Bioconjugate Chemistry

Review

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New Strategies for Rapid ^{18}F-Radiolabeling of Biomolecules for Radionuclide-Based In Vivo Imaging

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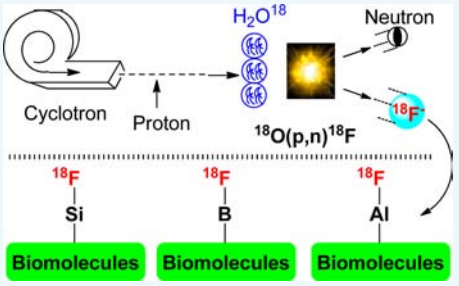
ABSTRACT: The increasing availability of highly active no-carrier-added [^{18}F]-fluoride makes its use in radiolabeling biomolecules attractive. By incorporating "fluorophilic" elements (Si, B, and Al) into biomolecules, recent advances offer mild and rapid ^{18}F-labeling approaches without HPLC purification at the radiosynthetic stage while maintaining sufficient specific activity. In this Topical Review, we will discuss the most recent strides in the field.



Fluorine-18 (^{18}F) is the most widely used PET (positron-emission tomography) radioisotope for clinical imaging because of its nearly ideal nuclear properties, including high positron emission abundance (β^+, 97%), low positron energy (0.635 MeV) resulting in limited positron migration (<2 mm), and suitable physical half-life (109.7 min).[1−5] Depending on the mode of production, no-carrier-added (NCA) [^{18}F]-fluoride ions can be readily obtained in an aqueous solution by proton irradiation of an [^{18}O]-H_2O target using a medical cyclotron (Figure 1, top). However, fluoride ions are very poorly nucleophilic in the presence of water. To improve its nucleophilicity, the [^{18}F]-fluoride is commonly trapped on an anion exchange resin, eluted with a small volume of an organic−aqueous solution (e.g., CH_3CN/H_2O) of an inorganic base (potassium carbonate) and a cryptand (kryptofix: K 2.2.2) or tetrabutylammonium hydrogen carbonate ($TBAHCO_3$). All water traces have to be removed by iterative azeotropic distillation, and the cryptand or ammonium enables solubilization of the [^{18}F]-fluoride ion in a polar aprotic solvent suitable for the subsequent labeling reaction. However, this complex automation process requires 80−110 °C temperatures and 20−30 min, and consumes radiochemical yield (Figure 1a, bottom).

To simplify the azeotropic evaporation procedure, in 2010 Lemaire and co-workers introduced an innovative elution method by using phosphazenes or guanidines (pK_a value of its conjugate acid: 23−28) as additives to replace the inorganic bases classically used in the resin eluent (Figure 1b, bottom).[6] Accordingly, an appropriate selection of solvent, protic additive, organic base, and temperature enables optimization of the reactivity of [^{18}F]-fluoride. Later, Wester's group presented another new drying strategy known as the "Munich method" (Figure 1c, bottom).[7] This technique consists of the elution of dry [^{18}F]-fluoride from a strong anion exchange cartridge (SAX) with lyophilized K2.2.2/potassium hydroxide complex ([K^+⊂2.2.2] OH^-) dissolved in anhydrous acetonitrile. These two promising procedures are fast (3−5 min) and fully devoid of complex azeotropic drying steps, and are well-suited to an automated setup. Furthermore, these approaches should also be useful for the direct labeling of sensitive biomolecules.

Large biological molecules, such as peptides, proteins, carbohydrates, and nucleic acids, often exhibit high affinity and high specificity for many pathogenic targets. Over the past decades, ^{18}F-radiolabeled biomolecules have been the focus of research due to their potential as molecular imaging probes and therapeutic agents. When labeling large biomolecules, minimizing steric and electronic alteration to the targeting molecules is less critical than that for small organic molecules, while the use of mild and efficient labeling conditions preferably in a single step is more important. In this context, the direct incorporation of several noncarbon elements (such as silicon, aluminum, and boron) into biomolecules as fluoride-binding sites for ^{18}F-radiolabeling has attracted much attention from chemists and clinicians in the molecular imaging community. Rapid and efficient labeling approaches, based on ^{18}F−Si and ^{18}F−B bond formation, as well as ^{18}F−Al chelation scaffolding, have appeared in the literature. In this Topical Review, we will discuss the most recent strides in the field.

From the seminal reports of Schirrmacher,[8] Choudhry,[9] and Ametamey,[10] the knowledge of the silicon-fluoride acceptor (SiFA) ^{18}F-labeling strategy has increased tremendously over the past years. Simple organofluorosilanes display poor kinetic stability, and the Si−F bond is prone to dissociation in the presence of water. To shield the Si−F bond from hydrolysis, the introduction of *tert*-butyl groups at the silicon atom is critical for [^{18}F]-SiFAs to achieve sufficient in vivo stability. However, the high lipophilicity of the peptide conjugates could

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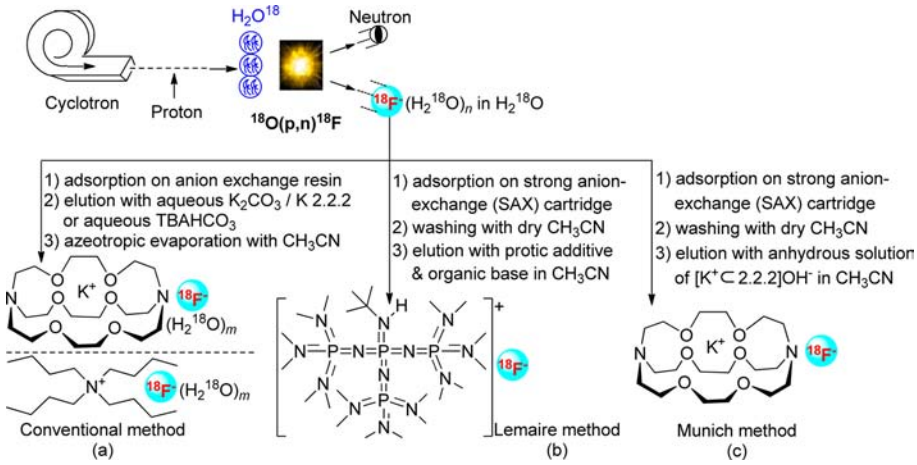

Figure 1. Production of no-carrier-added [^{18}F]-fluoride ions in an aqueous solution by proton irradiation of an [^{18}O]-H_2O target using a medical cyclotron (top). Preparation of highly active no-carrier-added [^{18}F]-fluoride (bottom): (a) anion exchange and elution with aqueous K_2CO_3/K 2.2.2 (or $TNAHCO_3$), then azeotropic evaporation (conventional method); (b) anion exchange and elution with CH_3CN solution of protic additive and organic base (Lemaire method); and (c) anion exchange and elution with anhydrous CH_3CN solution of $[K^+\subset 2.2.2]OH^-$ (Munich method).

affect its metabolism and biodistribution, generating unspecific uptake and leading to poor PET imaging quality. Several research groups have approached this problem by incorporating hydrophilic units into the SiFA-conjugated biomolecules to compensate for the high lipophilicity. For example, the group of Schirrmacher and Wängler successfully disclosed the use of aspartic acid (Asp), polyethylene glycol (PEG) spacers, and/or carbohydrates as lipophilicity-reducing auxiliaries for SiFA-peptides,[11−13] whereas Ametamey and co-workers nicely introduced the tartaric acid/L-cysteic acid-containing linkers as a silicon-based alternative with counterbalanced lipophilicity.[14,15]

The [^{18}F]-SiFA strategies can be subdivided into two labeling methods: the isotopic exchange (IE) reaction and the Si-leaving group procedure. The notable feature of the SiFA-IE labeling is that the labeling precursor and labeled radiotracer are chemically identical, eliminating the need to separate the radiotracer from its precursor. Starting from readily available [^{18}F]F^-/[^{18}O]H_2O, Wängler et al. recently developed an elegant combination of the SiFA-IE chemistry with the Munich method, providing a simple kit-production procedure for ^{18}F-radiolabeling of peptides (Figure 2, top).[16] Three general radiosynthons, including *p*-(di-*tert*-butylfluorosilyl)-benzaldehyde (SiFA-A: **1**), *N*-succinimidyl *o*-(di-*tert*-butylfluorosilyl)-benzoate (SiFB: **2**), and *p*-(di-*tert*-butylfluorosilyl)benzenethiol (SiFA-SH: **3**), were designed and used in the SiFA-IE chemistry (Figure 2: bottom). The SiFA-IE reaction proceeds in dipolar aprotic solvents at room temperature and below, avoiding the formation of radioactive side products during the IE. In addition to the SAX and the solid-phase extraction (SPE) cartridges, no equipment is required, thereby simplifying the entire drying and purifying procedure enormously. Moreover, the scope of this promising combination has also been extended to the labeling of proteins and affibodies.[17−19]

The ^{18}F-labeling of arylfluoroborates with the nucleophilic [^{18}F]-fluoride and near-quantitative carrier (from KHF_2) to yield [^{18}F]-organotrifluoroborates was first described by Perrin and co-workers in 2005.[20] The great potential advantage of this approach is that it entails only a single radioactive reaction step and is conducted in at least partially aqueous media without the need of the time-consuming azeotropic drying steps. However, this approach involves carrier ^{19}F, and the specific activity is

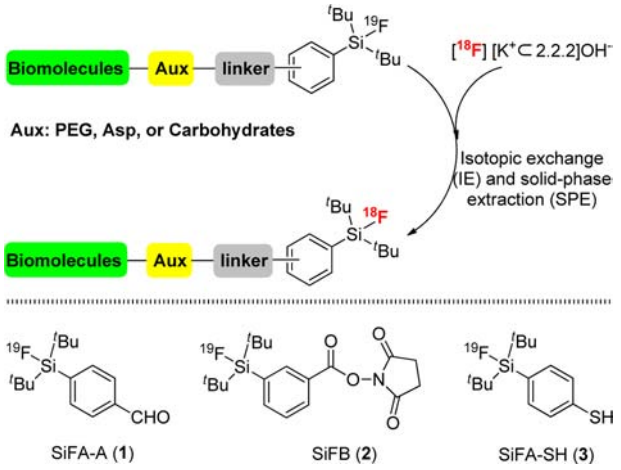

Figure 2. Labeling biomolecules through the combination of the Munich ^{18}F drying method with SiFA-IE chemistry (top), and three SiFA-radiosynthons (bottom).

relatively low. In addition, HPLC purification was needed, and in one case the in vivo stability could be questioned.[21,22]

Most recently, the same group developed an innovative one-step ^{18}F-labeling approach via an isotope exchange reaction on a zwitterionic ammoniomethyl-trifluoroborate ($AmBF_3$) moiety (Figure 3).[23] Three simple alkylammoniomethyl-trifluoroborates (**4**−**6**) were successfully designed and employed as radiosynthons. [^{18}F]-$AMBF_3$ appears to be metabolically stable as the anionic BF_3^- group is noncoordinating and bioorthogonal. For labeling, one lyophilized aliquot of $AMBF_3$-peptides was dissolved in an acidic buffer (pH ∼2.5) and transferred to the polypropylene tube into which no-carrier-added [^{18}F]-fluoride ion was eluted with saline. HPLC purification can be replaced with a simple reverse-phase Sep-Pak elution that provides radiotracer in high purity. Many peptides and proteins could be quickly labeled by this method in high radiochemical yield and at high specific activity.[24−26] For very acid-sensitive biomolecules, one-pot two-step approaches can be contemplated.

Fluoride ions are known to coordinate as ligands strongly to aluminum (Al^{3+}) (>670 kJ mol^{-1}). The first study using 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) and derivatives

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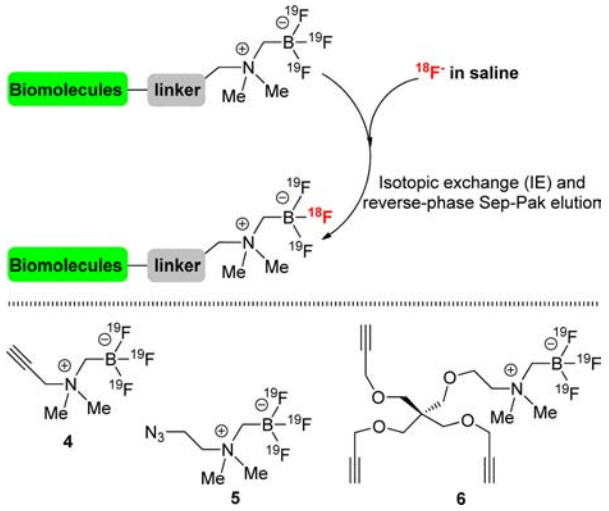

Figure 3. $AmBF_3$–IE reaction for ^{18}F-labeling biomolecules (top) and three $AmBF_3$-radiosynthons (bottom).

as chelators for ^{18}F-radiolabeling biomolecules was published by McBride and co-workers in 2009.[27−29] An aqueous solution of $[^{18}F]F^-/[^{18}O]H_2O$ was directly mixed with $AlCl_3$ in a pH 4.0 ± 0.2 optimal buffer to form the $Al^{18}F$ complex, which was moved into a solution of chelator-linked biomolecules and heated to 90−110 °C for several minutes. However, these early ligands usually suffer from the formation of unwanted hexadentate complexes with aluminum.[30,31]

With the identification of the pentadentate ligands (e.g., 1,4,7-triazacyclononane-1,4-diacetate motif with a methylphenyl-acetic acid: NODA-MPAA) as improved chelators for stable $Al^{18}F$ chelation, the investigators found that the NODA-MPAA-containing peptides could be formulated conveniently into a lyophilized kit and radiolabeled with $^{18}F^-$ in saline or $Na^{18}F$ in one step with good radiochemical yield and high specific activity (Figure 4).[32−36] The ^{18}F-radiolabeling products could

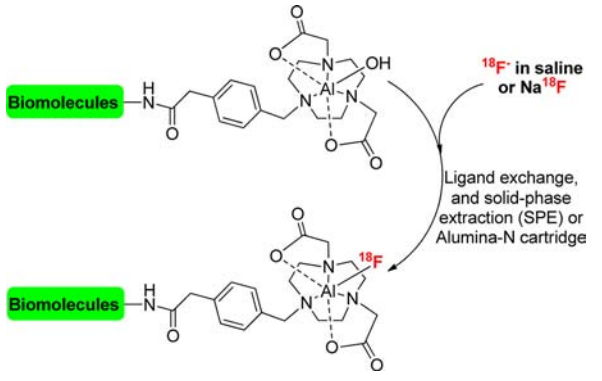

Figure 4. Labeling biomolecules through the formation of stable aluminum fluoride chelates.

be rapidly purified using an inexpensive and disposable Alumina-N cartridge or a reverse-phase SPE cartridge. Furthermore, excellent in vivo properties were also found for $Al^{18}F$-labeled affibody molecules and proteins.

Notably, the chemists and clinicians from China and the USA presented the first clinical report on the use of a simple and one-pot lyophilized kit for $Al^{18}F$-labeling PRGD2 peptide ($Al^{18}F$-NOTA-PRGD2, denoted as $[^{18}F]$-alfatide).[37] Nine patients with a primary diagnosis of lung cancer and one tuberculosis patient were examined by using both $[^{18}F]$-alfatide and $[^{18}F]$-FDG imaging. The entire radiosynthesis and purification was finished within 20 min in 42.1 ± 2.0% decay-corrected yield with >95% radiochemical purity. $[^{18}F]$-alfatide PET imaging identified all primary tumors, with mean standardized uptake values of 2.90 ± 0.10. Tumor-to-muscle and tumor-to-blood ratios were 5.87 ± 2.02 and 2.71 ± 0.92, respectively.

In summary, the recently disclosed approaches by the groups of Lemaire and Wessmann represent very efficient procedures for the fast production of highly active no-carrier-added $[^{18}F]$-fluoride. On the other hand, by incorporating silicon-, boron-, and aluminum-containing prosthetic groups into biomolecules, new advances offer mild and rapid ^{18}F-labeling approaches without HPLC purification at the radiosynthetic stage while maintaining sufficient specific activity.[38] These protocols could help meet the requirements for a true kit-like ^{18}F-labeling procedure. However, the application extension and clinical translation of these methodologies remain to be explored in more details.

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Notes

The authors declare no competing financial interest.

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