

Biodistribution and radiation dosimetry of ^{18}F -FTC-146 in humans

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ABSTRACT

The purpose of this study is to assess safety, biodistribution and radiation dosimetry in humans for the highly selective sigma-1 receptor (S1R) positron emission tomography (PET) agent ^{18}F -6-(3-fluoropropyl)-3-(2-(azepan-1-yl)ethyl)benzo[*d*]thiazol-2(3H)-one (^{18}F -FTC-146). **Methods.** Ten healthy volunteers (HV; five female, five male; age: 34.3 ± 6.5 years) were recruited, and written informed consent was obtained from all participants. Series of whole-body PET/magnetic resonance imaging (PET/MRI) examinations were acquired for up to three hours after injection (357.2 ± 48.8 MBq). Blood samples were collected and standard vital signs (heart rate, pulse oximetry, and body temperature) were monitored at regular intervals. Regions-of-interest were delineated, time-activity curves were calculated, and organ uptake and dosimetry was estimated using PMOD 3.7 and Organ Linear Internal Dose Assessment (OLINDA). **Results.** All subjects tolerated the PET/MRI examination well, and no adverse reactions to ^{18}F -FTC-146 were reported. High accumulation of ^{18}F -FTC-146 was observed in S1R dense organs such as the pancreas and spleen, moderate uptake in the brain and myocardium, and low uptake in bone and muscle. High uptake was also observed in the kidneys and bladder, indicating renal tracer clearance. The effective dose (ED) of ^{18}F -FTC-146 was 0.0259 ± 0.0034 mSv/MBq (range: 0.0215-0.0301 mSv/MBq). **Conclusion.** First-in-human studies with clinical-grade ^{18}F -FTC-146 were successful. Injection of ^{18}F -FTC-146 is safe, and absorbed doses are acceptable. The potential of ^{18}F -FTC-146 as an imaging agent for a variety of neuroinflammatory diseases is currently under investigation.

Key words: Sigma-1 receptor; Radiation dosimetry; Biodistribution; First-in-human; PET

INTRODUCTION

Sigma-1 receptors, a unique class of intercellular chaperone proteins, are widely distributed in the central nervous system and peripheral tissues. S1Rs modulate ion channels and other neurotransmitter systems, and are therefore involved in many biological mechanisms associated with pain, inflammation, neuronal protection, neurodegeneration, cancer, addiction, and psychiatric diseases.

S1Rs are expressed in both neurons and glial cells and are believed to have an important role in preserving and restoring neuronal function. Study of S1Rs may provide important insight into degenerative disorders such as Alzheimer's Disease, stroke, Parkinson's Disease and Amyotrophic Lateral Sclerosis (for review, see (1)). Prior studies suggest a strong link between S1Rs and important brain functions such as mood and cognition (2,3). In particular, stimulation of S1Rs dampened depression-like behavior in mice (4). Several studies have indicated that S1Rs also play a key role in nociception (5-7), and are known to interact with opioid receptors and modulate opioid activity (8,9). In particular, antinociceptive effects of S1R antagonists both when acting alone and in combination with opioids (to enhance opioid analgesia) have been reported at both central and peripheral sites (8,9). Emerging evidence for the involvement of S1Rs in various diseases makes the S1R a promising biomarker for research in diagnostic imaging and therapy.

PET is a highly sensitive imaging modality that employs specifically designed radioligands to quantify molecular processes *in vivo*. Several groups have developed S1R targeting radioligands with different pharmacophore structures, such as piperazines (10) and piperidines (11). However, only three compounds have thus far been utilized in clinical studies:

^{11}C -SA4503 ($K_i = 4.6$ nM (12)), ^{18}F -FPS ($K_i = 4.3$ nM (13,14)) and ^{18}F -fluspidine ($K_i = 0.59$ nM (15)). ^{11}C -SA4503 displays significant affinity for the sigma-2 receptor ($K_i = 63$ nM (16)) and vesicular acetylcholine transporters ($K_i = 50$ nM (17)); these interactions may confound imaging results when specifically interrogating for S1R. ^{18}F -FPS has shown unfavorable slow brain pharmacokinetics, which limits the clinical evaluation of S1Rs in the central nervous system. Recently, ^{18}F -fluspidine has been tested in healthy human subjects (18), and further clinical application is pending.

Since 2011, our group has been developing a highly selective S1R radioligand, ^{18}F -FTC-146 (Fig.1). The excellent selectivity (>1000-fold) for the S1R over the sigma-2 receptor and vesicular acetylcholine transporters demonstrates the high potential of ^{18}F -FTC-146 for selectively imaging the S1R. Preclinical studies (*i.e.*, cell line, wild-type and S1R knock-out mice, rats, and non-human primates) of ^{18}F -FTC-146 have shown excellent pharmacokinetic imaging properties and biosafety (19-21). Based on these favorable preclinical findings, we obtained exploratory Investigational New Drug status for clinical-grade ^{18}F -FTC-146 to allow first-in-human ^{18}F -FTC-146 studies (22).

The purpose of this study is to assess the safety, biodistribution, and radiation dosimetry for clinical-grade ^{18}F -FTC-146 in humans.

MATERIALS AND METHODS

Subjects

The study protocol was approved by the Stanford University Institutional Review Board, and is compliant with federal, state, and local regulation on medical research (clinical trial registration number, NCT02753101). Ten healthy volunteers (five female, five male; age: $34.3 \pm$

6.5 years) were recruited between February and April 2016 (Table 1), and written informed consent was obtained from each subject before commencing the study. Inclusion criteria were adults 18-50 years of age. Exclusion criteria included pregnancy, breastfeeding, MRI-incompatible materials and devices, and presence of pain, which was assessed using the Oswestry Disability Index, visual analog scale, and Short Form 36 Health Survey.

No specific patient preparation was requested (i.e., fasting, hydration, etc.) on the day of scanning. The volunteer's vital signs (heart rate, pulse oximetry, and body temperature) were monitored at regular intervals throughout the duration of imaging. To determine whether the injected dose of ^{18}F -FTC-146 affected blood measurements over time, blood specimens were obtained and analyzed (complete blood count with differential, renal function panel, and liver function panel) from each volunteer at three time points: 1) immediately prior to the injection of ^{18}F -FTC-146, 2) 24 hours after injection of ^{18}F -FTC-146 and 3) 7 days after injection of ^{18}F -FTC-146. Any unusual or adverse patient symptoms were recorded on the day of imaging as well as during follow-up.

Radiosynthesis

In-depth details regarding the synthesis and quality control of clinical-grade ^{18}F -FTC-146 are published elsewhere (22). In brief, ^{18}F -FTC-146 was synthesized via aliphatic nucleophilic substitution (^{18}F /tosylate exchange) using TRACERlab FX-FN. Tosylate precursor solution (2.5 mg in 1 mL anhydrous DMSO) was added into azeotropically dried $^{18}\text{F}/\text{K}_{222}/\text{K}_2\text{CO}_3$ complex, heated to 150°C for 15 min, and the crude product was purified on semi-preparative high-performance liquid chromatography. The ^{18}F -FTC-146 high-performance liquid chromatography

fraction was formulated in saline containing no more than 10% ethanol. The specific activity at end-of-bombardment was 173.9 ± 66.6 GBq/ μ mol.

PET Imaging and Reconstruction

The mean and standard deviation of the administered mass and activity of ^{18}F -FTC-146 was 1.4 ± 0.5 μ g (range: 0.57–2.44 μ g), and 357.2 ± 48.8 MBq (range: 269.0–419.2 MBq), respectively. All subjects underwent a series of PET/MR examinations scheduled at 0, 30, 60, 90, 120, 150 and 180 minutes post tracer administration on a time-of-flight PET/MR scanner (SIGNA PET/MR; GE Medical Systems, USA).

The first PET/MR examination started simultaneously with tracer administration and consisted of a 10-minute acquisition of the brain, followed by a whole-body (WB) PET/MR scan. Data was acquired for at least six bed positions with 2 min PET acquisition per bed together with simultaneous MRI scans (T1 and T2-weighted images) for anatomical reference and attenuation correction (2-point Dixon sequence). The PET photon attenuation coefficients at 511 keV were obtained by segmenting the MR-based attenuation correction images into air, lung, fat, and water (everywhere except the brain), which was registered to an atlas containing skull information.

For the first five subjects, WB scans covering head to mid-thigh were conducted, while for subjects 6-10, additional total-body scans (head to toe) were acquired at three time points (for details, see Table 2). The PET data was reconstructed using a fully 3D iterative ordered subsets expectation maximization algorithm (28 subsets, 2 iterations), and corrected for attenuation, scatter, dead time, and decay. Subjects were allowed to momentarily leave the scanner after the 30-minute scan, and were strongly encouraged to void their bladder.

Biodistribution and Radiation Dosimetry

Organs of interest (kidneys, brain, liver, pancreas, spleen, thyroid, urinary bladder, muscle, cortical bone, heart wall, brain, and marrow) were delineated using PMOD 3.7 (PMOD Technologies LLC, Zurich, Switzerland), and the corresponding standardized uptake values were calculated for each imaging time point. In addition, to estimate the total number of disintegrations (“residence times” in hours) in each organ, the total organ uptake was calculated based on the average (non-decay corrected) concentration data and standardized phantom organ volumes as implemented in PMOD 3.7. To avoid any underestimation of absorbed doses, the activity was normalized to account for 100% of the injected activity. The activity data was fitted by trapezoidal integration to the end of scanning, followed by isotope decay. The resulting residence times were imported to OLINDA/EXM software (23) for radiation dose estimations. The “remainder in the body” was calculated by subtracting the sum of the activity in all source organs from the total activity in the body. The total number of integrations for the bladder was determined using the urinary bladder model as implemented in OLINDA/EXM, with a 1-hour bladder-voiding interval and 100% renal excretion. The biological half-life of ^{18}F -FTC-146 was estimated from the WB activity data. The phantoms selected in OLINDA/EXM were the adult female and male phantoms, for female and male subjects, respectively. In addition, to allow for individual variations in organ mass, the phantom organ volumes were scaled according to the subject’s individual body weight as implemented in OLINDA/EXM. The ED was determined using the methodology defined in International Commission on Radiological Protection publication 60 (24).

RESULTS

All subjects tolerated the PET/MRI examination well. No adverse reactions to ^{18}F -FTC-146 were reported during the day of scanning or during the 7-day follow up period. As required by the Food and Drug Administration, a full assessment including blood pressure and blood count were performed for acute toxicity assessment, and no abnormal findings were observed. Subject 8 disclosed, after the end of scanning, low-grade muscle soreness due to performing intense exercise the day before. Hence, since Subject 8 was not an asymptomatic volunteer, Subject 8's results were eliminated from the biodistribution and dosimetry assessment.

All subjects were scheduled to be scanned at 30-minute intervals for up to 3 hours after tracer administration. However, the start time of each WB scan and the number of scans varied slightly between subjects due to logistics and patient comfort. In particular, the 60-minute WB was often delayed due to the encouraged bathroom break. The exact timing of the WB scans and total number of scans for the individual subjects are listed in Table 2.

^{18}F -FTC-146 Biodistribution and Dosimetry

Figure 2 shows the uptake pattern and biodistribution of ^{18}F -FTC-146 at six different time points after tracer administration in a healthy volunteer (subject 7; Fig. 2A) as well as the inter-subject variability between volunteers ($n=9$) at 30 minutes after tracer administration (Fig. 2B). The corresponding coronal and axial PET/MR images in Figure 3 show tracer distribution in several key areas of the body (subject 10). High accumulation of ^{18}F -FTC-146 was observed in S1R dense organs such as the pancreas, spleen, and thyroid, while moderate uptake was observed in the brain and myocardium, and low uptake in bone and muscle. Renal tracer clearance resulted in the expectedly high uptake observed in the kidneys and bladder. High accumulation of ^{18}F -FTC-146 was also observed in the veins of the arm on the side of injection (Fig. 2). Figure 4

shows the average (n=9) time-activity curves for 10 principle organs; the reported standardized uptake values are corrected for physical decay. A gradual tracer washout was observed in the lungs, kidneys, and bladder.

The absorbed dose estimates for the nine included participants are listed in Table 3. The bladder received the highest dose of all organs (0.1498 ± 0.0245 mSv/MBq), reflecting renal tracer clearance. The other major organs that received relatively high doses were the pancreas (0.0654 ± 0.0208 mSv/MBq), spleen (0.0637 ± 0.0117 mSv/MBq), kidneys (0.0577 ± 0.0080 mSv/MBq), and thyroid (0.0457 ± 0.0100 mSv/MBq). The thymus, testes, skin, marrow, ovaries, breasts, and adrenals received the lowest absorbed doses. The highest inter-subject variation in absorbed dose was observed in the bladder (range: 0.1230-0.1710 mSv/MBq) and pancreas (range: 0.0381-0.1100 mSv/MBq).

The mean ED of ^{18}F -FTC-146 was 0.0259 ± 0.0034 mSv/MBq (range: 0.0215-0.0301 mSv/MBq). With an injected ^{18}F -FTC-146 dose of 370 MBq and a 1-hour voiding interval, the patient would be exposed to an ED of 9.6 mSv. Correcting for individual subject body weight, the mean ED was 0.0245 ± 0.0034 mSv/MBq (range: 0.0177-0.0296 mSv/MBq), and the patient radiation exposure from ^{18}F -FTC-146 was 9.1 mSv.

DISCUSSION

This first-in-human PET/MRI study demonstrates the safety, biodistribution, and radiation dosimetry of clinical-grade ^{18}F -FTC-146. Multiple WB PET/MRI scans were conducted successfully in 10 volunteers, and no adverse reaction or clinical changes in vital signs were observed. The estimated absorbed doses to critical and radiation-sensitive organs are acceptable and considered to be safe.

The organs showing primary uptake of ^{18}F -FTC-146 are those known to have a high expression of S1R (25,26), such as the spleen, pancreas, heart wall, brain, normal groin and axillary lymph nodes, thyroid, and lungs. The primary route of tracer clearance was through the renal pathway, resulting in high uptake and gradual washout in the kidneys and bladder. While uptake was also observed in the small intestine, we believe that this accumulation occurred in the Peyer's patches of the small bowel's lymph node system. In addition, no uptake was observed in the gallbladder or in the colon over time. Hence, we conclude that the tracer excretes solely through the renal and not the hepatobiliary pathway.

A full assessment of radiometabolites from ^{18}F -FTC-146 administration in human plasma has been previously published (22). In brief, $43 \pm 7\%$ and $23 \pm 5\%$ of the peak radioactivity remained in circulation at 30 min and 120 min post-injection, respectively. Based on our preclinical studies, only intact ^{18}F -FTC-146 was present in the rat brain at 15, 30, and 60 min post-injection (19).

In contrast to tracer uptake in the skull observed in our previous non-human primate study (19), only insignificant radioactivity uptake in bone was detected in humans. Also, differences in tracer pharmacokinetic properties were observed between the two species; slow tracer washout was seen in monkeys unlike in human brain tissue where no gradual washout of ^{18}F -FTC-146 was detected within the 3-hour imaging session. The observed slower kinetics is likely due to high S1R binding affinity in the picomolar range. While slow tracer kinetics is not ideal for a neuroimaging probe, it facilitates high signal to background contrast, enabling potential detection of smaller foci related to disease, such as pain and nerve injury. In addition, high specific binding provides advantages for future translation of S1R-specific therapeutic strategies.

^{18}F -FTC-146 was retained in the veins of the arm that was injected, a phenomenon also observed in a recent human study with ^{18}F -fluspidine (18). In order to prevent this radiotracer retention in the vein, we are working to improve the tracer's solubility under physiological conditions by experimenting with different formulation strategies. No specific dosimetric assessment was conducted based on this uptake; the amount of tracer accumulation in the arm was included in the "remainder of the body".

The estimated ED of ^{18}F -FTC-146 was 0.0259 ± 0.0034 mSv/MBq, with an uppermost estimated individual ED of 0.0301 mSv/MBq. An injected dose of 370 MBq will expose the patient to 9.6 mSv (based on mean) or 11.1 mSv (based on max). Correcting for individual body weights, the highest radiation exposure was estimated to be 11.0 mSv. The estimated radiation doses are comparable to other ^{18}F -labeled radiopharmaceuticals (27), such as ^{18}F -FPPRGD2 (0.0396 ± 0.0181 mSv/MBq (28)) and the S1R radioligand ^{18}F -fluspidine (0.021 ± 0.013 mSv/MBq (18)). For comparison, radiation exposure from a standard ^{18}F -fluorodeoxyglucose PET examination is typically 6-7 mSv (27).

For radioactive agents used in clinical trials, dose limitations for adult research subjects are defined in the United States by the U.S. Food and Drug Administration (29). For blood forming organs, lens of the eye, gonads, and whole body, the radiation doses must not exceed 30 mSv per examination or 50 mSv per year. For all other organs, the limits for single and total annual dose are 50 mSv and 150 mSv, respectively. Based on the calculated whole-body dosimetric values, 1930 MBq of ^{18}F -FTC-146 can be injected in each patient per year, hence, five ^{18}F -FTC-146 PET acquisitions with 370 MBq can be conducted annually. For radiation-sensitive organs, such as the testes, ovaries and red marrow, the dosimetric calculations show

that the absorbed organ doses are well below the 30 mSv dose limit given by the Food and Drug Administration.

For the hybrid, whole-body PET/MR scanner, the MR-based attenuation correction methodology does not include correction for photon attenuation in bone. Hence, measured activity values in the PET images may be underestimated for tissue surrounded by a substantial amount of bone. However, Iagaru and colleagues (30) demonstrated that the image quality was improved and the measured activity values were higher in PET images obtained with PET/MRI compared to PET/computed tomography. Another study showed that the standardized uptake values based on PET/computed tomography and PET/MRI correlated well in normal organ tissues, except for the lungs, subcutaneous fat and blood pool (31). In addition, due to the high sensitivity of the current PET/MR scanner (32), we believe that the calculated ED values provide accurate estimates of the radiation exposure to patients.

¹⁸F-FTC-146 is a promising imaging agent for a variety of applications, as SIRs are believed to play an important role in cancer, chronic pain, and neurological disorders. We are currently investigating the potential of ¹⁸F-FTC-146 to image pain generators in the peripheral nervous system. The high selectivity and affinity of the tracer facilitate an excellent signal-to-noise ratio, which is necessary for such small imaging targets.

CONCLUSION

First-in-human studies with clinical-grade ¹⁸F-FTC-146 have been successful. Injection of ¹⁸F-FTC-146 is safe and absorbed doses are acceptable. The potential of ¹⁸F-FTC-146 as an imaging agent for chronic pain and neuroinflammatory diseases is currently under investigation.

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DISCLOSURE

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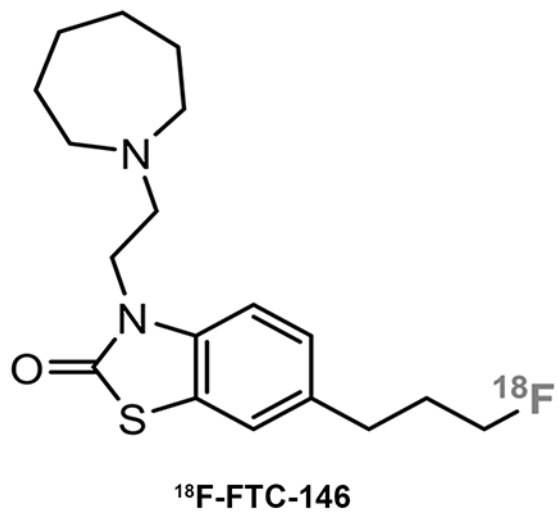


Figure 1. Chemical structure of ^{18}F -FTC-146.

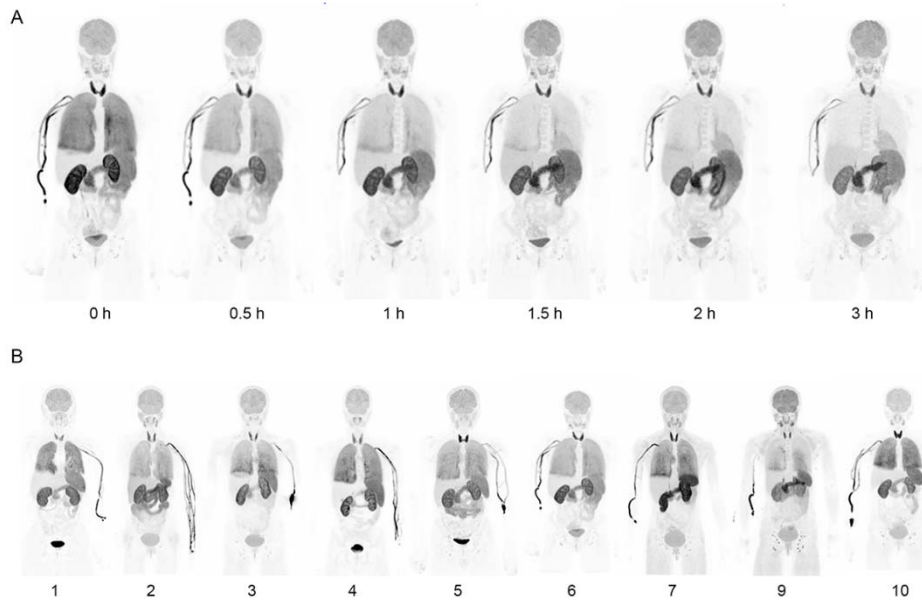


Figure 2. Whole-body PET Maximum-Intensity Projection (MIP) images at different time points after ^{18}F -FTC-146 administration in Subject 7 (A), and at 30 minutes after ^{18}F -FTC-146 administration in nine subjects (B).

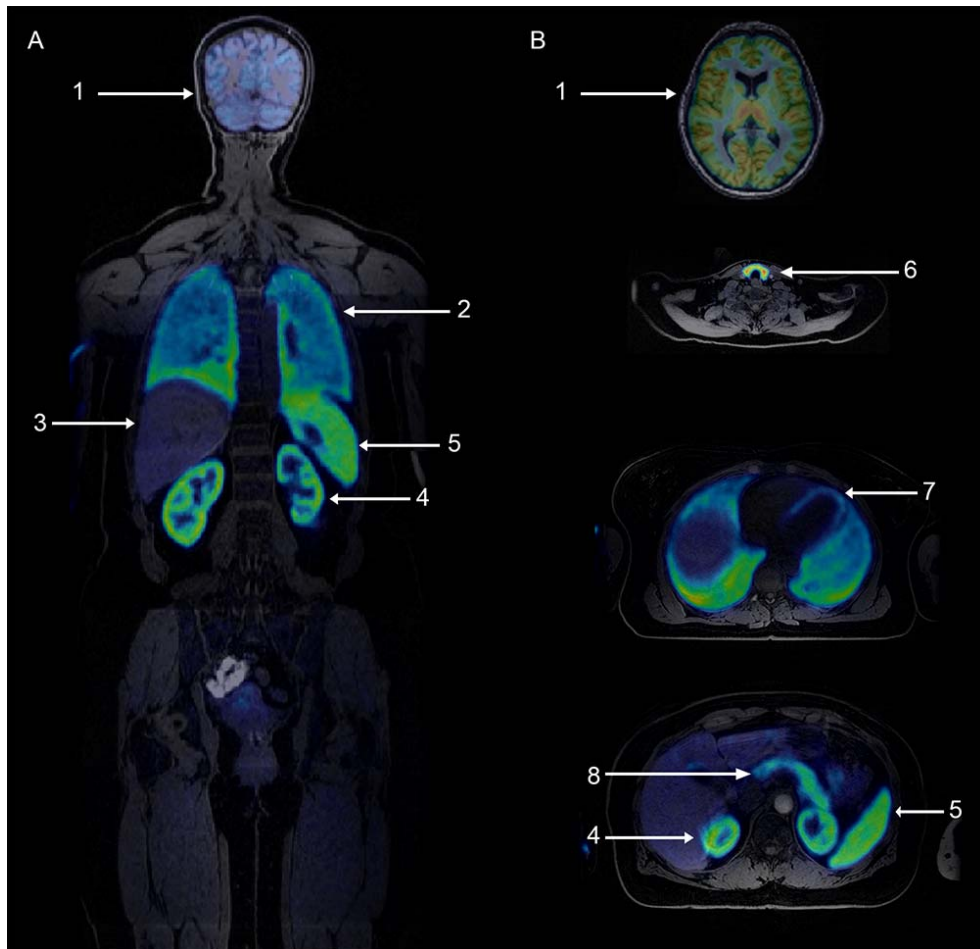


Figure 3. Simultaneous PET/MRI in coronal (A) and transverse (B) planes showing uptake in the principal organs 30 minutes after ^{18}F -FTC-146 injection in Subject 10. Brain (1), lungs (2), liver (3), kidneys (4), spleen (5), thyroid (6), heart (7), and pancreas (8).

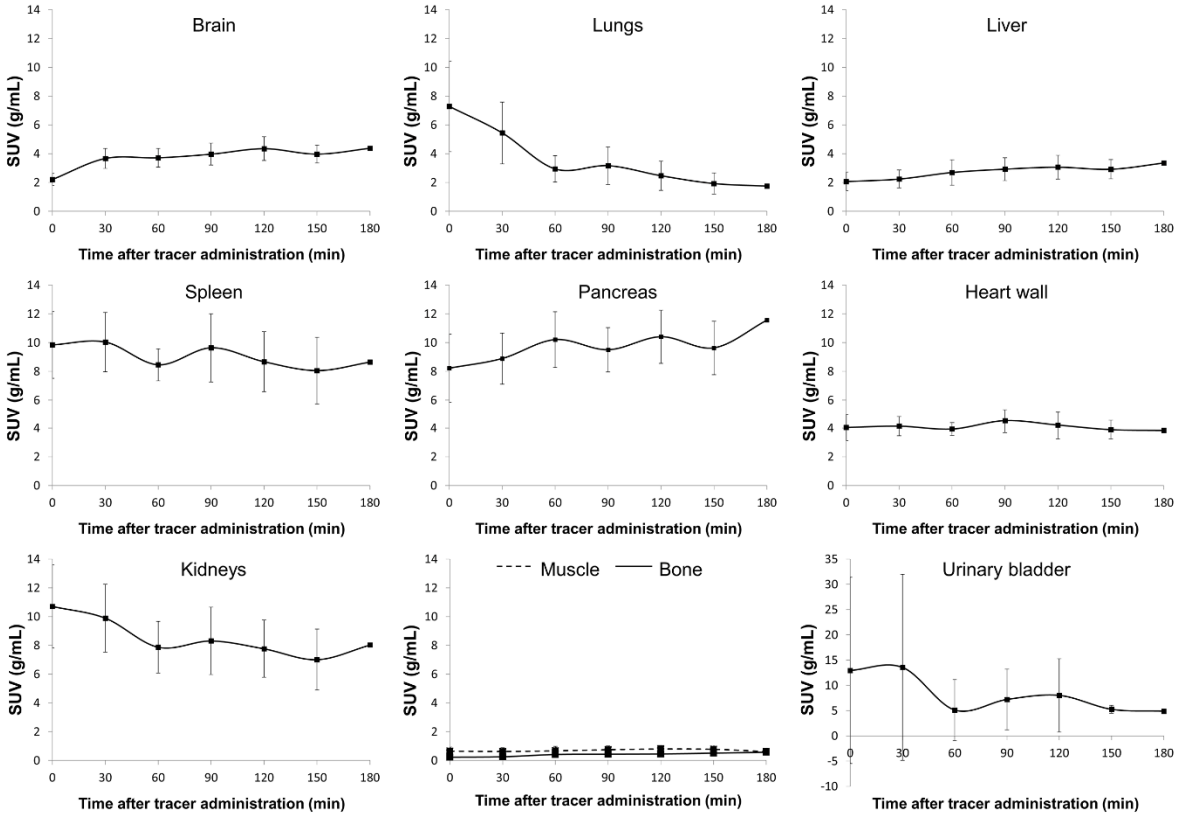


Figure 4. Average (n=9) time-activity curves for 10 principle organs. Error bars indicate \pm standard deviation. The Standardized Uptake Values (SUVs) at 180 min are based on a single subject only (no error bars). Note the scale difference on the y-axis for the urinary bladder.

Table 1: Subject demographics and administered ¹⁸F-FTC-146 dose data.

HV#*	Gender	Age	Height (cm)	Weight (kg)	Injected activity (MBq)
1	M	33	175.3	103.4	307.8
2	F	41	162.6	61.2	346.3
3	F	35	170.2	78.0	269.0
4	M	29	174.0	70.0	405.5
5	M	28	178.0	80.0	342.3
6	M	31	170.2	68.0	371.5
7	F	36	165.1	54.4	325.6
8	M	33	177.8	100.0	414.8
9	F	28	162.6	63.5	419.2
10	F	49	167.6	79.4	370.0
Mean		34.3	170.3	75.8	357.2
SD [†]		6.5	5.8	16.0	48.8

*HV = healthy volunteer; [†]SD = standard deviation.

Table 2: ¹⁸F-FTC-146 Imaging Protocol. Actual imaging start time points (minutes after tracer administration) and number of WB PET/scans for each volunteer.

HV#*	Start time after tracer injection for each PET/MR scan (min)							Number of WB [†] PET/MR scans
	0	30	60	90	120	150	180	
1	0	43		85	122			4
2	0	35	77	100	127			5
3	0	43		101	126			4
4	0	34	69	93	123			5
5	0	38	78	104	125			5
6	0	33 [‡]	76 [‡]		115	132 [‡]	172	6
7	0	31 [‡]	74 [‡]	102	126 [‡]	154		6
8	0	31 [‡]		80 [‡]	115	136 [‡]	172	6
9	0	32 [‡]	73 [‡]	100	129 [‡]	160		6
10	0	29 [‡]		78 [‡]	117	139 [‡]		5
Mean	0	34.9	74.5	93.7	122.5	144.2	172.0	5.2
SD [§]	0	4.9	3.3	10.1	5.1	12.1	0.0	0.8

*HV = healthy volunteer; [†]WB = whole body (head to mid thigh). [‡]Total body (TB; head to toe) scan coverage. [§]SD = standard deviation.

Table 3. ^{18}F -FTC-146 dosimetric data.

Target organ	Absorbed dose estimates (mSv/MBq)			
	Mean	SD*	Min	Max
Adrenals	0.0161	0.0023	0.0133	0.0193
Brain	0.0307	0.0054	0.0218	0.0406
Breasts	0.0094	0.0012	0.0077	0.0111
Gallbladder wall	0.0166	0.0021	0.0140	0.0208
LLI Wall	0.0171	0.0021	0.0131	0.0194
Small Intestine	0.0318	0.0122	0.0125	0.0558
Stomach wall	0.0150	0.0018	0.0123	0.0172
ULI wall	0.0171	0.0025	0.0120	0.0200
Heart Wall	0.0332	0.0075	0.0234	0.0436
Kidneys	0.0577	0.0080	0.0459	0.0717
Liver	0.0272	0.0087	0.0162	0.0480
Lungs	0.0262	0.0046	0.0215	0.0356
Muscle	0.0115	0.0026	0.0080	0.0154
Ovaries	0.0177	0.0021	0.0133	0.0195
Pancreas	0.0654	0.0208	0.0381	0.1100
Red Marrow	0.0152	0.0022	0.0124	0.0198
Osteogenic cells	0.0207	0.0038	0.0160	0.0274
Skin	0.0082	0.0010	0.0067	0.0096
Spleen	0.0637	0.0117	0.0419	0.0785
Testes	0.0105	0.0006	0.0098	0.0113
Thymus	0.0117	0.0017	0.0094	0.0139
Thyroid	0.0457	0.0100	0.0275	0.0643
Urinary bladder wall	0.1498	0.0245	0.1230	0.1710
Uterus	0.0216	0.0021	0.0174	0.0234
Total body	0.0145	0.0020	0.0119	0.0163
Effective dose	0.0259	0.0034	0.0215	0.0301

*SD = standard deviation.