

Purpose of Study

microPET® scanner has the capability of imaging a whole-body mouse in one scan. However, the absolute quantitative glucose metabolic images of a mouse, i.e. pixel values in glucose utilization rates (MRglc; in unit of mg/min/100g), have not been shown in the literature. Substantial blood loss was one of the drawbacks of sampling blood required by the quantitative microPET study. The goals of our study are to minimize the blood loss of the animal and to develop a computationally efficient method to measure the glucose metabolic rates in all major organs of a mouse using a FDG PET scan. We generate the whole-body glucose metabolic images of a mouse using a 45-minute FDG microPET scan and pixel-wise Patlak analysis. The input function was computationally derived by applying cluster analysis to the heart images and 2 blood samples taken at 9 and 45 minutes post-injection. User interventions in blood sampling and imaging processing were minimized. Our results demonstrated that the regional MRglc values obtained by this simplified method were comparable to those obtained by using the input function derived from 16 serial arterial blood samples.

Reliable FDG kinetics in mice was not shown in the literature due to the difficulty of blood sampling. We studied the FDG kinetics (i.e. glucose transportation rates and hexokinase activities) in some major tissues of the mice using 18 blood samples (~220 nL each) from the mouse. Good model fittings were shown in all studies (n=4). The R squares of the curve fittings are 0.90-0.99 for 4K-compartmental model and > 0.99 for the Patlak analysis. For the first time, more reliable glucose kinetics was demonstrated in living mice using FDG PET study with minimum blood loss and physiological disturbance.

Protocol:

In this study, mice were anesthetized with 2% isoflurane. For each mouse, FDG (~500 µCi in 60 µL) was injected 3 seconds after PET scan started. Sixty-minute list-mode PET data were acquired and 18 serial blood samples (220 nL each) were taken from a femoral artery during the scan. A 10-minute CT scan was taken afterward for attenuation correction. Only the 45-minutes list-mode data were used to generate the parametric images. Filtered-back-projection reconstruction was used.

(Figure 1) Images in this figure demonstrated the practical usefulness of our simplified method for measuring the regional glucose utilization rate in mice by generating the whole body parametric images of MRglc. The almost identical color intensities in two MRglc images illustrated that the MRglc obtained by the simplified method was comparable to those obtained by using the input function derived from 16 arterial blood samples. The glucose metabolic image has less background activities and is more physiologically meaningful as compared to the FDG distribution image.

(Figure 2) We generated the ratio images (mouse #1) of the two metabolic images and compared the mean values of different ROI to demonstrate the accuracy of this simplified 2-blood-sample technique. In all major organs with glucose uptakes, the ratios are close to 1. Using small blood volume, multiple blood samples, we showed some quantitative estimates of the FDG kinetics in some example tissues of a mouse (mouse #2). The goodness of model fittings was demonstrated in the plots of myocardial kinetics using a 4K-compartmental model and the Patlak analysis.

Scanner- microPET Focus 120 / microCAT I

Subject: 25g C57BL/6 normal male mouse
Instrument: microPET Focus 120 / microCAT I
Tracer / Contrast Agent(s): FDG

Kinetic Modeling:

1. Whole body parametric images in Figure 1 and mouse #1 of Figure 2 were generated by using pixel-wised Patlak graphical analysis.
2. FDG kinetics for mouse #2 in Figure 2 was obtained by drawing ROIs and generating the tissue time activity curves. The model fitting used either a conventional 4-parameters, 3-compartment FDG model or the Patlak graphical analysis.
3. The input function of two-blood-technique was generated by applying cluster analysis (n=4 clusters) and two-blood-sample-counts with the mouse heart images of PET scan.

Other Data Acquired:

During the sixty-minute PET scan, 18 serial blood samples (220 nL each) were taken from a femoral artery -- 10 samples in first 2 minutes and 8 samples afterward. A 10-minute CT scan was taken for attenuation correction purpose. For two-blood-sample technique, we only used blood samples taken at 9 minutes and 45 minutes.

¹²⁴I-NM404 In vivo Dual Modality Colonoscopy in a Live Mouse Fused microPET/microCT Images

Purpose of Study

To evaluate the utility of ¹²⁴I-NM404, a new dipeptide tumor agent which undergoes selective uptake and prolonged retention in malignant tumors (30/30 human and rodent xenograft and spontaneous tumor models), but unlike FDG does not localize in hyperplasias or inflammatory sites. Due to its long retention it has displayed significant therapeutic effect in several human xenografts in SCID mice. We published mouse microCT virtual colonoscopy in a Min mouse model, which develops non malignant colonic polyps, last year in PNAS (March 1, 2005) and now extend this study to dual modality virtual colonoscopy in live mice which entails fusing the tumor avid NM404 microPET data set with the beautiful anatomic microCT data sets both in vitro and in vivo. Because NM404 does not localize in adenomatous polyps, but does localize and remain in malignant tumors we see the malignant lesions lit up on as we fly through (Amira) the colon of a live mouse. This selectivity can be thought of as *virtual biopsy* and is totally noninvasive. We are using this technique to monitor growth and regression in this mouse model.

Protocol:

Mice are given cherry flavored NuLytle the night prior to scanning. Prior to scanning the animal is anesthetized with Nembutol (IP) and given a brief enema with warmed PBS to remove the remaining fecal remnants. The bowel is then insufflated with air, fiducial markers placed, and the mouse undergoes microPET scanning (20 minute acquisition). Following this, the scanning bed is moved to the microCAT II for a microCT scan (91 micron, 8 minute acquisition). Following the scanning, the animal is euthanized, the intestinal tract is removed, flushed with buffered saline and one end tied off with suture. The bowel is then filled with 2% barium suspension and sealed with suture. The contrast-filled excised intestine is then placed in formalin to fix the tissues. After 30 minutes, the excised bowel is scanned by microPET and microCT and the resulting images fused in Amira. Resulting 3D fly-throughs are generated with Amira. Contrast enhancement of the lumen allows subsequent generation of surface and volume-rendered images.

Scanner- microPET Focus 120 / microCAT I

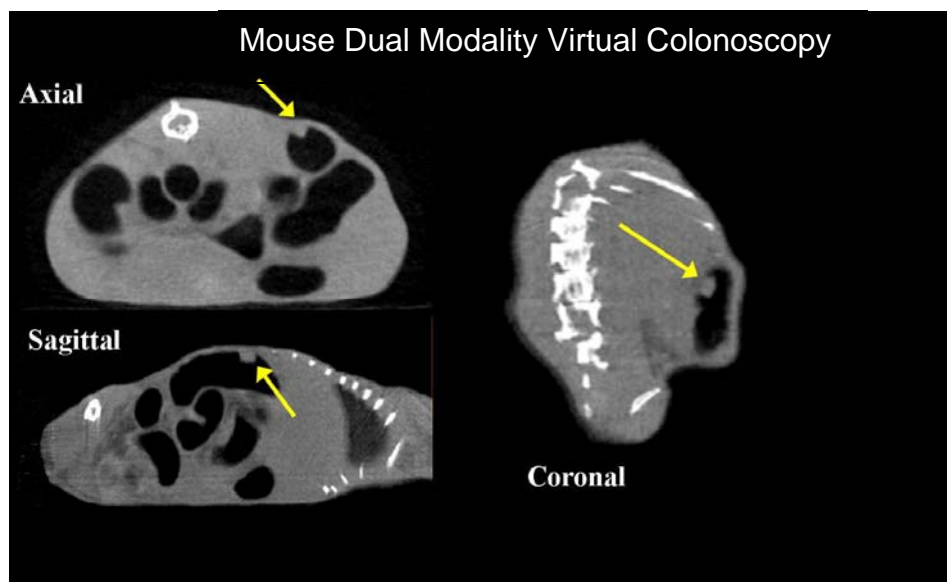
Subject: 25g C57BL/6 normal male mouse

Instrument: microPET Focus 120 / microCAT I

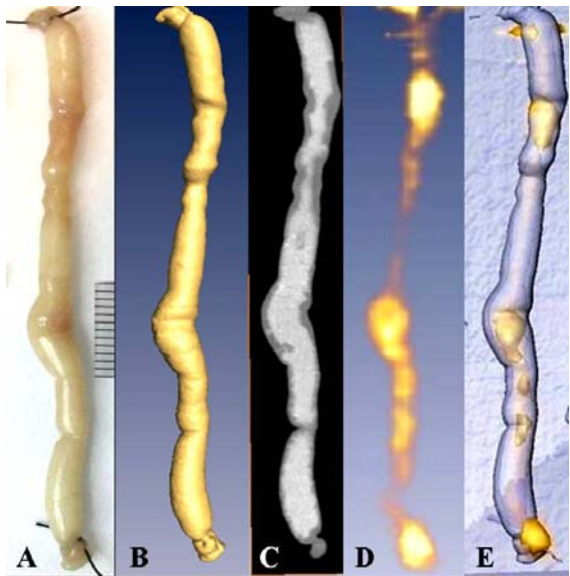
Tracer / Contrast Agent(s): FDG

Notes:

Due to its prolonged retention in tumor cells, NM404 can be scanned from 24-120 hours post iv injection. The long half life (4.2 days) of iodine-124 matches perfectly the pharmacokinetic profile of NM404. The prolonged uptake of NM404 is likely due to a decrease in the amount of phospholipase-D, an enzyme known to metabolize phospholipids like NM404, found in tumor cells relative to host tissue cells.



microCT images of an anesthetized mouse showing the presence of an intestinal tumor. Mouse was previously prepped overnight with NuLytle and the bowel was insufflated with air prior to scanning. Intestinal tumor is indicated with an arrow in the 3 views.



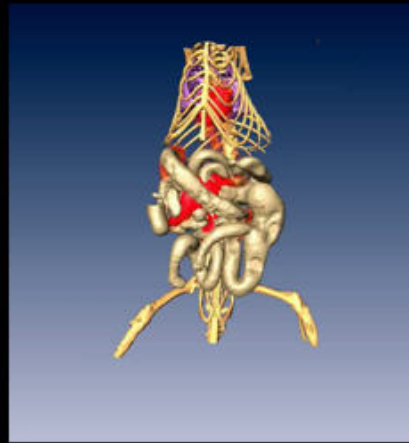
Dual Modality Virtual Colonoscopy

Excised BrF1 adenocarcinoma-bearing mouse small intestine. Photograph (A), surface-rendered microCT (B), coronal microCT slice (C), coronal microPET scan (D) 96 h post iv administration of ^{124}I -NM404, a new dipeptidic tumor agent, and the fused microPET and microCT surface-rendered image (E). The excised tissue was flushed with water, insufflated with 2% barium suspension, and fixed in formalin prior to scanning *ex vivo*. Malignant tumor avidity of NM404 is illustrated in D and E. Tumors in this model are characterized by wall thickening and a kinked appearance.

^{124}I -NM404 *In vivo* Dual Modality Colonoscopy in a Live Mouse Fused microPET/microCT Images



CT



Dual Modality
PET-CT

Data courtesy of University of Wisconsin, Madison, Jamey P. Weichert, Ph.D.