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>Genetic and pharmacological analysis of thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Bleeding, thrombosis, platelets</td>
</tr>
<tr>
<td>Expected duration of the project (yrs)</td>
<td>5</td>
</tr>
<tr>
<td>Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)</td>
<td>✓ Basic research</td>
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<tr>
<td></td>
<td>Translational and applied research</td>
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<td>Regulatory use and routine production</td>
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<td></td>
<td>Protection of the natural environment in the interests of the health or welfare of humans or animals</td>
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<td></td>
<td>Preservation of species</td>
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<td></td>
<td>Higher education or training</td>
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<td></td>
<td>Forensic enquiries</td>
</tr>
<tr>
<td></td>
<td>✓ Maintenance of colonies of genetically altered animals¹</td>
</tr>
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</table>

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

The Home Office, in line with the rest of HMG, has implemented the Government Security Classification (GSC). Details of the GSC can be found at [https://www.gov.uk/government/publications/government-security-classifications](https://www.gov.uk/government/publications/government-security-classifications). Please note that documents and emails you receive may contain specific handling instructions.

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All government information may be subject to an FOI request and subsequent assessment.

Version 1.5
Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)

Platelets are small circulatory cells that are essential to prevent bleeding. However, platelets also form a clot (called a thrombus) in an artery when an atherosclerotic plaque ruptures, which can block the artery. If a coronary artery is blocked, blood flow to the heart is reduced and can lead to a heart attack.

The aim of the project is to better understand how platelets are activated and how they contribute to thrombus formation.

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)?

Coronary heart disease leading to heart attacks is one of the biggest causes of death in the UK. The cause of death is often a clot (thrombus) inside a blood vessel supplying the heart. Drugs that reduce platelet activation and their contribution to thrombus formation could help reduce the incidence and burden of coronary heart disease. To develop such drugs, we need to better understand the molecular mechanisms that control platelet activation.

What species and approximate numbers of animals do you expect to use over what period of time?

This project proposes to use mice. Approximately 2650 mice will be used 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 end?

The majority of the animals maintained under this licence are not expected to show any detectable adverse effects. Some genetically altered mice that have platelet defects, however, may develop bleeding defects, in which case they will be kept under close observation in case of injury and receive special care. All animals will either be killed at end of procedures whilst terminally anaesthetised or otherwise humanely killed, after which various tissues samples will be taken for analysis.
### Application of the 3Rs

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

Where possible, we minimise the use of animals by using platelets from human volunteers. However, the experimental approaches that we can use with human platelets are limited. This is because platelets themselves do not have a nucleus. This means that they cannot be grown in culture and cannot be analysed through standard genetic techniques used in other cell types. Mouse gene knockouts provide a powerful approach to understand the role of a gene in platelet function. Mouse gene knockouts are mice that have been genetically altered so that they are missing a specific gene and the protein encoded by the gene. The increased specificity of this approach, compared to pharmacological tools, enables us to draw clear conclusions. Unfortunately, this cannot be applied to human platelets.

Moreover, platelets do not act in isolation from other cells. Rather, cardiovascular disease is a product of the interaction between multiple cells including platelets, vascular smooth muscle cells, endothelial cells and other blood cells. Our analysis of this complex process combines experiments on platelets in isolation from other cells, with experiments in a whole animal setting. This is vital to allow us to analyse gene function in the setting and context of these other cells.

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

Animal numbers bred for use on this Project will be minimised as far as possible by matching breeding to experimental requirements. Pilot studies and power calculations will be employed to refine the number of animals used.

The methods chosen will generate the greatest amount of data for the fewest animals used. We routinely expect to derive multiple data sets from a single animal, by extensive use of modern approaches that allow us to analyse very small blood samples.
### 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 are the species of choice for the proposed investigations because they are a good mammalian model with a well-characterised microcirculatory patterns and in particular platelet-endothelial interactions that are similar to humans. Studying thrombus formation in mice therefore provides valuable information that will further our understanding of human biology and diseases.

Genetically-altered mouse technologies are becoming increasing sophisticated, where genes can be deleted within specific cells whilst leaving the rest of the animal unaffected. Such genetically altered animals will be used wherever possible in this project and will greatly reduce the risk of adverse effect to the mouse. This is because only the platelets will be genetically altered, whilst all the other cells in the mouse will be normal.

<table>
<thead>
<tr>
<th>For Office Use Only</th>
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<tbody>
<tr>
<td>Will the project be subject to Retrospective Assessment?</td>
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