

Appendices

of the

**MRC Centre for Translational Research in
Neuromuscular Diseases**

Scientific Advisory Board Review

Friday 14th November 2014

i) MRC Centre Metrics summary 2013-2018

The proposed SMART metrics for the next funding period are listed in table below:

	Metric	Baseline	Target	How Outputs Measured	Qualitative outcomes
Resource generation					
1	Numbers of samples biobanked and distributed	1800	3000	Six monthly reporting of metrics and publication in annual report	High impact publications based on work utilising biobank samples
2	Numbers of patients enrolled in NMD cohorts	2000	3000	Six monthly reporting of metrics and publication in annual report	Patient availability for studies, greater patient engagement
3	Validated MR clinical endpoints for trials	8	16	Numbers of patients enrolled in MR studies of clinical outcomes annually	Publications, SOPs for MR evaluation, adoption as trial outcomes
4	Numbers of students enrolled in MRC training programme	9	18	Annual returns, time to PhD completion	Availability of highly trained cohort of scientists
5	Attendees at MRC conference, workshops and seminars	250pa	300pa	Numbers of participants, participant feedback, web hits on podcasts	Greater engagement of NMD clinical and academic community
6	Numbers of additional centres contributing to biobanks, cohorts, trials	0	2	Numbers of samples and patients reported six monthly and annual report	Greater engagement of NMD clinicians, patients
7	New high level science recruitment to MRC centre	4	6	Numbers of new staff attracted to MRC Centre	Greater critical mass
8	Number of industry partnerships	5	10	Numbers of industry contacts and contracts	Greater industry involvement in NMD
Know how					
9	Number of experimental medicine studies initiated	16	20	Numbers of orphan drugs associated to centres, trials initiated	Proof of principle studies completed, high impact publications
10	Number of new genes identified and classified	6	24	Numbers of new disease genes collected annually	Publications, new disease targets for therapies

11	New targets for antisense therapy in NMD	1	2	Numbers of experimental antisense studies annually	Grants, publications, new clinical studies
12	Initiation of a clinical study for stem cell therapy in NMD	0	1	Milestones to clinical study including safety, preclinical evaluation	Proof of principle clinical study, grants, publications
13	Numbers of experimental exercise studies initiated	1	4	Numbers of patients enrolled in exercise studies annually	Understanding the role of exercise in disease and therapy
14	Overall scientific/ academic output More than one PI Total PI NMD output	135 500	200 600	Numbers of joint papers and value of grants including MRC, EU	Increased high impact publications and grant awards

ii) MRC Centre renewal application 2012

1. Summary of Mission and Objectives.

Serious muscle wasting neuromuscular diseases (NMD) are individually rare but represent an important unmet health need affecting >150,000 UK children and adults. They cause life-long disability or premature death. **The Centre's mission is to translate science into experimental medicine and new treatments for children and adults with disabling/fatal neuromuscular diseases.**

The renewed Centre will operate as an MRC-Host University partnership with the following aims:

- Deliver new experimental medicine studies with clinical impact
- Develop and embed six core translational activities to consolidate experimental personalised medicine across the NMD field. These include: stratified cohorts, experimental trials support and coordination, MRI biomarker development, neuromuscular biobank, preclinical models and PhD capacity building training programmes
- Improve access to experimental medicine and new therapies for this neglected patient group
- Add value to major programmes of separately funded (>£60m) Centre PI discovery science

The key disease research themes underpinning the Centre's scientific strategy and major scientific and translational achievements in last four years:

1. Muscular Dystrophy (Muntoni, Morgan, Lochmüller, Straub, Morgan, Brown, Wells, Bushby) Delivered ground-breaking experimental medicine proof of principle trials of antisense oligonucleotide therapy in Duchenne muscular dystrophy (DMD) (MRC funded, *The Lancet* 2011)¹. Highlighted in the MRC Annual Review 10/11 www.mrc.ac.uk/sevenages. Trial design is underpinned by the first rare disease care guidelines to achieve UK NICE accreditation (*Lancet Neurology* 2010)². Four novel genes and novel molecular mechanisms recently discovered.

2. Neuromuscular Channelopathies (Hanna, Schorge, Koltzenburg, Bostock, Lochmüller, Palace, Beeson, Manniko, Kullmann) First phase II experimental trial showed clear efficacy of reprofiled mexiletine in genetic myotonia (*Neurology* 2011)³. New in vivo clinical electrophysiological tools for channelopathy diagnosis & genetic stratification (*Ann Neurol* 2011)⁴. Genetic evidence supporting a gating pore current as new pathophysiological mechanism identified (*Neurology* 09, 11, *J Physiol* 2010)⁵⁻⁷. New gene (GFPT1) discovered in congenital myasthenic syndrome (*Am J Hum Genet* 2011, *J. Neurology* 2011)^{8,9}.

3. Inherited Neuropathies (Reilly, Jessen, Hovarth, Koltzenburg, Greensmith, Houlden) First international multicentre phase II experimental trial in commonest genetic neuropathy (CMT1A) (*Lancet Neurology* 2010)¹⁰. New disease mechanism linked to accumulation of neurotoxic deoxysphingolipids causes sensory neuropathy (*J Biol Chem* 2010)¹¹. Discovery of four new genes for inherited neuropathies.

4. Inclusion Body Myositis (Hanna, Turnbull, Hilton-Jones, Houlden, Greensmith, Lochmüller) First safety and tolerability study of a non-licensed experimental compound to upregulate heat shock proteins in inclusion body myositis completed. This investigator led study met the primary outcome measure; manipulation of heat shock protein 70 pathway shown to be safe and tolerated in patients with inclusion body myositis; thereby facilitating an efficacy study of this new approach (*Neurology* 2012)¹².

5. Mitochondrial Diseases (Turnbull, Hanna, McFarland, Horvath, Duchon, Rahman, Taylor, Chinnery). Resistance and aerobic exercise therapy shown to be safe and effective in mtDNA deletion muscle disease (*Brain* 2010)¹³. Mitochondrial disease mitigated by idebenone therapy in an experimental medicine trial (*Brain* 2011)¹⁴ Mitochondrial DNA disease potentially preventable (*Nature* 2010 & MRC Perspectives 10/11 <http://perspectives.mrc.ac.uk/chapters/people-populations-and-body-systems>)¹⁵.

The original strategy and objectives for the Centre and their delivery over the past four years

We exceeded all agreed objectives; listed here in the same order as in the original application:

- New **critical mass** Francesco Muntoni, Jenny Morgan, Hanns Lochmüller, Rita Horvath, Richard Hughes (& entire Cochrane Neuromuscular Unit), Ros Quinlivan & teams all relocated to the Centre.
- We discovered **new genes, new pathophysiological mechanisms** and identified potential new targets in NMD (*Nature & Nature Genetics*)^{15,16}.
- We established the **national MRC neuromuscular biobank** with >1800 human cell lines used in >20 science projects and linked to international rare disease biobanks via Eurobiobank.
- We delivered a step change in **UK natural history/experimental personalised medicine studies** rising from just 3 to >30 with an increase in patients entered into experimental studies from 29 to >200

(*Lancet, Lancet Neurology & Brain*)^{1,2,10-14}. We lead international experimental medicine initiatives in the NMD field.

- We **utilise animal models** in imaging studies, to understand pathophysiology and as **preclinical models for potential therapeutics for a number of NMD**. These include novel generation antisense for modification of splicing in Duchenne and spinal muscular atrophy mouse models and assessment of hyperglycosylation strategies in dystroglycanopathies. We also use cell cultures from patients with muscular dystrophy and IBM to explore compound libraries for their therapeutic potential.
- We developed a major **education and training** translational research programme and trained ten MRC funded PhD students (two clinical, eight non-clinical). We attracted additional PhD students funded by other schemes.
- We established world-leading nationally coordinated **stratified experimental medicine patient cohorts** (now >2000 patients) in target NMD: these cohorts are a critical prerequisite for experimental medicine trials/personalised medicine. We provided highly visible, outward looking, collaborative, **nationally coordinated translational leadership** including web-seminars, PhD student retreats, workshops and a high profile MRC translational research annual meeting jointly with major UK Muscular Dystrophy Campaign charity attracting >250 scientists (as well as developing new patient partnerships (<http://www.cnmd.ac.uk>)).
- The Centre is an internationally recognised focal point for NMD research with **national and global collaborations** (Oxford Neuroscience and Cambridge MRC Mitochondrial Biology Unit, Europe, Japan, USA, Australia). We developed **industry partnerships** that delivered new experimental trials and MRI biomarker development (e.g. GSK, Senexis, Prosensa, Shire). We leveraged MRC Centre status to attract additional funding from grant organisations, host institutions & NHS Biomedical Research Centres >£60million.

None of this progress would have happened without critically important MRC support for the core activities and resulting leverage with host and other funders.

Vision, strategy and objectives for the future

Our ten-year vision is to consolidate the expertise and tools of the combined Centre to enhance experimental medicine in UK NMD. We will deliver new experimental medicine studies in each of the five disease themes. Our continued leadership will change UK NMD clinical practice and embed an experimental trials culture. Like UK cancer care now, UK NMD patients will have the option to enter national stratified cohorts & experimental medicine trials, or will have effective treatments. **Our strategy** is to develop the scientific excellence that delivers “know how” and the tools and resources that underpin successful translation. We will build on effective academic, industry, funder and patient partnerships.

Objectives for the Centre over the next five years

1. People to deliver translational research: build on critical mass and recruit two new world-class colleagues: Cossu (stem cell therapy) to London (UCL) and Senderek (neuropathy) to Newcastle (NCL). We will train more students in unrivalled and inspiring educational environments, and prioritise mentoring best young scientists.

2. Maximising added value of core areas to achieve “pull through” from discovery science into experimental medicine: core translational activities will continue to add value to discovery science and we will deliver new experimental medicine and natural history studies in each target disease. We will develop and refine stratified cohorts, biobanks, MRI biomarkers and additional outcome measures as essential platforms for experimental therapy studies. We will refine our use of preclinical cell and animal models to inform study design of novel experimental therapies. We will extend experimental trial culture to more UK clinicians and NMD patients.

3. Advancing neuromuscular gene discovery to identify new therapy targets and new biomarkers Centre PI programmes of next generation DNA sequencing will enable further genetic stratification of cohorts, identify new therapy targets & enhance diagnostics. Biobanked stratified patient material will be key to advance understanding of new gene disease pathophysiology & preclinical therapy development.

4. Antisense strategies to treat NMD: we will target other dystrophin gene exons using different antisense oligonucleotide (ASO) chemistries in collaboration with industry (AVI BioPharma and GSK/Prosensa). We will study a new generation of peptide conjugated antisense oligomers. We aim to develop applications of antisense technology to new NMD such as spinal muscular atrophy.

5. Stem cell therapies we are developing strategies to correct autologous DMD stem cells with a lentiviral vector. We will assess safety and efficacy using myogenic stem cells injected into a single human muscle. We will develop a safe, efficient method to transduce stem cells for systemic delivery.

6. Experimental medicine exercise physiology/therapy we will exploit the critical mass of expertise and new experimental exercise facilities we established with £2m host investment support across UCL and NCL. We will address key experimental questions in relation to molecular basis of exercise benefit and identify genetically stratified NMD groups for whom exercise is safe and effective.

7. Industry partnerships continuing strong industry partnerships will enable us to i) Develop and apply new experimental therapies e.g. antisense ii) Reprofile licensed drugs e.g. bezafibrate in mitochondrial disease and retigabine in channel disease iii) Develop MRI biomarkers iv) Use industry compound libraries to screen preclinical NMD models. Successful partnerships already exist with GSK; Prosensa; AVI, Shire, Senexis; Santhera, Trophos.

Funding requested from the MRC is £3.3 million. In addition, we have agreement for a further **£3.6 million of new host support** and agreed **£750k of new industry support** over the period 2013-2018.

2. Importance of UK Translational & Experimental Medicine Research in Neuromuscular Diseases

Unmet UK health burden of neuromuscular diseases

Neuromuscular diseases (NMD) are an important group of disabling conditions caused by impairment of peripheral nerve and/or skeletal muscle function causing premature death or major chronic disability, which may be compounded by cardio-respiratory involvement. Genetic examples include muscular dystrophy (~1 in 3500), Charcot Marie Tooth (CMT) neuropathy (~1 in 2500), channelopathies (~1 in 50-100,000) and mitochondrial diseases (~1 in 5000). Acquired examples include chronic inflammatory demyelinating neuropathy (CIDP) (~1 in 1500) and inclusion body myositis (IBM) (~1 in 10-50,000). NMD represent an important unmet health burden for the nation. This is despite the excellent clinical infrastructure provided by clinical centres and the nationally commissioned NHS funding for care and diagnosis of rarer NMD lead by MRC Centre PI's (e.g. mitochondrial disease, congenital muscular dystrophies & myasthenia and muscle channelopathies).

How the Centre fills a strategic need and how it has developed its approach to meeting the original mission.

In 2006, we identified a lack of national strategic focus to enable translation of science into patient benefit. There had been significant progress in NMD discovery science, frequently led by internationally high profile UK clinicians and scientists, but translation into patient benefit had been disappointing. The UK risked falling behind other countries such as France, Germany and the USA who had established nationally funded systems to support the NMD translational pipeline. UK progress was also hindered by a notable absence of a NMD experimental medicine trials culture. This was in sharp contrast to standard cancer clinical practice in which patients were routinely offered entry into registries, cohorts and experimental trials. **This MRC Centre, which has encapsulated a highly successful London-Newcastle collaboration, has led the UK efforts to link discovery research to experimental medicine in the last four years** via the initiation of **six core activities** specifically designed to help overcome translation "gap-1" from discovery science into experimental medicine:

- **Core-1 Stratified cohorts for personalised medicine:** development of highly phenotyped genetically stratified patient cohorts as an essential prerequisite for personalised medicine.
- **Core-2 Experimental trials support:** a system of coordination and support to link discovery science to innovative experimental trials in the five neuromuscular disease themes.
- **Core-3 Neuromuscular human cell biobank:** a resource of human fibroblasts/muscle cells for preclinical testing and discovery science linked to routine NHS diagnostic biopsy procedures.
- **Core-4 MRI biomarker outcome measure development:** physics development and systematic application of quantitative MRI as a biomarker and NMD outcome measure.
- **Core-5 Capacity building for future NMD translational research:** education and capacity building PhD programmes in NMD translational medicine.
- **Core-6 Animal NMD models:** improved linkage and collaboration between expert NMD clinical and animal scientists to evaluate validity & translatability of findings in animal models to humans.

The core activities were critical in adding value to discovery science and enabling delivery of experimental medicine studies in each disease theme: i) Dystrophin restoration in DMD¹, ii) Mexiletine in

muscle channelopathies³, iii) Vitamin C in Charcot Marie Tooth 1A¹⁰, iv) Heat shock protein upregulation in inclusion body myositis¹², v) Resistance and aerobic exercise in mitochondrial disease¹³, vi) Idefenone in mitochondrial disease¹⁴. The following case study provides one typical example of how the Centre added value and used the biobank facilities, stratified cohorts, MRI protocols, and experimental trials support to deliver a new DMD experimental study in London and Newcastle:

MRC Centre DMD exon skipping study: *The AVI-4658 study, co-funded by MRC & AVI BioPharma, recruited 19 boys with exon 51 eligible deletions. Its design was based on a previous proof of principle study which had utilised MRI as a measure of muscle damage. Recruitment occurred ahead of schedule and MRC Centre support enabled a) rapid access to large number of patients followed in London and Newcastle; b) effective links to UK Action DMD-TREAT-NMD registry; c) rapid interrogation of North Star UK DMD cohort, with longitudinal clinical functional data from >500 DMD boys. The MRC Centre infrastructure allowed us to contact and recruit boys who met strict entry criteria very rapidly. The MRC study coordinators were instrumental in setting up the study at London and Newcastle, coordinating rapid recruitment and maintaining the MRC cohorts. They also arranged research update newsletters for patients, transport and reimbursement. After consent, each patient underwent a skin biopsy to assess efficacy of antisense in inducing exon skipping in vitro. Fibroblasts were grown and stored in the MRC Biobank, where the research muscle samples were also stored after completion of the project. This proof of principle study confirmed dystrophin upregulation in vivo¹. In renewal, all Centre core activities will enable delivery of new antisense chemistry with industry.*

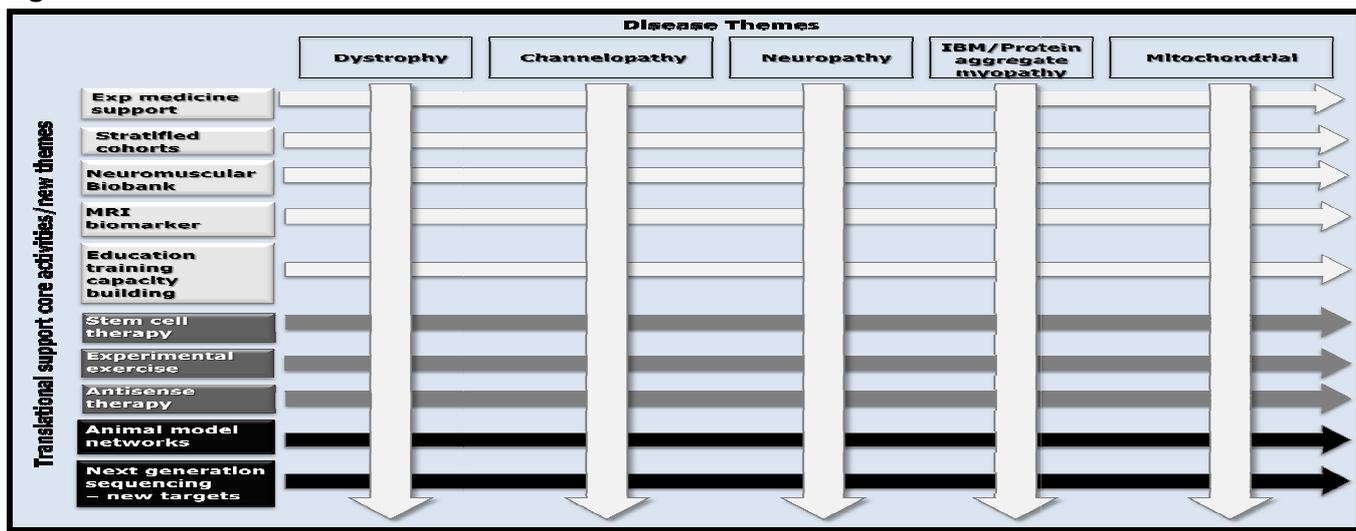
The primary focus of the MRC Centre in the next funding period is to embed and maximise the added-value of the Centre core activities to deliver more “pull through” of discovery science to new experimental treatments in each of five disease themes: muscular dystrophy, neuromuscular channelopathy, neuropathy, inclusion body myositis and mitochondrial disease. Core activities will enable us to maximise the potential of three important developments:

- Discovery science progress has improved pathophysiological understanding and identified more targets for pharmacological/genetic intervention. Progress will accelerate with next generation sequencing (NGS) DNA/RNA technology.
- Availability of animal models for preclinical optimisation of targets for “personalised” subsets of genetically stratified patients.
- Increased industry interest in rare disorders because of favourable regulations for orphan disease drug development and industry increasingly uses rare disorders as a route to market.

The **six MRC Centre core activities** will be developed and refined in the next funding period to maximise added value to separately funded (>£60m) programmes of discovery science lead by Centre PI's (examples of discovery science are in section 3 and in appendix II). **Matching 1-1 support in each core activity demonstrates very major UCL & NCL host commitment to a renewed MRC Centre.**

Figure 1 illustrates the Centre's five vertical disease themes and the interdependence of disease themes and core support areas: each theme has critical mass of discovery science supported by major programmes of separate funding (>£60m) that underpin the Centre's translational activities. The ten left-hand column boxes represent cross cutting themes that are the key tools of the Centre designed to add value by aiding and informing translation of discovery science into experimental patient studies. The top five light grey boxes on the left indicate the **core activities that are supported by the requested MRC funding (matched by host support)** and that cut across the vertical disease themes overcoming obstacles to translation into man. Also shown in this diagram are the new Centre experimental therapy directions in which the Centre has developed critical mass (three light grey boxes represent new therapy themes: stem cell therapy, experimental exercise therapy and antisense therapy). These therapy themes are separately funded, but major added value is achieved by linking with the Centre core activities. Finally, there are major independently funded programmes of next generation sequencing (NGS) and animal model research (shown as left hand column black boxes). NGS in the Centre has already lead to the discovery of new genes¹⁶ and new therapy targets by Centre PI's, and this will likely increase in renewal. (Please note: full details of all core activities, including all related outputs for the past four years, and other additional useful reviewer information, such as previous SAB reports, is available at a dedicated MRC Centre renewal reviewer web page at: <http://www.cnmd.ac.uk>)

Figure 1.



MRC Centre core activities and importance for experimental medicine

The Centre will continue to drive UK NMD experimental medicine by evolving the six core activities:

1. Centre core activity 1 - MRC Centre stratified cohorts for personalised medicine: an essential activity of the MRC Centre in renewal is to support and maximise the potential of the UK **MRC Centre stratified patient cohorts**. The MRC Centre patient cohorts, whose core diagnostic data are being aligned to stored biomaterials and accurate contemporary natural history studies, are crucial to deliver translational medicine. We are at the forefront of such efforts internationally. Samples of patients studied with targeted genetic based therapies can provide valuable correlates with treatment response and ultimately biomarker validation. Patients with rare conditions, meeting stringent inclusion criteria, can be identified rapidly for recruitment into experimental studies. Such cohorts are the basis for proof of principle studies of potential therapies in the preclinical phase (e.g. recent/planned Centre studies of antisense in Duchenne); they are the source of patients for definition of appropriate outcome measures and ultimately for early and late phase studies. Over the previous funding period we placed a high priority on the consolidation of clinical datasets, the extension of these datasets and co-ordination of registry and natural history cohort activity, all in relation to the stored samples in the MRC biobank. This activity enabled and linked with other investments: the MRC funded Centre mitochondrial cohort programme, the EU FP6 funded Network of Excellence TREAT-NMD; the EU FP7 funded BIO-NMD initiative and UK patient organisation funding e.g. Muscular Dystrophy Campaign (MDC). Our cohort work is a major collaboration with patient organisations and represents a very strong area of MRC Centre public engagement. We have started to link clinical data, patient level functional/outcome data, genetic data, biopsy data and biobank data for individual cases. The aim in renewal is to achieve a full integrated database combining all above data streams at the single patient level. Such a fully developed, internationally unrivalled, MRC Centre integrated stratified patient cohort database will drive personalised experimental medicine and collaborations internationally and with industry. **The MRC Centre linked cohorts now contain over 2000 patients across the five disease themes.** Examples of the experimental medicine studies they will support are provided in section 3 below.

i). **Muscular dystrophies (DMD, congenital muscular dystrophies, LGMD, FSHD, myotonic dystrophy)**: Centre investigators (FM, MH) lead on national natural history datasets (n>500) and on co-ordination of TREAT-NMD international patient registries (HL). (See <http://www.cnmd.ac.uk>).

ii). **Neuromuscular channelopathies**: Centre investigators (MH, HL, JP, DK) coordinate nationally commissioned channelopathy diagnostic services with >850 patients in the channelopathy cohort.

iii). **Inherited neuropathy cohort**: Centre investigator (MR) leads the MRC Centre cohort (n>1000) and co-leads the NIH inherited neuropathies consortium (<http://rarediseasesnetwork.epi.usf.edu/INC/>). Over 200 deeply phenotyped MRC Centre cases entered into the MRC-NIH natural history collaboration.

iv). **Inclusion body myositis cohort**: Centre investigators (MH, DT, JM, HL,) in collaboration with Oxford (DHJ) established a prospective cohort of IBM patients (n=164).

v). **Mitochondrial disease cohort**: the MRC Centre was crucial to a successful bid to the MRC Translational Medicine Board for funding the MRC Centre Mitochondrial Disease Patient Cohort (UK). This collaborative study (UCL, NCL & Oxford) includes >850 patients with a biochemical or genetic

diagnosis and detailed clinical assessment, and is the largest mitochondrial patient cohort world-wide generated through active collaboration and partnership across the MRC Centre.

2. Centre core activity 2 - MRC Centre experimental medicine support

We delivered a **ten-fold increase** in early phase experimental medicine clinical trials and natural history studies [2007 n=3; 2011 n=34] (see <http://www.cnmd.ac.uk>). There are > 200 NMD adults and children either currently involved in or who have completed MRC Centre experimental trials (including genetic therapy e.g. antisense¹, PTC 124, reprofiled drugs e.g. mexiletine³ or new compounds e.g. arimoclomol/idebenone)^{12,14} compared to <30 when the Centre commenced [2007 n=29; 2011 n=241]. There are now many additional funded studies at both early and advanced planning stages detailed in the scientific plan section 3 below, and also in the Centre Science programmes in appendix II. As detailed in the case study above, the MRC Centre translational support core activities remain an essential prerequisite for these studies at many levels, including trial co-ordination support and “know-how”. There are three new therapy themes; i) **Antisense** (described in section 3 & in appendix II), ii) **Stem cell therapy** (described in section 3 and in appendix II) iii) **Experimental exercise therapy** (described in appendix II).

3. Centre core activity 3 - MRC Centre neuromuscular cell biobank

The MRC Centre biobank has exceeded all milestones and provided valuable human muscle cell cultures for discovery research and preclinical therapy testing. Any child or adult undergoing an NHS diagnostic biopsy in UCL or NCL can now consent to donate part of the diagnostic sample to the MRC biobank. Currently, the MRC biobank has built a collection of > 1870 anonymised samples linked to patient data using a biobank ID and secure database. These include mostly myoblasts and fibroblasts but also urine, whole blood, serum and plasma. Patient data are updated against genetic reports. All cultures are mycoplasma tested. All myoblasts are tested for myogenicity and differentiation to myotube by fusing and desmin staining. More than 1000 lines have been shared with nine UCL groups, five NCL groups, and more than 50 groups outside the MRC Centre, confirming the national and international science resource we have created. In addition, more than 1000 frozen muscle biopsies are stored with consent for research in the UCL and NCL diagnostic pathology labs. Samples are distributed under a strict governance framework, with an institutional MTA, and only after having verified the ethical approval of the recipient lab for the planned study. The MRC Centre biobank is fully included in international biobanking frameworks such as EuroBioBank and BBMRI. **We will build on the success of the biobank in renewal and will:** i) Increase sample size by continuing routine collection of myoblast and/or fibroblast cells from each patient undergoing diagnostics and extend sample collection to other UK centres, ii) Systematically collect biomaterials from each patient enrolled in clinical trials or natural history studies at the Centre or collaborating partners (e.g. exon skipping in DMD; Jain natural history for LGMD2B; FOR-DMD steroid trial), iii) Introduce immortalisation of targeted myoblast samples using recently developed method (retroviral transduction with both telomerase and cyclin-dependent kinase 4 expressing vectors) with French collaborators at the Institute of Myology, iv) Introduce immortalisation of targeted fibroblast samples using the method previously used by NCL PIs (retroviral transfer of papillomavirus E6E7 genes) v) Introduce MyoD-transfect human fibroblasts to generate myogenic cells for selected patients where muscle biopsies cannot be obtained, vi) Collect muscle derived stem cells vii) Introduce additional measures of quality control (ISO certification). viii) Increase collection of fibroblasts from neuropathy patients to be available for separate studies to generate iPSCs. Studies to be supported by the MRC biobank are described in the science section 3 below and in appendix II.

4. Centre core activity 4 - MRC Centre MRI biomarker platform for the quantification of nerve and muscle pathology: the central aim of the **MRI platform** activity is, through methodological advances and systematic patient studies, to develop MRI measures of NMD activity and progression, applicable as timely, practical outcome measures in both single and multi-centre clinical trials. MRI will provide key non-invasive readouts underpinning new clinical studies within the five disease theme programmes of the Centre. We have developed MRI methods to reliably quantify muscle pathology as potential outcome measures in both primary myopathies and peripheral neuropathies in adult and paediatric patients. The use of ‘Dixon’ fat-water MRI to quantify muscle fat infiltration, a common pathological manifestation across the NMD, has been a unifying theme. We established a **platform infrastructure** across the Centre to enable this research. In London, through the MRC Centre, we established the UCL Neuromuscular MRI Research Group (www.ucl.ac.uk/neuromuscular-mri). In NCL, the existing experience of the MRI Centre (www.ncl.ac.uk/magres/) in assessing muscle pathology by MRI and spectroscopy was, through the support of the MRC Centre, extended to muscular dystrophies and cardiomyopathies. Cross-centre collaborations established the following **standardised methods and protocols** that can now be used as outcome measures in clinical trials: i) Quantitative Dixon lower-limb

fat-water methods optimised in Newcastle (Philips) and London (Siemens)^{17,18}; ii) Magnetization transfer (MT) MRI correlated with muscle strength in CMT1A supporting MT-MRI as an outcome measure¹⁹⁻²¹; iii) innovations to improve MR sensitivity¹⁹⁻²¹; iv) IDEAL-CPMG, which provides in a single scan muscle water and fat content and respective T₂ relaxation times²²; v) validated protocols for multi-parameter quantitative lower-limb muscle MRI with test-retest and normal age-dependence data; vi) Quantification of sciatic nerve hypertrophy, a potential disease marker in CMT1A²³; vii) quantification of early changes in cardiac structure, wall motion and energetics through the development of cardiac wall tagging and cardiac phosphorus spectroscopy; viii) the use of phosphorus magnetic resonance spectroscopy to detect metabolic abnormalities at rest and under exercise in skeletal muscle. The methods and protocols were applied in various **Patient Studies**: i) Multi-centre study involving Newcastle and London assessing quantitative MRI in Limb Girdle Muscular Dystrophy 2I (LGDM2I)^{17,18}; ii) Cross-sectional assessment of the localised mechanism of cardiac involvement in LGMD2I; iii) the identification of non-invasive metabolic biomarkers in skeletal muscle at rest and under exercise in LGMD2I; iv) a cross-sectional and longitudinal MRI investigation in inclusion body myositis (IBM) and Charcot-Marie-Tooth disease (CMT1A); v) Muscle histology vs. MRI in Duchenne muscular dystrophy²⁴. Recently initiated/planned funded studies include: i) MRI in progressive external ophthalmoplegia; ii) cross-sectional evaluation of MRI in non-dystrophic myotonias; iii) MRI in inflammatory neuropathies; iv) MRI to assess progression and therapy in periodic paralysis. The significant imaging and spectroscopy expertise in NMD across the Centre MRI groups has resulted in close **Industrial Links** with GlaxoSmithKline, Prosensa, AVI and Genzyme. Collaboration agreements including NMD MRI development are in place with Siemens and Philips. **Over the next five years** we will deploy MRC Centre-established MRI protocols in patient experimental medicine studies in the five disease themes and continue technical development to fully exploit MRI to provide non-invasive, objective readouts. We will extend anatomical coverage (upper limbs; diaphragm; 'whole-body' coverage), develop improved image segmentation and data analysis methods. We will investigate the potential of muscle diffusion-tensor imaging and apply multi-parametric methods to probe intra- and extramyocellular water and lipid distributions. A priority will be to establish MRI measures in pre-fatty infiltrated muscle where therapies may be most effective. We will develop high resolution 'whole-nerve' imaging and segmentation to quantify gross morphological changes, and through quantitative MRI assess the potential of "virtual nerve biopsy"; determining measures that relate to axonal loss, demyelination, inflammation, and conduction block. We will continue essential work to develop standardisation and validation of imaging methods and protocols across both MRC Centre sites and link with NMD centres across Europe & USA.

5. Centre core activity 5 - MRC Centre capacity building and training (see section 4 below).

6. Centre core activity 6 - MRC Centre NMD animal model translation strategy: many MRC Centre PI's have significant programmes of NMD animal model research (see other support). There are strong links with MRC Harwell (EF), and membership of the recent successful MRC mouse network bid (DT, FM, EF, LG, MR, MK, MH). Centre PI's agreed it was not realistic for the renewal to resource major animal research programmes. However, there are very important opportunities for us to add value to existing MRC investments by linking human clinical scientists and human cohorts with animal scientists and animal models to drive translation through, for example, informing animal model preclinical therapy assessment (also strongly highlighted by our SAB 2009 and 2011 who said "*the Centre is virtually uniquely placed to generate effective "cross talk" between NMD animal experts and clinical scientists*" - see SAB reports appendix III). The MRC Centre has a four-fold strategy to add value, support and inform existing MRC investments in NMD animal model research: i). A series of translational PhD projects in the Centre which utilise preclinical animal models in each of the major disease themes; ii). MRC Centre PI's will play an active role in optimising the success of the recently awarded MRC Neuromouse Consortium and build further links with MRC Harwell; iii). Centre PI's and PhD students will continue to utilise the successful MRC Centre NMD animal phenotyping laboratory established using the original Centre award allocation (50k). iv). We will establish a series of innovative national MRC Centre NMD animal-clinician scientist workshops with MRC Harwell to maximise "cross talk" and joint new projects between human and animal scientists. *The overarching aim of our animal model strategy, linked to other supported programmes, is to understand how reversible functional impairment turns into irreversible structural deficits and how experimental therapy can prevent, delay or compensate this.* This will be studied in three areas, namely: (i) *which factors control axonal transport and Schwann cell phenotype;* (ii) *which mechanisms dominate transition from ion channel abnormalities to structural change;* (iii) *how can better understanding of experimental therapy be harnessed for human trials,* (more details of the three areas provided in the animal model science theme appendix II).

3. Scientific plan

The scientific programmes that underpin and gain value from the Centre's core translational activities attract >£60m of separate grant income (see other support). Here we provide examples from four of the disease themes, illustrating how the Centre's core areas have added value to discovery science programmes, and we outline experimental medicine plans (details of the science in the fifth disease theme, IBM, are included in appendix II). *Each scientific programme will offer range of PhD projects.*

A. Muscular Dystrophy-discovery science and experimental medicine:

UCL lead: Francesco Muntoni (FM) NCL lead: Katie Bushby (KB),

Background/importance: muscular dystrophies cause progressive weakness and disability often with cardiorespiratory complications. Duchenne muscular dystrophy (DMD) is the most frequent childhood form, causing death in teens or early adult life. A high de-novo mutation rate means genetic counselling alone will not reduce incidence. Centre PIs also have strong expertise in other areas of dystrophy research. These include dystroglycanopathies, with an active programme of gene discovery (recent discovery of three novel genes), mouse model phenotyping and translational research using various genetic therapy and small molecule approaches, discussed in appendix II²⁵. Another area of strength includes the investigation of the therapeutic potential of stem cells in dystrophies (below and in appdx II).

Discovery science and experimental medicine we delivered

Antisense oligonucleotides (AOs) in DMD: this is an area of strong and effective multidisciplinary collaboration across the MRC Centre with multiple research projects involving clinician scientists and researchers. Centre investigators (FM, JM, KB, VS) have successfully completed a recent MRC funded phase IIa study using a morpholino (PMO) AO developed by the UK MDEX consortium to skip exon 51 (<http://www.mdex.org.uk/> PI-FM) in collaboration with an industrial partner AVI BioPharma¹. This experimental study followed the preclinical optimisation and identification of the lead AO compound for skipping exon 51 using muscle cells from the MRC Centre biobank^{26,27}.

New dystrophy discovery science and experimental medicine studies

There are major opportunities to take dystrophy discovery science into man over the next 1-5 years. These opportunities will be accelerated by the substantial value the MRC Centre can add in the areas of stratified cohorts, neuromuscular biobank & MRI biomarker outcome development. There are unrivalled translational research training opportunities. Several active projects are already at the in-man stage; others are currently being pursued at a preclinical level in cellular or animal models and will benefit from the carefully phenotyped and genotyped Centre cohorts.

Antisense oligonucleotides (AOs): MRC Centre investigators (FM, KB, VS) have obtained funding for collaborative industry sponsored studies with GSK/ Prosensa including a phase IIb study using a 2'OMe backbone AO designed to skip exon 51. A further study on non-ambulant older DMD patients who could benefit from exon 51 skipping is at the planning stage using 2'OMe AO. In collaboration with Prosensa we are also planning a phase I study of two novel 2'OMe AOs that target exons 45 & 53. MRC Centre investigators in collaboration with the MDEX consortium have identified a lead morpholino AO sequence to skip exon 53²⁸, which has been validated using patients' cells stored in the MRC biobank, and has undergone patent protection (a grant for an investigator-led phase I/IIa study being submitted). This will be a randomised placebo controlled dose escalation study and will also investigate the role of non invasive biomarkers (muscle MRI and serum miRNA) in monitoring disease progression and therapy response. We have just secured an Association Francaise Myopathies (AFM) consortium grant to develop outcome measures for non-ambulant DMD. This AFM grant will support an investigator-led collaborative clinical trial (in UCL, NCL and Paris) to assess safety of PMOs in non-ambulant DMD and to assess the value of the exploratory outcome measures being developed. In addition, this grant is focused on identifying safety and efficacy biomarkers to evaluate the effect of chronic PMO administration and determining optimal protein and RNA techniques to quantitatively assess efficacy of this genetic intervention. MRC centre PIs and the MDEX consortium also obtained a Wellcome Trust Health Innovation Challenge Fund grant, in which a new generation AO (a PMO linked to a peptide for improved skeletal and cardiac muscle targeting) is currently undergoing efficacy and safety testing in the mdx mouse model. The expectation is that a safe compound that is more efficient than current 2'OMe and PMO AOs will be found and we will proceed to a phase I trial in DMD boys eligible for exon 53 skipping using a peptide modified PMO. Currently, nine classes of peptide conjugations to the PMOs are being investigated by the Oxford and Cambridge members of the MDEX consortium and their efficacy is tested in vivo in the mdx mice in the MRC Centre. Significant recent consortium progress has identified peptides that improve skeletal and cardiac muscle PMO targeting *by more than ten-fold*. Preclinical studies will investigate route and dose optimisation including repeat low doses and assess biodistribution relevant for skeletal and heart muscle. Correction of heart dystrophin expression and function in mdx

mice will be assessed using cardiac conductance catheter techniques which are available in the Centre in NCL (VS). Some of these peptide modified PMOs also appear to be able to cross the blood brain barrier. Preclinical toxicology of the lead compound is expected in 2013. In other preclinical developments, collaborative work between JM FM and SH is also assessing the role of nanoparticles to improve AO uptake in tissues which are not targeted by the current AO chemistries such as cardiac muscle and brain. Both this and the peptide modified PMOs might have important implications for other conditions, such as spinal muscular atrophy, in which clinical applications of AOs are being planned in USA (ISIS) using a MOE backbone AO. Investigators in the MRC Centre also have expertise in this condition both from the clinical perspective and the modification of splicing to retain SMN2 exon 7²⁹. As discussed in appendix II, MRC Centre investigators recently identified a novel AO sequence which is very effective in improving life expectancy in a transgenic animal model of severe SMA.

Other therapeutic approaches: stem cells: PIs of the Centre (UCL:FM, JM, AT,OD, NCL: HL) are undertaking an MRC funded translational research project to identify an optimal stem cell³⁰; an efficient and safe lentiviral vector³¹; and an “opti-dystrophin” construct containing all the necessary regulator elements, including the nNOS binding site. We aim to perform a proof of principle study comparing a local injection of lentivirally-induced opti-dystrophin expressing autologous stem cells into a single human muscle. These stem cell projects will link to the expertise of Giulio Cossu who, thanks to UCL host support, joins the Centre in 2012. Cossu’s group will also pursue their pioneering work on the use of human artificial chromosomes (HACs) containing the whole dystrophin locus as a potential DMD therapy. Their recent work has shown that the dystrophin HAC (DYS-HAC) has efficacy in a dystrophic mouse cell model³². In renewal, efforts will focus on generating HACs which will be transferred into human dystrophic mesoangioblasts which will be challenged for their ability to repair dystrophic muscle and ameliorate the disease. The translation of this alternative strategy to trials will be greatly supported (value added) by the Centre experimental trials/cohorts core support (see appendix II). **Regarding gene therapy;** Centre PIs have recently initiated a collaboration with Genethon and Paris (Thomas Voit, Institute of Myologie) to recruit DMD boys with deletions eligible for exon 53 skipping in order to undertake a detailed function and MRI assessment of upper limb weakness progression. This is in preparation for a phase I study of an AAV vector expressing antisense sequences linked to a modified U7 small nuclear RNA. The vector will be delivered by perfusing a single upper limb in the first instance.

How the MRC Centre will add value to future studies: the Centre has been instrumental in delivering completed studies and will underpin planned experimental trials. The main added value relates to biobank, muscle imaging, experimental medicine support and stratified cohorts. **MRC Centre Biobank:** the biobank will be instrumental for continuing to optimise new target sequences for skipping other exons (or including exons in SMA). The biobank will also support studies on DMD stem cells; the dystroglycanopathy studies; and high throughput next generation sequencing studies on muscular dystrophies. **MRC Centre MRI biomarker development:** we will investigate the role of muscle imaging and spectroscopy using MRI in detecting changes related to the administration of AOs in mdx mice. This study will assess both short term effects of AO in reducing muscle inflammation and longer term effects on muscle anatomy. A dose response on MRI with different AO regimens will be assessed and correlated with the level of dystrophin in mdx muscle, and with serum biomarkers. Studies performed in NCL by VS will evaluate the effects of AO on cardiac function in mdx mouse models of DMD. These mdx mouse MRI studies will be paralleled by natural history studies of muscle MRI changes in DMD boys at different level of functional abilities, performed both in collaboration with industrial partners (Prosensa; GSK) and academic sponsors (MRC: Genethon). These studies will inform planned intervention studies using AOs to skip various exons in different DMD cohorts. **MRC Centre stratified cohorts:** all the studies above on exon skipping in DMD will benefit from the stratified MRC Centre supported North Star cohorts both for recruiting patients with eligible deletions and assessing inclusion criteria, and to assess and validate novel outcome measures relevant for non-ambulant DMD individuals. Indeed, these novel AO therapies are **highly personalised genetic therapies** and only a subgroup of DMD boys with eligible deletions can be recruited into such specific studies. **MRC Centre experimental medicine support:** the MRC trials coordinator will continue to be central to maintaining the stratified cohorts for personalised medicine and streamlining regulatory support and trial monitoring and delivery. These cohorts could also be instrumental for future post-marketing surveillance studies. In addition, maintaining accurate information on patients followed at the Centre will be essential for the efforts of various PIs in identifying novel genes. In this respect, a recent collaboration between FM and the Sanger Centre in Cambridge has led in the last few months to the identification of four novel genes responsible for a dystroglycanopathy; two novel congenital myopathy genes and one gene for a distal motor neuropathy. The recent identification, as part of a separate collaborative study, of a gene responsible for a congenital

myopathy, the function of which appears to be that of regulating satellite cells myogenesis, highlights the cross links between different aspects of this research program^{16,33}. These gene discoveries have revealed new therapeutic targets.

B. Inherited Peripheral Nerve Disorders: discovery science and experimental medicine

UCL lead: Mary Reilly (MR), NCL lead: Rita Horvath (RH).

Background/importance: The main inherited peripheral neuropathies are Charcot Marie Tooth disease (CMT), the distal hereditary motor neuropathies (HMN) and the hereditary sensory and autonomic neuropathies (HSAN). Severity varies, but patients most commonly have significant life-long disability.

What we have delivered and how the Centre will translate new discovery science into experimental medicine studies

Genetics: Using MRC Centre stratified cohorts, we identified many new causative mutations in a wide range of genes (e.g. Frabin, SH3TC2, TRPV4, Fam134B, PMP22, MPZ, MFN2). Based on MRC Centre cohort studies assessing mutation frequency in a UK population, we developed and implemented new genetic diagnostic algorithms for clinical practice.³⁴ Linked to the MRC cohorts we (MR,MH,JH,HH) secured new MRC and Wellcome funding (>£1m) for an Illumina platform next generation sequencer (HiSeq2000) to employ targeted & whole exome sequencing. We already identified a new gene causing the neuropathy Brown Vialetto von Laere syndrome (submitted), two new genes causing axonal CMT2 and also the FBXO38 gene in dominant HMN (submitted and see appendix II). In our MRC neuropathy cohorts, 45% of CMT2 cases and 80% of HMN and HSAN cases remain genetically undefined. ***In renewal***, new gene discovery using NGS will be an important activity. We could not do this research without maintaining/updating the MRC neuropathy cohorts (now >1000 patients). Developing links to patient biobanked fibroblasts (& generation of iPS cells) will be critical to enable functional studies of new genes. New gene discovery will, enable further genetic stratification, and reveal new therapy targets.

MRC Neuropathy Stratified Cohorts: the MRC neuropathy cohort enabled Centre investigators (MR, FM) to become leading partners in the international NIH (USA) funded inherited neuropathy rare disease consortium (RDCRC, MR is Co-Director). With new Centre investigator RH in NCL, we added 200 new NCL patients, further enhancing this national cohort for genetics, natural history studies and planned experimental trials. ***In renewal***, MR, RH and JS will continue to deeply phenotype and stratify the cohort employing clinical, neurophysiological, genetic, MRI and functional techniques. We will take advantage of recent advances in techniques to phenotype sensory deficits (MK) and continue to develop MRI Biomarkers utilising the cohort.

Development of Outcome Measures: developing validated, sensitive and responsive outcome measures in neuropathies is crucial for powered trials. We (MR) published the first validated composite scale (CMTNS) used as an outcome measure in CMT trials. Based on outcome data analysis from the MRC Centre experimental trial of ascorbic acid in CMT1A we refined the sensitivity and reported CMTNS2³⁵. The MRC Centre has enabled a major new direction for neuropathy outcomes research with development of quantitative muscle MRI as a biomarker of denervation. We developed a lower limb muscle MRI protocol in CMT patients (see MRI core activity earlier). Initial pilot cross sectional data indicates this MRI method is a more sensitive marker of early muscle denervation than current clinical or neurophysiological methods¹⁹. There is clear potential for MRC Centre MRI protocols to be biomarker outcomes in future neuropathy trials. ***In renewal*** we will i) study responsiveness of the new CMT scale (CMTNS2), ii) study the sensitivity/responsiveness of our new muscle MRI protocol in stratified cohorts of CMT, HMN & HSAN patients, iii) continue to identify more sensitive methods of measuring muscle power using isokinetic myometers (HUMAC) and compare with conventional MRC score methods.

Understanding Molecular Pathophysiology: better understanding of fundamental pathophysiology of neuropathy will help identify new treatment targets. Our discovery programme has produced new insights into disease pathogenesis. For example, we recently identified the first human null peripheral myelin protein (PMP22) patient and correlated human findings with the PMP22 null mouse. These data suggested PMP22 is especially important for cranial motor neurons and spinal sensory neurons in early development and differentially affects myelination between motor and sensory nerves³⁶. We also defined the function of the protein SH3TC2 and showed how mutations result in mis-targeting of SH3TC2 away from the recycling endosome as the fundamental molecular defect leading to CMT4C demyelinating neuropathy³⁷. ***In renewal*** we will focus on four areas; i) inherited protein folding disorders of the PNS, ii) mitochondrial function in inherited neuropathies, iii) pathophysiology of hereditary sensory and autonomic neuropathy type 1 (HSAN1) and iv) animal models and axonal transport (see appendix II).

1) Inherited Protein Folding Disorders of the PNS From the MRC neuropathy cohort we recently identified mutations in the small heat shock protein genes HSPB1 & HSPB8 in a large series of dHMN

and CMT2 cases. To understand the pathogenesis of this important group of motor nerve disorders we linked with expert groups across the MRC Centre encompassing clinical inherited neuropathy (MR), molecular genetics (HH, MR) and animal and *in vitro* functional modelling (LG,EF). The functional group (LG,EF) are studying the pathogenesis of peripheral motor disorders using different models including:

i) transgenic mice, ii) mice with endogenous mutations in genes associated with motor nerve degeneration, and iii) *in vitro* models of primary neurons virally transfected with relevant mutant genes. In order to examine sensory and motor systems in neuropathy mouse models, we will use the MRC Centre neuromuscular mouse phenotyping facility at UCL (LG, EF, MK). This facility has been used by MRC PhD students and investigators to analyse the phenotype of a number of mouse models of motor nerve disorders. We have also established confocal systems to study mitochondrial function and axonal transport. ***In renewal*** we will investigate how protein misfolding disorders cause motor nerve degeneration. We will initially focus on modelling our HSPB1 mutations, and in parallel we will study a recently generated knockout mouse (HSJ1) that develops a severe motor neuropathy. We will study axonal transport in axons of both primary motor neurons virally transfected with HSPB1 mutations and neurons from the HSJ1 knock out. We will also study axonal transport in motor neurons from a newly developed HSPB1 transgenic mouse in (*collaboration: L. Van den Bosch*). We will evaluate experimental compounds including, arimoclomol, which augments the heat shock response (we have already obtained MHRA approval for arimoclomol and have undertaken human experimental trials in the Centre in IBM) and has potential to ameliorate the effect of HSPB1 mutations. We will assess the effects of arimoclomol in HSPB1 mutant motor neurone cultures and transfected cellular models. We will use patient derived fibroblasts (biobank) to generate iPS cell derived motor neurons and study axonal transport.

2) Mitochondrial function in Inherited Neuropathies: we recently identified mutations in the mitochondrial gene (ATPase 6) in CMT2 (~2% of cases) with a predominantly motor phenotype. Functional data confirmed pathogenicity and phenotypic severity correlated with blood mutant load (submitted). These data indicate ATPase 6 mutations are the second commonest cause of CMT2 after the nuclear mitochondrial gene MFN2 mutations which has important genetic diagnostic implications. By whole exome analysis we recently identified a new nuclear mitochondrial biogenesis gene in CMT2. In one family we observed that the co-inheritance of a known pathogenic mutation in the variable loop of a mitochondrial tRNA gene for serine markedly worsened phenotypic severity, suggesting an important nuclear-mitochondrial interaction. ***In renewal*** we will use mitochondrial expertise across the MRC Centre to study both mtDNA and autosomal mitochondrial genes in inherited axonal neuropathies. Our plans include: i) studying the effect of recently identified mtDNA and nuclear gene mutations on axonal transport using iPS cell models ii) pursuing our recent discovery by investigating nuclear-mitochondrial interactions using cybrid systems and by evaluating mitochondrial gene expression patterns (with DT) iii) use the MRC Centre mitochondrial cohort to assess neuropathy involvement in detail.

3) Hereditary Sensory and Autonomic Neuropathy type 1 (HSAN1): from MRC Cohorts we published the largest series of HSAN1 patients with *SPTCL1* (subunit 1 of SPT enzyme) gene mutations. Recently, we discovered a new disease mechanism in which the *SPTCL1* mutation leads to a change in substrate specificity of the SPT enzyme resulting in generation of neurotoxic deoxysphingolipids (DSBs)¹¹. We recently discovered two novel *SPTCL2* (subunit 2 of SPT) mutations causing HSAN1. A pilot study in our *SPTCL1/2* cohorts shows DSB levels correlate with disease severity (unpublished). ***In renewal*** we will longitudinally assess whether DSB levels correlate with disease progression, and determine the best outcome measures for a planned trial of serine therapy (see below).

Clinical Trials: we recently completed a significant international experimental trial of high dose ascorbic acid (AA) in CMT1A¹⁰. MRC Centre cohorts allowed us to achieve full recruitment rapidly. Importantly, our study indicated that the AA efficacy reported in the CMT1A animal model was not reproduced in the human disease. The study provided important insights into outcome measure responsiveness. As part of the Centre exercise therapy theme we have started to investigate both resistance and aerobic exercise in inherited neuropathies. We showed that hip flexor fatigue limits walking in CMT³⁸ and have just completed a trial of the effect of increasing hip flexor strength on waking ability in CMT (data being analysed). ***In renewal*** we will undertake two initial experimental trials. First, a CMT aerobic exercise trial which we have designed in collaboration with NCL. Second, an experimental trial of serine therapy in patients with HSAN1 caused by *SPTCL1* or *SPTCL2* mutations.

How the MRC Centre core activities added value to future studies: all above studies have gained significant value from MRC Centre specialised experimental trials support, biobank access, stratified cohort development, MRI biomarker development and use of MRC centre mouse phenotyping facility. MRC Centre PhD students have undertaken neuropathy research. All planned studies will be catalysed by the MRC core activities.

C. Neuromuscular Channelopathies: discovery science and experimental medicine

UCL lead: Michael Hanna (MH), NCL lead: Hanns Lochmüller (HL).

Background/ importance: Genetic dysfunction of ion channels causes disorders with altered nerve and muscle excitability, impaired neuromuscular junction transmission or altered excitation contraction coupling. Clinical manifestations include neonatal myotonia and/or weakness that may be fatal, episodic and progressive muscle weakness, craniofacial and limb deformities, and cardiac arrhythmias³⁹.

Discovery science and experimental medicine we delivered

The MRC Centre channel group have taken advantage of Centre core activities to make discoveries:

Muscle channelopathy genetics: we comprehensively defined the genetic architecture of muscle channelopathies discovering large numbers of new pathogenic missense, nonsense and frameshift mutations in muscle voltage-gated ion channels (SCN4A, CACNA1S, KCNJ2, CLCN1)^{5,40}. We showed that large scale gene rearrangements and copy number variation in CLCN1 can cause severe drug resistant myotonia⁴¹. The Centre developed the world's largest genetically stratified muscle channelopathy cohort and linked it to our nationally commissioned diagnostic service as an invaluable platform enabling the MRC natural history and experimental medicine studies we delivered (MH)^{3,42,43}. New genotype-phenotype relationships discovered include first descriptions of neonatal hypotonia and stridor with genetic sodium channel fast inactivation defects, guiding changes in clinical practice^{44,45}.

Muscle channelopathy pathophysiological mechanisms: we tested the possibility that the commonest muscle channelopathy, hypokalaemic periodic paralysis (HypoPP), is caused by loss of voltage sensor positive charge in either the sodium (Nav1.4) or Calcium (Cav1.1) channel. In our cohort of >80 cases we found almost all harboured mutations of arginine residues that predict a gating pore current, identifying this as a common disease mechanism^{5,7}. We undertook a pharmacogenetic correlation study and showed that SCN4A or CACNA1S mutations that predict a proton selective gating pore current consistently respond to carbonic anhydrase inhibitors. In contrast, radical amino acid substitutions predicting a non-selective gating pore currents do not. This allows stratification and prediction of treatment response⁶.

Muscle excitation-contraction coupling disorders: we (FM MD) delineated the role of dysfunction of the sarcoplasmic calcium release channel RYR1 in human disease, used cohorts to define the phenotypic range of mutations, and implicated mitochondrial dysfunction in the pathophysiology⁴⁶.

Congenital myasthenic channelopathies: we discovered a gene associated with congenital myasthenic syndromes (CMS) (HL). Most known CMS genes encode structural components of the neuromuscular junction (NMJ) but we discovered mutations of the *GFPT1* gene (encoding an amino sugar synthesising enzyme) caused CMS with tubular aggregates. The exact NMJ function of GFPT1 is unclear, but has important implications for understanding synaptic physiology⁸. We characterised key clinical features in a large cohort of GFPT1 patients in the Centre and with Oxford (DB, JP)⁹.

Translational activities supported by the MRC Centre

Completed large multicentre natural history studies (NIH funded) in genetically stratified muscle channelopathies; in particular periodic paralysis and non-dystrophic myotonias. We defined precise natural history and outcome measures for experimental medicine studies^{3,42,43}.

Completed the first multicentre international randomised controlled experimental trial (NIH funded) in a muscle channelopathy: myotonia congenita³. We showed that reprofiling of the use-dependent sodium channel blocker mexiletine has a highly significant benefit ($p < .0001$) compared to placebo when assessed by validated patient reported outcome measure. This work has resulted in an orphan drug status application to the European Medicines Agency (EMA)³.

Developed new in vivo diagnostic electrophysiological protocols and techniques: (including first-in-man muscle sarcolemmal velocity recovery cycle measurements)⁴⁷ to diagnose, direct DNA testing and stratify muscle channelopathy patients^{4,47}.

Added value from the MRC Centre: All the above discovery and translational studies have gained significant added value from the MRC Centre through specialised experimental trials support, biobank access, stratified cohort development, MRI biomarker development, and training of the MRC Centre PhD students. All planned studies will be catalysed by the key core areas provided by the Centre.

New channelopathy discovery science and experimental medicine studies

Channel research benefits greatly from Centre core activities. Each project is associated with separate funding and multiple collaborations often bringing investigators outside the Centre into NMD research.

Discover new genes (MH, HH): 20% of patients with muscle channelopathies do not have mutations in known genes and undiscovered genes likely exist. MH, MR, HH have MDC/MRC/Wellcome funding (>£1m) for next generation sequencing to perform whole exome analysis, and we have identified 64 genetically undefined families from our stratified cohorts for this purpose.

Investigate relationship between genotype and phenotype (MH HH): we will ask whether gene modifiers, differential allelic expression and other epigenetic mechanisms can explain the poorly understood relationship between genotype and phenotype (funded by the MRC and MDC). These observations will extend to asking how genotype predicts drug response (supported by MRC and NIH). For example, the optimal treatment of HypoPP is not known. Although acetazolamide is sometimes effective in reducing attack severity, analysis of the MRC channel cohort showed ~50% of genetically proven HypoPP cases do not respond⁶. We found that patients with arginine to histidine substitutions in the voltage sensor region are more responsive to acetazolamide therapy than other mutations⁶. Indeed, we never observed a beneficial response with the R528G or R1239G substitutions in CACNA1A or with R672G in SCN4A. Thus our genetically stratified database has provided insight into the mechanism of this important drug. Further work will ask how variation in genes can impact drug response.

Understand the molecular pathophysiology of diseases caused by gating pore currents

(MH, SS, RM, DK). An aberrant gating-pore leak introduced by CACNA1S or SCN4A mutations has been proposed to be critical to the pathophysiology of HypoPP^{48,49}. MRC Cohort analysis enabled us to provide compelling genetic evidence supporting this hypothesis⁵. However, it is unknown how this leak explains the tendency for hypokalaemia to trigger paralysis or how it relates to progressive muscle degeneration. Our genetic study (see above) showed that the response to acetazolamide correlates with the cation selectivity of the predicted gating pore current: when the S4 arginines are substituted by histidines, the gating-pore current is highly proton selective and the disease responds to treatment, whereas other substitutions that lead to a non-selective gating-pore current are treatment unresponsive. Thus our genetic findings strongly implicate the trans-membrane proton gradient as central to the acetazolamide response. With this insight we will use carbonic anhydrase inhibition as a tool to understand how the cation shunt results in paradoxical depolarisation of the muscle fibre. This will also be informed by our recent genetic discovery in the MRC cohort that a new mutation affecting a negatively charged residue in S2 of NaV1.4 causes HypoPP. A potential unifying explanation is that this residue also lines the gating pore and possibly interacts with S4, and that its neutralisation allows a leak current through the pore.⁵⁰ This idea is supported by very recent NaV1.4 x-ray crystallography data⁵¹. We will test this hypothesis directly by measuring the gating pore current in vitro and relate the findings to other gating pore mutations in SCN4A and CACNA1S. These studies will be done in xenopus oocytes and also in mammalian cell lines, allowing channel function assessment at physiological temperatures. Human myoblasts from the MRC biobank are also being explored for functional characterisation, and in the case of CACNA1S some mutations are available in mouse strains (see studies of muscle degeneration below), and we are already refining patch clamp recording methods from acutely dissociated mouse muscle fibres. These recordings will allow assessment of the channel function within the native context of functional muscle fibres. We will also examine the contribution of ATP-gated K⁺ (K_{ATP}) channels to the effect of lowering the extracellular potassium concentration on membrane potentials. This channel is highly expressed in muscle fibres and its conductance exhibits an anomalous dependence on extracellular K⁺ concentration. Reduced K_{ATP} channel expression has already been shown in some patients with HypoPP⁵². We will ask if this is a general phenomenon and whether it depends on the nature of the gating-pore or other mutations. This work will improve pathophysiological understanding and may create druggable opportunities to test in genotyped patients.

Mechanisms of muscle degeneration in channelopathies (MH, MD): most patients with muscle channelopathies develop a severe myopathy but the mechanism is unknown and there is no treatment. We suspect calcium physiology is detrimentally altered by aberrant membrane excitability and there may be druggable opportunities. By extensively characterising the calcium physiology of cultured myoblasts from healthy human controls and biobank myoblasts from genotyped individuals with muscle channelopathies, and by evaluating calcium physiology in mouse models, we aim to identify new pathways implicated in channel myopathy. We have access to a knock-in mouse model of hyperkalemic periodic paralysis (Scn4a¹⁵⁹²) which has already shown a beneficial role of increased extracellular calcium and detrimental role of impairment of the sodium/potassium pump in myopathy development⁵³. We will also study mouse models of HypoPP caused by mutations of CACNA1S (Cacna1s¹²³⁹, Cacna1s⁵²⁸). We will compare the calcium handling of cultured myoblasts from this mouse with those of genotyped individuals with muscle channelopathies (MRC biobank) and healthy human controls. We also developed a method of studying calcium physiology in single muscle fibres, and will measure the resting [Ca²⁺], characteristics of any spontaneous [Ca²⁺] signals, and SR calcium release, which will be evoked by caffeine, by membrane depolarisation and by stimulation with acetylcholine.

Muscle channelopathies and new experimental medicine studies (MH, MK, DK): the Centre has enabled us to build a genetically stratified cohort of channelopathy patients for natural history

experimental medicine studies already delivered^{3,42,43}. Our recently completed experimental RC trial of reprofiled mexiletine established it is effective for many patients with myotonia congenita but ~30% remain drug resistant or tolerate mexiletine poorly³. Our cohort analysis has established that 50% of patients with HypoPP do not respond to carbonic anhydrase inhibitor therapy and this relates to genotype⁶. We will reprofile lacosamide, a novel anti-epileptic drug, that acts on sodium channels, and retigabine (which opens potassium channels) in genetically stratified mexiletine-resistant myotonia congenita patients. We will also test a novel KATP channel opening agent in the subgroup of acetazolamide-resistant patients with hypokalaemic periodic paralysis who have non-selective gating pore current S4 mutations. We will conduct these studies by combining our existing patient reported outcome measures (developed in the mexiletine trial^{42,43}) together with new muscle MRI biomarker secondary endpoints. Recent pilot work indicates MRI detectable reversible muscle water accumulation correlates with weakness in HypoPP patients. We will ask whether a reduction in MRI detectable muscle water is a useful surrogate marker for disease progression and treatment response.

Scientific discovery and experimental medicine plans in relation to ryanodine receptor channelopathies (FM, SR, MD): Ryanodine receptor mutations cause disabling core myopathy but the pathophysiology is unknown and there is no treatment⁴⁶. Morphological studies indicate that mitochondria are early targets in the disease but mitochondrial function has not been investigated. We have a funded programme of research to use biobank myotubes to fully evaluate mitochondrial function (see ryanodine channelopathy science programme in appendix II).

Scientific discovery and experimental medicine plans in congenital myasthenic channelopathies (HL, DB, JP FM, SR). Key areas of planned discovery i) New gene discovery next generation whole exome in families not accounted for by known genes. ii) Pathogenic mechanisms; we will establish model systems to study GFAT1 deficiency: patient material (muscle and muscle cells), down regulation of GFAT1 expression in cultured cells by siRNA and zebrafish as a GFAT1 deficient in vivo model; development of appropriate mouse models (in vivo electroporation, knock-out mice) (See appendix II).

D. Mitochondrial Diseases: discovery science and experimental medicine

NCL lead: Doug Turnbull (DT), UCL lead: Michael Hanna (MH).

Background Importance: Mitochondrial myopathies are increasingly recognised as an important cause of muscle disease. Myopathy may be isolated or be part of a multisystem disturbance in which muscle involvement is often prominent and disabling. The clinical severity varies from mild ptosis late in life to neonatal onset severe muscle weakness with respiratory failure. The underlying biochemical defect involves the mitochondrial phosphorylation system. Oxidative phosphorylation uniquely relies upon gene products of the mitochondrial and nuclear genome thus mitochondrial myopathies can be caused by mutations in either genome⁵⁴. Considerable progress has been made in improving the diagnosis and care of patients with mitochondrial myopathies at least in part by establishing the NHS Highly Specialised Services lead by Centre PIs (DT, MH) (UCL, NCL and Oxford) working closely together.

Discovery science and experimental medicine we delivered

Over the last five years we made several major advances including first completed randomised control trial¹⁴, the development of an extensive cohort of patients with accurate genotype and phenotype (MRC funded to UCL and NCL), new approaches to prevent transmission¹⁵ and significant evidence for the benefit of exercise¹³. We have therefore laid the foundations for real translational impact, and the next five years present a major opportunity to translate these advances into clinical practice by developing our experimental medicine programme, by linking with industry and performing informative trials on the stratified cohort. Our MRC support has enabled us to make considerable progress in our understanding and treatment of patients with mitochondrial disease and myopathies as highlighted in recent publications (see CVs). We would like to highlight the following areas:

- We made major insights into the pathogenesis of the mitochondrial myopathy seen in patients with HIV. This work showed that clonal expansion of pre-existing age-related somatic mtDNA mutations and a biochemical defect that can affect up to 10% of cells. These observations add weight to the role of somatic mtDNA mutations in the ageing process and raise the spectre of progressive iatrogenic mitochondrial myopathies emerging over the next decade⁵⁵.
- We pioneered new clinically relevant methods to prevent the transmission of mitochondrial myopathies and disease¹⁵. This work has important policy implications and in response the Secretary of State for Health requested the recent report from the HFEA (<http://www.hfea.gov.uk/6372.html>). This research was highlighted in the MRC Annual Review as one of the most compelling discoveries of 2010/11 by thinking about medical research challenges from a new angle (<http://perspectives.mrc.ac.uk/>).

- The MRC funded studies were crucial to a successful bid to MRC/NIHR Translational Medicine Board for funding of the MRC Centre for Translational Research in NMD - Mitochondrial Disease Patient Cohort (UK). This cohort allows careful stratification of patients and helped enable the first ever large-scale randomised controlled trial in patients with mitochondrial disease¹⁴. There are 12 on-going clinical studies involving patients registered in the cohort from both UCL & NCL.
- An award of Pump-Priming translational research initiative - MRC Muscle Assessment & Training Laboratory. The support from the translational research initiative has enabled us to develop exercise as a therapy for patients with NMD. These ongoing cross-Centre exercise studies have shown that not only is there improvement in strength and oxidative metabolism, but also improvement in quality of life and no adverse effects on mitochondrial function¹³
- Our previous MRC funded work led directly to funding by the NHS Highly Specialised Services Group for a multidisciplinary clinical service for all patients with rare mitochondrial disease in the UK with the centres at UCL, NCL and Oxford. We have a leading international role in the clinical care of patients with mitochondrial disease with the development of assessment scales⁵⁶ and guidelines (http://www.mitochondrialncg.nhs.uk/newcastle_guidelines.html)
- We have led the first multinational randomised controlled trial in the treatment of a mitochondrial disorder. Licensing negotiations are currently under way with the European Medicines Agency (EMA)¹⁴.

Added value from the MRC Centre core activities: a major added value has been the close working relationship of the MRC Neuromuscular Centre and NCL University Centre for Brain Ageing and Vitality supported by the BBSRC, EPSRC, ESRC and MRC as part of the cross-council Lifelong Health and Wellbeing Initiative (Director Turnbull); and the Newcastle NIHR Biomedical Research Centre (BRC) in Ageing and Chronic Disease (Director Chinnery). Both MRC Centres and the NIHR BRC Centres have a major interest in age-related muscle disease (particularly inclusion body myositis – see appendix II) and sarcopenia, and have worked together on developing exercise programmes and have jointly held workshops exploring the role of exercise as a potential therapy for muscle disease (<http://www.cnmd.ac.uk/>) A key component of the collaborative activity has been the support of supporting meetings, workshops and both clinical and non-clinical studentships. Finally, the award of MRC Pump-Priming translational research initiative-MRC Muscle Assessment and Training Laboratory was also dependent upon the support of both the MRC Neuromuscular Centre, NIHR BRC and Centre for Brain Ageing and Vitality.

New mitochondrial discovery science and experimental medicine studies

Our proposed studies are dependent upon core areas of support provided by the MRC Centre – the Biobank, MRC Mitochondrial Disease Cohort UK and exercise facilities at NCL and UCL.

Why is muscle so prominently involved in mitochondrial DNA disease? One intriguing aspect of mtDNA disease is the observation that muscle is the most severely or only affected tissue in patients with some mtDNA mutations^{57,58}. This observation is particularly intriguing because we know at least some of these mutations are present in the oocyte since low levels of the mutation are present in the monozygotic twin⁵⁹. We will use the clinical data present in the MRC Mitochondrial Disease Cohort and the type and degree of heteroplasmy of individual mtDNA mutations. In addition, we will explore the presence of mutations in muscle satellite cells and other tissues from the patients. Our hypothesis is that those mutations which are lost rapidly from satellite cells are those which should segregate most specifically to post-mitotic muscle.

Why do patients with mitochondrial myopathies get worse? Disease progression is often associated with progressive muscle involvement. Previous studies analysed repeat biopsies from a limited number of patients and suggested the mechanism of progression may depend on the particular mtDNA mutation. In some patients there is increased mtDNA mutation load whereas in others there is decreased mtDNA copy number^{57,60,61}. We will re-biopsy patients with different mtDNA mutations in whom we have detailed information on their clinical progression. We will determine the biochemical defect in individual muscle fibres, assess mtDNA mutation load and mtDNA copy number to explore the molecular mechanisms involved in progression for a number of specific mtDNA mutations, determining why these parameters change with time, by correlating the mtDNA changes with the associated respiratory chain deficiency in individual muscle fibres. These studies will provide crucial information on possible therapies since approaches which increase mtDNA copy number (e.g. exercise), could be an effective for some, but not all patients. These investigations will lead to planned intervention studies in stratified patient groups.

What is the response of mitochondrial myopathy patients' muscle to exercise? Several previous studies, including our own, have shown that exercise is beneficial for patients with mitochondrial myopathies¹³. The molecular studies on muscle biopsies have predominantly been limited to exploring

mutation load and copy number whilst there is considerable opportunity to explore the molecular mechanisms which will guide the type of training for individuals. We will use muscle biopsy samples, available in the MRC Biobank, to explore the molecular mechanisms in individual muscle fibres using both new biochemical techniques and RNA profiling^{62,63} of muscle fibres. These studies will link directly to the results of the exercise studies available for each individual patient.

Do licensed drugs known to induce mitochondrial biogenesis improve muscle strength and quality of life in mitochondrial myopathy? Emerging evidence from animal models has shown the effect of sirtuins, bezafibrate and rosiglitazone on mitochondrial biogenesis in healthy animals and animals with a tissue specific defect of oxidative phosphorylation. There is limited human data. We will carry out the first placebo-controlled studies of these drugs, evaluating the cellular and biochemical consequences of the drugs, and the clinical consequences of the drugs in terms of muscle and cardiac function, and quality of life. We will also study the way that these treatments interact with exercise. This work will translate some of our earlier studies into clinical practice, and shape the treatment of these disorders in the short-to-medium term future.

Is muscle regeneration a realistic option for patients with mitochondrial myopathies? For a group of patients with mitochondrial myopathies due to sporadic mtDNA disease, the causative mutation is present at high levels in mature muscle, but surprisingly at very low levels or absent in myoblasts from the same patient⁵⁹. Recent studies by MRC funded students have shown that in patients with sporadic large-scale single deletions, the mutation load is similar between satellite cells and mature muscle, but in some patients the mutation is lost rapidly during culture, whilst in others the loss is much slower. However, in all patients the level in replicating cells falls, and this may allow an opportunity for regenerating muscle to lower the level of mutated mtDNA in muscle. We will develop these studies by careful analysis of muscle biopsies from patients who have undertaken resistance exercise training, looking specifically at correlation of the amount of regeneration with mutation load.

4. Training Plans

Education, training and capacity building are major components of the MRC Centre. Our overarching aim is to build a community of translational research students, integrated between both sites and with existing Wellcome and NIHR funded-programmes, and create a self-supporting critical mass of talented future basic and clinical NMD scientists.

Overview: The key strategic training aim was to develop a four-year basic science and a three-year clinical science translational PhD programme to address the severe lack of capacity in the NMD field. We successfully developed and implemented both programmes (details of programmes, recruitment and metrics in appendix III). We delivered the original training strategy and met all objectives.

Recruitment: Eight MRC funded students were recruited to the four-year programme and two students to the clinical science programme (full details in appendix III). Given the huge demand (~forty applicants per post) we sought additional funds to enable more students to enter the programme. We recruited five additional basic science PhD students funded by other sources. For example our strong links with patient organisations enabled some PhD student funding. The training and educational activities of the MRC Centre have been extremely popular and include seminars, web-seminars, workshops and the flagship annual MRC Centre translational science conference (<http://www.cnmd.ac.uk/>).

People Development and Mentoring: The PhD programmes are jointly delivered between UCL and NCL with a clear focus on translational research. The first four students in the four-year basic science programme have now all submitted their PhDs. The final four students are on target to finish and submit in 2012. The details of the programmes, the supervision/mentoring arrangements and the appointed students and their project titles are given in appendix III. The unique feature of this PhD programme is that during the first six-week induction, the students attend clinics to see patients and had a series of lectures focused on NMD. Following induction, in the first year at UCL, the students rotated three-monthly through three PI laboratories of their choice. Following this rotation the students select their preferred project for their PhD. In the first year in NCL, the students undertake an MRes in Medical and Molecular Biosciences This is a one-year, full-time programme and provides a broad-based training in contemporary molecular biomedical sciences (details appendix III). Following the MRes students commence a three-year PhD project. The two students in the three-year clinical PhD programme undertook either a laboratory or clinical translational (e.g. development of MRI) project together with a significant clinical component (e.g. clinical trial, natural history study). All students are encouraged to attend the multiple scientific educational opportunities in the Centre (developed for all members, senior and junior in the Centre) during their PhD (details; appendix III) including the annual UK Neuromuscular Translational Conference, an annual dedicated neuromuscular clinical update course, monthly MRC

seminar series invited international speakers (also available as web-seminars), regular journal clubs, departmental research meetings and seminars, subject specific workshops and conferences. In addition, the students organised and ran very successful yearly science retreats (<http://www.cnmd.ac.uk/>). Trainee next destination is in appendix III.

Active Partnering with Stakeholders: the Centre successfully linked with both host universities to strengthen the training programmes. The links include both UCL and NCL students joining a week-long NMD module of the UCL Institute of Neurology MSc in Clinical Neurosciences. In addition, in Newcastle, students successfully joined the MRes in Medical and Molecular Biosciences as the first year of the four-year PhD programme. Strong links between the Centre and the host NHS Trusts enabled the basic science students to attend NMD clinics in the introductory six weeks in year one of the four-year programme. The expansion of the programme to include students funded by other sources e.g. MRC and Wellcome training fellowships, MDC, fellows from the NIH funded RDCRC, has greatly strengthened the training programmes. *Throughout the programme students frequently have opportunities to meet and be inspired by patients and families in order to understand the real impact of NMD on patients' lives.*

Strategic Capacity Building: the lack of capacity of trained UK NMD basic and clinical scientists was the major driver for developing this programme. The MRC funding has enabled us to train four basic science PhD students and one clinical scientist (with five more being trained). We are proud that all five students who completed the programme have continued as postdoctoral or clinical scientists in NMD.

Evaluation and Feedback: very positive feedback indicates we developed a successful and popular PhD programme. We will continually improve the programme as follows:

1) Align PhD programme projects: with the five disease themes, as they have the largest critical mass of world class expertise and the most imminent translational potential.

2) Link MRC Centre PhD students with new training opportunities: that are now available across UCL and NCL. These include a) a new UCL four-year clinical neurosciences modular PhD programme; b) the Wellcome Trust funded PhD programme in Translational Medicine and Therapeutics (Chinnery) in NCL; c) the NCL NIHR Training School developed through the NCL Biomedical Research Centre (Chinnery, BRC Director, Turnbull Theme lead); and c) the Wellcome Centre for Mitochondrial Disease in NCL (Turnbull, Chinnery, Taylor). NCL has developed MRes modules with taught programmes in translational medicine, clinical pharmacology, regenerative medicine, and mitochondrial medicine. Several modules are already delivered by e-learning. We will enable all students across both sites to share all educational opportunities including live web.

3). Build on the success of the Wellcome programme in Translational Medicine and Therapeutics.

We will consolidate links with industry through industrial placements and industry-shared training programmes. The NCL MRes module on therapeutics includes webcasts by industrial partners, which will be available to all UCL and NCL students. GSK have agreed to fund two CASE PhD studentships in MRI studies (see MRI theme in appendix II).

4). One year post CCST translational fellowships. There is a need to offer one-year translational fellowships to senior clinical trainees e.g. post-CCST. This is particularly important for trainees wishing to pursue a clinical translational NMD career (e.g. in clinical trials) and who will contribute to future UK trials networks. MR leads a European TREAT-NMD group that developed an NMD advanced fellowship now offered in the Centre (appendix III). We are not requesting MRC funding for this programme, but these trainees do benefit significantly from the Centre's educational and translational environment.

Future Plans: We intend to increase the capacity of our PhD programmes. We request MRC funding for nine PhD students to enter the four-year programme and have agreement for 1-1 host matched funding. GSK have agreed to provide two CASE PhD studentships for MRI development. We request MRC funding for two three-year clinical PhD students (one UCL, one NCL), also host-matched. In order for more clinician scientists to be trained in translational medicine we devised a brand new one year clinical science "pump priming" programme to allow very talented clinical trainees one year to obtain pilot data before applying for MRC training fellowships. We request four MRC "pump-prime" fellowships which will be host-matched.

5. Institutional commitment

Host institution commitment letters from UCL Provost and NCL Vice Chancellor attached as appendix I.

6. Management

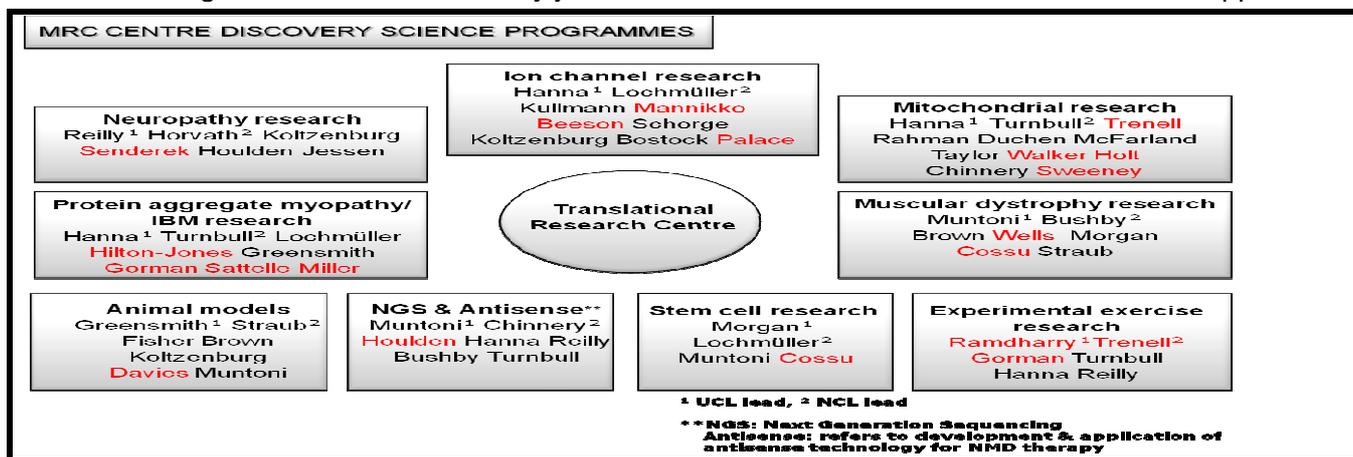
The Director had full institutional support and direct access to senior colleagues in both universities. At UCL, MH meets regularly with Alan Thompson, Dean of the Faculty of Brain Sciences. In NCL, KB & DT meet regularly with Chris Day, Pro-Vice Chancellor & Provost of Medical Sciences. This strong support

and clear alignment with host mission is reflected by the substantial 1-1 matching support (>£3.6m direct & indirect costs). We developed an effective and collegiate Centre management structure. This structure ensures delivery of key management functions: **operational, oversight, involvement, scientific & strategic**. The Director chairs a monthly steering committee in which UCL & NCL colleagues consider an agenda including standing items on each core translational activity. All meetings are minuted, are face to face whenever possible, or teleconferences. This format has proved an effective and productive mechanism to ensure efficient **operational** Centre running; ensures peer colleague **oversight** including allocation of resources and enables **strategic** planning. A particular strength of the NCL-UCL team is our extensive global reach (e.g. Turnbull: European & USA mitochondrial initiatives; Bushby-Straub-Muntoni: TREAT-NMD European network of excellence; Hanna: NIH consortium for channelopathies, North American Muscle Study Group scientific member, chairman British Myology Society, NIH NeuroNEXT links; Reilly: NIH genetic neuropathy consortium) ensuring an international dimension to strategy & regarding opportunity and influence. **Public/patient/science community involvement**: the steering committee successfully delivered the largest UK annual NMD translational research conference with the biggest UK patient organisation & Centre project partner—the Muscular Dystrophy Campaign and a series of successful patient & patient organisation days (<http://www.cnmd.ac.uk/>). The four annual meetings attracted >1200 delegates and rotated between UCL, NCL, Oxford. To ensure rigorous independent **scientific** review we established an international SAB including some of the most highly respected NMD world experts. The SAB visited the Centre three times to review science & translational delivery (see two detailed SAB reports appendix III & <http://www.cnmd.ac.uk/>). In the renewed Centre, the Director (Hanna) will work closely with five senior Co-Directors (UCL Co-Directors: Muntoni, Reilly, Koltzenburg, NCL Co-Directors: Bushby, Turnbull). See simple management diagram below:



7. Overview of Centre scientists contributing to the Centre's key research themes

In addition to previously attracting world class scientists (Muntoni, Morgan, Hughes, Lochmüller), two new eminent scientists will join the Centre in renewal: Giulio Cossu, muscle stem cell expert at UCL and Jan Senderek, a neuropathy expert at NCL. The Centre has critical mass of scientific and translational expertise in each disease-themed area. We have expertise in each new therapy theme (antisense, stem cells, exercise). In addition, new UCL, Kings, Newcastle, Manchester, Oxford and Cambridge collaborators have joined. Diagram illustrates the scientists that contribute to each of the disease themes. Investigators in red have recently joined. Centre PI CV's & science theme details in appendix II.



8. Evidence of outputs and outcomes

The MRC Centre has met the agreed objectives/metrics in relation to each of the core areas (see full pdf at <http://www.cnmd.ac.uk/>): **1.Neuromuscular trials:** we delivered a marked increase in natural history studies and experimental trials from n=3 to n>30. We tested new experimental therapies in man: antisense in DMD, heat shock protein upregulation in IBM, exercise therapy and idebenone in mitochondrial disease, mexilitine in muscle channelopathies & vitamin C in CMT1A, & published in high impact journals e.g.: Brain, Neurology, Lancet, Lancet Neurology^{1,3,10,12,13,14}. Patients in trials of new therapies has risen from n=29 to n>200 & we recruited >2000 patients into stratified cohorts. MRC experimental trials coordinators were crucial in supporting these significant increases & ensuring our very high success in recruiting of other centres world-wide (see SAB comments appendix). **2.Neuromuscular biobank:** we established a national MRC biobank of nerve and muscle tissues available to scientists which has added value to discovery science and preclinical testing of therapies (e.g. antisense in DMD). We far exceeded the original sample target (target 550 samples; achieved >1870). We provided cell lines to 53 different scientists (20 within the MRC Centre; also Europe, Japan, Australia). We have cell lines on >60 different NMD. 22 peer reviewed publications have arisen directly from biobank tissue research, and many others have used the biobank (see full publications appendix II). 5 MRC PhD student projects used the biobank (appendix II). **3.MRI Biomarker studies:** Development of NMD MRI biomarkers was a completely new initiative established by the MRC Centre. We applied qualitative MRI and developed quantitative MRI methodology in muscle/nerve: ***eight methodology techniques delivered and five new MRI patient studies delivered*** (listed in detail in section 2 above). **4.Animal studies:** we delivered on areas agreed. We established a comprehensive animal phenotyping facility that includes behavioural, histological and electrophysiological techniques. We developed novel electrophysiological assessment techniques including nerve excitability profiling and cardiac & skeletal muscle MRI. MRC investigators & PhD students used this facility. 19 peer reviewed publications in which the facility was utilised (appendix II) **5.Training and education:** all objectives/metrics delivered (appendix III). Established four-year translational research PhD programme. Successfully recruited all ten students (>40 applicants for each post). First five have submitted PhD's. **Partnerships industry:** we formed extensive industry experimental medicine partnerships to (GSK, Prosensa, Shire, Senxis, PTC, AVI). **Partnerships patient organisations:** we linked with the Muscular Dystrophy Campaign to establish the largest UK NMD translational research conference-now held four conferences >1200 delegates total. **Partnerships academic;** new links with Oxford (D.Hilton-Jones, K.Davies, M.Wood), Cambridge MRC MBU (J.Walker, I.Holt), **Public engagement:** held six Centre patient days for scientists to link with patients and families; two patient organisation days to enable links with Centre. **PI's publications:** we published > 500 peer reviewed publications 138 include more than one Centre PI. Centre PI's attract >£60m grant funding ~£14m from MRC. **Reputation:** MRC Centre has established an international reputation for translational experimental NMD research with global links (see SAB comments "*arguably the leading Centre in the world for experimental NMD*"). **Developing resources:** we developed a biobank, an animal phenotyping facility, a translational PhD programme, national visible leadership, a network of clinicians for trials (British Myology Society) and national stratified cohorts for personalised medicine and a NMD MRI platform. **Technologies:** we have systematically applied MRI and developed it as a biomarker and outcome measure in NMD-NIH now using our protocol. The proposed SMART metrics for the next funding period are listed in table below:

	Metric	Baseline	Target	How Outputs Measured	Qualitative outcomes
Resource generation					
1	Numbers of samples biobanked and distributed	1800	3000	Six monthly reporting of metrics and publication in annual report	High impact publications based on work utilising biobank samples
2	Numbers of patients enrolled in NMD cohorts	2000	3000	Six monthly reporting of metrics and publication in annual report	Patient availability for studies, greater patient engagement

3	Validated MR clinical endpoints for trials	8	16	Numbers of patients enrolled in MR studies of clinical outcomes annually	Publications, SOPs for MR evaluation, adoption as trial outcomes
4	Numbers of students enrolled in MRC training programme	9	18	Annual returns, time to PhD completion	Availability of highly trained cohort of scientists
5	Attendees at MRC conference, workshops and seminars	250pa	300pa	Numbers of participants, participant feedback, web hits on podcasts	Greater engagement of NMD clinical and academic community
6	Numbers of additional centres contributing to biobanks, cohorts, trials	0	2	Numbers of samples and patients reported six monthly and annual report	Greater engagement of NMD clinicians, patients
7	New high level science recruitment to MRC centre	4	6	Numbers of new staff attracted to MRC Centre	Greater critical mass
8	Number of industry partnerships	5	10	Numbers of industry contacts and contracts	Greater industry involvement in NMD
Know how					
9	Number of experimental medicine studies initiated	16	20	Numbers of orphan drugs associated to centres, trials initiated	Proof of principle studies completed, high impact publications
10	Number of new genes identified and classified	6	24	Numbers of new disease genes collected annually	Publications, new disease targets for therapies
11	New targets for antisense therapy in NMD	1	2	Numbers of experimental antisense studies annually	Grants, publications, new clinical studies
12	Initiation of a clinical study for stem cell therapy in NMD	0	1	Milestones to clinical study including safety, preclinical evaluation	Proof of principle clinical study, grants, publications
13	Numbers of experimental exercise studies initiated	1	4	Numbers of patients enrolled in exercise studies annually	Understanding the role of exercise in disease and therapy
14	Overall scientific/ academic output More than one PI	135	200	Numbers of joint papers and value of grants	Increased high impact publications

	Total PI NMD output	500	600	including MRC, EU	and grant awards
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9. Communications

We delivered highly visible strategic leadership and our communication plan engaged all stakeholders including: patients/patient organisations, funders, host Universities, host NHS institutions, host biomedical research centres, UK NMD clinicians and scientists, international colleagues/funders and UK and EU policy makers. **Patients:** investigators in NCL and UCL have a strong record of seeking and incorporating patient and carer opinions through the MRC Centre patient and patient organisation days held regularly (<http://www.cnmd.ac.uk/>). **Funders/scientists/clinician/charities:** we have strong visible links with major UK charities including the Muscular Dystrophy Campaign (MDC)-a project partner. We established the largest UK neuromuscular translational research science conference in partnership with the MDC. There have been four very successful conferences rotating nationally (UCL, NCL, Oxford) attended by 250-300 scientific delegates. **National clinician networks;** we established the British Myology Society; a UK network of NMD clinicians linked to trials and cohort building (<http://www.cnmd.ac.uk/>). **Policy makers:** we achieved the first NICE accreditation for NMD (DMD) and highlighted standards of care are improved within experimental trials. We are fully engaged with NHS commissioners and lead nationally commissioned NMD services and have direct links into EU policy making (KB). We link with UCL and MRC media offices as appropriate. (see <http://www.bbc.co.uk/news/health-16004112>) and (www.mitochondrialncg.nhs.uk/newcastle_index.html).

10. Exploitation

Our discoveries may include new mechanisms/genes/molecules, new diagnostics and new treatments and could create IP issues. Advice from UCL and NCL IP expertise will be sought early. UCL Business PLC manages the IP portfolio of UCL and provides a senior business manager (Chris Loryman c.loryman@uclb.com) to cover the commercial activities with an additional legal/commercial support team. In NCL there are specific links with the university commercial enterprise team and the senior manager contact for the MRC Centre is Martin Cox (martin.cox@ncl.ac.uk).

11. Ethics

All patient-related research will be done in full accordance with REC approval & in line with NCL & UCL R&D governance. Data Protection Preservation for sharing will be done according to MRC and OECD (www.oecd.org). All research/education is within clear governance framework of host universities/NHS organisations. All animal activities are undertaken in accordance with Home Office regulations. Ethical and clinical governance issues relating to biobank comply with UK and EU regulations. This Biobank is already linked to Eurobiobank: (http://www.eurobiobank.org/en/information/info_institut.htm).

12. Resources

The Centre mission is fully aligned with the experimental and translational mission of the host universities. Substantial new grant success, patient impact and publication output metrics of the Centre enabled us to make a strong case for host 1-1 matching with the MRC support requested. We request £3.3m from the MRC which will be more than matched by brand new host support totalling £3.6m, plus recruitment of Giulio Cossu to UCL and Jan Senderek to NCL. **Justification for MRC resources requested:** resources requested are specifically targeted to support and accelerate the core translational activities of the Centre which underpin the two over-riding Centre deliverables: **1. Increased scientific “know-how” in the area of NMD translational research and in particular the delivery of experimental medicine studies and new gene discovery, and 2. Resource generation to extend the tools which enhance UK competitiveness in this field by the embedding of a trial culture for UK NMD patients.** In renewal we are not requesting specific MRC support for animal model work which will be supported by other funded programmes of PI research. We established a successful core phenotyping facility with previous MRC Centre support which will continue to add value to Centre investigators work linked to MRC Harwell and Neuromouse consortium. We request support for innovative new workshops to encourage “cross-talk” between animal and clinical NMD scientists which we believe will add new value to existing MRC-animal work investments. **Core activities 1 & 2: Experimental medicine stratified cohorts and experimental trial co-ordination.** Two experimental medicine coordinator posts are requested from the MRC and these will be matched by host support. Each sister-site of the Centre will have two staff to ensure maintenance and development of the stratified cohorts and to ensure rapid trial design, protocol development and initiation and delivery of complex

experimental trials in children and adults. It is important to note that the rigour which stratified cohorts and experimental medicine studies require for regulatory approval and ongoing assessment to ensure compliance with regulations, and scientific excellence is high. Such studies cannot be initiated and completed without full-time dedicated support over the next five-year period. The work underpinning any given study may take months to deliver and ongoing vigilance and reporting requirements are also major complex tasks. Given the specific complexity of the studies in relation to first in man delivery and data quality for the cohort collections, dedicated support is essential in this area. These posts for five years each are critical for delivering the central mission of the Centre. Such important underpinning posts are not eligible for funding from other external sources. We have used these posts extremely effectively to increase experimental studies from 3 to >30 in just four years. In addition, we have maximally leveraged any NIHR host support e.g. in relation to NHS support costs for certain trials once the trials coordinators have completed all the administrative work to achieve NIHR portfolio status. However, the focus of NIHR is not experimental medicine studies in rarer diseases. The outcomes described under metrics 2, 3, 8, 9, 10, 11 & 13 depend on this MRC investment. **Core activity 3: Biobank support.** In the previous MRC Centre grant the UK NMD biobank was established and sample collection and distribution far exceeded projections, underpinning many high profile scientific publications and grant awards. In renewal we are extending the scope of the biobank towards generation of iPS cells and collection and distribution of samples to increased numbers of centres (metric 6). The biobank underpins a range of activities relating to metrics 1, 6, 9, 10, 11 and 12 and is also attracts industry links (metric 8). We request two biobank positions from the MRC matched by the hosts. This will provide two posts each at UCL and NCL to support existing burgeoning core activities and new developments (section 2 above). **Core activity 4: MRI Biomarker support.** The Centre is leading internationally in the generation of NMD MRI outcomes and the physics expertise underpinning this is essential to deliver metrics 3, 9 & 13. There is a real prospect that Centre-developed quantitative MRI sequences will become the standard outcome in NMD experimental medicine studies and we can consolidate an international leadership position. We request one physicist from the MRC matched by host support. MRI scan-time requested from MRC has been minimised. **Core activity 5. PhD students and training programmes.** The Centre PhD programme has been highly regarded and has generated new skilled scientists with 100% completion rates. We had >40 applicants for every post. We want to expand student numbers working in key scientific areas of the Centre, advance scientific “know-how” and provide the next generation of scientists. The PhD students through their work, enthusiasm and dynamism contribute to all deliverable metrics directly or indirectly. We have agreement for 1-1 matching from the host which will enable us to train a total of eighteen four-year non-clinical PhD students. It is extremely important the Centre trains the future clinical translational scientists so we request two three-year clinical PhD students. In addition, we request four one-year “pump-prime” translational clinical fellowships which will allow us to train excellent applicants to obtain pilot data for a year before applying for MRC training fellowships; these will also be host matched. **Director, PI support and administrative support.** Support for 20% of the Director’s time has been requested, matched by the host, allowing MH to devote at least 40% of his time to the Centre. In NCL 5% of the time of Co-Director KB has been requested, matched by the host, reflecting the importance of the successful UCL-NCL link. Support and co-ordination of the work of the Centre by the Co-Directors is a significant role (DT, FM, MK, MR); the host is providing the other Co-Director investigator costs to deliver these tasks ensuring the Centre once again exceeds its goals and targets. The administrative support for the Centre, although pivotal for the Centre’s success, is reduced to 50% from the MRC with 50% from the host.

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iii) MRC Report following renewal site visit by MRC 2012

**Neurosciences and Mental Health Board (NMHB) review
of the MRC Centre for Neuromuscular Disease Research, University College
London and Newcastle University**

Report of the Visiting Subcommittee

Site Visit 25 April 2012

1 Purpose of the Report

The purpose of this report is to make a recommendation to the Neurosciences and Mental Health Board (NMHB) as to the justification for renewal of Centre status in light of the Subcommittee's Terms of Reference (Annex 1) and the MRC expectations of Centres (Annex 2) and provide comment in relation to:

- the performance of the Centre over the past quinquennium,
- the underpinning research strategy of the Centre and its future development,
- the request for core resources and how these will be used to strengthen the Centre's research agenda.

This report summarises the discussions and conclusions of the NMHB visiting subcommittee.

2 Subcommittee membership

Professor Hugh Perry (chair)	Centre for Biological Sciences, University of Southampton and chair of MRC NMHB
Professor John Zajicek	Institute of Health Service Research, Plymouth University and MRC NMHB
Professor Richard Reynolds	Department of Medicine, Imperial College London
Professor Charles ffrench-Constant	MRC Centre for Regenerative Medicine, The University of Edinburgh
Professor Gerald Zamponi	Department of Physiology & Pharmacology, University of Calgary
Professor Richard Griffiths	Institute of Ageing and Chronic Disease, University of Liverpool

MRC Office

Dr Rob Buckle	NMHB Head of Theme
Dr Joanna Robinson	NMHB Programme Manager
Mr Tom Trehwella	MRC Reviews Team, administrative support
Ms Kerry O'Brien	MRC Reviews Team, observer

3 Declarations of Interest

Professor Charles ffrench-Constant declared that he was Director of the MRC Centre for Regenerative Medicine, University of Edinburgh, which will have future funding bids submitted to NMHB. The Subcommittee agreed that this did not represent a significant conflict of interest.

4 Introduction

The purpose of the site visit was to review the Centre status of the MRC Centre for Neuromuscular Disease Research (CNMD), which was seeking to continue MRC funding for a further five years. Current MRC policy guidelines are that Centre funding is normally time-limited to ten years.

The **CNMD** was set up in 2008 as a 'translational' Centre under the directorship of Professor Mike Hanna in response to an MRC call in 2006 to strengthen translational research. It is based across two sites (UCL and Newcastle), with the deputy director Professor Kate Bushby based in Newcastle, and also has strong affiliations to the MRC Functional Genomics Unit in Oxford and the MRC Mitochondrial Biology Unit in Cambridge.

The current Centre grant award for £2.60 million is due to end on 31 December 2012. The application for renewal of the CNMD for the next quinquennium requests a total of £3.38 million (80% MRC contribution). This application as a whole will be discussed by NMHB at its meeting in July 2012, together with the recommendations of this report.

The agenda for the site visit to University College London (UCL) can be found at [Annex 3](#). The visit provided an opportunity for the Subcommittee to meet with the Director and other members of the Centre to explore issues arising from the renewal application. The Subcommittee did not re-assess the quality of individual scientific research programmes, but evaluated how the Centre had performed against performance milestones over the past quinquennium and whether the Centre continued to meet the MRC criteria for Centre funding.

Summarised below are the conclusions and recommendations of the Subcommittee following the site visit. A summary of these conclusions was relayed to the Director and confirmed in writing at the end of the site visit.

5 Overall Assessment

The Subcommittee agreed that there was a strong strategic rationale for continuing investment in the CNMD for a further 5 years to allow the Centre to establish a national experimental medicine network in NMD by 2017. The Subcommittee recognised the strong institutional support being offered and was particularly supportive of Centre's plan to continue building upon its NMD cohorts, with a view to fully exploiting these genetically stratified cohorts in conjunction with biobanked materials to provide mechanistic understanding of NMD and develop new interventions.

The Subcommittee considered that more thought was required regarding certain aspects of the Centre renewal, in particular the validation of new MRI techniques and development of other surrogate biomarkers, as well as the development of better clinical outcome measures. While supportive of the training environment and complimentary of the training achieved to date, the Subcommittee did not consider that the balance between basic and clinical training proposed under the current bid was optimal. Similarly, while supportive overall for the development of biobank activities, the Subcommittee did not support the employment of the two requested post-docs and recommended a single biobank manager to oversee the proposed work. For a more detailed summary of the recommendations of the Subcommittee, see Section 7.

In light of the recommended changes, the Subcommittee requested that a revised budget plan be submitted to the Neuroscience and Mental Health Board reflecting their recommendations on training and biobank resourcing. In doing so, it was considered that some savings could be achieved to increase the value for money of the proposed Centre renewal, reducing the amount requested from MRC at 80% full economic cost to under £3 million.

Subject to these recommendations being incorporated by the Director, the Subcommittee recommended a score of **9** to the Board in recognition of the excellent quality of the

Centre, which it considered to be internationally competitive and leading edge in most areas.

6 Summary of the site visit

6.1 Past achievements and future strategic direction

Professor Hanna provided an overview of the Centre's vision, objectives and strategic need, outlining that the Centre would consist of five core areas of research (ion channels, mitochondria, neuropathy, inclusion body myositis and muscular dystrophy). All areas would be supported by the necessary critical mass of discovery science and infrastructure, including genetically stratified cohorts, biobanked materials, animal models and MRI biomarkers, and would be supported by training activities. Having delivered and exceeded its milestones of the first quinquennium - where, for example, patient enrolment in clinical NMD studies had increased dramatically since 2006 - the next phase of the Centre would further develop its existing activities with the aim of securing and embedding a national capability for experimental medicine in NMD by 2017.

Following Professor Hanna's presentation, the Subcommittee sought clarification on what new aspects were to be added in the next phase of the Centre. Professor Hanna explained that, as the tools for the research had now been developed, the Centre planned to move into new experimental medicine studies with matched host support in areas such as stem cell research in dystrophy, systematic development of exercise therapy and patient stratification for personalised medicine using next generation sequencing. Continued development of the application of MRI to NMD was also envisaged. Ultimately, following 10 years of Centre support, the vision would be for the Centre's work to become fully embedded within its host universities of UCL and Newcastle University such that it could continue in a self-sustaining manner.

Professor Hanna also clarified that clinical outcome measures, which are needed in addition to the planned surrogate outcome measures, are being developed in harmony with the existing clinical cohorts, with Centre PIs often leading an international effort in this area across rare diseases.

The Subcommittee asked how the Centre's 'national' strategy was being promoted, and with what degree of linkage to other institutions. Prof Hanna explained that, in the first funding period, the Centre had established national networks to facilitate recruitment of patients with neuromuscular diseases. They had also successfully established the twin site centre with UCL and Newcastle and were now cultivating increasing links to Cambridge's MRC Mitochondrial Biology Unit and Oxford's MRC Functional Genomics Unit. National networking was further encouraged by the annual NMD conference established by the Centre.

The biobank established by the Centre is also a national resource, with 1800 cell lines distributed to over 60 research groups during the previous funding period. The biobank is part of an EU network and available samples are listed online to facilitate the sharing of this resource nationally and internationally. For the future it is intended to establish immortalised muscle cell cultures within the biobank. The Centre had requested two post-doctoral positions as part of the biobank resource to support cell line development, preclinical assessment of patients in trials, back translational approaches, technical support and advice to other labs using cell lines. The Subcommittee questioned whether these were the most suitable roles for early career scientists in post-doctoral positions.

Further information was sought regarding the Centre's vision for a national pathway for treatment. Professor Hanna explained that the Centre envisaged neuromuscular disease needs being delivered through a network of regional clinical centres, but that Centre members were also inputting into guidance of standards of care at a national level, with a 'national definition set' of NMD recently established. Frameworks and guidance published by Prof Bushby had been NICE accredited. It is hoped that this momentum will lead the new National Commissioning Board to address NMD in the near future.

The Subcommittee requested some more information about the Centre's plans for the use of stem cells. Current effort focuses on identifying stem cell populations, modifying marker cells and attempting ex-vivo autologous transplantation. New expertise in this area had been acquired through the recruitment of Professor Giulio Cossu, who joined the Centre in 2012, and who had already established a progenitor phase I trial in Milan. He had also recently been awarded an MRC translational stem cell research grant to develop a novel cell therapy for Duchene Muscular Dystrophy (DMD) based upon transplantation of autologous mesoangioblasts engineered with a human artificial chromosome vector.

When questioned about their plans for the use of iPSC technologies, Centre members responded that a selective approach would be pursued. Fibroblasts were being collected from all consenting NMD patients and added to the biobank with a view to the future creation of immortalised cell lines, and in specific areas iPSC populations had already been established, for example in collaboration with Dr Chris Denning in Nottingham who was investigating DMD-patient derived cardiomyocytes. MyoD directed differentiation approaches were also being investigated. Most stem cell activity was to be funded through other grants and the Centre had not developed a strategic approach towards this area at present. The Subcommittee commented that the Centre was currently being too cautious in this area, which could present a major opportunity.

6.2 University strategy and commitment to the Centre; partnership with MRC and other stakeholders.

Professor Sir John Tooke and Professor Nick Wright provided an overview of the Centre's fit within the host institutions of UCL and Newcastle University respectively. UCL is organised into four faculties with cross-cutting domains, of which experimental medicine and neuroscience are of relevance to the Centre. Newcastle also incorporates two strategic themes which are of relevance to the Centre: ageing and health as well as societal challenges.

Both institutions expressed strong support for the Centre and, as submitted, planned to provide £3.6million in matched funding to support the Centre over the next five years (see Table 1, page 10). The Subcommittee asked how host support would change should the grant be re-configured following the Centre review. Both institutions stated that they were willing to consider any option which would strengthen the Centre and would consider re-configuring their support within the envelope of £3.6million offered.

A further area of discussion concerned linkage to bioindustry and the IP arrangements between institutions. To date, industry involvement has been pursued where scientific opportunities had arisen, e.g. in MRI and antisense technology. The institutions do not currently have a formal agreement concerning IP opportunities arising from the Centre, and were of the opinion that, while a formalised framework should be considered, the strong working relationships between the host universities may provide a more flexible basis for industry involvement than a complex formal IP agreement.

Mr Robert Meadowcroft, Chief Executive of the Muscular Dystrophy Campaign (MDC), then presented how the Centre is working with his charity and the NHS to provide a national plan and service standards in this disease area. Evidence of the success of this partnership is the NICE accreditation achieved by Professor Kate Bushby concerning framework and guidance for NMD. In support of the Centre, MDC provides project grants and PhD support, as well as some support for trial coordination for the Centre. In partnership with the Centre, MDC also organises patient information days to ensure the outcomes of the research are effectively communicated to patients.

6.3 Impact of Centre funding on delivery and future development of the science

The following key research theme leaders provided short presentations:

i) Professors Mutoni, Matthews and Bushby: Muscular Dystrophy

Professors Mutoni, Matthews and Bushby presented the Centre's approaches for translational research in Muscular Dystrophy. During the past quinquennium, multidisciplinary collaborations across the Centre had developed antisense oligonucleotide approaches to skipping exon 51 in DMD, leading to a phase IIa clinical study. New approaches as part of the Centre renewal were outlined to include: 1) further studies in collaboration with industry investigating the benefits of antisense oligonucleotides; 2) exploring the possibility of lentiviral stem cell delivery to single human muscle cells; 3) the use of human artificial chromosomes to repair muscle and 4) developing non-invasive biomarkers, in the form of MRI.

The goal of these projects will be to gain better mechanistic understanding of antisense oligonucleotide therapy through back translation and to use stratified medicine approaches to investigate treatment responses and to identify new genetic or pathway targets for treatment. The projects will rely on the Centre's existing and continuing infrastructure, specifically the biobank resource and the stratified cohorts established during the first quinquennium.

The Subcommittee questioned whether there would be challenges in establishing bespoke treatments for specific NMD subtypes due to the differences in local tissue environment surrounding the treatment area. Centre PIs explained that changes in inflammatory state had not been found so far, however, it was accepted that any regenerative approaches were likely to be very variable depending on the local environment or 'niche'.

The Subcommittee sought further clarification on how the existing cohorts could best be used to test antisense oligonucleotides, as these are a highly personalised treatment method within an already rare disease. The Centre PIs provided reassurance that, due to the registered information within the North-Star cohort, patients with the appropriate genotype and disease severity could be selected and that, in the future, there would be the opportunity to create a national screening programme to intervene at the earliest points of the disease.

Finally, further clarification was requested with regard to the challenge of using MRI to measure muscle, as this appeared to be more difficult than in MRI measurements of brain tissue. One challenge, which applies to both MRI of muscle and brain, is the harmonisation of studies across multiple centres. The main other challenge for MRI measurement of muscle is accurate quantitative measurement. As muscle has a more variable individual anatomy than the brain, it is more difficult to measure quantitatively, and such measures are unable to distinguish intracellular from extracellular water. A future opportunity will be the use of sodium imaging, planned in partnership with Oxford, which might also allow the assessment of changes at pre-symptomatic stages. In response to the Subcommittee's questions about longitudinal data for MRI measures, they were informed that some longitudinal MRI data is available for juvenile DMD patients, but not across major cohorts.

ii) Professor Kullmann: Channelopathies

Professor Kullmann highlighted that the Queen's Square site provides a referral centre for muscle channelopathies for the whole of the UK, providing clinical assessment, diagnosis, clinical neurophysiology, genetics, functional expression and treatments. The cohort established through this service includes over 1,600 patients and is therefore the largest cohort in this area worldwide. This patient database allows stratification according to the ion channel genotype and has allowed recruitment of patients to the clinical trials of Mexiletine for Myotonia.

The main impact of the Centre for this area of work has been the clinical trials as well as the dialogue with cohorts to drive new hypotheses. While the biobank has provided some support to this area in the past, this is expected to increase in the future.

When asked about what new questions this area of the Centre intends to address in the next funding period, Professor Kullmann spoke of plans to investigate the mechanisms of

paralysis, the assessment of new drugs and to study the molecular dynamics of ion channels in the diseases.

The Subcommittee questioned whether the development of new methods in this area was planned for the renewal period. Professor Kullmann explained that they had very recently implemented muscle cell recordings and were planning to develop new MRI techniques and scanning ion conductance microscopy. Asked about plans to implement medium to high throughput screening, he replied that there were no current plans for high-throughput screening of small molecules. Rather, the Centre planned to take a more hypothesis driven approach using molecular dynamic modelling. Following evidence from epilepsy concerning spliced isoforms, there are also plans to consider the role of spliced receptor types. Work on calcium channels has recently been published and these will now be considered in new cell models.

iii) Professor Turnbull: Mitochondrial myopathies

Professor Doug Turnbull provided an overview of past achievements and future plans in the area of mitochondrial myopathies. Past achievements included completion of a first randomised controlled trial and gathering evidence of the benefit of exercise to treat muscle disease caused by mitochondrial myopathies.

A pump-priming award from MRC's Strategy Board had allowed the establishment of facilities to assess the benefits of exercise to treat mitochondrial diseases, with the goal of understanding why exercise is beneficial and how this could be translated into a clinical setting. Using a supplementary award from MRC for £915k, the group were able to develop a patient cohort for mitochondrial disease, which now includes 900 patients with accurate genetic and biochemical data.

In the next funding period, the group plan to investigate the involvement of muscle in mitochondrial disease, investigate why patients get worse with age and who could benefit from exercise. Licensed drugs with effects on mitochondrial biogenesis will be 're-purposed' and trialled to improve muscle strength (with new funding recently attained through the MRC Stratified Medicine Initiative) and the group will also explore the possibility of using muscle stem cells for regenerative purposes. The advent of next generation sequencing technologies will also soon allow diagnosis for the third of NMD patients without any genetic aetiology, providing future options for counselling as well as the identification of novel drug targets.

The Subcommittee sought clarification on how cohort data was acquired and stored. For the mitochondrial cohort, all data are captured UK wide and then held centrally as a resource for the wider community. This approach is now being implemented for the other NMD cohorts coordinated through the CNMD.

6.4 Training and capacity building

The Subcommittee had the opportunity to meet students from both sites during a presentation of posters on their work within the Centre, who demonstrated enthusiasm for their science and a clear sense of engagement with the Centre.

The Centre's training programme was presented by Professors Reilly and Chinnery, who outlined the Centre's ambition to ensure all NMD centres across the UK have the capacity to participate in clinical trials. The NMD clinical community was already well connected through national conferences and academic societies, but the Centre wished to play a leading role through increasing national research capacity and by supporting the broader educational of scientists entering the field, for example through the provision of guidelines to underpin evaluations and cohort enrolment.

The submitted request for MRC training support for the new Centre included nine 4-year non-clinical PhD students, two 3-year clinical training fellowships and four 12 month

'pump-priming' clinical research fellowships. Each training position was to be matched by at least the same number of positions provided by the host Universities (see Table 1, page 10). The pump-priming fellowships were a new request, designed to encourage clinicians to consider a research career in this area.

The 4-year non-clinical PhD programme was designed to build upon existing approaches at Newcastle and UCL, where all students have three attachments in their first year before committing to a project. The placements of student rotations are designed around the core Centre theme, and each student is also supervised by an external expert. The Subcommittee questioned how the Centre ensured sufficient coverage of all relevant themes without prescribing a project to new students. The Centre's strategy involved education of new students, ensuring they were aware of the scientific and medical opportunities within each theme, and particularly in those themes requiring new students.

The Subcommittee agreed that the Centre had developed a very good training programme during the past 5 years, as exemplified by the quality of the students presenting posters, who were cognisant of the Centre's role and what it was providing. With regard to the new proposals, the Subcommittee was particularly supportive of the pump-priming approach to encourage clinical researchers in this area. However, the added value that might be provided through the request for a high number of PhD students was less clear.

6.5 Resources, facilities and management of the Centre

The Director joined the Subcommittee to discuss his aspirations and plans for the Centre over the next five years in more detail. When questioned about what will be achieved in the next 5 years, the Director summarised that the impact of the Centre should be to change clinical practice and ensure all enrolled patients have access to intervention studies as well as state of the art protocols and therapeutic development.

The Centre had been referred to as a national Centre at several points throughout the day; however, it was unclear how many institutions would be included within the Centre's work. Professor Hanna clarified that the aim was to build the Centre on the existing Newcastle-UCL collaboration but to engage Oxford and Cambridge-based researchers more fully. While the Centre PIs and studies would be concentrated in these Universities, the Centre would also aim for more comprehensive national coverage for the benefit of patients, using UK-wide inclusion of samples in the biobank, setting up clinical trial centres where necessary and ensuring that experimental medicine facilities were placed where most appropriate.

As current MRC policy expects Centres to be independent of core MRC support after 10 years of funding, the Subcommittee asked the Director about his plans for sustainability of the Centre beyond 2017. As had been mentioned by the host institutions earlier in the day, there was support from both universities to embed the Centre fully within their structures from 2017. By this point, it was anticipated that the experimental medicine tools and clinical networks would be well established.

In terms of management of the Centre, the Director explained that he employs a collegiate approach with monthly steering committees to ensure engagement across PIs. The Subcommittee expressed some concern over the Director's time commitment as he planned to spend 40% of his time on the Centre as well as holding the directorship of the UCL Institute of Neurology and undertaking his own research. The 40% commitment requested by the Director was defended on the basis of the need to driving linkage across the two Centre sites and beyond.

7 Subcommittee feedback

Following the site visit, the Subcommittee provided the following feedback to the Director:

7.1 Delivery during the current quinquennium

The Subcommittee commended the Director on his leadership of the Centre and his successful delivery of the twin-site Centre model since its inception.

The Committee agreed that the Centre had:

- made excellent progress over past five years, establishing itself as a nationally and internationally recognised focus for neuromuscular disease (NMD) research
- established valuable and unique clinical cohorts, with associated biobanking, providing a major resource for the Centre and beyond
- delivered against, and exceeded, the metrics set within the original Centre grant
- demonstrated significant leverage of other funding sources, including grant income and capital funds, to support its goals in experimental medicine
- provided added value through linkage to NMD research in Oxford and Cambridge
- established and harmonised assays and protocols across the two sites to underpin intervention studies in NMD patient groups
- had a major impact on patient enrolment in clinical trials in NMD
- catalysed the development of clinical networks nationwide
- helped to deliver a national care plan and service standards, for which the Centre was congratulated.

7.2 Future strategic direction

- The Subcommittee **supported**:
 - the vision of the Centre to establish a national experimental medicine network in NMD by 2017
 - the continued roll out of comprehensive and accessible databases to encompass all of the Centre's NMD cohorts, so that, by the end of the next funding phase, all patients' data will be prospectively captured
 - the Centre's ambition to further exploit genetically stratified cohorts, utilising biobanked material and immortalised cell lines to support back-translation for mechanistic understanding, as well as for intervention platforms.
- The Subcommittee agreed that **more consideration was needed** with regard to:
 - the validation of new MRI techniques and development of other surrogate biomarkers, e.g. using proteomics
 - the development of clinical outcome measures aligned to the specific features of the NMD cohorts being studied
 - establishing links to clinical trials units and methodological support available through these to inform experimental trial design and longer term translation to clinical impact
 - plans to build new stem cell programmes - this was considered to represent a major opportunity for the Centre over the next five years but, as presented, lacked clarity and ambition
 - whether results from proof of concept studies in rare diseases could translate to more common diseases areas, e.g. frailty
 - creating the best interface with industry and ensuring suitable IP arrangements are made with regards to multi-institutional activity
 - further developing the NMD biobank to be a long-term and fully utilised national resource.

7.3 Institutional support

- The strong level of institutional support and cross institutional integration was evident and was highly commended, as was the commitment from UCL and Newcastle to jointly support this area of work beyond the expected lifetime of the Centre.
- The Subcommittee recognised the added value provided through links with the Muscular Dystrophy Campaign, which was seen to be of benefit to both parties.

7.4 Training programme

The Subcommittee:

- agreed that the Centre had delivered a very successful training programme during its first quinquennium, and noted that the students presenting posters from both sites were very engaged and appeared to be well mentored, both scientifically and in terms of wider career advice
- was very supportive of the proposed pump-priming mechanism to encourage the best clinical trainees to enter clinical academia in this area.
- commented that the overall number of studentships to be trained at the Centre was high, taking into account the matched support being provided by the host Universities and the breadth of the overall training package requested. For comparative purposes, other Centres within the Neuroscience and Mental Health Board usually receive 2-3 students per annum in total.
- agreed that the most emphasis should be placed on encouraging clinical academics into this area of research, and was therefore not persuaded of the balance between clinical and non-clinical studentships requested.

7.5 Resources requested

The resources requested were supported with two exceptions:

- **The two post-doctoral fellows for the biobanking activities were not supported**, given that the roles did not look attractive career roles and that the research activities envisaged would be better supported through grant applications. Instead, consideration should be given to directing support to ensure delivery of a unified, national biobank, managed by the appropriate level of individual with responsibility to coordinate and promote the utilisation of this resource, e.g. by linking it to the recent investments in stem cell activities at the host institutions.
- **The training programme was not optimally configured.** The Subcommittee recommended that the investment in pump-priming awards in support of academic clinical fellows be increased at the expense of the proposed number of non-clinical studentships.

- **The Subcommittee requested that a revised budget plan be submitted to the Neuroscience and Mental Health Board reflecting the above recommendations.** In doing so it was considered that some savings could be achieved to increase the value for money of the proposed Centre renewal. The amount requested from MRC at 80% full economic cost should therefore be reduced to under £3 million in this revised budget.

The revised costings and justification are appended as Annex 4 [please, note, this will be added once submitted by the Director, expected before 25 May].

7.6 Score

In light of the above recommendations, the Subcommittee recommended a score of **9**. This recognised the excellent quality of the Centre, which was considered to be internationally competitive and leading edge in most areas.

PROTECT - PRIVATE

Matched funding provided by UCL		Matched funding provided by Newcastle University		Requested from MRC		
					100%	80%
1 Centre Director (0.2FTE)	£135,981	1 Co-Director (0.05FTE)	£29,950	1 Centre Director (0.2FTE)	£135,981	£108,785
-	-	-	-	1 Co-Director (0.05FTE)	£29,950	£23,960
2 Pump Prime Clinical Research Fellows (2FTE) 12 months each	£85,402	3 Pump Prime Clinical Research Fellows (3FTE) 12 months each	£150,993	4 Pump Prime Clinical Research Fellows (4FTE) 12 months each	£176,790	£141,433
1 Clinical Research Fellow (1FTE) 36 months	£133,863	1 Clinical Research Fellow (1FTE) 36 months	£158,092	2 Clinical Research Fellows (2FTE) 36 months each	£277,880	£222,305
1 Biobank Technician (1FTE)	£175,392	1 Biobank Technician (1FTE)	£143,092	2 Biobank Postdocs (2FTE)	£401,296	£321,037
1 MRI Physicist (1FTE)	£211,533	0.5 MRI Physicist (0.5FTE)	£97,776	1 MRI Physicist (1FTE)	£224,902	£179,922
1 Experimental Medicine Cohort Coordinator (1FTE)	£165,771	1 Experimental Medicine Cohort Coordinator (1FTE)	£192,671	2 Experimental Medicine Cohort Coordinators (2FTE)	£429,072	£343,257
0.5 Centre Administrator (0.5FTE)	£127,126	-	-	0.5 Centre Administrator (0.5FTE)	£127,126	£101,700
5 Non-clinical PhD students 48 months each	£311,800	4 Non-clinical PhD students 48 months each	£277,152	9 Non-clinical PhD students 48 months each	£675,952	£675,952 (e)
Directly Incurred Costs (PhD consumables)	£120,000	Directly Incurred Costs (PhD consumables)	£0	Directly Incurred Costs	£294,000	£235,200
Direct & Indirect Costs	£692,401	Direct & Indirect Costs	£422,757	Direct & Indirect Costs	£1,280,791	£1,024,632
Total FEC Request:	£2,159,269	Total FEC Request:	£1,472,483	Total FEC Request:	£4,053,740	£3,378,183

Table 1

Overview of funding requested as part of original application and matched funding offered by the host institutions.

Annex 1

Terms of Reference of the NMHB Subcommittee for the review of the MRC Centre for Neurodegeneration Research

1. To provide an assessment of past progress and achievement over the previous quinquennium
2. To assess and advise the Board on:
 - whether the strategic need for the Centre remains
 - the proposed Centre vision and strategy for advancement of the field, therapy, or clinical practice
 - the strength of commitment from the University and fit to University strategy
 - partnership with the MRC and other stakeholders
 - visibility of the Centre as a significant and strategic MRC investment and resource
 - impact of Centre funding on scientific delivery and development of future science and strategy
 - quality of the proposed training and plans for capacity building
 - resources and management arrangements for the Centre
 - metrics for the Centre; objectives for the next five years
 - justification for the resources requested.
3. To recommend to the Board whether Centre support for the next 5 years is justified, at what level of financial support, and the objectives to be met in the next five years.

Annex 2

MRC Expectations of Centres

MRC Centres are either:

- 1.** Internationally competitive centres of excellence, delivering a specific strategy in an area of strategic need which is of importance for UK medical research; or
- 2.** Have an explicit mission to become an internationally competitive centre of excellence with clear strategic direction in areas of importance for UK medical research within a realistic period.

MRC expects Centres to:

- be outward looking with high visibility as significant and strategic MRC investments, able to act as national or international focal points
- have dedicated commitment and investment from both partners (MRC and University)
- add value to high-quality scientific programmes that are already supported by grants from the MRC and other funders
- provide intellectually stimulating and well-resourced environments which will not only attract established researchers but will also encourage the most able young scientists to take up a career and remain in the UK
- become an International Centre of Excellence or deliver a specific strategy.
- meet a strategic need
- have a dedicated Director who is a leading, internationally renowned scientist and who will provide focussed scientific leadership and management
- demonstrate strategic impact .

Centres achieve this by:

- Providing leadership in focussed aspects of a field
- Delivering strategy in an area of importance for UK medical research, where appropriate
- Co-ordinating research projects and appointments to strengthen the scientific impact
- Creating or building on a critical mass of researchers where, together, these groupings will benefit research in a specific area
- Fostering internal and external collaborations
- Co-ordinating exceptional facilities to add value to research and training
- Engaging with the public

By the end of the agreed MRC Core Centre Grant period, the Centre should be internationally competitive and sustainable through research grant funding

Annex 3

**MRC Centre for Neuromuscular Diseases
Site Visit Agenda
Wednesday 25th April 2012**

Time	Session	Present
09:00-09:45	Private meeting of Subcommittee	Subcommittee
09:45-10:00	Session 1: Welcome and introductions	Subcommittee Centre Director Centre Senior Scientists & PIs Senior University Reps Charity Partners
10:00-10:35	Session 2: Strategic need and Centre vision, objectives and milestones Presentation [10 minutes]: Professor Michael Hanna Questions [10 minutes]	Subcommittee Centre Director Centre Senior Scientists & PIs Senior University Reps Charity Partners
10:35-11:10	Session 3: University strategy and commitment to the Centre. Partnership with MRC & other stakeholders. Visibility. Presentation [10 minutes]: Sir John Tooke, UCL Presentation [10 minutes]: Professor Nick Wright, NCL Presentation [5 minutes]: Mr Robert Meadowcroft, MDC Questions [10 minutes]	Subcommittee Centre Director Centre Senior Scientists & PIs Senior University Reps Charity Partners
11:10-11:30	Private meeting of Subcommittee	Subcommittee
11:30-12:30	Session 4: Impact of Centre funding on delivery and future development of the science Presentation [16 minutes]: Muscular Dystrophy Professors Francesco Muntoni, Kate Bushby & Paul Matthews Presentation [8 minutes]: Mitochondrial myopathies Professor Doug Turnbull Presentation [8 minutes]: Ion channel mutations of muscle and	Subcommittee Centre Director Centre Senior Scientists & PIs

	<p>nerve: mechanisms and therapeutic implications Professor Dimitri Kullmann</p> <p>Questions [30 minutes]</p>	
12:30-13:00	Private meeting of Subcommittee	Subcommittee
13:00-14:00	<p>Lunch</p> <p>Session 5:</p> <p>Poster presentations</p>	<p>Subcommittee</p> <p>PhD students</p> <p>Junior Faculty</p>
14:00-14:30	<p>Session 6:</p> <p>Training & Capacity Building</p> <p>Presentation [15 minutes]: Professors Mary Reilly and Patrick Chinnery</p> <p>Questions [15 minutes]</p>	<p>Subcommittee</p> <p>Centre Director</p> <p>Centre Senior Scientists & PIs</p>
14:30-14:50	Private meeting of Subcommittee	Subcommittee
14:50-15:30	<p>Session 7:</p> <p>Resources, facilities and management of the Centre.</p> <p>Leadership discussion with the Director.</p>	<p>Subcommittee</p> <p>Director</p>
15:30-16:00	Private meeting of Subcommittee to discuss management and resource issues, and to formulate the final conclusions and recommendations	Subcommittee
16:00	Final meeting with Director	<p>Subcommittee</p> <p>Director</p>

MRC Centre for Neuromuscular Diseases
UCL Institute of Neurology
Ground Floor, 8-11 Queen Square
London WC1N 3BG

iv) MRC Centre Antisense Strategic Application 2014

RNA therapeutics for neuromuscular disorders: An MRC Centre-MDEX Consortium partnership approach

A collaborative translational research application from the MRC Centre for Neuromuscular Diseases and the MDEX Consortium.

Key partners:

MRC Centre for Neuromuscular Diseases at UCL and NCL

UCL: Francesco Muntoni; Jenny Morgan;
Linda Greensmith; John Thornton; Tarek Yousry; Mary Reilly; Mike Hanna;
NCL: Volker Straub; Kate Bushby; Hanns Lochmüller; Steve Laval;
Doug Turnbull, Bob Lightowlers, Olliver Russel
Robert Taylor; Rita Horvath; Patrick Chinnery; Andrew Blamire;
Annemieke Aartsma-Rus (Leiden/ NCL)

MDEX Consortium (in addition to several of the members of the MRC Centre above).

Oxford: Matthew Wood; Samir El Andaloussi; Kay Davies
UCL: Steve Hart; Haiyan Zhou;
Cambridge: Mike Gait
RVC: Dominic Wells
RHUL: George Dickson

Strategic alliance and application of funding of the MRC Neuromuscular Centre and the MDEX Consortium:

This expression of interest describes the unique position in which neuromuscular translational research science is situated in UK, and the opportunities for further developments. This document summarises both the current expertise on antisense oligonucleotides (AOs) within the MDEX Consortium and the MRC Neuromuscular Centre core expertise. It also argues why a comprehensive and collaborative program of translational research between these 2 consortia, and in partnership with industry, will advance clinical science.

Why antisense oligonucleotides (AOs).

Experimental use of AOs in neuromuscular conditions is progressing very rapidly. Most of the experience is on Duchenne muscular dystrophy (DMD): in the years between 2007 and 2013 eight clinical trials using AOs to induce exon skipping in DMD have been performed and 2 more studies initiated. These trials have predominantly targeted DMD exon 51 with 2 different AO chemical backbones: the 2'OMe [*van Deutekom 2007, Goemans 2011*] and the morpholino (PMO) [*Cirak et al, 2011; Mendell 2013*]. The 2 companies involved in such trials are Prosensa, until recently in partnership with GSK for the 2'OMe chemistry targeting exon 51, 44, 45 and 53; and Sarepta Therapeutics (previously AVI, in partnership with the MDEX Consortium), currently targeting exon 51, with plans to initiate clinical trials with PMO targeting exons 50, 45 and 53. This latter effort (exon 53) is part of an EU funded consortium led by Francesco Muntoni (UCL/ and MDEX consortium, London) (<http://www.skip-nmd.eu/>).

AOs are also being used in motor neuron diseases. In 2009-2012 ISIS Pharmaceuticals performed a safety study of intrathecally delivered AOs (a methoxyethyl [MOE] modification) in amyotrophic lateral sclerosis (ALS) due to *SOD1* mutations (*Miller 2013*). Recently ISIS Pharmaceuticals completed a phase I study of another MOE AO administered intrathecally in spinal muscular atrophy (SMA) due to *SMN1* mutations; a phase II study with multiple repeated doses in the same condition is currently underway (<http://ir.isispharm.com/phoenix.zhtml?c=222170&p=irol-newsArticle&ID=1902404&highlight=>); and a phase III study will commence in 3Q2014.

Amongst muscular dystrophies DMD is uniquely placed to be targeted by AOs, as the underlying pathology facilitates the AOs uptake. Nevertheless there are limitations of the current AO approaches even for DMD. Preclinical studies and more recently the outcome of the clinical trials suggest that the PMO chemistry is more efficient in inducing exon skipping and dystrophin protein production compared to 2'OMe AOs, and in providing clinical benefit. However neither the 2'OMe nor the PMO chemistries target the heart effectively, hence further development will be required to improve skeletal and cardiac muscle targeting, also for DMD.

The MDEX Consortium

Members of the MDEX consortium (<http://www.mdex.org.uk/>) have been working for a decade on AO using the PMO chemistry and have previously completed on time and on budget 2 clinical trials on DMD (one DOH (*Kinali et al, 2009*) and the other MRC funded, *Cirak et al, 2011*). Importantly, the FDA has recently agreed a path forward for accelerated approval of this AO (developed with a DOH and MRC funds) in the USA.

In addition to taking forward a new clinical trial with the PMO chemistry targeting exon 53 – in collaboration with Sarepta and EU funding- members of the consortium are also working at next generation peptide conjugated PMO (PPMO) chemistries with improved efficacy in targeting skeletal and cardiac muscle (*Betts et al, 2012a, 2012b; Crisp et al, 2010; Yin et al, 2009, 2010a and 2010b, 2011; Muntoni & Wood 2012*). The advanced PPMO chemistry allows much greater potency of AO delivery and intracellular activity, and members of the consortium (Wood and Muntoni, lead two major programmes funded by Wellcome Trust HICF and Association Francaise Myopathies to develop advanced PPMO chemistry). PPMOs also have the potential to cross the blood brain barrier and hence target the central nervous system without the need of direct central nervous system (CNS) administration. Very recently a MRC DPFS grant was assigned to Wood (PI)- and Gait/Muntoni -to develop a PPMO which could cross the blood brain barrier for spinal muscular atrophy (SMA).

The MDEX consortium has unique multidisciplinary expertise is the access of validated methodologies to assess preclinical models and their response to therapeutic intervention including cardiac physiology with advanced imaging technologies. Unique animal models are available, including a pig model which closely reflects the clinical severity of the human condition (*Klymiuk 2013*); and the team at the RVC has recently received Wellcome Trust funding to develop a novel colony of dogs with an exon 50 deletion that has the reading frame restored when AOs targeting exon 51 are used (*Walmsley et al, 2010*). The MDEX consortium also has expertise in imaging and biochemical assays to allow study of the biodistribution of AOs.

Finally MDEX partners are involved and lead large-scale European Union funded projects to identify biomarkers (BIO-NMD, Neuromics), develop MRI protocols to assess therapeutic response in DMD trials (COST, BioIMAGE; GSK) and develop improved methods for oligonucleotide drug delivery (IMI, COMPACT), in addition to the SKIP-NMD EU funded clinical trial project.

MRC Centre expertise relevant for this application.

Several members of the MRC Centre are already involved in the MDEX consortium (Muntoni; Morgan; Bushby; Straub); in addition in the MRC Centre there is very relevant expertise that optimally complements the MDEX expertise. This expertise is on 3 main fronts: **1.** core funded MRC Centre activities (human muscle MRI imaging; biobanks; national cohorts of neuromuscular patients). Specifically the MRC Centre has developed innovative muscle MRI acquisition techniques and these are being tested in longitudinal cohorts of patients, and correlated to clinical outcomes (*Willis TA 2013; Hollingsworth al, 2013*). The Centre also hosts a very large tissue and cell biobank of deeply phenotyped patients. These cells, which include iPS cells, are used for development and optimisation of novel therapeutics (*Cirak et al, 2011; Dick et al, 2013*); relevant animal models are also available to MRC investigators studies.

2. unique clinical expertise in rare neuromuscular disorders, due to several National Specialist Commissioning services directed by PIs of the MRC Centre (Channelopathies; Limb girdle muscular dystrophies; Mitochondrial diseases; Congenital muscular dystrophies and myopathies; Glycogen storage myopathies), and other areas of international leadership such as on peripheral neuropathies; **3.** expertise on preclinical RNA therapies for mitochondrial diseases (antigenomic approaches). Specifically, the Newcastle group has previously developed an attractive strategy aimed at targeting mutant DNA in heteroplasmic mitochondrial DNA mutations, a common cause of neuromuscular disease. The aim is to suppress replication of the mutant DNA to push balance of wild type to mutated mtDNA across critical threshold (*Taylor 1997*). Initial work *in vitro* showed the viability of the approach at specifically binding and inhibiting replication of mutated mitochondrial DNA. Unfortunately *in vivo* studies have not yield the expected results, due to poor compound delivery through the double membrane of mitochondria to reach the target. Technological advances are required before this approach could be considered for human applications. This is a relevant example on the rationale of combining the expertise of the MRC mitochondrial group with the MDEX knowhow on novel AO chemistries such as PPMO.

Industry collaboration

Members of the MRC Centre and of the MDEX Consortium have strong links with different industrial partners interested in AO therapies ranging from Sarepta Therapeutics, Idera, AstraZeneca, ISIS Pharmaceuticals, Pfizer, Ugichem, Summit, Prosensa and Shire.

Proposed studies.

We propose to set up a comprehensive program of research linking the MRC Centre to the MDEX consortium related to RNA therapeutics for neuromuscular disorders, from the early discovery to first-in-man studies. We will concentrate on conditions in which there is a strong clinical base and patient population followed in the centre together with biobanked material and technical knowhow. Collaboration with industry to take forward the most promising candidate is available.

Our aims are therefore the following:

- i. Identify novel targets for AOs including conditions / genes not currently studied; ii
- ii. Identify novel modification of AOs for improved biodistribution and efficacy
- iii. Perform new first in human clinical trials of these new compounds.

These different aims will be carefully managed with a series of go-nogo milestones which will be agreed with the industrial partner(s), with whom the optimal target for clinical development will be negotiated, and supervised by an external SAB.

Regarding the identification of novel therapeutic targets, we will use the following techniques: RNA-targeted antisense knockdown; anti-gene targeted knockdown; and antisense mediated miRNA interference. Each laboratory will concentrate on a specific set of conditions.

Specifically we will

- i. Knockdown mutant disease genes in autosomal dominant disorders in which we have clear clinical evidence of absence of phenotype in patients with haploinsufficiency (the disease is caused by gain of pathological function of missense mutations). These include myopathies and neurogenic disorders, such as *RYR1* related core myopathies; collagen VI related muscular dystrophies; IBMPFD (inclusion body myopathy, Paget disease and fronto-temporal dementia due to VCP mutations); autosomal dominant neuropathies due to SPTLC1 or SPTCL2 mutations. We will induce allelic specific knock down by AO mediated splice switching resulting in out-of-frame deletions in the allele carrying the missense mutation; and by RNase H mediated RNA cleavage where AO may target any SNPs. We have a track record and expertise in allele specific knockdown (*Sibley et al, 2011; Scholefield et al, 2009; Abdelgany et al, 2009*). A similar strategy will be used to target genes pathologically activated in specific diseases, such as in Facio Scapulo Humeral Muscular Dystrophy (in which DUX4 gene can be targeted) (*Vanderplanck et al, 2011*) or expanded alleles such as in Oculopharyngeal muscular dystrophy, where we have already designed and are testing AOs which may be specific for steric blocking translational inhibition of poly-alanine expanded repeat allele RNA. (*Wheeler et al 2012; Leger et al 2013*).
- ii. Target miRNA binding sites at UTRs of genes of interest, inducing increased translational efficiency of target proteins. Specific examples are utrophin 3'UTR (*Basu et al, 2011*) for which there is already consolidated expertise in Oxford, and laminin $\alpha 1$ and $\alpha 4$ miRNA binding sites. We will target genes encoding proteins which, if upregulated, can compensate for the lack of the protein primarily deficient in DMD and Becker muscular dystrophies, and in MDC1A, respectively. A similar strategy (i.e. targeting the 3'UTR of the *DMD* gene) could also be used to enhance dystrophin translation in BMD (*Cacchiarelli et al 2011*).
- iii. Antigenomic therapies. We will combine our recent efforts to target AOs to mitochondria using novel AO chemistries described below. We will investigate the effect of different AO modifications and mitochondrial targeting molecules on sub-cellular localisation using microscopy techniques developed within the Turnbull group. We will explore efficacy of different AO chemistries such as conjugation to *peptide* targeting sequences, *RNA* targeting sequences, targeted diffusion across mitochondrial membranes and conjugation with other imported mitochondrial components. The Turnbull group has developed medium-high content imaging assays to assess localisation of oligonucleotides, enabling large scale screening. This strategy is aimed at preventing production of mtDNA encoded proteins. The MRC centre Biobank has access to extensive number of relevant cell lines and there are collaborations in place for testing in animal models of mitochondrial DNA disease.
- iv. Interfere with specific physiopathological processes, such as muscle atrophy, fibrosis and inflammation. We have already developed optimised reagents for the destructive exon skipping in the myostatin transcript in mice and men (*Kang et al, Malerba et al, Lu-Nguyen et al: see below*). Myostatin is a negative regulator of

muscle mass, and its effective knockdown or modulation of the expression of its receptor (ActRIIB) could have implication for a significant number of conditions. Along similar lines we will target pathways crucial for inflammation (IL-1 receptor accessory protein, *Yilmaz-Eliş et al, 2013*) and for fibrosis. This latter pathway could be targeted with AONs in different parts, by either targeting transforming growth factor beta1 (TGF- β 1) (*Takabate 2005*) or tissue inhibitor metalloproteinase-1 (TIMP-1, *Nie et al, 2001*).

Regarding the second aim, exploration of novel modified peptide modified PMO AO for increased efficacy and targeting to tissues.

These efforts encompass the various targeting strategies mentioned above. For example the 2OMe and PMO are not optimal AO chemistries for achieving anti-miR effects; the Gait lab has specific expertise on AO chemical modification to obtain maximal miRNA interference (*Torres et al 2011 and 2012; Fabani et al, 2008 and 2010*) and collaborations with groups focused on evaluating novel chemistry (*Lennox et al, 2013*) are also established in the Wood lab.

Re: peptide conjugated AOs (typically of PMO or PNA backbone chemistry); the most advanced peptides developed by the Gait and Wood labs are the Pip series developed jointly by Gait and Wood. (*Betts et al, 2012; Lehto et al, 2013; Yin et al, 2011; Crisp et al, 2010; Yin et al 2010; Ivanova et al, 2008*). The Pip6 series is currently the most advanced series in routine use in pre-clinical studies. Such compounds achieve high potency in muscle and heart tissues in vivo at ultra-low concentrations and Pip6a now also shows promise for direct trans-blood brain barrier CNS delivery in animal models of spinal muscular atrophy obviating the need for intrathecal delivery (see below).

Methods are in place to develop peptide-PMO (PPMO) compounds for novel targets as well as to optimise the delivery and targeting of such compounds to specific tissues. Gait in particular has developed novel methodologies for medium to high throughput screening of novel peptide conjugated oligonucleotides allowing more rapid screening of novel constructs (*Deuss et al, 2013*) – Pip9-PMO conjugates to target skeletal and cardiac muscle with far better efficacy, less frequent dosing. These new PPMO can therefore target cardiac muscle which is involved not only in DMD, but also in a number of other muscular dystrophies.

Brain delivery of AOs. We will be assessing the efficacy of modified AOs to target the blood brain barrier (BBB). While we have already achieved brain trans-BBB delivery and brain penetration using Pip-PMO technology, there are additional approaches to enhance and refine this, providing a route for systemic administration of CNS targeting oligonucleotide drugs. One approach to enhance AO uptake to the brain is to chemically conjugate them to targeting ligands for specific receptors on the brain microvasculature that mediate endocytosis or transcytosis, or to package them into multifunctional nanoparticles for targeted transport across the BBB. Nucleic acid aptamers are small with high affinity for their targets, non-immunogenic and can be chemically modified for in vivo applications and so may represent a novel targeting strategy to enhance the uptake of exon skipping AOs through the blood-brain barrier. Peptides, while of lower affinity than aptamers, have proven to be effective in mediating nanoparticle targeting through particle avidity and uptake into cells in vitro and in vivo. Systematic analysis of the capabilities of these modified AOs to cross the blood nerve barrier and target axons / the peripheral nerve will also be explored.

Regarding the translational applications, and first in human studies. We believe that it is realistic for us, in collaboration with an industrial partner, to identify a minimum of two conditions / AOs for which the preclinical data is sufficiently compelling to take the decision to perform proof of concept clinical trials. The final decision on which condition to target will be taken in collaboration with the industrial partner, with whom we will also plan to perform preclinical toxicology in order to derisk the experimental approach. Additional considerations will relate to the level of freedom to operate and, if appropriate, the level of evidence from existing animal models (already available in the Consortium).

We will prioritise the following AOs aiming at a clinical trials
Mitochondrial diseases; IBMPFD; dominant neuropathies and collagen VI related disorders. We will also target physiopathological processes (such as muscle mass; or fibrosis) in preclinical models. Provided the preclinical data will be compelling, we could consider to develop one of these AOs for clinical application.

Flow and prioritisation of work.

1. Aim 1, months 1-16.

Optimisation of gene target; assessment of efficacy of splice switching/ silencing in cellular (and/ or animal models) of at least 12 genetically different diseases (RYR1/ COL6/ FSHD/ OPMD/ IBMPFD/ peripheral neuropathies/ SMA/ SPTLC1 and different mitochondrial mutations/; MDC1A and dystrophin (miRNA targeting).

Milestone 1 (month 16): Identification of ≥ 8 optimal AOs for genes/ conditions currently not in AO clinical trials

2. Aim 2. Months 4-28.

Identification of optimal lead AO compounds for gene / miRNA targeting

We will assess the properties and tissue / organ targeting of different modified AO compounds as described in basic research aim B. In particular we will explore capacity of novel AO modification to target mitochondria and organs currently not easily accessible (such as peripheral nerve and brain). This, and the previous milestone (identification of optimal primary gene target sequence), and the in-vivo studies, will allow us to define the lead AOs.

Milestone 2 (month 28).

Identification of ≥ 6 advanced AO compounds based on pre-clinical efficacy data and biodistribution in relevant animal models which will be developed further for clinical applications.

3. Aim 3. Months 16-44.

Longitudinal assessment of novel clinical, imaging and serum biomarkers to monitor disease progression and efficacy of AO intervention in the 4 target diseases identified in milestone 2. As we plan to target conditions not currently involved in clinical trials, we aim to collect longitudinal data (functional; muscle MRI; serum biomarkers) which will be used as baseline to assess efficacy of therapeutic intervention. Specifically we will study correlation between muscle MRI and functional measures, as we have identified in DMD and in LGMD2I that muscle MRI has a higher sensitivity to detect progression of changes compared to functional measures.

Milestone 3 (month 44).

Have acquired natural history data and biomarkers profile for the at least 4 target diseases so that these could be used as exploratory endpoints in clinical trials

**4. AIM 4:
Safety, toxicology analysis of lead AO compounds. Months 28-44**

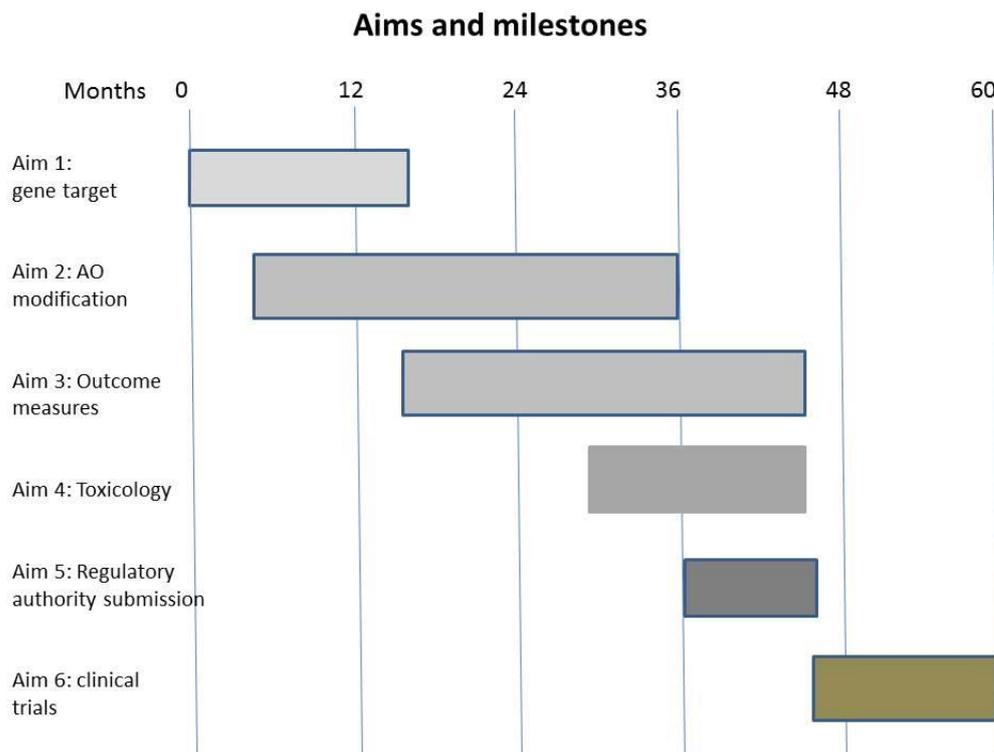
Following the identification of the lead compound, in collaboration with industrial partner, preclinical toxicology will be initiated for the lead compounds. Already during milestone 2 we will have performed exploratory preclinical toxicology in different animal models to de-risk compounds which could be considered for the more extensive regulatory toxicology.

Milestone 4 (month 44). Have performed preclinical toxicology of at least 4 of the novel AO targeting a novel gene target.

**5. Aim 5. Trial design and regulatory authority submission. Months 36-44
Milestone 5: Have submitted to regulatory authorities at the protocols for different diseases.**

**6. Aim 6 (Months 44-60). Completion of a dose escalating Phase I/II clinical trial targeting at least 2 different genes/ processes.
Milestone 6. Completion of at least 2 clinical trials**

Fig 1. Schematic representation of the aims and milestones is copied below



Industrial partnerships

We recognise that in order to take forward this ambitious plan of research it is necessary to have an effective partnership with industry interested in taking forward the options of taking one or more of the lead candidates forward.

We have already approached and discussed our approach with Pfizer which has agreed to provide a letter of expression of intent.

We also have had detailed meetings with 4 additional industrial partners; the documents relative to finalising the expression of interest with one of these partners is at the advanced stage of negotiations while 2 of the remaining partners have expressed an interest in provide in-kind support to our studies (in house expertise and materials).

Other partnerships.

The French Association for Myopathies AFM) is a large charity which funds much of the French translational research in the field of genetics and neuromuscular disorders. The MDEX Consortium is already receiving funding from AFM to develop novel AONs for Duchenne Muscular Dystrophy. The AFM has expressed an interest to be part of a translational; research consortium focused on taking forward novel antisense oligonucleotides for conditions not currently targeted by this approach. Further discussion between AFM, the MRC, the MDEX, the MRC centre and the MRC centre should be considered ahead of a submission to MRC.

Budgetary consideration

In terms of Budget required to perform the proposed program of research, we anticipate this project will require, for each Aim/ workpackage, the following resources:

Aim 1.

Optimising gene primary target, 0-16 months.

Partners involved.

UCL: 1.5 FTE RA (AO selection)

NCL: 1.5 FTE RA (AO selection)

RHUL: 1 FTE RA (AO selection)

RVC -----

Oxford: 1 FTE RA (AO selection)

Cambridge -----

Industrial partner -----

Anticipated budget: ~ £540,000

Aim 2. PPMO tissue targeting and exploratory toxicology. 4-34 months

Partners involved.

UCL: 1 FTE RA (peripheral nerve / brain targeting, month 16-34)

NCL: 1 FTE RA (mito + other targeting) 30

RHUL: 1 FTE RA (functional assessment in vivo) 30

RVC 1 FTE RA (functional assessment in vivo) 30

Oxford: 1 FTE RA (cardiac/ brain targeting/ functional assessment) 30

Cambridge 2 FTE RA (PPMO design) 30

Industrial partner -----

Anticipated budget: £ 1,680,000

Aim 3. Clinical and biochemical outcome measures. Months 16-44

Partners involved.

UCL:	3 FTE RA (2 CRF(1 paed one adult); 0.5 physio; 0.5 radiologist)
NCL:	3 FTE RA (1 CRF (1 paed one adult); 0.5 physio; 0.5 radiologist)
RHUL:	0.5 FTE RA (months 28-44)
RVC	0.5 FTE RA (months 28-44)
Oxford:	0.5 FTE RA (months 28-44)
Cambridge	-----
Industrial partner	-----

Anticipated budget: £ 800,000

Aim 4. Preclinical toxicology

Partners involved.

UCL:	0.1 wte
NCL:	-----
RHUL:	-----
RVC	-----
Oxford:	0.1 wte
Cambridge	-----
Industrial Partner	+

Anticipated budget: (contribution from the industrial partner(s))

Aim 5. Submission to regulatory authorities (months 36-44)

Partners involved.

UCL:	0.1 FTE
NCL:	0.1 FTE
RHUL:	-----
RVC	-----
Oxford:	-----
Cambridge	-----
Industrial Partner	+

Anticipated budget: ~£ 20,000 (academic contribution, the rest expected by industrial partner(s))

Aim 6. Clinical trial (months 44-60)

Partners involved.

UCL:	2 FTE CF; 1 FTE physio; 0.5 FTE coordinator; + 0.5 FTE physicist
NCL:	2 FTE CF; 1 FTE physio; 0.5 FTE coordinator; + 0.5 FTE physicist
RHUL:	-----
RVC	-----
Oxford:	-----
Cambridge	-----
Industrial Partner	+

Salary budget of the research teams: ~ £650,000 (note this budget does not contain drug costs or Clinical Research facility/ costs of specific exploratory measures, which will be required for the clinical trials at the 2 sites.

Budget summary.

Aim 1: £ 540,000

Aim 2: £1,680,000

Aim 3: £ 800,000

Aim 4: £ Industrial partner

Aim 5: £ 20,000

Aim 6: £ 650,000 + industrial partner

+1 scientific coordinator for the duration of the project (£280,000)

Total direct costs for academic partners: £ 3,970,000+

Note

The industrial partner(s) should contribute with the budget to perform the preclinical toxicology for the compounds (see Aim 4), so this budget could be devolved to the industrial partner after the go-nogo decision to take forward a clinical developmental programme.. The industrial partner(s) will also have the option to take the lead compounds forward and contribute to the funding of the phase I/II clinical trials involving the trial sites in London and Newcastle. Negotiation with AFM could also help to have potentially another funder involved in the translational research program.

References

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Appendix . Letter of collaboration from Pfizer



Pfizer Inc.
235 East 42nd Street
New York, NY 10017
www.pfizer.com

June 6, 2014

Professor Francesco Muntoni
Dubowitz Neuromuscular Centre
UCL Institute of Child Health
30 Guilford Street
London WC1N 1EH
United Kingdom

Re: Support for 'Exploration of Interest' Proposal to the Medical Research Council ("MRC") entitled "RNA therapeutics for neuromuscular disorders: A MRC Centre-MDEX Consortium partnership approach"

Dear Francesco:

I am writing to you to express our support and interest in your 'exploration of interest' proposal to the MRC. I can confirm that Pfizer views this therapeutics area as of one of significant unmet need and that the expertise and talent assembled by this team is very exciting. Furthermore, if the MRC were to express interest in this proposal, Pfizer would be interested in discussing with the council and consortium ways in which it might collaborate.

Best wishes,



Kevin Lee
Chief Scientific Officer, Rare Disease Research Unit

v) MRC Centre UK Translational Research Conference programmes 2013 & 2014



UK Neuromuscular Translational Research Conference 2013

Medical Sciences Teaching Centre, Oxford

Thursday 14th – Friday 15th March

PROGRAMME

Day 1 – Thursday 14th March

09:00 – 10.15 Registration and Coffee

10:15 – 10:30 Introduction
Professor Michael Hanna
UCL Institute of Neurology

10:30 – 13:00 Translational Research in Human Mitochondrial Diseases Chairs: Professors Patrick Chinnery (Newcastle University) and Massimo Zeviani (MRC Mitochondrial Biology Unit)

10:30 – 11:00 Evaluating new therapies in mitochondrial diseases
Professor Anu Suomalainen, University of Helsinki, Biomedicum-Helsinki

11:00 – 11:30 Developing new treatments in mitochondrial disease
Dr Werner Koopman, Radboud University Medical Centre

11:30 – 12:00 Exercise treatments in mitochondrial myopathies
Dr Grainne Gorman, Newcastle University

12:00 – 12:15 Evidence based treatments in mitochondrial diseases -
Challenges and pitfalls
Professor Patrick Chinnery, Newcastle University

12:15 – 12:30 *NDUFA4* mutations: a new cause of mitochondrial cytochrome c oxidase
linked neurological disease
Rob Pitceathly, UCL Institute of Neurology

12:30 – 12:45 Defective thiolation impairs mitochondrial translation offering a therapy
approach in reversible infantile respiratory chain deficiency
Veronika Boczonadi, Newcastle University

12:45 – 13:15 Late breaking abstracts

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

Day 2 - Friday 15th March

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

16:00 – 16:30

Gene therapy for DMD and OPMD

Professor George Dickson, Royal Holloway, University of London

16:30 – 16:45

Poster prizes and close



UK Neuromuscular Translational Research Conference 2014

ICH, 30 Guilford Street, London WC1N 1EH

Kennedy Lecture Theatre

Monday 3rd and Tuesday 4th March

PROGRAMME

Day 1 – Monday 3rd March

08:30 – 9:30 Registration and Coffee

9:30 – 9:45 Introduction
Professor Michael Hanna
UCL Institute of Neurology

09:45 – 12:30 Session 1: Cell-Based therapies and IPS Cells Chairs: Professor Jenny Morgan (UCL Institute of Child Health) and Professor Dame Kay Davies (University of Oxford)

09:45 – 10:15 Autologous cell therapy in oculopharyngeal muscular dystrophy (OPMD)
Professor Gill Butler-Browne
Institut De Myologie, Paris

10:15 – 10:45 Opti-dystrophin in DMD stem cells
Professor Jenny Morgan
UCL Institute of Child Health

10:45 – 11:15 Cell therapy for muscular dystrophies
Professor Giulio Cossu
Institute of Inflammation and Repair
University of Manchester

11:15 – 11:45 Coffee

11:45 – 12:00 Platform Presentation: Improving satellite cell regenerative potential in muscular dystrophy: an environmental issue
Dr A Pisconti
Department of Biochemistry, University of Liverpool

- 12:00 – 12:15 Platform Presentation: Designing 3D scaffolds that can support myogenic progression in skeletal muscle satellite cells
Dr Nicolas Figeac
King's College London
- 12:15– 12:30 Platform Presentation: iPS cells and human artificial chromosomes: novel therapeutic tools for muscle disorders
Dr Francesco Saverio Tedesco
Department of Cell and Developmental Biology, UCL
- 12:30 – 13:30 Posters and lunch**
- 13:30 – 14:30 Poster guided tours**
Muscular Dystrophies group a
Mitochondrial Disease
MRI
Glycosylation Disorders, Inclusion Body Myositis and Muscle Satellite cells and IPS Cells
- 14:30 – 17:30 Session 2: Protein Homeostasis and Neuromuscular Diseases**
Chairs: Professors Mary Reilly (UCL Institute of Neurology) and Hanns Lochmuller (Newcastle University)
- 14:30 – 15:00 Working towards first in human trials of prion immunotherapeutics
Dr Simon Mead
UCL Institute of Neurology
- 15:00 – 15:30 The role of the unfolded protein response in neurodegeneration: a new target for therapy
Professor Giovanna Mallucci
MRC Toxicology Unit, Leicester
- 15:30 – 16:00 Heat shock proteins and protein homeostasis in hereditary neuropathies
Professor Vincent Timmerman
University of Antwerp, Belgium
- 16:00 – 16:30 Coffee
- 16:30 – 17:00 Using proteomic profiling to decipher the pathogenesis of myofibrillar myopathies
Professor Rudolf Kley
University Hospital Bergmannsheil, Germany
- 17:00 – 17:15 Platform presentation: Mitochondrial abnormalities and increased oxidative stress in HSBP1 induced distal hereditary motor neuropathies
Dr Bernadett Kalmar
UCL Institute of Neurology

- 17:15 – 17:30 Platform presentation: Investigating the effects of pharmacological up-regulation of the heat shock response in a transgenic mouse model of inclusion body myopathy
Dr Mhoriam Ahmed
UCL Institute of Neurology
- 17:30 – 18:30 The Third Morgan-Hughes Thomas Lecture**
A gene for speed: ACTN3, athletes, evolution and impact on human health
Professor Kathryn North
Murdoch Children’s Research Institute, Australia
Introduced by Professor Mike Hanna
- 18:30 – 19:30 **Drinks Reception and Posters**
Introduced by Robert Meadowcroft, Muscular Dystrophy Campaign CEO

(followed by walk/coaches to Gala Dinner)
- 19:45 – 20:00 **Aperitif followed by Gala Dinner**
Grand Connaught Rooms
Great Queen Street
WC2B 5DA

(Dress code: smart / smart casual)

Day 2 – Tuesday 4th March

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

- 08:30 – 09:00 Tricyclo-DNA for the treatment of neuromuscular diseases
Professor Christian Leumann
University of Bern
- 09:00 – 09:30 AON development for SMA
Dr Arthur Burghes
Ohio State University
- 09:30 – 10:00 Peptide modified AONs for enhanced potency and tissue targeting
Professor Matthew Wood
University of Oxford
- 10:00 – 10:30 Antisense approaches to counter skeletal muscle atrophy and fibrosis: targeting myostatin and other strategies
Professor George Dickson
Royal Holloway – University of London
- 10:30 – 11:00 Coffee
- 11:00 – 11:30 **MRC Guest speaker**
The MRC in 2014 - evolution and strategy
Dr Declan Mulkeen
MRC Chief Science Officer
- 11:30 – 12:30 The Third Victor Dubowitz Lecture**
Molecular Therapies for Neuromuscular Diseases
Professor Jerry Mendell
Ohio State University
Introduced by Professor Francesco Muntoni
- 12:30 – 12:45** Platform presentation: Peptide-conjugated phosphodiarnidate morpholino treatment in mdx mice: cardiac dystrophin restoration and function
Dr Alison Blain
Institute of Human Genetics, Newcastle University
- 12:45 – 13:00** Platform presentation: High content screening identifies small molecules that remove nuclear foci, affect MBNL distribution and CELF1 protein levels via a PKC independent pathway in Myotonic Dystrophy cell lines
Dr Ami Ketley
School of Life Sciences, University of Nottingham, UK
- 13:00 – 14:00 Lunch**
- 14:00 – 15:00 Poster guided tours**

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

- 15:00 – 16:30** **Session 4: MRI in Neuromuscular Diseases**
Chairs: Professors Tarek Yousry (UCL Institute of Neurology) and Professor Volker Straub (Newcastle University)
- 15:00 – 15:30 Diffusion Tensor Imaging in Neuromuscular Disease
Professor Klaas Nicolay
Eindhoven University of Technology
- 15:30 – 16:00 Results from the Imaging DMD study
Doctor Lee Sweeney
University of Pennsylvania
- 16:00 – 16:15 Platform presentation: Quantitative lower limb muscle MRI in CMT1A demonstrates length-dependent fatty infiltration
Dr Matthew Evans
UCL Institute of Neurology
- 16:15 – 16:30 Platform presentation: Reducing the cost of MRI in neuromuscular clinical trials: acceleration of fat-fraction measurement in Becker muscular dystrophy by combined compressed sensing and parallel imaging
Dr Kieren Hollingsworth
Institute of Cellular Medicine, Newcastle University
- 16:30 – 17:00** **Poster prizes and close**

vi) MRC Centre Update in Neuromuscular Disorders course programmes 2013 & 2014



Update in Neuromuscular Disorders

Tuesday 7th - Friday 10th May 2013

***Clinical Neuroscience Lecture Theatre at 33 Queen Square, London
WC1N 3BG***

PROGRAMME

Day 1 - Tuesday 7 May

- | | |
|----------------------|---|
| 10:00 – 10:30 | Registration and coffee |
| 10:30 – 10:50 | DMD standards of care in clinical practice
Dr Adnan Manzur, UCL Institute of Child Health and Great Ormond Street Hospital |
| 10:50- 11:10 | Do we need to revise our practice: the example of corticosteroids
Dr Ros Quinlivan, MRC Centre for Neuromuscular Diseases and UCLH |
| 11:10 – 11:30 | Panel discussion |
| 11:30 – 11:50 | COFFEE |
| 11:50 – 12:30 | LGMD made easy
Professor Volker Straub, University of Newcastle |
| 12:30 – 13:00 | 3 illustrative cases |
| 13:00 – 14:00 | LUNCH |
| 14:00 – 14:25 | Structural congenital myopathies : pathology
Professor Caroline Sewry, UCL Institute of Child Health and Great Ormond Street Hospital |
| 14:25 - 15:00 | The congenital myopathies – 2013 update
Dr Heinz Jungbluth, Evelina Children's Hospital, London |

- 15:00 – 15:30** **TEA**
- 15:30– 16:00 Case presentation
-
- 16:00 – 16.30** **Approach to rarer congenital myopathies**
Professor Francesco Muntoni, UCL Institute of Child Health and
Great Ormond Street Hospital
- 16:30 – 17:30** **Special Guest speaker**
Thick filament disorders and distal arthrogryposis
Dr Anders Oldfors, University Hospital, Goteborg
- 17:30 – 18:30** **Drinks reception in the lecture theatre foyer**

Day 2 – Wednesday 8 May

AM: Congenital muscular dystrophies

- 09:00 – 09:30** **Congenital muscular dystrophy: classification update**
Professor Eugenio Mercuri, Catholic University, Rome
- 09:30 – 10:00** **Spectrum of brain involvement in CMD**
Dr Daniela Pilz, Cardiff School of Medicine
- 10:00– 10:40 Illustrative cases
- 10:40 - 11:10** **COFFEE**
- 11:10 – 11:40** **Therapeutic development in CMD**
Professor Francesco Muntoni, UCL Institute of Child Health and Great
Ormond Street Hospital
- 11:40 – 12:20** **Innovation in Neuromuscular disorders -where are we with stem
cell transplant in DMD?**
Professor Giulio Cossu, University College London
- 12:20 – 12:40** **Physiotherapy assessment and outcome measures for CMD**
Marion Main, UCL Institute of Child Health and Great Ormond Street
Hospital

- 12: 40 - 13.00** **Which outcome measures do really matter?**
Laura and Judith Merry, National Ambassadors for Trailblazers,
MDC Young campaigner's network
- 13:00 – 14:00** **LUNCH**
- 14:00 – 14:20** **Optimisation of spinal surgery neuromuscular programme**
Dr Stewart Tucker, UCL Institute of Child Health and Great Ormond Street Hospital
- 14:20 – 14:40** **Cardiac MRI in preoperative assessment in DMD**
Dr Andreas Brunklaus, Great Ormond Street Hospital
- 14:40 – 15:00** **Magnetic growth rods**
Mr Hilali Noordeen, Royal National Orthopaedic Hospital
- 15:00- 15:30 Panel discussion
- 15:30 – 15.45** **TEA**
- 15.45 – 16:05 **McArdle National Specialist Commissioned Service**
Dr Ros Quinlivan, MRC Centre for Neuromuscular Diseases and National
Hospital for Neurology and Neurosurgery
- 16:05 – 16:25 **Late onset Pompe disease: optimal screening**
Tracey Willis, Robert Jones and Agnes Hunt Orthopaedic Hospital

Day 3 – Thursday 9 May

- 09:00 – 09:45** **The diagnosis of CMT in 2013**
Professor Mary Reilly, UCL Institute of Neurology and National Hospital
for Neurology and Neurosurgery
- 09:45 – 10:15** Illustrative cases
Dr Matilde Laura, UCL Institute of Neurology and National Hospital for
Neurology and Neurosurgery
- 10:15 – 11:00** **Foot surgery in CMT**
Dishan Singh, Royal National Orthopaedic Hospital

- 11:00 – 11:30** **COFFEE**
- 11:30 – 12:15** **Myotonic dystrophy**
Dr Chris Turner, National Hospital for Neurology and Neurosurgery
- 12:15 – 13:00** **Mitochondrial myopathy- diagnosis, management and therapy**
Dr Andrew Schaefer, Newcastle upon Tyne Hospitals NHS Foundation Trust
- 13:00 – 14:00** **LUNCH**
- 14:00 – 14:45** **Muscle channelopathies: an update**
Professor Mike Hanna, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery
- 14:45 - 15:15** **Inflammatory myopathies and IBM**
Dr David Hilton Jones, John Radcliffe Hospital, Oxford
- 15:15 – 15:30** **TEA**
- 15:30 – 16:15** **Exome sequencing in neuromuscular disease**
Professor Henry Houlden, UCL Institute of Neurology
- 16:15 – 16:30** **Genetics of MND**
Professor Chris Shaw, King's College London

Day 4 – Friday 10 May 2013

For the CPC session at 15.20, please collect the CPC information sheet at Reception. Your responses are due in by lunchtime

- 09:00 – 09:30** **Muscular dystrophies in adult practice**
Dr Ros Quinlivan, MRC Centre for Neuromuscular Diseases and National Hospital for Neurology and Neurosurgery
- 09:30 – 10:15** **Rhabdomyolysis- a practical approach**
Dr Rob Pitceathly, MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology
- 10:15 – 11:00** **Mononeuropathies – causes and management**
Dr Hadi Manji, MRC Centre for Neuromuscular Diseases and National Hospital for Neurology and Neurosurgery

11:00 – 11:15	COFFEE
11:15 – 12:00	Current treatments and controversies in GBS management Dr Robert Hadden, King's College London
12:00 -12:30	Management of GBS in ITU Dr Nick Hirsch, National Hospital for Neurology and Neurosurgery
12:30- 13:30	LUNCH
13:15 – 14:00	An approach to muscle pain in adults Dr Matt Parton, MRC Centre for Neuromuscular Diseases and National Hospital for Neurology and Neurosurgery
14:00 – 14:30	Exercise intolerance and muscle disease Dr Mark Roberts, Greater Manchester Neurosciences Unit at Salford Royal NHS Foundation
14:30 – 15:00	MRI in adult neuromuscular disease Dr Jasper Morrow, MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology
15:00 – 15:20	TEA
15:20 – 15:50	CPC discussion Dr Wojtek Rakowicz, Imperial College School of Medicine
15:50 – 16:20	CPC conclusion Professor Mike Hanna, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery



Update in Neuromuscular Disorders
Monday 17th - Thursday 20th March 2014
Clinical Neuroscience Lecture Theatre at 33 Queen Square, London
WC1N 3BG

PROGRAMME

A summary of the CPC discussion on Thursday afternoon will be available from the registration desk throughout the course for delegates. Please complete and hand in your response to the registration desk by 12.45 on Thursday 20 March. There is a prize for the winning entry.

Day 1 – Monday 17 March

10:00 – 10:30 Registration and coffee

Morning Muscular dystrophies

10:30 – 10:45 DMD: Evolving natural history

Dr Adnan Manzur, ICH Dubowitz Neuromuscular Centre

10:45- 11:10 Experimental Therapies in DMD: where are we?

Professor Francesco Muntoni, ICH Dubowitz Neuromuscular Centre

11:10 – 11:30 Psychological aspects of participating in clinical trials

Professor Elena Garralda, Child and Adolescent Psychiatry, Imperial College

11:30 – 11:50 COFFEE

11:50 – 12:30 Limb girdle muscular dystrophies: old and new

Dr Anna Sarkozy, ICH Dubowitz Neuromuscular Centre

12:30 – 12:45 A study of families' perspective on participation in research trials

Naomi Antcliff and Dr Valeria Ricotti

Clinical Trials Unit, Great Ormond Street Hospital & ICH Dubowitz Neuromuscular Centre.

12:45 – 13:00 Illustrative cases

Dr Adeline Seow, Dubowitz Neuromuscular Centre, Great Ormond Street Hospital

13:00 – 14:00 LUNCH

- Afternoon** **Cardiac rhythm disorders in NMD**
- 14:00 – 14:30** **DMD: Cardiomyopathy and cardiac arrhythmia – (Brief: focus on arrhythmia risk and implications especially in young men/ evolving natural history)**
Professor Perry Elliott, Heart Hospital, London
- 14:30 – 15:00** **Cardiac Rhythm disorders in NMD - (briefing: EDMD; Myotonic dystrophy; myofibrillar myopathies)**
Juan Kaski, Great Ormond Street Hospital
- 15:00 – 15:30** **Case presentations**
Dr Adeline Seow, Dubowitz Neuromuscular Centre, Great Ormond Street Hospital
- 15:30 – 16:00** **TEA**
- 16:00 – 17:00** **Special guest speaker**
Therapeutic approaches to childhood mitochondrial diseases
Professor Rita Horvath, Newcastle University International Centre for Life
- 17:00 – 18:30** **Drinks reception and canopies in the lecture theatre foyer**

Day 2 – Tuesday 18th March

AM: Childhood Neurogenic Disorders

- 09:00 – 09:25 Spinal muscular atrophy**
Professor Victor Dubowitz, Emeritus Professor of Paediatrics, University of London
- 09:25 – 09:50 Outcome measures in SMA**
Professor Eugenio Mercuri, Catholic University, Rome
- 09:50 – 10:15 Illustrative cases**
Dr Luigi D'Argenzio. Dubowitz Neuromuscular Centre, Great Ormond Street Hospital
- 10:15 – 10:45 COFFEE**
- 10:45 – 11:30 CIDP in children: age-specific aspects, and what can be learned from adults**
Professor Rudolph Korinthenberg, Children's Hospital, University Hospital Freiburg
- 11:30 – 12:00 Illustrative cases**
Dr Anna Schugal, Dubowitz Neuromuscular Centre, Great Ormond Street Hospital
- 12:00 – 12:30 A treatable neuronopathy: Brown Vialetto Von Laere Syndrome**
Dr Shamima Rahman, Institute of Child Health
- 12:30 - 13.00 Illustrative cases**
Dr Anna Schugal, Dubowitz Neuromuscular Centre, Great Ormond Street Hospital
- 13:00 – 14:00 LUNCH**
- Afternoon Congenital myopathies and their differential diagnosis**
- 14:00 – 14:30 Overview on congenital myopathies**
Professor Francesco Muntoni, ICH Dubowitz Neuromuscular Centre
- 14:30 – 15:00 Vacuolar myopathies and other neuromuscular disorders associated with defective autophagy**
Dr Heinz Jungbluth, Childrens Neuroscience Centre, St Thomas' Hospital
- 15:00 – 15:30 Illustrative cases**
Dr Maria Sframeli, ICH, Great Ormond Street Hospital
- 15:30 – 15:50 TEA**
- 15:50 – 16.30 Myofibrillar Myopathies**
Prof Hanns Lochmuller, University of Newcastle
- 16.30 – 17:00 Late onset Glycogen Storage diseases: Differential diagnosis and therapeutic perspectives**
Tracey Willis, Robert Jones and Agnes Hunt Orthopaedic Hospital

Day 3 – Wednesday 19 March

- 09:00 – 09:45** **Distal inherited motor neuropathies**
Professor Mary Reilly, MRC Centre for Neuromuscular Diseases
- 09:45 – 10:15** **Illustrative cases**
Dr Alex Rossor, Kings College London
- 10:15 – 11:00** **CIDP update on diagnosis and pathogenesis**
Dr Mike Lunn, MRC Centre for Neuromuscular Diseases
- 11:00 – 11:30** **COFFEE**
- 11:30 – 12:15** **Practical approach to diagnosing and treating metabolic myopathies**
Dr Mark Roberts, Neurosciences, Salford
- 12:15 – 13:00** **Metabolic muscle disease in adults**
Dr Ros Quinlivan, MRC Centre for Neuromuscular Diseases
- 13:00 – 14:00** **LUNCH**
- 14:00 – 14:45** **Fatty acid oxidation disorders – making the diagnosis and options for treatment**
Dr Elaine Murphy, National Hospital for Neurology and Neurosurgery
- 14:45 - 15:15** **Familial amyloid polyneuropathies**
Professor Mary Reilly, MRC Centre for Neuromuscular Diseases
- 15:15 – 15:30** **TEA**
- 15:30 – 16:15** **MRI in adult neuromuscular disease**
Dr Jasper Morrow, MRC Centre for Neuromuscular Diseases
- 16:15 – 17.00** **Current approach to genetic diagnosis of inherited neuromuscular diseases**
Professor Henry Houlden, UCL Institute of Neurology

Day 4 – Thursday 20 March

09:00 – 09:30	Muscle channelopathies 2014 Mike Hanna, MRC Centre for Neuromuscular Diseases
09:30 – 10:15	Diagnosis and management of myotonic dystrophies Chris Turner, MRC Centre for Neuromuscular Diseases
10:15 – 11:00	Mitochondrial myopathies- diagnosis and management Dr Rob Pitceathly, King's
11:00 – 11:15	COFFEE
11:15 – 12:00	Acquired Myasthenia Gravis Professor Dimitri Kullman, UCL Institute of Neurology
12:00 - 12:45	Congenital Myasthenia Gravis Syndrome Professor David Beeson, Weatherall Institute of Molecular Medicine, Oxford
12:45 - 13:30	LUNCH
13:30 – 14:00	POEMs Syndrome Dr Mike Lunn, MRC Centre for Neuromuscular Diseases
14:00 – 14:30	Mononeuropathies Dr Hadi Manji, MRC Centre for Neuromuscular Diseases
14:30 – 15:00	Diagnosis and management of inflammatory myopathies Dr David Hilton-Jones, John Radcliffe Hospital, Oxford
15:00 – 15:20	TEA
15:20 – 15:50	CPC discussion Dr Carolyn Gabriel, Imperial College Healthcare NHS Trust
15:50 – 16:20	CPC conclusion Professor Mary Reilly, MRC Centre for Neuromuscular Diseases
16:20	Close of course

vii) MRC Centre Seminar Series 2013 & 2014

MRC Centre seminar series 2013 & 2014

2014

Mitochondrial quality control in mitochondrial neuropathies

Prof Jo Poulton
John Radcliffe Hospital, Oxford
3rd November, UCL Institute of Neurology

Understanding the early pathological events in amyotrophic lateral sclerosis

Prof Kevin Talbot
NDCN, University of Oxford
1st September, UCL Institute of Neurology

Application of antisense oligonucleotides for neuromuscular disorders

Dr Annemieke Aartsma-Rus
Department of Human Genetics, Leiden University Medical Centre
21st July, UCL Institute of Neurology

Chronic Inflammatory Demyelinating Polyneuropathy

David Cornblath MD
Johns Hopkins University, Baltimore, US
6th June, UCL Institute of Neurology

Glycomics in Health and Disease

Prof Anne Dell
Department of Life Sciences, Imperial College London
20th May, Newcastle

Dystroglycan Glycosylation during Muscle Development and Regeneration

Prof Kevin Campbell
University of Iowa
19th May, UCL Institute of Neurology

Therapeutic approaches to Childhood Mitochondrial Diseases

Prof Rita Horvath
MRC CNMD, Newcastle University
17th March, UCL Institute of Neurology

Alternative protein synthesis machinery in Drosophila germ line tissue

Professor Paul Lasko
James McGill Professor of Biology
McGill University, Montreal, Canada
11th March, Institute of Genetic Medicine, Newcastle

Diagnosis of inherited myopathies: next generation sequencing in action

Prof Kathryn North
University of Melbourne
6th March, UCL Institute of Neurology

Exercise as an experimental therapy in health and disease

Prof Fares Haddad, Professor Monty Mythen
Institute of Sports, Exercise and Health, UCLH
3rd February, UCL Institute of Neurology

Informatics Infrastructure for Genomic Medicine

Dr Paul Flicek,
Team Leader and Senior Scientist, European Molecular Biology Laboratory, European

Bioinformatics Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge
28th January, Institute of Genetic Medicine, Newcastle

2013

Unexpected twists and turns in the prion story

Dr Simon Mead
Clinical Lead of the UK National Prion Clinic,
National Hospital of Neurology & Neurosurgery
2nd December, UCL Institute of Neurology

Spinocerebellar ataxias: In search for a therapy

Professor Thomas Klockgether
University of Bonn, Germany
26th November, Institute of Genetic Medicine, Newcastle

Let's talk about developing a new drug for neuromuscular disease

Professor Paul Matthews
Head of Division of Brain Sciences, Imperial College
Vice President, Integrative Medicines Development, Neuroscience at GlaxoSmithKline
Honorary Professor, UCL Institute of Neurology
4th November, UCL Institute of Neurology

Unravelling demyelinating CMT

Dr Rhys Roberts
Wellcome-Beit Prize and Intermediate Clinical Fellow
Department of Clinical Neurosciences, University of Cambridge
7th October, UCL Institute of Neurology

Intraspinal Stem Cell Transplantation in ALS

Professor Eva Feldman
President, American Neurological Association
12th September, UCL Institute of Neurology

Standards of care in Myotonic Dystrophy

Dr Cynthia Gagnon, PhD,
Assistant Professor, School of Rehabilitation, University of Sherbrooke, Québec
4th September, UCL Institute of Neurology

The wide spectrum of brain malformations caused by tubulins and MT-related proteins dysfunction: Insights into cellular and pathophysiological mechanisms

Professor Jamel Chelly
INSERM, Paris
3rd September, Institute of Genetic Medicine, Newcastle University

McArdle Disease: Of Mice and Men

Dr Antoni Andreu
Head of the Neuromuscular and Mitochondrial Diseases Research Group,
Vall d'Hebron Research Institute, Barcelona
2nd September, UCL Institute of Neurology

The intriguing chaperone defect with DNAJB6 mutated LGMD1D

Professor Bjarne Udd
University of Tampere
21st May, Institute of Genetic Medicine, Newcastle University

Dissecting the pathogenesis of spinocerebellar ataxia type 3 using animal models

Professor Olaf Riess
University of Tuebingen
14th May, Institute of Genetic Medicine, Newcastle University

Thick filament disorders and distal arthrogryposis

Dr Anders Oldfors
University Hospital Goteborg
7th May 2013, UCL Institute of Neurology

Massively parallel sequencing for molecular diagnosis and gene identification in myopathies

Professor Jocelyn Laporte
University of Strasbourg
23rd April, Institute of Genetic Medicine, Newcastle University

Tailoring pigs as models for human monogenetic diseases, including DMD

Professor Eckhard Wolf
University of Munich
12th February, Institute of Genetic Medicine, Newcastle University

Molecular and cellular therapeutic strategies for spinal muscular atrophies

Professor Giacomo Comi
University of Milan
26th February, Institute of Genetic Medicine, Newcastle University

Antisense mediated exon skipping: a promising therapeutic approach for Duchenne muscular dystrophy and other rare diseases

Dr Annemieke Aartsma-rus
Leiden University Medical Center
29th January, Institute of Genetic Medicine, Newcastle University

Dystroglycan phosphorylation as a therapeutic target for DMD

Professor Steve Winder
Sheffield University
7th January, UCL Institute of Neurology

viii) MRC Centre supported British Myology Society annual meeting programmes 2013 & 2014

2013 MEETING PROGRAMME

Location:

Linbury Building, Worcester College

Wednesday 18th September

16:30-17:00 Tea

Commissioning Session

Chair: Michael Hanna

17:00-17:20 **Welcome and introduction**

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

17:20-17:40 **What you need to know about CRGs**

Dr Simon Hammans, Director Wessex Regional Muscle and Nerve Service, Southampton General Hospital

17:40-18:00 **Muscular Dystrophy Campaign & service developments**

Robert Meadowcroft, Chief Executive, Muscular Dystrophy Campaign

18:00-18:20 **NIHR Translational Research Collaboration**

Professor Patrick Chinnery, Director, Institute of Genetic Medicine Newcastle University

18:20-20:00 **An Update on Nationally Commissioned Services for:
Adults and Children with Rare Mitochondrial Diseases
Rare neuromuscular diseases
McArdle's Disease**

Neuroscience

Professor Kate Bushby, Institute of Genetic Medicine Newcastle University
Dr Robert McFarland, Wellcome Trust Centre for Mitochondrial Research
Dr Ros Quinlivan, MRC centre for Neuromuscular Diseases
Dr Jacqueline Palace, Oxford University Hospitals Trust

20:00 **AGM followed by Dinner at Worcester College**

21:00 **After-dinner talk**

Professor Victor Dubowitz

Thursday 19th September

Muscle Interest Group Session

Chair: Helen Roper

Birmingham Heartlands Hospital and Birmingham Children's Hospital

08:30-10:30 MIG case discussions

10:30-11:00 Coffee

Myotonic Dystrophy Session

Chair: Chris Turner

11:00-11:30 **Latest developments in therapy for Myotonic Dystrophy**

Dr Charles Thornton, University of Rochester Medical Center

11:30-12:10 **Review of the management of Myotonic Dystrophy including cardiac, respiratory, GI and sleep management and NICE Guidelines**

Dr Chris Turner, MRC Centre for Neuromuscular Diseases & Dr Mark Roberts, Salford Royal NHS Foundation Trust

12:10-12:30 **Management of Myotonic Dystrophy: cardiac aspects**

Professor Perry Elliott, UCL

12:30-13:30 Lunch

Congenital Myopathy Session: Review of latest developments in diagnosis and management

Chair: Francesco Muntoni

13:30-14:30 Case presentations

14:30-15:00 **Approach to rarer congenital myopathies**

Professor Francesco Muntoni, UCL Institute of Child Health and Great Ormond Street Hospital

15:00-15:30 **The congenital myopathies – 2013 update**

Dr Heinz Jungbluth, Evelina Children's Hospital, London

15:30-16:00 **Congenital Myopathy in Adults**

Dr Ros Quinlivan, MRC centre for Neuromuscular Diseases

16:00 Meeting close

2014 MEETING PROGRAMME

Location:

Wolfson College, Linton Road, Oxford OX2 6UD

Thursday 11th September

16:30-17:00 **Registration and Tea**

Session 1

Chair: Michael Hanna

- 17:00-17:10 **Welcome and introduction**
Professor Michael Hanna, Director, UCL Institute of Neurology and MRC Centre for Neuromuscular Diseases
- 17:10-17:20 **Muscular Dystrophy Campaign & service developments**
Robert Meadowcroft, Chief Executive, Muscular Dystrophy Campaign
- 17:20-17:50 **Enabling independence in the profoundly disabled**
Dr David Henderson-Slater, Nuffield Orthopaedic Centre
- 17:50-18:20 **The role of the rehabilitation team in NMD patient care**
Dr Margaret Phillips, University Hospital, Derby
- 18:20-18:50 **'Bridging the gap' an NHS England funded project**
Nic Bungay and Bobby Ancil, Muscular Dystrophy Campaign
- 18:50-20:00 **AGM**
Feedback from the BMS council (10 mins each)
BMS rules and Aims/ attracting new membership: Professor Mike Hanna
Training day for trainees: Dr Simon Hammans/ Dr David Hilton-Jones
Workforce planning: Dr Richard Petty
Neuromuscular curriculum: Dr Helen Roper
Standards of Care: Dr Michael Rose
Muscle pathology services: Professor Caroline Sewry/ Dr Janice Holton
North Star forms: late non-ambulant: Dr Ros Quinlivan
- 20:00 **Dinner at Wolfson College**
- 21:00 **After-dinner talk**
Professor Doug Turnbull

2014 Meeting programme contd...

Friday 12th September

Session 2

Chair: Simon Hammans

- 08:30-09:00 **Muscle Channelopathies; diagnosis and management**
Professor Mike Hanna, Institute of Neurology
- 09:00-09:30 **Diagnosis and management of DM2: Experience from Germany**
Professor Benedikt Schoser, Ludwig-Maximilians University of Munich
- 09:30-10:00 **An update on the Congenital Myasthenic Syndromes**
Professor David Beeson, University of Oxford
- 10:00-10:30 **Coffee**

Session 3

Chair: Ros Quinlivan

- 10:30-11:00 **Myofibrillar Myopathies: from patients to cell and animal models and back again**
Professor Rolf Schroeder, University of Erlangen
- 11:00-11:30 **An update on Mitochondrial Disease**
Professor Doug Turnbull, University of Newcastle
- 11:30-12:00 **Oculopharyngeal Muscular Dystrophy**
Dr Simon Hammans, Southampton General Hospital
- 12:00-12:30 **Adult DMD and North Star Network**
Professor Katie Bushby and Dr Ros Quinlivan
- 12:30-13:30 **Lunch**

Muscle Interest Group Session

Chair: Helen Roper

- 13:30-15:30 **MIG case discussions**
- 15:30-16:00 **Tea / Close**

16:00 **OXFORD MUSCLE MEETING (pls contact D Hilton-Jones or Monica Hofer)**

ix) MRC Centre Biobank supported research

APPENDIX ix

Research projects supported by the Biobank

Within UCL

Accelerate screening of PPMO drug candidates targeting exons 44,45,55, Jihee Kim

Advanced antisense oligonucleotide technology for exon skipping in DMD, Virginia Arechevala

Analysis of beta-dystroglycan in patients with GMPPB mutations after fibroblast transduction with MyoD adenovirus, Francesco Catapano

Beta-dystroglycan in diagnostics and therapeutics of DMD, Silvia Torelli

BIONMD, Irina Zaharieva

BVVL mutations in vitro, Amelie Pandraud

Charcot-Marie-Tooth disease and related disorders, Alex Rossor

Comparison of AONs designed to skip mutated dystrophin exons and restore dystrophin expression, Courtney Young

Contribution of human muscle derived stem cells to muscle regeneration, Jinhong Meng

Correcting pre-mRNA splicing in SMA, Haiyan Zhou

Correction of dystrophin duplications using zinc finger nucleases, Sarah Farmer

Correction of FKRP function via RNA trans-splicing, Sarah Farmer

Detecting neurofilament expression in plasma or serum from SMA patients, Haiyan Zhou

Developing antisense oligonucleotides as a therapy for neuromuscular diseases, Haiyan Zhou

Development of a collagen VI cyto blot, Virginia Arechevala

Development of an in vitro model of sporadic inclusion body myositis, Mhoriam Ahmed

Development of multi-functional muscle stem cells using human artificial chromosome vector for autologous cell therapy of DMD, Saverio Tedesco

Discover of therapeutic agents for the dystroglycanopathies, Elizabeth Stevens

Disease pathogenesis of ALS/MND in vitro, Philip McGoldrick

Dystrophin quantification and clinical correlations in BMD: implications for clinical trials, Silvia Torelli

Establishing the parameters for clinical trials of antisense oligonucleotide therapy in DMD, Irina Zaharieva

Finding new genes responsible for congenital muscular dystrophies and congenital myopathies, Tamieka Whyte

Flow cytometry for the analysis of α -dystroglycan glycosylation in fibroblasts from patients with dystroglycanopathies, Elizabeth Stevens

Functional characterisation of dopamine transporter deficiency syndrome, Manju Kurian

Functional studies in peripheral neuropathies, Elisavet Preza

Genetic and molecular analysis of dystroglycanopathies, Silvia Torelli

Genetic investigation on congenital muscular dystrophy and myopathy, Mattia Calissano

Identifying and validating pre-clinical biomarkers for diagnostics and therapeutics of NMDs, Irina Zaharieva

Integrins in congenital myopathies and CMD, Francesco Conti

Investigate how PD-related proteins may affect mitochondrial physiology or mitophagy, Marta Delgado Camprubi

Investigating Ca-imaging in SCA15, Sarah Wiethoff

Investigating GMPPB isoforms in patient cell lines with NMJ defects, Marianna Serrenti

Investigating mitochondrial dysfunction in CMT2 patient, Ellen Cottenie

Investigation into utrophin upregulation in DMD muscle, Nari Janghra

Investigation of nuclear encoded mitochondrial proteins and their role in the formation of mitochondrial DNA mutations, Rob Pitceathly

Investigation of the IGHMBP2 protein in fibroblasts, Ellen Cottenie

Juvenile dermatomyositis cohort biomarker study, Lucy Wedderburn

Metabolic profiling in human fibroblasts with mutations in proteins affecting mitochondrial function, Henry Houlden

Mitochondrial diseases: calcium signaling and mitochondrial turnover as novel therapeutic targets, Will Kotiadis

Mitochondrial dysfunction in lysosomal storage disorders, Laura Osellame

Mitochondrial function and riboflavin metabolism in human fibroblasts with BVVL mutations compared with controls, Henry Houlden

MyoD transduction and differentiation to analyse calcium transients in response to caffeine, Marta Fernandez-Fuente

Outcome measures in DMD: a natural history study, Karen Anthony

Phase 1/II clinical trial of antisense oligonucleotide therapy in DMD, Karen Anthony

Quantification of utrophin in non-regenerating muscle fibres in DMD and controls, Jennifer Morgan

Repair of dystrophin using nucleases, Francesco Conti

Restoring dystrophin expression in DMD, Karen Anthony

Role of F1F0-ATOPsynthase endogenous regulator IF1 in mtDNA diseases, Michelangelo Campanella

Shedding light on the pathophysiology of periodic paralysis, Neta Amior

The contribution of human stem cells to functional satellite cells, Soyon Chun

The role of the necrosome in DMD myofibre death, Max Bencze

The self-renewal of human muscle stem cells, Saverio Tedesco

Translational research in neuromuscular disorders: advanced dystrophin quantification for streamlined screening of RNA treatments, Virginia Arechevala
Uncovering the role of mitochondria in the pathogenesis of core myopathies, Iulia Oprea

Uncovering the role of mitochondrial dysfunction in core myopathies, Jenny Sharpe

VAP-1 contribution to muscle fibrogenesis and interference with diffusion of AONs, Silvia Torelli

Within NCL

Analysis of synaptogenesis in desminopathy. Steve Laval, Institute of Genetic Medicine, Newcastle University

Investigating the disease mechanisms in Leber hereditary optic neuropathy, Jennifer Duff. Institute of Genetic Medicine, Newcastle University

Investigating the role of ARMET and CRELD2 in the pathogenesis of human musculoskeletal diseases. Michael Briggs, Institute of Genetic Medicine, Newcastle University

Investigation of patients with combined respiratory chain deficiencies. Angela Pyle, Institute of Genetic Medicine, Newcastle University

Analysis of mtDNA in Chillingham Cow. Aurora Gomez-Duran, Institute of Genetic Medicine, Newcastle University

Analysis of mtDNA in Chillingham Cows. Angela Pyle, Institute of Genetic Medicine, Newcastle University

Analysis of patient cell line with an Ora1 mutation. Dr. Hue Hornig-Do, Institute of Ageing and Health, Newcastle University

Analysis of RNA in Patients with Glycogen Storage Diseases Type2 (Pompe). Matias Wagner, Institute of Genetic Medicine, Newcastle University

Anoctamin 5 analysis. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

Assessing copy number control regulation. Phillippa Carling, Institute of Genetic Medicine, Newcastle University

Assessing the feasibility of induced pluripotent stem cells to provide a disease model for age related macular degeneration. Dean Hallam, Institute of Genetic Medicine, Newcastle University

Cardiac abnormalities in mtDNA disease. Professor Doug Turnbull, Institute of Ageing and Health, Newcastle University

Characterizing a mutation in SPTLC2 in a family with HSAN I. Daniyal Daud, Institute of Genetic Medicine, Newcastle University

Collagen V analysis. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

Depletion and Repopulation of myoblasts. Phillippa Carling, Institute of Genetic Medicine, Newcastle University

Desmin/Myotilin. Teresinha Evangelista Northern Genetic Service, Newcastle

Determining the levels of potential biomarkers in samples from DMD and non-DMD patient cell lines. Dan Cox, Institute of Genetic Medicine, Newcastle University

Diagnosis of PDH Deficiency. Dr Robert McFarland, Institute of Ageing and Health, Newcastle University

Differences in satellite cell populations between extraocular and other skeletal muscles. Dr Cynthia Yu-Wai-Man, Institute of Genetic Medicine, Newcastle University

Disease mechanisms in dominant optic atrophy. Dr Florence Burté, Institute of Genetic Medicine, Newcastle University

Disturbance of mitochondrial dynamics in human genetic diseases. Kamil Sitarz, Institute of Genetic Medicine, Newcastle University

Disturbed interactions between mitochondria and the endoplasmic reticulum: implications for human disease. David Moore, Institute of Genetic Medicine, Newcastle University

Elucidating the causes of mitochondrial disease. David Lewis-Smith, Institute of Genetic Medicine, Newcastle University

Exon skipping as novel approach for dysferlinopathie. Isabella Houweling-Gazzoli, LUMC, Leiden, Netherlands

Exploring the role of mitochondrial abnormalities in myofibrillar and other myopathies. Amy Vincent, Institute of Ageing and Health, Newcastle University

Generation of iPSCs from patients with AMD. Dean Hallam, Institute of Genetic Medicine, Newcastle University

Genetic determination of patients with undetermined multiple deletions-related mitochondrial disease. GS Gorman, Institute of Ageing and Health, Newcastle University

Genetic Heterogeneity in BM. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

Genetic Heterogeneity in BM. Golar Torabi Farsani, Institute of Genetic Medicine, Newcastle University

Genetic heterogeneity in collagen VI related myopathy. Golar Torabi Farsani, Institute of Genetic Medicine, Newcastle University

Genetic heterogeneity in the collagen VI disorders. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

Genetic testing for LAMA2 carrier status. M Guglieri, Institute of Genetic Medicine, Newcastle University

Identification of gene defects in brain iron accumulation. Rita Horvath, Institute of Genetic Medicine, Newcastle University

Identification of novel biomarkers for neuromuscular disorders. Mattia Calissano, Institute of Genetic Medicine, Newcastle University

Identification of novel disease genes in combined respiratory chain deficiencies. Vivienne Neeve, Institute of Genetic Medicine, Newcastle University

Improving our understanding of autosomal dominant retinitis pigmentosa using PRPF31 patient specific induced pluripotent stem cells (iPSC). Adriana Buskin, Institute of Genetic Medicine, Newcastle University

Investigating ALG2 in patient fibroblasts. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

Investigating LHON disease. Aurora Gomez-Duran, Institute of Genetic Medicine, Newcastle University

Investigating ALG2 in patient fibroblasts. Golar Torabi Farsani, Institute of Genetic Medicine, Newcastle University

Investigating genotype-phenotype correlations in WFS1 positive fibroblast lines. Kamil Sitarz, Institute of Genetic Medicine, Newcastle University

Investigating glycosylation defects in GFPT1 patients. Juliane Mueller/ Jon Ingledew, Institute of Genetic Medicine, Newcastle University

Investigating the cellular impacts of PRPF31 mutations using patient specific induced pluripotent stem cells and in situ genetic correction with engineered zinc finger nucleases. M Lako, D Steel, Institute of Genetic Medicine, Newcastle University

Investigating the influence of VPA on POLG affected fibroblast lines. Kamil Sitarz, Institute of Genetic Medicine, Newcastle University

Investigating the mechanisms of clonal expansion of mtDNA deletions. Kim Clugston, Institute of Ageing and Health, Newcastle University

Investigating the molecular mechanisms of mitochondrial translation deficiencies. Rita Horvath, Zophia Chrzanowska-Lightowlers, Robert Lightowlers, Institute of Ageing and Health, Newcastle University

Investigating the molecular mechanisms of respiratory chain deficiency. Rob Taylor, Institute of Ageing and Health, Newcastle University

Investigating the RBCK1 gene as a cause of GSD Debbie Hicks. Institute of Genetic Medicine, Newcastle University

Investigation of CHKB deficiency in sample H7518. Volker Straub, Institute of Genetic Medicine, Newcastle University

Investigation of combined respiratory chain (RC) deficiencies. Rita Horvath, Institute of Genetic Medicine, Newcastle University

Investigation of combined respiratory chain deficiencies. Hue Hornig-Do, Institute of Ageing and Health, Newcastle University

Investigation of mitochondrial network in WFS1 mutated patients. Kamil Sitarz, Institute of Genetic Medicine, Newcastle University

Investigation of pathogenicity of COL12 variation. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

Investigation of patients with combined respiratory chain deficiencies. Veronika Boczonadi, Institute of Genetic Medicine, Newcastle University

Investigation of patients with combined respiratory chain deficiencies. Paul Smith, Institute of Genetic Medicine, Newcastle University

Investigation of possible aminoacyl tRNA synthetase defect. Zosia Chrzanowska-Lightowlers and Abdulraheem Almalki, Institute of Ageing and Health, Newcastle University

Investigation of possible aminoacyl tRNA synthetase defect. Rob Taylor, Institute of Ageing and Health, Newcastle University

Investigation of the mitochondrial network in WFS1 mutated fibroblast lines. Kamil Sitarz, Institute of Genetic Medicine, Newcastle University

Leber Hereditary Optic Neuropathy. David Moore, Institute of Genetic Medicine, Newcastle University

Localisation of telomerase in muscle stem cells. Gabrielle Saretzki, Institute of Genetic Medicine, Newcastle University

Mitochondrial Dynamics in a new mitochondrial diseases (with congenital muscular dystrophy and optic atrophy/peripgeral neuropathy). Kamil Sitarz, Institute of Genetic Medicine, Newcastle University

Mitochondrial fragmentation in PD. Gavin Hudson, Institute of Genetic Medicine, Newcastle University

Modelling Outer Retinal Disease with Induced Pluripotent Stem Cells. Valeria Chichagova, Institute of Genetic Medicine, Newcastle University

Molecular Analysis of mitochondrial tRNA proline mutation. Paul Smith, Institute of Genetic Medicine, Newcastle University

Molecular Analysis of mitochondrial tRNA tryptophan. Paul Smith, Institute of Genetic Medicine, Newcastle University

Molecular basis of reversible cox deficiency. Veronika Boczonadi, Institute of Genetic Medicine, Newcastle University

Molecular and biochemical characterization of human mitochondrial translation deficiencies. Veronika Boczonadi

mtDNA mutations and human disease. Aurora Gomez-Duran, Institute of Genetic Medicine, Newcastle University

Muscle targeted gene therapy for T2DM. Gillian Patterson. Institute of Cellular Medicine, Newcastle University

Neuromics studies. Debbie Hicks, Institute of Genetic Medicine, Newcastle University

New genes in Congenital Myasthenic Syndromes (CMS). Juliane Mueller, Institute of Genetic Medicine, Newcastle University

Optimal Mini-Dystrophin Construct for Gene Delivery to Skeletal Muscle. Mojgan Reza, Institute of Genetic Medicine, Newcastle University

Parkinson and mitochondrial pathogenesis. Aurora Gomez-Duran, Institute of Genetic Medicine, Newcastle University

Role of Mitochondrial Abnormalities in Disease. Sally Spendiff, Institute of Ageing and Health, Newcastle University

Studying the mechanism of deficient mitochondrial translation in human cells. Marina Bartsakoulia, Institute of Genetic Medicine, Newcastle University

Studying the molecular basis of reversible infantile cytochrome C oxidase myopathy. Veronika Boczonadi. Institute of Genetic Medicine, Newcastle University

Studying the pathmechanism of coenzyme Q10 deficiency. Rita Horvath, Institute of Genetic Medicine, Newcastle University

The Pathophysiology of Anoctaminopathy. Kirsty Russell, Institute of Genetic Medicine, Newcastle University

To investigate functions of candidates genes in mitochondrial disease with combined RC deficiency. Angela Pyle, Institute of Genetic Medicine, Newcastle University

To investigate functions of candidates genes in mitochondrial disease with combined RC deficiency. Dr Michael Keogh, Institute of Genetic Medicine, Newcastle University

Understanding mitochondrial deafness. Peter Kullar, Institute of Genetic Medicine, Newcastle University

Outside of UCL/NCL

A human induced pluripotent stem cell (hiPSC) model to study neutral lipid metabolism and its impact on liver stages of malaria parasites. Jaishree Tripathi, Wellcome Trust Sanger Inst. Hinxton, Cambridge and Stem Cell Inst, Cambridge University

A read-through drug for DMD, Carmen Bertoni, University of California

AAV-U7 for exon-skipping for dystrophin: pre-clinical tests in vitro, Vincent Mouly, Institut de Myologie, France

Adiponectin and skeletal muscle : potential role in Duchenne Muscular Dystrophy. Sophie Lecompte. Université Catholique de Louvain - IREC – EDIN, Brussels

Analysis of miRs in biomarker samples from utrophin modulator clinical trials in DMD patients. Jon Tinsley/Bob Holt, Tepnel, Hologic Ltd., Manchester

Analysis of RNA in patients with congenital myasthenic syndrome. Juliane Mueller/Dr. Rolf Stucka, Institute of Genetic Medicine, Newcastle University and Lab for Molecular Myology, Marchioninstr. 17,81377Munich, Germany

Analysis of RNA in patients with congenital myasthenic syndrome. Rolf Stucka & Dr. Juliane Mueller, lab for Molecular Myology, Munich, Germany

Antisense oligomer mediated splice switching in DMD cells. Steve Wilton/Sue Fletcher, Murdoch University, Perth, Australia

AON candidate screening in myogenic cell cultures from DMD patients with different mutations. Anneke Janson,

Biomarker discovery in dystrophinopathy. Jon Tinsley, Summit plc & Nordic

Bioscience, Denmark

BIO-NMD. A Ferlini, UNIFE (Italy)

Candidate gene and protein studies in disease, Sebahattin Cirak, Children's National Medical Center, USA

cDNA sequencing for laminin $\alpha 2$ mutations in fibroblast. Elena Pegoraro

Charcot-Marie-Tooth disease and related disorders, Majid Hafezparast, University of Sussex

Clinical and molecular manifestations of neuromuscular and neurogenetic disorders of childhood, Carsten Bonnemann, Porter Neuroscience Research Center, USA

Delivery of dysferlin protein to muscle cells. Haifan Yin, Tianjin Medical University, China

Determining the contractile function of skeletal muscle fibres from patients with various congenital myopathies, Julien Ochala, Kings College London

Determining the levels of a potential urinary biomarker in samples from DMD and non-DMD patients. Carl Morris, Pfizer, Cambridge MA, USA

Developing modulators of mitophagy as treatments for mitochondrial diseases, Joanna Poulton, Oxford University

Development and in vitro testing of a Dystrophin sensor needle.

Diagnosis of diseases using olfactory biosensor, Hwi Jin Ko, Seoul National University

Diagnostic Studies. Kim Bartlett

Diagnostic test for somatic FSHD mutation. Volker Straub/molecular diagnostic lab Straub, Muscle Immunoanalysis Unit, Dental School, Newcastle

Dystrophin messenger topography before and after antisense treatment in immortalised human myoblast cells, Alessandra Ferlini, Universita di Ferrara

Dystrophin mRNA analysis for patient GC45063. Volker Straub/Guys hospital, Genetics Unit, Guys Hospital

ER-mitochondrial communication in fibroblasts from CMT2A/MFN2 patients. Eric A. Schon, Columbia University, New York

Exon Skipping, Thomas Merritt, Oxford University

Fatty acid oxidation diagnostics. Marie Appleton

Functional mapping of dystrophin isoforms, Carl Adkin, University of Western Australia

Functions of mitochondrial miRNA and putative therapeutic targets in human muscle disorder. Vanessa Jahnke

Generation and analysis of neuromuscular junctions using motorneurons differentiated from iPS cells originated from SMA patients and human myoblasts. Brunhilde Wirth, Institute of Human Genetics, University of Cologne

Genome surgery of the DMD gene, Linda Popplewell, Royal Holloway University of London

Glutaric Aciduria biochemical testing. Patrick Chinnery / Kim Barlett. Royal Victoria Infirmary

Growth dependence of *Toxoplasma gondii* on host lipase. Frank Seeber, Robert Koch Institute, Berlin

Identification and characterization of novel EDMD alleles. Eric Schirmer, University of Edinburgh

Identification of a gene for CMT with cataracts. Jan Senderek/Dr. Rolf Stucka, Friedrich-Baur-Institut, Klinikum der Universität München, München, Germany

Identification of gene defects in combined respiratory chain (RC) deficiencies. Eric Shoubridge, Dept. of Molecular Neurogenetics, McGill University, Montreal, Quebec, Canada

Identification of novel biomarkers in DMD and Becker plasma. Francis Wilson, Summit plc, Abingdon, Oxfordshire, UK

Identifying and validating pre-clinical biomarkers for diagnostics and therapeutics of Neuromuscular Disorders. Cristina Al-Khalili Szigarto, School of Biotechnology, Royal Inst of Technology, Stockholm, Sweden

Immunodiagnosics and functional studies of ANO5 linked muscular dystrophy. Rumaisa Bashir, Institute of Biological & Biomedical Sciences, University of Durham

Immunodiagnosics of ANO5 linked muscular dystrophy. Rumaisa Bashir, Institute of Biological & Biomedical Sciences, University of Durham

Induced pluripotent stem cells and zebrafish models of dystroglycanopathies, Yung-Yao Lin, Wellcome Trust Sanger Institute

Institute for Inflammation and repair. Giulio Cossu, Institute for inflammation & repair, Manchester University

Investigate skin fibroblasts with acylcarnitine profile suggestive of glutaric aciduria type II.

Investigating expression of muscular dystrophy proteins. Rumaisa Bashir, Institute of

Biological & Biomedical Sciences, University of Durham

Investigating glycosylation defects in GFPT1 patients. Francois Foulquier/ Dr. Juliane Mueller, Glycobiology Unit UMR8576, University of Lille

Investigation of Col6a3 function in the nervous system. Juliane Winkelmann, Stanford University Winkelmann,

Measurement of GDF8 levels in DMD/BMD serum. Carl Morris, Pfizer, Cambridge MA, USA

Mitochondrial biogenesis and human disease, Antonella Spinazzola, Medical Research Council

Mitochondrial DNA diseases: development of cardiomyocytes from patients' fibroblasts (inducible pluripotent stem cells). Matthew Bates

Molecular and biochemical characterization of human coenzyme Q deficiency diseases. Placido Navas, University Pablo de Olavide, Seville, Spain

Muscular Dystrophy with Deafness, confirmation of a newly identified mutation in patient GC22984. Carsten Bönnemann/Volker Straub, Porter Neuroscience Research Centre, Bethesda, MD 20892-3705, USA

Myostatin and leakage biomarkers in muscular dystrophy serum samples. Carl Morris/Lochmuller, Pfizer, Cambridge MA, USA

Neuromics pannel/exome analysis. Volker Straub/Dr. Peter Bauer, Institute of Human Genetics, Tübingen University, Germany

New in vitro models of DMD by induced pluripotency in patient biopsies. Emily Dick, CBS, University of Nottingham

Novel insights into muscular dystrophy: role of COLVI, intramuscular adipose tissue and metabolic dysregulation, C Jimenez-Mallebrera, Hospital Sant Joan de Deu

P Chinnery/K Bartlett, Royal Victoria Infirmary, Newcastle

Peptide Nucleic Acids for inhibition of the replication of mutated mitochondrial DNA. Markus Lamla, Institute of Human Genetics, University of Ulm

Phenotypic analyses of cells from individuals with muscular dystrophy, Anne Bang, Sanford Medical Institute

Potential new CMD gene. Jan Senderek, Friedrich-Baur-Institut, Klinikum der Universität München, München, Germany

Promoting expression of the N-truncated dystrophin isoform in patients cell lines harboring 5' mutations through activation of the glucocorticoid-inducible DMD IRES: a

promising application for other 5' dystrophin's mutated patients, Nicholas Wein, Nationwide Children's Hospital, USA

Proteomic biomarker discovery in muscles and fluids (WP3) and Validation biomarkers in humans (WP4) for BIO-NMD. Peter-bram 'tHoen, LUMC, Leiden, Netherlands

Proteomics profiles in myofibrillar myopathies. Hanns Lochmuller/Rudi Kley/Anna Sarkozy, Bergmansheil Bochum, Germany

Quantification of fibrosis in DMD and Becker plasma using mass spec approaches. Jon Tinsley, Nordic Bioscience, Norway

Role of Bmi1 in maintenance and function of muscle satellite cells, Silvia Marino, Queen Mary's University of London

Role of nuclear envelope proteins in sporadic inclusion body myositis, Federico Roncaroli, Charing Cross Hospital

Role of Opa-1 and Mfn2 mutants in human skeletal muscle cells mitochondrial fusion and myogenic differentiation.

Role of polycomb group genes in human neuromuscular diseases, Silvia Dibenedetto, Queen Mary's University of London

Secondary pathogenetic mechanisms in XLMTM and CNM, Susan Treves, Universitatsspital Basel

SLC25 gene mutation associated with neuromuscular defect. Hanns Lochmuller/Prof. Luigi Palmieri, Dipartimento Bioscienze, Biotecnologie e Biofarmaceutica Palazzo ex, Facoltà di Farmacia (I piano) Campus Universitario "Ernesto, Via Edoardo Orabona, Italy

Splice intervention therapies for Duchenne muscular dystrophy and other genetic disorder, Sue Fletcher, University of Western Australia

Splice switching strategies to treat Duchenne muscular dystrophy. Sue Fletcher, Murdoch University, Perth, Australia

Study DMD Associated Heart Disease Using Patient iPS Cells. Lei Yang, Rangos Research center, University of Pittsburgh, Pittsburgh, PA, 15201, USA

Studying the role of CoQ10 deficiency in cerebellar ataxia. Marie Appleton , Royal Victoria Infirmary, Newcastle

The investigation of oligonucleotide therapy with application to human disease. Rebecca Moore, University of Nottingham

The role of mevalonate derived metabolites (isoprenoids) in statin-related and

mitochondrial myopathies. Marie Appleton, Royal Victoria Infirmary, Newcastle

The role of muscle in GARS neurodegeneration.

Treatment of hereditary cardiomyopathy. Jan Ksienzyk , University Hospital Heidelberg, Germany

Whole exome analysis in ataxia. Kim Barlett, Department of Clinical Biochemistry, Royal Victoria Infirmary, Newcastle

x) MRC Centre final SAB report 2011

Robert C. Griggs, M.D.
*Professor of Neurology, Medicine, Pediatrics,
Pathology & Laboratory Medicine and Center for
Human Experimental Therapeutics*



**MRC Centre for Translational Research in Neuromuscular Diseases
Second Scientific Advisory Board Review
21st November 2011**

1. Introduction: The Scientific Advisory Board reviewed extensive written material prior to the meeting. At the 21 November 2011 review the Board met with key London and Newcastle leaders and heard presentations from the Ph.D. and M.D., Ph.D. trainees in the Centre. The Centre Director and other leadership were admirably responsive to the previous SAB criticisms and advice. The SAB was unanimous in the opinion that the Centre has made outstanding progress and that the Centre is arguably the world's leading program for translational research in neuromuscular disease. Examples of specific strengths and accomplishments include:

- Integration of multiple experts and many investigative teams into interdisciplinary programs.
- Well-coordinated and synergistic collaboration across geographically-separate UK locations: Newcastle, London and recently Oxford.
- Similarly synergistic program development with international groups in the EU and USA.
- Established world leaders in each major area of research enterprise with the recent recruitment of additional highly-visible, internationally recognized expertise.
- Development of state-of-the-art infrastructure for phenotyping patients with neuromuscular disease.
- World leadership in developing prospective registries that have genotyped/phenotyped extraordinary numbers of patient with many neuromuscular diseases.
- A biobank that has already become both larger and more productive than other comparable facilities.
- Linkage of Centre institutions with outstanding facilities for animal model development and study.
- Development of a large portfolio of clinical trials under the leadership of Centre faculty.
- Creation of an outstanding training program with an astonishing applicant pool (50/slot)
- Establishing a successful prototype for addressing them many challenges of translational research in a subset of rare diseases
- Strong administrative leadership.

The SAB agreed that continuing the success of the Centre will require:

- Prioritizing amongst the many opportunities to target a limited number of diseases most susceptible to successful treatment .
- Similarly prioritizing amongst diseases for those most susceptible to stratified (personalized) care.
- Developing the systematic approach and bioinformatic expertise to capitalize on data from next generation sequencing.
- Building upon their expanded expertise in imaging for rigorous biomarker development and application.
- Continued fostering the careers of trainees to position them for leadership in translational research in the years ahead.

The SAB agreed that continuing the success of the Centre will require: (Continued)

- Developing/recruiting senior colleagues within the major areas of scientific enterprise.
- Continuing to link with international clinical trial networks --- in particular the recently-funded NIH NeuroNEXT infrastructure.

The SAB reviewed and discussed many key aspects of the Centre including:

Cell therapy: Using myogenic progenitor cells or myoblasts with or without *ex vivo* correction is a translational research focus of the MRC Centre. The goal is to repair chronically diseased skeletal muscle and to foster regeneration by replenishing an (exhausted) stem cell pool, possibly in combination with the transfer of therapeutic genes or gene repair approaches such as lentivirus-U7-mediated exon skipping. There is strong and internationally recognized expertise in this field (Muntoni, Morgan), and this will be further strengthened from January 2012 by the arrival of a world leader, Giuglio Cossu. His plan to transfer artificial chromosomes into stem cells in order to repair missing genes is innovative and requires proof of concept. The cell therapy approach is transformative to the field of muscular dystrophies. It ties in with MRC Centre competencies such as biobanking (Lochmueller), viral platform (Thrasher) and GMP-compliant cell therapy facilities (London, Newcastle) for future translation into clinical trials. The goal of setting up a first in human phase 1 trial for Duchenne muscular dystrophy within the next 5 years is ambitious but fits with the translational role of the Centre.

NextGen sequencing: MRC Centre investigators have already found 7 new causative genes using exome sequencing methods. Due to the unpublished nature of the data, the SAB did not learn details of the approach and data analysis but commends the Centre for heading in this innovative direction. The collaborative work on phenotyping and outcome measures will serve the investigators well in dissecting the genotype/phenotype correlations in newly identified disease genes. In subsequent studies, the investigators must have a 'pipeline' regarding prioritization of patients selected for exome sequencing, and then prioritization and validation methods for variants identified by NextGen sequencing.

Animal models: Even though the Animal Studies Core was given only limited support in the original MRC award (50k over five years) the Core has established a neuromuscular phenotyping lab for animal models and has piloted studies using MRI through use of other institutional resources. The animal studies core has also established a broad phenotypic screen that can readily be applied to a spectrum of disease models. In so doing the core is exceptionally strong in preclinical research that provides rationale and proof of concept in support of clinical trials. As examples, Francesco Muntoni plays a leading role in development of animal models of dystroglycanopathy, Martin Koltzenburg has developed important models of neuropathic pain, and Lizzie Fisher and their Harwell collaborators play a leading role in the International Mouse Phenotyping Consortium, including the MRC Neuromouse effort. A considerable strength in the MRC Centre is the cross-talk between basic and clinical researchers on designing preclinical studies that are based upon considerations of clinical feasibility. With their application of NextGen sequencing and discovery of new disease genes in patients, the Centre will be poised for decisions as to which mutations should be prioritized to develop animal models and move forward to understand mechanisms and to develop therapy. Although the MRC is not providing major support, the Animal Studies Core is essential to identify area(s) where UCL/NCL can lead toward better

preclinical studies that assess candidate therapies and reduce the failure rate of phase 2 clinical trials. Through rigorous design and conduct, and thorough reporting of preclinical proof of concept data that link basic and clinical scientists to ensure that only carefully triaged candidate therapeutics go to clinical trials. The MRC Centre can play a leading role by facilitating best practices through conferences, publications, and examples of their own choices as to what goes to clinical trial.

Biobank: The MRC Center for Neuromuscular Diseases has successfully created a national neuromuscular biobank: Human muscle and nerve tissues and cell cultures, with currently almost 2000 human cell lines that have been used in more than 20 scientific projects. The establishment of the biobank has allowed both Center investigators and also external centres to receive cell lines for their own research. The MRC has recruited biomaterials (20%) from external labs in the biobank. More than 600 samples were given out for research to 50 scientists, and there are already 13 research publications and 4 grant applications funded using the biobank (3 are joint applications between London and Newcastle). The MRC biobank is now linked to international rare disease biobanks via the Eurobiobank. The Centre has enabled structural support to create a national biobank for neuromuscular diseases with planned further integration into the Eurobiobank, including a certification for biobanking.

Imaging: The goal of MRI imaging in neuromuscular disease during the first cycle was to increase the use of strong MRI infrastructure to develop better biomarkers for neuromuscular diseases. They have applied quantitative MRI in IBM and CMT. Manuscripts are in preparation for test-retest reproducibility in healthy volunteers, cross sectional, and longitudinal studies. The Newcastle site took the lead on the first systematic, multi center study in LBMD2I. Twelve month follow up measurements are underway. The center has developed novel approaches to using existing hardware and software to systematically make quantitative measurements and apply them as a biomarker of patient phenotype. Such implementation will be important for ongoing and future clinical trials. One of the strengths of the Center is that the sites are using different hard and software. In this way, it is a model for future multicenter clinical trials in neuromuscular disease. Thus, data regarding intersite and test-retest reliability will be important for such future studies.

Clinical trials: The Centre infrastructure has made possible an increase in the number of experimental trials in from 8 to 30 --- many directed by Centre investigations. There are already 19 manuscripts based on these studies. The MRC Neuromuscular Centre has a unique resource for leadership in trials: First, world leadership and expertise in many diseases including the muscular dystrophies, channelopathies, mitochondrial diseases and inherited neuropathies. Second, the extensive registries maintained by the Centre facilitate trials because the patients are well characterized and are available for rapid recruitment. Registries within the Centre for Duchenne Muscular Dystrophy (DMD), channelopathies, mitochondrial diseases and inherited neuropathies are among the best in the world. The SAB was impressed by the successful rapid recruitment of patients for many of the trials, particularly since many trials in other centres fail because of inadequate recruitment; third, these registries position the Centre for participation in trials supported by industry and for international studies since both industry and other sites can count on well characterized patients that will be recruited. Examples include the internationally recognized antisense oligonucleotide trials to promote exon skipping in DMD that is funded by industry and the ascorbic acid trial in CMT1A in which investigators in Italy sought out and

partnered with the Centre for their project. Fourth, the excellent research in cell biology of neuromuscular diseases at UCL and Newcastle, facilitates a move into clinical trials since the infrastructure for trials is in place. Finally, the Centre is well-positioned to take the lead in developing new approaches to trial design and outcome measures because of its strong imaging expertise. (Examples include the use of MRI outcome measures for inclusion body myositis (IBM) and neuropathies as well as trials to measure the benefits of physical exercise in the neuropathies and mitochondrial disorders.)

Exercise: Newcastle has a long tradition of exercise science investigators and interventions in other (non-NMD) populations, and the MRC Centre proposes to leverage this expertise to the MRC neuromuscular centre. There is increasing international acknowledgement that exercise interventions are greatly needed in neuromuscular diseases. This will become increasingly important as combinatorial therapies are assessed in translational studies. An NIH NIAMS consensus panel made exercise interventions in neuromuscular diseases a top priority. Exercise interventions in neuromuscular disease becomes especially important in the context of combinatorial therapeutic modalities. Recent published studies from this MRC Centre (Becker muscular dystrophy) and other centers (polymyositis) have uniformly shown functional benefit from exercise as a therapeutic modality in neuromuscular disease. Bridging the exercise science and neuromuscular interventions areas within the context of the MRC Centre is a logical and appropriate extension of the Experimental Clinical Trials section. While outcome measures will need to be clarified in neuromuscular exercise interventions on Centre patients, the endpoint research in the context of natural history studies, coupled with the imaging surrogate endpoint research, will provide outstanding synergism between these three subsections of the Experimental Clinical Trial section. Centre investigators should highlight their previous research in Becker, and propose integrating exercise into prospective clinical trials with clear methods and end points to show the relevance and significance of their approach.

Training: The MRC Centre is training 7 graduate students and 2 clinical students for a Ph.Ds that are directly funded by the MRC Centre grant. The 9 students are concluding their training. These students were recruited from a vast number of applicants (~50/slot) reflecting the Centre's ability to attract outstanding trainees. The training program provides strong clinical perspective to Ph.D. candidates and an equally strong and broad basic science familiarity to M.D. clinician trainees. The presentations of the Centre's trainees were uniformly outstanding. In addition to the Centre-funded trainees, a much larger number of non clinical and clinical PhD trainees funded are integrated into many of the Centre' training venues. The SAB considers that this program has been highly successful justifying an expansion in the number of trainees (if possible) as well as continued mentoring and career launching of trainees who are finishing their program.

Host institution's commitments: Both UCL and Newcastle have made a substantial financial matching contribution (£3 million host support in total to match the application to the MRC). The fruits of the existing host commitment are broadly evident: major space commitments; outstanding facilities for phenotyping patients; major recruitments of new faculty in areas that have strengthened the Centre; establishment of a highly productive biobank; new imaging capability coming on board; expansion of training activities of the Centre to a much larger group of non-Center trainees. Furthermore, while not necessarily a by-product of the Centre, the appointments of Centre leadership and investigators into

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senior academic positions at the National Hospital (Prof. Hanna) and at Newcastle (Prof. Chinnery) inspires confidence that both institutions will maintain their high level of commitment to the Centre as well as reap broad benefits from the Centre's contributions.

The Scientific Advisory Board:

Eric Hoffman

John Porter

Louis Ptacek

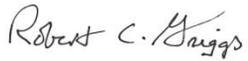
Michael Shy

Vincent Timmerman

Thomas Voit

Stephen Waxman

Robert C. Griggs, Chair,

 (signed for the SAB)

xi) MRC Centre staff list

MRC Centre staff list

Centre Director

Professor Michael Hanna

Centre Co Director, London

Professor Mary M. Reilly
Professor Francesco Muntoni
Professor Martin Koltzenburg

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

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

MRI Physicist, UCL

Dr Chris Sinclair

MRC Senior Research Associate (Stem Cell)

To be appointed

MRC CNMD Biobank London ICH/ION

Diana Johnson

CNMD Clinical Trials Co-ordinators, UCL

Daleen Lopez-Begg (Senior co-ordinator)
Gisela Barretto

MRC Centre Senior Administrators

Christine Oldfield
Zoe Scott

Centre Co Director, Newcastle

Professor Kate Bushby
Professor Doug Turnbull

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, Newcastle

Professor Andrew Blamire
Professor Kate Bushby
Professor Patrick Chinnery
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

MRI Physicist, Newcastle

Dr Paola Porcari

MRC CNMD Biobank Newcastle

Mojgan Reza
Dan Cox

CNMD Clinical Trials Co-ordinators, Newcastle

Becky Davis
Julia Maddison

xii) MRC Centre student list

MRC Centre Student List

UCL

MRC or Host or other Funded Non-Clinical PhD

Louise King
Andreea Manole
Charlotte Spicer
Michael Thor
Emma Wilson
Ione Meyer
Prasanth Sivakumar
Neta Amior
Qiang Gang
Alice Gardiner
Ellen Cottenie

MRC or Host or other Funded Clinical PhD

Dr Matthew Evans
Dr Umaiyal Kugathanan
Dr Alex Horga
Dr Helen Devine
Dr Karen Suetterlin
Dr Fatima Jaffer
Dr Renata Scalco

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
Calum Kirk
Golara Torabi Farsani
Michele Giunta
Mojan Reza
Morten Ritso

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