Amyotrophic lateral sclerosis: biological drivers of a complex disease.

Supervision:

Primary Supervisor: Prof Kevin Talbot (Head of NDCN and Professor of Motor Neuron Biology) Assoc. Prof Alex Thompson (MRC Clinician Scientist Fellow)
Day-to-Day Supervisor (Cellular): Dr Ruxandra Dafinca
Day-to-Day Supervisor (Computational): Avigail Taylor (IMCM Technical Lead in Bioinformatics)
GSK Supervisor: TBD (Andrew Goldfine as interim)

Summary:

Amyotrophic lateral sclerosis (ALS) causes progressive weakness due to loss of neurons within the corticomotoneuronal system. Despite decades of preclinical research and clinical trials, there remains only a single globally licensed disease-modifying therapy, with a small effect on survival. The upstream cellular and neuronal network-level events that lead to ALS are complex, and reflect significant disease heterogeneity, both in aetiology and progression between individuals. There is an urgent need for disease stratification to improve clinical translation.

This project will combine established pre-clinical cellular models with data generated in the IMCM ALS project from large patient cohorts to specifically establish the role of novel biomarkers in the pathogenesis of disease, by 1) identifying concordant changes using omics analysis of patient samples and cellular models, combined with large-scale genetics data 2) manipulating these pathways in cellular model systems and 3) testing GSK assets which target these pathways in cellular models.

The fellow will be trained in the analysis of complex omics and large-scale genetics datasets to align outputs from our current IMCM ALS project with data from pre-clinical modelling of ALS using induced pluripotent stem-cell models

iPSC models of ALS are well established in the Talbot group in the Kavli Institute (https://www.ndcn.ox.ac.uk/team/kevin-talbot). These models include combined cortical/spinal neuronal cultures, nerve-muscle co-cultures, and mixed neuronal/glial cultures. Key markers from OLINK proteomic signatures from the IMCM ALS project will be investigated in these models for their disease relevance.

Aims and Objectives:

Alignment with therapeutic area and key scientific theme(s):

This project closely aligns with the ALS theme of the IMCM. The joint Oxford-GSK ALS team have identified novel candidate biomarkers using proteomic analysis of our clinic cohorts. In order to understand how these biomarkers relate to the disease process and produce mechanistic insights to aid target engagement studies, we will now specifically investigate the pathways driving these biomarker changes in preclinical cellular models. This will be an iterative process which is likely to help focus the cohort analysis further by developing new biological insights into motor neuron degeneration.

Aims:

- Prioritise candidate pathways and biomarkers for mechanistic analysis
- Investigate mechanistic role of prioritised candidate pathways by manipulating cellular model systems
- Test GSK assets targeting these pathways in cellular models

Project delivery:

Kevin Talbot's group is based at the Kavli Institute for Nanoscience Discovery, a cross-Divisional University facility which brings together the biological and physical sciences to understand the cell. We have developed significant expertise in modelling ALS using induced pluripotent stem cells derived from patients attending the Oxford MND clinic:

i) spinal motor neuron and cortical neuron monoculture, demonstrating reproducible ALS-relevant phenotypes.

https://pubmed.ncbi.nlm.nih.gov/39440303/

https://pubmed.ncbi.nlm.nih.gov/38876108/

We have recently extended this work to the use of i) optogenetics to drive activity dependent phenotypes, analysable with multielectrode arrays ii) translatomics to identify novel disease signatures (manuscripts in preparation).

ii) spinal motor neuron/microglia co-culture, identifying specific mediators of microglial pathological effect on motor neurons

https://pubmed.ncbi.nlm.nih.gov/37736756/

https://pubmed.ncbi.nlm.nih.gov/35871163/

We are currently establishing more complex culture systems:

iii) spinal motor neuron/cortical neuron (+/- microglia) co-cultures

iv) spinal motor neuron/muscle co-cultures

These models will allow us to map network changes in proteomics signatures with specific aspects of the corticomotorneuronal axis in ALS to further develop our understanding of the relative contributions of upper and lower motor neurons to disease heterogeneity. All models are routinely being cultured in the group, allowing the fellow to focus on data analysis.

We have also jointly started developing pipelines (including extracellular vesicle proteomics) to cross-validate our cellular model systems with human biofluids from the ALS cohort.

We have expertise to analyse basic RNA sequening and proteomic data within the group but a joint project with the IMCM bioinformatics team and support from expertise within GSK would greatly enhance the power of our analysis and allow integration with our human biosample data.

Timelines:

Year 1:

Milestone 1 (1-12 months): the fellow will work with existing transcriptomic and proteomic data models generated by post-doctoral scientists in the group to establish pathway analysis which allows comparison of cellular models with proteomics data from the ALS IMCM project. There will also be an opportunity to develop, where relevant for the project, wet lab skills in culturing motor neurons, cortical neurons and microglia and analysing disease relevant phenotypes in response to oxidative stress and neuronal activity through optogenetics (cell survival, neurite outgrowth, mitochondrial bioenergetics, axonal transport, synaptic function).

Milestone 2 (6-12 months): a) complex co-cultures of spinal and cortical motor neurons with muscle/microglia will be analysed with proteomics and transcriptomics, b) targeted analysis of differentially expressed protein networks from OLINK data from our ALS cohorts.

Year 2:

Milestone 3 (months 13-18): the fellow will work with the IMCM bioinformatics core to analyse pathway data from the cellular omics readouts and link this to protein profiles from the ALS cohort studies. Candidate pathways and individual protein biomarkers will be prioritised based on overlapping alterations in cellular models and patient proteomics data, incorporating large-scale genetic data to provide evidence of causality.

Milestone 4 (months 19-30): the cellular model systems will be manipulated to alter expression of candidate molecules that are hypothesised to drive phenotypic changes.

Year 3:

Potential therapeutic assets in the GSK pipeline which target identified pathways will be analysed in our cell models, using our pathway analysis as a readout of disease engagement.

Research environment:

Provide additional information on support available for the fellow including:

- *brief details on whether the research group or institution are currently using similar methodologies or exploring similar hypotheses*
- *any additional financial or practical support specific to the research group or institution*
- *the extent and frequency of any clinical commitments expected of the fellow*

The IMCM brings together the very best scientific, clinical, technological and computational expertise from Oxford University and GSK to form a unique industry/academic partnership. The Institute will develop disease-agnostic platforms to change the clinical practice of pathology, helping to identify and validate early potential drug targets and biomarkers to predict disease progression. The fellow will benefit from the rich interdisciplinary environment of the IMCM but also from the broad range of translational research in the Oxforrd MND group. The proposed DPhil candidate will be embedded within the Oxford MND Care and Research Centre, led by Prof Kevin Talbot, Prof Martin Turner and Dr Alexander Thompson, which combines providing clinical care to 10% of people with ALS in the UK with a research portfolio spanning preclinical cellular disease models, world-leading longitudinal biofluid, imaging and neurophysiological cohort studies, and large scale epidemiological and genetic research in ALS. This project therefore provides a broad training in integrating pre-clinical models, patient data with developing expertise in clinical translation in ALS.