Accelerating the Development of Peptide-Based NET Tracers with ‘Next-Gen’ 18F Chemistry

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SiFA×NAMB-based syntheses of [18F]TATE

- We hypothesize that SiFA isotopic exchange reactions can be coupled with ‘NAMB’ techniques, allowing for the highly simplified and fully automated preparation of [18F]TATE and other peptide-based 18F-PET radiopharmaceuticals.

- The feasibility of labeling [18F]TATE (50 nmol) under NAMB conditions has been investigated (Fig. 3). Apart from the parameters in Table 1, we also tracked the efficiency of [18F]F-trap-and-release from our small (12 mg) QMA columns, which we 3D-print ourselves and also sell commercially.

Fig. 1. a)Canonical method for radiolabeling with [18F]F. A basic anion (usually carbonate) is used to elute [18F]F from QMA anion exchange resin, then water is removed via successive MeCN:HO aeotrope distillation (‘drydown’) steps. b) The ‘non-anhydrous, minimally basic’ (NAMB) method involves the trapping of [18F]F on small QMA columns, elution with non-basic anions, and subsequent nucleophilic 18F-fluorination in ‘damp’ reaction mixtures. No ‘drydown’ steps are required.

Merging New Technologies

- A ‘next generation’ direct (i.e. 1-step) labeling strategy called ‘Silicon-Fluoride Acceptor’ (aka SiFA) employs highly efficient 18F-for-18F isotopic exchange reactions to 18F-label di-tert-butyl-fluorosilane-modified peptide targeting vectors at room temp. Only nmol of 18F-peptide precursor is required to achieve high radiochemical yields, and thus high molarity radiochemicals can be obtained without HPLC purification.

- SiFA has led to the discovery of promising 18F-labeled octreotide derivative [18F]TATE (Fig. 2). When compared with [68Ga]Gal-DOTA-TOC in clinical NET imaging scans, [18F]TATE showed higher tumor uptake in most metastatic sites and comparable biodistribution in healthy tissues.

Fig. 2. Structure of [18F]TATE.

- Translation to automation has hamstrung clinical progress, owing to a radiosynthetic protocol that requires highly basic (hydroxide anion) [18F]F eluates that must be carefully titrated with small volumes (15 μL) of oxalic acid. As the 18F-peptide is sensitive to both the base and the acid alone, it must be quantitatively added to the reaction vessel via cannula after titration, a step that is difficult to automate.

- We introduced an alternative means to prepare reactive [18F]F called ‘Non-Anhydrous, Minimally Basic’ (NAMB) 18F-fluorination chemistry, in which [18F]F is eluted from smaller-than-usual anion exchange (AEX) quaternary methylammonium (QMA) columns with non-basic tetraalkylammonium salts, then used for nucleophilic 18F-fluorination reactions directly, despite reaction mixtures containing 3-5% water (Fig. 1b).4

Table 1. Summary of [18F]TATE syntheses. All elution efficiencies from QMA resin were >99%, except Entry 4 (66%). All reactions at room temp. Total syntheses times = 41-59 min. *Radiochemical conversion assayed by radio-TLC. †Non-delay-corrected radiochemical yield. ‡n=3 experiments.

Entry Eluate MeCN:H2O Water DMSO React. (min) RCC† NDC-RCC‡
1 7.3 (0.1 mL) 3 2.5 10 31 30
2 7.3 (0.1 mL) 3 2.5 20 37 25
3 7.3 (0.1 mL) 3 2.0 20 60-84 ‡ 37-52 ‡
4 9.1 (0.3 mL) 3 2.0 20 87 26
5 8.2 (0.3 mL) 6 2.0 20 70 49
6 8.2 (0.3 mL) 6 2.0 30 – 10

Fig. 3 Example radio-traces of the manual syntheses of [18F]TATE.

New PET agents for pancreatic cancer

- We intend to apply the ‘SiFA×NAMB’ radiolabeling strategy towards the design of new SiFA-bearing peptide receptor ligands which target certain pancreatic cancers (insulinomas).

- The overexpression of glucagon-like peptide 1 receptor (GLP-1r) in many insulinomas has led to nuclear imaging with radioalkylated exendin-4 analogues prior to surgery becoming common practice.

- Most GLP-1r-targeting radioprobes invented thus far employ metallic radioisotopes and tend to distribute into the kidneys, which can complicate pancreas imaging due to the proximity of the two organs.

- However, many 18F radio-peptides that contain lipophilic prosthetic groups clear quickly from the kidneys, making SiFA-bearing exendin-4 derivatives a worthy class of PET imaging agents for design and preclinical assessment.

References

5. General Science Innovations, Inc.

Fig. 4. Summary diagram of the automated synthesis of [18F]TATE.