1-(2'-Deoxy-2'-[^{18}F]fluoroarabinofuranosyl)cytosine

[^{18}F]FAC

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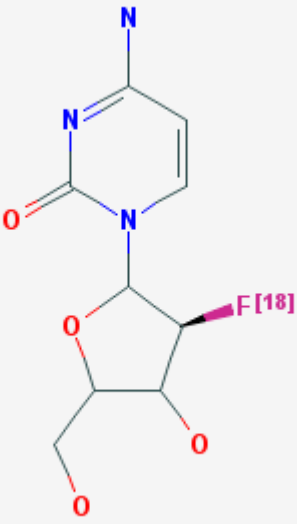
Chemical name:	1-(2'-Deoxy-2'-[^{18}F]fluoroarabinofuranosyl)cytosine
Abbreviated name:	[^{18}F]FAC
Synonym:	
Agent category:	Compound
Target:	Deoxycytidine kinase (DCK)
Target category:	Enzyme
Method of detection:	Positron emission tomography (PET)
Source of signal:	^{18}F
Activation:	No
Studies:	• *In vitro* • Rodents



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Background

[PubMed]

One of the characteristics of tumor cells is their unchecked proliferation. It is important to measure the proliferation rate of cancer lesions to help differentiate benign tumors from

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malignant tumors and to characterize malignant tumors among normal tissues. 2-[^{18}F]Fluoro-2-deoxy-D-glucose ([^{18}F]FDG) has been approved for cancer positron emission tomography (PET) imaging by the United States Food and Drug Administration. However, enhanced uptake of FDG as measurement of glycolysis occurs in inflammatory cells and lesions as well as in necrotic cells (1, 2). Thymidine (TdR) and TdR analogs are the standard markers for DNA synthesis, and [^{11}C]TdR has been used in PET to measure tumor growth rates *in situ*. Because of the short half-life of ^{11}C and the extensive metabolism of [^{11}C]TdR in the blood (3), 3'-deoxy-3'-[^{18}F]fluorothymidine (FLT) was developed for PET imaging. FLT is an analog of TdR and is phosphorylated by TdR kinase-1 (TK-1), an enzyme expressed during the DNA synthesis phase (S-phase) of the cell cycle (4). On the other hand, RNA synthesis occurs in all phases of the cell cycle except the M phase, even in slow-growing solid tumors. Tracers targeted to RNA synthesis could be used to visualize tumors with low TK-1 expression.

Phosphorylation of deoxyribonucleosides and their nucleoside analogs is carried out with deoxycytidine kinase (DCK) (5). DCK is ubiquitously expressed in normal tissues but is highly expressed in hematolymphoid tissues (spleen, thymus, and lymph nodes) and epithelial cells (6). Lymphoid cells and rapidly proliferating cells prefer the salvage pathway over the *de novo* pathway for DNA synthesis. 1-(2'-Deoxy-2'-fluoroarabinofuranosyl)cytosine (FAC) was found to be retained in proliferating T cells. FAC is taken up by cells and rapidly phosphorylated by DCK and trapped inside the cells. In this chapter, 1-(2'-deoxy-2'-[^{18}F]fluoroarabinofuranosyl)cytosine ([^{18}F]FAC) is being developed as a PET probe for imaging of epithelium, lymphoid tissues, and immune activation (6-8).

Related Resource Links:

- Chapters in MICAD (Nucleoside)
- Gene information in NCBI (DCK)
- Articles in Online Mendelian Inheritance in Man (OMIM) (DCK)
- Clinical trials ([^{18}F]FAC)

Synthesis

[PubMed]

Radu et al. (8) reported the synthesis of [^{18}F]FAC using 1-bromo-2-[^{18}F]fluoro-3,5-di-*O*-benzoyl-D-arabinofuranose sugar derivative. [^{18}F]FAC was purified with high-performance liquid chromatography with a radiochemical purity of >99% and radiochemical yields of 20%–30%. The specific activity of [^{18}F]FAC was >37 GBq/μmol (1 Ci/μmol).

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

In vitro cellular uptake assays with murine lymphoid cells from the thymus and spleen showed that $CD8^+$ T cells and $CD11b^+$ cells (macrophages and granulocytes) exhibited higher uptake of [^{18}F]FAC than did $CD4^+$ T cells (8). Activated mouse $CD8^+$ T cells (250 fmol/10^5 cells) showed >12-fold higher uptake of [^{3}H]FAC than did resting $CD8^+$ T cells (18 fmol/10^5 cells). NIH3T3 fibroblasts transfected with DCK and solute carrier family SLC29A1 genes showed ~1–2-fold higher uptake of [^{3}H]FAC than did control cells.

Animal Studies

Rodents

[PubMed]

Radu et al. (8) performed *ex vivo* biodistribution studies after injection of 7.4 MBq (200 μCi) [^{18}F]FAC in normal mice (n = 3). The radioactivity at 60 min after injection was highest in the urinary bladder (35% injected dose/gram (ID/g)), followed by the spleen (9% ID/g), thymus (7% ID/g), lymph nodes (5% ID/g), small intestine (5% ID/g), and large intestine (4% ID/g). The accumulation in the heart, kidney, lung, liver, and muscle was <4% ID/g. Whole-body PET imaging visualized [^{18}F]FAC accumulation in the thymus, spleen, intestines, liver, bone, and bone marrow at 60 min after injection. Fractionations of the cells from the thymus and spleen showed that the thymocytes, T cells, B cells, macrophages, and granulocytes had high accumulation of radioactivity. Analysis of thymus extract showed that [^{18}F]FAC and its phosphorylated derivatives (mono-, di-, and tri-phosphate metabolites) were detected at 60 min after injection. As a comparison, the spleen showed higher accumulation of [^{18}F]FAC (2.16 ± 0.48% ID/g) than of [^{18}F]FLT (1.02 ± 0.21% ID/g) or [^{18}F]FDG (1.69 ± 0.16% ID/g). [^{18}F]FAC PET imaging studies in a mouse model of antitumor immunity clearly visualized activated lymphoid organs (spleen and tumor-draining lymph nodes). Splenic $CD8^+$ T cells exhibited three-fold higher [^{18}F]FAC accumulation compared with naïve T cells. In a systemic autoimmunity model, PET imaging revealed increased numbers of [^{18}F]FAC-positive lymph nodes in B6.MRL-Fas^{lpr} autoimmune mice as compared with wild-type mice. Administration of 10 mg/kg dexamethasone (an immunosuppressive drug) decreased the numbers of [^{18}F]FAC-positive lymph nodes in B6.MRL-Fas^{lpr} mice.

Brewer et al. (6) demonstrated that the high uptake of [^{18}F]FAC in the intestines in normal mice was mainly contributed by the epithelial cells, with some contribution from T cells. Germ-free mice showed lower uptake in the intestine, whereas mice with immune inflammatory stimulation (transfer of T cells from colitic mice) showed higher uptake than the normal mice.

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

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