

Published in final edited form as:

Clin Cancer Res. 2011 December 15; 17(24): 7645–7653. doi:10.1158/1078-0432.CCR-11-1357.

2-(3-{1-Carboxy-5-[(6-[¹⁸F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [¹⁸F]DCFPyL, a PSMA-based PET Imaging Agent for Prostate Cancer

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Abstract

Purpose—We have synthesized and evaluated *in vivo* 2-(3-{1-carboxy-5-[(6-[¹⁸F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [¹⁸F]DCFPyL, as a potential imaging agent for the prostate-specific membrane antigen, PSMA. PSMA is upregulated in prostate cancer epithelia as well as in the neovasculature of most solid tumors.

Experimental Design—[¹⁸F]DCFPyL was synthesized in two steps from the *p*-methoxybenzyl (PMB) protected lys-C(O)-glu urea precursor using 6-[¹⁸F]fluoronicotinic acid tetrafluorophenyl ester ([¹⁸F]F-Py-TFP) for introduction of ¹⁸F. Radiochemical synthesis was followed by biodistribution and imaging with PET in immunocompromised mice using isogenic PC3 PSMA+ and PSMA− xenograft models. Human radiation dosimetry estimates were calculated using OLINDA/EXM 1.0.

Results—DCFPyL displays a K_i value of 1.1 ± 0.1 nM for PSMA. [¹⁸F]DCFPyL was produced in radiochemical yields of 36-53% (decay corrected) and specific radioactivities of 340 – 480 Ci/mmol (12.6 – 17.8 GBq/μmol, n = 3). In an immunocompromised mouse model [¹⁸F]DCFPyL clearly delineated PSMA+ PC3 PIP prostate tumor xenografts on imaging with PET. At 2 h post-injection, 39.4 ± 5.4 percent injected dose per gram of tissue (%ID/g) was evident within the PIP tumor, with a ratio of 358:1 of uptake within PIP to PSMA− PC3 flu tumor placed in the opposite flank. At or after 1 h post-injection, minimal non-target tissue uptake of [¹⁸F]DCFPyL was observed. The bladder wall is the dose-limiting organ.

Conclusions—These data suggest [¹⁸F]DCFPyL as a viable, new positron-emitting imaging agent for PSMA-expressing tissues.

Keywords

PSMA; PET; molecular imaging; prostate cancer; PC3

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Supplementary Data Available. HPLC traces and a normal mouse metabolism study for [¹⁸F]DCFPyL ([¹⁸F]3) are available online, free of charge at <http://clincancerres.aacrjournals.org/>.

INTRODUCTION

Prostate cancer (PCa) is the second leading cause of death from cancer in men in the United States (1). The vast majority of men dying of PCa succumb to metastatic, castration-resistant disease. Among the reasons to image PCa, including initial staging, therapeutic monitoring, guiding focal therapies and determining the location of recurrence after prostatectomy, one elusive but important goal is to image with a view to distinguishing indolent from aggressive disease. While no single marker is capable of providing that distinction, the prostate-specific membrane antigen (PSMA), a type II integral membrane protein over-expressed on prostate tumors, provides a step in that direction. Both disease-free survival and time to prostate-specific antigen (PSA) progression are decreased in patients with elevated levels of PSMA within their tumors (2, 3). PSMA expression has long been associated with androgen-independent disease (4). Recently Evans et al. demonstrated that a positron-emitting version of the anti-PSMA monoclonal antibody (mAb) J591 (5) was able to leverage PSMA expression into a non-invasive biomarker of androgen receptor signaling (6).

Several modalities have been applied to imaging PCa, but to study PSMA at high sensitivity *in vivo* others and we have focused on the radionuclide and optical molecular imaging techniques (7 – 18). PCa has not succumbed as readily to molecular imaging as other solid tumors as it is not easily visualized on positron emission tomography (PET) with [¹⁸F]fluorodeoxyglucose (FDG), the clinical gold standard, because PCa tends to grow slowly and is less metabolically active with respect to glucose transport and consumption. Another difficulty in imaging PCa with FDG, or any other radiopharmaceutical that is excreted through the urine, is the proximity of the prostate to the urinary bladder, which can obscure specific binding to intra-prostatic PCa. There are ways around that problem, including rapid scanning soon after voiding (before accumulation of radiotracer within the bladder), catheterization, and application of post-processing techniques (19). Accordingly, a variety of radiopharmaceutical imaging agents have been developed for PCa, including radiolabeled versions of choline (20, 21), [¹¹C]acetate (22 – 24), 1-amino-3-[¹⁸F]fluorocyclobutane-1-carboxylic acid ([¹⁸F]FACBC) (25), as well as a variety of radiolabeled antibodies specific for PSMA (26 – 29), (6), with several beginning to appear in clinical trials.

We have previously reported the development of *N*-[*N*-[(*S*)-1,3-dicarboxypropyl]carbamoyl]-4-[¹⁸F]fluorobenzyl-L-cysteine, [¹⁸F]DCFBC (9), with which we have initiated a Phase 1 trial (30). [¹⁸F]DCFBC showed 8 percent injected dose per gram (%ID/g) within PSMA+ PIP tumor, achieved at 60 min after injection, which decreased to 4.7% at 2 h post-injection. Nearly 2% ID/g in bone was present at most time points. In order to improve upon the pharmacokinetics of [¹⁸F]DCFBC, we have now synthesized 2-(3-{1-carboxy-5-[(6-[¹⁸F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [¹⁸F]DCFPyL ([¹⁸F]**3**), which uses the lys-C(O)-glu motif and contains a [¹⁸F]fluoropyridyl substituent, in analogy to a radioiodinated PSMA-binding ligand that we previously reported, which demonstrated high uptake within PSMA+ tumor and fast clearance from non-target tissues (11).

RESULTS

Chemical and Radiochemical Syntheses

The tosylate salt of **1**, previously described by us (10), was reacted with F-Py-TFP (31) to generate fluoropyridyl urea **2**. Deprotection afforded DCFPyL (**3**) in 81% yield (Figure 1). The ¹⁸F-labeled prosthetic group [¹⁸F]F-Py-TFP was prepared by a literature procedure (31) and used to generate [¹⁸F]DCFPyL ([¹⁸F]**3**) (Figure 1). The decay-corrected radiochemical yields of [¹⁸F]DCFPyL ([¹⁸F]**3**) ranged from 36 – 53% based on starting [¹⁸F]F[−] (n = 3)

with absolute yields of 7.7 – 10.4 mCi (285 – 385 MBq) after HPLC purification. The mean synthesis time was 128 min from the time of addition of [¹⁸F]F⁻. Starting from 44 – 61 mCi (1,628 – 2,257 MBq) of [¹⁸F]F⁻, the specific radioactivity of [¹⁸F]DCFPyL ([¹⁸F]**3**) ranged from 340 – 480 Ci/mmol (12.6 – 17.8 GBq/μmol).

PSMA Inhibition Assay

The K_i value for DCFPyL (**3**) was determined using a modification of the Amplex Red glutamic acid assay (32). The K_i value for DCFPyL (**3**) was 1.1 ± 0.1 nM, comparable to that of ZJ-43, which is 1.4 ± 0.2 nM when used as an internal reference.

Biodistribution

[¹⁸F]DCFPyL ([¹⁸F]**3**) was assessed for its *ex vivo* pharmacokinetics in non-obese diabetic severe-combined immunodeficient (NOD-SCID) mice bearing both PSMA+ PC3-PIP and PSMA- PC3-flu xenografts. Table 1 shows the %ID/g of radiochemical in selected organs. [¹⁸F]DCFPyL ([¹⁸F]**3**) showed clear PSMA-dependent uptake within PSMA+ PC3 PIP xenografts, reaching a value of 46.7 ± 5.8 %ID/g at 30 min post-injection (pi), which decreased by only about 10% over the ensuing 4 h. At 60 min pi the kidney, liver and spleen displayed the highest uptake. By that time, the urinary bladder also demonstrated relatively high uptake. However, that uptake includes excretion at all time points. Rapid clearance from the kidneys was demonstrated, decreasing from 74.1 ± 6.6 %ID/g at 30 min to 7.4 ± 0.9 %ID/g at 4 h. The relatively high values noted in kidney are partially due to high expression of PSMA within proximal renal tubules (33, 34). The ratio of uptake within PSMA+ PIP to PSMA- flu tumors ranged from 40:1 to over 1,000:1 over the 4 h time period of the study. A possible explanation for that increased tumor uptake of radiochemical over time could be due to ligand-mediated PSMA internalization within tumor cells (35, 36). Less retention in kidney relative to tumor over time could be due to a lower degree of internalization in this (normal) tissue and/or different metabolism of [¹⁸F]**3**, which does not promote retention of radiochemical in kidney. Relatively low bone uptake (< 1% ID/g at all time points) suggests little metabolic defluorination of [¹⁸F]DCFPyL ([¹⁸F]**3**).

Small Animal PET Imaging

Intense radiochemical uptake was seen only in the kidneys and PSMA+ PC3 PIP tumor after administration of [¹⁸F]DCFPyL ([¹⁸F]**3**) (Figure 2). As noted above for the *ex vivo* study, the intense renal uptake was partially due to specific binding of the radiotracer to proximal renal tubules (33, 34) as well as to excretion of this hydrophilic compound. By 3.5 h after injection, only the PSMA+ tumor is visible with no radiochemical background in liver or the gastrointestinal tract to obscure potential metastases.

Human Radiation Dosimetry Estimates

Table 2 lists source organ time-integrated activity coefficients for [¹⁸F]DCFPyL ([¹⁸F]**3**). Table 3 lists target organ absorbed doses. The organ with the highest mean absorbed dose per unit administered activity was the urinary bladder wall, 0.15 mGy/MBq, followed by the kidneys at 0.05 mGy/MBq. The absorbed dose to tissues listed in Table 3 that were not assigned a time-integrated activity coefficient reflects cross-fire photon contribution from organs that were assigned a time-integrated activity coefficient and contribution from radioactivity assigned to the remainder of the body. The effective dose based on the ICRP 60 tissue weighting factors was 13.6 μSv/MBq. Based on the dosimetry results a maximum of 9 mCi (331 MBq) can be administered without exceeding the 50 mGy critical organ dose limit (urinary bladder wall in this case), for a single administration of radioactive material for research use as specified in Code of Federal Regulations 21, part 361.

DISCUSSION

A variety of positron-emitting agents – as well as other techniques and modalities – for imaging PCa have been developed and have recently been reviewed elsewhere (37 – 39). With respect to PSMA specifically, in addition to imaging *per se*, PSMA affinity agents, such as low molecular weight compounds (40), antibodies (41) and aptamers (42), have been conjugated to and used to target nanoparticles and to deliver shRNA (43) to PSMA+ cells and tissues. Because PSMA is expressed in most solid tumor neovasculature (44 – 47), it may be used in principle as a general tumor imaging target with one clinical trial demonstrating imaging of non-prostate tumors (29). However, as stated at the outset, the main value of a PSMA-based imaging agent may be in providing an avenue through which to begin determining the aggressiveness of an individual prostate tumor. Furthermore, PSMA may also be used as an indicator of androgen receptor (AR) signaling within prostate tumors (48, 49), (6), which would provide a particularly important function for a PSMA-based imaging agent as new androgen receptor targeted drugs emerge (50). In this regard targeting PSMA may provide more information than targeting AR directly with an agent such as [¹⁸F]fluorodihydrotestosterone ([¹⁸F]FDHT) (51), as the AR will be occupied in patients treated with AR-based therapeutics. Positron-emitting progestins have been pursued as imaging agents for breast cancer for similar reasons (52), namely, that estrogen receptor, the target for [¹⁸F]fluoroestradiol, is largely occupied in patients undergoing antiestrogen therapy.

Among the positron emitting isotopes that are integrated into tumor-targeting agents of low molecular weight, including ¹¹C, ¹⁸F, ⁶⁴Cu, ⁸⁶Y, ⁸⁹Zr and ¹²⁴I, ¹⁸F is considered a particularly convenient radionuclide because of its nearly pure positron emission, isosterism with hydrogen, relative ease of incorporation into relevant affinity reagents at high specific radioactivity through ¹⁸F⁻ or a variety of prosthetic groups (as described here), and its relatively long physical half-life (110 min) enabling shipment of ¹⁸F-labeled radiotracers to sites distant from their production. Carbon-11-labeled PET agents are becoming increasingly viewed as being for proof-of-principle, with commercial entities demonstrating interest primarily in those labeled with ¹⁸F, particularly for indications outside of the central nervous system (CNS). The pharmacokinetics of most agents for use outside of the CNS, particularly those of low molecular weight, are more amenable to an ¹⁸F radiolabel than to ¹¹C, which may not have a sufficiently long physical half-life to enable washout from non-target sites during the imaging study. For those reasons we have chosen to focus on development of a new ¹⁸F-labeled PSMA imaging agent for PET.

Antibodies (53), (6), (27) and antibody fragments (54), aptamers (55) and low molecular weight PSMA-binding affinity agents (56), (9), (13), (18), (57) have recently been derivatized with positron-emitting isotopes. Those agents will have different indications, as they have widely varying pharmacokinetics, however, each class has demonstrated PSMA-specific binding in preclinical studies. In terms of specific, *in vivo* target tumor to non-target tumor uptake ratio, the radiolabeled mAbs ⁶⁴Cu-DOTA-3/A12 (53) and ⁸⁹Zr-DFO-J591 (27) both demonstrated values of approximately 3:1 at 48 h post-injection. But comparisons are difficult due to the differences in tumor models used and, importantly, the variable degree of PSMA expressed within them. Antibodies may have an advantage over agents of lower molecular weight due to their putative inaccessibility to apically positioned PSMA on non-malignant cells (27), suggesting enhanced tumor specificity for mAbs. PSMA-directed mAb fragments have not yet demonstrated selective uptake in PSMA-expressing tumors *in vivo* (54).

Among non-protein based PET imaging agents for PSMA, Rockey et al. have optimized conditions for conjugating ⁶⁴Cu to a PSMA-targeting aptamer, which has demonstrated

PSMA-mediated uptake in PSMA+ 22RV1 prostate tumor cells relative to PSMA- PC3 cells (55). So far low molecular weight imaging agents for PSMA fall into two classes, the ureas, such as [¹⁸F]DCFPyL ([¹⁸F]**3**), and the phosphoramidates (18). Both have a terminal glutamate at the P1' position, which enables productive binding to PSMA. Both are amenable to modification with bulky substituents that interact with the arginine patch or tunnel region on PSMA (58 – 60). In addition to ¹⁸F, the urea-based compounds have been functionalized with ¹¹C (56) and ⁶⁸Ga (13) for PET. A phosphoramidate has been radiolabeled with ¹⁸F and tested *in vivo* (18). As suggested above, it is challenging to compare the pharmacokinetics of these compounds because of the different models used between investigators and even within the same research group, due to the variable expression of PSMA between experiments within what is considered a PSMA+ cell line. For example, the PSMA+ PC3-PIP cell line expresses significantly lower PSMA than does PSMA+ LNCaP (61). However, we prefer the isogenic PSMA+ PIP vs. PSMA- flu comparison as the two cell lines are phenotypically identical, differing only in PSMA expression. We have also found that the PSMA+ PC3 PIP cells can lose PSMA expression after several passes. With those caveats in mind, [¹⁸F]DCFPyL ([¹⁸F]**3**) demonstrates 39.4% ID/g in PSMA+ PIP tumor with a PIP:flu uptake ratio of 358 at 2 h post-injection, while the ¹⁸F-labeled phosphoramidate showed 1.2% ID/g in LNCaP with an LNCaP:PC3 of 3.5 (18). However, renal and liver values for [¹⁸F]DCFPyL ([¹⁸F]**3**) were higher than for the ¹⁸F-labeled phosphoramidate, at 15.7 vs. 2.2% and 2.1 vs. 0.2%, respectively. [¹⁸F]DCFPyL ([¹⁸F]**3**) also compares favorably with the first generation ¹⁸F-labeled urea, [¹⁸F]DCFBC (9), demonstrating an 8-fold higher tumor uptake at 2 h post-injection. That is important because [¹⁸F]DCFBC has proved capable of delineating metastases from prostate cancer in human subjects in a recent, ongoing first-in-human trial (30).

Conclusions

Patterned after our previously reported radioiodinated PSMA-binding radiotracer that demonstrated high uptake within PSMA+ tumor and fast clearance from non-target tissues (11), [¹⁸F]DCFPyL ([¹⁸F]**3**) demonstrated high tumor and low normal tissue uptake and retention in PSMA+ PC3 PIP prostate tumor xenografts. The pharmacokinetics of [¹⁸F]DCFPyL ([¹⁸F]**3**) compare favorably with other low molecular weight agents that bind PSMA selectively. The pre-clinical results obtained with [¹⁸F]DCFPyL ([¹⁸F]**3**) warrant its further pursuit in a variety of clinical scenarios to help localize PCa.

EXPERIMENTAL SECTION

General Procedures

All reagents and solvents were purchased from either Sigma-Aldrich (Milwaukee, WI) or Fisher Scientific (Pittsburgh, PA). The tosylate salt of **1** was prepared according to a reported procedure (10). ¹H NMR spectra were obtained on a Bruker Avance 400 MHz Spectrometer. ESI mass spectra were obtained on a Bruker Esquire 3000 plus system. High-resolution mass spectra (HRMS) were performed by the Mass Spectrometry Facility at the University of Notre Dame using ESI by direct infusion on a Bruker micrOTOF-II. High performance liquid chromatography (HPLC) purification of DCFPyL (**3**) was performed on a Waters 625 LC system with a Waters 490E multiwavelength UV/Vis detector (Milford, MA).

[¹⁸F]Fluoride was produced by 18 MeV proton bombardment of a high pressure [¹⁸O]H₂O target using a General Electric PETtrace biomedical cyclotron (Milwaukee, WI). Solid-phase extraction cartridges (C₁₈ plus, Sep-Pak) were purchased from Waters Associates. Reverse phase radio-HPLC purification of [¹⁸F]DCFPyL ([¹⁸F]**3**) was performed using a Varian Prostar System with a Bioscan Flow Count PMT radioactivity detector (Varian

Medical Systems, Washington, DC). Radioactivity was measured in a Capintec CRC-10R dose calibrator (Ramsey, NJ). The specific radioactivity was calculated as the radioactivity eluting at the retention time of product during the semi-preparative HPLC purification divided by the mass corresponding to the area under the curve of the UV absorption.

2-(3-{1-carboxy-5-[(6-fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, **3**

To a solution of **1** (0.015 g, 0.018 mmol) in CH₂Cl₂ (1 mL) was added triethylamine (0.010 mL, 0.072 mmol), followed by 6-fluoro-nicotinic acid 2,3,5,6-tetrafluoro-phenyl ester (F-Py-TFP) (**31**) (0.005 g, 0.017 mmol). After stirring for 2 h at ambient temperature, the solvent was evaporated. The crude material was purified on a silica column using methanol/methylene chloride (5:95) to afford 0.009 g (65%) of compound **2**. ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 8.22 (m, 1H), 7.15-7.24 (m, 7H), 6.83-6.97 (m, 7H), 5.35-5.56 (m, 2H), 4.93-5.08 (m, 6H), 4.31-4.35 (m, 2H), 3.76 (m, 9H), 3.31-3.36 (m, 2H), 2.34 (m, 2H), 2.07 (m, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.54 (m, 3H), 1.23 (m, 2H). ESI-Mass calcd for C₄₂H₄₈FN₄O₁₁ [M + H]⁺ 803.3, found 802.9.

A solution of TFA in CH₂Cl₂ (1:1, 2 mL) was added to **2** (0.009 g, 0.011 mmol). The mixture was stirred at ambient temperature for 2 h, then concentrated on a rotary evaporator. The crude material was purified by HPLC (Econosphere C18 10 μ, 250 × 10 mm, H₂O/CH₃CN/TFA (92/8/0.1), 4 mL/min) to afford 0.004 g (0.009 mmol) (81%) of **3**. ¹H NMR (400 MHz, D₂O) δ 8.56 (s, 1H), 8.29 (m, 1H), 7.20 (m, 1H), 4.18-4.24 (m, 2H), 3.42 (m, 2H), 2.49 (m, 2H), 2.15 (m, 1H), 1.87-2.00 (m, 2H), 1.64-1.80 (m, 3H), 1.47 (m, 2H). ESI-Mass calcd for C₁₈H₂₄FN₄O₈ [M + H]⁺ 443.2, found 442.9. ESI-HRMS calcd for C₁₈H₂₄FN₄O₈ [M + H]⁺ 443.1573, found 443.1556.

Radiochemistry

2-(3-{1-Carboxy-5-[(6-[¹⁸F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [¹⁸F]DCFPyL ([¹⁸F]3**)**—In a vial containing 2 mg (0.002 mmol) of **1** and 0.005 mL of triethylamine was added [¹⁸F]F-Py-TFP (**31**) in 2 mL CH₂Cl₂. The reaction was heated at 45° C for 20 min followed by removal of solvent under a stream of nitrogen, addition of 0.1 mL of 3% anisole/TFA and further heating at 45°C for 10 min. The final product was obtained after HPLC purification (Econosphere C18 10μ, 250 × 10 mm, H₂O/CH₃CN/TFA [90/10/0.1], 4 mL/min) at a retention time of ~ 9.5 min, and was neutralized with 1M NaHCO₃, concentrated under vacuum to dryness, reconstituted in PBS (pH 7.4) and passed through a 0.22 μm syringe filter into an evacuated sterile vial.

PSMA Inhibition Assay—Cell lysates of LNCaP cell extracts were incubated with DCFPyL (0.01 nM – 100 μM) in the presence of 4 μM NAAG at 37°C for 2 h. The amount of released glutamate was measured by incubating with a working solution of the Amplex Red glutamic acid kit (Molecular Probes Inc., Eugene, OR, USA) at 37°C for 30 min. Fluorescence measurements were performed with a VICTOR³V multilabel plate reader (Perkin Elmer Inc., Waltham, MA, USA), with excitation at 490 nm and emission at 642 nm. Inhibition curves were determined using semi-log plots, and IC₅₀ values were determined at the concentration at which enzyme activity was inhibited by 50%. Assays were performed in triplicate with the entire inhibition study being repeated at least once to confirm affinity and mode of inhibition. Enzyme inhibitory constants (*K_i* values) were generated using the Cheng-Prusoff conversion (62, 63). Data analysis was performed using GraphPad Prism version 4.00 for Windows (GraphPad Software, San Diego, California).

Cell Lines and Tumor Models—LNCaP cells used in the PSMA inhibition assay were obtained from American Type Culture Collection (ATCC, Manassas, VA) and were

maintained as per ATCC guidelines. PC3 PIP (PSMA+) and PC3 flu (PSMA-) cell lines were obtained from Dr. Warren Heston (Cleveland Clinic) and were maintained as previously described (9). Cells were grown to 80 – 90% confluence in a single passage before trypsinization and formulation in Hank's balanced salt solution (HBSS, Sigma, St. Louis, MO) for implantation into mice. Animal studies were in compliance with guidelines related to the conduct of animal experiments of the local Animal Care and Use Committee. For biodistribution and imaging studies of [¹⁸F]DCFPyL ([¹⁸F]3), male NOD-SCID mice (Johns Hopkins University, in-house colony) were implanted subcutaneously with 1×10^6 PSMA+ PC3 PIP and PSMA- PC3 flu cells behind either shoulder. Mice were imaged or used in biodistribution studies when the tumor xenografts reached 3-5 mm in diameter.

Biodistribution—PSMA+ PC3 PIP and PSMA- PC3 flu xenograft-bearing SCID mice were injected *via* the tail vein with 100 μ Ci (3.7 MBq) of [¹⁸F]DCFPyL ([¹⁸F]3). In each case four mice were sacrificed by cervical dislocation at 30, 60, 120, 240 min pi. The heart, lungs, liver, stomach, pancreas, spleen, kidney, muscle, bone, small and large intestines, urinary bladder, and PC3 PIP and flu tumors were quickly removed. Stomach and other gastrointestinal contents were removed and the urinary bladder was emptied. A 0.1 mL sample of blood was also collected. Each organ was weighed, and the tissue radioactivity was measured with an automated γ counter (1282 Compugamma CS, Pharmacia/LKB Nuclear, Inc., Gaithersburg, MD). The %ID/g was calculated by comparison with samples of a standard dilution of the initial dose. All measurements were corrected for decay.

PET and CT Imaging—A single NOD-SCID mouse implanted with PSMA+ PC3 PIP and PSMA- PC3 flu xenografts was used for imaging. The mouse was anesthetized with 3% isoflurane in oxygen for induction and maintained under 1.5% isoflurane in oxygen at a flow rate of 0.8 L/min. Then the mouse was placed in the prone position on the gantry of a GE eXplore VISTA small animal PET scanner (GE Healthcare, Waukesha, WI) and injected intravenously with 0.38 mCi (14.1 MBq) [¹⁸F]DCFPyL ([¹⁸F]3) in 200 μ L of PBS. The images were acquired as a pseudodynamic scan, i.e., a sequence of successive whole-body images were acquired in two bed positions. The dwell time at each position was 1 min such that a given bed position (or mouse organ) was revisited every 3 min. An energy window of 250 – 700 keV was used. Images were reconstructed using the FORE/2D-OSEM method (one iteration, 16 subsets) and included correction for radioactive decay, scanner dead time, and scattered radiation. After PET imaging the mobile mouse holder was placed on the gantry of an X-SPECT (Gamma Medica Ideas, Northridge, CA) small animal imaging device to acquire the corresponding CT. Animals were scanned over a 8.9 cm field-of-view using a 230 μ A, 75 kVp beam. The PET and CT data were then co-registered using NIH AMIDE software (<http://amide.sourceforge.net/>).

Radiation Dosimetry—The human dosimetry values were obtained using the mouse biodistribution data. The mouse organ activity concentrations in %ID/g were converted to the human %ID/organ by setting the ratio of organ %ID/g to whole-body %ID/g in the mouse equal to that in humans and then solving for the human %ID/organ; the adult male phantom organ masses listed in the OLINDA/EXM 1.0 were used for the conversion (64). The human source organ time-activity curves were fitted using a monoexponential function. Since the biodistribution data were radioactive decay-corrected, only the biological removal constants were obtained from the curve fits, and the physical decay constant for ¹⁸F was added in obtaining the time-integrated activity coefficients (TIACs). The source organ TIACs in MBq-h/MBq were entered in the OLINDA/EXM 1.0 for the dose calculations. The dynamic voiding bladder model was used to obtain the TIAC for the urinary bladder contents. The whole-body clearance half-life (obtained as sum of sampled tissues, excluding

the tumors) was used as half-life to describe urinary bladder filling. All radioactivity was assumed eliminated *via* the urine, a one hour voiding interval was assumed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank CA92871 and CA134675 for financial support. We also thank James Fox for performing the imaging studies and Gilbert Green and Jianhua Yu for excellent technical support.

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Statement of Translational Relevance

Relative to other malignancies, prostate cancer (PCa) is an elusive target for molecular imaging. By targeting the prostate-specific membrane antigen (PSMA), [^{18}F]DCFPyL may provide insight into prognosis and androgen receptor (AR) signaling – an important target in PCa research – as well as a way to image and locally invasive disease and metastases. The initial indications for [^{18}F]DCFPyL will be in staging of patients with PCa diagnosed at biopsy or who present with a rising prostate-specific antigen (PSA) blood test after prostatectomy. Other indications include therapeutic monitoring in the context of standard chemotherapeutic agents, AR-based agents and possibly for emerging PSMA-based therapeutics. The superior pharmacokinetics of this compound, namely the high uptake in tumor vs. non-target tissues, the fact that it is a low molecular weight agent, that it can be radiolabeled with a widely available isotope (^{18}F), and its tractable radiation dosimetry profile all point toward rapid clinical translation through the exploratory Investigational New Drug (eIND) mechanism.

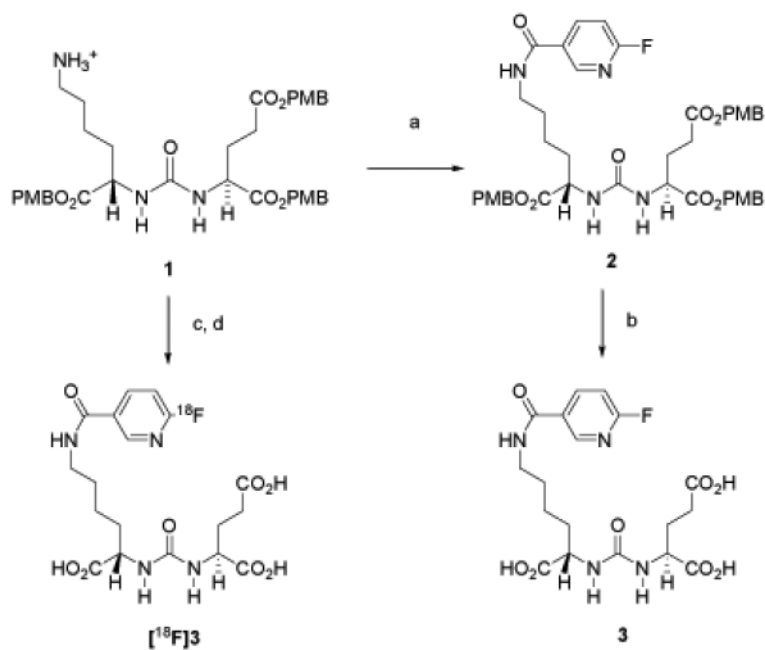


Figure 1. Synthesis of [¹⁸F]DCFpyL [¹⁸F]**3** and DCFpyL **3**. a) 6-Fluoro-nicotinic acid-2,3,5,6-tetrafluoro-phenyl ester, Et₃N, CH₂Cl₂; b) TFA/CH₂Cl₂; c) 6-¹⁸F-fluoro-nicotinic acid-2,3,5,6-tetrafluoro-phenyl ester; d) TFA/anisole.

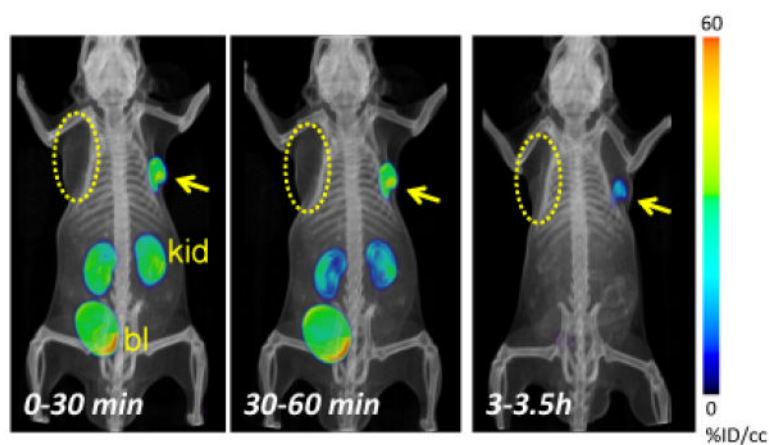


Figure 2.

PET-CT volume-rendered composite images representing the time course of radiochemical uptake after administration of [^{18}F]DCFPyL ([^{18}F]3). PSMA+ PC3 PIP (arrow) and PSMA–PC3 flu (dotted oval) tumors are present in subcutaneous tissues posterior to opposite forearms, as indicated. The mouse was injected intravenously with 0.38 mCi (14.1 MBq) [^{18}F]DCFPyL ([^{18}F]3) at Time 0. By 30 min post-injection radiochemical uptake was evident within the PIP tumor and kidneys. Radioactivity receded from kidneys faster than from tumor, and was not evident within kidneys by 3.5 h post-injection. Radioactivity within bladder was due to excretion. At no time was radiochemical clearly visualized within the flu tumor. kid = kidneys, bl = urinary bladder.

Table 1Biodistribution of [¹⁸F]3 in Tumor-Bearing Mice*

Organ	30 min	60 min	120 min	240 min
Blood	1.53±0.19	0.24 ±0.05	0.43 ±0.37	0.03 ±0.01
Heart	0.68 ±0.07	0.20 ±0.11	0.06 ±0.01	0.02 ±0.00
Lung	1.91 ±0.47	0.55 ±0.17	0.18 ±0.02	0.06 ±0.00
Liver	3.88 ±0.74	2.87 ±0.92	2.14±0.11	1.80 ±0.39
Stomach	1.50±1.12	0.35 ±0.34	0.08 ±0.03	0.02 ±0.00
Pancreas	1.02 ±0.53	0.26 ±0.13	0.08 ±0.00	0.03 ±0.01
Spleen	7.59 ±3.56	2.70 ±1.28	0.69 ±0.11	0.23 ±0.09
Kidney	74.1 ±6.6	42.3 ±19.0	15.7 ±3.3	7.42 ±0.89
Muscle	0.39 ±0.05	0.61 ±0.92	0.04 ±0.00	0.05 ±0.05
Bone	0.82 ±0.16	0.42 ±0.15	0.33 ±0.08	0.43 ±0.06
sm. Intest	0.79 ±0.11	0.31 ±0.12	0.11 ±0.07	0.05 ±0.01
lrg. Intest	0.73 ±0.04	0.40 ±0.17	0.12 ±0.05	0.06 ±0.01
Bladder (empty)	18.6± 18.1	9.88 ±4.92	6.44 ±4.42	1.54 ±1.79
PSMA+ PIP	46.7 ±5.8	44.2 ±9.7	39.4 ±5.4	36.6 ±4.3
PSMA- flu	1.17 ±0.41	0.36 ±0.14	0.11 ±0.02	0.03 ±0.01
PIP/flu	40	123	358	1220

* Values are in % ID/g SD; n = 4.

Table 2

Human source organ time-integrated activity coefficients

Source organ	Time-integrated activity coefficient (MBq-h/MBq)
Lower large intestine	4.23E-04
Small intestine	1.30E-03
Stomach	3.36E-04
Upper large intestine	4.23E-04
Heart wall	3.97E-04
Kidneys	7.47E-02
Liver	4.09E-02
Lungs	3.52E-03
Muscle	4.50E-02
Pancreas	1.48E-04
Spleen	2.98E-03
Urinary bladder contents	3.09E-01
Remainder	8.51E-01

Table 3

Estimated human organ absorbed dose

Target organ	Absorbed dose (mGy/MBq)
Adrenals	6.46E-03
Brain	4.84E-03
Breasts	3.97E-03
Gallbladder wall	6.48E-03
Lower large intestine wall	9.40E-03
Small intestine	7.53E-03
Stomach wall	5.27E-03
Upper large intestine wall	6.67E-03
Heart wall	3.26E-03
Kidneys	4.81E-02
Liver	7.38E-03
Lungs	3.01E-03
Muscle	3.95E-03
Ovaries	9.06E-03
Pancreas	4.38E-03
Red marrow	5.35E-03
Osteogenic cells	7.59E-03
Skin	3.84E-03
Spleen	6.57E-03
Testes	7.06E-03
Thymus	4.43E-03
Thyroid	4.45E-03
Urinary bladder wall	1.51E-01
Uterus	1.45E-02
Total body	5.71E-03
Effective dose equivalent (mSv/MBq)	1.80E-02
Effective dose (mSv/MBq)	1.36E-02