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 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:

Project Title (max. 50 characters)	Regenerative medicine therapy for renal injury	
Key Words (max. 5 words)	Regenerative medicine; cell therapy; kidney; injury	
Expected duration of the project (yrs)	5 years	
Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)	X	Basic research
	X	Translational and applied research
		Regulatory use and routine production
		Protection of the natural environment in the interests of the health or welfare of humans or animals
		Preservation of species
		Higher education or training
		Forensic enquiries
		Maintenance of colonies of genetically altered animals[1]

[1] At least one additional purpose must be selected with this option.

Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	Donated kidneys frequently have to be transported to the recipient. During this period of storage, the kidney will be damaged. Healthy kidneys can recover quite quickly, but kidneys from older donors often do not recover enough function to make them worth transplanting. Therefore potential donor organs are being discarded. We aim to develop a new treatment which involves injecting cells isolated from the recipient's own body fat into the donor kidney to improve the kidney's rate of recovery. We have shown that these fat-derived cells can improve the function of an injured kidney in animals. We now need to establish the safety of this treatment: do the cells remain in the kidney or do they migrate elsewhere in the body? If they leave the kidney do they form tumours or damage other organs?
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)?	In the UK there are over 25,000 patients whose lives are being sustained by kidney dialysis. A kidney transplant would improve the quality of life and survival of these patients dramatically. However there is a shortage of donor organs which means that many patients will not receive a new kidney. One solution is to use 'extended criteria donor' (ECD) kidneys. These kidneys tend to come from donors >60 years in which there has been a delay between death and transplantation. Consequently, ECD kidneys are at greater risk of subsequently failing which makes them an unattractive option. If we can show that cells derived from body fat improve the recovery of injured kidneys without causing harm to the animal, then we can progress towards a clinical trial in human volunteers. We are working with a transplant surgeon who will use an approved device to isolate cells and inject them into ECD kidneys in a 'first in man' clinical trial. Thus we anticipate that the proposed animal work will have direct clinical benefit in the next 5 years.

What species and approximate numbers of animals do you expect to use over what period of time?	We have requested authority for 5 years. We will use rats for the planned experiments. The majority of the animals will be standard laboratory rats. We will also use rats that have been genetically modified to make the protein found in fireflies which makes them glow. If we inject cells from the 'glowing' rats into the kidneys of normal animals we can easily track where the cells go using an imaging device. In addition, we will use rats with a compromised immune system to test the safety of the cell treatment, as transplant patients will be taking immunosuppressant drugs which in turn could increase the risk of tumour formation. The total number of rats required = 1080

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?	The main cause of harm to a donor kidney in storage is a lack of oxygen. In order to recreate this condition in an animal model we will use an experimental approach called ischaemia reperfusion injury (IRI). This is performed under anaesthesia and involves temporarily clamping the blood vessels that supply one of the animal's kidneys, so that blood flow is stopped. IRI causes damage to one of the kidneys; however because the second kidney remains intact the risk of death due to kidney failure is low. In order to introduce the therapeutic cells into the injured kidney, we need to inject the cells directly into the renal artery. This can be achieved in two ways; however both carry the risk of substantive blood loss as they involve creating a hole in a blood vessel under high pressure. We will perform a small pilot study to establish which method carries the least risk in our hands. Some risk remains that there will be blood loss which cannot be controlled during the operation. If that occurs, the animal will be killed without being allowed to recover from the anaesthetic. In some animals blood loss may be controlled, only for there to be subsequent internal bleeding upon recovery from the anaesthetic. Should this occur the animal will be killed. The cells that we will inject into the damaged kidney are expected to help repair the injuries, so their overall effect should be beneficial. If the cells leave the kidney we do not anticipate that they will cause any harm in normal rats. As transplant patients will be taking drugs to suppress their immune system, we will also establish what happens to fat-derived cells injected into rats with compromised immune systems. We know that transplant patients have a greater risk of developing cancer, so there is a risk that the injected cells may form a tumour in the immunocompromised rats. We will monitor the rats for up to 6 months to see if there is a greater risk of tumour formation; if this occurs the animal will be killed.

Application of the 3Rs				
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	Animals are necessary as we are trying to establish whether therapeutic cells injected into an injured kidney remain in the kidney or migrate elsewhere in the body where they could form tumours. We will be conducting experiments on cells and isolated kidneys to answer some of our questions; however ultimately we have to test the safety of the cell treatment in a whole animal.			
2. Reduction Explain how you will assure the use of minimum numbers of animals	The experiments are designed so that we are able to gain the most information from each animal. We have performed sample size calculations based on our experience with the model so that we know how many rats will be required to give statistically meaningful results.			
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.	We will use rats in this study because they share similar physiology with humans and they are large enough to perform the surgery necessary to induce IRI. The IRI model allows one kidney to be damaged while leaving the other kidney intact, therefore the animal is unlikely to develop renal failure. We will conduct a pilot study to identify the best method to inject therapeutic cells in the renal artery while minimizing blood loss, which is the biggest risk to the welfare of the animals.			
For Office Use Only				
Will the project be subject to Retrospective Assessment?[1]	Yes	No	Date due:	