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>
<thead>
<tr>
<th>Project Title (max. 50 characters)</th>
<th>Papillomavirus Life-Cycle Regulation</th>
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</thead>
<tbody>
<tr>
<td>Key Words (max. 5 words)</td>
<td>Papillomavirus, Epithelium, Tropism, Warts, Regression</td>
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<td>Expected duration of the project (yrs)</td>
<td>5 years</td>
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<td>Purpose of the project (as in Article 5)(^1)</td>
<td>Basic research Yes</td>
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<td></td>
<td>Translational and applied research Yes</td>
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<td>Regulatory use and routine production No</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 No</td>
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<td></td>
<td>Preservation of species No</td>
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<td></td>
<td>Higher education or training No</td>
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<td></td>
<td>Forensic enquiries No</td>
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<tr>
<td></td>
<td>Maintenance of colonies of genetically altered animals(^2) No</td>
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</tbody>
</table>

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

Our work aims to understand how the papillomavirus life-cycle is regulated at different epithelial sites, and how changes in the cellular microenvironment can regulate and suppress viral gene expression. Our goal is to understand why HPV-associated cancers are restricted primarily to certain ‘susceptible’ sites in the body. In addition, we aim to understand how the immune system controls the spread of HPV disease and can in some cases lead to disease-regression.

What are the potential benefits

Papillomaviruses cause a number of problematic

\(^1\) Delete Yes or No as appropriate.
\(^2\) At least one additional purpose must be selected with this option.
likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?

diseases in humans including recurrent respiratory papillomatosis, which can cause breathing difficulties in children, and cervical cancer, which can result from persistent infection by 'high-risk' types. How the course of disease is regulated depends both on the immune environment and on the specific epithelial site where infection occurs. Our ultimate goal is to develop clear approaches to control and eliminate recalcitrant papillomavirus infections in humans. This will have a major impact for individuals suffering from the problems of HPV infection.

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

The work will make use of a recently identified mouse papillomavirus (muSPV), which can produce productive lesions in immunocompromised mice. Because we are looking at different immune and genetic backgrounds as well as different epithelial sites, the questions that we are asking are quite complex. As a result, we expect to use up to 2000 mice during the course of the study. In addition we will use a low number of other animals (i.e. rats and guinea pigs (10 of each approx)) as controls. Although these can be infected by muSPV, they do not develop disease. A papillomavirus that infects rabbits (ROPV) will be used in a small number of cases to establish whether information generated in mice is likely to extend more generally to the papillomavirus group as a whole. A maximum of 30 rabbits will be used for this work.

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?

Papillomaviruses cause benign epithelial lesions that are self-limiting in immunocompetent hosts. In immunosuppressed animals the lesions can spread, but will always be restricted to the epithelium as papillomaviruses are epitheliotropic viruses. Because of their precise epithelial tropism, papillomavirus-induced lesions are straightforward to monitor visually, and any adverse effects can be addressed rapidly. At some epithelial sites, such as the oral cavity, extra care will be taken when monitoring lesion size. Similarly, immunosuppression regimes are expected to facilitate an increase in lesion size in infected animals, which will also warrant closer monitoring. The effects of HPV infection are likely to be mild or possibly moderate in some cases. If adverse effects become more serious than this the animals will be killed by a schedule 1 method.
### Application of the 3Rs

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

  The lab already makes extensive use of tissue culture and organotypic raft culture approaches to study the biology of papillomavirus infections. We are also very active in the analysis of virus expression and virus protein function in clinical specimens, and are using these to develop our hypothesis as to how HPV interacts with the epithelial cells that it infects. We cannot however mimic particular epithelial sites in the raft model and cannot properly investigate interactions with the immune system using these methods. As a result we will use the animal models to answer questions that cannot be properly addressed using other approaches in order to produce a more complete picture of how papillomaviruses function.

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

  To minimise animal numbers, the project will be run in a stepwise fashion, and will aim initially to understand how papillomavirus/epithelial tropisms are controlled, and how epithelial site regulates viral gene expression. Once we have a better understanding of this, we will consider the different immune cell backgrounds and also the local microenvironment as modulators of viral gene expression. A final part of the project will look at papillomavirus backgrounds in relation to genetic susceptibilities. By following a cautious approach, we expect to limited unnecessary animal usage. Although we indicate the use of 2000 mice over the course of 5 years, it is likely that the actual numbers used will be much lower than.

- **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 (harm) to the animals.

  Previously, the most appropriate animal model for the study of papillomavirus infections was the rabbit, and in our past studies we have made use of the Cottontail Rabbit (CRPV) and Rabbit Oral Papillomavirus systems (ROPV). These models were difficult to use, and we found that the rabbits often suffered significant weight loss upon immunosuppression. The identification of a mouse papillomavirus has been difficult to achieve, but recently a mouse papillomavirus has been described in the literature and has been reported to produce typical papillomas in immunocompromised mice. As a result we will now move our studies to the mouse model. Because the mouse papillomavirus is evolutionarily distinct from the papillomavirus types found in humans, we will carry out a limited number of comparative experiments in rabbits using the ROPV system. ROPV has some
similarities in life-cycle organisation to the papillomavirus types that cause important disease in humans. By using this combined approach however, coupled with the analysis of clinical material, we envisage that we can now confine the majority of our future work to mice. As mice are a well understood laboratory host animal, we expect to be able to minimise any adverse effects during our experiments.

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| Will the project be subject to Retrospective Assessment? | Yes [ ] No [ ] Date due: |

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1 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).