotypes associated with m.3243A>G mutation – implications for diagnosis and treatment

34. THE NATURAL HISTORY OF INCLUSION BODY MYOSITIS (IBM Net)
Status: Open to Recruitment
Sponsor: University College Hospitals
Funder: MDC
PI: Dr Matt Parton/Mike Hanna
Target 200; recruited 59
Inclusion body myositis (IBM) is probably the commonest muscle disease beginning in those aged over 50. It leads to progressive disability with, classically, a characteristic pattern of muscle involvement. However it is poorly understood: its cause is unknown, there is no conclusive diagnostic test and it has no treatment. Furthermore, information on the pattern and prognosis of IBM is more based on anecdote from clinical experience, rather than firm fact. The largest published series of data on the natural history of the illness followed only eleven patients for six months.
The current project seeks to better characterise IBM by gathering clinical data from as many cases as possible.
Serial standardised assessment (annually for five years) will chart disease progression and so both expand and strengthen knowledge of the natural history of the illness. Furthermore, establishment of a cohort of reliably-defined cases will build a valuable resource that could potentially form the starting-point for future studies.
For information on the status of recruitment please contact Dr. Pedro Machado at p.machado@ion.ucl.ac.uk

35. Kennedy's Disease – Study and Register
Status: Open
Sponsor: UCLH
PI: Hanna
Patients recruited: 50
The primary purpose of this study is to create a national register of patients with Kennedy's Disease (spinal and bulbar muscular atrophy) with a view to facilitating research into the disorder. In particular, we aim to systematically characterise diagnostic features of the disorder and their natural history and attempt to estimate the incidence and prevalence of Kennedy's disease in the United Kingdom. Furthermore we intend to assess the experience of patients with regard to specialist neurological, endocrinological and clinical genetic care and, by so doing, to establish best practice guidelines for the diagnosis and management of this disorder.
Kennedy's disease was first described as a separate entity in a series of 9 males in 2 families (Kennedy et al., 1968) and prior to this was not distinguished from adult-onset forms of spinal muscular atrophy. Kennedy described the disorder as being X-linked on the basis of his pedigrees, and the causative mutation in the X-chromosome was tracked in 1991 to the Androgen Receptor. The disease is caused by the expansion of an intragenic CAG triplet repeat in exon 1 of the gene which is translated into a polyglutamine segment in the AR protein. As such Kennedy's disease became the first in a series of 9 disorders now known to be caused by such expanded polyglutamine repeats (the others being Huntington's disease, dentato-rubral pallido-luysian atrophy and spino cerebellar ataxias).
The earliest clinical features are androgen insensitivity, postural hand tremor and muscle pains with subsequent development of motor neuropathy, bulbar signs and symptoms and a distal sensory neuropathy which is usually subclinical.
As the prognoses of these two conditions are very different it is clearly important that these patients are correctly identified and managed. Furthermore, patients with Kennedy's disease have an additional set of endocrine and metabolic problems over and above the more well-defined neurological deficits. The endocrine and metabolic aspects of the disorder in particular are poorly characterised and their relationship to the genotype is controversial. Their implications for patients in terms of morbidity has also not been investigated.
The study proposes to, if possible, interview and examine patients directly and attempt to gain a time course of the development of individual symptoms and signs. Wherever molecular genetic confirmation of the diagnosis has not already been performed by the referring hospital this will be performed by standard PCR methods with the prior explicit consent of the patient and the referring neurologist. Creatine kinase, and endocrine function (testosterone, luteinising hormone and sex-hormone binding globulin levels) will be assessed from blood samples by standard techniques. Pedigrees for the patients families will be obtained from the hospital notes, or from direct interview where this has been possible.
By creating a register of the United Kingdom's Kennedy's population we hope to obtain clear evidence of phenotype-genotype correlation and, over time, establish relationships with disease severity and prognosis.
For further information contact: Dr Pietro.Fratta, p.fratta@prion.ucl.ac.uk

36. Investigation of Human Neurological Ion Channel Disorders
Status: Open to recruitment
Sponsor: University College London Hospitals
PI: Prof. Hanna

Ion channels are membrane bound proteins that allow the flux of charged ions across cell membrane in excitable tissue including muscle and nerve. These ion channels are usually specific for a particular ion e.g. potassium or calcium. An increasing number of inherited and acquired neurological diseases are attributed to disorders of ion channels. The 'channelopathies' include non-dystrophic myotonia, periodic paralysis, episodic ataxias types 1 and 2 (EA1 and EA2), familial hemiplegic migraine types 1 and 3 (FHM1 and 3) and some forms of epilepsy. The mechanisms by which ion channel dysfunction causes disease are incompletely understood, but the genetic channelopathies have provided unique insights into because the properties of mutant channels can be studied with great precision with biophysical methods.
Although each of the known channelopathies is rare, there is considerable circumstantial evidence that genetic variability in ion channels plays a major role in idiopathic epilepsy and migraine. These disorders, which are characterised by normal brain development and function punctuated by episodes of abnormal excitability, show strong heritability although typically do not respect Mendelian patterns of inheritance. They represent an important disease burden to society. It remains to be determined whether such disorders are caused by many, individually rare genetic variants or by a few common polymorphisms affecting ion channel splicing, assembly, trafficking or function.

Several intense programmes of research are underway to identify genetic susceptibility factors in epilepsy and other paroxysmal neurological diseases. The purpose of this proposal however, is to take a complementary approach to gain an insight into the consequences of genetic variability, focusing primarily on KCNA1, mutations of which cause EA1(5) and CACNA1A mutations which cause EA2(6), and to document these at all levels from molecular biophysics to cellular excitability studied in individuals harbouring the mutations. Only by understanding the degree to which variability of ion channel properties can be tolerated by the organism, or conversely affect neuronal excitability in a detectable manner, will we be able to interpret the functional impact of coding polymorphisms that are staring to be reported in population studies.

This research project aims to consolidate and expand on previous work by collating clinical data and continuing to sequence candidate genes in patients suspected to have ion channel disorders, particularly in Episodic Ataxia Type 1 (KCNA1 gene) and Episodic Ataxia type 2 (CACNA1A gene). As the project progresses it is possible that further candidate genes will be identified and we will sequence these also. In vitro expression of new mutations will be performed in order to further study how these genetic mutations result in channel dysfunction.

37. AFM Natural History Study
Full Title: Outcome measures in Duchenne Muscular Dystrophy: A Natural History Study
Status: Open
Sponsor: UCL Institute of Child Health
Funder: AFM
PIs: Francesco Muntoni, Kate Bushby
Patients recruited: 40; target (UK) 15
Description: To document with quantified measurements the natural history of Duchenne Muscular Dystrophy. Several validated tools will be used to describe motor, orthopaedic and respiratory functions, quality of life and blood parameters along a 4 years follow-up study in ambulant and non-ambulant patients.
Objective(s)
Primary objective:
• To document with quantified measurements the natural history of Duchenne Muscular Dystrophy. Several validated tools will be used to describe motor, orthopaedic and respiratory functions, quality of life and blood parameters along a 4 years follow-up study in ambulant and non-ambulant patients.
Secondary objectives:
• Specific tests to ambulant and non-ambulant patients will be performed. All these tests should determine the most sensitive outcome measures to use in the assessment of efficacy of future therapies.
This prospective longitudinal natural history study will be performed in two cohorts of patients with DMD according to their level of functional motor ability (ambulant/non-ambulant). Inclusion criteria and methods will be different in the two cohorts and will be described separately.

38. Using Next Generation Sequencing to Unravel the Pathogenesis of Sporadic Inclusion Body Myositis (IBM) – The International IBM Consortium Genetic Study
Status: Open
Sponsor:
Funder: MRC
PI: Prof Hanna
Patients target: 400
The primary pathogenesis of IBM is not determined, although in IBM the aggregated proteins are in muscle tissue, many such as tau, alpha synuclein, TDP-43, beta amyloid and the prion protein are implicated in neurodegeneration. It is possible that the defective processes that lead to the formation of these abnormal protein deposits are likely to have important implications for many neurological disorders.
The vast majority of IBM is sporadic but there is significant evidence to suggest that genetic factors are important in IBM; these include the compact age at onset, insidious progression, clinical and pathological features, infrequent occurrence in twins, siblings and families. There have been several Mendelian genes identified in families with IBM phenotypes but these are rare. To investigate the pathogenesis of IBM further requires a genomic approach on large numbers of defined cases.
We will establish an international collaboration to collect IBM patient DNA and detailed clinical information to facilitate IBM research - The International IBM Consortium Genetic Study (IIBMCGS).
The number of IBM cases worldwide is not large enough for an effective genome wide association study (GWAS) but using next generation exome sequencing we can identify rare coding variants and high-risk genome wide variants in IBM. This technique has been used effectively in the identification of mutations that

cause Mendelian disorders and more recently found significant rare coding variants in type I diabetes and autism.
In this proposal we wish to employ exome sequencing to analyse 200 IBM cases and 200 normal muscle controls. We expect to identify a number of IBM rare variants that cluster in disease associated genes. We plan to replicate these findings in a further 700 IBM and 2200 controls. These data will be made publicly available (anonymously) to allow comparison with other muscle disorders and neurodegenerative conditions.

Closed Studies

39. NON-DYSTROPHIC MYOTONIAS: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDIES
Status: Closed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Hanna
Patients recruited: 20
This multi-centre project involves a prospective, cross-sectional and longitudinal natural history in non-dystrophic myotonias (NDM).
The aim is to collect standardized data from NDM patients, to include clinical symptoms, exam findings, as well as the results of strength, functional, and electrophysiological testing. Genetic testing will permit precise identification of individual NDM subtype. This information will allow for the identification and implementation of appropriate endpoints in studies of potential treatments.
This is a NIH funded study. Twenty patients were enrolled at the National Hospital for Neurology and Neurosurgery. *Under review for publication with Brain*

40. ANDERSEN-TAWIL SYNDROME: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDY
Status: Closed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Hanna
Patients recruited: 11 target >10
Andersen-Tawil syndrome is a neuromuscular disorder caused by a mutation in the KCNJ2 gene which codes for the inwardly rectifying potassium channel Kir2.1. A number of different mutations in this gene have already been identified in affected individuals. This disorder is characterised by the triad of periodic paralysis, developmental abnormalities and cardiac arrhythmias.
This project is a natural history trial into Andersen-Tawil Syndrome. The aim of the trial is to study the relationship between the genetic abnormalities underlying the disorder and the diverse clinical features. Eleven patients have been enrolled so far at the National Hospital for Neurology and Neurosurgery.

41. EPISODIC ATAXIA SYNDROME: GENOTYPE-PHENOTYPE CORRELATION AND LONGITUDINAL STUDY
Status: Closed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Hanna
Patients recruited: 36 target >20
Episodic Ataxia Syndrome is a rare, genetic disease that causes recurrent episodes of dizziness and incoordination.
The majority of cases are likely caused by an inherent genetic mutation. However in some patients the mutation is unidentifiable. The purpose of this study is to collect prospective standardized data from subjects to better define the clinical phenotype of the EAs and to establish clinically relevant endpoints for use in therapeutic trials.
The study will also :
- Fully characterize the clinical spectra and the natural history of genetically defined EA.
- Systematically investigate phenotypic differences between EA subjects harboring KCNA1/CACNA1A mutations and those that do not.

This proposal involves a multi-center cross-sectional data collection analysis as well as a prospective longitudinal study. Since EA is a chronic disease whose course is measured in years rather than months, the subjects will be followed longitudinally at a yearly interval for a period of two years. *Paper in draft form.*

42. PERIPHERAL NEUROPATHY OUTCOME MEASURES STANDARDISATION STUDY (PERINOMS)
Status: Closed
Sponsor: Erasmus Medical Center
PI: Dr M Lunn
Patients recruited: 110; overall target 120
The current study aims to expand the clinimetric knowledge on outcome measures at various levels of outcome (pathology, impairment, activity & participation limitation, and quality of life) in autoimmune polyneuropathies, particularly in GBS, CIDP, MMN, MGUSP, and autoimmune small fibre neuropathies (AI-SFN). Also, the general applicability of an autonomic symptoms scale plus some selected activity limitation scales will be examined.
Outcome measures will be assessed in a cross-sectional and longitudinal group of patients at the level of:
- Pathology: Intraepidermal nerve fibre (IENF) density will be assessed in patients with GBS, CIDP, MGUSP, and AI-SFN (in sarcoidosis). IENF density will be examined regarding its correlation with other outcome measures (validity), its reliability (intra-observer and inter-observer), and its responsiveness to clinical changes over time.
- Impairment: comparison studies, evaluating the validity, reliability, and responsiveness will be performed between MRC sumscore versus NIS motor subset, INCAT sensory sumscore versus NIS sensory sumscore, and hand-held Vigorimeter versus Jamar dynamometer. Also, the correlation of electrophysiological studies with other impairment outcome measures will be evaluated. Finally, the scientific soundness of the modified Dutch composite autonomic symptoms scale (mdCompass) will be examined.
- Activity limitation: comparison studies, evaluating the validity, reliability, and responsiveness will be performed between the ODSS and an overall neuropathy limitations scale (ONLS). Also, a newly devised weighted (based on Rasch analyses) activity and participation scale will be constructed, aiming specifically on the limitations in patients with polyneuropathy.
- Quality of life: Disease-specific versus generic quality of life measures will be assessed, determining their clinimetric soundness and by comparison studies in the various polyneuropathy groups.
The ultimate goal of the current study will be the presentation of a *specific* minimum core set of outcome measures to be used in future clinical and follow-up studies in patients with polyneuropathy, mainly those patients with autoimmune mediated polyneuropathies. The study will be performed in collaboration with several local, European, and USA neurological centres with great experience in dealing with inflammatory neurological disorders. *Due for publication shortly.*

43. OUTCOME MEASURES IN SMA TYPE II AND III
Status: Closed to recruitment
Sponsor: UCL Institute of Child Health
Funder: SMA Europe
PIs: Prof Muntoni; Kate Bushby
Patients recruited: 26; target (UK) 23
Description: The primary aim of this project is to establish, for the first time, a clinical network involving most of the leading neuromuscular centres in Europe and to enable them to have common outcome measures in order to be ready for forthcoming multi-centre trials on SMA type II and III
Objective(s)
Primary objective:
• To establish a clinical network involving most of the leading neuromuscular centres in Europe enabling them to have common outcome measures on SMA type II and III.
Secondary objectives:
• To ensure the functional scales used are suitable and clinically relevant for future trials, that we understand how the different measures relate to one another and how they may change over a 12 month period
This prospective longitudinal natural history study will be performed in two cohorts of patients with SMA type II and III identified according to their level of functional motor ability (ambulant/non ambulant). Inclusion criteria and methods will be different in the two cohorts and will be described separately. We have considerable retrospective data on SMA but very little planned data and none using the range of outcome measures proposed.
Further information can be obtained from the Trials Coordinator or Research Physiotherapist on 020 7905 2639.

Exercise Studies

Open Trials

44. Aerobic training in Charcot-Marie-Tooth disease and Inclusion Body Myositis.
Status: Recruiting
Sponsor: University College Hospitals
PI: Dr Gita Ramdharry
The specific objective of the present study is to investigate the effect of aerobic training in two common neuromuscular diseases (NMD): Charcot-Marie-Tooth disease (CMT) and Inclusion Body Myositis (IBM). These diseases result in progressive muscle wasting and substantial morbidity and disability. The effect of aerobic training on fitness levels, muscle strength and function will be systematically examined. This study will also monitor the safety, feasibility and impact on quality of life of this type of exercise training in these groups.
Sixty subjects, (30 from each disease group, aged between 18 and 75), will be recruited from the neuromuscular clinics at Queen Square. Both disease groups will be investigated concurrently with the same methods but will be viewed and analysed as separate studies. A crossover design will be used with training and control periods. The trial will span three years with each subject participating for a 34 week period. For the training intervention, participants will train in select local gyms and train on a bicycle ergometer.
The primary outcome measure for this study is maximum aerobic capacity during exercise testing. There will also be measures of muscle strength, body composition, and activity levels. In addition the study will investigate non-motoric effects of exercise such as mood, motivation, sleep and fatigue.

For further information please contact Dr Amanda Wallace, Amanda.wallace@uclh.nhs.uk

45. Full Title: Exploring the causes of falls and balance impairments in people with neuromuscular diseases
Status: Recruiting
Sponsor: University College Hospitals
Funder: NIHR
PI: Dr Gita Ramdharry
Falls are commonly reported by people with neuromuscular disorders but to date there has been little formal investigation of this problem. Frequent falling increases the risk of injury and reduces mobility due to avoidance of activities perceived to increase the threat of falls. The aim of this study is to ascertain falls risk from measurement of falls incidents, balance impairment and clinical presentation in people with different types of Charcot-Marie-Tooth (CMT), Distal Myopathy (DM) and Sensory Neuropathy (SN) with healthy controls. Measurements of static, anticipatory and reactive balance impairment and prospective falls events will be used to ascertain relationships with clinical presentation in people with different types of CMT, DM and SN. The three pathologies have been chosen for comparison as this will allow some discernment between the sensory and motor contributions to falls

47. PHYSICAL ACTIVITY AND INCLUSION BODY MYOSITIS
Status: Recruiting
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
PI: Dr M Trenell
Collaborating site MRC Centre London
Recruitment: 500 recruits expected, across 5 disease sites
The aim of this study is to collect data on day to day physical activity levels and metabolic control in individuals with chronic disease.
DESIGN:
Participants will be identified from chronic disease clinics by the following lead clinicians: Stroke-Prof Gary Ford, Neuromuscular disorders-Prof Kate Bushby, Metabolic disorders-Prof Roy Taylor, fatigue-Prof Julia Newton and Ageing-Prof Julia Newton. An equal sample of male and female participants will be used in the study which will be up to 100 patients in each disease group.
METHODOLOGY:
Step 1: Relevant practitioners will highlight possible candidates for the study.
Step 2: Visit 1: At the start of the study participants will either be asked to attend Newcastle University's Campus for Ageing and Vitality (Newcastle General Hospital), or if they are an inpatient will be visited on the ward. Participants will be provided with an information sheet about the study. They will be given the opportunity to talk with the team and ask questions. Once fully informed, participants will provide signed informed consent.
Participants will be asked to fill in a disease screening questionnaire at the start of the process. The height and weight of the participants will be recorded and this information will be entered into the physical activity monitors. Instructions will be provided as to how to use the monitors. A resting blood sample may also be taken at this point. This will be analysed for glucose, insulin, lipid profile and liver function.
Step 3: Participants will wear the arm monitors for five days including one weekend day. Step 4: Visit 2: At the end of the five day period participants will attend the research centre again or attend a pre-arranged session either at their home work place or on the ward to return the activity monitor. Here they will complete a brief physical activity questionnaire and two brief fatigue questionnaires. Data from the physical activity monitor will be fed into a computer. Each participant will be provided with a printout of their weekly activity levels and given the opportunity to discuss their results.

For information about recruitment contact Julia.maddsion@newcastle.ac.uk.

48. EXERCISE AND SARCOPENIA
Status: Recruiting
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust Funder: MRC
PI: Prof DM Turnbull
Collaborating site MRC Centre London
Target: 36
Sarcopenia, which is a complex multifactor process, has significant implications on quality of life, performance of daily activities, maintenance of independence and on projected healthcare costs.
Studies show that low physical activity correlates with poor mitochondrial function. Conversely, exercise correlates with better mitochondrial function, clinical improvement and improved perceived quality of life. Endurance training has been proven to be safe and efficacious in mitochondrial disease which may provide a model for the aging process albeit in an accelerated form with biochemical, histological and genetic changes seen in aged muscle also found in various mitochondrial conditions.
Aims:
1. To assess the rate and extent of motor unit loss in the eighth decade of life- cross-sectional (time 0) and longitudinal analysis (end of study)
2. To correlate the extent of motor unit loss with histological correlates and the development of sarcopenia
3. To assess the impact of exercise on the rate and extent of motor neuron loss
4. To observe whether endurance training initiated in late middle age prevents loss of muscle strength and mass in senescence
5. To assess the impact of neuronal loss on the inability to retain gains made in muscle strength following training after the 7th decade of life
6. To characterise effects of exercise upon neural activity, muscle oxidative capacity and mitochondrial and satellite cell plasticity with age.
Method: Thirty six (36) female participants, matched for body mass index who do not take regular exercise will be invited to participate: 40- 45 years (12), 60-65 years (12) and 80- 85 years (12). Inclusion criteria will be capacity to undertake cycling exercise and ability to give informed consent. Exclusion criteria will be co-existing active coronary artery disease or steroid therapy.
These patients will be recruited via the media and social support groups. All expenses (travel, accommodation and meals) will be paid for from the research grant.
The study will take place over 24 weeks. Participants will attend the study centre for 7 visits in total. The study will include 2 main visits at the beginning and end of the study. Each main visit will last 3 days. There will also be 5 one day visits.
For information about recruitment contact Julia.maddison@newcastle.ac.uk

49. A Randomised controlled trial of tailored home exercise versus advice and usual care for disability in people with immune mediated neuropathy
Status: Open
Sponsor: King's College London
Funder: GBS/CIDP
PI: Dr Lunn
Collaborating site KCL
Patients recruited: 0
Study design: A prospective parallel observer blind randomised controlled trial of a tailored home exercise programme (tHEP0 versus information about exercise and usual care (UC) that included a 12 month follow-up with economic evaluation of cost-effectiveness and cost-utility and a nested qualitative process evaluation.

Sample: People with stable motor neuropathy, with or without sensory neuropathy as a result of GBS, CIDP or PDN will be recruited. The sample seize is based on a 80% power calculation to detect a difference between mean change in overall disability sum score (ODSS) of 1 point using a 2-sided test at the 5% significance level based on a SD of 1.27 from pilot study data. Fifty four people (27 per group) will be needed; therefore 70 people will be recruited to allow for a 25% attrition rate at 12 months.

Closed Trials

50. STRENGTHENING HIP MUSCLES TO IMPROVE WALKING DISTANCE IN PEOPLE WITH CHARCOT- MARIE-TOOTH DISEASE
Status: Completed
Sponsor: University College London Hospitals
Funder: Muscular Dystrophy Campaign (MDC)
PI: Dr. Reilly
Patients recruited: 32 target: 32
Charcot-Marie-Tooth (CMT) disease is a form of hereditary peripheral neuropathy.
People with CMT present with weakness, wasting and sensory loss as a result of degeneration of the long peripheral nerves supplying the distal muscles.
The aim of this study will be to investigate the efficacy of a 16 week home based programme of training to increase hip flexor muscle strength and walking endurance. Additional measures of gait speed, exertion, fatigue, disability and general activity will also be recorded. Baseline impairment measures will be obtained to ascertain predictors of strength gains.

This study will use a single blinded, randomised cross over design to investigate if training the hip flexor muscles will strengthen the hip flexor muscle and improve walking endurance in people with all types of CMT.
The trial will include people aged between 18 and 70 years, who have been diagnosed with CMT on the basis of genetic tests (where possible), family history and neurophysiology testing. Each subject will be involved with the study for a 40 week period.
Journal of the Peripheral Nervous System, 2011; 16(S3):S115

51. EXERCISE TRAINING IN PATIENTS WITH MITOCHONDRIAL DISEASE: ASSESSING THE BENEFITS
Status: Closed
Sponsor: University Newcastle
Funder: Muscular Dystrophy Campaign (MDC)
PI: Prof Turnbull
Collaboration site MRC Centre London (Hanna)
Patients recruited: 6- 5 Newcaslte; 1 London
Mitochondrial myopathies are a very important group of muscle diseases associated with weakness, pain and fatigue. At present, treatment options are very limited.
Exercise therapy has been found to have some benefit in this group of patients and we wish to explore this further in terms of both strength and endurance.
The aim of this study is to demonstrate that strength exercise training is an effective approach to therapy in certain patients with mitochondrial myopathy, specifically those with sporadic mutations in mitochondrial DNA. Based on our previous research studies, we believe that such training will improve muscle strength, mitochondrial function, exercise tolerance and overall quality of life.
The main objectives are:
To confirm that endurance training in patients with mitochondrial abnormalities improves quality of life, exercise tolerance and oxidative capacity.

To determine the ability of resistance muscle strength training to improve skeletal muscle strength and oxidative capacity by incorporation of satellite cells into mature myofibres. Participants are expected to commit to an exercise training and testing over a period of 4 to 8 months.
The study will include patients between the ages of 18 and 65 years who have had a previous muscle biopsy showing a defect in skeletal muscle mitochondrial DNA that is either in the form of a sporadic point mutation or single large-scale deletion. Patients who have this type of mutation and do not have any family members that are affected and have no major cardiac involvement, hypertension, pulmonary or peripheral vascular disease that may complicate findings.

46. CARDIAC ADAPTATIONS TO EXERCISE IN MITOCHONDRIAL DISEASE
Status: Closed
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
PI: Prof D M Turnbull/Dr MI Trenell,
Patients recruited: 39
Twenty four people with mitochondrial disease will take part in the study. Participants will undergo cardiac, cognitive and movement examination and then they will be randomised into two groups. They will receive either; exercise counselling and support (n = 12) or continue standard care (n = 12) over a 16 week period. At the end of the 16 week period baseline measures will be repeated. Participants to be studied will have biopsy proven mitochondrial disease (age 18−60 years; BMI 20−35 kg/m2; and do not take part in regular exercise). Subjects with heart disease that would produce an adverse response to exercise will be excluded. Subjects with significant kidney disease or in vivo ferrous material will be excluded also as these are contra-indications to the use of gadolinium-based contrast agents and magnetic resonance imaging respectively. Magnetic resonance and echocardiographic evaluation of cardiac function as well as movement and cognitive function will be assessed at baseline and at 16 weeks. A progressive exercise test will be undertaken at baseline to establish maximal aerobic capacity and evaluate for an adverse response to exercise..
The patient exercise group will be matched with a control group of individuals without known mitochondrial disease who will undergo the same evaluation and training regime (n = 12)..
In total, the study will require each participant to attend the research facility for three visits for metabolic examination. The exercise groups will be requested to attend 48 exercise sessions over 16 weeks.

Imaging Studies

Open Trials

52. Full Title: Evaluation and Optimisation of Muscle Imaging Biomarkers in Support of Non-ambulant Duchenne Muscular Dystrophy Studies
Status: Open
Sponsor: UCL Institute of Child Health
Funder: GSK
PI: Prof Francesco Muntoni
Patient target: 15 (UK)
The primary objective of this study is to characterise the differential involvement of muscle groups occurring with disease progression (i.e. as a function of age) using skeletal muscle MRI so as to more precisely define which muscle groups could provide the best markers for therapeutic response in the non-ambulant boys.
The secondary objectives of this study are to

- Measure quantitative imaging changes in DMD muscle over the course of one year

using skeletal muscle and dynamic breathing MRI.

- Measure quantitative imaging changes in diaphragm movement occurring with disease progression (i.e. as a function of age) using dynamic diaphragmMRI.

For more information about the study please contact Dr Valeria Ricotti at v.ricotti@ich.ucl.ac.uk.

53. Magnetic Resonance Imaging Characteristics of Inflammatory Neuropathies – a pilot study
Status: Open to recruitment
Sponsor: University College London Hospitals
PI: Dr Lunn
Patients recruited: 20: 10 patient; 10 controls

The assessment of patients with peripheral nervous system (PNS) disease is currently mainly dependent on clinical examination, neurophysiological tests and occasionally nerve biopsy. Clarification of nerve imaging characteristics in chronic inflammatory demyelinating polyneuropathy (CIDP) could alleviate the need for invasive procedures such as nerve biopsy in cases where there is uncertainty in the clinical diagnosis.

Magnetic resonance imaging (MRI) has been widely applied to neurological diseases of the central nervous system, but to a much lesser extent diseases of the PNS. Research in inflammatory neuropathies has included traditional T1 and T2-weighted sequences; some more recent work in mainly focal entrapment neuropathies has looked at novel MRI sequences such as diffusion tensor imaging.

CIDP is an immune mediated condition characterised by progressive or relapsing motor and sensory deficits in all four limbs. It is a treatable condition and often responds to immunomodulatory treatment. Currently the diagnosis is based on a combination of clinical, neurophysiological and supportive criteria. Diagnosis can be difficult as the causative pathology is often proximally sited in the nerves, and their proximal portions are less anatomically accessible to neurophysiological examination.

Recent work in our unit has demonstrated that the sciatic nerve area in CIDP patients is significantly enlarged compared with controls, but with substantial overlap between the ranges of values obtained for disease and control groups. Since much of the pathology in CIDP is located at the nerve roots it is important to assess whether enlargement of the roots is able to differentiate between CIDP and controls.

There is no published research documenting the use of novel MRI techniques in patients with CIDP. Diffusion sequences and assessment of the magnetisation transfer ratio (MTR) of nerves may reveal diagnostic characteristics in diseased tissue, as is seen in the brain. **Aims:** We aim to clarify the use of MRI for the diagnosis of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMNCB). Using 3T MRI, we will use both conventional and novel quantitative MRI sequences to examine the nerve roots, plexuses, sciatic nerves and forearm nerves of 10 patients each with CIDP, MMNCB and 20 healthy volunteers. We will quantify nerve root cross sectional area in cervical and lumbar regions in patients with CIDP, MMN and healthy controls. We will explore imaging characteristics of the sciatic nerve in patients with CIDP versus healthy controls. We will define imaging characteristics at sites of conduction block in nerves of patients with MMNCB. In a separate group of patients with suspected inflammatory neuropathy we will compare MRI to pathological findings on nerve biopsy. MRI may be shown to be a useful non-invasive diagnostic tool.

For further information, contact Dr Jasper Morrow, j.morrow@ucl.ac.uk

54. MRI in IBM and CMT

Full Title: A Study of Quantitative Magnetic Resonance Imaging and the Clinical Features of Inclusion Body Myositis and Charcot Marie Tooth Disease
Status: Closed to recruitment

Sponsor: University College London Hospitals
Funder: MRC
PI: Prof T Yousry/Dr J Thornton
Patients recruited: 72: 40 patients; 32 controls

Magnetic resonance imaging (MRI) is a key tool in the diagnosis and management of a number of diseases. Despite the wide use of MRI in several clinical settings, so far its role in neuromuscular disease has not been well established. The current standard for the diagnosis of neuromuscular disorders includes clinical examination, electrophysiological investigations, biopsy and genetic testing. Due to the nature of the involvement of prominent muscles and peripheral nerves in these disorders it is proposed that MRI could play a prominent role in understanding of neuromuscular disease.

This study aims to investigate the use of MRI as a tool in the study of nerve and muscle diseases by focusing on two particular neuromuscular diseases, one primarily neuropathic and one principally myopathic. Two separate patient cohorts with neuromuscular disease will be recruited. Forty patients with Sporadic Inclusion Body Myositis (IBM) and 40 patients with genetically confirmed Charcot Marie Tooth Disease (CMT). In addition to the two patient cohorts, two groups of healthy volunteers each of size 40 will act as comparators for the disease groups. Each of the patients enrolled in the study will undergo an MRI scanning session in which the quantitative MR techniques developed in Phase 1 with the health volunteers will be applied. In addition to the MRI scanning sessions, each patient will undergo a clinical examination to record the main clinical features of their disease status including an electrophysiological nerve conduction assessment. In the final phase of the study, a sub-group of the patients will then be followed-up at 6 month intervals for 5 years in a longitudinal natural history study of IBM and CMT that focuses on the MR methods and clinical findings that were shown to be most illuminating.

Changes over time in the MRI parameters in the diseased groups and Healthy volunteers will be compared.

Objectives:

To detect, using quantitative magnetic resonance imaging (qMRI), the changes in the nerves and muscles of patients with inclusion body myositis or Charcot Marie Tooth disease, and to relate these changes to the measurable clinical and neurophysiological features in these diseases. This will allow the value of various qMRI techniques as markers of disease activity and progression to be tested.

Secondary objectives of the study include:

The development of novel quantitative MR techniques for targeted assessment of the human neuromuscular system.

To more fully characterise both the magnetic resonance imaging and clinical features of inclusion body myositis or Charcot Marie Tooth disease as compared with healthy individuals and to study the progression of these characteristics with time over a period of 5 years.

For more information about the study please contact Dr Jasper Morrow at j.morrow@ion.ucl.ac.uk.

55. A Study of Quantitative Magnetic Resonance Imaging to Monitor Disease Activity in Hypokalaemic Periodic Paralysis.
Status: Open to recruitment
Sponsor: UCL
Funder: MRC
PI: Hanna
Recruitment: 24: 12 patients; 12 controls

The commonest muscle channelopathy is hypokalaemic periodic paralysis caused by mutations in the voltage sensor regions of either the muscle sodium channel SCN4A or the muscle calcium channel CACN1AS. From childhood, patients experience disabling episodes of

complete muscle paralysis lasting hours to days. In the early years patients recover in between attacks but over time they develop a permanent fixed muscle weakness (myopathy) and often become wheelchair bound. Although there are established treatment strategies which we and other centres in USA and Europe employ and which can reduce attack frequency, we do not have sensitive methods to monitor disease activity or to determine if the treatment regime is fully effective.
Recent data indicate that muscle water content may be a key determinant of muscle function in patients with higher abnormal water content (oedema) correlating with more weakness. Preliminary published data indicates patients with less oedema may have a better prognosis. Furthermore, we currently make decisions to adjust standard treatments based on attack frequency only and this may not be the most reliable way to monitor actual disease activity in affected muscles. In this study we wish to evaluate abnormal muscle water content using MRI applied in the context of the normal current clinical practice and management in this patient group.
In this study we aim to show that patients with hypokalaemic periodic paralysis have abnormal muscle water on MRI which is inversely correlated with muscle strength and sensitive to changes over time. In a wider context than this study, similar techniques may be applied to other muscle diseases, where MRI could guide treatment in clinical practice and act as an outcome measure in clinical trials.
This study has two phases. The first phase is a period of MRI technique refinement in up to 10 healthy volunteers lasting up to two months. The main study phase is a longitudinal case control study and will study a minimum of twelve patients with hypokalaemic periodic paralysis and twelve healthy volunteers who will act as a comparison group for the patients. Assessments will be repeated at a four week interval to see if any changes in clinical parameters are reflected in changes on MRI parameters. One of the inclusion criteria for patient enrolment will be evidence of active disease in order to maximise differences between the two time points.
For further information contact Dr Jasper Morrow: j.morrow@ucl.ac.uk

56. Magnetic Resonance Imaging as an outcome measure in Motor Neuropathies: a pilot study
Status: Recruitment to open soon
Sponsor: UCL
PI: Hanna
The development of novel therapies for motor neuropathies necessitates the search for a reproducible outcome measure which can sensitively monitor disease progression. Muscle magnetic resonance imaging (MRI) is an excellent candidate due to its reproducibility and observer independence. We plan to investigate various parameters obtained through muscular MRI as longitudinal biomarkers in diseases of the motor neuron with different speeds of disease progression: amyotrophic lateral sclerosis (ALS), Kennedy's disease (KD) and distal hereditary motor neuropathy (dHMN). Using 3T MRI the research team will perform lower limb imaging with quantitative 3-point Dixon, magnetisation transfer and IDEAL-CPMG sequences in addition to standard qualitative T1 and STIR sequences in 12 patients each with ALS, KD and dHMN as well as 12 healthy volunteers. Detailed clinical data will be collected, including isokinetic and isometric lower limb strength. These assessments will be repeated at a 3 and 12 month interval in ALS patients and at a 6 and 12 month interval in dHMN and KD patients. We will analyse the value of quantitative MRI as an outcome measure in these conditions by analysing both correlation with clinical measures and sensitivity to change over time. Data from this study will be able to be used to establish sample size in clinical trials to evaluate novel therapeutic strategies in these diseases.
MRI has been widely applied to neurological diseases of the central nervous system, but to a much lesser extent diseases of the peripheral nervous system (PNS), and even less frequently to the diseases in this study.
The hypothesis is that MRI can detect changes in the muscles in patients with ALS, KD and dHMN.
The proposed project will take place in two phases, an initial cross-sectional case control study of all patients and volunteers followed by a longitudinal natural history study.

MRI imaging will be performed of thigh and calf muscles at 3 Tesla in a scanning session lasting approximately an hour. All participants will undergo standard MRI imaging with T1-weighted and STIR sequences. The following quantitative MRI techniques will be used: magnetization transfer imaging, T2 relaxometry with IDEAL-CPMG and 3-point Dixon fat quantification. We will not be using gadolinium contrast in this pilot study.
For further information contact Dr Jasper Morrow, j.morrow@ucl.ac.uk

Closed Studies

57. MRI IN FKRP-RELATED LGMD2I
Full-Title: A study using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) in Patients with Limb Girdle Muscular Dystrophy 2I; an assessment of muscle damage.
Status: Closed
Sponsor: Newcastle NHS Trust
Funder: MRC
PI - Prof V Straub
Re-defined in 1995, the LGMDs are face-sparing, proximally predominant, progressive muscular dystrophies with elevated creatine kinase levels and dystrophic features on muscle biopsy. In the current classification system, LGMDs are divided into autosomal dominant (LGMD1) and autosomal recessive (LGMD2) disorders with a superimposed lettering system denoting the chronological order of the chromosomal linkage.
Limb Girdle Muscular Dystrophy 2I (LGMD2I) is caused by a mutation in the fukutin related protein gene (FKRP)1 and manifests temporal variability. Clinically the age of onset, rate of progression and severity varies greatly between cases and even within the same family. They range from asymptomatic patients with mildly raised creatine kinase levels to those severely affected and non ambulant. The respiratory and cardiac complications, well known to occur in this type of muscular dystrophy, in 30% and 60% of patients respectively, occur independently of the general muscle weakness and also cardiac complications occur independently from respiratory compromise.
Magnetic Resonance imaging (MRI) has been increasingly used in imaging in patients with neuromuscular disorders over the past 5 years.
Studies have shown that whilst there is considerable overlap in muscle involvement there is also striking differences that can be of diagnostic value. In both patients with LGMD2A and LGMD2I there is a prominent pattern of involvement of the posterior thigh muscles, however in LGMD2A there is also selective involvement of the medial gastrocnemius and soleus muscles in the lower leg, which was not seen in LGMD2I. Although it is clearly demonstrated that MRI findings mirror those obtained from clinical examination, it has been reported recently that in fact MRI abnormalities can be detected in patients with neuromuscular disorders when clinical examination of particular muscle groups have been normal. MRI can therefore be useful to show early manifestations of a disease and to monitor the effect of early therapeutic interventions.
Beside MRI another non-invasive technique to consider is phosphorus magnetic resonance spectroscopy (P-MRS). P-MRS studies have demonstrated several metabolic abnormalities in the skeletal muscle of patients with Duchenne Muscular Dystrophy (DMD)/ Becker Muscular Dystrophy (BMD) and in the group of autosomal recessive LGMDs, associated with sarcoglycan deficiency (LGMD2C-F) . These changes are thought to be specific for dystrophies secondary to deficits in the dystrophin-glycoprotein complex. In these patients there appears to be an increased cytosolic pH in both groups, however there is also abnormal concentrations of phosphorylated compounds (in particular, decreased phosphocreatine and increased inorganic phosphate concentrations).
The study overall aim is to develop and evaluate non-invasive techniques to quantify muscle pathology and the rate of change over time in LGMD2I, which is potentially a useful tool for monitoring response to treatment and therapies. This shall be achieved by measuring static MRI over a 2 year period and comparing this to age matched adult controls including the quantitative 3-point Dixon technique for measuring fat. At the same time we will also be measuring the Pi and cytosolic pH, ATP and ADP via MRS to see whether a specific pattern of metabolic abnormality is detected in these patients.

For further information about the study please contact Dr. Jasper Morrow at j.morrow@ion.ucl.ac.u.k.

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