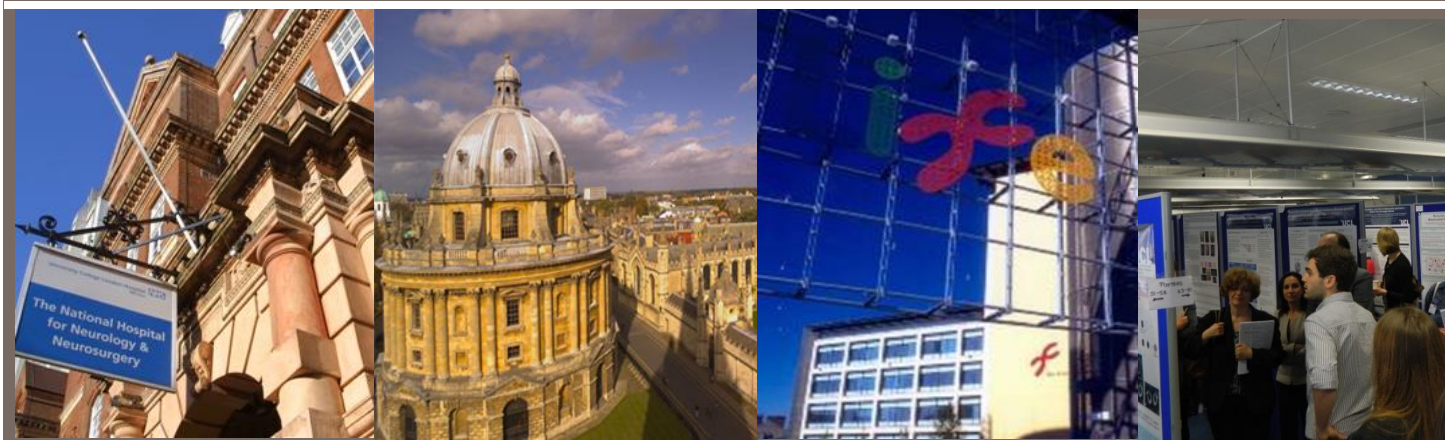
Muscular Dystrophy UK
Fighting muscle-wasting conditions

MRC Centre for Neuromuscular Diseases

Ninth UK Neuromuscular Translational Research Conference

22nd – 23rd March 2016



Medical Sciences Teaching Centre
Oxford
Oxford, OX1 3PL


MRC
Centre for
Neuromuscular Diseases


Muscular
Dystrophy UK
Fighting muscle-wasting conditions


Newcastle
University


UCL


wellcome trust centre for
Mitochondrial Research


NHS
National Institute for
Health Research


NUFFIELD DEPARTMENT OF
CLINICAL NEUROSCIENCES


MRC
Functional
Genomics
Unit


Cav
Centre for Ageing
and Vitality
at Newcastle University


MRC
Mitochondrial
Biology Unit

Table of Contents

Welcome to the UK Neuromuscular Translational Research Conference, Oxford 2016

Dear Colleagues,

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

Major translational themes this year include a wide ranging session on genomic therapies, an in-depth review of next generation biomarkers and a session tackling the difficult issue of defining and how to deal with big data.

We are delighted to welcome Professor David Beeson from the University of Oxford to deliver the third John Newsom-Davis lecture. Professor Beeson's renowned work on inherited neuromuscular junction disorders makes him the ideal person to deliver this lecture.

After our inaugural and very successful patient day at our conference in Newcastle last year, we are running another patient day this year the day before the conference itself.

The mission of the MRC Centre is to translate science into new experimental medicine trials and find treatments for children and adults with serious muscle wasting diseases. Collaborative working and interdisciplinarity represent a fundamental platform for successful translation. The MRC Centre works to bring together clinicians, scientists, patient organisations and patients in order to advance the UK translational research effort. This is a particularly exciting time in the field as 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 (renewed 2013-2018) 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 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 Newcastle University and was renewed for a further five years in 2013. The Centre continues to be closely linked to its partner NHS organisations, University College London Hospitals NHS Foundation Trust, Great Ormond Street Hospital for Children NHS 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 continue to build on in this current 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 125 high quality abstracts, and there will be platform presentations and dedicated poster sessions each day as well as guided poster discussions. This year will be the second time we add a poster flash session where abstracts are selected to be presented in 5 minute slots using only three slides. We hope this will prove a popular session. There will be five £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.

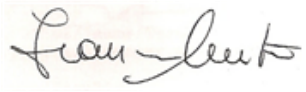
As the Centre Director, I would very much like to thank Professor Mary M. Reilly who has led the joint MRC-Muscular Dystrophy UK meeting scientific planning team: Professors Kate Bushby, Doug Turnbull, Francesco Muntoni, Professor Dame Kay E Davies, Professor Kevin Talbot and Dr Marita Pohlschmidt. I also sincerely thank Christine Oldfield and Dr Marita Pohlschmidt for their very hard work in organising 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 Oxford.

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

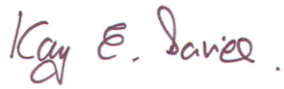
Professor Mary M. Reilly
Co-Director
MRC Centre for Neuromuscular Diseases
UCL Institute of Neurology



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
Newcastle University

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



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

Dr Marita Pohlschmidt
Director of Research,
Muscular Dystrophy UK

Professor Kevin Talbot
Head of the Division of Clinical Neurology
University of Oxford

Welcome to the Conference

Robert Meadowcroft, Chief Executive of Muscular Dystrophy UK

I am delighted to welcome you to Oxford and the 2016 UK Neuromuscular Translational Research Conference. We have expert speakers, interesting research posters and a great opportunity to develop and share ideas and I trust you enjoy your time here.

Muscular Dystrophy UK has supported this important conference since its inception and we welcome and encourage the opportunity it presents to bring scientists and clinical researchers together each year.

As a funder of research, we have invested more than £55million in backing cutting-edge research into neuromuscular conditions. We also make a major investment each year in improving specialist NHS care in the UK as well providing information, advice and support for families. We are planning to increase our support in the coming years of high-quality science and translational research here in the UK and through international partnerships to address a number of the rarer conditions such as nemaline myopathy and the Collagen VI disorders.

We share the concern of many families and supporters that every day counts in the race to develop effective treatments particularly for the more aggressive conditions that affect children. For many adults with a muscle-wasting condition, there is a similar focus on research and also an understanding that expert clinical care, retaining independence and enjoying the best possible quality of life are all important goals.

We are encouraged by the significant progress being made towards ensuring effective treatments although there are many questions that remain unanswered. We need to develop and refine the use of MRI and also develop additional outcome measures. The heterogeneity of many conditions underlines the need for better characterisation and an improved understanding of the natural history.

Nevertheless, we are very encouraged by the increase, year on year, in the number of clinical trials underway in the UK and indeed across the world. This led to the recognition that clinical trial capacity in the UK should be extended and Muscular Dystrophy UK is a major contributor to the 'Newcastle Plan' to ensure the UK does not turn away future trials in Duchenne muscular dystrophy and other neuromuscular conditions.

I must thank the scientists, the clinical researchers and clinicians joining us at Oxford for their outstanding efforts on behalf of patients and families. Across the world, there is a fight underway to beat muscle-wasting conditions and we can see much progress being made. I have to confess we are impatient and keen to accelerate the pace of progress towards effective treatments and cures.

I do hope you have an enjoyable and productive time here in Oxford and I give you my best wishes for your continuing endeavours.

Yours

Robert Meadowcroft
Chief Executive, Muscular Dystrophy UK

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 Newcastle University. The Centre is building on long-established UCL-Newcastle research and clinical links. The Centre has formed 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 £110m 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 Newcastle University. 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. 9100 patients entered into to our stratified cohorts.

- We are facilitating clinical trials in neuromuscular diseases 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.

- 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 2642 human cell lines that have been invaluable for translational research including preclinical therapy evaluation including using IPS cells.

- 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 fifteen PhD students have already graduated from this programme. A cadre of twenty-seven new students has been appointed since 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 continues to promote translational research and add value to basic science neuromuscular research themes currently active in London, Newcastle and other centres.

Looking to the future we aim to have embedded a trial-ready culture into routine neuromuscular UK practice by 2018. We plan that every patient attending one of our core or linked centres will have the opportunity to enrol in a natural history study or clinical trial as a matter of routine. We will have developed sensitive, validated and responsive outcome measures for our five core diseases and expanded our national registries to include all interested UK neuromuscular centres. The next challenge will be to systematically and rationally deliver the trials needed to test the increasing number of potential therapies. To do this we are planning to develop an Experimental Therapeutic Centre in Neuromuscular Diseases which will be the natural and necessary next step to ultimately deliver successful therapies to our patients.

About Muscular Dystrophy UK

Muscular Dystrophy UK is the charity bringing individuals, families and professionals together to beat muscle-wasting conditions. We are combining skills, knowledge and resources in the UK and working with others around the world so we can improve the quality of life for people affected, and bring treatments and cures closer to reality.

Since the charity was founded in 1959, we have invested more than £55m in high quality research into the underlying molecular basis of muscle-wasting conditions. This investment has achieved positive results hence the focus of our research funding has started to shift towards the development of treatments – the bench-to-bedside transfer of promising technology. Indeed, we are delighted to have laid the foundations for the first potential treatments for Duchenne and Becker muscular dystrophy, which are now in clinical trials.

Muscular Dystrophy UK aims to accelerate the transition of promising technology into the clinic by providing support to both scientists and clinicians. We fund basic science through to pre-clinical research and, where possible, to clinical trials. We also provide logistic and financial support to create platforms where clinicians and scientists can meet, exchange experiences and discuss ideas. This event, the Ninth UK Neuromuscular Translational Research Conference here in Oxford is one such platform.

We are also very keen to encourage early participation for UK patients in clinical trials. To ensure this, we continue to invest in the clinical trial infrastructure. We currently fund key posts of clinical trial co-ordinators and the national neuromuscular database to ensure vital patient data are available to clinicians and researchers.

With possible treatments for some conditions at last on the horizon, it is crucial that access to new drugs licensed for use in patients with neuromuscular conditions is as swift as possible. Muscular Dystrophy UK are leading the drive for fast access to emerging treatments for UK families.

Patient Organisations

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

UK Neuromuscular Translational Research Conference 2016
Medical Sciences Teaching Centre, Oxford, OX1 3PL

Tuesday 22 and Wednesday 23 March 2016

PROGRAMME

Day 1 – Tuesday 22nd March

08:45 – 09:15 **Registration and Coffee**

09:15 – 09:30 **Introduction**
Prof. Michael Hanna
UCL Institute of Neurology

09:30–11:00 **Session 1: Genomic Therapies**
Chairs: Prof. Francesco Muntoni and Prof. Dame Kay Davies

09:30 – 10:00 **Alternate translational initiation of dystrophin: clinical and therapeutic implications**
Prof. Kevin Flanigan, Nationwide Children's Hospital, Ohio
(abstract S01)

10:00 – 10:30 **From pathogenesis to therapy in spinal muscular atrophy**
Prof. Francesco Muntoni, UCL Institute of Child Health
(abstract S02)

10:30 – 11:00 **Antisense targeting of 3'end elements involved in DUX4 mRNA processing is an efficient therapeutic strategy for Facioscapulohumeral Dystrophy: a new gene silencing approach**
Dr. Julie Dumonceaux, Institut de Myologie, Paris
(abstract S03)

11:00 – 11:30 **Coffee**

11:30 – 11:45 Platform presentation 1 (merged)
Results of North Star Ambulatory Assessments in the Phase 3 Ataluren Confirmatory Trial in Patients with

Nonsense Mutation Duchenne Muscular Dystrophy (ACT DMD)
Prof. Francesco Muntoni, UCL Institute of Child Health
ACT DMD: Effect of Ataluren on Timed Function Tests in Nonsense Mutation Duchenne Muscular Dystrophy
Prof. Nathalie Goemans, University Hospitals Leuven, Belgium

(abstract P03 and P04)

11:45 – 12:00 Platform presentation 2
Cell therapy for muscular dystrophy: lessons learned and a road to efficacy
Prof. Giulio Cossu, University of Manchester
(abstract P02)

12:00 – 12:15 Platform presentation 3
Charcot-Marie-Tooth and Centronuclear myopathy induced mechanistic impairment in endocytosis
Tayyibah Ali, Imperial College London
(abstract P01)

12:15 – 12:30 Platform presentation 4
Intestinal Pseudo-obstruction in Adult m.3243A>G-Related Mitochondrial Disease: An Under-Recognised and Poorly-Managed Clinical Entity
Yi Ng, Newcastle University
(abstract P47)

12:30 – 13:00 Lunch

13:00 – 14:00 Poster guided tours session 1 of 3

14:00 – 17:30 Session 2: Next generation biomarkers
Chairs: Prof. Mary Reilly and Prof. Volker Straub

14:00 – 14:30 **Next generation in vivo imaging technologies in DMD - the BIOIMAGE-NMD programme**
Prof. Andy Blamire, Newcastle University
(abstract S04)

14:30 – 15:00 **MRI Biomarker Outcome Measures in Charcot-Marie-Tooth disease and Inclusion Body Myositis**
Dr. John Thornton, UCL Institute of Neurology
(abstract S05)

15:00 –15:30 **Integration of pharmacodynamic biomarkers into a drug regulatory pipeline: Vamorolone/VBP15 in DMD**
Prof. Eric Hoffman, ReveraGen BioPharma, Children's National Medical Center, Washington
(abstract S06)

15:30 – 16:00 **Coffee**

16:00 – 17:00 **Poster guided tour session 2 of 3**

17:00 – 17:30 **Session2: next generation biomarkers (ctd…)**
Qualification of Novel Methodologies European regulatory perspective
Dr. Maria Isaac, Senior Scientific Officer, EMA
(abstract S07)

17:30 – 17:45 Platform presentation 5
Human, Fly and Cell models of Riboflavin Transporter Neuronopathy
Andreea Manole, UCL Institute of Neurology
(abstract P66)

17:45 – 18:00 Platform presentation 6
Impaired mitochondrial function in neuronal cells harbouring a dominant glycyl-tRNA synthetase mutation
Veronica Boczonadi, Newcastle University
(abstract P65)

18:00 – 18:15 **Robert Meadowcroft**
CEO, MDUK

18:15 – 19:00 Drinks

19:30 **Gala Dinner**
Keble College *OX1 3PG (10 mins walk)*
(Dress code: smart / smart casual)

Day 2 – Wednesday 23rd March

08:30 – 09:30 **Poster guided tour session 3 of 3**

09:30 – 10:30 **Poster flash sessions** (see p.14 for list)
Chaired by Prof. Michael Hanna, UCL Institute of Neurology

10:30 – 12:30 **Session 3: Big Data**
Chairs: Prof. Hanns Lochmuller and Prof. Thomas Voit

10:30 – 11:00 **A Human Phenotype Ontology (HPO)-driven whole-genome analysis framework for effective identification of pathogenic regulatory variants in Mendelian disease**
Prof. Peter Robinson, Charité Hospital Berlin
(abstract S08)

11:00 – 11:30 **Big data, large sequencing challenges, and the technology behind it**
Dr. Ivo Gut, CNAG (National Centre for Genomic Analysis), Barcelona
(abstract S09)

11:30 – 12:00 **Coffee**

12:00 – 12:30 **Neurology and Neurodegeneration Genomics England Clinical Interpretation Partnership (Neuro-GeCIP)**
Prof. Henry Houlden, UCL Institute of Neurology
(abstract S10)

12:30 – 12:45 Platform presentation 7
Clinical and genetic analysis of CLCN1 mutations with dual inheritance pattern
Dr. Emma Matthews, UCL Institute of Neurology
(abstract P94)

12:45 – 13:00 Platform presentation 8
A GFPT1 deficient mouse model of Congenital Myasthenic Syndrome
Yasmin Issop, Newcastle University
(abstract P98)

13:00 – 14.00 **Lunch**

14:00 – 14:15 Platform presentation 9
Development of a cell-penetrating peptide for the delivery of antisense oligonucleotides to peripheral and CNS tissues of spinal muscular atrophy mice
Suzan M Hammond, University of Oxford
(abstract P84)

14:15 – 14:30 Platform presentation 10
Microvascular defect as potential peripheral target in spinal muscular atrophy
Haiyan Zhou , UCL Institute of Child Health
(abstract P85)

14:30 – 15.00 **MRC Strategic plan**
Kathryn Adcock
Head of Neurosciences and Mental Health
Medical Research Council

15:00 – 16:00 **John Newsom-Davis Lecture**
The congenital myasthenic syndromes: better treatments through an understanding of disease mechanisms
Prof. David Beeson, University of Oxford

16:00 – 16:30 Poster prizes and close

To Note: Those displaying posters. To allow for judging and poster sessions, posters should only be put up and taken down during these times.

Day 1 Tuesday 22 March
Posters up: 8.45 am to 9.15 am
Posters down: 18:15 – 18.45 pm

Day 2 Weds 23 March
Posters up: evening of 22nd 18.45 pm onwards OR by 8.15 am latest 23 March (first poster session of this day is at 8.30 am). Building access is from 8am.
Posters down: 16.30 onwards

Flash Poster Presentations List

Poster 116
Should the use of the Extended Myositis Antibody (EMA) panel be part of the routine work-up in suspected myositis?
Antoinette O' Connor, Cork University Hospital

Poster 117
The Revised Hammersmith Scale for Spinal Muscular Atrophy: Reliability, validity and results from a large international pilot
Danielle Ramsey, UCL Institute of Child Health

Poster 5
Muscle water T2 and fat fraction determination by NMRI as well as 31P-NMRS in a global multi-center dysferlinopathy study
Andy Blamire, Newcastle University

Poster 7
Habitual physical in patients with Myotonic Dystrophy type 1: an OPTIMISTIC sub study.
A. C. Jimenez Moreno, Newcastle University

Poster 6
Outcome measures for Duchenne muscular dystrophy from ambulant to non-ambulant: implications for clinical trials
Joana Domingos, UCL Institute of Child Health

Poster 49
Recessive Mutations in *TRMT10C* Cause Defects in Mitochondrial RNA Processing and Multiple Respiratory Chain Deficiencies
Kyle Thompson, Newcastle University

Poster 48
3D reconstruction and quantitative analysis of skeletal muscle mitochondrial networks in patients with mitochondrial disease
Amy Vincent, Newcastle University

Poster 103
Anti-cN1A autoantibody seropositivity is associated with increased mortality risk in Inclusion Body Myositis
James Lilleker, University of Manchester

Poster 99
Mutations in *COl13A1* cause a Congenital Myasthenic Syndrome
Judith Cossins, Weatherall Institute of Molecular Medicine, Oxford

Poster 102
Stabilization of Muscle Strength With Long-term AceER Treatment in Subjects with GNE Myopathy (GNEM): Results from an Open-Label Phase 2 Extension Study
Mary Hames (for Ed Conner), Ultragenyx Pharmaceutical

Poster List

Dystrophy

Guided Poster Session Leads:
Session a (Tue 1pm) Prof. Francesco Muntoni, Prof. Volker Straub
Session b (Tue 4pm) Prof. Dame Kay Davies, Prof. Thomas Voit
Session c (Wed am) Prof. Giulio Cossu, Dr. Aisling Carr

Session	Poster	Name	Surname	Title
a	5	Andy	Blamire	**Muscle water T2 and fat fraction determination by NMRI as well as 31P-NMRS in a global multi-center dysferlinopathy study**
a	6	Joanna	Domingos	**Outcome measures for Duchenne muscular dystrophy from ambulant to non-ambulant: implications for clinical trials**
a	7	Cecilia	Jimenez Moreno	**Habitual physical activity in patients with Myotonic Dystrophy type 1: an OPTIMISTIC sub study**
a	8	Emine	Bagdatlioglu	**Investigating the CNS in mouse models for Duchenne muscular dystrophy**
a	9	Corinne	Betts	**The Cmah-/-mdx mouse: an early onset model of cardiomyopathy for Duchenne muscular dystrophy**
a	10	David	Burns	**Utrophin modulation for the treatment of cardiomyopathy in mdx mice**
a	11	Kim	Down	**United Kingdom National Workshop on Duchenne Muscular Dystrophy Clinical Trial Capacity**
a	12	Stephanie	Carr	**Mini-dystrophins for gene therapy of Duchenne Muscular Dystrophy: is the C-terminus important for the function of the protein?**
a	13	Huijia	Chen	**Benefits of utrophin modulation therapy in the mdx mouse diaphragm**
a	14	Benjamin	Clarke	**Investigating necroptosis of muscle cells in vitro**
a	15	Janice	Clayton	**Extrapolation of 6-minute walking distance (6MWD) to predict loss of ambulation (LoA) with ataluren and placebo in nonsense-mutation Duchenne muscular dystrophy (nmDMD)**
a	16	Becky	Davis	**Setting up academic international clinical trials in rare diseases: a checklist to anticipate obstacles and facilitate processes**

a	17	Nathalie	Doorenweerd	**Cerebral diffusion weighted magnetic resonance spectroscopy suggests membrane damage or structural deficits in neuronal and glial cells in Duchenne muscular dystrophy patients**
a	18	Giulia	Ferrari	**Combining iPS cells and human artificial chromosomes for a genomic integration-free stem cell gene therapy of Duchenne muscular dystrophy**
b	19	Keith	Foster	**Cannabidiol increases oxidative and angiogenic potential in C2C12 myoblasts**
b	20	Nathalie	Goemans	**Development of a Prognostic Model for 1-year Change in 6-Minute Walk Distance (6MWD) in Patients with Duchenne Muscular Dystrophy (DMD)**
b	21	Nathalie	Goemans	**Reference values for the three-minute walk test, North Star Ambulatory Assessment and timed tests in typically developing boys aged 2.5-5 years**
b	22	Nathalie	Goemans	**Development of a patient-reported outcome measure for upper body function in Duchenne Muscular Dystrophy (Upper body PROM)**
b	23	Golnoush	Golshirazi	**Antisense Targeting of mRNA 3'UTR to Moderate Myostatin (GDF8) Expression for the Treatment of Myopathies**
b	24	Simon	Guiraud	**Second generation utrophin modulator for the therapy of Duchenne muscular dystrophy**
b	25	Matt	Hall	**The Sensitivity of the diffusion-weighted MRI signal decay curve to microstructural changes due to Duchenne Muscular Dystrophy**
b	26	Matt	Hall	**Fractional diffusion as a probe of microstructural change in a mouse model of Duchenne Muscular Dystrophy**
b	27	Persefoni	Ioannou	**NHE1 inhibition as a potential therapy to attenuate DMD pathology**
b	28	Cecilia	Jimenez Moreno	**Cardiac Magnetic Resonance Imagining (MRI): cross-sectional study of 20 Myotonic Dystrophy type-1 patients soon to start an exercise program**
b	29	E	Kaye	**Eteplirsen, a Phosphorodiamidate Morpholino Oligomer (PMO) for Duchenne Muscular Dystrophy (DMD): Clinical Update and Longitudinal Comparison to External Controls on Six-Minute Walk Test (6MWT)**

b	30	Yung Yao	Lin	**Isogenic human induced pluripotent stem cell based models for studying FKRP-deficient muscular dystrophy**
b	31	Rusia	Manuel	**Audit of DEXA scan surveillance in Duchenne muscular dystrophy**
b	32	Elena	Marrosu	**The application of allele-specific silencing therapeutic approach by antisense oligonucleotide in COL6A-related congenital muscular dystrophy**
c	33	Ursula	Moore	**Heterogeneous progression in Dysferlinopathy: a JAIN COS study update**
c	34	Louise	Moyle	**Can direct reprogramming of adult muscle satellite cells improve current hurdles impeding myoblast transplantation therapies?**
c	35	Nikoletta	Nikolenko	**Demographics and clinical characteristics**
c	36	Vicente	Pagalday	**Evaluation of a panel of new monoclonal antibodies to α-DG**
c	37	Maryna	Panamarova	**Generation of a mouse model of FSHD to reveal the DUX4 expression profile and dynamics**
c	38	Amaia	Paredes-Redondo	**Developing novel human isogenic cellular models for Duchenne muscular dystrophy**
c	39	Linda	Popplewell	**Development of Gene Editing Approaches for the Treatment of Duchenne Muscular Dystrophy (DMD)**
c	40	Agata	Robertson	**Global FKRP Registry**
c	41	Valentina	Sardone	**Dystrophin as a biochemical outcome measure in Duchenne Muscular Dystrophy clinical trials**
c	42	Volker	Straub	**Pattern recognition by semiquantitative radiological analysis in a large and multinational cohort of dysferlin patients**
c	43	Steve	Winder	**Repurposed Cancer Therapeutics as Treatments for DMD**
c	44	Libby	Wood	**UK Myotonic Dystrophy Patient Registry: A tool for clinical research**
c	45	Libby	Wood	**The UK FSHD Patient Registry: A Study of Scapular Fixation**
c	46	Nick	Zafeiropoulos	**Determination of tissue-water T2 of fat infiltrated upper limb skeletal muscle with MRI in Duchenne muscular dystrophy**

Mitochondrial Disease

Guided Poster Session Leads:
Session a (Tue 1pm) Prof. Robert Taylor, Prof. Henry Houlden
Session c (Wed am) Prof. Patrick Chinnery, Dr. Ros Quinlivan

Session	Poster	Name	Surname	Title
a	48	Amy	Vincent	**3D reconstruction and quantitative analysis of skeletal muscle mitochondrial networks in patients with mitochondrial disease**
a	49	Kyle	Thompson	**Recessive Mutations in TRMT10C Cause Defects in Mitochondrial RNA Processing and Multiple Respiratory Chain Deficiencies**
a	50	Enrico	Bugiardini	**A novel MT-ATP6 mutation causing complex spastic paraparesis associated with posterior predominant white matter changes**
a	51	Enrico	Bugiardini	**RNASEH1 mutations are a rare cause of CPEO with multiple mtDNA deletions**
a	52	Carl	Fratter	**Intra-uterine and postnatal growth failure resulting from maternally inherited mitochondrial DNA mutation m.3243A>G**
a	53	Sarah	Holmes	**Development and evaluation of individualised Exercise protocol for people with mitochondrial disease: a Service evaluation**
a	54	Louise	King	**Mitophagy deficiencies in mitochondrial DNA disease**
a	55	Julia	Maddison	**Reproductive decision making in mitochondrial patients: A qualitative investigation of women's experience**
a	56	Benjamin	O'Callaghan	**Impact of mtDNA mutations on the myogenic differentiation of IPSCs**
c	57	Olivia	Poole	**A mutation in a novel nuclear gene causing mitochondrial disease**
c	58	Joanna	Poulton	**Identifying novel pharmacological drugs to eliminate pathogenic heteroplasmic mtDNA by using a novel quantitative assay of mitophagy**
c	59	Iwona	Skorupinska	**Mortality in a cohort of mitochondrial patients**
c	60	Ewen	Sommerville	**Whole exome sequencing in undiagnosed late-onset mitochondrial DNA maintenance disorders**
c	61	Ewen	Sommerville	**A novel Celtic YARS2 founder mutation is associated with mitochondrial myopathy**

c	62	Katarzyna	Swist-Szulik	**The role of mitochondrial dysfunction in inflammatory crosstalk between immune cells and non-myeloid cells such as fibroblasts and myoblasts**
c	63	Maria Eleni	Anagnostou	**Characterisation of Polymerase gamma (POLG)-mutant fibroblasts with Alpers' and Alpers'-like disease**
c	64	Kyle	Thompson	**De novo dominant mutations in SLC25A4 cause severe early-onset mitochondrial disease and loss of mitochondrial DNA copy number**

Peripheral Nerve

Guided Poster Session Leads:
Session a (Tues 1pm) Prof. Mary Reilly, Prof. Dave Bennett
Session c (Wed am) Prof. Rita Horvath, Dr. Mike Lunn

Session	Poster	Name	Surname	Title
a	67	Boglarka	Bansagi	**Clinical and genetic characterisation of hereditary motor neuropathies**
a	68	Madga	Dudziec	**BALTiC study protocol: A feasibility analysis of home based BALance Training in people with Charcot-Marie-Tooth disease**
a	69	Matthew	Evans	**Defining the spectrum of intramuscular fat accumulation in hereditary sensory neuropathy type 1 using quantitative MRI.**
a	70	Umaiyal	Kugathasan	**Natural History Study in HSN1**
a	71	Juliane	Mueller	**Zebrafish as model for RNA metabolism related neurological disorders**
a	72	Gita	Ramdharry	**Patient & Public Involvement: How service user engagement has informed research into falls interventions in people with Charcot Marie Tooth Disease**
a	73	Alex	Rossor	**Facial Onset Sensory and Motor Neuronopathy: An extension of the FTD-MND spectrum**
a	74	Verna	Sarajarvi	**Developing allele-specific gene silencing as a therapeutic strategy for hereditary sensory neuropathy type I**
a	75	Teena	Shetty	**Incidence and Risk Factors for Neuropathy Following Primary Total Hip Arthroplasty**
c	76	Teena	Shetty	**Incidence and Risk Factors for Neuropathy Following Primary Total Knee Arthroplasty**

c	77	Mariola	Skorupinska	**Monitoring pregnancy in Charcot-Marie-Tooth disease: results of a survey**
c	78	James	Sleigh	**Dominant Gars mutations cause a sensory neuron fate switch in CMT2D mice**
c	79	Andreas	Themistocleous	**Neurological consequences of Non-Freezing Cold Injury**
c	80	Andreas	Themistocleous	**The Pain in Neuropathy Study (PiNS): A cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy**
c	81	Pedro	Tomaselli	**A de novo dominant mutation in the kinesin domain of KIF1A is a cause of autism spectrum disorder and axonal neuropathy**
c	82	Pedro	Tomaselli	**HNPP due to a heterozygous deletion of exons 4 and 5 of the PMP22 gene**
c	83	Emma	Wilson	**Cellular pathomechanisms of Hereditary Sensory Neuropathy Type 1 (HSN-1) in mammalian motor neurons**

Motor Neuron Disease

Guided Poster Session Leads:
Session a (Tues 1pm) Prof. Kevin Talbot, Dr. Pietro Fratta

Session	Poster	Name	Surname	Title
a	86	Fernando	Bartolome	**p62/SQSTM1 mutations induce limitation of mitochondrial substrates and energy metabolism impairments**
a	87	Melissa	Bowerman	**"Tweak/Fn14 pathway: at the crossroads of muscle atrophy and metabolic perturbations in spinal muscular atrophy**
a	88	Francesco	Catapano	**Dynamic dysregulation of microRNA-9, -206 and -132 in spinal muscular atrophy and the response to antisense oligonucleotide therapy**
a	89	Helen	Devine	**Retrograde Axonal Transport in human iPSC derived Motor Neurons**
a	90	Uros	Klickovic	**Magnetic resonance imaging as an outcome measure in motor neuron disorders**
a	91	Jakub	Scaber	**Absence of wide-spread mis-splicing in the preclinical phase of a native promoter driven TDP-43 mouse model of ALS**
a	92	Prasanth	Sivakumar	**Investigating dysfunctional RNA processing**

				in TDP-43 mouse mutants
a	93	David	Villaroel	**Role of PTPN23 in motor neuron neurotrophin signaling**

Channelopathies and Neuromuscular Junction Disorders

Guided Poster Session Leads:
Session b (Tues 4 pm) Prof. Michael Hanna, Prof. David Beeson

Session	Poster	Name	Surname	Title
b	95	Renata	Scalco	**RCT of Bumetanide in Hypokalaemic Periodic Paralysis**
b	96	Karen	Suetterlin	**Screening for Brody's Syndrome in an Undiagnosed Muscle Channelopathy Cohort**
b	97	Roope	Mannikko	**Loss of function mutations in SCN4A cause severe fetal hypokinesia or congenital myopathy**
b	99	Judith	Cossins	**Mutations in COl13A1 cause a Congenital Myasthenic Syndrome**
b	100	Ione	Meyer	**Investigating the role of nidogens, basement membrane proteins, at the neuromuscular junction in health and disease**
b	101	Pedro	Rodriguez Cruz	**Clinical features of the myasthenic syndrome arising from mutations in GMPPB**

Other Muscle Disease

Guided Poster Session Leads:
Session c (Wed am) Dr. David Hilton-Jones, Dr. Robert McFarland

Session	Poster	Name	Surname	Title
c	102	Mary	Hames	**Stabilization of Muscle Strength With Long-term AceER Treatment in Subjects with GNE Myopathy (GNEM): Results from an Open-Label Phase 2 Extension Study**
c	103	James	Lilleker	**Anti-cN1A autoantibody seropositivity is associated with increased mortality risk in Inclusion Body Myositis**
c	104	Qiang	Gang	**Analysing whole-exome sequencing data in a large cohort of sporadic inclusion body myositis and control individuals**
c	105	Katherine	Johnson	**The MYO-SEQ project: application of exome sequencing technologies to 1000 patients affected by limb-girdle weakness of unknown**

				origin
c	106	Pedro	Machado	**Baseline characteristics of a prospective natural history study of sporadic inclusion body myositis including MRI assessment**
c	107	Rusia	Manuel	**Schwartz- Jampel syndrome**
c	108	Oksana	Pogoryelova	**GNE myopathy: clinical presentation, mutation analysis and longitudinal observations from a Global Patient Registry Study**
c	109	Karolina	Rygiel	**Mitochondrial DNA rearrangements in sporadic Inclusion Body Myositis**
c	110	Renata	Scalco	**CAV3 mutations mimicking a metabolic myopathy: expanding the phenotypic spectrum of Caveolinopathies**
c	111	Renata	Scalco	**Effect of a multi-disciplinary approach to diagnosis and management for non-lysosomal skeletal muscle glycogen storage disorders**
c	112	Renata	Scalco	**Dantrolene as a possible prophylactic treatment for RYR1-related rhabdomyolysis**
c	113	Renata	Scalco	**Misdiagnosis in McArdle disease**
c	114	Charlotte	Spicer	**Investigating the effects of pharmacological up-regulation of the heat shock response in models of inclusion body myopathy**
c	115	Anna	Sarkozy	**STAC3 p.Trp284Ser, a hotspot mutation for congenital myopathy with distinctive dysmorphic features and malignant hyperthermia**

Diagnostics and Clinical Practice

Guided Poster Session Leads:
Session C (Wed am) Dr. Matilde Laura, Dr. Tracey Willis

Session	Poster	Name	Surname	Title
c	116	Antoinette	O'Connor	**Should the use of the Extended Myositis Antibody (EMA) panel be part of the routine work-up in suspected myositis?**
c	117	Danielle	Ramsey	**The Revised Hammersmith Scale for Spinal Muscular Atrophy: Reliability, validity and results from a large international pilot**
c	118	Aisling	Carr	**Optimising the IVIg service: an audit of monitoring and dosage**

c	119	Aisling	Carr	**Optimising the IVIg service: an audit of Daycare delivery**
c	120	Becky	Davis	**Clinical Research Activity in the Newcastle MRC Centre for Neuromuscular Disease**
c	121	Carolynne	Doherty	**Safety, tolerability and biological efficacy of Rituximab therapy in the Northern Irish Neuromuscular Clinic.**
c	122	James	Lilleker	**Using a Gene Sequencing Panel to Investigate Rhabdomyolysis**
c	123	Danielle	Ramsey	**The Revised Hammersmith Scale for Spinal Muscular Atrophy: Moving towards meaningful measurement, content validity from a patient/carer perspective**
c	124*	Debbie	Smith	**An update on FSHD2 diagnostic testing** ***(late poster withdrawal)****

Abstracts: Invited Speakers

Tuesday 22nd March 2016

S01

Alternate translational initiation of dystrophin: clinical and therapeutic implications

Kevin Flanigan[1,2], Tabatha Simmons[1], and Nicolas Wein[1].
[1]*Center for Gene Therapy, Research Institute of Nationwide Children's Hospital, Columbus, OH, USA*
[2] *Departments of Pediatrics and Neurology, Ohio State University, Columbus, OH, USA*

We recently identified an internal ribosome entry site (IRES) within exon 5 of the DMD gene that when active results in alternate translational initiation beginning within exon 6. As a result, patients carrying mutations that truncate the reading frame 5' of the IRES express an N-truncated dystrophin isoform that is highly functional, despite lacking the calponin homology domain 1 (CH1) of the actin binding domain 1 (ABD1). Consistent with genotype-phenotype correlations in Duchenne muscular dystrophy (DMD) patients, the IRES is not active in the presence of an exon 2 duplication but is active when exon 2 is deleted. We developed an AAV9.U7snRNA vector to induce skipping of exon 2, and have shown that in a DMD mouse model carrying a duplication of exon 2 (the Dup2 mouse), intramuscular (IM) or intravascular (IV) treatment results in functional and histopathologic improvement in skeletal muscle, and gene transfer at postnatal day 1 (P1) results in sustained correction of pathologic and physiologic defects. Preliminary studies in the Dup2 mouse using peptide-linked PMO antisense oligomers (PPMOs) show a similar degree of correction, suggesting multiple potential therapeutic routes to exon skipping. To model the applicability of this approach beyond exon 2 patients, we have used the same viral vector to treat human patient fibroblast-derived transdifferentiated myoblasts (FibroMyoD cells) harboring different mutations within exons 1 to 4, and shown abundant exon skipping and dystrophin expression. These results suggest that this exon-skipping approach offers a therapeutic route not only to patients with exon 2 duplications but with all mutations within the first four DMD exons, and supports the idea that early treatment of these patients will have longstanding and significant benefit resulting in a better outcome.

S02

From pathogenesis to therapy in spinal muscular atrophy

Francesco Muntoni
Dubowitz Neuromuscular Centre, Institute of Child Health and MRC Neuromuscular Centre, University College London, UK

Spinal Muscular Atrophy (SMA) is a common autosomal recessive disease due to the deficiency of Survival Motor Neuron (SMN) protein. In the great majority of patients this is secondary to homozygous deletions of the *SMN1* gene. A second gene, *SMN2*, is intact in all patients and encodes a related protein, but a single nucleotide difference from *SMN1* prevents efficient splicing of its exon 7, leading to a truncated transcript and an unstable protein. SMN is a protein evolutionary conserved and ubiquitously expressed in the cytoplasm and nucleus of all cells. It is part of a multiprotein complex involved in assembly of spliceosomes; 3'end processing of replication dependent histone mRNAs and axonal transport and local translation of mRNAs at the distal end of developing neurons. There is growing evidence that although motor neuron death appears to be a cell autonomous event, SMN deficiency is likely to induce defects elsewhere, which contribute to the motor neuron pathology. In my presentation I will summarise the main roles attributed to SMN and how they may contribute to SMA pathogenesis. In addition, I will discuss how the understanding of the genetic basis of SMA is being exploited for developing *SMN* gene specific therapies, which for the first time are addressing the primary defect in SMA patients.

S03

Antisense targeting of 3'end elements involved in *DUX4* mRNA processing is an efficient therapeutic strategy for Facioscapulohumeral Dystrophy: a new gene silencing approach

Anne-Charlotte Marsollier[1], Lukasz Ciszewski[2#], Virginie Mariot[1#], Linda Popplewell[2], Thomas Voit[1,§], George Dickson[2], **Julie Dumonceaux[1*]**

[1]*Sorbonne Universités UPMC Univ Paris 06, Inserm, CNRS, Centre de Recherche en Myologie (CRM), GH Pitié Salpêtrière, 47 bld de l'hôpital, Paris 13, France*

[2]*Centre of Biomedical Sciences, School of Biological Sciences, Royal Holloway University of London, Surrey, TW20 0EX UK*

[§]*Present Address: NIHR Biomedical Research Centre, Institute of Child Health, University College London, 30 Guilford Street, London WC1N1EH, UK*

Defects in mRNA 3' end formation have been described to alter transcription termination, transport of the mRNA from the nucleus to the cytoplasm, stability of the mRNA and translation efficiency. Therefore, inhibition of polyadenylation may lead to gene silencing. Here, we choose Facioscapulohumeral Dystrophy (FSHD) as a model to determine whether or not targeting key 3'end elements involved in mRNA processing using antisense oligonucleotide drugs can be used as a strategy for gene silencing within a potentially therapeutic context. FSHD is a gain-of-function disease characterized by the aberrant expression of the DUX4 transcription factor leading to altered pathogenic deregulation of multiple genes in muscles. Here we demonstrate that targeting either the mRNA polyadenylation signal and/ or cleavage site is an efficient strategy to downregulate *DUX4* expression and to decrease the abnormally high pathological expression of genes downstream of DUX4. We conclude that targeting key functional 3'end elements involved in pre-mRNA to mRNA maturation with antisense drugs can lead to efficient gene silencing and is thus a potentially effective therapeutic strategy for at least FSHD. Moreover polyadenylation is a crucial step in the maturation of almost all eukaryotic mRNAs, and thus all mRNAs are virtually eligible for this antisense-mediated knockdown strategy.

S04

Next generation in vivo imaging technologies in DMD - the BIOIMAGE-NMD programme

Andrew M. Blamire

Centre for In Vivo Imaging & Institute of Cellular Medicine, Newcastle University, UK

BIOIMAGE-NMD is an FP7 programme which aims to develop combined structural and molecular imaging biomarkers to detect therapeutic effects in patients with rare neuromuscular diseases, particularly Duchenne muscular dystrophy (DMD). The BIOIMAGE consortium is developing imaging acquisition and analysis methodologies based on diffusion MRI and drug radiolabelling to assess bio-distribution by positron emission tomography (PET, a nuclear medicine technique). Methods are evaluated in animal models and ongoing natural history and clinical trials in neuromuscular disorders.

Diffusion MRI generates image contrast based on the diffusibility of water within tissue. The measured diffusion coefficient is lower than true Brownian diffusion due to restrictions to motion imposed by tissue microstructure. Quantitation of diffusion therefore offers a non-invasive assessment of tissue structure. While used extensively in brain, applications of the same methods in muscle are sub-optimal. We have tailored the diffusion MRI acquisition to the muscle environment and compared imaging findings with histology in the *mdx* model over the lifespan. Our optimised methods reveal changes in tissue structure which are not seen using conventional muscle diffusion MRI. Quantitative data extracted from the diffusion scans indicate we can detect age and disease related changes in muscle fibre size distribution and overall permeability of tissue to water movement. Ongoing work is translating these methods to clinical scanners for initial studies in patients.

S05

MRI Biomarker Outcome Measures in Charcot-Marie-Tooth disease and Inclusion Body Myositis

John Thornton, Jasper Morrow, Christopher Sinclair, Arne Fischmann, Pedro Machado, Matthew Evans, Mary Reilly, Tarek Yousry, Michael Hanna.
MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, University College London, UK.

Irrespective of the primary molecular defect, neuromuscular disorder pathological processes include disturbance of intramuscular water distribution followed by intramuscular fat accumulation, both quantifiable by MRI. To meet the urgent need for responsive trial outcome measures, we investigated MRI biomarker longitudinal responsiveness, validity by correlation against functional measures, and sensitivity to early muscle water changes in patients with Charcot-Marie-Tooth disease 1A and inclusion body myositis. MRI-determined lower limb muscle fat fraction increased significantly over 12-months in both patient groups, and correlated with the relevant clinical functional scales. In muscles with fat fraction lower than the control group 95th percentile, T_2 was increased and MTR decreased in patients compared with controls. MRI outcome measure responsiveness greatly exceeded that of conventional severity indices, suggesting their use may markedly reduce the number of subjects required for adequately powered trials. MRI outcome measures can monitor intramuscular fat accumulation with high responsiveness, show validity by correlation with conventional functional measures, and detect muscle-water changes preceding significant intramuscular fat accumulation.

S06

Integration of pharmacodynamic biomarkers into a drug regulatory pipeline: Vamorolone/VBP15 in DMD

Eric Hoffman[1,2], Yetrib Hathout[2], Kristy Brown[2], Kanneboyina Nagaraju[1,2], John McCall[1], Paula Clemens[3], Kate Bushby[4]
[1]ReveraGen BioPharma, Rockville MD; [2] Children's National Medical Center, Washington DC; [3] University of Pittsburgh School of Medicine, Pittsburgh, PA; [4] Newcastle University, Newcastle, UK

The integration of circulating (blood) biomarkers into drug development pathways holds potential for acute and objective readouts of drug mechanism of action (pharmacodynamics biomarkers), or prediction of later clinical benefit (surrogate outcome biomarkers). Vamorolone/VBP15 is a small molecule, first-in-human drug that has potential for optimizing four subactivities of traditional glucocorticoids for DMD. It has removed transactivation (transcriptional activities associated with side effect profiles), retained transrepression (inhibition of NFkB and anti-inflammatory effects), enhanced plasma membrane stability properties, and changed from an agonist of mineralocorticoid receptor (prednisone) to an antagonist (eplerenone). We carried out a pharmacodynamics biomarker discovery of prednisone-treated DMD and inflammatory bowel disease patients. Pharmacodynamic biomarkers reflected safety aspects (adrenal suppression, insulin resistance, bone turnover), and efficacy aspects (myofiber membrane stability, fibrosis, inflammation). Both acute (within hours of a single dose) and chronic (months of daily treatment) biomarkers were defined. These are integrated into the clinical development program of vamorolone/VBP15 for acute measures of safety and dose selection, as well as confirmation of clinical outcome measures (objective read out less subject to placebo effect). Feedback from the EMA and FDA on the integration of pharmacodynamics biomarkers into the drug clinical path will be presented.

S07

Qualification of Novel Methodologies European regulatory perspective

Maria B Isaac MASc, MD, PhD, MFPM, Psychiatrist
Senior Scientific Officer
European Medicines Agency (EMA)
Maria.Isaac@ema.europa.eu

Disclaimer: The views expressed in this article are the personal views of the Authors and may not be understood or quoted as being made on behalf of or reflecting the official position of the European Medicines Agency or any of its Committees or Working Parties.

Scientific assessment of the potential for use of new methodologies (biomarkers, Clinical outcomes, new statistical methods) in clinical trials can be advanced in a structured fashion through the process of *qualification*, a process recently introduced by regulatory agencies including the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA). Regulatory qualification of a new method or tool for a defined context of use provides scientifically robust assurances to sponsors and regulators that accelerate appropriate adoption of new method into drug development and clinical practice. Such assurance saves time and money by removing the burden of proof on each individual sponsor to provide data to regulatory agencies on performance and validation. The aim is that the procedure will help at the time of the MAA, in the review of the new methodology, assurance for CHMP of acceptance of the new methodologies. The new clinical assessments tools thus enable drug development teams to use new clinical endpoints, potentially targeting new indications and better description of the clinical meaningfulness.

Wednesday 23rd March 2016

S08

A Human Phenotype Ontology (HPO)-driven whole-genome analysis framework for effective identification of pathogenic regulatory variants in Mendelian disease

Peter N Robinson[1], Max Schubach[1], Julius O. B. Jacobsen[2], Sebastian Köhler[1], Tomasz Zemojtel[1], Malte Spielmann[1], Marten Jäger[1], Harry Hochheiser[3], Nicole L. Washington[4], Melissa A. Haendel[5], Christopher J Mungall[4], Suzanna E Lewis[4], Tudor Groza[6], Giorgio Valentini[7], Damian Smedley[2]
[1]Charité-Universitätsmedizin Berlin,
[2] Skarnes Faculty Group, Wellcome Trust Sanger Institute, Hinxton, CB10 1SA, UK.
[3]Department of Biomedical Informatics and Intelligent Systems Program, University of Pittsburgh, Pittsburgh 15206 PA, USA
[4]Division of Environmental Genomics and Systems Biology, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA.
[5]Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland, Oregon 97239, USA
[6]Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Darlinghurst, NSW 2010, Australia
[7]Department of Computer Science, University of Milan, 20126 Milan, Italy

In this talk I will present phenotype matching algorithms that use the Human Phenotype Ontology to prioritise genes and diseases in the setting of genomic diagnostics and research. Whole-exome sequencing has enabled coding variants to be comprehensively investigated in research and diagnostic settings, and whole-genome sequencing has the potential to do the same for non-coding variation. However, interpretation of non-coding variants still constitutes a major challenge in Mendelian disease, especially for single-nucleotide and other small non-coding variants. To address this gap, we have developed a whole genome analysis framework, Genomiser, which combines phenotypic and genotypic information along with a Regulatory Mendelian Mutation (ReMM) score for predicting the relevance of variation in the non-coding genome. ReMM was implemented using a novel machine learning approach applied to a new high-quality set of manually curated regulatory Mendelian disease-associated variants, and significantly outperforms other state-of-the-art scoring methods. Genomiser additionally assesses allele frequency, regulatory sequences, and phenotypic relevance to rank variants. Overall, Genomiser is

able to identify causal regulatory variants as the top candidate in over 70% of simulated whole genomes, for the first time allowing effective detection and discovery of regulatory variants in Mendelian disease.

S09

Big data, large sequencing challenges, and the technology behind it

Ivo Glynne Gut
Centro Nacional de Análisis Genómico, CRG, Barcelona, Spain

Genomic analyses play an increasingly important role in any biomedical research project. Today genomic technologies provide exquisite resolution that can go as far as analysing genomics, transcriptomes and epigenomes even from individual cells. There are two main components that have been brought together. On one hand are high resolution sequencing devices that are used to generate the omic data and on the other the high-performance computers together with computational methods to deal with the vast amount of sequences that are generated. These days the major challenges lie in data analysis that keys itself up into primary and secondary data analysis. There is much emphasis on primary data analysis. Even if this is technically challenging and generally lacks good standards, the real issues are in secondary data analysis in which observations are used to derive biological or clinical results. Due to a lack of upstream standards and a limited willingness to share data much of the value of data generated is unfortunately lost. The state-of-the-art will be discussed. A lot remains to be done in this field.

S10

Neurology and Neurodegeneration Genomics England Clinical Interpretation Partnership (Neuro-GeCIP)

Henry Houlden for the Neuro-GeCIP
MRC Centre for Neuromuscular Diseases, The National Hospital for Neurology and Neurosurgery and UCL Institute of Neurology, Queen's Square, London WC1N 3BG.

Over the next two years, our linked Genome Medicine Centres (GMCs) around England will collect DNA and "omic" samples on an estimated 8,000 samples from trios and families with neurological and neurodegenerative diseases for whole genome sequencing by Genomics England. This includes rare and the more aggressive genetically undefined neuromuscular diseases and neurodegenerative disorders. The Neuro-GeCIP forms a wide group of clinicians and scientists interested in the optimisation, validation and interpretation of these genome data, to maximise the research potential of whole genome sequencing. This will improve our understanding of the genetic architecture of rare neurological disease, identify key pathways forming the foundations for future mechanistic studies and novel therapeutic interventions. The key aims of the Neurology and Neurodegeneration research plan include: 1. The development of data capture and similarity scoring algorithms to delineate phenotypic groups. 2. Gene discovery will lead to the identification of novel pathways. 3. Training and 4. Future collaboration with industry to use pathway discovery and identify new medicines.
We hope to involve all clinicians in the UK in the GeCIP that interested in neurological disorders to promote sample collection and advance the delivery of genome results back to patients.

S11

The congenital myasthenic syndromes: better treatments through an understanding of disease mechanisms

David Beeson[1], Judy Cossins[1], Richard Webster[1], Susan Maxwell[1], Kate Belaya[1], Wei-Wei Liu[1], Pedro Rodriguez-Cruz[1], Stephanie Robb[2], Jacqueline Palace[3]
[1]Neuoscience Group, WIMM, Oxford University, UK
[2]*UCL Institute of Child Health, London, UK*
[3]*Nuffield Department of Clinical Neuroscience, The John Radcliffe, UK*

The congenital myasthenic syndromes (CMS) are hereditary disorders of neuromuscular transmission with the number of cases recognised, at around 1:100,000 in the UK, increasing with improved diagnosis.

The advent of next-generation sequencing has facilitated the discovery of many genes that harbour CMS-associated mutations, and to date at least 22 have been identified. We highlight an emerging group of CMS, characterised by a limb-girdle pattern of muscle weakness which are caused by mutations in genes that encode proteins involved in the initial steps of the N-linked glycosylation pathway. Surprisingly although this pathway occurs in all mammalian cells, symptoms in our CMS patients are largely restricted to neuromuscular transmission and we speculate that the neuromuscular junction is particularly sensitive to defects in biochemical pathways affecting glycosylation. Since the characterisation of DOK7 CMS it has become clear that the β2-adrenergic receptor agonists, salbutamol and ephedrine, can be life-transforming if treatment is tailored for particular syndrome subsets where disease mechanisms have been elucidated. Examples of the dramatic patient improvement that can be achieved with tailored treatment will be demonstrated.

9th Annual Neuromuscular Translational Research Conference
22nd and 23rd March 2016
Posters and Platform Presentations
‡indicates a platform or flash presentation

Dystrophy

‡P01
Charcot-Marie-Tooth and Centronuclear myopathy induced mechanistic impairment in endocytosis
Tayyibah Ali, Andrew Shevchuk
Imperial College London
t.ali13@imperial.ac.uk

Background: In Charcot-Marie-Tooth peripheral neuropathy (CMT) and Centronuclear myopathy (CNM), mutations in various domains of the Dynamin 2 gene (DNM2), which occur in a tissue specific manner, have been identified. CMT is an inherited neuropathy characterized by muscle weakness and atrophy, and loss of touch sensation that occurs in 1 in 2,500 people making it currently one of the most common incurable inherited neurological disorders. CNM is a group of congenital myopathies characterised by cell nuclei being abnormally located in muscle cells. It is a slowly progressive myopathy characterized by generalized muscle weakness with variable severity, ranging from severe neonatal to mild late onset forms. DNM2 mutations cause axonal CMT (CMT2) and dominant intermediate CMT4 and autosomal dominant form of CNM.
DNM2 is a large GTPase involved in the scission of nascent vesicles during endocytosis and is also implicated in wide range of cellular processes such as membrane and cytoskeletal dynamics.
Current research has characterised the biochemical properties of DNM2 mutant however none have yet related these properties to functioning in the cell. Although mutations in DNM2 have been characterised biochemically, little is known about their influence on the dynamics of nanoscale morphological changes taking place in individual trafficking events. Such knowledge is critical for understanding of disease-related perturbations.
Aims: To determine the role of disease associated DNM2 mutations in endocytic vesicle formation and internalisation
Methods: In this study we used correlative Scanning Ion Conductance Microscopy (SICM) and fluorescence confocal (FC) microscopy developed in our lab that allows live imaging at super resolution. This was combined with electron microscopy, confocal analysis and biochemical assays to characterise the temporal and spatial recruitment of mutant dynamin 2 and their effect on formation and internalisation of individual endocytic pits.
Results: Utilising human skin fibroblasts from CMT and CNM patients as a model of study, we demonstrated R465W-DNM2 mutation causes dynamin-2 co-localisation with nascent pits in a stable manner, resulting in pits gradually flatten and dissipate without scission. We report the aberrant pit formation and clustering of R552H-DNM2. Both mutations are observed to adversely affect the average lifetime of clathrin coated pits compared to wild type DNM2 observed in human skin fibroblasts from healthy controls.
Conclusion: The applications of correlative SICM and FC live imaging have allowed for the first time the characterisation of DNM2 mutants in living cells at single vesicle level. The data acquired provides direct evidence that DNM2 mutations alter the kinetics of pit formation and internalisation in a mutation specific manner.

‡P02
Cell therapy for muscular dystrophy: lessons learned and a road to efficacy

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]*San Raffaele Hospital, Milan.*
[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.*
giulio.cossu@manchester.ac.uk

Background: Intra-arterial transplantation of mesoangioblasts proved safe and partially efficacious in pre-clinical models of muscular dystrophy. After completion of a toxicity study and an observational study on 28 DMD patients, five (age 8.5 to 12.4, two wheelchair-bound) were selected for a first-in-human, phase I-IIa clinical trial of intra-arterial HLA-matched donor cell transplantation.
Aims: Safety was the primary objective of the study, while engraftment of donor mesoangioblasts, dystrophin production and changes in force of contraction were the secondary objectives.
Methods: We administered escalating doses of donor-derived mesoangioblasts in limb arteries under immune-suppressive therapy. Four consecutive infusions were performed at two months intervals, preceded and followed by clinical and laboratory tests. Muscular MRI was performed every 6 months since recruitment. Two months after the last infusion a muscle biopsy was analyzed for the presence of donor derived DNA and dystrophin transcript and protein.
Results: We recorded a single SAE, a thalamic stroke that had no clinical consequences and whose correlation with mesoangioblast infusion remained unclear. MRI documented the advanced phase progression of the disease. Functional measures were transiently stabilized in 2/3 ambulant patients. Donor DNA was detected at very low level in muscle biopsies of 4/5 patients and donor-derived dystrophin in 1/5.
Conclusion: The study was relatively safe but efficacy was minimal, partly due to the advanced age of patients, partly to inefficient cell transplantation (Cossu et al. EMM 2015). We now plan: 1) to test in a pilot trial the efficiency of gene corrected autologous cells to cross-correct neighboring nuclei; 2) to implement (through *in vitro* assays) each step of transplantation; 3) to target (in large animals) also the diaphragm and the back muscles. This should lead to a new clinical protocol with autologous, genetically corrected cells that, administered to younger patients, may approach the threshold of clinical efficacy.

‡P03

Results of North Star Ambulatory Assessments in the Phase 3 Ataluren Confirmatory Trial in Patients with Nonsense Mutation Duchenne Muscular Dystrophy (ACT DMD)

Francesco Muntoni[1], Janbernd Kirschner[2], Xiaohui Luo[3], Gary Elfring[3], Hans Kroger[3], Peter Riebling[3], Tuyen Ong[3], Robert Spiegel[3], Stuart W. Peltz[3], and Katharine Bushby[4] for the Ataluren DMD Study Steering Committee
[1] *UCL Institute of Child Health, London, UK* [2] *University Medical Center Freiburg, Freiburg, Germany;* [3] *PTC Therapeutics, New Jersey, USA;* [4] *John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK*
f.muntoni@ucl.ac.uk

Background: Results of the Phase 3, randomized, double-blind, placebo-controlled ACT DMD trial have been reported. The NSAA is a validated functional scale to measure disease progression specifically in ambulant boys with DMD.
Aims: Examine the efficacy of ataluren in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) as assessed by the North Star Ambulatory Assessment (NSAA).
Design/Methods: ACT DMD enrolled males aged 7–16 years with nmDMD and baseline six-minute walk distance (6MWD) ≥150m and ≤80%-predicted. Eligible patients were randomized 1:1 to receive ataluren 10, 10, 20 mg/kg or placebo orally three times daily for 48 weeks. A subgroup analysis of patients with baseline 6MWD of 300–400m was pre-specified. The NSAA consists of 17 activities ranging from standing

from a chair to jumping. Each activity is scored as 0, 1, or 2; the sum of these 17 scores forms the total score, which is linearized to a 0 (worst) –100 (best) score.
Results: The intent-to-treat population of ACT DMD consisted of 228 patients (ataluren, n=114; placebo, n=114). Overall, patients who received ataluren gained a 1.5-point advantage in NSAA observed score compared with patients who received placebo (mean NSAA scores, ataluren: -7.0; placebo: -8.5; *p*=0.270). In the pre-specified subgroup of 99 patients with baseline 6MWD 300–400m, the advantage conferred by ataluren over placebo increased to 4.5 points (mean observed NSAA scores, ataluren: -5.7; placebo: -10.2; *p*=0.030).
Conclusions: Ataluren is the first drug to demonstrate a benefit to patients with nmDMD compared with placebo as assessed by NSAA scores; this benefit was especially pronounced in the subgroup of patients with baseline 6MWD 300–400m. NSAA results when combined with 6MWD results, provide complementary information on different aspects of motor function in nmDMD patients and further demonstrate the efficacy of ataluren in this patient population. More detailed analysis of NSAA domains will be presented.
Study Supported By: PTC Therapeutics Inc.
Disclosures: TBD

‡P04
ACT DMD: Effect of Ataluren on Timed Function Tests in Nonsense Mutation Duchenne Muscular Dystrophy
Katharine Bushby[1], Craig Campbell[2], Craig M. McDonald[3], Thomas Voit[4], Xiaohui Luo[5], Gary Elfring[5], Hans Kroger[5], Peter Riebling[5], Tuyen Ong[5], Robert Spiegel[5], Stuart W. Peltz[5] and Nathalie Goemans[6] for the Ataluren DMD Study Steering Committee
[1] John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK, [2] London Health Sciences Centre and Western University, Ontario, Canada, [3] University of California Davis, California, USA, [4] University College London, Institute of Child Health, London, UK, [5] PTC Therapeutics, New Jersey, USA, [6] University Hospitals Leuven, Belgium
kate.bushby@newcastle.ac.uk

Background: Ataluren is the first drug to treat the underlying cause of nmDMD by promoting readthrough of a premature stop codon to produce full-length functional dystrophin. It is approved in Europe for the treatment of nmDMD in ambulatory patients aged 5 years and older.
Aims: Determine the effects of ataluren on motor function in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) using timed function tests (TFTs).
Design/Methods: ACT DMD (Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy) is a Phase 3, randomized, double-blind, placebo-controlled study. Males 7–16 years of age with nmDMD and a screening six-minute walk distance (6MWD) ≥150m and <80%-predicted were randomized 1:1 to ataluren 40 mg/kg/day or placebo for 48 weeks. A pre-specified subgroup included patients whose baseline 6MWD was 300–400m. Secondary endpoints included TFTs: 10-meter walk/run; 4-stair climb; 4-stair descend. A meta-analysis of the overall ACT DMD population and the 'ambulatory decline phase' subgroup of the Phase 2b study (i.e., those patients meeting ACT DMD entry criteria) was pre-specified in the ACT DMD statistical plan.
Results: In the overall ACT DMD population (N=228), changes in the three TFTs presented below, favored ataluren over placebo: 10-meter walk/run, -1.2s (p=0.117); 4-stair climb, -1.8s (p=0.058); 4-stair descend, -1.8s (p=0.012). In the pre-specified subgroup (n=99), these differences increased to -2.1s, -3.6s, and -4.3s, respectively, and were statistically significant for the 4-stair climb (p=0.003) and 4-stair descend (p<0.001), and approached significance for 10-meter walk/run (p=0.066). Results are supported by the meta-analysis (N=291), which demonstrated significant differences in all three TFTs: 10-meter walk/run, -1.4s (p=0.025); 4-stair climb, -1.6s (p=0.018); 4-stair descend, -2.0s (p=0.004).
Conclusions: TFT results showed a benefit for ataluren in ACT DMD, and a larger treatment effect in the pre-specified baseline 6MWD 300–400m subgroup as well as the pre-specified meta-analysis of ACT DMD and the Phase 2b study decline subgroup.

Study Supported By: PTC Therapeutics Inc.
Disclosures: TBD

‡P05

Muscle water T2 and fat fraction determination by NMRI as well as 31P-NMRS in a global multi-center dysferlinopathy study

H. Reyngoudt, N. Azzabou, F.E. Smith, Pierre G. Carlier[1], **A. Blamire** & the JAIN COS Consortium[2], Kate Bushby[3]
[1] Institut de Myologie, AP-HP, G.H. Pitié-Salpêtrière 47-83, Boulevard de l'Hôpital, Paris, France[1]
[2] Magnetic Resonance Centre, Institute for Cellular Medicine, Newcastle University,
[3] The John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK

Background: The Jain COS Study investigates the natural history of dysferlinopathy over a three year period. MRI, Medical and physiotherapy assessments are obtained. An analysis of NMRI baseline data is presented. Subjects are assessed with NMRI/S annually.
Aims: Baseline NMRI data was analysed to act as a reference for disease progression in subsequent years.
Methods: Quantitative Nuclear Magnetic Resonance Imaging (NMRI) is used to determine disease progression and activity. This is performed with dedicated NMRI sequences based on fat/water separation (Dixon techniques) and muscle water T2 mapping (Multi-Slice Multi-Echo, MSME), respectively. Quantitative phosphorus NMR Spectroscopy (31P-NMRS) evaluates phosphate metabolism and pH.
NMRI was obtained bilaterally in thigh (n= 12) and leg muscles (n=7), in a large subset of 203 subjects across 14 centres. At three centres performed, 31P-NMRS in the Tibialis anterior muscle.
Results: Data was acquired in 124 patients: 62 males (11 to 71 years),62 females (15 to 86 years); 16 male and 15 female subjects were non-ambulant. Fat fraction values varied 1.3 % to 95.1 % in both leg and thigh muscles. Muscle water T2 values were on average 37.4 ± 6.5 ms and 38.9 ± 5.2 ms in leg and thigh muscles, respectively. Muscle water T2 was elevated (≥ 39 ms) in 59%, 70% and 69% for Vastus intermedius, Vastus lateralis and Vastus medialis muscle, respectively. For Tibialis posterior, Adductor magnus, Biceps femoris (Long Head) and Semimembranosus muscles, the percentage of muscles with elevated T2 was higher than 50%.
Conclusion Fat fraction and muscle water T2 values were determined in a large cohort, which will serve as a reference for evaluation of disease progression in subsequent years. Phosphorus metabolic information adds value to the evaluation of this neuromuscular pathology. Quantitative NMRI and NMRS can be used to monitor therapeutic efficacy in future clinical trials in dysferlinopathy.

‡P06

Outcome measures for Duchenne muscular dystrophy from ambulant to non-ambulant: implications for clinical trials

Domingos, J.[1]; Eagle, M.[2]; Moraux, A.[3]; Butler, J.[1]; Decostre, V.[3];Ridout, D.[4]; Mayhew, A. [2]; Selby, V.[1]; Reguiba, N.[3]; Guglieri, M.[2]; Van der Holst, M.[5]; Jansen, M.[6]; Verschuuren, J.G.M.[5]; de Groot, I.[6]; Niks, E.[5]; Servais, L.[3]; Hogrel, J.Y.[3];.Straub, V.[2]; Voit, T. [3,7]; Ricotti, V. [1] and Muntoni, F.[1]
[1]UCL Institute of Child Health, Dubowitz Neuromuscular Centre, London UK;
[2] John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle, UK;
[3]Institut de Myologie, Groupe Hospitalier Pitié Salpêtrière, Paris, France;
[4] Population, Policy and Practice Programme, UCL Institute of Child Health, London, UK;
[5]Leids Universitair Medisch Centrum, Leiden, Netherlands;
[6]Radboud University Medical Centre, Nijmegen, Netherlands;
[7] Biomedical Research Centre, UCL Institute of Child Health, London, UK
j.domingos@ucl.ac.uk

Background: Novel emerging therapies for Duchenne Muscular Dystrophy (DMD) require a deeper understanding of DMD natural history. Most information is available for ambulant subjects, with less data on non-ambulant. We aim to assess the natural history of DMD through a composite assessment tool capable of capturing disease progression linking ambulant and non-ambulant phases of the condition.
Methods: With a recruitment target of 80 DMD across 5 centres (London, Newcastle, Paris, Leiden and Nijmegen), subjects are assessed 6 monthly according to a shared protocol, with longitudinal data centrally collected and analysed. Assessments include 6-minute walk distance (6MWD), NorthStar Ambulatory Assessment (NSAA), Performance of Upper Limb (PUL) and MyoSet (i.e. MyoGrip MyoPinch and MoviPlate). We explored relationships between measures across the ambulant and non-ambulant stages.
Results: We currently have longitudinal data for 60 DMD patients, ranging from 5-19years old, 37 ambulant and 23 non-ambulant. The ambulant boys >7years old declined 20 meters/year ($p<0.01$) in relation to 6MWD and 1.7 NSAA points/year ($p<0.01$). The non-ambulant boys over 1 year lost 4.3 PUL scores ($p<0.001$) and 6% in FVC% ($p=0.01$). In relation to MyoGrip strength, the yearly loss was 340gr in the non-ambulant population ($p<0.01$). We compared MyoGrip strength with age/gender matched healthy controls; the percentage difference from expected mean was -45% for ambulant and -81% for non-ambulant boys. With this initial analysis we observed a correlation between the shoulder domain of the PUL and NSAA ($r=0.56$, $p<0.001$) and the 6MWD ($r=0.54$, $p<0.01$); and between MyoGrip strength and total PUL score ($r=0.57$, $p<0.001$). Analysis of 2 and 3 year follow up data is on-going.
Conclusion: Our on-going study offers a comprehensive concurrent natural history data including the non-ambulant DMD population.
Acknowledgments: L'Association française contre les myopathies (AFM) is gratefully acknowledged for funding this study

‡**P07**
Habitual physical activity in patients with Myotonic Dystrophy type 1: an OPTIMISTIC sub study
A.C. Jimenez-Moreno[1] H. Lochmuller[1] V.T. van Hees[2], S. J. Denton[2], M. Catt[2], M.I. Trenell[2]
OPTIMISTIC Consortium[3]
[1]. The John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle UK.
[2]. MoveLab Research Centre, Newcastle University, Newcastle UK
[3]. European Consortium of the OPTIMISTIC trial in Myotonic Dytrophy Type 1, van Engelen et al 2015.
a.c.jimenez-moreno@ncl.ac.uk

Background: The association between habitual physical activity (HPA) levels and clinical phenotype in other neuromuscular disorders has been shown. However, the level of HPA in patients with Myotonic Dystrophy type 1 (DM1) and its relationship with disease burden is unknown.
Methods: HPA measured for 15 consecutive days using an ankle worn triaxial accelerometer (GENEActiv, Activinsights Ltd, UK), fatigue (Checklist Individual Strength; CIS), disease burden (Muscular Impairment Rating Scale; MIRS) and cardiopulmonary fitness (six minute walk test 6MWD) were assessed in 29 patients with genetically proven DM1.
Results: 42 patients have been included on this analysis. Patients with DM1 had significantly lower levels of HPA than age matched healthy population references. CIS scores, 6MWD or age were not predictors of HPA levels. At baseline, 58.6% of the patients were classified as least active, in relation to activity levels, out of three possible categories. Differences in gender were observed, a mean HPA for women 16.2% higher than men but not statistical significant ($p= 0.14$), There were no significant differences in the mean levels of HPA amongst patients with MIRS score of 2 ($n=7$) or 3 ($n=8$), but patients with MIRS scores of 4 ($n=13$) showed a significant lower mean level of activity ($p<0.05$) and the few patients with a MIRS of 1 was dramatically more active than the rest. Patients still capable of running showed over 32% higher activity levels.
Patients reported outcomes related to their physical activity levels showed a strong correlation ($r = -0.65$, $p= 0.001$) with objective HPA, which is not always the case in diseases that characterize with chronic fatigue.

6MWT also showed a strong correlation with their HPA, factor that has been shown in other neuromuscular disease HPA study with Duchenne patients.
Conclusions: These results demonstrate objectively for the first time, low levels of HPA in DM1. This may constitute a potential modifiable risk factor in DM1 patients. Individual factors that may influence on this will be further analysed.

P08

Investigating the CNS in mouse models for Duchenne muscular dystrophy

E.Bagdatlioglu[1], P. Porcari[2], D. O'Hogain[2], E. Greally[1], A. Blamire[2], V.Straub[1]
[1] *The John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases at Newcastle, Institute of Genetic Medicine, Newcastle University, UK*
[2] *Newcastle Magnetic Resonance Centre, Campus for Ageing and Vitality, Newcastle University, UK*
emine.bagdatlioglu@newcastle.ac.uk

Background: Duchenne Muscular Dystrophy (DMD) is an X-linked recessive muscle wasting disease caused by mutations in the *DMD* gene. The large cytoskeletal protein dystrophin is also expressed within the central nervous system (CNS) where its function remains unknown. 1/3 of DMD boys exhibit cognitive problems ranging from reduced verbal intelligence to severe autism. The dystrophin deficient *mdx* mouse and an *mdx* strain also null for the Cmah gene (*Cmah-/-mdx*), similarly mutated in humans, served to analyse the effect of dystrophin deficiency on brain function.
Aims: To investigate brain changes using both qualitative and quantitative MRI techniques in combination with immunoanalysis of brain tissue.
Methods: T_1- and T_2-weighted magnetization sequences were established to gather brain volumetric measurements. Evans blue dye and T_1-w gadolinium enhancements were employed to assess blood-brain barrier (BBB) leakage.
Results: Immunoblotting revealed that *mdx* mice manifest a progressive reduction of aquaporin-4 (AQP4) expression, the major water channel of the CNS, with this effect exacerbated in *Cmah-/-mdx* mice. Total brain volume was significantly larger in *Cmah-/-mdx* mice compared to both aged matched *mdx* and WT mice. Interestingly, WT mouse brain expanded with increasing age. Temporalis muscle hypertrophy and a different head shape was observed in DMD mice, similar to recent findings in Duchenne boys. Cmah-/-*mdx* mice also exhibited numerous ventricular abnormalities including irregular ventricular shape and enlarged lateral ventricle (LV) volume, in contrast *Cmah-/-* mice showed a significant reduction in LV volume compared to both age matched *Cmah-/-mdx* and WT mice.
Conclusion: Enlarged lateral ventricles may be caused by impaired regulation of ion transport through the loss of interaction between dystrophin and AQP4. The BBB disruptions suggest defects in fluid handling in the brains of mutant mice. Taken together these two findings suggest that osmotic equilibrium may be involved in the pathology of the cognitive impairment seen in DMD.

P09

The *Cmah*$^{-/-}$mdx mouse: an early onset model of cardiomyopathy for Duchenne muscular dystrophy

Corinne A Betts, Richard Healicon, Tirsa LE van Westering, Vicky Ball, Damian J Tyler, Matthew JA Wood
Department of Physiology, Anatomy and Genetics, University of Oxford, South Parks Road, Oxford, OX1 3QX, UK

Background: Duchenne muscular dystrophy (DMD) is a devastating muscle wasting disorder caused by the lack of an integral structural protein called dystrophin. DMD boys develop severe cardiomyopathy by the second decade of life, and cardiorespiratory complications are a major cause of death amongst patients. The *mdx* mouse is the most widely used model for DMD, however it does not accurately recapitulate skeletal muscle pathology or the cardiac disease progression observed in patients. As such the *CMAH* mouse model, with a mutation in the *Cmah* gene on the *mdx* background, was developed and

reported to show a more severe phenotype then the *mdx* mouse. However, an extensive comparison of cardiac function, metabolic profile and pathology was not described between the two models.
Aims: Therefore, we set out to determine whether the *CMAH* mouse model is a more appropriate cardiac model of DMD.
Methods: Cardiac function (Magnetic Resonance Imaging) and metabolism (Dynamic Nuclear Polarisation) were measured in *CMAH* and *mdx* mice at 12 and 24 weeks of age. Markers of cardiac damage were assessed by qPCR.
Results: *CMAH* mice exhibit pronounced left ventricular (LV) dysfunction, characterised by reduced LV end-diastolic volume, stroke volume and cardiac output. This was accompanied by raised pyruvate dehydrogenase flux which indicates a switch from fatty acid metabolism towards glucose oxidation for energy requirement. Additionally, markers of cardiac damage were significantly raised in *CMAH* mice at an earlier time-point then *mdx* mice.
Conclusion: These events indicate that *CMAH* mice display earlier onset of cardiomyopathy, and may thus be a more appropriate model for assessing therapeutic benefit following treatment strategies for the disease.

P10

Utrophin modulation for the treatment of cardiomyopathy in *mdx* mice

David Burns[1], Simon Guiraud[1], Carolyn Carr[1], Huijia Chen[1], Sarah E. Squire[1], Ben Edwards[1], Arran Babbs[1], Nandini Shah[1], Adam Berg[1], Stephen G. Davies[2], Graham M. Wynne[2], Angela J. Russell[2]¶, David Elsey[3], Francis.X. Wilson[3], Jon M. Tinsley[3], Kay E. Davies[1]
[1]*MRC Functional Genomics Unit, University of Oxford,* [2]*Department of Chemistry, ¶Department of Pharmacology, University of Oxford.* [3]*Summit PLC, Abingdon*
david.burns@dpag.ox.ac.uk

Background: Duchenne muscular dystrophy (DMD) is a devastating muscle-wasting disease caused by lack of the cytoskeletal protein dystrophin. There is currently no cure for DMD although various promising approaches are progressing through clinical trials. Severe cardiomyopathy frequently occurs in DMD patients and is one of the main causes of death. In collaboration with Summit Therapeutics we have developed a first generation utrophin modulator, SMT C1100, which is about to enter phase 2 clinical trials. Second generation compounds with more robust metabolic profiles have also been developed. One of these second generation compounds, SMT022357, has produced promising results in the *mdx* mouse model.
Aims: By pharmacologically modulating the dystrophin-related protein utrophin, we are developing a therapy applicable to all DMD patients, regardless of their dystrophin mutation. Increasing the level of utrophin in the heart and restoring normal cardiac function will be crucial in increasing patients' lifespan.
Methods: SMT022357 increases utrophin levels in skeletal muscle, diaphragm and in the heart. Using cardiac MRI in 9 weeks old mice which have been treated with SMT022357 for 7 weeks we determined whether the increase in utrophin in the heart was associated with an improvement in cardiac function. Dobutamine stress testing was used to precipitate underlying cardiac pathologies in 9 weeks old *mdx* mice. Histological analysis was performed to correlate functional improvement and reduction in histopathology in *mdx* mice treated with SMT022357.
Results: Daily oral administration of SMT022357 increases the level of utrophin in the heart. This modulation was associated with an improvement in cardiac function and an improved response to dobutamine stress testing, as assessed by MRI. This was correlated with a reduction in cardiac fibrosis in SMT022357 treated *mdx* mice.
Conclusion: These results demonstrate that utrophin modulation can significantly reduce pathology in the heart in *mdx* mice. This validates the concept of increasing utrophin expression in the heart as a potential means to treat cardiomyopathy in all DMD patients.

P11

United Kingdom National Workshop on Duchenne Muscular Dystrophy Clinical Trial Capacity

Kate Bushby[1], Kim Down[1], Annemieke Aartsma-Rus[1,2], Becky Davis[1]
[1]Newcastle University John Walton Centre for Muscular Dystrophy Research, MRC Centre for Neuromuscular Diseases, UK; [2] Leiden University, Netherlands.
kate.bushby@newcastle.ac.uk

Patient organisations representing Duchenne muscular dystrophy (DMD) are concerned about the apparent lack of capacity for trials in DMD in the UK. Clinicians in larger centres are involved in multiple DMD studies and are reaching capacity, while smaller centres need support to develop their clinical trial capacity.
This workshop brought together a group of 75 people representing patient organisations, clinical staff from different centres as well as representatives from the National Institute for Health Research (NIHR) and industry both to assess the current situation and to develop a strategy to improve capacity and better utilise resources. These representatives met in Newcastle on the 10th of July, 2015 under the chairmanship of Annemieke Aartsma-Rus, the current chair of the TREAT-NMD Alliance.
Various speakers presented on the following topics: how a clinical trial site runs a clinical trial for DMD; the industry perspective on running a clinical trial in the UK; service delivery for DMD; the perspective of physiotherapists; National Institute for Health Research support for trials; and a US model for capacity building and supporting care.
The meeting concluded that the UK must continue to be one of the key "go to" countries for clinical trials in DMD. The Newcastle Plan was devised as the actions needed to ensure that the UK builds its clinical trial capacity for DMD and, by extrapolation, also other neuromuscular diseases. The plan includes three phases of development. A one year plan aims to immediately boost capacity at existing UK centres of excellence. A two year, or medium term plan aims to build excellence and capacity at existing sites that have trial experience but need resource. The aim of the five year plan is to ensure that all patients with DMD, including children and adults, have access to clinical research opportunities.

P12

Mini-dystrophins for gene therapy of Duchenne Muscular Dystrophy: is the C-terminus important for the function of the protein?

S. Carr, M. Reza, M. Ritso, S. Laval and H. Lochmuller.
John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University
s.carr2@ncl.ac.uk

Background: Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene, which generally disrupt the translational reading frame. In the milder, allelic form of the disease, Becker muscular dystrophy (BMD), the reading frame tends to remain intact. Gene therapy is a promising treatment; however the transcript is too large for packaging into viral vectors. This has led to design of mini- and micro-dystrophins, truncated yet functional versions of the gene based on deletions observed in BMD patients. The C-terminus of dystrophin is thought to anchor neuronal nitric oxide synthase (nNOS) to the sarcolemma via syntrophin. Recent studies have found that nNOS can localise to the sarcolemma in the absence of syntrophin, allowing the C-terminus to be removed from mini- and micro-dystrophins.
Aims: To ascertain whether the C-terminus is necessary for nNOS sarcolemmal localisation. Whether maintenance of the C-terminus confers therapeutic benefit.
Methods: Mdx mouse muscle was electroporated using mini-dystrophins with and without the C-terminus. Lentivirus containing mini-dystrophin or green fluorescent protein (GFP) was produced and used to transduce primary mdx cardiomyocytes. Area measurements of cells were taken to measure the hypertrophic response.
Results: Immunofluorescence of electroporated mdx muscle sections revealed that nNOS localized to the sarcolemma by mini-dystrophins regardless of whether they maintained the C-terminus. No significant reduction in hypertrophy observed in cells transduced with mini-dystrophin-lentivirus compared with untreated controls. Unexpectedly, a significant increase in hypertrophy was observed in cells transduced with control GFP-containing virus suggesting viral transduction increases hypertrophic response.

Comparison of different mini-dystrophin-containing lentivirus effects on the hypertrophic response of mdx cardiomyocytes revealed that the mini-dystrophin maintaining the entire C-terminus caused a significantly greater reduction in size than the mini-dystrophin completely missing this domain.
Conclusions: This data suggests that the C-terminus of dystrophin may be important in the functioning of the protein and further studies are required to determine the mechanism.

P13

Benefits of utrophin modulation therapy in the *mdx* mouse diaphragm

Simon Guiraud[1], **Huijia Chen**[1], Sarah E. Squire[1], Benjamin Edwards[1], David T. Burns[1], Nandini Shah[1], Arran Babbs[1], Stephen G. Davies*, Graham M. Wynne[2], Angela J. Russell[2¶], David Elsey[≠], Francis.X. Wilson[≠], Jon M. Tinsley[≠], Kay E. Davies[1]
[1]MRC Functional Genomics Unit, [2]Department of Chemistry, ¶Department of Pharmacology, University of Oxford. [≠]Summit Therapeutic plc
huijia.chen@dpag.ox.ac.uk

Background: Duchenne muscular dystrophy (DMD) is a severe muscle degenerative disease caused by genetic mutation in the dystrophin gene resulting in loss of dystrophin function. Affected individuals succumb to heart or respiratory failure by 30 years of age. Currently, there is no effective treatment for DMD and only a limited number of disease modifying drugs are progressing in clinical trials. We have previously demonstrated that the dystrophin-related protein utrophin, a structural and functional autosomal paralogue of dystrophin, can act as an effective surrogate to compensate the loss of dystrophin in *mdx* muscles. In partnership with Summit Therapeutics, we developed SMT C1100, an oral utrophin modulator that reduces dystrophic symptoms in the *mdx* mouse and successfully completed a Phase 1b trial with an excellent safety profile in DMD patients.
Aims and Methods: We are now exploring in the *mdx* mouse, future generations of utrophin modulators from the SMT C1100 series with improved physicochemical properties and a more robust metabolism profile. Unlike skeletal and cardiac muscles, the *mdx* diaphragm exhibits a highly dystrophic pathology and closely mimics the degeneration observed in DMD patients. By using histological and molecular methods, we evaluated and compared the benefits of the new generation of utrophin modulators in the *mdx* diaphragm.
Results: We have identified 2 compounds in the same chemical series as SMTC1100 with improved pharmacokinetics profiles. Daily oral administration of these utrophin modulators show efficient distribution to all skeletal muscles, heart and diaphragm of the *mdx* mouse and reduced muscular dystrophy. In particular, an effective rescue of calcium dysregulation, protection against muscle damage, necrosis and fibrosis were observed in the highly dystrophic *mdx* diaphragm, one of the most severely affected muscles in DMD.
Conclusion: Oral administration of small molecule utrophin modulators prevents muscular dystrophy and holds great promise to treat all DMD patients irrespective of their mutation.

P14

Investigating necroptosis of muscle cells *in vitro*

Benjamin Clarke[1,2], Jennifer Morgan[1,2], Maximilien Bencze[2].
[1]Dubowitz Neuromuscular Centre, Molecular Neurosciences Section, Developmental Neurosciences Programme, Institute of Child Health, University College London, WC1N 1EH and [2]MRC Centre for Neuromuscular Diseases, Queen Square, London, WC1 3BG.
benjamin.clarke.15@ucl.ac.uk

Background: Duchenne Muscular Dystrophy (DMD) is characterised by necrotic cell death of myofibres. This myonecrosis is accompanied by an infiltration of inflammatory cells that contribute to cell death via the release of pro-inflammatory cytokines. The mechanisms involved in necrosis triggered by inflammation remain elusive. A newly discovered mechanism of regulated necrosis, named necroptosis, can be triggered through pro-inflammatory signalling. This mechanism of cell death occurs when caspase

8 is inhibited and is dependent on receptor interacting kinase 1 and 3 (RIPK1/3). Preliminary data from our group suggests that necroptosis occurs in dystrophic muscle *in vivo*. Therefore better understanding of necroptosis in muscle may provide new targets for therapeutic intervention in DMD.
Aims: To determine whether skeletal muscle cells can execute necroptosis *in vitro*.
Methods: C2C12-derived myotubes and myoblasts were treated with a combination of pro-inflammatory cytokines and protein inhibitors. Cells were treated with the inhibitors of cell death, z-VAD.fmk (apoptosis) and Necrostatin-1s (necroptosis). Cell death was measured using CytoTox-Glo/Cell Titer-Glo assays. Levels of RIPK3 were determined by Western Blot and real time PCR.
Results: Cell death was induced in C2C12 myoblasts with TNF-α in the presence of inhibitors of pro-survival signalling. Pan-caspase inhibitor z-VAD.fmk did not significantly rescue dying cells however cell death was rescued by the RIPK1 inhibitor Necrostatin-1s, which is characteristic of necroptosis. Although immunoblotting and real time PCR suggested that myotubes express a significant amount of RIPK3, the same triggers of necroptosis did not induce death in this cell type. Therefore other triggers of necroptosis are currently being tested in myotubes.
Conclusion: C2C12 myoblasts and myotubes both express proteins required for necroptosis, suggesting that muscle cells can undergo this type of cell death. C2C12 myoblasts can elicit necroptosis however further work is required to assess the propensity of C2C12-derived myotubes to experience necroptotic cell death.

P15

Extrapolation of 6-minute walking distance (6MWD) to predict loss of ambulation (LoA) with ataluren and placebo in nonsense-mutation Duchenne muscular dystrophy (nmDMD)

Clayton J[12], Quinlivan R[2,3], Marshall J[4], Maronati M[1], Trifillis P[1], Park S[1], Sniecinski M[1], Souza M[1], Peltz S[1], Luo X, Elfring G[1]
[1] *PTC Therapeutics International Limited, Dublin, Ireland*
[2] *MRC Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, London UK*
[3] *Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, UK*
[4] *MAP BioPharma Limited, Cambridge, UK*
jclayton@ptcbio.com

Background: DMD is a severe, progressive, rare genetic muscle-wasting disease characterised by a rapid decline in physical functioning leading to children being fully wheelchair bound at 12-14 years old. Ataluren is the first licensed therapy for ambulant boys with nmDMD aged 5 and over. Emerging natural history data indicate the optimal window to detect a 48-week treatment effect in 6MWD is with a 300–400m baseline.
Aims: To predict the time to LoA with ataluren and placebo based on extrapolation of observed 6MWD from two randomised, placebo-controlled, double-blind trials: Study 007 and 020 (n=291).
Methods: A simulation model was used to predict the age of LoA in a cohort of patients using the 6MWD as the main parameter. Considering that a baseline 6MWD of 300-400m is the optimum range for demonstrating a treatment effect in 48 weeks, the primary analysis used a linear extrapolation of observed 48-week change in patients to estimate the time to 0m. A secondary analysis of non-linear extrapolation stratified by baseline 6MWD was also used.
Results: Both analyses demonstrated that ataluren could significantly delay time to LoA. Extrapolation of placebo in both analyses gave clinically valid ages at LoA comparable to UK natural history data (Ricotti, 2013). In the primary analysis, mean LoA for ataluren patients was age 25.6 - a LoA delay of 12.2 years. In the secondary analysis, LoA for ataluren patients was age 21.3 when starting at 436m and age 30.3 when starting at 500m (i.e. early treatment), representing delays in LoA of 7.1 and 15.7 years, respectively.
Conclusion: Using a modelling approach, two analyses extrapolating 48-week 6MWD study results showed that ataluren was predicted to delay LoA by 12.2 years on average (range 7.1-15.7 years). This represents a step change in treating nmDMD and demonstrates the importance of early treatment initiation.

P16

Setting up academic international clinical trials in rare diseases: a checklist to anticipate obstacles and facilitate processes

R. Davis[1] M. Guglieri[1], K. Hart[2], E. McColl[1], B. Herr, W. Martens[2], J. Wilkinson[1], M. Eagle[1], W. King[2], M. Brawn[2], M. McDermott[2], R. Tawil[2], D.Hirtz[3], J. Kirschner[4], K. Bushby[1,] R.C. Griggs[2],
[1]Newcastle University , Newcastle upon Tyne – UK; [2]University of Rochester School of Medicine and Dentistry, Rochester, NY, USA; [3]National Institute of Neurological Disorders and Stroke, NIH, USA; [4]University of Freiburg, Freiburg, Germany

FOR DMD is an academic led clinical trial in Duchenne Muscular Dystrophy. The trial was funded by NIH for 5 years (July 2010 to June 2015), anticipating that all sites (40 across USA, Canada, UK, Germany and Italy) would be open to recruitment from July 2011. However, study start-up was significantly delayed and recruitment did not start until January 2013.
The time from first contact to site activation across countries ranged from 6 months to 24 months. Reasons of delay were both global (drug procurement, budgetary constraints) and country specific (complexity and diversity of regulatory processes, contracting).
The push for new treatments in rare disease is being hindered by several factors, the divergent landscape of international clinical trial regulations one of them. Based on the FOR DMD experience, we have devised a checklist of steps to anticipate and minimize delays in academic international trial initiation but also identify obstacles that will require a concerted effort on the part of many stakeholders to mitigate.

P17

Cerebral diffusion weighted magnetic resonance spectroscopy suggests membrane damage or structural deficits in neuronal and glial cells in Duchenne muscular dystrophy patients

N. Doorenweerd[1,2,3,4], E. Ercan[1,3], M.T. Hooijmans[1], J. Burakiewicz[1], K.G. Hollingsworth[5], V. Straub[2], A. Webb[1], J.G.M. Hendriksen[6,7], J.J.G.M. Verschuuren[4], E.H. Niks[4], H.E. Kan[1,3], I. Ronen[1,3]
[1]Department of Radiology, C.J. Gorter Center for High Field MRI, Leiden University Medical Center, Leiden, The Netherlands
[2]John Walton Muscular Dystrophy Research Centre, International Centre for Life, Newcastle University, Newcastle upon Tyne, United Kingdom
[3]Leiden Institute for Brain and Cognition, Leiden, The Netherlands
[4]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands
[5]Newcastle Magnetic Resonance Centre, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, United Kingdom
[6]Department of Neurological Learning Disabilities, Kempenhaeghe Epilepsy Center, Heeze, The Netherlands
[7]Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands

Background: DMD is associated with learning disabilities and neurodevelopmental disorders in addition to progressive muscle weakness. Dystrophin is expressed in neuronal, glia and endothelial cells in which its function is unclear. Cerebral diffusion tensor imaging previously indicated microstructural alterations with increased water apparent diffusion coefficient (ADC) and reduced fractional anisotropy throughout the white matter. However, diffusion of water in biological tissues is non-specific, occurring inside, outside, and through cellular structures.
Aim: Determine the ADCs of cell-type specific brain metabolites using diffusion weighted spectroscopy (DWS).
Methods: DWS and T1-weighted MR scans were obtained in ten patients with DMD (mean age 16.2, range 10-22 years) and six age-matched controls. The DWS spectra were zero-order phased, eddy current and frequency shift corrected and quantified using LCModel with a simulated basis set to compute the ADCs of N-acetylaspartate (exclusively neuronal), creatine (ubiquitous) and choline (predominantly glial). Variances were assessed using an F-test and an unpaired t-test was used to assess differences in ADCs ($p<0.05$).

Results: ADCs of tNAA and Cho were significantly higher (p=0.036 and p=0.026 respectively) and tCr higher (p=0.054) in DMD patients. Variance was significantly higher in tNAA ADC in DMD patients (p=0.029).
Conclusion: Our results suggest that metabolite ADC increases are non-cell-type specific. Combined with earlier results of increased ADC of water this may indicate leaky membranes which allow exchange with the extracellular space, similar to that seen in muscle cells in DMD patients. Alternatively, there may be structural deficits, such as changes to mitochondria or the cytoskeleton, within the cells that are non-specific.

P18

Combining iPS cells and human artificial chromosomes for a genomic integration-free stem cell gene therapy of Duchenne muscular dystrophy

Giulia Ferrari[1], Hidetoshi Hoshiya[1], Martina Ragazzi[1] Tamara Casteels[1,#], Sara M. Maffioletti[1], Yasuhiro Kazuki[2], Francesco Muntoni[3], Mitsuo Oshimura[2], Francesco Saverio Tedesco[1]
[1]Department of Cell and Developmental Biology, University College London, WC1E 6DE London, United Kingdom.
[2]Department of Biomedical Science, Tottori University, 603-8503 Yonago, Japan.
[3]Developmental Neuroscience Programme, UCL Institute of Child Health and Great Ormond Street Hospital for Children, London WC1N 1EH, United Kingdom.
[#]Current address: Research Center for Molecular Medicine of the Austrian Academy of Sciences 1090 Vienna, Austria
f.s.tedesco@ucl.ac.uk

Background: Duchenne muscular dystrophy (DMD) is due to mutations of the X-linked dystrophin gene and primarily affects skeletal muscles, resulting in disability and premature death. The limited availability of large number of cells and the large size of the dystrophin gene (2.4Mb), represent substantial obstacles in the development of therapies for this incurable disease. Our promising gene and cell therapy approach combines human artificial chromosome (HAC)-based gene correction and iPS cell-mediated production of transplantable myogenic cells. Although these technologies have been successfully pioneered in our laboratory, safer strategies to translate them into future clinical protocols still need to be developed.
Aims: This study aims at generating safe, transplantable DMD iPS cell-derived myogenic cells genetically corrected with HACs containing the entire human dystrophin genetic locus.
Methods: DMD iPS cells have been generated with non-integrating strategies, including Sendai viruses and mRNAs. The genomic integration-free iPS cells are then differentiated into expandable and inducible myogenic cells using the myogenesis regulators MyoD.
Results: We generated and characterized three DMD iPS cell lines, one of them already genetically corrected with HAC. We then derived myogenic cells similar to skeletal muscle pericyte-derived mesoangioblasts, therefore showing the feasibility of our strategy. A novel HAC capable to induce MyoD-mediated differentiation without genomic integration was also developed.
Conclusion: The generation of HAC-corrected, DMD iPS cell-derived myogenic cells establish the basis for further pre-clinical studies exploring a new, safer genomic integration-free approach for ex vivo gene therapy of DMD.

P19

Cannabidiol increases oxidative and angiogenic potential in C2C12 myoblasts

Helen Foster, Wouter Eilers, Dammy Pinheiro-Fadeyi, Alistair Nunn & Keith Foster
University of Reading, Whiteknights, Reading, RG6 4UR, UK

Background: Progressive dysregulation of calcium (Ca^{2+}) homeostasis in DMD is an important factor the progression of muscle pathology. Calcium dysregulation impacts on mitochondrial function and reactive oxygen species (ROS) precipitating further cellular stresses and promoting a pro-inflammatory environment. Promoting an oxidative muscle phenotype enhances Ca^{2+} handling through an increase in

mitochondrial number and improves dystrophic muscle pathology. Cannabidiol (CBD) a non-psychoactive component of *Cannabis sativa* has been shown to be a powerful anti-oxidant, anti-inflammatory and promotes mitochondrial biogenesis which gives it the potential to be an effective candidate drug in the treatment of DMD.
Aims: Investigate the effect of CBD on C2C12 myoblasts to assess the potential of CBD as a novel treatment for DMD
Methods: C2C12 myoblasts were cultured in DMEM, 10% FCS, supplemented with 1, 5 or 25mM glucose. Metabolic activity of the cells was assessed by an MTS assay. Mitochondrial structure was visualized using MitoTracker Deep Red at 100x by confocal microscopy. Standard quantitative RT-PCR was performed within MIQE guidelines to assess gene expression profiles.
Results: CBD induces a biphasic metabolic response in C2C12 myoblasts. The glucose concentration in the culture media affects the CBD dose at which a peak increase in metabolic activity is observed. The observed increase in metabolic activity is not associated with an increase in cell number. CBD significantly induces the expression of mitochondrial transcription factor A and the mitochondrially encoded NADH dehydrogenase. CBD also significantly upregulates the Sirtuin1-PGC1a pro-oxidative pathway and the angiogenic factor VEGF-165. Of relevance to DMD, CBD also significantly promotes expression of gene involved in autophagy and protein stabilisation.
Conclusions: CBD shows great potential for inducing an oxidative phenotype in dystrophic muscle. In conjunction with CBD's known anti-inflammatory and anti-oxidant properties CBD is a novel candidate for the treatment of DMD. Studies are currently ongoing in the mdx mouse model of DMD.

P20

Development of a Prognostic Model for 1-year Change in 6-Minute Walk Distance (6MWD) in Patients with Duchenne Muscular Dystrophy (DMD)

Nathalie Goemans, James Signorovitch[2,3], Elyse Swallow[2], Jinlin Song[2], Susan J. Ward[3]
[1] *University Hospitals Leuven, Child Neurology, Leuven, Belgium*
[2]*Analysis Group, Inc., 111 Huntington Ave, 14th floor, Boston, MA USA*
[3]*The TAP Collaboration, One Broadway, 14th floor, Cambridge, MA, USA*
Nathalie.goemans@uzleuven.be

Background: Disease progression is inherently heterogeneous among individuals with DMD. The resulting variation in outcome measures can complicate clinical trial design and potentially cloud interpretation of results.
Aim: To develop a prognostic model for 1-year change in 6MWD among DMD patients, and to assess the additional predictive value of the model compared to commonly used factors (i.e., age, baseline 6MWD and steroid use).
Methods: Natural history data were collected from DMD patients at routine follow up visits approximately every 6 months over the course of 2 to 5 years. Patient demographics, treatment experience and ambulatory outcomes were recorded at each visit. Annualized changes in 6MWD were studied between all pairs of visits separated by ~1 year (8-16 months). Prediction models were developed using multivariable regression for repeated measures, and were evaluated using cross-validation.
Results: A total of n=171 ~1-year follow-up intervals from n=37 boys were included. Mean age was 9.4 years and mean 6MWD was 350.7 meters at the start of these intervals; 86% had received steroids. During the subsequent ~1-year, mean annualized change in 6MWD was -37.7 meters with a standard deviation (SD) of 95.9 meters. Predictions based on age, baseline 6MWD and steroid use explained 26% of variation in annualized 6MWD changes (R-squared = 0.26, residual SD=82.2 meters). A broadened prognostic model, adding timed 10-meter walk/run, 4-stair climb and rise from supine, as well as height and weight, significantly improved prediction, explaining 61% of variation in annualized 6MWD changes after cross-validation (R-squared=0.61, residual SD=59.6 meters).
Conclusion: A prognostic model incorporating timed function tests significantly improved prediction of 1-year changes in 6MWD. Explained variation was more than doubled compared to predictions based only

on age, baseline 6MWD and steroid use, indicating significant potential for broader prognostic models to inform clinical trial design and interpretation in DMD.

P21

Reference values for the three-minute walk test, North Star Ambulatory Assessment and timed tests in typically developing boys aged 2.5-5 years

Klingels, K.[1-2] ; Van Verdegem, L.[1] ; vanden Hauwe, M.[3] ; Buyse, G.[3] ; Goemans, N.[3]
[1] *KU Leuven, Department of Rehabilitation Sciences, Leuven, Belgium;*
[2] *REVAL Rehabilitation Research Center, BIOMED, Faculty of Medicine and Life Sciences, Hasselt University, Diepenbeek, Belgium.*
[3] *University Hospitals Leuven, Child Neurology, Leuven, Belgium*
Nathalie.goemans@uzleuven.be

Background: The 6-minute walk test is used to evaluate functional capacity in ambulant boys with Duchenne muscular dystrophy (DMD) and accepted as primary endpoint in registration-directed therapeutic studies. The feasibility of this test may be tackled by short attention span or developmental delay in younger children. Therefore, a shorter 3-minute walk test (3MWT) may potentially be a useful tool for assessing functional capacity in this age group.
Aims: 1) To generate reference values for the 3MWT, North Star Ambulatory Assessment (NSAA) and timed tests in typically developing boys aged between 2 years 6 months and 5 years
2) To describe the relation between the functional tests and anthropometric variables.
Methods: A total of 114 typically developing boys (mean 4 years 2 months) were recruited across four age subcategories (2.5-<3 years; 3-<4 years; 4-<5 years; 5-<6 years).
Results: The 3MWT was feasible for all participants, although more encouragements were needed to keep the attention of the very young ones. The three-minute walk distance (3MWD) increased significantly with age, from 160.4m ± 18.8m at 2.5 years to 209.7m ± 19.1m at 5 years. Median score (interquartile range, IQR) on the NSAA increased with age from 25 (23-27) at 2.5 years to 33 (33-34) at 5 years. For the timed tests (Gower's test, 10 m run and climb and descend four stairs), median values (IQR) for the total group were 2.6 (2.2-3.3), 4.1 (3.7-4.7), 2.3 (1.9-3.0) and 2.6 (2.1-3.7) respectively. The correlation coefficient between 3MWT and NSAA was 0.57 and high correlations were found between all timed tests. Correlations with age, height and weight varied between 0.56 and 0.79.
Conclusion: These reference values of the 3MWT, NSAA and timed tests according to age and height provide a useful tool to assess functional capacity in boys aged 2 years 6 months to 5 years.

P22

Development of a patient-reported outcome measure for upper body function in Duchenne Muscular Dystrophy (Upper body PROM)

Klingels K[*1,] Mayhew AG[*2,] Mazzone ES[3], Eagle M[2], Duong T[4], Ricotti V[5], Main M[5], Van den Hauwe M[6], Decostre V[7], Campion G[8], Werlauff U[9], De Groot I[10], Vroom E[11], Mercuri E[2,] **Goemans NM**[6]
on behalf of the Clinical Outcome group
[1]*KU Leuven, Department of Rehabilitation Sciences, Leuven, Belgium ;* [2]*Institute of Genetic Medicine, Newcastle Upon Tyne, UK;* [3]*Department of Paediatric Neurology, Catholic University, Rome, Italy,* [4]*Stanford University School of Medicine, Department of Neurology, Stanford, US;* [5]*Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London, UK;* [6]*University Hospitals Leuven, Department of Child Neurology, Leuven, Belgium;* [7]*Institut de Myologie, GH Pitié Salpetrière, Paris, France;* [8]*BioMarin, Leiden, The Netherlands;* [9]*The Danish National Rehabilitation Center for Neuromuscular Diseases, Aarhus , Denmark;* [10]*Radboud University Medical Centre, Nijmegen, The Netherlands;* [11]*Duchenne Parent Project, Veenendaal, The Netherlands. * both first authors*
Nathalie.goemans@uzleuven.be

Background: A multidisciplinary international Clinical Outcomes group consisting of clinicians, scientists, industries, patients and their advocacy groups designed the Performance of Upper Limb module (PUL) for

Duchenne Muscular Dystrophy (DMD), according to a contextual framework of upper limb function in both ambulant and non-ambulant individuals with DMD. This group also identified the need to develop in parallel a patient-reported outcome measure (PROM) to evaluate upper body function related to activities of daily living (ADL) that cannot be observed in a clinical setting.
Aims: To develop a questionnaire to assess upper body function in ADL specifically for patients with DMD across a wide age range and applicable in the different stages of the disease.
Methods: The developmental process included item generation from a systematic review of existing tools and expert opinion. Individuals with DMD were involved throughout the iterative process by offering their opinion on task difficulty and relevance. Also, cultural aspects affecting ADL were taken into consideration to make this tool applicable to the broad DMD community. Items were selected in relation to the different levels of the PUL from proximal to distal performance in order to cover the full range of upper body function across different domains of ADL.
Results: After pilot testing followed by iterative Rasch analyses redundant or clinically irrelevant items were removed. The final questionnaire consists of 32 items covering four domains of ADL (Food, Self-care, Household and environment, Leisure and communication) and is recommended for use in boys from 7 years of age. Test-retest reliability was excellent.
Conclusion: The Upper Body PROM was developed taken into account guidelines published by the US Food and Drug Administration, and applied modern psychometric methods. The main purpose is to be used for description of Natural History in DMD and to assess the efficacy of interventions.

P23

Antisense Targeting of mRNA 3'UTR to Moderate Myostatin (GDF8) Expression for the Treatment of Myopathies

Golnoush Golshirazi, George Dickson, Linda Popplewell
Centre of Biological Sciences, School of Biological Sciences, Royal Holloway University of London, Egham surrey, TW20 0EX
Golnoush.Golshirazi.2014@live.rhul.ac.uk

Background: Genetic deletion of Myostatin (*Mstn*), a member of the Transforming Growth factor-**β** family of signaling molecules**,** leads to the excessive growth of skeletal muscle, indicating that myostatin is a negative regulator of muscle mass. This led to the proposal that stimulating muscle growth in individuals with myopathies by myostatin reduction or blockade could potentially ameliorate symptoms without having to correct the primary cause of the disease itself. Furthermore, it has been shown that the inhibition of myostatin activity leads to improved muscle pathology, as well as function, in disease models. Myostatin is therefore implicated as a target for therapeutic strategies.
Aim: Evaluation of antisense phosphorodiamidate morpholino oligomers (PMOs) to target the 3' UTR of *Mstn* we aim to decrease myostatin expression, which would be applicable in patients with a variety of myopathies.
Methods: PMOs were designed following bioinformatics analysis of the *Mstn mRNA* 3'UTR in the human and mouse. In-vitro transfection of RD114 rhabdomyosarcoma cells with PMOs targeting the 3'UTR were carried out, followed by quantification of *Mstn* mRNA using real-time PCR. Off target effects of chosen PMO was assessed using BLASTN analysis.
Results: Our designed PMOs all showed significant decrease in Myostatin expression at various concentrations. No significant off target effects of PMOs were found in BLASTN analysis.
Conclusion: The work presented so far shows successful in-vitro knockdown of *Mstn,* and highlights the potential of targeting specific elements in the 3'UTR of genes for therapeutic purposes. This work is of potential significance in the treatment of patients with a wide range of myopathies including Duchenne muscular dystrophy.

P24

Second generation utrophin modulator for the therapy of Duchenne muscular dystrophy

Simon Guiraud[1], Sarah E. Squire[1], Benjamin Edwards[1], Huijia Chen[1], David T. Burns[1], Nandini Shah[1], Arran Babbs[1], Stephen G. Davies[2], Graham M. Wynne[2], Angela J. Russell[2¶], David Elsey[3], Francis. X. Wilson[3], Jon M. Tinsley[3], Kay E. Davies[1]
[1]MRC Functional Genomics Unit, [2]Department of Chemistry, ¶Department of Pharmacology, University of Oxford. [3]Summit Therapeutics plc
simon.guiraud@dpag.ox.ac.uk

Background: Duchenne muscular dystrophy (DMD) is a devastating, X-linked muscle-wasting disease caused by lack of the cytoskeletal protein dystrophin. There is currently no cure for DMD although various promising approaches (e.g. stop codon readthrough, exon skipping, gene therapy) are progressing through human clinical trials. In partnership with Summit Therapeutics, we previously developed SMT C1100, an oral small molecule utrophin modulator that reduces dystrophic symptoms in the *mdx* mouse and successfully completed a Phase 1b trial with an excellent safety profile in DMD patients. Second generation compounds is currently in development. These compounds illustrated by SMT022357 and structurally related to SMT C1100, present favourable chemical physical properties and a more robust metabolism profile.
Aims: By pharmacologically modulating the dystrophin-related protein utrophin, we aim to develop a therapy applicable to all DMD patients, regardless of the underlying genetic fault in the dystrophin gene, by targeting the primary defect and restoring sarcolemmal stability in all skeletal muscles including the diaphragm and in the heart.
Methods: After 5 weeks of daily oral treatment with SMT022357, potential benefits in skeletal, respiratory and cardiac muscles of 7 weeks old *mdx* mice were assessed using histological, molecular and physiological analysis.
Results: Pre-clinical *in vivo* studies in the *mdx* mouse demonstrate that daily oral administration of the second generation compound SMT022357 increases utrophin expression in target muscle groups, including the diaphragm and heart. This results in improved sarcolemmal stability and prevents dystrophic pathology through a significant reduction of regeneration, necrosis and fibrosis with no change in fibre type composition. These improvements combine to provide functional enhancement and protection of muscle from contraction induced damage.
Conclusions: The use of small molecules to increase utrophin expression in skeletal, respiratory and cardiac muscles emphasises the potential of utrophin modulation as a disease-modifying therapeutic strategy for all DMD patients, irrespective of their mutation in dystrophin.

P25
The Sensitivity of the diffusion-weighted MRI signal decay curve to microstructural changes due to Duchenne Muscular Dystrophy
Matt G Hall and Chris A Clark
Institute of Child Health, University College London, 30 Guilford St, London WC1N 1EH

Background: Duchenne Muscular Dystrophy is a muscle-wasting disorder affecting approximately 1 in 3600 boys worldwide. Progression of the disease can be difficult to quantify due to a lack of image-based biomarkers. Diffusion MRI is known to be a probe of microstructural change, but it is not clear *a priori* how sensitive it is to the changes associated with DMD.
Aims: We investigate the sensitivity of diffusion-weighted MRI to microstructural changes caused by DMD *in silico*. We synthesise diffusion-weighted measurements over a wide range of scan parameters for healthy tissue and in environments exhibiting pathological changes. Differences between the resulting curves are quantified using entropy, which provides a model-free measure of curve complexity. We compare changes from microstructure to changes due to noise alone.
Methods: Diffusion is simulated in an environment containing parallel cylinders which contain other, smaller cylinders. Cylinder sizes are drawn from distributions observed from histology of healthy mouse muscle and from an mdx disease model.

We simulate a baseline healthy substrate and several microstructural scenarios based on DMD pathology: (a) internal cylinders are reduced in size (b) cylinder walls made permeable and (c) outer cylinder radius distribution parameters changed to those observed in a mouse model of DMD pathology.
We synthesise diffusion-weighted measurements over a range of acquisition parameters and report the percentage change in entropy between the baseline and microstructural scenarios.
Results: Permeability causes the largest entropy change (60-80%), atrophy is also important (30-40%), with fibre distribution changes causing 4-5% entropy change. Rician noise alone (SNR=20) leads to a 0.2-0.8% change.
Conclusions: The diffusion weighted signal is sensitive to pathological changes in DMD, although in some cases the changes are subtle and require multiple acquisitions. Signal analysis is also challenging since conventional techniques, such as DTI, struggle to capture the form of variation in the curves.

P26

Fractional diffusion as a probe of microstructural change in a mouse model of Duchenne Muscular Dystrophy

Matt G Hall[1], Paola Porcari[2], Andrew Blamire[2], and Chris A Clark[1]
[1]*Institute of Child Health, University College London, London, UK*
[2]*Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle, UK*

Background & Aims: Duchenne Muscular Dystrophy (DMD) is a genetic muscle-wasting disorder affecting 1 in 3600 boys worldwide categorised by progressive degeneration of muscle tissue. Diffusion-weighted MRI is known to be sensitive to microstructural changes in tissue, but analysis of the data can be challenging.
Muscle tissue is hierarchical, and hence Fractional diffusion models are good candidates for image analysis. We apply this model to preclinical DWI data of mouse models of DMD and compare the results to histology. We find that parameters of the fractional diffusion model are sensitive to microstructural changes associated with DMD.
Methods: *Imaging:* Using a diffusion-weighted STEAM sequence on a 7T Varian scanner, we acquire images at six diffusion times and four different gradient strengths per diffusion time. TE/TR=4000/20ms, d=3ms. Muscle fibres align with the slice select direction, diffusion gradients, applied perpendicular to fibres.
Histology: The Gatrocnemius muscle was carefully removed from the left hindlimb of each mouse, mounted, frozen, and stained. Feret's diameter was measured using Image-J.
Modelling: We fit a three parameter Mittag-Leffler function using a Levenberg-Marquardt algorithm. Parameters represent a diffusivity, and two exponents related to the spatial and temporal properties of the diffusion process in the tissue. The properties are all sensitive to the microstructural environment experience by spins.
Results: Exponent images show localised darkening in mdx models which are not observed in wildtype. Histograms of parameter values from the central region of the Gastrocnemius show a similar shift to that observed in fibre radius histograms observed from histology.
Conclusions: Darkening in the exponent maps is present in both Mdx mice and not in either wildtype. Histology shows a change in tissue microstructure which supports the idea that the model used is sensitive to the microstructural changes caused by pathology. This suggests that darkened regions may be associated with disease regions.

P27

NHE1 inhibition as a potential therapy to attenuate DMD pathology

Persefoni Ioannou[1], Umar Burki[1], Elizabeth Greally[1], Steven Laval[1], Stefan Schaefer[2] and Volker Straub[1]
[1]*John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine*
Newcastle University, Newcastle Upon Tyne, UK; [2]*Peacock Pharma GmbH, Goch, Germany*

The absence of dystrophin in Duchenne Muscular Dystrophy (DMD) muscle cells results in increased membrane permeability and subsequent intracellular calcium overload. The dysregulation of calcium homeostasis that characterizes the DMD models is exacerbated by the increased activity of the Sodium/Hydrogen Exchanger 1 (NHE1). NHE1 overactivity leads to an increased influx of sodium, which in turn switches the Sodium/Calcium Exchanger (NCX) into reverse mode, resulting in an increased calcium influx. Selective NHE1 inhibitors can be used to reduce the sodium influx and thereby revert the NCX to normal mode with a subsequent decrease in the cellular calcium load. This observation has led to the hypothesis that the use of specific NHE1 inhibitors could improve the calcium homeostasis and alleviate pathology in DMD muscle.
The current study seeks to demonstrate the efficacy of a specific NHE1 inhibitor that has a good safety and potency profile in several pre-clinical studies. In order for the efficacy of the drug to be determined, eleven *mdx* mice were treated chronically via drug in chow. The calcium dynamics in both skeletal and cardiac muscles were studied using manganese enhanced molecular resonance imaging (MEMRI). At the end of the treatment the mice were sacrificed and tissues were harvested for histological analysis. Interestingly, four limb functional grip strength tests that were carried out throughout the treatment demonstrated a significant increase of the grip strength of the drug-treated mice in comparison to the vehicle-treated ones. The study will be supplemented with *in vitro* pH, sodium and calcium assays that will be used to verify the drug action.
The proposed studies with a first prototype NHE1 inhibitor are an important step towards potential clinical trials for dystrophinopathies with this class of compounds.

P28

Cardiac Magnetic Resonance Imaging (MRI): cross-sectional study of 20 Myotonic Dystrophy type-1 patients soon to start an exercise program

A.C. Jimenez-Moreno*, S. Cassidy**,DG. Jakovjevic**, H. Lochmüller*, G. Gorman**, and the OPTIMISTIC Consortium***
** The John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle UK.*
*** MoveLab Research Centre, Newcastle University, Newcastle UK*
****European Consortium of the OPTIMISTIC trial in Myotonic Dytrophy Type 1, van Engelen et al. 2015.*

Background: Cardiac MRI has shown to be a promising screening method to reveal early cardiac involvement in different neuromuscular diseases, including concentric hypertrophic remodeling and sub-endocardial dysfunction, even when standard cardiac evaluation (ECG and echocardiography) have shown normal results. A better understanding of any clinical variability in the myocardium of patients with myotonic dystrophy type 1 (DM1) requires a correlation of cardiac anthropometric results with any possible modifying clinical characteristics of the patient. This understanding would also benefit cardiac screening strategies, that are, to date, unclear.
Aims and Methods: To elucidate whether myocardial abnormalities could be identified in Myotonic Dystrophy type 1(DM1) patients without overt clinical cardiac involvement. A cohort of patients with genetically determined DM1 and high levels of perceived, were recruited from UK's OPTIMISTIC main-study sample population.
Results: 22 patients (only 5 females) have been scanned for baseline and half of these have proceeded to follow-up (at the time of the abstract). The sample has a 3:1 men-to women ratio, a mean age (SD) of 45 (14) and a mean time of active disease recalled of 17 (14) years. All patients have had an ECG within 12 months of study commencement and all demonstrated normal sinus rhythm; only one male patient reports to be taking cardiac medication at baseline. 13 of these (3 females) have been randomized to the active group that implies and increased level of physical activity as part of the therapy provided and in those that agreed to join a gym, proper exercising. Baseline cardiac parameters will be presented comparing both groups and relevant historical data.
Conclusions: Cardiac screening in DM1 patients has proven logistically difficult in the past; however, cardiac MRI appears to be a promising tool to measure cardiac functionality performance and disease progression over time.

P29

Eteplirsen, a Phosphorodiamidate Morpholino Oligomer (PMO) for Duchenne Muscular Dystrophy (DMD): Clinical Update and Longitudinal Comparison to External Controls on Six-Minute Walk Test (6MWT)

JR Mendell[1], N Goemans[2], L Rodino-Klapac[1], Z Sahenk[1], LP Lowes[1], LN Alfano[1], K Berry[1], E Peterson[1], S Lewis[1], K Shontz[1], J Shao[3], P Duda[3], C Donoghue[3], F Schnell[3], J Dworzak[3], B Wentworth[3], **EM Kaye[3]**, E Mercuri[4], DMD Italian Network[5]

[1]Nationwide Children's Hospital, Columbus, OH; [2]University Hospitals, Leuven, Belgium; [3]Sarepta Therapeutics, Inc., Cambridge, MA 02142; [4]Università Cattolica Rome, Italy; [5]Fondazione Telethon DMD Italian Network

Objective: DMD, a rare, degenerative, X-linked genetic disease results in progressive muscle loss and premature death, occurring in 1:3500-5000 males worldwide. DMD is primarily caused by frameshift-causing whole-exon mRNA deletions that prevent production of dystrophin protein. Eteplirsen, a PMO, is designed to induce production of internally-shortened dystrophin in patients amenable to exon 51-skipping.

Methods: In a 24-week double-blind placebo-controlled study, 12 boys aged 7-13 years were randomized to weekly intravenous infusions of 30/50 mg/kg eteplirsen or placebo, rolling-over to an ongoing open-label extension study (1:1 30/50 mg/kg). Clinical outcome measures included 6MWT and dystrophin expression. Routine safety assessments and cardiac monitoring were conducted.

External control (EC) data were obtained from the DMD Italian Network and the Leuven Neuromuscular Research Center. A cohort (N=13) comparable to the eteplirsen-treated boys was defined based on age at baseline, corticosteroid use, and genotype. 3 year longitudinal data were used for comparative analysis of 6MWT performance.

Results: At Year 3, a statistically significant treatment benefit of 151 meters on 6MWT was observed in eteplirsen-treated patients compared with EC ($p<0.01$). 2/12 (16.6%) eteplirsen patients lost ambulation by Year 1 with no additional losses observed, compared with 6/13 (46%) EC at Year 3.

Muscle biopsy analysis demonstrated exon 51-skipping in consented eteplirsen-treated patients (N=11) by RT-PCR and statistically significant increases ($p<0.001$) of dystrophin intensity and % dystrophin-positive fibers by immunohistochemistry over untreated DMD controls (N=9). Western blot confirmed dystrophin production in 9/11 patients.

No deaths, discontinuations due to AEs, or treatment-related SAEs were reported. LVEF on ECHO was stable over 3 years. AEs were generally mild and unrelated to study-drug.

Conclusions: After 3 years of eteplirsen-treatment, DMD patients had a mean 6MWT 151m longer ($p<0.01$) than that in the comparable external cohort. Correct mRNA and de novo dystrophin were detected using 3 complementary methods in nearly all eteplirsen treated patients.

P30

Isogenic human induced pluripotent stem cell based models for studying FKRP-deficient muscular dystrophy

Beatrice Lana[1], David Ryan[2], Evangelos Konstantinidis[1], Francesco Muntoni[3], Yung-Yao Lin[1]

[1]Blizard Institute, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK

[2]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, UK

[3]UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK

yy.lin@qmul.ac.uk

Background: Our research focuses on the study of allelic mutations in the putative glycosyltransferase *FKRP* gene, which cause a wide range of muscular dystrophy (MD). The most severe forms are characterized by an early onset of the MD phenotype associated with central nervous system (CNS) defects, but little is known about the molecular and cellular mechanisms underlying the CNS involvement.

Induced pluripotent stem cells (iPSC) can be differentiated to neurons for studying the CNS involvement. However, a major challenge of working with iPSC is the lack of an appropriate isogenic control, which minimizes the variability between different genetic backgrounds.
Aims: To address this problem, we aim to generate isogenic pairs of patient-specific and wildtype iPSC and use them as cell models to study the CNS involvement in FKRP-deficient MD.
Methods: We combined CRISPR/Cas9 technology (programmable RNA-guided DNA nuclease) with *piggy*Bac selection cassette. This approach allowed us to perform targeted gene correction in patient-specific iPSC and targeted gene mutation in wildtype iPSC. We then differentiated each isogenic pairs into neural stem cells.
Results: Upon CRISPR/Cas9-mediated homologous recombination, a targeting donor vector with the corrected or mutated sequence was successfully integrated into the genomic DNA of patient-specific or wildtype iPSC, respectively. The selection cassette was subsequently removed. PCR based genotyping and sequencing confirmed the achievement of a clean and biallelic targeted gene correction or mutation of FKRP.
Conclusion: We show that CRISPR/Cas9 mediated genome editing in combination with *piggy*Bac technology allow precise modification of the mammalian genome at single base-pair levels. Our protocol allows rapid and efficient genome editing in any desired genomic location without leaving footprints. These isogenic pairs can be differentiated into specific cell lineages and used for cell disease modelling. In the future, the isogenic iPSC MD models will be exploited for genetic and molecular screens aiming to identify therapeutic targets.

P31

Audit of DEXA scan surveillance in Duchenne muscular dystrophy

R Manuel[1], N Emery[1], H Unsworth[1], T Willis[1]
[1]*Robert Jones and Agnes Hunt hospital NHS trust, Oswestry*

Background: In Duchenne muscular dystrophy (DMD) glucocorticoids slows the decline of muscle strength and function. However, glucocorticoids have many side effects including bone demineralisation and increased risk of fractures. Bushby et al (Lancet Neurology, 2010) proposed a set of recommendations for the care and management of boys with DMD including close monitoring of bone mineral density. These were adopted by National Institute for Clinical Excellence in September 2011. This requires DEXA scan at age 3+ or within 6 months of commencing Glucocorticoid therapy and repeat DEXA scan annually.
Aim: Compare surveillance of bone mineral density in patients with DMD taking Glucocorticoids against the recommended standards.
Methods: Genetically confirmed DMD patients on glucocorticoid therapy were divided into pre-NICE guideline group and post-NICE guideline group. Age at diagnosis, age at commencing glucocorticoids, time intervals between commencement of glucocorticoids and initial scan, interval between subsequent follow up DEXA scans, fracture data were collected. The groups were sub-divided into fracture group and non-fracture group.
Results: In the pre-NICE guideline non fracture group (7) 57% of patients had the initial scan within 6 months of starting Glucocorticoids while in the fracture group (9) 82% of patients had this scan. In this non-fracture group 40% had the follow up scans in the recommended time frame (median 12.5months [12.5-23.5]) while in the fractured group no patients had all scans within the recommended time frames (median 17 months [14-23.5].
In the post-NICE guideline group (4) there is 100% adherence to the nice guideline. So far, no one sustained fracture in this group.
Conclusion: Our data suggests that adherence to the DEXA scan surveillance enable timely preventive treatment for fractures in DMD patients, although longer follow up in a larger group is needed to validate the findings.

P32

The application of allele-specific silencing therapeutic approach by antisense oligonucleotide in COL6A-related congenital muscular dystrophy

Elena Marrosu, Francesco Muntoni and Haiyan Zhou
Dubowitz Neuromuscular Centre, Molecular Neurosciences Section, Developmental Neurosciences Programme, Institute of Child Health, University College London, WC1N 1EH, UK.
elena.marrosu@ucl.ac.uk

Background: Allele-specific silencing by antisense oligonucleotide (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. The severe collagen VI-related congenital muscular dystrophy (CMD) variant, known as Ullrich CMD (UCMD), is caused by mutations in one of the three collagen 6 genes (*COL6A1, COL6A2 and COL6A3*). The fact that 50% of UCMD are caused by *de-novo* dominant mutations, and haploinsufficiency is not associated with clinical phenotypes in collagen 6 genes, provides the theoretical basis of using AON to selectively silence the mutant allele as a therapeutic strategy.
Aims: To develop a novel AON approach for collagen VI-related UCMD by using RNA-based therapeutic strategies for allele-specific silencing.
Methods and Materials: Skin fibroblast established from UCMD patients carrying dominant mutations in collagen 6 genes are used as cellular model in this study. AONs targeting either the specific mutations or the common SNPs are synthesized using a variety of chemical modifications. Small interfering RNAs (siRNAs) are investigated to compare their efficacy with AONs in selective allelic silencing. The efficiency is measured by PCR, quantitative real-time PCR and Sanger sequencing followed by immunohistochemical staining and flow cytometry of collagen 6 expression in extracellular matrix as functional readout.
Results: Our preliminary data showed AONs with specific backbone modifications displayed improved efficiency than ordinary AONs on allele-specific silencing when targeted the specific mutations. Further optimal designs are still required to reduce potential toxicity and increase specificity.
Conclusion: AONs have shown the potential in selectively silencing the mutant allele in collagen 6 gene *in vitro* in cellular models. Further improvement on the design of AONs to target common SNPs is still required for the wider application of this strategy in the therapy of UCMD.

P33

Heterogeneous progression in Dysferlinopathy: a JAIN COS study update

Ursula Moore, Meredith James, Karen Bettinson, Anna Mayhew, Michelle Eagle, Heather Hilsden, the Jain COS consortium, Kate Bushby
John Walton Neuromuscular Research Centre, Newcastle University

Background: Dysferlinopathy, or LGMD2b, is a disease caused by mutation in the protein Dysferlin. Clinically, mutations cause a wide spectrum of disease. Both distal and proximal phenotypes have been described. Age of presentation varies from congenital to 9th decade. Some patients progress rapidly from symptom onset whilst others remain mildly affected throughout life. This variability presents challenges for understanding the disease and developing clinical trial outcome measures. The JAIN foundation's international longitudinal clinical outcomes study aims to overcome this by collecting observational data from comprehensive assessments of a 203 patients. With year one visits complete, trends in progression are emerging.
Aims: To assess rate and character of progression of muscle symptoms and function over one year. To assess the utility of the current JAIN study protocol to fulfil the study's aims.
Methods: All patients enrolled in the Jain COS study who have completed year 1 visits. Statistical analysis to determine rate of change in physiotherapist assessments (Respiratory, muscle strength, timed tests, motor performance). Assessment of medical questionnaire responses to explore co-morbidities.
Results: Statistically significant decline in motor function is seen overall in the group. Some patients deteriorated more quickly while others remained static or even improved. Ankle swelling was common but no other co-morbidity appeared overrepresented. Medical questionnaires showed patient interest in

information about pregnancy and exercise.
Conclusions: In general, Dysferlinopathy is a progressive condition; however there is wide heterogeneity in the rate of progression. Reasons for this variability can now be explored in additional analysis. Physiotherapy assessments can be refined to include only relevant variables. Medical questionnaires should be adjusted to explore patient experience of exercise and pregnancy.

P34

Can direct reprogramming of adult muscle satellite cells improve current hurdles impeding myoblast transplantation therapies?

Louise A. Moyle[1,*], Mattia F.M. Gerli[1,*,#], Martina Ragazzi[1], Hiroshi Sakai[2], Ekin Ucuncu[1], Chrystalla Constantinou[1], Shahragim Tajbakhsh[2], Giulio Cossu[3] and Francesco Saverio Tedesco[1,⌘]
*[1]Department of Cell and Developmental Biology, University College London, WC1E 6DE London, UK; [2]Department of Developmental & Stem Cell Biology, Institut Pasteur, 75015 Paris, France; [3]Institute of Inflammation and Repair, University of Manchester, M13 9PL Manchester, UK; *These authors contributed equally to this work; [#]Current address: Massachusetts General Hospital, 02114 Boston, MA; ⌘Corresponding author (f.s.tedesco@ucl.ac.uk)*

Satellite cells are responsible for post-natal skeletal muscle regeneration; upon activation they proliferate as transient amplifying myoblasts, most of which fuse into regenerating myofibres. Despite the encouraging outcomes obtained from transplanting myoblasts into dystrophic animals and patients with localised forms of muscular dystrophy, results achieved in clinical trials with more severe forms of muscle diseases, such as Duchenne muscular dystrophy, showed limited efficacy. In addition to satellite cells, pericyte-derived mesoangioblasts can contribute to muscle regeneration and give rise to satellite cells. Crucially, when injected systemically they migrate through the vascular endothelium, circumventing the requirement for local intra-muscular injections. These cells have recently undergone clinical experimentation in a phase I/II first-in-human trial in five Duchenne patients (EudraCT no. 2011-000176-33). We hypothesised that by modulating pericyte specification factors, we might reprogram adult satellite cells into pericyte-like cells. Here we show that exposing adult satellite cells to pericyte lineage specifiers induces skeletal-to-smooth muscle lineage reprogramming. Treated cells acquire perivascular markers and functional properties, such as stabilisation of capillary networks. Importantly, preliminary data shows increased engraftment of reprogrammed cells upon both intramuscular and intra-arterial delivery in dystrophic mice. Interestingly, treated satellite cells also show up-regulation of Pax7, a marker normally found in quiescent satellite cells. Implying that treated cells acquire an intermediate stem cell phenotype between satellite cells and pericytes. These results extend our understanding of smooth/skeletal muscle lineage choice and provide evidence of a druggable pathway with potential clinical relevance, by enabling the systemic delivery of myoblasts to treat muscle diseases.

P35

DMD in Cyprus: Demographics and clinical characteristics

Nikolenko N.[1] [2], Yiangou A.[3], Lochmüller H.[1], Lavranos G.[2]
[1] The John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK.
[2]Open University of Cyprus, Faculty of Economics and Management, Nicosia, Cyprus.
[3]Aintree University Hospital NHS Trust, Mersey, UK.
nikoletta.nikolenko@newcastle.ac.uk

Background: Cyprus has a population of 865,900 and a centralized health system. Over the past years various interventions have been implemented, such as genetic counselling, national neonatal CPK screening program and steroid treatment, in order to reduce the disease incidence and increase the life expectancy of the Duchenne Muscular Dystrophy (DMD) patients.

Aims: The collection of epidemiological data to measure the prevalence and incidence of DMD in Cyprus from 1974-2009. The collection of medical data to provide an efficient selection of patients to clinical trials or therapy.
Methods: Patients suffering from DMD were identified through the Cyprus Muscular Dystrophy Association database. Registry data was collected from patients or their legal representatives following written informed consent. The inclusion criteria included male Cypriot residents with European Union nationality, neurological confirmation of DMD diagnosis.
Results: Since 1974 until today, 41 patients with DMD have been born in Cyprus, of which 41.5% are still alive. The prevalence of DMD in Cyprus for 2012 was approximately 2:100,000 population. The 35-year (1974-2009) incidence of DMD in Cyprus is 1:4,350 male births, with the highest between 1985-1989 (1:2,278) and the lowest between 2005-2009 (1:22,881).
Out of the 12 registered patients in the national DMD registry 58.3% lost their walking ability, 16.7% never took steroid treatment, 41.7% were diagnosed with cardiomyopathy and 50% used mechanical ventilation. The most common deletions (77.8% of the cases) occurred between exons 45-55. The duplications occurred between exons 3-6 and 12-17.
Conclusion: The interventions that have been implemented in the recent years may have helped to increase life expectancy of DMD patients and reduce the incidence of the disease in the population of Cyprus by preventing of having two or more individuals with the same disease in one family. However, the observation period may have been too short and the number of observations not statistically significant.

P36

Evaluation of a panel of new monoclonal antibodies to α-DG

Vicente Pagalday[1], Caroline Sewry[2,3], Glenn Morris [2], Susan C. Brown[1].
[1]Royal Veterinary College, London UK, [2]Wolfson Centre for Inherited Neuromuscular Disease, RJAH Orthopaedic Hospital, Oswestry, UK; [3]Dubowitz Neuromuscular Centre, UCL Institute of Child Health, University College London, London, UK.; Institute for Science and Technology in Medicine, Keele University, Keele, UK
Vicentepagalday@hotmail.com

Background: O-linked glycosylation of the central mucin-rich domain of alpha dystroglycan is key to mediating the binding to laminin, agrin and perlecan in the extracellular matrix. Mutations in up to 18 genes have now been associated with this group and are responsible for a spectrum of clinical phenotypes that range from Walker–Warburg syndrome and Muscle–Eye–Brain disease to milder forms of muscular dystrophy with onset in childhood or adult life. However, there are only limited quantities of antibodies to the core alpha dystroglycan protein and the main antibody used diagnostically is IIH6 which often produces a variable staining pattern that is sometimes difficult to interpret.
Aims: The laboratory of Prof. Glenn Morris has recently generated a new panel of monoclonal antibodies against the core epitope of alpha dystroglycan which we sought to characterise using immunocytochemistry and Western blotting.
Methods or Materials: Antibodies were air dried frozen sections overnight, washed and incubated with biotinylated anti mouse followed by streptavidin conjugated with either Alexa 488 or 594. Muscle samples (quadriceps of wild type mice) were run under native conditions on 3-8% Tris-Acetate gels (Novex). Proteins were blotted for 1hour onto PVDF membrane at 50V. Membranes were immunolabelled with antibody in PBST (phosphate buffered saline with tween) containing 5% milk for 1 hour, then washed and labelled with IgG conjugated with HRP and visualised with ECL.

Results: All monoclonals reacted with frozen mouse tissue and in some cases there was evidence of differences in labelling between individual muscles. Western blotting was successful only when using non denaturing conditions.

Conclusion: These staining protocols and antibodies will now be tested on human muscle biopsies with the aim of determining if different gene defects differentially alter the core alpha dystroglycan protein and establishing robust protocols that may be shared between different diagnostic laboratories.

P37

Generation of a mouse model of FSHD to reveal the DUX4 expression profile and dynamics

Authors: Maryna Panamarova[1], Alexandra Tassin[2], Louise Moyle[1,3], Alexandra Belayew[2], Peter S. Zammit[1]
[1] *Kings College London, London, UK*
[2] *University of Mons, Mons, Belgium*
[3] *University College London, London, UK*

Background: Facioscapulohumeral muscular dystrophy (FSHD) is characterised by a descending, often asymmetric, skeletal muscle atrophy. The genetic basis of the disease is linked to a loss of *D4Z4* macrosatellite repeats in chromosome 4q35. Contraction of the D4Z4 repeats facilitates DNA hypomethylation of the region, causing aberrant expression of the DUX4 retrogene, encoded by each D4Z4 unit. DUX4 expression is thought the primary cause of FSHD.
Aims: We aimed to a generate mouse model of FSHD to reveal the DUX4 expression profile and dynamics, to give insight into FSHD pathomechanisms and provide a platform for testing potential therapeutic strategies.
Methods: We generated a construct *DUX4p-nlacZ-pLAM* with the native human DUX4 promoter and pLAM region flanking a nuclear-localised (n)l*acZ* reporter gene. Using pronuclear injection of the construct, we have created transgenic mouse in which the expression dynamics of the pathogenic locus can be mapped.
Results: We first demonstrated the functionality of *DUX4p-nlacZ-pLAM* construct in cultured proliferating myoblasts and differentiated multinucleated myotubes. *DUX4p-nlacZ-pLAM* transgenic mice have now been generated and initial analysis of the F1 generation reveals rare nuclei containing β-galactosidase in skeletal muscle. We are now establishing multiple lines of *DUX4p-nlacZ-pLAM* mice and hope to report their further analysis at the meeting.
Conclusion: Through generating a transgenic mouse line that carries a native human configuration of DUX4 promoter and pLAM region, we aim to create an animal model that could be used for mapping the expression profile and dynamics of DUX4.

P38

Developing novel human isogenic cellular models for Duchenne muscular dystrophy

Amaia Paredes-Redondo[1], Yung-Yao Lin[1].
[1]*Blizard Institute, Queen Mary University of London, 4 Newark Street, London E1 2AT, UK*
yy.lin@qmul.ac.uk

Background: The most common form of muscular dystrophies in childhood is Duchenne muscular dystrophy (DMD). It is characterised by progressive muscle wasting caused by mutations in dystrophin gene without cure or effective treatment to date. To understand the pathogenesis of the disease, several animal models have been developed in the last years. In addition, there are DMD human myoblast models but they are difficult to populate well in vitro and in vivo, limiting their clinical applications. In view of the above, there is an unmet need of physiologically relevant human cellular models for studying the pathogenesis of DMD and testing therapeutic strategies. Patient-specific induced pluripotent stem cells (iPSC) can be differentiated into muscle fibres for modelling molecular and cellular mechanisms underlying DMD. Nevertheless, a major challenge is the use of appropriate control cells for analysis.
Aims: Our project is aimed to generate novel isogenic pairs of human cellular models for DMD that will be used to elucidate pathological mechanisms by comparing patient-specific cells with isogenic controls.
Methods and results: We used a rapid and efficient reprogramming protocol to reprogram patient fibroblasts into iPSC. We took three different patients' fibroblasts with three different mutations in the

dystrophin gene. After the reprogramming, we are characterising the iPSC lines by measuring the expression of pluripotent genes (e.g. Nanog, Oct4, Sox2) by qPCR and immunostaining.
Conclusions and perspectives: We will use CRISPR/Cas9 mediated genome editing technology to precisely correct the dystrophin gene mutations to get the isogenic control iPSC. Once the isogenic pairs of iPSC are established, we will induce the differentiation of these cells. In this way, we will get a powerful platform to study the molecular and cellular mechanisms underlying muscle pathogenesis in DMD, as well as to develop new therapeutic strategies to treat the disease.

P39

Development of Gene Editing Approaches for the Treatment of Duchenne Muscular Dystrophy (DMD)

Marc Moore, Denis Vallese, Hanna Kymalainen, George Dickson and **Linda Popplewell**
Centre of Biomedical Sciences, School of Biological Sciences, Royal Holloway University of London, Egham, Surrey TW20 0EX
linda.popplewell@rhul.ac.uk

Background: Current gene therapies being developed for DMD would either require repeat administration, carry an adverse immunological risk, or are restricted by mutation specificity, all of which would limit their clinical relevance. Such problems may be circumvented through the use of gene editing using designed endonucleases and various repair strategies.
Aims: Using endonucleases designed to target specific sites in the *DMD* and *mdx* genes, the aim was to develop permanent gene editing strategies that would respectively have high patient applicability and allow *in vivo* assessment of therapeutic efficacy.
Methods: Endonucleases (MGNs, TALENs, CRISPRs) were designed to target upstream of a *DMD* mutation hotspot and the *mdx* mutation, and at the 5' end of the *DMD* and *mdx* genes. *In vitro* cutting efficiency was assessed using enzyme mismatch cleavage or next generation sequencing. Full *DMD* gene repair and specific reading frame repair using designed donor repair templates were examined using (RT)-PCR. *In vivo* studies used a TALEN pair targeting upstream of the *mdx* nonsense stop mutation delivered as mRNAs or packaged into AAV vectors, both with and without a targeting repair template. Restoration of dystrophin protein expression was assessed using immunohistochemical staining.
Results: Specific DNA cleavage using all three endonucleases at all genomic locations targeted was demonstrated *in vitro*. Using a MGN targeting upstream of a *DMD* mutation hotspot and a targeting repair template, full *DMD* gene repair was established. When no repair template was supplied, NHEJ repair resulted in repair of the reading frame of both the *mdx* and *DMD* genes. *In vivo* studies revealed the potential of TALENs both with and without targeting repair templates to restore dystrophin protein expression.
Conclusions: The work presented here demonstrates the potential of gene editing to provide a permanent corrective gene therapy that with the correct design could hold high DMD patient applicability.

P40

Global FKRP Registry

Agata Robertson[*1], Olivia Schreiber-Katz[2], Laurence Bindoff[3], Jean-Pierre Laurent[4], Katherine Mathews[5], Anne Rutkowski[6], John Vissing[7], Maggie Walter[8], Lacey Woods[9], Volker Straub[1]
[1] *Newcastle University, UK;*
[2] *Hannover Medical School, Germany;*
[3] *University of Bergen, Norway;*
[4] *LGMD2I Research Fund, USA;*
[5] *University of Iowa Carver College of Medicine, USA;*
[6] *Cure CMD, USA;*
[7] *University of Copenhagen, Denmark;*
[8] *Ludwig-Maximilians University of Munich, Germany;*
[9] *Patient representative*

agata.robertson@ncl.ac.uk

Background: The Global FKRP Registry is an international registry for people with conditions caused by mutations in the *FKRP* gene: limb girdle muscular dystrophy 2I (LGMD2I) and, at the more severe end of the clinical spectrum, the congenital muscular dystrophies: MDC1C, Muscle-Eye-Brain Disease and Walker-Warburg Syndrome. The registry aims to ready the patient population for future clinical trials and to develop a better understanding of the natural history and prevalence of *FKRP*-related muscular dystrophies.
Aims and Methods: The Global FKRP Registry is a patient driven registry, whereby patients register and consent themselves online. The data is reported by both patients and their healthcare professionals. The clinical dataset collected includes: age of onset, presenting symptoms, family history, motor function and muscle strength, respiratory and cardiac function, medication, along with information on patients' quality of life and pain. Here we analyse this data to describe the characteristics of the patients within the Registry.
Results: There are currently 396 patients (53% female: 47% male) from 35 countries (28% Germany; 28% USA; 12% UK) represented in the Registry. The age range of patients is 1 to 76 years with diagnoses reported as LGMD2I (89%), MDC1C (3%), other *FKRP*-related MDs (5%), unspecified (4%). 75% of patients are reported as being ambulant, 22% as non-ambulant and 3 % as unspecified. The mutations reported within the Registry are: 62% homozygous for the common mutation (c.826C>A), 33 % heterozygous for the common mutation, 3% heterozygous with two unique mutations and 2% homozygous with a unique mutation which is not the common mutation.
Conclusion: The Global FKRP Registry has the potential not only to assist with clinical trial readiness but also to help with other areas of research and care such as gaining a better understanding of phenotype-genotype correlation, identifying the biomarkers and improving standards of care.

P41

Dystrophin as a biochemical outcome measure in Duchenne Muscular Dystrophy clinical trials

Valentina Sardone[1], Matthew Ellis[2], Silvia Torelli[1], Lucy Feng[1], Darren Chambers[1], Valeria Ricotti[1], Joana Pisco Domingos[1], Rahul Phadke[1,3], Caroline A Sewry[3], Jennifer Morgan[1], Francesco Muntoni[1]
[1]Dubowitz Neuromuscular Centre, UCL Institute of Child Health
[2]Department of Neurodegenerative Disease, UCL Institute of Neurology
[3]Great Ormond Street Hospital for Children, London

Background. Modified nucleic acids can be used as therapeutic molecules able to modify and correct genetic defects and splice switching antisense oligonucleotides (AON) are currently under investigation for treating Duchenne Muscular Dystrophy (DMD). Depending on the specific *DMD* gene out of frame deletion, it is possible to synthesize target AONs to induce exon skipping and restore the transcript reading frame, leading to the production of an internally deleted dystrophin protein. This treatment should prevent or delay muscle fiber degeneration and ameliorate disease progression. In DMD clinical trials, one of the primary biological endpoints is the restoration of the dystrophin protein in muscles of treated patients.
Aims. In order to evaluate the efficacy of such treatments, a reliable and reproducible method for the quantification of dystrophin protein is required. Our laboratory published a semi-quantitative immunohistochemistry method for quantifying dystrophin expression (1). However, this method is time consuming and partially user-dependent, so we sought to develop an automated method. **Material and methods.** Our new method involves the image acquisition of an entire transverse muscle section and the quantification of many relevant parameters (i.e number of fibers, fiber width and protein expression intensity). We have analyzed DMD, Becker Muscular Dystrophy (BMD) and control muscles stained with antibodies against sarcolemma components (to verify sarcolemma integrity) as well as dystrophin antibodies recognizing different protein epitopes. **Results.** We have compared the previously published method for quantifying dystrophin protein expression with the new automated method and here we are presenting our results.

Conclusion. We have developed an accurate and unbiased quantification of dystrophin expression for evaluating the efficacy of strategies aimed to restore dystrophin expression in DMD patients. Such methodology will be essential to determine the pharmacodynamic response of the muscle of boys with DMD recruited in clinical trials aimed at determining dystrophin restoration.

1. Arechavala Gomeza V.et al. Immunohistological intensity measurements as a tool to assess sarcolemma-associated protein expression. Neuropathol Appl Neurobiol. (2010) 36, 265–274

P42

Pattern recognition by semiquantitative radiological analysis in a large and multinational cohort of dysferlin patients

Volker Straub MD[1], Roberto Fernandez-Torron, MD [1,4] Jaume LLauger Rossello,[2,3], Jordi Díaz-Manera MD PhD[2,3], The Jain COS Consortium, Kate Bushby MD[1],

[1] *The John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Central Parkway, Newcastle upon Tyne, NE1 3BZ, UK*

[2] *Neuromuscular Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

[3] *Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Barcelona, Spain*

[4] *Neuromuscular Area. Biodonostia Health Research Institute. Neurology Service. Donostia University Hospital. Donostia-San Sebastian. Spain.*

Background: Muscle MRI was performed in 182 patients with a confirmed diagnosis of dysferlinopathy in 14 different centres, using 1.5T or 3T scanners from different manufacturers (Philips, General Electrics, Siemens).

Aims: To describe the pattern of pathology by muscle MRI in a large and multinational cohort of patients with dysferlinopathy

The semiquantitative analysis was perfomed on axial T1 weighted sequences by a blinded neurologist with experience in muscle MRI using the Mercuri scale modified by Fisher (0 to 4). 81-131 muscles were scored per patient. Statistical analysis was done using SPSS 21.0 and non parametric tests were used to analyze gender and symmetry differences.

Results: Half (50%) of the patients were male and half were female. The mean age at MRI was 38 ± 12.65 years (11-86 years). The mean age of first symptoms was 21.48 ± 8.48 years (1-60 years) and the mean disease duration to MRI was 16.8 ± 10 years (1-51 years). Serum CK activity at the time of the MRI was 4594 ± 4031 IU/l (209-23124). 136 patients (74.7%) were ambulant at the time of the MRI scan. The tensor fasciae latae, semimembranosus, semitendinosus, peroneus and soleus muscle were the most affected muscles (median Mercuri score of 4), followed by the gastrocnemius medialis, lateralis, subscapularis, extensor spinae, glutei minimus, adductor brevis, longus and magnus, quadriceps, tibialis anterior and long head of the biceps femoris muscles. The facial, cervical, pectoralis, trapezius, brachialis, triceps, arm, abdominal, gracilis and popliteal muscles were not usually affected. The femoral quadriceps, peroneus brevis, gastrocnemii and soleus muscle were more affected in female than in male patients ($p < 0.05$). There were statistically significant differences in symmetry in the right long head of the biceps femoris muscle ($p < 0.0001$).

Conclusion: The tensor fasciae latae, hamstring and peroneus muscles were the most affected muscles, followed by the femoral quadriceps and medial gastrocnemius. The facial, popliteal, piriformis and quadratus lumborum muscles were the least affected. The femoral quadriceps and calves muscles were more affected in female patients and differences in symmetry were significant in the long head of the biceps femoris.

P43

Repurposed Cancer Therapeutics as Treatments for DMD

Steve Winder, Gaynor Miller, Tracy Emmerson, & Emma Hoffman

Department of Biomedical Science, University of Sheffield, S10 2TN, UK.

s.winder@shef.ac.uk

By studying the fate of the dystrophin glycoprotein complex in Duchenne muscular dystrophy (DMD) we have identified tyrosine phosphorylation of dystroglycan, the key transmembrane laminin receptor, as central to the loss of the entire DGC from the sarcolemma.
Preventing phosphorylation of dystroglycan in *mdx* mice by mutation of a key tyrosine phosphorylation site ameliorates the dystrophic phenotype. Studies in mouse myoblasts also demonstrate that pharmacological treatment with proteasome or tyrosine kinase inhibitors can increase levels of non-phosphorylated dystroglycan. Furthermore by inhibiting tyrosine phosphorylation, ubiquitination or proteasomal degradation pharmacologically we can demonstrate a reduction in dystroglycan phosphorylation and a rescue of the dystrophic phenotype in *sapje* zebrafish, a fish model of DMD. Through the use of FDA approved cancer therapeutics, we can demonstrate significant improvement in *sapje* zebrafish swimming ability when treated with either tyrosine kinase or proteasome inhibitors. We have extended these studies into *mdx* mice and again certain drug regimen demonstrate improvements in muscle pathophysiology including muscle central nucleation, serum creatine kinase levels, restoration of dystroglycan and sarcoglycan to the sarcolemma and in physical parameters such as wire hanging times.
These studies demonstrate the utility of inhibiting dystroglycan tyrosine phosphorylation as a therapeutic strategy for DMD, particularly as several of the compounds that are effective are in existing clinical use. Obtaining orphan drug status for repurposed drugs could be a rapid and effective route to DMD therapy, either in their own right or as adjuncts to other therapies currently in or nearing the clinic.

P44

UK Myotonic Dystrophy Patient Registry: A tool for clinical research

L. Wood[(a)], A. Atalaia[(a)], C. Marini-Bettolo[(a)], M. Philips [(b)], D. Monckton [(c)] R. Orrell [(d)], M. Roberts [(e)], M. Rogers [(f)], M. Rose [(g)], D. Hilton-Jones [(h)], C. Turner [(i)], H. Lochmüller [(a)].
a) John Walton Muscular Dystrophy research Centre, Newcastle University, b) Department of Rehabilitation, Royal Derby Hospital, c)Institute of molecular and systems biology, University of Glasgow, d) Department of Clinical neuroscience, University College London, e) Department of neurology, Salford Royal hospital, f) Institute of medical genetics, University hospital of Wales, g) Kings College London h) Department of Clinical neurology, John Radcliffe Hospital, Oxford, i) National Hospital for Neurology and Neurosurgery, Queen Square, London
Elizabeth.wood2@ncl.ac.uk

Background

The UK Myotonic Dystrophy Patient Registry (www.dm-registry.org/uk) was established in May 2012 and is coordinated from the John Walton Muscular Dystrophy Research Centre (Newcastle) and collects clinical and genetic information about both DM1 and myotonic dystrophy type 2 (DM2) through an online portal. The data collected includes all items agreed at the 2009 TREAT-NMD and Marigold Foundation ENMC workshop.
Results: Of the 410 DM1 patients enrolled in the first two years 326 (79.5 %) report adult onset DM1 with 33 (8%) reporting childhood onset with symptoms beginning between the ages of 3 and 15, and 51 (12.4%) reporting infantile onset (symptoms at the age of 3 or younger). An even distribution is seen between genders (Female: 214, Male: 196) and a broad range of ages is present from 1 to 81 years old (mean 43.41 +/- 16.91), with the largest proportion, 62.7% between 30 and 59 years old**.** The two most commonly reported symptoms in the Registry are fatigue and myotonia, reported to some severity by 323 and 302 patients respectively. They both occur across all ages and are present in the congenital, childhood and adult onset forms of the condition. Dysphagia occurs mostly in patients also reporting myotonia and a statistically significant association can be seen between the two with more severe myotonic occurring more often in those with dysphagia ($p = < 0.0001$).
Conclusion: The UK Myotonic Dystrophy Patient registry is an example of a novel patient driven registry. Its success can be measured by its continuous growth and utilisation. The registry has successfully assisted the recruitment and planning of a number of commercial and academic studies, including EU

funded project OPTIMISTIC (www.optimistic-dm.eu). In addition to this purpose the registry also provides interesting and important data characterising the DM1 community in the United Kingdom.

P45

The UK FSHD Patient Registry: A Study of Scapular Fixation

Libby Wood, Teresinha Evangelista, Hanns Lochmüller
John Walton Muscular Dystrophy Research Centre, Newcastle University, UK.
Elizabeth.wood2@ncl.ac.uk

Background: The UK FSHD Patient Registry is a patient driven, clinician verified tool for clinical research. The registry shares a common dataset with many registries worldwide and is able to collect symptomatic information longitudinally. Between May 2012 and December 2015 583 individuals joined the Registry.
Methods: On the advice of patient organisations (MDUK and the FSHD Support Group) an additional questionnaire was included asking for information about the experiences and outcomes of scapular fixation. We present these results here.
Results: Fifty one patients (26 female, 25 male) in the UK FSHD Patient Registry have indicated they have had either unilateral (21) or bilateral (30) scapular fixation. More detailed information has been provided by 42 individuals. The operation was performed between the ages of 16 and 52 (mean 27.5) and the questionnaire has been completed between 2 and 45 years after the procedure. Thirty (71%) people were happy or very happy with the outcome of the procedure. In all cases (42) people expected increased mobility, 15 (36%) expected to experience a reduction in pain, 8 (19%) wanted to improve appearance or posture. When describing the ability to raise their arm 31 (74%) patients said this was considerably restricted before the operation, and one year later 18 (43%) described partial restriction, 5 (12%) were unrestricted and 8 (19%) remained considerably restricted.
Conclusion: The registry provides a useful tool to collect information from a heterogeneous population to assess the prevalence and utility of scapular fixation unbiased from any particular surgeon or clinical centre. The majority of patients questioned found the procedure a positive one and experienced increase in rotational mobility and the ability of raise arms over one year. Future work will aim to obtain more information from clinical and surgical colleagues involved in order to ascertain the methods used.

P46

Determination of tissue-water T2 of fat infiltrated upper limb skeletal muscle with MRI in Duchenne muscular dystrophy

Nick Zafeiropoulos[1], Valeria Ricotti[2], Matthew Evans[1,3], Jasper Morrow[3], Paul Matthews[4], Robert Janiczek[5], Tarek Yousry[1,3], Christopher Sinclair[1,3], Francesco Muntoni[2], and John Thornton[1,3]
[1]Neuroradiological Academic Unit, UCL Institute of Neurology, London, United Kingdom, [2]Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London, United Kingdom, [3]MRC Centre for Neuromuscular Diseases, London, United Kingdom, [4]Imperial College London, London, United Kingdom, [5]GlaxoSmithKline, London, United Kingdom

Background & Aims: MRI shows promise as a way of quantifying muscle tissue water in Duchenne muscular dystrophy (DMD). In this work a bi-exponential signal decay model was used to determine muscle-water T2 (T2m) in upper-limb fat-infiltrated skeletal muscles in non-ambulant Duchenne muscular dystrophy patients and healthy controls.
Methods: MR imaging was performed at 3T using a 12 spin-echo sequence without fat-suppression in 9 healthy volunteers and 12 DMD patients. The signal decay was fitted to a two-component model with a mono-exponential approximation for the fat decay component. An image slice at the centre of the dominant forearm was manually segmented into muscle regions of interest (ROIs) and T2m values averaged over all ROIs and corresponding histogram metrics calculated.
Results: Analysable T2 maps were obtained from all subjects after application of fit quality-control criteria. Mean T2m in volunteers was 31.5±1.4ms. The mean T2m in DMD of 30.7±2.1ms was not

statistically different from controls, in agreement with previous reports. ANOVA suggested significant differences for full width at quarter maximum (p=0.0032) and skewness (p=0.0016) of the distribution between patients and healthy controls.
Discussion: The signal model used here is simpler than previously presented in the literature and provides stable T2m estimates. More sophisticated approaches are likely to be appropriate for analysing data with more echo times and higher signal-to-noise ratio, particularly where determining a physically meaningful model of lipid compartmentalisation is a primary objective. Nevertheless, using our method we obtained forearm T2m values in both controls and DMD patients which are consistent with those previously reported (Wary et al., 2015), and appear largely independent of muscle fat content.

Mitochondrial Disease

‡P47

Intestinal Pseudo-obstruction in Adult m.3243A>G-Related Mitochondrial Disease: An Under-Recognised and Poorly-Managed Clinical Entity

Yi Shiau Ng[1], Catherine Feeney[1], Andrew M Schaefer[1], Paula Hynd[2,] Carol E Holmes[3], , Charlotte Alston[1], John P Grady[1], Mark Roberts[4], Mellisa Maguire[5], Alexandra Bright[1], Robert W Taylor[1], Yan Yiannakou[6], Robert McFarland[1], Doug M Turnbull[1], Gráinne S Gorman[1]

[1.] Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE2 4HH

[2.] Children's Services, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP

[3.] Department of Radiology, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP

[4.] The Greater Manchester Neuroscience Centre, Salford Royal NHS Foundation Trust, Salford, M6 8HD

[5.] Department of Neurology, The Leeds Teaching Hospitals NHS Trust, West Yorkshire, LS1 3EX

[6.] Department of Gastroenterology, County Durham and Darlington NHS Foundation Trust, Durham, DH1 5TW

Background: The m.3243A>G *MTTL1* mutation is the most common cause of mitochondrial DNA disease in adults manifesting with a wide range of clinical phenotypes. However there is a limited awareness of the prevalence and severity of gastrointestinal dysmotility and its management in m.3243A>G-related mitochondrial disease.
Aims: To provide insight into the severity, prevalence, and clinical outcome of patients with m.3243A>G-related mitochondrial disease presenting with intestinal pseudo-obstruction and develop expert opinion guidelines to optimise clinical management.
Methods: This was an observational cohort study of patients with m.3243A>G mutation recruited to the MRC Mitochondrial Disease Patient Cohort in Newcastle. We evaluated the clinical, molecular and radiological characteristics of patients who presented with severe intestinal pseudo-obstruction. Multivariate Cox regression analysis was applied to determine putative predictors of intestinal pseudo-obstruction.
Results: Between January 2009 and June 2015, 226 patients harbouring the m.3243A>G mutation were registered in the MRC Mitochondrial Disease Patient Cohort database (Newcastle). Thirteen percent of patients (n=30) developed severe intestinal pseudo-obstruction mimicking a mechanical obstruction (minimum prevalence rate: 0·53 per 100,000). The predictors of intestinal pseudo-obstruction were the presence of stroke-like episodes, cardiomyopathy, low body mass index and high m.3243A>G heteroplasmy level, irrespective of the presence of diabetes mellitus and gender.
Conclusion: Our findings suggest that severe intestinal pseudo-obstruction is under-recognised and often poorly managed in m.3243A>G–related mitochondrial disease. It is associated with patients with already high disease burden although it may rarely be the first clinical manifestation of m.3243A>G disease. High

morbidity and mortality are evident among those patients who were treated surgically. Based on these findings, we have developed expert opinion guidelines encompassing both acute and chronic treatment of gastrointestinal dysmotility, in order to optimize the management.

‡P48

3D reconstruction and quantitative analysis of skeletal muscle mitochondrial networks in patients with mitochondrial disease

A.E. Vincent[1], K. White[2], T. Davey[2], R.W. Taylor[1], D.M. Turnbull[1], M. Picard[1,3].
[1] *Wellcome Trust Centre for Mitochondrial Research, Institute of Neurosciences, Newcastle University, Newcastle upon Tyne, UK*
[2] *EM Research Services, Newcastle University, Newcastle upon Tyne, UK*
[3] *Division of Behavioral Medicine, Department of Psychiatry, Department of Neurology, College of Physicians and Surgeons, Columbia University, Columbia University Medical Center, New York, NY, USA*
a.vincent2@ncl.ac.uk

Background: Mitochondrial morphology and network organization are intrinsically linked to mitochondrial function. This fundamental relation has implications for understanding the mechanisms underlying energetic deficiency and clonal expansion of mitochondrial DNA (mtDNA) defects in muscle fibres. However, little is known about mitochondrial morphology and networking in skeletal muscle affected by mitochondrial disease.
Aim: To develop a quantitative method to analyse mitochondrial networks and morphology in skeletal muscle biopsies of patients with mitochondrial pathology.
Methods: Muscle fibers from patients with genetically defined mitochondrial disease (n=7), sarcopenia (n=1), or hypertrophic cardiomyopathy (n=1) were subject to serial block face scanning electron microscopy (SBF-SEM). Four muscle fibres per patient with 25-50 mitochondria each were reconstructed using IMOD software, and surface area (SA) and volume (V) measured for each mitochondrion and number of nanotunnels quantified. Building from the morphometric descriptor form factor, we developed a Mitochondrial Complexity Index ($MCI = SA^2/(4\pi V)$) and a compartment-based method to quantify shape complexity and degree of branching in 3D.
Results: Mitochondrial SA, V, MCI and degree of branching and nanotunelling exhibits large inter-individual variability, with less variation between fibres of the same patient or within a fibre. Mitochondria exhibited substantially more connections with each other in the cross-sectional plane of the muscle fibre than the longitudinal. Furthermore, three relatives with different *m.8344A>G* heteroplasmy levels exhibit large variations in mitochondrial morphology.
Conclusions: We have developed a 3D method to quantify mitochondrial morphology and degree of connectivity in human skeletal muscle biopsies. Our in depth morphological analysis of patients with molecularly defined mtDNA defects reveals that the mitochondrial network is more connected in cross-section than in the longitudinal plane of the muscle fibre, which could influence the spread of mtDNA mutations and respiratory chain deficiency within muscle fibres. This work reveals new mechanisms to understand the nature and progression of mitochondrial pathology.

‡P49

Recessive Mutations in *TRMT10C* Cause Defects in Mitochondrial RNA Processing and Multiple Respiratory Chain Deficiencies

Kyle Thompson[1], Metodi D. Metodiev[2], Charlotte L. Alston[1], Langping He[1], Zarah Assouline[3], Marlene Rio[3], N. Bahi-Buisson[3], Andrew Morris[4], Angela Pyle[5], Patrick F. Chinnery[5], Arnold Munnich[2,3], Robert McFarland[1], Agnès Rötig[2] and Robert W. Taylor[1]
[1]*Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK*
[2]*INSERM U1163, Université Paris Descartes-Sorbonne Paris Cité, Institut Imagine, 75015 Paris, France*
[3]*Departments of Pediatric, Neurology and Genetics, Hôpital Necker-Enfants-Malades, Paris, France*

[4]*Willink Biochemical Genetics Unit, Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester, M13 9WL, UK*
[5]*Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, NE1 3BZ, UK*
kyle.thompson@newcastle.ac.uk

Background: Mitochondrial disorders are clinically and genetically diverse since defective expression of mitochondrial (mt)DNA can be caused by mitochondrial or nuclear gene mutations. Recently, several mitochondrial disease patients have been diagnosed with mutations in genes encoding factors involved in mt-tRNA processing. By whole exome sequencing we identified two individuals with mutations in the *TRMT10C* gene encoding the mitochondrial protein, MRPP1. MRPP1, MRPP2 and MRPP3 form mt-RNase P, which is responsible for cleaving the 5' end of mt-tRNAs from polycistronic precursor RNAs. Additionally, a complex of MRPP1 and MRPP2 has m^1R9 methyltransferase activity. Methylation of mt-tRNAs at position 9 is a vital modification required for folding mt-tRNAs into the correct cloverleaf structure.
Aims: To validate and characterise the pathogenicity and functional effects of mutations in the *TRMT10C* gene.
Patients: We report 2 cases of mitochondrial disease, each presenting at birth with high CSF and serum lactate levels, hypotonia and deafness. Following whole exome sequencing, both affected individuals were found to harbor the c.542G>T, p.(Arg181Leu) mutation in *TRMT10C.* One patient was homozygous for this mutation, with the second patient heterozygous for this mutation and the c.814A>G, p.(Thr272Ala) mutation in the same gene.
Results: Analysis of patient fibroblasts revealed decreased protein levels of MRPP1 and components of respiratory complexes I and IV due to reduced mitochondrial protein synthesis. Patient fibroblasts also showed an increase in mt-RNA precursors indicative of defective mt-RNA processing. All of these defects were rescued following lentiviral transduction of wild type *TRMT10C*.
Conclusion: We confirm *TRMT10C* as a mitochondrial disease gene and have shown that the c.542G>T, p.(Arg181Leu) and c.814A>G, p.(Thr272Ala) mutations are pathogenic. These mutations affect MRPP1 stability and mt-tRNA processing without effects on m^1R9 methyltransferase activity.

P50

A novel MT-ATP6 mutation causing complex spastic paraparesis associated with posterior predominant white matter changes

Bugiardini E[1], Horga A[1], Woodward C[2], Sweeney MG[2], Hargreaves I[3], Pitceathly RDS[1], Houlden H[4], Quinlivan R[1], Hanna MG[1,4]
[1] *MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London*
[2]*Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London*
[3]*Neurometabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London*
[4]*Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London*
e.bugiardini@ucl.ac.uk

Background: Complex V (ATP synthase) comprises several subunits encoded by both nuclear and mitochondrial DNA. MT-ATP6 codes for one subunit and mutations in this gene are associated with a broad variety of phenotypes. The most frequently reported are Leigh syndrome and neuropathy ataxia and retinitis pigmentosa (NARP). More recently, the phenotype has been expanded to include tissue-specific phenotypes, including axonal Charcot-Marie-Tooth disease (CMT2).
Aim: The aim of this study is to describe a family with a novel variant in MT-ATP6 presenting with a new clinical phenotype.
Patients: A 41 year-old-lady presented with a history of global developmental delay, short stature, Asperger syndrome and progressive spastic paraparesis. In subsequent years she developed cataracts and tapeto-retinal degeneration, hearing impairment, diabetes and at 30 years old kidney failure requiring kidney transplantation. The parents are in their 70s and are unaffected. She has one brother and one

sister both asymptomatic. During the admission blood test, muscle biopsy and brain MRI were performed.
Result: CK were normal. Lactate was mildly elevated at 2.59 mmol/L. Muscle biopsy showed mild myopathic features and increased lipid content. Respiratory chain analysis demonstrated reduced complex II-III activity (0.018). BNGE showed a normal level of complex V. Muscle ubiquinone levels were normal. Brain MRI revealed posterior predominant white matter changes and cerebellar atrophy. Sequencing of mtDNA confirmed the frame shift mutation m.8618dup; p.Thr33Hisfs*32 in muscle (65%) and blood (20%). The extension of the analysis to the unaffected mother and sister detected lower level of heteroplasmy in blood (4% and 10% respectively).
Conclusion: We report a new variant in ATP6 associated with complex spastic paraparesis associated with white matter changes. This case expands the genotype and phenotype of ATP6 mutations.

P51

RNASEH1 mutations are a rare cause of CPEO with multiple mtDNA deletions

Bugiardini E[1], Pitceathly RDS[1], Poole O[1], Horga A[1], Manole A[2], Sweeney MG[3], Woodward C[3], Hargreaves I[4], Holton JL[5], Fratter C[6], Poulton J[7], Houlden H[2], Hanna MG[1,2]
[1] MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London
[2] Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London
[3]Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London
[4]Neurometabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London
[5] Department of neuropathology, UCL Institute of Neurology, Queen Square, London
[6]Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford
[7] Nuffield Department of Obstetrics and Gynaecology, University of Oxford
e.bugiardini@ucl.ac.uk

Background: Mitochondrial diseases are common inherited disorders caused by mutations in nuclear and mitochondrial encoded DNA.A subset of nuclear genes are involved in mitochondrial DNA maintenance and their dysfunction results in mtDNA depletion or multiple deletions. The clinical phenotype varies widely ranging from severe hepatocerebral disorders in infancy to adult onset chronic progressive ophtalmoplegia (CPEO). Recently a new gene (RNASEH1) causing CPEO and multiple deletions with adult onset has been described. RNASEH1 encodes an endonuclease (ribonuclease H1) that digests the RNA component of RNA-DNA hybrids and may have a role in mtDNA maintenance.
Aims: To identify RNASEH1 mutations in our cohort of patient with genetically undefined CPEO and/or mtDNA multiple deletions.
Methods: We included genetically undefined patients seen in our mitochondrial service satisfying the following criteria: 1) CPEO with/without multiple deletions; 2) multiple deletions irrespective of the phenotype. All 8 exons of RNASEH1 genes were analysed using Sanger sequencing.
Results: 63 patients were included in the study: 51 with CPEO (43% with associated multiple deletions); and 12 with multiple deletions with other mitochondrial phenotypes. We identified the homozygous RNASEH1 mutation (c.424G>A, p.Val142Ile) in four patients belonging to two separate families. The phenotype was similar to previously reported cases and was mainly characterized by CPEO, dysphagia, proximal weakness and cerebellar signs. One patient had clinical and electrophysiological features suggestive of sensory neuronopathy. Muscle biopsy showed COX negative fibres, ragged red fibres and multiple deletions in all cases.
Conclusion: RNASEH1 represents a relatively rare cause of CPEO and multiple deletions. The phenotype appears to be homogenous and it is characterized by CPEO, dysarthria and cerebellar signs. The presence of a sensory neuronopathy may be an additional feature of RNASEH1 mediated disease. As such RNASEH1 should be considered in patient presenting with sensory ataxia neuropathy dysarthria and ophthalmoplegia (SANDO) and negative POLG screening.

P52

Intra-uterine and postnatal growth failure resulting from maternally inherited mitochondrial DNA mutation m.3243A>G

Carl Fratter[1], Conrad Smith[1], Jo Lowndes[2], Fiona Ryan[3], Opope Wedi[4], Jo Poulton[4]
[1]*Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust*
[2]*Department of Clinical Genetics, Oxford University Hospitals NHS Foundation Trust*
[3]*Paediatric Endocrinology, The Children's Hospital, Oxford University Hospitals NHS Foundation Trust*
[4]*Nuffield Department of Obstetrics & Gynaecology, University of Oxford*
carl.fratter@ouh.nhs.uk

Background: Mitochondrial DNA diseases such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) are frequently heteroplasmic, mutant m.3243A>G mitochondrial DNA (mtDNA) co-existing with normal mtDNA. These diseases are usually progressive, the load of mutant mtDNA determining disease severity. Pregnant women carrying this mutation are at increased risk of developing pre-eclamptic toxaemia (PET), a systemic disorder of maternal hypertension with placental dysfunction causing growth retardation or miscarriage in their offspring.
Aims: To investigate the load of m.3243A>G mutant mtDNA in a MELAS family.
Methods: MtDNA mutant load in samples from family members (including blood, saliva and placenta from a newborn baby) was analysed by fluorescent restriction digest PCR and pyrosequencing.
Results: The asymptomatic daughter, GB, of the severely affected proband declined presymptomatic testing. GB's first two children were healthy but she had her third by Caesarean section at 30 weeks gestation for intra-uterine growth retardation and rising blood pressure, weighing 640g (0.4%ile). His placenta was also small at 90g. However, GB's blood pressure was normal until the end of the pregnancy. m.3243A>G mutant load in the newborn baby was 20% in blood, 22% in saliva, and 62-65% in placenta.
Conclusion: Low birth weight is common in families with m.3243A>G due to PET, but there was growth failure well ahead of the rise in blood pressure in this case. In view of the high mutant load in placenta, we infer that the growth failure may have been due to placental dysfunction resulting from mitochondrial disease.

P53

Development and evaluation of individualised Exercise protocol for people with mitochondrial disease: a Service evaluation

S. Holmes; G. Ramdharry; E. Bugiardini, O. Poole; N. James; M. G. Hanna
Centre for Neuromuscular Disease, University College London; University College London.
sarah.holmes@uclh.nhs.uk

Background: Mitochondrial diseases are inherited disorders of oxidative phosphorylation that may present with a multitude of clinical features. Limited treatments are available for people with Mitochondrial disease (M.D.). A number of studies have explored the use of exercise as a treatment. Exercise has been seen to be safe and beneficial in terms of improved aerobic fitness, and improved functional ability in this group (Trennel et al, 2006; Jeppensen et al 2006).
Aims:
• To critique relevant research and develop an individualised assessment and exercise protocol for people with a genetically confirmed diagnosis of mitochondrial disease;
• To pilot exercise protocol - exploring compliance, adherence and acceptability of the individualised exercise protocol within a service evaluation framework.
Methods: Patients attending the National Specialist Service for Mitochondrial Diseases at University College London Hospital, with confirmed diagnoses of Mitochondrial disease, will be asked for informed consent as part of physiotherapy assessment. Where consent is gained, patients will be screened and assessed using the exercise protocol. Screening includes assessment of cardiovascular risk factors, previous levels of physical activity and presence of diabetes. Prescribed exercise intensity is informed by this assessment of risk factors, following review by a cardiologist where appropriate. Heart rate monitors are provided and individuals are followed up via telephone at one month and three months.

Results: Our recruitment target is ten people with genetically confirmed diagnosis of M.D. Results will be collected at the end of the 12 week evaluation period. Primary outcomes (exercise frequency, intensity and duration) will be compared to the recommended exercise protocol.
Conclusion: The target date for completion is August 2016.

P54

Mitophagy deficiencies in mitochondrial DNA disease

King, L.[1,2], Sweeney M.[2] , Hanna M.[1] and Plun-Favreau, H.[2]
[1] *MRC Centre for Neuromuscular Disease, UCL Institute of Neurology, Queen Square, London*
[2] *University College London, Institute of Neurology, Queen Square, London*
louise.king.13@ucl.ac.uk

Mitophagy is the process of selective mitochondrial degradation that occurs to maintain efficient synthesis of ATP in the cell and avoids the toxic accumulation of damaged mitochondria. Dysfunction of mitochondria is linked to several neuromuscular and neurodegenerative disorders, due to the high energy requirements of skeletal muscle and the central nervous system. Within mitochondrial disease, mutated mitochondrial DNA (mtDNA) coexists with wild-type mtDNA in separate nucleoids and the severity of disease depends upon this ratio; therefore maintaining mitochondrial quality control processes is essential.
It has previously been shown that overexpression of Parkin, an E3 ubiquitin ligase recruited in mitophagy, can increase the ratio of wild-type mtDNA to mutant mtDNA in human cells (Suen *et al.,* 2010). Furthermore, it has also been suggested that mtDNA damage can induce mitophagy (Youle & Narendra, 2011).
The aim of this study was, firstly, to characterise the mitochondrial physiology for a range of pathogenic mutations, mutant loads and clinical phenotypes. Mitochondrial physiology data, including mitochondrial membrane potential, mitochondrial mass and network analysis, was collected from patient fibroblasts. In addition, patient fibroblasts were used to study the functioning of the PINK1/Parkin pathway of mitophagy in order to understand how mtDNA mutations at different levels of heteroplasmy can escape elimination by this pathway. Analysis of the ubiquitination of outer mitochondrial membrane proteins upon uncoupling of mitochondria showed defects in the functioning of the PINK1/Parkin pathway.

P55

Reproductive decision making in mitochondrial patients: A qualitative investigation of women's experience

Julia Maddison[1], Doug Turnbull[1], Jane Stewart[2] and Tim Rapley[3]
[1] *Institute of Neuroscience, Newcastle University, UK.* [2] *Newcastle Upon Tyne NHS Foundation Hospitals, UK.* [3] *Institute of Health and Society, Newcastle University, UK.*

Background: Mitochondrial disease is a group of disorders that are heterogeneous and are caused by defects in the mitochondrial DNA (mDNA) or in the nuclear DNA of a cell that affects mitochondrial maintenance. They are a clinically and genetically diverse group of disorders that are progressive and disabling. There are many issues that make determining the risk of maternally inherited disease difficult. With newly available and emerging reproductive techniques, mitochondrial patients have even more reproductive options than ever before to consider. There is currently no published research exploring how mitochondrial patients make reproductive decisions. Research into other genetic conditions does however give us a base to explore potentially similar factors affecting reproductive decision making in women with mitochondrial disease. Research into Huntington's disease for example has shown that lived/factual awareness of disease; personal values; concepts of future; risk mitigation and perceived social support impacted parental decision making. Studies into Duchenne Muscular Dystrophies have highlighted the importance of parental understanding of carrier and recurrence risk and that socio educational status can impact on this understanding.

Aims: We are interviewing up to 15 women in a retrospective group and up to 15 women who are currently or in the near future thinking about becoming pregnant.
Methods: Transcripts from semi structured interviews are being analysed using procedures from first-generation grounded theory, analytic induction and constructivist grounded theory.
Results: Preliminary analysis has allowed for the development of in-depth conceptual models for themes including Disclosure, Clinical Relationships, Impact of Diagnosis and Disease and the Transition State; from awareness and manageability to behaviours indicative of their perception of risk.
Conclusion: Continued collection and analysis of data will allow for further insight into experiences of these women and to the development of patient pathway and production of patient centred resources to support reproductive discussions with mitochondrial patients.

P56

Impact of mtDNA mutations on the myogenic differentiation of IPSCs

Ben O'Callaghan[1], Monika Madej[1], Jennifer Morgan[2], Henry Houlden[1], Mary M. Reilly[1], Michael G. Hanna[1]
[1]*MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London*, [2]*Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London*

Background: Mitochondrial disease mutations within mt-tRNA genes result in oxidative phosphorylation dysfunction. It is now appreciated that mitochondrial metabolism plays an important role in the maintenance of pluripotency or terminal differentiation. The switch from a glycolytic metabolic state to one which favours oxidative phosphorylation appears important for effective differentiation. Products of mitochondrial metabolism are substrates for chromatin modifying enzymes, possibly contributing to the importance of oxidative phosphorylation for differentiation.
Aims: To determine whether disease causing mt-tRNA mutations impair the myogenic differentiation of induced pluripotent stem cells (IPSCs).
Methods: Patient-derived and control fibroblasts were reprogrammed using non-integrating delivery methods. IPSC clones were selected and subjected to next generation sequencing of the mtDNA for quantification of mutation load. IPSCs were differentiated into myotubes using a recently published protocol which combines defined factors to recapitulate developmental stages of myogenesis (Chal et al., 2015). The efficiency of myogenic differentiation was assessed by qPCR and immunohistochemistry of stage specific differentiation markers.
Results: Clonal fibroblast lines have been subjected to reprogramming. Isogenic IPSC lines have been obtained due to segregation of mtDNA mutation (~100% vs ~0% mutation load) as a result of reprogramming. Selected IPSC clones are currently being differentiated into myotubes. The myogenic differentiation capacity appears to differ across patient derived cell lines. Preliminary results will be presented.
Conclusions: These results will provide new insight into the effect of mitochondriopathies on myogenic differentiation.
Chal, J. et al. Differentiation of pluripotent stem cells to muscle fiber to model Duchenne muscular dystrophy. Nature Biotechnology. 33, 962–9 (2015).
benjamin.o'callaghan.11@ucl.ac.uk

P57

A mutation in a novel nuclear gene causing mitochondrial disease

O.V.Poole[1], R.D.S. Pitceathly[1], C. Turner[1], E. Bugiardini[1], I. Barbosa[2], C. Deshpande[2], H. Houlden[3] and M.G. Hanna[1].
[1]*MRC Centre for Neuromuscular Diseases, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London UK*
[2]*South East Thames Regional Genetics Centre, Guy's and St Thomas' NHS Foundation Trust, Guy's Hospital, London, UK*
[3]*Department of Molecular Neuroscience, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London UK*

o.poole@ucl.ac.uk

Background: Mitochondrial diseases are a group of phenotypically, biochemically and molecularly heterogeneous genetic diseases resulting from diminished cellular energy production due to impaired oxidative phosphorylation. Typically multiple organ systems are involved. Disease causing mutations can reside in either the mitochondrial or nuclear genomes.
Aims: We performed whole exome sequencing to identify possible pathogenic nuclear DNA mutations in a patient with clinical and biochemical evidence of mitochondrial disease.
Patient: A 24 year old female of Pakistani origin, born of consanguineous parents, with a background of learning disability, presented with symptoms of distal myopathy at school age. This progressed slowly with time and she went on to develop chronic progressive external ophthalmoplegia, bilateral facial weakness, dysphagia, respiratory involvement and neuropathy. Blood lactate was 2.5, COX negative fibres were present on muscle biopsy and respiratory chain enzyme assays revealed low complex IV and complex I activity. Sequencing of her mitochondrial DNA was normal. There was the suggestion of multiple mitochondrial DNA deletions on long range PCR, but this was not confirmed with southern blot.
Results: Whole exome sequencing revealed the patient was homozygous for a mutation in *TRIAP1,* c.194delT (p.M65fs). *TRIAP1* plays a role in the maintenance of cardiolipin levels in mitochondria, a phospholipid found exclusively in mitochondria with many key functions including regulation of apoptosis. No disease causing mutations have previously been described in this gene.
Conclusion: We describe a mutation in a novel nuclear gene resulting in mitochondrial disease. Further work will include functional studies to elucidate the pathomechanism.

P58

Identifying novel pharmacological drugs to eliminate pathogenic heteroplasmic mtDNA by using a novel quantitative assay of mitophagy

Eszter Dombi[1]*, Alan Diot[1]*, Alex Hinks-Roberts[1], Tiffany Lodge[1], Chunyan Liao[1,2], Karl Morten[1], Stefen Brady[1,3], Carl Fratter[4], Janet Carver[1], Charlotte J Green[5], Grant Churchill[6], Heather Mortiboys[7] and **Joanna Poulton[1]**

** Equal first authors*
[1]Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Oxford, UK
[2]Present address Molecular Biology & Biotechnology, University of Sheffield[3]Present address Department of Neurology, York Hospital, Wigginton Road, York
[4] Oxford Molecular Genetics Laboratory, Churchill Hospital, Oxford, UK
[5]Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford, UK
[6]Department of Pharmacology, University of Oxford
[7]Sheffield Institute of Translational Neuroscience, University of Sheffield, Sheffield

Background: Mitochondrial diseases such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) are frequently heteroplasmic, where mutant m.3243A>G mitochondrial DNA (mtDNA) co-exists with normal mtDNA. These diseases are usually progressive, the load of mutant mtDNA determining disease severity.
Mitophagy is a cellular mechanism for the recycling of redundant or dysfunctional mitochondrial fragments. This process may be able to improve mtDNA quality in heteroplasmic disease and influence disease progression.
Aims and Methods: Measuring mitophagy is technically demanding. We used pharmacological modulators of autophagy to validate two techniques for quantifying mitophagy. First we used high throughput fluorescence microscopy, the IN Cell 1000 analyzer, to quantify mitochondrial co-localisation with LC3-II positive autophagosomes. Unlike conventional fluorescence and electron microscopy, this high-throughput system is sufficiently sensitive to detect transient low frequency autophagosomes.

Secondly, because mitophagy preferentially removes pathogenic mtDNA, we developed a heteroplasmy assay based on loss of the m.3243A>G mutants during culture conditions requiring oxidative metabolism ("energetic stress").
The effects of the pharmacological modulators on these two measures were consistent, confirming that the high throughput imaging output (autophagosomes co-localising with mitochondria) reflects mitochondrial quality control.
Results: We screened the NCC1 drug library for modulators of mitophagy. We found that metformin, the most commonly prescribed antidiabetic drug that is still sometimes used in Maternally Inherited Diabetes and Deafness (MIDD), inhibits mitophagy at clinically relevant concentrations under energetic stress. Idebenone, a drug used for treating patients with Leber's Hereditary Optic Neuropathy (LHON) was a weak inhibitor of mitophagy in cultures from MELAS patients carrying the m.3243A>G mutation. It significantly inhibited mitophagy in LHON/Leigh's disease due to the rare m.13051G>A mutation.
Conclusions: Metformin may be damaging to patients with heteroplasmic mtDNA disease because it inhibits mitophagy. Idebenone on the other hand may inhibit mitophagy because it benefits the impaired respiratory chain that underlies LHON pathology.

P59

Mortality in a cohort of mitochondrial patients

I. Skorupinska[1], E.Bugiardini[1], A. Horga[1], M.G Hanna[1]
[1]*MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London UK*

Background: Mitochondrial respiratory-chain diseases can be caused by mitochondrial DNA or nuclear DNA defects. The prevalence of mitochondrial DNA diseases has been estimated at 1 in 10,000 individuals, which makes them one of the most common inherited disorders. The true prevalence of mitochondrial respiratory-chain diseases is in fact higher if we include nuclear DNA disorders.
Several studies have evaluated prognostic factors for specific mitochondrial diseases. However few studies have specifically evaluated the cause of death and contributing factors.
Aims: The aim of this work was to identify the cause of death in adult patients with mitochondrial diseases attending a specialized mitochondrial disease clinic at the NHNN.
Methods: We reviewed records of all patients attending a specialized mitochondrial disease clinic that deceased in the last 25 years. Patients were screened if classified as having a mitochondrial disease based on the muscle biopsy results or genetic sequencing. Demographic and clinical data were collected from medical records. Causes of death were obtained from the death certificates.
Results: We retrieved death certificates of 23 patients with mitochondrial disease. The mean age of death was 48.04 ± 17.63 (SD), the range was 20-83. The main causes of death were cardiac (39%) and respiratory (26%). Two patients had an unexpected cardiac death: an m.3243A>G patient with only hearing loss and a patient with SANDO.
Conclusions: Cardiac disease was the leading cause of death in our cohort of mitochondrial patients irrespective of the phenotype.

P60

Whole exome sequencing in undiagnosed late-onset mitochondrial DNA maintenance disorders

Ewen W. Sommerville[1], Ilaria Dalla Rosa[2], Mariana C. Rocha[1], Angela Pyle[3], Patrick Yu-Wai-Man[3], Patrick F. Chinnery[4], Gráinne S. Gorman[1], Antonella Spinazzolla[2], Robert W. Taylor[1].
[1]*Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*
[2]*MRC National Institute for Medical Research, Mill Hill, London, UK*
[3]*Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK*
[4]*Department of Clinical Neurosciences, School of Clinical Medicine, University of Cambridge, Cambridge, UK*
e.w.sommerville@newcastle.ac.uk

Background: Progressive external ophthalmoplegia (PEO) is a mitochondrial DNA (mtDNA) maintenance disorder characterised by extraocular muscle paresis and skeletal muscle restricted multiple mtDNA deletions. After excluding mutations in known mtDNA maintenance genes, approximately 50% of patients remain without a diagnosis. Hence, whole exome sequencing (WES) to identify variants in the exons (coding regions) of all known genes is an attractive diagnostic tool.
Aims: To determine the genetic aetiology of a cohort of 22 patients presenting isolated to multisystem PEO-plus phenotypes with multiple mtDNA deletions.
Patient and Methods: Our proband was a 76 year old female presenting PEO, bilateral ptosis and diplopia. Muscle histochemistry showed 15% COX-deficient fibers and 3% ragged-red fibers (RRFs), while long-range PCR revealed the presence of multiple mtDNA deletions. Sequencing of *POLG*, *ANT1*, *C10orf2*, *POLG2*, *RRM2B*, *TK2* and *RNASEH1* was negative. Family history was negative. Rare exonic or splice-site variants occurring 1% or less in sequenced controls from several databases were identified and prioritised according to associated Gene-Ontology (GO-) terms: 'mitochondr', 'replication', 'DNA repair', 'helicase', 'ligase', 'polymerase', 'exonuclease', 'topoisomerase', 'nucleotide' or 'nucleoside'.
Results: The proband harboured a novel heterozygous (p.[Gly183Arg]) *GMPR* mutation. Studies to confirm pathogenicity included western blot analysis of OXPHOS, GMPR knockdown and rescue, and mitochondrial localisation. *In silico* modelling demonstrated that the mutation occurred in the highly conserved active site loop necessary for GMP binding, likely causing impaired function.
Conclusion: *GMPR* encodes guanosine monophosphate reductase, which is required for *de novo* synthesis of purine nucleotides and re-utilisation of free intracellular bases and nucleosides. The largely unknown role of GMPR in mtDNA maintenance demonstrates the difficulty of diagnosing late-onset mtDNA integrity disorders. We propose that this mutation is a novel, rare cause of PEO and multiple mtDNA deletions.

P61

A novel Celtic *YARS2* founder mutation is associated with mitochondrial myopathy

Ewen W. Sommerville[1], Yi S. Ng[1], Charlotte L. Alston[1], Tobias B. Haack[2], Maria E. Farraugia[3], Langping He[1], Micol Gilberti[4], Cristina Dallabona[4], Claudia Donnini[4], Holger Prokisch[2], Robert W. Taylor[1], Gráinne S. Gorman[1]
[1]*Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*
[2]*Institute of Human Genetics, Helmholtz Zentrum München, Neuherberg, Germany*
[3]*Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK*
[4]*Department of Life Sciences, University of Parma, Parma, Italy*
e.w.sommerville@newcastle.ac.uk

Background: *YARS2* encodes mitochondrial tyrosyl-acyl tRNA synthetase and is required for the conjugation of $tRNA^{tyr}$ and tyrosine. Recessive *YARS2* mutations have been associated with a clinical triad of myopathy, lactic acidosis and sideroblastic anaemia (MLASA). Similar phenotypes have been described in some patients with mutations of *PUS1*, *LARS2* and a *de novo* heteroplasmic *MT-ATP6* (m.8969G>A) mutation. Sideroblastic anaemia is also a prominent feature of Pearson's syndrome. *YARS2* mutations have predominantly been described in Middle East populations with variable phenotypes. Hence, this disorder may be underdiagnosed in other populations.
Aims: To delineate the clinical, molecular and genetic features of four Celtic patients harbouring *YARS2* mutations.
Patients and Methods: Patients were diagnosed by whole exome sequencing or targeted *YARS2* gene screening. Yeast modelling using *Saccharomyces cerevisiae* assessed pathogenicity of novel missense mutations. Immunoblotting assessed OXPHOS and YARS2 protein levels from fibroblasts and myoblasts of patient 1.
Results: All tested patients had lactic acidosis accompanied by generalised myopathy, global COX-deficiency and survived into adulthood. Only patients 2.1 and 2.2 exhibited sideroblastic anaemia.

Hypertrophic cardiomyopathy presented in three patients and preceded demise with respiratory insufficiency in patients 2.1 and 2.2. Patients 2.1 and 3 shared a homozygous p.[Leu392Ser] *YARS2* mutation. Patient 1 had compound heterozygous (p.[Cys369Tyr];[Val383_Glu388dup]) mutations. Yeast modelling correlated with patient phenotypes. Immunoblotting revealed no change in YARS2 protein levels and mild OXPHOS defects.
Conclusion: We propose that p.[Leu392Ser] is a founder mutation in Celtic populations. Absence of sideroblastic anaemia suggests that *YARS2*-related mitochondrial disease is variable and may not present as the classical MLASA phenotype. Hence, screening should be considered for patients of all ethnicities presenting generalised myopathy, lactic acidosis and prominent respiratory failure.

P62

The role of mitochondrial dysfunction in inflammatory crosstalk between immune cells and non-myeloid cells such as fibroblasts and myoblasts

Dr Katarzyna Swist-Szulik[1], Dr Lee Borthwick[2], Prof Doug Turnbull[1], Dr Robert McFarland[1], Prof Robert Taylor[1]
[1]Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle upon Tyne,UK, [2]Fibrosis Group, Newcastle upon Tyne, UK

Background: Mitochondria are intracellular organelles responsible for a wide range of metabolic processes and are the primary source of cellular energy. Mitochondria are also involved in activation of molecular platform called NRLP3 inflammasome and secretion of pro-inflammatory cytokine such as IL-1β in immune cells. Current studies indicate a role of mitochondrial dysfunction and inflammation in disease process seen in patients with inflammatory myopathies, neurodegenerative disease or sterile inflammation.
Aims: To characterise the nature and correlation between mitochondrial dysfunction and cytokine crosstalk between inflammatory cells like monocytes and non-immune cells like fibroblasts, myoblasts with induced and inherited mitochondrial dysfunction.
Methods: Monocytes were treated with LPS and benzylated ATP for inflammasome activation. Supernatants containing IL-1β from treated for inflammasomes monocytes as well as recombinant IL-1β were applied on fibroblasts and myoblasts with induced by Rotenone (Complex I inhibitor) and benzylated ATP mitochondrial dysfunction. ELISA tests were used to measure the content of IL-1β and IL-6 in supernatants. Immunohistochemistry was used to look at components of inflammasome platform and IL-6 on muscle sections with inflammatory myopathies.
Results: Mitochondrial dysfunction induced by Rotenone in monocytes increases level of released IL-1β. Fibroblasts and myoblasts do not release IL-1β via inflammasome pathway however release IL-6 in the presence of IL-1β in the dose dependent manner. Fibroblasts and myoblasts with induced mitochondrial dysfunction produce more IL-6 in comparison to healthy cells. IL-6 level increases in the presence of recombinant IL-1β in close correlation to the degree of mitochondrial dysfunction and in IL-1β dose dependent manner. IL-6 released by fibroblasts is in 90% inhibited by adding IL-1 receptor antagonist (IL-Ra) and anti-IL-1β antibodies what would suggest single cytokine crosstalk between IL-1β and IL-6.
Conclusions: The data indicate the presence of crosstalk between monocytes and fibroblasts and myoblasts on the cytokine level characterized by IL-1β and IL-6 relationship and mitochondrial dysfunction contributes to the level of secreted interleukins.

P63

Characterisation of Polymerase gamma (*POLG*)-mutant fibroblasts with Alpers' and Alpers'-like disease

Maria Eleni Anagnostou[1], Robert W. Taylor[1], Robert McFarland[1]
[1] *Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*
m.e.anagnostou@newcastle.ac.uk

Background: Alpers' syndrome is a rare hepatocerebral syndrome, characterised by intractable seizures and liver failure. Over 90% of Alpers' cases are caused by mutations located in the catalytic subunit of the polymerase gamma (*POLG*) gene, the only DNA polymerase known to exist in mammalian mitochondria. *POLG* mutations result in mitochondrial DNA (mtDNA) depletion in affected tissues leading to oxidative phosphorylation (OXPHOS) defects with consequent development of disease. However, the underlying mechanisms have been poorly characterised.
Aims: To characterise the basal mitochondrial function in patient-derived *POLG*-mutant fibroblasts, prior to transformation into neural progenitor cells (NPC's).
Methods: *POLG*-mutant fibroblasts were derived from 1 adult patient homozygous for the linker p.Ala467Thr mutation and 2 paediatric patients harbouring the p.Ala467Thr mutation in a compound heterozygous state with linker p.Leu428Pro and polymerase p.Thr914Pro mutations respectively. Experimentation involved: live cell imaging, real-time PCR, bioenergetics and western blotting with respect to appropriate controls.
Results: Morphological assessment of mitochondrial networks and nucleoids of *POLG*-mutant fibroblasts did not reveal significant abnormalities compared to controls. The mtDNA copy number of patient fibroblasts ranged from 46% to 70% of the control mean. Bioenergetics analysis revealed a trend of reduced baseline oxygen consumption rate ($p=0.0782$) and ATP production ($p=0.0662$) in patient fibroblasts, although not significantly. Further, protein expression of POLG did not show major alterations compared to controls as verified by western blotting.
Conclusion: Our findings suggest a mild dysfunction of mitochondrial respiration in *POLG*-mutant fibroblasts, which is not sufficient to recapitulate the disease phenotype. In line with literature, these results suggest that *POLG*-mutations exert tissue-specific effects. The investigation of neurons through direct conversion, will enable rapid disease modelling and inform the molecular mechanisms of epilepsy; the predominant manifestation of Alpers'.

P64

***De novo* dominant mutations in *SLC25A4* cause severe early-onset mitochondrial disease and loss of mitochondrial DNA copy number**

Kyle Thompson[1], Homa Majd[2], Karit Reinson[4], Christina Dallabona[3], Charlotte L. Alston[1], Langping He[1], Martin King[2], Tiziana Lodi[3], Katrin Õunap[4], Andres Piirsoo[4], Sanna Puusepp[4], Sander Pajusalu[4], Tuuli Metsvaht[4], Richard J. Rodenburg[5], Aviva Fattal-Valevski[6], Nitay Fraenkel[7], Ines Barbosa[8], Michael A. Simpson[8], Charu Deshpande[9], Roshni Vara[9], Penelope Bonnen[10], Simon Jones[11], Ileana Ferrero[3], Orly Elpeleg[7], Robert McFarland[1], Edmund Kunji[2] and Robert W. Taylor[1].
[1]*Wellcome Trust Centre for Mitochondrial Disease, Newcastle University, UK*
[2]*MRC Mitochondrial Biology Unit, Cambridge, UK*
[3]*Department of Life Sciences, University of Parma, Italy*
[4]*Department of Genetics, Tartu University Hospital, Tartu, Estonia*
[5]*Department of Pediatrics, Nijmegen Center for Mitochondrial Disorders, Nijmegen, The Netherlands*
[6]*Pediatric Neurology Unit, Dana Children Hospital, Tel-Aviv, Israel*
[7]*The Monique and Jacques Roboh Department of Genetic Research, Hadassah, Hebrew University Medical Center, Jerusalem, Israel*
[8] *Division of Genetics and Molecular Medicine, King's College London School of Medicine, London, UK*
[9] *Department of Genetics, Guy's and St. Thomas' NHS Foundation Trust, London, UK*
[10]*Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA*
[11]*Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK*
kyle.thompson@newcastle.ac.uk

Background: Mutations in *SLC25A4* encoding the mitochondrial ADP/ATP carrier AAC1 are a well-recognised cause of mitochondrial disease. Several heterozygous *SLC25A4* mutations have been associated with adult-onset autosomal dominant progressive external ophthalmoplegia (adPEO) and a qualitative mitochondrial DNA defect (multiple mtDNA deletions). There are also reports of recessive

SLC25A4 mutations in patients presenting in late childhood/early adulthood with mitochondrial myopathy and cardiomyopathy.
Aims: To confirm the pathogenicity of dominant *de novo* mutations in the *SLC25A4* gene identified by whole exome sequencing of 5 patients with severe, early-onset mitochondrial disease.
Patients: All affected individuals presented at birth, were ventilator-dependent and, where tested, revealed combined mitochondrial respiratory chain deficiencies associated with a marked loss of mitochondrial DNA copy number in skeletal muscle.
Results: An identical *de novo* heterozygous c.239G>A, p.(Arg80His) mutation was demonstrated in 4 of the 5 patients by whole exome sequencing, whilst the other case harboured a *de novo* c.703C>G, p.(Arg235Gly) mutation. Analysis of patient skeletal muscle samples confirmed a slight decrease of AAC1 protein levels with marked loss of respiratory chain components. Equivalent mutations were modelled in *S. cerevisiae* and shown to cause a severe respiratory phenotype. Furthermore, using recombinant protein expression in *L. lactis* we show that both mutant proteins exhibit greatly impaired ADP/ATP transport activity.
Conclusion: This is the first work to demonstrate pathogenic *de novo,* dominant mutations in severe paediatric cases of mitochondrial disease and expands the known phenotypes of *SLC25A4* mutations.

Peripheral Nerve

‡**P65**
Impaired mitochondrial function in neuronal cells harbouring a dominant glycyl-tRNA synthetase mutation
Veronika Boczonadi[1]*, Kathrin Meyer[2], Brian Kaspar[2], Marina Bartsakoulia[1], Juliane S. Mueller[1], Rita Horvath[1]*
[1]*Institute of Genetic Medicine, Wellcome Trust Centre for Mitochondrial Research, Newcastle University, Newcastle upon Tyne, UK;* [2]*Nationwide Children Hospital, Columbus, Ohio, US.*
veronika.boczonadi@ncl.ac.uk

Background: Dominant mutations in the gene GARS, encoding the glycyl-tRNA synthetase, have been identified in patients with Charcot–Marie–Tooth peripheral neuropathy type 2D (CMT2D) or distal spinal muscular atrophy type V (dSMA-V). Autosomal recessive mutations in *GARS* have been recently detected in patients with systemic mitochondrial phenotypes. While most tRNA synthetases have two different forms, one for the cytosol and another for the mitochondrial translation, GARS has a dual function in both mitochondria and the cytoplasm. The molecular mechanisms behind the diverse clinical presentations are not fully understood.
Aims: Here we investigated whether dominant GARS mutations could cause mitochondrial abnormalities which consequently contribute to peripheral neuropathy.
Methods: To overcome the fact that fibroblasts often do not express the mitochondrial defect in tissue specific phenotypes we have directly converted patient fibroblasts carrying a novel heterozygous mutation (c.647A>G; pHis216Arg) in the catalytic domain of GARS into neuronal progenitor cells (iNPCs) following recently published protocols. Mitochondrial function was assessed on both fibroblasts and iNPCs including immunoblotting, BN-PAGE analysis, mitochondrial oxygen consumption measurement and immunostaining.
Results: As we expected fibroblasts did not show a mitochondrial translation defect, however, patient iNPCs demonstrated a gradually increasing mitochondrial protein translation defect through conversion mainly affecting complex IV. This cell linage specific mitochondrial dysfunction was presented by reduced levels of mitochondrial complexes and more importantly, significantly decreased maximal mitochondrial oxygen consumption capacity was observed compared to control iNPCs.
Conclusions: Our data suggest that an abnormal mitochondrial translation in neurons contributes to CMT2D neuropathy.

‡P66

Human, Fly and Cell models of Riboflavin Transporter Neuronopathy

Andreea Manole, Amelie Pandraud, Dimitri M. Kullmann, Michael G. Hanna, Mary M. Reilly, James E.C. Jepson and Henry Houlden

MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London WC1N 3BG

andreea.manole.13@ucl.ac.uk

Background - First described in 1894, Brown-Vialetto-Van Laere (BVVL) or riboflavin transporter neuronopathy is a rare, autosomal recessive neurodegenerative disorder characterised by bilateral sensorineural hearing loss, cranial nerve palsies, respiratory insufficiency and severe sensorimotor neuropathy. Most infants rapidly become ventilator-dependent and die during childhood. Mutations in two riboflavin transporter genes, SLC52A2 and SLC52A3, have been identified.

Aims - A) The spectrum of genetic defects; B) The *in-vitro* cellular effects of SLC52A2 mutations and riboflavin on metabolism and mitochondrial function; and C) The *in-vivo* consequences of the loss of the SLC52A3 homologue and thus riboflavin deficiency in the fruit fly, *Drosophila melanogaster*.

Methods - We used Sanger sequencing to screen 130 patients exhibiting cranial neuropathies and sensorimotor neuropathy +/- respiratory insufficiency. We then performed functional assays and measured activities of mitochondria respiratory complexes in patients with SLC52A2 mutations. We also employed an RNAi-mediated gene knockdown of the *Drosophila* SLC52A3 homologue to recapitulate the loss-of-function phenotype of BVVLs.

Results - We identified 18 BVVLs cases summing 5 SLC52A2 and 14 SLC52A3 pathogenic mutations, of which 4 SLC52A2 and 10 SLC52A3 variants were not previously reported. Mitochondrial respiratory complex I and complex II activity and mitochondrial membrane potential were decreased in SLC52A2 mutation patients and carrier fibroblasts as a consequence of a deficit in riboflavin, FAD and FMN status confirmed by HPLC.

Global knockdown of the *Drosophila* riboflavin transporter homologue revealed mitochondrial deficits in complex I activity and riboflavin, FMN and FAD levels. In addition, the flies had severely reduced life span and locomotor activity, recapitulating the patients' phenotype and pathology.

Conclusions - Overall our findings confirm the pathogenetic role of SLC52A2 and SLC52A3 in BVVL, and thus highlight the important clinical and therapeutic implications.

P67

Clinical and genetic characterisation of hereditary motor neuropathies

Bansagi B[1],Evangelista T[1],Steele H[1],Whittaker R[2],Lochmüller H[1],Chinnery P[1],Horvath R[1]

[1] *MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK*

[2] *Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK*

Boglarka.Bansagi@ncl.ac.uk

Background: The distal hereditary motor neuropathies (dHMN) encompass clinically and genetically heterogeneous groups of disorders caused by lower motor neuron pathology. Various age of onset, clinical course and associated neurological features complicate the phenotype and serve for disease classification.

Aims: This study was designed to focus on the disease prevalence, phenotype characteristics, mutation detection rate, mutational spectrum and phenotype-genotype analysis within the group of hereditary motor neuropathies.

Methods: We included 105 patients from 72 families presenting either with length-dependent distal predominantly motor symptoms or with distal motor neuropathy as part of a complex clinical syndrome. All patients were further classified into one of the overlapping groups of pure dHMN, motor predominant CMT2 and complex motor neurono- or neuropathies. We performed mutational screen within these groups and detailed neurological and electrophysiology assessments were carried out in order to

determine phenotype-genotype correlations. We evaluated the efficacy of next generation techniques as a tool in gene and mutation discovery.
Results: Patient distribution was 65/105 in dHMN, 15/105 in motor predominant CMT2 and 25/105 in complex motor neurono- or neuropathies groups. The dHMN prevalence in North-England was calculated 2.2 affected individual per 100.000 inhabitants. Causative gene mutations were concluded in 45.8% of hereditary motor neuropathies. The mutation detection rate was 45% in the dHMN group. The molecular diagnosis was achieved in 19 index patients by whole-exome sequencing, in 11 index cases by IPN gene panel approach and in 3 by candidate gene testing.
Conclusion: We investigated the phenotypic variability and the genetic spectrum of motor neurono-neuropathies. The significant increase in the mutation detection rate can be attributed to the development of next generation techniques and international datasets. Increasing knowledge on disease pathways will not only help to identify new genes with shared pathomechanisms but will provide a basis for novel therapy approaches.

P68

BALTiC study protocol: A feasibility analysis of home based BALance Training in people with Charcot-Marie-Tooth disease

Dudziec, M.[1,2], Reilly, M.M. & Ramdharry[2], G.M.[1,2]
[1]*Faculty of Health Social Care and Education, Kingston University/St George's University of London, UK*
[2]*MRC Centre for Neuromuscular Diseases, London, UK*
m.dudziec@ucl.ac.uk

Background: Charcot-Marie-Tooth disease (CMT) is the most common inherited neuromuscular disorder. People with CMT develop slow, progressive neuropathy manifesting with distal weakness and sensory loss. People with CMT report a high incidence of falls with 85.9% of 108 respondents in a recent survey reporting falling in the preceding year (Ramdharry et al., 2011). Exploratory work investigating the causes of these balance impairment show that both weakness and loss of sensation are factors. So far, little work has been done to find physical rehabilitation strategies addressing the key contributors to balance impairment in this group.
Aims: This study will investigate whether falls education alone or falls education plus a 12 week home based exercise programme of proximal muscle strengthening and multi-sensory balance training has an effect on functional balance measures in people with CMT.
Methods: A single blinded randomised controlled design will be used to investigate whether the intervention has an effect on balance measures. Ambulant people with all types of CMT will be invited to participate. The intervention group will undergo resistance training of the leg muscles and multi-sensory balance exercises. Both groups will undergo falls management education focusing on the causes of falls. A blinded assessor will record the outcome measures: static and dynamic posturography, subjective and objective measures of strength, sensation, activity and function and falls diary records. A sample of participants will be invited to undergo an interview to explore their experience of balance difficulties, falls and their experience of the trial.
Conclusion: Clinical physiotherapists adopt a problem solving approach to treatment for functional difficulties. The potential future impact of the study will be to inform physiotherapists of efficacious treatment for improving balance in people with CMT. This feasibility work will inform a power calculation for a future larger study.

P69

Defining the spectrum of intramuscular fat accumulation in hereditary sensory neuropathy type 1 using quantitative MRI

M.R.B. Evans*, N. Bantan**, J.M. Morrow*, C.D.J. Sinclair*, S. Shah**, M.G. Hanna*, J.S. Thornton**, T.A. Yousry**, M.M. Reilly*
** MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK.*
*** Neuroradiological Academic Unit, UCL Institute of Neurology, London, UK.*

Background: HSN1 is a rare, predominantly sensory neuropathy. With serine identified as a potential treatment, this study aims to identify MRI outcome measures by defining the spectrum of intramuscular fat accumulation (IFA).
Methods: We performed lower limb 3-point Dixon 3T MRI in thirty HSN1 patients and nine matched controls. Muscle fat fraction (ff) was quantified at distal thigh, proximal calf and distal calf levels. IFA was graded as mild, moderate or severe based on mean muscle ff (<10%;10-60%;>60% respectively).
Results: Mean muscle ff was significantly greater in HSN1 than controls (12.0%vs2.0% thigh; 26.7%vs2.3% prox. calf; 37.8%vs4.0% distal calf). One patient had severe; and seven had mild IFA at all levels. 22 patients had moderate IFA at least one level.
Conclusion: Despite classification as a 'sensory' neuropathy, a wide spectrum of IFA was seen in HSN1, identifying IFA as a potential outcome measure, warranting further assessment of responsiveness in longitudinal studies.

P70

Natural History Study in Hereditary Sensory Neuropathy Type 1 (HSN1)

Umaiyal Kugathasan[1], Matilde Laurá[1], Matthew Evans[1,2], Chris Sinclair[2], Thorsten Hornemann[3], Saranya Suriyanarayanan[3], Rahul Phadke[4], Khadijah Miller[4], Giuseppe Lauria[5], Raffaella Lombardi[5], James Polke[6], Julian Blake[7], Henry Houlden[1], David Bennett[8] and Mary M Reilly[1]
[1]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK; [2]Academic Neuroradiological Unit, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, UK; *[3]Institute for Clinical Chemistry, University Hospital Zurich, Switzerland; [4]Division of Neuropathology, National Hospital for Neurology and Neurosurgery, London, UK; [5]3rd Neurology Unit, IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy; [6]Neurogenetics Unit, National Hospital for Neurology and Neurosurgery, London, UK; [7]Department of Clinical Neurophysiology, Norfolk and Norwich University Hospital, Norwich, UK; [8]Nuffield Department of Clinical Neurosciences, Oxford, UK.*
u.kugathasan@ucl.ac.uk

Background: HSN1 secondary to *SPTLC1/2* mutations is a rare, slowly progressive neuropathy resulting in profound sensory loss, especially nociception, and variable but often severe motor deficit. It 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 limiting factor for undertaking a clinical therapeutic trial.
Aim: To identify responsive outcome measures to be used in trials in HSN1 patients.
Methods: One year natural history study was conducted using a variety of assessment methods to cover the spectrum of deficits seen in this condition. These include CMT Neuropathy score (CMTNS), MRI of calves and thighs, computerised myometry, quantitative sensory testing (QST), comprehensive neurophysiological assessment, proximal thigh skin biopsy for intra-epidermal nerve fibre density (IENFD), 1-dSLs plasma levels and patient based questionnaires (Neuropathic Pain Symptom Inventory and SF-36). Standardised Response Mean, SRM (mean change/standard deviation of change) was used to compare responsiveness between tests. The MRI data is still being analysed.
Results: 35 patients were recruited: 31 with *SPTLC1* (C133W) and 4 with *SPTLC2* mutations. There was marked heterogeneity in the severity of the phenotype with males generally having a more severe phenotype. All the outcome measures when analysed using the whole cohort, showed low responsiveness (SRM <0.5). The exception to this is pressure pain thresholds (components of QST) where SRM as high as 0.74 is noted. A large floor effect is seen in neurophysiology, subset of QST and IENFD assessments and as a result low SRMs (ranging from 0.01-0.21) are seen.
Conclusions: Measures of change are limited by floor effects seen in the more severely affected patients. In addition to the ongoing MRI data analysis, further analysis is underway to determine if sub-classification based on severity at baseline or patient specific outcome measures can improve the responsiveness.

P71

Zebrafish as model for RNA metabolism related neurological disorders

Juliane S. Müller[1], Michele Giunta[1], Nandor Baranyi[1], Veronika Boczonadi[1] , Rita Horvath[1]
[1] *John Walton Muscular Dystrophy Research Centre and Wellcome Trust Centre for Mitochondrial Research, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK*
Juliane.mueller@ncl.ac.uk

Background: Abnormal RNA metabolism is the cause of many severe inherited neurological disorders. Recessive mutations in the subunits EXOSC3 and EXOSC8 of the exosome, which is responsible for the degradation and maturation of RNA in the cell, are known to cause pontocerebellar hypoplasia type 1, spinal muscular atrophy and central nervous system demyelination. Dominant mutations in the glycyl-tRNA synthetase GARS have been identified in patients with Charcot–Marie–Tooth neuropathy type 2D or distal spinal muscular atrophy type V. Interestingly, recessive mutations in GARS can cause a systemic mitochondrial disorder. The molecular pathology of exosome and GARS mutations has yet to be clarified. We are using zebrafish to model the molecular consequences of dominant and recessive mutations in vivo.
Methods: We designed antisense morpholino oligonucleotides targeting EXOSC8 and GARS to knock down gene expression in order to model recessive loss of function mutations. In addition, we are using the CRISPR/Cas9 system to create mutant zebrafish lines. To investigate dominant mutations, mRNA encoding EGFP-tagged GARS containing missense mutations is injected into zebrafish embryos at the one-cell stage. Antibody staining is used to visualise defects in muscle fibres and neuromuscular junctions in zebrafish embryos.
Results: Whereas morpholino injections are a quick model for a recessive disorder, they also carry the risk of unspecific off-target effects. We established the CRISPR/Cas9 technology for zebrafish in our lab and we are currently raising the first generation of EXOSC8 mutants. Injection of mutant GARS mRNA causes a developmental phenotype with abnormal somite and motor axon formation. Expression of GARS from the injected mRNA, however, is too short lived to investigate late onset phenotypes.
Conclusion: Zebrafish offers the possibility to create transient and stable models for different disorders. We hope that our results in zebrafish will contribute towards determining the molecular mechanisms of exosome and GARS mutations.

P72

Patient & Public Involvement: How service user engagement has informed research into falls interventions in people with Charcot Marie Tooth Disease

Ramdharry, G.M.[1,2], Dudziec, M.[1,2], Reilly, M.M.[2]
[1] Faculty of Health Social Care and Education, Kingston University/St George's University of London, UK
[2] MRC Centre for Neuromuscular Diseases, London, UK
g.ramdharry@ucl.ac.uk

Background: Patient and Public Involvement (PPI) is now a requirement of many funders for clinical research. The INVOLVE organisation defines PPI in research as *"research being carried out '**with**' or '**by**' members of the public rather than '**to**', '**about**' or '**for**' them".* One aspect is consultation to understand issues and identify research topics. Here we present the method and results of a focused PPI activity and how it has informed a research program for people with Charcot Marie Tooth disease.
Aims: Consult people with CMT on strategies they use to address the problem of poor balance and falls.
Methods: Two methods were used to collate responses from people with CMT:

(1) Two workshops were held as part of the CMT United Kingdom annual general meeting. Attendees were asked to discuss and answer two questions:
    1. What have you found improves your balance?
    2. What do you do or use to prevent falls?
(2) The CMT United Kingdom has a strong social media presence. They gave permission for the two questions to be posted on their Facebook page.

Responses from both sources were collated. Data was coded and thematic analysis was used to identify the emergent topics.
Results: In total, 76 suggested strategies were obtained for question 1 and 74 for question 2. For question 1, the four most common strategies used were 1) use of orthoses (22.4%); 2) walking aids (21.1%); 3) good footwear (19.7%); 4) regular exercise (17.1%). For question 2, the four most common strategies used were 1) paying attention and planning ahead (37.8%); using walking aids and support (28.4%); regular exercise (9.5%) and use of orthoses (6.8%).
Conclusion: These results have now been incorporated into a funded pilot home based falls management /exercise intervention, and a PhD studentship exploring the use of walking aids and the effect of orthoses on balance.
Acknowledgements: CMT United Kingdom charity

P73

Facial Onset Sensory and Motor Neuronopathy: An extension of the FTD-MND spectrum

Rossor AM[1], Jaunmuktane Z[2], Healy E[3], Holton J[2], Reilly MM[1]

1. *MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, WC1N 3BG*
2. *Department of Neuropathology, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, WC1N 3BG*
3. *Department of Neuropathology, Royal Victoria Infirmary, Belfast, BT12 6BA*

a.rossor@ucl.ac.uk

Background: Facial onset sensory and motor neuronopathy describes a clinical syndrome characterised by asymmetric facial numbness or paraesthesia, bulbar palsy and facial weakness which may progress to the upper limbs. Previous post mortem studies have reported TDP-43 inclusions in some but not all cases and it remains unclear whether FOSMN should be considered part of the FTD-MND spectrum.
Aims: To investigate whether there are TDP43 inclusions in post mortem tissue from a patient with a clinical diagnosis of FOSMN and features of the behavioural variant of FTD.
Methods: A post mortem examination was performed on a 54 year old gentleman with FOSMN who died of an aspiration pneumonia. A phosphorylation independent TDP43 antibody was used to label both normal nuclear TDP43 and pathological inclusions.
Results: Post mortem examination revealed a mild increase in microglial cells in the cerebral white matter and cortex and a more pronounced increase within the midbrain, pons, medulla and grey matter of the spinal cord. Neuronal cytoplasmic TDP43 inclusions with globular and skein morphology were seen in both anterior horn cells and dorsal root ganglia. TDP43 pathology was more prominent in the spinal cord and brainstem than in the neocortex and subcortical hemispheric white matter where it was rare. No amyloid-beta, tau or alpha-synuclein pathology was seen.
Conclusion:
This case provides further evidence that FOSMN is a neurodegenerative disease characterised by TDP-43 pathology. The association of cortical TDP43 inclusions and features of the behavioural variant of FTD suggest that FOSMN falls within the FTD-MND spectrum.

P74

Developing allele-specific gene silencing as a therapeutic strategy for hereditary sensory neuropathy type I

Verna Sarajarvi[1,2], Mary M. Reilly[2], Francesco Muntoni[1] and Haiyan Zhou[1]
1 Dubowitz Neuromuscular Centre, Molecular Neurosciences Section, Developmental Neurosciences Programme, Institute of Child Health, University College London, WC1N 1EH, UK.
2 MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and The National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK.
verna.sarajarvi.12@ucl.ac.uk

Background: Allele-specific silencing of gene expression is a potential therapeutic strategy for dominant genetic diseases in which haploinsufficiency is not pathogenic. Hereditary sensory neuropathy type 1 (HSN1) is most frequently caused by mutations in the *SPTLC1* gene. The most common mutation in *SPTLC1* in the UK HSN1 population is a missense variation (c.399T>G/p.C133W) in exon 5. Different approaches can be used to induce specific silencing of the mutant allele, including 1) antisense oligonucleotide (AON) to induce RNase H mediated RNA cleavage activated by RNA-DNA hybrids; and 2) small interfering RNAs (siRNAs) that cause mRNA degradation by activating the RNA-induced silencing complex.
Aims: In this study we aim to investigate the ability of different AON and siRNA approaches to specifically silence the mutant *SPTLC1* allele.
Materials and methods: A patient fibroblast cell line harbouring the dominant c.399T>G mutation was used as a cellular model. Different AONs targeting the mutation have been synthesised as Gapmer with phosphorothioate (PS) and 2'-O-methyl (2'-OMe), Locked nucleic acid (LNA) or 2'-deoxy-2'-fluoro-beta-D-arabinonucleic acid (2'FANA) chemistries, or as Multimer with PS and 2'FANA chemistries. A series of siRNAs targeting the dominant mutation are also being evaluated. PCR, Sanger sequencing and real-time PCR were used to investigate the efficiency of allele-specific silencing by AONs and siRNAs.
Results: Our preliminary data show that the silencing efficiency of Gapmer and Multimer AONs was concentration-dependent and varied with sequence length, target site and chemical modifications. We have identified a number of promising lead AONs that show a significant and specific suppression of the mutant allele. We are currently in the process of screening additional AONs and siRNAs.
Conclusion: Allele-specific gene silencing is a potential therapeutic strategy for HSN1. Further improvements to the design of AONs and siRNAs are required in order to improve the silencing efficacy and specificity.

P75

Incidence and Risk Factors for Neuropathy Following Primary Total Hip Arthroplasty

Authors: Joseph Nguyen[1], Edwin Su[1], Stephen Lyman[1], Erin Manning[1], Kelianne Cummings[2], Anita Wu[3], Mayu Sasaki[1], Aashka Dalal[1], Charlotte Ching[1], **Teena Shetty[1]**
[1]Hospital for Special Surgery, New York, NY, USA, [2]SUNY Downstate Medical Center, Brooklyn, NY, USA, [3]Carolinas HealthCare System, Charlotte, NC, USA
shettyt@hss.edu

Background: Post-surgical neuropathy is a rare, but potentially devastating complication following total hip arthroplasty (THA). Previous literature suggests that prevalence of post-operative neuropathy ranges from 0.2% to 1.9% in primary THA cases.
Aims: This study identifies potential risk factors for neuropathy after primary THA at a tertiary orthopedic institution.
Methods: Patients who developed neuropathy following THA between January 1, 1998 and December 31, 2013 were identified by electronic hospital records and matched with 2 controls. The controls were matched by surgical date. Patient and surgical variables were reviewed using data from patient charts. A multivariable logistic regression model was created to identify potential risk factors for neuropathy. Odds ratios (OR) were calculated from parsimonious stepwise models. Variables that had p-values of 0.10 or below were retained and p-values ≤0.05 were deemed statistically significant.
Results: There were 81 neuropathy cases identified out of 39,056 primary THAs (0.21%) performed at our institution during the study period. The cases were matched with 162 controls. The mean age of neuropathy cases was 63 years. Patients older than 50 years were found to be less at risk for developing neuropathy (OR 0.38). Conversely, patient history of smoking (OR 3.45), lumbar spine disease or surgery (OR 2.29), and spinal stenosis (OR 4.31) were associated with increased risk. Surgeries between 10AM to 1PM (OR 1.71) and 1PM or later (OR 3.98) were also found to increase risk.
Conclusion: The study demonstrates neuropathy is a rare complication following primary THA at our institution. Afternoon surgeries should be investigated, as personnel fatigue or shift change may be a cause for increased risk. Spinal stenosis and lumbar spine disease, and smoking history should be closely

monitored to inform the patient and surgeon for the potential increased risk of post-operative neuropathy following THA.

P76

Incidence and Risk Factors for Neuropathy Following Primary Total Knee Arthroplasty

Authors: Joseph Nguyen[1], Edwin Su[1], Stephen Lyman[1], Erin Manning[1], Kelianne Cummings[2], Anita Wu[3], Mayu Sasaki[1], Aashka Dalal[1], Charlotte Ching[1], **Teena Shetty[1]**

[1]Hospital for Special Surgery, New York, NY, USA, [2]SUNY Downstate Medical Center, Brooklyn, NY, USA, [3]Carolinas HealthCare System, Charlotte, NC, USA

shettyt@hss.edu

Background: Post-operative neuropathy following TKA is a rare, but potentially catastrophic complication. Previous literature reports the prevalence of neuropathy following primary TKA as 0.3% to 2.2% of patients.

Aims: This study identifies potential risk factors for neuropathy after primary TKA at a tertiary orthopedic institution.

Methods: Patients who developed neuropathy following TKA between January 1, 1998 and December 31, 2013 were identified by electronic hospital records and were matched with 2 controls. A multivariable logistic regression model was created to identify potential risk factors for neuropathy. Odds ratios (OR) were calculated from parsimonious stepwise models. Variables that had p-values of 0.10 or below were retained in the final model and p-values ≤0.05 were deemed statistically significant.

Results: There were 60 neuropathy cases identified out of 39,990 primary TKAs (0.15%) performed at our institution that were matched with 120 controls. The mean age and BMI of neuropathy cases was 67 years and 31.5 kg/m^2, respectively. Adjusting for all other variables in the model, females (OR 2.13) and patients with increasing BMI were found to be associated with increased risk of post-operative neuropathy. Patients with a history of lumbar spine disease or surgery (OR 11.8) and using low molecular weight heparin (LMWH) for thromboprophylaxis (OR 1.37) were found to be significant risk factors.

Conclusions: The study demonstrates neuropathy is a rare complication following primary TKA at our institution. Females have a higher incidence of lateral compartment disease leading to valgus alignment, which may explain the greater risk. Bleeding associated with LMWH may account for increased frequency of post-operative hematoma. Patients with increased BMI and those with a history of spinal disease or spinal surgery should be closely monitored to inform the patient and surgeon for the potential increased risk of neuropathy following TKA.

P77

Monitoring pregnancy in Charcot-Marie-Tooth disease: results of a survey

Mariola Skorupinska[1], Matilde Laurá[1], Karen Bull[1], Bridgette Byrne[2], Mary M. Reilly[1]

[1]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London UK, [2]Coombe Women and Infants University Hospital, Dublin

Background: Charcot Marie Tooth (CMT) disease is the most common inherited peripheral neuropathy. Patients frequently ask whether pregnancy will affect their CMT, whether CMT will affect their pregnancy, the optimal delivery and whether they or their child will have a higher risk of complications during pregnancy or delivery. So far only few studies address these questions. Currently guidelines for the management of pregnancy, delivery and postnatal care in CMT patients are not available.

Aim: To assess the impact of pregnancy on CMT and to assess how CMT affects pregnancy, the delivery and the care of the new born baby.

Methods: We designed a questionnaire, with expert help from an obstetrician with a special interest in pregnancy in patients with medical conditions, to assess the impact of pregnancy on CMT, to determine how CMT affects pregnancy, the delivery and the care of the new born baby. The questionnaire is divided in 4 parts (prior, during, after pregnancy and delivery) and includes 29 questions on impairment, falls,

pain, fatigue and respiratory complications during those periods; type of delivery, possible complications, details of anaesthesia and difficulties looking after the baby in the first couple of months.
Results: The survey is currently ongoing. So far 23 CMT women answered the questionnaire. Preliminary results show deterioration of CMT symptoms during pregnancy in 9 women (39%) which did not resolve after delivery in 4 women. So far none of the women reported any complications related to anaesthesia. 53% of deliveries were natural, 12% were assisted and 29% were caesarean which are similar to the normal population in UK.
Conclusions: The data acquired from this survey will provide valuable information on current practice and will inform future guidelines and standard of care in Charcot Marie Tooth disease.

P78

Dominant *Gars* mutations cause a sensory neuron fate switch in CMT2D mice

James N. Sleigh[1,2,], John Dawes[2], Steven J. West[2], Adriana Gómez-Martín[1], Gustavo Pregoni[1], M. Zameel Cader[2], Kevin Talbot[2], David L. Bennett[2], Giampietro Schiavo[1]
[1] *Sobell Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College London, London WC1N 3BG, UK*
[2] *Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK.*
j.sleigh@ucl.ac.uk

Charcot-Marie-Tooth disease (CMT) is a group of hereditary peripheral neuropathies that display characteristic motor and sensory dysfunction. CMT type 2D (CMT2D) is caused by dominant, toxic, gain-of-function mutations in the widely expressed, housekeeping gene *GARS*. *GARS* encodes glycyl-tRNA synthetase (GlyRS), which links the amino acid glycine to its cognate tRNA, thereby ensuring the fidelity of the genetic code. The mechanisms underlying selective nerve pathology in CMT2D remain a mystery, as does the cause of the mild-to-moderate sensory involvement that distinguishes CMT2D from the allelic disorder distal spinal muscular atrophy type V. To elucidate the origin of sensory pathology and thus illuminate features of the disease mechanism, we have analysed the sensory system in CMT2D $Gars^{C201R/+}$ mice. Culturing primary dorsal root ganglion (DRG) cells at one month of age, we have shown that mutant sensory neurons display no discernable defects in morphology or survival compared to wild-type cells. We do, however, find a selective reduction in the percentage of medium-to-large area neurons positive for NF200 (proprioceptive and mechanoreceptive cells). This phenotype, and the concomitant increase in small area peripherin^{+} neurons (pain-sensing nociceptive cells), is replicated in mutant DRG *in vivo*, and leads to behavioural defects in proprioception and mechanosensation, and a hypersensitivity to thermal and mechanical pain. Together with comparable L5 DRG cell counts and cleaved-caspase 3 protein levels between genotypes, this indicates that a possible peri- or pre-natal switch in sensory neuron fate is the cause of the sensory pathology. This work corroborates our previous finding that there appears to be a developmental component to CMT2D pathology (Sleigh *et al.* 2014 Hum Mol Genet 23: 2639-50), and will help to ultimately understand how specific molecular differences between sensory neuron subtypes during development selectively predispose them to the toxic effects of mutant GlyRS.

P79

Neurological consequences of Non-Freezing Cold Injury

Andreas C. Themistocleous*[1], Tom Vale*[1], David L.H. Bennett[1]
*The authors contributed equally to the work
[1] *Nuffield Department of Clinical Neurosciences, University of Oxford*
andreas.themistocleous@ndcn.ox.ac.uk

Non-freezing cold injury is a clinical syndrome that occurs when peripheral tissues are exposed to cold temperatures close to the freezing point of water for sustained periods. It is a common injury of military personnel of African and Caribbean descent as they are at 30 times increase risk of developing non-

freezing cold injury. Non-freezing cold induced injury causes significant long term morbidity, in particular severe neuropathic pain affecting the hands and feet. Very little is known about the underlying neurological deficits and the pathophysiological mechanisms for the neuropathic pain. Our aim was to investigate for evidence of peripheral neuropathy, and explore the relationships between pain symptomatology and peripheral sensory dysfunction. Patients were assessed using a detailed medical interview that included: questionnaires to assess severity and nature of pain, structured neurological examination, quantitative sensory testing (QST, using the protocol of the German Neuropathic Pain Network), skin biopsy for intraepidermal nerve fibre density (IENFD) measurement and nerve conduction studies. Six patients have currently been assessed. All patients had ongoing moderately severe neuropathic pain involving the hands and feet, with severe intermittent exacerbations caused by cold. Neurological exam showed loss of thermal sensitivity and pinprick sensitivity in the hands and feet. IENFD, normalised for age and gender, were reduced. QST results were variable with an overall loss of sensation across a number of sensory modalities. Nerve conduction studies were normal. Preliminary data supports the possibility that non-freezing cold induced injury causes a small fibre neuropathy. There is a symmetrical, distal loss of pinprick and temperature sensation, reduced intra-epidermal nerve fibre density of the distal leg and normal nerve conduction studies. We are currently recruiting and assessing more patients to confirm our initial findings.

P80

The Pain in Neuropathy Study (PiNS): A cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy

Andreas C. Themistocleous*[1], Juan D. Ramirez*[1], Pallai R. Shillo[2], Jonathan G. Lees[3], Dinesh Selvarajah[2], Christine Orengo[3], Solomon Tesfaye[2], Andrew S.C. Rice [4 5], David L.H. Bennett[1]
*The authors contributed equally to the work
[1] *Nuffield Department of Clinical Neurosciences, University of Oxford*
[2] *Diabetes Research Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, U.K.*
[3] *University College London*
[4] *Pain Research Group, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital Campus, London, UK*
[5] *Pain Medicine, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK*
andreas.themistocleous@ndcn.ox.ac.uk

Disabling neuropathic pain (NeuP) is a common sequel of diabetic peripheral neuropathy (DPN). We aimed to characterise sensory phenotype of patients with and without NeuP, assess screening tools for NeuP, and relate DPN severity to NeuP. The Pain in Neuropathy Study (PiNS) is an observational cross-sectional multicentre study. 191 patients with DPN underwent neurological examination, quantitative sensory testing, nerve conduction studies and skin biopsy for intra-epidermal nerve fibre assessment. A set of questionnaires assessed the presence of pain, pain intensity, pain distribution and the psychological and functional impact of pain. Patients were divided according to the presence of DPN, and thereafter according to the presence and severity of NeuP. The DN4 questionnaire demonstrated excellent sensitivity (88%) and specificity (93%) in screening for NeuP. There was a positive correlation between greater neuropathy severity ($r= 0.39$, $P < 0.01$), higher HbA1c ($r= 0.21$, $P < 0.01$), and the presence (and severity) of NeuP. DPN sensory phenotype is characterised by hyposensitivity to applied stimuli that was more marked in the moderate/severe NeuP group than the mild NeuP or no NeuP groups. Brush evoked allodynia was present in only those with NeuP (15%), the paradoxical heat sensation did not discriminate between those with (40%) and without (41.3%) NeuP. The 'irritable nociceptor' subgroup could only be applied to a minority of patients (6.3%) with NeuP. This study provides a firm basis to rationalise further phenotyping of painful DPN, for instance stratification of DPN patients for analgesic drug trials.

P81

A de novo dominant mutation in the kinesin domain of *KIF1A* is a cause of autism spectrum disorder and axonal neuropathy

Pedro J Tomaselli[1], Alexander M Rossor[1], Alejandro Horga[1], Matilde Laura[1], Henry Houlden[2], Mary M Reilly[1]
1. MRC Centre for Neuromuscular Diseases and National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK
2. Department of Neurogenetics, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, WC1N 3BG, UK.
p.tomaselli@ucl.ac.uk

Background: Recessive mutations in the kinesin family member 1A gene (*KIF1A*) have been reported as causative of hereditary sensory neuropathy and hereditary spastic paraplegia. More recently, de novo dominant mutations have been shown to cause a complex phenotype characterized by developmental delay, cerebellar ataxia, spasticity and peripheral neuropathy. Autism spectrum disorder (ASD) has never previously been reported in association with mutations in *KIF1A*.
Aims: To report the case of a 20-year old male with early onset spasticity, axonal neuropathy and ASD.
Methods: We performed whole exome sequencing to determine the genetic cause of our patient's phenotype. Variants were filtered to include only nonsynonymous variants, those with a minor allele frequency of <1% in the ExAc, 1.000 Genomes and EVS databases, and both dominant and recessive patterns of inheritance.
Results: We identified a de novo dominant mutation, c.38G>A (p.R13H), in *K1F1A* in a 20 year old male with spasticity, axonal neuropathy and ASD. This mutation is located within a highly conserved region, both between species and among the kinesin family of proteins, where it forms part of the ATP binding site of the kinesin motor domain.
Conclusion: Mutations in the KIF1A gene cause a complex phenotype that in addition to axonal neuropathy and spasticity now also includes autism spectrum disorder. The mutation in our patient affects the ATP-dependent motor domain and is likely to disrupt anterograde axonal transport leading to both neurodevelopmental (ASD) and neurodegenerative (peripheral neuropathy) phenotypes.

P82
HNPP due to a heterozygous deletion of exons 4 and 5 of the PMP22 gene

Pedro J Tomaselli[1], Alexander M Rossor[1], Roy Poh[2], James Polke[2], Matilde Laura[1], Henry Houlden[2], Mary M Reilly[1]
1. MRC Centre for Neuromuscular Diseases and National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK
2. Department of Neurogenetics, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, UK.
p.tomaselli@ucl.ac.uk

Background: Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant disease that is commonly caused by a 1,5Mb deletion of chromosome 17p resulting in haploinsufficiency of peripheral myelin protein 22 (PMP22).
Aim: To report the case of a patient with HNPP due to a partial deletion of *PMP22*.
Methods: Multiplex ligation-dependent probe analysis (MLPA) was used to identify deletion of the PMP22 gene.
Results: The proband presented with recurrent common peroneal nerve palsies beginning in the second decade of life. By the age of 40 he had developed a permanent right foot drop. Nerve conduction study demonstrated a patchy demyelinating neuropathy with bilateral prolonged median distal motor latencies and bilateral ulnar nerve slowing at the elbows. MLPA revealed a heterozygous deletion of exons 4 and 5 of the PMP22 gene.

Conclusions: Heterozygous deletion of exons 4 and 5 of PMP22 cause an identical phenotype to HNPP caused by the common 1.5 Mb deletion of chromosome 17p. Deletion of exons 4 and 5 are predicted to create a truncated protein that is unstable and rapidly degraded, leading to PMP22 haploinsufficiency.

P83

Cellular pathomechanisms of Hereditary Sensory Neuropathy Type 1 (HSN-1) in mammalian motor neurons

Emma Wilson[1, 2], Bernadett Kalmar[1], Maiya Kugathasan[1, 2], Andrey Abramov[3], Mary M Reilly[2], Linda Greensmith[1, 2]

[1]*Sobell Department of Motor Neuroscience and Movement Disorders,* [2]*MRC Centre for Neuromuscular Diseases,* [3]*Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square House, Queen Square, London WC1N 3BG*

Emma.wilson.09@ucl.ac.uk

Background: HSN-1 is a peripheral neuropathy most frequently caused by missense mutations in the **SPTLC1/ SPTLC2** genes, which code for two subunits of the enzyme serine palmitoyltransferase (SPT). SPT catalyzes the first and rate-limiting step of *de novo* sphingolipid synthesis. It has been proposed that mutations in SPT result in a change in enzyme substrate specificity which results in the production of two atypical sphinganines- deoxysphinganine (DSp) and deoxymethylsphinganine (DMSp), rather than the normal enzyme product, sphinganine (Sp). Levels of DSp and DMSp are elevated in the blood of HSN-1 patients and this is thought to cause the peripheral nerve damage characteristic of the disease. However, the underlying pathomechanism of how DSp and DMSp damage neurons remains elusive.
Aims and methods: DSp and DMSp-mediated neurotoxicity was examined in primary mouse motor neurons, by assessing cell survival and neurite outgrowth following exposure to different concentrations of Sp, DSp or DMSp. We also explored the potential mechanisms that underlie DSp/DMSp neurotoxicity, by characterizing mitochondrial function and changes in calcium regulation.
Results: The abnormal enzyme products DSp and DMSp have a dose-dependent, neurotoxic effect in primary motor neurons after just 24 hours of treatment. These abnormal sphingolipids not only cause significant neuronal death, but reduce neurite outgrowth. Within two hours of treatment with DSp and DMSp we also observed significant deficits in mitochondrial function and calcium handling, manifesting in an increase in mitochondrial calcium levels and a decrease in mitochondrial membrane potential.
Conclusions: Our results show that the aberrant sphinganines have a dose-dependent neurotoxic effect in primary motor neurons. Furthermore, DSp and DMSp have very rapid, deleterious effects on mitochondria and calcium signalling, and these effects may play a role in their neurotoxic effects.

Motor Neuron Disease

‡P84

Development of a cell-penetrating peptide for the delivery of antisense oligonucleotides to peripheral and CNS tissues of spinal muscular atrophy mice

Suzan M Hammond[1], Melissa Bowerman[1], Frank Abendroth[2], Gareth Hazell[1], Karin Meijboom[1], Corinne A Betts[1], Larissa Goli[1], Francesco Catapano[3], Haiyan Zhou[3], Francesco Muntoni[3], Michael J Gait[2], Matthew JA Wood[1]

[1]*Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, OX1 3QX, UK*
[2]*Medical Research Council, Laboratory of Molecular Biology, Cambridge CB2 0QH, UK*
[3]*Dubowitz Neuromuscular Centre, Institute of Child Health, University College London, London, WC1N 1EH, UK*

Spinal muscular atrophy (SMA) is a severe neuromuscular disorder which results from functional loss of the survival motor neuron 1 (*SMN1*) gene and is characterized by the degeneration of lower motor neurons and muscular atrophy. Humans carry a genomic duplication which gave rise to a second gene,

SMN2. A critical difference between *SMN1* and *SMN2* is a C to T substitution which leads to aberrant splicing of exon 7 and production of an unstable SMNΔ7 protein. Thus, *SMN1* expresses the full-length (FL) SMN protein while *SMN2* mostly produces the SMNΔ7 protein. Recently, the use of antisense oligonucleotides (ASOs) that bind *SMN2* mRNA, modify its splicing and induce exon 7 inclusion, has emerged as a viable therapy for SMA. ASOs show promise in SMA mice and successful improvements of patients in phase II clinical trials. However, they require invasive administration methods for adequate delivery to the CNS and do not provide systemic delivery to peripherally affected tissues. An alternate method is to covalently conjugate the ASO to a cell-penetrating peptide (CPP). We have developed such a peptide-conjugated ASO (Pip6a-PMO) that efficiently modulates splicing in peripheral and CNS tissues when delivered via a less invasive intravenous injection. In neonatal SMA mice, Pip6a-ASO significantly upregulates FL*SMN2* in CNS and peripheral tissues, rescues lifespan and overall improves the neuromuscular phenotype. Pip6a-ASO also crosses the blood brain barrier in adult mice, upregulating FL*SMN*2 transcripts in the spinal cord and brain. Following this success we aim to generate further CPPs that can more effectively penetrate CNS and peripheral tissues in adult mice and display an enhanced favorable toxicity profile. Here, we present the CPPs evaluated in neonatal SMA pups and adult WT mice that express human *SMN2*. Our goal is to develop a novel clinically amenable and relevant CPP-ASO approach for SMA.

‡P85

Microvascular defect as potential peripheral target in spinal muscular atrophy

Haiyan Zhou[1], Ying Hong[2], Palittiya Sintusek[1], Mariacristina Scoto[1], Simon Parson[3], Paul Brogan[2] and Francesco Muntoni[1]

[1] *Dubowitz Neuromuscular Centre, Molecular Neurosciences Section, Developmental Neuroscience Programme, Institute of Child Health, University College London, WC1N 1EH, UK.*

[2] *Infection, Inflammation and Rheumatology Section, Institute of Child Health, University College London, WC1N 1EH, UK.*

[3] *Department of Anatomy, Institute of Medical Sciences, University of Aberdeen, AB25 2ZD, UK.*

haiyan.zhou@ucl.ac.uk

Background: Spinal muscular atrophy (SMA) is an autosomal recessively inherited neuromuscular disorder caused by homozygous deletion in the Survival Motor Neuron gene 1 (SMN1). While SMA is considered to be a lower motor neuron disease where spinal motor neurons are the primary pathological target, increasing clinical and experimental reports indicate the involvement of additional peripheral organs in the pathogenesis of the disease.

Aims: Vascular defects have been reported in the severe transgenic mouse models of SMN deficiency, including reduced capillary density and hypoxia in spinal cord and skeletal muscle tissues. In this study we aimed to investigate the underlying molecular mechanisms for microvascular abnormalities in SMA mice. We also examined the intestine, to determine the involvement of the microvascular defect in the gastroenterological system.

Methods and Materials: Severe SMA mice, of the Taiwanese model, were used in our study. Spinal cord, skeletal muscle and intestine were collected at postnatal day 10 from untreated SMA mice, therapeutic antisense oligomer PMO25 treated SMA mice and controls. Expression of different angiogenic factors were measured both in mouse tissues and serum from SMA patients. Human umbilical vein endothelial cells (HUVEC) with SMN deficiency were used for vessel tube formation and cell migration studies. Capillary density, enteric neurons and inflammation in intestine of SMA mice were examined by immunohistochemical staining.

Results: SMN deficiency affects the function of endothelial cells *in vitro*. Dysregulation of angiogenic factors were detected in spinal cord and skeletal muscle in SMA mice and were restored to nearly normal level after efficacious PMO25 treatment. Altered circulating angiogenic factors were also detected in serum from SMA patients. A striking vascular defect was identified in the intestine of SMA mice and this defect responded to PMO25 treatment.

Conclusion: We have shown that there are significant abnormalities in the microvasculature in SMA. This defect appears to be systemic, affecting both central nervous system and peripheral structures. The microvascular defects respond to systemic PMO25 treatment in SMA mice.

P86

***p62/SQSTM1* mutations induce limitation of mitochondrial substrates and energy metabolism impairments**

Fernando Bartolome[1,2], Noemi Esteras[2], Tadashi Honda[3], Albena T. Dinkova-Kostova[4], John Hardy[2], Eva Carro[1], Andrey Y. Abramov[2].

[1]Neurosciences group, Instituto de Investigacion Hospital 12 de Octubre (i+12), Av Cordoba, Madrid, 28041, Spain; [2]Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London, WC1N 3BG;[3]Department of Chemistry and Institute of Chemical Biology & Drug Discovery, Stony Brook University, Stony Brook, New York 11794, USA; [4]Division of Cancer Research, School of Medicine, University of Dundee, Dundee DD1 9SY, UK

fbartolome.imas12@h12o.es

Background: A growing body of experimental evidence shows abnormal mitochondrial function related to patients with frontotemporal dementia and amyotrophic lateral sclerosis (FTD/ALS). Mutations in the same disease-causing genes have been reported in both diseases and they support the idea of an FTD-ALS continuum. *VCP* and *p62/SQSTM1* mutations which cause FTD/ALS have also been identified as causing Paget's Disease of the Bone.

Aims: In this work the role of p62/SQSTM1 in energy metabolism will be studied using live-cell imaging techniques.

Methods or Patients or Materials: Human dopaminergic neuroblastoma cell line (SH-SY5Y) where *p62/SQSTM1* will be transiently knock-down and fibroblasts from ALS patients carrying two independent pathogenic mutations in the *p62/SQSTM1* gene.

Results: p62 deficiency is associated with inhibited complex I mitochondrial respiration due to lack of NADH for the electron transport chain, but increased levels of NADPH. This inhibition resulted in lower mitochondrial membrane potential and higher mitochondrial ROS production. Pharmacological activation of transcription factor Nrf2 increased mitochondrial NADH levels and restored mitochondrial membrane potential in p62-deficient cells.

Conclusion: These findings highlight the implication of energy metabolism in pathophysiological events in FTD/ALS associated with p62 deficiency.

P87

Tweak/Fn14 pathway: at the crossroads of muscle atrophy and metabolic perturbations in spinal muscular atrophy

Melissa Bowerman[1], Karin Meijboom[1], Gareth Hazell[1], Corinne A Betts[1], Emily McFall[2], Marc-Olivier Deguise[2], Daniel Anthony[3], Rashmi Kothary[2], Linda C Burkly[4], Matthew JA Wood[1]

[1]*Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, OX1 3QX, UK*

[2]*Ottawa Hospital Research Institute, Regenerative Medicine Program, Ottawa, ON, K1H 8M5, Canada*

[3]*Department of Pharmacology, University of Oxford, Oxford, OX1 3QT, UK*

[4]*Biogen Idec, Cambridge, Massachusetts, USA*

melissa.bowerman@dpag.ox.ac.uk

Background: Spinal muscular atrophy (SMA) is characterized by loss of motoneurons and muscular atrophy. While motoneurons are the primary cellular target of this disease, therapeutic strategies alleviating muscle pathology improve lifespan and/or phenotype in SMA models. A combined therapeutic action at both neuronal and muscular sites is therefore the most pertinent approach towards SMA therapy. TWEAK is a cytokine of that binds the Fn14 receptor. Their interaction regulates denervation-induced muscle atrophy as well as muscle proliferation, differentiation, metabolism and atrophy.

Aims: Since neurodegeneration, muscle atrophy and metabolic perturbations typify SMA, we investigated the contribution of *Tweak* and *Fn14* to muscle pathology in SMA.
Methods: Skeletal and cardiac muscle from *Smn*$^{-/-}$*;SMN2* mice were assessed for expression of the TWEAK/Fn14 pathway and its downstream effectors.
Results: We have uncovered an aberrant expression of *Tweak* and *Fn14* mRNA in pre-symptomatic skeletal muscles of SMA mice. TWEAK and Fn14 interact with and regulate the expression of PGC-1α, Glut4, Mef2D and HKII, which all play key roles in muscle health and function. We show an abnormal expression of PGC-1α, Glut4, Mef2D and HKII in SMA skeletal muscle, in agreement with Tweak/Fn14 dysregulation. Finally, we demonstrate that Tweak, Fn14 and PGC-1α are also misregulated in the heart of pre-symptomatic SMA mice, another muscle pathologically affected in SMA.
Conclusion: We **hypothesize** that an aberrant expression of the TWEAK/Fn14 pathway in SMA muscle promotes and exacerbates muscle pathology and that modulation of this pathway may ameliorate disease pathogenesis. We will define the pathological role of TWEAK and Fn14 in SMA muscle as well as assess the therapeutic potential of manipulating TWEAK and Fn14 expression via genetic and pharmacological approaches. The **aim** of this project is to highlight TWEAK and Fn14 as novel muscle-specific molecular targets for SMA therapy that could eventually be combined with strategies targeting the CNS.

P88

Dynamic dysregulation of microRNA-9, -206 and -132 in spinal muscular atrophy and the response to antisense oligonucleotide therapy

Francesco Catapano, Irina T. Zaharieva, Mariacristina Scoto, Jennifer Morgan, Francesco Muntoni and Haiyan Zhou
Dubowitz Neuromuscular Centre, Developmental Neuroscience Programme, Institute of Child Health, University College London, WC1N 1EH, UK.
f.catapano@ucl.ac.uk

Background: Spinal muscular atrophy (SMA) is an autosomal recessive motor neuron disease due to mutations in the survival motor neuron-1 (*SMN1*) gene. It is characterized by the selective degeneration of lower motor neurons and limb and trunk muscle weakness due to the deficiency of SMN protein. Although SMA is currently incurable, experimental therapies such as antisense oligonucleotide (AON) and viral vector mediated SMN gene therapy have shown encouraging preclinical and clinical outcomes. MicroRNAs (miRNAs) are short (~22 nucleotides) non-coding RNAs that regulate gene expression by binding to specific mRNA targets and promoting their degradation or translational inhibition. Dysregulation of specific miRNAs has been extensively investigated in neuromuscular disorders such as Duchenne muscular dystrophy.
Aims and Methods: In this study we investigated the expression of miR-9, miR-206 and miR-132, selected based on their involvement in central nervous system and skeletal muscle development, in SMA mouse models with different severity (type I and III) at different stage of the disease (pre-symptomatic, symptomatic and end stage). We also investigated the response of these three miRNAs to experimental AON therapy targeting the *SMN2* gene in SMA mice.
Results: The expression of these miRNAs in spinal cord and skeletal muscle changed dynamically over time in both SMA and control mice. Significant dysregulation of all three miRNAs was observed in serum from SMA mice and correlated with disease progression. The abundance of these serum miRNAs was significantly reduced after effective AON therapy in SMA mice. There was also upregulation of miR-9 and miR-132 in serum samples from SMA patients.
Conclusions: We have characterized the expression of miR-9, miR-206 and miR-132 in SMA mice and patients. Our study provides support for the development of miRNAs as biomarkers to monitor disease progression and response to experimental therapy.

P89

Retrograde Axonal Transport in human iPSC derived Motor Neurons

Fellows AD[1], Devine HE[1,3], Hall C[2], Tyzack G[2], Greensmith L[1], Patani R[2], Schiavo G[1]
[1]Sobell Department of Motor Neuroscience and Movement Disorder, UCL Institute of Neurology, London. [2]Department of Molecular Neuroscience, UCL Institute of Neurology, London. [3]MRC Centre for Neuromuscular Disease, Queen Square, London.
alexander.fellows.13@ucl.ac.uk and h.devine@ucl.ac.uk

Background: Deficits in axonal transport have been previously observed in models of motor neuron diseases and motor sensory neuropathies. To date, studies have been largely undertaken in cell lines, embryonic stem cell-derived or primary motor neurons from animal models. However, these models may not truly recapitulate the full disease pathogenesis in humans. There is therefore a need to look at human motor neurons from control individuals and motor neuron disease patients. Induced pluripotent stem cells (iPSC) represent a ideal source for human motor neurons. In this study, we sought to investigate axonal transport in motor neurons derived from human iPSCs.
Aims: Determine whether it is possible to visualise retrograde axonal transport in motor neurons derived from iPSCs.
Methods: Control human iPSCs were differentiated into motor neurons using a protocol recently established in the Patani laboratory. Axonal transport was examined at two time points (Day 24 and 37 in vitro) by treating the cultures with a fluorescent atoxic tetanus toxin fragment, which enables the analysis of retrograde axonal transport of signalling endosomes. Using live cell imaging and motion analysis software we studied the characteristics of axonal transport in these cells.
Results: Our results show that it is possible to visualise retrograde axonal transport in human iPSC derived motor neurons.
Conclusions: Axonal transport may be a candidate for assessing functionality of motor neurons derived from iPSCs.

P90

Magnetic resonance imaging as an outcome measure in motor neuron disorders

Uros Klickovic, Chris Sinclair, Luca Zampedri, Jan Clarke, Aleksandra Pietrusz, Robin Howard, Andrea Malaspina, Richard Orrell, Nikhil Sharma, Katie Sidle, Michael Hanna, Linda Greensmith, Tarek Yousry, Jasper Morrow, Jonathan Thornton*, Pietro Fratta*
[#]*UCL Institute of Neurology, and *MRC Centre for Neuromuscular Diseases, Queen Square, London, WC1N 3BG, UK*

Background: The development of novel therapies for motor neuronopathies requires a reproducible outcome measure which can sensitively monitor disease progression. Muscle magnetic resonance imaging (MRI) has been widely applied to neurological diseases and is an excellent candidate due to its reproducibility and observer independence.
Aims: We aim to evaluate the use of MRI of skeletal muscle as an outcome parameter in diseases which primarily affect the motor neurons but have variable rates of disease progression: amyotrophic lateral sclerosis (ALS) and Kennedy's disease (KD). We rely on the hypothesis that MRI can detect changes of muscular fat content in those conditions.
Methods: With qualitative MRI techniques, including T1-weighted and STIR imaging, semi-quantitative volumetric imaging and 3-point Dixon fat-water quantification we will evaluate lower limb, upper limb and bulbar regions in 24 ALS patients, 12 KD patients as well as 18 healthy volunteers. We will collect detailed clinical data, including isokinetic and isometric limb strength and repeat these assessments at a 6 and 12 month interval.
Results: By analysing the value of quantitative MRI as an outcome measure in these conditions the results will investigate both correlation with clinical measures and sensitivity to change over time. Data from this study will inform regarding sample size in clinical trials to evaluate novel therapies in these diseases.
Conclusions: The search for biomarkers used as surrogate outcome parameters is an important step for the development of new drugs. Muscle MRI might serve as a useful monitoring parameter due to its reproducibility and objectivity.

P91

Absence of wide-spread mis-splicing in the preclinical phase of a native promoter driven TDP-43 mouse model of ALS

Jakub Scaber[1], David Gordon[1], Ruxandra Mutihac[1], Javier Alegre-Abarrategui[1], Javier Riancho[1], David Sims[3], Richard Wade-Martins[2], Andreas Heger[3], Kevin Talbot[1]

[1]*Nuffield Department of Clinical Neurosciences, University of Oxford, University of Oxford;* [2]*Computational Genomics Analysis and Training, Department of Physiology, Anatomy and Genetics, University of Oxford;* [3] *Department of Physiology, Anatomy and Genetics, University of Oxford*

jakub.scaber@ndcn.ox.ac.uk

Background: TDP-43 is the protein that accumulates in intracellular inclusions in amyotrophic lateral sclerosis (ALS) and mutations in TDP-43 account for up to 5% of familial ALS cases. To investigate the role of TDP-43 mutations in vivo, we developed a native promoter driven BAC transgenic human TDP-43 mouse with the M337V mutation. The mouse develops a robust motor phenotype and loss of nuclear TDP-43 in the spinal cord from 9 months of age.

Aims: Our aim was to investigate if splicing changes occur early or late in the disease course and to identify a pre-symptomatic phenotype of the M337V mutation.

Methods: RNA was extracted from whole spinal cords from three non-transgenic, three heterozygous wild-type and four M337V mice each at three and twelve months of age. Following library-prep with poly-A selection, sequencing was performed on the Illumina HiSeq2000 platform to a read depth of at least 26 million per sample.

Results: At 3 months 453 genes were differentially expressed between wild-type and M337V, increasing to 4207 genes at 12 months. At 12 months downregulated genes were significantly longer than upregulated genes. Differential splicing was observed at 12 months but not at 3 months.

Conclusion: Our M337V mouse developed a downregulation of long transcripts as well as differential splicing at the 12 month time point, when the mouse is symptomatic and shows TDP-43 mislocalisation in motor neurons. These changes are not seen in the presymptomatic spinal cord at three months, but early transcriptomic changes that may give clues to pathological events prior to TDP-43 misclocalisation are already observed.

P92

Investigating dysfunctional RNA processing in TDP-43 mouse mutants

Prasanth Sivakumar[1], Agnieszka Gromadzka[1], Cristian Bodo[1], Jack Humphrey[1,2], Warren Emmett[2], Tom Ricketts[3], Hugo Oliveira[3], Eric Wang[4], David Housman[4], Linda Greensmith[1], Emanuele Buratti[5], Francisco Baralle[5], Vincent Plagnol[2], Abraham Acevedo-Arozena[3], Elizabeth MC Fisher[1], Pietro Fratta[1]

[1]*MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London, UK*

[2]*UCL Genetics Institute, London, UK*

[3]*MRC Harwell, UK*

[4]*Koch Institute, MIT, Cambridge, USA*

[5]*International Centre for Genetic Engineering and Biotechnology, Trieste, Italy*

prasanth.sivakumar.14@ucl.ac.uk

Background: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neuromuscular disorder characterised by degeneration of both upper and lower motor neurons, resulting in muscular atrophy. Recently, RNA processing has been implicated in ALS pathology, notably the depletion of RNA-binding protein TDP-43 from the nucleus and its subsequent cytoplasmic aggregation in the vast majority of ALS cases. These aggregates are found in both sporadic and familial ALS, regardless of the genetic background, suggesting the importance of TDP-43 in disease progression. Therefore, our aim is to further investigate these genotypic consequences of aberrant TDP-43 activity.

Methods: We investigated two mouse models of TDP-43, each containing a single substitution within the coding region of the TDP-43 gene. One mutation is found in the second RNA recognition motif (RRM2),

and the other in the prion-like domain. RNA sequencing was used to examine cases of differential gene expression and alternative splicing events as a result of these mutations. Individual nucleotide resolution crosslinking and immunoprecipitation (iCLIP) will highlight changes in RNA-binding patterns of the TDP-43 mutants.
Results: Severe molecular dysregulation was identified in both mouse mutants, alongside contrasting changes in TDP-43 splicing activity. Mutation of RRM2 leads to a reduction in RNA binding, as well as instances of cryptic exon inclusion and changes to the TDP-43 autoregulation mechanism. The altered prion-like domain triggered novel 3' untranslated region splicing in TDP-43-regulated transcripts.
Conclusions: The array of RNA processing features disrupted by each TDP-43 mutation, alongside identification of changes in binding patterns between TDP-43 mutants and RNA via iCLIP, provides invaluable insight into possible mechanisms by which TDP-43 could contribute to the ALS phenotype. The results of the ongoing project will be presented.

P93
Role of PTPN23 in motor neuron neurotrophin signaling
Villarroel-Campos D[1]., Budzinska M[1]., Schiavo G[1].
[1] *UCL Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK.*
david.villarroel.15@ucl.ac.uk

Background: The correct sorting of proteins and organelles is a critical feature for neurons, and since they exhibit a highly polarized morphology, efficient axonal transport is essential for their function. Axonal transport is mediated by a diverse group of molecular motors which couple ATP hydrolysis to movement guided by cytoskeletal elements. Kinesin and dynein motor proteins are of particular interest for anterograde and retrograde axonal transport, respectively.
The dynein adaptor protein, Bicaudal D-homolog 1 (BICD1), recruits the dynein-dynactin complex to the trans-Golgi network and controls Golgi-ER trafficking. It also regulates the retrograde transport and sorting of neurotrophin receptors (NTR) in mouse embryonic stem cell-derived motor neurons (ES-MN). However the molecular mechanism controlling the latter process is not completely understood. In addition, recent results have identified the catalytically inactive histidine domain-protein tyrosine phosphatase (HD-PTP/PTPN23) as a novel BICD1 interacting protein.
Aims: The aim of this work is to characterize the role of PTPN23 in NTR trafficking.
Methods: The strategy includes the use of the mouse neuroblastoma cell line N2a and mouse embryonic stem (ES) cells, differentiated into motor neurons (ES-MN). Firstly, point mutations are introduced in PTPN23 to disrupt its binding to BICD1. A second approach involves PTPN23 being knocked down and the effect on NTR internalization, transport and sorting within the endocytic pathway analyzed in both conditions. Experimentally, it includes techniques such as immunocytochemistry, western blotting and live cell imaging using confocal microscopy. In addition, morphological changes and motor neuron survival (activation of apoptotic or survival signaling pathways) in those experimental conditions is also under evaluation.
Results and conclusions: Genetic manipulation of HD-PTP/PTPN23 expression influences neurotrophic signaling and thus, this protein is likely to play an important role in regulating endosomal trafficking.

Channelopathies and Neuromuscular Junction Disorders

‡P94
Clinical and genetic analysis of CLCN1 mutations with dual inheritance pattern
R. Sud[1], K. Suetterlin[1], S. Durran[1], D. Fialho[1], S. M[c]Call[1], R. Mannikko[1], M.G. Hanna[1] and **E. Matthews[1]**
MRC Centre for Neuromuscular Diseases, ION, UCL and National Hospital for Neurology and Neurosurgery, Queen Square, London
emma.matthews@ucl.ac.uk

Background: Myotonia congenita is a rare neuromuscular disorder due to mutations in the CLCN1 gene. Inheritance can be autosomal dominant or recessive. Some mutations have been reported in both dominant and recessive families although the mechanism for this dual inheritance pattern is not clear. Myotonia can also be caused by other gene mutations, namely SCN4A (paramyotonia congenita), ZNF9 (DM2) and DMPK (DM1). All of which are inherited in an autosomal dominant manner.
Aims: We sought to determine if there are examples of individuals both heterozygous and homozygous for the same CLCN1 mutations who are affected with myotonia in our UK cohort of channelopathy patients.
Methods: We reviewed the genetic and clinical data of channelopathy cases referred to the channelopathy service at Queen Square. Where indicated testing of other myotonia causing genes was also carried out.
Results: Data analysis is ongoing and will be presented in full. Preliminary findings show there are examples of families with dominant inheritance pattern attributed to a sole CLCN1 mutation who were later found to also have other gene mutations e.g. DM2. In addition there is one family in whom individuals both heterozygous and homozygous for the same CLCN1 mutation have myotonia.
Conclusion: CLCN1 mutations in tandem with other myotonia gene mutations can influence phenotype, complicate the interpretation of genetic results and lead to erroneous prediction of clinical affectation in family members. In addition some heterozygous individuals carrying CLCN1 mutations considered to be "recessive" can also display mild symptoms and signs. This has important implications for ensuring adequate genetic analysis is performed for optimal genetic counselling. Our data also suggests the likelihood of a CLCN1 mutation being dominant or recessive may be balanced along a spectrum as opposed to being truly dichotomous.

P95

RCT of Bumetanide in Hypokalaemic Periodic Paralysis

Renata S. Scalco, Iwona Skorupinska, Camille Blochet, Emma Matthews, Jasper Morrow, Michael G. Hanna, Doreen Fialho
MRC Centre for Neuromuscular Diseases, Institute of Neurology, UCL, London, United Kingdom
r.scalco@ucl.ac.uk

Background: Hypokalamic periodic paralysis (hypoPP) is a muscle channelopathy characterised by episodes of focal or generalised attacks of weakness accompanied by low serum potassium. Treatment of acute attacks is limited to potassium supplement either taken orally or intravenously. Recent animal studies suggested that bumetanide may be useful in treating both acute attacks as well as a preventative agent.
Aims: We designed a clinical trial to explore possible efficacy and safety aspects of bumetanide in hypoPP.
Method: Randomised double blind placebo controlled phase II clinical trial with a crossover design carried out at the MRC Centre for Neuromuscular Diseases, London, aiming to recruit a total of 12 participants. A focal attack of HypoPP is provoked by exercise in a hand muscle (using the McManis protocol) and participants receive either placebo or bumetanide as a single dose on two different occasions. Electrophysiological measurements are used to assess the severity and the duration of the attack.
Results: The results of the first participants are presented. There were no serious adverse events. Vital signs and serum potassium levels were stable over a period of 4 hours after treatment intake in all participants. Outcome measurements are discussed.
Conclusions: This is the first time bumetanide is utilised as a treatment option for patients with hypoPP. Interim results indicate that bumetanide is safe to use as a single dose in this patient group. The McManis test, used here as a procedure and an outcome measurement in a clinical trial for the first time, is well tolerated and produces reliable results.

P96

Screening for Brody's Syndrome in an Undiagnosed Muscle Channelopathy Cohort

K. Suetterlin[1], E.Healy[2], J.Molenaar[3], A.Oosterhof[4], Q.Gang[1], N. Voermans[3], D.Fialho[1], H. Houlden[1], R. Quinlivan[1], E. Matthews[1], J. Holton[2], M.G. Hanna[1]

1 = MRC Centre for Neuromuscular Diseases, 8-11 Queen Square, London, WC1N 3BG, England

2 = Department of Neuropathology, National Hospital for Neurology and Neurosurgery, London, WC1N 3BG, England

3 = Department of Neurology, Radboud University Medical Centre, Nijmegen, The Netherlands

4= Radboud Institute for Molecular Life Sciences, Department of Biochemistry, Radboud University Nijmegen Medical Centre, The Netherlands

karen.suetterlin@ucl.ac.uk

Background: *Brody's disease* is an autosomal recessive muscle condition caused by mutations in *ATP2A1*, the gene encoding the Sarcoplasmic Reticulum Calcium ATPase (SERCA1). Its estimated incidence is 1 in 10,000,000. The term *Brody's syndrome* has been proposed to describe those patients with reduced SERCA1 activity but no *ATP2A1* mutation. In contrast to Brody's disease, patients with Brody's syndrome may report a dominant mode of inheritance, are more likely to describe adult onset of symptoms, focal muscle involvement and complain of myalgia. The incidence of Brody's syndrome is not known. However, as SERCA activity is not routinely tested, it may be more common than currently recognised.
Aims: To investigate the presence of SERCA dysfunction in undiagnosed patients referred to our specialist channelopathy clinic with muscle stiffness or myalgia.
Patients: Channelopathy clinic lists were reviewed and undiagnosed patients whose primary complaint was of muscle stiffness or myalgia were identified. Only those patients who had undergone a muscle biopsy were selected. SERCA activity was determined as calcium-dependent ATPase activity in muscle homogenate. 11 patients were included.
Results: Two patients had significantly reduced SERCA activity. Both patients were screened for mutations in known muscle channel genes and were negative. Both had adult onset of symptoms, complained of myalgia as well as muscle stiffness and had varying degrees of generalised muscle hypertrophy. One patient reported a dominant family history. The other patient reported no family history. Neither patient has a mutation in ATP2A1. Exome analysis is ongoing.
Conclusion:
1. Brody's syndrome may be more common than previously thought.
2. SERCA activity testing is worth considering in the diagnostic work up of undiagnosed muscle stiffness or myalgia.
3. SERCA dysfunction may form part of a common final pathway in the genesis of muscle stiffness/myalgia of differing aetiology and as such could be an important therapeutic target.

P97

Loss of function mutations in *SCN4A* cause severe fetal hypokinesia or congenital myopathy

Irina Zaharieva[1*], **Michael G. Thor[0,2*]**, Emily Oates[3*], Clara Van Karnebeek[4], Glenda Hendson[4], Eveline Blom[5], Nanna Witting[6], Magnhild Rasmussen[7,8], Michael Gabbett[9], Gianina Ravenscroft[10], Maria Sframeli[1], Karen Suetterlin[0,2], Anna Sarkozy[1], Luigi D'Argenzio[1], Louise Hartley[11], Emma Matthews[0,2], Matthew Pitt[12], John Vissing[6], Martin Ballegaard[13], Christian Krarup[13], Andreas Slørdahl[14], Hanne Halvorsen[15], Cynthia Ye[4], Linhua Zhang[4], Nicoline Løkken[6], Ulla Werlauf[16], Mena Abdelsayed[17], Mark R. Davis[18], Lucy Feng[1], Rahul Phadke[1], Caroline A. Sewry[1], Jennifer E. Morgan[1,2], Nigel G. Laing[10], Hilary Vallance[4], Peter Ruben[17], Michael G. Hanna[0,2], Suzanne Lewis[4], Erik-Jan Kamsteeg[19], Roope Männikkö[0,2], Francesco Muntoni[0,1,2]

** These authors contributed equally to this work*

m.thor@ucl.ac.uk

[0]MRC Centre for Neuromuscular Diseases, 8-11 Queen Square WC1N 3BG, London, [1]Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London, WC1N 1EH, UK, [2]Department of Molecular Neuroscience, UCL Institute of Neurology, London, WC1N 3BG, UK, [3]Institute for Neuroscience and Muscle

Research, The Children's Hospital at Westmead, Sydney, NSW 2145, Australia, [4]Child and Family Research Institute, Centre for Molecular Medicine and Therapeutics, University of British Columbia, 4480 Oak Street, Vancouver, B.C. V6H 3V4, Canada, [5]Maastricht University Medical Center, Maastricht, 6211 LK, Netherlands, [6]Copenhagen Neuromuscular Center, Rigshospitalet, University of Copenhagen, Copenhagen, 2100, Denmark, [7]Department of Clinical Neuroscience for Children, Oslo University Hospital, 0424, Oslo, Norway, [8]Unit for Hereditary Neuromuscular Disorders, Oslo University Hospital, 0424, Oslo, Norway, [9]Genetic Health Queensland, Royal Brisbane & Women's Hospital & Griffith University, Brisbane, Australia, [10]The Harry Perkins Institute of Medical Research, University of Western Australia, Perth, 6009, Western Australia, Australia, [11]Department of Child Health, University Hospital Wales, Cardiff, CF14 4XW, UK, [12]Neurophysiology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH, UK, [13]Department of Clinical Neurophysiology, Rigshospitalet, University of Copenhagen, Copenhagen, 2100, Denmark, [14]Children's Clinic, St.Olavs hospital, Trondheim University Hospital, 7006 Trondheim, Norway, [15]Department of Pathology, University Hospital of North Norway, 9038 Tromsø, Norway, [16]The Danish National Rehabilitation Center for Neuromuscular Diseases, Aarhus, 8000 Denmark, [17]Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, V5A 1S6, Canada, [18]Department Molecular Genetics, Pathwest, QEII Medical Centre, Nedlands 6009, Western Australia, Australia, [19]Department of Human Genetics, Radboud University Medical Center, Nijmegen, 6500HB, The Netherlands

Background: *SCN4A* encodes the skeletal muscle sodium channel $Na_V1.4$, which is integral to action potential generation and propagation in the muscle. Dominant *SCN4A* gain of function mutations are a well-established cause of myotonia and periodic paralysis.
Methods: Using whole-exome sequencing, homozygous or compound heterozygous *SCN4A* mutations were identified in 11 individuals with congenital myopathy from six unrelated kindreds. Mutant $Na_V1.4$ channels were transiently expressed in HEK293 cells and *X. laevis* oocytes and functionally characterized by patch clamp and two-electrode voltage clamp, respectively.
Results: Heterozygous carriers were asymptomatic. Patients developed *in utero*- or neonatal-onset muscle weakness of variable severity. Seven cases resulted in death during the third trimester or shortly after birth. The remaining four had marked congenital or neonatal-onset hypotonia and weakness, as well as significant neonatal-onset respiratory and swallowing difficulties. Muscle biopsies showed typical myopathic features, including fiber size variability and fibrofatty tissue of varying severity; some biopsies showed non-specific structural abnormalities. All but one mutation resulted in either full or partial loss of function by reducing the current density, attenuating channel activation or enhancing fast inactivation. The only mutation without a detectable functional effect in HEK293 cells is a C-terminal frameshift mutation altering the sequence of the C-terminus and may cause muscle-specific changes in channel function. Each individual carried at least one full loss of function mutation.
Conclusion: We propose that the combined effect of heteroallelic loss of function mutations – one of which causes full loss of function – attenuates the action potential amplitude to a level insufficient to sustain normal muscle force. Full loss of function is a mechanism of pathophysiology not previously associated with *SCN4A* mutations. We hope these results will help improve the genetic diagnosis of patients with similar phenotypes.

‡P98
A GFPT1 deficient mouse model of Congenital Myasthenic Syndrome
Yasmin Issop, Steven H Laval, Hanns Lochmüller
John Walton Muscular Dystrophy Research Centre, MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, UK
y.issop@newcastle.ac.uk

Background: Congenital myasthenic syndromes (CMS) occur as a result of inherited mutations giving rise to impaired transmission at the neuromuscular junction (NMJ). Patients with mutations in *GFPT1* demonstrate a limb-girdle pattern of weakness, tubular aggregates in muscle biopsies, and an unusual

sparing of the ocular, facial and bulbar muscles. *GFPT1* encodes a ubiquitous protein in the hexosamine pathway which yields precursors required for protein and lipid glycosylation.
Aims: To breed and characterise a *Gfpt1* knockout mouse model.
Methods: Since homozygous knockout is embryonic lethal, we bred and will characterise the conditional muscle-specific *Gfpt1* knockout mouse model. We used immunofluorescence staining to look at structures at the synapse. The *Gfpt1* allele reports the activity of the promoter which we use to track the expression pattern.
Results: Heterozygous *Gfpt1* knockout mice display normal morphology of the NMJ. Furthermore, β-galactosidase activity shows ubiquitous GFPT1 expression in both muscle and non-muscle tissues. Muscle-specific *Gfpt1* knockout mice are viable and normal in appearance and bodyweight. These mice display lower hanging times when compared to wild type mice.
Outlook: We will use *in vitro* isometric force measurements to assess muscle contractile function. *In situ* force measurements and the four limb inverted screen test will be used to measure fatigable muscle weakness. Moreover, we will focus on the morphology of the synapse paying particular attention to the clustering properties of acetylcholine receptors and other proteins at the NMJ which are known to be glycosylated.
Conclusion: Embryonic lethality of homozygous *Gfpt1* knockout mice suggests that insertion of the *lacZ* gene-trap cassette in the *Gfpt1* gene generates a null allele. We show that any phenotype seen in the muscle-specific *Gfpt1* knockout mice is due to a deficiency of GFPT1 in skeletal and cardiac muscle only. Our data suggests that the muscle-specific *Gfpt1* knockout mouse demonstrates signs of muscle weakness.

‡P99

Mutations in *COl13A1* cause a Congenital Myasthenic Syndrome

Judith Cossins,[1] Pedro Rodríguez Cruz,[1,2] Susan Maxwell,[1] Jaqueline Palace,[2] Stephanie Robb,[3] Clare Logan,[4] Gabriel Chow,[5] Colin Johnson,[4] David Beeson.[1,2]
[1]Neurosciences Group, Weatherall Institute of Molecular Medicine, Oxford, UK; [2]Nuffield Department of Clinical Neurosciences, JR Hospital, Oxford, UK; [3]Dubowitz Neuromuscular Centre, Institute of Child Health and Great Ormond Street Hospital, London, UK; [4]Leeds Institute of Biomedical and Clinical Science, UK; [5]Department of Paediatric Neurology, Nottingham City Hospital, Nottingham University Hospitals NHS Trust, Hucknall Road, Nottingham, UK

Background: Congenital myasthenic syndromes (CMS) are a heterogeneous group of rare inherited disorders characterised by fatigable muscle weakness and caused by impaired signal transduction at the neuromuscular junction. Approximately 10% of UK patients with the disease do not have defined mutations in any of the 18 known causative genes.
Aims: To use next generation sequencing to identify novel a gene harbouring mutations which cause CMS, and to explore the underlying pathogenic mechanisms of these mutations.
Methods: Exome sequencing was carried out on three patients from two families who shared similar clinical features, including onset at birth, dysmorphic features, decrement on repetitive nerve stimulation and no response to pyridostigmine treatment. A homozygous frameshift variant c.1171delG (p.Leu392Sfs*71) and a homozygous splice site mutation c.523-1delG in *COL13A1* were identified. *COL13A1* encodes COL13A1, a ubiquitously expressed non-fibrillary transmembrane collagen. We show that COL13A1 is expressed at neuromuscular junctions in control muscle but not in muscle from the patient. Variant c.1171delG was engineered into mouse C2C12 myoblasts using CRISPR/Cas9 technology. After differentiation, myotubes showed reduced numbers of agrin-induced acetylcholine receptor clusters.
Conclusion: Together with data from mouse models our results indicate an important role of COL13A1 at both pre-and post-synaptic sites in NMJ development and stability, and define a new type of CMS which is refractory to acetylcholinesterase therapy.

P100

Investigating the role of nidogens, basement membrane proteins, at the neuromuscular junction in health and disease

Ione FG Meyer[1], James N Sleigh[1], Kinga Bercsenyi[2], Sergey Novoselov[1], Giampietro Schiavo[1]
[1]*Sobell Department of Motor Neuroscience and Movement Disorders, MRC Centre for Neuromuscular Disease, UCL Institute of Neurology, London WC1N 3BG, UK*
[2]*MRC Centre for Developmental Neurobiology, King's College London Guy's Campus, New Hunt's House, London, SE1 1UL*
i.meyer@ucl.ac.uk

Motor neuron death is a pathological hallmark of a number of neurodegenerative diseases including ALS and SMA. Growing evidence indicates that this degeneration begins at distal regions, with changes at the neuromuscular junction (NMJ) preceding motor neuron cell death and the onset of clinical symptoms. Interestingly, there appears to be a selective vulnerability of specific motor neuron classes (fast fatigable) and their innervated muscle fibre types. Taken together, these results suggest the existence of factors at the NMJ that influence vulnerability, or resistance, to degeneration. It is therefore important to increase our understanding of the reciprocal interactions between motor neurons and the motor endplate in health and disease. Our lab have recently identified a novel retrograde signalling pathway that involves the mobilisation and uptake by motor neurons of a group of extracellular proteins called nidogens, also known as entactins, from the basement membrane at the neuromuscular synapse. The binding affinity of nidogens for several components of the basement membrane indicates that these proteins are involved in stabilisation of the extracellular matrix. However, our results suggest an additional intracellular signalling role for nidogens. We aim to further investigate the physiological function of nidogens at the NMJ, by examining nidogen isoform expression in cultured motor neurons and *ex vivo* muscles using fluorescence microscopy. Co-localisation studies will also be performed to explore protein interactions, which may shed light on the role of nidogen signalling. This work will lead to a greater understanding of the processes regulating NMJ integrity, and thereby reveal potential targets for therapeutic intervention to combat NMJ pathology in devastating neurodegenerative diseases.

P101

Clinical features of the myasthenic syndrome arising from mutations in GMPPB

Pedro M Rodríguez Cruz [1,2], Katsiaryna Belaya [2], Wei Wei Liu [2], Susan Maxwell [2], Maria Farrugia [3], Richard Petty [3], Timothy J. Walls [4], Maryam Sedghi [5], Keivan Basiri [6], Janice L Holton [7], Robin Kennett [1], Francesco Muntoni [8], Jacqueline Palace [1], David Beeson [1].
[1] Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, Oxford, UK; [2] Neurosciences Group, Weatherall Institute of Molecular Medicine, Oxford, UK; [3] Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK; [4] Department of Neurology, Royal Victoria Infirmary, Newcastle upon Tyne, UK; [5] Medical Genetics Laboratory, Alzahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran; [6] Neurology Department, Neuroscience Research Centre, Isfahan University of Medical Sciences, Iran; [7] Department of Molecular Neurosciences, UCL Institute of Neurology, London, UK; [8] Dubowitz Neuromuscular Centre & MRC Centre for Neuromuscular Diseases, UCL Institute of Child Health, London, UK.
pedro.rodriguezcruz@gtc.ox.ac.uk

Background: Congenital myasthenic syndrome (CMS) due to mutations in *GMPPB* has recently been reported confirming the importance of glycosylation for the integrity of neuromuscular transmission.
Aims: Clinical characterisation of CMS patients with mutations in *GMPPB*
Methods: Review of case notes of CMS patients with mutations in *GMPPB* to identify the associated clinical, neurophysiological, pathological and laboratory features. In addition, serum creatine kinase (CK) levels within the Oxford CMS cohort were retrospectively analysed to assess its usefulness in the differential diagnosis of this new entity.
Results: All patients had prominent limb-girdle weakness with minimal or absent craniobulbar manifestations. Presentation was delayed beyond infancy with proximal muscle weakness.

Neurophysiology showed abnormal neuromuscular transmission only in the affected muscles, and myopathic changes. Muscle biopsy showed dystrophic features and reduced labeling of α-dystroglycan. In addition, myopathic changes were present on muscle MRI. CK was significantly increased in serum compared to other CMS subtypes. Patients were responsive to pyridostigimine alone or combined with 3,4-diaminopyridine and/or salbutamol.
Conclusions: Patients with GMPPB-CMS have a similar phenotype to other CMS subtypes harboring mutations within the early stages of the N-glycosylation pathway. Additional characteristics shared with the dystroglycanopathies include myopathic features and raised CK levels. This confirms that CMS can occur in the absence of classic myasthenic manifestations such as ptosis, ophthalmoplegia or facial weakness, and links myasthenic disorders with dystroglycanopathies.

Other Muscle Disease

‡P102

Stabilization of Muscle Strength With Long-term AceER Treatment in Subjects with GNE Myopathy (GNEM): Results from an Open-Label Phase 2 Extension Study

Lau H[1], Caraco Y[2], Pestronk A[3], **Conner E[4]**, Skrinar A[4], Koutsoukos T[4], Kakkis E[4]
[1]New York University School of Medicine, New York, NY, USA; [2]Hadassah-Hebrew University Medical Center, Jerusalem, Israel; [3]Washington University Medical Center, St. Louis, MO, USA; [4]Ultragenyx Pharmaceutical Inc., Novato, CA, USA

Background: GNEM is a rare, progressive, adult-onset myopathy caused by mutations in the GNE gene that encodes an enzyme responsible for sialic acid (SA) biosynthesis. The defect in SA biosynthesis leads to a loss of muscle strength in the upper (UE) and lower extremities (LE), and eventual loss of ambulation and functional independence. Aceneuramic acid, an investigational extended-release formulation (AceER) of SA, at 6g/day stabilized UE muscle strength compared with placebo or lower dose (3g/day) AceER for up to 48 weeks in a randomized Phase 2 study in adults with GNEM.
Aims: Long-term treatment with AceER was evaluated in an ongoing open-label extension.
Methods: In Part I of the extension, all subjects received open-label AceER at 6g/day for a mean 23.4 weeks. In Part II, all subjects received a combination of 6g/day AceER and immediate release SA for a total of 12g/day. Muscle strength was measured every 6 months using hand held dynamometry and assessed for individual muscle groups and as a UE composite score (UEC) comprising grip, shoulder abductors, elbow flexors, and extensors and a LE composite score (LEC) comprising the hip flexors, extensors, abductors, adductors, and knee flexors.
Results: All subjects (N=46) who completed the Phase 2 study entered the extension. Among the 24 subjects who had received 6g/day AceER in the original study, strength remained stable in 7 of 9 of the individual muscle groups making up the UEC and LEC at the Part II month 12 visit (LS means change < 1.0 kg from original study baseline). Mean grip (-2.46 kg) and hip abductors (-1.25 kg) strength decreased. AceER was well tolerated during long-term treatment. The most commonly reported AEs were gastrointestinal or consistent with underlying GNEM disease.
Conclusions: Treatment with AceER at 6g/day for approximately 2.5 years stabilized muscle strength in subjects with GNEM.

‡P103

Anti-cN1A autoantibody seropositivity is associated with increased mortality risk in Inclusion Body Myositis

J. Lilleker*[1,2], A. Rietveld*[3] U. A. Badrising[4] O. Benveniste[5] K. R. Gheorghe[6] M.G. Hanna[7] M. K. Herbert[8] D. Hilton-Jones[9] J. Lamb[10] B. Lecky[11] I.E. Lundberg[6] P. Machado[7] K. Mariampillai[5] J. Miller[12]
M. Parton[7] M. T. J. Peeters[3] S. Pye[1] M. E. Roberts[2] S. Sacconi[13] C. G. Saris[3] R. G. Cooper[2,10,14] G. J. M. Pruijn[8] H. Chinoy[1,2] B. G. M. van Engelen[3]

***Joint first authors**
[1] *Centre for Musculoskeletal Research, University of Manchester, UK.*
[2] *Salford Royal NHS Foundation Trust, UK.*
[3] *Department of Neurology, Center for Neuroscience Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands.*
[4] *Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands.*
[5] *Department of Internal Medicine, La Pitié-Salpêtrière Hospital, Paris, France*
[6] *Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Solna, Karolinska Institutet, Stockholm, Sweden*
[7] *MRC Centre for Neuromuscular Diseases, University College London, UK*
[8] *Department of Biomolecular Chemistry, Radboud Institute for Molecular Life Sciences and Institute for Molecules and Materials, Radboud University, Nijmegen, The Netherlands*
[9] *Nuffield Department of Clinical Neurosciences, Oxford University Hospitals, UK*
[10] *Centre for Integrated Genomic Medical Research, University of Manchester, UK*
[11] *Walton Centre for Neurology and Neurosurgery, Liverpool, UK*
[12] *The Newcastle upon Tyne Hospitals NHS Foundation Trust, UK*
[13] *Peripheral Nervous System, Muscle and ALS Department, Nice University Hospital, France.*
[14] *MRC/ARUK Institute of Ageing and Chronic Disease, University of Liverpool, UK.*

Background: Inclusion Body Myositis (IBM) pathogenesis is incompletely understood. Inflammatory and degenerative processes cause cumulative muscle damage. Recent identification of anti-cytosolic 5'-nucleotidase 1A (cN1A/NT5c1A) autoantibodies in ~1/3 of IBM patients offers insight into pathogenic mechanisms.
The utility of classifying IBM patients by anti-cN1A serotype has not been thoroughly investigated. In diseases with pathogenic circulating autoantibodies, serotype can predict disease course, including treatment response. We investigated the potential for a similar role for anti-cN1A testing in IBM.
Aims: To investigate the clinical utility of anti-cN1A autoantibody testing in IBM.
Methods: Data from four European IBM registries (UK, Netherlands, France, Sweden) were pooled. Anti-cN1A serotyping by ELISA was performed as previously described.
Cases were stratified by anti-cN1A serotype. For clinical characteristics, associations were investigated using logistic regression. For mortality and mobility-aid requirement analyses Kaplan-Meier curves were generated and Cox proportional hazards regression performed.
Results: Data from 309 IBM patients were analysed, 100 (32.4%) were anti-cN1A seropositive. Mean age at onset did not differ according to serotype (60.2 years SD=9.6). At onset, fewer seropositive patients had proximal arm weakness (6.1% vs. 22.2%, adjusted OR 0.22, 95%CI=0.08-0.58, p=0.002). A higher proportion of seropositive patients had excess cytochrome oxidase deficient fibres on muscle biopsy (86.7% vs. 70.6%, adjusted OR 3.10, 95%CI=1.26-7.61, p=0.014).
During follow-up, 68 patients died at a mean age of 77.8 years (SD=8.1). Adjusted mortality risk was higher in the seropositive group (HR 1.91, 95%CI=1.12-3.28, p=0.018), as was adjusted risk of mobility-aid requirement (HR 1.67, 95%CI=1.03-2.68, p=0.036).
Conclusions
Anti-cN1A seropositivity was associated with an increased risk of mortality and mobility-aid requirement, suggesting a more severe disease phenotype.
Further use of this serological method to interrogate IBM disease mechanisms are clearly required. Stratification of IBM by anti-cN1A serotype may prove important for future treatment decisions if disease modifying therapies for IBM become available.

P104

Analysing whole-exome sequencing data in a large cohort of sporadic inclusion body myositis and control individuals

Qiang Gang[1,3], Conceição Bettencourt[1,2]*, Pedro M. Machado[1,3,5]*, Stefen Brady[3,7], Janice L. Holton[3], Deborah Hughes[1], Estelle Healy[3], Matthew Parton[3], David Hilton-Jones[7], Perry B. Shieh[8], Merrilee

Needham[9], Christina Liang[10], Edmar Zanoteli[11], Leonardo Valente de Camargo[11], Boel De Paepe[12], Jan De Bleecker[12], Aziz Shaibani[13], Michela Ripolone[14], Raffaella Violano[14], Maurizio Moggio[14], Richard J. Barohn[15], Mazen M. Dimachkie[15], Marina Mora[16], Renato Mantegazza[16], Simona Zanotti[16], Alan M. Pittman[1,6], Andrew B. Singleton[17], Michael G. Hanna[1,3]**, Henry Houlden[1,3,4]**, The Muscle Study Group and The International IBM Genetics Consortium#

[1] Department of Molecular Neuroscience, [2] Department of Clinical and Experimental Epilepsy, [3] MRC Centre for Neuromuscular Diseases, [4] Neurogenetics Laboratory, Institute of Neurology, University College London, Queen Square, London WC1N 3BG, UK

[5] Centre for Rheumatology, Division of Medicine, University College London, Rayne Building, 4th Floor, 5 University Street, London WC1E 6JF, UK

[6] Reta Lila Weston Institute, UCL Institute of Neurology, 1 Wakefield Street, London WC1N 1PJ, UK

[7] Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, UK

[8] Department of Neurology, University of California Los Angeles, USA

[9] Western Australian Neurosciences Research Institute (WANRI), University of Western Australia and Murdoch University, Fiona Stanley Hospital, Perth, Australia

[10] Royal North Shore Hospital, New South Wales, Australia

[11] Department of Neurology, Medical School of the University of São Paulo (FMUSP), São Paulo, Brazil

[12] Ghent University Hospital, Department of Neurology & Neuromuscular Reference Centre, Ghent, Belgium

[13] Nerve and Muscle Center of Texas, 6624 Fannin, Suite 1670, Houston, Texas 77030 USA

[14] Neuromuscular Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Centre, University of Milan, Milan, Italy

[15] The University of Kansas Medical Centre, 2100 West 36th Ave., MS 2012, Kansas City KS 6616, USA

[16] Neuromuscular Diseases and Neuroimmunology Unit, Fondazione IRCCS Isitituto Neurologico C. Besta, Milano, Italy

[17] Laboratory of Neurogenetics, National Institute on Aging, National Institute of Health, Bethesda, Maryland, United States

g.gang@ucl.ac.uk

Background: Sporadic inclusion body myositis (sIBM) is the most common myopathy in individuals aged over 45 years. Clinico-pathologically overlapping inherited disorders indicates that genetic factors might be involved in sIBM pathogenesis. Based on the International IBM Genetics Consortium, whole-exome sequencing has been performed in a large cohort of 199 sIBM patients and 513 controls.

Aim: Our aim was to produce a high-quality exome dataset using a series of quality control techniques, to ultimately perform a case-control study to identify genetic factors associated with increased risk of sIBM.

Methods: All the 712 samples were sequenced on Illumina HiSeq2500 platform. Raw reads were aligned to a reference sequence (hg19) with *novoalign*. Local realignment around indels, variant calling with haplotypeCaller and variant quality score recalibration (VQSR) were calculated for each variant in a joint VCF file containing all samples according to the *Genome Analysis Toolkit* good practice. Sample quality control aimed to remove outliers including Freemix Fraction ≥0.03, missingness per sample >0.2, mismatching genders, heterozygosity rate outside the range of mean ±3SD, and duplicated/relatedness samples. Variant quality control was based on VQSR, linkage disequilibrium (LD) score, and missingness per variant at 0.1. A case-control association analysis will be performed on this cleaned high quality exome dataset.

Results: In sample quality control, of the total 712 samples, 49 were excluded for missingness (>20%) of the total variants, 47 were excluded for having mismatched genders to their recorded genders. Fourteen heterozygosity outliers and 13 duplicated/relatedness samples were removed. This left a total of 589 samples (IBM=135). In variant quality control, of the total 576014 variants, 136836 were removed for LD >0.5 and 36463 were removed for missing >10% genotype data. This left a total of 402715 variants.

Conclusion: A series of stringent quality control strategies was performed and this generated a cleaned high quality exome dataset for further case-control association analysis.

P105

The MYO-SEQ project: application of exome sequencing technologies to 1000 patients affected by limb-girdle weakness of unknown origin

Katherine Johnson[1], Marta Bertoli[1], Lauren Phillips[1], Kate Bushby[1], Hanns Lochmüller[1], Ana Topf[1], Volker Straub[1]

[1]*John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University*

The MYO-SEQ project is supported by Genzyme, Ultragenyx, LGMD2iFund, Samantha J Brazzo Foundation, LGMD2D Foundation and Kurt+Peter Foundation

Katherine.Johnson@ncl.ac.uk

Background: The symptoms of rare neuromuscular disorders often overlap, meaning it can be difficult to achieve a clinical diagnosis: there is thus a necessity for a more robust investigative approach. Genomic mutations are a large causative component of such disorders, with exonic variations capable of altering the function of encoded proteins. Here, we apply targeted whole exome sequencing (WES) to a cohort of undiagnosed patients with limb-girdle weakness. This approach should increase the diagnostic rates for causative mutations in disease-associated genes, while also expanding genotype-phenotype correlations.
Aims: The MYO-SEQ project aims to i) to contribute to the diagnostic pathway for patients affected by limb-girdle muscular dystrophy, and ii) to improve the diagnostic awareness of rare neuromuscular diseases.
Methods: One thousand patients were recruited by clinicians throughout Europe. Inclusion criteria stipulated that patients must present with limb-girdle weakness and elevated serum creatine kinase activity. Phenotypic data was collected using the PhenoTips software tool. WES with >250 ng DNA was completed at the Broad Institute, using Illumina exome capture and 38 Mb baited target. The variant call set was uploaded onto xBrowse and an analysis of 169 candidate genes was performed.
Results: The analysis of >500 patient samples from 14 different countries is now complete. We have annotated causal variants in 40% of these patients, with mutations identified in 52 of the 169 candidate genes. Of particular interest was the identification of a *TTN* founder mutation, associated with LGMD2J, in a Serbian sub-population. Causal variants were most frequently identified in *CAPN3* (LGMD2A), *DMD* (dystrophinopathies), *DYSF* (LGMD2B), *RYR1* (central core disease) and *COL6A2* (Bethlem myopathy).
Conclusion: Implementing WES enabled the detection of causal variants in previously undiagnosed patients with muscle weakness, in addition to the identification of a *TTN* founder mutation in Serbia. Our preliminary data have highlighted the value of WES in diagnosing rare neuromuscular diseases.

P106

Baseline characteristics of a prospective natural history study of sporadic inclusion body myositis including MRI assessment

Pedro M. Machado[1], Parul Houston[2], Angela Genge[3], Ingo Scholten[2], Linda Lowes[4], Didier Laurent[2], Dimitris A. Papanicolaou[5], Michael G. Hanna[1]

[1]*Medical Research Council Centre for Neuromuscular Diseases, University College London* [2]*Novartis Pharma AG, Basel, Switzerland*
Institute of Neurology, London, UK
[3]*Montreal Neurological Institute and Hospital, Montreal, QC, Canada*
[4]*Nationwide Children's Hospital, Columbus, OH, USA*
[5]*Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA*
p.machado@ucl.ac.uk

Background: Sporadic inclusion body myositis (sIBM) is a rare, debilitating, inflammatory and degenerative myopathy affecting people aged over 45 years. Limited data is available on longitudinal characterization of functional impairment, patient burden and the economic impact of sIBM.
Aims: Our aims are to characterize the clinical progression and functional impact of sIBM on patients over time assessed by functional performance measures and patient-reported outcomes, and to assess thigh muscle composition using MRI.

Methods: This longitudinal, prospective study is planned to recruit ~300 patients.
Patient-reported functional impact of sIBM over time as measured by the Sporadic Inclusion Body Myositis Physical Functioning Assessment (sIFA) is the primary outcome measure; functional performance as measured by the 6-Minute Walk Distance (6MWD), Quantitative Muscle Testing (QMT) are also being assessed. Demographics, medical history and functional assessments will be recorded at baseline and annually for 2 years. Muscle composition is being assessed by MRI in a subset of 30 patients.
Results: At cut-off date (31 July 2015), 137 patients (Men: 72.1%; Caucasians: 95.6%) with mean age (SD) of 68.5 (8.0) years were enrolled. Mean time from onset of symptoms to baseline visit was 10.3 (5.9) years and 65.6% patients had dysphagia. Mean total sIFA score was 48.3 (20.6) on a scale of 100 (highest degree of difficulty). Mean 6MWD was 302.1 (137.9) meters. Significant correlations were observed between sIFA and 6MWD. Correlations between lower body items of sIFA and QMT of quadriceps and thigh muscle volume as assessed by MRI were observed.
Conclusion: Findings from this study may help to determine clinical progression, functional impact, economic and humanistic burden of sIBM over time. sIFA is a valid tool to assess physical function in patients with sIBM.
Study supported by: Novartis Pharma AG, Basel, Switzerland.
Disclosures:
Parul Houston, Ingo Scholten, Didier Laurent, and Dimitris A. Papanicolaou are employees of Novartis and may be eligible for Novartis stock and stock options. Pedro M. Machado, Angela Genge and Michael G. Hanna serve as consultants to Novartis. Angela Genge was employed with Novartis from January–July 2014. Linda Lowes serves as a consultant to PTC, Sarepta, and Bristol-Myers Squibb. There was no payment from Novartis for participation in this abstract. Her institution has received grant support for clinical trials from Novartis. This study was sponsored by Novartis Pharma AG, Basel, Switzerland.

P107

Schwartz- Jampel syndrome

R Manuel[1], T Willis[1]
1 The Robert Jones and Agnes Hunt Orthopaedic hospital NHS Trust

Background: Schwartz-Jampel syndrome is a rare genetic disorder characterised by the association of dysmorphic features, myotonia and chondrodysplasia. Less than 100 cases have been reported in the literature. Mutations in the HSPG2 gene which encodes Perlecan causes this syndrome.
Patient characteristics: We report a case of a three year old girl presenting with waddling gait, multiple skeletal dysplasia, short stature, micrognathia, small mouth, narrow palpebral fissure and pursed lips. She has limited mouth opening with puckering of her mouth and face. Antenatally ultrasound scans showed shortening of upper limbs. At birth she had shortening of upper limbs, bowing of tibia and her skeletal survey was consistent with the diagnosis of Kniest dysplasia. She initially presented to the skeletal dysplasia clinic at 5 months of age with mild fixed flexion of elbows, fixed external rotation and restriction of abduction of both hips, bowing of the tibia and fixed adduction of the right foot. At age 3 she appeared to have myotonia, puckering of her lips, difficulty in opening of her month and more prominent stiffness in the cold and on eating cold food. Her eye examination showed right anisometropia and myopia.
Investigations: Needle EMG of the distal and proximal limb muscles at rest showed copious and continuous myotonic discharges of widely varying frequencies. X ray of her lower limbs and hips showed considerable dysplasia with dysplastic acetabulum.
Next generation sequencing was negative for COL2A1 gene associated with Kniest dysplasia. Homozygous mutation has been identified in the HSPG2 gene: c. 2563G>A,p.(Trp4188Ter) consistent with the diagnosis of Schwartz Jampel syndrome.
Conclusion: Schwartz- Jampel Syndrome is a rare disorder and should be considered in the differential diagnosis of a child presenting with triad of dysmorphic features, skeletal deformities and myotonia.

P108

GNE myopathy: clinical presentation, mutation analysis and longitudinal observations from a Global Patient Registry Study

Oksana Pogoryelova[1], *Phillip Cammish[1], Supriya Rao[2], Ed Conner[2] Ali Skrinar[2], Steffen Durinck[2], Hanns Lochmüller[1]*
[1] Newcastle University, John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK
[2] Ultragenyx Pharmaceutical Inc., Novato, CA, USA

Background: GNE myopathy is an ultra-rare autosomal recessive distal myopathy caused by mutations in the *GNE* gene resulting in reduced sialic acid synthesis. Clinical presentation varies from asymptomatic carriers to severely debilitating forms.
Aims: The aim of the analysis is to describe clinical presentation and progression of GNE myopathy using data collected via the GNE Myopathy Disease Monitoring Program (GNEM-DMP). The GNEM-DMP includes a hospital based/clinician reported natural history study and a global online patient self-reported registry.
Results: As of October 2015, 126 patients from 26 countries completed registry questionnaires including medical history, validated and non-validated health related questionnaires. In total 29 different *GNE* mutations were reported. Most of mutations 26/29 are missense and 3/29 are deletions with the frame shift. Clinical presentation at the onset most commonly included distal leg weakness (mean age 28.9), then progress to weakness in hands, difficulty climbing stairs, muscle spasms, twitching and pain (mean age 31.8), followed by difficulty sitting unaided, turning in bed and first indications to use a wheelchair or scooter (mean age 35.5). Lung function and cardiac function is compromised in 8.7% and 7.1% cases respectively. Pain (neck, shoulders, back and legs) was reported at an unexpectedly high rate -31.7%. Longitudinal observation was done using a Functional activity scale questionnaire (GNEM-FAS). From baseline to month 6, the most significant decrease in function was observed in the self-care domain (12.3%, n=15). Motor function and upper extremity domain score showed a very slight change. Longitudinal observations from the GNE myopathy DMP are continuing.
Conclusion: A high rate of pain and perceived drop in self-care ability suggest that better pain management and involvement of a social care provider could be beneficial in management of patients with GNE myopathy.

P109
Mitochondrial DNA rearrangements in sporadic Inclusion Body Myositis
K. A. Rygiel[a], H. Tuppen[a], A. Reeve[a], J. Miller[b], R. Taylor[a], D. M. Turnbull[a, b]
[a] *Mitochondrial Research Group (MRC Centre for Ageing and Vitality, Wellcome Trust Centre for Mitochondrial Research, Newcastle University, Institute of Neuroscience, Newcastle upon Tyne, UK)*
[b] *Department of Neurology (Royal Victoria Infirmary, Newcastle upon Tyne, UK)*
karolina.rygiel@ncl.ac.uk

Background: Mitochondrial abnormalities are pronounced in muscle from sIBM patients. Large-scale mitochondrial DNA (mtDNA) deletions have been considered the most common cause of respiratory deficiency in myofibres. A process called clonal expansion has been thought to drive accumulation of a single deletion in any one cell. An in-depth characterisation or these deletions in sIBM, however, have never been carried out.
Aims: The aim of this study was to characterise the type of mtDNA rearrangements in individual myofibres from muscle biopsies from patients with sIBM as well as assess their prevalence.
Patients and Methods: Open muscle biopsies from nine patients with diagnosed sIBM were used for laser-microdissection of individual myofibres, which were then used for downstream molecular analysis (PCR assays and sequencing).
Results: Using long-range PCR we found that about 15% myofibres harboured up to three different deletion species. We confirmed this result using single molecule PCR (smPCR) – 20% of myofibres

contained multiple deletions. Sequencing analysis revealed unusual deletion breakpoints spanning into the minor arc and removing origin of Light Strand Replication (OL). Quantitative real-time PCR demonstrated that almost 10% of all deletions removed OL and other genes located within the minor arc. Existence of OL-devoid mtDNA molecules is challenging to explain as OL is considered essential for mtDNA replication. One of the ways these molecules can replicate is when they contain duplicated regions. Indeed, a PCR-based assay designed to detect duplicated genomes confirmed their presence in muscle from our patients.
Conclusions: MtDNA rearrangements in sIBM are complex. Several species of large-scale, major and minor arc deletions can accumulate through clonal expansion in individual myofibres. Unusually large deletions are accompanied by duplicated regions of mtDNA, which allow replication of these molecules. The mechanism underlying formation of such complex rearrangements needs to be investigated further.

P110

***CAV3* mutations mimicking a metabolic myopathy: expanding the phenotypic spectrum of Caveolinopathies**

Renata Siciliani Scalco[1,2], Alice R. Gardiner[1], Rob Pitceathly[1,3], David Hilton-Jones[4], Anthony H Schapira[1], Chris Turner[1], Matt Parton[1], Mahalekshmi Desikan[1], Rita Barresi[5,6], Julie Marsh[5] , Adnan Y Manzur[7], Anne-Marie Childs[8], Lucy Feng[7], Elaine Murphy[9], Phillipa J Lamont[10], Gianina Ravenscroft[11], William Wallefeld[12], Mark R Davis[12], Nigel G Laing[11,12], Janice L. Holton[1], Doreen Fialho[1], Kate Bushby[6], Michael G Hanna[1], Rahul Phadke[1,7], Heinz Jungbluth[3,13,14], Henry Houlden[1], Ros Quinlivan[1,7]
[1]MRC Centre for Neuromuscular Diseases and Department of Molecular Neuroscience, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom
[2]CAPES Foundation, Ministry of Education of Brazil, Brasilia DF, Brazil
Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience,
[3]King's College London, London, United Kingdom
[4]Department of Clinical Neurology, West Wing, John Radcliffe Hospital, Oxford, United Kingdom
[5]NHS England HSS for Rare Neuromuscular Diseases, Muscle Immunoanalysis Unit, Dental Hospital Richardson Road, Newcastle upon Tyne, United Kingdom
[6]The John Walton Muscular Dystrophy Research Centre and MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom
[7]Dubowitz Neuromuscular Centre, UCL Institute of Child Health, Great Ormond Street Hospital, London, United Kingdom
[8]Leeds Teaching Hospitals, Leeds, United Kingdom
[9]Charles Dent Metabolic Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, United Kingdom
[10]Neurogenetic unit, Dept of Neurology, Royal Perth Hospital, Western Australia
[11]Harry Perkins Institute of Medical Research and the Centre for Medical Research, University of Western Australia, Nedlands, Australia
[12]Department of Diagnostic Genomics, Pathwest, QEII Medical Centre, Nedlands, Australia
[13]Department of Paediatric Neurology, Evelina Children's Hospital, Guy's & St Thomas NHS Foundation Trust, London, United Kingdom
[14]Randall Division for Cell and Molecular Biophysics, Muscle Signalling Section, King's College London, London, United Kingdom
r.scalco@ucl.ac.uk

Background: Rhabdomyolysis is often due to a combination of environmental trigger(s) and genetic predisposition; however, the underlying genetic cause remains elusive in many cases. Mutations in CAV3 lead to various neuromuscular phenotypes with partial overlap, including LGMD1C, rippling muscle disease, distal myopathy and isolated hyperCKemia.
Aims: To present a series of patients with exercise intolerance and rhabdomyolysis caused by mutations in CAV3.

Methods: Clinical phenotype, genetic findings, muscle biopsy analysis and immunoblotting are described in eight patients from six families.
Results: Symptoms included myalgia (n=7), exercise intolerance (n=6) and episodes of rhabdomyolysis (n=2). A previous heterozygous mutation in CAV3 (p.T78M) and three novel variants (p.V14I, p.F41S, p.F54V) were identified. Caveolin-3 immuno-labelling in sections was normal in 3/4 patients however, immunoblotting showed more than 50% reduction compared with controls in 5 patients.
Conclusion: This case series demonstrated that rhabdomyolysis can be caused by mutations in CAV3 and broadens the phenotypic spectrum of caveolinopathies. Defects in CAV3 should therefore be considered in patients presenting with rhabdomyolysis. Caveolin-3 expression may be normal on immunohistochemical study on sections, but immunoblotting proved to be a more sensitive method to detect reduced caveolin-3.

P111

Effect of a multi-disciplinary approach to diagnosis and management for non-lysosomal skeletal muscle glycogen storage disorders

Renata S. Scalco[1], Suzanne Blooth[1], Charlotte Ellerton[1], Richard Godfrey[1], Ayfer Kahraman[1], Ralph Wigley[2], Sherryl Chatfield[1], Rachel Carruthers[1], Mary Anne Preece[3], Richard Kirk[4], Patricia Turner[1], Helena Coskeran[1], Andrew Wakelin[5], Janice Holton[1,6], Jatin Pattni[1], Ros Quinlivan[1]
[1]*MRC Centre for Neuromuscular Diseases and Department of Molecular Neuroscience, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK*
[2]*Enzyme laboratory, Great Ormond Street Hospital For Sick Children NHS Foundation Trust , London, UK*
[3]*Department of Clinical Chemistry, Birmingham Children's Hospital, Birmingham, UK*
[4]*Sheffield Diagnostic Genetics Service, Sheffield Children's NHS Foundation Trust, Sheffield, UK*
[5]*Patient Representative, Association for Glycogen Storage Disease UK, London, UK*
[6]*Division of Neuropathology, Institute of Neurology, University College London, London, UK*
r.scalco@ucl.ac.uk

Background: The highly specialised national service for rare non-lysosomal muscle glycogen storage diseases (GSDs) is the only service world-wide offering multi-disciplinary care for patients, including: physician, physiotherapist, clinical nurse specialist, clinical psychologist, dietician, sports and exercise physiologist, patient advocate and a PhD student. Direct access to laboratory investigations and a clinical diagnostic and management service are provided. In addition to an MDT clinic, telephone clinics, information days for newly diagnosed patients and face-to-face therapy reviews are also offered.
Aims: Service evaluation.
Methods: Prospective audit of outcome measures used for the NHS commissioning for Quality and innovation (CQUIN).
Results: Data from approximately 236 (175 genetically confirmed) patients aged 5-75 years will be presented. The majority of patient had McArdle disease, with mutations in *PYGM* at R50x being the most common. Other diagnoses include: GSDVII, GSDXIII and GSDXV. Patients were referred from the UK and EU countries including: Isle of Man, Malta and Eire. The incidence of episodes of severe rhabdomyolysis defined as those requiring hospital visits within the past 12 months was 17% in new referrals and 2.8% in follow-up patients. Prospective data from functional walking assessments (12MWT), quality of life (SF36), dietetic assessments and genetic testing will be presented. A Patient Liaison Panel oversaw the production of the reference booklet for GPs and assisted with recruitment to the EUROMAC Registry and a clinical trial of Sodium Valproate.
Conclusion: This highly specialised multi-disciplinary national service demonstrates reduced frequency of rhabdomyolysis and other complications related to rare GSDs following clinical assessment. Patients could be divided into four clear cohorts on the basis of severity as assessed by the 12MWT which showed a positive correlation with quality of life. Improvements in walking distance and quality of life were seen in subsequent visits to the clinic, demonstrating functional improvement over time.

P112

Dantrolene as a possible prophylactic treatment for *RYR1*-related rhabdomyolysis

Renata Siciliani Scalco[1,2], Nicol C. Voermans[3], Heinz Jungbluth[4,5,6], Ros Quinlivan[1,7]

[1]*MRC Centre for Neuromuscular Diseases and Department of Molecular Neuroscience, University College London (UCL) Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK*

[2]*CAPES Foundation, Ministry of Education of Brazil, Brasilia, DF, Brazil*

[3]*Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands*

[4]*Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience (IoPPN), King's College London (KCL), London, UK*

[5]*Randall Division for Cell and Molecular Biophysics, Muscle Signalling Section, King's College London, London, UK*

[6]*Department of Paediatric Neurology, Evelina Children's Hospital, Guy's & St Thomas NHS Foundation Trust, London, UK*

[7]*Dubowitz Neuromuscular Centre, Great Ormond Street Hospital, London, UK*

r.scalco@ucl.ac.uk

Background: Acute muscle breakdown, also known as rhabdomyolysis (RM), may result from gene-environment interactions. Mutations in *RYR1* lead to various neuromuscular phenotypes including malignant hyperthermia susceptibility and RM.

Aims: We report the ad hoc use of oral dantrolene as a prophylactic treatment for *RYR1*-related RM in three patients.

Methods or Patients or Materials: Case series.

Results: Patients were prescribed 25mg of dantrolene to take orally up to a maximum of four times a day at the onset of symptoms in an attempt to stop progression of the RM episodes. Patient one intermittently took dantrolene at early onset of muscle symptoms (cramp or myalgia), reporting complete abatement of symptoms within 20-30 minutes. Patient two was able to resume symptom-free exercise by taking a single dose of dantrolene prior to physical activity (such as cycling). While taking dantrolene neither patient one nor two had an episode of myoglobinuria or RM. Patient three increased dantrolene dose up to four times daily when symptomatic. She has suffered four additional episodes of RM in the follow-up of six years, but with less severely elevated CK levels, not requiring intensive care unit admittance. None of the patients had drug-related side effects, in particular their liver function tests remained normal.

Conclusion: In the short term use of low dose dantrolene-associated benefits appear to outweigh risks in the management of patients with recurrent rhabdomyolysis due to mutations in *RYR1*, in particular ad hoc use during symptoms might possibly prevent or abort an attack of RM. Undertaking a randomised, double-blinded, placebo controlled clinical trial to assess risks and benefits of dantrolene in this group of patients could help to evaluate the role this drug in preventing RM due to *RYR1* mutations in the future.

P113

Misdiagnosis in McArdle disease

Renata Siciliani Scalco, Suzanne Booth, Richard Godfrey, Ros Quinlivan

MRC Centre for Neuromuscular Diseases and Department of Molecular Neuroscience, University College London Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK.

r.scalco@ucl.ac.uk

Background: McArdle disease (glycogen storage disease type V – GSDV) is an autosomal recessive disorder characterized by the absence of muscle glycogen phosphorylase. This results in impaired muscle metabolism with symptoms such as exercise intolerance and muscle pain beginning in childhood. Correct diagnosis is often delayed for decades following the first presentation to a doctor.

Aims: To investigate the frequency of misdiagnosis in patients with GSDV

Methods or Patients or Materials: Clinical information from 43 patients with genetically confirmed GSDV was reviewed.
Results: A high frequency of misdiagnosis was found (88%), most of them occurring in people under 20 years of age. Incorrect treatment was given to 47% of patients.
Conclusion: Data presented here demonstrated a variety of misdiagnoses prior to the correct diagnosis of GSDV, which has led to inappropriate treatment and which, in some cases, has even resulted in long term harm by exacerbating symptoms and, as a consequence, reducing quality of life still further. McArdle disease should be considered when evaluating patients presenting with myalgia, exercise intolerance and/or myoglobinuria. Early diagnosis of GSDV is important to prevent recurrent episodes of rhabdomyolysis, which can potentially be an acute life-threatening event resulting in compartment syndrome, acute renal failure and rarely death.

P114

Investigating the effects of pharmacological up-regulation of the heat shock response in models of inclusion body myopathy

Spicer, C. [1, 2] , Ahmed, M. [1, 2], Hanna, MG.[1] Greensmith, L. [1, 2]
[1]*MRC Centre for Neuromuscular Diseases, Queen Square, London, UK*
[2]*Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, Queen Square, London, UK*
charlotte.spicer.13@ucl.ac.uk

Sporadic inclusion body myositis (sIBM) is the most common acquired muscle disease affecting adults over the age of 50. Although the precise cause of sIBM remains unknown, the disease is characterised by both inflammatory and degenerative features. However, trials of anti-inflammatory agents have all been unsuccessful and to date there is no effective disease-modifying treatment for sIBM.
Protein mishandling in cells leads to the accumulation and aggregation of proteins, and this is characteristic of IBM pathology. Previous work in our lab has demonstrated that co-induction of the cytoprotective heat shock response (HSR) by treatment with Arimoclomol ameliorates IBM-like pathology in *in vitro* models of IBM by improving protein handling.
In order to test whether Arimoclomol was also effective in vivo, we undertook a pre-clinical trial of Arimoclomol in a transgenic mouse model of multisystem proteinopathy (MSP) caused by a mutation in the valosin-containing protein (VCP) gene. This model recapitulates many of the key features of sIBM in muscle. We examined changes in the muscle of the mutant (mVCP) mice to gain insight into the underlying pathomechanisms of the disease, using immunohistochemistry, western blot analysis, electron microscopy and imaging techniques and tested the effects of Arimoclomol on these pathological changes. In addition, we also obtained fibroblasts from patients with VCP mutations and examined whether these human cells also manifested any IBM-like pathology.
Histological examination of mVCP mice showed evidence of key IBM-like characteristics in muscle, including TDP-43 mislocalisation, ubiquitin-positive inclusions, mitochondrial damage and inflammatory cell infiltration. Treatment with Arimoclomol was found to significantly attenuate these pathogenic features in muscle *in vivo*.
These *in vivo* findings build upon our *in vitro* data and together suggest that Arimoclomol may be a potential therapeutic agent for the treatment of sIBM.

P115

***STAC3* p.Trp284Ser, a hotspot mutation for congenital myopathy with distinctive dysmorphic features and malignant hyperthermia**

Irina T. Zaharieva[1], Anna Sarkozy[1,2], Adnan Manzur[1,2], Gina O'Grady[3,4], Jenny Sharpe[5], Joanne Dixon[6], Gemma Poke[7], Emily C. Oates[8,9], Irene Colombo[10], Maria Sframeli[11], Lucy Feng[1,2], Rahul Phadke[1], Caroline A. Sewry[1,2], Michael Duchen[5], Jennifer E. Morgan[1,12], Susan Treves[13], Francesco Muntoni[1,2,12]
[1] *Dubowitz Neuromuscular Centre, UCL Institute of Child Health, London, UK*
[2] *Great Ormond Street Hospital, London, UK*

[3] *Institute for Neuroscience and Muscle Research, Children's Hospital at Westmead*
[4] *Starship Children's Health, Auckland, New Zealand*
[5] *Research Department of Cell & Developmental Biology, UCL, London, UK*
[6] *Genetic Health Service NZ, Christchurch, New Zealand*
[7] *Genetic Health Service NZ, Wellington, New Zealand*
[8] *Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Sydney, NSW 2145, Australia*
[9] *Discipline of Paediatrics and Child Health, Faculty of Medicine, The University of Sydney, Sydney, New South Wales, 2006, Australia*
[10] *Neuromuscular and Rare Disease Unit, Department of Neuroscience, University of Milan, Milano 20122, Italy*
[11] *Department of Neurosciences and NEMO SUD Clinical Centre, Messina, Italy*
[12] *MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, WC1N 3BG, UK*
[13] *Department of Anesthesia and Biomedicine, University Hospital Basel, Hebelstrasse 20, 4031 Basel, Switzerland*

Background: Congenital myopathies (CMyo) are a heterogeneous group of conditions caused by mutations in >20 genes. Recently, a homozygous p.Trp284Ser mutation in the *STAC3* gene was identified as causative for Native American Myopathy (NAM), characterized by congenital muscle weakness, susceptibility to malignant hyperthermia, multiple joint contractures, scoliosis, ptosis and facial dysmorphisms. STAC3, a muscle specific protein, is essential for maintaining the excitation-contraction coupling (EC) although the exact mechanism of its action is not known.
Aims: We describe 7 patients from 3 families carrying the homozygous p.Trp284Ser *STAC3* mutation, further expanding the current knowledge about this rare myopathy.
Methods: Two families were identified by whole exome sequencing, while a 3rd kindred was identified based on its distinctive clinical features.
Results: Affected individuals presented at birth mostly with hypotonia, talipes, feeding difficulties and failure to thrive. Main muscle findings were motor developmental delay and slowly progressive muscle weakness, with proximal more than distal, axial and facial distribution. All patients were ambulant at last examination (age range 3-14 years). A variable degree of respiratory impairment and scoliosis/kyphosis was present in most patients, while malignant hyperthermia was documented in 4. Dysmorphic features included ptosis, malar hypoplasia, facial weakness, high palate and dental malocclusion and overcrowding. Other less common findings were dysarthria, hearing loss and cryptorchidism. One child died at 3 years of age. CK was normal and muscle biopsy analysis showed mild myopathic changes. Preliminary analysis in fibroblasts from one patient indicated larger histamine evoked calcium concentration compared to control fibroblasts. Further functional characterization of the intracellular calcium handling in p.Trp284Ser myoblasts is ongoing.
Conclusions: Our results confirm *STAC3* as a novel cause of CMyo and malignant hyperthermia. The functional characterization of the p.Trp284Ser mutant will contribute to a better understanding of the role of *STAC3* in EC and in CMyo.

Diagnostics and Clinical Practice

---

‡P116

Should the use of the Extended Myositis Antibody (EMA) panel be part of the routine work-up in suspected myositis?

Antoinette O'Connor[1], Jennifer Mulhall[1], Sinead MJ. Harney[2], John G. Ryan[2], Grainne Murphy[2], Michael T. Henry[3], Peter Annis[4], Vincent Tormey[5], Aisling M. Ryan[1]
[1]Department of Neurology, [2]Rheumatology, [3]Respiratory Medicine, [4]Immunology, Cork University Hospital

[5]Department of Immunology, University Hospital Galway
antoinetteoconnor.aoc@gmail.com

Background: The discovery of unique autoantibodies has informed and altered our approach to the diagnosis and management of the inflammatory myopathies[1,2]. This study reports the initial experience of use of the Extended Myositis Antibody (EMA) panel in Cork University Hospital (CUH), the largest university teaching hospital in Ireland.
Aims: To determine the clinical utility and cost effectiveness of the EMA panel in suspected immune myopathy.
Methods: We conducted a retrospective review of the electronic and paper records of all patients who had an EMA assay performed from test introduction in April 2014 to March 2015. Demographic details, clinical presentation and requesting department were recorded. The use of additional investigations (electromyography, MRI, muscle biopsy, CT Thorax) and laboratory results were documented. We reviewed the utility of the assay in clarifying diagnosis, directing the investigative pathway and selecting the appropriate treatment.
Results: Twenty two patients (mean age:55, SD:15) had an EMA panel sent during the study period. The assay cost was €26.41 per sample analysed. The EMA panel was diagnostic in 27% (6/22) of cases. A positive EMA panel was of significant clinical utility in facilitating decisions on appropriate investigations, and need for onward referral to other, particularly respiratory, physicians. All patients with a positive EMA panel (n=6, 27%) experienced symptomatic improvement on receiving immunosuppressants.
Conclusion: This study illustrates the value of the EMA panel in defining a heterogeneous patient population into clinicoserological phenotypes, and consequently guiding investigation and treatment pathways.
References:
1. Hengstman GJD, Van Engelen BGM, Vree Egberts WTM, et al. Myositis specific autoantibodies: overview and recent developments. Curr Opin Rheumatol 2001 Nov;13:476–8.
2. Gunawardena H, Betteridge ZE, McHugh NJ. Myositis-specific autoantibodies: their clinical and pathogenic significance in disease expression. Rheumatology. 2009 Jun; 48(6):607–12.

‡117

The Revised Hammersmith Scale for Spinal Muscular Atrophy: Reliability, validity and results from a large international pilot

D. Ramsey[1], M.Scoto[1], A. Mayhew[2], M. Main[1], E. Mazzone[3], J. Montes[4], S. Dunaway[4], R. Salazar[4], A.M. Glanzman[7], A. Pasternak[6], R. De Sanctis[3], L. Fanelli[3], J. Quigley[6], E. Mirek[6], T. Duong[8], R. Gee[8], R. Muni Lofra[2], M. Civitello[5], G. Ramdharry[9], A. Wallace[10], K. Bushby[2], J. Day[8], B. Darras[6], D. De Vivo[4], R. Finkel[5], E. Mercuri[1,3], F. Muntoni[1]
[1]*Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital, London, UK*
[2]*John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, Newcastle University, UK*
[3]*Department of Paediatric Neurology, Catholic University, Rome, Italy*
[4]*Department of Neurology, Columbia University Medical Center, New York, USA*
[5]*Nemours Children's Hospital, University of Central Florida College of Medicine, Florida, USA*
[6]*Boston Children's Hospital, Boston, USA*
[7]*The Children's Hospital of Philadelphia, Philadelphia, USA*
[8]*Stanford University, Palo Alto, California, USA*
[9] *Faculty of Health Social Care & Education, Kingston University and St George's University of London, London, UK*
[10] *UCL Institute of Child Health, London, UK*
danielle.ramsey.12@ucl.ac.uk

Background: Robust outcome measures are essential to assess disease progression, stability, improvement and as a measure of treatment efficacy. Outcome measures currently used in SMA 2 and 3 capture progression of disease but have limitations at the two extremes of clinical severity, and require further validation regarding their psychometric properties. An international collaboration has been working together over the last two years to address this.
Aim: To develop a psychometrically robust outcome measure for the assessment of gross motor functional abilities in type 2 and 3 SMA.
Methods: An iterative process was undertaken to revise the HFMSE using a series of expert panels, pilots and psychometric analysis with the Rasch model. The resultant Revised Hammersmith Scale for SMA (RHS) was piloted in three international networks – SMA REACH UK, Italian SMA Network and PNCRN USA. Inter and intra-rater reliability was investigated in a UK group of neuromuscular physiotherapists via an online survey and videos.
Results: The RHS was piloted in 140 patients across the three international networks. Rasch analysis demonstrated very good fit of all 36 items to the construct of motor performance, good reliability, logical and hierarchical item progression in 27/36 items, and excellent targeting with minimal ceiling. The RHS differentiated between clinically different groups: SMA type ($p < 0.001$), World Health Organisation (WHO) motor milestones ($p < 0.001$), and ambulation status ($p < 0.001$). A strong positive correlation with the WHO $r = 0.868$, $p < 0.001$ confirmed construct and concurrent validity. A high level of agreement was identified for inter and intra-rater reliability (ICC 0.997).
Conclusion: Initial findings demonstrate the RHS is a psychometrically sound outcome measure for assessment of type 2 and 3 SMA, further work is required to remove a small floor effect. Work is ongoing to establish sensitivity to change over time.

P118

Optimising the IVIg service: an audit of monitoring and dosage

Authors: S Sarri-Gonzales, A Zarkali, G Bonifacio, C Englezou, V Van Hamel Parsons, H Renshaw, C Turner, MJ Parton, MG Hanna, H Manji, MM Reilly, MP Lunn, AS Carr
MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, Queen's Square, London

Background: Regular intravenous immunoglobulin (IVIG) is commonly used in the management of autoimmune neuromuscular conditions. In our tertiary neurological centre, 388 patients received 203,571 grams of IVIG (at a cost of £35/gram) in 2014/15 amounting to 3127 patient days (at a cost of £250/person/day). The vast majority (91.7%) was delivered through our Daycare Unit (DCU). Close medical supervision is required to maintain response, safety and manage cost.
Aims: The 2011 Department of Health set guidelines for monitoring and dosing in patients on long-term IVIg treatment. The recommendation was for annual assessment to establish:

1. Functionally important response (using at least 3 established outcome measures)
2. Safety and tolerance
3. Lowest dose for optimal symptom control

Methods: A new service was set up in July 2015 to provide regular consultant-led clinical review for all neuromuscular IVIg patients. Annual assessments were scheduled to coincide with peak and trough points in individual patient cycles. This audit prospectively documented achievement of DOH recommendations for timing and content of monitoring and any dose changes. Comparison was made with the preceding year (July 2014- June 2015).
Results: 90 established neuromuscular IVIg patients, 60% male were referred to the new service. 58.9% CIDP, 35.6% MMN, 4% inflammatory myopathy (blue recommendations), 2.5% other (grey recommendation). After 6 months an absolute reduction in IVIg dose of 472g/month, 4 treatment cessations and 6 less DCU treatment days/month had been achieved: equivalent to £18, 020/month cost reduction. Compliance with DoH recommendations for annual assessment improved from 60% (2013/14) to 89.7% (2014/15) to 100% (2015). Objective evidence of clinical response was documented using at

least 3 established outcome measures in 100% in the new service (mean: 1.5 outcome measures/patient in2014/15) with clear outcome reporting to pharmacy in 100% (35% in 2014/15).
Conclusion: The IVIg assessment services has optimised compliance with national guidelines and facilitated safe, stable reduction in mean monthly dose and DCU treatment days equivalent to an annual saving to the trust of £216,240.

P119

Optimising the IVIg service: an audit of Daycare delivery

Authors: A Zarkali, G Bonifacio, C Englezou, V Van Hamel Parsons, H Renshaw, G Ingle, S Sarri-Gonzales, G Plant, H Manji, MM Reilly, MP Lunn, AS Carr
MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, Queen's Square, London

Background
Regular intravenous immunoglobulin (IVIG) is commonly used in the management of autoimmune neuromuscular conditions. In our tertiary neurological centre, 388 patients received 203,571 grams of IVIG in 2014/15 amounting to 3127 patient days; the vast majority (91.7%) was delivered through our Daycare Unit.

Aims: We want to ensure that all patients receiving regular IVIG in our hospital will receive a clinical assessment ensuring safe administration of IVIG, without unnecessary waiting times.
Methods: We mapped the journey of a typical patient receiving IVIG and tried to minimise processes that did not add value. At regular intervals throughout the auditing process we organised workshops with juniors, consultants, nurses, managers and pharmacists to identify the drivers for delays and suboptimal assessments, and to raise awareness. Finally, we trialled a clerking proforma with prompts for risk factors and a '2-Step IVIG clinic' led by senior house officers on days with increased number of IVIG admissions. We continuously audited on a weekly basis a sample of 50% of all patients admitted to Daycare Unit for IVIG to assess the effect of our interventions.
Results: We audited a total of 45 patients over 4 weeks. With our interventions, the mean waiting time from arrival to IVIG administration was reduced by 28% from 71.2 (median 55, range 5 to 160) to 51.42 minutes (median 45, range 15 to 95). In addition, the clinical assessment prior to IVIG administration was significantly improved, with 100% of patients now being assessed for thromboembolism (from 45.5%), infection (from 90.9%) and comorbidities (from 72.7%) prior to IVIG infusion.
Conclusion: Our project highlights the importance of a multidisciplinary approach which allowed us to plan and implement significant changes in the Unit's structure. With all the team working together we managed to reduce unnecessary waiting times and ensure safe administration of IVIG.

P120

Clinical Research Activity in the Newcastle MRC Centre for Neuromuscular Disease

Becky Davis1, Julia Maddison2, Jodie Worley1, Professor Volker Straub1, Professor Hanns Lochmuller1 , Professor Doug Turnbull2 , Professor Patrick Chinnery1 , Professor Mike Trenell3 , Professor Rita Horvath 1 Dr Robert McFarland2, Dr Grainne Gorman2, Professor Robert Taylor2, Professor Kate Bushby1
1John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine ,University of Newcastle upon Tyne, Newcastle upon Tyne, UK; 2 Wellcome Trust Centre for Mitochondrial Research, Institute of Neuroscience, University of Newcastle upon Tyne, Newcastle upon Tyne, UK. 3 Institute of Cellular Medicine, University of Newcastle upon Tyne, UK, 4Newcastle Upon Tyne NHS Hospitals Foundation Trust.
Becky.davis@ncl.ac.uk

The Newcastle MRC Neuromuscular team encompasses a number of specialists performing world-class translational research to bring diagnosis, care and therapy to people with neuromuscular 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. We have a multidisciplinary team who work together on many clinical trials and studies in the adult and paediatric populations. Current and upcoming projects include drug and exercise intervention studies, translational research, natural history studies, registries, BioBanks, behavioural intervention and clinical outcome studies. 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 MHRA approval, Research Ethics Committee approval, 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) that is facilitated by the coordination team to produce the highest professional level of neuromuscular clinical research in Newcastle and the North East.

121

Safety, tolerability and biological efficacy of Rituximab therapy in the Northern Irish Neuromuscular Clinic

C M Doherty, J McConville.
Department of Neurosciences, Belfast Health and Social Care Trust, Northern Ireland.
carolynne.doherty@belfasttrust.hscni.net

Background: The monoclonal antibody Rituximab, directed against the CD20 antigen expressed by B lymphocytes has historically been used to manage haematological malignancies. Experience of use of Rituximab in neuromuscular conditions, particularly refractory myasthenia gravis, is growing despite the lack of clinical trial evidence to support its use. Published Rituximab regimens in auto-immune disease include low dose (100mg) high dose (1000mg) and dose by surface area (375mg/m^2).
Aims: We sought to retrospectively evaluate the safety, tolerability and biological efficacy of administration of low dose Rituximab in patients with refractory neuromuscular conditions in Northern Ireland.
Methods: Patients who had received either 100mg or 375mg/m^2 doses of Rituximab were identified. Data including demographics, exposure to other immunotherapies, adverse events, immunoglobulin profiles and lymphocyte subsets were collected.
Results: Rituximab (100mg) was effective at causing complete B cell depletion defined by an absolute CD19 positive count of <0.01x10^9/L in 7 of 8 cases. Infusions were tolerated in all patients. B cell counts became detectable (≥0.01) after a mean of 254 days (±42, 95% C-I). Immediate T cell lymphopenia was common where lymphocyte subsets were checked in the immediate post-transfusion stage (43% reduction in CD3 lymphocytes, average post-infusion CD3 count of 0.81).
Conclusion: This data provides supportive evidence that 100mg doses of Rituximab typically produce complete depletion of CD19 antigen expressing lymphocytes.

P122

Using a Gene Sequencing Panel to Investigate Rhabdomyolysis

James B Lilleker[1,2], Richard Kirk[3], Mandy Nesbitt[3], Reena Sharma[4], Mark E Roberts[1,2]
[1]*Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, UK*
[2]*University of Manchester, UK*
[3]*Sheffield Diagnostic Genetics Service, Sheffield Children's NHS Foundation Trust, UK*
[4]*Mark Holland Metabolic, Salford Royal NHS Foundation Trust, Salford, UK*

Background: A variety of genetic myopathies and metabolic disorders can predispose patients to rhabdomyolysis. Traditional diagnostic approaches have involved sequential candidate gene analysis. However, this is expensive and diagnostic delays are common.
Aims: We sought to investigate the diagnostic utility of a rhabdomyolysis gene sequencing panel (Sheffield Diagnostic Genetics Service).

Methods: A sequencing panel of 30 genes potentially associated with rhabdomyolysis was developed in Sheffield. Over a 12 month period all adult patients with rhabdomyolysis or hyperCKaemia felt clinically to be caused by a metabolic muscle disorder were investigated using this panel.
Results: A total of 21 patients (15M, 6F) with a mean age of 29 were studied. 12 patients presented with acute rhabdomyolysis, with others presenting with less acute exercise induced myalgia and hyperCKaemia. The median serum creatine kinase at presentation was 9,000 (IQR 2,000-16,000).
In 12 patients, no pathogenic mutations were identified. One patient was homozygous for a mutation in the *PYGM* gene, abnormalities which were not identified on 'hot-spot' screening. One patient was homozygous for a mutation in the *CPT2* gene. In this patient, muscle biopsy was avoided thanks to timely genetic diagnosis.
Seven other patients were found to be heterozygous for variants (some newly described) in one of the following genes: *FBP2*, *RYR1*, *HADHA*, *CPT2* and *AGL*. The pathogenic relevance of these findings remains uncertain although *in-silico* analysis suggested a pathogenic role in some cases.
Conclusions: A gene panel approach to genetic testing in rhabdomyolysis has the potential to reduce diagnostic delay and avoid unnecessary investigations. As well as identifying two pathogenic mutations, variants were identified which may have pathogenic relevance. Functional studies are required to understand the significance of these findings.

P123

The Revised Hammersmith Scale for Spinal Muscular Atrophy: Moving towards meaningful measurement, content validity from a patient/carer perspective

D. Ramsey[1], M.Scoto[1], F. Muntoni[1]
[1]*Dubowitz Neuromuscular Centre, UCL Institute of Child Health & Great Ormond Street Hospital, London, UK*
danielle.ramsey.12@ucl.ac.uk

Background: Functional outcome measures are frequently designed by professionals to assess body structures, functions and reflect real life activities. User involvement in the development of outcome measures is an essential part of scale construction. The Revised Hammersmith Scale for SMA (RHS) was designed by physiotherapists and clinicians to assess physical abilities of people with type 2 and 3 SMA. It is important to assess whether such scales represent real life activities and if what is measured is meaningful to patients, parents and carers.
Aim: To investigate content validity of the RHS from a patient/carer perspective in patients with type 2 and 3 SMA.
Methods: Two patient/parent focus groups were held by SMA REACH UK. Patients with type 2 and 3 SMA were invited together with their parents/carers. Each focus group was facilitated by SMA REACH UK Physiotherapist and involved thorough discussion of the RHS scale item by item. Participants were asked to explain what each item meant to them, and what activity it could represent/be useful for. Participants fed back their answers in a variety of methods, spoken, written on post-it notes or in the form of a structured workbook.
Results: Nineteen families participated in the workshop (SMA 2 = 6 families, SMA 3 = 3 families), 4 children with SMA contributed their perspective. Qualitative information was obtained from a patient/parent perspective for all 36 items of the RHS with regards what they mean and what activities they could represent.
Conclusion: We have established the patient/parent perspective of items included in the RHS scale. This study has anchored a clinically reported scale to 'real life' activities and given meaning from a patient perspective and is a valuable step towards identifying what is considered as a clinically minimal important difference. These results are also of relevance for the original Hammersmith Scale.

P124

An update on FSHD2 diagnostic testing

D. Smith[1], R. Whittington[1], P. Lunt[2], T. Evangelista[3], H. Lochmuller[3], M. Williams[1];

[1]*Bristol Genetics Laboratory, Bristol, United Kingdom,* [2]*Formerly: Dept of Clinical Genetics, St Michaels Hospital, Bristol, United Kingdom.* [3] *The Newcastle University, John Walton Muscular Dystrophy Research Centre. MRC Centre for Neuromuscular Diseases at Newcastle. Newcastle upon Tyne, UK*
debbie.smith@nbt.nhs.uk

Facioscapulohumeral muscular dystrophy (FSHD), affecting ~1 in 20,000 individuals, is an AD epigenetically-regulated disorder, with characteristic pattern of progressive muscle involvement commencing in the face and shoulder-girdle. Two clinically indistinguishable forms differ in molecular basis of epigenetic regulation, but are underpinned by hypomethylation of 4q35, causing aberrant DUX4 expression (toxic transcription factor). FSHD1 (OMIM158900) (95% cases) caused by contraction of D4Z4 repeats, results in allele-specific hypomethylation. FSHD2 (OMIM158901) (~3% of cases), contraction independent, is caused by mutations in SMCHD1, encoding a chromatin-modulating enzyme, resulting in global hypomethylation and chromatin relaxation of D4Z4 arrays. A permissive haplotype at 4q35 is required for clinical expression of FSHD1 and 2, necessitating digenic inheritance for FSHD2, increasing the complexity of genetic counselling.
BGL provides a UKGTN specialist diagnostic service for FSHD, processing >500 UK/international referrals annually. FSHD2 testing has been available since Jan 2014; clinically-typical (assessed by clinical proforma) deletion negative patients (4.8% referrals) are tested for FSHD2 by 4q35 methylation quantification followed by SMCHD1 sequencing of hypomethylated patients by Sanger or NGS (Focused Exome Agilent) We present an audit of FSHD2 positive cases (16 cases with 13 novel SMCHD1 mutations), and clinical data illustrating genotype-phenotype correlations associated with two different categories of SMCHD1 pathogenic mechanism, but seen in more equal proportion than previously reported (Lemmers *et al*.[1]). Negative cases may have mutations in other genes in the differential diagnosis for FSHD (Leidenroth *et al*.[2]), or other methylation controlling genes. An NGS gene panel to cover overlapping neuromuscular phenotypes is being trialled and results will be presented.

References

1. Lemmers, R *et al*. Inter-individual differences in CpG methylation at D4Z4 correlate with clinical variability in FSHD1&2. HMG (2014)
2. Leidenroth *et al*. Diagnosis by sequencing: correction of misdiagnosis from FSHD2 to LGMD2A by whole-exome analysis. EJHG.(2012) 1-5.

Current UK Neuromuscular Clinical Trials

MRC Centre CTIMPs Set-up Phase trials

1. Mesoangioblast-mediated exon 51 skipping, based upon a single intra-muscular injection of five non ambulant DMD patients: a non-randomized, open label, phase I/IIa study
Status: Set-up phase
Sponsor: University of Manchester
Funder: The Wellcome Trust
CI: Dr. Imelda Hughes
PI: Prof. Giulio Cossu

2. A Phase II Clinical Study to Assess the Activity and Safety of Utrophin Modulation with SMT C1100 in Ambulatory Paediatric Male Subjects with Duchenne Muscular Dystrophy (C11005)
Status: Set -up phase
Sponsor: Summit
CI: Prof. Muntoni
PI: Dr. Michela Guglieri

3. A phase IIb/III of Arimoclomol in IBM
Status: Set-up phase
Planned start date: TBC
Sponsor: UCL
Funder: UCL/FDA/Orphazyme (TBC)
PI: Prof. Michael Hanna
Recruitment target: 150

4. Multicentre, open-label, single arm study to evaluate long-term safety, tolerability, and effectiveness of 10 mg/kg olesoxime in patients with SMA
Status: Set-up phase
Sponsor: Roche
CI: Prof. Hanns Lochmüller
PI: Dr. Michela Guglieri

5. A Single-Blind, Phase 2 Study To Evaluate The Safety And Efficacy Of Tideglusib 400mg Or 1000mg For The Treatment Of Adolescent And Adult Congenital And Juvenile-Onset Myotonic Dystrophy
Status: Set-up phase
Sponsor: AMO Pharma
CI/PI: Prof. Hanns Lochmüller

MRC Centre CTIMPs Open Trials

6. Observational outcomes in testosterone treatment of pubertal delay in Duchenne Muscular Dystrophy
Status: Open to recruitment
Sponsor: Newcastle upon Tyne NHS Hospitals Foundation Trust
CI: Prof. Volker Straub
Recruitment target: 20; patients recruited: 1

7. A Phase III Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Sialic Acid Extended Release Tablets in Patients with GNE Myopathy (GNEM) or Hereditary Inclusion Body Myopathy (HIBM)
Status: Open to recruitment
Sponsor: Ultragenyx
Newcastle:
CI/PI: Prof. Hanns Lochmüller
Recruitment target: 15-20; patients recruited: 10

8. Phase Ib/II, double-blind, placebo-controlled, within-subject, dose escalation study to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of PF-06252616 administered to ambulatory boys with Duchenne Muscular Dystrophy
Status: Open to recruitment
Sponsor: PFIZER
Newcastle:
CI: Prof. Kate Bushby
PI: Dr. Michela Guglieri
Recruitment target: 3-5; Patients recruited: 4
London GOSH:
PI: Prof. Francesco Muntoni
Recruitment target: 3; Patients recruited: 4

9. A Phase III, Randomized, Double-blind, Sham-Procedure Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Infantile-onset Spinal Muscular Atrophy
Status: Open to recruitment
Sponsor: Ionis Pharmaceuticals (previously known as ISIS Pharmaceuticals)
London GOSH
PI: Prof. Francesco Muntoni
Recruitment target: 2-3; Patients recruited: 4
Newcastle:
PI: Prof. Volker Straub
Recruitment target: 1; Patients recruited: 1

10. A double-blind, randomised, multicentre, placebo-controlled, parallel-group study to evaluate the efficacy and safety of fingolimod 0.5 mg administered orally once daily versus placebo in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
Status: Ongoing but closed to recruitment
Sponsor: Novartis
PI: Dr. Michael Lunn
Recruitment target: 1-2; Patients recruited: 2

11. DMD Heart Protection Trial
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: Ongoing but closed to recruitment
Sponsor: Newcastle upon Tyne NHS Hospitals Foundation Trust
Funder: British Heart Foundation
Newcastle
PI: Dr. John Burke
Recruitment target: 20-30; Patients recruited: 26

London GOSH
PI: Prof. Francesco Muntoni
Recruitment target: 50-60; Patients recruited: 46

12. FOR-DMD

Duchenne muscular dystrophy: double-blind randomized trial to find optimum steroid regimen (FOR-DMD)

Status: Open to recruitment
Sponsor: University of Rochester
Funder: NIH
Newcastle
CI: Prof. Kate Bushby
PI: Prof. Volker Straub
Recruitment target: 10; Patients recruited: 10
London GOSH
PI: Prof. Francesco Muntoni
Recruitment target: 8; recruited: 5

13. PTC124-GD-019 Open label

An open-label study for previously treated Ataluren (PTC124®) patients with nonsense mutation dystrophinopathy

Status: Ongoing but closed to recruitment
Sponsor& Funder: PTC
Newcastle
CI/PI: Prof. Kate Bushby
Patients recruited: 11
London GOSH
PI: Prof. Francesco Muntoni
Patients recruited: 8

14. A phase III efficacy & safety study of Ataluren (PTC124) in patients with nonsense mutation dystrophinopathy (PTC Phase III) PTC124-GD-020-DMD

Status: Closed to recruitment
Sponsor: PTC
Funder: PTC
Newcastle
CI: Prof. Kate Bushby
PI: Dr. Michela Guglieri
Patients recruited: 4
London GOSH
PI: Prof. Francesco Muntoni
Patients recruited: 7

15. 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
Newcastle
CI/PI: Prof. Volker Straub
Patients recruited: 2

London GOSH
PI: Prof. Francesco Muntoni
Patients recruited: 2

16. **An Open-label, multicentre, 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
Patients recruited: 1

17. **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: Ongoing but closed to recruitment
Sponsor: Novartis
CI: Prof. Michael Hanna
PIs: Hector Chinoy; James Miller
Patients recruited: 44 (UK); 353 (WW)

18. Extension of the CBYM338B2203 phase IIb/III study to evaluate the long-term efficacy, safety and tolerability of intravenous BYM338 in patients with sporadic inclusion body myositis
Status: Open to recruitment
Sponsor: UCL
Funder: Novartis
PI: Prof. Michael Hanna
UK Recruitment target: 26 patients

19. A Phase II/III Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy
Status: Ongoing but closed to recruitment
Sponsor: Ionis Pharmaceuticals, Inc.
PI: Prof. Mary M Reilly
Patients recruited: 6
Global recruitment target: 195

20. A Pilot Study of Valproate Sodium for McArdle Disease
Status: Open to recruitment
Sponsor: UCL
Funder: Muscular Dystrophy UK
PI: Dr. Ros Quinlivan
Recruitment target: 8; Patients recruited: 6

21. 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: Open to recruitment
Sponsor: UCL

Funder: UCL Charities
PI: Dr. Doreen Fialho
Recruitment target: 12; Patients recruited: 5

22. PATH extension Study
Multicentre, open-label extension study to investigate the long-term safety and efficacy of IgPro20 in maintenance treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) in subjects completing study IgPro20_3004
Status: Ongoing but closed to recruitment
Sponsor: CSL Behring
PI: Dr. Michael Lunn
Recruitment target: 3; Patients recruited: 3

23. 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
CI: Prof. Volker Straub
Newcastle:
PI: Prof. Volker Straub
Recruitment target: 3-5; Patients recruited: 1
London GOSH:
PI: Prof. Francesco Muntoni
Recruitment target: 1-2; Patients recruited: 1

24. A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, and Pharmacokinetics Study (Part 1) Followed by an Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy (DMD) Amenable to Exon 53 Skipping
Status: Open to recruitment
Sponsor: Sarepta, EU Grant
London GOSH:
CI/PI: Prof. Francesco Muntoni
Recruitment target: 12; Patients recruited: 8
Newcastle:
PI: Prof. Volker Straub
Recruitment target: 12; Patients recruited: 5

25. **A Multi-Centre, Randomized, Double-Blind, Placebo-Controlled, Multiple- Dose Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of RO6885247 following 12 Weeks treatment in Adult and Paediatric Patients with Spinal Muscular Atrophy**
Status: Open to recruitment
Sponsor: F. Hoffmann-La Roche Ltd
Newcastle:
CI/PI: Prof. Hanns Lochmüller
Recruitment target: 7; Patients recruited: 4
London GOSH – not open yet
PI: Prof. Francesco Muntoni

26. **A Phase III Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy (PTC20e –PTC 20 is being extended)**
Status: Open to recruitment

Sponsor PTC therapeutics
Newcastle
CI: Prof. Kate Bushby
PI: Dr. Michela Guglieri
Recruitment target: 4; Patients recruited: 4
London GOSH
PI: Prof. Francesco Muntoni
Recruitment target: 6-9; Patients recruited: 8

27. SMT C11003

A placebo-controlled, multi-centre, randomized, double-blind, 3-period dose escalation study to evaluate the PK and safety of SMT C1100 in paediatric patients with Duchenne muscular dystrophy (DMD) who follow a balanced diet

Status: Ongoing but closed to recruitment
Sponsor: Summit Corporation plc
PI: Prof. Francesco Muntoni
Recruitment target: 4; Patients recruited: 4

28. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Study to Assess the Safety and Efficacy of UX007 in Subjects with Glucose Transporter Type 1 Deficiency Syndrome

Status: Ongoing
Sponsor: Ultragenyx
PI: Dr. Rita Horvath
Recruitment target: 3; patients recruited: 3

29. A randomized, double-blind, placebo-controlled trial of deferiprone in patients with pantothenate kinase-associated neurodegeneration (PKAN)- TIRCON2012V1

Status: Ongoing but closed to recruitment
Sponsor: ApoPharma Inc.
CI: Prof Patrick Chinnery
PI: Dr. Rita Horvath
Recruitment target: 8; patients recruited: 8

30. Long-term Safety and Efficacy Study of Deferiprone in Patients with Pantothenate Kinase-Associated Neurodegeneration (PKAN)- TIRCON2012V1-EXT

Status: Open Feb/Mar 2016
Sponsor: ApoPharma Inc.
CI: Prof Patrick Chinnery
PI: Dr. Rita Horvath
Recruitment target: 6; patients recruited: 0

31. A Feasibility Study of Bezafibrate in Mitochondrial Myopathy

Status: Ongoing
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
CI: Prof Patrick Chinnery
PI: Prof Rita Horvath
Recruitment target: 10 (gp 1 n=6, gp 2 n=4); patients recruited: 4

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

32. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (GSK Extension Study)

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/ Dosing suspended
Sponsor: GlaxoSmithKline
Funder: GlaxoSmithKline
Newcastle
CI/PI: Prof. Volker Straub
London GOSH
PI: Prof. Francesco Muntoni
Recruitment target: 8; Patients recruited: 8

33. 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 UK (MDUK)
PI: Prof. Mary M Reilly
Recruitment target: 50; Patients recruited: 50

34. Therapeutic trial of Mexiletine in Non-Dystrophic Myotonia
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. Michael Hanna
Recruitment target: 15; Patients recruited: 14

35. 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
Newcastle
CI: Prof. Kate Bushby
London GOSH
PI: Prof. Francesco Muntoni
Patients recruited: 11

36. 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. Francesco Muntoni
Patients recruited: 8

37. 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

Newcastle:
PI: Prof. Kate Bushby
London:
PI: Prof. Francesco Muntoni
Patients recruited: 19

38. Eculizumab for Myasthenia Gravis

A Randomised, Double-Blind, Placebo-controlled, Cross-over, Multicentre Study of Eculizumab in Patients with Generalised Myasthenia Gravis (GMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosupressants

Status: Completed
Sponsor/Funder: Alexion Pharmaceuticals, Inc.
PI: Prof. Dimitri Kullmann

39. Arimoclomol for Sporadic Inclusion Body Myositis (IBM)

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. Michael Hanna
Recruitment target: 12; Patients recruited: 12

40. 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. Dimitri Kullmann
Recruitment target: 40; Patients recruited: 39

41. GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (PRO051)

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
Newcastle
CI/PI: Prof. Volker Straub
London GOSH
PI: Prof. Francesco Muntoni
Recruitment target (UK): 8; Patients recruited (UK): 8

42. Therapeutic trial of lithium carbonate in MND/ALS (LiCALS)

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
Funder: Motor Neurone Disease Association, and NIHR
UCL PI: Dr. Richard Orrell
Recruitment target: 22; Patients recruited: 22

43. LiCALS Open Label Extension

LiCALS open label extension trial of lithium carbonate in amyotrophic 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
Recruitment target: 3; Patients recruited: 3

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

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
Recruitment target: 2; Patients recruited: 2

45. HYP HOP: Dichlorphenamide vs. Placebo for Periodic Paralysis

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. Michael Hanna
Recruitment target: 40; Patients recruited: 14

46. Phase II, multicentre, 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 Française contre les Myopathies
Newcastle
PIs: Prof. Hanns Lochmüller, Helen Roper
Recruitment target: 3
London GOSH
PI: Prof. Francesco Muntoni,
Recruitment target: 10
Recruitment target UK: 30

47. The PATH Study

Randomized, multicentre, 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)

Status: Completed
Sponsor: CSL Behring
PI: Dr. Michael Lunn
Recruitment target: 5; Patients recruited 6

48. SMT C1100 – A Phase I, Open-label, Single and Multiple Oral Dose, Safety, Tolerability and Pharmacokinetic Study in Paediatric Patients with Duchenne Muscular Dystrophy

Status: Completed
Sponsor & Funder: Summit
London GOSH
PI: Prof. Francesco Muntoni
Patients Recruited: 4

MRC Centre Natural History – Longitudinal Studies: Set-up Phase

49 Prospective. Longitudinal Study of the Natural History and functional status of patients with MyoTubular Myopathy (NatHis-MTM)
Status: Set-up phase
Sponsor: Institute of Myology
PI: Prof. Francesco Muntoni
Recruitment target: 6-8

50. LEMS Disease Registry – UK Proposal
Status: Set-up phase
Sponsor: BioMarin Europe Ltd
PI: Prof. Michael Hanna
Patients target: 10 from the NHNN

MRC Centre Natural History – Longitudinal Studies: Open Studies

51. PhenoDM1: Myotonic Dystrophy type 1 (DM1) deep phenotyping to improve delivery of personalised medicine and assist in the planning, design and recruitment of clinical trials.
Status: Open to recruitment
Sponsor: Newcastle upon Tyne NHS Hospitals Foundation Trust
Newcastle
PI: Prof. Hanns Lochmüller
Recruitment target: 200, patients recruited: 4
London NHNN
PI: Dr. Chris Turner
Recruitment target: 200, recruitment to start shortly

52. NIHR Pain Consortium (Bridge Neuropathic Pain)
Status: Open to recruitment
Funder: NIHR BioResource – Rare Diseases
Sponsor: Cambridge University Hospitals NHS Foundation Trust & University of Cambridge
London NHNN
PI: Prof. Mary M Reilly
Patients recruited: 3
Newcastle
PI: Prof. Rita Horvath
Patients recruited: 9

53. Becker Muscular Dystrophy - A Natural History Study to Predict Efficacy of Exon Skipping
Status: Open to recruitment
Sponsor: CINRG
Newcastle
CI: Prof. Kate Bushby
PI: Dr. Michela Guglieri
Recruitment target: 8; Patients recruited: 8

54. FSHD registry
Status: Ongoing
Funder: Muscular Dystrophy UK and TREAT-NMD Alliance
PI: Prof. Hanns Lochmüller
Patients recruited: 611

55. CMT: A Natural History study
Charcot-Marie-Tooth Disease and related disorders: A Natural History Study
Status: Ongoing
Sponsor: University College London Hospitals
Funder: National Institutes of Health (NIH – USA)
Recruitment target (UK):1000
London NHNN
CI: Prof. Mary M Reilly
Patients recruited: 904
London GOSH
PI: Prof. Francesco Muntoni
Patients recruited: 89
Newcastle
PI: Dr. Rita Horvath
Patients recruited: 59

56. MRC Centre Mitochondrial Disease Patient Cohort: A Natural History Study and Patient Registry
Status: Ongoing
Sponsor: Newcastle Upon Tyne Hospitals NHS Foundation
Funder: MRC
PIs: Dr. R McFarland, Prof. Michael Hanna, Dr. Doug Turnbull
Total recruitment target 1500
Recruitment to date: 1329
Newcastle: 672
UCL: 358
Oxford: 99
Satellites: 200

57. The Natural History of Inclusion Body Myositis (IBM Net)
Status: Ongoing
Sponsor: University College Hospitals
Funder: MDUK
PIs: Dr. Matt Parton, Prof. Michael Hanna
Recruitment target 120-150; Patients recruited: 85

58. Kennedy's Disease – Study and Register
Status: Ongoing
Sponsor: UCLH
CI: Prof. Michael Hanna
Patients recruited: 76

59. Investigation of Human Neurological Ion Channel Disorders
Status: Ongoing
Sponsor: University College London Hospitals
CI: Prof. Michael Hanna

Patients recruited: 66

60. AFM Natural History Study

Outcome measures in Duchenne Muscular Dystrophy: A Natural History Study
Status: Ongoing
Sponsor: UCL Institute of Child Health
Funder: AFM
London GOSH
PI: Prof. Francesco Muntoni
Patients recruited: 20
Newcastle
PI: Prof. Kate Bushby
Patients recruited: 20

61. The International IBM Consortium Genetic Study

Using Next Generation Sequencing to Unravel the Pathogenesis of Sporadic Inclusion Body Myositis (IBM)
Status: Ongoing
Funder: MRC
UK recruiting target: 400
London NHNN
CI: Prof. Michael Hanna
Patients recruited: 93
Newcastle
PI: Dr. Miller

62. Hereditary Inclusion Body Myopathy-Patient Monitoring Program (HIBM-PMP): A Registry and Prospective Natural History Study to Assess HIBM Disease

Status: Ongoing
Sponsor: Ultragenyx
Funder: Ultragenyx
CI/PI: Prof. Hanns Lochmüller
Recruiting target: 15-20; Patients recruited: 25

63. Biomarker Studies in MND/ALS

Characterisation of a panel of disease biomarkers in peripheral blood from individuals with motor neuron disease

Status: Ongoing but closed to recruitment
Sponsor: University College London Hospitals NHS Foundation Trust
Funder: Motor Neurone Disease Association
UCL PI: Dr. Richard Orrell
Patients recruited: 165

64. International Guillain-Barre' Syndrome (GBS) Outcome Study - IGOS

Status: Ongoing
Sponsor: Glasgow University
Funder: Wellcome Trust/GBS Support group
PI: Dr. Michael Lunn
Recruiting target: 10 from the NHNN, Patients recruited: 3

65. 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: Prof. Michael Hanna
Recruited patients: 65

66. Study of clinical and radiological changes in teenagers with Duchenne muscular dystrophy theoretically treatable with exon 53 skipping (Pre-U7)
Status: Closed to Recruitment
Sponsor: Genethon
Funder: Genethon
London GOSH
PI: Prof. Francesco Muntoni
Newcastle
PI: Prof. Volker Straub
Recruitment target: 5; Patients recruited: 5

67. SMA registry
Status: Ongoing
Funder: TREAT-NMD
PI: Prof. Hanns Lochmüller
Patients recruited: 400

68. UK Myotonic Dystrophy patient registry
Status: Ongoing
Funder: Myotonic Dystrophy Support Group, Muscular Dystrophy UK and TREAT-NMD Alliance
PI: Prof. Hanns Lochmüller
Patients recruited: 599

69. Global FKRP registry
Status: Ongoing
Funder: LGMD2I
PI: Prof. Volker Straub
Patients recruited: 396

70. GNE myopathy-Disease Monitoring Programme (GNE-DMP): A registry and prospective observational natural history study to assess HIBM disease
Status: Ongoing
Funder: Ultragenyx and Newcastle University
PI: Prof. Hanns Lochmüller
Patients recruited: 218

71. SMA REACH UK
Spinal Muscular Atrophy Research and Clinical Hub UK
Status: Ongoing
Funder: UK SMA charity: SMA TRUST
Sponsor: Great Ormond Street Hospital
London GOSH
CI: Prof. Francesco Muntoni
Recruitment target: 80; Patients recruited: 79
Newcastle
PI: Prof. Katie Bushby
Recruitment target: 70; Patients recruited: 23

72. OPTIMISTIC

Observational Prolonged Trial in Myotonic Dystrophy type 1 to Improve Quality of Life Standards, a Target Identification Collaboration

Status: Closed to recruitment
Funder: EU Seventh Framework Programme
Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust
Newcastle
CI/PI: Dr. Grainne Gorman
UK recruitment target: 72; Patients recruited: 64

73. FSHD – NH Study

A multicentre collaborative study on the clinical features, expression profiling, and quality of life of infantile onset facioscapulohumeral muscular dystrophy

Status: Closed to recruitment
Sponsor: CINRG
CI: Prof. Kate Bushby
PI: Dr. Michel Guglieri
Patients recruited: 9

74. Genotype-Phenotype in inherited neurodegenerative diseases

Status: Ongoing
Funder: Wellcome Trust
Sponsor: Newcastle upon Tyne NHS Hospitals Foundation Trust
PI: Prof. Patrick Chinnery
PI: Prof. Rita Horvath
Patients recruited: 225

75. CBYM338B2302: A Prospective Natural History Study in Sporadic Inclusion Body Myositis (sIBM)

Status: Ongoing but closed to recruitment
Sponsor: Novartis
PI: Dr Pedro Machado/ Prof. Michael Hanna
Recruitment target: 30; Patients recruited: 37

76. 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
Newcastle
CI/PI: Prof. Kate Bushby
Recruitment target: 20; Patients recruited: 43

77. Mito Exome Sequencing Study

Status: Ongoing
Sponsor: Guys and St Thomas
Funder: Lily Foundation
Newcastle
PI: Dr. Robert McFarland
Recruitment target: 25 families; Families recruited: 53 (158 participants)
London
CI: Dr. Charulata Deshpande

PI: Prof. Michael Hanna
Recruitment target: 100 families; Families recruited: 13

78. Reproductive Decision Making in Mitochondrial Disease
Status: Ongoing
Sponsor: Newcastle Upon Tyne NHS Foundation Trust
Funder: MRC
Newcastle
PI: Prof. Doug Turnbull
Recruiting target: 30; Patients recruited: 15

MRC Centre Natural History – Longitudinal Studies: Completed Studies

79. Validation of prognostic biomarkers in Charcot-Marie-Tooth disease type 1A
Status: completed
Funder: AFM
Sponsor: Newcastle upon Tyne NHS Hospitals Foundation Trust
PI: Prof. Rita Horvath
Recruitment target: 20; patients recruited: 20

80. Natural History study of Hereditary Sensory Neuropathy type 1 secondary to SPTLC1 and SPTLC2 mutations
Status: Completed
Sponsor: University College London Hospitals
PI: Prof. Mary M Reilly
Patients recruited: 35

81. Prospective evaluation of gastrostomy in MND (PROGAS). Prospective evaluation of gastrostomy in MND (PROGAS)
Status: Completed
Sponsor: Royal Free London NHS Foundation Trust
Start date: 2011
Funder: Motor Neuron Disease Association / South Yorkshire CLRN
UCL PI: Dr. Richard Orrell
Recruiting target: 6; Patients recruited: 6

82. Therapeutic trial of diaphragmatic pacing in MND/ALS (DiPALS)
A randomised controlled trial in patients with respiratory muscle weakness due to motor neurone disease of the NeuRx RA/4 Diaphragm Pacing System
Status: Completed
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
Recruiting target: 4; Patients recruited: 2

83. Incidence of complications of pregnancy in patients diagnosed with mitochondrial disease or carrying a mitochondrial DNA mutation
Status: Closed
Sponsor: Newcastle Upon Tyne NHS Foundation Trust

Funder: MRC
PI: Dr. Robert McFarland
UK Recruitment target: 200; Patients recruited: 151 (80 patients, 71 controls)

84. Non-Dystrophic Myotonias: Genotype and Phenotype correlation and longitudinal studies
Status: Completed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Michael Hanna
Patients recruited: 20

85. Andersen-Tawil Syndrome: Genotype and Phenotype correlation and longitudinal study
Status: Completed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Michael Hanna
Recruitment target >10; Patients recruited: 11

86. Episodic Ataxia Syndrome: Genotype-Phenotype correlation and longitudinal study
Status: Completed
Sponsor: University College London
Funder: National Institutes of Health (NIH – USA)
PI: Prof. Michael Hanna
Recruitment target >20; Patients recruited: 36

87. Outcome measures in SMA type II and III
Status: Closed
Sponsor: UCL Institute of Child Health
Funder: SMA Europe
London GOSH
PI: Prof. Francesco Muntoni
Newcastle
PI: Prof. Kate Bushby
UK Recruitment target: 23; Patients recruited: 26

88. Peripheral Neuropathy outcome measures standardisation study (PERINOMS)
Status: Completed
Sponsor: Erasmus Medical Center
PI: Dr. Michael Lunn
Recruitment target: 120; Patients recruited: 110

89. A Study of Biological Prognostic Factors for IGM Paraproteinemic Anti-Mag Associated Peripheral Neuropathy
Status: Completed
Sponsor: UCL
PI: Dr. Michael Lunn
Recruitment target: 45 patients

90. Standardized NBIA patient registry and natural history study
Status: Completed
Sponsor: University of Munich
PI: Prof. Patrick Chinnery

Recruitment target: 20; Patients recruited: 24

MRC Centre Exercise Studies: Set-up Studies

91. BALTiC study: A feasibility analysis of home based BALance Training in people with Charcot-Marie-Tooth disease:
Status: Set-up phase
Sponsor: St George's University of London
Funder: CMT United Kingdom
Planned start date: March 2016
PI: Dr. Gita Ramdharry
Recruitment target: 20

92. An exploration of the 12 minute walk test and its impact on McArdle patients' confidence levels and pain descriptions: A mixed methods study
Status: Set- up phase
Sponsor: UCLH
Funder: The National Brain Appeal, Small Acorns Fund and the Association for Glycogen Storage Disease (AGSD)-(UK).
CI & PI: Dr. Ros Quinlivan
Recruitment target: 21

MRC Centre Exercise Studies: Open Studies

93. Development a paediatric and adult home based assessment tool for monitoring symptoms of myasthenic syndromes.
Status: Ongoing
Sponsor: UCL / GOSH / UCLH
Funder: MyAware Charity & UCL impact
PI: Prof. Francesco Muntoni
Recruitment target: 120 (including adults and children); Patients recruited: 20 children & 30 adults.

94. Aerobic training in Charcot-Marie-Tooth disease and Inclusion Body Myositis.
Status: Ongoing but closed to recruitment
Sponsor: University College Hospitals
PI: Dr. Gita Ramdharry
Recruiting target: 60; patients recruited: 47

95. Physical Activity and Inclusion Body Myositis
Status: Ongoing
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
PI: Dr. M Trenell
Collaborating site MRC Centre London
Recruitment target: 500 across 5 disease sites

96. Exercise and Sarcopenia
Status: Ongoing
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust Funder: MRC
PI: Dr. Grainne Gormann
Collaborating site MRC Centre London (Recruitment at Newcastle only)
Recruitment target: 36; Patients recruited: 34

97. Exercise, cognition and brain vitality
Status: Ongoing
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
Newcastle
PI: Dr. Grainne Gorman
Patients recruited: 29

MRC Centre Exercise Studies: Closed Studies

98. Exploring the causes of falls and balance impairments in people with neuromuscular diseases
Status: Closed
Sponsor: University College Hospitals
Funder: NIHR
PI: Dr. Gita Ramdharry
Recruiting target: 30; Patients recruited: 30

99. Strengthening Hip muscles to improve walking distance in people with Charcot- Marie-Tooth disease
Status: Completed
Sponsor: University College London Hospitals
Funder: Muscular Dystrophy UK (MDUK)
PI: Prof. Mary M Reilly
Recruitment target: 32; Patients recruited: 32

100. Exercise training in patients with Mitochondrial disease: Assessing the benefits
Status: Closed
Sponsor: University Newcastle
Funder: Muscular Dystrophy UK (MDUK)
PI: Prof. Doug Turnbull
Collaboration site MRC Centre London (Hanna)
Patients recruited: 9 Newcastle; 0 London

101. Cardiac adaptations to exercise in Mitochondrial disease
Status: Completed
Sponsor: Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder: MRC
PI: Prof. Doug Turnbull/Dr. M Trenell
Patients recruited: 39

MRC Centre Imaging Studies: Open Studies

102. Brain imaging and cognition in patients with Duchenne muscular dystrophy
Status: Open to recruitment
Sponsor: Newcastle upon Tyne NHS Foundation Trust
Funder: MDUK
PI: Prof. Volker Straub
Recruitment target: 48; patients recruited: 0

103. A study using Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) in patients with Limb girdle muscular dystrophy 2I ; an assessment of skeletal and cardiac muscle damage
Sponsor: Newcastle upon Tyne NHS Hospitals Foundation Trust
Newcastle
Status: Ongoing
CI: Prof. Volker Straub
PI: Prof. Volker Straub
Recruiting target: 20; Patients recruited: 9
London - Due to open shortly
PI: Prof. Michael Hanna
Recruitment target: 6

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

105. Magnetic Resonance Imaging as an outcome measure in Motor Neuropathies: a pilot study
Status: Open to recruitment
Sponsor: UCL
PI: Prof. Michael Hanna
Patients recruited: 11

106. A study of Qualitative Magnetic Resonance Imaging in Channelopathies
Status: Ongoing, recruitment due to start
Sponsor: UCL
PI: Prof. Michael Hanna
Patients recruited: 0

MRC Centre Imaging Studies: Completed Studies

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

108. MRI in FKRP-Related LGMD2I
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: Completed
Sponsor: Newcastle NHS Trust
Funder: MRC
PI: Prof. Volker Straub
Recruited patients: 22

109. A Study of Quantitative Magnetic Resonance Imaging to Monitor Disease Activity in Hypokalaemic Periodic Paralysis.
Status: Completed
Sponsor: UCL
Funder: MRC
PI: Prof. Michael Hanna
Recruitment: 24 (12 patients; 12 controls)

110. Evaluation and Optimisation of Muscle Imaging Biomarkers in Support of Non-ambulant Duchenne Muscular Dystrophy Studies
Status: Completed
Sponsor: UCL Institute of Child Health
Funder: GSK
PI: Prof. Francesco Muntoni
UK Patient target: 15; Patients recruited: 15 patients - 10 controls

Delegate List 2016

Name	Surname	email	Organisation
Annemieke	Aartsma-Rus	a.m.rus@lumc.nl	Leiden University Medical Center
Kathryn	Adcock	Kathryn.Adcock@headoffice.mrc.ac.uk	MRC Headquarters Office
Tayyibah	Ali	t.ali13@ic.ac.uk	Imperial College London
Maria-Eleni	Anagnostou	deborah.little@ncl.ac.uk	Newcastle University
Naomi	Antcliff	naomi.anctliff@bmrn.com	Biomarin
Emine	Bagdatlioglu	emine.bagdatlioglu@newcastle.ac.uk	Newcastle University
Fernando	Bartolome	fbartolome.imas12@h12o.es	
laila	Bastaki	rouchelle@genpharmservices.com	genpharm
David	Beeson	david.beeson@ndcn.ox.ac.uk	University of Oxford
Maximilien	Bencze	m.bencze@ucl.ac.uk	UCL-ICH
Corinne	Betts	corinne.betts@dpag.ox.ac.uk	University of Oxford
Natalie	Birch	lakomska@doctors.net.uk	Queen Elisabeth University Hospital Glasgow
Andy	Blamire	andrew.blamire@newcastle.ac.uk	Newcastle University
Veronika	Boczonadi	veronika.boczonadi@ncl.ac.uk	Newcastle University
Sue	Booton		Sanofi Genzyme
Melissa	Bowerman	melissa.bowerman@dpag.ox.ac.uk	University of Oxford
Sue	Brown	scbrown@rvc.ac.uk	Royal Veterinary College
Enrico	Bugiardini	e.bugiardini@ucl.ac.uk	UCL Institute of Neurology
David	Burns	david.burns@dpag.ac.uk	University of Oxford
Karen	Butcher	karen@cmtuk.org.uk	CMTUK
Giles	Campion	giles.campion@bmrn.com	BioMarin Nederland B.V.
Stephanie	Carr	s.carr2@ncl.ac.uk	Newcastle University
Aisling	Carr	Aisling.Carr@uclh.nhs.uk	NHNN
Francesco	Catapano	f.catapano@ucl.ac.uk	UCL ICH
Mehool	Chavda		Sanofi Genzyme
Huijia	Chen	huijia.chen@dpag.ox.ac.uk	University of Oxford

Patrick	Chinnery	pfc25@medschl.cam.ac.uk	
Vanessa	Christie-Brown	vanessa@smatrust.org	The SMA Trust
Lukasz	Ciszewski	wtaz057@live.rhul.ac.uk	Royal Holloway-University of London
Chris	Clark	christopher.clark@ucl.ac.uk	UCL
Ben	Clarke	benjamin.clarke.15@ucl.ac.uk	UCL Institute of Neurology
Judith	Cossins	judith.cossins@imm.ox.ac.uk	University of Oxford
Giulio	Cossu	giulio.cossu@manchester.ac.uk	University of Manchester
Pedro	Cruz	pedro.rodriguezcruz@ndcn.ox.ac.uk	University of Oxford
Kay	Davies	kay.davies@dpag.ox.ac.uk	University of Oxford
Becky	Davis	becky.davis@ncl.ac.uk	Newcastle University
Helen	Devine	h.devine@ucl.ac.uk	UCL Institute of Neurology
George	Dickson	g.dickson@rhul.ac.uk	Royal Holloway - University of London
Carolynne	Doherty	carolynnedoherty@doctors.org.uk	Royal Victoria Hospital- Belfast
Joana	Domingos	j.domingos@ucl.ac.uk	UCL ICH
Nathalie	Doorenweerd	Nathalie.Doorenweerd@Newcastle.ac.uk	Newcastle University
Kim	Down	kim.down@ncl.ac.uk	Newcastle University
Magdalena	Dudziec	m.dudziec@ucl.ac.uk	St Georges University of London and Kingston University
Julie	Dumonceaux	julie.dumonceaux@upmc.fr	Institut de Myologie, Paris
Johannes	Dworzak		SAREPTA THERAPEUTICS
Matthew	Evans	matthew.evans@ucl.ac.uk	UCL Institute of Neurology
Alex	Fellows	alexander.fellows.13@ucl.ac.uk	Institute of Neurology
Lucy	Feng	Lucy.feng@gosh.nhs.uk	UCL ICH
Giulia	Ferrari	giulia.ferrari.14@ucl.ac.uk	UCL
Doreen	Fialho	d.fialho@ucl.ac.uk	NHNN/UCLH
Kevin	Flanigan	Kevin.Flanigan@nationwidechildrens.org	Nationwide Children's Hosp,

			Ohio
Diane	Frank		Sarepta Therapeutics
Carl	Fratter	carl.fratter@ouh.nhs.uk	Oxford Medical Genetics Laboratories- Oxford University Hospitals NHS Trust
Qiang	Gang	q.gang@ucl.ac.uk	UCL Institute of Neurology
Jesus	Garcia-Segovia	jesus.segovia@bmrn.com	BioMarin
Michele	Giunta	michele.giunta@ncl.ac.uk	Newcastle University
Nathalie	Goemans	nathalie.goemans@uzleuven.be	University Hospitals Leuven
Grainne	Gorman	deborah.little@ncl.ac.uk	Newcastle University
Simon	Guiraud	s.guiraud@dpag.ox.ac.uk	University of Oxford
Ivo	Gut	ivo.gut@cnag.crg.eu	CNAG (National Centre for Genomic Analysis), Barcelona
Matt	Hall	matt.hall@ucl.ac.uk	University College London
Mary	Hames	mhames@ultragenyx.com	Ultragenyx
Mark	Hamilton	markhamilton1@nhs.net	University of Glasgow
Suzan	Hammond	suzan.hammond@dpag.ox.ac.uk	University of Oxford
Michael	Hanna	m.hanna@ucl.ac.uk	UCL Institute of Neurology
David	Hilton-Jones	david.hilton-jones@ndcn.ox.ac.uk	John Radcliffe Hospital
William	Hind	whind@gwpharm.com	GW Pharmaceuticals
Eric	Hoffman		ReveraGen BioPharma, Children's National Medical Center, Washington
Sarah	Holmes	sarah.holmes@uclh.nhs.uk	NHNN- UCLH
Rita	Horvath	rita.horvath@ncl.ac.uk	Newcastle University
Henry	Houlden	h.houlden@ucl.ac.uk	UCL Institute of Neurology
Persefoni	Ioannou	P.Ioannou1@newcastle.ac.uk	Newcastle University

Maria	Isaac	maria.isaac@ema.europa.eu	Dr Maria Isaac, Senior Scientific Officer, EMA
Yasmin	Issop	y.issop@ncl.ac.uk	Newcastle University
Aura Cecilia	Jimenez Moreno	a.c.jimenez-moreno@ncl.ac.uk	Newcastle University
Katherine	Johnson	katherine.johnson@ncl.ac.uk	Newcastle University
Bernadett	Kalmar	b.kalmar@ucl.ac.uk	UCL Institute of Neurology
Jihee	Kim	jikim@rvc.ac.uk	Royal Veterinary College
Louise	King	louise.king.13@ucl.ac.uk	UCL Institute of Neurology
Richard	Kitson		BIOMARIN
Uros	Klickovic	uros.klickovic.15@ucl.ac.uk	UCL Institute of Neurology
Umaiyal	Kugathasan	u.kugathasan@ucl.ac.uk	UCL Institute of Neurology
Richa	Kulshrestha	Richa.Kulshrestha@nhs.net	Robert Jones and Agnes Hunt Orthopaedic Hospital
Beatrice	Lana	b.lana@qmul.ac.uk	Blizard Institute-Queen Mary University of London
Matilde	Laura	m.laura@ucl.ac.uk	UCL Institute of Neurology
Tracy	Lester	tracy.lester@ouh.nhs.uk	Oxford Genetics Laboratories
James	Lilleker	james.lilleker@manchester.ac.uk	University of Manchester
Yung-Yao	Lin	yy.lin@qmul.ac.uk	Blizard Institute-Queen Mary University of London
Hanns	Lochmuller	hanns.lochmuller@ncl.ac.uk	Newcastle University
Michael	Lunn	michael.lunn@uclh.nhs.uk	UCLH
Julia	Maddison	julia.maddison@ncl.ac.uk	Newcastle University
Monika	Madej	m.madej@ucl.ac.uk	UCL
Roope	Mannikko	r.mannikko@ucl.ac.uk	UCL Institute of

			Neurology
Andreea	Manole	andreea.manole.13@ucl.ac.uk	UCL Institute of Neurology
Rusia	Manuel	rusia@doctors.org.uk	The Robert Jones and Agnes Hunt Orthopaedic hospital NHS Trust
Elena	Marrosu	e.marrosu@ucl.ac.uk	UCL
Jade	Marshall	jade@mapbiopharma.com	MAP BioPharma Limited
Emma	Matthews	emma.matthews@ucl.ac.uk	UCL
Bobby	McFarland	deborah.little@ncl.ac.uk	Newcastle University
Robert	Meadowcroft	R.Meadowcroft@muscular-dystrophy.org	Muscular Dystrophy UK
Ione	Meyer	i.meyer@ucl.ac.uk	UCL Institute of Neurology
Joanna	Mitchell	jo@smatrust.org	The SMA trust
Jacky	Molyneaux	j.molyneaux@ucl.ac.uk	UCL Institute of Neurology
Catherine	Moody	Catherine.moody@headoffice.mrc.ac.uk	MRC Headquarters Office
Ursula	Moore	ursula.moore@ncl.ac.uk	John Walton muscular dystrophy research centre
Jenny	Morgan	Jennifer.morgan@ucl.ac.uk	UCL ICH
Jasper	Morrow	j.morrow@ucl.ac.uk	Queen Square Centre for Neuromuscular Diseases
Louise	Moyle	l.moyle@ucl.ac.uk	UCL
Juliane	Mueller	juliane.mueller@ncl.ac.uk	Newcastle University
Francesco	Muntoni	f.muntoni@ucl.ac.uk	UCL Institute of Child Health
Paul	Mylchreest		BioMarin
Kulandavelu	Nagendran	kulan.nagendran@bartshealth.nhs.uk	Barts Health NHS Trust
Yi	Ng	yi.ng@ncl.ac.uk	Newcastle University
Nikoletta	Nikolenko	nikoletta.nikolenko@ncl.ac.uk	Newcastle University
Ben	O Callaghan	benjamin.o'callaghan.11@ucl.ac.uk	UCL Institute of

			Neurology
Antoinette	O' Connor	antoinetteoconnor.aoc@gmail.com	
Chris	Oldfield	christine.oldfield@ucl.ac.uk	UCL Institute of Neurology
Mike	Oldridge	michael.oldridge@ouh.nhs.uk	Molecular Genetics-NHS
Richard	Orrell	r.orrell@ucl.ac.uk	UCL Institute of Neurology
Jane	Owens	jane.owens@pfizer.com	Pfizer
Ozge	Ozkaya	o.ozkaya@musculardystrophyuk.org	Muscular Dystrophy UK
Vicente	Pagalday	vicentepagalday@hotmail.com	Royal Veterinary College
Maryna	Panamarova	maryna.panamarova@kcl.ac.uk	Kings College London
Amaia	Paredes	a.paredesredondo@qmul.ac.uk	Blizard Institute-Queen Mary University of London
Latha	Parvataneni	lparvataneni@ptcbio.com	PTC Therapeutics
Mark	Perry	mark.perry@ucl.ac.uk	UCL- Institute of Child Health
Richard	Petty	richard.petty@nhs.net	private
Rahul	Phadke	r.phadke@ucl.ac.uk	National Hospital for Neurology and Neurosurgery- UCL Institute of Neurology
Lauren	Phillips	lauren.phillips@newcastle.ac.uk	Newcastle University
Oksana	Pogoryelova	oksana.pogoryelova@ncl.ac.uk	Newcastle University
Marita	Pohlschmidt	M.Pohlschmidt@musculardystrophyuk.org	MDUK
Chee Ling	Poole		Sanofi Genzyme
Olivia	Poole	o.poole@ucl.ac.uk	UCL Institute of Neurology
Linda	Popplewell	linda.popplewell@rhul.ac.uk	Royal Holloway University of London
Joanna	Poulton	joanna.poulton@obs-gyn.ox.ac.uk	University of Oxford
Ros	Quinlivan	r.quinlivan@ucl.ac.uk	NHNN
Sithara	Ramdas	sithara.ramdas@ouh.nhs.uk	Oxford University Hospitals NHS Trust

Gita	Ramdharry	g.ramdharry@sgul.kingston.ac.uk	Kingston University/St George's University of London
Danielle	Ramsey	Danielle.ramsey.12@ucl.ac.uk	UCL ICH
Mary	Reilly	m.reilly@ucl.ac.uk	UCL Institute of Neurology
Diana	Ribeiro	diana@actionduchenne.org	Action Duchenne
Valeria	Ricotti	v.ricotti@ucl.ac.uk	
Carlo	Rinaldi	carlo.rinaldi@dpag.ox.ac.uk	
Paul	Roberts		Sanofi Genzyme
Agata	Robertson	agata.robertson@ncl.ac.uk	Newcastle University
Peter	Robinson	peter.robinson@charite.de	Charité Hospital Berlin
Alex	Rossor	a.rossor@ucl.ac.uk	UCL Institute of Neurology
Karolina	Rygiel	deborah.little@ncl.ac.uk	Newcastle University
Verna	Sarajarvi	verna.sarajarvi.12@ucl.ac.uk	UCL Institute of Neurology
Valentina	Sardone	v.sardone@ucl.ac.uk	UCL Institute of Neurology
Anna	Sarkozy	Anna.Sarkozy@gosh.nhs.uk	GOSH
Renata	Scalco	r.scalco@ucl.ac.uk	UCL
Jenny	Sharpe	j.sharpe@musculardystrophyuk.org	Muscular Dystrophy UK
Prasanth	Sivakumar	prasanth.sivakumar.14@ucl.ac.uk	UCL Institute of Neurology
Mariola	Skorupinska	mariola.skorupinska@uclh.nhs.uk	NHNN
Iwona	Skorupinska	Iwona.Skorupinska@uclh.nhs.uk	NHNN
James	Sleigh	j.sleigh@ucl.ac.uk	University College London Institute of Neurology
Hassan	Sobati	HassanSobati@hotmail.com	SMA Trust
Ewen	Sommerville	e.w.sommerville@ncl.ac.uk	Newcastle University
Charlotte	Spicer	charlotte.spicer.13@ucl.ac.uk	UCL Institute of Neurology
Alison	Stevenson	a.stevenson@musculardystrophyuk.org	MDUK
Volker	Straub	volker.straub@ncl.ac.uk	Institute of Genetic

			Medicine- Newcastle University
Karen	Suetterlin	karen.suetterlin@ucl.ac.uk	UCL Institute of Neurology
Katarzyna	Swist-Szulik	katarzyna.swist-szulik@ncl.ac.uk	Mitochondrial Research Group
Kevin	Talbot	kevin.talbot@ndcn.ox.ac.uk	University of Oxford
Robert	Taylor	deborah.little@ncl.ac.uk	Newcastle University
Saverio	Tedesco	f.s.tedesco@ucl.ac.uk	University College London
Andreas	Themistocleous	andreas.themistocleous@ndcn.ox.ac.uk	University of Oxford
Kyle	Thompson	kyle.thompson@ncl.ac.uk	Newcastle University
John	Thornton	john.thornton@ucl.ac.uk	UCL Institute of Neurology
Jon	Tinsley	jon.tinsley@summitplc.com	Summit Therapeutics
Pedro	Tomaselli	p.tomaselli@ucl.ac.uk	UCL Institute of Neurology
Hersey	Underwood	nclear@gwpharm.com	GW Pharmaceuticals
David	Villaroel	david.villarroel.15@ucl.ac.uk	UCL
Amy	Vincent	a.vincent2@ncl.ac.uk	Newcastle University
Angela	Vincent	angela.vincent@ndcn.ox.ac.uk	University of Oxford
Thomas	Voit	t.voit@ucl.ac.uk	UCL Institute of Child Health
Ruth	Wake	ruth.wake@ncl.ac.uk	NUTH & Newcastle University
Susanne	Wang	susanne.wang@bmrn.com	BioMarin Pharmaceuticals-Inc.
Tracey	Willis	tracey.willis1@nhs.net	Robert Jones and Agnes Hunt
Emma	Wilson	emma.wilson.09@ucl.ac.uk	UCL Institute of Neurology
Steve	Winder	s.winder@shef.ac.uk	University of Sheffield
John	Winer	john.winer@uhb.nhs.uk	Queen Elizabeth Hospital
Libby	Wood	elizabeth.wood2@ncl.ac.uk	Newcastle University
Elizabeth	Wraige	elizabeth.wraige@gstt.nhs.uk	Evelina Children's

			Hospital
Tarek	Yousry	t.yousry@ucl.ac.uk	UCL Institute of Neurology
Angeliki	Zarkali	a.zarkali@ucl.ac.uk	National Hospital for Neurology and Neurosurgery
Haiyan	Zhou	Haiyan.zhou@ucl.ac.uk	UCL ICH

MRC Centre for Neuromuscular Diseases, UCL and Newcastle staff list

Centre Director Professor Michael Hanna	
Centre Co Directors, London Professor Mary M. Reilly Professor Francesco Muntoni	**Centre Co Directors, Newcastle** Professor Kate Bushby Professor Doug Turnbull
Centre Steering Committee Professor Linda Greensmith Professor Michael Hanna Professor Henry Houlden Professor Martin Koltzenburg Professor Dimitri Kullmann Professor Jenny Morgan Professor Francesco Muntoni Professor Mary M. Reilly Dr John Thornton Professor Tarek Yousry	**Steering committee ctd….** Professor Andrew Blamire Professor Kate Bushby Professor Patrick Chinnery Professor Rita Horvath Professor Hanns Lochmüller Professor Volker Straub Professor Robert Taylor Professor Doug Turnbull
Centre Principal Investigators, UCL Dr Chris Clark Professor Giulio Cossu Professor Michael Duchen Professor Elizabeth Fisher Professor Xavier Golay Professor Linda Greensmith Professor Michael Hanna Professor John Hardy Professor Henry Houlden Professor Kristjan Jessen Professor Dimitri Kullmann Dr Michael Lunn Professor Paul Matthews Professor Jennifer Morgan Professor Francesco Muntoni Dr Gita Ramdharry Professor Mary M. Reilly Professor Gipi Schiavo Dr Stephanie Schorge Dr John Thornton Professor Tarek Yousry Professor Martin Koltzenburg	**Centre Principal Investigators, Newcastle** Professor Andrew Blamire Professor Kate Bushby Dr Grainne Gorman Dr Kieren Hollingsworth Professor Rita Horvath Professor Hanns Lochmüller Dr Robert McFarland Dr James Miller Professor Volker Straub Professor Robert Taylor Professor Michael Trenell Professor Doug Turnbull **Centre Principal Investigator, Cambridge** Professor Patrick Chinnery
MRI Physicist, UCL Dr Chris Sinclair	**MRI Physicist, Newcastle** Dr Paola Porcari
MRC Senior Research Associate (Stem Cell) Monika Madej	**MRC CNMD Biobank Newcastle** Dr Mojgan Reza Dan Cox Lauren Phillips Rachel Jenkins
MRC CNMD Biobank London ICH/ION Vaishnavi Manoharan	**CNMD Clinical Trials Co-ordinators, Newcastle** Becky Davis Julia Maddison

MRC Centre for Neuromuscular Diseases, UCL and Newcastle staff list, ctd...

CNMD Clinical Trials Co-ordinators, UCL	**MRC Centre Senior Administrators**
Daleen Lopez-Begg (maternity leave)	Christine Oldfield
Camille Blochet	Zoe Scott (maternity leave)
Mariam Habib (maternity leave cover)	David Bull (maternity leave cover)

MRC Centre student list 2016

UCL

MRC or Host or other Funded Non-Clinical PhD

Ben O'Callaghan
Ben Clarke
Verna Sarajarvi
Ione Meyer
Prasanth Sivakumar
Louise King
Andreea Manole
Charlotte Spicer
Michael Thor
Emma Wilson
Neta Amior
Qiang Gang

MRC or Host or other Funded Clinical PhD

Dr Matthew Evans
Dr Umaiyal Kugathasan
Dr Helen Devine
Dr Karen Suetterlin
Dr Renata Scalco
Dr Olivia Poole
Dr Enrico Bugiardini
Dr Kate Maresh (starting April 2016)
Dr Pedro Tomaselli

Newcastle

MRC or Host or other Funded Non-Clinical PhD

Emine Bagdatlioglu
Ewen Sommerville
Amy Vincent
Stephanie Carr
Yasmin Issop
Persefoni Ioannou
Aura Cecilia Jimenez Moreno
Marina Bartsakoulia
Michele Giunta
Hadeel Alrohaif
Rachel Thompson

MRC or Host or other Funded Clinical PhD

Dr Yi Shiau Ng
Dr Claire Wood
Dr Boglarka Bansagi
Dr Katarzyna Swist-Szulik
Dr Elizabeth Harris
Dr Alexander Murphy
Dr Grace McMacken

Project Partners of the Centre

David Beeson, University of Oxford
David Bennett, University of Oxford
Hugh Bostock, UCL Institute of Neurology
Sebastian Brandner, UCL Institute of Neurology
Susan Brown, Royal Veterinary College
Kay E Davies, University of Oxford
George Dickson, Royal Holloway University of London
Lionel Ginsberg, UCL Institute of Neurology
Iain Hargreaves, National Hospital for Neurology & Neurosurgery
Steve Hart, UCL Institute of Child Health
Simon Heales, National Hospital of Neurology & Neurosurgery
David Hilton-Jones, John Radcliffe Hospital
Ian Holt, NIMR
Janice Holton, UCL Institute of Neurology
Richard Hughes, UCL Institute of Neurology
Heinz Jungbluth, Guy's & St Thomas' NHS Trust
Andrea Malaspina, Barts & The London
Roope Mannikko, UCL Institute of Neurology
Adnan Manzur, Great Ormond Street Hospital for Children
Robert Meadowcroft, Muscular Dystrophy UK
James Miller, Newcastle University Hospitals NHS Trust
Glenn Morris, Robert Jones and Agnes Hunt
Jackie Palace, University of Oxford
Matt Parton, National Hospital for Neurology & Neurosurgery
Rahul Phadke, UCL Institute of Neurology
Joanna Poulton, John Radcliffe Hospital
Ros Quinlivan, National Hospital for Neurology & Neurosurgery
Shamima Rahman, UCL Institute of Child Health
Stephanie Robb, Great Ormond Street Hospital for Children
Rhys Roberts, University of Cambridge
David Sattelle, UCL
Tony Schapira, UCL Institute of Neurology
Mary Sweeney, National Hospital for Neurology & Neurosurgery
Kevin Talbot, University of Oxford
Jan-Willem Taanmen, UCL
Veronica Tan, UCL Institute of Neurology
Francesco Tedesco, UCL
Alan Thompson, UCL
Adrian Thrasher, UCL Institute of Child Health
Chris Turner, National Hospital for Neurology and Neurosurgery
Professor Massimo Zeviani, University of Cambridge
Nic Wells, Royal Veterinary College
Matthew Wood, University of Oxford

MRC Centre Conference Planning Group 2016

Professor Mary Reilly
Professor Mike Hanna
Dr Marita Polschmidt
Professor Katie Bushby
Professor Doug Turnbull
Professor Kay Davies
Professor Kevin Talbot

Principal Investigators currently supported by Muscular Dystrophy UK

Prof David Abbot	University of Bristol
Prof David Beeson	University of Oxford
Dr Sue Brown	Royal Veterinary College
Prof Kate Bushby	Newcastle University
Prof Dame Kay Davies	University of Oxford
Prof George Dickson	Royal Holloway University of London
Prof Michael Duchen	University College London
Prof Thomas Gillingwater	University of Edinburgh
Prof Michael Hanna	UCL Institute of Neurology
Prof Darren Monckton	University of Glasgow
Professor Jennifer Morgan	UCL Institute of Child Health
Prof Francesco Muntoni	UCL Institute of Child Health
Dr Ros Quinlivan	National Hospital for Neurology & Neurosurgery
Dr Shamima Rahman	UCL Institute of Child Health
Dr Angela Russell	University of Oxford
Dr Andrew Shevchuk	Imperial College London
Dr Francesco Tedesco	University College London
Prof Dominic Wells	Royal Veterinary College
Dr Matthew Wood	University of Oxford
Dr Peter Zammit	King's College London

Institute of Child Health
University College London

MRC Centre for Neuromuscular Diseases

UPDATE IN NEUROMUSCULAR DISORDERS

Tuesday 3 - Friday 6 May 2016

At the Clinical Neuroscience Lecture Theatre, Lower Ground
33 Queen Square, London WC1N 3BG

This clinical course concentrates on childhood and adult neuromuscular disorders with an emphasis on clinical cases, natural history and management. This 4 day course is designed for specialists with an interest in neuromuscular disease; the first two days concentrating on paediatric neuromuscular disorders and the latter two days on adult neuromuscular disorders.

Course organisers:
Professor Francesco Muntoni and Dr Adnan Manzur, UCL Institute of Child Health and Great Ormond Street Hospital, Professor Mary Reilly and Professor Michael Hanna MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and UCLH Hospitals Foundation Trust.

SAMPLE COURSE CONTENT

- What's new in Duchenne muscular dystrophy?
- Natural history and clinical trials in Duchenne MD
- The limb girdle muscular dystrophies
- Optimal assessment and management of respiratory and cardiac complications of neuromuscular diseases
- Cardiac involvement in neuromuscular disease
- Congenital myasthenic syndromes
- Congenital muscular dystrophies
- Congenital myopathies
- Spinal muscular atrophy: management, natural history and therapeutic trials
- Inherited muscle channelopathies, myotonic dystrophies
- Inflammatory demyelinating neuropathies CIDP/MMN
- CPC
- Charcot Marie Tooth
- Diagnosis of CMT NGS
- Poem's syndrome
- Paraproteinaemic neuropathies
- Vasculitis
- Amyloid neuropathies
- Mitochondrial diseases – a clinical overview
- FSH
- Inflammatory muscle diseases
- Genetic and acquired inclusion body myositis
- Drug-induced neuropathies
- Motor neurone diseases

On-line registration http://onlinestore.ucl.ac.uk/browse/product.asp?compid=1&modid=2&catid=183

Costs for 2016 Early bird until 7 March	Day rate	Whole course
Consultants rate	150	500
Trainee rate (UK)	60	180
Trainee rate(non UK)	120	350
Allied professionals (physios, nurses)	110	320

Course co-ordinator Jacky Molyneaux (j.molyneaux@ucl.ac.uk) 0044 203 448 8111
http://www.cnmd.ac.uk/seminars_courses_workshops/courses_workshops RCP and RCPCH CPD approval have been applied for

The MRC Centre for Neuromuscular Diseases and Muscular Dystrophy UK would like to thank this year's sponsors for their generous support

SAREPTA
THERAPEUTICS

Sarepta Therapeutics is a biopharmaceutical company focused on developing RNA-targeted therapeutics to improve the lives of people affected by serious and life-threatening disorders such as Duchenne muscular dystrophy. Sarepta is committed to the continued evolution of the PMO platform for therapeutic use in a wide variety of diseases and is proud to support the 9th Annual Neuromuscular Translational Research Conference. Learn more about our leading RNA technologies and clinical research programs at www.sarepta.com

Ultragenyx is a development-stage biopharmaceutical company committed to bringing to market novel products for the treatment of rare and ultra-rare diseases. Ultragenyx has licensed rights to aceneuramic acid extended release and its potential use in treating GNE Myopathy from Nobelpharma, AAI Pharma, and the HIBM Research Group.

Sanofi, a global healthcare leader, discovers, develops and distributes therapeutic solutions focused on patients' needs. Sanofi has core strengths in diabetes solutions, human vaccines, innovative drugs, consumer healthcare, emerging markets, animal health and Genzyme. Sanofi is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY).

Sanofi Genzyme focuses on developing specialty treatments for debilitating diseases that are often difficult to diagnose and treat, providing hope to patients and their families.

BioMarin Europe Ltd.

BioMarin Pharmaceutical Inc. develops and commercialises promising new therapeutics for patients with severe and life-threatening diseases.
Headquartered in San Rafael, California, the company operates subsidiary offices in Europe, Latin America, Russia and the Middle East and since it was founded in 1997, the company has successfully advanced breakthrough products from bench, to market, to patients which is a testament to the company's passion and dedication to patients with serious unmet medical needs.

PTC Therapeutics, Inc. (PTC) is a biopharmaceutical company focused on the discovery and development of orally administered small-molecule drugs that target post-transcriptional control processes. Post-transcriptional control processes regulate the rate and timing of protein production and are essential to proper cellular function. While our discovery programs are directed at targets in multiple therapeutic areas, we are focusing particularly on the development of treatments for rare and very rare disorders, caused by nonsense mutations, including Duchenne Muscular Dystrophy (DMD).

Translarna™ (ataluren) is the first licensed treatment that addresses the underlying cause of DMD, ie the lack of dystrophin. It was approved in July 2014 by the EMA for the treatment of DMD resulting from a nonsense mutation in ambulatory patients aged 5 years and over.

PTC Therapeutics is pleased to support the 2016 Neuromuscular Translational Research Conference.


Roche


SANOFI GENZYME


BIOMARIN
BioMarin Europe Ltd.


PTC
THERAPEUTICS
Translating Science • Transforming Lives


Roche


SAREPTA
THERAPEUTICS


ultragenyx
pharmaceutical

MRC Centre for Neuromuscular Diseases, London

MRC Centre for Neuromuscular Diseases
Box 102
National Hospital for Neurology and Neurosurgery
Queen Square
London WC1N 3BG
020 3448 8013
cnmd.contact@ucl.ac.uk
www.cnmd.ac.uk

MRC Centre for Neuromuscular Diseases, Newcastle

Institute of Genetic Medicine
International Centre for Life
Central Parkway
Newcastle upon Tyne NE1 3BZ
0191 241 8737

Mitochondrial Research Group
The Medical School
Newcastle University
Newcastle Upon Tyne NE2 4HH

Muscular Dystrophy UK
61A Great Suffolk Street
London SE1 0BU
020 7803 4800
info@musculardystrophyuk.org
www.musculardystrophyuk.org
Registered Charity No. 205395 and
Registered Scottish Charity No. SC039445

RCP CPD reference: 103168