Unleashing the Healing Power of Hope

Animal Models in Cancer Research.

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Outline

- What is an animal model?
- Principles of model selection
- The process of using animals for research, testing or teaching at Roswell Park

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What is an Animal Model?

- Introduction- Types of models
  - *in vitro* assays
  - Computer simulations
  - Mathematical models
  - Animal models

Animals may model **analogous** processes (relating one structure or process to another) or **homologous** processes (comparative modeling).

Genetically Engineered Mice

- The primary driver of homologous modeling is the Genetically Engineered or Manipulated mouse.
- The rapid advancement of genomic sequencing and genomic manipulation improved the animal model selection based on phenotypic analogs of human processes.

Modeling Concepts

- One-to-one modeling vs many-to-many modeling.
  - **One-to-one** – A model tailored to demonstrate a similar phenotype to that which is being modeled.
    - Infectious disease
    - Spontaneous or induced monogenetic disease
  - **Many-to-many**- Results from analysis of a process in an organism in which each component of that process is evaluated at several levels.
    - System
    - Organ
    - Tissue
    - Cell

Many-to-many-modeling is more common

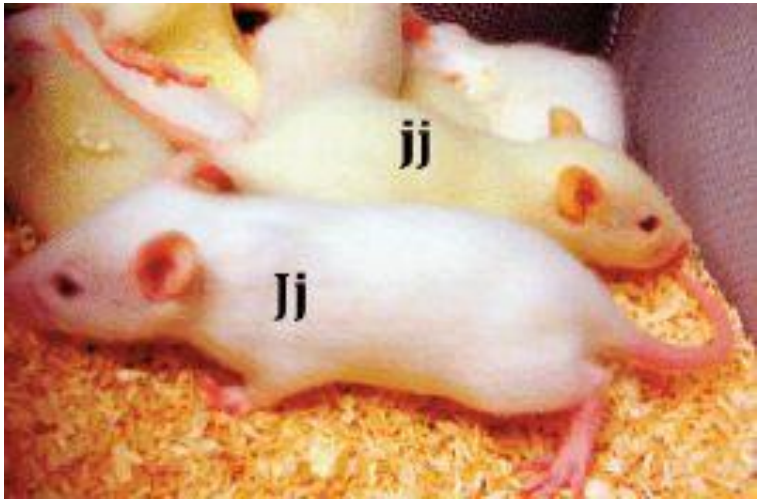
- Many of the most common diseases such as cancer are complex, often polygenic, with multiple interactive environmental influences.
- The advent of high-throughput techniques such as sequencing, proteomics and transcriptomics has facilitated the modeling process.
- Comparative genomics demonstrates the impressive degree of genetic conservation between common research species and humans.
- Although there are differences between mice and humans, new models are able to more accurately model human cancers by specifically controlling timing and location of mutations, even within single cells.

Animal Model Classification Spontaneous or Induced

- Spontaneous models – normal animals with phenotypic similarity to those of humans or by abnormal members of a species that arise through spontaneous mutations(s).
- Induced models- Animals handled by surgical, genetic, chemical or other manipulation resulting in an alteration to their normal physiologic state.

Examples of Spontaneous Mutations

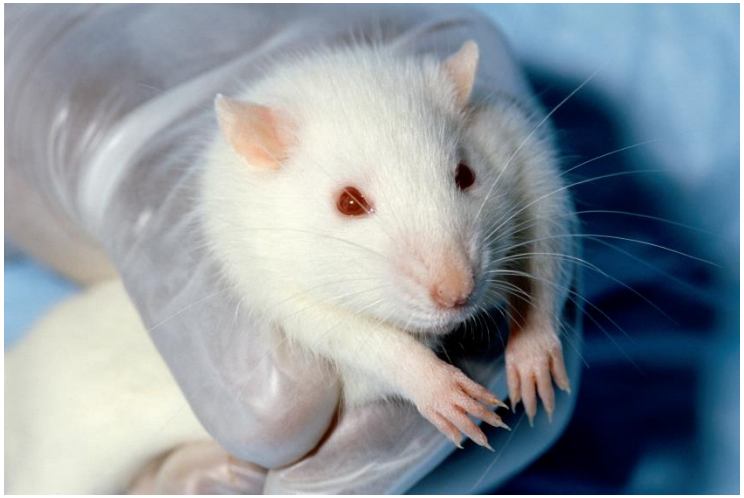
- Gunn rat- (Hereditary Hyperbilirubinemia) These rats are jaundiced due to a defect (lack of the enzyme uridine diphosphate glucuronyltransferase) which is transmitted as an autosomal recessive characteristic.



Spontaneous models
Type 1 Diabetes mellitus

- Non obese diabetic mouse

- BB Wistar rats



Spontaneous models

- SCID (Severe combined Immune deficient mouse)

- Nude mouse – Disruption of the FOX N1 gene

Other Spontaneous models

- Watanabe rabbit- hypercholesterolemia
- Brattleboro rats – Diabetes insipidus
- Obese chickens- Autoimmune thyroiditis
- Spontaneous Hypertensive Rats
- Dogs and mice with Duchenne X-linked Muscular dystrophy
- Dogs with hemophilia A and B

Induced models

- Helped unravel important concepts in physiology and medicine
  - Surgical models evolved in ability to perform-
    - Organ transplantation
    - Coronary bypass
    - Balloon angioplasty
    - Replacement of heart valves
    - Development of cardiac pacemakers
    - Discovery of insulin

Induced models continued…..

- Models induced by diet or administration of drugs and chemicals.
  - Alloxan and Streptozotocin- To induce diabetes as these drugs destroy the Beta cells of the islets of Langerhans.
  - Chemical mutagenesis approaches in mice and zebrafish.
  - Diet induced models – discovery of vitamins, trace minerals needs and pathogenesis of many diseases.

Most Commonly Used Animal Model

- The mouse

Mouse models

- The laboratory mouse is a powerful tool that scientists use to model human diseases and conditions in the search for better treatments and cures for humankind's most devastating diseases.
- Genetically and genomically, the human and the mouse are very similar, with many of the disease-related genes nearly identical.

Mouse models

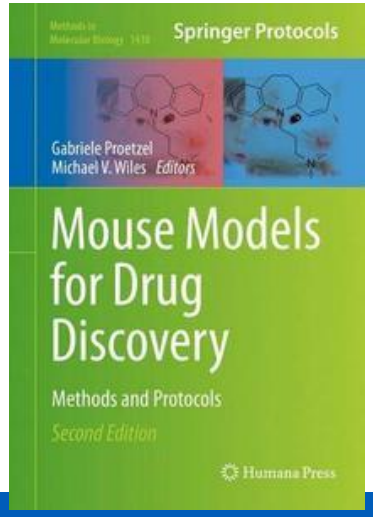
- The mouse is among the first mammalian species to have its genes modified with molecular tools.
- The ability to manipulate the mouse genome is what makes the mouse so relevant today.
- While we cannot change our own genomes, we can change those of mice, making small tweaks to individual mouse genes or even sequences within a specific gene allows scientists see what happens as a result.

Advantages associated with using the mouse are:

- Ability to genetically engineer new strains, including mice that can host patient tumors or specific gene mutations or a human immune system
- Availability of pure, inbred lines
- Opportunity to identify disease-causing gene mutations
- Platform for identifying modifying genes and background effects.

Drug Discovery

- Mouse models play an essential role in the drug discovery process.
- In preclinical trials, mouse models are key to demonstrating the metabolism and absorption, general safety and even efficacy of new medicines.



The most important advantage to using the mouse for biomedical research

- Ability to experimentally manipulate the mouse genome.
- Genes can be injected directly into the fertilized egg of a mouse, creating transgenic animals.
- Scientists developed techniques that allowed them to specifically target genes within the mouse genome – so-called “knockouts” –
- Thousands of mouse genes have been targeted in this fashion creating the Knockout Mouse Project (KOMP), and the International Knockout Mouse Consortium (IKMC)

Adding to the "Toolkit" Humanized Mouse models

- Mouse genes can be replaced with human genes to study gene function or to produce more human-like model systems in the mouse.
- The "NOD scid gamma" mouse lacks mature T or B cells and functional NK cells, is deficient in cytokine signaling, and can accept transplantation of virtually any human tissue.

Other Animal models for Cancer Research

- The woodchuck (Marmota monax)
- Viral hepatitis: evaluation of anti-viral compounds
- Hepatocellular carcinoma: evaluation of anti-neoplastic compounds
- Colony bred in captivity

Brought to Roswell Park

From Cornell University

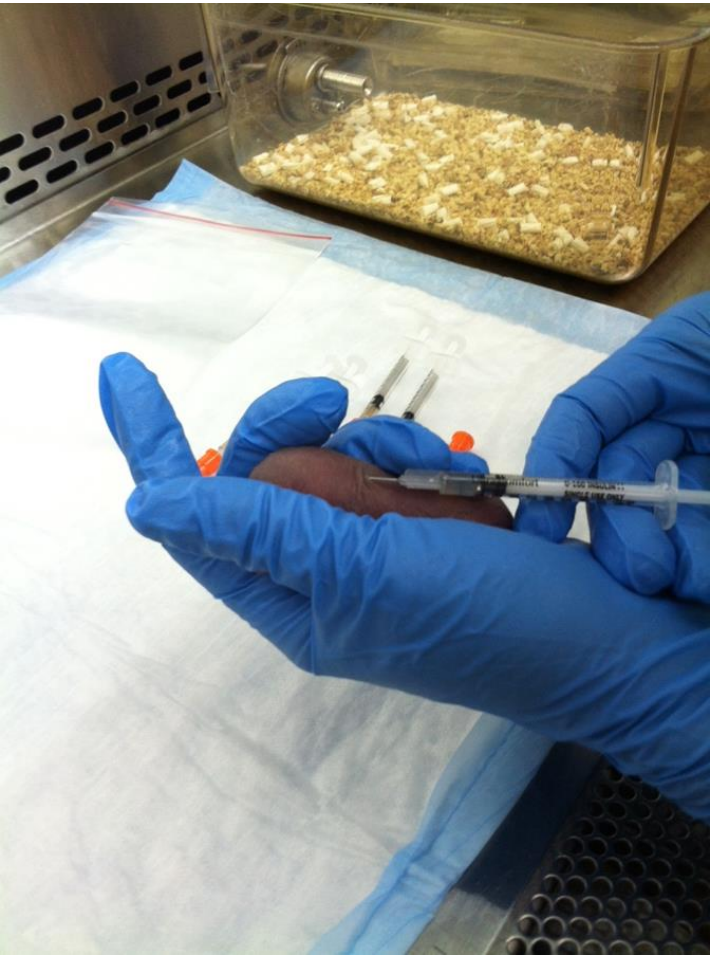
WHV + HCC Model

- Advantages:
  - Large animal model
  - Spontaneous HCC model in WHV (+)
  - Closely models development HCC in HBV+ individuals.

Model Creation

- A WHV(-) colony is maintained in our facility.
- Breeding occurs once a year

Creating the model



- To create the model, pups receive a subcutaneous injection of pooled WHV serum at 2-3 days of age

Viral Titers

- Viral titers are checked at 3,6 and 9 months of age to determine if the pups are carriers of the WHV.
- If positive they become very valuable research models for both anti viral studies and then for HCC research studies

Handling of the Woodchucks

Enrichment and Training to receive Liquid Diet

Repeated Dynamic Contrast Enhanced MRI Using a Vascular Access Port in Woodchucks *(Marmota monax)*

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Introduction:

The hepatitis-infected Eastern Woodchuck *(Marmota monax)* is the only large animal model of spontaneous Hepatocellular carcinoma (HCC) in the context of chronic hepatitis infection, making it ideally suited for translational studies of novel anti-neoplastic therapies (1, 3, 5, 6).

Magnetic Resonance Imaging (MRI) is a useful modality for non-invasive, long-term, longitudinal monitoring of tumor size and antineoplastic treatments in HCC (+) woodchucks and has been described previously (2).

Dynamic contrast enhanced-MRI (DCE-MRI) uses faster imaging and rapid injection of IV contrast material, allowing for more functional assessment of targeted drug effects such as tumor blood flow, in addition to monitoring tumor size, as most newer anti-neoplastic drugs target molecular pathways and do not produce the traditional tumor "shrinkage" seen with chemotherapy.

The aims of this study were to optimize methods for continuous IV access administration of the contrast agent Omniscan® during DCE-MRI by:

- Surgically implanting a vascular access port (VAP) in the medial Saphenous vein of HCC(+) woodchucks and
- Selecting the MRI compatible isoflurane machine as the method of choice to deliver safe and reliable anesthesia in metabolically compromised woodchucks.

Materials and Methods

1. **Animals.** 24-36 month old, male and female, WHV positive, HCC positive woodchucks.
   a. Woodchucks were infected at birth with dilute serum from standard infections pools derived from WHV+ carriers.
   b. Woodchucks were verified as HCC positive via abdominal ultrasound.
2. **Vascular access port (VAP) implantation.** VAPs were surgically implanted in the medial saphenous vein for administration of contrast agent during DCE-MRI.
   a. **VAP.** A 3-French x 6 inch/15 cM Hydromer coated polyurethane catheter (Model ROP VAP, Access Technologies, Skokie, IL) was used.
   b. **Anesthesia.** Two anesthetic protocols were used:
      i. **Inhalation anesthesia:** woodchucks were induced with 5% isoflurane in an induction box, and then maintained on 3-5% isoflurane administered via a facemask.
      ii. **Injectable anesthesia:** ketamine (50 mg/kg) and xylazine (5 mg/kg) were administer via IM injection.
   c. **Analgesia.**
      i. **Buprenorphine** was administered pre-emptively at a dose of 0.05 mg/kg SC. Woodchucks were re-assessed the following day, and additional buprenorphine was administered as needed.
      ii. **Marcaine** was dripped into the incision prior to closure.
   d. **Surgery.** Placement of VAPs in large animals has been previously described (4). A 1-inch incision was made on the medial surface of the rear limb near the stifle. The medial saphenous vein was isolated and ligated with 4-0 ethilon distally. A second, loose ligature was placed around the vein proximally. The vein was nicked between the 2 ligatures using microdissection scissors and the catheter tip of the port was advanced into the vein. The loose, proximal ligature was then tied. A subcutaneous pocket was made medial to the skin incision and the port of the catheter was inserted into it. The incision and subcutaneous tissue were closed routinely using 4-0 ethilon.
   e. **Port maintenance.** Ports were flushed twice weekly. The skin overlying the port was prepped aseptically with alcohol and betadine and then the port was flushed and locked with 5-10 cc of heparinized saline using a Huber needle (22 gauge x 1 inch, straight Huber point, All-Med Inc., Keene, NH).

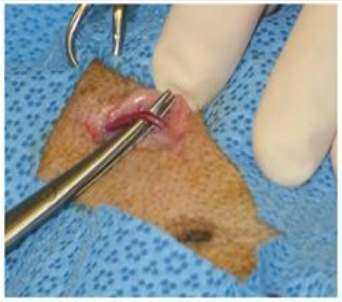

Fig 1: Surgical procedure to access medial Saphenous vein

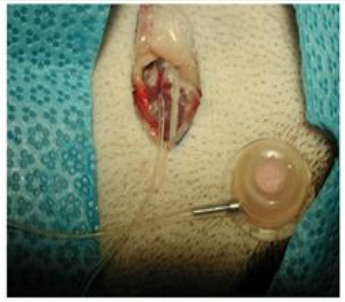

Fig 2: Surgical placement of a 3-French x 6 inch/15 cM VAP.

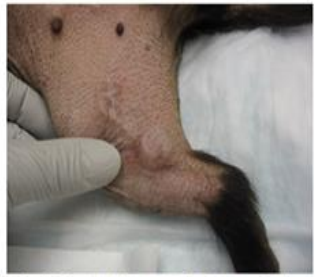

Fig. 3: : VAP implanted in the medial Saphenous vein of the rear limb.

Fig 4: Positioning of the woodchuck inside the head coil in the MRI. The power injector (arrow) is connected to the VAP.

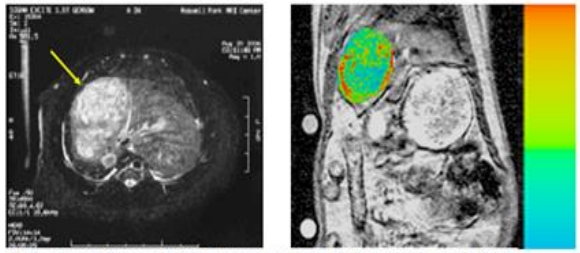

Fig 5: (A) Axial MRI image of a HCC (arrow) in a woodchuck. (B) Saggital MRI image of a HCC in a woodchuck with Ktrans overlay.

Materials and Methods, cont.

3. **Dynamic contrast enhanced-MRI:** DCE-MRI imaging was performed pre-treatment (baseline) on days 0 and 7, and post-treatment on days 7 and 28.
   a. **Anesthesia:**
      i. **Injectable anesthesia** was used initially, ketamine (50 mg/kg) and xylazine (5 mg/kg) via IM injection ± IV pentobarbital (2-6 mg/kg), but abandoned due to inconsistent anesthetic plane and side effects (poor anesthetic recovery, seizures, and cardiac arrest)
      ii. **Inhalant anesthesia:** a MRI-compatible isoflurane anesthesia machine was used. Woodchucks were induced with 5% isoflurane in an induction box, and then maintained on 3-5% isoflurane administered via a facemask.
   b. **VAP:** The skin overlying the port was prepped aseptically with alcohol and betadine, and the port was flushed with 5 cc of heparinized saline using a Huber needle. The Huber needle was connected to the power injector for administration of the contrast agent.
   c. **DCE-MRI:** Images were acquired in a 1.5 T clinical magnet using a Quad human head coil. Woodchucks were positioned inside the head coil in dorsal recumbency for imaging.
   d. **Contrast agent:** Gadolinium gadopectate (Omniscan, GE Healthcare Inc., Princeton NJ) was administered at minute 22 of the MRI through the VAP at a rate of 3 cc/second using a Spectris Solaris MRI contrast power injection system.
   e. **Image analysis:** Tumor size, Ktrans, AUC90, and percent necrotic tumor were calculated using published methods by Virtualscopics Inc.

Results:

VAPs were successfully placed in 18 woodchucks. There was localized reaction surrounding the VAPs in 3 animals, necessitating removal of the port. New VAPs were then successfully placed in the contralateral limb and maintained.

The implanted VAPs were maintained long-term in 17 out of 18 woodchucks. One woodchuck developed a complete catheter occlusion that was determined at necropsy to be due to a mechanical kink.

Nine woodchucks received isoflurane anesthesia for the DCE-MRI procedure, were successfully imaged, and recovered uneventfully from the procedure.

These techniques provide a practical approach to planning future studies of targeted anti-neoplastic therapies with translational potential in this unique animal model.

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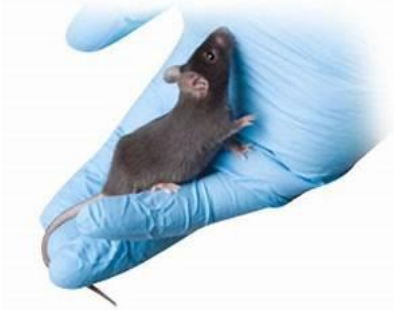
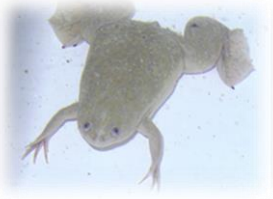
Research at Roswell Park

Planning Experiments using Animals?

Institute Animal Care and Use Committee (IACUC) Approval

- Whether you are performing research or testing on animals, or using animals for teaching, you must receive IACUC approval before any use of animals begins.


Getting Started

- Explaining Why the Use of Animals in Research is Important
- Some items on an animal protocol form such as
  - "How will the proposed use of animals improve the health of people or animals?"
  - "What is the experimental design of the animal studies planned?"

In general, there must be a compelling potential for benefit to human or animal health to warrant the use of animals

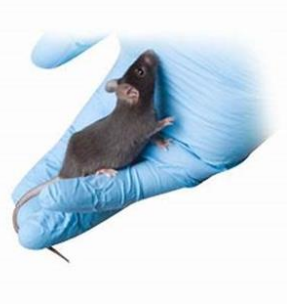
- Points to consider:
- If you are studying a human or animal disease or health concern.
- Because one of the IACUC members is a non-scientist try to use language that a high school student would understand.
- Make sure you explain medical terms, and define abbreviations the first time they are used.

Experimental Design

"What is the experimental design of the animal studies planned?"

- Keep in mind that the IACUC needs to understand the **proposed use of animals**.
- For more complex experiments it is very helpful to provide a flow chart to make the experimental design clear.
- The description of the animal procedures should stand by itself. Once again, define all abbreviations the first time they are used to facilitate comprehension.
- Try not to use technical language that only specialists in your field would understand.

Justifying the Species



- The presence of previous work in the biomedical literature that validates the use of a particular species in an animal model of a human disease.

- The existence of a large body of previous laboratory data that would have to be repeated if another species was used instead.

- Characteristics of the species that render it uniquely suited to the proposed research.
- Size, availability and cost.
- Availability of reagents or research tools unique to that species.
- **Cost savings alone is not an adequate justification for using a particular species! The justification should be based on sound scientific reasoning.**

Justifying the Number of Animals Requested

Some important points:

- A statistical analysis should be used to justify animal numbers. The goal is not to minimize the number of animals used but to determine the right number of animals for obtaining valid results.
- It is acceptable to ask for animals that will be used to perfect surgical or other techniques prior to initiating planned experiments.
- Studies on cadavers from other approved protocols in advance of any procedure on a live animal are strongly encouraged. By doing this, techniques can be perfected as much as possible before any live animals are used.
- It is also acceptable to ask for animals that will be used in pilot experiments in addition to animals requested for more robust experiments.

Description of the Animal Procedures

- Your descriptions must include:
- Nonsurgical methods, such as injections, administrations, sample collections, and food or water restriction. Routes and volumes of injections, etc., should be included.

- Surgical methods, to include aseptic technique, the surgical approach, suturing, perioperative care and monitoring, and postoperative analgesia.

- Anesthesia; requirement for and duration of pre-anesthetic fasting, drug agents used, routes of administration, duration of anesthesia, methods of anesthetic monitoring, and care during anesthetic recovery.

Testing

- Which of the following is helpful to the IACUC when reviewing an animal protocol?
  1. Frequent use of abbreviations and jargon to make responses shorter
  2. The use of highly technical language that proves complete scientific familiarity with the subject matter
  3. A description of proposed procedures on the animal protocol form that require the reviewer to refer back to other documents
  4. The use of a flowchart to illustrate complex experimental designs

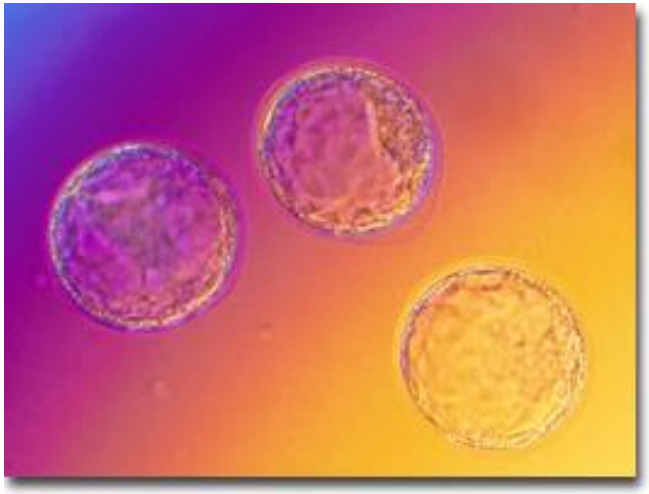
1. The use of a flowchart to illustrate complex experimental designs

Alternatives

- They described three important concepts now known widely as the "**three R's**":
- The purpose of these concepts is to minimize animal use and pain or distress while still achieving the critical scientific objectives that lead to advances in health and medicine.

The first "R" is replacement

- Replacement is simply replacing the use of animals with non-animal techniques.
- - Computer models.
- - Cell culture or tissue culture systems.
- - In vitro assays.



Practical examples of “Replacement" include:

- Use of cell culture techniques to replace animals as incubators for cell lines
- Use of immunologic bench assays to replace bioassays involving animals
- Use of computer software to model the pharmacokinetics of drugs in place of animal studies.

The second "R" is reduction

Reduction is simply reducing the number of animals used.

- Using appropriate group sizes to obtain statistically significant data.
- Performing multiple experiments simultaneously so that the same control group can be used for all the experiments.
- Sharing tissues with other investigators so that additional animals are not needed.
- Designing experiments so that animals serve as their own controls, when scientifically appropriate.
- Using newer instrumentation that improves precision and reduces the number of animals needed per data point.

The last "R" is refinement

- Refinement refers to changing experiments or procedures to reduce pain or distress in those animals that must be used.
- Examples of refinements include:
- - New anesthetics that allow rapid induction and reduced recovery times.
- - New analgesics that provide more extended pain relief postoperatively with less frequent administration.
- - New bleeding and injection techniques that cause less tissue damage or distress.
- - Improved surgical techniques that minimize trauma and the length of anesthesia.
- Check with the literature and your veterinarian to see if better techniques have evolved that reduce pain or distress on the animals.

Consider Alternatives

- The **Animal Welfare Regulations** require the IACUC to do two things regarding alternatives:
- Ensure that the principal investigator has considered alternatives if painful or distressing procedures are proposed.
- Evaluate a written narrative provided by the principal investigator that describes which source or sources were used to determine that alternatives were not available.

Organizations

There are a number of organizations that have active research programs into alternatives to animal use.

- They include the Johns Hopkins Center for Alternatives to Animal Testing (CAAT)
- Institute for In Vitro Sciences.

Avoiding Unnecessary Duplication

- You will be asked to document that your proposed work is not unnecessarily duplicative.
- Acceptance of new ideas in science is often dependent upon the ability of other scientists to duplicate published reports. The IACUC can allow duplication of previous work if convinced that it is important scientifically to do so.

USDA Pain/Distress Categories

- Even if you use non-USDA covered species (such as mice or rats) you will be required to place your animals into pain/distress categories.

- A simple yet useful definition of a painful or distressful procedure on an animal is this:

"A procedure that would cause pain or distress in a human."

Endpoint Criteria

- The **criteria used for intervention** in research studies to prevent unnecessary pain and distress are called "endpoint criteria" because they describe when it is time to:
- Euthanize an animal to prevent suffering.
- Discontinue a painful procedure.
- Remove an animal from a study.

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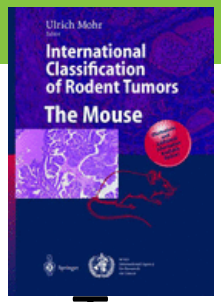
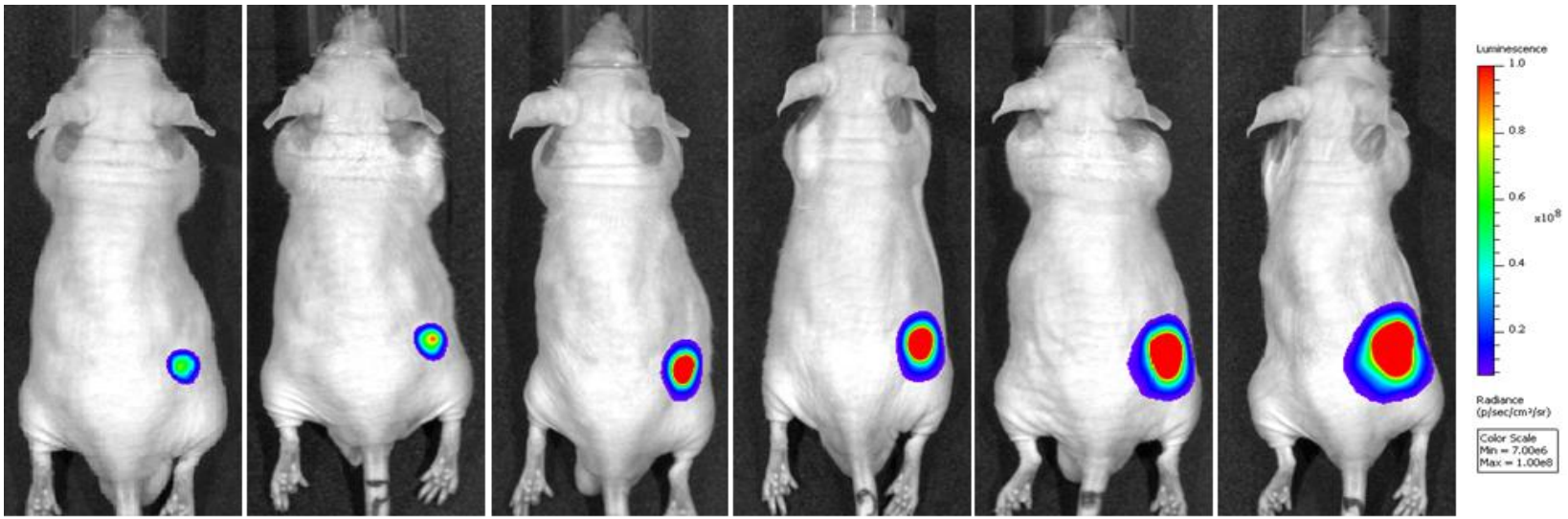
Common Examples of Endpoint Criteria

- Limit on weight loss as a percentage of body weight
- Sudden pain or distress that cannot be controlled with analgesics, sedatives or tranquilizers.
- Severe medical conditions that cannot be controlled with appropriate therapy (e.g. severe systemic infections, kidney or liver failure, heart disease).



At RPCI

- Tumor size as an endpoint often include maximum tumor volumes or tumor weight as a percentage of body weight, skin ulceration over the tumor, interference with normal gait or movement, and interference with normal feeding and drinking behaviors.

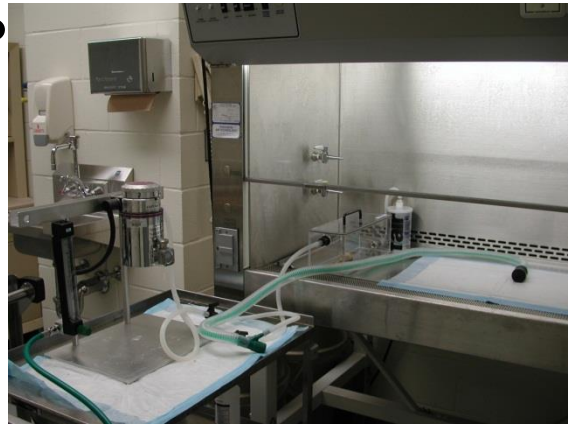


Surgery

- Surgery will be addressed in detail in your animal use protocol.
  - Sterile or aseptic technique
  - **General anesthesia**- a state of unconsciousness characterized by a complete lack of pain and sensory perception.
  - **Regional (or local) anesthesia** refers to preventing pain and sensory perception in one small part or a region of the body

Location

- The rooms that can be used for surgery vary depending on:
  1. The species
  2. Whether a surgery is major or minor
  3. Whether the surgery is survival or non-survival



Anesthesia and Analgesia

- Pre-anesthesia: A pre-anesthetic regimen may incorporate agents that will provide analgesia during the postoperative period. This is known as preemptive analgesia, since it provides analgesia before a painful stimulus (i.e. the initial incision) is applied.
- Anesthesia: The anesthetic regimen should provide a duration of anesthesia that matches the duration of the surgical procedure.

Postoperative Analgesia

- Plan which postoperative analgesics will be used at the time when the anesthetic regimen is established. The agent, dose, route, frequency, and duration of treatment should be discussed with and approved by a veterinarian.
- The Animal Welfare Regulations and PHS Policy stress the importance of using postoperative analgesics.

Postoperative Care for Survival Surgeries

- The animal should be monitored to make sure it is recovering properly
- **Documentation:**
  - For animals larger than rodents, individual health care records are usually maintained, with records of daily observations and treatments during the postoperative care period.
  - For smaller animals the use of a surgical cage card is required.

Personnel Training and Experience

- State your experience and training in performing the proposed procedures.
- Although academic degrees are useful indicators of educational experience, they are not often useful by themselves in evaluating an individual's experience in animal research.

Using Hazardous and Toxic Agents in Animals

- If your animal work requires the use of hazardous or toxic agents, there are many important considerations.
- **Infectious diseases**
- **Toxic chemicals** - including carcinogens, mutagens, biological toxins, and organic chemicals
- **Radioactive substances**
- **Recombinant DNA**

Housing Social Animals

- **Social animals** should be housed in pairs or groups whenever possible unless scientific, health, or behavioral considerations prevent it.
- Some justifications for single housing include:
- **Behavioral problems.** For instance, adult male C57BL/6 and BALB/c mice will fight if not raised together from birth.
- **Health problems.**
- **Scientific reasons.** If single housing must be used to achieve scientific objectives, then the IACUC may approve single housing.

Euthanasia

- Euthanasia literally means a "good death". A more appropriate simple definition is a "gentle death".

- Euthanasia techniques should result in a rapid loss of consciousness followed by cardiac or respiratory arrest and finally, the loss of brain function.

- Because it is necessary to euthanize most animals as part of experimental protocols, it is very important to use appropriate euthanasia techniques.

Euthanasia Training

- Personnel must be trained to properly and humanely perform euthanasia.

- Proper training for euthanasia is an area of emphasis because of the increased potential for harm to animals.

Methods of Euthanasia

- Euthanasia methods can be broadly separated into physical and nonphysical methods.
- **Physical methods** include cervical dislocation, decapitation, and exsanguinations. Usually under deep anesthesia.
- **Non-physical or pharmacologic methods** rely on drugs to cause loss of consciousness and death.

CO_2 Euthanasia Advantages

- CO_2 provides a rapid depression and anesthesia (narcosis).
- CO_2 is non-flammable and non-explosive.
- CO_2 does not introduce chemical residues into tissues.
- CO_2 does not result in distortion of cellular architecture.

Making Changes after You Receive Approval

- Some changes often considered significant are:

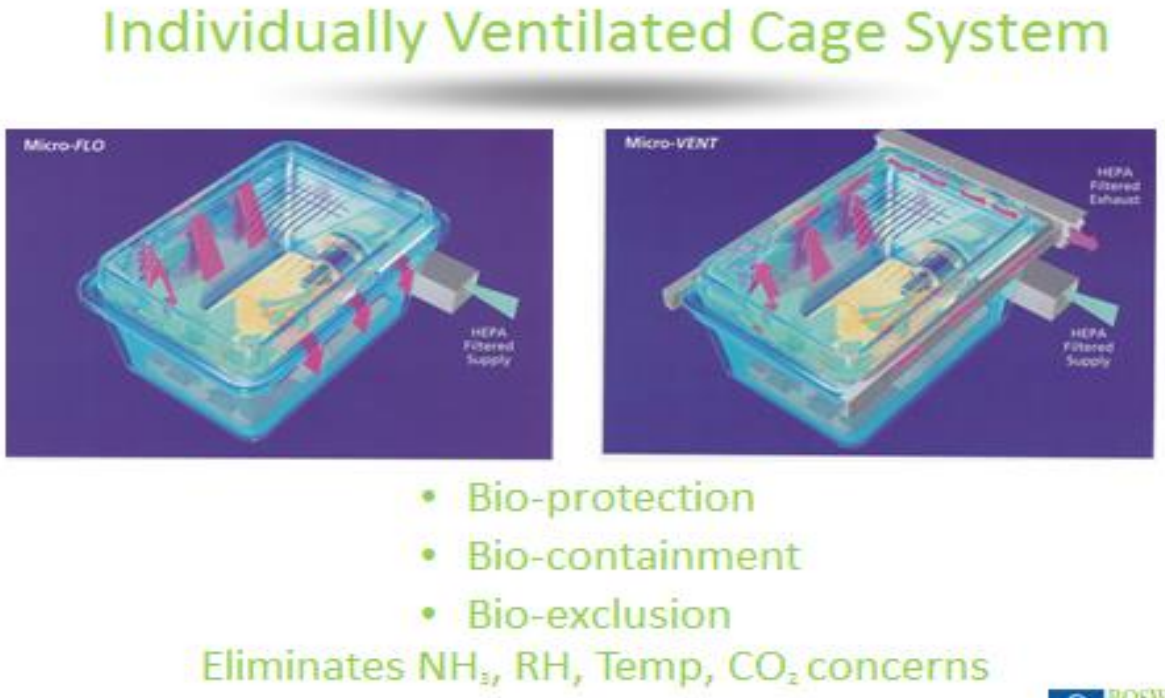
1. Drug dosage changes
2. Increasing the number of animals used
3. Addition of new drugs/agents
4. Performing an additional procedure
5. Changing procedures in any way that might increase the pain/distress category in which the animals are placed
6. Using animals approved for use on one of your protocols for use on another of your IACUC-approved protocols.

Services in the Laboratory Animal Shared Resource at RPCI

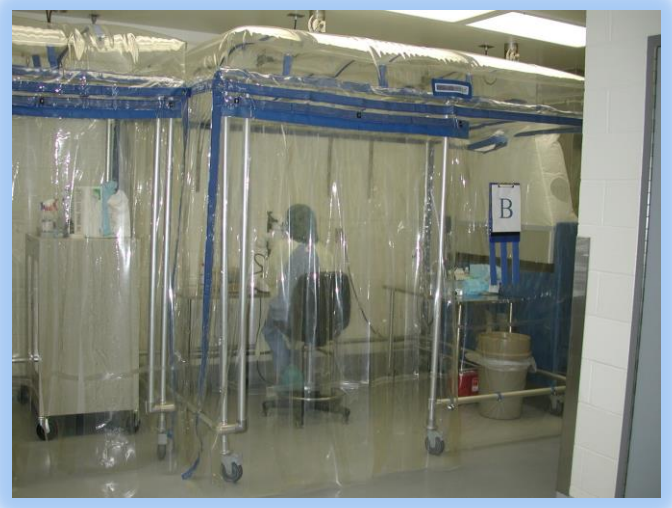
- Training in animal care and use
- Animal care
- Health Surveillance Program

Housing

- Our institution use micro-isolation cages, which are made of hard plastic and have a filter top to contain allergens and to protect animals from potential pathogens in the environment.



Laboratory Animal Shared Resources (LASR)



MRC Building

Main Animal Facility
45,000nsf

- ✓ 41 Animal Holding Rooms
- ✓ 13 Procedure rooms
- ✓ Bio-Bubble room
- ✓ Cage Processing Areas

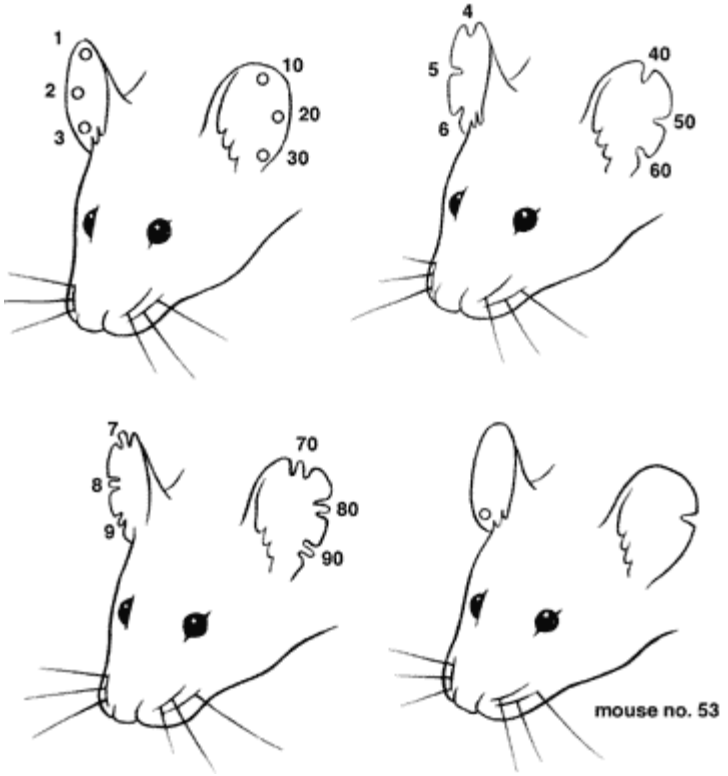
CCC Building

Additional 5,000nsf

- ✓ 22 Animal holding rooms
- ✓ Pre-Clinical MRI, GFP

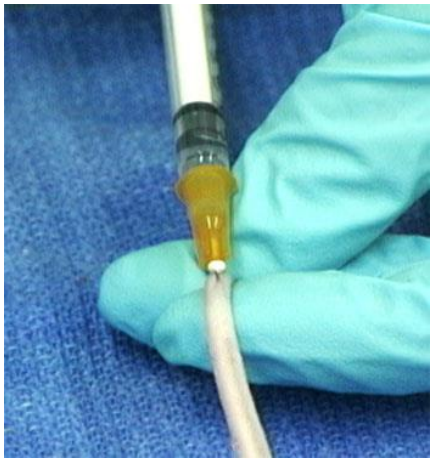
Animal identification

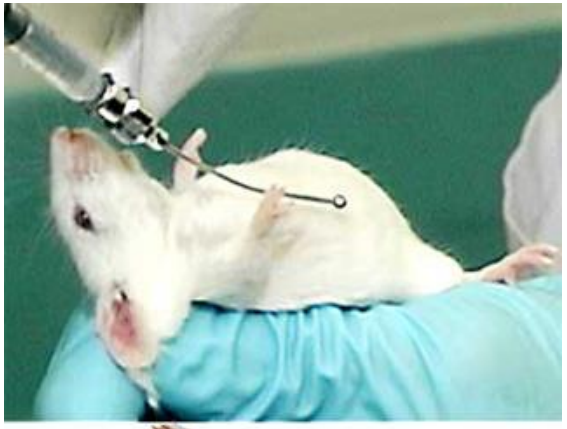
- Rodents can be identified with the numbers 1 through 99 by putting a hole, a notch, a double notch, or any combination of these three marks in one or both ears.

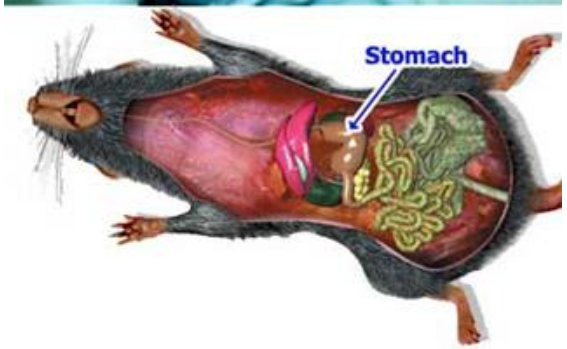


Common Routes of Drug administration in mice

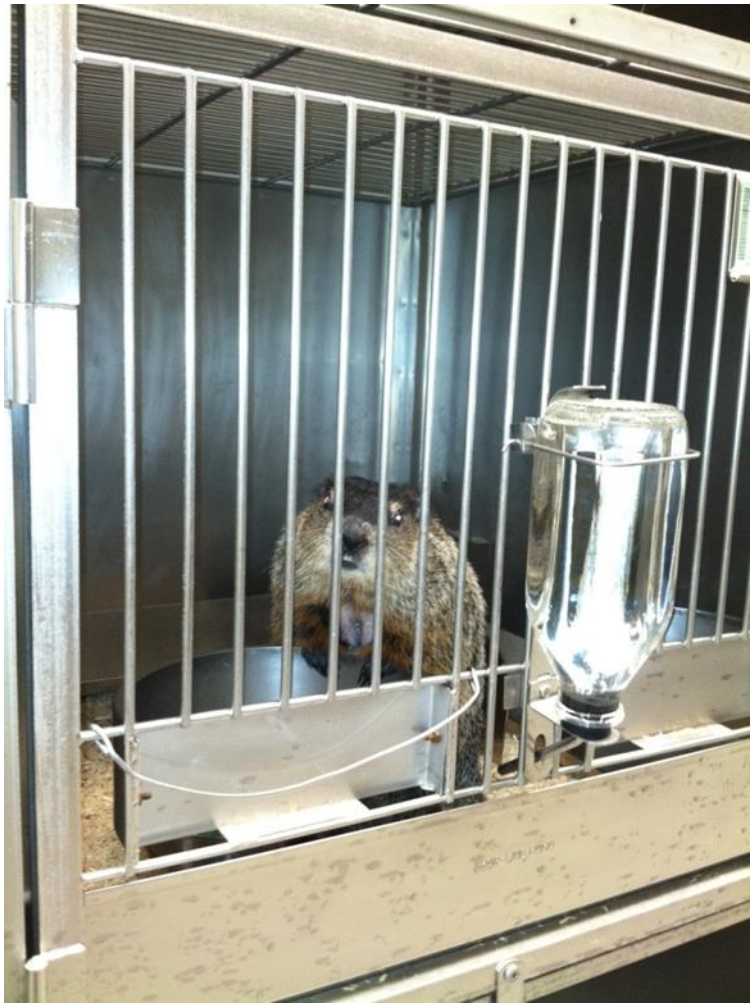
- Sub cutaneous
- Intraperitoneal
- Intravenous
- Oral Gavage







Woodchuck Colony at RPCI

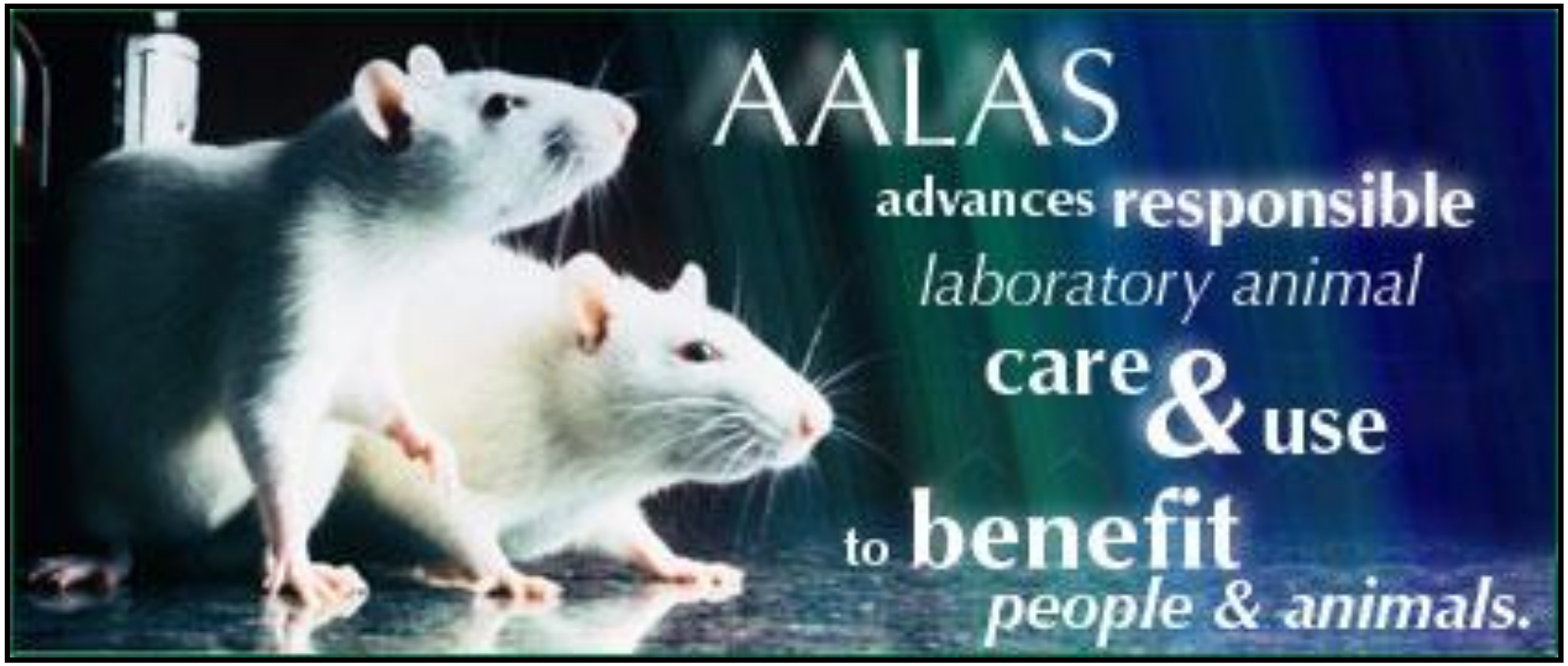


- Animal model for liver cancer

Final Comments

- Animal Research is Important
- By understanding more about animal research, you help your IACUC and the research community assure the American public that animal research is conducted according to the highest standards.
- Our society needs animal research and the accompanying medical advances that have reduced suffering and increased the quality of our lives.

Great Animal Care = Great Science



THANKS!