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WEILL CORNELL MEDICAL COLLEGE EDITION

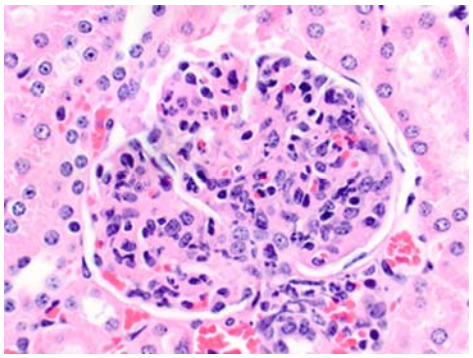
In Focus

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

New Necropsy Laboratory (C-704)

New Necropsy Lab Available for Investigators

The Laboratory of Comparative Pathology (LCP) has recently inaugurated a new state-of-the-art necropsy laboratory at its WCMC facility. This lab (C-704) is used by LCP staff, but is also available to investigative staff to perform necropsies on animals of any size, from mice to swine. The room is equipped with a downdraft necropsy table, two backdraft grossing stations, CO_2 for euthanasia of rodents, and a cooler for carcass storage and disposal. For reservation or questions regarding the use of this room, please contact the laboratory at (646) 888-2422 or lcp@med.cornell.edu.



Kidney (mouse) Spontaneous age-related glomerulonephritis.

Comparative Pathology- Important Tool in Scientific Discovery

Comparative pathology, the study of disease in various species, including humans, has contributed to the advancement of medical knowledge since the cellular basis of disease was first described in the 19th century by Rudolf Virchow, the Father of Modern Pathology. The core of pathology is formed by the study of four aspects of disease: its cause (etiology), mechanisms (pathogenesis), biochemical and morphologic manifestations (molecular and morphologic pathology), and functional consequences (clinical manifestations). Therefore, pathology is an integrative discipline: by combining the basic and clinical sciences, it contributes to a comprehensive understanding of disease. With the rapid growth in the development and use of animal models of human disease, the role of comparative pathology has expanded. As manipulations of the mouse genome has lead to the creation of increasingly sophisticated models, comparative pathology has become essential in their validation and use.

Comparative pathologists contribute a

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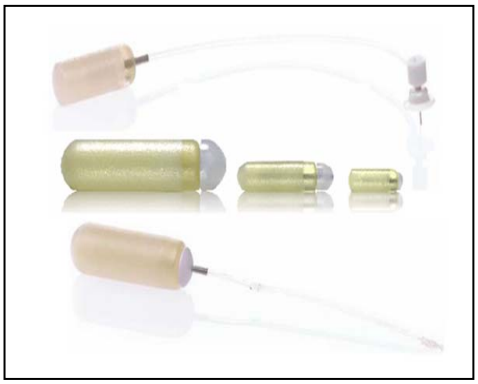

ALZET® pumps with catheter (bottom), brain infusion cannula (top) and polyethylene cap (middle three). From left to right the middle three catheters have reservoir volumes of 2 ml, 200 µL and 100 µL
(From: ALZET® Technical Information Manual).

Infusion Technology Update: Pump Delivery Systems

Testing promising pharmaceutical agents in animals has long been an important research methodology. Each new agent presents study design challenges such as establishing a delivery protocol. This protocol must integrate study duration, agent dose, delivery rate and solubility, delivery site and whether these parameters need to change during the study. Multiple methods exist to deliver these agents according to study needs, ranging from daily parenteral or enteral dosing, continuous rate infusion by osmotic pump or adjustable rate infusion by an external pump. This review discusses established pump delivery systems along with a new novel programmable, refillable tetherless system.

New experimental pharmaceuticals are generally first tested in mice and/or rats. Two technologies have reduced the need for repeated manual dosing by providing continuous dosing- implantable and tethered infusion pumps. Tetherless systems, such as implantable osmotic pumps, have benefited research by reducing researcher workload and animal stress. Osmotic pumps are most commonly used in rodents, but can also be used in larger animals such as non-human primates, pigs and rabbits.(1-2) Each pump delivers at a continuous delivery rate, but multiple volumes and rate settings are available. They are appropriate for use with many experimental agents including small peptides, antibodies and steroids.(3) These pumps can be placed subcutaneously or intraperitoneally with or without an attached catheter for intravenous, intra-arterial, intracerebral, or other location delivery. Serial implantation of these pumps is possible to provide long term delivery, changing delivery rates, washout periods or compound changes. Each implantation requires anesthesia and surgery which increases risks to research through infection or other inflammatory responses.(1,4) These pumps are low cost and require no initial equipment investment outside of surgical tools. The literature on use of these pumps is extensive citing greater than 11,000 articles.

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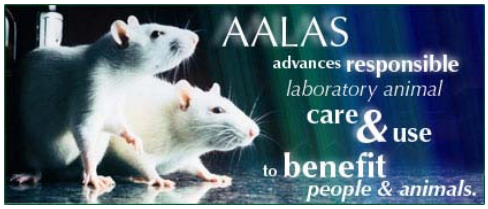


Important Notice:

VICRYL RECALL!

Contact RARC Vet Services for details.

http://sensiblemedicals.co.nz/supplies.

Laboratory Animal Technician Appreciation Week 2010

In February, The American Association for Laboratory Animal Science (AALAS) sponsored Laboratory Animal Technician Appreciation Week or "Tech Week." Tech Week was created a decade ago to recognize the contributions of animal care technicians by highlighting the important role they play in ensuring the health and well being of research animals. The celebration is officially scheduled for the first week of February in coordination with "Groundhog Day" and is meant to symbolize the technicians "coming out of the shadows".

For the past 7 years RARC has celebrated this occasion with a department luncheon for the combined WCMC and MSKCC staff. During the luncheon awards are presented to outstanding staff who have gone above and beyond the call of duty. In an effort to further staff education, we also invite guest speakers to discuss their research with animal. This year Dr. Jonathan Dyke a member of the Citibank Biomedical Imaging Center (CBIC) spoke about his work on atherosclerosis using a guinea pig model and Dr. Pat Zanzonico, Director of MSKCC's Small Animal Imaging Core (SAIC) detailed the state-of-the-art imaging facilities available to our investigative staff.

Please take a moment to thank the technicians who work in your area each day ensuring your animals are receiving the highest level of care.

Popular Suture Product Recall- Vicryl Rapide

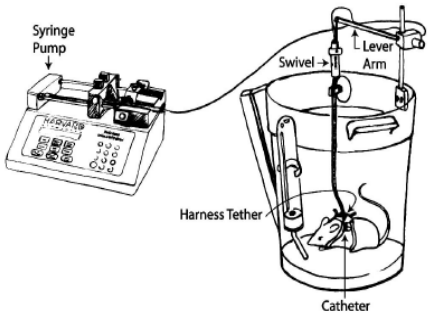
ETHICON has expanded a voluntary product recall of VICRYL RAPIDE suture material. This recall includes 37 lots of product that was produced during the May to June 2007 timeframe. The recall was initiated because of a defect in the packaging which could compromise the integrity of the product leading to premature suture degradation or impaired sterility. If you have VICRYL RAPIDE suture, please locate the lot number on the product and contact Veterinary Services (VS) to determine if that particular lot is included in the recall. VS can assist you with the return and replacement of this product.

Laboratory of Comparative Pathology Expansion

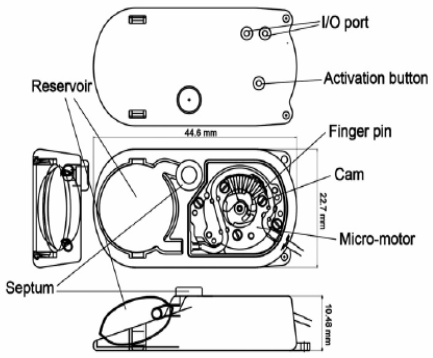
This spring the Laboratory of Comparative Pathology (LCP) opened a new WCMC necropsy and an adjacent histology laboratory at C-708. Combined with facilities at Memorial Sloan-Kettering, the LCP now offers the tri-institutional research community 2 state-of-the art necropsy facilities, which can provide integrated support services like radiography, gross tissue photography and subgross photography of specimens using our dissecting microscope. Other diagnostic and research services include bacteriology, hematology, serum chemistry and tissue collection in a variety of fixatives. The LCP now also offers cryostat sectioning and immunohistochemistry and immunofluorescence, as well as routine paraffin embedding for histostaining and a spectrum of special stains can be performed, such as a trichrome stain or picrosirius red for myocardial infarction assessment. The LCP's histotechnicians are skilled at orienting challenging samples such as mouse embryos or Zebrafish to meet research needs.

The LCP is uniquely distinguished from other prestigious biomedical institutions by providing 3 full time comparative pathologists and a fellow in comparative and genomic pathology to support our research community as well as offering diagnostic services to the large and varied laboratory animal population of our combined institutions. The spectrum of research projects range from imaging, tissue ablation or surgical studies, to small proof of concept experiments and large, pre-clinical safety studies for FDA submission. LCP pathologists offer consultation in experimental design, image, presentation or publication needs. Training sessions in necropsy techniques and tissue collection are also available through the LCP and offered free to the tri-institutional investigative community. The comparative pathologists and technicians of the LCP welcome the opportunity to meet with you and discuss how the expertise at the LCP can aid you in achieving your research goals. To contact the LCP, email: lcp@mskcc.org, call 646-888-2422 or 212-746-3399, or visit our website at: http://www.mskcc.org/mskcc/html/92362.cfm

Infusion Technology Update, cont.



A schematic of a mouse pump-tether system demonstrating modified cage with swivel and lever arm assembly. (From Nolan and Klein, 2002)



Configuration of the iPRECIO™ unit. The bottom view panel, the top view in the middle panel, and the side view in the lower panel. The weight of the iPRECIO™ unit is 10 g. (From: Abe et al. 2009)

A tethered system may be more appropriate for studies which require long term access (days to months) to a catheter for drug delivery or blood withdrawal.(5) Tethered systems also allow for simple alterations to infusion rates and solutions without anesthesia or surgery. These systems are available for animals ranging from mice to non-human primates. Rats are the most commonly used species for tethered infusion.(6) Specialized equipment and in some instances specialized caging is required for this technology.

The tethered catheter can be placed into any vessel, viscera or other cavity. Vascular access is most commonly achieved through the vena cava, tail vein or femoral vein.(5) After placement into the desired location, the distal portion of the catheter is exposed outside of the animal. A tether system then anchors and protects the catheter. These systems come in the form of jackets, harnesses, implantable buttons or tail cuffs. The externalized portion of the catheter extends to a pump delivery system, and requires protection against animal entanglement or chewing. This is achieved by running the catheter through a flexible metal spring attached to a swivel and lever arm that permits animal movement. This configuration prevents many rodent tethered systems from fitting within microisolator caging systems.

A syringe or peristaltic pump is required to drive the experimental compound through the catheter. Syringe pumps are better for low volumes and flow rates. These external pumps allow easy adjustment to the infusion rate and replacement of the infusion solution to test another compound or provide a washout period. Unlike osmotic pumps, the initial set-up cost of these tethered systems is substantial, but long term costs can be low.

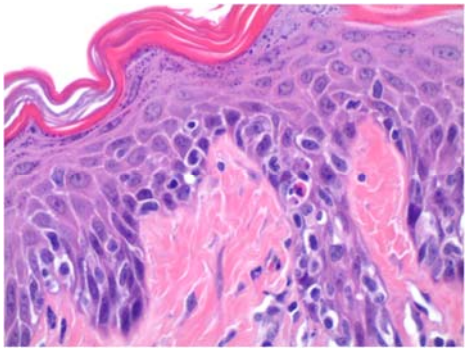
Programmable, ambulatory infusion pump technology has existed in human medicine for decades.(7) Its use in animal research has been reserved for animals of two to three kilograms or greater due to pump size.(7) An implantable, tetherless, refillable, programmable system has been developed for animals ranging in size from rats to larger species (iPRECIOTM, Primetech Corporation, Tokyo, Japan). Use in mice is precluded as each pump weighs approximately ten grams. The company believes that a lighter pump will be available within the next few years (C. Whelan, personal communication, April 10, 2010). This electromechanical infusion pump uses peristaltic action to deliver pharmaceutical agents according to a programmable infusion protocol.(8) Agents can be delivered at a continuous or variable rate. Up to ten variable flow rates (from 1.0 µl/hour to 30 µl/hour with 0.1 µl/hour increments) can be repeated in cycle loops to increase the number of variations in the infusion protocol. These programs can mimic bolus dosing or create dose response curves among other study designs. Also programmable are start and stop times and time delays to allow agent exchange. The life of the battery driven pump is determined by flow rate. The greater the set flow rate, the shorter the available infusion time, i.e. at 30 µl/hour the battery life is approximately 1 week, at 1 µl/hour, the battery life is approximately 6 months.(8)

The pump is designed to fit within the subcutaneous space of the animal. This superficial placement allows percutaneous access to the pump refill septum and underlying reservoir. Under sedation, the reservoir can be refilled to extend the experimental delivery period or emptied and refilled again to change experimental compounds or create washout periods. Two pumps can fit within the subcutaneous space of a rat to increase the amount of compound delivered, and pumps can be replaced as battery life expires. Pump replacement requires surgery.

This technology is still in its initial stages with few publications and proof of principle available. These pumps are associated with considerable cost. At start up, management software must be purchased to program the pumps and each pump is approximately $250.00. However, further development of this technology resulting in smaller programmable, refillable pumps could be of great benefit to research.

1. Strait KR, Orkin JL, Anderson DC, Muly EC. Chronic, Constant-Rate, Gastric Drug Infusion in Nontethered Rhesus Macaques (Macaca mulatta). J Am Assoc Lab Anim Sci.49(2):207-214. 2. Laham RJ, Hung D, Simons M. Therapeutic myocardial angiogenesis using percutaneous intrapericardial drug delivery. Clin Cardiol. Jan 1999;22(1 Suppl 1):I6-9. 3.ALZET Technical Information Manual. http://www.alzet.com/resources/index.html. Accessed April 20, 2010. 4. Hashimoto N, Maeshima Y, Satoh M, et al. Overexpression of angiotensin type 2 receptor ameliorates glomerular injury in a mouse remnant kidney model. Am J Physiol Renal Physiol. Mar 2004;286(3):F516-525. 5. Nolan TE, Klein HJ. Methods in vascular infusion biotechnology in research with rodents. ILAR J. 2002;43(3):175-182. 6. Nolan T, Loughnane M, Jacobson A. Tethered infusion and withdrawal in laboratory animals. ALN. 2008. www.alnmag.com. 7. Crowe M. Infusion technology: past, present and future. ALN. 2008. http://www.alnmag.com. 8. Abe C, Tashiro T, Tanaka K, Ogihara R, Morita H. A novel type of implantable and programmable infusion pump for small laboratory animals. J Pharmacol Toxicol Methods. Jan-Feb 2009;59(1):7-12.

Comparative Pathology, continued from page 1



Skin (mouse) Interface dermatitis caused by graft-versus-host disease.

unique perspective to biomedical research, as they are trained in veterinary or human medicine and pathology, and have a broad knowledge of the anatomy, physiology, and spontaneous pathology of a wide variety of animal species and strains. However, the number of pathologists trained in investigative comparative pathology and devoted to this discipline is small. In an article on the role of comparative pathology in research, Cardiff, Ward, and Barthold (1), noted: "Many investigators are forced to rely on their own 'Do-it-yourself' (DIY) pathology or on a local, albeit inexperienced, pathologist. As a result, the scientific literature is replete with erroneous interpretation of phenotype by DIY pathologists lacking expertise in mouse pathology. [This situation] has led to embarrassing and egregious errors. These are not trivial misinterpretations. Some … have had expensive consequences". This excerpt is followed by examples of unsubstantiated lesions, erroneous phenotypes, and misinterpretation of normal anatomical structures as lesions, which were published in high impact journals.

The interpretation of neoplastic and preneoplastic lesions in genetically engineered mice (GEMs) is an example that illustrates this problem. The study of GEM models of cancer represents a unique opportunity for understating the natural history of cancers: the correlation of molecular alterations with morphologic evidence of neoplastic transformation and progression can yield critical insights into cancer pathogenesis. However, preneoplastic and neoplastic lesions in new GEMs often represent a diagnostic challenge, even to the most experienced pathologists, and interpretation by untrained investigators has lead to erroneous conclusions (1). For this reason, funding agencies and editorial boards increasingly require the participation of a pathologist in cancer studies involving animal models. Additionally, the recognition of specific "genetic signatures" in animal tumors has become an interesting aspect of comparative pathology (2). As wisely stated by Rosai (3) as he discussed the value of H&E sections, "The amount of information that the examination of these samples [by a skilled observer] has provided is staggering. This should not be too surprising. After all, the microscopic appearance of a tumor … represents the grand synthesis of thousands of genes working in concert and sometimes in opposition".

Pathology has become essential in the phenotyping of new GEMs, not only for cancer models but for a wide variety of disease processes. By adopting a comprehensive approach which includes macroscopic and microscopic examination of all organ systems, standardized documentation and diagnosis of lesions, and incorporation of hematology and serum chemistry data, pathology contributes to the complete characterization of new GEMs. This approach has often led to the discovery of unexpected phenotypes which may not have been recognized by other methods.

CCMP's Laboratory of Comparative Pathology provides services and expertise in pathology and all major disciplines of laboratory medicine. The staff of the LCP is composed of three anatomic pathologists who are board certified by the American College of Veterinary Pathologists (ACVP), a consultant ACVP-certified clinical pathologist, one resident and one fellow in comparative pathology, and eight technologists with expertise in necropsy, histology, immunohistochemistry, hematology, serum chemistry, microbiology, parasitology, and serology. The primary role of the LCP staff is to provide analysis and diagnostic interpretation on animal specimens, but they are also available for consultation on the planning of studies and the choice of animal models, as they are familiar with the anatomy, physiology, and naturally occurring pathology of a wide variety of species and strains.

The LCP is open from Monday to Friday, 9 am to 5 pm, and can be reached at 646-888-2422 or lcp@med.cornell.edu. Additional information is available at http://intranet.med.cornell.edu/research/rarc/pat_lab/radl.html

References:

1. Cardiff RD, Ward JM, Barthold SW. One medicine – one pathology: are veterinary and human pathology prepared? Lab Invest 2008; 88:18-26.
2. Rosner A, Miyoshi K, Landesman-Bollag E, et al. Pathway pathology: histological differences between ErbB/Ras and Wnt pathway transgenic mammary tumors. Am J Pathol 2002; 161:1087-1097.
3. Rosai J. Why microscopy will remain a cornerstone of surgical pathology. Lab Invest 2007; 87:403-408.

UPCOMING SEMINARS

TECHNICALLY SPEAKING - INTRODUCTION TO RARC's VETERINARY SERVICES

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Christine Lieggi, DVM, DACLAM, Associate Director, Head of Veterinary Services

Place: MSKCC, RRL Room 116
Date: Wednesday, Sept. 22
Time: 2:00 - 3:30

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WHAT DO IACUC'S WANT?

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Andrew Nicholson, DVM, Ph.D., Director, Animal Research Protections Program, WCMC/MSKCC

Place: MSKCC, RRL Room 116
Date: Wednesday, Oct. 20
Time: 2:00 - 3:30