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)

Please attach the Non-technical Summary as generated by your application in ASPeL.

Project Title	Understanding peritoneal repair and internal scarring
Key Words	Surgery, scarring, abdomen, internal, repair
Expected duration of the project	5 year(s) 0 months

Purpose of the project (as in ASPA section 5C(3))

Purpose

Yes	(a) basic research;
	(b) translational or applied research with one of the following aims:
Yes	(i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants;
Yes	(ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
No	(iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes.
No	(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b);
No	(d) protection of the natural environment in the interests of the health or welfare of man or animals;
No	(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work;
No	(f) higher education or training for the acquisition, maintenance or improvement of vocational skills;
No	(g) forensic inquiries.

In this project, we will discover new medical treatments to prevent the formation of internal scars, or 'adhesions'. People often have to undergo operations which involve opening up their abdomens e.g. to cut out a tumour or an inflamed appendix. Sometimes a mesh or implant needs to be used to help repair the abdominal wall for instance if a bit of bowel has come through a weak section of the wall also called a hernia. A common complication after these operations is the development of adhesions which can glue our bowels together. These adhesions may be painful and can even cause our bowels to become twisted and blocked and stop working. This then requires a major operation to put things right, yet these second operations may themselves lead to more adhesions. Also if bacteria get into the abdomen and cause an infection, even more adhesions will form. Unfortunately, there are currently no good treatments to stop these scars forming.

We will work out how cells inside the abdomen form these internal scars after an operation and/or infection and then use this knowledge to block the process. We will also work out ways to grow scars outside of the body in the laboratory. This will make it easier for us to monitor how well our new therapies are working.

The aims of the project will be to:

1. Identify the different types of cells that are involved in the formation of adhesions and try to block their activity.

2. See whether these cells are more active at night or in the day to decide the best time to give new therapies to block adhesions forming.

3. Test new mesh implants used to repair the body wall and bowel to check they do not induce adhesions.

By the end of the project, we aim to have a list of new treatments which can then be tested on people who may be prone to recurrent adhesions.

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)?

Almost everyone who has an internal operation involving their abdomen will form adhesions. These internal scars may be associated with major complications such as severe long term pain, bowel blockage and infertility in women so represent a huge health problem world-wide. The cost of adhesion-related complications for the NHS are an estimated £152 million each year. At present, there are no good ways of preventing adhesion formation, and current therapies (e.g. membranes and gels) do not work in certain situations. Therefore any new ways to prevent adhesions forming would have enormous benefit for a large number of people. Also, because adhesions are associated with other abdominal diseases such as endometriosis, the results of our project could potentially have widespread benefits in a number of clinically important areas. This project aims to discover how internal scars form and then target these events to stop them forming. This will provide new treatments for

people these diseases. Of importance, our discoveries will also be relevant to animals. Horses, in particular, suffer from adhesions. These bands of scar tissue can cause their intestines to become twisted and this requires immediate surgery.

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

We will use mice as a part of our research studies. To better understand the processes involved we will also use mice that have been genetically altered that will help highlight the cells and molecules to target. Over the 5 years of this licence we may use up to 3000 animals.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?

We will inject factors into the abdomen of mice that are known to cause inflammation and internal scarring. These factors may include parts of bugs found in the bowel or chemical irritants such as peritoneal dialysis fluid. In some animals, we will perform abdominal surgery which may involve inserting a mesh implant in a similar manner to people having an operation for hernia repair. The level of severity is moderate. All animals will be humanely killed at the end of the study. Adverse effects including post-operative pain will be controlled using pain relief. After the procedures, mice will be provided with soft bedding, a mash diet and kept warm. All animals will be continually monitored for any adverse effects and will be humanely killed if approaching severity limit at any time-point in the study.

Application of the 3Rs

Replacement

State why you need to use animals and why you cannot use non-protected animal alternatives

Replacement

We have teased out some of the key events of scarring using cell culture systems in the laboratory. We have also analysed human adhesion scar tissue collected from patients undergoing surgery. However, more detailed studies looking at how factors, cells and pathways interact are now needed and require whole organisms that form blood clots between organs. These models will produce findings that we will be able to relate to patients as they involve mammals rather than frogs or fish.

Reduction

Explain how you will ensure the use of minimum numbers of animals

Reduction

We work closely with statisticians to ensure accurate calculations are performed to determine the minimum number of animals required to achieve our objectives. We will ensure that experiments are well planned before starting so that we are in the best position to generate statistically meaningful results. We will get as much information as possible from each animal by collecting multiple samples – blood, fluid, tissues - to be analysed.

Refinement

Explain the choice of animals 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.

Refinement

We have extensive expertise already using these mouse models under our previous licences and will make several refinements based on our experience. These include re-grouping mice a week after surgery rather than keeping them individually housed. Welfare checks will be continuous throughout the studies and we will explore the option of non-invasive imaging in the future. We work alongside many experts including surgeons so that we are sure that we use the most relevant models and experimental techniques to mirror what happens to patients as closely as possible. New developments and alternative models will be continually monitored and changes to experimental plan altered accordingly.