OLAC Newsletter

Office of Laboratory Animal Care

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What is Post-Approval Monitoring (PAM)?

Dana Glass-Mattie, DVM

Post-approval monitoring, referred to as PAM, is the name commonly used for the observation performed on IACUC approved protocols to ensure they are executed as they were written. The University of Tennessee, Knoxville recently began this program with my employment in the role of Director of Compliance Support (DACS). PAM is not currently a requirement of any regulatory body, per se, but is recommended to help larger institutes with a greater number of active protocols to have a method to maintain compliance within the system. Often times, especially with complicated protocols, a phenomenon called 'protocol drift' occurs which means that procedures originally written and approved get changed and these changes occur without being recognized by the principal investigator (PI), therefore, making the protocol noncompliant. The goal of the PAM program is to be a positive one and help identify any problems internally before outside regulatory agencies identify any.

My main job function is to identify protocols that have active animal work and go into the laboratory or field to watch the work being performed. These observations include looking for any changes in procedures, changes in personnel, animal problems, safety issues and work place issues that may need to be corrected. The PAM process will begin with a contact being made to a PI of an active protocol and a time set up to observe one or all of the procedures performed on the protocol. These observations will take place throughout the campus for both teaching and research protocols and beyond, for those involving field work. Once an observation takes place, I will inform the PI and lab staff of any obvious noncompliant issues and suggest methods in which to correct them which may include the submission of an amendment to the protocol. A formal report is sent to the PI by email, is included in the protocol file and will be reported at the next IACUC meeting. I am also available to help in the initial writing of protocols to help make sure they are written in a manner that makes it easier to stay compliant. The overall goal of the PAM office is to be a positive resource to help the University of Tennessee- Knoxville reflect an attitude of compliance. My office is located in Room 372 in the Ellington Plant Sciences Building and my phone number is 974-9074 for any questions or concerns.

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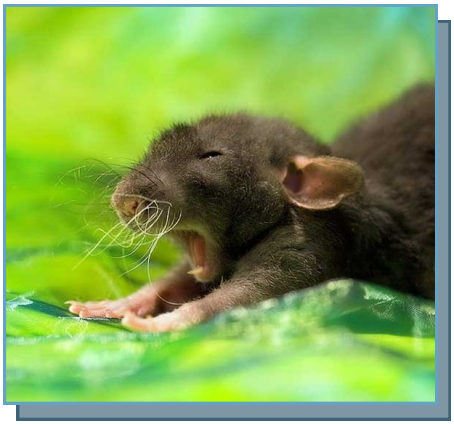
Tribromoethanol: To Use or Not To Use, That is the Question

William A. Hill, DVM, MPH, DACLAM



Tribromoethanol (TBE), formally available under the trade name Avertin, is a non-pharmaceutical grade anesthetic that has been used extensively for various manipulations in laboratory rodents due to ready availability, lack of state and federal drug regulations associated with use, and rapid anesthetic induction and recovery times.[1] Despite routine use, TBE use in rodents is controversial due to contradictory reports regarding the compound's efficacy and associated pathology and mortality.[2-7] Morbidities reported with TBE use in mice include intestinal ileus, peritonitis, muscle necrosis, serositis of abdominal organs, and death.[2,6,7] In an attempt to balance animal welfare concerns and investigator needs, many institutional animal care and use committees (IACUCs) have developed guidelines for TBE use, including prohibiting repeat use. The UTK IACUC Guidelines for Preparation and Use of Avertin in Mice can be found at http://iacuc.tennessee.edu/policies/avertin.shtml. Here at UTK, TBE is not recommended for repeated use however, the IACUC will consider requests for repeated dosing when adequate scientific justification is provided.

Investigators at UTK have recently presented findings of a study evaluating repeat administration of TBE in C57BL/6NHsd mice. To our knowledge, this is the first study to thoroughly evaluate the safety and efficacy of repeat TBE administration. In our study, intraperitoneal administration of TBE (500 mg/kg) did not produce morbidity, mortality, or pathologic changes following single or repeat administration. However, TBE failed to produce loss of pedal reflex after single administration. Nine of 10 animals reached a surgical plane of anesthesia following repeat TBE administration, yet anesthetic times varied widely. Based on these findings, our group urges caution in use of TBE in C57BL/6NHsd mice due to variable anesthetic effectiveness.

The UTK IACUC Guidelines for Preparation and Use of Avertin in Mice can be found at: http://iacuc.tennessee.edu/policies/avertin.shtml.

Notwithstanding TBE effectiveness, the National Institutes of Health Office of Laboratory Animal Welfare has articulated that use of non-pharmaceutical grade compounds such as TBE should be based on: scientific necessity; no availability of acceptable veterinary or human pharmaceutical-grade compounds; and specific review and approval by the IACUC. Various regimens using pharmaceutical grade anesthetics have been developed for use in mice.

Use of pharmaceutical grade anesthetics will satisfy regulatory guidance and likely result in less anesthetic variability. Please contact an OLAC veterinarian for assistance in selecting appropriate anesthetics for rodent species.

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Feral Mice in the Laboratory Animal Facility

Chris Carter BS, LVT, LATg

Feral mice are highly adaptive animals and frequently live in close proximity to humans. In their search for food and shelter mice frequently find their way into houses, office buildings, and even laboratory animal facilities. If all the right conditions are met such as the presence of food and a warm, safe place to nest, feral mice will inhabit the area and make it their permanent home. For this reason, it is important that safeguards such as general cleanliness, storage of feed and bedding above the floor, and barriers to entry are in place to prevent entry of wild mice.

Even when the best precautions are taken, wild mice can be very resourceful and are known to squeeze through an opening only ¼ inch in size. Wild mice should always be considered "dirty" animals because their health status is unknown and they can serve as host to a number of pathogens which could threaten the health status of our "clean" laboratory rodents. In addition to posing a threat to laboratory animals, wild mice have the potential to transmit zoonotic diseases to humans as well.

Sometimes feral mice are visible and they can be spotted scurrying across the floor, other times the presence of mouse droppings is the only sign that they are present in the facility. Mice prefer walls and corners to being out in the open, so placing a live trap along the wall will result in the best chance of catching the animal. Our laboratory animal facilities employ the use of live traps in all animal rooms and storage areas to maximize the chances that the mouse will be caught before it has a chance to cause problems.

If a live mouse is caught, the OLAC office should be contacted as quickly as possible to ensure that a blood sample can be obtained from the mouse. The blood sample will be sent out and a gross necropsy performed on the mouse. The information obtained from these procedures could provide an epidemiological linkage between the captured feral rodents and new diseases that may arise in the current laboratory animal population. Preventative strategies to keep feral mice at bay are an important part of the pest control plan in a laboratory animal facility and are a key ingredient to impeding the spread of adventitious agents to our rodent population.

The Animal Care and Use Program at UTK

Patricia Coan, DVM, PhD, DACLAM

Our animal care and use program includes The University of Tennessee Medical Center, Knoxville, TN; College of Education, Health and Human Sciences; College of Arts and Sciences; College of Veterinary Medicine (CVM); College of Agricultural Sciences and Natural Resources; and Agricultural Research and Education Centers.

The following dedicated animal facilities (DAF) comprise the core animal facilities on the UTK campus:

* Walters Life Sciences Laboratory Animal Facility (WLSLAF);
* Jesse Harris Laboratory Animal Facility (JHLAF);
* University of Tennessee Medical Center, Knoxville Laboratory Animal Facilities (UTMCKLAF); and
* UTK Veterinary Medical Center (VMC) DAFs, which include: CVM Laboratory Animal Facility (VMCLAF), Joe Johnson Animal Research and Teaching Unit (JARTU), CVM Cherokee Building A (VMCCBA).

The following Research and Education Centers comprise the animal facilities throughout the state:

* Dairy Research and Education Center (DREC)
* East Tennessee Research and Education Center (ETREC)
* Greeneville Research and Education Center (GREC)
* Highland Rim Research and Education Center (HRREC)
* Middle Tennessee Research and

The Animal Care and Use Program at UTK

Education Center (MTREC)

* Plateau Research and Education Center (PREC)

UTK's primary purpose is to move forward the frontiers of human knowledge and enrich and elevate society. The mission of the animal facilities at the University of Tennessee is to provide excellent service in support of research and teaching missions while concurrently providing for the safe and ethical treatment of the animals. External research funding at UTK increased to more than $208.5 million in FY 2011. The animal care and use program at UTK is AAALAC accredited and has 144 primary investigators (PI) with 301 currently active IACUC-approved protocols. The Office of Laboratory Animal Care (OLAC) is the centrally administered animal resource for UTK.

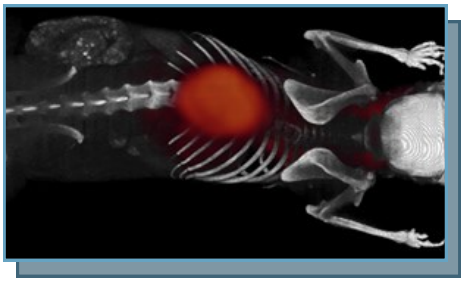
The Institutional Official (IO) is James P. Thompson, DVM, PhD. Oversight of the campus-wide animal care and use program is the responsibility of the Institutional Animal Care and Use Committee (IACUC) and the Attending Veterinarian (AV), Patricia N. Coan, DVM, PhD, DACLAM. The IACUC is appointed by the IO and the AV reports to Dr. Thompson. Due to the varied nature of teaching and research activities and the size of the UTK Campus, animal care is decentralized and several satellite facilities are maintained. The Office of Laboratory Animal Care (OLAC) is responsible for research animal care at UTMCK, JH, WLS, and Satellites. OLAC additionally provides veterinary care for some animals used in instructional activities at the College of Veterinary Medicine and for the Animal Science Department.

Other animals utilized at the CVM are provided veterinary care by Small Animal Clinical Sciences (SACS) veterinarians, Large Animal Clinical Sciences (LACS) veterinarians, or the most appropriate veterinary designee, as determined by the AV and IO. The REC's utilize the Ambulatory Service, members of the VMC veterinary faculty or private local veterinarians who have been granted designation by the IO and the AV to provide veterinary care to animals at the outlaying locations.

The decentralized evolution of the University of Tennessee's animal care and use program and the inclusion of units in the statewide REC's have resulted in a number of separately operated animal facilities. Although budget source and management practices may vary somewhat among facilities, the IACUC ensures that all practices and procedures are consistent with those described in the Animal Welfare Regulations, The Guide for the Care and Use of Laboratory Animals, The Guide for the Care and Use of Agricultural Animals in Research and Teaching, and university policies. The IACUC is responsible for semi-annual facility inspections, semi-annual program review, review and approval of standard operating procedures (SOPs), and review and approval of all teaching and research protocols involving vertebrate animals.

THE GRADUATE SCHOOL OF MEDICINE – MEDICAL CENTER KNOXVILLE (UTMCK)

Research at the UTMCK is focused in a variety of biomedical fields that include: the study of the renin-angiotensin system and its relationship to shock and sepsis; the correlation between hormone replacement therapy and vascular disease in women; small animal functional and anatomic imaging of novel tracers that target tumor antigens, angiogenesis, or amyloid-related biomarkers; and the in vivo study of immunoglobulin light chain-related pathologies. There is a strong emphasis on molecular and functional imaging and many of these research projects make use of the state-of-the-art small animal SPECT, PET and CT imaging facility located in UTMCK.



DEPARTMENT OF NUTRITION – JESSIE HARRIS (JH)

The major areas of animal based research in the Department of Nutrition include: obesity, diabetes, and oncology utilizing rats and mice. Zucker fatty rats are used as a genetic model of obesity. Athymic nude mice are used in xenograph experiments to study prostate cancer after it has metastasized to a secondary sight, such as bone. An ApcMin/ mouse model is used to study nutrient effects on intestinal tumorigenesis.

THE COLLEGE OF ARTS AND SCIENCES –WALTERS LIFE SCIENCES (WLS)

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Biochemistry, Cellular, and Molecular Biology (BCMB) faculty and students use wild-type mutant and transgenic mice to study germ cell development, cancer, aging, cell-cycle regulation, regulation of circadian rhythms and responses to fungal infections. Rabbits are used for production of polyclonal antibodies. Oocytes from frogs (Xenopus) are used for expression and biochemical analysis of membrane proteins. Research on vertebrate animals in the Department of Ecology and Evolutionary Biology include snake behavior, ecology, and phylogeography, and salamander population genetics and ecology. Faculty in the Department of Psychology study the vocal interactions of birds and effects of social stress in hamsters. Those faculty members in the Department of Microbiology who use the animal facility aggressively pursue research in immunology; virology; and microbial pathology. These investigators focus on research problems that use the mouse as the model animal. Typical research projects include studies on: virulence and population genetics of Toxoplasma gondii; cytomegaloviruses' modulation of the immune system; lipid-based virulence determinants in mycobacterial species; B cell responses to influenza infection and vaccination; and, viral immunology and memory T cell differentiation.

THE VETERINARY MEDICAL CENTER (VMC)

Research performed by VMC investigators includes clinical trials and applied and basic research using laboratory, exotic, avian, wildlife, and livestock species. Research emphasis areas involving animals include advanced imaging, oncology, and cancer cell biology, nutrition and metabolic disorders, vascular and degenerative disorders, rehabilitation, and veterinary public health. Teaching protocols include routine diagnostic and surgical procedures for companion animals and livestock.

THE COLLEGE OF AGRICULTURAL SCIENCES AND NATURAL RESOURCES (CASNR)

The College of Agricultural Sciences and Natural Resources strives to provide high-quality, experiential learning opportunities for our students to prepare them for careers in the animal and wildlife industries, biotechnology, and professional programs, including Veterinary Colleges, Pharmaceutical and Medical Schools and graduate programs. To support such, the Department of Animal Science provides classes covering hands-on instructional laboratories involving major food animal (swine, bovine, ovine, and poultry) and equine species. The live animal based instructional laboratories are coordinated by Animal Science faculty members. In wildlife, teaching faculty conduct demonstrations on small mammal, amphibian, and bird handling to prepare students for graduate school, veterinary school, or careers in natural resources. Research programs cover amphibian diseases and conservation concerns, zoonotic disease investigations, deer ecology and movements, bird behavior and ecology, fish conservation and restoration, and carnivore ecology.

TENNESSEE AGRICULTURAL RESEARCH AND EDUCATION CENTERS (REC)

Animal research by Tennessee Agricultural REC scientists are focused on food animals and are principally directed toward improving the efficiency of food animal production systems. Dairy and beef systems receive the major attention. The REC's maintain three research dairy herds and four research beef herds. Scientists use these research herds to explore issues related to food safety, animal health, reproduction efficiency, nutrition, and environmental impact. When called for by specific research protocols, swine, poultry, sheep, and fish are acquired in adequate quantities and maintained in appropriate facilities for duration of specific studies.

Spotlight on Models in Animal Research

Tim Sparer, PhD

Dr. Sparer received his BS from Northwestern University, PhD from Emory Medical School, and continued his training as postdoctoral fellow at Imperial College, London, UK and Stanford University Medical Center. He joined the UT Microbiology Department in 2003.

ANIMAL MODELS FOR VIRAL PATHOGENESIS, CANCER, AND ATHEROSCLEROSIS

The role of chemokines in different diseases is the overarching focus of my lab. Chemokines are small chemoattractant proteins. Their secretion leads to the attraction of multiple different cell types. Any cell of the body that is undergoing stress (i.e. physical trauma, viral infection, etc.) will release these proteins to alert and recruit cells of the immune system. Think of chemokines as the "early warning system" of body, informing it that there is a problem or invasion from outside. We are interested in how these chemokines contribute to viral spread within the host, atherosclerosis (i.e. hardening of the arteries), and cancer metastasis. Mouse models for studying chemokines within these different disease states have been essential.

One of our projects is to study how a chemokine produced from a common herpesvirus called cytomegalovirus (CMV) contributes to CMV dissemination and pathology. Human CMV is a ubiquitous herpesvirus with over 70% of humans infected. In most cases the initial infection with CMV occurs in childhood with little or no symptoms. As with all herpesviruses, after initial infection, the virus remains latent for the rest of their lives. Even though most people carry this virus for life, it is asymptomatic unless a person becomes immune compromised. This could occur during late stage AIDs, cancer therapies, or long-term suppression following organ transplantation. Once a person is immune suppressed the virus is reactivated and can lead to complications, death or organ rejection. In order to understand the role that chemokines play at each stage of infection, we use the mouse model of CMV infection. One of the features of CMV is its species specificity. This means that human CMV does not productively infect mice and mouse CMV does not infect humans. The only way to understand human CMV's lifecycle and to test potential vaccines/ treatments in vivo is to infect mice with mouse CMV. The mouse model for human CMV infection mimics many of the aspects of human CMV. Using this model along with recombinant mouse CMVs expressing host and viral chemokines, we seek to address the role of host and viral chemokines in viral dissemination and pathogenesis. By uncovering novel roles of these chemokines we hope to exploit its weakness for developing anti-virals that will minimize CMV pathology.

The mouse model for atherosclerosis allowed us to test the role that viral and host chemokines play in CMV-enhanced atherosclerosis. Atherosclerosis is the development of fat filled plaques lining the arteries. These plaques block the flow of blood leading to high blood pressure but more importantly they can rupture leading to a stroke or heart attack. Human CMV has been implicated as a contributor to the development of atherosclerotic plaques. We wanted to know how it was doing this. Because immune cells are one of the initiators of plaque formation, viral and host chemokines are probably responsible for some portion of atherosclerosis. One of the advantages of using mice is that mice have been generated that knock out specific genes allowing them to develop atherosclerosis either under a high fat diet or spontaneously. These atherosclerotic mice will allow us to see how CMV infection contributes to the inflammation that initiates atherosclerosis. Without these mouse models the effects of CMV and its role in atherosclerosis could not be discovered.

More recently my lab has branched out into the field of cancer biology with a focus on a chemokine receptor instead of the chemokine ligand. We have found that a common chemokine receptor, CXCR2, can undergo a single point mutation that locks it in the "ON" position. We hypothesized that once this protein is turned on, it could contribute to cancer metastasis. After all, 90% of cancer deaths are due to metastasized tumor cells instead of the primary tumor so an activated chemokine receptor could direct cancer cells to distant sites in the body and contribute to cancer mortality. We have made cell lines that express these mutated chemokine receptors and injected them into mice to measure how quickly the tumor grows and how well it can metastasize. Being able to measure the spread of the tumor cells to distant sites in the mouse will help us develop novel tools for combatting metastatic cancer initiated with this chemokine receptor. Without the mouse we would not be able to understand the role that chemokines and their receptors play in cancer development and metastasis.