NEW & UPDATED POLICIES

The Duke IACUC has approved one new policy and several updates / edits to the animal care / use policies (all are available on the Duke animal program website).

The Policy on Continuing Education for Animal Researchers & Care Staff is a new policy, many months in the making. This policy addresses specific language changes in the 8th Edition of The Guide and helps bring the Duke animal program in-line with The Guide. This is an important action, because the vast majority of our institution’s funding stream originates with federal agencies - all of which require allegiance to The Guide for continued access to federal funds. After reviewing The Guide language and considering several options for addressing the instructions therein, the IACUC determined that persons participating in the animal care & use program at Duke must complete three (3) continuing education (CE) hours every 12 months as a condition of continued access to animals.

An informal survey conducted prior to the IACUC’s decision suggested that most Duke persons obtain far more than 3 hours every 12 months as a routine and normal part of being a modern and progressive research scientist. As such, a requirement of 3 hours CE is more a matter of documentation of existing continuing educational efforts than an new unfunded expense. While the CE activities that qualify for CE credit are numerous (see the policy for details), individuals can obtain full CE credit simply by attending 3 Brown Bag Seminars, DLAR or DLC training sessions, or reading articles which will be selected by the IACUC and posted on the animal program web site. There is no reporting of the CE hours completed, but there is a checkbox on the protocol template (Sections F & G) that confirms three hours have been completed. It is the intent of the Committee to ‘trust and verify.’

The ‘trust’ component is letting the lab or the individual keep their own records and indicate accomplishment by a checkbox on the protocol template. The ‘verify’ component will occur during IACUC Semiannual Inspections or Post Approval Monitoring visits. The last validation tool will be a 5 slide web module on the OESO web site (same location as Animal Handler & safety training). Your OESO training page will notify you when the year is up and the re-validation of the CE module is required. Simply open the web module, read the first four slides, and check the box on the last slide. That’s it for another year.

Island of Lemurs: Madagascar


Academy Award® winner Morgan Freeman (Million Dollar Baby, Dolphin Tale) narrates the IMAX 3D® documentary Island of Lemurs: Madagascar, the incredible true story of nature’s greatest explorers—lemurs. The film reunites Freeman with Drew Fellman, who also wrote and produced the 2011 IMAX 3D documentary Born to Be Wild 3D, and director David Douglas, who served as director of photography on that film.

Captured with IMAX® 3D cameras, Island of Lemurs: Madagascar takes audiences on a spectacular journey to the remote and wondrous world of Madagascar. Lemurs arrived in Madagascar as castaways millions of years ago and evolved into hundreds of diverse species but are now highly endangered.

A presentation of Warner Bros. Pictures and IMAX Entertainment, Island of Lemurs: Madagascar will be released in select IMAX® and IMAX®3D theatres starting April 4, 2014. Click here to see the IMAX trailer for the movie.

A CULTURE OF COMPLIANCE

In 2005, the Duke animal program developed a strategic plan to move the campus toward greater compliance with animal care & use expectations. Each quarter since that time, the animal program has considered the status of the animal program’s compliance footprint. Overall, the report is good. The campus has continued a steady march toward a fully compliant animal care & use program.

Compliance is not easy for a campus of our size. We have approximately 4000 program participants working on over 750 approved animal use activities. But even so, we continue to sit between 80 and 90% total compliance with approved protocols, campus SOPs, & policy expectations for care/use of animals. In comparison to prior years, the general trend and annual averages was slightly down, although not significantly so and within a margin of error. Overall, compliance is good but remains shy of the IACUC-defined strategic goals:
1. Greater than 90% compliance for any 6 month period; &
2. No significant deficiencies during the reporting period; &
3. PI Self-Reporting of in-lab errors.

Continued on Page 3
TUMOR BURDEN POLICY
(In Rodents)

Tumor (cancer) implantation in research animals is a critically important experimental activity which also requires consideration of the effect of the tumor on the animal. Limiting the discomfort, pain and distress animals may experience during the conduct of biomedical research is important and is the primary force behind the animal welfare regulations that govern the use of animals in research. Outcomes of tumor studies vary depending on the species and strain of animals, the route of injection for transplantable tumors, and the subsequent cancer treatment. Death as an endpoint may be allowed by the IACUC only after full consideration of alternatives and only if scientifically acceptable for the proposed outcome. At all times, the well-being of the research animals must be balanced against requirements of the study.

Cancer studies can broadly be divided into two categories: biology and treatment: 1. Cancer biology is the study of how tumors grow and behave. The IACUC Tumor Policy is intended to limit the tumor burden and avoid excessive pain or distress, but still achieve the research goal. 2. Cancer treatment is the study of the response of tumors to chemical, radiologic or immunologic therapy. The purpose of all cancer treatments is to destroy or disable the cancer cells while minimizing damage to healthy tissues. The success of a treatment becomes a balance between cancer destruction and reduction of side effects.

Regardless of category, Endpoints and Assessment Tools should be used to assist with determining endpoints for tumor-related activities.

The Duke animal program policy addresses cumulative tumor burden. Animals showing any of the signs below will be euthanized, unless an exemption is provided by the Duke Attending Veterinarian or the IACUC. Whether single or multiple tumors (an unusual situation), the following restrictions apply:

1. Tumors that are ulcerated. If an exemption is provided for this condition, then the affected animals are required to be single housed (may require protocol amendment and / or alternate environmental enrichment or medical treatment),
2. Tumors where the animals chew on the lesion or pay undue attention to the lesion.
3. Tumors that interfere with 'normal' mouse functions (e.g. inability to eat, drink, or ambulate).
4. Tumor burden is greater than 10% of the baseline body weight (mice).
5. Tumor volume that exceeds (in mice) 2000 mm3 in size (which is roughly 10% baseline body weight).

NOTE 1: For the basis of this policy, tumors may be measured using the following formula:

\[ \text{Tumor Volume} = \frac{(\text{Width})^2 \times \text{Length}}{2} \]

NOTE 2: If tumors are spherical, a diameter of 1.5—1.6 cm will generate a 2000 cm³ tumor.

Other clinical signs that require veterinary intervention and are suggestive of tumor related disease such as metastases or ascites are extant:

\[ \Rightarrow \] Weight loss greater than 15%,
\[ \Rightarrow \] Significant abdominal distension, especially when it begins to compromise respiratory ability of animal,
\[ \Rightarrow \] Hunched posture with easily visible vertebral bodies,
\[ \Rightarrow \] Failure to eat or drink,
\[ \Rightarrow \] Absence (or abnormal) of fecal or urine output,
\[ \Rightarrow \] Rough hair coat,
\[ \Rightarrow \] Reluctance to move or abnormal gait,
\[ \Rightarrow \] Discharges or hemorrhage,
\[ \Rightarrow \] Abnormal behavior or vocalizations.

Additional characteristics which could be monitored/measured to assist with study endpoints include:

<table>
<thead>
<tr>
<th>Experimental Endpoint</th>
<th>Example</th>
<th>Clinical Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size</td>
<td>Estimated tumor mass not to exceed 10% of body weight</td>
<td>Frequent measurements of solitary tumor (1 cm³ = 1 gm)</td>
</tr>
<tr>
<td>Evidence of necrosis</td>
<td></td>
<td>Physical examination: scabbing, ulceration, exudate, anorexia, hypothermia, etc.</td>
</tr>
<tr>
<td>Evidence of sepsis</td>
<td></td>
<td>Restricted ambulation, inability to access food or water</td>
</tr>
<tr>
<td>Evidence of metastasis</td>
<td></td>
<td>Circling, blindness, dementia, convulsions</td>
</tr>
<tr>
<td>Evidence of local invasiveness</td>
<td></td>
<td>Inability to access or ingest food and water, inability to ambulate and keep clean</td>
</tr>
<tr>
<td>Physical Characteristics of Tumor(s)</td>
<td>Neurologic impairment</td>
<td>Evidence of dehydration</td>
</tr>
<tr>
<td>Tumor Location</td>
<td>Head/neck and extremities</td>
<td>Frequent weighing (3-5 times/week)</td>
</tr>
<tr>
<td>Moribund or Pre-moribund State</td>
<td>Define with specific clinical tests or signs</td>
<td></td>
</tr>
<tr>
<td>Cachexia, Chronic Wasting</td>
<td>Weight loss &gt;15% of normal body weight</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Dyspnea, rapid or labored breathing, coughing, rales</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Shock, hemorrhage, anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea (&gt;2 days' duration), vomiting</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Circling, blindness, dementia, convulsions, unresponsiveness</td>
<td></td>
</tr>
<tr>
<td>Signs of Organ or System Failure</td>
<td>Integument</td>
<td>Extensive hair loss, inflammation, self-trauma</td>
</tr>
</tbody>
</table>

Other signs that are identified as moribund state:

- Moribund state begins to compromise respiratory ability of animal
- Moribund or Pre-moribund State
- Signs of Organ or System Failure

Wishing you a wonderfully successful research month,
The **Policy on Counting Animals** was recently updated to reflect current and ongoing processes. The more significant change involves the definitions of embryo and pre-weaning. The new definitions are simpler and more global than the older rather focused and detailed definitions.

- **Embryonic/Fetal Animal**: From implantation to birth (in mammals): from shelled egg to hatching (in avian or reptile species); from egg to larva with unab sorbed yolk sac (in aquatics or reptiles).
- **Pre-weaning/fledgling**: Young animals requiring parental protection or nursing.
- **Adult**: Those animals which are ‘mature; or have aged beyond the weaning date (for the species) or are of an age able to reproduce; or are free swimming and no longer dependent upon the yolk sac (aquatics).

These new definitions are far simpler than the old definitions, and one step in the process of preparing our program for the implementation of the SmartLab animal program management system later this year. The Committee also added guidance regarding reporting animals produced by a Duke vendor/breeding core and counting (or not) animals in collaborative projects with sister institutions.

In both the **Enrichment for Primate** and the **Enrichment for Species Other Than Primates** policies, the Committee inserted common language regarding post-surgical care. Effectively immediately, researchers DO NOT require an exemption for single housing and/or restricted cage sizes less than the recommended standard caging size (e.g. ICU caging for use post-surgery rather than the normal cage) of immediate post-operative recovery patients. Post-operative recovery is defined as from the time of surgery up to 7 days post-surgery. Animals should retain the ability to make normal postural adjustments with adequate freedom of movement, including sitting, standing, and turning around - even in the smaller cage.

The **Policy on Fetal & Neonatal Euthanasia (Mouse/Rat)** was enhanced to bring it into full compliance with the AVMA policy. Two specific changes include: IACUC approval is required for all methods of euthanasia; and not expose any rodent younger than 15 days of age to CO2! In addition (and consistent with other policy language) the term 'pre-weaning' will be used to replace the references to neonate (neonate can be of different ages in different species/conditions).

The **Policy on Amendments to Approved Protocols** has been shifted to reflect actual practice:
- An increase in USDA-covered species go to Significant Change Subcommittee (SCSC); but special species (e.g., dogs, cats, primates) will be called to Full Committee.
- Section U (Exception to the rules, regulations, or practices) will be reviewed at SCSC and then recommended to the Full Committee.
- Non-pharmaceutical grade drugs will be reclassified as a 'minor with veterinary review' (generally approved in 4-5 business days).

The **Policy on Animal Transport Around Campus** was clarified to insure all understand that a transport cage (commonly called the 'chicken bucket' or 'chow mein box') is not a housing cage. The modifications identify parameters for transport and limit holding animals in a transport cage for not more than 3 hours.

Lastly there are several protocol changes that were necessary to both match *The Guide* expectations, improve consistency with current practices, and make things actually work better for the new SmartLab applications. Collectively these included:

- **Section B3**: This section has been updated to:
  1. Remove “alternative” as a required search term;
  2. Specify that two (2) databases are required;
  3. Include a link to the Duke University Medical Center library for lit search resources;
  4. Update the literature search database selections to include those considered most relevant by a Duke medical center librarian; and
  5. Change in question phrasing to focus upon all sources of pain or distress, not just procedural activities.

- **Section B12**: Insert the phrase “for which there is a pharmaceutical grade substance.” This address those situations were a non-pharm substance is preferred over a pharm-grade material.

- **Section B14**: Insert a reminder to capture unique rodent strains in the new MouseBase Registry.

- **Section F**: Addition of a Continuing Education (CE) certifying statement “I certify that I and all personnel on this protocol have (or will) obtain (ed) three <3> CE credits as required by the Policy on Continuing Education.”

- **Section G**: Addition of a Continuing Education (CE) certifying statement “I certify that I have (or will) obtain three <3> Continuing Education credits as required by the Policy on Continuing Education.”

---

**UPCOMING EVENTS**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb. 12</td>
<td>Brown Bag Seminar</td>
</tr>
<tr>
<td></td>
<td>Presenter: Dr. Anna Hampton:</td>
</tr>
<tr>
<td></td>
<td>Topic: R.U.N.C.? (Are You Non-Compliant?)</td>
</tr>
<tr>
<td></td>
<td>12:00-1:00 PM; JONES BUILDING AUDITORIUM RM 143</td>
</tr>
<tr>
<td>Feb. 20</td>
<td>Amendment meeting</td>
</tr>
<tr>
<td>Feb. 25</td>
<td>Brown Bag Seminar</td>
</tr>
<tr>
<td></td>
<td>Presenter: Dr. Debbie Vanderford:</td>
</tr>
<tr>
<td></td>
<td>Topic: The 7 Deadly Sins of Protocol Preparation</td>
</tr>
<tr>
<td></td>
<td>12:00-1:00 PM; JONES BUILD. AUDITORIUM RM 143</td>
</tr>
<tr>
<td>Feb. 27</td>
<td>New Protocol meeting</td>
</tr>
<tr>
<td>March 3</td>
<td>New Protocol deadline</td>
</tr>
<tr>
<td>March 6</td>
<td>Amendment meeting</td>
</tr>
<tr>
<td>March 10</td>
<td>Amendment deadline</td>
</tr>
<tr>
<td>March 20</td>
<td>Amendment meeting</td>
</tr>
<tr>
<td>March 24</td>
<td>Amendment deadline</td>
</tr>
</tbody>
</table>

---
While all non-complaint activities remained low, there are select areas which will be a focus for the animal program this coming year. As a general rule, the non-complaint actions are the result of momentary lapses of judgment, accidents, or areas where confusion existed between approved and anticipated procedures. The animal program continues to focus upon these issues as the core of on-going training activities.

**RESEARCH ANIMAL COORDINATORS**

**(A Status Report)**

The Duke animal program believes that a critical foundation for compliant activity begins with extending education and oversight to the bench-top. Research Animal Coordinators (RACs) are a critical component of the program’s success. RACs are research staff members who receive a higher level of education than the routine research member, and with the enhanced knowledge and skill-set can serve as a bench-top emissary of the animal program assisting with compliance and encouraging educated care & use practices. Since its inception, the animal program has graduated three cohorts of Research Animal Coordinators. A total of sixty-one (61) graduates to date, the animal program continues to find value in the process as the laboratories of the RACs are more in-tune with the compliance objectives of the institution and provide more timely capture and resolution of potentially significant compliance events. But the benefits are not just local. Eight RAC graduates have left the university, further extending Duke’s national impact of animal well-being and animal welfare.

Later this summer, the 4th course cycle will swell the working RACs to eighty-two (82) RACs, serving in over 100 laboratories around campus. The RACs are having a positive impact upon compliant behavior and corrective measures when behavior is less than desirable.

The IACUC has chosen to further leverage the RAC initiative by establishing a RAC Advisory Committee as an ad hoc participant in animal program processes. Thus far, the RAC Advisory Committee has reviewed and updated the Animal Handlers 1 on-line training (adopted by the IACUC in January 2013); and previewed the updated CO2 euthanasia training module (adopted by the IACUC in September 2013) and provided numerous suggestions to enhance clarity and understandability. During 2014, RACs will serve as beta-testers and trainers for the new Edstrom on-line IACUC Submission and Review module.

The next RAC course cycle will begin in the fall. For those interested, contact Bill Wade, RVT, LATg (w.wade@duke.edu) for registration information.

**NOTIFICATION OF HAZARDOUS WORK IN ANIMAL CARE AREAS**

When animal research involves the use of hazardous agents (i.e. infectious agents, hazardous chemicals, radiological agents, etc.) it is imperative that workers be notified of potential risks and how to work safely when such risks are present. The role of the researcher is to ensure that this information is provided to all research, animal care and occupational health staff. Here are some important highlights of working with hazardous agents.

Researchers must assure OESO and DLAR that all required signage is properly affixed and notification of pending (or ongoing) hazardous work has occurred prior to working with the agent in an animal use area. The PI, with support from OESO, will prepare a Standard Operating Procedure (SOP) that outlines the safe work practices for the animal use area when hazardous agents are employed. Personal Protective Equipment (PPE) is required, appropriate to the species and the hazardous agent being used. Staff should be trained on proper use of PPE.

Investigators must notify DLAR via written communication, preferably e-mail, at least 5 business days prior to the use of hazardous agents in animals. PI or research staff member must post hazard signs (available from OESO) in the appropriate areas. Information on the form must include; name of hazardous agent, building and room number, species in which agent will be used, emergency contact information for the PI and staff, copy of the SOP for safe handling of the agent being used. PI should provide all information to and notify:

- Dr. Randall Reynolds (randall.reynolds@duke.edu),
- Peg Hogan (hogan012@mc.duke.edu) or
- Dr. Francis Sun (francis.sun@duke.edu)

**AALAS LEARNING LIBRARY**

**(One way to satisfy the new annual C.E. requirement)**

All individuals with an active protocol have access to FREE web module training through the AALAS Learning Library training site.

If you or your lab staff are interested in obtaining a password for this research procedure and bio-methodology training, please contact Bill Wade @ 668.6722 or via e-mail at w.wade@duke.edu

**REMAINING IACUC SEMIANNUAL SITE VISIT SCHEDULE**

FEBRUARY 13TH: GSRB2
FEBRUARY 20TH: BRYAN – NANALINE DUKE – VSH-CARY
MARCH 6TH: GSRB2 ANNEX – JONES – RP 1-4 – GSRB1 – ENGINEERING
MARCH 13TH: DUKE MARINE LAB
MARCH 20TH: CARL – EYE CENTER – DLAR FARM – INDEPENDENCE PARK
APRIL 3RD: CCIF
APRIL 10TH: FOSTER ST. – BIOLOGY – FRENCH – CIEMAS
APRIL 17TH: DUKE NORTH/SOUTH – GHRB
MAY 1ST: VIVARIUM – MSRB1
MAY 8TH: LEMUR CENTER – MSRB2 – MESOCOSM
**Introduction**

Approximately 95 percent of all laboratory animals are mice and rats. Easily housed and bred, short lived (2-3 years), small, and relatively inexpensive, these rodents have become the animal model of choice for modern medical and scientific researchers. Because their physiology and genetic make-up closely resemble that of humans, rodents play an invaluable role in biomedical research. In the last decade, scientists discovered how to breed mice with genetic alterations that mimic human diseases. This capability has revolutionized medical research and dramatically increased the number of mice needed in medical science. The mouse genome contains essentially the same complement of genes found in the human genome, so studying how the genes work in mice is an effective way of discovering the role of a gene in human health and disease.

**Man-made, genetically altered rodents**

Transgenic and knockout rodents have been created with revolutionary new technology. While transgenic mice have had a foreign gene (a piece of DNA) artificially added to their genomes, knockout mice have had a specific gene “turned off” or made useless. A great deal of promising research relies on these genetically altered mice. Transgenic rats also have been used in medical studies and found to be better models than mice for studying certain human diseases. Genetically altered rodents have allowed scientists to observe what happens during the progression of Parkinson’s disease, cancer, cystic fibrosis, heart disease, memory loss, muscular dystrophy, and spinal cord injuries. Recently, the mouse and rat genomes were sequenced. This achievement promises to significantly advance biomedicine.¹

**Naturally occurring immunodeficient mice**

SCID (severe combined immune deficiency) mice and nude (or hairless) mice are born without thymus glands and lack functioning immune systems. These mice are very important models for studying both normal and malignant human tissue. They also are needed to develop and evaluate new drugs without risking human lives.²

**Alzheimer’s Disease**

Scientists have evidence that a buildup of plaques containing amyloid protein deposits in the brain is a characteristic feature of Alzheimer’s disease (AD), a disorder that affects patients’ memories and personalities. Rats and transgenic mice bred to carry a gene that over expresses human amyloid protein have become indispensable for understanding and evaluating new drugs to prevent or delay the onset of AD. And recently, researchers have shown that vaccinating these mice with modified amyloid protein slowed the progression of the disorder. Patients are now being tested to see if the vaccine is well tolerated and can help overcome AD.³

**Aging**

Measuring physiologic changes over an entire life span would take many decades to complete in humans. However, such studies can be accomplished on “fast forward” in normal mice and rats. Research has shown that a reduced intake of calories in rodents markedly increases longevity, retards physiological deterioration, delays, and in some cases, prevents the incidence of age-associated diseases.⁴

**Carcinogen Testing**

Scientists are evaluating several lines of knockout mice to study the mechanisms of carcinogenesis. They propose that such animals might be needed for routine testing of chemicals for carcinogenic potential. The results can be obtained more rapidly with fewer animals, and the outcome can be used effectively in chemical and drug safety assessments.⁵

**Cancer**

During the past decade much of our knowledge of how environmental agents damage DNA and cause mutations that enhance cancer risk has come from studies with rats and mice. Scientists have produced cancer resistant mice that lack the ability to produce cyclin D1, a protein found in abnormally high amounts in human breast cancers.
They propose that cyclin D1 therapy might be highly selective in inhibiting the growth of human breast cancer cells.  

**Cystic Fibrosis**  
Cystic fibrosis (CF) is a childhood disease characterized by chronic lung congestion and digestive problems. CF is incurable and patients rarely live to see the age of 30. Scientists now know that CF is caused by a small defect in the gene that manufactures CTRF, a protein that regulates the passage of salts and water in and out of cells. Studies with CTRF-deficient mice have shown that the disease results from a failure to clear certain bacteria from the lung, which leads to mucus retention and subsequent lung disease. These mice have become models for developing new approaches to correct the CF defect and cure the disease.  

**Drug Addiction**  
Rats trained to self administer cocaine have high predictive value for human addiction because they share common triggers of relapse. In mapping the brains of adult rats that kicked the cocaine habit, researchers found that in relapse, the “high” from cocaine occurs in an area separate from where the brain retains cocaine-seeking behavior. This finding opens the possibility for developing new targets for anti-craving medication.  

**Spinal Cord Injury**  
Scientists are using rats to study the mechanisms underlying long-term recovery of motor skills after spinal cord injury. They found that motor function is related to the number of intact axons, the part of the nerve cell that transmits signals to motor neurons. Recent studies have demonstrated that axonal sprouting or regeneration at the injury site correlates with functional recovery and can be enhanced by the application of certain growth factors to the spinal tract. Development of these approaches to neural repair may ultimately generate new strategies for treating human spinal cord injury.  

**Heart Attack**  
New research has revealed that the heart muscle regenerates to some extent after a heart attack. A new strategy for treating this condition is being studied in transgenic mice. Researchers are experimenting with injecting stem cells (primitive bone marrow cells) into the periphery of the injured area to stimulate self-repair. The studies showed that the cells promoted structural and functional repair of the damaged tissue.  

**References**  