Muscular Dystrophy Campaign

MRC Centre for Neuromuscular Diseases

Seventh UK Neuromuscular Translational Research Conference

3rd – 4th March 2014

UCL Institute of Child Health
30 Guilford Street
London WC1N 1EH

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

UK Neuromuscular Translational Research Conference London 2014

Dear Colleagues,

We are delighted that the MRC Centre has been renewed from 2013-2018 and to welcome you to London for this seventh annual scientific meeting. We are very pleased that this annual UK Neuromuscular Translational Research Conference continues to be jointly hosted with the Muscular Dystrophy Campaign. In addition, this year we have worked closely with colleagues in the London-Newcastle MRC Centre steering committee, the MRC Functional Genomics unit in Oxford and the Wellcome Trust Centre for Mitochondrial Research in Newcastle to develop the scientific translational research programme.

Major translational themes this year include stem cell technology and the emerging stem cell therapies; cellular protein homeostasis and its dysfunction in neuromuscular diseases; the rapidly growing field of antisense technology and its evolving role as a therapy in neuromuscular diseases and the increasing role of MRI biomarkers for diagnosis and disease/therapy monitoring.

We are delighted to welcome two world-leading neuromuscular clinician scientists who will deliver the two conference named lectures; Professor Kathryn North, Director of the Murdoch Children's Research Institute, University of Melbourne, Australia, will give the third Morgan-Hughes Thomas Lecture, and Professor Jerry Mendell, Director for Gene Therapy, Research Institute at the Nationwide Children's Hospital, Columbus, Ohio, will give the third Victor Dubowitz lecture.

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

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

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

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

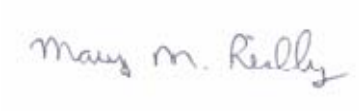
We have received 77 high quality abstracts, and there will be dedicated poster sessions each day as well as guided poster discussions. There will be £500 poster prizes for young investigators. Accepted abstracts will be published in a special supplement of the journal *Neuromuscular Disorders* with Professor Mary M. Reilly as the special guest editor.

As the Centre Director, I would very much like to thank Professor Mary M. Reilly who has lead the joint MRC-MDC meeting scientific planning team: Professors Kate Bushby, Doug Turnbull, Francesco Muntoni, Dame Kay E Davies, and Dr Marita Pohlschmidt. I also sincerely thank Christine Oldfield and Marita Pohlschmidt for their very hard work in organizing this meeting. I am very grateful for the interest, sponsorship and support of industry colleagues who are working with us to develop new therapies for patients with neuromuscular diseases.

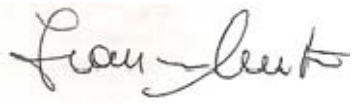
Once again this annual meeting has been oversubscribed. We are very encouraged that there continues to be such strong interest in neuromuscular translational research from throughout the UK and beyond.

We sincerely hope that you have a stimulating, productive and entertaining two days in London.

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



Professor Mary M. Reilly
Co-Director
MRC Centre for Neuromuscular Diseases
UCL Institute of Child Health

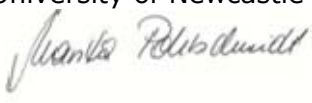


Professor Francesco Muntoni
Co-Director, ICH/GOS
MRC Centre for Neuromuscular Diseases
UCL Institute of Neurology

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

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

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



Dr Marita Pohlschmidt
Director of Research,
Muscular Dystrophy Campaign

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

I am writing on behalf of the Muscular Dystrophy Campaign to welcome you to the 2014 UK Neuromuscular Translational Research Conference organised in partnership between the MRC Centre for Neuromuscular Diseases and the charity.

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

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

The charity continues to campaign successfully for improvements in patient care and support by lobbying government and NHS decision makers in each part of the UK to ensure patients with neuromuscular disorders can access specialist care. We are particularly pleased to have secured NHS funding for a national network of more than 40 Care Advisor and Nurse Specialist posts across the UK – a hugely valued expansion in direct support to individual patients and families.

As we all recognise, without a well resourced clinical infrastructure, treatments have no effective route out of the laboratory, so I must thank all our clinical colleagues who have worked closely with us in putting the case for a high quality national neuromuscular service. As well as the impressive progress in research, improvements in clinical care have been achieved as a result of a collaborative effort over many years and the Muscular Dystrophy Campaign is widely recognised for our positive and influential role on behalf of all patients and families affected by the conditions, working with leading clinicians.

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

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

Robert Meadowcroft
Chief Executive, Muscular Dystrophy Campaign

About the MRC Centre for Neuromuscular Diseases

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

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

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

- One of our main objectives currently is to develop deeply phenotyped stratified cohorts of patients in the five disease areas we have prioritized, which are muscular dystrophies, neuromuscular channelopathies, inherited neuropathies, inclusion body myopathy and mitochondrial disease. Our biobanked samples are complimentary to these cohorts and to date we have c. 3000 patients entered into to our stratified cohorts.

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

first phase of the MRC Centre we delivered a step change and well over 3,000 patients were entered into natural history studies and clinical trials.

- A shortage of human cell lines and neuromuscular tissues currently hinders basic science efforts and in vitro testing of potential therapies. We have now established a unique UK biobank of human neuromuscular patient tissues and have collected over 1800 human cell lines that have been invaluable for translational research including preclinical therapy evaluation.

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

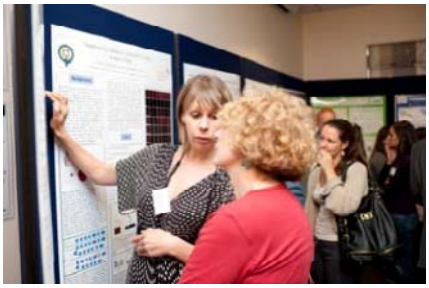
- We have developed new outcome measures and biomarkers for NM diseases. We continue to develop new MRI techniques which have started to change the way we assess and monitor neuromuscular disease in patients. We are taking advantage of major new MRI facilities in London and Newcastle to establish cutting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

- We recognise the critical importance of training the basic and clinical neuromuscular scientists of the future. The Centre has developed and delivered very successful four-year and three-year translational neuromuscular disease PhD programmes, and twelve PhD students have already graduated from this programme. A cadre of 15 new students (from over 200 applicants) has been appointed from 2013. We prioritise the provision of exciting and inspirational translational research environments to continue to train the next generation of basic and clinical neuromuscular scientists, building future capacity in the UK.

By developing these six 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 fighting muscle-wasting conditions. We are dedicated to beating muscular dystrophy and related neuromuscular conditions by finding treatments and cures and to improving the lives of everyone affected by them. The charity campaigns for specialist healthcare, helps people with muscle-wasting conditions to fight for their rights and get the essential services and equipment they need, and provides specialist education and development for health professionals.



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

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

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

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

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

Patient Organisations

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

UK Neuromuscular Translational Research Conference 2014
ICH, 30 Guilford Street, London WC1N 1EH
Kennedy Lecture Theatre

Monday 3rd and Tuesday 4th March

PROGRAMME

Day 1 – Monday 3rd March

08:30 – 9:30	**Registration and Coffee**
9:30 – 9:45	Introduction Professor Michael Hanna UCL Institute of Neurology
09:45 – 12:30	**Session 1: Cell-Based therapies and IPS Cells** **Chairs: Professor Jenny Morgan (UCL Institute of Child Health) and Professor Dame Kay Davies (University of Oxford)**
09:45 – 10:15	Autologous cell therapy in oculopharyngeal muscular dystrophy (OPMD) Professor Gill Butler-Browne Institut De Myologie, Paris
10:15 – 10:45	Opti-dystrophin in DMD stem cells Professor Jenny Morgan UCL Institute of Child Health
10:45 – 11:15	Cell therapy for muscular dystrophies Professor Giulio Cossu Institute of Inflammation and Repair University of Manchester
11:15 – 11:45	Coffee
11:45 – 12:00	Platform Presentation: Improving satellite cell regenerative potential in muscular dystrophy: an environmental issue Dr A Pisconti Department of Biochemistry, University of Liverpool

12:00 – 12:15 Platform Presentation: Designing 3D scaffolds that can support myogenic progression in skeletal muscle satellite cells
Dr Nicolas Figeac
King's College London

12:15– 12:30 Platform Presentation: iPS cells and human artificial chromosomes: novel therapeutic tools for muscle disorders
Dr Francesco Saverio Tedesco
Department of Cell and Developmental Biology, UCL

12:30 – 13:30 Posters and lunch

13:30 – 14:30 Poster guided tours
Muscular Dystrophies group a
Mitochondrial Disease
MRI
Glycosylation Disorders, Inclusion Body Myositis and Muscle
Satellite cells and IPS Cells

14:30 – 17:30 Session 2: Protein Homeostasis and Neuromuscular Diseases
Chairs: Professors Mary Reilly (UCL Institute of Neurology) and Hanns Lochmuller (Newcastle University)

14:30 – 15:00 Protein Homeostasis – what does it mean?
Dr Graham Jackson
UCL Institute of Neurology

15:00 – 15:30 The role of the unfolded protein response in neurodegeneration: a new target for therapy
Professor Giovanna Mallucci
MRC Toxicology Unit, Leicester

15:30 – 16:00 Heat shock proteins and protein homeostasis in hereditary neuropathies
Professor Vincent Timmerman
University of Antwerp, Belgium

16:00 – 16:30 Coffee

16:30 – 17:00 Using proteomic profiling to decipher the pathogenesis of myofibrillar myopathies
Professor Rudolf Kley
University Hospital Bergmannsheil, Germany

17:00 – 17:15 Platform presentation: Mitochondrial abnormalities and increased oxidative stress in HSBP1 induced distal hereditary motor neuropathies
Dr Bernadett Kalmar
UCL Institute of Neurology

17:15 – 17:30 Platform presentation: Investigating the effects of pharmacological up-regulation of the heat shock response in a transgenic mouse model of inclusion body myopathy
Dr Mhoriam Ahmed
UCL Institute of Neurology

17:30 – 18:30 The Third Morgan-Hughes Thomas Lecture
A gene for speed: ACTN3, athletes, evolution and impact on human health
Professor Kathryn North
Murdoch Children's Research Institute, Australia
Introduced by Professor Mike Hanna

18:30 – 19:30 **Drinks Reception and Posters**
Introduced by Robert Meadowcroft, Muscular Dystrophy Campaign CEO

(followed by walk/coaches to Gala Dinner)

19:45 – 20:00 **Aperitif followed by Gala Dinner**
Grand Connaught Rooms
Great Queen Street
WC2B 5DA

(Dress code: smart / smart casual)

Day 2 – Tuesday 4th March

08:30 – 11.30 **Session 3: Antisense Oligonucleotide Therapies**
Chairs: Professors Francesco Muntoni (UCL institute of Child Health) and Kate Bushby (University of Newcastle)

08:30 – 09:00 Tricyclo-DNA for the treatment of neuromuscular diseases
Professor Christian Leumann
University of Bern

09:00 – 09:30 AON development for SMA
Dr Arthur Burghes
Ohio State University

09:30 – 10:00 Peptide modified AONs for enhanced potency and tissue targeting
Professor Matthew Wood
University of Oxford

10:00 – 10:30 Antisense approaches to counter skeletal muscle atrophy and fibrosis: targeting myostatin and other strategies
Professor George Dickson
Royal Holloway – University of London

10:30 – 11:00 Coffee

11:00 – 11:30 **MRC Guest speaker**
The MRC in 2014 - evolution and strategy
Dr Declan Mulkeen
MRC Chief Science Officer

11:30 – 12:30 **The Third Victor Dubowitz Lecture**
Molecular Therapies for Neuromuscular Diseases
Professor Jerry Mendell
Ohio State University
Introduced by Professor Francesco Muntoni

12:30 – 12:45 Platform presentation: Peptide-conjugated phosphodiamidate morpholino treatment in mdx mice: cardiac dystrophin restoration and function
Dr Alison Blain
Institute of Human Genetics, Newcastle University

12:45 – 13:00 Platform presentation: High content screening identifies small molecules that remove nuclear foci, affect MBNL distribution and CELF1 protein levels via a PKC independent pathway in Myotonic Dystrophy cell lines
Dr Ami Ketley
School of Life Sciences, University of Nottingham, UK

13:00 – 14:00 **Lunch**

14:00 – 15:00 **Poster guided tours**

Muscular Dystrophies Group b
Muscle Channelopathies and Myasthenia Gravis
Peripheral Nerve Disease
Databases, Diagnostics and Clinical Practice and 'Other'

15:00 – 16:30 Session 4: MRI in Neuromuscular Diseases
Chairs: Professors Tarek Yousry (UCL Institute of Neurology) and Professor Volker Straub (Newcastle University)

15:00 – 15:30 Diffusion Tensor Imaging in Neuromuscular Disease
Professor Klaas Nicolay
Eindhoven University of Technology

15:30 – 16:00 Results from the Imaging DMD study
Doctor Lee Sweeney
University of Pennsylvania

16:00 – 16:15 Platform presentation: Quantitative lower limb muscle MRI in CMT1A demonstrates length-dependent fatty infiltration
Dr Matthew Evans
UCL Institute of Neurology

16:15 – 16:30 Platform presentation: Reducing the cost of MRI in neuromuscular clinical trials: acceleration of fat-fraction measurement in Becker muscular dystrophy by combined compressed sensing and parallel imaging
Dr Kieren Hollingsworth
Institute of Cellular Medicine, Newcastle University

16:30 – 17:00 Poster prizes and close

Abstracts: Invited Speakers

Monday 3rd March 2014

O01
Autologous cell therapy in oculopharyngeal muscular dystrophy (OPMD)

S. Périé[1,2,3,4], C. Trollet[2,3,4], V. Mouly[2,3,4], J. Larghero[5], K. Mamchaoui[2,3,4], B. Bouazza[2,3,4], M. Toy-Miou[6], J.P. Marolleau[5], B. Eymard[7], P. Laforêt[7], F. Chapon[8], G. Butler-Browne[2,3,4], J. Lacau St Guily[1,2,3,4]

[1]Service d'Oto-Rhino-Laryngologie et de Chirurgie Cervico-Faciale, Hôpital Tenon, Faculté de Médecine et Université Paris VI Pierre et Marie Curie, Assistance publique-Hôpitaux de Paris, 4, rue de la Chine, 75020 Paris, France

[2]Centre for Research in Myology/Institut de Myologie, UM76, UPMC Univ. Paris 6, Groupe hospitalier Pitié-Salpétrière, Faculté de Médecine Pierre et Marie Curie, 47, Boulevard de l'Hôpital, 75013 Paris, France

[3]INSERM U974, Paris, France

[4]CNRS UMR 7215, Paris, France

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant inherited, slow progressing, late onset degenerative muscle disorder, characterized by progressive eyelid drooping (ptosis) and difficulties with swallowing (dysphagia). The pharyngeal and cricopharyngeal muscles (CPM) are among the specific targets in OPMD. The genetic mutation is an abnormal expansion of a (GCG)n repeat in the coding region of the ubiquitously expressed poly(A) binding protein nuclear 1 (PABPN1) gene, leading to an expanded polyalanine tract at the N-terminal of the protein.

We have demonstrated that cell cultures isolated from non-affected OPMD muscles have a normal proliferation and differentiation phenotype, whereas cultures isolated from affected OPMD muscles have a reduced myogenicity as compared to control cells. Since OPMD is selectively expressed in a defined group of small muscles and satellite cells can be isolated and amplified from non-affected muscles, we conducted a phase I/II clinical trial in OPMD patients, consisting of the grafting of non affected autologous myoblasts into the pharyngeal muscle during a myotomy.

Results from this trial supports the hypothesis that a local injection of autologous myoblasts in the pharyngeal muscles is a safe procedure in OPMD patients. In addition a dose dependent improvement in swallowing was observed even though this was initially a phase I/II study of toxicity.

O02
Optidystrophin in DMD stem cells

J. Meng[1], J. Counsell[1], M. Reza[2], S. Laval[2], H. Lochmüller[2], A. Thrasher[1], F. Muntoni[1], J. Morgan[1]

[1]UCL Institute of Child Health, London, UK

[2]Institute of Genetic Medicine, Newcastle University, UK

Skeletal muscle stem or precursor cells derived from Duchenne Muscular Dystrophy (DMD) patients contribute to muscle regeneration following their transplantation into immunodeficient mouse models. However, they do not correct the dystrophin deficiency within the regenerated muscle fibres. This may be overcome by transducing such autologous stem cells with dystrophin constructs. Lentiviral vectors efficiently infect quiescent cells, including stem cells and, because they integrate into the host genome, give long-term, heritable, gene expression. However the drawback of lentiviral vectors is their limited cloning capacity (up to 10 kb). We have therefore designed dystrophin constructs that retain key functional elements and investigated their functionality in mdx mice. Lentiviral vectors containing these dystrophin constructs under the control of either the desmin or SFFV promoters were used to transduce DMD muscle stem cells. The function of these lentivirally-modified stem cells was investigated *in vitro* and their ability to regenerate skeletal muscle fibres and produce functional dystrophin was assessed in our *in vivo* mouse model.

O03

Cell therapy for muscular dystrophies

Cossu G[1,2,3], Previtali S[1], Napolitano S[1], Cicalese MP[1], Venturini M[1], Politi L[1], Marktel S[1], Noviello M. [1], Tedesco FS[1,3], Bonini, C[1]., Torrente Y[4] and Ciceri F[1]

[1]*Division of Regenerative Medicine, Department of Neurology and Bone Marrow Transplantation Unit, San Raffaele Scientific Institute,*

[2]*Institute of Inflammation and Repair, University of Manchester.*

[3]*Dept of Cell and Developmental Biology, University College London,*

[4]*Department of Neurological Sciences, University of Milan.*

Mesoangioblasts are progenitor cells, associated with the vasculature and able to differentiate into different types of mesoderm, including skeletal muscle (Minasi et al. Development 129, 2773, 2002). When mesoangioblasts were delivered intra-arterially to muscles of dystrophic mice and dogs they resulted in a significant functional amelioration (Sampaolesi et al. Science 301, 487, 2003; Nature 444, 574, 2006). Human adult mesoangioblasts, isolated and expanded in vitro from muscle biopsies, were shown to correspond to a subset of pericytes (Dellavalle et al. Nature Cell Biol. 9, 255, 2007).

Based on these results, a mono-centre, prospective, non-randomized, clinical phase I/II study of cell therapy with HLA-matched donor human mesoangioblasts in DMD patients started in June 2009, after a one year preliminary study (involving 28 DMD patients, aged 5-10), required to validate outcome measures. Starting on March 2011, three out of these patients (with an HLA-identical donor) underwent successive intra-arterial transplantations at escalating doses of cells, under a continuous regime of immune suppression. Two more patients have been treated the following year. Although the results from the last two patients are still being analyzed, preliminary results indicated safety, a transient stabilization of functional measures and the presence of donor cells and donor derived dystrophin in younger patients, Despite this encouraging trend, clinical efficacy appears still to be reached and new strategies are being devised to this aim and will be discussed.

O04

Protein homeostasis – what does it mean?

G.S. Jackson

MRC Prion Unit and Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK

The human proteome relies on interacting pathways to maintain integrity against both acute and chronic damage. Eukaryotic protein homeostasis, or proteostasis, is the active process required to maintain optimum cellular function and hence the health of an organism. Perturbations in proteostasis can lead to a range of disease states in humans including metabolic, oncological, cardiovascular, neuromuscular and neurodegenerative disorders. In many instances small deficiencies may have long term cumulative effects and there is the potential for intervention using biological and small molecule therapies to have curative actions.

O05

The role of the unfolded protein response in neurodegeneration: a new target for therapy

G. Mallucci

MRC Toxicology Unit, Leicester, UK

Neurodegenerative diseases are characterised by the accumulation of misfolded proteins and neuronal loss. We used prion-diseased mice to understand the link between protein misfolding and neurodegeneration. We found that rising levels of misfolded prion protein (PrP) generated by prion replication lead to sustained over-activation of the branch of the unfolded protein response (UPR) controlling the initiation of protein synthesis. This causes persistent repression of translation, resulting in the catastrophic loss of critical proteins and hence synaptic failure and neuronal death. Localised genetic manipulation of this pathway restored vital translation rates, preventing neurodegeneration in prion-diseased mice, leading us to predict that its pharmacological inhibition would give widespread neuroprotection by the

same mechanism. We have now shown that oral treatment with a specific inhibitor of the kinase PERK, a key mediator of this pathway, prevents development of clinical prion disease and produces marked neuroprotection throughout the brain in mice treated both at pre-clinical stage, and later in disease, when behavioral signs had emerged. Critically, the compound acts downstream, and independently, of the primary pathogenic process of prion replication and is effective despite continuing accumulation of PrP. The compound also prevents neurodegeneration in a tau transgenic mouse model. Thus the data support drug development programs targeting PERK and other members of this pathway for treatment of prion, and potentially other UPR-inducing, neurodegenerative diseases.

O06

Heat shock proteins and protein homeostasis in hereditary neuropathies

V. Timmerman

VIB and University of Antwerp, Belgium

Heat shock proteins (HSPs) are molecular chaperones that protect the cell from various types of stress. Although regulated by stress, some of these proteins are constitutively expressed and responsible for quality control and protein folding. Based on their molecular weight, the heat shock protein family mainly consists of two groups: large and small HSPs. The large HSPs require ATP for their functioning, whereas the small HSPs (HSPBs) are ATP independent. The latter bind improperly folded proteins and assist in the targeting process for refolding or degradation. These HSPBs are not only molecular chaperones but are also involved in many essential cellular processes such as apoptosis, autophagy, splicing, cytoskeleton dynamics and neuronal survival. Here I will focus on HSPB1 (HSP27) as mutations in this small heat shock protein cause an axonal type of Charcot–Marie–Tooth neuropathy (CMT2F). The special cellular and molecular architecture of the peripheral nerve represents a major challenge for the intracellular transport in axons extending for very long distances. Several studies have shown that mutations causing axonal CMT mainly impede the axonal transport. We found that some mutations in HSPB1 display a higher chaperone activity and an enhanced affinity to their client proteins. Tubulin came out as the most striking differential interacting protein, with hyperactive HSPB1 mutants binding more strongly to tubulin and microtubules (MT). This anomalous binding leads to a stabilization of the MT network in a MAP-like manner [Almeida-Souza et al., J Neurosci, 2011; 31: 15320–15328]. A transgenic mouse model for mutant HSPB1, recapitulating the features of CMT2F, confirmed the enhanced interaction of mutant HSPB1 with tubulin. At presymptomatic age the neurons in these animals show a hyperstable MT network, and at symptomatic age the MT network completely lost its stability as reflected by a marked decrease in tubulin acetylation levels [d'Ydewalle et al., Nat Med, 2011; 17: 968–974]. The remodeling capacity of MTs is essential for their proper function. MTs are predominantly formed at the centrosome, but can also originate from non-centrosomal sites. We demonstrated that HSPB1 plays a role in the control of the non-centrosomal MT formation. More specifically, HSPB1 regulates the balance between centrosomal and non-centrosomal MTs. HSPB1 can be detected specifically at sites of de novo forming non-centrosomal MTs, while it is absent from the centrosomes. In addition, we showed that HSPB1 binds preferentially to the lattice of newly formed MTs in vitro, suggesting that it functions by stabilizing MT seeds [Almeida-Souza et al., PLoS One, 2013; 8: e66541]. Mutations in HSPB1 have also been shown to disrupt the neurofilament (NF) network and cause their aggregation. Furthermore, mutations in the neurofilament light gene (NEFL) are associated with axonal CMT (CMT2E). Neurofilaments are the most abundant structural proteins in neurons and play a key role in neurodegeneration. We observed that transduction of neuronal cell lines with mutant HSPB1 affect the NFs axonal transport and binding to the anterograde motor protein kinesin. These deficits were also associated with an increased phosphorylation of NFs as well as an increased phosphorylation of the cyclin dependent kinase Cdk5, which mediates the NF phosphorylation. To confirm the role of Cdk5 in this process, we showed that inhibition of Cdk5 restored the NF phosphorylation and binding to kinesin [Holmgren et al., Acta Neuropathologica, 2013; 126: 93–108]. Altogether, specific mutations in HSPB1 affect the axonal transport via induced hyperphosphorylation of NFs and stabilization of the MT network.

O07

Using proteomic profiling to decipher the pathogenesis of myofibrillar myopathies

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Myofibrillar myopathies (MFM) are a group of genetically heterogeneous muscle disorders characterized by focal disintegration of myofibrils and by the formation of intramyoplasmic protein aggregates. We applied a highly sensitive proteomic approach to decipher the aggregate composition in different MFM subtypes. The aim was to identify novel disease-relevant proteins and subtype-specific proteomic profiles.

Skeletal muscle samples from 63 MFM patients were included in this study. Aggregate samples and intraindividual control samples were collected by laser microdissection and analyzed by a label-free mass spectrometric approach for identification and relative quantification of proteins. We detected more than **4000** different proteins and 108 of these showed a statistically highly significant accumulation in aggregate samples compared to controls. Z-disc and Z-disc-associated proteins constituted the most abundant group of over-represented proteins. We also identified chaperones and proteins involved in protein degradation, sarcolemmal and extracellular proteins, components of signaling pathways and regulators of myofibrillar organization. The comparison of MFM subtypes revealed many similar findings but also significant differences regarding the accumulation ratio and abundance of proteins in aggregates.

Our proteomic data provide important new insights into the composition of pathological protein aggregates in MFM and expand our knowledge about proteins that seem to be involved in pathogenesis. The detection of specific proteomic profiles for different MFM subtypes can be helpful for differential diagnosis.

O08

A gene for speed: *ACTN3*, athletes, evolution and impact on human health

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The human *ACTN3* gene encodes the protein α-actinin-3, a component of the contractile apparatus in fast skeletal muscle fibers. In 1999, we identified a common polymorphism in *ACTN3* (R577X) that results in absence of α-actinin-3 in more than one billion people worldwide, despite the *ACTN3* gene being highly conserved during human evolution. In 2003, we demonstrated that *ACTN3* genotype influences elite athletic performance, and the association between *ACTN3* genotype and skeletal muscle performance has since been replicated in athletes and non-athlete cohorts. We have also studied the evolution of the R577X allele during human evolution and demonstrated that the null (X) allele has undergone strong, recent positive selection in Europeans and Asian populations. We have developed an *Actn3* knockout mouse model that replicates α-actinin-3 deficiency in humans and has already provided insight into the role of α-actinin-3 in the regulation of skeletal muscle metabolism, fibre size, muscle mass and contractile properties. In particular, mouse muscle lacking α-actinin-3 uses energy more efficiently, with the fast fibers displaying metabolic and contractile properties of slow oxidative fibers. While this favors endurance activities, the trade off is that the muscle cannot generate the rapid contractions needed to excel in sprinting. We propose that the shift towards more efficient aerobic muscle metabolism associated with α-actinin-3 deficiency also underlies the adaptive benefit of the 577X allele. We have now shown that α-actinin-3 plays a role in regulating the activity of glycogen phosphorylase and calcineurin activity. Our current studies are focussed on the effect of *ACTN3* genotype on response to exercise, the onset and severity of muscle disease phenotype, glucose homeostasis, and weight gain in response to changes in diet.

O09

Tricyclo-DNA for the treatment of neuromuscular diseases

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Tricyclo-DNA (Tc-DNA) belongs to the class of conformationally constrained oligonucleotide analogues and shows increased biostability and RNA affinity. Tc-DNA has been used previously as antisense oligonucleotides (ASOs) *in vitro* acting either as steric block agents or as splice modulators. Specifically in the latter context Tc-DNA showed improved efficacy as compared to fully modified LNA or 2'OMe-RNA. More recently *in vivo* experiments of Tc-DNA gapmer ASOs targeted against scavenger receptor B1 (SR-B1) showed excellent activity for reducing SR-B1 in liver. The Tc-DNA 20-mer ASO also showed better activity than a corresponding 2'-MOE oligonucleotide in several extra-hepatic tissues such as kidney, heart, diaphragm, lung, fat, gastrocnemius and quadriceps. Currently we are evaluating Tc-DNA for exon skipping or inclusion in neuromuscular diseases such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA). In particular, we have performed a side by side efficacy test of a 2'OMe-RNA 20-mer, a Tc-DNA 15-mer (both as thioates) and a PMO 25-mer in the mdx mouse and found at isomolar concentrations higher exon skipping efficacy and dystrophin levels for Tc-DNA in all tissues.

Tuesday 4th March 2014

O10
Development of PMO antisense oligonucleotides for treatment of Spinal muscular atrophy

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Spinal muscular atrophy (SMA) is caused by loss or mutation of the *SMN1* gene and retention of the *SMN2* gene. The two genes differ from each other by a single nucleotide in exon 7 which alters the incorporation of exon 7 into the transcript. The loss of exon 7 results in a SMN protein that does not oligomerize efficiently and is rapidly degraded. Thus SMA results from a deficiency of SMN and the severity of SMA is dependent on the amount of SMN produced. There are a large number of both positive and negative regulators of splicing in both the *SMN1* and *SMN2* genes. Thus antisense oligonucleotides can be targeted to the negative regulators of exon 7 splicing to enhance incorporation of SMN exon 7. Essentially this can make the *SMN2* gene behave like *SMN1*. From variants that occur in the *SMN2* genes it is predicted that approximately a 25% increase in exon 7 incorporation will correct a two-copy *SMN2* type 1 SMA patient. To date two chemistries of antisense oligos (morpholino and MOE) have been shown to be effective in altering the splicing of the *SMN2* gene. We have used morpholino ASOs to block the negative ISS-N1 regulator of SMN exon 7. A single dose of PMO ASO directed at ISS-N1, administered by ICV at P0 to the delta7 SMA mouse, results in a marked increase in both full-length SMN as well as SMN protein. Furthermore, SMA mice show increased survival from 14 days to over 100 days with excellent correction of both compound muscle action potential (CMAP) and motor unit number estimation (MUNE). Relatively late correction at P6 resulted in improved survival and normalized CMAP in rescued animals. However MUNE was not significantly rescued. We have also investigated re-dosing of the PMO in 28–30 day animals by stereotactic injection. Interestingly, the naked PMO did not spread throughout the CNS and had no impact on SMA mouse survival. We have found a reagent which can be simply mixed with the PMO and results in widespread distribution of the ASO in the CNS of adult animals. When the PMO is re-dosed using this agent the *SMN2* gene has increased incorporation of SMN exon 7 in all areas of the CNS. Re-dosing of SMA animals via CNS delivery results in an additional 100-day increase in survival. We are now investigating other ASO sequences, including bi-functional ASOs and ISS-N2, to increase

SMN produced by *SMN2* and in turn survival of SMA mice. While MOEs using intrathecal delivery are in clinical trial the increased potency and very low toxicity of PMOs offers a second very attractive path for treatment of SMA.

O11

Peptide modified AONs for enhanced potency and tissue targeting

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Oligonucleotides to modulate pre-mRNA splicing have therapeutic potential for a wide range of inherited neuromuscular disorders. The classical example is Duchenne muscular dystrophy (DMD), where modulation of pre-mRNA splicing of the DMD gene can restore a viable reading frame and the expression of a functional protein isoform. This approach is currently being evaluated in clinical trials. A limitation of such methods is the poor ability to deliver oligonucleotides effectively to affected tissues including skeletal muscle, heart and brain. A possible solution to this problem is offered by the use of cell-targeting and cell-penetrating peptides conjugated to or complexed with the oligonucleotide of choice. Such compounds provide greatly improved delivery and enhanced potency and are being developed for future clinical studies in both DMD and for other neuromuscular disorders, such as spinal muscular atrophy.

O12

Antisense approaches to counter skeletal muscle atrophy and fibrosis: targeting myostatin and other strategies

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Myostatin, a secreted growth factor of the TGFβ family, is expressed in skeletal muscle and adipose tissue. Myostatin expression limits the size of muscle during development, and myostatin mutant animals exhibit dramatic increases in muscle mass, reduction in fat mass and resistance to diet-induced and genetic obesity. Inhibition of the myostatin pathway represents a potential therapeutic target to reverse muscle wasting in a range of disease situations such as muscular dystrophies and atrophies, sarcopenia, and disease-induced (COPD, cancer, diabetes) muscle cachexia. Use of blocking antibodies, and of natural or engineered inhibitory binding partners to myostatin such as myostatin propeptide, follistatin and soluble ActRIIB receptor fragments has resulted in increase in muscle mass. These protein delivery strategies are expensive, require repeated dosing, lead to fluctuating levels of active circulating reagent, and can be accompanied by undesirable immune responses. Another method to deliver these therapeuics is via gene therapy, involving the use of non-viral or viral vectors to provide a long term gene-based expression of myostatin inhibitors. Finally, there are oligonucleotide-based strategies to knock-down myostain via RNA interference or antisense mechanisms. Exon skipping is one antisense strategy for knocking down targeted transcripts, by interference with the natural pre-mRNA splicing pattern. We have designed, and evaluated the use of, antisense oligonucleotides of 2'O-methyl phosphorothioate and phosphodiamidate morpholino chemistry targeting the myostatin pre-mRNA to perturb its splicing and provide a mechanism to efficiently inhibit myostatin gene expression activity.

O13

Progress toward molecular-based therapies for muscular dystrophy

J.R. Mendell[1,2,3]

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Multiple therapies are evolving for muscular dystrophies. Two leading candidates include exon skipping and gene replacement therapies. Exon skipping mediated by an RNA modulator, eteplirsen (Sarepta Therapeutics®), provides a platform to build upon for a disease with limited treatment options. Eteplirsen is phosphorodiamidate morpholino

oligomer that modifies gene expression at a pre-mRNA level and heralds an unmatched safety profile. The drug was introduced to skip exon 51 of the DMD gene, targeting a domain of the gene with high mutation rate, potentially reaching 13% of the DMD population. A randomized, double blind protocol for six months demonstrated dystrophin production with open label extension of the study for more than 1 year showing stability in the distance walked on 6MWT. This consistency in walking distance that now extends for 2 years is of particular interest when considered in the context of potentially treating infants with DMD through implementation of a two-tier system of newborn screening (NBS) introduced in the state of Ohio (USA) that tests CK and DNA on the same dried blood card. The safety of eteplirsen might be considered a compelling reason to broaden the scope of NBS.
The initial effort toward gene replacement in DMD also provides a path forward. An unsuspected finding was an immune response to the transgene expressed in a deleted region of the DMD gene. Clinical trialists will be guided by this experience, as well as an immune response triggered by misfolding of newly expressed dystrophin epitopes localized within a defined amino acid pool that primed a cellular response to delivery of a therapeutic mini-dystrophin. In LGMD2D, a disease dominated by missense mutations, the immune system was far more receptive to gene transfer of alpha-sarcoglycan with full-length expression of the transgene. These clinical trials have paved the way forward for a gene delivery through the circulation. The initial approach to be employed utilizes a method of gene recirculation targeting the lower extremity of LGMD2D patients poised for clinical trial (IND 15800). We are also using an alternative approach to improve muscle strength through inhibition of the myostatin pathway by gene delivery of follistatin in Becker muscular delivery. Low (Cohort 1) and High (Cohort 2) dose cohorts received AAV1.CMV.follistatin injections to the quadriceps muscles and year 1 data will be available for presentation.
A novel delivery system has been extensively studied in a pre-clinical effort for adaptation of the dysferlin gene (LGMD2B), usually considered beyond the packaging limits of AAV. We have developed a unique dual vector system using AAV to deliver and express DYSF specifically in muscle. A 1 kb region of homology between two vectors (5' and 3') provided a substrate for recombination that spawns a full-length DYSF gene with successful protein expression and functional membrane repair following both intramuscular and systemic delivery of vectors. This approach is also primed for clinical trial.
These clinical and pre-clinical translational studies will be reviewed in this presentation

O14

Diffusion tensor imaging in neuromuscular disease

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Diffusion tensor magnetic resonance imaging (DTI) provides unique tools for the characterization of skeletal muscle microstructure. The utility of DTI arises from the fact that the Brownian motion of water molecules in skeletal muscle is highly anisotropic as it is strongly affected by the architecture of the tissue. For DTI multiple acquisitions are done that sensitize for diffusion effects in different spatial directions. The subsequent analysis of the directional data yields information on tissue-specific parameters like the apparent diffusion coefficient (ADC) and fractional anisotropy. Analysis of the data in terms of the diffusion tensor provides a means to deduce the direction of principal diffusion in each imaging pixel, which has been shown to correspond to the overall muscle fiber direction. With this information, three-dimensional reconstructions of the muscle architecture can be done, from which in turn key parameters that describe muscle function can be quantified. These parameters include physiological cross-sectional area, pennation angle and fiber length. This presentation will highlight recent advances in the application of DTI to skeletal muscle in general and to investigations in the setting of neuromuscular diseases in particular. For background reading see Refs. (1–7).

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7. Froeling M, Nederveen AJ, Nicolay K, Strijkers GJ. DTI of human skeletal muscle: the effects of diffusion encoding parameters, signal-to-noise ratio and T2 on tensor indices and fiber tracts. NMR in biomedicine 2013; 26(11): 1339–1352.

O15

Emerging results from the Imaging DMD study

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[1]Department of Physical Therapy, University of Florida; [2]Division of Statistics and Scientific Computation, The University of Texas at Austin; [3]Department of Pediatrics and Molecular Genetics & Microbiology, Powell Gene Therapy Center, University of Florida; [4]Oregon Health & Science University; [5]The Children's Hospital of Philadelphia; [6]Shriners Hospital for Children; [7]Department of Physiology and Functional Genomics, University of Florida; [8]Department of Physiology, University of Pennsylvania, USA

The Imaging DMD project is a natural history study to follow a cohort of 100+ DMD boys for five years with periodic MRI, MRS, and functional outcomes evaluations. Based on our studies to date, what are emerging as the most useful MR parameters in terms of sensitivity to disease progress and predictive value are: (1) fat fraction (% of muscle replace by fat) and (2) Quantitative T_2 imaging. Within the study we have observed the impact of corticosteroid initiation a small group of boys as well as make comparisons between boys on and not on steroids. The initiation of corticosteroids was associated with a significant decline in T_2 in 3 months, which was easily detected by both T_2-MRI and spectroscopic relaxometry. A cross-sectional comparison showed significantly lower T_2 values and fat fraction in boys treated with corticosteroids. Boys on corticosteroids showed significantly better performance on the timed functional tests, but no difference was noted in the 6 min walk. Boys on corticosteroids showed a slower progression in intramuscular Fat Fraction compared to corticosteroid naive boys. Our growing data set indicates that MR is well suited to be used as a biomarker in therapy development in DMD. It allows the quantitative assessment of the amount and health of defined skeletal muscles, which will correlate with specific functional measures. Muscle quality measured by MR is strongly related to functional test times/distances. MR measures show disease progression over 3 months. MR measures of muscle quality worsen over 1 year in boys whose functional performance remains stable or improves. MR measures of muscle quality may be able to predict loss of ambulation.

Poster List

Muscular Dystrophies

Guided Poster Session Leads:

Group a) Francesco Muntoni and Sue Brown (group a indicated by *)

Group b) Matt Parton and Katie Bushby (group b indicated by #)

001*	Alison	Blain	See Platform Presentations
002*	Tracey	Willis	Myosin myopathies; a family case study
003*	Rumaisa	Bashir	Development of anoctaminopathy immunodiagnostics using the novel ANO5-5F7 antibody
004*	Calum	Kirk	Pathophysiology of anoctaminopathy (LGMD2L)
005*	Francesco	Catapano	Detection of circulating miRNAs in serum in a mouse model of Collagen VI Deficiency
006*	Debbie	Smith	Development of FSHD2 diagnostic testing
007*	Jaipreet	Bharj	Control of transcription elongation is essential for cardiac and skeletal muscle development.
008*	Emma	Wilson	Development of a novel approach using TALE nucleases to correct duplications in the dystrophin gene.
009*	Houria	Bachtarzi	Adeno-associated virus (AAV)-mediated RNA interference to PABPN1 combined with an optimised resistant transgene for rescue of the muscle specific disease oculopharyngeal muscular dystrophy (OPMD)
010*	Jonathon	Tinsley	Utrophin modulators to treat Duchenne Muscular Dystrophy (DMD): Future clinical trial plans for SMT C1100 and biomarker development programme
011*	Louise	King	Elucidating the immune response to transplanted xenogeneic human mesoangioblasts for cell-based therapies of muscular dystrophies
012*	Morten	Ritso	Hypertrophy in Cardiomyocytes Isolated from mdx Embryos
013#	Rebecca	Fairclough	New orally available compounds which modulate utrophin expression for the therapy of Duchenne muscular dystrophy (DMD)
014#	Rebecca	Moore	Observations on Oligonucleotide Based Therapy for Myotonic Dystrophy

015#	Saam	Sedehizadeh	Longitudinal observational study of myotonic dystrophy type 1: baseline clinical characteristics
016#	Silvia	Torelli	Towards a consensus on biochemical outcome measures for Duchenne Muscular Dystrophy clinical trials
017#	Irina	Zaharieva	Whole exome sequencing in patients with congenital myopathies.
018#	Haiyan	Zhou	Developing allele-selective silencing by antisense oligonucleotide as a therapeutic strategy for autosomal dominant neuromuscular diseases
019#	Haiyan	Zhou	Low doses of antisense oligonucleotide to generate an intermediate mouse model of SMA and explore optimal timing for therapeutic intervention
020#	Mojgan	Reza	Optimised dystrophin mini-constructs for gene delivery
021#	Andrew	Douglas	Strategies for brain targeting using peptide-conjugated antisense oligonucleotides
022#	Ami	Ketley	See platform presentations
023#	Olav	Veldhuizen	SCOPE – DMD (Consortium for Products across Europe in Duchenne Muscular Dystrophy)

Mitochondrial Disease

Guided Poster Session Leads: Robert Taylor and Jo Poulton

024	Jenny	Sharpe	Loss-of-function mutations in MICU1 cause a brain and muscle disorder linked to primary alterations in mitochondrial calcium signalling
025	Daniel	Ives	Clearing cells of mutant mitochondrial DNA by restricting glycolysis
026	Jane	Newman	Can aerobic exercise improve function in patients with mitochondrial disease?
027	Yi	Ng	Sudden unexpected death in adults with m. 3243A>G mutation
028	Amy	Vincent	Investigating mitochondrial dysfunction in the myofibrillar and other protein aggregate myopathies
029	Marina	Bartsakoulia	Behr`s syndrome is a mitochondrial disease due to autosomal recessive mutations in the C12orf65 gene
030	Veronika	Boczonadi	Does a physiological COX isoform switch contribute to the clinical presentation of infantile reversible cytochrome c oxidase

			deficiency?
031	Ewen	Sommerville	Genotypic and phenotypic heterogeneity in adult-onset progressive external ophthalmoplegia (PEO) with mitochondrial DNA instability: a systematic review
032	Grainne	Gorman	Mutations in SPG7 cause chronic progressive external ophthalmoplegia through disordered mtDNA maintenance
033	Joanna	Poulton	Do modulators of mitophagy select pathogenic mtDNA mutations?

MRI

Guided Poster Session Leads: John Thornton and Jasper Morrow

034	Kieren	Hollingsworth	See platform presentations
035	Valeria	Ricotti	Upper Limb Muscle Fat-Water Quantification MRI in Non-Ambulant Duchenne Muscular Dystrophy
036	Chris	Sinclair	Texture Analysis of Muscle MRI Changes Over 1 Year
037	Pedro	Rodriguez Cruz	Muscle MRI in Congenital Myasthenics Syndromes
038	Jasper	Morrow	MRI quantification of fixed myopathy in hypokalaemic periodic paralysis identifies potential therapeutic window
039	Matthew	Evans	See platform presentations
040	Olav	Veldhuisen	BIOIMAGE-NMD (BIOIMAGE-Neuromuscular Diseases)

Muscle Channelopathies and Myasthenia Gravis

Guided Poster Session Leads: Dimitri Kullmann and David Beeson

041	Yasmin	Issop	Investigating the effect of AGRN mutations on acetylcholine receptor (AChR) clustering in vitro
042	Jonathan	Cheung	Pathogenic mechanisms of RAPSN mutations in congenital myasthenic syndromes
043	Karen	Suetterlin	Functional characterisation of the novel CLC-1 variants C179Y and A529V using Two-Electrode-Voltage-Clamp and review of ClC-1 structure–function

044	Michael	Thor	Mutations of the same S4 arginine residue in NaV1.4 can result in either myotonia or hypokalemic periodic paralysis
045	Saif	Huda	Seronegative Myasthenia Gravis- Clinical and Serological Features
046	Alice	Gardiner	Functional Investigation of a Novel Mutation Causing a New Phenotype for the KCNA1 Gene
047	Siobhan	Durran	Loss of Negative Charges within the Voltage Sensor Domain of Nav1.4 results in gating pore currents
048	Jacob	Ross	Integrins are required for synaptic transmission and development of the neuromuscular junction

Peripheral Nerve Disease

Guided Poster Session Leads: Matilde Laura and Kevin Talbot

049	Bernadett	Kalmar	See platform presentations
050	Andreea	Manole	Genetics of riboflavin channels
051	Aisling	Carr	Neuropathy phenotype in Hereditary Transthyretin Amyloidosis
052	Aisling	Carr	MFN2 deletion founder mutation in the UK population.
053	Umaiyal	Kugathasan	Identifying responsive outcome measures in hereditary sensory neuropathy type 1 (HSN1)
054	Alex	Rossor	A dominant negative mutation in FBXO38 is a cause of distal hereditary motor neuropathy (dHMN).
055	Helen	Devine	Are axonal transport deficits present in a novel mouse model of Spinal and Bulbar Muscular Atrophy?
056	Alex	Horga	Whole-exome sequencing in patients with sensory and motor inherited neuropathies
057	Ellen	Cottenie	IGHMBP2 mutations cause recessive axonal neuropathy: Genetic and functional characterisation in seven families.

Glycosylation Disorders, IBM, Muscle Satellite cells and IPS Cells

Guided Poster Session Leads: Henry Houlden and Dominic Wells

058	Jana	Haberlova	Psycho-organic symptoms as early manifestation of adult onset POMT1-related muscular dystrophy

059	Yung-Yao	Lin	Transcriptome analysis in a mouse model of FKRP-deficient muscular dystrophy
060	Elizabeth	Stevens	Shared defective glycosylation pathways link congenital myasthenic syndromes with the dystroglycanopathies
061	Qiang	Gang	Using exome sequencing to investigate disease-causing mutations of muscle disorders with protein aggregates
062	Mhoriam	Ahmed	(Also platform presentation) Investigating the effects of pharmacological up-regulation of the heat shock response in a transgenic mouse model of inclusion body myopathy
063	Addolorata	Pisconti	See platform presentations
064	Charlotte	Whitmore	The Effect of Calorie Restriction on Satellite Cell Function
065	Nicolas	Figeac	See platform presentations
066	Francesco	Tedesco	See platform presentations
067	Silvia	Dibenedetto	Characterisation of the expression of Polycomb Group Genes in human neuromuscular diseases.

Databases, Diagnostics and Clinical Practice, and Other

Guided Poster Session Leads: Ros Quinlivan and Janice Holton

068	Saif	Huda	Improving Diagnostic Sensitivity and Specificity of Musk Cell-Based Assays for Myasthenia Gravis
069	David	Lewis-Smith	Combining old dicta & new techniques to diagnose DOK7-related CMS
070	Renata	Scalco	EUROMAC: Disease registry for McArdle disease and other pure muscle glycogenolytic disorders presenting with exercise intolerance
071	Elizabeth	Harris	International Clinical Outcomes Study in Dysferlinopathy (COS): results of screening questionnaires in UK patients
072	Chris	Buxton	Unraveling the genetic cause in patients with inherited peripheral neuropathy using gene panel testing
073	Rita	Barresi	The National Diagnostic and Advisory Service for Limb-Girdle Muscular Dystrophies in Newcastle
074	Danielle	Ramsey	Improving standards of care and Translational Research in Spinal Muscular Atrophy (SMA) – Functional Scales

075	Tamieka	Whyte	Exome sequencing identifies EPG5 mutations in two siblings with a childhood onset vacuolar myopathy
076	Julia	Maddison	Clinical Research Activity in the Newcastle MRC Centre for Neuromuscular Disease
077	Golara	Torabi Farsani	Collagen XII; Novel disease-causing candidate gene for Bethlem-like patients

Abstracts: Posters and Platform Presentations

Muscular Dystrophies

P1 (Platform presentation)
Peptide-conjugated phosphodiamidate morpholino treatment in *mdx* mice: cardiac dystrophin restoration and function

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Cardiac failure is a major cause of mortality in Duchenne muscular dystrophy (DMD). Antisense-mediated exon skipping has the ability to correct out-of-frame mutations in DMD to produce truncated but functional dystrophin. Traditional antisense approaches have however been limited by their poor uptake into heart. The addition of cell penetrating peptides to antisense molecules has increased their potency and improved uptake into all muscles including heart.

We investigated the efficacy of Pip6a-PMO, for restoration of cardiac dystrophin and rescue of function. *mdx* mice were administered Pip6a-PMO fortnightly from 12 to 30 weeks (4 × 18 mg/kg then 8 × 12.5 mg/kg i.v) alongside mock-injected control mice. Cardiac function was analysed by MRI and conductance catheter at 32 weeks and muscles were harvested for dystrophin quantification.

Treatment with Pip6a-PMO resulted in a modest but significant restoration of dystrophin, sufficient to significantly improve cardiac output and normalise left ventricular volumes and contractile indices.

These encouraging data suggest that total restoration of dystrophin may not be required to significantly improve cardiac outcome in DMD patients and that it may be realistic to expect functional improvements with modest levels of dystrophin restoration, which may be achievable in future clinical trials.

P2
Myosin myopathies; a family case study

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Background: Hereditary myosinopathies have emerged as an important group of diseases with variable clinical and morphological expression depending on the mutated isoform and type and location of the mutation.

Distal arthrogryposis syndromes are associated with dominant mutations in developmental MyHC isoform genes (MYH3 and MYH8), whereas early-onset myopathies are associated with either dominant or recessive mutations affecting the type IIa MyHC (MYH2). These myopathies can have variable muscle weakness and ophthalmoplegia. Dominant mutations in the gene for slow/b cardiac MyHC (MYH7) is usually associated with scapuloperoneal myopathies, distal or limb-girdle muscle weakness, such as myosin storage myopathy and Laing distal myopathy.

Patients: We describe a consanguineous family presenting with axial, hip flexor, neck and facial weakness, opthalmoplegia and scoliosis. The proband, initially seen at age 4 years, had ophthalmoplegia, mild proximal and truncal weakness and a scoliosis. At the consultation his mother was also noted to have mild proximal and truncal weakness, ophthalmoplegia and ptosis (from her early 20's). She was 12 weeks pregnant and subsequently this child has developed similar problems. Ptosis, scoliosis and myopathy have been reported in other family members.

Results: The proband's biopsy shows features suggestive of a congenital myopathy with variation in fibre size, populations of smaller fibres and core like areas. A novel but apparent pathogenic recessive splice site mutation in MYH2 was identified.

Conclusions: Hereditary myosinopathies are emerging as an important group of diseases. MYH2 should be considered particularly if there is an early onset mild myopathy, particularly truncal and facial, and ophthalmolplegia.

P3

Development of anoctaminopathy immunodiagnostics using the novel ANO5–5F7 antibody

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Recessive mutations in the anoctamin 5 gene (ANO5) cause the muscular dystrophies LGMD2L and MMD3, designated the "anoctaminopathies". Many ANO5 mutations are being reported and of these the c.191dupA exon 5 mutation and the exon 20 R758C mutation are prevalent in Europe. ANO5 belongs to the anoctamin protein family consisting of ten human proteins, ANO 1–10, which have been functionally grouped into ion channels or dual ion channel/scramblases respectively. The function of ANO5 is not known nor the pathomechanisms involved in anoctaminopathy.

To improve ANO5 immunodiagnostics and increase our understanding of ANO5 function we have generated a monoclonal ANO5 antibody designated ANO5–5F7. We have demonstrated that ANO5–5F7 is a specific C-terminal ANO5 antibody. We have examined the immunodiagnostic potential of ANO5–5F7 antibody by immunoblotting anoctaminopathy muscle lysates ($n \geq 23$) and immunolabelling anoctaminopathy fibroblasts ($n = 5$) respectively. Our results demonstrate that ANO5–5F7 antibody is suitable for anoctaminopathy immunodiagnostics which requires a combined approach of immunoblotting muscle lysates and immunofluorescent analysis of cultured fibroblasts or myoblasts.

P4

Pathophysiology of anoctaminopathy (LGMD2L)

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Background: Anoctamin 5 (ANO5), suggested as function as calcium activated chloride channel, is the causative gene underlying LGMD2L and Miyoshi muscular dystrophy 3 (MMD3). These 'anoctaminopathies' are the third most common muscular dystrophies in the North of England. Like all LGMDs, LGMD2L is characterised by weakness of the shoulder and hip musculature, generally increasing in severity with age.

Aims: To understand the subcellular localisation of ANO5.

Methods: A GFP tagged ANO5 construct was co-transfected into cell lines with plasmids containing organelle specific markers for endosomes, endoplasmic reticulum, peroxisomes and Golgi apparatus. The same GFP tagged ANO5 construct was electroporated into the tibialis anterior (TA) muscles of mdx mice. GFP only, alternatively tagged ANO5 and mini-dystrophin constructs were also used as controls.

Results: Co-localisation data of GFP tagged ANO5 with organelle specific markers suggests that anoctamin 5 localises to the endosomes in both MIN6 and NIH3T3 cell lines. Electroporation of mouse muscle shows the presence of GFP positive fibres in specific muscle compartments.

Conclusion: The use of GFP tagged constructs in localisation studies is a valuable resource in further investigating ANO5 location and function, especially in light of the absence of a specific primary antibody. It allows for inference of protein location via visualisation of fluorescence patterns as well as further confirming localisation through staining of the GFP tag itself. The localisation data for ANO5 in this study suggest further routes of investigation into this proteins function and how distortion of this function leads to LGMD2L.

P5

Detection of circulating miRNAs in serum in a mouse model of Collagen VI Deficiency

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The highly heterogeneous group of congenital muscular dystrophies (CMDs) includes a range of myopathies, classified in groups based on the phenotype or the affected gene. At least 20 genes have been identified as causative for CMDs, among these are the 3 *COL6A* genes. Mutations disrupting *COL6A1, COL6A2 or COL6A3* genes result in impaired link between the muscle fibres and the extracellular matrix and lead to Ullrich CMD (UCMD) or Bethlem myopathy (BM). The development of a mouse model with targeted inactivation of the Col6a1 gene (*Col6a1*$^{-/-}$) has helped in understanding the disease mechanism. *Col6a1*$^{-/-}$ mice show an early onset myopathic disorder which resembles human UCMD and BM.
MicroRNAs are short (~20–23 nucleotides) non-coding RNAs that regulate gene expression by binding to specific mRNA targets and promoting their degradation or translational inhibition. Recent studies showed that specific serum miRNAs have dysregulated levels in Duchenne Muscular Dystrophy patients compared to healthy individuals and the level of miRNAs correlated with the clinical phenotype.
With the aim of identifying circulating miRNAs that are associated with the myopathic changes in UCMD and BM, we performed high-throughput expression profiling of miRNAs in serum of *Col6a1*$^{-/-}$ (n = 4) and wild type mice (n = 4). The preliminary data indicate a difference in the level of miRNAs between *Col6a1*$^{-/-}$ and wild type mice, which will be validated in the next weeks and presented at the meeting.

P6
Development of FSHD2 diagnostic testing
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Facioscapulohumeral muscular dystrophy, affecting 1 in 20,000 individuals, is characterised by progressive wasting of facial and upper body muscles. FSHD is caused by hypomethylation of chromosome 4q35, allowing expression of DUX4 (toxic to myoblasts). 95% of cases are FSHD1 (OMIM 158900) caused by contraction of D4Z4 repeats at 4q35 leading to allele specific hypomethylation and DUX4 expression in the presence of a permissive haplotype. ~2% of cases are due to an extended deletion of D4Z4. The remaining 3% of cases are FSHD2 (OMIM 158901), characterised by hypomethylation and chromatin relaxation of D4Z4 array (independent of size), allowing DUX4 expression.
Lemmers *et al.* (2012) identified mutations in *SMCHD1* (18p11.23) causing global hypomethylation of D4Z4 arrays, leading to DUX4 expression. Hartweck *et al* (2013) identified a region showing intense hypomethylation in FSHD2 (DR1). We have developed a novel pyrosequencing assay for quantification of methylation using 10 sites within DR1. A pilot UK cohort of 15 clinically typical FSHD1 negative patients (assessed by clinical proforma) and recruited/consented by geneticists/neurologists were assessed for hypomethylation. followed by *SMCHD1* sequencing. 9/15 patients had hypomethylation and candidate *SMCHD1* mutations were identified in all 9 patients (3 missense, 1 non-sense, 1 duplication, 2 deletions, 2 potential splice site). 3 patients without hypomethylation were sequence negative. Family studies are on-going.
This study has informed a UKGTN gene dossier application that has supported commissioning of testing for FSHD2 from April 2014 and will facilitate direct translation of this work into clinical service. We present the results of this study, illustrated by interesting cases.
R.L.F. Lemmers et al. (2012). Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nature Genetics, vol. 44, no. 12, pp. 1370–1374.
L. Hartweck, L. Anderson and R. Lemmers (2013). A focal domain of extreme demethylation within D4Z4 in FSHD2. Neurology, epub: 10.1212/WNL.0b013e31827f075c.

P7
Control of transcription elongation is essential for cardiac and skeletal muscle development
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Background: Gene expression is often regulated at the level of transcriptional elongation, when RNA polymerase II pauses along nascent mRNAs, effectively arresting gene transcription. Its activity is resumed following the recruitment of transcription elongation factors (TEFs). This level of regulation is widespread in particular among genes that are developmentally regulated, but its role in the development of specific organs is not well understood.
Aims and Methods: To determine whether the control of transcriptional elongation plays a role in development of cardiac and skeletal muscle *in vivo*, using zebrafish as a model organism.
Results: We knocked down expression of a specific TEF using antisense morpholino oligonucleotides in zebrafish. Morphants present with severe defects in cardiac development, including oedema, looping defects and absent circulation. In skeletal muscle, myofibres detach from the myosepta. These defects are similar to those observed in mutants for dystrophin and integrins. Surprisingly, expression of these genes was maintained in TEF morphants, suggesting that novel candidates may be involved. Global analysis of gene expression via microarray and RT-PCR shows deregulated expression of numerous genes involved in heart and skeletal muscle development.
Conclusions: The control of transcriptional elongation plays crucial roles in the development of cardiac and skeletal muscle, and suggests that alterations in this process may underlie cardiomyopathies and muscular dystrophy in patients.

P8

Development of a novel approach using TALE nucleases to correct duplications in the dystrophin gene

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Background: Duchenne Muscular Dystrophy (DMD), caused by a mutation in dystrophin, is the most common inherited muscular disease. DMD patients suffer progressive weakening of muscles, and ultimately heart and respiratory failure, leading to premature death.
Aims: Here we propose a genome editing method to remove duplications in the dystrophin gene (*DMD*) (cause of 5–10% of DMD cases). Transcription activator-like effector nucleases (TALENs) insert a DNA double strand break (DSB) in a specified region of the genome. By targeting TALENs to duplicated intronic regions of dystrophin, we aim to produce two DSBs flanking one copy of the duplicated region, leaving the cell to repair the DSBs by non-homologous end joining, removing the duplication.
Methods or Patients or Materials: TALENs have been introduced by transfection as well as integrated into a viral vector for delivery into HEK293 cells and patient-derived fibroblasts.
Results and Conclusion: We have identified a TALEN that targets with high efficiency the DMD gene. Current work is aimed at establishing a viral expression system and determining repair of duplications in DMD-derived cell lines.

P9

Adeno-associated virus (AAV)-mediated RNA interference to PABPN1 combined with an optimised resistant transgene for rescue of the muscle specific disease oculopharyngeal muscular dystrophy (OPMD)

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Background: OPMD is an autosomal dominant, late-onset muscle disorder, caused by a trinucleotide repeat expansion in PABPN1 resulting in an N-terminal expanded polyalanine tract and intracellular inclusions of aggregated expPABPN1. PABPN1 promotes interaction between the poly(A) polymerase and the cleavage and polyadenylation specificity factor and controls the length of mRNA poly(A) tails, mRNA export from the nucleus, and alternative poly(A) site usage.
Aims: We ought to design a gene therapy strategy based on RNA interference to silence mutant PABPN1, combined with a codon-modified sequence resistant to degradation using AAV as a vector.

Methods: Viral plasmids containing shRNA constructs (pAAV-sh131, pAAV-sh132, pAAV-sh133) and RNA polymerase III promoters were designed in collaboration with BENITEC BIOPHARMA. A viral plasmid expressing a codon-optimised PABPN1 under a muscle specific promoter (pAAV-spc512-OPTPAB) was synthesised by Geneart. Knock-down efficiency was assessed *in vitro* and *in vivo* (A17 mice) by western blotting and quantified using ImageJ.
Results: pAAV-sh131, pAAV-sh132 and pAAV-sh133 gave 40%, 90% and 95% knock-down of PABPN1 expression, respectively, *in vitro*. scAAV8 expressing sh133 injected into *TA* muscles gave 90% knock-down of PABPN1 expression *in vivo.* Co-transfection studies showed resistance of pAAV-spc512-OPTPAB to sh133 degradation *in vitro*.
Conclusion: PABPN1 can be efficiently knocked-down *in vitro* and *in vivo.* Studies are on-going to investigate PABPN1 knock-down and replacement on muscle function *in vivo.*

P10

Utrophin modulators to treat Duchenne Muscular Dystrophy (DMD): Future clinical trial plans for SMT C1100 and biomarker development programme

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Background: Utrophin modulation i.e. the re-programming of utrophin transcription such that utrophin RNA and protein is continually expressed in mature fibres is expected to be disease modifying in DMD. SMT C1100 is a small molecule utrophin modulator demonstrating significant benefit on the muscular dystrophy in the dystrophin deficient mdx mouse. These data led to the nomination of SMT C1100 as the candidate for evaluation in DMD clinical trials.
In 2012 we reported that SMT C1100 successfully completed a Phase 1 healthy volunteer trial in which an oral paediatric formulation was deemed safe and well tolerated with plasma levels well above those determined to be effective to modulate utrophin levels in cells and animals.
Aims: The first DMD patient trials of SMT C1100 have started with a safety and dose finding Phase 1b study in DMD boys with plans to follow on with a proof of concept Phase 2 study in 2014. In order for proof of concept to be demonstrated in patients, a multicomponent biomarker strategy has been implemented that comprises of two modules; (i) quantification of utrophin levels and evidence of reduction in muscle regeneration in muscle biopsies and (ii) quantification of specific miRNAs associated with fibre leakage and peptide markers of active fibrosis in serum samples.
Results: We aim to present the patient clinical trial plans and data from candidate biomarkers tested both in DMD samples and dystrophin deficient animals.

P11

Elucidating the immune response to transplanted xenogeneic human mesoangioblasts for cell-based therapies of muscular dystrophies

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Background: Mesoangioblasts are vessel-associated stem/progenitor cells derived from human skeletal muscle pericytes. Mesoangioblasts have the ability to differentiate into skeletal muscle myofibres and migrate across vessels walls, features that make their intra-arterial delivery desirable as treatment for muscular dystrophies. However, several unknown factors appear to cause sub-optimal engraftment of human mesoangioblasts into immune-deficient murine skeletal muscle (important to assess pre-clinical efficacy of the strategy). Therefore the overall aim of the project is to study the host mouse response to xenogeneic muscle stem cell transplantation, in particular, the recruitment and role of macrophages.
Methods: Mdx/scid mice were intramuscularly injected with human mesoangioblasts. One week later, gastrocnemius and quadriceps muscles were taken for FACS analysis to determine the infiltration of macrophages, whilst the tibialis anterior was taken for immunofluorescence analysis, to identify the position of macrophages around the transplanted human cells.
Results: Preliminary results showed that CD68+ cells/macrophages are the main identifiable subset of innate immunity cells present surrounding mesoangioblasts within the transplantation scar

(approximately 44%), followed by CD11b+ cells (approximately 2%). Further analyses are currently ongoing.
Conclusion: Mouse CD68+ macrophages are associated with transplanted human mesoangioblasts and may have a role in preventing their optimal xenogeneic engraftment.

P12
Hypertrophy in cardiomyocytes isolated from mdx embryos
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Background: Potential therapies for Duchenne Muscular Dystrophy (DMD) must target both skeletal and cardiac muscle tissues. However, there is a shortage of *in vitro* models of cardiomyocytes for testing therapies.
Aim: Here we propose a method that may be used as an assay for testing DMD therapies in cardiomyocytes.
Methods: Our protocol investigates cardiomyocytes isolated from mdx and C57BL/10 control mouse embryos. These cardiomyocytes are subjected to a serum content reduction and their hypertrophic response to this quantified by area and volume measurements.
Results: Both mdx and C57BL/10 mouse cardiomyocytes undergo a rapid hypertrophic response upon serum reduction. However, the overall increase in size is more drastic in dystrophic cells. It is possible to ameliorate the mdx cardiomyocyte hypertrophic response with various therapeutic compounds proposed as therapeutic agents in DMD.
Conclusion: Dystrophic cardiomyocyte hypertrophy can be used as an outcome measure for *in vitro* assessment of various therapeutics that target cardiac tissue.

P13
New orally available compounds which modulate utrophin expression for the therapy of Duchenne Muscular Dystrophy (DMD)
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DMD is a devastating X-linked muscle-wasting disease caused by lack of the cytoskeletal protein dystrophin. By pharmacologically modulating the dystrophin-related protein utrophin, we aim to develop a therapy applicable to all DMD patients by targeting the primary defect and restoring sarcolemmal stability. In partnership with Summit plc we previously developed SMT C1100; a small molecule utrophin modulator that reduced dystrophic symptoms in the mdx mouse. As a potential first-in-class molecule, SMT C1100 recently successfully completed a Phase 1 trial and DMD patients are currently being dosed in an ongoing Phase 1b trial.
The successful clinical progression to-date provides crucial proof-of-concept for the strategy we developed. We are now developing next generation utrophin modulators using an improved drug screening assay based on immortalised myoblasts from the utrophin luciferase knock-in mouse. This enables us to screen utrophin in its genomic context, better mimicking the *in vivo* situation and enabling identification of compounds which modulate utrophin through regulatory pathways outside of the 8.4 kb promoter fragment used in our previous screen. Screening a filtered subset (7000 molecules) from our 25,000-member compound collection, selected to maximise drug-like properties and the hit rate, has identified at least four structural classes which significantly increase utrophin in mouse and human DMD myoblasts. The compounds exhibit favourable solubility, stability, oral absorption and are well tolerated in the mouse. Structure-analogue relationship studies are well underway to allow us to improve compound effectiveness and optimise drug-like properties.

P14
Observations on oligonucleotide based therapy for myotonic dystrophy
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Background: One of the longstanding problems of oligonucleotide based therapies is efficient delivery of the oligonucleotides *in vivo*. In myotonic dystrophy (DM1) expanded CUG repeat (CUG^{exp}) mRNAs aggregate in the nucleus forming "foci". Unlike the situation in other conditions where the RNA target is cytoplasmic, in DM1 there is a requirement for nuclear delivery of oligonucleotides.
Aims: To assess the therapeutic usefulness of chemically modified oligonucleotides (CMOs).
Method: Testing CMOs effectiveness at disrupting nuclear foci in a cell based assay using high content imaging to visualise the number, size and intensity of foci. CMOs tested: deoxyribonucleic acids (DNA), Peptide nucleic acids (PNAs), 2'OMethyl (2'OMe), locked nucleic acids (LNAs) and morpholino oligonucleotides, tested on both DM fibroblast and myoblast lines.
Results: Initially two types of CMOs; PNA and 2'OMe, were seemingly taken up via gymnosis by DM cells, and removed foci at nanomolar concentrations. However further investigations using live cell and fluorescent imaging techniques demonstrated that fixing methods and insitu hybridisation procedures disrupt the localisation of the CMOs, giving false representation of nuclear delivery.
Conclusion: Using confocal microscopy we have demonstrated that CMOs of various types are up taken into the cells via gymnosis but do not cross the nuclear membrane. We are currently developing new methods to promote non-toxic nuclear delivery to improve CMOs suitability for therapeutic use.

P15
Longitudinal observational study of myotonic dystrophy type 1: baseline clinical characteristics
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Background: Myotonic dystrophy type 1 (DM1), an autosomal dominant inherited disease, is the most common form of adult-onset muscular dystrophy with a prevalence of 1 in 8000 worldwide. The molecular defect associated with DM1 consists of an expanded (CTG)n repeat (from 37 to several thousands) within the noncoding 3' untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome 19q35 with the number of repeats in lymphocytes broadly correlated with age at onset and severity of disease. Early weakness and atrophy of the tibialis anterior and finger flexor muscles reflect a distal to proximal slow progression of the disease with a highly variable phenotype. As therapeutic trials are being developed for DM1, methods to assess their effects on muscle function are needed.
Aim: The main aim is to gather data in a genotyped cohort of patients to identify outcome measures of muscle function and evaluate any changes in body composition (using dual-energy X-ray absorptiometry) and gene expression in vastus lateralis muscle biopsies over a 36 month follow-up study.
Baseline clinical data: Here, baseline clinical characteristics (manual muscle testing score, quantitative hand-held dynamometry for ankle dorsiflexion, grip dynamometry and 6 minute walk test according to a standardised protocol) of 31 patients currently recruited to the study are presented.

P16
Towards a consensus on biochemical outcome measures for Duchenne Muscular Dystrophy clinical trials
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Background: Experimental therapies aimed at restoring dystrophin expression are progressing through clinical trials, but their efficacy is difficult to reliably assess and compare due to a lack of standardised biochemical outcome measures to quantify dystrophin.

Aims: To compare dystrophin quantification methods and reach a consensus on the most reliable method.
Methods: Five laboratories performed a comparative analysis of a single reference set of normal and dystrophinopathy muscle biopsies using previously agreed standardised quantitative immunohistochemistry and western blotting protocols.
Results: Results were highly concordant with minimal inter- and intra-laboratory variability, particularly with quantitative immunohistochemistry. There was a good level of agreement between data generated by immunohistochemistry and western blotting, although immunohistochemistry was more sensitive. Furthermore, mean dystrophin levels determined by two alternative quantitative immunohistochemistry methods were essentially identical.
Conclusion: The combined use of quantitative immunohistochemistry and western blotting are reliable biochemical outcome measures for DMD clinical trials, and standardised protocols can be comparable between competent laboratories. The methodology validated here will facilitate the development of experimental therapies focused on dystrophin production and their regulatory approval.

P17
Whole exome sequencing in patients with congenital myopathies
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During the last decade a growing number of genes causing Congenital myopathies (CMs) have been discovered, however, additional novel genes are yet to be identified as genetic diagnosis has not been established in many patients with CMs.
We carried out whole exome sequencing (WES) in eighteen patients with CM, where mutations in suspected genes had been excluded. The WES was performed by deCODE genetics and the data analysed using deCODE Clinical Sequence Miner Tool.
Recently, a homozygous missense mutation in exon 10 of *STAC3* gene was identified in patients with Native American myopathy. Analysis of WES data in our cases identified a homozygous *STAC3* mutation in a patient with King-Denborough syndrome and core-like changes on muscle biopsy.
A second patient with a severe phenotype and muscle biopsy changes suggestive of nemaline myopathy, carried a homozygous missense mutation in *KLHL40*. Mutations in *KLHL40* have been very recently identified as a frequent cause of severe autosomal-recessive nemaline myopathy.
Two heterozygous truncating *TTN* mutations were detected in a patient with severe cardiomyopathy and muscle biopsy suggestive of a centronuclear myopathy (CNM), supporting the emerging data that *TTN* mutations should be investigated as causative in cases with unresolved CNM.
By applying WES, we were able to reveal the molecular defect in 3 out of 18 patients in whom mutations in recently described genes causing CM were identified, showing that these genes should be considered in diagnostic testing. The remaining cases carried mutations in potentially novel genes which are under investigation.

P18
Developing allele-selective silencing by antisense oligonucleotide as a therapeutic strategy for autosomal dominant neuromuscular diseases
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Background: Antisense oligonucleotide (AON) technology has been successfully applied as experimental therapies in neuromuscular disorders, e.g. in Duchene muscular dystrophy and spinal muscular atrophy, by manipulating pre-mRNA splicing. In addition to the strategies of exon skipping and exon inclusion, allelic-specific silencing by AON has recently been investigated in some neurodegenerative genetic diseases and has shown its therapeutic potential. This strategy is potentially applicable to dominant genetic disease in which haploinsufficiency is not pathogenic. In the paediatric neuromuscular field, typical common examples are congenital muscular dystrophy

caused by dominant mutations in the 3 *COL6A* genes and congenital core myopathies caused by dominant mutations in *RYR1* gene.
Aims: We aim to develop allele-specific targeting with AON to induce out-of-frame exon skipping and deplete the mutant allele by RNA nonsense-mediated decay. This strategy is theoretically feasible to specifically silence the allele where the dominant mutation resides while keeping the wild type allele intact.
Methods and Materials: Exonic single nucleotide polymorphisms (SNPs) in the *RYR1* gene with high frequency of heterozygosity were identified. AONs with 2'-O-methyl phosphorothiate chemistry were designed to target the candidate SNPs. Skipping of target exons and its consequences on the expression of RNA and protein were evaluated in an immortalized skeletal muscle cell line.
Results: Skipping of exon 51 in *RYR1* gene was confirmed at the RNA level by reverse transcript PCR and sequencing. Monoallelic expression of SNPs in exon 51 and its flanking exons were confirmed by cDNA sequencing. Furthermore, western blot showed the reduction of RyR1 protein in differentiated myotubes after AON treatment.
Conclusion: Allele-specific silencing by out-of-frame exon skipping induced by AON is a feasible approach as an experimental therapy for dominantly inherited congenital core myopathies caused by *RYR1* gene mutations.

P19
Low doses of antisense oligonucleotide to generate an intermediate mouse model of SMA and explore optimal timing for therapeutic intervention
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Background: The clinical subtypes of spinal muscular atrophy (SMA) range from the most severe form (type I), to intermediate type II, type III and the mild adult-onset (type IV). While the severe transgenic mouse models may mimic type I SMA with short lifespan and severe neuromuscular involvement, the mild mouse model is essentially free from clinical neuromuscular manifestation, therefore not recapitulating the phenotype of milder SMA patients.
Aims: We aim to: (1) generate an intermediate SMA mouse model which may mimic the less severe subtypes, e.g. type II and type III SMA; and (2) explore the therapeutic window in the less severe SMA mice.
Methods and Materials: Severe type I SMA mice [$(SMN2)2^{+/-}$; $smn^{-/-}$] were given a single low (sub-therapeutic) dose of a 25-mer Morpholino antisense oligomer (PMO25), designed to induce SMN2 exon 7 inclusion, at postnatal day 0 (PND0) or prenatally. A series of injections was performed thereafter at different time points. The investigated parameters include survival, splicing of *hSMN2* in organs and neuromuscular system pathology.
Results: The treated SMA mice exhibit a modestly extended lifespan with moderately improved neuromuscular histopathology. Sudden onset of hind limb paralysis was observed in most of the mice given a single low dose of PMO25 injected prenatally. The second administration of PMO25 at PND5-PND10 significantly improved the lifespan of these pre-treated and symptomatic mice. However, repeated injections at weekly intervals did not give any additional benefit.
Conclusion: We generated an intermediate SMA mouse model by administering severe SMA mice low dose of therapeutic morpholino oligomer. Our results also suggest that the window of therapeutic response in these intermediately affected mice is wider than in the severe SMA I mice.

P20
Optimised dystrophin mini-constructs for gene delivery
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The aim of our project is to obtain an optimal dystrophin construct that will be lentivirally-transduced into skeletal muscle stem cells derived from Duchenne muscular dystrophy (DMD) patients. These stem cells would restore functional dystrophin expression following their transplantation into dystrophin-deficient skeletal muscles. To this end, we have cloned several, different dystrophin truncated forms ranging from 4.2 kb to 8.4 kb cDNA, encoding various components of the dystrophin molecule that may be used in a lentiviral system focusing on

elongated transcript length and selected dystrophin domains. The constructs were assessed for functionality using intramuscular injection and electroporation into mdx muscle. The construction, cloning strategy and characterisation of the constructs as well as first functional results will be presented. We are aware of challenges to gene transfer approaches and know that further long-term experiments are required to assess the potential of this strategy, but this project may bring us closer to a robust and reproducible system for testing functionality of both engineered and naturally occurring dystrophin mutants.

P21

Strategies for brain targeting using peptide-conjugated antisense oligonucleotides

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Background: The blood–brain barrier (BBB) presents a major obstacle to systemic use of oligonucleotides to treat neuromuscular disorders. The ability of oligonucleotides to penetrate the BBB can be evaluated by assessing exon skipping in central nervous system (CNS) tissues of the *mdx* mouse model of Duchenne muscular dystrophy (DMD).
Aims: We have tested several putative brain-targeting peptides conjugated to phosphorodiamidate morpholino oligonucleotides (PPMOs) that induce *Dmd* exon 23 skipping. We have also investigated BBB morphology and permeability in *mdx* mice.
Methods: Mice were systemically administered with PPMOs and tissues subsequently assessed for exon 23 skipping. Fluorescently-labelled PPMOs were also injected and imaged to analyse distribution and clearance. BBB permeability was analysed by fluorescent tracer accumulation in brain following systemic injection. BBB morphology was assessed by immunofluorescence and electron microscopy.
Results: Single PPMO injections have not demonstrated BBB penetration or CNS exon skipping. However, tissue distribution is widespread, including accumulation in choroid plexus. BBB morphology is grossly normal in *mdx* mice and permeability similar to wild-type except at P14, where some increased permeability is seen.
Conclusion: Understanding PPMO uptake and kinetics will likely influence their ability to achieve CNS delivery. The BBB of *mdx* mice appears generally similar to wild-type in adults but there may be subtle developmental differences in permeability.

P22 (Platform presentation)

High content screening identifies small molecules that remove nuclear foci, affect MBNL distribution and CELF1 protein levels via a PKC independent pathway in myotonic dystrophy cell lines

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Myotonic dystrophy (DM) is a multi-system neuromuscular disorder for which there is no treatment. We have developed a medium throughput phenotypic assay, based on the identification of nuclear foci in DM patient cell lines using *in situ* hybridization and high-content imaging to screen for potentially useful therapeutic compounds. Two compounds that reduce and/or remove nuclear foci have been identified, Ro 31–8220 and chromomycin A3. Ro 31–8220 is a PKC inhibitor, previously shown to affect the hyperphosphorylation of CELF1 and ameliorate the cardiac phenotype in a DM1 mouse model. We show that the same compound eliminates nuclear foci, reduces MBNL1 protein in the nucleus, affects *ATP2A1* alternative splicing and reduces steady-state levels of CELF1 protein. We demonstrate this effect is independent of PKC activity and conclude that this compound may be acting on alternative kinase targets within DM pathophysiology.

P23

SCOPE-DMD (Exon Skipping COnsortium for Products across Europe in Duchenne Muscular Dystrophy)

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The SCOPE-DMD project builds on results from the TREAT-NMD and BIO-NMD European projects to investigate a personalised-medicinal product through to market for the treatment of Duchenne Muscular Dystrophy (DMD). The initial goal of the SCOPE-DMD project is to develop a therapy that can restore the expression of a functional dystrophin protein in a targeted DMD patient that would potentially benefit from skipping of exon 45 of the DMD gene. The project uses an innovative clinical study design and novel outcome measures to reduce development timelines. Based on extensive experience from classical clinical trials of two other AONs in DMD patients, the consortium has worked on a highly innovative development plan that if successful, could be applied to future clinical trials in DMD and other rare diseases. Also novel biomarkers and functional outcome measures will be incorporated in additional to more established ones. Multiple layers of expertise and scientific knowledge come together in this SCOPE-DMD project consortium to launch an innovative drug product but also to provide a regulatory and pathway-to-market precedence in order to benefit future patients with rare disorders getting earlier access to treatment.

Mitochondrial Disease

P24

Loss-of-function mutations in *MICU1* cause a brain and muscle disorder linked to primary alterations in mitochondrial calcium signalling

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Aims: Mitochondria play a key role in cellular Ca^{2+} homeostasis [1]. Mitochondrial Ca^{2+} uptake through the Mitochondrial Ca^{2+} Uniporter (MCU) links cytosolic Ca^{2+} signals to the regulation of oxidative phosphorylation, which matches energy supply with demand (e.g. during muscle contraction). Individuals with mutations in *Mitochondrial Calcium Uptake 1* (*MICU1*), a regulator of the MCU, have a novel disease phenotype characterised by proximal myopathy, learning difficulties

and a progressive extrapyramidal movement disorder [2]. We have therefore explored the pathophysiological consequences of the functional loss of MICU1.
Patients and Methods: Fibroblasts from skin biopsies from affected subjects were cultured and live cell fluorescence imaging used to probe mitochondrial function, morphology or Ca^{2+} signalling, which was also studied using luminescence measurements of aequorin targeted to the mitochondrial matrix or to the cytosol. Mitochondrial respiration was measured using high resolution respirometry using the Oroboros Oxygraph 2k.
Results: While mitochondrial membrane potential and mitochondrial respiration were normal, a significant number of MICU1-deficient cells displayed fragmented and Ca^{2+}-loaded mitochondria at rest. Rates of agonist-induced mitochondrial Ca^{2+} uptake were increased in patient derived fibroblasts while cytosolic Ca^{2+} responses were reduced. Viral expression of MICU1 rescued this phenotype. Dynamic measurements of agonist stimulated cytosolic and mitochondrial Ca^{2+} signals revealed that MICU1 deficiency causes a loss of physiological co-operative sigmoid regulation of mitochondrial Ca^{2+} uptake.
Conclusion: These findings reveal the role of *MICU1* as a signal-noise discriminator for mitochondrial Ca^{2+} handling. The loss of *MICU1* is associated with elevated mitochondrial Ca^{2+} loading even at resting cytosolic Ca^{2+} concentrations. This in turn leads to mitochondrial stress and ultimately to disease affecting the CNS and muscle.
Jenny Sharpe is supported by a PhD studentship from the Muscular Dystrophy Campaign.
[a]These authors contributed equally to this work. [b]A full list of members and affiliations appears in the Supplementary of doi:10.1038/ng.2851. [c]These authors jointly directed this work.
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P25
Clearing cells of mutant mitochondrial DNA by restricting glycolysis
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Mitochondrial disease can be caused by mutations in mitochondrial DNA, a 16kb circular genome encoding 13 proteins crucial to respiratory-chain function. Reducing the proportion of mutant mitochondrial DNA would provide a promising therapeutic avenue for a currently untreatable group of diseases. Previously it has been shown that the proportion of mutant mitochondrial DNA can increase or decrease depending on the nuclear background. To determine which features of the nuclear background are associated with clearance of mutant mitochondrial DNA, A549 cells, which can clear mutant mitochondrial DNA, were compared by microarray to a group of cell lines that increase the proportion of mutant mitochondrial DNA. A549 cells were found to exhibit features consistent with chronic glucose deprivation. To test this prediction, A549 cells maintaining stable levels of mutant mitochondrial DNA were treated with the glycolysis inhibitor and glucose deprivation mimetic 2-deoxy-glucose. 2-Deoxy-glucose treatment reduced the proportion of mutant mitochondrial DNA in a sub-population of A549 cells, which otherwise maintained stable levels of mutant mitochondrial DNA. This suggests that inhibition of glycolysis or glucose deprivation could be extended to treatment of mitochondrial disease in humans.

P26
Can aerobic exercise improve function in patients with mitochondrial disease?
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Background: Mitochondrial diseases are a heterogeneous group of genetic disorders, resulting in significant disability. Aerobic exercise is proposed as a potential therapy. Exercise capacity is improved by aerobic exercise, but the effect on disease burden and performance of daily tasks remains unknown.
Aims: Confirm that exercise is safe and explore the influence on everyday functional activities in mitochondrial disease.
Methods: Twelve patients (m3243A>G n = 10, 8344A>G n = 2) and 11 sedentary controls undertook a 16-week structured cycling exercise programme. Assessments of disease severity (Newcastle Mitochondrial Disease Assessment [NMDAS]), exercise capacity (VO_{2PEAK}), proximal muscle strength (dynamometry) and everyday function were undertaken.
Results: Exercise capacity improved (VO_{2PEAK}, mitochondrial patients 20 vs. 24, $p = 0.003$, controls 28 vs. 30 ml/kg/min, $p = 0.053$). No changes were detected in disease burden (NMDAS 22 vs. 23, $p = 0.684$), proximal muscle strength (1 vs. 2 nm/kg, $p = 0.657$) or daily function tasks (5 times sit to stand 13 vs. 12 seconds, $p = 0.158$, 10 m walk 8 vs. 7 seconds, $p = 0.477$, timed up and go 8 vs. 8 seconds, $p = 0.561$, 6 minute walk 480 vs. 471 m, $p = 0.821$). No adverse events were reported.
Conclusion: Aerobic exercise is safe and well tolerated. Improvements in exercise capacity did not alter disease burden or functional ability. Further work is required to define how rehabilitation should be tailored to benefit day to day function in mitochondrial disease.

P27
Sudden unexpected death in adults with m.3243A>G mutation
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Background: Heterogeneity of clinical phenotype associated with the m.3243A>G mutation is a significant diagnostic and prognostic challenge to clinicians. Current literature regarding disease progression in relation to this mutation focuses on individuals who are moderately or severely affected by the disease. We present two sudden unexpected deaths in individuals who were largely asymptomatic but harboured high urine mutation load.
Method: Multiple tissues from each patient were investigated including muscle, brain and heart. The degree of respiratory chain deficiency was determined using histochemical techniques and m.3243A>G mutation load by pyrosequencing.
Result: A high level of m. 3243A>G mutation load was detected in cardiomyocytes, brain and skeletal muscle for both patients. Mild left ventricular hypertrophy was identified in one case. There were 15–60% of COX deficient cardiomyocytes in both cases. Interestingly, the extensive respiratory chain deficiency observed in brain tissues from both of these individuals is similar to a patient severely affected by MELAS (Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like Episodes).
Conclusion: We propose that sudden unexpected death in asymptomatic individuals with high tissue heteroplasmy represents a new, but rare, phenotype. The exact mechanism of death in our cases is undetermined although cardiac cause is a strong possibility. This adds a further challenge to the increasingly complex counselling of asymptomatic carriers of the m.3243A>G mutation.

P28
Investigating mitochondrial dysfunction in the myofibrillar and other protein aggregate myopathies
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Background: Protein aggregate myopathies are a group of myopathies which include, among other diseases, myofibrillar myopathies. Myofibrillar Myopathies (MFMs) are characterised by aggregation

of the Z-disk proteins and myofibrillar destruction. Studies in MFM patients, to date, show a degree of mitochondrial dysfunction.
Aims: To investigate evidence of mitochondrial dysfunction in MFM patients and characterise the mechanisms which may underlie aberrant muscle mitochondrial redistribution.
Methods: Routine histology and oxidative enzyme histochemistry including sequential COX/SDH reactions were performed on cryosectioned muscle from patients with desminopathy (n = 7), myotilinopathy (n = 1), Zaspopathy (n = 1) and dysferlinopathy (n = 8), determining any evidence of mitochondrial respiratory dysfunction. To date mitochondrial DNA analysis has been performed on the dysferlinopathy group.
Results: We identified evidence of focal COX deficiency, with levels reaching 16% respiratory-deficient cells in some biopsies. Muscle pathology including fat replacement and basophilic inclusions were present in some patients. Mitochondrial genetic analysis focusing on the COX-deficient cells in dysferlinopathy patients has shown no abnormalities to date.
Future work: Further functional (immunohistochemical) and molecular genetic (mitochondrial DNA) studies are planned. Patient myoblasts will be subjected to live cell imaging to determine whether any abnormality in mitochondrial dynamic movement can be detected.

P29

Behr's syndrome is a mitochondrial disease due to autosomal recessive mutations in the *C12orf65* gene

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Behr's syndrome is a classical phenotypic description of childhood-onset optic atrophy combined with various neurological symptoms, including ophthalmoparesis, nystagmus, spastic paraparesis, ataxia, peripheral neuropathy and learning difficulties. Here we describe 4 patients with the classical Behr's syndrome phenotype who carry homozygous nonsense mutations in the *C12orf65* gene encoding a mitochondrial protein. *C12orf65* mutations have been previously reported with various clinical presentations, such as Leigh syndrome, SPG55, CMT6, syndromic intellectual disability, but a thorough review of these previous reports indicates that the phenotype of all patients with *C12orf65* mutations is compatible with Behr's syndrome. We think that *C12orf65* mutations are more frequent than previously suggested and *C12orf65* screening should be considered not only in mitochondrial respiratory chain deficiencies, but also in the inherited peripheral neuropathies, spastic paraplegias and ataxias, especially with pre-existing optic atrophy.

P30

Does a physiological COX isoform switch contribute to the clinical presentation of infantile reversible cytochrome c oxidase deficiency?

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Infantile reversible cytochrome c oxidase (COX) deficiency is a mitochondrial disorder by showing spontaneous recovery if infants surviving the first months of life. We identified the homoplasmic m.14674T>C mt-tRNAGlu mutation as a cause of this disease but this does not explain why all patients develop severe isolated myopathy and what triggers the timed recovery.
Some nuclear-encoded subunits of COX are present as tissue specific isoforms. Isoforms of subunit VIa and VIIa expressed in heart and skeletal muscle are different from isoforms expressed in liver, kidney and brain. Furthermore, in human skeletal muscle both forms of subunit VIIa have been demonstrated.
We studied, whether a physiological isoform switch of nuclear COX subunits takes place in normal infants and whether it contributes to the age-dependent manifestation or spontaneous recovery of infantile reversible COX deficiency myopathy. We performed immunohistochemistry and immunoblotting with antibodies against COXVI and COXVII isoforms in mice, in human skeletal

muscle of controls and patients in different ages (0–6 months, >1 year, adults) and in human muscle cells.
Both in mice and humans, the liver type isoforms gradually decreased, and the heart/muscle-type isoforms increased through development in the first weeks of life, confirming an age-dependent isoform switch. In skeletal muscle of a patient with reversible COX deficiency myopathy we proved the existence of the COXVI and COXVII isoform switch, although we could not confirm an association with the clinical recovery. However, understanding developmental changes of the COX isoforms may have implications for other mitochondrial diseases.

P31

Genotypic and phenotypic heterogeneity in adult-onset progressive external ophthalmoplegia (PEO) with mitochondrial DNA instability: a systematic review

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Background: Progressive external ophthalmoplegia (PEO) is an eye movement disorder characterised by extraocular muscle paresis and muscle restricted mitochondrial DNA (mtDNA) deletions. Patient classification is difficult due to overlapping clinical phenotypes and poor genotype-phenotype correlates. This is compounded by the fact that approximately half of PEO patients do not have a genetic diagnosis.
Aims: To review the phenotypic and genotypic manifestations of adult-onset PEO and to identify possible novel candidate genes.
Patients: Patients were identified in the literature using electronic searches from Scopus, Medline via PubMed and Genetics Abstracts databases (1st January 1970 to 8th November 2013). Adult patients presenting PEO (≥16 years) presenting with PEO and mtDNA instability and with a confirmed genetic diagnosis were selected. The criterion was extended when searching candidate novel genes.
Results: We identified 575 PEO patients, harbouring 12 known nuclear encoded genes (*TYMP*, *SLC25A4*, *POLG*, *C10ORF2*, *OPA1*, *POLG2*, *RRM2B*, *TK2*, *DGUOK*, *MPV17*, *MGME1*, and *DNA2*). Additional novel candidate genes (twenty in total), including several encoding proteins not predicted to localise to mitochondria, were also identified.
Conclusion: We propose to use the findings of this systematic review coupled to whole exome and targeted next-generation sequencing technology, to help direct the investigation of a large cohort of clinically well-defined, genetically undetermined adult patients with PEO and mtDNA instability.

P32

Mutations in *SPG7* cause chronic progressive external ophthalmoplegia through disordered mtDNA maintenance

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Background: Despite being a canonical presenting feature of mitochondrial (mt) disease, the genetic basis of progressive external ophthalmoplegia (PEO) remains unknown in a large proportion of patients.
Aims: To identify the causative gene in patients with genetically undetermined mtDNA maintenance disorders.
Methods: Whole exome sequencing, targeted Sanger sequencing and MLPA analysis were used to study 68 adult patients with PEO either with or without multiple mtDNA deletions in skeletal muscle. Functional studies included transcript analysis, proteomics, mitochondrial network analysis, single fibre mtDNA analysis and deep re-sequencing of mtDNA.

Results: Nine patients (eight probands) were found to carry compound heterozygous *SPG7* mutations, including three novel mutations: c.2221G>A; p.(Glu741Lys), c.2224G>A; p.(Asp742Asn), and c.861dupT; p.Asn288*, and seven previously reported mutations. We identified a further six patients with single heterozygous mutations in *SPG7*, including two further novel mutations: c.184–3C>T (predicted to remove a splice site before exon 2) and c.1067C>T; p.(Thr356Met). The clinical phenotype typically developed in mid adult life with either PEO/ptosis and spastic ataxia, or a progressive ataxic disorder. Functional studies revealed increased mitochondrial biogenesis in patient muscle, and mitochondrial fusion in patient fibroblasts associated with the clonal expansion of mtDNA mutations.
Conclusion: The SPG7 gene should be screened in patients in whom a disorder of mtDNA maintenance is suspected when spastic ataxia is prominent. The complex neurological phenotype is likely due to the clonal expansion of secondary mtDNA mutations modulating the phenotype, driven by compensatory mitochondrial biogenesis.
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P33
Do modulators of mitophagy select pathogenic mtDNA mutations?
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Mitochondrial diseases that result from maternally transmitted mitochondrial DNA (mtDNA) mutations occur in 1/400 individuals. In heteroplasmic diseases, the balance between co-existing mutant and wild type mtDNA usually underlies disease progression. Cellular mechanisms for maintaining mitochondrial quality include mitophagy, and this could be a critical determinant of disease severity. Previous investigators showed that mitophagy was increased by the drug phenanthroline, a metallopeptidase inhibitor. We reasoned that activating mitophagy with phenanthroline might potentially reduce the load of pathogenic mutant mtDNA in tissue culture cells.
We used a previously developed high throughput imaging for quantifying mitophagy in cultured primary fibroblasts bearing the common pathogenic A3243G mtDNA mutation, associated with the mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode syndrome (MELAS) and with diabetes mellitus and deafness.
We showed that phenanthroline significantly increased mitophagy in fibroblasts and reduced both the mitochondrial volume and mtDNA content. We conclude that phenanthroline activates mitophagy. However, there was little evidence that it reduced the load of mutant mtDNA. This suggests that both wild type and mutant mtDNA are turned over during mitophagy activated by phenanthroline.
We conclude that phenanthroline is a poorly selective activator of mitophagy. Modulators of mitophagy need to target mitochondria enriched for mutant mtDNA if they are to benefit patients with heteroplasmic mtDNA disease.

MRI

P34 (Platform Presentation)
Reducing the cost of MRI in neuromuscular clinical trials: acceleration of fat-fraction measurement in Becker muscular dystrophy by combined compressed sensing and parallel imaging
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Background: Fat fraction measurement in muscular dystrophy has an important role to play in future therapy trials. MRI could be more easily incorporated into trials in neuromuscular diseases if the acquisition time were markedly reduced, reducing trial cost and patient burden. This can be done by using combined compressed sensing and parallel imaging (CS-PI).
Aim: To demonstrate the use of accelerated fat-fraction MRI in Becker muscular dystrophy.

Methods: 8 patients with Becker muscular dystrophy were recruited and prospectively undersampled data at ratios of 3.65×, 4.94× and 6.42× were acquired in addition to fully sampled data: equivalent data were collected for reconstruction with standard PI. Fat fraction maps from 940 muscle regions of interest were computed and analysed.
Results: The CS-PI reconstructions are of sufficient quality to allow muscle delineation at 3.65× and 4.94× undersampling but some muscles were obscured at 6.42×. When plotted against the fat fractions from fully sampled data, non-significant bias and 95% limits of agreement of 1.65%, 1.95% and 2.22% were found for the three CS-PI reconstructions, while a 3.36× PI reconstruction yields 2.99%, 1.8 times worse.
Conclusion: 5× acceleration of muscle fat fraction measurement in muscular dystrophy is possible with this new technique and superior to conventional parallel imaging.

P35

Upper limb muscle fat-water quantification MRI in non-ambulant Duchenne Muscular Dystrophy

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Background: Outcome measures in Duchenne Muscular Dystrophy (DMD) rely on invasive and insensitive functional tests. Muscle MRI could offer a valuable alternative.
Aim: Here, fat-water quantification was used to compare fat-infiltration in the forearm muscles of non-ambulant DMD patients and healthy controls.
Methods: To date, 8 non-ambulant DMD patients (mean age: 13.6 years; mean duration of non-ambulation 20 months) and 10 volunteers (mean age:14.6 years) underwent 3T 3-Point Dixon imaging of the dominant forearm to measure muscle fat-fraction (f.f.). Ten forearm muscles were segmented and mean f.f. and cross-sectional area recorded. Patients also underwent physiotherapy evaluation: Performance of Upper Limb (PUL) module; wrist extension myometry; and EK2 performance of tasks in daily life interview. Time to loss of ambulation (LOA) was recorded.
Results: Overall mean f.f (±SD) in DMD was significantly higher than healthy controls: (13.4±11% vs 0.8±0.1%, $p = 0.002$). Total mean area was reduced in DMD (1735±331 mm^2) compared to healthy controls (2398±821 mm^2, $p = 0.04$). Overall f.f. correlated with LOA (Spearman $r = 0.8$, $p = 0.02$) and wrist extension myometry ($r = 0.8$, $p = 0.004$) with relationships also suggested between f.f and PUL ($r = -0.6$, $p = 0.09$) and with EK2 ($r = 0.6$, $p = 0.09$).
Conclusion: Initial data supports MRI fat quantification as a potential objective biomarker to monitor disease progression in the upper limb in DMD, showing significant correlation between putative MRI pathological indices and clinically meaningful endpoints.
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P36

Texture analysis of muscle MRI changes over 1 year

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Background: The appearance of skeletal muscle fat-infiltration on MRI is commonly evaluated using qualitative visual grading scales. However, texture analysis techniques allow the spatial distribution of pathology to be described quantitatively, potentially providing further insight into disease signatures and progression. Here we evaluated texture-based image homogeneity and contrast changes over one year in inclusion body myositis (IBM).
Methods: The thigh muscles of 17 patients with IBM (8f, mean age 60.1 y) and 24 healthy volunteers (10 f, 51.9 y) underwent 3-point Dixon water-fat imaging at 3T to measure fat-fraction (f.f.), repeated twice at a 1 year interval. The three hamstring muscles were segmented bilaterally and f.f gray level co-occurrence matrices were calculated for each muscle. Texture parameters

summarising the image homogeneity and contrast were calculated in addition to mean f.f. and the sensitivity to change over one year evaluated with the standardised response mean (SRM).
Results: Mean f.f. increased from 17.8±19.6% to 19.8±19.6% (mean±s.d.) over one year (SRM 0.76). Texture based contrast increased from 0.019±0.018 to 0.022±0.019 (SRM 0.34) and homogeneity decreased from 0.15±0.06 to 0.13±0.05 (SRM −0.49, all $p < 0.001$) over the same period. In the volunteer group there were no significant changes ($p > 0.3$ all parameters).
Discussion: Mean f.f. is the most sensitive parameter for assessing change over 1 year in IBM. However, texture-based parameters also convey information about the spatial distribution of pathology within muscles which may provide valuable disease-specific information for diagnosis, staging and prediction of progression using MRI.

P37
Muscle MRI in congenital myasthenic syndromes
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Background: Congenital Myasthenic Syndromes (CMS) are a group of heterogeneous inherited disorders caused by mutations encoding for proteins involved in the neuromuscular junction. Given that some CMS subtypes have shown myopathic changes on histology, they shall also demonstrate abnormal appearance on muscle MRI.
Aims: whether appearances on CMS muscle MRI is abnormal and can help to differentiate between the different CMS subtypes.
Subjects and Methods: 26 cases and 10 controls were included; sex (54% female); mean age 38.3±18.4years; CMS subtypes: DOK7(5), slow channel syndrome(5), AChRε(4), RAPSYN(3), COLQ(3), GFPT1(2), DPAGT1(3), ALG14(1). 3T-MRI was performed using T1 and STIR sequences through calves and thighs. Blinded analysis was performed by two experts reaching consensus. 38 muscles per subject were evaluated using a severity score (Mercury). Correlation between MRI appearance and clinical severity was investigated using QMG and ADL scales.
Results: The overall mean T1score was significantly increased in GFPT1 and DPAGT1 ($p < 0.05$). Some subjects with DOK7 and RAPSYN CMS also showed mild extensive or marked changes in T1. STIR images did not significantly differ from controls. Mean T1 score was correlated with age but not with QMG or ADL scales.
Conclusion: We found a wide range of MRI appearance from normal imaging to marked abnormality depending upon CMS subtype. T1 images seem to be especially abnormal in glycosylation pathway CMS subtypes. No muscle specific patterns were identified. Muscle MRI can have a role in differentiating CMS subtypes.

P38
MRI quantification of fixed myopathy in hypokalaemic periodic paralysis identifies potential therapeutic window
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Background: Hypokalaemic periodic paralysis (HypoPP) is a muscle channelopathy characterised by recurrent paralytic attacks. A proportion of patients also develop a fixed myopathy resulting in significant disability but this has not previously been quantified. The aim of this study was to quantify chronic muscle pathology in HypoPP using MRI.
Methods: Lower limb muscle MRI was performed at 3T in 12patients with HypoPP (9M/3F, age 42±12 y) and 12healthy controls (9M/3F, age 41±10 y). Fat fraction maps were generated using the 3-point Dixon fat-water separation method. Thigh and calf muscles were analysed using whole muscle regions of interest drawn by an observer blinded to diagnosis on a single axial slice respectively 20 cm above and 15 cm below the knee joint.

Results: Mean muscle fat fraction was significantly increased in patients compared with controls at both thigh (patients: 10.2±15.4%; controls 1.5±0.5%) and calf (8.3±10.5%; 1.7±0.6%) level. Muscle involvement was variable with greatest mean fat infiltration in adductor magnus (17.8%) and vastus medialis (14.7%) in the thigh and in medial gastrocnemius (15.9%) in the calf. Overall fat fraction correlated with age in patients (rho = 0.76, $p < 0.01$) but not controls (rho = 0.17, $p = 0.6$). The age-severity relationship appeared dichotomous with normal fat fraction in patients younger than 40 (1.8±1.2%), but significantly increased in patients older than 40 (15.5±14.2%).
Conclusion: There is clear evidence of fixed myopathy in HypoPP patients over 40 with muscle selective fat infiltration. This suggests a potential window for treatment before the age of 40 where effective therapy may prevent irreversible muscle damage.

P39 (Platform Presentation)
Quantitative lower limb muscle MRI in CMT1A demonstrates length-dependent fatty infiltration
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Background: Charcot–Marie–Tooth type 1A (CMT1A) is a length-dependent motor and sensory neuropathy which presents clinically with distal weakness. Qualitative MRI studies have demonstrated distally accentuated fatty atrophy of lower limb muscles. The aim of this study is to quantify fat fraction (FF) along a muscle's length.
Methods: We performed lower limb 3T MRI using the 3 point Dixon technique for fat quantification, in five patients with CMT1A, and in five healthy volunteers. Muscle FF was measured across 10 consecutive slices of the right calf, separated by 2 cm, in tibialis anterior (TA), medial gastrocnemius (MG) and peroneus longus (PL). A gradient was defined as a run of three adjacent slices with increasing or decreasing FF and a minimum average change of 0.5%/cm. All gradients are expressed as absolute differences in FF percentage.
Results: In healthy volunteers, mean FF was 1.4%, 2.2% and 5.3% in TA, MG and PL respectively, compared with 16.2%, 21.7% and 35.2% in patients with CMT1A. In patients with CMT1A, there was a distal FF gradient (higher FF distally) in TA and PL of +3.1%/cm and +3.3%/cm respectively. The pattern of fat infiltration in MG was more variable. A distal gradient was not present in healthy volunteers; although a small reverse gradient (higher FF proximally) was seen in 90% of TA and PL muscles: −1.1%/cm and −0.9%/cm respectively; a finding only present in 20% of muscles of patients with CMT1A.
Conclusion: Consistent with known pathophysiology, there is a clear distal FF gradient in TA and PL muscles in these patients with CMT1A. These findings have significant implications for accurate slice selection when analysing serial imaging: a difference of 1 cm in slice analysed will result in a difference of up to 8.9% in FF measured. This study is being continued in a larger cohort of patients with CMT.

P40
BIOIMAGE-NMD (BIOIMAGE-Neuromuscular Diseases)
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The project will develop methods for radiolabelling of AON and demonstrate the use of pre-clinical Positron Emission Tomography (PET)/MRI to assess the tissue targeting, bio-distribution and pharmacokinetics of AON in vivo.

The project aims are to deliver combined structural and molecular imaging biomarkers with proven utility for the detection of therapeutic effects in patients with rare neuromuscular diseases (NMD). The project will apply a simultaneous MRI/MRSI protocol in multi-centre clinical trials of AON therapy in DMD with the aim of establishing a clinical proof of principle that these imaging measures are effective biomarkers of therapeutic response.
BIOIMAGE-NMD will deliver PET/MRI and MRI/MRSI technologies for both drug development and clinical evaluation roles which will contribute to bringing personalized therapeutic interventions in rare diseases to the market.
The BIOIMAGE-NMD project hopes to provide new tools to assess treatments in early clinical trials of the AON therapeutics.

Muscle Channelopathies and Myasthenia Gravis

P41

Investigating the effect of *AGRN* mutations on acetylcholine receptor (AChR) clustering in vitro

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Background: Congenital myasthenic syndromes (CMS) occur as a result of genetically inherited mutations giving rise to impaired transmission at the neuromuscular junction (NMJ). Agrin is a key extracellular matrix proteoglycan responsible for the organisation of the postsynaptic membrane through aggregation of AChRs. We have identified *AGRN* gene mutations in the N-terminal domain in two families presenting with an unusual phenotype of a neuromuscular transmission defect in combination with a distal myopathy, however the significance of these changes remains unproven.
Aims: To demonstrate the AChR clustering properties of agrin in C2C12 myoblasts. To investigate the AChR clustering ability of mutant agrin proteins using an in vitro cluster assay.
Methods: C2C12 myotubes were treated with mutant agrin protein expressed by HEK293 EBNA transfected cells. The myotubes were then stained with fluorescently labelled alpha-Bungarotoxin to visualise AChR clustering.
Results: We observed clustering of AChRs on the postsynaptic membrane due to the activity of agrin which was dependent on the mutational status of the agrin used. Further data on the ability of mutant agrin proteins to cluster AChRs will be presented.
Conclusion: This study demonstrates that we can establish whether there is a correlation between mutations in the agrin gene and the CMS-like phenotype seen in the two families studied.

P42

Pathogenic mechanisms of *RAPSN* mutations in congenital myasthenic syndromes

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Background: *RAPSN* mutations contribute towards a major subtype of congenital myasthenic syndromes. Rapsyn interacts directly with acetylcholine receptors (AChR) at the postsynaptic membrane and is essential for the formation of AChR clusters. Mutations in the *RAPSN* gene have an overall effect of causing a deficiency of AChR at patient endplates, possibly through a variety of molecular mechanisms that disrupt rapsyn functions. *RAPSN*-CMS is autosomal recessive, with a common mutation, p.N88K, either homozygous or heterozygous in over 90% of patients.
Aims: We have investigated the pathogenic properties of newly identified *RAPSN* mutations in patients: p.E23K, p.H329P, p.R376W and p.H387Y and rarer mutations identified from patients who do not harbour the common mutation N88K: p.V45M, p.R91L, p.A153T.
Methods: Human full-length wild-type rapsyn cDNA was cloned into expression vectors (pEGFP-N1, pBabe-PURO). Mutations identified in patients were introduced by mutagenesis. AChR clustering assay was performed by infecting these *RAPSN* variants into *RAPSN*$^{-/-}$ myoblasts; and the expression levels and the stability of the protein were determined in TE671.
Results and Conclusions: The mutations investigated were all found to impair AChR cluster formation, but are likely to act through different molecular mechanisms.

The aim of our project is to obtain an optimal dystrophin construct that will be lentivirally-transduced into skeletal muscle stem cells derived from Duchenne muscular dystrophy (DMD) patients. These stem cells would restore functional dystrophin expression following their transplantation into dystrophin-deficient skeletal muscles. To this end, we have cloned several, different dystrophin truncated forms ranging from 4.2 kb to 8.4 kb cDNA, encoding various components of the dystrophin molecule that may be used in a lentiviral system focusing on elongated transcript length and selected dystrophin domains. The constructs were assessed for functionality using intramuscular injection and electroporation into mdx muscle. The construction, cloning strategy and characterisation of the constructs as well as first functional results will be presented. We are aware of challenges to gene transfer approaches and know that further long-term experiments are required to assess the potential of this strategy, but this project may bring us closer to a a robust and reproducible system for testing functionality of both engineered and naturally occurring dystrophin mutants.

P43

Functional characterisation of the novel CLC-1 variants C179Y and A529V using Two-Electrode-Voltage-Clamp and review of ClC-1 structure–function

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Background: Myotonia Congenita is caused by mutations in CLCN1 which encodes the skeletal muscle chloride channel ClC-1 [1]. Mutations are loss of function and result in sarcolemmal hyperexcitability, which manifests as myotonia, and patients describe as muscle stiffness. Chloride channels are homodimers. Each subunit contains its own pore, gate and voltage sensor which can be individually controlled by a fast gate, or in tandem via a common gating mechanism not as yet fully elucidated [2]. Mutations can be dominant or negative and for some mutations both modes of inheritance have been reported [1].

Aims:

1. To characterise the novel ClCN1 variants: c.1586C>T p.A529V and c.536G>A p.C179Y.
2. To use homology modelling of ClC-1 to map variants according to their functional effect to aid mechanistic insight.

Methods: Site directed mutagenesis of ClC-1 was followed by in *vitro* transcription and microinjection of RNA into xenopus oocytes. Mutant RNA was injected alone, or with WT RNA for co-expression studies. Expressed channels were examined 48-hours later using the two electrode voltage clamp technique.

A CLCN1 homology model was created using the PHYRE2 intensive modeller [3]. Mutations and conserved residues were mapped onto the homology model and, using sequence alignment, onto the crystal structure of a homologous eukaryotic chloride transporter [2].

Results: C179Y mutant channels significantly shift the voltage dependence of activation when expressed alone and when co-expressed with WT subunits. A529V mutants yield no or reduced currents when expressed alone but yield functional currents when co-expressed with WT. Both mutations are in or adjacent to conserved residues.

Conclusion: Functional assessment and homology mapping enables us to group mutations according to their functional effects and estimated location within the channel structure. A529V may block the pore or affect surface expression of channel proteins.

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P44

Mutations of the same S4 arginine residue in $Na_V1.4$ can result in either myotonia or hypokalemic periodic paralysis

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Background: Mutations of arginine residues in the voltage-sensor segment S4 in *SCN4A* encoding $Na_V1.4$ cause gating-pore currents and hypokalemic periodic paralysis (hypoPP). Mutations in the same S4 arginine, R222Q and R222W cause disparate patient phenotypes: hyperkalemic PP/myotonia and hypoPP, respectively.
Aims: To investigate the electrophysiological basis of the two phenotypes associated with R222Q and R222W.
Methods: The electrophysiological properties of R222Q, R222W and wildtype $Na_V1.4$ were compared using whole-cell patch clamp in HEK293 cells and two-electrode voltage clamp in *Xenopus* oocytes.
Results: A 20 mV hyperpolarizing shift in the voltage-dependence of activation was found in R222Q-expressing cells compared to wildtype and R222W. Both mutants also had minor effects in other parameters. Preliminary data suggest the presence of gating-pore currents in both mutant channels.
Conclusion: The hyperpolarizing shift in voltage dependence of activation of R222Q is expected to lower the activation threshold of sodium channel-driven activation, consistent with myotonia. Further work is required to determine whether the R222W and/or R222Q mutations introduce gating-pore currents, potentially underlying the HypoPP phenotype of R222W.
Replacing an arginine residue with two different amino acids results in contrasting electrophysiological and clinical phenotypes, suggesting that it is imperative to study all S4 arginine mutations to understand their functional role in muscle channelopathies.

P45

Seronegative myasthenia gravis – clinical and serological features

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Background: Acquired Myasthenia Gravis is an autoimmune channelopathy of the post-synaptic neuromuscular junction. Diagnosis is supported by clinical presentation, neurophysiology, and detection of Acetylcholine Receptor (AChR), Muscle Specific Kinase (MuSK), or Low Density Lipoprotein Related Protein (LRP4) antibodies. Despite clear autoimmune aetiology, a proportion of patients remain 'seronegative' (SNMG) and diagnostic confirmation can be challenging.
Aims: Our aim was to characterise the clinical and functional features of SNMG.
Methods: An international cohort of 293 suspected SNMG patients were tested by radioimmunoassay (RIA) and cell-based assays (CBA) for AChR, MuSK or LRP4 antibodies. SNMG sera were screened for binding to primary muscle cell lines (TE671 and CN21) and inhibition of agrin-induced AChR clustering in myotube cultures (C2C12).
Results: Of the 293 patients 7 patients were RIA/CBA(+) and 81 patients were RIA(−)/CBA(+). 212 patients were negative by both methods [M:F 1:1.4, median onset age 35.5 (1–63)]. Most of these patients had mild disease (MGFA ≤IIb) at onset (17/17) and follow-up (70% n = 61/87). Neurophysiology was positive in 65% (n = 28/43). Preliminary results suggest that these sera do not affect agrin-induced AChR clustering in C2C12s, although some seronegative sera bound to TE671 and CN21 muscle cell lines.
Conclusion: Myasthenia gravis patients without AChR, MuSK or LPR4 antibodies have relatively mild disease according to MGFA grading. Neurophysiology was supportive in only 65% of these patients. Our evidence suggests that some of these sera do bind to novel antigen(s) on muscle cells. The next stage will be to try to define the antigen(s) using immunoprecipitation and mass spectroscopy.

P46

Functional investigation of a novel mutation causing a new phenotype for the *KCNA1* gene

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Background: The *KCNA1* gene encodes the voltage-gated potassium channel Kv1.1, mutations in which cause Episodic Ataxia1 (EA1), a neuronal channelopathy. Kv1.1 is a homo-tetramer and is expressed in both neuronal and muscle cells. Whole exome sequencing on a large Paroxysmal

Exercise-Induced Dystonia pedigree revealed a segregating novel missense mutation in the voltage-sensing domain of *KCNA1.* This is a novel phenotype for this gene.
Aims: We predict that this mutation could provide a new disease mechanism for this gene by causing a gating pore current in the channel; the first seen in a human neuronal channelopathy and potentially explaining the novel phenotype. The aim is therefore to functionally investigate this mutation using electrophysiology.
Methods: We use the two-electrode voltage clamp technique to investigate the presence of a gating pore current. This was done on oocytes injected with the mutant RNA, WT, or a combination of the two at varying ratios.
Results and Conclusion: Despite predictions, this mutation did not appear to cause a gating pore current. Instead, the mutation caused loss-of-function: no currents were recorded in homomeric mutant channels. In simulated heterozygous condition the current amplitude was less than 25% of the WT, suggesting a dominant-negative effect of the mutant on the WT subunit.

P47
Loss of negative charges within the voltage sensor domain of $Na_v1.4$ results in gating pore currents
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Background: To date causative mutations that give rise to Hypokalaemic Periodic Paralysis (HypoPP) have been found in the S4 voltage sensing segments causing neutralisation of arginine residues of either $Ca_v1.1$ or $Na_v1.4$. While these mutations account for ~90% of HypoPP cases, ~10% of cases remain undiagnosed. We have previously shown that a novel Hypo PP mutation, p.Asp1420Gly, which affects a negative charge within the voltage sensor domain, causes an aberrant ionic leak current.
Aims: To investigate the electrophysiological properties of Asp1420Gly and the homologous negative charges within the voltage sensor domains.
Methods: The electrophysiological properties of negative charge voltage sensor mutations and wildtype $Na_V1.4$ were compared using two-electrode voltage clamp in *Xenopus* oocytes and patch clamp in HEK293 cells.
Results: In HEK cells Asp1420Gly main pore sodium currents were wildtype-like, suggesting that the gating pore current is the causative change of function for Asp1420Gly. Selectivity studies revealed that monovalent cations carry the Asp1420Gly gating-pore currents. However, some of the homologous mutations in other Nav1.4 domains resulted in gating-pore currents carried by chloride and had different voltage dependence than Asp1420 gating-pore currents.
Conclusion: Loss of the negative charges in S3 segments disrupts the negative charge cluster interactions with the voltage sensor allowing for an ionic leak to occur through the voltage sensor domain. This supports the notion that a gating pore current can be induced through loss of negative charges as well as positive gating charges.

P48
Integrins are required for synaptic transmission and development of the neuromuscular junction
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Background: Development of the neuromuscular junction (NMJ) depends on interactions between proteins in the nerve terminal, muscle fibre and in the synaptic cleft. Laminins play a central role, as they bind to presynaptic voltage-gated calcium channels and to dystroglycan in the muscle fibre. Integrin-α3 is a laminin receptor expressed in the presynaptic active zones, the sites of neurotransmitter release across the synaptic cleft.
Aims and Methods: To determine the function of integrin-α3 at the NMJ, using mice with a genetic ablation of the integrin-α3 gene.
Results: At embryonic day E18.5, $\alpha3^{-/-}$ mice present with abnormal assembly of active zone proteins and reduced synaptic transmission, as determined by electrophysiology. Ultrastructural studies reveal defective deposition of the basal lamina at the synaptic cleft. As $\alpha3^{-/-}$ mice die at

birth due to the failure of multiple systems, we used α3$^{+/-}$ mice to study the role of this protein in postnatal maturation of the NMJ. In adult α3-deficient mice, we find aberrant NMJ morphology and reduced expression of several active zone proteins.
Conclusions: Integrin-α3 is important for the assembly of active zones and of the synaptic basal lamina. The data suggests that defects in this protein may be associated with myasthenia in humans.

Peripheral Nerve Disease

P49
Mitochondrial abnormalities and increased oxidative stress in HSBP1 induced distal hereditary motor neuropathies
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Background: HSPB1 mutations cause Charcot-Marie Tooth (CMT) Disease Type 2/distal hereditary motor neuropathies (dHMN). HSPB1 is a cytosolic chaperone involved in the maintenance of the cytoskeleton, protects against protein misfolding and helps maintain the mitochondrial redox potential. Expression of mutant HSPB1 results in protein aggregationand mitochondrial axonal transport deficits (Ackerley et al., 2006; d'Ydewalle et al., 2011).
Aims: We examined the effects of HSPB1 mutations (Ser135Phe, Pro39Leu and Arg140 Gly) on mitochondrial characteristics in primary motor neurons (MNs) including mitochondrial membrane potential (Ψ^m), activities of mitochondrial complexes, oxidative stress and glutathione (GSH) levels.
Methods: GSH levels, Ψ^m and mitochondria-specific superoxide was measured using the appropriate dyes (monochlorobimane, TMRM and Mitosox, respectively) and time lapse microscopy in primary motoneurons expressing WT and mutant HSPB1. Mitochondrial Complex activities were measured by a biochemical assay. Superoxide production was also assessed by FACS.
Results: In HSPB1 mutant MNs, basal Ψ^m was normal, but there was a 20% reduction in rotenone response, indicating Complex II impairment, which was confirmed by a biochemical assay. Baseline superoxide levels were similar to WT, but under stress, there was elevated superoxide production in mutant HSPB1 MNs. Mitochondrial GSH levels were also reduced in mutant cells.
Conclusions: Axonal damage in HSPB1 induced CMT2 involves multiple interconnected pathways affecting mitochondria. Reduced GSH levels and complex II activity in mitochondria together result in an increased susceptibility to metabolic stress, resulting in oxidative stress and further mitochondrial damage. Together, these accumulating sub-lethal abnormalities may contribute to the slow axonal degeneration observed in CMT2/dHMN.
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P50
Genetics of riboflavin channels
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First described in 1894, Brown-Vialetto-Van Laere (BVVL) syndrome is a rare, autosomal recessive neurodegenerative disorder characterised by bilateral sensorineural hearing loss, cranial nerve palsies, respiratory insufficiency and severe sensorimotor neuropathy. Most infants who are diagnosed with this condition rapidly become ventilator dependent and die during childhood. Mutations in two riboflavin transporter genes *SLC52A2* and *SLC52A3* have recently been shown to underlie a number of severe cases of BVVL syndrome. The aim of this study was to investigate the scope of mutations occurring in these genes. We used Sanger sequencing to screen 25 patients for mutations in both *SLC52A2* and *SLC52A3*. Five patients were identified with novel mutations, appointed E1–5. E1 was a compound heterozygote for two missense mutations in *SLC52A3* localized in areas encoding transmembrane regions of the protein (I74M and V118M). E2 was a compound heterozygote for an insertion leading to a premature stop codon and a non-sense mutation in *SLC52A3*. E3 was a compound heterozygote for two missense mutations in *SLC52A2* (E77K and A288V) but also a homozygote and compound heterozygote for two missense mutations in *SLC52A3*

(F224C and G146R respectively). E4 was a compound heterozygote for two missense mutations in *SLC52A3* (G13R and G418D), while E5 was homozygous for one missense mutation in *SLC52A3* (R266W). Overall our findings confirm the pathogenetic role of *SLC52A2* and *SLC52A3* in BVVL and thus have important clinical and therapeutic implications.

P51

Neuropathy phenotype in hereditary transthyretin amyloidosis

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Background: Hereditary transthyretin amyloidosis (ATTR) is associated with progressive peripheral neuropathy, cardiac, gastrointestinal and autonomic failure due to dominantly inherited transthyretin mutations causing accelerated amyloid deposition. The neuropathy phenotype is less well described than cardiac manifestations.

Methods: A cross-sectional study of ATTR patients attending the National Hospital Inherited Neuropathy Clinic. Detailed clinical neurological and electrophysiological data were collected on all patients alongside correlating autonomic and cardiac assessments. Follow-up data was available on a subset.

Results: Thirty four patients (mean age at presentation = 62 years; 70.6% male) were assessed at least once; 19 cases (55.8%) had serial examinations, mean follow-up: 1.9 years. The genetic breakdown was 38.2% T60 A, 14.7% V30M, 8.8% I107F, 5.9% V122I, 32.4% individual mutations; 76.5% UK and/or Irish ancestry. 44.1% were treated (Diflunasil or liver transplant). 26.5% presented with neuropathy; 70.6% had neuropathy on follow-up. Positive and negative sensory phenomena were equally prevalent at presentation; with negative symptoms slightly more common in T60A patients ($p = 0.22$). A length-dependent, axonal, sensory followed by motor neuropathy was typical; 6.7% had patchy onset and 10% had demyelinating features. Mean MRC score at first examination was 62.5 with a mean reduction of 2.7 points/year and a trend to slower deterioration in the treated group (2.4 versus 3.0 points/year; $p = 0.77$).

Conclusion: The detection of measurable annual changes in MRC score is encouraging but monitoring of sensory deficits should also be quantifiable. This small but representative study mirrors difficulties observed in recent treatment trials regarding sensitivity of current outcome measures.

P52

***MFN2* deletion founder mutation in the UK population**

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Background: Mitofusion 2 (*MFN2*) mutations are the most common cause of axonal Charcot-Marie-Tooth disease (CMT2). The majority are usually inherited in an autosomal dominant manner but recessive and semi-dominant kindreds have also been described. We previously reported this deletion resulting in nonsense mediated decay, segregating with disease when present in *trans* with another pathogenic *MFN2* mutation.

Methods: Detailed clinical and electrophysiological data on five affected patients and, when available, their parents and relatives was collected. *MFN2* sequencing was performed followed by multiplex ligation probe amplification (MPLA assay) to identify large deletions when a heterozygous mutation was found. Haplotype analysis was also carried out.

Results: A severe early-onset CMT phenotype was seen in all cases: progressive distal weakness, wasting and sensory loss from infancy or early childhood. Optic atrophy (3/5) and wheelchair dependency by age 20 were common (4/5). All were compound heterozygous for a deletion of exon 7 and 8 in *MFN2* with another previously reported pathogenic mutation (Phe216Ser,

Thr362Met and Arg707Trp). Carrier parents and relatives were unaffected (age range: 32–65 years). Haplotype analysis confirmed that the deletion had a common founder in all families.
Conclusion: Here we present five patients with severe, early-onset CMT2 compound heterozygous for a deletion of exon 7 and 8 in *MFN2* with haplotype analysis confirming this deletion as a founder mutation in the UK population.

P53

Identifying responsive outcome measures in hereditary sensory neuropathy type 1 (HSN1)

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Background: HSN1 secondary to SPTLC1/2 mutations is associated with the accumulation of 1-deoxysphingolipids (1-dSLs) which are thought to be neurotoxic. L-serine has been shown to be a potential candidate therapy for HSN1. The lack of outcome measures is a major barrier to starting a definitive clinical trial.
Aim: To identify responsive outcome measures to be used in trials in HSN1 patients.
Methods: This is an ongoing longitudinal study in HSN1 patients. Assessments include: CMT Neuropathy score, MRI of calves and thighs, myometry, quantitative sensory testing (face, hand and foot), comprehensive neurophysiological assessment, proximal thigh skin biopsy for intraepidermal nerve fibre density, 1-dSLs plasma levels and questionnaires for pain and quality of life.
Results: 11 patients (4 females) have been evaluated so far. Average age was 51 years (21–67 yrs). Average CMTNS was 20 (3–35/36). Floor effect was noted in neurophysiological assessment of 4 patients (globally absent sensory and motor responses) and in QST in foot in majority of the patients and in hand in half the patients for all modalities. QST in face was abnormal in 2 patients (CMTNS = 29 and CMTNS = 28). Skin biopsy and MRI analysis are pending.
Conclusions: Results so far show significant variability between patients therefore a single outcome measure will be insufficient to measure disease progression. The assessments will need to be combined to create patient specific or severity specific methods of measuring diseases progression.

P54

A dominant negative mutation in *FBXO38* is a cause of distal hereditary motor neuropathy (dHMN)

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Background: The dHMNs are a genetically heterogeneous group of diseases characterised by distal lower motor neuron (MN) weakness. Only 20% of cases have mutations in known genes.
Aims: To identify the causative gene and underlying pathomechanism in a large unresolved dHMN pedigree.
Methods: We employed whole exome sequencing to identify a mutation in *FBXO38* in two unrelated families with dHMN. FBXO38 is a co-activator of KLF7 transcriptional activity, a transcription factor with a role in neuronal development and repair. We used luciferase reporter constructs to examine the effect of the FBXO38 mutation on KLF7 transcriptional activity. In

addition, we examined neurite outgrowth in primary mouse embryonic MNs infected with lentivirus expressing mutant FBXO38.
Results: We identified a p.Cys206Arg mutation in *FBXO38* as the causative mutation in two dHMN pedigrees. Mutant FBXO38 was found to impair KLF7-mediated transactivation of a KLF7-responsive promoter construct in both HEK293T cells and patient-derived fibroblasts. This transcriptional dysregulation was associated with impairment of neurite outgrowth in primary embryonic mouse MNs expressing mutant FBXO38.
Conclusions: The p.Cys206Arg mutation in FBXO38 is causative of dHMN, highlighting the importance of FBXO38 and KLF7 in MNs.

P55

Are axonal transport deficits present in a novel mouse model of spinal and bulbar muscular atrophy?

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Background: Spinal and bulbar muscular atrophy (SBMA) is an X-linked neurodegenerative disorder caused by an abnormal expansion of the CAG repeat in the androgen receptor (AR) encoding a polyglutamine (poly-Q) sequence in the protein. Expression of this abnormal protein leads to selective degeneration of lower motor neurons (MNs). Axonal transport deficits have been implicated in the pathogenesis of other MN and poly-Q diseases. However, although some reports have observed axonal transport deficits in mouse models of SBMA, we failed to detect any defects in the AR100 mouse model of SBMA.
Aims: To identify whether axonal transport deficits are present in the AR121 novel mouse model of SBMA which has 121 CAG repeats within the androgen receptor.
Methods: An atoxic tetanus toxin (TeNT Hc) will be used to visualise fast retrograde transport and mitotracker to simultaneously visualise mitochondrial transport. The tracking and measurement of transport kinetics will be undertaken using time-lapse confocal microscopy and motion analysis software. We will use these techniques to identify whether axonal transport defects are present in the AR121 mouse model.
Results and Conclusion: Work is ongoing and in progress. Preliminary results will be presented at the conference.

P56

Whole-exome sequencing in patients with sensory and motor inherited neuropathies

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Background: Identification of pathogenic mutations causing inherited sensory and/or motor neuropathies may be challenging, since more than 78 disease-related genes have been described. More than 85% of the mutations associated with known Mendelian diseases are located in protein-coding exons. Targeted capture and massive parallel sequencing of these genomic regions (whole-exome sequencing) has been demonstrated to be an efficient method for the identification of novel mutations and genes in patients with inherited neuropathies.
Objective: To report our experience with whole-exome sequencing in suspected inherited neuropathies.
Methods: After excluding mutations in inherited neuropathy-related genes according to the phenotype, whole-exome sequencing was performed in 59 individuals from 34 unrelated pedigrees. Enrichment of coding exons and flanking intronic regions was performed with Illumina TruSeq and Agilent SureSelect capture products. Sequencing was performed on HiSeq 1000 and 2000 platforms.
Results: From a total of 34 probands (24 familial cases; 10 sporadic cases), 3 (9%) had a demyelinating neuropathy, 6 (18%) had a sensory-motor axonal neuropathy, 16 (47%) had a predominantly sensory neuropathy, 8 (24%) had a predominantly motor neuropathy, and 1 (3%) had recurrent episodes of plexopathy, with or without additional neurologic features (e.g. ataxia, optic neuropathy). A definite pathogenic variant was identified in 6 different genes in 6 unrelated probands (5 familial cases and 1 sporadic case).

Conclusion: Our preliminary results suggest a success rate of 18% in the detection of disease-related genes in suspected inherited neuropathies. Analysis of the data is still in process and we envisage higher success rates.

P57

IGHMBP2 mutations cause recessive axonal neuropathy: Genetic and functional characterisation in seven families

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Background: Using a combination of linkage, exome and Sanger sequencing we identified seven families with slowly progressive, recessive CMT2 with compound heterozygous mutations in the *IGHMBP2* gene. Mutations in *IGHMBP2* normally lead to the much more severe SMARD1 phenotype where most children die before 1-year of age. Our patients had typical slowly progressive CMT2, with no respiratory/diaphragm weakness in adulthood.
Aims: Genetic and functional studies were performed to investigate this pathway and how these different mutations cause such diverse diseases.
Methods: After genetic analysis, skin fibroblasts and lymphoblasts were obtained in eight individuals to analyze the IGHMBP2 protein levels in affected and carrier patients. Co-immunoprecipitation was also performed to look for interacting proteins.
Results and Conclusion: IGHMBP2 levels in CMT2 patients were found to be higher than SMARD1 patients, but lower than controls and carriers. TDP43 was found to interact with IGHMBP2. Further studies are ongoing to uncover the pathways involved in the cause of disease.

Glycosylation Disorders

P58

Psycho-organic symptoms as early manifestation of adult onset POMT1-related muscular dystrophy

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Background: Mutations in *POMT1* gene were reported to cause a spectrum of muscular dystrophies characterised by abnormally glycosylated α-dystroglycan.
Case report: The older sister was followed for mental development delay since her infancy. From the age of 20 y she suffered from attacks of agitated behaviour, complained of hearing inner voices, intellectually deteriorated; in 15 y she was uncooperative uttering single words. At the age of 31 y limb girdle muscle weakness was noticed; 10 y later she was barely ambulant. Serum creatine kinase (CK) was 3000 UI/L. Brain MRI was normal. The younger sister was healthy until the age of 31 y when she started to suffer from hallucinatory symptoms and to deteriorate intellectually. Four years later moderate limb girdle muscle weakness was noticed. CK was 3656 UI/L. Brain MRI showed reduced volume of partial lobes with focal cortical dysplasia. Muscle biopsy showed myopathic features, fibre type disproportion and central nuclei; immunohistochemistry revealed reduction of α-dystroglycan labelling. The sequencing of the *POMT1* gene found a novel homozygous mutation c.251G>A in both sisters.
Conclusion: Our case report shows unusual phenotype of a novel homozygous mutation in the *POMT1* gene presenting with intellectual disability and psychotic symptoms, preceding the symptoms of limb-girdle weakness by several years.

P59

Transcriptome analysis in a mouse model of FKRP-deficient muscular dystrophy

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Allelic mutations in the putative glycosyltransferase gene *fukutin-related protein* (*FKRP*) lead to a wide range of muscular dystrophies associated with hypoglycosylation of alpha-dystroglycan, referred to as dystroglycanopathies. The severe forms are characterized by congenital onset of muscular dystrophy with central nervous system involvement. To date there is no effective treatment for any of these conditions. We aim to elucidate the neural pathogenesis of FKRP-deficient muscular dystrophies by studying the brain transcriptome in a mouse model of FKRP-deficient dystroglycanopathy.

We have performed transcriptome sequencing (RNAseq) using E18.5 brain tissues from six FKRP-deficient mutant mice and four homozygous wildtype littermates. Preliminary transcriptome analysis identified 1743 differentially expressed genes. Among these, up-regulated genes are predominately associate with extracellular matrix organisation, whereas down-regulated genes are required for neuron development. These results are consistent with the brain pathology of FKRP-deficient mice, exhibiting disrupted basement membrane and neuronal migration defects. Thus, a comprehensive analysis on tissue-specific transcriptome in FKRP-deficient mice will reveal the identity of the key genes and uncover their roles in disease pathogenesis, as well as critical targets for therapeutic strategies.

P60

Shared defective glycosylation pathways link congenital myasthenic syndromes with the dystroglycanopathies

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Altered glycosylation is a defining biochemical feature of a subset of congenital muscular dystrophies known as the dystroglycanopathies, as well as some forms of congenital myasthenic syndromes (CMS). Alpha-dystroglycan (α-DG) is a membrane glycoprotein integral to the dystrophin-glycoprotein-complex. It interacts with beta-dystroglycan and components of the extracellular matrix (ECM), including laminins. In the dystroglycanopathies, the glycosylation α-DG is reduced resulting in lower affinity binding to the ECM. In CMS caused by mutations in the genes *GFPT1*, *DPAGT1*, *ALG14*, and *ALG2* aberrant protein glycosylation or hexosamine biosynthesis is thought to compromise neuromuscular junction (NMJ) transmission. We found that some mutations in these genes also reduce the amount of O-mannosyl glycans on α-DG and/or the CT carbohydrate antigen (a glycan epitope expressed at the NMJ). This was assessed by flow cytometry and/or immunoblotting using antibodies which recognize these epitopes. While the link between the glycosylation required for normal NMJ transmission and α-DG function requires further investigation, this suggests a degree of overlap which could elucidate some of the pathomechanisms responsible for these diseases.

IBM

P61

Using exome sequencing to investigate disease-causing mutations of muscle disorders with protein aggregates

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Muscle disorders with protein aggregates are a spectrum of rare familial or sporadic neuromuscular conditions with marked clinical and genetic heterogeneity; they include disorders such as inclusion body myositis (IBM) and myopathies with tubular aggregates (TAM). The pathogenic pathways, and genetic factors are still not fully understood. Exome sequencing is a very effective method that provides a promising opportunity for the identification of rare disease-causing variants, further facilitating a much greater understanding of the biochemical pathways underlying the aetiology of these diseases.
Our group, based in the International IBM Consortium Genetic Study, has already recruited 154 patients with sporadic IBM (sIBM), two patients with familial IBM, 24 patients with TAM, one patient with cylindrical body myopathy, one patient with cytoplasmic body myopathy and 159 British controls. From current exome data, we have detected three known pathogenic mutations. We also selected a list of candidate genes from exome analysis, which we will further confirm by Sanger sequencing.
Analysis of the data is still in process, and we aim to (1) explore genes along the pathway of calcium homeostasis in patients with TAM; (2) compare genetic differences between blood and muscle samples at the DNA level; (3) identify high risk variants associated with sIBM.

P62 (Platform presentation and poster)
Investigating the effects of pharmacological up-regulation of the heat shock response in a transgenic mouse model of inclusion body myopathy

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Inclusion body myositis (IBM) is the commonest sporadic muscle disease affecting adults over the age of 50. Although the aetiology of this disease remains unclear, there is evidence for both inflammatory and myodegenerative processes in sIBM muscle pathology. In particular, abnormal protein aggregation is a characteristic feature of affected muscle, with evidence of ubiquitinated inclusion body formation, TDP-43 mislocalisation, mitochondrial dysfunction and ER stress.
The heat shock response (HSR) is an endogenous cytoprotective mechanism involved both in the regulation of normal protein folding and prevention of protein aggregation. Up-regulation of the HSR and the subsequent elevation in heat shock protein (Hsp) expression has been investigated as a potential therapeutic strategy in a number of neurodegenerative diseases.
Due to the sporadic nature of IBM there is no animal model in which to test potential therapies. However, mutations in the valosin containing protein (VCP) gene cause an hereditary form of the disease called Inclusion body myopathy with Paget's disease and frontotemporal dementia (IBMPFD). In this study, we characterised a transgenic mouse model of IBMPFD which has been reported to recapitulate many of the features of sporadic IBM in muscle, and examined the effects of pharmacological up-regulation of the HSR as a potential therapy for IBM.

Muscle Satellite Cells and IPS Cells

P63 (Platform presentation)
Improving satellite cell regenerative potential in muscular dystrophy: an environmental issue

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Background: Skeletal muscle has a remarkable regenerative capacity thanks to a population of resident stem cells termed satellite cells. The satellite cell niche, delimited by the adjacent myofibre and the surrounding basal lamina, maintains satellite cells quiescent, but its role on the long-term regenerative potential of skeletal muscle is unknown. The transmembrane proteoglycan syndecan-3

is expressed in satellite cells and regulates transduction of several signals from the niche into the satellite cell.
Methods: We used mouse genetics, histology, microscopy and behavioral tests to study the mechanisms that regulate satellite cell-niche interactions.
Results: When syndecan-3 is genetically ablated in mice, satellite cells lose their ability to adhere to the myofibre and to return quiescent after being activated by an injury. However, muscle regenerative capacity is not lost in syndecan-3 null mice. Indeed repeatedly injured syndecan-3 null muscles regenerate equally well as wild type muscles and develop a progressive myofibre hypertrophy. In dystrophic mice syndecan-3 knockout leads to an extraordinary amelioration of the dystrophic phenotype, including: reduced myofibre necrosis, muscle fibrosis and inflammation and improved muscle function, tested as time and distance run when mice are exposed to voluntary exercise.
Conclusions: Our data show that satellite cell-niche interactions regulate satellite cell homeostasis and regenerative potential both in healthy and dystrophic mice. The improvement of the dystrophic phenotype caused by syndecan-3 loss is associated with enhanced regenerative capacity and suggests syndecan-3 as a potential new therapeutic target for the management of muscular dystrophy and for the improvement of stem cell therapies.

P64
The effect of calorie restriction on satellite cell function
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Sarcopenia, the age-associated loss of skeletal muscle mass and function [1], is becoming an increasing societal and health problem, given the aging population in many countries. Caloric restriction without malnutrition has been shown to extend lifespan and reduce age-associated diseases in a variety of species, including the C57Bl/6 laboratory mouse strain, but not the DBA/2 strain [2].
We are currently investigating the behaviour of satellite cells using *in vitro* and *in vivo* techniques, from aging C57Bl/6 and DBA/2J male and female mice fed either *ad libitum* or a 40% calorie restriction regimen from 12 weeks of age.
Here, we present data showing that calorie restriction affects the function of satellite cells in both C57Bl/6 and DBA/2J mice, with potential downstream consequences for skeletal muscle regeneration.
1. Evans WJ. Skeletal muscle loss: cachexia, sarcopenia, and inactivity. The American Journal of Clinical Nutrition. 2010; 91(4): 1123S–1127S. Epub 2010/02/19.
2. Forster MJ, Morris P, Sohal RS. Genotype and age influence the effect of caloric intake on mortality in mice. FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 2003; 17(6): 690–2. Epub 2003/02/15.

P65 (Platform presentation)
Designing 3D scaffolds that can support myogenic progression in skeletal muscle satellite cells
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Background: Skeletal muscle can efficiently repair/regenerate after localised damage due to the presence of resident muscle stem cells, called satellite cells. However, this process has limitations, and is unable to restore significant muscle after severe trauma/loss, such as can occur following tumour removal or accidents. One strategy to facilitate larger scale muscle regeneration or replacement is transplantation of myogenic cells, together with a biocompatible scaffold to provide a supportive environment.
Aims: Our aim was to test different biocompatible 3D scaffolds for their ability to support myogenic progression of muscle satellite cells.
Methods: C2C12 myoblasts or primary murine satellite cells were seeded into three different biocompatible scaffolds in vitro (Collagen gel, polyethylene glycol-fibrinogen hydrogel (PEG-FN) and Fibrinogen-based gel) and their survival, proliferation, self-renewal and myogenic differentiation monitored.

Results: All three scaffolds supported C2C12 myoblast differentiation and fusion into multinucleated myotubes. However, although primary satellite cells embedded in these 3D scaffolds generally survived, they did not proliferate or differentiation well, with poor myotube formation observed.
Conclusion: Primary satellite cells require biomatrices with different properties to proliferate/differentiate successfully, compared to C2C12 myoblasts. We are currently testing further biomaterials for their ability to maintain myogenic progression in satellite cells as a step in designingD scaffolds that will eventually efficiently support *in vivo* transplantation of myogenic cells.

P66 (Platform presentation)
iPS cells and human artificial chromosomes: novel therapeutic tools for muscle disorders
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Background: Gene and cell therapy for Duchenne muscular dystrophy (DMD) is complex, since dystrophin is the largest human gene and skeletal muscle is the most abundant human tissue. We reported the amelioration of DMD mice by combining Human Artificial Chromosome (HAC)-mediated dystrophin gene-replacement with mouse mesoangioblast stem cell transplantation (using a HAC containing the entire dystrophin locus: DYS-HAC; PMID21849666). However, degeneration-regeneration cycles of dystrophic muscles may cause exhaustion of progenitors for autologous use, as recently shown (PMID22745439).
Aims: In order to translate DYS-HAC-mediated gene therapy to human mesoangioblasts, their proliferative capacity needs to be extended. Additionally, myogenic differentiation of iPS cells represents an ideal solution to bypass the limited availability of endogenous progenitors.
Methods: We describe transfer of a novel DYS-HAC into DMD mesoangioblasts reversibly immortalized to bypass replicative senescence. A method to obtain unlimited transplantable iPS cell-derived progenitors is also described.
Results: Reversible immortalization of DMD mesoangioblasts resulted in non-transformed cells that can be corrected with the DYS-HAC and transplanted into dystrophic mice. Moreover, differentiation of human dystrophic iPS cells resulted in progenitors that can be genetically-corrected and transplanted into dystrophic mice, providing therapeutic potential. Finally, application of this platform for disease modelling and bioengineering will be discussed.
Conclusion: This strategy provides evidence of pre-clinical safety and efficacy of HACs and iPS cells for cell-based therapies of muscular dystrophies.

P67
Characterisation of the expression of Polycomb Group Genes in human neuromuscular diseases
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Upon ageing and in the context of neuromuscular diseases the satellite cell-mediated regenerative capacity of the skeletal muscle is reduced, hence contributing to the decline in muscle function. Understanding the mechanisms that regulate the maintenance of muscle mass is therefore crucial for the development of novel therapeutic tools to sustain the regenerative process in neuromuscular disorders.
Polycomb group (PcG) proteins are transcriptional repressors that remodel chromatin through epigenetic modifications. In mouse models, two PcG proteins, Bmi1 and Ezh2, play a crucial role in skeletal muscle regeneration through regulation of self-renewal and proliferation of satellite cells. Thus, it is conceivable that modulation of the expression of these genes may be a viable tool to regulate satellite cell function in human neuromuscular pathologies.

To begin to understand the role of PcG proteins in the regenerative process of human muscle, we have performed immunofluorescence for Bmi1 and Ezh2, including co-localisation with markers of quiescent and activated satellite cells, in a wide spectrum of neuromuscular disorders, including inflammatory myopathies, DMD and MND. Cases that did not show histological abnormalities at the time of biopsy were considered normal comparators.
We show that both Bmi1 and Ezh2 are expressed in the human muscle during the regenerative process. A detailed characterisation of the expression pattern of these proteins will be presented, including a comparative assessment of the findings in human tissue and mouse models.

Databases, Diagnostics and Clinical Practice

P68

Improving diagnostic sensitivity and specificity of MuSK cell-based assays for myasthenia gravis

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Background: Acquired Myasthenia Gravis (MG) is an autoimmune channelopathy of the post-synaptic neuromuscular junction. Antibodies to the acetylcholine receptor and Muscle specific kinase can be detected by radioimmunoprecipitation assays (RIA) and cell-based assays (CBA).
Aim: To test and improve the sensitivity and specificity of the MuSK CBA
Patients and Methods: AChR and MuSK RIA(−) MG patients, positive controls, healthy controls, and other neurological disease controls were tested. Human Embryonic Kidney cells were transfected with MuSK and incubated with human sera (1:20). IgG binding to cell surface MuSK was detected using anti-human IgG (heavy and light chains) or anti-human IgG Fc(γ) antibody. End point titrations were carried out on positive controls.
Results: With anti-human IgG(H+L) MuSK positivity could be seen in 2/8 healthy controls and 3/17 other neurological disease controls. In some cases this coincided with the presence of IgM MuSK antibodies. The anti-human IgG Fc(γ) which is specific for the IgG class does not cross react with IgM antibodies, and was not positive in the healthy controls. Both secondary antibodies detected positive controls but the anti-human IgG Fc(γ) provided a slightly more sensitive as well as specific assay.
Conclusion: The light chains of IgG are shared between immunoglobulin isotypes. Other isotypes, in particular IgM may inadvertently be detected using anti-human IgG (H+L). An anti-IgG Fc(γ) appears more specific for IgG. The functional role and specificity of IgM in seronegative MG remains unclear and will form part of future work.

P69

Old dicta and new techniques

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Background: As students we are taught that differential diagnosis rests upon astute pattern-recognition within the clinical consultation which guides subsequent confirmatory investigations. As practising clinicians experience intermittently stresses the importance of critical clinical review and the limitations of our diagnostic techniques.
Aims: To evaluate how we discovered the cause of an isolated case of congenital non-progressive weakness.
Methods: In-depth clinical record review and whole exome sequencing.
Results: A 2-year old boy had difficulty walking and demonstrated a waddling gait and Gower's sign. There was no similar family history. Despite his weakness remaining non-progressive into adulthood he became unable to work because of fatigue. Congenital myaesthenia was considered but discarded in favour of a myopathy on the basis of two muscle biopsies, neurophysiology and an unsuccessful trial of pyridostigmine. However recent genetic tests including whole exome sequencing filtered for candidate myopathy genes failed to reach a molecular diagnosis. Comprehensive review prompted neurophysiological re-examination which demonstrated significant decrements in compound muscle action potentials on repetitive stimulation. Reinterrogation of the

exome data identified one pathological Dok7 variant. A second variant overlooked due to insufficient coverage was found by Sanger sequencing.
Conclusion: Powerful technological advances can greatly support the diagnostician but do not supersede traditional clinical reasoning. This case emphasises the importance of defining the clinical phenotype precisely to lead whole exome analysis.

P70

EUROMAC: Disease registry for McArdle disease and other pure muscle glycogenolytic disorders presenting with exercise intolerance

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Background: There is a demand for international cooperation on studies with larger cohorts of people with rare muscle disorders.
Aims: To create an international registry for McArdle Disease and very rare muscle glycogenolytic disorders registering patients across all European countries, collecting important natural history and epidemiological data.
Methods: EUROMAC is an European network which currently has 20 partners from 7 European countries and collaborators from Turkey and the USA. The registry will be accessed directly by patients via **http://euromacregistry.eu/**
The project will improve access to patient support bodies. Data on natural history and epidemiology of patients living in Europe will be analysed.
Standards of care will be developed, together with a plan to develop outcome measures for large multi-centre clinical trials.

P71

International Clinical Outcomes Study in Dysferlinopathy (COS): results of screening questionnaires in UK patients

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Mutations in *dysferlin* cause a variety of phenotypes collectively known as dysferlinopathies, including limb girdle muscular dystrophy type 2B and Myoshi Myopathy. There is a need to develop clinically validated outcome measures in dysferlinopathy in preparation for future clinical trials.
The International Clinical Outcomes Study for Dysferlinopathy (COS) is a multicentre international study, funded by The Jain Foundation and sponsored by Newcastle upon Tyne NHS Foundation Trust, which aims to develop and validate clinical outcome measures and will also collect information relating to the natural history of dysferlinopathy.

Data will be collected over 3 years, including physiotherapy and medical assessments, MRI and questionnaires. To date 124 patients have been recruited worldwide. We have analysed data from screening questionnaires in 39 UK patients.
In total 60 different mutations were identified. Mean age at symptom onset was 22.5 years and mean time to subsequent diagnosis was 5.9 years. Polymyositis was initially incorrectly diagnosed in 6/39 patients. Lower limbs were the most common first affected area (23/39), and muscle weakness the most frequent first symptom (20/39).
This data confirms that dysferlinopathies primarily present in young adulthood, often initially with lower limb symptoms, and are associated with significant allelic heterogeneity. Completion of this study will further enhance understanding of the natural history this variable condition.

P72

Unraveling the genetic cause in patients with inherited peripheral neuropathy using gene panel testing

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Inherited peripheral neuropathy (IPN) encompasses a clinically and genetically heterogeneous group of disorders. Advances in sequencing technology have made it feasible and cost effective to screen numerous causative genes simultaneously. We designed a panel assay comprising 56 genes associated with the common and the rare causes of different types of IPN. This is provided as a specialist UK Genetic Testing Network (UKGTN) service at Bristol Genetics Laboratory.
To date we have completed 80 cases referred by Neurologists and Geneticists across the UK. Excluding patients with PMP22 dosage abnormalities, a definite genetic diagnosis was achieved in 41% of CMT1 patients, whilst a further 18% have one or more candidate pathogenic variants requiring segregation studies. Similarly, 35% of the CMT2 patients had a definite genetic diagnosis and another 23% a probable one. Among dHMN patients, 43% had a pathogenic variant. 66% of HSAN patients had a candidate variant. A possible diagnosis was found in only 10% of patients with a poorly defined or complex clinical phenotype.
Our preliminary data indicate that gene panel testing is a powerful tool for genetic diagnosis in IPN. It provides high diagnostic yield, faster and at lower cost than sequential single gene screening. Accuracy and detail in phenotyping the patient is key to realising high detection rate, and variant interpretation. Family follow-up studies are often necessary to elucidate the clinical significance of novel variants. This brings added benefits, providing other affected relatives with a specific diagnosis and thereby more accurate information regarding prognosis and genetic risk.

P73

The national diagnostic and advisory service for limb-girdle muscular dystrophies in Newcastle

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A diagnostic service for Rare Neuromuscular Disorders was established in 2001 as a consortium of four Centres in the UK to advance diagnostics in such diseases. The service is now commissioned through NHS England and is managed by one of several Clinical Reference Groups with responsibility for different services. Newcastle is the national referral centre for the diagnosis of limb girdle muscular dystrophies (LGMDs), providing a nationally funded service for patients referred from England, Scotland and Wales. LGMDs are caused by at least eight genes with dominant inheritance and eighteen genes with a recessive inheritance. Patients' diagnosis is challenging due to the overlap in clinical presentation not only among different LGMD subtypes but also with other forms of muscular dystrophy. The diagnosis is ultimately resolved by identifying the primary gene defect, and protein analysis of muscle biopsies is a useful test for ruling in or out a significant number of these pathologies. In Newcastle we offer multidisciplinary assessment of LGMDs with specialist clinicians and physiotherapists and comprehensive laboratory diagnostics provided at both the protein and DNA levels. A research and development programme is in place to further characterise newly discovered disease-causing genes and their phenotypical spectrum. Our

approach is beneficial to patients as the specialised diagnostic expertise is concentrated in one centre leading to more effective diagnoses and management.

P74

Improving standards of care and translational research in spinal muscular atrophy (SMA) – functional scales

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Background: Recent discoveries and advances regarding SMA have led to the development of potential therapeutic treatments; consequentially there is the need for a robust clinical and research Network poised for designing valid outcome measures for clinical trials, and to collect longitudinal data on SMA.

Aims and Methods: SMA REACH UK (SMA Research And Clinical Hub UK) aims to establish national agreement on clinical and physiotherapy assessments, and standards of care for patients with SMA. The SMA REACH UK database will store longitudinal clinical and physiotherapy data facilitating translational research. This project will also ensure that functional scales are clinically relevant for future trials.

Physicians and physiotherapists from London, Newcastle, Rome and USA met in London (December 2013) to review the Expanded Hammersmith Functional Motor Scale for SMA (HFMSE), Upper Limb Module for SMA (ULM), and Performance Upper Limb Scale in conjunction with RASCH analysis information. Agreement on new exploratory scales for HFMSE and ULM was reached.

Results: The revised scales together with the North Star Ambulatory Assessment and 6 minute walk test are being tested prospectively across the participating sites.

Conclusion: It is anticipated SMA REACH UK will merge with the SMA Registry facilitating recruitment into clinical trials. Once the SMA REACH database, assessment tools and functional measures are finalised, national UK sites with a history of successful SMA enrolment will be invited to participate and collect high quality longitudinal data.

Other

P75

Exome sequencing identifies EPG5 mutations in two siblings with a childhood onset vacuolar myopathy

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Vici syndrome is a severe, recessively inherited multisystem disorder characterized by vacuolar myopathy, callosal agenesis, cataracts, cardiomyopathy, combined immunodeficiency and hypopigmentation. Ectopic P-Granules Autophagy Protein 5 Homolog (EPG5) has been identified as the primary cause of Vici syndrome. EPG5 encodes a protein that plays a crucial role in the later stages of the autophagy pathway during the clearance of autophagosomal cargo, as evidenced by defects in phagolysosome formation in the absence of *Epg-5.* Null mutations in this gene have consistently presented with a similar range of severe phenotypic features.

We present here a UK Caucasian sib pair presenting in the early teens with severely progressive proximal, axial and distal muscle weakness, elevated creatine kinase (5–10 times normal values), who developed respiratory insufficiency in the late teens. Muscle pathology showed a vacuolar myopathy. In collaboration with the Sanger Centre UK10K project whole exome sequencing was performed on the sisters. A heterozygous frame shift mutation was discovered in EPG5 which is also

present in their unaffected father (g.43534647G>A, c.721C>T, p.R241*). Further investigation into the EPG5 transcript by RT-PCR revealed a rearrangement in her other transcribed allele, in which non-coding material from the X chromosome was inserted into exon 23 of the EPG5 gene. We speculate that this inserted sequence partially disrupted the EPG5 protein function, hence the milder phenotype compared to typical Vici syndrome observed in these siblings.

P76

Clinical research activity in the Newcastle MRC Centre for Neuromuscular Disease

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The Newcastle MRC Neuromuscular team encompasses a number of specialists involved in the diagnosis, treatment, management and research into a broad spectrum of neuromuscular and mitochondrial diseases, ranging from Duchenne muscular dystrophy, congenital myopathies and limb girdle muscular dystrophies to mitochondrial cytopathies and inherited neuropathies. The team aims to use information gathered from translational research to offer patients suffering from genetic and acquired neuromuscular diseases the opportunity to take part in studies and clinical trials, which may lead to new treatments and improve the quality of life for all patients and their families. The clinical research team includes clinicians, clinical research associates, physiotherapists, research nurses, psychologists, physiologists, clinical trial coordinators/ project managers and PhD students working together on a number of studies in adult and paediatric patients. Current and pending projects include drug (17) and exercise intervention studies (7), translational research (6), natural history studies (9), registries (6), BioBanks (3), behavioral intervention (3) and clinical outcome studies (3). The team is active in the conception and design of local, national and international commercial and academic studies. The coordination team is responsible for obtaining Ethical and Research and Development approval, National Institute for Health Research support and adoption and study management throughout the whole process. Every member of the clinical research team is instrumental in conducting research in line with Good Clinical Practice (GCP) which is facilitated by the coordination team to produce the highest professional level of neuromuscular clinical research in Newcastle and the North East.

P77

Collagen XII; novel disease-causing candidate gene for Bethlem-like patients

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Background: Bethlem Myopathy characterized by progressive muscle weakness, joint contractures and late onset of symptoms. Mutations in collagen VIA genes have been defined for only 50% of Bethlem phenotypes.

Aim: a cohort of 24 Bethlem patients without mutations in the *COL6A* genes were analysed to identify potential disease-causing variants.

Methods and Results: 12 candidate genes including collagen VI binding partners were sequenced in this cohort but no disease-causing variants were found. Whole exome sequencing (WES) revealed two novel variants (c.C5893T: p.Arg1965Cys and c.G8357A: p.Gly2786Asp) in the *COL12A1* gene were identified in five patients from two families. Segregation of both variants showed an autosomal dominant pattern of inheritance. Collagen XII is a member of Fibril Associated Collagen with Interrupted Triple helices (FACIT collagens), important in stabilisation of other extracellular matrix (ECM) components [1]. In silico analysis revealed that c.G8357A: p.Gly2786Asp disrupted

conserved motif of GLY-X-Y in the triple-helical domain of the protein and c.C5893T: p.Arg1965Cys which creates an unpaired cystein residue. Immunofluorescence studies revealed an intracellular retention pattern of the mutant collagens in dermal fibroblasts of patients.
Conclusions: Our findings suggest a causative role for *COL12A1* in Bethlem myopathy.
Key words: Bethlem myopathy, *COL12A1*
1. Koch, M., Bohrmann, B., Matthison, M., Hagios, C., Trueb, B. and Chiquet, M. (1995) Large and small splice variants of collagen XII: differential expression and ligand binding. J. Cell Biol., 130, 1005–1014.

Sponsor Abstract

PTC Therapeutics

Development of a confirmatory phase 3, multicentre, randomized, double-blind, placebo-controlled study of ataluren in patients with nonsense mutation Duchenne muscular dystrophy

A Reha, R Spiegel, GL Elfring, J Barth, M Husain, SW Peltz, for the Ataluren DMD Study Steering Committee
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Background
Duchenne muscular dystrophy (DMD) is a progressive and fatal neuromuscular disorder, characterized by a relentless decline in physical function. A nonsense mutation (nm) in the dystrophin gene is the cause of DMD in ~13% of patients. Ataluren is an investigational oral drug designed to promote ribosomal read-through of premature stop codons caused by nonsense mutations, leading to production of full-length, functional protein.
Aims
To describe an ongoing, confirmatory, phase 3, placebo-controlled study designed to assess the efficacy and safety of ataluren in boys with nmDMD.
Methods
A total of 220 patients will be enrolled in the study. All patients will be male with a nonsense mutation in the dystrophin gene, aged 7–16 years, receiving a stable dose of corticosteroids, and have a screening 6-minute walk distance (6MWD) ≥150 m but below the protocol-specified %-predicted threshold. Patients will be randomized in a 1:1 ratio to placebo or ataluren 40 mg/kg/day. The primary endpoint is change in 6MWD over 48 weeks. Secondary efficacy measures include timed function tests, quality of life, North Star Ambulatory Assessment, and patient/parent-reported disease-related symptoms and activities of daily living.
Results
The design of this study reflects lessons learned from earlier trials and targets a study population to best show a treatment effect. In a retrospective subgroup analysis of patients in the phase 2b trial of ataluren in nmDMD who met the current study criteria, the difference between ataluren 40 mg/kg/day (n=30) vs placebo (n=31) in mean change in 6MWD over 48 weeks was ~50 m.
Conclusions
This study is designed to confirm the treatment effect of ataluren seen in the phase 2b ataluren trial and is anticipated to be one of the largest trials conducted in DMD.

Current UK Neuromuscular Clinical Trials

MRC Centre CTIMPs Set-up Phase trials

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

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

2. A Pilot Study of Valproate Sodium for McArdle Disease
Status: Set-up phase (REC submitted)
Sponsor: UCL
Planned start date: 2014
Funder: Muscular Dystrophy campaign
PI: Dr Ros Quinlivan
Recruitment target: 15
McArdle disease (Glycogen storage disease type V, GSDV) is an inherited metabolic disorder of skeletal muscle. Affected patients are unable to produce lactate during ischaemic exercise [McArdle 1951] because they have a congenital absence of the enzyme muscle glycogen phosphorylase, which is essential for glycogen metabolism [Mommaerts 1959, Schmidt and Mahler 1959]. The condition is caused by homozygous or compound heterozygous mutations in the muscle glycogen phosphorylase gene *(PYGM)* located at chromosome 11q13 [Beynon 2002]. This enzyme deficiency results in the inability to mobilise muscle glycogen stores that are normally required for energy during anaerobic metabolism. In affected people, symptoms of fatigue and cramp occur within minutes of initiating any activity and during strenuous activity such as lifting heavy weights or walking uphill, if the activity is continued despite severe cramping, a contracture occurs which leads to muscle damage (rhabdomyolysis), myoglobinuria and, when severe, acute renal failure.

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

Although most people with McArdle disease have complete absence of skeletal muscle phosphorylase, there are a small minority of patients who possess splice site mutations that enable production of very small amounts (1-2%) of functional enzyme [Vissing]. These people have a milder phenotype with less severe symptoms, and functional exercise assessments have shown better exercise capacity than typical patients with the condition. Findings from these atypical individuals suggest potential therapeutic agents might only need to produce very small amounts of enzyme for significant functional improvement. Furthermore, finding a therapeutic agent to 'switch on' expression of the foetal isoenzyme may be a potential therapeutic strategy.
Sodium Valproate (Valproic acid) is one of a group of drugs known as histone deacetylase inhibitors (HDACIs) that can affect gene expression by acetylating lysine residues, which in turn has a direct effect on chromatin [Thiagalingam 2003]. There is some evidence from animal studies to suggest that sodium valproate can 'switch on' the foetal phosphorylase isoenzyme.
A recent clinical trial of the drug in McArdle sheep that were given sodium valproate for three months showed the presence of phosphorylase positive muscle fibres, in the absence of muscle necrosis and/or regeneration [Howell 2010].

The current proposes an open label uncontrolled pilot study to evaluate safety and efficacy of Sodium valproate (slow release) 20mg /kg once daily for six months. 15 subjects, adult male and post menopausal women attending specialist centres for McArdle disease will be recruited across three sites: London, Copenhagen and Dallas.

3. A randomized, double-blind, placebo-controlled, multicenter, parallel group, dose-finding, pivotal, phase IIb/III study to evaluate the efficacy, safety and tolerability of intravenous BYM338 at 52 weeks on physical function, muscle strength, and mobility and additional long-term safety up to 2 years in patients with sporadic inclusion body myositis
Status: Set-up phase/ Investigator's meeting 4- 6 Feb 2014/REC submitted
Sponsor: Novartis
Planned start date: 2014
PI: Prof Michael Hanna
Recruitment target: 10
The purpose of this dose-finding study is to demonstrate that at least one dose regimen of BYM338 in sporadic inclusion body myositis (sIBM) patients improves physical function and mobility when compared to placebo after 52 weeks of treatment. The study will assess efficacy, safety, tolerability and pharmacodynamic effect of i.v. administration of BYM338 compared to placebo on lean body mass, muscle strength, physical function and mobility in sIBM patients.
The results will support marketing authorization applications for BYM338 as treatment for sIBM patients.
This is a multi-center, pivotal, randomized, double-blind, placebo-controlled, 4 arm dose-finding, phase IIb/III trial.

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

Specific Aims

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

5. Bumetanide in HypoPP
A randomised, double-blind, placebo-controlled, phase II clinical trial with a cross-over design assessing efficacy of a single dose of bumetanide in reducing focal attack severity in hypokalaemic periodic paralysis assessed using the McManis protocol
Status: Set-up phase
Sponsor: UCL
Funder: TBC
Planned start date: 2014
PI: Prof Michael Hanna
Recruitment target: 12
This is a planned phase II clinical trial, double-blind, randomised, placebo-controlled cross-over, single-site study to investigate the efficacy of bumetanide in patients with hypokalemic periodic paralysis (HypoPP). The objective is to

assess the efficacy of bumetanide in reducing severity and duration of acute attacks of weakness in HypoPP patients. Hypokalaemic periodic paralysis is an autosomal dominant muscle channelopathy with onset in the first or second decade, characterized by attacks of reversible flaccid paralysis lasting from several hours to days. These patients may have frequent attacks of weakness interfering with daily activities and work, and are often hospitalized for intravenous potassium treatment causing a significant economic burden. They may also progress to a chronic myopathy especially because there are no optimal treatments available nowadays.
Experimental evidence of the use of bumetanide in a mouse model of HypoPP has provided convincing evidence that it can abort paralytic attacks.
We would expect bumetanide to abort acute attacks of weakness faster and reduce their severity, reducing the likelihood of patients being hospitalized during severe attacks. Bumetanide will add as an adjuvant therapy to potassium intake during an attack.

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

MRC Centre CTIMPs Open Trials

7. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (GSK Extension Study)
Full Title: An open-label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne Muscular Dystrophy.
Status: Closed to recruitment
Sponsor: GlaxoSmithKline
Funder: GlaxoSmithKline
PIs: Prof Volker Straub, Prof Francesco Muntoni
Patients recruited: 8; target (UK) 8
Description: A Phase III, multicenter, open-label extension, study in male outpatients with Duchenne Muscular Dystrophy (DMD) who have participated in eitherDMD114117 or DMD114044. All subjects will receive 6mg/kg GSK2402968 weekly for a minimum period of two years or an intermittent dosing frequency of 6mg/kgGSK2402968 for a minimum period of two years.
Objective(s)
Primary objective:
• To evaluate the long term safety, tolerability and efficacy of subcutaneous 6mg/kg/weekGSK2402968 in subjects with DMD who have participated in either DMD114117 orDMD114044.
Secondary objectives:
• To evaluate the long-term PK of subcutaneous 6 mg/kg/week GSK2402968 in subjects with DMD who have participated in either DMD114117 or DMD114044.
• To evaluate the long-term impact on health-related quality of life (HRQoL) and functional outcomes of continued treatment with GSK2402968 in subjects with DMD who have participated in either DMD114117 or DMD114044.
• To evaluate DMD disease progression and outcomes (clinical, HRQoL and functional) in subjects who discontinue active treatment during the conduct of study (natural history component).
• To evaluate the long-term safety, efficacy and PK of an intermittent dosing option in those subjects unable to tolerate GSK2402968 6mg/kg/week dosing.

This study aims to enrol approximately 200 subjects. In the primary dosing arm, subjects will receive GSK2402968 6 mg/kg as subcutaneous injections once a week for a period of 104 weeks. Further information about this study can be obtained from the MRC Centre Clinical Trials Coordinator on 020 7905 2639.

8. The PATH Study
Full title: Randomized, multicenter, double-blind, placebo-controlled, parallel-group phase III study to investigate the efficacy, safety and tolerability of 2 different doses of Igpro20 (subcutaneous immunoglobulin) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) – the Path Study
Status: Open
Sponsor: CSL Behring
PI: Dr Michael Lunn
Patient target: 5; recruited 6
CIDP is an acquired neurological, demyelinating neuropathy with an assumed autoimmune-mediated pathogenesis. Due to its heterogeneous presentation and the limitations in the individual diagnosis procedures (clinical, serologic, and electrophysiological), the diagnosis relies on findings from multiple modalities. The probable autoimmune nature of the condition is most strongly suggested by response to immunotherapies such as intravenous immunoglobulins (IVIGs), plasmapheresis (PE), and corticosteroids.
In addition, despite less definitive published evidence of efficacy, corticosteroids are also considered as first-line therapy because of their long history of use.
Apart from IVIGs, there are currently no other medications approved for the treatment of CIDP; however experimental use of azathioprine, mycophenolate mofetil, methotrexate and cyclosporine are common and whilst there are also emerging reports of the use of B Lymphocyte antigen CD20 and anti-complement monoclonal antibody therapies, efficacy has not been established for any of these agents.
This is a prospective, multicenter, randomised, double-blind, placebo-controlled, parallel-group 3-arm study to investigate 2 different doses of SCIG IgPro20 compared to SC (subcutaneous) placebo for maintenance treatment of subjects with CIDP. Subjects on IVIG maintenance therapy experiencing CIDP relapse during an IVIG Withdrawal period will be administered the IVIG IgPro10 (1 loading dose and 3 or 4 maintenance doses every 3 weeks) during an IVIG Re-stabilization Period. Subjects with improved and maintained INCAT score at the last 2 assessments in the IVIG Re-stabilization Period will be randomised to 1 of 2 Igpro20 doses (0.2 or 0.4 g/kg body weight) or placebo during the SC Treatment Period.
IgPro20 is a ready-to-use formulation of human IgG with ≥98% purity for subcutaneous (SC) administration. Igpro20 is approved in the United States of America (US), in the EU, in Switzerland and Canada under the brand name Hizentra® for SC application in primary immune deficiency syndromes and is also under review by other regulatory agencies for use in primary and secondary immunodeficiencies.
IgPro10 is a ready-to-use liquid formulation of polyvalent IgG for intravenous (IV) application approved and marketed in several countries including the European Union (EU) and the US for use in primary immunodeficiency (PID) syndromes and for immune thrombocytopenic purpura (ITP). In the EU, IgPro10 is further approved for other conditions associated with immunodeficiencies resulting in the need for replacement therapy and in Guillian-Barre Syndrome (GBS) where IVIG is thought to have immunomodulatory effects on the peripheral nervous system. For the treatment of GBS and CIDP, a similar mode of action is assumed.
IgPro10 is currently under investigation in a confirmatory phase III study in subjects with CIDP.
Several randomised clinical studies have demonstrated the clinical efficacy and safety of using IVIGs to treat CIDP. IVIGs requires subjects to visit a clinic or hospital for 1 to 5 days on a regular basis, usually every 2 to 6 weeks. This study is being conducted to provide SCIG as an alternative treatment option for CIDP that allows subject (or their caregiver) to self-administer the product in the home setting.

9. DMD HEART PROTECTION TRIAL
Full-Title: A double-blind randomised multi-centre, placebo-controlled trial of combined ACE-inhibitor and beta-blocker therapy in preventing the development of cardiomyopathy in genetically characterised males with DMD *without* echo-detectable left ventricular dysfunction
Status: Open to recruitment
Sponsor: Newcastle NHS Foundation
Funder: British Heart Foundation
PI: Prof Muntoni
Recruitment target: 50-60 (GOSH) 20-30 (Newcastle)

Patients recruited: 42 (GOSH) 16 (Newcastle) (recruitment ends July 2014)
Duchenne muscular dystrophy [DMD] is an X-linked recessively inherited neuromuscular disorder due to a deficiency in the expression of the protein dystrophin on the inner aspect of cell sarcolemma. Its clinical course has traditionally been characterised by progressive weakness of proximal limb-girdle muscles and calf muscle hypertrophy. Duchenne-affected individuals typically lose ambulation and become wheelchair-dependent before the age of 13 and die from cardio-respiratory failure at around the age of 20 years. From the cardiology perspective, some 90% of males with DMD develop a severe, progressive form of cardiomyopathy. Twenty to 30% have evidence of left ventricular impairment on echocardiography by age 10 years. Abnormalities in left ventricular function are evident in an even larger proportion of patients at all ages when more sensitive imaging techniques, such as tissue Doppler, magnetic resonance or metabolic imaging, are deployed. Despite the severity of cardiac involvement in DMD, cardiologists have largely ignored this particular inherited form of cardiomyopathy. This is due to the fact that, because of their inability to exercise, cardiac symptoms only occur terminally in DMD patients when all cardiac reserve has been eroded. Even today in most hospitals, cardio-active drug therapy is only started in patients with DMD when overt heart failure is evident and, even then, is typically deployed tentatively for symptom control, without any expectation that it can prolong life. The objective of this trial is to determine whether the introduction of ACE inhibitor combined with beta-blocker therapy, before the onset of echo-detectable left ventricular dysfunction, can delay the age of onset and/or slow the rate of progression of cardiomyopathy compared to placebo in males with DMD. This is a double-blind randomised, placebo-controlled Phase III trial of combined ACE inhibitor and beta-blocker therapy (perindopril and bisoprolol) over a minimum of three years and a maximum of five years. 140 participants (70 per arm) are to be enrolled and randomised. For more information about the study please contact the trial coordinator on 020 7905 2639.

10. FOR-DMD
Full Title: Duchenne muscular dystrophy: double-blind randomized trial to find optimum steroid regimen (FOR-DMD)
Status: Open to recruitment
Sponsor: University of Rochester
Funder: NIH
PI: Prof Francesco Muntoni, Prof Volker Straub
Patients recruited: 2 (GOSH) 5 (Newcastle)
Target: 8
This is a multi-centre, double-blind, parallel group, 36-60 month study, comparing three corticosteroid regimens in wide use in DMD:

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

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

11. PTC124-GD-019 Open label
Full-Title: An open-label study for previously treated Ataluren (PTC124®) patients with nonsense mutation dystrophinopathy
Status: **Closed to recruitment**
Sponsor& Funder: PTC
Patients recruited: 8 (GOSH), 11 (Newcastle)
This study comprises a phase III, open-label study of ataluren in patients with nmDBMD who previously received ataluren at an investigator site in a prior PTC-sponsored clinical study.

Subjects will receive ataluren 3 times per day (TID) at respective morning, midday, and evening

doses of 10 mg/kg, 10 mg/kg, and 20 mg/kg, for approximately 96 weeks. Study assessments will be performed at clinic visits during screening, on the first day of ataluren dosing, and then every 12 weeks during the ataluren treatment period.

Primary Objective:

The primary objective of this study is to assess the long-term safety and tolerability of 10, 10, 20 mg/kg ataluren in patients with nmDBMD who had prior exposure to ataluren in a PTC-sponsored clinical trial.

Secondary objectives include the following:

- Ambulatory patients (able to run/walk 10 meters in ≤30 seconds) - To determine the effect of ataluren on ambulation and other aspects of physical function
- Nonambulatory patients (unable to run/walk 10 meters in ≤30 seconds) - To assess the effect of ataluren on activities of daily living, upper limb function, and pulmonary function
- All patients – To assess patient and/or parent/caregiver reports of changes in disease status:

Retrospectively during and after participation in previous studies (Studies 007 and 007e) and prospectively during the current study.

12. PROSPECTIVE EVALUATION OF GASTROSTOMY IN MND/ALS (PROGAS)
Full title: Prospective evaluation of gastrostomy in MND (PROGAS). Prospective evaluation of gastrostomy in MND (PROGAS).
Status: Ongoing
Sponsor: Royal Free London NHS Foundation Trust
Start date: 2011
Funder: Motor Neurone Disease Association / South Yorkshire CLRN
UCL PI: Dr Richard Orrell
Patients recruited: 6, target: open-ended

Difficulty in swallowing is a common problem in patients with MND. Patients with severe swallowing difficulty experience malnutrition, dehydration, choking and an increased risk of chest infections. Long-term nutritional support of patients with severe swallowing difficulty can be achieved by placing a feeding tube, known as a gastrostomy, directly into the stomach. However, the current practice of gastrostomy feeding is largely based on consensus and expert opinion rather than the outcomes of appropriately designed trials. Currently gastrostomy technique and timing of insertion within the disease course vary throughout the UK. There is a lack of evidence to suggest what the optimal timing for gastrostomy is, or which method is most appropriate. In addition, although gastrostomy is routinely performed, the benefits, such as improved survival and quality of life following gastrostomy, have not been proven. The main aim of this study is to develop evidence-based guidelines for gastrostomy use in patients with MND. Patients and carers will be recruited at the participating MND Centres around the UK. Questionnaires will be used to assess the safety, complications and benefits of the differing timings and methods of gastrostomy insertion. The results of this work will translate into the development of guidelines, which will optimise the benefit, and the patient and carer experience of gastrostomy. The principles will be readily applicable to patients with severe swallowing problems who are eligible for gastrostomy insertion due to other neurological diseases

13. THERAPEUTIC TRIAL OF diaphragmatic pacing IN MND/ALS (DiPALS)
Full title: A randomised controlled trial in patients with respiratory muscle weakness due to motor neurone disease of the NeuRx RA/4 Diaphragm Pacing System
Status: Ongoing
Sponsor: Royal Free London NHS Foundation Trust
Start date: March 2013
Funder: NIHR Health Technology Assessment Programme / Motor Neurone Disease Association / Department of Health subvention funding
UCL PI: Dr Richard Orrell
Patients recruited: target: 4 plus

Non Invasive Ventilation (NIV) therapy is the current standard treatment to help allow patients with MND/ALS to breathe. Patients wear a face mask over their nose or mouth or both and as they breathe in, the machine gives an extra push of air to support the patient's weak breathing muscles, enabling a bigger deeper breath. Some MND patients do not tolerate NIV due to the type of mask they have. During the day problems with using NIV include issues like claustrophobia, feeding and communication. Eventually respiratory muscle weakness will progress to a point at which intermittent/overnight NIV is ineffective. Diaphragm pacing (DP) is a means of increasing the strength of the main breathing muscle. The NeuRx RA/4 Diaphragm Pacing System has been developed for patients who are unable to control their diaphragms because of stable high spinal cord injuries or because they have a neuromuscular disease such as MND. The pacing wires are inserted into the diaphragm muscle during a small operation and are connected to a small portable box that the patient can easily carry about. The proposed study will assess if treatment with DP prolongs life and maintains quality of life when given in addition to current standard care with NIV. 108

patients will recruited to the study in up to 10 NHS hospitals in the UK. Patients will be randomised to either have NIV or receive DP in addition to NIV. Study participants will be required to complete outcome measures at 5 follow up time points (2, 3, 6, 9 and 12 months). Patients in the DP group will have additional visits for surgery and a 1 week post operative follow up. 12 patients (and their carers) from the DP group will also be asked to complete 2 qualitative interviews.

14. Full Title: A phase III efficacy & safety study of Ataluren (PTC124) in patients with nonsense mutation dystrophinopathy (PTC Phase III) PTC124-GD-020-DMD
Status: Open to recruitment
Sponsor: PTC
Funder: PTC
PI: Prof Francesco Muntoni, Dr Michela Guglieri
Patients recruited: 2 (GOSH) 3 (Newcastle)
Target: 3-5

A phase 3 efficacy and safety study of ataluren (ptc124) in patients with nonsense mutation dystrophinopathy

The primary objective of this study is to determine the ability of ataluren to slow disease progression as assessed by ambulatory decline (decrease in 6MWD) in patients with nonsense mutation dystrophinopathy.
Secondary endpoints have been chosen to evaluate changes in skeletal muscle function through assessment of proximal muscle function, as assessed by the time to run/walk 10 meters, time to ascend 4 stairs and time to descend 4 stairs and patient or parent/caregiver perception of physical functioning. Additional secondary endpoints have been selected to enhance understanding of the primary and secondary treatment effects. For example, a beneficial effect in physical function relative to placebo, as assessed by the North Star Ambulatory Assessment (NSAA), would compliment positive changes in ambulation proximal muscle function. Collection of patient and/or parent reported changes in disease status provides an opportunity to expand the implications of a drug effect on the patient's disease symptoms and activities of daily living.

15. Full Title: A phase IIb, open-label study to assess the efficacy, safety, pharmacodynamics and pharmacokinetics of multiple doses of PRO045 in subjects with Duchenne muscular dystrophy (PRO045)
Status: Open to recruitment
Sponsor: Prosensa
Funder: Prosensa
PI: Prof Francesco Muntoni, Prof Volker Straub
Patients recruited: 1 (GOSH) 2 (Newcastle)
Target: 4-5 (GOSH)
Primary objective: To assess the efficacy of PRO045 after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy.
Secondary objectives: To assess the safety and tolerability of PRO045 after 48 weeks of treatment in all study subjects with Duchenne muscular dystrophy including subjects from the dose-escalation phase of the study. To determine the pharmacokinetics of PRO045 at different dose levels after subcutaneous administration in subjects with Duchenne muscular dystrophy.
To assess the pharmacokinetics, bioavailability and safety of PRO045 following single intravenous dose administration at different dose levels.
To assess the pharmacodynamics of PRO045 at different dose levels after subcutaneous administration in subjects with Duchenne muscular dystrophy.
To assess trend in efficacy in all subjects with Duchenne Muscular Dystrophy not included in the primary objective after 48 weeks of treatment.

16. SMT C1100 – A Phase 1, Open-label, Single and Multiple Oral Dose, Safety, Tolerability and Pharmacokinetic Study in Paediatric Patients with Duchenne Muscular Dystrophy
Status: Open to Recruitment
Sponsor & Funder: Summit
PI: Prof F. Muntoni
Patients Recruited: 4 consented (GOSH)
Recruitment target 4 (GOSH), UK target 12
This will be an open-label, single and multiple oral dose study. Up to 12 patients with DMD will be enrolled onto the study. Primary Objective is to determine the safety and tolerability of single and multiple oral doses of SMT C1100 in patients with Duchenne Muscular Dystrophy (DMD). Secondary Objectives are to determine the single and multiple oral dose pharmacokinetics of SMT C1100 and its metabolites in patients with DMD.

SMT C1100 is the first in a new pharmacological class of orally available small molecules that act to modulate transcriptional control of utrophin. SMT C1100 is being developed with the potential to treat DMD independent of the dystrophin mutation, by maintaining production of utrophin to compensate, at least in part, for the loss of the dystrophin protein. Outcomes from non-clinical pharmacodynamic studies indicate that SMT C1100 increases utrophin mRNA and protein levels and improves muscle structure and function.

17. An Open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of repeated biweekly infusions of neoGAA in naïve and alglucosidasealfa treated late-onset Pompe disease patients.
Status: Open to recruitment
Sponsor: Genzyme
Funder: Genzyme
PI: Prof Volker Straub
Patient recruited: 0
Target: 1
Phase I, multicenter, multinational, open-label, ascending dose, repeated bi-weekly intravenous infusion study of neoGAA in:

- Group 1 – Late-onset Pompe disease patients naïve to treatment, 3 dose levels
- Group 2 – Late-onset Pompe disease patients previously treated with alglucosidasealfa, 3 dose levels

Objectives:
Group 1
To determine in treatment naïve patients with late-onset Pompe disease patients:

- The safety and tolerability of neoGAA
- The pharmacokinetic parameters of neoGAA
- The pharmacodynamic effects of neoGAA on skeletal muscle and other exploratory biomarkers
- The effect of neoGAA on exploratory efficacy endpoints

Group 2
To determine in alglucosidasealfa treated late-onset Pompe disease patients:

- The safety and tolerability of neoGAA
- The pharmacokinetic parameters of neoGAA
- The pharmacodynamic effects of neoGAA on skeletal muscle and other exploratory biomarkers
- The effect of neoGAA on exploratory efficacy endpoints

<u>MRC Centre CTIMPs Completed Trials</u>

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

19. THERAPEUTIC TRIAL OF MEXILETINE IN NON-DYSTROPHIC MYOTONIA
Full Title: A Phase II Randomised, Double-Blind, Placebo controlled, Cross-Over Study to Investigate the Efficacy of Mexiletine in Patients with Non-Dystrophic Myotonia
Status: Completed
Sponsor: University College London (UCL)
Funder: Food and Drug Administration (FDA – USA)
PI: Prof Hanna
Patients recruited: 14; target 15

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

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

20. A PHASE IIb EFFICACY AND SAFETY STUDY OF PTC124 IN SUBJECTS WITH NONSENSE MUTATION-MEDIATED DUCHENNE AND BECKER MUSCULAR DYSTROPHY Status: Completed
Sponsor: PTC Therapeutics
Funder: PTC Therapeutics
PIs: Prof Muntoni, Prof Bushby
Patients recruited: 11

Duchenne muscular dystrophy (DMD) is an X-linked genetic disorder affecting young boys. The condition is disabling and life-threatening. A small subset of boys are classified as having Becker muscular dystrophy (BMD), a phenotypically milder form of the dystrophic muscle disease.

In approximately 10 to 15% of boys with DMD and BMD the causative defect is the presence of a nonsense mutation in the dystrophin gene that truncates dystrophin protein production by introducing a premature stop codon into the dystrophin messenger ribonucleic acid (mRNA).

PTC124 is a novel, orally bioavailable, small-molecule drug that promotes ribosomal read-through of mRNA containing a premature stop codon. Through this mechanism of action, PTC124 has the potential to overcome the genetic defect in boys for whom a nonsense mutation causes DMD/BMD.

In vitro studies in cell lines with dystrophin nonsense mutations have shown that PTC124 can restore production of the missing dystrophin gene.

This is an international, multi-centre, randomised, double-blind, placebo-controlled, dose-ranging, efficacy and safety study.

The study primary aim is to evaluate the effect of PTC124 on ambulation as assessed by the distance walked during a 6-minute walk test (6MWT).

The double-blind arm of the study randomised 174 participants worldwide which are to be followed for a period of 12 months. At the completion of the blinded treatment, all compliant participants were eligible to receive open-label PTC124 in a separate extension study.

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

This work has been completed.

The preliminary findings from the Ataluren Study 007 did not show significant muscle improvement in the patients who participated in the study. The study was therefore discontinued. An update on this study was presented at the International Congress on Neuromuscular Diseases, Naples, Italy, 17-22 July 2010 by Professor Kate Bushby. Details of this presentation is available on www.ptcbio.com Briefly, analysis showed that, on average, patients treated with low-dose ataluren experienced better outcomes on measures of efficacy than patients treated with high-dose ataluren or placebo - this phenomenon is not unique for ataluren and has been observed with other drugs for other diseases. Further analysis of efficacy data is ongoing.

ANTISENSE OLIGONUCLEOTIDE INDUCED EXON SKIPPING IN DUCHENNE MUSCULAR DYSTROPHY

This initiative is led by the MDEX consortium (The MDEX consortium led by Professor Muntoni, is a multidisciplinary enterprise to promote translational research into muscular dystrophies, and is formed by the clinical groups of Professor Francesco Muntoni (UCL Institute of Child Health) and Professor Kate Bushby and Professor Volker Straub (Newcastle University), and scientists from Imperial College London (Professor Dominic Wells), UCL Institute of Child Health (Dr Jennifer Morgan), Royal Holloway University of London (Professor George Dickson and Dr Ian Graham), Oxford University (Dr Matthew Wood) and University of Western Australia (Prof Steve Wilton). In addition, the charities Muscular Dystrophy Campaign (MDC), Action Duchenne and Duchenne Family Support Group also participate in the Consortium, www.mdex.org.uk).

The current two trials led by the consortium are mentioned below.

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

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

23. ECULIZUMAB FOR MYASTHENIA GRAVIS
Full Title: A Randomised, Double-Blind, Placebo-controlled, Cross-over, Multicenter Study of Eculizumab in Patients with Generalised Myasthenia Gravis (GMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosupressants
Status: Closed
Sponsor/Funder: Alexion Pharmaceuticals, Inc.
PI: Prof Dimitri Kullmann
This is a randomized, double-blind, placebo-controlled, cross-over, multicenter study to evaluate the safety and efficacy of eculizumab for the treatment of patients with myasthenia gravis. Myasthenia gravis (MG) is an acquired autoimmune syndrome caused by the failure of neuromuscular transmission, which results from the binding of autoantibodies to proteins involved in signalling at the neuromuscular junction (NMJ). These proteins include the nicotinic AChR or, less frequently, a muscle-specific tyrosine kinase (MuSK) involved in AChR clustering.

Current available treatments for myasthenia gravis aim to modulate neuromuscular transmission, to inhibit the production or effects of pathogenic antibodies, or to inhibit inflammatory cytokines. There is currently no specific treatment that corrects the autoimmune defect in MG.
Eculizumab is a humanized murine monoclonal antibody that blocks the activation of complement by selectively binding to C5 and preventing the enzymatic cleavage of C5 to C5a and C5b. The blockade of complement activation at this point in the cascade has been shown to prevent the proinflammatory effects of both C5a and C5b, especially the chemotaxis of inflammatory cells, and MAC (C5b-9)-mediated cell activation and lysis. Since eculizumab effectively inhibits complement, especially MAC formation, it is a potentially effective therapeutic approach for diseases such as MG in which the formation of the MAC and/or the release of C5a leads to localized destruction of the postsynaptic NMJ membrane and play a important role in the disease process.
Patients will receive approximately 22 infusions including 11infusions of eculizumab and 11 infusions of placebo. The estimated duration of a patient's participation is approximately 41 weeks.
Wiley Periodicals, Inc. Published online March 2013, (wileyonlinelibrary.com) DOI 10.1002/mus.23839

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

25. **Investigation of the ability of Otelixizumab to inhibit in vitro antigen-specific T cell responses from Myasthenia Gravis patients**
Status: Completed
Sponsor/Funder: GlaxoSmithKline
PI: Prof Kullmann
Patients recruited: 39; target 40
Myasthenia Gravis (MG) is the best understood autoimmune disease (a disease in which the immune system attacks some part of the body). This attack is directed by various parts of the immune system.
There is a continued search for newer drugs that will be of benefit in the treatment of MG. Otelixizumab has been identified as a possible treatment for MG. However before clinical trials can be considered additional information is needed to determine how it interacts with the immune system of patients with MG.
In this study adult patients with MG will be invited to provide blood samples (50 ml) for research purposes. Blood collected from patients will be used for T-cell assay and autoantibody assay development. Patients may be asked to provide a repeat blood sample (additional 50ml) after 46 months following the initial collection to see if T cell activation changes over time. Up to 40 participants will be enrolled in the UK. The study is being sponsored by GlaxoSmithKline group of companies.
For information on recruitment contact Natalie James (natalie.James@uclh.nhs.uk).

26. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (PRO051)
Full Title: A phase II, double-blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy

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

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

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

29. GSK1223249 in MND/ALS (the Nogo-A study)

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

30. HYP HOP: DICHLORPHENAMIDE vs. PLACEBO FOR PERIODIC PARALYSIS
Full Title: Double-blind, placebo-controlled, parallel group, phase III study comparing dichlorphenamide vs. placebo for the treatment of periodic paralysis
Status: Completed
Sponsor: University Rochester
Funder: National Institutes of Health (NIH - USA)
PI: Prof Hanna
Patients recruited:14; target 40
This is a phase III trial into Periodic Paralysis. This proposal involves a multi-center, double-blind, placebo-controlled parallel group, nine-week studies comparing the effects of dichlorphenamide (DCP) vs. placebo in patients with period paralysis (Hyper, Hypokalemic periodic paralysis). The 9-week studies will investigate the prevention of attacks of weakness and it will be followed by 1-year extensions without placebo to compare the long term effects of DCP on the course of the diseases and on inter-attack weakness. Approximately 40 participants will be recruited from the United Kingdom.
Results in analysis

31. Pro053: Title: A Phase I/II, open-label, dose escalating with 48-week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of PRO053 in subjects with Duchenne muscular dystrophy
Status: Closed to Recruitment
Sponsor & Funder: Prosensa
PI: Prof F Muntoni, Prof Volker Straub
Patients Recruited: 1 (GOSH)
Recruitment target: 1-2

A Phase I/II, open-label study. The study consists of two phases; a single dose-escalation phase and a 48-week treatment phase. All subjects will have a screening period prior to their first dose of PRO053.
Efficacy, safety, pharmacokinetics (PK) and pharmacodynamic (PD) assessments will be conducted at regular intervals throughout the study.

Primary Objective is to assess the efficacy of PRO053 after 48 weeks treatment in ambulant subjects with Duchenne muscular dystrophy. Secondary objectives are to assess the safety and tolerability of PRO053 after single intravenous (IV) and subcutaneous (SC) doses and after 48 weeks of treatment in subjects with Duchenne muscular dystrophy; to investigate the pharmacokinetics PRO053 at different dose levels in subjects with Duchenne muscular dystrophy; to assess the pharmacodynamics of PRO053 at different dose levels in subjects with Duchenne muscular dystrophy; to assess efficacy trends of PRO053 in subjects with Duchenne Muscular Dystrophy not included in the primary analysis after 48 weeks of treatment.

32. Phase II, multicenter, randomized, adaptive, double-blind, placebo controlled Study to assess Safety and Efficacy of Olesoxime (TRO19622) in 3-25 year old Spinal Muscular Atrophy (SMA) patients
Status: Completed
Sponsor: TROPHOS

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

Natural History – Longitudinal Studies

Set-up Phase

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

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

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

35. Prospective. Longitudinal Study of the Natural History and functional status of patients with MyoTubular Myopathy (NatHis-MTM)
Status: set-up
Sponsor: Institute of Myology
PI: Prof Francesco Muntoni
Patients target: 6-8
Centronuclear myopathy (CNM) is an inherited neuromuscular disorder. It is a group of rare congenital myopathies characterized by the presence of hypotrophic myofibers with centrally placed nuclei on muscle biopsies. CNM exists in 3 forms: i) X-linked recessive (OMIM 310400), ii) autosomal dominant (OMIM 160150) and iii) autosomal recessive form (OMIM 255200). This study will be a multicentre international study in Europe and USA. Presently, there is no effective therapy to treat the muscle weakness in XLMTM patients. Current treatments include mainly respiratory, feeding and orthopedic management. These treatments improve muscular function, quality of life and longevity but do not directly target the disease mechanism. Primary objective of this study is to characterize the disease course in MTM patients using standardized evaluations. Secondary objectives are to identify prognostic variables of the disease; to identify the best outcome measure(s) for future treatment studies; to assess the immune response against AAV.

36. OPTIMISTIC
Observational Prolonged Trial in Myotonic Dystrophy type 1 to Improve Quality of Life Standards, a Target Identification Collaboration
Status: in set up
Funder: EU Seventh Framework Programme
Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust
PI: Dr Grainne Gorman
OPTIMISTIC is a two-arm, multi-centre, randomised controlled trial designed to compare a tailored behavioural change intervention against standard patient management regimes. It is expected that the trial and outcome work will lead to new clinical guidelines for DM1 management. The intervention comprises cognitive behavioural therapy (CBT) and graded physical activity, both of which aim to achieve a more active lifestyle. The effectiveness of this intervention, together with any adverse events associated with it, will be compared to standard patient management. Outcome measures will be measured at baseline, 5 months, 10 months (the end of the intervention period) and at 6-months post intervention (i.e. 16 months from baseline).

37. FSHD NH Study
A multicentre collaborative study on the clinical features, expression profiling, and quality of life of infantile onset facioscapulohumeral muscular dystrophy
This multicenter study will be conducted at participating US and International CINRG sites. Fifty individuals with infantile onset (diagnosed at <11 years of age) and genetically confirmed FSHD will be recruited for a cross-sectional study of pediatric FSHD. This will include children and youth (less than 18 years old) with FSHD who are currently followed in pediatric neuromuscular centers, as well as adults (18 years or older) with FSHD who are identified as having infantile onset of disease by chart review, clinical exam, and genetic confirmation. Our goal is to have close to

25 individuals with early infantile onset (<5 years) and 25 with late infantile onset (5 to 10 years) of FSHD in order to compare their clinical phenotypes and health-related outcomes.

Open Studies

38. FSHD registry
Status: Ongoing
The UK FSHD Patient Registry is a national registry for all people affected by facioscapulohumeral dystrophy living in England, Scotland, Wales and Northern Ireland. It is a patient driven online registry launched in May 2013. The main purpose of the registry is to facilitate and accelerate the recruitment into clinical research while also providing a resource to help plan and design clinical trials. In addition to collecting an internationally agreed dataset the registry is a platform for additional research questionnaires collecting information about pain, quality of life and scapular fixation. The registry is funded by the Muscular Dystrophy Campaign and supported by the TREAT-NMD Alliance.

39. CMT: A NATURAL HISTORY STUDY
Full Title: Charcot-Marie-Tooth Disease and related disorders: A Natural History Study
Status: Open to Recruitment
Sponsor: University College London Hospitals
Funder: National Institutes of Health (NIH – USA)
PI: Prof Reilly/Prof Muntoni
Patients recruited: 580; target (UK) 650
Charcot-Marie-Tooth Disease (CMT) and related disorders (distal hereditary motor neuropathy (dHMN) and hereditary sensory and autonomic neuropathy (HSAN)) are a clinically and genetically heterogenous group of disorders affecting approximately 1 in 2500 people.
People with this condition present with upper and lower limb weakness, wasting and sensory loss as a result of degeneration of the long peripheral nerves supplying the distal muscles. Despite the clinical similarities among patients with CMT the group is genetically heterogeneous. Advances have been made in identifying the genes that cause CMT and the molecular organisation of the peripheral nervous system (PNS) nevertheless the optimal management and treatment of the different variants of this disorder is not known and moreover natural history data is lacking for most forms of inherited neuropathies.
This is a 5 year study that will be conducted by four centres in United States and two centres in the UK (National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital). The aim of the project is to fully characterise the features of different types of CMT and the longitudinal progression of the disease. The data will also be used to establish clinical relevant endpoints for use in therapeutic trials. The identification and genetic characterisation of patients will facilitate the recruitment of participants for future therapeutic trials. Ultimately the information gained with this study will lead to the improvement in the treatment and management of CMT.
The study is also seeking to establish an appropriate paediatric impairment scoring method for CMT and establish a database for the inherited neuropathies. The study will include both adult and paediatric patients. Evaluations will consist of a neurological history and examination, nerve conduction velocity (NCV) study and in some selected cases skin biopsy.
This is a NIH funded study. At least fifty patients will be enrolled at the National Hospital for Neurology and Great Ormond Street Hospital.
For more information about the study please contact Dr. Matilde Laura at m.laura@ion.ucl.ac.uk.

40. Natural History study of Hereditary Sensory Neuropathy type 1 secondary to SPTLC1 and SPTLC2 mutations
Status: Open to Recruitment
Sponsor: University College London Hospitals
PI: Prof Reilly
Patients recruited: 32
Hereditary Sensory Neuropathy Type I secondary to SPTLC1 and 2 mutations is the commonest of the Hereditary Sensory Neuropathies. It is a slowly progressive neuropathy leading to profound loss of sensation especially pain and temperature sensation with variable but often severe motor involvement. Most patients have sensory complications such as recurrent ulcers; osteomyelitis and amputations are common. Over time, there is considerable disability requiring extensive carer support.

There is emerging evidence for the use of serine as a potential treatment option. This rapid progress has led to the possibility of a clinical therapeutic trial of serine in our UK HSN1 population.

A longitudinal study is now underway to determine the best way of measuring diseases progression in this condition which can be used in a clinical trial. We have a unique population within the United Kingdom where all the SPTCL1 patients (56) have a common mutation (C133W). Despite this, there is significant heterogeneity in the phenotype. A variety of assessment methods to cover the spectrum of deficits noted in this condition will be performed and repeated after a year. These include: CMT Neuropathy Score, comprehensive neurophysiological assessment, Quantitative Sensory Testing (DFNS protocol), muscle MRI studies of the thighs and calves, machine myometry, analysis of plasma DSB levels, upper thigh skin biopsy (epidermal nerve fibre density measurements) and patient questionnaires (SF36 and NPSI).

For more information contact: Dr Maiya Kugathasan, u.kugathasan@ucl.ac.uk

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

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

43. Kennedy's Disease – Study and Register
Status: Open
Sponsor: UCLH
PI: Prof Hanna
Patients recruited: 50

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

44. Investigation of Human Neurological Ion Channel Disorders
Status: ongoing
Sponsor: University College London Hospitals
PI: Prof Hanna
Ion channels are membrane bound proteins that allow the flux of charged ions across cell membrane in excitable tissue including muscle and nerve. These ion channels are usually specific for a particular ion e.g. potassium or calcium. An increasing number of inherited and acquired neurological diseases are attributed to disorders of ion channels. The 'channelopathies' include non-dystrophic myotonia, periodic paralysis, episodic ataxias types 1 and 2 (EA1 and EA2), familial hemiplegic migraine types 1 and 3 (FHM1 and 3) and some forms of epilepsy. The mechanisms by which ion channel dysfunction causes disease are incompletely understood, but the genetic channelopathies have provided unique insights into because the properties of mutant channels can be studied with great precision with biophysical methods.
Although each of the known channelopathies is rare, there is considerable circumstantial evidence that genetic variability in ion channels plays a major role in idiopathic epilepsy and migraine. These disorders, which are characterised by normal brain development and function punctuated by episodes of abnormal excitability, show strong heritability although typically do not respect Mendelian patterns of inheritance. They represent an important disease burden to society. It remains to be determined whether such disorders are caused by many, individually rare genetic variants or by a few common polymorphisms affecting ion channel splicing, assembly, trafficking or function. Several intense programmes of research are underway to identify genetic susceptibility factors in epilepsy and other paroxysmal neurological diseases. The purpose of this proposal however, is to take a complementary approach to gain an insight into the consequences of genetic variability, focusing primarily on KCNA1, mutations of which cause EA1(5) and CACNA1A mutations which cause EA2(6), and to document these at all levels from molecular biophysics to cellular excitability studied in individuals harbouring the mutations. Only by understanding the degree to which variability of ion channel properties can be tolerated by the organism, or conversely affect neuronal excitability in a detectable manner, will we be able to interpret the functional impact of coding polymorphisms that are staring to be reported in population studies.

This research project aims to consolidate and expand on previous work by collating clinical data and continuing to sequence candidate genes in patients suspected to have ion channel disorders, particularly in Episodic Ataxia Type 1 (KCNA1 gene) and Episodic Ataxia type 2 (CACNA1A gene). As the project progresses it is possible that further

candidate genes will be identified and we will sequence these also. In vitro expression of new mutations will be performed in order to further study how these genetic mutations result in channel dysfunction.

45. AFM Natural History Study
Full Title: Outcome measures in Duchenne Muscular Dystrophy: A Natural History Study
Status: Ongoing
Sponsor: UCL Institute of Child Health
Funder: AFM
PIs: Prof Francesco Muntoni, Prof Volker Straub
Patients recruited: 20 (GOSH) 18 (Newcastle)
Description: To document with quantified measurements the natural history of Duchenne Muscular Dystrophy. Several validated tools will be used to describe motor, orthopaedic and respiratory functions, quality of life and blood parameters along a 4 years follow-up study in ambulant and non-ambulant patients.

Primary objective is to document with quantified measurements the natural history of Duchenne Muscular Dystrophy. Several validated tools will be used to describe motor, orthopaedic and respiratory functions, quality of life and blood parameters along a 4 years follow-up study in ambulant and non-ambulant patients.
Secondary objectives are specific tests to ambulant and non-ambulant patients will be performed. All these tests should determine the most sensitive outcome measures to use in the assessment of efficacy of future therapies. This prospective longitudinal natural history study will be performed in two cohorts of patients with DMD according to their level of functional motor ability (ambulant/non-ambulant). Inclusion criteria and methods will be different in the two cohorts and will be described separately.

46. Using Next Generation Sequencing to Unravel the Pathogenesis of Sporadic Inclusion Body Myositis (IBM) – The International IBM Consortium Genetic Study
Status: Ongoing
Sponsor:
Funder: MRC
PI: Prof Hanna
Patients target: 400
The primary pathogenesis of IBM is not determined, although in IBM the aggregated proteins are in muscle tissue, many such as tau, alpha synuclein, TDP-43, beta amyloid and the prion protein are implicated in neurodegeneration. It is possible that the defective processes that lead to the formation of these abnormal protein deposits are likely to have important implications for many neurological disorders.
The vast majority of IBM is sporadic but there is significant evidence to suggest that genetic factors are important in IBM; these include the compact age at onset, insidious progression, clinical and pathological features, infrequent occurrence in twins, siblings and families. There have been several Mendelian genes identified in families with IBM phenotypes but these are rare. To investigate the pathogenesis of IBM further requires a genomic approach on large numbers of defined cases.
We will establish an international collaboration to collect IBM patient DNA and detailed clinical information to facilitate IBM research - The International IBM Consortium Genetic Study (IIBMCGS).
The number of IBM cases worldwide is not large enough for an effective genome wide association study (GWAS) but using next generation exome sequencing we can identify rare coding variants and high-risk genome wide variants in IBM. This technique has been used effectively in the identification of mutations that cause Mendelian disorders and more recently found significant rare coding variants in type I diabetes and autism.
In this proposal we wish to employ exome sequencing to analyse 200 IBM cases and 200 normal muscle controls. We expect to identify a number of IBM rare variants that cluster in disease associated genes. We plan to replicate these findings in a further 700 IBM and 2200 controls. These data will be made publicly available (anonymously) to allow comparison with other muscle disorders and neurodegenerative conditions.

47. Hereditary Inclusion Body Myopathy-Patient Monitoring Program (HIBM-PMP): A Registry and Prospective Natural History Study to Assess HIBM Disease
Status: Recruiting
Sponsor: Ultragenyx
Funder: Ultragenyx
PI: Prof Hanns Lochmuller
Patients recruited: 12
Target: 15-20
HIBM is a severe progressive myopathy that typically presents in early adulthood as weakness in the distal muscles of the lower extremities and progresses proximally, leading to a loss of muscle strength and function, and ultimately a wheelchair-bound state. The rate of progression is gradual and variable over the course of 10-20 years or longer. There is a need to better understand the disease-specific features of HIBM to heighten disease awareness; facilitate

early diagnosis; identify patients; expand knowledge of the clinical presentation, progression and variation of the disease; identify and validate biomarkers and other efficacy measures; inform on the design and interpretation of clinical studies of investigational products; and eventually to optimize patient management.

Up to 10 centers in North America, the European Union (EU), and the Middle East will participate in the HIBM prospective observational study (hereto referred to as the HIBM Natural History Study).
HIBM Disease Registry subjects may or may not be associated with a Study Site. Some disease registry subjects may enter only self-reported data and will not be associated with a clinical site. Other disease registry subjects who are in the same country as a natural history site may choose to have their data confirmed by one of those centers or opt-in to the HIBM Natural History Study.

The main objective of this program is to better understand HIBM.
The specific HIBM Disease Registry's objectives are to:
• Identify HIBM patients worldwide.
• Promote awareness and facilitate diagnosis of HIBM disease in the neuromuscular field.
• Obtain an assessment of the medical history, clinical presentation and progression of disease in HIBM patients and provide a connection for subjects to the broader HIBM community and associated programs.
• Provide customized information to subjects and their physicians that desire information on their disease status and progression.

The specific HIBM Natural History Study's objectives are to:
• Characterize HIBM disease presentation and progression over time using relevant clinical assessments of muscle strength and function.
• Obtain information to better characterize quality of life and understand the timing of significant life changing events in HIBM patients using patient-reported outcomes.

48. Full title: Prospective evaluation of gastrostomy in MND (PROGAS). Prospective evaluation of gastrostomy in MND (PROGAS).
Status: Ongoing
Sponsor: Royal Free London NHS Foundation Trust
Start date: 2011
Funder: Motor Neurone Disease Association / South Yorkshire CLRN
UCL PI: Dr Richard Orrell
Patients recruited: 6, target: open-ended
Difficulty in swallowing is a common problem in patients with MND. Patients with severe swallowing difficulty experience malnutrition, dehydration, choking and an increased risk of chest infections. Long-term nutritional support of patients with severe swallowing difficulty can be achieved by placing a feeding tube, known as a gastrostomy, directly into the stomach. However, the current practice of gastrostomy feeding is largely based on consensus and expert opinion rather than the outcomes of appropriately designed trials. Currently gastrostomy technique and timing of insertion within the disease course vary throughout the UK. There is a lack of evidence to suggest what the optimal timing for gastrostomy is, or which method is most appropriate. In addition, although gastrostomy is routinely performed, the benefits, such as improved survival and quality of life following gastrostomy, have not been proven. The main aim of this study is to develop evidence-based guidelines for gastrostomy use in patients with MND. Patients and carers will be recruited at the participating MND Centres around the UK. Questionnaires will be used to assess the safety, complications and benefits of the differing timings and methods of gastrostomy insertion. The results of this work will translate into the development of guidelines, which will optimise the benefit, and the patient and carer experience of gastrostomy. The principles will be readily applicable to patients with severe swallowing problems who are eligible for gastrostomy insertion due to other neurological diseases

49. THERAPEUTIC TRIAL OF diaphragmatic pacing IN MND/ALS (DiPALS)
Full title: A randomised controlled trial in patients with respiratory muscle weakness due to motor neurone disease of the NeuRx RA/4 Diaphragm Pacing System
Status: Ongoing
Sponsor: Royal Free London NHS Foundation Trust
Start date: March 2013
Funder: NIHR Health Technology Assessment Programme / Motor Neurone Disease Association / Department of Health subvention funding
UCL PI: Dr Richard Orrell
Patients target: 4 plus
Non Invasive Ventilation (NIV) therapy is the current standard treatment to help allow patients with MND/ALS to breathe. Patients wear a face mask over their nose or mouth or both and as they breathe in, the machine gives an extra push of air to support the patient's weak breathing muscles, enabling a bigger deeper breath. Some MND patients do not tolerate NIV due to the type of mask they have. During the day problems with using NIV include

issues like claustrophobia, feeding and communication. Eventually respiratory muscle weakness will progress to a point at which intermittent/overnight NIV is ineffective. Diaphragm pacing (DP) is a means of increasing the strength of the main breathing muscle. The NeuRx RA/4 Diaphragm Pacing System has been developed for patients who are unable to control their diaphragms because of stable high spinal cord injuries or because they have a neuromuscular disease such as MND. The pacing wires are inserted into the diaphragm muscle during a small operation and are connected to a small portable box that the patient can easily carry about. The proposed study will assess if treatment with DP prolongs life and maintains quality of life when given in addition to current standard care with NIV. 108 patients will be recruited to the study in up to 10 NHS hospitals in the UK. Patients will be randomised to either have NIV or receive DP in addition to NIV. Study participants will be required to complete outcome measures at 5 follow up time points (2, 3, 6, 9 and 12 months). Patients in the DP group will have additional visits for surgery and a 1 week post operative follow up. 12 patients (and their carers) from the DP group will also be asked to complete 2 qualitative interviews.

50. A Study of Biological Prognostic Factors for IGM Paraproteinemic Anti-Mag Associated Peripheral Neuropathy
Sponsor: UCL
Status: Open to recruitment
PI: Dr M. Lunn
Recruitment target: 45 patients
Anti-MAG neuropathies have a variable severity and some have a non-significant response to immunotherapies, but all have significant risks of potentially severe adverse effects from treatment. It seems important to find predictive factors in order to determine which patients have a high risk of evolution to severe disability so treatment would be targeted to appropriate patients. We suggest studying factors which could influence the disease evolution including molecules that regulate the monoclonal IgN secreting B-cells (BAFF, APRIL, inflammatory cytokines), molecules that may modulate the alteration of the blood-nerve barrier (inflammatory cytokines, VEGFs, angiopoietins).

This is a retrospective cohort study, including patients from the National Hospital for Neurology, London, UK, and from the University Hospital of Rennes, France.

The objective is to determine biological factors in blood and CSF that could be predictive of severity of neuropathies associated with IgM anti-MAG antibodies.

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

52. Identification of disease susceptibility genes associated with development and clinical characteristics of primary inflammatory muscle diseases, PM, DM and IBM

Status: Ongoing
Sponsor: University of Manchester
Funder: ARC
PI: Isenberg

PM, DM and IBM are a subset of inflammatory muscle disorders of unknown cause, currently classified under the umbrella term of idiopathic inflammatory myopathies (IIM). PM, DM and IBM are characterised by skeletal muscle inflammation and progressive muscle weakness, which can be debilitating and chronic in nature (occasionally fatal). Steroid and immuno-suppressive treatments are often only partially effective at reducing symptoms, and toxic side effects also limit their usefulness.
The cause of muscle inflammation in PM, DM and IBM is unknown. There is, however, increasing evidence that genetic factors, such as the polymorphisms around the complex HLA molecules, as well as certain inflammatory cytokines, are intimately involved in both the development and expression (in terms of disease severity and organs targeted for damage) of these conditions. Many of the inflammatory mechanisms responsible for the pathological changes of PM, DM and IBM are similar to those mediating damage in other inflammatory diseases, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), so it seems likely that genetic factors will similarly be involved in the development and expression of PM, DM and IBM.

Establishing the extent of involvement of these genetic mechanisms in PM, DM and IBM is of great importance, since understanding the aetiological mechanisms of any disease may eventually permit the development of specific and therefore more effective therapies.
Primary Objectives:
To identify and characterise the disease susceptibility genes associated with the development and clinical characteristics of the primary inflammatory muscle diseases, PM, DM and IBM.
Secondary:
To gain further insights into the aetiological mechanisms responsible for the development of the primary muscle diseases PM, DM and IBM and ultimately identify new therapeutic targets for treatment.

53. Full Title: Study of clinical and radiological changes in teenagers with Duchenne muscular dystrophy theoretically treatable with exon 53 skipping (Pre-U7)
Status: Open to Recruitment
Sponsor: Genethon
Funder: Genethon
PI: Prof Volker Straub/Prof Francesco Muntoni
Patients to recruit: 4-5

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

54. BIOMARKER STUDIES IN MND/ALS
Full title: Characterisation of a panel of disease biomarkers in peripheral blood from individuals with motor neuron disease
Sponsor: University College London Hospitals NHS Foundation Trust
Start date: May 2009
Funder: Motor Neurone Disease Association
UCL PI: Dr Richard Orrell

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

55. SMA registry
PI: Prof Lochmuller
Status: Ongoing
The UK SMA (Spinal Muscular Atrophy) registry is for all patients living the UK and Ireland who are affected by all types of Spinal Muscular Atrophy. The aim of the registry is to encourage genetically diagnosed SMA patients to register so that they may be considered for relevant clinical trials, receive the most up to date information regarding standards of care for their disease and help provide the research community with an understanding of disease prevalence. People with SMA, or the parents/guardians of children with SMA, can register themselves online. The UK SMA registry was set up in 2008 as a collaboration between TREAT-NMD and the Jennifer Trust for Spinal Muscular Atrophy, and is part of the TREAT-NMD Global SMA Registry. Since 2012, the registry is supported by the Jennifer Trust.

56. UK Myotonic Dystrophy patient registry
PI: Prof Lochmuller
Status: Ongoing
The UK Myotonic Dystrophy Patient Registry is an online patient driven resource launched in May 2012. The primary aim of the registry is to facilitate and accelerate the planning, design and recruitment of clinical research while also providing a snapshot of the myotonic dystrophy population in the UK. The registry collects an internationally agreed dataset with the majority of information provided by the patient themselves, additional clinical and genetic details are provided by their neuromuscular specialist. The registry is funded by the Myotonic Dystrophy Support Group and Muscular Dystrophy Campaign with support from the TREAT-NMD Alliance.

57. Global FKRP registry
PI: Prof Straub
Status: Ongoing
The Global FKRP Registry is an international registry for all persons affected by conditions caused by a mutation in the *Fukutin-Related Protein* (*FKRP*) gene, namely Limb Girdle Muscular Dystrophy type 2I (LGMD2I), and also the rarer conditions Congenital Muscular Dystrophy type 1C (MDC1C), Muscle Eye Brain Disease and Walker-Warburg Syndrome. The Registry aims to facilitate recruitment into clinical trials by identifying patients more readily, accelerate research, and provide more detailed knowledge about the natural history and prevalence of FKRP-related muscular dystrophies, whilst keeping patients informed. The Registry was set-up in 2011 as an online patient driven registry and is currently supported by the LGMD2I Research Fund.

58. GNE myopathy-Disease Monitoring Programme (GNE-DMP): A registry and prospective observational natural history study to assess HIBM disease
PI: Prof Straub
Status: Ongoing
The Disease Monitoring Program is a public-private partnership between Ultragenyx Pharmaceutical Inc. (USA) and Newcastle University (UK). The program was designed to collect data on clinical presentation and progression of GNE myopathy to improve knowledge and support treatment development. The unique structure of the program allows a combination of longitudinal data collected through an online global patient registry and a hospital based natural history study in a single platform. The Natural History study is performed by selected centres in Europe, Middle East and North America. Anonymous data gathered through the registry will be accessible to the medical and research community, patients, families and patient organisations upon approval from the Steering Committee and Ethical Committee in the hope that this information will provide insight into the disease, and help drive clinical trials and research that could lead to better treatment strategies.

59. SMA REACH UK
Spinal Muscular Atrophy Research and Clinical Hub UK
Status: Open to recruitment
Funder: UK SMA charity: SMA TRUST
Sponsor: Great Ormond Street Hospital
Chief Investigator: Prof Francesco Muntoni
Newcastle PI: Prof Katie Bushby
Target: ~70
The primary aim of this project is to establish the first national clinical and research network named SMA REACH UK (SMA Research And Clinical Hub UK) to establish a national agreement on clinical and physiotherapy assessment and standards of care. We propose designing, piloting and expanding an electronic database created to streamline

the collection of data for patients with SMA. This UK SMA database would be a unique infrastructure started at GOSH and Newcastle which would soon be built up and accessible to specialist centres across the UK who treat patients with SMA.

Closed Studies

60. NON-DYSTROPHIC MYOTONIAS: GENOTYPE AND PHENOTYPE CORRELATION AND LONGITUDINAL STUDIES
Status: Closed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof Hanna
Patients recruited: 20
This multi-centre project involves a prospective, cross-sectional and longitudinal natural history in non-dystrophic myotonias (NDM).
The aim is to collect standardized data from NDM patients, to include clinical symptoms, exam findings, as well as the results of strength, functional, and electrophysiological testing. Genetic testing will permit precise identification of individual NDM subtype. This information will allow for the identification and implementation of appropriate endpoints in studies of potential treatments.
This is a NIH funded study. Twenty patients were enrolled at the National Hospital for Neurology and Neurosurgery.
Brain 2013 Jul; 136 (Pt 7):2189-200. DOI: 10.1093/brain/awt133. Epub 2013 Jun PMID: 23771340 [PubMed - in process]

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

62. EPISODIC ATAXIA SYNDROME: GENOTYPE-PHENOTYPE CORRELATION AND LONGITUDINAL STUDY
Status: Closed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof Hanna
Patients recruited: 36 target >20
Episodic Ataxia Syndrome is a rare, genetic disease that causes recurrent
episodes of dizziness and incoordination.
The majority of cases are likely caused by an inherent genetic mutation. However in some patients the mutation is unidentifiable. The purpose of this study is to collect prospective standardized data from subjects to better define the clinical phenotype of the EAs and to establish clinically relevant endpoints for use in therapeutic trials.
The study will also:
- Fully characterize the clinical spectra and the natural history of genetically defined EA.
- Systematically investigate phenotypic differences between EA subjects harboring KCNA1/CACNA1A mutations and those that do not.
This proposal involves a multi-center cross-sectional data collection analysis as well as a prospective longitudinal study. Since EA is a chronic disease whose course is measured in years rather than months, the subjects will be followed longitudinally at a yearly interval for a period of two years. *In press with Brain*

63. OUTCOME MEASURES IN SMA TYPE II AND III
Status: Complete

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

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

65. Jain Foundation natural history and clinical outcomes study of dysferlinopathy (limb-girdle muscular dystrophy type 2B)
Status: closed to recruitment
Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: Jain Foundation
PI: Prof Katie Bushby
Recruitment: 37 (Newcastle)

Target: 20
A clinical outcome study for Dysferlinopathy. To define the natural history of dysferlinopathy in a large unselected patient group with respect to age and nature of onset, progression and presence of complications via existing and expanded registries and databases. Study a selection of possible outcome measures for dysferlinopathy trials over a three year period in a multicentre evaluation of 150 patients based in centres of excellence for muscular dystrophy diagnosis and management. Extend the existing registry activities co-ordinated by the Jain Foundation to ensure a comprehensive

Exercise Studies

Open Trials

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

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

68. PHYSICAL ACTIVITY AND INCLUSION BODY MYOSITIS
Status: Recruiting
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
PI: Dr M Trenell
Collaborating site MRC Centre London
Recruitment: 500 recruits expected, across 5 disease sites

The aim of this study is to collect data on day to day physical activity levels and metabolic control in individuals with chronic disease.

DESIGN:
Participants will be identified from chronic disease clinics by the following lead clinicians: Stroke-Prof Gary Ford, Neuromuscular disorders-Prof Kate Bushby, Metabolic disorders-Prof Roy Taylor, fatigue-Prof Julia Newton and Ageing-

Prof Julia Newton. An equal sample of male and female participants will be used in the study which will be up to 100 patients in each disease group.

METHODOLOGY:
Step 1: Relevant practitioners will highlight possible candidates for the study.
Step 2: Visit 1: At the start of the study participants will either be asked to attend Newcastle University's Campus for Ageing and Vitality (Newcastle General Hospital), or if they are an inpatient will be visited on the ward. Participants will be provided with an information sheet about the study. They will be given the opportunity to talk with the team and ask questions. Once fully informed, participants will provide signed informed consent.

Participants will be asked to fill in a disease screening questionnaire at the start of the process. The height and weight of the participants will be recorded and this information will be entered into the physical activity monitors. Instructions will be provided as to how to use the monitors. A resting blood sample may also be taken at this point. This will be analysed for glucose, insulin, lipid profile and liver function.

Step 3: Participants will wear the arm monitors for five days including one weekend day. Step 4: Visit 2: At the end of the five day period participants will attend the research centre again or attend a pre-arranged session either at their home work place or on the ward to return the activity monitor. Here they will complete a brief physical activity questionnaire and two brief fatigue questionnaires. Data from the physical activity monitor will be fed into a computer. Each participant will be provided with a printout of their weekly activity levels and given the opportunity to discuss their results.

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

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

Closed Trials

70. STRENGTHENING HIP MUSCLES TO IMPROVE WALKING DISTANCE IN PEOPLE WITH CHARCOT- MARIE-TOOTH DISEASE
Status: Completed
Sponsor: University College London Hospitals
Funder: Muscular Dystrophy Campaign (MDC)
PI: Prof Reilly
Patients recruited: 32 target: 32
Charcot-Marie-Tooth (CMT) disease is a form of hereditary peripheral neuropathy.
People with CMT present with weakness, wasting and sensory loss as a result of degeneration of the long peripheral nerves supplying the distal muscles.
The aim of this study will be to investigate the efficacy of a 16 week home based programme of training to increase hip flexor muscle strength and walking endurance. Additional measures of gait speed, exertion, fatigue, disability and general activity will also be recorded. Baseline impairment measures will be obtained to ascertain predictors of strength gains.
This study will use a single blinded, randomised cross over design to investigate if training the hip flexor muscles will strengthen the hip flexor muscle and improve walking endurance in people with all types of CMT.
The trial will include people aged between 18 and 70 years, who have been diagnosed with CMT on the basis of genetic tests (where possible), family history and neurophysiology testing. Each subject will be involved with the study for a 40 week period.
Results published Journal of the Peripheral Nervous System, 2011; 16(S3):S115

71. EXERCISE TRAINING IN PATIENTS WITH MITOCHONDRIAL DISEASE: ASSESSING THE BENEFITS
Status: Closed
Sponsor: University Newcastle
Funder: Muscular Dystrophy Campaign (MDC)
PI: Prof Turnbull
Collaboration site MRC Centre London (Hanna)
Patients recruited: 6- 5 Newcastle; 1 London
Mitochondrial myopathies are a very important group of muscle diseases associated with weakness, pain and fatigue. At present, treatment options are very limited.
Exercise therapy has been found to have some benefit in this group of patients and we wish to explore this further in terms of both strength and endurance.
The aim of this study is to demonstrate that strength exercise training is an effective approach to therapy in certain patients with mitochondrial myopathy, specifically those with sporadic mutations in mitochondrial DNA. Based on our previous research studies, we believe that such training will improve muscle strength, mitochondrial function, exercise tolerance and overall quality of life.
The main objectives are:
To confirm that endurance training in patients with mitochondrial abnormalities improves quality of life, exercise tolerance and oxidative capacity.
To determine the ability of resistance muscle strength training to improve skeletal muscle strength and oxidative capacity by incorporation of satellite cells into mature myofibres.
Participants are expected to commit to an exercise training and testing over a period of 4 to 8 months.
The study will include patients between the ages of 18 and 65 years who have had a previous muscle biopsy showing a defect in skeletal muscle mitochondrial DNA that is either in the form of a sporadic point mutation or single large-scale deletion. Patients who have this type of mutation and do not have any family members that are affected and have no major cardiac involvement, hypertension, pulmonary or peripheral vascular disease that may complicate findings.

72. CARDIAC ADAPTATIONS TO EXERCISE IN MITOCHONDRIAL DISEASE
Status: Closed
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
PI: Prof D M Turnbull/Dr MI Trenell,
Patients recruited: 39

Twenty four people with mitochondrial disease will take part in the study. Participants will undergo cardiac, cognitive and movement examination and then they will be randomised into two groups. They will receive either; exercise counselling

and support (n = 12) or continue standard care (n = 12) over a 16 week period. At the end of the 16 week period baseline measures will be repeated. Participants to be studied will have biopsy proven mitochondrial disease (age 18−60 years; BMI 20−35 kg/m2; and do not take part in regular exercise). Subjects with heart disease that would produce an adverse response to exercise will be excluded. Subjects with significant kidney disease or in vivo ferrous material will be excluded also as these are contra-indications to the use of gadolinium-based contrast agents and magnetic resonance imaging respectively. Magnetic resonance and echocardiographic evaluation of cardiac function as well as movement and cognitive function will be assessed at baseline and at 16 weeks. A progressive exercise test will be undertaken at baseline to establish maximal aerobic capacity and evaluate for an adverse response to exercise.

The patient exercise group will be matched with a control group of individuals without known mitochondrial disease who will undergo the same evaluation and training regime (n = 12)..

In total, the study will require each participant to attend the research facility for three visits for metabolic examination. The exercise groups will be requested to attend 48 exercise sessions over 16 weeks.

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

Imaging Studies

Set-up Phase

73. A study of Qualitative Magnetic Resonance Imaging in Channelopathies
Status: Set-up
Sponsor: UCL
PI: Prof M Hanna
The skeletal muscle channelopathies are a heterogenous group of diseases caused by mutations in voltage-gated skeletal muscle ion channels. Broadly speaking, they can be divided into the non-dystrophic myotonias (NDM) and the periodic paralyses (PP).

The objective of this retrospective study is to define the presence, frequency and pattern of MRI abnormalities in the lower limbs of patients with genetically proven PP compared with healthy volunteers. Furthermore, we will describe differences in MRI abnormalities in the subsets of PP.
It will involve approximately 40 patients with genetically confirmed periodic paralysis. To allow blinded analysis, in addition to the MRI scans available from 12 healthy volunteers involved in a previous research study, 12 healthy volunteers will undergo standard clinical lower limb MRI.

For more information about the study please contact Dr Matthew Evans at matthew.evans@ucl.ac.uk

Open Trials

74. Full Title: Evaluation and Optimisation of Muscle Imaging Biomarkers in Support of Non-ambulant Duchenne Muscular Dystrophy Studies
Status: Open to recruitment
Sponsor: UCL Institute of Child Health
Funder: GSK
PI: Prof Francesco Muntoni
Patient target: 15 (UK) Recruited 15 patients, 10 controls
The primary objective of this study is to characterise the differential involvement of muscle groups occurring with disease progression (i.e. as a function of age) using skeletal muscle MRI so as to more precisely define which muscle groups could provide the best markers for therapeutic response in the non-ambulant boys.
The secondary objectives of this study are to

- Measure quantitative imaging changes in DMD muscle over the course of one year using skeletal muscle and dynamic breathing MRI.
- Measure quantitative imaging changes in diaphragm movement occurring with disease progression (i.e. as a function of age) using dynamic diaphragmMRI.
  For more information about the study please contact Dr Valeria Ricotti at v.ricotti@ucl.ac.uk.

75. Magnetic Resonance Imaging Characteristics of Inflammatory Neuropathies – a pilot study

Status: Open to recruitment
Sponsor: University College London Hospitals
PI: Dr Lunn
Patients recruited: 20: 10 patient; 10 controls

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

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

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

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

There is no published research documenting the use of novel MRI techniques in patients with CIDP. Diffusion sequences and assessment of the magnetisation transfer ratio (MTR) of nerves may reveal diagnostic characteristics in diseased tissue, as is seen in the brain. **Aims:**

We aim to clarify the use of MRI for the diagnosis of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMNCB). Using 3T MRI, we will use both conventional and novel quantitative MRI sequences to examine the nerve roots, plexuses, sciatic nerves and forearm nerves of 10 patients each with CIDP, MMNCB and 20 healthy volunteers. We will quantify nerve root cross sectional area in cervical and lumbar regions in patients with CIDP, MMN and healthy controls. We will explore imaging characteristics of the sciatic nerve in patients with CIDP versus healthy controls. We will define imaging characteristics at sites of conduction block in nerves of patients with MMNCB. In a separate group of patients with suspected inflammatory neuropathy we will compare MRI to pathological findings on nerve biopsy. MRI may be shown to be a useful non-invasive diagnostic tool.

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

76. MRI in IBM and CMT
Full Title: A Study of Quantitative Magnetic Resonance Imaging and the Clinical Features of Inclusion Body Myositis and Charcot Marie Tooth Disease
Status: Ongoing
Sponsor: University College London Hospitals
Funder: MRC
PI: Prof T Yousry/Dr J Thornton / Prof M Hanna / Prof M Reilly
Patients recruited: 72: 40 patients; 32 controls

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

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

then be followed-up at 6 month intervals for 5 years in a longitudinal natural history study of IBM and CMT that focuses on the MR methods and clinical findings that were shown to be most illuminating.
Changes over time in the MRI parameters in the diseased groups and Healthy volunteers will be compared.
Objectives:
To detect, using quantitative magnetic resonance imaging (qMRI), the changes in the nerves and muscles of patients with inclusion body myositis or Charcot Marie Tooth disease, and to relate these changes to the measurable clinical and neurophysiological features in these diseases. This will allow the value of various qMRI techniques as markers of disease activity and progression to be tested.
Secondary objectives of the study include:
The development of novel quantitative MR techniques for targeted assessment of the human neuromuscular system. To more fully characterise both the magnetic resonance imaging and clinical features of inclusion body myositis or Charcot Marie Tooth disease as compared with healthy individuals and to study the progression of these characteristics with time over a period of 5 years.
For more information about the study please contact Dr Jasper Morrow at j.morrow@ucl.ac.uk.
Submitted to European Radiology

77. Magnetic Resonance Imaging as an outcome measure in Motor Neuropathies: a pilot study
Sponsor: UCL
PI: Prof Hanna
The development of novel therapies for motor neuropathies necessitates the search for a reproducible outcome measure which can sensitively monitor disease progression. Muscle magnetic resonance imaging (MRI) is an excellent candidate due to its reproducibility and observer independence. We plan to investigate various parameters obtained through muscular MRI as longitudinal biomarkers in diseases of the motor neuron with different speeds of disease progression: amyotrophic lateral sclerosis (ALS), Kennedy's disease (KD) and distal hereditary motor neuropathy (dHMN). Using 3T MRI the research team will perform lower limb imaging with quantitative 3-point Dixon, magnetisation transfer and IDEAL-CPMG sequences in addition to standard qualitative T1 and STIR sequences in 12 patients each with ALS, KD and dHMN as well as 12 healthy volunteers. Detailed clinical data will be collected, including isokinetic and isometric lower limb strength. These assessments will be repeated at a 3 and 12 month interval in ALS patients and at a 6 and 12 month interval in dHMN and KD patients. We will analyse the value of quantitative MRI as an outcome measure in these conditions by analysing both correlation with clinical measures and sensitivity to change over time. Data from this study will be able to be used to establish sample size in clinical trials to evaluate novel therapeutic strategies in these diseases.
MRI has been widely applied to neurological diseases of the central nervous system, but to a much lesser extent diseases of the peripheral nervous system (PNS), and even less frequently to the diseases in this study.
The hypothesis is that MRI can detect changes in the muscles in patients with ALS, KD and dHMN.
The proposed project will take place in two phases, an initial cross-sectional case control study of all patients and volunteers followed by a longitudinal natural history study.
MRI imaging will be performed of thigh and calf muscles at 3 Tesla in a scanning session lasting approximately an hour. All participants will undergo standard MRI imaging with T1-weighted and STIR sequences. The following quantitative MRI techniques will be used: magnetization transfer imaging, T2 relaxometry with IDEAL-CPMG and 3-point Dixon fat quantification. We will not be using gadolinium contrast in this pilot study.
For further information contact Dr Jasper Morrow, j.morrow@ucl.ac.uk

Closed Studies

78. MRI IN FKRP-RELATED LGMD2I
Full-Title: A study using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) in Patients with Limb Girdle Muscular Dystrophy 2I; an assessment of muscle damage
Status: Closed
Sponsor: Newcastle NHS Trust
Funder: MRC
PI: Prof V Straub
Re-defined in 1995, the LGMDs are face-sparing, proximally predominant, progressive muscular dystrophies with elevated creatine kinase levels and dystrophic features on muscle biopsy. In the current classification system, LGMDs are divided into autosomal dominant (LGMD1) and autosomal recessive (LGMD2) disorders with a superimposed lettering system denoting the chronological order of the chromosomal linkage.
Limb Girdle Muscular Dystrophy 2I (LGMD2I) is caused by a mutation in the fukutin related protein gene (FKRP)1 and manifests temporal variability. Clinically the age of onset, rate of progression and severity varies greatly between cases and even within the same family. They range from asymptomatic patients with mildly raised creatine

kinase levels to those severely affected and non ambulant. The respiratory and cardiac complications, well known to occur in this type of muscular dystrophy, in 30% and 60% of patients respectively, occur independently of the general muscle weakness and also cardiac complications occur independently from respiratory compromise. Magnetic Resonance imaging (MRI) has been increasingly used in imaging in patients with neuromuscular disorders over the past 5 years.
Studies have shown that whilst there is considerable overlap in muscle involvement there is also striking differences that can be of diagnostic value. In both patients with LGMD2A and LGMD2I there is a prominent pattern of involvement of the posterior thigh muscles, however in LGMD2A there is also selective involvement of the medial gastrocnemius and soleus muscles in the lower leg, which was not seen in LGMD2I. Although it is clearly demonstrated that MRI findings mirror those obtained from clinical examination, it has been reported recently that in fact MRI abnormalities can be detected in patients with neuromuscular disorders when clinical examination of particular muscle groups have been normal. MRI can therefore be useful to show early manifestations of a disease and to monitor the effect of early therapeutic interventions.
Beside MRI another non-invasive technique to consider is phosphorus magnetic resonance spectroscopy (P-MRS). P-MRS studies have demonstrated several metabolic abnormalities in the skeletal muscle of patients with Duchenne Muscular Dystrophy (DMD)/ Becker Muscular Dystrophy (BMD) and in the group of autosomal recessive LGMDs, associated with sarcoglycan deficiency (LGMD2C-F) . These changes are thought to be specific for dystrophies secondary to deficits in the dystrophin-glycoprotein complex. In these patients there appears to be an increased cytosolic pH in both groups, however there is also abnormal concentrations of phosphorylated compounds (in particular, decreased phosphocreatine and increased inorganic phosphate concentrations).
The study overall aim is to develop and evaluate non-invasive techniques to quantify muscle pathology and the rate of change over time in LGMD2I, which is potentially a useful tool for monitoring response to treatment and therapies. This shall be achieved by measuring static MRI over a 2 year period and comparing this to age matched adult controls including the quantitative 3-point Dixon technique for measuring fat. At the same time we will also be measuring the Pi and cytosolic pH, ATP and ADP via MRS to see whether a specific pattern of metabolic abnormality is detected in these patients.
For further information about the study please contact Dr. Jasper Morrow at j.morrow@ucl.ac.u.k.
LGMD2I Longitudinal paper accepted by PLOS ONE

79. A Study of Quantitative Magnetic Resonance Imaging to Monitor Disease Activity in Hypokalaemic Periodic Paralysis.
Status: Completed
Sponsor: UCL
Funder: MRC
PI: Prof Hanna
Recruitment: 24: 12 patients; 12 controls
The commonest muscle channelopathy is hypokalaemic periodic paralysis caused by mutations in the voltage sensor regions of either the muscle sodium channel SCN4A or the muscle calcium channel CACN1AS. From childhood, patients experience disabling episodes of complete muscle paralysis lasting hours to days. In the early years patients recover in between attacks but over time they develop a permanent fixed muscle weakness (myopathy) and often become wheelchair bound. Although there are established treatment strategies which we and other centres in USA and Europe employ and which can reduce attack frequency, we do not have sensitive methods to monitor disease activity or to determine if the treatment regime is fully effective.
Recent data indicate that muscle water content may be a key determinant of muscle function in patients with higher abnormal water content (oedema) correlating with more weakness. Preliminary published data indicates patients with less oedema may have a better prognosis. Furthermore, we currently make decisions to adjust standard treatments based on attack frequency only and this may not be the most reliable way to monitor actual disease activity in affected muscles. In this study we wish to evaluate abnormal muscle water content using MRI applied in the context of the normal current clinical practice and management in this patient group.
In this study we aim to show that patients with hypokalaemic periodic paralysis have abnormal muscle water on MRI which is inversely correlated with muscle strength and sensitive to changes over time. In a wider context than this study, similar techniques may be applied to other muscle diseases, where MRI could guide treatment in clinical practice and act as an outcome measure in clinical trials.
This study has two phases. The first phase is a period of MRI technique refinement in up to 10 healthy volunteers lasting up to two months. The main study phase is a longitudinal case control study and will study a minimum of twelve patients with hypokalaemic periodic paralysis and twelve healthy volunteers who will act as a comparison group for the patients. Assessments will be repeated at a four week interval to see if any changes in clinical

parameters are reflected in changes on MRI parameters. One of the inclusion criteria for patient enrolment will be evidence of active disease in order to maximise differences between the two time points.
For further information contact Dr Jasper Morrow: j.morrow@ucl.ac.uk
Data in analysis

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RCP CPD reference: 87837