motor neurone disease association

Information Sheet E

Research we fund

We are a leader in the funding and promotion of cutting-edge motor neurone disease (MND) research both within the UK and across the world. This information sheet will provide you with a brief overview of the portfolio of research grants we award.

The **Association-wide strategy** for the future will guide us until the end of 2021 – access it here: www.mndassociation.org/strategy2017.

Our research aims are outlined in our **research strategy**, which can be downloaded from here: www.mndassociation.org/ourplan.

You can also view our **research goals and priorities** for action here: www.mndassociation.org/research-strategy.

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How do we decide what research we fund?

Decisions to award research grants are made following rigorous peer review and guidance from the MND Association's Biomedical Research Advisory Panel (for biomedical and clinical research) and Healthcare Research Advisory Panel (for healthcare research). Peer review is extremely important in research and is used to ensure that all of the projects that we fund are of the highest calibre and can realistically achieve the aims of the project.

What types of research does the Association fund?

All of the research projects that the MND Association funds have clear clinical relevance and/or therapeutic potential.

- **Biomedical projects** are laboratory-based. They aim to identify potential causes of MND, increase scientific understanding of the mechanisms of motor neurone degeneration and develop potential new treatments.

- **Clinical projects** are not laboratory based but still aim to increase understanding of the underlying biology of MND. These include projects such as measures of disease progression.

- **Healthcare projects** are not laboratory based but aim to establish ways of improving care and quality of life of people living with MND. These projects include looking at quality of life factors and new assistive devices such as the Sheffield Support Snood.

How much do research projects cost the Association?

The MND Association awards research funding annually under four different schemes: the Project grant scheme, the PhD Studentship scheme, the MRC/MND Association Lady Edith Wolfson Clinical Research Fellowship scheme and the Non-Clinical Fellowships scheme. We are currently committed to funding projects that fall into the following categories:

- **Biomedical projects** are usually awarded a maximum of £255,000 for up to three years to allow an in depth investigation of an area of research.

- **PhD Studentships** are a cost-effective means of conducting biomedical and clinical research (see above for explanations), while ensuring high calibre graduates can undertake a PhD training in MND-related research. These projects are awarded approximately £100,000 over three years.

- **MND Association/MRC Lady Edith Wolfson Clinical Research Fellowships** are jointly funded by the Association and the Medical Research Council (MRC). They support clinicians (practising doctors) wishing to pursue scientific research and aim to strengthen the links between laboratory and clinic. Our financial commitment to these fellowships varies between £86,000 and £280,000 for up to five years.

- **Non-Clinical Fellowships** aim to retain and develop early and mid-career MND researchers conducting biomedical or clinical research. These fellowships are for up to four years, with the financial award for these projects varying from up to £270,000 for a junior fellowship and up to £440,000 for a senior fellowship.

Our research portfolio

In the following pages we explain more about 74 of the research projects that we fund and what this research means to you. We categorise the research projects we fund into five themes: causes, models of MND, healthcare, markers of disease progression and developing treatments.

If you are looking for a particular researcher or institution, please refer to the index on pages 43-45.

- **Causes**

  These projects aim to understand what causes motor neurones to die. This is essential to allow the development of treatments. Only by understanding what goes wrong in MND can scientists know how to design and where to target drugs and other therapies.

- **Models of MND**

  One way in which to understand the function of a gene and how this goes wrong in a disease, or the impact of a biochemical pathway malfunctioning, is to use a model. This might be in mice or isolated cells in a dish. These projects aim to develop new and better models of MND to better understand the causes of MND.

- **Healthcare**

  These projects aim to increase the quality of life of people living with MND, as well as improving care. The projects have a direct impact on people living with MND here and now.

- **Markers of disease progression**

  There is currently no diagnostic test for MND and no specific 'biomarker' to monitor the disease. These projects aim to find a marker of disease progression to speed up diagnosis, prognosis and disease monitoring of MND.

- **Developing treatments**

  These projects aim to test the effectiveness of potential treatments. They aim to test potential treatments from the laboratory stage to the clinical trial environment.

The projects listed below are divided into sections by their themes and organized chronologically by their start date. For each project you can find (**a**) title of the study (amended for non-scientific audience), (**b**) researchers responsible for the project, (**c**) home institution of each researcher and *an institution where the research project is taking place*, (**d**) amount of grant awarded, (type of project) and duration of the project, (**e**) start date of the project, (**f**) project ID number (used by researchers and the Association staff) and (**g**) brief description of the project.

Causes

Currently funding:

The function of C9ORF72 in MND

- Prof Chris Miller and Dr Wendy Noble
- *King's College London*
- £94,051 (PhD Studentship) over 3 years (+10 months extension)
- Start date: October 2013
- Our Ref: 863-792

In 2011 mistakes in the gene C9ORF72 were identified as the most common cause of inherited MND. Since then, researchers from around the world have been trying to find a way to open-up and reveal more about this MND-causing gene.

The aim of this research project is to gain insight into the function of the C9ORF72 protein (made by the C9ORF72 gene). Specifically, the researchers will use advanced microscopy to find the location of C9ORF72 within cells, investigate the consequences of varying the amount of the C9ORF72 protein produced on overall function of motor neurones, and investigate whether C9ORF72 is involved in a specific process called 'transcription'.

Update: PhD student Ambra Annibali has successfully created a new antibody for detecting the C9ORF72 protein. She hopes to use this to determine where the C9ORF72 protein is found within the motor neurones and how this protein may cause MND in some individuals.

The UK Whole Genome Sequencing project

- Professors Ammar Al-Chalabi, Chris Shaw, Dame Pam Shaw and Karen Morrison
- *King's College London*, University of Sheffield and University of Southampton
- £849,471 (Biomedical project) over 3 years
- Start date: August 2014
- Our Ref: 984-797

This project aims to sequence over 1,500 genomes (a genome represents the total genetic make-up of an individual) utilising the samples already collected in the UK MND DNA Bank. By collaborating with Project MinE, this unique international collaboration aims to further identify more of the rarer predisposing genetic factors involved in the disease.

Update: The second batch of 672 samples from the UK MND DNA Bank were sequenced in 2016. A further 384 samples have been sent for sequencing this year. The study now aims to sequence around 1,800 genomes.

Once the UK samples and all the other genomes have been sequenced, the researchers can begin to look at the DNA in detail to find out more about how our genes influence the onset and speed of progression of the disease.

Shining a light on stem cells to find out more about MND

- Dr Richard Wade-Martins and Dr Colin Akerman
- *University of Oxford*
- £95,826 (PhD Studentship) over 3 years
- Start date: October 2014
- Our Ref: 867-792

This project will use induced pluripotent stem cell (iPSC) technology to study human motor neurones 'in a dish' to find out more about how these motor neurones function and what goes wrong in MND.

Dr Wade-Martins hopes to engineer these motor neurones so that they become activated by light. In this way, he can selectively activate motor neurones only, instead of the many other types of neurones found in the nervous system, allowing him to view the functioning of motor neurones in exquisite detail.

Studying axon development in early stage motor neurones

- Prof Catherina Becker
- *University of Edinburgh*
- £87,418 (PhD Studentship) over 3 years
- Start date: October 2014
- Our Ref: 871-792

In MND, motor neurones degenerate at the end of an axon, where the cell connects with the muscle. The researchers propose to study this part of the motor neurone in detail using zebrafish in order to further our understanding of the connection between the motor neurones and the muscles. Inevitably, the research may lead to the identification of potential drug targets for MND.

The role of mitochondria in C9ORF72-related MND

- Dr Kurt De Vos and Dr Andrew Grierson
- *University of Sheffield*
- £86,917 (PhD Studentship) over 3 years
- Start date: February 2015
- Our Ref: 870-792

Mitochondria are the cell’s batteries that provide them with energy. Earlier research has linked damage to mitochondria as a contributor to why motor neurones die in MND. Based on preliminary evidence, Dr De Vos aims to find how the C9ORF72 protein causes damage to the mitochondria, where it happens and what might be done to prevent it.

Understanding and preventing the protein build-up that can cause cells to die

- Dr Jacqueline Mitchell and Prof Chris Shaw
- *King's College London*
- £240,050 (Biomedical project) over 3 years
- Start date: April 2015
- Our Ref: 828-791

Prior research has already shown that build-up of the protein TDP-43 is found in the majority of cases of MND (irrespective of whether it was caused by an inherited genetic mistake).

Dr Mitchell and her team at King's College London have created several new mouse models to investigate how TDP-43 causes motor neurones to die in MND.

By studying affected cells from these models, the team is seeking to find out how this protein contributes to the disease occurring and what measures might be taken to prevent it. By identifying how this protein causes MND, we can develop new drugs to slow down or halt the progression of the disease.

Motor neurone signalling and the effects of RNA in MND

- Dr Pietro Fratta
- *University College London*
- £280,000 (Total award value of £1,160,000 MND Association/ MRC Lady Edith Wolfson Clinical Research Fellowship) over 4 years
- Start date: April 2015
- Our Ref: 946-795

This Clinical Scientist Fellowship will allow Dr Fratta to find out what RNA molecules are present in the cell body of the motor neurone as well as in the nerve fibres.

RNA is the cell's copy of our genetic material known as DNA; Dr Fratta is hoping to establish if the transport of RNA molecules along the nerve fibres is impaired and, if so, whether there are particular versions of RNA that are particularly important for motor neurone health and survival.

Validating and testing potential MND-causing genes

- Prof Chris Shaw and Dr Han-Jou Chen
- *King's College London*
- £216,526 (Biomedical project) over 3 years
- Start date: April 2015
- Our Ref: 985-797

The use of more advanced and faster DNA sequencing methods have led to the identification of further five possible MND-causing genes. This project, jointly funded with the MRC, will study these genes further, specifically looking at a part of a gene called the exome. The exome is the part containing instructions that make proteins, and it is the proteins that directly affect the function or structure of cells.

The disease-causing effects of the proteins produced by these five genes will be studied in nerve cells grown in the laboratory. Those proteins that have the greatest toxic effects will be tested further in fruit flies and zebrafish. This will tell us more about the toxicity of these proteins, and may show precisely how they damage nerve cells.

We are grateful for the support of the Heaten-Ellis Trust in funding this project.

Using iPSCs to understand the interplay between C9ORF72 and TDP-43

- Prof Kevin Talbot and Dr Ruxandra Dafinca
- *University of Oxford*
- £228,332 (Biomedical project) over 3 years (+12 months extension)
- Start date: July 2015
- Our Ref: 832-791

In previous research these researchers began to understand more about how the C9ORF72 gene defect causes human motor neurones to die. These studies were conducted using nerve cells created from patients' skin cells using induced pluripotent stem cell (iPSC) technology.

In this research project Dr Dafinca and Prof Talbot will look at the electrical activity of the nerve cells, how the nerves connect to muscle and how different parts of the cell contribute to cells dying. They will use motor neurones from people with two different forms of inherited MND (those with either C9ORF72 or TDP-43 mutations) to see any differences and similarities between them.

Using iPSCs to understand what happens to human motor neurones in MND

- Dr Gareth Miles and Prof Siddharthan Chandran
- *University of St Andrews* and University of Edinburgh
- £87,347 (PhD studentship) over 3 years
- Start date: September 2015
- Our Ref: 878-792

Researchers can create human motor neurones exhibiting signs of MND in the lab by taking skin cells from a person living with MND and reprogramming them into motor neurones. This is called induced pluripotent stem cell (iPSC) technology.

Dr Miles has previously found that these motor neurones lose their ability to produce an electrical nerve impulse. In this new project he plans to investigate why these electrical properties change by looking at proteins called 'ion channels' that regulate the flow of electrical messages between cells.

By understanding the reasons why motor neurones lose their normal function, we can aim to design and develop new treatments that target this process.

Identifying changes in the brain tissue in MND and FTD

- Dr Olaf Ansorge and Prof Kevin Talbot
- *University of Oxford*
- £96,892 (PhD studentship) over 3 years
- Start date: October 2015
- Our Ref: 877-792

Some people with MND will also develop frontotemporal dementia (FTD), meaning that cells in several parts of the brain are affected. Commonly, these people will carry a gene mutation known as C9ORF72. Some people with the C9ORF72 gene mutation will only develop MND. Other people with the same mutation will only develop FTD, and some people will develop both conditions.

Looking at post-mortem brain tissue down the microscope, we can observe three typical signs signalling that the cells are affected. They will either see tangled TDP-43 protein, a tiny fragment of C9ORF72 protein or a clump of C9ORF72 RNA. Using brain tissue from the Oxford Brain Bank, Dr Ansorge and Prof Talbot aim to identify which brain cells are most susceptible and whether there is genetic variation within specific regions of the brain that could help explain the differences between the two diseases.

Studying the detailed structure of SOD1 and TDP-43

- Prof Samar Hasnain, Dr Svetlana Antonyuk and Dr Gareth Wright
- *University of Liverpool*
- £207,081 (Biomedical project) over 3 years
- Start date: October 2015
- Our Ref: 833-791

Proteins often bump into each other within the cell, however, in some cases this interaction can cause shape and structural damage. The SOD1 and TDP-43 proteins become damaged in MND, forming deposits within the motor neurones that cause the cells to become sick and die. Why this happens is not yet understood.

This project aims to study the SOD1 and TDP-43 proteins in exquisite detail using X-ray scattering and X-ray crystallography to better understand these proteins in order to identify potential drug targets. These techniques allow the researchers to work out the importance of changing one or two atoms in a protein, giving a far more detailed approach at understanding these proteins within the cell.

Understanding how TDP-43 interacts with RNA to test new drugs

- Professors Annalisa Pastore and Gian Gaetano Tartaglia
- *King's College London* and University Pompeu Fabra
- £221,595 (Biomedical project) over 3 years
- Start date: October 2015
- Our Ref: 840-791

TDP-43 is found to form deposits within motor neurones in nearly all cases of MND. This projects aims to understand the structure of the TDP-43 protein and how the protein forms deposits within the motor neurones.
By studying how the TDP-43 protein interacts with RNA (the cell's copy of our genetic material known as DNA) the team aims to use this information to test small RNA-like drugs to prevent TDP-43 from forming deposits within the motor neurones.

Identifying genetic susceptibility factors in MND

- Prof Ammar Al-Chalabi
- *King's College London*
- £134,207 (Biomedical project) over 2 years
- Start date: November 2015
- Our Ref: 844-791

In 2014 Prof Al-Chalabi applied a mathematical model to MND, which identified that six distinct steps are needed to trigger this disease. One of these steps is likely to be genetic. This project will compare the data from population-based MND registers with genetic data to better understand the genetic risk of MND.

In particular, this project will focus on the C9ORF72 and ATXN2 genes, which have been found to be a risk factor in apparently sporadic cases of MND.

Investigating jumping DNA as a genetic risk factor for MND

- Prof John Quinn, Dr Gerald Schumann, Dr Vivian Bubb, Dr Gerome Breen and Prof Ammar Al-Chalabi
- *University of Liverpool*, Paul Ehrlich Institute and King's College London
- £204,435 (Biomedical project) over 3 years
- Start date: November 2015
- Our Ref: 843-791

The majority of cases of MND are believed to be caused by a combination of subtle genetic, lifestyle and environmental factors. This project aims to identify whether 're-shuffling' of DNA in the very early embryo might be responsible for events later in life.

By using brain tissue and genetic data already available the group will use powerful computers to look for evidence of this re-shuffling through the identification of stretches of DNA known as 'retrotransposons' or 'jumping DNA'.

Identifying genetic causes of MND in specific populations

- Dr Russell McLaughlin, Prof Orla Hardiman and Prof Daniel Bradley
- *Trinity College, Dublin*
- £252,997 (Junior Non-Clinical Fellowship) over 3 years (+9 months extension)
- Start date: January 2016
- Our Ref: 957-799

In this research fellowship, Dr McLaughlin will study the impact of ancestry on the development of MND. The study will involve sequencing the genetic code of over 1000 Irish individuals, 700 of whom have ALS (amyotrophic lateral sclerosis, a form of MND).

Using these sequences, large family trees can be constructed. It is likely that these will link ALS patients previously assumed to be unrelated. These 'superfamilies' will give researchers a greater chance of identifying rarer gene variants linked to ALS development. The project may answer other questions, such as why certain populations seem to be more affected than others.

Studying the role of TDP-43 mutations in the transport of RNA

- Dr Martina Hallegger, Prof Jernej Ule and Dr Rickie Patani
- *University College London*
- £389,977 (Senior Non-Clinical Fellowship) over 4 years
- Start date: January 2016
- Our Ref: 959-799

Abnormal deposits, or aggregates, of the TDP-43 protein are found in the majority of cases of MND, making it a key feature of the disease. These deposits cause damage to the motor neurones. There is a part of the TDP-43 protein which is heavily linked to the development of TDP-43 deposits - this is called the low-complexity (LC) domain.

Dr Hallegger will look at how mutations in the LC domain are linked to MND. She will do this by studying motor neurones generated from induced pluripotent stem cells (iPSCs). Understanding the 'knock on' effects of LC domain mutations, and how these might lead to protein deposits, could enable the development of more targeted therapeutic interventions.

Understanding how MND alters the way cells generate and use energy

- Dr Scott Allen, Prof Dame Pam Shaw and Dr Andrew Grierson
- *University of Sheffield*
- £247,954 (Senior Non-Clinical Research Fellowship) over 3 years
- Start date: January 2016
- Our Ref: 956-799

In MND, the way that cells use nutrients and generate energy from them is thought to be altered. This leads to weight loss, which is common in people who have MND. Dr Allen's research is aiming to improve our understanding of how MND alters the cells' ability to use energy sources such as carbohydrates and fats.

This research should reveal which pathways in the cell are being disrupted. Using this information Dr Allen will be able to investigate if nutritional supplementation can help restore these cellular pathways. Addressing this would help re-balance the way cells use and store energy and try and counteract weight loss in people with MND.

Using a new method to find rare MND-causing genes

- Dr Ashley Jones, Prof Ammar Al-Chalabi and Prof Jeffrey Macklis
- *King's College London* and Harvard University
- £265,000 (Junior Non-Clinical Fellowship) over 3 years
- Start date: March 2016
- Our Ref: 958-799

For approximately 5-10% of people living with MND, the cause of the disease is primarily due to a mistake within the genes. However, for the majority of cases of MND, genes are thought to play a more subtle role and it is becoming increasingly difficult to find these genes.

In this Non-Clinical Fellowship, Dr Jones is aiming to use a new way to find the rare genes associated with MND that would otherwise be 'invisible'. He will create a list of candidate MND-causing rare genes using information on how motor neurones develop, together with data from Project MinE. This will guide him towards rare genes to prioritise for further investigation, by studying post-mortem brain tissue and through DNA sequencing. Identifying these may give promising candidates for gene-based therapies.

Gene-Environment database and analysis system

- Prof Ammar Al-Chalabi and Prof Richard Dobson
- *King's College London*
- £171,478 (Biomedical project) over 3 years
- Start date: March 2016
- Our Ref: 829-791

Genetic research into MND generates huge amounts of data. This project is a collaboration between MND researchers and bioinformaticians (those with expertise in computing, statistics and biology). The aim is to develop a system that will let researchers easily share genetic, clinical and epidemiological information, as well as adding new information as it becomes available.

The resource will speed up the identification of genetic factors involved in MND, but will also serve as a platform for unpicking genetic, lifestyle and environmental interactions.

Gene-hunting in Middle-Eastern MND cases

- Dr Bradley Smith, Dr Marc Gotkine and Prof Chris Shaw
- *King's College London* and Hebrew University of Jerusalem
- £125,000 (Biomedical project) over 2 years
- Start date: September 2016
- Our Ref: 847-791

The researchers at King's College London have teamed up with a research group in Israel to test out a novel approach to identifying genes linked to the rare inherited form of MND. A big advantage of this new technique is that it requires less participants to take part – making the research quicker and more feasible. Families from the Middle East are more likely to have common ancestor than European families, which makes it easier to identify genes that are linked to MND. This research is a 'proof of principle' study. If new genes are successfully identified using this approach, the methods can be applied to other groups of families with the rare, inherited form of MND.

Earlier research studies in small groups of closely matched people with inherited MND have shown that the results can have important and wide reaching implications for understanding all forms of MND. The first part of the study will involve genetic analysis of blood samples from these families. The second part will investigate the role of new gene mutations linked to MND – how does the fault in the gene causes motor neurones to die.

Understanding and targeting autophagy in MND-FTD

- Dr Rob Layfield, Prof Mark Searle and Dr Marios Georgiou
- *University of Nottingham*
- £197,652 (Biomedical project) over 3 years
- Start date: August 2016
- Our Ref: 845-791

This project will follow up on Prof Layfield's previous findings showing that a specific mutation in the SQSTM1 gene disrupts cells' waste disposal system (autophagy). Using already developed cell models, the team will now investigate whether these disruptions can occur due to other mutations in the SQSTM1 gene and in two other genes that are also crucial for autophagy (OPTN and TBK1).

The researchers will then test a number of drugs known to enhance autophagy and that are currently used to treat diseases other than MND. The most promising drugs will then be tested in fly models before considering them as a potential treatment for MND and the associated frontotemporal dementia (FTD).

Exploring the body's defence machinery to tackle protein clumping

Prof Mike Cheetham and Dr Adrian Isaacs

- *University College London*
- £92,537 (PhD studentship) over 3 years
- Start date: September 2016
- Our Ref: 881-792

A defect in the C9ORF72 gene is the most common cause of the rare inherited form of MND. One way it may exert harmful effects is through causing certain proteins, called dipeptide proteins, to clump in the neurones. The body has natural defence mechanisms (molecular chaperones) that usually stop these clumps from forming. The aim of this studentship it to test which parts of this defence machinery are effective against the clumps caused by the C9ORF72 defect using cell models and human motor neurones created from adult stem cells.

The researchers will assess how the clumps form in motor neurones, and test if they can prevent it by harnessing parts of the defensive machinery, or by boosting the machinery with drugs. Results from this work could identify potential future targets for drugs to reduce the damaging effects of the C9ORF72 defect.

The role of glycospingo-lipids in MND

- Prof Frances Platt and Dr David Priestman
- *University of Oxford*
- £96,252 (PhD studentship) over 3 years
- Start date: October 2016
- Our Ref: 883-792

There is an unexplored link between MND and rare diseases called lysosomal storage diseases. Lysosomes are a part of the cell where larger molecules, no longer required, are broken down for 'recycling and disposal'. One type of molecule that the lysosomes break down are glycosphingo-lipids (GSLs). The team has recently found a link between GSLs and MND.

This project will investigate the role of a specific GSL in MND, using patient blood samples, cell lines and post-mortem tissues, as well as various samples from mouse models. The team will also test whether they can delay MND progression by targeting GSLs with therapies. This study will open up a new perspective on MND and could lead to new directions for MND research and therapies.

Regulation of neuronal transport system by TBK1 and its relevance to MND

- Prof Giampietro Schiavo and Dr Pietro Fratta
- *University College London*
- £92,842 (PhD Studentship) over 3 years
- Start date: October 2016
- Our Ref: 880-792

Motor neurones are long cells running from the spinal cord to various parts of the body. Their function is to transmit messages from the spinal cord to the muscles to cause a muscle contraction. Motor neurones need to keep themselves in working order to transmit these messages. To do this they have an internal transport system ensuring that they have maintenance materials, fuel and nutrients in the right place at the right time along the cell.

This research will investigate how a protein called Rab7, involved in organising motor neurone transport, is affected in MND. Specifically, it is thought that faults in a protein called TBK1, known to malfunction in MND, have an indirect effect on the correct function of Rab7.

Using nuclear magnetic resonance to understand aggregation of TDP-43

- Prof John Christodoulou and Dr Lisa Cabrita
- *University College London*
- £91,970 (PhD studentship) over 3 years
- Start date: January 2017
- Our Ref: 882-792

The protein clumps found within the neurones of people with MND often contain the TDP-43 protein. Building on work achieved during a previous MND Association studentship, the student employed on this project will study the detailed structure of TDP-43.

The student will use nuclear magnetic resonance (NMR), a state-of-the-art technique that can provide information about the arrangement of the atoms that comprise the protein. They will use NMR to study the protein within cells, which will help us to understand how and why TDP-43 protein forms clumps and the role of these clumps in the disease process. This information will eventually be used to design and develop small molecules (drugs) that may stop or reverse this process.

Committed to funding

Using iPSCs to investigate mechanisms of toxic protein accumulation in C9ORF72-related MND/FTD

- Prof Kevin Talbot and Dr Ruxandra Dafinca
- *University of Oxford*
- £98,526 (PhD studentship) over 3 years
- Start date: April 2017
- Our Ref: 889-792

Mutations in the C9ORF72 gene lead to formation of protein clumps in the motor and cortical neurones, causing them to die (common cause of MND and FTD). This project aims to specify which of three previously identified mechanisms of protein accumulation leads to neuronal degeneration.

The researchers will use iPSC technology in which motor and cortical neurones are created from skin cells of healthy people and people with the C9ORF72 gene mutation. They will then introduce a virus causing protein accumulation and observe for the location and function of the clumps within neurones. Specific drugs will then be tested on their potential to remove the toxic virus from the neurones, findings of which could lead to identification of a new therapy.

Is reduced dynein function a cause and a risk factor of MND?

- Prof Luc Dupuis and Dr Majid Hafezparast
- *University de Strasbourg* and University of Sussex
- £240,000 (Biomedical project) for over 3 years
- Start date: July 2017
- Our Ref: 852-791

One of the reasons why motor neurones degenerate in MND is thought to be due to errors in transport along the neuronal axon. This has been found to be concurrent with mutations of the dynein protein, known to support the neuronal transportation system.

This project will explore the effect of the dynein protein on disruptions of the transportation system by introducing different amounts of dynein into mice. The mice with normal and lower or no levels of dynein will then be observed for changes in movements and muscle strength, indicating expression and progression of the disease. Results will inform about the role of dynein in developing MND and whether it can be targeted as a potential therapeutic mechanism.

Understanding the role of Calcyclin in developing MND and Alzheimer's disease

- Dr Bradley Smith, Dr Salvatore Adinolfi and Prof Corinne Houart
- *King's College London*
- £95,746 (PhD studentship) over 3 years
- Start date: October 2017
- Our Ref: 888-792

The grantees have recently found that mutations in the *ANXA11* gene are responsible for approximately 1% of all cases of MND. In looking at how ANXA11 mutations cause motor neurones to die, they have highlighted damage to a protein called calcyclin. Little is known about whether calcyclin causes motor neurones to die in MND or whether it has been 'caught up in the cross fire' of other damaging effects.

This research project will investigate the role of calcyclin in MND in more detail in order to understand more about the shape and chemistry of the protein and where it is found in people with MND. They will do so by using post-mortem tissue from people who donated their brain and spinal cord for research and by modelling the function of calcyclin in a zebrafish model of MND.

Exploring the role of RNA processing and long gene regulation in ALS

- Dr Vincent Plagnol, Dr Pietro Fratta and Dr Adrian Isaacs
- *University College London*
- £92,843 (PhD studentship) over 3 years
- Start date: Autumn 2017
- Our Ref: 885-792

Several of the genes that have been associated with MND are implicated in the processing of RNA, the intermediate stage between DNA and proteins. RNA molecules are also involved in controlling lots of cell processes. This project is aimed at looking into the role of RNA dysregulation in order to identify key genes and pathways involved in developing MND.

A technique called 'RNA-Seq' can be used to study all the RNA in a specific cell type. The student will analyse RNA-Seq data from various animal models and human material already generated by teams in the Institute of Neurology at University College London. They will specifically look at the 'long genes 'as there is evidence that long genes are particularly important in the nervous system. The team hopes that this method will uncover novel insights into the factors that cause MND and that may potentially be targeted by drugs.

Models of MND

Currently funding

Development of a new C9ORF72 mouse and cellular model using BAC technology

- Dr Javier Alegre
- *University of Oxford*
- £240,906 (Biomedical project) over 3 years (+20 months extension)
- Start date: January 2013
- Our Ref: 814-791

Previous work at Oxford, with MND Association funding, looked at the development of mouse models with the TDP-43 and FUS genes. In this project Dr Alegre will look at using bacteria artificial chromosome (BAC) technology to develop a new mouse model of the C9ORF72 gene that can be 'switched' on and off. He will also use the same technology to develop a new cellular model by inserting the C9ORF72 gene into human motor neurone cell lines.

Creating a zebrafish C9ORF72 model of MND

- Dr Andrew Grierson and Dr Kurt De Vos
- *University of Sheffield*
- £92,354 (PhD Studentship) over 3 years (+4 months extension)
- Start date: October 2013
- Our Ref: 864-792

This project aims to create a zebrafish model for studying C9ORF72. They will do this by removing or blocking the C9ORF72 gene, and determining whether the zebrafish develop MND. This will allow the research group to learn about the role of C9ORF72 in the brain and spinal cord, and to determine the effect of defective C9ORF72 in the context of an animal model.

The second aim is based on some new evidence from recent experiments in Sheffield that C9ORF72 regulates the way that cells are able to break down damaged components. This process is called autophagy. This project will directly test whether C9ORF72 defects associated with MND lead to disruption of autophagy in the developed zebrafish model.

Update: PhD student Natalie Rounding has found that a mutation of the C9ORF72 gene in zebrafish gives rise to defects in the start of autophagy. Zebrafish with the C9ORF72 mutation have apparently normal motor function up to 12 months of age, but do show some changes in their behaviour.

Investigating C9ORF72 and TDP-43 proteins in a fruitfly model of MND

- Dr Frank Hirth and Prof Chris Shaw
- *King's College London*
- £94,878 (PhD Studentship) over 3 years
- Start date: February 2014
- Our Ref: 868-792

C9ORF72 has been previously shown to lead to protein deposits in the motor neurones. Dr Hirth will develop a fruitfly model to study these protein deposits and how they lead to MND. The protein TDP-43 also forms deposits in motor neurones affected by the C9ORF72 gene, and this research will study the relationship between these two protein deposits and how they cause MND.

Understanding the role of FUS in a mouse model of MND

- Prof Vladimir Buchman
- *Cardiff University*
- £236,362 (Biomedical project) over 3 years (+6 months extension)
- Start date: April 2014
- Our Ref: 822-791

This project aims to study in detail how MND develops and the role of FUS protein in a mouse model of the disease. The project also aims to create another mouse model that produces a different FUS protein that is unable to bind to RNA (the cell's copy of our genetic material – DNA). Studying these different FUS proteins will enable the researchers to try and find out what leads to motor neurone damage in MND and the role of FUS.

Understanding FUS to help develop future therapies in the mouse

- Prof Elizabeth Fisher, Dr Abraham Acevedo-Arozena and Dr Anny Devoy
- *University College London* and MRC Harwell
- £112,690 (Biomedical project) over 3 years
- Start date: October 2014
- Our Ref: 874-792

This project aims to develop a mouse model of MND to find out more about the FUS protein and how it causes MND. The researchers have created a mouse model by inserting the human FUS gene, allowing the researchers to study the effect of the 'human' FUS gene in the mouse.

The aim of this project is to characterise this new mouse model in terms of the behaviour, physiological, cellular and molecular changes, as well as creating new mouse models to understand more about the role of the FUS protein in MND.

By creating a mouse model that contains abnormal FUS protein, the researchers hope to better understand the disease and highlight potential targets for future therapies.

Development of a C9ORF72 zebrafish model

- Dr Tennore Ramesh, Prof Dame Pam Shaw and Dr Adrian Higginbottom
- *University of Sheffield*
- £107,972 (PhD Studentship) over 3 years
- Start date: February 2015
- Our Ref: 875-792

C9ORF72 is the most common genetic cause of inherited MND and frontotemporal dementia (FTD). However, researchers still do not know how it causes the motor neurones to die in MND.

This project will develop a C9ORF72 zebrafish model of MND to investigate the toxicity of the mutation in more detail. By clever genetic engineering the reading of the mutated C9ORF72 can be turned on or off to further understand its toxicity. The researchers will aim to identify whether the expression of RNA, protein or both lead to motor neurone death.

The researchers have previously used a similar approach in the SOD1 zebrafish, with the aim of creating a C9ORF72 zebrafish model to better understand the disease and screen potential drugs.

Developing a drug screen using neurones from a TDP-43 mouse model

- Prof Kevin Talbot and Dr David Gordon
- *University of Oxford*
- £228,042 (Biomedical project) over 3 years
- Start date: July 2015
- Our Ref: 831-791

The researchers have developed a new TDP-43 mouse model of MND that accurately reflects the symptoms of the disease and levels of the TDP-43 protein as seen in humans.

This project will use cultured nerve cells from this new mouse model to screen a large library of drugs to identify molecules. By creating an automated computerised imaging system that can detect the TDP-43 protein within the cells, the researchers aim to screen thousands of compounds in a short space of time. This will identify any promising drugs quickly, which can then be tested in the new TDP-43 mouse model and human cells.

Using DNA Bank samples to create iPSC models of MND

- Prof Chris Shaw, Prof Jack Price and Prof Siddharthan Chandran
- *King's College London* and University of Edinburgh
- £488,979 (Biomedical project) over 3 years
- Start date: October 2015
- Our Ref: 80-970-797

Induced pluripotent stem cell (iPSC) technology has enabled researchers to create and study living human motor neurones in the lab, derived originally from patient skin cells.

This project aims to use the already collected white blood cell samples within the UK MND DNA Bank to create a larger number of new iPSC models of MND. Ultimately creating an MND iPSC cell bank, these models will enable researchers to better understand the disease and screen potential new drugs.

Creating a C9ORF72 mouse model of MND

- Prof Stuart Pickering-Brown and Prof Stuart Allan
- *University of Manchester*
- £188,245 (Biomedical project) over 3 years
- Start date: October 2015
- Our Ref: 841-791

Mouse models of MND allow researchers to understand more about the disease and how it affects the whole body. Developing new models that better reflect the disease in humans is essential in allowing researchers to further understand it and develop effective treatments.

Prof Pickering-Brown has demonstrated the ability to insert the human C9ORF72 gene and replicate the symptoms of MND using cultured cells. In this project the researchers will insert this gene into a mouse and 'switch' the gene on and off to investigate the role of dipeptide repeat proteins in MND.

Humanizing TDP-43 in the mouse

- Prof Elizabeth Fisher, Dr Abraham Acevedo-Arozena and Dr Anny Devoy
- *University College London* and MRC Harwell
- £91,843 (PhD Studentship) over 3 years
- Start date: December 2015
- Our Ref: 876-792

Researchers have previously identified the TDP-43 gene as a cause of inherited MND. Interestingly, although these mutations are only identified in a small number of inherited cases of MND, clumps of the protein TDP-43 are being found in the majority of MND cases.

How mutations in the gene TDP-43 cause the loss of motor neurones is still not fully understood, and this project aims to develop a new mouse model that better models the human disease.

By inserting the human TDP-43 gene into mice and completely removing the existing equivalent mouse gene, the researchers aim to create and study a more accurate model of MND with a view to future therapies.

Creating a 'protein-only' C9ORF72 mouse model

- Dr Adrian Isaacs, Prof Elizabeth Fisher and Dr Anny Devoy
- *University College London*
- £230,075 (Biomedical project) over 3 years
- Start date: May 2016
- Our Ref: 834-791

A mistake in the C9ORF72 gene has been found to be the most common genetic cause of the rare inherited form of MND. Previous research has shown that the proteins made by the gene are highly toxic, and this project will aim to create mouse models that express these toxic proteins.

This project will initially create mouse embryonic stem cells expressing the toxic form of the C9ORF72 protein before ultimately using these cells to create new mouse models of this form of MND. Once generated, these mouse models will then allow the researchers to study the effect of the C9ORF72 protein in detail.

Identifying common points of neuronal dysfunction in the MND-FTD spectrum using fruitfly and iPSC models

- Dr Sean Sweeney and Dr Paul Genever
- *University of York*
- £87,246 (PhD studentship) over 3 years
- Start date: October 2016
- Our Ref: 884-792

In previous work, the team created a model of MND in fruit flies (Drosophila). They have found a link between two key cell processes thought to be involved in MND development and certain parts of DNA that are activated. Activation of these forms of DNA in MND has been suspected for some time and it could be a key cause of damage in MND.

In this PhD the student will be trained in the use and interpretation of fruit fly genetics to image these processes to understand the relationships between them and DNA activation. In parallel, they will generate human stem cell models of MND to create human neurones in order to image and confirm what they find in the fruit flies. Through this, they hope to uncover a process that is contributing to neurone death in MND patients with the eventual aim of stopping it with new therapies.

Observing MND-related changes in the brain of mice with TDP-43 protein

- Dr Jemeen Sreedrahan and Prof Michael Coleman
- *The Barbraham Institute*
- £54,900 (Biomedical project) over 1 year
- Start date: December 2016
- Our Ref: 849-791

The TDP-43 protein is known to be one of the factors causing MND. To explore how exactly it causes motor neurones in the brain and spinal cord to die, changes within the brain need to be observed over time, as the disease progresses.

This project will work with mice whose TDP-43 genes were modified to mimic the changes that occur in people with MND. To track the progress of the disease, the mice will be subjected to tests examining their motor and cognitive (thinking) abilities and mutation-related changes in their nervous system will be monitored. Specific interest will be given to the mutations occurring in the pre-symptomatic stage to identify potential biomarkers (unique biological fingerprints) of the disease.

Targeting disease pathways of juvenile MND using mice models and iPS cells

- Prof Linda Greensmith, Dr Bilal Malik and Dr Rickie Patani
- *University College London*
- £197,346 (Biomedical project) over 3 years
- Start date: January 2017
- Our Ref: 851-791

Mutations in the Senataxin gene (SETX) are known to cause a rare form of juvenile MND (ALS4). To understand what goes wrong in motor neurones carrying this mutation, the cellular changes occurring in the earliest stages of the disease need to be identified first.

This project will work with mice with the SETX mutation and human motor neurones reprogrammed from stem cells of people with ALS4 (using iPSC technique). The researchers will specifically observe disruptions in the neuronal transport system and formation of stress granules in the neurones. By comparing the findings from mice and human stem cells, the researchers hope to determine a common cause of neuronal death in SETX-related MND.

Committed to funding

Exploring mechanisms causing TDP-43 depositions in a fruitfly model

- Dr Frank Hirth
- *King's College London*
- £95,747 (PhD studentship) over 3 years
- Start date: February 2017
- Our Ref: 890-792

The two biggest areas of research into why motor neurones die in MND are studies of the C9ORF72 gene and clumps or depositions of the TDP43 protein. Using a fruitfly model of MND with the faulty C9ORF72 protein, this project will examine what is happening in the early stages of the disease by looking at how faulty C9ORF72 affects the accumulation of the TDP43 protein.

Investigating changes in miR-9 and their effect on autophagy

- Dr Rob Layfield and Dr Federico Dajas-Bailador
- *University of Nottingham*
- £89,500 (PhD studentship) over 3 years
- Start date: October 2017
- Our Ref: 887-792

Degeneration of motor neurones in MND is not likely to be caused by just one single factor. This project will look at the interplay of disturbances in microRNA and dysfunction of the cells' waste disposal system (autophagy), occurring due to mutations in the TDP-43 gene, and how these two adverse processes together contribute to the death of motor neurones.

The researchers will use skin cells from people with MND with mutations of the TDP-43 gene and transform them into motor neurones (iPSC technology). They will then observe which particular microRNAs are critical in neuronal death and whether these have a negative impact on other MND-related genes known to be implicated in autophagy.

Healthcare

Currently funding

Is ALS/FTD different from FTD?

- Prof Julie Snowden, Dr Matthew Jones and Dr Jennifer Thompson
- *University of Manchester*
- £84,720 (PhD Studentship) over 3 years
- Start date: October 2014
- Our Ref: 872-792

Some people with MND develop an increasingly recognised form of dementia, known as frontotemporal dementia (FTD). The main symptoms include alterations in decision making, behaviour and difficulty with language.

The relationship between MND and FTD is not well understood and this project aims to establish whether MND combined with this form of dementia is different to FTD on its own. This research offers the potential to improve identification of the people with FTD who are also at risk of developing MND, leading to improved care and quality of life.

The MND Register of England, Wales and Northern Ireland

- Prof Ammar Al-Chalabi and Prof Kevin Talbot
- *King's College London* and *University of Oxford*
- £411,627 (Healthcare project) over 5 years
- Start date: October 2014
- Our Ref: 926-794

MND is believed to affect 5,000 people in the UK at any one time, however, the true figure is not known as there is currently no way of recording this information.

The MND Register will aim to capture this information. Research into the number of people living with MND in the UK could give important clues to the cause of the disease and identify gene-environment interactions. By recording the information of people living with MND in the UK we can get an accurate number of how many people in the UK are affected, as well as co-ordinate better care. An important first step will be developing the database for the project.

We are grateful for the support of the Betty Messenger Charitable Foundation in funding this project.

Evaluating a new neck support for people living with MND (the Sheffield Support Snood)

- Prof Christopher McDermott
- *University of Sheffield*
- £19,955 (Healthcare project) over 1 year (+7 months extension)
- Start date: April 2015
- Our Ref: 928-794

Neck weakness is an extremely distressing problem in MND, and it is very difficult as a clinician to treat this. Current neck supports available are often restricted and do not suit everyone. This is because they are designed for other purposes, such as immobilising the necks of individuals after trauma.

After working with people living with MND, designers, clinicians and engineers, Prof McDermott developed the Sheffield Support Snood.

The Snood was initially trialled in 26 people living with MND, and this next stage of the project – the '100 Collars' project - will evaluate the Snood in a larger number of people in order to provide the necessary wider consumer testing needed for a commercial partner to take on the manufacture of the product.

Gathering information on disease features and care needs of people with MND in Scotland

- Dr Danielle Leighton and Prof Siddharthan Chandran
- *University of Edinburgh*
- £63,546 (Fellowship, jointly funded with Chief Scientist Office, Scotland) over 3 years
- Start date: August 2015
- Our Ref: 986-797

In this project Dr Leighton will gather information on the clinical and cognitive characteristics of all cases of suspected MND in Scotland over a two year period. Newly collected data will be added to the existing Scottish Motor Neurone Disease Audit, Research and Trials (SMART-MND) register.

The specific features of a person's MND will be taken, alongside an assessment of their behaviour and memory using the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). This will assist in grouping patients into different disease subtypes. Being able to group people together will help study the genetic causes behind different types of MND in more detail.

In the long-term it is hoped that this data can be compared to those from other centres in the UK and to the MND Register of England, Wales and Northern Ireland.

Studying language changes in MND

- Prof Orla Hardiman and Dr Niall Pender
- *Trinity College, Dublin*
- £75,125 (PhD Studentship) over 3 years
- Start date: February 2016
- Our Ref: 879-792

Some people with MND may have difficulties with thinking, language, memory and behaviour, which may interfere with activities of daily living and with decision-making (eg regarding treatment options and future care plans). This study aims to investigate the frequency and nature of language difficulties compared to changes in other aspects of thinking and behaviour, and to study how these changes evolve as the disease progresses.

Participants (75 people with MND and 75 matched controls) will be asked to take part in a neuropsychological assessment soon after diagnosis. They will also be invited to undergo an MRI brain scan. The assessment and the brain scan will be repeated every four months, ideally at least three times. This will help in classifying the disease as different subtypes in order to increase diagnosis accuracy and treatment options for the future. Moreover, repeat assessments will help in gaining a better understanding of how the different subtypes of MND change over time.

Genetic testing will identify those participants with the C9ORF72 gene mutation as this is known to cause cognitive change either with or without motor symptoms. Language changes will be compared between those with and without this genetic change.

Measuring quality of life in MND

- Prof Carolyn Young and Prof Dyfrig Hughes
- *The Walton Centre* and Bangor University
- £296,703 (Healthcare project) over 3 years
- Start date: April 2016
- Our Ref: 929-794

This project aims to develop patient-reported outcome measures and a model of quality of life for people with MND. It is part of a wider study called TONiC, and participants will be asked to fill out a questionnaire pack in order to identify factors affecting quality of life.

The project will also look at the health costs associated with MND, both to families and the healthcare system. This will help with future economic evaluations of new medicines and interventions in MND.

Update: TONiC has been rolled out into a number of clinics across the UK. To find out more please visit: www.mndassociation.org/tonic.

Practical management of cognitive and neuropsychiatric symptoms in MND

- Prof Eneida Mioshi, Prof Michael Hornberger, Prof Lee Shepstone and Dr David Dicks
- *University of East Anglia*
- £199,956 (Healthcare project) over 3 years
- Start date: October 2016
- Our Ref: 934-794

Aside from the main symptoms involving muscle atrophy, people with MND also show a number of concurrent behavioural and cognitive (thinking) symptoms, including general loss of interest and empathy or problems with planning and decision-making.

This project aims to develop a new toolkit that would help patients and their carers to deal with these additional psychological symptoms. The toolkit will be based on an input from MND patients and their carers and subjected to clinicians' use in practice. Changes in the patients' and carers' quality of life over time will be used as an outcome measure.

The final step of this project is to create a set of guidelines that would act as an official document helping patients, carers and professionals to manage behavioural and cognitive changes in MND.

Markers of disease progression

Currently funding

Developing the Biomarkers in Oxford Project

- Prof Martin Turner
- *University of Oxford*
- £240,013 (Total award value of £1,600,089 MND Association/ MRC Lady Edith Wolfson Clinical Research Fellowship) over 5 years
- Start date: August 2013
- Our Ref: 944-795

Biomarkers in Oxford (BioMOx) is a research project with the aim of identifying a diagnostic and prognostic biomarker for MND.

Advanced MRI brain scans and analysis of spinal fluid and blood have revealed several biomarker candidates, and shown that their combination improves accuracy. This project will test these in people who are at risk of developing inherited MND, particularly in those with the C9ORF72 mutation.

The aim of this project is to identify a biomarker for MND and enable more efficient organisation of clinical trials, as well as effective care-planning.

Update: This project is now recruiting people who are at risk of developing inherited MND (known as pre-symptomatic) to take part. To find out more please visit http://www.mndassociation.org/biomox.

Developing a blood test for MND by linking changes in the brain and spinal cord

- Dr Andrea Malaspina, Dr Ian Pike and Prof Linda Greensmith
- *Queen Mary University of London* and University College London
- £160,408 (Biomedical project) over 3 years (+6.5 months extension)
- Start date: October 2013
- Our Ref: 817-791

Dr Malaspina and colleagues are investigating if changes in the brain and spinal cord can be linked to chemicals in the blood to give a ‘fingerprint’ of MND. This would lead the way towards developing a blood test to confirm a diagnosis of MND, and provide a much needed tool to track the effectiveness of drugs in clinical trials.

We are grateful for the support of the Garfield Weston Foundation in funding this project.

Update: This project is now recruiting people living with MND and healthy individuals to take part. Please visit www.mndassociation.org/alsbiomarkerstudy to find out more.

In 2014 Dr Malaspina and Dr Turner presented results of their joint biomarker study. They identified neurofilament light chain as a potential blood-based prognostic biomarker for MND.

Defining disease progression in ALS: A novel analytical approach using existing clinical and imaging datasets

- Prof Mara Cercignani, Prof Nigel Leigh, Dr Andy Simmons, Prof Daniel Alexander and Prof Ammar Al-Chalabi
- *University of Sussex*, University College London and King's College London
- £77,117 (PhD studentship) over 3 years
- Start date: January 2014
- Our Ref: 865-792

Although conventional brain magnetic resonance imaging (MRI) scans are often normal in people with MND, more sophisticated MRI techniques have shown changes in the structure of the brain. A limitation of even the most recent MRI techniques is that they provide a snapshot of the brain at a single moment in the course of the illness. Only a description of how these MRI changes evolve over time as the disease advances will tell us how the nerve cell damage is evolving area by area in relation to the individual's symptoms.

This studentship project will use MRI scans that have already been obtained from many studies at King's College London over the past 16 years. By applying new concepts in medical computing to this data this project will identify how MRI changes evolve in sequence, even using scans done on a single occasion. This will allow the integration of imaging information with clinical features, linking insights into the evolution of physical changes in the brain with clinical features to develop a new and objective method to 'stage' disease progression and to detect brain abnormalities early in the disease.

Micro RNAs as a biomarker of disease progression

- Prof Linda Greensmith, Dr Andrea Malaspina, Prof Eran Hornstein, Prof Elizabeth Fisher, Dr Pietro Fratta, Prof Adriano Chio and Dr Johnathan Rohrer
- *University College London*, Queen Mary University, Weizmann Institute of Science and University of Torino
- £229,328 (Biomedical project) over 3 years
- Start date: January 2016
- Our Ref: 839-791

The development of a biomarker for MND is of upmost importance in diagnosing and monitoring disease progression. Previous research has suggested micro RNAs (miRNAs) present in the blood may be used as a biomarker.

miRNAs are short forms of RNA, the cell's copy of our genetic material DNA, that are found to be stable in the blood. This project aims to observe changes in miRNA within a large set of already collected patient samples and also in mouse models of MND. The researchers will also test a potential drug that has been previously shown to normalise miRNA levels.

Development of confocal endomicroscopy for MND research

- Prof Richard Ribchester, Dr Paul Skehel and Prof Thomas Gillingwater
- *University of Edinburgh*
- £176,443 (Biomedical project) over 2 years
- Start date: January 2016
- Our Ref: 838-791

Diagnosis of MND is usually made after a number of diagnostic tests have been performed. This includes investigation of the health of the connections made by motor neurones at the neuromuscular junction using EMG or muscle biopsy – a highly invasive and painful procedure.

This project aims to develop a different approach called confocal endomicroscopy. This non-invasive approach uses a probe (only 1.5mm in diameter), which is applied to the surface of the muscle. This probe is also connected to a powerful microscope, enabling live observation at the neuromuscular junction. Already tested in mice, the researchers aim to develop this technique towards the clinic to enable an earlier diagnosis of MND.

Looking for non-coding RNA biomarkers in the blood and CSF

- Dr Majid Hafezparast, Prof Nigel Leigh, Prof Sarah Newbury and Dr Martin Turner
- *University of Sussex* and University of Oxford
- £120,405 (Biomedical project) over 2 years
- Start date: April 2016
- Our Ref: 836-791

There are currently no robust biomarkers of diagnosis and disease progression in MND, with diagnosis being based on clinical examination.

This project will use a new method for cataloguing a group of molecules called non-coding RNAs in the blood and cerebral spinal fluid (CSF) of people living with MND and healthy individuals.

Ten of the most promising non-coding RNAs, which show changes in the blood and CSF samples from people with MND will then be validated as potential biomarkers in order to provide an earlier diagnosis and monitor disease progression.

A Multicentre Biomarker Resource Strategy in ALS: AMBRoSIA

- Prof Martin Turner, Dr Andrea Malaspina and Prof Dame Pam Shaw
- *University of Oxford*, Queen mary University and University of Sheffield
- £2,006,835 (Biomedical project) over 5 years
- Start date: August 2016
- Our Ref: 972-797

In order to diagnose MND faster, we need to better understand the causes of the disease. One way to do so is to identify the unique fingerprints – MND biomarkers – by obtaining biological samples from people with MND.
Over the span of five years, this study will collect blood, urine and skin cells from 900 people with MND as well as from over 400 people without the disease. We are also seeking to identify biomarkers that predict how MND progresses, and why people with MND progress at different rates. This has important implications for clinical trials.

The blood and urine samples will be subjected to an extensive analysis to search for chemicals that might act as MND biomarkers. The skin cells will be reprogrammed into motor neurones using an iPSC technology and used to test the effects new drugs can have on motor neurones, exploring the possibility that different drugs may work for different subtypes of MND. The extensive collection of samples will also act as a resource to future researchers investigating MND.

Using surface EMG recordings to measure muscle fasciculations

- Dr James Bashford, Prof Chris Shaw and Prof Kerry Mills
- *King's College London*
- £117,646 (Clinical Research Fellowship) over 3 years
- Start date: October 2016
- Our ref: 947-795

Muscle fasciculations ('rippling' of a muscle under the skin) are a common symptom of MND. So far, muscle fasciculations have been measured by inserting a fine needle into muscles, a procedure which can be very painful. In this project, Dr Bashford will use a much less invasive technique called surface electromyography (EMG) that allows measuring fasciculations from electrodes placed on the skin.

Fasciculations will be recorded from arms and legs of people with MND at multiple stages within 12 months to observe changes over time. These will then be compared to the patients' muscle strength to track the progress of the disease. The results of this study will help to better understand the role fasciculations play in MND. Moreover, the use of surface EMG might also be used to help test potential new therapies in the future.

How do genetic variations affect biomarkers? (NECTAR)

- Dr Janine Kirby and Dr Pietro Fratta
- *University of Sheffield* and University College London
- £382,000 (Biomedical project) over 3 years
- Start date: November 2016
- Our Ref: 974-797

This project is complementary to the AMBRoSIA programme, which aims to identify biomarkers for diagnosing MND and monitoring its progression more accurately. We know that MND progresses at different rates, and so we hope that it will be possible to identify biomarkers that characterise subgroups of MND too.

The NECTAR project will use the blood samples collected as part of the AMBRoSIA programme and conduct genetic analysis on these samples, looking for genetic mutations and variations known to be linked to MND. The results of these analyses will be used for research, to see if there are specific biomarkers that characterise the genetic forms of MND. There will also be the option for the person with MND, their families and future family members to find out the results of their genetic analysis - in other words, whether they are carriers of MND-related genes.

Committed to funding

Development and validation of a new combined approach for tracking the progress of MND

- Mr Matt Gabel, Prof Nigel Leigh and Prof Mara Cercignani
- *University of Sussex*
- £101,455 (Junior Non-clinical Fellowship) over 2 years
- Start date: Spring 2017
- Our ref: 966-799

Researchers are developing a range of ways to measure how MND progresses over time. These might be to identify a set of chemicals where their levels change in the blood or in the cerebrospinal fluid (the fluid that surrounds our brain and spinal cord). Another method that researchers are working on is to look at the change in patterns in brain scans over time.

Until recently, no-one has looked at how these measures of disease progression compare against each other. In his PhD project, Matt Gabel applied a mathematical model to look at all the data to see the overall sequence of events. For example, were changes in a brain scan seen before changes in the chemicals in blood? In his fellowship he will build on these ideas to confirm whether or not this mathematical model works, using data from people with MND from international collaborators.

Developing treatments

Currently funding

Investigating how axons degenerate in MND using flies and mice to develop a therapy

- Dr Jemeen Sreedrahan, Prof Marc Freeman and Prof Robert Brown
- *The Babraham Institute* and University of Massachusetts Medical School
- £237,270 (Total award value of £1,226,157.92 MND Association/ Lady Edith Wolfson Clinical Research Fellowship) over 4 years
- Start date: June 2013
- Our Ref: 943-795

This project aims to investigate how axons, long projections of neurones that transport messages within motor neurones, can be protected. This could lead to identification of new ways to treat MND.

Update: Dr Sreedrahan has developed a fly model of MND to study the TDP-43 gene, which is known to be involved in axon degeneration. They identified three genes, two of which were new discoveries. These genes have a role in controlling the effects of TDP-43.

Next, the researchers will try and confirm these results in a mouse model. The results found from these models will then be verified using human motor neurones grown in a dish. This project has the potential to open up new avenues of research for the treatment of MND.

Developing models to test new treatments for MND

- Dr Richard Mead and Prof Dame Pam Shaw
- *University of Sheffield*
- £125,000 (Total award value of £250,000 Kenneth Snowman-MND Association lectureship) over 4 years
- Start date: May 2014
- Our Ref: 983-797

Developing disease models is important for furthering our understanding of MND and allows researchers to screen potential new drugs for a beneficial effect before they can be given to humans, by means of a clinical trial. Dr Mead hopes to develop our understanding of MND through mouse models of the disease and to transfer this knowledge to develop new therapies.

Update: To date Dr Mead has identified a new mouse model of MND, based on defects in the TDP-43 protein. He is currently using this mouse model to test a potential compound. The next steps will be to screen over 300,000 compounds and develop new therapies in collaboration with chemists at Sheffield and with the pharmaceutical company AstraZeneca.

Dr Mead is also moving into cell therapy to test a stem cell treatment in this mouse model with a leading stem cell company.

Restoring muscle function with transplanted stem-cell derived motor neurones

- Prof Linda Greensmith, Dr Barney Bryson and Dr Ivo Lieberam
- *University College London* and King's College London
- £229,160 (Biomedical project) over 3 years
- Start date: August 2014
- Our Ref: 825-791

This study will use stem cell technology to restore muscle function in a mouse model of MND. The researchers will transplant stem-cell derived motor neurones and then guide them to where they are needed using light.

The researchers aim to restore function to the muscles that are responsible for breathing, and develop an optical stimulator, which can then be implanted into the body to stimulate the transplanted cells for long periods of time. If successful, this technique could form the basis of future treatments that could potentially restore muscle function in MND.

Protecting against oxidative stress in MND

- Prof Dame Kay Davies and Dr Peter Oliver
- *University of Oxford*
- £95,826 (PhD Studentship) over 3 years
- Start date: October 2014
- Our Ref: 869-792

During the early stages of MND it is proposed that motor neurones are more susceptible to an imbalance of oxygen within the cells, known as oxidative stress. Prof Davies has previously shown that increasing the levels of the gene Oxr1 can protect motor neurones from death caused by oxidative stress and delay MND in mice.

The aim of this project is to understand more about the role of Oxr1 in the protection of motor neurones in MND, as well as to determine if increasing levels could be a protective treatment approach.

Preventing TDP-43 deposits in motor neurones

- Prof Marcus Rattray, Dr David Hicks and Dr Ritchie Williamson
- *University of Bradford*
- £174,965 (Biomedical project) over 3 years
- Start date: August 2015
- Our Ref: 837-791

Deposits of the protein TDP-43 that are found within the motor neurones in the majority of cases of MND are considered a pathological hallmark of the disease. The events that cause TDP-43 proteins to deposit within the motor neurones are currently unknown.

In previous research, activation of the Unfolded Protein Response (UPR) causes the protein TDP-43 to form abnormal deposits within motor neurones. This project will aim to identify what pathways link the UPR and TDP-43 deposition within the motor neurones and whether reversing the accumulation of TDP-43 has an effect on slowing the progression of MND. The researchers will then aim to screen hundreds of compounds that may potentially reverse this process.

Correcting the early damage seen in interneurones in the zebrafish

- Dr Johnathan McDearmid, Dr Tennore Ramesh and Prof Dame Pam Shaw
- *University of Leicester* and University of Sheffield
- £160,900 (Biomedical project) over 3 years
- Start date: November 2015
- Our Ref: 835-791

Previous research in humans and zebrafish has shown that before symptoms arise in MND, early changes occur in the interneurones (the cells linking the upper and lower motor neurones).

Using zebrafish, this project will investigate if the early defects that occur in interneurones can be targeted as a potential treatment for MND, in order to slow, or even prevent, the onset of symptoms. These studies will be conducted looking specifically at the electrical activity of the interneurones.

Testing the effect of antisense oligonucleotides on iPSC-derived motor neurones

- Prof Kevin Talbot and Prof Mathew Wood
- *University of Oxford*
- £96,252 (PhD studentship) over 3 years
- Start date: July 2016
- Our Ref: 886-792

Understanding how the C9ORF72 gene mutation leads to MND by damaging nerve cells is vital for developing potential new treatments. The Talbot group has generated motor neurones with the C9ORF72 mutation using groundbreaking induced pluripotent stem cell (iPSC) technology.

They have been working on a targeted method to alter the RNA made from the C9ORF72 gene, using short stretches of molecules, known as antisense oligonucleotides (ASOs). They plan to study the effect of ASOs on their cell lines using a new technique called TRAP (translating ribosome affinity purification).

The team will compare the effects of the ASOs on the C9ORF72 iPSC cells with those originating from healthy people and also with a third set of cells in which the C9ORF72 mutation has been 'cut out'. By testing the effects of different ASO molecules on the cells, they will find out if this is a potential therapeutic strategy for MND.

Novel therapeutic strategies to prevent toxicity in C9ORF72-related MND

- Dr Guillaume Hautbergue and Dr Lydia Castelli
- *University of Sheffield*
- £169,358 (Biomedical project) over 2 years
- Start date: August 2016
- Our Ref: 846-791

Cells within our body contain a number of separated compartments, each carrying out specific functions. The blueprint for making up thousands of proteins is housed in the form of genes, in a compartment in the centre of the cell, the nucleus. A copy of the blueprint is created for each protein and is transported into the 'open plan' part of the cell, known as the cytoplasm. These copies serve as individual instruction manuals for the building of each protein. The copies are known as RNA.

Damage to the C9orf72 gene is the commonest cause of inherited MND. The toxicity of the C9orf72 gene is linked to the transport system between the nucleus and the cytoplasm of the motor neurone. Researchers have recently found that a protein called SRSF1/F2 can help reduce this toxicity. In this project, the researchers hope to confirm the role of SRSF1/F2 in the C9orf72 form of MND in fly and human models of the disease. They will also investigate how it might be possible to reduce SRSF1/F2 safely as a possible treatment option.

Investigating the efficacy and safety of low-dose interleukin-2 treatment to control neuroinflammation in ALS (MIROCALS)

- Prof Nigel Leigh
- *University of Sussex*
- £316,440 (Healthcare project) over 3 years
- Start date: September 2016
- Our Ref: 80-971-797

The Modifying Immune Response and Outcomes in Amyotrophic Lateral Sclerosis (MIROCALS) study will aim to investigate interleukin-2 as a potential treatment for MND.

Interleukin-2 has been used for many years to treat cancer, however, at low doses it is much safer but still effective against a number of immune diseases. Because the immune system is thought to be involved in causing damage in MND, the researchers believe it may be beneficial in treating MND too.

This study will aim to start recruiting 216 people living with MND in the UK and France in **spring 2017.**

The role of exosomes in MND and the therapeutic effect of mesenchymal stem cells

- Prof Giambattista Bonanno and Prof Pam Shaw
- *Universita di Genova* and University of Sheffield
- £170,000 (Biomedical project) over 2 years
- Start date: January 2017
- Our Ref: 848-791

Many researchers around the world are investigating the potential of stem cells as a therapy for MND, however, its benefits are not proven. We know that a particular type of stem cell, the mesenchymal stem cell (MSCs), found in the bone marrow, have shown beneficial effects in mice with MND. However, it is unclear how MSCs are beneficial. We know that little ‘packets’, or compartments, of MSCs known as exosomes break off from the MSCs. Within these packets are chemicals that affect the role of support cells around motor neurones.

Professor Bonanno and colleagues will investigate whether these exosomes have a beneficial effect in MND on their own, in mice and human cell models of MND. This could have important implications for future stem cell trials.

Committed to funding

Investigating viability of newly created neurone-muscle connections in mice

- Dr Barney Bryson, Prof Linda Greensmith and Prof Giampietro Schiavo
- *University College London*
- £272,579 (Senior Non-clinical Fellowship) over 3 years
- Start date: August 2017
- Our ref: 965-799

The cause of muscle weakness in MND is caused by the disruption of the connections between a motor neurone and a muscle. This project will use stem cells from mice that were transformed into motor neurones and use these to create new muscle-neurone connections. These will be implanted back into the mice and observed for how well the neurones connect with muscles (innervation).

The researchers will then identify the chemicals that promote successful innervation that could potentially be used in developing new therapies, focused on preventing the breakdown of muscle-neurone connections. Moreover, this study has the potential to contribute to the development of a new therapy based on replacing damaged motor neurones and restoring lost muscle function.

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Research involving animals: Approximately three fifths of the research projects we fund do not involve the use of animals. With those that do, we and the researchers we fund are committed to ensuring that the welfare of the animals is considered at all times. For more information on how we approach funding MND research involving animals, go to www.mndassociation.org/animalresearch.

Research we fund: A selection of these research projects are highlighted on our website (www.mndassociation.org/researchwefund).

If you'd like more information about any of the research projects we fund, please contact the Research Development team at research@mndassociation.org or on 01604 611880.

Last revised: February 2017