Project summary

Describe the aims and objectives of the project.

Peripheral nerves respond to changes at the surface or inside our body, the brain then interprets these responses in terms of tactile or visceral sensations, such as heat, touch, or pain. Until now, accepted scientific

theory has held that only the central nervous system could interpret and analyse such sensations. The peripheral nerves were seen to be a mainly wiring network, relaying information to and from the central nervous system by delivering messages to the ‘control centre’ (the brain), which then tells the body how to react. Our recent findings challenge this view and suggest that peripheral nerves could be capable of interpreting their environment and modulating pain. My overarching goal is to develop a comprehensive mechanistic understanding of how peripheral nerves can regulate and control pain. These studies will change current view on the principles of pain processing and will provide new ideas for the treatment of pain.

What are the potential benefits that will derive from this project?

I believe that this programme of work will lead to the development of improved, novel means by which both acute and chronic pain can be controlled; these new means may reduce side effects of traditional analgesics (e.g. addiction, tolerance). Thus, the ultimate impact of this research should be with patients suffering from acute or chronic pain. The economic costs associated of chronic pain reach tens or even hundreds of billions annually. Enabling individuals to return to work more promptly, or indeed to avoid absences, through the development of new approaches to pain control and treatment, may have a tremendous positive impact on national economy and, therefore, the nation’s international competitiveness, which in turn should further enhance individuals’ quality of life.

What types and approximate numbers of animals will you use over the course of this project?

Rats and mice (including transgenic mice). We estimate usage of approximately 175 mice and 150 rats p.a. Mice are needed as extensive transgenic approaches that are suggested here are only available in mice. On the other hands, rats as larger animals, allow better success rates for some surgical approaches suggested. The research that has led up to this proposal has been performed on mice and rats.

What are the expected adverse effects and endpoints for animals used in this project?

Some of the experiments (pain models) will be of moderate severity. Lesions to peripheral nerves or peripheral inflammation may result in moderate hyperalgesia and in some distress associated with it. At the end of each experiment animals will be humanely sacrificed using the Schedule 1 procedure.

Replacement

Why can’t your project use non-animal alternatives?

Pain management is an unmet clinical need as many types of pain (i.e. neuropathic pain) cannot be successfully treated with current medications. Therefore the experiments with mammals are necessary. However, our programme does involve a large body of mathematical modelling of pain processing as per our earlier published work. We also abundantly use experiments with the in vitro systems, such as expression systems, to replace animal tissue.

Reduction

How will you ensure that the number of animals used will be kept to a minimum?

Our aim is to reduce the number of animal experiments whenever possible. A large share of our experiments is done with cultured neurons. This is a very efficient way of animal usage since a culture from one animal usually provides enough material for up to a week of experiments. In the in vivo experiments we will keep the group size

to a minimum sufficient to detect significant changes between the groups. Mathematical modelling will also be extensively used.

Refinement

Why are your choices of animal, model, and method the most refined?

The species of choice for this work are rat and mice. These species offer a well characterised models that are used widely in pain research. Mice are needed because they are currently the species of choice for gene manipulation, which will be used in this programme. Rats are larger animals and some surgical procedures used in this programme have better success rates on rats because of this. Moreover, confirmation of findings in two mammalian species ensures broad applicability of these findings. Moreover, the part of the nervous system responsible for pain sensation is well conserved between rodents and human. We will only use pain models that are well established in the field. In most cases in these models animals only experience relatively mild distress, close to the threshold of feeling discomfort. As animals are checked daily, signs of significant discomfort will result in immediate sacrifice of the animal with humane schedule 1 procedure.