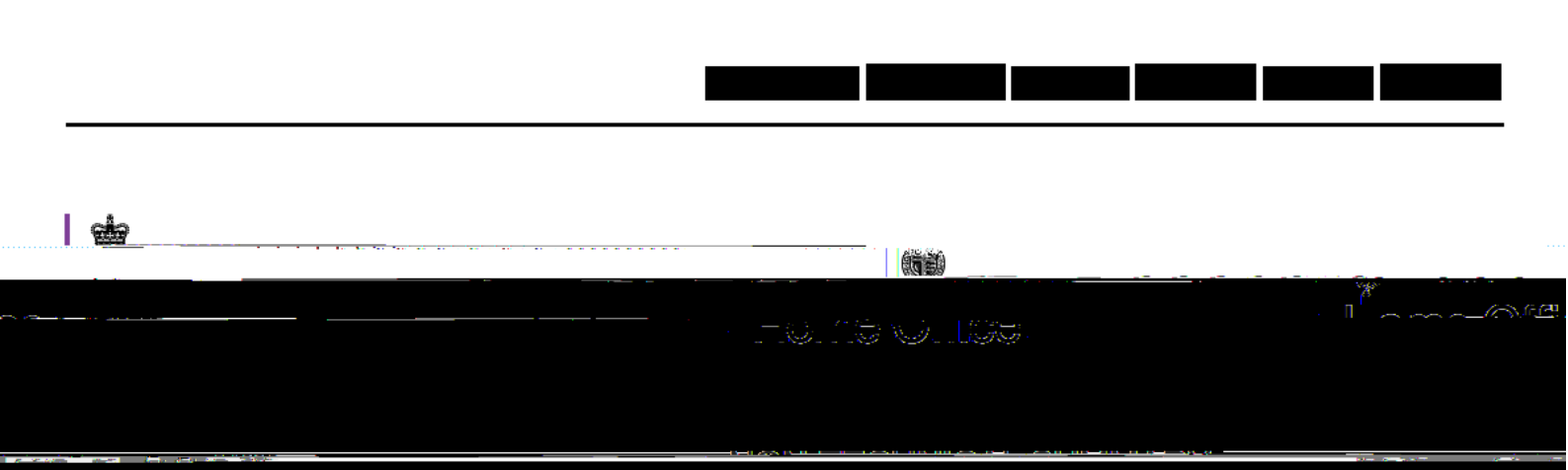

What's the aim of this project?

Our aim is to increase our understanding of the molecular and cellular processes that enable a healthy lifespan and that, when deregulated, can cause or worsen diseases such as immuno-deficiencies, chronic inflammation and type-2 diabetes.

Potential benefits likely to derive from the project, for example how science might be advanced or how humans, animals or the environment might benefit - these could be short-term benefits within the duration of the project or long-term benefits that accrue after the project has finished.

Why is it important to undertake this work?

A better understanding of the biological mechanisms underlying human health and the causes of complex diseases will allow us to better treat such diseases in the future, by enabling us to use rational strategies in the development of more efficient therapeutics with fewer undesirable side-effects.

What outputs do you think you will see at the end of this project?

The expected benefit from this project is that we will gain a better understanding of the complex

Typical procedures done to animals, for example injections or surgical procedures, including duration of the experiment and number of procedures.

Explain why you are using these types of animals and your choice of life stages.

We will use mice, as they are the best understood and most widely used mammalian laboratory animal, with excellent means for generating and interpreting the effects of genetic modifications. Most of the mice will be used at young adult life stage, some will be compared to old mice, and a few will be tested throughout their lifespan. We will compare young and old mice because some phenotypes, such as inflammation and metabolic syndrome are age-dependent.

Typically, what will be done to an animal used in your project?

The majority of mice will be used for the generation and maintenance of genetically modified strains or for the collection of cells and tissues for analysis ex vivo after the animals are humanely killed. Some mice will be aged, so their inflammatory, immune and metabolic responses can be compared to those of young mice. Some mice will be given single injections to challenge,l be givTnM[illegible]

We will use group sizes that can confidently detect significant differences, determined largely by past experience, and also from the published literature, with help from the Institute's statistician where needed.

What steps did you take during the experimental design phase to reduce the number of animals being used in this project?

Which animal models and methods will you use during this project? Explain why these models and methods cause the least pain, suffering, distress, or lasting harm to the animals.

Wherever possible, mice will be used for isolation of primary cells and tissues after they were humanely killed, rather than for *in vivo* experimentation. The minimum number of animals will always be used that yield meaningful results, and with the lowest possible relevant severity procedure to address a specific question.

We will work in cell lines to evaluate potential functional impacts of genetic modifications prior to generating new mouse strains. In new genetically modified mouse strains, we will undertake pilot studies and test isolated primary cells to evaluate phenotype prior to using relevant *in vivo* models, starting with mild severity procedures and progressing to moderate severity depending on evidence gathered.

We use bacterial infections to challenge the immune system of mice and evaluate their ability to clear these infections. These infections would cause some of the mice to develop clinical signs and even die, if these mice were kept for several days after the infection. We will limit the period of time that infected animals are kept so that we can detect an inflammatory or immune response, without clinical signs or deaths expected.

Bone marrow transplantation may cause up to 5% of mice to die from failed engraftment. Use of this procedure is justified because it informs on the cell types involved in an inflammatory or immune response, thus minimising the need for additional mouse strains. Treatment of the mice with antibiotics and careful timing and dosing of the transplant material will be used to refine this procedure and minimise harm.

Why can’t you use animals that are less sentient?

sampling to reduce stress to these animals. Mice on these long-term studies, and all our breeders, have extra enrichment in their cages to further eliminate stress. In rare cases where it will be required that we induce and maintain general anaesthesia, we will use modern anaesthetics and continuous monitoring.

What published best practice guidance will you follow to ensure experiments are conducted in the most refined way?

We will follow PREPARE and local campus guidelines.