mnda
motor neurone disease
association

Research we fund
2022

Research

We are a leader in the funding and promotion of cutting-edge motor neuron disease (MND) research, both within the UK and across the world. All of the research projects we fund have clear clinical relevance and/or therapeutic potential. You can find out more about the **research we fund in 2022** on the following pages, in order of their theme. Research studies that involve animals (e.g. fruit flies, zebrafish, mice) are marked with **A**. Co-investigators also include PhD students, post-doctoral researchers, research assistants, and technicians.

What types of research projects do we fund?

Our research projects are categorised into four themes that range from 'bench to bedside'. This means that some projects try to identify the causes of MND and develop models to study the disease, others aim to find unique biomarkers in people with MND to help speed up diagnosis and track progression of the disease, some hope to turn the most promising compounds into drugs that will treat the disease, and others are aim to improve the quality of life and care of people living with MND.

Identifying therapeutic targets

Understanding the causes of MND, focusing on the pivotal biochemical processes involved in the disease that will provide a starting point for the development of new treatments.

Developing treatment pipeline

Turning the most promising scientific discoveries into potential new treatments. New treatments that have been proven safe and effective by all other methods are then carefully tested in people.

Understanding clinical progression

Developing a detailed understanding of how the disease manifests and progresses in humans to ensure that fundamental laboratory research can be clearly linked to the 'real world' events occurring in people with MND.

Improving standards of care

Ensuring that the clinical management of MND is informed by the priorities of people living with the disease and their families, and is supported by a strong evidence base.

How do we decide what research we fund?

Peer review (scrutiny by experts in the field) is essential in research and is used to ensure all projects we fund are of the highest calibre and can realistically achieve the aims of the project. 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). The types of research we support are listed below:

Project grant (Biomedical or Healthcare)

We are committed to playing a key role in ending MND. Our **biomedical** research programme delivers significant and measurable advances in understanding and treating the disease. We only fund research of the highest scientific excellence and greatest relevance to MND.

The MND Association has a longstanding record of supporting **healthcare** research and therapeutic trials. Our goal is that healthcare research we fund will lead to improvements in treatment, disease management and quality of life for people with MND, their families and carers and strengthen the case for statutory funding of high-quality MND care. Some of our healthcare projects are co-funded by Marie Curie.

Grants of up to **£255,000** are offered for up to **3 years** to allow for an in-depth investigation of an area of research.

PhD Studentship

We have a track record of attracting and funding promising young, or early career stage, scientists to develop their careers in MND research through our successful PhD studentship programme. Grants are offered up to the value of **£100,000** for up to **3 years**. This is a cost-effective method that allows high calibre candidates to undertake PhD training in MND-related projects.

Small grant

We offer small grants that are of variable amounts to facilitate the rapid follow-up of important new findings. Small pump-priming grants are considered on an 'ad-hoc' basis.

The Lady Edith Wolfson Fellowship Programme

Clinical Research Fellowship

Jointly funded by the Medical Research Council (MRC), these grants support clinicians wishing to pursue scientific research and aim to strengthen the links between laboratories and clinics.

Non-Clinical Fellowship

Since 2015, the MND Association has awarded non-clinical fellowships to nurture and retain the best post-doctoral researchers at early and mid-career levels, usually conducting biomedical research, with the aim to develop them into MND research leaders of the future. Fellowships are awarded at two levels, depending on the experience of the applicant: **Junior** or **Senior**. Our non-clinical fellowships are currently funded with generous support from several donors and MND Association branches and groups.

NEUROHACK (950-793)		**Therapeutic targets**
Lead investigator	Dr Ahmad Al Khleifat	
Lead institution	King's College London	
Co-investigators	Prof David Llewellyn, Dr Janice Ranson, Prof Richard Everson and Dr Laura Winchester	
Cost: £10,000	**Type of grant:** Small grant (Biomedical)	January 2022
Neurohack is an "invention marathon" designed to spark innovation, promote diversity, attract and educate the brightest and deepen collaborations. Applicants will spend 4 days collaborating to address a challenging set of scientific problems related to clinical and genomic data, using machine learning and artificial intelligence. This includes a challenge specific to MND relating to exploring genetic variation longevity to inform drug discovery. The most promising ideas will be awarded £10,000 pilot grants to continue to investigate their potential.		

Dissecting the pathobiology of MND using the FUS Delta14 mouse model (867-791) **A**		**Therapeutic targets**
Lead investigator	Dr Anny Devoy	
Lead institution	King's College London	
Co-investigators	Dr Marc-David Ruepp and Dr Helene Plun-Favreau	
Cost: £100,000	**Type of grant:** Project grant (Biomedical)	January 2019 - March 2022
The aim of this study is to identify and investigate the earliest disease-specific changes that occur in MND in order to identify key cellular changes that contribute to the death of motor neurons. The project will take advantage of a new FUS mouse model of MND to investigate the interaction of mutant FUS with two important cellular structures – the endoplasmic reticulum and mitochondrion – which are essential for maintaining energy, and thus the health of cells, especially neurons. ***Supported by the Hornsby Lonsdale Charitable Trust and the Mid Kent MND Association Branch***		

Identification of Arfaptin-2 as a potential therapeutic target for MND (944-793) **A**		**Therapeutic targets**
Lead investigator	Dr Ke Ning	
Lead institution	University of Sheffield	
Co-investigators	Prof Dame Pamela Shaw, Dr Tennore Ramesh and Anushka Bhargava (Student)	
Cost: £9,734	**Type of grant:** Small grant (Biomedical)	December 2020 - June 2022
A key feature of MND is the presence of protein clumps (aggregates) within neurons. Studies into other neurodegenerative diseases have shown that a protein called Arfaptin-2 gathers at the sites of protein clumps and stops them from being removed. In contrast to this, there is one form of the Arfaptin-2 protein which has protective properties and seems to regulate the breakdown of the protein aggregates. This protective form of the protein is called HC-ARFIP-2 and it has been found to activate the degradation of the protein clumps and increase motor neuron survival in MND affected cells. This project aims to test the action of HC-ARFIP-2 on more MND cell models, to further observe its effects on protein aggregation, and in zebrafish models of MND to see the effect it has on symptoms and progression of the disease. The study will assess whether ARFIP2 may be a novel therapeutic target for MND.		

Role of immune-related autophagy and inflammation in C9MND/FTD (862-791) **A**		**Therapeutic targets**
Lead investigator	Prof Kurt De Vos	
Lead institution	University of Sheffield	
Co-investigators	Dr Andrew Grierson and Dr Emma Smith	
Cost: £226,197	**Type of grant:** Project grant (Biomedical)	September 2018 - July 2022

This project will investigate MND caused by a C9orf72 defective gene which results in inflammation when the waste removal system of the cell, a process called autophagy, is not working properly and causes a build-up of toxic waste. The researchers will test a number of drugs that increase the autophagy process using zebrafish and in cells donated by patients, to see if these potential treatments reduce inflammation which it is hoped might benefit MND patients.

Supported by The Astor Foundation and The Mackintosh Foundation

Investigating MND as a disease of the Tripartite Synapse (863-791) **A**		**Therapeutic targets**
Lead investigator	Prof Gareth Miles	
Lead institution	University of St Andrews	
Co-investigators	Prof Siddharthan Chandran and Dr Matthew Broadhead	
Cost: £236,987	**Type of grant:** Project grant (Biomedical)	December 2018 - July 2022

Changes in the connections between neurons, called synapses, and dysfunction of the main supportive cells of the nervous system, called glial cells, contribute to motor neuron loss in MND. This project will investigate the changes in synapses and glial cells in MND in mouse models, post-mortem tissue obtained from people with MND and combinations of motor neurons and glial cells from skin samples of people with MND.

Supported by Robert Barr's Charitable Trust

Investigating immune system involvement in MND using a novel in-vitro human neuromuscular junction model (949-793)		**Therapeutic targets**
Lead investigator	Dr Nassar Al-Shanti	
Lead institution	Manchester Metropolitan University	
Co-investigators	Dr Amina Chaouch and Dr Emma Hodson-Tole	
Cost: £2,500	**Type of grant:** Small grant (Biomedical)	February 2022 - Jul 2022

The connections between nerve cells and muscle cells, called neuromuscular junctions (NMJ's), are formed and regulated by interactions of chemicals that are produced by nerve cells, muscle cells and immune cells. Altered communications between these chemicals is thought to play a role in the damage to the NMJ's that we see in MND. Previous research has identified that one subset of immune cells, called T-cells, are contributors to impaired muscle cell regeneration in the disease. This project is looking at T-cells to determine the exact role that these play in the impaired development and regeneration of NMJs in MND. To achieve this, the team will use a cell model of NMJ's and expose them to T-cells collected from those with MND to observe the effects these have on the NMJ's and compare these results to NMJ's that are exposed to T-cells from healthy individuals. This could help us to further understand how the immune system is involved in the development of MND and may highlight potential therapeutic targets.

Unravelling TDP-43 autoregulation: routes to therapy for MND-FTD (865-791)		**Therapeutic targets**
Lead investigator	Dr Jemeen Sreedharan	
Lead institution	King's College London	
Co-investigators	Dr Michael Niblock	
Cost: £238,600	**Type of grant:** Project grant (Biomedical)	October 2018 - September 2022
At the centre of almost all cases of MND is an imbalance in a protein called TDP-43. This work will find ways to correct this by testing thousands of potential gene therapies at the same time to potentially reduce TDP-43 to normal levels. These studies could yield targets for therapy that will be important for most people with MND. This project grant includes small grant funding to conduct screening experiments at the Crick Institute. ***Supported by the Childwick Trust and MND Association Branches and Groups***		

Understanding RNA dysfunction using novel RNA-seq technologies (893-792)		**Therapeutic targets**
Lead investigator	Prof Pietro Fratta	
Lead institution	University College London	
Co-investigators	Prof Giampietro Schiavo, Dr Maria Secrier, Dr Thomas Cunningham, Dr Vincent Plagnol and Samuel Bryce-Smith (PhD student)	
Cost: £100,000	**Type of grant:** PhD Studentship	November 2019 - December 2022
Correct processing of RNA (molecules that carry information to make proteins from DNA) is crucial for survival. Proteins called TDP-43 and FUS are important for the processing of RNA. This project will help understand how changes in TDP-43 and FUS impact on motor neuron RNA and survival. Molecular changes occurring in early stages of disease can be identified using RNA-sequencing (RNA-seq) technology. This knowledge will be invaluable for developing effective therapeutics and the project will allow application of cutting-edge technology to numerous MND mouse and human cell models. ***The Masonic Charitable Foundation PhD Studentship***		

Characterisation of induced pluripotent stem cell models for MND (941-793)		**Therapeutic targets**
Lead investigator	Dr Agnes Nishimura	
Lead institution	King's College London	
Co-investigators	Erin Hedges (PhD Student)	
Cost: £15,651	**Type of grant:** Small Grant (Biomedical)	January 2021 - December 2022
The use of cell models is important to further our understanding of MND and allows researchers to screen potential new drugs for a beneficial effect in the lab. Induced pluripotent stem cells (iPSCs) can be generated by obtaining cells from people with MND and altering them using specialist technology to replicate diseased motor neurons. This project allows a continuation of previous research project, in which 35 new cell lines of MND-like cells were generated for use in future research. Currently only 6 of these cell lines have undergone the rigorous testing and quality control checks needed to be accepted by the European Collection of Authenticated Cell Cultures (ECACC) - a collection of high-quality cell lines run by Public Health England who can supply cells for researchers to use. This grant will enable the remaining 29 generated cell lines to undergo the necessary quality testing so that they can be accepted by the ECACC and be used in future MND research.		

TDP-43 and p62 in MND-FTD: when a molecular handshake goes wrong* (970-799) **A**		**Therapeutic targets**
Lead investigator	Dr Daniel Scott	
Lead institution	University of Nottingham	
Co-investigators	Prof Rob Layfield, Prof James McInerney and Barry Shaw	
Cost: £254,116	**Type of grant:** Non-Clinical Fellowship (Junior)	August 2019 - January 2023

A recently discovered interaction or 'molecular handshake' between TDP-43 protein (that builds-up in and is toxic to diseased motor neurons) and another protein called p62 (which controls key cellular 'waste-disposal' systems) could be harmful in affected individuals. The purpose of this fellowship is to understand the effect this interaction might have on motor neurons and to investigate the utility of targeting p62 to prevent the build-up of toxic TDP-43 as a potential therapeutic strategy in MND.

The Lady Edith Wolfson Fellowship Programme
Supported by the Payne-Gallwey Charitable Trust

Converging minor intron splicing defects in MND* (872-791)		**Therapeutic targets**
Lead investigator	Dr Marc-David Ruepp	
Lead institution	King's College London	
Co-investigators	Dr Sarah Mizielinska and Niamh O'Brian	
Cost: £223,386	**Type of grant:** Project grant (Biomedical)	January 2020 - February 2023

The aim of this project is to identify which specific defects in minor intron splicing are shared between FUS, TDP-43 and C9orf72 gene mutations. To do this, human stem cells will be exposed to the various MND causing gene mutations and then will be grown into nerve cells. Cells with mutations in FUS (which can cause a very aggressive form of MND) and TDP-43 (the protein most commonly aggregated in MND) have already been created and now cells with the most common gene mutation (C9orf72) will be created. The project will look for changes in the minor intron splicing process to find potential new targets for drug development across all MND types.

Supported by the Bruce Wake Charitable Trust
and MND Association Branches and Groups

Characterisation of novel C9orf72 dipeptide repeat knock-in mice* (876-791) **A**		**Therapeutic targets**
Lead investigator	Prof Adrian Isaacs	
Lead institution	University College London	
Co-investigators	Prof Elizabeth Fisher, Prof Linda Greensmith and Dr Carmelo Milioto	
Cost: £175,000	**Type of grant:** Project grant (Biomedical)	April 2021 - March 2023

One of the genetic changes that is linked to MND occurs in the C9orf72 gene and the mutation can cause five unwanted different proteins to be made. Funding from a previous grant allowed the development of a novel mouse model expressing one of these proteins, called polyGR, as seen in those with C9orf72 MND to study. This project will use this mouse model to look at the effects of the toxic polyGR protein on motor neurons and how it leads to neuronal cell death and identify the disease pathways involved in driving the disease. Therefore, this project will conduct a detailed characterisation of the mouse model which provides an opportunity to get new insights into the toxic protein, disease mechanisms in C9orf72 MND and should identify new pathways for therapeutic intervention.

Understanding the role of NEAT1 in MND (968-799) **A**		**Therapeutic targets**
Lead investigator	Dr Tatyana Shelkovnikova	
Lead institution	University of Sheffield	
Co-investigators	Prof Vladimir Buchman and Prof Dame Pamela Shaw	
Cost: £389,513	**Type of grant:** Non-Clinical Fellowship (Senior)	September 2018 - May 2023

An RNA molecule called NEAT1 forms the scaffolding of small compartments in a cell's nucleus (called paraspeckle). It has been suggested the way NEAT1 is created may be altered and that these changes might be common to both sporadic and familial MND and differentiate them from FTD. This project will model NEAT1 in human motor neurons and fruit flies and observe how it responds to stress and toxicity within neurons. Understanding the adverse processes regulated by NEAT1 might provide a potential target for therapy.

The Lady Edith Wolfson Fellowship Programme

Investigating early protein translation deficits in mice/iPSC models* (868-791) **A**		**Therapeutic targets**
Lead investigator	Prof Pietro Fratta	
Lead institution	University College London	
Co-investigators	Dr Thomas Cunningham, Prof Elizabeth Fisher, Dr Bernadett Kalmar, Prof Rickie Patani, Prof Giampietro Schiavo, Dr Maria Secrier and Dr Matthew Keuss	
Cost: £209,295	**Type of grant:** Project grant (Biomedical)	July 2020 - June 2023

A new mouse line bearing mutations in the FUS gene develops an aggressive MND phenotype over 3 months. This project will thoroughly characterise these mice and their motor neuron loss to make the novel tool available to the MND research community. Secondly, these mice and patient-derived cells will be used to determine whether the making of new proteins is impaired and if it is an early mechanism of disease. The findings of the project could help in development of new therapeutic strategies to modify disease progression.

MND's next top model: evaluating iPSC models by protein aggregates* (971-799)		**Therapeutic targets**
Lead investigator	Dr Dezerae Cox	
Lead institution	University of Cambridge	
Co-investigators	Prof Sir David Klenerman and Prof Chris Shaw	
Cost: £155,052	**Type of grant:** Non-Clinical Fellowship (Junior)	July 2021 - June 2023

This project aims to use sensitive imaging techniques to enhance understanding of toxic protein aggregates. Preventing toxic protein aggregates being formed and causing damage are possible ways to treat MND, and the presence of these aggregates could be used for early disease diagnosis. However, detailed understanding of the shape, size and properties of these aggregates has been hampered by their low abundance and the fact they can form many different types of clumps. It remains unclear how well cellular models used in MND research best represent the real disease. Therefore, this project will also characterise and compare the protein aggregates formed in cellular models and patient-derived tissue to determine which cell model is most realistic.

The Lady Edith Wolfson Fellowship Programme
Supported by the Cambridgeshire MND Association Branch

Role of microglia-released microRNA in MND Pathology (897-792) **A**		**Therapeutic targets**
Lead investigator	Prof Majid Hafezparast	
Lead institution	University of Sussex	
Co-investigators	Prof Nigel Leigh, Dr Lisa Mullen, Prof Sarah Newbury and Libby Moody (PhD Student)	
Cost: £88,153	**Type of grant:** PhD Studentship	October 2020 - September 2023

Microglia (immune cells in the brain) are activated to release a number of proteins and chemicals which modulate the function of neighbouring motor neurons but at high levels can damage these cells. Recent data show that lab-grown microglia also release a group of molecules known as microRNAs (miRNAs) with different expression in non-activated and activated states. There is increasing evidence that miRNAs released from microglia play an important role in cell-to-cell communication by modulating the expression of genes in adjacent cells. This PhD project will use normal and mutant mouse models of MND, cell and molecular biology techniques, alongside bioinformatics tools to identify the key disease-associated miRNAs and the genes targeted by these miRNAs.

Supported by the East Sussex MND Association Branch

Identifying disease modifying interactors of FUS at synapses* (894-792) **A**		**Therapeutic targets**
Lead investigator	Dr Caroline Vance	
Lead institution	King's College London	
Co-investigators	Dr Anny Devoy and Sara Tacconelli (PhD student)	
Cost: £97,310	**Type of grant:** PhD Studentship	October 2020 - September 2023

The project investigates how FUS protein functions normally in the brain by identifying proteins that it interacts with at synapses (point of contact for brain cells) and seeing how these differ in disease. Two different and well-characterised mouse models of MND-FUS will be used to identify common pathways affected in disease. One recapitulates an early-onset aggressive fatal model of the human disease and the other models non-fatal late-onset. Advanced imaging will also be used to investigate how manipulating the FUS-interacting proteins within brain cells in a dish can reverse a known cellular defect (transport of proteins). This will identify potential therapeutic pathways for intervention in relevant disease cell types.

Supported by the West Sussex South and West Sussex North MND Association Branches

Role of axonal transport in cell models carrying MND mutations (973-799) **A**		**Therapeutic targets**
Lead investigator	Dr Andrew Tosolini	
Lead institution	University College London	
Co-investigators	Prof Giampietro Schiavo and Prof Rickie Patani	
Cost: £142,423	**Type of grant:** Non-Clinical Fellowship (Junior)	November 2021 - October 2023

Healthy motor neurons work by transmitting signals from the brain and spinal cord to muscles to allow us to move, speak and breathe. This relies on a complicated process known as 'axonal transport', which refers to the movement of important molecules and organelles (subunits of a cell that have specific functions) up and down motor neuron cells. When people have MND, this transport process doesn't work as well so the molecules and organelles that cells normally need to survive get stuck in the wrong places. Dr Tosolini's research, which uses motor neurons developed from people with MND or from mice, will focus on understanding this process, and how it might be restored to normal.

The Lady Edith Wolfson Fellowship Programme

Longitudinal multi-omics of host-microbe dynamics (874-791)		**Therapeutic targets**
Lead investigator	Prof Chris McDermott	
Lead institution	University of Sheffield	
Co-investigators	Prof Dame Pamela Shaw, Dr Johnathan Cooper-Knock and Dr Sarah Boddy	
Cost: £188,331	**Type of grant:** Project grant (Biomedical)	January 2021 - December 2023

We know that MND is the result of complex interactions between genetics and the environment. One way in which the environment can affect the body and even the brain is through bacteria within our gut, which is linked to features such as diet, exercise, and antibiotic use. Gut bacteria are relatively easy to manipulate making them an ideal target for design of new treatments. This study will aim to determine whether gut bacteria influence the development and severity of MND by comparing gut bacteria in MND patients and controls who have a matched diet, BMI and environment. Measures of gut bacteria will also be integrated with sequencing of patient's genomes to capture both sides of the gene-environment interaction.

Supported by the PF Charitable Trust and the Sylvia Waddilove Foundation

Role of repetitive proteins in C9orf72-MND waste disposal dysfunction (896-792) **A**		**Therapeutic targets**
Lead investigator	Dr Sarah Mizielinska	
Lead institution	King's College London	
Co-investigators	Dr Patricia Gomez-Suaga and Olivia Houghton (PhD student)	
Cost: £97,311	**Type of grant:** PhD Studentship	February 2021 - January 2024

Defects in the C9orf72 gene can produce repetitive proteins which disrupt the cells' waste disposal system (called autophagy). If waste is not cleared effectively from brain cells, it builds up and clumps together affecting cell function and eventually leading to cell death. Autophagy requires certain proteins to be transported between the nucleus and cytoplasm. This project will investigate 1) how repetitive proteins disrupt autophagy and how this is related to the dysfunction of transport, 2) how that overlaps with loss of the C9orf72 protein and how the autophagy disruption affects the clearance of key disease-related cargo and 3) the therapeutic potential of autophagy inducers. This will hopefully help design new therapies to prevent the death of brain cells and thus the normal functioning in C9orf72-related MND.

Supported by the Bruce Wake Charitable Trust

Glial engulfment of human synapses in MND (977-799) **A**		**Therapeutic targets**
Lead investigator	Dr Zsofia Laszlo	
Lead institution	University of Dundee	
Co-investigators	Dr Christopher Henstridge and Prof Jeremy Lambert	
Cost: £149,929	**Type of grant:** Non-clinical Fellowship (Junior)	February 2022 - January 2024

Glial cells, a type of cell found in the brain and spinal cord, help to ensure that neurons are functioning correctly and maintain connections between neurons and muscles. In some neurological diseases, glial cells become toxic and consume synapses (connections which enable messages to be sent from one neuron to another to be passed to the muscles) causing these connections to be lost. This project aims to investigate the link between toxic glial cells and synapse loss in MND using cell models and post mortem brain tissue to observe the action of the toxic glial cells on synapses. It will provide new insights into the role of glial cells in MND and may potentially highlight ways to delay or prevent synapse loss which could help to slow the progression of the disease.

The Lady Edith Wolfson Fellowship Programme

Spatiotemporal diversity of cellular and molecular mechanisms in MND (950-795) **A**		**Therapeutic targets**
Lead investigator	Prof Rickie Patani	
Lead institution	University College London	
Cost: £150,000	**Type of grant:** Clinical Research Fellowship	March 2019 - February 2024

To understand precisely what goes wrong in MND and where, this project uses induced pluripotent stem cell (iPSC) technology. This is where skin cells from patients are 'tricked' into becoming stem cells and are then transformed into motor nerves. New problems are identified within messages that normally make the protein, also with misplacement and malfunction of these proteins. As well as the motor nerves, 'supporting' cells called astrocytes are found to be co-conspirators in MND. Another major aspect of the proposed work is understanding how ageing makes these cells vulnerable to MND. Studying these aspects will help to identify key processes that can then guide new therapy development.

The Lady Edith Wolfson Fellowship Programme

Investigating the role of NEK1 in MND (895-792) **A**		**Therapeutic targets**
Lead investigator	Prof Kurt De Vos	
Lead institution	University of Sheffield	
Co-investigators	Dr Andrew Grierson and Natalie Pye (PhD student)	
Cost: £88,475	**Type of grant:** PhD Studentship	March 2021 - February 2024

Mutations in the NEK1 gene are predicted to cause less NEK1 protein to be produced, thus not enough to do its job. The aim of this project is to understand why loss of NEK1 function causes MND by investigating precisely what NEK1 does and how it might connect to the cellular waste disposal process called autophagy. This knowledge could be used to correct the defects.

Supported by the Yorkshire Dales MND Association Branch

Natural and synthetic chaperones for SOD1-related MND* (969-799)		**Therapeutic targets**
Lead investigator	Dr Gareth Wright	
Lead institution	University of Essex	
Co-investigators	Prof Samar Hasnain and Prof Malcolm Jackson	
Cost: £289,590	**Type of grant:** Non-Clinical Fellowship (Senior)	April 2019 - March 2024

SOD1 is a protein found in all human cells but sometimes it misfolds into abnormal shapes that are toxic to motor neurons, leading to their death. This project will search for drug molecules that help it fold properly and create synthetic proteins that will remove it using the cellular recycling system. Ultimately the project will help us understand what causes those instances of MND where SOD1 misfolding is present and find therapeutic applications.

The Lady Edith Wolfson Fellowship Programme

Investigating metabolic dysfunction in models of MND (943-793) **A**		**Therapeutic targets**
Lead investigator	Dr Scott Allen	
Lead institution	University of Sheffield	
Co-investigators	Dr Heather Mortiboys, Prof Dame Pamela Shaw, Prof Daniela Zarnescu and James Lee (student)	
Cost: £10,000	**Type of grant:** Small grant (Biomedical)	October 2020 - April 2024

This funding tops up a studentship at University of Sheffield which investigates metabolic dysfunction in MND and how it may influence disease progression. It is known that there are problems with the way that energy is produced and used within motor neurons in MND. The part of the cell that is responsible for energy supply and use is called the mitochondria. This project will use stem cells from MND patients and turn them into motor neurons and another type of cell which helps to protect and support motor neurons, called astrocytes. These cells will be used to observe any abnormalities in the mitochondria and increase our understanding of what is going wrong with energy processes in motor neurons. The project will also assess these mitochondrial alterations in fruit flies. This could identify therapeutic targets which may help to combat the metabolic dysfunction seen in MND.

Understanding how NEK1 and C21ORF2 mutations contribute to MND (877-791)		**Therapeutic targets**
Lead investigator	Prof John Rouse	
Lead institution	University of Dundee	
Co-investigators	Dr Ivan Munoz	
Cost: £218,197	**Type of grant:** Project grant (Biomedical)	November 2021 - April 2024

There are known to be over 40 genetic causes of MND and one of these is a change in the gene that makes the NEK1 protein. This gene change causes a faulty version of the NEK1 protein to be produced, meaning that it no longer works as it should within the cell. Inside cells, NEK1 usually partners with another protein called C21ORF2 and faulty versions of this protein have also been associated with the development of MND. This project aims to further our knowledge of how NEK1 and C21ORF2 work together in healthy cells and their normal functions. Knowing more about the actions of NEK1 and C21ORF2 in healthy cells will aid in gaining a better understanding of how faulty versions of these proteins behave in MND and how they contribute to the development of the disease.

Role of transposable elements in MND development & progression (875-791)		**Therapeutic targets**
Lead investigator	Prof John Quinn	
Lead institution	University of Liverpool	
Co-investigators	Dr Vivian Bubb, Dr Alfredo Iacoangeli, Prof Ammar Al-Chalabi, Dr Johnathan Cooper-Knock, Dr Abigail Pfaff, Prof Sulev Koks and Dr Aleksey Shatunov	
Cost: £189,210	**Type of grant:** Project grant (Biomedical)	July 2021 - June 2024

The DNA changes that influence MND may be within genes (the instructions for forming proteins) or within the intervening stretches of DNA. It used to be thought that the 'non-gene' DNA was unimportant and was rarely studied until recently. This is partly because the tools used to study the whole genome sequence (WGS) data did not work as well for the sequences of connecting DNA, which are more likely to contain similar or repeating sequences. The researchers propose to re-analyse the WGS data generated by Project MinE to improve the sequence information especially for the non-gene DNA. They will specifically study sequences known as 'transposable elements', aiming to identify MND-associated differences in these sequences between people with MND and controls. When differences are identified, they will be studied further to determine if they have a role in initiation or progression of MND.

Supported by the MND Association Wirral group and Cheshire Branch

Functionally characterising changes in 'non-coding' regions of DNA (899-792)		**Therapeutic targets**
Lead investigator	Dr Johnathan Cooper-Knock	
Lead institution	University of Sheffield	
Co-investigators	Dr Laura Ferraiuolo and Calum Harvey (PhD student)	
Cost: £81,529	**Type of grant:** PhD Studentship	September 2021 - August 2024

Much of the understanding of the genetic causes of MND has resulted from the identification of genes that encode proteins and harbour a mutation (change in the DNA sequence). However, less work has been done to look for genetic causes in the 'non-coding' regions which are stretches of DNA that don't carry instructions to make proteins for our cells but work to regulate the actions of genes. This study will analyse genetic data, collected from healthy and diseased motor neurons, to better understand the functions of non-coding DNA between different cell types. This data will be used to identify new genetic risk factors and mechanisms driving MND. Discoveries will then be used to develop cell and animal models and identify drug targets.

Supported by the Barbara Naylor Trust

Capturing cell-type specific miRNA deregulation in MND using human stem cell models (974-799)		**Therapeutic targets**
Lead investigator	Dr Hamish Crerar	
Lead institution	University College London	
Co-investigators	Prof Rickie Patani, Dr Giulia Tyzack and Dr Raphaelle Luisier	
Cost: £150,000	**Type of grant:** Non-clinical Fellowship (Junior)	September 2022 - August 2024

While research made great strides in discovering what is changing at a cellular level, we still have limited understanding as to why. One of these events is the incorrect placement and processing of a molecule known as RNA, which in its various forms is essential for the correct function of motor neurons, the cells most affected in MND. The main aim of this project is to investigate whether a class of small RNA molecules, known as miRNA, are affected in MND and, if they are, whether they are a cause or consequence of the disease. Promising recent studies have shown that pharmacologically manipulating these small RNA molecules can be used to treat disease. Identifying the molecules affected could allow this same technology to be applied to treat MND.

The Lady Edith Wolfson Fellowship Programme

Impact of TDP-43 on translation and response to axon damage in MND (951-795) **A**		**Therapeutic targets**
Lead investigator	Prof Pietro Fratta	
Lead institution	University College London	
Cost: £175,000	**Type of grant:** Clinical Research Fellowship	October 2019 - September 2024

TDP-43 is a protein important for the specific transport of RNA to different locations in the axons and in the response of cells to stress and damage. This project will combine novel mouse models and patient cell lines to investigate how TDP-43 impacts the response of motor neurons to damage in the axons, and the relevance of this response pathway in ALS. It will help to understand how changes in TDP-43 impact motor neuron survival. This information will be essential to develop effective therapeutics.

The Lady Edith Wolfson Fellowship Programme

Exploring striatal neuron dysfunction in C9orf72 MND-FTD cells (900-792)		**Therapeutic targets**
Lead investigator	Dr Matthew Livesey	
Lead institution	University of Sheffield	
Co-investigators	Dr Laura Ferraiuolo and Manpreet Atwal (PhD student)	
Cost: £88,529	**Type of grant:** PhD Studentship	October 2021 - September 2024

Research has shown that MND doesn't just affect motor neurons (nerve cells needed for muscle movement), but also other parts of the brain that control our ability to think, interact and formulate words. One of these regions is called the striatum. Studies into the role of the striatum have indicated that, when damaged, it may contribute to the cognitive impairments commonly seen in people with MND and related frontotemporal dementia (FTD). This project will use samples from people living with a common genetic form of MND-FTD (C9orf72) to grow striatum nerve cells in the lab. The function of these cells will be measured using sophisticated electronics and then compared to healthy cells to see if there is a difference. The work will pinpoint functional impairment in MND nerve cells which may lead to strategies to come up with new therapies to target this brain region in MND.

Mapping signatures of rare MND genes: a means to identify key MND functional pathways (881-791)		**Therapeutic targets**
Lead investigator	Dr Bradley Smith	
Lead institution	King's College London	
Co-investigators	Dr Claire Troakes, Dr Andrew King, Prof Ammar Al-Chalabi and Dr Caroline Vance	
Cost: £199,562	**Type of grant:** Project grant (Biomedical)	May 2022 - October 2024

This project aims to identify neuropathological signatures (signatures of disease in the nervous system) in post-mortem tissue from MND cases that had mutations (a change in the biological instructions) within common and rare MND genes. Specifically, the project will look at key players within RNA biology such as RNA Binding Proteins. Once these neuropathological signatures have been identified then the project will move on to mapping these signatures from cases with an unknown genetic cause. This will help to establish the significance and frequency of these signatures and highlight relevant pathways of disease which can then become potential therapeutic targets.

Using statistical models and machine learning to find MND subgroups (869-791)		**Therapeutic targets**
Lead investigator	Dr Alfredo Iacoangeli	
Lead institution	King's College London	
Co-investigators	Prof Ammar Al-Chalabi and Prof Richard Dobson	
Cost: £166,384	**Type of grant:** Project grant (Biomedical)	October 2019 - March 2025

Current classifications of MND do not readily translate to relevant subgroups for treatment, nor do they reliably predict clinically important factors like survival. Machine learning is a method to use computers to find patterns in data. A particular form of machine learning, latent class cluster analysis, was previously applied to clinical information from neurologists and showed that MND can be considered as five subtypes. These subtypes strongly predicted survival, and more recently were the basis of a genetic study that found two genes that predict disease progression rate. Biological information can now be used to refine the subgrouping further to find new subtypes of MND for personalised medicine.

Identifying the early biochemical signature of MND (952-795)		**Therapeutic targets**
Lead investigator	Dr Alex Thompson	
Lead institution	University of Oxford	
Co-investigators	Prof Martin Turner, Prof Kevin Talbot and Prof Huw Morris	
Cost: £200,000	**Type of grant:** Clinical Research Fellowship	April 2020 - April 2025

The project will use disease models and post mortem tissue to study the genetic alterations that predispose people to MND in the years before symptoms begin (presymptomatic). By measuring the levels of thousands of proteins in cerebrospinal fluid (the fluid closest to the cells affected by MND) Dr Thompson aims to detect MND-related changes occurring in the nervous system long before the start of MND symptoms. This will hopefully shed light on the mechanisms that lead to the development of MND, paving the way for new therapies. It may also help to develop ways of predicting when MND will begin in order to allow earlier treatment of MND, even before symptoms develop. Although the study focuses on gene carriers, its findings are likely to be applicable to sporadic ALS.

The Lady Edith Wolfson Fellowship Programme
Supported by the Freshfield Foundation

Understanding the role of FUS and RNA binding proteins in MND (976-799) **A**		**Therapeutic targets**
Lead investigator	Dr Nicol Birsa	
Lead institution	University College London	
Co-investigators	Prof Pietro Fratta and Prof Jernej Ule	
Cost: £269,943	**Type of grant:** Non-clinical fellowship (Senior)	September 2022 - August 2025

FUS is a protein that regulates the production of other proteins and is known to be dysfunctional in MND. This project aims to understand how the disruptions to protein production caused by FUS alter the function of nerve cells and their connection to muscles. Once it is understood how nerve cells are damaged, the project will move on to investigating if it is possible to correct this damage. Understanding the changes to nerve cells in MND is crucial to designing new and effective treatments.

Investigating Dipeptide-Repeat Protein toxicity in C9orf72-related MND (906-792) **A**		**Therapeutic targets**
Lead investigator	Dr Ryan West	
Lead institution	University of Sheffield	
Co-investigators	Prof Kurt De Vos and Charlotte Gale (PhD Student)	
Cost: £93,409	**Type of grant:** PhD Studenship	October 2022 - September 2025

Mutations in the C9orf72 gene are the most common genetic cause of MND and lead to the production of 5 toxic proteins called dipeptide repeat proteins (DPR's) , which accumulate in neurons. It has previously been found that two of these five DPRs cause the structural framework that gives a cell structure and shape (cytoskeleton), to become disorganised. Using fruit fly models of C9orf72 MND, this project aims to investigate the theory that some DPR's bind to proteins involved in regulating the cytoskeleton and cause them to stick together in clumps in the cell. This may cause disorganisation of the cytoskeleton in nerve cells and lead to neurodegeneration. It will use drug-screening facilities to screen existing drugs which are known to stabilise the cytoskeleton as potential therapeutic treatments for MND. In addition to identifying potential drugs for the treatment of MND this study will also help unravel biological mechanisms underpinning the disease.

Cystatin C in human MND (907-792)		**Therapeutic targets**
Lead investigator	Dr Robin Highley	
Lead institution	University of Sheffield	
Co-investigators	Prof Kurt De Vos and Sarah Granger (PhD Student)	
Cost: £93,547	**Type of grant:** PhD Studentship	October 2022 - September 2025

Two types of abnormal protein clumps have been identified in MND. While TDP-43 clumps have been studied extensively, protein clumps known as Bunina bodies are less understood. These clumps are composed of a protein known as cystatin C (hCC) which plays a key role in autophagy (a mechanism used to remove faulty proteins). hCC dysfunction is likely to cause autophagy failure and thus TDP-43 clumps and cell dysfunction. This project aims to better understand the role of hCC/Bunina bodies in our brains in MND and how hCC may impact TDP-43 clump formation and autophagy. If these disease mechanisms can be understood, researchers will gain a better understanding of ways to potentially stop or slow the disease process.

Targeting MND-dysregulated microRNAs in astrocytes (905-792) **A**		**Therapeutic targets**
Lead investigator	Prof Rob Layfield	
Lead institution	University of Nottingham	
Co-investigators	Dr Daniel Scott, Dr Federico Dajas-Bailador, Dr Sebastian Serres and Dr David Boocock	
Cost: £93,570	**Type of grant:** PhD Studentship	October 2022 - September 2025

Astrocytes are cells within the nervous system that serve to 'protect' neurones and keep them healthy. In MND, this protection can be reduced due to the malfunction of a protein called Nrf2. In some cases of MND, malfunction of another critical protein called TBK1 can exaggerate this effect, ultimately leading to motor neurone death. miR-340 is a naturally occurring biomolecule which has the potential to control levels of both these proteins in human cells. The aim of this project is to establish highly sensitive analytical methods to allow measurement of levels of Nrf2, TBK1 and more than 100 other MND-associated proteins in different biological samples. The project will then compare protein levels between human astrocytes and motor neurones and their changes when miR-340 are added to cells. These findings will underpin experiments that explore the therapeutic potential of blocking miR-340 in human astrocytes which are predicted to increase levels of Nrf2 and TBK1 proteins, making astrocytes more protective and increasing motor neurone survival.

Molecular mechanisms of TDP-43 in MND (904-792) **A**		**Therapeutic targets**
Lead investigator	Dr Frank Hirth	
Lead institution	Kings College London	
Co-investigators	TBC	
Cost: £104,726	**Type of grant:** PhD Studenship	October 2022 - September 2025

One of the key features in almost all cases of MND, including the most common genetic form related to changes to the C9orf72 gene, is the accumulation of a protein called TDP-43 in the nerve cells of the brain and the spinal cord. Recent research investigating the early changes caused by TDP-43 and C9orf72 found that the activation of an immune response pathway is harmful. This studentship aims to test the hypothesis that this pathway is a characteristic of the pre-symptomatic (has the disease but is not showing any symptoms) phase of MND which then leads to the onset and progression of the disease. Further understanding of mechanisms underlying the early events that affect TDP-43 will help develop new strategies for targeted and lasting treatment of MND.

Developing a AAV-GRN gene therapy for MND (903-792) **A**		**Therapeutic targets**
Lead investigator	Dr Younbok Lee	
Lead institution	King's College London	
Co-investigators	Prof Chris Shaw	
Cost: £104,744	**Type of grant:** PhD Studentship	October 2022 - September 2025
To cure motor neuron disease, it is essential to first understand which neural mechanisms are altered in the brain or spinal cord. Progranulin (PGRN) is glycoprotein secreted by cells in the brain which plays a key role in the lysosome (breaks down cells and removes waste). Defects in lysosomes could lead to the build-up of pathogenic TDP-43 seen in many cases of MND. The aim of this project is to characterise the role of each of the 8 GRNs (which make up PGRN) and identify which GRNs are protective against lysosomal defects and neuronal death. Any protective GRNs will then be used in a type of gene therapy and tested as a therapeutic strategy in animal models of MND.		

Supported by the UK Government BEIS/DH Medical Research Charity Support Fund
In December 2021, 82 medical research charities across the UK, including the MND Association, were awarded support from a new government fund called the UK Government BEIS/DH Medical Research Charity Support Fund. The fund aims to help charities to continue to support the work of Early-Career Researchers, despite the effects of the COVID pandemic, and enabling them to become the next generation of research leaders. The projects marked with an asterisk (*) in this research theme are being supported by this fund.

Developing strategies to promote muscle reinnervation in MND (965-799) **A**		**Treatment pipeline**
Lead investigator	Dr Barney Bryson	
Lead institution	University College London	
Co-investigators	Prof Linda Greensmith and Prof Giampietro Schiavo	
Cost: £286,079	**Type of grant:** Non-Clinical Fellowship (Senior)	August 2017 - July 2022

This project uses stem cells from mice transformed into motor neurons which will be used to create new muscle neuron connections. These will be implanted back into the mice and observed for how well the neurons connect with muscles. The researchers will then identify the chemicals that promote successful innervation. This study has the potential to contribute to the development of a new therapy by replacing damaged motor neurons and restoring lost muscle function.

The Lady Edith Wolfson Fellowship Programme

Lighthouse 2 and TRICALS clinical trials (947-793)		**Treatment pipeline**
Lead investigator	Prof Ammar Al-Chalabi	
Lead institution	Kings College London	
Cost: £43,645	**Type of grant:** Small grant (Clinical)	November 2021 - October 2022

Clinical trials are vitally important when investigating potential treatments for the MND community. However, running these trials can be time-intensive and requires nurses/clinical studies officers. This small grant will help to fund a nurse/clinical studies officer for a year at King's College London, for use in the Lighthouse 2, a phase 3 clinical trial investigating the use of Triumeq (an antitretroviral) in people with MND. The nurse/clinical studies officer will also help with TRICALS, a European clinical trials platform designed to accelerate the process of carrying out phase 2/3 trials in MND. This recruitment will provide a necessary additional resource, allowing for these trials to run and improving the ability of the trial centre to open more trials.

PRELUDE (Personalised treatment with Lithium Carbonate for Unc13a Determined MND) trial (80-110-950)		**Treatment pipeline**
Lead investigator	Prof Ammar Al-Chalabi	
Lead institution	King's College London	
Co-investigators	Dr Michael van Es and Prof Matthew Kiernan	
Cost: £519,665	**Type of grant:** Project grant (Healthcare)	July 2020 - July 2024

PRELUDE (Personalised treatment with Lithium Carbonate for Unc13a Determined MND) is a major new international, multi-centre, phase III clinical trial to investigate the effect of lithium carbonate on survival in MND patients carrying a specific mutation in a gene called Unc13a. Multiple centres from across the UK (led by Prof Ammar Al-Chalabi at King's College London), Europe and Australia will participate. If successful, this trial could provide an effective new treatment to one in every six people with MND. The trial is expected to begin in 2021.

Supported by the Greendale Charitable Foundation, the Payne-Gallwey Charitable Trust and MND Association Branches and Groups

Development of an SRSF1-targeted gene therapy for C9orf72 MND/FTD (878-791) **A**		**Treatment pipeline**
Lead investigator	Dr Guillaume Hautbergue	
Lead institution	University of Sheffield	
Co-investigators	Prof Mimoun Azzouz and Prof Dame Pamela Shaw	
Cost: £50,000	**Type of grant:** Project grant (Biomedical- LifeArc)	August 2021- July 2024
Mutations in the C9orf72 gene lead to repeated sections within the RNA (instructions the cell uses to make the protein) and these faulty pieces of RNA are transported out of the nucleus of the cell and into the cytoplasm. A protein called SRSF1 is involved in the transport of the RNA to the cytoplasm, where toxic proteins called dipeptide repeat proteins (DPR's) are made from the faulty RNA. Previous research has shown that reducing the amount of SRSF1 protein in the cells inhibits the movement of the repeated sections of RNA from the nucleus and prevents the DPR's from being made. This project will further develop a novel gene-therapy which has already shown promise in animal models of MND. This study aims to gather more data on the new gene therapy, including the best route of delivery of the therapy, the dose needed to lead to maximum beneficial effects and long-term effects of the therapy in mice. This additional data could be used to apply for a clinical trial of the gene therapy in the future.		

Development of RAR class ligands for treatment of MND (882-791) **A**		**Treatment pipeline**
Lead investigator	Prof Peter McCaffery	
Lead institution	University of Aberdeen	
Co-investigators	Dr Guy Bewick, Dr Iain Greig and Victoria Gorberg	
Cost: £241,796	**Type of grant:** Project grant (Biomedical)	April 2022 - March 2025
Deficiency of the retinoic acid receptor (RAR) system, that occurs in the central nervous system, has been thought to be a signature of MND. A group of drugs have been developed called "dual potency retinoids" (RAR-Ms) which can help restore RAR function and have the potential to reverse abnormalities caused by SOD1 and C9orf72 mutations. This project will take selected RAR-Ms through pre-clinical trials (laboratory tests prior to testing in humans) to determine their potential to treat MND.		

Clinical progression

A new strategy for clinical trials and personalised therapy in MND (870-791)		**Clinical progression**
Lead investigator	Prof Ammar Al-Chalabi	
Lead institution	King's College London	
Co-investigators	Dr Ahmad Al Khleifat	
Cost: £119,767	**Type of grant:** Project grant (Biomedical)	August 2019 - January 2022

Analysis of MND clinical trial data generally assumes it is one disease, rather than multiple diseases representing different underlying pathologies, but knowing how to subgroup patients for targeted trials is essential. Imaging based subgrouping methods such as brain scanning do not exist, and subgrouping based on disease hallmarks from brain and spinal cord tissue is not feasible while the affected person is alive. The purpose of this project is to generate a DNA fingerprint for each person in an ongoing clinical trial 'MIROCALS' to understand why some people are likely to respond to treatment and others are not. The analysis will also extend to the biggest MND genetic project in the world (Project MinE) to ensure observations are not biased.

Factors influencing MND disease course - establishing a TONiC-MND bioresource (991-797)		**Clinical progression**
Lead investigator	Prof Carolyn Young	
Lead institution	Walton Centre for Neurology and Neurosurgery	
Co-investigators	Dr Roger Mills, Prof John Quinn, Prof Ammar Al-Chalabi, Prof Andrea Malaspina	
Cost: £30,000	**Type of grant:** Small grant (Biomedical)	May 2021 - April 2022

The aim of this project is to establish a repository of biosamples for a large cohort of people with MND, by using participants in an already established research study (TONiC). TONiC is the largest study of factors influencing quality of life. The study collects a significant amount of data, including MND symptoms and quality of life, which can be used to provide information about the progression (clinical stage) of the disease. This information, along with the collected biosamples will help to identify disease biomarkers (indicator of disease) and therapeutic targets.

Supported by the Freshfield Foundation and the Wirral MND Association Group

Measuring cognitive and behavioural impairment in MND-FTD (892-792)		**Clinical progression**
Lead investigator	Prof Laura Goldstein	
Lead institution	King's College London	
Co-investigators	Prof Ammar Al-Chalabi, Dr Silia Vitoratou and Lyndsay Didcote (PhD student)	
Cost: £100,074	**Type of grant:** PhD Studentship	October 2018 - June 2022

Assessment of changes in thinking and behaviour in people with MND is done using screening tools which offer a fast evaluation in the clinic. Due to the variety of tests there are and their different rules and criteria, various conclusions might be drawn from the different tests, potentially leading to people with MND being offered inadequate care. This project will compare different screening tools and see how they agree in terms of diagnosing behavioural and cognitive change in people with MND. Findings from this project will inform clinicians and researchers about the implications of using different measures.

Clinical progression

Determining the gut microbiota in early MND patients (860-791)		**Clinical progression**
Lead investigator	Dr Nikhil Sharma	
Lead institution	University College London	
Co-investigators	Prof Pietro Fratta, Prof Andrea Malaspina, Dr Jane Macnaughtan, Dr Vincenzo Libri and Dr Ian Jeffery	
Cost: £100,015	**Type of grant:** Project grant (Biomedical)	August 2019 - July 2022

It has recently been discovered that a functional link exists between the brain and microbes in the gut (microbiota). As microbiota have the ability to control immune cells in the brain (microglia) and the intestines, they have the potential to regulate cellular inflammation. Therefore, it is possible that manipulating the microbiome of people with MND might lead to reduction of inflammation in the central nervous system. This project will explore the association between the microglia and microbiome to establish it as a potential route for therapy.

Supported by MND Association Branches and Groups

A Multicentre Biomarker Resource Strategy in ALS: AMBRoSIA (972-797)		**Clinical progression**
Lead investigator	Prof Martin Turner	
Lead institution	University of Oxford	
Co-investigators	Prof Andrea Malaspina, Prof Dame Pamela Shaw, Dr Jennifer Davies and Dr Trong Khoa Pham	
Cost: £2,102,701	**Type of grant:** Project grant (Biomedical)	August 2016 - December 2022

This project will collect blood, urine and skin cells from 900 people with MND and over 400 people without the disease. The blood and urine samples will be subjected to an extensive analysis to search for MND biomarkers. Skin cells can be reprogrammed into motor neurons using iPSC technology. These are used to test the effects of new drugs on motor neurons. It also allows researchers to explore the possibility that different drugs may work for different subtypes of MND. The extensive collection of samples will also act as a resource for future research.

Supported by The Linbury Trust in memory of Annette Page, prima ballerina, the London City Swim Foundation, and the PF Charitable Trust

Predicting disease course in the C9orf72 BAC mouse model of MND (871-791) **A**		**Clinical progression**
Lead investigator	Dr James Alix	
Lead institution	University of Sheffield	
Co-investigators	Dr Johnathon Cooper-Knock, Dr Richard Mead, Prof Visakan Kadirkamanathan, Dr John Day and Sophie Badger	
Cost: £220,001	**Type of grant:** Project grant (Biomedical)	October 2019 - December 2022

An extremely valuable mouse model has been developed to display many of the hallmarks of the human condition, including its unpredictability. This project will examine the mice in detail using a variety of tests that look at how different parts of the brain and spinal cord work. Advanced mathematical methods will be used to develop a way to detect when the disease starts and predict how it is going to progress. The results will enable scientists to better understand the disease and how it develops to enable better research studies to be designed and develop new treatments.

Supported by MND Association Branches and Groups

Clinical progression

NECTAR - Screening component of AMBRoSIA (974-797)		**Clinical progression**
Lead investigator	Prof Janine Kirby and Prof Pietro Fratta	
Lead institution	University of Sheffield & University College London	
Cost: £382,000	**Type of grant:** Project grant (Biomedical)	November 2016 - January 2023
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.		

Developing MND prognostic biomarkers based on brain function (972-799)		**Clinical progression**
Lead investigator	Dr Roisin McMackin	
Lead institution	Trinity College Dublin	
Co-investigators	Prof Orla Hardiman, Prof Richard Carson and Dr Bahman Nasseroleslami	
Cost: £149,052	**Type of grant:** Non-Clinical Fellowship (Junior)	April 2021 - March 2023
MND affects each patient in a different way, with symptoms emerging and progressing at highly variable, unpredictable rates. Therefore, some treatments may work in subsets of MND patients but not in others. It is now established that patients often experience cognitive and behavioural problems. The aim of this project is to develop ways to measure brain function changes that can predict patient symptoms and improve understanding of the biology of why MND has different effects on different people. This will be conducted by measuring how well the brain and spinal cord are functioning over time, while profiling movement and non-movement symptoms in a large group of patients. By identifying patterns of dysfunction, patients will be categorised into subgroups with similar prognosis then tested if these measures can predict individual patients' symptoms in future. This is expected to facilitate earlier, more informative diagnoses for patients and improve detection of effective therapies in clinical trials. ***The Lady Edith Wolfson Fellowship Programme***		

Risk variants and genetic architecture of MND (879-971)		**Clinical progression**
Lead investigator	Dr Russell McLaughlin	
Lead institution	Trinity College Dublin	
Co-investigators	Ross Byrne	
Cost: £155,811	**Type of grant:** Project grant (Biomedical)	September 2021 - August 2023
This project aims to reanalyse datasets of over 150,000 MND patients and healthy subjects to address three important components of MND risk (factors that impact whether you will be diagnosed with MND) which have not been thoroughly investigated. The components of risk to be investigated are sex-specific genetic factors, population-specific genetic risk factors and overlap of genetic risk between MND and other neurological diseases. Acknowledging the genetic complexity of MND will help to better understand mechanisms involved in disease risk and is central to developing effective therapies and genetic counselling strategies.		

Advancing therapy development in MND - Martin Turner Professorship (989-797)		**Clinical progression**
Lead investigator	Prof Martin Turner	
Lead institution	University of Oxford	
Cost: £1,000,000	**Type of grant:** Project grant (Biomedical)	December 2018 - November 2023
This 5-year plan offers an important advance in understanding the core systems-level neurobiology of MND. For a multi-factorial, complex disorder of cortical dysfunction, it is clear that combinations of biomarkers are needed. Neuroimaging is a leading approach to develop more sensitive trial outcome measures, with the added value of biofluid analysis to clarify clinical variation. The aim of this professorship is to exploit the unique insights of neuroimaging, integrated with targeted analysis of cerebrospinal fluid (CSF), to develop sensitive outcome measures for the therapeutic era in MND.		

A whole-genome sequencing approach to advance precision medicine and study patient subgroups in MND (946-793)		**Clinical progression**
Lead investigator	Dr Alfredo Iacoangeli	
Lead institution	King's College London	
Co-investigators	Prof Ammar Al-Chalabi	
Cost: £15,000	**Type of grant:** Small grant (Biomedical)	October 2020 - March 2024
Sequencing of the whole genome (the complete set of genes/genetic material in an organism) is now relatively cheap and quick, which has resulted in sequencing the genome of over 10,000 people with MND and healthy controls. This small grant will help fund a PhD studentship alongside a pharmaceutical company and King's College London, which will help to exploit the potentials of whole genome sequencing in MND. It is hoped that understanding the genetic variant types/factors underlying MND will help to identify subgroups with more similar genetic causes and clinical outcomes that can then be translated to a more personalised approach to care and treatment.		

Reclassifying MND/FTD subgroups using next-generation diagnostics (975-799)		**Clinical progression**
Lead investigator	Dr Ahmad Al Khleifat	
Lead institution	King's College London	
Co-investigators	Prof Ammar Al-Chalabi	
Cost: £131,999	**Type of grant:** Non-clinical Fellowship (Junior)	January 2022 - March 2024
Currently, we do not know the best way to subgroup and classify neurodegenerative diseases since overlapping disease mechanisms are often not taken into account. Reclassifying these diseases will allow for the best targeted therapeutic approaches and potential treatments. This project involves reclassifying these diseases based on a combination of biological measures. This will include genetic profile, epigenetics (a system controlling whether genes are switched on or off) and the level of a nerve protein found in the blood called neurofilament. The variations of these three areas will be analysed for both MND and Frontotemporal dementia (FTD) and machine learning will then be used to find patterns that correspond to different subgroups. If this allows for the formation of new subgroups, these can be used group people together for clinical trials and to understand the underlying biology of the conditions.		

The Lady Edith Wolfson Fellowship Programme

Clinical progression

Identification of non-coding RNA biomarkers for disease prognosis and progression in MND (880-791)		**Clinical progression**
Lead investigator	Prof Majid Hafezparast	
Lead institution	University of Sussex	
Co-investigators	Dr Andre Altmann, Prof Nigel Leigh, Dr Greig Joilin	
Cost: £169,988	**Type of grant:** Project grant (Biomedical)	May 2022 - April 2024
Biomarkers (an indicator of disease) are important in helping to diagnose and track progression of MND. 7 non-coding RNA molecules (ncRNA), which can be found in the blood, have already been used to predict if a sample is from a person with MND. Currently, these ncRNAs cannot track the speed of progression. This project looks to identify ncRNA biomarkers that change over time so they can be used to both predict and track disease progression. This could allow the behaviour of MND to be predicted more accurately and aid in treatment development.		

Developing a home-based stimulation-free motor unit number estimate in MND (901-792)		**Clinical progression**
Lead investigator	Prof Chris Shaw	
Lead institution	King's College London	
Co-investigators	Dr James Bashford and Judith Bilgorai (PhD Student)	
Cost: £97,700	**Type of grant:** PhD Studentship	October 2021 - September 2024
This PhD studentship aims to develop and test a new and convenient way to regularly monitor patient neurodegeneration over long timeframes. The method will use non-invasive surface muscle recordings which will be used to analyse key features of neuromuscular activity and the number of functional neurons at a given time. For the first time, these assessments will be able to be made in patients' homes which will allow patients to be tested more frequently. This method will not only bring about a greater understanding of how neurons change over time but could provide researchers with a validated way of tracking improvements to new drugs in clinical trials. ***Supported by the Heaton-Ellis Trust***		

Neuroimaging and neurochemical biomarkers of brain ageing in MND (898-792)		**Clinical progression**
Lead investigator	Dr James Cole	
Lead institution	University College London	
Co-investigators	Prof Andrea Malaspina and Ayodeji Ijishakin (PhD Student)	
Cost: £79,780	**Type of grant:** PhD Studentship	October 2021 - September 2025
This project looks at the effects of MND on brain volume by using MRI scans. MRI scans of those with both fast and slow progressing forms of MND will be taken in order to determine a 'brain age' prediction for patients, these will be compared to MRI scans of healthy individuals (controls). This study aims to develop a neuroimaging MND database and enable a new clinical approach to disease classification and prognosis. The study will also assess blood biomarkers known as neurofilaments which are released into the blood and CSF upon neuron damage, and their concentration increases with brain age. This will act as a secondary measure for the predicted 'brain age' of those with MND. The study could lead to neuroimaging and blood neurofilament levels being used in combination to act as biomarkers of MND and allow more accurate disease classification to be established.		

Developing Motor Unit MRI as a diagnostic tool for motor neuron diseases (902-792)		**Clinical progression**
Lead investigator	Prof Andrew Blamire	
Lead institution	University of Newcastle	
Co-investigators	Prof Roger Whittaker and Dr Yujiang Wang	
Cost: £94,500	**Type of grant:** PhD Studentship	September 2022- September 2025
There is an urgent need for new diagnostic strategies for MND. For decades, the time from symptom onset to diagnosis has remained largely unchanged, preventing early access to treatment. This studentship will make developments to a new type of MRI scan called motor unit MRI (MUMRI). The scan can take images of multiple muscles simultaneously across the whole limb and identify the motor units (MU), structures composed of motor nerves and muscle fibres which control muscle movement. Crucially, this takes only 3 minutes, is entirely non-invasive, pain-free and has the potential to automatically measure abnormalities in muscles inaccessible to needle electromyography (current diagnosis strategy). The study will test MUMRI in MND patients to determine the diagnostic value. The methods developed in this studentship will directly contribute to the design of a large scale MUMRI trial for the diagnosis of MND which will be the next step towards adoption of the method into routine clinical use.		

Web-based psychological intervention to reduce distress in MND (891-792)		**Standards of care**
Lead investigator	Prof Lucy Yardley	
Lead institution	University of Southampton	
Co-investigators	Dr Laura Dennison, Dr Adam Geraghty and Cathryn Pinto (PhD student)	
Cost: £79,612	**Type of grant:** PhD Studentship	October 2018 - March 2022

Emotional distress often leads to poor quality of life and potentially a poor prognosis. To support people with MND and their carers who are going through a great deal of emotional distress, this project aims to review existing therapy interventions and create an internet-based therapy intervention. As these interventions are web-based, they would be more practical for people with MND as they can access them from home.

Supported by the Isle of Wight and East Dorset and New Forest MND Association Branches

A prospective observation of secretion problems in MND (ProSec) (960-794)		**Standards of care**
Lead investigator	Prof Chris McDermott	
Lead institution	University of Sheffield	
Co-investigators	Prof Stephen Walters and Dr Sarah Boddy	
Cost: £124,728	**Type of grant:** Project grant (Healthcare - Marie Curie)	July 2017 - June 2022

As many as half of people with MND may have problems with excess saliva and for most of those, the symptom is not well managed. This project will be collecting information on how excess saliva is treated and how well the treatment worked. The need for more research into the management of excess saliva was highlighted by the MND NICE guideline and a recent research priority setting exercise.

Supported by the Jersey MND Association Branch

Developing a web-based decision aid for gastrostomy in MND (963-794)		**Standards of care**
Lead investigator	Dr Sally Wheelwright	
Lead institution	University of Southampton	
Co-investigators	Dr Anne Hogden, Dr Alejandra Recio-Saucedo, Prof Claire Foster, Prof Karen Morrison, Dr Sophia Taylor and Prof Chris McDermott	
Cost: £94,576	**Type of grant:** Project grant (Healthcare - Marie Curie)	December 2018 - June 2022

Gastrostomy is offered to people with MND as a palliative care intervention when weight loss becomes problematic, with the assumption that it is the best method to provide long-term nutritional support. However, there is currently little evidence on increased survival, and the impact on patient and carer quality of life. As the decision about whether to undergo gastrostomy is a difficult one, this project aims to support this decision-making process by developing a patient decision aid.

Supported by MND Association Branches and Groups

Understanding experiences of inherited MND to develop Healthtalk (941-794)		**Standards of care**
Lead investigator	Prof Louise Locock	
Lead institution	University of Aberdeen	
Co-investigators	Prof Martin Turner, Prof Sue Ziebland, Adam Barnett, Ruth Sanders and Jade Howard	
Cost: £51,123	**Type of grant:** Project grant (Healthcare)	October 2019 - July 2022

This study will interview families affected by inherited forms of MND to help build a new section on the research-based website "Healthtalk". The interview will include investigating how families make decisions around issues including predictive genetic testing and reproductive choices, how families communicate around the disease, and how they deal with genetic information. The resource will be a lasting source of information used to help support families affected by inherited MND, others going through similar experiences, and help train doctors, nurses, GPs and other health professionals to understand inherited MND.

Supported by the Grace Trust and the Oakdale Trust

Evaluation of post-gastrostomy management in MND (PostGas) (935-794)		**Standards of care**
Lead investigator	Prof Chris McDermott	
Lead institution	University of Sheffield	
Co-investigators	Dr Harris Stavroulakis and Dr Sarah Boddy	
Cost: £208,308	**Type of grant:** Project grant (Healthcare)	June 2017 - October 2022

Gastrostomy was found to be an effective way to manage malnutrition and resulting weight loss. However, research suggested that lack of information on nutrition after gastrostomy leads to continuing weight loss. This study will review current practices of post-gastrostomy nutritional care and explore reasons why some patients continue to lose weight after gastrostomy. This study is a continuation of the ProGas project, investigating the best gastrostomy methods in MND.

Supported by the Holbeck Charitable Trust and the Hamamelis Trust

Practical management of cognitive symptoms in MND - MiND Toolkit (934-794)		**Standards of care**
Lead investigator	Prof Eneida Mioshi	
Lead institution	University of East Anglia	
Co-investigators	Prof Michael Hornberger, Prof Lee Shepstone, Dr Godwin Mamutse and Dr Ratko Radakovic	
Cost: £300,697	**Type of grant:** Project grant (Healthcare)	May 2017- December 2022

This project aims to develop a new toolkit to help patients and their carers to deal with behavioural and cognitive symptoms, including general loss of interest and empathy. The toolkit will be based on input from MND patients and their carers and subjected to clinicians' use in practice. The final step of this project is to create a set of guidelines to act as an official document helping patients, carers and professionals to manage behavioural and cognitive changes in MND.

Supported by the Stanley Grundy Foundation, the Leslie Mary Carter Charitable Trust and the John Jarrold Trust

UK MND Clinical Studies Group Co-ordinator (942-794)		**Standards of care**
Lead investigator	Prof Chris McDermott	
Lead institution	University of Sheffield	
Co-investigators	Stacy Young	
Cost: £54,789	**Type of grant:** Project grant (Healthcare)	January 2021 - December 2022

This grant covers continued funding for a MND Speciality Coordinator who supports the UK Motor Neurone Disease Clinical Studies Group. The group consists of neurologists, palliative care specialists, patients, carers and other healthcare professionals interested in MND clinical research. They work to increase the number of studies for people with MND to participate in across the UK. The coordinator ensures that eligible studies are included on the UK Clinical Research Network portfolio and that studies have access to support, enabling them to recruit and deliver their research effectively. The COVID-19 pandemic has had a huge impact on MND clinical research so the coordinator role will be essential in getting things up and running again and helping researchers adapt to the new ways of working that will be needed post pandemic.

Who am I? Does spirituality enhance resilience amongst MND carers (938-793)		**Standards of care**
Lead investigator	Dr Belinda Hornby	
Lead institution	University of Central Lancashire	
Co-investigators	Prof Nicola Graham-Kevan and Emma Yates	
Cost: £2,000	**Type of grant:** Small grant (Healthcare)	April 2020 - March 2023

This study looks at the psychological impact of MND on carers; from diagnosis to the death of a loved one. Spirituality can be defined as 'personhood' and it is thought that traumatic life events, such as a loved one getting a diagnosis of MND, can cause changes to the carer's spirituality. It has been recognised by hospices that the patient and family require psychological support alongside the palliative end of life care. This study aims to assess the issues that MND carers are facing and how they might have an impact on their spirituality. There are two parts to this study; the first being a review of current research to establish a reliable summary of previous studies and the second part recruiting care givers of those with MND to be interviewed to determine how the issues they face may have an impact on their spirituality.

Understanding living with tracheostomy ventilation for MND (968-794)		**Standards of care**
Lead investigator	Dr Eleanor Wilson	
Lead institution	University of Nottingham	
Co-investigators	Prof Christina Faull and Johnathon Palmer	
Cost: £121,617	**Type of grant:** Project grant (Healthcare)	April 2022 - March 2024

Supporting breathing via a tube in the neck (Tracheostomy Ventilation – TV) is not often used by people living with MND in the UK when compared to other countries. This project aims to explore and better understand the realities of living with TV. This will be done by completing interviews about the experiences of daily living with people living with MND who have TV, family members and healthcare professionals. This project will help provide updated information for patients and families and may enable greater choice about their care. Additionally, it will help contribute to national guidance and training for healthcare professionals.

Testing an online peer-to-peer support programme for family caregivers (964-794)		**Standards of care**
Lead investigator	Prof Louise Rose	
Lead institution	King's College London	
Co-investigators	Dr Michelle Ramsay, Dr Anu Tandon, Prof Doug McKim, Trevor Murrells, Dr Esther Hobson, and Prof Chris McDermott	
Cost: £136,696	**Type of grant:** Project grant (Healthcare - Marie Curie)	November 2021 - October 2024

Family caregivers of those with MND can experience exceptional burden and significant decline in psychological wellbeing due to MND's profoundly debilitating effects and intensive support needs. Despite the recognised impact of caregiving, data about effective interventions that provide direct practical and psychosocial support is scarce. People who have experienced the same health problem and have similar characteristics (peers), can be a key source of emotional, informational, and affirmational support. Online peer support is a flexible, more accessible and low cost form of support. Although peer support programmes for family caregivers of people with MND exist, data about them is limited. Therefore, this study has developed an online peer support programme, completed usability testing and now will test its effectiveness on caregiver psychological wellbeing and caregiver burden.

Supported by MND Association Branches and Groups

The MND Register of England, Wales and Northern Ireland (965-794, 966-794)		**Standards of care**
Lead investigator	Prof Ammar Al-Chalabi & Prof Kevin Talbot	
Lead institution	King's College London & University of Oxford	
Cost: £541,968	**Type of grant:** Project grant (Healthcare)	January 2022 - December 2024

MND affects around 5,000 people in the UK at any one time, but the true figure is not known. The MND Register aims to capture this information across England, Wales and Northern Ireland. The number of people living with MND could give important clues to the cause of the disease and identify gene-environment interactions, and give us an accurate number of how many people within the UK are affected to help coordinate better care.

Supported by the Betty Messenger Charitable Foundation

Developing a patient decision aid to support genetic testing in MND (967-794)		**Standards of care**
Lead investigator	Dr Alisdair McNeill	
Lead institution	University of Sheffield	
Co-investigators	Prof Chris McDermott and Prof Hilary Bekker	
Cost: £169,614	**Type of grant:** Project grant (Healthcare)	April 2022 - March 2025

Mutations in genes (changes in the biological instruction) can alter the function of the gene and cause MND. These mutations can be hereditary, so can be passed on from parents to children. People with MND are not offered genetic testing as often as they could be. There are many benefits to having genetic testing, including being eligible to take part in a clinical trial for the specific gene mutation. The aim of this project is to develop a decision aid which highlights the pros and cons of genetic testing, allowing people to have informed discussions with doctors and make a decision that they are comfortable with. This aid aims to support doctors, people with MND and families and help improve access to genetic testing.

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Bold = Principal investigator; PhD = PhD student; CF = Clinical Research Fellow; NCF = Non-Clinical Fellow

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