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	Regulation of Glomerular Barrier Function in Health and Disease
Key Words	
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.

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

The overall focus of this research is to determine how the kidney filters are maintained in health and disrupted in disease. The experiments I propose will improve our understanding of the biology of kidney filters before applying this knowledge to test therapies that will prevent or stabilise the effects of glomerular disease in animal models. These studies will be the prelude to human studies of new treatments.

- We aim to find early biomarkers for kidney disease. We have already shown that mice with glomerular disease show very early structural changes in glomeruli and using proteomics we have identified new potential biomarkers.
- We aim to find mechanisms that cause kidney disease to progress in severity. We have shown that disrupting the ability of glomeruli to respond to mechanical forces can affect the progression of glomerular disease.
- We aim to identify and test new therapies for glomerular disease in zebrafish and mice.

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)?

Chronic kidney disease (CKD) is a huge public health concern, affecting more than 10% of the global population and substantially increasing their mortality. When kidneys fail, renal replacement therapy with dialysis or transplantation is necessary but costs are escalating and replacement therapies are not universally accessible. Strategies to improve early detection of CKD and targeted therapy to prevent disease progression would have significant impact on improving human health. This research programme aims to identify early disease biomarkers and also new therapies for early intervention in CKD. As such this research could have significant impact on the early detection and treatment of kidney disease.

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

Mice 2000 over five years Zebrafish 150,000 over five years

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?

The project has a 'Moderate' severity level. We will use breeding programmes so that, typically, clinically healthy parents (each carrying a mutant gene) are mated to produce litters containing animals with two mutant genes. The latter animals will have kidney and urinary tract malformations. Glomerular injury will be induced by removing kidney tissue or the administration of substances (e.g. chemicals, peptides, antibodies). Therapies (e.g. chemicals, peptides, antibodies or non harmful virus vectors) will be delivered to animals. In experiments, when the interventions are mild or moderate, we will cautiously follow the progress of mice in the year after birth. Should signs of ill health become apparent, the animal will be killed by a humane method.

Application of the 3Rs

Replacement

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

Replacement

We aim to determine whether new therapies can prevent or treat glomerular disease

Glomerular cell culture models alone provide limited insights into mechanisms of glomerular disease and response to therapies.

Currently there is no alternative to using live animals for preclinical models.

In addition the administration of treatments to whole animals we ensure that we can detect any (albeit unanticipated side effects) on other organs.

Reduction

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

Reduction

We will also study zebrafish as an alternative vertebrate model. It has a very simple embryonic kidney, with a glomerulus and 'proximal tubule' similar to those found in mammals. The inclusion of zebrafish in the current study is highly desirable because large numbers of embryos can be quickly generated and it is simple to manipulate gene

expression in these embryos. Therefore, the information obtained from zebrafish studies can complement and inform the mouse studies and reduce the number of experiments we will need to perform in mice.

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

At present, the mouse represents the best species with which to test the efficacy of new therapies for glomerular disease. It has a kidney of similar structure and anatomical complexity (e.g. with glomeruli and branching collecting ducts) to human organs. Our experiments are proposed in mice after they are born when they will be closely monitored. Particular attention will be paid to their weights and behaviour. Should these parameters deviate markedly and/or persistently from normal, mice will be humanely killed.