Project Details	
Project Code	MRCNMH25Ex Housden
Title	Understanding motor neuron disease using a powerful combination of model systems
Research Theme	Neuroscience & Mental Health
Summary	The aim of this project is to understand the mechanisms that cause motor neuron disease (MND) so that new treatments can be developed. This is important because MND is a devastating disease that results in death only three years after diagnosis. There are no cures and our understanding of why people develop the disease is limited. This project will use cutting edge techniques to investigate the mechanisms underlying MND, leading to effective therapies in the future.
Description	The aim of this project is to investigate the cellular mechanisms underlying motor neurone disease (MND) to facilitate the development of new therapies in the future. This is important because MND has a short life expectancy (3 years from diagnosis), the impact on quality of life is severe and there are currently no effective treatments. There is a clear need to gain a better understanding of the disease to inform the development of effective therapies. Our approach to uncovering mechanisms of MND is to use genetic interaction analysis to gain insight into the genes and pathways that are involved in loss of viability in MND cells. We have developed Drosophila cell culture models expressing mutant version of human proteins known to be associated with MND (SOD1, FUS and TDP43) and have demonstrated that these models share characteristics with human models of the disease (e.g. alterations in cell viability and protein localisation). Using these new models, we have screened for genetic interactions between two mutant forms of TDP43 and approximately 350 kinases. This has resulted in the identification of several candidate genetic interactions that are now being validated. In addition, we have profiled transcriptional changes that occur when mutant forms of TDP43 are expressed. These datasets provide a powerful basis for mechanistic analysis. A major problem in determining mechanisms of human disease is that knowledge and candidate therapies identified in cell culture systems are not always relevant in patients. We have developed methods to overcome this issue by cross comparing between cell models derived from distant genetic backgrounds. Specifically, by comparing Drosophila cells to human cells modelling the same disease, it is possible to distinguish mechanisms and drug targets that are relevant across diverse systems from those that are specific to one system. This results in mechanistic understanding and candidate drug targets with a high chance of relevance in the clinic. In this project, the student will compare results between Drosophila cells, Drosophila in vivo models and human iPSC models of MND to gain new knowledge of the underlying mechanisms that are likely to be relevant to patients. Initially, the student will build on our previous work by extending the genetic interaction screens to cover 150 additional genes for which clinically approved chemical inhibitors already exist (Objective 1). By focusing on this gene set, identified genes and pathways have a high chance of rapid translation towards new therapies. Using these data

	combined with the previous screen results and the transcriptomic data, the student will then use computational approaches to map pathways associated with MND (Objective 2). Finally, the student will investigate the identified pathways using two diverse models of MND. The first is an in vivo Drosophila model and the second is an iPSC model. By investigating these new pathways in Drosophila cells, in vivo and using human cell models, we can apply a filter to remove MND-linked mechanisms that are specific to a single model system and focus on those pathways that are common between diverse genetic environments. This greatly increases the chances that our results will be relevant to human patients. Objective 1: To map genetic interactions with 150 potential drug targets. Objective 2: To map biological pathways involved in MND using computation methods During this objective, the student will guide the data analysis approach and choosing the most appropriate method for the task. For example weighted gene co-expression network analysis (WCNA), similarity network fusion (SFN) and/or topological data analysis (TDA), with guidance from Professor Krasimira Tsaneva-Atanasova. Objective 3: To validate novel MND pathways using human iPSC and Drosophila in vivo models The student will decide which genes and pathways to pursue based on advice from the supervisors and their own literature-based analysis of the candidates. These decisions will be guided with input from Prof. James Hodge, who has extensive experience in characterisation of fly models of neurodegenerations. Overall, we expect this project to address an important biological question, which will lead to significant impact on human health in the future. The project will also provide the student with a broad range of skills that will be invaluable in many different future careers.
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