MRC Centre PhD Students, Research Fellows and Projects

Since Centre Inception (2008)

Clinical current students (by start date)

Menelaos Pipis

Start date: August 2017
PhD Project Title: The causes and pathogenesis of inherited peripheral neuropathies
Supervisors: Professor Mary M Reilly, Dr Alexander M Rossor
Funding Source: National Institute of Health Fellowship (Inherited Neuropathy Consortium)
Length of studentship: 3 years

Project Description:
Charcot-Marie-Tooth (CMT) and related conditions are the commonest inherited neuromuscular diseases with a population prevalence of 1 in 2500. As a scientific community we have entered an exciting therapeutic era, where advances in cell biology and animal models of CMT are paving the way for rational treatments and this has accelerated the need to improve our diagnostic rate and accuracy. Despite the discovery of more than 90 causative CMT genes through the advent and use of next-generation sequencing (NGS) technologies, there are still patients with specific subtypes of CMT, such as CMT2 and distal Hereditary Neuropathy (dHMN) that remain without a genetic diagnosis. Through the use of whole exome and whole genome sequencing, I endeavour to identify new pathogenic genetic variants of CMT and through functional assays and where possible transcriptomic analysis, study the effect of non-coding variants in the pathogenesis of CMT.

Laura Nastasi

Photo not supplied

Start date: March 2017
PhD Project Title: A natural history study of adults with Duchenne Muscular Dystrophy living in the UK
Supervisors: Dr Ros Quinlivan, Professor Michael Hanna
Funding Source: Muscular Dystrophy UK Clinical Training
Length of studentship: 4 years (plus 6-month extension for maternity leave)

Project Description:
Duchenne muscular dystrophy (DMD) is an inherited progressive disorder affecting about 2,500 boys living in the UK. Co-ordinated multidisciplinary care and corticosteroid treatment has increased the life expectancy of DMD boys, resulting in a new population of affected adults who would have previously died in their late teens or early 20s. Adult neurologists have still limited experience and expertise in the management of adult patients with DMD, and standards of care for adults need to be implemented. In addition, significant molecular advances have now created opportunities to test new therapies in patients with DMD, but no systems are in place to facilitate this process among non-ambulant patients.
The purpose of this study is to develop a clinician-reported outcome tool able to capture significant functional changes in adult Duchenne in order to assess the natural history of a large cohort of adults with DMD living in the UK in the corticosteroid era, with the main focus to improve standard of care across the nation and to inform clinical trial design.

Publications:
1. Effect of botulinum toxin treatment on quality of life in patients with isolated lingual dystonia and oromandibular dystonia affecting the tongue. Nastasi L, Mostile G, Nicoletti A, Zappia M, Reggio E, Catania S.J Neurol. 2016 Jun 8
2. Subacute combined degeneration of the spinal cord presenting with pseudoathetosis of the upper limbs. Reggio E, Lanzafame S, Giliberto C, Nastasi L, Nicoletti A, Zappia M. Eur J Neurol. 2013 Jan;20(1): e26-7. doi: 10.1111/ene.12008. PubMed PMID: 23279443.
3. Man-in-the-barrel syndrome due to Klippel-Feil deformity. Giliberto C, Giuffrida S, Nastasi L, Cicirata F, Platania N, Albanese V, Zappia M. Eur J Neurol. 2013 Jan;20(1): e24-5. doi: 10.1111/ene.12002. PubMed PMID: 23279442.
4. Advanced ossification of the posterior longitudinal ligament in a mildly symptomatic patient. A case report and literature review. Conte G, Viglianesi A, D'Amore A, Chiaramonte R, Pecoraro C, Nastasi L, Giuffrida S, Pero G, Chiaramonte I. Neuroradiology J. 2011 Aug 31;24(4):643-7. Epub 2011 Sep 2. PubMed PMID: **24059724.**

Enrico Bugiardini

Start Date: June 2016
PhD Project Title: Clinical, functional and genetic characterization of mitochondrial diseases
Supervisors: Professor Mike Hanna, Professor Henry Houlden
Funding source: NCG
Length of studentship: 3 years

Project Description:
Mitochondrial diseases are a group of conditions caused by a dysfunction of the mitochondrial respiratory chain, which is under the dual control of nuclear, and mitochondrial DNA (mtDNA). Mutation of either the nuclear or the mitochondrial genome may cause mitochondrial disease. In recent years several nuclear genes have been associated with mitochondrial function and diseases but there are still several patients without a genetic diagnosis. My main project is focused on studying those patients who still do not have a diagnosis and applying next generation sequencing techniques (genes panel or exome sequencing). The first step will be the identification of new genes causing mitochondrial disease or new clinical manifestations of known genes. This will have a direct clinical benefit for the patient in terms of management and genetic counselling. The second step will be studying the mechanism underlying the mitochondrial damage caused by those nuclear genes. A better understanding of mitochondrial function/dysfunction holds the clue for future therapy focused on restoring mitochondrial efficiency. As mitochondrial disease often presents with muscle symptoms I will extend the analysis to patients affected by muscle diseases.
Finally as well as the genetic studies I am involved in a clinical study through the MRC Centre Mitochondrial Disease Patient Cohort. This represents a national registry containing all the clinical, genetic and demographic information of patients affected by mitochondrial disease in UK. I am directly involved in the collection and

analysis of data of patients belonging to the London site. One specific study that is ongoing is evaluating the cause of death in patients with mitochondrial diseases. A better understanding of this may have direct implication on clinical management of people affected by mitochondrial diseases.

Significant Publications:

Long-term Safety and Efficacy of Mexiletine for Patients with Skeletal Muscle Channelopathies. JAMA Neurol. 2015 Dec 1;72(12):1531-3. PMID: 26658970 Suetterlin KJ, **Bugiardini E**, Kaski JP, Morrow JM, Matthews E, Hanna MG, Fialho Clinical and genetic characterization of leukoencephalopathies in adults. Brain. 2017 May 1;140(5):1204-1211. PMID: 28334938. Lynch DS, Rodrigues Brandão de Paiva A, Zhang WJ, Bugiardini E, Freua F, Tavares Lucato L, Macedo-Souza LI, Lakshmanan R, Kinsella JA, Merwick A, Rossor AM, Bajaj N, Herron B, McMonagle P, Morrison PJ, Hughes D, Pittman A, Laurà M, Reilly MM, Warren JD, Mummery CJ, Schott JM, Adams M, Fox NC, Murphy E, Davagnanam I, Kok F, Chataway J, Houlden H.
Clinicopathologic and molecular spectrum of RNASEH1-related mitochondrial disease. Neurol Genet. 2017 May 2;3(3):e149. PMID: 28508084. Bugiardini E, Poole OV, Manole A, Pittman AM, Horga A, Hargreaves I, Woodward CE, Sweeney MG, Holton JL, Taanman JW, Plant GT, Poulton J, Zeviani M, Ghezzi D, Taylor J, Smith C, Fratter C, Kanikannan MA, Paramasivam A, Thangaraj K, Spinazzola A, Holt IJ, Houlden H, Hanna MG, Pitceathly RDS.
Homozygous mutation in HSPB1 causing distal vacuolar myopathy and motor neuropathy. Neurol Genet. 2017 Jul 6;3(4):e168. PMID: 28702508 Bugiardini E, Rossor AM, Lynch DS, Swash M, Pittman AM, Blake JC, Hanna MG, Houlden H, Holton JL, Reilly MM, Matthews E.

Kate Maresh

Start Date: April 2016
PhD Project Title: Deep phenotyping of the central nervous system in dystrophinopathies
Supervisor: Professor Francesco Muntoni
Funding source: MRC Centre Grant
Length of studentship: 3 years. Maternity leave Jan ’17 – Oct’17
Project Description:
Duchenne muscular dystrophy (DMD) and its milder allelic variant, Becker muscular dystrophy (BMD), are X-linked neuromuscular conditions caused by mutations in the *DMD* gene. In DMD, a lack of dystrophin leads to progressive muscle inflammation and damage, and many patients also exhibit symptoms related to central nervous system (CNS) dysfunction, including non-progressive learning difficulties, attention deficit disorder, anxiety and autism.
The function of dystrophin in the brain is not known. The dystrophin gene contains 7 promoter regions, each coding for different tissue-specific dystrophin isoforms. Full length dystrophin (Dp427) is expressed in muscle, brain and cerebellar Purkinje cells, and a number of shorter isoforms are also specifically expressed in the central nervous system (CNS). Mutations which lead to loss of the shortest isoforms correlate with increased cognitive impairment in

DMD, but the genotype-phenotype association is less clear in BMD and in other aspects of CNS function.
A mouse model of DMD (*mdx* mouse), which lacks the full-length Dp427 isoform of dystrophin, exhibits enhanced defensive behaviour and freezing response. Dp427 localises to the postsynaptic region of GABA-ergic neurons in the mouse, and in the *mdx* mouse there is impaired GABA-ergic signaling in the amygdala, which is involved in the fear response. These behaviours in the mouse have been improved in mdx mice treated with exon-skipping antisense oligonucleotide treatments, suggesting that at least some of the CNS effects of lack of dystrophin may be reversible.
I will conduct deep-phenotyping of the CNS phenotype in DMD and the milder allelic Becker muscular dystrophy (BMD) variant patients with the following aims:

- to develop a standardised testing protocol of neuropsychology tests to be used in DMD & BMD
- to perform structural and functional brain MRI and electroretinography (ERG) studies in a subset of patients
- to correlate the findings of these studies with the location of the *dystrophin* mutations in a phenotype-genotype analysis

Grace McMacken

Start date: September 2015
PhD Project Title: Adrenergic Signalling and Congenital Myasthenic Syndromes
Supervisors: Professor Hanns Lochmüller, Dr Andreas Roos
Funding Source: Association of British Neurologists/Guarantors of Brain Clinical Research Training Fellowship
Length of studentship: 3 years

Project Description: Therapies acting on the sympathetic nervous system have been shown to have beneficial effects in several neurological diseases. More recently, sympathomimetics have been shown to be beneficial with certain types of congenital myasthenic syndromes (CMS). However, the mechanism by which the sympathetic nervous system exerts these effects on neuromuscular transmission is not understood. The aim of this project is to explore the mode of action of sympathomimetics at the neuromuscular junction (NMJ) development and structure, and to characterise the principle route by which adrenergic modulation exerts a physiological effect.
The effect of the adrenergic agonists salbutamol and ephedrine will be studied in vivo using CMS zebrafish and mouse models which closely resemble the human disease, allowing the analysis of pre and post-synaptic effects of these drugs throughout NMJ maturation. An understanding of the effect of sympathomimetics at the NMJ will be instrumental in order to target treatment to the most appropriate patient groups, and will facilitate the development of more targeted therapies, which benefit skeletal muscle function while minimizing systemic side effects.

Olivia Poole

Start Date: August 2015
PhD Project Title: Mitochondrial disease: clinical studies and molecular mechanisms
Supervisors: Professor Mike Hanna, Dr Rob Pitceathly
Funding source: Lily Foundation
Length of studentship: 3 years

Project Description:
Mitochondrial diseases encompass a phenotypically, biochemically and genetically heterogeneous group of disorders caused by impaired oxidative phosphorylation. Their complexity is, in part, related to the dual genomic expression of mitochondrial proteins which are encoded by both nuclear and mitochondrial DNA. The main aim of my project is to identify novel nuclear genes underpinning mitochondrial dysfunction, using next generation sequencing technology, and to characterise the pathological effects of these mutations using functional studies. My research will also evaluate the clinical impact of mitochondrial disease on organ function

Significant Publications: Poole, O. V., Hanna, M. G., & Pitceathly, R. D. (2015). Mitochondrial Disorders: Disease Mechanisms and Therapeutic Approaches. *Discovery medicine*, 20(111), 325-331. PMID:26645904

Alexander Murphy

Start date: August 2014
PhD Project Title: Magnetic resonance imaging of cardiomyopathy secondary to neuromuscular disease and the dystrophinopathies
Supervisors: Professor Straub, Dr Hollingsworth, Dr Bourke.
Funding source: Bioimage NMD
Length of studentship: 3 years

Project description:
Neuromuscular outcome measurements should be reliable, sensitive, clinically relevant and linked to the underlying disease process. This PhD project explores the use of MRI as a neuromuscular outcome measure for some types of muscular dystrophy. Although MRI has been used in several ways to measure neuromuscular disease progression, so far it has not been able to quantify fibrosis within skeletal or cardiac muscle. LGMD2I, one of the most

common types of LGMD has previously only been described with MRI in a one year follow up study. My work will examine:
1. Whether a novel gadolinium-based contrast agent can accurately quantify fibrosis within skeletal and cardiac muscle.
2. Whether the same contrast agent is sensitive enough to detect changes in fibrosis due to administration of an anti-fibrotic.
3. Whether MRI can be used to detect disease progression in a cohort of patients with LGMD2I over a five year period and then compare this to existing neuromuscular outcome measures.
4. Whether MRI can be used to detect disease progression within the heart using novel methods of measurement.
5. Whether MRI can be improved as an outcome measure by reducing acquisition times.

Relevant publications:
Murphy AP, Straub V. The Classification, Natural History and Treatment of the Limb Girdle Muscular Dystrophies. Journal of Neuromuscular Diseases, vol. 2, no. s2, pp. S7-S19, 2015

Elizabeth Harris

Start date: October 2013
PhD Project Title: Next generation sequencing and deep phenotyping in limb girdle muscular dystrophies
Supervisors: Professor Kate Bushby, Professor Volker Straub, Dr Ana Topf
Funding Source: Muscular Dystrophy UK Clinical Training and Research Fellowship
Length of studentship: 3 years (plus 8 month extension for maternity leave)

Project Description:
Limb girdle muscular dystrophies (LGMD) are a clinically and genetically heterogeneous group of rare disorders that cause progressive weakness and wasting of proximal muscles. Although the number of genes known to cause LGMD has increased in recent years there remains a small proportion of patients in who a genetic diagnosis is not achieved. This project applies whole exome sequencing to identify the pathogenic genetic variants underlying LGMD, which may be in known or novel disease genes.
Once diagnosed, obtaining a comprehensive understanding of the phenotype and progression of these rare diseases is essential for the design of successful clinical trials. I clinically assess patients with genetically confirmed LGMD type 2B, due to mutations in the dysferlin gene as part of an international multicentre natural history study, and analysis of data from this study is also performed as part of this project.

Significant Publications:
1. Harris E, Bladen CL, Mayhew A, James M, Bettinson K, Moore U, et al. The Clinical Outcome Study for dysferlinopathy: An international multicenter study. Neurology Genetics. 2016 Aug;2(4):e89. PubMed PMID: 27602406. Epub 2016/09/08. eng.
2. Steele HE, Harris E, Barresi R, Marsh J, Beattie A, Bourke JP, et al. Cardiac involvement in hereditary myopathy with early respiratory failure: A cohort study. Neurology. 2016 Sep 6;87(10):1031-5. PubMed PMID: 27511179. Epub 2016/08/12. eng.

3. Figueroa-Bonaparte S, Hudson J, Barresi R, Polvikoski T, Williams T, Topf A, et al. Mutational spectrum and phenotypic variability of VCP-related neurological disease in the UK. Journal of neurology, neurosurgery, and psychiatry. 2016 Jun;87(6):680-1. PubMed PMID: 26105173. Pubmed Central PMCID: PMC4893144. Epub 2015/06/25. eng.
4. Nasim Vasli*, Elizabeth Harris*, Jason Karamchandani, Eric Bareke7, Jacek Majewski, Norma B. Romero et al. Recessive mutations in the kinase ZAK cause a congenital myopathy with fiber type disproportion. *Accepted for publication in Brain, August 2016. * denotes that these authors contributed equally to this work*

Helen Devine

Start Date: September 2013 (maternity leave April 2014 to Apr 2015), (maternity leave Aug 2016 to Aug 2017)
PhD Project Title: The Pathogenesis of Spinal Bulbar Muscular Atrophy
Supervisors: Professor Michael Hanna, Professor Linda Greensmith, Dr Rickie Patani
Funding source: Kennedy's fund followed by MRC Clinical Research Training Fellowship
Length of studentship: 3 years

Project Description:
Spinal and Bulbar Muscular Atrophy (SBMA) is a neurodegenerative disorder caused by a polyglutamine repeat in the Androgen Receptor gene. It leads to a motor neuron (MN) disease in males who present with weakness in bulbar and limb muscles in their fourth to sixth decade. Previous research in SBMA has been performed in cell and rodent models which do not truly recapitulate the human disease; there is, therefore, a need for a human model. This is possible using induced pluripotent stem cells (iPSCs). Although SBMA is a rare disease, it is particularly interesting as it has parallels to both other MN diseases and other polyglutamine disorders such as Huntington's Disease which also have a neurodegenerative phenotype.
The goals of my project are to:
1. Develop a human model of SBMA by differentiating iPSCs from SBMA patients into bulbar and spinal MN and astrocytes co-cultured with iPSC spinal MN
2. Investigate pathways of neurodegeneration implicated in MN disease: axonal transport deficits, protein mishandling and aggregation, endoplasmic reticulum stress, mitochondrial dysfunction and the role of disturbed astroglial-neuronal interaction
3. Determine if MN deficits can be ameliorated. Compounds which target protein mishandling and axonal transport are currently available for assessment

Significant Publications:
Peripheral neuropathy in complex inherited diseases: an approach to diagnosis.
Rossor AM, Carr AS, Devine H, Chandrashekar H, Pelayo-Negro AL, Pareyson D, Shy ME, Scherer SS, Reilly MM.
J Neurol Neurosurg Psychiatry. 2017 Oct;88(10):846-863.
The translational potential of human induced pluripotent stem cells for clinical neurology
Devine H, Patani R. Cell Biol Toxicol. 2017 Apr;33(2):129-144.
Whittaker RG, Devine HE, Gormon GS, Schaefer AM, Horvath R, Ng Y, Nesbitt V, Lax NZ, McFarland R, Cunningham MO, Taylor RW, Turnbull DM Epilepsy in adults with

mitochondrial disease: A cohort study (2015) *Annals of Neurology* 78(6) 949-57 PMID: 26381753
Devine H, Parton M (2015) Tips from the shop floor: Seizure: Acute management and investigation *British Journal of Hospital Medicine*
Devine H, Rohrer J (2015) Next Generation Neurology: The ABNT mentoring program *ACNR* 15(3):17
Tallantyre E, Devine H (2014) The Shape of Training: what is it and how does it affect neurology? *ACNR* 14 (4): 22-24

Next destination: My aim is to apply for further funding after completion of my PhD in order to continue my research whilst completing my neurology training.

Karen Suetterlin

Start Date: September 2013 (maternity leave January 2015 to October 2015) (maternity leave 12 May 2016 to Jan 2017)
PhD Project Title: A Molecular Pathophysiological Study of the Skeletal Muscle Channelopathies
Funding source: EU FP7 Research and innovation followed by MRC Research fellowship
Supervisor: Professor Michael Hanna, Dr Emma Matthews, Dr Roope Männikkö
Length of studentship: 4 years

Project Description:
Myotonia congenita is caused by mutations in the chloride channel gene. Mutations are found throughout the entire channel, can be dominant or recessive and in some cases both patterns of inheritance have been reported for the same mutation. This makes genetic counselling and determining the likely clinical significance of new variants very difficult.
To try to address this I used our large data set to investigate how functional characterisation and variant location might help estimate the risk of a variant being disease causing and/or associated with a dominant mode of inheritance. I functionally characterised 5 novel chloride channel variants and built a homology model of a chloride channel in its functional form as a dimer. I mapped over 80 variants that have been functionally characterised by our centre onto this model and categorised over 200 patients with these variants according to their reported inheritance pattern of clinical symptoms. Variants clearly clustered on the model according to their functional effect and associated inheritance pattern. Combining a variant's location and functional effect with the associated inheritance pattern has enabled us to provide a framework to assess the risk of an associated dominant mode of inheritance and highlight those variants most likely to be benign polymorphisms.
In the second part of my PhD I will investigate progressive age related weakness in periodic paralysis and normal ageing. My hypothesis is that age related changes may reduce the muscle's homeostatic reserve to deal with the chronic consequences of single ion channel dysfunction. I will investigate how excitation-contraction coupling and the skeletal muscle 'channelome' change with age in periodic paralysis and normal muscle. I will also look at the effect of prolonged depolarisation, as occurs during an attack of paralysis, on the muscle as a whole and how age affects this. My aim is to improve our understanding of the

mechanisms involved in the development of progressive age related weakness and how acute attacks of paralysis may contribute to permanent weakness in periodic paralysis.

Significant Publications:
Zaharieva IT, Thor MG, Oates EC, van Karnebeek C, Hendson G, Blom E, et al. Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or 'classical' congenital myopathy. Brain : a journal of neurology. 2015. Epub 2015/12/25.
Suetterlin KJ, Bugiardini E, Kaski JP, Morrow JM, Matthews E, Hanna MG, et al. Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies. JAMA neurology. 2015;72(12):1531-3. Epub 2015/12/15.
Suetterlin K, Turner C. Diagnosis and management of headache. Br J Hosp Med (Lond). 2014;75(12):C178-82. Epub 2014/12/10.
Suetterlin K, Mannikko R, Hanna MG. Muscle channelopathies: recent advances in genetics, pathophysiology and therapy. Current opinion in neurology. 2014;27(5):583-90. Epub 2014/09/05.
Suetterlin K & Hanna, M.G. Muscle Channelopathies. Chapter 116. International Neurology: A Clinical Approach. 2nd Edition. Wiley Blackwell. In press, to be published April 2016.

Renata Scalco

Start Date: Sept 2013
PhD Project Title: Translational research studies in exercise related muscle disorders
Supervisors: Professor Michael G Hanna, Dr Ros Quinlivan, Dr Doreen Fialho
Funding source: CAPES Foundation, Ministry of Education of Brazil
Length of studentship: 3 years

Project Description:
Translational research (TR) is the research that transfers knowledge from basic science to clinical setting thus making findings from basic science useful for practical applications and aiming to improve patient care within a relatively short period. This PhD research will translate knowledge from animal models of Hypokalaemic Periodic Paralysis (HypoPP) and McArdle Disease to identify new treatments for both conditions. It includes two phase II clinical trials: an open label uncontrolled pilot study to evaluate safety and efficacy of sodium valproate in McArdle Disease; and an RCT of Bumetanide in HypoPP. Outcome measurements including neurophysiology, exercise functional tests and muscle biopsy analysis will be assessed for the benefit of future studies.
A further project aims to evaluate a group of patients presenting with exercise induced rhabdomyolysis. This involves clinical and histopathological studies as well as genetic testing using next generation sequencing. The identification of new well-characterised patient cohorts will facilitate future translational studies.

Significant Publications:
Scalco RS, Nastasi L, Hanna MG, Quinlivan R. Re-audit on Unplanned Hospital Admissions in Patients with Neuromuscular Diseases. Technical Report: http://www.musculardystrophyuk.org/app/uploads/2017/11/Unplanned-admissions.web-Final.pdf

Scalco RS, Morrow JM, Booth S, et al. Misdiagnosis is an important factor for diagnostic delay in McArdle disease. Neuromuscul Disord. 2017 Sep;27(9):852-855.
Scalco, RS, Snoeck M, Quinlivan R, et al. Exertional rhabdomyolysis: Physiological response or manifestation of an underlying myopathy? BMJ Open Sport & Exercise Medicine. In press
Neuromuscul Disord. 2016 Aug;26(8):504-510.
Scalco RS, Voermans NC, Piercy RJ, et al. Dantrolene as a possible prophylactic treatment for RYR1-related rhabdomyolysis. Eur J Neurol. 2016 Aug;23(8):e56-7.
Scalco RS, Gardiner AR, Pitceathly RD, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015 May 2;10:51.

Next destination: Apply for Post-doc in Translational Research

Maiya Kugathasan

Start Date: April 2013 (maternity leave Jan 17 – Oct 17)
PhD Project Title: Hereditary Sensory Neuropathy Type 1 secondary to SPTLC1/2 mutations: Pathogenesis and treatment
Supervisors: Professor Mary M Reilly & Professor Linda Greensmith
Funding source: NIH Rare Disease Inherited Neuropathy Fellowship (1 year), MRC Centre Grant, followed by MRC clinical training fellowship (3 years)
Length of studentship: 4 years

Project Description:
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. At the National Hospital for Neurology and Neurosurgery, we have the largest cohort of patients with this condition in the world. We have a unique population within the United Kingdom where all the SPTCL1 patients have a common mutation (C133W). 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.
My project has three aims. Firstly, to investigate the role of deoxysphingolipids in HSN1 using primary motor neuron and DRG culture models. Secondly to investigate the therapeutic potential of L-serine supplementation using induced pluripotent stem cell derived sensory neurons from patients' fibroblasts (Professor Bennett's lab in Oxford). Thirdly, to identify outcome measures for a therapeutic trial in HSN1 patients by undertaking a one year natural history study.

Next destination: PhD to be submitted March 2018. Clinical reg training from April 2018

Non-clinical current students (by start date)

Alaa Khan

Photo not provided
Start date: Nov 2016
Project title: Genetic investigation of inherted neuromuscular disorders
Supervisors: Prof. Henry Houlden, Prof. Mary Reilly, Dr. Daniah Trabzoni
Funding Source: Saudi Government
Duration: 4 years full time

Project description:
Understanding the genetic basis of neuromuscular disorders is the main focus of my Ph.D. Although the molecular pathogenesis of many neuromuscular disorders has been explained, a definitive genetic diagnosis remains unsolved for many cases suggesting the high heterogeneity of inherited neuromuscular disorders. I am currently analyzing the exome data for different neuromuscular disease, their correlations with clinical manifestations, looking for newly associated genes and their pathways involved in the pathogenesis. My approach involves bioinformatics analysis and combination techniques including Next-generation sequencing (focused or full exome and genome sequencing).

Matthew Jennings

Start date: October 2016
PhD Project Title: Elucidating the mechanisms by which ER stress and mitochondrial mechanisms contribute and interact in the pathophysiology of inherited peripheral neuropathies and how modulation of these mechanisms may provide therapeutic pharmacological targets.
Supervisors: Professor Rita Horvath, Dr. Andreas Roos
Funding Source: MRC Discovery Medicine North
Length of studentship: 3.5 years

Project Description:
Peripheral neuropathies (Charcot-Marie-Tooth disease) encompasses a range of inherited neurological disorders causing slow, progressive loss of function of motor and sensory peripheral nervous systems resulting in disability. A specific genetic deficit causing the condition can now be identified in the majority of patients, but despite this no disease-modifying treatments are currently available and the exact mechanism of disease for most genetic mutations is not well-agreed. The project aims to utilise modern molecular approaches to identify common features of peripheral neuropathies in and between different disease sub-groups.

Part of the project will use multi-targeted proteomics to investigate blood protein alterations in of neuropathy patients, giving insight into the involvement of biological pathways in

disease pathophysiology and for the establishment of much-needed biomarkers. Another part will look specifically into the pathophysiology of cells affected by CMT-associated mutations in genes encoding aminoacyl-tRNA synthetase proteins, utilising patient cells transdifferentiated to induced-neural progenitor cells and non-biased molecular techniques to determine cellular abnormalities in a disease-appropriate cell type. Via feedback between these two elements the project will improve the understanding of the cellular and molecular characteristics of peripheral neuropathy, and thereby contribute to the development of disease-modifying treatments.

Publications:
Boczonadi V, Jennings MJ, Horvath R. The role of tRNA synthetases in neurological and neuromuscular disorders. FEBS letters. 2017 Dec 30.

Emily O'Connor

Start date: June 2016
PhD Project Title: Structural and molecular changes in the pre-synapse in disorders of the neuromuscular junction
Supervisors: Professor Hanns Lochmüller, Professor Clarke Slater, Dr Andreas Roos
Funding Source: Kindness for Kids
Length of studentship: 3 years

Project Description:
Congenital myasthenic syndromes (CMS) are a group of rare, inherited disorders characterised by compromised function of the neuromuscular junction (NMJ). Patients present with fatigable muscle weakness that can affect the ocular, bulbar and skeletal muscles. We described mutations in a novel causative gene, MYO9A, encoding for an unconventional myosin. Mutations were present in three patients showing a severe neonatal phenotype with both respiratory and bulbar involvement.
The aim of this project is to characterise the role of MYO9A at the NMJ using a range of techniques in cell culture models and in vivo using both zebrafish and mouse models of MYO9A-CMS. Understanding more about the underlying pathophysiology is crucial for the identification of novel therapeutic targets for this disorder, as current treatments used in CMS are systemic in their action with a range of side effects and can even have detrimental effects on patients of certain genotypes. Novel therapeutic options will therefore be trialled both in vitro and in zebrafish to determine a selection of candidates that may be considered for further analysis.
Publications:
Emily O'Connor, Ana Töpf, René Zahedi, Yasmin Issop, Sally Spendiff, Daniel Cox, Andreas Roos, Hanns Lochmüller (in press) Clinical and research strategies for limb-girdle congenital myasthenic syndromes. Ann. N.Y. Acad. Sci.
Kieran A. Boyle, Maria Gutierrez-Mecinas, Erika Polgár, Nicole Mooney, Emily O'Connor, Takahiro Furuta, Masahiko Watanabe, Andrew J. Todd (2017) A quantitative study of neurochemically defined populations of inhibitory interneurons in the superficial dorsal horn of the mouse spinal cord. Neuroscience 363 120-133.

Benjamin O'Callaghan

Start Date: September 2015
PhD Project Title: The impact of mitochondrial impairment on histone acetylation profiles
Supervisors: Professor Henry Houlden, Professor Jenny Morgan
Funding source: UCL matched funding (MRC Centre Grant)
Length of studentship: 4 years

Project Description:
During my first 3 month rotation I looked at the effect mutations in mitochondrial DNA have on the differentiation of induced pluripotent stem cells (IPSCs) into myotubes. Mitochondrial diseases are a heterogeneous group of disorders caused by genetic dysfunction of mitochondrial oxidative phosphorylation. IPSCs derived from mitochondrial disease patients and appropriate differentiation towards affected cell types (e.g. muscle and neurons) represents an excellent model to explore disease mechanisms for novel targeted therapeutic intervention.
Mutations in a potassium channel gene KCNJ18 have recently been associated with TPP however this has been disputed due to the high prevalence in healthy control individuals. During my second rotation I looked into the genetics of TPP with particular focus on KCNJ18 and the closely related KCNJ12 genes.
Environmental stressors are thought to play an important role in the initiation and progression of amyotrophic lateral sclerosis (ALS). Recent evidence has revealed that stress granules might represent a focal point linking external stress with genetic susceptibility. During my final 3 month rotation I have been optimising an *in vitro* model of motor neuron injury to investigate the cellular localisation of RNA-binding proteins associated with ALS.

Benjamin Clarke

Start Date: September 2015
PhD Project Title: The role of the heat shock response in mitochondrial dysfunction in motor neuron disease
Funding source: UCL matched funding (MRC Centre Grant)
Length of studentship: 4 years
Project Supervisors: Dr Bernadett Kalmar, Prof Linda Greensmith

Project description:

Mitochondrial dysfunction has been implicated in contributing to the death of motor neurons in Amyotrophic lateral sclerosis (ALS). Heat shock proteins are a family of pro-survival chaperones known to possess anti-aggregation and anti-apoptotic capabilities which aid motor neuron survival. Several heat shock proteins localise to mitochondria although their roles in motor neurons are not fully understood. My PhD project will investigate the importance of heat shock proteins to mitochondrial dysfunction in models of ALS and attempt to ameliorate mitochondrial dysfunction through the pharmacological upregulation of heat shock proteins.

Verna Sarajarvi

Start Date: September 2015
PhD Project Title: Investigating cellular pathomechanisms of Charcot-Marie-Tooth disease
Funding source: UCL matched funding (MRC Centre Grant)
Length of studentship: 4 years
Project Supervisors: Prof Linda Greensmith, Dr Bernadett Kalmar, Prof Mary Reilly

Project description: Charcot-Marie-Tooth (CMT) disease is a group of peripheral neuropathies with over 80 causative genes identified to date. Despite the identification of several CMT-causing mutations, the underlying pathomechanisms of disease remain unclear and there are currently no disease modifying treatments available.
In my PhD project I use *in vitro* disease models to investigate the pathomechanisms involved in CMT and to compare the pathomechanisms across a range of CMT-causing mutations.

Hadil Alrohaif

Start date: September 2015
MD Project title: Next generation sequencing in diagnostics and disease gene discovery: A systematic assessment of integrated genomic platforms in rare neuro-genetic disease
Supervisors: Professor Hanns Lochmüller, Dr Ana Topf, Rachel Thompson
Funding source: Kuwaiti Government
Length of studentship: 3 years

Project description:

This project will take a systematic bioinformatics approach in evaluating three integrated genomic platforms used in prioritising genes and variants from next generation sequencing (NGS) projects in neurogenetic disease. Up to 1,000 WES/WGS datasets will be available for analysis, on at least two platforms each. These platforms, namely: RD-Connect (CNAG, Barcelona, academic), Seqr(Broad Institute, Boston, academic) and Clinical Sequence Analyser (WuXi NextCODE, commercial), will be initially assessed for sensitivity, specificity and diagnostic yield of solved and unsolved cases. An in-depth analysis of VCF filtering algorithms, variant annotation, user filtering options, and integration with relevant genomic, phenotypic and bioinformatics applications will be carried out and compared across platforms. Findings will be used in an attempt to further develop diagnostics and disease gene discovery in rare neurological disease. My hypothesis is that through standardization of the bioinformatics pipeline, integration of machine-readable deep phenotypic information, and matchmaking the number of correctly solved cases can be increased. In addition, the comparison between platforms will reveal strengths and weaknesses which may aid developers to design and implement improvements.

Ione Meyer

Start Date: Sept 2014
PhD Project Title: 'Investigating nidogens, basement membrane proteins, at the neuromuscular junction in health in disease'
Supervisors: Professor Giampietro Schiavo, Professor Elizabeth Fisher
Funding source: MRC Centre Grant
Length of studentship: 4 years

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

NMJ integrity, and thereby reveal potential targets for therapeutic intervention to combat NMJ pathology in devastating neurodegenerative diseases

Stephanie Carr

Start date: September 2014
PhD project title: Cardiac targeted therapy studies in Duchenne Muscular Dystrophy
Funding source: Barbour Foundation
Length of studentship: 4 years (1 year MRes + 3 years PhD)
Supervisor: Prof Hanns Lochmüller

Project description:
In patients with Duchenne Muscular Dystrophy (DMD), both skeletal and cardiac muscle lack dystrophin protein and degenerate progressively, leading to loss of independence and premature death. While the primary genetic defect is identical for the heart and skeletal muscle, the symptoms and severity are often dissociated pointing towards different secondary, organ-specific events and pathways. Moreover, several innovative therapies that are currently in clinical development such as exon skipping via antisense oligonucleotides seem to be more efficient in the dystrophin-deficient muscle than the heart. To understand the different pathways acting in the dystrophic heart and to develop therapies targeting the heart in DMD, we have generated a specific, new assay.
For our assay, we culture primary heart cells from dystrophin-deficient mdx mice (cardiomyocytes) and subject them to stress via serum starvation. Unlike healthy dystrophin-positive cardiomyocytes, mdx cells show a specific hypertrophic response that can be partially reversed by cardio-protective drugs. Therefore, this assay can be utilized to assess therapeutic interventions (drugs or genetic) for whether they show benefit for dystrophic heart cells. Moreover, data obtained through RNA sequencing of different time points in the hypertrophic response of the dystrophic cells in comparison with the normal cells, revealed a number of pathways that are specific for dystrophin-deficiency and some that are specific for the heart. This project will continue to use this assay to test therapies for potential efficacy in the heart as well as using it as a tool to investigate specific genes and pathways involved in the hypertrophic response.

Persefoni Ioannou

Start Date: September 2014

PhD Project Title: NHE1 inhibition as a potential therapy for Duchenne Muscular Dystrophy (DMD)
Supervisor: Professor Volker Straub
Funding source: MRC, Barbour Foundation
Length of studentship: 3 years

Project Description:
The absence of dystrophin in Duchenne Muscular Dystrophy (DMD) muscle cells results in increased membrane permeability and subsequent intracellular calcium overload. The dysregulation of calcium homeostasis that characterizes the DMD models is exacerbated by the increased activity of the Sodium/Hydrogen Exchanger 1 (NHE1). NHE1 over-activity leads to an increased influx of sodium, which in turn switches the Sodium/Calcium Exchanger (NCX) into reverse mode, resulting in an increased calcium influx. Selective NHE1 inhibitors can be used to reduce the sodium influx and thereby, revert the NCX to normal mode with a subsequent decrease in the cellular calcium load. This observation has led to the hypothesis that the use of specific NHE1 inhibitors could improve the calcium homeostasis and alleviate pathology in DMD muscle.
The current study seeks to demonstrate the efficacy of a specific NHE1 inhibitor that has shown a good safety and potency profile in several pre-clinical studies. The study employs a series of methods including manganese-enhanced molecular resonance imaging (MEMRI), histological analysis, and functional grip strength test, in order to assess the efficacy of the drug after *in vivo* treatment of *mdx* mice, a DMD model. The study will be supplemented with *in vitro* pH, sodium and calcium assays that will be used to verify the drug action.
The proposed studies with a first prototype NHE1 inhibitor are an important step towards potential clinical trials for dystrophinopathies with this class of compounds.

Prasanth Sivakumar

Start Date: September 2014
PhD Project Title: Investigating dysfunctional RNA processing in TDP-43 mouse mutants
Supervisors: Professor Elizabeth Fisher, Pietro Fratta
Funding source: MRC Centre Grant
Length of studentship: 4 years

Project Description:
Amyotrophic lateral sclerosis (ALS) is a rapidly progressive disorder characterised by degeneration of both upper and lower motor neurons, resulting in muscular atrophy. Recently, RNA processing has been implicated in ALS pathology, notably the depletion of RNA-binding protein TDP-43 from the nucleus and its subsequent cytoplasmic aggregation in the vast majority of ALS cases. My aim is to investigate the genotypic consequences of aberrant TDP-43 activity on RNA processing. Changes to the motor neuron transcriptome will be analysed using newly developed techniques enabling cell-specific gene expression analysis, and through these methods I hope to further our understanding of the role TDP-43 dysfunction plays in ALS.

Studies completed clinical students:

Boglarka Bansagi

Start date: February 2014 – March 2017
PhD Project Title: Clinical and genetic characterisation of hereditary motor neuropathies
Supervisors: Professor Rita Horvath
Funding Source: MRC studentship
Length of studentship: 3 years

Project Description:
The aim of the clinical project is to enhance the national cohort of Charcot Marie Tooth disease with patients 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 project is primarily focused on the subgroup of distal hereditary motor neuropathies (dHMN). We plan to identify new genes and establish further subclassification of dHMN on a clinico-genetic basis. This will provide us with new insights of the pathomechanisms of the disease and will hopefully allow us to identify biomarkers in this subgroup.

Significant publications:
Balreira A, Boczonadi V, Barca E, Pyle A, Bansagi B, Appleton M, Graham C, Hargreaves IP, Rasic VM, Lochmüller H, Griffin H, Taylor RW, Naini A, Chinnery PF, Hirano M, Quinzii CM, Horvath R. ANO10 mutations cause ataxia and coenzyme Q_{10} deficiency. J Neurol 2014;261(11):2192-2198.
Herrmann DN, Horvath R, Sowden JE, Gonzalez M, Sanchez-Mejias A, Guan Z, Whittaker RG, Almodovar JL, Lane M, Bansagi B, Pyle A, Boczonadi V, Lochmüller H, Griffin H, Chinnery PF, Lloyd TE, Littleton JT, Zuchner S. Synaptotagmin 2 mutations cause an autosomal-dominant form of lambert-eaton myasthenic syndrome and nonprogressive motor neuropathy. Am J Hum Genet 2014;95(3):332-339.
Boczonadi V, Bansagi B, Horvath R. Reversible infantile mitochondrial diseases. J Inherit Metab Dis 2015;38(3):427-435.
Cottenie E, Kochanski A, Jordanova A, Bansagi B, Zimon M, Horga A, Jaunmuktane Z, Saveri P, Rasic VM, Baets J, Bartsakoulia M, Ploski R, Teterycz P, Nikolic M, Quinlivan R, Laura M, Sweeney MG, Taroni F, Lunn MP, Moroni I, Gonzalez M, Hanna MG, Bettencourt C, Chabrol E, Franke A, von Au K, Schilhabel M, Kabzińska D, Hausmanowa-Petrusewicz I, Brandner S, Lim SC, Song H, Choi BO, Horvath R, Chung KW, Zuchner S, Pareyson D, Harms M, Reilly MM, Houlden H. Truncating and missense mutations in IGHMBP2 cause Charcot-Marie Tooth disease type 2. Am J Hum Genet 2014;95(5):590-601.
Evangelista T, Bansagi B, Pyle A, Griffin H, Douroudis K, Polvikoski T, Antoniadi T, Bushby K, Straub V, Chinnery PF, Lochmüller H, Horvath R. Phenotypic variability of TRPV4 related neuropathies. Neuromuscul Disord 2015;25(6):516-521.
Bansagi B, Antoniadi T, Burton-Jones S, Murphy SM, McHugh J, Alexander M, Wells R, Davies J, Hilton-Jones D, Lochmüller H, Chinnery P, Horvath R. Genotype/phenotype

correlations in AARS-related neuropathy in a cohort of patients from the United Kingdom and Ireland. J Neurol 2015; 262(8):1899-1908.
Bansagi B, Griffin H, Ramesh V, Duff J, Pyle A, Chinnery PF, Horvath R. The p.Ser107Leu in BICD2 is a mutation 'hot spot' causing distal spinal muscular atrophy. Brain 2015;138(Pt 11):e391.
Whittaker RG, Herrmann DN, Bansagi B, Hasan BA, Lofra RM, Logigian EL, Sowden JE, Almodovar JL, Littleton JT, Zuchner S, Horvath R, Lochmüller H. Electrophysiologic features of SYT2 mutations causing a treatable neuromuscular syndrome. Neurology 2015;85(22):1964-1971.

Next destination: Applying for clinical work at University of Leuven

Matthew Evans

Start Date: April 2013 – March 2016
PhD Project Title: Development and application of Neuromuscular MRI
Supervisors: Professor Mary M Reilly, Dr John Thornton, Professor Michael Hanna
Funding source: Host matched funding (UCLH BRC)
Length of studentship: 3 years

Project Description:
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.

Significant Publications:
Evans M, Manji H. Progress in Peripheral nerve disease research in the last two years. *J Neurol* (2013) 260:3188–3192. DOI 10.1007/s00415-013-7121-x
MRB Evans, H Manji. Neurology in Africa – Howlett. A Book review. *J Neurol Neurosurg Psychiatry.* doi:10.1136/jnnp-2014-308919.
Matthew RB Evans, Jasper M Morrow. The pupillary examination. *Br J Hosp Med (Lond).* 2015 Apr;76(4):C50-4. doi: 10.12968/hmed.2015.76.4.C50.
Matthew R B Evans, Matilde Laurá, Hoskote Chandrashekar, Mary M Reilly. Cervical spinal cord compression complicating the clinical course of Charcot-Marie-Tooth type 1. *BMJ Case Rep.* 2015. doi:10.1136/bcr-2015-213486.
Rossor AM, Evans MR, Reilly MM. A practical approach to the genetic neuropathies. *Pract Neurol.* 2015 Apr 21. pii: practneurol-2015-001095. doi: 10.1136/practneurol-2015-001095.
Carr AS, Pelayo-Negro AL, Jaunmuktane Z, Scalco RS, Hutt D, Evans MR, Heally E, Brandner S, Holton J, Blake J, Whelan CJ, Wechalekar AD, Gillmore JD, Hawkins PN, Reilly MM. Transthyretin V122I amyloidosis with clinical and histological evidence of amyloid neuropathy and myopathy. *Neuromuscul Disord.* 2015 Feb 14. pii: S0960-8966(15)00036-X. doi: 10.1016/j.nmd.2015.02.001.

Carr AS, Pelayo-Negro AL, Evans MR, Laurà M, Blake J, Stancanelli C, Iodice V, Wechalekar AD, Whelan CJ, Gillmore JD, Hawkins PN, Reilly MM. A study of the neuropathy associated with transthyretin amyloidosis (ATTR) in the UK. *J Neurol Neurosurg Psychiatry*. 2015 Aug 4. pii: jnnp-2015-310907. doi: 10.1136/jnnp-2015-310907.

Next destination: Consultant Neurologist, St George's

Katarzyna Swist-Szulik

Start date: October 2013 (research associate part-time), May 2014 (MRC studentship) – May 2017
PhD Project Title: Does mitochondrial dysfunction influence NLRP3 inflammasome activation and other cell signalling pathways?
Supervisors: Professor Sir Doug Turnbull, Dr Robert McFarland, Professor Rob Taylor, Professor Derek Mann and Dr Lee Borthwick (Fibrosis and Inflammation Group)
Funding Source: MRC studentship
Length of studentship: 3 years

Project Description: The project aims to improve our understanding of the role of mitochondrial dysfunction in inflammatory responses in both myeloid and non-myeloid cells and investigate the hypothesis that cells with mitochondrial injury can influence signalling transduction pathways and inter-cellular interactions. We have identified that fibroblasts and myoblasts with induced mitochondrial dysfunction by Rotenone (complex I inhibitor) and recombinant interleukin IL-1β produce extremely high levels of interleukin IL-6 in dose dependent manner. In experiments using a migration assay we demonstrated that fibroblasts and myoblasts with induced mitochondrial injury attract far more immune cells, such as THP1 immortalised monocytes, than healthy cells. Pro-inflammatory interleukin IL-6 appears to play an important role in the migration of these immune cells. These findings may be relevant to disease processes presenting with both mitochondrial and inflammatory components.

Next destination: Consultant Paediatrician, Newcastle Upon Tyne Hospitals

Yi Ng

Start date: August 2013
PhD Project Title: Understanding the phenotype-genotype correlation in mitochondrial disease
Supervisors: Dr Robert McFarland, Professor Sir Doug Turnbull and Professor Rob Taylor
Funding Source: MRC Clinical PhD Studentship
Length of studentship: 3 years

Project Description:
The MRC Mitochondrial Disease Patient Cohort is a national collaborative project that has been launched since 2009. The main aims are to better understand the phenotypic and genotypic heterogeneity of mitochondrial disease and facilitate patient recruitment for basic science research and clinical study. To date, more than 1150 patients are registered in the cohort database and more than 55% of patients are recruited in Newcastle.
My PhD study is integrated with this cohort project. The cores are to clinically deep phenotype patients and family pedigrees affected by mitochondrial disease caused by different genetic mutations, analyse their disease burdens using Newcastle Mitochondrial Disease Adult Scale (NMDAS) and other investigations (such as brain, cardiac and gastrointestinal imaging) in order to better elucidate the natural history. Ultimately, these findings hopefully could be translated back to clinical practice by providing more accurate data on genetic counselling, prognostication and streamline the guidance on disease management.

Significant publications:
Ng YS, Feeney C, Schaefer AM, Holmes CE, Hynd P, Alston CL, Grady JP, Roberts M, et al. Pseudo-obstruction, stroke and mitochondrial dysfunction: A lethal combination. Annals of neurology. Jul 25 2016.
Ng YS, Grady JP, Lax NZ, Bourke JP, Alston CL, Hardy SA, Falkous G, Schaefer AG, Radunovic A, Mohiddin SA, Ralph M, Alhakim A, Taylor RW, McFarland R, Turnbull DM, Gorman GS (2015) Sudden adult death syndrome in m.3243A>G-related mitochondrial disease: an unrecognized clinical entity in young, asymptomatic adults. European heart journal
Ng YS, Alston CL, Diodato D, Morris AA, Ulrick N, Kmoch S, Houstek J, Martinelli D, et al. The clinical, biochemical and genetic features associated with RMND1-related mitochondrial disease. Journal of medical genetics. Jul 13 2016.
Ng Y, Turnbull D (2015) Mitochondrial disease: genetics and management. Journal of neurology:1-13 (60%)
Anagnostou ME, NG YS, Taylor RW, McFarland R. Epilepsy due to mutations in the mitochondrial polymerase gamma (POLG) gene: a clinical and molecular genetic review (Joint first author, accepted in Epilepsia on 26th July 2016)

Next destination: NIHR Clinical Lectureship in Neurology (50% in clinical neurology and 50% ongoing research with the Wellcome Centre for Mitochondrial Research in Newcastle).

Alex Horga

PhD Dates: 2011- 2015

PhD Title: Peripheral neuropathy and mitochondrial disease

Supervisors: Professor Mary M Reilly & Professor Michael Hanna

Project Description:
Dr Horga is a clinical research fellow undertaking a PhD in peripheral neuropathy and mitochondrial disease with Professor Reilly and Professor Hanna. He has completed a clinical study on peripheral neuropathy in patients with progressive external ophthalmoplegia and is currently working with whole-exome sequencing to determine the genetic basis of inherited neuropathies and mitochondrial diseases.

Publications whilst at MRC Centre:

Horga A, Pitceathly RDS, Blake JC, Woodward CE, Zapater P, Plant GT, Houlden H, Sweeney MG, Hanna MG, Reilly MM. Peripheral neuropathy predicts nuclear gene defect in patients with mitochondrial ophthalmoplegia. [in preparation]

Liu Y-T, Laura M, Hersheson J, Horga A, Jaunmuktane Z, Brandner S, Pittman A, Hughes D, Polke JM, Sweeney MG, Proukakis C, Janssen JC, Auer-Grumbach M, Zuchner S, Shields K, Reilly MM, Houlden H. Extended phenotypic spectrum of KIF5A mutations: from spastic paraplegia to axonal neuropathy. **Neurology** [in press]
2013
Horga A, Raja Rayan DL, Matthews E, Sud R, Fialho D, Durran SCM, Burge JA, Portaro S, Davis MB, Haworth A, Hanna MG. Prevalence study of genetically–defined skeletal muscle channelopathies in England. **Neurology** 2013;80(16):1472-1475.

Pérez-Miralles F, Sastre-Garriga J, Tintoré M, Nos C, Perkal H, Río J, Edo MC, Horga A, Castilló J, Auger C, Huerga E, Rovira A, Montalban X. Clinical impact of early brain atrophy in clinically isolated syndromes. **Mult Scler** 2013 May 7 [*Epub ahead of print*]

Vidal-Jordana A, Sastre-Garriga J, Pérez-Miralles F, Tur C, Tintoré M, Horga A, Auger C, Río J, Nos C, Edo MC, Arévalo MJ, Castilló J, Rovira A, Montalban X. Early pseudoatrophy on natalizumab is due to white matter volume changes. **Mult Scler** 2013 Jan 14 [*Epub ahead of print*]

2012
Costa C, Arrambide A, Tintoré M, Castilló J, Sastre-Garriga J, Tur C, Río J, Vidal-Jordana A, Auger C, Nos C, Rovira A, Comabella M, Horga A, Montalban X. Value of NMO-IgG determination at the time of presentation as CIS. **Neurology** 2012; 78(20):1608-1611.

Cantó E, Reverter F, Morcillo-Suárez C, Matesanz F, Fernández O, Izquierdo G, Vandenbroeck K, Rodríguez-Antigüedad A, Urcelay E, Arroyo R, Otaegui D, Olascoaga J,

Saiz A, Navarro A, Sánchez A, Domínguez C, Caminero A, Horga A, Tintoré M, Montalban X, Comabella M. Chitinase 3-like 1 plasma levels are increased in
A. Horga 9 April 2013
patients with progressive forms of multiple sclerosis. **Mult Scler** 2012; 18(7): 983-990.

2011
Horga A, Castilló J, Río J, Tintoré M, Auger C, Sastre-Garriga J, Edo MC, Pérez-Miralles F, Tur C, Nos C, Huerga E, Comabella M, Rovira A, Montalban X. An observational study of the effectiveness and safety of natalizumab in the treatment of multiple sclerosis. **Rev Neurol** 2011; 56(6): 321-330.

Horga A, Tintoré M. Natalizumab in the treatment of relapsing-remitting multiple sclerosis. **Neurología** 2011 26 (6), 357-368.

Peiró AM, Climent L, Zapater P, Horga A, Horga JF. Ketanserin potentiates morphine-induced antinociception mediated by kappa-receptor activation. **Pharmacol Res** 2011; 64(1): 80-84.

Next destination: (Current) Consultant Neurologist, Hospital Clínico San Carlos, Madrid

Pedro Machado

Month / Year Started April 2010 (Clinical Research fellow, PhD not undertaken in UCL)

Research Work: Development of a Research Portfolio in Inclusion Body Myositis

Project Description:
The broad aims of the project are: 1) to support a wide range of IBM research activities, including the national collection of IBM protocolised data; 2) to deep phenotype IBM patients at the clinical, serologic, histopathological, genetic, and MRI level, and to link all these data in order to improve our understanding of the disease; 3) to develop and validate new biomarkers and responsive outcome measures in IBM; 4) to establish an International IBM Consortium Genetic Study; 5) to establish productive links with industry and to support new clinical trials in IBM (eg. the Bimagrumab (Novartis) and the Arimoclomol (Orphazyme) trials).

Supervisor: Professor Michael G. Hanna

Significant Publications whilst at Centre
Ahmed M*, Machado PM*, Miller A*, Spicer C, Herbelin L, He J, Noel J, Wang Y, McVey AL, Pasnoor M, Gallagher P, Statland J, Lu C-H, Kalmar B, Brady S, Sethi H, Samandouras G, Parton M, Holton JL, Weston A, Collinson L, Taylor JP, Schiavo G, Hanna MG, Barohn RJ, Dimachkie MM, Greensmith L (*joint first authors). Targeting protein homeostasis as a novel therapeutic approach in Sporadic Inclusion Body Myositis. Science Translational Medicine 2016 (manuscript accepted for publication).

Morrow JM, Sinclair CD, Fischmann A, Machado PM, Reilly MM, Yousry TA, Thornton JS, Hanna MG. MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study. Lancet Neurol. 2016 Jan;15(1):65-77. doi: 10.1016/S1474-4422(15)00242-2. Epub 2015 Nov 6. PubMed PMID: 26549782; PubMed Central PMCID: PMC4672173.

Gang Q, Bettencourt C, Houlden H, Hanna MG, Machado PM. Genetic advances in sporadic inclusion body myositis. Curr Opin Rheumatol. 2015 Nov;27(6):586-94. doi: 10.1097/BOR.0000000000000213. PubMed PMID: 26335925.

Rothwell S, Cooper RG, Lundberg IE, Miller FW, Gregersen PK, Bowes J, Vencovsky J, Danko K, Limaye V, Selva-O'Callaghan A, Hanna MG, Machado PM, Pachman LM, Reed AM, Rider LG, Cobb J, Platt H, Molberg Ø, Benveniste O, Mathiesen P, Radstake T, Doria A, De Bleecker J, De Paepe B, Maurer B, Ollier WE, Padyukov L, O'Hanlon TP, Lee A, Amos CI, Gieger C, Meitinger T, Winkelmann J, Wedderburn LR, Chinoy H, Lamb JA; Myositis Genetics Consortium. Dense genotyping of immune-related loci in idiopathic inflammatory myopathies confirms HLA alleles as the strongest genetic risk factor and suggests different genetic background for major clinical subgroups. Ann Rheum Dis. 2015 Sep 11. pii: annrheumdis-2015-208119. doi: 10.1136/annrheumdis-2015-208119. [Epub ahead of print] PubMed PMID: 26362759.

Gang Q, Bettencourt C, Machado PM, Fox Z, Brady S, Healy E, Parton M, Holton JL, Hilton-Jones D, Shieh PB, Zanoteli E, De Paepe B, De Bleecker J, Shaibani A, Ripolone M, Violano R, Moggio M, Barohn RJ, Dimachkie MM, Mora M, Mantegazza R, Zanotti S, Hanna MG, Houlden H; Muscle Study Group and the International IBM Genetics Consortium. The effects of an intronic polymorphism in TOMM40 and APOE genotypes in sporadic inclusion body myositis. Neurobiol Aging. 2015 Apr;36(4):1766.e1-3. doi: 10.1016/j.neurobiolaging.2014.12.039. Epub 2015 Jan 14. PubMed PMID: 25670332; PubMed Central PMCID: PMC4378665.

Herbert MK, Stammen-Vogelzangs J, Verbeek MM, Rietveld A, Lundberg IE, Chinoy H, Lamb JA, Cooper RG, Roberts M, Badrising UA, De Bleecker JL, Machado PM, Hanna MG, Plestilova L, Vencovsky J, van Engelen BG, Pruijn GJ. Disease specificity of autoantibodies to cytosolic 5'-nucleotidase 1A in sporadic inclusion body myositis versus known autoimmune diseases. Ann Rheum Dis. 2015 Feb 24. pii: annrheumdis-2014-206691. doi: 10.1136/annrheumdis-2014-206691. [Epub ahead of print] PubMed PMID: 25714931; PubMed Central PMCID: PMC4699257.

Machado PM, Ahmed M, Brady S, Gang Q, Healy E, Morrow JM, Wallace AC, Dewar L, Ramdharry G, Parton M, Holton JL, Houlden H, Greensmith L, Hanna MG. Ongoing developments in sporadic inclusion body myositis. Curr Rheumatol Rep. 2014 Dec;16(12):477. doi: 10.1007/s11926-014-0477-9. Review. PubMed PMID: 25399751; PubMed Central PMCID: PMC4233319.

Machado PM, Dimachkie MM, Barohn RJ. Sporadic inclusion body myositis: new insights and potential therapy. Curr Opin Neurol. 2014 Oct;27(5):591-8. doi: 10.1097/WCO.0000000000000129. PubMed PMID: 25159931; PubMed Central PMCID: PMC4248565.

Gang Q, Bettencourt C, Machado P, Hanna MG, Houlden H. Sporadic inclusion body myositis: the genetic contributions to the pathogenesis. Orphanet J Rare Dis. 2014 Jun 19;9:88. doi: 10.1186/1750-1172-9-88. Review. PubMed PMID: 24948216; PubMed Central PMCID: PMC4071018.

Hiscock A, Dewar L, Parton M, Machado P, Hanna M, Ramdharry G. Frequency and circumstances of falls in people with inclusion body myositis: a questionnaire survey to explore falls management and physiotherapy provision. Physiotherapy. 2014 Mar;100(1):61-5. doi: 10.1016/j.physio.2013.06.002. Epub 2013 Aug 15. PubMed PMID: 23954023

Machado P, Brady S, Hanna MG. Update in inclusion body myositis. Curr Opin Rheumatol. 2013 Nov;25(6):763-71. doi: 10.1097/01.bor.0000434671.77891.9a. Review. PubMed PMID: 24067381; PubMed Central PMCID: PMC4196838.

Cortese A, Machado P, Morrow J, Dewar L, Hiscock A, Miller A, Brady S, Hilton-Jones D, Parton M, Hanna MG. Longitudinal observational study of sporadic inclusion body myositis:

implications for clinical trials. Neuromuscul Disord. 2013 May;23(5):404-12. doi: 10.1016/j.nmd.2013.02.010. Epub 2013 Mar 11. PubMed PMID: 23489664.
Machado P, Miller A, Holton J, Hanna M. Sporadic inclusion body myositis: an unsolved mystery. Acta Reumatol Port. 2009 Apr-Jun;34(2A):161-82. Review. PubMed PMID: 19474772.

Next Destination:
(initial) Clinical Research Associate, UCL/UCLH/NHNN
(most recent) NIHR Researcher and Honorary Consultant in Rheumatology and Muscle Diseases, UCL/UCLH/NHNN

Alex Rossor

PhD Dates: 2010-2014

PhD Title: A clinical and in-vitro study of the distal hereditary motor neuropathies

Supervisors: Professor Mary M Reilly, Professor Linda Greensmith

Project Description:
During my PhD I investigated the pathomechanisms of Hereditary Motor Neuropathy (HMN) and undertook a natural history study of patients with distal HMN.
During the first part of my PhD I investigated the pathomechanism of dHMN due to homozygous mutations in the heat shock protein HSJ1, using primary motor neurons (MNs) from HSJ1 knockout mice. Using live cell confocal imaging I examined mitochondrial axonal transport and ER calcium levels, but found no evidence of axonal transport deficits or ER stress.
In the second part of my PhD I examined the pathomechanism of dHMN due to a novel mutation in FBXO38. FBXO38 modulates the transcriptional activity of KLF7; a transcription factor with a role in neuronal development and repair. I therefore examined neurite outgrowth in lentivirus-infected primary MNs and demonstrated a reduction in neurite outgrowth in mutant FBXO38 infected MNs.
During the latter part of my PhD I identified a mutation in a new disease gene, BICD2, in a family with a form of Spinal Muscular Atrophy (SMA) termed lower extremity dominant SMA. BICD2 is a dynein adaptor protein and using immunoprecipitation I found that two disease mutations in BICD2 increase dynein binding affinity.
In the final part of my PhD I performed a genetic study of the HMNs and showed that mutations in HSPB1 are the most common cause of dHMN. I also evaluated plasma neurofilament heavy chain (NFH) as a biomarker of disease activity in the inherited neuropathies but was unable to detect a difference between patients and healthy volunteers. This would suggest that plasma NFH levels are not a suitable biomarker of disease activity in the inherited neuropathies.

Significant Publications whilst at Centre:

Rossor AM, Oates EC, Salter HK, Liu Y, Murphy SM, Schule R, Gonzales MA, Scoto M, Phadke R, Sewry CA et al. Reply: The p.Ser107Leu in BICD2 is a mutation “hot spot” causing distal spinal muscular atrophy. Brain. 2015; epub ahead of print 26063657
Rossor AM, Evans MRB, Reilly MM. A practical approach to the genetic neuropathies. Pract Neurol. 2015;**15**:187–98. PMID:25898997
Scoto M*, **AM Rossor***, MB Harms, S Cirak, M Calissano, S Robb, AY Manzur, AM Arroyo, AR Sanz, S Mansour, et al. The clinical phenotype of congenital Spinal Muscular Atrophy with lower limbs predominance (SMA-LED) due to mutations in the tail domain of the Cytoplasmic Dynein Heavy Chain 1 (*DYNC1H1)*. Neurology. 2015;**84**:668-79. ***These authors contributed equally to this work PMID: 25609763
Rossor AM*, EC Oates*, HK Salter, Y Liu, SM Murphy, R Schule, MA Gonzales, M Scoto, R Phadke, CA Sewry, et al. Phenotypic and molecular insights into Spinal Muscular Atrophy due to mutations in Bicaudal-D2. Brain. 2015;**138**:293–310. ***These authors contributed equally to this work
PMID: 25497877
Rossor, A. M., F. Perry, A. Botha and F. Norwood (2014). "Opsoclonus myoclonus syndrome due to squamous cell carcinoma of the oesophagus." BMJ Case Rep. pii: bcr2013202849. doi: 10.1136/bcr-2013-202849.
PMID: 24591387
Sumner CJ, d’Ydewalle C, Wooley J, Fawcett KA, Hernandez D, Gardiner AR, Kalmar B, Baloh RH, Gonzalez M, Zuchner S, Stanescu HC, Kleta R, Mankodi A, Cornblath DR, Boylan KB, Reilly MM, Greensmith L, Singleton AB, Harms MB, **Rossor AM**, Houlden H. Dominant mutation of *FBXO38* causes distal spinal muscular atrophy with calf predominance. *Am J Hum Genet*. 2013;93(5):976-83.
PMID: 24207122
Rossor AM, Polke J, Houlden H, Reilly MM. Clinical Implications of Genetic Advances in Charcot-Marie-Tooth Disease. *Nature Reviews Neurology*. 2013;9(10):562-571
PMID: 24018473
Oates EC*****, **Rossor AM***, Hafezparast M et al. Mutations in BICD2 cause Dominant Congenital Spinal Muscular Atrophy and Hereditary Spastic Paraplegia. *Am J Hum Genet*. 2013;92(6):965-73 * These authors contributed equally to this work.
PMID: 23664120
Cottenie E, Menezes MP, **Rossor AM** et al. Rapidly progressive asymmetrical weakness in Charcot-Marie-Tooth disease type 4J resembles chronic inflammatory demyelinating polyneuropathy. *Neuromuscul Disord*. 2013;23(5):399-403
PMID: 23489662
Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. *Journal of neurology, neurosurgery, and psychiatry* 2012;83(7):706-10.
PMID: 22577229
Rossor AM, Murphy S, Reilly MM. Knee bobbing in Charcot-Marie-Tooth disease. *Practical neurology* 2012;12(3):182-3
PMID: 22661351
Rossor AM, Davidson GL, Blake J, et al. A novel p.Glu175X premature stop mutation in the C-terminal end of HSP27 is a cause of CMT2. *Journal of the peripheral nervous system : JPNS* 2012;17(2):201-05. PMID: 22734906
Jaffer F, Murphy SM, Scoto M, et al. BAG3 mutations: another cause of giant axonal neuropathy. *Journal of the peripheral nervous system : JPNS* 2012;17(2):210-16.
PMID: 22734908

Rossor AM, Kalmar B, Greensmith L, Reilly MM. The distal hereditary motor neuropathies. *J Neurol Neurosurg Psychiatry*. 2011
PMID: 22028385
Next Destination:

Following my PhD I returned to full time clinical training in neurology. I am currently undertaking a post CCT fellowship in neuromuscular diseases and in August 2016 will start a Wellcome Trust Post Doctoral Clinical Fellowship in Professor Schiavo's laboratory as part of the Centre for Neuromuscular Diseases.

Next destination: (current) Wellcome trust post doctoral fellowship for clinicians and honorary consultant neurologist

Jasper Morrow

PhD dates: 2009 - 2014

PhD Title: Development of Quantitative MRI as an Outcome Measure in Neuromuscular Diseases

Supervisors: Professor Michael Hanna, Professor Mary M Reilly and Professor Tarek Yousry

Lack of sensitive outcome measures is a major obstacle to clinical trials in many neuromuscular diseases (NMD). Lower limb muscle MRI allows non-invasive visualisation of acute and chronic pathology in NMD. This thesis assessed the reliability, validity and responsiveness of quantitative MRI in chronic neuromuscular diseases.

A comprehensive quantitative MRI protocol of lower limb muscles was developed including T1, T2, fat fraction and magnetisation transfer ratio (MTR) measurements. The protocol was assessed for reliability and sensitivity to physiological variation in 47 healthy volunteers with 15 rescanned at a two week interval. This protocol was then performed together with detailed clinical assessments and isokinetic/isometric dynamometry in 20 patients with inclusion body myositis (IBM), 20 patients with Charcot-Marie-Tooth disease (CMT) and matched health volunteers twice at a 12 month interval.

In the healthy volunteers, the inter-scan and inter-observer reliability was high (ICC 0.62-0.99) despite small observed physiological variation of between subjects. Fat fraction, T2 and MTR showed significant correlations with subject age in thigh and calf muscles and with subject weight in thigh muscles whereas gender did not influence quantitative parameters. Cross-sectional analysis showed strong correlations with both muscle strength and clinical severity measures demonstrating validity of MRI measurements as outcome measures. Longitudinal assessment demonstrated that excellent sensitivity to change of MRI measures; in particular muscle fat fraction quantification exceeded that of myometry and clinical measurements with standardised response mean over 12 months of 1.1 in IBM and 0.8 in CMT indicating a high level of responsiveness. Annual change in fat fraction could be predicted based on baseline MRI measurements, providing the opportunity to improve SRM further. This thesis demonstrates the reliability, validity and responsiveness of quantitative MRI as an outcome measure providing a comprehensive practical protocol for clinical trials in NMD.

Significant Publications:

Finlayson S, Morrow JM, Rodriguez Cruz PM, Sinclair CDJ, Fischmann A, Thornton JS, Knight S, Norbury R, White M, Al-Hajjar M, Carboni N, Jayawant S, Robb SA, Yousry TA, Beeson D, Palace J. Muscle MRI in congenital myasthenic syndromes. Muscle Nerve. 2016 Jan 20; PMID: 26789134

Pitceathly RDS, Morrow JM, Sinclair CDJ, Woodward C, Sweeney MG, Rahman S, Plant GT, Ali N, Bremner F, Davagnanam I, Yousry TA, Hanna MG, Thornton JS. Extra-ocular muscle MRI in genetically-defined mitochondrial disease. Eur Radiol. 2016 Jan;26(1):130–137. PMID: 25994195

Morrow JM, Sinclair CDJ, Fischmann A, Machado PM, Reilly MM, Yousry TA, Thornton JS, Hanna MG. MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study. Lancet Neurol. 2016 Jan;15(1):65–77. PMCID: PMC4672173

Suetterlin KJ, Bugiardini E, Kaski JP, Morrow JM, Matthews E, Hanna MG, Fialho D. Long-term Safety and Efficacy of Mexiletine for Patients With Skeletal Muscle Channelopathies. JAMA Neurol. 2015 Dec 1;72(12):1531–1533. PMID: 26658970

Morrow JM, Reilly MM. Early detection of nerve injury in transthyretin-related familial amyloid polyneuropathy. Brain. 2015 Mar;138(Pt 3):507–509. PMID: 25713400

Machado PM, Ahmed M, Brady S, Gang Q, Healy E, Morrow JM, Wallace AC, Dewar L, Ramdharry G, Parton M, Holton JL, Houlden H, Greensmith L, Hanna MG. Ongoing developments in sporadic inclusion body myositis. Curr Rheumatol Rep. 2014 Dec;16(12):477. PMCID: PMC4233319

Morrow JM, Sinclair CDJ, Fischmann A, Reilly MM, Hanna MG, Yousry TA, Thornton JS. Reproducibility, and age, body-weight and gender dependency of candidate skeletal muscle MRI outcome measures in healthy volunteers. Eur Radiol. 2014 Jul;24(7):1610–1620. PMCID: PMC4046083

Willis TA, Hollingsworth KG, Coombs A, Sveen M-L, Andersen S, Stojkovic T, Eagle M, Mayhew A, de Sousa PL, Dewar L, Morrow JM, Sinclair CDJ, Thornton JS, Bushby K, Lochmuller H, Hanna MG, Hogrel J-Y, Carlier PG, Vissing J, Straub V. Quantitative magnetic resonance imaging in limb-girdle muscular dystrophy 2I: a multinational cross-sectional study. PLoS ONE. 2014;9(2):e90377. PMCID: PMC3938727

Fischmann A, Morrow JM, Sinclair CDJ, Reilly MM, Hanna MG, Yousry T, Thornton JS. Improved anatomical reproducibility in quantitative lower-limb muscle MRI. J Magn Reson Imaging. 2013 Oct 7; PMID: 24123788

Morrow JM, Matthews E, Raja Rayan DL, Fischmann A, Sinclair CDJ, Reilly MM, Thornton JS, Hanna MG, Yousry TA. Muscle MRI reveals distinct abnormalities in genetically proven non-dystrophic myotonias. Neuromuscul Disord. 2013 Aug;23(8):637–646. PMID: 23810313

Morrow JM, Reilly MM, Hanna MG. Reliability and accuracy of skeletal muscle imaging in limb-girdle muscular dystrophies. Neurology. 2013 Jun 11;80(24):2276. PMID: 23905174

Cortese A, Machado P, Morrow J, Dewar L, Hiscock A, Miller A, Brady S, Hilton-Jones D, Parton M, Hanna MG. Longitudinal observational study of sporadic inclusion body myositis: implications for clinical trials. Neuromuscul Disord. 2013 May;23(5):404–412. PMID: 23489664

Morrow JM, Pitceathly RDS, Quinlivan RM, Yousry TA. Muscle MRI in Bethlem myopathy. Case Reports. 2013 Apr 16;2013(apr16 1):bcr2013008596–bcr2013008596.

Cottenie E, Menezes MP, Rossor AM, Morrow JM, Yousry TA, Dick DJ, Anderson JR, Jaunmuktane Z, Brandner S, Blake JC, Houlden H, Reilly MM. Rapidly progressive asymmetrical weakness in Charcot-Marie-Tooth disease type 4J resembles chronic inflammatory demyelinating polyneuropathy. Neuromuscul Disord. 2013 Mar 12; PMID: 23489662

Pitceathly RDS, Tomlinson SE, Hargreaves I, Bhardwaj N, Holton JL, Morrow JM, Evans J, Smith C, Fratter C, Woodward CE, Sweeney MG, Rahman S, Hanna MG. Distal myopathy with cachexia: an unrecognised phenotype caused by dominantly-inherited mitochondrial polymerase γ mutations. J Neurol Neurosurg Psychiatr. 2013 Jan;84(1):107–110. PMID: 22933815

Willis TA, Hollingsworth KG, Coombs A, Sveen M-L, Andersen S, Stojkovic T, Eagle M, Mayhew A, de Sousa PL, Dewar L, Morrow JM, Sinclair CDJ, Thornton JS, Bushby K, Lochmüller H, Hanna MG, Hogrel J-Y, Carlier PG, Vissing J, Straub V. Quantitative Muscle MRI as an Assessment Tool for Monitoring Disease Progression in LGMD2I: A Multicentre Longitudinal Study. PLoS ONE. 2013;8(8):e70993. PMID: 23967145
Sinclair CDJ, Morrow JM, Hanna MG, Reilly MM, Yousry TA, Golay X, Thornton JS. Correcting radiofrequency inhomogeneity effects in skeletal muscle magnetisation transfer maps. NMR Biomed. 2012 Feb;25(2):262–270. PMID: 21796708
Sinclair CDJ, Morrow JM, Miranda MA, Davagnanam I, Cowley PC, Mehta H, Hanna MG, Koltzenburg M, Yousry TA, Reilly MM, Thornton JS. Skeletal muscle MRI magnetisation transfer ratio reflects clinical severity in peripheral neuropathies. J Neurol Neurosurg Psychiatr. 2012 Jan;83(1):29–32. PMID: 21613652
Sinclair CDJ, Miranda MA, Cowley P, Morrow JM, Davagnanam I, Mehta H, Hanna MG, Koltzenburg M, Reilly MM, Yousry TA, Thornton JS. MRI shows increased sciatic nerve cross sectional area in inherited and inflammatory neuropathies. J Neurol Neurosurg Psychiatr. 2011 Nov;82(11):1283–1286. PMID: 20971754
Morrow JM, Reilly MM. The Babinski sign. Br J Hosp Med (Lond). 2011 Oct;72(10):M157–159. PMID: 22041660

Next Destination:
Consultant Neurologist, National Hospital for Neurology & Neurosurgery, & Lister Hospital, Stevenage

Robert Pitceathly

PhD Dates: 2009 - 2013

Phd Title: Clinical and Molecular Genetic Studies in Mitochondrial Disease

Supervisors: Professor Michael G Hanna, Professor Shamima Rahman

Project Description:
The research undertaken whilst working towards my PhD at the MRC Centre for Neuromuscular Diseases aimed to establish the molecular basis of mitochondrial disease in adult patients attending the Queen Square UK Specialised Service for Rare Mitochondrial Disease out-patient clinic, and evaluate genotype/phenotype correlations. Both novel clinical syndromes and molecular causes of disease were identified and new insights into the protein structure of the respiratory chain were elucidated.

Significant Publications whilst at Centre
Pitceathly RDS, Rahman S, Wedatilake Y, et al. *NDUFA4* mutations underlie dysfunction of a cytochrome *c* oxidase subunit linked to human neurological disease. *Cell Rep.* 2013 Jun 27;3(6):1795–805.
Morrow JM, **Pitceathly RDS**, Quinlivan R, Yousry T. Muscle MRI in Bethlem Myopathy. *BMJ case reports*. Published Online: 2013 Apr 16;2013.
Nesbitt V, **Pitceathly RDS**, Turnbull DM, et al. The UK MRC Mitochondrial Disease Patient Cohort Study: clinical phenotypes associated with the m.3243A>G mutation - implications for diagnosis and management. *J Neurol Neurosurg Psychiatry.* 2013 Aug;84(8):936-8.
Pitceathly RDS, Smith C, Fratter C, et al. Adults with *RRM2B*-related mitochondrial disease have distinct clinical and molecular characteristics. *Brain.* 2012 Nov;135(Pt 11):3392-403.
Pitceathly RDS, Tomlinson SE, Hargreaves I, et al. Distal myopathy with cachexia: an unrecognised phenotype caused by dominantly-inherited mitochondrial polymerase γ mutations. *J Neurol Neurosurg Psychiatry*. 2013 Jan;84(1):107-10.
Pitceathly RDS, Murphy SM, Cottenie E, et al. Genetic dysfunction of *MT-ATP6* causes axonal Charcot-Marie-Tooth disease. *Neurology*. 2012 Sep 11;79(11):1145-54.
Pitceathly RDS, Rahman S, Hanna MG. Single deletions in mitochondrial DNA - Molecular mechanisms and disease phenotypes in clinical practice. *Neuromuscul Disord*. 2012 Jul;22(7):577–86.
Elson JL, Sweeney MG, Procaccio V, Yarham JW, Salas A, Kong Q-P, van der Westhuizen FH, **Pitceathly RDS**, et al. Towards a mtDNA locus-specific mutation database using the LOVD platform. *Hum Mutat.* 2012 Sep;33(9):1352-8.
Pitceathly RDS, Fassone E, Taanman J-W, et al. Kearns-Sayre syndrome caused by defective R1/p53R2 assembly. *J Med Genet*. 2011;48(9):610–617.

Next Destination:
(initial)
StR Neurology, South London Deanery
(most recent)
NIHR Academic Clinical Lecturer in Neurology

Dipa Raja Ryan

PhD Dates: 2009-2015

PhD Title: A Clinical and Genetic Study of the Skeletal Muscle Channelopathies

Supervisors: Professor M Hanna, Professor D Kullmann

Project Description:
My project aimed to increase the current understanding of the clinical and genetic basis of the skeletal muscle channelopathies. It investigated the overall prevalence in England as 1.12/100,000 and determined the individual minimum prevalence of each disease, which has not previously been documented. I also conducted a detailed phenotype study of periodic paralysis (PP),
paramyotonia congenita (PMC) and sodium channel myotonia (SCM), which was the first comparative study of these diseases. In the process it uncovered the marked similarity between
PMC and SCM and suggested that these may be a spectrum of one disease, rather than two distinct diseases as traditionally thought. It provided the first systematic study of pregnancy and anaesthetics in a large number of channelopathy patients, identifying a marked increase in severity of symptoms during pregnancy that has not previously been documented.
To widen the spectrum of genetic diagnosis and techniques in this group of diseases, this project identified the first cases of large scale rearrangements in CLCN1 causing myotonia congenita. I also utilised whole exome sequencing, to increase the genetic diagnosis rate, including two cases that may be explained by variations in RYR1 and another case in which a genetic diagnosis of Liddle's syndrome may underlie secondary PP. This suggests that RYR1 variations may account for some unconfirmed cases and others may be explained by genetic causes of secondary PP.
Finally I conducted the UK part of an international study presenting convincing evidence of the efficacy of mexiletine in non-dystrophic myotonia in a double-blind placebo-controlled trial. It demonstrated improvement of the primary outcome measure of patient-reported stiffness and the majority of secondary outcome measures assessed.

Significant Publications whilst at Centre:
Morrow, J. M., Matthews, E., Raja Rayan, D. L. , Fischmann, A., Sinclair, C. D. J., Reilly, M. M.,
Thornton, J.S., Hanna, M.G., Yousry, T. A. (2013). Muscle MRI reveals distinct abnormalities in genetically proven non-dystrophic myotonias. Neuromuscular Disorders, 23(8), 637-646. PMID: 23810313
Horga, A., Rayan, D. L. R. , Matthews, E., Sud, R., Fialho, D., Durran, S. C. M., Burge, J.A., Portaro S.,Davis, M.B., Haworth, A., Hanna, M. G. (2013). Prevalence study of genetically defined skeletal muscle channelopathies in England. Neurology, 80(16), 1472-1475. PMID: 23516313
Trivedi, J. R., Bundy, B., Statland, J., Salajegheh, M., Rayan, D. R. , Venance, S. L., Wang, Y., Fialho,
D., Matthews E., Cleland, J., Gorhm, N., Herbelin, L., Cannon, S. Amato, A., Griggs, R.C., Hanna,
M.G., Barohn, R.J., CINCH Consortium. (2013). Non-dystrophic myotonia: prospective study

of objective and patient reported outcomes.. Brain, 136(Pt 7), 2189-2200. PMID: 23771340
Statland, J. M., Bundy, B. N., Wang, Y., Rayan, D. R. , Trivedi, J. R., Sansone, V. A., Salajegheh, M. K.,et al. (2012). Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. JAMA: the journal of the American Medical Association, 308(13), 1357-65. PMID: 23032552
Statland, J. M., Bundy, B. N.,Wang, Y., Trivedi, J. R., Raja Rayan, D. , Herbelin, L, et al and the CINCH Consortium. (2012). A quantitative measure of handgrip myotonia in non-dystrophic myotonia.. Muscle Nerve, 46(4), 482-489. PMID: 22987687
Raja Rayan DL , Haworth A, Sud R, Matthews E, Fialho D, Burge J, Portaro S, Schorge S, Tuin K,
Lunt P, et al. A new explanation for recessive myotonia congenita: Exon deletions and duplications in CLCN1. Neurology 78(24):1953-1958 12 Jun 2012. PMID: 22649220

Next destination:
Neurology SpR Training post in London at Royal Free Hospital and National Hospital for Neurology and Neurosurgery

Jennifer Spillane

Phd Dates: 2009-2013

PhD Title: Clinical and functional studies in autoimmune disorders of neuromuscular transmission

Project Description:
I combined clinical and laboratory based research to study the autoimmune disorders of neuromuscular transmission; Myasthenia Gravis (MG) and Lambert Eaton Myasthenic Syndrome (LEMS). I examined the long term outcome of patients with MG focusing on outcome following thymectomy and prognosis following a severe exacerbation of Myasthenia Gravis. In the lab. I used a variety of techniques including immunohistochemistry, electrophysiology and synaptic vesicle imaging to examine how LEMS antibodies affect neuromuscular transmission.

Supervisors: Professor DM Kullmann, Professor MG Hanna

Significant Publications whilst at Centre
Spillane, J., Beeson, D.J., and Kullmann, D.M. (2010). Myasthenia and related disorders of the neuromuscular junction. J. Neurol. Neurosurg. Psychiatry *81*, 850–857. PMID: 20547629
Spillane, J., and Kullmann, D. (2010). History central to diagnosing myasthenia gravis. The Practitioner *254*, 15–18, 2. PMID:2113318
Leite, M.I., Coutinho, E., Lana-Peixoto, M., Apostolos, S., Waters, P., Sato, D., Melamud, L., Marta, M., Graham, A., Spillane, J., et al. (2012). Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. Neurology *78*, 1601–1607. PMID: 22551731
Rajakulendran, S., Viegas, S., Spillane, J., and Howard, R.S. (2012). Clinically biphasic myasthenia gravis with both AChR and MuSK antibodies. J. Neurol. *259*, 2736–2739. PMID: 22955633
Spillane, J., Higham, E., and Kullmann, D.M. (2012). Myasthenia gravis. BMJ *345*, e8497. PMID: 23261848
Finlayson, S., Spillane, J., Kullmann, D.M., Howard, R., Webster, R., Palace, J., and Beeson, D. (2013). Slow channel congenital myasthenic syndrome responsive to a combination of fluoxetine and salbutamol. Muscle Nerve *47*, 279–282.
Spillane, J., Hayward, M., Hirsch, N.P., Taylor, C., Kullmann, D.M., and Howard, R.S. (2012). Late recurrent thymoma in myasthenia gravis: a case series. J. Neurol. Neurosurg. Psychiatry *83*, 1030–1031. PMID: 22767383
Spillane, J., Hayward, M., Hirsch, N.P., Taylor, C., Kullmann, D.M., and Howard, R.S. (2013). Thymectomy: role in the treatment of myasthenia gravis. J. Neurol. *260*, 1798–1801. PMID: 23508539
Spillane J, Fialho D, Hanna MG. (2013) Diagnosis of skeletal muscle channelopathies. Expert Opin Med Diagn 2013 Nov;7(6):517-29, PMID: 24066928
Spillane, J., Hirsch, N.P., Kullmann, D.M., Taylor, C., and Howard, R.S. (2014). Myasthenia gravis--treatment of acute severe exacerbations in the intensive care unit results in a favourable long-term prognosis. Eur. J. Neurol. *21*, 171–173. PMID:23398500

Spillane J., Ermolyuk Y., Cano-Jaimez M., Lang B., Vincent A., Volynski KE., Kullmann DM. (2014). Lambert-Eaton syndrome IgG inhibits transmitter release via P/Q Ca^{2+} channels. Neurology. 2015 Jan 14 PMID:25589670
Spillane J, Kullmann DM, Hanna MG. Genetic neurological channelopathies: molecular genetics and clinical phenotypes. J Neurol Neurosurg Psychiatry (2016) Jan; 87 (1) 37-48 PMID: 26558925

Next Destination:
Royal Free Hospital and NHNN, Queen Square (to complete SpR training in Neurology)

Adrian Miller

PhD Dates: 2008-2014

PhD Title: Development of New Therapeutic Strategies for Sporadic Inclusion Body Myositis

Supervisors: Professors M Hanna and L Greensmith

Project Description:

This translational project incorporated two strands. First, IBM-relevant pathological outcome measures were developed and characterised in vitro, using primary satellite cell cultures either transfected with beta-amyloid or exposed to inflammatory mediators. Using this model, the effects of heat shock response augmentation, using the heat shock factor co-inducer Arimoclomol, were examined. The second arm of the project established a Phase IIa safety and tolerability study of Arimoclomol in patients with IBM.

Next Destination:
(Initial) continued in clinical neurology training
(Most recent) Consultant Neurologist with subspecialty interest in NM disease

James Burge

PhD Dates: 2008 - 2012

PhD Title: Mechanisms of Phenotypic Variability in Myotonia Congenita

Supervisors: Professor MG Hanna, Dr. S. Schorge

Project Description:
The severity of Myotonia Congenita varies not only across individuals with different CLCN1 genotypes, but also within a pedigree, and can even fluctuate over time within a single individual in response to environmental circumstances. The functional consequences of eight naturally occurring sequence variants in the skeletal muscle chloride channel gene, CLCN1, were examined by whole cell patch-clamp of HEK293T cells expressing the gene product, ClC-1, in order to investigate potential differences in their mechanisms of pathogenicity. G276D and G523D caused complete loss of function, while S289G produced altered kinetics and a marked depolarizing shift of voltage dependence. H369P, A566T and M646T all tested normal in the HEK293T assay despite strong clinical support for pathogenicity. Their mechanism of pathogenicity may rely on muscle-specific processes that are not faithfully recapitulated in HEK293T cells. W118G and P744T were selected as examples of variants for which pathogenicity is unclear from the clinical evidence. The former is present in controls, but over-represented in the Myotonia Congenita population. The latter is present in an individual who also harbours a large deletion in CLCN1. Both variants tested normal in the HEK293T assay.

A potent trigger for worsening of myotonia in some female patients is pregnancy. In order to clarify the role of sex hormones in non-genomic modulation of skeletal muscle excitability, the effects of progesterone and oestrogen on endogenous chloride currents through the wildtype ClC-1 of mouse skeletal muscle were tested by whole cell patch clamp. Progesterone and oestrogen rapidly reduced the chloride conductance and shifted its voltage dependence, thus a non-genomic mechanism exists in skeletal muscle linking sex hormones to ClC-1. However the effect was only significant at 500 times the highest physiological concentration encountered in pregnancy.

The macroscopic chloride conductance of a membrane expressing wildtype ClC-1 was simulated in Matlab. The simulation improves on published models by recapitulating both time-dependence and voltage-dependence of the channel through a method based on independent representations of the fast and the slow gates. The applicability of the model for the purposes of exploring the effects of specific mutations was assessed by attempting to simulate the currents through S289G channels; the effects of S289G could be mimicked by slowing and inverting the kinetics of the fast gate and shifting the fast gate opening probability to more depolarized potentials. The mechanism of low chloride conductance myotonia and electrical factors likely to impact on its severity are discussed in the context of experiments conducted in a model of myotonic muscle. Slowing of ClC-1 kinetics alone did not produce myotonia, but could lower the threshold for myotonia caused by shifts in voltage dependence. Muscle fibre diameter is an important factor in the propensity to myotonia, which can be driven by asynchrony between surface and t-tubular action potentials in large muscle fibres. Increasing muscle fibre diameter could underlie the age-dependence of symptom onset in Myotonia Congenita, and differences in diameter could contribute to phenotypic variability, including male-female differences.

Significant Publications:
First author:
Burge JA, Hanna MG Novel Insights into the Pathomechanisms of Skeletal Muscle Channelopathies. Curr Neurol Neurosci Rep. 2012; 12(1):62-9.
Burge J. From alpha to omega: a paradox is unraveling in hypokalaemic periodic Paralysis ACNR 2012;11(6): 20
Burge J, Hanna MG, Schorge S. Non-genomic actions of progesterone and 17b-estradiol on the chloride conductance of skeletal muscle. Muscle Nerve 2013 Apr 26 (epub ahead of print)

Burge J, Hanna MG Channelopathies of skeletal muscle in Rabi N. Tawil and Shannon Venance (eds.), Neuromuscular Disorders (Wiley-Blackwell).
Contributor
Tan SV, Matthews E, Barber M, Burge JA, Rajakulendran S, Fialho D, et al. Refined exercise testing can aid dna-based diagnosis in muscle channelopathies. Ann Neurol 2011;69(2):328-340.
Dipa L Raja Rayan, Andrea Haworth, Richa Sud, Emma Matthews, Doreen Fialho, James Burge, Simona Portaro, Stephanie Schorge, Kiki Tuin, Peter Lunt, Meriel McEntagart, Antonio Toscano, Mary B Davis, and Michael G Hanna A new explanation for recessive Myotonia Congenita - exon deletions and duplications in CLCN1 Neurology 2012;78(24):1953-8
Michell AW, Gaitatzis A., Burge J., Reilly M.M., Kapoor R., Koltzenburg M., Isolated motor conduction block associated with infliximab. J.Neurol.2012; 259(1):1578-60
Raheem O, Penttila S, Suominen T, Kaakinen M, Burge J, Haworth A, et al. New immunohistochemical method for improved myotonia and chloride channel mutation diagnostics. Neurology 2012;79(22):2194-200.
Horga A, Raja Rayan DL, Matthews E, Sud R, Fialho D, Durran SC, Burge JA, Portaro S, Davis MB, Haworth A, Hanna MG. Prevalaence study of genetically defined skeletal muscle channelopathies in England. Neurology 2013; 80(16):1472-5

Next destination:
(Initial) National Hospital for Neurology & Neurosurgery, Queen Square, London
(Current) Consultant, Kings College Hospital NHS Foundation Trust, Denmark Hill, London

Emma Matthews

PhD Dates: 2006 - 2013

PhD Title: The skeletal muscle channelopathies: phenotype, genotype and pathogenesis

Supervisors: Professor Michael Hanna and Dr Stephanie Schorge

Project Description:
The skeletal muscle channelopathies are a group of inherited disorders due to the dysfunction of voltage gated channels in the sarcolemma resulting in abnormal membrane excitability. Simplistically they are broadly divided into those that result from an “over excited” membrane (the non-dystrophic myotonias) and those due to an inexcitable one (the periodic paralyses). Skeletal muscle channelopathies were described clinically long before they were genotyped or hypotheses regarding pathogenesis fully evolved. My thesis explored the phenotype, the genotype and recent insights into the pathogenesis.
Detailed clinical and neurophysiologic examination of a large group of patients identified new aspects of the phenotype including neonatal presentations with important implications for early life care. Morphological findings were also expanded with the

presence of inflammatory infiltrates, not previously described in the channelopathies. Extensive DNA sequencing of causative genes was undertaken in a carefully genotyped cohort. In hypokalaemic periodic paralysis an exclusive relationship between mutations and the channel voltage sensor emerged which related closely to recent electrophysiological evidence of a “gating pore” disease mechanism. A small but significant minority of cases remained however where no mutation was found. The implication of other potential genetic mechanisms or even undescribed genes in these cases was discussed.
Current drug therapies were also examined in three separate cohorts and evidence suggested
acetazolamide, a commonly prescribed treatment, may only be effective in 50-60% of those with hypokalaemic periodic paralysis. A tentative relationship between efficacy and genotyped also emerged.
Patch clamp studies showed significant loss of function of the main alpha pore of the sodium channel in periodic paralysis but the implications of this in light of the “gating pore” hypothesis were discussed. Tentative explorations were made as to the viability of performing future studies in myoctes as opposed to the traditional HEK cell model with early experiments illustrating limitations.

Significant Publications arising from PhD:

Muscle MRI reveals distinct abnormalities in genetically proven non-dystrophic myotonias. Morrow JM, **Matthews E**, Raja Rayan DL, Fischmann A, Sinclair CD, Reilly MM, Thornton JS, Hanna MG, Yousry TA. Neuromuscul Disord. 2013 Aug;23(8):637-46.
Non-dystrophic myotonia: prospective study of objective and patient reported outcomes. Trivedi JR, Bundy B, Statland J, Salajegheh M, Rayan DR, Venance SL, Wang Y, Fialho D, **Matthews E**, Cleland J, Gorham N, Herbelin L, Cannon S, Amato A, Griggs RC, Hanna MG, Barohn RJ; CINCH Consortium. Brain. 2013 Jul;136(Pt 7):2189-200.
Prevalence study of genetically defined skeletal muscle channelopathies in England. Horga A, Raja Rayan DL, **Matthews E**, Sud R, Fialho D, Durran SC, Burge JA, Portaro S, Davis MB, Haworth A, Hanna MG. Neurology. 2013 Apr 16;80(16):1472-5
Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. Statland JM, Bundy BN, Wang Y, Rayan DR, Trivedi JR, Sansone VA, Salajegheh MK, Venance SL, Ciafaloni E, **Matthews E**, Meola G, Herbelin L, Griggs RC, Barohn RJ, Hanna MG; Consortium for Clinical Investigation of Neurologic Channelopathies. JAMA. 2012 Oct 3;308(13):1357-65.
A quantitative measure of handgrip myotonia in non-dystrophic myotonia. Statland JM, Bundy BN, Wang Y, Trivedi JR, Raja Rayan D, Herbelin L, Donlan M, McLin R, Eichinger KJ, Findlater K, Dewar L, Pandya S, Martens WB, Venance SL, **Matthews E**, Amato AA, Hanna MG, Griggs RC, Barohn RJ; CINCH Consortium. Muscle Nerve. 2012 Oct;46(4):482-9
A new explanation for recessive myotonia congenita: exon deletions and duplications in CLCN1. Raja Rayan DL, Haworth A, Sud R, **Matthews E**, Fialho D, Burge J, Portaro S, Schorge S, Tuin K, Lunt P, McEntagart M, Toscano A, Davis MB, Hanna MG. Neurology. 2012 Jun 12;78(24):1953-8.
A case of necrotizing myopathy with proximal weakness and cardiomyopathy. **Matthews E**, Plotz PH, Portaro S, Parton M, Elliott P, Humbel RL, Holton JL, Keegan BM, Hanna MG. Neurology. 2012 May 8;78(19):1527-32.
Acetazolamide efficacy in hypokalemic periodic paralysis and the predictive role of genotype. **Matthews E**, Portaro S, Ke Q, Sud R, Haworth A, Davis MB, Griggs RC, Hanna MG. Neurology. 2011 Nov 29;77(22):1960-4.
Sodium and chloride channelopathies with myositis: coincidence or connection? **Matthews E**, Miller JA, MacLeod MR, Ironside J, Ambler G, Labrum R, Sud R, Holton JL, Hanna MG. Muscle Nerve. 2011 Aug;44(2):283-8.
Refined exercise testing can aid DNA-based diagnosis in muscle channelopathies.

Tan SV, **Matthews E**, Barber M, Burge JA, Rajakulendran S, Fialho D, Sud R, Haworth A, Koltzenburg M, Hanna MG. Ann Neurol. 2011 Feb;69(2):328-40.
Infantile onset myofibrillar myopathy due to recessive CRYAB mutations. Forrest KM, Al-Sarraj S, Sewry C, Buk S, Tan SV, Pitt M, Durward A, McDougall M, Irving M, Hanna MG, **Matthews E**, Sarkozy A, Hudson J, Barresi R, Bushby K, Jungbluth H, Wraige E. Neuromuscul Disord. 2011 Jan;21(1):37-40. Epub 2010 Dec 3
Stridor as a neonatal presentation of skeletal muscle sodium channelopathy. **Matthews E**, Manzur AY, Sud R, Muntoni F, Hanna MG. Arch Neurol. 2011 Jan;68(1):127-9.
Muscle channelopathies: does the predicted channel gating pore offer new treatment insights for hypokalaemic periodic paralysis? **Matthews E**, Hanna MG. J Physiol. 2010 Jun 1;588(Pt 11):1879-86.
Multi-minicore disease and atypical periodic paralysis associated with novel mutations in the skeletal muscle ryanodine receptor (RYR1) gene. Zhou H, Lillis S, Loy RE, Ghassemi F, Rose MR, Norwood F, Mills K, Al-Sarraj S, Lane RJ, Feng L, **Matthews E,** Sewry CA, Abbs S, Buk S, Hanna M, Treves S, Dirksen RT, Meissner G, Muntoni F, Jungbluth H. Neuromuscul Disord. 2010 Mar;20(3):166-73.
The non-dystrophic myotonias: molecular pathogenesis, diagnosis and treatment. **Matthews E**, Fialho D, Tan SV, Venance SL, Cannon SC, Sternberg D, Fontaine B, Amato AA, Barohn RJ, Griggs RC, Hanna MG; the CINCH Investigators.Brain. 2010 Jan;133(Pt 1):9-22.
A patient with episodic ataxia and paramyotonia congenita due to mutations in KCNA1 and SCN4A. Rajakulendran S, Tan SV, **Matthews E**, Tomlinson SE, Labrum R, Sud R, Kullmann DM, Schorge S, Hanna MG. Neurology. 2009 Sep 22;73(12):993-5.
Voltage sensor charge loss accounts for most cases of hypokalemic periodic paralysis. **Matthews E**, Labrum R, Sweeney MG, Sud R, Haworth A, Chinnery PF, Meola G, Schorge S, Kullmann DM, Davis MB, Hanna MG. Neurology. 2009 May 5;72(18):1544-7.
Neonatal hypotonia can be a sodium channelopathy-recognition of a new phenotype. **Matthews E**, Guet A, Mayer M, Vicart S, Pemble S, Sternberg D, Fontaine B, Hanna MG. Neurology. 2008 Nov 18;71(21):1740-2.
Possible New Treatments in Muscular Dystrophy. **Matthews E**, Hanna MG. Advances in Clinical Neuroscience and Rehabilitation. 2008 March/April: 24-26.
What causes paramyotonia in the United Kingdom? Common and new SCN4A mutations revealed. **Matthews E**, Tan SV, Fialho D, Sweeney MG, Sud R, Haworth A, Stanley E, Cea G, Davis MB, Hanna MG. Neurology. 2008 Jan 1;70(1):50-3.
Skeletal-muscle channelopathies: periodic paralysis and nondystrophic myotonias. Ryan AM, **Matthews E**, Hanna MG. Curr Opin Neurol. 2007 Oct;20(5):558-63.

Next destination:

(initial): SPR Neurology Royal Free Hospital and National Hospital for Neurology and Neurosurgery
(current):Senior research fellow, UCL MRC CNMD

Doreen Fialho

PhD Dates: 2004 - 2009

PhD Title: Clinical, genetic and electrophysiological study of skeletal muscle channelopathies - new insights into Myotonia congenita and Andersen-Tawil syndrome

Supervisors: Professor Michael G. Hanna, Professor Dimitri M. Kullmann

Project Description:
This PhD focussed in particular on myotonia congenita, a skeletal muscle channelopathy characterised clinically by muscle stiffness and caused by mutations in the skeletal muscle chloride channel gene *CLCN1* .The project involved detailed genotype-phenotype analysis in an initial myotonia congenita cohort. The findings allowed the development of a screening strategy in a larger cohort. In total twenty-three novel novel mutations were identified. A high proportion of dominant mutations were observed to cluster in exon 8 of *CLCN1*. Four of these mutations were expressed using the Xenopus laevis oocyte expression system and loss of function and a dominant-negative effect in co-expression were demonstrated. The same expression system was also utilised to study the non-genomic effect of sex hormones on CLC-1 channel function. Novel inhibitory effects were found with application of testosterone and progesterone but not 17beta-estradiol. A further part of this study looked into repeat size of genes DMPK and ZNF9 causing myotonic dystrophy as a potential modifier of non-dystrophic myotonia. Andersen-Tawil syndrome is a rare skeletal muscle channelopathy characterised by the triad of periodic paralysis, cardiac arrhythmias and dystrophic features. A UK cohort of 17 families was investigated. Novel mutations and unusual clinical features were identified.

Significant Publications during PhD:
Matthews E, Fialho D, Tan SV, Venance SL, Cannon SC, Sternberg D, Fontaine B, Amato AA, Barohn RJ, Griggs RC, Hanna MG; CINCH Investigators. The non-dystrophic myotonias: molecular pathogenesis, diagnosis and treatment. *Brain.* 2010; 133: 9-22; PMID 19917643
Fialho D, Kullmann DM, Hanna MG, Schorge S. Non-genomic effects of sex hormones on CLC-1 may contribute to gender differences in myotonia congenita. *Neuromuscul Disord.* 2008;18(11): 869-72; PMID 18815035
Matthews E, Tan SV, Fialho D, Sweeney MG, Sud R, Haworth A, Stanley E, Cea G, Davis MB, Hanna MG. What causes paramyotonia in the United Kingdom? Common and new SCN4A mutations revealed. *Neurology*. 2008;70(1):50-3; PMID 18166706
Fialho D, Hanna MG. Periodic Paralysis. Handb Clin Neurol. 2007;86:77-106; PMID 18808996
Fialho D, Schorge S, Pucovska U, Davies NP, Labrum R, Haworth A, Stanley E, Sud R, Wakeling W, Davis MB, Kullmann DM, Hanna MG. Chloride channel myotonia: exon 8 hot-spot for dominant-negative interactions. *Brain*. 2007;130:3265-74; PMID 17932099
Venance SL, Cannon SC, Fialho D, Fontaine B, Hanna MG, Ptacek LJ, Tristani-Firouzi M, Tawil R, Griggs RC; CINCH investigators. The primary periodic paralyses: diagnosis, pathogenesis and treatment. *Brain*. 2006;129(Pt 1):8-17; PMID 16195244

Fialho D, Chan YC, Allen DC, Reilly MM, Hughes RA. Treatment of chronic inflammatory demyelinating polyradiculoneuropathy with methotrexate. *J Neurol Neurosurg Psychiatry*. 2006;77(4):544-7; PMID 16543541
Chan YC, Allen DC, Fialho D, Mills KR, Hughes RA. Predicting response to treatment in chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry*. 2006;77(1):114-6; PMID 16361609
Horvath R, Hudson G, Ferrari G, Futterer N, Ahola S, Lamantea E, Prokisch H, Lochmuller H, McFarland R, Ramesh V, Klopstock T, Freisinger P, Salvi F, Mayr JA, Santer R, Tesarova M, Zeman J, Udd B, Taylor RW, Turnbull D, Hanna M, Fialho D, Suomalainen A, Zeviani M, Chinnery PF. Phenotypic spectrum associated with mutations of the mitochondrial polymerase gamma gene. *Brain*. 2006;129(Pt 7):1674-84; PMID 16621917
Hudson G, Deschauer M, Taylor RW, Hanna MG, Fialho D, Schaefer AM, He LP, Blakely E, Turnbull DM, Chinnery PF. POLG1, C10ORF2, and ANT1 mutations are uncommon in sporadic progressive external ophthalmoplegia with multiple mitochondrial DNA deletions. *Neurology*. 2006;66(9):1439-41; PMID 16682683
Davies NP, Imbrici P, Fialho D, Herd C, Bilsland LG, Weber A, Mueller R, Hilton-Jones D, Ealing J, Boothman BR, Giunti P, Parsons LM, Thomas M, Manzur AY, Jurkat-Rott K, Lehmann-Horn F, Chinnery PF, Rose M, Kullmann DM, Hanna MG. Andersen-Tawil syndrome: new potassium channel mutations and possible phenotypic variation. *Neurology*. 2005;11;65(7):1083-9; PMID 16217063

Next Destination:
2007-2010 Specialist Registrar in Clinical Neurophysiology at King's College Hospital NHS Trust leading to CCT in Clinical Neurophysiology May 2010
Since 2010 I have 2 consultant posts (part-time):

1. **Consultant Clinical Neurophysiologist and Honorary Senior Lecturer at the National Hospital for Neurology and Neurophysiology, UCLH and the MRC Centre for Neuromuscular Diseases, UCL, London**
2. **Consultant Clinical Neurophysiologist at King's College Hospital NHS Foundation Trust, London**

Studies completed non- clinical students

Michele Giunta

Start Date: November 2013
PhD Project Title: Exosomal Protein Deficiencies: How Abnormal RNA Metabolism Results in Childhood-Onset Neurological Diseases
Supervisors: Prof Rita Horvath, Prof. Patrick Chinnery, Dr. Veronika Boczonadi
Funding Source: Marie-Curie "MEET" studentship
Length of studentship: 3 years (+ up to 1 year unfunded to write up)

Project Description: Abnormal RNA metabolism is frequently associated with severe neurological disorders such as pontocerebellar hypoplasias and motor neuron disease. The exosome complex is an important RNA processing machinery within the cell and its correct functions are emerging as fundamental for correct neurodevelopment.
My work aims to study the function and defects of the exosome complex which cause neurological disorders in patient cell lines and in zebrafish models of defective exosomal proteins.

Significant publications:
Boczonadi V, Müller JS, Pyle A, Munkley J, Dor T, Quartararo J, Ferrero I, Karcagi V, Giunta M, ….. ,Chinnery PF, Edvardson S, Horvath R. EXOSC8 mutations alter mRNA metabolism and cause hypomyelination with spinal muscular atrophy and cerebellar hypoplasia. *Nat Commun.* 2014 Jul 3;5:4287. DOI:10.1038/ncomms5287
Müller JS, Giunta M, Horvath R. Exosomal Protein Deficiencies: How Abnormal RNA Metabolism Results in Childhood-Onset Neurological Diseases. *J Neuromuscul Dis.* 2015;2(Suppl 2):S31-S37. DOI: 10.3233/JND-150086
Giunta M, Edvardson S, Xu Y, Schuelke M, Gomez-Duran A, Boczonadi V, Elpeleg O, Müller JS, Horvath R. Altered RNA metabolism due to a homozygous RBM7 mutation in a patient with spinal motor neuropathy. *Hum Mol Genet.* 2016 May 18. pii: ddw149. [Epub ahead of print] DOI:10.1093/hmg/ddw149

Next destination: Postdoc research - Wellcome Trust Centre for Mitochondrial research, Newcastle University

Ewen Sommerville

Start Date: Sept 2013
PhD Project Title: Identifying Novel Genes in Mitochondrial Disease
Supervisors: Professor Robert W. Taylor and Dr Gráinne S. Gorman
Funding source: MRC DTP Studentship
Length of studentship: 3 years (+ up to 1 year unfunded to write up)

Project Description: Whole exome sequencing (WES) is a targeted next-generation sequencing technology for the identification of all variants in the exons (coding regions) of all known genes. Mendelian mitochondrial disease has particularly benefitted from WES for attaining genetic diagnoses, due to the vast clinical and genetic heterogeneity of affected patients.
My studentship aims to utilise WES to provide diagnoses for two mitochondrial disease patient cohorts with poor phenotype-genotype correlations:-
(i) Adult-onset progressive external ophthalmoplegia (PEO) with multiple mitochondrial DNA (mtDNA) deletions. This mtDNA maintenance disorder is characterised by extraocular paresis and skeletal muscle restricted multiple mtDNA deletions. Affected patients present broad phenotypes ranging from indolent PEO to fatal multisystem PEO-plus. Furthermore, identification of pathogenic variants is further complicated since both autosomal dominant and recessive variants have been associated with this disorder.
(ii) Early-onset mitochondrial translation disorders. This typically affects patients within the first decade of life and is characterised by multiple mitochondrial respiratory chain complex deficiencies.
Both mtDNA maintenance and mitochondrial translation require the tight coordination of a vast set of nuclear-encoded proteins. Hence, WES allows the rapid identification of pathogenic variants by filtering of all associated nuclear-encoded genes. Following identification, characterisation of novel candidate disease genes seek to understand the underlying pathological mechanisms and to translate findings into potential therapeutic strategies.

Significant Publications:
Ewen W. Sommerville, Yi Shiau Ng, Charlotte L. Alston, Cristina Dallabona, Micol Gilberti, Langping He, Charlotte Knowles, Sophie L. Chin, Andrew M. Schaefer, Gavin Falkous, David Murdoch, Cheryl Longman, Marianne de Visser, Laurence A. Bindoff, John M. Rawles, John C.S. Dean, Richard K. Petty, Maria E. Farrugia, Tobias B. Haack, Holger Prokisch, Robert McFarland, Douglass M. Turnbull, Claudia Donnini, Robert W. Taylor, Gráinne S. Gorman (2016) Clinical features, molecular heterogeneity and prognostic implications in YARS2-related mitochondrial myopathy. JAMA Neurol (In Press).

Renata Oliveira, Ewen W. Sommerville, Kyle Thompson, Joana Nunes, Angela Pyle, Manuela Grazina, Patrick F. Chinnery, Luísa Diogo, Paula Garcia, Robert W. Taylor (2016) Lethal neonatal LTBL associated with biallelic EARS2 variants: case report and review of the reported neuroradiological features. JIMD Rep DOI:10.1007/8904_2016_581

Robert Kopajtich, Thomas J. Nicholls, Joanna Rorbach, Metodi D. Metodiev, Peter Freisinger, Hanna Mandel, Arnaud Vanlander, Daniele Ghezzi, Rosalba Carrozzo, Robert W. Taylor, Klaus Marquard, Kei Murayama, Thomas Wieland, Thomas Schwarzmayr, Johannes A. Mayr, Sarah F. Pearce, Christopher A. Powell, Ann Saada, Akira Ohtake, Federica Invernizzi, Eleonora Lamantea, Ewen W. Sommerville, Angela Pyle, Patrick F. Chinnery, Ellen Crushell, Yasushi Okazaki, Masakazu Kohda, Yoshihito Kishita, Yoshimi Tokuzawa, Zahra Assouline, Marlène Rio, François Feillet, Bénédict Mousson de Camaret, Dominique Chretien, Arnold Munnich, Björn Menten, Tom Sante, Joél Smet, Luc Régal, Abraham Lorber, Asaad Khoury, Massimo Zeviani, Tim M. Strom, Thomas Meitinger, Enrico S. Bertini, Rudy Van Coster, Thomas Klopstock, Agnès Rötig, Tobias B. Haack, Michal Minczuk, Holger Prokisch (2014) Mutations in GTPBP3 cause a mitochondrial translation defect associated with hypertrophic cardiomyopathy, lactic acidosis, and encephalopathy. Am J Hum Genet 95(6): 708-720. DOI:10.1016/j.ajhg.2014.10.017
Ewen W. Sommerville, Patrick F. Chinnery, Gráinne S. Gorman, Robert W. Taylor (2014) Adult-onset Mendelian PEO Associated with Mitochondrial Disease. J Neuromuscul Dis 1(2): 119-133. DOI:10.3233/JND-140041

Next destination: Postdoc assoc. Baylor College of Medicine

Amy Vincent

Start date: September 2013
PhD Project Title: Investigating mitochondrial dysfunction in mitochondrial myopathy and other myopathies
Supervisors: Professor Sir Doug Turnbull, Professor Rob Taylor, Dr Rita Barresi
Funding Source: MRC DTP studentship
Length of studentship: 3 years (+ up to 1 year unfunded to write up)

Project Description:
Mitochondrial DNA mutations and mitochondrial respiratory chain deficiency arise in a mosaic pattern within the skeletal muscle of patients with mitochondrial myopathy. However, they are also found in a number of other myopathies and in aging skeletal muscle.
My work looks to investigate mitochondria dysfunction and associated pathogenic mechanisms in both mitochondrial and other myopathies. This is being approached from three angles:
1) Characterising mitochondrial dysfunction in myofibrillar myopathy, dysferlinopathy and centronucelar myopathy and looking for potential links to disease pathology.
2) Attempting to understand mechanisms and factors effecting clonal expansion of mitochondrial DNA mutations.
3) Looking to make links between mitochondrial morphology, ultrastructure and function.

Significant publications:
Amy E. Vincent, John P. Grady, Mariana C. Rocha, Charlotte L. Alston, Karolina A. Rygiel, Rita Barresi, Robert W. Taylor, Doug M. Turnbull: *Mitochondrial dysfunction in myofibrillar myopathy*. Neuromuscular Disorders 08/2016; DOI:10.1016/j.nmd.2016.08.004 (in press)

Amy E. Vincent, Hannah S. Rosa, Charlotte L. Alston, John P. Grady, Karolina A. Rygiel, Mariana C. Rocha Rita Barresi, Robert W. Taylor, Doug M. Turnbull: *Dysferlin mutations and mitochondrial dysfunction*. Neuromuscular Disorders 08/2016; DOI:10.1016/j.nmd.2016.08.004 (in press)
Amy E Vincent, Yi Shiau Ng, Kathryn White, Tracey Davey, Carmen Mannella, Gavin Falkous, Catherine Feeney, Andrew M Schaefer, Robert Mcfarland, Grainne S Gorman, Robert W Taylor, Doug M Turnbull, Martin Picard: *The Spectrum of Mitochondrial Ultrastructural Defects in Mitochondrial Myopathy*. Scientific Reports 09/2016; 6. DOI:10.1038/srep30610
Martin Picard, Amy E Vincent, Doug M. Turnbull: *Expanding Our Understanding of mtDNA Deletions*. Cell Metabolism 07/2016; 24(1). DOI:10.1016/j.cmet.2016.06.024
Virgilio J. J. Cadete, Sonia Deschênes, Alexanne Cuillerier, François Brisebois, Ayumu Sugiura, Amy Vincent, Doug Turnbull, Martin Picard, Heidi M. McBride, Yan Burelle: *Formation of Mitchondrial-derived vesicles is an active and physiologically relevant mitochondrial quality control process in the cardiac system*. The Journal of Physiology 06/2016; DOI:10.1113/JP272703
Karolina A. Rygiel, Helen A. Tuppen, John P. Grady, Amy Vincent, Emma L. Blakely, Amy K. Reeve, Robert W. Taylor, Martin Picard, James Miller, Doug M. Turnbull: *Complex mitochondrial DNA rearrangements in individual cells from patients with sporadic inclusion body myositis*. Nucleic Acids Research 04/2016; 44(11). DOI:10.1093/nar/gkw382
Mariana C Rocha, John P Grady, Anne Grünewald, Amy Vincent, Philip F Dobson, Robert W Taylor, Doug M Turnbull, Karolina A Rygiel: *A novel immunofluorescent assay to investigate oxidative phosphorylation deficiency in mitochondrial myopathy: Understanding mechanisms and improving diagnosis*. Scientific Reports 10/2015; 5. DOI:10.1038/srep15037

Next destination: Postdoc research assoc at University of Newcastle Wellcome Centre for Mitochondrial Research w/ D Turnbull

Yasmin Issop

Start Date: September 2013
PhD Project Title: A GFPT1 Deficient Mouse Model of Congenital Myasthenic Syndrome
Supervisors: Professor Hanns Lochmüller & Dr Andreas Roos
Funding source: MRC/Barbour Foundation
Length of studentship: 3 years

Project Description:
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 breed and characterise a Gfpt1 knockout mouse model. We will investigate the consequence of GFPT1 deficiency on the glycosylation of skeletal muscle and neuromuscular junction proteins in mice. We will determine whether GFPT1 deficiency results in a modification of glycosyl residues on these proteins and whether this affects acetylcholine receptor clustering at the neuromuscular junction.

Next destination: Associate Medical Publications Manager at Excerpta Medica in London.

Michael Thor

Start Date: Sept 2013
PhD Project Title: Molecular and cellular pathological mechanisms of skeletal muscle channelopathies and related disorders
Supervisors: Drs Roope Männikkö & Stephanie Schorge
Funding source: MRC Centre Grant
Length of studentship: 4 years

Project Description:
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.

Significant Publications:
Loss-of-function mutations in SCN4A cause severe foetal hypokinesia or 'classical' congenital myopathy.
Zaharieva IT, Thor MG, Oates EC, van Karnebeek C, Hendson G, Blom E, Witting N, Rasmussen M, Gabbett MT, Ravenscroft G, Sframeli M, Suetterlin K, Sarkozy A, D'Argenzio L, Hartley L, Matthews E, Pitt M, Vissing J, Ballegaard M, Krarup C, Slørdahl A, Halvorsen H, Ye XC, Zhang LH, Løkken N, Werlauff U, Abdelsayed M, Davis MR, Feng L, Phadke R, Sewry CA, Morgan JE, Laing NG, Vallance H, Ruben P, Hanna MG, Lewis S, Kamsteeg EJ, Männikkö R, Muntoni F.
Brain. 2015 Dec 22. pii: awv352. [Epub ahead of print]

Next destination: Postdoc, Benfenati Lab, Genoa, Italy.

Emma Wilson

Start Date: Sept 2013
PhD Project Title: Cellular pathomechanisms and therapeutic strategies in Hereditary Sensory Neuropathy type 1 (HSN-1)
Supervisors: Professor Linda Greensmith, Professor Mary Reilly, Dr Bernadett Kalmar
Funding source: MRC Centre Grant
Length of studentship: 4 years

Project Description:
My project investigates an inherited disease of the peripheral nervous system called Hereditary Sensory Neuropathy type 1 (HSN-1). HSN-1 presents in patients with both motor and sensory dysfunction to differing extents. I use motor and sensory neuronal models to investigate the underlying pathomechanisms causing this disease and develop potential therapeutic treatments.

Next destination: Postdoc in Hunter James Kelly Research Institute, University at Buffalo, USA. Feltri Lab, project concerning prohibitin-2 and its role in myelination during development and potential role in neuropathy.

Louise King

Start Date: Sept 2013
PhD Project Title: Mitophagy deficiencies in mitochondrial DNA disease
Supervisors: Helene Plun-Favreau, Professor Mike Hanna and Dr Mary Sweeney
Funding source: MRC Centre Grant
Length of studentship: 4 years

Project Description:
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.

Significant Publications:

A recessive Nav1.4 mutation underlies congenital myasthenic syndrome with periodic paralysis.
Habbout K, Poulin H, Rivier F, Giuliano S, Sternberg D, Fontaine B, Eymard B, Morales RJ, Echenne B, King L, Hanna MG, Männikkö R, Chahine M, Nicole S, Bendahhou S.
Neurology. 2016 Jan 12;86(2):161-9. doi: 10.1212/WNL.0000000000002264. Epub 2015 Dec 11.
PMID: 26659129

Andreea Manole

Start Date: Sep 2013
PhD Project Title: Genetic and Functional Investigation of an Inherited Neuropathy and a Channelopathy: Brown-Vialetto-Van Laere Syndrome and Episodic ataxia 1
Supervisors: Professor Henry Houlden, Professor Dimitri Kullmann and Professor Mike Hanna
Funding source: MRC Centre
Length of studentship: 4 years

Project Description:
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.

Significant Publications:
Severe axonal neuropathy is a late manifestation of SPG11
Manole A, Chelban V, Haridy N A, Berardo A, Reilly MM , Houlden H
J Neurol. 2016 in press
Genetic and phenotypic characterization of complex hereditary spastic paraplegia.
Kara E, Tucci A, Manzoni C, Lynch DS, Elpidorou M, Bettencourt C, Chelban V, Manole A, Hamed SA, Haridy NA, Federoff M, Preza E, Hughes D, Pittman A, Jaunmuktane Z, Brandner S, Xiromerisiou G, Wiethoff S, Schottlaender L, Proukakis C, Morris H, Warner T, Bhatia KP, Korlipara LV, Singleton AB, Hardy J, Wood NW, Lewis PA, Houlden H.
Brain. 2016 Jul;139(Pt 7):1904-18. doi: 10.1093/brain/aww111. Epub 2016 May 23.
PMID: 27217339
A novel KCNA1 mutation in a family with episodic ataxia and malignant hyperthermia.
Mestre TA, Manole A, MacDonald H, Riazi S, Kraeva N, Hanna MG, Lang AE, Männikkö R, Yoon G.
Neurogenetics. 2016 Jun 8. [Epub ahead of print]
PMID: 27271339
Charcot-Marie-Tooth disease type 2C and scapuloperoneal muscular atrophy overlap syndrome in a patient with the R232C TRPV4 mutation.
Koutsis G, Lynch D, Manole A, Karadima G, Reilly MM, Houlden H, Panas M.

J Neurol. 2015 Aug;262(8):1972-5. doi: 10.1007/s00415-015-7800-x. Epub 2015 Jun 6. No abstract available.
PMID: 26048687
Recent advances in bulbar syndromes: genetic causes and disease mechanisms.
Manole A, Fratta P, Houlden H. Curr Opin Neurol. 2014 Oct;27(5):506-14. doi: 10.1097/WCO.0000000000000133. Review.
PMID: 25159929
Riboflavin Transporter Deficiency Neuronopathy.
Manole A, Houlden H.
In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.
2015 Jun 11. PMID: 26072523

Next destination: Postdoc research – Salk institute, California

Charlotte Spicer

Start Date: Sep 2013

PhD Project Title: Investigating the effects of pharmacological up-regulation of the heat shock response in models of inclusion body myopathy
Supervisors: Professor Linda Greensmith, Professor Michael Hanna
Funding source: MRC Centre Grant
Length of studentship: 4 years

Project Description:
This PhD project involves characterising the histopathology in 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. 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. In addition, we have obtained fibroblasts from patients with VCP mutations and will examine whether these human cells also manifest any IBM-like pathology.

Significant Publications:
Targeting protein homeostasis in sporadic inclusion body myositis.
Ahmed M, Machado PM, Miller A, Spicer C, Herbelin L, He J, Noel J, Wang Y, McVey AL, Pasnoor M, Gallagher P, Statland J, Lu CH, Kalmar B, Brady S, Sethi H, Samandouras G, Parton M, Holton JL, Weston A, Collinson L, Taylor JP, Schiavo G, Hanna MG, Barohn RJ, Dimachkie MM, Greensmith L. Targeting protein homeostasis in sporadic inclusion body myositis. Sci Transl Med. 2016 Mar 23;8(331):331ra41. PubMed. PMID: 27009270

Next destination: Viva planned for April 2018, seeking postdoc research position after this.

Emine Bagdatlioglu

Start date: September 2013
PhD Project Title: The application of MR imaging in the dystrophin deficient mouse brain: developing outcome measures for diagnostic and therapy development
Funding source: MRC Centre Grant
Supervisors: Professor Volker Straub & Professor Andrew Blamire

Project description: 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.

Next destination: Neuroscience Postdoc Research

Aura Cecilia Jimenez Moreno

Start Date: September 2014
PhD Project Title: Assessing habitual physical activity in Myotonic Dystrophy type 1 and its impact on disease severity
Supervisors: Professor Hanns Lochmüller, Dr. Grainne Gorman and Dr. Sarah Charman
Funding source: MRC, Barbour Foundation and Conacyt Mexico.
Length of studentship: 3 years

Project Description:
Myotonic Dystrophy type 1 (DM1) is the most common muscular dystrophy in adults and due to a mutation on the DMPK gene it manifests with an heterogeneous phenotype. However, one of the symptoms patient report to impact more on their daily life functionality has been fatigue which with the underlying progressive muscle weakness leads to a sedentary behaviour associated with poor health outcomes and distinctive physiological consequences in healthy adults.
In different debilitating disorders, the association between habitual physical activity (HPA) levels and clinical phenotype has been shown and has also been suggested for DM1. However a valid objective outcome measure is required to quantify this and demonstrate if there is any association between these two variables, HPA and disease burden.
The aim of my PhD is to validate the use of an accelerometer to measure HPA in DM1 and analyze its association with disease burden at baseline and prospectively over time. This study is part of an ongoing international trial oriented to increase physical activity in DM1 with the aim to improve patients quality of life and reduced fatigue severity and variables to consider include, functional outcomes, patient reported outcomes, blood biomarkers and cardiac function analyzed by MRI.

Relevant Publications:
van Engelen B and the **OPTIMISTIC Consortium**. Cognitive behaviour therapy plus aerobic exercise training to increase activity in patients with myotonic dystrophy type 1 (DM1) compared to usual care (OPTIMISTIC): study protocol for randomised controlled trial. Trials. 2015;16(1):224.

Next destination: Research assoc at Newcastle w/ Grainne Gorman. EU-IMI founded project in neuromuscular diseases.

Marina Bartsakoulia

Start Date: September 2013
PhD Project Title: Mitochondrial translation deficiencies
Supervisors: Professor Rita Horvath, Dr Veronika Boczonadi and Professor Patrick Chinnery
Funding Source: Randerson Foundation
Length of Studentship: 3 years (+ up to 1 year unfunded to write up)

Project Description:
Mitochondrial disorders comprise a large group of heterogeneous disorders which are characterized by impairments in the cellular energy production. One of the great challenges of mitochondrial disease is the variety of clinical features present in patients. Mitochondrial disorders affect more than one organ leading to complex multisystem dysfunctions. Tissues, in which the metabolic demand is higher, such as skeletal muscle, neurons, liver or heart are typically affected. Mutations in both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) often lead to mitochondrial disorders. Hence, efficient mitochondrial function is critically dependent on concerted action of the two genomes. There is not much available to date to

treat mitochondrial disease. Vitamin supplements, pharmacological agents and exercise therapy are common strategies used in individuals suffering from mitochondrial disorders. My project focuses on the reversibility and tissue specificity of mitochondrial translation deficiencies and therefore I will investigate the effect of L-cysteine and N-acetyl-cysteine supplementation on mitochondrial translation deficiencies and the tissue specificity presentation of some translational deficiencies.

Significant Publication:
Bartsakoulia M, Müller SJ, Gomez-Duran A, Patrick Yu Wai Man, Boczonadi V, Horvath R: *Cysteine Supplementation May be Beneficial in a Subgroup of Mitochondrial Translation Deficiencies*, Journal of Neuromuscular Disorders 9/2016, DOI: 10.3233/JND-160178
Pyle A, Ramesh V, Bartsakoulia M, Boczonadi V, Gomez-Duran A, Herczegfalvi A, Blakely EL, Smertenko T, Duff J, Eglon G, Moore D, Yu-Wai-Man P, Douroudis K, Santibanez-Koref M, Griffin H, Lochmüller H, Karcagi V, Taylor RW, Chinnery PF, Horvath R.: *Behr's Syndrome is Typically Associated with Disturbed Mitochondrial Translation and Mutations in the C12orf65 Gene*, Journal of Neuromuscular Diseases 2014;1(1):55-63, DOI: 10.3233/JND-140003

Next destination: Postdoc research - University of Patras, Greece

Qiang Gang

Start Date: Sept 2012
PhD Project Title: Genetic investigations of sporadic inclusion body myositis and myopathies with structural abnormalities and protein aggregates in muscle
Supervisors: Professor Henry Houlden, Professor Michael Hanna & Dr Conceição Bettencourt
Funding source: Host Impact (UCL)
Length of studentship: 3 years

Project Description:
Using whole-exome sequencing to investigate the pathogenesis of sporadic inclusion body myositis (IBM) and tubular aggregate myopathies (TAM). Both diseases are rare and the causes are unknown, and it is suggested that genetic factors might be involved in the disease process. Whole-exome sequencing is an advanced and cost-efficient approach to explore the genetic changes of the whole protein-coding region. We aim to identify the genetic risk factors associated with sporadic IBM and the disease-causing genes for TAM, and to improve our understanding of these diseases.

Significant Publications:
Rare variants in SQSTM1 and VCP genes and risk of sporadic inclusion body myositis. Gang Q, Bettencourt C, Machado PM, Brady S, Holton JL, Pittman AM, Hughes D, Healy E, Parton M, Hilton-Jones D, Shieh PB, Zanoteli E, Camargo LV, De Paepe B, De Bleecker J, Shaibani A, Ripolone M, Violano R, Moggio M, Barohn RJ, Dimachkie MM, Mora M, Mantegazza R, Zanotti S, Singleton AB, Hanna MG, Houlden H; Muscle Study Group and the International IBM Genetics Consortium. 2016 (Accepted by Neurobiology of Aging)

The effects of an intronic polymorphism in TOMM40 and APOE genotypes in sporadic inclusion body myositis.
Gang Q, Bettencourt C, Machado PM, Fox Z, Brady S, Healy E, Parton M, Holton JL, Hilton-Jones D, Shieh PB, Zanoteli E, De Paepe B, De Bleecker J, Shaibani A, Ripolone M, Violano R, Moggio M, Barohn RJ, Dimachkie MM, Mora M, Mantegazza R, Zanotti S, Hanna MG, Houlden H; Muscle Study Group and the International IBM Genetics Consortium. Neurobiol Aging. 2015 Apr;36(4):1766. PMID:25670332
Genetic advances in sporadic inclusion body myositis.
Gang Q, Bettencourt C, Houlden H, Hanna MG, Machado PM. Curr Opin. 2015 Nov;27(6):586-94.PMID:26335925
Sporadic inclusion body myositis: the genetic contributions to the pathogenesis.
Gang Q, Bettencourt C, Machado P, Hanna MG, Houlden H. Orphanet J Rare. 2014 Jun 19;9:88. PMID:24948216

Co-author publication:
Ongoing developments in sporadic inclusion body myositis.
Machado PM, Ahmed M, Brady S, Gang Q, Healy E, Morrow JM, Wallace AC, Dewar L, Ramdharry G, Parton M, Holton JL, Houlden H, Greensmith L, Hanna MG. Curr Rheumatol Rep. 2014 Dec;16(12):477.PMID:25399751

Next destination: Clinical training

Neta Amior

Start Date: Sept 2010 (currently in CRS)
PhD Project Title: Developing models to study the mechanisms of weakness and myotonia in Periodic Paralysis
Supervisors: Professor Michael Duchen and Professor Mike Hanna
Funding source: Host Impact (UCL)
Length of studentship: 3 years (+ 1 yr extended funding)

Project Description: Periodic paralysis (PP) is a disorder caused by mutations of skeletal voltage gated ion channels, characterised by episodic attacks of paralysis. Although these eventually subside, patients develop progressive muscle weakness and frequently, myopathy. The relationship between this progression and the associated mutations is not understood. I propose that the longer term defect might result from disordered calcium signalling and its impact on mitochondrial function. I therefore sought disease models in order to study these aspects of muscle signalling. These were:
A model derived from patients: Patient derived fibroblasts were virally transduced with MyoD to generate myoblasts, which were differentiated into myotubes. This process proved too inefficient to collect adequate data.
A pharmacological model: generated by treating neonatal rat myotube cultures with barium and low extracellular potassium to simulate attacks of PP. The model was validated using membrane potential sensitive dyes and by electrophysiological techniques. Treated cultures displayed more frequent spontaneous calcium fluctuations. Mitochondrial membrane potential was not affected by the treatment, but expression of TFAM, a regulator of

mitochondrial transcription, was upregulated, suggesting activation of retrograde signalling pathways.
A mouse model: collaborators at MRC Harwell generated mice carrying a mutation (c.1744A>G; p.Ile582Val) equivalent to a novel point mutation in *SCN4A,* one of the ion channel genes associated with PP. Measurements *in-vivo* established that affected mice show muscle weakness and delayed fatigue during tetanic responses. Calcium handling and mitochondrial function were analysed in single isolated myofibres. Calcium handling was not affected, however control fibres typically had a bigger mitochondrial membrane potential and more interfibrillar mitochondria, indicating that mitochondrial bioenergetics were affected.
I describe several approaches that could be used to investigate the progressive weakness and myopathy in PP, and assess the relative merits of each approach.

Significant Publications:
Novel mutations in human and mouse SCN4A implicate AMPK in myotonia and periodic paralysis. / Corrochano, Silvia; Männikkö, Roope; Joyce, Peter I.; McGoldrick, Philip; Wettstein, Jessica; Lassi, Glenda; Rayan, Dipa L Raja; Blanco, Gonzalo; Quinn, Colin; Liavas, Andrianos; Lionikas, Arimantas; Amior, Neta; Dick, James; Healy, Estelle G.; Stewart, Michelle; Carter, Sarah; Hutchinson, Marie; Bentley, Liz; Fratta, Pietro; Cortese, Andrea; Cox, Roger; Brown, Steve D. M.; Tucci, Valter; Wackerhage, Henning; Amato, Anthony A.; Greensmith, Linda; Koltzenburg, Martin; Hanna, Michael G.; Acevedo-Arozena, Abraham. In: Brain, Vol. 137, No. 12, 01.12.2014, p. 3171-3185.

Next destination: Post-doctoral research Hebrew University, Jerusalem w/ Rachel Nechushtai

Mhoriam Ahmed

PhD Dates: Oct 2008 - 2011

Phd Title: Investigating the effects of pharmacological up-regulation of the heat shock response in an *in-vitro* model of sporadic inclusion body myositis

Project Description:
Sporadic inclusion body myositis (sIBM) is the commonest acquired muscle disease affecting adults over the age of 50. Although the aetiology of this disease remains unclear, there is evidence for both inflammatory and myodegenerative processes in sIBM muscle pathology. In particular, abnormal protein aggregation is a characteristic feature of affected muscle, with inclusions incorporating several well studied proteins including amyloid-beta precursor protein (β-APP), amyloid-beta (Aβ), phosphorylated tau and heat shock proteins (HSPs) among many others.
The heat shock response (HSR) is involved both in the regulation of normal protein folding and the disaggregation of aggregated proteins. Therefore, in this study, we examined the effects of pharmacological up-regulation of the HSR in an *in vitro* model of sIBM. Using primary muscle cultures derived from neonatal rats, we found that transfection with β-APP results in an over-expression of this protein, increased protein aggregation and cytotoxicity. Pharmacological up-regulation of the HSR was found to significantly improve cell survival and

reduce protein aggregation in transfected cells. These results led to the examination of the protein degradation pathways autophagy and proteasomal degradation. Over-expression of β-APP revealed dysfunction in both these pathways. Pharmacological upregulation of the HSR improved autophagy however did not appear to have an effect on proteasomal function.

Supervisors: Professor Linda Greensmith and Professor Jenny Morgan

Significant Publications whilst at Centre:
Ongoing Developments in Sporadic Inclusion Body Myositis Curr Rheumatol Rep. 2014; 16: 477. PMCID: PMC4233319

Next Destination:
Following my PhD, I continued with my project in Professor Greensmith's lab where I am currently investigating upregulation of the heat shock response in an in vivo model of multiproteinopathy

Alex Clark

PhD Dates: Sept 2008 – Nov 2012

PhD Title : The use of microfluidic chambers to study action potential propagation and stimulus transduction in sensory neurons *in vitro*

Project Description:
Primary afferent sensory neurons are incredibly long cells, often traversing distances of over one metre in humans. Cutaneous sensory stimuli are transduced in the periphery by specialised end-organs or free nerve endings which code the stimulus into electrical action potentials that propagate towards the central nervous system. Despite significant advances in our knowledge of sensory neuron physiology and ion channel expression, many commonly used techniques fail to accurately model the primary afferent neuron in its entirety. *In vitro* experiments often focus on the cell somata and neglect the fundamental processes of peripheral stimulus transduction and action potential propagation.
We have used ratiometric calcium imaging performed in compartmentalised sensory neuron cultures. these can be used to directly and accurately compare the sensitivity and functional protein expression of isolated neuronal regions *in vitro*. Using these specialised cultures, we demonstrate that the nerve terminals of cultured DRG neurons can be depolarised to induce action potential propagation, which has both TTX-resistant and TTX-sensitive components. Furthermore, we show that there is a differential regulation of proton sensitivity between the sensory terminals and somata in cultured sensory neurons. We also demonstrate that capsaicin sensitivity is highly dependent on embryonic dissection age.
This approach enables a comprehensive method to study the excitability and regional sensitivity of cultured sensory neurons on a single cell level. Examination of the sensory terminals is crucial to further understand the properties and diversity of DRG sensory neurons.

Supervisors: Professor Martin Koltzenburg, Professor Giampietro Schiavo

Next Destination: University of Oxford - Post-doctoral research associate

Ellen Cottenie

PhD Dates: Sept 2011 – 2015

Phd Title: Genetic and functional investigation of inherited neuropathies

Project Description:
Focus was applied on finding genetic causes of inherited neuropathies, mainly Charcot-Marie-Tooth disease, by using both old and new genetic techniques and the accompanying functional investigations to prove the pathogenicity of the variants found. Mutations in *ATPase 6*, the first mitochondrially encoded gene responsible for an isolated neuropathy, were found in five families with CMT2 by a traditional Sanger sequencing

approach. The same approach was used to expand the phenotype associated with *FIG4* mutations, known as CMT4J. Compound heterozygous mutations were found in a patient with a proximal and asymmetric weakness and rapid deterioration of strength in a single limb, mimicking CIDP. Several appropriate cohorts were screened for mutations in candidate genes with the traditional Sanger sequencing approach; however, no new pathogenic genes were found. In the case of the *HINT1* gene, the originally stated frequency of 11% could not be replicated and a founder effect was suggested, underlying the importance of considering the ethnic background of a patient when screening for mutations in neuropathy-related genes. After the incorporation of exome sequencing, five CMT families were provided with a genetic diagnosis due to mutations in three novel genes and two previously known pathogenic genes. Many more families are currently under investigation and candidate genes have been found in some. Lastly, a series of divergent functional techniques was used to investigate the pathogenicity of *IGHMBP2* mutations in 11 families with CMT2. *IGHMBP2* mutations normally lead to SMARD1 and fibroblast and lymphoblast studies indicate that the IGHMBP2 protein levels are significantly higher in CMT2 than SMARD1, but lower than controls, suggesting that the clinical phenotype differences correlate to the IGHMBP2 protein levels.
Supervisors: Professor Mary M. Reilly, Professor Henry Houlden, Professor Mike Hanna

Significant Publications whilst at Centre

Absence of HINT1 mutations in a UK and Spanish cohort of patients with inherited neuropathies.
Horga A, Cottenie E, Tomaselli PJ, Rojas-García R, Salvado M, Villarreal-Pérez L, Gamez J, Márquez-Infante C, Houlden H, Reilly MM.
J Neurol. 2015 Aug;262(8):1984-6. doi: 10.1007/s00415-015-7851-z. Epub 2015 Jul 21.
PMID: 26194197

Truncating and missense mutations in IGHMBP2 cause Charcot-Marie Tooth disease type 2.
Cottenie E, Kochanski A, Jordanova A, Bansagi B, Zimon M, Horga A, Jaunmuktane Z, Saveri P, Rasic VM, Baets J, Bartsakoulia M, Ploski R, Teterycz P, Nikolic M, Quinlivan R, Laura M, Sweeney MG, Taroni F, Lunn MP, Moroni I, Gonzalez M, Hanna MG, Bettencourt C, Chabrol E, Franke A, von Au K, Schilhabel M, Kabzińska D, Hausmanowa-Petrusewicz I, Brandner S, Lim SC, Song H, Choi BO, Horvath R, Chung KW, Zuchner S, Pareyson D, Harms M, Reilly MM, Houlden H.
Am J Hum Genet. 2014 Nov 6;95(5):590-601. doi: 10.1016/j.ajhg.2014.10.002. Epub 2014 Oct 30.
PMID: 25439726 Free PMC Article

Mutations in γ adducin are associated with inherited cerebral palsy.
Kruer MC, Jepperson T, Dutta S, Steiner RD, Cottenie E, Sanford L, Merkens M, Russman BS, Blasco PA, Fan G, Pollock J, Green S, Woltjer RL, Mooney C, Kretzschmar D, Paisán-Ruiz C, Houlden H.
Ann Neurol. 2013 Dec;74(6):805-14. doi: 10.1002/ana.23971.
PMID: 23836506 Free PMC Article

Mutations in BICD2 cause dominant congenital spinal muscular atrophy and hereditary spastic paraplegia.
Oates EC, Rossor AM, Hafezparast M, Gonzalez M, Speziani F, MacArthur DG, Lek M, Cottenie E, Scoto M, Foley AR, Hurles M, Houlden H, Greensmith L, Auer-Grumbach M, Pieber TR, Strom TM, Schule R, Herrmann DN, Sowden JE, Acsadi G, Menezes MP, Clarke NF, Züchner S; UK10K, Muntoni F, North KN, Reilly MM.
Am J Hum Genet. 2013 Jun 6;92(6):965-73. doi: 10.1016/j.ajhg.2013.04.018. Epub 2013 May 9.
PMID: 23664120 Free PMC Article

Rapidly progressive asymmetrical weakness in Charcot-Marie-Tooth disease type 4J resembles chronic inflammatory demyelinating polyneuropathy.
Cottenie E, Menezes MP, Rossor AM, Morrow JM, Yousry TA, Dick DJ, Anderson JR, Jaunmuktane Z, Brandner S, Blake JC, Houlden H, Reilly MM.

Neuromuscul Disord. 2013 May;23(5):399-403. doi: 10.1016/j.nmd.2013.01.010. Epub 2013 Mar 13.
PMID: 23489662
Genetic dysfunction of MT-ATP6 causes axonal Charcot-Marie-Tooth disease.
Pitceathly RD, Murphy SM, Cottenie E, Chalasani A, Sweeney MG, Woodward C, Mudanohwo EE, Hargreaves I, Heales S, Land J, Holton JL, Houlden H, Blake J, Champion M, Flinter F, Robb SA, Page R, Rose M, Palace J, Crowe C, Longman C, Lunn MP, Rahman S, Reilly MM, Hanna MG.
Neurology. 2012 Sep 11;79(11):1145-54. doi: 10.1212/WNL.0b013e3182698d8d. Epub 2012 Aug 29.
PMID: 22933740 Free PMC Article

Siobhan Durran

PhD Dates: Sept 2010 – March 2014

PhD Title: Genetic and Molecularstudies of skeletal muscle channelopathies

Supervisors: Professor M Hanna, Dr Mary Sweeney and Dr Roope Manniko

Project description:
The aim of this PhD project was to investigate the genetic and molecular aspects of the skeletal muscle channelopathies, in particular periodic paralysis. A number of genetic studies were conducted to identify the causative mutations in a cohort of patients who did not have a genetic diagnosis following routine diagnostic screening. A number of mutations were identified within the coding region of the *SCN4A* gene. SCN4A encodes for the voltage gated sodium channel, Nav1.4. Those mutations which were of particular interest were then studied further to determine what effect they had on channel functioning.

Next destination:
Patent attorney, Intellectual Property Law

Alice Gardiner

Phd Dates: 2011-2015

PhD Project Title: A Genetic Investigation of the Muscle and Neuronal Channelopathies: From Sanger to Next – Generation Sequencing

Project Description:
The channelopathies are a rare group of neurological diseases, caused by voltage-gated ion channel dysfunction as a result of genetic mutation. Whilst some of the genetic causes are known, genetic and phenotypic heterogeneity can make identifying the causative mutation difficult, and many patients are without a genetic diagnosis.
This project used a range of sequencing technologies to further investigate the genetic basis of the channelopathies. Traditional Sanger sequencing was used sequence patients with paroxysmal dyskinesias. Additionally, both small custom and large off the shelf next generation sequencing panels were employed to investigate patients with a range of episodic muscle and brain phenotypes. Lastly, whole exome sequencing was undertaken on families with previously unexplained hereditary channelopathy phenotypes.

Supervisors: Professor Henry Houlden and Professor Mike Hanna

Significant Publications whilst at Centre:
PRRT2 gene mutations: from paroxysmal dyskinesia to episodic ataxia and hemiplegic migraine.
Neurology. 2012 Nov 20;79 (21):2115-21.
PMID:2307702
The clinical and genetic heterogeneity of paroxysmal dyskinesias.
Brain. 2015 Dec;138(Pt 12):3567-80
PMID: 26598494

Next destination:
Higher Pharmacopoeial Scientist, Medicine and Healthcare product Regulatory Agency

Anna Gray

PhD Dates: 2010-2014

PhD Project Title: Investigation of disease progression, outcome measures and therapeutic intervention in a mouse model of spinal and bulbar muscular atrophy (SBMA)

Project Description:
Spinal and bulbar muscular atrophy (SBMA), otherwise known as Kennedy's disease is an adult onset, X-linked lower motor neuron disease, caused by a mutation in the gene that encodes the androgen receptor (AR) protein. Although understanding of disease pathogenesis has advanced considerably following the identification of the disease causing mutation (La Spada et al. 1991), no tolerable disease-modifying treatments have yet been developed.
The AR100 transgenic mouse model of SBMA, developed by Albert La Spada and Colleagues, was shown to convincingly recapitulate the slowly progressive neuromuscular phenotype and lower motor neuron degeneration seen in SBMA patients (Sopher et al. 2004). In addition, disease pathogenesis was gender specific and androgen dependent, both key aspects of human SBMA; therefore presenting an ideal tool for the study of disease progression and therapeutic strategies in this disease.
My PhD project involved a longitudinal pathophysiological and histological characterisation of disease progression in AR100 mice, so that therapeutic interventions used in preclinical trials could be targeted to key disease stages. Disease was shown to first manifest in skeletal muscle, prior to any motor neuron degeneration, which was only present in late stage disease. These findings challenge the traditional view of SBMA as a primary motor neuron disorder. AR100 mice were treated with arimoclomol, a novel pharmacological co-inducer of the endogenous heat shock response, from the time point at which motor deficits first manifest (6 months) until a designated end point (18 months). Finally, in collaboration with experts in MRI, skeletal muscle MRI was developed as a non-invasive biological marker, to longitudinally monitor disease progression and response to therapeutic intervention. These studies focussed on imaging of the lower hindlimb muscles. This approach is directly translatable to the clinical setting and may allow a more direct transition between preclinical studies and patients.

Supervisor(s): Professor Linda Greensmith & Professor Michael Hanna

Significant Publications whilst at Centre:
Montague K, Malik B, **Gray AL**, La Spada AR, Hanna MG, Szabadkai G, Greensmith L. Endoplasmic reticulum stress in spinal and bulbar muscular atrophy: a potential target for therapy. *Brain*. 2014 Jul 137(Pt 7):1894-906. PMID: 24898351.

Novoselov SS, Mustill WJ, **Gray AL**, Dick JR, Kanuga N, Kalmar B, Greensmith L. Molecular chaperone mediated late-stage neuroprotection in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *PLoS One*. 2013 Aug 30;8(8):e73944. PMID: 24023695.

Malik B, Nirmalananthan N, **Gray AL**, La Spada AR, Hanna MG, Greensmith L. Co-induction of the heat shock response ameliorates disease progression in a mouse model of

human spinal and bulbar muscular atrophy: implications for therapy. *Brain*. 2013 Mar 136(3):926-943. PMID: 23393146.

Fratta P, Malik B, **Gray A**, La Spada AR, Hanna MG, Fisher EM, Greensmith L. FUS is not dysregulated by the spinal bulbar muscular atrophy androgen receptor polyglutamine repeat expansion. *Neurobiol Aging*. 2013 May 34(5):1516.e17-19. PMID: 23062703.

Acevedo-Arozena A, Kalmar B, Essa S, Ricketts T, Joyce P, Kent R, Rowe C, Parker A, **Gray A**, Hafezparast M, Thorpe JR, Greensmith L, Fisher EM. A comprehensive assessment of the SOD1G93A low-copy transgenic mouse, which models human amyotrophic lateral sclerosis. *Dis Model Mech.* 2011 Sep 4(5):686-700. PMID: 21540242.

Next destination: Research associate: University of Manchester
Current: Research Associate in Graphene Neuroscience and Neuropathology

Yo-Tsen Liu

Phd Dates: 2010-2014

PhD Title: Genetics and Pathogenesis of Inherited Neuropathies

Project Description:
Inherited neuropathies are a clinically and genetically heterogeneous group of diseases. More than 51 causative genes have been recognised as the aetiologies, however, there are still patients whose disease-causing genes have not been identified, particularly those presenting with complex and atypical phenotypes in a combination of the involvement of the central nervous system (CNS) and the peripheral nervous system (PNS) and even other organs. The major objective of my PhD was to establish the genetic diagnosis in patients affected by inherited neuropathies or complex syndromes. To achieve the objective, an integrative approach combining conventional Sanger sequencing and the next generation sequencing (NGS) technology was taken. The efficiency and limitations of NGS in genetic diagnosis were also investigated. My research projects were accordingly divided into the following parts: (1) screening of disease-causing mutations in newly-identified genes or rare genes for inherited neuropathies, (2) screening of disease-causing mutations in genes responsible for other disorders which may be also associated with peripheral neuropathies, (3) whole exome sequencing in small families or sporadic patients who are difficult to approach by conventional gene searching methods, (4) targeted resequencing in patients with inherited neuropathies and related disorders. Identification of disease-causing mutations of these phenotypes will help unravelling the underlying pathomechanisms. Therefore, the second objective of my PhD aimed to study functional consequences and pathologic roles of the identified mutations in cellular models.

Supervisors: Professor Mary M Reilly, Professor Henry Houlden, Dr Matilde Laura

Significant Publications whilst at Centre:

Liu YT, Laurá M, Hersheson J, Horga A, Jaunmuktane Z, Brandner S, Pittman A,

Hughes D, Polke JM, Sweeney MG, Proukakis C, Janssen JC, Auer-Grumbach M, Zuchner S, Shields KG, Reilly MM, Houlden H. Extended phenotypic spectrum of KIF5A mutations: From spastic paraplegia to axonal neuropathy. Neurology. 2014 Aug 12;83(7):612-9. doi: 10.1212/WNL.0000000000000691. Epub 2014 Jul 9. PubMed PMID: 25008398; PubMed Central PMCID: PMC4141994.
Liu YT, Hersheson J, Plagnol V, Fawcett K, Duberley KE, Preza E, Hargreaves IP, Chalasani A, Laurá M, Wood NW, Reilly MM, Houlden H. Autosomal-recessive cerebellar ataxia caused by a novel ADCK3 mutation that elongates the protein: clinical, genetic and biochemical characterisation. J Neurol Neurosurg Psychiatry. 2014 May;85(5):493-8. doi: 10.1136/jnnp-2013-306483. Epub 2013 Nov PubMed PMID: 24218524; PubMed Central PMCID: PMC3995328.
Tucci A, Liu YT, Preza E, Pitceathly RD, Chalasani A, Plagnol V, Land JM, Trabzuni D, Ryten M; UKBEC, Jaunmuktane Z, Reilly MM, Brandner S, Hargreaves I, Hardy J, Singleton AB, Abramov AY, Houlden H. Novel C12orf65 mutations in patients with axonal neuropathy and optic atrophy. J Neurol Neurosurg Psychiatry. 2014 May;85(5):486-92. doi: 10.1136/jnnp-2013-306387. Epub 2013 Nov 6. PubMed PMID: 24198383; PubMed Central PMCID: PMC3995331.
Gonzalez M, McLaughlin H, Houlden H, Guo M, Yo-Tsen L, Hadjivassilious M, Speziani F, Yang XL, Antonellis A, Reilly MM, Züchner S; Inherited Neuropathy Consortium. Exome sequencing identifies a significant variant in methionyl-tRNA synthetase (MARS) in a family with late-onset CMT2. J Neurol Neurosurg Psychiatry. 2013 Nov;84(11):1247-9. doi: 10.1136/jnnp-2013-305049. Epub 2013 Jun 1. PubMed PMID: 23729695; PubMed Central PMCID: PMC3796032.
Murphy SM, Ernst D, Wei Y, Laurà M, Liu YT, Polke J, Blake J, Winer J, Houlden H, Hornemann T, Reilly MM. Hereditary sensory and autonomic neuropathy type 1 (HSANI) caused by a novel mutation in SPTLC2. Neurology. 2013 Jun 4;80(23):2106-11. doi: 10.1212/WNL.0b013e318295d789. Epub 2013 May 8. PubMed PMID: 23658386; PubMed Central PMCID: PMC3716354.
Fawcett K, Mehrabian M, Liu YT, Hamed S, Elahi E, Revesz T, Koutsis G, Herscheson J, Schottlaender L, Wardle M, Morrison PJ, Morris HR, Giunti P, Wood N, Houlden H. The frequency of spinocerebellar ataxia type 23 in a UK population. J Neurol. 2013 Mar;260(3):856-9. doi: 10.1007/s00415-012-6721-1. Epub 2012 Oct Erratum in: J Neurol. 2013 Mar;260(3):860. PubMed PMID: 23108490.
Murphy SM, Laura M, Fawcett K, Pandraud A, Liu YT, Davidson GL, Rossor AM, Polke JM, Castleman V, Manji H, Lunn MP, Bull K, Ramdharry G, Davis M, Blake JC, Houlden H, Reilly MM. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry. 2012 Jul;83(7):706-10. doi: 10.1136/jnnp-2012-302451. Epub 2012 May 10. PubMed PMID: 22577229; PubMed Central PMCID: PMC3736805.

Next Destination:
Neurology consultant, Taipei Veterans General Hospital, Japan

Amelie Pandraud

PhD Dates: 2010 – 2013

PhD Title: A genetic and functional investigation of inherited neuropathies: Charcot-Marie-Tooth disease and Brown-Vialetto-Van Laere syndrome

Project Description:
The thesis focuses on two inherited neuropathies: Charcot-Marie-Tooth disease and Brown-Vialetto-Van Laere Syndrome. Methods utilised to investigate these diseases are both genetics- and molecular biology-based.

Charcot-Marie-Tooth Disease: CMT is an inherited motor and sensory neuropathy. Although most CMT type 1A patients carry the same sized chromosome 17 duplication containing the PMP22 gene, they exhibit a wide range of severities both within and between families. Furthermore, some cases of demyelinating CMT (CMT1) remain without a genetic diagnosis. The thesis seeks to identify the genetic factors modifying the CMT1A phenotype by analysing variants in the PMP22 gene and its promoter region in a cohort of CMT1A cases, and by genotyping CMT1A cases on an Immunochip to determine whether common variants associated with autoimmune and inflammatory diseases account for some of the disease heterogeneity in CMT1A. A mutational screening of demyelinating CMT genes is also performed and exome sequencing is used to search for novel genetic causes of demyelinating CMT. The genetic causes of selected canine neuropathies are also investigated.

Brown-Vialetto-Van Laere syndrome: BVVL is a rare, generally recessive motor neuron disease with early onset. A severe sensory-motor neuropathy is part of the phenotype. Mutations have been found in genes encoding riboflavin transporters, leading to flavin deficiency. Riboflavin is necessary for the synthesis of FAD and FMN, which play a role in energy metabolism. To further characterise the aetiology of the disease, the known genes were screened in patients with BVVL-like phenotypes and exome sequencing was used to search for novel BVVL-associated genes. Mitochondrial dysfunction was investigated as a potential pathway leading to neuronal damage in BVVL. Three cell models are used: patient fibroblasts as well as a neuroblastoma cell line and mouse motor neurons in which one of the riboflavin transporters has been knocked down

Supervisors: Professor M Reilly and Professor H Houlden

Significant Publications whilst at Centre

Kara E, Kiely AP, Proukakis C, Giffin N, Love S, Hehir J, Rantell K, Pandraud A, Hernandez DG, Nacheva E, Pittman AM, Nalls MA, Singleton AB, Revesz T, Bhatia KP, Quinn N, Hardy J, Holton JL, Houlden H. A 6.4 Mb duplication of the α-synuclein locus causing frontotemporal dementia and Parkinsonism: phenotype-genotype correlations. JAMA Neurol. 2014 Sep;71(9):1162-71. doi: 10.1001/jamaneurol.2014.994. PubMed PMID: 25003242; PubMed Central PMCID: PMC4362700.
Foley AR, Menezes MP, Pandraud A, Gonzalez MA, Al-Odaib A, Abrams AJ, Sugano K, Yonezawa A, Manzur AY, Burns J, Hughes I, McCullagh BG, Jungbluth H, Lim MJ, Lin JP, Megarbane A, Urtizberea JA, Shah AH, Antony J, Webster R, Broomfield A, Ng J, Mathew AA, O'Byrne JJ, Forman E, Scoto M, Prasad M, O'Brien K, Olpin S, Oppenheim M, Hargreaves I, Land JM, Wang MX, Carpenter K, Horvath R, Straub V, Lek M, Gold W, Farrell MO, Brandner S, Phadke R, Matsubara K, McGarvey ML, Scherer SS, Baxter PS, King MD, Clayton P, Rahman S, Reilly MM, Ouvrier RA, Christodoulou J, Züchner S, Muntoni F, Houlden H. Treatable childhood neuronopathy caused by mutations in riboflavin transporter RFVT2. Brain. 2014 Jan;137(Pt 1):44-56. doi: 10.1093/brain/awt315. Epub 2013 Nov 19. PubMed PMID: 24253200; PubMed Central PMCID: PMC3891447.
Nalini A, Pandraud A, Mok K, Houlden H. Madras motor neuron disease (MMND) is

distinct from the riboflavin transporter genetic defects that cause Brown-Vialetto-Van Laere syndrome. J Neurol Sci. 2013 Nov 15;334(1-2):119-22. doi: 10.1016/j.jns.2013.08.003. Epub 2013 Aug 13. PubMed PMID: 24139842; PubMed Central PMCID: PMC4068726.
Koutsis G, Pandraud A, Karadima G, Panas M, Reilly MM, Floroskufi P, Wood NW, Houlden H. Mutational analysis of PMP22, EGR2, LITAF and NEFL in Greek Charcot-Marie-Tooth type 1 patients. Clin Genet. 2013 Apr;83(4):388-91. doi: 10.1111/j.1399-0004.2012.01910.x. Epub 2012 Jul 5. PubMed PMID: 22765307
Johnson JO, Gibbs JR, Megarbane A, Urtizberea JA, Hernandez DG, Foley AR, Arepalli S, Pandraud A, Simón-Sánchez J, Clayton P, Reilly MM, Muntoni F, Abramzon Y, Houlden H, Singleton AB. Exome sequencing reveals riboflavin transporter mutations as a cause of motor neuron disease. Brain. 2012 Sep;135(Pt 9):2875-82. doi: 10.1093/brain/aws161. Epub 2012 Jun 26. PubMed PMID: 22740598; PubMed Central PMCID: PMC3437022.

Voermans NC, Kleefstra T, Gabreëls-Festen AA, Faas BH, Kamsteeg EJ, Houlden H, Laurá M, Polke JM, Pandraud A, van Ruissen F, van Engelen BG, Reilly MM. Severe Dejerine-Sottas disease with respiratory failure and dysmorphic features in association with a PMP22 point mutation and a 3q23 microdeletion. J Peripher Nerv Syst. 2012 Jun;17(2):223-5. doi: 10.1111/j.1529-8027.2012.00402.x. PubMed PMID: 22734911.
Bryson JB, Hobbs C, Parsons MJ, Bosch KD, Pandraud A, Walsh FS, Doherty P, Greensmith L. Amyloid precursor protein (APP) contributes to pathology in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis. Hum Mol Genet. 2012 Sep 1;21(17):3871-82. doi: 10.1093/hmg/dds215. Epub 2012 Jun 7. PubMed PMID: 22678056.
Murphy SM, Laura M, Fawcett K, Pandraud A, Liu YT, Davidson GL, Rossor AM, Polke JM, Castleman V, Manji H, Lunn MP, Bull K, Ramdharry G, Davis M, Blake JC, Houlden H, Reilly MM. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry. 2012 Jul;83(7):706-10. doi: 10.1136/jnnp-2012-302451. Epub 2012 May 10. PubMed PMID: 22577229; PubMed Central PMCID: PMC3736805.
Koutsis G, Pandraud A, Polke JM, Wood NW, Panas M, Karadima G, Houlden H. Novel peripheral myelin protein 22 (PMP22) micromutations associated with variable phenotypes in Greek patients with Charcot-Marie-Tooth disease. Brain. 2012 Aug;135(Pt 8):e217, 1-6; author reply e218, 1-2. doi: 10.1093/brain/aws034. Epub 2012 Mar 1. PubMed PMID: 22382358; PubMed Central PMCID: PMC3407418.
Koutsis G, Karadima G, Pandraud A, Sweeney MG, Paudel R, Houlden H, Wood NW, Panas M. Genetic screening of Greek patients with Huntington's disease phenocopies identifies an SCA8 expansion. J Neurol. 2012 Sep;259(9):1874-8. PubMed PMID: 22297462.

Next destination:
Senior Molecular Pathologist in Neurodegeneration at Eli Lilly and Company

Phil McGoldrick

Phd Dates: 2008 – 2012

Phd Title: Investigating New Mouse Models of Amyotrophic Lateral Sclerosis

Project Description:
Research into the pathophysiology of ALS has been heavily dependent upon transgenic mice overexpressing mutant human proteins. Although these models have many advantages, to date they have not provided extensive translational benefits. In a complementary and alternative approach, my project was based upon characterising mutant mice generated by ENU mutagenesis. This method causes mutations in endogenous mouse genes, thereby avoiding overexpression artefacts and modelling disease in a more physiological setting.
I initially began my project examining mice with mutations in *Tardbp*, the gene encoding TDP-43. Mutations in *TARDBP* are not only causative of ALS, but cytoplasmic aggregation of TDP-43 is a pathological hallmark of approximately 97% of all ALS cases. Alongside 4 mutant TDP-43 lines, I also examined a mutant *Sod1* line, as mutations in *SOD1* are the second most commonly known cause of ALS. Study of these mutant lines was primarily done using combination of *in vitro* characterisation of primary embryonic motor neurons, including live cell imaging of mitochondrial function, and *in vivo* physiological techniques to assess motor function.
In addition to these ENU-induced ALS models, I was also able to work in collaboration with other groups on: transgenic mice overexpressing human wildtype *FUS*, *Zfp106* knock-out mice and *Scn4a* ENU mutant mice.

Supervisor(s): Professor Linda Greensmith & Professor Elizabeth Fisher

Significant Publications whilst at Centre:
Mitchell JC, **McGoldrick P**, Vance C, Hortobagyi T, Sreedharan J, Rogelj B, Tudor EL, Smith BN, Klasen C, Miller CC, Cooper JD, Greensmith L, Shaw CE . Overexpression of human wild-type FUS causes progressive motor neuron degeneration in an age- and dose-dependent. Acta Neuropathol. 2013 Feb;125(2):273-88. doi: 10.1007/s00401-012-1043-z. Epub 2012 Sep 9. fashion. . http://www.ncbi.nlm.nih.gov/pubmed/22961620
McGoldrick P, Joyce PI, Fisher EM, Greensmith L..Rodent models of amyotrophic lateral sclerosis. Biochim Biophys Acta. 2013 Sep;1832(9):1421-36. doi: 10.1016/j.bbadis.2013.03.012. Epub 2013 Mar 21. http://www.ncbi.nlm.nih.gov/pubmed/23524377
Ricketts T*, **McGoldrick P***, Fratta P, de Oliveira HM, Kent R, Phatak V, Brandner S, Blanco G, Greensmith L, Acevedo-Arozena A, Fisher EM. A nonsense mutation in mouse Tardbp affects TDP43 alternative splicing activity and causes limb-clasping and body tone defects. PLoS One. 2014 Jan 21;9(1):e85962. doi: 10.1371/journal.pone.0085962. eCollection 2014. http://www.ncbi.nlm.nih.gov/pubmed/24465814
Joyce PI, **Mcgoldrick P**, Saccon RA, Weber W, Fratta P, West SJ, Zhu N, Carter S, Phatak V, Stewart M, Simon M, Kumar S, Heise I, Bros-Facer V, Dick J, Corrochano S, Stanford MJ, Luong TV, Nolan PM, Meyer T, Brandner S, Bennett DL, Ozdinler PH, Greensmith L, Fisher EM, Acevedo-Arozena A.A novel SOD1-ALS mutation separates central and peripheral

effects of mutant SOD1 toxicity.Hum Mol Genet. 2015 Apr 1;24(7):1883-97. doi: 10.1093/hmg/ddu605. Epub 2014 Dec 2. http://www.ncbi.nlm.nih.gov/pubmed/25468678

Next destination:
University Of Toronto, Postdoctoral Fellow. Supported by ALS Association Milton Safenowitz Postdoctoral Fellowship

Alice Neal

Phd Dates: 2008 - 2012

Phd Title: Satellite cell Subpopulations and Environmental Mediators of their Function: Implications for Stem Cell Therapy in Skeletal Muscle

Project Description:
Satellite cells are myogenic cells found between the basal lamina and the sarcolemma of the muscle fibre. Satellite cells are the source of new myofibres; as such, satellite cell transplantation holds promise as a treatment for muscular dystrophies. There is a need to investigate factors that enable satellite cell survival and/or proliferation post engraftment in order to obtain the optimal donor
cell and host environment for efficient satellite cell transplantation. I have investigated sex differences in mouse satellite cell populations across the lifespan in vitro and in vivo. I show that satellite cell number and myogenic regulator factor expressions differ according to sex and developmental stage. Despite this, I show that engraftment efficiency is not mediated by the age or sex of the host
or the donor. I hypothesise that there are two distinct satellite cell populations: one for muscle growth and maintenance and one for muscle regeneration. I have used high dose ionising radiation to separate radio resistant from radio sensitive satellite cells. I demonstrate that radio resistant satellite cells do not contribute to growth but are able to contribute to host muscle regeneration post
transplantation and have compared their expression profiles using microarray. I hypothesise that satellite cells able to survive high dose ionizing radiation are the same population of satellite cells that are able to survive transplantation. Engraftment efficiency is greatly improved if host muscle is exposed to ionizing radiation prior to engraftment. I demonstrate that elimination of the host satellite cell pool is not sufficient to account for the improved engraftment efficiency with radiation and I have therefore investigated the role of the vasculature as a mediator of radiation induced improvement in engraftment efficiency.

Supervisor: Professor Jennifer Morgan

Significant Publications whilst at Centre:
The satellite cell in male and female, developing and adult mouse muscle: distinct stem cells for growth and regeneration. Neal A, Boldrin L, Morgan JE PLoS ONE. 2012 PMID 22662253
Donor Satellite cell Engraftment is Significantly Augmented when the Host Niche Structure is Preserved and Endogenous Satellite Cells are Incapacitated. Boldrin L, **Neal A**, Zammit PS, Muntoni F, Morgan JE. Stem Cells . 2012. PMID 22730231

Next destination
Post doctoral Research Scientist. Ludwig Institute for Cancer Research, University of Oxford.

Alasdair Wood
PhD dates: Sept 2008 – Dec 2012
PhD Title: Glycosylation Deffects and LGMD
Supervisors: Volker Straub, Juliane Mueller, Rita Barresi and Steve Laval
Next destination: Postdoctoral research, Monash University, Melbourne

Amy Innes
Phd Dates: 2007-2010
Phd Title: Characterisation of Novel Mutations within Heat Shock Protein 27 causing CMT2 F and dHMN II
Supervisor: Professor L Greensmith, Prof H Houlden
Next destination: Post grad MBBS, St George's university of London

Kieren Lythgow
PhD dates: Sept 2007 – Jul 2010
PhD Title: Bioinformatic approaches in mitochondrial disease
Supervisor: Patrick Chinnery
Next destination: Systems Administrator/Bioinformatician, Barts and the London

Sally Spendiff
PhD dates: Sept 2007 - **Nov 2011**
PhD Title: Investigating mitochondrial DNA mutations in muscle stem cells
Supervisors: Doug Turnbull and Hanns Lochmüller (situated in the mitochondrial research group)
Next destination: Postdoctoral research (Myology), Newcastle University

Elspeth Hutton
PhD Dates: Nov 08-Jan 2012
PhD Title: The skin as a window on mechanisms of neuropathy and neuropathic pain
Supervisors: Prof Martin Koltzenburg and Prof Mike Lunn
Next destination: Research fellow, Van Cleef centre for Nervous Diseases, Monash University, Australia