MY NAME'5 DODDIE foundation

mnda motor neurone disease association

CATAPULT Medicines Discovery

Guiding Principles for ALS Drug Discovery and Development

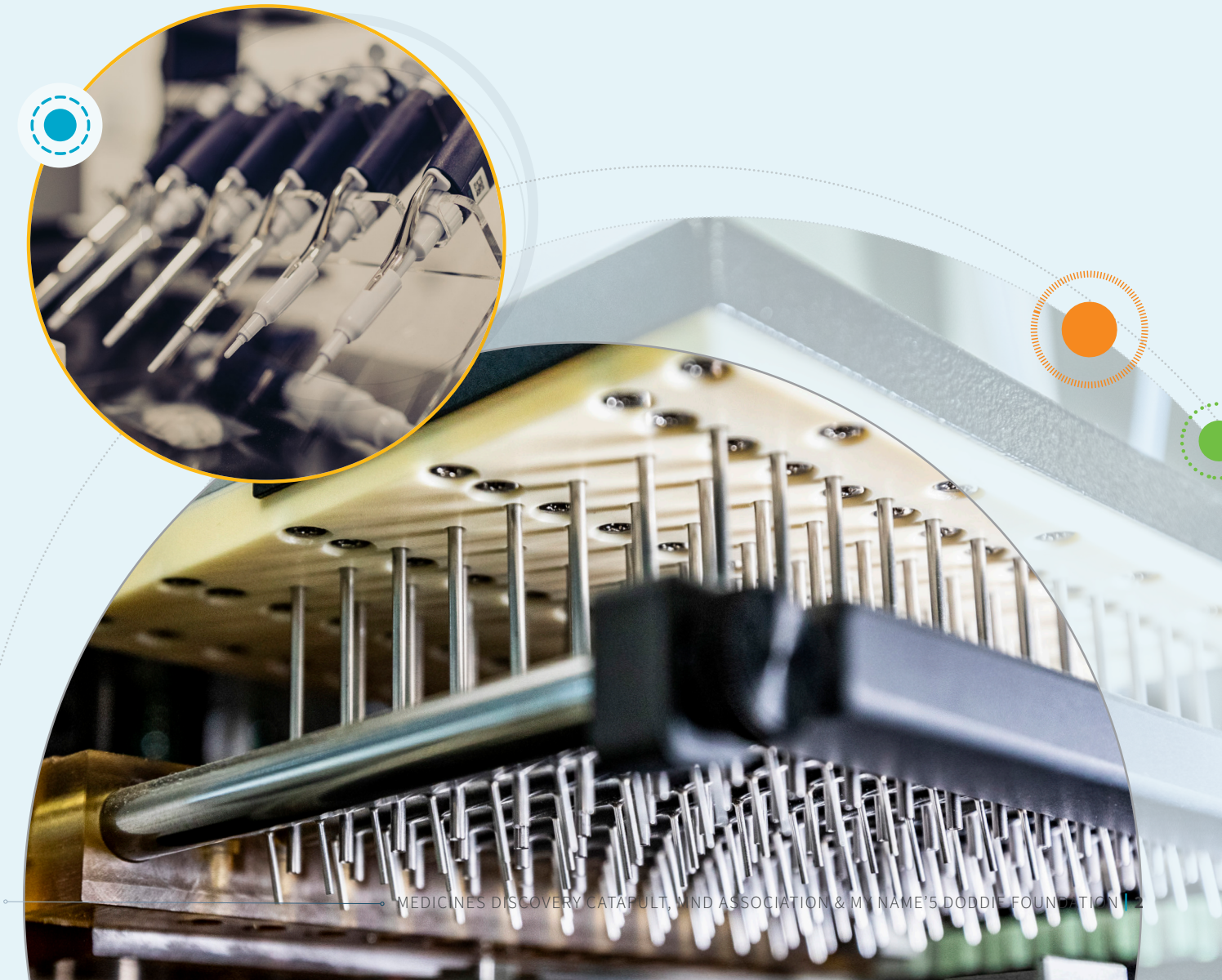
Consensus Workshop

Introduction

Since 2020, three UK-based organisations; Medicines Discovery Catapult, MND Association and My Name'5 Doddie Foundation have been working together to galvanise the cross-sector ALS research community to identify key opportunities and challenges to accelerating drug discovery. A key challenge identified was the need for more consensus on what constitutes a robust preclinical pathway and data package in ALS.

To address this, an Expert Steering Group was convened over a period of 9 months. The Group discussed the factors governing the barriers to translating advances in basic science into effective therapies and suggested Guiding Principles for de-risking clinical trials of novel therapeutics by an enhanced evidenced-based approach to preclinical studies.

To enable community consensus on these Guiding Principles, a workshop of global leading experts in ALS drug discovery and development was convened in June 2022. Before the workshop, a White Paper outlining the Guiding Principles proposed by the Expert Steering Group was circulated to all delegates. Delegates were invited to complete a survey to provide their input on whether they agreed on the proposed Principles.



Survey Results

26 people, including people with MND, academic and industry researchers and funders, completed the survey.

In general, there was a strong consensus across survey respondents, with over 80% of respondents (21/26) strongly agreeing or agreeing that the Guiding Principles developed were a fair representation of the actions required to achieve successful translation in ALS.

Three survey respondents disagreed due to a number of reasons including: the need for better collaboration between industry and academia and because the White Paper was too Euro-centric.

The survey highlighted three key areas in which respondents' opinions differed. These three areas were discussed in further detail during the workshop and are summarised in this report:

1. An agreed approach for Biomarkers
2. Replicating preclinical findings
3. The ability to implement the Guiding Principles in future ALS drug discovery and development efforts

Workshop Conclusions

There was a high level of agreement with the Guiding Principles outlined within the White Paper produced by the Expert Steering Group, and in general, an enthusiasm for the paper to be published and disseminated widely. Workshop attendees felt that it would be important for funders and other stakeholders in the ALS community to commit to the recommendations outlined in the white paper, to ensure their adoption. It was also felt that the paper should become a living document and be updated every 2-5 years to ensure its continued relevance.

Workshop attendees emphasised that the White Paper should not be seen to be too prescriptive or to stifle innovation. Instead, it should be clear that the recommendations represent a snapshot in time of what the community currently believe to be best practice in ALS drug discovery and development. It should also be caveated that each ALS therapeutic programme will vary and not all Principles will be relevant for every programme. It was generally agreed that the White Paper provides an opportunity for the ALS community to come together around a shared vision for effective and impactful ALS drug discovery and can provide a platform for continued progress for patient benefit.

Topic 1

An Agreed Approach for Biomarkers

Workshop attendees were asked to discuss the recommendation made by the Expert Steering Group that Biomarkers for target engagement and disease monitoring are critical tools for ALS drug discovery, and that NFL should be measured as part of every clinical study. It was first agreed that defining the different kinds of biomarkers relevant for ALS drug discovery and development would be useful:

Term	Definition	State-of-Play in ALS
Biomarker	A measurable indicator of a biological state or condition. Includes Molecular, Functional, Imaging and Behavioural approaches	-
Diagnostic Biomarker	Used to accurately diagnose disease or predict individuals that are more likely to be susceptible to disease	No molecular diagnostic biomarkers specific to ALS, however there is evidence from familial studies that NFL levels begin to rise on disease emergence
Prognostic Biomarker	Used to predict likelihood of a particular out-come e.g., rate of disease progression	NFL levels on diagnosis often used to predict rate of disease progression
Predictive Biomarker	Used to identify a population of patients most likely to respond to a specific therapy	Some familial mutations e.g., SOD1 used for patient stratification of genetic therapies
Target Engagement Pharmacodynamic (PD) Biomarker	Used to demonstrate that a therapeutic is engaging the target of interest *Proof of Mechanism – PoM	N/A - Specific to therapeutic in development
Downstream PD Biomarker	Used to demonstrate that a therapeutic has engaged its target and is modulating a relevant downstream pathway *Proof of principle - PoP	N/A - Specific to therapeutic in development
Monitoring Biomarker	Used to monitor whether a therapeutic has any effect on disease; ideally translatable from preclinical models to human	Emerging evidence that NFL could represent a good monitoring biomarker, however further data is needed to support its validation

PD Biomarkers

Overall, workshop attendees agreed that it is critical for every therapeutic programme to develop effective PD Biomarkers of target engagement and downstream pathways. These Biomarkers will be specific to the therapeutic programme and should be used to demonstrate target engagement in iPSCs, *in vivo* and in Experimental Medicine studies as a Go/No Go criterion for onwards development.

Monitoring Biomarkers

It was also agreed that effective Monitoring Biomarkers are needed and that ideally this would be a matrix of biomarkers including molecular, functional, and behavioural biomarkers. From a patient's perspective, having an objective measure of disease progression would provide more confidence in clinical trials. However, it is felt that not having a good biomarker should not halt progress. As a field we are still not close to achieving this and the best molecular Monitoring Biomarker available at the time of the workshop is NFL, which does still not have enough data to provide full confidence in its alignment to disease state. It was agreed that it is critical to continue to build a pool of evidence to support NFL as a future Monitoring Biomarker for NFL, and to do this it would be useful for all clinical studies to collect longitudinal patient biofluid samples and to measure NFL as an exploratory endpoint, as well as a range of other biomarkers. Sharing this data openly would be very beneficial for the community.

There was also consensus that additional efforts to identify and validate novel Monitoring Biomarkers are critical. Industry raised the challenges for them in accessing high quality longitudinal samples (in particular cerebral spinal fluid (CSF) samples) from well characterised patient cohorts. It was also discussed that the development of a consortium of industry, academic and clinical centres where high quality longitudinal patient samples could be shared and analysed precompetitively to identify and cross-validate novel Monitoring Biomarkers, would be a valuable exercise. In addition, it was highlighted that accessing early diagnostic samples and including them in Biomarker studies should be prioritised to ensure the full disease trajectory is included in studies. Samples should be sought from patients with ALS and other conditions known to mimic ALS, as well as healthy controls.

Predictive Biomarkers

From a regulatory perspective, effective stratification of people with ALS into different subgroups to enable enrichment of specific sub-types that are more likely to respond to therapies in Clinical Studies would be hugely beneficial. This enrichment would reduce burden on clinical trials and reduce the need to show an effect in every ALS patient. There are already examples of effective patient stratification have taken place in ALS. A notable example is for Clinical Studies Tofersen, which is only suitable for people with a SOD1 mutation and people with ALS were therefore only eligible for the Study if they had a SOD1 mutation. There are many new adaptive trials in development or delivery in ALS which can enable precision medicine approaches based on the use of effective predictive biomarkers

Although precision medicine may be an attractive approach for future ALS therapeutic strategies, consideration does need to be made to the implications of stratifying an already small patient population. The majority of ALS patients do not meet the current inclusion criteria for clinical studies, further stratification could therefore create ultra-rare patient subgroups with implications on the ability to recruit adequate numbers to power high quality clinical studies. An alternative could be to conduct post-hoc analysis of studies to identify responders based on patient subpopulations. However, this means conducting larger and more costly trials, and potentially means enrolling ALS patients into trials without a sound hypothesis for therapeutic benefit.

Topic 2

Replicating Preclinical Findings

Workshop attendees were asked to discuss the recommendations made by the Expert Steering Group that preclinical findings in ALS should be independently replicated before promising assets are progressed to clinical studies. In discussing this, the workshop attendees felt the need to better define the following terms:

Replication: Repeating a study with the same methodology and experimental setup, either in the same or an independent lab

Validation: Repeating the finding using a different methodology or experimental setup (e.g., a different relevant model) to provide additional confidence in a hypothesis

Overall, it was agreed that replication should only be necessary where there is a lack of confidence in the way that the original studies were delivered, or where the hypothesis had been tested in only one model or experimental setup. In contrast, all breakout groups agreed that providing additional hypothesis validation would enable researchers to build confidence in a therapeutic approach, using different tools and methodologies. Whether or not this also requires independent replication was debated, however all agreed the key is to generate strong confidence in the hypothesis being tested, through well designed experiments.

Barriers to enabling the delivery of replication studies were highlighted, including the increased time it would take for a new therapeutic to reach the clinic, which would need to be carefully explained to the patient community. In addition, in academia accessing the funding required to deliver these studies, as well as cultural barriers such as the perceived lack of academic "impact" of replication studies is a significant challenge.

In discussing different approaches that could be employed for the delivery of validation or replication studies, the following were identified:

1. Development of an academic-CRO consortium where world-class models and approaches from academia could be delivered through independent CROs, in partnership with leading academics. This could enable innovators to access reliable and independent expertise and capabilities to build confidence in a therapeutic approach, however how this would be funded was questioned.

2. Targeted funding approaches where multiple projects could be delivered in parallel by multiple organisations to build robust bodies of evidence around promising targets or therapeutic interventions e.g., a Consortium or organisation could fund more than one research team (academic, industry, CRO) to independently test the same hypothesis.

Topic 3

The Ability to Implement the Guiding Principles in Future ALS Drug Discovery and Development Efforts

Survey respondents highlighted the need for a focused effort to be placed on implementing the Guiding Principles within the ALS community, to overcome potential barriers to their realisation. Workshop attendees were asked to discuss potential barriers and opportunities to ensure active adoption.

The key feedback from workshop attendees was the need to carefully position the White Paper, to ensure it is not seen as a prescriptive document. Instead, it should act to bring the ALS community together onto the same playing field and enable researchers to fully understand the potential needs and requirements of an ALS therapeutic programme to foresee potential gaps and challenges and address them early. It was felt that the outputs of the White Paper should be used to influence funding priorities, and ensure the right funding, infrastructure and networks are in place for effective ALS drug discovery. Finally, it was highlighted that people with ALS do not have the luxury of time and so the White Paper should instil the same sense of urgency and speed progress, not hold it back.

Workshop attendees identified mechanisms to help ensure the implementation of the Guiding Principles:

Communicate

Publish and disseminate widely.

Commit

Ensure funders and investors are committed and aligned, and understand the cost implications required to bring the roadmap to life. For example, Guiding Principles could be implemented within funding calls to ensure all researchers are aware of them and assess their research against them to enable best practice and to identify potential pitfalls early.

Celebrate Success

Host an annual workshop or meeting e.g., at the Annual International Symposium on ALS/MND, where examples of best practice according to the white paper are identified and celebrated.

Iterate

Keep the White Paper up to date by reviewing and republishing every 2-5 years, considering evolutions within the field.

Next Steps

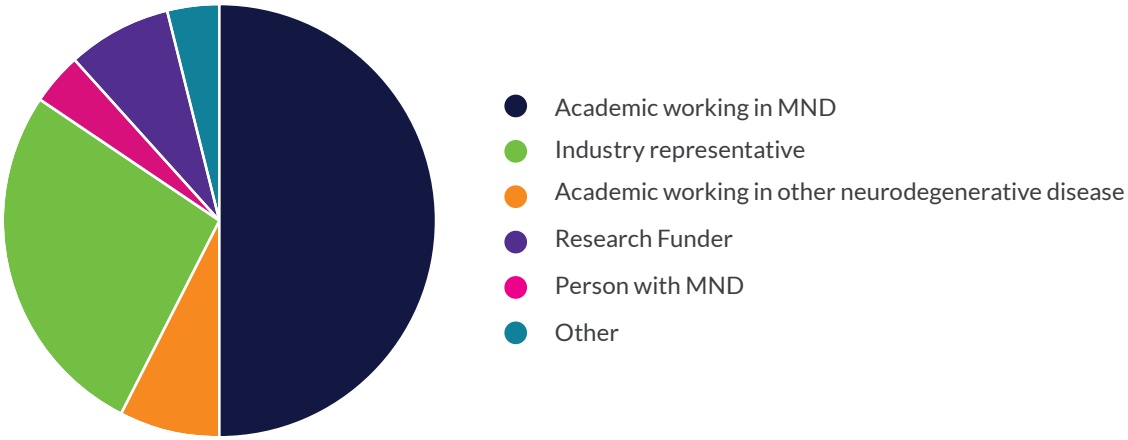
Overall, there was a strong consensus from the workshop attendees that the White Paper produced represents an accurate overview of Guiding Principles for effective ALS drug discovery and development. The participants were keen that the White Paper be disseminated within the community, with the caveat that it is not made too prescriptive, and many ideas for how it can be updated and evolved were discussed.

Following the workshop, the White Paper will be updated taking into account the feedback gratefully received at the workshop. It is the intention of the Expert Steering Group to submit the paper for peer-reviewed publication and explore the ideas suggested at the workshop to ensure its dissemination and uptake within the ALS community. We hope that this will provide a platform and shared understanding on the current state of play in ALS drug discovery and development, on which future cross-sector collaborative efforts can be enabled to accelerate the quest for a cure and bring effective treatments to people with ALS, faster.

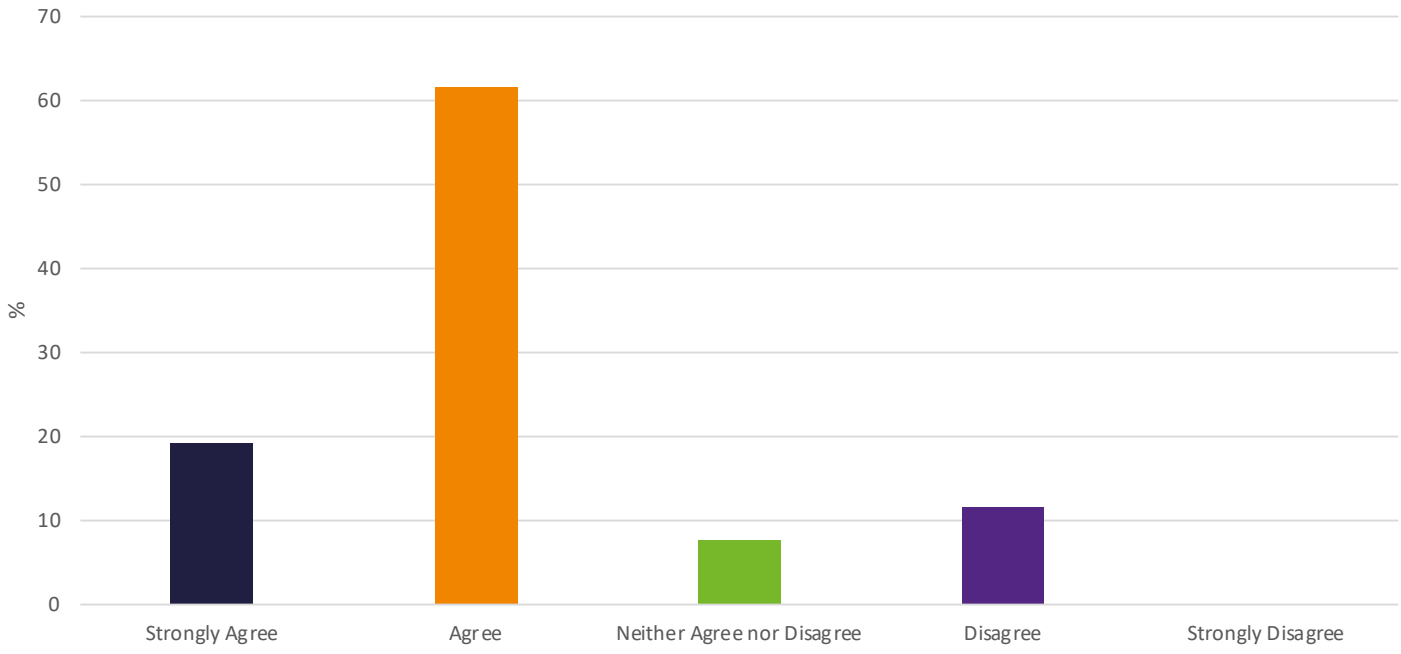
Appendix 1

Survey Results

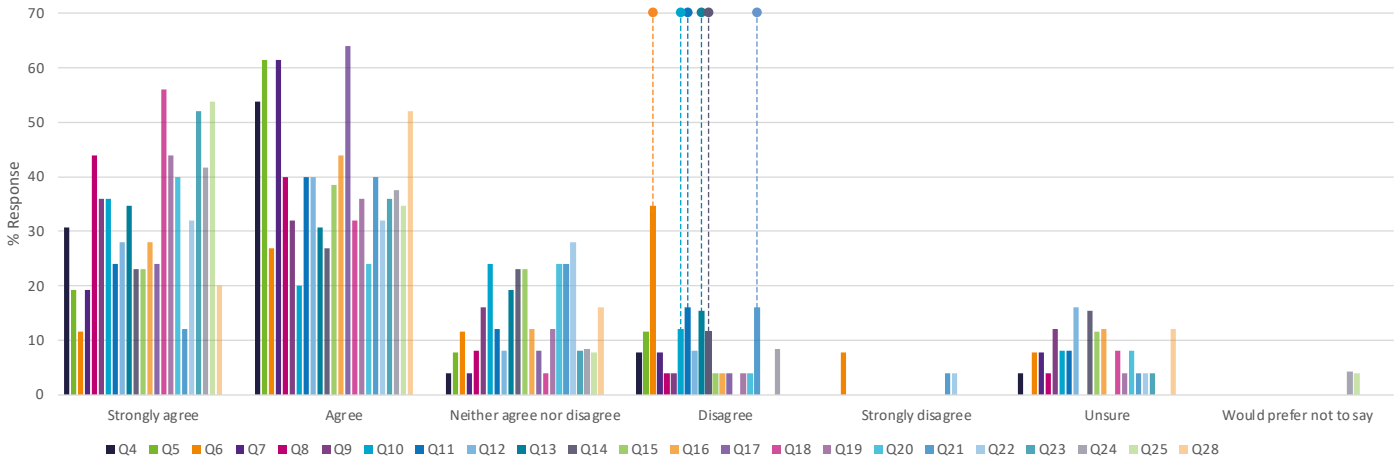
Survey Respondents by Category



Respondent agreement with the following statement "The considerations outlined in the Roadmap are a fair representation of the actions required to increase the chance for successful translation in ALS drug discovery and development"



Summary of survey respondents to all questions in the survey, highlighting a strong consensus with the majority of respondents strongly agreeing or agreeing to most questions. Questions where multiple respondents disagreed have been highlighted and were the focus of discussions at the workshop.



- **Q6.** All ALS therapeutics undergoing development shouldbe able to achieve all aspects of the roadmap in order to meet the criteria for pharma in-licensing or investment and onwards progression towards the clinic.
- **Q10.** Understanding if biomarkers to measure disease modification can be identified is crucial before progression to clinical studies.
- **Q11.** Neurofilament light chain (NFL) should be measured in every study as a biomarker of treatment response.
- **Q13.** Understanding if a patient stratification approach can be identified is crucial before progression to clinical studies.
- **Q14.** Pre-clinical findings should be replicated in an additional independent lab using the same experimental set-up.
- **Q21.** Confirming functional response in an Experimental Medicine study is an essential step ahead of progressing to clinical trial.

Appendix 2

Workshop Attendees

The following people attended and contributed to discussions at a virtual workshop on 6 June 2022. **We would like to thank all the workshop attendees for sharing their time, insights and feedback with us.**

First Name	Last Name	Institution	Position
Adrian	Isaacs	UCL	Principle Investigator
Alessia	Auber	Evotec	Principal Scientist
Ammar	Al Chalabi	Kings College London	Professor of Neurology & Complex Disease
Andrea	Malaspina	Queen Square Institute of Neurology	Professor of Neurology
Anna	Ambrosini	Fondazione AriSLA	Chief Scientific Officer
Anne	Phelan	Benevolent AI	CSO
Bhuvaneish	T Selvaraj	Anne Rowling Regenerative Neurology Clinic, University of Edinburgh	Group Leader
Brian	Dickie	MND Association	Director of Research
Carolyn	Young	Walton Centre NHS Trust	Neurologist
Caterina	Bendotti	Institute for Pharmacological Research Mario Negri IRCCS	Head of Lab
Colin	Stubberfield	PrecisionLife	SVP Drug Discovery
David	Fischer	Charles River	Chief Technology Officer (Early Discovery)
David	Setters	Living with MND	Living with MND
Derek	Sheader	LifeArc	Business Development Manager
Fernando	Vieira	ALS Therapy Development Institute	CEO and CSO
Gareth	Miles	University of St Andrews	Professor of Neuroscience/Head of School
Giampietro	Schiavo	University College London	Deputy Director, Queen Square Institute of Neurology
Guhan	Nagappan	Glaxo SmithKline	Senior Scientific Director
James	Berry	Mass General Hospital	Neurologist
Jamie	Timmons	Amylyx	Head of Scientific Communications
Janine	Kirby	University of Sheffield	Professor of Neurogenetics
Jean	Waters	Living with MND	Living with MND
Jeremy	Shefner	Barrow Neurological Institute	Chief Medical Officer for Clinical Research
Jessica	Lee	Medicines Discovery Catapult	Head of Patient-Focused Partnerships
Jill	Richardson	MSD	Executive Director, Head of UK Neuroscience
Jinsy	Andrews	Columbia University	Director of Neuromuscular Clinical Trials
Jo	Latimer	MRC	Head of Neurosciences and Mental Health

Kate	Holmes	National Institute for Health and Care Research	Head of Collaborations
Kevin	Talbot	Oxford University	Head of Department, Nuffield Department of Clinical Neurosciences
Kuldip	Dave	The ALS Association	Vice President Research
Laura	Ferraiuolo	University of Sheffield	Professor of Cellular Neuroscience and Metabolism
Laura	Caberlotto	Evotec	Senior Research Leader
Laura	Ajram	Medicines Discovery Catapult	Partnership Lead, Neuroscience
Leann	Quinn	Charles River Laboratories	Business Development
Lee	Coney	Cell and Gene Therapy Catapult	Head of Development
Linda	Greensmith	University College London	Science Director UCL QS MND Centre; Head of Department
Ludo	Van Den Bosch	KU Leuven & VIB	Full Professor
Majid	Hafezparast	University of Sussex	Professor of Molecular Neuroscience
Meera	Swami	Eisai	External Innovation Manager
Melissa	Bowerman	Keele University	Senior Lecturer in Rare Genetic Diseases
Merit	Cudkowicz	Massachusetts General Hospital	Chief, Neurology
Neil	Miller	NRG Therapeutics Ltd	CEO
Nick	Cole	MND Association	Head of Research
Nicola	Ticozzi	Istituto Auxologico Italiano, University of Milan	Neurologist
Nicola	Waters	Living with MND	Living with MND
Nicola	Heron	Medicines Discovery Catapult	Chief Business Officer
Nigel	Leigh	Brighton and Sussex Medical School	Professor of Neurology
Oliver	Freeman	AstraZeneca	Associate Director
Pamela	Shaw	University of Sheffield	Professor of Neurology, Director of SITraN
Paul	Wright	LifeArc	MND Translational Challenge Lead
Pavel	Balabanov	European Medicines Agency	Head of Office, Therapies for Neurological and Psychiatric Disorders
Pietro	Fratta	UCL	Professor of Neuroscience
Priya	Viswanathan	NIHR	Research Collaboration Manager
Richard	Rutter	NRG Therapeutics	CSO
Richard	Mead	University of Sheffield	Senior Lecturer
Sean	McGrath	My Name'5 Doddie Foundation	Medical Strategy Lead
Thomas	Nieland	Verge Genomics	Director, Head of Target Validation & Exploratory Biology
Tom	Gillingwater	University of Edinburgh	Professor of Anatomy

Medicines Discovery Catapult
md.catapult.org.uk
@MedDiscCat
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