08 February 2016

Project title	**Type 2 immunity in infection and tissue homeostasis**		
Key words	Helminth infection, cytokines, macrophages, wound repair, allergy		
Expected duration of the project (years)	5		
Purpose of the project	Basic research	Yes	
	Translational and applied research	Yes	
	Regulatory use and routine production		No
	Protection of the natural environment in the interests of the health or welfare of humans or animals		No
	Preservation of species		No
	Higher education or training		No
	Forensic enquiries		No
	Maintenance of colonies of genetically altered animals		No
Objectives of the project	Infection with multicellular parasites (helminths) leads to what is called a 'type 2' immune response. For reasons that are not fully understood, this arm of the immune system is involved not only in combatting infection with these large parasites but regulating wound repair and the body's energy balance. We strive to understand how the cells and proteins that are expanded during a type 2 immune response mediate these different functions.		
Potential benefits likely to derive from this project	Helminths infect over a quarter of the human population and the vast majority of wild and domestic animals. Although rarely fatal, they affect mental and physical development in humans and can cause severe debilitating disease. The also represent an enormous economic burden to the livestock industry. Our findings will help develop strategies, such as vaccination, for controlling these diseases. In particular, we study parasites that in humans cause elephantiasis and river blindness. We also study parasites of the intestine that first migrate through the lung. These lung migrating parasites are very common in people living in developing countries. The type 2 immune response also is a major cause of allergy, asthma and tissue scarring (fibrosis). Fibrosis is a major cause of death worldwide but little is understood of		

	its root causes. We expect our work to reveal important details of how these diseases develop, helping in the future development of therapies. Diseases of metabolism are considered a major challenge for the western world and increasingly in developing countries. The unexpected discovery that cells and proteins of the 'type 2' immune response interact with fat cells to regulate metabolism will open the doors for novel approaches to treating obesity and diabetes. Most of the work we do is fundamental research designed to unravel the details of the interactions between cells of the immune system and the rest of the body. Therefore, we don't expect to generate or test therapies directly. However, the work we do will provide important knowledge for those involved in direct translational programmes.
Species and approximate numbers of animals expected to be used, and anticipated period of time	The majority of animals we will use will be mice. We expect to use approx. 55,000 over 5 years. Approx. half of these will be used for breeding strains that have specific gene modifications needed to test particular hypothesis. We will also use approx. 5000 jirds and rats to maintain life cycles of the helminth parasites.
Expected adverse effects and the likely/expected level of severity. What will happen to the animals at the end.	The vast majority of animals will experience no adverse effects or only mild adverse affects. The parasite infections are generally well tolerated and will rarely even reach moderate severity. Some manipulations that make animals more susceptible to infection may increase the severity from mild to moderate. All animals will be killed before they exceed moderate severity limits.
Application of the 3 Rs	
1. Replacement Why do animals need to be used, and why non-animal alternatives cannot be used.	Our studies rely on looking at the immune response to infection or other conditions in the context of the whole body. We cannot replicate these processes outside the body. No alternatives for exist for parasite migration through the body, wound repair in the tissues, effect of dietary manipulation on parasite survival exist. Further, these processes involve multiple body systems. In particular we study how cells move through the body during disease, whether they expand at the site of infection and injury by dividing or whether they come in from the blood. These processes are tightly regulated by multiple systems in the body and cannot be studied in cell culture

	or artificial model systems. Whenever possible, we use cell culture systems to address specific questions.
2. Reduction How the use of minimum numbers of animals will be assured	Our experiments are carefully designed such that the results will be clearly interpretable using the smallest number of mice. We consult statisticians whenever necessary to ensure this is the case. Additionally, we carefully discuss our experiments as a team to design experiments to take full advantage of all tissues in the animal. For example one person may be studying the body cavities while another studies the liver, and another the intestine, all in the context of a particular helminth infection. Thus, different tissues from one mouse can be used to answer multiple questions. This is a routine process in the lab. Additionally, through careful assessment of animal strains used, we have over the past 5 years dramatically reduced the numbers of animals needed for maintenance of parasite life cycles.
3. Refinement Reasons for the choice of species and why the animal model(s) to be used are the most refined, having regard to the objectives. General measures to be taken to minimise welfare costs (harms) to the animals.	We use a variety of helminth models that infect different tissues of the body. When the natural host is a mouse, the mouse is used to keep parasites alive (none can be maintained in culture). In some cases, rats or jirds are more susceptible to infection and then these are used to maintain the parasite, so that we can use the fewest animals possible. We use inbred laboratory mice for the vast majority of our experimental work because of the enormous range of reagents that are available. These can be used to assess in detail the mechanisms by which the cells and proteins ofa the type 2 immune response cause wound repair, changes in metabolism and killing of parasites. For example, we use a parasite that migrates through the lung before it reaches the intestine. This model allows us to study mechanisms of worm killing in the lung and intestine, while at the same time studying how the lung is repaired, and how poor repair leads to long term lung problems. Animals are closely monitored for any ill affects, typically by visual assessment and weighing. Weight loss can predict ill effects before they are seen visually.