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Biosafety Guidance for Working with Viral Vectors

USC Environmental Health & Safety

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Contents

Introduction

Viruses naturally possess the ability to enter cells and seize the cell's machinery to express their viral genes to make progeny virions. Using viruses as vectors allows scientists to take advantage of this feature to deliver and express genes of interest. Viral vectors are common tools used in molecular biology as a delivery system for genetic materials into cells that may normally be difficult to transfect. Viral vectors are constructed by replacing wild type viral genes with transgenes of interest. The viral genomes removed are usually viral replication genes so that the vector is rendered safer than wild-type virus.

Biosafety Concerns

While viral vectors are modified in such a way to minimize the risks when handling them and are considered safer than their wild-type parent virus, there are biosafety concerns that must be addressed during construction and use of them.

Replication competence

Most viral vectors are designed to be replication deficient. During the construction of viral vectors, genes critical for replication are usually removed to make room for the transgene of interest. For some vectors (e.g., lentiviruses), virion genes required for propagation are packaged on different plasmids or viruses (helper viruses). This allows the virus to replicate within the packaging cell line. By splitting viral production genes across multiple plasmids, the number of recombination events required to produce a replication competent virus is increased. The result is production of viral vector particles with the gene of interest but without the pathogenic properties of the wild-type virus. While these vectors are designed to be replication deficient, it is impossible to completely control for the possibility of the generation of replication competent virus or reversion to wild type virus through recombination. One way to mitigate these potential hazards is to incorporate replication competent viral testing into the viral production operating procedures.

Off Target Effects

For viral vectors that integrate into the host cell genome, off target effects such as insertional mutagenesis can be a safety concern. Integration into genes that are important for cell division or programmed cell-death can potentially result in oncogene activation or tumor-suppressing gene inactivation. While unlikely to occur, integrating vectors that have a wide host cell range (e.g., VSV-g pseudotyped vectors) may also carry a greater risk of unintentional germline integration.

Transgene Hazards

The gene of interest can present a hazard itself and transgene properties should be evaluated during the risk assessment process. Transgenes that are known oncogenes or have high oncogenic potential present a higher biosafety risk. Additionally, transgenes that encode either apoptotic or toxin molecules can increase biosafety risk.

General Biosafety Requirements

All research involving viral vectors must be reviewed and approved by the Institutional Biosafety Committee (IBC). For experiments that falls under Section III-A, -B, -C, or -D of the *NIH Guidelines*, the Principal Investigator must submit a protocol to the IBC which contains the following information prior to initiation:

- the source(s) of DNA
- the nature of the inserted DNA sequences
- the host(s) and vector(s) to be used
- if an attempt will be made to obtain expression of a foreign gene, and if so, indicate the protein that will be produced
- the containment conditions that will be implemented as specified in the *NIH Guidelines*.

Research involving viral vectors that do not fall under Section III-D of the *NIH Guidelines*, likely fall under Section III-E and require IBC notice simultaneous with initiation. For example, experiments in which all components derived from non-pathogenic prokaryotes and non-pathogenic lower eukaryotes fall under Section III-E.

General Biosafety Measures

Standard Microbiological Practices must be followed in all labs conducting research with viral vectors. These practices include:

- Work surfaces are decontaminated once a day and after any spill of viable material.
- All contaminated liquid or solid wastes are decontaminated before disposal.
- Mechanical pipetting devices are used; mouth pipetting is prohibited.
- Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. Food may be stored in cabinets or refrigerators outside of lab areas designated and used for this purpose only.
- Persons wash their hands: (i) after they handle materials involving organisms containing recombinant or synthetic nucleic acid molecules and animals, and (ii) before exiting the laboratory.
- All procedures are performed carefully to minimize the creation of aerosols.
- Personal protective equipment (PPE) is available and is appropriate for the risk of exposure to viable organisms containing recombinant or synthetic nucleic acid molecules
- Contaminated materials that are to be decontaminated at a site away from the laboratory are placed in a durable leak-proof container which is closed before being removed from the laboratory

BSL-2 Biosafety Measures:

In addition to following the standard microbiological practices listed above, BSL-2 labs must also:

- Limit or restrict access to the laboratory when work with organisms containing recombinant or synthetic nucleic acid molecules is in progress
- Post BSL-2 signage on the lab door
- Provide laboratory personnel with specific training in handling pathogenic agents
- Wear the appropriate PPE while working in the laboratory. Before leaving for non-lab areas, this protective clothing must be removed and left in the lab or covered with a clean coat not used in the laboratory.

- Minimize the use of sharps as much as possible. Needles should not be bent, sheared, replaced in the needle sheath or guard, or removed from the syringe following use.
- Use a biosafety cabinet (BSC) whenever procedures with a high potential for creating aerosols are conducted or when high concentrations or large volumes of organisms containing recombinant or synthetic nucleic acid molecules are used.

General Animal Biosafety Measures

- Wear gloves when handling experimental animals and when skin contact with the agent is unavoidable. Special care should be taken to avoid skin contamination with organisms containing recombinant or synthetic nucleic acid molecules.
- Viral vectors transported to the animal facility must be contained in a non-breakable sealed primary container and then enclosed in a non-breakable sealed secondary container. All containers, primary and secondary, should be disinfected before transport.
- Animals should be restrained (chemical or physical) prior to agent administration.
- Any incident (e.g., animal bites, needlesticks) involving viral vectors must be immediately treated and reported.

ABSL-2 Biosafety Measures

- Personnel shall be required to have specific training in handling pathogenic viral vectors
- For viral vector administration under ABSL-2 containment, work should be conducted in a biosafety cabinet. Examples of work that should be performed in a BSC include:
    - opening tubes
    - vector administration
    - cage changing
- When the animal research requires special provisions for entry (e.g., vaccination), a warning sign incorporating the universal biosafety symbol must be posted on all access doors to the animal work area. The sign must include information regarding:
    - the agent
    - the animal species
    - the name and telephone number of the Animal Facility Director or other responsible individual
    - any special requirements for entering the laboratory

Adeno-associated Viruses (AAV)

Adeno-associated viruses are small, non-enveloped viruses with single-stranded linear DNA. They are members of the Parvoviridae family and there are 12 serotypes. Of the most commonly used viral vectors in research, AAV are some of the smallest (4.8 Kb) with small packaging capacities. To replicate, AAV require helper viruses (wild type adenovirus or herpesvirus). In the absence of these helper viruses, AAV can stably integrate into the host cell genome. AAV vectors are non-pathogenic and can infect dividing and non-dividing (quiescent) cells making them preferred viral vectors for many applications.

Potential Health Hazards

While there are no known diseases associated with any AAV human serotype, insertional mutagenesis is a theoretical possibility due to the ability of AAV to integrate into the host cell genome.

Lab Hazards

- Mucous membrane exposure, parenteral inoculation (e.g., needlesticks, animal bites), ingestion, inhalation of aerosols
- There has been at least 1 reported potential laboratory-acquired infection that involved recombinant AAV and wild-type adenovirus.

Containment

- For most uses- BSL-1/ABSL-1
- Exceptions:
    - Presence of helper virus (adenovirus or herpes virus)- BSL-2/ABSL-2
    - Packaging in human cell lines- BSL-2
    - Potentially hazardous transgenes (e.g., oncogenes, toxins)- BSL-2/ABSL-2
- The IBC may raise containment if deemed necessary.

Disinfection/Decontamination

AAV tends to be more resistant to some disinfectants due to being small, non-enveloped viruses. Isopropanol and hydrogen peroxide have been shown to be ineffective disinfectants for AAV and should not be used for spills or for routine decontamination. Effective disinfectants include 10% bleach (0.5% sodium hypochlorite), 70% ethanol, 2% glutaraldehyde, and 0.25% sodium dodecyl sulfate. AAV can be inactivated by autoclave (121°C for 1hr).

Adenoviruses

Adenoviruses are medium-sized, non-enveloped viruses with double-stranded linear DNA. They are members of the family Adenoviridae and there are close to 100 different serotypes with over 40 being human pathogens. Adenoviral vectors are non-integrating and are a popular choice in gene therapy research due to their high transduction efficiencies, ability to infect many cell types, and high level of transgene expression.

Potential Health Hazards

Exposure to adenovirus can cause a wide range of symptoms including bronchitis (coughing, shortness of breath), sore throat, fever, diarrhea, and pink eye. Infections can be more severe in very young and immunocompromised individuals. NOTE: Adenoviral vectors do not have to be replication competent to cause corneal and conjunctival damage.

Lab Hazards

- Mucous membrane contact, parenteral inoculation (e.g., needlesticks, animal bites), inhalation of aerosols, ingestion
- There have been at least 10 lab exposures with one resulting in a lab-acquired infection (wild type adenovirus). Transmission primarily occurs through inhalation of aerosolized droplets, ingestion, or mucus membrane contact.

Containment

- BSL-2/ABSL-2 for activities with materials and cultures known or reasonably expected to contain adenoviral vectors and for activities with experimentally infected animals.
- Adenovirus must be administered to animals under ABSL-2 conditions. Animals must be housed under ABSL-2 conditions for 72 hours after adenovirus administration, after which animals may be moved to ABSL-1 housing. The IBC may raise containment if deemed necessary.

Disinfection/Decontamination

Adenoviral vectors are relatively stable and resistant to dehydration because they are non-enveloped viruses. Isopropanol and hydrogen peroxide have been shown to be ineffective disinfectants for adenovirus and should not be used for spills or for routine decontamination. Effective disinfectants include 10-20% bleach (0.5-1% sodium hypochlorite), 70% ethanol, 2% glutaraldehyde, and 0.25% sodium dodecyl sulfate (SDS). Adenovirus can be inactivated by autoclave (121°C for 1hr).

Lentiviruses

Lentiviruses are enveloped retroviruses that are characterized by a long incubation period, immune evasion, and persistent infections in their natural hosts. They have single stranded and linear RNA that is reverse transcribed to produce DNA upon entry into the host cell. This DNA transcript then integrates into the host's genome. Lentiviruses have the ability to integrate into the genome of non-dividing cells, a feature that distinguishes lentiviruses from other retroviruses. There are 5 recognized serotypes with HIV-derived vectors being the most commonly used lentiviruses in biomedical research.

Potential Health Hazards

Infection with lentivirus (HIV) can cause initial symptoms that are flu-like. Symptoms can be more severe in very young and immunocompromised individuals. Infection is persistent and lifelong due to their ability to integrate into the host chromosome and the ability to evade host immunity.

Lab Hazards

- The main routes of transmission include parenteral inoculation, mucous membrane contact and ingestion. Aerosol transmission is unknown.
- The major risks to be considered for research with HIV-1 based lentivirus vectors are:
    - potential for generation of replication-competent lentivirus (RCL), and
    - potential for oncogenesis

  These risks can be mitigated by the nature of the vector system (and its safety features) or exacerbated by the nature of the transgene insert encoded by the vector.
- There have been at least 5 reported laboratory acquired infections with HIV (splashing of infected materials, inapparent skin exposure, puncture wounds) and at least 20 lentivirus occupational exposures reported to the NIH. HIV-1 infection of a laboratory worker with a replication-competent recombinant clone was reported in 2016.

Containment

- BSL-2/ABSL-2 is often appropriate in the laboratory setting for research involving the use of advanced lentivirus vector systems that have multiple safety features and that segregate vector and packaging functions onto four or more plasmids.
- Lentivirus must be administered to animals under ABSL-2 conditions. Animals must be housed under ABSL-2 conditions for 72 hours after lentivirus administration, after which animals may be moved to ABSL-1 housing. The IBC may raise containment if deemed necessary.

Disinfection/Decontamination

Lentiviruses are susceptible to many disinfectants including 10-20% bleach (0.5-1% sodium hypochlorite) and to a lesser extent ethanol. Lentivirus can be inactivated by UV light, pH higher or lower than the optimal level of 7.1, and autoclave (121°C for at least 30min).

Retrovirus / Moloney Murine Leukemia Viruses (MMLV)

Moloney murine leukemia virus (MMLV) is an enveloped single-stranded RNA gammaretrovirus that gets its name from its ability to cause cancer in mice. Like other retroviruses, MMLV randomly integrates into the host cell genome. The host range of recombinant MMLV depends on the specificity of the viral envelope. Ecotropic vectors only infect rodent cells whereas amphotropic vectors can potentially infect a wide range of cell types. Pseudotyping MMLV with the VSV-g envelope, for example, changes the specificity of binding and entry into cells allowing MMLV to infect both mammalian and non-mammalian cells. Additionally, MMLV can transduce hard to transfect dividing cells (cell division is required for infection) making it a popular gene delivery system for several applications.

Potential Health Hazards

Pseudotyped MMLV that infects human cells can result in insertional mutagenesis that can lead to the development of malignancies. In a human gene therapy trial using MMLV, 2 out of 10 patients developed leukemia as a result of integration in proximity to an oncogene.

Lab Hazards

The main routes of transmission include parenteral inoculation, mucous membrane exposure, contact with tissues and body fluids of infected animals.

Containment

- Ecotropic MMLV: BSL-1/ABSL-1
- Amphotropic or VSV-g pseudotyped vectors containing biological toxin or gene with oncogenic potential: BSL-2/ABSL-2

Disinfection/Decontamination

MMLV is susceptible to common lab disinfectants including 10-20% bleach (0.5-1% sodium hypochlorite), 70% ethanol, Cidex (2.4% glutaraldehyde), and quaternary ammonium disinfectants.

Other Viral Vectors

Baculovirus

Baculovirus is a lytic, enveloped DNA virus that infects insects. Baculovirus vectors are mainly used to produce high levels of recombinant proteins in insect cells as they have large cloning capacity and low cytotoxicity. Wild type virus is non-pathogenic to humans but recombinant virus using mammalian specific promoters allows for gene expression in mammalian cell lines. Most baculovirus vectors can be handled at BSL-1/ABSL-1. Baculovirus pseudotyped with VSV-g can transduce human cell lines and should be handled at BSL-2/ABSL-2. The transgene should be taken into consideration during the risk assessment process (e.g., oncogenes, mammalian-specific toxin). Baculovirus is susceptible to common disinfectants including 10% bleach and 70% ethanol and be inactivated by autoclaving (121°C, 30 min).

Herpes simplex virus (HSV)

Herpesviruses include infectious human viruses such as HSV-1 and HSV-2 that can infect cells lytically and some cells (e.g., neurons) latently. They are large, enveloped double stranded DNA viruses that remain episomal. Once infected with HSV-1 or HSV-2, the virus travels to the nervous system where it remains in a latent state. While infections are usually mild (e.g., cold sores), some cases can become more severe (e.g., meningoencephalitis). HSV-1 is the most common herpesvirus used as a viral vector system. The HSV-1 vector system has a large insert capacity and a broad host cell range and can efficiently transduce neurons. HSV is prone to recombination and there are concerns that vector infection could result in reactivation from latency since 50-90% of the population possess antibodies to HSV-1. HSV-1 vectors must be handled at BSL-2 and animals infected with HSV-1 must be handled and housed in ABSL-2. HSV-1 is highly susceptible to common disinfectants including 70% ethanol and 10% bleach and is inactivated by low pH and autoclaving (121°C, 30min).

Vesicular stomatitis virus (VSV)

Vesicular stomatitis viruses are enveloped, single-stranded, negative-sense RNA viruses. VSV is in the family *Rhabdoviridae*, genus *Vesiculovirus*. There are 8 main serotypes (Indiana, New Jersey, Cocal, Alagoas, Isfahan, Chandipura, Maraba, and Piry) and several laboratory-adapted strains. VSV is zoonotic and causes flu-like illness in infected humans. Applications for VSV vectors include vaccine vector development and oncolytic virotherapy. In these applications, VSV often remains replication competent. The advantages of VSV as a vector include high transgene expression, wide infection range, and a simple structure. VSV-Indiana 1 serotype strains (e.g., Glasgow, Mudd-Summers, Orsay, San Juan) and VSV-New Jersey serotype strains (e.g., Ogden, Hazelhurst) can be handled at BSL-2. Animals infected with VSV vectors must be housed in ABSL-2. VSV is susceptible to 10% bleach and is inactivated by autoclaving 121°C, 30min) and low pH.

Rabies Virus (RV)

Rabies virus is an enveloped, single-stranded, negative-sense RNA virus that is neurotropic and characterized by its wide host range among mammals. RV vectors are commonly employed in neuronal tracer and circuit studies. RV vectors are made replication-deficient by deleting the envelope B19-glycoprotein gene which renders the virus incapable of spreading trans-synaptically. RV cannot integrate in the genome and recombination risks are low. Vectors can be pseudotyped with an envelope protein that is not found in mammals. This prevents the virus from being able to infect mammalian cells except for those that have been genetically modified to express the envelope receptor. RV vectors must be handled at BSL-2. Animals infected with virus must be housed in ABSL-2. Rabies virus is susceptible to UV light, desiccation, and low or high pH. RV is inactivated by 70% isopropyl alcohol, 10% bleach, iodides, and autoclaving (30min at 121°C).

Emergency Procedures

Spills

All laboratories conducting recombinant or synthetic nucleic acid research, including the use of viral vectors, must have a plan for handling spills. Most spills in BL-1 and BL-2 labs can be handled by lab personnel. Procedures for handling biological spills can be found on the Biological Safety website. For questions regarding spills, contact the Biosafety Officer (803-777-1625).

The following items should be conveniently accessible in laboratories using viral vectors, and all lab personnel must know the location of these materials:

1. Gloves (latex or nitrile)
2. Lab coat or disposable gown
3. Safety glasses or goggles
4. Disinfectant solution
    a. A freshly prepared 10% bleach solution is effective for the decontamination of most biological spills.
5. Tongs, forceps, dustpan, broom
    a. A mechanical device (e.g., forceps, tongs) must be used to remove sharps without using gloved hands
6. Absorbent materials (e.g., paper towels)
7. Signage to post at lab entrance for controlling access ("Biohazard Spill – Do Not Enter")
8. Biohazard bags for collecting all contaminated disposable materials generated during the cleanup, and a puncture-resistant biohazard sharps container if spill involves contaminated sharps
9. A copy of all applicable biological spill procedures

NIH Guidelines Incident Reporting:

The NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines) states that "…any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" must be reported to NIH within 30 days. Certain types of accidents must be reported on a more expedited basis. Spills or accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to NIH.

Any spill or accident involving recombinant or synthetic nucleic acid molecule research of the nature described above or that otherwise leads to personal injury or illness or to a breach of containment must be reported to NIH Office of Science Policy (OSP). These kinds of events might include skin punctures with needles containing recombinant or synthetic nucleic acid molecules, the escape or improper disposition of a transgenic animal, or spills of high-risk recombinant or synthetic materials occurring outside of a biosafety cabinet. Failure to adhere to the containment and biosafety practices articulated in the *NIH Guidelines* must also be reported to NIH OSP.

Report any incident involving recombinant or synthetic nucleic acids, including viral vectors, to the Biosafety Office as soon as possible for further investigation. The Biosafety Office will coordinate the submission of all reports to the NIH.

Viral Vector Biosafety Summary Table

Viral Vector	Risk Group	BSL-	ABSL-	Decontamination	Additional Information
Adeno-associated viral vector (AAV)	RG1 or RG2 (helper virus, oncogene/toxin transgene)	1	1	10% bleach, 70% ethanol 2% glutaraldehyde, and 0.25% sodium dodecyl sulfate; inactivated by autoclave (121°C for 1hr).	BSL-1/ABSL-1 for most applications; BSL-2/ABSL-2 for presence of helper virus (adenovirus or herpes virus), packaging in human cell lines, potentially hazardous transgenes (e.g., oncogenes, toxins) Isopropanol should not be used as a disinfectant for AAV
Adenoviral vector	RG2	2	2	10% bleach (0.5% sodium hypochlorite), 70% ethanol, 2% glutaraldehyde, and 0.25% sodium dodecyl sulfate; inactivated by autoclave (121°C for 1hr).	Isopropanol should not be used as a disinfectant for Adenoviral vectors
Lentiviral vector (HIV)	RG2+ or RG3	2	2*	Susceptible to 10-20% bleach and to a lesser extent ethanol; inactivated by UV light and autoclave (121°C for at least 30min).	* Animals must be housed under ABSL-2 conditions for 72 hours after lentivirus administration, after which animals may be moved to ABSL-1 housing
Moloney murine leukemia viral vector (MMLV)	RG1 (ecotropic) RG2 (amphotropic)	1 or 2^	1 or 2**	10-20% bleach, 70% ethanol, Cidex (2.4% glutaraldehyde), and quaternary ammonium disinfectants	^Amphotropic or VSV-g pseudotyped vectors containing biological toxin or gene with oncogenic potential must be handled at BSL-2/ABSL-2 ** Animals must be housed under ABSL-2 conditions for 72 hours after MMLV administration, after which animals may be moved to ABSL-1 housing
Baculovirus vector	RG1^^	1	1	10% bleach and 70% ethanol; inactivated by autoclave (121°C, 30 min).	^^ Baculovirus pseudotyped with VSV-g should be handled at BSL-2/ABSL-2
Vesicular stomatitis viral vector (VSV)	RG2	2	2	Susceptible to 10% bleach; inactivated by autoclaving 121°C, 30min) and low pH	Alcohols are not effective disinfectants against VSV
Herpes simplex viral vector (HSV)	RG2	2	2	Highly susceptible to common disinfectants including 70% ethanol and 10% bleach; inactivated by low pH and autoclaving (121°C, 30min)	50-90% of the population possess antibodies to HSV-1 Animals infected with HSV-1 are to remain housed in ABSL-2 through duration of experiment
Rabies viral vector (RV)	RG2	2	2	Susceptible to common disinfectants including 70% isopropanol and 10% bleach; inactivated by low or high pH and autoclaving (121°C, 30min)	

Resources

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