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Review Article

Fluorine-18-radiolabeled pharmaceuticals for imaging with positron emission tomography, excluding [^{18}F]-fluorodeoxyglucose

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Introduction

Nuclear medicine uses radiopharmaceuticals for the imaging or treatment of various diseases. The pharmacological characteristics of the radiopharmaceutical determine the behavior of the agent in the human body, whereas the radionuclide part determines the radiation properties of the tracer. In recent years, nuclear medicine has focused on tumor imaging and various tracers labeled with technetium-99m (^{99m}Tc), gallium-67 (^{67}Ga), indium-111 (^{111}In) and thallium-201 (^{201}Tl) have been used. Unfortunately, these radiopharmaceuticals in combination with planar scintigraphy or single photon emission tomography do not have the clinically desired sensitivity and specificity and are of limited value in current clinical practice.

Improvements in imaging technology and developments in radiopharmaceutical design have led to the widespread use of positron emission tomography (PET). This technique differs from conventional nuclear medicine imaging modalities by the use of radioactive isotopes that emit positrons. Such positron emission radionuclides can be made in a cyclotron and the most frequently applied radionuclides in PET are carbon-11 (^{11}C), nitrogen-13 (^{13}N) and fluorine-18 (^{18}F). Due to a surplus in positive particles, these radionuclides are unstable and decay by electron capture or positron emission. For positron emission the energy of the nucleus should be at least 1022 keV. Once emitted, the positron combines with an electron found on its way and the 2 antiparticles annihilate, translating their energy in the creation of 2 photons of 511 keV each, emitting under an angle of 180°. PET cameras detect the 2 photons via 2 opposite detectors, the so-called coincidence detection, and events detected within 12 ns are recorded and with the use of electronic and mathematical techniques the three-dimensional distribution of the positron emitting radionuclides can be determined. The resolution of a PET camera is typically 4-5 mm and is seriously restrained by the fact that after emission, a positron travels (a few mm) before the annihilation takes place. One of the great advantages of PET is the possibility to quantify radioactivity, therefore allowing for the quantitative assessment of radiopharmaceutical accumulation and biodistribution in the human body. PET can be combined with computerized tomography (CT) to obtain a better anatomic overview and this is done by the use of image fusion from a PET and CT machine at 2 different locations or as a single apparatus comprising both imaging modalities.

The great potential of PET lies in its ability to elucidate tissue function. This originates in the use of the radionuclides ^{11}C, ^{13}N and ^{18}F which can be incorporated into radiopharmaceuticals used to probe various biochemical pathways. For this reason, nuclear medicine, especially when carried out with PET tracers, is often referred to as "*in vivo* biochemistry". It goes without saying that it is closely related to "molecular imaging" as it depicts and eventually quantifies molecular metabolic processes. The radionuclide half-lives of ^{11}C and ^{13}N are 20 min and only 2 min, respectively. Thus, tracers containing these isotopes can only be used at the site of production. ^{18}F, however, has a half-life of approximately 2 h and can be shipped to institutions a few hours away from the production site. Therefore, it is possible to use [^{18}F]-labeled tracers for PET without having a cyclotron and, thus, these radiopharmaceuticals are of great interest for those

institutions who do not wish to invest in a production site including a medical cyclotron.

As said, many nuclear medicine developments have been directed towards the field of tumor imaging. PET has evolved into a technique that is a well-established, routine procedure in lung and colorectal cancer as well as in melanoma, head and neck cancer and lymphoma. PET has not only proven its value in the diagnostic spectrum but also shown its capability in the field of therapy monitoring and tumor viability testing. For these applications, 2-[18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) has been used extensively and its diagnostic accuracy has proven to be extremely high, often in the range of 90-100% (1).

The accumulation of [18F]-FDG in malignant lesions is based on the increased sugar metabolism in tumor tissue and is thus relatively aspecific (2). Therefore, other [18F]-labeled PET agents are often of great interest as these may reflect more disease-specific characteristics. Various labeling methods have been investigated to label compounds with 18F. Recently, an extensive review of these methods has been presented by Okarvi and interested readers are referred to this article (3) and others (4, 5). It has been recognized that there is a bright future for these agents, widening the spectrum of PET applications. It is the aim of this review to highlight recent advances and potential clinical applications of the various [18F]-labeled radiopharmaceuticals for PET in oncology. As [18F]-FDG has been reviewed recently in this journal (6), this agent has been excluded from the present review.

Amino acids

The hypermetabolic state of malignant cells involves increased peptide and protein biosynthesis. An increased protein biosynthesis rate in local tissue is associated with both repair processes in response to neoplastic cell formation and increased proliferation of normal and malignant cells. Measurement of protein synthesis can be carried out using [18F]-labeled amino acids because of the great variety in the amino acid composition of proteins and because amino acids serve as substrates for various other biochemical pathways. However, measurement of peptide/protein synthesis requires careful selection of the amino acid to be labeled.

[18F]-α-Methyltyrosine ([18F]-AMT)

Carboxyl-labeled amino acids such as L-[1-11C]-tyrosine have demonstrated a high uptake rate in various types of malignancy and a low uptake in benign lesions (7). This tracer appears to be suited to measure protein synthesis and thus synthesis of an [18F]-labeled tyrosine compound was encouraged. After initial studies in mice (8, 9), the clinical potential for tumor detection was investigated in tumors of the brain (10) and in the musculoskeletal system (10, 11) (Fig. 1). These investigations are only academic in nature since tumor detection is easily achieved with CT or MRI. The clinical value with regard to therapy follow-up has not been published.

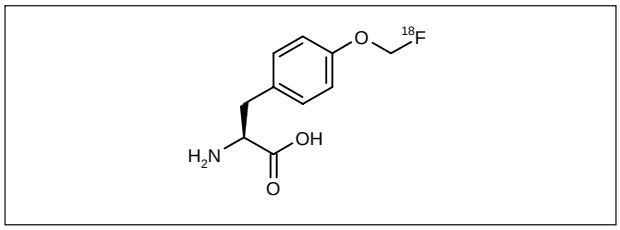

Fig. 1. [18F]-α-Methyltyrosine.

[18F]-Ethyl-L-tyrosine ([18F]-FET)

[18F]-FET is a recently described amino acid analogue that has shown high accumulation in experimental colon and mammary tumors (12). Biodistribution studies in mice revealed high *in vivo* stability and low accumulation in nontumor tissue (13). [18F]-FET has been compared with [11C]-labeled methionine in patients with brain tumors and uptake and image contrast appeared to be very similar (14), although a high tissue specificity was not obtained.

[18F]-Phenylalanine ([18F]-Phe)

The clinical value of [11C]-labeled methionine has been demonstrated in patients with glioma, particularly in the prediction of histological grade and where follow-up and prognosis are concerned (15, 16). The high physiological uptake of this [11C]-labeled agent in the abdomen is a drawback and for that reason [18F]-Phe was proposed for imaging and staging of these brain tumors (17, 18).

cis-4-[18F]-Fluoroproline (cis-[18F]-Fpro)

Tumor growth is associated with enhanced collagen synthesis and since proline and hydroxyproline are major constituents of mammalian collagen, [18F]-labeled proline may be a potentially effective tracer to study tumor cell growth (19). The tumor uptake of *cis*-[18F]-Fpro has been demonstrated in various animal models. Although some evidence suggests that this tracer reflects collagen synthesis in humans, no relevant accumulation was seen in malignant tissue in a series of patients with urological tumors (19, 20) (Fig. 2).

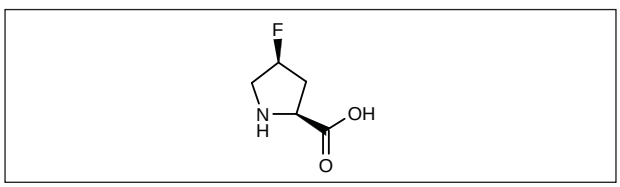

Fig. 2. *cis*-4-[18F]-Fluoroproline.

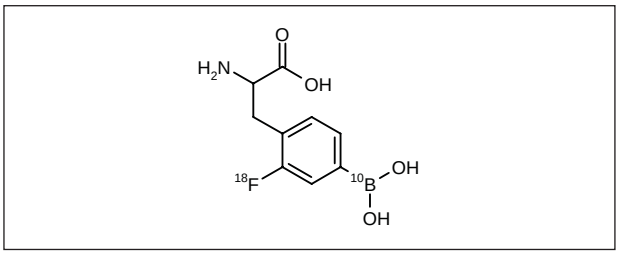

Fig. 3. 4-Borono-2-[^{18}F]-fluoro-D,L-phenylalanine.

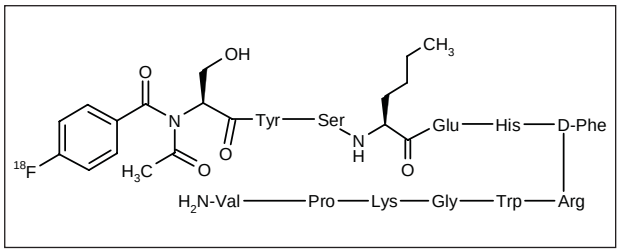

Fig. 5. [^{18}F]-α-Melanocyte stimulating hormone.

4-Borono-2-[^{18}F]fluoro-D,L-phenylalanine ([^{18}F]-BPA)

BPA is a target molecule for boron capture neutron therapy. This therapy involves the capture of thermal neutrons in the boron nucleus after which alpha particles for local radiation therapy are emitted (21) (Fig. 3). Avid uptake of [^{18}F]-BPA has been demonstrated in melanoma tissue in animals and human studies have revealed the accumulation of this agent in glioma and melanoma (22, 23). This is an important finding, as the quantitative uptake determination would allow for the assessment of boron levels in the tumor necessary for accurate neutron dosimetry. Although boron capture therapy presents various difficulties in clinical practice (*e.g.,* patients need to be irradiated with thermal neutrons from nuclear reactors), this approach holds considerable promise for highly effective tumor ablation after initial surgical therapy.

Peptides

[^{18}F]-(Arg-Gly-Asp)-containing glycopeptide

This RGD-containing peptide can be used as a ligand for the cell adhesion receptor $\alpha_v\beta_3$ integrin, a cell adhesion receptor involved in tumor growth, local invasiveness and metastatic potential (24), as well as tumor-induced angiogenesis (25). Adding a sugar moiety to the RGD-containing peptide improved the pharmacokinetics by increasing activity concentration in the blood and significantly reducing liver uptake (26). When this agent was examined in mice bearing murine osteosarcoma and human melanoma models, it was concluded that it is suitable for determination of the $\alpha_v\beta_3$ integrin status and therapy monitoring (27) (Fig. 4).

[^{18}F]-α-Melanocyte stimulating hormone (α-MSH)

α-MSH is a tridecapeptide that binds to its melanocortin 1 (MC1) receptor (involved in skin pigmentation and the melanizing response after exposure to UV radiation) of melanoma tissue (28) and labeling of this peptide for melanoma detection was proposed. The result is [^{18}F]-α-MSH (Fig. 5). However, a low labeling efficiency prevented adequate PET imaging (29). In this regard, one may wonder whether the scintigraphic detection of these skin lesions is clinically useful. If visual inspection of the skin would reveal a suspect lesion, good clinical practice would call for a biopsy and subsequent tissue characterization, whereas in the case of metastases, other imaging techniques would be employed. We believe, therefore, that further efforts to prepare [^{18}F]-α-MSH should not be undertaken.

[^{18}F]-Octreotide

Various types of human tumors, notably neuroendocrine tumors, small cell lung cancers and medullary thyroid carcinoma, express somatostatin receptors in a high density. Different synthetic peptides have shown high binding to human somatostatin receptors and octreotide is one of them. In nuclear medicine,

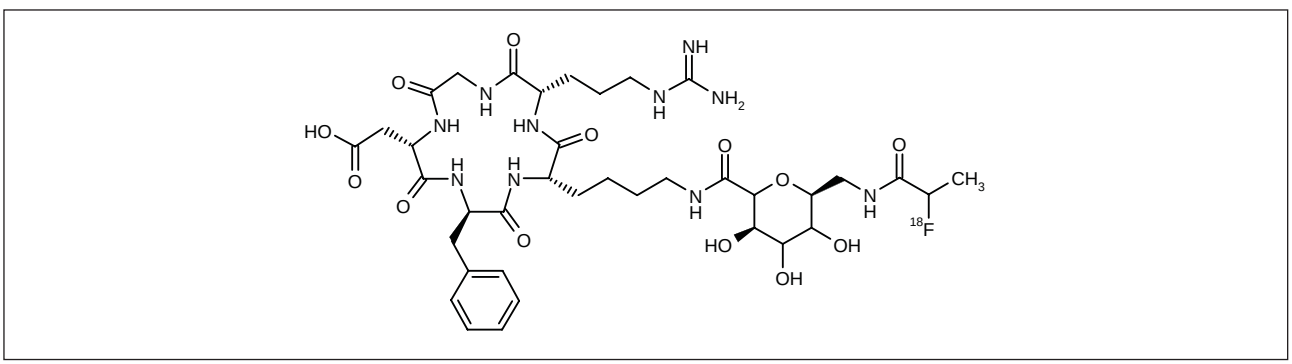

Fig. 4. [^{18}F]-(Arg-Gly-Asp) RGD-containing glycopeptide.

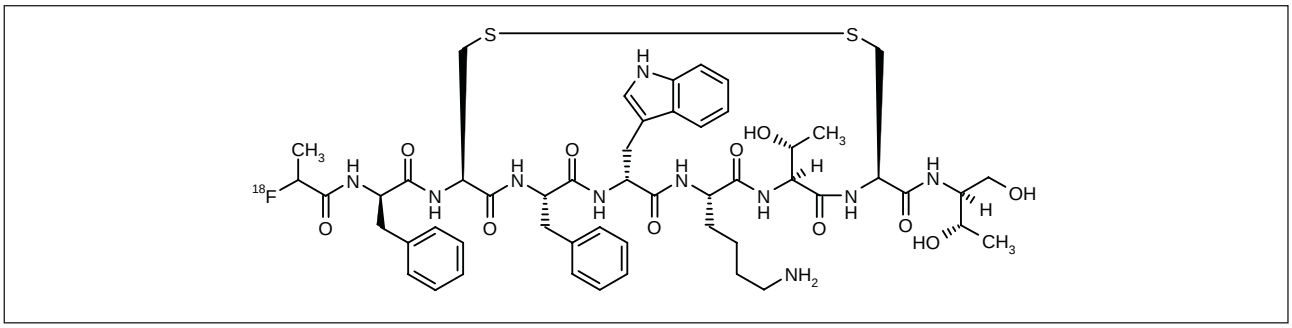

Fig. 6. [18F]-Octreotide.

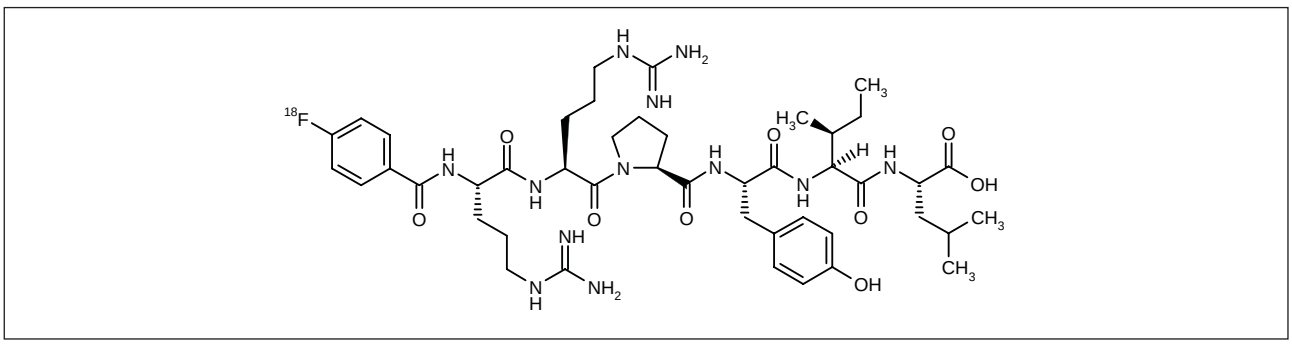

Fig. 7. [18F]-Neurotensin(8-13) analog.

[111In]-labeled octreotide has been used extensively and has an established role in the diagnostic and therapeutic arsenal to treat cancer patients. [18F]-Octreotide was synthesized (30) (Fig. 6) but has been largely overshadowed by [111In]-octreotide, which is easily available and has a well defined clinical usefulness (31). The only role for [18F]-octreotide might be in PET where accurate quantification of somatostatin receptors would be useful for therapy monitoring.

[18F]-Neurotensin(8-13) analogues

Different tumors overexpress the neurotensin receptor 1 and [18F]-labeled neurotensin was proposed for imaging of these malignancies and for quantification of receptor expression (32) (Fig. 7). Initial experiments in mice, however, have shown considerable proteolytic degradation of the agent, preventing its use in PET (32).

[18F]-Vasoactive intestinal peptide (VIP)

This 28-amino acid peptide has broad biological activity in various cells and tissues, mediating growth and proliferation of normal and malignant cells. Increased VIP receptor expression occurs in various tumors, including adenocarcinomas, breast cancer and pancreas carcinoma. VIP has been labeled with 123I and clinical studies have demonstrated its uptake in a large variety of primary tumor and metastases. It is therefore questionable as to whether there would be a role for [18F]-VIP in clinical practice, except for accurate quantification of receptor density (33).

Proteins

Only a few efforts have been undertaken to label proteins with 18F. This is not surprising, since fluorination of these large and complicated compounds may not preserve biological activity and reactivity. Efforts have been undertaken to label erythropoietin (EPO) and transferrin to study EPO receptors in erythroleukemia and iron uptake in cancer cells, respectively (34-36).

The limited success of radiolabeled monoclonal antibodies for cancer detection and treatment has resulted in a loss of interest in radiolabeling these compounds with 18F.

Steroids

16α-[18F]-Fluoroestradiol-17β (FES)

Estrogen receptors can be targeted with estradiol and the imaging of these receptors has been accomplished with [123I]- or [18F]-labeled estradiol (Fig. 8). FES has proven to be suitable for tumor imaging (37), predicting of

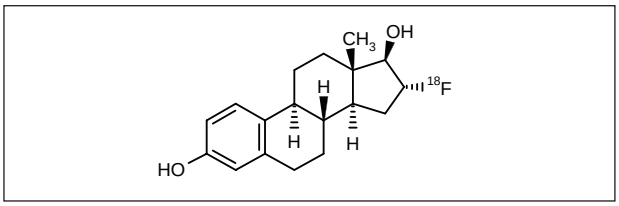

Fig. 8. 16α-[^{18}F]-Fluoroestradiol-17β.

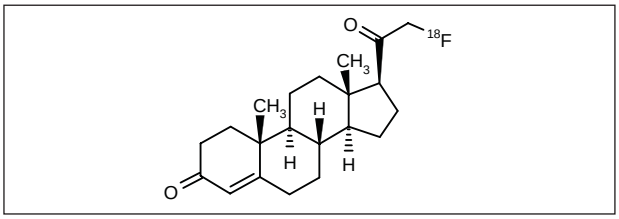

Fig. 9. [^{18}F]-Nor-progesterone.

hormone therapy (38) and monitoring tamoxifen (a nonsteroidal estrogen antagonist) response in breast cancer (39). Its main indication is the prediction of therapeutic effect of tamoxifen therapy in patients with breast carcinoma. Furthermore, it has been used to study estrogen receptor expression in meningioma (40).

In addition to FES, another compound suitable for estrogen receptor imaging has been proposed and 17α-ethynyl-16β-[^{18}F]-fluoro-11β-methoxyestradiol ([^{18}F]-FMOX) was synthesized and tested. Clinical evaluation of this fluorinated compound, however, did not demonstrate better targeting characteristics than FES (41).

Other steroids

To visualize and quantify progesterone receptors in tumor tissue, norprogesterone has been labeled with ^{18}F (Fig. 9). Rapid biotransformation of this agent after i.v. injection in patients has stopped further evaluation of this compound. After the initial publication by Verhagen *et al.* (42), no further reports of this radiotracer have appeared in the literature.

The detection and quantification of androgen receptors in, for example, metastatic prostate cancer has been achieved with 16β-[^{18}F]-5α-dihydrotestosterone (43) and with 7α-[^{18}F]-fluoro-17α-methyl-5α-dihydrotestosterone (44) with reasonable success. Such radiotracers may be effective in better understanding the pathophysiology of this disease. Whether these labeled testosterone derivatives would be of help clinically remains to be seen.

Hypoxia agents

The most important nonsurgical treatment for cancer is radiotherapy. However, for a number of tumors, radiotherapeutic treatment may fail due to hypoxia (PO_2 < 5 mm) of tumor tissue. Identification and quantification of hypoxia in these tumors may, therefore, predict outcome and identify patients who might benefit from concomitant radiosensitizing therapy to overcome the hypoxia effect (45-47). Furthermore, it can be used to measure the response of targets to therapeutic interventions (48).

Several invasive procedures have been developed to measure the degree of oxygenation in tumors. They are predictive of response to therapy, but none of these is suitable for routine clinical use due to their technical complexity, inconvenience and inability to produce repeated measures. In light of this, it is understandable that noninvasive imaging with hypoxia-directed radiopharmaceuticals would be of great clinical utility in cancer patients. Most such radiopharmaceuticals in development use 2-nitroimidazole as targeting moiety. Nitroimidazoles are selectively trapped in hypoxic but not viable cells. The nitro group undergoes enzymatic reduction in all tissues, but is immediately oxidized back to the starting material in the presence of normal levels of oxygen. On the other hand, at extremely low levels of oxygen, the nitro group is further reduced, resulting in reactive intermediates that can bind to cellular macromolecules. Labeled to an appropriate radioisotope (^{18}F), 2-nitroimidazole represents the basis for PET imaging of hypoxia (49). Several [^{18}F]-labeled 2-nitroimidazoles have been synthesized: [^{18}F]-fluoromisonidazoles ([^{18}F]-FMISO) (48-54) (Fig. 10), [^{18}F]-fluoroerythronitroimidazole ([^{18}F]-FETNIM) (55, 56) (Fig. 11), 2-(2-nitroimidazol-1*H*-yl)-*N*-(3-[^{18}F]-fluoropropyl)acetamide ([^{18}F]-EF1) (57, 58) (Fig. 12), [^{18}F]-2-(2-nitroimidazol-1*H*-yl)-*N*-(3,3,3-trifluoropropyl)acetamide ([^{18}F]-EF3) (59) (Fig. 13), [^{18}F]-2-(2-nitroimidazol-1*H*-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide ([^{18}F]-EF5) (60) (Fig. 14) and [^{18}F]-fluoroetanidazole ([^{18}F]-FETA) (61, 62).

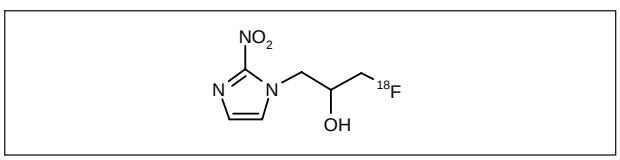

Fig. 10. [^{18}F]-Fluoromisonidazole.

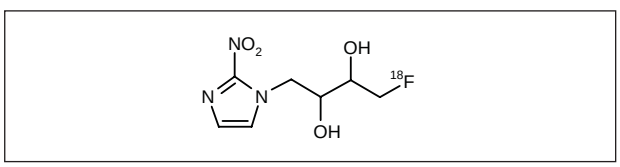

Fig. 11. [^{18}F]-Fluoroerythronitroimidazole.

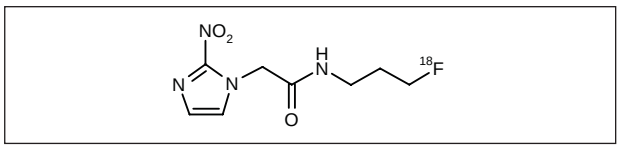

Fig. 12. 2-(2-Nitro-1*H*-imidazol-1-yl)-*N*-(3-[^{18}F]-fluoropropyl)acetamide ([^{18}F]-EF1).

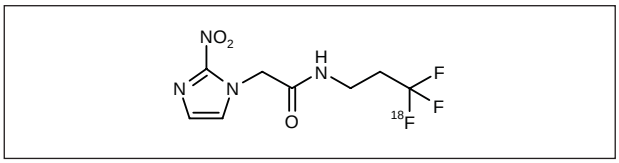

Fig. 13. [18F]-2-(2-Nitroimidazol-1*H*-yl)-*N*-(3,3,3-trifluoropropyl)-acetamide ([18F]-EF3).

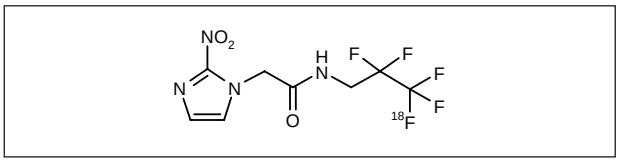

Fig. 14. [18F]-2-(2-Nitroimidazole-1*H*-yl)-*N*-(2,2,3,3,3-pentafluoropropyl)acetamide ([18F]-EF5).

Of these compounds, the first to be developed and the most investigated is [18F]-FMISO (63). It has been reported that [18F]-FMISO can be used to quantify regional hypoxia in human tumors such as non-small cell lung cancer (64), nasopharyngeal carcinoma (65, 66), prostate cancer, hepatocellular carcinoma (50) and other malignancies (67). However, synthesis of [18F]-FETNIM is easier and less costly (68) and more hydrophilic than [18F]-FMISO. Although it has been demonstrated that [18F]-FETNIM can detect tumor hypoxia (55, 68), a study by Kaisa *et al.* (56) showed that uptake of [18F]-FETNIM in head and neck cancer is highly variable, a significant limitation of the compound.

The oxygen dependence of cellular uptake of EF5 was initially tested in two cell lines (69), after which its tumor specificity and oxygen dependency was demonstrated in a rat glioma model (70). Furthermore, *in vivo* experiments in mice and rats provided evidence that this agent can be used as an *in vivo* predictive assay of individual tumor hypoxia and resultant therapy resistance (71, 72). The labeling of EF5 with the radionuclide 18F has paved the way for use in patients and the reporting of the first clinical results will only be a matter of time (60).

Although few relevant *in vitro* and *in vivo* data have been reported for other [18F]-labeled hypoxia agents (57), developments in this area are interesting and will undoubtedly lead to further investigations. An independent marker of the oxygenation of tissue could have many useful clinical applications of which cancer is only one. Another application to consider is anaerobic, odontogenic infection in patients undergoing radiation therapy for head and neck tumors (65).

Gene therapy

The directed introduction and expression of new genetic information in cells of an organism for therapeutic purposes is known as gene therapy and was introduced in the early 1980s. Since 1989, many clinical trials with different targets, such as hereditary monogenic disease (*e.g.*, cystic fibrosis), multifactorial disease (*e.g.*, diabetes), infectious disease (*e.g.*, AIDS) and cancer, have been and continue to be carried out.

Some possible strategies for gene therapy in cancer are the induction of cell death using genes which encode for toxic products, stimulation of the immune system to recognize and destroy cancer cells, and inhibition of "cancer genes". At present, gene therapy in cancer patients holds promise, as new gene-based treatments may improve tumor control with far less morbidity than conventional surgery and chemotherapy (73, 74).

There are several methods to monitor the expression of the reporter gene once it is introduced into the desired tissue (75, 76). Conventional methods include (i) tissue biopsy followed by immunohistochemistry or histochemical staining for reporter gene protein, (ii) *in situ* hybridization with probes targeted for reporter gene mRNA and (iii) sampling of blood in cases in which the reporter gene product is a protein secreted into the blood stream. An important shortcoming of these methods is the fact that they do not allow the noninvasive assessment of the location and magnitude of gene expression in the body. Other methods include green fluorescent protein and luciferase gene expression and they have provided a way to image reporter gene expression in some living animals transparent to light. However, these imaging techniques are very limited as well and would not work in humans. Thus, noninvasive and quantitative imaging of reporter gene expression in living animals and in humans would be a valuable development (75) permitting longitudinal examinations of both somatically transferred DNA in experimental animals and patients and transgenic constructs expressed in experimental animals (76, 77).

At present, clinical investigations are directed at the monitoring of human gene therapy in tumors transduced with the herpes simplex virus type 1-thymidine kinase (HSV1-tk) (75). HSV1-tk is a commonly studied suicide gene for cancer gene therapy and has been investigated in many different clinical trials (78). The HSV1-tk gene is introduced into target cells and codes for the formation of viral thymidine kinase (HSV1-TK). HSV1-TK converts acycloguanosine prodrugs to toxic compounds that destroy the target cells (75, 76, 78). The following [18F]-labeled acycloguanosine derivatives have been developed to image HSV1-tk expression with PET: 9-[(3-[18F]-fluoro-1-hydroxy-2-propoxy)methyl]guanine ([18F]-FHPG) (75, 79-85) (Fig. 15a), 8-[18F]-fluoroganciclovir ([18F]-FGCV) (75-77, 85, 86) (Fig. 15b),

8-[18F]-fluoropenciclovir ([18F]-FPCV) (76, 85, 87, 88) (Fig. 15c) and 9-(4-[18F]-fluoro-3-hydroxymethylbutyl)guanine ([18F]-FHBG) (78, 83, 85, 89-92) (Fig. 15d).

[18F]-FHPG

The results of *in vitro* studies in human colon cancer cells and *in vivo* studies in tumor-bearing nude mice suggest that [18F]-FHPG is a potential *in vivo* PET imaging

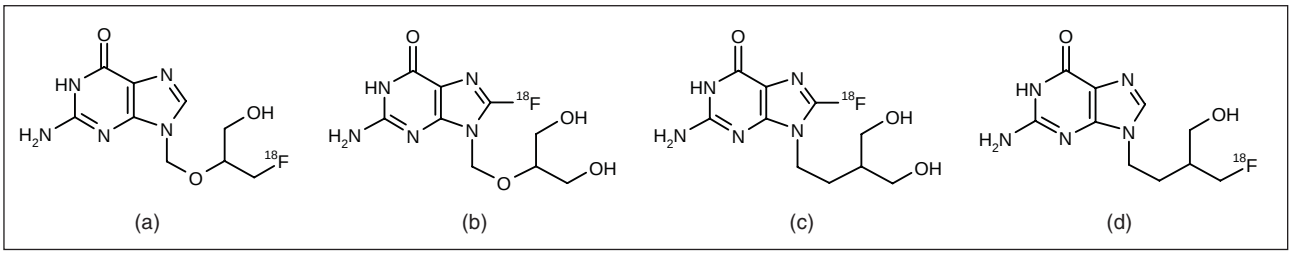

Fig. 15.a) 9-[(3-[^{18}F]-Fluoro-1-hydroxy-2-propoxy)methyl]guanine (FHPG); b) 8-[^{18}F]-Fluoroganciclovir (FGCV); c) 8-[^{18}F]-Fluoropenciclovir (FPCV); d) 9-[4-[^{18}F]-Fluoro-3-(hydroxymethyl)butyl]guanine (FHBG).

agent for monitoring gene incorporation and expression in gene therapy of cancer (81). In C6 rat glioma cells, [^{18}F]-FHPG was shown to be a promising tracer for monitoring HSV1-tk gene expression *in vivo* with PET (80). In a murine model, a high specificity for HSV1-tk expression was shown (82).

[^{18}F]-FGCV

After an initial study in a murine model with [^{18}F]-FGCV and micro PET imaging (86), further investigations with [^{18}F]-FGCV as a PET reporter probe for noninvasive and repeated imaging of HSV1-tk gene expression with PET were discontinued. Additional studies demonstrated that [^{18}F]-FGCV associates with HSV1-tk. It is useful in the quantification of HSV1-tk reporter gene expression, but there is a lower accumulation of [^{18}F]-FGCV as compared with ganciclovir for similar levels of HSV1-tk expression (75).

[^{18}F]-FPCV

[^{18}F]-FPCV can be used as a PET reporter probe to image HSV1-tk gene expression in animals (76). In a study using cell cultures and mice, [^{18}F]-FPCV was compared to [^{18}F]-FGCV in monitoring the expression of HSV1-tk reporter gene (88). The results from this test indicate that [^{18}F]-FPCV is a better reporter probe than [^{18}F]-FGCV for imaging lower levels of HSV1-tk gene expression *in vivo*.

[^{18}F]-FHBG

[^{18}F]-FHBG is a [^{18}F]-labeled analogue of the antiviral drug penciclovir. It is reported to be superior to [^{18}F]-FPCV as a PET reporter probe for monitoring HSV1-tk gene expression *in vitro* (92). The stability, dosimetry and safety of [^{18}F]-FHBG was studied in healthy human volunteers (78). The agent was found to have desirable *in vivo* characteristics including stability, rapid blood clearance, low background signal and biosafety, and also has an acceptable radiation dosimetry in humans.

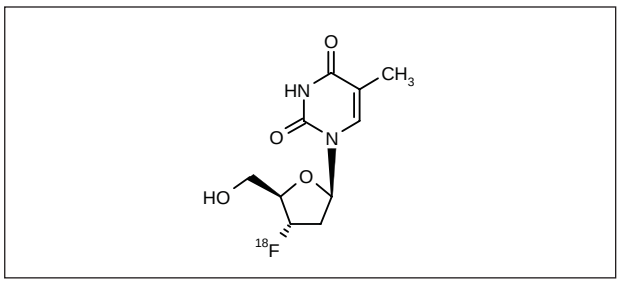

Fig. 16. 3'-Deoxy-3'-[^{18}F]-fluorothymidine ([^{18}F]-FLT).

Proliferation

As mentioned previously, [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) is the most widely used agent for imaging tumors with PET. However, [^{18}F]-FDG is not a highly selective tracer for tumor imaging or for the assessment of proliferation since glucose is used in many cell types. Moreover, because [^{18}F]-FDG is also taken up by inflammatory cells, it is impossible to differentiate between malignancy and inflammatory processes. In order to detect areas of increased proliferative activity and measure the rate of cellular proliferation, various more specific [^{18}F]-labeled agents have been developed: 3'-deoxy-3'-[^{18}F]-fluorothymidine ([^{18}F]-FLT) (93-101) (Fig. 16), 5-[^{18}F]-fluorouracil ([^{18}F]-FU) (102-107) (Fig. 17), [^{18}F]-fluorocholine/[^{18}F]fluoromethyl-dimethyl-2-hydroxyethylammonium ([^{18}F]-FCH) (108-113) (Fig. 18),

[^{18}F]-fluorodeoxyadenosine ([^{18}F]-FAD) (114), 5-[^{18}F]-2'-deoxyuridine ([^{18}F]-FdUrd) (115) and 2'-fluoro-5-([^{18}F]-methyl)-1-β-D-arabinofuranosyluracil ([^{18}F]-FMAU) (93).

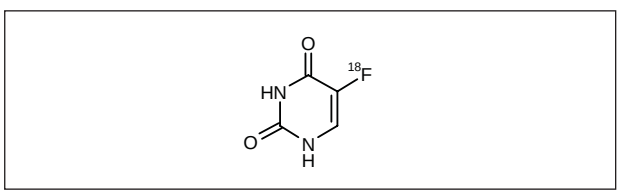

Fig. 17. 5-[^{18}F]-Fluorouracil ([^{18}F]-FU).

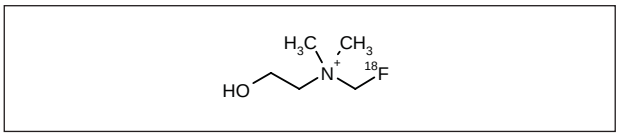

Fig. 18. [18F]-Fluorocholine ([18F]-FCH).

[18F]-FLT

3'-Deoxy-3'-[18F]-fluorothymidine ([18F]-FLT), an [18F]-labeled thymidine analogue, is retained in proliferating cells after phosphorylation by thymidine kinase 1. Thymidine kinase 1 activity is a measure of cellular proliferation. This was illustrated in patients with brain tumors, in which cases a high target-to-nontarget ratio was obtained due to proliferating tumor cells in contrast to the non- or virtually nonproliferating brain cells (2, 99). Breast cancer and its lymph node metastases, as well as thoracic tumors are well depicted using [18F]-FLT PET, which is facilitated by the low uptake of [18F]-FLT in the mediastinum and axillary and pulmonary tissue (2, 97, 98). Normalization of tumoral uptake of [18F]-FLT after chemotherapy is indicative of efficient treatment (100).

Abdominal PET imaging with [18F]-FLT is also possible. Although physiologic retention is seen in the liver, kidney and bladder, various tumors of the gastrointestinal tract can be imaged including malignant lesions in the stomach, esophagus, colon and pancreas (101).

[18F]-FU

5-Fluorouracil (FU) is a widely used drug for chemotherapy, especially of nonresectable carcinomas of the colon and breast (102, 103). The agent arrests cell proliferation by blocking thymidylate synthase, the enzyme that catalyzes *de novo* synthesis of the DNA precursor thymidylate, resulting in the formation of defective fluorinated RNA and DNA. 5-FU can only be toxic after cell uptake and phosphorylation to fluoronucleotides (102). Two studies showed that PET imaging with [18F]-FU is a valuable tool to determine FU chemotherapy outcome before beginning therapy. Only patients with a high uptake of [18F]-FU demonstrated a response to therapy (106, 107). The use of [18F]-FU PET has revealed various problems, including low tumor uptake and rapid catabolism of this radiolabeled agent, which hampers the interpretation of the PET images (102, 103). Studies in rats and a trial involving 6 patients showed that eniluracil (5-ethynyluracil), an inhibitor of the catabolic enzyme dihydropyrimidine dehydrogenase which leads to an increase in plasma FU half-life, increased tumor accumulation of [18F]-FU relative to host tissues (102, 103).

[18F]-FCH

Choline is considered a vitamin necessary for the synthesis of phospholipids in cell membranes and various other biochemical functions (116). Choline metabolism in tumor cells is directed primarily towards membrane synthesis (proliferation) and the *de novo* synthesis of choline is negligible in tumor cells (113). This makes [18F]-FCH a logical and theoretically attractive agent for PET tumor imaging. Its efficacy has been shown clinically in the evaluation of metastatic prostate cancer and recurrent brain cancer (108, 110, 111).

Sigma receptors

Recently, it was shown that different [18F]-radiolabeled compounds that bind to sigma receptors may be useful in oncology for detecting tumors by PET. Sigma receptors have been studied extensively and at least 2 different subtypes, σ1 and σ2 receptors, have been identified. It appears that sigma receptors (a distinct class of receptors expressed in liver, kidneys, endocrine glands and the central nervous system) are overexpressed on different cancer cells (117). Furthermore, it has been found that σ2 receptors may serve as biomarkers of tumor proliferation. Proliferative cells of mouse mammary carcinoma had 10 times more σ2 receptors per cell than quiescent mouse mammary carcinoma cells (118). The various ligands that have been proposed for selective imaging of sigma receptors are described below.

N-*(*N*-Benzylpiperidin-4-yl)-2-[18F]fluorobenzamide (2-FBP)*

Binding assays and biodistribution studies in mice revealed that [18F]-2-FBP is suitable as a radioligand of sigma receptors in PET scanning (119) (Fig. 19). This agent has been used as a ligand in PET imaging in breast tumor-bearing mice. Results of this study suggest that [18F]-2-FBP may be a potential ligand for PET imaging of breast cancer (120).

2-[18F](N-Fluorobenzylpiperidin-4-yl)4-iodobenzamide

This compound has been synthesized to evaluate its potential in PET scanning. Animal studies revealed that it is useful to map sigma sites *in vivo* with PET. However, among the various drawbacks there is high liver and adrenal uptake and slow hepatic clearance (121).

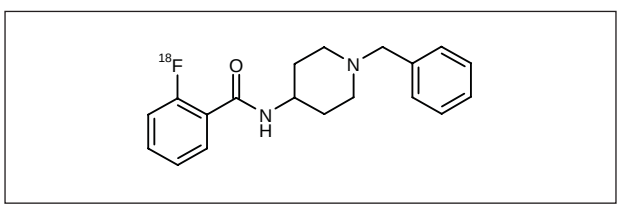

Fig. 19. *N*-(*N*-Benzylpiperidin-4-yl)-2-[18F]fluorobenzamide.

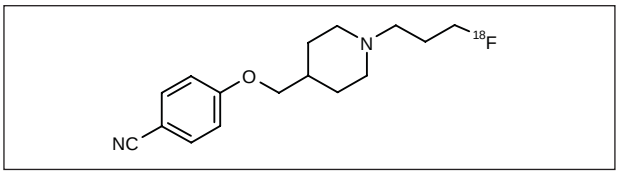

Fig. 20. [18F]-1-(3-Fluoropropyl)-4-(4-cyanophenoxymethyl)-piperidine.

[18F]-Fluoroethyl SA-4503 ([18F]FE-SA-4503)

SA-4503 (1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride) has been found to be a potent and selective agonist for the sigma1 receptor subtype in the brain (122). An [18F]-fluoroethyl analogue has been prepared and evaluated in animals to investigate its suitability for *in vivo* measurement of sigma receptors with PET. It was concluded that [18F]-FE-SA-4503 showed specific binding to sigma receptors in animal tissues, making further evaluation of this compound in PET scanning suitable (123).

[18F]-1-(3-Fluoropropyl)-4-(4-cyanophenoxymethyl)-piperidine

This compound has been synthesized and examined in animal studies as a selective high-affinity ligand for sigma1 receptors. It appeared that this compound, with its appropriate lipophilicity, can be used as a receptor targeted imaging agent, thus making it suitable for the *in vivo* evaluation of σ_1 receptors (124) (Fig. 20).

[18F]N-(4'-Fluorobenzyl)-4-(3-bromophenyl)acetamide

Biodistribution studies were conducted with this compound (Fig. 21) in mice bearing mammary adenocarcinoma. This tracer was found to have high affinity for σ_1 and σ_2 receptors and that blocking the σ_1 receptor resulted in a higher tumor to background ratio, thus making it suitable for σ_2-selective imaging. It has also been compared with [18F]-FDG and [125I]-IUDR and it appears that selective σ_2 receptor imaging with this compound may be a better anatomic imaging agent for breast cancer than [18F]-FDG and a better functional imaging agent than [125I]-IUDR (125). However, it remains to be determined whether it is a more appropriate than [18F]-FLT as an imaging agent for measuring the proliferative status of breast tumors.

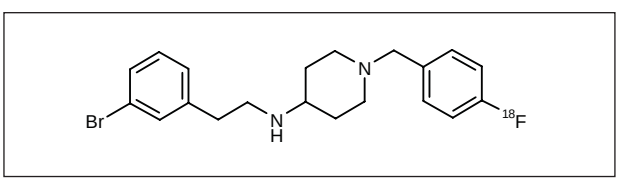

Fig. 21. [18F]-*N*-(4'-fluorobenzyl)-4-(3-bromophenyl)acetamide.

Discussion

In this article we discussed various new radiopharmaceuticals labeled with the radionuclide 18F that could be used for PET imaging in centers where cyclotron are not available for the preparation of [11C]- or [13N]-labeled compounds. The relatively long half-life of around 2 h for 18F makes this isotope suitable for shipment and would enable its use in more distant PET centers with a radiopharmaceutical laboratory but no isotope production facilities. For this review, we selected those agents that hold promise for clinical use and provide additional information to CT and MRI, which are primary tools for (differential) diagnosis. In contrast with CT and MRI, PET allows the study of kinetics and biological processes at a cellular level. Therefore, this method is suited for tumor grading and the detection of vital tumor tissue after irradiation or surgery. In addition, PET enables easy and rapid whole body imaging which is of the utmost importance for detection of metastases and, thus, for tumor staging.

The present communication highlights developments in this field but many of these radiopharmaceuticals have not yet been tested in humans and are only in a development phase. However, we hope to have pointed out in which direction progress is going. If only 1 of 10 of the experimental compounds mentioned in this article were to be clinically available within 5 years, it would signify a step forward in cancer diagnosis and treatment. These radiopharmaceuticals provide unique information that cannot be obtained with other imaging modalities and they offer the additional value in the clinical management of patients. This so-called "*in vivo* biochemical" information on tumor status can be of great significance for subsequent therapy decisions such as radiation therapy/chemotherapy or further surgical intervention.

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