G: NON-TECHNICAL SUMMARY (NTS)

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

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 programme of work clearly using non-technical terms which can be understood by 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 will 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 www.gov.uk/research-and-testing-using-animals.

Word limit; 1000 words

Project Title	Regulation miR-29 targets in wound repair
Key Words	Cutaneous wounds, microRNA-based therapy
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;
No	(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.

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

Non-healing skin ulcers are becoming more common so the need to find improved skin regeneration is becoming ever more important. If we are to develop efficient ways to improve skin repair, we need to understand the mechanisms underlying normal and impaired healing. For my project, I am seeking to

further describe functions of small ribonucleic acids (RNA) molecules, miR-29s, which I identify as regulators of the top layer of the skin called the epidermis. Our aim is to develop new ways to promote wound healing, caused by massive burns, reconstructive surgery, genetic diseases of the skin, or diabetes. The long-term goal of the project is to utilize miR-29 to improve skin regeneration in patients suffering from large acute wounds, bedsores, and diabetic ulcers.

Our overall objectives are to:

1. Identify the underlying molecular mechanisms that contribute to dysregulated wound healing.
2. Contribute to scientific knowledge related to chronic wounds.
3. Identify potential new therapeutic strategies to promote healing in diabetic and elderly humans and animals.

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)?

We hope this study will develop the potential for gene and cell-based therapies to aid patients with chronic wounds and reduce the need for limb amputation. In addition, we hope this study will benefit animals with diabetes and elderly animals, particularly pet dogs and cats, which like human patients, develop complications associated with chronic wounds.

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

Over a 5 year period: 2720 mice (2400 for breeding purposes and 320 for experimental procedures)

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?

Animals will be monitored for adverse events using score sheets developed in conjunction with the NVS and NACWO. This will allow objective measurement of clinical signs associated with the adverse event to determine when the humane end-point has been reached. A rapid reduction in body weight (>15%), loss of appetite for greater than 24h, subdued behaviour and pilo-erection for up to 24h will result in the animal being culled by schedule 1 killing or exsanguination under terminal anaesthesia. This study is designed to understand how microRNAs control normal wound environment and how this mechanism can be potentially used to improve a diabetic or aged wound environment. Anaesthetised mice will two receive small (6 mm diameter) wounds on their skin so that we can compare the processes involved in wound healing in wild-type (normal) mice with the miR29a deletion. We will apply the short nucleotides to the wounds that we believe will enhance wound healing, in order to find the best treatment for chronic wounds. After surgery, mice will be provided with pain relief and monitored closely for any signs of distress. Distress in mice after this type of surgery is very rare, however, if there is any indication of suffering we will seek veterinary advice. Strategies to minimise adverse effects due to our treatment, as well as minimise the number of animals needed for these studies include testing the effects of the factors we are putting on the wounds in cell culture first. In this way we will be able to identify the most promising candidate factors without using animals. This will reduce the chances of inducing an adverse effect and reduce the number of animals needed to accomplish the objective.

Application of the 3Rs

Replacement

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

Replacement

We have to use animals in this study because understanding how different types of skin cells interact with wound healing in a pathological environment must be studied in the complete physiological setting. That way, we get an accurate picture of this process. Mice are the least sensitive animals that accurately mimic disease in humans. Also, we cannot use humans for these experiments because we would not be able to modify their genes nor track the in vivo transfections with siRNAs.

Reduction

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

Reduction

By reading the scientific literature, we will avoid repeating anything that has already been done. For example, previous studies found virtually no correlation between wounds within the same animal, suggesting that use of wound biological replicates is acceptable for the accurate estimation of the histological measurements. By consulting with colleagues that have expertise in our area, we will refine our experimental design. We will also test potential therapeutic treatments in cell culture models of wounds before we work with animals. **This will reduce the chances of inducing an adverse effect and reduce the number of animals needed to accomplish the objective.** To plan for our animal work, we have consulted a statistician to establish the minimum number of animals required for each study. Also, where possible, we will use two wounds per animal to reduce the number of animals required.

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 minimize welfare costs (harms) to the animals.

Refinement

After surgery, mice will be provided with pain relief and monitored closely for any signs of distress. Distress in mice after this type of surgery is very rare, however.

The species and models we have chosen are based on how well they mimic systemic response to wounding in humans, their sensitivity (they are the least sensitive models we can use for our study), how well-characterised they are, and our expertise. The animals will be given anaesthesia when they undergo wounding. They will also be given pain killers so when they wake up they will not have any discomfort. They will be watched closely to make sure they do not show any signs of being in pain or becoming ill. If they appear to be in pain or appear unwell, veterinary advice will be sought.