



InFocus

Center of Comparative Medicine & Pathology
Research Animal Resource Center
Laboratory of Comparative Pathology



Individual housing cubicles accommodate reverse light cycle housing and flexibility.

State-of-the-Art S-3 Vivarium Reopens

RARC recently reopened the vivarium on the third floor of the S building located on 71st St. The state-of-the-art facility was extensively renovated with partial support from an NIH Extramural Research Facility Construction Grant. The vivarium contains the Research Animal Surgical Facility (RASf), holding rooms for both large and small animals, procedure laboratories, and a large animal necropsy. RASf, overseen by Dr. Rodolfo Ricart and his staff, contains 2 operating rooms with a portable C-arm fluoroscope, a pharmacy, and a recovery suite. RASf supports large animal model development as well as surgical training courses using large animals. Importantly, the facility is located in close proximity to the Citigroup Biomedical Imaging Center allowing easy transport of animals in which advanced imaging technologies are used.

Ketamine, an Old Drug with Newly Discovered Properties: Implications for research

Ketamine is a dissociative anesthetic agent, whose pharmacological effects were first discovered in 1965.¹ This phencyclidine derivative was first used in human clinical practice in the 1970's but due to its hallucinogenic side effects and the development of new anesthetic agents, its use became restricted.^{1,2} Its current use is limited to provide anesthesia to uncooperative children, battlefield emergencies and veterinary medicine, where it is frequently employed.¹ In the research setting it is commonly used to anesthetize laboratory rodents, notably mice, rats and rabbits, as part of a cocktail of agents including various tranquilizers and/or analgesics.^{1,3}

Ketamine is the only anesthetic available that produces analgesia, amnesia, suppression of anxiety, and has a lack of cardiopulmonary depressant effects.^{1,3} It is believed to induce dissociative anesthesia by reducing activation in the thalamocortical structures and increasing activity in the limbic system and hippocampus.² Ketamine is an effective anesthetic in animals capable of producing anesthetic stages I and II. Its analgesic effects are due to the inhibition of NMDA (N-methyl-D-aspartate) receptors and nitric oxide synthase reducing the production of the neurotransmitter nitric oxide, which both have a role in pain perception.¹ Ketamine is metabolized in the liver by cytochrome P450 and is then excreted via the kidneys.^{2,3}

Clinical effects of ketamine include bronchodilation; increases in blood pressure, stroke volume, heart rate, and cerebral blood flow in spontaneously breathing patients; and, a decrease in ischemic neuronal injury.^{3,4} Cardiovascular effects are attributed to an increase in sympathetic tone. Ketamine does not cause significant respiratory depression at clinical doses, but at higher doses it can decrease respiratory rates.

In some animal models and under certain conditions, ketamine has been



S-3 Vivarium contains a state-of-the-art necropsy



Research Animal Surgical Suite with 2 ORs which can be combined for training exercises



Additional Senior Clinical Veterinarian joins CCMP

We are extremely pleased to announce that Dr. Rodolfo J Ricart Arbona, MLAS, DVM has rejoined the CCMP staff and now serves as a Senior Clinical Veterinarian in RARC serving both the Weill Medical College of Cornell University and the Memorial Sloan-Kettering Cancer Center.

Dr. Ricart received his Masters in Laboratory Animal Science from Hahnemann University School of Medicine. He obtained his veterinary degree at The Ohio State University. After graduating from veterinary school he completed a small animal medicine and surgery internship at Oradell Animal Hospital. Dr. Ricart completed a postdoctoral fellowship in our Tri-Institutional Training Program in Laboratory Animal Medicine and Science in 2009. He received board certification in laboratory animal medicine in 2010 while working at the New York State Psychiatric Institute. His interests include animal models in neuroscience, colony health management and large animal anesthesia.

Dr. Ricart can be reached at 212-746-9265 or email at ricartar@mskcc.org or rjr2004@med.cornell.edu.

NEW LCP SERVICE: Whole Slide Scanning

The Laboratory of Comparative Pathology (LCP) is pleased to announce the addition of a new whole slide scanning service that will complement its existing histology and anatomic pathology services. This technology, an Aperio ScanScope system, produces a high resolution digital version of a slide, which can be used for viewing, sharing, annotating, analyzing, and archiving any slide based material (limited to bright field microscopy at this time). By using Aperio's ImageScope software, available as a free download, slides can be viewed on a continuum of magnifications, from 1x to the maximum scanned resolution (up to 40x). Image analysis can also be performed on whole slide images, but additional software may be required for some types of analysis. For more information and detailed instructions regarding this service, please visit our website at: http://www.med.cornell.edu/research/rea_sup/slide_services.html or contact us at lcp@mskcc.org or 646-888-2422.

Biosecurity Update: Feral Mice Pose a Major Risk

Wild rodents pose a significant risk to our mouse colonies as they carry a number of pathogens that could cause devastating disease outbreaks. RARC implements measures to prevent this from happening. During vivaria construction wall penetrations are carefully sealed to prevent entry of rodents. In addition, we have an active pest control program that traps rodents in our facilities to alert us to any feral incursion.

During the past 10 years we have never trapped a feral rodent inside one of our animal rooms, only cage escapees as determined based on careful observation including coat color, size, shape of the head, the presence of markings or signs of genotyping as well as behavior. In addition, captured rodents are routinely tested for infectious agents; it is easy to differentiate feral from lab bred mice based on their disease profile.

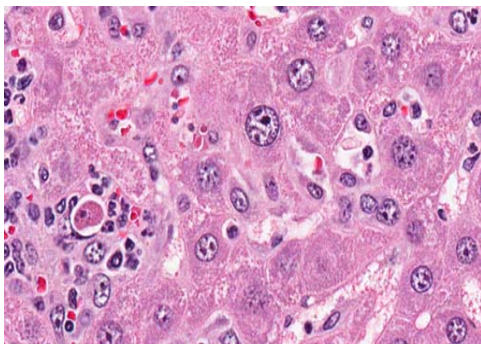
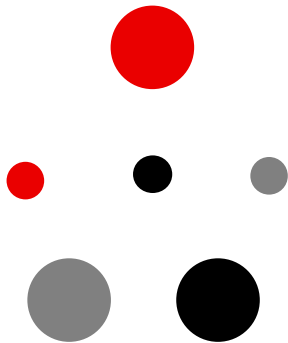
If rodents are observed in laboratories or support areas, or if a mouse escapes in your laboratory and is not captured, please contact Lab Ops to have live traps placed to aid in capturing and removing these mice. If you capture a mouse, please contact RARC immediately and we will evaluate the animal to determine the risk it poses to our facility. We appreciate your collaboration.

Bar Code System Upgrade

Earlier this year, RARC implemented an upgrade to the *eCensus* bar coding system. The protocol number on which the animals are purchased and/or used is now included on and linked to the bar code sticker for easier tracking. Each animal holding room is now stocked with bar code labels which include the PI's name as well as protocol number. For PI's with multiple protocols, bar code labels are provided for each approved protocol. Investigators are responsible for placing the correct bar code label on each new cage that is generated. We have not required changes to bar codes labels on existing cages. Please be very careful when placing new barcodes on your cage cards as there have been several instances in which bar codes with the wrong protocol number were used. If you maintain a stock of bar code labels without protocol numbers, please contact us at RARC_HO@med.cornell.edu for replacement labels and discard your current label inventory. The updated request form can be found on RARC's web site. If you have any questions or concerns, please contact Husbandry and Operations Management.



Dr. Rodolfo J Ricart-Arbona, MLAS, DVM former Fellow of CCMP's Tri-Institutional Training Program returns in a new role.



**Mouse liver, hepatitis, H&E stain.
Image captured from scanned slide.**

Ketamine: Implications for Research, cont. from pg. 1

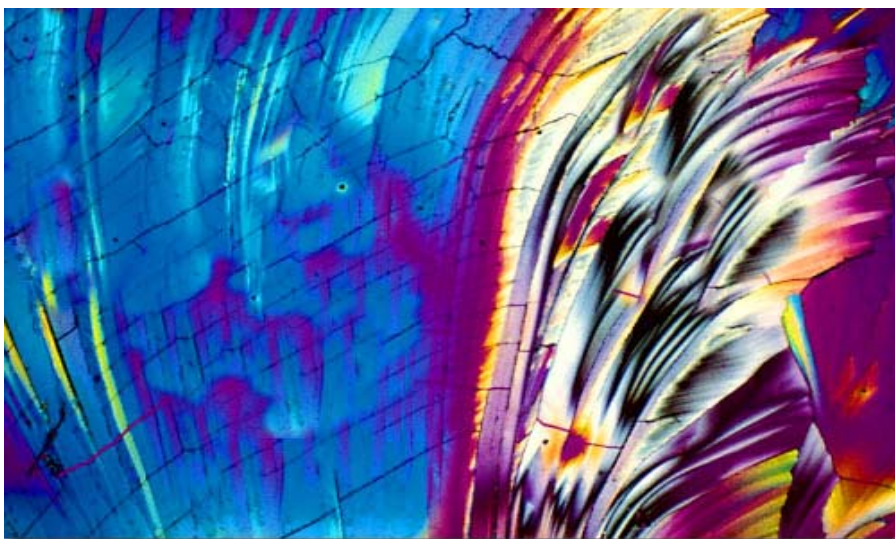


Ketamine HCl anesthetic produces analgesia, amnesia, and suppression of anxiety without cardiopulmonary depression.

found to cause neurotoxicity.⁴ In rodents, extreme inhibition of normal NMDA receptor activity has been shown to lead to poor nerve cell survival, reduction in normal signaling pathways, and acute, temporary vacuolar changes in the brain.^{4,5} Pregnant and neonatal rhesus monkeys may also develop neuronal cell death after being exposed to ketamine for a 24 hour period.^{2,6} Therefore, ketamine may not be an ideal drug to use during procedures that require hours of anesthesia.

Ketamine has also been shown to have immunologic effects. It is anti-inflammatory; in endotoxic patients it reduces pro-inflammatory cytokine production.⁷ In several models of bacterial infection/sepsis, ketamine improved survival and suppressed IL-6, IL-8, IL-12, IFN- γ , and TNF α production.^{7,8} Treatment with ketamine was also shown to significantly decrease activation and phagocytosis by macrophages.^{8,9} Ketamine can also inhibit dendritic cell maturation and prevent them from priming a Th1 type immune response.¹⁰ It can also effect exocytosis in mast cells.¹¹ Ketamine's effects on tumor metastasis is controversial. In one study ketamine was shown to promote tumor metastasis and significantly suppress natural killer cell activity.¹² In another, ketamine was found to significantly reduce, the number of lung metastases.¹³

Ketamine is a very popular and effective anesthetic agent useful for many research applications. Nonetheless, it may be an inappropriate anesthetic to use depending on experimental goals. Careful consideration should be taken when using ketamine in studies highly dependent on immune system function.



Photomicrograph of ketamine (Ketalar). The *Molecular Expressions* Pharmaceutical Collection.

<http://micro.magnet.fsu.edu/pharmaceuticals/index.html>

References:

1. Aroni F, Iacovidou N, Dontas I, et al. Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. *J Clin Pharmacol* 2009;49:957-964.
2. Sinner B, Graf BM. Ketamine. *Handb Exp Pharmacol* 2008:313-333.
3. Craven R. Ketamine. *Anaesthesia* 2007;62 Suppl 1:48-53.
4. Himmelseher S, Durieux ME. Revising a dogma: ketamine for patients with neurological injury? *Anesth Analg* 2005;101:524-534, table of contents.
5. Hayashi H, Dikkes P, Soriano SG. Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. *Paediatr Anaesth* 2002;12:770-774.
6. Stikker W, Jr., Zou X, Hotchkiss CE, et al. Ketamine-induced neuronal cell death in the perinatal rhesus monkey. *Toxicol Sci* 2007;98:145-158.
7. Takahashi T, Kinoshita M, Shono S, et al. The effect of ketamine anesthesia on the immune function of mice with postoperative septicemia. *Anesth Analg*;111:1051-1058.
8. Kawasaki C, Kawasaki T, Ogata M, et al. Ketamine isomers suppress superantigen-induced proinflammatory cytokine production in human whole blood. *Can J Anaesth* 2001;48:819-823.
9. Li CY, Chou TC, Wong CS, et al. Ketamine inhibits nitric oxide synthase in lipopolysaccharide-treated rat alveolar macrophages. *Can J Anaesth* 1997;44:989-995.
10. Ohta N, Ohashi Y, Fujino Y. Ketamine inhibits maturation of bone marrow-derived dendritic cells and priming of the Th1-type immune response. *Anesth Analg* 2009;109:793-800.
11. Fujimoto T, Nishiyama T, Hanaoka K. Inhibitory effects of intravenous anesthetics on mast cell function. *Anesth Analg* 2005;101:1054-1059, table of contents.
12. elamed R, Bar-Yosef S, Shakhar G, et al. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental, and halothane, but not by propofol: mediating mechanisms and prophylactic measures. *Anesth Analg* 2003;97:1331-1339.
13. Forget P, Collet V, Lavand'homme P, et al. Does analgesia and condition influence immunity after surgery? Effects of fentanyl, ketamine and clonidine on natural killer activity at different ages. *Eur J Anaesthesiol*;27:233-240.

ASK RARC: How do I prepare transport boxes for shipping animals?

Rodents to be shipped to other institutions must be transported in an appropriate shipping crate. RARC uses commercial shipping crates to distribute rodents worldwide. To request shipping materials, please submit a completed "Request for Shipping Materials for Rodents" form to the Facility Manager at the vivarium where the animals are housed. This form is available on RARC's website as well in RARC's main office. Please note, requests should be made at least 48 hours prior to use.

"How do I know what to request?"

Each shipping crate can be divided into four compartments. Each compartment can hold one cage of mice. For example, if you are shipping 3 cages of mice, you will need 1 crate, 2 dividers and 3 gel packs. If you are shipping rats or are in need of assistance, please contact RARC's Husbandry and Operations Management at RARC_HO@med.cornell.edu and we will be happy to assist you. We highly recommend taping the dividers in the crates to ensure security. If you are shipping more than four cages, multiple crates should be requested. Shipping materials are picked up at the RARC main office. A copy of RARC's "Guidelines for Packing Mice for Shipment to Other Institutions" is also included with your shipping materials and must be followed.

"How do I actually pack the animals?" You will need the following supplies to complete the packing process: a marker, packing tape, a copy of the health certificate (obtained using RARC's eCertificate system), labels printed with the shipping address, gel pack(s) (hydration supplement), and at least one scoop of rodent feed.

Each crate compartment must contain a packet of shipping gel (the packet must be cut open to ensure the animals have access to the contents) and a scoop of rodent feed. Cage cards, identifying the animals must be attached to the top of the exterior of the crate (if placed inside, the animals may eat them). We suggest you mark the cage cards and the side of the crate for each section with matching numbers or letters so that the cage card can be easily associated with the animals in a specific compartment. We also recommend that the shipper retains a copy of the cage cards in case they are lost in transit.

Finally, the crate lid is snapped into position. You must ensure you start with the correct end of the lid. There are hooks on the side of the lid that has "Live Animals" printed on the edge. This is the edge to slide into place first. Once the

lid is securely snapped into place, it will not easily open. If you have difficulty with this step, please ask a member of RARC's staff for help.

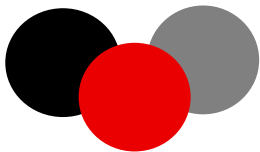
Animals should be packed on the morning of the day they are being shipped. The courier picks the shipping crates up from next to the service elevators in each of the WCMC Facilities. You need to place a copy of the health certificate in an envelope and secure it to the top of the crate with the shipping address noticeable. You should also place additional shipping address labels on at least one side of the crate as an extra security measure. The waybill (if needed) should be left loose on top of the crate.

"Who arranges shipment?"

RARC has established services with two couriers, World Courier and Marken. The shipping lab is responsible for assuming all transportation costs. World Courier requires a waybill which you can obtain from RARC and will be included in the shipping materials when requested. A waybill is not needed if using Marken. If you have further questions about shipping of the animals, please contact RARC's Billing and Purchasing Coordinators @ 212-746-1026.



Standard shipping crate divided into 4 compartments each provided with food and water (gel pack).



After inserting hooks into the lip of the crate, the lid is secured by "snapping" it into place.



Crate ready for shipment with envelope containing the health certificate and cage cards taped to the lid.

UPCOMING SEMINARS

WHAT A DIFFERENCE A LAB MAKES! INTRODUCTION TO THE LABORATORY OF COMPARATIVE PATHOLOGY & GEM PHENOTYPING SERVICE

**Sebastien Monette, DVM, MVSC, DACVP
Comparative Pathologist**

Place: MSKCC, ZRC Room 105
Date: Tuesday, May. 17
Time: 2:00 - 3:30

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HANDLING & EXPERIMENTAL TECHNIQUES IN RODENTS

**Vicki Giroffi, MPS, BS, RLATG,
RARC Education & QA Specialist
WCMC/MSKCC**

Place: MSKCC, RRL Room M-107
Date: Tuesday, July 19
Time: 2:00 - 3:30