NON-TECHNICAL SUMMARY (NTS)

Project Title (max. 50 characters)	Mechanisms of skeletal repair and pain
Key Words (max. 5 words)	Fractures, bone, joint, pain
Expected duration of the project (yrs)	5

Purpose of the project as in ASPA section 5C(3) (Mark all boxes that apply)		
	x	Basic research
	x	Translational and applied research
		Regulatory use and routine production
		Protection of the natural environment in the interests of the health or welfare of humans or animals
		Preservation of species
		Higher education or training
		Forensic enquiries
		Maintenance of colonies of genetically altered animals[1]

Describe the objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed)	The number of fractures worldwide increases dramatically due to the ageing population and the consequent rise in skeletal diseases such as osteoporosis and osteoarthritis The process of fracture healing is both long and arduous and inflammatory nociceptive pain is also associated with skeletal tissues damage and the resulting inflammatory process. The ultimate goal of our programme is to reduce fracture risk in the ageing population, to improve fracture healing and to minimise bone pain.
What are the potential benefits likely to derive from this project (how science could be advanced or humans or animals could benefit from the project)?	This project will provide information on the basic science that underpins skeletal remodelling and repair processes, their modulations by mechanical and biological factors and their interactions. We expect to determine the mechanical and biological environments that promote optimal blood flow to bone, chondrogenesis and osteogenesis for bone repair. This is a timely project due to the massive clinical need to address fragility fractures in the elderly and in skeletal diseases. Bone pain is also a serious complication after fractures and new therapeutic options for treating and preventing skeletal pain are required.

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[1] At least one additional purpose must be selected with this option.

What species and approximate numbers of animals do you expect to use over what period of time?	We will use a maximum of 3000 mice and rats, mainly mice. Rodents are appropriate species because their fundamental skeletal biology is very similar to humans. Well-established models of diabetes, osteoporosis and osteoarthritis that develop the full spectrum of characteristics of these diseases are available in rodents The numbers of rodents to be used are based on experience and calculations which we have undertaken that estimate the minimum number required to detect statistically valid differences between groups.
In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected level of severity? What will happen to the animals at the end?	All surgical procedures (ovariectomy, neurectomy, induction of osteoarthritis and fractures) to be undertaken are performed in rodents and do not exceed "moderate" in severity. We have developed over the years appropriate animal models of skeletal diseases and protocols that aimed at investigating the remodelling and repair responses of skeletal tissues to their mechanical and biological environment. All these experiments are performed by appropriately trained experimenters and are essential for the success of this project. Animals will be sacrificed by a Schedule 1 or non-Schedule 1 method where necessary at the end of experiments.
Application of the 3Rs	
1. Replacement State why you need to use animals and why you cannot use non-animal alternatives	Many aspects of our work are being achieved through the use of laboratory based in vitro cell and tissue cultures, which allow identification of the most likely treatments to be validated in vivo. This replacement reduces the numbers of animals used. The integrated physiological environment of the living animal is still essential to elucidate the patho-physiological mechanisms of fracture healing prior to application in advancing clinical management of fractures in both veterinary and human patients.
2. Reduction Explain how you will assure the use of minimum numbers of animals	We always aim to reduce the numbers of animals we use. Power analyses are always applied in order to identify the minimum number of animals that we need to use in order to answer the specific question being posed. Wherever it is possible we will also exploit contra-lateral limbs as controls in order to reduce further the numbers of animals. Our techniques and appropriate training of experimenters will also minimise the number of animals used.

3. Refinement Explain the choice of species and why the animal model(s) you will use are the most refined, having regard to the objectives. Explain the general measures you will take to minimise welfare costs (harms) to the animals.	The strategy used would minimise the animal suffering which will be limited in our studies by our strict monitoring of severity limits. Our use of surgical approaches will be kept to a minimum. Appropriate pain relief during our protocols will be achieved through appropriate levels of analgesia. Pain relief will be provided unless scientifically justified in a small number of animals.