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Laboratory Animal PET/SPECT-CT Imaging for Biomedical Research

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Abstract

Small laboratory animal models are being increasingly used as a biomedical research tool in several human diseases such as cancer, cardiovascular diseases, endocrine disorders and obesity. For the last couple of years, molecular and functional imaging become a powerful techniques for studying spatial and temporal distribution of new drugs and their target affinity non-invasively in animal models. Hence non invasive imaging modalities such as positron emission tomography (PET), single photon emission computed tomography (SPECT), X-ray, magnetic resonance imaging, fluorescence and bioluminescence have emerged for rapid and accurate screening of the new molecules. This review focuses on nuclear imaging modalities mainly SPECT and PET, which allow whole body survey of the animal and quantitation of target affinity. While establishing such facilities, accessibility to vivarium, work flow, availability of radiotracers, regulatory requirements and trained human resource needs to be considered. The readout data requires dedicated software for viewing and quantitation eg. VIVID, PMOD, AMIDE and Micro View. Therefore, a perfect amalgamation of instrumentation, facility logistics and work flow that is required for efficiently managing such a facility has been elaborately reviewed in this article.

Key words: Small Animal Imaging, microPET, microSPECT, microCT, preclinical imaging

Introduction

Small laboratory animals such as mice and rats have been integral part of biomedical research since past few decades (Mukerjee, 1997). Recently, the role of these animals expanded dramatically in the last decade due to introduction of multimodality imaging techniques (Koo *et al.,* 2006). The opportunities opened up to investigate new animal model systems non-invasively in several fields of biomedical research such as cancer, cardiovascular diseases, endocrine disorders and obesity(Sanz and Fayad, 2008){Kang`, 2003}. The dedicated small animal imaging systems such as micro PET (Positron Emission Tomography), microSPECT (Single Photon Emission Computed Tomography), microCT (X-ray Computed Tomography), Optical, microMRI (Magnetic Resonance Imaging), and Ultrasound has opened new avenues to refine and revisit several fields of biomedical research involving small rodents (Jiang *et al.*, 2000; Holdsworth and Thornton, 2002; Wernick and Aarsvold, 2004; Ntziachristos *et al.,* 2005; Kagadis *et al.*, 2010). *In vivo* molecular and functional imaging of animals has become a powerful approach for studying spatial and temporal distribution of new drugs and their target affinity non-invasively in animal models (Shah *et al.,* 2014; Chaudhari, 2015). These imaging technologies are in demand due to their unprecedented abilities to monitor and measure in vivo biological and pharmacologic processes as a function of time in the same animals. Similarly, there is an increase in availability of several imaging probes for molecular and functional measurement for PET and SPECT and different contrast agents for CT (Dean and Plewes, 1984; Ralph and Umar, 2001; Cai and Chen, 2008). These developments have led to need for comprehensive, multimodality imaging facilities that are well equipped and planned for handling radioisotopes, labeling compounds, dose administration in laboratory animals, housing these animals after administration of radioactive probes for performing successful imaging experiments (Cook *et al.,* 2012). At ACTREC, Tata Memorial Centre, we have planned and established such a facility to support research interests of multiple disciplines. This facility includes support for training, study scheduling, data acquisition, archiving, image display, and analysis. The facility designed to satisfy both research and regulatory requirements and critically planned to create a logistic workflow for process of handling radioisotopes (Cai and Chen, 2008), animals and data. Along processes for procurement of PET and SPECT radiotracers, regulatory requirements for transport of radiotracers from the source facilities were set (King *et al.,* 2002).

The important factor in designing of such facility includes consideration for different animal experimentation protocols and procedures. The short-term animal holding space is a key consideration in this regard. The space preferably adjacent to imaging suite having individually ventilated cage racks is suitable for holding animals. This holding area has animal cage changing station with filter-top assembly to prevent radioactive contamination while changing cages in the holding room and for personnel safety in this area (Klaunberg and Davis, 2008).

Separate work area for radioactive work and animal experimentation is required for preparation of animals before imaging studies. Radioactive work area should be separate for PET and SPECT radioisotopes while animal experimentation area for performing dose administration, minor animal experimentation procedures such as vein catheterization, oral dosing, blood withdrawals etc. should be adjacent to imaging room (Francis, 1991).

Instrumentation:

The instrumentation details of microPET, microSPECT and microCT has been mentioned in detail (Wernick and Aarsvold, 2004). There are few completely digital systems are available and as an example details about GE Flex Triumph trimodality has been explained here (Fig-1). GE Flex Triumph microPET /SPECT and microCT is a trimodality imaging platform on single axis, with advanced detector system providing high resolution images of laboratory animals (Larsson, 2011). The scanner is well equipped with preplumbed inhalation anesthesia for laboratory animals while imaging procedures are performed (Hildebrandt *et al*., 2008; Larsson, 2011). Isoflurane is a safe anesthesia for rodents and does not interfere significantly with tracer distribution in routine imaging work (Hildebrandt *et al.,* 2008). The imaging beds are also equipped with temperature, respiratory sensors and ECG measurement device. Heating mechanism in imaging bed maintains animal body temperature while imaging procedures prevent mortality of the animals. Image reconstruction, processing, visualization, analysis and quantitation are carried out with various software such as AMIRA, VIVID, PMOD and AMIDE (Zaidi, 2013). The PET tracers are obtained from Medical Cyclotron Facility, RMC located in Tata Memorial Hospital Parel, Mumbai on as and when required basis. Similarly SPECT isotopes are obtained from in-house radiopharmacy.

microPET:

PET is being used increasingly to advance the understanding of cellular and molecular processes that are altered in cancer initiation and progression. Compared with other molecular imaging technologies, PET enables highly sensitive and quantitative measurements of biological and biochemical processes *in vivo* through specific labeling of organic compounds (or close analogs) with positron emitters, such as ^{18}F and ^{11}C (Kumar *et al.,* 2014; Bose, 2015). LAB PET4 microPET scanner has one-to-one coupled phoswich-Avalanche Photodiode (APD) detector. A single APD sitting at an angle is optically coupled with a pair of scintillation crystals consisting of one Lu1.9Y0.1SiO5 (LYSO) and one Lu0.4Gd1.6SiO5 (LGSO) with the size of 2 x 2 x 12/14 mm^3 respectively. This side-by-side configuration provides high

Fig-1. GE Flex Triumph microPET /SPECT and microCT trimodality scanner**.**

spatial resolution and the scintillators are coupled directly to the APDs to achieve optimal energy resolution (Schambach *et al*., 2010; Yao *et al.,* 2012).

microSPECT:

micro-SPECT systems in preclinical research have witnessed tremendous growth in last decade. ACTREC has advanced digital single head micro-SPECT scannerhaving solid-state CZT (Cadmium Zink Telluride) detector. CZT detector technology enable multiple radioisotope studies due to its high energy resolution (4.5%) (Verger *et al.,* 2007). The detector is mounted on a rotating gantry, which is common for microSPECT and microCT scanner. There are no photomultiplier tubes unlike conventional NaI gamma camera system. This scanner is well equipped with high resolution parallel hole, single and multiple pinhole low energy collimators, which are useful for imaging animals in various research protocols. The achievable resolution using this scanner is ~0.5 mm after date reconstruction (Khalil *et al.,* 2011).

microCT:

The anatomical imaging in preclinical cancer research provides important information about the structural changes in the bone and soft tissue (Jaiswal *et al.,* 2013; Thummuri *et al*., 2015). microCT is commonly used for localization purpose, precise information on location of the lesion can be achieved by co-registration with microPET / SPECT images. The other applications of microCT includetumor vascularity mapping, bone metastasis imaging and evaluating novel contrast agents (Jaiswal *et al.,* 2013). GMI XO microCT scanner provides images with ~ 50 microns resolution andallows faster whole body image acquisition.High resolution (HRES) scanning is used for specimens and in this mode 15-30 micron resolution can be obtained (Schambach *et al.,* 2010).

Facilities engaged in animal imaging work for various projects from academia and industryshould be approved by the regulatory authority and the facility should be appropriately designed with scanner room, radiopharmacy, animal experimental area, animal holding room and radioisotope waste storage room (Klaunberg and Davis, 2008).

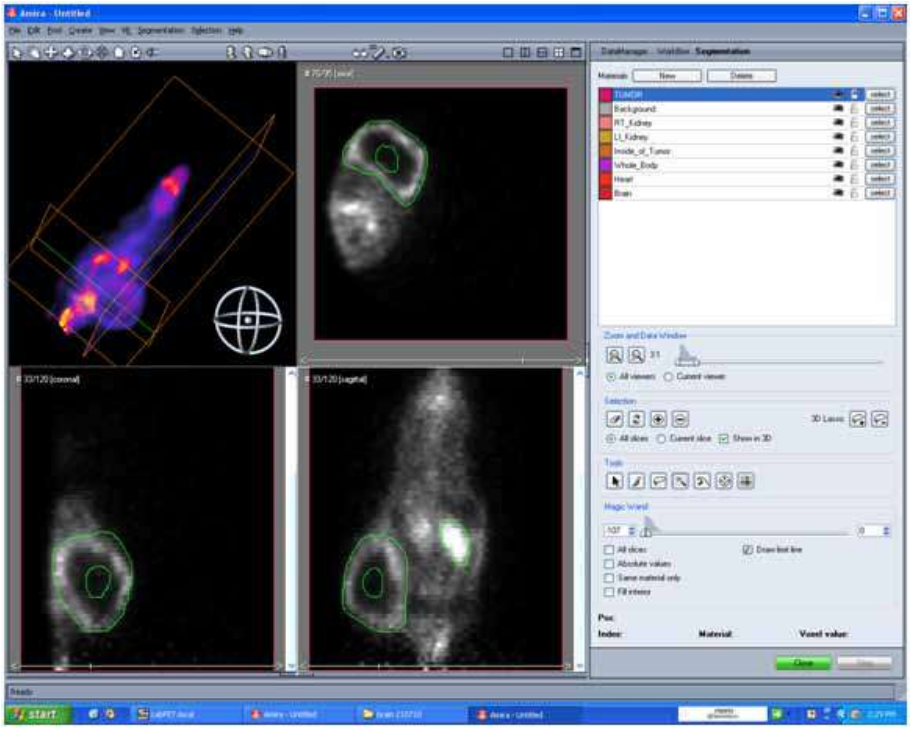

Fig-2. The representative image of whole body scan of immune-compromised SCID mouse xenograft model 2 hours post injection of 18F-fluro-deoxy glucose has been provided here. Volumetric analysis of tumor uptake and visualization of image data using AMIRA platform.

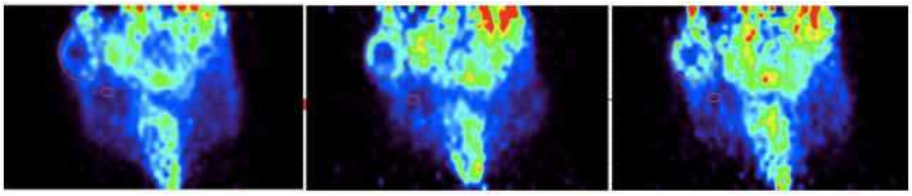

Fig-3.Tumor uptake of FDG at 15min, 1hr and 2hr post injection in immune compromised SCID mouse xenograft model .

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