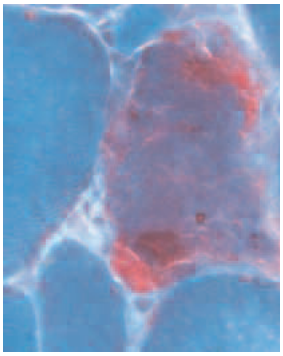
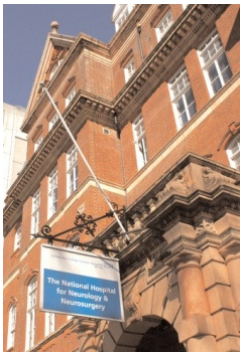
Muscular Dystrophy Campaign

50 years of support

MRC Centre for Neuromuscular Diseases

UK Neuromuscular Translational Research Conference

26 -27 March 2009

International Centre for Life
Times Square
Newcastle Upon Tyne
NE1 4EP

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Welcome to the second annual meeting of the London Newcastle MRC Centre for Translational Research in Neuromuscular Diseases

UK Neuromuscular Translational Research Conference 2009

Dear Colleagues,

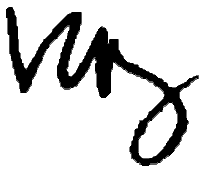
We are delighted to welcome you to Newcastle for this second annual scientific meeting of the first MRC funded centre for translational research in neuromuscular diseases. We are pleased that this UK Neuromuscular Translational Research Conference is jointly hosted with the Muscular Dystrophy Campaign. The MRC centre aims to bring together clinicians, scientists, patient organisations and patients in order to advance UK translational research in neuromuscular diseases. This is a particularly exciting time in the field as a range of basic science discoveries are revealing an increasing number of therapeutic targets. The centre aims to work with all its partners to support the development of a trials culture for patients with neuromuscular diseases. We will continue to work hard to form effective research and clinical links with as many other UK neuromuscular groups as possible.

The MRC Centre is a joint partnership between the Institute of Neurology, Queen Square UCL, the Institute of Child Health, UCL and the University of Newcastle-upon-Tyne. The centre is 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.

Over the next two days this conference aims to showcase a wide range of high quality scientific neuromuscular research from many UK groups, European colleagues and industry partners. There are focussed sessions on translational research developments in muscle disease, peripheral nerve disease and neuromuscular channelopathies. In addition, there are sessions on exercise therapy in neuromuscular disease and the importance of collaborative networks in delivering translational research. We have received over 65 high quality abstracts and there will be dedicated poster sessions each day. We are delighted that Professor Dame Kay E Davis will deliver the first John Walton Lecture and that Professor Chris Kennard will discuss translational research in the context of the MRC.

We would like to thank the joint MRC-MDC meeting planning team for all their hard work organising this meeting. We are delighted that there has been such an enormous interest from throughout the UK and beyond.

We sincerely hope that you have a stimulating and entertaining two days in Newcastle.



Professor Michael G Hanna
Director,
MRC Centre for Neuromuscular Diseases

Professor Katie Bushby
Deputy Director Newcastle,
MRC Centre for Neuromuscular Diseases

Welcome from Philip Butcher – CEO of the Muscular Dystrophy Campaign

Welcome to the UK Neuromuscular Translational Research Conference in Newcastle. This is the second conference organised in partnership between the MRC Centre for Neuromuscular Diseases and the Muscular Dystrophy Campaign.

After last year's tremendous success, we are delighted to support the conference again as it brings together scientists and clinical researchers working in the field of neuromuscular disorders to present their newest research findings. The scientific programme looks both exciting and enticing – in particular we look forward to hearing the latest results of the first promising potential treatments that are now emerging.

This year the Muscular Dystrophy Campaign commemorates its 50th birthday and we are very proud to have supported research into neuromuscular disorders for half a century. During this time our families and supporters have raised more than £50 million to fund cutting edge science and to help researchers in the UK become major players on an international platform.

This year the conference coincides with the annual meeting of the MDC Physiotherapists, Occupational Therapists and Care Professional Networks. These are initiatives established by the Muscular Dystrophy Campaign which aim to bring together professionals working with people affected by neuromuscular disorders and their carers. Considering that most conditions are rare, these networks are essential for the sharing of knowledge and expertise and help to develop national standards of best practice guidelines.

Over the last year the charity has been successful in campaigning for improvements in patient care and support. By building coalitions with families, parliamentarians and health professionals, we have been lobbying the Government and NHS decision makers to ensure all people with neuromuscular disorders can access specialist care. This has led to £1 million additional investment in neuromuscular services in the South West of England and we now aim to replicate this success across the UK.

There may be challenging times ahead but we will continue to work hard to build on the achievements of our research investments into neuromuscular disorders to date. It is clear that working across disciplines, geographies and national boundaries is the key to success as we forge ahead as one team. Together we are stronger.

Mr Philip Butcher

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. In the UK there is a large gap between major science discoveries and patient benefit in these important disorders. This gap is larger in the UK than in other countries such as Germany, France and the USA who have already moved forward with translational research initiatives. The new MRC Centre aims to reduce this gap by establishing a 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 neuromuscular research groups and 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 is to translate basic science findings into 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 £20m of grant income will underpin the activities of the Centre. The Centre is developing 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 identified five key areas which we consider to be current obstacles to effective translation of basic science findings into patient benefit. These are: 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 and Newcastle (NCG services). The MRC Centre is working closely with TREAT-NMD, the pan-European network of excellence, as the UK implementation partner. A list of current trials appears on page 48.

- 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 cell lines for translational research.

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

- We believe that the application of new MRI techniques has the potential to revolutionise the assessment and monitoring of neuromuscular disease in both animal models and 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 a brand new four-year neuromuscular disease PhD programme, and eight science PhD students have now been appointed to this programme. We are ensuring that exciting translational research environments to train a new 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 all muscle disease. 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 muscle disease.

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

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, the focus of this research has begun to shift towards the search for treatments for these conditions.

Translational research involves a 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 the 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 will ultimately benefit the patient.

The Muscular Dystrophy Campaign aims to ease this transition by providing support to both scientists and clinicians. We fund basic research through to pre-clinical research and where possible clinical trials. As well as monetary help, we aim to provide a platform where clinicians and scientists can meet and discuss ideas.

One of our strategic aims is to fast-track promising treatment approaches when they are close to clinical trial and to ensure a rapid transition from bench to bedside. A major focus of the last year has been to support and encourage initiatives to promote translational research in order to help remove some of the barriers faced by scientists and clinicians. We currently support research across a range of disciplines from the basic science through to research looking at treatment approaches for a number of conditions.

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 that these sessions will be of interest to you and provide you with an update of the recent research advances that the scientists and clinical researchers have made.

We are proud to announce that in 2009 we are Tesco Charity of the Year. This year also sees us mark our 50th anniversary.

Patient Organisations

The MRC centre and the Muscular Dystrophy Campaign aim to develop strong links with all neuromuscular patient organisations, and are delighted that the following organisations are represented at this meeting.

Programme

Day 1 – Thursday 26th March

09:00 – 10:15	Registration	
10.15 – 10:30	Introduction	Professor Mike Hanna, Institute of Neurology
10:30 – 12:30	**Focus on muscle disease** Chairs: Professors Francesco Muntoni & Kate Bushby	
10:30 – 11:00	Sporadic inclusion body myositis (sIBM): from the inflammation to degeneration; impact on therapeutic interventions	Professor Marinos Dalakas, Imperial College London
11:00 – 11:30	How to examine the mdx mouse	Professor Volker Straub, Newcastle University
11:30 – 12:00	Restoring Dystrophin Expression in Duchenne Muscular Dystrophy: A Phase I/II Clinical Trial Using Morpholino Antisense Oligomers	Professor Francesco Muntoni, Institute of Child Health, UCL
12:00 – 12:15	Platform presentation: Mutations in TACO1 cause juvenile onset Leigh-syndrome with optic atrophy	Dr Rita Horvath, University of Newcastle
12:15 – 12:30	Platform presentation: How much dystrophin is required to restore normal muscle function?	Dr Paul Sharp, Imperial College
12:30 – 14:00	Posters – Scotswood Suite Lunch – Mezzanine	
14:00 – 16:00	**Focus on peripheral nerve disease** Chairs: Dr Mary Reilly and Professor Kristjan Jessen	
14:00 – 14:30	The control of nerve development, pathology and repair by c-Jun and Notch in Schwann cells	Professor Kristjan Jessen, University College London
14:30 – 15:00	Teasing out targets: the application combinatorial glycomics to peripheral nerve autoimmunity	Professor Hugh Willison, University of Glasgow
15:00 – 15:30	Update on Charcot Marie Tooth disease	Dr Mary Reilly, Institute of Neurology, UCL
15:30 – 15:45	Platform presentation: Association between magnetization transfer ratio and muscle strength in Chronic Inflammatory Demyelinating Polyneuropathy	Dr Chris Sinclair, Institute of Neurology

15:45 – 16:00	Platform presentation: Patients from an unusual family co-segregating myotonic dystrophy and Charcot-Marie-Tooth disease present with an imperfect CTG repeat allele at the DM1 locus	Claudia Braida, University of Glasgow
16:00 – 16:30	**The MRC and translational research** Introduction by Prof Mike Hanna	Professor Chris Kennard, Chairman of the MRC Neurosciences and Mental Health Research Board
16:30 – 17:45	Posters – Scotswood Suite Tea – Foyer	
17:45 – 18:45	**The John Walton lecture** Introduction by Professor Doug Turnbull, University of Newcastle Therapeutic opportunities in DMD	Professor Dame Kay E Davies, University of Oxford
19:00 - 20:00	Drinks reception, Visitor Centre Introduced by Phil Butcher, Muscular Dystrophy Campaign	
20:00	Dinner - Scotswood Suite	

Day 2 – Friday 27th March

08:45 – 09:20	**Network Translational Research** Chair: Professor Doug Turnbull	
08:45 – 09:00	The Smartnet Clinical Network – creation of a national standardised assessment tool and natural history database for Spinal Muscular Atrophy	Anna Mayhew, Institute of Child Health, UCL
09:00 – 09:20	'We just live from day to day': Tricky transitions for young men with Duchenne Muscular Dystrophy (DMD) and their families	David Abbott, University of Bristol
09:20 – 11:20	**Exercise therapy and muscle disease** Chair: Professor Doug Turnbull	
09:20 – 09:50	EastEnders to Exercise: the cross talk between basic science and clinical care	Dr Mike Trenell, University of Newcastle
09:50 – 10:20	A currently ongoing trial: exercise training in FSHD based on a model of functional health status	Professor Baziel Van Engelen, University Medical Centre Nijmegen
10:20 – 10:50	Assessment and Management of McArdle disease	Dr Ros Quinlivan, RJAH Orthopaedic Hospital

10:50 – 11:20	Physical Activity and Barriers to Exercise for People with Neuromuscular Disease	Dr Margaret Phillips, University of Nottingham
11:20 – 11:50	Coffee - Foyer Posters – Scotswood Suite	
11:50 – 12:50	**Molecular therapies** Chair: Professor Dame Kay Davies	
11:50 – 12:20	Oculopharyngeal muscular dystrophy: biology and therapeutic strategies	Professor David Rubinsztein, University of Cambridge
12:20 – 12:50	Exon skipping for DMD, from lab to clinical reality	Gerard Platenburg, Prosensa
12:50 – 14:20	Posters – Scotswood Suite Lunch – Mezzanine MDEX meeting, Blaydon Room	
14:20 – 16:20	**Neuromuscular channelopathies** Chairs: Professors Mike Hanna and Hanns Lochmüller	
14:20 – 14:50	Translational research in muscle channelopathies	Professor Michael Hanna, Institute of Neurology, UCL
14:50 – 15:20	In vivo electrophysiology in neuromuscular channelopathies	Professor Martin Koltzenburg, Institute of Neurology, UCL
15:20 – 15:50	Molecular mechanisms in congenital myasthenia	Professor David Beeson, University of Oxford
15:50 – 16:20	Congenital myasthenic syndromes - diagnosis and therapy	Professor Hanns Lochmüller, Newcastle University
16:20 - 16:30	Close	

Speaker Abstracts

Sporadic Inclusion Body Myositis (sIBM): from the inflammation to degeneration; impact on therapeutic interventions

Professor Marinos C. Dalakas
Imperial College, South Kensington, London SW7 2AZ, UK

In sporadic Inclusion Body Myositis (sIBM), the most prevalent acquired myopathy above the age of 50, chronic inflammatory features co-exist with degeneration. The inflammatory cells invade non-vacuolated fibers while the vacuolated fibers are not invaded by T cells implying two independent processes, a primary immune process with antigen-driven T cells, and a degenerative process in which β-amyloid and related proteins may play a role. The specific immunopathologic marker of the MHC-1/CD8 lesion, distinguishes the antigen-driven inflammatory cells seen in PM and IBM from the non-specific, secondary inflammation seen in inflammatory dystrophies. In IBM, the autoinvasive CD8+ inflammatory cells form immunological synapses with the MHC-1 expressing muscle fibers based on the clonal expansion of the autoinvasive $CD8^+$ cytotoxic T cells that persist over time, and the upregualtion of proinflammatory cytokines, chemokines, and co-stimulatory molecules. The degenerative process of IBM is highlighted by the accumulation of β-amyloid, cleaved from amyloid precursor protein (APP), as well as cell-stress or degeneration-associated molecules, such as αB-crystallin, tau and ubiquitin, associated with intracellular protein aggregation. The chronic overexpression of MHC-1 can also exert stressor effect on muscle fibers. In IBM, but not the controls, there appears to be an interrelationship between inflammatory and degeneration-associated molecules based on the observations that: a) the mRNA of APP significantly correlates with endomysial inflammation and with the levels of chemokines and IFN-γ; b) cytokines and stressor proteins, such as IL-1β, iNOS and αB-crystallin, co-localize with β-amyloid and MHC-1; c) IFN-γ, TNF-α and IL-1β enhance the production of cytokines in cultured myotubes and augment the expression of APP and β-amyloid leading to intracellular protein aggregation; and d) IFN-γ induces autophagy in human myotubes that clear β-amyloid. These observations highlight the concept that in IBM inflammation and degeneration act in concert with each other and suggest that treatment strategies targeting the chronic inflammatory response may suppress muscle degeneration. Promising agents capable of affecting both processes will be discussed and the clinicopathologic observations from the recently conducted trial with CAMPATH, a T cell-depleting monoclonal antibody, in sIBM patients will be presented.

How to examine the *mdx* mouse

Professor Volker Straub
Institute of Human Genetics, Newcastle University, International Centre for Life, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK, MRC Centre for Neuromuscular Diseases, Institute of Neurology, Queen Square, London WC1N 3BG, UK

Over the past century, the mouse has developed into the premier mammalian model system for genetic research because of its close genetic and physiological similarities to humans, as well as the ease with which its genome can be manipulated and analyzed. Mouse models mimicking human diseases are also playing an important role in testing novel treatment strategies, but one obstacle in the interpretation of results from such studies is the lack of standard operating procedures (SOPs) that serve as a reference point for mouse assessment. At present, the variety of animal models, readout parameters and experimental protocols available makes it difficult to compare results and conclusions of different laboratories, therefore hindering a straight and efficient translation into clinical studies. One of the most commonly used and best characterized mouse models for a genetic disease is the *mdx* mouse for Duchenne muscular dystrophy. To assure that results from pre-clinical studies in the *mdx* mouse can be impartially interpreted and compared, an international consortium of experts has been established to standardize and disseminate functional, histological and biochemical assessment criteria for the *mdx* mouse. Consortium meetings were organized by the Wellstone Center (Washington, USA) and by TREAT-NMD, with the generous support of the Foundation to Eradicate Duchenne. In a first step, currently used readout parameters were sought in the literature. In a second step, the parameters were prioritized with special regard to their applicability in clinics and the possibility to predict improvement in clinical practice. The consortium has used a process of systematic review and validation to ensure the robustness of the SOPs. Each SOP was developed by dedicated working groups and examined by an administration team for accuracy and consistency with the established SOP format. Finally, the SOP was reviewed and approved by an expert outside the working group to obtain a broad acceptance by end users before being uploaded to the TREAT-NMD website.

Restoring dystrophin expression in duchenne muscular dystrophy: a phase I/II clinical trial using morpholino antisense oligomers

Professor Francesco Muntoni
Dubowitz Neuromuscular Centre, Institute of Child Health, UCL, 30 Guilford Street, London WC1N 3JH, UK, MRC Centre for Neuromuscular Diseases

Background: Mutations in the *DMD* gene that disrupt the open reading frame (ORF) cause Duchenne muscular dystrophy (DMD), a fatal, progressive disease, where either no, or truncated and unstable, dystrophin is produced. Modulation of pre-RNA splicing with antisense oligonucleotides (AOs) can correct the open reading frame and produce truncated, yet functional dystrophin in human myoblasts in vitro, in animal models of DMD and in DMD patients. We conducted the first phase I/II clinical trial to test morpholino AO (AVI-4658) designed to skip dystrophin exon 51 following its intra-muscular injection in seven patients harbouring deletions responsive to skipping exon 51. The safety and ability of this AO to skip exon 51 and produce dystrophin protein were investigated. *Methods*: The efficacy of the AO was tested first on each patient's fibroblasts in vitro. Each subject received a low (0.09 mg) or high (0.9 mg) dose of AVI-4658 via IM injections into the extensor digitorum brevis (EDB) foot muscle; the contralateral muscle received an equivalent volume of saline. Bilateral EDB biopsies were obtained 3-4 weeks later. Safety was evaluated and local exon skipping and dystrophin expression assessed. *Results:* There was no adverse event related to the administration of the AVI-4658. All patients showed specific exon 51 skipping at the RNA level and those injected at the higher AO dose showed sarcolemmal dystrophin expression in a variable number of fibres. *Conclusion* :Our results show that, following intramuscular injection, AVI-4658 is safe and induced skipping of exon 51, leading to dystrophin protein production in vivo. AO-induced exon skipping offers one of the most promising therapeutic strategies for DMD and this study forms the basis for future systemic studies.
Acknowledgements: The Authors wish to thank the participating patients and the charities Muscular Dystrophy Campaign, Action Duchenne and the Duchenne Family Support Group for the support to our study. This work was funded by the Department of Health. The authors also wish to thank the support of AVI Biopharma in the supply of AVI-4658, Mr Chambers and Miss Kim for their help processing samples and Drs Jungbluth, Gosalakkal, Roper, Quinlivan and Chils for referring their patients for this study.

The control of nerve development, pathology and repair by c-Jun and Notch in Schwann cells

Professor Kristjan Jessen
University College London, Gower Street, London WC1E 6BT, UK, MRC Centre for Neuromuscular Diseases,

Dedifferentiation of myelinating Schwann cells is a key feature of nerve injury and demyelinating neuropathies. This talk will present evidence that this dedifferentiation depends on the activation of specific intracellular transcriptional regulators in Schwann cells that act as negative regulators of myelination and drive the dedifferentiation programme. Two factors will be discussed in this context, Notch and c-Jun. Notch, which controls Schwann cell generation and proliferation and is a timer of myelination, is activated in injured nerves where it accelerates demyelination. Activation of Notch, even in uninjured nerves. is sufficient to induce demyelination. c-Jun is also activated in injured nerves where it drives demyelination and is required for the correct generation of the denervated Schwann cell phenotype. The realization that myelination is subject to negative as well as positive controls contributes significantly to the understanding of Schwann cell plasticity. Negative regulators are likely to have a major role during injury, because they promote the transformation of damaged nerves to an environment that fosters neuronal survival and axonal regrowth. A striking example of this will be shown in the case of c-Jun. In neuropathies, however, activation of these pathways is likely to be harmful because they may be key contributors to demyelination, a situation which would open new routes for clinical intervention.

Teasing out targets: the application combinatorial glycomics to peripheral nerve autoimmunity.

Professor Hugh Willison
Glasgow Biomedical Research Centre, University of Glasgow, 120 University Place, Glasgow G12 8TA, UK

Clinical studies have identified serum anti-ganglioside antibodies in Guillain-Barré syndrome cases and related chronic neuropathies. Gangliosides are a family of ~50 structurally distinct sialic acid-containing glycosphingolipids highly enriched in the nervous system. Anti-GM1 and -GD1a antibodies characterise the motor axonal form of GBS and anti-GQ1b/GT1a antibodies characterise Miller Fisher syndrome (MFS). Evidence suggests these antibodies arise through molecular mimicry with sialic acid containing bacterial lipopolysaccharides (LOS) and are the principle pathogenic mediators of the disease, and pathogenic antibodies can be isolated from mice immunised with bacterial LOS. Using *in vivo* and *ex vivo* mouse nerve preparations as a model system, we have shown complement-dependent destructive effects induced by anti-ganglioside antibodies at clinical, physiological and morphological levels. Neural injury can be exaggerated or attenuated by manipulating the levels of the ganglioside target, and complement inhibition can attenuate the pathological procession. The observation that glycolipid complexes (GSCs) act as both *de novo* antigens and inhibitory domains for anti-glycolipid antibody binding in GBS adds substantial

combinatorial complexity to screening assays that are typically limited in diversity. We have recently devised combinatorial glycolipid macroarrays to investigate the frequency of GSC complex antibodies in disease and control groups, including a large Dutch GBS cohort. It is now possible to screen a high number of potential antigens in their combinatorial complexity to identify the target antigen(s) in autoimmune neuropathy. New data will be presented outlining the power of this method in identifying novel antigens.

Update on Charcot Marie Tooth disease

Dr Mary M Reilly
MRC Centre for Neuromuscular Diseases and Department of Molecular Neurosciences, The National Hospital for Neurology and Neurosurgery and Institute of Neurology, Queen Square, London WC1N 3BG, UK

Charcot-Marie-Tooth disease (CMT) is the commonest inherited neuromuscular disorder affecting 1 in 2,500. CMT is classified into CMT1 (demyelinating) and CMT2 (axonal). The first causative gene (chromosome 17 duplication containing the peripheral myelin protein 22 (PMP22)) was identified in 1991 and there are now more than 30 causative genes known. In recent years research has been directed into studying the pathogenesis of the various genetic subtypes of CMT in order to identify potential therapeutic strategies. Most work has been done on CMT1A secondary to the chromosome 17 duplication and this has led to drug trials which are currently underway. Other trials are being planned for CMT1B secondary to myelin protein zero (MPZ) point mutations.

This update will focus on translational research. Specifically it will address how the identification of the causative genes and studying the pathogenesis of the various CMT subtypes has begun to be translated into clinical based research and treatments for patients. An example of a subtype of CMT (CMT1A), in which the translational research is well advanced will be discussed as well as examples of those subtypes of CMT (especially CMT2), where research is still at a very basic stage.

The Smartnet Clinical Network – Creation of a national standardised assessment tool and natural history database for Spinal Muscular Atrophy

Dr Anna Mayhew
Dubowitz Neuromuscular Centre, Institute of Child Health, UCL, 30 Guildford Street, London WC1N 1EH, UK

Objective: To develop a standard neuromuscular measurement tool for the assessment of children and young adults with Spinal Muscular Atrophy (SMA) in order to optimise their management and to create a national database to collect natural history data on type II and type III SMA. Background: The Smartnet Clinical Network UK was established in August 2006 following the appointment of a project co-ordinator and clinical collaboration between the major Paediatric Neuromuscular centres and some adult based centres involved in the care of individuals affected by SMA. A similar initiative had already been successfully established in UK through North Star, a network designed to establish standardised assessment procedures in ambulant Duchenne Muscular Dystrophy boys and collect these longitudinal data onto a national database. Increasingly there has been a need to establish standardised assessment procedures as clinical trials become more likely and regulatory authorities require more comprehensive measures of progress. Methods: To establish the optimum motor function scales for use within the physiotherapy assessment, existing motor function scales were reviewed by an expert group, and consensus was achieved on choice of 3 motor function measures, as follows: For non-ambulant children – Hammersmith Functional Motor Scale (HFMS) - This has been used in clinical trials already both in UK and overseas. For ambulant children and adults - Slightly modified North Star Ambulatory Assessment, originally designed for use in Duchenne Muscular Dystrophy, but now adapted for the use in ambulant SMA. Its advantage is that it is familiar to UK therapists and has been compiled in a robust fashion. For non-ambulant children, teenagers and adults - Egen Klassifikation for SMA, which is a robust functional questionnaire highly relevant to affected individuals. It can be used where clinic time is short or if patients are unwilling or unable to perform a motor assessment. An adjunct to this project was collaboration with the original author of the EK scale, Birgit Steffensen and Professor Mercuri in Rome to establish a revised scale for use in SMA that included questions on bulbar function, fatigue and hand function. This has resulted in the EK2 -a 17 item questionnaire. A manual has been produced detailing assessment techniques for this patient group. Results: Through the activities of the project coordinator and the network, medical and physiotherapy assessment proformas have been produced and are in circulation. A web-based national clinical database has been developed in order to review the natural history of SMA, facilitate multicentre clinical audit and review services. The database is hosted on a joint website with the North Star project and is due to go live by February 2009. Future developments: It is hoped that with further funding the work can be extended to cover the adult population more comprehensively and new outcome measures can be evaluated and correlations between measures assessed. We gratefully acknowledge the financial support of Jennifer Trust for Spinal Muscular Atrophy and Muscular Dystrophy Campaign.

"We just live from day to day": Tricky transitions for young men with Duchenne Muscular Dystrophy (DMD) and their families

David Abbott
Norah Fry Research Centre, University of Bristol, 3 Priory Road, Clifton, Bristol BS8 1TX, UK

Aim: to explore the tensions around transition to adulthood for a group of young men living with a life limiting illness. Methods: postal survey of families with a son with DMD aged 15+ in 3 English regions. Also, qualitative interviews with 40 young men with DMD and their families. Explored current arrangements, views and experiences of health and social care services, hopes for the future and possible barriers to a successful transition to adulthood. Results: findings suggest that families were reluctant to think about the future whilst at the same time, wanting, as far as possible, opportunities to do the 'normal things of youth and adulthood'. Formal processes of transition planning were rarely successful, if in place at all. Significant barriers to post 16/school services existed and social and relationship opportunities for young people were limited. Conclusion: young people with DMD and their families tread a difficult tightrope between not thinking about the future, alongside trying to ensure that young men have a 'good life'. This necessarily involves some degree of planning for the future. Statutory services were not routinely offering helpful, individualised support. As a result, young men in the study did run the risk of becoming isolated at home and not having age-appropriate and engaging ways of spending their time.

EastEnders to Exercise: the cross talk between basic science and clinical care

Mike Trenell
Newcastle University, School of Biomedical Sciences, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

Muscle contraction is one of the most powerful known modulators of muscle function. Contraction activates signalling pathways which can promote growth and maintain healthy function. A lack of contraction takes away these stimuli, but also activates different pathways, promoting muscle breakdown and reduction in function. Despite the power of muscle contraction, our knowledge of how daily activities such as watching television or exercise influence muscle function of people with neuromuscular disease is very limited. This cannot be better highlighted by three commonly asked questions by people with neuromuscular problems:

1) Is movement safe?
2) What types of movement/exercise should I do?
3) How much should I do?

Our ability to answer these questions will only happen when we bring together teams of basic and clinical researchers. The presentation will outline some of the key questions about exercise and its use in clinical care and also provide a background about how these questions could be addressed.

A currently ongoing trial: exercise training in FSHD based on a model of functional health status

Professor Baziel van Engelen
The Radboud University Nijmegen Medical Centre, 6500 HC Nijmegen, The Netherlands

Symptomatic treatment in FSHD:
As long as we do not have a definite cure for FSHD, symptomatic treatment is the best we can do for our FSHD patients.
Fatigue is a main symptom in FSHD**:**
One of the main symptoms in FSHD is severe fatigue. It is not only a *frequent* (61%) but also a *relevant* symptom in FSHD.
A model of determinants of severe fatigue:
In a longitudinal study, we (Kalkman et al.2007) have built a model of perpetuating factors for fatigue in patients with FSHD, using structural equation modelling. Perpetuating factors contributing to fatigue were physical activity, pain, sleep disturbances and muscle strength (through physical activity). As for the treatment of severe experienced fatigue, theoretically, all these factors could be targeted, but from a practical viewpoint physical activity can probably be influenced most easily. In addition, from all factors, physical activity had the strongest direct influence on experienced fatigue.
Model of severe fatigue as the starting point of a trial in FSHD**:**
Therefore, based on this model, we propose to alleviate severe experienced fatigue by improving the activity level in patients with FSHD either through exercise or cognitive behavioural therapy (CBT). Both treatment modalities have the potential to improve the level of physical activity and will be compared to no specific treatment at all. At present, there is preliminary evidence that strength training of the arm (elbow flexors) and leg (ankle extensor) muscles can improve dynamic strength in FSHD. (Van der Kooi et al., 2004). Only one trial has been done to

investigate low-intensity aerobic exercises in FSHD, indicating improved maximal oxygen uptake and workload without signs of muscle damage (Olsen et al., 2005). Hence, it is still unknown how exercise may influence the individual level of activity, experienced fatigue, social participation or quality of life in patients with FSHD. CBT has not yet been applied in FSHD, but has been proven to alleviate experienced fatigue in Chronic Fatigue Syndrome (Whiting et al, 2001; Prins et al, 2001) and in cancer survivors (Gielissen et al, 2007).

Assessment and management of McArdle disease

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Mc Ardle disease is a rare metabolic myopathy caused by genetic absence of muscle phosphorylase. Patients present with exercise induced cramping and fatigue. Diagnosis is frequently delayed, but in the majority of British Caucasian patients diagnosis can be confirmed by testing for the two hot spot mutations: R50X and G205S, in the PYGM gene. Muscle biopsy demonstrates complete absence of muscle. Phosphorylase, the brain (foetal) isoform is present in regenerating fibres. Affected patients have significantly impaired quality of life due to limited exercise tolerance and many suffer from chronic fatigue which is probably secondary to a sedentary life-style. Increasing dietary carbohydrate, giving pre-exercise glucose and a regular programme of aerobic exercise can be helpful in improving exercise capacity. Advances in translational research may lead to new pharmacological treatments in the future. Testing of any new drug requires an appropriate tissue and animal model. Clinical evaluation of any treatment requires a functional exercise assessment. We use a 12 minute walking assessment which combines a heart rate assessment together with ratings of perceived pain using the BORG scale. This assessment can identify a second wind phenomenon and is easy to perform in a clinical setting.

An Exploratory Study of Physical Activity and Perceived Barriers to Exercise in Ambulant People with Neuromuscular Disease Compared with Unaffected Controls

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The reasons why physical activity and exercise may be beneficial to people with neuromuscular disease have been explained in the previous talks. In this presentation I will discuss what physical activity people with neuromuscular disease are participating in at present and what barriers prevent them from participating more. An exploratory study[1] confirmed that physical activity, approximated by both questionnaire and minutes spent at greater than resting heart rate (minutes above flex heart rate), was less and barriers to exercise greater in number in thirteen ambulatory people with a range of neuromuscular conditions, compared with eighteen healthy controls. Time spent in physical activity, as assessed by the EPIC–Norfolk Physical Activity Questionnaire-2, was 38.4 hours per week (hpw), interquartile range (IQR) 31.7hpw in the neuromuscular group, compared with 62.5hpw, IQR 16.2hpw in the control group, $p<0.004$. Time spent in physical activity as assessed by time above flex heart rate was a mean of 129 (SD 243) minutes per day active compared to 283 (SD 215) minutes per day in the control group, $p < 0.05$. The number of perceived barriers was greater in participants with a neuromuscular condition, with a mean of 7 barriers (S.D.4.2, 95% C.I.4.2–9.3) for neuromuscular disease participants and 3 (S.D.2.1, 95% C.I. 2.3–4.4) for controls ($p<0.05$), and specific barriers differed. As those with different conditions may benefit from intervention with different types and amounts of physical exercise our next step was to assess whether these findings are confirmed for specific conditions and to obtain further details on the types of physical activity those with neuromuscular conditions are participating in. This study is a UK multicentre questionnaire study with Muscle Clinics in Cardiff, Oxford, Leicester, Derby, Nottingham, Oswestry and Newcastle contributing to it. It includes those with facioscapulohumeral, myotonic and limb girdle muscular dystrophy, and will be analysed to assess degree of activity in each condition separately, compared with unaffected controls. Recruitment of patients is almost finished and a preliminary analysis of that data will be presented.

[1] Physical Activity and Barriers to Exercise in Ambulant People with Neuromuscular Disease. N. Davey, K. Tsintzas, M.Phillips. Neuromuscular Disorders 2005, 15: (9-10) TP4.05

Oculopharyngeal Muscular Dystrophy – Pathogenesis and therapeutic strategies

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Oculopharyngeal muscular dystrophy (OPMD) is a late onset, progressive muscular dystrophy caused by the abnormal expansion of a $(GCG)_n$ trinucleotide repeat in the coding region of the poly-(A) binding protein nuclear 1 (*PABPN1*) gene. This results in a polyalanine expansion mutation, which is thought to confer a toxic gain-of-function on mutant PABPN1. There is currently no effective therapeutic treatment for OPMD. Our previous studies

have suggested that compounds that prevent mutant PABPN1 aggregation may be beneficial for OPMD. I will describe how molecular and chemical chaperones alleviate the toxicity of OPMD in cell-based and mouse models of the diseases. In addition, our studies have highlighted the possibility that enhanced apoptosis underlies OPMD pathogenesis. We found that wild-type PABPN1 over-expression could reduce mutant PABPN1 toxicity in both cell and mouse models of OPMD. In addition, wild-type PABPN1 provided some protection to cells against pro-apoptotic insults distinct from the OPMD mutation, such as staurosporine treatment and Bax expression. Conversely, PABPN1 knockdown (which itself is not toxic) made cells more susceptible to apoptotic stimuli. The protective effect of wild-type PABPN1 was mediated by its regulation of X-linked inhibitor of apoptosis (XIAP) protein translation. This normal activity of PABPN1 was partially lost for mutant PABPN1; elevated levels of XIAP are seen in mice expressing a wild-type but not a mutant PABPN1 transgene. This raised the possibility that a compromise of the anti-apoptotic function of PABPN1 might contribute to the disease mechanism of OPMD.

Translational Research in Muscle Channelopathies - Genetics, Disease Mechanisms and Treatment Trials
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The skeletal muscle channelopathies are caused by mutations in key voltage-gated ion channels that determine muscle fibre membrane excitability at rest and during activity. Patients present with isolated or combined clinical phenotypes which can include; periodic paralysis (PP), mild or severe myotonia, cardiac arrhythmias or progressive disabling myopathy. Advances in our understanding of genetics and molecular pathophysiology are paving the way for translation into new clinical trials. As part of the NCG funded muscle channel service (rare neuromuscular disease consortium) we have identified a large number of new mutations allowing correlations between genotype and clinical/electrophysiological phenotype. It is now clear that “gain of function” point mutations in the voltage gated sodium channel (SCN4A) result in delayed/altered channel inactivation and associate with a range of phenotypes including hyperkalaemic periodic paralysis, paramyotonia congenita and pure sodium channel myotonia. In addition, we have recently defined transient neonatal hypotonia as a sodium channelopathy. In contrast, the molecular pathophysiology of the commonest form of periodic paralysis, hypokalaemic periodic periodic paralysis-HypoPP, is not determined. Although mutations in the voltage gated calcium channel CACNA1S frequently cause HypoPP, mutant channel expression studies have shown only subtle channel functional defects not sufficient to account for the sustained membrane depolarisation typical of HypoPP attacks. We have recently shown that “loss of positive charge” point mutations in the S4 regions of both CACNA1S and SCN4A cause HypoPP in 74/83 (90%) of UK families. This finding supports the hypothesis that HypoPP is caused by a non-alpha pore, S4 gating pore leak. Some patients with periodic paralysis have Andersen’s syndrome characterised by PP, cardiac arrhythmias and specific craniofacial features. Most UK Andersen’s families studied have point mutations in the voltage independent potassium channel gene KCNJ2. All KCNJ2 mutations we have expressed induce a dominant negative effect on the tetrameric potassium channel predicting impaired membrane repolarisation. Myotonia congenita is the commonest inherited myotonia and associates with over 70 different recessive or dominant mutations in the dimeric voltage gated muscle chloride channel which determines the resting membrane potential.

Despite major advances in genetics, molecular pathophysiology and diagnostics there are no established treatments that have been rigorously proven to prevent attacks, reduce myopathy and improve quality of life in patients with muscle channelopathies. Recent neuromuscular Cochrane reviews concluded that there is insufficient evidence to recommend any treatment as the standard. Even though certain medications such as acetazolamide and mexiletine are widely prescribed they are not licensed for these indications. Randomised control trial evidence is required to establish standard treatments for patients with muscle channelopathies. The MRC Centre is now completing natural history studies in muscle channelopathies and is commencing funded international multi-centre trials in periodic paralysis and myotonia congenita.

Neurophysiological investigations of neuromuscular channelopathies
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Nerve conduction studies (NCS) and electromyography (EMG) are the main neurophysiological techniques used to investigate patients with suspected neuromuscular channelopathies. While standard NCS are often normal or show only subtle changes, needle EMG can aid in the differential diagnosis by showing (i) myotonic discharges in muscle channelopathies, (ii) neuromyotonic discharges in hereditary or acquired disorders affecting potassium channels in the peripheral nerve or (iii) increased jitter on single fibre EMG in disorder of the neuromuscular junction. The addition of exercise tests has provided additional tools to diagnose muscle channelopathies. The principle of these

tests is to simulate neurophysiologically patterns of post-exercise weakness by monitoring the amplitude of muscle compound action potentials (CMAPs) in response to short or long periods of exercise. Characteristic patterns of abnormalities are linked to defined mutations in muscle ion channels. Recent work has demonstrated that temperature challenges can increase the diagnostic yield in these conditions. Nerve excitability studies, using paradigms pioneered by Hugh Bostock from the UCL Institute of Neurology, have provided a versatile tool to study ion channel function in peripheral nerves of human volunteers, patients and in animal models in vivo and in vitro. The principle of the technique is similar to that of voltage clamp studies: Currents are measured to maintain a constant target amplitude of the compound action potential of a peripheral motor or sensory nerve in response to different stimulus configurations or conditioning stimuli. The technique has potential to (i) discover difference in ion channel functions in normal control subjects, (ii) as a novel diagnostic method for peripheral nerve channelopathies and (iii) as a translational tool for drug discovery studies. Neurophysiological techniques using skin nerve preparations of rodents have emerged as useful method to investigate ion channel abnormalities on a single unit level. These techniques allow more detailed investigations into the mechanisms leading to abnormal ion channel function in myelinated fibres as well as unmyelinated fibres.

Pathogenic mechanism underlying synaptic dysfunction in congenital myasthenic syndromes

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Congenital myasthenic syndromes (CMS) comprise a group of inherited disorders of synaptic transmission at the neuromuscular synapse. As part of the NCG-funded 'Advisory and diagnostic service for rare neuromuscular disease' in Oxford we provide the service for CMS and have identified more than 180 different underlying mutations. A feature CMS is that many patients do respond to treatments, but the type of treatment and its effectiveness will depend upon the underlying pathogenic mechanism. We therefore aim to define the molecular mechanism for each mutation identified and feed this information back to the clinic. This will highlight new mutations in the AChR □-subunit gene, in cholineacetyltransferase (CHAT), and in the most recent protein in which CMS mutations have been characterized, Dok-7. Dok-7 is thought to interact with the juxtamembrane phosphotyrosine binding domain (PTB) motif of MuSK and amplify signalling in the MuSK/AChR clustering pathway. We screened CMS patient DNA for mutations in the *DOK7* gene and identified 17 different recessive mutations in 40 unrelated kinships. All but one were found to have at least one allele harbouring a frameshift in exon 7 of *DOK7* that encodes the C-terminal domain. Analysis of the effects of selected *DOK7* mutations showed altered number, size and complexity of AChR clusters. Wild-type or mutant Dok-7 was introduced into C2C12 myotubes and cell surface AChR was visualised using α-bungarotoxin-alexafluor 594. Over-expression of wild type Dok-7 induced many large AChR clusters, some of which had complex branched shapes. Mutations in Dok-7 always resulted in fewer, less complex, clusters, but the severity varied with each mutation. AChR at the motor endplates in biopsies from patients with DOK7 CMS have normal AChR density, but have small, less well developed neuromuscular junctions. It is likely that the DOK7 mutations impair MuSK signaling crucial for maintaining synaptic structure at the neuromuscular junction and thus lead to the synaptopathy that characterizes this disorder.

Congenital myasthenic syndromes - diagnosis and therapy

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Congenital myasthenic syndromes (CMS) are a genetically and phenotypically heterogeneous group of rare hereditary disorders affecting neuromuscular transmission. The understanding of the molecular basis of the different types of CMSs has evolved rapidly in recent years. After the identification of mutations in the subunits of the nicotinic acetylcholine receptor (AChR), other genes encoding post-, pre- or synaptic proteins were determined as candidate genes for CMS; to date, mutations in ten different genes have been shown to cause CMS. Pathogenic mechanisms leading to an impaired neuromuscular transmission modify AChRs or endplate structure or lead to decreased acetylcholine synthesis and release. However, the genetic background of many CMS forms is still unresolved. A precise molecular classification of CMS type is of paramount importance for the diagnosis, counselling and therapy of a patient, as different drugs may be beneficial or deleterious depending on the molecular background of the particular CMS.

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Poster Abstracts

1. FER1L5: Enhanced expression in dysferlin deficient muscle and defective muscle membrane repair following inhibition highlights this novel ferlin a potential compensatory protein of dysferlin.

Usha Ramachandran[1], Jens Reimann[2], William Lostal[3], Khalil Saleki[1], Louise Anderson[4], Isabelle Richard[3] and Rumaisa Bashir[1].

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Mutations in the dysferlin gene cause limb-girdle muscular dystrophy type 2B (LGMD2B) and Miyoshi myopathy (MM) collectively termed the dysferlinopathies. Dysferlin mutations result in the sarcolemmal deficiency of dysferlin protein in patient muscle which is also characterized by plasma membrane lesions and defective membrane repair. Dysferlin is predicted to function in vesicle trafficking pathways and sarcolemmal repair although the mechanisms are still poorly understood. Following a membrane disruption dysferlin accumulates at the wound site in normal muscle fibers and these cells repair their torn membranes rapidly in contrast to dysferlin deficient muscle fibers which are defective in membrane resealing. It has been proposed that dysferlin present at the sarcolemma and in vesicles mediates in the generation of a "membrane patch" at the disruption site for resealing.The research in our laboratory has focused on identifying and characterising compensatory proteins of dysferlin. Through bioinformatic analysis we have previously reported the existence of three novel ferlin genes which have been designated *FER1L4*, *FER1L5* and *FER1L6* respectively. By performing homology modeling and sequence analysis of ferlin C2 domains we have shown that some of these domains have distinct features allowing the *in-silico* functional subgrouping of the ferlin proteins into two groups, dysferlin-like and otoferlin-like. Dysferlin, myoferlin and FER1L5 have been sub-grouped together as the dysferlin-like ferlins. Since we observed high gene expression of FER1L5 in skeletal muscle which is also elevated during myoblast fusion like dysferlin and myoferlin we hypothesized that FER1L5 may have a role in muscle membrane fusion. To test this hypothesis we have examined the distribution of FER1L5 relative to dysferlin and myoferlin, in cultured muscle cells and the role of FER1L5 in myoblast fusion and membrane repair. We have previously reported that FER1L5 is present in vesicles which share similar properties with dysferlin and myoferlin vesicles. We will now present data implicating FER1L5 in membrane repair. Consistent with this finding we will also show that the expression of FER1L5 is enhanced in dysferlin deficient muscle. The data emerging from our studies suggests that FER1L5 operates in similar vesicular trafficking pathways as dysferlin and may act as a compensatory protein in dysferlin deficiency.

2. Identifying Novel Genetic causes for Bethlem Myopathy and Ullrich Congenital Muscular Dystrophy

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Collagen VI disorders form a clinical spectrum of muscle disease from Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD) to autosomal recessive myosclerosis myopathy. However, genetic investigations in muscle diseases which clinically resemble collagen VI disorders reveal mutations in the classical collagen VI loci in only approximately 50% of cases, indicating genetic heterogeneity. We wanted to investigate the underlying pathological mechanism in these diseases by elucidating the genetic pathology underlying the remaining 50% of patients in two well defined cohorts. As a result of our ongoing studies into the collagen VI diseases we have a panel of 20 patients who have a clinically characterised muscle disease which resembles collagen VI disease. However, extensive mutation detection at the classical collagen VI structural loci has been unable to uncover any pathogenetic mutations. Whilst we cannot rule out cryptic mutations in these genes, it is more likely that most if not all of these patients have mutations in other loci which produce a clinically related muscle disease. We performed molecular genetic analysis on an assembled list of candidate loci which may be involved in these diseases including associated extracellular matrix components (such as biglycan, decorin, tenascin-X, collagen V and integrin alpha-9) and enzymes involved in collagen biosynthesis (such as lysyl hydroxylase and collagen Prolyl 4-hydroxylase). Since experience tell us that disease causing genes can often not be predicted, collaboration with colleagues in Turkey and Saudi Arabia have enabled us to assemble a second patient group, a novel collection of large consanguineous families from segregating diseases which resemble collagen VI related pathologies. Targeted linkage analysis in these families indicated whether they were segregating mutations in classical collagen VI loci. Those families which did not link to the classical collagen VI loci underwent further, genome wide, linkage analysis to identify the genomic regions containing putative loci which, when mutated, are causative in these disorders.

3. Investigating the molecular genetic basis of multiple respiratory chain complex deficiency

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Multiple respiratory chain deficiency (MRCD) is a complex mitochondrial disease characterised by the reduction in activity of multiple respiratory chain complexes of oxidative phosphorylation system (OXPHOS). Mutations in several mitochondrial DNA (mtDNA) and nuclear genes involved in mitochondrial translation have recently been reported in MRCD patients, indicating that MRCD may be caused by a generalized defect in mitochondrial translation. In this study we investigated 37 MRCD individuals who had previously undergone full mitochondrial genome screening to exclude mtDNA mutations, and in whom both mtDNA depletion and mtDNA rearrangements had also been excluded. Our study investigated to what extent translational repression occurred in patients with MRCD and whether MRCD could be attributed to nuclear mutations in three mitochondrial translation elongation factor genes (*EFG1*, *EFTu* and *EFTs*) and one mitochondrial ribosomal subunit gene (*MRPS16*). *In vivo* labeling of mitochondrial polypeptides in two of five patient cell lines showed a significant reduction in mitochondrial translation. The results indicate that MRCD in our patients is not necessarily caused by mitochondrial translational repression. DNA sequencing analysis of 37 MRCD patients revealed three heterozygous non-synonymous variants G1990A (p.V664I), T860A (p.L287H) and C34T (p.Y12H) detected in *EFG1*, *EFTs* and *MRPS16,* respectively. Further analysis of the observed amino acid substitutions indicated a potentially pathogenic effect for Y12H found in *MRPS16* whilst the remaining substitutions did not occur in evolutionary conserved positions. The absence of unequivocal, disease-causing mutations in *EFG1*, *EFTs*, *EFTu* and *MRPS16* in our patient cohort would suggest further genetic heterogeneity in patients with MRCD.

4. Mutations in *TACO1* cause juvenile onset Leigh-syndrome with optic atrophy

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Objective: We describe the clinical presentation in a single family caused by mutations in the translation activator of cytochrome c oxidase 1 (*TACO1*) gene, suggesting a novel function in mammalian mitochondrial translation. Background: Leigh syndrome and deficiency of cytochrome c oxidase (COX), the terminal enzyme in the mitochondrial respiratory chain may be caused by mutations in different COX assembly genes or COX subunit genes. Design/Methods: Here we report the clinical, neuroimaging, muscle biopsy and genetic findings of five members of a big consanguinous family affected by a juvenile-onset Leigh syndrome and optic atrophy. Results: The index patient developed a slowly progressive Leigh syndrome. Neurological examination at 10 years of age indicated bilateral optic atrophy and spastic tetraparesis with mild mental retardation. Laboratory analysis detected increased lactate levels in serum and CSF. Brain MRI revealed bilateral, symmetric hyperintense lesions of the basal ganglia, typical for Leigh syndrome. Muscle biopsy showed generalized COX deficiency. Biochemical analysis of the respiratory chain enzymes in skeletal muscle and fibroblasts confirmed a severe isolated COX deficiency. The patient's 3 siblings and one cousin presented with similar, but milder manifestation, and most patients preserved ambulation into the twenties. We identified a specific defect in the translation of the COX I subunit in fibroblasts from the index patient and the defect was mapped to chromosome 17q. A homozygous single base pair insertion causing a premature stop was identified in *CCDC44,* which we called *TACO1*. Conclusions/Relevance: The clinical presentation of *TACO1* mutations in our family is a juvenile-onset Leigh syndrome and optic atrophy. Screening for *TACO1* mutations in further patients is recommended. Furthermore, the detection of a new pathomechanism, specifically affecting translation of a single mitochondrial-encoded protein (COX I) opens new insights to search for possible gene defects in human mitochondrial disease.

5. Autosomal dominant Progressive External Ophthalmoplegia (adPEO) due to mutations in the *PEO1* gene: a clinical, histochemical and molecular survey of 30 patients

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Progressive External Ophthalmoplegia (PEO) is a common manifestation of patients with mitochondrial myopathy, characterised by a progressive paralysis of the extraocular muscles leading to ptosis and ophthalmoparesis. The molecular genetic defect involves either primary mutations in the mitochondrial genome (mtDNA), commonly single, large-scale mtDNA rearrangements or mtDNA point mutations, or mutations in nuclear-encoded mtDNA maintenance proteins leading to secondary mtDNA changes such as multiple mtDNA deletions. Mendelian forms of PEO are caused by mutations in five known genes – *POLG*, *POLG2*, *SLC25A4* (*ANT1*), *OPA1* and *PEO1*, which encodes Twinkle, the mtDNA helicase. Patients with adPEO and PEO1 mutations typically present with extraocular muscle involvement alone, with little evidence of the clinical heterogeneity seen in other patients who present with multiple mtDNA deletions and mutations in other mtDNA maintenance genes (e.g. *POLG*). Here we present a cohort of 30 patients from 22 different families in whom we have identified pathogenic *PEO1* mutations at three Mitochondrial Diagnostic Centres in Oxford, Munich and Newcastle. We review the clinical presentations, histochemical and mtDNA findings and distribution of mutations – including 7 unreported *PEO1* variants - throughout the gene. As expected, ptosis (29/30 patients) and ophthalmoparesis (28/30) were almost universal clinical features, with 57% (17/30) reporting fatigue and 37% (11/30) having mild proximal myopathy. Features consistent with CNS involvement (migraine, epilepsy, visual impairment) were rarely described, however in 27% (8/30) of the patients mild cardiac abnormalities were reported. Whilst *POLG* remains the most commonly mutated gene in patients with multiple mtDNA deletions in muscle, the contribution of *PEO1* mutations to this cohort is likely to be underestimated.

6. Nuclear-mitochondrial DNA sequences: implications for mitochondrial genetics and diagnostics

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The integration of mitochondrial DNA (mtDNA) into the nuclear genome is a common mechanism among many taxa. The majority of nuclear-mitochondrial DNA sequences (NUMTs) reside in the nuclear genome as pseudogenes. The accidental amplification of NUMTs can pose serious problems when investigating mitochondrial diseases. Mitochondrial genome disease-associated biomarkers must be rigorously authenticated to eradicate any contamination with paralogous nuclear pseudogenes. Previous studies have explained how a gene is transposed into the nucleus, but fail to explain the mechanism controlling gene loss from mtDNA. Sequence analysis was performed to investigate an existing database of 263 known mtDNA deletions to the nuclear genome using BLASTN. Automated computational techniques were developed to analyse the resulting data generated from the BLAST analysis. Homologous sequences detected in the nuclear genome were collated to generate a consensus list of Human NUMTs. The size and number of NUMTs varies greatly among species, being highly abundant in plant genomes and absent in others such as fish belonging to the order *Tetraodon*. These techniques can then be applied to a multi-genome wide study to highlight the mechanisms involved in mtDNA transfer and integration.

7. Is the *mdx* mouse a suitable model for the neurological aspects of Duchenne muscular dystrophy?

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In the absence of dystrophin, Duchenne muscular dystrophy patients can have a range of neurological complaints, including low IQ, night blindness and auditory processing problems. The dystrophin glycoprotein complex (DGC) is understood to be the functional unit of dystrophin in all cellular contexts, and in most parts of the body dystrophin shares the core of the DGC with a heterodimeric partner, alpha-dystrobrevin. This is particularly true in the brain, which is the major site of alpha-dystrobrevin expression. Alpha-dystrobrevin, however, is subject to complex patterns of alternative promoter use, alternative splicing, and alternative polyadenylation, generating a large number of functionally distinct isoforms. We show that mice and rats specifically lack one promoter and one coding exon of alpha-dystrobrevin which are present in most other mammals. The promoter (which gives rise to isoforms alpha-dystrobrevin-4 and -5) and the coding exon (which encodes a novel syntrophin binding site) are used almost exclusively in the brain in humans, where they contribute to a substantial proportion of alpha-dystrobrevin molecules produced. We argue that as mice and rats lack over half of the brain alpha-dystrobrevin isoforms present in humans, this makes them poor models for the study of the DGC and its disorders in the central nervous system.

8. Registry of Outcome Measures; a tool for muscle research and trials

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Objective: To provide a valuable, web based self help tool for choosing outcome measures (OMs) for clinical studies and trials in neuromuscular disease (NMD). Background: The choice of OMs for clinical studies and trials in muscle disease is an important one. Making the right choice is likely to be improved by having as much information on the available OMs and their characteristics as possible. However finding this information can be time consuming. Even worse each study that does this may duplicate the effort. At present imperfect choices may have been made in previous studies and even studies for the same disease and intervention have used different OMs making meta-analysis or comparison of findings difficult. Methods: With European funding and as part of the TREAT NMD consortium we have launched a web based registry which catalogues potentially useful OMs for NMDs. Information about OMs can be entered by investigators for the benefit of the research community. Investigators can browse the OMs, read about their basic characteristics and find links to manuals, references and other resources that will facilitate the choice and use of these OMs. Results: We have a growing number of OM records. We have a forum for discussion of the OMs and we are now disseminating ideas for the systematic review of the OMs so as to allow an informed choice of OMs for particular NMD studies and trials. The ROM can be accessed at http://www.researchrom.com/ Conclusion: We are confident that the ROM will become a valuable tool for muscle research and an important part of the effort for promoting translational research.

9. The effect of the host muscle environment on donor satellite cell-derived skeletal muscle regeneration.

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Satellite cells, located under the basal lamina of adult skeletal muscle fibres, have stem cell properties, being able to regenerate skeletal muscle and to reconstitute the satellite cell pool following their grafting into irradiated *mdx*-nude host muscles. However, satellite cell engraftment within non-irradiated *mdx*-nude host muscle is minimal. Other injury regimes have been shown to augment donor-derived skeletal muscle regeneration, but no systematic comparison has yet been made between the different injury regimes. Here, we compare the extent of donor-derived satellite cell skeletal muscle regeneration in host muscles that have been either not treated, or irradiated with 18Gy, or injected with snake venom, or cryodamaged, prior to grafting. Our data suggest that ablation of host satellite cells is crucial for efficient donor-derived skeletal muscle regeneration, although other factors appear to be required for optimal engraftment.

10. The role of extracellular matrix components on satellite cell function.

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Muscular Dystrophy (MD) is a heterogeneous group of genetic disorders that leads to progressive muscle fibre degeneration and necrosis, followed by muscle weakness, finally resulting in failed muscle regeneration. Dystroglycanopathies are a group of MDs, in which α-dystroglycan protein is hypoglycosylated leading to reduced binding of the extracellular matrix (ECM) to the intracellular cytoskeleton of muscle fibres, thereby causing muscle instability and defective signalling with the surrounding environment. Mutations in the putative glycosyltransferases *FKRP* or *LARGE* lead to dystroglycanopathies. Even though the pathology of the disease is well defined, the consequences of the mutations in *FKRP* and *LARGE*, and the associated hypoglycosylation of α-dystroglycan on muscle regeneration have never been studied. We aim to identify, whether there are defects in the adult stem cell population of skeletal muscle, referred to as satellite cells (SCs), in recently generated $FKRP^{/-}$ and $LARGE^{myd-/-}$ mouse models that block muscle regeneration, or if satellite cells are unaffected by the mutations in these models and their function is inhibited by the pathological environment. Firstly, we compared the effect of different ECM proteins on SC activation, proliferation and differentiation *in-vitro*. We investigated SC behaviour on different substrates using Fibronectin, Laminin-1 and Matrigel. Here we report our initial findings based on satellite cell cultures isolated from single fibres of wild type mice. In the next step, we will compare our results to the proliferative behaviour of SCs isolated from *FKRP* and *LARGE* mutant mice. Exploring the role of ECM components on SC proliferation and differentiation is important to further understand and potentially mimic the stem cell niche, therefore improving the efficiency of stem cell engraftment.

11. Immunohistological intensity measurements as a tool to measure sarcolemma associated protein expression

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The quantification of sarcolemma-associated protein levels in muscle biopsies is of particular relevance to the disease process of several muscular dystrophies, but is complicated by the relative low levels of protein present. We have developed a comparative method to evaluate differences in expression of these proteins by using immunohistological techniques and analysis software readily available. Captured images are analysed by the operator using an imaging system to measure intensity corresponding to the expression of these proteins. To validate this system, transverse cryosections of skeletal muscles taken from biopsies from patients suffering from Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD) and normal controls were immunostained with antibodes to dystrophin, β-dystroglycan, α-sarcoglycan, utrophin and spectrin and analysed. DMD patients' biopsies are characterised by the lack of dystrophin protein, while BMD patients show decreased amounts compared to normal controls. We were able to show that this system is able to accurately distinguish between the different sets of patients. We are confident that this method will have added value to the techniques routinely used in diagnostic laboratories, in particular in assessing the efficacy of potential treatments designed to increase amounts of dystrophin protein.

12. Pax3/Pax7 transcriptional activity is required both *in vitro* and *in vivo* for muscle differentiation.

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Pax3 and Pax7 are paired-box transcription factors with common and divergent functions that are involved in developmental and adult myogenesis. They are transcriptionally active in satellite cells, the main cell source in muscle regeneration, both in their quiescent and proliferative phases, whilst they become silenced upon differentiation into muscle fibres. Constitutive expression of Pax3 or Pax7 either in satellite cells, or in C2C12 myoblasts lacking either protein, causes increased cell proliferation and decreased cell size. Accordingly, expression of dominant-negative constructs leads to reduced cell division, combined with a dramatic increase in cell size. Interestingly, following grafting into irradiated muscles in *mdx*-nude host mice, C2C12 cells that had been retrovirally infected with Pax3/Pax7 constructs are able to contribute to muscle regeneration, but, if dominant-negative constructs are constitutively expressed, the myogenic cells do not differentiate into myofibres. These findings show that Pax3/Pax7 transcriptional activity is required for myogenic differentiation, and provide evidence for a novel role in their coordination of cell growth and division.

13. Diagnosis of Bethlem Myopathy: a Biochemical Approach

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Collagen VI is component of the extracellular matrix and comprises three different peptide chains a1(VI), a2(VI) and a3(VI), each encoded by distinct genes: *COL6A1*, *COL6A2*, and *COL6A3*, respectively. Mutations in any of these genes leads to Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD). The gold standard diagnostic test for BM and UCMD is molecular genetic testing, however the large size of the collagen VI genes (107 coding exons, 150 kb genomic DNA) makes it expensive and time-consuming. Immunohistochemistry (IHC) on muscle biopsy is useful in the diagnosis of UCMD where loss of labelling is strongly suggestive of mutation in one of the collagen VI genes. This test is much less informative for BM as the labelling is frequently normal or only subtly reduced. Currently, the most reliable test to guide molecular genetic testing for BM is immunofluorescent labelling of collagen VI in fibroblast cultures. Interpretation of data still retains a degree of subjectivity requiring considerable expertise during examination. In an effort to strengthen the existent diagnostic capabilities we appraised immunoblot analysis as an alternate means to quantify the expression of collagen VI in muscle and fibroblasts. This was undertaken in skeletal muscle and skin fibroblasts from patients with molecular diagnosis of BM or UCMD and disease controls where genes other than *Col6* have been implicated. The

development and validation of a quantitative and less subjective assay could provide a useful diagnostic test to recognize subtle collagen VI abnormalities and guide molecular testing for BM.

14. A new approach for the detection of collagen VI defects: FACS analysis may be a useful tool

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Background & aim: Collagen VI is a major extracellular matrix (ECM) protein and mutations in COL6A1, COL6A2 and COL6A3 genes cause Ullrich congenital muscular dystrophy (UCMD) and Bethlem myopathy (BM). UCMD shares some clinical features with BM, such as contractures but displays a more severe course. Also recently some patients have been reported to have a collagen VI related disorder without carrying any mutation in COL6A genes. Currently, there are 2 routine methods for the diagnosis of collagen VI disorders: 1. Double immunofluorescence labelling in muscle 2. Analysis of collagen VI production by fibroblasts. Double labelling technique is not sensitive enough to detect all BM cases, since milder cases are indistinguishable from controls. Often muscle samples are not available. Analysis of collagen VI production from fibroblasts is difficult to assess and it can be subjective. An added problem is the fact that this technique is very time consuming (up to 3weeks). The aim of our study is to find out if the Fluorescence Analysis Cell Sorting (FACS) analysis may be useful technique for the detection of collagen VI abnormalities alone or in combination with current techniques. Methods: Fibroblasts from explants of skin biopsies (3 molecularly confirmed UCMD patients, 3 BM patients and 5 controls) were grown in Dulbecco's modified Eagles medium, containing 20% fetal bovine serum, L-glutamine and antibiotics (penicillin, streptomycin and neomycin), in 5% CO2 at 37 ˚C. L-ascorbic acid phosphate (50µl/ml) was added 24hours before the test. *Immunostaining of fibroblasts*:Cells were harvested with a non enzymatic cell dissociation solution and fixed with 2% paraformaldehyde for 5 min. Then cells were immunolabelled with primary collagen VI antibody (Chemicon, MAB1944). Cells were treated in 2 ways: Permeabilisation diluted in PBS or without permeabilisation 0.02%Tween20/PBS for 1 hour. After washing 3 times with PBS (with or without 0.02%Tween20), PE conjugated with anti-mouse was applied for 30 min. Finally, cells were filtered before the FACS analysis. Results and findings:No differences in the number of positive cells were found between control fibroblasts (98.2±0.28%). UCMD patients showed a marked reduction of collagen VI expression (around 70%), while BM patients showed variable degrees of reduction (ranging between 30 and 50%). Conclusion: FACS analysis may be a useful tool for the detection of collagen VI abnormalities in conjunction with current routine methods. Also unlike the routine culture and immunocytochemistry methods, this technique is quantitative and considerably less time consuming and expensive.

15. Dynamic DNA in myotonic dystrophy

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Myotonic dystrophy type 1 (DM1) is the most common of about 20 diseases associated with inheriting an abnormally large unstable DNA simple sequence repeat. In DM1 patients these repeats occur in the non-coding region of the *DMPK* gene. Most unusually, the number of transmitted repeats is genetically highly unstable. An increase in the number of repeats passed on from one generation to the next causes a decreasing age of onset, whilst an increase in the number of repeats throughout the lifetime of the patient contributes toward the progressive nature of the symptoms. New quantitative data, collected from small pool PCR analysis of allele length in blood cells from 145 DM1 patients reveals the extent and nature of the variation of allele length within and between patients. We are developing mathematical models using a range of deterministic and stochastic simulation techniques that capture the key features of the mechanism underlying allele length evolution. These models have biological parameters, some of which can be measured experimentally and some of which must be inferred indirectly. Parameter estimation (recovering unknown parameters from experimental data) and model selection (rating competing models that are attempting to describe the biological processes) are important steps towards obtaining an explanatory model that can be used for simulation and prediction. Bayesian inference is being used increasingly in genetics as it provides a solid foundation for parameter estimation and model selection and we are developing modern Bayesian techniques involving Markov chain Monte Carlo in order to calibrate our models

against the biological data. These models can then be used to predict age of onset and severity of the symptoms with greater precision. This has potential for improving prognostic information for patients as well as providing a deeper understanding of the underlying biological process.

16. How much dystrophin is required to restore normal muscle function?

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Duchenne muscular dystrophy (DMD) is a progressive muscle degenerative disorder caused by mutations in the gene encoding for the dystrophin protein, which provides a crucial structural link between the extracellular matrix and the internal cytoskeleton and increases sarcolemmal stability during muscle contraction. A potential therapy for DMD consists of using antisense oligonucleotides to redirect gene transcript processing in order to correct the reading frame of the dystrophin gene when it is disrupted by mutations. A number of studies have shown that a phosphorodiamidate morpholino oligmer (PMO) is able to skip the mutated exon in the *mdx* mouse model of DMD and restore expression of dystrophin. However, a crucial weakness in these studies is the limited evaluation of muscle function following treatment with PMOs. Therefore, we conducted a comprehensive study of muscle function following intramuscular delivery of PMO, which included isometric force measurements and most importantly resistance to eccentric contraction mediated damage. Furthermore, by varying the dose and volume administered to the muscles of *mdx* mice, we were able to assess the relationship between dystrophin expression and improvements in muscle function. Interestingly, we found a highly significant correlation between the number of dystrophin positive fibres and improved resistance to eccentric contractions, but no correlation with specific force. These findings clearly establish the need to conduct stress inducing protocols when assessing the efficacy of potential treatments for DMD, and indicate the necessary levels of dystrophin required to improve muscle function in patients with DMD.

17.Epidemiology of Mitochondrial Point Mutations

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Mitochondrial DNA (mtDNA) mutations are a major cause of genetic disease, but their prevalence in the general population has not been previously reported. We determined the frequency of ten mitochondrial point mutations in 3168 neonatal-cord-blood samples from sequential live births, 27tilized27 matched maternal-blood samples to estimate the *de novo* mutation rate. DNA analysed was from the North Cumbria Community Genetics (NCCGP) program, which collected samples from the north west of the UK and had a high participation rate. Screening of mutations 27tilized Sequenom MALDI-TOF technology. Mitochondrial DNA mutations were detected in 15 offspring (0.54%, 95% CI = 0.30-0.89%). Of these live births, 0.00107% (95% CI = 0.00087-0.0127) harboured a mutation not detected in the mother's blood, providing an estimate of the *de novo* mutation rate. The most common mutation was m.3243A→G. m.14484T→C was only found on sub-branches of mtDNA haplogroup J. In conclusion, at least one in 200 healthy humans harbours a pathogenic mtDNA mutation that potentially causes disease in the offspring of female carriers. The exclusive detection of m.14484T→C on haplogroup J implicates the background mtDNA haplotype in mutagenesis. These findings emphasise the importance of developing new approaches to prevent transmission.

18.IBM-like phenotype evolving from steroid-responsive inflammatory myopathy with atypical inflammatory characteristics

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We describe two patients presenting with clinical and laboratory features of an inflammatory myopathy not typical of either polymyositis (PM) or sporadic inclusion body myositis (sIBM), as currently defined. Both patients had CK levels >2000 U/L and EMG features including increased insertional activity and myopathic discharges usually seen in acute inflammatory myopathies. Both also responded initially to steroids but then evolved an IBM phenotype with relative steroid resistance. Biopsies from both patients showed features typical of sIBM, including rimmed vacuoles, COX negative fibres and sarcoplasmic inclusions on EM. However, the inflammation in both cases initially comprised significant numbers of perimysial B-cells and plasma cells, as well as cytotoxic T-cells, together with elements of the membrane attack complex, indicating a significant autoimmune component to the immunopathology in the early phase of the disease. Serial biopsy in one case showed a progressive reduction in inflammation and an increase in rimmed vacuoles and dystrophic features over time. Tests for recognised myositis-

associated and myositis-specific antibodies were negative but both patients demonstrated several distinct bands of similar molecular weight. These autoreactivities may identify muscle autoantigens bound to HLA Class I molecules on the muscle surface membranes. Both cases fulfilled the current operative pathological criteria for sIBM but had an atypical phenotype at presentation and unusual inflammatory characteristics. Cases of this type may represent a condition intermediate between PM and IBM or a stage in the evolution of the classical sIBM phenotype.

19. Cardiac Involvement in Adult Pompe Disease

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Introduction: Adult Pompe disease (Acid Maltase Deficiency, Glycogen Storage Disease type II) is characterised by a progressive, predominantly central and proximal myopathy, with diaphragmatic involvement presenting as respiratory compromise. In the infantile and juvenile onset cases cardiomyopathy is common and in infants can be the presenting feature. However, cardiac involvement in adult onset cases is not usually considered. We report four cases where dilated cardiomyopathy was a significant factor in disease manifestations. Patients and methods: We currently have 29 patients under review with Pompe disease proven by finding a reduced level of alpha-glucosidase in white cells. All patients are symptomatic with either myopathy and/or respiratory involvement. As part of the assessment before starting enzyme replacement therapy, all patients have a 12 lead ECG and a standard echocardiogram. Where cardiac disease is found further tests are done. Of the 29 patients studied, 7 have Asian origins. Results: Of those screened, 5 have been found to have abnormal tests. One had left ventricular hypertrophy on ECG and echocardiogram thought to be due to their long standing hypertension. Of the other 4, they all had a dilated left ventricle with mild reduction in ejection fraction in two cases. One patient had atrial fibrillation. Of these 4 cases 2 were of Asian origin and all had symptom onset before the age of 21 years, Discussion: While this is a small patient cohort, and we cannot be 100% sure that there are not any other causes for the cardiac disease despite full investigation, we feel that there are some cases of early onset adult Pompe disease where cardiac involvement may occur. We would recommend that screening for cardiac disease is undertaken as part of the routine screening for Pompe patients.

20. High incidence of Vitamin D Deficiency in Patients with Pompe Disease.

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Introduction: Pompe disease (acid maltase deficiency, glycogen storage disease type II), caused by a deficiency of the lysosomal enzyme alpha-glucosidase, presents clinically in adults with a progressive proximal myopathy, usually with the lower limbs more affected than the upper, with or without diaphragmatic involvement. In some patients the respiratory symptoms can be more prominent than those attributable to skeletal muscle involvement. In addition, a few patients can also have difficulty in swallowing. As part of our protocol for assessing patients prior to starting enzyme replacement therapy, we performed several nutritional investigations including Vitamin D status. We were particularly interested in vitamin D levels because of the influence these may have on overall muscle function. Patients and methods: Levels of $25(OH)_2$ vit D2 and 3 were assayed using standard tandem mass spectrometry techniques Normal levels were taken as a total of both forms of vitamin D above 20 ng/ml with border line levels being from 15-19 ngs/ml inclusive. All patients had a standard dietary assessment as part of their history. 29 patients are under review with Pompe disease and results are available for 28 of these. Of the 28 only 5 have some swallowing problems and 1 of these is fed via a “PEG”. No patients had a history of fractures suggesting osteoporosis and none were on supplements. Results: Of 29 patients tested 14 had low levels and three had borderline levels. Subsequent review did not reveal any relationship to severity of disease, ethnicity, gender, or dietary preferences. All patients had calcium and phosphate levels within the normal range, although in most patients these were at the lower end of normal. Discussion: The cause of these findings is unclear. However, poor dietary intake and immobility leading to decreased exposure to sunlight may be two factors. As vitamin D deficiency can cause muscle weakness and bone disease we suggest that measurement of vitamin D with replacement therapy when low levels are found should become standard management for all Pompe patients.

21. Mitochondrial Copy Number in Human Oocytes and Embryos

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Mitochondrial DNA (mtDNA) diseases are an important cause of muscle disease and are often caused by mutations in mitochondrial genes. MtDNA is strictly maternally inherited, so that a woman with mtDNA disease due to a mitochondrial DNA mutation is at significant risk of passing the defect to her children. It is not possible to predict how severely affected her children will be, however, as the level of mutant mtDNA that is transmitted to her offspring can vary dramatically. This is due to the mitochondrial genetic bottleneck which restricts the number of mtDNA molecules passed to the next generation. This is thought to involve a massive reduction in the mtDNA content although the precise developmental stage at which this occurs in humans is not known. Therefore, we have used quantitative realtime PCR to determine the mtDNA content in human oocytes and preimplantation embryos at different stages of development to try and identify the mitochondrial genetic bottleneck. This analysis revealed that human oocytes and embryos contain vast numbers of mtDNA and that the mtDNA content is extremely variable. Despite this huge variation, however, the average mtDNA content did not differ significantly at each developmental stage. These results indicate that there is no sharp reduction in the mtDNA content during the developmental stages studied and suggest that the mitochondrial genetic bottleneck is occurring at an earlier stage of development.

22. Investigating mitochondrial DNA mutations in Satellite Cells

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Mitochondrial myopathies are a group of progressive muscle disorders caused by mutations – either single base substitutions or large-scale rearrangements - in the mitochondrial genome (mtDNA). Whilst mtDNA point mutations tend to be maternally-inherited, large-scale mtDNA deletions arise sporadically, yet it is not currently known at which stage of development the mtDNA deletion arises. The use of eccentric contractions to damage muscle and thus induce muscle stem cell (satellite cell) activation has been suggested as a possible intervention for these patients. In the presence of heteroplasmy, it is hoped this will favourably shift the balance of deleted to wild type mtDNA, thereby decreasing mtDNA mutation load in affected tissues. However, the absence of sporadic mtDNA mutations in satellite cells needs to be confirmed, as previous investigations examining mtDNA deletions in satellite cells have focused on myoblasts, the cultured progeny of these satellite cells. Here we describe the use of Fluorescently Activated Cell Sorting (FACS) using NCAM to isolate satellite cell samples for the analysis of mtDNA mutation load. NCAM-positive cells from patients with the m.3243A>G mutation, and those with single, large-scale mtDNA deletions were chosen for investigation. Using a sensitive, fluorescent PCR-RFLP assay to determine mutation load, we were able to detect the m.3243A>G transition at a level of 50% in the satellite cell pool obtained from a patient previously shown to harbour this mutation in muscle homogenate at 56% mutation load. We are currently using an mtDNA deletion-specific real-time PCR assay to determine the exact level of mtDNA deletion in the satellite cells of a patient with CPEO due to a single, large-scale mtDNA deletion. Potentially these techniques will allow us to determine exactly which patients will benefit from attempts to activate satellite cells in order to shift the balance of wild type to mutated mtDNA in muscle.

23. Morphological, stem cell and myosin abnormalities in the dystrophic embryo reveal an embryonic basis for muscular dystrophy

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Examination of embryonic myogenesis of two distinct but functionally related, skeletal muscle dystrophy mutants (*mdx* and *cav-3*$^{-/-}$) establishes for the first time that key elements of the pathology of DMD and LGMD type 1C originate in disruption of the embryonic cardiac and skeletal muscle patterning processes. Disruption of myogenesis occurs earlier in *mdx* than *cav-3*$^{-/-}$ consistent with the milder phenotype of LGMD-1c and the earlier (E9.5) expression of dystrophin. Myogenesis is severely disrupted in *mdx* embryos with developmental delay, myotube morphology and displacement defects, and aberrant stem cell behaviour. In *cav-3*$^{-/-}$ there is a more restricted phenotype comprising hypaxial muscle defects, excess, malformed hypertrophic myotubes, 2-fold increase in myonuclei and reduced FMyHC content. Both have cardiac defects and both exhibit aberrant stem cell behaviours including, hyperproliferation and apoptosis of cultured embryonic myoblasts and depletion of pax-7+ cells. In double mutant (*mdxcav*) embryos these phenotypes are exacerbated. These data establish a key role for dystrophin in early muscle formation and demonstrate that caveolin-3 and dystrophin are essential for correct fibre-type specification and emergent stem cell function. These data plug a significant gap in the natural history of MD and will be invaluable in establishing earlier diagnosis for DMD/LGMD and in designing earlier treatment protocols leading to better clinical outcome for these patients

24. Late-onset Pompe disease with normal muscle biopsy findings

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We describe a 44-year-old man who presented in 2004 with limb weakness which developed over seven years. He had calf hypertrophy and limb girdle weakness on examination and a serum creatine kinase of >700 IU/L. Electromyography (EMG) showed mixed denervation and myopathic abnormalities. Quadriceps muscle biopsy showed non-specific changes and a clinical diagnosis of limb-girdle muscular dystrophy (LGMD) was made. The patient himself suggested a diagnosis of Acid Maltase deficiency (AMD). The diagnosis was confirmed initially by demonstrating vacuolation in the patient's lymphocytes and significantly decreased and leukocyte ox-glucosidase (GAA) activity. The genetic mutations giving rise to the enzyme deficiency have now been elucidated and may help explain the late presentation. We conclude that late-onset AMD should be considered in the differential diagnosis of all individuals presenting with the clinical features of LGMD.

25. An important improvement of severe respiratory failure secondary to multidisciplinary management in a case of Carnitine palmitoyltransferase II (CPT II) deficiency

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Background and objective: Carnitine palmitoyltransferase II (CPT II) deficiency is the most common cause of exercise-induced rhabdomyolysis, myoglobinuria, renal failure, proximal muscle weakness and pain in young adults. A lack of this enzyme impairs mitochondrial oxidation of long-chain fatty acids. The respiratory failure during infections is a rare but potentially life-threatening complication of the CPT II deficiency. We report a case of a 43-year-old male, who developed, after a respiratory infection, a severe respiratory failure and showed a striking improvement of muscular and respiratory aspects through a multidisciplinary approach. Case report: In March 2008 a 43-year-old chinese male developed a rapidly progressive dyspnea and was admitted to the Emergency Area of Niguarda Cà Granda Hospital. His medical history was positive for CPT-II deficiency with onset in adolescence, characterized by episodes of weakness after exercise. The family history was negative for neuromuscular disorders. After an initial approach with non invasive ventilation without any clinical improvement, the patient was intubated and, then, tracheostomized. At admission in our Centre the neurological examination showed moderate/severe proximal weakness (Medical Research Council scale: 3-4) associated with muscular hypotonia at four limbs. The patient was dependent by invasive ventilation. An appropriate management with mechanical ventilatory support, in-exsufflator technique, motor rehabilitation and dietary restriction (low fat increased carbohydrate intake and carnitine and riboflavin supplements) brought about complete resolution with an excellent outcome. Discussion: Decreased utilization of long-chain fatty acids and decreased availability of ketone bodies can deprive the muscle of crucial sources of energy and, in certain conditions, may precipitate myoglobinuria. A severe respiratory failure can represent a life-threatening complication of the CPTII deficiency, but a multidisciplinary management can significantly improve the outcome of complicated cases.

26. Multidisciplinary management of an elective C-section in a wheelchair bound limb girdle muscular dystrophy (LGMD2C)

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We describe the groundwork and the management of a 24 years old wheelchair bound primigravida with severe limb girdle muscular dystrophy (type 2C) that came to our attention at her 29th week of pregnancy. LGMD2C is an autosomal recessive form of limb-girdle muscular dystrophy with a variable severity of the clinical condition. The described patient lost ambulation at the age of 9 yrs presented with diffuse muscle weakness, severe restrictive lung disease, which required non-invasive positive pressure ventilation (FVC: 430 ml;11% pred), and marked complicated scoliosis; echocardiography revealed mildly decreased left ventricular function. Fetal assessment was normal. After discussion with the obstetrician, the neonatologist and the pneumologist, elective Caesarean delivery was deemed the best management. Despite the fact that neuroaxial anaesthesia had an increased risk of failure due to the profound lumbar lordosis, epidural anaesthesia was attempted. Before the procedure patient underwent a training with caught assist machine (in-exsufflator) to prevent atelectasias (for a better management of atelectasias) and to ameliorate the VC through lung expansion. After catheter insertion a sensory block was titrated to a T4 level. This was well tolerated by both mother and fetus. A healthy baby was delivered with Apgar scores of 9 and 10. Postoperatively the mother was transferred to the intensive care unit. After 24 hrs, the patient returned tour neuromuscular unit. This case illustrates successful multidisciplinary management of a severely compromised

patient with limb-girdle muscular dystrophy undergoing, at 32 weeks' gestation, elective Caesarean section surgery through the use of combined spinal-epidural anaesthesia.

27. Attenuated muscle regeneration in dysferlin-deficient mice

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Mutations in dysferlin gene cause limb-girdle muscular dystrophy type 2B, Miyoshi Myopathy and distal myopathy with anterior tibial onset, collectively called dysferlinopathies. Dysferlin-deficient patients are characterized by adult onset, slow progressive, high serum CK and a prominent inflammatory infiltrate. Dysferlin is a type II membrane protein containing six C2 domains and one transmembrane domain. To date, the functions of dysferlin are still unclear. Our previous studies demonstrated that dysferlin proteins translocated from the cytoplasmic space to sarcolemma during muscle regeneration and the biopsies of dysferlinopathy patients showed an excess of immature fibers compared to other types of muscular dystrophy. All these results indicate that dysferlin might play a role in muscle regeneration. To test this hypothesis, muscle regeneration was induced by injecting 0.2µg of notexin into the right tibials anterior (TA) muscle of 12 to 14 weeks old wild type C57BL/10 and dysferlin-deficient C57BL/10.SJL-dysf mice. The left TA was used as a non-injected control. The muscles were harvested and analyzed at 2, 3, 5, 7, 14 and 28 days after injury. The muscles were completely destroyed within 2 days after notexin injection in both strains. In wild type animals, the damaged fibers were completely removed and replaced by regenerating fibers at day 7 after notexin injection. Although the regenerating fibers were also observed in dysferlin-deficient mice, abundant of damaged fibers were still found even at 28 days after injury in dysferlin-deficient mice. Moreover, the dystrophic pathology was observed after three times of notexin injection cycles in dysferlin-deficent animals whilst the regeneration is completed in the wild type. All these data confirmed the attenuation of muscle regeneration in dysferlin-deficient animals. Here we propose the functions of dysferlin protein in muscle regeneration and the pathomechanism of dysferlinopathies.

28. Development of an *in-vitro* model of inclusion body myositis (IBM) in primary rat muscle cultures.

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Inclusion body myositis (IBM) is the most common acquired muscle disease affecting adults over the age of 50. The disease is a significant cause of disability in this age group and, at present, this debilitating disease remains untreatable. Although IBM has long been considered as an immune-mediated disorder, immune-based therapies have not proved beneficial. However, IBM muscle displays additional degenerative features which distinguish it from the established primary inflammatory myopathies, so that in addition to myofibre infiltration by cytotoxic T-Cells, the presence of intracellular protein aggregates, vacuolation and proteasomal dysfunction suggests that a complex pathological process is involved. It is therefore likely that a broader therapeutic approach may be necessary for the treatment of IBM. Our aim is to use primary muscle cultures derived from neonatal rats to model the inflammatory and degenerative aspects of IBM in order to investigate the underlying pathophysiology of the disease. To establish a reliable and reproducible *in vitro* model of IBM, it is necessary to establish muscle cultures of high purity from digested muscle, so that contamination with fibroblasts, adipocytes and other non-myogenic cells is minimal. This is particularly important when undertaking biochemical analysis of primary cell cultures. This work reports on the use of different methods of isolating satellite cells, muscle stem cells, from the total digested muscle cell population using differential centrifugation as well as differential adhesion methods including Immunopanning, Fluorescence Activated Cell Sorting (FACS) and Magnetic Activated Cell Sorting (MACS).

29. Minced muscle autograft in partially resected urethra improves urinary continence in male rats.

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Satellite cells are mononucleated cells located at the periphery of the muscle fibre, between the sarcolema and the extracellular matrix. They are normally quiescent in adult muscles and considered as stem cells. When they are activated, they proliferate in order to increase myonuclei number in young muscle fibres or to regenerate injured fibres. In this study, we researched how to optimize the muscular regeneration of the urethral striated sphincter as it is injured after prostatectomy, leading to urinary incontinence. Currently, injections of cultivated myogenic cells result of temporary functional improvement but the fate of the injected cells remains uncertain. Furthermore, myogenic cells lose partly their regenerative capacities when they are cultivated outside their natural environment and injected in a host muscle. As an alternative we propose the implantation of fragments of freshly minced muscle

which preserves the “cellular niche” occupied by the satellite cells. For this purpose, we filled the gap resulting from the resection of a piece of urethra in male rat with fragments of rectus abdominus muscle, since such a resection is done in man during radical prostatectomy. When evaluated 28 days after surgery, autografted rats returned to continence with micturition cycles and sphincter activity close to normal, whilst control sutured animals remained fully incontinent without urethral activity. Thus, this easy to use technique should offer the prospective to prevent incontinence following prostatectomy in man.

30. *In vitro* Investigation of Potential Therapies for Inclusion Body Myositis

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Inclusion body myositis (IBM) is the commonest acquired muscle disease affecting people over 50 years old. Clinically characterised by progressive, muscle weakness and atrophy, IBM is a disabling condition. The classic pathological findings on muscle biopsy in IBM reflect a combination of inflammatory and degenerative features. The relative contributions of these components are unclear but interactions between the two are increasingly evident. Stemming from the traditional classification of IBM as one of the primary inflammatory myositides, several common immunotherapies have been the subject of clinical trials. None, however, has demonstrated efficacy. It is therefore possible that successful treatments of IBM may require broader mechanistic targets than selected facets of autoimmunity. We propose that such an approach may be represented by the Heat Shock Response (HSR) which involves the upregulation of a family of cytoprotective ‘molecular chaperones’ called Heat Shock Proteins (HSPs). Their actions have been demonstrated both to dampen inflammatory processes, via inhibition of the proinflammatory transcription factor NFkB, and to reduce cytotoxic intracellular accumulation of protein. Therefore, pharmacological augmentation of the HSR appears an attractive approach and has been achieved by several compounds, with benefit in models of other of neuromuscular diseases. To investigate this therapeutic potential in IBM, we have developed a primary cell *in vitro* system using neonatal rats in which potential IBM treatments, including manipulation of the HSR, can be characterised. Relevant cellular stressors which model IBM pathology include overexpression of β-amyloid precursor protein via lipofectamine-mediated plasmid transfection and exposure to key inflammatory cytokines, IL1β and TNFα. Using this model we are presently comparing a number of potential therapeutic agents targeting the inflammatory and degenerative features of IBM.

31. Muscle satellite cells are a functionally heterogeneous population

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Satellite cells are the resident stem cells of growing and adult skeletal muscle. Here we have examined the properties of satellite cells from muscles distributed throughout the body. There was marked heterogeneity in satellite cell myogenicity: soleus-derived satellite cells differentiated well, while those from the masseter, proliferated extensively but were less myogenic. Importantly, although the masseter muscle, unlike limb muscles, is not somite-derived, masseter-derived satellite cells are able to efficiently regenerate muscle when grafted into hindlimb muscles. We next investigated whether satellite cells from within the same muscle showed marked heterogeneity, and found that the proliferative, differentiative and self-renewal capacity of individual satellite cells associated with the same myofibre differed markedly. In conclusion, satellite cells are a heterogenous population: ranging from cells that proliferate extensively and give rise to both many new myonuclei and satellite cells, to others that divide only a few times before differentiating, but do not self-renew.

32. Reduced expression of fukutin related protein (FKRP) in mice results in a model for FKRP related muscular dystrophies.

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Mutations in fukutin related protein (FKRP) are responsible for a common group of muscular dystrophies ranging from adult onset limb girdle muscular dystrophies to severe congenital forms with associated structural brain involvement, including Muscle Eye Brain Disease. A common feature of these disorders is the variable reduction in the glycosylation of skeletal muscle alpha-dystroglycan. In order to gain insight into the pathogenesis and clinical variability, we have generated two lines of mice, the first containing a missense mutation and neomycin cassette, FKRP-NeoTyr307Asn and the second containing the FKRPTyr307Asn mutation alone. We have previously associated this missense mutation to a severe muscle-eye-brain phenotype in several families. Homozygote *Fkrp*-NeoTyr307Asn mice die soon after birth and show a reduction in the laminin-binding epitope of alpha-dystroglycan

in muscle, eye and brain, and have reduced levels of FKRP transcript. Homozygous *Fkrp*Tyr307Asn mice showed no discernible phenotype up to 6 months of age, contrary to the severe clinical course observed in patients with the same mutation. These results suggest the generation of a mouse model for FKRP related muscular dystrophy requires a knock-down rather than a knock-in strategy in order to give rise to a disease phenotype.

33. The role of muscle MRI in the diagnosis of muscle disorders with rigid spine

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Background: Muscle disorders associated with rigid spine often show considerable clinical overlap. Accurate diagnosis may be complicated as genetic testing is time consuming, expensive and results are sometimes difficult to interpret. Muscle MRI is increasingly being used as a diagnostic adjunct in muscle disorders but is undoubtedly underused due to the perception that it requires expert detailed interpretation. Objective: To evaluate the sensitivity of visual analysis of T1 weighted axial thigh and calf muscle MRI in differentiating 5 subgroups of muscle disorders associated with rigid spine including RSMD1 (associated with mutations in SEPN1), Bethlem myopathy and Ullrich congenital muscular dystrophy (both due to mutations in collagen 6) , autosomal dominant Emery Dreifuss (due to mutations in Lamin AC) and LGMD2A (associated with mutations in Calpain). Materials and Methods: Retrospective review of MRI muscle scans from 83 patients. Patients were included if they had a diagnosis of one of the 5 disorders listed above and had at least one MRI of thigh and leg muscles. Scans were assessed by 5 reviewers including 3 neurologists, and 2 radiologists who were blinded to clinical and genetic information. Scans were independently reviewed and a consensus opinion reached. The pattern of muscle involvement was compared to published data for the various disorders and then classified as: typical for a specific disorder; consistent but with other changes; different; or uninformative. Scoring systems based on the involvement of individual muscles were avoided in favour of a simpler 'gestaltic' impression of the overall pattern of muscle involvement. Results: 67 of 83 (80%) scans were classified as typical with a further 7 scans (8%) classified as consistent with one of the 5 conditions. These findings correlated with genetic results in all but one scan (1%) where a capainopathy scan was incorrectly classified as typical of a collagen 6 disorder. Approximately 10% of scans were uninformative due to very mild or normal findings, the majority in patients with Bethlem myopathy. Sensitivity of MRI diagnosis was 75% overall (92% in RSMD1, 85% in collagen 6 disorders and 88% in calpainopathy). In Emery Dreifuss muscular dystrophy the sensitivity for 'typical' changes was 46%, but a further 46% were classified as consistent with EDMD but with features overlapping those seen in calpainopathy. Good consensus was found among examiners. Conclusion: Muscle MRI is a useful clinical adjunct when investigating muscle disorders associated with rigid spine. It is a simple and sensitive assessment tool and is helpful in investigating cases where the clinical diagnosis is uncertain.

34. Transgenic Mice Overexpressing human LARGE: Implications for therapeutic interventions in muscular dystrophy.

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Much attention has recently been focused on the biochemical properties of LARGE and its potential as a therapeutic agent in some forms of muscular dystrophy. LARGE is one of a number of known or putative glycosyltransferase enzymes that underlie a group of muscular dystrophies commonly referred to as the "dystroglycanopathies". They share the common pathological feature of a *hypo*glycosylated form of □-dystroglycan. The forced overexpression of LARGE results in *hyper*glycosylation of □-dystroglycan in cell lines from both normal and dystroglycanopathy patients where ligand binding is restored. To address the potential of LARGE as a therapeutic agent we have generated several mouse lines expressing a human LARGE transgene tagged with the V5 epitope under the control of a synthetic CMV/chicken β-actin promoter (pCAGGS). We have 33abeling33ized these mice in detail in order to assess the consequence of □-dystroglycan hyperglycosylation *in vivo*. Henotypically, mice harbouring the LARGE transgene were indistinguishable from their wild type litter mates at the gross morphological level. Analysis of tissue sections from young mice (<6 weeks old) using histology, immunohistochemistry and western blotting of showed a variable pattern of transgene expression: highest in skeletal muscle and cardiac muscle with little or no expression in brain, kidney and liver. High levels of transgene expression were correlated with □-dystroglycan hyperglycosyaltion as determined either by 33abeling with antibody IIH6 or increased laminin binding on an overlay assay. In skeletal muscle, expression was highly variable between fibres. Staining for other components of the DGC and extracellular matrix ligands was normal. No abnormal muscle

pathology was seen. Analysis of older mice (>6 months of age) showed that the level of transgene expression remained constant with time. However, histological analysis of skeletal muscle sections from aged showed evidence of an increase in connective tissue infiltration and a significant increase in central nucleation. In addition, physiological testing revealed decrease resistance to eccentric exercise in aged mice. The generation and careful analysis of these LARGE overexpressing transgenic lines has important implications for any potential therapies based on the upregulation of this gene in the dystroglycanopathies.

35. Patients from an unusual family co-segregating myotonic dystrophy and Charcot-Marie-Tooth disease present with an imperfect CTG repeat allele at the *DM1* locus

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The DM1+CMT++ family is an unusual three-generation family in which all 14 patients co-segregate both myotonic dystrophy type 1 (DM1) and Charcot-Marie-Tooth disease (CMT) (LOD score = 8.03). In this family, we identified an imperfect CTG repeat allele at the *DM1* locus with the following structure: $(CTG)_x$ $(GGC)_3$ G $(CCG)_{20}$ $(CCGCTG)_{14}$ $(CTG)_{35}$. The interrupted 3'-end of the array appeared to be genetically stable with only minor variants observed within and between family members. In contrast, the pure CTG repeat tract at the 5'-end of the array was unstable in the soma and in the germline. The expanded (>86 repeats) CTG tract at the 5'- end of the array explains the classic DM1 symptoms such as myotonia and cataracts observed in this family. Two mechanisms might explain the CMT symptoms in this family: a novel effect on the downstream genes; and/or a novel RNA gain-of-function mediated by the presence of CCG and CGG repeats, analogous to the RNA gain of function observed in fragile X associated tremor ataxia syndrome. Similar imperfect CTG repeat alleles containing CCGCTG and/or CCG repeats were also identified in other DM1 patients with an unusual molecular diagnosis. These findings, suggest that imperfect CTG repeat alleles are present in more DM1 patients than previously realised and probably accounts for some of the otherwise enigmatic symptomatic variation observed within and between DM1 families. These data emphasise the need for performing a more detailed molecular characterisation of the mutation in individual families, which should lead to provision of more accurate prognoses.

36. Mutations in the Frabin gene can cause a variable phenotype and lead to protein truncation.

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Charcot–Marie–Tooth disease (CMT) is a clinically and genetically heterogeneous group of disorders and is the most common inherited neuromuscular disorder, with an estimated overall prevalence of 1 in 2500 individuals. The clinical phenotype includes progressive distal muscle weakness and atrophy, foot deformities, gait problems and sensory loss. Autosomal recessive (AR) CMT is clinically and genetically heterogeneous. The number of genes for AR CMT has rapidly increased over the last few years with AR axonal and demyelinating CMT genes being identified. The AR CMT phenotype is usually more severe and has an earlier onset than AD CMT there are often additional clinical features such as scoliosis, vocal cord problems or cranial neuropathies that can give clinical clues to the genetic cause. The frequency of AR CMT is much less than AD overall, although this may change as the number of AR genetic causes are identified. In certain regions of the world such as the Mediterranean basin and the Gypsy communities there is a high rate of consanguinity and the frequency of AR CMT is much higher than the dominant form and may account for over 50% of the CMT cases. De Sandre-Giovannoli et al identified the CMT4H locus on chromosome 12p11.21-q13.11 in two large consanguineous families. Clinically these families had severe childhood onset demyelinating CMT with frequent focally folded myelin seen on Sural nerve biopsy. The CMT4H gene was recently identified and five mutations in six AR CMT families were reported in the Frabin gene. This gene is a GDP/GTP nucleotide exchange factor specific to Cdc42, a member of the Rho family of small GTP binding proteins. The two papers reporting Frabin mutations carried out functional studies and confirmed the Frabin proteins ability to induce Cdc42-mediaed cell shape changes and observed that mutant Frabin induced fewer microspikes in rat primary motorneurons and Schwann cells. We follow a number of Irish and English families with AR demyelinating CMT with varying degrees of disease severity. We screened the entire Frabin gene in our family cohort and identified a homozygous R275X mutation in a family from Northern Ireland. This family had an unusually mild slowly progressive phenotype even when the

two affected cases were in their middle ages although nerve conduction studies still showed severe demyelination. Examination of mRNA from lymphoblasts showed that this stop mutation caused very little non-sense mediated mRNA decay and the predominant mRNA species was the mutant form that translates into a truncated protein.

37. Association between magnetization transfer ratio and muscle strength in Chronic Inflammatory demyelinating Polyneuropathy

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Objectives: Quantitative MRI techniques hold promise as outcome markers in trials of new therapies in disorders of nerve and muscle. The purpose of this study was to examine for the first time the relationship between magnetization transfer ratio of muscle [1], which characterises tissue microstructure, and clinical disease severity as measured by manual muscle testing in a group of patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), an acquired peripheral neuropathy [2]. *Methods:* Nine adult patients suffering from CIDP and ten healthy control subjects were scanned on a 1.5T scanner (GE Healthcare, Milwaukee, WI). An interleaved 2D gradient echo sequence was used to measure the magnetization transfer ratio (MTR) in 5mm axial slices of both lower legs (TR/TE = 1500/7 ms) using an abdominal phased array receive coil and a magnetization transfer saturation pulse offset by 2kHz. A radiologist placed manual regions of interest on the resulting spatial MTR maps over the four principle muscle compartments in the lower leg (the posterior superficial compartment (PSC), posterior deep compartment (PDC), anterior compartment (AC) and lateral compartment (LC)) for both the right and left lower legs of the CIDP patients and healthy controls. The clinical severity of the CIDP patients was measured by manual muscle strength testing [3] of ankle dorsiflexion by a neurologist using the standard 5 point MRC Score ordinal scale of manual muscle strength. An MRC score of 0 corresponds to the most severe impairment and 5 corresponds to healthy status. *Results:* The mean MTR in the ROIs placed over of the anterior muscle compartment (AC) correlated strongly with the MRC strength score for ankle dorsiflexion in both the right and left legs of the CIDP patients, showing a reduced MTR with reduced clinical muscle function. (Spearman's correlation coefficient 0.91, p=0.001 right leg and =0.83, p=0.006 left leg). (Fig 1 & 2) The mean MTR measured in the other three muscle compartments (PSC, PDC, LC) did not significantly correlate with MRC score for ankle dorsiflexion which is consistent with the chosen clinical strength test being primarily a measure of muscle function in the anterior compartment of the lower leg. The group median MTR of the CIDP group was reduced compared to the healthy control group when tested in each of the four muscle compartments for both right and left legs, further supporting the hypothesis that reduced MTR is a good indicator of pathology in CIDP (two-tailed Mann-Whitney U Test, $p<0.05$ for all 4 muscle groups except left lateral compartment ($p=0.053$)). MTR combined across all muscle compartments and both legs was also significantly less in CIDP than in controls (CDIP median(IQR)=39.3(35.1,45.8), Controls 50.5(47.2,50.8), reduction significant at p=0.03 level, two tailed Mann-Whitney test). *Conclusions This* study shows for the first time that the magnetization transfer ratio measured in the lower leg muscles of patients suffering from CIDP is consistently reduced compared to healthy controls and thus provides an appropriate characterization of tissue pathology. Furthermore, investigations specific to the anterior musculature of the leg show that reduced MTR is directly correlated with reduced muscle strength and function as tested by standard clinical methods. These findings strongly support quantitative MRI in general and MTR in particular as a potential biomarker of clinical status in CIDP which could prove potentially useful in therapeutic trials in CIDP and other neuromuscular diseases.[1] McDaniel et. Al. *Journal Computer Assisted Tomography*, 23, p609, 1999, [2] Saperstein, D. et. Al. *Muscle & Nerve,* 24, p311, 2001, [3] MRC(1975) *Aids to the investigation of the peripheral nervous system*, HM Stationary Office Synopsis: Magnetization transfer ratio (MTR) maps were made of the lower legs of nine patients suffering from chronic inflammatory demyelinating polyneuropathy (CIDP) and ten healthy control subjects. Measurements of the clinical severity of the CIDP patients were made by manual muscle strength testing of ankle dorsiflexion. The median MTR of the CDIP group was significantly lower than the controls. A reduction in MTR in the anterior compartment of the leg was correlated significantly with reduced clinical muscle strength, supporting the potential use of quantitative MR methods such as MTR as a surrogate biomarker of disease severity in trial of therapies for neuromuscular conditions.

38. Deletion of *smn-1*, the *Caenorhabditis elegans* orthologue of the spinal muscular atrophy gene, results in locomotor dysfunction and reduced lifespan

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Spinal Muscular Atrophy (SMA) is one of the most common genetic causes of infant mortality and is characterized by degeneration of lower motor neurons. The gene responsible has been identified as *Survival Motor Neuron* (*SMN*). The invertebrate model organism *Caenorhabditis elegans* contains *smn-1*, the orthologue of human *SMN*. *C. elegans smn-1* is expressed in various tissues including the nervous system and body wall muscle and knockdown of *smn-1* by RNA interference produces severe developmental defects such as embryonic lethality. Here we show that the *smn-1(ok355)* deletion, which removes most of *smn-1* including the translation start site, produces a pleiotropic phenotype including late larval arrest, reduced lifespan, sterility, impaired locomotion as well as pharyngeal pumping defects. Mutant worms develop to late larval stages due to the maternal contribution of SMN-1 protein which allows investigation of its functions beyond embryogenesis. We show here that neuronal- but not muscle-directed expression of *smn-1* partially rescues the growth arrest of *smn-1(ok355)* worms. This finding agrees well with recent studies on tissue specific rescue in a mouse SMA model. The deletion mutant *smn-1(ok355)* therefore provides a useful platform for functional analysis of an invertebrate orthologue of the human SMN protein and for high-throughput drug / RNAi screening for modifiers of the pathogenesis of SMA. **References:** Briese M. et al (2008) Human Mol Genet (in press: epub ahead of publication) Briese M. et al (2006) Invert Neurosci 6, 5-12 Briese M. et al (2005) Bioessays 27, 946-957Culetto E. et al (2000) Human Mol Genet 9, 869-877Miguel-Aliaga, I. (1999) Human Mol Genet 8, 2133-2143

39. Differential weakness of the ulnar and median bellies of flexor digitorum profundus is a useful indicator of an inflammatory neuropathy: A new clinical sign?

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Inflammatory neuropathies are linked by their presumed immune mediated pathogenesis. They include primary diseases of the nervous system such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and systemic diseases that involve the peripheral nervous system (PNS) e.g. primary systemic vasculitis Inflammatory neuropathies are characteristically patchy. Non-inflammatory diseases of the PNS, where nerves are affected by a primary systemic disease e.g. diabetes, neuropathies are typified by symmetrical distal length dependent damage. Flexor digitorum profundus (FDP) receives dual 36nnervations to its lateral (FDP II) and medial (FDP V) bellies. Innervation is more proximal than that to the small muscles of the hand with no difference in length of 36nnervations between the median and ulnar nerves. The aim of the study was to determine if clinically evident differential weakness between muscle groups in the hand was a good predictor of inflammatory demyelinating neuropathy. Ninety sequential unselected patients attended in the MRC Centre for Neuromuscular Disease were blindly examined and MRC power scores from the distal muscles of the arm were recorded. Differential weakness of FDP II and FDP V is able to differentiate inflammatory demyelinating neuropathies from other neuropathies with a sensitivity of 70.4% and a specificity of 90%. Differential muscle weakness of FDP II and FDP V may be helpful in support of a clinical diagnosis and guide further investigation and treatment, especially where there is diagnostic uncertainty.

40. Chronic Inflammatory Demyelinating Polyradiculoneuropathy, Morvan's Syndrome and Myasthenia Gravis in a single patient: Efficacy of Rituximab

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Rituximab is a chimeric antibody directed against human CD 20 molecules and following injection rapidly depletes peripheral B-cells. Studies have demonstrated that rituximab is effective in various autoimmune diseases including myasthenia gravis and Morvan's syndrome. Inflammatory demyelinating polyradiculoneuropathy (CIDP) can be effectively treated with prednisolone, intravenous immunoglobulin (IVIG) and plasma exchange (PE). The efficacy of rituximab in CIDP is yet to be proven. Biological studies indicate a role for CD20 lymphocytes and antibodies being important in the pathogenesis of CIDP and anecdotal evidence to support use of rituximab is beginning to emerge from clinical cases. We present a case report of a 76 year old man with CIDP, Morvan's syndrome and probable myasthenia gravis who responded to rituximab following the failure of other therapies.

41. Complications of sural nerve biopsy: an audit at the National Hospital for Neurology and Neurosurgery.

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Approximately 70-100 peripheral nerve biopsies are performed annually at the MRC Centre for Neuromuscular Disease to assist in the diagnosis of peripheral neuropathies. Sural nerve biopsy is increasingly infrequent as less invasive techniques of diagnosis advance. Peripheral nerve biopsies are targeted to abnormal nerves, usually to exclude vasculitis, amyloidosis, malignant infiltration of the nerve or to confirm demyelinating neuropathies in atypical or non-responsive cases. Published complication rates for sural nerve biopsy vary from 10-30% depending upon the complications quoted and the follow up period. We wished to explore the current rates of complications from our service and compare these to other quoted complication rates and evidence from international guidelines. We present these data at this meeting.

42. Does the clinical and electrophysiological phenotype help distinguish acquired from inherited chronic peripheral sensory ataxic states?

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Background: Sensory ataxia is a common problem seen in peripheral nerve clinics. The differential is wide and when the syndrome is chronic, the distinction between acquired inflammatory and inherited disorders can be challenging. Aim: To compare and contrast the clinical and electrophysiological phenotypes of patients with acquired and inherited chronic peripheral sensory ataxia. Methods: Patients from a tertiary peripheral nerve clinic were recruited and assessed. These included 4 patients with proven Sjogren's syndrome (diagnosed using clinical phenotype, immunological profile, and histology including lip biopsy) and chronic sensory ataxic neuronopathy and 4 patients with sensory ataxic neuropathy, dysarthria and ophthalmoparesis (SANDO) who had multiple mtDNA deletions in muscle and recessive *POLG1* gene mutations. Results: Clinically the sensory syndrome seen in patients with Sjogren's was more asymmetric and associated with more positive sensory phenomena as compared to the SANDO group. Electrophysiologically, there tended to be a non-uniform and asymmetric reduction in sensory nerve action potentials (SNAPs) in those patients with Sjogren's. The patients with SANDO exhibited uniformly absent SNAPs without any asymmetry. One patient had subclinical motor involvement. Conclusion: It is crucial to correctly diagnose patients with chronic peripheral sensory ataxia to allow appropriate management with either immunomodulatory therapy or genetic counseling and family tracing. The presence of positive sensory phenomena, clinical asymmetry and electrophysiological uniformity/non-uniformity are useful distinguishing features in establishing an acquired or genetic basis as the cause of chronic peripheral sensory ataxic syndromes. This is particularly pertinent in those patients with a monosymptomatic presentation of mitochondrial disease. Further work is needed to confirm these potentially important findings in a larger sample.

43. Characterisation of novel mutations within HSP27 causing Charcot-Marie-Tooth Diesease 2F and distal Hereditary Motor Neuropathy II

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Heat shock proteins (Hsps) are a highly conserved, ubiquitously expressed family of stress response proteins whose expression is increased in response to cellular stress. HSPs can function as molecular chaperones, facilitating protein folding, preventing protein aggregation, or targeting improperly folded proteins to specific degradative pathways. Heat shock protein 27 (HSP27) is a well characterised small Hsp that plays a role in normal neuronal functions such as axonal growth as well as cell survival, inhibiting apoptosis and protecting against oxidative stress. Recently mutations have been discovered in the HSP27 gene that lead to both Charcot-Marie-Tooth Disease 2F and distal Hereditary Motor Neuropathy II (dHMN) (Houlden et al, 2008). We have recently identified a number of unique HSP27 mutations that cause dHMN and the aim of this study is to examine the molecular and pathogenic mechanisms by which these mutations result in disease. Initially, three HSP27 mutations were replicated by site-directed mutagenesis. The effects of transfection with each of the mutant HSP27 constructs as well as control, wildtype HSP27 on neurons in vitro is currently being examined using SH-SY5Y and Neuro-2A cell lines. In order to establish and compare the effects of the various mutant HSP27s, in the first instance we will examine the effects on cell survival, neurite outgrowth and aggregate formation. We hope that the results of this study will increase our understanding of the pathomechanism of the disease causing effects of HSP27 mutations. Since there is currently no effective treatment for dHMN, it is imperative that we increase our understanding of the disease mechanism in order to identify therapeutic targets for this disease.

44. Intermediate Charcot-Marie-Tooth disease with tongue hemiatrophy due to de novo point mutation in the neurofilament light chain gene

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A 34 year old woman with a progressive sensorimotor neuropathy with onset in infancy without family history is presented. Unusual clinical features were the presence of right tongue hemiatrophy and marked asymmetry in upper limb strength. The patient also had early onset sensorineural deafness. Neurophysiology showed absent sensory responses and motor conduction velocities in the intermediate range. Genetic testing demonstrated a de novo point mutation resulting in a single amino acid substitution in the neurofilament light chain gene, c.293A>G (p.Asn98Ser) which was absent in both parents. Although tongue amyotrophy has been described previously in patients with autosomal recessive CMT, it is rare in autosomal dominant forms, and tongue hemiatrophy has not previously been described. The two previous patients described with this mutation also had de novo mutations, however clinical age of onset varied, as did associated features (1,2). References 1. Yoshihara T, Yamamoto M, Hattori N, Misu K, Mori K et al. Identification of novel sequence variants in the neurofilament-light gene in a Japanese population: analysis of Charcot-Marie-Tooth disease patients and normal individuals. Journal of the Peripheral Nervous System, 2002; 7:221–224 2. Jordanova A, De Jonghe P, Boerhkoel CF, Takashima H, et al. Mutations in the neurofilament light chain gene (NEFL) cause early onset severe Charcot-Marie-Tooth disease. Brain, 2003; 126: 590-597

45. Chaperone co-induction improves neuromuscular function in a mouse model of Spinal and Bulbar Muscular Atrophy.

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Spinal and Bulbar Muscular Atrophy (SBMA) is an inherited neurodegenerative disorder in which a CAG repeat expansion in the androgen receptor gene results in dysfunction and death of brainstem and spinal cord motoneurons. Although the disease mechanisms are poorly understood, evidence suggests that androgen receptor misfolding and aggregation plays a key pathogenic role. We phenotyped transgenic mice expressing a mutant human androgen receptor containing 100 CAG repeats (AR100 mice) and demonstrated late-onset weakness closely resembling the human disease. We show that treatment with arimoclomol, a heat shock protein co-inducer, significantly delays disease progression in AR100 mice. AR100 mice begin to develop subtle neuromuscular deficits at around 12 months of age with marked muscle wasting and motoneuron loss by 18 months. Mice were treated with arimoclomol orally from 12 months of age for 6 months. and prepared for physiological analysis of muscle force and motor unit survival. Arimoclomol-treated AR100 mice demonstrated significant improvements in hind-limb muscle function, increased motor unit and motoneuron survival. These results suggest that arimoclomol is a promising therapeutic strategy for SBMA and may have potential for treatment of other neuromuscular conditions in which protein aggregation is a prominent pathophysiological feature.

46. Introduction of a dynein mutation does not alter neuromuscular function in a mouse model of Spinal and Bulbar Muscular Atrophy.

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Spinal and Bulbar Muscular Atrophy (SBMA) is an inherited neurodegenerative disorder in which a CAG repeat expansion in the androgen receptor gene results in dysfunction and death of brainstem and spinal cord motoneurons. Although disease mechanisms are poorly understood evidence suggests that androgen receptor misfolding and aggregation and that axonal transport is disrupted. Mutations in the dynein heavy chain gene have been shown to improve the phenotype of mouse models of amyotrophic lateral sclerosis whilst exacerbating the phenotype of Huntington's disease models. We crossed AR100 SBMA mice with Loa mice carrying a mutation in the dynein heavy chain gene. Surprisingly, AR100/Loa double heterozygotes do not show a phenotype significantly different from that of AR100 mice even at a late stage of disease. These results suggest that the pathophysiology of SBMA is markedly different from that of ALS and Huntington's disease, and that autophagic clearance of aggregate-prone proteins and disruption of axonal transport are not as critical for motoneuron survival.

47. The Smartnet Clinical Network – Creation of a national standardised assessment tool and natural history database for Spinal Muscular Atrophy

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Objective: To develop a standard neuromuscular measurement tool for the assessment of children and young adults with Spinal Muscular Atrophy (SMA) in order to optimise their management and to create a national database to collect natural history data on type II and type III SMA.
Background:The Smartnet Clinical Network UK was established in August 2006 following the appointment of a project co-ordinator and clinical collaboration between the major Paediatric Neuromuscular centres and some adult based centres involved in the care of individuals affected by SMA. A similar initiative had already been successfully established in UK through North Star, a network designed to establish standardised assessment procedures in ambulant Duchenne Muscular Dystrophy boys and collect these longitudinal data onto a national database. Increasingly there has been a need to establish standardised assessment procedures as clinical trials become more likely and regulatory authorities require more comprehensive measures of progress.
Methods:To establish the optimum motor function scales for use within the physiotherapy assessment, existing motor function scales were reviewed by an expert group, and consensus was achieved on choice of 3 motor function measures, as follows: For non-ambulant children –Hammersmith Functional Motor Scale (HFMS) - This has been used in clinical trials already both in UK and overseas. For ambulant children and adults - Slightly modified North Star Ambulatory Assessment, originally designed for use in Duchenne Muscular Dystrophy, but now adapted for the use in ambulant SMA. Its advantage is that it is familiar to UK therapists and has been compiled in a robust fashion. For non-ambulant children, teenagers and adults - Egen Klassifikation for SMA, which is a robust functional questionnaire highly relevant to affected individuals. It can be used where clinic time is short or if patients are unwilling or unable to perform a motor assessment. An adjunct to this project was collaboration with the original author of the EK scale, Birgit Steffensen and Professor Mercuri in Rome to establish a revised scale for use in SMA that included questions on bulbar function, fatigue and hand function. This has resulted in the EK2 -a 17 item questionnaire. A manual has been produced detailing assessment techniques for this patient group.
Results:Through the activities of the project coordinator and the network, medical and physiotherapy assessment proforma's have been produced and are in circulation. A web-based national clinical database has been developed in order to review the natural history of SMA, facilitate multicentre clinical audit and review services. The database is hosted on a joint website with the North Star project and is due to go live by February 2009.
Future developments: It is hoped that with further funding the work can be extended to cover the adult population more comprehensively and new outcome measures can be evaluated and correlations between measures assessed. We gratefully acknowledge the financial support of Jennifer Trust for Spinal Muscular Atrophy and Muscular Dystrophy Campaign.

48. "We just live from day to day": Tricky transitions for young men with Duchenne Muscular Dystrophy (DMD) and their families

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Aim: to explore the tensions around transition to adulthood for a group of young men living with a life limiting illness. Methods: postal survey of families with a son with DMD aged 15+ in 3 English regions. Also, qualitative interviews with 40 young men with DMD and their families. Explored current arrangements, views and experiences of health and social care services, hopes for the future and possible barriers to a successful transition to adulthood. Results: findings suggest that families were reluctant to think about the future whilst at the same time, wanting, as far as possible, opportunities to do the 'normal things of youth and adulthood'. Formal processes of transition planning were rarely successful, if in place at all. Significant barriers to post 16/school services existed and social and relationship opportunities for young people were limited. Conclusion: young people with DMD and their families tread a difficult tightrope between not thinking about the future, alongside trying to ensure that young men have a 'good life'. This necessarily involves some degree of planning for the future. Statutory services were not routinely offering helpful, individualised support. As a result, young men in the study did run the risk of becoming isolated at home and not having age-appropriate and engaging ways of spending their time.

49. Assessing the effects of exercise-induced stress on the Fiona mouse model

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Background and Aim: Characterized by the severe progressive wastage of skeletal muscle, Duchenne muscular dystrophy is a crippling disease that is caused by the absence of the cytoskeletal protein dystrophin. *Utrophin* is a paralogue of *dystrophin*. The Fiona mouse is an *mdx* (dystrophin-deficient) transgenic mouse that over-expresses the full-length utrophin protein in skeletal muscle. Various studies have shown that it is completely rescued and does not display any of the dystrophic characteristics of *mdx* mice. However, these studies have only been performed on sedentary mice. My aim is to see if Fiona mice continue to display this rescued phenotype after an extended period of sustained exercise-induced stress, or whether they revert to the dystrophic phenotype.
Methods: 4-week old C57/BL6 and *mdx* mice were divided into two groups – 'sedentary' and 'run'. Those in the

'run' group were made to run on a treadmill at12 m.min^{-1} for 30 minutes, twice a week, for 8 weeks. After the end of the trial, muscle samples were dissected out and subjected to a range of tests. This protocol will be repeated for the Fiona mice once the desired number is obtained. Results: Muscle physiology tests show a significant decrease in maximum isometric force produced by the extensor digitorum longus (EDL) muscle caused by exercise in *mdx* but not C57/BL6 mice. Leftward shifts in the force-frequency curves were seen for both groups of mice. Increased centronucleation was seen in muscle sections of *mdx* mice but not of C57/BL6. No change in α-naphthyl staining was seen in either group. Increased utrophin staining was seen in muscle sections of both groups. Western blot data so far show no increase in utrophin in exercised *mdx* mice compared to non-exercised mice. These are important control data that will be used during analysis of the Fiona mice data.

50. Resistance training in patients with single, large-scale deletions of mitochondrial DNA

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Mitochondrial myopathies are a group of progressive muscle disorders caused by mutations in the mitochondrial genome (mtDNA). Despite progress in the diagnosis and management of patients, there remains a need for effective treatments, and one proposed treatment is exercise training. Tissue variation in mtDNA heteroplasmy levels has been found to exist in patients with sporadic mtDNA mutations. Despite high abundance in mature skeletal muscle, levels of the causative mutation are low or undetectable in satellite cells. The activation of these mitotic cells and subsequent shifting of wild-type mtDNA genomes to mature muscle has been proposed as a means of restoring a more normal mitochondrial genotype and function in these patients. As resistance exercise is known to serve as a stimulus for satellite cell induction within active skeletal muscle, this study sought to assess the therapeutic potential of resistance training in 8 patients with single large-scale mtDNA deletions by assessing: physiological determinants of peak muscle strength and oxidative capacity and muscle biopsy-derived measures of damage, mtDNA mutation load, level of oxidative impairment and satellite cell numbers. Our results show that 12 weeks of progressive overload leg resistance training led to: (1) increased muscle strength; (2) myofibre damage and regeneration; (3) increased proportion of NCAM-positive satellite cells; (4) improved muscle oxidative capacity. Taken together, we believe these findings support the notion of resistance exercise-induced mitochondrial gene-shifting in muscle containing satellite cells which have low or absent levels of deleted mtDNA. Further investigation is warranted to refine parameters of the exercise training protocol in order to maximize the training effect on mitochondrial genotype and treatment potential for patients with specific, sporadic mutations of mtDNA in skeletal muscle.

51. The role of the peroxisome proliferator-activated receptor (PPAR)δ agonist GW501516 in alleviating muscle pathology in the *mdx* mouse

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Duchenne muscular dystrophy (DMD) is a severe muscle wasting disorder caused by mutations in the cytoskeletal protein dystrophin. By pharmacologically upregulating the dystrophin-related protein utrophin, our aim is to develop a therapy for DMD by reconstructing the dystrophin-associated protein complex. Recently, signalling pathways involving PPARδ coactivator 1α (PGC-1α) and PPARδ have been identified as novel therapeutic targets in DMD through their ability to upregulate utrophin and activate genes involved in oxidative metabolism (Handschin 2007, Miura 2007). We have tested the effect of delivery of the PPARδ agonist GW501516 in the *mdx* mouse. GW501516 treatment gave a marginal increase in utrophin RNA and protein levels. Improvements in muscle physiology included greater resistance to mechanical stress as determined by a reduction in the percentage force drop following eccentric contractions. Furthermore, an increase in the frequency required to produce a certain force suggested improved Ca^{2+} handling in treated muscle. However, there was no reduction in the number of centrally nucleated fibres or serum creatine kinase. Overall these data show that GW50516 treatment results in some improvement of the dystrophic phenotype in the *mdx* mouse.

52 Upgrading U7snRNA to complete efficient rescue of dystrophin by exon-skipping in DMD patients

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Most cases of Duchenne muscular dystrophy (DMD) are caused by mutations that disrupt the dystrophin mRNA reading frame. In many cases, skipping of a single exon could supposedly restore the reading frame, giving rise to a shorter but still functional quasi-dystrophin protein. It has previously been proposed to use small nuclear RNAs, especially U7snRNA, to shuttle antisense sequences designed to mask key elements involved in the splicing of targeted exons. Our present project focuses on the upgrading of U7snRNA to complete rescue of dystrophin by exon-skipping in DMD patients. We indeed developed bifunctional U7snRNAs carrying a complementary sequence to the targeted exon and a free tail harbouring canonical binding sites for the heterogeneous nuclear ribonucleoproteins A1/A2 (hnRNP) that are powerful splicing repressors. The presence of this generic strong silencer tail could indeed circumvent the always tricky and time-consuming specific optimization required for each new exon-target. We first focused on the exon 51 of the dystrophin gene and therefore designed new tailed U7snRNA constructs. Each construct has been inserted into lentiviral vectors for *in vitro* analysis on myoblasts from DMD patients. After transduction of these cells with lentiviral vectors encoding the tailed U7-ex51, we confirmed the skipping of the exon 51 by nested RT-PCR and dystrophin restoration by Western blot. By Comparison with their controls with a mutated tail, we could show that the skipping efficiency of these constructs was due to the tail carrying silencer motifs, therefore confirming its splicing repressor action, and not the annealing sequence to the exon. Furthermore, we demonstrated the efficacy of these constructs *in vivo* in transgenic mice carrying the entire human DMD locus (hDMD mice) after intramuscular injection of AAV vectors encoding the bifunctional U7 snRNA. These very encouraging results on exon 51 provide evidence that bifunctional U7snRNA can achieve efficient exon-skipping *in vitro* and *in vivo*. These new constructs offer therefore very promising tools for clinical treatment of DMD, but also powerful and versatile tools to modulate pre-mRNA splicing in a wide range of applications.

53. Functional constraints on the dystrophin rod domain: relevance to the design of minidystrophin constructs and induced exon-skipping therapies

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The dystrophin rod domain is the site of the vast majority of DMD and BMD mutations and comprises over 75% of the length of the protein. For most purposes the rod domain is considered to be an inert structural rod whose only function is to separate the actin-binding N-terminus from the membrane-binding C-terminus. Our phylogenetic analysis, however, shows that some form of powerful functional constraint has resulted in specific regions of the rod domain being substantially more conserved (over periods of hundreds of millions of years) than would be expected for a mere structural rod. We suspect that these regions are involved in mediating specific protein-protein interactions, and examine the implications of this for the rational design of therapeutic minidystrophin constructs, for our understanding of BMD phenotypic variation, and for consideration when designing exon-skipping therapies (where a "BMD" transcript is created).

54. Chemical rescue of paralysis in a *Caenorhabditis elegans* model of Inclusion Body Myositis by inhibitors of β-amyloid aggregation

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Inclusion Body myositis (IBM) is the commonest acquired muscle disease affecting people over 50 years old. It is one of a group of muscle disorders characterized by muscle weakness and degeneration in addition to chronic muscle inflammation. Histologically, IBM is characterized by atrophic muscle fibers with internal nuclei containing rimmed vacuoles and abnormal protein aggregates and filamentous inclusions mainly consisting of amyloid deposits derived from amyloid precursor protein (APP) and hyperphosphorylated tau. Remarkably, despite the inflammation component of the disease, IBM patients are only poorly responsive to anti-inflammatory drugs suggesting that inflammation per se may not be the primary cause of the pathology. We have deployed a *C. elegans* transgenic line over-expressing human amyloid 1-42 peptide in the muscles as a model with which to study IBM and to search for novel routes to therapy. This *C. elegans* line becomes paralyzed shortly after the induction of amyloid expression in the muscles, which makes it an easily-recordable phenotype useful for exploring candidate treatments to alleviate the paralysis. We report on the actions of two novel chemicals, which inhibit amyloid

aggregation and partially rescue the amyloid-induced phenotype. **References:** Wu Y, W.Z., Butko P, Christen Y, Lambert MP, Klein WL, Link CD, Luo Y. (2006) Amyloid-beta-induced pathological behaviors are suppressed by Ginkgo biloba extract EGb 761 and ginkgolides in transgenic Caenorhabditis elegans. *J. Neurosci.,* **26,** 13102-13.
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55. Nucleofection: An optimal method for testing the efficacy of morpholino antisense oligonucleotide induced exon-skipping in primary myoblasts.

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Duchenne muscular dystrophy (DMD) is a lethal muscle degenerative disorder resulting from a loss of dystrophin expression. Antisense oligonucleotides (AON) can be used to modify splicing of the primary transcript to restore the reading frame and hence protein expression. Using a phosphorodiamidate morpholino oligomer (PMO) that targets the 5' donor splice site of intron 23 in the *mdx* mouse model of DMD, we have compared the effects of differing methods of delivering a PMO into primary *mdx* myoblasts *in vitro*. Our findings indicate that the use of nucleofection to administer PMO results in higher levels of exon skipping than previously reported methods. We confirm these observations using a PMO targeting exon 51 in primary cultures from DMD patients.

56. Results of Two Years Treatment with Enzyme Replacement Therapy with rh-alpha-glucosidase (Myozyme) in Adult Onset Pompe Disease.

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Introduction: Adult Pompe disease (Acid Maltase Deficiency, Glycogen Storage Disease type II) is characterised by a progressive, predominantly central and proximal myopathy, with diaphragmatic involvement presenting as respiratory compromise. It is caused by a deficiency in lysosomal alpha-glucosidase. Until recently the disease slowly progressed with increasing muscle weakness and respiratory failure. With the advent of enzyme replacement therapy (ERT) it is hoped that prognosis will be significantly improved. We report our experience of ERT in 6 adult patients at 2 years. Patients were treated with rh-alpha-glucosidase (Myozyme ®) in a dose of 20 mg/kgm body weight every two weeks intravenously. Assessments were performed every 4 months and consisted of full history and examination together with pulmonary function tests. These consisted of standard measurements performed both standing or lying, or standing and sitting where patients could not lie down. Some patients had sitting and lying if they could not stand. In addition we performed SNIPs where ever possible. All patients showed some improvement. The best was the 62 year old male who was bed bound when first seen and ventilated for 24 hours. He can now walk with a zimmer frame for about 50 yards. He can tend to his everyday care relieving the burden from his wife. His ventilator is now used for only 10 hours over night. The slowest response was in the 41 year old male. However, there was improvement in his respiratory function tests and his exercise tolerance also significantly improved. There were no complications. All 6 patients tolerated the ERT well with no reported reactions. For the last 9 months, 5 of the patients have been receiving their therapy in their own home. Conclusion: While the patients treated for 2 years are few in number, we feel that the results in our patients are very encouraging. The treatment would seem to be safe and efficacious.

57. Myoprotective effects of erythropoietin (EPO) and riluzole after ventral root avulsion injury in the adult rat

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Long-term nervous denervation of skeletal muscle results in severe muscle atrophy. This muscle atrophy results in permanent deficits in the contractile ability of the muscle, with replacement of the muscle with fibrotic material. Normally, the myogenic satellite cells become activated to help regenerate the muscle, but if there is no peripheral

nerve re-innervation, the satellite cells fail to enhance muscle regeneration and undergo apoptosis. This causes a dramatic reduction in number of satellite cells with long-term denervation. Even if nervous innervation is restored, it may be too late to reverse the loss of the satellite cells and further degenerative effects on muscle function. Using a ventral root avulsion model of muscle denervation we have investigated the potential myoprotective effects of erythropoietin (EPO) and riluzole. Adult rats received an avulsion injury of the L3-6 ventral roots followed by one of 4 treatment regimes: 1) EPO administered immediately after the injury and again 24 hours later (N=8); 2) riluzole administered every day for the 1st week then every other day for the 2nd week (N=5); 3) a combination treatment of EPO and riluzole (N=5); 4) untreated (N=5). After a 2 weeks survival period, rats were sacrificed and the spinal cord and soleus muscles were removed. Analysis of motoneuron survival showed that in untreated avulsion only animals, around 30% of motoneurons as compared to the contralateral side had died by 2 weeks post injury and in those animals treated with EPO or riluzole this was reduced to 15%. Additionally, the expression of EPOR in avulsed motoneurons was decreased in untreated animals compared to treated animals. The results suggest that EPO has protective effects on the motoneurons and this in turn affects the expression of the receptor. Analysis of soleus muscles in EPO treated rats showed a reduction in the number of atrophic fibres in the denervated muscle compared to the untreated animals and there were fewer inflammatory cells within the denervated muscles. Normally, EPO-R is down regulated during muscle cell differentiation and is not detected in mature muscle fibres, but is co-expressed with satellite cell markers. We find that in the atrophying muscle fibres there are more EPO-R positive muscle fibres, we also find that EPO-R expression is lost from satellite cells. The EPO treated muscles have significantly fewer of these EPO-R positive fibres, and EPO-R is maintained by the satellite cells. Riluzole increased the number of satellite cells, but was not effective at preventing the muscle fibre atrophy. The combination of EPO and riluzole had synergistic effects, preventing the muscle fibre atrophy and increasing the number of satellite cells. Therefore, these results suggest that EPO and riluzole are able to act as a survival and growth factor for both denervated motoneurons and muscle, maintaining proliferation and preventing apoptosis of stimulated muscle satellite cells and may therefore play a role in muscle development and repair.

58. Genotype-dependent responses to Beta-adrenergic blockade in mouse models of muscular dystrophy-associated cardiomyopathy

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The value of β-adrenergic receptor blockers (BB) in treating cardiomyopathy associated to muscular dystrophy is not yet established, and we do not know if all cardiomyopathies respond to BB. We tested the effects of a β_1-selective BB on cardiac haemodynamics in two different animal models for muscular dystrophy and cardiomyopathy. A clinically relevant dose of metoprolol was given orally (2.5 g/ kg BW/ day through the drinking water) over 8 weeks to *mdx* mice (model for Duchenne muscular dystrophy) and δ-sarcoglycan-deficient (*Sgcd*$^{-/-}$) mice (model for Limb Girdle Muscular Dystrophy type 2F), started at an early stage in the development of cardiomyopathy. *In vivo* cardiac function was assessed using pressure-volume loops in treated and untreated *mdx*, *Sgcd*$^{-/-}$ and wild-type mice (WT). In both the WT and *mdx* mice there is a beneficial reduction in afterload (E_a) and an increase in stroke volume. Contractility (preload recruitable stroke work, PRSW) is also improved in the *mdx* mice. In contrast, in the *Sgcd*$^{-/-}$ mice we found a marked deterioration with prolonged relaxation (Tau), reduced stroke volume, stroke work and an increased mortality during dobutamine infusion. Heart rate was significantly reduced in WT and *Sgcd*$^{-/-}$, though not *mdx* mice. In conclusion, BB may not necessarily be beneficial in all cardiomyopathies, and reduction in heart rate may not predict a positive outcome. Clinical trials of BB in muscular dystrophy-associated cardiomyopathy patients may need to stratify patients by genotype.

59. Efficient and fast functional screening of micro-dystrophin constructs *in vivo* and *in vitro* for therapy of Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is an X-linked, lethal genetic disorder affecting the skeletal muscle compartment, which is caused by mutation(s) in the dystrophin gene. Gene delivery of micro-dystrophin constructs using Adeno-Associated Virus (AAV) and antisense-mediated exon-skipping restoring the genetic reading frame are two of the most promising therapeutic strategies for DMD. Both approaches utilize micro-dystrophin proteins either directly as a desired construct for gene delivery using the capacity-limited AAV vectors or as the therapeutic outcome of gene splicing. Although functionality of the resulting artificial dystrophin proteins can be predicted *in*

silico, experimental evidence usually obtained in transgenic mice is required prior to human trials. However, the enormous number of potential constructs makes screening assays for dystrophin protein function *in vitro* and *in vivo* highly desirable. In the present study we wanted to assess fast and efficient evaluation methods of artificial dystrophin proteins with potential therapeutic relevance. We generated four new micro-dystrophins with large in-frame deletions of the rod domain that were evaluated *in vivo* using intramuscular injection followed by electroporation into Tibialis Anterior (TA) and *in vitro* using a primary-derived immortalized mdx myoblast cell line. All four constructs showed functionality *in vivo* with correct localization and recruitment of the Dystrophin-Glycoprotein Complex (DGC) proteins to the sarcolemma. All four constructs also significantly reduced the number of centro-nucleated fibres in dystrophin-positive fibres compared to dystrophin-negative (non-transfected) fibres. This evidenced the functionality at the cellular level with alleviation of the dystrophic pathology. Experiments where mdx myoblasts expressing the micro-dystrophin constructs were exposed to hypo-osmotic stress indicated that the constructs protected against membrane damage and recruited the DGC proteins back to the sarcolemma *in vitro*. Based on our results dystrophin functionality can be tested efficiently and consistently using simple methods, which are relatively fast and do not require the need for transgenic mouse models, viral vector production and viral vector *in vivo* tests.

60. Stem cell transplantation in MNGIE (mitochondrial neuro gastrointestinal encephalopathy): The first UK patient and world experience.

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A 41 year old female was diagnosed with MNGIE with biochemical and genetic confirmation of thymidine phosphorylase mutations. She had experience deteriorating neurological function (progressive external ophthalmoplegia, demyelinating neuropathy) and gastrointestinal deterioration (with the necessity of two years feeding by total parenteral nutrition), with a probably fatal diagnosis. After full discussion of the imperfectly known benefits of haematopoietic stem cell transplantation (HSCT), with the patient, family, ethical and funding agencies, a transplant was planned using an HLA matched sibling with normal thymidine phosphorylase genes. At 13 months post transplant the patient remains well, with apparent improvement in appetite and well being, but no definite objective improvement in weight, GI function or neurological as yet. Previously high levels of plasma thymidine reverted to normal following transplantation. World experience of HSCT in MNGIE was discussed recently at a consensus conference. HSCT in this disabling and fatal disease is a promising treatment. HSCT in MNGIE has particular challenges. We advocate that HSCT should only be undertaken as part of a collaboration using the experience gained to date.

61. New loss of positive charge mutations in muscle channel S4 voltage sensors cause hypokalaemic periodic paralysis

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Several missense mutations of muscle CACNA1S and SCN4A genes occur in hypokalemic periodic paralysis (HypoPP). These mutations affect arginine residues in S4 voltage sensors. In most published reports 70% of cases are due to CACNA1S mutations, and 10% to SCN4A mutations with approximately 20% of cases remaining genetically undefined. As 80% of cases are accounted for by direct sequencing of only 3 S4 segments this may be the only analysis available in a diagnostic setting. We undertook direct automated DNA sequencing of all regions of CACNA1S and SCN4A coding for all S4 segments of both genes (8 in total) for 83 patients with hypoPP. Using this approach we genotyped approximately 90% of our cohort. 64/83 harboured the common mutations in CACNA1S in the S4 segments of protein domains II and IV. Of the remaining 19 cases mutations were found in 10, including 3 previously unknown changes (1 in CACNA1S and 2 in SCN4A) and the first mutations to be described in channel domains I and III. In total 65/83 (78%) cases were due to CACNA1S mutations, 9/83 were due to SCN4A mutations (11%) and only 9/83 (11%) were undefined. All mutations affected arginine residues, consistent with the gating pore cation leak hypothesis of HypoPP. Arginine mutations in S4 segments underlie approximately 90% of cases of HypoPP. Identification of these novel mutations involving novel protein domains leads to a number of testable hypothesis regarding the contribution of dysfunction of the S4 voltage sensors to the pathogenesis of hypoPP.

62 Complement-fixing antibodies in seronegative myasthenia and their correlation with clinical and neurophysiological severity

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Myasthenia gravis (MG) is caused by antibodies against neuromuscular junction proteins, resulting in fatiguable weakness. Most patients have antibodies against the nicotinic acetylcholine receptors (AChRs) or muscle specific kinase (MuSK). The remaining patients, termed seronegative myasthenia (SNMG) have clinical similarities to AchR antibody positive myasthenia, but do not have easily detectable antibodies by conventional radioimmunoprecipitation techniques. We have recently developed a cell-based assay (CBA) using clustered AchRs which improves the sensitivity of antibody detection in SNMG (Leite, Jacob et al, 2008) but the pathogenicity of these antibodies is not yet demonstrated directly. Here we asked whether there was a correlation between single fibre electromyography (SFEMG) findings and the antibodies, and also whether we could passively transfer SNMG to mice. The low affinity/avidity AchR antibodies detected by the CBA were shown to be predominantly of the IgG1 subclass and had the ability to activate complement in-vitro. This was demonstrated by the deposition of activated complement components C3b and membrane attack complex (MAC) on the cell surface. Neurophysiological abnormalities significantly correlated with antibody levels (using both conventional techniques and cell-based assays). Patients with complement-fixing antibodies were found to have more severe neuromuscular transmission defects, probably suggesting the pathogenic potential of these antibodies. To further prove the pathogenicity of these antibodies, purified IgG from 2 SNMG patients were transferred to mice. Although phenotypic weakness could not be elicited, significant reduction in miniature end-plate potential (MEPP) amplitudes was demonstrated. Reduction in MEPP amplitudes is characteristic of experimental myasthenia. Further, these animals were also found to have deposition of activated complement components near their neuromuscular junctions. These experiments indicate that low affinity/avidity AchR antibodies have the ability to fix complement, are potentially pathogenic and their presence correlates with the degree of neurophysiological abnormalities. The testing of these antibodies in SNMG patients would improve the diagnostic sensitivity and guide the clinician in commencing appropriate pharmacological therapies.

63. A mutation in the *Caenorhabditis elegans* nicotinic acetylcholine receptor α subunit, *unc-63*, provides a model for fast channel congenital myasthenia

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The nematode *Caenorhabditis elegans* is an established model organism for studying neurobiology since many synaptic molecular components are conserved both in the worm and humans. The *unc-63* alpha subunit of the *C. elegans* nicotinic acetylcholine receptor (nAChR) plays an important role in fast cholinergic synaptic transmission at the nematode neuromuscular junction. Here we show that worms with the *unc-63(x26)* allele, with its alpha C151Y mutation that disrupts the cys-loop, have deficient muscle function as displayed by impaired thrashing locomotion compared to wild-type worms. Single-channel recordings from muscle cells of the mutant strain show a reduced number of active patches, a 100-fold reduced frequency of opening events, and abnormally reduced duration of channel openings, similar to that observed in patients with fast-channel congenital myasthenia syndromes (FCCMS). Interestingly, a mutation in the equivalent position in the human muscle nAChR epsilon subunit (epsilon C128S) is associated with a FCCMS due to nAChR deficiency at the endplate. Therefore, disruption of the cys-loop results in qualitatively similar actions on both nematode and human receptors. Therapy for FCCMS is limited in variety and success with 3,4-diaminopyridine (3,4-DAP) and anticholinesterase drugs such as pyridostigmine bromide (PB). We show that PB and 3,4-DAP can partially rescue the motility defect seen in *unc-63(x26)*, making this the first candidate *C. elegans* model for screening for drugs aimed at ameliorating the consequences of mutations in nAChRs associated with FCCMS.

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64. A deletion mutation in the ion channel pore of the muscle acetylcholine receptor reduces channel conductance and underlies a congenital myasthenic syndrome (CMS)

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Muscle acetylcholine receptor ion channels (AChR) mediate neurotransmission by depolarising the post-synaptic membrane in response acetylcholine (ACh) released from motorneuron synapses. Disruption of this process can lead to myasthenic syndromes characterised by fatigable muscle weakness. Loss of synaptic AChR and/or kinetic

abnormalities of AChR function can underlie this disruption and lead to various forms of CMS. In this study we have investigated a 47 yr woman with onset of a CMS at birth. She displays progressive bulbar, respiratory and generalised limb weakness plus ptosis and opthalmoplegia. She has had a positive response to high dose pyridostigmine (900mg/day) but 3,4 diaminopyridine gave no improvement. She has non-consanguinous parents, no affected family members and 4 unaffected children. At aged 45 she suffered a respiratory arrest with hypoxic brain injury. The patient's DNA was directly sequenced, which revealed a Proline to Arginine substitution at position 282 (□P282R) and the deletion of a phenylalanine residue at position 266 (□□F266), one on each allele of the AChR epsilon subunit gene (CHRNE). Transfection of HEK 293 cells with AChRs containing either of these mutations showed reduced but not abolished surface expression. Receptor complexes precipitated with an anti-□-subunit antibody were reduced by 50% for □□F266, but were severely reduced to 18% of wildtype for □P282R AChR. Single channel analysis of □P282R mutant AChR at low [ACh] (500 nM) showed greatly reduced burst duration, with the longest burst population only 1.25 ± 0.2 ms (n=4). However, for □□F266 AChR channels, the longest burst duration population was not different from wildtype AChR (4.39 ± 0.6 ms vs. 4.68 ± 0.7 ms, n= 5 each). Cluster open probability at higher [ACh] was also unchanged for □□F266 AChR channels (EC_{50} 8.6 □M compared with 8.9 □M for wildtype AChR). Interestingly, single channel conductance was significantly reduced in □□F266 AChR channels (42.7 ± 1.4 pS compared with 70.9 ± 1.6 pS for wildtype, n= 8 and 6 respectively). □□F266 is the first reported CMS mutation which affects AChR conductance. Since the deleted residue is within the critical pore-lining region of the M2 transmembrane domain of the □-subunit it is remarkable functional channels are expressed. Since channel gating is not altered the reduction in conductance is the crucial change underlying this pathogenic mutation. From these data we conclude this patient's CMS is the result of a combination of a low expression/fast channel mutation (□P282R) and a reduced conductance/reduced expression mutation (□□F266).

65. Analysis of neuromuscular junction proteins in zebrafish embryos

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Congenital myasthenic syndromes (CMS) arise from genetic defects that affect transmission at the neuromuscular junction (NMJ). Causal mutations in presynaptic nerve terminal, synaptic cleft, and postsynaptic apparatus proteins have been identified. We are studying the functions of proteins involved in CMS pathogenesis in order to gain a better understanding of disease mechanisms. We chose zebrafish as model organisms to study NMJ proteins: Transparency and external embryonic development of zebrafish allow in vivo imaging of the earliest steps in NMJ formation not accessible in mammals. Furthermore, mutations that are lethal in mammals at early stages of development can be studied in the zebrafish. We are particularly interested in the function of Dok-7 and Lrp4 at the zebrafish NMJ. Mutations in the *DOK7* gene cause a limb-girdle form of CMS. The Dok-7 protein has been shown to interact with the muscle-specific kinase MuSK and play an important role in acetylcholine receptor clustering at the NMJ. Lrp4 has recently been described to be part of the same signalling pathway by linking nerve-derived agrin and MuSK. We downregulate protein expression by injection of antisense morpholino oligonucleotides into fertilised zebrafish eggs; abnormalities of NMJ development in the injected embryos will hint towards the role of the targeted protein during NMJ formation. Our results may help to better understand the development of CMS in patients with *DOK7* mutations. Furthermore, zebrafish may be a suitable model organism for testing novel treatments for CMS patients.

66. The genetic skeletal muscle channelopathies: Genotype-Phenotype correlation and longitudinal studies

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The skeletal muscle channelopathies are rare Mendelian disorders caused by mutations in genes that encode ion channel subunits. As members of the CINCH group (Consortium for the Clinical Investigation of Neurological Channelopathies), the MRC centre for neuromuscular diseases are involved in the first large scale multi-centre natural history trial of the non-dystrophic myotonias (NDM) and Andersen-Tawil syndrome (ATS). The non-dystrophic myotonias encompass a spectrum of heterogeneous disorders ranging from myotonia congenita (MC), to paramyotonia congenita (PMC) through to the potassium aggravated myotonias with muscle stiffness being the cardinal symptom. ATS is characterized phenotypically by the triad of periodic paralysis, cardiac dysrhythmias and dysmorphic facies. Mutations in the potassium channel gene, *KCNJ2* underlie the disorder. The aims of the trials are as follows: to characterize the phenotypic spectrum associated with specific genetic defects; to collate information on symptom progression; to evaluate investigations used in the diagnoses and to assess endpoints for future treatment trials.

67. Multiple mitochondrial DNA deletions, COX negative fibres and slowly progressive cognitive decline with psychiatric features

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Background: Multiple deletions of mitochondrial DNA (mtDNA) arising from nuclear gene defects have been described in a spectrum of disorders ranging from the severe early-onset Alpers syndrome to mild cases of progressive external opthalmoplegia (PEO). Cognitive impairment is an unusual presenting feature. We report a patient who presented with a history of slow cognitive decline and psychiatric features. Case history: The patient presented at the age of 50 years with an 18 month history of memory problems, poor concentration and a diminished capacity for arithmetic. He had a long history of depression. He subsequently developed mild unsteadiness and involuntary jerky movements of his limbs which progressed slowly over 10 years. He also gave a 3 years history of regular diarrhoea and steady weight loss of 8kg. Examination: Observation revealed myoclonus of his arms. He had mild eye and limb cerebellar signs. He had normal limb power, increased tone in his legs, bilateral upgoing plantars and a mild distal sensory neuropathy. There was no ptosis, but he had restriction of upgaze. Investigations: MRI brain scan showed scattered deep white matter and basal ganglia changes of ischaemic origin with no focal abnormality. Detailed neuropsychological testing revealed moderate cognitive impairment predominantly implicating subcortical and bi-temporal regions. Muscle histology revealed a higher proportion of COX negative fibres than expected for age. Respiratory chain enzyme analysis demonstrated a reduction in complex II+/-III activity. Multiple mtDNA deletions were present on long PCR analysis. Complete sequencing of *POLG*, *SLC25A4* and a targeted screen of *PEO1* did not identify any mutations. A screen for MNGIE was also negative using the thymidine phosphorylase assay. Conclusion: This patient has a mitochondrial disorder with a prominent cognitive and psychiatric presentation. The presence of multiple deletions of his mtDNA points to a nuclear gene defect; however sequencing of *POLG* was negative for mutations. We have also excluded three other nuclear genes commonly associated with multiple mtDNA deletions, namely *PEO1, SLC25A4* and *TYMP*. It seems likely that this is driven by an as yet unidentified nuclear gene involved in mtDNA maintenance.

68. Electrodiagnosis of muscle channelopathies in clinical practice

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We have investigated whether specialized electrophysiology including the long and short exercise tests can guide genetic testing in patients with skeletal muscle channelopathies. We evaluated a cohort of patients with suspected muscle channelopathies who underwent specialized electrophysiology and genetic analysis in our centre. We collected genetic and clinical neurophysiology data on 115 consecutive patients with a suspected muscle channelopathy seen in our clinic over 18 months (April 2007 to October 2008). We correlated previously reported patterns of specialised electrophysiological [SE] abnormalities with final genotype. We demonstrated that SE accurately predicted the responsible channel in all myotonic syndromes due to SCN4A mutations and in the vast majority of myotonic syndromes due to CLCN-1 mutations. Only two patients with CLCN1 mutations were incorrectly identified as sodium channel mutations using SE. In patients with genetically confirmed periodic paralysis who underwent exercise testing, the long exercise test was abnormal in over 90%. These data indicate that specialised electrophysiology is a useful adjunct to the clinical assessment of muscle channelopathy patients and helps to direct genetic testing more efficiently.

Clinical Trials

Clinical trials linked to the MRC Centre and supported by different funding agencies including the Medical Research Council, Muscular Dystrophy Campaign, UK Department of Health, National Institutes of Health (USA), Food and Drug Administration (USA), AVI Biopharma and PTC Therapeutics.

Open Trials

RANDOMISED DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF LONG-TERM ASCORBIC ACID TREATMENT IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

Status: Follow-up phase. Closed to recruitment
Sponsor: University College London
Funder: Muscular Dystrophy Campaign (MDC)
PI: Dr. Reilly

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 has been running now almost for two years and it is now in the follow-up phase. Fifty participants were enrolled in the UK site at the National Hospital for Neurology and Neurosurgery.

For information about the study please contact Dr. Matilde Laura at m.laura@ion.ucl.ac.uk.

A PHASE IIb EFFICACY AND SAFETY STUDY OF PTC124 IN SUBJECTS WITH NONSENSE MUTATION-MEDIATED DUCHENNE AND BECKER MUSCULAR DYSTROPHY

Status: Closed to recruitment
Sponsor: PTC Therapeutics
Funder: PTC Therapeutics
PIs: Prof. Muntoni, Prof. Bushby

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 approximately10 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 will be eligible to receive open-label PTC124 in a separate extension study.

(Ataluren is now the non-proprietary generic name for PTC124).

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.

RESTORING DYSTROPHIN EXPRESSION IN DUCHENNE MUSCULAR DYSTROPGY: A PHASE I/II CLINICAL TRIAL USING AVI-4658

Status: completed. Closed to recruitment
Sponsor: Imperial College London
Funder: Department of Health (DoH)
PIs: Prof. Muntoni

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].

DOSE-RANGING STUDY OF AVI-4658 TO INDUCE DYSTROPHIN EXPRESSION IN SELECTED DUCHENNE MUSCULAR DYSTROPHY (DMD) PATIENTS – (Systemic study)

Status: Open to recruitment
Sponsor: AVI Biopharma
Funder: Medical Research Council (MRC) and AVI Biopharma
PIs: Prof. Muntoni

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 is being conducted in London and Newcastle.

For information on the status of recruitment please contact Gisela Barreto, Trials Coordinator (MRC centre London site) at Gisela.barreto@uclh.nhs.uk or Geoff Bell, Trials Coordinator (MRC centre Newcastle site) at geoff.bell@nuth.nhs.uk.

Planned Trials

HYP HOP: DICHLORPHENAMIDE vs. ACETAZOLAMIDE FOR PERIODIC PARALYSIS

Status: Set-up Phase
Sponsor: University College London (UCL)
Funder: National Institutes of Health (NIH - USA)
PI: Prof. Hanna

This is a phase III trial into Periodic Paralysis planned to start in 2009. This proposal involves a multi-centre, double-blind, placebo-controlled parallel group, nine-week studies comparing the effects of acetazolamide (ACZ) vs 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 double-blind extensions without placebo to compare the long term effects of DCP vs ACZ 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.

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: REC review is now pending
Sponsor: University College London (UCL)
Planned Start date: June 2009
Funder: Food and Drug Administration (FDA – USA)
PI: Prof. Hanna

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.

Approximately fifteen participants will be enrolled in the UK at the National Hospital for Neurology and Neurosurgery.

For information on the status of recruitment please contact Dr. Emma Matthews at e.matthews@ion.ucl.ac.uk or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk

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: REC Review is now pending
Sponsor: University College London (UCL)
Planned start date: June 2009
Funder: Medical Research Council (MRC)
PI: Prof. Hanna

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.

For information on the status of recruitment please contact Dr. Adrian Miller at a.miller@ion.ucl.ac.uk or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

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

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 Dr. James Burge at James.burge@uclh.nhs.uk or Gisela Barreto, Trials Coordinator at Gisela.barreto@uclh.nhs.uk.

Natural History – Longitudinal Studies

NON-DYSTROPHIC MYOTONIAS: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDIES

Status: Closed to recruitment
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Hanna

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.

For more information about the study please contact Dr. Emma Matthews at e.matthews@ion.ucl.ac.uk.

ANDERSEN-TAWIL SYNDROME: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDY

Status: Open to recruitment
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Hanna

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.

Eight patients have been enrolled so far at the National Hospital for Neurology and Neurosurgery.

For information on the status of recruitment please contact Dr. Sanjeev Rajakulendran at s.rajakulendran@ion.ucl.ac.uk.

Exercise Studies

STRENGTHENING HIP MUSCLES TO IMPROVE WALKING DISTANCE IN PEOPLE WITH CHARCOT- MARIE-TOOTH DISEASE

Status: REC Approved. Open to recruitment
Sponsor: University College London Hospitals
Funder: Muscular Dystrophy Campaign (MDC)
PI: Dr. Reilly

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 included 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.

For information about recruitment contact Alex Pollard, Research Physiotherapist at a.pollard@ion.ucl.ac.uk.

EXERCISE TRAINING IN PATIENTS WITH MITOCHONDRIAL DISEASE: ASSESSING THE BENEFITS

Status: Recruiting
Sponsor: University Newcastle
Funder: Muscular Dystrophy Campaign (MDC)
PI: Prof. Turnbull

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 will be:

1) To confirm that endurance training in patients with mitochondrial abnormalities improves quality of life, exercise tolerance and oxidative capacity.
2) 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.

For information about recruitment contact Geoff Bell at geoff.bell@nuth.nhs.uk or Caroline Hodgson at c.hodgson@ncl.ac.uk.

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