Making Preclinical PET/CT More Accessible

Positron emission tomography (PET) is a non-invasive quantitative 3D imaging technique that utilizes the naturally occurring positron decay of radionuclides to provide visualization of a wide-range of biological events. As a powerful clinical imaging tool, PET/CT is used to track molecules within the body with high sensitivity and specificity. PET/CT is being increasingly utilized in preclinical imaging due to improved access to imaging probes, better detector technology and need to provide *in vivo* imaging results using a clinically relevant modality.

PerkinElmer and Sofie Biosciences have partnered together to bring the latest generation *in vivo* imaging technology to preclinical investigators with the innovative G8 PET/CT system. The G8 is the world's first lightweight benchtop PET/CT scanner and delivers high-impact results in a lab-friendly footprint as shown in the workflow video below. It facilitates high sensitivity and high resolution PET scanning integrated with a sub-minute, low dose microCT. The G8 provides fully quantitative data, while maintaining workflow advantages including docking stations with imaging chambers, integrated anesthesia and intuitive imaging protocol creation menus. This highly versatile system is designed to integrate into your current preclinical research workflow in a broad-range of applications from oncology to immunology, drug discovery and radiotracer probe development.

To view video outlining the G8 PET/CT workflow, visit https://www.youtube.com/watch?v=6P25jdQQfuE

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Table 1: Outline of the low radiotracer activity that can be imaged on the G8 PET/CT.

AUTHOR	G4 OR G8	RADIOTRACER	LOWEST ACTIVITY USED (uCi)	(MBq)	APPLICATION*
Bansal et al. 2015	G4	89Zr(HPO4)2, 89Zr-labeled hMSCs	2.00	0.07	Novel 89Zr cell labeling PET cell tracking
Gu et al. 2013	G4	64Cu-minibody, 18F-FDG	3.70	0.14	Performance testing of high sensitivity PET Imaging system
Yang et al. 2016	G4	89Zr(HPO4)2, 89Zr-labeled hMSCs	7.50	0.28	PET tracking to determine therapeutic value of human adipose tissue in AVF
Hal.ler et al. 2015	G4	18F-AzaFol, 18F-fallypride	10.0	0.37	Chick and mouse comparision for PET probe uptake and stability
Meimetis et al. 2015	G4	89Zr-DFO-BODIPY-trastuzumab	10.0	0.37	Multimodal. Imaging of Antibodies with PET
Boros et al. 2016	G4	89Zr– L4/L5, 89Zr-DFO	10.0	0.37	Novel Immunoconjugation of 89Z for PET
Peng et al. 2014	G4	11C-PBR28	13.0	0.48	PET to investigate role of acetyl-coA in neurodegeneration
Lazari et al. 2014	G4	18F-FLT, 18F-FDG,18F-fallypride	20.0	0.74	Fully Automated Production of Diverse 18F-Labeled PET Tracers
Evdokimov et al. 2014	G4	18F-FMT	20.0	0.74	Development of novel CNS PET probe
Faltermeier et al. 2015	G4	18F-FDG	20.0	0.74	PET Imaging to identify kinases driving prostate cancer metastasis
Evdokimov et al. 2015	G4	18F-2-DFR, 18F-DFA	20.0	0.74	Development of PET probe for liver function imaging
Kim et al. 2016	G4	18F-CFA	20.0	0.74	Development of a PET probe for deoxycytidine kinase activity imaging
Hermann et al. 2013	G4	18F-FDG	25.0	0.93	Evaluation of a Bench-Top Preclinical PET Scanner
Lozier et al. 2015	G4	18F-FDG	25.0	0.93	Assessment of LIN28 oncogenic driver in neuroblastoma using PET
van der Meulen et al. 2015	G4	44Sc-DOTANOC	27.0	1.00	Evaluation of 44Sc biodistribution *in vivo* with PET
Seo et al. 2015	G4	64Cu-NOTA-UCNPs	40.0	1.48	Assessment of Radiolabeled Upconverting Nanoparticles with PET
Witney et al. 2014	G4	18F-FPIA	50.0	1.85	Preclinical Evaluation of a novel PET Imaging Agent for Tumor Detection
Song et al. 2016	G4	18F-FMISO	50.0	1.85	PET to assess oxygen changes after high-dose radiation therapy
Mueller et al. 2016	G8	152Tb-DOTANOC	90.0	3.33	152Tb-DOTANOC for PET radiolanthanide imaging
Farkas et al. 2016	G8	64Cu- and 68Ga-labeled NODAGA-folate	94.0	3.48	64Cu- and 68Ga-Based PET Imaging of Folate Receptor-Positive Tumors
Jang et al. 2013	G4	64Cu-Sar-chTNT-3	100	3.70	PET to assess the use of chemotherapy to improves the biodistribution of antibodies
Hu et al. 2015	G4	18F-FDG	100	3.70	Nanoparticle-mediated radiopharmaceutical.-excited fluorescence *in vivo* imaging
Mueller et al. 2016	G8	149Tb -DOTANOC	190**	7.03	Alpha-PET with terbium-149 in mice
Domnanich et al. 2016	G8	44Sc/68Ga-labeled DOTA/NODAGA- peptides	270**	9.99	44Sc for labeling of DOTA- and NODAGA peptides
Moon et al. 2015	G4	68GA-DOTA-IO-GUL	276**	10.2	Development PET/MR probe for PSMA targeting

** All studies conducted in mice* *** Due to tracer high life and study design, higher doses were needed prior to imaging*

The G8 PET/CT Overcomes Barriers to Wide Adoption of Preclinical PET/CT

Many barriers prevented PET from becoming a ubiquitous preclinical imaging modality. Historically, preclinical PET has been limited to imaging cores that could provide a dedicated technician to run the system with PET physics expertise. The G8 was specifically designed to overcome such barriers and make PET/CT a more accessible preclinical imaging modality. **We developed five features to achieve this goal – high PET sensitivity and resolution, compact benchtop footprint, rapid whole body scanning and fast reconstruction, intuitive user interface and integrated animal management:**

With the **highest sensitivity** on the market, the G8 can detect very low levels of radioactivity (as shown in Table 1), reducing the amount of activity that needs to be injected. This can be a game-changer in probe development, where yields are often low, and studies looking at immune responses, where large doses of carrier or radioactivity could elicit unexpected therapeutic effects. The sensitivity of 14% is made possible due through a) High atomic number (Z=83) of the BGO crystal detectors as this increases the probability of a photoelectric event at the first interaction site b) The arrangement of the four panel detector heads as they are placed closely together (unlike classic ring design) thus closer to the animal and emitted photons and c) Improved crystal cutting that reduces the gaps between adjacent crystals and increases the packing fraction. In addition, BGO allows for the increased sensitivity without compromising spatial resolution requires lower detector thickness, leading to reduced parallax errors and better spatial resolution due to reduced inter-crystal scatter and more accurate event positioning. A scanner with high sensitivity lowers the doses of radioisotopes that are needed to obtain high image quality. In turn, this results in less exposure to the animal and the investigator, and offers opportunities for greater cost savings. Moreover, the flat-panel architecture results in a **highly uniform spatial resolution** (1.4 mm) across the field of view and this allows for finer sampling of signal and clearer results. Conventional ring-based systems suffer from reductions in resolution as the target moves away from the isocenter of the imaging field. Sample images can be found in Figure 1.

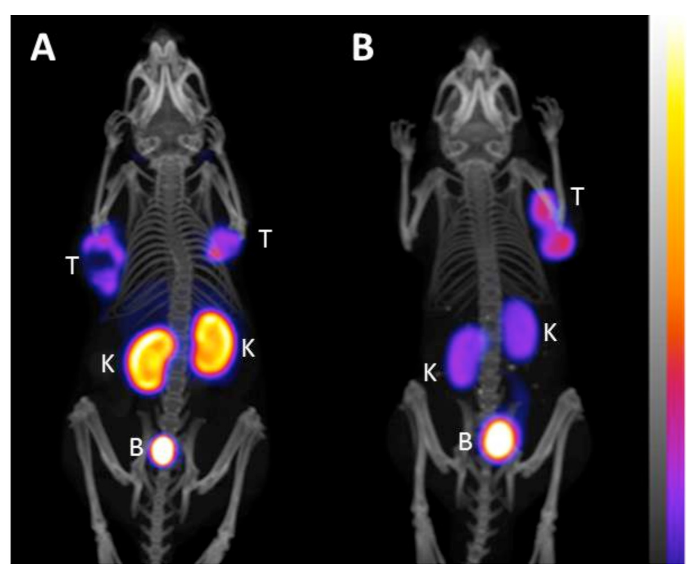

Figure 1: High resolution images of novel radiotracer probes imaged on the G8 PET/CT **(A)** ^{18}F-AzaFol static PET/CT scan in a nude mouse with cervical cancer xenografts **(B)** ^{44}Sc labelled PSMA-617 static PET/C scan of SCID mouse with LNCaP prostate cancer xenograft T = Tumor, K = Kidney and B = Bladder *(All images courtesy of Dr. Cristina Müller ETH, Zurich, Switzerland and used with permission.).*

The G8 is a compact lightweight and designed to fit on a benchtop. The system measures 26" x 24'' x 28" (Length, Width, Height) and does not require a dedicated room unlike many large-bore systems. The unit is self-shielded therefore does not require expensive site modifications. The compact size not only affords flexibility with respect to placement within the laboratory, but reduces the infrastructural modifications required when installing larger systems. Because the system is modular it can be moved from lab to lab, including behind barriers or next to radiochemistry preparation areas.

The G8 provides rapid whole body scanning and reconstruction. The 3D ML-EM reconstruction of 10 min static scan on the G8 is < 2 min. This enables quick "Go" or "No Go" decisions for new drug and tracer probe development. The G8 is designed to image an entire mouse in one scan, facilitating dynamic scanning to monitor probe uptake and distribution. Other systems, which can be configured with one or three PET rings, do not have large enough fields of view in the one-ring configuration to image an entire mouse. To accomplish this, multiple images need to be taken and stitched together. This means that dynamic imaging of probe uptake and distribution cannot be acquired. In addition, the G8 runs reconstructions on the acquisition PC following the scan, allowing additional scans to be run. Other systems often require off-loading of data to a reconstruction workstation before scanning can continue.

The G8 has a user friendly interface i.e. users new to PET can run the G8. The G8 software contains multiple user-friendly modes and is designed with easy workflow and access to expertise. This allows for higher imaging throughput and flexibility for users when needed. The modes are **1) General User** - designed specifically for researchers who do not have an in-depth knowledge of PET imaging and the various parameters that can be used to define a scan protocol. Users can select from a dropdown of optimized imaging workflows. The workflows have been validated and allow for collection, reconstruction and analysis of the data; **2) Physicist User** - enables a more experienced PET imaging researcher to make modifications to all user profiles e.g. adding new Isotopes or modifying any of the parameters associated with the imaging workflows and enables increased compliance and data integrity across all user profiles; **3) Administrator User** - lets the user quickly create reports for billing and grant reconciliation, track user data and setup new user profiles.

The G8 also provides an integrated animal management system. This reduces workflow times to match those of multiple-mice large bore scanners. The animal is housed in a purpose designed animal bed that has integrated heating and gas anesthesia units that deliver a steady flow of gas at 6psi and heat at 37 degrees Celsius. When the animal bed is locked into place the bed is illuminated illustrating a connection has been achieved between bed and the anesthesia unit and that anesthesia is being delivered to the subject. In addition to assisting in animal handling, the cassettes serve as pathogen barriers, protecting your animal from any outside contamination during the imaging session. This management system, enables high throughput, consistent and reliable imaging by removing the guesswork out of anesthesia delivery. Moreover animal vital signs are monitored live via a video-based real-time camera and lead-glad window. This also allows the researcher to closely monitor the mouse's respiratory cycle. The system also enables a live video monitoring of the animal while imaging is occurring.

For more information on the G8 PET/CT, visit us at www.perkinelmer.com/preclinical-pet-imaging

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