MRC Centre for Translational Research in Neuromuscular Diseases

Third Scientific Advisory Board Review

14th November 2014

at

the MRC Centre for Neuromuscular Diseases UCL
8-11 Queen Square, London
MRC Centre for Translational Research in Neuromuscular Diseases

Scientific Advisory Board Review

SAB 2014

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8-11 Queen Square, London
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1. Executive Summary

The MRC Centre for translational research in Neuromuscular Diseases was established in February 2008 following the first five year MRC award of ~£3m. With critical strategic advice from the SAB in 2011 the Centre was successfully renewed in 2013 for a further five years. In renewal there were approximately matching host and MRC contributions producing a total funding envelope of ~£6m. In renewal this resource has been effectively split equally by the Director between the two MRC Centre partner sites in London UCL and Newcastle for the period 2013-2018.

The mission of the Centre is to translate science into experimental medicine and new treatments for children and adults with disabling fatal neuromuscular diseases

A national strategic research partnership: the MRC Centre is a translational research partnership that builds on long established clinical and research links and complimentary expertise. It brings together colleagues at the UCL Institutes of Neurology and Child Health with those at the Institute of Genetic Medicine and the Wellcome Centre for Mitochondrial Research at Newcastle University. The Centre works with very large adult and paediatric patient populations drawn from across the UK and cared for at the major co-located NHS Foundation Trust Hospitals; the National Hospital for Neurology and Neurosurgery, Queen Square, Great Ormond Street Hospital and Newcastle-upon-Tyne University Teaching Hospitals.

Overcoming obstacles translating science into patient benefit: in establishing the Centre the partner investigators recognised that despite significant scientific advances in genetic and acquired neuromuscular diseases, there were generally no effective treatments for patients. Across the Centre there are separately funded research groups with critical mass focussed on five broad disease areas which are the main MRC Centre “disease themes”; muscular dystrophies, channelopathies, peripheral neuropathies, inclusion body myopathy and mitochondrial diseases. At the Centre’s inception the partner investigators aimed to add value to these separately funded disease-orientated research programmes by addressing what we considered to be key gaps in the translation of science into experimental medicine. We therefore established a strategic multidisciplinary translational research framework and six “core activities” funded by the MRC Centre that addressed the following key obstacles to effective translation 1) lack of stratified patient cohorts for personalised medicine 2) insufficient support and “know-how” to deliver experimental medicine neuromuscular trials 3) insufficient availability of human patient neuromuscular tissues for preclinical science 4) lack of sensitive biomarkers and limited application of MRI biomarkers 5) lack of scientific translational research training programmes for scientists and clinicians in neuromuscular diseases 6) lack of linkage and collaboration between expert clinical and animal scientists to assess validity and translatability of findings in animal models to humans. Specific collaborative core activities in each of these areas were established in the first phase of the Centre and we delivered and exceeded all milestones which were set by the MRC in each core area. The core activities were critical in adding value to discovery science and enabling delivery of experimental medicine studies in each disease theme and published in top-tier journals. 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.

**Vision for the Centre beyond 2018**

An embedded experimental network as part of specialist clinical practice and a new Centre focused on neuromuscular disease experimental therapeutics

The core funded activities of the Centre will need to be embedded into host institutions by 2018 and this will be a strategic priority over the next three years. In UCL plans have commenced to embed into a new Department of Neuromuscular Diseases and in NCL the John Walton Muscular Dystrophy Research Centre will be established. **For both institutions linking effectively with the renewal of the NIHR BRCs will be important for continuing host support.**

By 2018 we envisage a mature experimental medicine network with UK wide web-based entry of patients into curated cohorts and biobanking linked to routine clinical practice in the NHS. Embedded core activities and the experimental medicine network will be an essential platform from which we will develop a new centre focused on driving delivery of experimental therapeutics in neuromuscular diseases. Over the period 2018-2028 we aim to be at the forefront internationally in finding effective disease modifying therapies and/or possible preventative therapies by early interventions in paediatric populations and by preimplantation techniques.

The new **National Neuromuscular Experimental Therapeutics Centre** will aim to deliver more experimental studies at pace utilising the network and the platform established and embedded during the first ten years. The new centre will work in an innovative partnership with industry from its inception. Continued development of new outcome measures including new and evolving sensitive MRI, proteomic, RNA and metabolomic biomarkers will be important.

**The advice we need from the SAB 2014 team:** in addition to assessing progress to date against milestones we would like the SAB 2014 team to advise us on our future strategy beyond 2018. Specifically we want the SAB to explore and stress test the need for and deliverability of such a new centre and help us identify its optimal characteristics and capabilities. We need to determine which of a number of possible approaches to new therapies a new centre will prioritise including antisense, cell based therapy, gene therapy, exercise, drug repurposing and others. We also need to consider the optimal configuration of innovative core activities of such a new centre and demonstrate how they would add value to the existing programmes of independently funded research in each of our disease themes. New cores should enable more rapid delivery of new therapy trials and new therapies. They could include preclinical development core activities in each new therapy area and a core activity linked to innovative biomarker development which could for example include next generation MRI biomarker applications. An educational PhD programme would remain fundamental to a new centre with a focus on training and developing therapy focussed translational clinician scientists.

We need to consider and have SAB input and advice regarding the national and international funding landscape for such a new therapeutics centre. In the UK the MRC and the Wellcome...
Trust tend to fund preclinical research and experimental medicine trials. The National Institute for Health Research (NIHR - this is the clinical research arm of the NHS) tends to clinical research and fund larger phase II/III trials. There is overlap and a potential funding positioning opportunity in the rare diseases space. We envisage a possible national strategic partnership funding model that could include MRC, Wellcome and NIHR. International partnerships (Europe and USA) as well as industry partnerships will also be very important. There are specific opportunities to work closely with the so called NIHR BRCs (biomedical research centres which are NHS funded university based research centres) present in both UCL and NCL. Importantly the five year renewal process for BRCs will commence in 2015. A number of our Centre PIs have important links and leadership roles in each of these different funding agencies i.e. Wellcome, MRC, NIHR, Europe and USA and a coordinated strategic approach needs to be considered.

We consider that a new Neuromuscular Experimental Therapeutics Centre could be positioned for partnership funding and could have a unique role in catalysing development and delivery of therapies for rare neuromuscular diseases.
2. MRC Centre: Background and Vision beyond 2018

Background to MRC Centres

MRC Centres are specific funding schemes that are significant and strategic investments that can act as national and international focal points. There are 24 across all biomedical science in England, of which four are in neurology related areas and one in Neuromuscular Diseases.

The 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 & 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 and demonstrate strategic impact
- Have a dedicated Director who is leading to provide focussed scientific leadership and management

Centres are expected to achieve this by:
- Providing leadership in focussed aspects of a field
- Delivering strategy in an area of importance for UK medical research
- 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. Centres are usually funded for 10 years after which it is anticipated core activities will be embedded in host institutions. New Centres that are clearly different and innovative can be developed that utilise embedded platforms.

This MRC Centre for Translational Research in Neuromuscular Diseases

Direct funding envelope of over £9m in 10 years: The MRC Centre for Translational Research in Neuromuscular Diseases was established in February 2008 following the first five year MRC award of ~£3m. With critical strategic advice from the SAB the Centre was
successfully renewed in 2013 for a further five years. In renewal there were approximately matching host and MRC contributions producing a total funding envelope of ~£6m. In renewal this resource has been effectively split equally by the Director between the two MRC Centre partner sites in London UCL and Newcastle for the period 2013-2018.

The mission of the Centre is to translate science into experimental medicine and new treatments for children and adults with disabling fatal neuromuscular Diseases

A national strategic research partnership: the MRC Centre is a translational research partnership that builds on long established clinical and research links and complimentary expertise. It brings together colleagues at the UCL Institutes of Neurology and Child Health with those at the Institute of Genetic Medicine and the Wellcome Centre for Mitochondrial Research at Newcastle University. The Centre works with very large adult and paediatric patient populations drawn from across the UK and cared for at the major co-located NHS Foundation Trust Hospitals; the National Hospital for Neurology and Neurosurgery, Queen Square, Great Ormond Street Hospital and Newcastle-upon-Tyne Teaching Hospitals.

Overcoming obstacles translating science into patient benefit: in establishing the Centre the partner investigators recognised that despite significant scientific advances in genetic and acquired neuromuscular diseases, there were generally no effective treatments for patients. Across the Centre there are separately funded research groups with critical mass focussed on five broad disease areas which are the main “disease themes” of the MRC Centre; muscular dystrophies, channelopathies, peripheral neuropathies, inclusion body myositis and mitochondrial diseases. At the Centre’s inception the partner investigators aimed to add value to these separately funded disease orientated research programmes by addressing what we considered to be key gaps in the translation of science into experimental medicine. We therefore established a strategic multidisciplinary translational research framework that addressed the following key obstacles to effective translation 1) lack of stratified patient cohorts for personalised medicine 2) insufficient support to deliver experimental medicine trials 3) insufficient availability of human patient neuromuscular tissues for preclinical science 4) lack of sensitive biomarkers and limited application of MRI biomarkers 5) lack of scientific translational research training programmes for scientists and clinicians in neuromuscular diseases 6) lack of linkage and collaboration between expert clinical and animal scientists to assess validity and translatability of findings in animal models to humans. Specific collaborative core activities in each of these areas were established in the first phase of the Centre and we delivered and exceeded all milestones which were set by the MRC for each core area. Continuing core activities of the Centre:

- **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 DMD\(^1\), ii) Mexiletine in muscle channelopathies\(^3\), iii) Vitamin C in Charcot Marie Tooth 1A\(^10\), iv) Heat shock protein upregulation in inclusion body myositis\(^12\), v) Resistance and aerobic exercise in mitochondrial disease\(^13\), vi) Idebenone in mitochondrial disease\(^14\).

**The key disease research themes underpinning the Centre’s scientific strategy and major scientific and translational achievements in the first five years of the MRC Centre:**

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](http://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 identified.


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, Duchen, 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)\textsuperscript{14} Mitochondrial DNA disease potentially preventable (Nature 2010 & MRC Perspectives 10/11 \url{http://perspectives.mrc.ac.uk/chapters/people-populations-and-body-systems})\textsuperscript{15}

The original strategy and objectives for the Centre and their delivery over the first five years 2008-2013

We exceeded agreed objectives in first phase of the Centre:

- 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)\textsuperscript{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)\textsuperscript{1,2,10-14}. We lead international experimental medicine initiatives in the NMD field.
- We utilised 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 used 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 (>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 (\url{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 2013-2018

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 aim to recruit new world-class colleagues. 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.

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 **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 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 had already lead to the discovery of new genes and new therapy targets by Centre PI’s in the first 5 years of the centre and this is continuing in the renewed centre (see individual disease theme reports).

**Figure 1.**
The Separately funded disease-based programmes that link to the MRC Centre

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. The diagram below illustrates the scientists that contribute to each of the disease themes. Investigators in red have recently joined.

Evidence of outputs and outcomes against agreed outputs for 2013-2018

The MRC Centre is on target to meet / exceed all the agreed objectives/metrics in relation to each of the core areas (see metrics summary appendix i).: 1. MRC Centre Experimental medicine trials: we have delivered a marked increase in experimental medicine trials from n=10 to n=16 with an increase of patients recruited into trials from 507 in February 2013 to 772 in October 2014. Details of the trials are given in section 5, a, ii). MRC experimental trial coordinators are crucial in supporting these significant increases & ensuring our very high success in recruiting which is particularly noteworthy when compared to other centres in our international collaborations. 2. MRC Centre Stratified Cohorts: we have also delivered a marked increase in the number of stratified cohorts from 12 in February 2013 to 23 in October 2014 with a corresponding increase in patients recruited into stratified cohorts from 2896 in February 2013 to 5423 in October 2014. These cohorts are critical for our experimental medicine trials and also for the development of sensitive and responsive
outcome measures. Details of the stratified cohorts are given in section 5, a, iii). MRC experimental trial coordinators continue to be crucial in supporting these significant increases & ensuring our very high success in recruiting. **3. MRC Centre Neuromuscular biobank:** our established national MRC biobank of nerve, muscle and skin derived tissues continues to grow and to be available to scientists and continues to add value to discovery science and preclinical testing of therapies (e.g. antisense in DMD). In February 2013 we had 1932 biobanked samples and by October 2014 we have banked 2392 samples. We have successfully extended sample collection to other UK centres and are introducing a range of new activities (detailed in 5.a.i)). The MRC Centre biobank has benefited a large number of basic, translational research and research & development projects within the centre and generated high-profile publications. These studies include BIO-NMD, Neuromics, PreU7, Pro045 and SKIP-NMD DMD skipping studies, AFM natural history study, longitudinal HSN1 studies, Dysferlinopathy natural history study, For DMD study, HIBM study, Optimistic study and MyoSeq study. More than 200 research projects based at UCL, NCL and internationally are currently benefitting from the samples supplied by the biobank (Appendix ix) supporting research into neuromuscular and other disorders. To date, the research has been published in 44 articles (section 7) acknowledging the contribution of the MRC Centre biobanks.

**4. MRI Biomarker studies:** Development of NMD MRI biomarkers was a completely new initiative established by the MRC Centre. In the first 5 years we applied qualitative and developed quantitative MRI methodology to develop MRC Centre MRI protocols and we are now using these in patient experimental medicine studies and stratified cohort studies and also continuing technical development to fully exploit MRI to provide non-invasive, objective readouts. As an example we have demonstrated that lower-limb fat-fraction is a responsive outcome measure correlating with muscle strength and clinical scales in CMT1A and IBM over 1 year (manuscript submitted); 2 year follow-up data collection is ongoing. Details of our MRI programme are in section 5.a.iv). **5. Animal studies:** Although the MRC Centre does not directly fund animal research, animal models continue to be of importance to the centre and several Centre PI’s have significant programmes of research that involve NMD animal models. The MRC Centre does support a series of translational PhD projects in the Centre which utilise preclinical animal models in each of the major disease themes (details of MRC Centre animal projects are given in 5.a.vi). We have also developed strong links with MRC Harwell and several PIs are members of the MRC Mouse Network. The MRC Centre enables human clinical scientists with human cohorts to link with animal scientists working with animal models to work projects towards translation, for example by informing animal model preclinical therapy assessment. **6. Training and education:** our training programme remains a central priority for the Centre and we are recruiting to target. In our renewal we were awarded (jointly by the MRC and our host universities) 16 four-year non clinical, 4 three-year clinical and 13 one-year clinical pump priming posts. To date we have appointed 14 non clinical PhDs and 9 clinical PhDs with plans in pace to appoint the rest throughout the 5 year centre cycle. The MRC Centre also continues to provide a range of highly valuable training and educational activities for centre PIs and postdocs (details of MRC training programme are given in 5.a.v).
**Partnerships industry**: we have formed extensive industry experimental medicine partnerships to (GSK, Prosensa, Shire, Senexis, PTC, AVI). **Partnerships patient organisations**: we continue to link with the Muscular Dystrophy Campaign to deliver the largest UK NMD translational research conference – we have now held seven conferences, with >1800 delegates total. **Partnerships academic**: we have new links with Oxford (D. Hilton-Jones, K. Davies, M. Wood), Cambridge MRC MBU (J. Walker, M. Zeviani), **Public engagement**: we have held >10 Centre patient days for scientists to link with patients and families; **PI's publications**: we published > 350 peer reviewed publications. 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 and continues to work hard to develop this reputation further.

**Vision for the Centre beyond 2018**

**An embedded experimental network as part of specialist clinical practice and a new Centre focused on neuromuscular disease experimental therapeutics**

The core funded activities of the Centre will need to be embedded into host institutions by 2018 and this will be a strategic priority over the next three years. In UCL plans have commenced to embed into a new Department of Neuromuscular Diseases and in NCL the John Walton Muscular Dystrophy Research Centre will be established. For both Institutions linking effectively with the renewal of the NIHR BRCs will be important for continuing host support.

By 2018 we envisage a mature experimental medicine network with UK wide web-based entry of patients into curated cohorts and biobanking linked to routine clinical practice in the NHS. It is our aim that these embedded activities and this experimental medicine network will be an important platform from which we will develop a new centre focused on driving delivery of experimental therapeutics in neuromuscular diseases. Over the period 2018-2028 we aim to find effective disease modifying therapies or possible preventative therapies by early interventions in paediatric populations.

The new Neuromuscular Experimental Therapeutics Centre will aim to deliver increasing numbers of experimental studies utilising the network and the platform. The new Centre will work in partnership with industry from its inception. Outcome measures including new and evolving sensitive MRI, proteomic, RNA and metabolomic biomarkers will be potentially important tools.

The current PIs with the SAB need to explore and stress test the viability and deliverability of such a new Centre. We need to determine which of a number of possible approaches to new therapies it will prioritise including antisense, cell based therapy, gene therapy, exercise and drug repurposing.

We also need to determine what the core funding in such a new centre proposal will be dedicated to. An educational PhD programme would remain a key feature of a new centre with a focus on training and developing translational clinician scientists. However, other resource allocations will depend on the final configuration of the Centre but possibilities
might include core activities to develop antisense molecules for different neuromuscular targets and a more systematic approach to developing new experimental sensitive biomarkers.

We also need to explore the national and international environment for a new therapeutics centre. In the UK the MRC funds experimental medicine trials whereas later phase larger trials are commonly funded by the National Institute for Health research (NIHR) although for rare diseases the distinction is less clear. We currently envisage the MRC being the major funder of such a new centre. At the same time we would aim to work increasingly closely with the NIHR and the NIHR BRCs (the biomedical research centres which the NIHR fund in both UCL and NCL). A number of our centre PIs, including Patrick Chinnery and Michael Hanna have senior roles in developing and delivering the UK NIHR rare disease strategy.

Internationally we have established strong links both in Europe and the US as we recognise and have shown that for many rare diseases international collaborations are essential to deliver clinical trials and new treatments. Many of our PIs have senior strategic leadership roles in European rare disease networks including Hanns Lochmuller who is chair of the Interdisciplinary Scientific Committee in IRDiRC and co-ordinator of RD Connect: an IRDiRC flagship programme on omics and data sharing. Katie Bushby is co-ordinator of the European Joint Action for Rare Diseases, the major EU policy think tank for Rare Diseases. Volker Straub leads a COST Action on MRI (MYO MRI). Several centre PIs at both sites are work package and activity leaders in Neuromics, another large IRDiRC project. These roles mean that the MRC Centre and any future therapeutics centre are well placed to closely link and lead European initiatives. A number of our PIs have also established strong links with collaborators in the US including in a number of NIH funded projects (Mary Reilly is a co-director of an NIH funded rare disease consortium), Katie Bushby is co-PI of the NIH funded DMD steroid trial FOR DMD) and Mike Hanna has completed a number of international trials in both IBM and channelopathies with US collaborators demonstrating that all the regulatory obstacles to running these critical international trials can be overcome.

We therefore consider that a new Neuromuscular Experimental Therapeutics Centre could be positioned to have a unique role in developing and delivering therapies for rare neuromuscular diseases internationally.

As a bridge to such a new Centre for experimental therapeutics an application for a possible strategic award in antisense applications to neuromuscular conditions beyond DMD has been developed and will be discussed (appendix vi). We will also present possible new therapeutic directions in relation to each disease theme areas.
3. **Aims of SAB visit 14th November 2014**

*International Scientific Advisory Board*

Berch Griggs (Chair)
Rick Barohn (*in absentia*)
Eric Hoffmann
Silvère van der Maarel
John Porter (*in absentia*)
Louis Ptáček
Michael Shy
Vincent Timmerman
Thomas Voit
Stephen Waxman

Following the renewal of the MRC Centre in 2013 the mission, vision and aims of the centre were clearly defined and a set of six core activities and five key disease themes have been identified to deliver these aims. Milestones have been set against which the progress of the centre would be measured.

**Requirements of the SAB visit**

1. To evaluate the progress in each of the six core activities against the agreed milestones.
2. To evaluate the progress made in the five key disease themes.
3. To provide advice on the future direction of the centre from 2018 onwards.
4. To advise if there are any areas we are lagging behind the field, new areas we should be developing or any opportunities we may be missing.

**Methods and tools to assist SAB evaluation**

1. Detailed SAB review document provided in advance of the SAB visit
2. Oral presentations by MRC Centre PIs
3. Poster scientific presentations by junior faculty MRC Centre PhD students and senior research fellows.
4. Discussions with MRC Centre director, co-directors, PIs, PhD students and clinical fellows.

**Feedback from the SAB to the centre**

It is anticipated that during the closed session on the 14th November the SAB will have discussions that will be the basis of brief verbal report to the MRC Centre director at the end of the SAB visit and be the basis of a written report to be sent to the MRC Centre director within one month of the visit.
4. Programme for SAB visit 14th November

8.30am  Coffee

9.00am  Introduction, overview of MRC Centre, aims of SAB visit.  Hanna

9.30 - 11.00  MRC Centre progress and look forward

09.30 - 10.00  Muscular Dystrophy  Muntoni / Bushby
10.00 - 10.30  Channelopathies  Hanna/Kullmann/Lochmüller
10.30 - 11.00  Inherited neuropathies  Reilly/Horvath

Coffee

11.30 - 12.00  IBM  Hanna / Greensmith / Lochmüller
12.00 - 12.30  Mitochondrial disorders  Turnbull/Chinnery
12.30 - 13.30  Lunch and posters; PhD student and post-doc poster presentations  SAB / students
13.30 - 14.00  Private meeting of SAB with students  SAB / students

14.00 - 15.45  MRC Centre post 2018 – where next?

14.00 - 14.20  MRI  Straub / Yousry
14.20 - 14.50  Strategic award application – update  Muntoni / Hanna
14.50 - 15.20  National / international environment (BRC, Europe, USA)  Hanna / Chinnery
15.20 - 15.45  Discussion

Tea

16.15 - 18.00  SAB closed session  SAB
18.00  Feedback to MRC Centre  SAB / Director / others

19.00  Drinks and Dinner  All
5. Achievements to date and plans for the next 3 years

a. Reports against milestones in six core centre activities

i) Biobank

UCL lead: Francesco Muntoni (FM), NCL lead Hanns Lochmüller (HM)

Summary

The MRC for Neuromuscular Diseases Biobank was established in 2008 as a unique resource of human plasma, serum, DNA, urine, muscle tissue and myoblast and fibroblast cell cultures from defined neuromuscular disorders. These materials are available to the basic science community for research purposes. Deliverables include: (i) Increasing 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. Target = 3000 (since the start of the biobank sample collection); (ii) Systematically collect biomaterials from each patient enrolled in clinical trials or natural history studies at the Centre or collaborating partners; (iii) Introducing 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) Introducing immortalisation of targeted fibroblast samples using the method previously used by NCL PIs (retroviral transfer of papillomavirus E6E7 genes); (v) Introducing MyoD-transfect human fibroblasts to generate myogenic cells for selected patients where muscle biopsies cannot be obtained; (vi) Collecting muscle derived stem cells; (vii) Introducing additional measures of quality control (ISO certification); (viii) Increasing collection of fibroblasts from neuropathy patients to be available for separate studies to generate iPS cells. The MRC Centre biobank has benefited a large number of basic, translational research and research & development projects within the Centre and generated high-profile publications.

Progress against deliverables

The biobanks have stored nearly doubled the target sample size as of September 2014. See table below.

<table>
<thead>
<tr>
<th>Sample type stored*</th>
<th>London</th>
<th>Newcastle</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC133+</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>678</td>
<td>662</td>
</tr>
<tr>
<td>Myoblasts</td>
<td>615</td>
<td>663</td>
</tr>
<tr>
<td>Frozen muscle</td>
<td>153</td>
<td>0</td>
</tr>
<tr>
<td>Frozen skin</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Immortalised fibroblasts</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Immortalised myoblasts</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Peripheral blood lymphocytes</td>
<td>76</td>
<td>0</td>
</tr>
<tr>
<td>Plasma</td>
<td>165</td>
<td>347</td>
</tr>
<tr>
<td>Sample Type</td>
<td>London</td>
<td>Newcastle</td>
</tr>
<tr>
<td>-------------</td>
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<td>-----------</td>
</tr>
<tr>
<td>Serum</td>
<td>168</td>
<td>518</td>
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<tr>
<td>Synovial cells</td>
<td>10</td>
<td>0</td>
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<tr>
<td>Urine</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>134 (RNA)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1932</td>
<td>2392</td>
</tr>
</tbody>
</table>

*DNA is collected from patients routinely in both UCL and NCL and stored in the respective genetic biobanks and not included in these figures.

Both centres have been collecting skin, muscle, blood and urine samples from patients enrolled in numerous clinical trials and natural history studies at the Centre or with collaborating partners. These studies include BIO-NMD, Neuromics, PreU7, Pro045 and SKIP-NMD DMD skipping studies, AFM natural history study, longitudinal HSN1 studies, Dysferlinopathy natural history study, FOR DMD study, HIBM study, Optimistic study and MyoSeq study. Both centres have been immortalising myoblasts and fibroblasts. In Newcastle, 31 samples have been immortalised including 13 fibroblast and 18 myoblast lines using with a retrovirus expressing the E6E7 gene region from human papillomavirus. In London, 11 myoblasts have been immortalised using the retroviral transduction with both telomerase and cyclin-dependent kinase 4 expressing vectors. MyoD-transfection of human fibroblasts and the purification of muscle derived stem cells are established techniques in the London centre with 11 muscle derived stem cells (AC133+ myoblasts) established. We have also increased the collection of fibroblasts from neuropathy patients, collecting 35 skin biopsies from HSN1 patients through the HSN1 longitudinal study in London and 8 skin biopsies from CMT patients in both centres. Newcastle is currently obtaining ISO certification. Current centres for sample collection are listed below:

- Institute of Genetic Medicine, Newcastle University
- Welcome Trust Centre for Mitochondrial research, Newcastle University
- Royal Victoria Infirmary Hospital, Newcastle University
- Freeman Hospital Orthopaedic Centre, Newcastle
- Great Ormond Street Hospital for Children, London
- National Hospital for Neurology & Neurosurgery, London
- Guys and St Thomas’ NHS Trust, London
- Royal National Orthopaedic Hospital, Stanmore
- RJAH Orthopaedic Hospital, Oswestry (new site from August 2014)

**Support from the biobank**

Biobank resources have been extensively used. Please refer to the below table for sample distribution numbers.

<table>
<thead>
<tr>
<th>Samples distributed</th>
<th>London</th>
<th>Newcastle</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC133+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DNA</td>
<td>4</td>
<td>255</td>
</tr>
<tr>
<td>Fibroblasts</td>
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<td>538</td>
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<td>Count1</td>
<td>Count2</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Myoblasts</td>
<td>153</td>
<td>264</td>
</tr>
<tr>
<td>Frozen muscle</td>
<td>328</td>
<td>0</td>
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<tr>
<td>Frozen skin</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immortalised fibroblasts</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Immortalised myoblasts</td>
<td>43</td>
<td>20</td>
</tr>
<tr>
<td>Peripheral blood lymphocytes</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Plasma</td>
<td>47</td>
<td>303</td>
</tr>
<tr>
<td>Serum</td>
<td>54</td>
<td>709</td>
</tr>
<tr>
<td>Synovial cells</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urine</td>
<td>13</td>
<td>58</td>
</tr>
<tr>
<td>Other</td>
<td>28 (whole blood)</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1026</td>
<td>2158</td>
</tr>
</tbody>
</table>

More than 200 research projects based at UCL, NCL and internationally have benefited from the samples supplied by the Biobanks (Appendix 1) supporting research into neuromuscular and other disorders. To date, the research has been published in 44 articles (Appendix 2) acknowledging the contribution of the Biobanks.

**Research projects supported by the MRC Centre biobank and Publications**

A list of research projects supported by the MRC Centre biobank in UCL, NCL and external users is given in appendix ix and resulting publications are outlined in section 7.
ii) **Experimental medicine trials**

**UCL lead: Michael Hanna (MH), NCL lead: Katie Bushby (KB)**

One of the main aims of the MRC Centre is to translate discovery science into treatments for patients and as such experimental medicine trials are a critical part of our activities. As can be seen in Table 1, we had 10 drug or exercise trials in process before February 2013 and currently have 16 open drug and exercise trials. We had 507 patients enrolled in experimental trials before February 2013 and currently have 772 patients enrolled in trials (Table 2, Figure 1).

**Table 1: MRC Centre Experimental Medicine Trials and Stratified Cohorts**

MRC Centre 2013 – 2014 Overall Studies Status

<table>
<thead>
<tr>
<th></th>
<th>Pre Feb 2013</th>
<th></th>
<th>Post Feb 2013</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
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<td>Open</td>
<td>Closed</td>
<td>Open</td>
<td>Closed</td>
</tr>
<tr>
<td>Drug Trials</td>
<td>5</td>
<td>12</td>
<td>11</td>
<td>18</td>
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<tr>
<td>Exercise trials</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>3</td>
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<tr>
<td>MRI studies</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>NH/Cohort</td>
<td>12</td>
<td>5</td>
<td>23</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 2: MRC Centre Trials and Stratified Cohorts Recruitment numbers**

<table>
<thead>
<tr>
<th></th>
<th>Total in 2013</th>
<th>Total in 2014</th>
<th>Increase 2013-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials</td>
<td>507</td>
<td>772</td>
<td>265</td>
</tr>
<tr>
<td>NH/Cohorts</td>
<td>2896</td>
<td>5423</td>
<td>2527</td>
</tr>
</tbody>
</table>

**Figure 1: MRC Centre Trials and Stratified Cohorts Recruitment numbers**

The MRC Centre trials are listed below and discussed in more detail in each of the disease sections.
<table>
<thead>
<tr>
<th>Trial Title</th>
<th>Recruitment Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>An open-label extension study of the long-term safety, tolerability and efficacy of GSK 2402968 in subjects with Duchenne Muscular Dystrophy</td>
<td>8</td>
</tr>
<tr>
<td>Randomized, multicenter, double-blind, placebo-controlled, parallel-group phase III study to investigate the efficacy, safety and tolerability of 2 different doses of IgPro20 (subcutaneous immunoglobulin) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) - The Path Study</td>
<td>6</td>
</tr>
<tr>
<td>DMD Heart Protection Study: A double-blind randomised multi-centre, placebo-controlled trial of combined ACE-inhibitor and beta-blocker therapy in preventing the development of cardiomyopathy in genetically characterised males with DMD without echo-detectable left ventricular dysfunction</td>
<td>77</td>
</tr>
<tr>
<td>FOR-DMD: Duchenne muscular dystrophy: double-blind randomised trial to find optimum steroid regimen</td>
<td>11</td>
</tr>
<tr>
<td>PTC124-GD-019 Open Label: An open-label study for previously treated Ataluren (PTC124®) patients with nonsense mutation dystrophinopathy</td>
<td>19</td>
</tr>
<tr>
<td>A phase III efficacy &amp; safety study of Ataluren (PTC124) in patients with nonsense mutation dystrophinopathy (PTC phase III) PTC124-GD-020-DMD</td>
<td>10</td>
</tr>
<tr>
<td>PRO045: A phase IIb, open-label study to assess the efficacy, safety, pharmacodynamics and pharmacokinetics of multiple doses of PRO045 in subjects with Duchenne muscular dystrophy</td>
<td>3</td>
</tr>
<tr>
<td>NeoGAA: An open-label, multicenter, multinational, ascending dose study of the safety, tolerability, pharmacokinetics, pharmacodynamics and exploratory efficacy of repeated biweekly infusions of neoGAA in naïve and alglucosidase alfa treated late-onset Pompe disease patients.</td>
<td>1</td>
</tr>
<tr>
<td>A randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose-finding, pivotal, phase IIb/III study to evaluate the efficacy, safety and tolerability of intravenous BYM338 at 52 weeks on physical function, muscle strength, and mobility and additional long-term safety up to 2 years in patients with sporadic inclusion body myositis</td>
<td>41</td>
</tr>
<tr>
<td>A Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ISIS 420915 in Patients with Familial Amyloid Polyneuropathy</td>
<td>6</td>
</tr>
<tr>
<td>PRO053: A Phase I/II, open-label, dose escalating with 48-week treatment study to assess the safety and tolerability, pharmacokinetics, pharmacodynamics and efficacy of PRO053 in subjects with Duchenne muscular dystrophy.</td>
<td>2</td>
</tr>
<tr>
<td>Randomised Double-Blind Placebo-Controlled Trial of Long-Term Ascorbic Acid Treatment in Charcot-Marie-Tooth Disease Type 1A</td>
<td>50</td>
</tr>
<tr>
<td>Therapeutic Trial of Mexiletine in Non-Dystrophic Myotonia: A Phase II Randomised, Double-Blind, Placebo-Controlled, Cross-Over Study to Investigate the Efficacy of Mexiletine in Patients with Non-Dystrophic Myotonia</td>
<td>14</td>
</tr>
</tbody>
</table>
| PTC 124 GD 007: A Phase IIb Efficacy and Safety Study of PTC124 in 11
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Protocol Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>A Phase 2a Study of Ataluren (PTC124) in Non-ambulatory Patients with Nonsense-Mutation-Mediated Duchenne/Becker Muscular Dystrophy (Protocol Number -PTC124-GD-008-DMD)</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Restoring Dystrophin Expression in Duchenne Muscular Dystrophy: A phase I/II Clinical Trial Using AVI-4658</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Dose-Ranging Study of AVI-4658 to Induce Dystrophin Expression in Selected Duchenne Muscular Dystrophy (DMD) Patients (Protocol number AVI-4658-28)</td>
</tr>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Eculizumab for Myasthenia Gravis: A Randomised, Double-blind, Placebo-controlled, Cross-over, Multicenter Study of Eculizumab in Patients with Generalised Myasthenia Gravis (GMG) who have Moderate to Severe Muscle Weakness Despite Treatment with Immunosuppressants</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Arimoclomol for Sporadic Inclusion Body Myositis (IBM): A Randomised, Double-blind, Placebo-controlled Pilot Study Assessing the Safety and Tolerability of Arimoclomol in Adult Patients with Sporadic Inclusion Body Myositis</td>
</tr>
<tr>
<td></td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Investigation of the ability of Otelixizumab to inhibit in vitro antigen-specific T cell responses from Myasthenia Gravis Patients</td>
</tr>
<tr>
<td></td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>GSK/Prosensa clinical trial in DMD boys with study drug GSK2402968 (PRO051/DMD114117)): A phase II, double-blind, exploratory, parallel-group, placebo-controlled clinical study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant subjects with Duchenne muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>DMD114349 An open-label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne Muscular Dystrophy (PROSENSA DMD extension)</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Therapeutic Trial of Lithium Carbonate in MND/ALS(LiCALS): A double-blind, randomised, placebo controlled trial of lithium carbonate in patients with amyotrophic lateral sclerosis</td>
</tr>
<tr>
<td></td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>LiCALS Open Label Extension Trial of Lithium Carbonate in amyotrophic Lateral Sclerosis</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>GSK1223249 in MND/ALS (the Nogo-A study): A Phase I, multi-centre, randomised, placebo-controlled, double-blind, single and repeat dose escalation of a drug to treat ALS</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>HYP HOP: Dichlorphenamide vs. Placebo for Periodic Paralysis: Double-blind, placebo-controlled, parallel-group, phase III study comparing dichlorphenamide vs. placebo for the treatment of periodic paralysis</td>
</tr>
<tr>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Phase II, multicentre, randomised, adaptive, double-blind, placebo-controlled safety and efficacy of olesoxime (TRO19622) in 3-25 year old non-ambulant Spinal Muscular Atrophy (SMA) patients</td>
</tr>
<tr>
<td></td>
<td>13</td>
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<tr>
<td></td>
<td>SMT C1100 - A phase I, Open-label, Single and Multiple Oral Dose,</td>
</tr>
<tr>
<td>Study Title</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Safety, Tolerability and Pharmacokinetic Study in Paediatric Patients with</td>
<td></td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td></td>
</tr>
<tr>
<td>Aerobic training in Charcot-Marie-Tooth disease and Inclusion Body Myositis</td>
<td>28</td>
</tr>
<tr>
<td>Exploring the causes of falls and balance impairments in people with</td>
<td>54</td>
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<tr>
<td>neuromuscular diseases</td>
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<tr>
<td>Physical activity and inclusion body myositis</td>
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<tr>
<td>Exercise and Sarcopenia</td>
<td>24</td>
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<tr>
<td>Strengthening Hip Muscles to Improve Walking Distance in People with</td>
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</tr>
<tr>
<td>Charcot-Marie-Tooth Disease</td>
<td></td>
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<tr>
<td>Exercise Training in patients with Mitochondrial Disease: Assessing the</td>
<td>10</td>
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<tr>
<td>Benefits</td>
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</tr>
<tr>
<td>Cardiac Adaptations to Exercise in Mitochondrial Disease</td>
<td>39</td>
</tr>
<tr>
<td>Magnetic Resonance Imaging Characteristics of Inflammatory Neuropathies-a</td>
<td>20</td>
</tr>
<tr>
<td>pilot Study</td>
<td></td>
</tr>
<tr>
<td>MRI in IBM and CMT: A Study of Quantitative Magnetic Resonance Imaging and</td>
<td>72</td>
</tr>
<tr>
<td>the Clinical Features of Inclusion Body Myositis and Charcot-Marie-Tooth</td>
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<tr>
<td>Disease</td>
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<tr>
<td>Magnetic Resonance Imaging as an outcome measure in Motor Neuropathies: a</td>
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<tr>
<td>pilot study</td>
<td></td>
</tr>
<tr>
<td>MRI in FKRP-Related LGMD2I: A Study using Magnetic Resonance Imaging (MRI)</td>
<td>22</td>
</tr>
<tr>
<td>and Magnetic Resonance Spectroscopy (MRS) in Patients with Limb Girdle</td>
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<tr>
<td>Muscular Dystrophy 2I; an assessment of muscle damage</td>
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<tr>
<td>A Study of Quantitative Magnetic Resonance Imaging to Monitor Disease</td>
<td>24</td>
</tr>
<tr>
<td>Activity in Hypokalaemic Periodic Paralysis</td>
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</tr>
<tr>
<td>Evaluation and Optimisation of Muscle Imaging Biomarkers in Support of</td>
<td>25</td>
</tr>
<tr>
<td>Non-ambulant Duchenne Muscular Dystrophy Studies</td>
<td></td>
</tr>
<tr>
<td>Stratifying Patients with Leber Hereditary Optic Neuropathy (LHON) for</td>
<td></td>
</tr>
<tr>
<td>Idebenone Therapy Trial (SPLI-TT) – set to recruit March 2015. EME-MRC</td>
<td>0</td>
</tr>
<tr>
<td>funded</td>
<td></td>
</tr>
</tbody>
</table>
iii) Stratified cohorts

UCL lead: Francesco Muntoni (FM), NCL lead: Doug Turnbull (DT)

One of the main aims of the MRC Centre is to translate discovery science into treatments for patients and as such developing carefully phenotyped stratified cohorts is a major aim of the Centre in in this grant cycle. As can be seen in Table 1, we had 12 stratified cohort studies ongoing before February 2013 and currently have 23 stratified cohorts. We had 2896 patients enrolled in stratified cohorts before February 2013 and currently have 5423 patients enrolled in stratified cohorts (Table 2, Figure 1).

Table 1: MRC Centre Experimental Medicine Trials and Stratified Cohorts

<table>
<thead>
<tr>
<th>MRC Centre 2013 – 2014 Overall Studies Status</th>
<th>Pre Feb 2013</th>
<th>Post Feb 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Open</td>
<td>Closed</td>
</tr>
<tr>
<td>Drug Trials</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Exercise trials</td>
<td>5</td>
<td>3</td>
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<tr>
<td>MRI studies</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>NH/Cohort</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2: MRC Centre Trials and Stratified Cohorts Recruitment numbers

<table>
<thead>
<tr>
<th>Recruitment Nos.</th>
<th>Total in 2013</th>
<th>Total in 2014</th>
<th>Increase 2013-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials</td>
<td>507</td>
<td>772</td>
<td>265</td>
</tr>
<tr>
<td>NH/Cohorts</td>
<td>2896</td>
<td>5423</td>
<td>2527</td>
</tr>
</tbody>
</table>

Figure 1: MRC Centre Trials and Stratified Cohorts Recruitment numbers

The MRC Centre stratified cohorts are listed below and discussed in more detail in each of the disease sections.
<table>
<thead>
<tr>
<th>Cohorts/NH Title</th>
<th>Recruitment Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRC Centre Mitochondrial Disease Patient Cohort: A Natural History Study and Patient Registry</td>
<td>1123</td>
</tr>
<tr>
<td>North Star</td>
<td>917</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth Disease and related disorders: A Natural History Study</td>
<td>665</td>
</tr>
<tr>
<td>UK Myotonic Dystrophy patient registry</td>
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iv) MRI biomarkers

UCL lead: Tarek Yousry (TY), NCL lead: Volker Straub (VS)

We aim to deploy MRC Centre-established MRI protocols in patient experimental medicine studies and continue technical development to fully exploit MRI to provide non-invasive, objective readouts.

Patient Studies

In preparation for experimental medicine studies in the five MRC Centre disease themes we are undertaking MRI natural history studies in a number of patient cohorts.

We are undertaking cohort characterization using muscle MRI in natural history studies for Dysferlinopathy and DMD, accelerated MRI in cardiac and skeletal muscle imaging in DMD, BMD and DM1 patients, and the pre-clinical development and clinical application of diffusion tensor imaging in dystrophin-deficiency.

Along with the JAIN Foundation we are coordinating an international clinical outcome study for Dysferlinopathy involving 15 worldwide study locations across the USA, Europe, Japan and Australia (commenced 2012). This study aims to determine which outcome measures are most effective at measuring changes in the disease. Medical and physiotherapy assessments will be made as well as muscle MRI on 6 occasions over 3 years to evaluate muscle degeneration through T2 mapping and fat mapping, and 31P- magnetic resonance spectroscopy to determine metabolic changes.

In a separate GSK-sponsored investigation acquisitions are complete for an upper-limb MRI natural history study in non-ambulant DMD boys. Forearm measurements at baseline, 6 and 12 month follow up show robust progressive fat-fraction increase, before significant change in functional measures (presented at WMS 2014; manuscript in preparation).

We have completed baseline and 1 year follow up in MRC Centre for Neuromuscular Diseases prospective MRI IBM and CMT1A study. We have published reproducibility and normative control data (Morrow 2014) and have demonstrated that lower-limb fat-fraction is a responsive outcome measure correlating with muscle strength and clinical scales (manuscript submitted); 2 year follow-up data collection is ongoing.

We have completed a study of quantitative magnetic resonance imaging to monitor disease activity in hypokalaemic periodic paralysis (Symposium Neuoradiologica; Istanbul 2014).

We have been awarded an UCLH NIHR Biomedical Research Centre project grant (£251,259; 2014-2017) for a study characterising skeletal muscle MRI in closely phenotyped amyotrophic lateral sclerosis (ALS) subjects.

MRI Biomarker Development

Across the MRC Centre we are pursuing technical development to fully exploit MRI to provide non-invasive, objective readouts.
We have pioneered the development of accelerated MRI in the IMPRESS (Imaging using Compressed Sensing) project (PI Dr Kieren Hollingsworth, Medical Research Council 2012-2015, £370k). We have validated accelerated imaging by using combined compressed sensing and parallel imaging (CS-PI) in a cross-sectional cohort of ambulant adults with Becker muscular dystrophy. We established that a reduction in scanning time of up to 5 times was possible without losing anatomical delineation or suffering loss of accuracy of fat fraction, as well as the optimum values for the reconstruction. This technique will now be deployed in longitudinal studies of DMD and myotonic dystrophy (DM1). We will also extend this scan acceleration technology to the analysis of early stage cardiac impairment, again using adult Becker muscular dystrophy as our exemplar cohort, for both cine imaging and cardiac tagging. We aim to reduce the number and length of the breath holds currently required to make cardiac assessments. Ultimately we are driving towards a comprehensive muscle and cardiac examination lasting less than 30 minutes, with attendant benefits for clinical trial cost and patient comfort.

We are involved in an EU funded programme called BIOIMAGE-NMD (commenced Oct 2013), which is coordinated from Newcastle and is developing new imaging approaches to quantify muscle structure by MRI and apply these in both a natural history study in DMD and in AON treatment trials alongside our SME partner Prosensa Therapeutics. Method developments using diffusion MRI techniques have been implemented on a preclinical system and evaluated in vitro and in vivo using the *mdx* model. Further, with our European partners within the BIOIMAGE consortium (Paris, Leiden) we are currently translating these methods into clinical protocols. We are progressing plans for a natural history imaging study in DMD, which will chart muscle degeneration through T2 mapping, fat mapping and metabolic changes through 31P- magnetic resonance spectroscopy. To maximise the information obtained in individual boys we are working alongside the AFM funded clinical natural history study coordinated by Prof Muntoni.

Current work also involves plans for the development of sodium MRI with the goal to assess relative intra and extracellular sodium levels. This has already been shown by others to be feasible based on differences in sodium T1 and demonstrated in boys with DMD. We aim to implement the method in Newcastle where it can be used both in natural history and planned NHE1-inhibitor treatment studies. Funding for the required clinical sodium coil was obtained from the MRC call and we are in negotiation with coil manufacturers to ensure that the purchased coil has optimum characteristics for these challenging measurements. We are also developing a small scale sodium coil for our preclinical MRI scanner which will again allow us to do translation work between patients and transgenic models.

We have developed protocols with extended anatomical coverage for fore-arm and diaphragm acquisition in upper limb longitudinal MRI in non-ambulant DMD boys study (upper-limb MRI presented at UK Neuromuscular Translation Research meeting March 2014; ISMRM May 2014; WMS Oct 2014; MRI diaphragm excursion results presented WMS Oct 2014; paper in preparation);
To investigate MRI measures in pre-fatty infiltrated muscle where therapies may be most effective, our Study of Quantitative Magnetic Resonance Imaging to Monitor Disease Activity in Hypokalaemic Periodic Paralysis (Symposium Neuroradiologica; Istanbul 2014) used the UCL-developed IDEAL CPMG sequence to provide muscle T2 water changes independently of fatty infiltration. The data is being used to develop optimised IDEAL fat-water separation and new data-fitting models.

In healthy volunteers we have shown that in non-fat suppressed T2 relaxometry and magnetisation transfer acquisitions, fat-adjusted T2 and MTR age and gender dependencies, showing that we can measure biologically relevant MRI changes in the healthy muscle independent of fat content (Morrow et al. 2014).

The MRC Centre for Neuromuscular Diseases prospective MRI IBM and CMT1A study has shown evidence for muscle-water T2 & MTR changes independent of fat fraction prior to marked pathological fat infiltration (paper submitted).

As a first step towards high resolution ‘whole-nerve’ imaging we have obtained ethical and institutional approval for a pilot study in multi-focal motor neuropathy with conduction block, to commence January 2015.

Standardisation and validation of imaging methods and protocols across both MRC Centre sites and link with NMD centres across Europe & USA remains a core centre activity, exemplified by the participation in the MYO-MRI eCOST Action BM1304, “Applications of MR imaging and spectroscopy techniques in neuromuscular disease: collaboration on outcome measures and pattern recognition for diagnostics and therapy development”, (Proposer Volker Straub), to fund European collaboration which specifically aims to improve diagnosis and understanding of muscle pathology; Develop multicentric imaging outcome measures; explore new contrasts, targets and imaging techniques for NMD and explore strategies for muscle imaging texture analysis

Two publications have resulted from the multi-centre LGMD2I Study led by Newcastle Centre researchers (Willis 2013, 2014).

Centre investigators lead MRI protocol design and analysis for a two-centre (London-Iowa) international study of quantitative MRI in CMT1A study to establish the feasibility of multi-centre investigations in this disease incorporating or the first time distal lower-limb 3D Dixon fat-water imaging.

**Funding and publications**

All of the above studies are funded by both by the MRC Centre and other grants obtained by the MRI group in the MRC Centre (see section 8) and have resulted in the publications outlined in section 7.
v) Education and training

UCL lead; Mary Reilly, NCL lead; Patrick Chinnery

MRC Centre PhD programme

The cornerstone of our training programme is our MRC Centre non-clinical and clinical PhD programme.

- In the first phase of our Centre we developed a 4-year non-clinical PhD programme. In UCL for the first year, the students have an induction programme including attending clinics to see patients and have a series of lectures focused on neuromuscular diseases. Following induction, in the first year at UCL, the students rotate three-monthly through three PI laboratories of their choice. Following this rotation the students select their preferred project for their PhD. During the year the students have regular teaching, lectures and seminars.

In the first year in the 4 year non-clinical PhD programme in NCL, the students undertake a Masters by Research (MRes) “Neuromuscular Diseases – Bench to Bedside” which has been developed by the MRC neuromuscular group in NCL utilising the skills and knowledge of the neuromuscular staff and selected pre-eminent colleagues. The course covers the entire breadth of translational science in neuromuscular diseases, from the basic physiology of muscle and neuromuscular transmission, through basic science models, clinical diagnostics, experimental therapeutics to clinical trials and patient benefit.

In both UCL and NCL, the students spend the next 3 years in a neuromuscular centre laboratory doing a PhD. Highlights of the programme include the opportunity to attend the yearly 4 day neuromuscular course in ION and all students have to present their work by poster and in some cases by platform presentations at our yearly neuromuscular translational research conference. A new development in the last three years is the students’ retreat that the students organise and run once a year which has proved very popular and educational.

- In the 3 year clinical PhD programme the students undertake 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 including the annual UK Neuromuscular Translational Research Conference, an annual dedicated neuromuscular clinical update course, monthly MRC seminar series with invited international speakers (also available as web-seminars), regular journal clubs, departmental research meetings and seminars, subject specific workshops and conferences.

- A further development in the renewed Centre is that all PhDs whether clinical or non-clinical now are aligned with our five MRC Centre key disease themes.
Metrics of MRC Centre PhD programme

As shown in Table 1 below, we were awarded 16 four-year non clinical, 4 three-year clinical and 13 one-year clinical pump priming posts in the renewed centre. These posts were equally funded by the MRC and by the host universities UCL and NCL. To date we have appointed 14 non clinical PhDs and 9 clinical PhDs with plans in place to appoint the rest throughout the 5 year Centre cycle.

Table 1: MRC Centre Studentships from February 2013

<table>
<thead>
<tr>
<th>Studentships awarded in Centre Renewal 2013</th>
<th>Appointed</th>
<th>To be appointed</th>
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<tr>
<td>Non Clinical 4 year posts</td>
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<tr>
<td>UCL – 9</td>
<td></td>
<td>Non-clinical PhD (4 yrs.)</td>
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<td></td>
<td></td>
<td>UCL – 2 (2014)</td>
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<td></td>
<td></td>
<td>NCL – 4 (2013)</td>
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<tr>
<td></td>
<td></td>
<td>NCL – 3 (2014)</td>
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<tr>
<td>Clinical posts *</td>
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<tr>
<td>12 yrs (4x3year)</td>
<td></td>
<td>Appointed Clinical PhD posts**</td>
</tr>
<tr>
<td>13 yrs (13x1year)</td>
<td></td>
<td>UCL – 5 (2013)</td>
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<tr>
<td></td>
<td></td>
<td>NCL – 4 (2014)</td>
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<td></td>
<td></td>
<td>Further appts. to be made in 2015</td>
</tr>
</tbody>
</table>

*yrs. awarded

** alternative funding also used

In the renewed centre the MRC were keen we appointed clinical fellows for one year (pump priming posts) and that they would then be encouraged to apply for their own MRC training fellowships which are very prestigious and competitive. This became difficult to do as the training system for specialist registrars (SPRs) in neurology in the UK changed in 2013 so that SPRs had to take the full three years off for a predetermined period so the flexibility of the one year posts was not possible. To overcome this we have introduced a system where we appoint clinical PhDs for three years (using a mixed funding model with MRC, host university and other funders) but after 1 year the students have to apply for a MRC training fellowship if they are doing an appropriate project. This model allows recycling of the MRC funding and has been very effective in allowing us to attract and appoint the best PhD students. Our first appointed PhD student (Maiya Kugathasan, appointed 2013 in UCL) applied successfully for a 3 year MRC fellowship this year and one further clinical PhD has now applied and another is in the process of applying.
Post PhD mentoring and career progression

One of the most important aims of the MRC Centre is to train clinical and non-clinical neuromuscular scientists to develop a critical mass of researchers and clinicians in the UK for the future. We therefore provide ongoing mentoring and career advice for our PhD students and carefully monitor career progression post PhD. Table 2 lists the post-PhD destinations of all the clinical and non-clinical PhD students for the first 5 year grant cycle (2008-2013). To date we have been very successful at helping our trainees secure further positions in neuromuscular diseases. Most of our trainees are either in post-doctoral positions in neuromuscular diseases or are clinical trainees or consultants in neuromuscular diseases. One of our non-clinical PhDs is now doing a medical degree and one is a bioinformatician.

A further training aim in the MRC Centre renewal was to work with industry to develop joint MRC Centre / industry PhD studentships (CASE studentships). We have successfully done this with GSK and have appointed two CASE studentships in MRI neuromuscular diseases, both of whom started in 2014.

We train many other students, post docs and senior fellows in the MRC Centre (35 in the first 5 year grant cycle) who are funded by sources other than the MRC but who benefit from the educational and training opportunities in the MRC Centre.

The SAB will get an opportunity to view posters prepared by the MRC Centre students and to talk to the students during the SAB visit but as the current students have all been appointed in 2013 / 2014 we have also arranged for a number of our more senior post docs and fellows to present posters of their work so that the SAB can get a comprehensive view of the training the centre provides.

Table 2: MRC Students Post-PhD Destination

<table>
<thead>
<tr>
<th>MRC Centre Non-Clinical PhD students, UCL</th>
<th>PhD Dates</th>
<th>Post-PhD Destination</th>
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<tbody>
<tr>
<td>Dr Mhoriam Ahmed</td>
<td>2007 – 2011</td>
<td>Neuromuscular Post-Doc, UCL Institute of Neurology</td>
</tr>
<tr>
<td>Dr Alex Clark</td>
<td>2008 – 2012</td>
<td>iPS Post-Doc, Division of Clinical Neurology, University of Oxford</td>
</tr>
<tr>
<td>Dr Amy Innes</td>
<td>2007 – 2011</td>
<td>Postgraduate MBBS, St George’s University of London</td>
</tr>
<tr>
<td>Dr Phil McGoldrick</td>
<td>2008 – 2012</td>
<td>Neuromuscular Post-Doc, University of Toronto</td>
</tr>
<tr>
<td>Dr Alice Neal</td>
<td>2008 - 2012</td>
<td>Post-Doc, Ludwig Cancer Research, University of Oxford</td>
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<table>
<thead>
<tr>
<th>MRC Centre Clinical PhD students, UCL</th>
<th>PhD Dates</th>
<th>Post-PhD Destination</th>
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<tbody>
<tr>
<td>Name</td>
<td>Years</td>
<td>Position/Institution</td>
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<tr>
<td>Dr Adrian Miller</td>
<td>2008-2011</td>
<td>Neurology SpR training, London</td>
</tr>
<tr>
<td>Dr Jasper Morrow</td>
<td>2009-2012</td>
<td>Consultant Neurologist, National Hospital for Neurology &amp; Neurosurgery, &amp; The Lister Hospital, Stevenage</td>
</tr>
<tr>
<td>MRC Centre Non-Clinical PhD students, Newcastle</td>
<td></td>
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<tr>
<td>Dr Alastair Wood</td>
<td>2008-2012</td>
<td>Neuromuscular Post-Doc, Australian Regenerative Medicine Institute, Monash University, Western Australia</td>
</tr>
<tr>
<td>Dr Sally Spendiff</td>
<td>2007-2011</td>
<td>Neuromuscular Post-Doc, McGill University, Montreal, Canada</td>
</tr>
<tr>
<td>Dr Kieren Lythgow</td>
<td>2007-2011</td>
<td>Bioinformatician, Public Health England</td>
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**Other MRC Centre educational activities**

The MRC Centre provides an ongoing extensive portfolio of educational and training opportunities. Particular highlights include:

- The yearly MRC Centre UK Translational Research Conference. This conference organised jointly by the MRC Centre and the charity Muscular Dystrophy Campaign (MDC) has become the main neuromuscular meeting in the UK with an average of 300 participants yearly. This is a particular highlight for our students and senior fellows and post docs who get to present their research findings yearly. We have made this meeting truly national by alternating the meeting between London, Newcastle and Oxford. The programmes for the 2013 (Oxford) and the 2014 (London) meetings are given in appendix v.

- We run a very popular and successful 4 day neuromuscular course which is a comprehensive update covering all neuromuscular diseases in UCL yearly and which attracts about 100 attendees yearly many of whom are international. The programmes for the 2013 and 2014 courses are given in appendix vi.
vi) Animal models

UCL lead: Linda Greensmith (LG), NCL lead: Volker Straub (VS)

Although the MRC Centre does not have funding to directly support animal research, animal models continue to be of importance to the Centre and several Centre PIs have significant programmes of research that involve NMD animal models. We have strong links with MRC Harwell (EF, LG), and several PIs are members of the MRC Mouse Network (DT, FM, EF, LG, MR, MK, MH). The MRC Centre enables human clinical scientists with human cohorts to link with animal scientists working with animal models to work projects towards translation, for example by informing animal model preclinical therapy assessment.

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.

A number of animal models of neuromuscular disorders are currently being investigated by MRC Centre PIs and have been utilised by several of the Centre PhD students. Some examples of the current animal models of NMD under study by Centre PIs include:

**Inclusion Body Myositis (IBM):** We have now established colonies of two lines of mice expressing human VCP mutations that model Inclusion body myopathy with Paget's disease of bone and frontotemporal dementia (IBMPFD), and hereditary inclusion body myopathy. Dr Mhoriam Ahmed in LG's lab is leading on this project along with MRC Student Charlotte Spicer.

**Muscle Channelopathies:** Analysis of mice with mutations in SCN4A by Centre PIs MH, MK and LG, in collaboration with MRC Harwell have shown that AMPK plays a role in myotonia and periodic paralysis. This study involved Centre PhD student Phil McGoldrick and Postdoc Roope Männikkö.

**Motor Nerve Disorders and Inherited Neuropathies:**

**Distal Hereditary Motor Neuropathy (dHMN):** a homozygous splice mutation in the HSJ1 gene (DNAJB2) which decreases the expression of the 2 main isoforms HSJ1a and HSJ1b has been identified as a novel rare variant of dHMN. This mutation causes a loss-of-function of HSJ1 and is linked to a pure lower motor neuron disease. This study has been undertaken in LG’s lab with MRC Students Alex Rossor and Anna Gray.

**Charcot-Marie-Tooth disease type 1A (CMT type1A):** using the C3 mouse model of CMT type1A, Centre PIs (KJ, MK) have shown that Schwann cell c-Jun is elevated in nerves of C3 mice. This elevation of c-Jun in the Schwann cells of C3 nerves serves to prevent loss of myelinated sensory axons, particularly in distal nerves, suggesting that Schwann cells have two contrasting functions in CMT type 1A: on the one hand they are the genetic source of the disease, on the other, they respond to it by mounting a c-Jun-dependent response that significantly reduces its impact.
Spinal Bulbar Muscular Atrophy (SBMA): We continue to work with the AR100 mouse model of SBMA (Kennedy’s Disease) in which we have undertaken a preclinical trial of Arimoclomol (Malik et al, 2013). More recently we have established a new colony of mice that model a more aggressive form of SBMA and which express 121 CAG repeats (AR121 mice). This work has been undertaken in LG’s lab with MRC Centre students Anna Gray and Helen Devine.

Motor Neuron Disorders (MND): Centre PIs (EF, LG) use a number of models of MND, including the most widely used and best characterised mutant SOD1 mouse model. These groups have also been collaborating with MRC Harwell to identify and characterise mice with endogenous point mutations in the new ALS-causing genes TDP-43 and FUS. This work has been undertaken as part of a large collaborative project in the EF and LG labs with their co-supervised MRC Student Phil McGoldrick.

Centre PIs have also been studying transgenic mice that over express the molecular chaperone HSJ1. Overexpression of HSJ1 is capable of protecting motor neurons in the mutant SOD1 mouse model of ALS. Centre PhD student Anna Gray in LG’s lab contributed to this study.

The Centre has very recently established a colony of mice with mutations in the Senataxin gene (SETX). SETX mutations are known to be causative for a form of juvenile onset ALS (ALS4) and have also been shown to be a rare cause of hereditary motor neuropathy. Characterisation of these mice will be undertaken in LG’s lab with MRC Student Helen Devine.

Duchenne Muscular Dystrophy (DMD): Centre PIs (JEM, FM) use the mouse model for DMD (the mdx mouse) to investigate the mechanisms of muscle fibre death and whether this can be prevented (lead by postdoctoral research associate Dr Maximilien Bencze; in collaboration with LG). Immunodeficient mdx mice (mdx nude) are used in stem cell transplantation studies. Work on stem cells of human origin that have been lentivirally transduced to express dystrophin has been done in collaboration with Hanns Lochmuller, Adrian Thrasher and Olivier Danos. PhD student Bruno Doreste is working on factors within irradiated host muscle that enhance donor mouse satellite cell engraftment.

Spinal Muscular Atrophy (SMA): In SMA transgenic mice, the Smn gene is knocked out and the human SMN2 gene is introduced. Mice that carry at least one copy of endogenous Smn gene show no phenotype; Mice that have no Smn gene but two copies of human SMN2 gene (Smn +/-; (SMN2)2+/+) show severe phenotypes similar to type I SMA patients and a very short lifespan about 10 days; Mice that carry no copy of Smn gene but four copies of human SMN2 gene (Smn +/-; (SMN2)2+++) show mild phenotypes with only tail and ears necrosis and a normal life expectancy. Studies led by Centre postdoc Dr Haiyan Zhou in FM’s laboratory include: investigation of the molecular pathogenesis of SMA, evaluation of potentially therapeutic strategies (e.g. antisense oligonucleotide therapy and small molecules) and motor functional studies of neurodegeneration and response to therapeutic intervention (in collaboration with LG).
ii). MRC Centre PI’s play an active role in optimising the success of the MRC Neuromouse Consortium and have strong links with MRC Harwell

We collaborate closely with the one of the world’s major mouse genetics establishments, the MRC Mammalian Genetics Unit, Harwell, in the development and analysis of new models of disease. Recently, this has involved the NEUROMOUSE CONSORTIUM, which was set up by Professor Elizabeth Fisher, a member of the MRC Centre for Neuromuscular Disease, and is co-run with Professor Doug Turnbull, Dimitri Kullmann, Francesco Muntoni and others. The Neuromouse Consortium aims to help disperse mouse models relevant to human disease to the neuro-behavioural community in the UK, and also to provide experts in human and mouse neurological and psychiatric disease who can give essential insight and advice to Harwell on phenotyping platforms for the analysis of mouse models, and on genes for the prioritisation of specific mutants. While current efforts have focussed on models related to motor neuron disease, Harwell has been advised by Professor Dimitri Kullmann on electrophysiology and related platforms and has been making efforts to generate a new model for Professor Muntoni.

iii). Centre PI’s and PhD students continue to utilise the successful MRC Centre NMD animal phenotyping laboratory at UCL established using the original Centre award allocation (50k).

This facility is used on a regular basis by LG and EF’s laboratory in the phenotyping of all of their NMD mouse models, and by MRC Centre Students and postdocs.

iv). We participate in regular meetings on neuromuscular animal models.

The MRC Mouse Network continues to organise regular meetings to update members on lines produced, phenotyping tests being performed, and any phenotyping results of interest to date.

MRC Harwell also continues to offer regular training courses to which MRC Centre staff and students are invited. These include the following recent courses:

i) Bioinformatics of Mutant Mouse Resources: designed to give participants an understanding of high-throughput phenotype data, enabling them to interpret this data, compare it against other phenotype sources and identify mouse models of relevance to their clinical domain of interest.

ii) Understanding and Using the Light Microscope, intended for those new to light microscopy, with practical sessions and expert advice on how to operate both basic microscopes and advanced research instruments.

iii) Mouse Embryo and Spermatozoa Cryopreservation training course, covering the techniques needed to store and use frozen sperm and embryos, and a robust method of IVF.

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. We have studied this in three key areas:

(i) **Abnormalities of axonal transport**: have emerged as a key factor in several NMDs. Centre PIs have examined axonal transport in vivo e.g. in mouse models of MND (Loa and mSOD1 mice) and in vitro in models of motor neuropathies (HSPB1, loa) and CMT1A (C3).

(ii) **How do neuromuscular channelopathies cause muscle degeneration?** We have examined mouse models of muscle channelopathies (periodic paralysis) with mutations of Na (SCN4A) and calcium (CACNA1S) channels and RyRs.

(iii) **Mouse therapy studies**:

a) **Protein Aggregation/IBM**: using the mutant VCP mouse model of IBMPFTD, LG’s lab has examined the effects of manipulation of muscle cell protein homeostasis including heat shock protein and proteosomal regulation. The results indicate that long term treatment with Arimoclomol significantly ameliorates the histopathological features of IBM in muscle, resulting in improved muscle strength – study undertaken by MRC Centre Postdoc Mhoriam Ahmed with Centre PhD student Charlotte Spicer.

b) **Ion Channel Disease**: we have developed translational neurophysiological biomarkers of nerve excitability profiling for application in rodents, non-human primates and human volunteers and patients for drug discovery studies. Using the mutant SOD1 mouse model of ALS, Centre PIs (HB and LG) have developed a theoretical model of mouse motor nerve excitability, and validated it by application to recordings from mouse axons with membrane potential altered by polarizing currents using multiple excitability tests. Multiple excitability measures of nerves in mutant SOD1 mice before and during disease progression indicated a modest membrane depolarization in SOD1(G93A) axons at symptom onset, possibly due to deficient energy supply. However, previously described excitability changes in ALS patients, suggesting altered sodium and potassium conductances, were not seen in the mice. This suggests that those changes relate to features of the human disease that are not well represented in this animal model.

c) **Muscular Dystrophy**: we are examining a) the optimal type of donor muscle stem cells for systemic delivery and are using lentiviral vectors to transduce these cells with the largest possible dystrophin construct (opti-dystrophin); b) undertaking a proof of principle study of autologous stem cells lentivirally-transduced to express opti-dystrophin; c) using cardiac MRI to monitor natural history and effects of therapy on cardiac function in the Mdx mouse.

**Funding and publications**

All of the above studies are funded by a variety of grants obtained by the groups using animal models in the MRC Centre (see section 8) and have resulted in the publications outlined in section 7
b. Achievements in five key disease themes

i) Muscular Dystrophy

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

Stem cells in muscular dystrophy:

PIs of the Centre (UCL: FM, JM, NCL: HL) have undertaken an MRC-funded translational research project to identify an optimal stem cell that could be used for systemic delivery in Duchenne Muscular Dystrophy (DMD) (Meng 2014); an efficient and safe lentiviral vector; and an “opti-dystrophin” construct containing all the necessary regulatory elements, including the nNOS binding site.

Dystrophin constructs were electroporated into the dystrophic mouse mdx muscle, to investigate dystrophin expression, number of dystrophin+ fibres, restoration of the sarcoglycan complex and fibre morphology. This identified 3 constructs that were put into lentiviral vectors driven by the desmin (Jonuschies 2014) and SFFV (spleen focus-forming virus) promoters. Skeletal muscle stem cells obtained from DMD boys and processed in the MRC Biobank were lentivirally-transduced and cells were transplanted into muscles of immunodeficient mdx mice. Muscle fibres expressing human dystrophin were formed within the regenerated host muscles, but expression of dystrophin and restoration of nNOS within regenerated fibres was dependent on the construct and the promoter used.

We aim to follow on from this work by performing a proof of concept clinical trial assessing a local injection of lentivirally-induced opti-dystrophin expressing autologous stem cells into a single DMD muscle.

FST: Our current research projects are focusing on developing novel gene and cell therapy strategies based upon human artificial chromosomes (HACs) and induced pluripotent stem (iPS) cells (Benedetti et al., FEBS J 2013). We are developing next-generation multifunctional HACs containing the entire dystrophin locus (DYS-HAC), which will be transferred into human dystrophic myogenic progenitors. Genetically-corrected cells will be then challenged for their ability to repair dystrophic muscle and ameliorate the disease. Proof-of-principle of the potential of this approach using mouse cells was reported by us a few years ago (Tedesco et al, Sci Transl Med 2011). We are also finalising a project in which we have translated that same approach to human myogenic stem/progenitor cells (Benedetti S et al., in preparation). One of these projects was also funded by the MRC with a translational stem cell grant (MR/J006785/1; in collaboration with Prof. Cossu). This project specifically deals with the generation of a novel DYS-HAC containing: 1) a floxed immortalizing sequences to allow cell expansion and a suicide gene as a safety system; 2) an inducible MyoD cDNA to drive differentiation “on demand”; 3) additional copies of the full-length human dystrophin cDNA to increase dystrophin expression by transplanted cells. We are approaching completion of this multifunctional DYS-HAC using an innovative gene synthesis technology and the above construct will be mainly used for muscle-derived stem/progenitor cells.
Another important research line in the laboratory deals with the use of iPS cell-derived myogenic progenitors (Tedesco et al., Sci Transl Med 2012; Li O et al., F1000 Res 2013; Gerli et al., JoVE 2014). We are exploiting this technology for both disease modelling (for drug screening) and cell therapy in muscle diseases. In the case of cell therapy, we have also recently obtained funding from the Muscular Dystrophy Campaign to merge the DYS-HAC and iPS cell platforms to develop a novel cell therapy strategy for Duchenne muscular dystrophy. Work on this new project will start in January 2015.

Finally, we are also exploring the use on biomaterials in combination with stem cells for muscle disorders. In this context funding from the MRC was also secured with Dr Richard Day (UCL Division of Medicine) to improve delivery and function of myoblasts using soluble microcarriers (MR/L002752/1).

GC: The goal of current research is to optimise a cell-gene therapy protocol that may be applied to a large number of monogenic, recessive muscular dystrophies and, also, to other recessive diseases of the mesoderm. Intra-arterial delivery of the stem/progenitor cells represents the unique feature (already validated in patients) of the protocol: in the presence of inflammation, a common feature of these diseases, endothelium is activated and mesoderm progenitors can cross the micro-vessel wall to evenly distribute in downstream tissue. However mesoderm stem cells, such as mesoangioblasts (Mab) or mesenchymal stem cells (MSC) are significantly less efficient than leukocytes and this reduces the overall efficiency of the process, also considering the need to survive, proliferate, migrate and differentiate in an inflamed and sclerotic tissue to finally correct the genetic defect. To this aim we will optimise each individual step of the transplantation protocol in vitro, by enhancing: a) adhesion to endothelium (through exposure to cytokines and/or vasoactive drugs and/or transient expression of adhesion molecules); b) crossing the endothelium: using Boyden chambers coated with activated endothelium, and differentiated myotubes (for muscular dystrophy) or beads coated with chemo-attractants (for fibrillonapathies) in the lower chamber and testing molecules that may enhance the process; c) migration and ECM remodelling: myofibres or chemoattract-covered beads will be overlaid with ad hoc produced ECM complex that may mimic the diseased environment. Degradation of “diseased” ECM and replacement with a “healthy’ one can be monitored, in the case of muscle by fusion with myofibres (using fluorescent cells) and by measuring mechanical properties of these matrices; d) gene correction: we will co-culture an excess of mutant cells with wt or genetically corrected cells and will measure the amount of wt protein produced. As gene correction strategy we have modified (by insertion of an inducible MyoD) a lentivector expressing small nuclear RNA (snRNA), engineered to skip exon 51 (De Angelis et al. PNAS 2002). The rationale of this approach is based on the assumption that one donor nucleus will produce snRNA that, after assembling with nuclear proteins in the cytoplasm, will enter all neighbouring nuclei of the same cluster, thus amplifying gene correction.
Antisense Oligonucleotides (AON) in muscular dystrophy.

The activities on AON development in DMD have been focused on a number of different directions. i. investigator led studies targeting other DMD exons; ii. Collaboration in multicentric industry sponsored (Prosensa/ GSK) studies focused on skipping several exons in DMD boys; iii. In depth assessment of patients with Becker muscular dystrophy (BMD) including clinical features and dystrophin protein quantification on muscle biopsies, to help in planning the DMD studies; iv. Biomarker discovery to facilitate assessment of experimental therapies in DMD.

Regarding the Investigator led studies, FM has obtained a grant from the EU commission to develop a novel morpholino AON to target exon 53. The study involved centres in London, Newcastle; Rome; Paris and will be performed in collaboration with Sarepta. A new sequence which skips exon 53 at high efficiency has been identified using DMD cells stored in our Biobank; and the preclinical toxicology has now been completed. Regulatory authorities have granted authorisation for beginning dosing in UK, and we expect to start this clinical trial before the end of 2014.

Regarding the collaboration in industry sponsored clinical trials, the London and Newcastle centres are involved in an exon 51 phase IIb study (Voit, 2014); and recently started two phase Ib/2A studies for exon 53 and 45. All these studies performed in collaboration with industry are performed using a 2’OMe AON backbone.

Regarding the in depth assessment of patients with BMD phenotype, we have recently published our results of assessing in detail the clinical phenotype and protein production of a subset of BMD patients who carry deletions equivalent to those of DMD boys in which AON are used (Anthony et al, 2014).

Finally, re: the use of biomarkers, we have recently published a collaborative London-Newcastle study focused on the role of miRNA in DMD and BMD clinical course (Zaharieva et al, 203).

Antisense oligonucleotides (AON) have also been developed for other conditions, and specifically for spinal muscular atrophy (SMA). In particular a highly effective AON designed to induce SMN2 exon 7 retention has been developed [Zhou 2013; Millipant, 2013]. In collaboration with Matthew Wood (Oxford University, PI), in 2014 FM has obtained a DPFS grant from the MRC to assess the feasibility of developing a highly efficient AON that targets SMN2 and also crosses the blood brain barrier. This latter feature could potentially have implications for conditions other than SMA.

Other experimental therapies for Duchenne muscular dystrophy.

FM has conducted as a Chief Investigator coordinating 4 paediatric sites in UK (London; Manchester; Birmingham; Leeds) a phase Ib dose escalation study aiming at assessing the safety, PK and PD of SMTC1100, an orally bioavailable drug developed for the upregulation of utrophin. This study was sponsored by Summit plc and the result of this study will be presented at the World Muscle Society meeting in 2014 [Muntoni et al, 2014].
In parallel, the group at UCL ICH (FM; JM) is working together with Summit to develop and validate novel biochemical outcome measures to allow to document utrophin levels in DMD muscle, so that a validated assay could be used in the upcoming phase II study, of which FM will also be the chief investigator.

**Funding and publications**

All of the above studies are funded by both by the MRC Centre and other grants obtained by the muscular dystrophy groups in the MRC Centre (see section 8) and have resulted in the publications outlined in section 7.

**Added value from MRC Centre core activities**

Biobank. We use biobanked tissue for selecting sequences to target for antisense studies. For example the recent EU FP7 SKIP NMD grant targeting exon 53 had sequence selected entirely based on MRC Biobank

We also use stored cells for iPS work (in collaboration with Tedesco; and with Yung-Yao Lin)

We use stored cells for investigating feasibility of skipping duplication (collaborative work with Wilton- Australia)

We have used and published work on muscle biopsy studies focused on assessing dystrophin expression in DMD and BMD and methodologies for detecting dystrophin expression that could inform study design for clinical trials (paper in press in Neurology).

Biobank is also facilitating biomarker studies

It is facilitating optimal methods for utrophin quantification studies for informing future Summit phase II studies

Experimental medicine trials. DMD. We are currently involved in the following:

1. Skipping exon 45; 53; 51 with Prosensa (3 studies industry sponsored)
2. Skipping exon 53 (UCL/ Sarepta sponsored)
3. Summit utrophin upregulation phase Ib

MRI Biomarker. Excellent collaboration between GSK/ and Institute of Neurology for upper limb muscle MRI (longitudinal) and diaphragm, in non-ambulant DMD
ii) Neuromuscular Channelopathies

**UCL- Lead Michael Hanna (MH) NCL Lead Hanns Lochmuller (HM)**

**BACKGROUND/IMPORTANCE:** Dysfunction of ion channels causes neurological disorders with altered nerve and muscle excitability, impaired neuromuscular junction transmission or altered excitation-contraction (EC) coupling. Clinical manifestations include myotonia, episodic and progressive muscle weakness, myopathies and myasthenia.

**DISCOVERY SCIENCE AND EXPERIMENTAL MEDICINE**

**Muscle channelopathy genetics:** We have previously discovered many pathogenic changes in muscle ion channels in the world’s largest genetically stratified muscle channelopathy cohort established in the Centre (MH see publication list). Studying genetically undefined patients using whole exome sequencing we have identified a novel mutation affecting the sodium channel Nav1.4 in previously undefined congenital myopathy. This is a novel phenotype to be associated with Nav1.4. (FM MH in prep) We have also systematically established the prevalence of skeletal muscle channelopathies and common mutations in England (MH Neurology). We have built a cohort of deeply phenotyped patients without variants in known disease causing genes who are undergoing next generation sequencing.

**Muscle channelopathy genotype-phenotype correlation:** We established mexiletine as the first evidence based treatment for non-dystrophic myotonia in an international multicentre trial. (MG JAMA 2012) We additionally reviewed a cohort of 71 of our own patients. The data indicates those with chloride channel mutations require a higher dose of Mexiletine and are more likely to be non-responders than patients with sodium channel mutations. An exaggerated male/female ratio for Myotonia Congenita was also observed and in vitro work demonstrated a direct effect of sex hormones on chloride channel function. We previously described neonatal phenotypes of sodium channel myotonia. Further identified cases (both our own unpublished observations and published others) suggest a phenotype-genotype correlation with G1306E mutation. This has implications for best treatment as mexiletine efficacy is thought to vary with mutation.

**Molecular pathophysiology:** We have been awarded an MRC research grant to improve our facilities to study the gating pore currents identified as the major pathomechanism in hypokalaemic periodic paralysis. This includes setting up a cut-open voltage clamp system (gold standard for gating pore current measurements), establishing GLT dysgenic cell line for Cav1.1 channel expression, and developing myoblast cell lines derived from HypoPP patients. We have been invited to submit a full application for an NIHR grant to study the effects of mutation on efficacy of sodium channel blockers and whether combined drug therapy has additional or synergistic benefits in sodium channel myotonia.

**Mechanisms of muscle degeneration in channelopathies:** Most patients with muscle channelopathies develop a severe myopathy but the mechanism is unknown and there is no treatment. We used MRI to study muscle changes in myotonia congenita and showed varying degrees of fatty infiltration in patients. This is consistent with the observation of a proportion of patients developing a fixed weakness and provides outcome measures for
muscle degeneration. We have also participated in characterization of a novel mouse model of Hyperkalemic PP (MH Brain in press) The mice display progressive decrease in muscle function and will provide a valuable model for studies on muscle degeneration.

**Muscle channelopathies and new experimental medicine studies:** Bumetanide is an inhibitor of Na-K-Cl co-transporter that has been shown efficacious therapy in two mouse models of HypoPP. Funding, study ethics and plan are in place to start a clinical trial in humans in the Centre in the near future.

**RyR channelopathies:** Ryanodine receptor mutations cause disabling core myopathy. We have recently shown that RyR1 deficiency in congenital myopathies concomitantly alters the expression pattern of several proteins involved in calcium homeostasis including of the α1 subunit of the DHPR and show disruption of the organization of the EC coupling machinery\(^5\). This may influence the manifestation of these diseases.

**Congenital myasthenic channelopathies:** Using whole-exome sequencing on patients with congenital myasthenia, distal muscle weakness and atrophy reminiscent of a distal myopathy we identified new mutations in the gene encoding agrin (Lochmuller in press) This proteoglycan was previously found mutated in more typical forms of congenital myasthenic syndrome. Our findings expand the spectrum of congenital myasthenic syndromes due to agrin mutations.

**Funding and publications**
All of the above studies are funded by both by the MRC Centre and other grants obtained by the channelopathy group in the MRC Centre (see section 8) and have resulted in the publications outlined in section 7.

**Added value from MRC Centre core activities**
The channelopathy group has benefited significantly form the infrastructure offered by the MRC Centre. We have been able to establish and expand a **stratified cohort** of approximately 1700 deeply phenotyped channelopathy patients, many of whom have participated in natural history and MRI studies, and clinical treatment trials. This stratified cohort has allowed accurate **MRI biomarkers** to be identified as well as better understanding of genotype-phenotype correlations which in turn prioritises our molecular targets for study. The mix of skill and facilities at the centre involved in the characterisation of a **mouse model** of hyperkalaemic periodic paralysis provides further opportunity to significantly progress in molecular pathophysiology.
iii) Inherited Neuropathies

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

New genes:

- Using next generation sequencing to identify new genes for inherited neuropathies was one of our main aims for 2013-2018. We have identified 6 new genes to date; two genes for autosomal dominant CMT2, *MARS* (MR, JNPP 2013) and a novel gene (MR, AJHG 2014 submitted); two genes for hereditary motor neuropathy, *BICD2* (MR, AJHG 2013) and *FBOX38* (MR, AJHG 2013) and two genes for complex neuropathies *EXOSC8* which causes spinal muscular atrophy, pontocerebellar hypoplasia and hypomyelination (RH, Nat Comm 2014) and *SYT2* which causes non progressive motor neuropathy with Lambert-Eaton myasthenic syndrome (RH, AJHG 2014).

- In addition we have identified multiple new mutations in our cohort in known inherited neuropathy genes and published novel phenotypes for many of these genes including *C12orf65, IGHMBP2, ADCK3, COX10, FIG4, SPTLC2* and *TRPV4* (see MR and RH publications, section 8) and a selection of genotype / phenotype studies including the usefulness of the presence of peripheral neuropathy to predict the genotype in mitochondrial ophthalmoplegia (MR, Brain 2014).

- We have also developed, instituted and published a guide to the use of next generation sequencing in inherited neuropathies (MR, Nat Reviews Neurol 2013).

MRC Neuropathy stratified cohorts.

- Prior to February 2013, we already had a neuropathy cohort in the UCL part of the centre (MR) and since renewal we have, as planned, extended that cohort and currently have 1900 deeply phenotyped patients (1500 UCL; 400 NCL) as well as a further 1400 in our inherited neuropathy DNA registry (3300 in total). Internationally the UCL site is part of the NIH funded inherited neuropathy consortium and has contributed 631 patients to the total of 2618 patients recruited to this natural history study from 16 sites.

- In the MRC Centre UCL/NCL cohort we have a project studying HMN, HNPP, hereditary sensory neuropathy type 1, the CMTNS responsiveness, familial amyloid polyneuropathy, rare forms of inherited neuropathy, the effects of pregnancy on CMT and the types of orthopaedic procedures used in CMT patients. We also have an active program of biobanking blood and fibroblasts from skin and in selected cases nerve and skin biopsies for our pathogenetic studies.

- In UCL we are specifically studying the responsiveness of a newly developed MRI neuromuscular protocol in longitudinal studies in CMT1A and HSN1.
Understanding Molecular Pathophysiology

- Deepening our understanding of the pathogenesis of a wide range of inherited neuropathies to help develop therapies was a further aim for 2013-2018.
- In the hereditary motor neuropathies we have studied the pathogenesis of the two new genes we have identified. We have shown that BICD2, a major protein involved in retrograde axonal transport is likely to cause HMN due to perturbation of BICD2-dynein-dynactin-mediated trafficking and impair neurite outgrowth (MR, AJHG 2013) and that FBXO38, needed for regulation of genes required for neuronal axon outgrowth and repair is likely to cause HMN by transcriptional dysregulation with an associated impairment of neurite outgrowth (MR, UCL).
- In HSN1 secondary to SPTLC1/SPTLC2 mutations we have shown that the deoxysphingolipids (DSBs) which are produced when a mutation alters the substrate specificity of the SPT enzyme, are toxic to both sensory and motor neurones and have an ongoing project studying IPS cells from patients and looking at the potential of both serine and antisense oligonucleotide therapy for this group of patients (MR, UCL).
- In investigating the pathogenesis of complex neuropathies, we developed and successfully used a zebrafish model to investigate the major disease mechanisms in the complex spinal muscular atrophy, pontocerebellar hypoplasia and hypomyelination syndrome in which we had identified EXOSC8 mutations, and showed that the neurodegeneration was caused by a defect in mRNA metabolism (RH, Nat Comm 2014)(RH, NCL).

Clinical trials

- In our NCL site, we have completed a clinical trial as part of an international study: “Validation of prognostic biomarkers in CMT1A”. This is a multicentre international study (coordinated by Dr. Michael Sereda, Gottingen, Germany) including 8 partners from 7 European countries. In NCL we performed detailed clinical investigations and collected skin biopsies for biomarker research in 20 patients with CMT1A. The data of 300 CMT1A patients from all partners are currently being evaluated.
- In our UCL site, we are currently enrolling into a trial of aerobic exercise for CMT1A which has a unique trial design for CMT of delivering the exercise through local gyms coordinated by the trials physiotherapists.
- Our UCL site (together with the National Amyloid Centre, UCL) are a site for the first antisense oligonucleotide trial in an inherited neuropathy i.e. TTR-related Familial Amyloid Polyneuropathy being run by ISIS.

Funding and publications

All of the above studies are funded by both by the MRC Centre and other grants obtained by the neuropathy groups in the MRC Centre (see section 8) and have resulted in the publications outlined in section 7.
Added value from MRC Centre core activities

The inherited neuropathy group has had major benefit from the MRC Centre. The joint centre between London and Newcastle has enabled initially the setting up of a dedicated CMT clinic in Newcastle during the first cycle of the grant and in the last 18 months the support from the experimental medicine trial coordinators has allowed us to setup a joint MRC Centre inherited neuropathy stratified cohort which currently has 1900 deeply phenotyped patients entered. The use of this cohort and also fibroblasts from the MRC Centre biobank has been instrumental in helping both new gene discovery and functional studies in these new genes in both sites of the centre. The experimental medicine trial coordinators have also helped the setting up of and the coordination of the ongoing aerobic exercise study in CMT in UCL. The MRI biomarker development in UCL has allowed us to develop a biomarker which is responsive over 1 year in CMT1A which will be revolutionary in future clinical trials.
iv) Inclusion Body Myositis (IBM)

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

The IBM group aims to understand the causes of IBM, develop cell & animal models and to identify novel therapeutic strategies.

1) IBM Natural History Study: a prospective IBM patient cohort is established, this cohort is being deeply phenotyped at the clinical, serologic, histopathological and MRI level and outcome measures/MRI biomarkers for experimental trials are being developed. 2) Development of in vitro models of IBM: we established 2 cell culture systems modelling “degenerative” or “inflammatory” components of IBM. Muscle cells in vitro were transfected with β-APP (to model protein mishandling) or exposed to inflammatory mediators IL1β, TNFα and IFNγ (to model inflammation). In both models cells recapitulated pathological characteristics of IBM including: i) formation of ubiquitinated intracellular inclusions immunoreactive for β-APP, AB-42, TDP-43, p-Tau, caspase-3 Hsp70 and p62; ii) increased expression of MHC Class I; iii) mitochondrial dysfunction & iv) cytoplasmic translocation of TDP-43. ER stress & activation of the NFκB cascade, potential central pathogenic mechanisms in IBM. 3) Establishing cellular outcome measures: we established in vitro readouts of IBM pathology for drug screens for IBM: i) cell survival; ii) inclusion body formation; iii) cytoplasmic translocation of TDP-43; iv) activation of NFκB cascade; v) ER Stress. 4) Screening novel compounds: using this in vitro model we examined effects of pharmacological manipulation of the Heat Shock Response (HSR), an endogenous cellular defence pathway on IBM-like pathology. We found that Arimocromol, a co-inducer of the transcription factor HSF-1 that drives expression of Heat Shock Proteins ameliorated several IBM-relevant features. We established a new collaboration with a small drug discovery company Senexis (Cambridge) that develop compounds to target formation of amyloid. Two of these compounds are effective at attenuating the IBM-like pathology observed in our cellular models. These compounds merit further investigation in animal models & for safety and tolerability as a first step in man. 5) MRC Centre-First in IBM man experimental safety study: We undertook an investigator-lead placebo controlled safety and tolerability study of Arimocromol in 24 IBM patients with pre and post treatment muscle biopsy. Initial data confirms safety and tolerability and an efficacy study in currently being planned. This project represents a fundamental step in a translational research programme in IBM that we have established in the MRC Centre. This approach is novel in the field as all previous pharmaceutical efforts have concentrated on immunosuppression and to date all such trials have been negative. 6) Assessing Arimocromol in the VCP mouse. This recent transgenic mouse represents the best characterized & pathologically representative model of IBM available. This mouse carries a mutation of Valosin Containing Protein (VCP) which is intimately related to TDP-43 function & is implicated in other conditions such as motor neuron disease. The VCP mouse recapitulates the pathology of human IBMFTDPD, in which muscle shares key pathological features with sporadic IBM, including cytoplasmic translocation of TDP-43, activation of NFκB cascade & inflammation. We will employ a blinded treatment regimen with longitudinal physiological, behavioural & histological analysis of mice carrying mutated or wildtype VCP to determine if manipulation of the HSR produces functional or pathological benefits in vivo. This study may have wider implications
for NMD & treatments, e.g. the sarcopenia of ageing shares several characteristics with IBM, several muscular dystrophies also display an inflammatory component that is driven by NFkB activation, which we hypothesize will be inhibited in vivo by Arimoclomol treatment, as it is in vitro. 7) MRI Biomarkers: our recent work shows that qMRI parameters in muscles in IBM patients prospectively followed over 12 months show consistent significant reductions that correlate with reduced power. These data indicate MRI can now be included as a clinical trial outcome. 8) Genetics: we formed an international IBM genetic consortium (Europe, USA, Australia) & established a large DNA bank of IBM patients. With MRC funding (£853866 2012-2015) we will undertake NGS to identify rare protein coding variants that associate with IBM and undertake functional characterization. 9) Exercise physiology: We are currently investigating aerobic training in IBM on fitness levels, muscle strength and function using a randomised crossover design with training and control periods. 10) Links with industry and new clinical trials: We have established productive links with industry in order to support new clinical trials in IBM. A phase IIb/III multicentre clinical trial sponsored by Novartis is ongoing; this study will test a new humanised intravenous monoclonal antibody against the myostatin receptor (BYM338/Bimagrumab). The myostatin pathway is a central negative regulator of myogenesis during development and periods of muscle regeneration in postnatal life. This pathway is of major interest as a target for therapeutic manipulation in neuromuscular conditions characterised by progressive muscle atrophy and weakness. We continue to collaborate with Orphazyme (owns rights to Arimoclomol) to undertake the first human efficacy trial in IBM. In collaboration with Novartis, we are starting a new prospective, multinational, multicentre study IBM study aimed at understanding of the natural history of IBM over time by evaluation of the functional, economic and humanistic burden of disease. In order to assess the changes in muscle quality and composition MRI imaging will be performed in a subset of IBM patients at UCL only.

All MRC Centre core activities will add value and enable the IBM programme including stratified cohort and experimental trial support, MRI biomarker, Biobank, PhD studentships and animal models and phenotyping unit.

Funding and publications

All of the above studies are funded by both by the MRC Centre and other grants obtained by the IBM group in the MRC Centre (see section 7) and have resulted in the publications outlined in section 6.

Added value from MRC Centre core activities

Collaboration in a rare disease such as IBM is essential to advance knowledge. The MRC Centre for Neuromuscular Diseases has proved to be the ideal platform to support collaborative work in IBM, combining the expertise of the London and Newcastle Centres. The existence of the Centre has allowed developing further the research infrastructure to support patient-centred research into IBM, enhancing patient recruitment for clinical trials, observational studies (IBM stratified cohort) and biobanking. Sharing of ideas and protocols between the two centres has acted as a catalyst to translate IBM research into the development of new IBM medicines and biomarkers, particularly MRI biomarkers. The
MRC Centre for Neuromuscular Diseases has also allowed the establishment of a collaborative network able to provide unique opportunities to train health professionals on IBM.
v) Mitochondrial Diseases

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

Progress

Ongoing or recently completed clinical studies

1. MRC Centre Mitochondrial Disease Patient Cohort: Natural History Study and Patient Registry – this now includes 1113 patients. This cohort study is proving invaluable in our management of disease (see below).

2. Exercise in Sarcopenia – this includes 22 subjects of varying ages who are undergoing training regime to determine the effect on mitochondrial defects causing sarcopenia.

3. Cardiac adaptations to aerobic exercise in Mitochondrial Disease – this study that included 39 patients has been completed and has shown that exercise is beneficial for patients with mitochondrial disease with no adverse cardiac events.

4. Exercise training for adults with neuro muscular weakness and limited physical activity: optimising the benefits – this study recruited 15 patients and explored the benefits of high intensity exercise in neuromuscular disease.

5. Exercise training in patients with single deletion mitochondrial disease: Assessing the benefits – this study involved 6 patients and looked at the benefits of resistance and endurance exercise.

6. Assessing cognition in patients with mitochondrial disease – this study recruited 84 patients and showed that cognitive impairment is common in mitochondrial disease and is devising strategies to help patients cope with their difficulties.

7. Complications of pregnancy in patients with mitochondrial disease – this study included 155 patients and have recently been completed. The results will advise us how to manage patients with mitochondrial disease in the future.

8. Reproductive Decision Making in Female Mitochondrial Patients: A study to explore retrospective and current reproductive decision making – this study has recently been started and currently includes 3 patients.

9. Investigating the changes in muscle over time in patients with mitochondrial disease – this study includes 22 patients who have undergone repeat muscle biopsy and has stopped recruiting with the laboratory studies on going.

10. Genotype and Phenotype of inherited mitochondrial disease – this study is to look at hearing impairment in patients with mitochondrial disease and 30 patients have been approached for inclusion.

11. Sequencing nuclear genes causing mitochondrial disorders using NGS-Exome Study – this is a collaboration with Guy’s hospital and 14 families have been included.

12. 100,000 Genomes Project – this nationwide study includes 33 of our patients.

13. Peripheral neuropathy in patients with progressive external ophthalmoplegia – this study that retrospectively evaluated 116 patients with progressive external ophthalmoplegia has been recently completed (see below).
14. Renal disease in adult patients with mitochondrial disease – this cross-sectional study aimed to investigate the prevalence and nature of renal disease in adult patients with mitochondrial disease (see below).

15. Mortality in adult patients with mitochondrial disease – this is an ongoing retrospective study evaluating the cause of death of patients with mitochondrial disease. The results will be used to improve the assessment and management of patients in the future.

16. Clinical trial of nicotinamide riboside in mitochondrial disease – in this study we will establish methodology for the evaluation of new treatments in mitochondrial myopathy, and provide proof-of-principle safety and preliminary efficacy data for nicotinamide riboside in an adaptive, double blind, randomised, placebo-controlled trial (see below).

Experimental studies

Clinical studies with impact on patients

**Single, large-scale deletions of mitochondrial DNA** are a common cause of mitochondrial disease and cause a broad phenotypic spectrum ranging from mild myopathy to devastating multi-system syndromes such as Kearns-Sayre syndrome. Studies to date have been inconsistent on the value of putative predictors of clinical phenotype and disease progression such as mutation load and the size or location of the deletion. Using a cohort of 87 patients with single, large-scale mitochondrial DNA deletions we demonstrate that a variety of outcome measures are significantly ($p < 0.05$) correlated with the size of the deletion, the deletion heteroplasmy level in skeletal muscle, and the location of the deletion within the genome. Furthermore, we have used mixed modelling techniques to model the progression of disease according to these predictors, allowing a better understanding of the progression over time of this strikingly variable disease. In this way we have developed a new paradigm in clinical mitochondrial disease assessment and management that sidesteps the perennial difficulty of ascribing a discrete clinical phenotype to a broad multi-dimensional and progressive spectrum of disease, establishing a framework to allow better understanding of disease progression.

**m.3243A>G mitochondrial DNA mutation** is the most common genetic cause of mitochondrial disease. The clinical presentation associated with the mutation is extremely varied, including four classically recognised mitochondrial syndromes [mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), Leigh Syndrome, Chronic Progressive External Ophthalmoplegia (CPEO) and maternally-inherited diabetes and deafness (MIDD)], but also a wide spectrum of other phenotypes. Understanding of disease progression for patients harbouring this mutation is limited. We utilised a cohort of 156 subjects carrying the m.3243A>G mutation (both patients and asymptomatic carriers) to quantify the association between heteroplasmy (measured in urinary sediment), age, and disease progression. We demonstrate that both age and mitochondrial DNA heteroplasmy are associated with the majority of phenotypic features including deafness, diabetes mellitus, cerebellar ataxia, and myopathy, but other features such as seizures, whilst being associated with m.3243A>G heteroplasmy, are not associated with age. Age is more
strongly associated with many phenotypic features than heteroplasmy. Deafness and diabetes mellitus are shown to be strongly associated with each other, but are not negatively associated with any other features. We also show that both m.3243A>G heteroplasmy and age are strongly associated with overall disease burden progression (p<0.0001), and demonstrate that genetic familial lineage is a significant modulator of disease burden (p<0.0001). We have also identified that there are patients with high levels of m.3243A>G heteroplasmy who have a relatively low disease burden.

**Peripheral neuropathy in patients with progressive external ophthalmoplegia.** Progressive external ophthalmoplegia (PEO) is a common presenting feature of mitochondrial disease caused by mitochondrial and nuclear DNA defects. Peripheral neuropathy is also a frequent manifestation of mitochondrial disease although its prevalence varies among the different genetic aetiologies. Based on clinical observations, we investigated whether the presence of peripheral neuropathy could predict the underlying genetic defect in patients with PEO. We analysed clinical data from 116 patients with genetically defined mitochondrial disease and PEO. We observed that the prevalence of peripheral neuropathy is a rare clinical feature in patients with a single mitochondrial DNA deletion and that peripheral neuropathy is an independent predictor of a nuclear DNA defect (odds ratio 8.43, 95% CI 2.24-31.76, p=0.002). This observation will facilitate future development of diagnostic algorithms to aid clinicians when selecting and interpreting molecular genetic investigations.

**Renal disease in adult patients with mitochondrial disease.** Renal disease is a common feature of mitochondrial disease in children. However, little is known about the effects of mitochondrial disease on kidney function in adults. We investigated the extent and nature of renal involvement in a cohort of 117 adult patients with genetically confirmed mitochondrial disease by measuring established markers of tubular and glomerular dysfunction. We observed that abnormalities in urinary protein and metabolite excretion are common in adult patients with mitochondrial disease, that they exist in the absence of elevated serum creatinine levels, and that they cannot be attributed exclusively to the effects of diabetes. These observations have important clinical implications for devising appropriate screening strategies of renal involvement in adults with mitochondrial disease.

**Clinical trial of nicotinamide riboside in mitochondrial disease.** Mitochondrial diseases cause severe neuromuscular and multisystem disease in children and adults and are associated with significant morbidity and mortality. A recent Cochrane systematic review found no treatments of proven benefit in patients with mitochondrial disease. Pre-clinical studies in animal models of mitochondrial disease have shown that the induction of mitochondrial biogenesis leads to improvements in respiratory chain activity accompanied by physiological improvements in muscle function and life-span. Pathways related to mitochondrial biogenesis are targets for Sirtuin1 (Sirt1), a nicotinamide adenine dinucleotide (NAD+)-dependent protein deacetylase. Nicotinamide riboside, a natural NAD+ precursor, enhances the activity of Sirt1 and other sirtuins, and supplementation with nicotinamide riboside has been shown to improve the respiratory chain defect and exercise intolerance in two separate mouse models of mitochondrial disease. This strategy is potentially translatable into therapy of human mitochondrial disease irrespective of the underlying genotype, as the ultimate aim is to increase the overall residual activity of the
respiratory chain rather than correct the specific genetic defect. In this study we will establish methodology for the evaluation of new treatments in mitochondrial myopathy, and provide proof-of-principle safety and preliminary efficacy data for nicotinamide riboside in an adaptive, double blind, randomised, placebo-controlled trial.

**Stratifying Patients with Leber Hereditary Optic Neuropathy (LHON) for Idebenone Therapy Trial.** Our preliminary work showed that low-dose idebenone appeared to increase the rate of visual recovery in patients with this classical mitochondrial disorder, LHON. Data from this trial underpinned a successful MRC-EME application (£750K) to treat 105 patients with LHON with 900mg for 48 weeks stratified by genotype. Trial agreements are in place and recruitment will start in the new year 2015.

**New diagnostic tools**

Some of the challenges of mitochondrial disease is establishing a diagnosis and then understanding the molecular mechanisms. Whilst the use of NGS has allowed remarkable recent progress (see below), new diagnostic techniques are required to enable the proper evaluation of tissues (particularly muscle) obtained from patients. The mainstay of diagnostic investigations is the use of cytochrome c oxidase histochemistry which is invaluable in terms of establishing if a mitochondrial defect is present in many patients. This technique however has some limitations particularly given there is no reliable histochemical method to detect one of the commonest respiratory chain defects seen in patients, complex I deficiency. We have developed a new diagnostic procedure which involves fluorescent immunocytochemistry using four different antibodies on the same section. This technique highlights different signatures of immunoreactivity depending on the nature of the underlying molecular genetic defect and will be useful for directing research investigations in the future, particularly in determining response to therapeutic interventions. In addition, this technique can be automated and has the potential to play a major role in the investigation of mitochondrial dysfunction in the future.

**Mitochondrial gene discovery and molecular mechanisms**

**mtDNA-related mitochondrial disease:**

Our studies have identified novel mitochondrial DNA (mtDNA) mutations associated with multisystem and myopathic presentations of paediatric and adult-onset mitochondrial disease, delineating the mechanisms leading to molecular pathology in muscle and the central nervous system. Utilising the patients registered on the MRC Centre Mitochondrial Disease Patient Cohort (UK), we have extended these studies to delineate and model disease progression (see above), the nature of mtDNA mutations within muscle satellite cells and mechanisms underlying mtDNA mutation accumulation for a sub-group of pathogenic mtDNA mutations, single, large-scale mtDNA deletions.

**Nuclear mtDNA mutations:**

We have used whole exome sequencing (WES) and targeted capture arrays to elucidate the molecular basis of mitochondrial disease in our clinically- and biochemically-characterised cohorts of patients with mitochondrial disease. We have sequenced a cohort of ~60 patients with biochemical evidence of multiple respiratory chain complex
abnormalities indicative of a generalised mitochondrial protein synthesis defect, identifying an unprecedented high rate of disease gene discovery (approximately 70% of the individuals) including known genes, previously unrecognised genotype: phenotype correlations and a number of new disease genes; confirmatory functional studies have been completed for some of these genes including \textit{ELAC2}, \textit{FBXL4}, \textit{TRIT1} and \textit{APOPT1} whilst these are continuing for other examples. Mechanistic studies have led to the identification of the molecular mechanisms underlying reversible infantile respiratory chain deficiency and to the reassignment of the NDUFA4 protein to mitochondrial respiratory chain complex IV. We have also used WES to delineate the molecular basis of undiagnosed adult-onset mitochondrial PEO with multiple mtDNA deletions, identifying \textit{SPG7} mutations as an important cause and describing new clinical phenotypes associated with other recessive mtDNA maintenance disorders.

**Funding and publications**

All of the above studies are funded by both by the MRC Centre and other grants obtained by the mitochondrial groups in the MRC Centre (see section 8) and have resulted in the publications outlined in section 7.

**Added value from MRC Centre core activities**

Progress in the mitochondrial theme is entirely dependent on the interaction between UCL and Newcastle and support from the core activities. The stratified cohort is the largest well characterised cohort of mitochondrial patients internationally and is leading the development of guidelines and interventions. Support from the clinical trials coordinator is crucial to the success of the cohort and the numerous studies that have developed from this unique group of patients. In addition, the opportunity to train both clinical fellows and PhD students, plus the access to tissues form the Biobank has enabled critical new studies to be developed"
6. MRC Centre current PhD students and projects post 2013 start

Year 1

**Ione Meyer**
Year 1 Non-Clinical UCL – started September 2014 and currently in induction 6 week period.

**Prasanth Sivakumar**
Year 1 Non-Clinical UCL – started September 2014 and currently in induction 6 week period.

**Aura Cecilia Jimenez Moreno**
Year 1 Non-Clinical Newcastle (3 Year PhD) - started Sept 2014
‘MD type 1. as part of the multicentre trial OPTIMISTIC’
Supervisor: Professor Hanns Lochmüller

Co-ordination of the OPTIMISTIC Trial in the UK site (which is based at Newcastle).
OPTIMISTIC: Observational Prolonged Trial In Myotonic dystrophy type 1 to Improve Quality of Life - Standards, a Target Identification Collaboration.
OPTIMISTIC is the first ever project to focus on myotonic dystrophy and involves an international multicentre intervention (France, Germany, United Kingdom and the Netherlands).
OPTIMISTIC will investigate the effect of exercise training and cognitive behavioural therapy (CBT) on patients with myotonic dystrophy in order to find new and innovative ways to improve quality of life; In doing so protocols and guidelines will be developed specifically for this complex disease. Over 200 patients will be involved in this project across Europe and recruitment is expected to start in 2014. In addition OPTIMISTIC will utilise this opportunity to work towards standardising cardiac screening procedures and to carry out genetic analysis to better develop prognosis tools. Furthermore OPTIMISTIC aims to
develop and validate clinically significant outcome measures that can be used in future clinical trials. Newcastle will be the site responsible for cardiac MRI screenings.

**Stephanie Carr**  
Year 1 Non-Clinical Newcastle (MRes in Neuromuscular Diseases) – started Sep 2014

‘Molecular and stem cell therapy for Duchenne Muscular Dystrophy’  
Supervisor: Professor Hanns Lochmüller

Outline of PhD project as advertised – Ms Carr began her MRes in Sept 2014. ‘Gene therapy and stem cell therapy are molecular approaches that may be applicable to all patients with DMD regardless of their specific mutation once proven effective and safe. In contrast to therapeutic approaches targeting RNA, they also have the potential for permanently restoring dystrophin to muscle following a single application. Previous work has focussed on identifying suitable stem cells for autologous transplantation including iPS cells (MRC grant with Chris Denning; Dick et al 2011; Dick et al 2013), identifying suitable vector systems and dystrophin constructs for gene transfer into stem cells or into muscle directly (MRC grant with Jenny Morgan; Meng et al, submitted), and establishing tests in vitro and in vivo to assess the benefit of such therapeutic approaches (Jorgensen et al, 2011; M Ritso unpublished; M Reza unpublished). Preliminary results show that dystrophin-deficient, primary cardiomyocytes show a hypertrophy response to stress that can be utilized for the assessment of pharmacological or molecular therapeutic interventions. In addition, we have generated optimized dystrophin constructs that are small enough to be packaged into lentiviral and AAV vectors, but restore nNOS binding to the sarcolemma. The project will test which of the nNOS-binding sites are essential, and whether nNOS-restoring dystrophin constructs are superior in restoring function in dystrophin-deficient cardiac and skeletal muscle as compared to conventional micro- or mini-dystrophin molecules. Optimized dystrophin constructs will be tested in both stem cell and gene transfer experiments utilizing the in vitro and in vivo assays mentioned above.’

**Persefoni Ioannou**  
Year 1 Non-Clinical Newcastle (3 year PhD) – started Sep 2014

‘Establishing contrast enhanced magnetic resonance imaging as a non-invasive outcome measure in a pre-clinical drug development study for Duchenne muscular dystrophy’  
Supervisors: Professor Volker Straub, Dr Steven Laval & Dr Umar Burki
NHE-1 inhibition represents a novel promising therapeutic strategy to attenuate DMD pathology. The current study seeks to demonstrate the efficacy of a specific NHE-1 inhibitor that has shown a good safety and potency profile in several pre-clinical studies using real-time imaging of calcium handling in mouse models of DMD. Calcium flux will be monitored in vivo by manganese enhanced MRI (MEMRI) which allows the monitoring of calcium intake in both skeletal and cardiac muscle. The imaging study will be supported by functional muscle testing and tissue analysis. The proposed studies with a first prototype NHE-1 inhibitor are an important step towards potential clinical trials for DMD with this class of compounds.

**Boglarka Bansagi**
Year 1 Clinical, NCL – started Feb 2014

‘Clinical and genetic characterisation of hereditary motor neuropathies’
Supervisor: Professor Rita Horvath

The aim of the clinical project is to enhance the national cohort of Charcot Marie Tooth disease with patients recently diagnosed in North England. This cohort will enable us to proceed with natural history and genetic studies in this gross patient group both nationwide and locally. The research part of the project is primarily focused on the subgroup of distal hereditary motor neuropathies (dHMN). With the goal of new genes discovery we plan to establish further subclassification of dHMN on a clinicogenetic basis. This will provide us with new insights of the pathomechanism of the disease and will hopefully allow us to identify biomarkers in this subgroup.

**Claire Wood**
Year 1 Clinical, NCL – started Jun 2014

Qualitative and quantitative MRI for the assessment of genetic muscle disease

**Supervisors:**
Newcastle - Professor Volker Straub, Dr Kieren Hollingsworth, Dr Tim Cheetham
London- Professor Tarek Yousry

In a number of inherited muscle diseases, the pattern of selective muscle involvement detected by MRI can be pathognomonic and help guide genetic testing, target the optimal muscle for biopsy, and explore disease mechanisms. MRI for diagnostic purposes,
however, is still not applied in a standardised fashion across neuromuscular centres and often depends on the interest of individual investigators. Pooling these data will help to define the spectrum of selective patterns of pathology; answer questions about why certain muscles are spared from pathology despite ubiquitous protein expression and to better understand disease onset, progression and pathophysiology. The first part of my PhD will involve helping to establish an online inventory of muscle MRIs from neuromuscular centres across Europe and qualitatively review the images alongside associated clinical information.

During the second part of my PhD I will design and implement a clinical trial to determine the effects of low dose versus high dose testosterone on muscle function in adolescents with Duchenne Muscular Dystrophy, utilising quantitative muscle MRI techniques.

Kataryzna Swist-Szulik
Year 1 Clinical, NCL - started Jun 2014

‘Does inherited and acquired mitochondrial dysfunction influence the NLRP 3 inflammasome activation?’
Supervisors: Professor Doug Turnbull, Professor Rob Taylor, Professor Robert McFarland

Mitochondria are required for maintaining the cellular energy level and their health is vital for cell viability. Mitochondria are as well in the crossroad of innate responses and inflammation signaling cascades culminating in activation of nuclear factor-kB (NF-kB), mitogen-activated protein kinases (MAPKs) and interferon regulatory factors (IRFs) which control the expression of pro-inflammatory cytokines. During cellular injury and necrosis damaged mitochondria leak mitochondrial damage-associated molecular patterns (DAMPs) such as mtDNA, mitochondrial ATP, mitochondrial ROS into the cytosol and activate the inflammasome, a multi-protein molecular platform that upon activation of caspase-1 promotes the secretion of pro-inflammatory cytokines IL-1β and IL-18. There are the evidence that mitochondrial stress and dysfunction are monitored by inflammasome through three main mechanisms including extracellular ATP/P2X7 signaling and ion fluxes, ROS signaling and lysosome degradation. Recent studies suggested a role of NLRP3 inflammasome activation and IL-1β in diabetes, atherosclerosis, neurodegenerative disease such as Alzheimer’s disease, muscle inflammation in Limb Girdle Muscular Dystrophy (LGMD) and Inclusion body myositis. The main research questions are focused on the influence of mitochondrial dysfunction in NLRP3 inflammasome stimulation as well as their role in non-immune cells such as myoblasts and fibroblasts. The aim of my project is to develop and optimize monocyte, fibroblasts and muscle models and be able to test NLRP3 inflammasome activation in the cell stress environment.
Year 2

**Louise King**
Year 2 Non-Clinical UCL – started Sep 2013

‘Mitophagy deficiencies in mitochondrial DNA disease’
Supervisors: Helene Plun-Favreau, Mike Hanna and Mary Sweeney

Mitochondrial DNA (mtDNA) mutations are associated with numerous severe disorders, which primarily affect muscle and neural tissues. The clinical severity of patients is highly dependent on the proportion of mutant mtDNA present in affected tissues; therefore maintaining mitochondrial quality control processes is essential. Mitophagy is the process of selective mitochondrial degradation that occurs to maintain efficient synthesis of ATP in the cell and avoids the toxic accumulation of damaged mitochondria, and it has been suggested that mtDNA damage can induce this process. We aim to characterize the effect of particular mtDNA mutations, involving different aspects of oxidative phosphorylation, on the process of mitophagy.

**Andreea Manole**
Year 2 Non-Clinical, UCL – started Sep 2013

‘Genetic and functional characterisation of episodic ataxia 1’
Supervisors: Prof Henry Houlden, Prof Dimitri Kullmann and Prof Mike Hanna

During my PhD I will reprogram fibroblasts from patients with episodic ataxia 1, a disease that arises as a result of mutations in a type of potassium channels, into human induced pluripotent stem cells. I will then characterize these cells by looking at pluripotency markers, karyotype and identity. Finally I will differentiate them into cortical neurons, describe their properties and treat them for the disease.
Charlotte Spicer  
Year 2 Non-Clinical, UCL – started Sep 2013

‘Investigating the effects of pharmacological up-regulation of the heat shock response in a transgenic mouse model of inclusion body myopathy’  
Supervisor: Professor Linda Greensmith

This PhD project involves characterising a transgenic mouse model of a hereditary form of inclusion body myopathy, which recapitulates many of the features of sporadic inclusion body myositis in muscle. We aim to examine the underlying pathomechanisms and changes in the muscle of the mutant mice both in vivo and in primary muscle cultures. From this, we hope to obtain outcome measures which can be used to assess the therapeutic effects of Arimoclomol, a pharmacological co-inducer of the heat shock response.

Michael Thor  
Year 2 Non-Clinical, UCL – started Sep 2013

‘Molecular and cellular pathological mechanisms of skeletal muscle channelopathies and related disorders’  
Supervisors: Drs Roope Mannikko & Stephanie Schorge

Skeletal muscle channelopathies are a group of neuromuscular disorders where mutations disrupt the normal function of ion channels. I am interested in using electrophysiological techniques to study how pathogenic mutations in the NaV1.4 sodium and CaV1.1 calcium channels affect their function, and how they relate to the patient phenotype. By the end of this project, I hope to have significantly advanced our understanding of how mutations in related channels can lead to similar electrophysiological properties and clinical manifestations, as well as how different mutations within a single channel can lead to different diseases. This is a useful step towards predicting genotype-phenotype relationships in patients with channelopathies, to optimize therapeutic intervention and ultimately improve patient outcome.
Emma Wilson
Year 2 Non-Clinical, UCL – started Sep 2013

‘Cellular pathomechanisms and therapeutic strategies in a primary motoneuron model of Hereditary Sensory and Autonomic Neuropathy type 1 (HSAN-1)’
Supervisors: Professor Linda Greensmith, Professor Mary Reilly, Dr Bernadett Kalmar

Having completed my rotation project year I am now beginning my three year PhD project in Linda Greensmith’s laboratory. The project investigates Hereditary Sensory and Autonomic Neuropathy type 1 (HSAN-1), which presents with both sensory and motor involvement, to different extents. The main aims of the project are to investigate the cellular pathomechanisms underlying neurotoxicity in HSAN-1, as well as to develop more robust primary motoneuron models of this disease, in which potential therapeutic treatments can be tested.

Matthew Evans
Year 2 Clinical, UCL – started April 2013

‘Development and application of Neuromuscular MRI’
Supervisors: Professor Mary Reilly, Dr John Thornton, Professor Michael Hanna

As we move closer toward clinical trials of treatments for inherited neuromuscular diseases, the need for a valid, reliable and responsive outcome measure becomes increasingly important. My research is focussed on further refining quantitative MRI as an outcome measure in patients with neuromuscular disease, and the application of improved MRI analysis methods to both the cross sectional and longitudinal assessment of various neuromuscular diseases currently being studied at the MRC Centre including inclusion body myositis and Charcot-Marie-Tooth disease.
**Maiya Kugathasan**  
Year 2 Clinical, UCL – started April 2013

‘Hereditary Sensory Neuropathy Type 1 secondary to SPTLC1/2 mutations: Pathogenesis and treatment’  
Supervisors: Professor Mary Reilly & Professor Linda Greensmith

Hereditary Sensory Neuropathy Type 1 (HSN1) secondary to SPTLC1/2 mutations is a rare, slowly progressive neuropathy leading to profound sensory loss with variable but often severe motor involvement. Recent studies have shown that mutations in these two genes, which encode an enzyme, lead to the build of atypical metabolites called deoxysphingolipids which are postulated to be neurotoxic. This project has three aims. Firstly, to investigate the role of deoxysphingolipids in HSN1 and establish disease models. Secondly to investigate the therapeutic potential of L-serine supplementation using induced pluripotent stem cell derived sensory neurons from patients' fibroblasts. Thirdly, to identify outcome measures for a therapeutic trial in HSN1 patients.

**Karen Suetterlin**  
Year 2 Clinical, UCL – started Sep 2013

‘A molecular pathophysiological study of the skeletal muscle channelopathies’  
Supervisors: Professor Hanna, Dr Roope Mannikko & Dr Emma Matthews

The first part of my PhD has focused on the non-dystrophic myotonias. I have reviewed our myotonic patient cohort to understand adverse effects and efficacy rates of mexiletine in a clinical setting. Using techniques in molecular biology, electrophysiology and bioinformatics I have investigated the molecular pathophysiology of Myotonia Congenita and gained some novel insights into muscle chloride channel structure/function.

For the second part of my PhD, I plan to investigate the effect of age on excitation-contraction coupling and the skeletal muscle 'channelome' in both normal subjects and those with periodic paralysis. I hope to understand whether the myopathy observed in periodic paralysis is precipitated by normal age-related changes that reduce the muscle's ability to cope with single ion channel dysfunction and/or whether periodic paralysis myopathy might represent an accelerated version of the muscle weakness that occurs with normal ageing.
Helen Devine  
Year 2 Clinical, UCL – started Sep 2013

‘The Pathogenesis of Spinal Bulbar Muscular Atrophy’  
Supervisors: Prof Michael Hanna and Prof Linda Greensmith

The aim of my project is to identify the mechanism(s) of motor neuron loss in spinal bulbar muscular atrophy (SBMA) as potential target(s) for treatment of this incurable condition. I am investigating axonal transport and protein homeostasis in a mouse model of SBMA and in induced pluripotent stem cells generated from patients with SBMA. I will also be performing an MRI study to assess neuromuscular changes in SBMA patients over time as a potential outcome measure for a clinical trial.

Emine Bagdatlioglu  
Year 2 Non-Clinical, NCL – started Sept 2013

‘The application of MR imaging in the dystrophin deficient mouse brain: developing outcome measures for diagnostic and therapy development’  
Supervisors: Professor Volker Straub & Professor Andrew Blamire

Duchenne muscular dystrophy (DMD), a fatal X-linked recessive disease, is the most common and best characterised form of muscular dystrophy. Although the dystrophin protein, encoded by the DMD gene, is most abundantly expressed in muscle, it is also expressed in the Central Nervous System (CNS). Intellectual impairment is recognised as a disease symptom in DMD and approximately one third of boys with DMD have some degree of cognitive deficit ranging from reduced verbal intelligence to severe autism. Our lack of knowledge about brain pathology in DMD is reflected in the limited number of studies of the CNS in mouse models of DMD, with hardly anything known about the anatomical or electrophysiological correlates in the mouse brain. The major focus of this project is the development and application of quantitative MRI, including diffusion tensor imaging (DTI) methods to access structural and metabolic brain pathology in mouse models of DMD. The imaging studies will be complemented by histological investigations and immunoanalysis of brain tissue. The overall aim of this research is to use MRI to develop imaging biomarkers that can be used for preclinical studies in DMD mouse models.
Amy Vincent
Year 2 Non-Clinical, NCL - started Sept 2013

‘Investigating mitochondrial dysfunction in myofibrillar myopathies and other protein aggregate myopathies’

Supervisors: Professor Doug Turnbull, Professor Robert Taylor & Dr Rita Barresi
Protein aggregate myopathies are a group of myopathies which include, among other diseases, myofibrillar myopathies (MFM). Also in this group of conditions are actinopathies, myosinopathies, central core disease and inclusion body myositis. MFM are characterized by focal myofibrillar destruction and accumulation of myofibrillar elements as protein aggregates, normally containing desmin. MFM variants differ considerably both in genetics and clinical presentation and studies in MFM patients, to date, show a degree of mitochondrial dysfunction. This project is looking at a group of myofibrillar myopathy patients and some dysferlinopathy patients to see what, if any, respiratory defect they have in their muscle. We will then look for molecular genetic mutations, rearrangements and deletions in the mitochondrial DNA. Subsequently we will investigate mitochondrial dynamics and movement in muscle and how this differs in myofibrillar myopathy patients.

Yasmin Issop
Year 2 Non-Clinical, NCL – Started Sept 2013

‘Understanding the Molecular Mechanisms Underlying Congenital Myasthenic Syndromes’
Supervisors: Professor Hanns Lochmuller and Dr Steven Laval

Congenital Myasthenic Syndromes (CMS) are inherited neuromuscular transmission defects characterised by fluctuating muscle weakness and fatigability. CMS differ in terms of severity, course of the disease, inheritance pattern and treatment options depending on the underlying molecular defect, making them a paradigm for individualized medicine. We have identified mutations in the GFPT1 gene giving rise to a novel form of CMS. GFPT1 encodes a ubiquitous protein in the hexosamine pathway which yields precursor substrates required for protein and lipid glycosylation. The aims of this project are to investigate the
consequence of GFPT1 deficiency on these two types of glycosylation for skeletal muscle and NMJ proteins in tissue culture and mice. We will determine whether GFPT1 deficiency results in a modification of glycosyl residues on these proteins and whether that affects acetylcholine receptor clustering at the NMJ.

**Ewen Sommerville**

Year 2 Non-Clinical, - Started Sept 2013

‘Identifying new genes in mitochondrial disease’

Supervisors: Professor Rob Taylor, Dr Gráinne Gorman & Professor Patrick Chinnery

Whole exome sequencing (WES) is a targeted next-generation sequencing technology for the identification of variants in the exons (coding regions) of all known genes, which constitutes approximately 1% of human genomic DNA. WES has been successfully applied to mitochondrial disease patients, particularly those with translational disorders, with mutations of genes including MTO1, EARS2, and AARS2 identified. My research aims to identify genes, using WES, whereby mutations cause adult-onset progressive external ophthalmoplegia (PEO) and skeletal muscle restricted multiple mitochondrial DNA (mtDNA) deletions in cohort of thirteen clinically well-defined patients, with phenotypes ranging from indolent PEO to multi-system PEO plus disorders. Candidate variants will be confirmed by functional analysis of patient cells lines and where possible, cell complementation experiments.

**Yi Shiau NG**

Year 2 Clinical, Newcastle – Started Aug 2013

‘Phenotypes and genotypes in adult mitochondrial disease’

Supervisors: Dr Robert McFarland, Professor Doug Turnbull & Professor Robert Taylor

The establishment of the MRC Mitochondrial Disease Patient Cohort database provides an excellent opportunity to analyse the phenotypic heterogeneity across different age groups
and genotypes in mitochondrial disease. Essentially, my project is to deep phenotype adult patients recruited in Newcastle (n=591 to date) by utilising a wealth of clinical and laboratory data collected in the database. Another key component is to examine individual disease burden and progression over time based on the Newcastle Mitochondrial Disease Assessment Scale (NMDAS). The outcomes that I would like to achieve are to identify prognostic factors that could facilitate more accurate patient counselling and to develop genotypic specific (m.3243A>G and POLG) clinical guidelines that hopefully can lead to a better care.
7. PI publications since renewal centre February 2013
Publications with authors from both UCL and NCL are marked with a diesis (‡).

Andrew Blamire


Blain A, Greally E, Laval S, Blamire AM, Straub V, MacGowan GA. (2013). Beta-blockers, left and right ventricular function, and in-vivo calcium influx in muscular dystrophy cardiomyopathy.


Kate Bushby


Patrick Chinnery


Chinnery PF. One complex world of mitochondrial parkinsonism Brain 2013 Aug;136(Pt 8):2336-41. PMID:23884808


**Michael Duchen**


Kotiadis VN, Duchen MR, Osellame LD. Mitochondrial quality control and communications with the nucleus are important in maintaining mitochondrial function and cell health. Biochim Biophys Acta. 2014 Apr;1840(4):1254-65. Epub 2013 Nov 6. Review. PMID: 24211250


Grainne Gorman


Charlotte L. Alston, Andrew M. Schaefer, Pravrutha Raman, Nicola Solaroli, Kim J. Krishnan, Emma L. Blakely, Langping He, Kate Craig, Mark Roberts, Aashish Vyas, John Nixon, Rita Horvath, Douglass M. Turnbull, Anna Karlsson, Grainne S. Gorman, Robert W. Taylor. Late-onset respiratory
failure due to TK2 mutations causing multiple mtDNA deletions Neurology. 2013;81:2051-3 PMID: 24198295


Linda Greensmith


JC Mitchell, P McGoldrick, CA Vance, T Hortobagyi, J Sreedharan, B Rogelj, EL Tudor, BN Smith, C Klasen, CC Miller, JD Cooper, L Greensmith & CE Shaw (2013)


# Joint Senior Authors


Michael Hanna


Robert D.S. Pitceathly, Shamima Rahman, Yehani Wedatilake, James M. Polke, Sebahattin Cirak, A. Reghan Foley, Anna Sailer, Matthew E. Hurles, Jim Stalker, Iain Hargreaves, Cathy E. Woodward, Mary G. Sweeney, Francesco Muntoni, Henry Houlden, UK10K Consortium, Jan-Willem Taanman, Michael G. Hanna. NDUFA4 Mutations Underlie Dysfunction of a Cytochrome c Oxidase Subunit Linked to Human Neurological Disease, Cell Reports, 06 June 2013

Ke Q et al. Rare disease centers for periodic paralysis: China vs the US and UK. Muscle Nerve. 2013 July 28. PMID: 23893386


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Kieren Hollingsworth


Rita Horvath


**Kristjan Jessen**


**Martin Koltzenburg**


In press:


**Dimitri Kullmann**


Kullmann DM. Brain. Editorial. 2014 May;137(Pt 5):1273. PMID: 24771396


Ruiz AJ, Kullmann DM. Ionotropic receptors at hippocampal mossy fibers: roles in axonal excitability, synaptic transmission, and plasticity. Front Neural Circuits. 2013 Jan 9;6:112. eCollection 2012. PMID: 23316138


Hanns Lochmüller


Mike Lunn


Robert MacFarland


Yarham JW, Blakely EL, Alston CL, Roberts ME, Ealing J, Pal P, Turnbull DM,

**James Miller**


**Jenny Morgan**


Francesco Muntoni


Gita Ramdharry


Mary Reilly


Stevens JC, Murphy SM, Davagnanam I, Phadke R, Anderson G, Nethisinghe S, Bremner F, Giunti P, Reilly MM. The ARSACS phenotype can include supranuclear gaze palsy and lipofuscin skin deposits. JNNP 2013; 84; 114-116. PMID: 23123642

Stephanie Schorge


Volker Straub


Rob Taylor


PMID:23849775


PMID:23849775

Mitochondrial DNA deletions in muscle satellite cells: implications for therapies.
PMID:23847047

SURF1 deficiency: a multi-centre natural history study.
PMID:23829769

Schaefer AM, Walker M, Turnbull DM, Taylor RW.
Endocrine disorders in mitochondrial disease.
PMID:23769710

Defining cardiac adaptations and safety of endurance training in patients with m.3243A>G-related mitochondrial disease.
PMID:23742928

Clinical, biochemical, cellular and molecular characterization of mitochondrial DNA depletion syndrome due to novel mutations in the MPV17 gene.
Pathogenic mitochondrial tRNA point mutations: nine novel mutations affirm their importance as a cause of mitochondrial disease.
PMID:23696415

Recessive desmin-null muscular dystrophy with central nuclei and mitochondrial abnormalities.
PMID:23575897

Jalil A, Usmani HA, Khan MI, Blakely EL, Taylor RW, Vassallo G, Ashworth J.
Bilateral paediatric optic neuropathy precipitated by vitamin B12 deficiency and a novel mitochondrial DNA mutation.
PMID:23572439

Zamzami MA, Duley JA, Price GR, Venter DJ, Yarham JW, Taylor RW, Catley LP, Florin TH, Marinaki AM, Bowling F.
Inosine triphosphate pyrophosphohydrolase (ITPA) polymorphic sequence variants in adult hematological malignancy patients and possible association with mitochondrial DNA defects.
PMID:23547827

Whittaker RG, Hall E, Mansoor MK, Taylor RW, Turnbull DM.
Incidence of carpal tunnel syndrome in adult patients with mitochondrial disease.
PMID:23521646

Initial development and validation of a mitochondrial disease quality of life scale.
PMID:23433484

‡Nesbitt V, Pitceathly RD, Turnbull DM, Taylor RW, Sweeney MG, Mudanohwo EE, Rahman S, Hanna MG, McFarland R.
The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m.3243A>G mutation--implications for diagnosis and management.
PMID:23355809

Lax NZ, Gnanapavan S, Dowson SJ, Alston CL, He L, Polvikoski TM, Jaros E, O'Donovan DG, Yarham JW, Turnbull DM, Dean AF, Taylor RW.
Early-onset cataracts, spastic paraparesis, and ataxia caused by a novel mitochondrial tRNAGlu (MT-TE) gene mutation causing severe complex I deficiency: a clinical, molecular, and neuropathologic study.


John Thornton


Doug Turnbull

Chinnery PF, Craven L, Mitalipov S, Stewart JB, Herbert M, Turnbull DM
The challenges of mitochondrial replacement
PLoS Genetics 10(4) e1004315
Apr-14
24762741

Reeve A, Simcox E, Turnbull D
Ageing and Parkinson's disease: why is advancing age the biggest risk factor?
Ageing Research Reviews 14, 19-3
Mar-14
24503004

Baines HL, Turnbull DM, Greaves LC
Human stem cell ageing: do mitochondrial DNA mutations have a causal role?
Aging Cell 13(2) 201-5
Apr-14
24382254

Discrete gait characteristics are associated with m.3243A>G and m.8344A>G variants of mitochondrial disease and its pathological consequences.
Journal of Neurology 261(1) 73-82
Jan-14
24150688

Campbell G, Krishnan KJ, Deschauer M, Taylor RW, Turnbull DM
Dissecting the mechanisms underlying the accumulation of mitochondrial DNA deletions in human skeletal muscle
Human Molecular Genetics
in press 2014

Prenatal testing in mitochondrial disease
European Journal of Human Genetics
doi: 10.1038/ejhg.2014.35

Distal weakness with respiratory insufficiency caused by the m.8344A>G "MERFF" mutation
Neuromuscular Disorders 24, 533-536
2014

Rygiel KA, Miller J, Grady JP, Rocha MC, Taylor RW, Turnbull DM
Mitochondrial and inflammatory changes in sporadic Inclusion Body Myositis
Neuropathology and Applied Neurobiology
doi: 10.1111/nan.12149
Clonal expansion of secondary mtDNA deletions associated with spinocerebellar ataxia type 28
JAMA Neurology
in press 2014

Disease progression in patients with single, large-scale mitochondrial DNA deletions
Brain 137 (2) 323-334
Feb-14
24277717

Therapeutic potential of somatic cell nuclear transfer for degenerative disease caused by mitochondrial DNA mutations.
Science Reporter 4, 3844
2014
24457623

Late-onset respiratory failure due to TK2 mutations causing multiple mtDNA deletions
Neurology 81(23) 2051-3
Dec-13
24198295

Mitochondrial DNA deletions in muscle satellite cells: implications for therapies.
Human Molecular Genetics 22(23) 4739-47
Dec-13
23847047

Extraocular muscle atrophy and central nervous system involvement in chronic progressive external ophthalmoplegia.
PLoS One 8(9): e75048
2013
24086434

No excess of mitochondrial DNA deletions within muscle in progressive multiple sclerosis
Campbell. GR, Reeve AK, Ziabreva I, Reynolds R, Turnbull DM, Mahad DJ
Multiple Sclerosis 19(14) 1858-66
Dec-13
23787892


Pathogenic mitochondrial tRNA point mutations: nine novel mutations affirm their importance as a cause of mitochondrial disease.

Human mutation

May-13

Initial development and validation of a mitochondrial disease quality of life scale.
Neuromuscular disorders : NMD
Apr-13
23433484

Roger G Whittaker, Elizabeth Hall, Muhammad K Mansoor, Robert W Taylor, Douglass M Turnbull
Incidence of carpal tunnel syndrome in adult patients with mitochondrial disease.
Journal of the peripheral nervous system : JPNS
Mar-13

Martin Picard, Doug M Turnbull
Linking the metabolic state and mitochondrial DNA in chronic disease, health, and aging.
Diabetes
Mar-13
PMC3581215

Picard M, Turnbull D M
Linking the metabolic state and mitochondrial DNA in chronic disease, health, and aging.
Diabetes
Mar-13
23431006

Nichola Z Lax, Sharmilee Gnanapavan, Sarah J Dowson, Charlotte L Alston, Langping He, Tuomo M Polvikoski, Evelyn Jaros, Dominic G O'Donovan, John W Yarham, Douglass M Turnbull, Andrew F Dean, Robert W Taylor
Early-onset cataracts, spastic paraparesis, and ataxia caused by a novel mitochondrial tRNAGlu (MT-TE) gene mutation causing severe complex I deficiency: a clinical, molecular, and neuropathologic study.
Journal of neuropathology and experimental neurology
Feb-13

The m.3291T>C mt-tRNA(Leu(UUR)) mutation is definitely pathogenic and causes multisystem mitochondrial disease.
Journal of the neurological sciences
Feb-13
PMC3560033
Tarek Yousry


8. Successful new grant applications since renewal of centre February 2013

Andrew Blamire
EU FP7
BIOIMAGE-NMD – Novel Imaging technologies for muscle disease
€5.96 million
October 2013 – March 2017

Kate Bushby
Commission of the European Communities
RARE – Best practices
£28,571
October 2013 – December 2016

European Commission
TREAT-NMD Operating Grant
Split award value £35,657
January – December 2013

NIHR
Senior Investigator Award
£75,000
April 2013 – January 2018

Great Ormond Street Hospital Children’s Charity
Improving standards of care and translational research in spinal muscular atrophy
£29,507
April 2013 – March 2015
Muscular Dystrophy Campaign
MDC Clinical Trials Coordinator
£75,335
June 2013 – June 2015
Muscular Dystrophy Campaign
High throughput sequence analysis to identify genetic causes of limb girdle muscular dystrophies
£60,000
October 2013 – September 2016
Duchenne Parent Project
DMD liaison post at TREAT-NMD office
£18,518
October 2013 – March 2014
Parent Project Muscular Dystrophy
DMD Liaison post at TREAT-NMD office
£22,500
April – September 2014
Children’s National Medical Center
Project 3 – accelerating the agenda for academic networking in post marketing surveillance for RD
Drug development
£88,888
January – December 2014

**Patrick Chinnery**

Medical Research Council
Clinical research capabilities call.
The Newcastle University Single Cell Functional Genomics Unit (NUSCU).
£1.98M. PI
2014-2017

Wellcome Trust
Clinical Research Training Fellowship to Dr Michael Keogh (103396/Z/13/Z).
The role of inherited and acquired mitochondrial DNA mutations in dementia with Lewy bodies
£221K
2014 - 2017

Wellcome Trust
Senior Clinical Fellowship 2nd Renewal (101876/Z/13/Z)
Genetic factors modulating the expression of mitochondrial disease.
£1.3M. PI
2013 – 2018

Medical Research Council
Maximising the value of MRC Brain Banks: high-throughput genomic studies to enrich data available to the research community.
£1.7M. Newcastle PI
2013 – 2015

Medical Research Council
High throughput genomics and transcriptions of the human development biology resource.
£891K. PI
2013 – 2015

Wellcome Trust
Clinical Research Training Fellowship to Dr Peter Kullar.
Defining the cellular and molecular mechanisms of mitochondrial deafness
£225K
2013 – 2016

**Chris Clark**

The Commission of the European Communities
FP7-HEALTH-2013-INNOVATION-1
BIOIMAGE-NMD
£498,992
December 2013 – December 2016

UCL Capital Equipment
State of the art magnetic resonance imaging
October 2013
£250,000

**Michael Duchen**

SLMS Capital Equipment Fund To develop a high throughput high content imaging platform at UCL
£300,000
2013

GSK/BBSRC CASE
PhD studentship Mitochondria as therapeutic targets in human disease
£101,520
2013-2017

Action Medical Research
Mitochondrial quality control pathways as therapeutic targets in genetic mitochondrial disease
£200,243
2013-2016

Eisai Therapeutic Innovations Group (TIG)
Funding for screening mPTP inhibitors 2 positions for 3 years plus consumables
2014-2017
Total investment not explicit

GSK
Post-Doc: To develop small molecule inhibitors of the permeability transition pore
£143,000
2014-2015 (to be funded on an annual basis but with promise of renewals)

EPSRC
Post-Doctoral Fellowship for Tom Blacker
2013-2014

Grand Challenge PhD Studentship (collaboration with Ken Smith)
£69,000
2013-2016

**Elizabeth Fisher**

Motor Neurone Disease Association
PhD studentship - Characterising a novel delta14 Fus mouse model
£112,690 With Dr Abraham Acevedo
Oct 2014 to Sept 2017

Medical Research Council
New humanised mouse models for dissecting the pathobiology of disease, using FUS-ALS as a paradigm
£994,155
Sept 2014 to August 2017

Medical Research Council
Investigating a neuronal subcellular transcriptome by the novel technique of RNA TU-tagging, in a normal and ALS-related mouse model
£466,205
April 2014 to Sept 2016

Grainne Gorman

Observational Prolonged Trial in Myotonic dystrophy type 1 to Improve QoL-Standards, a Target Identification Collaboration. Collaborative FP7 Project (Newcastle PI: Gorman): 3-year project
£233,400
2013-2016

Linda Greensmith

The Graham Watts Bequest Program
Grant for Research into Motor Neuron Disease
2013-2018
£654,000

The Sobell Foundation/Brain Research Trust
£175,000
2013-2018

Motor Neuron Disease Association
A targeted proteomic analysis for biomarkers discovery in ALS
A Malaspina, I Pike and L Greensmith
£135,408
2013-2016

UCL Hospitals Biomedical Research Centre Neuroscience Programme
The role of sphingolipids in the pathomechanism of hereditary sensory neuropathy type 1 HSN1
M Reilly (PI), M Laurá, B Kalmar and L Greensmith
£96,360
2013-2015

Medical Research Council
New humanised mouse models for dissecting the pathobiology of disease, using FUS-ALS as a paradigm
E Fisher (PI), L Greensmith and G Schiavo
£994,155
2014-2017

Motor Neuron Disease Association
Optogenetically-controlled restoration of muscle function in MND model mice using engrafted ES-derived motor neurons
L Greensmith, B Bryson and I Lieberam
£229,160
2014-2017

Foundation Thierry Latran
Optogenetically-Controlled Restoration of Muscle Function in ALS
€160,000
2014-2016

Michael Hanna

Medical Research Council
MRC Centre for Neuromuscular Diseases Centre Renewal
£2.8 million
2013-2018

UCLH/NIHR BRC
Matched funding for MRC Centre for
£493,106
2013-2019

GOS BRC
With F. Muntoni Matched funding for MRC Centre for Neuromuscular Diseases
£282,714
2013-2018

Lilly Foundation
Clinical Research fellow 2014-2016
£124,000

Neuromics FP7
Channelopathies – for Karen Stevens
£193,000
2013-2017

UCLH BRC
A randomized, double-blind, placebo controlled
Fast Track phase Ila experimental pilot trial assessing efficacy of a single
dose or repurposed bumetanide in genetically defined hypokalaemic periodic paralysis assessed
using the electrophysiological McManus protocol
Co grant holder w/ Doreen Fialho
£40,000
2013-2014

Action Medical Research
Mitochondrial quality control pathways as therapeutic targets in genetic mitochondrial disease
Co-grant holder w/ Michael Duchen
£192,243
2013-2016

NIHR
Rare Diseases Translational Research Collaboration - IBM
£250,000
2013-2014

NIHR
Rare Diseases Translational Research
Co-grant holder w/ Francesco Muntoni 01/11/13-31/12/14  £200,000
Mike Hanna Collaboration – DMD

NIHR
Rare Disease TRC Postdoctoral Fellowship IBM – Pedro Machado
£401,333
2014-2017

NIHR
Rare Disease TRC Postdoctoral Fellowship Channels – Emma Matthews
£363,060
2014-2017

MRC
Periodic paralysis: from molecules to mice
Co-grant holder with R Männikkö
2014-2017
£464,146

Wellcome Trust
Synaptopathies: genetics, biophysics and circuit mechanisms of paroxysmal neurological disorders
Co-I
£4,194,451
2014-2019

Kieren Hollingsworth

No new grant awards since Feb 2013

Rita Horvath

European Research Council (ERC)
Reversibility and tissue specificity of mitochondrial translation defects in early childhood
Starter Grant - Consolidator (309548)
Role; PI
£1,139,280,00
2013-2018

FP7-PEOPLE-ITN (Marie-Curie Action)
Mitochondrial European Educational Training MEET (317433)
Role Co-Investigator with Patrick Chinnery in Newcastle, supervisor of a PhD student
total £3,042,664.00, Newcastle: €577,798.57
2013-2016

**Dimitri Kullmann**

Medical Research Council
Gene therapy for refractory epilepsy
£3.1m
2014-2019

Wellcome Trust
Synaptopathies: genetics, biophysics and circuit mechanisms of paroxysmal neurological disorders
£4,194,451
2014-2019

Medical Research Council
Periodic paralysis: from molecules to mice
£467,547
2014-2017

**Hanns Lochmüller**

European Commission
TREAT-NMD Operating Grant
Split award value £35,657
2013 – 2018

Medical Research Council (MRC)
MRC - Centre for Neuromuscular Diseases
Split award value £95,796
2013 – 2018

Association Francaise Contre les Myopathies
Coordination of the global patient registries for neuromuscular disorders
£35,714
2013 – 2015

Duchenne Parent Project
Coordination of the global patient registries for neuromuscular disorders
£15,892
2013 – 2015

European Commission
3GB-test proposal
£9,019
2013 - 2014

Eli Lilly and Co (USA)
Lilly & Co (USA)
£70,000
2013 – 2014

Jennifer Trust for Spinal Muscular Atrophy
Jennifer Trust UK SMA Co-ordinator
£10,000
2013 - 2014

PTC Therapeutics, Inc.
Patient Registry (Lochmuller)
£10,826
2013 – 2013

Mike Lunn
Cochrane Neuromuscular Disease Group
Quinquennial Renewal
£700,000
2014 – 2019

Robert McFarland
Wellcome Trust
Public Engagement Programme
£287K Co-PI
2014 – 2017

Ryan Stanford Appeal
PhD Studentship ‘Fight Alpers’
£50K Co-PI
2014-2017

Lily Foundation Award,
Improving the molecular genetic diagnosis of mitochondrial disease
£44K Co-PI
2014-2016

NIHR RCF Award
Development and evaluation of a national diagnostic strategy for paediatric mitochondrial disease
£49K. Co-PI
2013-2014

Jenny Morgan
Muscular Dystrophy Campaign.
The effect of modulating the dystrophic skeletal muscle environment on donor stem cell engraftment. P.I (Co-applicant Dr Silvia Torelli
£111,225.
2014-2018

UCL Therapeutic Innovation Fund.
Pharmacological inhibition of programmed necrosis in dystrophic skeletal muscle.
£47,077
2014-2015

Muscular Dystrophy Campaign.
Mechanisms of myonecrosis in Duchenne Muscular Dystrophy: can we control the death of muscle fibres?
£174,944
2014-2017

**Francesco Muntoni**

SMA Trust
Improving standards of care and translational research in SMA
£ 264,000 Muntoni PI.
2013-2014

NIHR
NIHR Rare Disease Initiative: Neuromuscular Diseases: Deep Duchenne muscular dystrophy phenotyping Muntoni PI.
£355,000
2013-2016

Cure CMD
Serum miRNA in dystroglycanopathies.
$ 25,000 Muntoni PI.
2014-2105

MRC
Peptide Conjugated oligonucleotides for splice switching therapy of SMA
£1,008,000 Muntoni Co-PI
2014-2017

Summit Plc
A phase Ib study of C11002 in Duchenne Muscular Dystrophy. Muntoni CI
2013-2014.

AFM
A multicentre natural history study on DMD
€ 852,000 Muntoni Coordinator and CI.
2014-2017

Genethon
Pre-U7 natural history study
£50,836
2014-2016.

MDC
Allele-selective suppression by antisense oligonucleotide as a therapeutic strategy for collagen VI-related congenital muscular dystrophy. Muntoni PI
£59,134
2014-2015

**Gita Ramdharry**

Clinical Research Network
Funding for a 6 month research physiotherapist
£17,561
2014

NIHR
Research for Patient Benefit grant based at UCLH NHS trust.
Principle Investigator.
Aerobic training in neuromuscular diseases. (grant number PB-PG 0711-25151-G613)
£194K
2013

Co-applicant for NIHR HTA grant [13/30/02]
Orthotic management of instability of the knee in neuromuscular disease.
PI Dr Catriona Mcdaid, University of York
£158,860
2013

Clinical Research Network funding for a 6 month research physiotherapist
£19,006
2013

**Mary Reilly**

MRC
training fellowship for Dr Umaiyal Kugathasan
HSN1 secondary to SPTCL1/SPTLC2 mutations: Pathogenesis and treatment
£144,849
2014-2017

CMT UK
grant for MRI scanning
£30,000
2013-2016

BRC
Hereditary Sensory Neuropathy type 1 (HSN1): exploring the role of 1-deoxysphingolipids (1-dSLs) in the pathogenesis of the disease and defining outcome measures for a clinical trial. PI
£99,360
2013-2015

MRC
Centre grant renewal for London Newcastle Centre for Neuromuscular disease (Co-Director)
£2.8 million
2013-2018

**Stephanie Schorge**
MRC Programme grant
Gene therapy for refractory epilepsy
£3.1M. PI: D Kullmann, Co-Is: S Schorge, M Walker
2013

Wellcome Trust Strategic Award
Synaptopathies: genetics, biophysics and circuit mechanisms of paroxysmal neurological disorders
~£4.2M. PI: D Kullmann
2014; 5 Years,

MRC research grant
Functional significance of neuronal sodium channel splicing in epilepsy and pain
£500,156
2013

European FP7 grant
EpiMiRNA Partner (Work package leader and UCL PI).
Total funding to to UCL £~400,000
2013

Volker Straub

Action Medical Research
NHE1 inhibitors to treat Duchenne muscular dystrophy
Split award value £103,438
2014-2016

British Heart Foundation
Cardiomyocyte regeneration in non-ischaemic cardiomyopathy
Split award value £8,066
2014-1026

Action Duchenne
Exosomes: a novel therapeutic approach for the treatment of dystrophinopathies
£71,441
2014-2015

COST Office
Applications of MR imaging and spectroscopy techniques in neuromuscular disease: collaboration
on outcome measures and pattern recognition for diagnostics and therapy development
£72,666
2014

European Commission BIOIMAGE-NMD
Novel Imaging technologies for muscle disease
Split award value: £534,088
2013-2017

European Commission
SCOPE-DMD
£730,067
2013-2016

Medical Research Council
MRC - Centre for Neuromuscular Diseases
Split award value: £95,796
2013-2018

UCL
MRC Centenary Award
£11,226
2013

European Commission TREAT-NMD Operating Grant
Split award value £42,789
2013

Rob Taylor

The Lily Foundation
Diagnosis of mitochondrial disease using whole exome sequencing.
£90,000 co-PI with D.M. Turnbull and R. McFarland
2014-2016

John Thornton

MRC
Next generation MRI brain imaging platform for dementia research: from microstructure to function
Grant to substantially upgrade research MRI platform (Co-I, PI T. Yousry)
£1.4M
2014

UCLH NIHR BRC Neuroscience Programme
Big Questions Funding Call; Novel biomarkers in amyotrophic lateral sclerosis (Co-I, PI L. Greensmith)
£251,259
2014-2017

Doug Turnbull

Wellcome Trust
Wellcome Trust Centre for Mitochondrial Research Public Engagement Enhancement
£286,551
2014-2017

Newcastle University Hospitals NHS Trust
RCF - Salary funding for Grainne Gorman
£200,010
2014-2016
e-Therapeutics
Collaboration - testing compounds
£112,665
2013-2014

MRC
Centre for Ageing and Activity
£2,907,201
2014-2019

MRC
Centre for Brain Ageing & Activity Bridging funding
£342,971
2014-2014

Newcastle Healthcare Charity
The importance of mitochondrial dysfunction in the pathogenesis of osteoporosis
£157,489
2013-2016

NIHR
BRC - Treating mitochondrial dysfunction - mechanisms underlying response to specific compounds
£25,002
2013-2017

Novartis Institutes for BioMedical Research Inc
Monogenetic mitochondrial disorders
$100,000
2013-2017

Wellcome Trust
Eve’s Curse: the Art of mitochondrial disease
£7,000
2013-2014

NIHR
BRC - NHS Service Support for Mitochondrial theme
£98,428
2013-2017

Tarek Yousry

MRC
A next-generation MRI brain imaging platform for dementia research: from microstructure to function
£1,217,068
2014 – 2016

MS Society of GB
Imaging research to facilitate treatments for multiple sclerosis
£1,350,000 April 2013 – March 2018

MRC
MRC Centre for Neuromuscular disease PI for imaging
£3.2M
2013-2017

Wellcome Trust & MRC
A systematic investigation into the pathogenesis and course of PD’s syndrome
£5.9M
2010-2015

The Stroke Association & BHF
Microbleeds and genetic risk factors to predict the risk of intracranial haemorrhage in patients treated with anticoagulation
£939k
2010-2015
9. Management structure of MRC Centre

Management of the Centre
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 (>£3.7m 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: North American Muscle Study Group co-chair, chairman British Myology Society, NIH NeuroNEXT links; Reilly: NIH genetic neuropathy consortium, president elect international Peripheral Nerve Society (PNS)) ensuring an international dimension to strategy & regarding opportunity and influence.

Public/patient/science community involvement: the steering committee successfully delivers 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 seven annual meetings attracted >1800 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 during the first 5 years of the centre (see SAB report 2011, appendix x). In the renewed Centre, the Director (Hanna) works closely with five senior Co-Directors (UCL Co-Directors: Muntoni, Reilly, Koltzenburg, NCL Co-Directors: Bushby, Turnbull). See simple management diagram below:
MRC Centre Partners

The Newcastle upon Tyne Hospitals NHS Foundation Trust

University College London Hospitals NHS Foundation Trust

Great Ormond Street Hospital for Children NHS Trust

TREAT-NMD Neuromuscular Network

Muscular Dystrophy Campaign

UCL PARTNERS

Institute of Child Health
University College London

ICH Mail
Centre for Neuromuscular Diseases, London

Centre for Neuromuscular Diseases
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Institute of Genetic Medicine
International Centre for Life
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