The contribution of neurons and microglia to pathogenesis of TDP-43 related ALS

Acronym: TDPBAC

Principal Investigator: Kevin Talbot

Grant: 170 000€

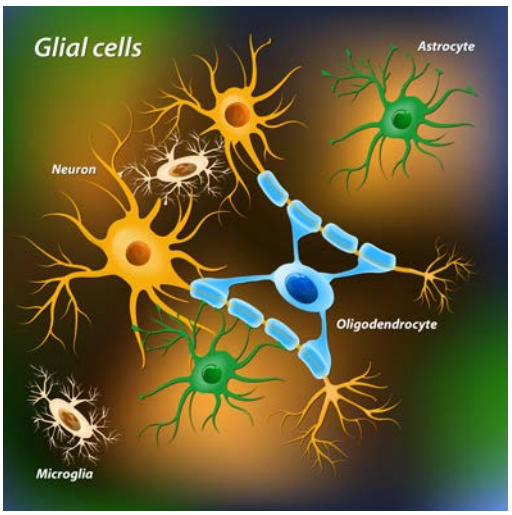
Duration: two years

Summary of the research project

This project is being carried out in the laboratory of Professor Kevin Talbot in the Nuffield Department of Clinical Neurosciences at the University of Oxford and will be co-led by Dr David Gordon.

The RNA-binding protein TDP-43 is central to the pathogenesis of ALS. In affected motor neurons, TDP-43 characteristically becomes depleted from the nucleus and mislocalised to the cytoplasm, where it forms the major protein component of insoluble, ubiquitinated inclusions. The group have produced a novel mouse model of ALS based on inserting a single copy of the human TDP-43 gene with an ALS-causing mutation into the mouse genome, allowing more realistic expression, closer to that observed in patients with ALS. This mouse develops progressive weakness from about 6 months of age and has a reduced lifespan.

Although most studies in ALS have focused research on the mechanisms of degeneration of the motor neuron itself, a growing body of evidence has implicated non-neuronal cells such as glia in disease onset and progression in ALS. This is often referred to as a 'non-cell autonomous' mechanism, meaning that it may be the interaction of several cell types, not just motor neurons acting alone, which is responsible for neurodegeneration.



This project takes advantage of a special feature of the mouse model. The way it was constructed means that the expression of mutant TDP-43 can be switched off selectively in different cell types by crossing the mouse with another mouse line expressing the enzyme Cre-recombinase in either motor neurons or in microglia.

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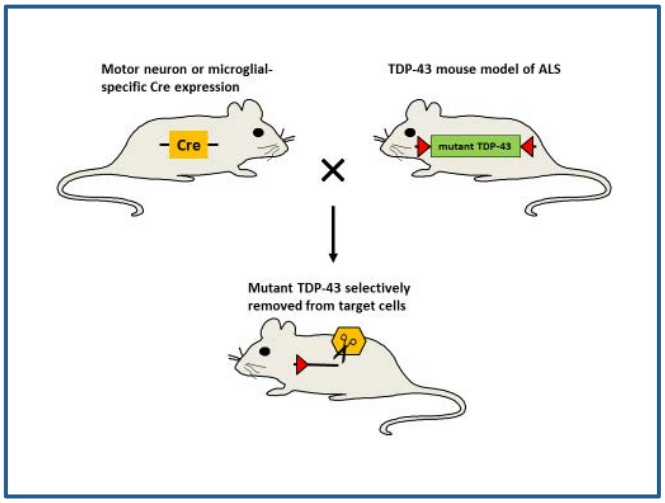
The aim of the project is to inactivate the transgene in motor neurons to establish whether neurodegeneration still occurs or whether expression of mutant TDP-43 is absolutely necessary to trigger ALS pathogenesis. Similarly, the mutation will be inactivated in microglia to see if this improves or eliminates the neurodegenerative phenotype. Understanding the relative contribution of these two cell types will help target therapies for ALS.

Schematic presentation of the research project:



Research team from left to right:
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