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Review

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Advancing BNCT: A Concise Review on ^{18}F Labeling of Tracers

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ABSTRACT

Boron neutron capture therapy (BNCT) stands at the forefront of cancer treatment, offering a pioneering approach to enhance the rate of recovery for patients who show noncompliance to conventional therapies. The ^{18}F labeling of BNCT tracers signifies a groundbreaking leap in molecular imaging. Hence, the aim of this brief review is to outline the radiofluorination strategies utilized for BNCT tracers. Radiofluorination of L-BPA, a ligand of L-type amino acids, can be carried out via electrophilic as well as nucleophilic substitution reactions. It's solubility can be elevated by complexing it with fructose to form BPA-fructose complex, followed by radiolabeling with ^{18}F. In addition to electrophilic and nucleophilic radiofluorination, we have briefly presented the radiofluoro exchange method, which is applicable for amino acids having trifluoroborate groups, i.e., FBY (fluoroboronotyrosine), featuring both imaging and therapeutic functionalities. Furthermore, this review offers an inclusive array of radiofluorination strategies employed for other BNCT tracers, including o-carborane and fenbufen boronopinacol.

Key Words: BNCT, ^{18}F radiolabeling, BPA, FBPA, FBY, PET

1. Introduction

Boron Neutron Capture Therapy (BNCT) is projected as a dynamic therapeutic approach that combines stable nonradioactive ^{10}B isotopes with a neutron beam, demonstrating a non-invasive methodology to combat cancer (1). Despite its natural abundance being only 20%, ^{10}B becomes a highly potent agent against malignant cells after neutron bombardment. The activated neutron, with energy up to the epithermal level, enables ^{10}B to penetrate tissues up to 10 cm (2). The selection of ^{10}B depends on its exceptional interaction cross-section, approaching 3837 barns with thermal neutrons (3). BNCT is based on a biological mechanism where one can selectively eradicate tumor cells while shielding the surrounding healthy cells. This intricate approach not only elevates the therapeutic efficacy but also buffers the adverse effects commonly related to traditional

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radiotherapy modalities by finely tuning the treatment parameters (4). ^{10}B isotope, when subjected to thermal neutrons, undergo a transformation resulting in the production of unstable ^{11}B isotopes, which further initiate a nuclear reaction yielding a cascade of highly energetic particles, including ^{7}Li (0.175 MeV/μm) and ^{4}He (0.150 MeV/μm) along with the emission of gamma rays, as illustrated in Figure 1 (5). The ^{4}He (0.150 MeV/μm) particles generated in this process effectively damage DNA double strands, leading to the death of cancer cells. To effectively target tumor lesions, maintaining the optimal *in vivo* concentration of ^{10}B, typically 2 mM (10^{9} atoms/cell or 20–50 μg of ^{10}B/g), is crucial for successful BNCT (6). Moreover, the irradiation time of thermal neutrons is also a paramount for optimization of BNCT results, ensuring an ample accumulation of ^{10}B in tumor compared to healthy tissues that is approximately three times higher concentration in tumor than in the background tissue. Attaining a tumor boron concentration of ≥20 ppm is essential for the success of BNCT (7). Excitingly, BNCT exhibits promising clinical outcomes, particularly in treating head and neck cancers and meningiomas, with successful responses witnessed even at T/N ratios as low as 2.1 (8).

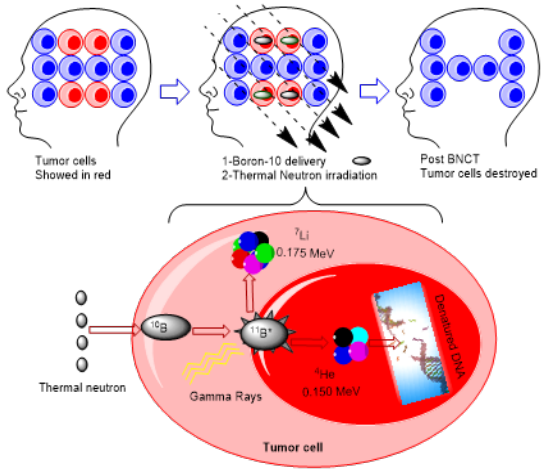


Figure 1. Schematic overview of the BNCT principle.

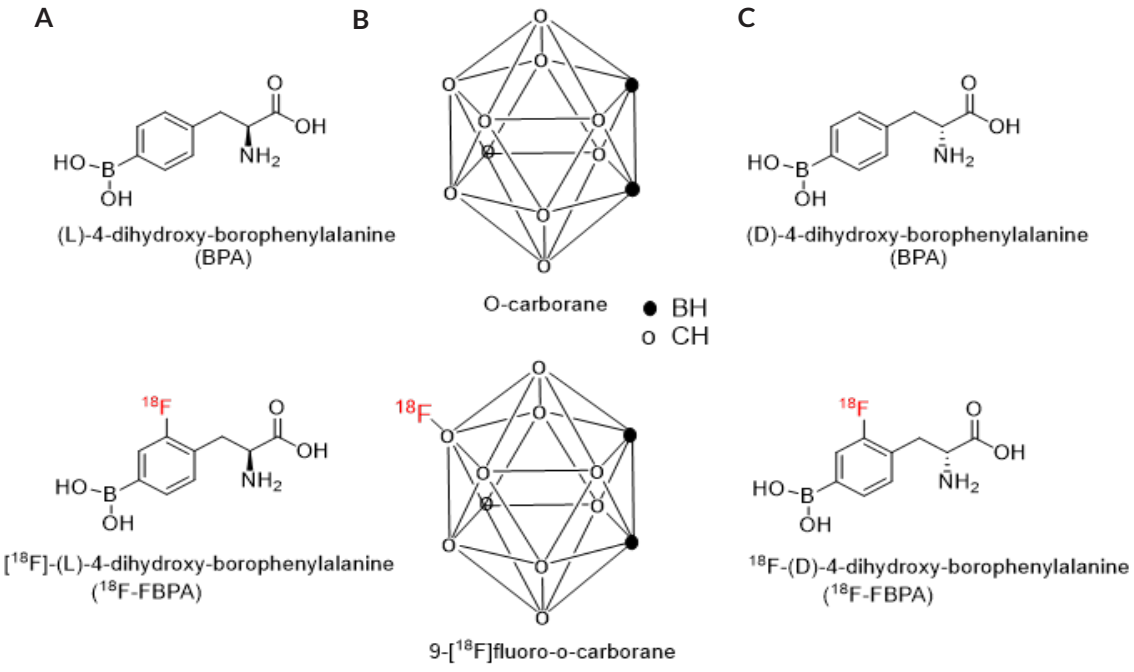


Figure 2. Pioneering boron carriers for BNCT: The most recent innovations (A) L-BPA structure and its PET tracers. (B) O-carborane structure and its PET tracer. (C) D-BPA structure along with its PET tracer.

The leading boron carriers, BPA (Boronophenylalanine) and BSH (Sodium Borocaptate), (Figure 2) marked the BNCT era showing the significant potential during initial assessment. BPA, because of its affinity for tumor tissues, helps in selective boron accumulation in malignant cells, elevating the efficacy of neutron irradiation while sparing healthy surrounding tissue. Despite nonspecific tumor uptake shown by these BNCT tracers, clinical trials in the United States and Japan have utilized the phenylalanine derivative enriched with ^{10}B (9). This initial success initiated the foundation for future progress in boron carrier design and application, shaping the trajectory of BNCT research and clinical practice.

PET is regarded as a cornerstone approach in nuclear imaging, crucial for assessing the pharmacokinetics and dosimetry of labeled BNCT tracers (10). This imaging modality is helpful for real-time visualization of *in vivo* dynamics and quantitative monitoring of drugs due to the extended half-life of radionuclides employed. During a PET scan, positrons emitted by isotopes such as fluorine (^{18}F) and copper (^{64}Cu) annihilate with electrons, thus producing two gamma rays. These gamma rays are subsequently detected by the PET scanner, resulting in the formation of high-resolution images with superior sensitivity, uncovering metabolic activity and diseases. Renowned for its enhanced spatial resolution (2–4 mm) and capacity for quantification, PET imaging surpasses SPECT imaging in clinical utility (11-14). Given the phenomenal nuclear decay of ^{18}F, along with its resilient half-life of 109.7 minutes and marginal positron emission energy of 635 keV, it ensures unparalleled imaging accuracy. Hence, this radionuclide promptly proved as the 'workhorse' of positron-emission tomography (PET), a reign unyielding for over three decades. With nucleophilic fluoride $[^{18}F]F^-$ and radiofluorine gas $[^{18}F]F_2$ as primary sources, PET imaging provides invaluable insights into drug behavior (15, 16). This review explores the intersection of ^{18}F radiolabelling of BNCT tracers against brain tumors, promising a paradigm shift in cancer therapy.

2. ^{18}F labeling of BNCT tracers

Successful incorporation of radioisotopes into BNCT drug candidates unveils the subtleties of their pharmacokinetic properties, offering efficient insights into efficacy and optimal neutron irradiation timing for the drug. Various methods exist for radiohalogenation of boron clusters as halogens exhibit diverse chemistry, offer-

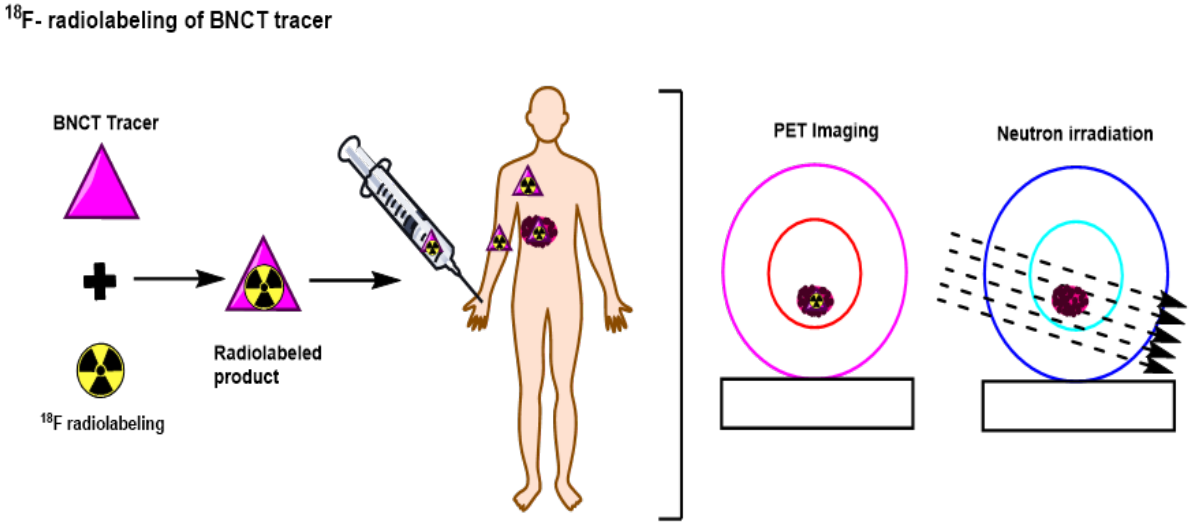


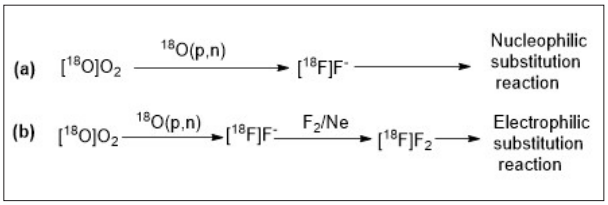
Figure 3. Pictorial representation of ^{18}F radiolabeling of the BNCT tracer.

ing a broad range of radioactive elements with diverse emission modes. Among the halogen family, fluorine-18 (^{18}F) stands out as a captivating choice for radiolabeling BNCT tracers, where BNCT tracer is allowed to react with ^{18}F, followed by its injection into the patient. Subsequent to injection PET imaging is performed to assess the distribution of tracer, followed by determination of appropriate timing for neutron irradiation (Figure 3).

Fluorine-18 an indispensable radionuclide imperative for biomedical imaging, produced in state-of-the-art cyclotrons via distinct nuclear reactions, as shown in Table 1 (17). It is important to note that among all possible reactions, the methodologies dominating the others are the ^{20}Ne(d,α)^{18}F and ^{18}O(p,n)^{18}F reaction. These production leads to the formation of two chemical entities: aqueous [^{18}F] fluoride ion ([^{18}F]F$^-$) and [^{18}F] fluorine gas ([^{18}F]F$_2$). The nucleophilic [^{18}F]F$^-$ is produced by single step reaction (Scheme 1a) with no-carrier-added (n.c.a.) which allows the synthesis of radiotracers with high specific activity, contrary to nucleophilic route, [^{18}F]F$_2$ for electrophilic substitution is produced by two step reaction (Scheme 1b) and is available only in carrier-added (c.a.) form which results the low specific activity of radiotracers (18). The first reaction, ^{18}O(p,n)^{18}F reaction, can produce both [^{18}F]F$^-$ and [^{18}F]F$_2$, but we need to separate [^{18}F]F$^-$ from the target and its activation for nucleophilic substitution reaction, providing a wide array of uses, thereby expanding the horizons of radiopharmaceutical research and clinical imaging. In addition to nucleophilic and electrophilic route BNCT tracer can also be radioflourinated by halogen exchange reaction as discussed later in section 2.3.

Table 1. Nuclear reactions for ^{18}F production.

Nuclear reaction	Energy range (MeV)	Nuclear abundance
^{18}O(p,n)^{18}F	4-14	0.2
^{16}O(^{3}He,p)^{18}F	1-15	99.7
^{16}O(^{4}He,np)^{18}F	20-40	99.7
^{16}O(^{4}He,2n)^{18}Ne:^{18}F	10-5	99.7
^{20}Ne(d,α)^{18}F	0-15	90.5
^{20}Ne(p,2pn) ^{18}F	30-40	90.5
^{20}Ne(3He,αp) ^{18}F	10-40	90.5

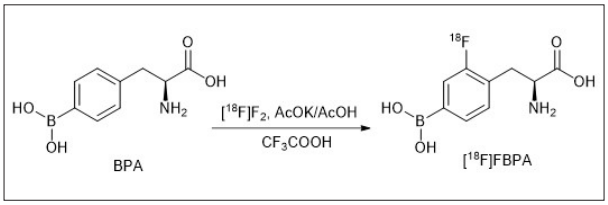


Scheme 1. The reaction route for the generation of radioflourine source (a) [^{18}F]F- for nucleophilic radioflourination (b) synthesis of [^{18}F]F$_2$ for electrophilic substitution.

2.1. Electrophilic radiofluorination of BNCT tracers

Due to the technical ease of using [^{18}F]fluorine gas, which requires no modification and can be employed directly as received from the target, electrophilic ^{18}F radiofluorination was historically the most preferred procedure (19). The pioneering *in vivo* PET investigation using BPA was made possible when Ishiwata and his co-workers carried out the reaction of fluorine substitution into the meta position of the boronic acid-substituted aromatic ring via electrophilic route, leading to the formation of [^{18}F]FBPA, which represents a radiofluorinated structural analog of BPA, as elucidated in Scheme 2 (20).

^{18}F-FBPA has shown high lipid affinity and was deployed to examine the boron level in brain tumors (21, 22). Remarkably, brain uptake of ^{18}F-FBPA revealed a progressive increase over time, reaching its peak at 120 minutes



Scheme 2. Radioflourination of BPA via electrophilic substitution.

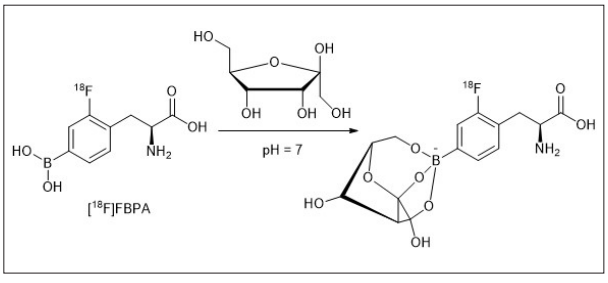
post-injection and constant afterwards. Moreover, its high accumulation and retention in the tumor are observed by PET imaging (23). The compound ^{18}F-FBPA exists as D- and L-isomers, as illustrated in Figure 2. Excitingly, (D)-^{18}F-FBPA demonstrates superiority with respect to achieving a significantly elevated tumor-to-blood (T/B) ratio. For instance, in the rat glioma model, the D-isomer manifests a striking T/B ratio of 6.93, notably surpassing the lower ratio of 1.45 exhibited by its L-isomer counterpart (24). D-FBPA shows fast clearance and possesses the unique metabolic pathway of being excreted via the kidneys instead of the liver, emphasizing its upbeat therapeutic relevance (25).

Despite numerous promising attributes of ^{18}F-FBPA, it's limited solubility in aqueous media poses a challenge. Kabalka *et al*. proposed an intriguing solution to enhance solubility of FBPA by complexing it with fructose in a two-step process. This procedure encompasses the synthesis of ^{18}F-FBPA via electrophilic substitution reaction, followed by its conjugation with fructose through a dehydration reaction, resulting in the formation of the FBPA-fructose complex as illustrated in Scheme 3 (26, 27). It is important to note that the ^{18}F-FBPA complex with fructose exhibits elevated solubility in water, but its biodistribution deviate from both ^{18}F-FBPA and BPA when administered independently.

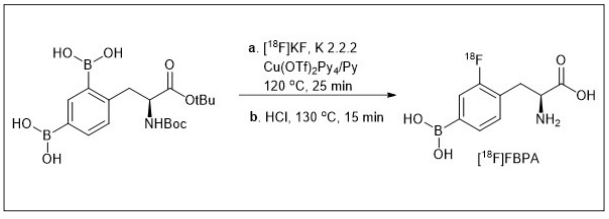
Electrophilic radiofluorination is limited because the molar activity obtained by this procedure is only about 100 MBq/μmol, hence it is only applicable to those compounds which adhere to the tracer principle, and an administered dose of approximately 0.5 mg proves sufficient (28). Another downside of this method is the exclusive use of targets capable of withstanding and resisting the harmful F_2 gas. Due to these reasons, methods utilizing electrophilic substitution are scarce in clinical setups.

2.2. Nucleophilic radioflourination of BNCT tracers

In contrast to [^{18}F]F_2 gas, the formation of [^{18}F]F^- by utilizing the ^{18}O(p,n)^{18}F nuclear reaction is preferred these days and is able to deliver very high specific activity of up to 300 GBq because of an improved target system (20, 29, 30). The process of nucleophilic radiofluorination involves separating [^{18}F]F^- from the target using anion-exchange resin, azeotropic drying in a reactor, adding the precursor to be labeled and heating, deprotecting functional groups if necessary, separating the final product by chromatography, and then formulating the drug. While nucleophilic radiofluorination holds great potential, unwanted fluorodeboronation can occur during the reaction. To address this complication, a novel strategy has emerged. The pioneering ^{18}F nucleophilic radiofluorination of the BNCT tracer was conducted by utilizing a diborono precursor, leading to the formation of ^{18}F-FBPA (Scheme 4). This reaction is catalyzed by copper triflate and yields an unprecedented specific activity by substituting the boron moiety ortho to the ring while preserving the structural coherence of the other boron group. By deliberately fluorinating only



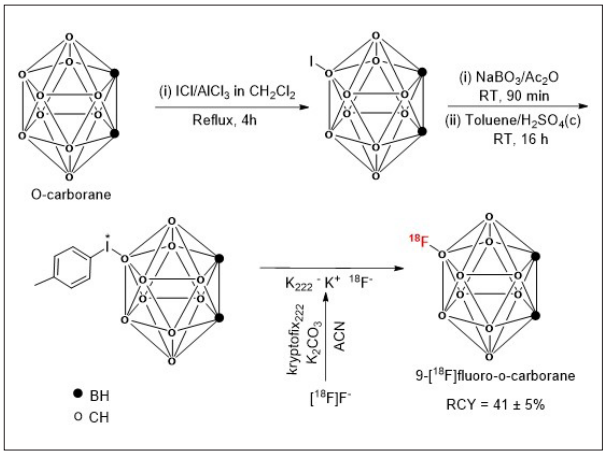
Scheme 3. Synthesis of [^{18}F]FBPA-fructose complex for enhanced aqueous solubility.



Scheme 4. Synthesis of ^{18}F labeled BPA analogue [^{18}F]FBPA via nucleophilic radioflourination of diborono precursor.

one group while preserving the second boron-containing group, one can achieve combined imaging and therapeutic potential within the same precursor, thus conserving the basic structure of the parent BPA compound (31).

Carboranes are clusters of carbon, hydrogen, and boron known for their stability and ability to incorporate ^{10}B in tumor, making them effective candidates for Boron Neutron Capture Therapy (BNCT). As of now, only ortho-carborane has been reported to undergo ^{18}F labeling. The initial method involved an electrophilic radiofluorination reaction, resulting in the formation of 9-fluoro-o-carborane with a 21% radiochemical yield (32). However, challenges persist in the production of $[^{18}F]F_2$. Therefore, preference is given to the use of fluoride ion



Scheme 5. Synthetic route towards the radioflourination of o-carborane resulting in the formation of 9-[^{18}F]fluoro-o-carborane.

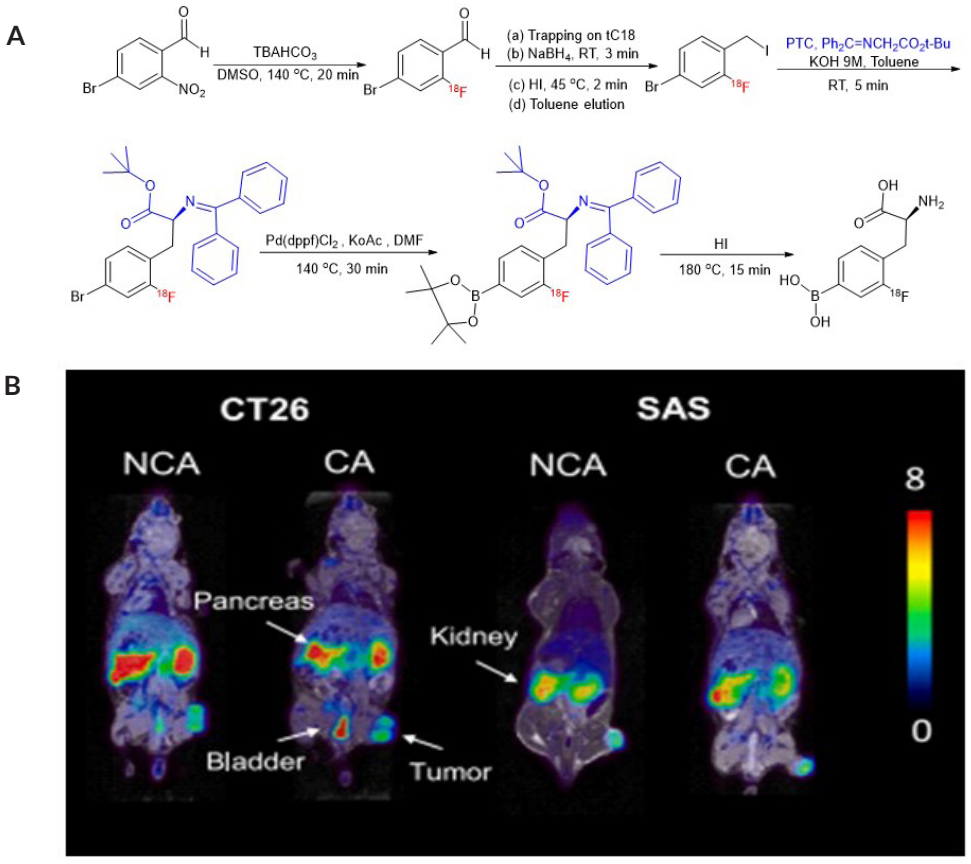


Figure 4. (A) Schematics of no-carrier-added [^{18}F]FBPA synthesis. (B) MicroPET/MR images of CT26 and SAS tumor-bearing mice IV injected with 37 MBq of carrier-added and no-carrier-added [^{18}F] FBPA-Fr after 60 minutes of injection. Adapted with permission from (34) copyright 2023, Elsevier B.V.

([^{18}F]F$^-$) as the labeling agent due to its production at a multi-gigabecquerel level. In a recent study, nucleophilic radiofluorination of o-carborane was conducted using [^{18}F]F$^-$ as the labeling agent, yielding 9-[^{18}F]fluoro-o-carborane with a good radiochemical yield of 44% (decay corrected) (Scheme 5) (33).

To overcome the challenge of lower radiochemical yield associated with radioflourination reaction of BNCT tracers, Chang *et al.* pioneered a novel strategy to synthesize no-carrier-added (NCA) [^{18}F]FBPA via nucleophilic substitution. Their methodology not only leads to high yield and purity but also provides a comparative analysis of the biological attributes of NCA and carrier-added (CA) [^{18}F]FBPA. During the synthesis of NCA [^{18}F]FBPA, various steps were involved starting from the 4-bromo-2-nitrobenzaldehyde precursor and following it's radiofluorination, alkylation, borylation, and hydrolysis as delineated in Figure 4a (34). Biodistribution and microPET analysis allowed for the examination of *in vivo* profiles of both NCA and CA [^{18}F]FBPA. *In vitro* studies has shown the elevated accumulation of NCA [^{18}F]FBPA compared to its CA counterpart across both SAS and CT-26 cell lines. It is important to note that there was no observable difference in tumor uptake between mice administered with NCA and CA [^{18}F]FBPA (Figure 4b). Hence, the authors concluded that many factors decide the path and destination of the drug, thus opening up a new avenue for evaluating the detailed pharmacokinetics of this drug.

2.3 Radioflourination of BNCT tracers via ^{18}F/^{19}F exchange reaction

Even though various remarkable observations were made using ^{18}F-FBPA as BNCT precursor, its substandard uptake in the tumor as well as its instability were focal points for researchers. To ensure improved therapeutic effects by utilizing the heteroatomic nature of the fluoride ion, various aliphatic as well as aromatic trifluoroborate ions were synthesized as the most promising theranostic precursors for BNCT (35, 36). It is important to note that the stability of these groups depends on the nature of the attached moiety, whether it is electron-withdrawing or electron-donating. Aryltrifluoroborates having electron-withdrawing groups at the ortho- or para- position are more stable than those of meta-substituted ones. Moreover, the substitution of trialkylphosphonium further elevates the stability of trifluoroborate precursors, leading to a further delay in decay for up to 3397 hours, as shown in Figure 5 (37).

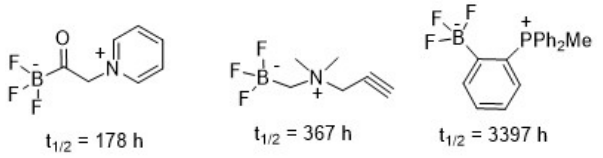
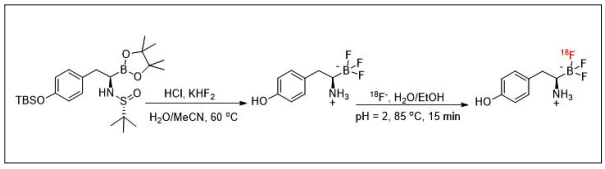


Figure 5. Structure of representative triflouroborates and their half-lives; increase in stability by electron withdrawing group.



Scheme 6. Synthesis of fluoroboronotyrosine [FBY] and ^{18}F labeled fluoroboronotyrosine [^{18}F]-FBY.

These trifluoroborates possess a more stable boron atom for targeting tumors while concurrently allowing for PET imaging when undergo radiofluorination reactions via ^{19}F to ^{18}F exchange. A representative compound of this class, fluoroboronotyrosine (FBY), having zwitterion-like character, was synthesized by the reaction of boronic ester with HI in acidic media, followed by it's radiolabeling via radio-fluoro exchange reaction in >50% radiochemical yield (Scheme 6) (38).

In contrast to BPA, this novel BNCT tracer proves superior with respect to high stability, solubility in aqueous media, and elevated uptake in the tumor. However, the boron concentration, a key determinant for BNCT,

is yet to be determined in humans. In 2022, Confalonieri L *et al.* were able to synthesize a number of BNCT tracers by complexing sugar with trifluoroborate moiety (Figure 6). Nevertheless, these precursors were deterred from further analysis because of their instability as well as insufficient brain accumulation (39).

3. Radiofluorination of Cholangiocarcinoma-Specific Boron Compounds

A revolutionary investigation emerged when Yeh *et al.* unveiled the synthesis of fenbufen boronopinacol (FBPin), a COX-2 selective boron carrier. Following it's synthesis, radiolabeling with ^{18}F was carried out via electrophilic substitution reaction, yielding orth-[^{18}F]F-FBPin)] and meta-[^{18}F]F-FBPin)] positional isomers in 2% and 6% yield respectively, as depicted in Figure 7a (40).

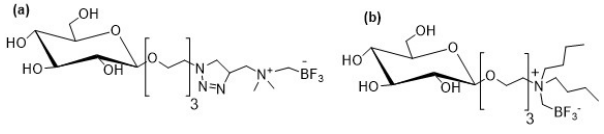


Figure 6. Structure of two representative organotriflouroborate.

The binding affinity and pharmacokinetics of the compound [^{18}F]FFBPin were studied in CCA rats. A [^{18}F]FFBPin-based PET scan was performed, depicting a concentration range of ^{10}B as 0.8-1.2 ppm in the liver and 1.2-1.8 ppm in the tumor. Moreover, a low T/B ratio suggests these compounds are unfavorable agents for imaging liver cancer or as BNCT tracers. Additionally, it is essential to note that the synthesized precursor has shown moderate selectivity for COX-2/COX-1. CCA rats treated with boron neutron capture therapy have shown a more pronounced decrease in tumor dimension compared to those treated with neutron capture therapy, as shown in Figure 7b and 7c.

Briefly summarizing the methodologies employed for ^{18}F labeling of BNCT tracers Table 2 outlines the merits and demerits of various BNCT tracers labeled with ^{18}F through electrophilic, nucleophilic, and ^{18}F/^{19}F exchange reactions. Conventionally, electrophilic radiofluorina-

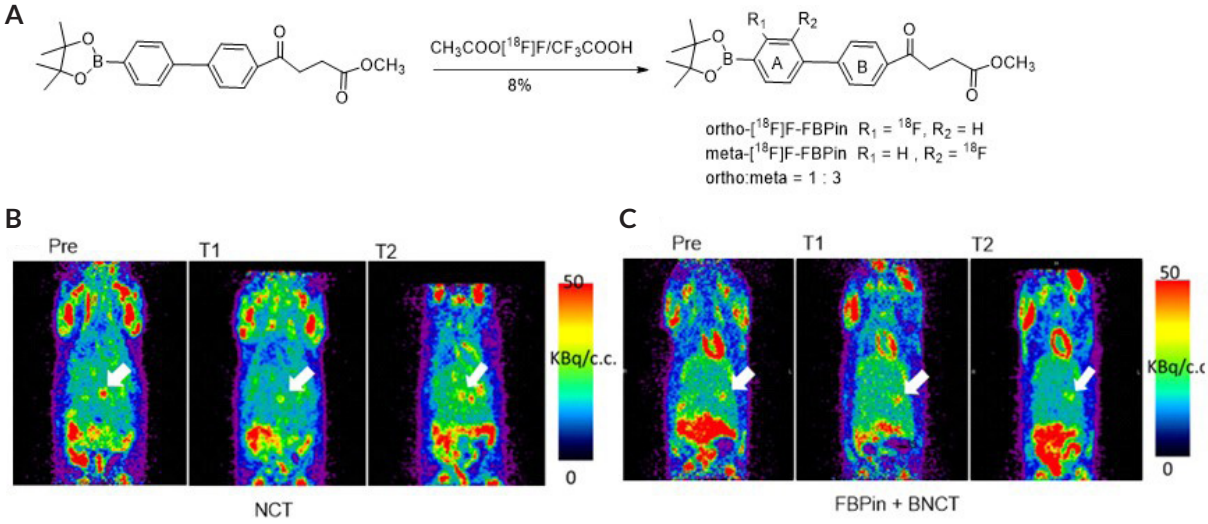
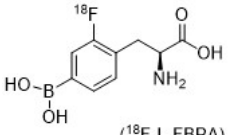
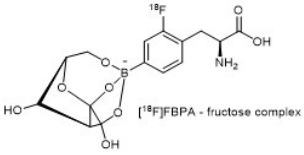
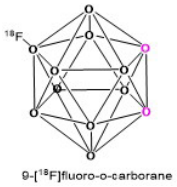
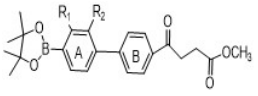
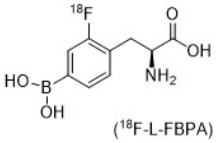
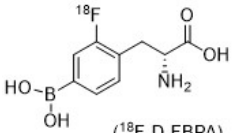
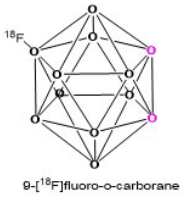
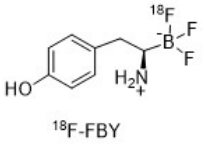


Figure 7. (A) Synthesis of [^{18}F]F-FBPin via electrophilic radioflourination for targeting COX-2 overexpressed cholangiocarcinoma tumor, (B) CCA rat images before and after sequential NCT treatment without tracer, (C) CCA rat images after treating with combine FBPin and BNCT. Adapted with permission from [40], copyright 2017, Elsevier B.V.

Table 2. Radiant Pros and Tricky Cons in Crafting 18F labeled BNCT tracers.

Nuclear reaction	^{18}F reagent	Advantages	Disadvantage	Ref
Electrophilic radioflourination				
	$[^{18}F]F_2$	Potential BNCT tracers demonstrate high accumulation and retention in tumors.	Limited aqueous solubility, less molar activity of approximately 100 MBq/μmol obtained.	[20]
	$[^{18}F]F_2$	Higher solubility in aqueous media.	Bio distribution profile deviate from ^{18}F-FBPA and BPA	[26]
	$[^{18}F]F_2$	Simple one step labeling protocol.	Only o carborane can be radioflourinated in 21% yield.	[32]
	$[^{18}F]F_2$	COX-2 selective boron carrier, can diagnose challenging cholangiocarcinoma.	Mixture of ortho and meta isomers formed, low T/B ratio, least potential agent for BNCT.	[40]
Nucleophilic radioflourination				
	$[^{18}F]F^-$	Potential BNCT tracer obtainable in very high specific activity upto GBq.	Limited solubility in water and uncertain boron concentration in tumor.	[30]
	$[^{18}F]F^-$	High T/B ratio, fast clearance, excretion via kidney.	Limited aqueous solubility.	[25]
	$[^{18}F]F^-$	High radiochemical yield of 44%.	This method is only applicable for o-carboranes.	[33]
Radiofluoroexchange (^{18}F/^{19}F) reaction				
	^{18}F/^{19}F exchange reaction	> 50% radiochemical yield, high stability, solubility in aqueous media and higher uptake in the tumor.	This method is only applicable for o-carboranes	[38]

tion was considered the preferable procedure due to the ease of using [^{18}F]F_2, which requires no preceding modification, but its clinical utility is restricted. BPA and o-carboranes possess the ability to be radiolabeled via both electrophilic and nucleophilic modes, each process having its upsides and downsides. Furthermore, the ^{18}F radiolabeling strategy for the BPA-fructose complex and fenbufen boronopinacol are also listed in Table 2, along with their assets and liabilities. It is important to note that flouroboronotyrosine (FBY) undergoes labeling via ^{18}F/^{19}F exchange reaction with a radiochemical yield of more than 50%. It is also crucial to emphasize that the choice of radiolabeling strategy is dependent on numerous factors such as required yield, substrate compatibility, scalability of the reaction, and its specific application.

4. Conclusion and future perspectives

The worldwide challenge of cancer has attracted the attention of the scientific community to develop favorable, potent, and risk-free strategies. In this regard, BNCT has emerged as an optimistic avenue. This review is in depth discussion of ^{18}F labeling of the most widely used tracer in the field of BNCT. The electrophilic, nucleophilic and halogen exchange strategy each of which offered noticeable benefits and shortcomings are explored. While electrophilic method is simple to carry out, nucleophilic leads to higher yield and more broader tracer selectivity. Contrary to these two methodologies halogen exchange route provide high yield, stability and compatibility of the drug. It is very critical to emphasize that there is no single method that is acceptable worldwide. So by integrating these methods and exploring hybrid strategies might give superior outcome for example dual labeling (^{18}F/^{11}C) of BNCT tracer can help scientist to get dynamic imaging and hence made them able to examine metabolic processes of patient in real time. This perpetual practice of radiofluorination sparks transformative advancements in BNCT, revealing new horizons in radiochemistry and ultimately proving beneficial in reshaping the future of medical science.

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