Home Office

NON-TECHNICAL SUMMARY

Establishing PKC-superfamily members as targets for new cancer therapeutics

Project duration

5 years 0 months

Project purpose

- (a) Basic research
- (b) Translational or applied research with one of the following aims:
  - (i) Avoidance, prevention, diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants.

Key words

Cancer, kinases, drugs, cardiovascular, colorectal

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?

Amongst the key changes in cancers are those associated with a family of cellular regulators, referred to as protein kinases. Here we address the cancer-associated actions, interventions and physiological liabilities of members of a subfamily of protein kinases, termed the protein kinase C family. We will determine if inhibition of aPKCi impacts tumour growth. We will determine if PKCe inhibition/loss is associated with reduced tumour formation. We will assess the phenotype of PKN family loss and assess impact on tumour incidence. We will assess the in vivo actions and hence drug opportunities for the two penetrant cancer mutations in PKCa and PKCb.

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 are seeking to improve cancer patient treatment options through validating and enabling drug development programmes directed at specific molecular targets. During the course of this licence we will test the effects and potential liabilities of genetic removal of PKN subfamily members in the context of a prostate cancer model (PKN3) and a colorectal cancer model (PKN1-3). We will test directly the consequences on aPKCi inhibition in the context of mutant Ras driven lung cancer in a series of different genetic models of disease. We will test the validity of PKCe as a target for intervention in p53 mutant tumours both through genetic ablation and also through inhibition. For PKCa/b we will assess whether gain/loss of catalytic activity affords a druggable opportunity. All studies will be written up and disseminated to the wider research community and we anticipate that one or more of these studies will lead to progression of drugs into Phase 1 trials in patients.

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?

It is expected that we will use 10000 mice during the course of these studies. These will include embryos, but most mice will be used as adults.

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?

The adverse effects will relate to tumour formation and any stress associated with possible heart hypertrophy (for one subfamily of genes). For the majority of the tumour formation studies, we are breeding tumour prone genetically modified strains where we have knowledge of the timing of tumour formation and hence can actively monitor animals at the appropriate time to ensure that animals do not suffer unexpected effects. The crosses and treatments we propose to perform are based on ex vivo

experiments where we have observed suppressive effects of interventions and hence the expectation is that we will suppress tumour development or progression and hence reduce the tumour-associated adverse effects seen in these strains.

In the case of the PKN2 knockout, in the context of PKN1/3 loss, we are seeking to induce colorectal cancer with a well-tested promotion protocol. There is the possibility of inflammation associated with this protocol, however careful monitoring will be applied to ensure that if this occurs then any associated adverse effect is limited. In respect of this genetic manipulation, the expectation is that there will be a reduced tumour burden with loss of this gene subfamily and hence no additional adverse effects. A related colorectal induction protocol is also to be used where we wish to test directly a drug intervention against another member of this gene family (PKCe). Here a less inflammatory protocol is to be employed which works in the particular genetic background; there is little likelihood of an inflammatory response here. As above, these manipulations are expected to reduce tumour burden and hence reduce adverse effects. For the PKCb knock-in mutation it is anticipated that this might promote an earlier induction of leukaemia/lymphoma in the HTLV-1 tax genetic background (itself prone to these cancers). Close monitoring will be applied for these strains. For PKCa it is also possible this will promote disease, hence we will implement close monitoring of this strain.

All animals will be humanely euthanised at the end of the experiments or once the humane endpoint is met

Replacement

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

Extensive *ex vivo* studies have been carried out on the genes under investigation here, leading to specific predictions regarding reliance of certain tumour types on the action of a subset of these genes. However, these predictions are not sufficient to define them as viable drug targets in human cancer, as they rely upon monocultures of tumour cells not accounting for the complexity of the *in vivo* environment; it is noted also that these genes are widely expressed in normal tissues. Hence to understand whether the dependencies observed *ex vivo* contribute to *in vivo* tumour formation and progression, and whether targeting these genes offers a therapeutic opportunity, demands data from a suitable *in vivo* model organism. The gene family under investigation is comprised of 12 genes (PKC superfamily) and is uniquely present in mammals with a limited repertoire present in other model organisms, ranging from 1 in yeast to 5 in drosophila. For those genes specifically under investigation here, non-mammalian model organisms do not provide either the complexity of the mammalian family (not represented or only in part) nor the context (e.g. stroma, vasculature, genetically engineered tumour models) in which to assess roles in tumour behaviour and the potential liabilities for patient intervention.

Reduction

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

The fundamental principles of breeding mice will be observed. As a general principle experiments will be designed to employ the least number of mice in order to derive a statistically sound answer. Specific advice on design and analysis has come from individuals who have extensive experience of work with the tumour models we intend to assess.

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.

The complexity of the mammalian gene family is represented in mice alongside the tumour models, making mice currently the only choice for these *in vivo* target validation studies.

We will employ good husbandry practices including regular monitoring of all animals. Through this good practice we will closely monitor the welfare of our animals and look for any reaction to experimental procedures. We will increase monitoring following any acute procedure. We will utilise humane endpoints to minimise suffering and especially in any cases of unexpected / additional suffering. The use of humane endpoints will be considered carefully at the stage of experimental design, and reviewed throughout experiments in light of our observations.