

# Generation of Transgenic Rodents under the *NIH Guidelines*: A Proposed Exemption

Jane Flint, Ph.D.  
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# Agenda

- **Current *NIH Guidelines* requirements for the generation of transgenic rodents that may be contained at Biosafety Level (BL) 1**
- **Rationale for proposed exemption to the *NIH Guidelines* for generation of certain BL1 transgenic rodents through mating**
- **Presentation from the NIH Animal Research Advisory Subcommittee on Genetically Modified Animals**
- **Proposed exemption language**

# **Current *NIH Guidelines***

## **Section III-E**

- **Section III-E of the *NIH Guidelines* covers experiments that are of low biosafety risk, i.e. may be conducted at BL1 and may be initiated upon registration with the Institutional Biosafety Committee**
  - IBC review and approval is still required.

# Current *NIH Guidelines*

## Section III-E-3 Experiments Involving Transgenic Rodents

- Experiments that involve the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic rodents) and require BL 1 containment may be initiated upon registration with the IBC
- Under the *NIH Guidelines*, “generation” of a transgenic rodent includes mating between two different transgenic rodents or mating of a transgenic rodent and a non-transgenic rodent if the purpose is to create a new transgenic rodent
  - Breeding of two identical transgenic rodents to maintain a line is not subject to this section of the *NIH Guidelines*

# Impetus for Considering an Exemption for Mating of Certain Transgenic Rodents

- Transgenic rodents that may be contained under BL1 conditions do not pose an appreciable biosafety risk to humans
- The *NIH Guidelines* currently exempts the purchase or transfer of transgenic rodents that require BL1 containment (Appendix C-VI)

# **Impetus For Considering an Exemption for Mating of Certain Transgenic Rodents**

- **The overwhelming majority of matings of transgenic rodents that require BL1 containment will result in a rodent that can be housed at BL1 and would therefore not pose an appreciable risk to human health**
- **While each registration is not a significant burden, the total number of registrations required leads to an administrative burden on the IBC and researchers that does not appear to be commensurate with the biosafety risk**

# Experts Consulted

- **HUGHES**, Stephen H., Ph.D.  
Director, HIV Drug Resistance Program  
Chief, Retroviral Replication Laboratory; and Head, Vector Design and Replication Section  
National Cancer Institute-Frederick
- **OVITT**, Catherine, Ph.D.  
Assistant Professor of Biomedical Genetics  
University of Rochester Medical Center, School of Medicine and Dentistry
- **PARKER-THORNBURG**, Jan, Ph.D.  
Associate Professor, Biochemistry and Molecular Biology  
Manager, Genetically Engineered Mouse Facility  
M. D. Anderson Cancer Center
- **BENNINK**, Jack R., Ph.D.  
Deputy Chief, Laboratory of Viral Diseases, NIAID
- **CLARK**, Terri R., DVM  
Acting Director, Office of Animal Care & Use, Office of Intramural Research  
Office of the Director
- **CUSHMAN**, Samuel W., Ph.D.  
Chief, Experimental Diabetes, Metabolism & Nutrition Section, NIDDK
- **PICKEL**, James, Ph.D.  
Chief, Nat. Institute of Mental Health Transgenic Core, NIMH
- **TORREY**, Ted A., Ph.D.  
Senior Scientist  
Comparative Medicine Branch, NIAID
- **Members of NIH Animal Research Advisory Subcommittee on Genetically Modified Animals**

# **Presentation on Biosafety and Mating of BL1 Transgenic Rodents**

**NIH Animal Research Advisory  
Subcommittee on Genetically Modified  
Animals**

**James Pickel, Ph.D.  
Chief, Transgenic Core  
National Institute of Mental Health, NIH**

# **Presentation on Biosafety and Mating of BL1 Transgenic Rodents**

**Transgenic rodents that may be housed BL-1 conditions don not pose a appreciable health risk.**

**Transgenic rodents have been used for scientific research for three decades.**

**Early transgenes were endogenous genes, or exogenous reporters (galactosidase, luciferase, green fluorescent protein).**

**Component systems allow inducible gene expression or conditional gene modification. (tet-activation, CRE recombinase)**

**Systems that allow inducible ablation or activation of specific cell types.**

# **Presentation on Biosafety and Mating of BL1 Transgenic Rodents**

**Historically, no risk has been seen from the mating of transgenic rodents that could themselves be houses in BL-1 conditions.**

**The use of these research models has increased.**

**The use of research animals that do carry a risk to human health is already registered.**

**The proposed changes identify additional transgenic matings that should not be exempt from registration.**

**Guidelines are made more robust when experiments that do pose a risk are accurately identified.**

# Proposed Language

# Proposed Exemption: Mating of Transgenic Rodents

- The mating of two different transgenic rodents or the mating of a transgenic rodent with a non-transgenic rodent with the intent of creating another transgenic rodent that requires BL1 containment, will be exempt from the NIH Guidelines if:
  - Both parental rodents require BL1 containment,  
AND

# Proposed Exemption: Mating of Transgenic Rodents

–Each parental transgenic rodent does not contain any one of the following genetic modifications:

- a) A transgene that codes for amyloid or a prion; or
- b) More than 50% of the genome of an exogenous virus from a single family; or
- c) Expression of the transgene is under the control of a retroviral long terminal repeat;

**AND**

–It is anticipated that the transgenic rodent that results from this mating will not:

- a) Contain more than 50% of an exogenous viral genome from a single family; or
- b) Contain a transgene that codes for amyloid or a prion.