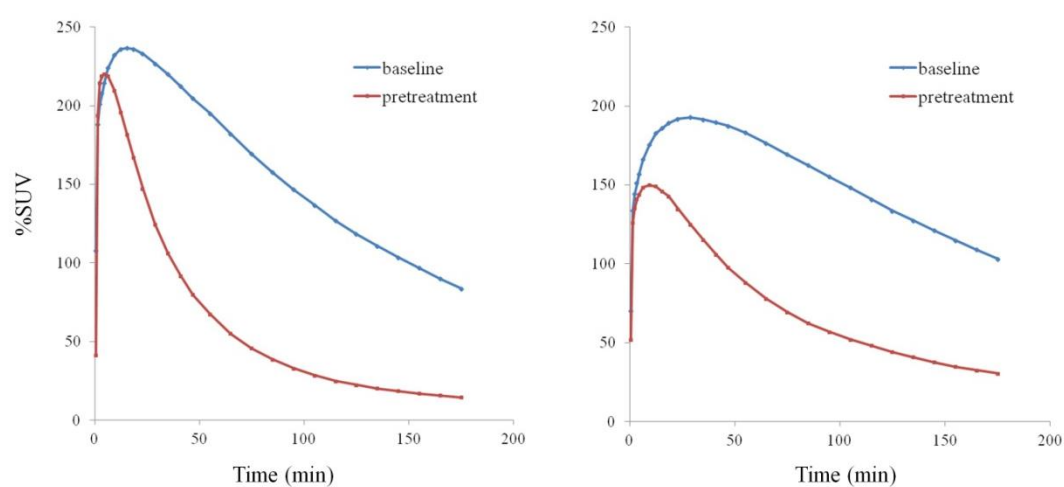
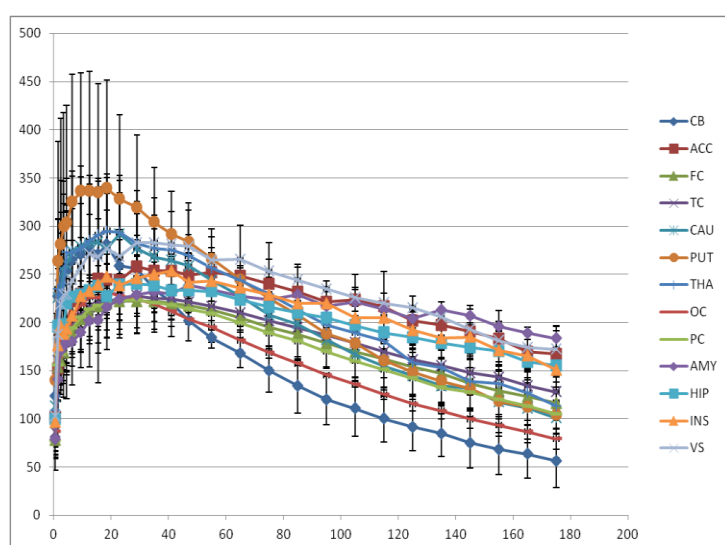


Supplemental Fig. 1. An example set of VOIs on the MRI/PET images

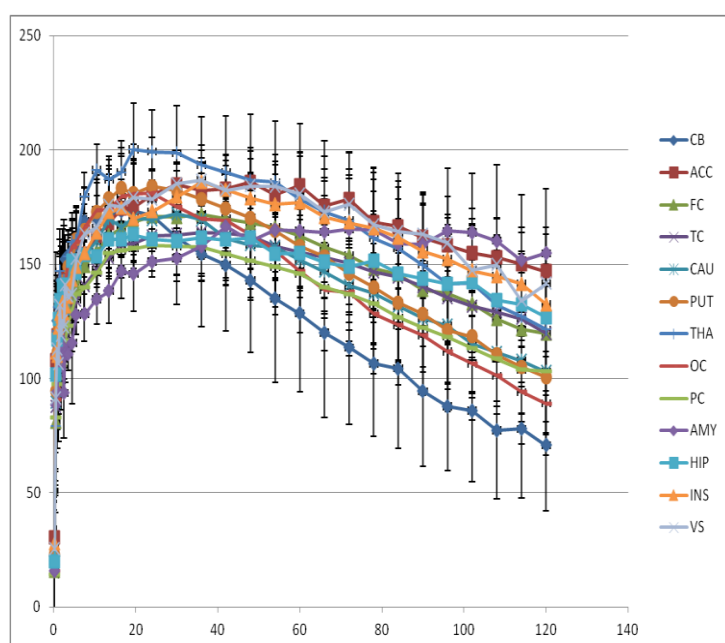


Supplemental Fig. 2. Whole brain time activity curves of ^{18}F -PF-06684511 at the baseline and pretreatment with LY2886721 (left: NHP 1 and right: NHP 2). %SUV: radioactivity in the brain (MBq/cc)/injected radioactivity(MBq) \times body weight (g) \times 100 (%).

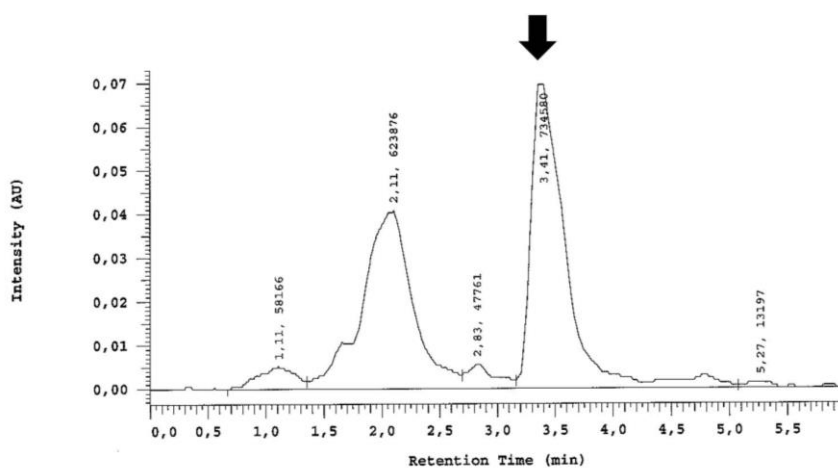
A.



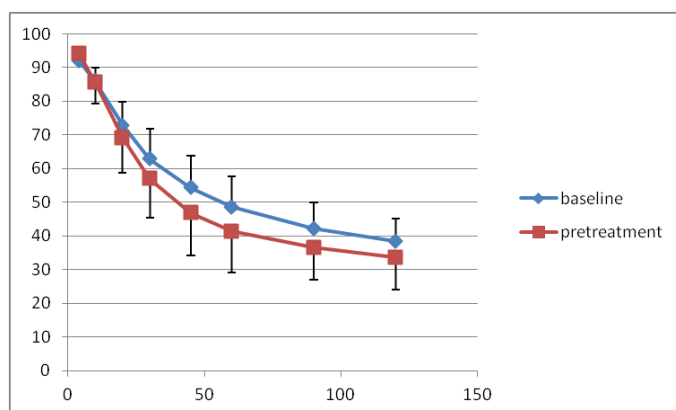
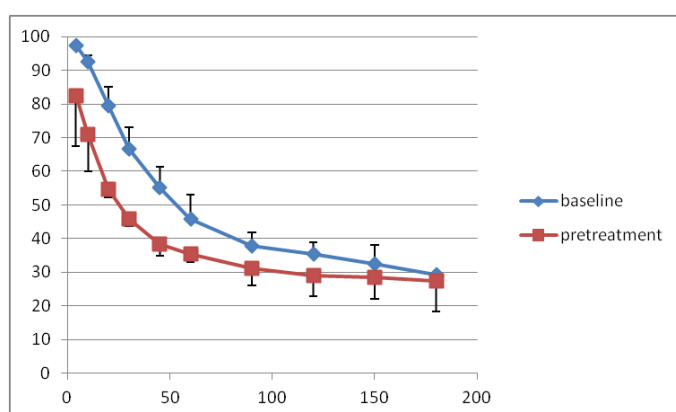
B.



Supplemental Fig. 3. Average time activity curves of ^{18}F -PF-06684511. A: 180-minute baseline PET measurements in the baseline/blocking study (n=2). B: 120-minute baseline PET measurements in the occupancy study (n=4). X-axis is time (minute) and Y-axis is % SUV.

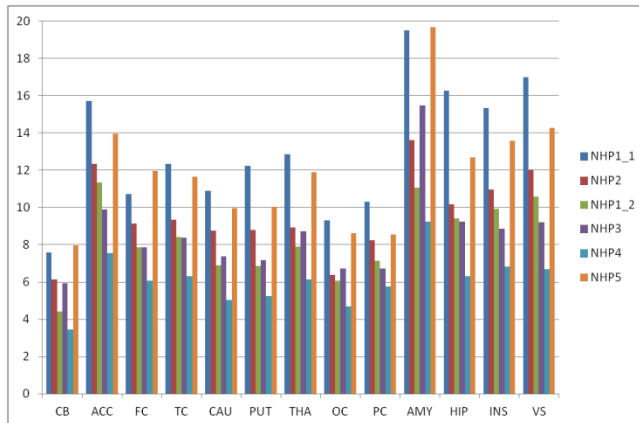


Supplemental Fig. 4. Radio-HPLC chromatogram at 45min in NHP 1 at the baseline. Black arrow indicates the peak of ^{18}F -PF-06684511.

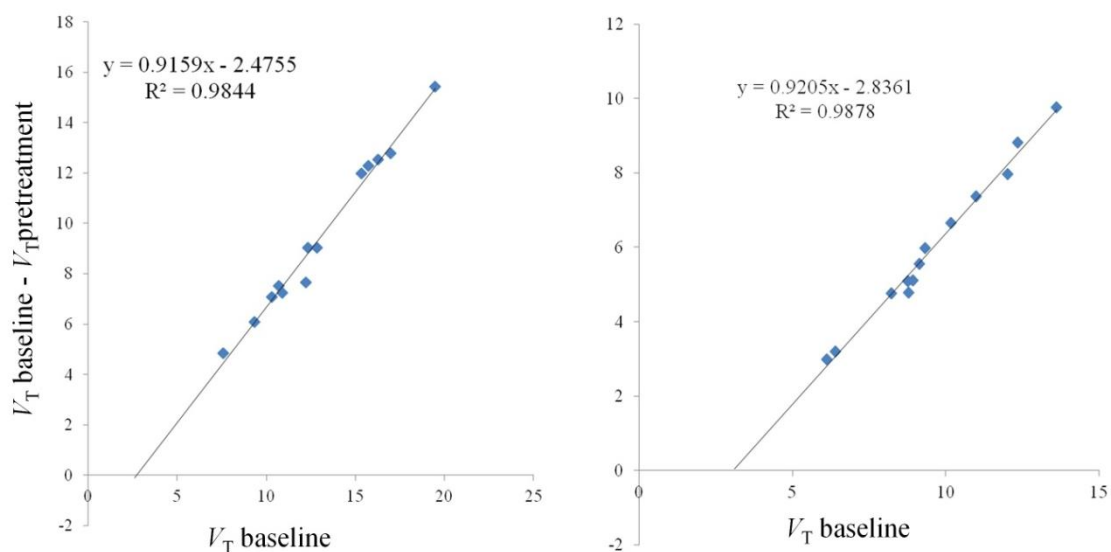


Supplemental Fig. 5. Average percent fraction of unmetabolized ^{18}F -PF-06684511 in the plasma. Upper: 180-minute PET measurements in the baseline/blocking study (n=2). Lower:

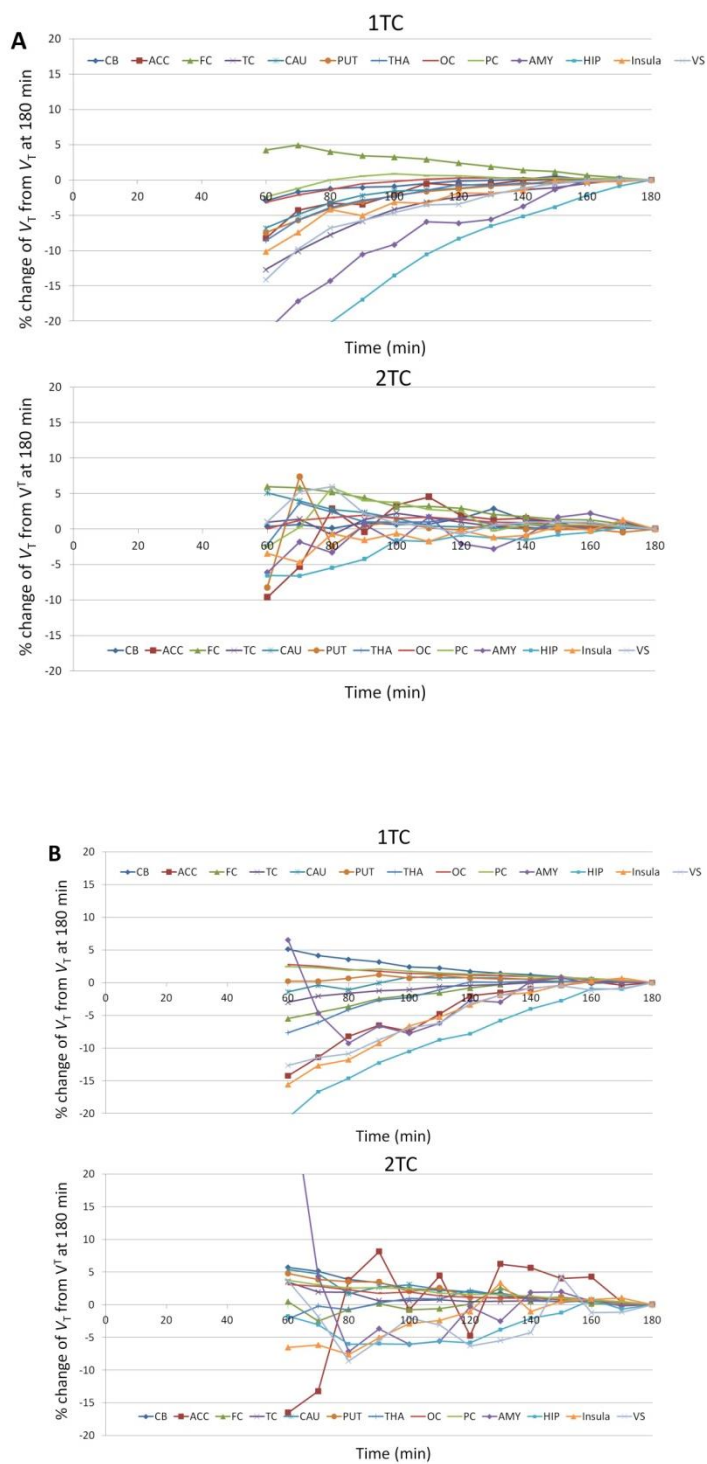
120-minute PET measurements in the occupancy study (n=4). X-axis is time (minute) and Y-axis is %fraction of unmetabolized radioligand.



Supplemental Fig. 6. Individual V_T values estimated by 2TC of 5 monkeys. X-axis is the brain regions and Y-axis is V_T values.



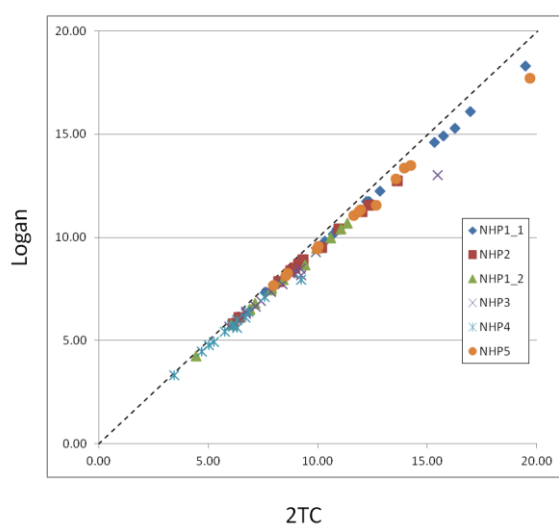
Supplemental Fig. 7. Lassen plots using V_T estimated with 2TC (left: NHP 1 and right: NHP 2).



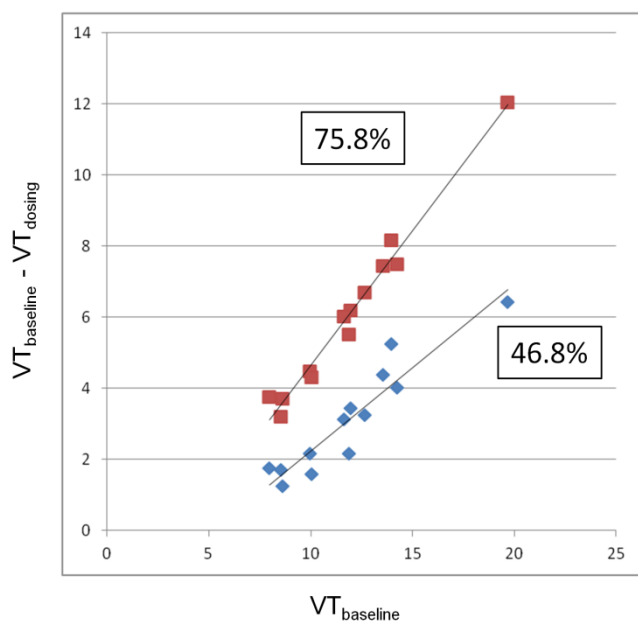
Supplemental Fig. 8. Time stability of V_T values. (A: NHP 1 and B: NHP2)



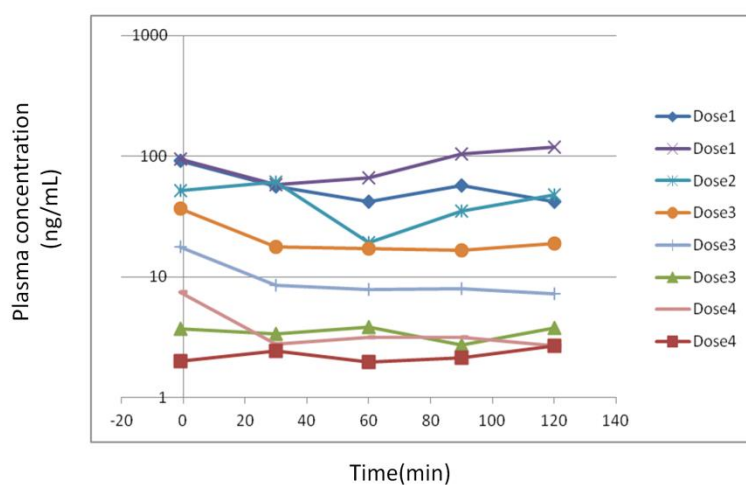
Supplemental Fig. 9. Examples of Logan plots in putamen (PUT), hippocampus (HIP) and cerebellum (CB).



Supplemental Fig. 10. Correlation of V_T values between 2TC and Logan plot.

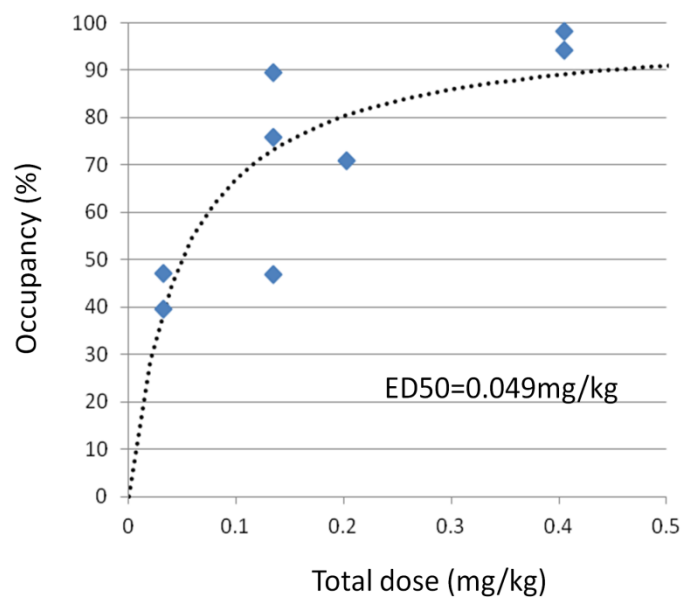


Supplemental Fig.11. Examples of Lassen plots in the occupancy study with PF-06663195.



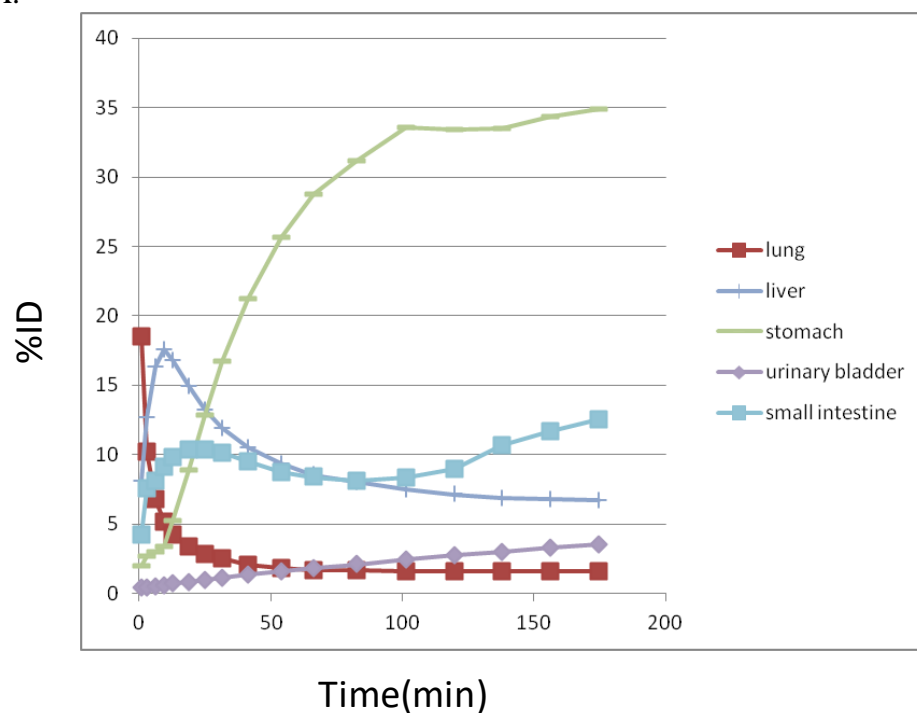
	Bolus (mg/kg)	Constant (mg/hr/kg)
Dose1	0.266	0.064
Dose2	0.133	0.032
Dose3	0.089	0.021
Dose4	0.022	0.005

Supplemental Fig. 12. The time courses of the plasma concentration of PF-06663195 in the occupancy study.

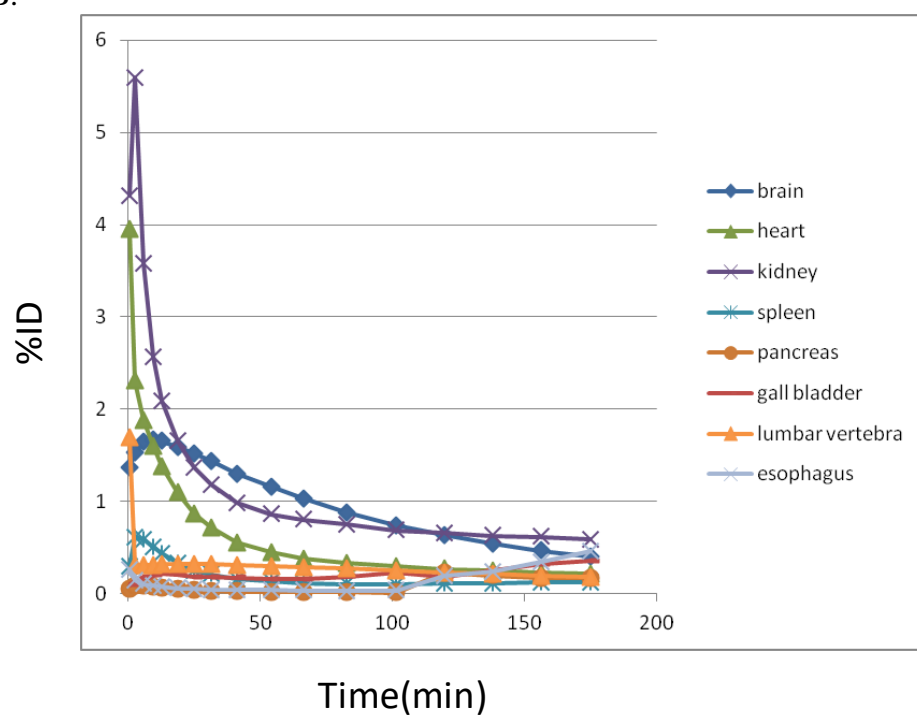


Supplemental Fig. 13. The relationship between the total administered dose of PF-06663195 and BACE1 occupancy in the occupancy study.

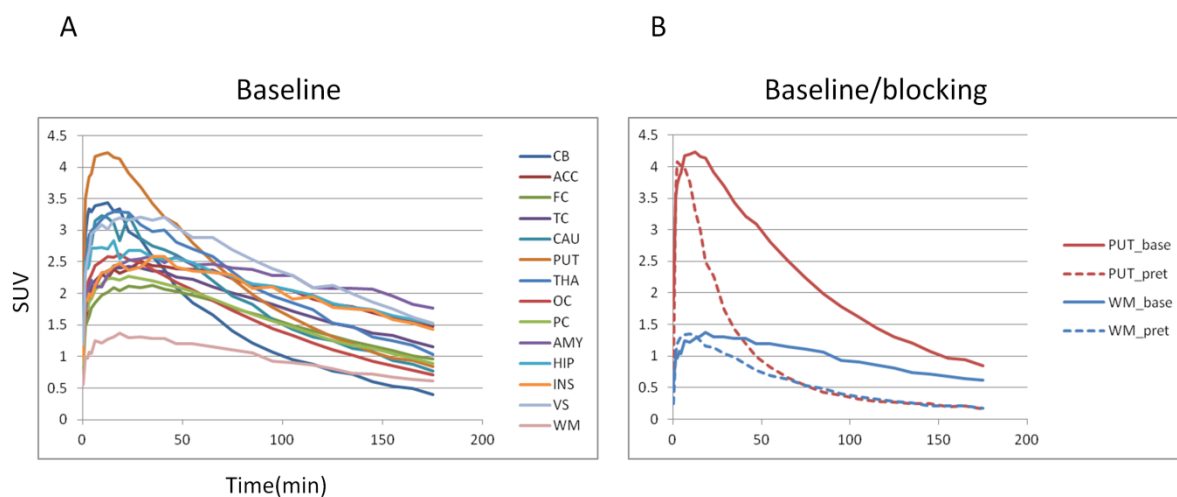
A.



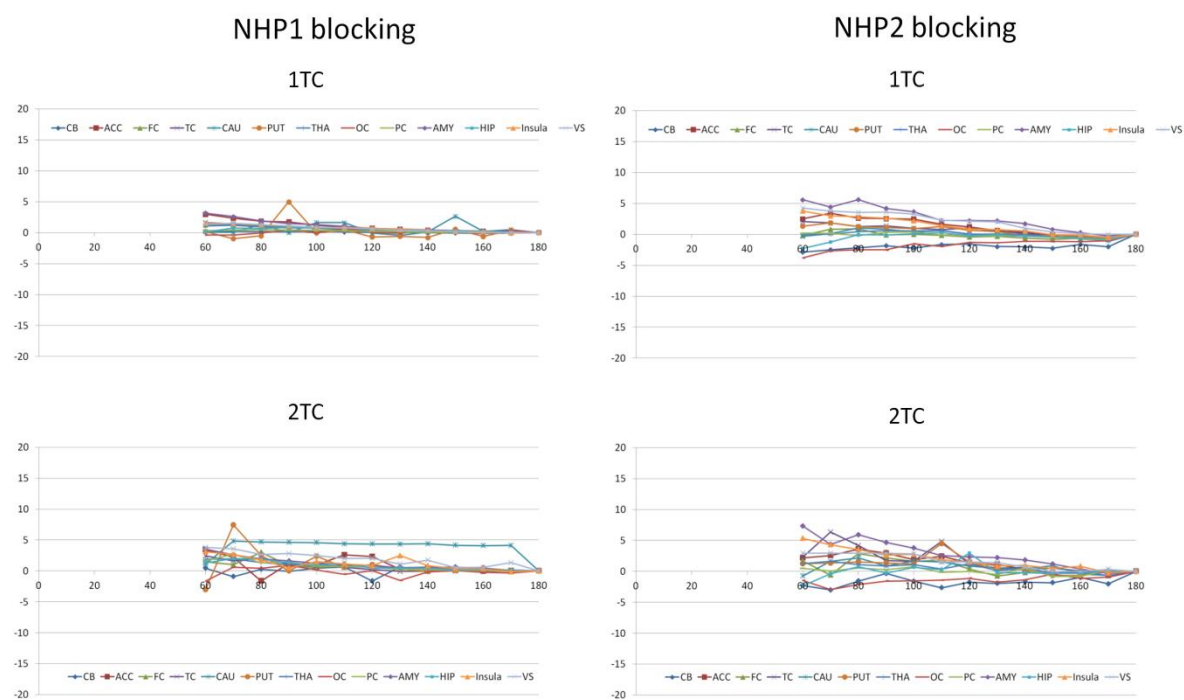
B.



Supplemental Fig. 14. The time course of organ uptake of ^{18}F -PF-06684511 in NHP 7 in the whole-body dosimetry experiment (A: Higher uptake organs and B: Lower uptake organs).



Supplemental Fig. 15. A. The time activity curves of ^{18}F -PF-06684511 in NHP 1 including the white matter (WM). B. The change of the time activity curves of putamen (PUT) and white matter after 5 mg/kg of LY2886721.



Supplemental Fig. 16. Time stability of V_T values estimated by 1TC and 2TC of 2 NHPs in the baseline/blocking study.

Supplemental Table 1. Kinetic parameters estimated by one-tissue compartment analysis

Monkey 1		baseline												
	CB	ACC	FC	TC	CAU	PUT	THA	OC	PC	AMY	HIP	INS	VS	
K1	0.23	0.12	0.11	0.13	0.21	0.27	0.19	0.15	0.13	0.13	0.15	0.13	0.17	
k2	0.030	0.008	0.010	0.011	0.019	0.022	0.015	0.017	0.012	0.0068	0.010	0.0085	0.011	
VT	7.54	15.47	10.72	12.01	10.65	11.97	12.63	9.26	10.27	18.63	14.85	15.04	16.50	
pretreatment with LY2886721														
K1	0.24	0.15	0.14	0.16	0.28	0.34	0.22	0.20	0.16	0.15	0.19	0.16	0.21	
k2	0.087	0.043	0.043	0.048	0.075	0.075	0.058	0.064	0.048	0.038	0.051	0.049	0.051	
VT	2.72	3.43	3.17	3.30	3.73	4.52	3.77	3.14	3.22	4.05	3.66	3.33	4.17	
Monkey 2		baseline												
	CB	ACC	FC	TC	CAU	PUT	THA	OC	PC	AMY	HIP	INS	VS	
K1	0.12	0.12	0.11	0.09	0.12	0.13	0.13	0.10	0.10	0.08	0.09	0.11	0.11	
k2	0.020	0.010	0.012	0.010	0.014	0.015	0.014	0.015	0.012	0.0060	0.010	0.010	0.0091	
VT	6.12	11.99	9.04	9.27	8.72	8.76	8.81	6.39	8.22	13.35	9.56	10.70	11.58	
pretreatment with LY2886721														
K1	0.15	0.10	0.11	0.10	0.12	0.14	0.15	0.12	0.11	0.092	0.12	0.11	0.11	
k2	0.049	0.029	0.029	0.029	0.033	0.035	0.038	0.037	0.031	0.024	0.034	0.030	0.028	
VT	3.13	3.54	3.60	3.36	3.68	4.00	3.83	3.18	3.46	3.85	3.52	3.62	4.05	

CB: cerebellum, ACC: anterior cingulate cortex, FC: frontal cortex, TC: temporal cortex, CAU: caudate, PUT: putamen, THA: thalamus, OC: occipital cortex, PC: parietal cortex, AMY: amygdala, HIP: hippocampus, INS: insula, VS: ventral striatum.

Supplemental Table 2. Kinetic parameters estimated by two-tissue compartment analysis

Monkey 1		baseline											
	CB	ACC	FC	TC	CAU	PUT	THA	OC	PC	AMY	HIP	INS	VS
K1	0.24	0.13	0.11	0.14	0.24	0.30	0.22	0.16	0.13	0.15	0.19	0.14	0.20
k2	0.040	0.014	0.011	0.028	0.068	0.053	0.056	0.024	0.016	0.042	0.051	0.038	0.040
k3	0.021	0.043	0.005	0.069	0.148	0.089	0.160	0.046	0.027	0.143	0.077	0.179	0.117
k4	0.073	0.064	0.094	0.050	0.070	0.076	0.070	0.110	0.103	0.031	0.022	0.057	0.048
VT	7.59	15.72	10.70	12.34	10.89	12.23	12.85	9.32	10.31	19.48	16.26	15.32	16.97
pretreatment with LY2886721													
K1	0.25	0.15	0.14	0.17	0.29	0.47	0.23	0.21	0.16	0.16	0.26	0.17	0.21
k2	0.11	0.081	0.066	0.12	0.089	0.68	0.11	0.081	0.076	0.060	0.53	0.053	0.058
k3	0.061	0.31	0.35	0.74	0.019	1.17	0.23	0.026	0.24	0.34	0.88	0.012	0.029
k4	0.25	0.37	0.71	0.50	0.16	0.21	0.28	0.11	0.46	0.62	0.13	0.16	0.22
VT	2.75	3.44	3.18	3.31	3.65	4.57	3.80	3.22	3.23	4.05	3.73	3.35	4.18

Monkey 2		baseline											
	CB	ACC	FC	TC	CAU	PUT	THA	OC	PC	AMY	HIP	INS	VS
K1	0.12	0.12	0.11	0.10	0.13	0.13	0.15	0.10	0.10	0.084	0.11	0.14	0.11
k2	0.036	0.018	0.022	0.021	0.032	0.017	0.089	0.021	0.013	0.019	0.033	0.104	0.018
k3	0.55	0.035	0.064	0.011	0.15	0.011	0.28	0.51	0.014	0.12	0.068	0.29	0.035
k4	0.67	0.042	0.085	0.011	0.12	0.10	0.065	1.37	0.24	0.059	0.030	0.040	0.039
VT	6.12	12.35	9.13	9.33	8.77	8.78	8.93	6.39	8.22	13.61	10.17	10.98	12.03
pretreatment with LY2886721													
K1	0.15	0.10	0.11	0.10	0.12	0.14	0.15	0.12	0.11	0.092	0.12	0.11	0.11
k2	0.050	0.030	0.030	0.034	0.045	0.036	0.041	0.039	0.031	0.024	0.035	0.031	0.028
k3	0.046	0.016	0.0019	0.130	0.412	0.038	0.251	0.039	0.019	0.0087	0.0056	0.0018	0.0092
k4	0.19	0.95	0.19	0.80	1.19	0.84	3.40	0.71	0.97	0.57	0.20	0.24	0.82
VT	3.13	3.54	3.58	3.36	3.67	4.00	3.82	3.18	3.47	3.85	3.52	3.60	4.06

CB: cerebellum, ACC: anterior cingulate cortex, FC: frontal cortex, TC: temporal cortex, CAU: caudate, PUT: putamen, THA: thalamus, OC: occipital cortex, PC: parietal cortex, AMY: amygdala, HIP: hippocampus, INS: insula, VS: ventral striatum.

Supplemental Table 3. V_T values estimated by Logan graphical analysis

	CB	ACC	FC	TC	CAU	PUT	THA	OC	PC	AMY	HIP	INS	VS
NHP1_base	7.31	14.89	10.14	11.75	10.38	11.73	12.24	8.89	9.82	18.30	15.29	14.61	16.08
NHP1_block	2.64	3.23	3.04	3.13	3.58	4.31	3.55	3.12	3.12	3.81	3.54	3.14	3.91
NHP2_base	5.81	11.56	8.69	8.90	8.34	8.38	8.50	6.10	7.84	12.74	9.49	10.38	11.25
NHP2_block	3.03	3.34	3.43	3.19	3.47	3.76	3.61	3.13	3.31	3.62	3.37	3.40	3.77

Supplemental Table 4. The average numbers of disintegrations in the source organs of two NHPs in the whole-body dosimetry experiment

Brain	2.20E-02
Gallbladder Contents	1.55E-02
LLI	1.60E-02
Small Intestine	1.59E-01
Stomach	5.77E-01
ULI	8.72E-02
Heart Wall	2.00E-02
Kidneys	2.00E-02
Liver	2.47E-01
Lungs	6.10E-02
Pancreas	5.95E-04
Spleen	3.00E-03
Urinary Bladder Contents	1.52E-01
Remainder	1.22E+00

Supplemental Table 5. Average human radiation doses estimates (adult male model) of two NHPs

Target Organ	Estimated dose	
	mSv/MBq	rem/mCi
Adrenals	1.48E-02	5.46E-02
Brain	5.08E-03	1.88E-02
Breasts	6.99E-03	2.59E-02
Gallbladder Wall	4.35E-02	1.61E-01
LLI Wall	2.26E-02	8.37E-02
Small Intestine	4.57E-02	1.69E-01
Stomach Wall	2.22E-01	8.23E-01
ULI Wall	5.13E-02	1.90E-01
Heart Wall	2.05E-02	7.57E-02
Kidneys	2.25E-02	8.32E-02
Liver	3.66E-02	1.35E-01
Lungs	1.66E-02	6.11E-02
Muscle	9.31E-03	3.45E-02
Ovaries	1.60E-02	5.90E-02
Pancreas	2.61E-02	9.65E-02
Red Marrow	9.30E-03	3.45E-02
Osteogenic Cells	1.13E-02	4.18E-02
Skin	6.14E-03	2.27E-02
Spleen	1.89E-02	6.99E-02
Testes	7.71E-03	2.85E-02
Thymus	8.01E-03	2.96E-02
Thyroid	6.54E-03	2.42E-02
Urinary Bladder Wall	8.00E-02	2.97E-01
Uterus	1.68E-02	6.22E-02
Total Body	1.11E-02	4.10E-02
Effective dose equivalent	3.54E-02	1.31E-01
Effective dose	4.34E-02	1.61E-01