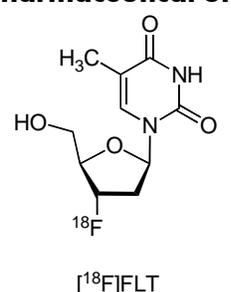


Radiopharmaceutical Name	3'-deoxy-3'-[¹⁸ F]-fluorothymidine Abbreviations: [¹⁸ F]fluorothymidine, FLT	
Radiopharmaceutical Image	Normal Biodistribution	Radiopharmaceutical Structure  [¹⁸ F]FLT
Radionuclide	¹⁸ F Half-life 109.7 minutes Emission: positron Emax 1.656 MeV	
MICAD	http://www.ncbi.nlm.nih.gov/books/NBK23373/	
Molecular Formula and Weight	C ₁₀ H ₁₃ FN ₂ O ₄ 244.2 g atom mole ⁻¹	
General Tracer Class	Investigational Diagnostic PET Radiopharmaceutical	
Target	Proliferating tissue, primarily cancers	
Molecular Process Imaged	Thymidine kinase I (TK1) activity is thought to be proportional to cellular proliferation and DNA synthesis by the salvage pathway. (J Biol Chem 263:8350, 1988)	
Mechanism for in vivo retention	Fluorothymidine is an analog of the nucleoside thymidine (deoxythymidine) but the 3'-F atom prevents FLT from following the full biochemical pathway of thymidine. FLT is transported from the blood into cells by active transport, it does not freely diffuse across the cell membrane. Once in the cell, FLT is a substrate for thymidine kinase I (TK1) and is phosphorylated but is not incorporated into DNA. The assumption is that the concentration of FLT nucleotides in cells is proportional to TK1 activity and therefore to cellular proliferation. Phosphorylated FLT cannot exit the cell. FLT is not a substrate for thymidine phosphorylase and so is not significantly degraded in vivo and is retained in the cells. One advantage of FLT is that it is only a substrate for TK1	

	and not for mitochondrial TK2 and so it is a more specific tracer compared with other fluorinated tracers for cellular proliferation.
Metabolism	FLT is not dephosphorylated in vivo but conjugated FLT is cleared via the kidneys and excretion in the urine.
Radiosynthesis	<p>[¹⁸F]FLT was first described by Grierson and Shields using a nucleophilic fluorination but the synthesis was low yield. (Nature Medicine 1998,1334; J Nucl Med 39:22P,1998; J Label Compd Radiopharm 42,Suppl1:S525,1999; Nucl Med Biol 27:143,2000.</p> <p>Other investigators have improved the synthesis with different leaving and protective groups that are somewhat analogous to the radiosynthesis of FDG. The newer approaches are described in Nucl Med Biol 30:151, 2003; Nucl Med Biol 29:263,2002; J Radioanal Nucl Chem 243:843,2000; J Label Compd Radiopharm 43:1211,2000.</p> <p>Unlike FDG the radiosynthesis of FLT can lead to many complex and potentially toxic side products and the FLT has to be purified. The most reliable purification is by HPLC but some recent papers describe solid phase extraction strategies.</p>
Availability	FLT is investigational and can only be used in humans under an approved IND. Available from some central radiopharmacies at several academic centers. The NCI Cancer Imaging Program (CIP) provides documents that can aid in the CMC process and synthesis http://imaging.cancer.gov/programsandresources/cancer-tracer-synthesis-resources
Status with USP / EuPh	USP and EuPh Monographs are under development as of early 2012.
Recommended Activity and Allowable mass	As FLT is investigational, there is no current set standard for the amount of radiation to be administered or the maximum nonradioactive FLT that may be administered. Typical activities are 185 to 370 MBq (5 to 10mCi) maximum injected dose. The IND held by NIH requires a radiochemical purity of no less than 95% and no more than 5 mcg of nonradioactive FLT and no more than 5 mcg of other UV-absorbing impurities.
Dosimetry	The effective dose equivalent is reported to be 0.028 ± 0.012 mSv/MBq for the standard adult male and 0.033 ± 0.012 mSv/MBq for the standard adult female. The critical organ is the urinary bladder wall and the dose depends on the voiding schedule: 0.18 mGy/MBq in males with voiding at 6 hrs and 0.08 mGy/MBq with voiding at 2 and 6 hrs post injection (J Nucl Med 44:1482,2003).
Pharmacology and Toxicology	Pharmacology / toxicology was initially assessed for FLT (non-radioactive) when it was under investigation as an antiviral. FLT had unacceptable toxicity at much greater doses than those for the radioactive tracer. The NCI IND for FLT provides a detailed section of pharm/tox and will provide investigators a letter to reference their IND if requested.

<p>Current Clinical Trials</p>	<p>The NIH clinical trials registry (www.clinicaltrials.gov) should be consulted for a list of current trials using FLT. As of early 2012, it listed 45 clinical trials with 36 in the United States in 37 states. Of these 45 clinical trials, 23 were recruiting or preparing to recruit subjects. Almost all of the clinical trials are for using FLT to image cancer and evaluate response to treatment and included lymphoma, breast, head and neck, brain, cervical, pancreatic, esophageal, kidney, lung, colorectal and neuroendocrine cancers. Two pediatric clinical trials in brain / CNS cancer were also listed. Multicenter trials of FLT as an imaging agent are underway including ACRIN clinical trials under the NCI IND and pharmaceutical company sponsored trials under the Clinical Trials Network IND.</p>
<p>Reference Site / Person</p>	<p>The best reference at this time for the state of FLT trials is clinicaltrials.gov or the NCI CIP website and contacts through that website (http://imaging.cancer.gov/programsandresources/cancer-tracer-synthesis-resources)</p>
<p>Imaging Protocol</p>	<p>The imaging protocol for FLT has not been standardized yet. No patient fasting is required. The ACRIN website is a useful source of protocol information. http://acrin.org/ Typically the procedure involves IV infusion by pump of 5-10 mCi radioactivity and dynamic scanning is started immediately at the start of tracer infusion. Following 60 to 90 min of dynamic scanning, a torso survey is typically acquired. If dynamic images are not acquired, the emission PET scan should be obtained at approximately 60±10 min after injection. In some protocols, blood samples are drawn at 15, 30 and 60 min after infusion and analyzed to correct the input function for FLT-glucuronide in plasma. This substantially improves the accuracy of estimating FLT flux and is important for protocols designed to follow response to therapy.</p>
<p>Human Imaging Experience</p>	<p>Listed below are selected early references but the use of FLT PET/CT is growing so rapidly that either MICAD or PubMed should be searched to find the most recent reports of human imaging studies.</p> <p>Dittmann H, Dohmen BM, Kehlbach R, et al. Early changes in [¹⁸F]FLT uptake after chemotherapy: an experimental study. <i>Eur J Nucl Med Mol Imaging</i>. 2002;29(11):1462–1469.</p> <p>Barthel H, Cleij MC, Collingridge DR, et al. 3'-deoxy-3'-[¹⁸F]fluorothymidine as a new marker for monitoring tumor response to antiproliferative therapy in vivo with positron emission tomography. <i>Cancer Res</i>. 2003;63(13):3791–3798.</p> <p>Vesselle H, Grierson J, Muzi M, et al. In vivo validation of 3'-deoxy-3'-[(¹⁸F)]fluorothymidine ([¹⁸F]FLT) as a proliferation imaging tracer in humans: correlation of [¹⁸F]FLT uptake by positron emission tomography with Ki-67 immunohistochemistry and flow cytometry in human lung tumors. <i>Clin Cancer Res</i>. 2002;8(11):3315–3323.</p> <p>Buck AK, Halter G, Schirrmeister H, et al. Imaging proliferation in lung tumors with PET: ¹⁸F-FLT versus ¹⁸F-FDG. <i>J Nucl Med</i>. 2003;44(9):1426–1431.</p>

Wagner M, Seitz U, Buck A, et al. 3'- $[^{18}\text{F}]$ fluoro-3'-deoxythymidine ($[^{18}\text{F}]$ -FLT) as positron emission tomography tracer for imaging proliferation in a murine B-Cell lymphoma model and in the human disease. *Cancer Res.* 2003;63(10):2681–2687.

Cobben DC, Jager PL, Elsinga PH, et al. 3'- ^{18}F -fluoro-3'-deoxy-L-thymidine: a new tracer for staging metastatic melanoma? *J Nucl Med.* 2003;44(12):1927–1932.

Smyczek-Gargya B, Fersis N, Dittmann H, et al. PET with $[^{18}\text{F}]$ fluorothymidine for imaging of primary breast cancer: a pilot study. *Eur J Nucl Med Mol Imaging.* 2004;31(5):720–724.

Dittmann H, Dohmen BM, Paulsen F, et al. $[^{18}\text{F}]$ FLT PET for diagnosis and staging of thoracic tumours. *Eur J Nucl Med Mol Imaging.* 2003;30(10):1407–1412.

Spence AM, Muzi M, Link JM, et al. NCI-sponsored trial for the evaluation of safety and preliminary efficacy of FLT as a marker of proliferation in patients with recurrent gliomas: safety studies. *Mol Imaging Biol.* 2008;10(5):271-80.

Spence AM, Muzi M, Link JM, et al. NCI-sponsored trial for the evaluation of safety and preliminary efficacy of 3'-deoxy-3'- $[^{18}\text{F}]$ fluorothymidine (FLT) as a marker of proliferation in patients with recurrent gliomas: preliminary efficacy studies. *Mol Imaging Biol.* 2009;11(5):343-55.

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