Home Office

NON-TECHNICAL SUMMARY

Kinase signalling in neuronal development and function

Project duration

5 years 0 months

Project purpose

- (a) Basic research

Key words

Brain development, brain tumour, neurodegeneration, epilepsy

Retrospective assessment

The Secretary of State has determined that a retrospective assessment of this licence is not required.

Objectives and benefits

Description of the project's objectives, for example the scientific unknowns or clinical or scientific needs it's addressing.

What's the aim of this project?

Our main goal is to discover novel mechanisms that play important roles in brain development and function. Kinases are enzymes that have critical functions in all cells. Role of several different kinases in neuronal development and function is not well understood. Learning more about kinases and

defining the molecular pathways that they regulate could be useful in designing therapeutics. We work on several kinases: their function range from preventing tumor formation, enabling correct brain cell formation to enabling correct wiring of the nervous system. Deficiencies in kinases can cause neurodevelopmental disorders such as CDKL5 Deficiency Disorder. Children with CDD have very early onset seizure that are difficult to control. Our research contributes to clarify cellular mechanisms that are regulated by CDKL5, and are defective in patients. We also work on kinases, whose deficiencies cause brain tumour or neurodegeneration in mice. By studying these mouse models we learn more about the mechanisms that play roles during tumour development or neurodegeneration. We then strive to translate our findings to therapies by connecting with clinicians.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

What are the potential benefits that will derive from this project?

We will discover novel kinase substrates and validate these in vivo. This will reveal signalling pathways that may be also used in different cell types and organisms. We will determine roles of kinase substrates and phosphorylations in vivo. Our novel substrates can be used as molecular read outs of signalling cascades and may be biomarkers for diseases. We have ongoing collaborations with multiple pharmaceutical industry partners. Novel discoveries can be translated into drug discovery research by our partners.

Species and numbers of animals expected to be used

What types and approximate numbers of animals will you use over the course of this project?

5 years 10000 mice and 150 rats

Predicted harms

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?

In vast majority of cases we will cull animals under terminal anaesthesia to remove tissue for histological or physiological examinations. We will also use standard killing procedures to cull animals without anaesthesia. Breeding genetically altered animals are non-invasive. Our main experimental approach involves histological and microscopic analysis of post-mortem tissues and physiological analysis of organs isolated from transgenic animals. Our second experimental approach is to obtain acute slices for electrophysiology. Animals will be anaesthetized prior to decapitation. We will also make primary cultures from our embryos obtained using schedule 1 methods.

Replacement

State why you need to use animals and why you cannot use non-animal alternatives.

Our project's goal is to discover mechanisms that play a role in the formation of connections between brain cells with each other. Brain circuitries that we are planning to work on to understand the molecular basis of their formation cannot be produced elsewhere. Non-animal models cannot replace testing hypothesis, that may be generated by the non-animal work, in animals. Nevertheless, much of the work in this project is to be done using ex-vivo material. Prior work from other groups and our in vitro work supports this project.

Before embarking on any animal experiments, we will collect as much evidence as possible to determine whether a candidate genetic or environmental manipulation has a reasonable chance of success and providing information within *in vivo* systems. Evidence will be collected from our own experiences and previous results as well as by surveying the mammalian and other literature. In addition, we will use non-regulated procedures to collect expression data from fixed non-GM mammalian tissues and functional/expression data from genetically and/or environmentally manipulated *in vitro* mammalian cell lines and/or early chick and fish embryos.

Reduction

Explain how you will assure the use of minimum numbers of animals.

We have restricted our analysis to few standard and most relevant time points. We will collect data and complete analysis from smaller cohorts before deciding on requirements for more numbers.

Refinement

Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.

We use rodents as model organisms. Neuronal circuitry in rodents have been studied over decades and cell types and physiological properties are well defined. In addition battery of behavioural tests and imaging methods are available. Finally, numerous transgenic lines exist, by use of conditional knockout techniques we are able to narrow down cell types in which kinases are deleted. Animals are monitored regularly and humane endpoints will be adhered to in communication with NACWO and NVS. Enrichment in home cages will be provided where possible.