G. NON TECHNICAL SUMMARY (NTS)

Project title: Cellular senescence, plasticity and cancer: new frontiers and novel tools for diagnosis and therapy
Duration of project - years: 5
Duration of project - months: 0

Purpose of the project (as in ASPA Section 5C(3)):
(a) basic research: YES
(b) translational or applied research with one of the following aims:
   (i) avoidance, prevention, diagnosis or treatment of disease, ill-health or other abnormality, or their effects, in man, animals or plants: YES
   (ii) assessment, detection, regulation or modification of physiological conditions in man, animals or plants: NO
   (iii) improvement of the welfare of animals or of the production conditions for animals reared for agricultural purposes: NO

(c) development, manufacture or testing of the quality, effectiveness and safety of drugs, foodstuffs and feedstuffs or any other substances or products, with one of the aims mentioned in paragraph (b): NO
(d) protection of the natural environment in the interests of the health or welfare of man or animals: NO
(e) research aimed at preserving the species of animal subjected to regulated procedures as part of the programme of work: NO
(f) higher education or training for the acquisition, maintenance or improvement of vocational skills: NO
(g) forensic inquiries: NO

Keywords:
Damage, Premalignant tumours, Cancer, Diagnostic tools, Therapeutic tools

Describe the aims and objectives of the project (e.g. the scientific unknowns or scientific/clinical needs being addressed):
Cancer is a leading cause of morbidity and mortality worldwide. We are interested in the processes and molecular mechanisms that can contribute to the origin of cancer. When cells are afflicted by different types of damage (such as lung cells exposed to smoke, or skin cells exposed to ultraviolet radiation from the sun) they undergo a defence mechanism that results in a permanent stop of the division cycle. These damaged cells are usually eliminated by the immune system. However, when damage is permanent (as in chronic smokers), the system is deregulated, and damaged cells accumulate forming premalignant lesions or tumours that the immune system is not able to eliminate. These aberrant cells cannot execute their specific functions properly. Instead, their functions are altered, and they secrete a complex cocktail of inflammatory and tumour-producing factors in the surrounding tissue, which transforms nearby cells ultimately promoting cancer. We have strong evidence (in vitro and in vivo) of a causal role between these damaged or aberrant cells and the origin of cancer.

Importantly, we are developing tools capable of targeting these premalignant cells, which include novel probes and drugs. We aim to detect precancerous lesions and eradicate them in order to limit their progression to malignant tumours.
In conclusion, the main goals of our project are:

i. to gain insight into mechanisms and processes that lie at the origin of cancer, thereby increasing our fundamental knowledge.

ii. to develop novel diagnostic and therapeutic interventions, thereby meeting an existing clinical need.

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)?

The overall purpose is a better understanding of the mechanisms that contribute to cancer initiation, which remains a formidable challenge in oncology. Such knowledge is crucial to develop novel diagnostic and treatment methods. To do so, it is important to isolate precancerous cells in order to identify the cellular type of origin and to characterise them. We also aim to validate novel probes and drugs to detect early-phase cancers and to implement novel therapeutic interventions. Our final goal is to expand our new therapies from preclinical studies to early-phase clinical trials. High-risk groups for cancer (for instance patients with a smoking history) may benefit from our technologies. In addition, the mouse models generated during our experimental approaches will be valuable to other scientists interested in cancer early detection and development of novel anti-cancer therapies.

What types and approximate numbers of animals do you expect to use and over what period of time?:

Mice have been widely used in cancer research and provide unique opportunities to manipulate their genes, 85% of which are shared with humans. Our work focuses exclusively on mice as animal models of human diseases. We anticipate the use of up to 10000 mice over 5 years, 7000 genetically altered mice obtained from our protocol 5, and 3000 obtained from projects with authority to distribute them.

In the context of what you propose to do to the animals, what are the expected adverse effects and the likely/expected levels of severity? What will happen to the animals at the end?:

In most cases, damage or tumour induction will have not a significant impact on the animals’ general well-being. We will mainly focus our experiments on initial and intermediate stages of cancer progression. Short-term discomfort may result directly at the administration site, but the animals are expected to recover quickly. In case the mice show any signs of discomfort or pain, they will receive analgesics in order to reduce the administration-related effects. In rare occasions tumour induction may result in sudden death without preceding signs. Damage and tumour initiation will be a cause of genetic manipulation, the direct use of carcinogens or tumour cell implantation. Different substances, to either induce tumours or to be used as therapies once the tumours are established, will be administered directly through the blood stream, in the abdominal cavity or given orally. After tumour induction, the animals will be monitored closely for any evidence of tumour growth by imaging techniques (internal tumours) or by direct observation (subcutaneous tumours). Discomfort resulting in clinical signs such as hunched posture in combination with inactivity or respiratory distress will result in individual animals being removed.
being culled. For other procedures such as treatment modalities with novel probes and drugs, most animals will show no more than mild clinical signs. In case of mice showing hunched posture in combination with inactivity or loss of body weight, mice will be culled. At the end of experiments, all animals will be sacrificed.

Application of the 3Rs
Replacement:
Identification of the cell of origin of cancer and the processes and mechanisms promoting malignant transformation of cells remains a challenge. Cancer initiation is a complex multi-step phenomenon that is modulated by different causal incidents (damage, inflammation, etc.), the properties of precancerous cells, and the surrounding tissue. Tissue environment may involve numerous cellular types and states (e.g. immune cells, damaged cells, proliferative cells, etc.). At present, it is essential to use animal models able to reproduce realistically the mechanisms, processes, tissue environment and complexity of events that contribute to the initiation and progression of cancer in humans.

To replace animal models we refer to cell cultures and the use of human tissues, whenever possible.

Reduction:
Bio-statisticians at the University of Cambridge will be consulted for advice on the proposed experimental designs and methods of analysis of the results. Calculations will be made to ensure that what is deemed to be a significant effect can be detected with the number of animals assigned to every single experiment. This quantitative assessment ensures that minimal numbers of animals are used. Damaged tissues, premalignant lesions, and tumours will be collected to perform complementary laboratory studies. Animals will be regularly followed up by imaging techniques in order to reduce the number of mice used. Different tissues will be collected at the end of the experiment to do a wide range of studies, avoiding this way duplication of experiments. We will perform pilot experiments to test our initial hypotheses/ideas on small numbers of animals. We will pay special attention to controlling sources of variability related to the environment, animals, animal handlers and the experimental procedures. To control the sources of variability we will use randomised experimental designs and blinded operators.

Refinement:
Our proposed mouse models replicate human cancer. Biological mechanisms and functions differ substantially in non-mammals organisms, especially in invertebrates. Consequently, mice represent the best species able to generate data likely to be directly applicable to human disease.

Animal suffering is minimised by the use of appropriate anaesthetics and analgesia. Animals will be terminated before they show sustained signs of discomfort or pain.

We have considered best practice guidelines, and proper husbandry/care measures and environmental conditions to improve the animals' quality of life.