Chapter 12
PET Radiopharmaceuticals in Oncology Beyond FDG

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Abstract Several imaging modalities to diagnose cancer, which include computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, optical imaging, and gamma scintigraphy, have been previously used. For instance, CT and MRI provide considerable anatomic information about the location and the extent of tumors, but do not adequately differentiate residual or recurrent tumors from edema, radiation necrosis, or gliosis. On the other ultrasound images provide limited information about local and regional morphology with blood flow. Similarly optical imaging showed promising results, but did not demonstrate the ability to detect deep tissue penetration. Notably, radionuclide imaging modalities are diagnostic cross-sectional imaging techniques that map the location and concentration of radionuclide-labeled compounds. Moreover, molecular imaging agents are making it possible to "see" the molecular makeup of the tumor and its metabolic activity beyond tumor location, size, shape, and viability. Other technological limitations include nuclear images, which can provide a very accurate definition of metabolically active areas, but miss anatomic features. As a result, new imaging modalities have combined nuclear images with CT scans for treatment planning. The hybrid scanners combine anatomic and functional images taken during a single procedure, without having to reposition the patient between scans. In this chapter, multiple ligands beyond clinical standard 18F-fluorodexoyglucose are reviewed.

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12.1 Molecular Imaging in Oncology

CT and MRI assess the effectiveness of cancer therapy (e.g., volumetric and morphological changes), whereas the endpoints rely almost exclusively on the analysis of biopsies by molecular and histopathological methods. While these methods provide microscopic data of the general heterogeneous process, nuclear imaging measures blood flow and metabolic patterns of the target organs. Therefore, a predictive nuclear biomarker is needed to assess clinical endpoints adequately and allow precise measurements of tumor targets on a whole-body image, upon administration of a functional radiolabeled agent. These mechanism-based agents provide image-guided therapy, which may help to decide whether it is better for the patient to discontinue an ineffective treatment at an earlier phase. Molecular imaging agents play a major role in drug discovery and development because of their ability to quantify drug properties in vivo. For example, positron emission tomography (PET) agents show high sensitivity and specific activities, since they are made through a nuclear transformation and use carrier-free forms of isotopes. Thus, PET agents do not produce detectable pharmacologic effects but provide important information concerning the characterization of various diseases such as the central nervous system (epilepsy, psychosis, dementia, Alzheimer's disease) [1–4] and cardiovascular system diseases (myocardial viability) [5]. At the same time it also helped determcine cancer staging, cancer restaging, and treatment planning for malignant diseases [6]. In addition, molecular imaging helps to control and monitor dosage for increased safety and effectiveness. The trends for PET agent's development in oncology are to assist in determining optimal therapeutic dose, to delineate differential diagnosis between inflammation/infection and recurrence, to determine sensitive or resistant to treatment responses, and thus to select the patients who may be good candidates for therapy. Below are the molecular targets for pathway-activated imaging systems.

12.2 Glucose Transporter Target

2-Deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG)-PET has been used to diagnose [7–9] and stage tumors [10–20], myocardial infarction [21], and neurologic diseases [22, 23]. ^{18}F-FDG was developed in 1976 for the specific purpose of mapping brain glucose metabolism in living humans. After the first synthesis of ^{18}F-FDG via an electrophonic fluorination with ^{18}F gas, small-volume enriched water targets were developed, which made it possible to produce large quantities of [^{18}F] fluoride ion via high yield ^{18}O(p,n)^{18}F reaction. This was followed by a major milestone, resulting in the development of a nucleophilic fluorination method that produced ^{18}F-FDG in very high yields. These advances and the remarkable properties of ^{18}F-FDG have largely overcome the limitations of the 110-min half-life of ^{18}F. Although ^{18}F-FDG has been successfully used to image tumors with high glycolytic activity [24]

in the past two decades, it has several limitations that give rise to false-positive/false-negative diagnosis and poor predictive value of tumor response to chemoradiation therapy [25]. For instance, FDG has poor contrast in brain tumor due to the high uptake of glucose in normal brain tissue [26, 27], and exhibits poor differentiation between tumors and inflammatory tissue due to the high uptake of FDG by granulocytes and macrophages [28] .

To improve the diagnosis, prognosis, planning, monitoring, and prediction of cancer treatment results, radiolabeled N-acetylglucosamine of the hexosamine biosynthetic pathway (HBP) has been used as an alternative to PET FDG [29–32]. Glucose and glutamine are substrates in the synthesis of GlcNAc via the HBP and key nutrients for cancer cells. Glutamine is a precursor amino acid for the synthesis of glucosamine, a prominent initiator in the HBP [33]. Briefly, fructose-6-phosphate from the glycolytic pathway combines with glutamine in the presence of the initiating enzyme glutamine–fructose-6-phosphate amidotransferase (GFAT) to synthesize glucosamine-6-phosphate. Subsequent enzymatic steps lead to the production of uridine diphosphate N-acetylglucosamine (GlcNAc), a substrate for O-linked glycosylation that is regulated by the terminating enzyme *O-linked* GlcNAc (O-GlcNAc) *transferase (OGT).* OGT is the enzyme responsible for the addition of a single GlcNAc residue to the hydroxyl groups of serine and/or threonine residues of target proteins. The HBP terminating in O-GlcNAc cycling (O-GlcNAcylation) has been implicated in cellular signaling cascades and regulation of transcription factors involved in cancer biology [34–37]. In fact, O-GlcNAc glycosylation on the serine or threonine residues of nuclear and cytosolic proteins is common and occurs frequently in all multicellular eukaryotes [38]. O-GlcNAc is part of posttranslational modification reactions and appears to modify many nucleocytoplasmic proteins, such as the transcription factors NF-κB and NFATc1. NF-κB and NFATc1 are both downstream targets of O-GlcNAc modification during T- and B-cell activation [39]. However, these transcription factors are constitutively activated in cancers and play an important role in growth and survival [40]. The chelator ethylenedicysteine (EC) was conjugated to glucosamine to mimic a GlcNAc analog called ethylenedicysteine-N-glucosamine (ECG). Radiolabeled ECG has been reported as a promising imaging agent in various tumor models in rodents [29, 31], as well as in humans [30].

12.3 Amino Acid Transporter Target

Radiolabeled amino acids are an alternative in characterizing tumors because of their much higher accumulation in tumors than in normal tissues and their rapid blood clearance. In keeping with the higher uptake, the expression of amino acid transporters is upregulated in cancer cells [41, 42], which indirectly measure cell proliferation [43], and assessment of their activities provides the potential of differential diagnosis and early prediction of treatment responses. Although ^{11}C-methionine is useful for metabolic imaging of tumors by PET [44], it has too

many metabolic pathways, which makes it difficult to obtain a rate constant [20, 21]. Furthermore, it is difficult to image tumors that have slow uptake because of its short half-life. Among all radiolabeled amino acids, aromatic amino acids are more suitable due to the easier chemistry alteration and characterization. However, aromatic amino acids tend to decarboxylate [45], which reduce its ability to get into cells via amino acid transporters. To circumvent these potential limitations, placement of a methyl group at the alpha position could retard metabolism, and hence, greater effort could be then directed toward the ^{18}F- and $^{123/124}$I-labeled amino acids such as 2-[^{18}F] fluoromethyl-L-phenylalanine [46], position 2- and 3-L-[^{18}F] flour-α-methyl tyrosine (FAMT) [47–49], and ^{123}I-labeled L-3-[^{123}I] iodo-α-methyltyrosine (^{123}I-AMT) [50, 51]. L-type amino acid transporter system (LAT), especially LAT1 subtype, is the only system that can transport large neutral amino acids with aromatic rings such as tyrosine, phenylalanine, and tryptophan [52, 53]. LAT family is known to form heterodimers, which contain a chaperone-like heavy chain 4F2hc, and a 12-time-folding transmembrane light chain, which is unique to each subtype [54]. Previous clinical studies showed that uptake of FAMT in the tumor was closely correlated with LAT1 expression and cellular proliferation [41, 48]. Its analog, ^{123}I-AMT, has also been used for SPECT studies on brain and pancreatic tumors [55–57]. High accumulation of ^{123}I-AMT in tumors was reported upon PET examination with ^{124}I-AMT, which was carried out in patients with brain tumors [57]. Though AMT shows very promising clinical results, the cost of using such isotope is prohibitive. Therefore, it is desirable to develop a radiotracer with easier chemistry and more affordable isotope that can be used clinically in most major medical facilities. Few promising chelator–amino acid conjugates in animal studies have been reported [58–60].

12.4 Estrogen Receptor Target

The presence of sex hormone receptors in both primary and secondary breast tumors is an important indicator for both prognosis and choice of therapy of the disease. Currently, receptors are determined by in vitro analysis of biopsy specimens and the use of antiestrogen antibodies. Tamoxifen is the therapy of choice for estrogen receptor-positive (ER+) tumors. The detection and measurement of ER+ tumors by the use of a radiolabeled ligand should provide a useful tool for the diagnosis of primary and secondary tumors. This approach may assist in selecting and following the most favorable therapy, as well as predicting its outcome. To this end a number of variations of substituted estradiol [61, 62] and tamoxifen [63] have been prepared. These compounds have been relatively successful in detecting ER-rich tissue in vivo, such as breast cancer, ovarian cancer, endometriosis, uterine carcinoma, and meningioma. These compounds may predict the response to anticancer therapy agents.

12.5 Tumor Hypoxia Target

The success to the noninvasive detection of the hypoxic fraction of tumors by nuclear molecular imaging is that it allows physicians to select patients for additional or alternative treatment regimens that may circumvent or overcome the ominous impact of tumor hypoxia and improve disease control [64]. Misonidazole (MISO) is a hypoxic cell sensitizer, and labeling it with different radioisotopes could be useful for differentiating a hypoxic but metabolically active tumor from a well-oxygenated active tumor by PET or planar scintigraphy. The nitro group of nitroimidazole (NIM) is enzymatically reduced by ribonucleoside reductase within viable hypoxic cells [65, 66]. ^{18}F-FMISO and clinically user-friendly chelator-based hypoxia tracers have been used to assess the hypoxic component in brain ischemia, myocardial infarction, and various tumors [51, 67]. Moreover, the assessment of tumor hypoxia prior to radiation therapy would provide a rational means to select patients for treatment with radiosensitizing or bioreductive drugs (e.g., mitomycin C). It is also possible to select proper modalities of radiotherapy (proton, neutron vs. photon) by correlating tumor uptake results with tumor response.

12.6 Lipid Metabolism Target

An elevated level of phosphatidylcholine has been found in tumors, which is the most abundant phospholipid in the cell membranes of all eukaryotic cells and provides a potential target for tumor imaging. This elevation is thought to be the result of increased uptake of choline, a precursor of the biosynthesis of phosphatidylcholine. Malignant tumors show a high proliferation and increased metabolism of cell membrane components that will lead to an increased uptake of choline [54]. Thus, radiolabeled choline can be used as a PET marker for imaging cell proliferation in prostate cancer, brain tumors, and many other types of tumors that lack the urinary radioactivity seen with ^{18}F-FDG [68, 69].

12.7 Tumor Cell Proliferation Target

Noninvasive imaging assessment of tumor cell proliferation could be helpful in the evaluation of tumor growth potential and the degree of malignancy and treatment response in the early assessment, prior to changes in tumor size. Radiolabeled nucleoside/nucleotide analogs should provide proliferative imaging information of primary and secondary tumors. They may also assist in selecting and following the most favorable choice of nucleoside/nucleotide therapy and in following its outcome. ^{18}F-Fluorothymidine (FLT) was developed in an attempt to improve the understanding of the biologic behavior of malignant tumors, which should lead to

better prognostic evaluation, treatment follow-up, and patient management. However, ^{18}F-FLT shows a lower accumulation in tumors than ^{18}F-FDG, since it only accumulates in the cells that are in the S phase of the cell cycle. This demonstrates a low sensitivity for nodal staging [70], which indicates that there is still room to develop better markers of cell proliferation biomarkers.

12.8 Gene Expression Target

Radiolabeled pyrimidine and purine probes to image herpes simplex virus type 1 thymidine kinase (HSV-1-*tk*) expression and other reporter genes by PET have been developed [71–73]. For example, pyrimidinenucleoside (e.g., FIAU, 2′-fluoro-2′-deoxy-5-iodo-1-β-D-ribofuranosyl-uracil[FIRU],2′-fluoro-2′-5-methyl-1-β-D-arabinofuranosyl-uracil [FMAU], 2′-fluoro-2′-deoxy-5-iodovinyl-1-β-D-ribofuranosyluracil [IVFRU]), acycloguanosine([9-[(2-hydroxy-1-(hydroxymethyl) ethoxy)methyl]-guanine (GCV) and 9-[4-hydroxy-3-(hydroxymethyl)butyl] guanine (PCV)]), and other 18F-labeled acycloguanosine analogs such as 8-fluoro-9-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl]guanine(FGCV),8-fluoro-9-[4-hydroxy-3-(hydroxymethyl)guanine (FHBG), were developed as reporter substrates to image wild-type and mutant HSV-1-*tk* expression. Recently, imaging, pharmacokinetics, and dosimetry of ^{18}F-FHBG were reported in healthy volunteers as a first step to image the HSV-1-*tk* reporter expression in clinical gene therapy trials. The difficulty with these probes is that HSV-1-*tk* enzyme expression depends on HSV-1-*tk* gene transduction with adenoviral vectors. The level of HSV-1-*tk* enzyme expression is likely to be different in diverse types of transuded cells and tissues, thus limiting the application. Understanding the proliferative activity of tumors could aid in the selection of optimal therapy, by estimating patient prognosis and selecting the proper management.

In summary, in order to improve the diagnosis, prognosis, planning, and monitoring of the cancer treatment, it is important to characterize tumor tissue extensively by the development and application of more tumor-specific pharmaceuticals. Radiolabeled ligands as well as radiolabeled antibodies have opened a new era in scintigraphy detection of tumors and have undergone extensive preclinical evaluation.

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