Supporting Information

Binding Mode of Human Norepinephrine Transporter Interacting with HIV-1 Tat

Charles Adeniran,[1,2,3] Yaxia Yuan,[1,2] Sarah E. Davis,[4] Ciai Lin,[4] Jiahui Xu,[4] Jun Zhu,[4] and Chang-Guo Zhan[1,2,*]

[1]*Molecular Modeling and Biopharmaceutical Center, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536.*

[2]*Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, 789 South Limestone Street, Lexington, KY 40536.*

[3]*Department of Chemistry, University of Kentucky, 505 Rose Street, Lexington, KY 40506.*

[4]*Department of Drug Discovery and Biomedical Sciences, South Carolina College of Pharmacy, University of South Carolina, Columbia, SC 29208.*

Correspondence to:
Chang-Guo Zhan, Ph.D.
Director, Molecular Modeling and Biopharmaceutical Center (MMBC)
Director, Chemoinformatics and Drug Design Core of CPRI
Endowed College of Pharmacy Professor in Pharmaceutical Sciences
Professor, Department of Pharmaceutical Sciences
College of Pharmacy
University of Kentucky
789 South Limestone Street
Lexington, KY 40536
Phone: 859-323-3943
FAX: 859-257-7585
E-mail: zhan@uky.edu

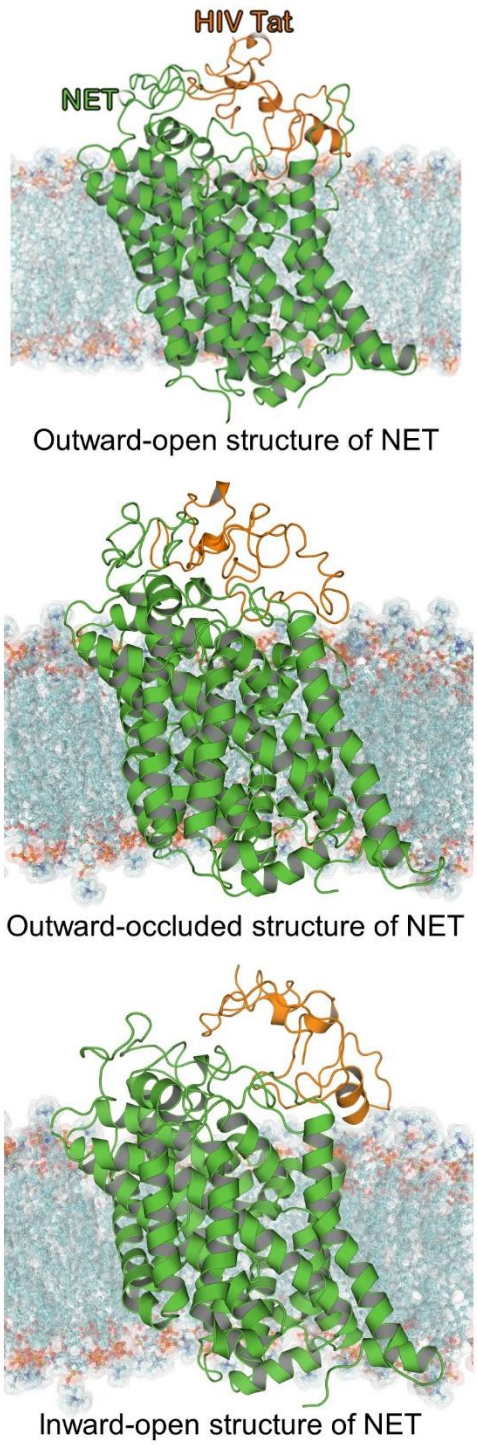

Figure S1. Docked structures of HIV-1 Tat binding with hNET in the outward-open state (upper panel), outward-occluded state (middle panel), and inward-open state (bottom panel). Using the docked binding structures, the binding energies were estimated by using the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) approach with the MMPBSA.py script[1] in

the Amber18 program. For the MM/GBSA calculations, the Generalized Born equation was solved using igb=5 and the ionic strength was set to the default 0.00 mM. The atomic radius scaling factor used in the solvation calculations was set to 1.2. For each binding system, the total binding energy was calculated as the sum of five individual components of the MM/GBSA method which includes van der Waals, electrostatic, internal, non-polar and polar solvation energy terms. As well known, the MM/GBSA calculations generally overestimate the binding affinities of protein-ligand or protein-protein binding interactions.[2,3] Nevertheless, the relative magnitudes of the calculated binding energies are reasonable.[2,3] Based on the MM/GBSA binding energy calculations, the HIV-1 Tat-hNET binding energy was -685.1431 kcal/mol for the outward-open state or -255.0876 kcal/mol for the outward-occluded state or -207.6646 kcal/mol for the inward-open state, suggesting that HIV-1 Tat most favorably bind with the outward-open structure of hNET.

References

1. Kollman, P. A.; Massova, I.; Reyes, C.; Kuhn, B.; Huo, S.; Chong, L.; Lee, M.; Lee, T.; Duan, Y.; Wang, W.et al., Calculating Structures and Free Energies of Complex Molecules: Combining Molecular Mechanics and Continuum Models. *Accounts of Chemical Research* **2000,** *33* (12), 889-897.

2. Yang, J.-F.; Williams, A. H.; Penthala, N. R.; Prather, P. L.; Crooks, P. A.; Zhan, C.-G., Binding Modes and Selectivity of Cannabinoid 1 (CB1) and Cannabinoid 2 (CB2) Receptor Ligands. *ACS Chemical Neuroscience* **2020,** *11* (20), 3455-3463.

3. Zheng, F.; Chen, X.; Kim, K.; Zhang, T.; Huang, H.; Zhou, S.; Zhang, J.; Jin, Z.; Zhan, C.-G., Structure-Based Design and Discovery of a Long-Acting Cocaine Hydrolase Mutant with Improved Binding Affinity to Neonatal Fc Receptor for Treatment of Cocaine Abuse. *The AAPS Journal* **2020,** *22* (3), 62.