An Administrative Viral Vector Policy For Animal Research

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Introduction

Every day viruses and viral vectors are used as common biotechnology tools by researchers coming from various backgrounds (engineering, chemistry, nanotechnology).

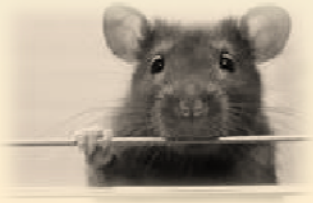
This presentation will address the safety considerations and recommendations involved with the use of viral vectors in animal models at a major California university

UC Berkeley's (UCB) Policy on the Use of Viral Vectors

- UC Berkeley must follow:
  - National Institutes of Health (NIH) Guidelines for the Use of Recombinant DNA Molecules because it receives NIH funding
  - the State of California **8 CCR §5199.1 -Aerosol Transmissible Diseases – Zoonotic Standard and 8 CCR §5193 – Bloodborne Pathogens** for work with viral vectors and animals

Pre-requisites

- Use of viral vectors and animals at UC Berkeley requires the review and approval of:
  - Animal Care and Use Committee (**ACUC)** and
  - Committee on Laboratory and Environmental Biosafety Committee (**CLEB**).
- Medical surveillance requirements vary based on the experiment protocol



Risk Assessment

Risk Assessment:

Safety Considerations

- **All** viral and viral vector usage must factor:
  - Intrinsic Pathogenicity of the Virus
  - Transgene Inserted
  - Tropism
  - Concentration/Volume of Culture
  - Helper Virus
  - Recombination

Risk Assessment:

Safety Considerations

- Evaluation if wild-type (replication competent) viral vectors is capable of causing disease in humans:
  - **Does the wild type virus potentially cause disease in humans or animals?**
  - **Does the nature of the inserted transgene amplify the risk?**
  - **Has a sequence been deleted that makes this recombinant virus safe to use? E.g. E1 region in adenoviral vector**

Risk Assessment:

Safety Considerations

- Nature of the inserted transgene:
  - ***is reviewed by CLEB***
  - ***may change the biosafety level e.g.***
    - hazardous to humans e.g. oncogene ↑
    - tracking marker e.g. GFP ↓

Risk Assessment:

Tropism

- Viral vectors usually have an affinity to infect a target cell.
- Questions asked to assert the risk of use:
  - ***What is the desired tropism (e.g. MMLV-murine cells)***
  - ***Does the replication-deficient, recombinant virus has potential to infect in-vivo others than the target cells ?***
  - ***Is this a gene therapy experiment where the tropism of the cells may be other than the target cells and consequently, may lead to serious adverse event in a human subject? (currently no gene therapy experiments are undergoing at UC Berkeley)***

Risk Assessment:

Recombination/Helper Virus

- Reconstitution of RCV (Replication Competent Virus) virus from replication deficient viral vectors is reviewed upon:
  - ***Titer of viral particles used***
  - ***Volume of culture***
  - ***Sequence of vector that was deleted for replication incompetency***
  - ***Type of culture: single batch versus continuous***

Risk Assessment:

Recombination/Helper Virus

- Reconstitution of RCV (Replication Competent Virus) virus from replication deficient viral vectors is reviewed upon:
  - ***recombination (e.g., at higher concentrations)?***
    - ***mutation or other untoward event (e.g., forming natural E-1 region in replication-deficient Adenovirus)?***
    - ***use of helper virus***
  - ***changes of the vector tropism (e.g. addition of vsv-g glycoprotein or pseudotyping of an ecotropic murine retrovirus, such as MMLV, allowing potential infection of other mammalian cells)***

Risk Assessment:

Recombination/Helper Virus

- Viral vectors may be affected by the presence of other viruses. To assert the risk of use ask if:
  - ***Other viruses are used simultaneously? (e.g., the use of replication deficient sindbis virus with other viruses to form a wild type alpha virus)***
  - ***The use of the vector may amplify the risks and subsequently lead to serious adverse event in a human subject gene therapy experiment (e.g., the use of lentivirus vector in an HIV patient)?***

Housing Consideration

Procedures and training

- Procedures and training must cover:
  - Biohazard signage
  - Cage labeling
  - Transport within and outside of vivarium
  - Personal Protective Equipment
  - Use of BSL-2 procedure room
  - Exiting the BSL-2 procedure room
  - Disposal of carcasses and cages

Where to do it?

- UC Berkeley challenges:
  - Shortage of space in ABSL2
  - Spaces in old buildings adopted to contain ABSL-1 vivariums
  - Vivaria in multiple locations on the Campus

Where to do it?

- UC Berkeley challenges:
  - Use of specialty equipment not easily transported/decontaminated in and out of the BSL2 (e.g. stereotaxic setups)
  - Limited possibilities to upgrade the existing ABSL-1 facilities to ABSL-2

Needed to do the right thing

- **Close collaboration with:**
  - Occupational Health Physician
  - Veterinarian
  - Scientific community
  - Animal handlers

Where to do it?

- **Use of:**
  - Adenoviruses
  - Herpes viruses
  - Retroviruses
  - Sindbis virus, Vaccinia virus
  - Murine Viruses: CMV, Herpes Virus, MMLV, MSCV
- **IN Designated ABSL-2 facility**

Where to do it?

- Procedures involving use of replication deficient viral vectors can be done with BSL-2 practices in designated areas of animal facilities with restricted access
  - PPE required
  - Special signage
  - Cage labeling
  - Short term housing possible

Housing Considerations

- Viral vector origin, replication deficiency, shedding of the viral particle, kind of host tissue where the virus will be injected all may be used to lower housing containment level
- Burden of proof is on the Investigator to provide valid scientific information concerning shedding of the metabolized viral particles

Housing Considerations

- Some Risk Group 2 recombinant viral vectors used with animals can be used with:
  - Biosafety Level 2 procedures for inoculations
  - Case by case for housing
    - ABSL2 for procedures/injections
    - ABSL1 for housing (inoculations where viruses cannot reproduce, e.g., lentivirus in ocular tissue)

Use of shared space

- Users of shared space that have both ABSL-2 and ABSL-1 agents must address:
  - Transportation
  - PPE
  - Door and cage signage
  - Disinfection
  - Room cleaning
- Example: Whole body imaging facilities used by many researchers

Summary

ABSL-2 containment for all procedures with viral vectors

- Location of procedures:
  - isolated ABSL-2 or
  - space designated as BSL-2 procedure room
- Housing:
  - ABSL-2 or
  - ABSL-1 based on the agent, protocol review and approval

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UC Berkeley Policy