ITGA3 and ITGB5 are promising druggable targets for treating Squamous Cell Carcinoma that control activity of TP53, JUN and ATF2 transcription factors on promoters 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 data set that contains *transcriptomics* data. The study is done in the context of *Squamous Cell Carcinoma*. 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: TP53, JUN, MYBL2, ATF2 and NFATC1. The subsequent network analysis suggested

- integrins
- PP2A

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 {(2Z)-4-AMINO-2-[(4-METHOXYPHENYL)IMINO]-2,3-DIHYDRO-1,3-THIAZOL-5-YL}(4-METHOXYPHENYL)METHANONE.

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
SRR349741.fastq	Transcriptomics
SRR349742.fastq	Transcriptomics
SRR349748.fastq	Transcriptomics
SRR349749.fastq	Transcriptomics

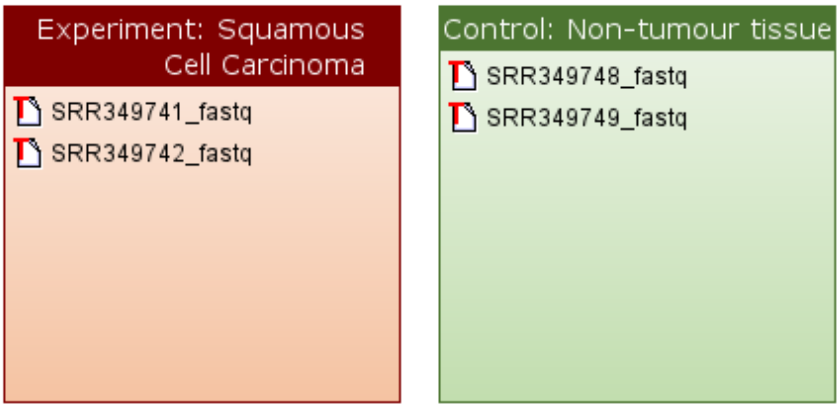


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

3. Results

We have compared the following conditions: Experiment: Squamous Cell Carcinoma *versus* Control: Non-tumour tissue.

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: Squamous Cell Carcinoma" with "Control: Non-tumour tissue". 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: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.*

See full table →

ID	Gene description	Gene symbol	logFC	logCPM	PValue	FDR
ENSG00000115758	ornithine decarboxylase 1	ODC1	7.17	10.32	2.21E-11	6.44E-8
ENSG00000148053	neurotrophic receptor tyrosine kinase 2	NTRK2	6.48	9.32	5.21E-11	1.14E-7
ENSG00000113140	secreted protein acidic and cysteine rich	SPARC	6.14	10.69	2.91E-9	2.03E-6
ENSG00000163359	collagen type VI alpha 3 chain	COL6A3	5.68	9.13	2.4E-8	1E-5
ENSG00000120708	transforming growth factor beta induced	TGFBI	5.24	8.77	6.25E-10	6.08E-7
ENSG00000134871	collagen type IV alpha 2 chain	COL4A2	5.14	7.97	1.36E-10	2.38E-7
ENSG00000186340	thrombospondin 2	THBS2	5.1	8.46	2.19E-7	5.04E-5
ENSG00000146648	epidermal growth factor receptor	EGFR	4.92	9.64	4.36E-6	5.44E-4
ENSG00000144824	pleckstrin homology like domain family B member 2	PHLDB2	4.9	8.29	3.7E-9	2.03E-6
ENSG00000145824	C-X-C motif chemokine ligand 14	CXCL14	4.89	8.54	1.11E-7	3.05E-5

*Table 3. Top ten **down-regulated** genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.*

See full table →

ID	Gene description	Gene symbol	logFC	logCPM	PValue	FDR
ENSG00000136155	sciellin	SCEL	-7.36	10.74	2.01E-12	1.76E-8
ENSG00000163209	small proline rich protein 3	SPRR3	-6.39	14.08	2.27E-5	2E-3
ENSG00000143369	extracellular matrix protein 1	ECM1	-6.04	10.66	2.28E-9	1.82E-6
ENSG00000189334	S100 calcium binding protein A14	S100A14	-6	10.05	7.93E-10	6.95E-7
ENSG00000229732	novel transcript		-5.88	12.56	3.53E-9	2.03E-6
ENSG00000086548	CEA cell adhesion molecule 6	CEACAM6	-5.82	9.92	2.89E-10	3.61E-7
ENSG00000171401	keratin 13	KRT13	-5.76	14.53	2.55E-8	1.02E-5
ENSG00000087128	transmembrane serine protease 11E	TMPRSS11E	-5.67	9.79	2.03E-8	8.91E-6
ENSG00000197632	serpin family B member 2	SERPINB2	-5.5	8.35	1.72E-10	2.51E-7
ENSG00000165272	aquaporin 3 (Gill blood group)	AQP3	-5.46	10.95	2.63E-6	3.78E-4

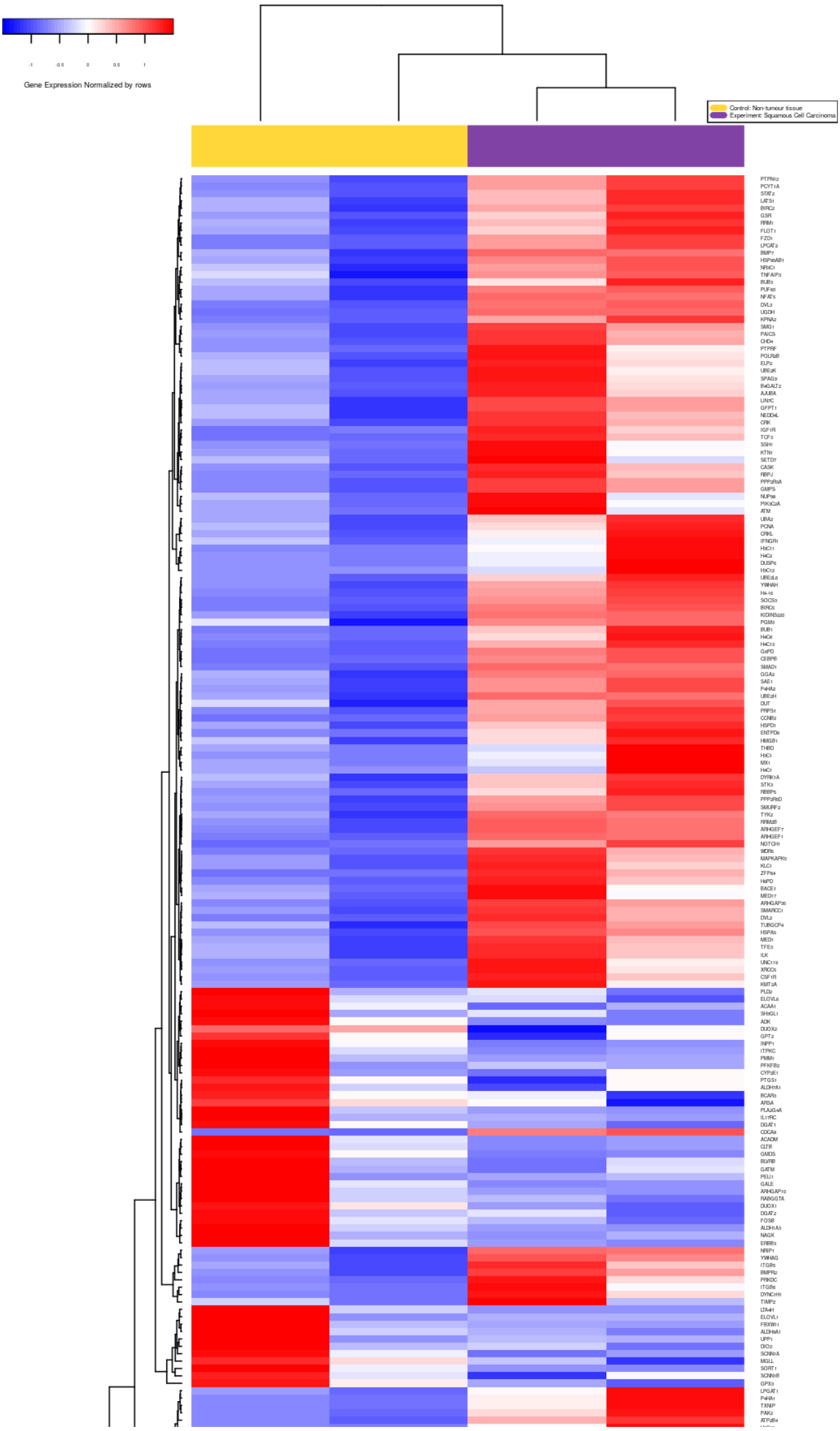
3.2. Functional classification of genes

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: Squamous Cell Carcinoma vs. Control: Non-tumour tissue

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


-1
-0.5
0
0.5
1
Gene Expression Normalized by rows
Control: Non-tumour tissue
Experiment: Squamous Cell Carcinoma
PTPN12
PCYT1A
STAT2
LATS1
BIRC2
GSR
RRM1
FLOT1
FZD1
LPCAT2
BMP7
HSP90AB1
NPTXR
TNFAIP3
BUB3
PUF60
NFAT5
DVL3
UGDH
KPNA2
SMG1
PAICS
CHD4
PTPRF
POLR2B
ELP2
UBE2K
SPAG9
B4GALT2
AJUBA
LIN7C
GFPT1
NEDD4L
CRK
IGF1R
TCF3
SSH1
KTN1
SETD7
CASK
RBPJ
PPP2R5A
GMPS
NUP98
PRKCBA
ATM
UBA2
PCNA
CRKL
IFNGR1
HIST1H1
H4C2
DUSP6
HIST1H2
UBE2L6
YWHAH
H4-16
SOCS3
BIRC5
KIDINS220
PGM3
BUB1
H4C8
H4C13
G6PD
CEBPB
SMAD1
GGA2
SAE1
P4HA2
UBE2H
DUT
PRPS1
CCNB2
HSPD1
ENTPD4
HMGB1
THBD
HIST1H1C
MX1
H4C1
DYRK1A
STK3
RBBP5
PPP2R5D
SMURF2
TYK2
RRM2B
ARHGEF7
ARHGEF1
NOTCH1
WDR5
MAPKAPK5
KLC1
ZFP64
HSPD1
BACE1
MED17
ARHGAP35
SMARCC1
DVL2
TUBGCP4
HSPA5
MED1
TFE3
ILK
UNC119
XRCC5
CSF1R
KMT2A
PLD2
ELOVL6
ACAA1
SH3GL1
ADK
DUOX2
GPT2
INPP1
ITPKC
PMM1
PFKFB2
CYP2E1
PTGS1
ALDH1A1
BCAR3
ARSA
PLA2G4A
IL1RAP
DGAT1
CDC42
ACADM
CLTB
GMDS
BUB1B
GATM
PELI1
GALE
ARHGAP10
RABGGTA
DUOX1
DGAT2
FOSB
ALDH1A3
NAGK
ERBB3
NRP1
YWHAG
ITGB5
BMPR2
PRKDC
ITGB6
DYNC1H1
TIMP2
LTA4H
ELOVL1
FBXW11
ALDH3A1
UPP1
DIO2
SCNN1A
MGLL
SORT1
SCNN1B
GPX3
LPGAT1
P4HA1
TXNIP
PAK2
ATP2B4

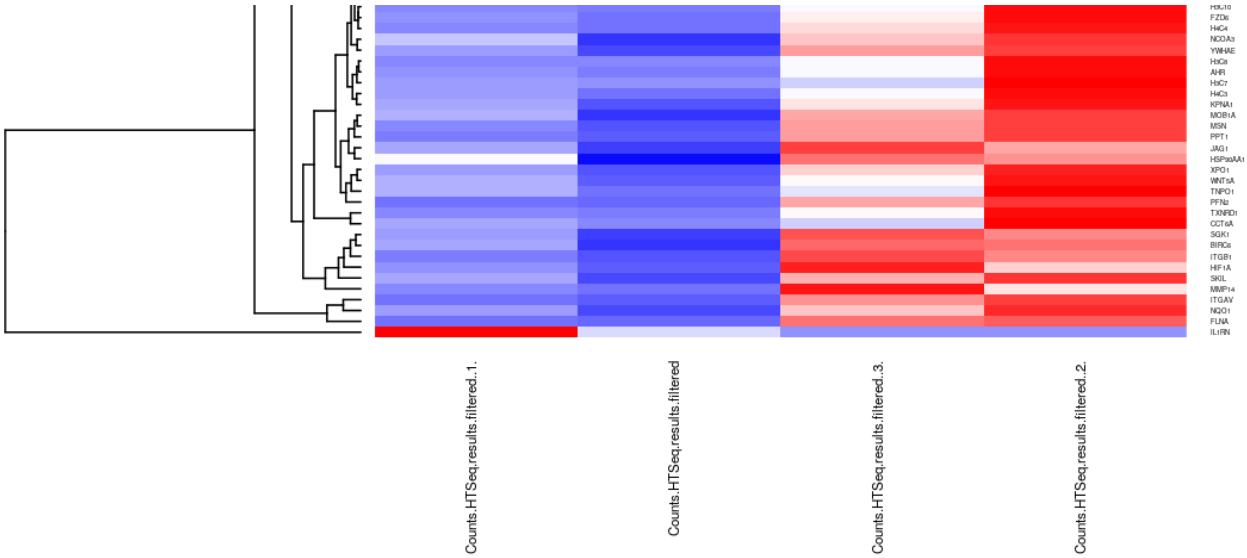


Figure 2. Heatmap of genes enriched in Transpath categories. The colored bar at the top shows the types of the samples according to the legend in the upper right corner.
See full diagram →

Up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue:

1436 significant up-regulated genes were taken for the mapping.

GO (biological process)

Figure 3. Enriched GO (biological process) of up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.

Full classification →

TRANSPATH® Pathways (2022.1)

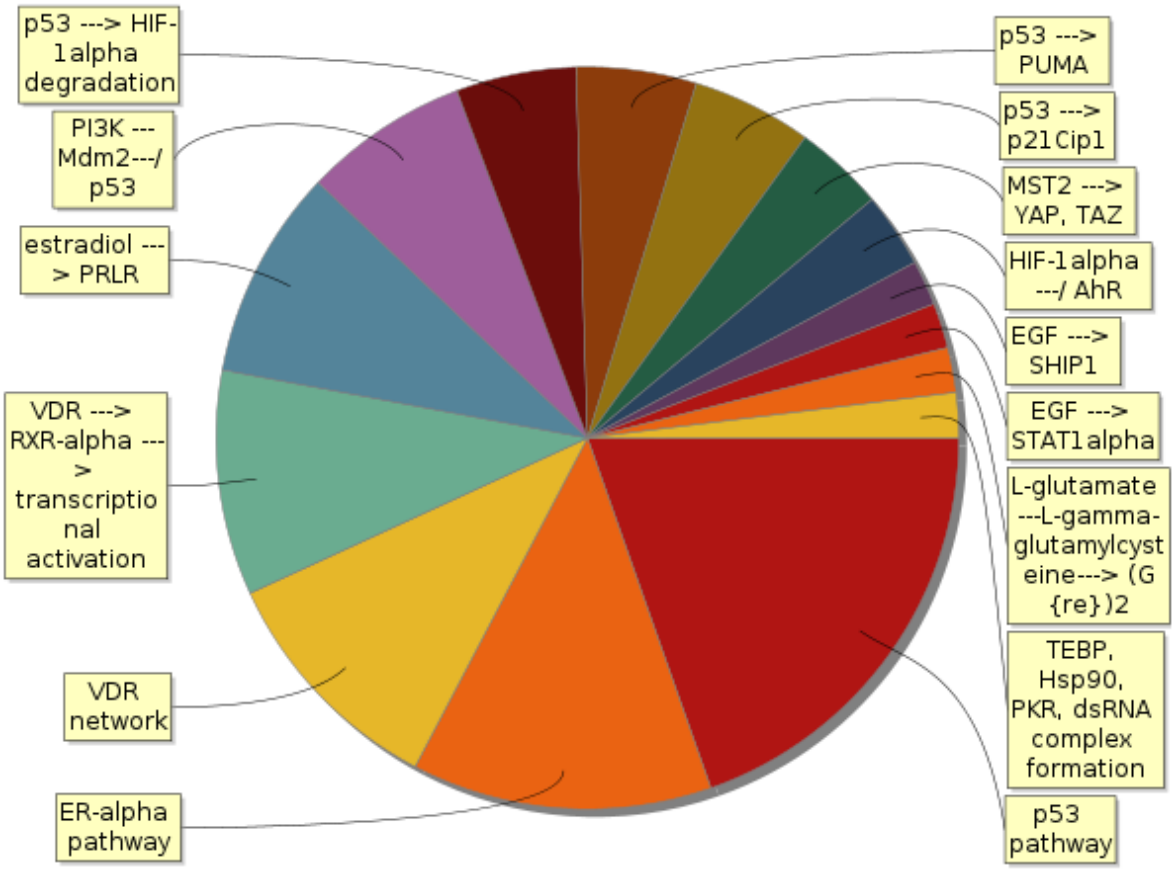


Figure 4. Enriched TRANSPATH® Pathways (2022.1) of up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.

Full classification →

HumanPSD(TM) disease (2022.1)

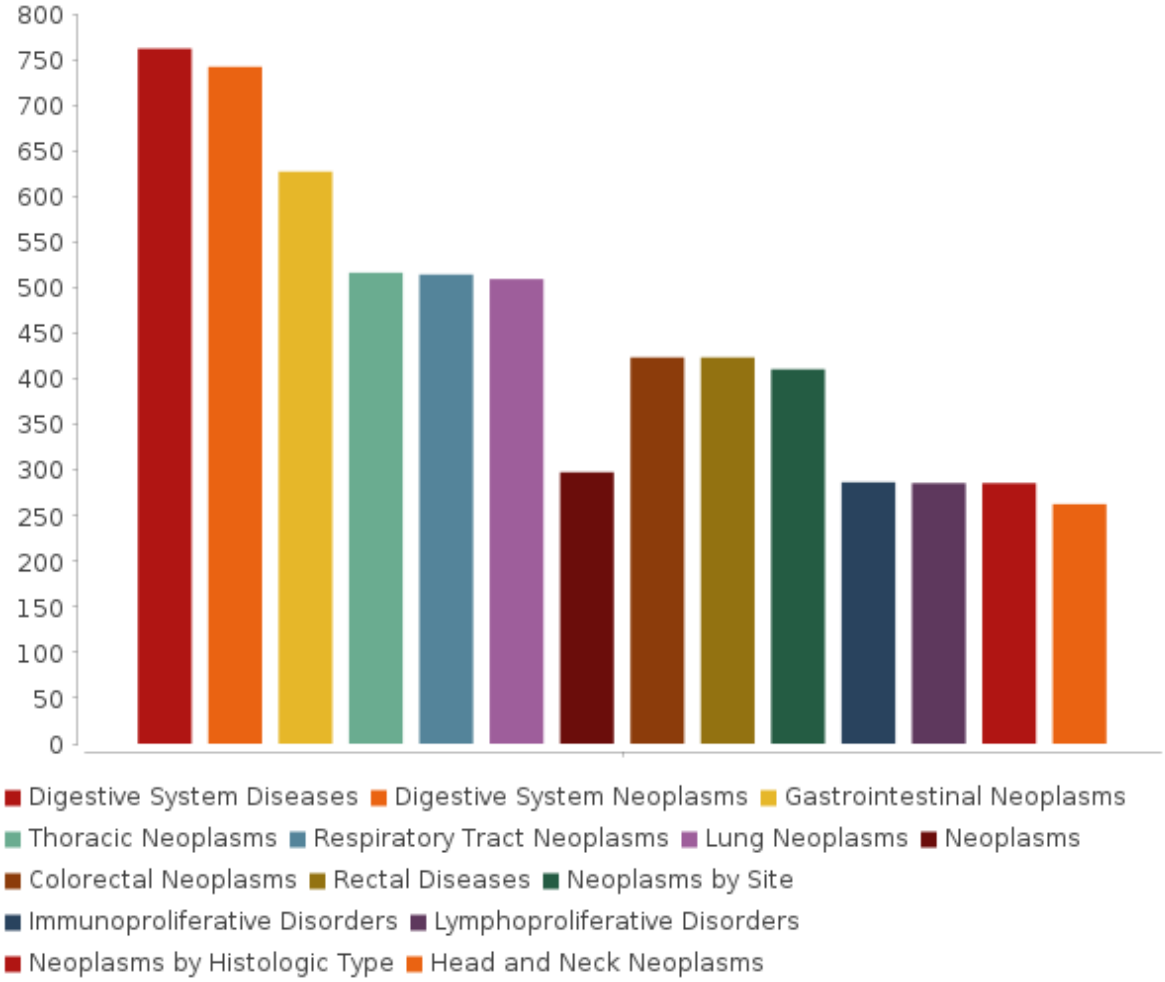


Figure 5. Enriched HumanPSD(TM) disease (2022.1) of up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

Full classification →

Down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue:

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

GO (biological process)

Figure 6. Enriched GO (biological process) of down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.

Full classification →

TRANSPATH® Pathways (2022.1)

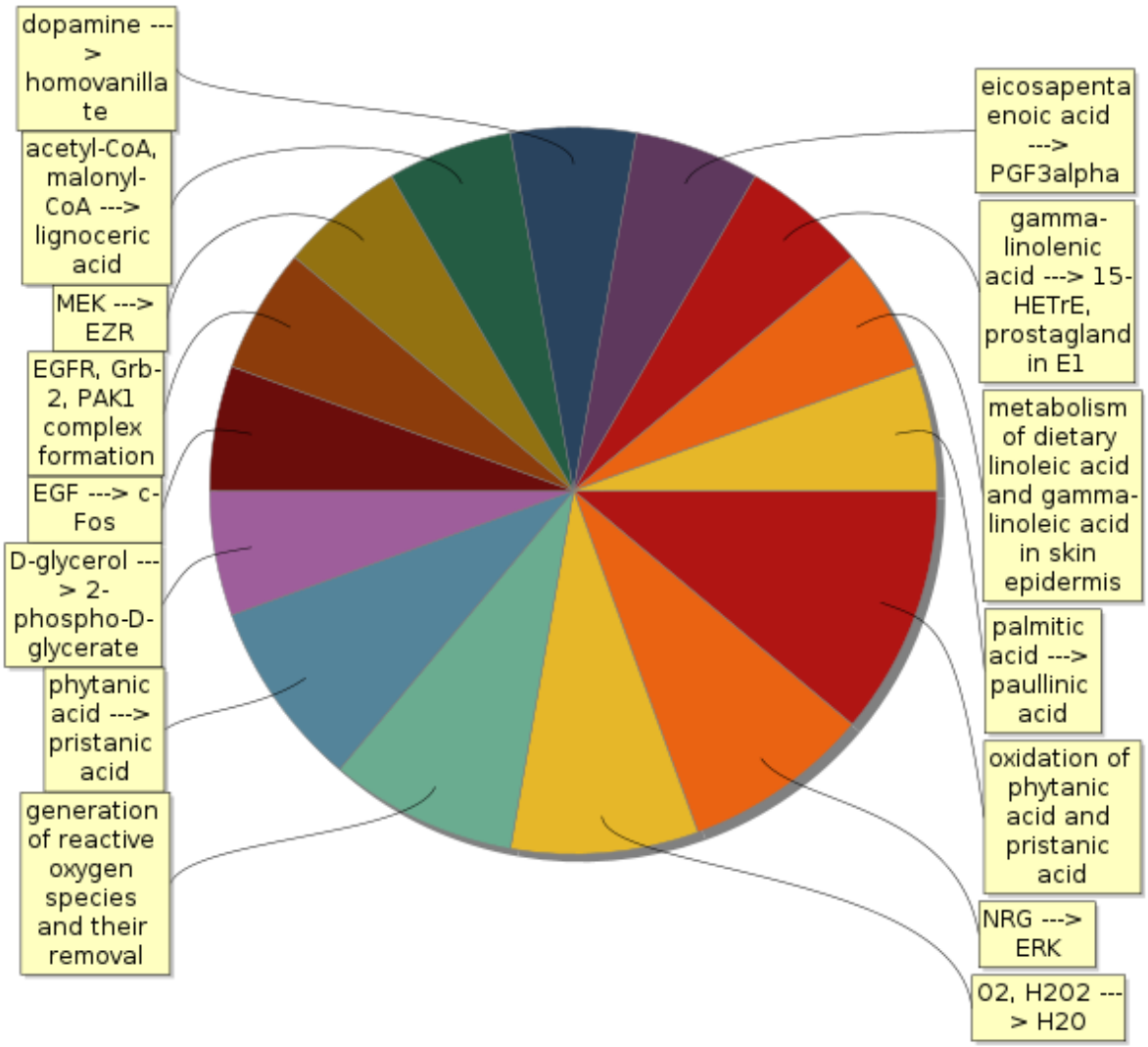


Figure 7. Enriched TRANSPATH® Pathways (2022.1) of down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.

Full classification →

HumanPSD(TM) disease (2022.1)

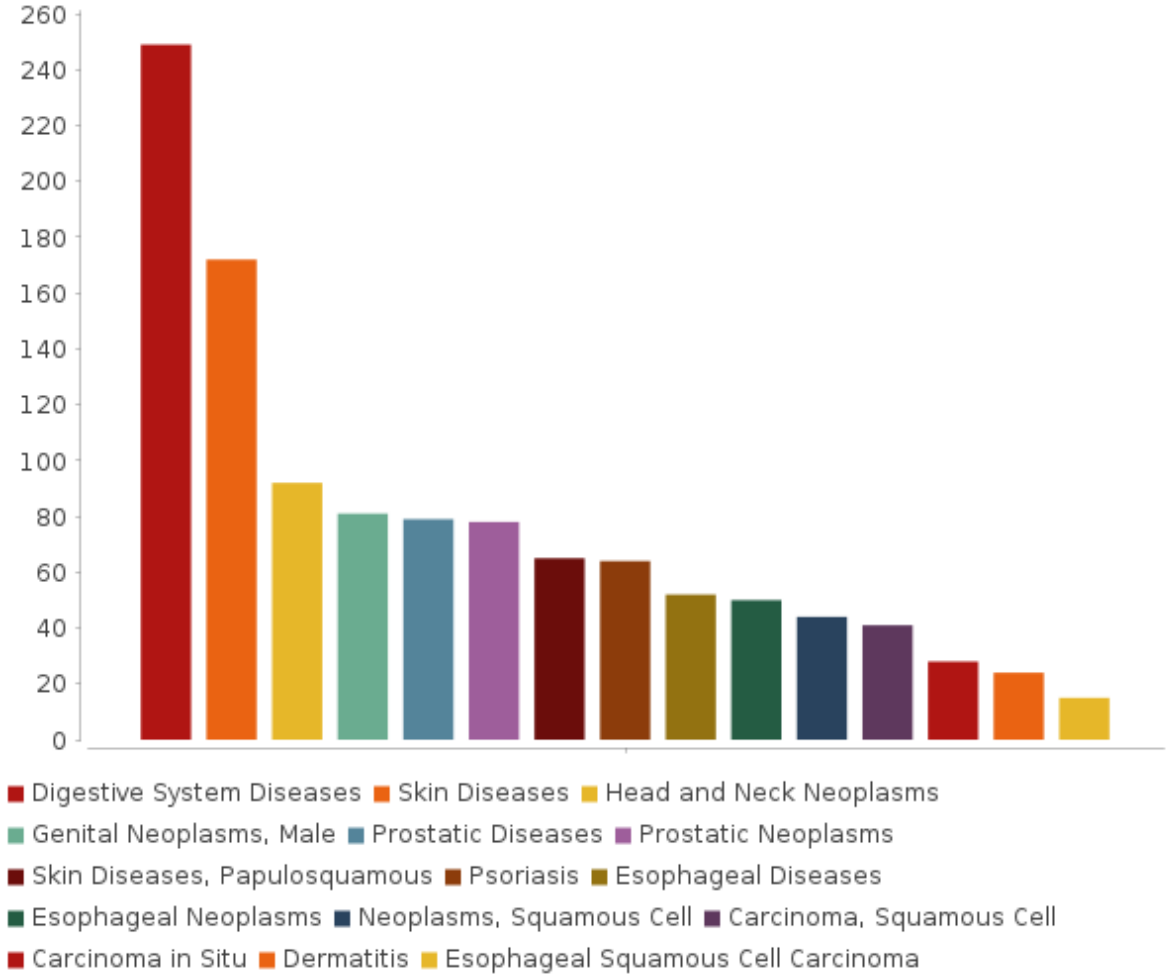
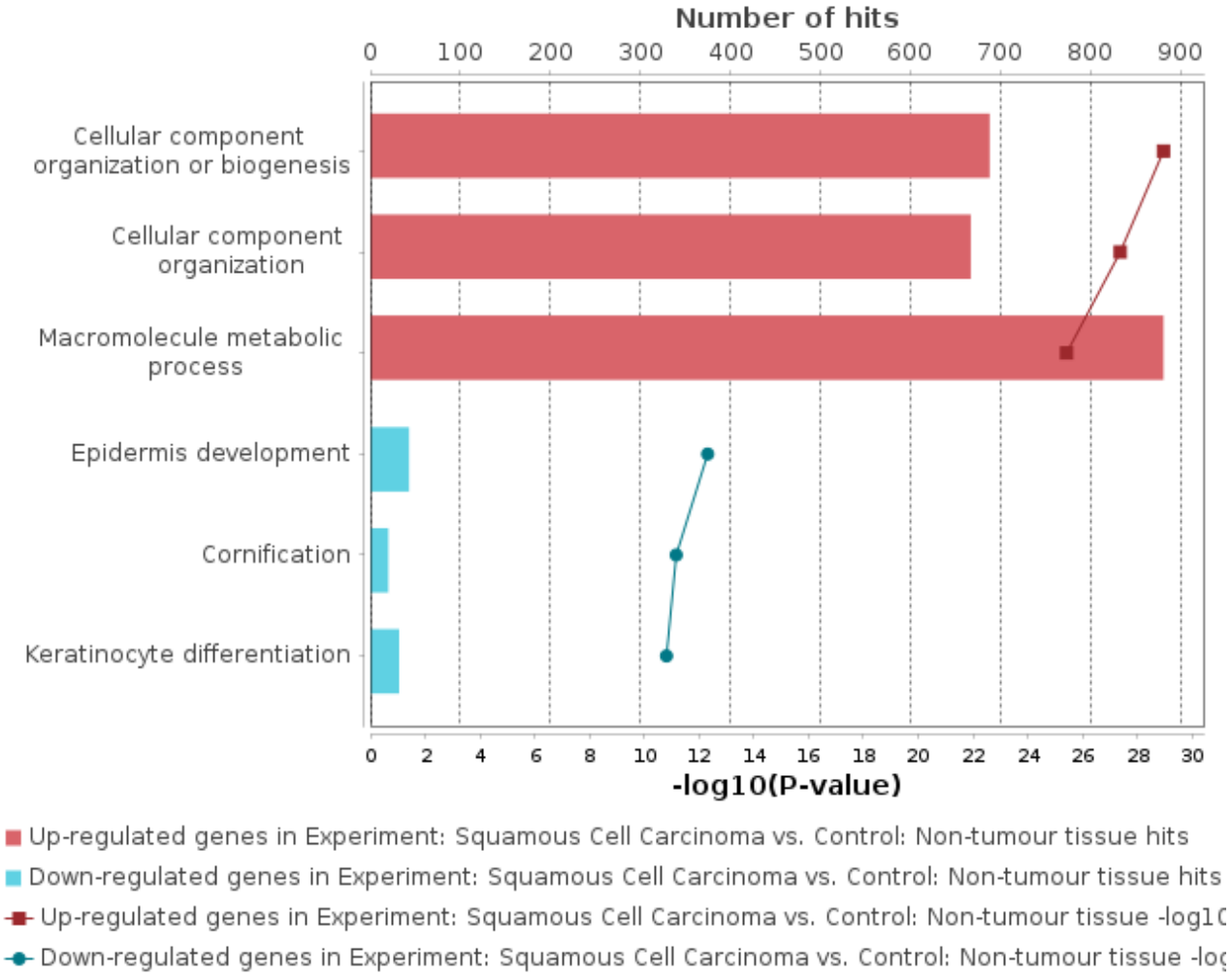


Figure 8. Enriched HumanPSD(TM) disease (2022.1) of down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

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

We analyzed mutations that were revealed in the potential enhancers located upstream, downstream or inside the ***target genes*** (see Table 4). We identified 646 mutations potentially affecting gene regulation. Table 5 shows the following lists of PWMs whose sites were lost or gained due to these mutations. Weighting of mutations was done in respect to the significance

of the change in TF affinity binding to the sequence. Mutations that maximally affected the change of binding affinity received higher weights. These PWMs were put in focus of the CMA algorithm that constructs the model of the enhancers by specifying combinations of TF motifs (see more details of the algorithm in the Methods section).

Table 4. Mutations revealed in Experiment: Squamous Cell Carcinoma versus Control: Non-tumour tissue
See full table →

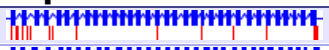
ID	Gene symbol	Gene schematic representation	Number of variations
ENSG00000146648	EGFR		21
ENSG00000083857	FAT1		16
ENSG00000134871	COL4A2		13
ENSG00000186340	THBS2		10
ENSG00000226445	ENSG00000226445		9
ENSG00000145012	LPP		8
ENSG00000114999	TTL		7
ENSG00000142173	COL6A2		7
ENSG00000152291	TGOLN2		7
ENSG00000157214	STEAP2		7

Table 5. PWMs whose sites were lost or gained due to mutations in Experiment: Squamous Cell Carcinoma and Control: Non-tumour tissue
See full table →

ID	P-value (gains)	P-value (losses)	yesCount (gains)	yesCount (losses)
V$EGR1_07	4.62E-2	1.4E-24	5	1134
V$E2F7_04	3.89E-2	5.74E-23	11	744
V$GLI2_05	2.49E-2	1.26E-22	11	2807
V$E2F3_05	1.58E-2	3.63E-25	27	1467
V$E2F1_Q4_01	1.5E-2	1.86E-27	11	1490
V$TFCP2_06	2.67E-3	1.98E-16	7	3313
V$GCM1ELK3_01	9.76E-5	1.1E-15	23	2012
V$RUNX3_01	5.78E-6	2.84E-24	151	1895
V$E2F1_05	3.15E-7	6.44E-27	39	1042
V$TEF_05	2.01E-7	1.39E-18	452	538
V$E2F7_01	2.67E-11	5.68E-16	73	153
V$MEIS1ELF1_01	2.18E-11	1.3E-16	2061	1805
V$TFDP1_03	1.1E-12	5.83E-24	275	1398
V$SP1_Q2_01	1.03E-15	1.82E-2	201	5
V$GLI2_Q3	3.26E-17		862	
V$OSX_Q3	5E-18	4.62E-2	352	5
V$GCM1_08	4.97E-18		852	
V$ZNF282_03	1.42E-18		789	
V$GLI1_Q3	1.29E-19		833	
V$MECP2_02	3.52E-20	1.39E-3	738	39

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: Squamous Cell Carcinoma vs. Control: Non-

tumour tissue).

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: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.

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$ZFP281_01 0.96; N=2
V$P53_Q3 0.96; N=3
V$SOX9_02 0.96; N=2
V$CEBP_01 0.98; N=3
V$FOSL2_02 0.93; N=1
V$MYBL2_06 0.98; N=2

Module width: 139

Module 2:

V$BCL11A_02 0.90; N=2
V$WT1_Q6_02 0.94; N=2
V$MECP2_02 0.96; N=1
V$IRF3_11 0.74; N=2
V$JUN_09 0.87; N=1
V$E2A_Q2 0.96; N=2

Module width: 144

Model score (-p*log10(pval)): 11.07
Wilcoxon p-value (pval): 4.80e-24
Penalty (p): 0.475
Average yes-set score: 3.84
Average no-set score: 1.83
AUC: 0.84
Separation point: 2.74
False-positive: 26.94%
False-negative: 19.35%

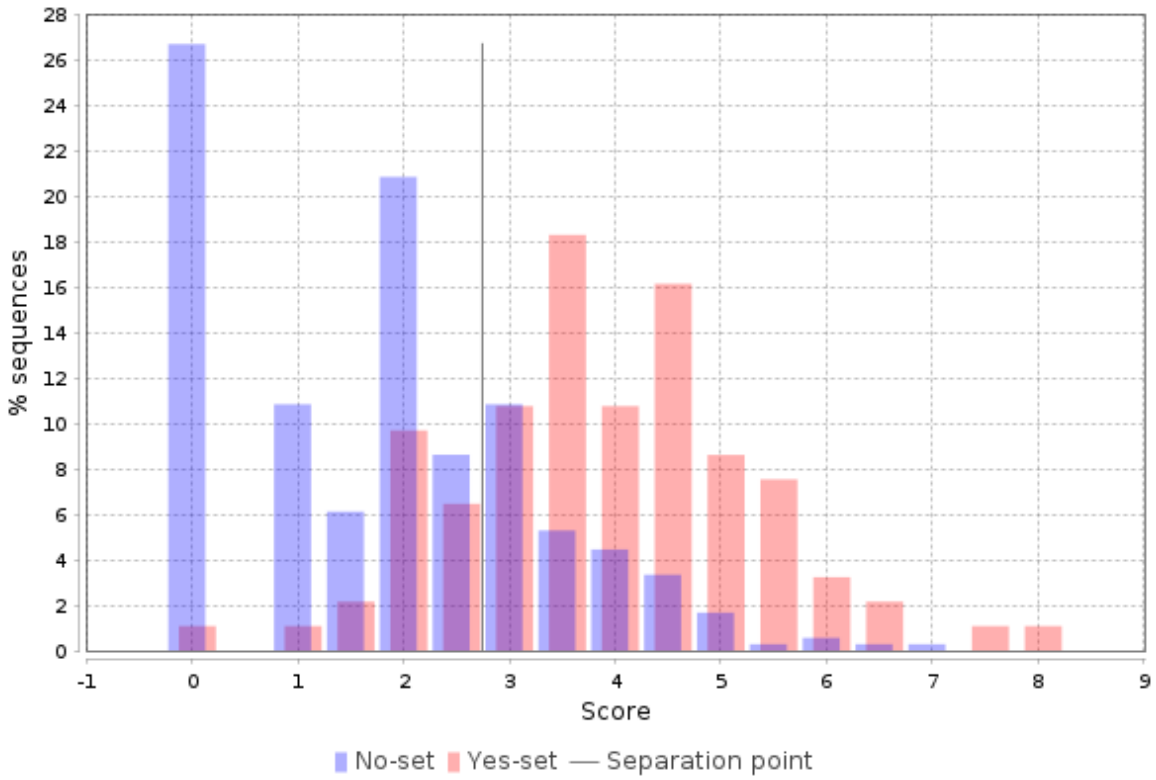


Table 6. List of top ten up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*

See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000173486	FKBP2	FKBP prolyl isomerase 2	8.11	SOX-9(h), p53(h), c-Jun(h), Fra-2(h), MeCp2(h), BCL-11A(h), WT1(h)...
ENSG00000172216	CEBPB	CCAAT enhancer binding protein beta	7.93	SOX-9(h), BCL-11A(h), Fra-2(h), c-Jun(h), p53(h), E2A(h),Myf-6(h),MyoD(h),Myogenin(h), WT1(h)...
ENSG00000135040	NAA35	N-alpha-acetyltransferase 35, NatC auxiliary subunit	7.28	p53(h), SOX-9(h), C/EBPalpha(h), IRF-3(h), MeCp2(h), BCL-11A(h), WT1(h)...
ENSG00000146242	TPBG	trophoblast glycoprotein	7.25	p53(h), BCL-11A(h), WT1(h), IRF-3(h), C/EBPalpha(h), Fra-2(h), ZNF281(h)
ENSG00000075240	GRAMD4	GRAM domain containing 4	7.12	E2A(h),Myf-6(h),MyoD(h),Myogenin(h), p53(h), Fra-2(h), SOX-9(h), c-Jun(h), ZNF281(h), WT1(h)...
ENSG00000135999	EPC2	enhancer of polycomb homolog 2	6.97	SOX-9(h), Fra-2(h), p53(h), C/EBPalpha(h), BCL-11A(h), E2A(h),Myf-6(h),MyoD(h),Myogenin(h)
ENSG00000242498	ARPIN	actin related protein 2/3 complex inhibitor	6.96	WT1(h), BCL-11A(h), IRF-3(h), SOX-9(h), c-Jun(h), Fra-2(h), p53(h)...
ENSG00000145337	PYURF	PIGY upstream reading frame	6.89	ZNF281(h), WT1(h), MeCp2(h), p53(h), SOX-9(h), IRF-3(h), BCL-11A(h)
ENSG00000184232	OAF	out at first homolog	6.89	SOX-9(h), E2A(h),Myf-6(h),MyoD(h),Myogenin(h), IRF-3(h), BCL-11A(h), p53(h), WT1(h), ZNF281(h)
ENSG00000249780		pseudogene similar to part of mitochondrially encoded cytochrome c oxidase III (MT-CO3)	6.79	C/EBPalpha(h), p53(h), Fra-2(h), SOX-9(h), E2A(h),Myf-6(h),MyoD(h),Myogenin(h), IRF-3(h), BCL-11A(h)

Enhancer model potentially involved in regulation of target genes (down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue).

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: Squamous Cell Carcinoma vs. Control: Non-tumour tissue.

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$GCM1_08	V$SOX10_12	V$TGIF1_04	V$NFATC1_02	V$SNAI2_01
0.89; N=3	0.67; N=3	0.75; N=3	0.80; N=3	0.93; N=3

V$CDX2_Q5
0.87; N=1

Module width: 92

Module 2:

V$ATF2_09	V$NFATC1_09	V$AP1_Q6_01	V$NKX25_08	V$NFATC1_05
0.82; N=2	0.61; N=3	0.94; N=2	0.98; N=2	0.95; N=1

V$GLI1_Q3
0.95; N=1

Module width: 106

Model score (-p*log10(pval)): 15.22
Wilcoxon p-value (pval): 8.37e-33
Penalty (p): 0.475
Average yes-set score: 6.82
Average no-set score: 5.31
AUC: 0.79
Separation point: 5.66
False-positive: 40.22%
False-negative: 14.72%

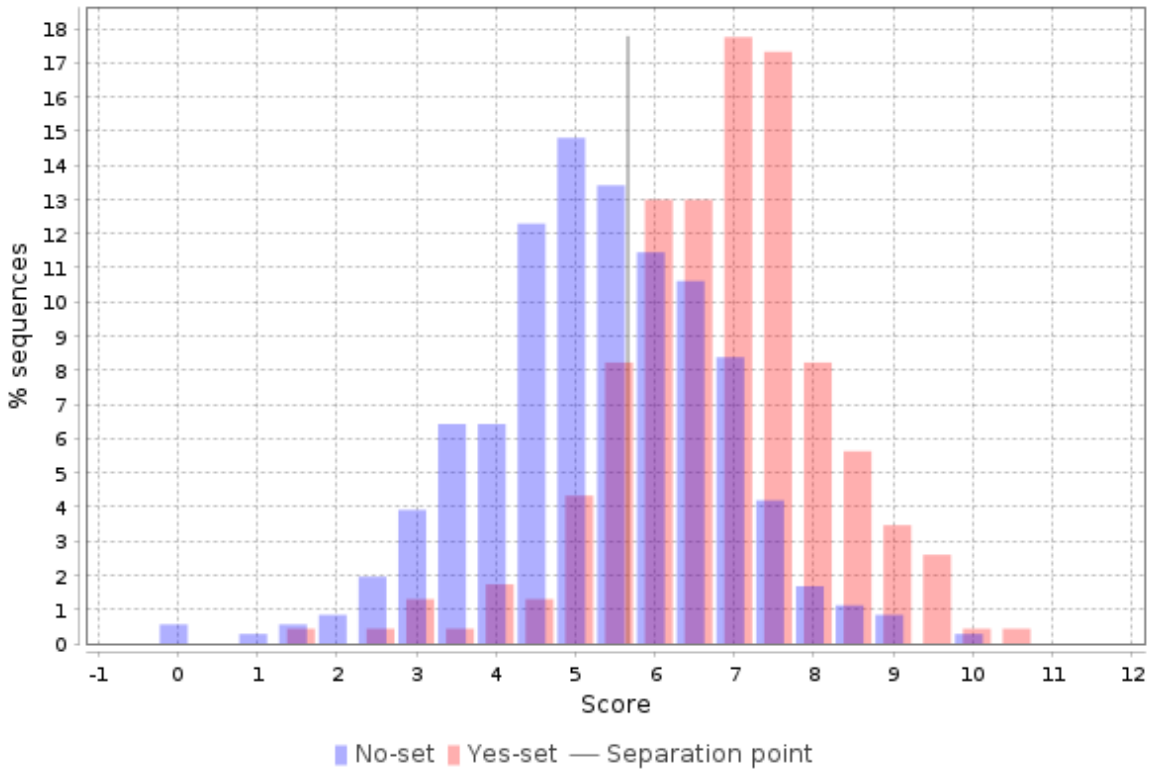


Table 7. List of top ten down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue with identified enhancers in their regulatory regions. ***CMA score*** *- the score of the CMA model of the enhancer identified in the regulatory region.*

See full table →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000172819	RARG	retinoic acid receptor gamma	11.51	NFATc1(h), FosB(h),Fra-1(h),Fra-2(h),JunB(h),JunD(h),c-Fos(h),c-Jun(h), ATF-2(h), TGIF-1(h), SNAI2(h), GCMa(h)
ENSG00000092203	TOX4	TOX high mobility group box family member 4	10.84	NKX-2.5(h), NFATc1(h), FosB(h),Fra-1(h),Fra-2(h),JunB(h),JunD(h),c-Fos(h),c-Jun(h), ATF-2(h), GCMa(h), SOX-10(h), SNAI2(h)
ENSG00000101276	SLC52A3	solute carrier family 52 member 3	10.78	ATF-2(h), NFATc1(h), FosB(h),Fra-1(h),Fra-2(h),JunB(h),JunD(h),c-Fos(h),c-Jun(h), NKX-2.5(h), SNAI2(h), GCMa(h)
ENSG00000170915	PAQR8	progestin and adipoQ receptor family member 8	10.5	NKX-2.5(h), ATF-2(h), NFATc1(h), FosB(h),Fra-1(h),Fra-2(h),JunB(h),JunD(h),c-Fos(h),c-Jun(h), SNAI2(h), TGIF-1(h), SOX-10(h)...
ENSG00000138411	HECW2	HECT, C2 and WW domain containing E3 ubiquitin protein ligase 2	10.48	SOX-10(h), GCMa(h), TGIF-1(h), GLI1(h), NFATc1(h), ATF-2(h), NKX-2.5(h)
ENSG00000026751	SLAMF7	SLAM family member 7	10.31	FosB(h),Fra-1(h),Fra-2(h),JunB(h),JunD(h),c-Fos(h),c-Jun(h), GCMa(h), NFATc1(h), SOX-10(h), TGIF-1(h), CDX-2(h)
ENSG00000134107	BHLHE40	basic helix-loop-helix family member e40	10.24	GLI1(h), NKX-2.5(h), FosB(h),Fra-1(h),Fra-2(h),JunB(h),JunD(h),c-Fos(h),c-Jun(h), NFATc1(h), ATF-2(h), SNAI2(h), GCMa(h)
ENSG00000201302	SNORA65	small nucleolar RNA, H/ACA box 65	10.22	SNAI2(h), SOX-10(h), GCMa(h), TGIF-1(h), NFATc1(h), ATF-2(h), GLI1(h)...
ENSG00000081913	PHLPP1	PH domain and leucine rich repeat protein phosphatase 1	10.22	SNAI2(h), GCMa(h), TGIF-1(h), NKX-2.5(h), NFATc1(h), ATF-2(h)
ENSG00000154319	FAM167A	family with sequence similarity 167 member A	10.22	SNAI2(h), TGIF-1(h), GCMa(h), ATF-2(h), NFATc1(h), GLI1(h), NKX-2.5(h)...

On the basis of the enhancer models we identified transcription factors potentially regulating the ***target genes*** of our interest. We found 15 and 16 transcription factors controlling expression of up- and down-regulated genes respectively (see Tables 8-9).

*Table 8. Transcription factors of the predicted enhancer model potentially regulating the differentially expressed genes (up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue). **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 →

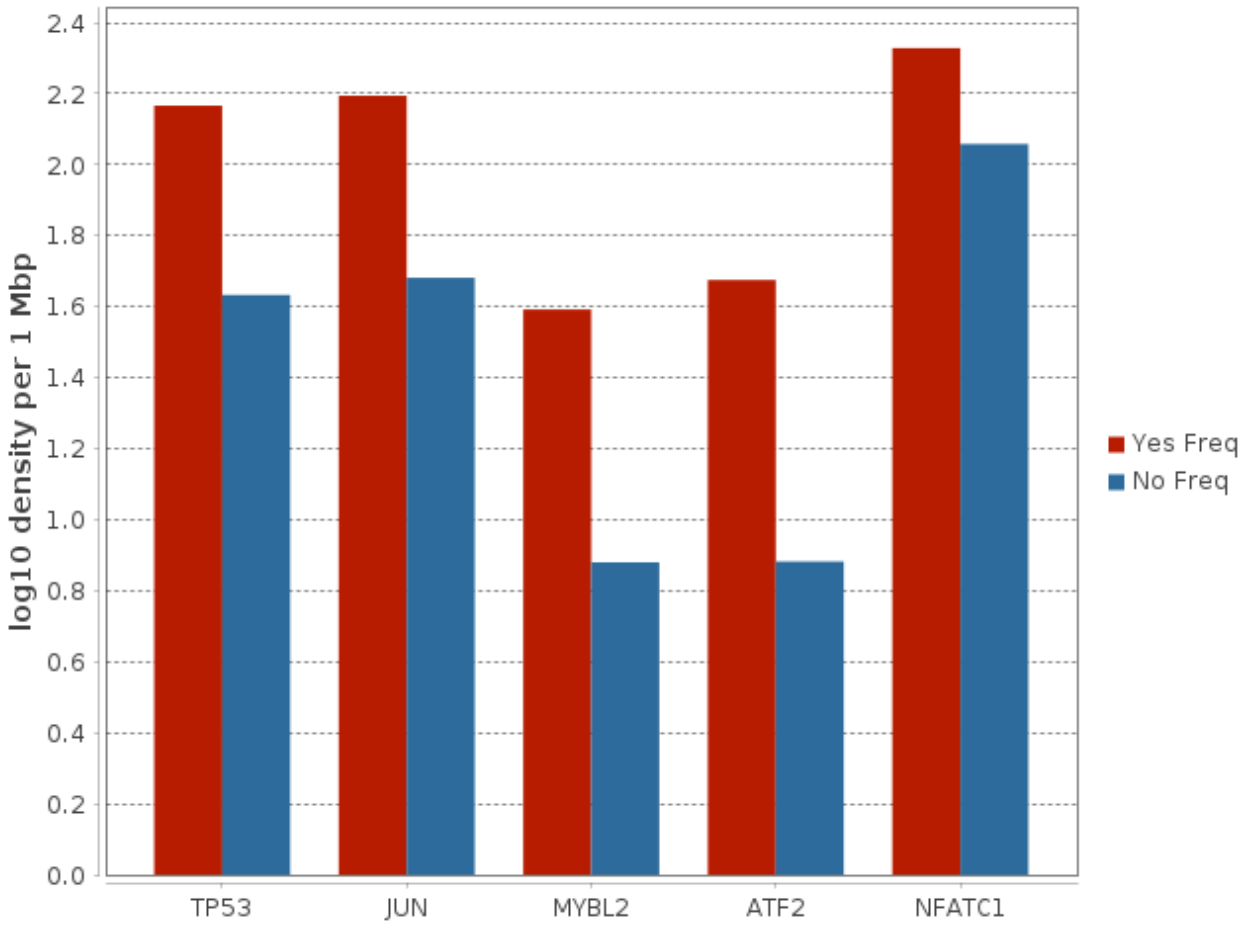
ID	Gene symbol	Gene description	Regulatory score	Yes-No ratio
MO000019548	TP53	tumor protein p53	4.03	3.41
MO000019469	JUN	Jun proto-oncogene, AP-1 transcription factor subunit	2.69	3.26
MO000021901	MYBL2	MYB proto-oncogene like 2	2.28	5.16
MO000019418	CEBPA	CCAAT enhancer binding protein alpha	2.28	2.15
MO000024984	MYOG	myogenin	2.17	6.45
MO000026074	FOSL2	FOS like 2, AP-1 transcription factor subunit	2.12	3.26
MO000028758	ZNF281	zinc finger protein 281	2	2.12
MO000019612	MYOD1	myogenic differentiation 1	1.92	5.16
MO000032492	TCF3	transcription factor 3	1.86	2.58
MO000018993	SOX9	SRY-box transcription factor 9	1.79	9.67

*Table 9. Transcription factors of the predicted enhancer model potentially regulating the differentially expressed genes (down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue). **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
MO000082535	ATF2	activating transcription factor 2	2.27	6.21
MO000019469	JUN	Jun proto-oncogene, AP-1 transcription factor subunit	2.17	5.82
MO000020760	NFATC1	nuclear factor of activated T cells 1	2.13	1.86
MO000018137	FOS	Fos proto-oncogene, AP-1 transcription factor subunit	2.06	15.52
MO000007834	JUND	JunD proto-oncogene, AP-1 transcription factor subunit	1.99	5.43
MO000082447	FOSB	FosB proto-oncogene, AP-1 transcription factor subunit	1.9	6.21
MO000007830	JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	1.82	6.98
MO000025684	FOSL1	FOS like 1, AP-1 transcription factor subunit	1.75	4.97
MO000026074	FOSL2	FOS like 2, AP-1 transcription factor subunit	1.65	6.98
MO000028767	SNAI2	snail family transcriptional repressor 2	1.62	1.46

The following diagram represents the key transcription factors, which were predicted to be potentially regulating differentially expressed genes in the analyzed pathology: TP53, JUN, MYBL2, ATF2 and NFATC1.



3.4. Finding master regulators in networks

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

Table 10. Signaling proteins whose structure and function is damaged by the mutations in Experiment: Squamous Cell Carcinoma and Control: Non-tumour tissue

See full table →

ID	Title	Mutation count	Consequence	Codons
MO000208420	GJB3(h)	2	stop_gained	tGg/tAg
MO000109306	PSMA4(h)	1	stop_lost	Tga/Cga
MO000119197	wolframin(h)	1	stop_gained	Caa/Taa
MO000144222	APT2(h)	1	stop_lost	Tag/Cag
MO000172130	c3orf1(h)	1	NMD_transcript_variant,stop_lost	tGa/tCa
MO000175986	oas2(h)	1	stop_lost	tAg/tGg
MO000189841	ZSWIM1(h)	1	stop_gained	tGg/tAg
MO000212738	EMC10(h)	1	stop_lost	taG/taT
MO000219203	PSMG1(h)	1	NMD_transcript_variant,stop_lost	Taa/Caa
MO000222634	TCP11L1(h)	1	NMD_transcript_variant,stop_gained	Cag/Tag

Top 10 mutated proteins for Experiment: Squamous Cell Carcinoma and Control: Non-tumour tissue were used in the algorithm of master regulator search as a list of nodes of the signal transduction network that are removed from the network during the search of master regulators (see more details about the algorithm in the Methods section). These master regulators appear to be the key candidates for therapeutic targets as they have a master effect on regulation of intracellular pathways that activate the pathological process of our study. The identified master regulators are shown in Tables 11-12.

*Table 11. Master regulators that may govern the regulation of **up-regulated** genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, transcriptomics data.*

See full table →

ID	Master molecule name	Gene symbol	Gene description	logFC	Total rank
MO000018003	PP2A(h)	PPP2CA, PPP2R3A, PPP2R3B, PPP2R5A, PPP2R5B, PPP2R5C, PPP2R5D	protein phosphatase 2 catalytic subunit alpha, protein phosphatase 2 regulatory subunit B''alpha, pr...	1.93	232
MO000090791	RPTPzeta-L(h)	PTPRZ1	protein tyrosine phosphatase receptor type Z1	3.37	267
MO000017291	integrins	ITGA1, ITGA2B, ITGA3, ITGA4, ITGA5, ITGA6, ITGA8, ITGA9, ITGAL, ITGAV, ITGB1, ITGB2, ITGB3, ITGB4, I...	integrin subunit alpha 1, integrin subunit alpha 2b, integrin subunit alpha 3, integrin subunit alph...	3.47	295
MO000019674	p110alpha(h)	PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	2.32	302
MO000032571	RhoC(h)	RHOC	ras homolog family member C	3.09	319
MO000031006	ATM(h)	ATM	ATM serine/threonine kinase	2.15	453
MO000030928	DNA-PKcs(h):XRCC6(h)	PRKDC, XRCC6	X-ray repair cross complementing 6, protein kinase, DNA-activated, catalytic subunit	1.98	461
MO000151172	TRIM18(h)	MID1	midline 1	1.43	497
MO000020249	26S proteasome(h)	PSMA7, PSMC2, PSMC3, PSMC5, PSMD4, PSMD5	proteasome 20S subunit alpha 7, proteasome 26S subunit, ATPase 2, proteasome 26S subunit, ATPase 3, ...	1.71	532
MO000279620	EGF-ECD:(EGFR-p170{pY1016}{pY1092}{pY1110}{pY1172}{pY1197})2:Grb-2:Sos1{pY}:Ras-C{farC}{metC}:GTP:Ra...	CSNK2A1, CSNK2A2, CSNK2B, EGF, EGFR, GRB2, HRAS, KRAS, KSR1, MAP2K2, NRAS, RAF1, SOS1	HRas proto-oncogene, GTPase, KRAS proto-oncogene, GTPase, NRAS proto-oncogene, GTPase, Raf-1 proto-o...	4.92	541

*Table 12. Master regulators that may govern the regulation of **down-regulated** genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, transcriptomics data.*

See full table →

ID	Master molecule name	Gene symbol	Gene description	logFC	Total rank
MO000033299	pim1(h)	PIM1	Pim-1 proto-oncogene, serine/threonine kinase	-2.6	77
MO000033396	DUSP5(h)	DUSP5	dual specificity phosphatase 5	-4.43	80
MO000022222	MKP-1(h)	DUSP1	dual specificity phosphatase 1	-2.29	85
MO000056491	KAT2B(h)	KAT2B	lysine acetyltransferase 2B	-2.74	89
MO000137304	DUSP5(h)	DUSP5	dual specificity phosphatase 5	-4.43	114
MO000036550	MKP-7(h)	DUSP16	dual specificity phosphatase 16	-1.71	119
MO000103285	MKP-7-isoform1(h)	DUSP16	dual specificity phosphatase 16	-1.71	148
MO000102190	PTK6-isoform1(h)	PTK6	protein tyrosine kinase 6	-3.89	153
MO000041952	calpain-1(h)	CAPN1	calpain 1	-1.23	163
MO000021356	EGFR(h) {pY}	EGFR, ERBB2, ERBB3, ERBB4	epidermal growth factor receptor, erb-b2 receptor tyrosine kinase 2, erb-b2 receptor tyrosine kinase...	-2.19	173

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.

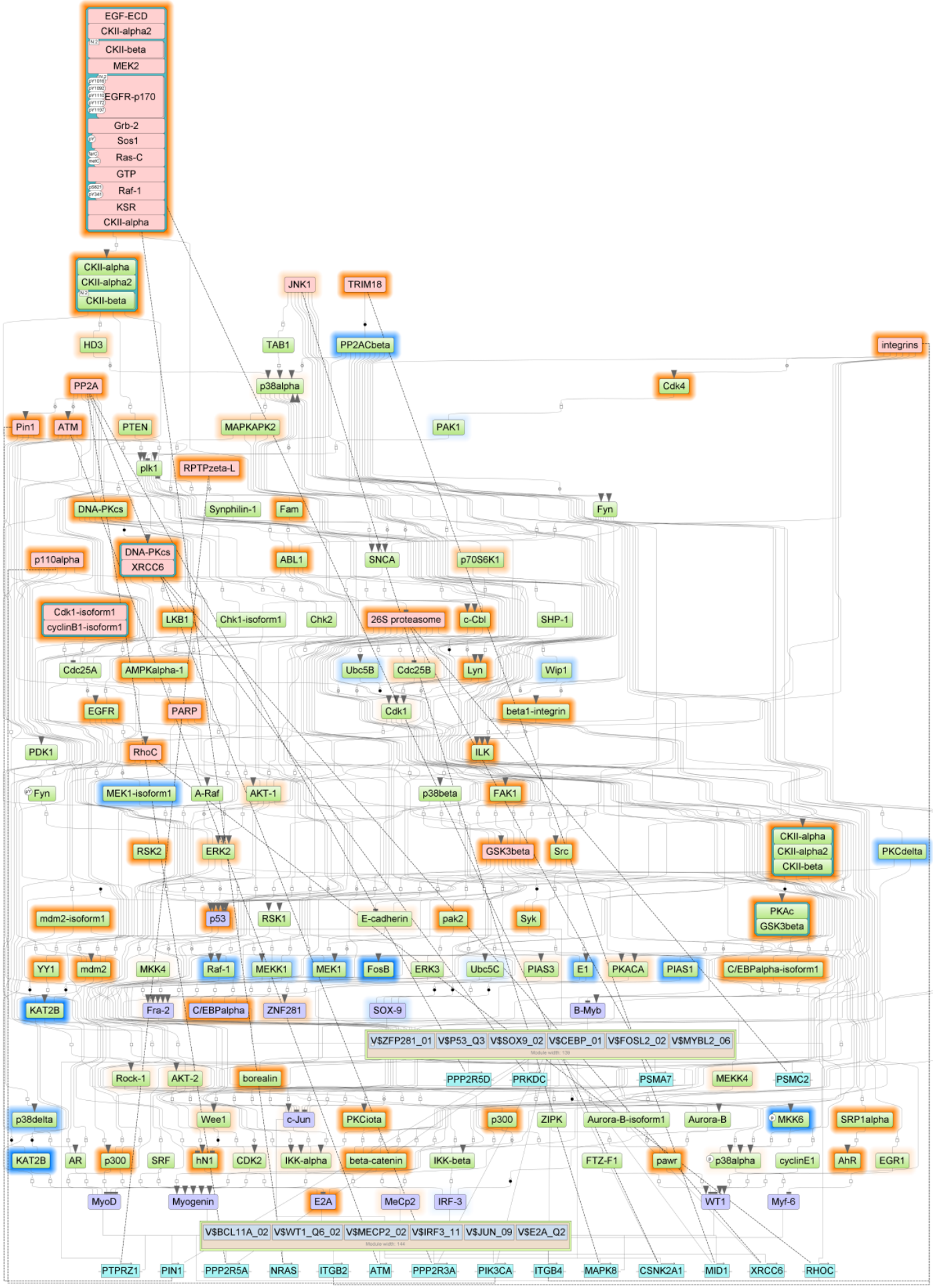


Figure 9. Diagram of intracellular regulatory signal transduction pathways of up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, 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 →

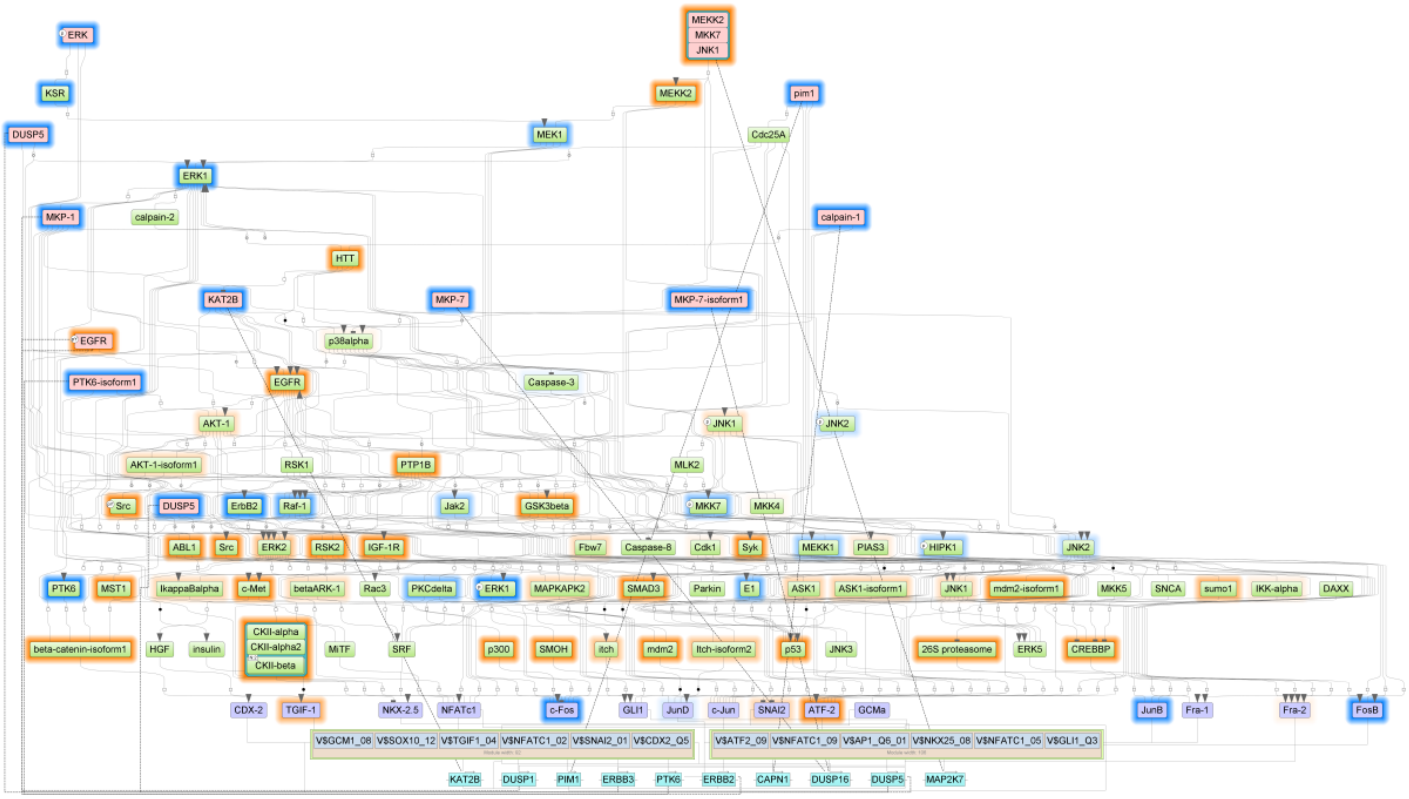


Figure 10. Diagram of intracellular regulatory signal transduction pathways of down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate 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 13. 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
ITGA3	integrin subunit alpha 3	2	3.47	295
ITGB5	integrin subunit beta 5	2	3.47	295
ITGA6	integrin subunit alpha 6	1	3.47	295
PSMA7	proteasome 20S subunit alpha 7	2	1.71	532
NTRK2	neurotrophic receptor tyrosine kinase 2	43	6.48	578
ODC1	ornithine decarboxylase 1	3	7.17	585

Table 14. 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.*

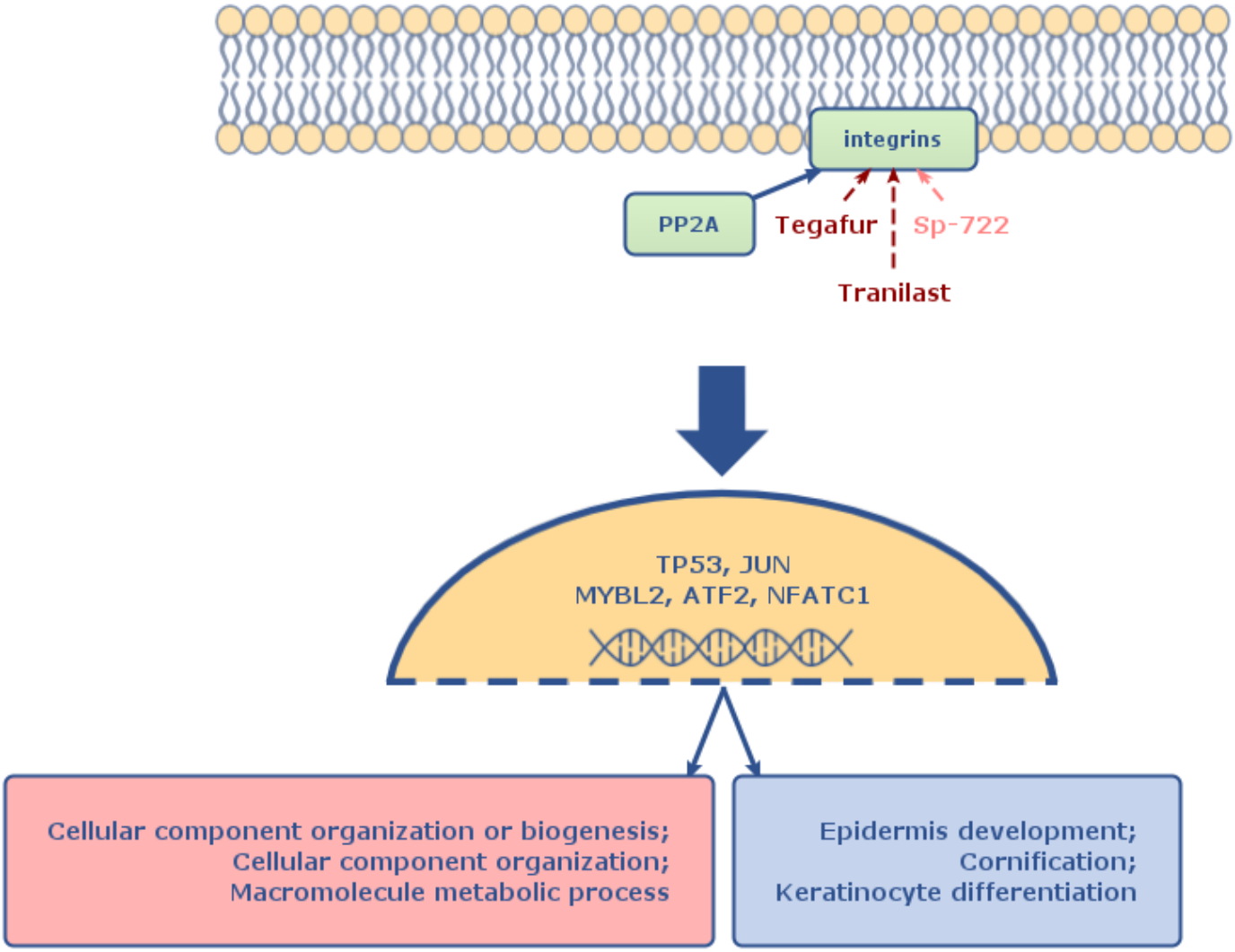
See full table →

Gene symbol	Gene Description	Druggability score	logFC	Total rank
ITGA3	integrin subunit alpha 3	6.21	3.47	295
ITGB5	integrin subunit beta 5	6.21	3.47	295
ITGA6	integrin subunit alpha 6	6.21	3.47	295
ITGB6	integrin subunit beta 6	6.21	3.47	295
PSMC5	proteasome 26S subunit, ATPase 5	3.43	1.71	532
PSMD5	proteasome 26S subunit, non-ATPase 5	3.43	1.71	532

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:

- integrins
- PP2A

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: Tranilast, Tegafur and Sp-722, 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 16 and 17), 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 15. 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
Methotrexate	CCND1, NR3C1, BAX, BIRC5	66	7	Phase 3: Carcinoma, Squamous Cell, Acute Disease, Alopecia, Alopecia Areata, Anemia, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Anger, Anterior Wall Myocardial Infarction, Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis, Arteritis, Arthritis, Arthritis, Juvenile, Arthritis, Psoriatic, Arthritis, Rheumatoid, Asthma, Atherosclerosis, Autoimmune Diseases, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Carcinoma, Carcinoma, Transitional Cell, Cardiac Complexes, Premature, Cardiovascular Diseases, Central Nervous System Neoplasms, Chikungunya Fever, Choriocarcinoma, Choroid Plexus Neoplasms, Chronic Urticaria, Coronary Artery Disease, Coronary Disease, Crohn Disease, Dermatitis, Dermatitis, Atopic, Dermatomyositis, Down Syndrome, Drug-Related Side Effects and Adverse Reactions, Eczema, Edema, Encephalomyelitis, Ependymoma, Erythema, Fibrosis, Gestational Trophoblastic Disease, Giant Cell Arteritis, Glioma, Glycogen Storage Disease, Glycogen Storage Disease Type I, Glycogen Storage Disease Type II, Graft vs Host Disease, Granuloma, Granulomatosis with Polyangiitis, Head and Neck Neoplasms, Hearing Loss, Hearing Loss, Sensorineural, Heart Failure, Hematologic Neoplasms, Histiocytosis, Histiocytosis, Langerhans-Cell, Hodgkin Disease, Hydatidiform Mole, Immune System Diseases, Infarction, Inflammation, Inflammatory Breast Neoplasms, Ischemia, Joint Diseases, Kidney Neoplasms, Leukemia, Leukemia, B-Cell, Leukemia, Biphenotypic, Acute, Leukemia, Erythroblastic, Acute, Leukemia, Large Granular Lymphocytic, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Megakaryoblastic, Acute, Leukemia, Monocytic, Acute, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Acute, Leukemia,	Carcinoma, Squamous Cell (FDA)

				Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Promyelocytic, Acute, Leukemia, T-Cell, Liver Cirrhosis, Liver Cirrhosis, Biliary, Lupus Erythematosus, Systemic, Lymphohistiocytosis, Hemophagocytic, Lymphoma, Lymphoma, B-Cell, Lymphoma, Extranodal NK-T-Cell, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Non-Hodgkin, Lymphoma, Primary Cutaneous Anaplastic Large Cell, Lymphoma, T-Cell, Lymphoma, T-Cell, Cutaneous, Macular Edema, Medulloblastoma, Meningeal Carcinomatosis, Mucositis, Multiple Myeloma, Multiple Sclerosis, Mycoses, Mycosis Fungoides, Myelitis, Myelodysplastic Syndromes, Myelodysplastic-Myeloproliferative Diseases, Myeloproliferative Disorders, Myocardial Infarction, Myocardial Ischemia, Myositis, Neoplasm Metastasis, Neoplasms, Neoplasms, Connective Tissue, Neoplasms, Connective and Soft Tissue, Neoplasms, Second Primary, Neoplasms, Squamous Cell, Nervous System Neoplasms, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Osteoarthritis, Osteopetrosis, Osteosarcoma, Pars Planitis, Pemphigoid, Bullous, Peritoneal Fibrosis, Polymyalgia Rheumatica, Polymyositis, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Precursor T-Cell Lymphoblastic Leukemia-Lymphoma, Pregnancy, Ectopic, Preleukemia, Psoriasis, Rage, Ranula, Recurrence, Retroperitoneal Fibrosis, Rhabdoid Tumor, ST Elevation Myocardial Infarction, Sarcoidosis, Sarcoma, Sclerosis, Spondylarthritis, Spondylarthropathies, Spondylitis, Spondylitis, Ankylosing, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Syndrome, Trophoblastic Neoplasms, Ureteral Neoplasms, Urethral Neoplasms, Urinary Bladder Neoplasms, Urticaria, Uterine Cervical Neoplasms, Uveitis, Uveitis, Intermediate, Vascular Diseases, Vasculitis, Vitiligo, Vitreoretinopathy, Proliferative	
Cisplatin	CDK1	15	12	Phase 4: Carcinoma, Squamous Cell, Adenocarcinoma, Anemia, Carcinoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Small Cell, Esophageal Neoplasms, Head and Neck Neoplasms, Lung Neoplasms, Lymphoma, Lymphoma, Mantle-Cell, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, Medulloblastoma, Neoplasms, Neoplasms, Germ Cell and Embryonal, Small Cell Lung Carcinoma, Uterine Cervical Neoplasms	Carcinoma, Squamous Cell (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 16. 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	MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, BIRC5, PKMYT1, MAPK1, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA,	98	8	Phase 3: Carcinoma, Squamous Cell, 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, 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, Ovarian Neoplasms, Pancreatic Intraductal Neoplasms, Pancreatic Neoplasms, Rectal Neoplasms, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Thoracic Neoplasms

	MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R			
Sorafenib	ROCK2, MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, SGK1, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, RPS6KB1, MAPK1, HIPK2, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2,	97	4	Phase 2: Carcinoma, Squamous Cell, 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, 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,

	ABL2, CSF1R			Neurofibrosarcoma, Oropharyngeal Neoplasms, Osteosarcoma, Ovarian Neoplasms, 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
Gefitinib	MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, MAPK1,	96	7	Phase 3: Carcinoma, Squamous Cell, Adenocarcinoma, Adenocarcinoma of Lung, Adenocarcinoma, Bronchiolo-Alveolar, Brain Neoplasms, Carcinoma, Carcinoma, Non-Small-Cell Lung, Colorectal Neoplasms, Head and Neck Neoplasms, Lung Neoplasms, Neoplasm Metastasis, Neoplasms, Neoplasms, Second Primary, Rectal Neoplasms, Squamous Cell Carcinoma of Head and Neck, Thoracic Neoplasms, Urinary Bladder Neoplasms

	FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R			
Lapatinib	MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, BIRC5, PKMYT1, MAPK1, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2,	95	3	Phase 2: Carcinoma, Squamous Cell, Adenocarcinoma, Adenoma, Astrocytoma, Bile Duct Neoplasms, Brain Neoplasms, Breast Diseases, Breast Neoplasms, Breast Neoplasms, Male, Carcinoma, Carcinoma, Acinar Cell, Carcinoma, Adenoid Cystic, Carcinoma, Ductal, Carcinoma, Ductal, Breast, Carcinoma, Hepatocellular, Carcinoma, Mucoepidermoid, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Small Cell, Carcinoma, Transitional Cell, Carcinoma, Verrucous, Central Nervous System Neoplasms, Cholangiocarcinoma, Colorectal Neoplasms, Cysts, Dermoid Cyst, Diarrhea, Digestive System Neoplasms, Endometrial Neoplasms, Ependymoma, Esophageal Neoplasms, Esophageal Squamous Cell Carcinoma, Fibroma, Gallbladder Neoplasms, Gastrointestinal Neoplasms, Glioblastoma, Glioma, Gliosarcoma, Head and Neck Neoplasms, Inflammatory Breast Neoplasms, Intestinal Neoplasms, Laryngeal Diseases, Laryngeal Neoplasms, Liver Neoplasms, Lung Neoplasms, Medulloblastoma, Melanoma, Nasopharyngeal Carcinoma, Neoplasm Metastasis, Neoplasms, Neoplasms, Second Primary, Neoplasms, Unknown Primary, Neoplastic Cells, Circulating, Nervous System Neoplasms, Neurilemmoma, Neurofibroma, Neurofibromatoses, Neurofibromatosis 1, Neurofibromatosis 2, Neuroma, Neuroma, Acoustic, Oligodendroglioma, Oropharyngeal Neoplasms, Pancreatic Neoplasms, Paranasal Sinus Neoplasms, Pharyngeal Neoplasms, Pituitary Diseases, Pituitary Neoplasms, Prolactinoma, Prostatic Neoplasms, Rectal Neoplasms, Recurrence, Salivary Gland Neoplasms, Sarcoma, Small Cell Lung Carcinoma, Spinal Cord Neoplasms, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Thymoma, Tongue Neoplasms, Urinary Bladder Neoplasms, Uterine Cervical Neoplasms, Uterine Neoplasms

	CLK1, CDK2, ABL2, CSF1R			
Sunitinib	MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, MAPK1, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R	94	4	Phase 2: Carcinoma, Squamous Cell, 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, 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, Ovarian Neoplasms, 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 17. 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	ROCK2, MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, CDK4, SYK, SGK1, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, CDK1, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, RPS6KB1, MAPK1, HIPK2, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R	85	Phase 2: ACTH-Secreting Pituitary Adenoma, Adenoma, Carcinoma, Non-Small-Cell Lung, Cystic Fibrosis, Cysts, Fibrosis, Pituitary ACTH Hypersecretion, Pituitary Neoplasms
Tofacitinib	ROCK2, MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, SGK1, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, RPS6KB1, MAPK1, FGFR3, NTRK2,	85	Phase 4: Alopecia, Alopecia Areata, Aortic Arch Syndromes, Arteritis, Arthritis, Arthritis, Psoriatic, Arthritis, Rheumatoid, COVID-19, Colitis, Colitis, Ulcerative, Disease, Granuloma, Granulomatosis with Polyangiitis, Infections, Lung Diseases, Lung Diseases, Interstitial, Necrosis, Rheumatic Fever, ST Elevation Myocardial Infarction, Spondylarthritis, Systemic Vasculitis, Takayasu Arteritis, Ulcer, Vasculitis

	YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R		
1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea	ROCK2, MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, SGK1, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, RPS6KB1, MAPK1, HIPK2, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R	84	N/A
ruboxistaurin	ROCK2, MAP4K4, MARK3, ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, SYK, SGK1, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, MET, CSNK1E, EPHA4, TTK, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, RPS6KB1, MAPK1, HIPK2, FGFR3, NTRK2, YES1, BRAF, FER, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R	84	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
Flavopiridol	MAP4K4, MARK3,	84	Phase 2: Adenocarcinoma, Brain Abscess, Breast

	ABL1, NEK7, PAK2, PRKACA, GSK3B, MAP3K11, CDK4, SYK, EIF2AK2, TYK2, IGF1R, JAK1, MAPK8, TGFBR1, SRC, MAP3K5, CSNK2A2, PRKD3, CSNK1G2, STK11, CSNK1G1, MAP4K3, WEE1, STK4, PTK2, LYN, MAPKAPK2, CSNK2A1, AKT2, PLK4, STK3, RPS6KA3, CAMK2G, CDK6, MET, CSNK1E, EPHA4, TTK, CDK1, PRKAA1, CSNK1D, EGFR, PTK2B, HCK, AKT1, AURKA, MAP3K20, PKMYT1, MAPK1, FGFR3, NTRK2, YES1, BRAF, FER, XIAP, PIK3CA, MAP3K4, TGFBR2, CLK1, CDK2, ABL2, CSF1R	Neoplasms, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Embolism, Endometrial Neoplasms, Esophageal Neoplasms, Germinoma, Granuloma, Head and Neck Neoplasms, Hodgkin Disease, Hypereosinophilic Syndrome, Immunoblastic Lymphadenopathy, Kidney Neoplasms, Leukemia, Leukemia, Basophilic, Acute, Leukemia, Eosinophilic, Acute, Leukemia, Erythroblastic, Acute, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Megakaryoblastic, Acute, Leukemia, Monocytic, Acute, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Acute, Leukemia, Prolymphocytic, Leukemia, T-Cell, Leukemia-Lymphoma, Adult T-Cell, Liver Neoplasms, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, B-Cell, Lymphoma, B-Cell, Marginal Zone, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Cutaneous, Lymphomatoid Granulomatosis, Melanoma, Multiple Myeloma, Mycoses, Mycosis Fungoides, Myelodysplastic Syndromes, Neoplasms, Neoplasms, Germ Cell and Embryonal, Neoplasms, Plasma Cell, Ovarian Neoplasms, Pancreatic Neoplasms, Peritoneal Neoplasms, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Prostatic Neoplasms, Sarcoma, Seminoma, Sezary Syndrome, Stomach Neoplasms, Testicular Neoplasms, Thromboembolism, Waldenstrom Macroglobulinemia

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 18. 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
{(2Z)-4-AMINO-2-[(4-METHOXYPHENYL)IMINO]-2,3-DIHYDRO-1,3-THIAZOL-5-YL}(4-METHOXYPHENYL)METHANONE	CCND1, CDK6, CCND3, CCNB1, CLK1, CCNA2, CDK1, CDK2, CCNB2, CDK4	100	7.59
Iodophenyl	RPS6KA3, ROCK2, MAP4K4, MARK3, NEK7, PAK2, GSK3B, CSNK1E, PRKAA1, ILK, CSNK1D, SGK1, EIF2AK2, TAOK2, AKT1, AURKA, TAOK1, ATM, LMTK2, PKMYT1, RPS6KB1, TBK1, ATR, HIPK2, MTOR, CSNK2A2, CSNK1G2, ROCK1, PRKDC, STK11, BRAF, BUB1, MAP4K3, CSNK1G1, STK4, PIK3CA, MAPKAPK2, IRAK1, CSNK2A1, AKT2, STK3	100	6.42
3-Bromo-7-Nitroindazole	RPS6KA3, CDK6, CCND3, CCNB1, GSK3B, CDK1, CCNB2, CDK4, CCND1, PTK2B, AKT1, CCNA2, CDK2, AKT2, RPS6KB1	100	6.14
O6-CYCLOHEXYLMETHOXY-2-(4'-SULPHAMOYLANILINO) PURINE	CCND1, CDK6, CCND3, CCNB1, CCNA2, CDK1, CDK4, CCNB2, CDK2	100	5.68
6-CYCLOHEXYLMETHYLOXY-5-NITROSO-PYRIMIDINE-2,4-DIAMINE	CCND1, CDK6, MTOR, CCND3, CCNB1, CCNA2, CDK1, CDK4, CCNB2, CDK2	100	5.64

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Erlotinib, seliciclib and {(2Z)-4-AMINO-2-[(4-METHOXYPHENYL)IMINO]-2,3-DIHYDRO-1,3-THIAZOL-5-YL}(4-METHOXYPHENYL)METHANONE. These drugs were selected for acting on the following targets: NTRK2 and CCNB2, 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 19. 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	82
Abiraterone	Prostatic Neoplasms, Castration-Resistant	N/I
Abiraterone acetate	Prostatic Neoplasms, Castration-Resistant	N/I
Acalabrutinib	Lymphoma, Mantle-Cell	N/I
Acitretin	Psoriasis	N/I
Ado-trastuzumab emtansine	Breast Neoplasms|Neoplasms	71
Afatinib	Carcinoma, Non-Small-Cell Lung	46
Aflibercept	Colorectal Neoplasms|Diabetic Retinopathy|Edema|Vascular Diseases|Wet Macular Degeneration	8
Alectinib	Carcinoma, Non-Small-Cell Lung	22
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	83
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	76
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	38
Azacitidine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes|Preleukemia|Syndrome	52
Belinostat	Lymphoma, T-Cell, Peripheral	54
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	17
Bexarotene	Lymphoma, T-Cell|Lymphoma, T-Cell, Cutaneous	13
Bicalutamide	Prostatic Neoplasms	35
Binimetinib	Melanoma	N/I
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	63
Bosutinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	77
Brentuximab vedotin	Hodgkin Disease|Lymphoma|Lymphoma, Large-Cell, Anaplastic|Lymphoma, T-Cell, Peripheral	N/I
Brigatinib	Carcinoma, Non-Small-Cell Lung	48
Buserelin	Prostatic Neoplasms	N/I
Cabazitaxel	Prostatic Neoplasms, Castration-Resistant	80
Cabergoline	Drug-Related Side Effects and Adverse Reactions|Pituitary	N/I

	Neoplasms	
Cabozantinib	Thyroid Neoplasms	40
Capecitabine	Breast Neoplasms|Colonic Neoplasms|Colorectal Neoplasms	14
Carboplatin	Carcinoma, Non-Small-Cell Lung|Lung Neoplasms|Neoplasms|Neuroendocrine Tumors|Ovarian Neoplasms|Retinoblastoma	N/I
Carfilzomib	Multiple Myeloma	59
Carmustine	Astrocytoma|Glioblastoma|Hodgkin Disease|Medulloblastoma|Multiple Myeloma|Neoplasms	N/I
Ceritinib	Carcinoma, Non-Small-Cell Lung	71
Cetuximab	Colorectal Neoplasms	33
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	15
Cladribine	Leukemia, Hairy Cell	8
Clofarabine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	39
Cobimetinib	Melanoma	N/I
Copanlisib	Lymphoma, Follicular	91
Crizotinib	Carcinoma, Non-Small-Cell Lung	91
Cyproterone acetate	Prostatic Neoplasms	N/I
Dabrafenib	Melanoma	29
Dacomitinib	Carcinoma, Non-Small-Cell Lung	87
Daratumumab	Multiple Myeloma	N/I
Dasatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid, Chronic-Phase|Precursor Cell Lymphoblastic Leukemia-Lymphoma	89
Decitabine	Anemia, Refractory|Anemia, Refractory, with Excess of Blasts|Leukemia, Myelomonocytic, Chronic|Myelodysplastic Syndromes	6
Degarelix	Cardiovascular Diseases|Prostatic Neoplasms|Vascular Diseases	13
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	18
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	41
Doxorubicin	Neoplasms|Multiple Myeloma|Carcinoma, Ovarian Epithelial|Ovarian Neoplasms|Leukemia, Lymphoid|Breast Neoplasms|Lymphoma, Follicular|Thyroid Neoplasms|Triple Negative Breast Neoplasms|Glioma	75
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	30
Elotuzumab	Multiple Myeloma	4
Enasidenib	Leukemia, Myeloid, Acute	N/I
Encorafenib	Colorectal Neoplasms|Melanoma	39

Enfortumab vedotin	Carcinoma, Transitional Cell|Neoplasms	N/I
Entrectinib	Carcinoma, Non-Small-Cell Lung	52
Enzalutamide	Prostatic Neoplasms|Prostatic Neoplasms, Castration-Resistant	N/I
Epirubicin	Breast Neoplasms	39
Erdafitinib	Urinary Bladder Neoplasms	52
Eribulin	Breast Neoplasms|Drug-Related Side Effects and Adverse Reactions|Neoplasms	N/I
Erlotinib	Carcinoma, Non-Small-Cell Lung|Neoplasms|Pancreatic Neoplasms	98
Erlotinib hydrochloride	Carcinoma, Non-Small-Cell Lung|Gastrointestinal Stromal Tumors	N/I
Estramustine	Prostatic Neoplasms	15
Ethinyl Estradiol	Acne Vulgaris|Neoplasms	17
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	88
Exemestane	Breast Neoplasms	N/I
Fedratinib	Primary Myelofibrosis	N/I
Finasteride	Hyperplasia|Neoplasms|Prostatic Hyperplasia	N/I
Flavopiridol	Leukemia, Lymphocytic, Chronic, B-Cell	84
Fluorouracil	Skin Neoplasms|Neoplasms, Basal Cell|Neoplasms, Second Primary|Neoplasms, Squamous Cell|Neoplasms|Colorectal Neoplasms|Pancreatic Neoplasms	80
Fluoxymesterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	28
Flutamide	Premenstrual Dysphoric Disorder|Premenstrual Syndrome|Prostatic Neoplasms	60
Fulvestrant	Breast Neoplasms	13
Gefitinib	Carcinoma, Non-Small-Cell Lung	96
Gemcitabine	Breast Neoplasms|Carcinoma, Non-Small-Cell Lung|Ovarian Neoplasms|Pancreatic Neoplasms	64
Gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	N/I
Gilteritinib	Leukemia, Myeloid, Acute	67
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	75
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	73
Idarubicin	Leukemia, Myeloid, Acute	N/I
Idelalisib	Leukemia, Lymphocytic, Chronic, B-Cell|Lymphoma, Follicular	34
Ifosfamide	Neoplasms	N/I
Imatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Mastocytosis, Systemic|Neoplasms	90
Inotuzumab ozogamicin	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	N/I
Ipilimumab	Carcinoma, Renal Cell|Melanoma	N/I
Irinotecan	Colorectal Neoplasms	79
Ivosidenib	Leukemia, Myeloid, Acute	N/I
Ixabepilone	Breast Neoplasms	N/I
Ixazomib	Multiple Myeloma	N/I
Lapatinib	Breast Neoplasms	95

Larotrectinib	Neoplasm Metastasis	65
Lenalidomide	Brain Abscess|Lupus Erythematosus, Cutaneous|Myelodysplastic Syndromes|Neoplasms, Plasma Cell	N/I
Lenvatinib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	16
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	71
Lorlatinib	Carcinoma, Non-Small-Cell Lung	75
Masoprocol	Keratosis, Actinic	N/I
Medroxyprogesterone Acetate	Depression|Depression, Postpartum|Depressive Disorder|Metrorrhagia|Neoplasms|Uterine Hemorrhage	57
Megestrol acetate	Acquired Immunodeficiency Syndrome|Bites and Stings|Breast Neoplasms|Pain|Wasting Syndrome	22
Methotrexate	Neoplasms|Breast Neoplasms|Head and Neck Neoplasms|Ovarian Neoplasms|Lymphoma, T-Cell, Peripheral|Brain Neoplasms|Colorectal Neoplasms|Neuroblastoma|Carcinoma, Squamous Cell	66
Methyltestosterone	Breast Neoplasms|Hypogonadism|Puberty, Delayed	N/I
Midostaurin	Leukemia, Mast-Cell|Leukemia, Myeloid, Acute|Mastocytosis, Systemic	82
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	12
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	74
Nilotinib	Blast Crisis|Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Leukemia, Myeloid, Chronic-Phase	51
Nilutamide	Prostatic Neoplasms	N/I
Nintedanib	Fibrosis|Idiopathic Pulmonary Fibrosis	76
Niraparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms	73
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	2
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	61
Olaratumab	Sarcoma	N/I

Osimertinib	Carcinoma, Non-Small-Cell Lung	55
Oxaliplatin	Colonic Neoplasms|Colorectal Neoplasms|Neoplasms|Rectal Neoplasms	54
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	85
Palbociclib	Breast Neoplasms	78
Panitumumab	Colorectal Neoplasms	68
Panobinostat	Multiple Myeloma	6
Pazopanib	Carcinoma|Carcinoma, Renal Cell|Sarcoma	94
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	48
Pertuzumab	Breast Neoplasms	40
Pomalidomide	Multiple Myeloma	6
Ponatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive|Precursor Cell Lymphoblastic Leukemia-Lymphoma	76
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	72
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	10
Rucaparib	Carcinoma, Ovarian Epithelial|Fallopian Tube Neoplasms|Peritoneal Neoplasms|Prostatic Neoplasms, Castration-Resistant	60
Ruxolitinib	Graft vs Host Disease|Polycythemia|Polycythemia Vera|Primary Myelofibrosis|Thrombocytosis	51
Selinexor	Multiple Myeloma	58
Selumetinib	Neurofibromatosis 1	N/I
Siltuximab	Giant Lymph Node Hyperplasia	N/I
Sirolimus	Angiomyolipoma|Constriction, Pathologic|Coronary Restenosis|Eye Diseases|Immune System Diseases|Kidney Failure, Chronic|Lipoma|Tuberous Sclerosis	93
Sonidegib	Carcinoma, Basal Cell	N/I
Sorafenib	Carcinoma, Hepatocellular|Carcinoma, Renal Cell|Thyroid Neoplasms	97
Sunitinib	Adenoma|Carcinoma, Renal Cell|Digestive System Neoplasms|Gastrointestinal Neoplasms|Gastrointestinal Stromal Tumors|Intestinal Neoplasms	94
Talazoparib	Breast Neoplasms	54
Tamoxifen	Breast Diseases|Cystic Fibrosis|Cysts|Fibroadenoma|Fibrocystic Breast Disease|Hemorrhage|Menorrhagia|Menstruation Disturbances|Metrorrhagia|Neoplasms	55
Tamsulosin	Calculi|Coronary Artery Disease|Heart Diseases|Hernia|Hernia,	N/I

	Inguinal|Inflammation|Ischemia|Lithiasis|Lower Urinary Tract Symptoms|Myocardial Ischemia|Prostatic Hyperplasia|Ureteral Calculi|Urinary Calculi|Urolithiasis|Urologic Diseases	
Temozolomide	Astrocytoma|Nervous System Neoplasms	22
Temsirolimus	Carcinoma, Renal Cell	90
Teniposide	Precursor Cell Lymphoblastic Leukemia-Lymphoma	49
Thalidomide	Brain Abscess|Immune System Diseases|Multiple Myeloma|Neoplasms, Plasma Cell	26
Tivozanib	Carcinoma, Renal Cell	3
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	2
Toremifene	Breast Neoplasms	N/I
Trabectedin	Leiomyosarcoma|Liposarcoma	N/I
Trametinib	Carcinoma, Non-Small-Cell Lung|Melanoma	70
Trastuzumab	Breast Neoplasms|Neoplasms	57
Tretinoin	Lentigo	79
Triptorelin	Fatty Liver|Hypogonadism|Infertility, Female|Prostatic Neoplasms	69
Tucatinib	Breast Neoplasms	14
Valrubicin	Urinary Bladder Neoplasms	N/I
Vandetanib	Thyroid Neoplasms	90
Vemurafenib	Melanoma	41
Venetoclax	Leukemia, Lymphocytic, Chronic, B-Cell|Leukemia, Myeloid, Acute	N/I
Vinblastine	Glioma	1
Vincristine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	18
Vinorelbine	Carcinoma, Non-Small-Cell Lung	35
Vismodegib	Carcinoma, Basal Cell	N/I
Vorinostat	Lymphoma, T-Cell, Cutaneous	69
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 data set that contains *transcriptomics* data. The study is done in the context of *Squamous Cell Carcinoma*. 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 {(2Z)-4-AMINO-2-[(4-METHOXYPHENYL)IMINO]-2,3-DIHYDRO-1,3-THIAZOL-5-YL}(4-METHOXYPHENYL)METHANONE

These drugs were selected for acting on the following targets: NTRK2 and CCNB2, 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: Tranilast, Tegafur and Sp-722. 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.

- integrins
- PP2A

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.

8. References

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Supplementary material

1. Supplementary table 1 - Detailed report. Composite modules and master regulators (up-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue).

2. Supplementary table 2 - Detailed report. Composite modules and master regulators (down-regulated genes in Experiment: Squamous Cell Carcinoma vs. Control: Non-tumour tissue).
3. Supplementary table 3 - Detailed report. Pharmaceutical compounds and drug targets.

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