4-[^{18}F]Fluorobenzoyl-Arg-Arg-Natl-Cys-Tyr-Cit-Lys-D-Lys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2

4-[^{18}F]F-T140

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Chemical name:	4-[^{18}F]Fluorobenzoyl-Arg-Arg-Natl-Cys-Tyr-Cit-Lys-D-Lys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2	
Abbreviated name:	4-[^{18}F]F-T140	
Synonym:	4-[^{18}F]F-TN14003	
Agent category:	Peptide	
Target:	Chemokine receptor 4 (CXCR4)	
Target category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal:	^{18}F	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structure not available in PubChem.

Background

[PubMed]

Chemokine receptors are G-protein–coupled receptors directing cell movement toward higher concentrations of chemokines. Chemokine receptor 4 (CXCR4) and its ligand, stromal cell–derived factor-1 (SDF-1 or CXCL12), are known to play a major role in the migration of progenitor cells during embryonic development of the central nervous, cardiovascular, and hematopoietic systems (1, 2). In addition, this CXCR4-SDF-1 receptor

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system has a function in the development, progression, and spread of various cancers (3), and the CXCR4 acts as a co-receptor for human immunodeficiency virus (HIV) on $CD4^+$ T cells (4). It has also been suggested that CXCR4/SDF-1 interaction participates in the pathogenesis of neurodegenerative and inflammatory conditions (5). CXCR4 is expressed by many different types of cancers, and overexpression of CXCR4 in cancers indicates poor prognosis with aggressive and metastatic tumors and resistance to chemotherapy (6).

CXCR4 is considered to play an important role in HIV infections and cancers. It is critical to perform imaging studies to measure CXCR4 levels under *in vivo* conditions for various pathological and physiological conditions (7). ^{99m}Tc-SDF-1 has been used with single-photon emission computed tomography (SPECT) to determine changes in CXCR4 expression in the heart after a myocardial infarction. ^{64}Cu-1,1'-[1,4-Phenylenebis(methylene)]-bis[1,4,8,11-tetraaza-cyclotetradecane] (^{64}Cu-AMD3100), an inhibitor of CXCR4 activity, has been studied with positron emission tomography (PET) (8). An ^{111}In-labeled CXCR4 antagonist peptide, ^{111}In-Ac-TZ14011, has been developed for SPECT imaging of CXCR4 expression in xenograft tumors in mice (9). Tamamura et al. (10) identified a 14-amino-acid peptide (T140, Arg-Arg-Natl-Cys-Tyr-Cit-Lys-D-Lys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2) with high anti-HIV and CXCR4 antagonistic activities *in vitro*. Jacobson et al. (11) radiolabeled T140 with 4-[^{18}F]fluorobenzoic acid ([^{18}F]FBA) to form 4-[^{18}F]fluorobenzoyl-Arg-Arg-Natl-Cys-Tyr-Cit-Lys-D-Lys-Pro-Tyr-Arg-Cit-Cys-Arg-NH_2 (4-[^{18}F]F-T140) for PET imaging of tumor CXCR4 expression with a high tumor/background ratio.

Related Resource Links:

- Chapters in MICAD (CXCR4)
- Gene information in NCBI (CXCR4)
- Articles in Online Mendelian Inheritance in Man (OMIM) (CXCR4)
- Clinical trials (CXCR4)
- Drug information in FDA (CXCR4)

Synthesis

[PubMed]

Jacobson et al. (11) prepared 4-[^{18}F]F-T140 with a two-step synthesis in a modular system. The T140 peptide precursor with protecting groups on both lysine residues was purchased (Pro-Immune). [^{18}F]FBA was synthesized using standard nucleophilic radiofluorination ([^{18}F]KF/Kryptofix 2.2.2) reaction with 50%–60% yield and >99% radiochemical purity. [^{18}F]FBA and the T140 peptide with protecting groups in dimethylformamide were incubated for 40 min at room temperature, followed by hydrazine hydrolysis of the protecting groups for 10 min at room temperature. 4-[^{18}F]F-T140 was purified with high-performance liquid chromatography, with a radiochemical purity of >99% and a specific activity of 7 ± 2 GBq/μmol (0.19 ± 0.05 Ci/μmol) at the end

of synthesis. The overall decay-corrected yield was 15 ± 5% (n = 6). The total synthesis time was not reported.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

Chinese hamster ovary (CHO) cells were transfected with human CXCR4 (7×10^5 binding sites/cell). A receptor-binding assay was performed with ^{125}I-SDF-1. 4-F-T140 exhibited 50% inhibition concentration (IC_{50}) value of 2.5 nM (11). 4-F-T140 exhibited a similar IC_{50} value to inhibit Jurkat T cell migration in response to SDF-1.

Animal Studies

Rodents

[PubMed]

Jacobson et al. (11) performed *ex vivo* biodistribution studies of 1.9 MBq (0.050 mCi) 4-[^{18}F]F-T140 in nude mice (n = 3/group) bearing the CHO and CHO-CXCR4 tumor xenografts at 1, 2, and 3 h after injection. Accumulation in the CXCR4-expressing organs increased with time. The spleen exhibited 8 ± 1% injected dose/gram (ID/g) at 1 h and 12 ± 2% ID/g at 3 h. Accumulation in bone marrow increased from 0.78 ± 0.22% ID/g at 1 h to 2.6% ± 0.65% ID/g at 3 h. The blood accumulation was unexpectedly high for a small peptide, with 14.7 ± 2.6% ID/g at 3 h. Accumulation in the liver, intestine, and kidneys was low (<5% ID/g). 4-[^{18}F]F-T140 exhibited a slightly higher accumulation in the CHO-CXCR4 tumors at 1–3 h (~2.3% ID/g) than in the CXCR4-negative CHO tumors (~1.7% ID/g) at the same time point ($P > 0.05$). The similar accumulation in both tumors suggested that the blood flow in both tumors was similar. Co-injection of excess 4-F-T140 (10–50 μg) significantly reduced ($P < 0.05$) the accumulation of 4-[^{18}F]F-T140 in the blood, spleen, bone marrow, and CXCR4-negative tumors at 3 h after injection, whereas the accumulation in the CHO-CXCR4 tumor was significantly increased ($P < 0.05$). Red blood cells were responsible for 95% of radioactivity in the blood, which was reduced to 44% by excess 4-F-T140, allowing 4-[^{18}F]F-T140 to be accessible to binding to the CHO-CXCR4 tumor. The tumor/muscle and tumor/blood ratios were 2.94 ± 0.16 and 0.19 ± 0.04, respectively, at 3 h after injection of only 4-[^{18}F]F-T140. Co-injection with 10 μg 4-F-T140 increased the tumor/muscle and tumor/blood ratios to 21.6 ± 7.14 and 27.05 ± 8.70, respectively. Co-injection with 50 μg 4-F-T140 produced tumor/muscle and tumor/blood ratios of 10.41 ± 5.30 and 6.15 ± 2.65, respectively.

The whole-body distribution of 4-[^{18}F]F-T140 was also assessed with PET imaging at 2 h after injection in mice bearing CHO and CHO-CXCR4 tumor xenografts. Both tumors were clearly visualized along with the abdomen area. In another experiment with mice bearing only a CHO-CXCR4 tumor, co-injection of excess 4-F-T140 increased radioactivity in the tumor.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No publication is currently available.

NIH Support

Intramural Research Program

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