**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/](http://scienceandresearch.homeoffice.gov.uk/animal-research/)).

**WORD LIMIT: 1000 WORDS**

Please complete the following:

<table>
<thead>
<tr>
<th>Project Title (max. 50 characters)</th>
<th>Preclinical therapies for pulmonary hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Cardiovascular, pulmonary, genetics, therapy</td>
</tr>
<tr>
<td>Expected duration of the project (yrs)</td>
<td>5 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>x Basic research</td>
<td></td>
</tr>
<tr>
<td>x Translational and applied research</td>
<td></td>
</tr>
<tr>
<td>x Regulatory use and routine production</td>
<td></td>
</tr>
<tr>
<td>x Protection of the natural environment in the interests of the health or welfare of humans or animals</td>
<td></td>
</tr>
<tr>
<td>x Preservation of species</td>
<td></td>
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<tr>
<td>x Higher education or training</td>
<td></td>
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<tr>
<td>x Forensic enquiries</td>
<td></td>
</tr>
<tr>
<td>x Maintenance of colonies of genetically altered animals¹</td>
<td></td>
</tr>
</tbody>
</table>

¹At least one additional purpose must be selected with this option.

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<table>
<thead>
<tr>
<th><strong>Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)</strong></th>
<th>The overall objective of this project is to find and test new treatments for a rare condition known as pulmonary arterial hypertension (PAH), which is characterised by severe high blood pressure in the arteries supplying the lungs. Patients with PAH have a very limited life expectancy despite existing drug treatments. A major breakthrough in understanding and treating this condition was the identification of genetic mutations in certain genes. Our research aims to understand how these mutations cause disease and, based on this knowledge, to design more effective therapies to treat the condition.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>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)?</strong></td>
<td>The major potential benefit from this project is the identification of new drug targets and new drugs to treat or prevent PAH in patients and their relatives. Even with currently available treatments, which don’t directly treat the underlying cause, 3-year survival is only 60-70%. We aim to develop treatments that treat the main cause of the disease. We also plan to explore how long these drugs remain in the body and if most of the drug makes it to the lungs. In addition, our research increases knowledge of how PAH occurs and progresses.</td>
</tr>
<tr>
<td><strong>What species and approximate numbers of animals do you expect to use over what period of time?</strong></td>
<td>This project will use rats and mice, including genetically modified mice. We anticipate the use of a maximum of 23,500 mice and 11,200 rats over a 5 year period.</td>
</tr>
</tbody>
</table>
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 majority of our protocols involve the use of genetically modified mice that develop PAH, or require the exposure to certain agents or environmental factors that stimulate the development of PAH. We then use drugs or other substances to try to prevent or reverse the disease. Most of our measurements are carried out at the end of any protocol once the animal is anaesthetised and the animal is not allowed to recover from the anaesthetic. In some protocols we make measurements in anaesthetised animals using non-invasive imaging techniques so that we can follow the course of PAH in each animal. Very occasionally we use a severe protocol that determines the effect of a drug on survival of rats with PAH. Ultimately in patients we want to improve survival, so we sometimes need to show that a drug improves survival in animals. Overall the expected level of severity in our protocols is mild-moderate. At the end of each protocol animals are humanely killed, usually under terminal anaesthesia.
**Application of the 3Rs**

1. **Replacement**
   State why you need to use animals and why you cannot use non-animal alternatives
   
   We use information from human genetic studies and from tissues and cells from patients with PAH to identify the most promising ways of treating PAH. We also use tissue culture of human cells in the laboratory to provide important information before embarking on animal experiments. Ultimately, before deciding whether to take a new treatment forward into patients, we need to test the approach in an animal model of PAH to see whether it is capable of preventing or reversing the key aspects of the disease. Cell-based studies are not appropriate for looking at drug stability in the blood and for examining if drugs are effectively reaching the lungs after they have been administered. For these studies, we need to use animals.

2. **Reduction**
   Explain how you will assure the use of minimum numbers of animals
   
   First, we only test treatments in animals for which there is a sound scientific basis, based on our finding patients with PAH and human tissues and cells. When we embark on a study in animals we calculate the minimum number of animals required to provide an answer, for example whether a drug reverses PAH. In addition, because we can measure the development of PAH in individual animals using non-invasive imaging techniques, this reduces the number of experimental groups required to determine whether a treatment works. For examining drug half-life and distribution in the body, we will perform longitudinal studies to reduce the numbers of animals needed.

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.
   
   Rats and mice are the lowest vertebrate group in which models of PAH have been developed and are thus the most appropriate species to study. We require the use of both rats and mice because rats, but not mice, develop pulmonary hypertension in response to certain stimuli and develop more severe PAH (more similar to the human pathology) in response to certain stimuli. On the other hand, mice provide better genetic models of disease. The introduction of sophisticated imaging techniques and measurements similar to those used in patients with PAH means that the number of groups of animals can be reduced. Animals are monitored at least daily to check for any signs of distress. If an animal shows any features of reaching moderate severity it will be humanely killed. We work closely with the veterinary surgeon who advises on methods to reduce welfare costs in our experiments.

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| Will the project be subject to Retrospective Assessment? | Yes | No | Date due: | 29 March 2021 |

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