G: NON-TECHNICAL SUMMARY (NTS)

NOTE: The Secretary of State considers the provision of a non-technical summary (NTS) is an essential step towards greater openness and requires one to be provided as part of the licence application in every case. You should explain your proposed project clearly using non-technical terms which will be understandable to a lay reader. You should avoid confidential material or anything that would identify you, or others, or your place of work. Failure to address all aspects of the non-technical summary may render your application incomplete and lead to it being returned.

This summary will be published (examples of other summaries can be viewed on the Home Office website at http://scienceandresearch.homeoffice.gov.uk/animal-research/).

(WORD LIMIT: 1000 WORDS) KEYWORDS (Insert up to 5 keywords)
Axon degeneration; Alzheimer's disease; motor neuron disease; peripheral neuropathy; ageing

- Summarise your project (1-2 sentences)

This project studies mechanisms of nerve degeneration as a model for axon loss in a range of neurodegenerative conditions including Alzheimer's disease, motor neuron disease and peripheral neuropathies. It also studies the loss of axons during normal ageing.

- Objectives: Explain why you are doing this project. Describe the scientific unknown(s) or clinical or service need you are addressing. Give a brief scientific background or other explanation of why the work is needed.

Axons are 'wires' carrying signals from one nerve cell to another. They are essential for nervous system function and vulnerable to physical injury, toxins, viruses, metabolic defects and inherited disorders. This contributes to multiple sclerosis, motor neuron disease, Alzheimer's disease, glaucoma and peripheral neuropathies. There is no effective treatment for axon degeneration in any disorder.

We aim to identify methods to prevent axon degeneration. In 2001 we found a protein that delays axon degeneration and have built on this to identify drugs that have the same effect. Two main aims are to test their efficacy in a mouse model of an axonal disorder and to identify more effective ways to prevent axon degeneration.

We will study chemotherapy induced peripheral neuropathy (CIPN) because it is an excellent candidate for prophylactic treatment. CIPN is a lifelong chronic pain condition in many cancer survivors caused by their chemotherapy. It also limits chemotherapeutic dose, and hence the cancer therapy itself. As it involves only temporary axonal stress during chemotherapy at predictable times, CIPN is a model disorder for preventing axon degeneration. If successful, this knowledge could be applied to other axonal disorders.

The skills we have developed for studying axons put us in a unique position to study axon pathology in other disorders. We will investigate how the essential flow of molecules and organelles along axons is disrupted in Alzheimer's disease and motor neuron disease. This is important because the early stages of both disorders, when treatment has the best chance, involve massive loss of distal axons and synapses.
We lose a huge number of axons during normal ageing: 40% of nerve endings in our skin by 80 years and 45% of brain white matter by 80. This underlies the normal decline in mobility, memory, vision and other functions, and helps explain why ageing is the biggest risk factor for neurodegenerative disease. Initial studies suggest diet and exercise significantly alter age-related axon loss and we aim to understand the extent and timing of dietary intervention or exercise that are required.

- **Outline the general project plan.**

We will collaborate with a fly genetics group to identify genes that regulate axon degeneration files and then validate their effects in mice, because confirmation in mammals is essential to know the full meaning of the data from flies. This combination of initial screening in flies and confirmation of the most important results in mice dramatically reduces the number of experiments needed in mice. We will then piece these steps together into a molecular pathway, using cell culture methods where possible, to identify the best points to intervene using drugs. We will test the effect of one drug type, that we have already found to block axon degeneration, as a potential prophylactic method to prevent CIPN.

We will also study mechanisms of axon loss both in normal ageing and in mouse models of the age-related neurodegenerative disorders Alzheimer's disease and motor neuron disease. These studies will focus particularly on the decline in the delivery of essential molecules and organelles to nerves as we age and in many neurodegenerative diseases, a process known as axonal transport. Non-harmful transgenes allow us to image and quantify axonal transport in mice, a method that is impossible in humans. This approach also allows us to study what influences this axonal transport using whole nerves, thereby generating data that is much more physiologically relevant than in cell culture or in simpler species such as flies.

- **Predicted harms:** Give a brief description of the procedures to be applied to the animals used in this project and describe the expected adverse effects.

Genetically altered mice with varying degrees of hindlimb paralysis will be used to model human neurodegenerative disorders. Nerve degeneration in mice or rats, induced surgically or by drugs injected into tissues, is important to identify factors that alter the course of degeneration. Mouse or rat models of CIPN will be used to test whether drugs can block the development of hypersensitivity to normally non-painful stimuli. Mouse models of obesity will be used to understand how this combines with normal ageing to cause axon loss.

- **Predicted benefits:** Outline in a few sentences how science will advance, or people or animals will benefit from this project.

Our work will advance scientific understanding of nerve degeneration and other cell death mechanisms. We are very likely to identify new genes that influence nerve degeneration and we also aim to translate this knowledge into novel drugs. In the long term this should benefit patients with a range of neurodegenerative conditions and in the short term we will promote public understanding of nervous system degeneration, and factors that cause it, through open access publishing and regular public engagement.
• Estimate the numbers of animals of each species to be used; explain what types of animal will be used and why you chose the particular types of animal. Explain how you will ensure that you use the minimum number of animals.

Most experiments will use mice (1-2000 per year) because their genome is well understood and models of the relevant human diseases have been established. A few will use rats (up to 100 per year) because some disorders are better modelled in rats than mice. Numbers will be minimised through careful use of pilot experiments, good experimental planning, use of cell culture methods and collaboration with groups using invertebrates.

• Demonstration of compliance with the 3Rs: State why you have to use animals and cannot use non-animal alternatives. Where appropriate, say how you will use non-animal studies in parallel with the project.

Replacement is used wherever possible, mostly through fly and cell culture studies, but confirming important results in a mammalian nervous system is essential. Without this, misunderstandings about disease mechanisms could eventually require more animals to clarify. For ‘Reduction’ see section above and for ‘Refinement’ see below.

Human studies are important for confirming key animal data but cannot replace animals. Many human tissues are only obtained at disease endstage (death), human ageing studies are extremely slow and human genetic diversity and wide-ranging lifestyles complicate data interpretation.

• Explain why the protocols and the way they are carried out should involve the least suffering.

Experiments are refined to minimise suffering using sterile conditions, anaesthetics, humane methods of killing, and targeting pathology to subsets of cells to avoid whole-animal suffering. The welfare of each animal is monitored daily by animal care staff, veterinary staff and/or scientists. If in rare circumstances an animal has an unexpectedly severe response to a drug or an operation, or where an infection develops, treatment is given where possible and if necessary the animal is humanely killed.