08 February 2016

Project title	**Development of new models of FTLD/MND**		
Key words	neurodegeneration; dementia; transgenic; mouse; disease		
Expected duration of the project (years)	5		
Purpose of the project	Basic research	Yes	
	Translational and applied research	Yes	
	Regulatory use and routine production		No
	Protection of the natural environment in the interests of the health or welfare of humans or animals		No
	Preservation of species		No
	Higher education or training		No
	Forensic enquiries		No
	Maintenance of colonies of genetically altered animals	Yes	
Objectives of the project	To develop novel mouse models of frontotemporal lobar degeneration (FTLD)/motor neuron disease (MND) in which to study mechanisms of disease and find new treatments. There is significant overlap between FTLD and MND with ~15% of patients presenting with both diseases. MND is a devastating disease, causing progressive paralysis and loss of life typically within just 2-5 years of onset. There are currently no treatments for these diseases. To generate the mice we will introduce a genetic modification (in the C9orf72 gene) that has been identified as being present in one out of every twelve patients diagnosed with FTLD/MND (i.e. we will be creating transgenic mice).		
Potential benefits likely to derive from this project	The primary potential benefit of this project is the generation of novel models of FTLD/MND that can be used to develop new treatments. Detailed studies of disease mechanisms are not possible in humans and therefore new mouse models of FTLD/MND would greatly improve our knowledge in this field. There are no disease-modifying treatments at present for FTLD/MND and therefore potential future benefits could be significant if this new knowledge helps to identify novel ways of treating the disease that could be tested in patients.		

Species and approximate numbers of animals expected to be used, and anticipated period of time	All studies will be in mice. Over the five year period of the project the maximum number of mice we expect to use is ~2500 mice. The majority (~2000) of these will be for breeding purposes and for maintenance of transgenic lines with around 500 animals to be used in actual experimental procedures.
Expected adverse effects and the likely/expected level of severity. What will happen to the animals at the end.	We will be assessing behavioural changes in the mice to find out if these are similar to what is observed in FTLD/MND patients. In addition we will assess pathological changes in the brain of the transgenic mice. The tests to be used are quite straightforward and do not involve any stress or harm to the animal. They will be used to assess co-ordination, learning, social interaction and motivation. Wherever possible we will use tests that rely on normal mouse behaviours such as nest building and burrowing. No surgery or other invasive procedures will be used. Animals will receive some simple injections and will occasionally have blood taken. Since we are generating completely new transgenic mice we do not know at this stage what adverse effects will be observed. However as we are trying to model a severe human disease like MND it is possible that the animals will be affected quite badly, for example showing problems with movement and eventual paralysis. Based on very recent studies in mice with C9orf72 related modifications effects range from none, the mice being completely normal, to hindlimb paralysis and reduced survival starting at 20-40 weeks. We will monitor all our animals very closely and immediately stop studies if there is any indication of adverse effects that are causing the animal pain, suffering or distress. The primary humane end point will be when animals show extreme weakness in both hindlimbs, defined as the inability to dorsiflex (bend).
Application of the 3 Rs	
1. Replacement Why do animals need to be used, and why non-animal alternatives cannot be used.	Studying mechanisms involved in neurological diseases such as FTLD/MND is extremely complex and in addition to pathological changes in the brains of FTLD/MND patients, the disease is characterised by profound changes in behaviour, which it is not possible to study in vitro. The proposed animal studies are complementary to a much greater programme of work on FTLD/MND using human samples, cell lines and model organisms such as the nematode C.elegans.

2. Reduction How the use of minimum numbers of animals will be assured	Pathological and behavioural end points proposed in this project are well established in studies of dementia and other neurological disease and experiments are therefore planned based on previously published data or our own experience. We will use the minimum number of animals that can answer the desired scientific objectives and will extract all relevant information in the data by using appropriate statistical analysis. Studies will be designed using the newly released Experimental Design Assistant (EDA) from the NC3Rs (https://www.nc3rs.org.uk/experimental-design-assistant-eda).
3. Refinement Reasons for the choice of species and why the animal model(s) to be used are the most refined, having regard to the objectives. General measures to be taken to minimise welfare costs (harms) to the animals.	Although it is possible to use animals with a lower degree of neurophysiological sensitivity (e.g. zebrafish, drosophila, C.elegans) as models of dementia these organisms do not allow one to mimic fully the brain pathology and behavioural changes associated with FTLD/MND. In contrast mice allow one to model the disease more closely, hopefully leading to a better understanding of disease mechanisms and the discovery of new treatments. All animals will be closely monitored for adverse effects caused by the genetic modification. Should there be severe behavioural changes then animals will be humanely killed immediately.