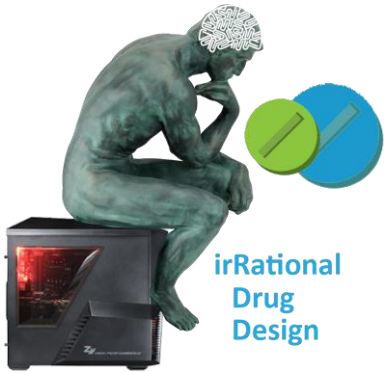
Laboratory of Rational Drug-Design

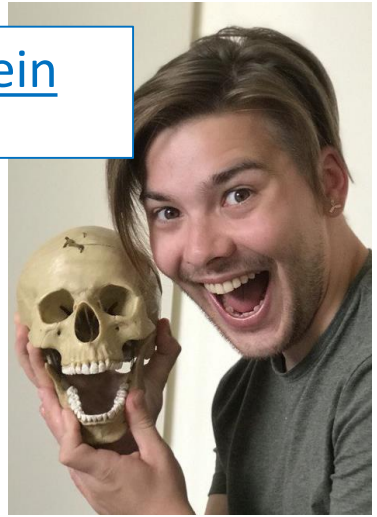


…or

How to make drugs online (fast)

Polina Avdiunina
Lomonosov MSU

Ilya Mazein
SPBSU



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Institute of Science and Technology (IST) Austria

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“Application” of the RationalDrugDesign Lab:

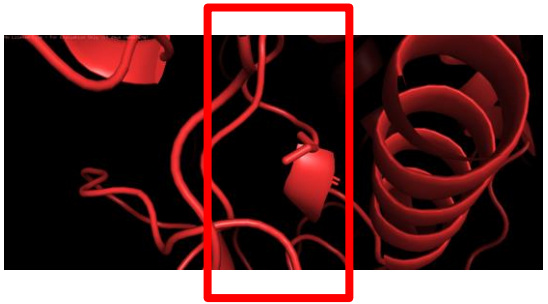
Several proteins, where mutations change interaction with low-molecular compounds, will be selected as "targets" to investigate...

- ...how the course of biochemical processes would change, if there were modifications in the encoding genes ?

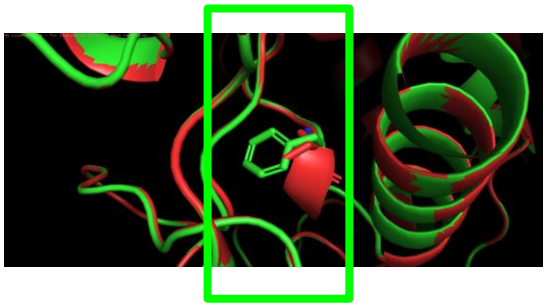
- ...how the "external pressure" (e.g. when cancer develops , the variants that accelerate the growth of the tumor and reduce the "feedback" of cancer cells to the immune response\medications are fixed) influences the accumulation of these changes ?

Mutations in binding sites can dramatically change protein-ligand interactions

MPO p.Ser406Phe (PDB id 5QJ3)



Δaff prot+lig = 3.7 kcal/mol



We can:

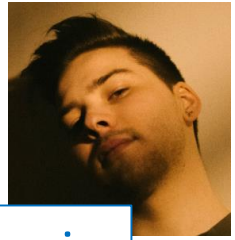
- estimate the binding energy of the protein-ligand complex (ΔG_native) using computational methods (molecular docking)
- predict the structure of an altered protein for each mutation in the active site
- re-estimate the binding energy of the protein-ligand complex for the mutant structure (ΔG_mutant)
- compare the binding energies of the ligand "before" and "after" mutation (ΔGG_native_vs_mutant) - to evaluate the mutation effect

Gene statistics
by cancer/ non-cancer substitutions

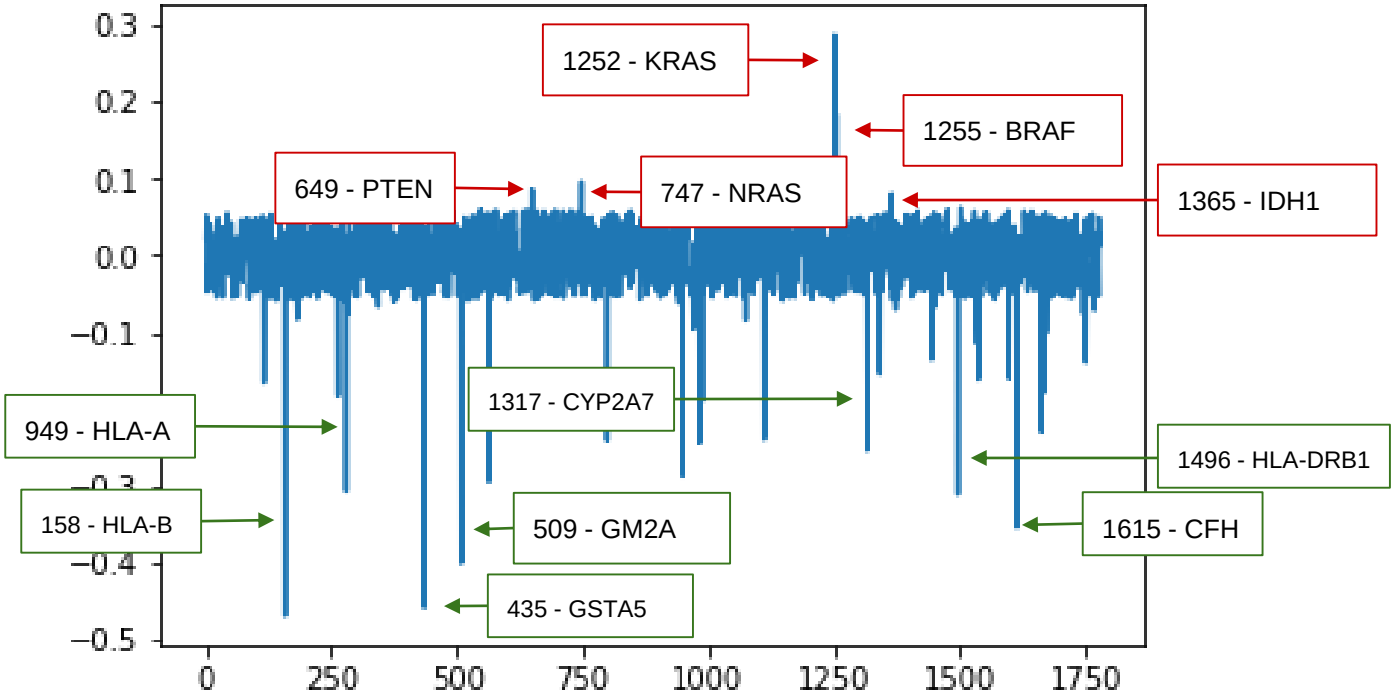
Polina Avdjunina

	cancer_mut	ancer_partner	noncancer_mut	oncancer_partner	cancer_ratio1	noncancer_ratio1	Entry	Entry name
ENSG00000000003	0	0	0	0	0	0	O43657	TSN6_HUMAN
ENSG00000000005	0	0	0	0	0	0	Q9H2S6	TNMD_HUMAN
ENSG00000000419	0	0	0	0	0	0	O60762	DPM1_HUMAN
ENSG00000000457	0	0	0	0	0	0	Q8IZE3	PACE1_HUMAN
ENSG00000000460	0	0	0	0	0	0	Q9NSG2	CA112_HUMAN
ENSG00000000938	0	67	0	52	0	0	P09769	FGR_HUMAN
ENSG00000000971	6	6	2282	1	0.002621231979	0.996941896	P08603	CFAH_HUMAN
ENSG00000001036	0	26	0	79	0	0	Q9BTY2	FUCO2_HUMAN

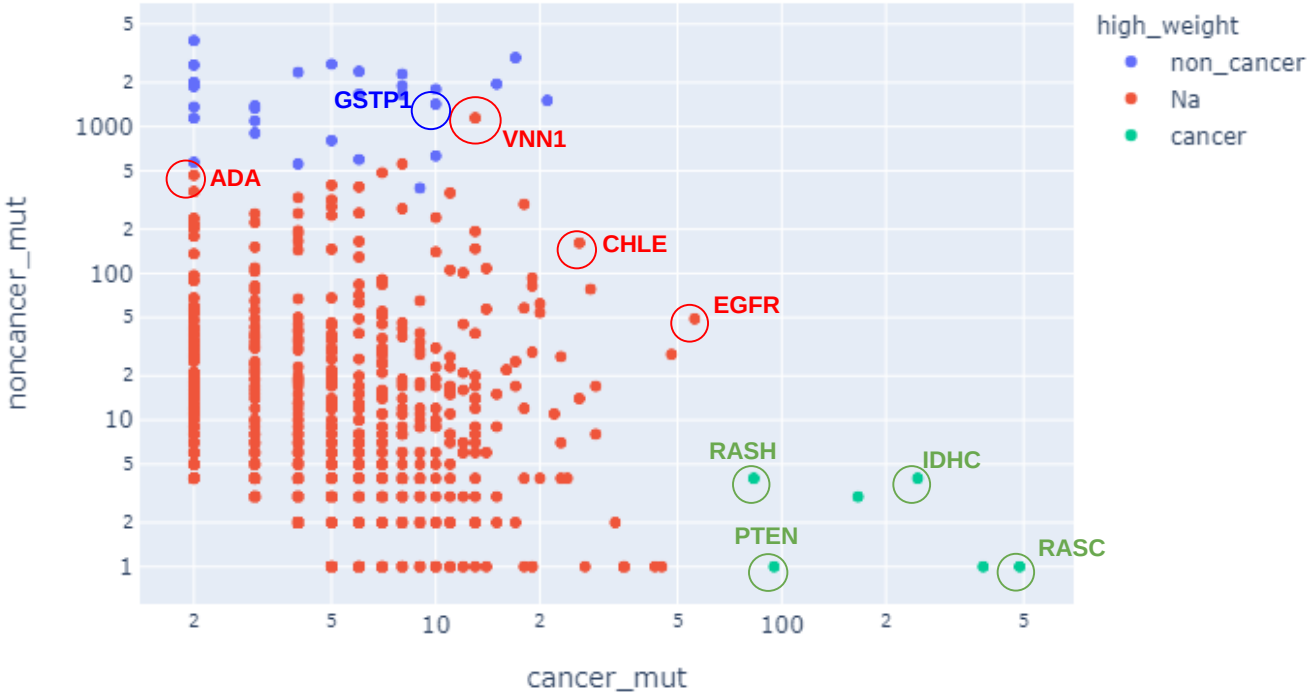
Results of “weighing” genes and mutations in cancer/ non-cancer using a neural network



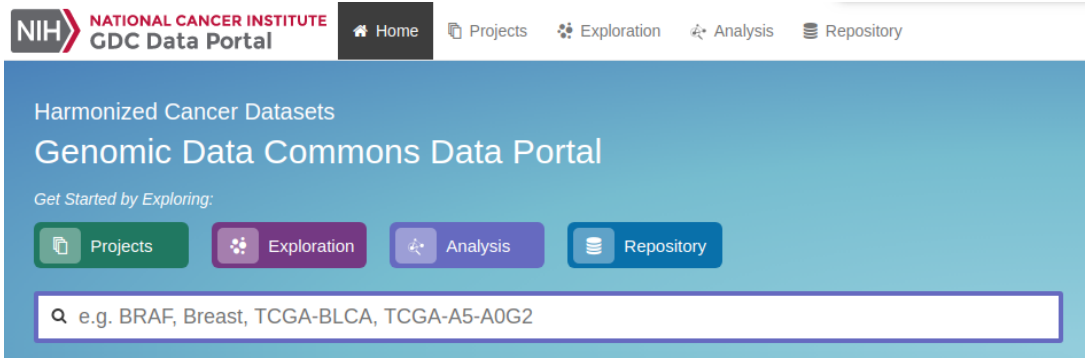
Ilya Mazein



Cancer and noncancer mutation ratio in proteins (potential targets are labeled)



Expression data

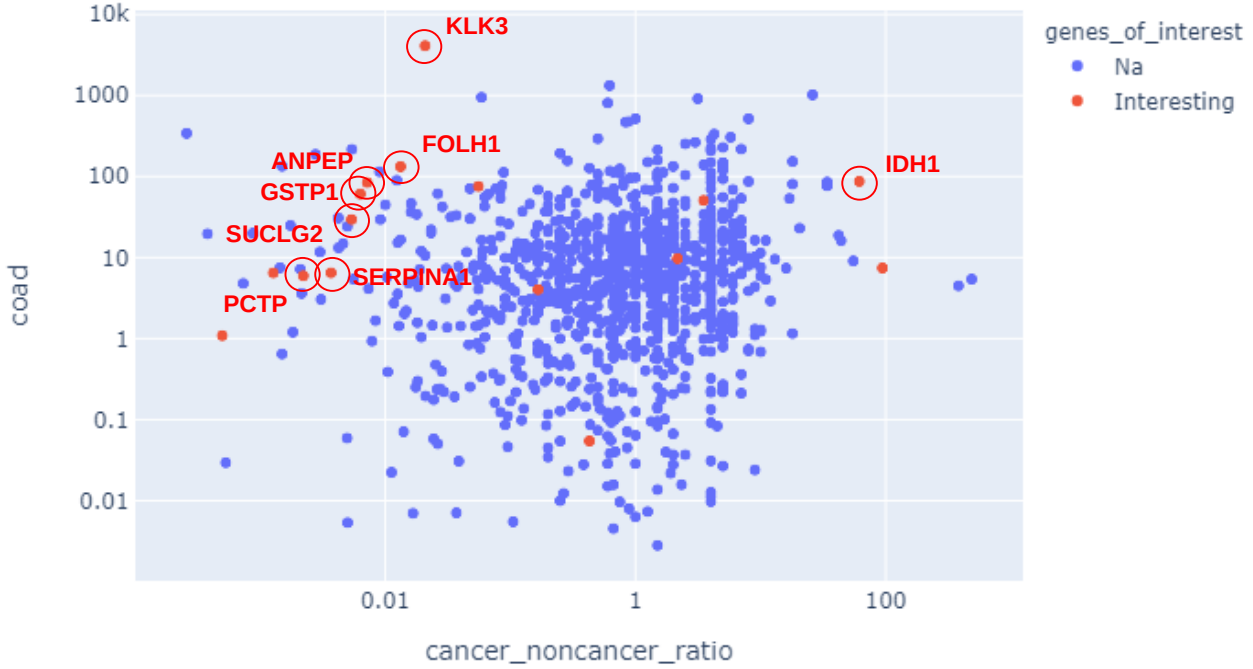


LAML - Acute Myeloid Leukemia
COAD - Colon adenocarcinoma
SARC - Sarcoma
BRCA - Breast invasive carcinoma
STAD - Stomach adenocarcinoma

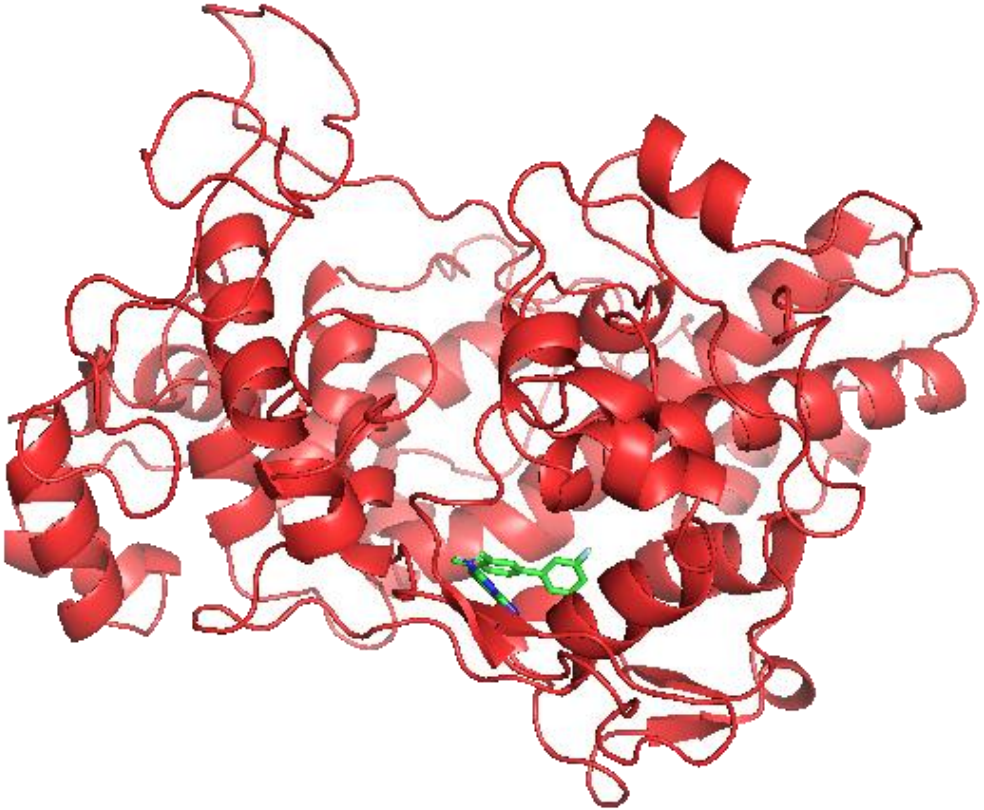
The Cancer Genome Atlas (TCGA), a landmark cancer genomics program, molecularly characterized over 20,000 primary cancer and matched normal samples spanning 33 cancer types.

0	laml	coad	sarc	brca	stad
ENSG00000242268	0.5995147415	0.006248980119	0.09526469736	0.04709657817	0.04507780221
ENSG00000270112	0.04120642704	0.006292379457	0.006890074374	0.009918158787	0.007855314444
ENSG00000167578	4.909340557	3.157504208	3.963034007	3.429264724	3.511829221
ENSG00000273842	0.006839131779	0.0006457108529	0.01034013262	0.003800154148	0.01969620953
ENSG00000078237	3.225871504	2.221692368	3.283359889	3.606900554	5.311345814

Cancer and noncancer mutation ratio
VS
gene expression in colon cancer (COAD)
(potential targets are labeled)



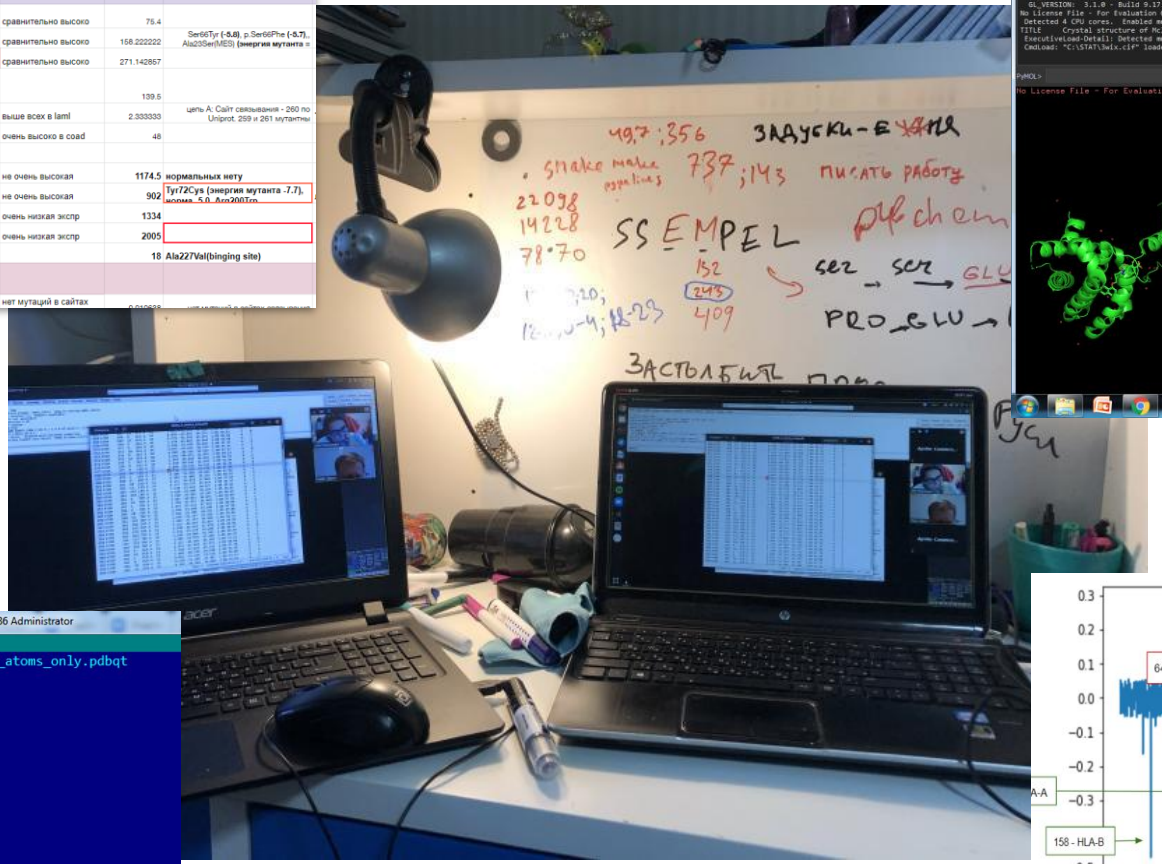
Methods of molecular docking and modelling

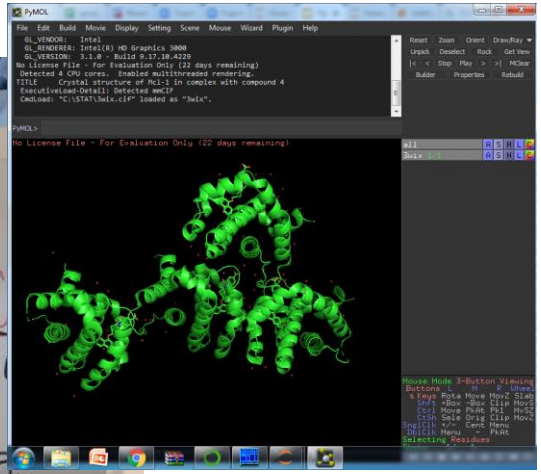


Docking is like that, just not with dogs, but with molecules.
Everything to optimize energy costs

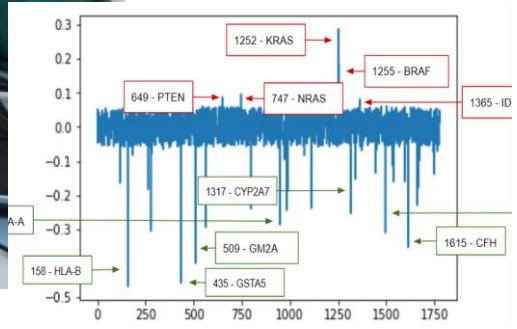
That is how our working process looked like

хорошие PDB-структуры	ген	высоко ли экспрессируется	соотношение нерак/рак	примеры очень ПОНЯТНЫХ мутаций в активномсайте
6S1X	FOLH1	сравнительно высоко	75.4	
6Y1E,11GS	GSTP1	сравнительно высоко	158.222222	Ser66Tyr (-5.8), p.Ser66Phe (-5.7), Ala235er(MES) (энергия мутанта =
мало нормальных структур, почти все	SERPINA1	сравнительно высоко	271.142857	
	ANPEP		139.5	
	MPO	выше всех в laml	2.333333	цепь A: Сайт связывания - 260 по Uniprot, 259 и 261 мутантны
	KLK3	очень высоко в coad	48	
	KLK6			
6T6R	ERAP1(на стадии	не очень высокая	1174.5	нормальных нету
1LN2 (4 цепи) - НО можно взять 1LN1	PCTP (на стадии	не очень высокая	902	Tyr72Cys (энергия мутанта -7.7), норма -5.0, Arg200Trp
4XVL	DPOLN	очень низкая экспр	1334	
4dkx	RAB6C	очень низкая экспр	2005	
3wix	MCL1		18	Ala227Val(binging site)
	RTEN	нет мутаций в сайтах		

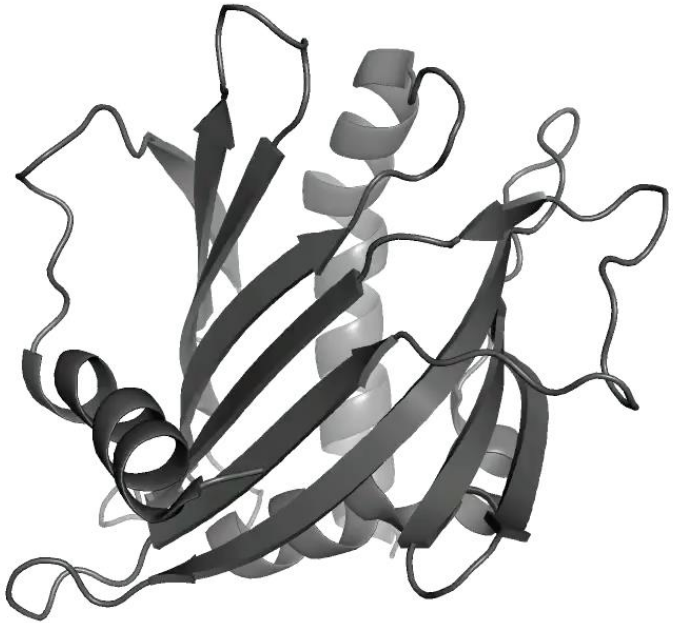





```
edit config.conf - Far 3.0.4455 x86 Administrator
C:\SMTB\config.conf
receptor = 11gs_mut_A_atoms_only.pdbqt

center_x = 7
center_y = 3
center_z = 18

size_x = 30
size_y = 30
size_z = 30

exhaustiveness = 8
```



Visualization of mutation frequency (in binding site)



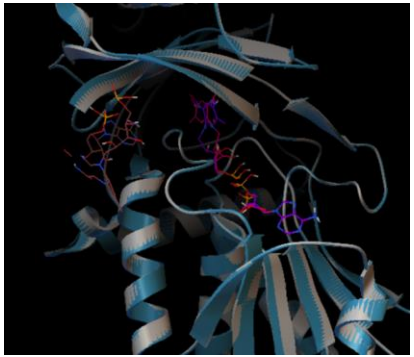
Receptor: phosphatidylcholine transfer protein
Ligand : 1,2-dilinoleoyl -sn-glycero-3-phosphocholine

our Holy Graal

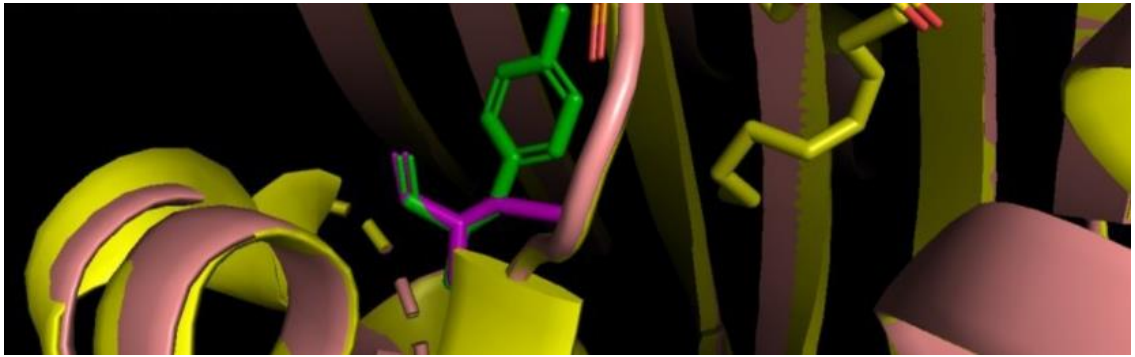
Criteria:

- Mutation from a protein that is rarely mutated in cancer
- This protein is highly expressed in cancer
- This mutation disrupts interaction protein-ligand
- This mutation is frequently mentioned in GNOMAD

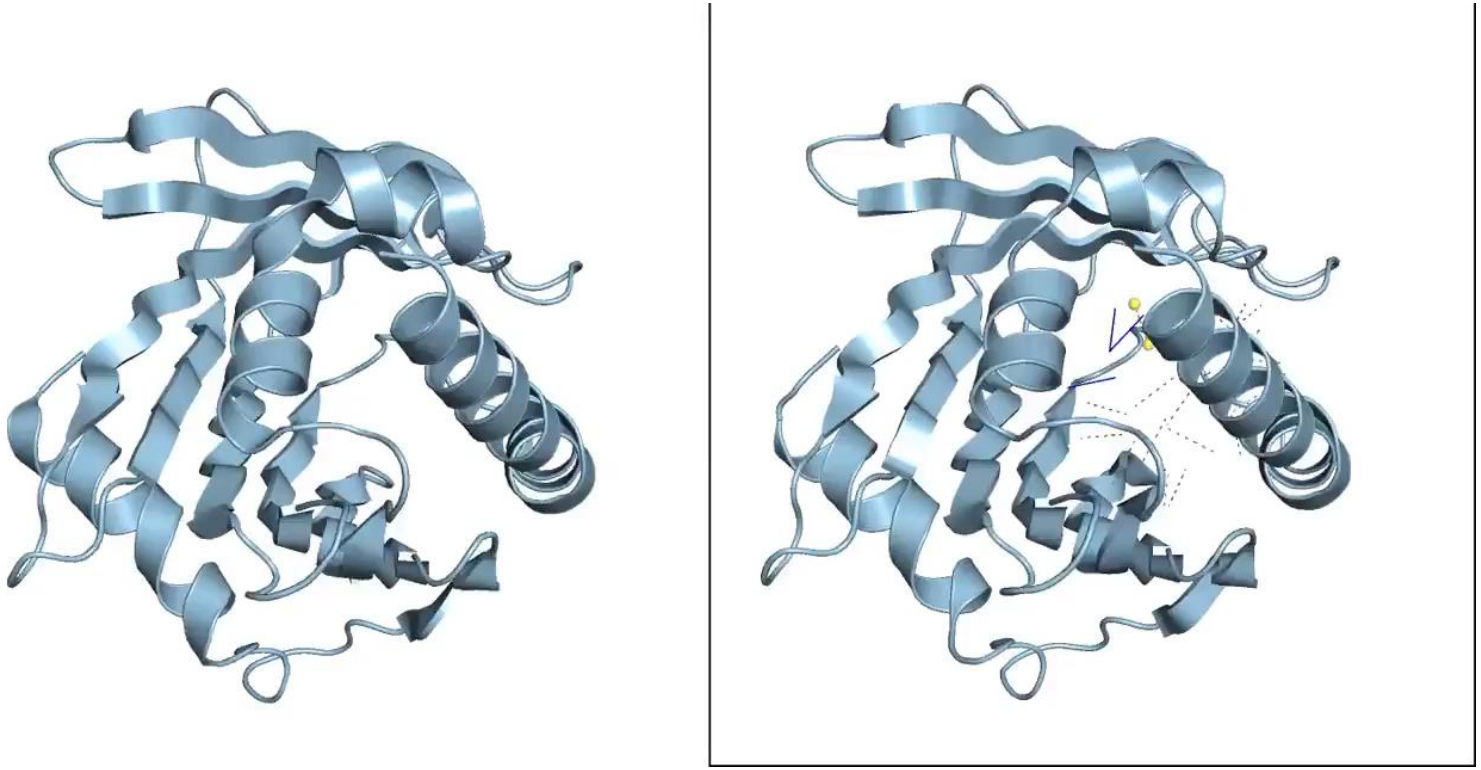
D-amino acid oxydase, **Asp46Glu**



Phosphatidylcholine transfer protein, **Tyr72Cys**



Example of specific mutation in binding sites



Receptor: phosphatidylcholine transfer protein
Ligand: 1,2-dilinoleoyl -sn-glycero-3-phosphocholine
Mutation: Tyr72Cys

RationalDrugDesign laboratory results:

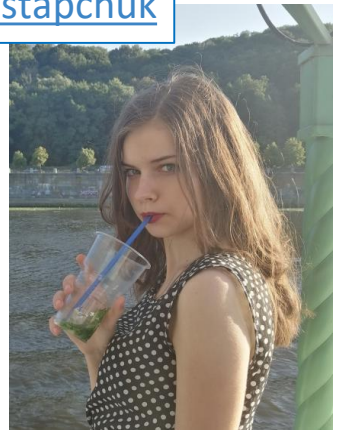
- For the analysis, proteins that were previously prioritized by the neural network were selected, as well as the ones that are highly expressed in cancer and have significant differences in the number of mutations in tumor and healthy tissues
- Structures of selected proteins with the most interesting mutations were modeled (SwissModel)
- Interaction of the selected proteins with their ligands were modeled (Vina AutoDock)
- A comparison of free energies of ligand binding in normal and mutated binding sites was made - and mutations that adversely affect the ability of a protein to bind to a ligand were identified

Acknowledgments

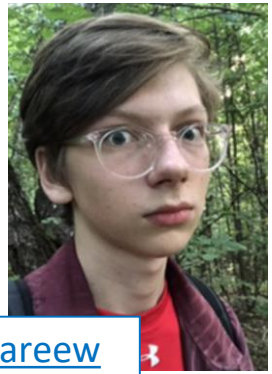
SMTB

ZIMIN FOUNDATION

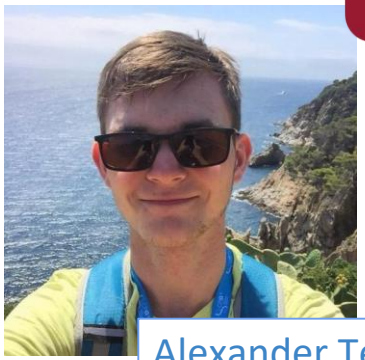
Ivanka Ostapchuk



Lisa Viner



Artem Salimgareew



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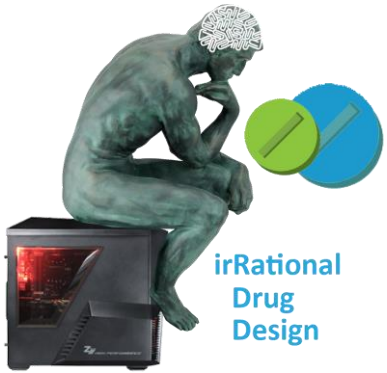

…or

How to make drugs online (fast)