INVESTIGATING THE ROLE OF TDP43, RECENTLY FUNDED MUTATED GENE CAUSATIVE OF ALS, IN MOTOR NEURONS

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Grant: € 100 000

Some forms of amyotrophic lateral sclerosis (ALS) arise because the affected individuals have a mutation in a particular gene. This mutated gene can be inherited in families and give rise to 'familial' ALS. One such gene is SOD1, which when in its mutant form, causes inherited ALS. Recently, in 2008 and 2009, a series of papers published in the biomedical press have shown that another gene, called TDP43 is also causative, when mutated, for ALS in the human population.

Both SOD1 and TDP43 are very important for our understanding of ALS because they give us a way to work out the biology of the disorder, and how mutations in these genes disrupt this normal biology. For TDP43, comparatively little is known about its function, other than it seems to be mainly involved in the processing and metabolism of a chemical called RNA that is important to the function of all cells, including motor neurons.

Once a new mutant gene for a human disease has been found, such as TDP43, the next step in trying to understand its function and to understand the aberrant biology caused by its mutation is to put a similar mutation into the same gene into a mouse. This approach makes sense because we share almost all our genes with mice as we both come from a common ancestor, and so our genes are doing similar things and giving out similar instructions to our cells. Many laboratories are now making genetically modified mice called transgenic mice and knock out mice, in a bid to find out more about TDP43. Although these mice will be very useful for improving our understanding of TDP43 biology, they have one major drawback in that they either have greatly elevated levels of the mutant TDP43 protein, or have no TDP43 at all. However, our group has a different kind of genetically modified mouse, which is unique and which more faithfully represents the physiology of a human patient. This mouse, like human patients, has a single change in its DNA in TDP43, this is an analogy of what is found in human ALS patients with TDP43 mutations. Thus this mouse will greatly complement the current studies of TDP-43 transgenic and knock out mice, and, we believe, will provide a better system in many respects for developing both conventional and gene based therapeutics.

IN SUMMARY

We have put together a 3 year proposal with one postdoctoral researcher to fully characterize an important new mouse model of TDP43-induced ALS that potentially reflects the physiological and biochemical levels of mutant TDP43 found in human ALS cases. Working in our own experienced laboratories and with an existing group of world-class collaborators we will analyze this mouse in order to give the ALS community an important new tool for ALS research and a resource for the development of conventional and gene based therapeutics. This project is the beginning of a long-term and much larger study aimed at generating new mouse models to understand human ALS, and without this 3 years of funding we simply cannot capitalize on our finding of the mutation or carry out the essential analyses described above to make this mouse strain useful and informative for the ALS community.

TEAM

Professor Elisabeth Fisher and Professor Linda Greensmith work at the Institute of Neurology (ION) part of University College London, a multidisciplinary neuroscience centre with a long standing history of achievements and the top 4* RAE(Research Assessment Exercise) rating. Together with the adjacent National Hospital for Neurology and Neurosurgery, ION forms one of the world's pre-eminent neuroscience centers. Elisabeth Fisher is in the Department of Neurodegenerative Disease, within the MRC Prion Unit - Prof. John Collinge is Head and gives his full support and access to Unit facilities and expertise. Linda Greensmith is in the Sobell Department of Motor Neuroscience and Movement Disorders and leads a lab focused on the study of cellular and systems biology of peripheral neurons and has a particular interest in ALS. Dr Abraham Acevedo is a program leader at the Medical Research Council Mammalian Genetics Unit, a premier mouse genetics establishment, and a pioneering centre in the use of mouse ENU mutagenesis. Its main focus is the development of new mouse models of human diseases with particular emphasis on phenotypic pipelines, with wide expertise on neurobehavioral genetics.

Investigating the role of TDP43 in motor neurons through studying a unique *Tdp43* mutant mouse

Call for projects 2009
Grant: 100 000 €
Project Duration: 2 years

Investigators: Elizabeth Fisher (PI), Linda Greensmith, UCL Institute of Neurology, London; & Abraham Acevedo, MRC Harwell, Oxford

Updated results December 2012

TDP43 is a gene that causes ALS when it is mutated. In trying to understand the biology of TDP43 and what happens when it is altered and causes disease, reliable animal models are needed. We have characterized mouse models that have single 'point mutations' within the endogenous *mouse* Tdp43 gene, similar to what is seen in humans.

Funding from the Thierry Latran Foundation enabled us to study these mice. We found that these mice have defects in 'RNA metabolism'. It is important to understand the mechanism of these defects as abnormalities of RNA processing are currently thought to play a crucial role in the pathogenesis of ALS. The mouse model we created will contribute to these studies.