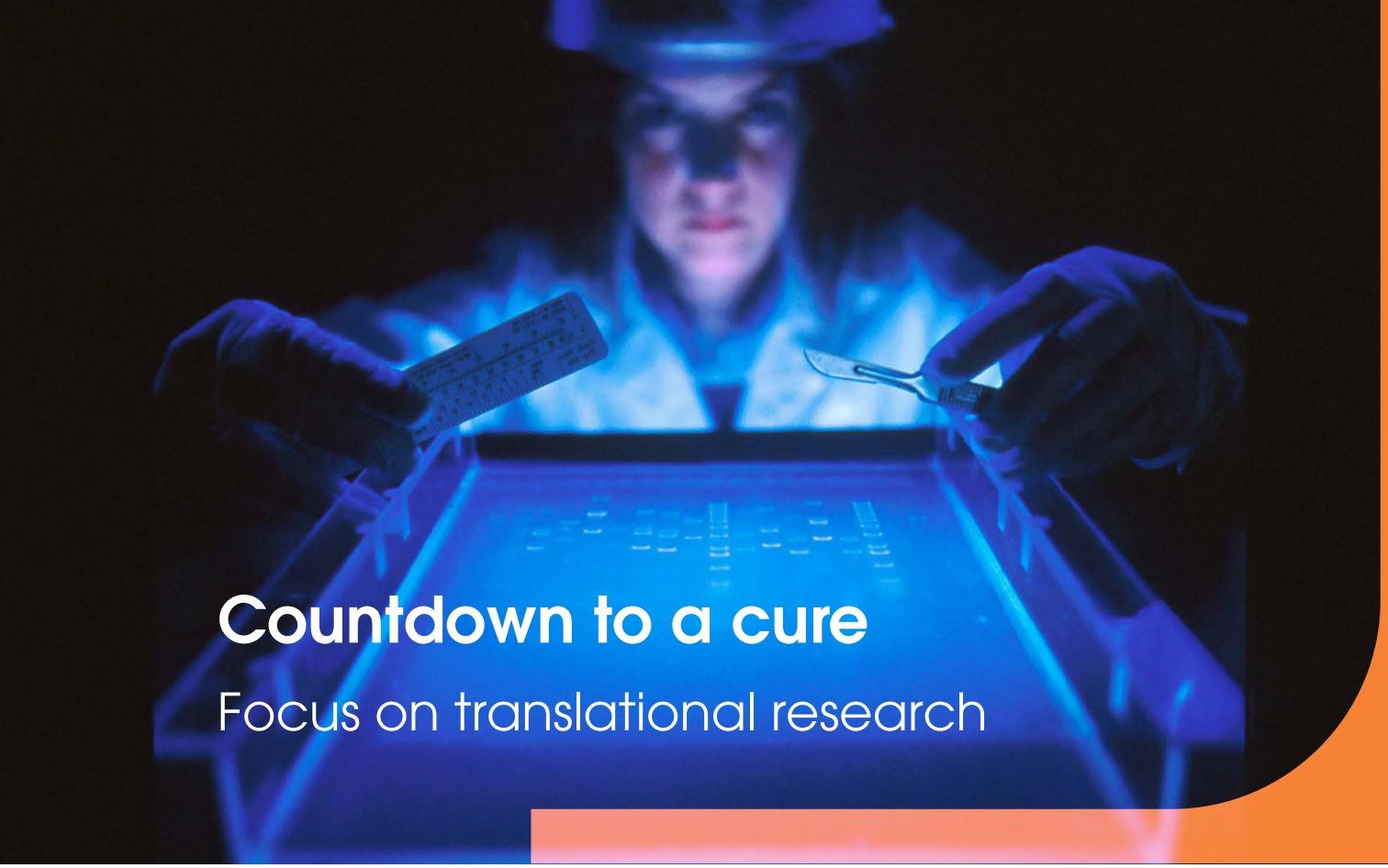
mnda
motor neurone disease
association

Countdown to a cure

How translational research is helping the MND Association to fight MND



Countdown to a cure

Focus on translational research

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"*Countdown to a cure* is a showcase of the innovative research we are funding, the international expert researchers whose careers we help develop to keep the expertise in the field of MND research..."

Dr Brian Dickie MBE, MND Association

Foreword

The MND Association funded its first research project in 1980, and our commitment to research has grown ever since. The scale of our research has expanded vastly. But crucially, our scientific understanding of MND means our focus is shifting - from what causes MND, to what we can do about it.

The path from bench work in the lab to approved prescription medicine is long, challenging, and incredibly expensive. It costs smaller research charities a lot of money to sponsor research. Due to the huge cost of drug development and clinical trials it is important to provide robust scientific evidence to encourage industry to invest in MND.

In the last few decades, research has revealed MND is a complex disease. As a result, we are seeing a wide range of new potential opportunities to treatment emerging from the lab, aimed at tackling MND in different ways. This provides opportunities to identify 'low risk, high return' approaches, such as finding treatments for types of MND caused by specific genetic mutations, to encourage industry to invest into MND research.

Countdown to a cure showcases the innovative research we fund, the international expert researchers whose careers we develop, and our investment in new and better ways to carry out clinical trials. It reflects our research strategy that has evolved to integrate new approaches made possible with advances in technology and milestone discoveries, taking what we have learned so far about what causes MND and translating it into potential treatments. We can be cautiously optimistic and hopeful about the future.

Partnerships are crucial to our strategy, joining up the scientific community and the various funders who invest in MND research. We are increasingly seeing examples of collaboration between various funders, streamlining research into large initiatives bringing together expertise within the UK and internationally.

On behalf of the Association, I would like to thank all the donors, funders and partners who have contributed to and supported our research. Your support and partnership for the future is vital. Together, we share common ground to understand, treat and – ultimately – defeat MND.

Dr Brian Dickie MBE, MND Association

July 2024

Our translational research programme

Translational research: new ways to tackle MND

A major challenge in MND research lies in the disconnect between basic research (discovery science) carried out in the labs to better understand the disease, and bringing pre-clinical findings into clinical development. This crucial stage is where new treatment development often fails. One of the ways **translational research** tackles this issue is by integrating clinical knowledge and advances in technology at an early stage in the drug development pathway.

Translational research frequently involves a team with multidisciplinary expertise working together, including chemists, bioinformaticians, lab researchers, and healthcare professionals. An overview of the drug development process, and how translational components link the stages together, is shown in the infographic below.

The UK is a leader in MND research, as demonstrated by the continued interest from leading pharmaceutical companies, investment by the government, and the recent initiation of the UK MND Research Institute (see feature on page 15). This positions the MND Association well as a facilitator of groundbreaking research within a strengthening UK ecosystem in accordance with our own research strategy.

Due to recent successes in translational research, MND is rapidly becoming a disease area attracting more funding. In 2021, the medical research charity LifeArc announced a commitment of up to £100 million in funding towards neurodegenerative diseases; MND features heavily in the investment portfolio as the LifeArc 'MND translational challenge'. Shortly after, the patient-led campaign group **United To End MND** successfully campaigned for £50 million commitment from the UK government to accelerate the search for new treatments for MND.

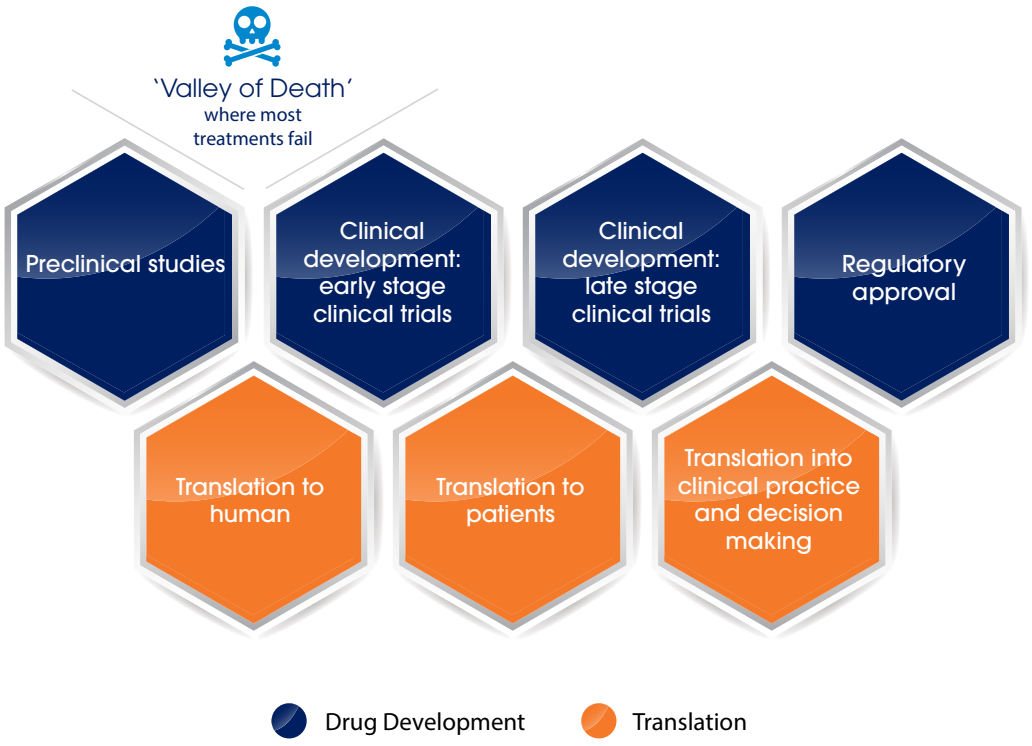
Today, the MND Association funds a range of translational research. To ensure this programme accelerates and yields new treatments, we are working together with numerous partners in the UK and across the world to pursue long-term multifaceted research initiatives, such as the **UK MND Research Institute, EXPERTS-ALS**, **TRICALS**, and **MND-SMART**. We will continue to focus on funding work to move research findings from the bench to the bedside'.

We are especially grateful for funds raised for translational research by Kevin Sinfield CBE and his team, through the 7in7in7 Challenge.

For more information, please contact Dr Sophie Nyberg, Research Programmes and Partnerships Manager, at sophie.nyberg@mndassociation.org

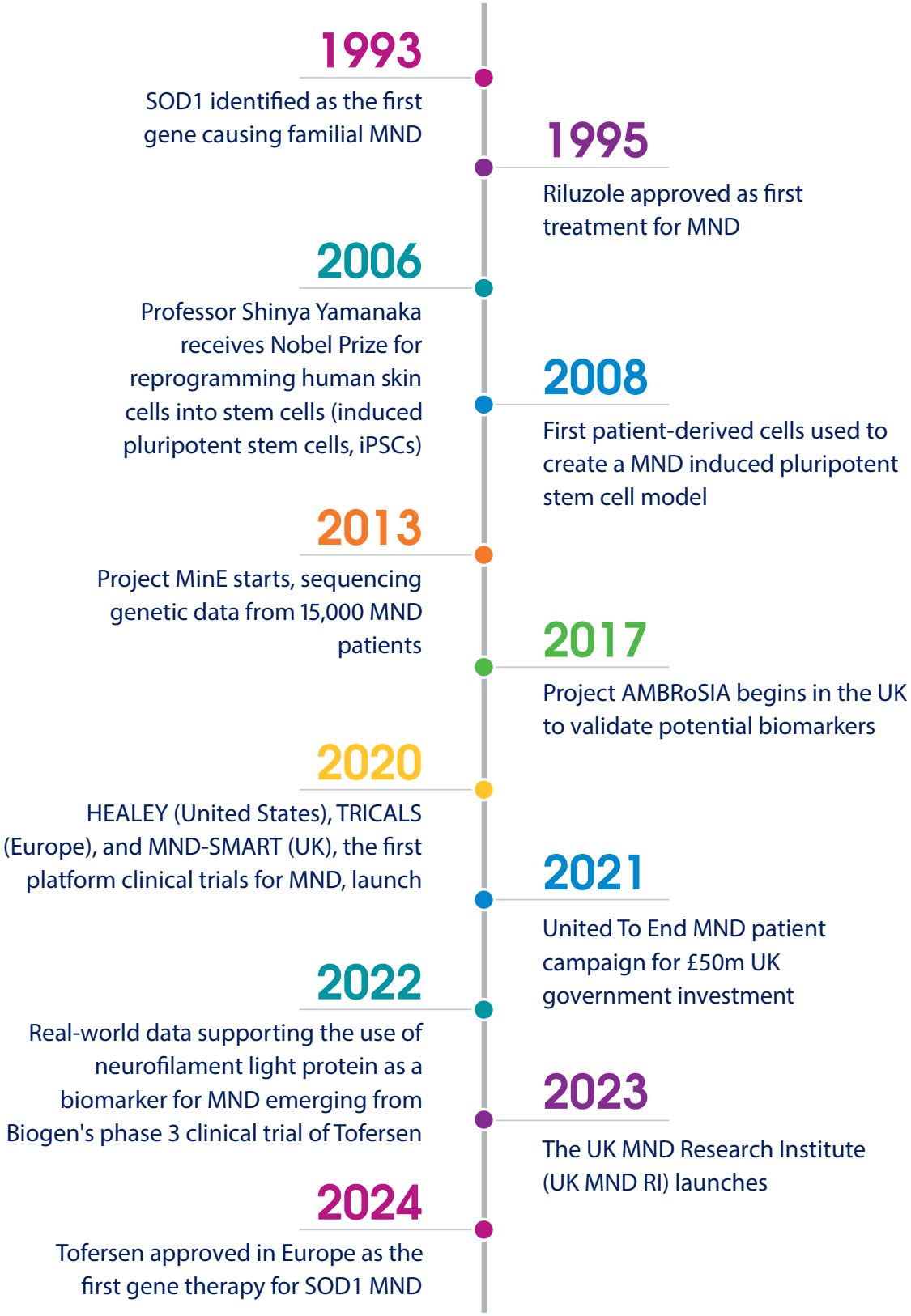
Translational research bridges the gap between laboratory-based research and the testing of potential therapies in clinical trials, aiming to move research ***'from bench to bedside'***.

Overview of the translational research pathway



MND research milestones driving translational research

A few highlights of historical milestones driving translational research in MND, in the UK and internationally.



Translational research we fund

The MND Association funds a variety of translational MND research. We work closely together with academics, industry partners and other charities.

As of 2024, we fund 6 large translational research projects in partnership with other organisations. Of these, three projects emerged from discoveries recently funded by the Association and another two from the original gene discoveries by Association funded scientists[1], illustrating the vital role of discovery science in generating new ideas for translation. We have also contributed £1 million towards the **UK MND Research Institute (UK MND RI)** (page 15) which has a strong translational focus.

1 FUS and TDP-43

MND Association, LifeArc and My Name'5 Doddie Foundation Translational Research Fund

In 2022, the MND Association announced a **Translational Research Fund** jointly with LifeArc and My Name'5 Doddie Foundation, funding projects to a total value of £1.5 million.

The funding call was opened to accelerate promising new treatments for MND that are on the translational pathway, from early drug discovery to pre-clinical validation and early stage (phase 1/2) clinical trials.

"People living with MND urgently need effective treatments to slow or stop progression of the disease. By joining forces, we have been able to create a unique fund that has supported these promising translational projects. This kind of funding is crucial to help us develop a pipeline of potential treatments and rigorously assess whether they hold potential for the treatment of MND."

Jessica Lee, Director of Research, My Name'5 Doddie Foundation

2023 MND Association research portfolio at a glance

109 grants

£20.7 million value

230 researchers

Including:

- **35** Biomedical Project grants
- **12** Healthcare Project grants
- **18** Small grants
- **24** Studentships
- **3** Clinical fellowships
- **13** Non-clinical fellowships
- **3** Pre-fellowships
- **1** Professorship
- **1** Special grant – UK MND Research Institute

Developing a cell therapy approach to restore lost muscle function in MND

In MND the connection between the brain and muscles is depleted as motor neurons die, eventually leading to muscle wasting and paralysis. **Dr Barney Bryson's** approach involves a unique strategy with the potential to restore paralysed muscles.

Neurons made from human stem cells are genetically modified to be activated by light, and then grafted into nerves close to the spinal cord to allow direct control over paralysed muscles where signals from the brain are blocked.

Dr Bryson's team at **University College London** has recently shown this approach works in a MND SOD1 mouse model. After making the neurons from stem cells, the neurons were transplanted into the mouse where they grew and connected with muscle cells. Neurons activated by light caused muscle contractions and prevented muscle wasting.

The findings could ultimately be developed into an assistive therapy in humans, controlled by Bluetooth and connected to a brain machine interface (BMI) to control muscles. More research is needed to confirm if this approach will work with human motor neurons.

Dr Barney Bryson, University College London

For more information read this academic paper: Bryson et al (2024), *eLife* 12:RP88250.

Co-funders: LifeArc, My Name's Doddie Foundation, mnda motor neurone disease association

Targeting TDP-43 dysfunction via UNC13A in sporadic MND and frontotemporal dementia

Professor Pietro Fratta, University College London

Dysfunction in the protein TDP-43 occurs in 97% of all MND cases. This suggests developing new therapies targeting TDP-43 may help a large proportion of people with MND.

Professor Pietro Fratta, based at the Institute of Neurology at **University College London**, is one of the recipients of the £1.5 million MND Translational Research Fund. Professor Fratta was awarded an MND Association **Lady Edith Wolfson Fellowship** in 2019.

The Translational Research Fund project involves developing new cutting-edge **antisense oligonucleotide (ASO) therapies** for MND. Antisense oligonucleotides are fragments of DNA that bind mRNA, leading to its destruction.

Professor Fratta's lab has shown that when TDP-43 alterations occur in MND, the gene UNC13A is incorrectly edited, which in turn leads to a reduction of this protein that is needed to keep neurons healthy. By making and testing ASOs to target this erratic gene editing event, the researchers believe levels of UNC13A can be restored to reduce TDP-43 dysfunction. The aim is to find the best ASO candidate that could be translated into human trials for treating TDP-43 related MND.

Co-funders: LifeArc, My Name's Doddie Foundation, mnda motor neurone disease association

Spotlight: An innovative gene therapy programme for *C9Orf72* mutations in MND

Professor Guillaume Hautbergue, in collaboration with **Professor Mimoun Azzouz** and **Professor Dame Pamela Shaw** at the **Sheffield Institute for Translational Neuroscience (SITraN)**, has been awarded a grant to carry out work on an innovative gene therapy programme in MND. The grant is a part of the **Philanthropic Fund** portfolio that LifeArc and the MND Association co-fund.

The gene therapy programme aims to correct mutations in the C9Orf72 gene, the most common genetic cause of MND and frontotemporal dementia (FTD). The mutation causes a misread in the gene which results in toxic proteins forming.

Professor Hautbergue's previous work funded by the MND Association has shown that the protein SRSF1 is critical to the process that makes toxic proteins, by exporting misprinted C9Orf72 from the nucleus into the cell cytoplasm where they are used to produce toxic proteins.

The approach is to correct the effects of the C9Orf72 mutations with an engineered harmless gene therapeutic virus, lowering the amounts of the SRSF1 protein to stop the export of misprinted transcripts. The research is conducted in collaboration with **Cell and Gene Therapy Catapult**, an independent centre to advance the growth of the UK cell and gene therapy industry.

This gene therapy programme could potentially lead ground-breaking research into early-stage clinical trials for one of the most common forms of these incurable neurodegenerative diseases within the next few years.

Building on this success, Professor Hautbergue is the Non-Executive Director of a biotechnology spin-out company, **Crucible Therapeutics**. The company recently secured £5 million in investment, demonstrating the impact of translating basic research to the clinic.

Co-funders: LifeArc mnda motor neurone disease association

"The MND Association has played a special role all along my career in translational research, from junior group leader to a senior investigator. It provided my very first grant for the SRSF1 programme. The research ultimately yielded a full gene therapy programme with the support of LifeArc and MND Association. Full circle! Thank you to the MND Association which has been present all along this journey."

Professor Guillaume Hautbergue, Sheffield Institute for Translational Neuroscience (SITraN)

"Genetic therapy approaches to lower the level of SRSF-1 decreases the production of dipeptide repeat proteins which contribute to motor neuron injury in C9-MND. We are hugely grateful to the translational programme supported by the MND Association and Life Arc which has allowed the preclinical work to move forward positively and the creation of the spin-out company Crucible Therapeutics which we hope will allow this treatment approach to be taken step by step towards clinical trials for patients".

Professor Dame Pamela Shaw, Sheffield Institute for Translational Neuroscience

Adenoviral gene therapy to correct FUS mutations in MND

Certain genetic mutations lead to a type of motor neuron disease (MND) that is rapidly progressive and often affects young people. **Fused in Sarcoma (FUS)** is one such example, accounting for 5% of inherited MND cases and 1% of sporadic cases.

Mutations in the FUS gene cause toxic protein to build up in the cell cytoplasm, where it disturbs cellular metabolism and ultimately causes neuronal cell death.

Dr Younbok Lee at **King's College London** is a recipient of the LifeArc and MND Association **Philanthropic Fund**, and is developing innovative ways to treat MND caused by FUS mutations via gene silencing.

The ability to deliver genes to neurons provides a tool to modify dysfunctional genes, such as FUS. A crucial aspect of this development is ensuring that the gene delivery vectors are non-toxic and suitable for incorporation into clinical trials.

Dr Lee is using a 'clinic-ready' adenoviral-associated vector (AAV) virus carrying instructions to motor neurons to stop mutant FUS RNA from being made. If shown to be an efficient therapy in pre-clinical models and in clinical trials, in the future this gene therapy could be delivered to the spinal cord of FUS patients in a single operation to provide lifelong protection.

Co-funders: LifeArc, mnda motor neurone disease association

"Our programme is profoundly fortunate to receive financial support from the philanthropic MND Association/ LifeArc funding initiative. This support is instrumental in enabling us to fine-tune the RNA vectors so they can effectively target and silence the mutated FUS gene. This step is critical as it lays the groundwork for developing a viable treatment.

Through our efforts, we hope to bring a new hope and improved quality of life for those affected by this debilitating disease."

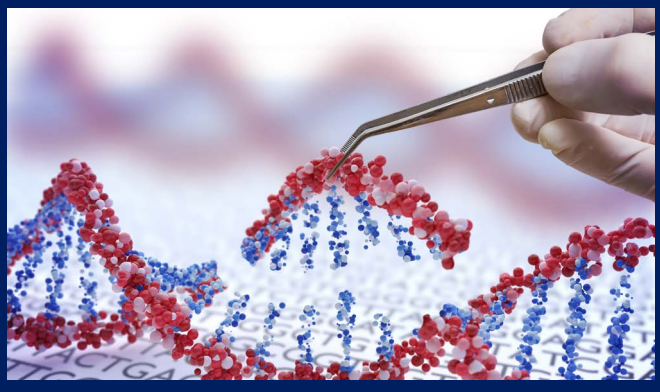
Dr Younbok Lee, King's College London

Adenoviruses are ancient viruses that can be genetically engineered to lose their viral activity, but still retain their natural abilities to enter cells in the body without activating an immune response.

Adenoviral-associated vectors (AAVs) can be used to deliver cargo in the form of genes to their destination.

Because certain types of AAVs have evolved over millions of years to target the central nervous system, AAVs are a powerful tool for translational neuroscience.

Gene therapy via AAVs is increasingly being used to target neurodegeneration. In 2016, SPINRAZA® (nusinersen) (Biogen) was the first ever gene therapy treatment approved for use to treat Spinal Muscular Atrophy, available via the NHS.



Human MND in a dish: a translational research toolkit

To make breakthroughs in finding new treatments we need the right toolkit to help us study underlying mechanisms of the disease. Cell-based models are increasingly being used for translational MND research, as cells can be grown on a large scale to test new therapeutics. More importantly, cells can be sampled from people living with MND and could reveal new insights into disease mechanisms when grown at scale.

Induced Pluripotent Stem Cells (iPSCs)

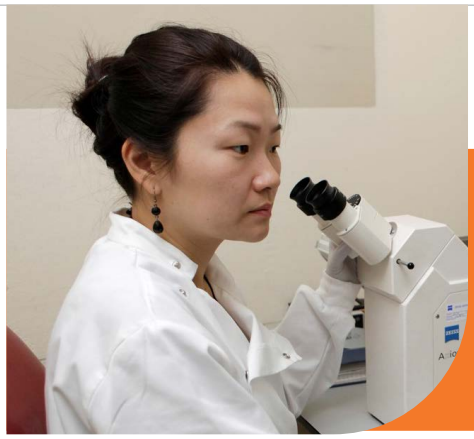
iPSCs are a particularly versatile tool for translational research. Cells from skin biopsies collected from patients grown in a petri dish are genetically reprogrammed using Nobel Prize winning technology (Yamanaka, 2012) to 'reset' into a stem cell state, before they are programmed into cell types that are relevant to the disease.

Reprogramming provides an opportunity for researchers to create disease models directly from patients who have the disease, which reduces the number of animal models that are used and provides the ideal model for looking at the disease instead of using animal models as a proxy.

Professor Christopher Shaw (King's College London) and **Dr Agnes Nishimura (Queen Mary University London)** have reprogrammed 35 iPSC cell lines from the **MND Collections** biobank to model MND. The samples were originally donated from patients with mutations in TDP-43, C9Orf72 and other more novel genes including Annexin 11 and Arpp21.

The cell lines can be converted into motor neurons and other nervous system support cells that together act as a sophisticated model to understand what is killing the motor neurons and other disease mechanisms, as well as a model to test new therapeutics directly on motor neurons that are affected by MND.

The cell lines have passed rigorous quality control checks according to the MRC and Wellcome Trust funded Human Induced Pluripotent Stem Cells (HipSci) initiative (http://www.hipsci.org), meaning they can be shared with the wider research community with assurance that the cells meet the quality standards for them to be used as MND models in academic studies and in industry.



Dr Agnes Nishimura, Queen Mary University London

Organoids

Cell models used for MND research are usually grown as a two-dimensional model in a petri dish or flask with a flat surface. However, the brain is a three-dimensional (3D) organ. Recently through advances in technology, new models are being developed where the cells grow in a 3D environment.

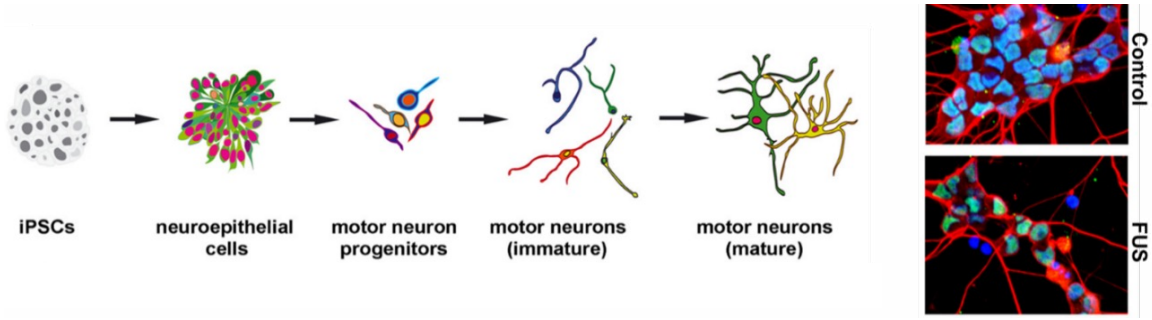
Organoids are simplified organs grown in 3D. Multiple cell types, in this case motor neurons and their support cells, are grown together and allowed to arrange themselves similar to how they might assemble in the brain.

Dr Matthew Broadhead and **Professor Gareth Miles (University of St Andrews)** have been working on making iPSC organoids in order to investigate how motor neurons make physical connections with other cells.

The team, in collaboration with **Professor Jeroen Pasterkamp (Utrecht University)**, is investigating how the synapses, which are structures neurons use to communicate with each other and other cells, behave in C9Orf72 forms of MND compared to healthy controls. Using a cutting edge microscopy approach, scientists can investigate synapses in thorough detail and examine how structurally dysfunctional synapses may differ compared to healthy ones.

In the longer term organoids can be used to assess synapses in this 3D environment to understand why synapses are vulnerable in MND and how they could be preserved as a possible treatment.

Co-funders: ALS CURE PROJECT mnda motor neurone disease association



Stages of converting iPSCs to motor neurons (left), and micrographs (right)representing healthy control motor neurons compared to FUS mutated motor neurons.

Tofersen, a Neurofilament Light chain case study

In 2022, pharmaceutical company **Biogen** presented findings on its phase 3 clinical trial of tofersen (QALSODY), an antisense oligonucleotide therapy against misfolded SOD1 protein.

Neurofilament light (NFL) chain levels were reduced in the blood of participants receiving the treatment, but not the control group.

The tofersen trial was the first real-world evidence case for using NFL as a biomarker for MND disease progression and treatment efficacy, with the US Food and Drug Administration (FDA) commenting on NFL as a "reasonably likely surrogate marker of clinical benefit".

NFL can be used together with other disease progression measurements, such as the ALSFRS-R functional rating scale which assesses activities of daily living in patients.

"AMBRoSIA is proving the power of having a larger, multi-centre resource of samples collected over time. The greater understanding of a range of biomarkers across the clinical variations we see in MND has been pivotal in taking a leading candidate, neurofilament light chain (NFL), to the next stage of development.

NFL levels in the blood reflect the rate of disability progression across groups of MND patients. Lower levels are associated with slower rates of progression and vice versa. Coupled to the relative stability of an individual's NFL levels as the disease progresses, there is hope of using NFL lowering as an objective signal of likely clinical benefit."

Professor Martin Turner, Oxford University, Project AMBRoSIA co-lead investigator

Progress in the hunt for biomarkers

Project AMBRoSIA (A Multicentre Biomarker Resource Strategy in ALS), one of the world's most comprehensive MND sample collections, has enabled research into the discovery and validation of biomarkers in the largest study of its kind to be funded by the MND Association. The funds predominantly comprised donations from the hugely successful Ice Bucket challenge campaign in 2014 as well as support from The Linbury Trust in memory of Annette Page, The Bruce Wake Charitable Trust and Cookies Fund, raised by friends, family and supporters of Paul Cook.

Three participating world class research centres in Oxford, London and Sheffield led by **Professor Martin Turner, Professor Andrea Malaspina** and **Professor Dame Pamela Shaw** respectively, have been working on identifying a biomarker for MND. The project recruited 525 people living with MND along with 398 people without MND as a control group, from whom to obtain biological samples every 3 months.

The samples (including blood, skin, urine, and cerebrospinal fluid) contained in Project AMBRoSIA being made available to the research community as a biobank has facilitated research that led to the discovery of a particular MND biomarker: **neurofilament light chain (NFL)**, a structural protein holding the neurons together, released by the cells as they die. The NFL study originated from the **BioMOx** study (Professor Martin Turner, Oxford University) and **ALS Biomarkers Study** (Professor Andrea Malaspina, University College London).

The AMBRoSIA-led validation of NFL as a biomarker for MND has already had major implications for clinical trials, as an increasing number of trials have started incorporating neurofilament measurements both for disease progression and to assess whether a given treatment works.

In 2023, the **Sean M. Healey International Prize for Innovation in ALS** was awarded to the team responsible for establishing neurofilament biomarkers as an early diagnostic and prognostic biomarker for ALS. The team included Professors Robert Bowser, Barrow Neurological Institute, USA; Martin Turner, Oxford University, UK; Michael Benatar, University of Miami, USA; Andrea Malaspina, UCL; Markus Otto, University Medicine Halle, Germany, and Biogen Therapeutics, Cambridge, USA. The prize was presented at the 34th International Symposium on ALS/MND in Basel, Switzerland by Merit Cudkowicz, MD, Director of the Healey & AMG Center at Mass General and Regan Healey.

Advances in personalised medicine

Patient stratification channels the power of translational research into personalised medicine, and involves categorising patients with similar disease traits and symptoms into groups.

Most clinical trials treat MND as a single disease, but in reality MND is a complex disease with variations in symptoms, progression rate, and causes. As such every person with MND has their own unique journey. Because of this complexity one person might respond to a particular treatment that is ineffective for the next person.

By increasing our understanding of the similarities and differences between 'sub-groups' of people with MND, through patient stratification, it could enable scientists to predict who might respond to any given treatment – enabling personalised medicine. This could help doctors recommend clinical trials most likely to benefit the patient.

Patient stratification to improve clinical trial design

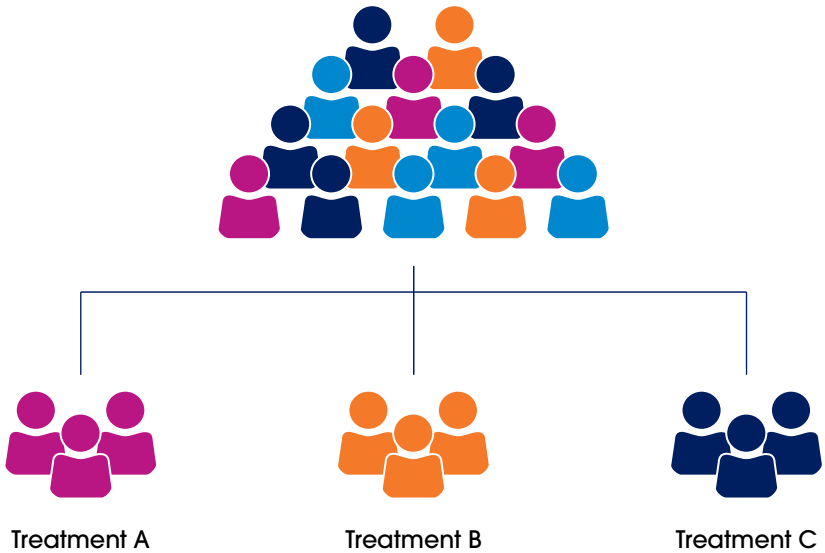
The MND Association is funding a patient stratification project led by **Professor Ammar Al-Chalabi** and **Dr Ahmad Al Khleifat (King's College London)** which aims to develop a new strategy for clinical trials and personalised therapy in MND.

Currently, clinical trials fail to consider the complexity of MND, including different disease progression and causes. This project aims to create and test a personalised genetic approach to MND clinical trials by combining datasets from 3 major studies: the international genome sequencing study Project MinE, the ENCALS survival prediction tool, and genetic data from the MIROCALS clinical trial.

This type of study, where the genetic makeup of an individual affects clinical trial design, has not been performed previously in MND trials but has been shown in three previous studies of lithium in MND to be an effective approach. Creating subgroups based on genetics can generate distinct groups both for underlying MND characteristics and for response to different treatments.

The project aims to use data from the **MIROCALS** clinical trial to understand why some people respond to treatments and others don't, and sequencing data from >10500 patients from **Project MinE** will support these findings.

The MND Association is also co-funding Dr Al Khleifat's Junior Fellowship in precision medicine together with the **ALS Association**.



Precision Medicine

Categorising people with MND into groups can help address the complexity of MND by providing different treatments to different groups, depending on the specific causes of MND in that population.

Mining whole genome data for clues with Project MinE

Project MinE is a worldwide genome sequencing consortium that started in 2013 in the Netherlands, and now includes a total of 21 participating countries. It is a unique collaboration and the largest international genetics study on MND to date.

Project MinE is a big data project 'mining' the full DNA profiles of at least 15,000 people with MND and 7,500 control subjects to identify gene variants contributing to the risk of developing sporadic MND.

MND Collections (p. 18) is an MND Association-funded resource combining more than 3000 blood samples and clinical information from people living with MND as well as from healthy donors, collected between 2003 and 2012. Over 2000 samples from this world class biobank have been genetically sequenced through the Project MinE consortium. This is the largest contribution of samples by any country outside of the Netherlands.

The Project MinE sequencing datasets are available online and accessible to researchers, and the data mining continues to identify genes associated with MND. In 2022 a paper resulting from the project was published, reporting 15 new genetic profiles with increased risk for developing MND.

There is a personalised medicine component to Project MinE as big data generated on genetic causes of MND enables the targeting of individual patients' disease processes. By knowing the mutations someone has it is possible to test the effects of new treatments specifically targeted to someone's genetic background in pre-clinical models and clinical trials. For instance, the **TRICALS-MAGNET** trial (p. 20) for people with an UNC13A mutation was formed based on Project MinE data.

Such large-scale research on the genetics of MND is unprecedented. In addition to the discovery of new MND genes, the consortium has also had international impact by sharing data to enhance the **ENCALS** (European Network for the Cure of ALS) survival prediction model, and received the prestigious Healey Center International Prize for Innovation in ALS in 2020.

Project MinE consortium members and patient ambassadors (27th International Symposium on MND/ALS, Dublin, 2016)

Partnerships

Joined up thinking, joined up funding

The MND Association has an established reputation of funding world leading research that has a strategic focus and is backed by appropriate governance, as demonstrated by being a long standing member of the Association of Medical Research Charities. All our research is peer reviewed by independent experts to ensure we only fund the highest quality research.

Finding new treatments for MND cannot be achieved in isolation. Tackling the disease needs to be coordinated - not just between researchers and industry, but also with other funders, policy makers, and through interactions with regulatory bodies such as the Medicines and Healthcare Regulatory Agency in the UK.

A report published by the National Institute for Health Research in 2023[1] on the rare disease landscape showed that MND received the largest amount of funding in the rare diseases portfolio, 8% of a total of £1.1 billion invested by charities and the Government between 2016-2021. Furthermore, the BioIndustry Association and the Association of the British Pharmaceutical Industry reported that 4% of all rare diseases research projects undertaken by industry were MND projects, among the five most researched rare diseases.

1 Reference: https://openresearch.nihr.ac.uk/documents/3-45

Collaboration with industry is essential for finding new treatments for MND and getting them to the market. Most of the MND Association translational research initiatives described throughout this impact report are partnerships, such as the joint **Translational Research Fund** with LifeArc and My Name'5 Doddie Foundation, the **UK MND Research Institute**, and the two platform clinical trials **MND-SMART** and **EXPERTS-ALS**. The Association's translational research portfolio illustrates how the research funding landscape is changing to be increasingly collaborative, and that these national initiatives reflect how 'joined up funding' is a commitment to 'joined up thinking'.

Investing in people

The Association has partnerships to develop and retain talented researchers and clinicians specialising in MND. This includes a long-standing partnership with the **Medical Research Council**, co-funding the **Lady Edith Wolfson Fellowships**, which develops clinical and non-clinical fellows into the future leaders in MND research. As of 2024, we are funding 16 Fellows through the Lady Edith Wolfson programme.

In addition, we fund 3 **Pre-fellowships** (administered by **MND Scotland**) to facilitate MND researchers obtaining fellowships. We have also recently entered into a partnership with the **National Institute for Health and Care Research (NIHR)**, creating new co-funded opportunities for health and social care professionals to further their specialisation in MND at a PhD or postdoctoral level.

"The MND Association is working together with a range of stakeholders, from other charities to industry and academic labs, to facilitate finding new treatments for MND. Collaboration is essential to move away from siloed research to co-ordinated large-scale efforts. Through partnerships we will continue to strengthen and transform the world leading MND research carried out in the UK."

Dr Sophie Nyberg, Research Programmes and Partnerships Manager, MND Association

The UK MND Research Institute

UK MND RI

Launched in 2023 after the **United To End MND campaign** led by people with MND, the **UK MND Research Institute (UK MND RI)** is a partnership between researchers, doctors, patients, charities and the government. To date £4.25 million has been awarded by multiple charities (the MND Association, LifeArc, MND Scotland, My Name '5 Doddie Foundation) and the Government. There are six participating centres in the institute, all leaders in MND research.

The UK MND RI aims to accelerate the discovery of effective therapies for MND by:

- Developing better tests – both biomarkers and patient reported - to measure MND progression
- Improving MND registers so more data can be gathered about the disease, to gain a more complete picture of MND in the UK
- Increasing our understanding of which patients are more likely to respond to a particular drug
- Providing support for people to participate in clinical trials more easily
- Developing better processes and tests in the lab to develop possible new therapeutics, and to fast-track them into clinical trials.

The UK MND RI is a multi-centre and multidisciplinary research partnership with expertise from across the UK, which allows for studying a complex disease such as MND in a much more coordinated way.

The UK MND RI aims to link together current MND research projects as vital parts of UK research infrastructure, such as the **MND Register** and **Project ALS-Biomarkers**. This involves integrating remote biosampling within the MND Register, to ultimately collect samples from everyone in the UK recently diagnosed with MND. Obtaining biosamples from a large population enables better insights into disease progression and better biomarkers. A pilot for integrating remote biosamples collection is being led by University College London, King's College London and the University of Oxford.

"The UK MND Research Institute networks the strengths of each MND researcher in the UK into a coordinated programme of work that will accelerate the search for a cure. No other country has the leading institutions working together nationally like this, and it is only possible because of the partnership between patients, patient-led charities, medical charities, government funders and industry, together with scientists and clinicians, all with the same aim of ending MND."

Professor Ammar Al-Chalabi, Co-Director, UK MND Research Institute

The work undertaken by the UK MND RI aims to break the impasse in MND research, using a strategy to nationally coordinate work across the entire translational pathway. The partnership is ideally placed to progress, with national infrastructure, large sample numbers, and internationally renowned expertise. The partnership has been made possible by bringing together patients, charities, scientists, clinicians, and industry to accelerate finding new treatments for MND.

mnda motor neurone disease association · MY NAME'5 DODDIE foundation · MND Scotland Making time count · LifeArc · UKRI Medical Research Council · NIHR National Institute for Health Research

Industry partnerships: essential for translational MND research

By Lucie Bruijn, PhD MBA
Therapeutic Area Biomarker Lead, Novartis

Collaboration is key to the success and advancement of therapies for ALS and there can be no better evidence of this than the remarkable achievement by Biogen in 2023 with the conditional approval by the Food and Drug Administration (FDA) of antisense therapy for those people living with ALS carrying the SOD1 mutation (QALSODY™). This could not have happened without academic-industry partnerships and philanthropic funding.

An additional milestone is the first conditional approval for MND by the FDA based on soluble biomarkers, neurofilaments, as indirect markers of clinical benefit. The observation that these markers significantly lowered upon treatment with the SOD1 antisense therapy, well before a clinical benefit could be identified, will impact future trial designs to best identify treatments that will benefit people living with MND.

So why are industry partnerships important?

Over the years the interest and investment by industry in the development of treatments for MND has grown exponentially, fuelled by an increased understanding of the disease, and growing academic and industry partnerships (spearheaded by organisations such as the MND Association). Importantly, academic colleagues developing model systems and validating potential pathways involved in MND provide opportunities for industry to apply their skills and technology to develop interventions that may become successful therapies. The more 'de-risked' an approach with strong supportive data is, the more likely the industry partner will commit resources to develop the therapy.

> *"The more 'de-risked' an approach with strong supportive data, the more likely the industry partner will commit resources to develop the therapy."*

Dr Bruijn, who received the International Alliance of ALS/MND Associations Humanitarian Award in 2023 for her impactful contributions to MND research.

The MND community has contributed significantly to building the necessary tools to facilitate drug development, such as the generation of induced pluripotent stem cells from people carrying specific disease mutations with direct relevance to human biology. The investments into Project MiNE to identify mutations in genes and risk factors linked to the disease has enabled the discovery of new targets, the starting point to develop new therapies. In addition, access to biosamples (cerebrospinal fluid, plasma, and post-mortem tissues) through initiatives such as Project AMBRoSIA provide the necessary tools to develop biomarkers and to better design clinical trials.

Clinical trial design has benefited from a growing understanding that the input of people living with the disease is critical for successful enrolment into trials. Through databases such as PROACT, industry can mine prior clinical trial data to better design studies minimising the number of patients required on placebo. Innovative and adaptive trial designs such as platform trials (successfully used in the cancer field) enable the exploration of multiple interventions to improve efficiencies. Academic and industry partners are collaborating on the development of new biomarkers, soluble, imaging, digital and clinical end-points through pre-competitive consortia.

The MND field is well poised for advancements in therapies and together with a global community of academic and industry experts in partnership with people living with MND and their families this is an extremely hopeful time for significant progress.

The MND Register

The **MND Register** has been set up with MND Association funding to gather information on every individual with MND in England, Wales and Northern Ireland, and is co-led by Professor Ammar Al-Chalabi (King's College London) and Professor Kevin Talbot (Oxford University). Information can be used to gain a better understanding of how many people have MND, as this is currently estimated. Knowing where in the country people with MND are located facilitates better care planning. It will also enable patterns in geographical variation and distribution to be observed, providing the potential to compare data from other countries and to identify possible disease clusters.

As of 2024, there are 46 sites actively enrolling onto the Register including neurology clinics and MND Association funded Care Centres, covering an area of 22 million people. 5200 participants have been recruited onto the Register so far. The project was supported by The Betty Messenger Charitable Foundation, The William Brake Foundation and a family foundation that wishes to remain anonymous.

MND REGISTER
England, Wales & Northern Ireland

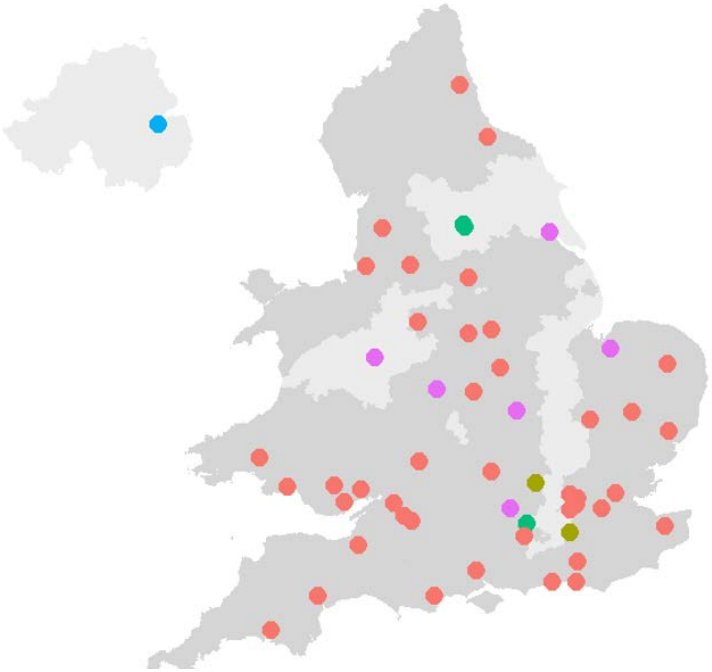
Phase 2 the MND Register

Phase 2 of MND Register began in 2022 and is set to continue until 2025. The purpose of Phase 2 is to:

- Expand data collection to cover 100% of England, Wales and Northern Ireland
- Collect environmental and non motor symptom information
- Linking together the Register with other MND research projects
- Regularly provide cleaned datasets to other MND researchers

Sites participating in the MND Register

Postcodes from which data is collected from people with MND in dark gray, areas to be enrolled in light gray. Red dots represent currently participating sites, other colours are in different stages of onboarding.



Future of the Register

A team led by Professor Chris McDermott (Sheffield Institute for Translational Neuroscience, UK) is currently working on a telemedicine app **Telehealth in Motor Neuron Disease (TiM)**. The aim is for the app to eventually be rolled out to all sites participating in the Register, linking use of the app together with the Register. TiM will allow people living with MND to sign up and complete questionnaires, such as for symptoms, remotely. The app will also act as a gateway to research and trial participation, able for instance to send 'push' notifications to app users regarding clinical trials nearby that are recruiting.

The Register is also being integrated into the UK MND Research Institute as a hub for research studies to link data between different projects, and other large NHS datasets. Each person on the MND Register will be allocated a unique identifier code so that valuable data can be shared between researchers.

The recent United To End MND campaign, which resulted in a pledge of £50 million from the UK government towards MND research, was successful in part because of the MND Register. Research is a number one priority for families affected by MND and our understanding of the disease is rapidly increasing, leading to new insights which were not conceivable when data was initially collected.

Partnerships with industry

QurAlis

QurAlis is a US-based biotechnology company focused on developing precision medicines for MND, frontotemporal dementia and other neurodegenerative diseases. In particular, treatments are focused on protein pathways that are dysfunctional in MND. Neuronal protein Stathmin-2 has been identified as a target of interest due to its dysfunction in familial and sporadic MND cases.

QurAlis obtained lymphoblast cell lines (LCLs) from patients with rare genetic mutations backgrounds from the MND Association resource MND Collections, which after transforming to iPSC lines have been used as an integral part of the company's R&D programme. The iPSC lines have been used as an MND cell model for disease studies and drug screening studies.

QurAlis presented advances in the Stathmin-2 programme at the 33rd International Symposium on ALS/MND in 2023, and have begun a phase 1 clinical trial of QRL-201, the lead Stathmin-2 compound.

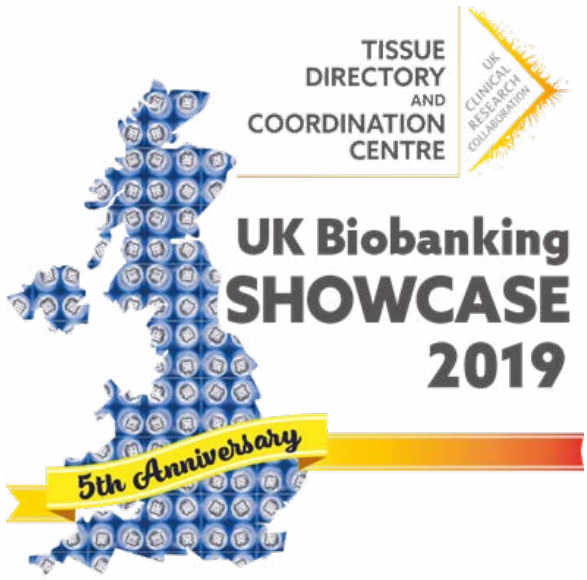
QurAlis™

MND Collections

The MND Collections is a resource combining DNA and cell lines from more than 3,000 blood samples and accompanying clinical information; as well as epidemiology data from 400 participants, including people with MND, controls and family members.

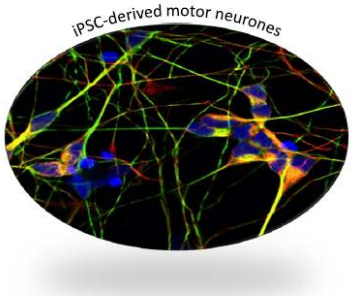
The MND Collections was established to provide the international research community with a resource to identify and understand causative and disease modifying factors in motor neurone disease. Sample collection concluded and the resource became fully accessible in 2012, with more than 75 publications to date and samples or data shared with over 20 countries.

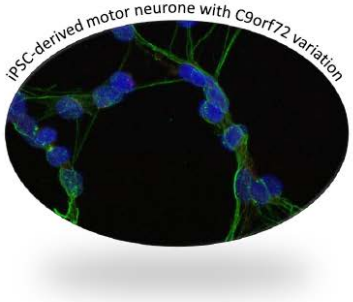
The resource is available to academic and industry researchers, following a formal application process to the MND Association Biomedical Research Advisory Panel. In addition to immortalised lymphocyte cell lines (LCLs) created from each blood sample, over 30 iPSC cell lines created in collaboration with Professor Christopher Shaw (King's College London) are also available.



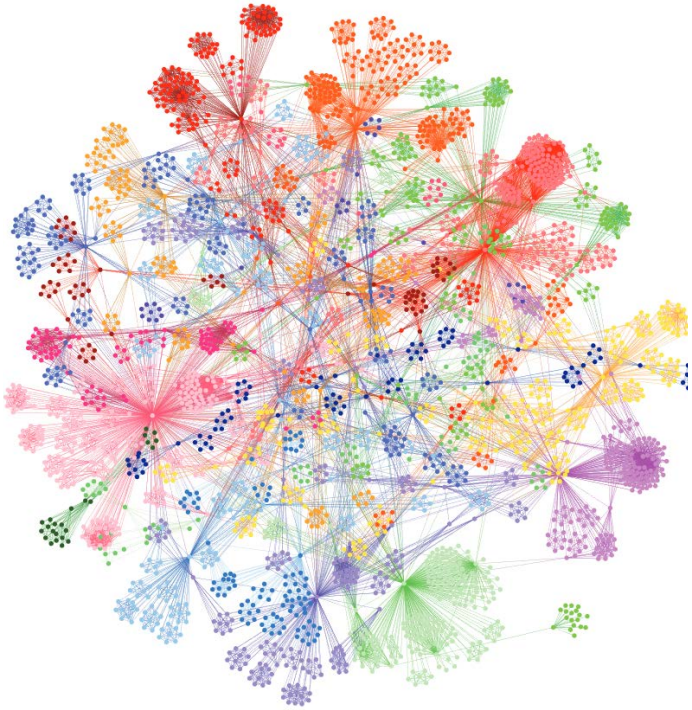
The MND Collections won **UK Biobank of the Year** in 2019, demonstrating the impact that the research studies, wider collaborations, and engagement that the resource has facilitated.

For further information, email **mndcollections@mndassociation.org**





PrecisionLife: Connecting Patient Data and Artificial Intelligence to Advance MND Research



The MND Association is working together with Oxford based biotechnology company **PrecisionLife**, using an artificial intelligence (AI)-based approach to analyse large disease population datasets to generate much deeper understanding of complex diseases like MND.

Previously PrecisionLife, used its platform analysis for **Project MinE** datasets and identified 33 new genes associated with increased risk for MND. More recently, PrecisionLife was granted access to extended clinical sample records from the **MND Collections**, the MND Association biobank.

The latest project, in collaboration with King's College London, aims to analyse genetic data from 1388 already sequenced samples together with additional information from MND Collections, including disease severity, age of death, and MND subtype diagnosis. Combining genetic data with clinical details and epidemiological studies means the analysis can find different groups of people with MND who share the same risk factors and disease progression. The insights created by this AI platform can also be used to build models that can predict risk of developing MND in a more personalised way.

The project is an excellent example of the large amounts of information that can be obtained from MND Collections and Project MinE. The resulting data will be used to develop new ways to evaluate disease risk and progression, and to deliver potential new treatments to people living with MND. The advances in AI technology also mean that results are generated in a much faster timescale than has previously been possible, which speeds up the process of getting a treatment into clinical trials.

These studies have also catalysed a new strategic partnership between PrecisionLife and LifeArc, as part of the LifeArc MND translational challenge.

"The MND Association has been pivotal in facilitating the data analysis collaboration between PrecisionLife and the King's College teams, and enabling the translational collaboration with LifeArc that will develop multiple new MND drug targets arising from this project. This is a major step forward bringing together academic and commercial researchers for the development of new therapeutic approaches and diagnostic tools that simply would not have been possible without the unwavering support of the MND Association."

Dr Steve Gardner, CEO and co-founder, PrecisionLife

Translational research in clinical trials

Clinical trials are the final steps of the translational research pathway, turning treatments that have been shown to be efficient in preclinical research into therapies for patients.

The best models of human MND are humans, so incorporation of additional translational research studies into clinical trials can give information on disease mechanisms, or indicate why a treatment has been successful or failed for subgroups of patients. Three case studies on clinical trials incorporating translational components are included below.

TUDCA-ALS

TUDCA-ALS was a phase 3 European trial assessing the use of tauroursodeoxycholic acid (TUDCA) for MND. Previous trials have shown the compound to delay degeneration of motor neurons.

The TUDCA-ALS trial announced negative top-line results in 2024, but further data analysis continues. Biosamples are kept at a biobank accessible to researchers, and will be used for further exploratory analysis, such as whether a differential response is seen in slow versus fast progressing participants. In addition, the study is evaluating whether treatment has an effect on the biomarker neurofilament light, and more exploratory biomarkers TIMP-1, and MMP-9.

TUDCA-ALS was funded by the European Union's Horizon 2020 research and innovation program.

MIROCALS

The phase 2b trial MIROCALS, assessing low-dose interleukin-2 for MND, was preceded by IMODALS, a phase 2a trial. The IMODALS results included a saw a significant and dose-dependent increase in T_{reg} cell numbers. Participants were classified as low, moderate or high responders depending on the amount of upregulation of regulatory T cells (T_{regs}).

Cells isolated from the blood of IMODALS participants were analysed with transcriptomics to map the full RNA contents of the cells and assess the immune 'thumbprint' of each participant, and IL-2 was found to lead to a reduction in pro-inflammatory markers in both the low and high responders.

Similar analyses are being undertaken to increase the understanding of differing results observed in MIROCALS participants, in which participants with more slow progressing forms of MND (as seen by lower levels of Neurofilament heavy protein) had a more pronounced response to IL-2, and demonstrate how translational research can pinpoint a mechanism for how a new treatment works, and whether the mechanism differs depending on the degree of response from a participant.

MIROCALS was funded through a European Commission H2020 award (No 633413) with additional support provided by Programme Hospitalier de Recherche Clinique, MND Association (supported by the J P Moulton Charitable Foundation and the Garfield Weston Foundation), My Name'5 Doddie Foundation, MND Scotland, Association pour la Recherche sur la Sclerose Laterale Amoytrophique, AFM-Telethon and the Alan Davidson Foundation.

PRELUDE (TRICALS-MAGNET)

Data from Project MinE has been used to re-analyse past clinical trial data assessing the efficacy of lithium for treating MND. Whilst the trial did not show a benefit of lithium for MND, *post hoc* analysis indicated that the treatment could be beneficial in a specific subgroup of participants with variations in the **UNC13A** gene, corresponding to approximately 16% of patients.

Previously UNC13A had been implicated in worsening survival in MND, but analysis of Project MinE data showed for the first time that UNC13A gene status can affect the outcome of a trial. Lithium reduced the risk of death from 60% to 30% in participants with the UNC13A mutation, an effect that was not seen in the overall participant population.

A new phase 3 clinical trial, PRELUDE (**P**e**R**sonalis**E**d treatment with **L**ithium carbonate for **U**nc13a **DE**termined ALS), is currently repeating the study of lithium carbonate specifically in people with the UNC13A variant. PRELUDE is a sub-study of TRICALS-MAGNET, an international platform trial for finding new MND treatments. The outcome of the former clinical trial and subsequent post hoc analysis illustrates that people with MND who have mutations in specific genes may need specific treatments, and the findings are a step towards personalised medicine in MND.

The PRELUDE study is funded by the MND Association, with generous contributions from the Greendale Charitable Foundation, P F Charitable Trust, the Payne-Gallwey Charitable Trust, the Mason le Page Charitable Trust, Hollick Family Foundation and Tony Hopper's friends and family.

EXPERTS-ALS

EXPErimental Route To Success in ALS (**EXPERTS-ALS**) is an early-stage experimental medicine platform spanning multiple centres in the UK, pre-screening drugs ready for Phase 3 clinical trials.

The 5-year programme will focus on identifying and prioritising new treatments, and testing them in a clinical platform using blood neurofilament light chain (NFL) levels as a marker of efficiency. The biomarker development workstream will help with understanding the molecular and overall changes as a result of treatment, and to identify mechanisms behind groups of participant responders and non-responders.

The programme is primarily funded by £4.8 million from the Government as a part of the £50 million pledge resulting from the United To End MND campaign, though the MND Association together with LifeArc and My Name '5 Doddie Foundation are contributing with additional funding to extend the length of the trial platform.

Drugs have to be tested in phase 3 clinical trials to show if they will benefit patients. However, these large trials are expensive and time-consuming and their success rate to date has been very low. This is partly because the drugs put forward for testing have often been chosen largely on data from laboratory studies, rather than evidence from clinical research studies.

The EXPERTS-ALS programme will screen drugs in patients, looking for early signals of benefit found in blood tests. A 'go' or 'no-go' decision can be reached within a few months and successful drugs prioritised for testing in the larger phase 3 trials, offering a higher chance of a positive outcome.

How EXPERTS-ALS fits into the MND drug discovery landscape

New drugs identified in pre-clinical drug discovery, and repurposed drugs, will be prioritised and tested via EXPERTS-ALS. Successful candidates, as shown by reduced neurofilament levels in participants receiving treatment, will be put forward for phase 3 clinical trials, such as platform clinical trials MND-SMART and TRICALS.

"Findings on neurofilament light chain and the recent Tofersen trial paves the way for EXPERTS-ALS. Sophisticated statistical analysis models, only possible with the data from projects like AMBRoSIA, suggest that evidence of a human signal of likely clinical benefit from NFL measurement can be obtained within 6 months and in a group of less than 50 patients. Any positive drugs can then be prioritised for the more traditional phase 3 trials needed to properly test whether the drug is indeed capable of slowing down the progress of MND."

Professor Martin Turner, EXPERTS-ALS co-lead investigator

Co-funders: NIHR | National Institute for Health and Care Research · mnda motor neurone disease association · LifeArc · MY NAME'5 DODDIE foundation

Platform clinical trials: MND-SMART

An innovative UK wide platform led by clinicians, world leading scientists, and statisticians, the MND Systematic Multi-arm Adaptive Randomised Trial (**MND-SMART**) aims to identify new treatments that will slow disease progression and improve quality of life.

MND-SMART is a **platform clinical trial**, a concept originally used in cancer trials, in which multiple treatments are trialled in parallel. Having multiple 'arms' (treatments) in a trial allows many therapies to be tested at the same time with the flexibility to discontinue treatments that are shown to be ineffective and add new drugs as trial data is examined at regular intervals.

First launched in 2020, MND-SMART originated in partnership with patient groups and is the first UK wide platform clinical trial for MND.

As of 2023, MND-SMART had recruited 746 people across 22 sites in all 4 nations of the UK. In 2023, drugs Trazodone and Memantine were discontinued at a trial checkpoint as no significant benefit was observed, and there are plans to introduce new treatment arms in 2024 and 2025. In 2023 the MND Association joined together with MND Scotland, the primary charity funders, and the Alan Davidson Foundation to fund the addition of a new treatment to the trial, maintain the existing trial infrastructure, and open additional trial sites to increase opportunities for people with MND in the UK to participate.

Snapshot of the arms of the MND-SMART platform trial in 2023.

There are plans with a new phase of the trial to open more arms, partly in collaboration with industry. Selection of new candidates involves a translational component, with an interdisciplinary team of scientists using state-of-the-art research techniques. Large libraries of potential new drugs are tested in iPSC-based MND models to assess whether the drugs have effects on motor neuron survival, and assessing effects on TDP-43 aggregation and reducing neuroinflammation, before being prioritised as candidates in the trial.

"We are delighted to be contributing to the continued development of the MND-SMART clinical trial platform. The hope is that through continuing public support, collaboration and partnership working, we will find effective treatments and, ultimately, a cure for this devastating disease."

Dr Brian Dickie MBE, MND Association

MND–SMART
Clinical trials for MND

"Like the MND Association, MND Scotland aspires to a world without MND and this can only be achieved through the identification of disease modifying treatments. It is so important that people with MND are offered the opportunity to participate in a clinical trial and MND-SMART provides the UK wide infrastructure to help make that possible. We're proud to work in direct partnership with the MND Association, and alongside the Alan Davidson Foundation, to realise a further five years of support for this essential resource. This builds on the previous contributions from MND Scotland and My Name'5 Doddie Foundation and is an excellent example of the MND charities working collaboratively to enable significant change."

Dr Jane Haley MBE, Director of Research, MND Scotland

Co-funders: MND Scotland Making time count; mnda motor neurone disease association; Alan Davidson Foundation; MY NAME'5 DODDIE foundation; EUAN MACDONALD CENTRE Vital research into motor neuron disease

Our 'bench to bedside' translational research portfolio spans innovative and novel programmes alongside more established activities to ensure that progress towards finding new possible treatments for MND accelerates, using skills and resources of research partners in the UK and internationally.

Dr Nick Cole, Head of Research, MND Association

Motor Neurone Disease Association
Francis Crick House
6 Summerhouse Road
Moulton Park
Northampton
NN3 6BJ

Tel: 01604 250505
www.mndassociation.org

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