
Introduction

Bioimaging of Laboratory Animals: The Visual Translation of Molecular Insights

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A Department of Energy report released in 1987 stated in a visionary prediction that “Knowledge of the human genome is as necessary to the continuing progress of medicine and other health sciences as knowledge of human anatomy has been for the present state of medicine” (Barnhart 1989). The pursuit of this knowledge has marked an era of rapid genomics-based discovery that continues to yield unique insights into connections between disease and molecular factors. One key method for transforming these initial insights into direct evidence of disease pathogenesis is molecular imaging. Imaging techniques that have been customized for laboratory animals provide scientists with the unprecedented ability to link detailed molecular understanding with the complexity of whole organism physiological responses and anatomical detail. The advancement of knowledge derived from the mammalian genome is likely to depend on the context provided by the unique blending of our knowledge of anatomy with the translational application of imaging technology.

The primary objective of this *ILAR Journal* issue focused on laboratory animal imaging is to provide readers with a compendium of reviews that describe the methods, the limitations, and a few examples of the most common applications of small animal imaging to human disease. Because most disease processes are dynamic, there are inherent limitations to using static tissue-based techniques to study dynamic processes. Among these is that a large number of animals is needed for every experiment to enable the processing of tissue at given time points of interest, and histopathological examination of these tissues using standard microscopy is a daunting task. In addition, there is a degree of variability introduced when the control level of a factor is determined by comparing different animals instead of using each animal as its own control. Experimental designs of longitudinal studies pose particular limitations because a certain degree of understanding about the kinetics of

a disease process is critical to the appropriate timing of tissue collections.

The imaging modalities available for use with laboratory animals provide a means to explore the molecular mechanism of several diseases, minimize many of the limitations of static tissue-based techniques, and, most importantly, decrease the numbers of animals required. In fact, depending on the application, it is possible to reduce the number of animals required per study by as much as 80% to 90%. This feature is noteworthy because, perhaps unique to the *ILAR Journal*, there is an intentional effort to publish reviews that include considerations specifically relevant to animal care and use.

The first article, by Brenda Klaunberg and Judith Davis, presents an overview of key considerations for laboratory animal imaging center design. This review not only is relevant to readers considering new facility design but also can provide a series of quick checks for existing centers as well as strategies for improvement. Contributing authors Isabel Hildebrandt, Helen Su, and Wolfgang Weber then discuss anesthesia for in vivo imaging of small animals in the context of how animal preparation differs among imaging modalities, and how the imaging procedures themselves can affect animal physiology. A general overview of practical considerations in rodent cardiac imaging is provided by Kennita Johnson as a segue to detailed reviews of specific imaging techniques. This article is a good source of baseline information about the particular challenges of cardiac imaging.

The contributions of imaging technology to the biomedical sciences are incontrovertible. In fact, one has only to list the number of Nobel prizes awarded to scientists in nuclear magnetic resonance (NMR) and magnetic resonance imaging (MRI) to appreciate the importance and recognition this field has received. These include the 2003 Nobel Prize for Physiology and Medicine awarded to Paul Lauterbur and Peter Mansfield for the development of MRI. Earlier NMR-related Nobel Prizes were awarded for Chemistry (Kurt Wüthrich in 2002, Richard R. Ernst in 1991) and Physics (Felix Bloch and Edward M. Purcell in 1952 and Isidor I. Rabi in 1944; <http://nobelprize.org>).

The first manuscript describing the MRI of a rat was published almost 25 years ago, and the technique continues to evolve and expand the scientific advances made possible

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by the application of MRI to laboratory animals. Two recent reports showcase the ever expanding potential for MRI application to laboratory animals. The use of dynamic contrast-enhanced MRI (DCE-MRI) to detect vascular permeability and study the inflammatory response and vascular remodeling associated with chronic airway inflammation in rat models is a prominent example of this expansion (Tigani et al. 2007). Moreover, the application of DCE-MRI in this context highlighted the translational potential for this method to study vascular permeability in humans in the clinical setting. In another study, MRI was used effectively to overcome one of the critical limitations in the stem cell field, with the detection and following of transplanted stem cells over a period of days in live animals (Ebert et al. 2007).

In this issue, Bastiaan Driehuys and colleagues provide a timely review of MRI that includes a discussion of the technical advances of this established technology. An exciting extension of MRI, functional MRI (fMRI), is presented by Anna Roe and Li Chen, who review the use of high-resolution fMRI to obtain maps of cortical activation in nonhuman primates. The application of this technique to brain physiology is an evolving area. One of the most promising aspects of fMRI is that it can provide maps of brain activities with millimeter spatial resolution. Deeper insight into the functioning of a neuronal network has been achieved by adding dynamic information to functional maps.

Over the last decade, many diagnostic imaging techniques developed for human use have become available for application to disease processes in laboratory animals. These include computed tomography (CT or microCT), single photon emission computed tomography (SPECT), positron emission tomography (PET), intravascular ultrasound, optical coherence tomography, near-infrared fluorescence and spectroscopic imaging, and bioluminescence imaging. CT, PET, and SPECT can also provide information that makes it possible to produce 3-dimensional (3D) images. A comprehensive review of small animal PET imaging was contributed by Gary Hutchins, Michael Miller, Victor Soon, and Timothy Receveur. This well-established clinical technique has only recently been effectively translated for use in laboratory animals. These authors make a compelling case for the strong translational potential of small animal PET while providing the reader with relevant discussion of some of the hurdles that must be addressed to fully engage the potential of this technology.

Multispectral imaging allows the separation of five or more fluorophores, with each signal quantitated and visualized separately. There are several advantages of this technique with respect to sensitivity, quantitation, and multiplexing, and these are thoroughly characterized in the article by Richard Levenson, David Lynch, Hisataka Kobayashi, Joseph Backer, and Marina Backer. These authors provide evidence to support the view that microscopy-based multispectral techniques offer scientists an excellent complement to other in vivo imaging techniques.

Similarly, multiphoton microscopy can be viewed as a cell-based, functional complement to anatomic imaging. The availability of labeled fluorophores enables investigators to study dynamic events with subcellular resolution in the functioning organ. As outlined for multispectral imaging, the use of multiple and varied fluorophores makes it possible to examine three different or interactive processes simultaneously. Furthermore, the extended ability to obtain 3D volumetric data makes quantitative time-based analysis possible. Kenneth Dunn and Timothy Sutton provide an elegant review of this emerging technology in their article entitled “Functional Studies in Living Animals Using Multiphoton Microscopy.”

The discovery of bioluminescence (a form of luminescence, or “cold light” emission) has been applied for use as a biotechnology tool via luciferase systems (Contag and Ross 2002). These systems have been widely used in biomedical research, and bioluminescence imaging represents the live animal application of this technology. Kurt Zinn and colleagues provide a comprehensive review of the current uses of noninvasive bioluminescence imaging in small animals.

Animal studies continue to enhance our understanding of the genetic, molecular, and cellular components of human disease, and the use of imaging can in some cases promote direct animal-to-human translational application. The development of novel animal models will extend our understanding of the biological basis of many diseases and yield a greater appreciation for the impact of any number of factors. In “Brain Imaging in Nonhuman Primates: Insights into Drug Addiction,” Michael Nader and Paul Czoty describe a salient example of success and opportunity in translating preclinical understanding of an extremely challenging and complex disease from animals to humans. A recent review on mouse imaging in drug discovery offers another example of translational benefits from a preclinical animal model in the context of pharmaceutical development (Beckmann et al. 2007).

I believe the articles in this issue of the *ILAR Journal* provide a useful general resource both for experts in this area and for the novice on this vast topic. The contributing authors have included many references for previously published review articles. I hope that this issue will spark the pursuit of broader understanding and widespread application of imaging methodology for laboratory animals.

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