Supporting Information

Deep Docking: A Deep Learning Platform for Augmentation of Structure Based Drug Discovery

Francesco Gentile[†,‡], Vibudh Agrawal[†,‡], Michael Hsing[†], Anh-Tien Ton[†], Fuqiang Ban[†], Ulf Norinder[▽,‖], Martin E. Gleave[†], Artem Cherkasov[†,*]

[†]*Vancouver Prostate Centre, University of British Columbia, Vancouver, British Columbia, V6H3Z6, Canada*

[▽]*Swetox, Unit of Toxicology Sciences, Karolinska Institutet, Forskargatan 20, SE-151 36 Södertalje, Sweden*

[‖]*Department of Computer and Systems Sciences, Stockholm University, Box 7003, SE-164 07 Kista, Sweden*

[*]acherkasov@prostatecentre.com

Table of Contents

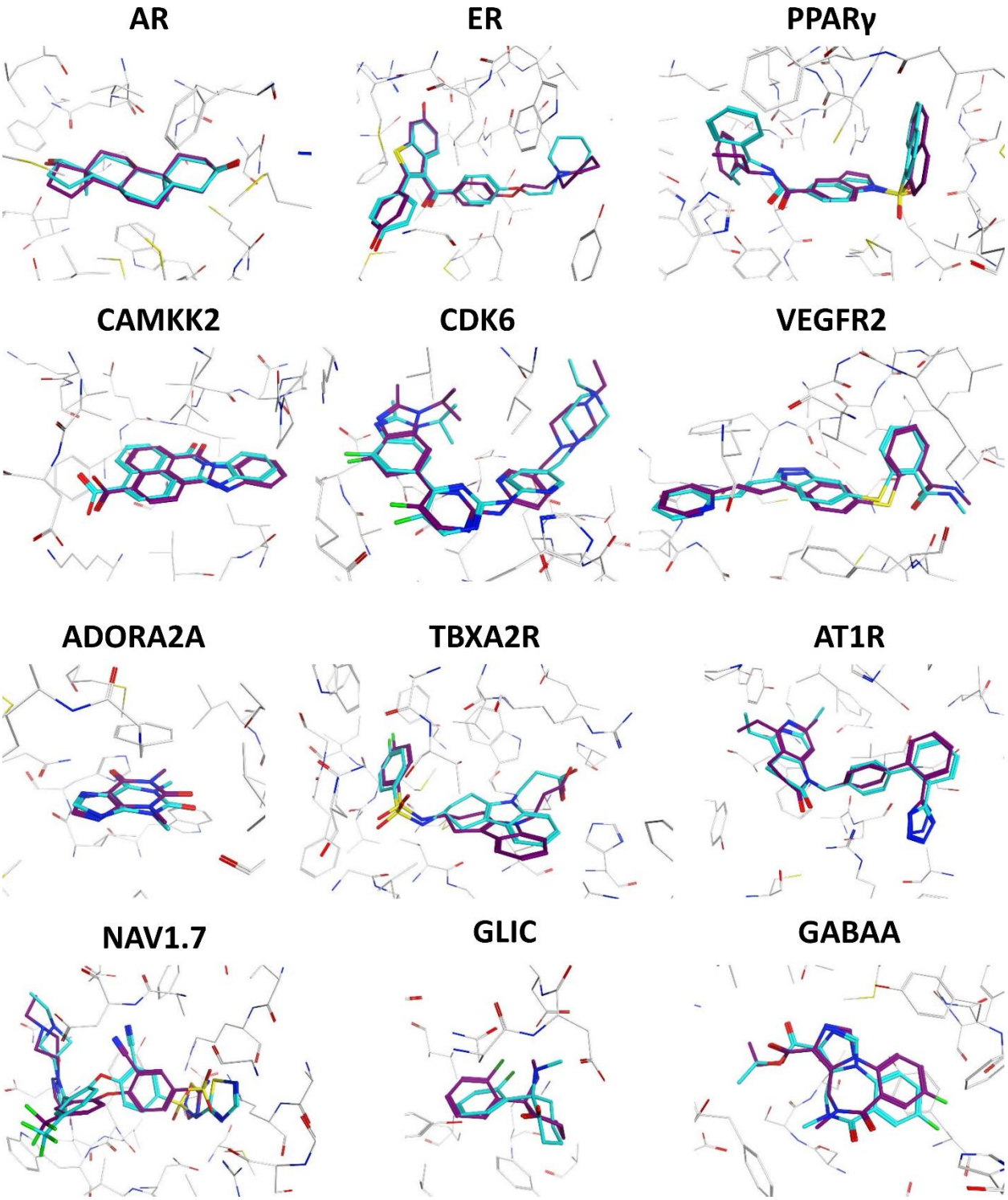

Figure S1. Results of FRED docking of native ligands to their receptor structures. Superposition of x-ray binding poses (cyan carbons) and docking poses (purple carbons) of the ligands for the 12 investigated systems.

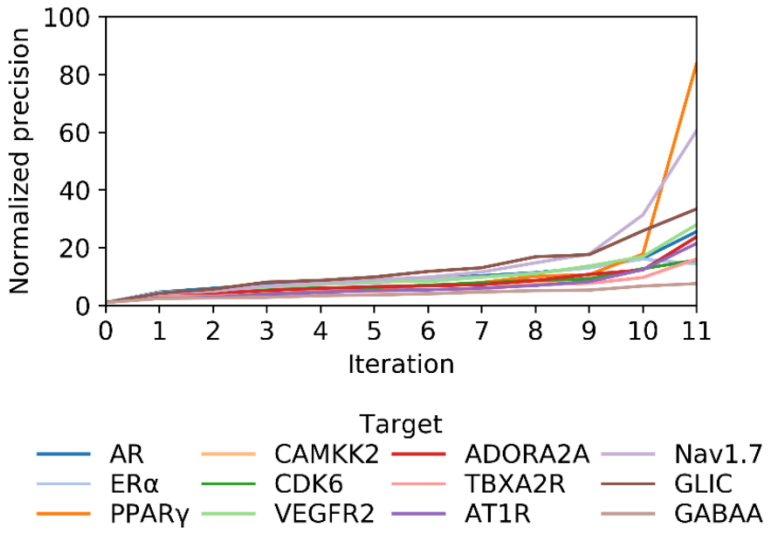

Figure S2. Normalized precision of *DD* models for molecules scoring below the score cutoff of the last iteration in random 1 million molecules sampled at each iteration. Values are normalized by dividing them by initial values (percentages of virtual hits in the entire ZINC15 database, random precisions).

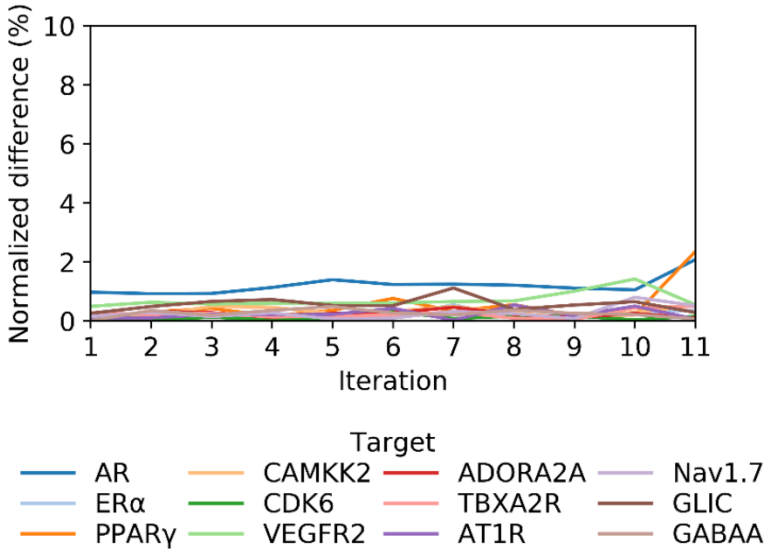

Figure S3. Normalized differences between number of *DD* hits inferred from the test set and obtained by applying *DD* models to ZINC15, calculated as $\frac{|hits_{test} - hits_{real}|}{\min(hits_{test}, hits_{real})} \cdot 100$

Table S1. Protein targets selected for evaluating *DD*.

Family	Target	Ligand	PDB	Resolution (Å)	Therapeutic Significance
Nuclear receptors	AR	Dihydrotestosterone	1T7R[1]	1.40	Prostate Cancer[2]
	ERα	Raloxifene	1ERR[3]	2.60	Breast cancer, osteoporosis, menopausal symptoms[2]
	PPARγ	SR-2067	4R06[4]	2.22	Diabetes[2]
Kinases	CAMKK2	STO-609	2ZV2[5]	2.40	Prostate cancer, metabolic hepatic diseases[5-6]
	CDK6	Abemaciclib	5L2S[7]	2.27	Breast cancer[8]
	VEGFR2	Axitinib	4AG8[9]	1.95	Multiple cancer types[8]
G protein-coupled receptors	ADORA2A	Theophylline	5MZJ[10]	2.00	Myocardial perfusion imaging, inflammation, neuropathic pain, Parkinson's disease[11]
	TBXA2R	Ramatroban	6IIU[12]	2.50	Cardiovascular diseases, asthma[13]
	AT1R	ZD-7155	4YAY[14]	2.90	Hypertension[15]
Ion channels	Nav1.7	GX-936	5EK0[16]	3.53	Pain[17]
	GLIC	Anesthetic ketamine	4F8H[18]	2.99	General anesthetics[18]
	GABAA	Flumazenil	6D6T[19]	3.86	Benzodiazepine overdose[19]

Table S2. Number of active ligands for each target, obtained from DUD-E.

Target	Active ligands
AR	1,084
ERα	1,314
PPARγ	1,290
VEGFR2	2,319
ADORA2A	3,095

Supplementary references

1. Hur, E.; Pfaff, S. J.; Payne, E. S.; Grøn, H.; Buehrer, B. M.; Fletterick, R. J., Recognition and accommodation at the androgen receptor coactivator binding interface. *PLoS biology* **2004,** *2* (9), e274.
2. Moore, J. T.; Collins, J. L.; Pearce, K. H., The nuclear receptor superfamily and drug discovery. *ChemMedChem: Chemistry Enabling Drug Discovery* **2006,** *1* (5), 504-523.
3. Brzozowski, A. M.; Pike, A. C.; Dauter, Z.; Hubbard, R. E.; Bonn, T.; Engström, O.; Öhman, L.; Greene, G. L.; Gustafsson, J.-Å.; Carlquist, M., Molecular basis of agonism and antagonism in the oestrogen receptor. *Nature* **1997,** *389* (6652), 753.
4. van Marrewijk, L. M.; Polyak, S. W.; Hijnen, M.; Kuruvilla, D.; Chang, M. R.; Shin, Y.; Kamenecka, T. M.; Griffin, P. R.; Bruning, J. B., SR2067 Reveals a Unique Kinetic and Structural Signature for PPARgamma Partial Agonism. *ACS Chem Biol* **2016,** *11* (1), 273-83.
5. Kukimoto-Niino, M.; Yoshikawa, S.; Takagi, T.; Ohsawa, N.; Tomabechi, Y.; Terada, T.; Shirouzu, M.; Suzuki, A.; Lee, S.; Yamauchi, T., Crystal structure of the Ca2+/calmodulin-dependent protein kinase kinase in complex with the inhibitor STO-609. *Journal of Biological Chemistry* **2011,** *286* (25), 22570-22579.
6. Penfold, L.; Woods, A.; Muckett, P.; Nikitin, A. Y.; Kent, T. R.; Zhang, S.; Graham, R.; Pollard, A.; Carling, D., CAMKK2 promotes prostate cancer independently of AMPK via increased lipogenesis. *Cancer research* **2018,** *78* (24), 6747-6761.
7. Chen, P.; Lee, N. V.; Hu, W.; Xu, M.; Ferre, R. A.; Lam, H.; Bergqvist, S.; Solowiej, J.; Diehl, W.; He, Y.-A., Spectrum and degree of CDK drug interactions predicts clinical performance. *Molecular cancer therapeutics* **2016,** *15* (10), 2273-2281.
8. Roskoski, R., Properties of FDA-approved small molecule protein kinase inhibitors. *Pharmacological research* **2019**.
9. McTigue, M.; Murray, B. W.; Chen, J. H.; Deng, Y.-L.; Solowiej, J.; Kania, R. S., Molecular conformations, interactions, and properties associated with drug efficiency and clinical performance among VEGFR TK inhibitors. *Proceedings of the National Academy of Sciences* **2012,** *109* (45), 18281-18289.
10. Cheng, R. K.; Segala, E.; Robertson, N.; Deflorian, F.; Doré, A. S.; Errey, J. C.; Fiez-Vandal, C.; Marshall, F. H.; Cooke, R. M., Structures of human A1 and A2A adenosine receptors with xanthines reveal determinants of selectivity. *Structure* **2017,** *25* (8), 1275-1285. e4.
11. de Lera Ruiz, M.; Lim, Y.-H.; Zheng, J., Adenosine A2A receptor as a drug discovery target. *Journal of medicinal chemistry* **2013,** *57* (9), 3623-3650.
12. Fan, H.; Chen, S.; Yuan, X.; Han, S.; Zhang, H.; Xia, W.; Xu, Y.; Zhao, Q.; Wu, B., Structural basis for ligand recognition of the human thromboxane A 2 receptor. *Nature chemical biology* **2019,** *15* (1), 27.
13. Hirata, T.; Narumiya, S., Prostanoid receptors. *Chemical reviews* **2011,** *111* (10), 6209-6230.
14. Zhang, H.; Unal, H.; Gati, C.; Han, G. W.; Liu, W.; Zatsepin, N. A.; James, D.; Wang, D.; Nelson, G.; Weierstall, U.; Sawaya, M. R.; Xu, Q.; Messerschmidt, M.; Williams, G. J.; Boutet, S.; Yefanov, O. M.; White, T. A.; Wang, C.; Ishchenko, A.; Tirupula, K. C.; Desnoyer, R.; Coe, J.; Conrad, C. E.; Fromme, P.; Stevens, R. C.; Katritch, V.; Karnik, S. S.; Cherezov, V., Structure of the Angiotensin receptor revealed by serial femtosecond crystallography. *Cell* **2015,** *161* (4), 833-44.
15. Dasgupta, C.; Zhang, L., Angiotensin II receptors and drug discovery in cardiovascular disease. *Drug discovery today* **2011,** *16* (1-2), 22-34.
16. Ahuja, S.; Mukund, S.; Deng, L.; Khakh, K.; Chang, E.; Ho, H.; Shriver, S.; Young, C.; Lin, S.; Johnson, J., Structural basis of Nav1. 7 inhibition by an isoform-selective small-molecule antagonist. *Science* **2015,** *350* (6267), aac5464.
17. Vetter, I.; Deuis, J. R.; Mueller, A.; Israel, M. R.; Starobova, H.; Zhang, A.; Rash, L. D.; Mobli, M., NaV1. 7 as a pain target–from gene to pharmacology. *Pharmacology & therapeutics* **2017,** *172*, 73-100.
18. Pan, J.; Chen, Q.; Willenbring, D.; Mowrey, D.; Kong, X.-P.; Cohen, A.; Divito, C. B.; Xu, Y.; Tang, P., Structure of the pentameric ligand-gated ion channel GLIC bound with anesthetic ketamine. *Structure* **2012,** *20* (9), 1463-1469.
19. Zhu, S.; Noviello, C. M.; Teng, J.; Walsh, R. M., Jr.; Kim, J. J.; Hibbs, R. E., Structure of a human synaptic GABAA receptor. *Nature* **2018,** *559* (7712), 67-72.