JUNE 2017

ADVANCE

Dr Tim Chataway, Vyoma Modi, Michell Cardoso and Dr Mary-Louise Rogers Credit: Flinders University

New biomarker to track MND

In a world-first, research supported by the MND Research Institute of Australia (MNDRIA) has led to the discovery of a new and simple test to monitor disease progression in people with MND and evaluate drugs under investigation in MND clinical trials.

Levels of $p75^{ECD}$, a region of protein present in urine after nerve injury, were found to increase as MND progressed. This suggests that $p75^{ECD}$ can be used as a biomarker that reflects motor neurone degeneration in people with MND. $p75^{ECD}$ is the first biological-fluid based biomarker of MND progression to be identified.

The study, led by Flinders University researchers Drs Mary-Louise Rogers and Stephanie Shepheard, and Professor Michael Benatar from the University of Miami, was published in the prestigious journal *Neurology* in February 2017.

p75 is a protein, which supports neurone growth during embryonic development. After birth, levels of p75 on neurones decrease unless the nervous system is injured in some way. A region of p75 protein – $p75^{ECD}$– is shed from injured nerves and subsequently found in the urine of all people with MND. This means it can be detected easily and consecutive urine samples can be used to monitor the amount of nerve injury and progression of MND.

This discovery is not a treatment. However, it is a new biomarker that can be used to track disease progression in people with MND and measure the effectiveness of treatments being tested in clinical trials. Currently, progression of MND in clinical trials is monitored using the ALS-FRS questionnaire to observe symptoms, and physical tests which look at things like hand muscle strength and breathing. A biomarker found in urine, which is easy to collect, provides an objective measure to assess clinical trials.

More research in larger numbers of people with MND will help to refine the use of $p75^{ECD}$ as a biomarker. This research was supported by seven organisations including MNDRIA.

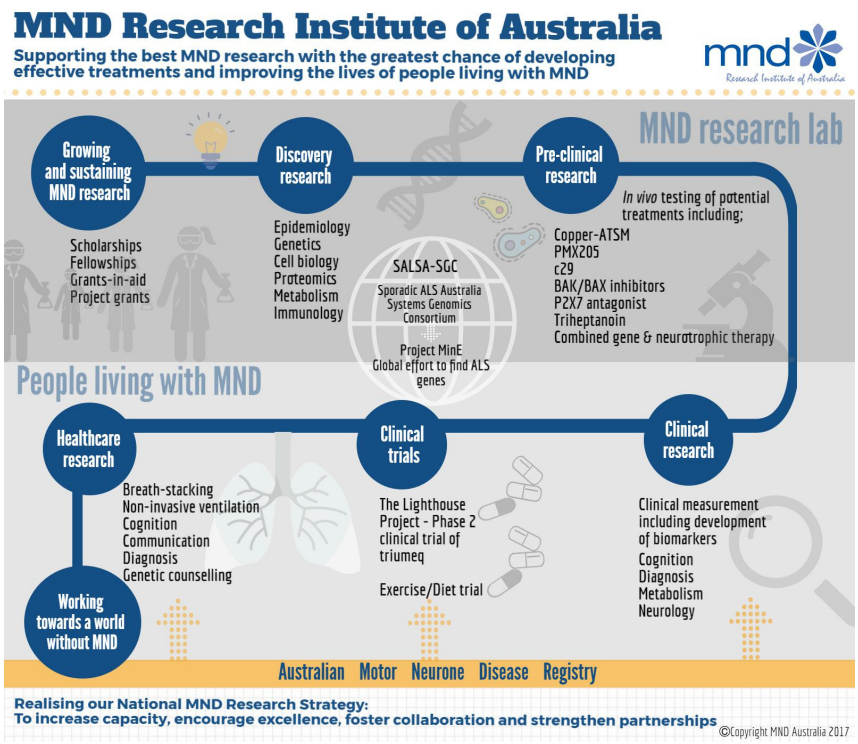
Detecting $p75^{ECD}$ is a non-invasive, painless test offering advantages over other biomarker tests that involve lumbar punctures and cerebrospinal fluid.

The MND Research Institute of Australia (MNDRIA) has built and sustained MND research in Australia for the last 30 years.

mnd Research Institute of Australia

From the Executive Director Research

The FDA approval of edaravone to treat MND in the US in May 2017 signals a hopeful chapter for the MND community. It is the first drug to be approved specifically for MND in 22 years. Clinical trials have shown edaravone slows the progression of MND in a subset of people. MND Australia is currently in discussions regarding plans for edaravone approval in Australia.



It takes an average of 12 years, millions of dollars and the collaborative efforts of many scientists for a drug to travel from the research laboratory to the patient. Recent advances in molecular medicine have enabled researchers to better understand what causes disease and consequently improve the potential of developing new treatments.

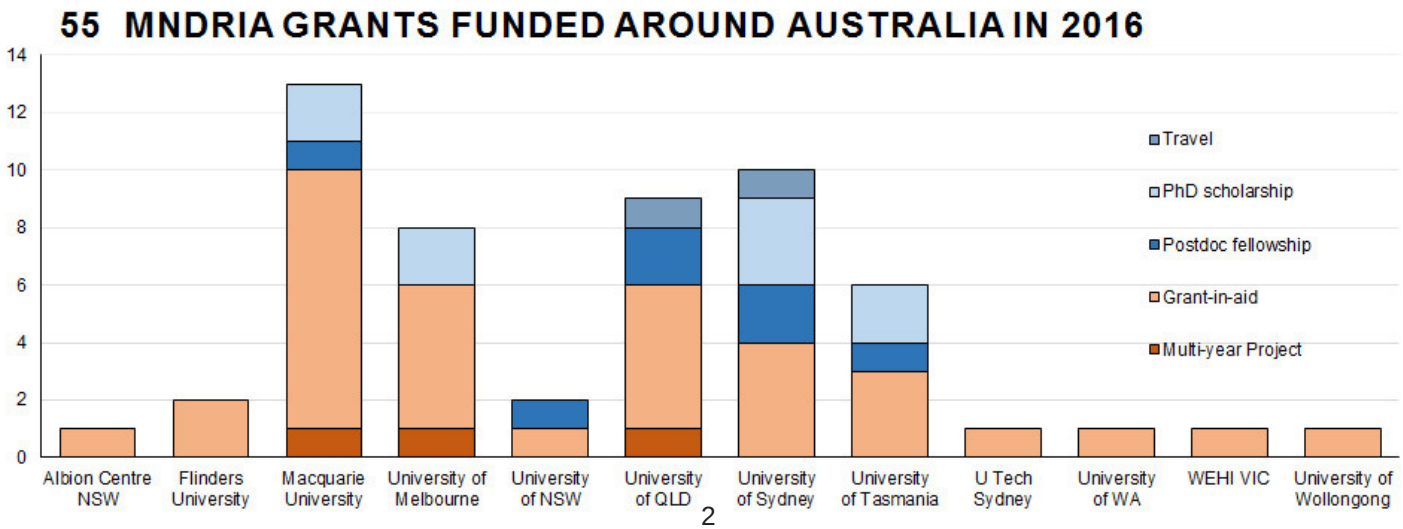
Thanks to the generosity of the community, MNDRIA has been able to support a comprehensive research program (pictured above) that covers discovery research through to healthcare. MNDRIA only funds the best research and has leveraged funding to maximise the community's investment through organisations like the National Health and Medical Research Council and by forging international links such as with Project MinE, a global effort to identify MND genes.

The past year has seen some significant progress in MND research supported by MNDRIA. MNDRIA is proud to report some of these success stories in this new look *Advance*. I hope you enjoy the read. For progress reports from research supported in 2016, visit www.mndresearch.org.au/reports2016. More than $5 million was invested in 55 research projects across 12 institutions in 2016 as shown in the chart below.

I took on the Executive Director Research role in April and would like to express my deep appreciation to Janet Nash who has led MNDRIA for 12 years to become the thriving organisation it is today. Janet remains with the research team managing all aspects of MNDRIA grants and finance.

We recently celebrated National Volunteer Week to acknowledge the contribution of Australia's volunteers. I would like to thank Clare Watson from the University of Wollongong for her assistance in writing for our website and Bhagya Warnakulasuriya for her fabulous analytical skills. I also thank long-serving volunteers Alan Hauserman and Maureen Burmeister for their steadfast support. To all our donors and supporters in the community, my heartfelt thanks for every dollar you raise for MND research. Please continue to support MNDRIA.
We can change, and we are changing, the future of MND.

Dr Stephanie Williams



PMX205 reduces MND symptoms and extends the life of mice

A study supported by MNDRIA and led by University of Queensland researchers Associate Professor Trent Woodruff and Dr John Lee has found a novel drug called PMX205 extends the life of mice that have a SOD1 mutation.

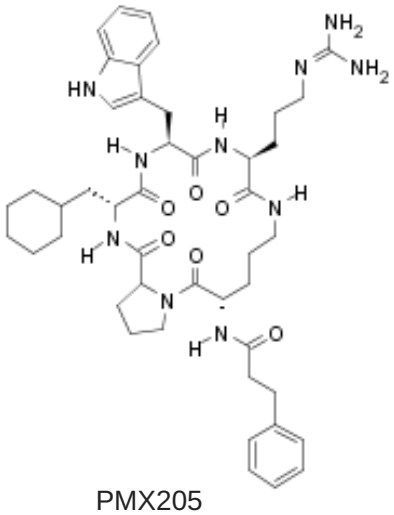
The research, published in the *British Journal of Pharmacology* earlier this year, also found PMX205 slowed disease progression and significantly increased the muscle strength of mice.

In human terms, the researchers hope these findings could mean people with MND retain their motor function for longer and also live longer, if treated with PMX205.

PMX205 blocks a key component of the immune system called “complement C5a.” C5a is involved in inflammation, which is the body’s response to injury. C5a is increased in the brains and blood of people with MND, and is thought to speed up the death of motor neurones. PMX205 is an inhibitor of C5a and dampens down inflammation, preventing further damage to the body.

More studies are now underway to determine the safety of PMX205 before it can be tested in humans. To date, PMX205 has only been tested in the familial SOD1-G93A model. However, the inflammatory pathway is likely to be active in all forms of MND. Future studies are planned to test PMX205 in sporadic MND models.

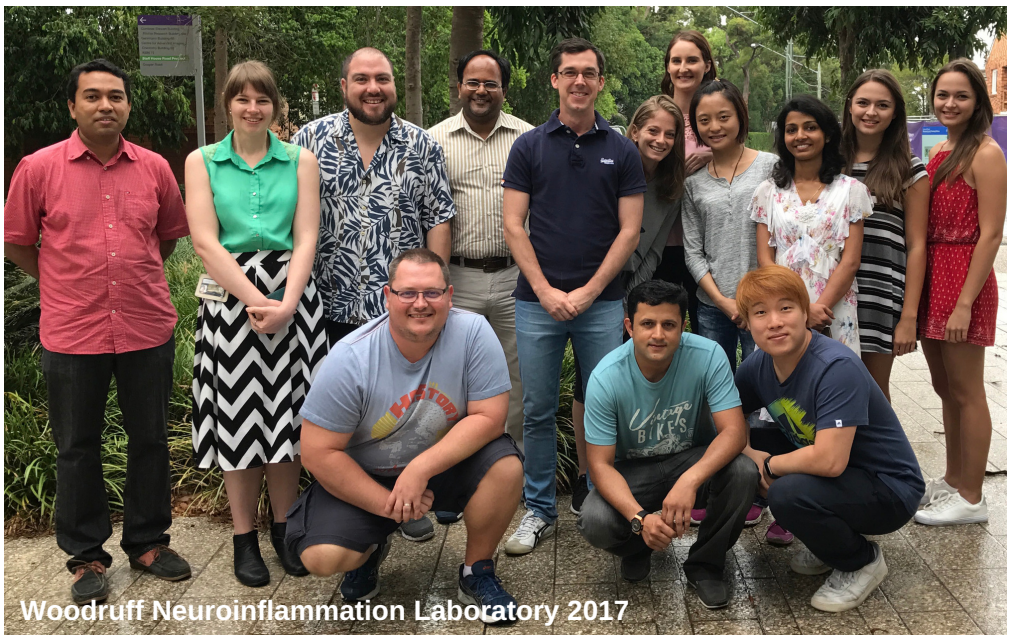
This research is expected to lead to clinical trials of PMX205. Formal preclinical safety and toxicity studies need to be successfully completed first, and this will take about two years before human testing can occur. The drug has obtained FDA (Food and Drug Administration) and EMA (European Medicines Agency) ‘orphan drug’ approval, which allows for an accelerated progression to human trials. The first clinical trials in healthy volunteers with PMX205 are currently anticipated to commence in Australia in late 2018.



PMX205

If PMX205 is found to be safe in healthy volunteers, clinical trials in patients with MND may be possible during 2019, with Australia as one potential site of these trials.

This research was supported by the National Health and Medical Research Council and MNDRIA.



Woodruff Neuroinflammation Laboratory 2017

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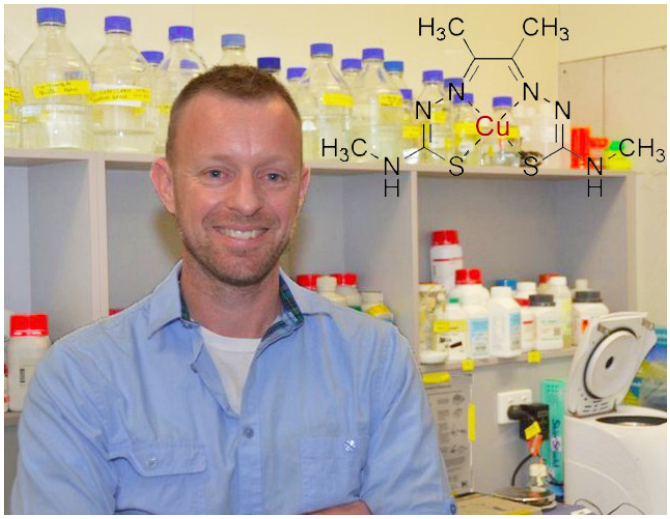
Potential MND treatment in the pipeline

When a Phase I clinical trial to test the safety of copper-ATSM began in November 2016, it signalled the start of a new era for MND research in Australia … the research effort had reached a stage where it could start delivering potential treatments to be tested in people.

This first-in-human study marks a major milestone for The University of Melbourne's Dr Peter Crouch and his team. It has been a long journey to get to this point. No less than 10 years, numerous scientists and more than $4 million.

The idea to investigate copper-containing compounds began as a collaboration between Drs Kevin Barnham, Tony White and Paul Donnelly, all based at The University of Melbourne at the time. They were working on Alzheimer's disease and Parkinson's disease. 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 dedicated funding from MNDRIA for copper-ATSM as a potential treatment for MND and the award of a $25,000 zo-ee MND Research Grant to Drs Li, Barnham, Donnelly, White and Crouch in 2008.

The rest is history. 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?



MND Fact
People living with MND have an average life expectancy of **2.5 years** from the time of diagnosis

MNDRIA's investment to support three projects that aim to assist developing copper-ATSM as a potential therapeutic:

Betty Laidlaw MND Research Grant
Copper malfunction in motor neurone disease: a therapeutic target for sporadic MND

zo-ee MND Research Grant
Proteomic investigation of functional copper deficiency in MND

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

MNDRIA has now invested more than $1.2 million in copper-ATSM research. Notably, Dr Crouch and colleagues published their latest findings in the journal *Scientific Reports* earlier this year. Their research over the last decade has led to the Phase I copper-ATSM clinical trial sponsored by Collaborative Medicinal Development Pty Ltd. This began in Sydney late in 2016 and more recently in Melbourne. 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.

Only 10% 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. Dr Crouch has been able to leverage MNDRIA funding to get support from several agencies including the National Health and Medical Research Council, the Australian Research Council, The University of Melbourne, and MND Victoria. Dr Crouch and his team continue to undertake research that feeds new information into the clinical setting. 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.

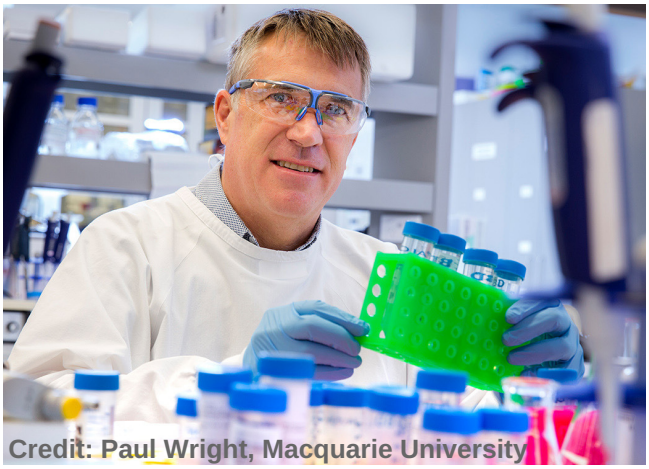
MND Australia Leadership Grant

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 may 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.



Credit: Paul Wright, Macquarie University

These huge studies have led to the discovery of eight new MND genes in the past four years: *ERBB4*, *SS18L1, TUBA4A, TBK1, CCNF, SFPQ, C21orf2* and *NEK1*. Several of these discoveries have translated into new diagnostic tests for familial MND. Importantly, Associate Professor Blair and his team led the international effort that found *CCNF* mutations are responsible for disease in a subset of MND families from Australia, Canada, Spain, Italy, Japan, the UK and USA. This major finding was published in the prestigious journal *Nature Communications* in April 2016. The team has now developed cell and animal models based on mutant *CCNF* to understand the biology of motor neurone death and to assess new therapeutic strategies for familial and sporadic MND.

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, some 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.

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

Meet Associate Professor Tracey Dickson, cellular neuroscientist

As a young student studying science at the University of Tasmania, Tracey Dickson had no idea that she would later become Deputy Director of the Menzies Institute for Medical Research, University of Tasmania.

“I was never quite sure of what I wanted to be, and initially began a law degree. It wasn’t until I had finished my honours degree in microbiology and started working as a research assistant in a neuroscience lab that I realised that I wanted to follow my interest in the brain further,” she says.

Associate Professor Tracey Dickson has been committed to researching the mechanisms of MND for the last 15 years.

“I think to be a successful researcher you need to be passionate and dedicated but also pretty stubborn and resilient. Your best ideas often don’t work out the way that you thought they might. This sometimes leads to a breakthrough, but more often this means going back to the drawing board.”

Associate Professor Dickson’s perseverance is spurred by the experiences of people living with MND, their families and carers as well as a strong desire to make a difference.

“I think I am affected by all people with MND who I meet: each is unique and it is such an unfair and unrelenting disease. However, when I've met

people who are diagnosed with young families, I can’t help but think about my own life and family, and how lucky I am."

Associate Professor Dickson's team is working to understand the role of toxicity in motor neurone death. There is evidence from many areas of clinical and laboratory medical research that in MND the motor neurones are dying because of a toxicity that is triggered by their over-activity. New evidence shows that this toxic cascade is initially triggered by the death or dysfunction of another type of neurone in the brain – the interneuron. Using this knowledge, Associate Professor Dickson and her team hope to develop an intervention to stop toxicity and halt MND progression.

A gift with global reach

Beryl Bayley was a long-term MNDRIA donor. Her generous bequest left to MNDRIA is helping clinicians around the world to diagnose MND more easily and reliably, and advancing researchers' understanding of MND onset and progression.

The diagnosis of MND is often clinically difficult and sometimes a person must be reviewed over many months before the diagnosis becomes certain. Beryl Bayley MND Postdoctoral Fellow, Dr Parvathi Menon, and the team at Westmead Hospital and the University of Sydney have extensively used a novel technique – threshold-tracking transcranial magnetic stimulation – to expedite diagnosis.

"This tool is a reliable diagnostic aid that helps people with MND receive an earlier definitive diagnosis. Patients can then begin to manage their care and treatment," says Dr Menon.

Transcranial magnetic stimulation (TMS) devices generate magnetic fields to stimulate nerve cells in the brain. Researchers can then measure the activity of nerves and detect abnormalities in electrical function. People living with MND typically have overactive nerves in their brain (hyperexcitability).

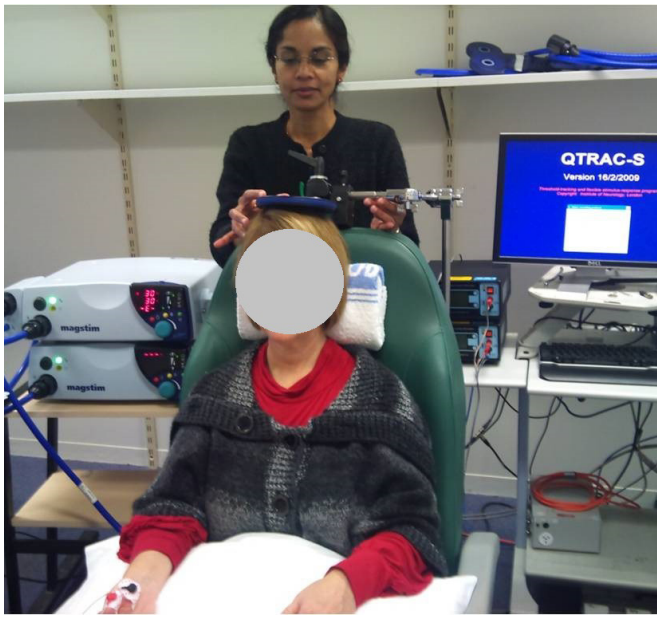
Brain hyperexcitability can be a red flag for MND

Dr Menon is a neurologist and clinical researcher with specialised training in the electrical function of the brain and nerves. The Beryl Bayley MND Postdoctoral Fellowship has enabled her to routinely use threshold-tracking TMS for MND diagnosis and to understand mechanisms underlying MND disease onset and progression. Research conducted by Dr Menon and colleagues on the use of threshold-tracking TMS as a diagnostic tool has been published in the reputed international journal, *Lancet Neurology*.

Dr Menon believes that problems caused by MND start in the brain and then spread to the spinal nerves and muscles. It is important to understand how MND progresses so that researchers can work towards developing targeted therapies.

Beryl Bayley's legacy: The Beryl Bayley MND Postdoctoral Fellowship

- **2015 – 2017:** Dr Parvathi Menon, Westmead Hospital, The University of Sydney. *Insights into ALS pathophysiology from patterns of disease progression*
- **2016 – 2018**: Dr Michelle Farrar, The University of NSW. *Motor neurone diseases in children and young people – understanding pathophysiology and developing treatment approaches*
- **2017 – 2019:** Dr Emma Devenney, Brain and Mind Centre, The University of Sydney. *Behaviour, cognition, eye-movements and psychiatric disease in C9orf72 MND and FTD; a cross modal-approach to facilitate early and accurate diagnosis*



MND Facts
Each day in Australia two people are diagnosed with MND and two people die with MND

The mean time from onset to confirmation of diagnosis is 10 to 18 months

Get involved

MND Connect 2017

MND Connect brings together the community, researchers and clinicians in an interactive forum to discuss MND research.
When: Saturday 11 November 2017
Where: Charles Perkins Centre
The University of Sydney

Annual MND Australia Research Conference

This is Australia's pre-eminent meeting of MND researchers. It is open to MND researchers as well as the broader MND community.
When: Friday 10 November 2017
Where: Charles Perkins Centre
The University of Sydney

Participate in research

Familial MND research project

If you are from a family in which there is a known MND gene, you are invited to participate in an interview by telephone to discuss your experiences of familial MND, receiving genetic information, and any subsequent decisions made. Contact Ashley Crook: ashley.crook@mq.edu.au or 02 9812 3720.

ALS Quest

ALS Quest is an online questionnaire to find out how our environments affect the likelihood of developing MND. To get the most accurate data possible, the researchers need people with and without MND to complete the questionnaire. Visit alsquest.org

MND Fact
More than 2,000 people have MND in Australia of whom 60% are male and 40% are female

Governance

MND Australia is the principal member of the MND Research Institute of Australia.
The governance and operations of both organisations are the responsibility of MND Australia.

Directors

The board of MND Australia consists of an independent elected President and a nominated representative from each member MND Association board, the chair of the MNDRIA Research Committee and up to three independent directors.

Research Committee

The MNDRIA Research Committee reviews research grant applications and determines the distribution of funds within the set policies and criteria for scientific assessment.

Research Committee Members
Chairman: Professor Matthew Kiernan, NSW
Associate Professor David Berlowitz, VIC
Associate Professor Ian Blair, NSW
Associate Professor Tracey Dickson, TAS
Professor Simon Foote, ACT
Professor Glenda Halliday, NSW
Dr Susan Mathers, VIC
Professor Pamela McCombe, QLD
Dr Shyuan Ngo, QLD
Professor Dominic Rowe AM, NSW
Professor Dominic Thyagarajan, VIC
Dr Bradley Turner, VIC
Professor Steve Vucic, NSW
Professor Naomi Wray, QLD

Donations

Research funded by the MND Research Institute of Australia is dependent on donations.
To contribute to this vital work, please send your gift to:
MND Research Institute of Australia
PO Box 430, North Sydney, NSW 2059

Donations can be made by cheque (payable to MND Research Institute of Australia) or credit card (Visa or MasterCard) or online at www.mndresearch.org.au

All donations of $2 and over are tax deductible.

ABN: 46 789 710 580

Bequests

Your Will can provide an important way of making a gift that can have lasting influence on MND research and give hope for the future.

If you would like to consider the MND Research Institute of Australia in your Will by providing a Bequest from your Estate, please contact your solicitor.

For more details on how your bequest can help MND research: www.mndresearch.org.au/leaveagift
Phone Stephanie Williams, Executive Director Research on 02 8287 4988 or email stephaniew@mndaustralia.org.au

Thank you