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>Glioblastoma treatment and resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Words (max. 5)</td>
<td>Cancer, brain, rodent, treatment, resistance</td>
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<tr>
<td>Expected duration of the project (yrs)</td>
<td>5</td>
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<tr>
<td>Purpose of the project (as in section 5C(3))¹</td>
<td></td>
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<tr>
<td>Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)</td>
<td>The aim of this project is to develop models of brain cancer using tumour cells from patients and use them to study how tumour growth and response to treatment varies between patients and over time.</td>
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<td></td>
<td><em><strong>Can patient-derived animal models tell us how patients will respond to treatment?</strong></em></td>
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<td></td>
<td>We will use the data of how animals respond to treatment and compare it with what happens to the patients then examine the clinical data to see if the models can in fact predict patient response.</td>
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<td></td>
<td>These data will tell us if we can use these models to test drug combinations to select those suitable for use in clinical trials.</td>
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<tr>
<td></td>
<td><em><strong>Can patient-derived animal models tell us how patients become resistant to treatment?</strong></em></td>
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¹ Delete Yes or No as appropriate.
² At least one additional purpose must be selected with this option.
We will use tumours from in treated and untreated animals to identify the cells that dominate and drive treatment resistance.

Examination of the genetics changes in these resistant cells will help us to identify new therapeutic targets in patients.

We can then go back to our animal models to test new treatments to identify those most appropriate to evaluate in clinical trials.

**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 use patient derived cell lines to generate mouse models of glioblastoma, which are more representative of the human disease than we currently have.

We will use these models to study how tumour growth and response to therapy varies between patients and over time. These data will inform how we can place patients into groups and more accurately target the right drug to the right patient.

We will use the models to investigate how tumours evolve in treated and untreated animals. This will help us to understand how minor cell populations can result in recurrent and treatment-resistant disease.

By analysing the mechanisms of this resistance we will be able to identify ways to circumvent the resistance and improve patient survival.

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

<table>
<thead>
<tr>
<th>Species</th>
<th>Mice</th>
<th>Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 3070 mice over 5 years</td>
<td>Up to 2750 rats over 5 years</td>
<td></td>
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</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?**

Tumour burden will be limited to the minimum required for a valid scientific outcome. In all cases, the general health and condition of an animal will remain the overriding determinant, in accordance with the NCRI Guidelines for the Welfare and Use of Animals in Cancer Research.

Most animals on protocol 19b1 (~70%) are expected to exhibit clinical signs of mild severity. Less than 5% of these will need to be humanely killed to ensure the moderate severity limit is not breached.

General adverse signs may include:
- Weight loss (<20% of pre-op weight) or rapid weight loss (>10% pre-op weight in less than 24 hours)
- Poor feeding or drinking (<24 hours post-op)
- Wound infection (<1% of animals)

Signs associated with tumour growth may include:
- persistent weight-loss >15%;
- food & water intake <40% of normal for more than 72 hours
- limb weakness or reduced mobility
- A single generalised seizures lasting >2 minutes

At the end of the experiments animal will be humanely killed

### Application of the 3Rs

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

- Cells in a dish are unable to recapitulate the complex signals driving tumour growth.
- To evaluate treatment response demonstration of effects in animals is essential.
- Analysis of how animals process a drug is vital to inform the design of early phase clinical trials (fore example dosing schedules).
- We aim to use our models to help us make decisions about how to treat patients so the data we generate must be as robust as possible.

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

- The use of inbred strains will be considered wherever possible in order to minimise variability and where possible transgenic animals designed to address specific questions will be used. This will use smaller numbers of animals compared to crude non-transgenic alternatives.
- Statistical analysis will be performed to ensure the number of animals used is the minimum necessary to generate a valid result.
- In vitro and in silico studies will be used where appropriate and the data used to design studies which use the least number of animals.

**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.

- The use of models using cells derived from individual patients represents a step-change in refinement.
- These animals are a more accurate re-capitulation of the human condition. Hence, fewer animals are required in many biological studies to obtain a given effect or to look for a biomarker.
- There is also growing evidence that cells from an individual GB patient will generate an in vivo model that retains the molecular & genetic features of the patient from whom the cells came.
- The programme will also use mice (or rats) in order to take advantage of genetically modified animals that can reduce the number of animals used in an experiment (e.g. use of immunocompromised mice to avoid repeated injection of
immunosuppressant drugs).

Pilot studies will be used to both refine the techniques used in each experiment and to minimise the number of animals used.

<table>
<thead>
<tr>
<th>For Office Use Only</th>
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<tbody>
<tr>
<td>Will the project be subject to Retrospective Assessment?¹</td>
<td>Yes</td>
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</table>

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).

Version 1.4