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Review Article

Positron emission tomography (PET) imaging with ^{18}F-based radiotracers

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Abstract: Positron Emission Tomography (PET) is a nuclear medicine imaging technique that is widely used in early detection and treatment follow up of many diseases, including cancer. This modality requires positron-emitting isotope labeled biomolecules, which are synthesized prior to perform imaging studies. Fluorine-18 is one of the several isotopes of fluorine that is routinely used in radiolabeling of biomolecules for PET; because of its positron emitting property and favorable half-life of 109.8 min. The biologically active molecule most commonly used for PET is 2-deoxy -2-^{18}F-fluoro-β-D-glucose (^{18}F-FDG), an analogue of glucose, for early detection of tumors. The concentrations of tracer accumulation (PET image) demonstrate the metabolic activity of tissues in terms of regional glucose metabolism and accumulation. Other tracers are also used in PET to image the tissue concentration. In this review, information on fluorination and radiofluorination reactions, radiofluorinating agents, and radiolabeling of various compounds and their application in PET imaging is presented.

Keywords: Fluorine-18, positron emission tomography (PET), PET radiopharmaceuticals

Introduction

The chemistry of fluorine has been popular since 1948, when Cady et al. [1] published in the first series of papers on the hypofluorite compounds, including the oxygen-fluorine group, -OF. Trifluoromethyl hypofluorite, CF_3OF, was prepared by catalytic fluorination of methanol (CH_3OH). Cady also achieved the first synthesis and characterization of xenon hexafluoride, which is of particular interest to chemists, because xenon, as one of the noble gases, shuns other elements, refusing to take part in any kind of chemical bond [1]. Extensive research on fluorine chemistry has continued ever since.

Fluorine is the most electronegative element in the periodic table. When bound to carbon, it forms the strongest bonds in organic chemistry, and this makes fluorine substitution attractive for the development of pharmaceuticals and a wide range of specialty materials. The C-F bond, although highly polarized, gains stability from the resultant electrostatic attraction between the polarized atoms. The C-F bond and its characteristics have been described extensively in a review [2]. The C-F bond is commonly found in pharmaceuticals and agrochemicals because it is generally metabolically stable and fluorine acts as a bioisostere of the hydrogen atom. An estimated one fifth of pharmaceuticals contain fluorine, including several top-selling drugs [3], such as 5-fluorouracil (5-FU) [4, 5], flunitrazepam (Rohypnol) [6], fluoxetine (Prozac) [7, 8], paroxetine (Paxil) [9], ciprofloxacin (Cipro) [10, 11], mefloquine [12, 13], and fluconazole [14, 15]. Other examples of use include the fluorine-substituted ethers, volatile anesthetics such as the commercial products methoxyflurane [16], enflurane [17, 18], and isoflurane [19].

Based on information from the Isotopes of Fluorine Wikipedia page [20], fluorine has several isotopes, ^{19}F, ^{18}F, ^{17}F, ^{20}F, and ^{21}F. Except for ^{19}F, these isotopes are radioactive and have very short half-lives, especially ^{17}F, ^{20}F and ^{21}F. ^{19}F and ^{18}F are used by the scientific community, especially ^{18}F, which has a half-life of 109.8 min. ^{18}F emits a positron that collides

with an electron, which is called an "annihilation reaction" and produces two photons with 511 Kev (gamma radiation) 180° apart [21-23]. Because of its short half-life and positron emission, ^{18}F is widely used in molecular imaging of biological and biochemical processes, including early detection of many diseases and assessment of treatment response by positron emission tomography (PET) [24-34].

PET is a nuclear medicine imaging technique that produces a three-dimensional image of functional processes in the body [27, 28]. The system detects pairs of gamma rays emitted indirectly through an annihilation reaction by a positron-emitting radionuclide, such as ^{18}F, which has been injected into the body through a biologically active molecule as a carrier. Three-dimensional images of the radiotracer concentrations within the body are then reconstructed by a computer using appropriate software and analysis. The biologically active molecule most commonly used for PET is 2-deoxy-2-^{18}F-fluoro-β-D glucose (^{18}F-FDG), an analogue of glucose, which is used for early detection of tumors [29-31] and assessment of response to cancer therapy [24, 26]. The concentration of tracer accumulation (i.e., the PET image) provides information about tissue metabolic activity in terms of regional glucose metabolism, which is known to be increased in cancer cells compared with normal cells. Although ^{18}F-FDG is the most common PET tracer, other ^{18}F-labeled molecules are also used in PET imaging of tumor proliferation [32-34], herpes simplex virus-1 thymidine kinase (HSV1-tk) gene expression [35-38], and many receptor-ligand interactions [39-42]. The present review describes the wide variety of fluorinating agents and radiofluorination reactions for synthesis of various radiolabeled compounds and their application in PET imaging.

Fluorinating agents, radiofluorination and synthesis of ^{18}F-labeled compounds

Fluorine forms very strong covalent or ionic bonds to most other elements [43]. The strength of the C-F bond and the small size of the fluorine atom (Van der Waals radius: 1.35 Å; hydrogen: 1.20 Å) give rise to a range of valuable chemical, physical, and biological properties in organic molecules that contain one or more fluorine atoms attached to carbon. However, because of the reactivity and hazards of elemental fluorine and hydrogen fluoride, the task of introducing fluorine into organic molecules has been a particular challenge to synthetic chemists and has led to the development of specialized fluorination technologies and reagents. Elemental fluorine, F_2, is one of the most chemically reactive substances known, owing to the relative weakness of the F-F bond and the great strength of its bonds to most other elements, including hydrogen, carbon, and silicon [43]. Fluorine can behave as both a fluorinating agent and a powerful oxidant. It reacts readily with almost every other element and attacks many common materials, often with near-explosive violence.

Electrophilic fluorination

Electrophilic fluorination reactions are performed using elemental fluorine [44-53]. Xenon fluorides, especially the difluoride, can be used in the selective fluorination of substrates, such as arenes, alkenes, and active methylenes, and in the fluoro-decarboxylation of carboxylic acids [54, 55]. A variety of N-fluorinated amines, quaternary salts, amides, and sulfonamides have been proposed as reagents for selective electrophilic fluorination under mild conditions [56]. These are usually stable, easily handled solids, and they provide a range of fluorinating power from mild to moderate, depending on the structure of the reagent and the nature of the substrate. Several electrophilic fluorinating agents for radiofluorination have been reported: trifluoromethyl-^{18}F-hypofluorite (CF_3-O^{18}F) [57], acetyl-^{18}F-hypofluorite (CH_3-CO_2^{18}F) [47], perchloryl-^{18}F-fluoride (^{18}F-$FClO_3$) [50], xenon difluoride (Xe$^{18}F_2$) [54, 55], 1-^{18}F-fluoro-2-pyridone, N-^{18}F-fluoropyridinium triflate, and N-^{18}F-fluoro-N-alkyl sulfonamide [52].

One of the most applicable electrophilic fluorination uses ^{18}F-F_2, in which fluorine is highly polarized with a partial positive charge. Under this condition, electron-rich substrates, such as alkenes, aromatic compounds, and carbanions, can attack as nucleophiles and become fluorinated [44-49, 58]. Thus, uracil has been radiofluorinated with ^{18}F-F_2 in the presence of acetic anhydride and a trace of acetic acid for the synthesis of 5-^{18}F-FU (**Figure 1A**) for PET imaging [58, 59]. Although ^{18}F-F_2 seems to be the fluorinating agent, the actual fluorinating agent is thought to be CH_3-COO^{18}F, which is formed in situ during the reaction. ^{18}F-F_2 was produced in the cyclotron and bubbled into a solution of uracil in acetic anhydride and a trace amount of acetic acid at room temperature.

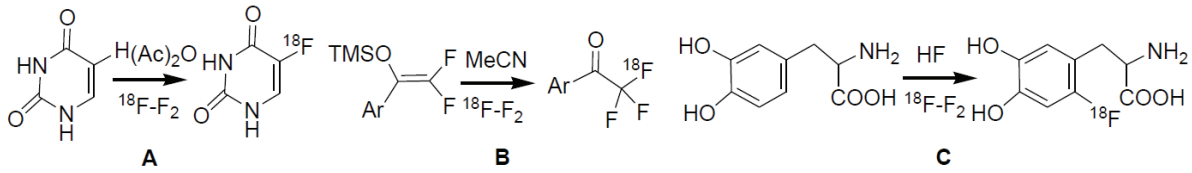

Figure 1. Electrophilic fluorination; Syntheses of ^{18}F-5-fluorouracil (A), ^{18}F-a-trifluoromethyl ketones (B), and ^{18}F-fluorodopa (C).

After the ^{18}F-F_2 gas was collected, the reaction mixture was neutralized with $NaHCO_3$ solution and diluted with HPLC solvent, and purified by HPLC. The radiochemical yield was around 40%. It should be noted that 40% yield in this reaction is very high; because 50% of the radioactivity is consumed and 50% is lost as the leaving group in the reaction.

Another example of electrophilic fluorination is the synthesis of ^{18}F-labeled α-trifluoromethyl ketones, for which ^{18}F-F_2 has been used as an electrophilic fluorinating agent in the reaction (**Figure 1B**) [44, 45]. Reactions of 2,2-difluoro-1-aryl-1-trimethylsiloxyethenes with ^{18}F-F_2 at low temperature produced ^{18}F-labeled α-trifluoromethyl ketones. Radiolabeled products were isolated by purification using column chromatography on silica gel in 22%-28% yields (decay-corrected [d. c.]). Radiochemical purity was >99% with specific activities of 15-20 GBq/mmol at the end of synthesis (EOS). The synthesis time was 35-40 min from the end of bombardment (EOB). This reaction differs from that of 5-^{18}F-FU synthesis; in this synthesis ^{18}F is added to an enol ether derivative in contrast to the addition-elimination reaction in 5-^{18}F-FU synthesis.

^{18}F-Labeled fluorodopa has also been synthesized using a direct electrophilic reaction with ^{18}F-F_2 [46, 48], (**Figure 1C**). The same compound has been synthesized by reacting another electrophilic fluorine, ^{18}F-acetyl hypofluorite, with a partially blocked dopa derivative in acetic acid [47], as well as electrophilic fluorination with an acetyl hypofluorite, demercuration and destanillation reactions [46-49]. Luxen et al. reviewed and reported on the production of 6-^{18}F-fluoro-L-DOPA and its metabolism in vivo [49]. That review critically appraised methods for the synthesis of 6-^{18}F-fluoro-L-3,4-dihydroxyphenylalanine (6-FDOPA) that is based on labeling by nonregioselective electrophilic fluorination, regioselective fluorodemetalation, or nucleophilic substitution. Luxen et al. gave recommendations for the standardization of labeling procedures, the optimization of radiochemical yield, and the assurance of product quality. Studies of the metabolism of 6-FDOPA in vivo were also reviewed to emphasize the importance of the biochemical component during the development of this tracer for PET. An approach to synthesize a no-carrier-added electrophilic agent, ^{18}F-perchloryl fluoride ($^{18}FClO_3$), has been reported [50] (**Figure 2A**); however, the radiochemical yields in this electrophilic fluorination were quite low (1%-6%).

^{18}F-FDG has also been synthesized by electrophilic fluorination (**Figure 2B**). Reaction of acetyl ^{18}F-hypofluorite (^{18}F-CH_3COOF) prepared by the reaction of ^{18}F-F_2 with solid sodium acetate trihydrate with the appropriate glycal/solvent combination, followed by hydrolysis, produced 2-^{18}F-FDG with a radiochemical yield of 95% [51].

^{18}F-NFSi has been prepared from sodium dibenzenesulfonamide and reacted in the presence of silyl enol ethers and allylsilanes to deliver ^{18}F-labeled fluorinated ketones and allylic fluorides, respectively. Radiosynthesis of the fluorinated A ring of vitamin D_3 has been successfully completed using this reagent (**Figure 2C**) [52]. Electrophilic fluorination is quite fast and efficient, making it a highly desirable synthetic method to obtain radiopharmaceuticals labeled with ^{18}F. However, the products suffer from low specific activity owing to the carrier-added nonradioactive fluorine. Electrophilic radiofluorination has also been summarized in a book edited by Tressaud and Hauf [53]; therefore, no further description of electrophilic radiofluorination is given in this review.

Nucleophilic fluorination

Inorganic and other ionic fluorides are used as nucleophilic fluorinating agents. The fluoride ion is normally the least nucleophilic of the halides.

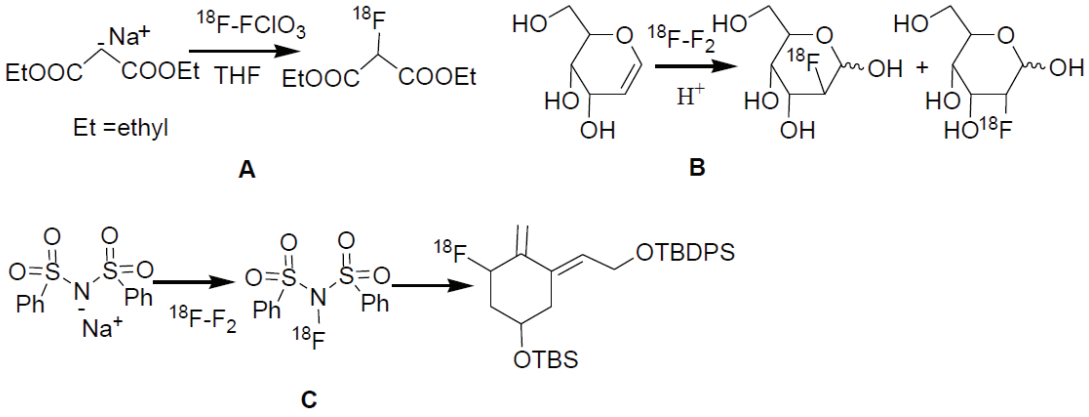

Figure 2. Electrophilic fluorination with ^{18}F-perchloryl fluoride (A), synthesis of ^{18}F-FDG (B), and radiosynthesis of the fluorinated A-ring of vitamin D_3 (C).

Nevertheless, halogens can be displaced in alkyl halides, since the high stability of alkyl fluorides and the poor leaving group ability of F^- can cause the equilibrium to be shifted. Dipolar aprotic solvents, such as N,N-dimethylformamide (DMF) and acetonitrile (MeCN), tend to give the best fluorination results, and in view of the low solubility of metal fluorides, addition of crown ether can be beneficial; alternatively, the much more soluble tetraalkylammonium fluorides can be employed as the fluorinating species. In aromatic systems, displacement of chloride (halex fluorination) can be achieved in high-boiling-point polar aprotic solvents, including dimethyl sulfoxide and sulfolane. The most common fluoride source in these reactions is potassium fluoride, although other fluorides, including cesium fluoride (CsF), are sometimes used, and improved results can often be obtained if the fluoride ion is solubilized by means of a thermally stable phase-transfer catalyst such as tetraphenylphosphonium chloride [60]. Detailed information about the aromatic nucleophilic substitution reactions of fluoride has been reported previously by Vlasov [61]. The fluoride ion can behave as a base, a hydrogen bond electron donor, and a nucleophile; the behavior and detailed applications of fluoride have been reviewed by Clark [62].

Although various fluorinating agents (both electrophilic and nucleophilic) have been reported in organic fluorination reactions [43, 62], only two agents are suitable for radiofluorination reactions with ^{18}F: ^{18}F-F_2 for electrophilic fluorination and ^{18}F-fluoride for nucleophilic reactions. A number of nuclear reactions are used to produce radioactive fluorine (^{18}F). The most common reaction is the bombardment of ^{18}O-oxygen using the nuclear reaction ^{18}O(p,n)^{18}F [63]. The other common reaction, particularly for the production of the electrophilic fluorine ^{18}F-F_2, is the ^{20}Ne(d,α)^{18}F reaction on natural neon [64]. ^{18}F-F_2 can also be produced by bombardment of ^{18}O-oxygen gas in a two-step process: bombardment of ^{18}O-O_2 followed by bombardment of the target again in the presence of a trace amount of F_2 gas to extract ^{18}F-F_2. The final product is a mixture of $^{18/19}$F-F_2, which is known as "carrier-added ^{18}F-F_2". This reagent is used for electrophilic substitution reactions [44-48].

^{18}F-Fluoride is produced by the nuclear reaction on ^{18}O-water using the same nuclear reaction mentioned above, ^{18}O(p,n)^{18}F, and the product is obtained as H^{18}F in ^{18}O-water. The ^{18}O-water (after bombardment) is generally passed through an ion-exchange cartridge, which traps the ^{18}F-fluoride and allows the free ^{18}O-water to be recovered. The ^{18}F-fluoride is then isolated from the ion-exchange cartridge by elution with K_2CO_3 solution to get K^{18}F or with tetrabutylammonium bicarbonate to get $Bu_4N^{18}F$. For K^{18}F, the solution collected from the ion-exchange cartridge is mixed with a solution of Kryptofix 2.2.2 in MeCN. Alternatively, the ^{18}F-fluoride can be eluted from the ion-exchange cartridge using a solution of K_2CO_3 in water (13 mg/ml) and Kryptofix in MeCN (15 mg/mL) at a ratio of 1:3 with a total volume of 1 mL. In addition to these two types of ^{18}F-fluoride, very few other

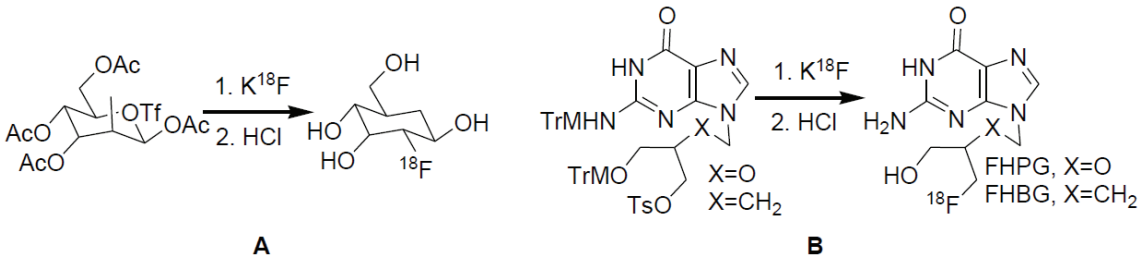

Figure 3. Nucleophilic fluorination; synthesis of ^{18}F-FDG (A), and ^{18}F-FHPG & ^{18}F-FHBG (B).

agents have been developed (described later). Other nuclear reactions can be used for the production of ^{18}F; these have been described in detail in various sources [65, 66] and are not discussed in this review.

The nucleophilic radiofluorination reaction has been used to synthesize many compounds, including ^{18}F-FDG (**Figure 3A**) [29]. Given the popularity and wide use of ^{18}F-FDG, this compound has been synthesized using both nucleophilic and electrophilic reactions [29, 51]. However, nucleophilic reactions with K^{18}F/Kryptofix and automated synthesis modules are the most commonly used method [29]. For the nucleophilic reaction, the precursor compound is a 2′-triflate of mannose acetate, which is commercially available. It is radiofluorinated with K^{18}F/Kryptofix 2.2.2. and hydrolyzed by acid (HCl), and purified by a series of columns to remove free fluoride and all other impurities; then the final pure product is sterilized by filtering through a 0.22-μm Millipore filter. Other reports on the production and quality control analysis of ^{18}FDG have been reviewed recently and are available in the literature [67].

Acycloguanosine analogues have been radiolabeled with K^{18}F/Kryptofix by nucleophilic fluorination [35, 68]. Two compounds have been synthesized by this method: 9-[(3-^{18}F-fluoro-1-hydroxy-2-propoxy)methyl)] guanine (^{18}F-FHPG) and 9-[4-^{18}F-fluoro-3-hydroxymethyl-butyl) guanine] (^{18}F-FHBG). Precursor compounds with tosylate as a leaving group were prepared in multiple steps and then radiofluorinated with K^{18}F/Kryptofix at high temperature (110°C-120°C) (**Figure 3B**). The crude product was hydrolyzed with HCl, neutralized, and purified by HPLC. The radiochemical yields were 10%-12% (d. c.) with >99% purity and 1000 mCi/μmole specific activity at EOS. Another synthesis of ^{18}F-FHPG was reported with di-tosylate as a precursor, but this method produced lower yields [69]. The biological efficacy of ^{18}F-FHPG and ^{18}F-FHBG in PET imaging differ, and ^{18}F-FHBG has been recognized as the most useful PET probe to detect HSV1-tk gene expression. As a result, many other investigators [70-74] have attempted to improve the radiochemical yields of ^{18}F-FHBG; however, none have been successful. Automated synthesis of ^{18}F-FHBG has been reported and is currently used for preclinical and clinical applications [72, 74].

Nucleophilic radiofluorination has been extended to the synthesis of ^{18}F-labeled adenosine analogues [75]. The syntheses of two adenosine analogues, 2′-deoxy-2′-^{18}F-fluoro-9-β-D-arabinofuranosyladenine (^{18}F-FAA) and 3′-deoxy-3′-^{18}F-fluoro-9-β-D-xylofuranosyladenine (^{18}F-FXA) have been reported (**Figure 4A** and **4B**). Adenosine was converted to its bis-methoxytrityl-2′- and 3′-triflate derivatives in multiple steps. Each triflate was reacted with Bu$_4$N^{18}F to produce the corresponding ^{18}F-fluorinated intermediates, which yielded the desired compounds by acidic hydrolysis. Crude preparations were purified by HPLC to obtain the desired pure products. The radiochemical yields were 10%-18% (d. c.) for 2′-^{18}F-FAA and 30%-40% (d. c.) for 3′-^{18}F-FXA. Radiochemical purity for both compounds was >99%, and specific activity was >74G Bq/μmol at EOS. The synthesis time was 90-95 min from EOB.

A radiofluorination method similar to the synthesis of ^{18}F-FDG has been developed and reported by Alauddin et al. for the radiosynthesis of a five -member fluorosugar derivative [76]. In this reaction, fluorination of a sugar fluorosulfonate ester by ^{18}F-fluoride in the form of either Bu$_4$N^{18}F or K^{18}F/Kryptofix produced a high-yield product of the fluorinated sugar derivative.

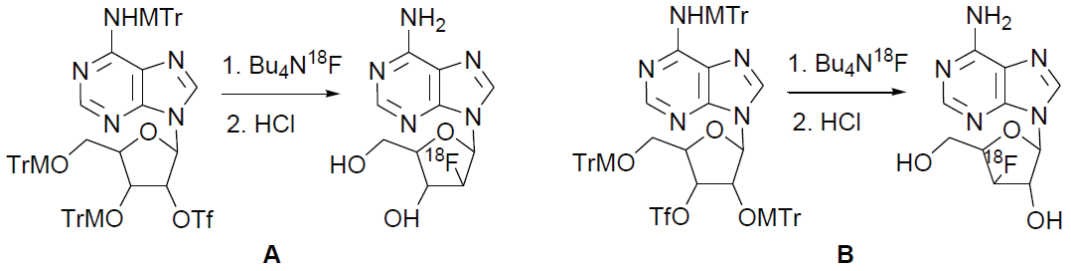

Figure 4. synthesis of 2′- deoxy-2′-^{18}F-fluoro-arabino-adenosine (A) and 3′- deoxy-3′-^{18}F-fluoro-xylo-adenosine (B).

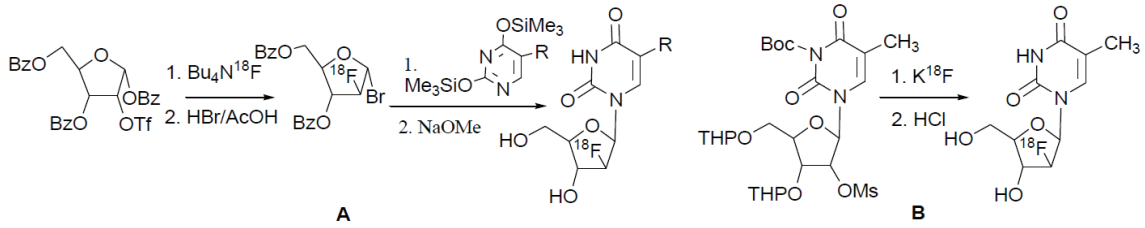

Figure 5. Four-step synthesis of 2′-deoxy-2′-^{18}F-fluoro-1-β-D-5-substituted-arabionofuranosyluracil (A), and two-step synthesis of 2′-deoxy-2′-^{18}F-fluoro-1-β-D-5-methyl-arabionofuranosyluracil (B).

1,3,5-Tri-O-benzoyl-α-D-ribofuranose-2-fluorosulfonate ester has been reacted with $Bu_4N^{18}F$ as the fluorinating agent under a variety of experimental conditions, producing the 2-^{18}F-fluoro-arabino sugar benzoate ester in 30%-40% yields [76]. This method was extended to the radiosynthesis of a series of 2′-fluoro-arabino-pyrimidine nucleoside analogues, as shown in **Figure 5A** [77-79].

These compounds include 2´-deoxy-2´-^{18}F-fluoro-1-β-D-arabinofuranosyluracil (^{18}F-FAU), 2´-deoxy-2´-^{18}F-fluoro-5-methyl-1-β-D-arabinofuranosyluracil (^{18}F-FMAU), 2´-deoxy-2´-^{18}F-fluoro-5-ethyl-1-β-D-arabinofuranosyluracil (^{18}F-FEAU), 2´-deoxy-2´-^{18}F-fluoro-5-fluoro-1-β-D-arabinofuranosyluracil (^{18}F-FFAU), 2´-deoxy-2´-^{18}F-fluoro-5-chloro-1-β-D-arabinofuranosyluracil (^{18}F-FCAU), 2´-deoxy-2´-^{18}F-fluoro-5-bromo-1-β-D-arabinofuranosyluracil (^{18}F-FBAU), and 2´-deoxy-2´-^{18}F-fluoro-5-iodo-1-β-D-arabinofuranosyluracil (^{18}F-FIAU). Synthesis of these compounds involves a four-step methodology (**Figure 5A**): 1) radiolabeling of an arabino sugar derivative, 2) conversion of the ^{18}F-fluorosugar to its 1-bromosugar derivative, 3) coupling of the 1-bromo-2-^{18}F-fluorosugar with a protected pyrimidine base, and 4) hydrolysis of the protecting groups of the coupled products. Briefly, 2-deoxy-2-^{18}F-fluoro-1,3,5-tri-O-benzoyl-α-D-arabinofuranose was prepared by the reaction of the respective 2-ribotriflate with $Bu_4N^{18}F$. The fluoro-sugar was converted to its 1-bromo derivative and coupled with protected thymine or its 5-substituted analogues. The crude product mixture was hydrolyzed in a strong base such as Na-OMe and purified by HPLC to obtain radiolabeled FMAU or its 5-substitued analogues, depending on the starting 5-substituted thymine derivatives. The radiochemical yield of the desired products was 20%-25% (d. c.) in four steps with an average of 22%. Radiochemical purity was >99%, and the average specific activity was 2300 mCi/μmol at EOS. A similar radiofluorination method was performed on the unnatural sugar, L-sugar derivative, for the synthesis of L-nucleoside analogues [79]. The chemistry and fluorination reactions were identical to those described above (**Figure 5A**), except that the starting sugar derivative was prepared from L-sugar.

It should be noted that direct fluorination of a pyrimidine nucleoside at the 2′-arabino position has been deemed to be extremely difficult, if not impossible [80]. The four-step synthesis of the 2′-fluoro-arabino-pyrimidine nucleoside analogues was developed to meet this challenge

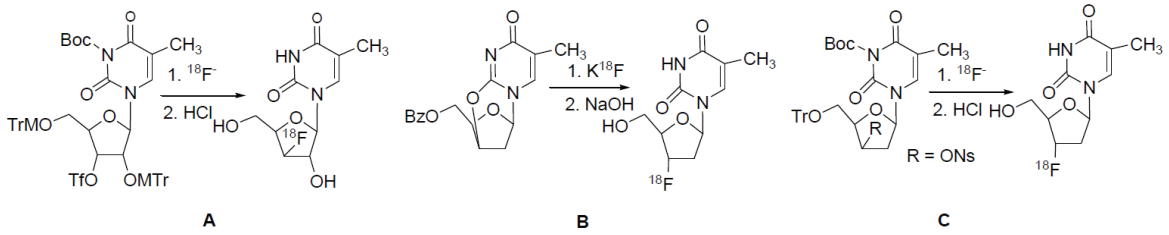

Figure 6. Synthesis of ^{18}F-FMXU (A), and ^{18}F-FLT (B) and (C).

and subsequently adapted for radiosynthesis by major modifications [77, 78]. This problem of direct fluorination at the 2′-arabino position was reported in the early 1960s and has remained unsolved. Recently, direct fluorination of the intact pyrimidine nucleoside analogue at the 2′-carbon with an arabino configuration has been achieved and reported [81]. The method (**Figure 5B**) demonstrated that direct fluorination of a pyrimidine nucleoside at the 2′-arabino position, although extremely difficult, is not impossible [81]. A novel precursor, 2′-methanesulfonyl-3′,5′-O-tetrahydropyranyl-N^3-Boc-5-methyl-1-β-D-ribofuranosiluracil, was synthesized in multiple steps. Radiofluorination of this precursor with K^{18}F/Kryptofix produced 2′-deoxy-2′-^{18}F-fluoro-3′,5′-O-tetrahydropyranyl-N^3-Boc-5-methyl-1-β-D-arabinofuranosiluracil. Acid hydrolysis followed by HPLC purification produced the desired ^{18}F-FMAU. The average radiochemical yield was 2.0% (d. c.) from EOB. Radiochemical purity was >99%, and specific activity was >1800 mCi/μmol at EOS. Synthesis time was 95-100 min from EOB. This direct fluorination is a novel method for the synthesis of ^{18}F-FMAU, and the method should be suitable to produce other 5-substituted pyrimidine analogues, including ^{18}F-FEAU, ^{18}F-FIAU, ^{18}F-FFAU, ^{18}F-FCAU, and ^{18}F-FBAU. However, further development is necessary to improve radiochemical yields in this method.

Nucleophilic radiofluorination has been used for synthesis of the 3′-xylo-thymidine analogue, 3´-deoxy-3´-^{18}F-fluoro-1-β-D-xylofuranosyluracil (^{18}F-FMXU) [82] using a protected pyrimidine nucleoside substrate with triflate as the leaving group and Bu$_4$N^{18}F as the fluorinating agent. 5-Methyluridine was converted to its dimethoxytrityl derivatives and then converted to its 3´-triflate followed by derivatization to the respective N^3-t-Boc product. The triflate was reacted with Bu$_4$N^{18}F to produce the intermediate fluoro compound, which yielded the desired product by acid hydrolysis (**Figure 6A**). The crude product was purified by HPLC to obtain the desired product, ^{18}F-FMXU. Radiochemical yields were 25%-40% (d. c.), with an average of 33% in four runs. Radiochemical purity was >99%, and specific activity was >74 GBq/μmol at EOS. The synthesis time was 67-75 min from EOB. In this synthesis, it is worth noting that the fluorination reaction was performed on the intact pyrimidine nucleoside derivative. Direct fluorination of a pyrimidine nucleoside at the 2′-arabino position has been deemed to be extremely difficult, if not impossible [80]; however, fluorination at the 3′-position with fluorine in the up configuration was successful [82], as for fluorine in the down position of 3′-^{18}F-fluoro-3′-deoxy-thymidine (^{18}F-FLT) synthesis.

^{18}F-FLT has been synthesized by radiofluorination of various precursors using K^{18}F/Kryptofix as the nucleophilic fluorinating agent (**Figure 6B** and **6C**) [83, 84]. ^{18}F-FLT is a well-known compound in the field of PET imaging of tumor proliferation because it targets human thymidine kinase (TK1). It was first reported by Wilson et al. [83] as a carrier-added synthesis method. Thymidine was converted to 5′-trityl-3′-mesyl-lyxothymidine then radiofluorinated with KF/K^{18}F/crown ether to obtain the protected $^{18/19}$F-FLT in low specific activity. Later, Grierson and Shields reported on their extensive investigation of the radiosynthesis of FLT using alternative precursors [84]. The radiochemical yields were always quite low, owing to the competition between elimination and fluorination reactions. The elimination product was observed as the major product when a stoichiometric amount of fluoride was used in the fluorination reaction. However, in radiosynthesis, the yields are somewhat better than those in nonradioactive synthesis, because only a very small amount of ^{18}F-fluoride is used in the radiosynthesis. Many

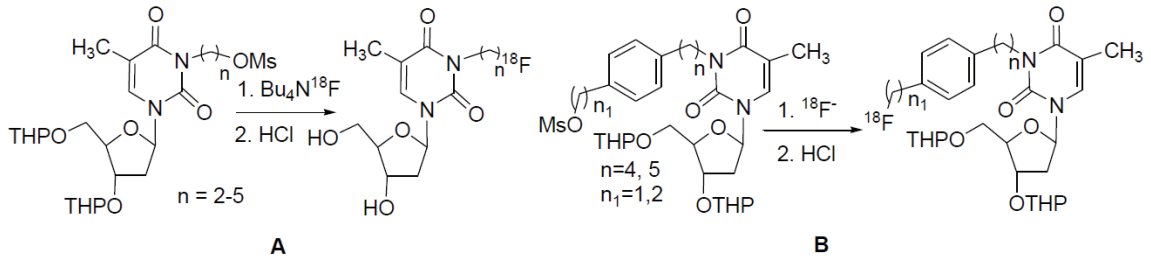

Figure 7. Nucleophilic fluorination, synthesis of synthesis of N^3-substituted thymidine analogues.

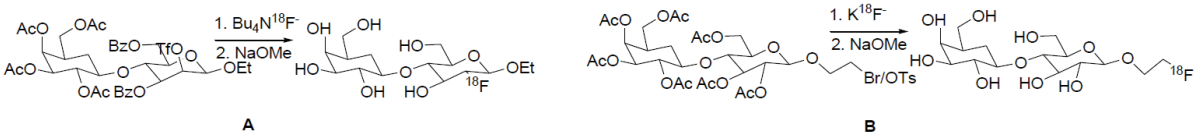

Figure 8. Radiosynthesis of Et-^{18}FDL (A) and ^{18}F-FEL (B).

other investigators [85-91] have attempted to improve the yield of ^{18}F-FLT by modifying the synthesis method using different precursors, but no improvement has yet been achieved. Production of ^{18}F-FLT using an automated synthesis module has been reported [89-91], and now clinical-grade ^{18}F-FLT is produced by this method.

Nucleophilic radiofluorination has been used to synthesize a series of N^3-substituted thymidine analogues using the appropriate substrates with mesylate as the leaving group and $Bu_4N^{18}F$ as the fluorinating agent (**Figure 7A** and **7B**) [33, 92-94].

Syntheses of the appropriate precursor compounds, 3´,5´-O-bis-tetrahydropyranyl-[N^3-substituted] thymidine mesylates, were synthesized in multiple steps. Radiofluorination of these precursors was performed using either $Bu_4N^{18}F$ or K^{18}F/kryptofix in dry MeCN. Hydrolysis of the protecting groups followed by HPLC purification yielded the desired N^3-substituted products. The radiochemical yields of these compounds varied from 5% to 10% (d. c.) with a short carbon-chain length at the N^3-position and from 35% to 48% with a longer chain length. Radiochemical purity was >99%, and specific activity was >74 GBq/μmol at EOS. The synthesis time was 80-90 min from EOB.

Radiosynthesis of two novel lactose derivatives as PET tracers for pancreatic cancer have been reported; these are ethyl-2-deoxy-2-^{18}F-fluoro-4-O-β-D-galactopyranosyl-β-D-glucopyranoside (Et-^{18}FDL) and 1′-^{18}F-fluoroethyl-β-D-lactose (^{18}F-FEL) [95, 96]. For Et-^{18}F-FDL, a precursor compound was prepared by multistep synthesis [95]. Radiofluorination reactions were performed on the precursor using n-$Bu_4N^{18}F$ in dry MeCN at 80^{o}C to prepare the ^{18}F-labeled intermediate compounds, and the crude product was purified by HPLC. The protecting groups were hydrolyzed with a base to obtain Et-^{18}FDL. **Figure 8A** shows the radiosynthesis of the lactose derivative Et-^{18}FDL. The radiochemical yields of Et-^{18}FDL were 65%-72% (d. c.), with an average of 68%. Radiochemical purity was >99%, and specific activity was >74 GBq/μmol at EOS. The synthesis time was 80–85 min from EOB.

Radiosynthesis of ^{18}F-FEL was performed on two different precursors; 1'-bromoethyl-2',3',6',2,3,4,6-hepta-O-acetyl-β-D-lactose and 1'-p-toluenesulfonylethyl-2',3',6',2,3,4,6-hepta-O-acetyl-β-D-lactose (**Figure 8B**) [96]. Radiofluorination was performed on the precursor compounds and the reaction mixture was passed through a silica gel Sep-pack cartridge and eluted with EtOAc. The crude product 1'-^{18}F-fluoroethyl-2',3',6',2,3,4,6-hepta-O-acetyl-β-D-lactose was purified by HPLC and hydrolyzed with a base. After hydrolysis of the protecting groups, the ^{18}F-FEL was neutralized, diluted with

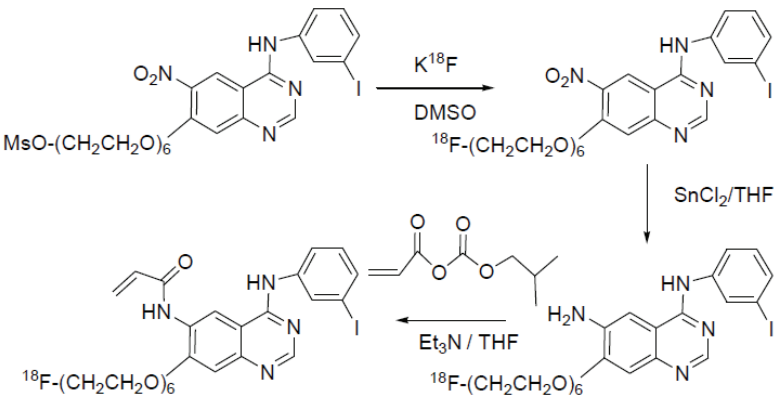

Figure 9. Nucleophilic fluorination, synthesis of ^{18}F-F-PEG$_6$-IPQA.

saline, filtered through a sterile Millipore filter, and analyzed by radio-thin layer chromatography. The average radiochemical yield was 9% (d. c.) with >99% radiochemical purity and specific activity of 55.5 GBq/μmol (EOS). The synthesis time was 80-85 min from EOB. It appeared that fluorination on the side chain was less efficient than that in the sugar ring. Thus, the radiochemical yield of ^{18}F-FEL was much lower than that of Et^{18}F-FDL.

A novel substrate for histone deacetylase (HDAC), ^{18}F-fluoroacetamido-hexanoic anilide (^{18}F-FAHA), has been synthesized by nucleophilic fluorination [97]. The precursor compound 6-(bromo-acetamido)-1-hexanoicanilide, with bromine as the leaving group, was synthesized in multiple steps. The radiofluorination reaction was performed using either n-Bu$_4$N^{18}F or K^{18}F/Kryptofix, and the crude product was purified by HPLC. The radiochemical yields were 9%-13% (d. c.), with an average of 11% using K^{18}F/Kryptofix, and specific activity was >2 GBq/μmol at EOS. The synthesis time was 67-75 min from EOB.

A novel radiotracer, ^{18}F-Fluoro-(polyethylene glycol)$_6$-iodophenylquinazolineanilide (^{18}F-F-PEG$_6$-IPQA) for PET imaging of epidermal growth factor receptor (EGFR) expression/activity in non-small cell lung cancer (NSCLC), has been described along with its radiosynthesis [98]. A mesylate precursor was synthesized in multiple steps, and the radiofluorination reaction was performed using K^{18}F/Kryptofix (**Figure 9**). The fluorinated intermediate compound was reduced to an amino derivative and then treated with acryloyl isobutyl carbonate, followed by HPLC purification to obtain the desired product. Decay-corrected radiochemical yields of ^{18}F-PEG$_6$-IPQA were 3.9%-17.6%, with an average of 9.0%. Radiochemical purity was >97%, and specific activity was 34 GBq/μmol at EOS. Although it is only briefly described here, this synthesis involved more steps than those used in simple fluorination and purification methodology [98].

^{18}F-Fluoroacetate (^{18}F-FAC) has been synthesized by reaction of an ester of acetic acid containing a suitable leaving group [99, 100] (**Figure 10A**). Precursor compounds O-mesyl glycolate ethyl ester (OMs) and O-tosyl glycolate ethyl ester (OTs) were reacted with Bu$_4$N^{18}F in MeCN at 100°C by nucleophilic substitution reaction. The radiochemical yields were quite high: 77% for OMs and 63% for OTs; however, the final yield (recovery) was only 24.5%. Synthesis time was 70-90 min from EOB. Radiochemical purity and specific activity were not reported [99]. In another report, the radiosynthesis method was automated, and the product was obtained in 50% yield (d. c.) within 32 min, with radiochemical purity of >99% [100]. Recently, a simplified method was reported that involved distillation of the intermediate product followed by hydrolysis and HPLC purification

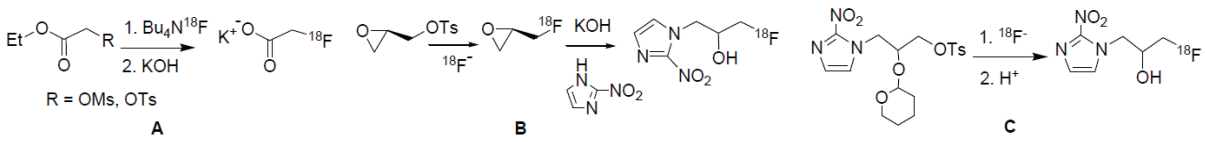

Figure 10. Radiosynthesis of ^{18}F-fluoroacetate (A), synthesis of ^{18}F-Fmiso (B) and (C).

[101].

^{18}F-Fluormisonidazole (^{18}F-FMISO) has been synthesized and reported by various authors [102-106]. Two main strategies for synthesis have been reported in the literature: 1) nucleophilic substitution with ^{18}F-fluoride on a protected precursor followed by deprotection and purification [103-105]; and 2) radiofluorination on an epoxide to produce the intermediate ^{18}F-epifluorohydrin followed by coupling to 2-nitroimidazole [102, 106]. Grierson et al. [102] proposed a two-step synthesis producing ^{18}F-FMISO with a high yield (40% from EOB), high purity (>99%), and a specific activity of 37 TBq/mmol (**Figure 10B**). Through this method, the fluoroalkylating agent ^{18}F-epifluorohydrin is first obtained by displacing (2R)-(−) glycidyl tosylate. ^{18}F-FMISO is then obtained by reaction of ^{18}F-epifluorohydrin with 2-nitroimidazole and further purification through HPLC. The most promising methods for ^{18}F-FMISO synthesis seems to be nucleophilic substitution of the tosylate-leaving group by ^{18}F-fluoride on the tetrahydropyranyl-protected precursor 1-(2'-nitro-1'-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluenesulfonylpropanediol (NITTP), with hydrolysis of the protecting group (**Figure 10C**). An automated synthesis of ^{18}F-FMISO by this method has been reported in the literature, in which either HPLC or Sep-Pak cartridge (Waters, Milford, MA, USA) was used for the purification of the radiotracer [103]. The radiochemical yield obtained with NITTP was 60% (d. c.) and reproducible, with a radiochemical purity ≥97% and a specific activity of about 34 TBq/mmol (EOS) [103].

Most recently, ^{18}F-labeled peptides have been reported by Al^{18}F labeling method [107-111]. This is a new methodology, a bifunctional chelating agent such as NOTA derivative has been labeled with ^{18}F through an ionic bond between Aluminum and fluoride. The labeling chemistry is as simple as shake and bake, for example, the chelating agent was mixed with $AlCl_3$ solution in acetate buffer in an appropriate pH, then ^{18}F-fluoride solution was added and the mixture heated for 15 min at 90-100°C. After work up, the crude product was conjugated with peptide and purified by 3 mL Sephadex G50-80 spin column and used for in vitro and in vivo imaging studies. Labeling of peptides using prosthetic group such, as 4-^{18}F-fluoro-benzoate, remains beyond the scope of this review.

Application of ^{18}F-labeled compounds in molecular PET imaging

5-^{18}F-fluorouracil (5-^{18}F-FU)

5-FU is a known chemotherapeutic drug for the treatment of cancers such as carcinoma of the colon and breast. However, a key limitation of 5-FU for therapeutic application is its rapid catabolism in vivo. 5-Ethynyluracil is an analogue of 5-FU that prevents catabolism of 5-FU, so 5-^{18}F-FU was developed for PET imaging and pharmacokinetic modeling of 5-FU [112-114]. It was demonstrated that blocking the catabolism of ^{18}F-FU by 5-ethynyluracil made it possible to measure the transport and anabolism of ^{18}F-FU in tumors by kinetic modeling and PET [59]. Such information may be useful in predicting tumor response to 5-FU. However, the use of ^{18}F-FU in PET imaging is limited owing to its in vivo catabolism.

^{18}F-Fluoro-deoxy-glucose (^{18}F-FDG)

^{18}F-FDG has been approved by the US Food and Drug Administration for clinical application in PET imaging, and it is routinely used for many applications, including the assessment of glucose metabolism in the heart, lungs, and brain. It is also used for imaging tumors in oncology, where dynamic images are usually analyzed in terms of standardized uptake values (SUVs). ^{18}F-FDG is taken up by cells, phosphorylated by hexokinase [115], and retained by tissues with high metabolic activity, such as most types of malignant tumors. As a result, FDG-PET can be used for diagnosis, staging, and monitoring treatment of cancers, particularly Hodgkin disease, non-Hodgkin lymphoma, colorectal cancer, breast cancer, melanoma, and lung cancer, among others. FDG-PET has also been approved for use in diagnosing Alzheimer disease [116]. Application of ^{18}F-FDG in early detection of malignant tumors and treatment follow-up is extremely wide, and many clinical trials are in progress [117]; therefore, a detailed description of the applications of ^{18}F-FDG is beyond the scope of this review.

^{18}F-Pyrimidine nucleoside analogues

A series of pyrimidine nucleoside analogues, including ^{18}F-FAU, ^{18}F-FMAU, ^{18}F-FEAU, ^{18}F-FFAU, ^{18}F-FCAU, ^{18}F-FBAU, ^{18}F-FIAU, and ^{18}F-FLT, have been radiolabeled with ^{18}F [77-82]. Two less

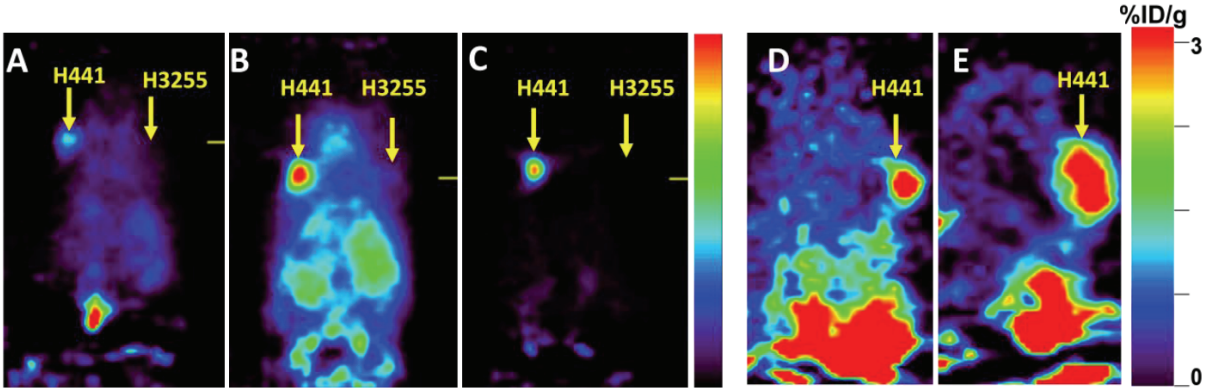

Figure 11. PET images of tumor-bearing mice using ^{18}F-L-FMAU (A), ^{18}F-D-FMAU (B), ^{18}F-FLT (C), N^3-^{18}F-FET (D) and N^3-^{18}F-FPrT (E).

well-known analogues, ^{18}F-L-FMAU and ^{18}F-FMXU, have also been reported [79, 82]. Among these analogues, only ^{18}F-FLT has been extensively studied as a proliferation marker in PET imaging of tumors and, in some cases, to assess treatment response in cancer patients. ^{18}F-FMAU has been widely used in animal models but has limited use in humans. Studies in dogs and patients with advanced cancer have been performed to assess imaging of DNA synthesis using ^{18}F-FMAU [118-120]. Because ^{18}F-FMAU accumulates in the DNA of cancer cells as opposed to ^{18}F-FLT, ^{18}F-FMAU has been investigated as a PET probe for imaging DNA synthesis [118-120]. Thus, ^{18}F-FMAU has an advantage over ^{18}F-FLT for accurate measurement of cellular proliferation as indicated by DNA synthesis. It has also been demonstrated that ^{18}F-FMAU is superior to ^{18}F-FLT for PET imaging in lung cancer patients with metastases to the brain [119, 120]. A comparative study of ^{18}F-L-FMAU, ^{18}F-D-FMAU, and ^{18}F-FLT was performed that demonstrated that all three tracers are good PET imaging agents for detecting lung cancer xenografts in nude mice [32]. **Figure 11 (A-C)** shows PET images of human lung cancer xenografts in nude mice. ^{18}F-L-FMAU (**Figure 11A**) is accumulated into the fast-growing tumor H441, but not in the slow-growing tumor H3255. ^{18}F-D-FMAU (**Figure 11B**) is also accumulated into the H441 tumor genografts, but not in the H3255. Similarly, ^{18}F-FLT (**Figure 11C**) has a high accumulation into the fast-growing tumor H441 without any accumulation into the slow-growing tumor H3255. As the images show, all three compounds are good candidates for PET imaging of fast-growing tumor proliferation. Although these compounds have been demonstrated to be good markers for imaging fast-growing tumors, further studies are necessary to establish them as PET probes in various slow-growing and moderate-growing tumor models. Other pyrimidine nucleoside analogues, including ^{18}F-FMAU, ^{18}F-FFAU, ^{18}F-FCAU, ^{18}F-FBAU, ^{18}F-FIAU, and ^{18}F-FEAU, have been used as markers for PET imaging of HSV1-tk gene expression as described later.

^{18}F-Labeled N^3-substituted thymidine analogues

A series of N^3-substituted thymidine analogues have been radiolabeled with ^{18}F [33, 92-94]; however, only limited studies have been performed in vitro and in vivo. Toyohara et al. [121] demonstrated that N^3-fluoroethylthymidine (N^3-FET) and N^3-fluoropropylthymidine (N^3-FPrT) have phosphorylation rates of 47% and 26%, respectively compared with thymidine (100%). However, a follow-up in vivo PET imaging study conducted by the same group of investigators demonstrated a lack of accumulation of N^3-^{18}F-FET in subcutaneous tumor xenografts in mice [122], which contradicted their previously reported in vitro enzyme assay results. In another report, it was demonstrated that accumulations of N^3-^{18}F-FET and N^3-^{18}F-FPrT in fast-growing tumor tissue 2 h after injection were 1.81±0.78 and 2.95±1.14 percent injected dose per gram (%ID/g), respectively, and tumor-to-muscle ratios were 5.57±0.82 and 7.69±2.18, respectively [33]. **Figure 11** (**D** and **F**) shows PET images of N^3-^{18}F-FET (**Figure 11D**) and N^3-^{18}F-FPrT (**Figure 11E**) in H441 tumor-bearing nude mice; both compounds show a very high accumulation

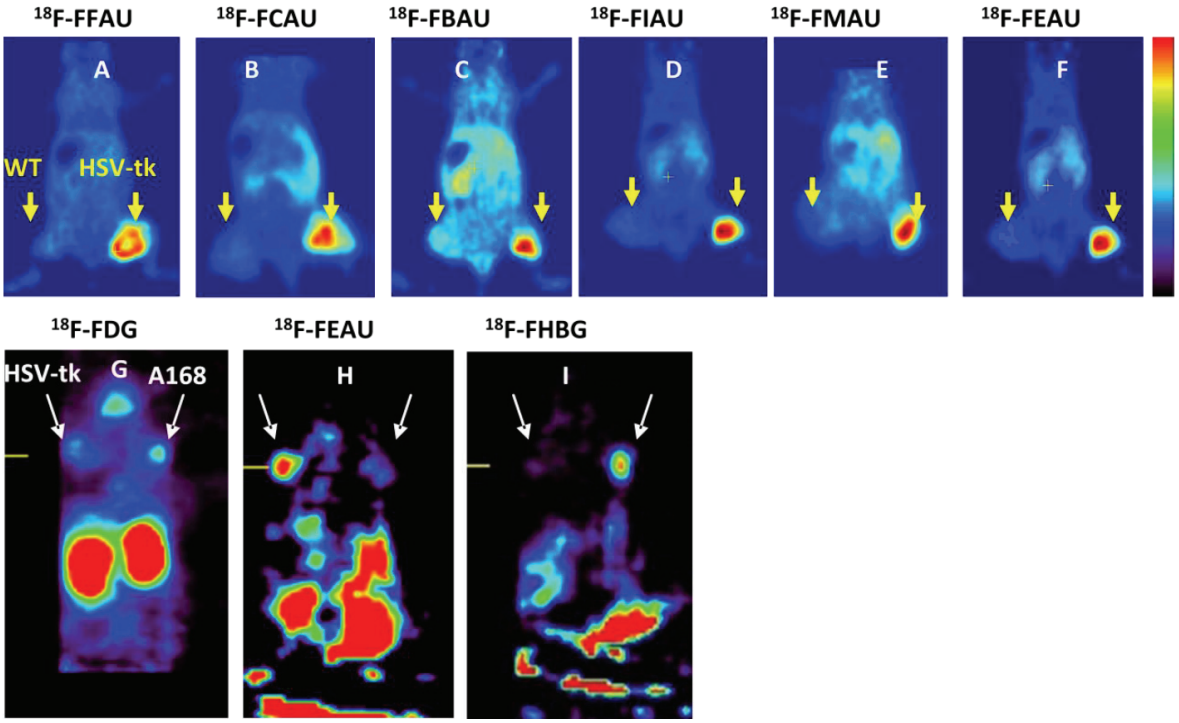

Figure 12. PET images of wild-type tumor (left flank) and HSV1-tk expressing tumor (right flank) on nude mice using ^{18}F-FFAU (A), ^{18}F-FCAU (B), ^{18}F-FBAU (C), ^{18}F-FIAU (D), ^{18}F-FMAU (E), and ^{18}F-FEAU (F). PET images of HSV1-tk and HSV1-A168Htk gene expression using ^{18}F-FDG (G), ^{18}F-FEAU (H) and ^{18}F-FHBG (I).

in the tumor xenografts. Although these compounds have been demonstrated to be good markers for imaging fast-growing tumor, further studies are necessary to establish them as PET probes in various growth rates of tumor models.

^{18}F-FLT

^{18}F-FLT has been widely used in clinical applications for early detection of many types of cancers and assessment of treatment response of cancer therapy. ^{18}F-FLT has been extensively studied as a proliferating marker in PET imaging of tumors and, in some cases, to assess treatment response of cancer patients. ^{18}F-FLT has been used for the diagnosis and grading of brain tumors [123], malignant lymphoma [124], lung cancer [125], colorectal cancer [126], and esophageal cancer [127] by PET. The literature on the applications of ^{18}F-FLT is quite large, so only a few examples have been referenced here [123-130]. Furthermore, ^{18}F-FLT is currently in multicenter clinical trials; therefore, this review will not further describe FLT.

Pyrimidine nucleoside analogues, including ^{18}F-FMAU, ^{18}F-FFAU, ^{18}F-FCAU, ^{18}F-FBAU, ^{18}F-FIAU, and ^{18}F-FEAU, have been used as markers for PET imaging of HSV1-tk gene expression. For example, ^{18}F-FMAU was studied for PET imaging of HSV1-tk gene expression in tumor-bearing nude mice [131]. It was demonstrated that accumulation of ^{18}F-FMAU in HSV1-tk expressing tumor was 24-times higher than that of ^{18}F-FHBG 2 h after injection. Similarly, ^{18}F-FFAU, ^{18}F-FCAU, ^{18}F-FBAU, ^{18}F-FIAU, and ^{18}F-FEAU have been shown to be excellent agents for PET imaging of HSV1-tk gene expression (**Figure 12A-F**) [132-134]. All compounds are excellent PET imaging agents for HSV1-tk gene expression. However, some of these compounds, especially ^{18}F-FMAU and ^{18}F-FIAU, are also substrates for TK1; therefore, total radioactivity accumulation of these compounds into the tumor cells represents a combination of phosphorylation by TK1 and HSV1-tk. Among these PET imaging agents, ^{18}F-FEAU has been accepted as the most useful probe for imaging HSV1-tk gene expression because it is more specific for HSV1-tk than ^{18}F-FMAU and ^{18}F-FIAU. This specificity has been demonstrated in PET imaging studies of native HSV1-tk and mutated HSV1-tk gene expression

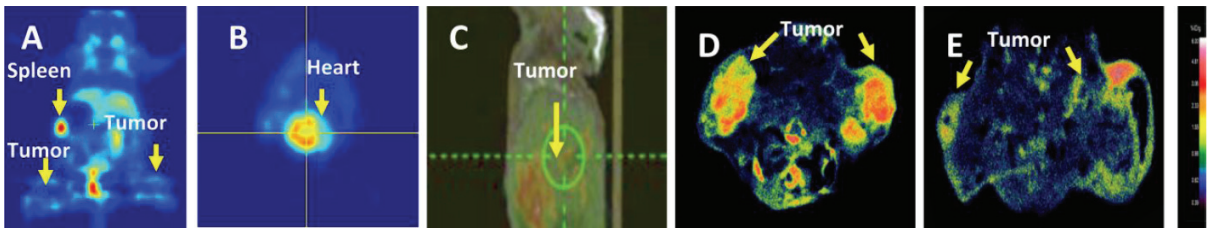

Figure 13. PET images of 18F-FAA (A) and 18F-FXA (B); PET image of an orthotopically implanted pancreatic tumor xenograft in a nude mouse (C); and PET images of xenografts expressing EGFR using 18F-PEG6-IPQA in mice before therapy (D) and after therapy (E).

in animal models [135-137].

^{18}F-Purine nucleoside, acycloguanosine

Among the purine nucleoside analogues, ^{18}F-FHPG was developed first [131], and studies have been performed both in vitro and in vivo to determine its utility for PET imaging [38]. PET imaging using ^{18}F-FHPG in rats bearing xenografts with rat glioma C_6 cells showed significantly more accumulation in transduced tumors (HSV1-tk–positive) than in wild-type tumors [38]. Much attention has been given to the PCV analogue ^{18}F-FHBG with regard to both its synthesis and its use in biological studies [37, 38, 135-144] because the efficacy of PCV as an antiviral drug is better than that of ganciclovir. ^{18}F-FHBG has been extensively studied in animal models using the mutated HSV1-tk gene sr39-HSV1-tk, because FHBG is quite sensitive to sr39-HSV1-tk-that is, FHBG is taken up more readily by sr39-HSV1-tk than by the native HSV-tk. Most of the biological studies using ^{18}F-FHBG and PET have been performed by Gambhir et al., including human dosimetry and clinical studies [138-143]. Comparative studies between FHBG and FEAU have been performed by others. Recently, it was demonstrated that HSV1-A168H-TK selectively phosphorylates the purine derivative ^{18}F-FHBG without phosphorylating the pyrimidine nucleoside ^{18}F-FEAU [144]. PET image of rats expressing HSV1-tk and HSV1-A168Htk (**Figure 12G-I**) were taken using ^{18}F-FDG, ^{18}F-FEAU and ^{18}F-FHBG. PET with ^{18}F-FDG (**Figure 12G**) shows both tumors on the shoulders, with ^{18}F-FEAU (**Figure 12H**) shows only wild-type HSV1-tk expressing tumor; and PET with ^{18}F-FHBG (**Figure 12I**) shows only HSV1-A168tk expressing tumor [144].

Molecular PET imaging of HSV1-tk gene expression is a fast-growing field, and although a large number of studies have been done in animal models, only a limited number of clinical studies have been performed in humans using ^{18}F-FHBG [141-143]. ^{18}F-FEAU being more sensitive PET probe than ^{18}F-FHBG remains unexplored for PET imaging HSV1-tk gene expression in humans. Further studies on ^{18}F-FEAU in large animals are needed to establish its application for routine use in humans.

^{18}F-Purine nucleoside, adenosine analogues

^{18}F-Labeled analogues of adenosine, ^{18}F-FAA and ^{18}F-FXA, have been evaluated in tumor-bearing nude mice [146]. In vivo biodistribution studies of ^{18}F-FAA and ^{18}F-FXA showed that these compounds are not substrates for HSV1-tk [146]. Uptake of ^{18}F-FAA in tumor was 3.3 times higher than that in blood. Maximum uptake of ^{18}F-FAA was in the spleen, and that of ^{18}F-FXA was in the heart. No uptake of ^{18}F-FXA occurred in tumors. Biodistribution results were supported by micro-PET images, which also showed very high uptake of ^{18}F-FAA in spleen and visualization of tumors, and high uptake of ^{18}F-FXA in the heart. It was suggested that ^{18}F-FAA may be useful for tumor imaging (**Figure 13A**) and that ^{18}F-FXA has potential as a heart imaging agent for PET (**Figure 13B**) [146].

Et-^{18}F-FDL

Lactose derivatives are relatively new compounds; although Et-^{18}F-FDL was synthesized earlier, biological studies of its potential as a tumor imaging agent have only been reported recently [147]. Et-^{18}F-FDL accumulates in the peritumoral area of pancreatic cancer. **Figure 13C** shows a PET image of an orthotopically implanted pancreatic tumor xenograft in a nude mouse. The area represented by the circle is the pancreas and its surrounding area, where the

radioactivity has accumulated. Et-^{18}F-FDL has a high potential in PET imaging of pancreatic cancer, however, further studies in large animals are needed for clinical translation of the compound in patient studies.

^{18}F-FPEG$_6$-IPQA

This compound was also developed only recently [98]. PET with ^{18}F-FPEG$_6$-IPQA in tumor-bearing mice was shown to distinguish H3255 NSCLC xenografts expressing L858R mutant EGFR from H441 and PC14 xenografts expressing EGFR or H1975 xenografts with L858R/T790M dual mutation in the EGFR kinase domain, which confers resistance to EGFR inhibitors (e.g., gefitinib). The T790M mutation was found to prevent the ^{18}FF-PEG$_6$-IPQA from forming an irreversible bond to EGFR. It has been suggested that PET with ^{18}F-FPEG$_6$-IPQA could be used to select NSCLC patients for individualized therapy with small-molecule inhibitors of EGFR kinase (i.e., gefitinib and erlotinib). **Figure 13 D** and **F** shows PET images of xenografts expressing EGFR using ^{18}F-PEG6-IPQA in mice; PET image of tumors before therapy (**Figure 13D**) and after treatment with gefitinib (**Figure 13E**) clearly demonstrated that therapy can be assessed by PET with ^{18}F-F-PEG$_6$-IPQA, and ^{18}F-F-PEG$_6$-IPQA was found to be specific for EGFR expression in tumor-bearing rats [148]. Whole-body biodistribution kinetics, metabolism, and radiation dosimetry estimates of ^{18}F-F-PEG$_6$-IPQA in nonhuman primates have also been reported [149], and the compound is now available for clinical translation and should be studied in humans for clinical use.

^{18}F-FAHA

FAHA is a new compound, and only limited studies have been reported. Of these, only one is a full research article [150]. In that study, ^{18}F-FAHA and its metabolite ^{18}F-FAC were prepared, and their in vivo biodistributions and pharmacokinetics were determined in baboons. ^{18}F-FAHA metabolism and its sensitivity to HDAC inhibition using suberoylanilide hydroxamic acid (SAHA) were assessed in arterial plasma and by in vitro incubation studies. ^{18}F-FAHA was rapidly metabolized to ^{18}F-FAC, and both labeled compounds entered the brain. A kinetic analysis taking into account the uptake of peripherally produced ^{18}F-FAC indicated that SAHA inhibited the binding of ^{18}F-FAHA in the baboon brain dose-dependently. The rapid metabolism of ^{18}F-FAHA to ^{18}F-FAC in the periphery complicated the quantitative analysis of HDAC in the brain, but dose-dependent blocking studies with SAHA and kinetic modeling indicated that specific interaction of ^{18}F-FAHA in the brain did occur. Further in vivo studies are needed to establish the utility of this compound for PET imaging.

^{18}F-FAC

Biodistribution studies have been performed comparing ^{18}F-FAC with ^{11}C-acetate (^{11}C-ACE) in normal Sprague-Dawley male rats and CWR22 tumor-bearing nu/nu mice [151]. A small-animal PET study of ^{18}F-FAC in CWR22 tumor-bearing nu/nu mice and a whole-body PET study in a baboon have also been performed to examine defluorination [151]. The rat biodistribution study showed extensive defluorination, which was not observed in the baboon PET study, as indicated by the SUVs (SUVs of iliac bones and femurs were 0.26 and 0.3 at 1 h and 0.22 and 0.4 at 2 h, respectively). CWR22 tumor-bearing nu/nu mice showed tumor uptake of 0.78±0.06 %ID/g for ^{11}C-ACE compared with 4.01±0.32 % ID/g for ^{18}F-FAC. For most organs-except blood, muscle, and fat-the tumor-to-organ ratios at 30 min after injection were higher for ^{18}F-FAC, whereas the tumor-to-heart and tumor-to-prostate ratios were similar. All of these data indicate that ^{18}F-FAC may be a useful alternative to ^{11}C-ACE for the detection of prostate tumors by PET.

The use of ^{18}F-FAC as a specific PET tracer of glial cell metabolism was evaluated in rodent models of glioblastoma, stroke, and ischemia-hypoxia [152]. Enhanced uptake of ^{18}F-FAC was observed as 6.98±0.43 %ID/g, and a tumor-to-normal brain tissue ratio of 1.40 was reported in orthotopic U87 xenografts, compared with healthy brain tissue. The extent of lesions as determined by ^{18}F-FAC PET correlated with that determined by magnetic resonance imaging. After transient middle cerebral artery occlusion in the rat brain, elevated uptake of ^{18}F-FAC (1.00±0.03 %ID/g; lesion-to-normal ratio, 1.90) depicted the ischemic territory and correlated with infarct volumes as determined by 2,3,5-triphenyltetrazolium chloride staining and with the presence of activated astrocytes detected by anti-glial fibrillary acidic protein. Ischemia-hypoxia, induced by permanent ligation of the common carotid artery with transient hypoxia,

resulted in persistent elevation of ^{18}F-FAC uptake within 30 min of the induction of hypoxia. These data support further evaluation of ^{18}F-FAC PET for the assessment of glial cell metabolism associated with neuroinflammation [152]. In fact, ^{18}F-FAC has been recently studied in nonhuman primates to determine pharmacokinetics, metabolism, biodistribution, radiation dosimetry, and toxicology, for future clinical trials [101].

^{18}F-Fluorodopa

^{18}F-Fluorodopa has been extensively used for PET imaging of the brain [153]. PET is used to assess the integrity of the nigrostriatal dopaminergic neurons in Parkinson's disease. ^{18}F-Dopa has been used in longitudinal studies to measure the progression of Parkinson's disease and the effects of medications and intracerebral transplants [153]. The significance of changes in PET indices in such studies depends largely on the reproducibility of the F-Dopa PET measurements. Repeated ^{18}F-Dopa PET scans were made in 12 subjects with Parkinson disease to measure scan-to-scan variations. ^{18}F-Dopa has been extensively studied, and a vast literature is available, including clinical trials [154], therefore, it is not described in further details.

^{18}F-FMISO

^{18}F-FMISO is a well-established PET imaging agent for hypoxia [155]. A study of ^{18}F-FDG, ^{18}F-FAC, and ^{18}F-FMISO compared the biodistributions, pharmacokinetics, and imaging characteristics of these three tracers for PET in a sarcoma- and inflammation-bearing mouse model. The inflammatory lesions were clearly visualized by ^{18}F-FDG/micro-PET, and the tumor-to-muscle and inflammatory lesion-to-muscle ratios derived from micro-PET imaging were 6.79 and 1.48 for ^{18}F-FMISO, 8.12 and 4.69 for ^{18}F-FDG, and 3.72 and 3.19 for ^{18}F-FAC 4 h after injection. Among these, the tumor-to-inflammation ratio was the highest (4.57) for ^{18}F-FMISO compared with that of ^{18}F-FDG (1.73) and ^{18}F-FAC (1.17), whereas ^{18}F-FAC had the highest bioavailability (area under concentration of radiotracer vs. time curve, 116.2 h×%ID/g). The results demonstrated the potential of ^{18}F-FMISO/PET in distinguishing tumors from inflammatory lesions [155]. ^{18}F-FMISO/PET has also been reported to be useful in assessing in advanced head and neck cancer treated with chemoradiation incorporating a hypoxia-targeting chemotherapy agent [156]. Many studies besides these have been done, including clinical trials [157], which remain beyond the scope of this review.

^{18}F-Labeled peptides

^{18}F-Labeled peptides using Al^{18}F has been minimally used for PET imaging [107, 111]. The in vivo stability of the ionic ^{18}F-fluoride remains to be further tested in different animal models although PET images have been reported. With successful and in vivo metabolic stability, this class of labeling methodology will have wide and extensive application in molecular PET imaging.

Summary and conclusion

The radioisotopic forms of fluorine, such as ^{18}F with its short half-life, have made organofluorines useful for determining diagnosis, prognosis, and treatment effects in many diseases, including cancer, by PET. In general, two forms of ^{18}F-fluorine are available for radiolabeling of biomolecules: electrophilic ^{18}F (^{18}F-F_2) and nucleophilic ^{18}F (^{18}F-fluoride). Use of ^{18}F-F_2 results in products with low specific activity, and that of ^{18}F-fluoride results in products with high specific activity, unless a carrier is added. ^{18}F-F_2 also produces other electrophilic species, such as $CH_3COO^{18}F$, in situ for electrophilic substitution reactions. Because ^{18}F-F_2 produces products with low specific activity, their application and use are limited. By contrast, nucleophilic ^{18}F (^{18}F-fluoride) is widely used in radiofluorination of desirable compounds with high specific activity. ^{18}F-fluoride can also be handled much easily than ^{18}F-F_2, which is produced and delivered as a gas.

^{18}F-Fluoride can be utilized in different forms, such as the salt of an organic base ($Bu_4N^{18}F$) or an inorganic metal ($K^{18}F$). Each of these two forms of ^{18}F-fluoride has some advantages; for example, $Bu_4N^{18}F$ is soluble in organic solvents and can thus be used without any crown ether. $K^{18}F$, however, requires a crown ether, such as Kryptofix 2.2.2., which makes the fluoride soluble in organic solvents and forms a complex with potassium to generate naked fluoride to act as a nucleophile. Handling $Bu_4N^{18}F$ is tricky, because it becomes unstable at high temperatures when it has been dried from water, caus-

ing many reactions to fail. K^{18}F/Kryptofix is much better in this context, because it can be dried at a relatively higher temperature and remain stable to react with the precursor; therefore, chances of a failed experiment are rare. Other fluorinating agents, such as ^{18}F-perchloryl fluoride and ^{18}F-NF, have very limited application. Therefore, further research is necessary to develop the routine use of these agents in radiofluorination reactions.

A wide variety of compounds that contain fluorine have been radiolabeled with ^{18}F either by electrophilic or nucleophilic reactions. The most popular compound is ^{18}F-FDG, which is routinely used in PET imaging of cancer patients to determine their prognosis and treatment response. ^{18}F-FDG has been synthesized by both electrophilic and nucleophilic reactions with ^{18}F; however, as a routine process, nucleophilic fluorination is used. A series of nucleoside analogues, including pyrimidine and purine nucleosides, have been radiolabeled with ^{18}F using nucleophilic fluorination reactions. Among the pyrimidine nucleoside analogues, ^{18}F-FLT and ^{18}F-FMAU have been used as markers to detect cellular proliferation, and ^{18}F-FEAU has been used to detect HSV1-tk gene expression. ^{18}F-FLT has been extensively studied, including in multicenter clinical trials; however, limited studies have been done on ^{18}F-FMAU. Of the purine nucleoside analogues, only ^{18}F-FHBG has been extensively studied, and it is used to detect -gene expression. Adenosine analogues require further studies to establish their application. The ^{18}F-labeled lactose derivatives, ^{18}F-FAHA, ^{18}F-FAC, and ^{18}F-PEG$_6$-IPQA, have been reported in limited studies, and further work is in progress. ^{18}F-Florodopa and ^{18}F-FMISO are well-established compounds; many studies have been performed on them, and clinical trials are in progress. Many other radiolabeled fluorine compounds have also been described in the literature but are not included in this review. ^{18}F -Labeled compounds is thus large and useful in many applications, providing avenues of research for years to come

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