Supplemental materials:

Drug Concentration Asymmetry in Tissues and Plasma for Small Molecule-Related Therapeutic Modalities

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Table S1. Free drug concentration in tissue and plasma of selected drugs at pharmacokinetic steady state

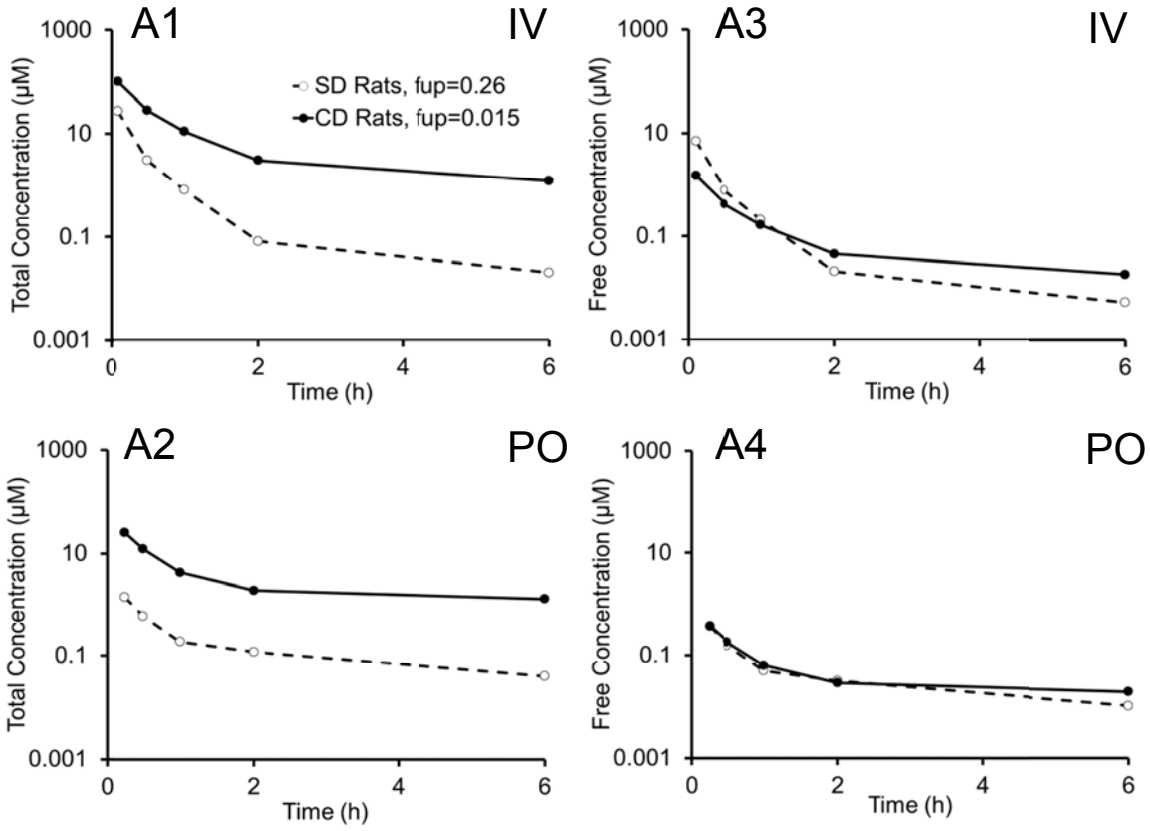
Free drug Concentration (μg/ml)	SY55551 (Deguchi et al., 1992)	Methotrexate (Ekstrom et al., 1996)	Cefminox (Deguchi et al., 1992)	Cefpodoxime (Liu et al., 2005)	Cefixime (Liu et al., 2005)
$C_{plasma,u}$	75 - 90	14.7	250	0.6*	0.3*
$C_{liver,u}$	64.2	17.6			
$C_{lung,u}$	68.7				
$C_{muscle,u}$	72.7	15.2		0.6*	0.3*
$C_{adipose,u}$			253		
*: $AUC_{0\text{-}24\ h}$					

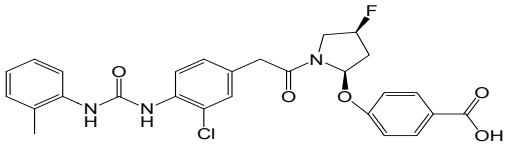
Table S2. Determination of K_p and $K_{p,uu}$ of in vivo rat livers in vitro rat hepatocytes in media

	Concentration (ng/mL)		K_p					$K_{p,uu}$		Fold Difference
Compounds	**In Vivo Plasma**	**In Vivo Liver**	**In Vivo Liver to Plasma**	**In Vitro K_p[A]**	**Plasma f_{up}**	**Liver $f_{u,liver}$ or $f_{u,cell}$**	**$f_{u,media}$**	**In Vitro[A]**	**In Vivo**	**in Vivo $K_{p,uu}$ /in Vitro $K_{p,uu}$**
Cerivastatin	261 ± 70	6717 ± 960	27 ± 8.0	27± 2.6	0.016 ± 0.001	0.017 ± 0.001	0.022 ± 0.003	21 ± 2.0	29 ± 8.5	1.4
Fluvastatin	245 ± 34	8990 ± 1490	37 ± 7.4	27± 1.8	0.011 ± 0.001	0.013 ± 0.001	0.016 ± 0.001	22 ± 1.5	44 ± 8.7	2.1
Rosuvastatin	14 ± 3.7	178 ± 50	13 ± 2.2	35 ± 0.6	0.044 ± 0.009	0.19 ± 0.02	0.19 ± 0.02	35 ± 0.6	57 ± 9.5	1.6
Pravastatin	33 ± 19	171 ± 15	6.7 ± 4.5	8.3 ± 0.8	0.54 ± 0.02	0.18 ± 0.02	0.49 ± 0.06	3.0 ± 0.3	2.2 ± 1.5	0.8
PF-04991532	172 ± 67	1170 ± 364	7.1 ± 2.0	8.9 ± 0.1	0.12 ± 0.01	0.096 ± 0.02	0.12 ± 0.01	7.1 ± 0.1	5.7 ± 1.6	0.8
PF-05187965	76 ± 21	323 ± 13	4.4 ± 1.0	10 ± 0.4	0.27 ± 0.01	0.15 ± 0.02	0.36 ± 0.01	4.2 ± 0.2	2.4 ± 0.57	0.6

A. In Vitro K_p rat hepatocytes and media with 4% BSA (Riccardi et al., 2016, 2017).

Figure S1. In Vivo effect of PPB on the total (A1 and A2) and free (A3 and A4) plasma concentration of compound D01-4582 in CD rats and SD rats. Its unbound fraction in CD rat and SD rat plasma was 0.015 and 0.26, respectively. Data is from Ito et al., 2007.





D01-4582

Figure S2: Figure S2: The distribution profiles of TFV, TFV-DP and phosphatidyl choline (PC, 16:0/OH) in colorectal tissue sections of four subjects. Research subjects (HIV-negative, men who have sex with men healthy volunteers (n=4)) received TFV enemas at two different time points (3 and 24 h) and two doses (low, 1.76 mg/mL in 125 mL and high, 5.28 mg/mL in 125 mL TFV concentrations). MALDI-MSI analysis was performed using colorectal biopsies and ion images (distribution profiles) were generated at a spatial resolution of 50 µm. TFV and TFV-DP exhibited heterogeneous distribution across colorectal tissue sections whereas the localization of phosphatidyl choline (PC, 16:0/OH) was relative homogeneous. The highest signal intensity (100%) is represented by the red color whereas blue color depicts the lowest signal (0%) of the ion of interest. Scale bar, 1 mm. These data were published recently (Seneviratne et al., 2018).

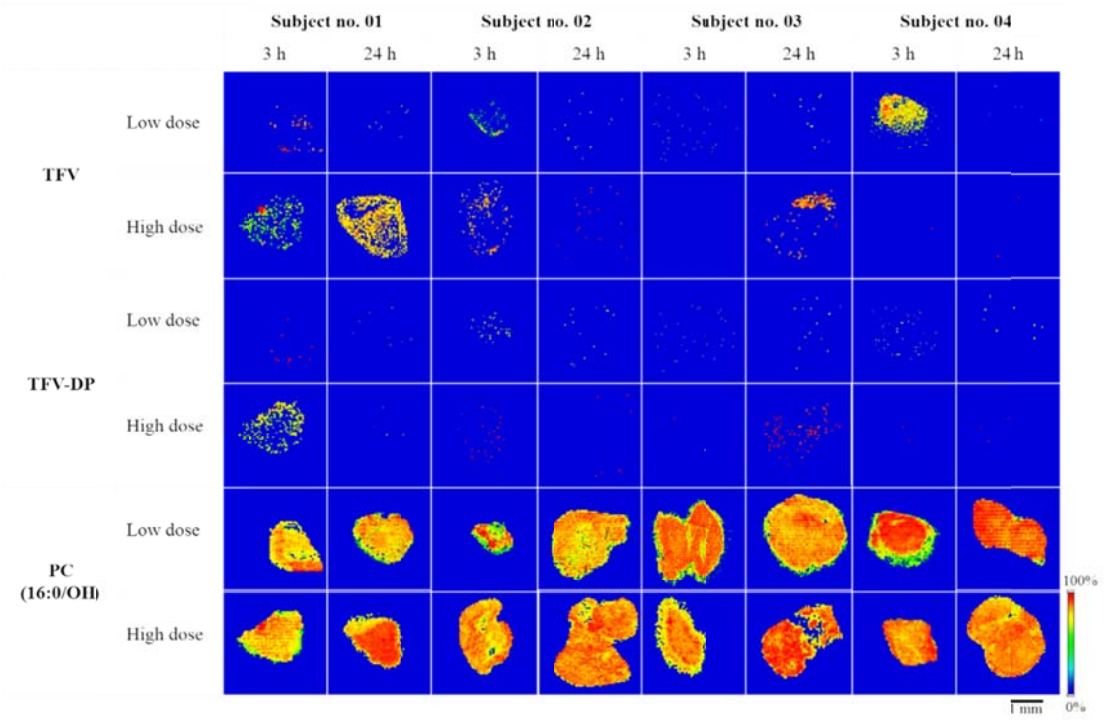


Figure S3**.** The schematic depicts multiple equilibrium processes that determine the drug distribution to the brain, the extent of drug distribution described by K_p and $K_{p,uu}$. The non-specific binding of a drug to components of plasma and brain can have a significant influence on K_p; however, $K_{p,uu}$ is not confounded by non-specific drug binding and represents the true transport equilibrium across the BBB. BBB, blood−brain barrier; K_p, brain-to-plasma ratio; $K_{p,uu}$, unbound partition coefficient; fu, unbound (free) fraction.

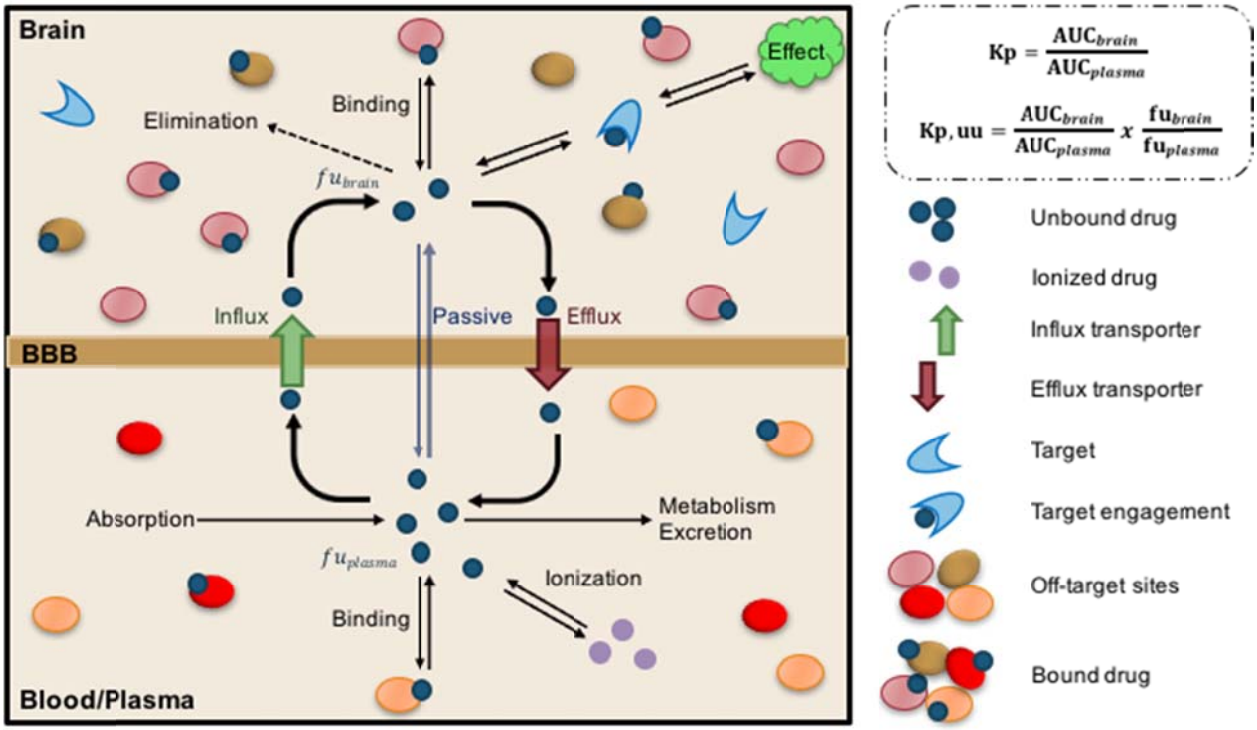
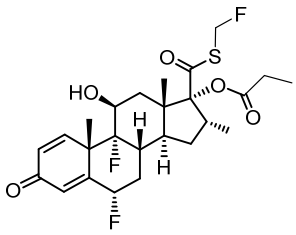
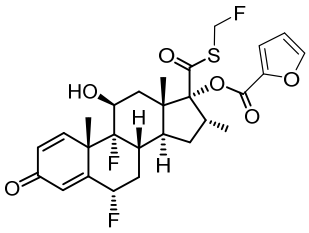


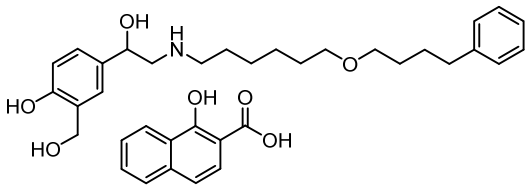
Figure S4. Structures of representative inhaled, lung targeted compounds.



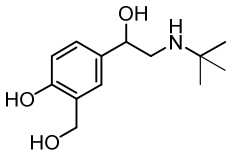
Fluticasone Propionate



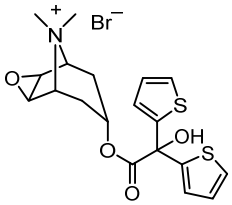
Fluticasone Furoate



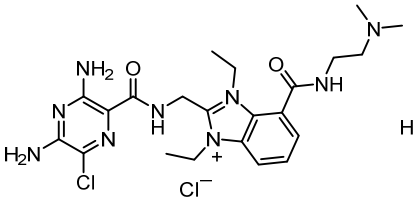
Salmeterol Xinafoate



Salbutamol



Tiotropium Bromide



Compound 3.05

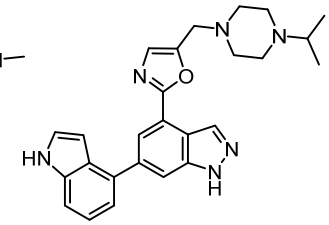


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Figure S5. Types of NPs that have been investigated as therapeutics and diagnostics