

Supporting Information

Pain Chemogenomics Knowledgebase (Pain-CKB) for Systems Pharmacology Target Mapping and PBPK Modeling Investigation of Opioid Drug-Drug Interactions

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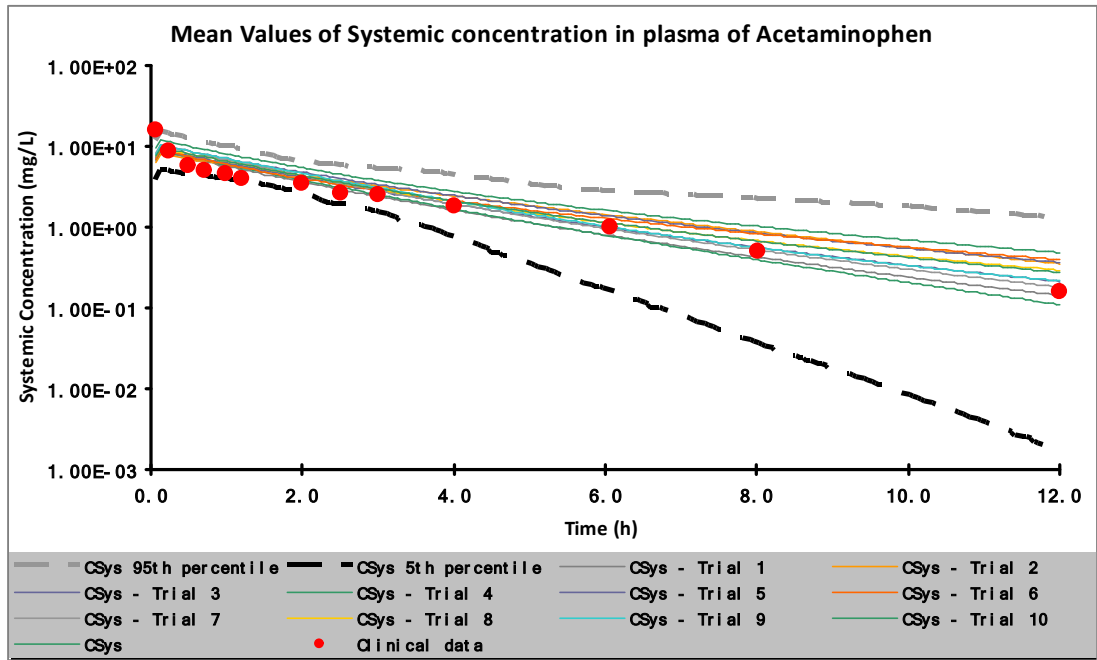


Figure S1. Observed and simulated concentration–time profiles of acetaminophen 650 mg iv infusion over 5 min. The simulated results were generated using 10 trials of 10 virtual healthy volunteers. Observed data¹ were highlighted in red dots while the simulated results, mean value, and the 95th/5th percentile of the simulation were shown by corresponding lines.

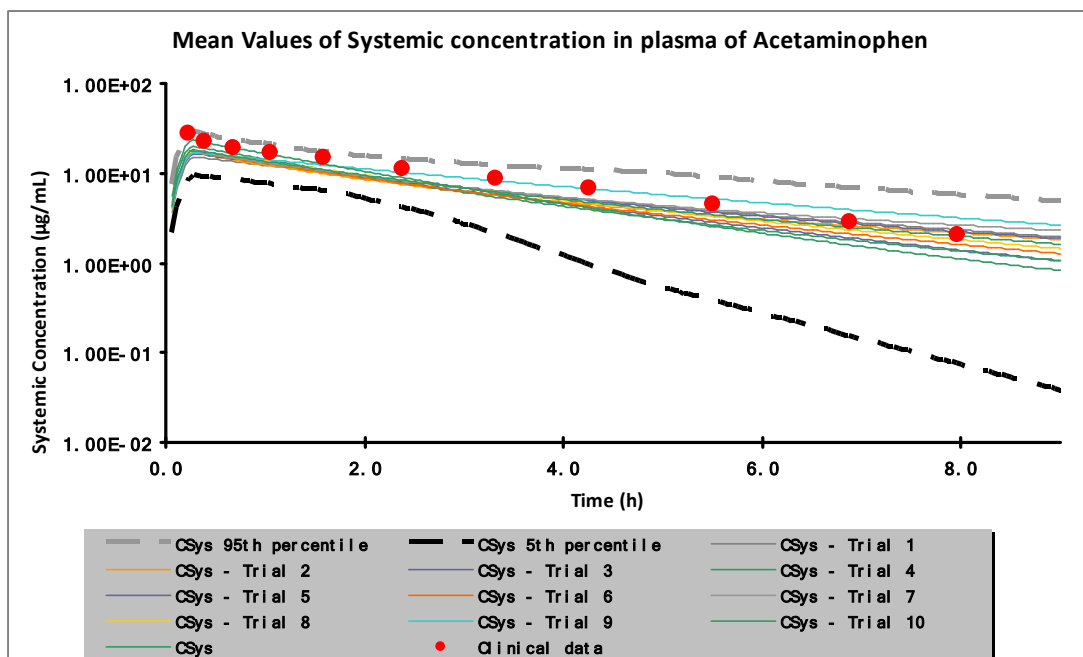


Figure S2. Observed and simulated concentration–time profiles of acetaminophen 1000 mg iv infusion over 15 min. The simulated results were generated using 10 trials of 10 virtual healthy Japanese volunteers. Observed data² were highlighted in red dots while the simulated results, mean value, and the 95th/5th percentile of the simulation were shown by corresponding lines.

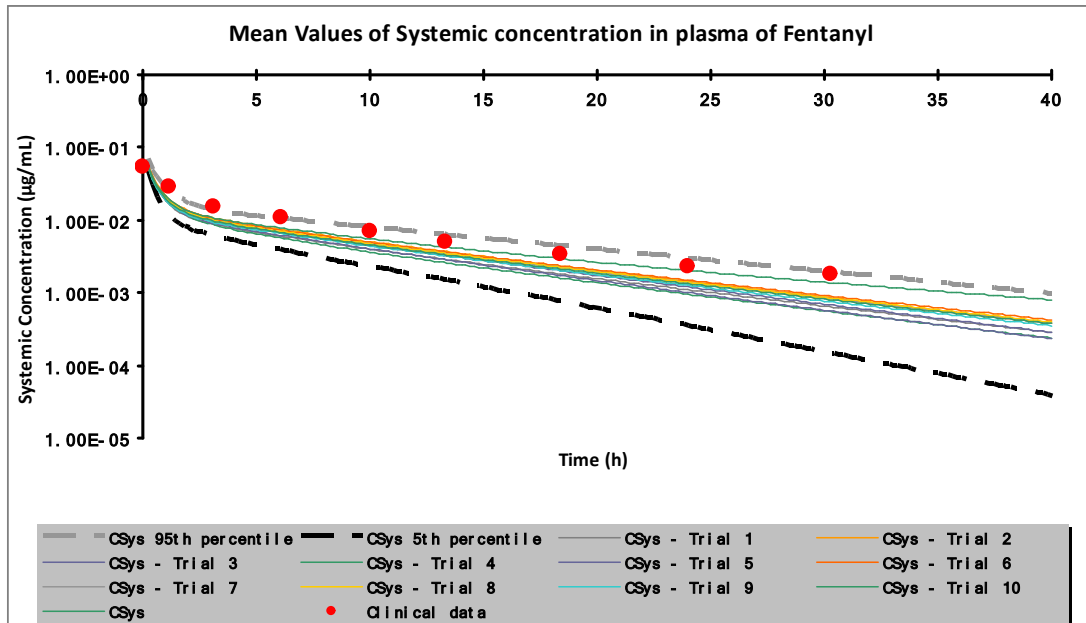


Figure S3. Observed and simulated concentration–time profiles of fentanyl 100 µg/kg iv bolus. The simulated results were generated using 10 trials of 10 virtual healthy volunteers. Observed data³ were highlighted in red dots while the simulated results, mean value, and the 95th/5th percentile of the simulation were shown by corresponding lines.

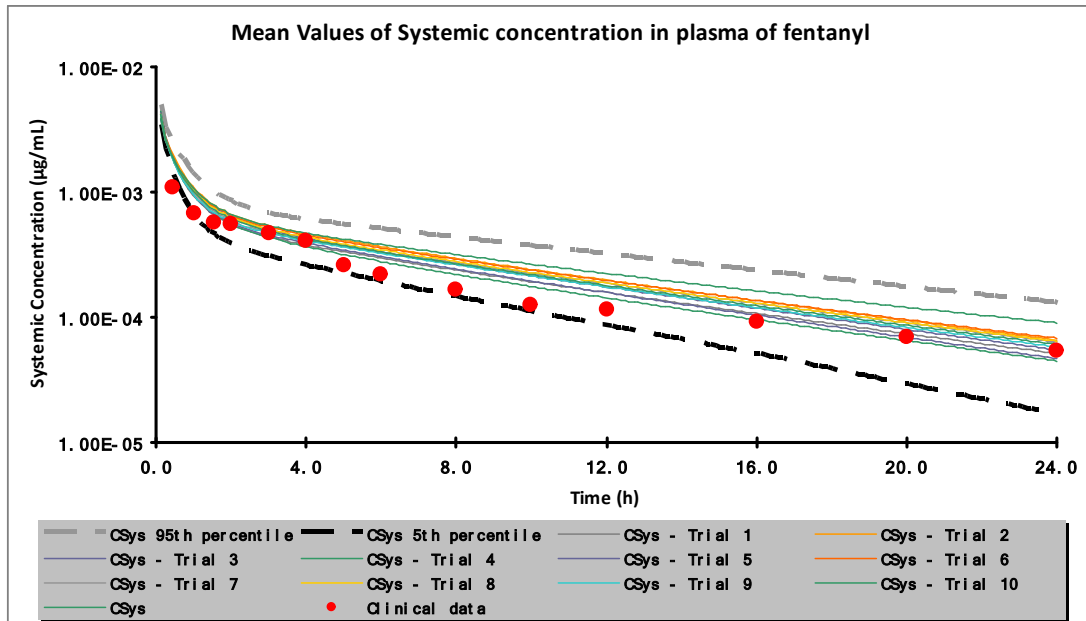


Figure S4. Observed and simulated concentration–time profiles of fentanyl 5 µg/kg iv bolus. The simulated results were generated using 10 trials of 10 virtual healthy volunteers. Observed data⁴ were highlighted in red dots while the simulated results, mean value, and the 95th/5th percentile of the simulation were shown by corresponding lines.

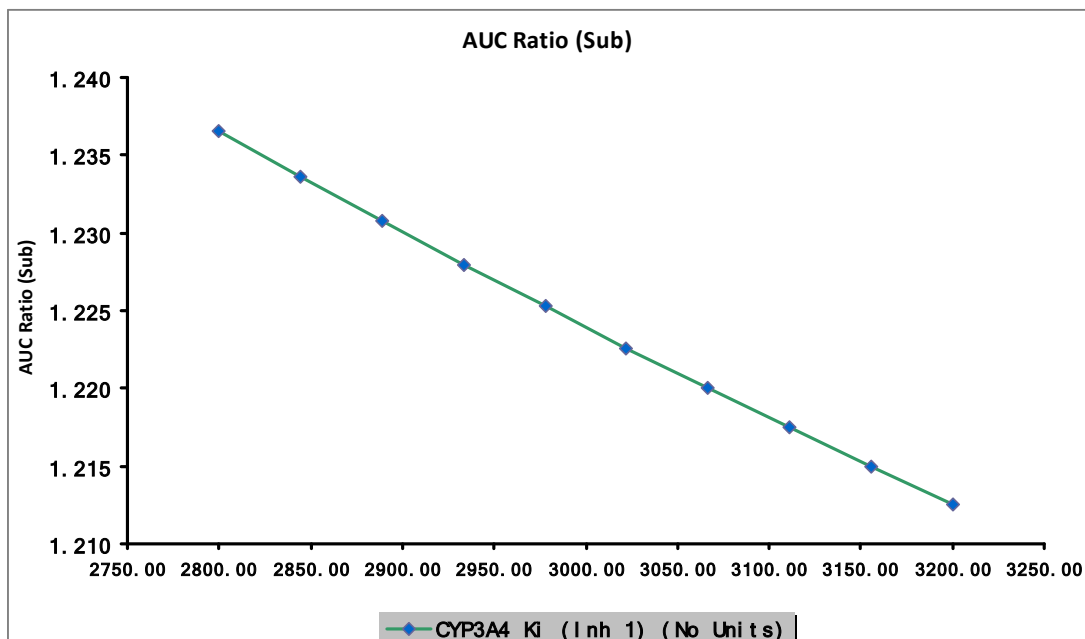
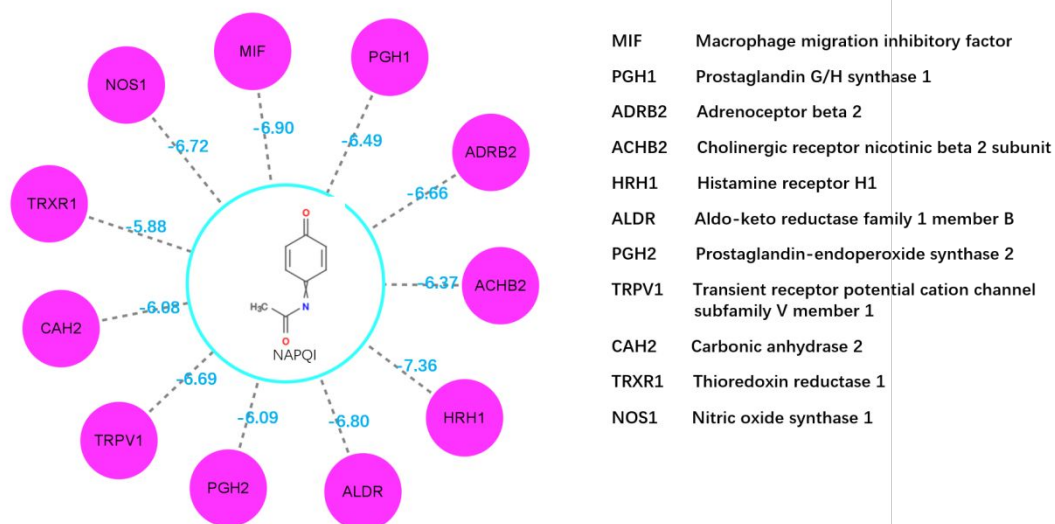


Figure S5. The AUC Ratio of fentanyl with acetaminophen when Ki value is ranged in 2800-3200 μM . The dosage of fentanyl and acetaminophen (inhibition substrate) is 0.003 mg/kg and 80000 mg.



MIF	Macrophage migration inhibitory factor
PGH1	Prostaglandin G/H synthase 1
ADRB2	Adrenoceptor beta 2
ACHB2	Cholinergic receptor nicotinic beta 2 subunit
HRH1	Histamine receptor H1
ALDR	Aldo-keto reductase family 1 member B
PGH2	Prostaglandin-endoperoxide synthase 2
TRPV1	Transient receptor potential cation channel subfamily V member 1
CAH2	Carbonic anhydrase 2
TRXR1	Thioredoxin reductase 1
NOS1	Nitric oxide synthase 1

Figure S6. Computational systems pharmacology-target mapping (CSP-Target Mapping) for NAPQI. The purple dots and dashed lines represent the predicted targets and interaction. Our algorithm predicted NAPQI may bind to TrxR.

References

1. Scavone, J. M., Greenblatt, D. J., Blyden, G. T., Luna, B. G., and Harmatz, J. S. (1990) Validity of a Two-Point Acetaminophen Pharmacokinetic Study, *Ther. Drug Monit.* 12, 35-39.
2. Imaizumi, T., Obara, S., Mogami, M., Iseki, Y., Hasegawa, M., and Murakawa, M. (2017) Population pharmacokinetics of intravenous acetaminophen in Japanese patients undergoing elective surgery, *J. Anesth.* 31, 1-9.
3. Brusset, A., Levron, D. J. C., Olivier, P., Schlumberger, S., Moing, J. P. L., Dubois, C., Guilmet, D., Valide, L., Guenoun, T., and Fischler, M. (1999) Comparative Pharmacokinetic Study of Fentanyl and Sufentanil after Single High-Bolus Doses, *Clin. Drug Invest.* 18, 377-389.
4. Saari, T. I., Laine, K., Neuvonen, M., Neuvonen, P. J., and Olkkola, K. T. (2008) Effect of voriconazole and fluconazole on the pharmacokinetics of intravenous fentanyl, *Eur. J. Clin. Pharmacol.* 64, 25-30.