07 April 2016

Project title	**Preclinical evaluation of cancer therapeutics**		
Key words	cancer, chemotherapy, immuno-oncology		
Expected duration of the project (years)	5		
Purpose of the project	Basic research		No
	Translational and applied research	Yes	
	Regulatory use and routine production	Yes	
	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		No
Objectives of the project	• Identify tolerated dose levels of test drugs and side effects not predicted by cell culture based model systems. • Study the effects of the drug on the body, and also the effects of the body on the drug. • Demonstrate that anticancer activity can be shown at specified doses and with dosing schedules that are tolerated. • Identify the best tumour models to use pre-clinically that correspond with a specific therapeutic target.		
Potential benefits likely to derive from this project	The aim of the data generated in these studies is to provide pre-clinical supporting information for clinical trial applications. A drug requiring evaluation will be supplied to Epistem along with summary evidence supporting the rationale for testing the agent. By having a much more thorough investigation into the efficacy and mechanism of action of a drug they will be able to make a more informed decisions on whether to proceed into clinical trials, reducing the risk of later stage failures. This will speed up the clinical trials and make them less expensive. The benefit is therefore a reduced number of unproductive human volunteer studies (and a reduced risk of adverse effects) and most importantly the development of improved and more effective		

	therapeutics. The benefit to patients will be the identification of new anti- cancer drugs. These studies will help identify the best potential drugs early in the drug development process.
Species and approximate numbers of animals expected to be used, and anticipated period of time	We would expect to run 150 studies on behalf of sponsors using approximately 7,500 mice and 1,150 rats over the 5 year duration of this project licence.
Expected adverse effects and the likely/expected level of severity. What will happen to the animals at the end.	Side effects of tumour treatment can include lethargy, anaemia, loss of appetite, diarrhoea, dysuria, bruising, bleeding or peripheral neuropathy. Animals exhibiting these signs will be humanely killed. This is likely to manifest as weight loss. A general dose limiting sign will be a 15% loss in bodyweight, and animals showing this will be considered unwell. Any mouse reaching a 20% bodyweight loss, or any rat reaching a 25% bodyweight loss along with other signs of distress will be humanely killed (schedule 1 method). Subcutaneous tumours may grow to a size that could cause discomfort or interfere with the animals' ability to satisfy thirst or hunger. Also, tumours could ulcerate through the skin dependent on the cancer type, or if intra-tumoural therapy is administered. Animals will be killed if their ulcers do not heal within 48 hours or if their tumour reaches more than 15mm in any direction. Injection at the tumour site may cause temporary bleeding which should stop within a few hours of injection. In the unlikely event that bleeding does not cease, and if the animal shows signs of discomfort, it will be humanely killed. Orthotopic (implanted at the natural tumour site, eg a breast cancer cell line injected into the mammary fat pad) tumours may have site specific adverse effects and elicit metastatic disease. Metastatic disease will be monitored by imaging of the whole body wherever possible. However if such techniques cannot be employed using a specific model, any deviations in physiology or behaviour will be treated as indicative of metastatic disease, and animals will be humanely killed when there is loss of condition consistent with the severity limit as defined by the Home Office regulation.

	For leukaemias, animals may gradually become weak, lethargic and lose body weight. Infiltration of the spleen or liver can lead to enlargement of these organs which may be palpable. Any animals showing signs of distress or symptoms at the limit of moderate severity will be humanely killed. Immunocompromised mice will be maintained in Individually Ventilated Cages in a barrier environment to avoid unwanted infections. If animals develop unwanted infections or surgical wound complications, they will be given antibiotic treatment after advice is sought or will be humanely killed. Animals will receive analgesia following surgical procedures such as bone marrow aspiration or orthotopic tumour implantation. Prolonged periods of anaesthesia can lead to animals losing body temperature. To counteract this, animals will be warmed throughout the procedure, either by the use of heating mats, warm air blowers or temperature regulated stages. All work will comply with the UKCCCR (United Kingdom Co-ordinating committee on Cancer Research) guidelines for the welfare of animals in experimental procedures.
Application of the 3 Rs	
1. Replacement Why do animals need to be used, and why non-animal alternatives cannot be used.	The programme requires that the models used are ones which closely mirror human disease. All compounds to be tested would have previously been screened in relevant *in vitro* models to determine those candidates suitable for *in vivo* testing. Rodents (rats and predominantly mice) are suitable for these studies as the work cannot be conducted in lower vertebrates, invertebrates or cell lines due to the poor resemblance of these options to the clinical setting. Animal models address issues which current in vitro tests cannot accurately determine.
2. Reduction How the use of minimum numbers of animals will be assured	Animal models will be restricted to the minimum number of animals needed for a statistically valid result. The number of animals used will be the minimum safely necessary to allow meaningful statistical analysis of the data generated. The most important aspect of the proposed programme of work that will reduce the number of animals used is careful selection of drugs, on the basis of preclinical data. Only those potential drugs that offer a realistic prospect of

	therapeutic exploitation will be investigated. The investment by the team in the purchase of small animal imaging technology also reduces animal numbers in these experiments. The development of disease can be followed in each animal over time, abrogating the need to humanely kill satellite groups to examine disease progress, and thereby reducing total animal numbers.
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.	Rodents provide a cost and time effective platform in general for most pre-clinical testing. For the purposes of oncology testing, the use of higher species is not required because there is a wealth of knowledge on different types of cancer in rodents, as well as decades of in-house expertise with such models. Internal expertise, and more recent technological advances, such as the use of whole body imaging, allows for a more refined study design that will minimise the number of animals. These techniques will maximise the output and will provide a more thorough assessment. They will also help in selecting the best models.