Private & confidential: *Please be aware that the contents of this form may be made public resulting from the "Freedom of information Act". Personal details will not be released.*

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:

<table>
<tr><td>Project Title (max. 50 characters)</td><td colspan="3">Circadian mechanisms underlying organ rejection</td></tr>
<tr><td>Key Words (max. 5 words)</td><td colspan="3">Circadian, transplant, organ rejection</td></tr>
<tr><td>Expected duration of the project (yrs)</td><td colspan="3">5</td></tr>
<tr><td>Purpose of the project (as in section 5C(3)[1]</td><td colspan="3"><table>
<tr><td>Basic research</td><td>Yes</td><td></td></tr>
<tr><td>Translational and applied research</td><td>Yes</td><td></td></tr>
<tr><td>Regulatory use and routine production</td><td></td><td>No</td></tr>
<tr><td>Protection of the natural environment in the interests of the health or welfare of humans or animals</td><td></td><td>No</td></tr>
<tr><td>Preservation of species</td><td></td><td>No</td></tr>
<tr><td>Higher education or training</td><td></td><td>No</td></tr>
<tr><td>Forensic enquiries</td><td></td><td>No</td></tr>
<tr><td>Maintenance of colonies of genetically altered animals[2]</td><td>Yes</td><td></td></tr>
</table></td></tr>
</table>

[1] Delete Yes or No as appropriate.
[2] At least one additional purpose must be selected with this option.

Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	Rejection of a transplanted organ remains one of the biggest challenges in transplantation. Despite use of drugs to supress the immune system the transplanted kidney will be rejected in 10% of kidney recipients in the first 12 months damaging the organ. This programme of work will identify whether organ rejection is under local control from our body clock. It will then go on to identify which pathways and cell types are involved. **The twenty-four hour circadian clock** Virtually all aspects of how our body functions are mapped onto 24 hour rhythms, orchestrated by internal body clocks. These internal clocks help anticipate changes in our environment so that our bodies can respond appropriately. Circadian dysfunction is now considered to be a contributory factor to the incidence and severity of a wide range of body functions including sleep, blood pressure, heart rate and immune function. **The circadian clock and immune function** There are clear links between circadian rhythms and the function of our immune system. Firstly, immune cells and immune organs possess a clock which ticks over. Furthermore, immune cells demonstrate variation in their function according to time of day. This is exemplified in animal experiments e.g. the outcome of pneumonia is altered by what time of day the illness is contracted. **Organ Transplantation** Organ transplantation is performed due to end stage organ failure. The main complications after organ transplantation are due to the immune system attacking the transplanted organ termed “rejection”. Currently most transplant recipients have to take immunosuppressant drugs to prevent or treat this rejection. These drugs all have significant side effects causing a reduced quality of life for the transplant recipient. Despite this the drugs have to be used since current demand for organs outstrips supply reducing the chance of re-transplantation.

	Objectives of the project: This project is investigating whether timing of transplantation affects rejection of the organ. In addition we will study how transplantation itself can affect the body clock and the downstream consequences of this disruption on the immune system.
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)?	The primary benefit of this project relates to new knowledge about circadian mechanisms altering rejection of the transplanted organ. In particular, the work outlined in this project will establish whether a circadian clock affects transplant organ rejection and provide detailed information about which components of the immune system (i.e. which cytokines/chemokines and which inflammatory cell types) are impacted by the circadian clock after transplantation. The aim is to publish the findings in academic journals, since the information will be of interest to both scientists and clinicians. The more long term and substantial benefits of this research relate to the possibility that new molecular targets may be identified, , for which pharmaceutical products could be developed. Finally, a greater understanding of how the clock impacts on organ rejection after transplantation may change clinical practice since it is now possible to preserve organs outside of the body allowing transplantation to be performed at the optimal circadian time.
What species and approximate numbers of animals do you expect to use over what period of time?	3800 mice over 5 years
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	The overall project will be classed as moderate severity. Animals may have a degree of suffering from the transplanted grafts and also from the chemical compounds we give them to modulate the immune system. Suffering will be minimised through environmental enrichment and administration of pain

end?	killers. If despite these interventions the mice still show suffering then we will end the experiment early. At the end of the experiment tissue and cells will be collected to monitor the relevant endpoint of the study (organ rejection , immune activation or circadian rhythm).
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	Currently there is no laboratory model of rejection as it involves a number of cell types and recognition of foreign tissue. Some of our work will be done in the laboratory where we will try and recreate a specific part of the rejection process that we are seeing in the animals.
2. Reduction Explain how you will assure the use of minimum numbers of animals	Initially pilot studies will be done to see how many animals are needed to generate robust data. After this information has been collected we will work with our biostatistician in order to ensure that the experiments use the least number of animals to produce robust results
3. 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.	Mice will be used in the model and we have already created several validated mouse lines with altered body clocks. Furthermore transplant experiments have been performed in mice for over 40 years therefore the biology is well understood minimising the welfare cost to the animal. The mice will be closely monitored and be given painkillers, antibiotics or extra food if necessary. If the animal is still experiencing a welfare cost then the experiment will be ended early.
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Will the project be subject to Retrospective Assessment?[1]	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).