



Performing world class translational  
research to bring diagnosis, care  
and therapy to people with  
neuromuscular disease



## Message from Lord Walton of Detchant

I graduated in medicine from Newcastle Medical School in 1945 after a shortened wartime course. After military service I returned to Newcastle to become a medical registrar, so as to train in neurology. I joined Professor Nattrass as his research assistant in order to carry out research into the muscular dystrophies and other neuromuscular diseases. He and I published a landmark paper in 1954 in *Brain*, introducing a new classification of the muscular dystrophies, and I decided to spend such time as I could spare from my clinical duties to study this group of diseases.

In 1954 I received a Nuffield Foundation Fellowship to work for a year at the Massachusetts General Hospital in Boston, USA, and lectured on muscle disease in many US centres. I then received a major research grant from the Muscular Dystrophy Association of America, which enabled me on my return to the UK to appoint a number of clinical research assistants and fellows in biochemistry, neuropathology and clinical neurophysiology, all of whom contributed massively to our research programme. Happily, the US research grant was followed by others from Canada, from Muscular Dystrophy UK, and later from the Wellcome Trust and the Medical Research Council.

I became a Consultant Neurologist at Newcastle General Hospital (NGH) in 1958 and persuaded the then Regional Hospital Board to add on to the new Regional Neurological Centre 2 floors of research laboratories in order to house the research programme. Later still, major donations, one from an anonymous donor and others from supporters of Muscular Dystrophy UK and local Tyneside benefactors, enabled me to build a block of muscular dystrophy research laboratories at the NGH. Research in Newcastle was enhanced by many fellows who came from countries across the world. These were halcyon days when many papers, based upon work done in the department, regularly appeared in peer-reviewed journals. We were also successful in obtaining an endowed chair and senior lectureship in Experimental Neurology, funded by Action Research for the Crippled Child.

When, in 1983 with a rather heavy heart, because of burgeoning national commitments, I left Newcastle to move to Oxford, it was a source of immense comfort to me to note the way research on neuromuscular disease in Newcastle continued to develop and to prosper with outstanding success, led by so many of those, like the remarkable Kate Bushby, Volker Straub, Hanns Lochmüller and Rita Horvath. They have given me an immense honour by naming the research centre in the Institute of Genetic Medicine at Newcastle University the John Walton Muscular Dystrophy Research Centre. I am humbled but nevertheless deeply honoured by this accolade, of which I am immensely grateful and also very proud.

# About the centre

Newcastle has a long history as a centre of international excellence in muscle disease diagnosis, care and research. The team here has grown substantially over the years and now comprises a group of experts across many fields within muscular dystrophy who together form the John Walton Muscular Dystrophy Research Centre.

Our partnerships with regional, national and international life science and research partners, mean that we are also extremely well-placed to make our contribution to the idea of a Northern Powerhouse which aims to boost economic growth and prosperity in the north of England.



# Our vision

On the 24th November 2014, the John Walton Muscular Dystrophy Research Centre was launched.

It is now time to consider our forward vision.

These are exciting times for research in the field of neuromuscular diseases. In recent years we have seen great progress in our understanding of the genetic, genomic, molecular and physiological underpinnings of many neuromuscular disorders. This has led to the first clinical trials based on molecular and genetic mechanisms of disease. It is clear that the most promising times for translational research in these diseases still lie ahead.

The John Walton Centre is uniquely poised to make a decisive contribution to therapy delivery for patients with neuromuscular diseases.

Our Centre brings together a unique breadth of expertise and experience relating to translational research in neuromuscular disease. Over the past decade, the group has grown exponentially and we are very proud to deliver excellent care and diagnosis whilst being at the forefront of clinical and basic research directed to therapy delivery, supported by internationally directed networking, tools and resources.

These principles are encompassed in our mission statement:

*Performing world class translational research to bring diagnosis, care and therapy to people with neuromuscular disease*

Supported by our many partners, and working with University College London as the MRC Centre for Neuromuscular Diseases, our vision is to establish a physical centre where our multidisciplinary team can work with state of the art facilities to take the next steps that will enable therapy delivery to patients whilst enhancing access to the latest high quality care.

By achieving our vision, we will be able to provide diagnosis and opportunities to participate in research for all people living with neuromuscular disease, identify new therapeutic targets and so develop better, more effective treatments across all neuromuscular conditions. We will continue to put patients at the heart of everything that we do at the John Walton Centre, improving quality of life now and for future generations.

This will lead to a step change in our approach: bringing therapies to patients faster, whilst also also enhancing the experience and outcomes for patients under our care.





# John Walton Muscular Dystrophy Research Centre

*‘Performing world class translational research to deliver diagnosis, care and therapy to people with neuromuscular disease.’*

## Clinical care

We provide ongoing lifelong care for around 2000 patients with inherited neuromuscular disease from the north of England. Our team provides diagnosis, care and management via specialized clinics for paediatric and adult disease as well as for specific disorders such as myotonic dystrophy, congenital myasthenic syndromes and arthrogryposis.

We take our clinical team out to 8 locations across the north of England and provide training and education to medical and other professionals in this region and beyond. We have led on the generation of standards of care and work with colleagues across the region to co-ordinate and deliver multidisciplinary care enabling excellent outcomes. Patients attending our clinics value access to research via natural history studies, biobanking and registry initiatives and clinical trials. We work closely with patient organisations across the different disorders seen in the centre.

## Diagnostic services

Since 2001 we have led the nationally commissioned service for rare neuromuscular diseases. The Centre specifically provides the diagnostic and advisory service for limb girdle muscular dystrophies and overlapping diseases, based on a multidisciplinary approach including specialised muscle biopsy analysis, directed genetic testing and clinical assessment. Over 9000 patients have accessed this service over the last 14 years from all over the UK and abroad.

We have responded to the promise of next generation sequencing technologies with the introduction of specialised gene panels, and contribute in this area to Genomics England. Patients benefit from a precise diagnosis, allowing specific genetic counselling, prognostic and management guidance as well as access to registries and research programmes in these rare diseases.

## Basic research

By combining state-of-the-art methods for translational medical research, our lab-based team conducts comprehensive studies towards the genetic, biochemical and cellular understanding of neuromuscular disorders and therapies for these conditions. We focus on the identification of disease-causative genes, biomarkers and modifiers and the pathophysiological characterization of the diseases, making use of model systems, MRI studies and patient-derived material. Our research outputs contribute towards development of treatments for different patient populations, including studying and optimising therapeutic compounds to deliver better, safer and more effective treatments. The 4 directors of the centre have cumulatively published more than 1,000 articles in peer-reviewed journals, including top-rated discovery journals such as *Nature* and *Science*. Our research has obtained significant funding from research councils (MRC and ERC), Wellcome Trust, European Commission, charities and public-private partnerships.

## Clinical research

Our team has pioneered the establishment and training for outcome measures for clinical research in NMDs. We are a leading site for international patient studies and clinical trials. Our expertise, experience and facilities lead to our current involvement in 20 patient studies, 8 to assess the natural history of a number of neuromuscular diseases and 12 interventional drug trials. Patients currently participating in these studies are from across at least 8 different disease groups. This number has continuously grown and will further increase in 2016, with at least 7 new studies planned. Recruitment of patients into studies and trials in our Centre is supported by the use of disease-specific patient registries. Registries also serve to keep patients informed about current research activities, to contact them when new clinical trials are about to start and also to collect natural history data outside clinical studies. We have been instrumental in the set-up of many of these national and international registries.

## Networks & collaborations

We have a long tradition of working to establish networks and collaborations with stakeholders from across the neuromuscular and rare disease landscape, with an experienced team dedicated to the underlying infrastructure and coordination that allows research to happen. We have had great success in securing funding for collaborative EU projects and since 2007 have participated in a funded portfolio totalling €73 million, putting us firmly at the centre of the European neuromuscular and rare disease community.

Newcastle currently leads numerous funded projects involved in coordinating translational research and we collaborate with 22 national and 157 international patient organisations, research institutions and industry partners. Over the last 5 years these activities have brought in excess of €9m in grant funding to Newcastle.

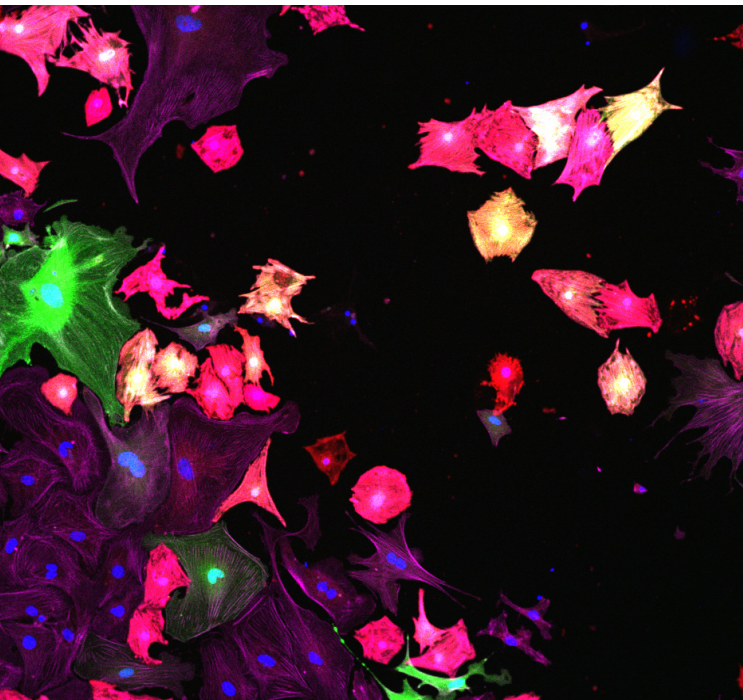


# Examples of our impact

We can demonstrate the impact of our activities across many disease areas, including:

Charcot-Marie-Tooth Disease  
Congenital Myasthenic Syndromes  
Duchenne Muscular Dystrophy  
Facio-Scapulo-Humeral Muscular Dystrophy  
GNE Myopathy  
Limb Girdle Muscular Dystrophies  
Mitochondrial Myopathies  
Myotonic Dystrophy  
Myotubular Myopathy  
Spinal Muscular Atrophy

The following case studies provide some examples.



# From basic research to personalised medicine

Ellie was diagnosed with congenital myasthenic syndrome when she was a baby, after being admitted to hospital with breathing difficulties and spending several months in intensive care, where doctors also noticed that her muscles were abnormally weak and fatigable. When she was 4 years old, it was discovered that the genetic defect responsible for her condition was a mutation in the CHAT gene. This causes problems with the transmission of signals from the nerves to the muscles. Knowing the genetic cause of the condition allows Ellie to receive a treatment that helps the signals get through, and this improves Ellie's symptoms.

The John Walton Centre is one of the few places in the world where people are working on all aspects of Ellie's condition. One group of lab researchers is studying animal models of her disease to try to better understand the mechanisms that stop the signals from the nerves getting through to the muscles, and to work out ways of treating this. Another group looks at genome sequences from people who have the same symptoms as Ellie but whose genetic diagnosis has not been found yet, to try to find the genetic fault and so give them a diagnosis and access to treatments. And of course, the doctors, nurses and physiotherapists who see Ellie every 6 months are experts in congenital myasthenic syndrome and can give Ellie care and treatments tailored to her specific condition. This joined up approach to the disease, with everything from lab research to expert care under one roof, is one of the things that makes the John Walton Centre truly unique.

Left: Heart cells from a mouse which have been stained in various colours to help identify different proteins.

# Leading in care standards and outcome measures

Patients with Duchenne Muscular Dystrophy (DMD) are typically diagnosed at the age of around 4 years when their parents report that their son (most affected people are boys) cannot run like other children and has frequent falls. The condition is progressive, and untreated boys lose the ability to walk around the age of 9 and die before the age of 20. Over the past 25 years the team in Newcastle has shaped the assessment and treatment of patients with DMD globally, with significant contribution in the UK to the development, implementation and dissemination of NICE accredited standards of care. We hope that most of the patients at our Centre can now be expected to retain ambulation into their teens and survive into adulthood with a far greater quality of life than was possible previously.

We have a range of exciting new DMD related projects in the pipeline. With the award of a recent EU grant, we will be leading a European trial of a novel compound, VBP15, which has been developed by our collaborators in Washington DC. The trial will include a number of innovative outcome measures, including MRI protocols and novel biomarkers. This is a promising molecule to replace steroids as standard of care in DMD. VBP15 offers the promise of benefits of steroid treatment but without the side effects.

Alongside our work in antisense oligonucleotide therapy and other novel agents, we believe that these strategies offer even greater prospects of enhanced wellbeing and survival for people with DMD. Increasing our portfolio to include advanced therapies such as gene therapy is a key target of our vision for the future.

# Novel diagnostics enabling trial readiness

Limb girdle muscular dystrophies (LGMDs) are a group of more than 30 different genetic muscle diseases that are typically characterized by progressive weakness and wasting of the shoulder and pelvic girdle muscles. Diagnostic facilities at the John Walton Muscular Dystrophy Research Centre are supported by the Rare Diseases Advisory Group Service for Neuromuscular Diseases (NHS England) and patients with limb girdle weakness from all over the UK are seen by our team in Newcastle for diagnostic and treatment advice. All the individual forms of LGMD are extremely rare and despite improved diagnostics a curative therapy is currently lacking for any of them. Medical care consists of the symptomatic treatment of complications, aiming to improve life expectancy and quality of life.

A prerequisite for successful drug development programs is a good understanding of the diseases' natural history. For 2 forms of LGMD associated with the genes for dysferlin (LGMD2B) and FKRP (LGMD2I), we coordinate natural history studies to assess outcome measures and biomarkers in international patient cohorts. Both studies apply magnetic resonance imaging (MRI) techniques for quantifying disease progression in a non-invasive and longitudinal fashion at early disease stages and with great sensitivity. Based on the collected imaging data, it is now important to determine which parameters are the most sensitive indicators of disease progression and how they correlate with clinical changes over time relative to physical assessment outcomes. These 2 studies, which are supported by patient organisations, will hopefully help us to use MRI as an outcome measure when we start clinical trials in LGMD2B and LGMD2I.



# Gene discovery impacting treatment options

At the John Walton Muscular Dystrophy Research Centre we study a very rare form of mitochondrial myopathy - reversible infantile myopathy. This condition results in children developing generalised muscle weakness shortly after birth meaning that they are not able to breathe, eat or move. Therefore, they require vigorous life sustaining measures such as assisted ventilation and tube feeding. However, the condition spontaneously starts to recover around 6 months of age, whereby muscle strength is regained and a near complete recovery is seen by the age of 2 years.

Our group here in Newcastle has found the mitochondrial DNA mutation that causes this disease. This meant that when Patrick showed severe symptoms after birth, he was able to be tested for this mutation. This meant that decisions about Patrick's care could be made in the knowledge that, by keeping him alive through his first 6 months, he was likely to be able to make a good recovery and lead a near-normal life in the future.

In addition to this clear and direct benefit to individual patients with reversible infantile myopathy, the latest research at the centre is investigating this rare disorder further to understand what it is that triggers patients' recovery. Muscle biopsies of patients before and after the recovery are studied and a small t-RNA molecule involved in the production of essential mitochondrial proteins has been shown to play a key role in the disease mechanism. This is critical because our findings inform research towards potential new and life-changing therapies for children with other mutations by trying to trigger recovery in them too.

5 day old zebrafish

# Patient involvement in research

Simon is 35 years old and affected by myotonic dystrophy. Over the last 10 years, he has developed weakness and cramping in his hands, swallowing difficulties and severe fatigue, as well as an arrhythmia in his heart. These symptoms were explained when the genetic fault was found by testing in Newcastle 5 years ago. Currently, there is no curative treatment for the condition.

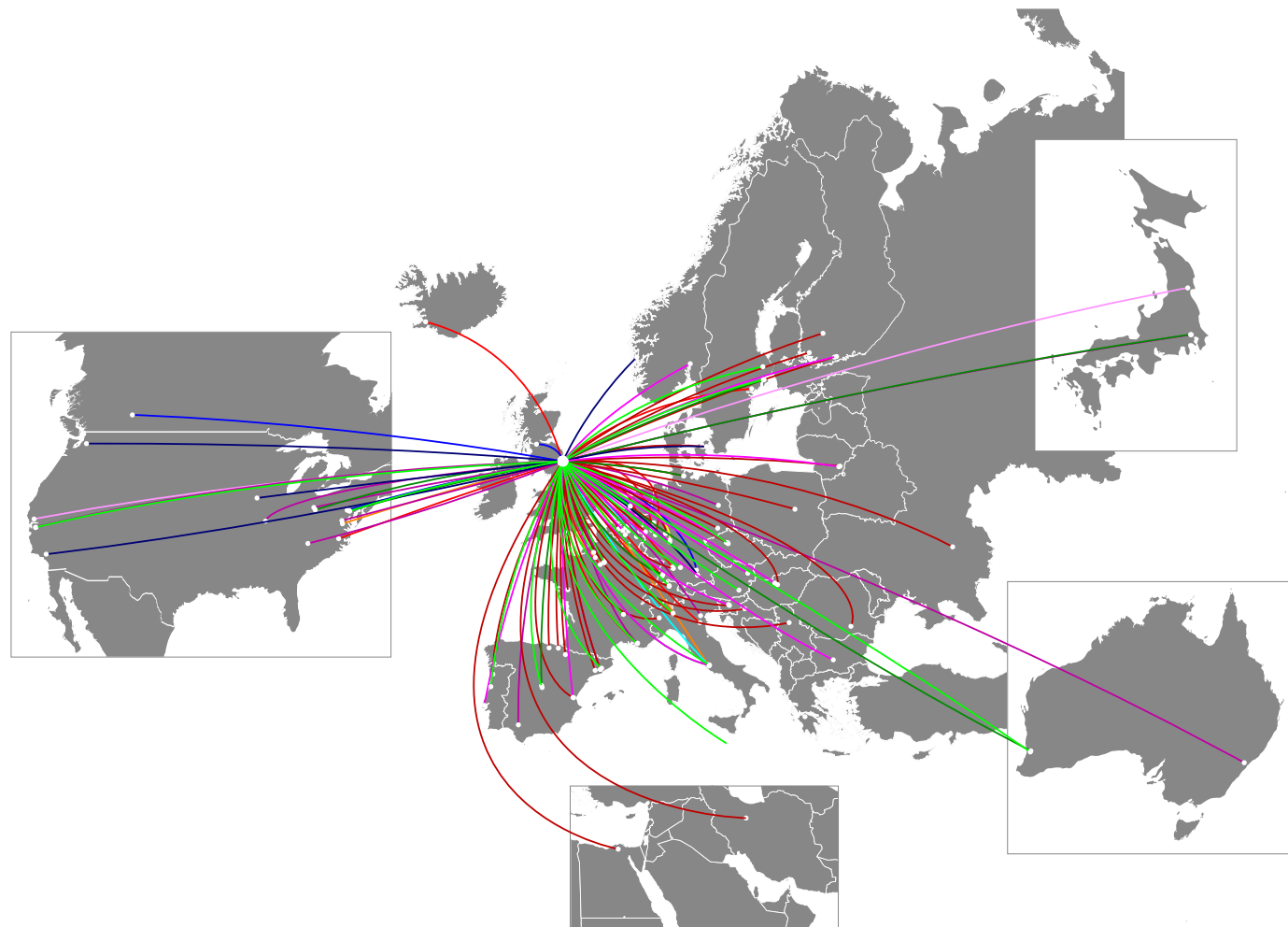
Simon is seen by the multidisciplinary team here at the Centre and he also signed up to the UK patient registry for myotonic dystrophy to hear about opportunities to take part in research. He recently enrolled in Optimistic, a clinical study run in 4 European countries which tests the impact of cognitive behavioural therapy and exercise on patients with myotonic dystrophy. Optimistic is the first large multi-centre study for myotonic dystrophy in Europe. Newcastle is the only UK centre for this study and has enrolled more than 50 patients. Participating in the study means attending half-day appointments every fortnight to receive the treatment, give blood samples and undergo tests. Simon feels less fatigued and more active since he started participating and will hear by the end of 2016 whether this treatment has a positive effect in the majority of patients. This would mean it might become standard treatment on the NHS. Simon also donated a tiny piece of his skin to the Newcastle biobank so that skin cells could be grown in a petri dish. These cells were reprogrammed to become stem cells and then heart cells which can be used to test the effects of drugs and other therapies in tissue culture – exciting new techniques employed here at the Centre that can help find out the causes of heart problems without having to touch the heart itself.

# International collaboration and networking

A real strength of the John Walton Muscular Dystrophy Research Centre is our leadership of international collaborative projects which bring together researchers, policy makers, patient organisations and industry partners from around the world. This is particularly important for rare-disease trial and drug development because both the patients and the researchers are spread across the globe. One key example is RD-Connect - a global infrastructure project, led from Newcastle, that links genomic data with registries, biobanks, and clinical bioinformatics tools to produce a central research resource for rare diseases. The linked resources provided via RD-Connect enabled us recently to make a new gene discovery for a patient seen here in Newcastle.

Thanks to our networking, their genome was able to be sequenced in Reykjavik and their proteome was analysed in Leiden. The findings from these analyses are being held in Cambridge and Barcelona and are made available to other doctors and researchers across the world. Because we have linked in to this process a system developed in Toronto to look for patients with shared findings, we found a matching patient in London. The really important impact of this global collaboration is that not only does the original patient benefit from having a diagnosis for the first time in their life, but their data can also be accessed to find diagnoses for other patients with the same condition. Defining new diseases like this offers for the first time ways to study the molecular pathophysiology of these conditions and understand pathways for therapies.

## Our collaborations



## With thanks to our funders who include





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The Newcastle upon Tyne Hospitals



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