P B A C

presidential biosafety advisory committee

IMPLEMENTATION DIRECTIVE

RISK ASSESSMENT OF LENTIVIRAL VECTORS

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McMaster University

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INTRODUCTION

The use of lentiviral vectors for gene transfer has resulted in the need to evaluate constructs on a case by case basis, taking into consideration the modifications. The Public Health Agency of Canada (PHAC) provides guidance on assessment of risk for the use of genetically modified viruses. This is found in the Canadian Biosafety Standards and Guidelines (CBSG), 2013.

GUIDANCE INFORMATION

4.3.2.1 GENETICALLY MODIFIED ORGANISMS (CBSG)

The use of rDNA technologies to create GMOs may increase or decrease the risk group and/or containment level relative to the risk group and/or containment level of the parental organism, depending on factors such as the gene(s) being transferred, the modification to genes already present in the organism (e.g., point mutations, deletions), the expression of the gene(s) in the recombinant organism, the biological containment offered by the host organism, the interactions between the gene(s) being transferred and the host vector systems, and the viability of the host vector systems.

The containment requirements need to be assessed when genetic manipulations are performed that:

- alter the pathogenicity or virulence of recombinant pathogens;
- affect pharmacological activities (e.g., resistance to antibiotics) of recombinant pathogens;
- delete genetic material or introduce novel genetic material with potentially adverse effects (e.g., insertion of an oncogene);
- induce the production of toxins by recombinant microorganisms;
- broaden the host range or cell tropism of recombinant pathogens;
- create novel mechanisms or undesirable traits in transgenic animals;
- produce attenuated strains of recombinant pathogens that have lost virulence factors; and
- produce host bacterial or viral vector systems with limited ability to survive outside the containment zone.

Factors to consider when assessing GMOs should include the following:

- containment level of the recipient organism;
- containment level of the donor organism;
- replication competency of the GMO;
- property of the donor segment incorporated into the recombinant particle;
- potential pathogenic factors associated with the donor segment; and
- novel hazards of the GMO that may not be well characterized.

4.3.2.2 Viral Vectors (CBSG)

The risks associated with viral vector systems can be assessed by examining the considerations for GMOs outlined in section 3.3.2.1, along with the choice of vector system, the safety features engineered into the system, and the nature of the transgene(s) in the vector. The use of retroviral vector systems, including lentiviral vectors derived from type 1 human immunodeficiency virus (HIV-1), raises other possible risks that should be assessed. The major risks involving viral vector systems include:

- potential for generation and propagation of replication competent retrovirus (RCR);
- potential for oncogenesis;
- potential for increased pathogenicity; and
- potential for seroconversion, even with non-replicating viruses.

Operational Procedures for Work with Lentiviruses

The Presidential Biosafety Advisory Committee (PBAC) has performed a risk assessment, and in April 2010 has put forth the following conditions for work with lentiviruses at BSL2:

1. minimum 3 plasmid system
2. virus is replication defective
3. expressed transgene is a known gene that is not classified as an oncogene
4. expressed shRNA depletes a known gene that is not classified as a tumor suppressor

If at least one of the conditions listed above is not met, then BSL2+ operational procedures will apply. These operational procedures are found in the *PBAC Implementation Directive – Operational Procedures for Use at BSL2+.*

Mechanism to Monitor PID Effectiveness

- Listing of BSL2+ lentiviral use by #BUP, #workers trained
- User feedback directly related to the PID