Applications of Small Animal Imaging with PET, PET/CT, and PET/MR Imaging

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- Computed tomography (CT)
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Molecular imaging includes a range of techniques meant to visualize molecular events at the cellular level in living organisms in a noninvasive fashion. In the preclinical setting, the most interesting molecular imaging techniques are PET[1] and MR imaging with molecular contrast agents that allow in vivo accurate quantitation or semiquantitation of many molecular phenomena. Another important technique is CT with or without vascular or liver contrast agents. CT does not provide molecular information but is useful for observing the morphology of tissues and lesions (eg, to accurately measure a tumoral mass over time) because it is very fast and complements the data obtained by PET and MR imaging.

It is now possible for one to purchase small animal PET, MR imaging, and CT scanners, but the future includes the production of hybrid scanners. Currently, small animal PET/CT scanners are available, whereas only prototypes of PET/MR imaging scanners are available. The most common way to combine data from these methods consists of post acquisition image coregistration.

Oncology is by far the field of preclinical research in which all of these imaging techniques are most frequently applied, but cardiovascular and neurologic research protocols can also take advantage of these innovative approaches. For example, PET is used to provide information about tumoral metabolic activity[2,3] and allows for the exploration of different metabolic pathways in physiologic and pathologic tissues. The main advantage of small animal PET and MR imaging over standard methods of preclinical experimentation requiring ex vivo examination is the possibility to analyze the same animal more than once over time, allowing one to observe the response of a disease condition to a new therapeutic agent or the development of disease, thereby significantly reducing the number of animals employed and increasing the reliability of the results.

Furthermore, the use of small animal PET technology allows for the detection of very low (picomolar) concentrations of radiotracers with great sensitivity even with very small uptake variations.[1] Although less sensitive than PET, MR imaging produces high resolution imaging.

Another interesting characteristic of preclinical molecular imaging is summarized in the word "translational." By employing the same technology (PET, MR imaging, or CT) in the experimental setting and in clinical practice, the step between preclinical science and clinical applications in human patients is shortened, reducing the overall time required to effectively verify the

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clinical utility of a new approach. One significant example in this field is the in vivo testing of new radiolabeled compounds designed to increase the specificity of PET imaging for a specific disease. The creation of animal models of human disease for in vivo testing of new compounds avoids the human translation of compounds that do not bind to the disease site or are not specific for the disease process of interest.

The translational applicability of these techniques, the possibility of accurate quantitation,[3] the high spatial resolution (1 mm for PET and <1 mm for MR imaging and CT) which is very important when studying small animals such as rodents in vivo, the high sensitivity, and the possibility of using targeted probes to increase the specificity of disease characterization are features that make these procedures desirable in the preclinical scenario despite their relatively high cost when compared with standard ex vivo studies.

APPLICATIONS OF SMALL ANIMAL PET

In the literature, the vast majority of studies employing a small animal PET scanner have not compared the results of PET with those of other preclinical imaging procedures but instead taken into consideration histochemical analyses or autoradiography to verify imaging results. This approach is mainly due to the high costs of the scanners, which makes it difficult to access the multiple modality technology. In the future, more complementary imaging techniques will be employed for evaluation of the same animal models.

Oncology

Small animal PET allows one to noninvasively measure a range of tumor-relevant parameters at the cellular and molecular level, which can be observed longitudinally over time. Studies to evaluate tumor response to a therapeutic intervention can achieve statistical significance using smaller groups of animals, because tumor cell physiology and tumor burden can be accurately determined before and after therapeutic intervention.

The most widely employed PET imaging probe is [18F]-2-fluoro-2-deoxy-D-glucose (FDG), which achieves tumor-specific accumulation because tumor cells have a higher rate of glucose uptake and metabolism (glycolysis) than normal tissues. FDG is generally used in oncology to predict cancer cell engraftment[4] and to measure the response to therapy. [18F]-3'-fluoro-3'-deoxy-L-thymidine (FLT) and its analogues (eg, [18F]-1-(2'-deoxy-2'-fluoro-β-D-arabinofuranosyl)thymine) are another family of compounds that are widely used in preclinical PET because they demonstrate the proliferative index of tumor masses with an accuracy that is far higher for animal models of cancer than for human patients.[5]

Many other PET probes have either been developed or are under development to obtain tumor specificity via a variety of tumor-specific mechanisms. The development of targeted radiolabeled ligands has enabled PET to image many aspects of in vivo tumor biology. Radiolabeled annexin-V, arginine-glycine-aspartic acid (RGD) peptide, vascular endothelial growth factor (VEGF), and $\alpha_v\beta_3$ integrin have been successfully tested in tumor models as well as models of cardiac infarction. The pharmacokinetics and pharmacodynamics of radiolabeled anticancer therapeutics can, in principle, also be monitored by these methods, leading to rapid improvements in drug dose scheduling or design.

The effects of receptor therapies (eg, inhibitors of androgen receptors, estrogen receptors, and epithelial growth factor receptor) can theoretically be predicted owing to the in vivo demonstration of the receptor after injection of a particular radiolabeled ligand.[3]

The literature includes studies on a wide number of PET radiolabeled compounds for preclinical evaluation of specific molecular events. It would be difficult to provide a complete list of all proposed compounds for oncological studies from the past decade in this article.

Cardiology

The applications of small animal PET imaging in preclinical cardiology can basically be divided into measurement of myocardial viability, measurement of myocardial perfusion, measurement of cardiac function, and targeting of specific processes (eg, angiogenesis, apoptosis, and injected stem cells following myocardial infarction).

The imaging of myocardial viability is based on the use of FDG. This approach relies on the concept that all viable myocardial cells (especially under conditions of hyperinsulinism) have increased glucose uptake. The signal obtained from the heart resembles the distribution of viability. Fibrotic and infracted areas are obviously hypometabolic.[6,7] Regarding the evaluation of myocardial perfusion, [13N]-NH_3 and [15O]-H_2O are suitable radiotracers for this application, and their use is already standard for human studies. Another possible way of assessing myocardial perfusion is to use [11C]-acetate with dynamic image acquisition, because the myocardial blood flow measured with [15O]-H_2O and [11C]-acetate is directly correlated. Acetate has several