

## HOME OFFICE LICENSING

Since the last meeting, the ERP Certificate Holder's Advisory Group has recommended three applications for amendments to existing project licences and three applications for continuation project licences. The Committee is asked to receive and note these applications, which were:

### Application

**Project Title: Mechanisms of plasticity in the visual cortex**

An application to continue work from an existing Project Licence. The application has been granted by the Home Office, and the project abstract is reproduced below for further information.

**Project Title: Brain mechanisms underlying configural/episodic memory in animals**

An application to continue work from an existing Project Licence. The application has been granted by the Home Office, and the project abstract is reproduced overleaf for further information.

**Project Title: Analysis of behavioural plasticity in rodents**

An application to continue work from an existing Project Licence. The application is currently with the Home Office, and the project abstract is reproduced overleaf for further information.

### Amendments:

**Project Title: Regulation of Peripheral Receptors for Biogenic Amines**

An application to amend an existing Project Licence. The application has been granted by the Home Office, and the lay summary is reproduced below for further information.

**Project Title: Thalamic and Cortical Mechanisms of Sleep and Absence Epilepsy**

An application to amend an existing Project Licence. The application was to update authority to import animals onto the project using the new Home Office administration method for "Better Regulation". The application was approved by BSC Chair's action, as this licence automatically qualified for attention from BSC, which did not meet over the Summer period.

**Project Title: Immune responses during persistent virus infection**

An application to amend an existing Project Licence. The application is currently with the Home Office, and the lay summary is reproduced below for further information.

BSO  
25 September 2010

## Lay Summary and Abstracts from Applications Processed by CHAG

Please note – These are for information only – no assessment by the Committee is needed

### Application 1 -Mechanisms of plasticity in the visual cortex

**Abstract:** This project aims at understanding at a cellular and subcellular level how the mammalian visual system adapts in both childhood development and adulthood to the visual environment and changing visual experience. Work over the past 50 years has greatly increased our knowledge of visual development as well as of disorders of vision such as amblyopia ('lazy eye'), but the underlying mechanisms of plasticity (the constant changes and adaptation taking place in the visual system) have only recently begun to be unravelled.

In order to achieve a more detailed understanding of plasticity, animals will be reared in a variety of visual environments that will provide them with either an impoverished or selectively enhanced visual experience. A small glass window will then be implanted into the skull above the visual cortex. The activity of the visual cortex will be imaged repeatedly using two different techniques of which one allows an overview over the patterns of activity in an entire area of cortex while the other enables us to visualise the activity of a smaller number of individual neurons. By labelling different types of neurons with specific dyes we will be able to monitor over time how their visual responses change dependent on visual experience. We will further examine the role certain proteins play in plasticity, by studying knock-out mice lacking the genes encoding those proteins. Some of these genes are known to be mutated in human developmental disorders of the brain such as in Fragile-X. A detailed understanding of their role in cortical development may help identify strategies to treat them in the future.

Since normal sensory input to the brain cannot be studied in the dish, there is no alternative to using live animals for this work. The use of modern imaging techniques as well as longitudinal assessment of individual animals at multiple time points will keep the number of animals to the necessary minimum. Animals will be anaesthetised and additionally given analgesics preoperatively in order to avoid them feeling any pain during surgical procedures. Animals undergoing longitudinal tests will be examined daily in order to identify early signs of pain or distress, or of infections as the most common adverse effect.

For the majority of the experiments in this project mice will be used. They are not only the most widely used mammalian species (and therefore a large body of existing data is available for comparison), they are the only mammalian species for which genetically modified subjects are readily available, which is crucial for this project. For functional MRI studies, rats and tree shrews will be used because their larger brains are more suitable for the lower spatial resolution of MRI. In addition, anatomical similarities between tree shrew and primate brains allow better comparison with human subjects.

Our study will help to gain a more detailed understanding not only of visual disorders such as amblyopia but of developmental brain disorders (such as Fragile-X) in general. Such knowledge may lead to developing new approaches to treatment of these conditions.

## Application 2 -Brain mechanisms underlying configural/episodic memory in animals

**Abstract:** 1. This project aims to identify the psychological and neural systems that underpin the encoding, storage and retrieval of configural/episodic memory in normal animals and animal models of human dementia.

2. Episodic memory binds together information about the time and the place where an event occurred. The importance of episodic memory is highlighted by the fact that it is one of the first cognitive domains to deteriorate in brain disorders, such as Alzheimer's disease. Nevertheless, the psychological and neural mechanisms of episodic memory remain largely unknown. This project will examine how and why brain diseases influence this type of memory. To do so we will use novel behavioural procedures to interrogate configural/episodic memory processes in animals and assess theories regarding their synaptic and systems level substrates. We will then examine how animal models of cognitive disorders such as schizophrenia and dementia (including Alzheimer's disease) and putative interventions influence the psychological and neural substrates of memory.

3. Animals are required for this work because we will need access to psychological, neural and synaptic levels of analysis in order to understand how the brain achieves the capacity for memory and importantly how disease processes influence memory mechanisms. As this research provides analysis at both behavioural and synaptic levels there is no feasible alternative that could replace the use of a living animal.

4. The protocols require the use of animals that are healthy and motivated to demonstrate learning and memory. As such, the level of suffering is kept to a minimum.

5. The project requires the use of rats and mice. Psychological and neural theories of learning have been studied extensively in rodents and thus provide a rich background of information to inform the design of effective and efficient experimental procedures. In addition, a number of the leading genetic models of human cognitive disorders are based in rodents.

6. The procedures include the use of genetically modified mice. The adverse effects of the mutations will be minimal and they typically result in only mild memory impairment and will not affect the special senses or maintenance behaviours. In addition, we will use surgical procedures to remove neurons in specific brain regions. In some experiments, we may record the firing activity of groups of neurons. Acute trauma is minimised by appropriate anaesthetic and analgesic procedures. Some procedures will involve administering drugs. The compounds will usually be well characterised and the dose ranges will be chosen to reduce side effects and typically will be designed to improve learning and memory.

7. The primary benefit from this project is: (1) new knowledge concerning the psychological and neurobiological processes supporting configural/episodic memory and (2) new knowledge regarding how animal models of human cognitive disorders and putative intervention strategies influence memory processes. The main output will be via publications in academic journals. We have active collaborations with industry and this information will be used to promote the translation of animal work to human clinical trials.

### Application 3 - Analysis of behavioural plasticity in rodents

**Abstract:** This project will deal with the analysis in rodents of the molecular and cellular mechanisms underlying learning, memory formation and some neuropsychiatric disorders such as drug addiction, Parkinson's (PD), Huntington's (HD) and Alzheimer's (AD) disease. In recent years it has become clear that all alterations occurring in the brain during normal and pathological cognitive processing are directly or indirectly related to neuronal cell signalling processes. One key unanswered question relates to the relative contribution of different brain areas such as the hippocampus, the amygdala, the striatum and various cortical areas in these processes. For instance, diseases such as PD, HD and drug addiction are believed to be mainly but not exclusively related to dysfunction in the striatum, a brain region involved in motor control and reward based behaviour.

The general aim of the proposed research is to understand how genes and environment interact in producing measurable behavioural responses and brain diseases. The mouse and the rat will be the model systems, since no alternative exist to the use of animals for studying behavioural responses. Rodents are the most common species to perform such genetic studies in which specific gene mutations can be introduced either in the germline or directly in the adult brain using viral vectors. In addition, the use of rodent is cost effective in comparison to other species. Animals with unique genetic features will be generated either via breeding, standard molecular genetics or via surgical techniques. In addition, pharmacological rodent models will also be used, also in combination with the genetically altered models. However, the number will be kept to the minimum by performing a substantial part of the work using in vitro systems such as tissue culture cells and molecular modelling. Suffering will be kept to a low level by extensively using anaesthetics and appropriated post-operative care. Subsequently, animals will be subjected to mild behavioural procedures in order to monitor both motor and cognitive functions. All the behavioural tests will be from mild to moderate and animals will be subjected to investigation for a short period of time.

Altogether, this project will allow us to reach a better understanding of the physiology of the brain and will provide a solid basis for innovative therapies for neuropsychiatric diseases such as drug addiction, PD, HD or AD. More specifically, the newly generated animals models can be used in the future for testing hypotheses related to the pathogenesis of the above brain diseases.

### Amendment 1 -Regulation of Peripheral Receptors for Biogenic Amines

**Lay summary:** The project aims to determine how the reactivity of peripheral organs of the body, such as the heart, blood vessels, the lungs, gut and bladder, to substances that occur naturally in the body are altered by disease. Knowledge about the reactivity to these substances will be important in the development and use of drugs to correct abnormalities in these organs in disease.

This project will investigate models of diseases of the peripheral organs of the body. Diseases of the heart will include angina and heart attack; of the blood vessels, hypertension and diabetes; of the lungs, asthma and chronic obstructive pulmonary disease (bronchitis) and viral infections; of the gut, inflammatory bowel disease; and of the bladder, urinary incontinence through overactive bladder. Control of the function of all these peripheral organs is brought about in the body

by a range of local substances called biogenic amines that are released from nerves and other cellular sources. Familiar examples include adrenaline and histamine. Many drugs that are currently used to treat these diseases or are potential new drugs work by either mimicking the effects of these biogenic amines or blocking their effects. Clearly the effectiveness of these drug approaches to treating disease depends on the sensitivity or reactivity of the organ, such as the heart, to the biogenic amine. But little is known about how the disease itself affects the sensitivity. If the disease causes an increase in reactivity to a biogenic amine then a drug that mimics its action or increases the amount of it in the body will be less effective than in a person not exhibiting the disease. Most drugs are tested initially in disease-free animals and then disease-free human volunteers. It is therefore necessary to have models of these diseases in animals for the early evaluation of the effectiveness and safety of new drugs before they can be safely given to humans. This project is aimed at determining how the disease process itself affects the reactivity of the peripheral organs to the very substances that control their activity. The levels of these controlling substances may be altered by disease - there are very effective buffering systems in the body to increase or decrease the levels of these substances. We also want to know how the reactivity of the organs is affected by changes in the levels of the controlling substances. Does reactivity increase to compensate for a loss of a controlling substance that may occur in disease? This project is aimed at understanding how the reactivity of the organs of the body is altered by disease and by the substances that control organ activity. This knowledge will enable us to design more effective and safer drugs for the treatment of diseases of these organs and to manage the use of existing drugs more effectively and to reduce their side effects.

The experiments to be undertaken in this project require the use of animals. Diseases of the cardiovascular, respiratory, gastrointestinal and urogenital systems including angina, hypertension, asthma, inflammatory bowel disease and urinary incontinence are disorders of the whole body, not simply of cells. They result from a complex set of disturbances in which the affected organs of the body interact with each other. It is impossible to study these interactions outside the context of a whole body. Humans will always be the experimental subject of choice, and advances in technology increasingly allow us to undertake more sophisticated non-invasive studies in humans. However, it is still impossible to be able to study humans in the depth needed to obtain new insights into the underlying mechanisms for changes in reactivity of the organs. Insects do not provide a viable alternative to animal use since their evolutionary development is too distant from humans to obtain meaningful data relevant to humans and mammalian models must therefore be used. Rodents, particularly mice and rats, have the enormous advantage that there are a wide range of commercially available antibodies for detection of proteins in their tissues. These proteins include the receptors and mediators that are altered by disease. We can also measure physiological changes in the cardiovascular, respiratory, gastrointestinal and urogenital systems of small laboratory animals such as rats, guinea-pigs and mice easily and without stress. Whenever possible, however, studies will use alternatives to animals. Computer simulations of the diseases in question are not feasible until the results of studies like the ones proposed are known. Only then will it be possible for the data generated to be fed into a database along with complementary data from other related studies that will enable crude models of the diseases to be established. When feasible, pilot experiments will be performed in cells grown in culture in the laboratory rather than in whole animals. Such pilot studies will identify suitable drugs and their doses for subsequent administration to animals. They will also identify whether prolonged exposure to drugs to be studied leads to tolerance in a simple single cell system. This will facilitate reduction and replacement of animals particularly if this approach leads to similar or complementary conclusions to those obtained from studies carried out in whole animals.

## Amendment 3 -Immune responses during persistent virus infection

### Lay summary:

#### 1. What the changes are:

**Alteration to of protocol 19b 1 subsection 3.** This allows us to increase the dose of irradiation that we expose mice to prior to haematopoietic stem cell transfer.

The irradiation dose listed on our existing license has been shown by collaborators at Cardiff to lead to incomplete graft of stem cells. Stem cell grafts are an important aspect of our experimentation that enables us to dissect the roles that cells both from the immune system, and also non-immune cells such as epithelial cells that are infected by viruses, play in protecting the body from virus infections. This technique therefore affords important insight into how different immune molecules that we target with therapies and vaccines actually work. It is therefore imperative that the technique uses the optimal dose of radiation to ensure a successful stem cell graft, and we wish to use a radiation doses (1000-1100 rads) that have been reported in numerous World-class journals to enable complete grafts of donor stem cells (Banks et al, JI, 2005, 174:7217; Lee et al, Nat Immunol, 2008, 9:917).

#### Species and number to be used

The proposed alteration to this procedure is refining current protocols to ensure the success of future experiments. No additional mice are required.

#### 2. Effects on the animals:

**Alteration to of protocol 19b 1 subsection 3.**

Based on previous experience from international collaborators we do not envisage any adverse effects. To ensure that the mice do not suffer from opportunistic infections following exposure to this increased radiation dose, mice will receive the stem cell transfer no more than 24 hours after irradiation, and will be treated with antibiotics for 3 weeks after exposure.

#### 3. Brief summary of the cost-benefit ratio of the proposal:

##### a) Costs to the animals:

No more mice will be required for these studies. Instead, we will ensure the success of the stem cell experiments. This will ensure that we obtain accurate data from each experiment performed.

##### b) Potential benefits:

Understanding the exact immune mechanisms that protect the body from viruses will help with the design of safe therapies and vaccinations. Therefore, the efficient design of stem cell transfer experiments will assist in this process.

##### c) How the benefits outweigh the costs:

With the procedures in place (stem cell transfer soon after irradiation and antibiotics treatment), the chance of adverse effects related to an increase in radiation exposure will be minimal. In contrast, the accurate information that we will gain from these experiments could have potentially massive implications for vaccines and other therapies that protect us from cytomegalovirus and other important viruses including HIV and influenza.