Trimodal PET/SPECT/CT Preclinical Imaging and Studies in Oncology

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Integrated preclinical PET/SPECT/CT imaging systems can supply flexible and quantitative datasets that can be a highly valuable component of a preclinical imaging suite. Preclinical $^{18}$F-FDG PET imaging is commonly used for quantitative assessment of therapeutic efficacy (Marini et al., 2013), in studies of imaging protocols (Massallo et al., 2013), as well as in determining molecular mechanisms of tumor biology (Rosenfeldt et al., 2013). SPECT imaging has been used in studies evaluating novel SPECT tracers (Mendoza-Sánchez et al., 2010, Ocampo-García et al., 2011a), assessing novel sentinel lymph node (SLN) imaging agents (Ocampo-García et al., 2011b), as well as in targeted radiotherapy (Vilchis-Juárez et al., 2014). In addition to providing anatomical landmarking, CT imaging can be used to monitor changes in normal lung volume with tumor progression using relatively minimal labor (Davison et al., 2013a; b).

The Albira PET/SPECT/CT system provides high resolution PET and SPECT imaging with automated CT image fusion for anatomical reference (Spinks et al., 2014). The continuous crystal technology employed in the Albira PET system provides real time and true depth-of-interaction (DOI) detection on the detector level, as well as corrections for decays, scatters, randoms, and attenuation corrections, and is calibrated to quantitative activity units (kBq/cc). The CT system is calibrated to Hounsfield Units (HU) allowing for reliable image quantitation and segmentation. Additionally, the system is compatible with the Bruker Multimodal Animal Bed, facilitating sample transfer between the BioSpec® MRI, ICON™ MRI, micro-CT 1176, and optical imaging systems like the In-Vivo Xtreme™. All Albira systems are provided standard with a package of PMOD (PMOD Technologies LTD; Zurich, Switzerland; www.pmod.com) software modules that allow for some of the most advanced analysis applications in preclinical oncology. Below we provide a brief review of a select range of published PET, SPECT, and/or CT studies in oncology.

PET Imaging: Tumor Biology and Therapies

$^{18}$F-FDG PET is used in the clinic for staging a range of cancers. $^{18}$F-FDG PET imaging offers broad tumor imaging specificity owing to the hyper-metabolic profile of tumors relative to healthy tissues. Genetic, molecular, and therapeutic agents may modify the metabolic profile of tumor cells or cells with oncogenic potential. In a recent study reported in Nature, Rosenfeldt et al. (2014) investigated the relationship between autophagy, p53 status, and tumor development, further elucidating the biological and molecular influence of autophagy in oncology. In a pancreatic ductal carcinoma (PDAC) mouse model that contains an activated Ki-Ras oncogenic allele, mice which were lacking essential autophagy genes were refractory to the
more severe tumor development. However, when critical autophagy genes were missing and p53 was also missing, PDAC mice exhibited accelerated tumor development. Albira PET imaging allowed for quantitative imaging of tumor development in those study animals. 18F-FDG PET imaging and standard uptake value (SUV) (quantitative measurement of 18F-FDG) of p53-/-/autophagy competent versus p53-/-/autophagy incompetent PDAC mice is displayed and reported in this study.

While Metformin is one of the most common drugs prescribed to treat type 2 diabetes, recent reports indicate that Metformin treatment results in increased gastrointestinal 18F-FDG uptake unrelated to tumor development that can complicate staging for abdominal cancers. Massollo et al. (2013) evaluated untreated, pulsed, and prolonged Metformin treatment protocols in a preclinical model (see Figure 1 left). The results of these studies indicate that the 18F-FDG activity associated with Metformin treatment is likely due to the increased pAMPK activity of colonic enterocytes. In this study preclinical PET imaging and kinetic analysis including image derived arterial input function were performed to measure intestinal 18F-FDG uptake.

Intriguingly, there is also some evidence indicating that Metformin may inhibit tumor growth. A recent study by Marini et al. (2013) showed that the likely mechanism-of-action is a hexokinase inhibitory activity. Using preclinical PET imaging Marini et al. (2013) were able to measure the tumor glucose consumption in Metformin treated model animals (see Figure 2 left). These studies demonstrate the utility of the Albira PET system in a range of preclinical oncology imaging and analysis applications.

SPECT Imaging: Novel Agents and Therapies

While clinical PET imaging has expanded significantly in the past decade, SPECT imaging is still very commonly used and is more widely available. Vigorous research into new and improved SPECT agents continues. For example, Ocampo-García et al. (2011a) reported on a kit for preparing gold nanoparticle (Au-NP) multimeric receptor-specific 99mTc radiopharmaceuticals. Lys3-bombesin, Arg-Gly-Asp (RGD) and thiol-mannose agents with evidence of specificity for gastrin releasing peptide-receptor (GRPr; upregulated in some cancers), αvβ3 integrin (marker associated with neo-angiogenesis commonly upregulated in tumors), and SLN retention (likely based on uptake/retention by macrophage residing in LN) respectively, were generated. Interestingly, the mannose agent showed greater SLN signal retention compared to controls and the GRP-r agent exhibited specificity for PC3 tumor in vivo (Mendoza-Sánchez et al., 2010, Ocampo-García et al., 2011b).
Recently, Vilchis-Juárez (2014) evaluated a 177Lu-AuNP-RGD candidate radiotherapeutic agent in a C6 glioma tumor model. Here, Albira SPECT imaging (see Figure 3 above) was utilized to evaluate 177Lu-AuNP-RGD biodistribution and targeting while 18F-FDG-PET imaging was used to evaluate therapeutic response. While SPECT imaging remains clinically relevant and widely available, high performance preclinical SPECT systems like the Albira S102 or S108 configuration will provide critical insights into developments in both tracers and therapeutics. A trimodal system providing for both SPECT and PET imaging in conjunction with anatomical CT can provide valuable insight into both radiotracer targeting using SPECT and therapeutic response using 18F-FDG-PET as illustrated in the study above.

**MicroCT Imaging: Lung Metastasis and Lung Tumor Progression**

CT imaging in bi- or trimodal platforms provides critical anatomical context for combined functional PET and/or SPECT imaging. CT imaging has also been used to detect lung tumor metastasis and lung tumor progression. Many of the protocols reported include low throughput and labor intensive gated CT imaging and manual or semi-automated nodule discovery methods. Recently, Davison et al. (2013a) reported on a relatively high throughput protocol for non-gated CT imaging and lung volume segmentation (Wathen et al., 2012) applicable for models of lung tumor development.

Here, relatively rapid scans were made and simple segmentation of the lung volume was performed to obtain a metric measurement of normal (non-tumor) lung volume. Individual nodules are not identified using this protocol, but instead a decrease in normal lung volume corresponds to an increase in overall tumor burden. Figure 4 (above) shows the 3-dimensional display of lung volume segmentation with lung cancer progression. Davison et al. (2013b) subsequently utilized this protocol in a study on the molecular role of antioxidant activity in lung tumor metastasis. Here they demonstrated that antioxidant deficient tumor cells were inhibited in their ability to metastasize. This protocol may be applied to other studies of lung tumor development.
Conclusions
Preclinical nuclear imaging is particularly valuable where quantitative and kinetic analysis is required. The Albira tri-modal PET/SPECT/CT system has been employed in range of preclinical studies in oncology. These studies have advanced efforts in novel radiotracers/therapeutics development, and in basic studies of molecular tumor biology.

References


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