

08 February 2016

<b>Project title</b>	<b>Pathophysiology of heart failure</b>		
Key words	Heart Failure, Calcium, $\beta$ -adrenergic, Ultrastructure		
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	<p>Diseases affecting the heart still occur at very high rates and have poor outcomes with most people diagnosed with heart failure not surviving for more than five years. There are some characteristic changes in the properties of the heart in diseases such as heart failure or atrial fibrillation which lead to a decrease in the hearts ability to pump blood (reduced contractility) and render it more susceptible to life threatening disturbances in the rhythm of the heart (arrhythmias). In this project we aim to understand the molecular, cellular and tissue mechanisms that are responsible for the hearts reduced contractility and increased susceptibility to arrhythmias in heart disease.</p> <p>A second aim of this project is to use explanted hearts to understand the mechanisms that cause some patients who receive a heart transplant to reject the donated heart. This will be achieved by mapping the content of cells in the heart that cause rejection and how this changes when explanted hearts are preserved with different solutions.</p>		
Potential benefits likely to derive from this project	<ul style="list-style-type: none"> <li>• Academic knowledge furthering understanding of the mechanisms causing heart failure and associated medical problems</li> <li>• Potential to identify new targets for drugs or devices to treat people with heart failure</li> </ul>		

	<ul style="list-style-type: none"> <li>Understanding the factors that lead to rejection of hearts used for transplantation could modify clinical practice and reduce the need for immunosuppressant drugs in transplant recipients</li> </ul>
Species and approximate numbers of animals expected to be used, and anticipated period of time	Sheep, approximately 800 over 5 years
Expected adverse effects and the likely/expected level of severity. What will happen to the animals at the end.	The severity level of the protocols undertaken is expected to be one of either unclassified (performed under terminal anaesthesia), mild or moderate. The majority of animals will however undergo moderate procedures with the expected adverse effect to mainly be the development of heart failure. Animals will be closely monitored for the onset of the signs of heart failure and once these become evident they will be humanely killed and tissues harvested for <i>in vitro</i> experiments.
<b>Application of the 3 Rs</b>	
1. Replacement Why do animals need to be used, and why non-animal alternatives cannot be used.	<ul style="list-style-type: none"> <li>The muscle cells within the heart are terminally differentiated and are not amenable to long term cell culture</li> <li>Diseases such as heart failure are systemic and can not be fully reproduced using tissue culture approaches</li> <li>Computer models are not 'clever' enough to predict the outcomes of the systemic influences occurring in conditions such as heart failure on the function of the heart</li> <li>Diseased human heart tissue is of limited availability and also suffers from being derived from highly variable disease causes and subject to multiple, again varying, treatment strategies.</li> <li>Healthy human heart tissue is even less available than diseased tissue</li> </ul>
2. Reduction How the use of minimum numbers of animals will be assured	<ul style="list-style-type: none"> <li>Tissues derived from each animal are used across multiple projects thus reducing numbers required</li> <li>Experimental design is key to performing this programme of work</li> <li>Where it is possible we will use non animal alternatives such as cell lines or computer models</li> </ul>

	to test the validity of hypotheses before undertaking animal experiments
<p>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.</p>	<ul style="list-style-type: none"> <li>• Procedures are refined to be as minimally invasive</li> <li>• We employ as clinically relevant approaches as possible</li> <li>• Animals are housed in social groups wherever possible or, if they have to be singly housed, this is within sight of /proximity to group housed animals in the same room</li> </ul>