Hong Kong University Guidance Document on Genetic Modification (GM) work

1. Introduction

This document forms part of the University of Hong Kong Health and Safety Policy and is issued with the approval of the University Biosafety Committee and the University Health, Safety and Wellbeing Committee. All employees and students must observe those parts of the University Health and Safety Policy that are relevant to their own work as well as observing any additional local requirements.

The policy covers general arrangements for work with genetically modified biological materials. It is complementary to guidance issued for work involving genetically modified viral vectors. If your work involves such vector systems please refer to the guidance appropriate for your system.

The policy is intended to ensure standards within Hong Kong University match internationally accepted best practice. Extensive guidance produced by various expert technical advisory committees from the World Health Organisation, the United Kingdom, Australia and the United States of America has been incorporated into this document.

2. Genetic Modification and the Law in Hong Kong

2.1 The Occupational Safety and Health Ordinance

In 1997 the Hong Kong government enacted The Occupational Safety & Health Ordinance – Chapter 509 (CAP 509). This states that:-

"Every employer must, so far as reasonably practicable, ensure the safety and health at work of all the employer's employees. This includes:-

(i) maintenance and provision of equipment and machinery (plant) and adopting safe systems of work,

(ii) arrangements for safe handling, and transport of plant and substances,

(iii) the provision of appropriate information, instruction, training and supervision."

The penalty for failing to comply with the legislation is a fine of up to HK$200,000 and for flagrant violations can include up to 6 months imprisonment.

While potential hazards arising from genetic modification are not specifically mentioned in the ordinance they may be considered to be covered by the general duty of all

employers under CAP509 to provide a safe place of work and the issues mentioned in (i), (ii), and (iii) above indicate the areas for particular concern specified by the legislation.

2.2 Common Law

In the event of an accident involving personal injury the injured person (or his/her representative) can institute legal action to obtain compensation from the wrongdoer. In the circumstances of an accident on University premises it is most likely that it would be the University that was taken to court, but depending on circumstances, it is possible that members of staff or even students could be cited in legal action.

Liability for such a claim would probably be based on whether any one was negligent or required safety measures were ignored. While it would be up to the court to decide what constitutes negligence and what safety measures were required they would probably look to international best practice as a guide for their judgment. It is the specific intention of Biosafety Policy and the University to meet international standards as specified in the WHO publication Laboratory Biosafety (Third edition) and the US NIH/CDC Biosafety in Microbiological and Biomedical Laboratories 5th Edition (BMBL).

It is worth noting that compensation payments in civil courts tend to be greater than the fines imposed after breaches of criminal law. While civil litigation in Hong Kong is not on the scale of that in the UK or USA compensation awards have been substantial in a number of cases.

2.3 The Cartagena Protocol and GM work

The "Convention on Biological Diversity" is an international treaty that entered into force on 29 December 1993 and has been signed by over 190 parties. As a means of furthering the aims of the treaty "The Cartagena Protocol on Biosafety to the Convention on Biological Diversity" was adopted as a supplementary agreement in 2000 to provide for the safe transfer, handling and use of genetically modified organisms (GMOs) [termed living modified organisms – LMO's by the protocol] that may have adverse effects on the conservation and sustainable use of biological diversity.

In September 2005 China ratified the Cartagena protocol and shortly after the Hong Kong government also announced its intention to ratify the protocol. The legislation (The Genetically Modified Organisms (Control of Release) Ordinance, Cap. 607, and its subsidiary legislation, the Genetically Modified Organisms (Documentation for Import and Export) Regulations) was introduced to implement the protocol and took effect on 1 March 2011.

The Ordinance controls the release into the environment and the transboundary

movement of GMOs, and makes provision for a number of related matters such as a register of GMO's that have been approved for release and requirements for risk assessment. The focus of the ordinance is on the **deliberate release** of transgenic plants but also covers other organisms such as recombinant bacteria and transgenic mice. Almost all the various provisions for control of deliberate release do not apply to organisms intended for contained use. **Consequently the various provisions for control of deliberate release do not apply to almost all of the Universities operations other than the appropriate labeling of living modified organisms imported or exported from Hong Kong**. Further details that are relevant for import, export or deliberate release of GM material, including clarifying definitions, are provided in a separate guidance document on the import and export of biological materials.

3. Evidence of Risks from GM work

GM work has a long history of safe use, and has been an essential technique in many disciplines for decades. Almost all of those working with GM organisms will complete their careers without ever coming across adverse consequences of any kind arising from the application of this technology in their work. This is because the vast majority of applications of the technology are intrinsically safe. However, there are an extremely limited number of examples where use of the technology resulted in the exact opposite, a potentially catastrophic event which in one case had the potential to become impossible to contain. A common feature of these events is that the outcomes were not anticipated beforehand, but with hindsight the nature of the experiment could have been predicted to merit caution. There are also common features which may be relevant to work undertaken at HKU. What follows are three examples of situations involving the application of GM technology which had or could have had very severe outcomes.

3.1 Ectromelia virus engineered to express IL-4

Researchers were interested in an ethically acceptable biological control strategy to reduce wild mouse numbers. The intention was to sterilize female mice by exposing them to a natural mouse virus engineered to express major sperm proteins. The aspiration was that wild mouse populations would respond to viral infection by mounting an immune response that included a response to the virally-expressed sperm proteins. As a result of infection with GM virus, female mice would mount an immune response to sperm after insemination that would render them inferterile. It was assumed that, if desired, it would be possible to protect a population of mice by vaccinating them against the viral vector used to express sperm proteins.

The research team became interested in augmenting the immune response of mice to facilitate this strategy. To do so they engineered an Ectromelia (mousepox) virus to express the immunomodulator IL-4. Ectromelia is a pathogen in mice, but different mouse strains vary in their susceptibility. They found that administration of recombinant virus expressing IL-4 was lethal to mice that were not immunized against mousepox, even in mouse strains that were known

to show a level of natural resistance to this virus. However, much to their surprise and concern, they found that prior immunization of mice against ectromelia did not offer them any protection against the IL-4 expressing virus. Recombinant IL-4 ectromelia demonstrated similar levels of lethality in experimental infection both naïve and immunized mouse populations. (Jackson et al., J Virol. 2001 Feb; 75(3): 1205–1210).
For further background see: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2816623/#b4

The outcome of this study was of great concern for three reasons:

i) Had this virus escaped containment it would have been impossible to control its spread in natural mouse populations. The ecological effects of eliminating mouse populations in this way are unknown but potentially very serious. In addition, it is difficult to avoid human contact with mice and in other parts of the world rodents are the reservoir of a number of serious zoonotic viral diseases such as hantaviruses and arenaviruses.
ii) The ectromelia virus is related to the recently extinct variola virus (smallpox). This disease was a serious threat to human health worldwide before eradication efforts based on immunization succeeded in the late 1970's. Variola engineered to express IL-4 could well render immunization against smallpox completely ineffective.
iii) This GM technique offers a general strategy for defeating disease prevention by immunization, the main countermeasure available against a wide variety of viral infections in humans and animals.

3.2 Mechanism of Smallpox Immune Evasion

Researchers used published DNA sequences to engineer a protein – known as SPICE – produced by the smallpox virus. The study revealed the ways in which, and the extent to which, this protein defeats the human immune system. The principle mechanism of SPICE action was by inactivation of complement components C3b and C4b, preventing complement-mediated viral clearance. Though the findings may facilitate development of protective medicines, they may also reveal ways to increase the virulence of the closely-related vaccinia virus (which is used in the smallpox vaccine). http://www.pnas.org/content/99/13/8808.long

3.3 TGN1412 clinical trial

Upregulation of T cell responses is desirable clinically in a number of contexts where there are limited number of activated T cells. Examples include rheumatoid arthritis and B-cell lymphoma. To this end CD28 superagonists are of interest as they are able to stimulate regulatory T cells regardless of T cell receptor activation. One such substance in TGN1412, a humanized genetically engineered anti-CD28 antibody. After promising results in vitro and in non human primates (NHP), where there the recombinant protein had the desired effects and was well tolerated, a phase 1 clinical trial was undertaken in 2006. Equivalent doses 500 times lower than used in the NHP study were given to six healthy volunteers. All six human volunteers developed

life-threatening conditions involving multiorgan failure for which they were moved to intensive care unit. It is thought that some of the volunteers will never fully recover from the effects of the trial.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2269728/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964774/

Experimental modulation of immune system function, whether intentional or reasonably forseeable as a consequence of work with pleiotropic gene products, is an aspect of a number of experimental strategies employed at HKU. All of the above strategies involved immunomodulation, and in two cases severe adverse consequences were not predicted.

4. Predicting Risks from the insert in GM work

In addition to immunomodulators there are other types of manipulation which also have the potential to cause adverse effects. Examples are manipulations that could promote recombination in human cells, induce expression of oncogenes and inactivate tumour suppressors. Going beyond this, even if a gene product does not fall into one of these defined categories of likely harmful gene products, if from knowledge of its properties some kind of adverse event is reasonably forseeable then given the responsibility under CAP 509 to prevent harm in the workplace, a risk assessment of some GM work is required. Further discussion of this point and a suggested pragmatic approach using OMIM to identify gene products with the potential to cause harm can be found in Bergmans et al. Environ. Biosafety Res. 7 (2008) pp 1–9, available at the following link:

https://www.cambridge.org/core/services/aop-cambridge-core/content/view/5730B6F9816A046629E7FA797B08C810/S1635792208000018a.pdf/identification_of_potentially_hazardous_human_gene_products_in_gmo_risk_assessment.pdf

5. Risk Assessment of GM work

If the outcome of a GM risk assesment is that adverse effects cannot be ruled out, the consequence is that work at BSL-2 or ABSL-2 will provide an adequate level of risk control in almost all cases. The University Safety Office is able to advise on how to set up a new BSL-2 lab, and in practice this is usually a quite straightforward process. However, to work at this level does impose its own costs, so it is important to conduct a robust risk assessment to ensure that these precautions are justified.

It is University policy that all biological work that involves operating at Biosafety Level 2 or 3 as well as all work with virus vectors and clinical samples should be assessed for the risk involved. If a GM experiment could be reasonably foreseen to have an adverse effect then a GM risk assessment should be performed, even if a viral vector or known pathogen is not involved. Clearly in the majority of cases the absence of a vector system will make an adverse event unlikely, but given the extreme examples outlined in section 3 it is still worth asking whether an adverse outcome is inconceivable given the experimental strategy to be employed.

The basic steps involved in carrying out any risk assessment can be found along with examples in the University risk assessment guidance document on the Safety Office website. The document also gives guidance on when an assessment is considered suitable and sufficient, who should carry out the assessment, the role of the PI or research group leader and other practical considerations.

5.1 Work with Micro-organisms and their Genetic Modification

Micro-organisms are categorized into a hazard group. This forms the basis of the risk assessment which determines the level of containment under which the work must be undertaken. Additional control measures may then need to be assigned depending on the route of infection of the particular micro-organism and the nature of the work. The NIH/CDC list of categorisations of biological agents according to risk, is the approved list for work in the University.

All work with virus vectors and micro-organisms of hazard level 2 or 3, must be formally risk assessed and the assessment approved by the Biosafety Committee before the project commences.

The University Biological Safety Officer is the point of contact to submit all risk assessments to the Biosafety Committee. In most straightforward cases he/she can give provisional approval for a project which will then be looked at by the whole committee at a full meeting. In the case of more complex assessments and all Class 3 work the whole committee will be circulated by e-mail and consensus arrived at before approval.

Please note this is not just work being funded externally and encompasses all relevant biological agent work carried out by undergraduate students, research assistants, PhD students, Post Docs and PIs. Any format for a risk assessment will be considered, however, staff are encouraged to use the forms which will be provided on the Safety Office website. This includes copies of blank and model risk assessment forms are available for a variety of pathogens including work with viral vectors. The forms and associated guidance serve as an aide-memoir of the points to consider during the risk assessment procedure, as well as helping to keep information in a consistent manner.

Applicants for financial support from external granting agencies or university sources of finance can follow the approval procedures currently in place detailed on the Safety Office website under the Safety Manual and Research proposals – Safety Approval procedures subheading. Risk assessment can be submitted at any time in the year and it would probably be prudent to avoid submission around the times RGC grants are due. It is the policy of the committee to give a response to the applicant within 7 working days. To assist in working to deadlines every effort will be made to reply within 48hrs although this may not always be possible.

It should be noted that one risk assessment written to encompass an organism or a set of functional pathways in an organism may cover more than a single project.

Heads of Departments shall be responsible for ensuring that PIs carry out a risk for all biological work and where the agent used is a viral vector or a class 2 or 3 micro-organism they shall ensure that the approval of the Biosafety Committee is obtained before the work is started.

5.2 Work with Animals and Plants

In general work with genetically modified animals and plants where viral vectors are NOT involved is very likely to pose no more risk than already presented by the host organism, as the consequences of any genetic modification will be confined to the organism it affects. However, the potential hazards associated with handling animals and plant materials must always be considered, and reference made to suitable sources of information to ascertain any precautionary measures required, before the work commences. If an experiment could cause a biologically active substance to be released, or the strategy employed may be able to affect the experimenter or other organisms in the vicinity, a generic GM risk assessment should be undertaken. If the outcome suggests that BSL-2 or higher containment is required the risk assessment should be submitted to the University Biological Safety committee for approval. If a GM risk assessment has already been submitted eg. as part of the CULATR application process then an additional submission to the University Biological Safety Committee is not required.