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Standard Operating Procedure (SOP) for safely operating and conducting husbandry of mice exposed to human origin substances while generating patient-derived xenografts.

DEFINITIONS

PCRA – The Pre - Clinical Research Authority includes all animal facilities of the Technion

PDX – Patient-Derived Xenografts in mice

ABSL1 – Animal Biosafety Level, suitable for work with laboratory animals involving well characterized agents that are not known to cause disease in immunocompetent adult humans, and present minimal potential hazard to personnel and the environment

ABSL2 – Animal Biosafety Level, suitable for work with laboratory animals infected with agents associated with human disease and pose moderate hazards to personnel and the environment. It also addresses hazards from ingestion as well as from percutaneous and mucous membrane exposure.

PPE – Personal Protective Equipment

PURPOSE

1. To outline the proper procedures for safely operating and conducting husbandry of rodents exposed to (hazardous) human tissues, grafts, cells and substances.
2. To reduce the risk of primary or secondary exposure of researchers and animal care staff to hazardous agents/substances metabolized or excreted from PDX animals within the animal facility.

RESPONSIBILITY

1. The Pre - Clinical Research Authority (PCRA) Manager ensures that:
 - 1.1 All technical and animal care staff is adequately trained to perform the husbandry practices described.
 - 1.2 Implementation of the procedures described

- 1.3 Animal housing rooms dedicated for PDX mice are clearly labeled with the hazardous agent present and specific safety practices implemented.
- 1.4 Appropriate personal protective equipment (PPE) is available.
- 1.5 Safety practices have been communicated to the relevant personnel.
2. It is the responsibility of the animal care staff to:
 - 2.1 Read, understand, and follow the procedures described.
 - 2.2 Review study protocol, room signage, and relevant SDSs prior to implementing the procedures described.

Safety Procedures:

1. All patient tissues and mice carrying patient tumors pose a possible health threat as the human tissue could still retain human pathogenic agents.
2. All researchers and animal care staff in PDX rooms have to be immunized against hepatitis B.
3. Animals administered uncharacterized primary human tumor resections, tissue explants, blood, or other primary human or patient-derived xenografts (PDX) has to be housed in **ABSL- 2 containment (for details please refer to sections 10)**
4. Proper Identification cards and signs should be posted on the cages.
5. Xenografts that were primary human-derived will be characterized by polymerase chain reaction (PCR), enzyme linked immunosorbent assay (ELISA), or other appropriate methodology, by a certified laboratory (e.g. IDEXX Bioresearch, RAMBAM hospital diagnostic laboratories, Blood bank etc.), prior to implantation or during passage of xenografts from F1 to F2 recipient mice.
6. The PCRA manager will authorize one of the PCRA veterinarian to handle the samples namely, packing, shipping, record kipping and follow up.
7. If such grafts are shown to be free of human agents of concern, the characterized recipient mice are eligible for housing at ABSL-1 (at the determination of the veterinarian)
8. Human agents of concern that primary human-derived specimens must be tested for and found to be absent of in order to eligibilize recipient mice for housing at **ABSL-1** include (at least):
 - 8.1 Mycoplasma spp.

- 8.2 Human immunodeficiency virus 1 (HIV1), and 2 (HIV2),
- 8.3 Hepatitis virus B
- 8.4 Hepatitis virus C
- 8.5 Hepatitis virus A
- 8.6 Human T-lymphotropic virus 1 (HTLV1) and 2 (HTLV2).
- 8.7 In some circumstances additional agents will be tested as specified by the Biosafety officer for example, Herpes simplex 1, Herpes simplex 2, Human cytomegalovirus, Human herpes virus 6, Human herpes virus 8, Human adenovirus, Human papillomavirus 16 & 18 (HPV), Lymphocytic choriomeningitis virus, Varicella virus, Epstein-Barr virus, Treponema pallidum and Hantaviruses (Hantaan, Seoul, Sin Nombre viruses).
9. Test results or written assurances provided by other diagnostic laboratories or sources of primary human specimens (e.g., blood bank) may be considered by PCRA veterinarians in conjunction with the biosafety officer to determine whether an acceptable assurance of the absence of hazard is provided to make recipient animals of the specimen eligible for housing at **ABSL-1**.
10. Here are some outlines (some highlights relating to the subject) for **ABSL-2 procedures**
 - 10.1 PPE minimum requirements include
 - 10.1.1 Eye protection
 - 10.1.2 Respirators
 - 10.1.3 Disposable gown
 - 10.1.4 Gloves,
 - 10.1.5 Shoe covers.
 - 10.1.6 Additional PPE if required by signage must also be donned
 - 10.2 As some procedures (surgeries, tissue derivations, cage and bedding changing) have the potential to produce hazardous fumes, dust, or aerosols, these must be performed in either a HEPA-filtered ventilated cage changing station, or a **Class II Type A2 Biosafety Cabinet** or chemical fume hood, as appropriate for the procedure, while wearing PPE listed above or required by the protocol.
 - 10.3 All procedures are carefully performed to minimize the creation of aerosols
 - 10.4 Work surfaces are cleaned and decontaminated before and after use.

- 10.5 All wastes from the animal room will be disposed of as hazardous waste namely autoclaved or incinerated.
- 10.6 Soiled microisolator caging is autoclaved.
- 10.7 When working in cage wash with cages that housed those animals a 3M8835 respirator is recommended.

EMERGENCY RESPONSE

In case of personal contamination when human derived materials (blood or other potentially infectious materials) are involved please act as follows:

1. If contact with potentially infectious material (e.g. human blood, tissues or other) occurs **on skin** or if there is a **cut or puncture** with a contaminated object (broken glass, needle, etc.)
 - **WASH / FLUSH AREA FOR 15 MINUTES** with soap and water
2. If contact with potentially infectious material (e.g. human blood, tissues or other) occurs **in the eyes or on mucous membrane**
 - **WASH / FLUSH AREA FOR 15 MINUTES** with water or normal saline.
3. **REPORT to YOUR SUPERVISOR (IF AVAILABLE)**
4. **Seek IMMEDIATE Medical** advice and Follow-up - please go to the near emergency room and notify the doctors that you have been exposed to human origin substance, which may be infected with blood born pathogen
5. **Complete the Incident Report Form** which is to be remitted to the Health and Safety Unit Office.

For additional information, https://docs.google.com/forms/d/e/1FAIpQLSe-3Qpnl7x9rPkuo0IsgV3G0yOMXbVXY_YZWD9TGdPBOfl-w/viewform