GPT2 (Alanine aminotransferase 2) computational docking - Phase 2

Docking of natural ligands (PLP and L-alanine) vs. Docking of drugs

Residues binding to natural substrates	Residues binding to Hydroxychloroquine	Residues binding to Remdesivir	Residues binding to Dexamethasone	Residues binding to Favipiravir	Residues involved in protein-protein interaction downstream
SER188	ARG170	ARG169	ARG169	GLY342	**TYR349**
ARG350	ARG169	GLU407	TYR343	SER340	**ARG110**
LYS341	GLN303	TYR166		**LYS341**	**GLY345**
ARG312	**ARG312**	GLN303		**ASN94**	**ASN94**
PHE313		**PHE313**		TYR440 (pi-pi)	**GLN80**
ASP304		**ASP304**	**ASP304**	LEU498 (pi-alkyl)	**CYS347**
VAL306	**VAL306**	**VAL306**	**VAL306**	MET439 (pi-alkyl)	**ARG81**
ARG313		LYS406			**ASN412**
		PHE402			

We see that every drug has at least 1 amino acid common with the binding site of the ligand, thus we hypothesise that every drug will impede the natural functioning of the protein.

SPACER analysis for allosteric interactions was thus not performed.

COMMON PROTEINS IN TWO DATABASES - STRING and BIOGRID

GOT1 - A co-fractionation experiment showed the proteins as complexed (Wan C. 2015)

Other likely candidates

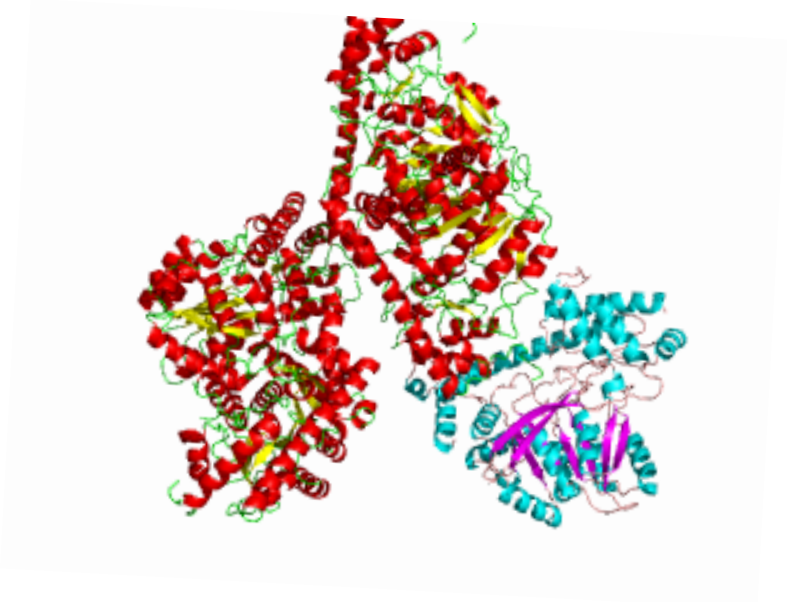
AGX1 - Determined by genetic interference assay that both proteins interact, Study was done in yeast, not humans.

(Multiple knockout analysis of genetic robustness in the yeast metabolic network.
Deutscher D, Meilijson I, Kupiec M, Ruppin E
Nat Genet. 38(9):993-8 (2006).)

No protein-protein docking studies found

Protein-protein docking to be done between GPT2 and GOT1

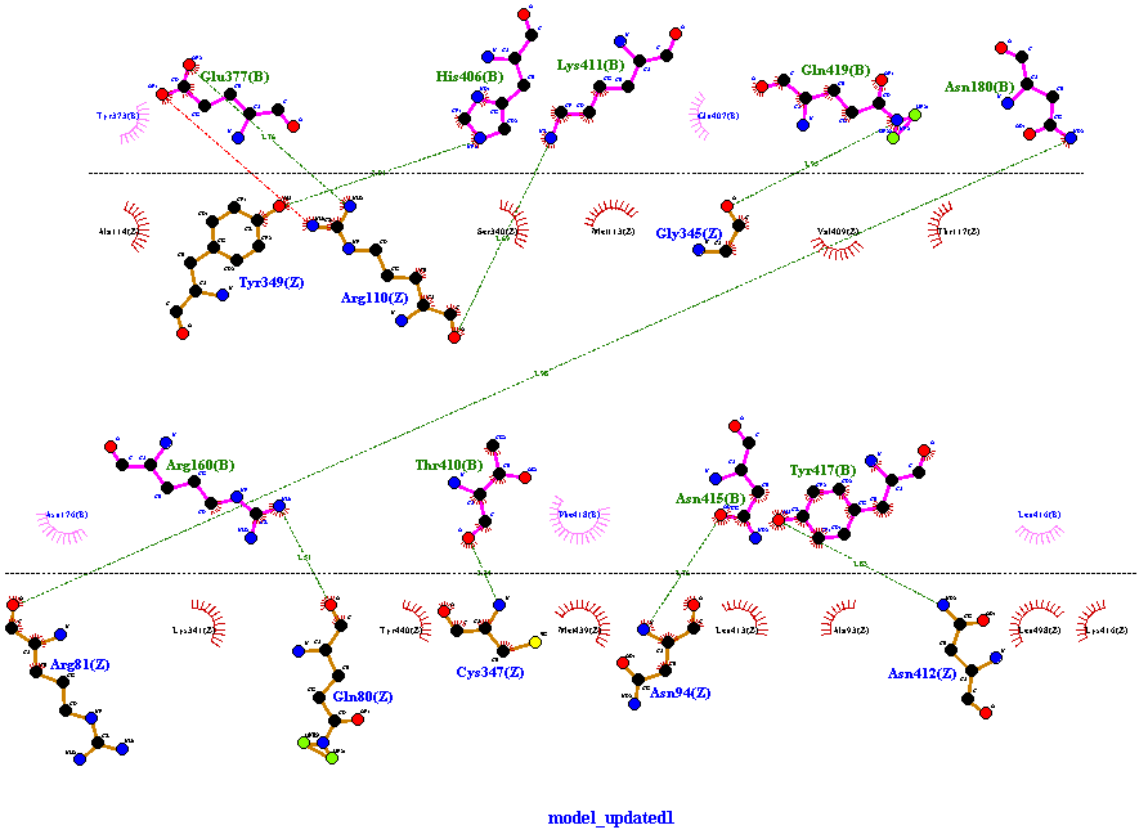
GPT2 - Alanine aminotransferase 2
GOT1 - Aspartate aminotransferase
Docking done by ClusPro 2.0



Docking model 1 - GPT2 in cyan and magenta, GOT1 in red and yellow

DOCKING SCORES

Cluster	Members	Representative	Weighted Score
0	46	Center	-772.3
		Lowest Energy	-864.0
1	29	Center	-714.2
		Lowest Energy	-863.5
2	28	Center	-735.9
		Lowest Energy	-813.8
3	26	Center	-716.6
		Lowest Energy	-864.9
4	23	Center	-778.8
		Lowest Energy	-826.0
5	20	Center	-778.7
		Lowest Energy	-873.7
6	20	Center	-815.4
		Lowest Energy	-860.8
7	20	Center	-777.1
		Lowest Energy	-777.1
8	20	Center	-734.7
		Lowest Energy	-768.7
9	19	Center	-810.2
		Lowest Energy	-810.2

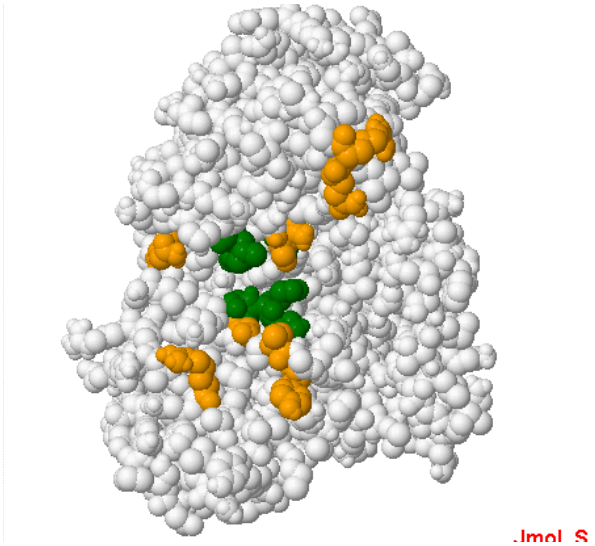


2D Interaction map for pose 0 (here, Z is GPT2 and B is a chain of GOT1)

No.	Residue
1	TYR349
2	ARG110
3	GLY345
4	ARG81
5	GLN80
6	CYS347
7	ASN94
8	ASN412

Residues of alanine aminotransferase interacting in the protein protein complex

SPACER Allostery Analysis of protein



Favipiravir binding site (in green) and GOT1 protein binding site in Orange

A D-PQ matric was made, and the following data was retrieved.

Drug	Interaction score with GOT-1 binding site
Favipiravir	0.4
Dexamethasone	0.25
Hydroxychloroquine	0.24
Remdesivir	0.24

References (for using ClusPro 2.0) -

Vajda S, Yueh C, Beglov D, Bohnuud T, Mottarella SE, Xia B, Hall DR, Kozakov D. New additions to the ClusPro server motivated by CAPRI. *Proteins: Structure, Function, and Bioinformatics.* 2017 Mar; 85(3):435-444. pdf

Kozakov D, Hall DR, Xia B, Porter KA, Padhorny D, Yueh C, Beglov D, Vajda S. The ClusPro web server for protein-protein docking. *Nature Protocols.* 2017 Feb;12(2):255-278. pdf

Kozakov D, Beglov D, Bohnuud T, Mottarella S, Xia B, Hall DR, Vajda, S. How good is automated protein docking? *Proteins: Structure, Function, and Bioinformatics.* 2013 Dec; 81(12):2159-66. Pdf

(For using SPACER)

1. **Mitternacht S, Berezovsky IN (2011) Coherent conformational degrees of freedom as a structural basis for allosteric communication. PLoS Comput Biol 7: e1002301.**

Other servers used -

1. **LIGPLOT**
2. **Discovery Studio**
3. **SPRING database**
4. **BIOGRID database**