

PLCG2 and MAP2K3 are promising druggable targets for treating Non-Small-Cell Lung Carcinoma and Lung Neoplasms that control activity of JUN, JUNB and EP300 transcription factor on promoters of genes carrying sequence variations

Demo User

geneXplain GmbH

info@genexplain.com

Data received on 10/04/2022 ; Run on 12/11/2022 ; Report generated on 12/11/2022

Genome Enhancer release 3.1 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2022.2)



Abstract

In the present study we applied the software package "Genome Enhancer" to a data set that contains *genomics* data. The study is done in the context of *Non-Small-Cell Lung Carcinoma and Lung Neoplasms*. The goal of this pipeline is to identify potential drug targets in the molecular network that governs the studied pathological process. In the first step of analysis pipeline discovers transcription factors (TFs) that regulate genes activities in the pathological state. The activities of these TFs are controlled by so-called master regulators, which are identified in the second step of analysis. After a subsequent druggability checkup, the most promising master regulators are chosen as potential drug targets for the analyzed pathology. At the end the pipeline comes up with (a) a list of known drugs and (b) investigational active chemical compounds with the potential to interact with selected drug targets.

From the data set analyzed in this study, we found the following TFs to be potentially involved in the regulation of the genes carrying sequence variations: JUN, JUNB and EP300. The subsequent network analysis suggested

- MKK3:Dyrk1B
- PLCgamma2
- BRCA1

as the most promising molecular targets for further research, drug development and drug repurposing initiatives on the basis of identified molecular mechanism of the studied pathology. Having checked the actual druggability potential of the full list of identified targets, both, via information available in medical literature and via cheminformatics analysis of drug compounds, we have identified the following drugs as the most promising treatment candidates for the studied pathology: Erlotinib, ruboxistaurin, 6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazol-5-one and 3-[1-(3-Aminopropyl)-1h-Indol-3-Yl]-4-(1-Methyl-1h-Indol-3-Yl)-1h-Pyrrole-2,5-Dione.

1. Introduction

Recording "-omics" data to measure gene activities, protein expression or metabolic events is becoming a standard approach to characterize the pathological state of an affected organism or tissue. Increasingly, several of these methods are applied in a combined approach leading to large "multiomics" datasets. Still the challenge remains how to reveal the underlying molecular mechanisms that render a given pathological state different from the norm. The disease-causing mechanism can be described by a re-wiring of the cellular regulatory network, for instance as a result of a genetic or epigenetic alterations influencing the activity of relevant genes. Reconstruction of the disease-specific regulatory networks can help identify potential master regulators of the respective pathological process. Knowledge about these master regulators can point to ways how to block a pathological regulatory cascade. Suppression of certain molecular targets as components of these cascades may stop the pathological process and cure the disease.

Conventional approaches of statistical "-omics" data analysis provide only very limited information about the causes of the observed phenomena and therefore contribute little to the understanding of the pathological molecular mechanism. In contrast, the "upstream analysis" method [1-4] applied here has been devised to provide a casual interpretation of the data

obtained for a pathology state. This approach comprises two major steps: (1) analysing promoters and enhancers of genes carrying sequence variations for the transcription factors (TFs) involved in their regulation and, thus, important for the process under study; (2) re-constructing the signaling pathways that activate these TFs and identifying master regulators at the top of such pathways. For the first step, the database TRANSFAC® [6] is employed together with the TF binding site identification algorithms Match [7] and CMA [8]. The second step involves the signal transduction database TRANSPATH® [9] and special graph search algorithms [10] implemented in the software "Genome Enhancer".

The "upstream analysis" approach has now been extended by a third step that reveals known drugs suitable to inhibit (or activate) the identified molecular targets in the context of the disease under study. This step is performed by using information from HumanPSD™ database [5]. In addition, some known drugs and investigational active chemical compounds are subsequently predicted as potential ligands for the revealed molecular targets. They are predicted using a pre-computed database of spectra of biological activities of chemical compounds of a library of 2245 known drugs and investigational chemical compounds from HumanPSD™ database. The spectra of biological activities for these compounds are computed using the program PASS on the basis of a (Q)SAR approach [11-13]. These predictions can be used for the research purposes - for further drug development and drug repurposing initiatives.

2. Data

For this study the following experimental data was used:

Table 1. Experimental datasets used in the study

File name	Data type
NCI-H1975	Genomics

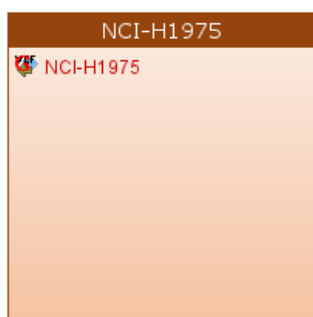


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

3. Results

We have analyzed the following condition: NCI-H1975.

3.1. Identification of target genes

In the first step of the analysis **target genes** were identified from the uploaded experimental data. The most frequently mutated genes were used as target genes.

Table 2. Top ten the most frequently mutated genes in NCI-H1975.

[See full table](#) →

ID	Gene description	Gene symbol	Gene schematic representation	Number of variations	Gene weight	Weighted score
ENSG00000034152	mitogen-activated protein kinase kinase 3	MAP2K3		105	287.18	861.55
ENSG00000178104	phosphodiesterase 4D interacting protein	PDE4DIP		128	318.48	636.96
ENSG00000168702	LDL receptor related protein 1B	LRP1B		63	159.83	319.66
ENSG00000081479	LDL receptor related protein 2	LRP2		54	141.29	282.59
ENSG00000115414	fibronectin 1	FN1		36	91.63	274.89
ENSG00000101680	laminin subunit alpha 1	LAMA1		47	127.8	255.6
ENSG00000107611	cubilin	CUBN		46	115.81	231.61
ENSG00000171105	insulin receptor	INSR		27	73.94	221.81
ENSG00000076555	acetyl-CoA carboxylase beta	ACACB		26	72.98	218.94
ENSG00000160145	kalirin RhoGEF kinase	KALRN		42	108.48	216.96

3.2. Functional classification of genes

A functional analysis of genes carrying sequence variations was done by mapping the genes to several known ontologies, such as Gene Ontology (GO), disease ontology (based on HumanPSD™ database) and the ontology of signal transduction and metabolic pathways from the TRANSPATH® database. Statistical significance was computed using a binomial test. Figures 2-4 show the most significant categories.

The most frequently mutated genes in NCI-H1975:

300 top mutated genes were taken for the mapping.

GO (biological process)

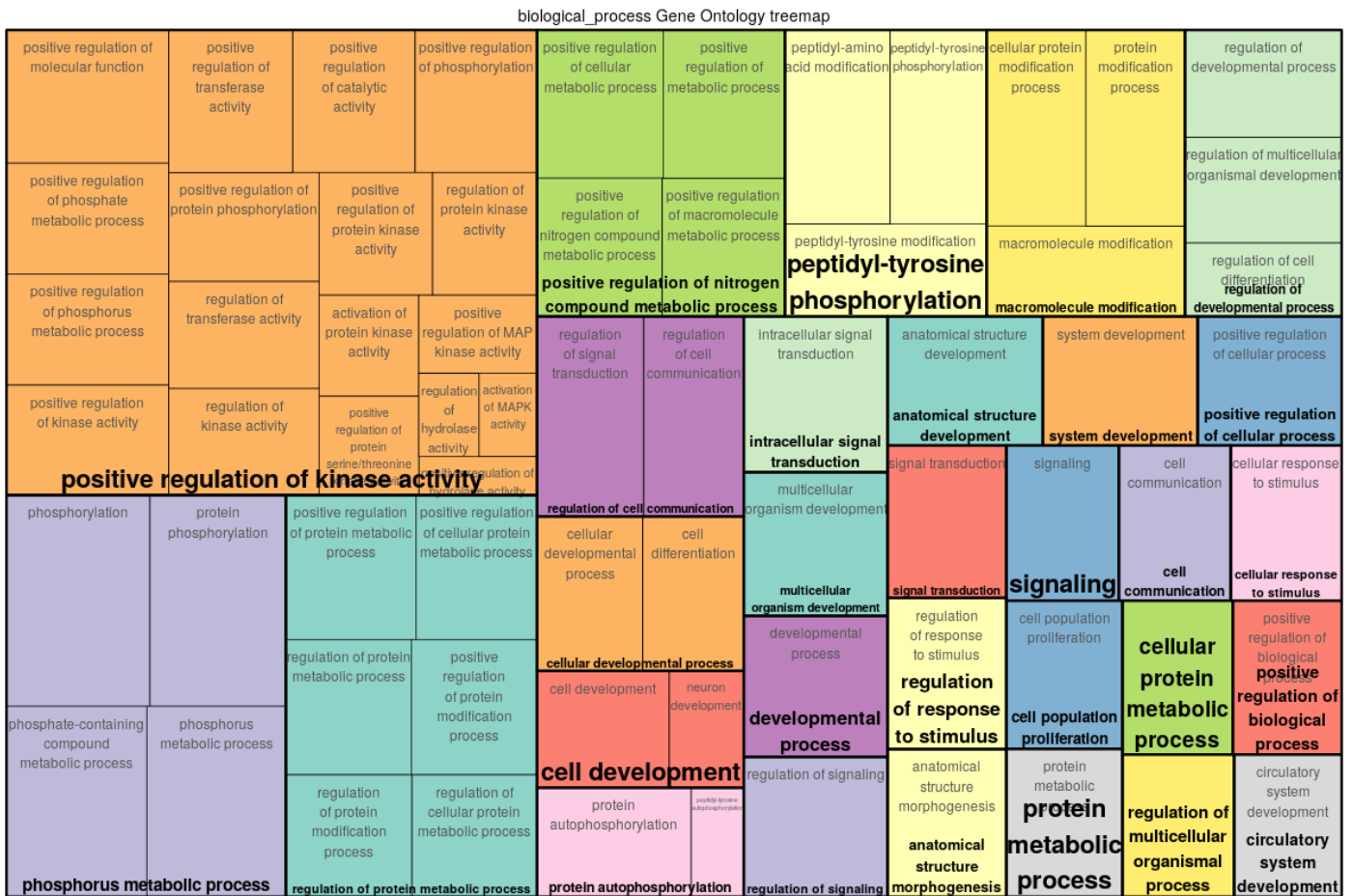


Figure 2. Enriched GO (biological process) of the most frequently mutated genes in NCI-H1975.

[Full classification →](#)

TRANSPATH® Pathways (2022.2)

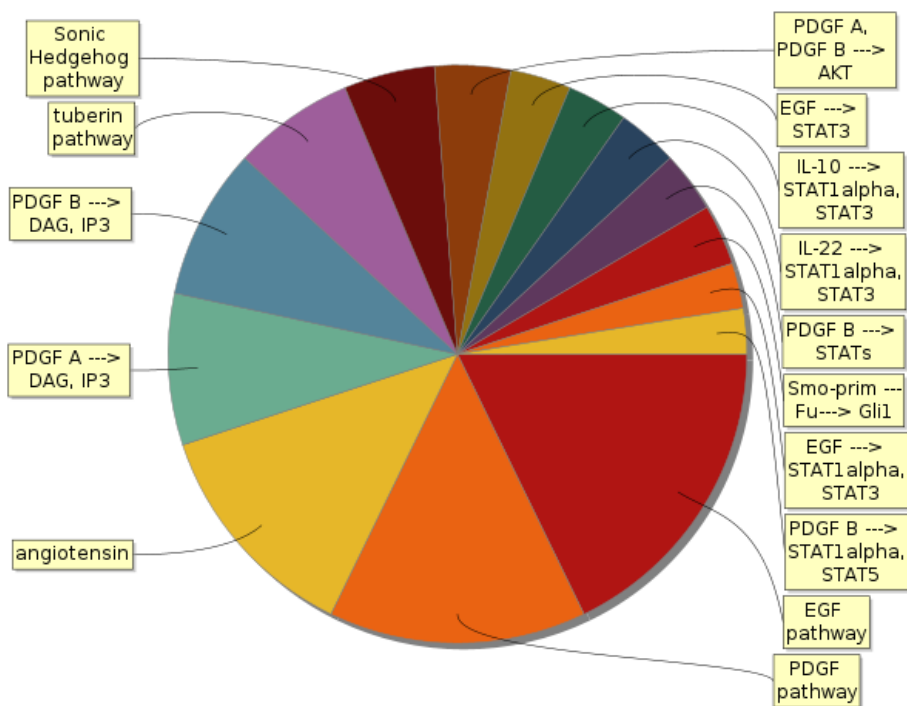
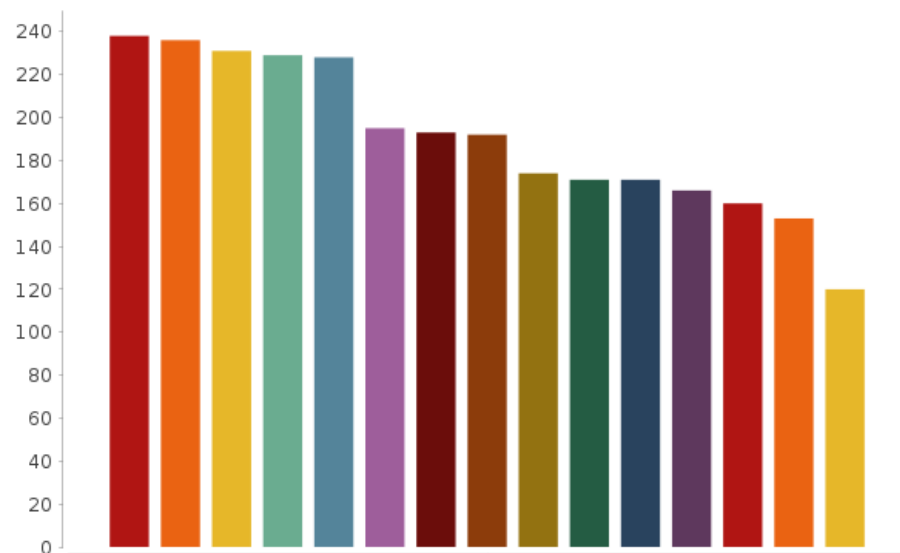


Figure 3. Enriched TRANSPATH® Pathways (2022.2) of the most frequently mutated genes in NCI-H1975.

[Full classification →](#)

HumanPSD(TM) disease (2022.2)

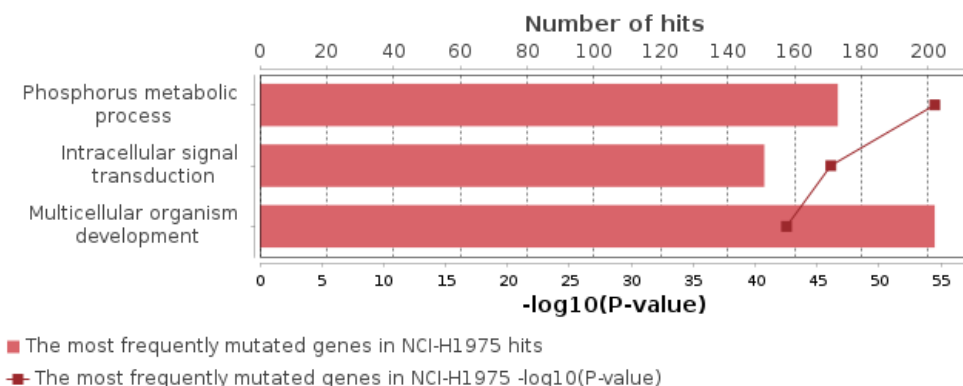


- Respiratory Tract Diseases ■ Lung Diseases ■ Thoracic Neoplasms
- Respiratory Tract Neoplasms ■ Lung Neoplasms ■ Neoplasms, Germ Cell and Embryonal
- Neoplasms, Nerve Tissue ■ Neuroectodermal Tumors ■ Genital Diseases, Female
- Bronchial Neoplasms ■ Carcinoma, Bronchogenic ■ Carcinoma, Non-Small-Cell Lung
- Genital Neoplasms, Female ■ Endocrine Gland Neoplasms
- Neoplasms, Connective and Soft Tissue

Figure 4. Enriched HumanPSD(TM) disease (2022.2) of the most frequently mutated genes in NCI-H1975. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

[Full classification →](#)

The result of overall Gene Ontology (GO) analysis of the genes carrying sequence variations of the studied pathology can be summarized by the following diagram, revealing the most significant functional categories overrepresented among the observed (genes carrying sequence variations):



3.3. Analysis of enriched transcription factor binding sites and composite modules

In the next step a search for transcription factors binding sites (TFBS) was performed in the regulatory regions of the **target genes** by using the TF binding motif library of the TRANSFAC® database. We searched for so called **composite modules** that act as potential condition-specific **enhancers** of the **target genes** in their upstream regulatory regions (-1000 bp upstream of transcription start site (TSS)) and identify transcription factors regulating activity of the genes through such **enhancers**.

Classically, **enhancers** are defined as regions in the genome that increase transcription of one or several genes when inserted in either orientation at various distances upstream or downstream of the gene [8]. Enhancers typically have a length of several hundreds of nucleotides and are bound by multiple transcription factors in a cooperative manner [9].

In the current work, we use the Genomics data from the "Yes VCF track" track to predict positions of potential **enhancers** where the observed sequence variations may influence the gene expression in the pathology under study. We scan 5kb flanking regions and the body of all genes caring the variations, with a sliding window of 1100bp size and find the position of the window with the maximal sum of the mutation weights, where we then perform the search for potential condition-specific enhancers (CMA model search).

We analyzed mutations that were revealed in the potential enhancers located upstream, downstream or inside the **target genes** (see Table 3). We identified 6914 mutations potentially affecting gene regulation. Table 4 shows the following lists of PWMs whose sites were lost or gained due to these mutations. Weighting of mutations was done in respect to the significance of the change in TF affinity binding to the sequence. Mutations that maximally affected the change of binding affinity received higher weights. These PWMs were put in focus of the CMA algorithm that constructs the model of the enhancers by specifying combinations of TF motifs (see more details of the algorithm in the Methods section).

Table 3. Mutations revealed in the most frequently mutated genes

[See full table →](#)

ID	Gene symbol	Gene schematic representation	Number of variations
ENSG00000178104	PDE4DIP		155
ENSG00000034152	MAP2K3		105
ENSG00000154358	OBSCN		82
ENSG00000155657	TTN		79
ENSG00000237298	TTN-AS1		77
ENSG00000168702	LRP1B		64
ENSG00000008128	CDK11A		62
ENSG00000268575	ENSG00000268575		62
ENSG00000081479	LRP2		54
ENSG00000198796	ALPK2		54

Table 4. PWMs whose sites were lost or gained due to mutations in the most frequently mutated genes

[See full table](#) →

ID	P-value (gains)	P-value (losses)	yesCount (gains)	yesCount (losses)
V\$ZBTB33_07	4.34E-2	4.45E-8	23	499
V\$ATF4_Q5	2.31E-2	7.92E-7	7	1830
V\$CREB_02	8.05E-3	1.28E-8	967	772
V\$CREB_Q2	6.15E-3	2.52E-9	973	1063
V\$CREB_Q4	6.15E-3	2.52E-9	973	1063
V\$CREB1_17	3.23E-3	1.88E-7	12	1190
V\$CREB_Q3	2.97E-3	1.37E-8	622	701
V\$ATF6B_05	3.6E-4	2.26E-7	58	167
V\$SALL2_01	2.95E-4	5.78E-8	25	74
V\$HIF1A_Q5	1.79E-4	7.69E-9	124	298
V\$PAX3_05	2.35E-5	6.41E-8	1994	1272
V\$ZBTB33_05	1.06E-5	1.06E-7	137	450
V\$ELK1_03	4.65E-6	5.15E-10	3372	4616
V\$ELK1_04	4.65E-6	1.32E-8	3372	4386
V\$HES1_03	4.47E-6	4.42E-7	43	44
V\$KLF8_Q5	6.49E-16	2.69E-2	251	28
V\$SALL2_02	5.71E-16	3.54E-2	128	8
V\$KR3_02	5.13E-16	2.13E-5	295	63
V\$GCM1_08	1.71E-16		1059	
V\$SP1_08	2.9E-17	2.76E-2	226	10

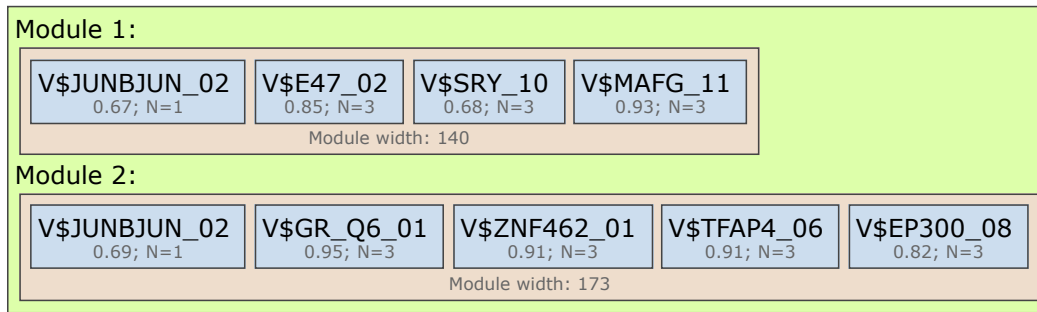
We applied the Composite Module Analyst (CMA) [8] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the enhancers by specifying combinations of TF motifs (from TRANSFAC®) whose sites are most frequently clustered together in the regulatory regions of the studied genes. CMA identifies the transcription factors that through their cooperation provide a synergistic effect and thus have a great influence on the gene regulation process.

Enhancer model potentially involved in regulation of target genes (the most frequently mutated genes in NCI-H1975).

To build the most specific composite modules we choose top mutated genes as the input of CMA algorithm. The obtained CMA model is then applied to compute CMA score for all the most frequently mutated genes in NCI-H1975.

The model consists of 2 module(s). Below, for each module the following information is shown:

- PWMs producing matches,
- number of individual matches for each PWM,
- score of the best match.



Model score (-p*log10(pval)): 28.72

Wilcoxon p-value (pval): 3.05e-56

Penalty (p): 0.517

Average yes-set score: 11.20

Average no-set score: 8.98

AUC: 0.79

Separation point: 10.67

False-positive: 21.11%

False-negative: 33.00%

The AUC of the model achieves value significantly higher than expected for a random set of regulatory regions
Z-score = 3.09

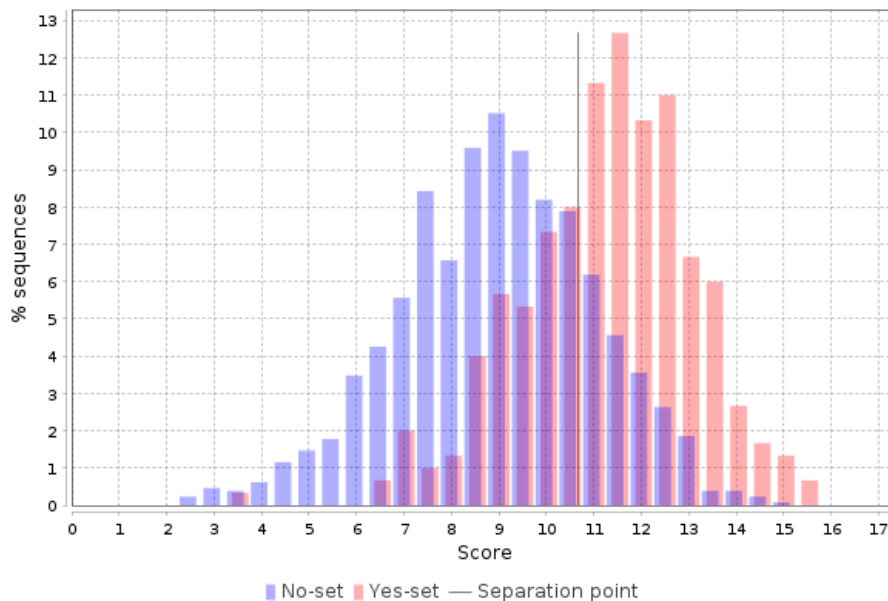


Table 5. List of top ten the most frequently mutated genes in NCI-H1975 with identified enhancers in their regulatory regions. **CMA score** - the score of the CMA model of the enhancer identified in the regulatory region.

[See full table →](#)

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000153944	MSI2	musashi RNA binding protein 2	15.7	MafG(h), E2A(h), GR(h), p300(h), AP-4(h), ZNF462(h), JunB(h),c-Jun(h)...
ENSG00000078401	EDN1	endothelin 1	15.6	p300(h), GR(h), AP-4(h), ZNF462(h), JunB(h),c-Jun(h), E2A(h), SRY(h)...
ENSG00000163918	RFC4	replication factor C subunit 4	15.51	p300(h), GR(h), SRY(h), JunB(h),c-Jun(h), AP-4(h), E2A(h), ZNF462(h)...
ENSG00000125375	DMAC2L	distal membrane arm assembly complex 2 like	15.38	E2A(h), GR(h), AP-4(h), ZNF462(h), JunB(h),c-Jun(h), SRY(h), p300(h)
ENSG00000132522	GPS2	G protein pathway suppressor 2	15.3	p300(h), AP-4(h), GR(h), SRY(h), ZNF462(h), JunB(h),c-Jun(h), E2A(h)...
ENSG00000132507	EIF5A	eukaryotic translation initiation factor 5A	15.3	p300(h), AP-4(h), GR(h), SRY(h), ZNF462(h), JunB(h),c-Jun(h), E2A(h)...
ENSG00000080224	EPHA6	EPH receptor A6	15.27	SRY(h), E2A(h), GR(h), ZNF462(h), p300(h), JunB(h),c-Jun(h), MafG(h)...
ENSG00000107242	PIP5K1B	phosphatidylinositol-4-phosphate 5-kinase type 1 beta	15.26	p300(h), JunB(h),c-Jun(h), SRY(h), GR(h), AP-4(h), ZNF462(h), E2A(h)...
ENSG00000165966	PDZRN4	PDZ domain containing ring finger 4	15.25	E2A(h), MafG(h), SRY(h), JunB(h),c-Jun(h), AP-4(h), GR(h), p300(h)...
ENSG00000074181	NOTCH3	notch receptor 3	15.19	p300(h), E2A(h), SRY(h), JunB(h),c-Jun(h), MafG(h), ZNF462(h), AP-4(h)...

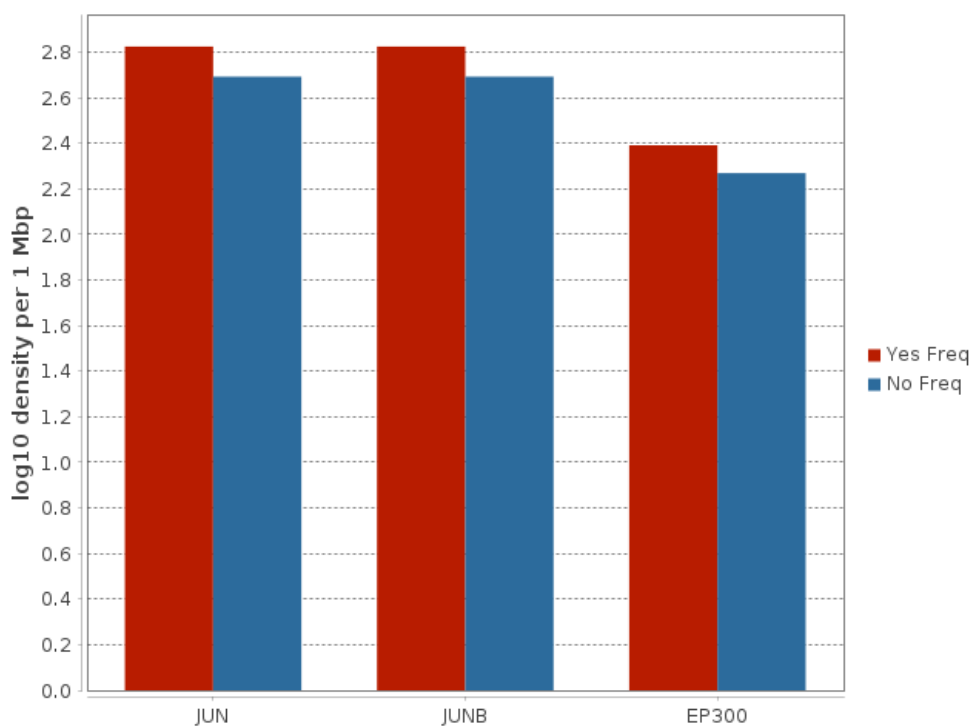
On the basis of the enhancer models we identified transcription factors potentially regulating the **target genes** of our interest. We found 9 transcription factors controlling expression of the genes associated with genomic variations (see Table 6).

Table 6. Transcription factors of the predicted enhancer model potentially regulating the genes carrying sequence variations (the most frequently mutated genes in NCI-H1975). **Yes-No ratio** is the ratio between frequencies of the sites in Yes sequences versus No sequences. It describes the level of the enrichment of binding sites for the indicated TF in the regulatory target regions. **Regulatory score** is the measure of involvement of the given TF in the controlling of expression of genes that encode master regulators presented below (through positive feedback loops).

[See full table →](#)

ID	Gene symbol	Gene description	Regulatory score	Yes-No ratio
MO000019469	JUN	Jun proto-oncogene, AP-1 transcription factor subunit	4.39	1.36
MO000007830	JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	3.39	1.36
MO000056654	EP300	E1A binding protein p300	3.02	1.33
MO000031266	NR3C1	nuclear receptor subfamily 3 group C member 1	2.96	1.48
MO000032492	TCF3	transcription factor 3	2.66	2.41
MO000092587	ZNF462	zinc finger protein 462	2.22	1.26
MO000028667	MAFG	MAF bZIP transcription factor G	2.08	2.83
MO000024660	TFAP4	transcription factor AP-4	1.91	1.65
MO000025328	SRY	sex determining region Y	1.85	1.59

The following diagram represents the key transcription factors, which were predicted to be potentially regulating genes carrying sequence variations in the analyzed pathology: JUN, JUNB and EP300.



3.4. Finding master regulators in networks

In the second step of the upstream analysis common regulators of the revealed TFs were identified. We identified 10 signaling proteins whose structure and function is highly damaged by the mutations (see Table 7).

Table 7. Signaling proteins whose structure and function are damaged by the mutations in the most frequently mutated genes

[See full table →](#)

ID	Title	Mutation count	Consequence	Codons
MO000139573	Myomegalin(h)	12	stop_gained	Cga/Tga,tGg/tAg,tgG/tgA
MO000009403	MKK3(h)	6	NMD_transcript_variant,stop_gained	Cag/Tag
MO000018990	BMP4(h)	1	stop_lost	Tga/Cga
MO000032335	RSK1(h)	1	NMD_transcript_variant,stop_lost	Tga/Cga
MO000032374	raptor(h)	1	stop_gained	CTg/TAg
MO000035011	SRPK1(h)	1	stop_gained	tCa/tGa
MO000059823	PDI(h)	1	NMD_transcript_variant,stop_lost	Tga/Cga
MO000109306	PSMA4(h)	1	stop_lost	Tga/Cga
MO000133935	RhoBP(h)	1	stop_gained	Cag/Tag
MO000162220	COH1(h)	1	stop_gained	taT/taG

Top 10 mutated proteins for the most frequently mutated genes were used in the algorithm of master regulator search as a list of nodes of the signal transduction network that are removed from the network during the search of master regulators

(see more details about the algorithm in the Methods section). These master regulators appear to be the key candidates for therapeutic targets as they have a master effect on regulation of intracellular pathways that activate the pathological process of our study. The identified master regulators are shown in Table 8.

Table 8. Master regulators that may govern the regulation of the most frequently mutated genes in NCI-H1975. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, genomics data.

[See full table](#) →

ID	Master molecule name	Gene symbol	Gene description	Total rank	Weighted score
MO000011150	PLCgamma2(h)	PLCG2	phospholipase C gamma 2	422	146.68
MO000021981	BRCA1(h)	BRCA1	BRCA1 DNA repair associated	498	148.7
MO000016677	EGFR(h)	EGFR	epidermal growth factor receptor	499	133.24
MO000009086	MEKK1(h)	MAP3K1	mitogen-activated protein kinase kinase kinase 1	503	70.47
MO000020139	Pyk2-isoform1(h)	PTK2B	protein tyrosine kinase 2 beta	521	152.88
MO000101469	LRRK2(h)	LRRK2	leucine rich repeat kinase 2	521	152.41
MO000035261	Ret(h)	RET	ret proto-oncogene	539	60.87
MO000036741	MKK3(h):Dyrk1B(h)	DYRK1B, MAP2K3	dual specificity tyrosine phosphorylation regulated kinase 1B, mitogen-activated protein kinase kina...	541	861.55
MO000042124	MKK3:Dyrk1B:PHS 2:HNF-1alpha	DYRK1B, HNF1A, MAP2K3, PCBD2	HNF1 homeobox A, dual specificity tyrosine phosphorylation regulated kinase 1B, mitogen-activated pr...	541	861.55
MO000078695	MKK3-isoform1(h)	MAP2K3	mitogen-activated protein kinase kinase 3	541	861.55

The intracellular regulatory pathways controlled by the above-mentioned master regulators are depicted in Figure 5. This diagram displays the connections between identified transcription factors, which play important roles in the regulation of genes carrying sequence variations, and selected master regulators, which are responsible for the regulation of these TFs.

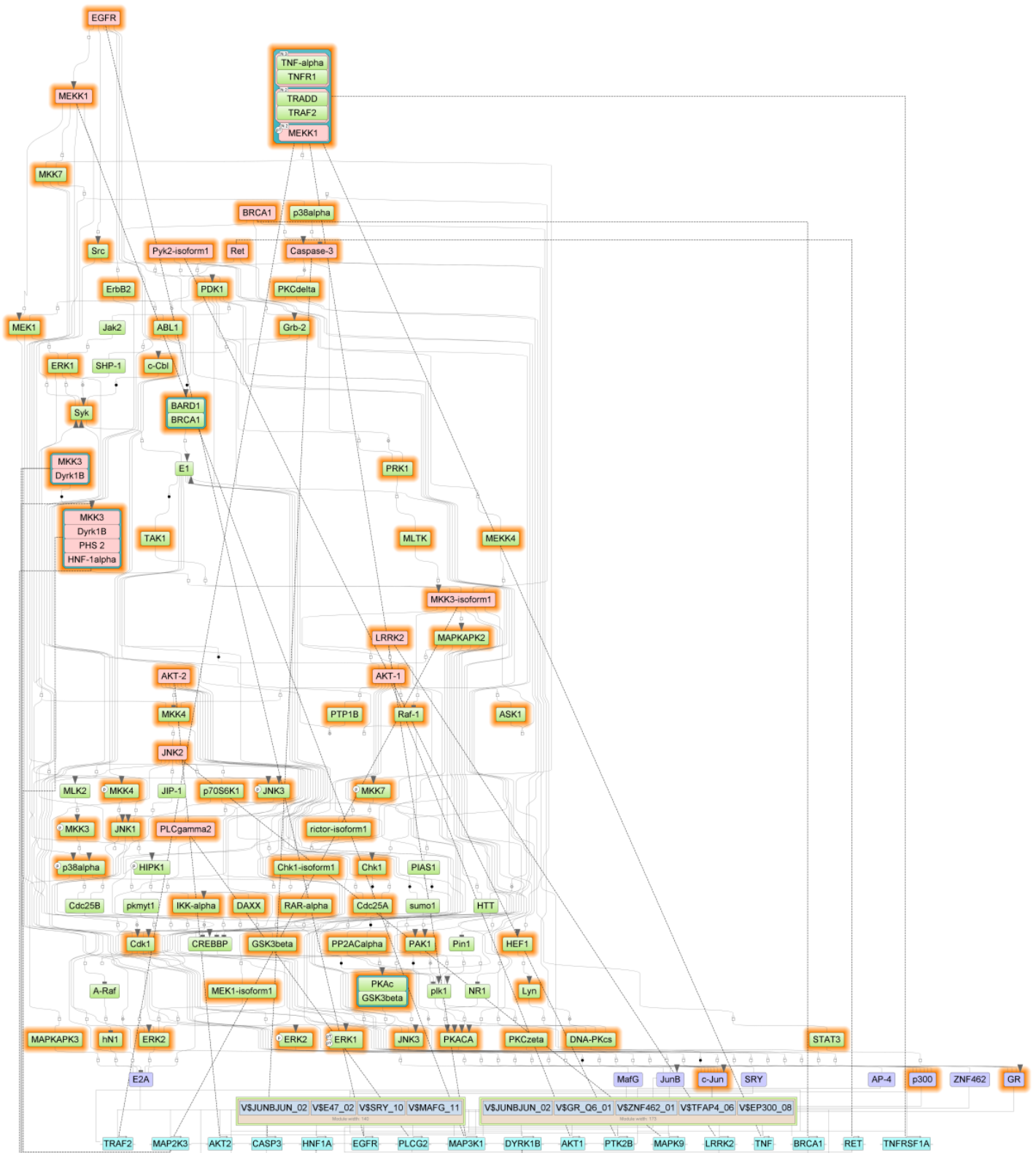


Figure 5. Diagram of intracellular regulatory signal transduction pathways of the most frequently mutated genes in NCI-H1975. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have been added to the network during the search for master regulators from selected TFs. Orange frames highlight molecules presented in original mapping.

[See full diagram →](#)


4. Finding prospective drug targets

The identified master regulators that may govern pathology associated genes were checked for druggability potential using HumanPSD™ [5] database of gene-disease-drug assignments and PASS [11-13] software for prediction of biological activities of chemical compounds on the basis of a (Q)SAR approach. Respectively, for each master regulator protein we have computed two Druggability scores: HumanPSD Druggability score and PASS Druggability score. Where Druggability score represents the number of drugs that are potentially suitable for inhibition (or activation) of the corresponding target either according to the information extracted from medical literature (from HumanPSD™ database) or according to cheminformatics predictions of compounds activity against the examined target (from PASS software).

The cheminformatics druggability check is done using a pre-computed database of spectra of biological activities of chemical compounds from a library of all small molecular drugs from HumanPSD™ database, 2507 pharmaceutically active known chemical compounds in total. The spectra of biological activities has been computed using the program PASS [11-13] on the basis of a (Q)SAR approach.


If both Druggability scores were below defined thresholds (see Methods section for the details) such master regulator proteins were not used in further analysis of drug prediction.

As a result we created the following two tables of prospective drug targets (top targets are shown here):

 **Table 9.** Prospective drug targets selected from full list of identified master regulators filtered by Druggability score from HumanPSD™ database. **Druggability score** contains the number of drugs that are potentially suitable for inhibition (or activation) of the target. The drug targets are sorted according to the **Total rank** which is the sum of three ranks computed on the basis of the three scores: keynode score, CMA score and expression change score (logFC, if present). See Methods section for details.

[See full table →](#)

Gene symbol	Gene Description	Druggability score	Total rank	Weighted score
PLCG2	phospholipase C gamma 2	1	422	146.68
MAP2K3	mitogen-activated protein kinase kinase 3	29	587	861.55
MMP2	matrix metalloproteinase 2	42	713	99.11
IFNB1	interferon beta 1	3	806	61.2
MERTK	MER proto-oncogene, tyrosine kinase	30	853	139.22
TEC	tec protein tyrosine kinase	28	858	56.3

 **Table 10.** Prospective drug targets selected from full list of identified master regulators filtered by Druggability score predicted by PASS software. Here, the **Druggability score** for master regulator proteins is computed as a sum of PASS calculated probabilities to be active as a target for various small molecular compounds. The drug targets are sorted according to the **Total rank** which is the sum of three ranks computed on the basis of the three scores: keynode score, CMA score and expression change score (logFC, if present). See Methods section for details.

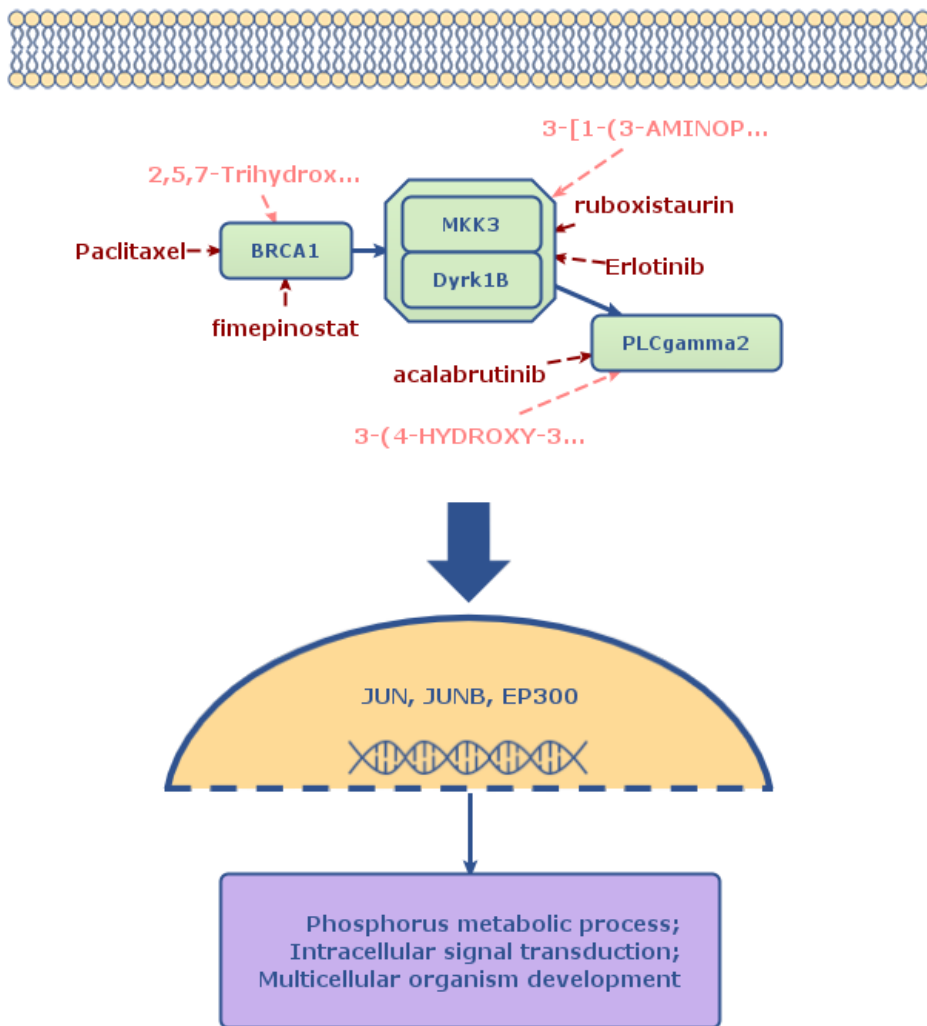
[See full table →](#)

Gene symbol	Gene Description	Druggability score	Total rank	Weighted score
PLCG2	phospholipase C gamma 2	39.67	422	146.68
MAP2K3	mitogen-activated protein kinase kinase 3	6.28	587	861.55
ITGB6	integrin subunit beta 6	0.7	658	126.26
MMP2	matrix metalloproteinase 2	19.17	713	99.11
IFNB1	interferon beta 1	12.36	806	61.2
MERTK	MER proto-oncogene, tyrosine kinase	8.67	853	139.22

Below we represent schematically the main mechanism of the studied pathology. In the schema we considered the top two drug targets of each of the two categories computed above. In addition we have added two top identified master regulators for which no drugs may be identified yet, but that are playing the crucial role in the molecular mechanism of the studied pathology. Thus the molecular mechanism of the studied pathology was predicted to be mainly based on the following key master regulators:

- MKK3:Dyrk1B
- PLCgamma2
- BRCA1

This result allows us to suggest the following schema of affecting the molecular mechanism of the studied pathology:



Drugs which are shown on this schema: 3-(4-HYDROXY-3-METHOXYPHENYL)-2-PROPENOIC ACID, 2,5,7-Trihydroxynaphthoquinone, Erlotinib, 3-[1-(3-AMINOPROPYL)-1H-INDOL-3-YL]-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE, Paclitaxel, ruboxistaurin, fimepinostat and acalabrutinib, should be considered as a prospective research initiative for further drug repurposing and drug development. These drugs were selected as top matching treatments to the most prospective drug targets of the studied pathology, however, these results should be considered with special caution and are to be used for research purposes only, as there is not enough clinical information for adapting these results towards immediate treatment of patients.

The drugs given in dark red color on the schema are FDA approved drugs or drugs which have gone through various phases of clinical trials as active treatments against the selected targets.

The drugs given in pink color on the schema are drugs, which were cheminformatically predicted to be active against the selected targets.

5. Identification of potential drugs

In the last step of the analysis we strived to identify known activities as well as drugs with cheminformatically predicted activities that are potentially suitable for inhibition (or activation) of the identified molecular targets in the context of specified human diseases(s).

Proposed drugs are top ranked drug candidates, that were found to be active on the identified targets and were selected from 4 categories:

1. FDA approved drugs or used in clinical trials drugs for the studied pathology;
2. Repurposing drugs used in clinical trials for other pathologies;
3. Drugs, predicted by PASS to be active against identified drug targets and against the studied pathology;
4. Drugs, predicted by PASS to be active against identified drug targets but for other pathologies.

Proposed drugs were selected on the basis of Drug rank which was computed from the ranks sum based on the individual ranks of the following scores:

- Target activity score (depends on ranks of all targets that were found for the selected drug);
- Disease activity score (weighted sum of number of clinical trials on disease(s) under study where the selected drug is known to be applied or PASS Disease activity score - cheminformatically predicted property of the compound to be active against the studied disease(s));
- Clinical validity score (applicable only for drugs predicted on the basis of literature curation in HumanPSD™ database (Tables 12 and 13), reflects the number of the highest clinical trials phase on which the drug was tested for any pathology).

You can refer to the Methods section for more details on drug ranking procedure.

Based on the Drug rank, a numerical value of Drug score was calculated, which reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. Drug score values belong to the range from 1 to 100 and are calculated as a quotient of maximum drug rank and the drug rank of the given drug multiplied by 100.

If sufficient information regarding the known associations between predicted drugs and variants identified in the studied pathology was found, this will be reflected in the **Somatic variants** column of the FDA approved and repurposed drugs used in clinical trials tables. Details on these variant-drug associations can be found in the [Molecular Tumor Board \(MTB\) report](#) generated for the studied pathology.

Top drugs of each category are given in the tables below:

Drugs approved in clinical trials for Oncology



Table 11. Clinically approved (FDA, EMA, etc.) drugs for the studied pathology (most promising and clinically approved treatment candidates selected for the identified drug targets on the basis of literature curation in [HumanPSD™](#) database)

[See full table](#) →

Name	Target names	Drug score	Disease activity score	Disease trial phase	Somatic variants	Approved
Erlotinib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, BIRC5, ERBB3, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, IL2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K1, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, ILK, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA,	100	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Carcinoma, Renal Cell, Disease Progression, Gastrointestinal Stromal Tumors, Neoplasms, Pancreatic Neoplasms	EGFR:T790M:resistance:A1, EGFR:L858R:response:A1	Carcinoma, Non-Small-Cell Lung (ClinicalTrials , ClinicalTrials , ClinicalTrials , DailyMed , Pubmed)

	MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, ERBB4, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2				
Gefitinib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCC, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1,	99	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms	EGFR:T790M:resistance:A2, EGFR:L858R:response:A1
					Carcinoma, Non-Small-Cell Lung (FDA) Lung Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials)

	DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2						
Crizotinib	EPHB2, FGFR3, MET, PKN2, SRC, NTRK1, NTRK2, ABL1, KDR, PDGFRB, MST1R, BTK, PRKD1, TEK, RET, AKT2, CSF1R, IGF1R, RPS6KB1, PDPK1	96	19	Phase 4: Carcinoma, Non-Small-Cell Lung, Lymphoma, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Non-Hodgkin			Carcinoma, Non-Small-Cell Lung (FDA)
Trametinib	MAPK1, PARP1, CASP7, MAP2K2, MAP2K7, CASP3, MAP2K1, CASP9, MAPK3	93	16	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Astrocytoma, Fibroma, Ganglioglioma, Ganglion Cysts, Ganglioneuroma, Glioblastoma, Glioma, Melanoma, Neoplasms, Neurocytoma, Neurofibroma, Neurofibromatosis, Neurofibromatosis 1, Neuroma, Oligodendroglioma			Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA)
Osimertinib	MAPK1, ERBB3, EGFR, MAPK4, ERBB2, AKT1, PTK6, BLK, ERBB4, MAPK3, AKT2	92	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms	EGFR:T790M:response:A1		Carcinoma, Non-Small-Cell Lung (FDA) Lung Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials)
dacomitinib	MAPK1, ERBB3, PARP1, EGFR, SRC, ERBB2, AKT1, ERBB4, MAPK3, AKT2	92	22	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms			Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA, PUBMED)
Ceritinib	MAPK1, PARP1, EGFR, STAT3, MAPK4, CASP3, AKT1, BAX, MAPK3, AKT2, IGF1R, INSR	92	14	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms, Sarcoma			Carcinoma, Non-Small-Cell Lung (FDA, Pubmed)
lorlatinib	EGFR, PTK2, PTK2B, NTRK1, NTRK2, FES, FER	91	19	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms			Carcinoma, Non-Small-Cell Lung (FDA, Pubmed)
Paclitaxel	MAPK8, PIK3CG, LIF, PIK3CA, CASP3, E2F1, MMP2, BIRC5, CDK1, MAPK3, BRCA1, TP53	90	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Adenocarcinoma, Breast Neoplasms, Carcinoma, Carcinoma, Large Cell, Carcinoma, Ovarian Epithelial, Carcinoma, Squamous Cell, Neoplasms, Neuroendocrine Tumors, Ovarian Neoplasms, Squamous Cell Carcinoma of Head and Neck, Triple Negative Breast Neoplasms			Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA, FDA)
capmatinib	MAPK1, ERBB3, GAB1, MET, MTOR, MAPK4, PARP1, EGFR, STAT3, PTK2, AKT1, MAPK3, AKT2, TP53	90	11	Phase 3: Carcinoma, Non-Small-Cell Lung, Sarcoma			Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA)
Afatinib	ERBB3, EGFR, ERBB2, ERBB4, PDPK1	88	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Carcinoma, Carcinoma, Squamous Cell, Neoplasms	EGFR:T790M:resistance:A1, EGFR:L858R:response:A1		Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA)
Gemcitabine	EGFR, SRC, CASP8, ERBB2,	88	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms,			Carcinoma, Non-Small-

	HRAS, CHEK1, BRCA1			Adenocarcinoma, Carcinoma, Carcinoma, Renal Cell, Histiocytosis, Lymphohistiocytosis, Hemophagocytic, Lymphoma, Lymphoma, Extranodal NK-T-Cell, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, Neoplasms, Pancreatic Neoplasms, Syndrome	Cell Lung (ClinicalTrials, FDA)
selpercatinib	FGFR3, FLT1, FGFR1, RET, FLT4	85	12	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Carcinoma, Medullary, Carcinoma, Neuroendocrine, Neoplasms, Thyroid Diseases, Thyroid Neoplasms	Lung Neoplasms (FDA) Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA)
Alectinib	DRD2, YAP1, AKT1, RET, AKT2	83	18	Phase 4: Carcinoma, Non-Small-Cell Lung, Lymphoma	Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA, Pubmed, Pubmed)
brigatinib	PARP1, EGFR, CASP3, IGF1R	78	14	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Carcinoma, Neoplasms	Carcinoma, Non-Small-Cell Lung (FDA)
amivantamab	EGFR, MET	74	14	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms	Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA, FDA)
Methotrexate	NR3C1, IL2, NTRK1, HGF, BAX, E2F1, BIRC5	72	12	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Aortic Arch Syndromes, Arteritis, Arthritis, Arthritis, Juvenile, Arthritis, Psoriatic, Arthritis, Rheumatoid, Brain Abscess, Burkitt Lymphoma, Carcinoma, Cardiac Complexes, Premature, Churg-Strauss Syndrome, Cicatrix, Collagen Diseases, Crohn Disease, Demyelinating Diseases, Dermatitis, Dermatitis, Atopic, Disease, Eczema, Edema, Enteropathy-Associated T-Cell Lymphoma, Eye Diseases, Glycogen Storage Disease, Glycogen Storage Disease Type I, Glycogen Storage Disease Type II, Gout, Graft vs Host Disease, Granuloma, Granulomatosis with Polyangiitis, Graves Ophthalmopathy, Immunoblastic Lymphadenopathy, Joint Diseases, Leukemia, Leukemia, Lymphoid, Leukemia, Promyelocytic, Acute, Lung Diseases, Lung Diseases, Interstitial, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, B-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Cutaneous, Lymphoma, T-Cell, Peripheral, Macular Edema, Mediastinal Neoplasms, Medulloblastoma, Meningeal Carcinomatosis, Meningeal Neoplasms, Meningitis, Microscopic Polyangiitis, Mucopolysaccharidoses, Mucopolysaccharidosis I, Mucopolysaccharidosis II, Multiple Sclerosis, Multiple Sclerosis, Relapsing-Remitting, Mycoses, Mycosis Fungoides, Myelitis, Neoplasm Metastasis, Neoplasms, Neoplasms, Germ	Lung Neoplasms (DailyMed)

					Cell and Embryonal, Neoplasms, Second Primary, Neuritis, Optic Neuritis, Osteoarthritis, Panniculitis, Polyarteritis Nodosa, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Pregnancy, Ectopic, Pregnancy, Tubal, Psoriasis, Rage, Recurrence, Rheumatic Diseases, ST Elevation Myocardial Infarction, Sarcoidosis, Sarcoidosis, Pulmonary, Sclerosis, Spondylarthritis, Spondylarthropathies, Spondylitis, Spondylitis, Ankylosing, Syndrome, Systemic Vasculitis, Takayasu Arteritis, Thalassemia, Uveitis, Uveitis, Anterior, Vasculitis, Vitiligo, alpha-Thalassemia, beta-Thalassemia	
entrectinib	NTRK1, NTRK2	71	10	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms	Carcinoma, Non-Small-Cell Lung (FDA , Pubmed)	
icotinib	EGFR	71	21	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Neoplasms, Neoplasms, Second Primary	Carcinoma, Non-Small-Cell Lung (ClinicalTrials , ClinicalTrials , ClinicalTrials) Lung Neoplasms (ClinicalTrials , ClinicalTrials)	
Vinorelbine	BAX, BRCA1	70	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Breast Neoplasms, Neoplasms	Carcinoma, Non-Small-Cell Lung (ClinicalTrials , ClinicalTrials , FDA) Lung Neoplasms (ClinicalTrials , ClinicalTrials , ClinicalTrials , ClinicalTrials , PUBMED)	
mabocertinib	EGFR	68	12	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Neoplasms	Carcinoma, Non-Small-Cell Lung (ClinicalTrials , FDA)	
Etoposide	XIAP, BAX, E2F1, CASP9	66	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Burkitt Lymphoma, Carcinoma, Small Cell, Cytokine Release Syndrome, Enteropathy-Associated T-Cell Lymphoma, Hematologic Neoplasms, Histiocytosis, Hodgkin Disease, Immunoblastic Lymphadenopathy, Leukemia, Leukemia, Lymphoid, Leukemia, Myeloid, Acute, Lymphadenopathy, Lymphatic Diseases, Lymphohistiocytosis, Hemophagocytic, Lymphoma, Lymphoma, B-Cell, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, Medulloblastoma, Neoplasms, Neoplasms, Germ Cell and Embryonal, Panniculitis, Precursor Cell Lymphoblastic Leukemia-Lymphoma,	Lung Neoplasms (ClinicalTrials , ClinicalTrials , DailyMed)	

				Retinoblastoma, Small Cell Lung Carcinoma, Syndrome	
tepotinib	MAPK1, MET, MAPK4, CDH1, GSK3B, MAPK3	59	3	Phase 2: Carcinoma, Non-Small-Cell Lung, Carcinoma, Carcinoma, Hepatocellular, Colorectal Neoplasms, Neoplasms, Rectal Neoplasms, Stomach Neoplasms	Carcinoma, Non-Small-Cell Lung (ClinicalTrials, DailyMed, FDA, FDA)
sotorasib	KRAS	56	7	Phase 2: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Carcinoma, Neoplasms, Pancreatic Neoplasms, Sarcoma	Carcinoma, Non-Small-Cell Lung (ClinicalTrials, FDA, FDA)
Docetaxel	BAX, HRAS	47	24	Phase 4: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Breast Neoplasms, Carcinoma, Carcinoma, Squamous Cell, Chemical and Drug Induced Liver Injury, Colorectal Neoplasms, Head and Neck Neoplasms, Neoplasms, Neoplasms, Second Primary, Prostatic Neoplasms, Squamous Cell Carcinoma of Head and Neck, Triple Negative Breast Neoplasms, Wounds and Injuries	Carcinoma, Non-Small-Cell Lung (FDA, FDA) Lung Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials)
Ketamine	DRD2	28	6	Phase 4: Lung Neoplasms, Abscess, Adenocarcinoma, Agnosia, Alcohol Withdrawal Delirium, Anemia, Anemia, Sickle Cell, Anhedonia, Anxiety, Anxiety Disorders, Apnea, Behavior, Bipolar Disorder, Brain Abscess, Brain Injuries, Brain Injuries, Traumatic, Breast Neoplasms, Bronchial Spasm, Burns, COVID-19, Cataract, Cerebral Hemorrhage, Cholangitis, Cholecystitis, Cholelithiasis, Cholelithiasis, Chronic Disease, Cleft Lip, Cluster Headache, Cognition Disorders, Cognitive Dysfunction, Colonic Neoplasms, Consciousness, Constipation, Coronary Artery Disease, Critical Illness, Cystitis, Cysts, Delayed Emergence from Anesthesia, Delirium, Dental Caries, Depression, Depression, Postpartum, Depressive Disorder, Depressive Disorder, Major, Depressive Disorder, Treatment-Resistant, Disease, Dissociative Disorders, Diverticulitis, Diverticulitis, Colonic, Diverticulum, Emergence Delirium, Fibromyalgia, Fractures, Bone, Fractures, Closed, Fractures, Multiple, Gallstones, Headache, Heart Arrest, Heart Defects, Congenital, Heart Diseases, Heart Septal Defects, Heart Septal Defects, Atrial, Heart Valve Diseases, Hematologic Neoplasms, Hemorrhage, Hemorrhoids, Hernia, Hernia, Inguinal, Hyperalgesia, Hyperventilation, Hypotension, Hypoxia, Ileus, Infections, Inflammation, Intraoperative Complications, Joint Dislocations, Lacerations, Lithiasis, Liver Failure, Low Back Pain, Lung Diseases, Lung Diseases, Obstructive, Mental Disorders, Muscle Rigidity, Musculoskeletal Diseases, Myofascial Pain Syndromes, Nausea, Neoplasms, Neuralgia, Nose Deformities, Acquired, Opioid-Related	Lung Neoplasms (ClinicalTrials, ClinicalTrials)

Disorders, Pain, Paranoid
Disorders, Pathological
Conditions, Anatomical,
Pneumonia, Pneumonia,
Aspiration, Poisoning,
Postoperative Cognitive
Complications, Postoperative
Complications, Postoperative
Nausea and Vomiting, Pressure
Ulcer, Problem Behavior, Prostatic
Neoplasms, Psychomotor
Agitation, Psychoses, Substance-
Induced, Psychotic Disorders,
Pulmonary Atelectasis,
Pulmonary Disease, Chronic
Obstructive, Rectal Neoplasms,
Respiratory Distress Syndrome,
Respiratory Distress Syndrome,
Newborn, Respiratory
Insufficiency, Respiratory Tract
Infections, Retinal Diseases, Rib
Fractures, Schizophrenia,
Scoliosis, Shared Paranoid
Disorder, Shock, Shock, Septic,
Sleep Apnea Syndromes, Sleep
Apnea, Obstructive, Sleep Wake
Disorders, Spasm,
Spondylolisthesis,
Stomatognathic Diseases, Stress
Disorders, Post-Traumatic, Stress
Disorders, Traumatic, Stress
Disorders, Traumatic, Acute,
Subarachnoid Hemorrhage,
Substance Withdrawal
Syndrome, Substance-Related
Disorders, Suicidal Ideation,
Suicide, Suicide, Attempted,
Syndrome, Tension-Type
Headache, Tic Disorders, Tooth
Diseases, Tooth, Impacted,
Trigeminal Neuralgia, Ulcer,
Unconsciousness, Urinary
Bladder Calculi, Vomiting,
Wounds and Injuries

The ***Disease trial phase*** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

Drugs approved in clinical trials



Table 12. Drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in *HumanPSD™* database)

See full table →

Name	Target names	Drug score	Disease activity score	Disease trial phase
Sorafenib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, CHEK2, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, HIPK2, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, MAPK13, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2	98	14	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Acute Disease, Breast Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Renal Cell, Digestive System Diseases, Digestive System Neoplasms, Fibroma, Fibromatosis, Aggressive, Gastrointestinal Diseases, Gastrointestinal Neoplasms, Hepatoblastoma, Intestinal Diseases, Intestinal Neoplasms, Kidney Neoplasms, Leukemia, Leukemia, Monocytic, Acute, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Liver Diseases, Liver Neoplasms, Melanoma, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Glandular and Epithelial, Pancreatic Neoplasms, Recurrence, Sarcoma, Sarcoma, Myeloid, Skin Neoplasms, Thrombosis, Thyroid Diseases, Thyroid Neoplasms, Vaccinia
Sunitinib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, SIRT1, TGFB2, PRKD2	97	16	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Adenoma, Adenoma, Islet Cell, Brain Neoplasms, Breast Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Islet Cell, Carcinoma, Renal Cell, Colorectal Neoplasms, Gastrointestinal Stromal Tumors, Glioblastoma, Kidney Diseases, Kidney Neoplasms, Liver Neoplasms, Neoplasms, Neoplasms by Site, Pancreatic Neoplasms, Prostatic Neoplasms, Rectal Neoplasms, Recurrence, Urogenital Neoplasms, Urologic Neoplasms
Vandetanib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, VEGFA, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, MST1R, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, CDK1, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2	97	14	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Carcinoma, Carcinoma, Medullary, Carcinoma, Neuroendocrine, Neoplasms, Thyroid Diseases, Thyroid Neoplasms
Pazopanib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9,	96	13	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Anemia, Carcinoma, Carcinoma, Renal Cell, Chondrosarcoma, Chondrosarcoma,

PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, FGF1, BLK, SLK, INSR, NEK2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFBR2, PRKD2

Mesenchymal, Dilatation, Pathologic, Epistaxis, Fibrosarcoma, Glomus Tumor, Granular Cell Tumor, Hemangiosarcoma, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Leiomyosarcoma, Liposarcoma, Myosarcoma, Neoplasms, Nerve Sheath Neoplasms, Neurofibrosarcoma, Osteosarcoma, Ovarian Neoplasms, Ranula, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Clear Cell, Sarcoma, Synovial, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis

motesanib	<p>TEC, BMP1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFBR2, PRKD2</p>	94	12	Phase 3: Carcinoma, Non-Small-Cell Lung, Lung Neoplasms, Leukemia, Myelodysplastic Syndromes, Neoplasms, Preleukemia, Primary Myelofibrosis, Syndrome
-----------	--	----	----	---

The **Disease trial phase** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

Repurposing drugs



Table 13. Repurposed drugs used in clinical trials for other pathologies (prospective drugs against the identified drug targets on the basis of literature curation in *HumanPSD™* database)

See full table →

Name	Target names	Drug score	Maximum trial phase
ruboxistaurin	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, PRKCG, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, CHEK2, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, HIPK2, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, MAPK13, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKCB, PRKD2	74	Phase 3: Diabetes Mellitus, Diabetes Mellitus, Type 1, Diabetes Mellitus, Type 2, Diabetic Neuropathies, Diabetic Retinopathy, Edema, Macular Edema, Nervous System Diseases, Peripheral Nervous System Diseases, Retinal Diseases
1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, CHEK2, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, HIPK2, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, IKBKB, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, MAPK13, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2	74	Phase 2: Arthritis, Arthritis, Rheumatoid, Psoriasis
midostaurin	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, PRKCG, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, TNF, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, IL2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, CASP3, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, CASP7, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2	74	Phase 3: Anemia, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Myelodysplastic Syndromes, Preleukemia, Syndrome
Tofacitinib	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4, CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, MAPK13, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKD2	74	Phase 4: Alopecia, Alopecia Areata, Aortic Arch Syndromes, Arteritis, Arthritis, Arthritis, Psoriatic Arthritis, Rheumatoid, COVID-19, Colitis, Colitis, Ulcerative, Disease, Embolism, Granuloma, Granulomatosis with Polyangiitis, Infections, Lung Diseases, Lung Diseases, Interstitial, Necrosis, Rheumatic Fever, ST Elevation Myocardial Infarction, Spondylarthritis, Spondylitis, Spondylitis, Ankylosing, Systemic Vasculitis, Takayasu Arteritis, Thromboembolism, Ulcer, Vasculitis
bms-387032	TEC, BMPR1A, IKBKE, ABL1, PAK2, PRKACA, GSK3B, MAP3K11, SYK, NEK6, ERBB2, LIMK1, MAPK3, MAP2K6, JAK1, MELK, MAPK8, PRKCG, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, BTK, WEE1, MAPK11, FLT1, PRKCD, LYN, AKT2, PDPK1, MAPK10, NTRK1, KDR, PRKCA, CSNK1E, TTK, PDGFRA, RAF1, CDK7, MAPK14, CSNK1D, HCK, CHEK1, PTK6, RIPK2, FGFR3, CDK9, PKN2, RPS6KA2, NTRK2, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, BLK, SLK, INSR, NEK2, MAP2K2, MAP2K3, CSK, PRKD1, TEK, PKN1, PIP5K1A, TYK2, IGF1R, MAP3K5, MAPK4, PDGFRB, MAP2K1, MAP4K3, RIPK1, STK4,	74	Phase 1: Leukemia, Lymphocytic, Chronic, B-Cell, Lymphoma, Mantle-Cell, Multiple Myeloma, Neoplasms

CAMK2A, PTK2, MAPKAPK2, FES, PLK4, DAPK3, ACVR1B, CAMK2G, MET, PRKAA2, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PRKCH, ACVR2A, PTK2B, PRKG1, AKT1, AURKA, MAP3K20, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, MERTK, PRKCE, FGFR1, PAK3, FER, CAMKK1, ZAP70, PIK3CA, TGFB2, PRKCB, PRKD2

The **Maximum trial phase** column reflects the maximum clinical trials phase in which the drug was studied for any pathology.



Table 14. Prospective drugs, predicted by **PASS** software to be active against the identified drug targets with predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool **PASS**)

[See full table](#) →

Name	Target names	Drug score	Target activity score
6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazol-5-one	CAMK2D, PRKACG, PRKCG, CAMK2G, PRKCH, PRKD3, CAMK2A, PRKACA, PRKD1, PRKCZ	97	3.46
K101	CDC25A, PTPRD, TNFSF11, PTPN1, TNF, PTPRC, PTPN11, PTPN22, TNFRSF1B, PTPRT, PTEN, CDC25C, PTPRU	83	0.35
Camptothecin	HIF1A, CASP3	81	0.31
LE-SN38	HIF1A, CASP3	80	0.29
Etoposide	CASP8, HIF1A, CASP3, CASP9, RELA	80	0.25



Table 15. Prospective drugs, predicted by **PASS** software to be active against the identified drug targets, though without cheminformatically predicted activity against the studied disease(s) (drug candidates predicted with the cheminformatics tool **PASS**)

[See full table](#) →

Name	Target names	Drug score	Target activity score
3-[1-(3-Aminopropyl)-1h-Indol-3-Yl]-4-(1-Methyl-1h-Indol-3-Yl)-1h-Pyrrole-2,5-Dione	CDK6, CAMK2G, GRK2, PRKAA2, PRKCQ, PRKACA, GSK3B, PRKCA, BLK, CDK1, CDK4, CDK7, RPS6KA1, PRKAA1, NEK2, SGK1, PRKCH, PRKD1, PKN1, MAP2K6, LRRK2, GRK6, PRKCG, CDK9, PKN2, RPS6KA2, GRK5, PRKD3, PRKCE, PRKCZ, CAMK2D, PRKACG, CAMK2A, SIRT1, PRKCD, PRKCI, CDK5, GRK3, PRKCB	97	29.85
Rbt205 Inhibitor	CDK6, CAMK2G, GRK2, PRKAA2, PRKCQ, PRKACA, GSK3B, PRKCA, BLK, CDK1, MAP2K4, CDK4, CDK7, RPS6KA1, PRKAA1, SGK1, PRKCH, PRKD1, PKN1, MAP2K6, LRRK2, GRK6, PRKCG, CDK9, RPS6KA2, PKN2, GRK5, PRKD3, PRKCE, PRKCZ, CAMK2D, PRKACG, PTK2, CAMK2A, SIRT1, PRKCD, PRKCI, CDK5, GRK3, PRKCB, DAPK3	97	28.43
3-[1-(3-AMINOPROPYL)-1H-INDOL-3-YL]-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE	CDK6, CAMK2G, GRK2, PRKAA2, PRKCQ, PRKACA, GSK3B, PRKCA, BLK, CDK1, MAP2K4, CDK4, CDK7, RPS6KA1, PRKAA1, SGK1, PRKCH, PRKG1, CHEK1, PRKD1, MAP2K6, PKN1, RPS6KB1, LRRK2, DYRK1B, GRK6, PRKCG, CDK9, RPS6KA2, PKN2, GRK5, PRKD3, PRKCE, PRKCZ, CAMK2D, MAPK12, PRKACG, CAMK2A, SIRT1, PRKCD, PRKCI, CDK5, GRK3, CHEK2, PRKCB, DAPK3	96	33.12
7-[4-(Dimethylamino)Phenyl]-N-Hydroxy-4,6-Dimethyl-7-Oxo-2,4-Heptadienamide	HDAC4, HDAC2, HDAC3	95	1.62
(1S,6BR,9AS,11R,11BR)-9A,11B-DIMETHYL-1-[(METHYLOXY)METHYL]-3,6,9-TRIOXO-1,6,6B,7,8,9A,10,11,11B-DECAHYDRO-3H-FURO[4,3,2-DE]INDENO[4,5-H][2]BENZOPYRAN-11-YL ACETATE	PIK3CG, PI4K2A, PIK3R2, RELA, PIK3C3, PLK3, SGK1, NEK6, HIF1A, PIK3CA, PI4KB, PIP5K1B, PIP5K1A	95	4.58

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Erlotinib, ruboxistaurin, 6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazol-5-one and 3-[1-(3-Aminopropyl)-1h-Indol-3-Yl]-4-(1-Methyl-1h-Indol-3-Yl)-1h-Pyrrole-2,5-Dione. These drugs were selected for acting on the following targets: MAP2K3, PRKD1 and LRRK2, which were predicted to be active in the molecular mechanism of the studied pathology.

The selected drugs are top ranked drug candidates from each of the four categories of drugs: (1) FDA approved drugs or used in clinical trials drugs for the studied pathology; (2) repurposing drugs used in clinical trials for other pathologies; (3) drugs, predicted by **PASS** software to be active against the studied pathology; (4) drugs, predicted by **PASS** software to be repurposed from other pathologies.

Supplementary drug info

In addition to the approved and repurposed drugs proposed by Genome Enhancer, below the **Supplementary drug info** table is given, which contains an extended list of drugs used for treatment of neoplasms. Those drugs which were predicted by Genome Enhancer as prospective treatment candidates for the studied case (both approved and repurposed) have a respective **Predicted Drug Score** assigned to them. This value on a scale from 1 to 100 reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. The **Predicted Drug Score** column

contains the "-" (Not Identified) value in case the drug targets of the respective treatment were not found in the molecular mechanism of the studied pathology.

Table 16. Supplementary drug info: extended list of drugs used for treatment of neoplasms with respective drug scores predicted for the studied pathology.

Drug	Disease	Predicted Drug Score	Somatic variants
Abarelix	Prostatic Neoplasms	10	
Abemaciclib	Breast Neoplasms	68	
Abiraterone	Prostatic Neoplasms, Castration-Resistant	-	
Abiraterone acetate	Prostatic Neoplasms, Castration-Resistant	-	
Acalabrutinib	Lymphoma, Mantle-Cell	63	
Acitretin	Psoriasis	36	
Ado-trastuzumab emtansine	Breast Neoplasms Neoplasms	78	
Afatinib	Carcinoma, Non-Small-Cell Lung	88	EGFR:T790M:resistance:A1, EGFR:L858R:response:A1
Aflibercept	Colorectal Neoplasms Diabetic Retinopathy Edema Vascular Diseases Wet Macular Degeneration	22	
Alectinib	Carcinoma, Non-Small-Cell Lung	83	
Alemtuzumab	Brain Abscess Leukemia, Lymphocytic, Chronic, B-Cell Multiple Sclerosis Multiple Sclerosis, Relapsing-Remitting Sclerosis	-	
Alitretinoin	Sarcoma, Kaposi	-	
Alpelisib	Breast Neoplasms	58	
Altretamine	Ovarian Neoplasms	-	
Aminolevulinic acid	Keratosis Keratosis, Actinic	-	
Anagrelide	Thrombocytopenia, Essential Thrombocytosis	-	
Anastrozole	Breast Neoplasms Hypersensitivity Obesity Obesity, Morbid Recurrence Weight Loss	-	
Apalutamide	Prostatic Neoplasms, Castration-Resistant	-	
Aprepitant	Nausea Neoplasms Postoperative Nausea and Vomiting	-	
Arsenic trioxide	Leukemia, Promyelocytic, Acute	75	
Atezolizumab	Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell Triple Negative Breast Neoplasms	-	
Avelumab	Carcinoma, Merkel Cell Carcinoma, Renal Cell Carcinoma, Transitional Cell	-	
Axitinib	Carcinoma, Renal Cell	88	
Azacitidine	Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes Preleukemia Syndrome	48	
Belinostat	Lymphoma, T-Cell, Peripheral	68	
Bendamustine	Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Lymphoid	-	
Bevacizumab	Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms Corneal Neovascularization Diabetic Retinopathy Dilatation, Pathologic Edema Epistaxis Glaucoma Hemorrhage Macular Degeneration Macular Edema Neoplasm Metastasis Neoplasms Neovascularization, Pathologic Optic Nerve Diseases Pterygium Rectal Neoplasms Retinal Detachment Retinal Diseases Retinal Vein Occlusion Telangiectasia, Hereditary Hemorrhagic Telangiectasis Vitreous Hemorrhage	28	
Bexarotene	Lymphoma, T-Cell Lymphoma, T-Cell, Cutaneous	26	
Bicalutamide	Prostatic Neoplasms	33	
Binimetinib	Melanoma	73	
Blinatumomab	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-	
Bortezomib	Brain Abscess Glomerulonephritis Glomerulonephritis, IGA Kidney Diseases Multiple Myeloma Neoplasms, Plasma Cell Nephritis Renal Insufficiency	61	
Bosutinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	69	
Brentuximab vedotin	Hodgkin Disease Lymphoma Lymphoma, Large-Cell, Anaplastic Lymphoma, T-Cell, Peripheral	-	
Brigatinib	Carcinoma, Non-Small-Cell Lung	78	
Buserelin	Prostatic Neoplasms	-	
Cabazitaxel	Prostatic Neoplasms, Castration-Resistant	77	
Cabergoline	Drug-Related Side Effects and Adverse Reactions Pituitary Neoplasms	4	
Cabozantinib	Thyroid Neoplasms	88	
Capecitabine	Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms	23	
Carboplatin	Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms Neuroendocrine Tumors Ovarian Neoplasms Retinoblastoma	-	
Carfilzomib	Multiple Myeloma	80	
Carmustine	Astrocytoma Glioblastoma Hodgkin Disease Medulloblastoma Multiple Myeloma Neoplasms	9	

Ceritinib	Carcinoma, Non-Small-Cell Lung	92	
Cetuximab	Colorectal Neoplasms	42	
Cinacalcet	Anemia Calcinosis Cardiovascular Diseases Hyperparathyroidism Hyperparathyroidism, Secondary Kidney Diseases Kidney Failure, Chronic Neoplasm Metastasis Neoplasms Parathyroid Neoplasms Renal Insufficiency Vascular Calcification Vascular Diseases Vision Disorders	-	
Cisplatin	Carcinoma, Squamous Cell Neoplasms Uterine Cervical Neoplasms Carcinoma, Non-Small-Cell Lung Esophageal Neoplasms Carcinoma	81	ERCC2:K751Q:resistance:B2
Cladribine	Leukemia, Hairy Cell	43	
Clofarabine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	22	
Cobimetinib	Melanoma	81	
Copanlisib	Lymphoma, Follicular	78	
Crizotinib	Carcinoma, Non-Small-Cell Lung	96	
Cyproterone acetate	Prostatic Neoplasms	21	
Dabrafenib	Melanoma	61	
Dacomitinib	Carcinoma, Non-Small-Cell Lung	92	
Daratumumab	Multiple Myeloma	-	
Dasatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid, Chronic-Phase Precursor Cell Lymphoblastic Leukemia-Lymphoma	90	
Decitabine	Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes	17	
Degarelix	Cardiovascular Diseases Prostatic Neoplasms Vascular Diseases	61	
Denosumab	Arthritis, Rheumatoid Bone Diseases Bone Diseases, Metabolic Breast Neoplasms Hyperparathyroidism Hyperparathyroidism, Primary Metabolic Diseases Neoplasm Metastasis Neoplasms Osteoporosis Osteoporosis, Postmenopausal Prostatic Neoplasms	72	
Dexrazoxane	Breast Neoplasms Cardiomyopathies	3	
Dienogest	Menorrhagia	33	
Dinutuximab	Neuroblastoma	-	
Docetaxel	Breast Neoplasms Carcinoma, Non-Small-Cell Lung Prostatic Neoplasms Squamous Cell Carcinoma of Head and Neck Stomach Neoplasms	47	
Doxorubicin	Neoplasms Multiple Myeloma Carcinoma, Ovarian Epithelial Ovarian Neoplasms Leukemia, Lymphoid Breast Neoplasms Lymphoma, Follicular Thyroid Neoplasms Triple Negative Breast Neoplasms Glioma	82	
Durvalumab	Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell	-	
Dutasteride	Alcoholism Hyperplasia Hypertrophy Neoplasms Prostatic Hyperplasia	-	
Duvelisib	Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular	60	
Elotuzumab	Multiple Myeloma	57	
Enasidenib	Leukemia, Myeloid, Acute	-	
Encorafenib	Colorectal Neoplasms Melanoma	78	
Enfortumab vedotin	Carcinoma, Transitional Cell Neoplasms	-	
Entrectinib	Carcinoma, Non-Small-Cell Lung	71	
Enzalutamide	Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant	-	
Epirubicin	Breast Neoplasms	52	
Erdafitinib	Urinary Bladder Neoplasms	80	
Eribulin	Breast Neoplasms Drug-Related Side Effects and Adverse Reactions Neoplasms	-	
Erlotinib	Carcinoma, Non-Small-Cell Lung Neoplasms Pancreatic Neoplasms	100	EGFR:T790M:resistance:A1, EGFR:L858R:response:A1
Erlotinib hydrochloride	Carcinoma, Non-Small-Cell Lung Gastrointestinal Stromal Tumors	-	
Estramustine	Prostatic Neoplasms	5	
Ethinyl Estradiol	Acne Vulgaris Neoplasms	9	
Everolimus	Angiomyolipoma Arthrogyryposis Astrocytoma Breast Neoplasms Carcinoma, Renal Cell Cysts Idiopathic Pulmonary Fibrosis Kidney Diseases, Cystic Kidney Failure, Chronic Lipoma Neuroendocrine Tumors Primary Graft Dysfunction Sclerosis Tuberous Sclerosis	88	
Exemestane	Breast Neoplasms	-	
Fedratinib	Primary Myelofibrosis	16	
Finasteride	Hyperplasia Neoplasms Prostatic Hyperplasia	23	
Flavopiridol	Leukemia, Lymphocytic, Chronic, B-Cell	76	
Fluorouracil	Skin Neoplasms Neoplasms, Basal Cell Neoplasms, Second Primary Neoplasms, Squamous Cell Neoplasms Colorectal Neoplasms Pancreatic Neoplasms	75	
Fluoxymesterone	Breast Neoplasms Hypogonadism Puberty, Delayed	3	

Flutamide	Premenstrual Dysphoric Disorder Premenstrual Syndrome Prostatic Neoplasms	5	
Fulvestrant	Breast Neoplasms	69	
Gefitinib	Carcinoma, Non-Small-Cell Lung	99	EGFR:T790M:resistance:A2, EGFR:L858R:response:A1
Gemcitabine	Breast Neoplasms Carcinoma, Non-Small-Cell Lung Ovarian Neoplasms Pancreatic Neoplasms	88	
Gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	-	
Gilteritinib	Leukemia, Myeloid, Acute	79	
Glasdegib	Leukemia, Myeloid, Acute	-	
Goserelin	Atrophy Breast Neoplasms Bulbo-Spinal Atrophy, X-Linked Endometriosis Muscular Atrophy Myoma Prostatic Neoplasms	13	
Histrelin	Puberty, Precocious	-	
Homoharringtonine	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	66	
Ibritumomab	Lymphoma, B-Cell Lymphoma, Follicular	-	
Ibrutinib	Graft vs Host Disease Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, B-Cell, Marginal Zone Lymphoma, Mantle-Cell Waldenstrom Macroglobulinemia	87	
Idarubicin	Leukemia, Myeloid, Acute	30	
Idelalisib	Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular	71	
Ifosfamide	Neoplasms	-	
Imatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Mastocytosis, Systemic Neoplasms	90	
Inotuzumab ozogamicin	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-	
Ipilimumab	Carcinoma, Renal Cell Melanoma	58	
Irinotecan	Colorectal Neoplasms	72	
Ivosidenib	Leukemia, Myeloid, Acute	-	
Ixabepilone	Breast Neoplasms	-	
Ixazomib	Multiple Myeloma	-	
Lapatinib	Breast Neoplasms	92	
Larotrectinib	Neoplasm Metastasis	71	
Lenalidomide	Brain Abscess Lupus Erythematosus, Cutaneous Myelodysplastic Syndromes Neoplasms, Plasma Cell	60	
Lenvatinib	Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms	91	
Letrozole	Breast Neoplasms Cysts Fibroma Myofibroma Myoma Ovarian Cysts Syndrome	51	
Leuprolide	Hot Flashes Ovarian Hyperstimulation Syndrome Prostatic Neoplasms Puberty, Precocious	16	
Levamisole	Ascariasis Colonic Neoplasms Helminthiasis	-	
Levonorgestrel	Epilepsy Hyperplasia Menorrhagia	25	
Lomustine	Brain Neoplasms Hodgkin Disease	-	
Lonafarnib	Breast Neoplasms Carcinoma, Non-Small-Cell Lung Central Nervous System Neoplasms Colorectal Neoplasms Gliosarcoma Head and Neck Neoplasms Leukemia, Myelomonocytic, Chronic Liver Neoplasms Lymphoma Myelodysplastic Syndromes Ovarian Neoplasms Urethral Neoplasms Urinary Bladder Neoplasms	31	
Lorlatinib	Carcinoma, Non-Small-Cell Lung	91	
Masoprocol	Keratosis, Actinic	30	
Medroxyprogesterone Acetate	Depression Depression, Postpartum Depressive Disorder Metrorrhagia Neoplasms Uterine Hemorrhage	39	
Megestrol acetate	Acquired Immunodeficiency Syndrome Bites and Stings Breast Neoplasms Pain Wasting Syndrome	37	
Methotrexate	Neoplasms Breast Neoplasms Head and Neck Neoplasms Ovarian Neoplasms Lymphoma, T-Cell, Peripheral Brain Neoplasms Colorectal Neoplasms Neuroblastoma Carcinoma, Squamous Cell	72	
Methyltestosterone	Breast Neoplasms Hypogonadism Puberty, Delayed	-	
Midostaurin	Leukemia, Mast-Cell Leukemia, Myeloid, Acute Mastocytosis, Systemic	74	
Mitotane	Adrenocortical Carcinoma	-	
Mitoxantrone	Autoimmune Diseases Autoimmune Diseases of the Nervous System Demyelinating Autoimmune Diseases, CNS Immune System Diseases Leukemia, Myeloid, Acute Multiple Sclerosis Myelitis Myelitis, Transverse Nervous System Diseases Neuromyelitis Optica Prostatic Neoplasms, Castration-Resistant	33	
Mogamulizumab	Mycosis Fungoides Neoplasms Sezary Syndrome	-	
Moxetumab pasudotox	Leukemia, Hairy Cell Neoplasms	-	
Necitumumab	Carcinoma, Non-Small-Cell Lung Neoplasms	-	
Nelarabine	Precursor T-Cell Lymphoblastic Leukemia-Lymphoma	-	

Neratinib	Breast Neoplasms	85	
Nilotinib	Blast Crisis Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid, Chronic-Phase	59	
Nilutamide	Prostatic Neoplasms	-	
Nintedanib	Fibrosis Idiopathic Pulmonary Fibrosis	90	
Niraparib	Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms	70	
Nivolumab	Carcinoma, Non-Small-Cell Lung Kidney Neoplasms Neoplasms Lung Neoplasms Melanoma	-	
Obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	-	
Octreotide	Acromegaly Adenoma Ascites Carcinoid Tumor Fistula Pancreatic Fistula Pituitary Diseases Renal Insufficiency Vipoma	38	
Ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	-	
Olaparib	Breast Neoplasms Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Ovarian Neoplasms Pancreatic Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant	60	
Olaratumab	Sarcoma	-	
Osimertinib	Carcinoma, Non-Small-Cell Lung	92	EGFR:T790M:response:A1
Oxaliplatin	Colonic Neoplasms Colorectal Neoplasms Neoplasms Rectal Neoplasms	66	
Paclitaxel	Acute Coronary Syndrome Angina Pectoris Arteriosclerosis Breast Neoplasms Carcinoma, Non-Small-Cell Lung Cardiovascular Diseases Coronary Artery Disease Coronary Disease Coronary Stenosis Heart Diseases Myocardial Ischemia Ovarian Neoplasms Vascular Diseases	90	
Palbociclib	Breast Neoplasms	71	
Panitumumab	Colorectal Neoplasms	58	
Panobinostat	Multiple Myeloma	44	
Pazopanib	Carcinoma Carcinoma, Renal Cell Sarcoma	96	
Pembrolizumab	Carcinoma, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Non-Small-Cell Lung Carcinoma, Renal Cell Carcinoma, Transitional Cell Hodgkin Disease Melanoma Neoplasms Stomach Neoplasms	-	
Pemetrexed	Carcinoma, Non-Small-Cell Lung Mesothelioma	-	
Pentostatin	Leukemia, Hairy Cell	18	
Pertuzumab	Breast Neoplasms	80	
Pomalidomide	Multiple Myeloma	16	
Ponatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Precursor Cell Lymphoblastic Leukemia-Lymphoma	91	
Pralatrexate	Lymphoma, T-Cell, Peripheral	-	
Radium Ra 223 Dichloride	Prostatic Neoplasms, Castration-Resistant	-	
Ramucirumab	Stomach Neoplasms	-	
Rasburicase	Hyperuricemia Leukemia Lymphoma Neoplasms Syndrome Tumor Lysis Syndrome	-	
Regorafenib	Colorectal Neoplasms	87	
Relugolix	Prostatic Neoplasms	-	
Ribociclib	Breast Neoplasms	58	
Rituximab	Arthritis Arthritis, Rheumatoid Granulomatosis with Polyangiitis Leukemia Leukemia, Lymphoid Lymphoma Lymphoma, B-Cell Lymphoma, Follicular Lymphoma, Non-Hodgkin Myelitis Neuromyelitis Optica Purpura Purpura, Thrombocytopenic Purpura, Thrombocytopenic, Idiopathic Thrombocytopenia	-	
Romidepsin	Lymphoma, T-Cell, Cutaneous	74	
Rucaparib	Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant	74	
Ruxolitinib	Graft vs Host Disease Polycythemia Polycythemia Vera Primary Myelofibrosis Thrombocytosis	74	
Selinexor	Multiple Myeloma	34	
Selumetinib	Neurofibromatosis 1	84	
Siltuximab	Giant Lymph Node Hyperplasia	-	
Sirolimus	Angiomyolipoma Constriction, Pathologic Coronary Restenosis Eye Diseases Immune System Diseases Kidney Failure, Chronic Lipoma Tuberous Sclerosis	89	
Sonidegib	Carcinoma, Basal Cell	-	
Sorafenib	Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms	98	
Sunitinib	Adenoma Carcinoma, Renal Cell Digestive System Neoplasms Gastrointestinal Neoplasms Gastrointestinal Stromal Tumors Intestinal Neoplasms	97	
Talazoparib	Breast Neoplasms	52	
Tamoxifen	Breast Diseases Cystic Fibrosis Cysts Fibroadenoma Fibrocystic Breast Disease Hemorrhage Menorrhagia Menstruation Disturbances Metrorrhagia Neoplasms	60	

Tamsulosin	Calculi Coronary Artery Disease Heart Diseases Hernia Hernia, Inguinal Inflammation Ischemia Lithiasis Lower Urinary Tract Symptoms Myocardial Ischemia Prostatic Hyperplasia Ureteral Calculi Urinary Calculi Urolithiasis Urologic Diseases	-
Temozolomide	Astrocytoma Nervous System Neoplasms	-
Temsirolimus	Carcinoma, Renal Cell	82
Teniposide	Precursor Cell Lymphoblastic Leukemia-Lymphoma	40
Thalidomide	Brain Abscess Immune System Diseases Multiple Myeloma Neoplasms, Plasma Cell	72
Tivozanib	Carcinoma, Renal Cell	86
Tocilizumab	Arthritis Arthritis, Juvenile Arthritis, Rheumatoid Behavior Cytokine Release Syndrome Giant Cell Arteritis Neurobehavioral Manifestations Oral Manifestations Psychotic Disorders Schizophrenia Tic Disorders	-
Topotecan	Small Cell Lung Carcinoma	59
Toremifene	Breast Neoplasms	31
Trabectedin	Leiomyosarcoma Liposarcoma	-
Trametinib	Carcinoma, Non-Small-Cell Lung Melanoma	93
Trastuzumab	Breast Neoplasms Neoplasms	70
Tretinoin	Lentigo	75
Triptorelin	Fatty Liver Hypogonadism Infertility, Female Prostatic Neoplasms	64
Tucatinib	Breast Neoplasms	71
Valrubicin	Urinary Bladder Neoplasms	-
Vandetanib	Thyroid Neoplasms	97
Vemurafenib	Melanoma	65
Venetoclax	Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Myeloid, Acute	-
Vinblastine	Glioma	55
Vincristine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	53
Vinorelbine	Carcinoma, Non-Small-Cell Lung	70
Vismodegib	Carcinoma, Basal Cell	-
Vorinostat	Lymphoma, T-Cell, Cutaneous	75
Zoledronate	Arthritis Bone Marrow Diseases Brain Abscess Chronic Kidney Disease-Mineral and Bone Disorder Chronic Periodontitis HIV Infections Hypersensitivity Infections Kidney Diseases Metabolic Diseases Multiple Myeloma Neoplasms Neoplasms, Plasma Cell Neoplasms, Second Primary Osteitis Osteoarthritis Periodontitis Pleural Effusion, Malignant Prostatic Neoplasms Renal Insufficiency, Chronic Thalassemia Wounds and Injuries	-

6. Conclusion

We applied the software package "Genome Enhancer" to a data set that contains *genomics* data. The study is done in the context of *Non-Small-Cell Lung Carcinoma and Lung Neoplasms*. The data were pre-processed, statistically analyzed and genes carrying sequence variations were identified. Also checked was the enrichment of GO or disease categories among the studied gene sets.

We propose the following drugs as most promising candidates for treating the pathology under study:



Erlotinib, ruboxistaurin, 6,7,12,13-tetrahydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazol-5-one and 3-[1-(3-Aminopropyl)-1h-Indol-3-Yl]-4-(1-Methyl-1h-Indol-3-Yl)-1h-Pyrrole-2,5-Dione

These drugs were selected for acting on the following targets: MAP2K3, PRKD1 and LRRK2, which were predicted to be involved in the molecular mechanism of the pathology under study.

The identified molecular mechanism of the studied pathology was predicted to be mainly based on the following key drug targets:



MKK3:Dyrk1B, PLCgamma2 and BRCA1

These potential drug targets should be considered as a prospective research initiative for further drug repurposing and drug development purposes. The following drugs were predicted as, matching those drug targets: 3-(4-HYDROXY-3-METHOXYPHENYL)-2-PROPENOIC ACID, 2,5,7-Trihydroxynaphthoquinone, Erlotinib, 3-[1-(3-AMINOPROPYL)-1H-INDOL-3-YL]-4-(1H-INDOL-3-YL)-1H-PYRROLE-2,5-DIONE, Paclitaxel, ruboxistaurin, fimepinostat and acalabrutinib. These drugs should be considered with special caution for research purposes only.

In this study, we came up with a detailed signal transduction network regulating genes carrying sequence variations in the studied pathology. In this network we have revealed the following top master regulators (signaling proteins and their

complexes) that play a crucial role in the molecular mechanism of the studied pathology, which can be proposed as the most promising molecular targets for further drug repurposing and drug development initiatives.

- MKK3:Dyrk1B
- PLCgamma2
- BRCA1

Potential drug compounds which can be affecting these targets can be found in the "Finding prospective drug targets" section.

7. Methods

Databases used in the study

Transcription factor binding sites in promoters and enhancers of genes carrying sequence variations were analyzed using known DNA-binding motifs described in the [TRANSFAC®](https://genexplain.com/transfac) library, release 2022.2 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transfac>).

The master regulator search uses the [TRANSPATH®](https://genexplain.com/transpath) database (BIOBASE), release 2022.2 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transpath>). A comprehensive signal transduction network of human cells is built by the software on the basis of reactions annotated in [TRANSPATH®](https://genexplain.com/transpath).

The information about drugs corresponding to identified drug targets and clinical trials references were extracted from [HumanPSD™](https://genexplain.com/humanpsd) database, release 2022.2 (<https://genexplain.com/humanpsd>).

The Ensembl database release Human104.38 (hg38) (<http://www.ensembl.org>) was used for gene IDs representation and Gene Ontology (GO) (<http://geneontology.org>) was used for functional classification of the studied gene set.

Genomic data processing

When analyzing a list of genomic variations (from input vcf file or computed by Genome Enhancer from SNP list or from fastq files), first of all, we compute a specific mutation weight (w_1) for each variation depending on its location in gene body and gene flanking regions (-1000 upstream and +1000 downstream of the gene body).

$w_1 = 0.7$ for variations in exon area

$w_1 = 1.3$ for variations in promoter region (-1000bp upstream and 100bp downstream of TSS),

$w_1 = 1.0$ for variations in other locations.

Next, VCF track (Yes track), provided as input or created by Genome Enhancer from SNP list or fastq files, is compared to Random VCF track (No track) of 10000 random human variations. On both tracks we calculate the score delta values (differences between PWM score values of the TF sites with the reference or with the alternative allele of the considered variation). For each variation we find then the maximal score delta values at each PWM leading either to the gain or to the loss of TF site (with the alternative allele). For selecting the maximum score delta values we consider both directions of DNA strand. Next, by going through all variations we compute two p-values for each PWM – the p-value of site losses and p-value of site gains. The p-values are computed using cumulative Binomial distribution estimating the random chances to observe the found high number of lost or gained TF sites in Yes track in the comparison to the No track. The PWM cut-offs are optimized to obtain the most extreme p-values. We further take top 20 best matrices by p-value from each: gained and lost sites and calculate the mutation weights on the Yes track on the basis of the obtained 40 matrices. Each mutation is assigned with a respective matrix that got the maximum delta value either for the site gain or for the site loss (changed the binding affinity most significantly). This delta is then compared to other delta values that were computed for the respective matrix on the No track. The eventual weight that reflects the transcription factor binding affinity change caused by the mutation is calculated as follows:

$w_2 = -\log_{10}(\text{NoGr} / \text{NoAll})$, if $\text{NoGr} > 0$

$w_2 = -\log_{10}(1.0 / (2.0 * \text{NoAll}))$, if $\text{NoGr} = 0$

where NoGr is the number of deltas from the No track that appeared to be greater than the inspected delta and NoAll is the total number of deltas in the No track. The resulting track is then constructed that contains all sites of the initial Yes track together with the additional weights reflecting the transcription factor binding affinity change caused by the mutation.

The list of 40 matrices most affected by variations will be further used in composite modules search described in the next section.

Total Gene mutation weight is the sum of the weights w_1 of all variations located inside the gene body and in the gene flanking regions summed up with the weight w_2 that reflects the transcription factor binding affinity change caused by the mutation. This weight is calculated by estimating the importance of a certain mutation in terms of gains or losses of binding sites caused by it.

Next, a weighted score is calculated for all genes with the following formula:

Weighted score = $\text{In_disease} * \text{In_transpath} * \text{Gene mutation weight}$, where

$\text{In_disease} = 2.0$ for genes assigned to selected diseases,

$\text{In_transpath} = 1.5$ for genes mapped to Transpath pathways,

and $\text{In_disease} = \text{In_transpath} = 1.0$ in all other cases.

At the next step, 300 genes with highest weighted score are selected for further CMA model search.

The mutation weights ($w = w_1 + w_2$) are also used to find the regulatory regions of the genes most affected by the variations/SNP. A sliding window of 1100 bp is used to scan through the intronic, 5' and 3' regions of the genes and a region is selected with the highest sum of the mutation weights.

Methods for the analysis of enriched transcription factor binding sites and composite modules

Transcription factor binding sites in promoters and enhancers of differentially expressed genes were analyzed using known DNA-binding motifs. The motifs are specified using position weight matrices (PWMs) that give weights to each nucleotide in each position of the DNA binding motif for a transcription factor or a group of them.

We search for transcription factor binding sites (TFBS) that are enriched in the enhancers under study as compared to a background set of promoters of housekeeping genes. We denote study and background sets briefly as Yes and No sets. In the current work we used a workflow considering promoter sequences of a standard length of 1100 bp (-1000 to +100). The error rate in this part of the pipeline is controlled by estimating the adjusted p-value (using the Benjamini-Hochberg procedure) in comparison to the TFBS frequency found in randomly selected regions of the human genome (adj.p-value < 0.01).

We have applied the CMA algorithm (Composite Module Analyst) for searching composite modules [7] in the promoters and enhancers of the Yes and No sets. We searched for a composite module consisting of a cluster of 10 TFs in a sliding window of 200-300 bp that statistically significantly separates sequences in the Yes and No sets (minimizing Wilcoxon p-value). Each composite module is forced to include at least one matrix that was identified as matrix causing the significant change in the transcription factor binding affinity as the result of the observed mutation.

Methods for finding master regulators in networks

We searched for master regulator molecules in signal transduction pathways upstream of the identified transcription factors. The master regulator search uses a comprehensive signal transduction network of human cells. The main algorithm of the master regulator search has been described earlier [3,4]. The goal of the algorithm is to find nodes in the global signal transduction network that may potentially regulate the activity of a set of transcription factors found at the previous step of the analysis. Such nodes are considered as most promising drug targets, since any influence on such a node may switch the transcriptional programs of hundreds of genes that are regulated by the respective TFs. In our analysis, we have run the algorithm with a maximum radius of 12 steps upstream of each TF in the input set. The error rate of this algorithm is controlled by applying it 10000 times to randomly generated sets of input transcription factors of the same set-size. Z-score and FDR value of ranks are calculated then for each potential master regulator node on the basis of such random runs (see detailed description in [9]). We control the error rate by the FDR threshold 0.05.

Methods for analysis of pharmaceutical compounds

We seek for the optimal combination of molecular targets (key elements of the regulatory network of the cell) that potentially interact with pharmaceutical compounds from a library of known drugs and biologically active chemical compounds, using information about known drugs from HumanPSD™ and predicting potential drugs using PASS program.

Method for analysis of known pharmaceutical compounds

We selected compounds from HumanPSD™ database that have at least one target. Next, we sort compounds using "Drug rank" that is the sum of the following ranks:

1. ranking by "Target activity score" ($T\text{-score}_{PSD}$),
2. ranking by "Disease activity score" ($D\text{-score}_{PSD}$),
3. ranking by "Clinical validity score".

"Target activity score" ($T\text{-score}_{PSD}$) is calculated as follows:

$$T\text{-score}_{PSD} = -\frac{|T|}{|T| + w(|AT| - |T|)} \sum_{t \in T} \log_{10} \left(\frac{\text{rank}(t)}{1 + \text{maxRank}(T)} \right),$$

where T is set of all targets related to the compound intersected with input list, $|T|$ is number of elements in T , AT and $|AT|$ are set set of all targets related to the compound and number of elements in it, w is weight multiplier, $\text{rank}(t)$ is rank of given target, $\text{maxRank}(T)$ equals $\text{max}(\text{rank}(t))$ for all targets t in T .

We use following formula to calculate "Disease activity score" ($D\text{-score}_{PSD}$):

$$D\text{-score}_{PSD} = \begin{cases} \sum_{d \in D} \sum_{p \in P} \text{phase}(d, p) \\ 0, D = \emptyset \end{cases},$$

where D is the set of selected diseases, and if D is empty set, $D\text{-score}_{PSD} = 0$. P is a set of all known phases for each disease, $\text{phase}(p, d)$ equals to the phase number if there are known clinical trials for the selected disease on this phase and zero otherwise.

The clinical validity score reflects the number of the highest clinical trials phase (from 1 to 4) on which the drug was ever tested for any pathology.

Method for prediction of pharmaceutical compounds

In this study, the focus was put on compounds with high pharmacological efficiency and low toxicity. For this purpose, comprehensive library of chemical compounds and drugs was subjected to a SAR/QSAR analysis. This library contains 13040 compounds along with their pre-calculated potential pharmacological activities of those substances, their possible side and toxic effects, as well as the possible mechanisms of action. All biological activities are expressed as probability values for a substance to exert this activity (Pa).

We selected compounds that satisfied the following conditions:

1. Toxicity below a chosen toxicity threshold (defines as Pa , probability to be active as toxic substance).
2. For all predicted pharmacological effects that correspond to a set of user selected disease(s) Pa is greater than a chosen effect threshold.
3. There are at least 2 targets (corresponding to the predicted activity-mechanisms) with predicted Pa greater than a chosen target threshold.

The maximum Pa value for all toxicities corresponding to the given compound is selected as the "Toxicity score". The maximum Pa value for all activities corresponding to the selected diseases for the given compound is used as the "Disease activity score". "Target activity score" (T-score) is calculated as follows:

$$T\text{-score}(s) = \frac{|T|}{|T| + w(|AT| - |T|)} \sum_{m \in M(s)} \left(pa(m) \sum_{g \in G(m)} IAP(g) optWeight(g) \right),$$

where $M(s)$ is the set of activity-mechanisms for the given structure (which passed the chosen threshold for activity-mechanisms Pa); $G(m)$ is the set of targets (converted to genes) that corresponds to the given activity-mechanism (m) for the given compound; $pa(m)$ is the probability to be active of the activity-mechanism (m), $IAP(g)$ is the invariant accuracy of prediction for gene from $G(m)$; $optWeight(g)$ is the additional weight multiplier for gene. T is set of all targets related to the compound intersected with input list, $|T|$ is number of elements in T , AT and $|AT|$ are set set of all targets related to the compound and number of elements in it, w is weight multiplier.

"Druggability score" (D-score) is calculated as follows:

$$D\text{-score}(g) = IAP(g) \sum_{s \in S(g)} \sum_{m \in M(s,g)} pa(m),$$

where $S(g)$ is the set of structures for which target list contains given target, $M(s,g)$ is the set of activity-mechanisms (for the given structure) that corresponds to the given gene, $pa(m)$ is the probability to be active of the activity-mechanism (m), $IAP(g)$ is the invariant accuracy of prediction for the given gene.

8. References

1. Kel A, Voss N, Jauregui R, Kel-Margoulis O, Wingender E. Beyond microarrays: Finding key transcription factors controlling signal transduction pathways. *BMC Bioinformatics*. **2006**;7(S2), S13. doi:10.1186/1471-2105-7-s2-s13
2. Stegmaier P, Voss N, Meier T, Kel A, Wingender E, Borlak J. Advanced Computational Biology Methods Identify Molecular Switches for Malignancy in an EGF Mouse Model of Liver Cancer. *PLoS ONE*. **2011**;6(3):e17738. doi:10.1371/journal.pone.0017738
3. Koschmann J, Bhar A, Stegmaier P, Kel A, Wingender E. "Upstream Analysis": An Integrated Promoter-Pathway Analysis Approach to Causal Interpretation of Microarray Data. *Microarrays*. **2015**;4(2):270-286. doi:10.3390/microarrays4020270.
4. Kel A, Stegmaier P, Valeev T, Koschmann J, Poroikov V, Kel-Margoulis OV, and Wingender E. Multi-omics "upstream analysis" of regulatory genomic regions helps identifying targets against methotrexate resistance of colon cancer. *EuPA Open Proteom*. **2016**;13:1-13. doi:10.1016/j.euprot.2016.09.002
5. Michael H, Hogan J, Kel A et al. Building a knowledge base for systems pathology. *Brief Bioinformatics*. **2008**;9(6):518-531. doi:10.1093/bib/bbn038
6. Matys V, Kel-Margoulis OV, Fricke E, Liebich I, Land S, Barre-Dirrie A, Reuter I, Chekmenev D, Krull M, Hornischer K, Voss N, Stegmaier P, Lewicki-Potapov B, Saxel H, Kel AE, Wingender E. TRANSFAC and its module TRANSCOMP: transcriptional gene regulation in eukaryotes. *Nucleic Acids Res*. **2006**;34(90001):D108-D110. doi:10.1093/nar/gkj143
7. Kel AE, Gössling E, Reuter I, Cheremushkin E, Kel-Margoulis OV, Wingender E. MATCH: A tool for searching transcription factor binding sites in DNA sequences. *Nucleic Acids Res*. **2003**;31(13):3576-3579. doi:10.1093/nar/gkg585
8. Waleev T, Shtokalo D, Konovalova T, Voss N, Cheremushkin E, Stegmaier P, Kel-Margoulis O, Wingender E, Kel A. Composite Module Analyst: identification of transcription factor binding site combinations using genetic algorithm. *Nucleic Acids Res*. **2006**;34(Web Server issue):W541-5.
9. Krull M, Pistor S, Voss N, Kel A, Reuter I, Kronenberg D, Michael H, Schwarzer K, Potapov A, Choi C, Kel-Margoulis O, Wingender E. TRANSPATH: an information resource for storing and visualizing signaling pathways and their pathological aberrations. *Nucleic Acids Res*. **2006**;34(90001):D546-D551. doi:10.1093/nar/gkj107
0. Boyarskikh U, Pintus S, Mandrik N, Stelmashenko D, Kiselev I, Evshin I, Sharipov R, Stegmaier P, Kolpakov F, Filipenko M, Kel A. Computational master-regulator search reveals mTOR and PI3K pathways responsible for low sensitivity of NCI-H292 and A427 lung cancer cell lines to cytotoxic action of p53 activator Nutlin-3. *BMC Med Genomics*. **2018**;11(1):12. doi:10.1186/1471-2105-7-s2-s13
1. Filimonov D, Poroikov V. Probabilistic Approaches in Activity Prediction. Varnek A, Tropsha A. *Cheminformatics Approaches to Virtual Screening*. Cambridge (UK): RSC Publishing. **2008**;:182-216.
2. Filimonov DA, Poroikov VV. Prognosis of specters of biological activity of organic molecules. *Russian chemical journal*. **2006**;50(2):66-75 (russ)
3. Filimonov D, Poroikov V, Borodina Y, Glorizova T. Chemical Similarity Assessment Through Multilevel Neighborhoods of Atoms: Definition and Comparison with the Other Descriptors. *ChemInform*. **1999**;39(4):666-670. doi:10.1002/chin.199940210

Thank you for using the Genome Enhancer!

In case of any questions please contact us at support@genexplain.com

Supplementary material

1. [Supplementary table 1 - Detailed report. Composite modules and master regulators \(the most frequently mutated genes in NCI-H1975\).](#)
2. [Supplementary table 2 - Detailed report. Pharmaceutical compounds and drug targets.](#)

Disclaimer

Decisions regarding care and treatment of patients should be fully made by attending doctors. The predicted chemical compounds listed in the report are given only for doctor's consideration and they cannot be treated as prescribed medication. It is the physician's responsibility to independently decide whether any, none or all of the predicted compounds can be used solely or in combination for patient treatment purposes, taking into account all applicable information regarding FDA prescribing recommendations for any therapeutic and the patient's condition, including, but not limited to, the patient's and family's medical history, physical examinations, information from various diagnostic tests, and patient preferences in accordance with the current standard of care. Whether or not a particular patient will benefit from a selected therapy is based on many factors and can vary significantly.

The compounds predicted to be active against the identified drug targets in the report are not guaranteed to be active against any particular patient's condition. GeneXplain GmbH does not give any assurances or guarantees regarding the treatment information and conclusions given in the report. There is no guarantee that any third party will provide a refund for any of the treatment decisions made based on these results. None of the listed compounds was checked by Genome Enhancer for adverse side-effects or even toxic effects.

The analysis report contains information about chemical drug compounds, clinical trials and disease biomarkers retrieved from the HumanPSD™ database of gene-disease assignments maintained and exclusively distributed worldwide by geneXplain GmbH. The information contained in this database is collected from scientific literature and public clinical trials resources. It is updated to the best of geneXplain's knowledge however we do not guarantee completeness and reliability of this information leaving the final checkup and consideration of the predicted therapies to the medical doctor.

The scientific analysis underlying the Genome Enhancer report employs a complex analysis pipeline which uses geneXplain's proprietary Upstream Analysis approach, integrated with TRANSFAC® and TRANSPATH® databases maintained and exclusively distributed worldwide by geneXplain GmbH. The pipeline and the databases are updated to the best of geneXplain's knowledge and belief, however, geneXplain GmbH shall not give a warranty as to the characteristics or to the content and any of the results produced by Genome Enhancer. Moreover, any warranty concerning the completeness, up-to-dateness, correctness and usability of Genome Enhancer information and results produced by it, shall be excluded.

The results produced by Genome Enhancer, including the analysis report, severely depend on the quality of input data used for the analysis. It is the responsibility of Genome Enhancer users to check the input data quality and parameters used for running the Genome Enhancer pipeline.

Note that the text given in the report is not unique and can be fully or partially repeated in other Genome Enhancer analysis reports, including reports of other users. This should be considered when publishing any results or excerpts from the report. This restriction refers only to the general description of analysis methods used for generating the report. All data and graphics referring to the concrete set of input data, including lists of mutated genes, differentially expressed genes/proteins/metabolites, functional classifications, identified transcription factors and master regulators, constructed molecular networks, lists of chemical compounds and reconstructed model of molecular mechanisms of the studied pathology are unique in respect to the used input data set and Genome Enhancer pipeline parameters used for the current run.