PDGFRA and DUSP9 are promising druggable targets for treating Ovarian Neoplasms that control activity of STAT3, MAZ and HNF4A transcription factors on of differentially expressed genes

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Genome Enhancer release 3.3 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2023.2)

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: STAT3, MAZ, EP300, HNF4A and FOSL1. The subsequent network analysis suggested

- EAC
- IGFBP-5
- PDGFRalpha
- CDK2
- MKP-4

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: Imatinib, midostaurin 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

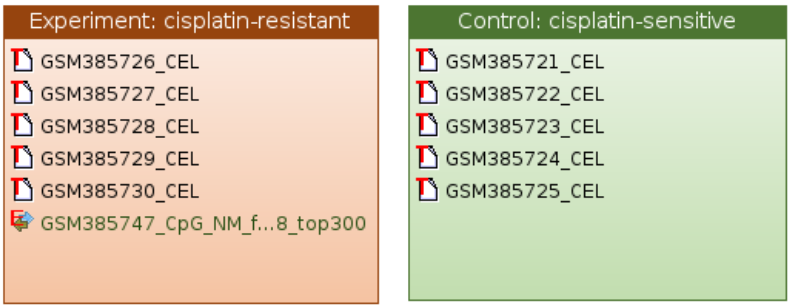


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

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 applied the Limma tool (R/Bioconductor package integrated into our pipeline) and compared gene expression in the following sets: "Experiment: cisplatin-resistant" with "Control: cisplatin-sensitive". Limma calculated the LogFC (the logarithm to the base 2 of the fold change between different conditions), the p-value and the adjusted p-value (corrected for multiple testing) of the observed fold change. As a result, we detected 4060 upregulated genes (LogFC>0.1) out of which 3350 genes were found as significantly upregulated (p-value<0.1) and 4162 downregulated genes (LogFC<-0.1) out of which 3351 genes were significantly downregulated (p-value<0.1). See tables below for the top significantly up- and downregulated genes. Below we call **target genes** the full list of up- and downregulated genes revealed in our analysis (see tables in Supplementary section).

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

ID	Gene symbol	Gene description	logFC	P.Value	adj.P.Val
ENSG00000123700	KCNJ2	potassium inwardly rectifying channel subfamily J member 2	5.37	6.79E-14	7.28E-11
ENSG00000064218	DMRT3	doublesex and mab-3 related transcription factor 3	4.03	7.48E-12	2.59E-9
ENSG00000099139	PCSK5	proprotein convertase subtilisin/kexin type 5	3.93	1.35E-14	2.07E-11
ENSG00000197705	KLHL14	kelch like family member 14	3.89	9.84E-13	4.22E-10
ENSG00000129038	LOXL1	lysyl oxidase like 1	3.54	2.27E-10	3.24E-8
ENSG00000133083	DCLK1	doublecortin like kinase 1	3.24	8.07E-13	3.76E-10
ENSG00000141431	ASXL3	ASXL transcriptional regulator 3	3.14	1.36E-11	3.64E-9
ENSG00000126950	TMEM35A	transmembrane protein 35A	3.05	1.6E-12	6.15E-10
ENSG00000164692	COL1A2	collagen type I alpha 2 chain	2.86	2.21E-10	3.24E-8
ENSG00000138378	STAT4	signal transducer and activator of transcription 4	2.86	3.04E-10	3.75E-8

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

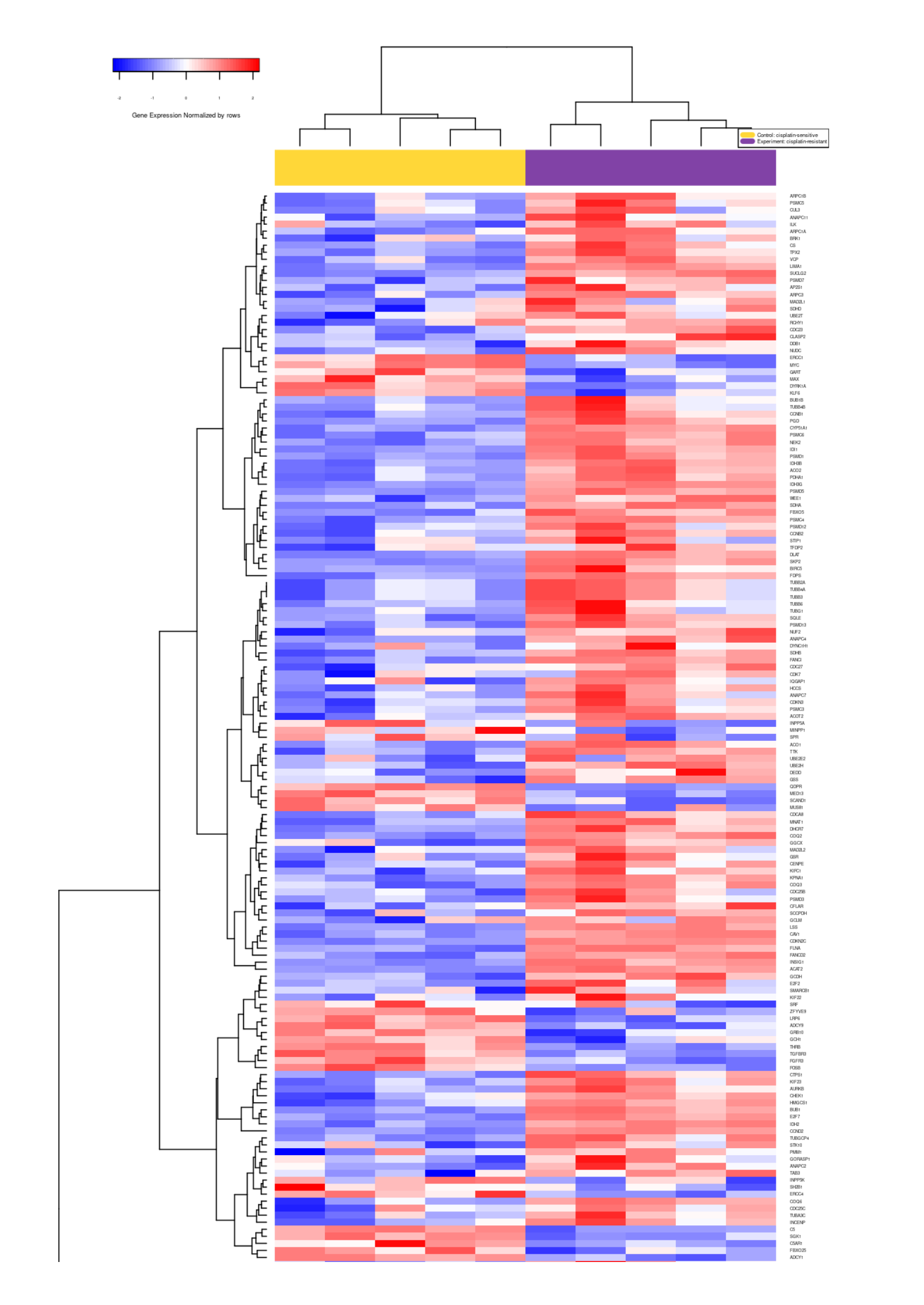
ID	Gene symbol	Gene description	logFC	P.Value	adj.P.Val
ENSG00000127324	TSPAN8	tetraspanin 8	-6.39	1.5E-15	4.04E-12
ENSG00000139292	LGR5	leucine rich repeat containing G protein-coupled receptor 5	-6.24	5.76E-18	6.18E-14
ENSG00000149968	MMP3	matrix metallopeptidase 3	-5.16	2E-13	1.65E-10
ENSG00000163359	COL6A3	collagen type VI alpha 3 chain	-5.08	5.33E-16	1.9E-12
ENSG00000169908	TM4SF1	transmembrane 4 L six family member 1	-4.94	1.59E-16	8.54E-13
ENSG00000153233	PTPRR	protein tyrosine phosphatase receptor type R	-4.6	5.98E-13	3.21E-10
ENSG00000166670	MMP10	matrix metallopeptidase 10	-4.45	9.28E-15	1.66E-11
ENSG00000106511	MEOX2	mesenchyme homeobox 2	-4.26	3.66E-12	1.35E-9
ENSG00000145431	PDGFC	platelet derived growth factor C	-4.14	3.26E-14	4.37E-11
ENSG00000060718	COL11A1	collagen type XI alpha 1 chain	-3.65	9.63E-11	1.75E-8

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
ARPC1B
PSMC5
CUL3
ANAPC11
ILK
ARPC1A
BRK1
CS
TPX2
VCP
LIMA1
SUCLG2
PSMD7
AP2S1
ARPC3
MAD2L1
SDHD
UBE2T
RCHY1
CDC23
CLASP2
DDB1
NUDC
ERCC1
MYC
GART
MAX
DYRK1A
KLF6
BUB1B
TUBB4B
CCNB1
PGD
CYP51A1
PSMC6
NEK2
IDI1
PSMD1
IDH3B
ACO2
PDHA1
IDH3G
PSMD5
WEE1
SDHA
FBXO5
PSMC4
PSMD12
CCNB2
STIP1
TFDP2
DLAT
SKP2
BIRC5
FDPS
TUBB2A
TUBB4A
TUBB3
TUBB6
TUBG1
SQLE
PSMD13
NUF2
ANAPC4
DYNC1H1
SDHB
FANCI
CDC27
CDK7
IQGAP1
HCCS
ANAPC7
CDKN3
PSMC3
ACOT2
INPP5A
MINPP1
SPR
ACO1
TTK
UBE2E2
UBE2H
DEDD
GSS
QDPR
MED13
SCAND1
MUS81
CDCA8
MNAT1
DHCR7
COQ2
GGCX
MAD2L2
GBR
CENPE
KIFC1
KPNA1
COQ3
CDC25B
PSMD3
CFLAR
SCCPDH
GCLM
LSS
CAK1
CDKN2C
FLNA
FANCD2
INSIG1
ACAT2
GCDH
E2F2
SMARCB1
KIF22
SRF
ZFYVE9
LRP6
ADCY9
GRB10
GCH1
THRB
TGFBR3
FGFR3
FOSB
CTPS1
KIF23
AURKB
CHEK1
HMGCS1
BUB1
E2F7
IDH2
CCND2
TUBGCP4
STK10
PMM1
GORASP1
ANAPC2
TAB3
INPP5K
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COQ6
CDC25C
TUBA3C
INCENP
C5
SGK1
CSAR1
FBXO25
ADCY1

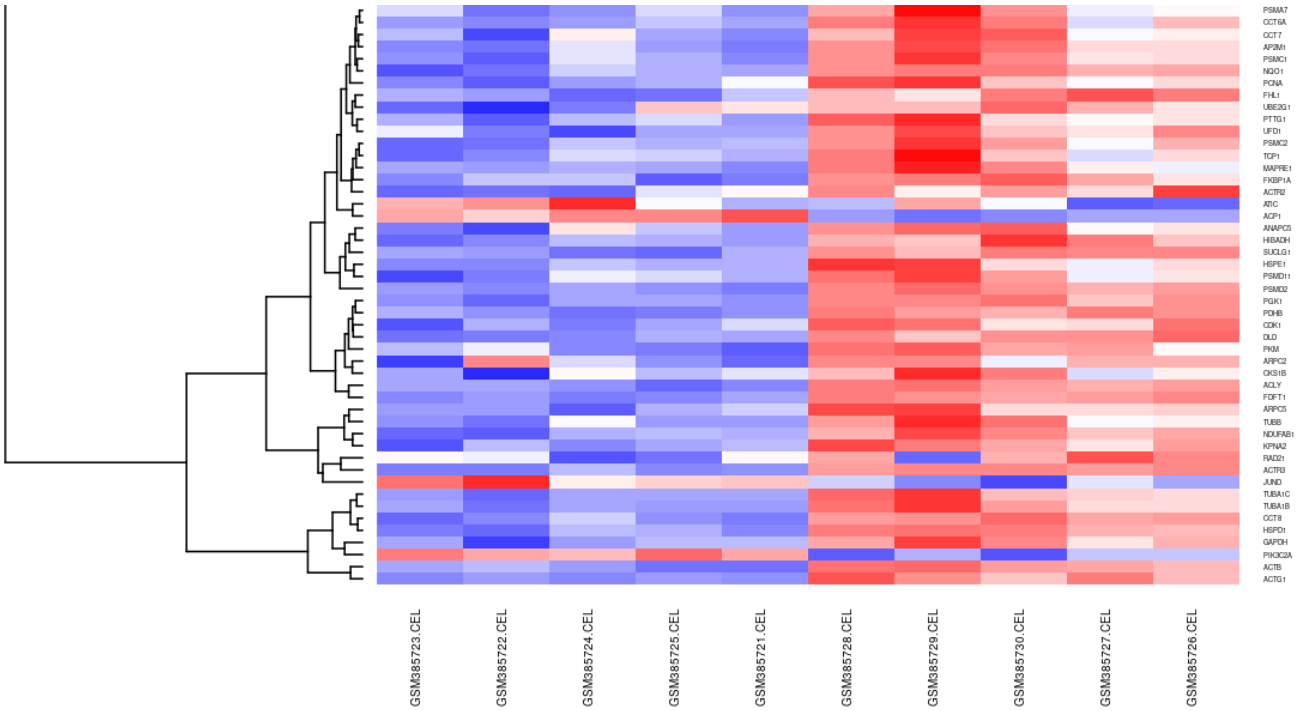


Figure 2. Heatmap of genes enriched in Transpath categories. The colored bar at the top shows the types of the samples according to the legend in the upper right corner.
See full diagram →

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

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

GO (biological process)

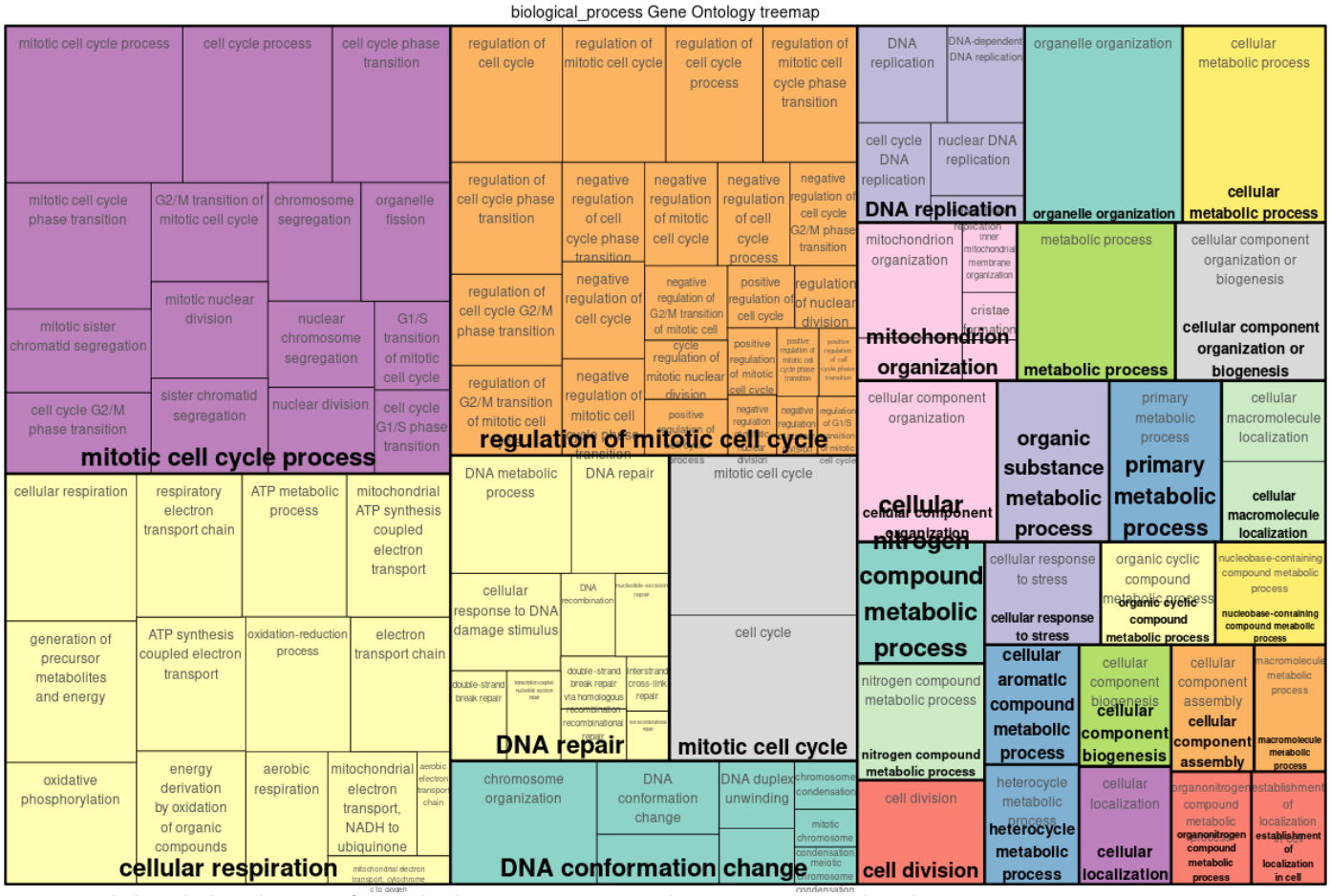


Figure 3. Enriched GO (biological process) of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

TRANSPATH® Pathways (2023.2)

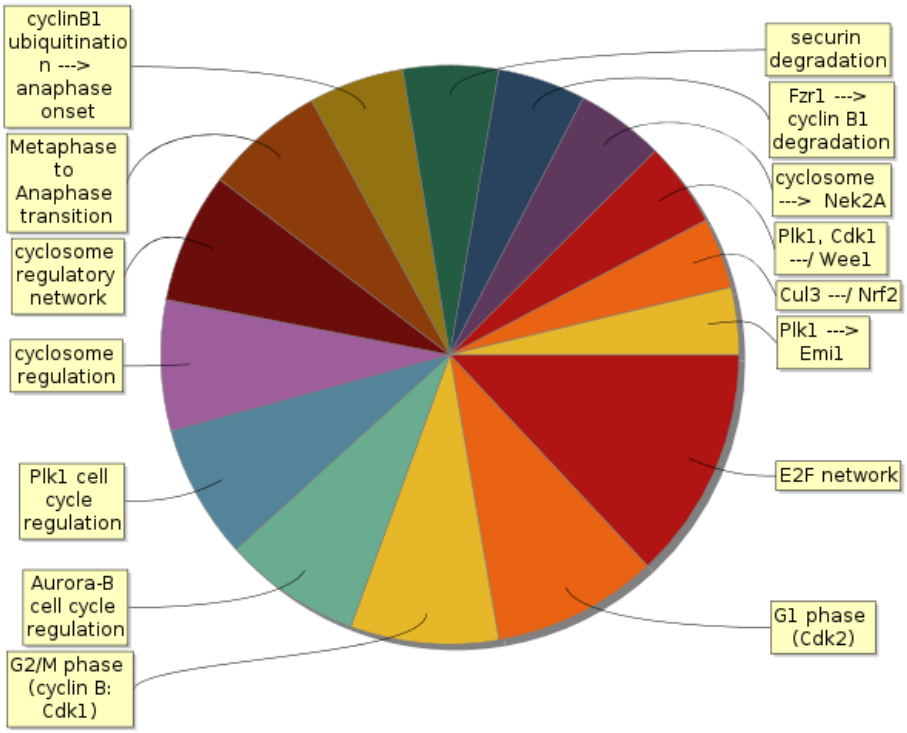


Figure 4. Enriched TRANSPATH® Pathways (2023.2) of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

HumanPSD(TM) disease (2023.2)

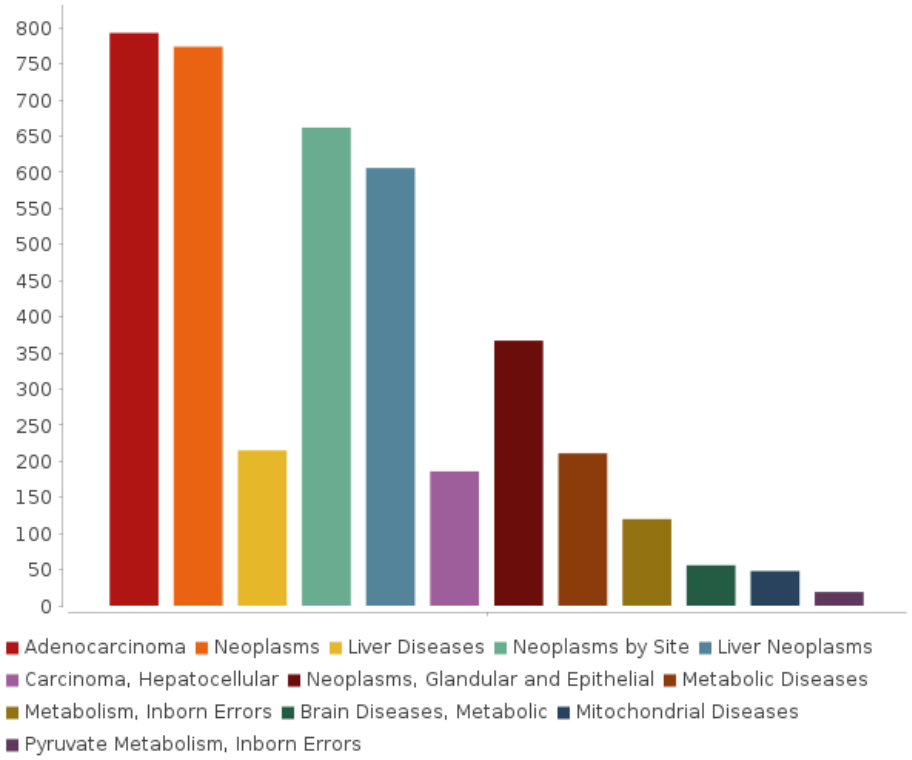


Figure 5. Enriched HumanPSD(TM) disease (2023.2) of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.
Full classification →

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

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

GO (biological process)

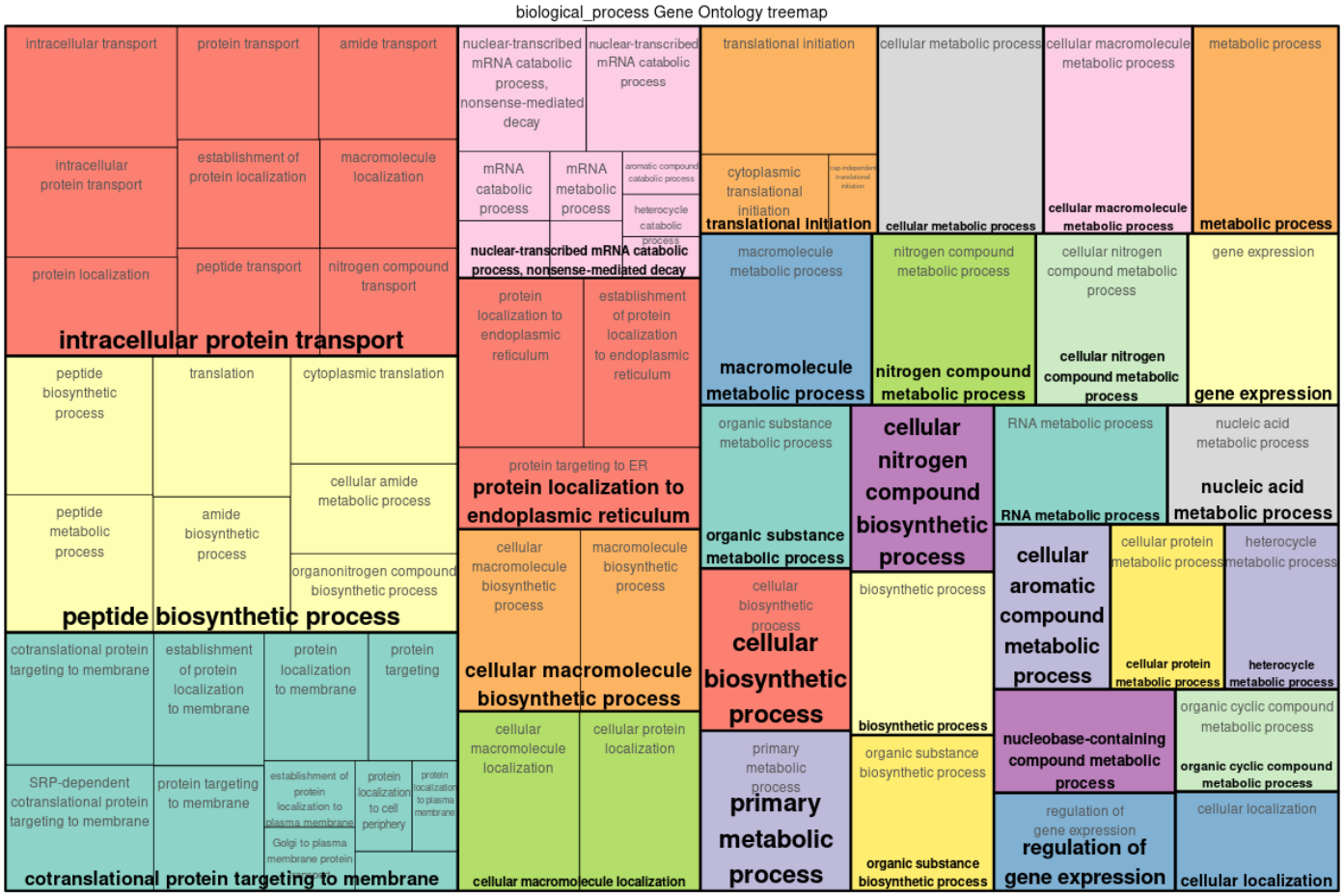


Figure 6. Enriched GO (biological process) of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.

Full classification →

TRANSPATH® Pathways (2023.2)

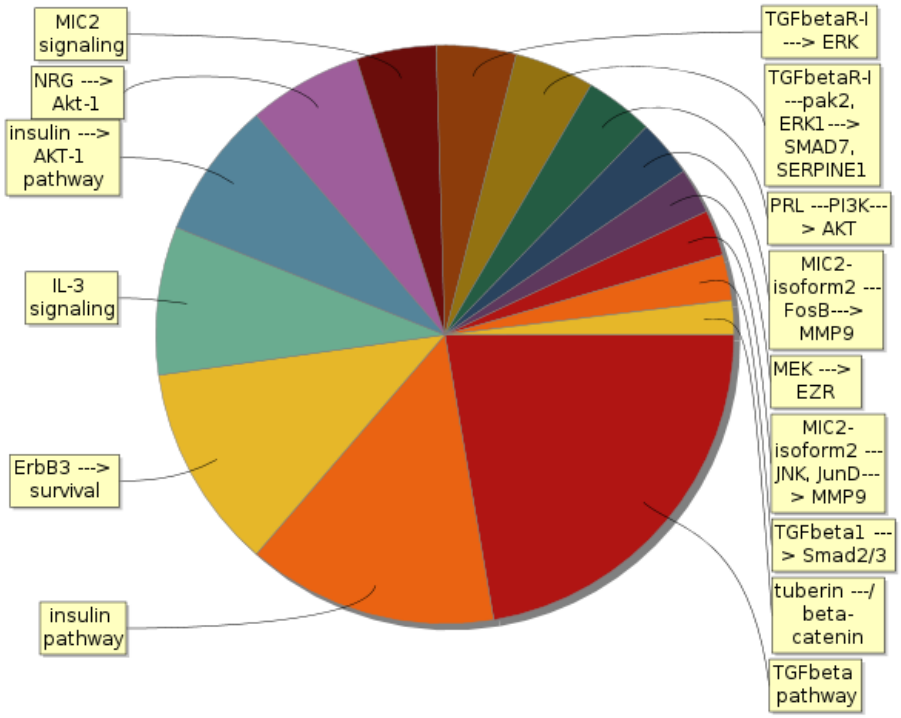


Figure 7. Enriched TRANSPATH® Pathways (2023.2) of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive.
Full classification →

HumanPSD(TM) disease (2023.2)

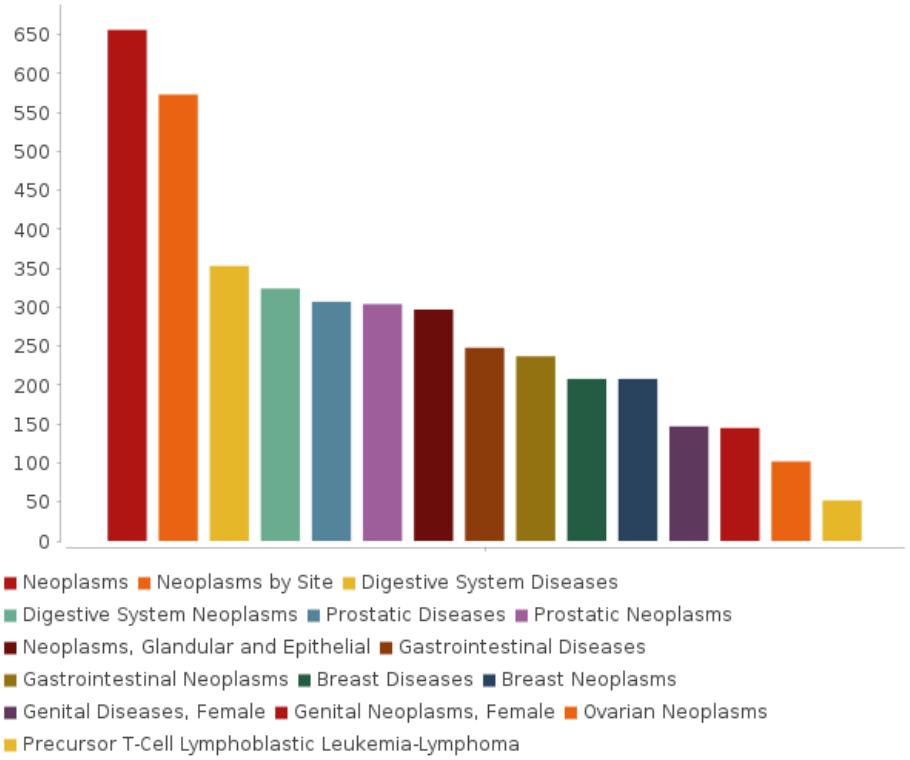
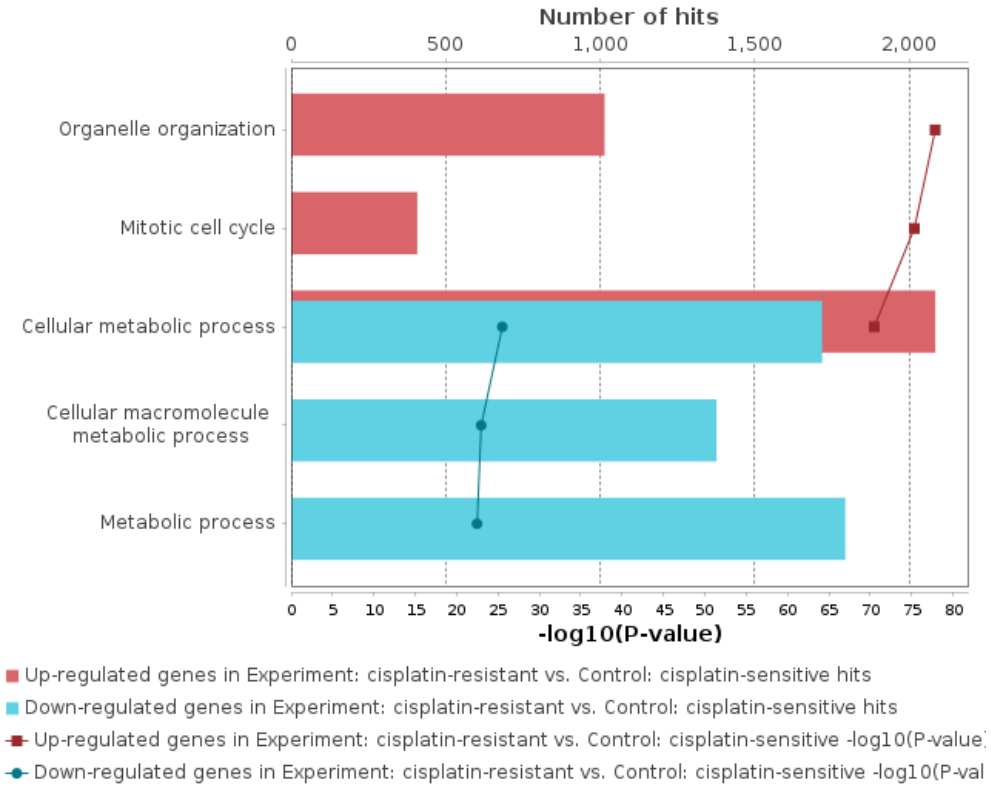


Figure 8. Enriched HumanPSD(TM) disease (2023.2) of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.
Full classification →

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].

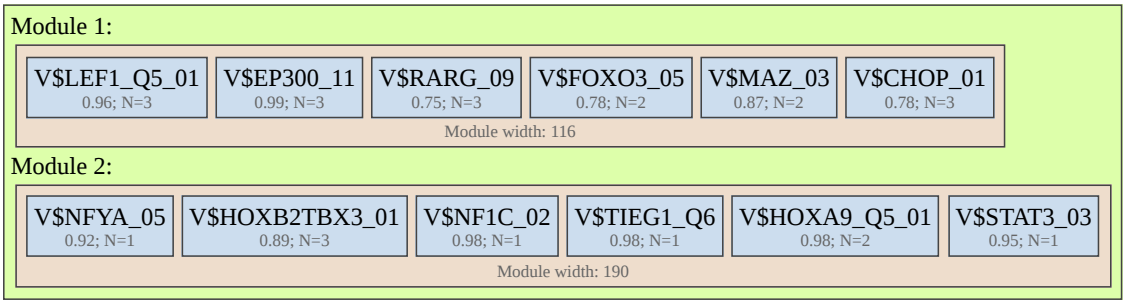
In the current work we use the Epigenomics data from the track(s) "GSM385747_CpG_NM.fixed.hg38.top300" to predict positions of potential ***enhancers*** regulating the differentially expressed genes revealed by comparative epigenomics analysis. We took genomic regions -550bp upstream and 550bp downstream 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)): 14.49
Wilcoxon p-value (pval): 2.86e-31
Penalty (p): 0.475
Average yes-set score: 5.57
Average no-set score: 4.36
AUC: 0.74
Separation point: 5.23
False-positive: 24.60%
False-negative: 36.67%

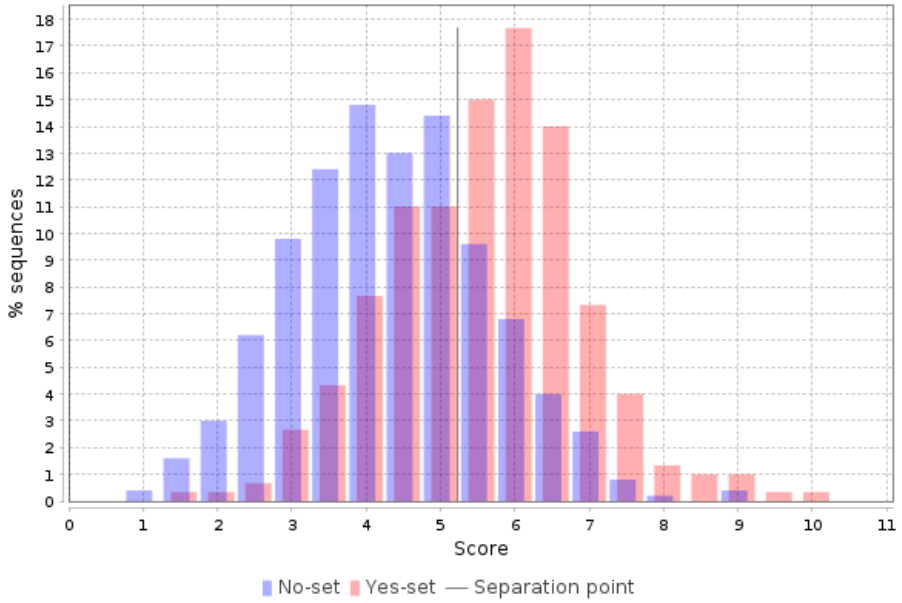


Table 4. List of top ten up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*
See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000104812	GYS1	glycogen synthase 1	10.13	p300(h), C/EBPalpha(h),DDIT3(h), NF-1C(h), KLF10(h), NF-YA(h), LEF-1(h), FOXO3(h)...
ENSG00000183207	RUVBL2	RuvB like AAA ATPase 2	9.97	LEF-1(h), p300(h), C/EBPalpha(h),DDIT3(h), NF-1C(h), KLF10(h), NF-YA(h), FOXO3(h)...
ENSG00000183479	TREX2	three prime repair exonuclease 2	9.89	NF-1C(h), NF-YA(h), KLF10(h), p300(h), RAR-gamma(h), LEF-1(h), FOXO3(h)...
ENSG00000134369	NAV1	neuron navigator 1	9.88	Hox-A9(h), LEF-1(h), MAZ(h), KLF10(h), NF-YA(h), NF-1C(h), p300(h)...
ENSG00000198843	SELENOT	selenoprotein T	9.68	C/EBPalpha(h),DDIT3(h), LEF-1(h), FOXO3(h), KLF10(h), NF-YA(h), Hox-A9(h), NF-1C(h)
ENSG00000189091	SF3B3	splicing factor 3b subunit 3	9.6	LEF-1(h), RAR-gamma(h), C/EBPalpha(h),DDIT3(h), KLF10(h), FOXO3(h), p300(h), Hox-A9(h)...
ENSG00000107984	DKK1	dickkopf WNT signaling pathway inhibitor 1	9.58	FOXO3(h), LEF-1(h), p300(h), C/EBPalpha(h),DDIT3(h), MAZ(h), NF-1C(h), KLF10(h)
ENSG00000205105	COX17P1	COX17 pseudogene 1	9.43	STAT3(h), NF-1C(h), NF-YA(h), FOXO3(h), LEF-1(h), KLF10(h), p300(h)...
ENSG00000052802	MSMO1	methylsterol monooxygenase 1	9.34	p300(h), RAR-gamma(h), C/EBPalpha(h),DDIT3(h), LEF-1(h), MAZ(h), FOXO3(h), NF-YA(h)...
ENSG00000170759	KIF5B	kinesin family member 5B	9.19	LEF-1(h), Hox-A9(h), NF-YA(h), NF-1C(h), p300(h), KLF10(h), C/EBPalpha(h),DDIT3(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.

Module 1:

V$MSX2_04	V$E2F2_11	V$SMAD1_01	V$HNF4A_03	V$AML2_Q3
0.95; N=2	0.87; N=3	0.88; N=2	0.85; N=1	0.97; N=2

Module width: 108

Module 2:

V$TCF3_01	V$HSF2_01	V$FRA1_Q6_01	V$TCF4_06	V$BEN_01	V$MAZ_Q6
0.88; N=2	0.96; N=2	1.00; N=1	0.91; N=2	0.95; N=3	0.94; N=3

Module width: 96

Model score (-p*log10(pval)): 15.25
Wilcoxon p-value (pval): 4.94e-32
Penalty (p): 0.487
Average yes-set score: 5.43
Average no-set score: 3.97
AUC: 0.75
Separation point: 4.54
False-positive: 38.60%
False-negative: 22.00%

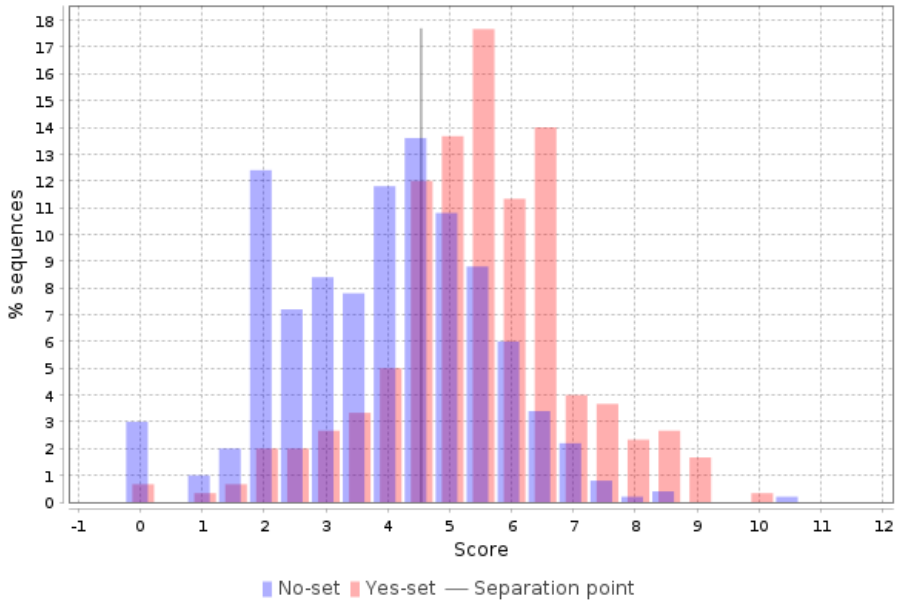


Table 5. List of top ten down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*

See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000152782	PANK1	pantothenate kinase 1	10.98	SMAD1(h), GTF2IRD1(h), MSX-2(h), E2F-2(h), MAZ(h), HSF2(h), TCF-7L1(h)
ENSG00000186660	ZFP91	ZFP91 zinc finger protein, atypical E3 ubiquitin ligase	10.67	HNF-4alpha(h), TCF-7L1(h), SMAD1(h), E2F-2(h), HSF2(h), MAZ(h), GTF2IRD1(h)
ENSG00000025796	SEC63	SEC63 homolog, protein translocation regulator	9.84	GTF2IRD1(h), HSF2(h), MAZ(h), TCF-7L1(h), TCF-7L2(h), MSX-2(h), SMAD1(h)...
ENSG00000143162	CREG1	cellular repressor of E1A stimulated genes 1	9.76	E2F-2(h), SMAD1(h), GTF2IRD1(h), TCF-7L1(h), TCF-7L2(h), MAZ(h), HSF2(h)
ENSG00000171206	TRIM8	tripartite motif containing 8	9.6	HSF2(h), TCF-7L1(h), MAZ(h), SMAD1(h), E2F-2(h), GTF2IRD1(h)
ENSG00000159023	EPB41	erythrocyte membrane protein band 4.1	9.58	MSX-2(h), HNF-4alpha(h), SMAD1(h), GTF2IRD1(h), HSF2(h), TCF-7L1(h), TCF-7L2(h)...
ENSG00000108840	HDAC5	histone deacetylase 5	9.58	GTF2IRD1(h), HSF2(h), TCF-7L1(h), MAZ(h), MSX-2(h), SMAD1(h)
ENSG00000118689	FOXO3	forkhead box O3	9.57	GTF2IRD1(h), MAZ(h), SMAD1(h), TCF-7L1(h), E2F-2(h), HNF-4alpha(h)
ENSG00000237438	CECR7	cat eye syndrome chromosome region, candidate 7	9.38	GTF2IRD1(h), SMAD1(h), TCF-7L2(h), TCF-7L1(h), HNF-4alpha(h), E2F-2(h), MAZ(h)
ENSG00000162104	ADCY9	adenylate cyclase 9	9.33	E2F-2(h), GTF2IRD1(h), MAZ(h), TCF-7L1(h), HSF2(h)

On the basis of the enhancer models we identified transcription factors potentially regulating the ***target genes*** of our interest. We found 14 and 11 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 →

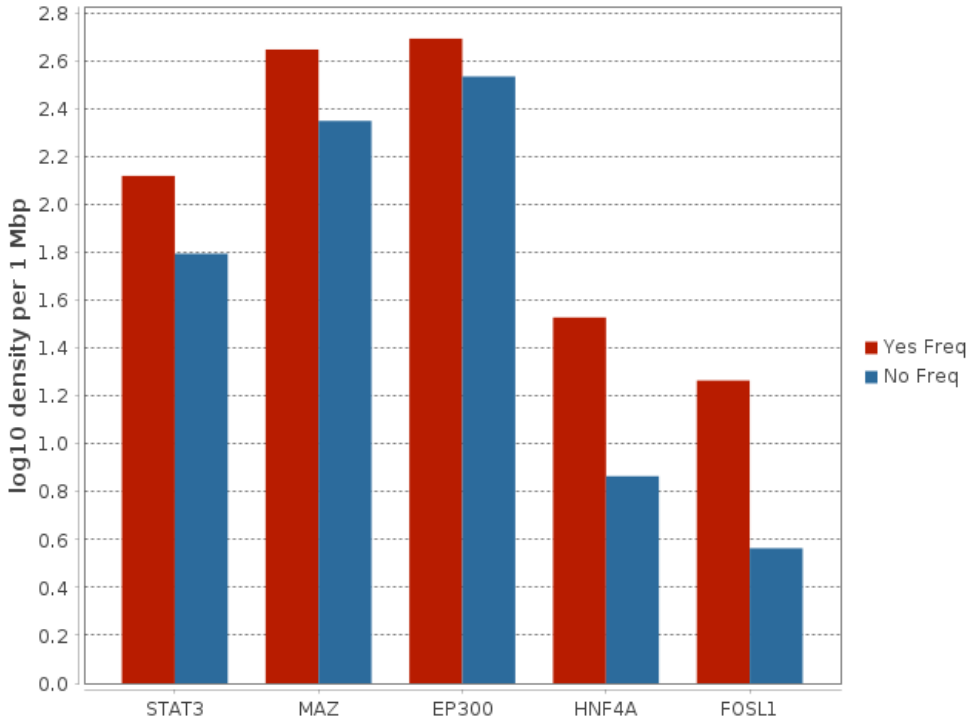
ID	Gene symbol	Gene description	Regulatory score	Yes-No ratio
MO000013123	STAT3	signal transducer and activator of transcription 3	3.46	2.11
MO000105384	MAZ	MYC associated zinc finger protein	2.83	1.99
MO000056654	EP300	E1A binding protein p300	2.79	1.44
MO000019418	CEBPA	CCAAT enhancer binding protein alpha	2.59	1.36
MO000020701	FOXO3	forkhead box O3	2.53	1.2
MO000025939	NFYA	nuclear transcription factor Y subunit alpha	2.3	1.96
MO000020832	DDIT3	DNA damage inducible transcript 3	2.21	1.23
MO000159782	LEF1	lymphoid enhancer binding factor 1	1.79	1.82
MO000119037	HOXA9	homeobox A9	1.74	2
MO000024750	NFIC	nuclear factor I C	0	2.69

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
MO000027755	HNF4A	hepatocyte nuclear factor 4 alpha	2.13	4.6
MO000105384	MAZ	MYC associated zinc finger protein	2.1	2.19
MO000025684	FOSL1	FOS like 1, AP-1 transcription factor subunit	1.78	5.02
MO000019609	SMAD1	SMAD family member 1	1.74	1.43
MO000046011	HSF2	heat shock transcription factor 2	1.73	2.09
MO000026882	TCF7L2	transcription factor 7 like 2	1.61	2.51
MO000026845	TCF7L1	transcription factor 7 like 1	1.54	1.47
MO000004278	E2F2	E2F transcription factor 2	1.54	2.29
MO000070133	GTF2IRD1	GTF2I repeat domain containing 1	1.38	1.09
MO000026238	RUNX3	RUNX family transcription factor 3	1.35	2.72

The following diagram represents the key transcription factors, which were predicted to be potentially regulating differentially expressed genes in the analyzed pathology: STAT3, MAZ, EP300, HNF4A and FOSL1.



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
MO000041170	EAC(h)	CYLD	CYLD lysine 63 deubiquitinase	0.95	87
MO000129050	EAC-isoform1(h)	CYLD	CYLD lysine 63 deubiquitinase	0.95	105
MO000129049	EAC-isoform2(h)	CYLD	CYLD lysine 63 deubiquitinase	0.95	145
MO000021736	CDK2(h)	CDK2	cyclin dependent kinase 2	0.8	165
MO000032712	MKP-4(h)	DUSP9	dual specificity phosphatase 9	0.75	197
MO000010977	PDGFRalpha(h)	PDGFRA	platelet derived growth factor receptor alpha	2.83	238
MO000112248	PDGFRalpha-isoform1(h)	PDGFRA	platelet derived growth factor receptor alpha	2.83	260
MO000256764	PDGFRalpha-isoform3(h)	PDGFRA	platelet derived growth factor receptor alpha	2.83	260
MO000256763	PDGFRalpha-isoform2(h)	PDGFRA	platelet derived growth factor receptor alpha	2.83	262
MO000021740	cyclinA(h):CDK2(h)	CDK2	cyclin dependent kinase 2	0.8	278

*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
MO000170234	RNF4(h)	RNF4	ring finger protein 4	-0.89	102
MO000129772	PTP-SL(h)	PTPRR	protein tyrosine phosphatase receptor type R	-4.6	151
MO000033272	SGK-1(h)	SGK1	serum/glucocorticoid regulated kinase 1	-1	201
MO000007566	InsR(h)	INSR	insulin receptor	-0.39	221
MO000005412	Fyn(h)	FYN	FYN proto-oncogene, Src family tyrosine kinase	-0.82	235
MO000117508	TC-PTP(h)	PTPN2	protein tyrosine phosphatase non-receptor type 2	-0.63	239
MO000170233	RNF4-isoform1(h)	RNF4	ring finger protein 4	-0.89	243
MO000286780	RNF4-isoform2(h)	RNF4	ring finger protein 4	-0.89	243
MO000337356	Cdc23(h):APC7(h):Cdc16(h):APC5(h):APC4(h):Cdc27(h):ANAPC2(h):APC1(h):ANAPC16(h)	ANAPC1, ANAPC16, ANAPC2, ANAPC4, ANAPC5, ANAPC7, CDC16, CDC23, CDC27	anaphase promoting complex subunit 1, anaphase promoting complex subunit 16, anaphase promoting comp...	-0.89	286
MO000034462	SGK-1(h){pT256}	SGK1	serum/glucocorticoid regulated kinase 1	-1	294

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.

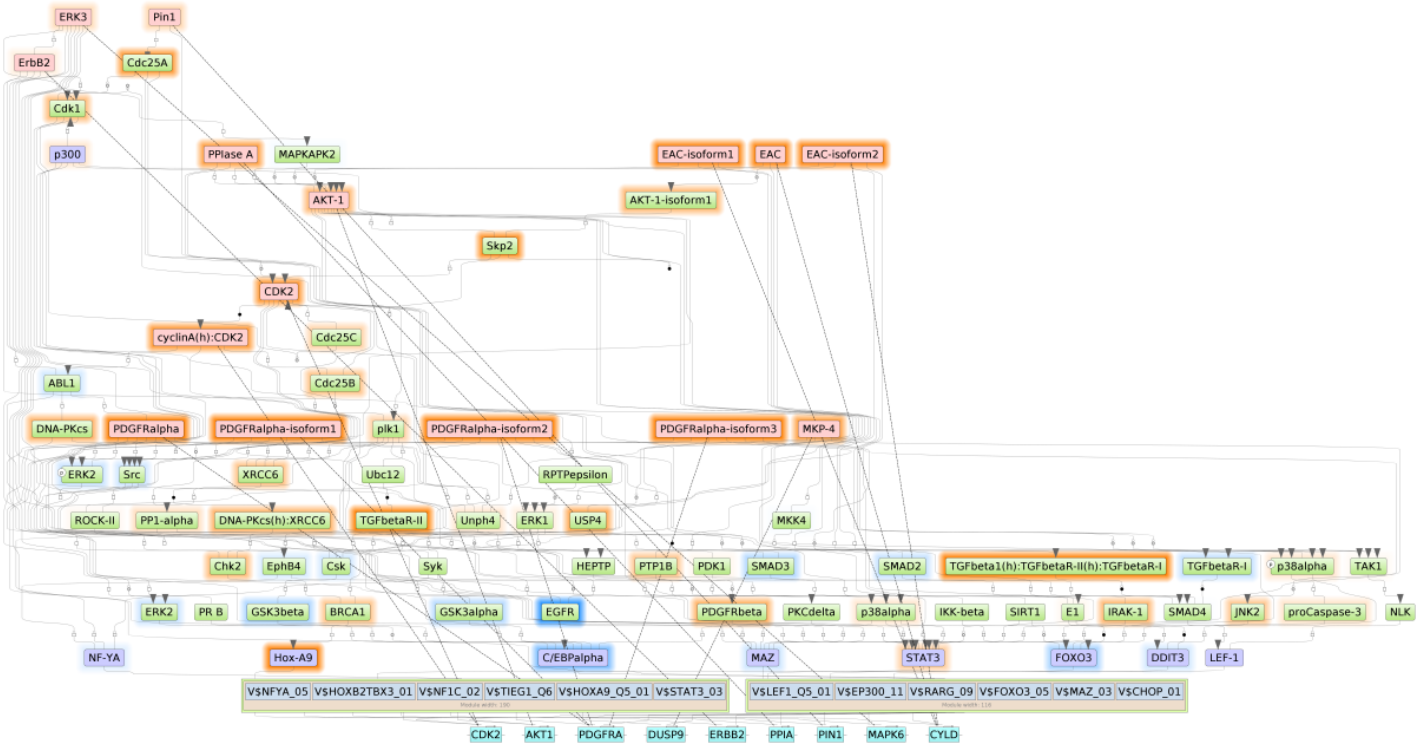


Figure 9. Diagram of intracellular regulatory signal transduction pathways of up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, 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 →

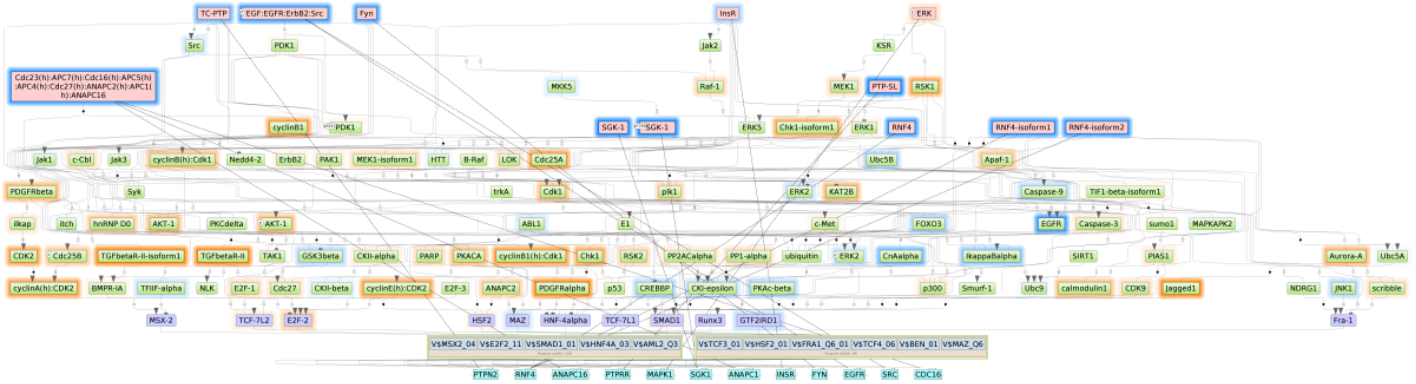


Figure 10. Diagram of intracellular regulatory signal transduction pathways of down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate 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
PDGFRA	platelet derived growth factor receptor alpha	55	2.83	262
IGFBP5	insulin like growth factor binding protein 5	2	2	377
AURKB	aurora kinase B	50	1.03	433
BIRC5	baculoviral IAP repeat containing 5	43	0.67	569
CAPN1	calpain 1	1	0.66	747
PSMD1	proteasome 26S subunit, non-ATPase 1	2	1.22	792

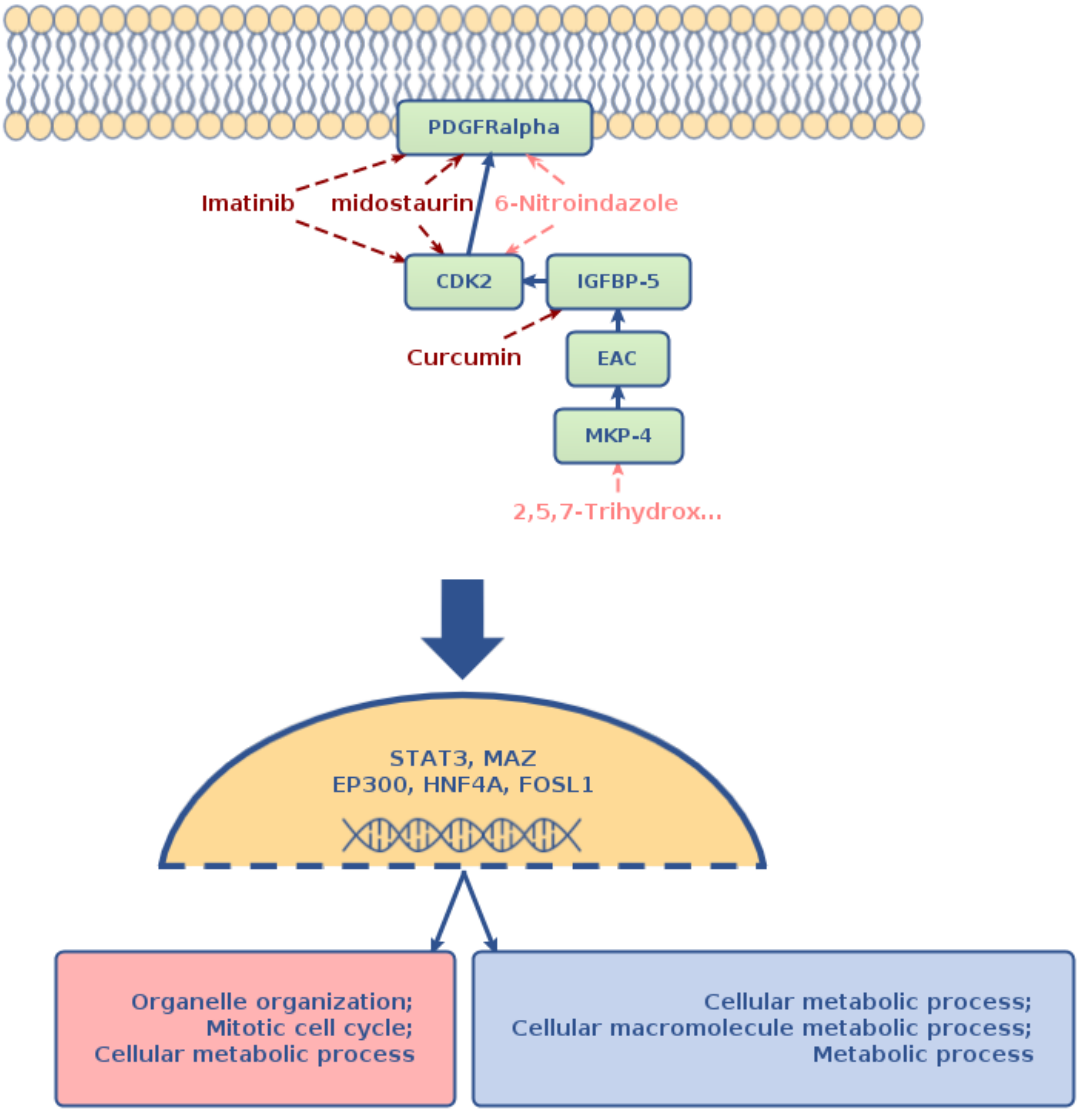
*Table 11. Prospective drug targets selected from full list of identified master regulators filtered by Druggability score predicted by PASS software. Here, the **Druggability score** for master regulator proteins is computed as a sum of PASS calculated probabilities to be active as a target for various 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
DUSP9	dual specificity phosphatase 9	4.91	0.75	197
PDGFRA	platelet derived growth factor receptor alpha	6.48	2.83	262
AURKB	aurora kinase B	1.99	1.03	433
PSMC4	proteasome 26S subunit, ATPase 4	1.28	1.22	792
PSMC6	proteasome 26S subunit, ATPase 6	1.28	1.22	792
PSMC1	proteasome 26S subunit, ATPase 1	1.28	1.22	792

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:

- EAC
- IGFBP-5
- PDGFRalpha
- CDK2
- MKP-4

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: 2,5,7-Trihydroxynaphthoquinone, Imatinib, midostaurin, 6-Nitroindazole and Curcumin, 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	PIK3CA, CASP3, E2F1, BIRC5, CDK1, CDK2, MAPK3, BRCA1	82	6	Phase 3: Ovarian Neoplasms, Adenocarcinoma, Anus Diseases, Anus Neoplasms, Arterial Occlusive Diseases, Ascites, Atherosclerosis, Biliary Tract Neoplasms, Breast Neoplasms, Bronchial Diseases, Carcinoma, Carcinoma, Adenosquamous, Carcinoma, Bronchogenic, Carcinoma, Large Cell, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Pancreatic Ductal, Carcinoma, Squamous Cell, Carcinosarcoma, Cholangiocarcinoma, Choriocarcinoma, Cystadenocarcinoma, Cystadenocarcinoma, Serous, Cysts, Digestive System Diseases, Digestive System Neoplasms, Endocrine Gland Neoplasms, Endocrine System Diseases, Endodermal Sinus Tumor, Endometrial Neoplasms, Esophageal Neoplasms, Esophageal Squamous Cell Carcinoma, Fallopian Tube Neoplasms, Gallbladder Neoplasms, Gastrointestinal Diseases, Gastrointestinal Neoplasms, Genital Diseases, Genital Diseases, Female, Genital Neoplasms, Female, Germinoma, Head and Neck Neoplasms, Infarction, Intestinal Diseases, Intestinal Neoplasms, Lung Diseases, Lung Neoplasms, Lymphatic Metastasis, Lymphoma, Lymphoma, Non-Hodgkin, Melanoma, Myocardial Infarction, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Germ Cell and Embryonal, Neoplasms, Nerve Tissue, Neoplasms, Squamous Cell, Neoplasms, Unknown Primary, Ovarian Diseases, Pancreatic Diseases, Pancreatic Neoplasms, Pelvic Neoplasms, Peripheral Arterial Disease, Peritoneal Neoplasms, Plaque, Atherosclerotic, Recurrence, Respiratory Tract Diseases, Respiratory Tract Neoplasms, Sarcoma, Seminoma, Sex Cord-Gonadal Stromal Tumors, Spina Bifida Occulta, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Teratoma, Testicular Neoplasms, Thoracic Neoplasms, Triple Negative Breast Neoplasms, Urinary Bladder Neoplasms, Uterine Cervical Neoplasms	Ovarian Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)
Doxorubicin	MAPK14, PIK3CB, PIK3CA, BAX, BIRC5, BRCA1, CDKN1B	78	11	Phase 4: Ovarian Neoplasms, Brain Abscess, Breast Neoplasms, Burkitt Lymphoma, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Ovarian Epithelial, Leukemia, Leukemia, Lymphoid, Lymphoma, Lymphoma, B-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Non-Hodgkin, Mediastinal Neoplasms, Multiple Myeloma, Myosarcoma, Neoplasms, Neoplasms, Plasma Cell, Obesity, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Rhabdomyosarcoma, Sarcoma	Ovarian Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, DailyMed)
Gemcitabine	ERBB2, HRAS, CHEK1, BRCA1	75	6	Phase 3: Ovarian Neoplasms, Adenocarcinoma, Adenoviridae Infections, Biliary Tract Neoplasms, Breast Neoplasms, Bronchial Diseases, Bronchial Neoplasms, Carcinoma, Carcinoma in Situ, Carcinoma, Acinar Cell, Carcinoma, Bronchogenic, Carcinoma, Hepatocellular, Carcinoma, Non-Small-Cell Lung, Carcinoma, Pancreatic Ductal, Carcinoma, Transitional Cell, Cholangiocarcinoma, Cysts, Digestive System Diseases, Digestive System Neoplasms, Drug-Related Side Effects and Adverse Reactions, Embolism, Endocrine Gland Neoplasms, Endocrine System Diseases, Fallopian Tube Neoplasms, Fibrosis, Gallbladder Neoplasms, Gastrointestinal Diseases, Gastrointestinal Neoplasms, Genital Neoplasms, Female, Head and Neck Neoplasms, Hepatoblastoma, Hodgkin Disease, Immunoblastic Lymphadenopathy, Infections, Intestinal Diseases, Intestinal Neoplasms, Liver Cirrhosis, Liver Neoplasms, Lung Diseases, Lung Neoplasms, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, 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, Nerve Tissue, Neoplasms, Unknown Primary, Pancreatic Cyst, Pancreatic Diseases, Pancreatic Neoplasms, Pelvic Neoplasms, Peritoneal Neoplasms, Pharyngeal Diseases, Pharyngeal Neoplasms, Recurrence, Respiratory Tract Diseases, Respiratory Tract Neoplasms, Thoracic Neoplasms, Thromboembolism, Triple Negative Breast Neoplasms, Urinary Bladder Neoplasms	Ovarian Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA)
Olaparib	PARP1	52	7	Phase 3: Ovarian Neoplasms, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Endometrial Neoplasms, Fallopian Tube Neoplasms, Lung Neoplasms, Neoplasms, Peritoneal Neoplasms, Prostatic Neoplasms	Ovarian Neoplasms (FDA, FDA)

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
Imatinib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, BIRC5, PIM2, CDK8, MAPK9, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	96	3	Phase 2: Ovarian Neoplasms, Acute Lung Injury, Angiomyoma, Asthma, Blast Crisis, Brain Abscess, COVID-19, Carcinoma, Carcinoma, Adenoid Cystic, Carcinoma, Transitional Cell, Chordoma, Colonic Neoplasms, Cysts, Dermatofibrosarcoma, Desmoplastic Small Round Cell Tumor, Edema, Endometrial Neoplasms, Eosinophilia, Familial Primary Pulmonary Hypertension, Fibroma, Fibrosarcoma, Fibrosis, Gastrointestinal Stromal Tumors, Genital Diseases, Male, Glioblastoma, Gliosarcoma, Head and Neck Neoplasms, Hematologic Diseases, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Hypereosinophilic Syndrome, Hypertension, Hypertension, Pulmonary, Idiopathic Pulmonary Fibrosis, Intestinal Neoplasms, Leiomyoma, Leiomyomatosis, Leukemia, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Accelerated Phase, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic-Phase, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Loiasis, Lung Diseases, Lung Injury, Lymphangioleiomyomatosis, Lymphangiomyoma, Lymphoma, Lymphoma, Non-Hodgkin, Mastocytosis, Mastocytosis, Systemic, Melanoma, Meningioma, Mesothelioma, Mesothelioma, Malignant, Multiple Sclerosis, Myelodysplastic Syndromes, Myeloproliferative Disorders, Myoma, Neoplasms, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neurofibroma, Neurofibroma, Plexiform, Neurofibromatoses, Neurofibromatosis 1, Osteosarcoma, Polycythemia, Polycythemia Vera, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Diseases, Prostatic Neoplasms, Pulmonary Arterial Hypertension, Pulmonary Edema, Pulmonary Fibrosis, Respiratory Distress Syndrome, Respiratory Distress Syndrome, Newborn, ST Elevation Myocardial Infarction, Sarcoma, Sarcoma, Ewing, Sarcoma, Kaposi, Scleroderma, Diffuse, Scleroderma, Localized, Scleroderma, Systemic, Sclerosis, Severe Acute Respiratory Syndrome, Skin Neoplasms, Stomach Neoplasms, Syndrome, Thrombocythemia, Essential, Thrombocytosis, Tuberculosis, Urinary Bladder Neoplasms, Wounds and Injuries
Erlotinib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, ILK, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, BIRC5, PIM2, CDK8, MAPK9, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	95	2	Phase 2: Ovarian Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Adenocarcinoma, Bronchiolo-Alveolar, Adenocarcinoma, Mucinous, Adenoma, Adenomatous Polyposis Coli, Adenomatous Polyps, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Brenner Tumor, Carcinoid Tumor, Carcinoma, Carcinoma, Endometrioid, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Colorectal Neoplasms, Cystadenocarcinoma, Cystadenocarcinoma, Mucinous, Cystadenocarcinoma, Serous, Cysts, Diffuse Intrinsic Pontine Glioma, Digestive System Diseases, Endocrine Gland Neoplasms, Ependymoma, Esophageal Diseases, Esophageal Neoplasms, Fallopian Tube Neoplasms, Fibrosarcoma, Gallbladder Neoplasms, Glioblastoma, Glioma, Gliosarcoma, Head and Neck Neoplasms, Laryngeal Neoplasms, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Acute, Lung Neoplasms, Lymphoma, Lymphoma, Non-Hodgkin, Medulloblastoma, Melanoma, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Myeloma, Myosarcoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasm Recurrence, Local, Neoplasms, Neoplasms, Unknown Primary, Nerve Sheath Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroendocrine Tumors, Neurofibrosarcoma, Osteosarcoma, Pancreatic Neoplasms, Paranasal Sinus Neoplasms, Pharyngeal Neoplasms, Polycythemia, Polycythemia Vera, Polyps, Precancerous Conditions, Psoriasis, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Sarcoma, Sarcoma, Ewing, Small Cell Lung Carcinoma, Thymoma, Thymus Neoplasms, Urinary Bladder Neoplasms, Wilms Tumor
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, TYRO3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3	95	3	Phase 2: Ovarian Neoplasms, Anemia, Brain Abscess, Brain Neoplasms, Carcinoid Tumor, Carcinoma, Carcinoma, Islet Cell, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Transitional Cell, Central Nervous System Neoplasms, Cholangiocarcinoma, Chondrosarcoma, Chondrosarcoma, Mesenchymal, Corneal Neovascularization, Desmoplastic Small Round Cell Tumor, Dilatation, Pathologic, Drug-Related Side Effects and Adverse Reactions, Edema, Endocrine Gland Neoplasms, Epistaxis, Fibrosarcoma, Gallbladder Neoplasms, Gastrinoma, Gastrointestinal Neoplasms, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Glomus Tumor, Glucagonoma, Granular Cell Tumor, Hemangioendothelioma, Hemangioendothelioma, Epithelioid, Hemangiopericytoma, Hemangiosarcoma, Hemorrhage, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Hypertension, Insulinoma, Intestinal Neoplasms, Leiomyosarcoma, Liposarcoma, Lung Neoplasms, Lymphedema, Macular Degeneration, Malignant Carcinoid Syndrome, Melanoma, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 1, Multiple Myeloma, Myosarcoma, Neoplasms, Neovascularization, Pathologic, Nerve Sheath Neoplasms, Nervous System Neoplasms, Neuroendocrine Tumors, Neurofibrosarcoma, Osteosarcoma, Pancreatic Neoplasms, Paraganglioma, Paraganglioma, Extra-Adrenal, Pheochromocytoma, Ranula, Recurrence, Rhabdomyosarcoma, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Clear Cell, Sarcoma, Synovial, Small Cell Lung Carcinoma, Solitary Fibrous Tumors, Somatostatinoma, Stomach Neoplasms, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis, Urinary Bladder Neoplasms
Vandetanib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G,	94	2	Phase 2: Ovarian Neoplasms, Astrocytoma, Brain Abscess, Breast Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Endocrine Gland Neoplasms, Fallopian Tube Neoplasms, Glioblastoma, Glioma, Gliosarcoma, Lung Neoplasms, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 2a, Multiple Endocrine Neoplasia Type 2b, Multiple Myeloma, Neoplasm Metastasis, Neoplasms, Neoplasms, Plasma Cell, Oligodendroglioma, Peritoneal Neoplasms, Pleural Effusion, Pleural Effusion, Malignant, Sarcoma, Squamous Cell Carcinoma of Head and Neck, Thyroid Diseases, Thyroid Neoplasms, Urinary Bladder Neoplasms

	MET, MAPK6, TTK, CDK1, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, PIM2, CDK8, MAPK9, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2			
Gefitinib	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, TYRO3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, PIK3CA, TGFBR2, PAK1, CDK5, CSNK2A1, CDK2, PRKD2, PLK4, STK3	94	3	Phase 2: Ovarian Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Brain Neoplasms, Breast Neoplasms, Carcinoid Tumor, Carcinoma, Carcinoma, Islet Cell, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Fallopian Tube Neoplasms, Gastrinoma, Gastrointestinal Neoplasms, Glioblastoma, Glucagonoma, Head and Neck Neoplasms, Insulinoma, Intestinal Neoplasms, Lung Diseases, Lung Neoplasms, Malignant Carcinoid Syndrome, Mesothelioma, Mesothelioma, Malignant, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms, Squamous Cell, Neuroblastoma, Neuroendocrine Tumors, Peritoneal Neoplasms, Recurrence, Respiratory Tract Diseases, Respiratory Tract Neoplasms, Sarcoma, Sarcoma, Synovial, Somatostatinoma, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Thoracic Neoplasms, Urinary Bladder Neoplasms, Vipoma

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
midostaurin	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, PIK3CB, WEE1, PTK2, CASP3, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, PIM2, CDK8, MAPK9, CASP7, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	89	Phase 3: Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute
Lapatinib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, BIRC5, PIM2, CDK8, MAPK9, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	89	Phase 3: Breast Diseases, Breast Neoplasms, Liver Neoplasms, Neoplasm Metastasis, Neoplasms
Flavopiridol	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, PIK3CB, WEE1, PTK2, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, CDK1, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, PIM2, CDK8, MAPK9, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	88	Phase 2: Embolism, Head and Neck Neoplasms, Lymphoma, Lymphoma, B-Cell, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Neoplasms, Sarcoma, Thromboembolism
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, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	88	Phase 2: Cystic Fibrosis, Cysts, Fibrosis
Vatalanib	STK10, IKBKE, PAK2, PRKACA, MAP3K11, NEK2, NEK6, ERBB2, MAPK3, MAP2K6, TYK2, MELK, PRKD3, PDGFRB, MAP2K1, MAP4K3, WEE1, PTK2, CSNK2A1, PLK4, STK3, RPS6KA3, CAMK2G, MET, MAPK6, TTK, CDK1, PDGFRA, RAF1, AURKB, CDK7, RPS6KA1, MAPK14, PLK1, AKT1, AURKA, CHEK1, MAP3K20, PIM2, CDK8, MAPK9, CDK9, TYRO3, PIK3CA, TGFBR2, PAK1, CDK5, CDK2, PRKD2	88	Phase 3: Colonic Neoplasms, Colorectal Neoplasms, Neoplasms, Rectal Neoplasms

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, PSMD13, PSMA7, PSMC3, PSMD2, PSMD1, PSMD14, PSMD5, PSMC6, CASP3, PSMD11, PSMC4, PSMC1, PSMC2, PSMD12, PSMD7, PSMD3	99	1.83
N-(4-MORPHOLINE)CARBONYL-B-(1-NAPHTHYL)-L-ALANINE-L-LEUCINE BORONIC ACID	PSMC5, PSMD13, PSMA7, PSMC3, PSMD2, PSMD1, PSMD14, PSMD5, PSMC6, PSMD11, PSMC4, PSMC1, PSMC2, PSMD12, PSMD7, PSMD3	98	1.43
2,5,7-Trihydroxynaphthoquinone	MAPK14, CDC25A, MAPK9, POR, CDKN3, MAPK6, CDC25B, DUSP14, DUSP9, MAPK3, BRCA1, TNS2, HSP90AA1	95	0.58
7-[4-(Dimethylamino)Phenyl]-N-Hydroxy-4,6-Dimethyl-7-Oxo-2,4-Heptadienamide	HDAC8, HDAC9	94	0.44
6-Nitroindazole	RPS6KA3, CAMK2G, CDK9, PRKD3, GRK5, PDGFRB, PRKACA, CDK1, PDGFRA, RPS6KA1, CDK7, HSP90AA1, SOD1, PAK1, CHEK1, CDK5, IRAK1, MAPK3, CDK2, CHEK2, MAP2K6	93	2.09

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Imatinib, midostaurin and Bortezomib. These drugs were selected for acting on the following targets: PDGFRA and PSMC4, which were predicted to be active in the molecular mechanism of the studied pathology.

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

Supplementary drug info

In addition to the approved and repurposed drugs proposed by Genome Enhancer, below the ***Supplementary drug info*** table is given, which contains an extended list of drugs used for treatment of neoplasms. Those drugs which were predicted by Genome Enhancer as prospective treatment candidates for the studied case (both approved and repurposed) have a respective ***Predicted Drug Score*** assigned to them. This value on a scale from 1 to 100 reflects the potential activity of the respective drug on the overall molecular mechanism of the studied pathology. The ***Predicted Drug Score*** column contains the "-" (Not Identified) value in case the drug targets of the respective treatment were not found in the molecular mechanism of the studied pathology.

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

Drug	Disease	Predicted Drug Score
Abarelix	Prostatic Neoplasms	-
Abemaciclib	Breast Neoplasms	23
Abiraterone	Prostatic Neoplasms, Castration-Resistant	-
Abiraterone acetate	Prostatic Neoplasms, Castration-Resistant	-
Acalabrutinib	Lymphoma, Mantle-Cell	-
Acitretin	Psoriasis	27
Ado-trastuzumab emtansine	Breast Neoplasms|Neoplasms	80
Afatinib	Carcinoma, Non-Small-Cell Lung	26
Aflibercept	Colorectal Neoplasms|Diabetic Retinopathy|Edema|Vascular Diseases|Wet Macular Degeneration	1
Alectinib	Carcinoma, Non-Small-Cell Lung	21
Alemtuzumab	Brain Abscess|Leukemia, Lymphocytic, Chronic, B-Cell|Multiple Sclerosis|Multiple Sclerosis, Relapsing-Remitting|Sclerosis	-
Alitretinoin	Sarcoma, Kaposi	-
Alpelisib	Breast Neoplasms	52
Altretamine	Ovarian Neoplasms	-
Aminolevulinic acid	Keratosis|Keratosis, Actinic	-
Anagrelide	Thrombocythemia, Essential|Thrombocytosis	-
Anastrozole	Breast Neoplasms|Hypersensitivity|Obesity|Obesity, Morbid|Recurrence|Weight Loss	-
Apalutamide	Prostatic Neoplasms, Castration-Resistant	-
Aprepitant	Nausea|Neoplasms|Postoperative Nausea and Vomiting	-
Arsenic trioxide	Leukemia, Promyelocytic, Acute	75
Atezolizumab	Carcinoma, Non-Small-Cell Lung|Carcinoma, Transitional Cell|Triple Negative Breast Neoplasms	-
Avelumab	Carcinoma, Merkel Cell|Carcinoma, Renal Cell|Carcinoma, Transitional Cell	-
Axitinib	Carcinoma, Renal Cell	72
Azacitidine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes|Preleukemia|Syndrome	9
Belinostat	Lymphoma, T-Cell, Peripheral	43
Bendamustine	Leukemia, Lymphocytic, Chronic, B-Cell|Leukemia, Lymphoid	-
Bevacizumab	Breast Neoplasms|Colonic Neoplasms|Colorectal Neoplasms|Corneal Neovascularization|Diabetic Retinopathy|Dilatation, Pathologic|Edema|Epistaxis|Glaucoma|Hemorrhage|Macular Degeneration|Macular Edema|Neoplasm Metastasis|Neoplasms|Neovascularization, Pathologic|Optic Nerve Diseases|Pterygium|Rectal	-

	Neoplasms|Retinal Detachment|Retinal Diseases|Retinal Vein Occlusion|Telangiectasia, Hereditary Hemorrhagic|Telangiectasis|Vitreous Hemorrhage	
Bexarotene	Lymphoma, T-Cell|Lymphoma, T-Cell, Cutaneous	-
Bicalutamide	Prostatic Neoplasms	13
Binimetinib	Melanoma	46
Blinatumomab	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-
Bortezomib	Brain Abscess|Glomerulonephritis|Glomerulonephritis, IGA|Kidney Diseases|Multiple Myeloma|Neoplasms, Plasma Cell|Nephritis|Renal Insufficiency	66
Bosutinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	70
Brentuximab vedotin	Hodgkin Disease|Lymphoma|Lymphoma, Large-Cell, Anaplastic|Lymphoma, T-Cell, Peripheral	-
Brigatinib	Carcinoma, Non-Small-Cell Lung	36
Buserelin	Prostatic Neoplasms	-
Cabazitaxel	Prostatic Neoplasms, Castration-Resistant	66
Cabergoline	Drug-Related Side Effects and Adverse Reactions|Pituitary Neoplasms	-
Cabozantinib	Thyroid Neoplasms	45
Capecitabine	Breast Neoplasms|Colonic Neoplasms|Colorectal Neoplasms	-
Carboplatin	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms|Neuroendocrine Tumors|Ovarian Neoplasms|Retinoblastoma	-
Carfilzomib	Multiple Myeloma	74
Carmustine	Astrocytoma|Glioblastoma|Hodgkin Disease|Medulloblastoma|Multiple Myeloma|Neoplasms	13
Ceritinib	Carcinoma, Non-Small-Cell Lung	76
Cetuximab	Colorectal Neoplasms	-
Cinacalcet	Anemia|Calcinosis|Cardiovascular Diseases|Hyperparathyroidism|Hyperparathyroidism, Secondary|Kidney Diseases|Kidney Failure, Chronic|Neoplasm Metastasis|Neoplasms|Parathyroid Neoplasms|Renal Insufficiency|Vascular Calcification|Vascular Diseases|Vision Disorders	-
Cisplatin	Carcinoma, Squamous Cell|Neoplasms|Uterine Cervical Neoplasms|Carcinoma, Non-Small-Cell Lung|Esophageal Neoplasms|Carcinoma	61
Cladribine	Leukemia, Hairy Cell	8
Clofarabine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	-
Cobimetinib	Melanoma	42
Copanlisib	Lymphoma, Follicular	79
Crizotinib	Carcinoma, Non-Small-Cell Lung	51
Cyproterone acetate	Prostatic Neoplasms	-
Dabrafenib	Melanoma	15
Dacomitinib	Carcinoma, Non-Small-Cell Lung	59
Daratumumab	Multiple Myeloma	-
Dasatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid, Chronic-Phase|Precursor Cell Lymphoblastic Leukemia-Lymphoma	92
Decitabine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes	10
Degarelix	Cardiovascular Diseases|Prostatic Neoplasms|Vascular Diseases	38
Denosumab	Arthritis, Rheumatoid|Bone Diseases|Bone Diseases, Metabolic|Breast Neoplasms|Hyperparathyroidism|Hyperparathyroidism, Primary|Metabolic Diseases|Neoplasm Metastasis|Neoplasms|Osteoporosis|Osteoporosis, Postmenopausal|Prostatic Neoplasms	-
Dexrazoxane	Breast Neoplasms|Cardiomyopathies	-
Dienogest	Menorrhagia	-
Dinutuximab	Neuroblastoma	-
Docetaxel	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Prostatic Neoplasms|Squamous Cell Carcinoma of Head and Neck|Stomach Neoplasms	44
Doxorubicin	Neoplasms|Multiple Myeloma|Carcinoma, Ovarian Epithelial|Ovarian Neoplasms|Leukemia, Lymphoid|Breast Neoplasms|Lymphoma, Follicular|Thyroid Neoplasms|Triple Negative Breast Neoplasms|Glioma	78
Durvalumab	Carcinoma, Non-Small-Cell Lung|Carcinoma, Transitional Cell	-
Dutasteride	Alcoholism|Hyperplasia|Hypertrophy|Neoplasms|Prostatic Hyperplasia	-
Duvelisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	10
Elotuzumab	Multiple Myeloma	32
Enasidenib	Leukemia, Myeloid, Acute	-
Encorafenib	Colorectal Neoplasms|Melanoma	55
Enfortumab vedotin	Carcinoma, Transitional Cell|Neoplasms	-
Entrectinib	Carcinoma, Non-Small-Cell Lung	-
Enzalutamide	Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	-
Epirubicin	Breast Neoplasms	58
Erdafitinib	Urinary Bladder Neoplasms	86
Eribulin	Breast Neoplasms|Drug-Related Side Effects and Adverse Reactions|Neoplasms	-
Erlotinib	Carcinoma, Non-Small-Cell Lung|Neoplasms|Pancreatic Neoplasms	95
Erlotinib hydrochloride	Carcinoma, Non-Small-Cell Lung|Gastrointestinal Stromal Tumors	-
Estramustine	Prostatic Neoplasms	21
Ethinyl Estradiol	Acne Vulgaris|Neoplasms	29
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	55
Exemestane	Breast Neoplasms	-

Fedratinib	Primary Myelofibrosis	-
Finasteride	Hyperplasia|Neoplasms|Prostatic Hyperplasia	12
Flavopiridol	Leukemia, Lymphocytic, Chronic, B-Cell	88
Fluorouracil	Skin Neoplasms|Neoplasms, Basal Cell|Neoplasms, Second Primary|Neoplasms, Squamous Cell|Neoplasms|Colorectal Neoplasms|Pancreatic Neoplasms	82
Fluoxymesterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	-
Flutamide	Premenstrual Dysphoric Disorder|Premenstrual Syndrome|Prostatic Neoplasms	50
Fulvestrant	Breast Neoplasms	-
Gefitinib	Carcinoma, Non-Small-Cell Lung	94
Gemcitabine	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Ovarian Neoplasms|Pancreatic Neoplasms	75
Gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	-
Gilteritinib	Leukemia, Myeloid, Acute	68
Glasdegib	Leukemia, Myeloid, Acute	-
Goserelin	Atrophy|Breast Neoplasms|Bulbo-Spinal Atrophy, X-Linked|Endometriosis|Muscular Atrophy|Myoma|Prostatic Neoplasms	-
Histrelin	Puberty, Precocious	-
Homoharringtonine	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	84
Ibritumomab	Lymphoma, B-Cell|Lymphoma, Follicular	-
Ibrutinib	Graft vs Host Disease|Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, B-Cell, Marginal Zone|Lymphoma, Mantle-Cell|Waldenstrom Macroglobulinemia	60
Idarubicin	Leukemia, Myeloid, Acute	-
Idelalisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	26
Ifosfamide	Neoplasms	-
Imatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Mastocytosis, Systemic|Neoplasms	96
Inotuzumab ozogamicin	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-
Ipilimumab	Carcinoma, Renal Cell|Melanoma	-
Irinotecan	Colorectal Neoplasms	64
Ivosidenib	Leukemia, Myeloid, Acute	-
Ixabepilone	Breast Neoplasms	-
Ixazomib	Multiple Myeloma	-
Lapatinib	Breast Neoplasms	89
Larotrectinib	Neoplasm Metastasis	39
Lenalidomide	Brain Abscess|Lupus Erythematosus, Cutaneous|Myelodysplastic Syndromes|Neoplasms, Plasma Cell	-
Lenvatinib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	67
Letrozole	Breast Neoplasms|Cysts|Fibroma|Myofibroma|Myoma|Ovarian Cysts|Syndrome	-
Leuprolide	Hot Flashes|Ovarian Hyperstimulation Syndrome|Prostatic Neoplasms|Puberty, Precocious	-
Levamisole	Ascariasis|Colonic Neoplasms|Helminthiasis	-
Levonorgestrel	Epilepsy|Hyperplasia|Menorrhagia	-
Lomustine	Brain Neoplasms|Hodgkin Disease	-
Lonafarnib	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Central Nervous System Neoplasms|Colorectal Neoplasms|Gliosarcoma|Head and Neck Neoplasms|Leukemia, Myelomonocytic, Chronic| Liver Neoplasms|Lymphoma|Myelodysplastic Syndromes|Ovarian Neoplasms|Urethral Neoplasms|Urinary Bladder Neoplasms	54
Lorlatinib	Carcinoma, Non-Small-Cell Lung	10
Masoprocol	Keratosis, Actinic	-
Medroxyprogesterone Acetate	Depression|Depression, Postpartum|Depressive Disorder|Metrorrhagia|Neoplasms|Uterine Hemorrhage	20
Megestrol acetate	Acquired Immunodeficiency Syndrome|Bites and Stings|Breast Neoplasms|Pain|Wasting Syndrome	-
Methotrexate	Neoplasms|Breast Neoplasms|Head and Neck Neoplasms|Ovarian Neoplasms|Lymphoma, T-Cell, Peripheral|Brain Neoplasms|Colorectal Neoplasms|Neuroblastoma|Carcinoma, Squamous Cell	47
Methyltestosterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	-
Midostaurin	Leukemia, Mast-Cell|Leukemia, Myeloid, Acute|Mastocytosis, Systemic	89
Mitotane	Adrenocortical Carcinoma	-
Mitoxantrone	Autoimmune Diseases|Autoimmune Diseases of the Nervous System|Demyelinating Autoimmune Diseases, CNS|Immune System Diseases|Leukemia, Myeloid, Acute|Multiple Sclerosis|Myelitis|Myelitis, Transverse|Nervous System Diseases|Neuromyelitis Optica|Prostatic Neoplasms, Castration-Resistant	37
Mogamulizumab	Mycosis Fungoides|Neoplasms|Sezary Syndrome	-
Moxetumomab pasudotox	Leukemia, Hairy Cell|Neoplasms	-
Necitumumab	Carcinoma, Non-Small-Cell Lung|Neoplasms	-
Nelarabine	Precursor T-Cell Lymphoblastic Leukemia-Lymphoma	-
Neratinib	Breast Neoplasms	63
Nilotinib	Blast Crisis|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid, Chronic-Phase	71
Nilutamide	Prostatic Neoplasms	-
Nintedanib	Fibrosis|Idiopathic Pulmonary Fibrosis	76
Niraparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms	63
Nivolumab	Carcinoma, Non-Small-Cell Lung|Kidney Neoplasms|Neoplasms|Lung Neoplasms|Melanoma	-
Obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	-
Octreotide	Acromegaly|Adenoma|Ascites|Carcinoid Tumor|Fistula|Pancreatic Fistula|Pituitary Diseases|Renal Insufficiency|Vipoma	30
Ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	-
Olaparib	Breast Neoplasms|Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Ovarian Neoplasms|Pancreatic Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	52

Olaratumab	Sarcoma	-
Osimertinib	Carcinoma, Non-Small-Cell Lung	60
Oxaliplatin	Colonic Neoplasms|Colorectal Neoplasms|Neoplasms|Rectal Neoplasms	25
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	82
Palbociclib	Breast Neoplasms	-
Panitumumab	Colorectal Neoplasms	-
Panobinostat	Multiple Myeloma	6
Pazopanib	Carcinoma|Carcinoma, Renal Cell|Sarcoma	95
Pembrolizumab	Carcinoma, Hepatocellular|Carcinoma, Merkel Cell|Carcinoma, Non-Small-Cell Lung|Carcinoma, Renal Cell|Carcinoma, Transitional Cell|Hodgkin Disease|Melanoma|Neoplasms|Stomach Neoplasms	-
Pemetrexed	Carcinoma, Non-Small-Cell Lung|Mesothelioma	-
Pentostatin	Leukemia, Hairy Cell	-
Pertuzumab	Breast Neoplasms	71
Pomalidomide	Multiple Myeloma	-
Ponatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Precursor Cell Lymphoblastic Leukemia-Lymphoma	33
Pralatrexate	Lymphoma, T-Cell, Peripheral	-
Radium Ra 223 Dichloride	Prostatic Neoplasms, Castration-Resistant	-
Ramucirumab	Stomach Neoplasms	-
Rasburicase	Hyperuricemia|Leukemia|Lymphoma|Neoplasms|Syndrome|Tumor Lysis Syndrome	-
Regorafenib	Colorectal Neoplasms	74
Relugolix	Prostatic Neoplasms	-
Ribociclib	Breast Neoplasms	-
Rituximab	Arthritis|Arthritis, Rheumatoid|Granulomatosis with Polyangiitis|Leukemia|Leukemia, Lymphoid|Lymphoma|Lymphoma, B-Cell|Lymphoma, Follicular|Lymphoma, Non-Hodgkin|Myelitis|Neuromyelitis Optica|Purpura|Purpura, Thrombocytopenic|Purpura, Thrombocytopenic, Idiopathic|Thrombocytopenia	-
Romidepsin	Lymphoma, T-Cell, Cutaneous	32
Rucaparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	75
Ruxolitinib	Graft vs Host Disease|Polycythemia|Polycythemia Vera|Primary Myelofibrosis|Thrombocytosis	36
Selinexor	Multiple Myeloma	-
Selumetinib	Neurofibromatosis 1	29
Siltuximab	Giant Lymph Node Hyperplasia	-
Sirolimus	Angiomyolipoma|Constriction, Pathologic|Coronary Restenosis|Eye Diseases|Immune System Diseases|Kidney Failure, Chronic|Lipoma|Tuberous Sclerosis	92
Sonidegib	Carcinoma, Basal Cell	-
Sorafenib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	94
Sunitinib	Adenoma|Carcinoma, Renal Cell|Digestive System Neoplasms|Gastrointestinal Neoplasms|Gastrointestinal Stromal Tumors|Intestinal Neoplasms	94
Talazoparib	Breast Neoplasms	38
Tamoxifen	Breast Diseases|Cystic Fibrosis|Cysts|Fibroadenoma|Fibrocystic Breast Disease|Hemorrhage|Menorrhagia|Menstruation Disturbances|Metrorrhagia|Neoplasms	23
Tamsulosin	Calculi|Coronary Artery Disease|Heart Diseases|Hernia|Hernia, Inguinal|Inflammation|Ischemia|Lithiasis|Lower Urinary Tract Symptoms|Myocardial Ischemia|Prostatic Hyperplasia|Ureteral Calculi|Urinary Calculi|Urolithiasis|Urologic Diseases	-
Temozolomide	Astrocytoma|Nervous System Neoplasms	-
Temsirolimus	Carcinoma, Renal Cell	71
Teniposide	Precursor Cell Lymphoblastic Leukemia-Lymphoma	54
Thalidomide	Brain Abscess|Immune System Diseases|Multiple Myeloma|Neoplasms, Plasma Cell	-
Tivozanib	Carcinoma, Renal Cell	75
Tocilizumab	Arthritis|Arthritis, Juvenile|Arthritis, Rheumatoid|Behavior|Cytokine Release Syndrome|Giant Cell Arteritis|Neurobehavioral Manifestations|Oral Manifestations|Psychotic Disorders|Schizophrenia|Tic Disorders	-
Topotecan	Small Cell Lung Carcinoma	41
Toremifene	Breast Neoplasms	9
Trabectedin	Leiomyosarcoma|Liposarcoma	-
Trametinib	Carcinoma, Non-Small-Cell Lung|Melanoma	79
Trastuzumab	Breast Neoplasms|Neoplasms	45
Tretinoin	Lentigo	60
Triptorelin	Fatty Liver|Hypogonadism|Infertility, Female|Prostatic Neoplasms	63
Tucatinib	Breast Neoplasms	70
Valrubicin	Urinary Bladder Neoplasms	-
Vandetanib	Thyroid Neoplasms	94
Vemurafenib	Melanoma	51
Venetoclax	Leukemia, Lymphocytic, Chronic, B-Cell|Leukemia, Myeloid, Acute	-
Vinblastine	Glioma	-
Vincristine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	-
Vinorelbine	Carcinoma, Non-Small-Cell Lung	50
Vismodegib	Carcinoma, Basal Cell	-
Vorinostat	Lymphoma, T-Cell, Cutaneous	67

Zoledronate	Arthritis|Bone Marrow Diseases|Brain Abscess|Chronic Kidney Disease-Mineral and Bone Disorder|Chronic Periodontitis|HIV Infections|Hypersensitivity|Infections|Kidney Diseases|Metabolic Diseases|Multiple Myeloma|Neoplasms|Neoplasms, Plasma Cell|Neoplasms, Second Primary|Osteitis|Osteoarthritis|Periodontitis|Pleural Effusion, Malignant|Prostatic Neoplasms|Renal Insufficiency, Chronic|Thalassemia|Wounds and Injuries	-

6. Conclusion

We applied the software package "Genome Enhancer" to a 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:

These drugs were selected for acting on the following targets: PDGFRA and PSMC4, 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:

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: 2,5,7-Trihydroxynaphthoquinone, Imatinib, midostaurin, 6-Nitroindazole and Curcumin. 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.

- EAC
- IGFBP-5
- PDGFRalpha
- CDK2
- MKP-4

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 2023.2 (geneXplain GmbH, Wolfenbüttel, Germany) (https://genexplain.com/transfac).
The master regulator search uses the TRANSPATH® database (BIOBASE), release 2023.2 (geneXplain GmbH, Wolfenbüttel, Germany) (https://genexplain.com/transpath). A comprehensive signal transduction network of human cells is built by the software on the basis of reactions annotated in TRANSPATH®.
The information about drugs corresponding to identified drug targets and clinical trials references were extracted from HumanPSD™ database, release 2023.2 (https://genexplain.com/humanpsd).
The Ensembl database release Human104.38 (hg38) (http://www.ensembl.org) was used for gene IDs representation and Gene Ontology (GO) (http://geneontology.org) was used for functional classification of the studied gene set.

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 - Up-regulated genes
2. Supplementary table 2 - Down-regulated genes
3. Supplementary table 3 - Detailed report. Composite modules and master regulators (up-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive).
4. Supplementary table 4 - Detailed report. Composite modules and master regulators (down-regulated genes in Experiment: cisplatin-resistant vs. Control: cisplatin-sensitive).
5. Supplementary table 5 - Detailed report. Pharmaceutical compounds and drug targets.

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

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