22 February 2016

Project title	**Understanding vision, developing therapies**		
Key words	Retina, retinitis pigmentosa, sight, melanopsin, vision		
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	Yes	
Objectives of the project	There are two related objectives. On the one hand, we want to understand how a newly discovered light sensing mechanism (melanopsin) and the long established rod and cone photoreceptors work together to allow us to see and to drive a range of subconscious responses to light. We understand quite a lot about how the retina and brain measure small differences in light intensity in order to help us see. However, in our everyday life the amount of light falling on our retina varies enormously over space and time. Our work to date tells us that those big differences in light intensity are in part measured by melanopsin. We now would like to determine how vision is influenced by changing light levels and how melanopsin helps us see. We would also like to know how melanopsin and the other photoreceptors adjust our biology in ways in which we are not even aware – especially keeping us alert and setting the phase of our biological clocks. As part of that work we will also determine what happens to these aspects of vision in diseases that affect the retina. This brings us to the second major objective, assessing ways of restoring vision in blindness. Loss of rod and cone photoreceptors is a common cause of blindness in people. We have recently shown that it is possible to recover vision in mice with an equivalent condition by introducing a photosensitive protein into the retina that remains when		

	rods and cones disappear. We now need to understand that therapy better. How well can it work? What limits its performance? Can we find alternatives that work even better?
Potential benefits likely to derive from this project	Blindness caused by rod and cone loss is quite common (around 1:2500 people) and currently untreatable. If we can develop new therapies for this condition it will make a big difference to people with those conditions. Understanding how melanopsin vision works is also very important. In modern industrialised societies people spend much of their time under artificial light and viewing electronic visual displays. These differ fundamentally from what we experience outdoors. If we better understand how the visual system works we will be able to design these artificial systems better, improving our visual experience and ensuring that lights not only help us see but also have appropriate sub- conscious effects. Its increasingly clear that artificial light at night can have deleterious health effects, the same likely is true to a lesser extent during the day. It is unrealistic to expect people to stop using artificial light, but we can do our best to make sure that it is appropriately designed.
Species and approximate numbers of animals expected to be used, and anticipated period of time	Approximately 10100 Mice and 300 Rhabdomys (African striped mouse) over 5 years.
Expected adverse effects and the likely/expected level of severity. What will happen to the animals at the end.	Most of the mice will not suffer pain or distress because they will be used for breeding, observations of voluntary behaviour, or killed for tissue collection. The majority of the rest will experience transient mild distress associated with inducing and recovering from anaeasthesia, short term restriction of food and water, or swimming in a maze to find an escape platform. The highest severity level we expect would be moderate, and that might be reached in those animals undergoing recovery surgery to implant transponders or cranial electrodes or inject substances into the eye. The main concern here is post-operative pain during wound healing and we will alleviate that with analgesics. The relatively small number of mice undergoing recordings from electrodes implanted into their brain will have a small additional weight on their head associated with the electrode mounting and, transiently, the ultra-

	light weight wire we use to connect to the recording apparatus. All animals will be killed at the end of experiments.
Application of the 3 Rs	
1. Replacement Why do animals need to be used, and why non-animal alternatives cannot be used.	Sight is an emergent property of the brain and retina that can only be studied in animals. It cannot be recreated with computer simulations, or tissues/cells grown in the lab. It is possible to study the process of photoreception outside animals and we will take advantage of this to replace animals as a first screen of potential improvements to our gene therapy. Only the strategies that prove most promising in vitro will be taken through to trial in mice.
2. Reduction How the use of minimum numbers of animals will be assured	Wherever possible we use electrodes that record simultaneously from many parts of the brain, which allows us to record a lot of data from a single animal and reduce the numbers used in total. We use statistical power calculations, randomise treatment allocations and analyse blind to treatment wherever possible in order to maximise efficiency.
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 have chosen mice because i.) they share many features of our own visual system; ii.) there is a large amount of baseline information in this species upon which to build; and iii.) there are a range of transgenic models that allow us to ask important questions. One way in which mice are unlike us is that they have rather few cone photoreceptors. There is an obvious need to also work in an animal with more cones. The conventional models would be cats or primates. We have instead chosen an animal with lower sentient ability (an African mouse species, Rhabdomys pomilio) that is diurnal and has a cone rich retina and higher acuity. Over the course of my previous project licence, we introduced refinements to electrophysiological and behavioural experiments that ensure we do NOT have to train mice to recognise aversive stimuli (mild electric shock), or restrain conscious animals to achieve our objectives.