^{18}F-Fluorination of Unactivated C-H Bonds in Branched Aliphatic Amino Acids: Direct Synthesis of Oncological PET Imaging Agents

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Supporting Information Placeholder

ABSTRACT: A mild and selective photocatalytic C-H ^{18}F-fluorination reaction has been developed that provides direct access to ^{18}F-fluorinated amino acids. The biodistribution and uptake of three ^{18}F-labelled leucine analogues via LAT1 mediated transport in several cancer cell lines is reported. PET imaging of mice bearing PC3 (prostate) or U87 (glioma) xenografts using 5-[^{18}F]-fluoro-homoleucine showed high tumor uptake and excellent tumor visualization, highlighting the utility of this strategy for rapid tracer discovery for oncology.

Positron emission tomography (PET) uses radioisotopes to interrogate specific physiological processes in real time and in living systems.[1] Thus, PET is ideally suited for the early detection of tumors and metastases, and is an established modality for diagnosis, staging, and treatment planning of various malignancies.[2,3] The selective imaging of cancers with PET often exploits radiotracers that target aberrant cellular metabolism or increased protein expression.[4] For example, the widely used cancer diagnostic 2-deoxy-2-[^{18}F]fluoro-D-glucose[4,5] ([^{18}F]FDG (**1**), Figure 1) takes advantage of the increased glucose up-

take and glycolysis in many tumors. Increased amino acid (AA) uptake through over-expression of AA transporters is also a signature feature in cancers, and radiolabeled AAs (e.g., **2**[6] and **3**[7]) are highly sought as imaging agents.[2,3,8] The uptake of AAs by L-type AA transporters (LATs)[9] is a particularly appealing target for PET radiotracers. Most notably, the LAT1 isoform transports branched and aromatic AAs, and is highly upregulated in several cancers (e.g., prostate, breast and brain) and at metastatic sites.[9a]

Among the wide range of AAs transported by LAT1, leucine plays a uniquely important role in cancer biology as large cellular concentrations of leucine are required to trigger mTORC1 activation and support accelerated protein synthesis.[10] Not surprisingly then, L-1-[^{11}C]leucine represents a promising PET imaging agent.[11] Unfortunately, its widespread use is limited by a reliance on the rapidly decaying radionuclide ^{11}C ($t_{1/2}$ = 20.4 min), which restricts use to PET clinics with on-site cyclotron facilities. The longer lived radionuclide ^{18}F ($t_{1/2}$ = 109.8 min) is incorporated in the leucine mimic [^{18}F]FACBC (**4**),[12] which was recently approved by the US FDA for recurrent prostate cancer imaging.[12a] Recently, the boramino acid [^{18}F]Leu-BF$_3$ (**5**) was also reported,[13] adding to the repertoire of radiolabeled leucine mimics. Notwithstanding these and other advances,[8] there is no general synthetic strategy to effect selective ^{18}F-labeling of AAs such as leucine without significantly altering the parent structure or relying on prosthetic groups. Here, we describe the direct radiofluorination[14] of unprotected, branched aliphatic amino acids. The PET imaging of mice bearing subcutaneous PC3 or U87 xenografts using a new ^{18}F-labeled analogue of leucine highlights the potential for this convenient reaction to rapidly access amino acid-derived imaging agents for cancer.
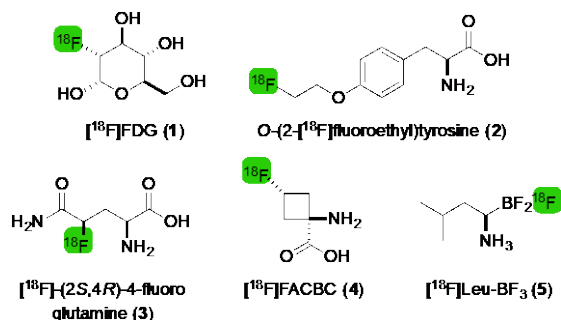

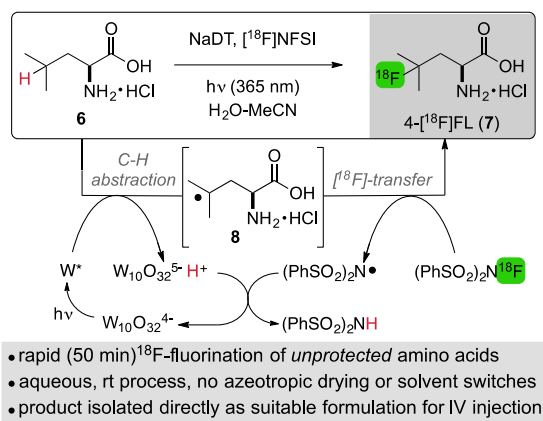**Figure 1.** Radiotracers for PET imaging in oncology and ^{18}F-labeled analogues of leucine.

Figure 2. Decatungstate-catalyzed C-H fluorination applied to the production of 4-[¹⁸F]fluoroleucine (4-[¹⁸F]FL (**7**)).

We recently reported the decatungstate-catalyzed fluorination of unactivated C-H bonds,[15a] and have applied this strategy to the selective fluorination of aliphatic[15a,15b] and benzylic[15c] C-H bonds. This reaction involves hydrogen atom abstraction by a photoactivated decatungstate catalyst[16] followed by fluorine atom transfer[17] from *N*-fluorobenzene-sulfonimide (NFSI) to the resultant carbon radical (e.g. **8**, Figure 2). Considering the high degree of selectivity observed for C-H fluorination at the branched position in esters of leucine[15b] and valine,[15a] we contemplated development of the photocatalytic C-H ¹⁸F-fluorination reaction depicted in Figure 2 using [¹⁸F]NFSI,[18] a reagent that has been developed by Gouverneur and Luthra.[18,19] This unique process would provide direct access to 4-[¹⁸F]FL (**7**)[20] or other radiolabeled AA substrates for LAT1 from readily available or natural AAs (e.g., **6**).
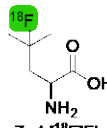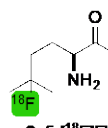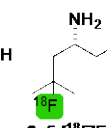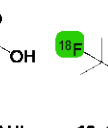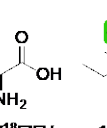
We began by exploring the fluorination of L-leucine·HCl using conditions previously reported by us for the large scale (~50 g) non-radioactive synthesis of 4-fluoroleucine methyl ester.[15b] We were pleased to discover that this mild process is also compatible with direct fluorination of the unprotected amino acid, and that 4-FL could be produced in modest yield (~20%) after 1 h. Several reactor configurations (batch and flow) were evaluated and ultimately, a narrow-bore PTFE tube wrapped around a BLB lamp[21] proved optimal, with ~60% conversion to 4-FL observed after only 40 min. While separable by HPLC,[21] the removal of leucine from 4-FL was ultimately deemed unnecessary as plasma concentrations of leucine range from 100-150 μM,[22] making it unlikely that residual leucine would interfere with the pharmacokinetic performance of the tracer. It was eventually found that a strong cation exchange resin retained the 4FL/leucine mixture and not NFSI, NHSI or other reaction by-products, and that the purified AA mixture could then be rapidly eluted using aqueous base (without requirement for HPLC).

The synthesis of [¹⁸F]NFSI was accomplished using a modified version of the reaction reported by Luthra and Gouverneur.[18] For our purposes,[23] a 5-10 min cyclotron irradiation of [¹⁸O]O₂ produced [¹⁸F]F₂ gas[24] from which ~1.5 GBq was trapped in the NaN(SO₂Ph)₂ → [¹⁸F]NFSI reaction mixture. Rapid (<5 min) purification of [¹⁸F]NFSI using a C18 SepPak afforded a solution of [¹⁸F]NFSI (0.2-0.5 GBq) in H₂O-CH₃CN with an impurity profile similar to that reported previously.[18,21] Critically, this modified process avoids the drying of [¹⁸F]NFSI by azeotropic distillation (110 °C, 20 min) required for other uses of this reagent.[18] The optimized photocatalytic C-H ¹⁸F-fluorination of L-leucine then simply involved adding the H₂O-CH₃CN solution of [¹⁸F]NFSI to a slurry of NaDT and L-leucine·HCl in H₂O. This mixture was irradiated for 40 min and purified as described for 4-FL above (Table 1). The specific activity for the 4-[¹⁸F]FL thus produced was ~7 MBq/μmol,[23] and the radiochemical purity of this material was >97%. The radiochemical yield for *isolated and purified* 4-[¹⁸F]FL (from [¹⁸F]NFSI) is 23±3.3% (n = 4, decay corrected) with a radiosynthesis time of 50 min. Repetition of this reaction using DL-leucine provided (±)-4-[¹⁸F]FL and allowed us to confirm by chiral HPLC that no racemization occurred during radiofluorination.[21] It is notable that while this method uses low specific activity (SA) [¹⁸F]F₂ gas (~1 GBq μmol⁻¹),[18] which may not be suitable for many purposes, clinically relevant doses of several amino acid radiotracers have been manufactured via this process.[19c,25]

We next examined the uptake of 4-[¹⁸F]FL in cancer cell lines LNCaP, PC3 and MCF7 showing various expression levels of LAT1. Notably, there was significant uptake in MCF7 cells, lower uptake in PC3 cells and almost no uptake in LNCaP cells,[21] which mirrors the expected LAT1 mRNA expression levels (RMA log2) in these cell lines of 13.05 (MCF7), 10.40 (PC3) and 6.49 (LNCaP).[26] The uptake of 4-[¹⁸F]FL in both PC3 and MCF7 cells was also significantly blocked by the addition of 2-amino-2-norbornanecarboxylic acid (BCH), a LAT1 inhibitor,[27] suggesting that LAT1 is largely responsible for their 4-[¹⁸F]FL uptake. However, analysis of the biodistribution of 4-[¹⁸F]FL in healthy mice showed high bone accumulation (Figure 4), which is indicative of *in vivo* defluorination of the radiotracer and an obvious barrier to its further clinical development.

The *in vivo* defluorination of 4-[¹⁸F]FL is consistent with the propensity for this molecule to undergo γ-lactone formation, liberating fluoride.[28] As rate of lactone formation is strongly influenced by ring size,[29] we contemplated the radiosynthesis of 5-[¹⁸F]fluoro-homoleucine (5-[¹⁸F]FHL (**8**)), 5-[¹⁸F]fluoro-β-amino-homoleucine (5-[¹⁸F]FBAHL (**9**)), 3-[¹⁸F]fluorovaline

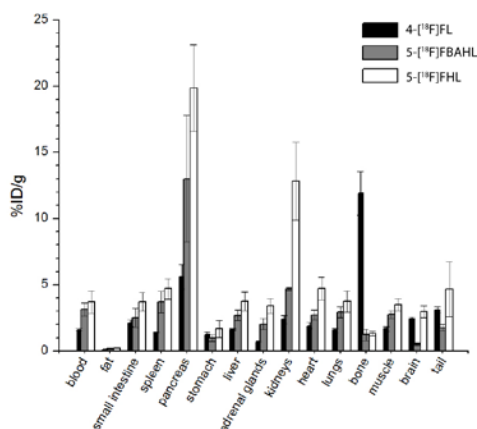**Table 1.** ^{18}F-Fluorination of unprotected branched aliphatic amino acids.[a]

[18]F-labelled amino acid	7: 4-[18F]FL	8: 5-[18F]FHL	9: 5-[18F]FBAHL	10: 3-[18F]FV	11: 3-[18F]FI
radiochemical yield (%)[b,c]	23.3 ±3.3%	27.9 ±3.3%	29.8 ±0.7%	6.4 ±0.4%	<5%[d]
specific activity (MBq/μmol)[e]	7.1 ± 1.9	6.3 ± 0.9	2.6 ± 0.6	3.4 ± 1.6	ND
bone uptake (%ID/g)[b]	11.9 ±1.6	1.6 ±0.1	1.2 ±0.4	ND	ND

[a] See Supporting Information for reaction conditions. All radiosynthesis times including purification were less than 60 min and the radiochemical purity of each tracer was >97%; [b] all experiments repeated ≥ 3 times; [c] RCYs determined from [18F]NFSI and are decay corrected; [d] produced as an inseparable 1.2:1 mixture of 3-[18F]FI:4-[18F]FI; [e] see SI for effective SA values that take into account residual parent AA.

(3-[18F]FV (**10**)), and 3-[18F]fluoroisoleucine (3-[18F]FI (**11**)).[30] It was expected that defluorination of these amino acids via β- or δ-lactone formation would be greatly attenuated. Moreover, in addition to transporting branched aliphatic and aromatic amino acids, a recent report by Kanai[31] highlighted the efficient transport of homoleucine and β-aminohomoleucine by LAT1 in HeLA S3 cells. As summarized in Table 1, 5-[18F]FHL (**8**) and 5-[18F]FBAHL (**9**) could be readily prepared and purified without modification to the process established for 4-[18F]FL.[21] The radiofluorination of valine and isoleucine afforded 3-[18F]FV (**10**) and mixtures of 3- and 4-[18F]FI (e.g., **11**) albeit in lower RCY owing to decreased rate of these reactions, which is consistent with our earlier findings from the fluorination of aliphatic esters.[15a] The biodistribution of both **8** and **9** was examined in healthy mice (Figure 3) and we were delighted to find that neither of these radiotracers showed any appreciable accumulation of activity in the bone at 60 min post injection (PI). The uptake of 5-[18F]FHL (**8**) was also examined in a panel of LAT1-expressing cancer cell lines that included LNCaP, PC3, MCF7 and U87 (glioma).[21] Again, uptake in these cancer cell lines correlated well with their expected mRNA expression levels for LAT1[26] and was substantially blocked by addition of the LAT1 inhibitor BCH,[27] suggesting that transport of this radiotracer is significantly mediated by LAT1.

The uptake of 5-[18F]FHL (**8**) in several cancer cell lines and its improved biodistribution over 4-[18F]FL inspired us to undertake an imaging study using this tracer in mice bearing human glioma (U87) or prostate cancer (PC3) xenografts. Biodistribution studies indicated high tumor accumulation (5.9±0.7 %ID/g (n=4) for U87, 5.6±3.2 %ID/g (n=5) for PC3 at 60 min pi) of 5-[18F]FHL was observed with both U87 and PC3 xenografts.[21] Combined with low background uptake, 5-[18F]FHL provided excellent tumor visualization and

high tumor contrast ratios as evidenced in Figure 4.[21] Excretion of 5-[18F]FHL occurred predominantly by renal clearance, with accumulation observed in the pancreas, kidneys and bladder. Tissue time activity curves[21] obtained in selected organs using dynamic images showed rapid accumulation of 5-[18F]FHL in the tumors and pancreas, peaking shortly before 10 minutes, followed by slow efflux. Low uptake was observed in muscles and bone, further evincing the improved *in vivo* stability of 5-[18F]FHL over the L-leucine derivative 4-[18F]HL.

Figure 3. Biodistribution at 60 min pi of 4-[18F]FL (**7**), 5-[18F]FHL (**8**) and 5-[18F]FBAHL (**9**) in healthy mice.

In summary, we have developed a mild ^{18}F-labeling strategy that selectively replaces the tertiary C-H bond in branched aliphatic amino acids with a C-^{18}F bond. Importantly, this process obviates both complicated precursor synthesis and the use of prosthetic groups. The uptake of both 4-[18F]FL and 5-[18F]FHL in several cancer cell lines was investigated and found to correlate well with LAT1 expression, highlighting their potential as metabolic PET imaging agents. However, the biodistribution of these two radiotracers differed significantly, with 4-[18F]FL displaying high bone uptake suggestive of *in vivo* defluorination. The imaging ability of 5-[18F]FHL was examined in mice bearing human glioma and prostate cancer xenografts and high accumulation was found in the tumors, which provided excellent tumor visualization and no significant defluorination was observed. Notably, this convenient radiofluorination should enable rapid proof-of-feasibility studies on a variety of related amino acids and biomolecules and support high throughput production of radiotracers.
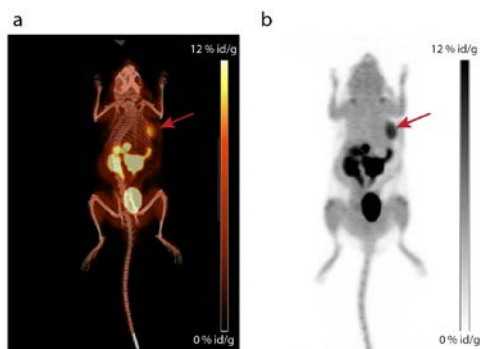
Figure 4. PET imaging of 5-[¹⁸F]FHL in mice bearing human glioma (U87) xenografts. Maximum intensity projection images overlaid on CT (a) and standalone PET images (b) of the biodistribution of 5-[¹⁸F]FHL at 60 min show high accumulation of 5-[¹⁸F]FHL in the tumor (red arrow).

ASSOCIATED CONTENT

Supporting Information includes experimental procedures, characterization, cell uptake, biodistribution and imaging data (PDF) (http://pubs.acs.org)

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Notes
The authors declare no competing financial interest.

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TOC Graphic

^{18}F-fluorination of branched aliphatic amino acids
Rapid radiosynthesis in aqueous medium
No racemization, no HPLC purification required