PSMA7 and PSMD5 are promising druggable targets for treating Ovarian Neoplasms that control activity of SMAD2, CTNNB1 and FOS transcription factors on of differentially expressed genes

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Genome Enhancer release 3.0 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2022.1)

Abstract

In the present study we applied the software package "Genome Enhancer" to a multiomics data set that contains *transcriptomics and epigenomics* data. The study is done in the context of *Ovarian 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 differentially expressed genes: SMAD2, CTNNB1, STAT3, FOS, TAL1 and SP1. The subsequent network analysis suggested

- TGFbetaR-II
- Nek2A
- 26S proteasome
- Cdk1-isoform1:cyclinB1-isoform1

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, seliciclib and Bortezomib.

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 deviced 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 differentially expressed genes 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
GSM385721.CEL	Transcriptomics
GSM385722.CEL	Transcriptomics
GSM385723.CEL	Transcriptomics
GSM385724.CEL	Transcriptomics
GSM385725.CEL	Transcriptomics
GSM385726.CEL	Transcriptomics
GSM385727.CEL	Transcriptomics
GSM385728.CEL	Transcriptomics
GSM385729.CEL	Transcriptomics
GSM385730.CEL	Transcriptomics
GSM385747_CpG_NM.fixed.hg38.top300	Epigenomics

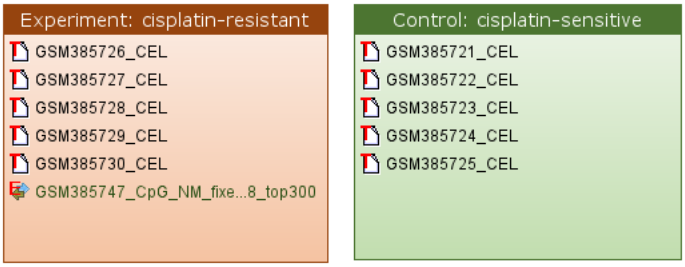


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

3. Results

We have compared the following conditions: Experiment: cisplatin-resistant *versus* Control: cisplatin-sensitive.

3.1. Identification of target genes

In the first step of the analysis ***target genes*** were identified from the uploaded experimental data. We compared gene expression in "Experiment: cisplatin-resistant" with "Control: cisplatin-sensitive". Genes were ranked according to the fold-change and 300 most up-regulated genes (see Table 2) and 300 most downregulated genes (see Table 3) were selected for further analysis.

*Table 2. Top ten **up-regulated** genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.*
See full table →

ID	Gene description	Gene symbol	logFC	CI.025	CI.975	AveExpr	t	P.Value	adj.P.Val	B	modLog10P	sig
ENSG00000123700	potassium inwardly rectifying channel subfamily J member 2	KCNJ2	5.37	5.05	5.69	7.78	36.67	6.79E-14	7.28E-11	22.22	13.17	13.
ENSG00000064218	doublesex and mab-3 related transcription factor 3	DMRT3	4.03	3.68	4.39	5.1	24.86	7.48E-12	2.59E-9	17.77	11.13	11.
ENSG00000099139	proprotein convertase subtilisin/kexin type 5	PCSK5	3.93	3.73	4.13	6.35	41.88	1.35E-14	2.07E-11	23.63	13.87	13.
ENSG00000197705	kelch like family member 14	KLHL14	3.89	3.6	4.18	7.21	29.41	9.84E-13	4.22E-10	19.74	12.01	12.
ENSG00000129038	lysyl oxidase like 1	LOXL1	3.54	3.12	3.95	5.01	18.68	2.27E-10	3.24E-8	14.33	9.64	9.6
ENSG00000133083	doublecortin like kinase 1	DCLK1	3.24	3	3.47	7.04	29.9	8.07E-13	3.76E-10	19.93	12.09	12.
ENSG00000141431	ASXL transcriptional regulator 3	ASXL3	3.14	2.86	3.43	6.45	23.65	1.36E-11	3.64E-9	17.18	10.87	10.
ENSG00000126950	transmembrane protein 35A	TMEM35A	3.05	2.82	3.29	6.15	28.24	1.6E-12	6.15E-10	19.27	11.79	11.
ENSG00000164692	collagen type I alpha 2 chain	COL1A2	2.86	2.53	3.2	7.84	18.72	2.21E-10	3.24E-8	14.36	9.65	9.6
ENSG00000138378	signal transducer and activator of transcription 4	STAT4	2.86	2.52	3.2	5.64	18.23	3.04E-10	3.75E-8	14.03	9.52	9.5

*Table 3. Top ten **down-regulated** genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.*
See full table →

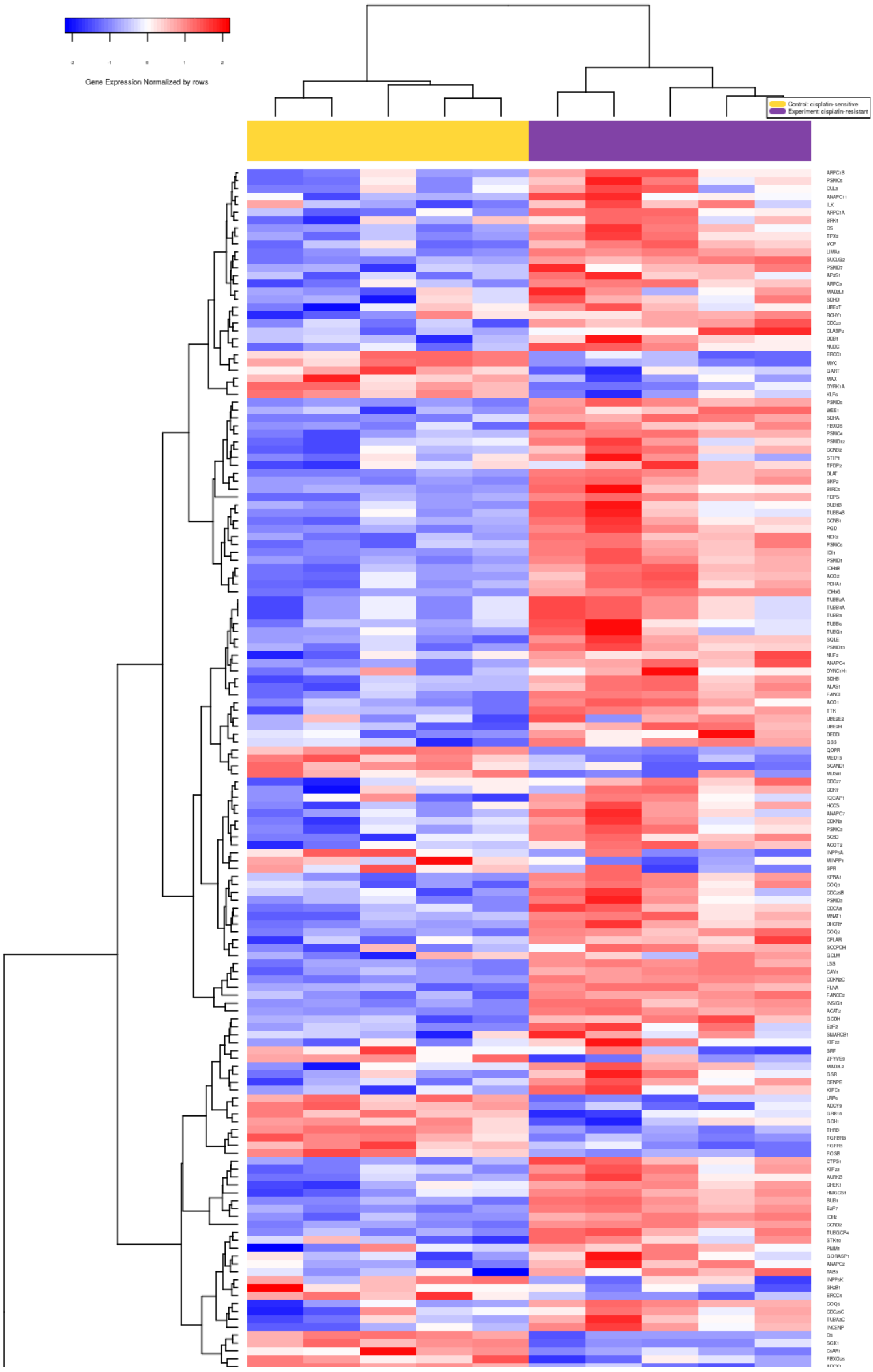
ID	Gene description	Gene symbol	logFC	CI.025	CI.975	AveExpr	t	P.Value	adj.P.Val	B	modLog10P	s
ENSG00000127324	tetraspanin 8	TSPAN8	-6.39	-6.66	-6.11	6.28	-50.15	1.5E-15	4.04E-12	25.43	14.82	-
ENSG00000139292	leucine rich repeat containing G protein-coupled receptor 5	LGR5	-6.24	-6.41	-6.07	6.28	-79.11	5.76E-18	6.18E-14	29.18	17.24	-
ENSG00000149968	matrix metallopeptidase 3	MMP3	-5.16	-5.5	-4.83	6.79	-33.55	2E-13	1.65E-10	21.23	12.7	-
ENSG00000163359	collagen type VI alpha 3 chain	COL6A3	-5.08	-5.29	-4.88	7.95	-54.61	5.33E-16	1.9E-12	26.23	15.27	-
ENSG00000169908	transmembrane 4 L six family member 1	TM4SF1	-4.94	-5.11	-4.76	7.72	-60.29	1.59E-16	8.54E-13	27.1	15.8	-
ENSG00000153233	protein tyrosine phosphatase receptor type R	PTPRR	-4.6	-4.92	-4.27	5.36	-30.65	5.98E-13	3.21E-10	20.21	12.22	-
ENSG00000166670	matrix metallopeptidase 10	MMP10	-4.45	-4.68	-4.23	8.31	-43.19	9.28E-15	1.66E-11	23.95	14.03	-
ENSG00000106511	mesenchyme homeobox 2	MEOX2	-4.26	-4.62	-3.91	4.34	-26.38	3.66E-12	1.35E-9	18.47	11.44	-
ENSG00000145431	platelet derived growth factor C	PDGFC	-4.14	-4.38	-3.91	4.99	-38.95	3.26E-14	4.37E-11	22.87	13.49	-
ENSG00000060718	collagen type XI alpha 1 chain	COL11A1	-3.65	-4.04	-3.25	5.67	-20.08	9.63E-11	1.75E-8	15.21	10.02	-

3.2. Functional classification of genes

A functional analysis of differentially expressed genes was done by mapping the significant up-regulated and significant down-regulated 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 3-8 show the most significant categories.

Heatmap of differentially expressed genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive

A heatmap of all differentially expressed genes playing a potential regulatory role in the system (enriched in TRANSPATH® pathways) is presented in Figure 2.


-2
-1
0
1
2
Gene Expression Normalized by rows
Control: cisplatin-sensitive
Experiment: cisplatin-resistant

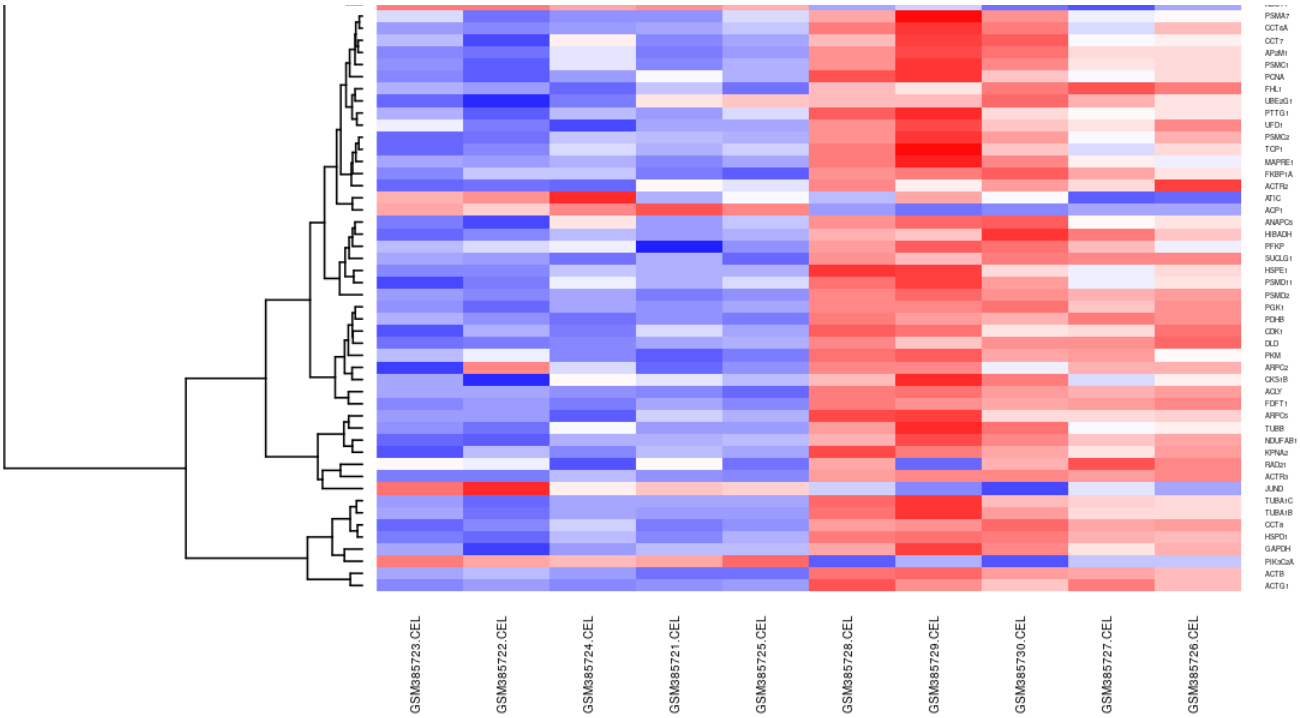


Figure 2. Heatmap of genes enriched in Transpath categories. The colored bar at the top shows the types of the samples according to the legend in the upper right corner.
See full diagram →

Up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive:

3350 significant up-regulated genes were taken for the mapping.

GO (biological process)

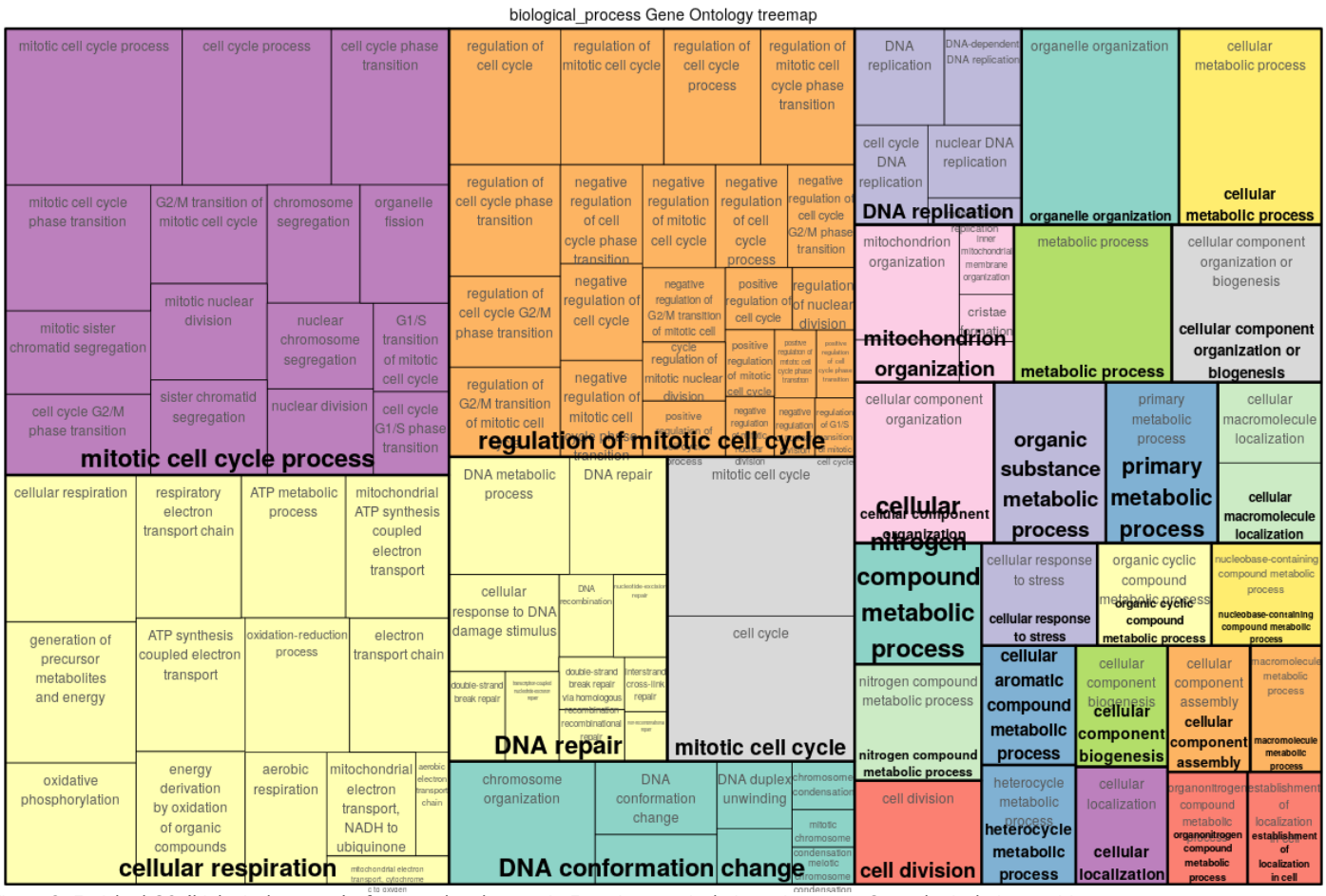


Figure 3. Enriched GO (biological process) of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

TRANSPATH® Pathways (2022.1)

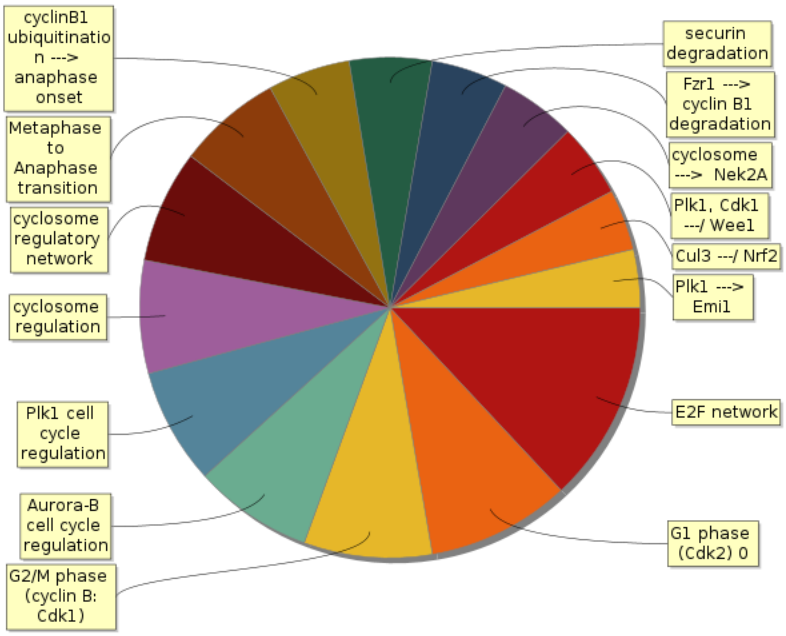


Figure 4. Enriched TRANSPATH® Pathways (2022.1) of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

HumanPSD(TM) disease (2022.1)

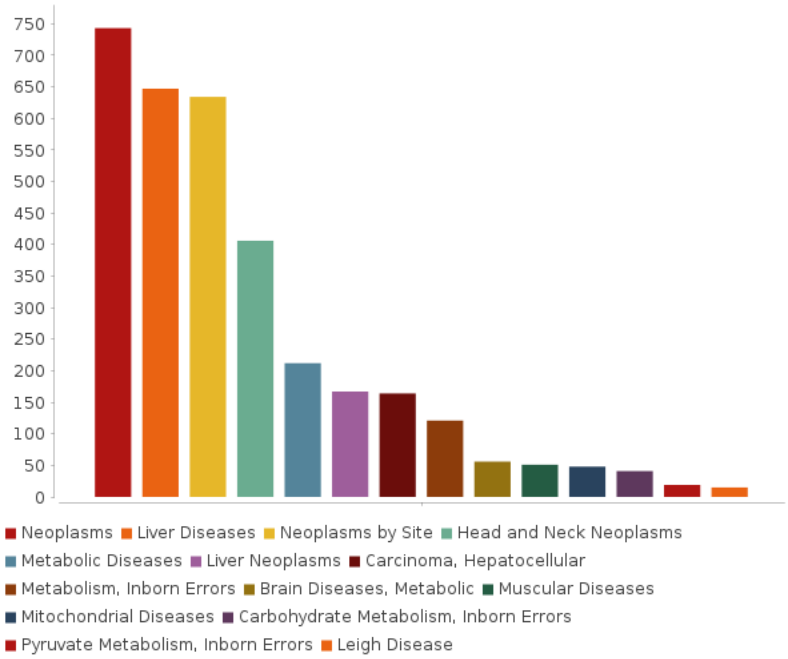


Figure 5. Enriched HumanPSD(TM) disease (2022.1) of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.
Full classification →

Down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive:

3351 significant down-regulated genes were taken for the mapping.

GO (biological process)

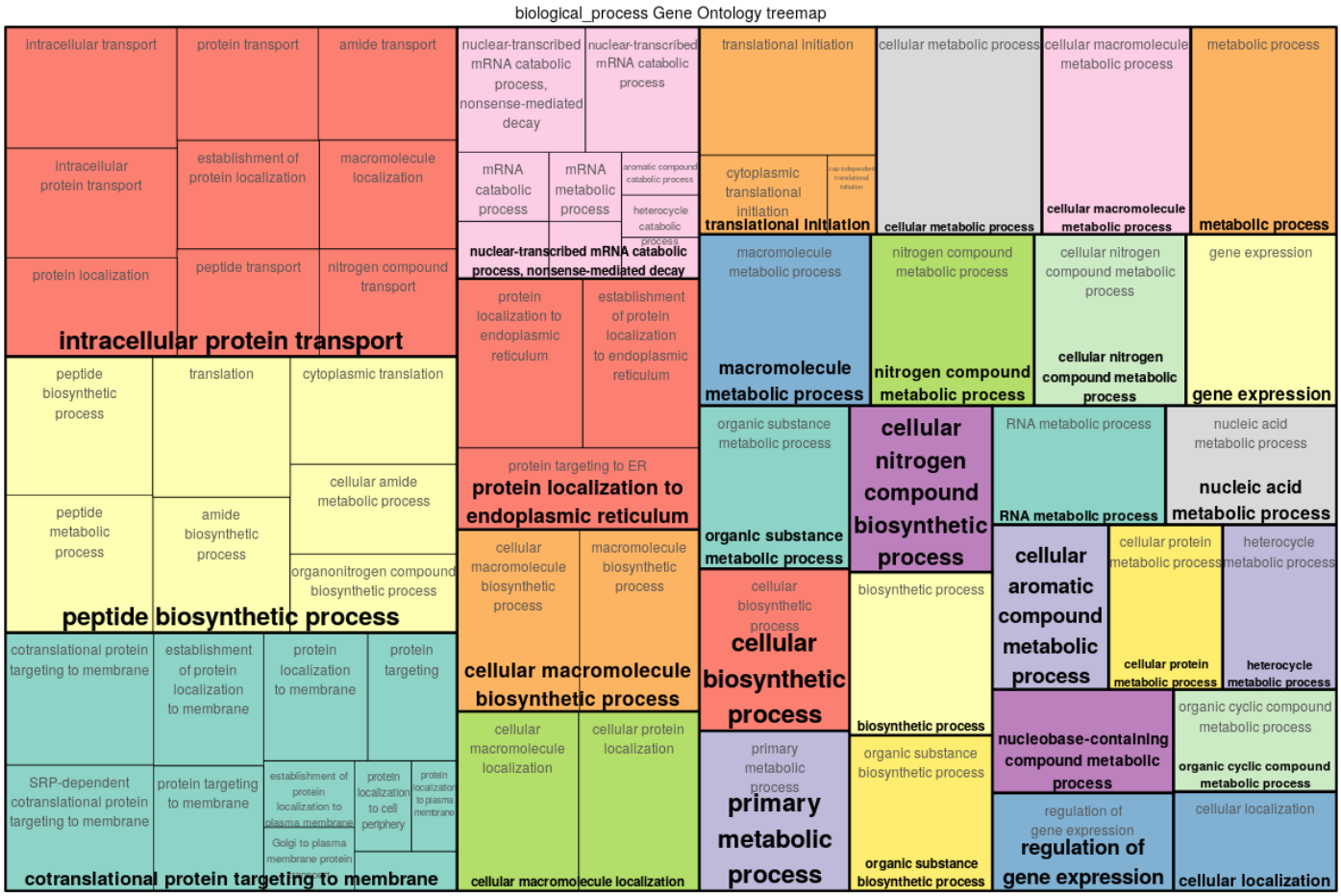


Figure 6. Enriched GO (biological process) of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

TRANSPATH® Pathways (2022.1)

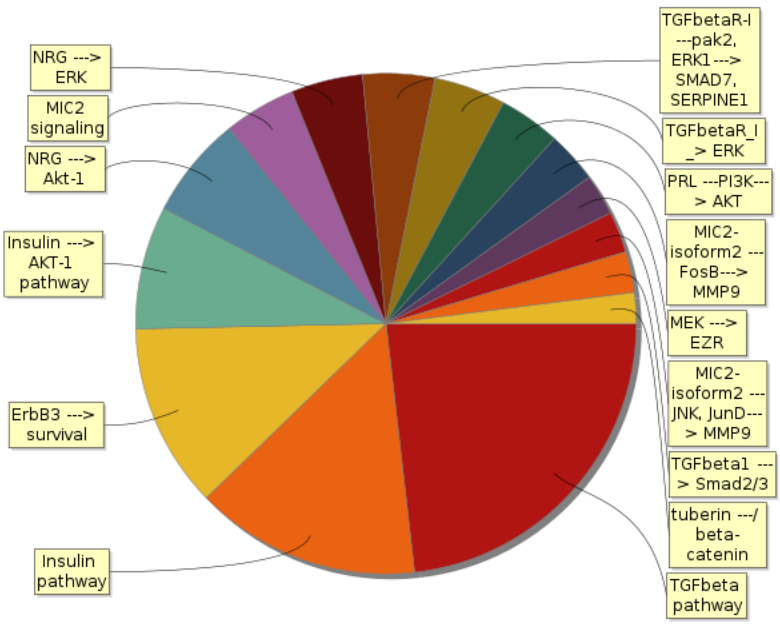


Figure 7. Enriched TRANSPATH® Pathways (2022.1) of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

HumanPSD(TM) disease (2022.1)

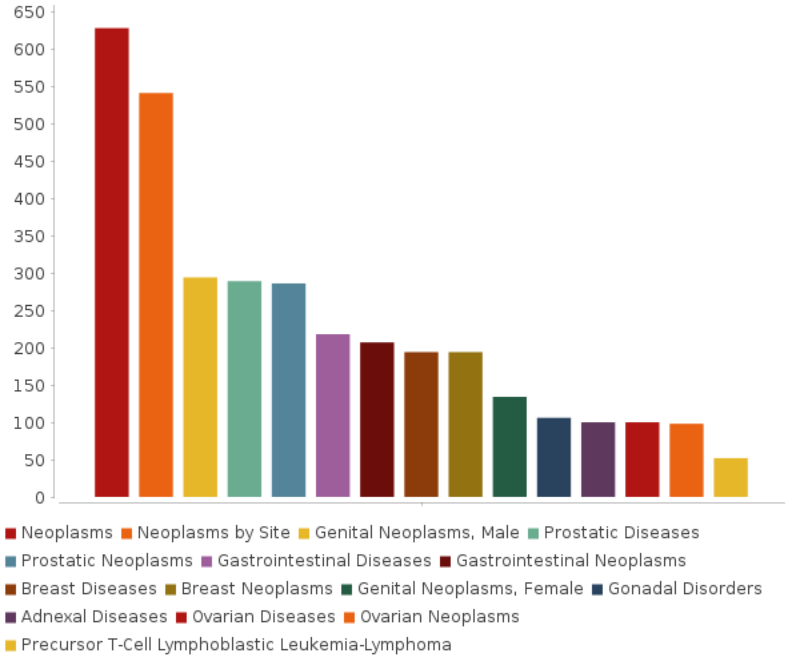
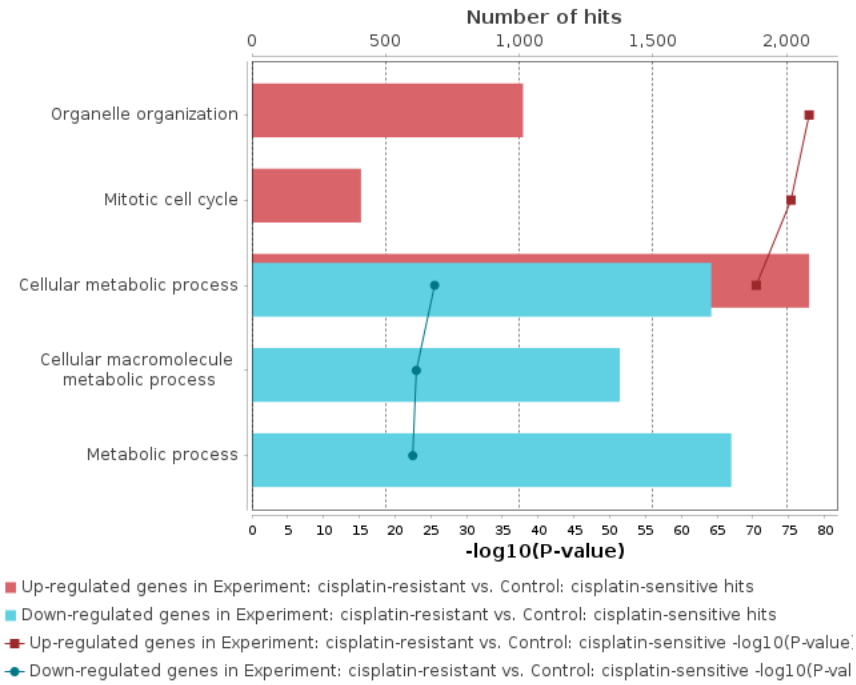


Figure 8. Enriched HumanPSD(TM) disease (2022.1) of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

Full classification →

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



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 Epigenomics data from the track(s) "GSM385747_CpG_NM.fixed.hg38.top300" to predict positions of potential ***enhancers*** regulating the differentially expressed genes revealed by comparative epigenomics analysis. We took genomic regions -550bp upstream and 550bp downstream from the middle point of each interval of the track and check if these regions are located inside the 5kb flanking areas of the differentially expressed genes (or inside the body of the genes). In such cases, these genomic regions are used for the search for potential condition-specific enhancers. In all other cases when the differentially expressed genes did not contain epigenomic peaks in their body or in the 5kb flanking regions we used the upstream regulatory regions of these genes (-1000bp upstream and 100bp downstream of TSS) for the search for condition-specific enhancers.

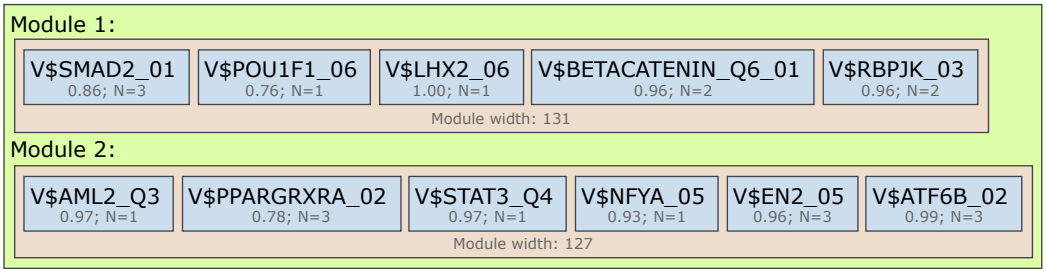
We applied the Composite Module Analyst (CMA) [8] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the

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 (up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive).

To build the most specific composite modules we choose top 300 significant up-regulated genes as the input of CMA algorithm. The obtained CMA model is then applied to compute CMA score for all up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.

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)): 10.69
Wilcoxon p-value (pval): 1.12e-22
Penalty (p): 0.487
Average yes-set score: 3.75
Average no-set score: 2.60
AUC: 0.71
Separation point: 3.47
False-positive: 28.80%
False-negative: 40.33%

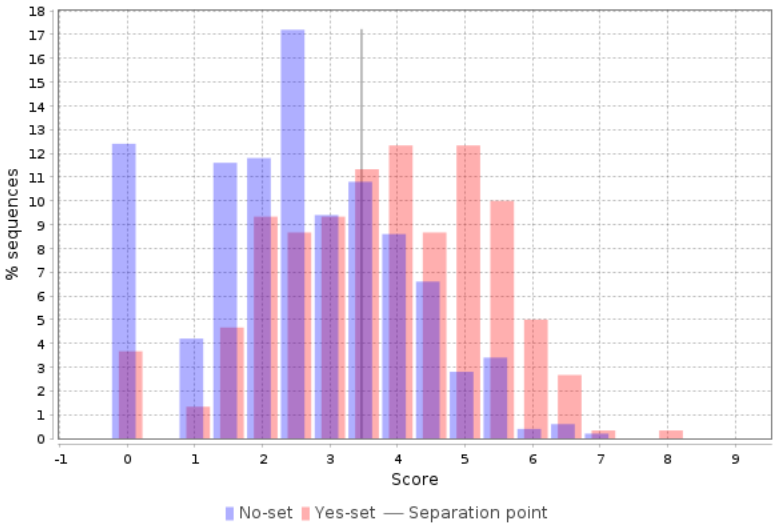


Table 4. List of top ten up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*

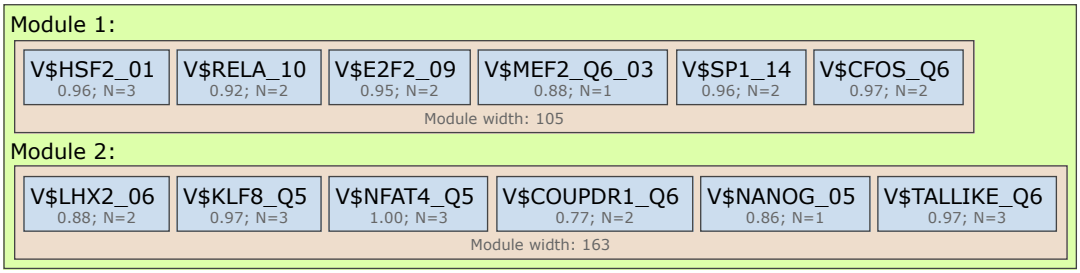
See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000170043	TRAPPC1	trafficking protein particle complex 1	8.78	NF-YA(h), ATF-6beta(h), PPARgamma(h),RXRalpha(h), RBP-Jkappa(h), SMAD2(h), beta-catenin(h)
ENSG00000241506	PSMC1P1	proteasome 26S subunit, ATPase 1 pseudogene 1	8.69	PPARgamma(h),RXRalpha(h), NF-YA(h), Lhx2(h), EN-2(h), beta-catenin(h), SMAD2(h), POU1F1(h)...
ENSG00000108439	PNPO	pyridoxamine 5'-phosphate oxidase	8.46	RBP-Jkappa(h), SMAD2(h), beta-catenin(h), PPARgamma(h),RXRalpha(h), NF-YA(h), POU1F1(h), Lhx2(h)
ENSG00000088247	KHSRP	KH-type splicing regulatory protein	8.09	SMAD2(h), NF-YA(h), Lhx2(h), PPARgamma(h),RXRalpha(h), beta-catenin(h), POU1F1(h)
ENSG00000130203	APOE	apolipoprotein E	8.06	SMAD2(h), beta-catenin(h), POU1F1(h), RBP-Jkappa(h), PPARgamma(h),RXRalpha(h), NF-YA(h)
ENSG00000181827	RFX7	regulatory factor X7	7.85	NF-YA(h), Runx3(h), PPARgamma(h),RXRalpha(h), SMAD2(h), beta-catenin(h), POU1F1(h), Lhx2(h)
ENSG00000135778	NTPCR	nucleoside-triphosphatase, cancer-related	7.71	PPARgamma(h),RXRalpha(h), STAT3(h), EN-2(h), beta-catenin(h), POU1F1(h), NF-YA(h), Lhx2(h)
ENSG00000139163	ETNK1	ethanolamine kinase 1	7.65	beta-catenin(h), POU1F1(h), STAT3(h), EN-2(h), PPARgamma(h),RXRalpha(h), NF-YA(h)
ENSG00000114405	C3orf14	chromosome 3 open reading frame 14	7.65	POU1F1(h), SMAD2(h), beta-catenin(h), ATF-6beta(h), STAT3(h), PPARgamma(h),RXRalpha(h)
ENSG00000204439	C6orf47	chromosome 6 open reading frame 47	7.48	PPARgamma(h),RXRalpha(h), STAT3(h), POU1F1(h), SMAD2(h), RBP-Jkappa(h), beta-catenin(h)

Enhancer model potentially involved in regulation of target genes (down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive).

To build the most specific composite modules we choose top 300 significant down-regulated genes as the input of CMA algorithm. The obtained CMA model is then applied to compute CMA score for all down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.

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)): 15.49
Wilcoxon p-value (pval): 2.28e-33
Penalty (p): 0.475
Average yes-set score: 4.03
Average no-set score: 2.67
AUC: 0.75
Separation point: 3.52
False-positive: 28.20%
False-negative: 32.67%

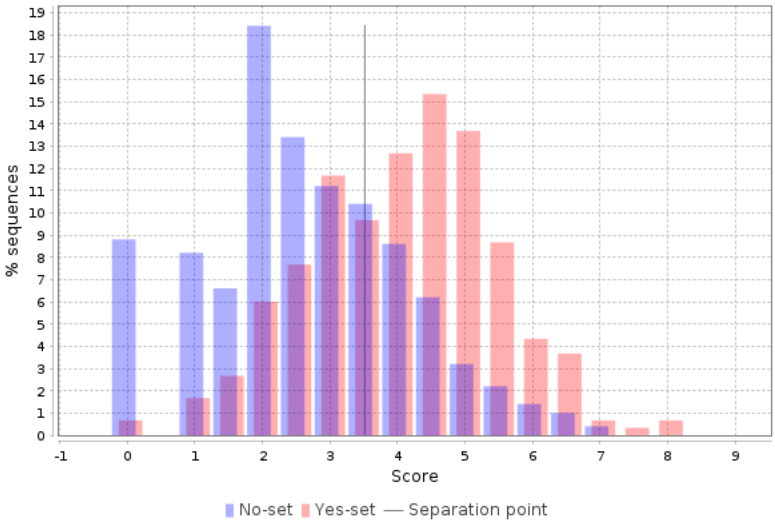


Table 5. List of top ten down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*
See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000163697	APBB2	amyloid beta precursor protein binding family B member 2	8.96	NF-kappaB-p65(h), COUP-TFI (h),COUP-TFII(h), MEF-2A(h),MEF-2B(h),MEF-2C(h),MEF-2D(h), Lhx2(h), NANOG(h), c-Fos(h), NFATc3(h)...
ENSG00000052126	PLEKHA5	pleckstrin homology domain containing A5	8.92	NFATc3(h), HSF2(h), NANOG(h), COUP-TFI (h),COUP-TFII(h), NF-kappaB-p65(h), E2F-2(h), Sp1(h)
ENSG00000181788	SIAH2	siah E3 ubiquitin protein ligase 2	8.61	HSF2(h), KLF8(h), NANOG(h), Sp1(h), E2F-2(h), c-Fos(h), NFATc3(h)
ENSG00000150455	TIRAP	TIR domain containing adaptor protein	8.26	HEN2(h),Lyl-1(h),Tal-1(h), NF-kappaB-p65(h), COUP-TFI (h),COUP-TFII(h), NFATc3(h), KLF8(h), c-Fos(h)
ENSG00000152782	PANK1	pantothenate kinase 1	8.09	E2F-2(h), Lhx2(h), MEF-2A(h),MEF-2B(h),MEF-2C(h),MEF-2D(h), HSF2(h), HEN2(h),Lyl-1(h),Tal-1(h), NF-kappaB-p65(h), NFATc3(h)...
ENSG00000116667	C1orf21	chromosome 1 open reading frame 21	8.06	NFATc3(h), Lhx2(h), KLF8(h), NANOG(h), Sp1(h), HSF2(h), NF-kappaB-p65(h)...
ENSG00000164116	GUCY1A1	guanylate cyclase 1 soluble subunit alpha 1	7.92	COUP-TFI (h),COUP-TFII(h), HSF2(h), MEF-2A(h),MEF-2B(h),MEF-2C(h),MEF-2D(h), Lhx2(h), NFATc3(h), NANOG(h)
ENSG00000284461		novel transcript	7.86	NANOG(h), COUP-TFI (h),COUP-TFII(h), NF-kappaB-p65(h), HEN2(h),Lyl-1(h),Tal-1(h), NFATc3(h), HSF2(h), E2F-2(h)...
ENSG00000176783	RUFY1	RUN and FYVE domain containing 1	7.77	NFATc3(h), NANOG(h), COUP-TFI (h),COUP-TFII(h), HSF2(h), NF-kappaB-p65(h), E2F-2(h)
ENSG00000204682	MIR1915HG	MIR1915 host gene	7.76	Sp1(h), NF-kappaB-p65(h), NFATc3(h), HSF2(h), COUP-TFI (h),COUP-TFII(h), NANOG(h), Lhx2(h)

On the basis of the enhancer models we identified transcription factors potentially regulating the ***target genes*** of our interest. We found 12 and 18 transcription factors controlling expression of up- and down-regulated genes respectively (see Tables 6-7).

*Table 6. Transcription factors of the predicted enhancer model potentially regulating the differentially expressed genes (up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive). **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 →

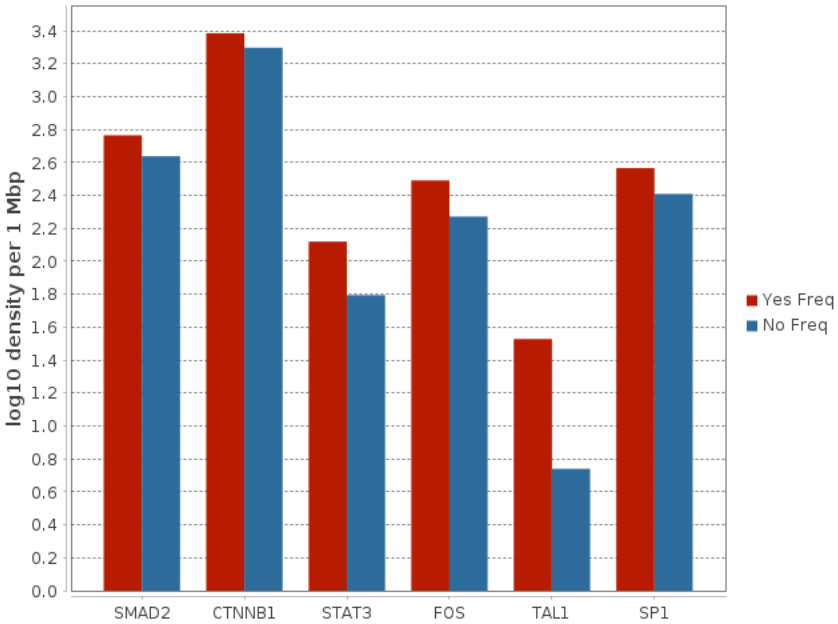
ID	Gene symbol	Gene description	Regulatory score	Yes-No ratio
MO000057829	SMAD2	SMAD family member 2	3.15	1.34
MO000017049	CTNNB1	catenin beta 1	3.1	1.22
MO000013123	STAT3	signal transducer and activator of transcription 3	2.72	2.11
MO000019619	RXRA	retinoid X receptor alpha	2.32	5.85
MO000025939	NFYA	nuclear transcription factor Y subunit alpha	2.19	1.96
MO000033565	PPARG	peroxisome proliferator activated receptor gamma	2.19	5.02
MO000030964	RBPJ	recombination signal binding protein for immunoglobulin kappa J region	1.94	10.03
MO000026238	RUNX3	RUNX family transcription factor 3	1.84	4.6
MO000084573	POU1F1	POU class 1 homeobox 1	1.55	1.63
MO000026059	LHX2	LIM homeobox 2	0	2.02

*Table 7. Transcription factors of the predicted enhancer model potentially regulating the differentially expressed genes (down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive). **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
MO000018137	FOS	Fos proto-oncogene, AP-1 transcription factor subunit	2.91	1.66
MO000032489	TAL1	TAL bHLH transcription factor 1, erythroid differentiation factor	2.78	6.14
MO000033308	SP1	Sp1 transcription factor	2.62	1.43
MO000079319	RELA	RELA proto-oncogene, NF-kB subunit	2.57	1.57
MO000031322	MEF2C	myocyte enhancer factor 2C	2.57	2.79
MO000085555	MEF2D	myocyte enhancer factor 2D	2.42	1.35
MO000084966	MEF2A	myocyte enhancer factor 2A	2.2	4.06
MO000004278	E2F2	E2F transcription factor 2	1.92	2.29
MO000095459	KLF8	Kruppel like factor 8	1.92	1.58
MO000134485	NANOG	Nanog homeobox	1.92	1.67

The following diagram represents the key transcription factors, which were predicted to be potentially regulating differentially expressed genes in the analyzed pathology: SMAD2, CTNNB1, STAT3, FOS, TAL1 and SP1.



3.4. Finding master regulators in networks

In the second step of the upstream analysis common regulators of the revealed TFs were identified. 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 Tables 8-9.

*Table 8. Master regulators that may govern the regulation of **up-regulated** genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, transcriptomics and epigenomics data.*

See full table →

ID	Master molecule name	Gene symbol	Gene description	logFC	Total rank
MO0000017448	TGFbetaR-II(h)	TGFBR2	transforming growth factor beta receptor 2	2.79	259
MO0000092591	Cdk1-isoform1(h):cyclinB1-isoform1(h)	CCNB1, CDK1	cyclin B1, cyclin dependent kinase 1	0.83	271
MO0000021736	CDK2(h)	CDK2	cyclin dependent kinase 2	0.8	311
MO0000032335	RSK1(h)	RPS6KA1	ribosomal protein S6 kinase A1	0.76	383
MO0000202927	TGFbetaR-II-isoform2(h)	TGFBR2	transforming growth factor beta receptor 2	2.79	400
MO0000083753	TGFbetaR-II-isoform1(h)	TGFBR2	transforming growth factor beta receptor 2	2.79	401
MO0000041170	EAC(h)	CYLD	CYLD lysine 63 deubiquitinase	0.95	405
MO0000022448	cyclinB1(h)	CCNB1	cyclin B1	0.83	421
MO0000021740	cyclinA(h):CDK2(h)	CDK2	cyclin dependent kinase 2	0.8	426
MO0000043727	Nek2A(h){p}	NEK2	NIMA related kinase 2	0.53	433

*Table 9. Master regulators that may govern the regulation of **down-regulated** genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, transcriptomics and epigenomics data.*

See full table →

ID	Master molecule name	Gene symbol	Gene description	logFC	Total rank
MO0000129772	PTP-SL(h)	PTPRR	protein tyrosine phosphatase receptor type R	-4.6	181
MO0000280531	rictor-isoform1(h):mTOR(h):SIN1(h):mLST8(h)	MAPKAP1, MLST8, MTOR, RICTOR	MAPK associated protein 1, MTOR associated protein, LST8 homolog, RPTOR independent companion of MTO...	-0.58	206
MO0000165201	mTOR(h):rictor(h):mLST8(h):SIN1(h):Protor-1(h)	MAPKAP1, MLST8, MTOR, PRR5, RICTOR	MAPK associated protein 1, MTOR associated protein, LST8 homolog, RPTOR independent companion of MTO...	-0.58	207
MO0000122429	SIN1(h):rictor(h):mTOR(h)	MAPKAP1, MTOR, RICTOR	MAPK associated protein 1, RPTOR independent companion of MTOR complex 2, mechanistic target of rapa...	-0.55	222
MO0000054152	mTOR(h):rictor(h)	MTOR, RICTOR	RPTOR independent companion of MTOR complex 2, mechanistic target of rapamycin kinase	-0.55	229
MO0000090102	rictor-isoform1(h)	RICTOR	RPTOR independent companion of MTOR complex 2	-0.55	233
MO0000122463	mTOR(h):rictor(h):mLST8(h):SIN1(h)	MAPKAP1, MLST8, MTOR, RICTOR	MAPK associated protein 1, MTOR associated protein, LST8 homolog, RPTOR independent companion of MTO...	-0.58	233
MO0000054153	rictor(h)	RICTOR	RPTOR independent companion of MTOR complex 2	-0.55	235
MO0000129771	PTP-SL alpha(h)	PTPRR	protein tyrosine phosphatase receptor type R	-4.6	299
MO0000129778	PTP-SL delta(h)	PTPRR	protein tyrosine phosphatase receptor type R	-4.6	299

The intracellular regulatory pathways controlled by the above-mentioned master regulators are depicted in Figures 9 and 10. These diagrams display the connections between identified transcription factors, which play important roles in the regulation of differentially expressed genes, and selected master regulators, which are responsible for the regulation of these TFs.

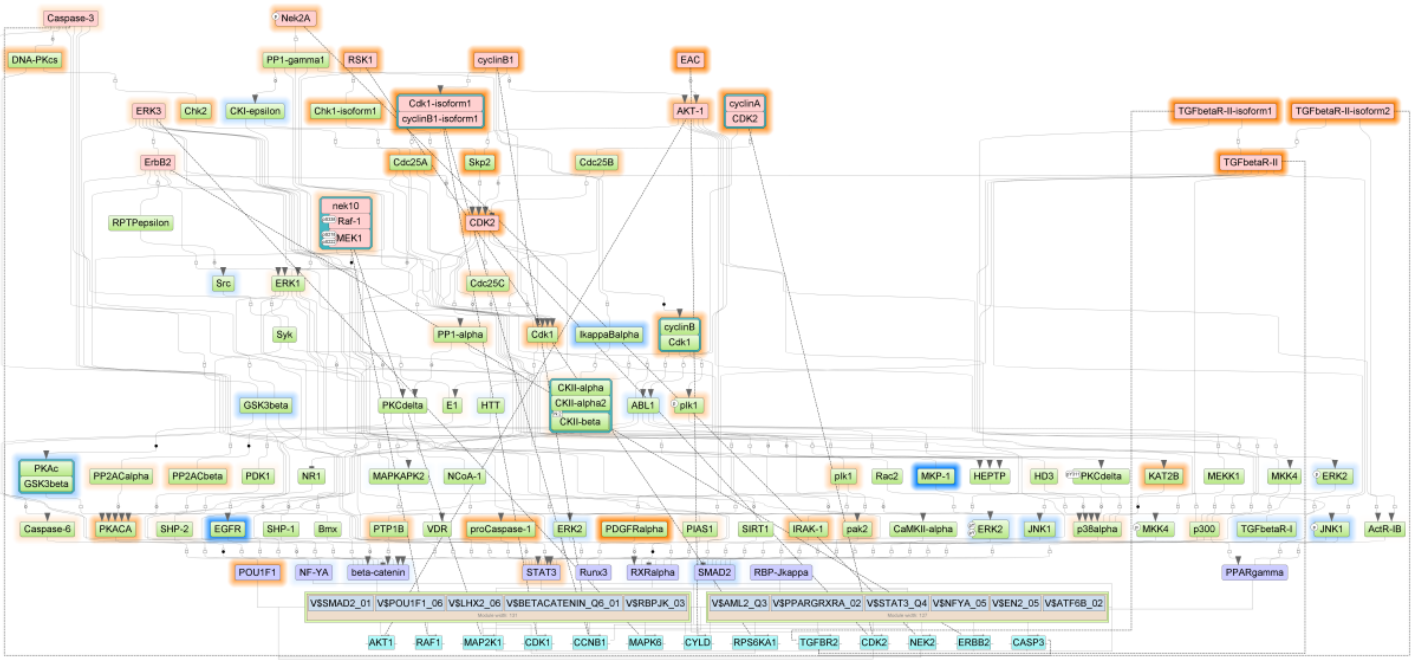


Figure 9. Diagram of intracellular regulatory signal transduction pathways of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have been added to the network during the search for master regulators from selected TFs. Orange and blue frames highlight molecules that are encoded by up- and downregulated genes, resp.

See full diagram →

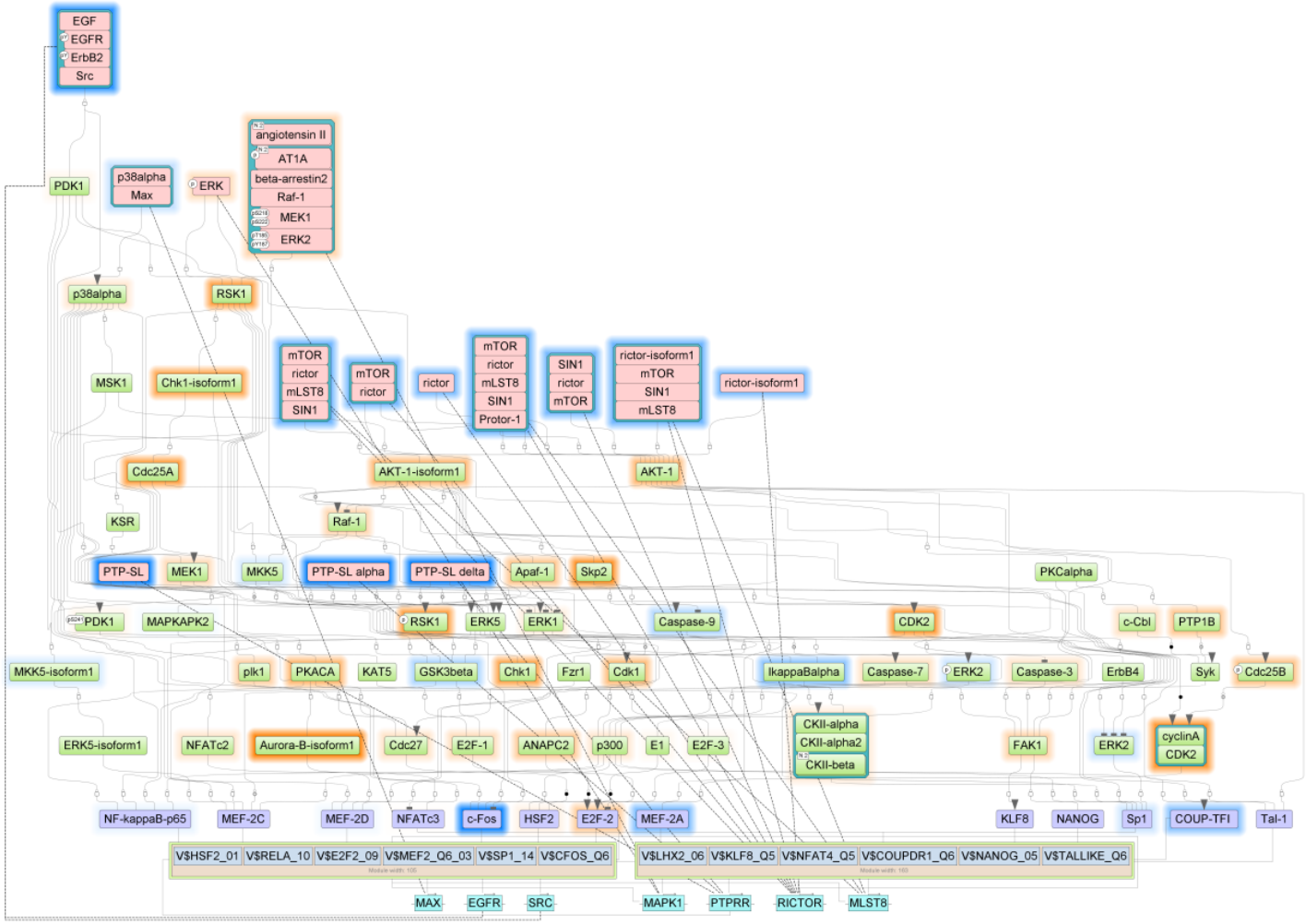


Figure 10. Diagram of intracellular regulatory signal transduction pathways of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have been added to the network during the search for master regulators from selected TFs. Orange and blue frames highlight molecules that are encoded by up- and downregulated genes, resp.

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 10. 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	logFC	Total rank
PSMA7	proteasome 20S subunit alpha 7	2	0.52	438
NEK2	NIMA related kinase 2	33	0.53	704
AURKB	aurora kinase B	45	1.03	704
CCNA2	cyclin A2	15	0.8	720
APOE	apolipoprotein E	10	1.2	781
PIK3R3	phosphoinositide-3-kinase regulatory subunit 3	1	0.88	789

*Table 11. 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.*

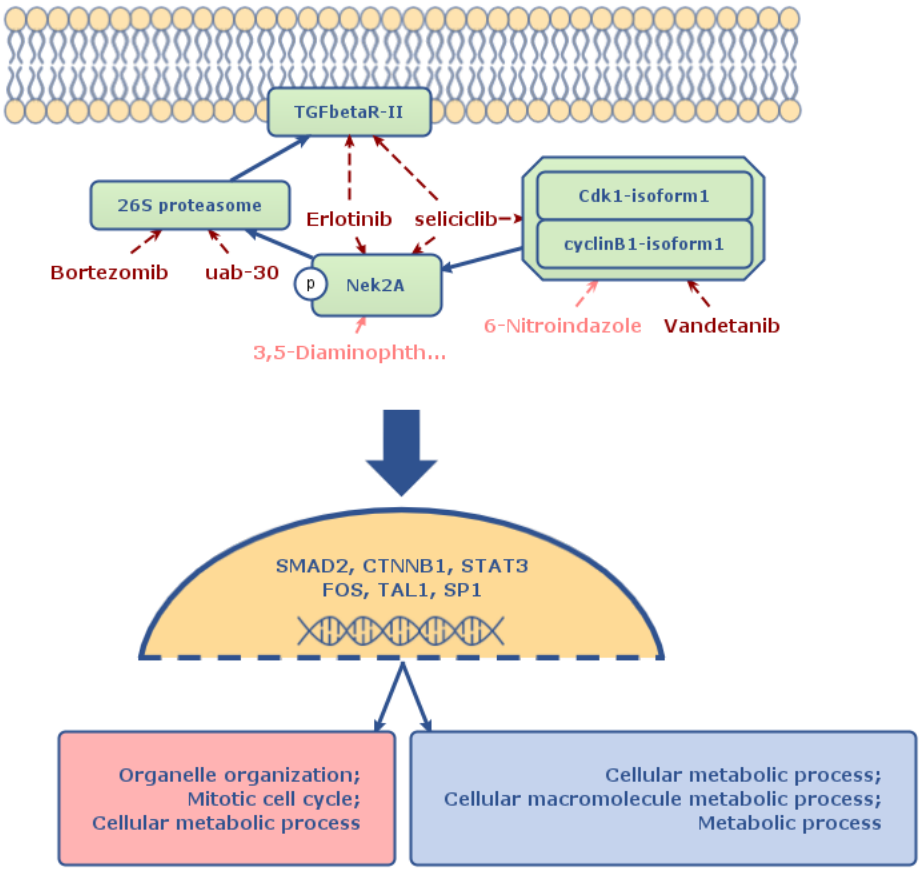
See full table →

Gene symbol	Gene Description	Druggability score	logFC	Total rank
PSMD5	proteasome 26S subunit, non-ATPase 5	1.28	0.52	438
PSMA7	proteasome 20S subunit alpha 7	2.17	0.52	438
GRK5	G protein-coupled receptor kinase 5	10.65	1.13	456
DUSP9	dual specificity phosphatase 9	4.91	0.75	675
NEK2	NIMA related kinase 2	2.82	0.53	704
AURKB	aurora kinase B	1.99	1.03	704

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:

- TGFbetaR-II
- Nek2A
- 26S proteasome
- Cdk1-isoform1:cyclinB1-isoform1

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: Vandetanib, Bortezomib, 6-Nitroindazole, Erlotinib, seliciclib, 3,5-Diaminophthalhydrazide and uab-30, 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 13 and 14), 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.

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

Drugs approved in clinical trials for Oncology

Table 12. Clinically approved (FDA, ENA, 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	Approved
Paclitaxel	FASN, PIK3CA, CASP3, E2F1, BIRC5, CDK1, CDK2, MAPK3, BRCA1	90	12	Phase 4: Ovarian Neoplasms, Acute Coronary Syndrome, Adenocarcinoma, Aneurysm, Angina Pectoris, Angina, Unstable, Arteriosclerosis, Breast Neoplasms, Carcinoma, Carcinoma, Large Cell, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Squamous Cell, Cardiovascular Diseases, Constriction, Pathologic, Coronary Artery Disease, Coronary Disease, Coronary Restenosis, Coronary Stenosis, Diabetes Mellitus, Dilatation, Pathologic, Heart Diseases, Hyperplasia, Infarction, Ischemia, Lung Neoplasms, Myocardial Infarction, Myocardial Ischemia, Neoplasms, Neuroendocrine Tumors, Pancreatic Neoplasms, Peripheral Arterial Disease, Peripheral Vascular Diseases, Squamous Cell Carcinoma of Head and Neck, Thymoma, Thymus Neoplasms, Triple Negative Breast Neoplasms, Vascular Diseases	Ovarian Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)
Doxorubicin	MAPK14, HMGCR, PIK3CB, PIK3CA, BAX, BIRC5, BRCA1, CDKN1B	86	12	Phase 4: Ovarian Neoplasms, Brain Abscess, Breast Neoplasms, Burkitt Lymphoma, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Ovarian Epithelial, Enteropathy-Associated T-Cell Lymphoma, Immunoblastic Lymphadenopathy, Leukemia, Leukemia, Lymphoid, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, B-Cell, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoproliferative Disorders, Mediastinal Neoplasms, Multiple Myeloma, Myosarcoma, Neoplasms, Neoplasms, Plasma Cell, Obesity, Panniculitis, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Rhabdomyosarcoma, Sarcoma, Urinary Bladder Neoplasms, Wilms Tumor	Ovarian Neoplasms (FDA)
Gemcitabine	ERBB2, HRAS, CHEK1, BRCA1	78	7	Phase 3: Ovarian Neoplasms, Adenocarcinoma, Adenocarcinoma, Clear Cell, Adenocarcinoma, Mucinous, Adenoviridae Infections, Aggression, Bile Duct Neoplasms, Biliary Tract Neoplasms, Brain Neoplasms, Breast Neoplasms, Brenner Tumor, Bronchial Diseases, Bronchial Neoplasms, Carcinoma, Carcinoma in Situ, Carcinoma, Acinar Cell, Carcinoma, Adenosquamous, Carcinoma, Bronchogenic, Carcinoma, Ductal, Carcinoma, Endometrioid, Carcinoma, Hepatocellular, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Pancreatic Ductal, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Cystadenocarcinoma, Cystadenocarcinoma, Serous, Cysts, Digestive System Diseases, Digestive System Neoplasms, Drug-Related Side Effects and Adverse Reactions, Embolism, Endocrine Gland Neoplasms, Endocrine System Diseases, Epstein-Barr Virus Infections, Fallopian Tube Neoplasms, Fever, Fibrosis, Gallbladder Neoplasms, Gastrointestinal Diseases, Gastrointestinal Neoplasms, Genital Neoplasms, Female, Head and Neck Neoplasms, Hepatoblastoma, Hernia, Hernia, Ventral, Hodgkin Disease, Hydrothorax, Hypersensitivity, Hyperthermia, Immunoblastic Lymphadenopathy, Infections, Intestinal Diseases, Intestinal Neoplasms, Kidney Neoplasms, Klatskin Tumor, Leiomyosarcoma, Liver Cirrhosis, Liver Neoplasms, Lung Diseases, Lung Neoplasms, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, B-Cell, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, Mesothelioma, Mesothelioma, Malignant, Muscle Neoplasms, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Diseases, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasm Recurrence, Local, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Germ Cell and Embryonal, Neoplasms, Glandular and Epithelial, Neoplasms, Nerve Tissue, Neoplasms, Second Primary, Neoplasms, Unknown Primary, Osteosarcoma, Pancreatic Cyst, Pancreatic Diseases, Pancreatic Intraductal Neoplasms, Pancreatic Neoplasms, Pelvic Neoplasms, Peritoneal Neoplasms, Pharyngeal Diseases, Pharyngeal Neoplasms, Prostatic Neoplasms, Recurrence, Renal Insufficiency, Respiratory Tract Diseases, Respiratory Tract Neoplasms, Sarcoma, Small Cell Lung Carcinoma, Thoracic Neoplasms, Thromboembolism, Triple Negative Breast Neoplasms, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms, Uterine Cervical Neoplasms, Virus Diseases	Ovarian Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA)
Ionafarnib	BIRC5	61	3	Phase 2: Ovarian Neoplasms, Breast Neoplasms, Carcinoma, Ovarian Epithelial, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Glioblastoma, Hepatitis, Hepatitis A, Hepatitis D, Hepatitis D, Chronic, Kidney Neoplasms, Leukemia, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Liver Diseases, Liver Neoplasms, Neoplasms, Progeria, Syndrome, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms	Ovarian Neoplasms (FDA)
Olaparib	PARP1	53	12	Phase 4: Ovarian Neoplasms, Breast Neoplasms, Carcinoma, Ovarian Epithelial, Neoplasms	Ovarian Neoplasms (FDA, FDA)
Methotrexate	BAX, E2F1, BIRC5, CDKN1B	48	2	Phase 2: Ovarian Neoplasms, Acquired Immunodeficiency Syndrome, Acute Disease, Adenocarcinoma, Anemia, Anemia, Aplastic, Anemia, Diamond-Blackfan, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Anemia, Sickle Cell, Anger, Anterior Wall Myocardial Infarction, Arteritis, Arthritis, Arthritis, Juvenile, Arthritis, Psoriatic, Arthritis, Rheumatoid, Asthenia, Astrocytoma, Atherosclerosis, Autoimmune Diseases, Basal Cell Nevus Syndrome, Blast Crisis, Bone Marrow Failure Disorders, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Burkitt Lymphoma, COVID-19, Carcinoma, Carcinoma, Basal Cell, Carcinoma, Merkel Cell, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Cardiac Complexes, Premature, Central Nervous System Neoplasms, Central Serous Chorioretinopathy, Chronic Urticaria, Churg-Strauss Syndrome, Colitis, Colitis, Ulcerative, Colorectal Neoplasms, Constriction, Pathologic, Coronary Artery Disease, Coronary Disease, Coronavirus Infections, Dermatomyositis, Disease, Down Syndrome, Drug-Related Side Effects and Adverse Reactions, Edema, Enteropathy-Associated T-Cell Lymphoma, Ependymoma, Erythema, Fibroma, Fibromatosis, Aggressive, Gestational Trophoblastic Disease, Giant Cell Arteritis, Glioblastoma, Graft vs Host Disease, Granuloma, Granulomatosis with Polyangiitis, HIV Infections, Head and Neck Neoplasms, Heart Failure, Hematologic Diseases, Hematologic Neoplasms, Hemoglobinuria, Hemoglobinuria, Paroxysmal, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Histiocytosis, Histiocytosis, Langerhans-Cell, Hodgkin Disease, Hypereosinophilic Syndrome, Immune System Diseases, Immunoblastic Lymphadenopathy, Infarction, Infections, Inflammation, Intestinal Neoplasms, Intraocular Lymphoma, Ischemia, Kidney Neoplasms, Leukemia, Leukemia, B-Cell, Leukemia, Biphenotypic, Acute, Leukemia, Erythroblastic, Acute, Leukemia, Hairy Cell, Leukemia, Large Granular Lymphocytic, Leukemia, Lymphocytic, Chronic, B-Cell,	Ovarian Neoplasms (FDA)

				Leukemia, Lymphoid, Leukemia, Megakaryoblastic, Acute, Leukemia, Monocytic, Acute, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Accelerated Phase, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Acute, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Neutrophilic, Chronic, Leukemia, Prolymphocytic, Leukemia, Promyelocytic, Acute, Leukemia, T-Cell, Leukemia-Lymphoma, Adult T-Cell, Lung Neoplasms, Lupus Erythematosus, Systemic, Lymphadenopathy, Lymphatic Diseases, Lymphohistiocytosis, Hemophagocytic, Lymphoma, Lymphoma, AIDS-Related, Lymphoma, B-Cell, Lymphoma, B-Cell, Marginal Zone, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Large-Cell, Immunoblastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Cutaneous, Lymphoma, T-Cell, Peripheral, Lymphomatoid Granulomatosis, Lymphoproliferative Disorders, Macular Edema, Medulloblastoma, Meningeal Carcinomatosis, Mesothelioma, Mesothelioma, Malignant, Microscopic Polyangiitis, Mucositis, Multiple Myeloma, Multiple Sclerosis, Muscle Weakness, Myasthenia Gravis, Mycoses, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic-Myeloproliferative Diseases, Myeloproliferative Disorders, Myocardial Infarction, Myocardial Ischemia, Myositis, Nasal Polyps, Nasopharyngeal Neoplasms, Necrosis, Neoplasm Metastasis, Neoplasm, Residual, Neoplasms, Neoplasms, Connective Tissue, Neoplasms, Connective and Soft Tissue, Neoplasms, Germ Cell and Embryonal, Neoplasms, Plasma Cell, Neoplasms, Second Primary, Nervous System Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neurofibroma, Neurofibroma, Plexiform, Neurofibromatoses, Neurofibromatosis 1, Neurotoxicity Syndromes, Neutropenia, Nevus, Osteopetrosis, Osteosarcoma, Pancytopenia, Pars Planitis, Pemphigus, Pharyngeal Neoplasms, Pica, Plasmablastic Lymphoma, Plasmacytoma, Polyarteritis Nodosa, Polycythemia, Polycythemia Vera, Polymyalgia Rheumatica, Polyps, Precancerous Conditions, Precursor B-Cell Lymphoblastic Leukemia-Lymphoma, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Precursor T-Cell Lymphoblastic Leukemia-Lymphoma, Pregnancy, Ectopic, Preleukemia, Primary Myelofibrosis, Psoriasis, Pulmonary Valve Stenosis, Ranula, Rectal Neoplasms, Retinoblastoma, Rhabdoid Tumor, ST Elevation Myocardial Infarction, Sarcoma, Schizophrenia, Scleroderma, Diffuse, Scleroderma, Systemic, Sclerosis, Severe Combined Immunodeficiency, Sezary Syndrome, Shwachman-Diamond Syndrome, Sjogren's Syndrome, Skin Neoplasms, Spondylitis, Spondylitis, Ankylosing, Squamous Cell Carcinoma of Head and Neck, Stenosis, Pulmonary Vein, Still's Disease, Adult-Onset, Suicide, Syndrome, Synovitis, Systemic Vasculitis, Teratoma, Thrombocythemia, Essential, Thrombocytopenia, Thrombocytosis, Trophoblastic Neoplasms, Ulcer, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms, Urticaria, Uveitis, Uveitis, Intermediate, Uveitis, Posterior, Vasculitis, Virus Diseases, Vitiligo, Vitreoretinopathy, Proliferative, Waldenstrom Macroglobulinemia, Wiskott-Aldrich Syndrome	
Dexamethasone	BIRC5, GSTP1, CDK2	45	11	Phase 4: Ovarian Neoplasms, Abdominal Pain, Acute Coronary Syndrome, Acute Lung Injury, Adrenal Hyperplasia, Congenital, Adrenal Insufficiency, Adrenocortical Hyperfunction, Adrenogenital Syndrome, Ageusia, Agnosia, Aneurysm, Aneurysm, Dissecting, Ankle Fractures, Anosmia, Anterior Cruciate Ligament Injuries, Apnea, Arm Injuries, Arthritis, Asthma, Atrial Fibrillation, Brain Abscess, Breast Neoplasms, Bronchiolitis, Bronchiolitis, Viral, Burkitt Lymphoma, COVID-19, Calculi, Capsule Opacification, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Cataract, Cleft Lip, Cognitive Dysfunction, Colitis, Conjunctivitis, Conjunctivitis, Allergic, Constipation, Constriction, Pathologic, Corneal Edema, Corneal Endothelial Cell Loss, Coronavirus Infections, Cough, Crohn Disease, Croup, Deafness, Deglutition Disorders, Delayed Graft Function, Delirium, Depression, Developmental Dysplasia of the Hip, Diabetes Mellitus, Diabetic Retinopathy, Digestive System Diseases, Dissociative Disorders, Drug-Related Side Effects and Adverse Reactions, Dry Eye Syndromes, Dysphonia, Edema, Encephalitis, Encephalitis, Viral, Endophthalmitis, Enterocolitis, Enterocolitis, Necrotizing, Epiretinal Membrane, Epstein-Barr Virus Infections, Exfoliation Syndrome, Eye Diseases, Femoral Neck Fractures, Fractures, Bone, Gastrointestinal Diseases, Gastrointestinal Neoplasms, Gingival Recession, Glaucoma, Glaucoma, Open-Angle, Graft vs Host Disease, Graves Disease, HELLP Syndrome, Hand Injuries, Headache, Hearing Loss, Hearing Loss, Sensorineural, Heart Failure, Hematoma, Hematoma, Subdural, Hematoma, Subdural, Chronic, Hemorrhage, Hernia, Hip Dislocation, Hip Dislocation, Congenital, Hip Fractures, Histiocytosis, Hoarseness, Hyaline Membrane Disease, Hyperglycemia, Hyperplasia, Hypertension, Hypocalcemia, Hypoparathyroidism, Hypospadias, Hypotension, Infections, Infertility, Inflammation, Inflammatory Bowel Diseases, Intervertebral Disc Displacement, Intestinal Diseases, Intestinal Neoplasms, Intestinal Obstruction, Intra-Articular Fractures, Iridocyclitis, Ischemia, Joint Diseases, Keloid, Keratoconjunctivitis, Keratoconjunctivitis Sicca, Keratoconus, Kidney Calculi, Kidney Diseases, Kidney Failure, Chronic, Laryngitis, Leg Injuries, Leukemia, Leukemia, Lymphoid, Leukemia, Monocytic, Acute, Low Back Pain, Lung Diseases, Lung Diseases, Obstructive, Lung Injury, Lung Neoplasms, Lymphohistiocytosis, Hemophagocytic, Lymphoma, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, Macular Degeneration, Macular Edema, Malnutrition, Mediastinal Neoplasms, Meibomian Gland Dysfunction, Meningitis, Migraine Disorders, Multiple Myeloma, Myocarditis, Myofascial Pain Syndromes, Nausea, Neoplasms, Neoplasms, Plasma Cell, Neuralgia, Neuritis, Ocular Hypertension, Olfaction Disorders, Opioid-Related Disorders, Osteoarthritis, Osteoarthritis, Hip, Osteoarthritis, Knee, Otitis, Otitis Media, Otitis Media with Effusion, Otitis Media, Suppurative, Pain, Pancreatic Neoplasms, Papilledema, Pars Planitis, Pericarditis, Peripheral Arterial Disease, Peripheral Vascular Diseases, Pharyngitis, Pneumonia, Poroma, Post-Traumatic Headache, Postoperative Cognitive Complications, Postoperative Complications, Postoperative Hemorrhage, Postoperative Nausea and Vomiting, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Premature Birth, Prostatic Hyperplasia, Prostatic Neoplasms, Pruritus, Pterygium, Pulmonary Disease, Chronic Obstructive, Purpura, Purpura, Thrombocytopenic, Purpura, Thrombocytopenic, Idiopathic, Radiculopathy, Radius Fractures, Recurrence, Renal Insufficiency, Respiratory Distress Syndrome, Respiratory Distress Syndrome, Newborn, Respiratory Insufficiency, Retinal Detachment, Retinal Diseases, Retinal Vein Occlusion, Rotator Cuff Injuries, Rupture, ST Elevation Myocardial Infarction, Shoulder Impingement Syndrome, Shoulder Injuries, Sinusitis, Sjogren's Syndrome, Sleep Apnea Syndromes, Sleep Apnea, Obstructive, Spinal Stenosis, Spondylosis, Status Asthmaticus, Stress Disorders, Post-Traumatic, Suppuration, Syndrome, Synovitis, Systemic Inflammatory Response Syndrome, Temporomandibular Joint Disorders, Temporomandibular Joint Dysfunction Syndrome, Tendinopathy, Tenosynovitis, Thrombocytopenia, Tinnitus, Tonsillitis, Tooth, Impacted, Trigger Finger Disorder, Trismus, Tuberculosis, Tuberculosis, Meningeal, Urethral Stricture, Uveitis, Uveitis, Anterior, Uveitis, Intermediate, Uveitis, Posterior, Vascular Diseases, Virus Diseases, Vision Disorders, Vitamin D Deficiency, Vomiting, Wounds and Injuries	Ovarian Neoplasms (ClinicalTrials, ClinicalTrials)

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 13. 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
Erlotinib	STK10, RPS6KA3, CAMK2G, MET, IKBKE, MAPK6, PAK2, PRKACA, TTK, MAP3K11, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, NEK2, PLK1, NEK6, ERBB2, AKT1, AURKA, CHEK1, MAP3K20, BIRC5, MAPK3, MAP2K6, TYK2, MELK, PIM2, CDK8, MAPK9, CDK9, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3	97	6	Phase 3: Ovarian Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Brain Neoplasms, Carcinoma, Carcinoma, Acinar Cell, Carcinoma, Adenosquamous, Carcinoma, Hepatocellular, Carcinoma, Large Cell, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Colorectal Neoplasms, Disease Progression, Esophageal Neoplasms, Fallopian Tube Neoplasms, Head and Neck Neoplasms, Lip Neoplasms, Lung Neoplasms, Mouth Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms, Second Primary, Pancreatic Intraductal Neoplasms, Pancreatic Neoplasms, Rectal Neoplasms, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Thoracic Neoplasms
Pazopanib	STK10, RPS6KA3, CAMK2G, MET, IKBKE, MAPK6, PAK2, PRKACA, TTK, MAP3K11, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, NEK2, PLK1, NEK6, ERBB2, AKT1, AURKA, CHEK1, MAP3K20, MAPK3, MAP2K6, TYK2, MELK, PIM2, CDK8, MAPK9, CDK9, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2,	97	7	Phase 3: Ovarian Neoplasms, Carcinoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Chondrosarcoma, Chondrosarcoma, Mesenchymal, Dilatation, Pathologic, Epistaxis, Fibrosarcoma, Glomus Tumor, Granular Cell Tumor, Hemangiosarcoma, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Leiomyosarcoma, Liposarcoma, Lung Neoplasms, Myosarcoma, Neoplasms, Nerve Sheath Neoplasms, Neurofibrosarcoma, Osteosarcoma, Ranula, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Clear Cell, Sarcoma, Synovial, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis

	PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3			
Sorafenib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, CHEK2, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, HIPK2, PIM2, CDK8, MAPK9, CDK9, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	94	4	Phase 2: Ovarian Neoplasms, Acute Disease, Adenocarcinoma, Adenocarcinoma of Lung, Adenocarcinoma, Follicular, Adenoma, Adenoma, Liver Cell, Adrenocortical Carcinoma, Astrocytoma, Bile Duct Neoplasms, Biliary Tract Neoplasms, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Breast Neoplasms, Male, Carcinoid Tumor, Carcinoma, Carcinoma, Ductal, Carcinoma, Hepatocellular, Carcinoma, Islet Cell, Carcinoma, Medullary, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Carcinoma, Verrucous, Carcinosarcoma, Central Nervous System Neoplasms, Cholangiocarcinoma, Colonic Neoplasms, Colorectal Neoplasms, Desmoplastic Small Round Cell Tumor, Digestive System Neoplasms, Disease Progression, Endocrine Gland Neoplasms, Esophageal Neoplasms, Fallopian Tube Neoplasms, Fibroma, Fibrosarcoma, Fibrosis, Gallbladder Neoplasms, Gastrinoma, Gastrointestinal Neoplasms, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Glucagonoma, Head and Neck Neoplasms, Hemangiosarcoma, Hepatitis, Hepatitis A, Hepatitis B, Hepatitis C, Hepatoblastoma, Hepatopulmonary Syndrome, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Hypertension, Hypertension, Portal, Immunoblastic Lymphadenopathy, Insulinoma, Intestinal Neoplasms, Keloid, Kidney Diseases, Kidney Neoplasms, Klatskin Tumor, Laryngeal Diseases, Laryngeal Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Biphenotypic, Acute, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Promyelocytic, Acute, Leukemia, T-Cell, Leukemia-Lymphoma, Adult T-Cell, Liver Cirrhosis, Liver Diseases, Liver Neoplasms, Lung Neoplasms, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Large-Cell, Immunoblastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Cutaneous, Lymphoma, T-Cell, Peripheral, Malignant Carcinoid Syndrome, Melanoma, Mesothelioma, Mesothelioma, Malignant, Metaplasia, Mixed Tumor, Mullerian, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 2a, Multiple Endocrine Neoplasia Type 2b, Multiple Myeloma, Myelodysplastic Syndromes, Myeloproliferative Disorders, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Glandular and Epithelial, Neoplasms, Plasma Cell, Neoplasms, Second Primary, Neoplasms, Squamous Cell, Neoplasms, Unknown Primary, Nerve Sheath Neoplasms, Nervous System Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurofibroma, Neurofibromatoses, Neurofibromatosis 1, Neurofibrosarcoma, Oropharyngeal Neoplasms, Osteosarcoma, Pancreatic Neoplasms, Paranasal Sinus Neoplasms, Peritoneal Neoplasms, Pharyngeal Neoplasms, Plasmablastic Lymphoma, Plasmacytoma, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Prostatic Neoplasms, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Rhabdomyosarcoma, Embryonal, Salivary Gland Neoplasms, Sarcoma, Sarcoma, Ewing, Sarcoma, Synovial, Skin Neoplasms, Small Cell Lung Carcinoma, Somatostatinoma, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Syndrome, Testicular Neoplasms, Thrombosis, Thyroid Cancer, Papillary, Thyroid Carcinoma, Anaplastic, Thyroid Diseases, Thyroid Neoplasms, Tongue Neoplasms, Triple Negative Breast Neoplasms, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms, Uterine Cervical Neoplasms, Uveal Neoplasms, Vaccinia, Vipoma, Wilms Tumor
Vandetanib	STK10, RPS6KA3, CAMK2G, MET, IKBKE, MAPK6, PAK2, PRKACA, TTK, CDK1, MAP3K11, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, NEK2, PLK1, NEK6, ERBB2, AKT1, AURKA, CHEK1, MAP3K20, MAPK3, MAP2K6, TYK2, MELK, PIM2, CDK8, MAPK9, CDK9, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2,	93	3	Phase 2: Ovarian Neoplasms, Adenocarcinoma, Adenocarcinoma, Follicular, Biliary Tract Neoplasms, Brain Abscess, Breast Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Carcinoma, Verrucous, Cholangiocarcinoma, Colorectal Neoplasms, Endocrine Gland Neoplasms, Fallopian Tube Neoplasms, Gallbladder Neoplasms, Gastrointestinal Stromal Tumors, Glioblastoma, Gliosarcoma, Head and Neck Neoplasms, Kidney Neoplasms, Leiomyoma, Leiomyomatosis, Leukemia, Leukemia, Myeloid, Lung Neoplasms, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 2a, Multiple Endocrine Neoplasia Type 2b, Multiple Myeloma, Myoma, Neoplasm Metastasis, Neoplasms, Neoplasms, Plasma Cell, Peritoneal Neoplasms, Pleural Effusion, Pleural Effusion, Malignant, Precancerous Conditions, Prostatic Neoplasms, Rectal Neoplasms, Sarcoma, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Thyroid Cancer, Papillary, Thyroid Diseases, Thyroid Neoplasms, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms, von Hippel-Lindau Disease

	PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3			
Sunitinib	STK10, RPS6KA3, CAMK2G, MET, IKBKE, MAPK6, PAK2, PRKACA, TTK, MAP3K11, SIRT2, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, NEK2, PLK1, NEK6, ERBB2, AKT1, AURKA, CHEK1, MAP3K20, MAPK3, MAP2K6, TYK2, MELK, PIM2, CDK8, MAPK9, CDK9, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3	93	3	Phase 2: Ovarian Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Adenocarcinoma, Clear Cell, Adenocarcinoma, Follicular, Adenoma, Adenoma, Islet Cell, Adenomyoepithelioma, Adrenocortical Carcinoma, Ascites, Astrocytoma, Barrett Esophagus, Blast Crisis, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Breast Neoplasms, Male, Carcinoid Tumor, Carcinoma, Carcinoma, Acinar Cell, Carcinoma, Adenoid Cystic, Carcinoma, Adenosquamous, Carcinoma, Endometrioid, Carcinoma, Hepatocellular, Carcinoma, Islet Cell, Carcinoma, Medullary, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Papillary, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Carcinosarcoma, Carotid Body Tumor, Central Nervous System Neoplasms, Cholangiocarcinoma, Colonic Neoplasms, Colorectal Neoplasms, Conjunctival Neoplasms, Cystadenocarcinoma, Cystadenocarcinoma, Serous, Cysts, Edema, Endocrine Gland Neoplasms, Endometrial Neoplasms, Ependymoma, Esophageal Neoplasms, Fallopian Tube Neoplasms, Fibroma, Fibromatosis, Aggressive, Fibrosarcoma, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Head and Neck Neoplasms, Hemangioblastoma, Hemangiopericytoma, Hemorrhagic Fever, Ebola, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Inflammatory Breast Neoplasms, Intestinal Neoplasms, Kidney Neoplasms, Laryngeal Diseases, Laryngeal Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Hairy Cell, Leukemia, Large Granular Lymphocytic, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Mast-Cell, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Accelerated Phase, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Acute, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Prolymphocytic, Liposarcoma, Liver Neoplasms, Lung Neoplasms, Lymphoma, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Non-Hodgkin, Macular Degeneration, Macular Edema, Melanoma, Meningioma, Mesothelioma, Mesothelioma, Malignant, Mixed Tumor, Mullerian, Multiple Myeloma, Myelodysplastic Syndromes, Myoepithelioma, Myosarcoma, Nasopharyngeal Carcinoma, Neoplasm Metastasis, Neoplasms, Neoplasms, Germ Cell and Embryonal, Neoplasms, Hormone-Dependent, Neoplasms, Plasma Cell, Neoplasms, Unknown Primary, Nervous System Neoplasms, Neuroendocrine Tumors, Neurofibroma, Neurofibroma, Plexiform, Neurofibromatoses, Neurofibromatosis 1, Oligodendroglioma, Oropharyngeal Neoplasms, Osteosarcoma, Pancreatic Neoplasms, Paraganglioma, Paranasal Sinus Neoplasms, Peritoneal Neoplasms, Pharyngeal Neoplasms, Pheochromocytoma, Pica, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Neoplasms, Ranula, Rectal Neoplasms, Retinal Vein Occlusion, Salivary Gland Neoplasms, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Kaposi, Skin Neoplasms, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Syndrome, Teratoma, Testicular Neoplasms, Thymoma, Thymus Neoplasms, Thyroid Cancer, Papillary, Thyroid Diseases, Thyroid Neoplasms, Triple Negative Breast Neoplasms, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms, Urogenital Neoplasms, Urologic Neoplasms, Uterine Cervical Neoplasms, Uterine Neoplasms, Uveal Neoplasms, Virus Diseases, von Hippel-Lindau Disease

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

Repurposing drugs

Table 14. 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
seliciclib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, CHEK2, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, CDK1, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, HIPK2, PIM2, CDK8, MAPK9, CDK9, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	80	Phase 2: ACTH-Secreting Pituitary Adenoma, Adenoma, Carcinoma, Non-Small-Cell Lung, Cystic Fibrosis, Cysts, Fibrosis, Pituitary ACTH Hypersecretion, Pituitary Neoplasms
midostaurin	STK10, RPS6KA3, CAMK2G, MET, IKBKE, MAPK6, PAK2, PRKACA, TTK, MAP3K11, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, NEK2, PLK1, NEK6, ERBB2, AKT1, AURKA, CHEK1, MAP3K20, MAPK3, MAP2K6, TYK2, MELK, PIM2, CDK8, MAPK9, CDK9, PRKD3, PDGFRB, MAP2K1, MAP4K3, PIK3CB, WEE1, PTK2, PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3	79	Phase 3: Anemia, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Myelodysplastic Syndromes, Preleukemia, Syndrome
Vatalanib	STK10, RPS6KA3, CAMK2G, MET, IKBKE, MAPK6, PAK2, PRKACA, TTK, CDK1, MAP3K11, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, NEK2, PLK1, NEK6, ERBB2, AKT1, AURKA, CHEK1, MAP3K20, MAPK3, MAP2K6, TYK2, MELK, PIM2, CDK8, MAPK9, CDK9, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3	79	Phase 3: Colonic Neoplasms, Colorectal Neoplasms, Neoplasms, Rectal Neoplasms
1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, CHEK2, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, HIPK2, PIM2, CDK8, MAPK9, CDK9, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	79	N/A
ruboxistaurin	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, CHEK2, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, HIPK2, PIM2, CDK8, MAPK9, CDK9, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	79	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

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

No prospective drugs were found, which would be predicted by PASS software to be active against the identified drug targets and would be predicted to have biological activity against the studied disease(s).

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
Bortezomib	PSMC5, PSME3, PSMD13, PSMA7, PSMC3, PSMD2, PSMD1, PSMD14, PSMD5, PSMC6, CASP3, PSMD11, PSMC4, PSMC1, PSMC2, PSMD12, PSMD7, PSMD3	98	2.05
N-(4-MORPHOLINE)CARBONYL-B-(1-NAPHTHYL)-L-ALANINE-L-LEUCINE BORONIC ACID	PSMC5, PSME3, PSMD13, PSMA7, PSMC3, PSMD2, PSMD1, PSMD14, PSMD5, PSMC6, PSMD11, PSMC4, PSMC1, PSMC2, PSMD12, PSMD7, PSMD3	98	1.61
Camptothecin	HIF1A, CASP3, LGALS1	97	0.82
Topotecan	HIF1A, CASP3, LGALS1	97	0.81
LE-SN38	HIF1A, CASP3, LGALS1	97	0.78

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Erlotinib, seliciclib and Bortezomib. These drugs were selected for acting on the following targets: NEK2 and PSMD5, 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 **N/I** (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
Abarelix	Prostatic Neoplasms	N/I
Abemaciclib	Breast Neoplasms	15
Abiraterone	Prostatic Neoplasms, Castration-Resistant	N/I
Abiraterone acetate	Prostatic Neoplasms, Castration-Resistant	N/I
Acalabrutinib	Lymphoma, Mantle-Cell	N/I
Acitretin	Psoriasis	12
Ado-trastuzumab	Breast Neoplasms|Neoplasms	83

emtansine		
Afatinib	Carcinoma, Non-Small-Cell Lung	34
Aflibercept	Colorectal Neoplasms|Diabetic Retinopathy|Edema|Vascular Diseases|Wet Macular Degeneration	41
Alectinib	Carcinoma, Non-Small-Cell Lung	23
Alemtuzumab	Brain Abscess|Leukemia, Lymphocytic, Chronic, B-Cell|Multiple Sclerosis|Multiple Sclerosis, Relapsing-Remitting|Sclerosis	N/I
Alitretinoin	Sarcoma, Kaposi	N/I
Alpelisib	Breast Neoplasms	60
Altretamine	Ovarian Neoplasms	N/I
Aminolevulinic acid	Keratosis|Keratosis, Actinic	N/I
Anagrelide	Thrombocythemia, Essential|Thrombocytosis	N/I
Anastrozole	Breast Neoplasms|Hypersensitivity|Obesity|Obesity, Morbid|Recurrence|Weight Loss	N/I
Apalutamide	Prostatic Neoplasms, Castration-Resistant	N/I
Aprepitant	Nausea|Neoplasms|Postoperative Nausea and Vomiting	N/I
Arsenic trioxide	Leukemia, Promyelocytic, Acute	68
Atezolizumab	Carcinoma, Non-Small-Cell Lung|Carcinoma, Transitional Cell|Triple Negative Breast Neoplasms	N/I
Avelumab	Carcinoma, Merkel Cell|Carcinoma, Renal Cell|Carcinoma, Transitional Cell	N/I
Axitinib	Carcinoma, Renal Cell	60
Azacitidine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes|Preleukemia|Syndrome	17
Belinostat	Lymphoma, T-Cell, Peripheral	58
Bendamustine	Leukemia, Lymphocytic, Chronic, B-Cell|Leukemia, Lymphoid	N/I
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	N/I
Bexarotene	Lymphoma, T-Cell|Lymphoma, T-Cell, Cutaneous	N/I
Bicalutamide	Prostatic Neoplasms	9
Binimetinib	Melanoma	50
Blinatumomab	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	N/I
Bortezomib	Brain Abscess|Glomerulonephritis|Glomerulonephritis, IGA|Kidney Diseases|Multiple Myeloma|Neoplasms, Plasma Cell|Nephritis|Renal Insufficiency	78
Bosutinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	66
Brentuximab vedotin	Hodgkin Disease|Lymphoma|Lymphoma, Large-Cell, Anaplastic|Lymphoma, T-Cell, Peripheral	N/I
Brigatinib	Carcinoma, Non-Small-Cell Lung	37
Buserelin	Prostatic Neoplasms	N/I
Cabazitaxel	Prostatic Neoplasms, Castration-Resistant	73
Cabergoline	Drug-Related Side Effects and Adverse Reactions|Pituitary Neoplasms	N/I
Cabozantinib	Thyroid Neoplasms	17
Capecitabine	Breast Neoplasms|Colonic Neoplasms|Colorectal Neoplasms	N/I
Carboplatin	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms|Neuroendocrine Tumors|Ovarian Neoplasms|Retinoblastoma	N/I
Carfilzomib	Multiple Myeloma	72
Carmustine	Astrocytoma|Glioblastoma|Hodgkin Disease|Medulloblastoma|Multiple Myeloma|Neoplasms	43
Ceritinib	Carcinoma, Non-Small-Cell Lung	70
Cetuximab	Colorectal Neoplasms	N/I
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	N/I
Cisplatin	Carcinoma, Squamous Cell|Neoplasms|Uterine Cervical Neoplasms|Carcinoma, Non-Small-Cell Lung|Esophageal Neoplasms|Carcinoma	77
Cladribine	Leukemia, Hairy Cell	5
Clofarabine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	N/I
Cobimetinib	Melanoma	48
Copanlisib	Lymphoma, Follicular	82
Crizotinib	Carcinoma, Non-Small-Cell Lung	27
Cyproterone acetate	Prostatic Neoplasms	N/I
Dabrafenib	Melanoma	24
Dacomitinib	Carcinoma, Non-Small-Cell Lung	57
Daratumumab	Multiple Myeloma	N/I
Dasatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid, Chronic-Phase|Precursor Cell Lymphoblastic Leukemia-Lymphoma	91
Decitabine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes	48
Degarelix	Cardiovascular Diseases|Prostatic Neoplasms|Vascular Diseases	40
Denosumab	Arthritis, Rheumatoid|Bone Diseases|Bone Diseases, Metabolic|Breast Neoplasms|Hyperparathyroidism|Hyperparathyroidism, Primary|Metabolic Diseases|Neoplasm Metastasis|Neoplasms|Osteoporosis|Osteoporosis, Postmenopausal|Prostatic Neoplasms	N/I
Dexrazoxane	Breast Neoplasms|Cardiomyopathies	N/I
Dienogest	Menorrhagia	N/I
Dinutuximab	Neuroblastoma	N/I
Docetaxel	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Prostatic Neoplasms|Squamous Cell Carcinoma of Head and Neck|Stomach Neoplasms	62
Doxorubicin	Neoplasms|Multiple Myeloma|Carcinoma, Ovarian Epithelial|Ovarian Neoplasms|Leukemia, Lymphoid|Breast Neoplasms|Lymphoma, Follicular|Thyroid Neoplasms|Triple Negative Breast Neoplasms|Glioma	86
Durvalumab	Carcinoma, Non-Small-Cell Lung|Carcinoma, Transitional Cell	N/I
Dutasteride	Alcoholism|Hyperplasia|Hypertrophy|Neoplasms|Prostatic Hyperplasia	N/I
Duvelisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	9
Elotuzumab	Multiple Myeloma	36
Enasidenib	Leukemia, Myeloid, Acute	N/I
Encorafenib	Colorectal Neoplasms|Melanoma	52
Enfortumab vedotin	Carcinoma, Transitional Cell|Neoplasms	N/I
Entrectinib	Carcinoma, Non-Small-Cell Lung	N/I
Enzalutamide	Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	N/I

Epirubicin	Breast Neoplasms	61
Erdafitinib	Urinary Bladder Neoplasms	58
Eribulin	Breast Neoplasms|Drug-Related Side Effects and Adverse Reactions|Neoplasms	N/I
Erlotinib	Carcinoma, Non-Small-Cell Lung|Neoplasms|Pancreatic Neoplasms	97
Erlotinib hydrochloride	Carcinoma, Non-Small-Cell Lung|Gastrointestinal Stromal Tumors	N/I
Estramustine	Prostatic Neoplasms	18
Ethinyl Estradiol	Acne Vulgaris|Neoplasms	30
Everolimus	Angiomyolipoma|Arthrogryposis|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	67
Exemestane	Breast Neoplasms	N/I
Fedratinib	Primary Myelofibrosis	N/I
Finasteride	Hyperplasia|Neoplasms|Prostatic Hyperplasia	N/I
Flavopiridol	Leukemia, Lymphocytic, Chronic, B-Cell	89
Fluorouracil	Skin Neoplasms|Neoplasms, Basal Cell|Neoplasms, Second Primary|Neoplasms, Squamous Cell|Neoplasms|Colorectal Neoplasms|Pancreatic Neoplasms	77
Fluoxymesterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	N/I
Flutamide	Premenstrual Dysphoric Disorder|Premenstrual Syndrome|Prostatic Neoplasms	45
Fulvestrant	Breast Neoplasms	N/I
Gefitinib	Carcinoma, Non-Small-Cell Lung	91
Gemcitabine	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Ovarian Neoplasms|Pancreatic Neoplasms	78
Gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	N/I
Gilteritinib	Leukemia, Myeloid, Acute	60
Glasdegib	Leukemia, Myeloid, Acute	N/I
Goserelin	Atrophy|Breast Neoplasms|Bulbo-Spinal Atrophy, X-Linked|Endometriosis|Muscular Atrophy|Myoma|Prostatic Neoplasms	N/I
Histrelin	Puberty, Precocious	N/I
Homoharringtonine	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	76
Ibritumomab	Lymphoma, B-Cell|Lymphoma, Follicular	N/I
Ibrutinib	Graft vs Host Disease|Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, B-Cell, Marginal Zone|Lymphoma, Mantle-Cell|Waldenstrom Macroglobulinemia	58
Idarubicin	Leukemia, Myeloid, Acute	N/I
Idelalisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	26
Ifosfamide	Neoplasms	37
Imatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Mastocytosis, Systemic|Neoplasms	86
Inotuzumab ozogamicin	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	N/I
Ipilimumab	Carcinoma, Renal Cell|Melanoma	N/I
Irinotecan	Colorectal Neoplasms	70
Ivosidenib	Leukemia, Myeloid, Acute	N/I
Ixabepilone	Breast Neoplasms	N/I
Ixazomib	Multiple Myeloma	N/I
Lapatinib	Breast Neoplasms	83
Larotrectinib	Neoplasm Metastasis	N/I
Lenalidomide	Brain Abscess|Lupus Erythematosus, Cutaneous|Myelodysplastic Syndromes|Neoplasms, Plasma Cell	N/I
Lenvatinib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	65
Letrozole	Breast Neoplasms|Cysts|Fibroma|Myofibroma|Myoma|Ovarian Cysts|Syndrome	N/I
Leuprolide	Hot Flashes|Ovarian Hyperstimulation Syndrome|Prostatic Neoplasms|Puberty, Precocious	N/I
Levamisole	Ascariasis|Colonic Neoplasms|Helminthiasis	N/I
Levonorgestrel	Epilepsy|Hyperplasia|Menorrhagia	N/I
Lomustine	Brain Neoplasms|Hodgkin Disease	N/I
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	61
Lorlatinib	Carcinoma, Non-Small-Cell Lung	12
Masoprocol	Keratosis, Actinic	N/I
Medroxyprogesterone Acetate	Depression|Depression, Postpartum|Depressive Disorder|Metrorrhagia|Neoplasms|Uterine Hemorrhage	15
Megestrol acetate	Acquired Immunodeficiency Syndrome|Bites and Stings|Breast Neoplasms|Pain|Wasting Syndrome	N/I
Methotrexate	Neoplasms|Breast Neoplasms|Head and Neck Neoplasms|Ovarian Neoplasms|Lymphoma, T-Cell, Peripheral|Brain Neoplasms|Colorectal Neoplasms|Neuroblastoma|Carcinoma, Squamous Cell	48
Methyltestosterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	N/I
Midostaurin	Leukemia, Mast-Cell|Leukemia, Myeloid, Acute|Mastocytosis, Systemic	79
Mitotane	Adrenocortical Carcinoma	N/I
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	56
Mogamulizumab	Mycosis Fungoides|Neoplasms|Sezary Syndrome	N/I
Moxetumomab pasudotox	Leukemia, Hairy Cell|Neoplasms	N/I
Necitumumab	Carcinoma, Non-Small-Cell Lung|Neoplasms	N/I
Nelarabine	Precursor T-Cell Lymphoblastic Leukemia-Lymphoma	N/I
Neratinib	Breast Neoplasms	52
Nilotinib	Blast Crisis|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid, Chronic-Phase	44
Nilutamide	Prostatic Neoplasms	N/I
Nintedanib	Fibrosis|Idiopathic Pulmonary Fibrosis	76
Niraparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms	65
Nivolumab	Carcinoma, Non-Small-Cell Lung|Kidney Neoplasms|Neoplasms|Lung Neoplasms|Melanoma	N/I
Obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	N/I
Octreotide	Acromegaly|Adenoma|Ascites|Carcinoid Tumor|Fistula|Pancreatic Fistula|Pituitary Diseases|Renal Insufficiency|Vipoma	31
Ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	N/I

Olaparib	Breast Neoplasms|Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Ovarian Neoplasms|Pancreatic Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	53
Olaratumab	Sarcoma	N/I
Osimertinib	Carcinoma, Non-Small-Cell Lung	62
Oxaliplatin	Colonic Neoplasms|Colorectal Neoplasms|Neoplasms|Rectal Neoplasms	36
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	N/I
Panitumumab	Colorectal Neoplasms	N/I
Panobinostat	Multiple Myeloma	21
Pazopanib	Carcinoma|Carcinoma, Renal Cell|Sarcoma	97
Pembrolizumab	Carcinoma, Hepatocellular|Carcinoma, Merkel Cell|Carcinoma, Non-Small-Cell Lung|Carcinoma, Renal Cell|Carcinoma, Transitional Cell|Hodgkin Disease|Melanoma|Neoplasms|Stomach Neoplasms	N/I
Pemetrexed	Carcinoma, Non-Small-Cell Lung|Mesothelioma	N/I
Pentostatin	Leukemia, Hairy Cell	N/I
Pertuzumab	Breast Neoplasms	77
Pomalidomide	Multiple Myeloma	N/I
Ponatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Precursor Cell Lymphoblastic Leukemia-Lymphoma	25
Pralatrexate	Lymphoma, T-Cell, Peripheral	N/I
Radium Ra 223 Dichloride	Prostatic Neoplasms, Castration-Resistant	N/I
Ramucirumab	Stomach Neoplasms	N/I
Rasburicase	Hyperuricemia|Leukemia|Lymphoma|Neoplasms|Syndrome|Tumor Lysis Syndrome	N/I
Regorafenib	Colorectal Neoplasms	69
Relugolix	Prostatic Neoplasms	N/I
Ribociclib	Breast Neoplasms	N/I
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	N/I
Romidepsin	Lymphoma, T-Cell, Cutaneous	36
Rucaparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	57
Ruxolitinib	Graft vs Host Disease|Polycythemia|Polycythemia Vera|Primary Myelofibrosis|Thrombocytosis	N/I
Selinexor	Multiple Myeloma	39
Selumetinib	Neurofibromatosis 1	35
Siltuximab	Giant Lymph Node Hyperplasia	N/I
Sirolimus	Angiomyolipoma|Constriction, Pathologic|Coronary Restenosis|Eye Diseases|Immune System Diseases|Kidney Failure, Chronic|Lipoma|Tuberous Sclerosis	79
Sonidegib	Carcinoma, Basal Cell	N/I
Sorafenib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	94
Sunitinib	Adenoma|Carcinoma, Renal Cell|Digestive System Neoplasms|Gastrointestinal Neoplasms|Gastrointestinal Stromal Tumors|Intestinal Neoplasms	93
Talazoparib	Breast Neoplasms	48
Tamoxifen	Breast Diseases|Cystic Fibrosis|Cysts|Fibroadenoma|Fibrocystic Breast Disease|Hemorrhage|Menorrhagia|Menstruation Disturbances|Metrorrhagia|Neoplasms	47
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	N/I
Temozolomide	Astrocytoma|Nervous System Neoplasms	N/I
Temsirolimus	Carcinoma, Renal Cell	78
Teniposide	Precursor Cell Lymphoblastic Leukemia-Lymphoma	38
Thalidomide	Brain Abscess|Immune System Diseases|Multiple Myeloma|Neoplasms, Plasma Cell	N/I
Tivozanib	Carcinoma, Renal Cell	70
Tocilizumab	Arthritis|Arthritis, Juvenile|Arthritis, Rheumatoid|Behavior|Cytokine Release Syndrome|Giant Cell Arteritis|Neurobehavioral Manifestations|Oral Manifestations|Psychotic Disorders|Schizophrenia|Tic Disorders	N/I
Topotecan	Small Cell Lung Carcinoma	38
Toremifene	Breast Neoplasms	18
Trabectedin	Leiomyosarcoma|Liposarcoma	N/I
Trametinib	Carcinoma, Non-Small-Cell Lung|Melanoma	82
Trastuzumab	Breast Neoplasms|Neoplasms	47
Tretinoin	Lentigo	61
Triptorelin	Fatty Liver|Hypogonadism|Infertility, Female|Prostatic Neoplasms	54
Tucatinib	Breast Neoplasms	69
Valrubicin	Urinary Bladder Neoplasms	N/I
Vandetanib	Thyroid Neoplasms	93
Vemurafenib	Melanoma	41
Venetoclax	Leukemia, Lymphocytic, Chronic, B-Cell|Leukemia, Myeloid, Acute	N/I
Vinblastine	Glioma	N/I
Vincristine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	N/I
Vinorelbine	Carcinoma, Non-Small-Cell Lung	66
Vismodegib	Carcinoma, Basal Cell	N/I
Vorinostat	Lymphoma, T-Cell, Cutaneous	64
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	N/I

6. Conclusion

We applied the software package "Genome Enhancer" to a multi-omics data set that contains *transcriptomics and epigenomics* data. The study is done in the context of *Ovarian Neoplasms*. The data were pre-processed, statistically analyzed and differentially expressed genes 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, seliciclib and Bortezomib

These drugs were selected for acting on the following targets: NEK2 and PSMD5, 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:

TGFbetaR-II, Nek2A, 26S proteasome and Cdk1-isoform1:cyclinB1-isoform1

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: Vandetanib, Bortezomib, 6-Nitroindazole, Erlotinib, seliciclib, 3,5-Diaminophthalhydrazide and uab-30. 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 differentially expressed genes 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.

- TGFbetaR-II
- Nek2A
- 26S proteasome
- Cdk1-isoform1:cyclinB1-isoform1

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 differentially expressed genes were analyzed using known DNA-binding motifs described in the TRANSFAC® library, release 2022.1 (geneXplain GmbH, Wolfenbüttel, Germany) (https://genexplain.com/transfac).
The master regulator search uses the TRANSPATH® database (BIOBASE), release 2022.1 (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®.
The information about drugs corresponding to identified drug targets and clinical trials references were extracted from HumanPSD™ database, release 2022.1 (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.

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 promoters and enhancers under study as compared to a background sequence set such as promoters of genes that were not differentially regulated under the condition of the experiment. 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).

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-score$_{PSD}$*),
2. ranking by "Disease activity score" (*D-score$_{PSD}$*),
3. ranking by "Clinical validity score".

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

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

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, *rank(t)* is rank of given target, *maxRank(T)* equals *max(rank(t))* for all targets *t* in *T*.

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

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

where *D* is the set of selected diseases, and if *D* is empty set, *D-score$_{PSD}$=0*. *P* is a set of all known phases for each disease, *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.

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Supplementary material

1. Supplementary table 1 - Detailed report. Composite modules and master regulators (up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive).
2. Supplementary table 2 - Detailed report. Composite modules and master regulators (down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive).
3. Supplementary table 3 - Detailed report. Pharmaceutical compounds and drug targets.

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