$25 MILLION

25 MILESTONES

Changing the future of motor neurone disease

mnd
Research Institute of Australia

$25 Million, 25 Milestones: Changing the future of motor neurone disease was launched on 10 November 2017 at the *13th MND Australia Research Conference: Investing in Innovation, Partnering for Progress* by Federal Assistant Minister for Health, the Honourable Dr David Gillespie MP.

Acknowledgement
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$25 Million, 25 Milestones: Changing the future of motor neurone disease
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Cover:
Within a dish, two young neurones interlace, forming connections and providing mutual support for growth.

Nadia Cummins
Queensland Brain Institute

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Foreword

There are currently more than 2,000 people living with motor neurone disease (MND) in Australia. For the vast majority, their diagnosis comes out of the blue, with no known family history. MND can strike anyone at any time. It insidiously robs individuals of their ability to move, swallow, communicate and breathe. Each day, at least two Australians are diagnosed with this debilitating condition and two more will die. The cost of MND to Australia is estimated to have been $2.37 billion in 2015. The human cost of this devastating disease is incalculable.

MND refers to a group of progressive neurological diseases in which motor neurones degenerate and die. Amyotrophic lateral sclerosis (ALS) represents 70 per cent of MND cases and with average survival of 2.5 years from disease onset, is the most malignant form of MND. MND occurs sporadically in about 90 to 95 per cent of cases, developing without any identifiable cause. Familial or inherited MND accounts for about 5 to 10 per cent of all MND cases. Clinically, the sporadic and familial forms of MND are indistinguishable. Less common forms of MND include isolated bulbar palsy and progressive muscular atrophy, which may progress to ALS, as well as spinal muscular atrophy and primary lateral sclerosis.

While there is still much to learn about MND, understanding of this complex condition globally has transformed over the last decade. The Motor Neurone Disease Research Institute of Australia (MNDRIA) has played an integral role in this transformation. More than $25 million has been invested in Australian health and medical research over 30 years. The community has donated every dollar, including more than $7 million via the State MND Associations. This incredible effort is a testament to the community's commitment to changing the future of MND. Every dollar of each donation goes to supporting research excellence identified through a rigorous process. MNDRIA supports only the best research with the greatest chance of developing effective treatments and improving the lives of people with MND.

MNDRIA funds and promotes a comprehensive research program from discovery to healthcare. In April 2017, all researchers who have been funded by MNDRIA were invited to make a submission to the organisation about their research achievements. Twenty-five significant MND research milestones were identified. Firstly, the development of the MND research workforce has been fundamental to building research capacity and collaboration in Australia with over $5.3 million invested in a range of postdoctoral fellowships since 2002. Most fellowship recipients continue to work in MND and/or neurological diseases, with several rising to be among the world's leading MND researchers. MNDRIA PhD scholarships co-funded with the National Health and Medical Research Council (NHMRC) and MNDRIA PhD scholarship Top-up Grants have also helped to attract a number of early career researchers to the field. The second milestone in this report is another important capacity-building initiative known as the SALSA-SGC, a national consortium of researchers at nine centres working together to find the genes involved in sporadic MND. This collaborative program was established in 2015 thanks to the generosity of the community participating in the 2014 ALS/MND Ice Bucket Challenge. A further 23 milestones outlined in this report demonstrate how MNDRIA research has:

- Advanced our understanding of the causes of MND
- Provided significant insights into many clinical aspects of MND
- Identified new diagnostic and prognostic tools
- Identified potential MND treatments now undergoing further testing
- Supported clinical trials
- Contributed to improving care.

These findings are pivotal to the incremental progress of MND research with implications for people with MND, their families and clinicians. Each milestone highlighted in this report is another step forward in defeating MND.

The achievements of MNDRIA would not have been possible without the contributions of all donors, bequestors and supporters, particularly those who have sponsored named grants.

MNDRIA is the research arm of MND Australia – the national peak organisation representing all across Australia who share the vision of a world without MND.

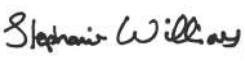
MNDRIA's long history began when founding members led by Dr Dawn Thew and Dr Brian Somerville established the ALS Research Foundation in 1984. Their goal was to raise $1 million for MND research with a vision to understand the causes, find effective treatments and ultimately cure MND. The Foundation became MNDRIA in 1986 and awarded its first modest grant-in-aid in 1987 to Professor Garth Nicholson at the University of Sydney to investigate the genetic basis of familial MND. By 1991, four projects were supported totaling $86,000. An expert Research Committee ensured only the best applications were funded through a review process. The Research Committee was chaired initially by Dr Dawn Thew (1986 – 1994) then by Professors David Burke (1995 – 1998), Edward Byrne (1999 – 2001), Perry Bartlett (2002 – 2004) and Dominic Rowe (2005 – 2014). Many dedicated experts have freely given their time to the Research Committee over the years and all have been approved by the NHMRC as suitably qualified to assess research proposals.

In the early years MND Associations, as members of MNDRIA, participated in executive roles, with MND NSW and MND Victoria also providing vital administration assistance. In 2004, MNDRIA members recognised the need to employ a professional to manage increasing funds and to effectively administer grants allocated. In early 2005, Janet Nash, the MND NSW Information Manager and long-time supporter of MNDRIA was employed as Executive Officer. A firm foundation had been established but changes enabled MNDRIA to go through a period of growth and consolidation. The introduction of named grants inspired donors to raise their targeted level of support to give a close connection to the research they were supporting. In 2009, MNDRIA reached its original funding goal with $1 million allocated to research through individual donations, State MND Association contributions and bequests. The following year, MNDRIA amalgamated with MND Australia, marking a turning point in its history with accountability to the MND Australia Board increasing professionalism and capacity.

While MNDRIA largely supported grants-in-aid to seed innovative projects as well as fellowships and scholarships as part of workforce development, special grants to support major initiatives were provided from time to time when exceptional funds became available. These include the MND Australia Leadership Grant (2013 – 2016), the MND Australia Ice Bucket Challenge Grant (2015 – 2018) and the Betty Laidlaw MND Research Grant (2016 – 2018). These special awards support outstanding and established researchers when funds are made available through large donations. In 2015, Professor Matthew Kiernan was elected to chair the expert Research Committee and growth of MNDRIA has continued. This year, more than $3.3 million will be awarded for research to commence in 2018.

Research is the only way to stop MND. Continued investment in Australian scientists at the forefront of MND research is vital to understanding the causes, developing effective treatments and moving towards a cure for MND sooner. MNDRIA is indebted to the intellect and dedication of MND researchers across the nation as well as the generosity of donors and supporters who fund this research. The enormity of this benevolence reflects the immense impact of MND on the community and the collective determination to end MND. As we acknowledge the achievements of the last 30 years and look to the future, we remain focused on working together for a world without MND.

Professor Matthew Kiernan
Chairman, MNDRIA Research Committee



Dr Stephanie Williams
Executive Director Research, MND Australia

10 November 2017

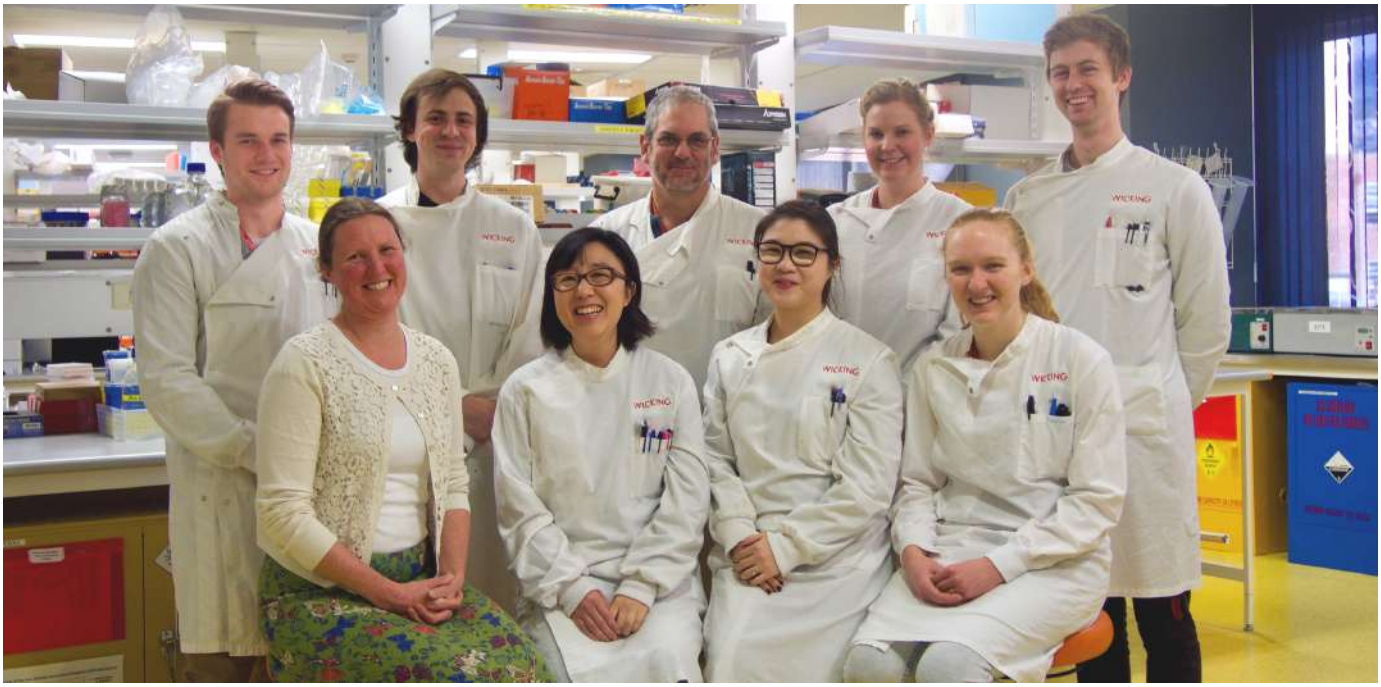
MNDRIA Research Committee members past and present whose collective expertise has ensured MNDRIA funds only the best research with the greatest chance of changing the future of MND.

Prof Perry Bartlett FAA	1990 – 2014
A/Prof David Berlowitz	2008 –
A/Prof Ian Blair	2012 –
Prof David Burke AO	1986 – 1998
Prof Edward Byrne AC	1990 – 2001
A/Prof Tracey Dickson	2014 –
A/Prof Mark Duncan	1998 – 1999
Prof Simon Foote	2015 –
Prof Peter Gage FAA	1986 – 2005
Prof Sonny Gubbay	1995 – 1999
Prof Clive Harper	1986 – 2001
Professor Glenda Halliday	2015 –
Prof Matthew Kiernan	2006 –
Prof Trevor Kilpatrick	1998 – 2005
Prof James Lance AO CBE	1986 – 1997
Dr Cecilie Lander	1990 – 1997
Prof Nigel Laing AO	2008 – 2016
Dr Andrew MacLaine-Cross	1991 – 1995
Prof Frank Mastalgia	2000 – 2008
Dr Susan Mathers	2006 –
Prof Pamela McCombe	1998 –
Prof James McLeod AO	1986 – 1997
Dr Shyuan Ngo	2017 –
Prof John Pollard AO	1998 – 2013
Prof Dominic Rowe AM	2002 –
Prof Robert Rush	1995 – 2008
Prof Norman Saunders	1998 – 2005
Dr Brian Somerville	1986 – 1997
Prof Greg Stuart	2008 – 2009
Dr Dawn Thew	1986 – 1999
Prof Dominic Thyagarajan	2008 –
Dr Bradley Turner	2017 –
Prof James Vickers	2006 – 2013
Prof Steve Vucic	2012 –
Dr David Williams	1986 – 1997
Prof Naomi Wray	2015 –

MNDRIA is indebted to many volunteers and particularly acknowledges:
Valda Retallic
Dympna Flanagan
Jo Thomson
Graham Lang
Paula Trigg
who helped to lay the foundations for the Motor Neurone Disease Research Institute of Australia.

Building Australia's MND workforce

For 30 years MNDRIA's $25 million investment in only the best research has grown and sustained Australia's world-class MND workforce. At the heart of this burgeoning community is the intellect and dedication of MND researchers from across the nation who work tirelessly to improve the lives of people impacted by MND. In this report, we celebrate the ingenuity that is strengthening research capacity and the passion that drives scientific endeavour. We acknowledge the motivation of researchers who are augmenting local MND expertise, reigniting careers, nurturing gently, leading confidently and pursuing their personal best in a quest to end MND.



To nurture is to lead

For more than a decade, MND research at the University of Tasmania has been fuelled by stalwart researchers, nurturing leadership and the financial backing of MNDRIA. This winning combination has led to advances in understanding the mechanisms behind the degeneration of axons that occur in people who have MND. Researchers at the University have identified changes in axonal structural proteins in MND and pinpointed one of these proteins – the microtubule – as a potential target for preventing axon degeneration.

Associate Professor Anna King heads up the MND research team at the Wicking Dementia Research and Education Centre (The Wicking Centre), University of Tasmania. During her 13-year career she has seen the team grow to today's nine-strong hub of MND researchers. This growth is partly attributed to grants from MNDRIA. Associate Professor King has benefited from 11 MNDRIA grants in the last 12 years, amounting to around $900,000.

Associate Professor King's MND research career began in 2004 under the mentorship of Professor James Vickers, Professor Roger Chung and Associate Professor Tracey Dickson. "I couldn't remember much," she jokes when recalling her return to the bench after spending 10 years raising her two children.

Photo:
Associate Professor Anna King and the MND research team at the Wicking Dementia Research Centre, University of Tasmania

Associate Professor King was working on her thesis, *Unravelling the cellular pathology leading to neurodegeneration in MND* when she was awarded a Nina Buscombe award by MND Victoria to attend the 16th International Symposium of ALS/MND in Dublin in 2005. At this point, she became hooked on MND research. She describes a welcoming international research community where "help is freely given, ideas are shared and excellence in research is paramount".

Associate Professor King's early research interests focused on determining the mechanisms by which the connections between nerve cells are lost in neurodegenerative diseases. By the late stages of her PhD, her strength of research and commitment to MND was recognised when she was awarded MNDRIA's most prestigious accolade – the Bill Gole MND Postdoctoral Fellowship – for her project, *Investigating the causes and consequences of axonal pathology in ALS*.

In 2009, MNDRIA awarded a Grant-in-aid to support Associate Professor King's research on axonal degeneration. The culmination of research funded by this grant and a grant from the University of Tasmania allowed her to secure a large project grant from the National Health and Medical Research Council (NHMRC) in 2011. This provided the impetus to grow the MND research group at The Wicking Centre. At this point, Associate Professor King stepped up to a leadership role in which she mentored students and early postdoctoral researchers. Since 2013, MNDRIA Grants-in-aid have provided seed funding for Associate Professor King's group, allowing them to pursue research in axonal and synaptic protection strategies and to secure a major NHMRC project grant in 2015.

The nurturing environment of The Wicking Centre is a linchpin in the MND group's success. Associate Professor King relishes this aspect of her role. She describes great satisfaction in guiding students through the early stages of their careers to become mature researchers who go on to forge new, independent paths of discovery.

Associate Professor King currently leads a group of researchers and supervises eight PhD and three honours students, many on projects related to MND. Adding to this very full professional plate is her recent appointment as Associate Director (Research) for The Wicking Centre. Reflecting on her career, Associate Professor King remarks on the growth of MND research in her field and believes that the pieces are beginning to come together. She remains hopeful that research outputs will one day translate to positive findings to treat or prevent MND.

MNDRIA funding

zo-ee MND Research Grant (2006) *Unravelling the cellular pathology underlying neuronal degeneration in MND*

Bill Gole MND Postdoctoral Fellowship – Anna King (2008 – 2011) *Investigating the causes and consequences of axonal pathology in ALS*

MNDRIA travel grant (2008) *ALS/MND International Symposium in Birmingham*

Mick Rodger Benalla MND Research Grant (2009) *The role of distal axonal degeneration in ALS*

Grant-in-aid (2013) *Axonal protection in ALS*

Grant-in-aid (2013) *Interneuron dysfunction in ALS; a new target for therapeutics*

Bill Gole MND Postdoctoral Fellowship – Jacqueline Leung (2014 – 2016) *Investigating the role of oligodendrocytes in ALS*

Grant-in-aid (2014) *ALS/FTLD proteins in axon function and role in disease*

Grant-in-aid (2015) *Inhibitory regulation of motor neurones: A new target mechanism for ALS?*

Grant-in-aid (2017) *Determining the role of oligodendrocytes in TDP-43 mediated ALS*

Grant-in-aid (2017) *Staying connected: determining targets to protect neuronal circuitry in ALS*

Thanks to the Rodwell Foundation, the Bill Gole MND Postdoctoral Fellowship has been awarded each year since 2005, in memory of Bill Gole who died from MND. It encourages early career researchers to study MND. The Fellowship has left a momentous legacy. About 90 per cent of recipients continue to work in the fields of MND and/or neurological diseases with several recipients rising to be among Australia's leading MND researchers.

Bill Gole MND Postdoctoral Fellows

2005 Roger Chung (Tas)
2005 Valerie Hansen (NSW)
2006 Ian Blair (NSW)
2007 Julia Morahan (NSW)
2008 Anna King (Tas)
2008 Jennica Winhammer (NSW)
2009 Justin Yerbury (NSW)
2010 Shu Yang (NSW)
2011 Catherine Blizzard (Tas)
2011 Rachel Duff (WA)
2012 Shyuan Ngo (Qld)
2013 Kelly Williams (NSW)
2014 Jacqueline Leung (Tas)
2015 James Howells (NSW)
2016 Fleur Garton (Qld)
2017 Jennifer Fifita (NSW)

Photo: Bill Gole

Investing in leaders

It is said great leaders are not born, they are made.

With this in mind, the MND Australia Leadership Grant was established to develop the leadership skills of an outstanding mid-career researcher as well as assist in building an MND research team.

The project had to be a totally new idea that could lead to effective treatments for MND. Developing MND research leaders is an important part of MNDRIA's remit to build and sustain MND research in Australia. Creating an inspiring vision for the future along with teams who engage with that vision form the foundation of MNDRIA's research strategy to ultimately find a cure for MND.

In 2013, MNDRIA awarded the MND Australia Leadership Grant to Macquarie University's Associate Professor Ian Blair to undertake a four-year project to investigate the genetic basis of MND. Not only does this approach help to provide a window to understand why motor neurones degenerate in MND, it also gives clues to where diagnosis and therapeutics may be targeted. Four years on, the list of achievements is overwhelming and tells a phenomenal success story from the discovery of new MND genes and 25 research publications to the formation of a new centre for MND research.

Without a doubt, the four-year award has helped Associate Professor Blair to undertake strategic research with long-term outcomes that extend beyond the usual short-term goals of smaller grants. Longer-term funding enabled a research framework, with patient recruitment, research training and infrastructure. This in turn increased the team's capacity for strategic research, enabling them to lead genetic studies and also to generate genetic data for Australia's role in large-scale international research consortia where thousands of DNA samples are needed to find new genes. Associate Professor Blair and his team are part of the International Familial ALS Consortium and Project MinE, the largest genetic study ever attempted in sporadic MND.

MNDRIA funding
MND Australia Leadership Grant – Ian Blair (2013 – 2016) *Investigating the pathogenic basis of familial MND*

The MND and Me Foundation, Commonwealth Bank Enterprise Services, Scanlon Foundation, Rodwell Foundation and many other generous donors contributed funds to the MND Australia Leadership Grant.

> "The MND Australia Leadership Grant provided an outstanding researcher with the opportunity to shine, inspire and build MND research capacity for the future ...
>
> Four years on, the list of achievements is overwhelming and tells a phenomenal success story from the discovery of new MND genes and 25 research publications to the formation of a new centre for MND research.

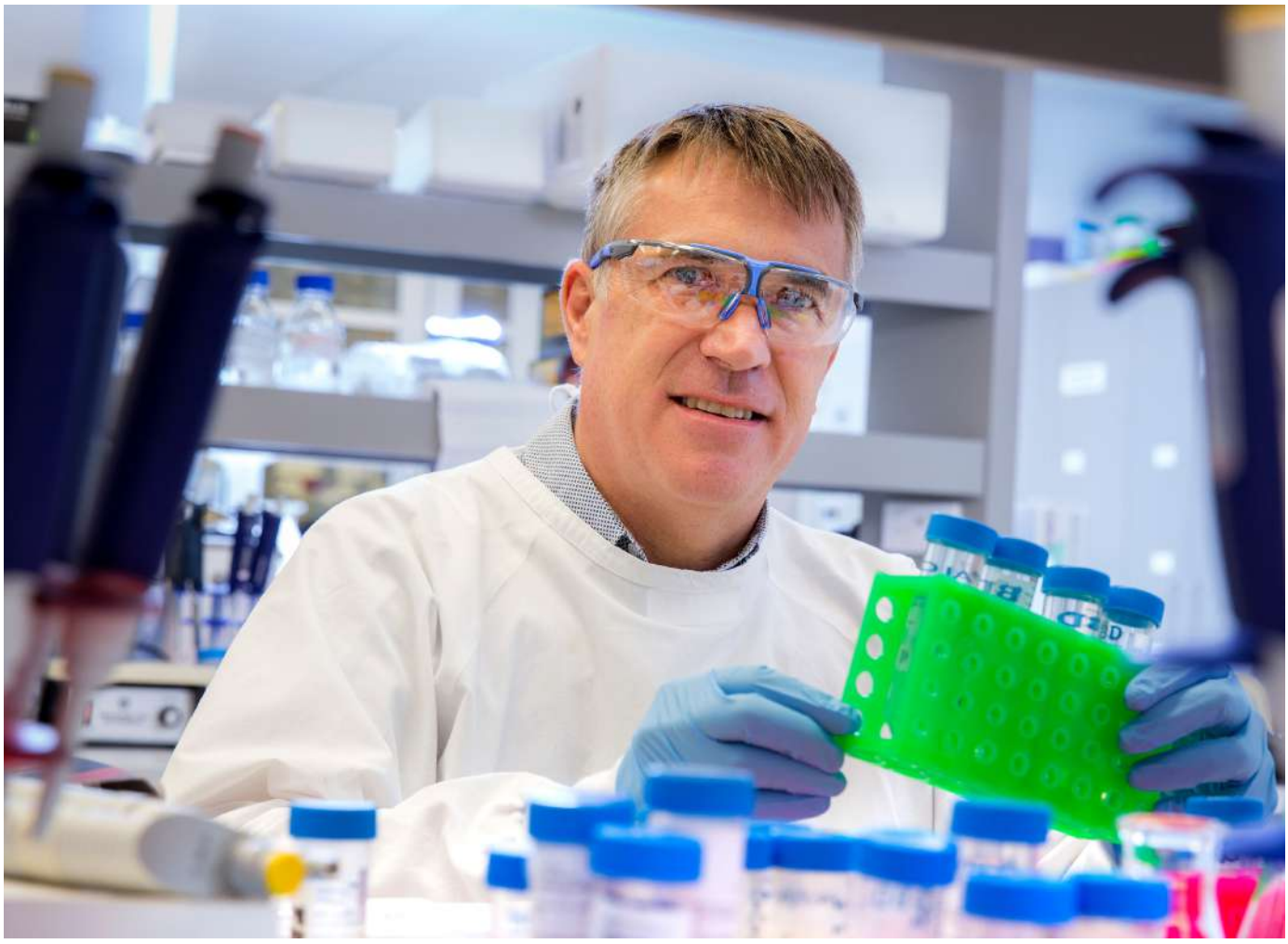
All these efforts and achievements have helped to build MND research capacity. Associate Professor Blair says he has been able to leverage MNDRIA support by winning National Health and Medical Research Council of Australia grants. These have secured employment for research staff as well as ongoing research projects for coming years, thus increasing and accelerating research output. The MND Australia Leadership Grant also partly supported the MND studies of five PhD students and three Masters students. All but one have continued with MND research.

The culmination of these achievements has been the 2017 formation of the Macquarie University Centre for MND Research, which comprises over 70 staff and students dedicated to MND research. Associate Professor Blair is the Centre Director. The genetics and genomics program led by Associate Professor Blair was the catalyst for an MND research program, which has subsequently resulted in the new multidisciplinary Centre aiming to solve MND.

While it is debatable whether leadership is about nature, nurture or both, two things are very clear. The MND Australia Leadership Grant provided an outstanding researcher with the opportunity to shine, inspire and build MND research capacity for the future. The discoveries made by Associate Professor Blair and his team have significantly advanced our understanding of what causes MND, formed the basis of new diagnostic tests for familial MND, and provided new leads for treatment strategies.

Photo:
Associate Professor Ian Blair, Macquarie University

Credit: Paul Wright, Macquarie University



Blazing the trail

Associate Professor Tracey Dickson and Dr Catherine Blizzard are two trailblazers whose encouraging and motivating leadership has been key to building their talented MND team at the Menzies Institute for Medical Research, University of Tasmania.

Associate Professor Dickson's dedication to researching the mechanisms of MND spans 15 years of which the last five years have been truly transformational. Joined at the helm by Dr Blizzard in 2011, the duo has been awarded MNDRIA funding amounting to almost $1.2 million to grow a critical mass of researchers who are making inroads into understanding the cellular mechanisms underlying MND.

The team has established a novel mouse model of MND to study the cellular environment of the central nervous system. They found that changes in this environment can lead to the characteristic die back of neuromuscular junctions, one of the earliest pathologies seen in MND patients, and also a phenomenon seen in SOD1 mouse models. They found that changes in the central nervous system precede pathology at the muscle and the disturbance is triggered by death or dysfunction of another type of neurone in the brain – the interneuron. They are now targeting this pathway as a means of potentially slowing the progression of MND.

These research advances have been built on a solid base of nine MNDRIA grants including those generously funded by the zo-ee group and the Simko and Stanford families as well as two PhD Scholarship Top-up Grants. MNDRIA funding has enabled Associate Professor Dickson and Dr Blizzard to recruit six talented young researchers, train them to be MND research leaders of the future and develop a program of research dedicated to the goal of a world without MND.

MNDRIA has also bolstered Dr Blizzard's career in MND, firstly in 2011 when she was awarded MNDRIA's foremost award, a Bill Gole Postdoctoral MND Research Fellowship to fund her project, *Investigating the cause of site specific excitotoxicity in ALS.*

More recently, in 2016 Dr Blizzard became the inaugural recipient of the Betty Laidlaw MND Research Prize. The Prize rewards an outstanding mid-career researcher with a demonstrated background of excellence in neuroscience research to undertake an innovative project with the potential to lead to effective treatments for MND.

MNDRIA funding
zo-ee MND Research Grant (2007) *Unravelling the cellular pathology underlying neuronal degeneration in MND*

Grant-in-aid (2009) *The role of distal axonal degeneration in ALS*

Bill Gole MND Postdoctoral Fellowship – Catherine Blizzard (2011 – 2013) *Investigating the cause of site specific excitotoxicity in ALS*

Grant-in-aid (2013) *Axonal protection in ALS*

zo-ee MND Research Grant (2013) *Interneuron dysfunction in ALS: A new target for potential therapeutics?*

PhD Scholarship Top-up Grant – Jayden Clark (2013 – 2015) *Targeted axonal protection in ALS*

PhD Scholarship Top-up Grant – Rosie Clark (2013 – 2015) *Interneuron dysfunction in ALS: A new target for potential therapeutics?*

Grant-in-aid (2014) *Synaptic alterations in ALS: A novel therapeutic target?*

Grant-in-aid (2015) *Synaptic dysfunction: An early mechanism of TDP-43 pathogenesis in ALS?*

Grant-in-aid (2015) *Inhibitory regulation of motor neurons: A new target mechanism for ALS?*

Grant-in-aid (2016) *Investigating synaptic dysfunction in ALS*

Stanford Family MND Collaboration Grant (2016) *Inhibitory dysfunction in the cortex: Tackling MND from the top down*

Jenny Simko MND Research Grant (2016) *Interneuron dysfunction in ALS: A systematic human pathology analysis*

Betty Laidlaw MND Research Prize – Catherine Blizzard (2017) *TDP-43 misprocessing drives synaptic deficits that leads to ALS*

Photo:
Dr Catherine Blizzard and Associate Professor Tracey Dickson, Menzies Institute for Medical Research, University of Tasmania

The Betty Laidlaw MND Research Prize will be awarded each year until 2019, thanks to the generosity of philanthropists, John and Betty Laidlaw. Betty is living with a slowly progressive form of MND.

Photo:
Dr Catherine Blizzard receiving the inaugural Betty Laidlaw MND Research Prize from John Laidlaw AO

Dr Blizzard's research aims to understand why nerve cells in the motor cortex of the brain are vulnerable to MND. Her project *TDP-43 misprocessing drives synaptic deficits and ALS* will investigate how defective function of TDP-43 alters nerve cell communication and how these changes lead to nerve cell death. They have identified that TDP-43 is involved in synaptic disturbances that may drive this MND pathology.

As proven masters of the work/life juggle, Associate Professor Dickson and Dr Blizzard are an inspiration to other women who aspire to forge their path in science leadership. While Associate Professor Dickson claims that her best research decision was choosing her partner and family, there is no doubt her perseverance, resilience and intelligence have allowed her to become one of Australia's leading MND researchers and Deputy Director of the Menzies Institute for Medical Research.

Under the duo's excellent leadership, the MND puzzle pieces are falling into place. The team is on the edge of uncovering why motor neurones are so vulnerable to excitability dysfunction in MND and are trialling novel therapeutic agents targeted at stopping this dysfunction in its tracks.

Growing Australian ingenuity

In 2006, while Dr Adam Walker was settling into life as a PhD student at the Florey Institute in Melbourne, over at the University of Pennsylvania, Professor Virginia Lee had made a landmark discovery in MND research. She found that TDP-43 proteins form brain aggregates in people with MND and that TDP-43 aggregations are common across a range of neurodegenerative diseases.

Fascinated by this line of research, Dr Walker attended a conference in Melbourne at which Professor Lee spoke about her discoveries. Fortuitously, Dr Walker was seated next to Professor Lee at the conference dinner. He was in awe of her enthusiasm and dedication to research. They kept in touch and Professor Lee invited Dr Walker to visit her labs.

With support from MND Victoria's Nina Buscombe Award to attend the International ALS/MND Symposium in Toronto in 2007, Dr Walker also made the trip to the University of Pennsylvania Centre for Neurodegenerative Disease Research (CNDR). He had expected a casual visit, but after a morning of back-to-back interviews with senior researchers, it became evident that he was in the middle of a postdoctoral interview. By his own admission he was "young and naïve".

Despite his lack of preparation, Dr Walker impressed the interviewers and was invited to do postdoctoral studies at the CNDR. He describes his four-year stint as an "eye-opening experience". Under the mentorship of Professor Lee, Dr Walker grew an understanding of neurodegenerative diseases with similar pathologies and acquired the technical skills to study transgenic mouse models.

Dr Walker returned to Australia in 2015 to work with Associate Professor Julie Atkin and Professor Roger Chung at the Centre for MND Research at Macquarie University. His return was enabled by MNDRIA through the awarding of the Cure for MND Foundation Research Grant for his project on pre-clinical therapeutic testing using the TDP-43 mouse model. With further financial support through MNDRIA's MonSTaR Foundation MND Research Grant, Dr Walker has formed a burgeoning independent research group – the Neurodegeneration Pathobiology Laboratory – within the Centre for MND Research. The group is focused on studying the mechanisms of MND and working towards developing new therapeutic avenues.

MNDRIA funding
Cure for MND Foundation Research Grant (2016) *Pre-clinical therapeutic testing and biochemical changes associated with neurone survival in a validated TDP-43 mouse model of MND*

MonSTaR Foundation MND Research Grant (2017) *New proteins and pathways contributing to TDP-43-mediated neurodegeneration*

Photo:
Dr Adam Walker and members of the Neurodegeneration Pathobiology Laboratory, Centre for MND Research at Macquarie University

Credit: Chris Stacey, Macquarie University

Importantly, MNDRIA funding has allowed Dr Walker to expand and develop the first Australian colony of new TDP-43 MND mice that he characterised during his time at CNDR. These mice are the first to develop both MND-like TDP-43 pathology and a progressive disease phenotype similar to people living with MND. They are an important new resource for both understanding how the disease develops and for testing new MND drugs. These mice are being used in multiple studies with collaborators throughout Australia and the USA and will allow Dr Walker's team to identify new treatments for people living with MND.

The funding from MNDRIA also allowed Dr Walker to gather preliminary data to show the feasibility of his research, which has led to the award of an NHMRC project grant and three Cure for MND Foundation Translational Research project grants, all beginning in 2017 and all focused on developing MND treatments.

Dr Walker's research achievements have been recognised by the NHMRC with the awarding of a four-year RD Wright Biomedical Career Development Fellowship starting in 2018. He will move to the Queensland Brain Institute in early 2018 to take up the position of Ross Maclean MND Research Fellow, and aims to continue growing his research team and accelerating research to take us closer to a world without MND.

Research from the heart

The heart-felt desire to improve the lives of people with MND motivated both Nicole Sheers and Camille Paynter to undertake PhDs in MND research. They have each received a Postgraduate Scholarship, co-funded by MNDRIA and NHMRC, which has given them time and funds to build on their clinical expertise to provide better care options for people living with MND.

Ms Sheers is a senior respiratory physiotherapist with the Victorian Respiratory Support Service at Austin Health. Her career path, which spans 20 years, has been defined by a strong desire to help people. Over the last decade, Ms Sheers has worked with people with MND; an experience that she has found most rewarding. She comments that "helping someone to sleep, breathe and cough can greatly improve symptoms and quality of life."

When she decided to study a PhD, Ms Sheers knew her focus must also be a passion. Her thesis is investigating the effects of breath-stacking on respiratory function in people with neuromuscular disease (see page 43).

As a speech pathologist, Ms Paynter's clinical expertise is the management of adults with acquired speech, language or swallowing disorders of neurological origin. Difficulties in these areas have a significant impact on both the person with MND and their family. Impairment in communication can also make it difficult for people to express their health care needs, resulting in vulnerability.

Ms Paynter's clinical interest has also been shaped by personal experience, having witnessed a friend live with MND. "The burden of communication loss on my friend and his family motivates me to conduct research to benefit people with MND and their caregivers," she says. Ms Paynter is researching the impact of communication impairment on health care decision-making involvement for people with MND and their caregivers.

Photo:
Nicole Sheers and research assistant test a patient's breathing

Looking for the smoking gun behind sporadic MND

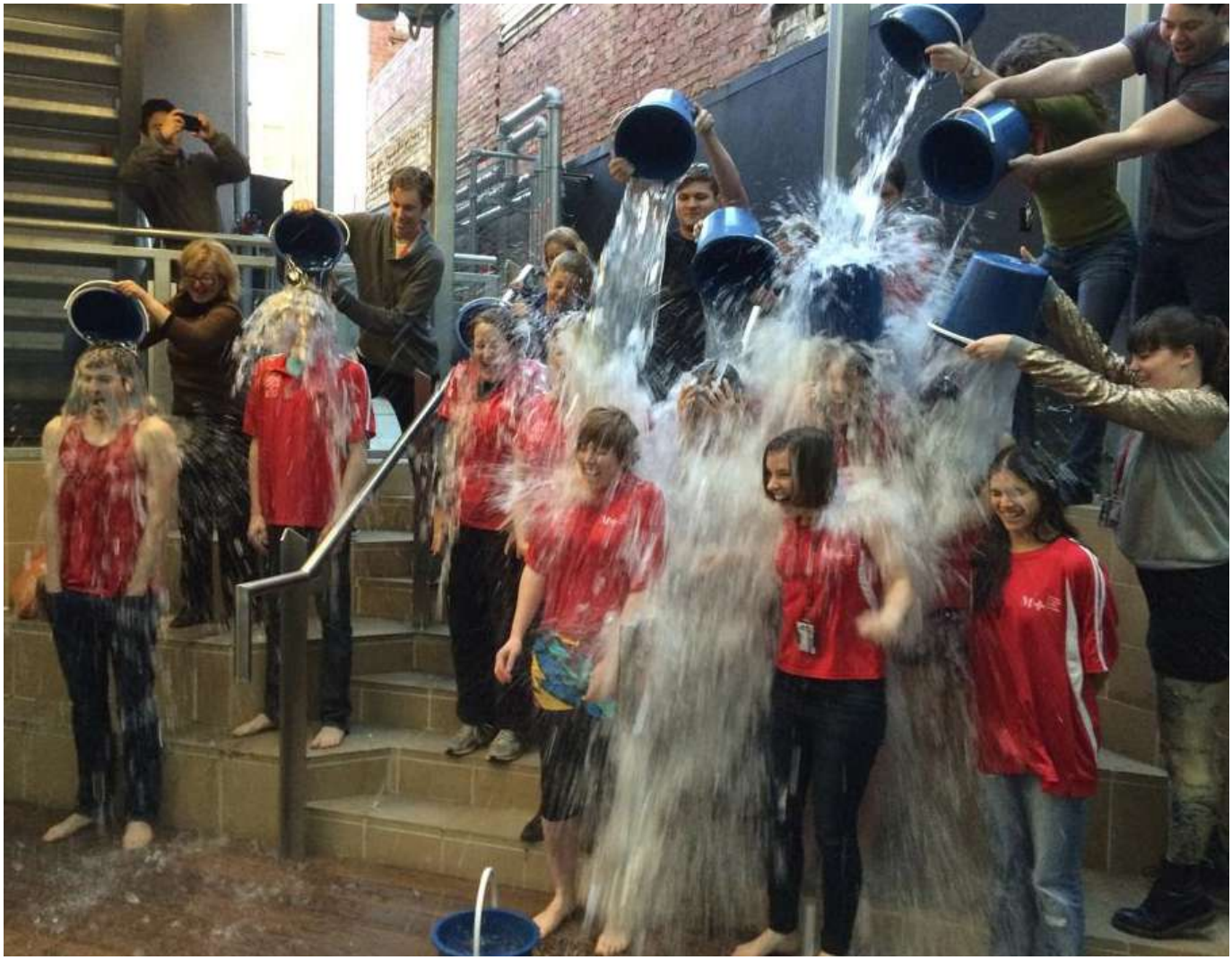
The Ice Bucket Challenge swept the world in 2014. From the rich and famous to the everyday person, more than 17 million people took on the challenge, gasping in the wake of a bucket of ice and water dumped over their heads. Critics described the campaign as a narcissistic fad. Yet the reality is the actions of the ice-bucketeers have had far-reaching consequences, raising awareness as well as over US$220 million worldwide for ALS/MND and accelerating the pace of discovery for more effective treatments.

In Australia, over $3 million was donated to support MND research and care. Donations from 30,000 Australians funded a $1.05 million MND Australia Ice Bucket Challenge Grant awarded by MNDRIA in 2015 to Professor Naomi Wray based at the University of Queensland and Associate Professor Ian Blair from Macquarie University. Their mission: to understand the genetic causes of sporadic MND. About 90 to 95 per cent of MND cases are sporadic. For the vast majority of people with MND, their diagnosis comes out of the blue with no known family history. Like heart disease and diabetes, sporadic MND is a complex disease influenced by many genetic and environmental risk factors.

MNDRIA funding
MND Australia Ice Bucket Challenge Grant (2015 – 2018) *Sporadic ALS Australian Systems Genomics Consortium (SALSA-SGC)*

Principal Investigators
Professor Naomi Wray: Institute for Molecular Biosciences, University of Queensland, Brisbane and Associate Professor Ian Blair: Macquarie University

Photo:
Staff from Menzies Institute for Medical Research, University of Tasmania, take the Ice Bucket Challenge, 2014

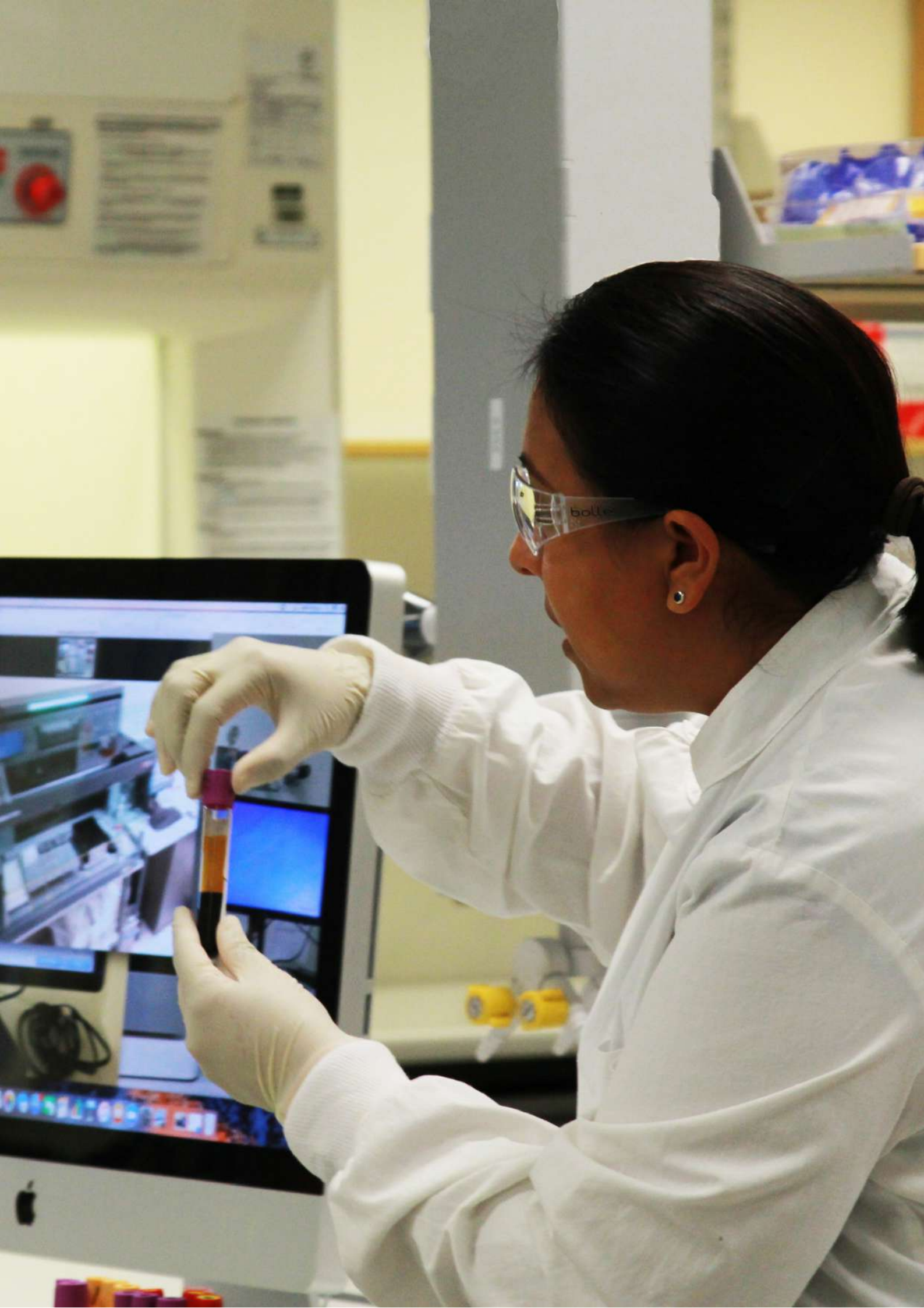


MNDRIA funding has enabled Professors Wray and Blair to set up a consortium that brings together 16 researchers from nine MND centres across Australia. Known as the SALSA-SGC (the Sporadic ALS Australian Systems Genomics Consortium), the group has built an integrated infrastructure to collect and analyse samples from Australians with sporadic MND. The program is undoubtedly ambitious and not for the faint hearted; coordinating nine centres to form a consortium is no easy task. Project Manager Anjali Henders drives SALSA at the coalface. At the outset, she coordinated meetings to help researchers at different centres agree on the types of information they should collect. Meanwhile, training sessions involving all sites ensured protocols for collection and handling of samples were the same across Australia. Researchers at each site were also provided with the necessary ethics documents to facilitate their Human Research Ethics Committee submissions to allow them to collect and analyse samples. The team has recently completed the design and build of a secure online database for managing the collection of demographic and clinical data, and tracking biological samples.

The bid to better understand the genes involved in sporadic MND is now well underway. The SALSA team is looking for variations in genes known as mutations and also single nucleotide polymorphisms (SNPs) to see if they are associated with disease. Another key research angle involves investigating methylation of genes. Methylation or the addition of a methyl group to DNA occurs normally to regulate gene activity. However, over a lifetime DNA methylation can change, perhaps in response to environmental exposures. These changes can switch off genes inappropriately, leading to disease. By comparing the DNA of those with MND to those without MND, researchers can identify multiple new genes that play a role in sporadic MND. Because everyone carries some genetic risk factors for MND, thousands of blood samples are needed to be able to draw solid conclusions. SALSA feeds into a global effort to find genes underlying sporadic MND, known as Project MinE, which has 17 countries participating.

Chief Investigators
Dr Beben Benyamin: Institute for Molecular Biosciences, University of Queensland; Associate Professor Robert Henderson: Royal Brisbane and Women's Hospital; Professor Matthew Kiernan: RPA Hospital/Brain and Mind Centre/Prince of Wales Hospital; Professor Nigel Laing: University of WA; Dr Susan Mathers: Calvary Health Care Bethlehem; Professor Pamela McCombe: Royal Brisbane and Women's Hospital, University of Queensland Centre for Clinical Research; Professor Garth Nicholson: Concord Hospital; Professor Roger Pamphlett: University of Sydney; Professor Dominic Rowe: Macquarie University Hospital; Dr David Schultz: Flinders Medical Centre; Professor Peter Visscher: Queensland Brain Institute, University of Queensland; Professor Steve Vucic: Westmead Hospital; Dr Kelly Williams: Macquarie University; Dr Qiongyi Zhao: Queensland Brain Institute, The University of Queensland

Photo:
Staff from Queensland Brain Institute take the Ice Bucket Challenge, 2014



As at November 2017, SALSA has recruited and collected data from 377 people with MND from NSW, Queensland, Victoria and WA, at multiple time points. The Consortium has also conducted SNP analysis on 400 individuals, which includes samples collected from NSW, Queensland, Victoria and WA. The data are now being analysed as part of a much bigger MND study of 1700 people. Importantly, Professors Wray and Blair were able to leverage MNDRIA funding to win additional support from the National Health and Medical Research Council for this larger study.

Further research is now looking at DNA methylation and sequencing the complete genetic make-up (whole genome) of people with MND. Methylation typing of 1200 samples began in June 2017. Whole genome sequencing and analysis of samples from 110 people is also underway. These samples will then be shared with the international effort, Project MinE. In addition, a questionnaire to investigate genetic and environmental risk factors will also help to understand sporadic MND. Participants will be invited through their local SALSA-affiliated clinic to complete the 40-minute online questionnaire via a secure web-link. Funded by the UK Halpin Trust, this initiative is another example of MNDRIA's funding leading to support from other sources.

The Ice Bucket Challenge has left an enduring legacy to Australia. Thanks to the community's generosity, a framework to understand the genetic basis of sporadic MND has been established and paves the way to ultimately find new treatments for MND. SALSA's research is designed to ensure information about differences between people is fed back into other lines of investigation, so that research uses all clues that can be provided from people with sporadic MND as well as familial MND. Biobanking through SALSA will provide a resource for researchers with different interests for many years.

In 2016, Australian samples contributed to the follow-up confirmation part of a major study published in the prestigious journal *Nature Genetics* that found a new gene, *C21orf2*, is associated with risk of developing MND, as well as implicating several other potential genes. SALSA is now geared up to fully contribute to the next international study. As sample sizes get bigger globally, the SALSA team is confident more genes associated with MND will be found. Over the last five years, genetics studies in other complex diseases have been illuminating and their results have been meshed with a wide range of knowledge sometimes leading to drug repurposing or a whole new angle of research not previously considered. The researchers hope the same will be true for MND.

Associate Investigators
Professor Ammar Al-Chalabi: King's College, England; Professor Jan Veldink: University Medical Centre, Netherlands; Professor Leonard van den Berg: Director of ALS Center, University Medical Centre, Netherlands; Ms Anjali Henders: Institute for Molecular Biosciences, University of Queensland, Australia

Investigators who are working on implementing SALSA in Western Australia
Professor Merilee Needham: Fiona Stanley Hospital, Dr Phillipa Lamont: Royal Perth Hospital, Dr Robert Edis: Royal Perth Hospital

Research aims

1: To establish an Australian Consortium for Systems Genomics in ALS

2: To share and harmonise protocol for optimised collection of phenotypic data and biological samples collected win ALS research clinics across Australia

3: To undertake genome wide SNP and methylation typing to the Australia-wide genomics data resource.

4: To undertake whole genome sequencing of ALS cases and controls as part of the international Project MinE effort

Photo:
Anjali Henders, University of Queensland

Changing the future of MND

Progress in science is incremental. Each of the following milestones is a step towards effective treatments, improved care and ultimately a cure for MND. In celebrating these successes we recognise the many more failures each researcher has had to endure. We most gratefully acknowledge these brilliant minds and their tenacity, patience and hard work to end MND.

Mutations in the *TDP-43* gene linked to MND

Protein aggregates containing ubiquitin have been recognised as a pathological hallmark of MND and frontotemporal dementia since the late 1980s. In 2006, studies identified misfolded TDP-43 as a principal component of these aggregates. While these studies were seminal, they had no way to definitively show that TDP-43 played a direct pathogenic role. Indeed, it was unknown whether abnormal TDP-43 was a cause of MND or merely a by-product of cells dying.

Science in brief
In collaboration with a group led by Professor Chris Shaw at Kings College London, Associate Professor Ian Blair and colleagues undertook a screen of Australian and UK MND families. They identified a change in the DNA sequence of the gene that encodes TDP-43 in an Australian case, then identified that Australian and English relatives who also had the disease carried the same change in their DNA. Separately, the researchers performed a genome-wide scan in the Australian MND family to independently locate the gene defect that was causing MND. This showed that the disease gene was restricted to a region on chromosome 1 that contains the gene that codes for the TDP-43 protein. Members of the family who did not have the disease had no change in the DNA sequence of the *TDP-43* gene. Together, these discoveries confirmed that the change in the DNA sequence was a mutation and the likely cause of the disease. They further identified a mutation in a sporadic MND case.

Impact
The research published in the prestigious journal, *Science,* showed that mutant *TDP-43* represented a proverbial “smoking gun” and established a clear pathogenic role for abnormal TDP-43 in MND. This was an exciting finding that opened a new chapter in MND research.

Next steps
The discovery of *TDP-43* mutations was quickly validated by others who reported mutations in MND families from many cohorts worldwide. These mutations offered a unique opportunity to develop cell and animal models to investigate the mechanisms by which abnormal TDP-43 leads to formation of protein aggregates and motor neurone loss. Models based on mutant TDP-43 are now used widely in MND research. Also, the subsequent discovery of mutations in FUS, a protein that is highly similar in function to TDP-43, implicated a common mechanism underlying motor neurone death. Both TDP-43 and FUS are RNA-binding proteins, and defective RNA metabolism is now widely recognised as a mechanism underlying MND.

Co-author Kelly Williams has continued a successful career in this field of MND research and was subsequently awarded a Bill Gole MND Postdoctoral Fellowship.

Milestone
Discovering that mutations in the *TDP-43* gene cause MND

Principal investigator
Associate Professor Ian Blair, ANZAC Research Institute

Publication
Sreedharan*, J., Blair*, I.P., Tripathi*, V.B., Hu, X., Vance, C., Rogelj, B., Ackerley, S., Durnall, J.C., Williams, K.L, Buratti, E., Baralle, F., de Belleroche, J., Mitchell, J.D., Leigh, P.N., Al-Chalabi, A., Miller, C.C., Nicholson*, G., Shaw*, C.E. (2008) *TDP-43* mutations in familial and sporadic ALS. *Science*

MNDRIA funding
Bill Gole MND Postdoctoral Fellowship – Ian Blair (2006–2007) *Identification of novel genes involved in motor neurone degeneration*

Photo:
Genomic sequencing – an essential tool for identifying new genes associated with MND

A new genetic link between MND and FTD

Researchers from Macquarie University and the University of Wollongong led a large international study which discovered mutations in a gene that causes both MND and frontotemporal dementia (FTD). This is the second gene to be discovered that is linked to both MND and FTD.

Science in brief
Mutations in a gene known as *CCNF* were found in patients from diverse international backgrounds including Australia, Canada, Italy, Spain, Japan, the USA and United Kingdom. Mutations were initially found in patients with the inherited forms of disease, and subsequently also found in the sporadic forms.

The researchers were then able to go one step further with the discovery of evidence for a potential common mechanism by which *CCNF* mutations cause both MND and FTD. A hallmark feature of most MND and FTD patients is the presence of clusters of abnormal proteins in the dying nerves. The clusters include a signature protein called TDP-43. *CCNF* makes a protein called cyclin F that is directly involved in protein breakdown and recycling in motor neurones. However, mutations in cyclin F impair its normal function in motor neurones, causing protein accumulation including TDP-43. This ultimately leads to the death of motor neurones.

Impact
This is a significant advance in understanding the biology of MND and FTD. Abnormal protein degradation and protein accumulation inside motor neurones are a fundamental pathological feature of both diseases. The researchers have identified potential mechanisms by which mutations in cyclin F contribute to protein accumulation and impair function in motor neurones.

Critically, the abnormal *CCNF* gene represents another smoking gun that will allow researchers to mimic the disease in the laboratory, to better understand the cause and help develop and test therapies. The identification of new MND genes adds to current DNA diagnostic testing regimes.

Next steps
The role of cyclin F in motor neurones is not known. Researchers have made advances to understand how and why mutations to cyclin F impair normal function causing downstream consequences to cell pathways. Some of these cell pathways, when defective, are involved with causing protein accumulation that leads to motor neurone death. The researchers are now working on characterising the relationship between these cell components and cyclin F. They are also investigating how the mutated form of cyclin F causes irregularities to some of these proteins, which may be potential targets for therapeutic design.

Milestone
Discovering mutations in the *CCNF* gene cause both MND and FTD

Principal investigators
Associate Professor Ian Blair, Dr Kellly Williams and Dr Albert Lee: Macquarie University

Publications
Williams, K.L, Topp S., Yang, S. Smith B., Fifita, J.A., Warraich, S.T., Zhang, K.Y, Farrawell, N., Vance, C., Hu, X., Chesi, A., Leblond, C.S., Lee, A., Rayner, S.L., Sundaramoorthy, V., Dobson-Stone, C., Molloy, M.P., van Blitterswijk, M., Dickson, D.W., Petersen, R.C., Graff-Radford, N.R., Boeve, B.F., Murray, M.E., Pottier, C., Don E., Winnick, C., McCann, E.P., Hogan, A., Daoud, H., Levert, A., Dion, P.A., Mitsui, J., Ishiura, H., Takahashi, Y., Goto, J., Kost, J., Gellera, C., Gkazi, A.S., Miller, J., Stockton, J., Brooks, W.S., Boundy, K., Polak, M., Muñoz-Blanco, J.L, Esteban-Pérez, J., Rábano, A., Hardiman, O., Morrison, K.E., Ticozzi, N., Silani, V., de Belleroche, J., Glass J.D., Kwok, J.B., Guillemin, G.J., Chung, R.S., Tsuji, S., Brown, R.H., García-Redondo, A.. Rademakers, R., Landers, J.E., Gitler, A.D., Rouleau, G.A., Cole N.J., Yerbury J.J., Atkin, J.D., Shaw, C.E., Nicholson, G.A., Blair, I.P. (2016) *CCNF* mutations in ALS and frontotemporal dementia. *Nat. Commun.*

Lee, A., Rayner, S.L., Gwee, S.S.L., De Luca, A., Shahheydari, H., Sundaramoorthy, V., Ragagnin, A., Morsch, M., Radford, R., Galper, J., Freckleton, S., Shi, B., Walker, A.K., Don, E.K., Cole, N.J., Yang, S., Williams, K.L., Yerbury, J.J., Blair, I.P., Atkin, J.D., Molloy, M.P., and Chung, R.S., Pathogenic mutation in the ALS/FTD gene, CCNF, causes elevated Lys48-linked ubiquitylation and defective autophagy. *Cell Mol Life Sci.*

Lee, A., Rayner, S.L., De Luca, A., Gwee, S.S.L., Morsch, M., Sundaramoorthy, V., Shahheydari, H., Ragagnin, A., Shi, B., Yang, S., Williams, K.L., Don, E.K., Walker, A.K., Zhang, K.Y., Yerbury, J.J., Cole, N.J., Atkin, J.D., Blair, I.P., Molloy, M.P., Chung, R.S. (2017) Casein kinase II phosphorylation of cyclin F at serine 621 regulates the Lys48-ubiquitylation E3 ligase activity of the SCF(cyclin F) complex. *Open Biol.*

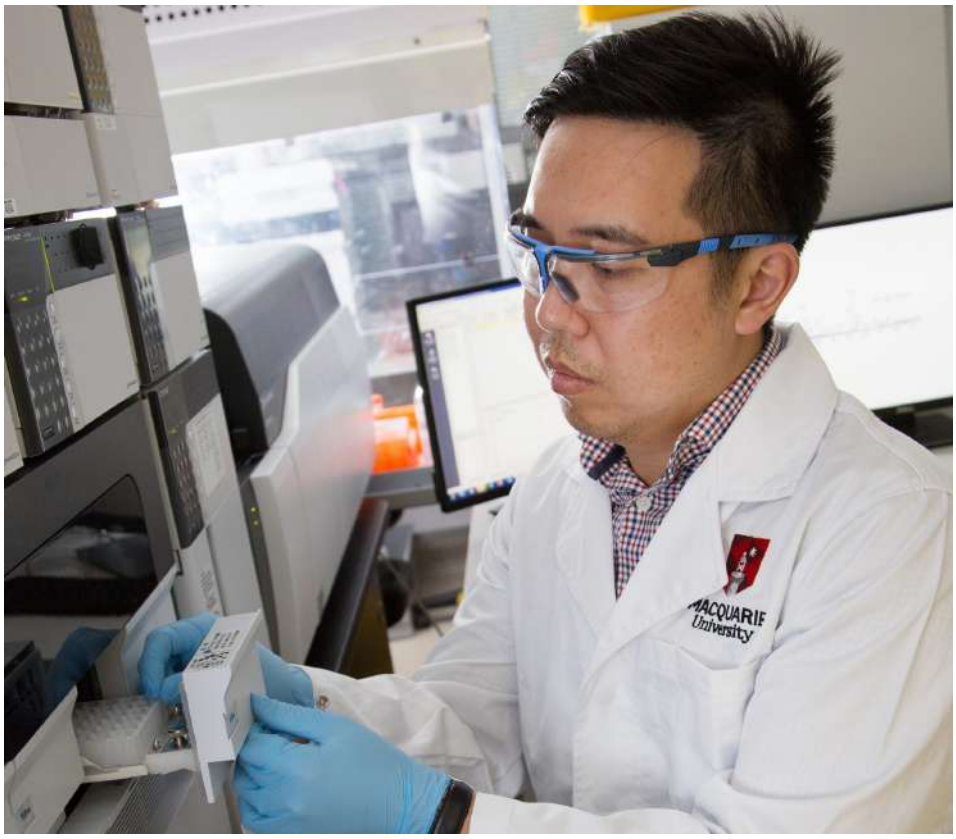


Photo:
Dr Albert Lee, Macquarie University

Credit: Chris Stacey, Macquarie University

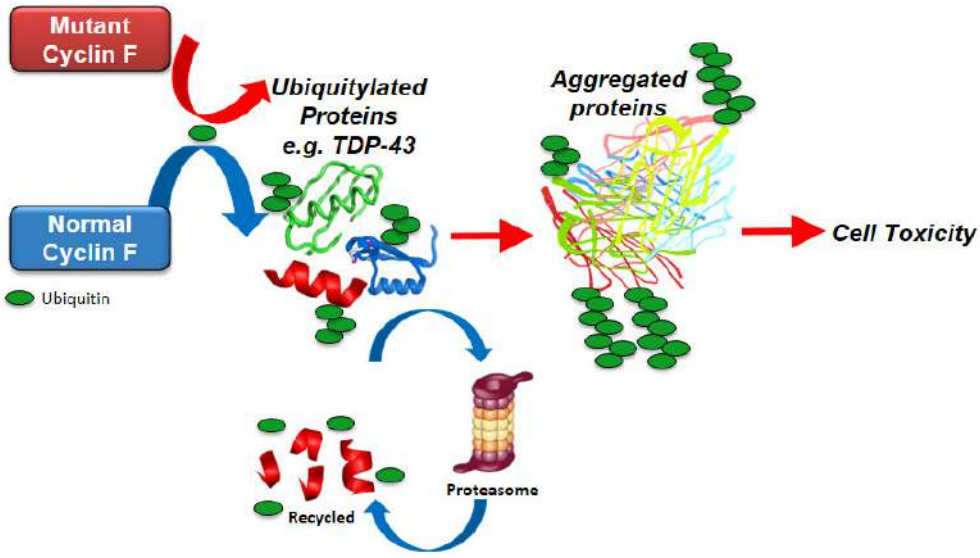


Diagram:
Normal cyclin F (blue arrows) is responsible for tagging proteins (ubiquitylation) for recycling by the proteasome to be reused by the cell. MND-linked mutations in cyclin F (red arrows) cause increased aggregation of ubiquitylated proteins leading to neuronal toxicity and death.

Publications continued
Hogan, A.L., Don, E.K., Rayner, S.L., Lee, A., Laird, A.S., Watchon, M., Winnick, C., Tarr, I.S., Morsch, M., Fifita, J.A., Gwee, S.S.L., Formella, I., Hortle, E., Yuan, K.C., Molloy, M.P., Williams, K.L., Nicholson, G.A., Chung, R.S., Blair, I.P., Cole, N.J. (2017) Expression of ALS/FTD-linked mutant CCNF in zebrafish leads to increased cell death in the spinal cord and an aberrant motor phenotype. *Hum Mol Genet.*

MNDRIA funding
MND Australia Leadership Grant – Ian Blair (2013 – 2017) *Investigating the pathogenic basis of familial ALS*

Bill Gole MND Postdoctoral Fellowship – Kelly Williams (2013 – 2015) *Investigating the molecular basis of ALS*

Grant-in-aid (2016) *Identifying mechanisms responsible for ubiquitination of TAR DNA-binding protein 43 (TDP-43) in ALS pathogenesis*

Grant-in-aid (2017) *Investigating the regulatory roles of cyclin F phosphorylation in the development and prevention of ALS*

Photo: Associate Professor Justin Yerbury and Professor Stephen Hawking, University of Cambridge, April 2017

Associate Professor Yerbury likens his research findings to Professor Hawking's work in physics and cosmology:

> "There are almost as many protein molecules in a human body as there are stars in the universe and we liken the deposits of proteins within motor neurones to black holes. They are dense accumulations that attract a whole range of proteins that become lost to the cell when they are sucked in. The biological properties of motor neurones make them vulnerable to this attack.

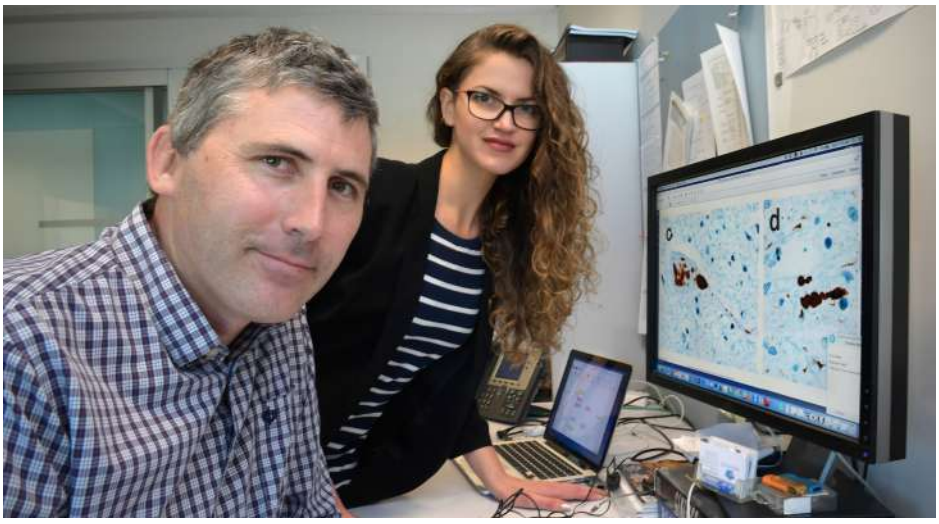
New light shed on motor neurone vulnerability

Associate Professor Justin Yerbury led a large international collaborative research project that has shed light on why motor neurones degenerate, and other types of neurones and tissues in the body remain unaffected in MND. Partners in the project were the University of Wollongong, University of NSW, University of Cambridge, CRG Barcelona, Universitat Pompeu Fabra and North Western University.

Science in brief
Protein deposits are found in affected motor neurones in all cases of MND, regardless of genetic background. The researchers discovered that more than 60 proteins found in these deposits are "supersaturated". This means the proteins exist inside motor neurones at such high levels that they exceed their solubility and are always on the brink of aggregating out of the watery solution that fills up cells. Notably, these proteins are highly supersaturated only in motor neurones, not in other tissue types. Further, these proteins do not normally interact with each other. The results suggest that a unifying feature among all cases of MND is a dangerous collapse of the motor neurone's ability to maintain all of the proteins in cells at sustainable levels.

Impact
Devising an effective treatment for MND is proving to be particularly challenging. The dozens of genes that are associated with MND are involved in a diverse range of cellular processes making it difficult to pinpoint a common underlying cause of MND that can be targeted therapeutically. Another mystery of MND is why motor neurones become diseased and degenerate, while billions of other neurones in the brain are unaffected.

Importantly, the research findings from this study suggest that motor neurones are particularly vulnerable to losing protein homeostasis (equilibrium), and this may underlie their susceptibility to dysfunction and degeneration. This finding shines a light on a potential target for therapeutic intervention; to develop an effective way to elevate the activity of mechanisms that maintain protein equilibrium in motor neurones. This will be important as part of a treatment strategy.



Next steps
Several molecular mechanisms are involved in maintaining equilibrium of the billions of protein molecules. Researchers have made headway in understanding the importance of one of these mechanisms – the ubiquitin-proteasome system (UPS). The preliminary data from this project indicates that boosting the activity of the UPS has striking ability to protect motor neurones from the damaging breakdown of protein equilibrium that occurs in MND. Researchers are working on ways to target and augment the UPS as a novel therapeutic strategy, and have worked up a nanoparticle-based system to efficiently deliver therapeutic compounds to motor neurones.

Milestone
Ascertaining why motor neurones are more susceptible than other types of neurones to dysfunction and degeneration

Principal investigator
Associate Professor Justin Yerbury: University of Wollongong

Publication
Ciryam, P., Lambert-Smith, I. A., Bean, D. M., Freer, R., Cid, F., Tartaglia, G. G., Saunders, D. N., Wilson, M. R.,Oliver, S. G., Morimoto, R. I., Dobson, C. M., Vendruscolo, M., Favrin, G., Yerbury, J. J. (2017) Spinal motor neurone protein supersaturation patterns are associated with inclusion body formation in ALS. *PNAS*

MNDRIA funding
Bill Gole MND Postdoctoral Fellowship – Justin Yerbury (2009 – 2012) *Probing molecular mechanisms of microglial and astrocyte activation in ALS*

zo-ee MND Research Grant (2015) *Monitoring accumulation of ubiquitin chains in ALS – Developing a potential imaging tool for monitoring preclinical disease progression*

Cunningham Family MND Research Grant (2016) *Development of a biocompatible functionalised liposome drug delivery system to increase efficiency of delivery to motor neurons*

Photo:
Associate Professor Justin Yerbury and Isabella Lambert-Smith, University of Wollongong

Investigating the link between protein accumulation and oxidative stress in MND

MND is characterised by accumulation of proteins in nerve cells. A signature protein found in these protein clumps is TDP-43. Associate Professor Anthony White and his team investigated different protein interactions in cell and animal models of MND and found a protein called hnRNP K is adversely affected by changes in TDP-43 metabolism.

Science in brief
hnRNP K binds directly to TDP-43 and accumulates in the cytoplasm of cells when TDP-43 is mislocalised. The researchers also found altered hnRNP K processing leads to abnormal oxidative stress responses in MND models. Oxidative stress occurs when there are too many damaging oxygen free radicals in the body. It is a major factor in neurodegeneration including MND. Importantly, hnRNP K adversely affected a neuroprotective protein Nrf2 in cell and animal models of MND. This suggests a key role for hnRNP K in linking neurotoxicity of TDP-43 accumulation to oxidative stress in MND.

Impact
Oxidative stress is recognised as a major contributor of dysfunction and death of cells in ALS and other forms of MND, however the cause of this is still unknown. Associate Professor White and his team have identified a major link between a protein known to drive MND, TDP-43, and impaired action of the main cellular protector, Nrf2. Much research is aimed at developing Nrf2-based protective strategies and this research will provide a major step forward in development of these strategies for treatment of MND patients.

Next steps
The researchers will investigate how hnRNP K affects Nrf2 responses in patient-derived brain cell cultures. They will also investigate how Nrf2 inducers, which are potential therapeutic compounds for treating MND, affect Nrf2 responses in different patient-derived cells. This will help to understand how individual patients respond to Nrf2 induction therapies.

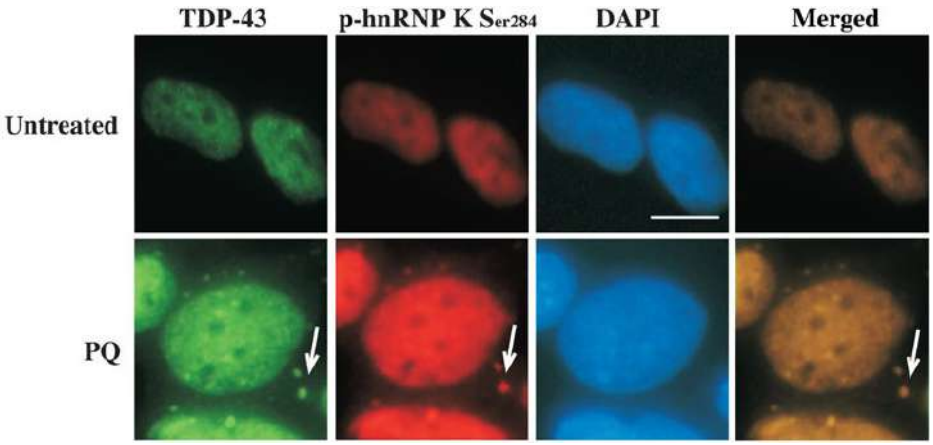


Photo:
The image shows co-localisation of TDP-43 and phophophorylated hnRNP K in stress granules in cells (arrow) after induction of oxidative stress with paraquat (PQ).

Milestone
Discovering that hnRNP K impairs the neuroprotective action of Nrf2, which leads to oxidative stress in MND

Principal investigator
Associate Professor Anthony White: University of Melbourne

Publications
Moujalled, D., James, J.L., Parker, S.J., Lidgerwood, G.E., Duncan, C., Meyerowitz, J., Nonaka, T., Hasegawa, M., Kanninen, K.M., Grubman, A., Liddell, J.R., Crouch, P.J., White, A.R. (2013) Kinase inhibitor screening identifies cyclin-dependent kinases and glycogen synthase kinase 3 as potential modulators of TDP-43 cytosolic accumulation during cell stress. *PLoS One.*

Moujalled, D., James, J.L., Yang, S., Zhang, K., Duncan, C., Moujalled, D.M., Parker, S.J., Caragounis, A., Lidgerwood, G., Turner, B.J., Atkin, J.D., Grubman, A., Liddell, J.R., Proepper, C., Boeckers, T.M., Kanninen, K.M., Blair, I., Crouch, P.J., White, A.R. (2014) Phosphorylation of hnRNP K by cyclin-dependent kinase 2 controls cytosolic accumulation of TDP-43. *Hum. Mol. Genet.*

Moujalled, D., Grubman, A., Acevedo, K., Yang, S., Ke, Y.D., Moujalled, D.M., Duncan, C., Caragounis, A., Perera, N.D., Turner, B.J., Prudencio, M., Petrucelli, L., Blair, I., Ittner, L.M., Crouch, P.J., Liddell, J.R., White, A.R. (2017) TDP-43 mutations causing ALS are associated with altered expression of RNA-binding protein hnRNP K and affect the Nrf2 antioxidant pathway. *Hum. Mol. Genet.*

MNDRIA funding
Grant-in-aid (2011) *Does TDP-43 aggregation cause translation arrest in motor neurones?*

Terry Quinn MND Research Grant (2012) *Targeting kinases to control TDP-43 and FUS accumulation in MND*

Cliff Smith MND Research Grant (2013) *The role of RNA binding protein hnRNP K in motor neurone degeneration*

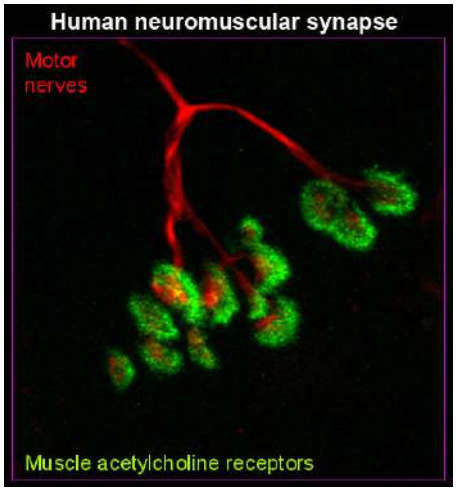
Neuromuscular synapses: hidden players in MND

Associate Professor Peter Noakes and his colleagues are investigating the cellular and molecular changes that occur between motor nerves and muscle cells in newly diagnosed MND patients in the early stages of the disease.

Science in brief
The researchers have revealed that there is a loss of adhesion between motor nerve endings and muscle, brought about in part by the decline in the levels of the adhesion molecules laminins α-4, and -5. They have also discovered that MuSK, a molecule normally found in muscle at the site of motor nerve-muscle connections is also lost. Laminins α-4 and -5 keep the motor nerve connected to the muscle, while MuSK triggers the collection of ion channels in the muscle membrane needed for muscle contraction.

Studies in MND model mice support the idea that the decline in the levels of laminins α-4, -5 and MuSK occurs very early, well before muscle weakness and MND symptoms. Furthermore, researchers have also shown that a loss of these molecules contributes to muscle weakness that occurs naturally as part of the ageing process in older mice. Together, these findings suggest that nerve-muscle molecules such as laminins and MuSK are key driving forces of muscle weakness in MND and ageing.

Impact
Research from MND models and MND patients has revealed that heightened motor nerve activity is an early feature of MND. This heightened activity can lead to increased release of chemicals from motor nerve endings such as acetylcholine, a chemical that controls muscle contraction. If not regulated, acetylcholine degrades motor nerve-muscle connections. This degradation is countered by maintaining motor nerve-muscle adhesion and activation of MuSK in the muscle. Associate Professor Noakes and his colleagues believe that improving motor nerve-muscle adhesion and the levels of laminins alpha-4, -5 and MuSK in the muscle of MND patients could slow the loss of nerve-muscle connections and hence slow the rate of muscle weakness, thereby providing a better quality of life for patients.



Next steps
Associate Professor Noakes and his collaborators aim to examine the stability of human nerve-muscle connections in culture using cells derived from MND patients and control donors who do not have MND. They hope this culture system will provide a means to manipulate motor nerve-muscle adhesion and/or the levels of MuSK to improve the stability and function of motor nerve-muscle connections. They are also aiming to collect muscle cells from MND patients and control donors, and measure their ability to collect ion channels in muscle needed to promote effective muscle contraction by motor nerves. They then hope to improve the levels of MuSK in muscle to see if this will in turn increase the collection of ion channels in muscle, thereby improving muscle contraction.

Milestone
Discovering the decline in levels of laminins α-4, -5 and MuSK cause a loss of adhesion between motor nerve endings and muscle

Principal investigator
Associate Professor Peter Noakes:
University of Queensland

Publications
Lee, K.M., Chand, K.K., Hammond, L.A., Lavidis, N.A., Noakes, P.G. (2017) Functional decline at the aging neuromuscular junction is associated with altered laminin α-4 expression. *Aging*

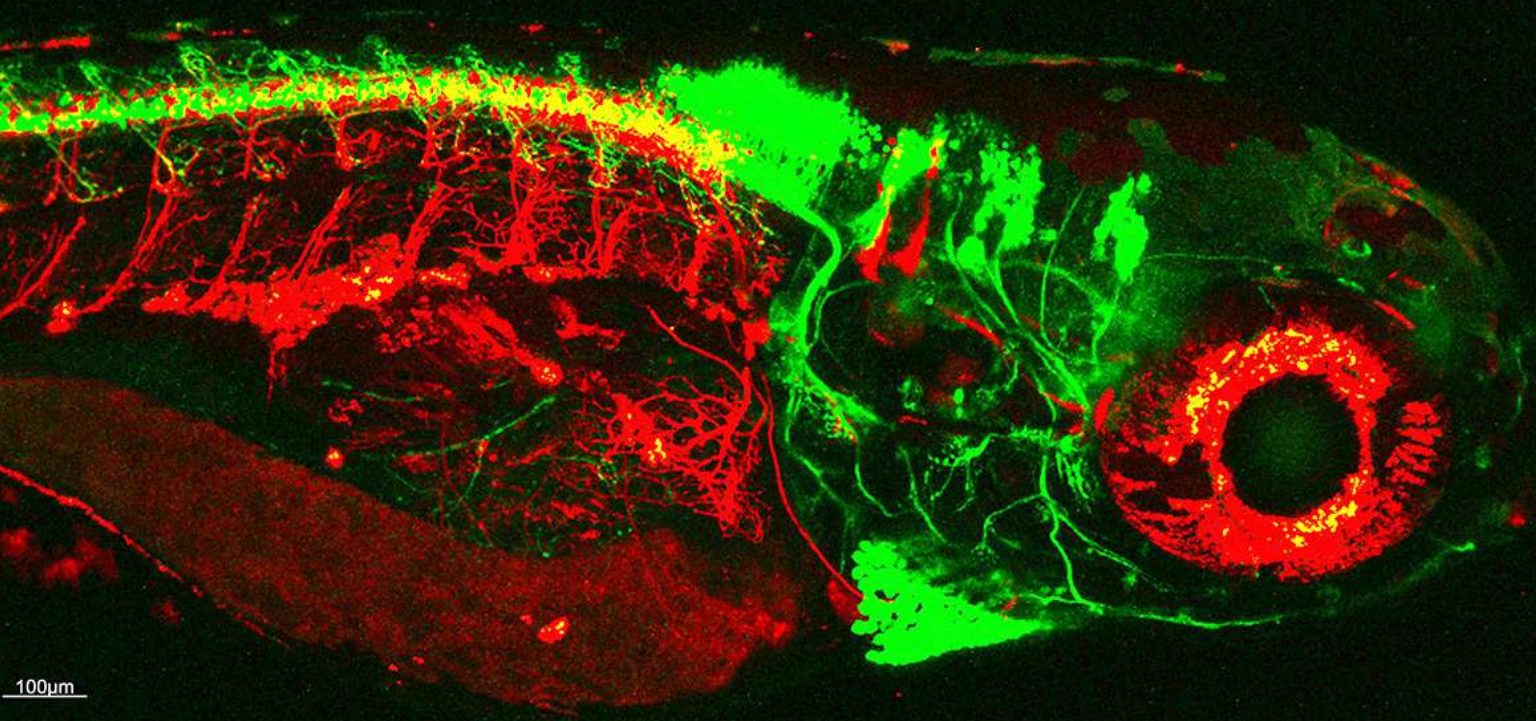
Chand, K.K., Lee, K.M., Lavidis, N.A., Noakes, P.G. (2017) Loss of laminin α-4 results in pre- and postsynaptic modifications at the neuromuscular function. *FASEB J.*

Fogarty, M.J., Klenowski, P.M., Lee, J.D., Drieberg-Thompson, J.R., Bartlett, S.E., Ngo, S.T., Hilliard, M.A., Bellingham, M.C., Noakes, P.G. (2016) Cortical synaptic and dendritic spine abnormalities in a presymptomatic TDP-43 model of ALS. *Sci Rep.*

Fogarty, M.J., Mu, E.W., Noakes, P.G., Lavidis, N.A., Bellingham, M.C. (2016) Marked changes in dendritic structure and spine density precede significant neuronal death in vulnerable cortical pyramidal neuron populations in the SOD1(G93A) mouse model of ALS. *Acta Neuropathol Commun.*

MNDRIA funding
Grant in-aid (2014) *Stability of neuromuscular connections in MND*

Grant in-aid (2017) *Targeting neuromuscular stability in MND*



"Visualising cells interacting in a living organism is absolutely fascinating, each and every time. Contributing to research that is moving us closer to finding an effective MND treatment is what gets me out of bed every morning.

Dr Marco Morsch

Tracking proteins to understand how MND spreads

Dr Marco Morsch and his team have established a novel technique to visualise the fate of MND proteins in neurones before and after they die.

Science in brief
In a world-first demonstration, the researchers were able to track the movement of disease proteins in real time and show their uptake into neuroprotective cells known as microglia, which had been attracted towards the dying neurones. This was the first time this process has been visualised in a living animal. Moreover, the researchers were able to show the spread of these disease proteins into the surrounding tissue and that this process was significantly altered when microglia were absent.

Impact
Investigating whether aggregated proteins are released from a stressed or dying motor neurone in a living experimental model will help researchers understand the role these proteins play in causing familial and sporadic MND. The zebrafish is a useful model as these visualisation studies cannot be tackled in rodents or humans. Importantly, this model will become an excellent tool to evaluate potential therapies aimed at blocking the spread of neurone death.

Next steps
Real-time characterisation of proteins in cells establishes a strong foundation for future funding applications for the next stages of this research. The spread and transfer of MND aggregates may be a common mechanism for both sporadic and familial MND and is therefore important for all MND cases. Importantly, if these neuroprotective cells are responsible for controlling the spread of neurodegeneration, this would uncover new targets for disease-modifying therapies.

Milestone
Establishing a novel technique to track the real-time movement of disease proteins in living animals

Principal investigator
Dr Marco Morsch: Macquarie University

Publications
Morsch, M., Radford, R.A.W., Don, E.K., Lee, A., Hortle, E., Cole N.J., Chung, R.S. (2017) Triggering cell stress and death using conventional UV laser confocal microscopy. *J Vis Exp*.

Don, E.K., Formella, I., Badrock, A.P., Hall, T.E., Morsch, M., Hortle, E., Hogan, A., Chow, S., Serene, S., Gwee, L., Stoddart, J.J., Nicholson, G., Chung, R., Cole, N.J. (2016) A Tol2 gateway-compatible toolbox for the study of the nervous system and neurodegenerative disease. *Zebrafish*

MNDRIA funding
Cure for MND Foundation Research Grant (2016) *Does the transfer of ALS protein aggregates between motor neurones trigger neurodegeneration?*

Photo:
Live florescent zebrafish showing brain and spinal cord neurones (green) and motor neurones (red)

Identifying targets to protect nerve cell connectivity

One of the key features in MND is the degeneration of axons that are responsible for signalling between regions of the nervous system, and to the muscles, in order to make muscles contract. The term “lateral sclerosis” refers to the scarring in the spinal cord, which is present in MND tissue and represents the loss of these axons as they descend from the brain to the spinal cord.

Science in brief
Associate Professor Anna King and her team have developed models to investigate mechanisms by which the axons degenerate and to test therapeutics that can provide protection. They have found that a specific structural protein, the microtubule, is affected in degenerating axons, and that stabilising this protein may prevent degeneration of axons.

Impact
Axons can initiate their own degeneration independently of the cell body, but it is not known how this occurs. Protecting the nerve cells alone may not be enough to maintain the connections between nerve cells and it may be necessary to target the axons with protective agents. This research has led to further investigating the mechanism involved in the degeneration of axons and to test therapies that can alter and stabilise the microtubules in both cell and animal models. It is hoped that these therapies could be used in the future to protect axons either alone or in combination with therapies that protect the nerve cells.

Next steps
The researchers are currently focusing on determining how dysfunction of proteins associated with MND, such as TDP-43, affect microtubules or other structural proteins. The researchers hope this work will lead to “axoprotective” strategies, which may be used alone or in combination therapies to prevent motor neurone decline and maintain connectivity between the nervous system and the muscles.

> I think the outputs are beginning to come from our research and my biggest hope is that these outputs can quickly translate to some positive findings to treat or prevent MND.
>
> *Associate Professor Anna King*

Milestone
Discovering damage to microtubule protein in degenerating axons

Principal investigator
Associate Professor Anna King: Wicking Dementia Research Centre, University of Tasmania

Publications

King, A. E., Dickson, T. C., Blizzard, C. A., Woodhouse, A., Foster, S. S., Chung, R. S., Vickers, J. C. (2011). Neuron-glia interactions underlie ALS-like axonal cytoskeletal pathology. *Neurobiol Aging*

King, A. E., Blizzard, C. A., Southam, K. A., Vickers, J. C., Dickson, T. C. (2012). Degeneration of axons in spinal white matter in G93A mSOD1 mouse characterised by NFL and α-internexin immunoreactivity. *Brain Res.*

Hosie, K. A., King, A. E., Blizzard, C. A., Vickers, J. C., Dickson, T. C. (2012). Chronic excitotoxin-induced axon degeneration in a compartmented neuronal culture model. *ASN Neuro*

King, AE., Southam, K.A., Dittmann, J., Vickers, J.C. (2013) Excitotoxin-induced caspase-3 activation and microtubule disintegration in axons is inhibited by taxol. *Acta Neuropathol Commun.*

Liu, Y., Atkinson, R. A., Fernandez-Martos, C. M., Kirkcaldie, M. T., Cui, H., Vickers, J. C., King, A. E. (2014). Changes in TDP-43 expression in development, aging, and in the neurofilament light protein knockout mouse. *Neurobiol Aging*

Atkinson, R. A., Fernandez-Martos, C. M., Atkin, J. D., Vickers, J. C., King, A. E. (2015) C9ORF72 expression and cellular localization over mouse development. *Acta Neuropathol Commun.*

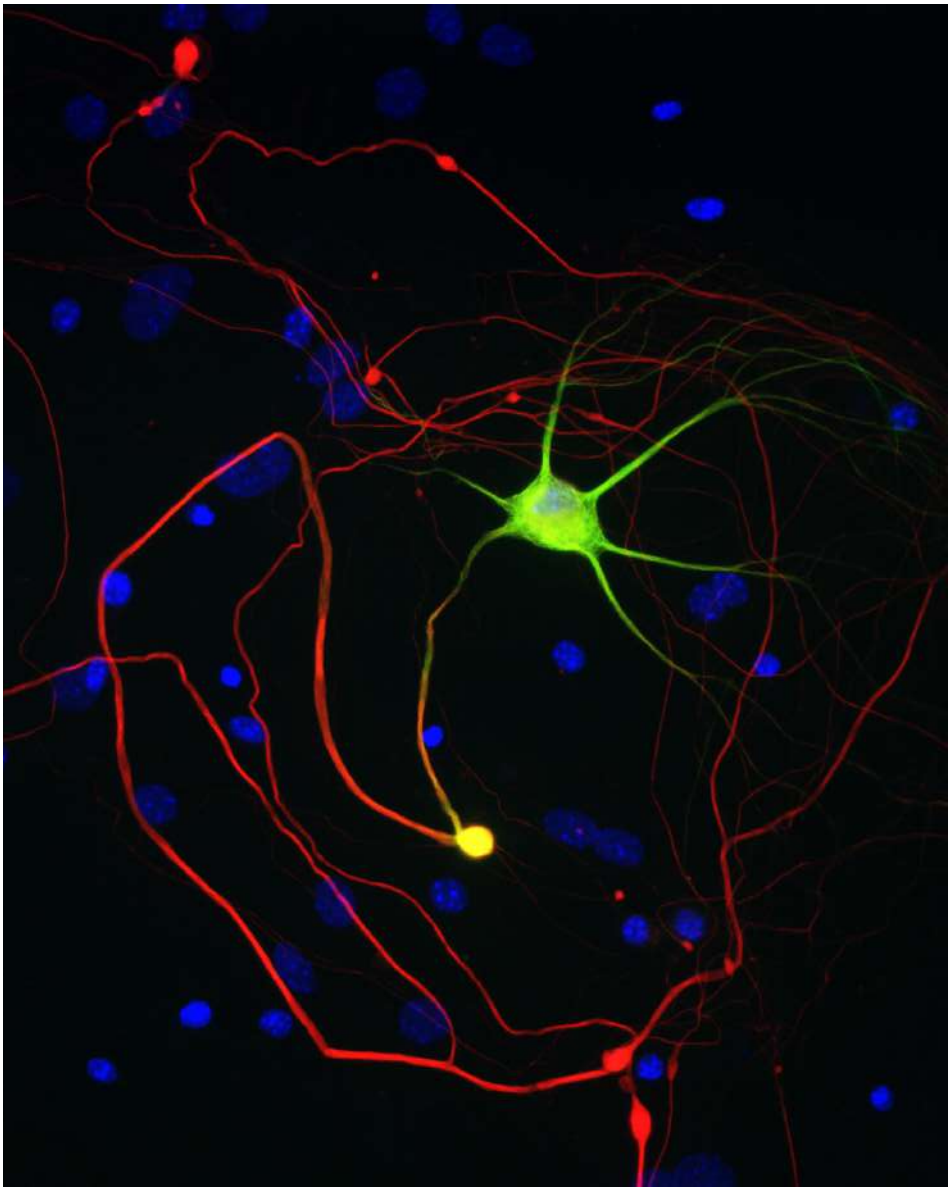


Photo:
A motor neurone growing in a culture dish. The cell body is in green and the red labelling shows the axon, which communicates with the muscle. The axon is swollen and tortuous, as seen by the yellow and red swellings. These arise from failure of microtubules to transport their cargoes, which are made in the cell body (green), along the axon to the synapse. These changes to axons could prevent them from communicating with the muscles and results in loss of motor function.

MNDRIA funding
Bill Gole MND Postdoctoral Fellowship – Anna King (2008 – 2010) I*nvestigating the causes and consequence of axonal pathology in ALS*

Mick Rodger MND Research Grant (2013) *Axonal protection in ALS*

Grant-in-aid (2014) *ALS/FLTD proteins in axon function and role in disease*

Grant-in aid (2017) *Staying connected: determining targets to protect neuronal circuitry in ALS*

A molecular link between MND and SMA

Dr Bradley Turner and his team uncovered a common molecular pathway that links MND to another disease called childhood spinal muscular atrophy (SMA).

Science in brief
The research team discovered that an essential protein called “SMN” (survival motor neurone protein) that is missing in children with SMA is also deficient in people living with MND, and MND cell and animal models. The researchers have demonstrated that boosting SMN levels in multiple mouse models of MND significantly slows disease progression, protects motor neurones and suppresses harmful inflammation. This suggests SMN-elevating therapies may be effective in both SMA and MND.

Impact
This research provides new insights into why motor neurones are selectively affected and unites two diseases of motor neurones – MND and SMA – through a common disease pathway. SMN deficiency in motor neurones could therefore be an important risk factor for MND and an enticing therapeutic target. These findings raise the important clinical implication that SMN-elevating therapeutics, both in development and approved for SMA, may also be effective for MND.

Next steps
Dr Turner and colleagues are working with Dr Mary-Louise Rogers at Flinders University to develop and evaluate a novel "gene therapy" approach to seek out and refill motor neurones with SMN for both MND and SMA. This powerful gene therapy approach could tackle MND and SMA in one unprecedented hit.

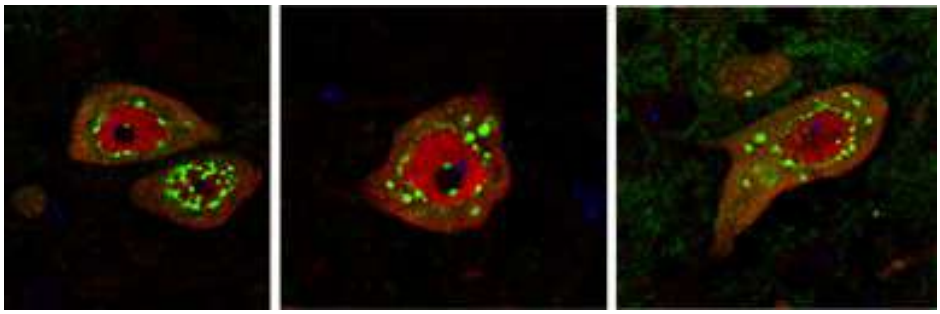


Photo:
SMN gene therapy (green) refilling motor neurones (red) in spinal cords of MND mice

Milestone
Boosting SMN levels in mouse models of MND slows disease progression, protects motor neurones and suppresses inflammation

Principal investigator
Dr Bradley Turner: Florey Neuroscience Institute and Florey Institute of Neuroscience and Mental Health

Publications
Perera, N.D., Sheean, R.K., Crouch, P.J., White, A.R., Horne, M.K., Turner, B.J. (2016) Enhancing survival motor neurone expression extends lifespan and attenuates neurodegeneration in mutant TDP-43 mice. *Hum. Mol. Gen.*

Turner, B.J., Alfazema, N., Sheean, R.K., Sleigh, J.N., Davies, K.E., Horne, M.K., Talbot, K. (2014) Overexpression of survival motor neurone improves neuromuscular function and motor neurone survival in mutant SOD1 mice. *Neurobiol Aging*

MNDRIA funding
Grant-in-aid (2010) *A role for survival motor neurone protein in MND?*

Mick Rodger MND Research Grant (2012) *Exploring the therapeutic potential of survival motor neurone protein for MND*

Cure for MND Collaboration Initiative Grant (2015) *A synergistic approach for treatment of MND using neurotrophic and gene therapy*

This powerful gene therapy approach could tackle MND and SMA in one unprecedented hit.

Degeneration of the cerebellum in sporadic MND

Despite containing more neurones than any other brain region, the human cerebellum has been largely overlooked in the study of MND. In 2011, a distinct pathological lesion was identified in this brain region in patients with an "expansion mutation" in the *C9ORF72* gene. This led researchers to postulate that cerebellar degeneration may be a distinguishing feature of patients with this gene mutation.

Science in brief
Amidst the subsequent surge of interest in the cerebellum in patients with the *C9ORF72* expansion, Dr Rachel Tan's research focused on patients with sporadic MND who did not have the *C9ORF72* expansion. Surprisingly, her research demonstrated significant cerebellar grey matter degeneration in these patients. Furthermore, Dr Tan identified distinct patterns of cerebellar degeneration that were associated with patients' performance on cognitive, neuropsychiatric and motor tasks. This finding indicated the important involvement of the cerebellum in these brain functions. Dr Tan's research went on to study patients with an intermediate repeat expansion in the *ATXN2* gene which is a major risk factor for MND. This work demonstrated a significant loss of Purkinje neurones in the cerebellar vermis.

Impact
This research highlights the need for future studies to focus on the cerebellum in MND. Distinct patterns of cerebellar degeneration in sporadic MND highlight the importance of including cerebellar assessments in patients with MND, both from a diagnostic and disease monitoring perspective.

Next steps
Dr Tan's research is further investigating whether cerebellar assessments using current and novel brain mapping techniques have the potential to elucidate disease-specific profiles and develop *in vivo* markers for diagnosis and monitoring disease progression in MND.

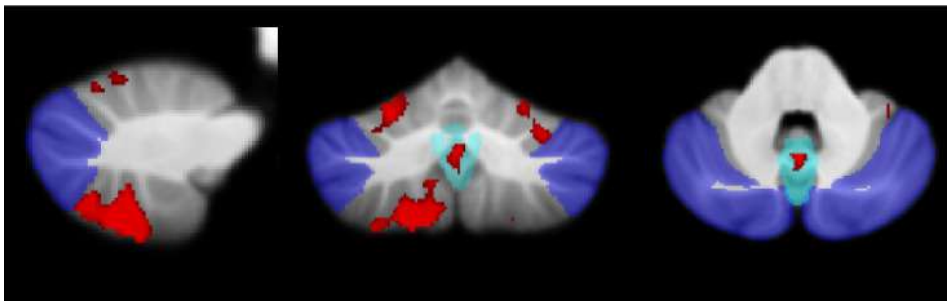


Photo:
Neuroimaging analysis of the cerebellum of patients with MND. Red indicates regions in which cerebellar degeneration correlate with motor function as measured on the ALS functional rating scale (ALS-FRS)

Milestone
Discovering degeneration in the cerebellum of people with sporadic MND who did not have the *C9ORF72* expansion

Principal investigator
Dr Rachel Tan: Neuroscience Research Australia, University of New South Wales and University of Sydney

Publications
Bae*, J., Ferguson*, M., Tan, R.H., Mioshi, E., Simon, N., Burrell, J., Vucic, S., Hodges, J.R., Kiernan, M.C., Hornberger, M. (2016) Dissociation of structural and functional motor system integrity in ALS and behavioral variant frontotemporal dementia. *J Clin Neurol.*

Tan, R.H., Kril, J.J., McGinley, C., Hassani, M., Masuda-Suzukake, M., Hasegawa, M., Mito, R., Kiernan, M., Halliday, G.M. (2016) Cerebellar neuronal loss in ALS cases with intermediate repeat expansions in the ATXN2 gene. *Ann. Neurol.*

Tan, R.H., Devenney, E., Dobson-Stone, C., Kwok, J., Hodges, J., Kiernan, M., Halliday, G., Hornberger, M. (2014) Cerebellar integrity in the ALS- frontotemporal dementia continuum. *PLoS ONE.*

MNDRIA funding
Mick Rodger Benalla MND Research Grant (2013) *Are polyglutamine repeats the mystery proteins in the novel p62 lesions in MND?*

Grant-in-aid (2015) *Histopathological changes in functional zones of the cerebellum across the MND-* frontotemporal dementia *continuum*

World-first biomarker to track MND progression

Biomarkers can be used to track disease progression in people living with MND and measure the effectiveness of treatments in clinical trials. Currently, progression of MND is monitored using the ALS Functional Rating Scale – Revised (ALSFRS) questionnaire. Dr Mary-Louise Rogers and her team have identified a biomarker found in urine, which is easy and painless to collect and provides an objective measure of MND progression.

Science in brief

$p75^{ECD}$ is a region of a protein present in urine after nerve injury. Dr Mary-Louise Rogers and her team conducted groundbreaking research that showed for the first time, a biological fluid-based biomarker known as $p75^{ECD}$ increases in concentration as disease progresses in MND patients sampled regularly over a two-year period. The findings provide a quantifiable measure of the severity of motor neurone degeneration in MND and predicted the future course of disease. They also suggest that analysing levels of the protein $p75^{ECD}$ in urine samples from people with MND may determine whether therapies are having any effect.

The study was published in *Neurology* in March 2017. It was a collaboration between Drs Mary-Louise Rogers and Stephanie Shepheard from Flinders University and Professor Michael Benatar from the University of Miami, as well as Dr David Schultz from the Flinders Medical Centre and Repatriation General Hospital.

Impact

This is an important finding for people living with MND because it paves the way for determining if new drugs used in future clinical trials are working or not. The finding provides a quantifiable measure of the severity of motor neurone degeneration in MND, and offers a unique opportunity to use $p75^{ECD}$ as a biomarker of drug effect in MND trials of treatments. $p75^{ECD}$ has the potential to transform the conduct of clinical trials, making it easier to decide which experimental therapies are worthy of further investigation.

Next steps

Dr Rogers and her team are now further investigating the role of $p75^{ECD}$ in MND, and also planning to incorporate urinary $p75^{ECD}$ in upcoming clinical trials of treatments for MND as a biomarker of disease progression.

Milestone

Developing the first biological fluid-based biomarker to track MND progression

Principal investigators

Dr Mary-Louise Rogers: Flinders University

Publication

Shepheard, S.R., Wuu, J., Cardoso, M., Wiklendt, L., Dinning, P.G., Chataway, T., Schultz, D., Benatar, M., Rogers, M-L. (2017) Urinary $p75^{ECD}$: a prognostic, disease progression, and pharmacodynamic biomarker in ALS. *Neurology*

Shepheard, S., Chataway, T., Schultz, D., Rush, R.A,, Rogers M-L. (2014) The extracellular domain of neurotrophin receptor p75 as a candidate biomarker for ALS. *PLOS One*

MNDRIA funding

Grant-in-aid (2010) *A biomarker for MND*

Grant-in-aid (2013) *Biomarker for determining outcomes of MND treatments in animal trials*

Rosalind Nicholson MND Research Grant (2014) *A biomarker to track progression of MND in humans and MND mice*

Photo:
Vyoma Modi, Michell Cardosa and Dr Mary-Louise Rogers, Flinders University

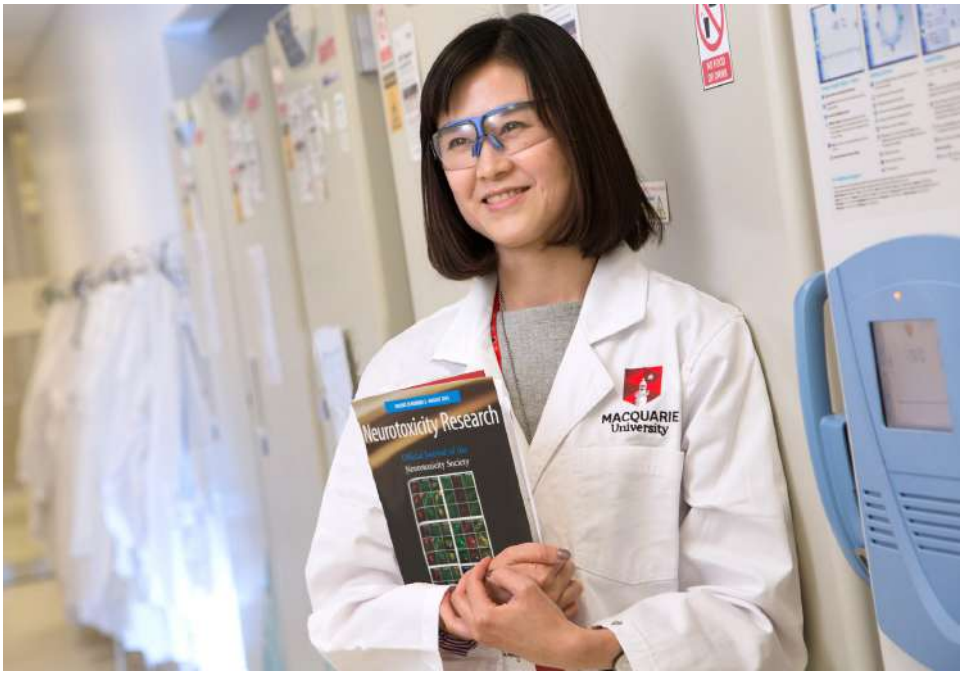
Credit: Flinders University

Creating a cell model to find biomarkers for MND

Dr Shu Yang has developed a pipeline to recruit patient samples and grow fibroblast cells from MND patient skin biopsies; establishing a fibroblast biobank as a valuable model for MND research.

Science in brief
Since 2013, fibroblasts from 28 patients and 14 controls have been banked with numbers growing every month. This renewable resource of MND patient cells is ready for use within a short time frame after biopsy collection, which is critical given the rapid progression of MND. Dr Yang has identified MND-related characteristics in fibroblast cells from some patients, including the reduced capacity to remove unwanted proteins. These findings were published in *Neurotoxicity Research* as the cover story in August 2015. Dr Yang's research also demonstrated that MND shows striking clinical variability among patients, with a subset of patients incapable of clearing specific proteins from their cells. This tells us that different molecular processes can lead to the loss of motor neurones.

Impact
It is critical to identify biomarkers to classify MND patients with certain clinical presentation or genotypes, so these patients can be enrolled in suitable clinical trials. Non-neuronal cells from MND patients, such as fibroblasts, are ideal for this purpose because they are readily obtained and grown in a short time. In this study, researchers used a relatively simple and quick assay to measure the rate of protein degradation, which may prove useful in diagnosis, prognosis and patient selection for clinical trials.



Next steps
Dr Yang's current research is following up whether any of the cell-based MND-related characteristics she has identified can be used as a biomarker to classify MND patients and facilitate diagnosis and prognosis for MND. Using a protein degradation assay, she is screening a larger number of patients, as well as patient samples collected at different disease stages, to see whether this assay can predict disease progression. She will also select the group of patients with insufficient protein degradation to search for the cause of this abnormality, which may provide us with novel targets for therapeutic development.

Milestone
Establishing a fibroblast biobank as a model for MND research

Principal investigator
Dr Shu Yang: ANZAC Research Institute and Macquarie University

Publication
Yang, S., Zhang, K.Y., Kariawasam, R., Bax, M., Fifita J.A., Ooi, L., Yerbury, J.J., Nicholson, G.A, Blair, I.P. (2015) Evaluation of skin fibroblasts from ALS patients for the rapid study of pathological features. *Neurotox Res.*

MNDRIA funding
Bill Gole MND Postdoctoral Fellowship – Shu Yang (2010 – 2013) *Investigating the role of recently identified mutant genes in MND pathogenesis*

Grant-in-aid (2016) *Ubiquitin proteasome system dysfunction as a biomarker for the diagnosis and prognosis of MND*

Photo:
Dr Shu Yang, Macquarie University holding *Neurotoxicity Research* featuring her research on the cover

Credit: Chris Stacey, Macquarie University

"Uncovering environmental factors that increase our risk of developing MND is a big challenge and requires a team effort. With continued support we can meet the challenge.

Associate Professor Kenneth Rodgers

Looking for environmental triggers for MND

Blue-green algae (cyanobacteria) form blooms and scums on waterways around the world. Blue-green algae can release a chemical known as β-Methylamino-L-alanine (BMAA), which has been implicated as an environmental toxin that may cause MND in some patients. In the USA, hot spots of MND have been linked to living close to lakes with frequent algal blooms.

Science in brief
Associate Professor Kenneth Rodgers and colleagues investigated ways in which BMAA could harm neurones. The researchers discovered that BMAA competed with the natural nutrient L-serine leading to damage to critical proteins in neurones. These findings led to a Phase I clinical trial conducted in the USA by Dr Paul Cox and colleagues to determine the safety of L-serine in MND patients, the results of which were published in February 2017. This initial trial showed that high doses of L-serine were protective and, based on these positive results, the study has now been approved for a Phase IIa clinical trial.

Impact
A combination of environmental and lifestyle factors interacting with genes likely contribute to the development of MND. Only about 5 to 10 per cent of MND runs in families. Sporadic MND accounts for about 90 to 95 per cent of people with MND, where only one person in a family has the disease and the causes are unknown.

Identifying environmental factors linked to complex diseases like MND can be challenging. This research built on increasing evidence implicating BMAA exposure as a risk factor for the development of MND, and has provided the foundation for a clinical trial that is investigating the use of L-serine to halt or reverse the neurological damage caused by BMAA.

Next steps
Associate Professor Rodgers, collaborator Professor Gilles Guillemin and their teams are currently carrying out an environmental survey of the distribution of BMAA in Australian freshwater. They are trying to link exposure to BMAA as well as a range of environmental toxins, including pesticides and heavy metals to an increased risk of MND.

Milestone
Discovering BMAA damages proteins in neurones and devising a clinical trial to determine the safety of L-serine to treat the damage caused by BMAA

Principal investigator
Associate Professor Kenneth Rodgers: University of Technology Sydney

Publications
Main, B.J., Rodgers, K.J. (2017) Assessing the combined toxicity of BMAA and Its Isomers 2,4-DAB and AEG *in vitro* using human neuroblastoma cells. *Neurotox Res.*

Rodgers, K.J., Main, B.J., Samardzic, K. (2017) Cyanobacterial neurotoxins: their occurrence and mechanisms of toxicity. *Neurotox Res.*

Bradley, W.G., Miller, R.X., Levine, T.D., Stommel, E.W., Cox, P.A. (2017) Studies of environmental risk factors in ALS and a Phase 1 clinical trial of L-serine. *Neurotox Res.*

Levine, T.D., Miller, R.G., Bradley, W.G., Moore, D.H., Saperstein, D.S., Flynn, L.E., Katz, J.S., Forshew, D.A., Metcalf, J.S., Banack, S.A., Cox. P.A. (2017) Phase I clinical trial of safety of L-serine for ALS patients. *Amyotroph Lateral Scler Frontotemporal Degener.*

Main, B.J., Dunlop, R.A., Rodgers, K.J. (2016) The use of L-serine to prevent BMAA induced proteotoxic stress *in vivo*. *Toxicon.*

MNDRIA funding
Grant-in-aid (2015) S*tudies investigating the non-protein amino acid BMAA, as an environmental trigger for MND*

Cure for MND Foundation Research Grant (2016) *Identification of environmental risk factors for sporadic MND in Australia*

Photo:
Blue-green algae bloom

Credit: Anne Colville

Targeting metabolism to treat MND

Dr Shyuan Ngo and colleagues at the University of Queensland, Royal Brisbane and Women's Hospital, and the Wesley Hospital are studying metabolic changes in people living with MND to identify new treatment pathways that might slow the progression of MND and prolong survival.

Science in brief
Researchers from this multicentre project studied energy expenditure in 59 MND patients. They found that resting energy expenditure increased dramatically in about half of the patients. This increase in metabolic rate is associated with symptom progression and survival. The team also found that an inability of neurones and skeletal muscle to receive, use, and generate energy efficiently may change the way that some MND patients use energy. This research highlights new pathways that can be targeted to improve outcomes for people living with MND.

Impact
Researchers have identified a metabolic change in patients that dramatically impacts survival. This is important because improving our understanding of factors that are linked to disease duration will lead to the development of treatments that might universally slow disease progression. Having confirmed similar changes in energy expenditure in an MND mouse model, the research team is now conducting pre-clinical studies to improve energy use in MND mice, with the hope that this will slow disease progression. As part of these studies, researchers are repurposing drugs used to treat metabolic diseases. If successful, these studies will uncover a range of new treatment options for people with MND.

Next steps
To accelerate research in identifying treatments to improve energy use in MND, Dr Ngo's team and collaborators are collecting muscle biopsies from MND patients to generate muscles in the dish. They are also developing new methods to turn skin cells of MND patients into motor neurones that are similar to those found in the brain and spinal cord. They will use these muscles and neurones to study the complex cellular processes that control energy use. By identifying why skeletal muscle and neurones from MND patients use energy differently, the team aims to discover more specific processes that can be targeted to improve the survival of these cells. Because these cells are being used to model the muscle and neurones of each patient, they offer an opportunity to develop treatments that suit the specific needs of each patient.

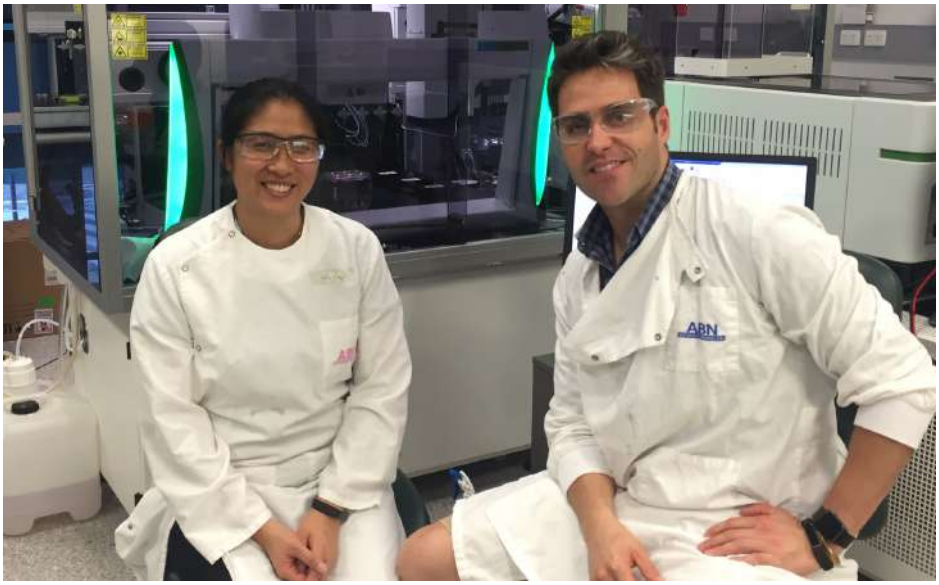


Photo: Dr Shyuan Ngo and Dr Frederik Steyn, University of Queensland

Milestone
Discovering an increase in resting energy expenditure in some people living with MND, which is associated with symptom progression and survival

Principal investigators
Dr Shyuan Ngo, Dr Frederik Steyn and Professor Pamela McCombe: University of Queensland; Associate Professor Robert Henderson: Royal Brisbane and Women's Hospital

Publications
Ioannides, Z.A., Steyn, F.J., Henderson, R.D., McCombe, P.A., Ngo, S.T. (2017) Predictions of resting energy expenditure in ALS are greatly impacted by reductions in fat free mass. *Cogent Medicine*

Ioannides, Z.A., Steyn, F.J., Henderson, R.D., McCombe, P.A., Ngo, S.T. (2017) Anthropometric measures are not accurate predictors of fat mass in ALS. *Amyotroph Lateral Scler Frontotemporal Degener.*

Ngo, S.T., Steyn, F.J., Huang, L., Mantovani, S., Pfluger, C., Woodruff, T.M., O'Sullivan, J.D., Henderson, R.D., McCombe, P.A. (2015) Altered expression of metabolic proteins and adipokines in patients with ALS. *J. Neurol. Sci.*

Palamiuc, L., Schlagowski, A., Ngo, S.T., Vernay, A., Grosch, S., Henriques, A., Boutillier, A.L., Zoll, J., Echaniz-Laguna, A., Loeffler, J.P., René, F. (2015) A metabolic switch towards lipid use in glycolytic muscle is an early pathologic event in a mouse model of ALS. *EMBO Mol Med.*

Ngo, S.T. Steyn, F.J., and McCombe, P.A. 2014. Body mass index and dietary intervention: implications for prognosis of ALS. *J. Neurol. Sci.*

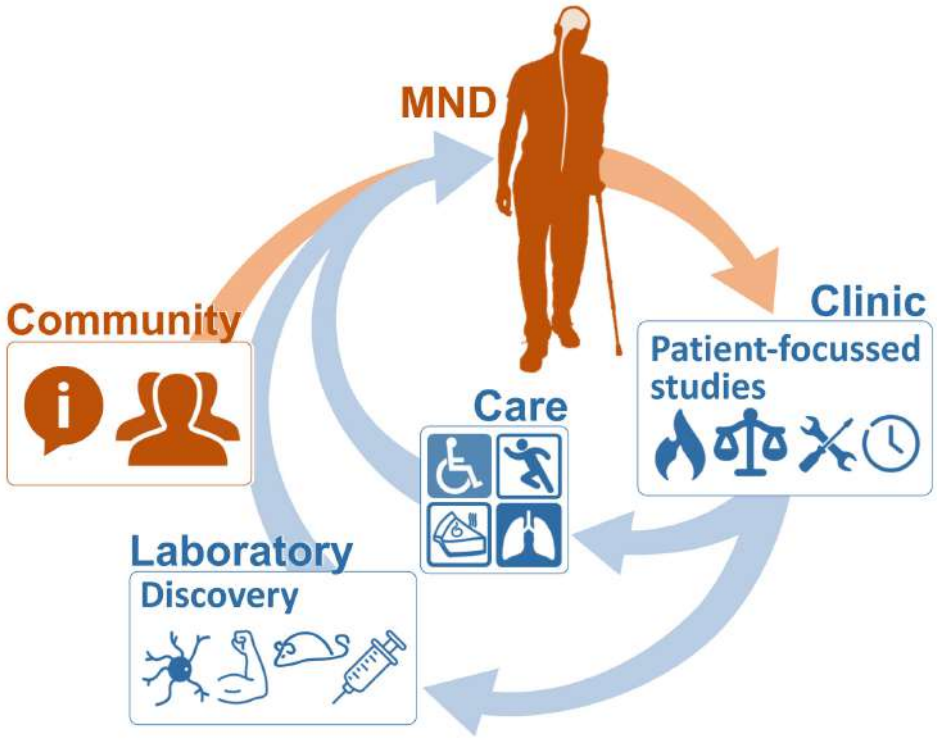


Diagram:
This translational approach to research begins with Drs Ngo and Steyn working with MND patients in the clinic. Their research uses laboratory models of disease, which include muscle tissues and neurones derived from the clinic patients, as well as mouse models of MND. Importantly, the MND community is kept engaged through the delivery of information about advances in research, and how this could benefit care. The loop is closed by implementing research findings back in the clinic.

MNDRIA funding
Bill Gole MND Postdoctoral Fellowship – Shyuan Ngo (2012 – 2015) *Investigating the causes and consequences of hypermetabolism in ALS*

Cunningham Collaboration MND Research Grant (2015) *A multicentre study of the impact of metabolic balance and dietary intake on the clinical parameters of disease progression*

Cunningham Family MND Research Grant (2016) *Metabolic and gut dynamics in MND: Identifying novel strategies to meet energy needs in patients*

Charcot Grant – Shyuan Ngo (2017) *Metabolic exploration in neurodegenerative disease (MEND): synergy between derangements in systemic and muscle metabolism in MND*

> We have found that people living with MND often develop a pragmatic outlook on life, with many finding strength in knowing that their involvement in research could lead to treatments to help others. That's why the MND community plays an integral part in our process of discovery.
>
> *Dr Frederik Steyn and Dr Shyuan Ngo*

Novel biomarkers to assess MND progression

Biomarkers can be used to track disease progression in people living with MND and measure the effectiveness of treatments in clinical trials.

Science in brief
Associate Professor Robert Henderson and colleagues have explored biomarkers using blood (serum neurofilaments), electrophysiology (MUNE) and imaging biomarkers (DTI). Their findings have been published in numerous international journals.

An important "spin-off" from this work has been advancing the understanding of the clinical features (phenotype) of MND. The researchers have classified MND according to upper motor neurone involvement (stiffness and spasticity) and lower motor neurone involvement (weakness and wasting). They have shown how lower motor neurone involvement correlates with survival. A collaboration with Professor Matthew Kiernan from the University of Sydney enabled a larger number of MND patients to participate in this research.

Impact
The search for biomarkers that can be used in clinical trials continues. The blood/urine neurofilaments appear to be the most promising. This research is important to people with MND because MND is variable in disease presentation and progression. A common method of classifying MND is needed for assessing disease progression particularly in clinical trials.
At the 27th International Symposium of ALS/MND 2016 held in Dublin, Professor Ben Brooks who devised the El Escorial criteria for the diagnosis of MND urged the international clinical MND community to use the Brisbane-Sydney method of grading clinical involvement.

Next steps
The researchers plan to use their biomarkers in early phase clinical trials to be conducted at the Royal Brisbane and Women's Hospital. They will continue to explore neurofilament biomarkers and collaborate with others to have the clinical phenotype widely used in assessing disease progression.

Photo:
Associate Professor Robert Henderson, Royal Brisbane and Women's Hospital and University of Queensland

Milestone
Devising a method of using clinical phenotype to assess MND progression

Principal investigator
Associate Professor Robert Henderson: Royal Brisbane and Women's Hospital and University of Queensland

Publications

Devine, M.S., Ballard, E., O'Rourke, P., Kiernan, M.C., McCombe, P.A., Henderson, R.D. (2015) Targeted assessment of lower motor neurone burden is associated with survival in ALS. *Amyotroph Lateral Scler Frontotemporal Degener*

Devine, M.S., Pannek, K., Coulthard, A., McCombe, P.A., Rose, S.E., Henderson, R.D. (2015) Exposing asymmetric gray matter vulnerability in ALS. *Neuroimage Clin.*

McCombe, P.A., Pfluger, C., Singh, P., Lim, C.Y., Airey, C., Henderson, R.D. (2015) Serial measurements of phosphorylated neurofilament-heavy in the serum of subjects with ALS. *J Neurol Sci.*

Devine, M.S., Kiernan, M.C., Heggie, S., McCombe, P.A., Henderson, R.D. (2014) Study of motor asymmetry in ALS indicates an effect of limb dominance on onset and spread of weakness, and an important role for upper motor neurones. *Amyotroph Lateral Scler Frontotemporal Degener.*

Drovandi, C., Pettitt, A.N., Henderson, R.D., McCombe, P.A. (2014) Marginal reversible jump Markov chain Monte Carlo with application to motor unit number estimation. *Comput Stat Data Anal.*

Devine, M., Farrell, A., Woodhouse, H., McCombe, P.A., Henderson, R.D. (2013) A developmental perspective on bulbar involvement in ALS. *Amyotroph Lateral Scler.*

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Baumann, F., Henderson, R.D., Ridall, P.G., Pettitt, A.N., McCombe, P.A. (2012) Use of Bayesian MUNE to show differing rate of loss of motor units in subgroups of ALS. *Clin Neurophysiol.*

"It is encouraging to see patients getting involved in clinical research to better understand this disease – we need reliable biomarkers to assess disease progression and for clinical trials, and we need to think out of the box.

Associate Professor
Rob Henderson

Publications continued

Baumann, F., Henderson, R.D., Gareth Ridall, P., Pettitt, A.N., McCombe, P.A. (2012) Quantitative studies of lower motor neurone degeneration in ALS: evidence for exponential decay of motor unit numbers and greatest rate of loss at the site of onset. *Clin Neurophysiol.*

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Ngo, S.T., Baumann, F., Ridall, P.G., Pettitt, A.N., Henderson, R.D., Bellingham, M.C., McCombe, PA. (2012) The relationship between Bayesian motor unit number estimation and histological measurements of motor neurons in wild-type and SOD1(G93A) mice. *Clin Neurophysiol.*

Raffelt, D., Tournier, D., Rose, S., Ridgway, G.R., Henderson, R.D., Crozier, S., Salvado, O., Connelly, A. (2012) Apparent fibre density: a novel measure for the analysis of diffusion-weighted magnetic resonance imaging. *Neuroimage*

Rose, S., Pannek, K., Bell, C., Baumann, F., Hutchinson, N., Coulthard, A., McCombe, P.A., Henderson, R.D. (2012) Direct evidence of intra- and interhemispheric corticomotor network degeneration in ALS: an automated MRI structural connectivity study. *Neuroimage.*

Rose, S., Rowland, T., Pannek, K., Baumann, F., Coulthard, A., McCombe, P., Henderson, R.D. (2012) Structural hemispheric asymmetries in the human precentral gyrus hand representation. *Neuroscience.*

McCombe, P.A., Henderson, R.D. (2011) The role of immune and inflammatory mechanisms in ALS. *Curr Mol Med.*

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MNDRIA funding

Grant-in-aid (2010) *Novel markers of MND*

Charles and Shirley Graham MND Research Grant (2013) *Use of biomarkers to understand ALS*

Graham Lang Memorial MND Research Grant (2015) *Blood biomarkers in ALS: translation into clinical practice of pNfH and search for additional biomarkers using proteomics*

MonSTaR Foundation MND Research Grant (2016) *Using biomarkers to explore heterogeneity of MND*

Empowering decision-making about care

Dr Anne Hogden and her team are developing decision-making tools to help people living with MND make decisions about their care.

Science in brief
The researchers assembled an expert panel of MND patients, carers, health professionals, researchers and State MND Association representatives. They asked the panel members to identify aspects of care that would benefit from decision tool support. From an initial list of 56 topics, six high-priority areas were chosen to develop into tools. These were gastrostomy, assisted ventilation, genetic testing, end of life care location, communication equipment and advance care planning.

Impact
People living with MND need services that provide timely, skilled care in response to changing priorities and needs. Decision support tools that are co-designed with patients, carers and health professionals can be tailored to a patient's specific needs, to optimise their participation in decision-making with health professionals, and promote patient and carer quality of life. The decision-making model that underpins this work has informed the MND guidelines for the UK National Institute for Health and Care Excellence (NICE). The NICE Guidelines aim to improve care for people with MND from the time of diagnosis to managing symptoms and preparing for end of life care.

Next steps
Development of the decision-making tools is underway, following linkage of the project with Macquarie University's Professional and Community Engagement (PACE) program. Undergraduate students from science, engineering and IT are developing web-based prototypes of the tools, for patients, families and health professionals to use on tablet or computer. This study is also linked to projects investigating decision-making for genetic testing and gastrostomy. Once prototypes are complete, they will be reviewed by the expert panel, and then undergo usability testing in MND clinics.

Milestone
Developing decision-making tools to help people with MND make decisions about care

Principal investigator
Dr Anne Hogden: Macquarie University

Publication
Hogden, A., Greenfield, D., Caga, J., Cai, X. (2016) Development of patient decision support tools for MND using stakeholder consultation: a study protocol. *BMJ Open*

MNDRIA funding
MND Victoria Research Grant
(2015) *Decision support tools for MND multidisciplinary care*

Breathing support improves care and survival in MND

For over 25 years, a collaborative team from Respiratory and Sleep Medicine and the Institute for Breathing and Sleep at Austin Health, and Calvary Healthcare Bethlehem in Melbourne, has worked to understand how assistance with breathing overnight affects survival in MND. As MND progresses, the breathing muscles weaken and mechanical ventilation support overnight can relieve symptoms and improve overall survival.

Science in brief
In 2016, the team led by Professor David Berlowitz and Associate Professor Paul Talman published data which showed that the overall pattern of muscle weakness exhibited by people with MND early in their disease affects how much improvement in survival will be provided by non-invasive ventilation. The paper showed that most people who started non-invasive ventilatory support overnight lived longer than those who were not able to use it. The median increase in survival with non-invasive ventilation use was 13 months compared with the median survival advantage of two to four months expected with riluzole, the most commonly used drug in MND.

Impact
This research is important for people living with MND and their carers because it shows that even those who have swallowing and speech difficulties early in the disease may benefit from breathing assistance overnight. It also showed that multidisciplinary care, specifically attention to breathing support by respiratory care teams, improves survival. Furthermore the researchers showed long-term, careful collection of clinical information in registries is key to improving care in MND. The generous support of over 1,000 patients and their families made the findings possible.

Next steps
The research team is continuing to collect and analyse data provided by patients and their families. They are working to determine breathing test values that will help decide the best time for individuals to start non-invasive ventilation. They are also testing whether assistance with coughing using a simple bag and mask can improve breathing during the day.

Milestone
Ascertaining that people with MND who use non-invasive ventilation overnight have a median increase in survival of 13 months

Principal investigator
Professor David Berlowitz: Institute of Breathing and Sleep, Austin Health

Publication
Berlowitz, D. J., Howard, M.E., Fiore Jr., J.F., Vander Hoorn, S., O'Donoghue, F.J., Westlake, J., Smith, A., Beer, F., Mathers, S., Talman, P. (2016) Identifying who will benefit from non-invasive ventilation in ALS/MND in a clinical cohort. *J. Neurol. Neurosurg. Psychiatry*

MNDRIA funding
Mick Rodger MND Research Grant (2011) *Identifying who will benefit from non-invasive ventilation in MND in a clinical cohort*

Cortical hyperexcitability an early feature of MND

Although described 150 years ago, the pathophysiological mechanisms underlying MND remain a matter of debate, particularly the site of disease onset and the factors that govern disease progression.

Science in brief
Research conducted by Professor Steve Vucic and his team, in collaboration with Professor Matthew Kiernan's team at the Brain and Mind Centre, has established that cortical hyperexcitability is an early feature in both sporadic and familial forms of MND and linked to the process of neurodegeneration, thereby confirming a central origin of MND. Subsequently, Professor Vucic and his team undertook a series of studies that established cortical hyperexcitability is a process specific to MND, by comparing ALS patients with non-ALS mimic neuromuscular disorders. These findings excluded the possibility that cortical hyperexcitability was a secondary response to muscle weakness.

Impact
These findings have identified novel treatment targets that are currently under assessment in two clinical trials being conducted by the NEALS consortium in the USA. They have also influenced cell rescue therapy strategies in MND, particularly directing the site of stem cell injections towards the central nervous system.

In addition to uncovering potential novel treatments, research conducted by Professors Vucic and Kiernan has led to the development of a much-needed diagnostic investigation for MND – threshold tracking transcranial magnetic stimulation (TMS). This diagnostic tool enables earlier diagnosis and recruitment into clinical trials, potentially providing maximum benefit for neuroprotective therapies under investigation. Furthermore, this technology can be used to monitor efficacy of novel treatments at an early stage of development to prevent unnecessary and costly clinical trials.

Professor Vucic has published extensively on the use of the threshold tracking TMS in high impact journals. His work published in the prestigious, *Lancet Neurology* (2015) was highlighted at the European Academy of Neurology meeting held in Berlin, Germany in June 2015. Threshold tracking TMS was also highlighted in *Nature* as an important medical discovery in 2011.

Next steps
The researchers aim to gain further insights into the mechanisms mediating the rapid pattern of disease spread in sporadic and familial forms MND over the next 3–5 years. They have combined neurophysiological studies using TMS with next-generation neuroimaging, in a longitudinal setting to follow changes in brain and nerve function.

In addition, threshold tracking TMS technology has been commercialised under the trade name MAGXCITE with a commercial partner Magstim (Wales, UK) and will be translated into clinical practice by early-2018. This is an example of translation into clinical practice and will provide a painless and readily accessible parameter to diagnose and provide a prognosis for MND patients.

Milestone
Establishing that cortical hyperexcitability forms a pathophysiological basis for MND and developing a diagnostic tool for MND

Principal investigator
Professor Steve Vucic: University of Sydney

Publications

Menon, P., Geevasinga, N., Yiannikas, C., Howells, J., Kiernan, M.C., Vucic, S. (2015) Threshold tracking TMS: a novel diagnostic investigation for ALS. *Lancet Neurol.*

Geevasinga, N., Menon, P., Nicholson, G.A., Ng, K., Howells, J., Kril, J., Yiannikas, C., Kiernan, M.C., Vucic, S. (2015) Cortical function in asymptomatic carriers and patients with c9orf72 carriers. *JAMA Neurol.*

Geevasinga, N., Menon, P., Howells, J., Nicholson, G.A., Kiernan, M.C., Vucic, S. (2015) Axonal ion channel dysfunction appears to be a pathophysiological feature of C9ORF72 ALS. *JAMA Neurol.*

Vucic, S., Lin, C.Y., Cheah, B., Murray, J., Menon, P., Krishnan, A.V., Kiernan, M.C. (2013) Riluzole exerts central and peripheral modulating effects in ALS. *Brain*

Vucic, S., Nicholson, G.A., Kiernan, M.C. (2008) Cortical hyperexcitability precedes the onset of familial ALS. *Brain*

Vucic, S., Howells, J., Trevillion, L., Kiernan, M.C. (2006) Assessment of cortical excitability using threshold tracking techniques. *Muscle Nerve*

Vucic, S., Kiernan, M.C. (2006) Novel threshold tracking techniques suggest that cortical hyperexcitability is an early feature of MND. *Brain*

MNDRIA funding

MND NSW Clinical Research Scholar – Steve Vucic (2005 – 2006) *Site of origin and patterns of neuronal degeneration in MND*

Photo:
Professor Steve Vucic (University of Sydney) with Jodie Bell

Credit: Western Sydney Local Health District

Combating the inflammatory response in MND

Associate Professor Trent Woodruff and colleagues have demonstrated that a key component of the immune system called "complement c5a" is activated in the brain and blood of patients with MND and in MND mouse models.

Science in brief
C5a is an extremely potent driver of the inflammatory response and appears to accelerate the progression of MND by increasing the generation of inflammatory mediators, which are neurotoxic to motor neurones.

The researchers tested a promising C5a inhibitor or drug called PMX205 in rodent models of MND. They showed PMX205 can significantly slow MND progression in these models when treated either before, or after the onset of disease. The research, published in the *British Journal of Pharmacology* in April 2017, also found PMX205 significantly increased the muscle strength of mice that have a SOD1 mutation.

Impact
PMX205 is a promising drug that targets an inflammatory pathway known to exacerbate MND. Research must be conducted in animal models to assess effectiveness and safety of a drug before testing in humans. The researchers hope their findings will ultimately translate to a treatment that means people with MND retain their motor function for longer and also live longer.

Next steps
Associate Professor Woodruff's current work aims to define the precise mechanisms by which C5a drives MND progression, as well as examining this pathway further in patients with MND. He and his team have also partnered with a pharmaceutical company, called Alsonex Pty Ltd, and together they are now moving PMX205 on the path towards human trials. A key step is to demonstrate a good safety profile of PMX205 in animals, before the researchers begin testing the drug in human volunteers. They are also investigating other immune targets for their role as potential therapeutic targets for MND.

Milestone
Discovering that PMX205 slows MND progression in rodent models of MND

Principal investigators
Associate Professor Trent Woodruff and Dr John Lee: University of Queensland

Publications
Lee, J.D., Kumar, V., Fung, J.N., Ruitenberg, M.J., Noakes, P.G., Woodruff, T.M. (2017) Pharmacological inhibition of complement C5a-C5aR1 signalling ameliorates disease pathology in the hSOD1(G93A) mouse model of ALS. *Br. J. Pharmacol.*

Wang, H.A., Lee, J.D., Lee, K.M., Woodruff, T.M., Noakes, P.G. (2017) Complement C5a-C5aR1 signalling drives skeletal muscle macrophage recruitment in the hSOD1(G93A) mouse model of ALS. *Skeletal Muscle.*

MNDRIA funding
MNDRIA Postdoctoral Fellowship – John Lee (2016 – 2018) *The role of C3aR signalling in slowing down the disease progression of MND*

Charles and Shirley Graham MND Research Grant (2015) *Therapeutic targeting of the NLRP3 inflammasome using a potent and orally active inhibitor in experimental MND*

PMX205 – Road to clinical trial

ADME: Absorption, distribution, metabolism and excretion testing conducted on drugs prior to testing in humans
IND: Investigational New Drug status granted by the US Food and Drug Administration, which allows new drugs to be administered to humans

Can breathing exercises help people with MND?

People living with MND represent a significant proportion of patients seen at the Victorian Respiratory Support Service, a state-wide service that provides specialised respiratory management for people who require ventilatory support at home. In 2017, there were over 100 people living with MND using ventilatory support at home in Victoria.

Science in brief
Ms Sheers is conducting a clinical trial to investigate whether doing specialised breathing exercises every day slows the decline in breathing function or improves cough effectiveness of people with MND.

Participants perform a number of different breathing tests and complete questionnaires at the baseline visit, before being randomly allocated to perform one of two different types of breathing exercises. People are asked to do their assigned exercises twice a day for a 3-month period, with each exercise session taking between 5-10 minutes. Researchers visit people in their home to review progress at the 1-month and 2-month mark. The final 3-month visit repeats these breathing tests and questionnaires to assess changes in breathing, cough and quality of life.

The study is over 50 per cent complete and people with MND who are participating have reported no significant difficulties with the trial. This research will help people living with MND, their families, carers and clinicians understand what treatments maintain the best ability to breathe and cough as MND progresses.

Impact
Although use of a mask ventilator (non-invasive ventilation) helps people with breathing muscle weakness live longer, it only addresses one aspect of the respiratory problems. Respiratory complications such as chest infections or pneumonia are also common towards the end of someone's disease, so improving cough or breathing function could improve people's symptoms and quality of life. A weak cough, a soft voice and losing the ability to take a deep breath are all distressing symptoms faced by some people with MND. This study aims to help with these symptoms.

Next steps
The researchers are continuing to recruit clinical trial participants and collect data. They are starting to analyse baseline data, specifically the relationship between people's lung function, cough and whether they have experienced any respiratory tract infections. With better understanding of these factors, they can then tailor respiratory interventions at the appropriate stage of a person's disease.

Photo:
Participant undergoing follow-up breathing tests in their home

Milestone
Conducting a clinical trial to investigate whether doing specialised breathing exercises slows the decline in breathing function or improves cough effectiveness of people with MND

Principal investigator
Nicole Sheers: Institute of Breathing and Sleep, Austin Health

MNDRIA funding
NHMRC/MNDRIA Co-funded Postgraduate Scholarship (2015) *Lung volume recruitment in neuromuscular disease: Can 'breath-stacking' improve lung function, respiratory symptoms and quality of life for people with neuromuscular disease?*

Copper-ATSM: A potential MND treatment

The idea to investigate copper-containing compounds as a possible treatment for MND began as a collaboration between Drs Kevin Barnham, Tony White and Paul Donnelly, all based at The University of Melbourne over 10 years ago. They were working on Alzheimer's disease and Parkinson's disease at the time. As luck would have it, they had an opportunity to test copper-ATSM in an MND mouse model under the auspices of Dr Qiao-Xin Li, also at The University of Melbourne. The researchers were thrilled to find the project was an immediate success; treating the MND model mice diminished severity of disease symptoms and extended survival. These data led to the first project to focus on investigating copper-ATSM as a potential treatment for MND. The project commenced in 2008 and was led by Drs Li, Barnham, Donnelly, White and Crouch.

Science in brief
Since the initial project, Dr Crouch and his team's focus has been to address some fundamental research questions. What is the full therapeutic potential of copper-ATSM? How does it work? Will it work in people with MND? To answer these questions they have adopted multiple, complementary lines of investigation, including assessments performed on mice treated with the drug and biochemical analyses performed using brain and spinal cord tissue from people who had MND. The expanded knowledge gained from this research provides an ever-increasing opportunity to ensure that the successful outcomes generated from MND model mice will translate to an effective drug for people with MND.

Impact
This research over the last decade has led to the Phase I copper-ATSM clinical trial sponsored by Collaborative Medicinal Development Pty Ltd, which began in Sydney in late 2016, and more recently, in Melbourne in 2017. Dr Crouch and his team have achieved what is often referred to as "bench-to-clinic" research. This means that an idea, initially developed then tested in the research laboratory, has withstood the rigours of scientific interrogation to the point where it has become feasible to begin testing in people.

Next steps
Dr Crouch and his team continue to undertake research that feeds new information into the clinical setting. Only 10 per cent, of drugs that begin preclinical testing ever make it to human clinical trials. Getting to this point needs many factors to align including financial support. A possible treatment resulting from this research is still many years away. Analysis of data from the clinical trial will give researchers a clearer picture on whether copper-ATSM should be tested in larger studies to further investigate its potential.

Milestone
Discovering copper-ATSM diminishes the severity of MND symptoms and extends survival of MND model mice, which led to a Phase I copper-ATSM clinical trial

Principal investigator
Dr Peter Crouch: University of Melbourne

Publications
Hilton, J.B., Mercer, S.W., Lim, N.K.H., Faux, N.G., Buncic, G., Beckman, J.S., Roberts, B.R., Donnelly, P.S., White, A.R., Crouch, P.J. (2017) CuII(atsm) improves the neurological phenotype and survival of SOD1G93A mice and selectively increases enzymatically active SOD1 in the spinal cord. *Sci. Rep.*

Dang, T.N.T, Lim, N.K.H., Grubman, A., Li, Q.X., Volitakis, I., White, A.R., Crouch, P.J. (2014) Increased metal content in the TDP43 (A315T) transgenic mouse model of frontotemporal lobar degeneration and ALS. *Front Aging Neurosci.*

Roberts, B.R, Lim, N.K.H., McAllum, E.J., Donnelly, P.S., Hare, D.J., Doble, P.A., Turner, B.J., Price, K.A., Lim, S.C., Paterson, B.M., Hickey, J.L., Rhoads, T.W., Williams, J.R., Kanninen, K.M., Hung, L.W., Liddell, J.R., Grubman, A., Monty, J.F., Llanos, R.M., Kramer, D.R., Mercer, J.F.B., Bush, A.I., Masters, C.L., Duce, J.A., Li, Q.X., Beckman, J.S., Barnham, K.J., White, A.R., Crouch, P.J. (2014) Oral treatment with CuII(atsm) increases mutant SOD1 *in vivo* but protects motor neurones and improves the phenotype of a transgenic mouse model of ALS. *J. Neurosci.*

McAllum, E.J., Lim, N.K.H., Hickey, J.L., Paterson, B.M., Donnelly, P.S., Li, Q.X., Liddell, J.R., Barnham, K.J., White, A.R., Crouch, P.J. (2013) Therapeutic effects of CuII(atsm) in the SOD1-G37R mouse model of ALS. *Amyotroph Lateral Scler Frontotemporal Degener.*

> I've always loved working in the lab; if there were more hours in the day, I'd spend them at the bench. I feel that our work on copper-ATSM is getting close to something very significant. So now, more than ever, I find it very hard to down tools at the end of the day. Fridays come too soon, and weekends are too long.
>
> *Dr Peter Crouch*

Photo:
Dr Peter Crouch, University of Melbourne

MNDRIA funding

zo-ee MND Research Grant (2008) *The use of copper-ATSM treatment to identify cellular mechanisms of motor neurone degeneration in ALS*

Betty Laidlaw MND Research Grant (2016) *Copper malfunction in MND: a therapeutic target for sporadic MND*

Jenny Barr Smith MND Collaboration Grant (2016) *Drug-specific biomarkers to facilitate clinical translation of copper-ATSM as a potential therapeutic for MND*

zo-ee MND Research Grant (2016) *Proteomic investigation of functional copper deficiency in MND: implications for copper-ATSM as a novel therapeutic*

Testing the benefits of an enriched diet and swallowing exercises

Eating, drinking and speaking are important parts of life and people with MND experience a rapid decline in these functions. Research suggests that active swallowing exercises may prolong the ability to eat and drink safely, and prolong the ability to speak. However, no thorough studies have been conducted. Animal studies suggest a diet enriched with extra virgin olive oil may be effective in slowing the progression of MND, with improved maintenance of weight status and muscle function.

Science in brief
Professor Vicki Flood is conducting a pilot study to evaluate the effects of diet changes combined with active swallowing exercises on swallowing function, speech and weight status of people with MND. The research is also investigating changes in the quality of life of participants. This study brings together a multidisciplinary team of health professionals in neurology, speech pathology and dietetics. Professor Flood's team is working with Professor Steve Vucic and Dr Parvathi Menon (Westmead Hospital) and Dr Hans Bogaardt (University of Sydney).

Professor Flood is creating and testing suitable recipes for people with MND, and is receiving feedback on the enriched diet intervention throughout the pilot study. A total of 45 people with MND will participate in the pilot of the clinical trial. The study is currently recruiting participants.

Participants in the study are randomly assigned to one of three different groups: the exercise only group; the extra virgin olive oil diet group; and the exercise combined with extra virgin olive oil diet group. Swallowing function, speech function, weight, muscle mass, diet intake and quality of life will be assessed in participants.

Impact
People with MND experience weakening muscles, which results in speech and swallowing disorders. This is the first study to evaluate the effects of active swallowing exercises and/or a diet enriched with extra virgin olive oil on disease progression, weight, muscle function and quality of life.

Next steps
If the results from this pilot study are feasible and promising, researchers will run a larger multi-site clinical trial.

Milestone
Conducting the first study to evaluate the effects of an enriched diet and swallowing exercises on speech and weight of people living with MND

Principal investigator
Professor Vicki Flood: University of Sydney

MNDRIA funding
Jenny Simko MND Research Grant (2017)
The effects of active exercise combined with an enriched diet on swallowing, speech function and weight in patients with MND: a randomised trial

Animal studies suggest a diet enriched with extra virgin olive oil may be effective in slowing the progression of MND, with improved maintenance of weight status and muscle function.

The Lighthouse Project

Approximately 8 per cent of human genes have retroviral origins. Human endogenous retroviruses (HERVs) infected animals and humans over millions of years of evolution and eventually became part of our genetic makeup. HERVs were only discovered about 20 years ago and it is still not known exactly how they may be related to causing human diseases. However, there is very good evidence that in animals these viruses are associated with a number of neurological conditions. HERV-K has been directly linked to motor neurone damage and has been found in the brain tissue of patients with MND.

Science in brief
The Lighthouse Project is a Phase 2 open-label clinical trial conducted at four centres in Australia. The study aims to determine the safety and tolerability of an anti-retroviral therapy known as Triumeq in 40 people with MND and provide preliminary data on whether it is able to slow down the progression of MND. Triumeq is already used to treat HIV infection safely and effectively.

Impact
The Lighthouse Project is the first clinical trial in the world to use modern combination anti-retroviral therapy in people with MND.

Next steps
All participants have been recruited and more than 60 per cent have completed the study. Analysis of data from the trial will give researchers a clearer picture on whether Triumeq should be tested in larger studies to further investigate its potential.

Researchers will analyse two recently discovered biomarkers in 20 people who have completed the trial. This will help to assess whether Triumeq has had a positive effect on people with MND. Blood and urine samples were taken from each participant before, during, and after treatment and stored. Dr Mary-Louise Rogers from Flinders University will supervise analysis of a biomarker found in urine called p75 (see page 30). Dr Andrea Malaspina from the Blizard Institute in London will oversee analysis of a neurofilament light-chain biomarker found in blood.

Milestone
Conducting the first Phase 2 clinical trial of an antiretroviral therapy for MND

Chief investigator
Professor Julian Gold: The Albion Centre

MNDRIA funding
Cure for MND Collaboration Initiative Grant (2016) *Pilot trial of antiretroviral therapy for ALS*

"It was the first time I had seen a patient with SMA type 1 get stronger, start to roll, then sit, celebrate successive birthdays and ride a tricycle. We realised this was a huge first step forward that could change the course of SMA.

Dr Michelle Farrar

Bringing an emerging SMA treatment to Australia

Dr Michelle Farrar is at the forefront of an exciting therapeutic era. She was a collaborator in ENDEAR, a pioneering study that identified the first emerging treatment – nusinersen – for spinal muscular atrophy (SMA).

SMA is the number one genetic cause of death in infants, affecting 1 in 11,000 children. Like adult MND, SMA affects the motor neurones of the spinal cord, causing muscle weakness and wasting.

Until now, the treatment of SMA has focused on managing complications caused by weakness, feeding and breathing difficulties. There has been no specific treatment for SMA. This has changed with positive results from recent clinical trials that have shown nusinersen significantly prolongs survival and also improves motor function such as head control, ability to roll, sit and stand.

Science in brief
SMA is caused by abnormalities in the *SMN1* (Survival Motor Neuron 1) gene. When the *SMN1* gene does not function properly, the SMN protein cannot be produced, which causes motor neurones in the spinal cord and brainstem to die. Nusinersen works by helping a "back-up gene" called *SMN2* to produce more of the SMN protein.

Impact
Dr Farrar is leading an Australian team participating in SMA clinical trials to evaluate the safety and efficacy of new potential therapies. She played a key role in establishing an expanded access program to enable patients with the most severe type of SMA access to the unapproved treatment while it is under review by the Therapeutic Goods Administration. Currently, nusinersen must be injected into the spinal fluid of infants affected by SMA several times a year.

In November 2016, Australia's first infant with SMA type 1 joined eight other infants worldwide to be given nusinersen outside a clinical trial. Since then, a further eight infants and children have commenced treatment via the expanded access program in Sydney. The children are making motor gains that have never been seen prior to this lifesaving treatment; for example, improvement in head control, and the ability to roll and sit. This is having huge implications for clinical care, with all aspects of supportive care changing and under discussion.

Next steps
Dr Farrar's ongoing research will provide new insights into the development of novel therapies. It will contribute to gaining new knowledge of the long-term benefits and any side effects of emerging treatments. The expanded access program has highlighted the challenges for early diagnosis, and the need for increasing SMA awareness among health professionals and the community. Importantly, newborn screening presents an opportunity to enable early initiation of treatment before the onset of symptoms.

There are a number of promising SMA drugs in the research pipeline. The strategy of increasing SMN protein levels to improve the survival or motor neurones provides a new therapeutic direction that could also benefit other types of MND in the future. Animal studies have suggested increasing the SMN protein may have some benefit in MND.

Milestone
Contributing to the development of nusinersen, a world-first emerging treatment for SMA

Principal investigator
Dr Michelle Farrar: University of NSW

MNDRIA funding
Beryl Bayley MND Postdoctoral Fellowship – Michelle Farrar (2016 – 2018) *MND in children and young people – understanding pathophysiology and developing treatment approaches*

SMA is the number one genetic cause of death in infants, affecting 1 in 11,000 children. Like adult MND, SMA affects the motor neurones of the spinal cord, causing muscle weakness and wasting.

Research on the radar

MNDRIA is committed to funding the best novel research to change the future of MND. The following projects have the potential to improve the lives of people impacted by MND and take us closer to realising our vision of a world without MND.

Dr Jean Giacomotto (Queensland Brain Institute, University of Queensland) has developed an innovative genetic approach, which opens new avenues to both study and reproduce MNDs in the zebrafish. Using this technology, he has generated the first stable model of spinal muscular atrophy and is working on developing models of ALS. By generating several MND models, Dr Giacomotto aims to further study the different molecular and cellular pathways involved in motor neurone degeneration and try to find drugs, which could block or slow this process.

MNDRIA funding
Grant-in-aid (2017) *New and innovative polygenic approach for understanding and modelling MNDs in zebrafish*

Dr Jennifer Fifita (Macquarie University) is carrying out research to identify novel gene mutations that cause MND. Her work has led to the identification of five candidate gene mutations in a family with several cases of MND. Further work is now in progress to test these gene mutations in animal models to learn more about their potential novel role in MND. This work helps to provide a greater understanding of the underlying causes of MND, new cell and animal models to study MND as well as new MND genes to add to DNA diagnostic testing regimes.

MNDRIA funding
PhD Scholarship MND Top-up Grant (2013 – 2015) *Examining the role of novel molecules causing MND*

Bill Gole MND Postdoctoral Fellowship – Jennifer Fifita (2017 – 2019) *Investigating the molecular and pathological origins of ALS*

Dr Jacqueline Leung's (Wicking Dementia Research Centre, University of Tasmania) research is focused on understanding the role of a cell type called the oligodendrocyte in MND. Oligodendrocytes have an important role in producing myelin, the insulating layer around the neuronal processes, which allows the rapid signal transmission between neurones. Loss of myelin is present in MND; however, the cause of this loss is currently not known. Dr Leung has identified the potential involvement of pathogenic proteins, TDP43 and SOD1, which may be a therapeutic target for the repair of myelin in MND.

MNDRIA funding
Bill Gole MND Postdoctoral Fellowship – Jacqueline Leung (2014 – 2016) *Investigating the role of oligodendrocytes in ALS*

Grant-in-aid (2017) *Identifying the role of oligodendrocytes in disease onset and progression in ALS*

Associate Professor Ronald Sluyter, Dr Diane Ly and Associate Professor Justin Yerbury (University of Wollongong) have found a drug that blocks a nerve cell communication pathway – known as the ATP-P2X7 pathway – slows MND progression in mice. They hope this drug will offer a potential new approach to treat MND in people. They are currently investigating whether a new, improved drug targeting this cell communication pathway can slow MND progression even further in mice. If successful, this drug may be considered for testing in people diagnosed with MND. Future opportunities also exist to test this new approach with other approaches to potentially offer a combined therapy.

MNDRIA funding
Stanford Family MND Research Grant (2017) *Establishing the therapeutic potential of the P2X7 receptor ion channel in ALS*

Dr Adam Walker (Macquarie University) and his team are studying mice with MND-like TDP-43 pathology. These mice have a progressive disease phenotype similar to people living with MND and are an important new resource for both understanding how the disease develops and for testing new MND drugs. These mice are being used in multiple studies with collaborators throughout Australia and the USA to allow researchers to identify new treatments for people living with MND.

MNDRIA funding
Cure for MND Foundation Research Grant (2016) *Pre-clinical therapeutic testing and biochemical changes associated with neurone survival in a validated TDP-43 mouse model of MND*

MonSTaR Foundation MND Research Grant (2017) *New proteins and pathways contributing to TDP-43-mediated neurodegeneration*

Dr Mehdi Van den Bos (Westmead Hospital, University of Sydney) is using newly developed neurophysiological techniques to investigate excitatory and inhibitory cortical networks in people with MND. He aims to find out how an imbalance of nerve excitation and inhibition affects the daily experience of people with MND. Dr Van den Bos hopes these findings will guide future therapies to slow down or stop the advance of MND.

MNDRIA funding
Stanford Family MND Research Grant (2017) *Pathophysiological mechanisms underlying ALS: insights from novel cortical functional techniques*

Dr Karin Borges and colleagues at the University of Queensland are working on a treatment they hope has the potential to slow the progression of MND. Their research found a fatty acid derivative called triheptanoin reduced motor neurone loss by a third in an MND animal model. Loss of limb strength and body weight were also delayed. Triheptanoin has already been used safely for 15 years for energy metabolism disorders and neuromuscular disorders. The researchers are expanding their investigations in animal models to determine whether triheptanoin is suitable for testing as a potential treatment on people with MND.

MNDRIA funding
MNDRIA Grant-in-aid (2017) *Triheptanoin to improve energy metabolism in MND*

Dr Parvathi Menon (Westmead Hospital, University of Sydney) uses threshold tracking transcranial magnetic stimulation (TMS) to look at brain hyperexcitability and its changes during the course of MND. Her work was published in the reputed international journal, *Lancet Neurology* in 2015. Dr Menon is studying brain changes associated with MND onset and progression to find pathways that may be modified to halt disease progression.

MNDRIA funding
Beryl Bayley MND Postdoctoral Fellowship (2015) *Insights into ALS pathophysiology from patterns of disease progression*

Professor Samar Aoun (Curtin University) has investigated the Australian practice in breaking the news of an MND diagnosis. Almost 40 per cent of patients/family carers have reported to be dissatisfied with their experience of the diagnosis delivery. Professor Aoun's research has found areas for improvement around delivery with more empathy, length of consultation, period of follow up and referral to State MND Associations. The findings provide an evidence base for developing protocols to improve communication skills and alleviate the emotional burden associated with breaking bad news.

MNDRIA funding
Graham Lang Memorial Grant (2014) *Best practice in breaking the news of an MND diagnosis*

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