Small Animal Imaging Center Design, David B. Stout Ph.D., Arion F. Chatziioannou Ph.D., Timothy P. Lawson DVM, Robert W. Silverman BS, Sanjiv S. Gambhir MD Ph.D., and Michael E. Phelps Ph.D., September 2006

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The UCLA Crump Institute for Molecular Imaging was designed and built to support the research interests of a wide range of investigators from multiple disciplines.

Biomedical research utilizing small animals, such as mice and rats, has expanded dramatically in the past few years as molecular biology and imaging techniques open new opportunities to investigate models of disease. The growing number of mouse and rat experiments, coupled with an increasing number of dedicated small animal imaging systems, such as microPET®, optical, microCAT, microMR, ultrasound, and microSPECT, has necessitated a common technical center for imaging small animals using these devices and to guide further technology development to meet the scientific needs for which these technologies are employed. These new imaging systems provide investigators unprecedented abilities to examine and measure in-vivo biological and pharmacologic processes over time in the same animals. Increasingly sophisticated molecular probes and tool sets allow researchers to examine multiple processes at once in the same animal by using different light wavelengths (optical), various molecular imaging probes (PET, SPECT), and different contrast agents (MR, CT), as well as to define the anatomical structures in which these processes take place. This, in turn, has led to a demand for comprehensive, mul-timodality imaging facilities that can house animals, support imaging systems, and provide investigators with the tools, methods, and other infrastructure necessary for successful imaging experiments. At the UCLA Crump Institute for Molecular Imaging, we have designed and built such a facility to support the research interests of a wide range of investigators from multiple disciplines. The facility includes support for investigator training, study scheduling, data acquisition, archiving, image display, and analysis. The design requirements to satisfy both research and regulatory oversight have been critically examined to create a streamlined process for handling animals and data.

At our institution, the facility must be capable of handling large numbers of animals from multiple investigators who utilize a wide range of imaging modalities, including microPET,® bioluminescent/fluorescent optical imaging systems, microCAT, and digital autoradiography (Figure 1). Each of these systems has various support requirements, including: dose-drawing equipment, well counters, anesthesia, isolated imaging specifications, maintenance and monitoring of biological functions, biosafety cabinets, computer infrastructure, data archiving, and image analysis tools.

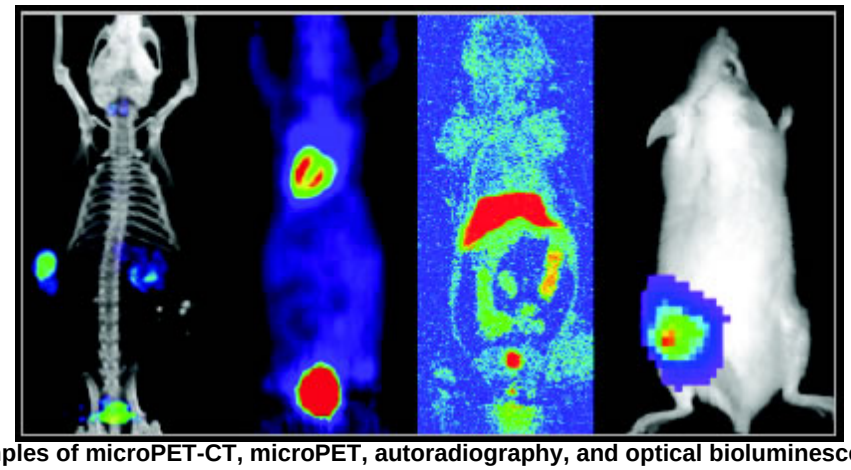

Figure 1. Examples of microPET-CT, microPET, autoradiography, and optical bioluminescence images in mice.

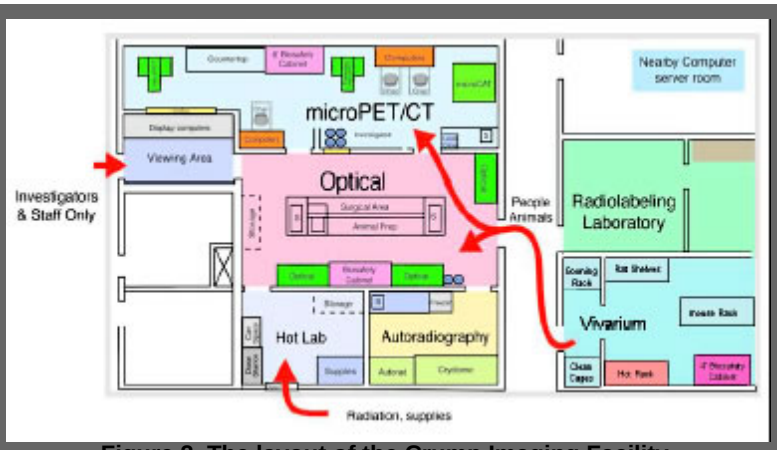

Figure 2. The layout of the Crump Imaging Facility.

The complexity of imaging systems and animal models requires that the imaging center provide specialized training and support, even for investigators who have a wide range of familiarity with imaging processes. For some imaging methods, such as optical imaging,1this only requires appropriate training and occasional support for supplies, service, and software upgrades. Other imaging methods, such as PET,2,3require dedicated staff, cyclotron time, and radiochemistry support for experiments. In particular, the use of ionizing radiation (radioisotopes), instruments that produce radiation (microCT4), or require radiation for use and calibration (microPET®) require oversight by staff trained in radiation safety.

To meet the demands of investigators, we have designed, built, and put into routine use a comprehensive small animal imaging technical center. A large number of design criteria were considered to ensure the best workflow of animals, personnel and data through the facility.

Design Issues

Facility Layout

Equipment layout should be designed to optimize the workflow of people, animals, and radiation pathways and exposure. The detailed specifications for each device are available from the equipment vendors and attention must be given to provide proper power, heating, cooling, and access to the various systems. Consideration must also be given to allowing space for oxygen tank replacement, investigator cart storage, ability to open instrument access panels, and sufficient space for multiple people to work in the same room together.

Animal Housing, Handling, and Preparation

An essential part of the imaging facility is an adjacent animal housing and preparation location. This room has a dedicated “hot” rack for cage storage of radioactive animals, a ventilated cage rack for mice, shelves for rat cage storage, and a biosafety cabinet. When investigators bring their animals for imaging experiments, they can store the animals for the duration of the study in this vivarium space. This saves considerable time and regulatory oversight for all involved parties, as well as standardization of research approvals. The inclusion of this space in our facility is the single most appreciated support feature by both users and the oversight agencies.

Using Immunocompromised Animals

The majority of imaging experiments make use of immunocom-promised animals, primarily SCID and nude mice. To maintain the health of the animals over the course of imaging experiments, which can last several weeks, a pathogen barrier must be maintained around the animals at all times. We have addressed this challenge by constructing imaging chambers to house the animals during the imaging process (Figure 3). Mice are positioned and placed within the chamber using sterile techniques inside a biosafety cabinet, which provides a sterile laminar flow of air over the workspace. Chambers have been designed for both microPET® and microCAT imaging (Figure 3a)5, as well as for optical imaging (Figure 3b).

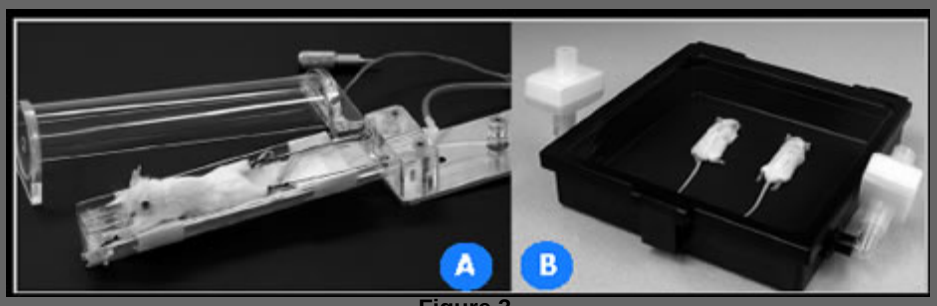

Figure 3.
Chambers designed for imaging mice in microPET/CT (A) and optical systems (B).

Anesthesia and Standard Operating Procedures

Imaging experiments are typically designed to non-invasively monitor biologic processes over time, either in the same animals on different days or in short-term individual experiments using a group of animals undergoing the same procedure. A common procedure is to look at a baseline condition and compare image data acquired at various time points after an intervention, which might be viral vectors, gene activation/deactivation in transgenics, cell transplants, drug therapies, or radiotherapy. Using the same methods to acquire data, image comparisons over time takes advantage of any systemic biases, since it is presumed that conditions are the same in both measurements. It is therefore advantageous to create standard operating procedures (SOPs) for all imaging work. SOPs are also useful for obtaining approval from review committees and regulatory agencies, since nearly all the imaging work in the facility follows the same methods and protocols.

All microPET® and microCAT imaging in rodents is done using the imaging chamber (Figure 3a). The chamber is designed to provide gas anesthesia, which maintains a constant level of sedation and avoids movement artifacts that can occur when injected anesthetics begin to wear off. A constant level of anesthesia is essential for all imaging systems, particularly those sensitive to any movement during acquisition such as microCT and microMR. By providing gas anesthesia, the need for investigators to purchase and track usage of controlled substances like ketamine or pentobarbital is reduced or eliminated. Animals can become hypothermic in as little as five minutes at standard room temperature, due in part to the large airflow in the facility to cool the imaging systems. For this reason, we also heat all of the imaging chambers and boxes used to induce anesthesia and keep animals sedated during tracer uptake and imaging.

In collaboration with a vendor, we designed a gas anesthesia system capable of handling all imaging requirements in an easy to use manner (Figure 4). The manifold system has orifices that provide constant specific flow rates to various locations, eliminating the need for flow valves that require constant adjustments as demand for anesthesia varies. Anesthetic gas is turned on or off using a simple cutoff switch located at each point of use location. All anesthetic waste gases are captured using a separate manifold system and vented out of the facility, eliminating the expense and need for constant changing of charcoal filters.

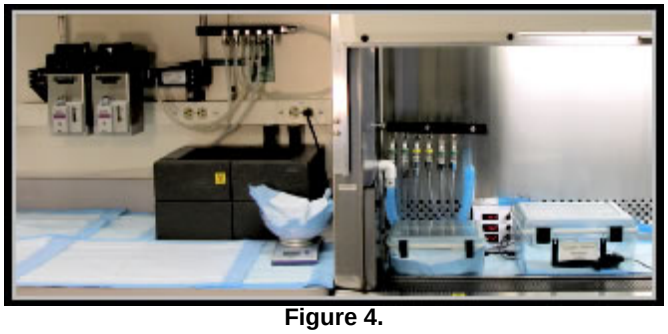

Figure 4.
Wall mounted gas anesthesia vaporizers and manifold system, adjacent biosafety cabinet with heated induction boxes. Note lead enclosure for radioactive sharps container.

MicroPET® and MicroCAT™

Of all the equipment in the facility, the microPET® imaging system requires the highest level of planning and support. Use of the system requires either purchasing radioisotopes or obtaining them from a dedicated cyclotron with automated, semi-automated, or traditional chemical synthesis support. In either case, scheduling of experiments, delivery and use of radiolabeled probes, imaging study, tomographic image reconstruction, and archiving of large image data require a high degree of personnel support, instrumentation, and coordination. These systems require ancillary equipment such as gas anesthesia, biosafety hoods, counter space, and storage space for supplies and incidental equipment, and additional computers for database and image display. Space must also be provided for lead brick shielding to house sources, radioactive needle containers, hot animals, and for unspecified shielding needs.

Optical Imaging

Our facility houses three bioluminescent optical imaging systems,1two of which are capable of imaging fluorescence.6Investigators attend a two-hour training seminar that covers scheduling, use, and archiving of data, followed by a hands-on training session. Most people do not need further training or help beyond this initial session. All supplies, including Luciferine, Coelenterazine, solutions, gloves, filters, etc. are provided as part of a recharge fee. Since the optical systems are easy for investigators to learn and operate, and are used in a more qualitative fashion, these instruments are located in a central core area that is available for use around the clock. Access to imaging any day or time is particularly useful for imaging biological processes, which progress on their own timeframe and may not be well suited to a typical workday/weekly schedule.

Autoradiography

Though the cryomicrotome and digital imaging system are less frequently used, they are a critical part of the

validation of new imaging compounds labeled with 14C, 3H, and positron-emitting radionu-clides.7The infrequent use of these devices by investigators makes it more efficient, although not necessary, to use the facility staff to run the equipment.

Data Tracking, Archiving, and Retrieval

For microPET®and microCAT, the staff assigns each new animal a unique ID number using a simple Excel spreadsheet. Each imaging session is assigned a specific ID number, which is generated from our internal archiving website after entering information related to the investigator, radiolabeled probe, and animal ID.8The session ID is used to retrieve images and is the primary identification of the imaging experiment. All information related to the specific imaging session is entered into a database, including the injected probe, injection time, reconstruction parameters, and any information that the investigator may specify.

Results and Discussion

In the three years since the creation of the imaging facility, over 30,000 imaging experiments have been conducted. These include dual and tri modality imaging sessions and longitudinal studies using the same animals, sometimes lasting up to several months.9,10Investigators have benefited from the consolidation of the imaging devices, associated technologies, and the support of centralized staff. Bringing together the investigators into one facility has also increased the interaction between different research groups and enhanced the collaboration and shared learning of techniques. Students, staff, and post-docs have the opportunity to learn from each other, particularly the small tricks and details of animal imaging that can save time and resources, as well as from their diverse science backgrounds and interests.

The gas anesthesia systems, combined with integrated heating to prevent hypothermia, has nearly eliminated loss of animals during the imaging procedures and stabilized body functions during experimental protocols. By providing gas anesthesia to all investigators, we have also reduced the amount of time due to complications associated with each investigator individually purchasing, storing, and handling paperwork for the use of injectable anesthetics that are controlled substances, such as ketamine, xylazine, and pentobarbital.

The centralized vivarium space located adjacent to the imaging facility has also saved considerable time for researchers by eliminating the need to locate and transport animals to and from remote animal storage locations. The separation of radioactive animals to a dedicated rack for isotope decay enables the veterinary staff to service the non-radioactive cages, thus investigators do not need to worry about animal husbandry, except for the short time during radioactive decay. Inclusion of a biosafety cabinet allows for cage changing of immunocompromised animals and also a location for procedures such as viral injections. Access to the vivarium is simplified by having the same badge-activated locks as the adjacent imaging facility; there are no special codes or keys required.

The co-localization of equipment has also facilitated the training of new researchers. The facility was designed to have sufficient space to hold small workshops and is located adjacent to a conference room with suitable space for holding training seminars for up to 30 people. Part of the ongoing support for the facility includes routine training, research seminars, and workshops, so the ability to hold seminars nearby and sufficient space to hold workshops within the facility is a useful feature.

Investigators have benefited from the central facility and the use of SOPs through faster authorizations from animal use, radiation, and biosafety committees. The oversight committees also benefit from the reduced time and questions when reviewing authorization requests, having a centralized location for inspections and the knowledge that the imaging experiments are conducted using SOPs, usually under the supervision of the facility manager. With the fast pace of research, the ability to get quick authorizations and fast access to the imaging systems and the analysis of data resulting from them improves the overall quality of research, satisfaction of the users, and accelerates their science.

Conclusions

We have designed, built, and put into routine use a small animal imaging facility to handle the needs of a wide range of imaging experiments using microPET®, microCAT, bioluminescence, and fluorescence optical imaging systems and autoradiogra-phy. The overall design facilitates the increasingly common use and comparisons of multiple imaging modalities applied to a wide range of biological and pharmacological problems. Consolidation of the imaging devices centralizes staffing and increases communication and collaboration between investigators, creating a more productive environment that better utilizes our resources to support a large number of investigators from many different disciplines.

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