Unlocking the secrets of MND

MND Association Research Report 2008
Unlocking the secrets of MND

At the Motor Neurone Disease (MND) Association we are committed to raising the funding needed to support national and international research efforts in order to realise our vision of a World Free of MND. Investing in MND research is a top priority of our membership and we believe that right now there has never been a better time to harness the recent, unprecedented advances in science, medicine and technology for the benefit of people living with this cruel disease. We are seeking to achieve this by funding research projects in hospitals, universities and commercial laboratories, nationally and internationally.

In November 2006, we launched our six-year Research Strategy. This Strategy has taken an innovative approach as we focus on generating a research environment that allows more collaborative activity. Our Strategy is strengthening and progressing the links between new developments in the labs and potential treatments for people living with the disease, known as translational research. We are also creating new scientific leaders in the field.

Our Research Strategy lays out a number of activities necessary to develop a sustainable translational research platform within the UK which will facilitate the regular testing of new effective treatments. Over the past 18 months we have been working towards achieving our principal strategic themes and making good progress.

Alongside this, we have been preparing the ‘fertile ground’ that will encourage greater investment by industry and major funding bodies in future clinical trials. This will expand the clinical research workforce, enhance expertise, improve standards of care in the management of MND and strengthen the network of centres able to recruit patients and perform trials.

One of our biggest achievements has been the success of the MND Association Research Foundation which has played a critical role in raising the profile of MND research and significantly contributed to raising an additional £6 million for research. Through our Research Foundation campaigning work we have secured Government commitment that will inject at least £7.5 million in high quality research awards in the coming years, through the UK Medical Research Council.

Our work is bringing us one step closer to unlocking the secrets of MND. There is still much more work to be done. We may not yet see the light at the end of the tunnel but we are moving firmly in the right direction.

Dr Brian Dickie
Director of Research Development
Motor Neurone Disease Association

"One of the hardest things about my dad’s diagnosis of MND was that we didn’t know the cause. I got involved in research because it asks the question - why do people get the disease? Answering this is fundamentally important to the quest for more effective treatments and finding a cure."

Dr Emily Goodall, MND researcher (cover image)

What is MND?

- MND is a rapidly progressive, fatal disease that can affect any adult at any time.
- We don’t know the cause of over 95% of cases and there is currently no cure or effective treatment.
- Five people die every day in the UK from MND.
- There are around 5,000 people living with MND in the UK at any one time.
- MND attacks the nerves that control movement. As these nerves die, muscles weaken and waste. MND leaves people locked in a failing body, unable to move, walk or talk but the mind usually remains alert.

MND research: taking an innovative approach
Identifying the causes of MND

Whilst it is simplistic to think in terms of ‘find the cause and you find the cure’, understanding the causes of MND is arguably the single most important springboard for further research activity.

To understand what causes MND we need to be able to identify the specific predisposing genes and the environmental factors that determine whether someone will develop the disease. This will lead to more effective treatments and will allow medical professionals to diagnose MND at an earlier stage.

Gene hunting

Prof Ammar Al-Chalabi has been leading a study to find genes that contribute to MND, in collaboration with US, Dutch and French researchers. It is currently the largest study of its kind with access to over 4,000 DNA samples so far and more on the way. Half of these samples are from people with MND and the remainder are from people who do not have the disease. Samples from the MND Association DNA Bank are contributing to this study.

By analysing the samples, Prof Al-Chalabi and his colleagues are hoping to identify the genetic factors which could predispose people to MND, influence the age it starts, or affect how fast it progresses. Once this link is made it will provide important clues as to the underlying causes of MND and could allow researchers to pinpoint effective treatments.

“The MND Association DNA Bank is making it possible to find genetic contributions to MND,” explains Prof Al-Chalabi who is based at King’s College London. “Because each DNA sample is coupled with other information, like the age at which MND began or the pattern of MND, we will also be able to search for genes that influence the way MND behaves. We are now collecting samples linked with very detailed lifestyle questions which will allow researchers to see if there are any ways in which lifetime exposures and personal genetics might act together to increase risk.”

A research breakthrough - TDP-43

MND Association funding to researchers at King’s College London in spring 2008 has contributed to the discovery of a mutation in the TDP-43 gene (the gene that makes a protein called TDP-43).

This gene has been identified as a direct cause of Amyotrophic Lateral Sclerosis (ALS) which is the most common form of MND. This is only the second ALS-causing gene to be identified since MND was first characterised over 130 years ago.

Although the TDP-43 gene appears to be a direct cause of MND in less than 1% of cases, the protein that the gene produces appears to be involved in up to 90% of MND cases.

Researchers are excited that this discovery could be relevant to many forms of MND. We believe this discovery will contribute to the biggest surge in international research activity since the discovery of mutations in the SOD1 gene as a cause of MND in 1993.
Creating new disease models

Developing MND lab models, based on human genetic research, is a fundamental step in checking that the genes researchers have identified do indeed cause MND. Creating new animal and human lab models will allow greater comparative research and ‘cross referencing’ to take place. This will help us identify the pivotal events responsible for the death of motor neurones. We need to develop many MND models in order to work out what is going wrong and to help identify potential treatments.

“Modelling in animals has been very useful for MND research and over the last 20 years this approach has changed dramatically,” says Dr Linda Greensmith at University College London. “A mouse model, created using a gene damaged in a rare inherited form of MND (the SOD1 gene), has been incredibly useful and has really led to an explosion in the amount of research undertaken into the disease. It has also been the source of most of our learning in understanding why motor neurones die.

“Unfortunately many of the effective treatments designed for the SOD1 mouse have failed to translate into positive clinical trials for people affected by MND and there has been much discussion about the validity of this model in MND research.

“This controversy demonstrates the need to develop other models of MND, not only in mice but also in other species such as flies and fish, which all offer different advantages to the MND researcher.”

Consistency in practice

To ensure that MND models are used effectively, it is essential for all researchers to work to the same high standards to reduce factors which may inadvertently skew research results.

We are committed to raising standards worldwide and have been involved in an international initiative to develop ‘bench-mark’ guidelines for MND research. These guidelines have now been adopted within our research-funding criteria.

It is essential that we set high, rigorous research standards as this will directly impact the quality of MND research.

One major focus within our Research Strategy has been to address the issues of using SOD1 mice by including strict best practice guidelines within our funding criteria.

Dr Adina Michael-Titus from the University of London believes that dietary fatty acids may protect motor neurones from dying. When she and her colleague, Dr Andrea Malaspina, submitted a proposal to investigate this further, we saw an opportunity to combine her novel idea with the expertise of Dr Caterina Bendotti who is based at the eminent Mario Negri Institute in Milan, Italy. Dr Bendotti has great expertise in using the SOD1 mouse and she was involved in producing the best practice guidelines.

A partnership between the research labs in London and Milan has been established, strengthening the quality of the research and forming a basis for further international collaborative MND research.
Identifying a predictable disease-specific ‘fingerprint’ or ‘biomarker’ is essential to MND research. This is a unique set of substances that help identify whether someone has MND.

Diagnosing MND is a very lengthy process due to the lack of a definitive diagnostic test with people waiting months or even years for a certain diagnosis. Moreover, doctors and researchers are desperate for more accurate ways of measuring the progression of MND and the effects of potential treatments during clinical trials.

Specific MND biomarkers may provide evidence linking what is happening in lab models of MND to the progression of the disease in patients.

Biomarker studies can be cross sectional (samples taken only once from people living with MND) or longitudinal (samples taken at more than one time-point and correlated with the progression of the disease). Longitudinal samples are much more powerful, but for practicality and cost, they have not been attempted in any scale around the world and, to our knowledge, never in the UK.

We are now funding two longitudinal studies at the University of London and University of Oxford and it is hoped that these two projects will make significant progress in identifying MND biomarkers.

Dr Martin Turner at the University of Oxford has been awarded a Medical Research Council/MND Association Lady Edith Wolfson Clinical Research Fellowship. His research focuses on identifying MND biomarkers.

“Biomarkers might be changes visible on research MRI scans, or substances measurable in the blood or spinal fluid. The discovery of such biomarkers could change the way that clinical trials are organised, allowing beneficial drugs to be identified more quickly and ineffective drugs to be discounted sooner.”

“My biomarker project aims to study around 70 people living with MND and also people who are not affected by the disease, for one day every six months. Patients will be recruited from two MND Association Care Centres as they attend their routine appointments. In this way we hope to build up a large cohort of people who have been carefully followed through their individual disease pathway, providing the best chance for biomarker discovery.”

“I’m desperate for researchers to find a cure for MND. I would love to see my young children grow up and to see a world free of this devastating disease.”

Sarah Ezekiel, living with MND
“The vision of a world free of MND is hugely ambitious, but I agree with the MND Association that the skill and dedication of scientists make this goal achievable in our lifetime.”

Prof Colin Blakemore, renowned Neuroscientist, President of the MND Association

“My father died from MND when I was 11. His mother, his sister, and his grandmother died too from the disease. We found out that we have a familial type of MND in our family and I have since lost my sister and cousin to the disease. It has been very difficult at times living with a sentence over my head worrying that every little ache or pain may be an onset to MND. We need to find a cure.”

Pete Inchley, affected by MND

“Hearing the latest results from the lab is what gets me out of bed every morning. We need to find out what causes motor neurone degeneration if we are to cure MND.”

Prof Chris Shaw, MND researcher

“My husband was diagnosed with MND over 23 years ago and then nothing was known and there was no help available. We’ve come so far in such a short time which shows there is light in the darkness. I look forward to understanding this terrible disease.”

Olga Camm, affected by MND
MND research is exciting work because there is a groundswell of medical and scientific opinion that MND is a disease that can be conquered. Defeating it through innovative fundamental research should only be a matter of time and resources.

Prof Richard Ribchester, MND researcher

“I come from a long line of women who lived well into their 90s, so when I was diagnosed with MND, I felt like I’d been robbed of half my life. I’m now only 50, and I’m dying. I’m dying for a cure.”

Ashley Morgan, living with MND

“The selective loss of motor neurones that causes MND is the great challenge of this disease. It is a deep mystery and we must find out the solution.”

Dr Isabella Fogh, MND researcher

“MND research is important to me. I was a dance teacher and I would love to be able to dance again. Why do we have to wait so long for someone to tell us there is a trial for a potential cure?”

Keith Ten-Pow, living with MND

“MND research is exciting work because there is a groundswell of medical and scientific opinion that MND is a disease that can be conquered. Defeating it through innovative fundamental research should only be a matter of time and resources.”

Prof Richard Ribchester, MND researcher
Expanding the scientific and clinical research base

By 2012 we want everybody in the UK who is diagnosed with MND to have the opportunity to take part in clinical research. This means we need to make sure there are clinicians whose knowledge and expertise will enhance the success of such research. As clinical research and trials are becoming increasingly sophisticated, it is essential that the very best MND clinicians are not only involved, but that they also work closely together.

Prof P Nigel Leigh is Director of the MND Care and Research Centre at King’s College Hospital in London as well as an internationally renowned researcher into MND and other neurodegenerative conditions. He has helped to organise many clinical trials for MND in the UK, including the trial of riluzole which is now licensed for use as it slows the progression of MND.

“Our philosophy at King’s, by no means realised, is that everyone who comes in to our clinic should have the opportunity to participate in clinical research. This might involve simply donating blood to the MND Association DNA Bank, consenting to having their data entered anonymously into our database or by joining a specific clinical project or drug trial.

“Everyone diagnosed with MND should have access to research and it should involve all aspects of the disease from working out why motor neurones die through to palliative care.

“There are very many important MND research questions to be answered, too few funded projects and therefore far less participation than there could be.”

Since 2006 we have been assisting the Department of Health with the development of an MND research programme within the Dementias and the Neurodegenerative Disease Research Network (DeNDRoN). This initially focused upon research studies on how to best manage disease symptoms but we are now developing plans with DeNDRoN to perform ‘phase II’ clinical drug trials. These are the next step in determining whether or not a drug benefits patients.

Healthcare research

We view healthcare research with the same importance as clinical research as it ensures that people living with MND receive the very best care. The complex nature of MND combined with the variation in the availability of multidisciplinary healthcare can result in widespread differences in the provision of care and support. These inequalities are due in part to the lack of evidence on which to base healthcare decisions. This impacts on the quality of life and survival times.

Healthcare research is crucial because it provides us with the evidence needed to influence Health and Social Care Commissioners when we are campaigning for better standards of care.

Prof Pam Shaw at the University of Sheffield is leading a healthcare research project which is evaluating the benefits of a ‘cough-assist’ device.

“For people with MND who have respiratory weakness and use non-invasive ventilation (NIV), the inability to cough effectively is a major problem. Poor coughing ability causes considerable distress and can lead to serious chest infections.

“Our healthcare research project aims to establish whether a mechanical ‘cough-assist’ device can reduce chest infections and hospital admissions and improve the quality of life for MND patients who need to use NIV. If improvements are documented then our study will provide the evidence base to support wide implementation of this new standard of respiratory care for the benefit of MND patients across the UK.”
Establishing clinical research networks

Hannah Nixon is a DeNDRoN research nurse working with people affected by MND, neurologists, and health care professionals to establish, develop and coordinate MND research in the UK.

She says: “The DeNDRoN network brings together expertise and enthusiasm to drive forward MND clinical research. Those living with MND who are involved in research can ensure that their own perspective is considered. I really believe that it empowers an individual as they are making a stand against the disease by contributing to the unanswered questions surrounding MND which will help those in the future.”

The MND Association

DNA Bank

Our DNA Bank holds the DNA samples of over 2,000 people with MND and their family members and carers. It was the first MND research study to be adopted by DeNDRoN. The collection of samples will aid genetic research.

Alex Deytrikh is living with MND and has donated a DNA sample. He says:

“The DNA Bank is crucial as it provides a foundation building block on which the research community can continue its search for the cause or causes of MND. Consequently, the DNA Bank represents, in a tangible form, a degree of hope for MND sufferers that progress is truly being made to unravel the MND conundrum.”

Alex Deytrikh has donated a DNA sample for MND research

Establishing clinical research networks

There are huge logistical implications in setting up clinical research but by working in partnership with DeNDRoN we are beginning to overcome these barriers.

DeNDRoN has been critical to the development of MND clinical research in the UK as its network of centres provides the infrastructure needed for such research to take place.

“...When Pat, my late wife, was offered a place on a clinical trial we were both for it. I didn’t have to persuade her to take part. Pat wanted to be included to be able to do something to help others.

“We willingly took part in the trial and we didn’t hold any false illusions for it. We knew that taking part could benefit someone else with MND in the future.”

Selwyn Evans, who lost his wife Pat to MND
Developing scientific expertise

Good researchers are at the heart of good research, whether in the lab or in the clinic. But good MND research can only be sustained if there is an effective programme to recruit, train, and support the career development of the next generation of researchers.

Our research strategy holds a commitment to increase our PhD programmes. Previously we supported six PhD projects at any one time, but now this figure has risen to 11.

Progress in MND research activity has moved a significant step forward as the first Medical Research Council/MND Association Lady Edith Wolfson Clinical Research Fellowships have been awarded. This fellowship scheme is the first major initiative to arise from our Research Foundation campaign.

The Fellowships are an exciting development as they will allow us to attract the best young clinicians, develop their scientific expertise and place them at the heart of translating knowledge from the lab to the MND clinic.

To see a world free of MND, we also need to develop a global MND research workforce. Every year we organise the International Symposium on ALS/MND, and this premier annual gathering of MND research experts plays a vital role in forging partnerships and generating international collaboration in the field of MND research.

Establishing the next generation of MND researchers is crucial

In the summer of 2008, Dr Robin Highley based at the University of Sheffield was awarded one of our first Clinical Research Fellowships.

“Sheffield is a centre of international excellence for MND research. I am enormously looking forward to working in this vibrant environment, and am immensely grateful to the MND Association and the Medical Research Council for funding this project.

“My project will hopefully generate data about the chain of events that causes a motor neurone to die. Such knowledge may be used to develop drugs designed to interrupt this process and allow motor neurones to survive, and thereby either slow or, ideally, stop the disease progression.”
Making our vision a reality

Our Research Strategy lays out a number of activities necessary to help us achieve our vision of a World Free of MND. They are:

- Identifying the causes of MND
- Creating new disease models
- Ensuring consistency of practice in preclinical testing
- Identifying biomarkers
- Building a trained workforce
- Developing influencing capacity
- Improving standards of clinical and healthcare research.

Since our Strategy was implemented in 2006, we have made significant progress:

- New causes of MND have been identified and we are supporting the development of new disease models based on these discoveries. (Pages 3 & 4)
- We have strengthened our funding criteria to ensure that all research is in accordance with the highest internationally agreed standards. (Page 4)
- We are supporting the first studies in the UK that compare changes in body biochemistry throughout the course of MND. (Page 5)
- We have invested in strengthening the research workforce, though PhD Studentship and Clinical Fellowship Programmes. (Page 10)
- We are actively collaborating with the UK Medical Research Council and the Dementias and Neurodegenerative Diseases Research Network, and are progressing our plans to strengthen international translational research activity. (Pages 8, 9 & 10)

Through our clinical and healthcare research funding programmes and our collaboration and influencing with other funders we aim to put ourselves at the heart of international MND research.

There are more scientists and clinicians around the world working on MND than ever before, reflecting the belief that we are, at last, beginning to understand the disease process. It is through such understanding that we will eventually develop effective treatments for this devastating condition.

“MND is like a jigsaw with a million pieces and with more research we can put it together.”

Lembit Öpik MP, Chair of Patrons, MND Association

For more information about our Research Strategy go to: www.mndassociation.org/researchreport
There is more going on in MND research now than at any other time. I find huge inspiration in the knowledge that when I finish my work for the day, the MND researchers in Australia are just beginning theirs.

Dr Martin Turner, Oxford, UK