Annual Report 2012

Centre of Research Excellence in Neuromuscular Disorders (CRE-NMD) and Australasian Neuromuscular Network (ANN)

www.ann.org.au

Australian Government
National Health and Medical Research Council

Australasian Neuromuscular Network

Who we are

The CRE-NMD will enable us to implement an Australia-wide multidisciplinary approach to neuromuscular disorders, and consolidate a national network of excellence in these areas to link in with international networks.

The CRE-NMD will reduce the burden of neuromuscular disorders, and promote excellence and innovation in research and clinical practice so that the latest in diagnosis and therapy is available throughout Australia.

Executive Report

Welcome to the inaugural report for the Centre for Research Excellence in Neuromuscular Disorders (CRE-NMD). The establishment of the CRE-NMD brings together researchers who have worked together for more than 15 years, and who are at the forefront of gene discovery and translational research in neuromuscular disorders.

The CRE-NMD will translate ‘best evidence’ from our clinical and laboratory-based research, including gene discovery, disease mechanism and therapy development, into ‘best clinical practice’ under two themes of diagnosis and prevention and treatment. The CRE-NMD will consolidate our place at the forefront of neuromuscular research internationally.

It will foster future research leaders and international partnerships to ensure the sustainability of excellence in neuromuscular research, and ultimately vastly improve health outcomes and quality of life for thousands of patients and their carers.

Since the establishment of the CRE-NMD in January 2012, we have worked towards developing a sustainable model for collaborative research. Firstly, we have built the Australasian Neuromuscular Network (ANN), which through well defined steering groups aims to disseminate and communicate the important research being conducted under the goals of the CRE-NMD grant. The ANN is well placed to continue leveraging funding to ensure longevity and sustainability of the research collaborations established through the CRE-NMD.

Secondly, the CRE-NMD supports a number of outstanding research fellows (clinicians, physiotherapists and researchers) and PhD students at key research sites in Australia (WA, VIC, NSW). The focus on supporting and providing high quality training for early career researchers will contribute to a sustainable future for research in neuromuscular disorders across Australia. A number of our early career researchers presented at our most recent annual meeting in Sydney in March 2013. This was a unique opportunity for all chief investigators, associate investigators and early career researchers to share knowledge and forge new collaborations.

Lastly, to work towards our ongoing sustainability and in recognition of the global reach of both the CRE-NMD and ANN, investigators and associate investigators from the CRE-NMD were invited to formally partner with European Union groups on an FP7 rare disease research program. With successful matching of NHMRC funding, the research program aims to address improving diagnostics, developing clinical guidelines and standards of care and developing shared platforms for data analysis and repositories. The CRE-NMD and ANN are leading this initiative for neuromuscular disorders and will pave the way for other rare diseases that impact Australians and in areas where we have national and international leadership and expertise.

CRE-NMD/ANN Executive

Prof Kathryn North

Prof Nigel Laing

A/Prof Monique Ryan

A/Prof Nigel Clarke

A/Prof Joshua Burns

Introduction

The CRE-NMD's research program will translate 'best evidence' from our clinical and laboratory-based research, including gene discovery, disease mechanism and therapy development, into 'best clinical practice' under two themes of diagnosis and prevention and treatment.

We will instigate a national collaborative diagnostic network involving multidisciplinary clinics and testing laboratories, to ensure that all patients have access to an accurate genetic diagnosis to inform prevention through prenatal diagnosis and to guide prognosis and surveillance. We will investigate prevention strategies built on population screening methods and build a coordinated clinical trials program so that potential new treatments developed in Australia and overseas will be quickly accessible to all individuals regardless of where in Australia they live. We will also develop a nationally integrated training program, using our comprehensive and complementary expertise in laboratory and translational research to provide an unparalleled experience for future clinical and laboratory

research leaders. The CRE-NMD will thus be the national hub for consolidating and expanding our national research and training initiatives.

The CRE-NMD will engage with the clinical and research community through the Australasian Neuromuscular Network (ANN). The ANN has over 300 members from Australia and New Zealand with representation from clinical care, allied health, pathology, nursing, research, and patient advocacy and parent groups. The ANN aims to address deficiencies in timely diagnosis and treatment, fragmented research efforts, shortcomings in data collection and lack of effective care for all individuals regardless of where they live.

Within the themes of Diagnosis and Prevention, Clinical Care, Clinical Trials and Research, the ANN will underpin and aims of the CRE-NMD, as the goals of the CRE-NMD and ANN are complementary. The CRE-NMD and the ANN will turn best evidence in best practice through a number of key initiatives:

- Improving diagnosis and prevention
- Developing best practice in diagnosis, care and treatment
- Training the clinicians and researchers of the future
- Expanding patient registries
- Enhancing clinical trial readiness
- Establishing a national clinical trials network
- Promoting research collaboration

The CRE-NMD will take Australia's existing research and clinical activities in this field to a new level, positioning us as an international leader in translational research in neuromuscular disorders.

Specifically, the CRE-NMD aims to achieve the following major outcomes:

• **Instigation of a national diagnostic network** to coordinate diagnosis to increase access, efficiency and diagnostic accuracy, decrease costs and develop research patient cohorts.

• **Accelerated gene discovery.** We have established large and unique patient cohorts and will use state-of-the-art next-generation sequencing technologies to find the causative genes for disorders where it was previously impossible to do so. We predict that within the next 10 years, almost all Australian NMD patients will have access to an accurate genetic diagnosis, which is essential for guiding management, for prediction of recurrence risk, for prevention through prenatal diagnosis, and, increasingly, for eligibility for clinical trials of new therapies.

• **National patient registries for each NMD.** Registries represent an important interface between researchers and patients and are the first port of call for enrolling patients in

clinical trials. They also enable clinical research into natural history and genotype-phenotype correlation.

• **Establishment of the applicability of population screening programs** for NMDs, aimed at reducing the health, social and economic burden of NMDs in Australia.

• **Australian leadership in phase II/III clinical trials for NMDs within a national clinical trials framework.** We have already established two centres with the expertise to participate in international clinical trials. The CIs and AIs on this proposal are developing novel therapeutic agents as part of their laboratory-based studies of new drugs (CIA, CIF), gene up-regulation (CIB), exon skipping (AIA) and stem cell therapy (AID, AIE). Our allied health CIs (CID, CIH) are pioneering physical therapy and rehabilitation trials targeting day-to-day difficulties of patients with NMDs. The CRE-NMD will enable us to initiate and lead new clinical trials and to engage all states to ensure patients have equal access to state-of-the-art therapies.

• **The development of a nationally integrated research training program** will draw together early career researchers in medicine, science and allied health from all states, promote interchange of staff and students, and encourage collaborative projects between sites.

The CRE-NMD will consolidate our place at the forefront of neuromuscular research internationally. We are currently leaders in gene discovery and diagnosis, and the CRE-NMD will elevate us to leaders, rather than participants, in the treatment of NMDs. The CRE-NMD will enable Australia to build a critical mass in all areas of basic and clinical research into disorders of muscle and nerve. It will foster future research leaders and international partnerships to ensure the sustainability of excellence in neuromuscular research, and ultimately vastly improve health outcomes and quality of life for thousands of patients and their carers.

Our Staff

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Our Team

CHIEF INVESTIGATORS

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Prof Kathryn Refshauge

Dr Michael Buckley

Prof Catriona McLean

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Prof Garth Nicholson

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Victoria (Alfred Hospital/Monash)

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Marnee Mackay	CRE-NMD Phd
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Dr Paula Bray

Dr Leanne Mills

Elena Mamontov Nursing update

Our Early Career Researchers

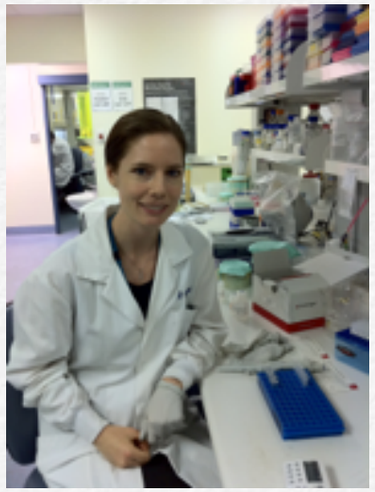
Education and training of healthcare professionals plays a crucial role in the improvement of patient diagnosis and care. Many trainees have limited access to specialty clinics, particularly adult neurologists in training who do not see neuromuscular cases unless they attend a specialist clinic. The CRE-NMD/ANN will identify and publicise training opportunities for medical trainees as well as nursing and allied health professionals, via the website and newsletter.

Zoë Davidson is an Accredited Practising Dietitian specialising in paediatric nutrition. Her recent doctoral research focused on advancing the evidence base for the nutritional management of boys with Duchenne muscular dystrophy. A key component of this research is a randomised control trial investigating the use on nutriceuticals in DMD for which recruitment is ongoing. Her PhD research also included a retrospective evaluation of growth in DMD; and investigating Vitamin D requirements for boys using corticosteroids. Zoë is continuing research in this area during her postdoctoral period as she embarks on a research post with Murdoch Children's Research Institute funded by the CRE. Zoë also lectures into the Bachelor of Nutrition and Dietetics and Bachelor of Nutrition Science programs at Monash University.

Currently, Zoë is continuing to coordinate the nutriceuticals study with sites running at the Royal Children's Hospitals in Melbourne and Brisbane. A new site will opening for recruitment in Sydney in 2013. Other research that Zoë is progressing includes:

- the development and evaluation of nutritional guidelines for DMD;
- a longitudinal study to assess energy expenditure and body composition of young boys with DMD; and
- a retrospective study investigating the relationship between dystrophin mutation and cardiac outcomes in DMD.

Zoe plans to extend her research program into other neuromuscular disorders including spinal muscular atrophy and congenital muscular dystrophy during 2013.



Rachael Duff is a postdoctoral research fellow working under Bill Gole and has worked in the area of neuromuscular genetics for fifteen years. Rachael's PhD, which was an investigation of the genetic causes of several neurodegenerative disorders, was completed in 2008 at UWA under the supervision of Professors Nigel Laing, Steve Wilton and Frank Mastaglia. The work resulted, amongst other findings, in the successful identification of a mutation in FLNC responsible for a novel form of distal myopathy. Between 1999 and 2009, Rachael worked at the Neurodegenerative Disorders Centre located at the Australian Neuromuscular Research Institute's high throughput genetic screening facility.

In 2009, Rachael relocated to the United Kingdom to complete a post-doctoral position at the National Heart and Lung Institute (NHLI), Imperial College, London. Working with Professors Bill Cookson and Miriam Moffatt, projects involved investigating the role of microbial flora on the development and progression of respiratory conditions using molecular biology techniques and bioinformatics.

Since returning to Nigel Laing's Laboratory in October 2010, Rachael has been awarded a three year Bill Gole postdoctoral fellowship from the Motor Neurone Disease Research Institute of Australia. The fellowship project involves the use of next generation sequencing technologies and bioinformatics to identify disease causing genes in motor neurone disease. Rachael also has funding from the Australian Mitochondrial Disease Foundation to develop and validate Next Generation Techniques for the diagnosis of mitochondrial disease.

Gina Ravenscroft is a postdoctoral researcher, holder of an Australian National Health and Medical Research Council Early Career Fellowship, within Prof Nigel Laing's Molecular Neurogenetics Laboratory in Western Australia. Gina joined Prof Laing's group as a PhD student after obtaining her undergraduate degree and Honours qualifications majoring in Physiology at the University of Western Australia.

Her main research interests include identification of disease genes and mechanisms for neuromuscular foetal akinesias and strongman syndrome; and investigating routes to therapy for a group of severe congenital muscle diseases caused by mutations in the skeletal muscle alpha-actin gene.

The foetal akinesias are a clinically and genetically heterogenous group of disorders in which the unifying feature is lack of foetal movement[1]. Most cases are lethal during the prenatal or early postnatal period. Other characteristics of this disease entity include: joint contractures, pterygia, polyhydramnios, hydrops, respiratory hypoplasia, craniofacial abnormalities and reduced muscle mass. A number of foetal akinesia cases are due primarily to muscle defects and some also present with pathologies seem in the congenital myopathies and dystrophies. The overlap in structural lesions observed in foetal akinesia and the congenital myopathies as well as overlap in disease genes have lead some to hypothesise that some of the foetal akinesias and the congenital myopathies may represent a disease continuum rather than separate disease entities. Despite some success in recent years at identifying the genetic cause of cases of foetal akinesias, the vast majority of published cases do not have a genetic diagnosis. The overall success rate for published cohort studies of the foetal akinsias is only ~ 25%. With the emergence of next generation sequencing (NGS) it is now possible to meet the need for genetic diagnosis of the foetal akinesias. To date we have performed NGS of probands from 20 foetal akinesia families: this has resulted in the identification of two novel foetal akinesia-nemaline myopathy genes (three families), and a genetic diagnosis in a further six families where previously this was not possible[2]. The two new genes are responsible for a significant number of recessive foetal akinesia-nemaline myopathy cases worldwide.

Strongman syndrome, a newly recognised entity described by Dr Bernard Brais in the French-Canadian population in Quebec, in which patients present with excessive muscle strength and

bulk, in the absence of training. Patients also exhibit numerous medical complications: muscle fatigue, cramping, poor sleep; and in some cases life-threatening compartment syndrome and rhabdomyolysis. In collaboration with Drs Brais and Phillipa Lamont, we are trying to unlock the genetic cause/s of strongman syndrome in Australian patients using NGS.

Dr Ravenscroft, is also involved in projects investigating potential therapeutics for skeletal muscle alpha-actin based congenital myopathies[3], using mouse models[4-6]. The main focus currently, is using up-regulation of the foetal actin isoform, cardiac alpha-actin, to replace the missing or defective skeletal muscle alpha-actin gene in mouse models of recessive and dominant disease, respectively. This includes investigation of viral delivery of actin.

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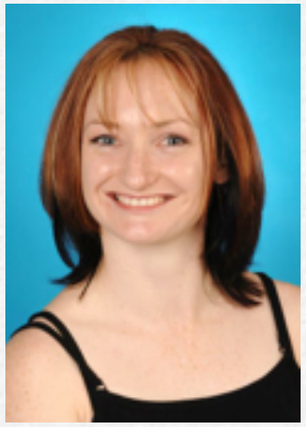
2. Ravenscroft, G., Thompson, E.M., Todd, E.J., Yau, K.S., Kresoje, N., Sivadorai, P., Friend, K., Riley, K., Manton, N.D., Blumbergs, P., et al. (2013). Whole exome sequencing in foetal akinesia expands the genotype-phenotype spectrum of GBE1 glycogen storage disease mutations. Neuromuscul Disord 23, 165-169.

3. Nowak, K.J., Ravenscroft, G., and Laing, N.G. (2013). Skeletal muscle alpha-actin diseases (actinopathies): pathology and mechanisms. Acta Neuropathol 125, 19-32.

4. Nowak, K.J., Ravenscroft, G., Jackaman, C., Filipovska, A., Davies, S.M., Lim, E.M., Squire, S.E., Potter, A.C., Baker, E., Clement, S., et al. (2009). Rescue of skeletal muscle alpha-actin-null mice by cardiac (fetal) alpha-actin. J Cell Biol 185, 903-915.

5. Ravenscroft, G., Jackaman, C., Bringans, S., Papadimitriou, J.M., Griffiths, L.M., McNamara, E., Bakker, A.J., Davies, K.E., Laing, N.G., and Nowak, K.J. (2011). Mouse models of dominant ACTA1 disease recapitulate human disease and provide insight into therapies. Brain 134, 1101-1115.

6. Ravenscroft, G., Jackaman, C., Sewry, C.A., McNamara, E., Squire, S.E., Potter, A.C., Papadimitriou, J., Griffiths, L.M., Bakker, A.J., Davies, K.E., et al. (2011). Actin nemaline myopathy mouse reproduces disease, suggests other actin disease phenotypes and provides cautionary note on muscle transgene expression. PLoS ONE 6, e28699



Leigh Waddell has a PhD in improving the diagnosis of muscular dystrophies. Leigh is employed as the Laboratory and Diagnostics Manager for the INMR, and is a postdoctoral scientist coordinating the gene discovery research with Dr Nigel Clarke.

As part of a research project into gene discovery, we have sent 249 samples from 125 families with neuromuscular disorders, collated from around Australia and New Zealand, to the Broad Institute for whole exome sequencing (protein coding regions of genome). The majority of these samples have previously been analysed through the INMR standard research-based diagnostic testing processes, which typically achieves ~50% diagnosis but excludes the common forms of muscular dystrophy such as Duchenne muscular dystrophy, Facioscapulohumeral muscular dystrophy and the myotonic dystrophies. The preliminary results on the first 88 samples (33 families) demonstrate a 73% diagnostic rate; 19 families with mutations in known genes and 5 in novel genes.

Dr Emily C. Oates is a Clinical Geneticist and is currently enrolled in a PhD.

Emily is a clinical geneticist with a long-standing interest in both clinical and basic science-based medical research – particularly genetics-focussed research. She worked on numerous research projects during her undergraduate Medical Science and Medical degrees. After completing clinical training in paediatrics, and advanced clinical training in clinical genetics, she recommenced her research career by enrolling in a full time PhD in 2010 at The Institute for Neuroscience and Muscle Research. Whilst undertaking her PhD, she has maintained her clinical skills by continuing to work as Neurogenetics fellow in the Children's Hospital at Westmead Neurogenetics Clinic. Her primary clinical and research interests are outlined below:

Clinical Genetics

As a clinical geneticist Emily has developed expertise in the careful evaluation of family and clinical history, examination findings, and the interpretation of relevant investigations to

establish an accurate clinical diagnosis, an important first step in establishing a formal genetic diagnosis, and in formulating an effective clinical management plan. She is currently developing expertise in the use of new technologies e.g. next generation sequencing, to establish genetic diagnoses in previously undiagnosed individuals. She also has a keen interest in the provision of accurate, well-considered genetic counselling, and in the education of clinical genetics trainees.

Clinical management of paediatric neuromuscular diseases and Neurofibromatosis Type 1 (NF1)

Emily has worked as a clinical geneticist in the CHW-based tertiary referral Neurogenetics clinic for over four years, and during this time have been actively involved in the management of a range of nerve and muscle disorders, and in the management of an autosomal dominant genetic disorder, NF1, in hundreds of children. In the final year of her training, she incorporated current best practice guidelines, and recommendations from local consultants into a guideline for management of Duchenne muscular dystrophy patients for use by the CHW Neurogenetics team - which remains in active use. She has also participated in the conduct of clinical trials for novel pharmacological and gene-based therapies for neurogenetic disorders, and has first and middle author publications arising from my NF1-related clinical work.

Centronuclear myopathy (CNM), and non-5q Spinal Muscular Atrophy (SMA)

During the last three years, Emily has been undertaking a PhD, supervised by Dr Nigel Clarke, Professor Kathryn North, and Dr Biljana Ilkovski. Her research has focussed on the further-evaulation of the clinical, pathological and genetic basis of two paediatric neuromuscular disorders; CNM, and an atypical lower-limb predominant form of SMA (an anterior horn cell disease which is quite distinct from the better known recessive SMA caused by deletions and mutations of the SMN1 gene on chromosome 5q). She has several publications arising from this work, including first author publications in Brain, and The American Journal of Human Genetics. During the course of her PhD she has played a key role in the exciting discovery of a new Dominant SMA gene, BICD2, and is now leading an international research collaboration to further-characterise disorders caused my mutations within this gene. The ultimate goal of this research is improved genetic diagnosis rates for patients with these disorders, and the identification of novel targets for effective future therapies.

Childhood-onset disorders of nerve and muscle result in severe weakness, chronic disability and early death. Almost half the children with neuromuscular disorders do not have a specific diagnosis, which adversely affects their medical care, provision of accurate genetic counselling, and access to potential new

therapies. The overseas phase of this project will be with one the world's leading paediatric neuromuscular centres, where Emily will learn to apply state of the art next generation sequencing techniques, muscle MRI analysis and biomarker technologies to the task of neuromuscular diagnosis. Emily will at first be applying these skills to the detailed analysis of Australian Centronuclear Myopathy and Dominant Spinal Muscular Atrophy patient cohorts established during the course of her PhD, with the aim of improving genetic diagnosis rates for patients with these diagnoses. If time permits, she will also be undertaking studies to analyse the effects of mutations on cell function, to further-confirm pathogenicity, and to gain further insight into the underlying mechanism(s) of disease. Emily will then return to Australia to apply these same skills to the task of improving genetic analysis rates in Australasian paediatric neuromuscular patients, including patients seen by myself, and other clinical members of the Children's Hospital at Westmead Neurogenetics clinic, as well as patients from centres around Australia and New Zealand. With its potential to significantly improve genetic diagnosis rates in Australasian neuromuscular patients, this project is anticipated to have a significant impact on lives of this vulnerable patient group, and their families, within just a few short years. In addition to its clinical relevance, the project will form the foundation of a future research career which, it is hoped, will contribute to a body of high quality gene discovery-related research, and eventually lead to development of effective pharmacological and gene-based therapies.

Sarah Sandaradura is a clinical genetics trainee, who is currently completing a MPhil through the Institute of Neuroscience and Muscle Research at the Children's Hospital at Westmead, supervised by Professor Kathryn North and Dr Nigel Clarke. She completed her medical training in New Zealand, before moving to Australia to train in Clinical Genetics. Sarah's research focuses on nemaline myopathy and includes a natural history study on nemaline myopathy, though which she hopes to gain evidence for genotype-phenotype correlation, and a survey of parents of children on tyrosine, looking at the benefits and side effects of this medication. This project has also involved clinical characterisation of a new disease gene for nemaline myopathy, identified through use of exome sequencing.

Our Goals

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Transforming the management of
neuromuscular disorders
from ‘compassionate assistance’ to
targeted therapy and prevention

Diagnosis and Prevention

A diagnostic network will link research and diagnostic laboratories across states to promote the continuous and rapid translation of new tests into standardised best practice diagnostic protocols. Its aims is to coordinate a national collaborative diagnostic service and research network for neuromuscular disorders that is cost-effective, maximises availability and minimises duplication of laboratory services.

Currently there is no coordination of testing between states. Core disorders that are tested for and the separate tests undertaken vary between laboratories and no list exists of what tests are available and their locations

Diagnostic testing has been developed within a number of Australasian research laboratories based on individual interests. While this has significantly improved the diagnosis for a number of individual conditions – usually free of charge - this decentralised and non-systematic approach to testing is not sustainable in the long-term, and is not best practice to ensure the optimal health outcomes for patients on a national scale. The diagnostic services provided by research laboratories are vulnerable to changing research priorities. An integrated network linking research and diagnostic laboratories would promote the continuous and rapid translation of new tests to standardised diagnostic protocols. In addition, there is no process for the transfer of tests developed within research laboratories into NATA accredited routine testing laboratories. Clinicians do not know what tests are available or where within Australia. The RACP is undertaking a study to assess how best to coordinate testing, however in the meantime the CRE-NMD/ANN has developed a list that will be made available on the ANN website and will be updated on a regular basis. In addition, the Federal Government has established a working party to look into developing a national diagnostic network. The CRE-NMD is represented through membership within the working party.

A list of genetic tests available in NATA accredited laboratories is available on the ANN website
http://www.ann.org.au/neuromuscular-gene-tests/

Improving diagnosis: Accelerating gene discovery

Next Generation Sequencing (NGS) is the ‘next step’ in molecular diagnosis. The goal of improving the molecular diagnostic success rate (aim is 90%) and accelerating gene discovery and establishing a national diagnostic network is underpinned by NGS. It is a powerful tool, best described by Prof Nigel Laing from his own personal experience:

Between 1993 and 2011, 15 new genes were discovered

Since March 2012, more than 5 new genes have been discovered.

While the rate at which whole exomes can been screened is increasing rapidly (within 1-2 years, new machines will be able to screen up to 50 exomes in 4 hours), and the cost per sample is also rapidly decreasing to approx. $1000, the enormity and complexity of the data generated requires interpretation by experts. Diagnosis using NGS is complex and includes a pre-analytical component of clinic- pathological diagnosis and an interpretative post-analytical component.

Muscle Bank

A muscle bank will provide a valuable resource for researchers, to understand the mechanisms of disease, improve diagnosis and identify novel genes and potential new therapies.

The muscle bank will be based on the successful Australian Brain Bank Network. The Brain Bank has collected 996 tissues in Victoria, there are 119 continuing projects and 500 publications have resulted from the tissue made available through the bank. An internet-based database would be developed to store the de-identified muscle information. This would be held nationally but the physical tissue would be stored locally within each laboratory. This has to be done prospectively. Tissue already collection cannot be used due to inadequate consent. Requests for tissue would be made via the website and a scientific advisory committee would oversee the application process. All samples made available through the bank must be consented for diagnosis and research purposes. Each site will need to ensure that they are handling and storing material in a standardised way and that consent is in place - the ANN will develop generic consent and information forms that can be broadly circulated.

Researchers can search the central database and formally apply for tissue to be sent to them. Each application is assessed by an Advisory Board - ethics approval must be in place by the institution so the Advisory Board’s role is to review the research protocol and if the requested tissue is available.

Population Screening using NGS

The clinical diagnosis of Duchenne muscular dystrophy (DMD) is often delayed until the age of 4-6 years, by which time there may be multiple affected younger boys within the sibship or affected boys born to other women in the family who did not know that they were carriers. Many other NMDs are recessive, meaning that they affect children in families with no family history. Population screening has been associated with decreased incidence of specific diseases within specific populations eg. Tay Sachs. DMD screening occurs in a small number of countries, and has generated much controversy and debate.

The US is currently undertaking a pilot study supported by the CDC (Annals of Neurology) and, in Australia, Nigel Laing and Klair Bailey have funding for a feasibility study of DMD screening that is being run in collaboration with NSW Newborn Screening.

Telepathology

Telepathology uses the internet to transfer high quality pathology images between distant locations for the purpose of diagnosis, education and research. The virtual slide system uses an automated digital slide scanner to create a digital image file of an entire glass slide. The file is then stored and can be viewed over the internet.

The ANN/CRE-NMD would utilize telepathology in diagnosis to discuss difficult or interesting cases, and it would also play a role in the national diagnostic network. Images would also be uploaded onto the website along with clinical information as a teaching tool. The implementation of telepathology will improve diagnostic capacity within Australasia.

Treatment

Australia is considered, along with the US, UK and Europe, as a viable first line site in which to conduct clinical trials. Our strengths are that we have experience and world-class expertise in neuromuscular disorders, in diagnosis, clinical care and research. In addition, we are a relatively small neuromuscular community with a positive history of close collaboration.

It will take a significant increase in funding to establish clinical trials in each state. In the meantime, the ANN will support local evaluator training to support less intensive trials that can be undertaken through local clinics.

Progress has been made in the development of disease specific outcome measures. NSW and VIC are leading studies to develop outcome measures for clinical trials. The CRE-NMD is supporting PhD scholarships for allied health students to undertake studies to determine normative data against which disease specific outcome measures can be identified.

The next five (5) years will be challenging, however there has been progress towards identifying clinical trial projects that can perform at sites without established clinical trial infrastructure. The Neutriceuticals trial will be undertaken across VIC, QLD and NSW, and the VIC serial casting in DMD project has been expanded into Sydney Children’s Hospital.

There has also been progress towards providing training for allied health professionals and their involvement in clinical trials. There are fellowships provided through VIC and NSW, however there needs to also be a more formal exchange of trainees and encouragement and support for new trainees to specialize in neuromuscular disorders.

Our minimum standards guidelines for establishing a multi-disciplinary clinic will provide much needed evidence to leverage funding. This funding will not only allow the establishment of clinics, but it will support the recruitment of dedicated nurse clinic coordinators and the training of associated specialists in the area of neuromuscular disorders.

Enhanced clinical trial readiness

The CRE-NMD provided support for Michelle Eagle from the UK to lead a clinical trials workshop for physiotherapists as part of the Duchenne Foundation's Riding the Wave Conference and RCH organized a training day for 55 physiotherapists in August. NSW is also providing training for local allied health professionals as part of the serial casting project.

Establishment of a national clinical trials network

There is increasing involvement of allied health professionals in clinical trials. NSW, VIC and WA are all leading studies with allied health involvement.

NSW: physiotherapy and podiatry

Congenital myopathy - tyrosine questionnaire

Curcumin –1 year follow-up pilot study

Nemaline myopathy – vibration study

Sleep parameters in DMD

Vic: physiotherapy, dietetics, OT, sleep therapists

Sleep parameters in DMD

Genetics: extended family support program

Physiotherapists' study of complementary medicine

Physiotherapists' study of serial casting in DMD

Physiotherapists' development of standardised assessment methods in NM clinic

Sleep parameters in DMD, SMA

OT study of upper extremity function in DMD

Psychological profiling in DMD, BMD and carriers

Review of transition services

WA: neonatal screening

Clinical Trials Update - National and International

VICTORIA

Some highlights of clinical trials that the Royal Children's Hospital is currently participating in:

- DMD114349 – An open label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne muscular dystrophy.
- Open-label PTC GD-019 study-anticipation of enrolment of 4-6 children in this study.
- The RCH research physiotherapists are also undertaking a survey of use of traditional and complementary therapies in patients seen in our NM clinic.
- Ongoing involvement in the CINRG UC Davis natural history study.
- Ongoing study on serial casting in selected patient of ambulant boys with DMD.
- Ongoing study of Nutriceuticals in DMD (collaboration with Zoe Davidson and Helen Truby from Monash University, Department Nutrition and Dietetics).
- Study of bone mineral density and zoledronic acid in boys with DMD (collaboration with A/Prof Margaret Zacharin, paediatric endocrinologist), RCH.

NEW SOUTH WALES

Some highlights of clinical trials that the Children's Hospital at Westmead is currently participating in:

- Congenital myopathy - progressing well with the tyrosine questionnaire
- Curcumin – Sarah Sandadura is involved in a 1 year follow-up pilot study
- LaminA and Centronuclear myopathy – single family trials of novel therapies (pre-treatment)
- Nemaline myopathy – vibration study
- DMD114349 – An open label extension study of the long-term safety, tolerability and efficacy of GSK2402968 in subjects with Duchenne muscular dystrophy.
- Open-label PTC GD-019 study-anticipation of enrolment of 4-6 children in this study.
- Ongoing study of Nutriceuticals in DMD (collaboration with Zoe Davidson and Helen Truby from Monash University, Department Nutrition and Dietetics).

Reliable Measures

A/Prof Joshua Burns is leading the 1000 Norms project which has two CRE-NMD supported PhD students taking normative data to establish an online repository of normative data for use internationally.

National clinical trials network

Allied health and Nursing steering groups have been established through the ANN to progress the goal of supporting the objective of clinical trial readiness at more centre's in Australia. Currently, NSW and VIC participate in international trials.

Physio training day- Organisation of one day training workshop at Royal Children's Hospital Melbourne on 10 August 2012 for community physiotherapists, to equip them to provide physiotherapy management at a consistently high standard in line with the current international standards of care. Organised by Kate Carroll, Chiara Tewierik, Rachel Kennedy, Katy de Valle - 50 physios attended

Dr Michelle Eagle CRE training- The CRE-NMD supported travel for an international expert to complete training in QLD to provide evaluator training for physiotherapists. This training is a requirement for all clinical trials, as trained evaluators are required to take the primary outcome measures.

Serial casting- a collaborative study of serial casting in boys with DMD is currently underway across VIC and NSW (PI: Dr Kate Caroll, The Royal Children's Hospital, Melbourne).

To ensure our patients are clinical trial ready for trials undertaken anywhere in the world, the CRE-NMD has supported and contributed to the expansion of registries through the Neuromuscular Disorders Registry Advisory Committee led by Dr Hugh Dawkins.

Registries

The Duchenne muscular dystrophy, Spinal muscular atrophy and Myotonic dystrophy registries are operational in Australia and New Zealand, with FSHD and Congenital muscular dystrophy to follow.

New Zealand has benefited enormously from inclusion in the ANN and with support from Dr Hugh Dawkins – the MDANZ has a database of 60-70 conditions covered by a single ethics application, and to date 175 patients have uploaded their information into the DMD registry.

Develop guidelines in neuromuscular disorders in an Australian context

Establishment of multi-disciplinary clinics

A draft guideline for the establishment of a multi-disciplinary clinic was circulated for discussion and comment. This guideline will provide a minimum standard of care and will also

provide a useful and powerful tool to leverage funding from local and state governments. Once finalized the document will be broadly circulated, including ensuring that state health departments receive a copy and will be available on the ANN website.

The guidelines are being developed to be of most relevance for clinicians who do not have specific expertise in neuromuscular disorders but are looking for guidance. The guidelines will also provide a template for neuromuscular clinical services.

Gap analysis

The CARE-NMD survey will be implemented throughout Australia and New Zealand. The survey was developed by Janbernd Kirschner to evaluate current practices and has been run in 7 countries with a 64% response rate.

The survey will be a powerful tool to gather evidence for a business case requesting support for establishing new and expanding existing clinics.

The results of the survey will also provide important information for patients who can use it to affect change.

Top 10 guidelines for Australia

A survey of ANN members was undertaken to ascertain where standards of care and guidelines are needed. Nine (9) people responded to the survey ahead of the workshop.

All respondents identified the following disorders as needing specific standards of care to be developed: Becker, CMT, Congenital MD, Congenital myopathy, DMD, Emery-Dreifuss, FSHD, Friedreich's Ataxia, Limb girdle, SMA and Peripheral neuropathy

The top 3 areas requiring the development of clinical care guidelines were:

- Rehabilitation Management including: exercise, stretching, physiotherapy, occupational therapy; orthotics and assistive devices; postural management; pain management
- Pulmonary assessment, monitoring and management
- Cardiac monitoring assessment and management

A working party will be established to modify existing standards of care for an Australian application and prioritise areas for the development of clinical care guidelines.

A snapshot of clinical care around Australia and NZ

In South Australia, a clinic is held once a month, with support from the MDASA and the Rehabilitation department.

In Queensland, a clinic is held once a month, and also includes attendance by a respiratory specialist and cardiologist. Home outreach has been undertaken through Montrose. The clinic is in need of a nurse coordinator – a nurse has been assigned to the clinic but is not dedicated to the neuromuscular clinic.

In Victoria, there are ongoing issues with transition. Royal Children's Hospital has met with transition services to improve the process.

In New South Wales, there is no coordinated planning across adult care for caring for patients affected by neuromuscular disorders. There is a dedicated adult clinic at Royal North Shore Hospital and their clinicians participate in a transition clinic held at The Children's Hospital at Westmead There has been a significant level of support provided by MDNSW, with caseworkers being provided to assist patients through the transition process. A social worker and genetic counselor work with the patients from high school and meet every year or two. Merrilee Needham has funding for a research project around transition – a useful project to benchmark services.

Transition continues to be an issue for most states, with the exception of Western Australia. In WA, transition guidelines have been developed. Phillipa Lamont attends clinics in adult hospitals and is supported by a coordinator and respiratory and cardiology physicians. WA provides an ideal model for other states to aspire to.

In New Zealand, there is resistance among adult neurologists (there is a perception that all of the interesting cases are neuromuscular), however transition clinics occur in Auckland with attendance from respiratory physicians but not in Wellington.

Research

The CRE-NMD/ANN will promote and facilitate the sharing of information and expertise between basic and clinical researchers, clinicians and clinician researchers, to accelerate improved outcomes for patients.

A collaborative network would allow large cohorts of patients to be included in gene discovery, screening and linkage studies, as part of a research work-up to underpin diagnostics, registries and clinical trials.

It is through research effort, for example, that the introduction of next generation sequencing and the analysis of large data sets (informing diagnosis and inclusion in registries) will be developed for translation into diagnostic laboratories.

We are in the process of developing a national integrated secure database that will store patient data combining clinical, molecular and pathology data with longitudinal standardised assessments. This resource will be invaluable for clinical researchers in studies of natural history and genotype/phenotype correlation, and will provide a platform for research collaborations.

The development of a patient database goes hand in hand with gene discovery and improved diagnosis and clinical trial readiness. For example, when a new gene is described, a search of the database can be made for a clinical phenotype associated

with the gene and then a search for those who don't have a diagnosis.

National patient database

Basic epidemiological data and information on the natural history of many rare diseases is very limited. However, this knowledge is essential to assess the impact of preventive or treatment activities and the implementation of best practice guidelines. Rare disease patient databases underpin improving clinical care and we aim to identify existing databases and prioritise and expand the collection of data for other rare diseases.

Australia is slowly developing patient registries, however they contain very limited information to largely determine if patients are eligible to enrol in a trial (eg. ambulant/non-ambulant; genetic diagnosis; walk time over a certain distance).

A critical step in the design of a clinical trial protocol is a more detailed database of patient information that is collected from researchers, clinicians and pathologists – a comprehensive set of data that describes the progression of the disease over time. This provides researchers and pharmaceutical companies with sufficient information to ensure that the outcome measures (how to determine the success of the trial) and the treatment are well designed for maximum benefit to the patient.

The proposed database for housing patient data and availability of muscle for research use will be a national centralised repository that will share inter-operability with existing registries established through the OPHG. The database will be incorporated into platforms that are to be developed as part of the RDConnect, RAREBestpractice and Neuromics programs.

The database will not duplicate the information stored in registries (post-diagnosis), but will add and link additional detailed levels of data on sub-sets of patients for gene discovery and investigator led genotype/phenotype and natural history studies (pre-diagnosis).

A working party will be established to develop an implementation plan and will address issues such as ethics, information to be stored in the database, access, retrieving data from existing databases to populate the national database and data entry (resourcing is being sought from patient groups, with an additional option of utilizing students as part of cohort studies).

Research studies

Over 15 research studies are underway in Australia, with details available on the ANN website.

- Centronuclear myopathy
- Congenital fibre type disproportion

- Congenital muscular dystrophy
- DMD: Serial casting in ambulant boys
- DMD: Survey of attitudes to population screening
- Dystrophinopathies
- Facioscapulohumeral dystrophy
- Foetal akinesia/hypokinesia
- Inclusion body myositis
- Limb girdle muscular dystrophy
- Myotonic dystrophy
- Nemaline myopathy
- Non-myotonic dystrophy
- Spinal muscular atrophy
- Syndrome of cerebellar ataxia with prominent motor and sensory neuropathy and chronic cough

Appointments/ Presentations/Awards

4

Appointments/Presentations/Awards

Laing

Appointments

Chair, WMS 2012

World Muscle Society - Chair Local Organising Committee WMS Annual Congress 2012, Perth, Western Australia. (October 9th - 13th)

European Neuromuscular Centre (ENMC) International Consortium on Nemaline Myopathy and Related Disorders - Co-convenor

World Muscle Society - Member of Executive Board

"Neuromuscular Disorders" - Member of Editorial Board 1999 onwards, Associate Editor 2009 onwards.

World Federation of Neurology Research Group on Neuromuscular Diseases - Executive Committee Member

Presentations

4th Biennial Human Variome Project Meeting, UNESCO, Paris, 11th – 15th June.

Burns

Appointments

Co-Director, Arthritis and Musculoskeletal Research Group, The University of Sydney

Member, NHMRC Research Translation Faculty (contribute to policy and strategies in research)

Member, Network Clinical Education Committee (NCEC), Sydney Children’s Hospitals Network (Randwick and Westmead)

Presentations

Keynote: Science of orthoses and footwear for pain and disability. In: IVO Congress 2012, 29–31st March 2012, Sydney, Australia.

Invited: Treating CMT in Children. In: 38. Jahrestagung der Gesellschaft für Neuropädiatrie [3th German Neuropaediatric Congress] 19- 22 April 2012, Munster Germany.

Keynote: Orthotic therapy for pain, disability and deformity. In: Podiatry New Zealand Biennial Conference 13-15 September, 2012, Auckland, New Zealand.

Keynote: Fine-tuning the prescription of footwear. In: Podiatry New Zealand Biennial Conference 13-15 September, 2012, Auckland, New Zealand.

Keynote: Gait analysis in the management of children with Cerebral Palsy. In: Podiatry New Zealand Biennial Conference 13-15 September, 2012, Auckland, New Zealand.

Keynote: Neurological disorders: Know when to hold them and when to refer them. In: Australian Podiatry Association (Queensland) Conference, 12 – 13 October 2012, Brisbane, Australia.

Keynote: Mechanism of effective orthotic and footwear therapy. In: 2012 International Conference of Korean Society of Sport Biomechanics & 2012 Korea Footwear Biomechanics Symposium. 26-27th October, 2012, Busan, South Korea.

Invitations

Burns J. Assessment and treatment of CMT in Children. In: Grand Rounds Department of Neurology University Hospital of Muenster 20 April 2012, Munster Germany.

Burns J. Assessment and treatment of CMT in Children. In: Grand Rounds C Besta Neurological Institute 22 April 2012, Milan, Italy.

Burns J. Treating CMT to help you get up and go. In: Victoria Charcot-Marie-Tooth Disease Awareness Day, Austin Repat Hospital, 27th May 2012, Melbourne, Australia.

Free paper: Burns J, Ouvrier R. Shy R. Estilow T. Reilly M. Acsadi G. Shy M. Finkel R. Charcot-Marie-Tooth disease Paediatric Scale: validation of an outcome measure of disability. In: Joint Congress of the 12th International Child Neurology Congress and the 11th Asian and Oceanian Congress of Child Neurology, Brisbane, Australia 27 May-1 June, 2012.

Media release: Validation of the CMT Pediatric Scale as an outcome measure of disability

Ryan

Appointments

Member, Muscular Dystrophy Association of Australia

Convenor, Royal Children's Hospital Multidisciplinary Neuromuscular Clinic

Head, Royal Children's Hospital Neuromuscular Program

Board Member, Duchenne Foundation Australia

Member, Executive Board, Cooperative International Neuromuscular Research Group (US)

Member, Therapeutics Subcommittee, Cooperative International Neuromuscular Research Group (US)

Member, Therapeutics Strategy Committee, FSH Global Research Foundation

Editorial Board, Journal of Clinical Neuroscience [Australasia]

Member, Executive Board, Australia and New Zealand Child Neurology Society

Member, Planning and Scientific Program Committees, 12th International Child Neurology Congress, Brisbane Australia

Member, Advisory Committee, National Duchenne Registry

Member, Scientific Program Committee, Australian and New Zealand Association of Neurologists

Member, Paediatric Written Examination Committee, Royal Australasian College of Physicians

Member, Australian Polio Expert Committee, Australian Government Dept of Health and Ageing

Investigator, Acute Flaccid Paralysis Study, Australian Paediatric Surveillance Unit

Reviewer, Paediatric Dosing Resource Australian Medicines Handbook

Member, Clinical Ethics Case Response Group, Royal Children's Hospital

Board Member, Medical Staff Association Executive, Royal Children's Hospital

Australasian Representative, T-TACT (Therapeutics Advisory Committee), TREAT-NMD

Presentations

Victorian Podiatry Conference, Melbourne Australia

8th International Conference Improving the Use of Electromyography in Paediatrics, London UK

International Child Neurology Congress June 2012:

a. Early onset infantile neuropathies (International Child Neurology Congress June 2012)

b. CMT case studies (International Child Neurology Congress June 2012)

c. Debate on newborn screening in DMD (International Child Neurology Congress June 2012)

Presentations: E Yiu

a. Research advances in paediatric CMT

b. A novel locus for X-linked CMT

Presentations: K Howell

a. Microarray analysis suggests an extended spectrum of dystrophinopathies

Invitations

Muscular Dystrophy Association of Australia

Common muscular dystrophies affecting children

Australian Podiatry Association

Neurological disorders affecting the lower limbs in children

Victorian Palliative Care Service

Palliative care in children with neuromuscular disorders

North

Appointments

Executive Member of TREAT-NMD Alliance

TREAT-NMD international task force – invited member

Awards

GlaxoSmithKline Australia Award for Research Excellence

Member of the Order of Australia (AM) for service to medicine in the field of neuromuscular and neurogenetics research, paediatrics and child health as a clinician and academic, and to national and international professional associations

Ramaciotti Medal for Excellence in Biomedical Research

Invitations

Victoria University Melbourne March 2012

Gage Conference, Canberra April 2012

International Child Neurology Congress May 2012 (three platform presentation)

International Neurofibromatosis Symposium, New Orleans June 2012

1st Brazilian Symposium on Genomics and Sports, Sao Paolo, June 2012

World Muscle Society, Perth October 2012

Achievements

1. A published list of diagnostic tests available for neuromuscular genes in Australia on the ANN website
2. Whole exome sequencing and Next Generation Sequencing has been trialled and is progressing well
3. The rate of diagnosis has increased from 50% to 60%
4. A specimen procedures manual has been developed to standardise the collection and processing of samples
5. A national patient database is in development
6. Over 8 novel disease genes have been discovered
7. A pilot study examining the feasibility of population screening for Duchenne Muscular Dystrophy (DMD) is underway
8. Supported and contributed to the expansion of registries through the Neuromuscular Disorders Registry Advisory Committee led by Dr Hugh Dawkins

   Status: DMD, myotonic dystrophy and SMA are operational in both Australia and NZ with FSHD and congenital muscular dystrophy to follow (all link to TREAT-NMD global registry and myotonic will also link into the US registry)

9. Training opportunities have been provided for physiotherapists
10. Developed guidelines for the establishment of multi-disciplinary clinics

    Status: Draft document for feedback

11. Whole exome sequencing has been trialled in WA and NSW

12. Submission of three (3) successful NHMRC-EU applications: Neuromics (CIA Laing), RDConnect (CIA Dawkins), RAREBestpractice (CIA North) – to provide additional funding for key CRE-NMD/ANN aims including gene discovery, development of guidelines and inter-operability of existing registries and databases and guidelines for the development of future databases. The initial focus will be on neuromuscular disorders and will expand to rare diseases.

Funding

5

In addition to the $2.5M awarded in 2012 to establish the CRE in Neuromuscular Disorders, our researchers have also been awarded over $3M to support the goals of the CRE and ANN.

NHMRC Project Grants

1022707 Kathryn North, Nigel Laing, Kristen Nowak, Nigel Clarke, Michael Buckley

Neuromuscular Disorders: Gene Discovery and Disease Mechanism $772,350

1026933 Nigel Laing, Kristen Nowak, Kathryn North, Nigel Clarke

Approaches to therapy for the skeletal muscle actin diseases $881,175

Fellowships

1035828 Nigel Clarke

Advancing the diagnosis and treatment of inherited muscle disorders $391,076

1036656 Transferring new genes to improve the condition and function of diseased skeletal muscle $315,828

NHMRC-EU

1055131 Kathryn North and Hugh Dawkins

Improving health outcomes for chronic rare diseases and reducing inequality of care $614,128

1055295 Nigel Laing

Improving diagnosis of rare disorders $999,242

Publications

6

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Our Supporters

We are very grateful for the ongoing support from Genzyme, and thank Lynda Rigby in particular for her friendship and support of our research and the broader neuromuscular community.

The CRE-NMD/ANN has a number of community partners and is a member of TREAT-NMD. The relationship with advocacy and patient groups is a very important part of the CRE-NMD/ANN.

TREAT-NMD
Neuromuscular Network

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