Preclinical PET Imaging in Studies of Candidate Therapeutics

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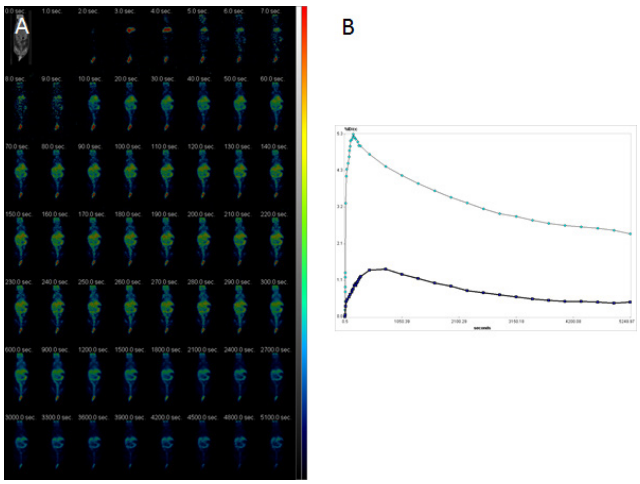
Clinical and preclinical non-invasive PET imaging is employed in the development and validation of therapeutic agents for cancer and neurological disorders, and a range of other diseases.[1,2,3] Reported studies have used numerous agents including ^{18}FDG, ^{18}FLT, ^{18}FMISO and ^{18}FAZA as early biomarkers of drug efficacy.[2,4] Preclinical PET imaging has been proven in studies of therapeutic targeting and biodistribution, drug target interactions, pharmacodynamics and toxicology.[5] These methods have helped facilitate the development of therapeutic agents that are now clinically available.[6] Probably two of the most common uses of preclinical PET imaging in drug discovery are studies of compound targeting and biodistribution and therapeutic efficacy. Here, we will provide a brief introduction to preclinical PET imaging for such studies.

Targeting and Biodistribution

Targeting validation and pharmacokinetics (PK)/ pharmacodynamics (PD) are important components of drug/ therapeutic development. PET imaging is a particularly useful tool for therapeutic tracking studies *in vivo* because it can provide tomographic distribution information with excellent temporal and spatial resolution (Figure 1). In fact, PET imaging arguably provides superior tracking capability compared to other preclinical imaging modalities, including SPECT. This is due to simultaneous PET detection in all projections and excellent sensitivity. Additionally, complex dynamic imaging/analysis can be performed using blood sampling and kinetic models. These advanced methods provide valuable information about distribution kinetics and receptor densities.

Figure 1



Preclinical PET imaging supports quantitative tomographic biodistribution studies. This example study of ^{11}C dynamic PET imaging demonstrates the temporal resolution and quantitative value that can be leveraged in drug biodistribution studies. (A) ^{11}C-Acetate biodistribution over 90 minutes in a dynamic PET acquisition. CT image shown top left. (B) Corresponding liver (teal) and muscle (purple) SUV (%ID/cc) plots over the time course show quantitative regional ^{11}C uptake. Ninety minutes image reconstruction was made at 10 x 1 second + 29 x 10 seconds + 17 x 300 seconds. Images were acquired using the Bruker Albira II PET/CT. Courtesy of Erin R. Snay and Frederick H Fahey, Boston Children's Hospital.

Using appropriate methods, biodistribution of small molecules, nanoparticles, radiotherapeutics and therapeutic antibodies can be determined using PET imaging. Typically, a given class of therapeutics is matched with an appropriate class of radionuclide. The best therapeutic-isotope pairing is based on chemistry/compound requirements and biodistribution time-course profiles. For example, small molecule biodistribution and function would potentially be modified by inclusion/tagging with radionuclides that are not incorporated in the natural compound structure. In this case, ^{11}C may be substituted within the native carbon compound structure, thereby preserving the function and biodistributiion properties of the compound. ^{11}C however has a relatively short half-life (see Table 1). While potentially appropriate for studies of small molecules that may have relatively short biodistribution time-courses, it may not be compatible with larger therapeutics, which typically have longer biodistribution courses. Antibodies, for example, typically have a relatively long biodistribution course and may therefore be paired with isotopes with longer half-lives such as ^{89}Zr and ^{124}I.[1,7]

Table 1

^{18}F; Fluor-18	109 min
^{11}C; Carbon-11	20 min
^{89}Zr; Zirkonium-89	78.4 min
^{124}I; Iodine-124	100.3 min

Common PET isotopes (and half-life minutes) used in PET biodistribution studies. Appropriate pairing of therapeutic agents and isotopes is an important factor in PET biodistribution studies.

Therapeutic Efficacy

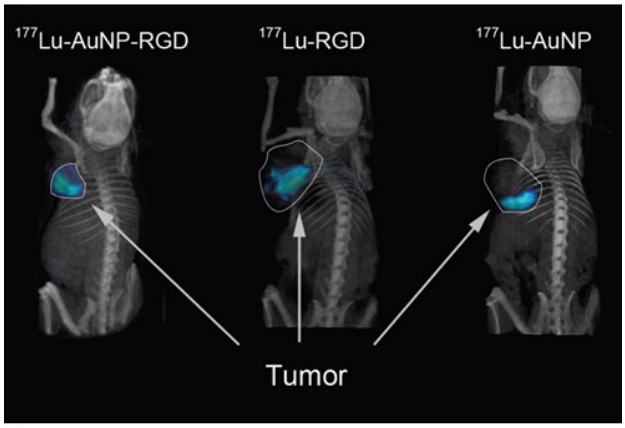
Preclinical PET is also commonly employed in studies of therapeutic response. Functional PET tracers can be used for quantitative dynamic studies of therapeutic response. ^{18}FDG (glucose metabolism) is probably used most commonly in studies of therapeutic efficacy. Still, ^{18}FLT (proliferation), ^{18}FAZA and ^{18}FMISO (hypoxia) and a range of custom tracers have been employed for the detection of angiogenesis, perfusion, protein synthesis and receptor density in therapeutic models. Here we will provide a few examples of studies employing preclinical PET to evaluate therapeutic response in cancer and neurological disease treatment models.

Some recent studies in cancer therapeutics using preclinical PET imaging have evaluated the potential of new combination treatments.[8,9] Combination therapies can provide better efficacy in part because multiple molecular targets can be addressed. Additionally, combination therapies can reduce the incidence of drug resistance. A typical treatment regimen for glioblastoma consists of Temozolamide (Tmz) combined with radiation (Rad) therapy. Llaguno-Munive et al. (2013)[8] recently evaluated Mifepristone (Mife), in a murine glioblastoma model, as a priming agent to the standard Tmz-Rad therapy. Using ^{18}FDG-PET imaging, the combination therapy Rad + Tmz + Mife was found to suppress tumor growth more than Rad + Mife, Tad + Tmz, or Rad therapies alone. Ultimately, this combination therapy could help reduce the incidence of treatment resistance in some patients.

Preclinical PET imaging has also been employed in studies of radiation therapeutics.[10,11] Recently, Vilchis-Juárez (2014)[11] evaluated a ^{177}Lu-AuNP-RGD candidate radiotherapeutic agent in a C6-glioma tumor model. A preclinical trimodal imaging system was utilized, employing ^{18}FDG-PET to evaluate therapeutic efficacy, and SPECT to monitor retention/clearance of the agent at the tumor site (Figure 2). The ^{177}Lu-AuNP-RGD compound significantly decreased tumor SUV values.

Figure 2

A



B

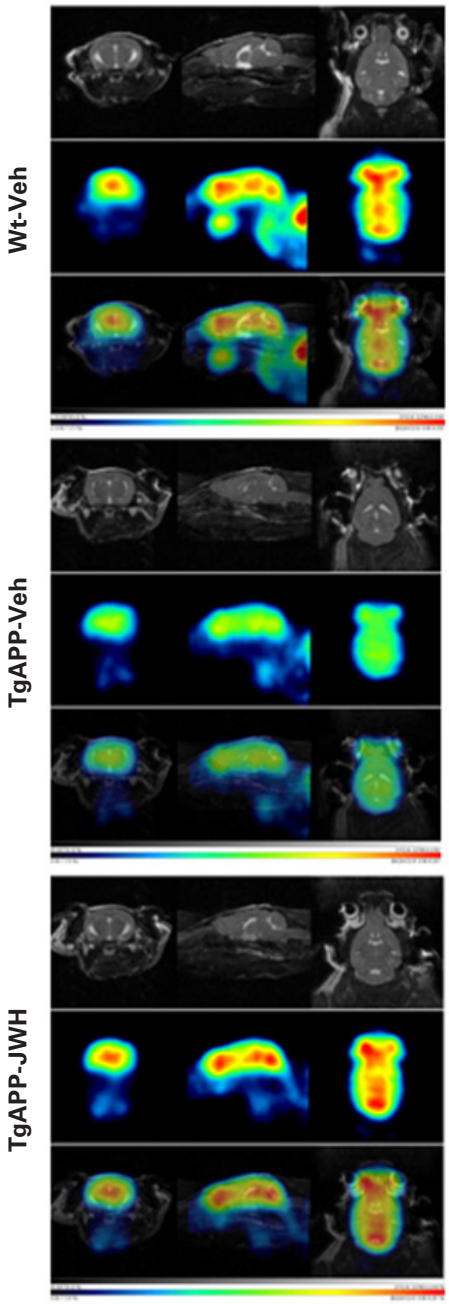
Treatment group	SUV
^{177}Lu-AuNP-RGD	0.335 ± 0.099*
^{177}Lu-AuNP	0.584 ± 0.107*†
^{177}Lu-RGD	2.740 ± 0.260*†
Control	6.539 ± 0.052

Combined PET and SPECT imaging in the study of a new cancer ^{177}Lu radiotherapeutic. (A) SPECT/CT imaging of C6-glioma tumor mice receiving ^{177}Lu-AuNP-RGD (left), ^{177}Lu-RGD (center) and ^{177}Lu-AuNP (right). (B) ^{18}FDG-PET imaging reveals the greatest reduction in tumor ^{18}FDG SUV when treated with ^{177}Lu-AuNP-RGD. This research was originally published in J. Biomed. Nanotechnolo[11] © American Scientific Publishers.

PET imaging is also proven in preclinical therapeutics studies of neurological diseases, including Parkinson's disease and Alzheimer's disease. Glucose metabolism can be a useful biomarker of many neurological disorders, given that normal brain glucose metabolism is modified by many neurological disease states and can be readily monitored by ^{18}FDG-PET. Fernandez et al. (2011)[12] evaluated a novel Rasagiline Mesylate (RM) PLGA preparation, designed to provide a controlled release, in a Rotenone rat model of Parkinson's disease. ^{18}FDG-PET revealed a 40 % increase in striatum glucose metabolism with RM PLGA treatment and *in vivo* efficacy compared to standard RM delivery, providing a possibly better therapeutic delivery with potential for improved compliance.

Current Alzheimer's disease (AD) therapeutics primarily target symptoms of the disease. New agents that directly target the underlying causes of AD are required to abate AD progression more effectively. Transgenic Tg APP 2576 mice are a suitable model for evaluating AD therapeutics. Martin-Moreno et al. (2012)[13] evaluated a new candidate therapeutic synthetic cannabinoid JWH in Tg APP mice using FDG-PET (Figure 3). Here, Tg APP mice showed a significant increase in metabolic activity in the hippocampus and cortical regions, measured by ^{18}FDG-PET. Additionally, reduced inflammation and an increase in Aβ clearance was observed with the candidate therapeutic. Studies like this have the potential to advance therapeutics toward more effective AD treatment options.

Figure 3



Oral administration of JWH cannabinoid rescues brain glucose metabolic activity in TgAPP mice. *In vivo* metabolic imaging by ^{18}FDG-PET, combined with MR for anatomical reference. Top: Wild mouse treated with vehicle. Middle: Tg APP mouse treated with vehicle. Bottom: Tg APP mouse treated with JWH showing rescued ^{18}FDG activity. This research was originally published by Martín-Moreno et al.[13]

Conclusion

Preclinical PET imaging provides excellent temporal resolution for *in vivo* therapeutic tracking studies. Approaches for tracking a range of therapeutics have been demonstrated using preclinical PET, including small molecules, antibodies, cells and radiotherapeutics. Using appropriate functional PET tracers, early therapeutic response can be assessed in preclinical disease models, including oncology and neurology models.

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