

G: NON-TECHNICAL SUMMARY (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed project clearly using non-technical terms which will be understandable to a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary may render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at <http://scienceandresearch.homeoffice.gov.uk/animal-research/>).

(WORD LIMIT: 1000 WORDS)

Please complete the following:

Project Title (max. 50 characters)	Circadian regulation of processes underlying chronic inflammation		
Key Words (max. 5 words)	Biological clocks, inflammation, arthritis, immune system, colitis		
Expected duration of the project (yrs)	5		
Purpose of the project (as in section 5C(3) ¹)	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

¹ Delete Yes or No as appropriate.

	Forensic enquiries		No
	Maintenance of colonies of genetically altered animals ²	Yes	
Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	The work outlined in this project will investigate how the biological clock regulates the processes which cause chronic inflammation. This will generate insight into how chronic inflammatory diseases might be better treated in the clinic. Although there are several different types of drugs used to treat chronic inflammatory diseases, these are not always effective in every patient, and many are associated with negative side effects. This work is aimed at finding new targets for which to develop drug treatments, and also to establish whether by taking existing anti-inflammatory drugs at certain times of the day we can improve how effective they are.		
What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?	This project will bring about a greater understanding of how the body's biological clock regulates the disease processes that cause chronic inflammatory diseases. It is hoped that in the long-term this will advance the way in which these disorders are medically treated. We hope to identify new targets for drug treatments, but also consider the possibility of altering how current therapies are utilised. For example, by administering a drug at a specific time of the day we may be able to improve how effective it is in treating the disease, and also reduce the occurrence of unwanted side-effects.		
What species and approximate numbers of animals do you expect to use over what period of time?	This project will utilise approximately 9050 mice over a period of 5 years.		
In the context of what you	Breeding		

² At least one additional purpose must be selected with this option.

<p>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?</p>	<p>This project covers the breeding of a number of genetically altered lines of mice, which have alterations in their biological clock. This includes animals in which a key part of the clockwork machinery has been deleted from either the whole animal or just one particular cell type. These lines of mice are unlikely to show any adverse effects. Additionally, mice will be bred which spontaneously develop arthritis as they grow older. This is likely to cause a moderate degree of discomfort and pain. These animals may be used to look at how the disease changes at different times of day, or to harvest blood that can be purified and administered to other animals as a way of inducing arthritis.</p> <p>Induction of arthritis</p> <p>This project will use several different ways of inducing arthritis, each of moderate severity. Either by injecting biological components derived from other animals or injecting collagen under the skin. Each method results in the animal developing localised inflammation and swelling within the paws. Samples will be taken from these animals either during the disease state (e.g. blood samples) or at the end of the experiment (e.g. cells and tissue). This arthritic state will cause a moderate degree of discomfort and pain, and animals will be monitored and scored accordingly.</p> <p>Induction of chronic inflammatory bowel disease</p> <p>Mice may be administered a chemical in the drinking water which causes inflammation within the gut, resulting in a moderate severity disease much like chronic inflammatory bowel disease in humans. This results in weight loss and diarrhoea. Treatment periods with this chemical will be limited, and the experiment will be ended if animals show signs of severe weight loss.</p> <p>Surgical intervention</p> <p>Animals may be surgically treated in a number of instances. Firstly, devices may be implanted under</p>
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	<p>the skin that record the animal's body temperature and activity. Secondly, a small pellet may be implanted under the skin that slowly releases a hormone. Finally, the adrenal glands (organs responsible for releasing the hormone corticosterone) may be removed. All of these procedures are well tolerated and not associated with any adverse effects. Through the use of proper surgical techniques and administration of antibiotics, post-operative infections will be avoided. Pain relief will be provided during and after surgery.</p>
<p>Application of the 3Rs</p>	
<p>1. Replacement</p> <p>State why you need to use animals and why you cannot use non-animal alternatives</p>	<p>Animal models are essential to address the research questions raised in this project. Computational modelling and <i>in vitro</i> techniques are insufficient to model the complex interactions between the mammalian circadian clock and the immune system. The animal studies outlined in this project will be supported by additional techniques which utilise cells harvested from either naive, healthy mice or from humans.</p>
<p>2. Reduction</p> <p>Explain how you will assure the use of minimum numbers of animals</p>	<p>Animal husbandry</p> <p>Where our studies involve breeding lines of mice that have been genetically altered, we take care to breed the minimum number of mice possible to provide us with animals to use experimentally, but also to maintain an efficient breeding colony. This is achieved by effective communication and co-ordination with our staff in the animal unit, and by keeping up-to-date accurate records.</p> <p>Laboratory techniques</p> <p>By taking advantage of the large array of cutting edge technologies available to us, we aim to obtain the maximum information possible from the fewest animals possible. Laboratory techniques which we routinely use allow us to generate large data sets from single samples and thereby reduce the need to repeat experiments to generate more experimental tissue.</p> <p>Experimental design</p>

	<p>Experimental design is critical to reducing the numbers of animals used. A statistical expert has been consulted regarding the planning of this project and has helped in informing the correct statistical tests to use in order to generate robust reliable conclusions.</p>
<p>3. Refinement</p> <p>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.</p>	<p>Choice of animal models</p> <p>1. Inflammatory arthritis. Mouse models of inflammatory arthritis are widely studied models of the human disorder rheumatoid arthritis. These models produce a disease characteristically very similar to the human condition. Such models are often used in the early stages (pre-clinical) of the development of new drugs to treat rheumatoid arthritis. These models are classified as moderate severity, and provoke inflammation in the joints, which will lead to a degree of pain and discomfort in the animals. Due to the nature of the study, it will not be possible to use analgesia during this phase as it would severely compromise the disease model. Once mice begin to show signs of arthritis, they will be maintained in this phase for the minimum time possible in order to achieve the objective outlined in this project.</p> <p>In order to minimise suffering, animals showing excessive signs of joint inflammation (as determined by regular assessment using a 16 point scale) will be removed from the experiment and be humanely euthanised. Mice will be group housed and provided with nesting material and environmental enrichment wherever possible.</p> <p>2. Chronic inflammatory bowel disease Administration of a chemical in the drinking water provokes an inflammatory response within the gut. We aim to optimise the dosing schedule to induce a mild/moderate localised chronic inflammation, which is essential to address our research goals. Animals will be monitored regularly for signs of ill health (significant weight loss, loss of condition) and will be held in this chronic inflammatory state for the minimum time possible</p>

	<p>in order to achieve our research objectives.</p> <p>3. Surgical removal of the adrenals and implantation of pellets</p> <p>Where it is necessary to undertake a surgical procedure, pain relief will be provided to these animals, and animals will be group housed and provided with environmental enrichment.</p> <p>General welfare measures</p> <p>Animals will be group housed wherever possible, and provided with environmental enrichment. When an animal is undergoing a procedure, they will be monitored regularly for disease progression (where appropriate) and for signs of adverse effects. Animals undergoing surgical intervention will be provided with analgesics.</p>						
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Will the project be subject to Retrospective Assessment? ¹	<table border="1"> <tr> <td data-bbox="695 867 786 932">Yes</td> <td data-bbox="786 867 873 932">No</td> <td data-bbox="873 867 1377 932">Date due³:</td> </tr> <tr> <td data-bbox="695 932 786 968"></td> <td data-bbox="786 932 873 968"></td> <td data-bbox="873 932 1377 968"></td> </tr> </table>	Yes	No	Date due ³ :			
Yes	No	Date due ³ :					

³ The retrospective assessment should be completed, agreed with the establishment AWERB, and submitted to the Home Office within 3 months of this date (or when the project terminates if earlier).