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)

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	Dysregulation of skin homeostasis
Key Words	Skin, Inflammation, Delayed healing, Psoriasis, Graft
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.
Yes	(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):

The aims of the project are:

1. To use and develop research models that can be used to test new treatments to improve the healing of wounds, particularly in settings where healing may be impaired such as the elderly and diabetics.
2. To use and develop research models that can be used to test new treatments for inflammatory skin conditions such as psoriasis.
3. To provide research models that can be employed to refine and further improve existing treatments for human skin diseases and treatments that promote healing of injured/damaged skin.
4. To support basic research into normal skin biology, healing and diseases of the skin in humans.
5. To apply 3Rs methodology to the development of experimental models for skin research.

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)?

Improved decision making during preclinical development of drugs to treat human skin damage cause by injury and inflammation, which will accelerate the process of getting new treatments into clinical trials. Improved understanding of skin biology which will help to identify targets for new drugs that can treat and help repair damaged human skin. Improved experimental models for skin research.

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

We anticipate using around 2050 mice and 200 rats over the entire period of the project.

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?

In studies investigating new treatments for delayed wound healing, small wounds may be made to the skin on the back on the animals, under anaesthesia. Delayed healing in humans may be the result of ageing, disease like diabetes, or infection. Some young female mice may have their ovaries removed surgically under anaesthesia, in order to replicate the effects of ageing. Animals may also undergo surgery under anaesthesia in order to implant devices to constantly deliver a small dose of a drug. The expected adverse event for all these procedures is post-operative discomfort which will be controlled by analgesia. The study of delayed healing due to diabetes involves the use of diabetic mice or rats; a mouse strain that develops diabetes due to a genetic mutation may be used, or diabetes may be induced (rats and mice) by administration of a chemical agent. Diabetic animals may show excessive weight gain or loss (chemically-induced diabetes), and may eat and drink more that usual; they will also produce more urine. Diabetic animals can develop cataracts and older animals can show heart and nerve problems, similar to humans with diabetes. Diabetic animals will have clean cages and bedding provided on a more frequent basis and will be examined carefully to monitor any muscle loss. If diabetic symptoms cause the animal distress then it will be humanely killed.

Animals may be challenged with inflammatory stimuli to mimic infection of the skin; this may result in localised discomfort.

In some studies, animals will undergo surgery to receive a skin graft. The expected adverse event is post-operative discomfort which will be controlled by analgesia.

In all studies, there may be localised discomfort at the site where drugs are injected or applied. It may also be important to house animals on their own for a short period of time to prevent them from licking wounds or grafts on other mice; this may affect the healing process or may alter exposure to any drug applied directly to the skin. Single housing may cause mild stress to the animals, and extra environmental enrichment can be provided to help with this.

Overall, the expected level of severity is moderate and humane end points will be applied to all protocols in order to maintain this. All animals are humanely killed at the end of a study so that tissues can be harvested for histopathology, gene expression and protein analysis.

Application of the 3Rs

Replacement

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

Replacement

Cell culture models will be employed for activity screening of treatments, prior to any animal studies being performed; however, the use of animal models for the pre-clinical efficacy testing of drugs that may have the potential for the treatment of wound healing in humans is still justified. Skin is the largest organ of the body. It stops us from becoming dehydrated; it provides a first line defence against infection; it is a sensory organ detecting touch, hot/cold and pain; it helps regulate body temperature and protects internal body tissues from injury. In order to fulfil these many roles, skin consists of many different types of cell. Cell culture models cannot fully replicate the multiple cellular interactions that occur in living animals. Use of models that use short-term maintenance of surgical tissue samples from animals or humans lack a blood supply and neuronal connections; they are also difficult to standardise, due to the many donor variables that are associated with each piece of available tissue.

Reduction

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

Reduction

All experiments are conducted according to current best practice. Statisticians from academia and from independent companies are consulted to ensure the rigour of our experimental design and analyses. We are promoting multi-user studies to improve both the efficiency of animal usage and the robustness of individual studies.

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

Mice are the least sentient species most suitable for these studies. In some instances, a rat model may be more appropriate. Rodent models of skin healing and inflammation are well-characterised and demonstrate broad similarities with human skin biology. We have refined many aspects of running the models, including the optimisation of study design, based on the statistical analysis of historical data. We have increased the number of different data read-outs that can be obtained from a single study. Studies run for the minimum period of time sufficient to achieve their objective(s) and appropriate humane end points are employed.