

DYRK1B and PCBD2 are promising druggable targets for treating Colorectal Neoplasms that control activity of AR, GCM1 and ZEB1 transcription factor on promoters of genes carrying sequence variations

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



Abstract

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

From the data set analyzed in this study, we found the following TFs to be potentially involved in the regulation of the genes carrying sequence variations: AR, GCM1 and ZEB1. The subsequent network analysis suggested

- Jak1
- PML
- MKK3:Dyrk1B:PHS 2:HNF-1alpha
- 26S proteasome

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: Vatalanib, seliciclib, Camptothecin and Iodophenyl.

1. Introduction

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

Conventional approaches of statistical "-omics" data analysis provide only very limited information about the causes of the observed phenomena and therefore contribute little to the understanding of the pathological molecular mechanism. In contrast, the "upstream analysis" method [1-4] applied here has been devised to provide a casual interpretation of the data obtained for a pathology state. This approach comprises two major steps: (1) analysing promoters and enhancers of genes carrying sequence variations for the transcription factors (TFs) involved in their regulation and, thus, important for the process under study; (2) re-constructing the signaling pathways that activate these TFs and identifying master regulators at the top of such pathways. For the first step, the database TRANSFAC® [6] is employed together with the

TF binding site identification algorithms Match [7] and CMA [8]. The second step involves the signal transduction database TRANSPATH® [9] and special graph search algorithms [10] implemented in the software "Genome Enhancer".

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

2. Data

For this study the following experimental data was used:

Table 1. Experimental datasets used in the study

File name	Data type
CRC_variants	Genomics

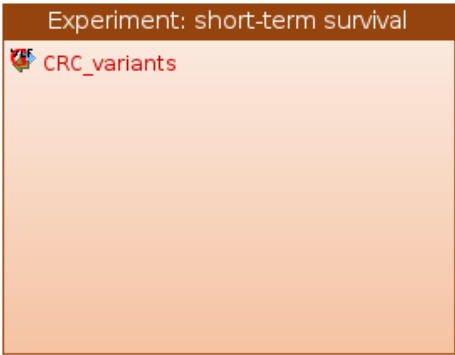


Figure 1. Annotation diagram of experimental data used in this study. With the colored boxes we show those sub-categories of the data that are compared in our analysis.

3. Results











We have analyzed the following condition: Experiment: short-term survival.

3.1. Identification of target genes

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

Table 2. Top ten the most frequently mutated genes in Experiment: short-term survival.

[See full table →](#)

ID	Gene description	Gene symbol	Gene schematic representation	Number of variations	Gene weight	Weighted score
ENSG00000132570	pterin-4 alpha-carbinolamine dehydratase 2	PCBD2		172	417.02	625.54
ENSG00000228716	dihydrofolate reductase	DHFR		56	131.61	394.83
ENSG00000176890	thymidylate synthetase	TYMS		44	112.04	336.12
ENSG00000242086	MUC20 overlapping transcript	MUC20-OT1		147	331.16	331.16
ENSG00000003402	CASP8 and FADD like apoptosis regulator	CFLAR		43	110.11	330.34
ENSG00000169894	mucin 3A, cell surface associated	MUC3A		68	162.39	324.79
ENSG00000067057	phosphofructokinase, platelet	PFKP		92	215.16	322.74
ENSG00000204525	major histocompatibility complex, class I, C	HLA-C		71	158.24	316.47
ENSG00000248923	MT-ND5 pseudogene 11	MTND5P11		126	304.61	304.61
ENSG00000134086	von Hippel-Lindau tumor suppressor	VHL		43	96.68	290.05

3.2. Functional classification of genes

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

Figures 2-4 show the most significant categories.

The most frequently mutated genes in Experiment: short-term survival:

300 top mutated genes were taken for the mapping.

Full classification →



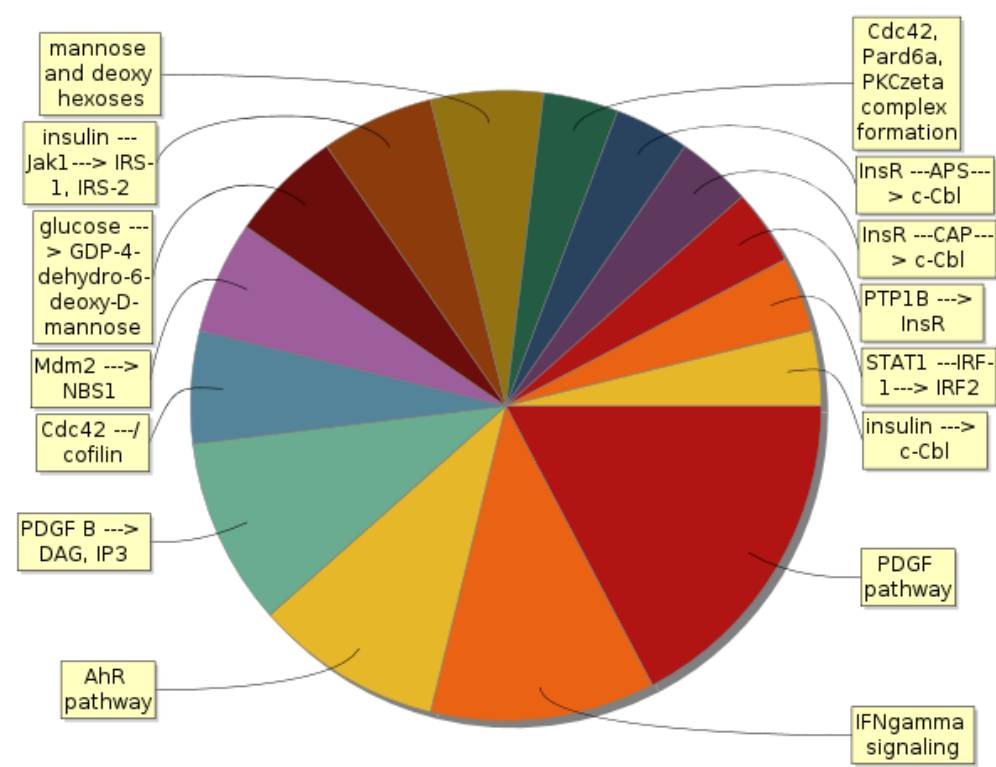


Figure 3. Enriched TRANSPATH® Pathways (2023.2) of the most frequently mutated genes in Experiment: short-term survival.
[Full classification →](#)

HumanPSD(TM) disease (2023.2)

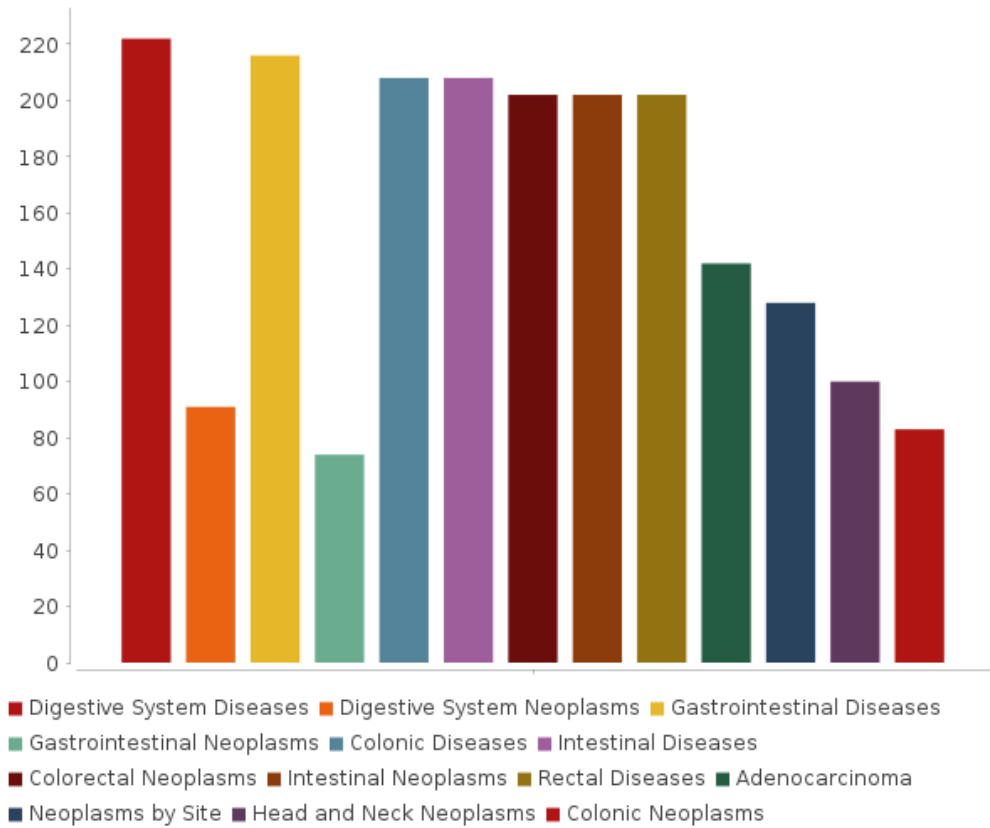
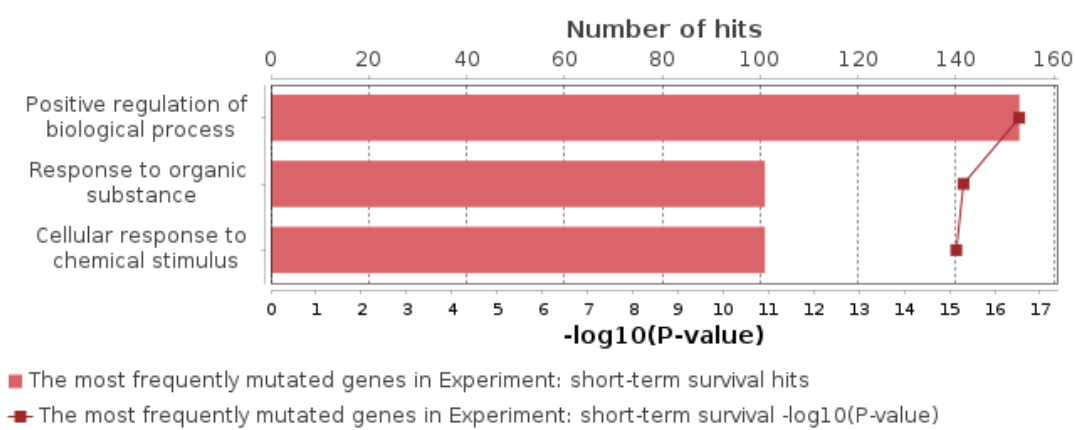


Figure 4. Enriched HumanPSD(TM) disease (2023.2) of the most frequently mutated genes in Experiment: short-term survival. The size of the bars correspond to the number of biomarkers of the given disease found among the input set.

[Full classification](#) →

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



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

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

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

In the current work, we use the Genomics data from the "Yes VCF track" track to predict positions of potential **enhancers** where the observed sequence variations may influence the gene expression in the pathology under study. We scan 5kb flanking regions and the body of all genes

caring the variations, with a sliding window of 1100bp size and find the position of the window with the maximal sum of the mutation weights, where we then perform the search for potential condition-specific enhancers (CMA model search).

We analyzed mutations that were revealed in the potential enhancers located upstream, downstream or inside the **target genes** (see Table 3). We identified 23927 mutations potentially affecting gene regulation. Table 4 shows the following lists of PWMs whose sites were lost or gained due to these mutations. Weighting of mutations was done in respect to the significance of the change in TF affinity binding to the sequence. Mutations that maximally affected the change of binding affinity received higher weights. These PWMs were put in focus of the CMA algorithm that constructs the model of the enhancers by specifying combinations of TF motifs (see more details of the algorithm in the Methods section).

Table 3. Mutations revealed in the most frequently mutated genes

[See full table](#) →

ID	Gene symbol	Gene schematic representation	Number of variations
ENSG00000132570	PCBD2		660
ENSG00000248923	MTND5P11		459
ENSG00000247627	MTND4P12		374
ENSG00000230021	ENSG00000230021		360
ENSG00000249119	MTND6P4		279
ENSG00000242086	MUC20-OT1		252
ENSG00000198868	MTND4LP30		245
ENSG00000263963	ENSG00000263963		245
ENSG00000154237	LRRK1		230
ENSG00000244921	MTCYBP18		225

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

[See full table](#) →

ID	P-value (gains)	P-value (losses)	yesCount (gains)	yesCount (losses)
V\$OTX2_06	3.65E-2	8.72E-14	25	70
V\$GSC_04	3.12E-2	3.07E-11	5	82
V\$ZBTB33_07	1.06E-2	8.27E-12	13	611
V\$ZBTB33_05	6.47E-3	6.92E-10	12	535
V\$MATH1_Q2	1.99E-3	3.66E-12	204	389
V\$E2A_03	1.6E-3	1.14E-12	231	387
V\$MAFG_12	3.44E-5	3.47E-10	34	1295
V\$E2F8_03	1.22E-6	1.32E-9	63	1618
V\$MYBL2_04	1.81E-12	1.1E-10	2161	2211
V\$CGBP_01	8.67E-23	4.62E-12	1755	1497
V\$E2F1DP1RB_01	1.88E-25	1.47E-9	3568	3831
V\$E2F4DP1_01	1.88E-25	1.14E-10	3568	4126
V\$SP1_02	1.18E-26	1.56E-2	250	6
V\$KLF8_Q5	6.06E-27	6.79E-3	313	214
V\$PAX5_Q6	4.25E-27	1.83E-3	1935	2567
V\$E2F1_Q6	3.25E-28	3.18E-2	2073	14
V\$E2F1DP2_01	2.9E-31	1.81E-11	3552	3615
V\$E2F3_12	1.1E-31	3.12E-2	1493	5
V\$E2F_Q4_02	1.46E-35	2.93E-2	2015	55
V\$E2F1_Q4	2.31E-36		903	

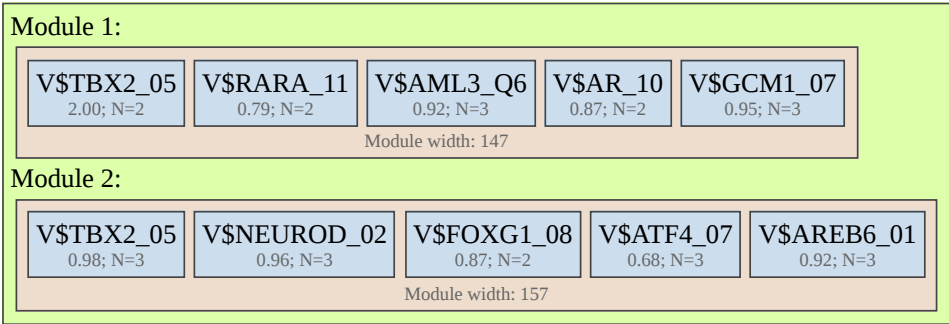
We applied the Composite Module Analyst (CMA) [8] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the enhancers by specifying combinations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

Enhancer model potentially involved in regulation of target genes (the most frequently mutated genes in Experiment: short-term survival).

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

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

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



Model score (-p*log10(pval)): 24.22
Wilcoxon p-value (pval): 4.79e-49
Penalty (p): 0.501
Average yes-set score: 8.58
Average no-set score: 6.57
AUC: 0.77
Separation point: 8.04
False-positive: 20.80%
False-negative: 37.00%

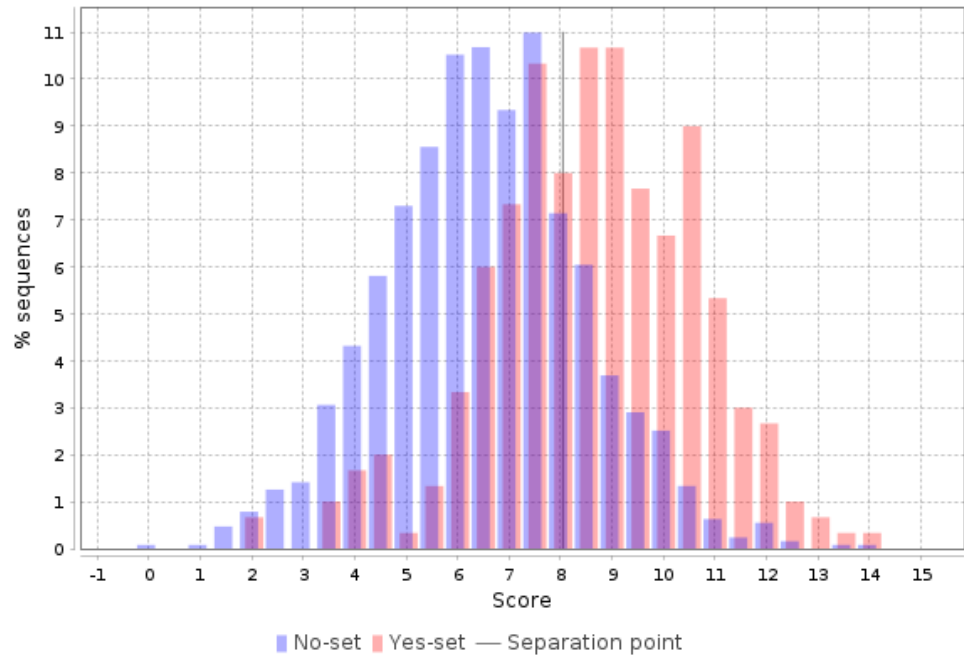


Table 5. List of top ten the most frequently mutated genes in Experiment: short-term survival with identified enhancers in their regulatory regions. **CMA score** - the score of the CMA model of the enhancer identified in the regulatory region.

[See full table](#) →

Ensembl IDs	Gene symbol	Gene description	CMA score	Factor names
ENSG00000145214	DGKQ	diacylglycerol kinase theta	16.99	ZEB1(h), ATF-4(h), TBX2(h), NeuroD1(h), AR(h), RAR-alpha(h), GCMa(h)...
ENSG00000141956	PRDM15	PR/SET domain 15	14.74	TBX2(h), ATF-4(h), FOXG1(h), NeuroD1(h), ZEB1(h), RAR-alpha(h), Runx2(h)...
ENSG00000132881	CPLANE2	ciliogenesis and planar polarity effector 2	14.65	GCMa(h), Runx2(h), RAR-alpha(h), AR(h), ZEB1(h), ATF-4(h), NeuroD1(h)...
ENSG00000167613	LAIR1	leukocyte associated immunoglobulin like receptor 1	14.62	ZEB1(h), RAR-alpha(h), GCMa(h), Runx2(h), AR(h), FOXG1(h), TBX2(h)...
ENSG00000147649	MTDH	metadherin	14.36	NeuroD1(h), GCMa(h), ZEB1(h), FOXG1(h), RAR-alpha(h), ATF-4(h), TBX2(h)...
ENSG00000142396	ERVK3-1	endogenous retrovirus group K3 member 1	14.25	Runx2(h), GCMa(h), AR(h), RAR-alpha(h), TBX2(h), FOXG1(h), ATF-4(h)...
ENSG00000283103		novel transcript, antisense to ERVK3-1	14.25	Runx2(h), GCMa(h), AR(h), RAR-alpha(h), TBX2(h), FOXG1(h), ATF-4(h)...
ENSG00000149781	FERMT3	fermitin family member 3	14.25	ZEB1(h), TBX2(h), ATF-4(h), FOXG1(h), NeuroD1(h), GCMa(h), RAR-alpha(h)...
ENSG00000204188	GGNBP1	gametogenetin binding protein 1 (pseudogene)	14.2	Runx2(h), RAR-alpha(h), GCMa(h), TBX2(h), ZEB1(h), AR(h), NeuroD1(h)...
ENSG00000301110	BAK1	BCL2 antagonist/killer 1	14.2	Runx2(h), RAR-alpha(h), GCMa(h), TBX2(h), ZEB1(h), AR(h), NeuroD1(h)...

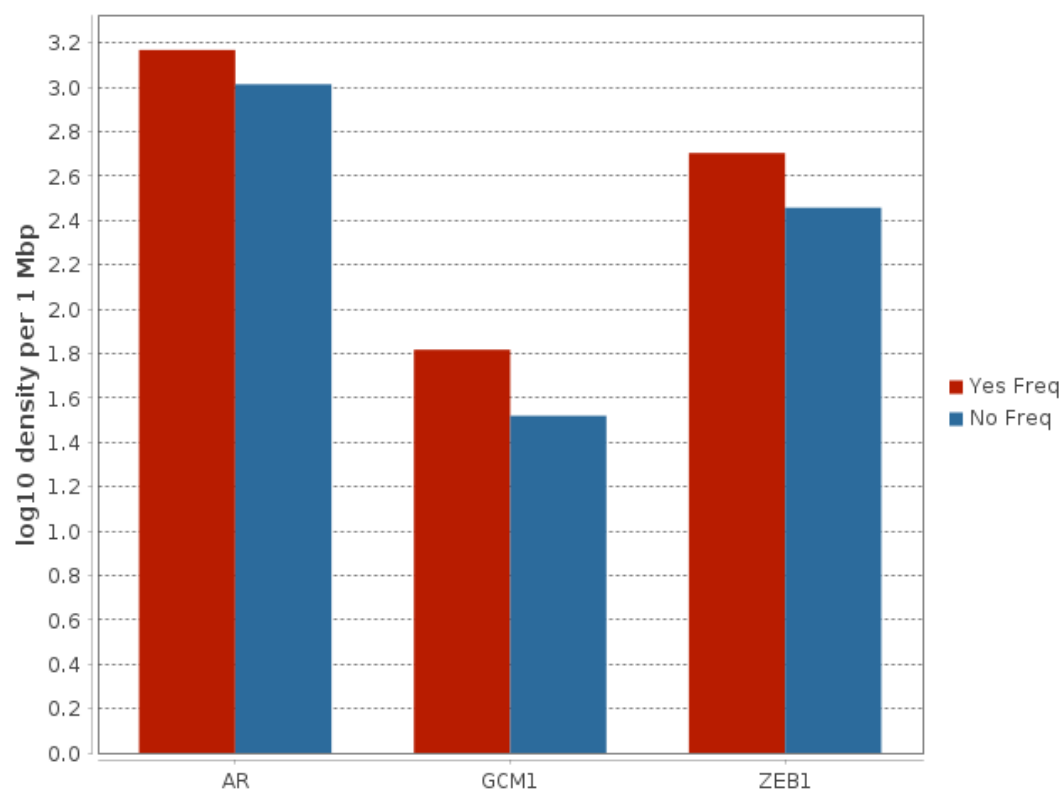
On the basis of the enhancer models we identified transcription factors potentially regulating the **target genes** of our interest. We found 9 transcription factors controlling expression of the genes associated with genomic variations (see Table 6).

Table 6. Transcription factors of the predicted enhancer model potentially regulating the genes carrying sequence variations (the most frequently mutated genes in Experiment: short-term survival). **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
MO000021454	AR	androgen receptor	4.23	1.43
MO000026306	GCM1	glial cells missing transcription factor 1	3.7	1.99
MO000139677	ZEB1	zinc finger E-box binding homeobox 1	3.44	1.76
MO000033904	RARA	retinoic acid receptor alpha	3.31	1.72
MO000028384	NEUROD1	neuronal differentiation 1	3.18	4.57
MO000026285	RUNX2	RUNX family transcription factor 2	2.95	2.01
MO000019140	ATF4	activating transcription factor 4	2.94	2.06
MO000028209	TBX2	T-box transcription factor 2	2.82	1.61
MO000026342	FOXG1	forkhead box G1	0	1.61

The following diagram represents the key transcription factors, which were predicted to be potentially regulating genes carrying sequence variations in the analyzed pathology: AR, GCM1 and ZEB1.



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 174 signaling proteins whose structure and function is highly damaged by the mutations (see Table 7).

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

[See full table](#) →

ID	Title	Mutation count	Consequence	Codons
MO000138949	Drp1(h)	13	NMD_transcript_variant,stop_gained	Gaa/Taa
MO000206935	C11orf74(h)	12	stop_gained	Gaa/Taa
MO000211774	DPAGT1(h)	10	NMD_transcript_variant,frameshift_variant	ttc/ttTc
MO000019673	p85alpha(h)	9	stop_gained	Cga/Tga
MO000190658	GPSM2(h)	9	stop_gained	Gaa/Taa
MO000093071	chd8(h)	8	stop_gained	taC/taA
MO000113258	MYPT1(h)	8	NMD_transcript_variant,frameshift_variant	aga/aAga
MO000127741	SMC4L1(h)	8	stop_gained	Cga/Tga
MO000214698	MS4A6A(h)	8	NMD_transcript_variant,frameshift_variant	-/T,ttA/ttTa
MO000035319	kinectin(h)	7	NMD_transcript_variant,frameshift_variant	-/A

Top 100 mutated proteins for the most frequently mutated genes were used in the algorithm of master regulator search as a list of nodes of the signal transduction network that are removed from the network during the search of master regulators (see more details about the algorithm in the Methods section). These master regulators appear to be the key candidates for therapeutic targets as they have a master effect on regulation of intracellular pathways that activate the pathological process of our study. The identified master regulators are shown in Table 8.

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

[See full table](#) →

ID	Master molecule name	Gene symbol	Gene description	Total rank	Weighted score
MO000079043	PML-4(h)	PML	PML nuclear body scaffold	133	135.49
MO000045014	PML(h)	PML	PML nuclear body scaffold	247	135.49
MO000019401	Jak1(h)	JAK1	Janus kinase 1	316	131.69
MO000019259	c-Cbl(h)	CBL	Cbl proto-oncogene	383	91.31
MO000031189	PKCdelta(h)	PRKCD	protein kinase C delta	422	66.82
MO000042124	MKK3:Dyrk1B:PHS 2:HNF-1alpha	DYRK1B, HNF1A, MAP2K3, PCBD2	HNF1 homeobox A, dual specificity tyrosine phosphorylation regulated kinase 1B, mitogen-activated pr...	437	625.54
MO000098746	PHS 2(h)	PCBD2	pterin-4 alpha-carbinolamine dehydratase 2	437	625.54
MO000135817	HNF-1alpha(h):PHS 2(h)	HNF1A, PCBD2	HNF1 homeobox A, pterin-4 alpha-carbinolamine dehydratase 2	437	625.54
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, ...	439	90.46
MO000007566	InsR(h)	INSR	insulin receptor	458	106.38

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

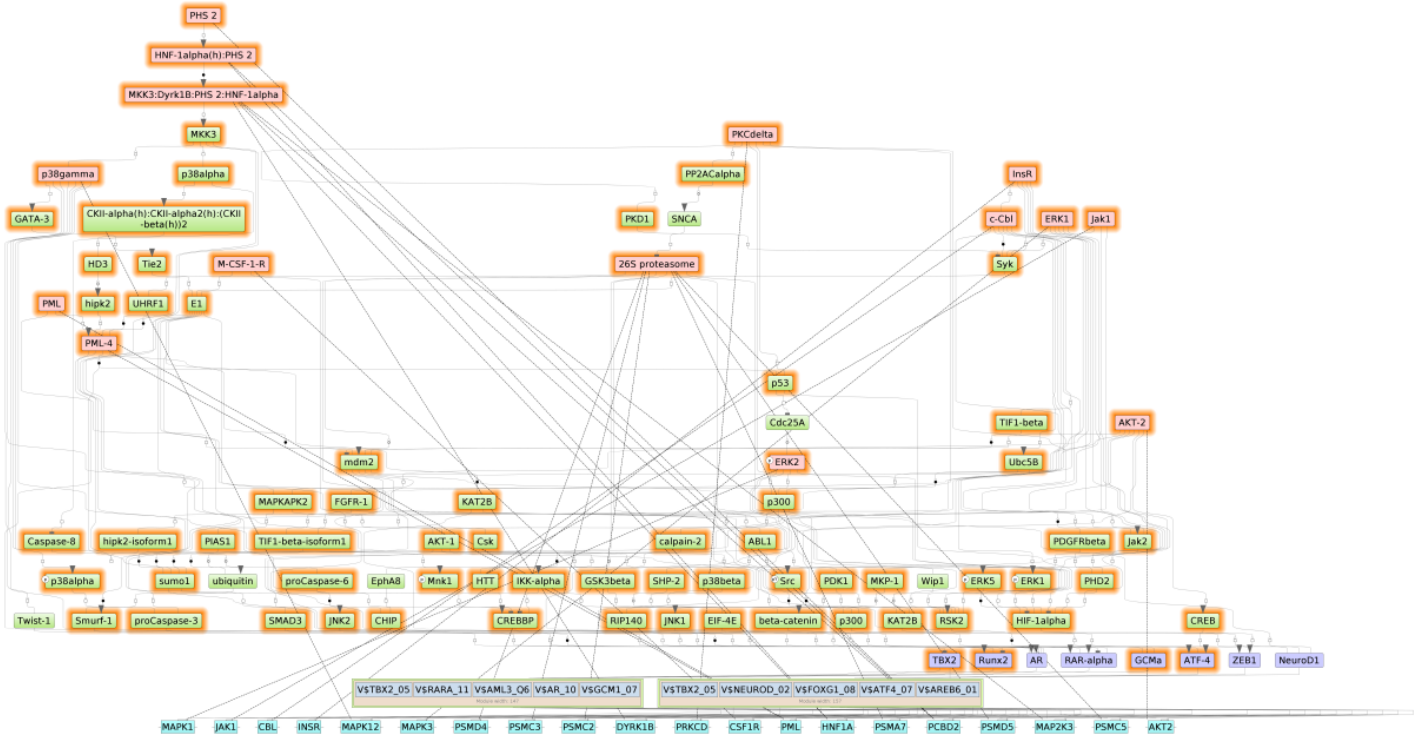


Figure 5. Diagram of intracellular regulatory signal transduction pathways of the most frequently mutated genes in Experiment: short-term survival. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have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

[See full diagram](#) →

4. Finding prospective drug targets

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

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

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

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



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

[See full table](#) →

Gene symbol	Gene Description	Druggability score	Total rank	Weighted score
DYRK1B	dual specificity tyrosine phosphorylation regulated kinase 1B	27	437	625.54
PSMA7	proteasome 20S subunit alpha 7	2	439	90.46
ITGAL	integrin subunit alpha L	14	637	189.03
ITGA3	integrin subunit alpha 3	2	637	189.03
ITGB5	integrin subunit beta 5	2	637	189.03
ITGA6	integrin subunit alpha 6	1	637	189.03



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

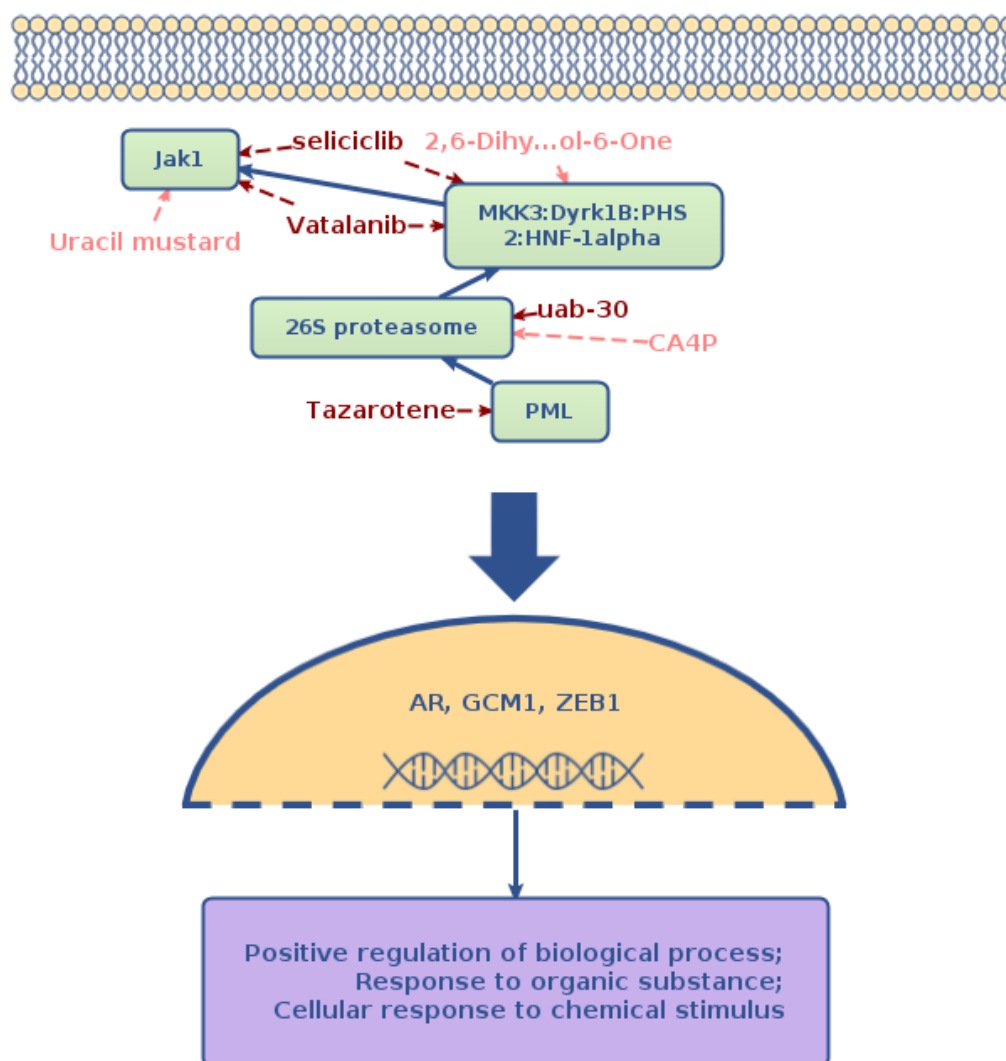
[See full table](#) →

Gene symbol	Gene Description	Druggability score	Total rank	Weighted score
DYRK1B	dual specificity tyrosine phosphorylation regulated kinase 1B	16.35	437	625.54
PCBD2	pterin-4 alpha-carbinolamine dehydratase 2	0.35	437	625.54
PSMC5	proteasome 26S subunit, ATPase 5	1.28	439	90.46
PSMD5	proteasome 26S subunit, non-ATPase 5	1.28	439	90.46
PSMA7	proteasome 20S subunit alpha 7	2.48	439	90.46
PSMD4	proteasome 26S subunit, non-ATPase 4	1.28	439	90.46

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:

- Jak1
- PML
- MKK3:Dyrk1B:PHS 2:HNF-1alpha
- 26S proteasome

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



Drugs which are shown on this schema: 2,6-Dihydroanthra[1,9-cd]pyrazol-6-one, Tazarotene, CA4P, Uracil mustard, seliciclib, Vatalanib and uab-30, should be considered as a prospective research initiative for further drug repurposing and drug development. These drugs were selected as top matching treatments to the most prospective drug targets of the studied pathology, however, these results should be considered with special caution and are to be used for research purposes only, as there is not enough clinical information for adapting these results towards immediate treatment of patients. The drugs given in dark red color on the schema are FDA approved drugs or drugs which have gone through various phases of clinical trials as active treatments against the selected targets.

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

5. Identification of potential drugs

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

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

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

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

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

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

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

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

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

Drugs approved in clinical trials for Oncology



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

[See full table](#) →

Name	Target names	Drug score	Disease activity score	Disease trial phase	Approved
Regorafenib	KIT, MAPK1, ABL1, KDR, FGFR2, PDGFRB, FGFR1, BRAF, PDGFRA, RAF1, FLT4, MAPK11, EPHA2, FLT1, AKT1, DDR2, TEK, MAPK3, RET, AKT2	94	6	Phase 3: Colorectal Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Gastrointestinal Stromal Tumors, Glioblastoma, Neoplasm Metastasis, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (FDA)
encorafenib	MAPK10, MAPK1, MAPK8, MAPK9, MAPK7, MAPK6, BRAF, MAPK3, MAP2K4, RAF1	83	3	Phase 3: Colorectal Neoplasms, Biliary Tract Neoplasms, Melanoma, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, FDA)
Fluorouracil	CASP8, CASP3, BAX, ITGAL, FAS, BIRC5, CDKN1A	79	11	Phase 4: Colorectal Neoplasms, Bowen's Disease, Breast Neoplasms, Carcinoma, Carcinoma, Basal Cell, Carcinoma, Squamous Cell, Digestive System Neoplasms, Gastrointestinal Neoplasms, Glaucoma, Head and Neck Neoplasms, Hypopigmentation, Intestinal Neoplasms, Keratosis, Keratosis, Actinic, Neoplasms, Neoplasms, Basal Cell, Neoplasms, Squamous Cell, Photosensitivity Disorders, Postoperative Complications, Skin Diseases, Skin Neoplasms, Squamous Cell Carcinoma of Head and Neck, Vitiligo	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials)
Oxaliplatin	CTNNB1, IGF2, CDH1, AKT1, AKT2	72	11	Phase 4: Colorectal Neoplasms, Colonic Neoplasms, Digestive System Neoplasms, Gastrointestinal Neoplasms, Intestinal Neoplasms, Neoplasms, Postoperative Complications, Rectal Neoplasms	Colorectal Neoplasms (FDA, PUBMED)
Aflibercept	VEGFA, PGF	56	4	Phase 2: Colorectal Neoplasms, Astrocytoma, Brain Neoplasms, Carcinoid Tumor, Carcinoma, Carcinoma, Merkel Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Cataract, Central Serous Chorioretinopathy, Choroidal Neovascularization, Corneal Neovascularization, Diabetic Retinopathy, Edema, Esophageal Squamous Cell Carcinoma, Eye Diseases, Glioblastoma, Hemorrhage, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Lung Neoplasms, Macular Degeneration, Macular Edema, Neoplasm Metastasis, Neoplasms, Neovascularization, Pathologic, Pseudoxanthoma Elasticum, Pterygium, Rectal Neoplasms, Retinal Degeneration, Retinal Diseases, Retinal Neovascularization, Retinal Vein Occlusion, Retinitis, Retinitis Pigmentosa, Small Cell Lung Carcinoma, Squamous Cell Carcinoma of Head and Neck, Vitreous Hemorrhage, Wet Macular Degeneration, Xanthomatosis	Colorectal Neoplasms (FDA)
Irinotecan	MAPK10, BIRC5, CDKN1A	47	12	Phase 4: Colorectal Neoplasms, Neoplasms, Neuroblastoma, Rectal Neoplasms	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)
Bevacizumab	FCGR2A, VEGFA	46	12	Phase 4: Colorectal Neoplasms, Carcinoma, Ovarian Epithelial, Cataract, Corneal Neovascularization, Diabetic Retinopathy, Dilatation, Pathologic, Edema, Epistaxis, Fallopian Tube Neoplasms, Glaucoma, Hemorrhage, Ischemia, Macular Edema, Neoplasm Metastasis, Neoplasms, Neovascularization, Pathologic, Optic Nerve Diseases, Ovarian Neoplasms, Peritoneal Neoplasms, Pterygium, Rectal Neoplasms, Retinal Detachment, Retinal Diseases, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis, Vitreous Hemorrhage	Colorectal Neoplasms (FDA, FDA)
Panitumumab	EGFR	39	5	Phase 3: Colorectal Neoplasms, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (FDA)

Cetuximab	FCGR2A, EGFR	34	11	Phase 4: Colorectal Neoplasms, Carcinoma, Carcinoma, Squamous Cell, Head and Neck Neoplasms, Liver Neoplasms, Neoplasm Metastasis, Neoplasms, Rectal Neoplasms, Squamous Cell Carcinoma of Head and Neck	Colorectal Neoplasms (FDA, FDA)
Capecitabine	CDKN2A	22	12	Phase 4: Colorectal Neoplasms, Neoplasms, Rectal Neoplasms	Colorectal Neoplasms (ClinicalTrials, ClinicalTrials, ClinicalTrials, FDA, FDA)

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

Drugs approved in clinical trials



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

[See full table](#) →

Name	Target names	Drug score	Disease activity score	Disease trial phase
Vatalanib	BMPR1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUAK1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, CDK1, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFB2, FYN	96	3	Phase 3: Colorectal Neoplasms, Colonic Neoplasms, Neoplasms, Rectal Neoplasms
Sunitinib	BMPR1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1,	96	3	Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Ascites, Astrocytoma, Barrett Esophagus, Blast Crisis, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Transitional Cell, Central Nervous System Neoplasms, Colonic Neoplasms, Endocrine Gland Neoplasms, Endometrial Neoplasms, Esophageal Neoplasms, Fibroma, Fibromatosis, Aggressive, Fibrosarcoma, Gastrointestinal Stromal Tumors, Glioblastoma, Glioma, Gliosarcoma, Hemangioblastoma, Hemangiopericytoma, Histiocytoma, Histiocytoma, Benign Fibrous, Histiocytoma, Malignant Fibrous, Intestinal Neoplasms, Kidney 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,

AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, CAMKK1, EPHB1, SIRT1, TGFB2, FYN

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, Non-Hodgkin, Melanoma, Meningioma, Multiple Myeloma, Myelodysplastic Syndromes, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasms, Neoplasms, Germ Cell and Embryonal, Neoplasms, Hormone-Dependent, Neoplasms, Plasma Cell, Nervous System Neoplasms, Neuroendocrine Tumors, Neurofibroma, Neurofibromatosis, Neurofibromatosis 1, Ovarian Neoplasms, Pancreatic Neoplasms, Paraganglioma, Pheochromocytoma, Pica, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Neoplasms, Ranula, Rectal Neoplasms, Recurrence, Sarcoma, Sarcoma, Alveolar Soft Part, Skin Neoplasms, Small Cell Lung Carcinoma, Solitary Fibrous Tumors, Stomach Neoplasms, Syndrome, Teratoma, Testicular Neoplasms, Thymoma, Thymus Neoplasms, Thyroid Diseases, Thyroid Neoplasms, Urinary Bladder Neoplasms, Uterine Neoplasms, von Hippel-Lindau Disease

Sirolimus	ROCK2, MARK3, PRKACA, GSK3B, NEK2, SGK1, NEK6, BAX, RPS6KA5, CSK, PRKD1, MAPK3, MELK, MAPK8, CAMKK2, MAP2K1, FGF2, PRKCZ, MAPK12, MAPK11, MAPKAPK2, CHEK2, AKT2, STK3, PDPK1, IKBKB, MAPK10, RPS6KA3, ITGAL, PRKCA, IL10, PRKAA1, AURKB, RPS6KA1, HSP90AA1, MAPK14, CSNK1D, PLK1, AKT1, CHEK1, TP53, RPS6KB1, MAPK1, HIPK2, PIM2, MAPK9, MTOR, PAK4, PIM3, MAPK13, CAMKK1, CTLA4	95	3	Phase 2: Colorectal Neoplasms, Acute Disease, Adenocarcinoma, Adenoma, Adenoma, Islet Cell, Adenomatous Polyposis Coli, Adenomatous Polyps, Alzheimer Disease, Amyotrophic Lateral Sclerosis, Anemia, Anemia, Aplastic, Anemia, Hemolytic, Anemia, Hemolytic, Autoimmune, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Anemia, Sickle Cell, Angina Pectoris, Angina, Unstable, Angiofibroma, Angiomyolipoma, Angiomyoma, Aphasia, Aphasia, Primary Progressive, Arteriovenous Malformations, Atrophy, Autoimmune Lymphoproliferative Syndrome, Blast Crisis, Bone Marrow Failure Disorders, Brain Abscess, Brain Stem Infarctions, Breast Neoplasms, Bronchiolitis, Bronchiolitis Obliterans, Bronchiolitis Obliterans Syndrome, Burkitt Lymphoma, COVID-19, Carcinoma, Carcinoma, Endometrioid, Carcinoma, Hepatocellular, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Squamous Cell, Chordoma, Choroidal Neovascularization, Cockayne Syndrome, Cognitive Dysfunction, Congenital Abnormalities, Coronary Artery Disease, Coronary Disease, Cysts, Dementia, Depression, Depressive Disorder, Diabetes Mellitus, Diabetes Mellitus, Type 1, Diabetic Retinopathy, Dilatation, Pathologic, Edema, Endometrial Neoplasms, Epidermolysis Bullosa, Epidermolysis Bullosa Simplex, Epilepsy, Epistaxis, Erythema, Esophageal Squamous Cell Carcinoma, Eye Diseases, Fanconi Anemia, Fanconi Syndrome, Fibroma, Fibrosarcoma, Fibrosis, Frontotemporal Dementia, Ganglion Cysts, Ganglioneuroblastoma, Genital Diseases, Genital Diseases, Female, Geographic Atrophy, Giant Lymph Node Hyperplasia, Glioblastoma, Glioma, Gliosarcoma, Glomerulonephritis, Glomerulonephritis, IGA, Gout, Graft vs Host Disease, Graves Ophthalmopathy, Hamartoma, Hamartoma Syndrome, Multiple, Head and Neck Neoplasms, Hemangioma, Hemangioma, Hemangiosarcoma, Hematologic Diseases, Hematologic Neoplasms, Hemolysis, Hemophilia A, Hemophilia B, Hodgkin Disease, Hyperinsulinism, Hypertension, Hyperuricemia, Hypoglycemia, Immunologic Deficiency Syndromes, Infarction, Inflammatory Bowel Diseases, Intestinal Neoplasms, Intracranial Arteriovenous Malformations, Ischemia, Kasabach-Merritt Syndrome, Kidney Diseases, Kidney Diseases, Cystic, Kidney Failure, Chronic, Klippel-Trenaunay-Weber Syndrome, Leiomyoma, Leiomyomatosis, Leiomyosarcoma, Leukemia, Leukemia, Biphenotypic, Acute, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, 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, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Plasma Cell, Leukemia, Prolymphocytic, Leukemia, Prolymphocytic, T-Cell, Leukemia, Promyelocytic, Acute, Lipoma, Liposarcoma, Liver Neoplasms, Lung Neoplasms, Lupus Erythematosus, Systemic, Lupus Nephritis, Lymphangioleiomyomatosis, Lymphangioma,
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Lymphangiomyoma, Lymphatic Abnormalities, Lymphedema, Lymphoma, Lymphoma, B-Cell, Lymphoma, B-Cell, Marginal Zone, Lymphoma, Follicular, Lymphoma, Large B-Cell, Diffuse, Lymphoma, Large-Cell, Anaplastic, Lymphoma, Large-Cell, Immunoblastic, Lymphoma, Mantle-Cell, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoproliferative Disorders, Macular Degeneration, Macular Edema, Melanoma, Metabolic Diseases, Motor Neuron Disease, Mouth Neoplasms, Multiple Myeloma, Multiple System Atrophy, Myelodysplastic Syndromes, Myelodysplastic-Myeloproliferative Diseases, Myeloproliferative Disorders, Myocardial Infarction, Myocardial Ischemia, Myoma, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasm, Residual, Neoplasms, Neoplasms, Plasma Cell, Neovascularization, Pathologic, Nephritis, Nerve Sheath Neoplasms, Neurilemmoma, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurofibroma, Neurofibromatosis, Neurofibromatosis 1, Neurofibrosarcoma, Neutropenia, Osteosarcoma, Ovarian Diseases, Ovarian Neoplasms, Pancreatic Neoplasms, Pancytopenia, Panuveitis, Parkinson Disease, Pars Planitis, Peripheral Arterial Disease, Peripheral Vascular Diseases, Peritoneal Fibrosis, Pharyngeal Neoplasms, Pica, Pick Disease of the Brain, Plasmablastic Lymphoma, Plasmacytoma, Pneumonia, Polycystic Kidney Diseases, Polycystic Kidney, Autosomal Dominant, Polyps, Post-Acute COVID-19 Syndrome, Precancerous Conditions, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Neoplasms, Pulmonary Fibrosis, Purpura, Purpura, Thrombocytopenic, Purpura, Thrombocytopenic, Idiopathic, Rage, Rectal Neoplasms, Recurrence, Renal Insufficiency, Renal Insufficiency, Chronic, Retinal Diseases, Retroperitoneal Fibrosis, Rhabdomyosarcoma, Rhabdomyosarcoma, Embryonal, ST Elevation Myocardial Infarction, Sarcoidosis, Sarcoma, Sarcoma, Alveolar Soft Part, Sarcoma, Ewing, Sarcoma, Kaposi, Sarcoma, Synovial, Scleritis, Sclerosis, Severe Acute Respiratory Syndrome, Severe Combined Immunodeficiency, Shy-Drager Syndrome, Squamous Cell Carcinoma of Head and Neck, Stomach Neoplasms, Sturge-Weber Syndrome, Syndrome, Telangiectasia, Hereditary Hemorrhagic, Telangiectasis, Thalassemia, Thrombosis, Tongue Neoplasms, Triple Negative Breast Neoplasms, Tuberous Sclerosis, Uveitis, Uveitis, Intermediate, Uveitis, Posterior, Vascular Diseases, Vascular Malformations, Vitiligo, Waldenstrom Macroglobulinemia, Wet Macular Degeneration, alpha-Thalassemia, beta-Thalassemia

Sorafenib	<p> BMPR1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK3, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, IKBKB, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, </p>	94	2	<p> Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenoma, Adenoma, Liver Cell, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Bile Duct Neoplasms, Biliary Tract Neoplasms, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Carcinoid Tumor, Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Islet Cell, Carcinoma, Medullary, Carcinoma, Neuroendocrine, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Desmoplastic Small Round Cell Tumor, Digestive System Neoplasms, Endocrine Gland Neoplasms, Fibrosarcoma, 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, Insulinoma, Intestinal Neoplasms, Kidney Diseases, Kidney Neoplasms, Leiomyosarcoma, Leukemia, Leukemia, Monocytic, Acute, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Chronic, Liver Diseases, Liver Neoplasms, Lung Neoplasms, Lymphoma, Malignant Carcinoid Syndrome, Melanoma, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Endocrine Neoplasia Type 2a, Multiple Endocrine Neoplasia Type 2b, Multiple Myeloma, Myelodysplastic Syndromes, Myosarcoma, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasms, Neoplasms by Histologic Type, Neoplasms by Site, Neoplasms, Glandular and Epithelial, Neoplasms, Plasma Cell, Nerve Sheath Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroectodermal Tumors, Primitive, Peripheral, Neuroendocrine Tumors, Neurofibrosarcoma, Osteosarcoma, Ovarian Neoplasms, Pancreatic Neoplasms, Pharyngeal Neoplasms, Plasmacytoma, Preleukemia, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Sarcoma, Sarcoma, Ewing, Sarcoma, Synovial, Somatostatinoma, Syndrome, Thyroid Diseases, Thyroid Neoplasms, Urinary Bladder Neoplasms, Vaccinia, Vipoma </p>
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	PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN		
Erlotinib	BMP1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BIRC5, BMX, ERBB3, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K1, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, ILK, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, ERBB4, PAK3, BRAF, FER, CAMKK1, EPHB1, TGFB2, FYN	94	2

Phase 2: Colorectal Neoplasms, Adenocarcinoma, Adenocarcinoma of Lung, Adenocarcinoma, Bronchiolo-Alveolar, Adenocarcinoma, Mucinous, Adenoma, Adenomatous Polyposis Coli, Adenomatous Polyps, Brain Abscess, Brain Neoplasms, Breast Neoplasms, Brenner Tumor, Carcinoid Tumor, Carcinoma, Carcinoma, Endometrioid, Carcinoma, Non-Small-Cell Lung, Carcinoma, Ovarian Epithelial, Carcinoma, Renal Cell, Carcinoma, Small Cell, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Cholangiocarcinoma, Cystadenocarcinoma, Cystadenocarcinoma, Mucinous, Cystadenocarcinoma, Serous, Cysts, Diffuse Intrinsic Pontine Glioma, Digestive System Diseases, Endocrine Gland Neoplasms, Ependymoma, Esophageal Diseases, Esophageal Neoplasms, Fallopian Tube Neoplasms, Fibrosarcoma, Gallbladder Neoplasms, Glioblastoma, Glioma, Gliosarcoma, Head and Neck Neoplasms, Laryngeal Neoplasms, Leukemia, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Acute, Lung Neoplasms, Lymphoma, Lymphoma, Non-Hodgkin, Medulloblastoma, Melanoma, Mesothelioma, Mesothelioma, Malignant, Multiple Endocrine Neoplasia, Multiple Myeloma, Myosarcoma, Nasopharyngeal Neoplasms, Neoplasm Metastasis, Neoplasm Recurrence, Local, Neoplasms, Neoplasms, Unknown Primary, Nerve Sheath Neoplasms, Neuroblastoma, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neuroendocrine Tumors, Neurofibrosarcoma, Osteosarcoma, Ovarian Neoplasms, Pancreatic Neoplasms, Paranasal Sinus Neoplasms, Pharyngeal Neoplasms, Polycythemia, Polycythemia Vera, Polyps, Precancerous Conditions, Psoriasis, Rectal Neoplasms, Recurrence, Rhabdomyosarcoma, Sarcoma, Sarcoma, Ewing, Small Cell Lung Carcinoma, Thymoma, Thymus Neoplasms, Urinary Bladder Neoplasms, Wilms Tumor

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

Repurposing drugs



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

[See full table](#) →

Name	Target names	Drug score	Maximum trial phase
seliciclib	BMPRI1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, CDK4, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, IKBKB, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, CDK1, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN	90	Phase 2: Cystic Fibrosis, Cysts, Fibrosis
1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea	BMPRI1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, IKBKB, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN	90	Phase 2: Arthritis, Arthritis, Rheumatoid, Psoriasis
pi-103	BMPRI1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, IKBKB, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN	90	N/A
ruboxistaurin	BMPRI1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, PRKCZ, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, CHEK2, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, HIPK2, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, IKBKB, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN	90	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

MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN

Tofacitinib	BMPR1A, IKBKE, ABL1, FGFR2, JAK3, PAK2, PRKACA, GSK3B, MAP3K11, SYK, EPHA1, NEK6, EIF2AK2, ERBB2, MAPK3, MAP2K6, AXL, JAK1, MELK, MAPK8, SRC, CAMKK2, PRKD3, CSNK1G2, MAP4K1, STK11, CSNK1G1, CLK4, MAPK12, PLK3, WEE1, MAPK7, MAPK11, FLT1, PRKCD, LYN, CSNK2A1, AKT2, STK3, PDPK1, MAPK10, KDR, MAPK6, PRKCA, CSNK1E, PDGFRA, RAF1, AURKB, CDK7, MAPK14, CSNK1D, EPHB3, DDR2, CHEK1, PTK6, BMX, PIM2, RIPK2, FGFR3, RPS6KA2, PAK4, NTRK2, TYRO3, PIM3, YES1, NUA1, CAMK2D, ITK, MAP3K4, PAK1, CLK1, CDK5, PRKACB, RET, ABL2, CSF1R, STK10, ROCK2, MAP4K4, MARK3, MAP3K10, SLK, INSR, NEK2, SGK1, MAP2K2, MAP2K3, EPHA2, RPS6KA5, CSK, PRKD1, TEK, PKN1, TYK2, IGF1R, MAP3K5, CSNK2A2, TNK2, PDGFRB, MAP2K1, MAP4K3, STK4, CAMK2A, PTK2, MAPKAPK2, PLK4, RPS6KA3, CAMK2G, MET, PRKCQ, EPHA4, MAP2K4, PRKAA1, RPS6KA1, FLT4, EGFR, PLK1, PTK2B, AKT1, AURKA, JAK2, MAP3K20, PKMYT1, RPS6KB1, KIT, MAPK1, DYRK1B, EPHB2, MAPK9, GSK3A, MERTK, EPHA3, EPHB4, PRKCE, FGFR1, PAK3, BRAF, FER, MAPK13, CAMKK1, EPHB1, TGFB2, FYN	90	Phase 4: Alopecia, Alopecia Areata, Aortic Arch Syndromes, Arteritis, Arthritis, Psoriatic Arthritis, Rheumatoid, COVID-19, Colitis, Colitis, Ulcerative, Embolism, Granuloma, Granulomatosis with Polyangiitis, Necrosis, ST Elevation Myocardial Infarction, Spondylarthritis, Spondylitis, Systemic Vasculitis, Takayasu Arteritis, Thromboembolism, Ulcer, Vasculitis
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The **Maximum trial phase** column reflects the maximum clinical trials phase in which the drug was studied for any pathology.



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

[See full table](#) →

Name	Target names	Drug score	Target activity score
Camptothecin	HIF1A, CASP3	79	0.31
Topotecan	HIF1A, CASP3	79	0.31
Eucalyptol	VEGFA, TLR3, TLR4, VEGFD, KDR, FLT1, FLT4	79	0.31
LE-SN38	HIF1A, CASP3	78	0.29
Ouabain	STAT3, CASP8, HIF1A, CASP3, STAT1, RELA	75	0.19



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

[See full table](#) →

Name	Target names	Drug score	Target activity score
Iodophenyl	STK10, ROCK2, MAP4K4, MARK3, PAK2, GSK3B, SLK, VRK1, NEK2, SGK1, NEK6, EIF2AK2, TAOK2, RPS6KA5, MELK, CSNK2A2, TNK2, CSNK1G2, MAP4K1, STK11, MAP4K3, CSNK1G1, STK4, NEK10, MAP4K2, MAPKAPK2, IRAK1, CSNK2A1, CHEK2, AKT2, PDPK1, STK3, RPS6KA3, PIK3CG, IRAK4, PINK1, CSNK1A1, CSNK1E, RAF1, PRKAA1, RPS6KA1, AURKB, ILK, CSNK1D, MASTL, HIPK1, AKT1, AURKA, CHEK1, TAOK1, ATM, LMTK2, PKMYT1, RPS6KB1, TBK1, ATR, RIPK2, PIM2, HIPK2, MTOR, GSK3A, RPS6KA2, PAK4, PIM3, PRKDC, NUA1, PAK3, PASK, BRAF, PAK1, CDK5	96	19.26
2,6-Dihydroanthra[1,9-Cd]Pyrazol-6-One	MAPK10, RPS6KA3, IRAK4, CDK6, CAMK2G, CSNK1A1, STAT1, PAK2, EPHA4, CSNK1E, CDK1, MAP2K4, CDK4, AURKB, CDK7, PRKAA1, HSP90AA1, CSNK1D, SGK1, EPHA1, MAP2K3, PTK2B, AKT1, AURKA, CHEK1, PKN1, MAP2K6, MAPK8, MAPK9, EPHB2, DYRK1B, GSK3A, PAK4, PRKD3, CSNK1G2, EPHA3, PAK3, CLK4, CSNK1G1, CAMK2D, EPHB1, CAMK2A, PAK1, CLK1, IRAK1, CDK5, CHEK2, AKT2	96	12.26
Rbt205 Inhibitor	RPS6KA3, CDK6, CAMK2G, GRK2, MAP3K10, PRKCQ, PRKACA, GSK3B, PRKCA, CDK1, MAP2K4, CDK4, CDK7, RPS6KA1, PRKAA1, SGK1, PRKD1, PKN1, MAP2K6, RPS6KA2, GSK3A, GRK5, PRKD3, PRKCE, PRKCZ, CAMK2D, PTK2, CAMK2A, SIRT1, PRKCD, PRKCI, CDK5, PRKACB	95	17.29
Uracil mustard	ABL1, FGFR2, JAK3, INSR, SYK, EPHA1, EIF2AK2, EPHA2, ERBB2, TEK, CSK, AXL, TYK2, MELK, JAK1, IGF1R, SRC, PDGFRB, TNK2, WEE1, PTK2, FLT1, PRKCD, LYN, MET, KDR, EPHA4, PDGFRA, FLT4, MST1R, EGFR, EPHB3, PTK2B, DDR2, PTK6, JAK2, KIT, BMX, RIPK2, ERBB3, EPHB2, FGFR3, MTOR, NTRK2, TYRO3, MERTK, EPHB4, EPHA3, YES1, FGFR1, ERBB4, FER, ITK, EPHB1, FYN, RET, CSF1R, ABL2	94	10.13
7-[4-(Dimethylamino)Phenyl]-N-Hydroxy-4,6-Dimethyl-7-Oxo-2,4-Heptadienamide	HDAC4, HDAC2, HDAC3, HDAC1	92	3.2

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: Vatalanib, seliciclib, Camptothecin and Iodophenyl. These drugs were selected for acting on the following targets: DYRK1B, HIF1A and MTOR, which were predicted to be active in the molecular mechanism of the studied pathology.

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

Supplementary drug info

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

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

Drug	Disease	Predicted Drug Score	Somatic variants
Abarelix	Prostatic Neoplasms	-	
Abemaciclib	Breast Neoplasms	42	
Abiraterone	Prostatic Neoplasms, Castration-Resistant	-	
Abiraterone acetate	Prostatic Neoplasms, Castration-Resistant	-	
Acalabrutinib	Lymphoma, Mantle-Cell	43	
Acitretin	Psoriasis	33	
Ado-trastuzumab emtansine	Breast Neoplasms Neoplasms	79	
Afatinib	Carcinoma, Non-Small-Cell Lung	76	
Aflibercept	Colorectal Neoplasms Diabetic Retinopathy Edema Vascular Diseases Wet Macular Degeneration	56	
Alectinib	Carcinoma, Non-Small-Cell Lung	50	
Alemtuzumab	Brain Abscess Leukemia, Lymphocytic, Chronic, B-Cell Multiple Sclerosis Multiple Sclerosis, Relapsing-Remitting Sclerosis	-	
Alitretinoin	Sarcoma, Kaposi	-	
Alpelisib	Breast Neoplasms	-	
Altretamine	Ovarian Neoplasms	-	
Aminolevulinic acid	Keratosi Keratosi, Actinic	-	
Anagrelide	Thrombocythemia, Essential Thrombocytosis	-	
Anastrozole	Breast Neoplasms Hypersensitivity Obesity Obesity, Morbid Recurrence Weight Loss	22	
Apalutamide	Prostatic Neoplasms, Castration-Resistant	-	
Aprepitant	Nausea Neoplasms Postoperative Nausea and Vomiting	-	
Arsenic trioxide	Leukemia, Promyelocytic, Acute	64	
Atezolizumab	Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell Triple Negative Breast Neoplasms	-	
Avelumab	Carcinoma, Merkel Cell Carcinoma, Renal Cell Carcinoma, Transitional Cell	-	
Axitinib	Carcinoma, Renal Cell	91	
Azacitidine	Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes Preleukemia Syndrome	26	
Belinostat	Lymphoma, T-Cell, Peripheral	72	
Bendamustine	Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Lymphoid	-	
Bevacizumab	Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms Corneal Neovascularization Diabetic Retinopathy Dilatation, Pathologic Edema Epistaxis Glaucoma Hemorrhage Macular Degeneration Macular Edema Neoplasm Metastasis Neoplasms Neovascularization, Pathologic Optic Nerve Diseases Pterygium Rectal Neoplasms Retinal Detachment Retinal Diseases Retinal Vein Occlusion Telangiectasia, Hereditary Hemorrhagic Telangiectasis Vitreous Hemorrhage	46	
Bexarotene	Lymphoma, T-Cell Lymphoma, T-Cell, Cutaneous	5	
Bicalutamide	Prostatic Neoplasms	4	
Binimetinib	Melanoma	66	
Blinatumomab	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-	
Bortezomib	Brain Abscess Glomerulonephritis Glomerulonephritis, IGA Kidney Diseases Multiple Myeloma Neoplasms, Plasma Cell Nephritis Renal Insufficiency	57	
Bosutinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	82	
Brentuximab vedotin	Hodgkin Disease Lymphoma Lymphoma, Large-Cell, Anaplastic Lymphoma, T-Cell, Peripheral	-	
Brigatinib	Carcinoma, Non-Small-Cell Lung	57	

Buserelin	Prostatic Neoplasms	-	
Cabazitaxel	Prostatic Neoplasms, Castration-Resistant	72	
Cabergoline	Drug-Related Side Effects and Adverse Reactions Pituitary Neoplasms	13	
Cabozantinib	Thyroid Neoplasms	83	
Capecitabine	Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms	22	
Carboplatin	Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms Neuroendocrine Tumors Ovarian Neoplasms Retinoblastoma	-	XRCC1:Q399R:sensitivity/response:B2
Carfilzomib	Multiple Myeloma	72	
Carmustine	Astrocytoma Glioblastoma Hodgkin Disease Medulloblastoma Multiple Myeloma Neoplasms	-	
Ceritinib	Carcinoma, Non-Small-Cell Lung	83	
Cetuximab	Colorectal Neoplasms	34	
Cinacalcet	Anemia Calcinosis Cardiovascular Diseases Hyperparathyroidism Hyperparathyroidism, Secondary Kidney Diseases Kidney Failure, Chronic Neoplasm Metastasis Neoplasms Parathyroid Neoplasms Renal Insufficiency Vascular Calcification Vascular Diseases Vision Disorders	-	
Cisplatin	Carcinoma, Squamous Cell Neoplasms Uterine Cervical Neoplasms Carcinoma, Non-Small-Cell Lung Esophageal Neoplasms Carcinoma	74	XRCC1:Q399R:sensitivity/response:B2
Cladribine	Leukemia, Hairy Cell	55	
Clofarabine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	34	
Cobimetinib	Melanoma	78	
Copanlisib	Lymphoma, Follicular	84	
Crizotinib	Carcinoma, Non-Small-Cell Lung	91	
Cyproterone acetate	Prostatic Neoplasms	-	
Dabrafenib	Melanoma	15	
Dacomitinib	Carcinoma, Non-Small-Cell Lung	81	
Daratumumab	Multiple Myeloma	-	
Dasatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid, Chronic-Phase Precursor Cell Lymphoblastic Leukemia-Lymphoma	94	
Decitabine	Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes	-	
Degarelix	Cardiovascular Diseases Prostatic Neoplasms Vascular Diseases	59	
Denosumab	Arthritis, Rheumatoid Bone Diseases Bone Diseases, Metabolic Breast Neoplasms Hyperparathyroidism Hyperparathyroidism, Primary Metabolic Diseases Neoplasm Metastasis Neoplasms Osteoporosis Osteoporosis, Postmenopausal Prostatic Neoplasms	39	
Dexrazoxane	Breast Neoplasms Cardiomyopathies	8	
Dienogest	Menorrhagia	-	
Dinutuximab	Neuroblastoma	-	
Docetaxel	Breast Neoplasms Carcinoma, Non-Small-Cell Lung Prostatic Neoplasms Squamous Cell Carcinoma of Head and Neck Stomach Neoplasms	30	
Doxorubicin	Neoplasms Multiple Myeloma Carcinoma, Ovarian Epithelial Ovarian Neoplasms Leukemia, Lymphoid Breast Neoplasms Lymphoma, Follicular Thyroid Neoplasms Triple Negative Breast Neoplasms Glioma	77	
Durvalumab	Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell	-	
Dutasteride	Alcoholism Hyperplasia Hypertrophy Neoplasms Prostatic Hyperplasia	-	
Duvelisib	Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular	66	
Elotuzumab	Multiple Myeloma	77	
Enasidenib	Leukemia, Myeloid, Acute	-	
Encorafenib	Colorectal Neoplasms Melanoma	83	
Enfortumab vedotin	Carcinoma, Transitional Cell Neoplasms	-	
Entrectinib	Carcinoma, Non-Small-Cell Lung	66	
Enzalutamide	Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant	-	
Epirubicin	Breast Neoplasms	47	
Erdafitinib	Urinary Bladder Neoplasms	89	

Eribulin	Breast Neoplasms Drug-Related Side Effects and Adverse Reactions Neoplasms	-
Erlotinib	Carcinoma, Non-Small-Cell Lung Neoplasms Pancreatic Neoplasms	94
Erlotinib hydrochloride	Carcinoma, Non-Small-Cell Lung Gastrointestinal Stromal Tumors	-
Estramustine	Prostatic Neoplasms	6
Ethinyl Estradiol	Acne Vulgaris Neoplasms	4
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	78
Exemestane	Breast Neoplasms	-
Fedratinib	Primary Myelofibrosis	60
Finasteride	Hyperplasia Neoplasms Prostatic Hyperplasia	41
Flavopiridol	Leukemia, Lymphocytic, Chronic, B-Cell	90
Fluorouracil	Skin Neoplasms Neoplasms, Basal Cell Neoplasms, Second Primary Neoplasms, Squamous Cell Neoplasms Colorectal Neoplasms Pancreatic Neoplasms	79
Fluoxymesterone	Breast Neoplasms Hypogonadism Puberty, Delayed	8
Flutamide	Premenstrual Dysphoric Disorder Premenstrual Syndrome Prostatic Neoplasms	39
Fulvestrant	Breast Neoplasms	52
Gefitinib	Carcinoma, Non-Small-Cell Lung	89
Gemcitabine	Breast Neoplasms Carcinoma, Non-Small-Cell Lung Ovarian Neoplasms Pancreatic Neoplasms	72
Gemtuzumab ozogamicin	Leukemia, Myeloid, Acute	8
Gilteritinib	Leukemia, Myeloid, Acute	70
Glasdegib	Leukemia, Myeloid, Acute	-
Goserelin	Atrophy Breast Neoplasms Bulbo-Spinal Atrophy, X-Linked Endometriosis Muscular Atrophy Myoma Prostatic Neoplasms	-
Histrelin	Puberty, Precocious	-
Homoharringtonine	Leukemia, Myelogenous, Chronic, BCR-ABL Positive	77
Ibrutinomab	Lymphoma, B-Cell Lymphoma, Follicular	8
Ibrutinib	Graft vs Host Disease Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, B-Cell, Marginal Zone Lymphoma, Mantle-Cell Waldenstrom Macroglobulinemia	83
Idarubicin	Leukemia, Myeloid, Acute	36
Idelalisib	Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular	67
Ifosfamide	Neoplasms	-
Imatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Mastocytosis, Systemic Neoplasms	89
Inotuzumab ozogamicin	Precursor B-Cell Lymphoblastic Leukemia-Lymphoma	-
Ipilimumab	Carcinoma, Renal Cell Melanoma	25
Irinotecan	Colorectal Neoplasms	47
Ivosidenib	Leukemia, Myeloid, Acute	-
Ixabepilone	Breast Neoplasms	-
Ixazomib	Multiple Myeloma	-
Lapatinib	Breast Neoplasms	89
Larotrectinib	Neoplasm Metastasis	63
Lenalidomide	Brain Abscess Lupus Erythematosus, Cutaneous Myelodysplastic Syndromes Neoplasms, Plasma Cell	38
Lenvatinib	Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms	91
Letrozole	Breast Neoplasms Cysts Fibroma Myofibroma Myoma Ovarian Cysts Syndrome	21
Leuprolide	Hot Flashes Ovarian Hyperstimulation Syndrome Prostatic Neoplasms Puberty, Precocious	-
Levamisole	Ascariasis Colonic Neoplasms Helminthiasis	-
Levonorgestrel	Epilepsy Hyperplasia Menorrhagia	-
Lomustine	Brain Neoplasms Hodgkin Disease	-
Lonafarnib	Breast Neoplasms Carcinoma, Non-Small-Cell Lung Central Nervous System Neoplasms Colorectal Neoplasms Gliosarcoma Head and Neck Neoplasms Leukemia, Myelomonocytic, Chronic Liver	33

	Neoplasms Lymphoma Myelodysplastic Syndromes Ovarian Neoplasms Urethral Neoplasms Urinary Bladder Neoplasms	
Lorlatinib	Carcinoma, Non-Small-Cell Lung	71
Masoprocol	Keratosi, Actinic	15
Medroxyprogesterone Acetate	Depression Depression, Postpartum Depressive Disorder Metrorrhagia Neoplasms Uterine Hemorrhage	16
Megestrol acetate	Acquired Immunodeficiency Syndrome Bites and Stings Breast Neoplasms Pain Wasting Syndrome	-
Methotrexate	Neoplasms Breast Neoplasms Head and Neck Neoplasms Ovarian Neoplasms Lymphoma, T-Cell, Peripheral Brain Neoplasms Colorectal Neoplasms Neuroblastoma Carcinoma, Squamous Cell	34
Methyltestosterone	Breast Neoplasms Hypogonadism Puberty, Delayed	-
Midostaurin	Leukemia, Mast-Cell Leukemia, Myeloid, Acute Mastocytosis, Systemic	89
Mitotane	Adrenocortical Carcinoma	-
Mitoxantrone	Autoimmune Diseases Autoimmune Diseases of the Nervous System Demyelinating Autoimmune Diseases, CNS Immune System Diseases Leukemia, Myeloid, Acute Multiple Sclerosis Myelitis Myelitis, Transverse Nervous System Diseases Neuromyelitis Optica Prostatic Neoplasms, Castration-Resistant	35
Mogamulizumab	Mycosis Fungoides Neoplasms Sezary Syndrome	-
Moxetumomab pasudotox	Leukemia, Hairy Cell Neoplasms	27
Necitumumab	Carcinoma, Non-Small-Cell Lung Neoplasms	-
Nelarabine	Precursor T-Cell Lymphoblastic Leukemia-Lymphoma	-
Neratinib	Breast Neoplasms	79
Nilotinib	Blast Crisis Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid, Chronic-Phase	82
Nilutamide	Prostatic Neoplasms	-
Nintedanib	Fibrosis Idiopathic Pulmonary Fibrosis	92
Niraparib	Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms	44
Nivolumab	Carcinoma, Non-Small-Cell Lung Kidney Neoplasms Neoplasms Lung Neoplasms Melanoma	-
Obinutuzumab	Leukemia, Lymphocytic, Chronic, B-Cell	-
Octreotide	Acromegaly Adenoma Ascites Carcinoid Tumor Fistula Pancreatic Fistula Pituitary Diseases Renal Insufficiency Vipoma	47
Ofatumumab	Leukemia, Lymphocytic, Chronic, B-Cell	-
Olaparib	Breast Neoplasms Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Ovarian Neoplasms Pancreatic Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant	41
Olaratumab	Sarcoma	-
Osimertinib	Carcinoma, Non-Small-Cell Lung	84
Oxaliplatin	Colonic Neoplasms Colorectal Neoplasms Neoplasms Rectal Neoplasms	72
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	78
Palbociclib	Breast Neoplasms	43
Panitumumab	Colorectal Neoplasms	39
Panobinostat	Multiple Myeloma	59
Pazopanib	Carcinoma Carcinoma, Renal Cell Sarcoma	88
Pembrolizumab	Carcinoma, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Non-Small-Cell Lung Carcinoma, Renal Cell Carcinoma, Transitional Cell Hodgkin Disease Melanoma Neoplasms Stomach Neoplasms	-
Pemetrexed	Carcinoma, Non-Small-Cell Lung Mesothelioma	-
Pentostatin	Leukemia, Hairy Cell	17
Pertuzumab	Breast Neoplasms	87
Pomalidomide	Multiple Myeloma	17
Ponatinib	Leukemia, Myelogenous, Chronic, BCR-ABL Positive Precursor Cell Lymphoblastic Leukemia-Lymphoma	87
Pralatrexate	Lymphoma, T-Cell, Peripheral	-
Radium Ra 223 Dichloride	Prostatic Neoplasms, Castration-Resistant	-
Ramucirumab	Stomach Neoplasms	-

Rasburicase	Hyperuricemia Leukemia Lymphoma Neoplasms Syndrome Tumor Lysis Syndrome	-
Regorafenib	Colorectal Neoplasms	94
Relugolix	Prostatic Neoplasms	-
Ribociclib	Breast Neoplasms	54
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	8
Romidepsin	Lymphoma, T-Cell, Cutaneous	77
Rucaparib	Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant	66
Ruxolitinib	Graft vs Host Disease Polycythemia Polycythemia Vera Primary Myelofibrosis Thrombocytosis	76
Selinexor	Multiple Myeloma	25
Selumetinib	Neurofibromatosis 1	80
Siltuximab	Giant Lymph Node Hyperplasia	-
Sirolimus	Angiomyolipoma Constriction, Pathologic Coronary Restenosis Eye Diseases Immune System Diseases Kidney Failure, Chronic Lipoma Tuberous Sclerosis	95
Sonidegib	Carcinoma, Basal Cell	-
Sorafenib	Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms	94
Sunitinib	Adenoma Carcinoma, Renal Cell Digestive System Neoplasms Gastrointestinal Neoplasms Gastrointestinal Stromal Tumors Intestinal Neoplasms	96
Talazoparib	Breast Neoplasms	30
Tamoxifen	Breast Diseases Cystic Fibrosis Cysts Fibroadenoma Fibrocystic Breast Disease Hemorrhage Menorrhagia Menstruation Disturbances Metrorrhagia Neoplasms	64
Tamsulosin	Calculi Coronary Artery Disease Heart Diseases Hernia Hernia, Inguinal Inflammation Ischemia Lithiasis Lower Urinary Tract Symptoms Myocardial Ischemia Prostatic Hyperplasia Ureteral Calculi Urinary Calculi Urolithiasis Urologic Diseases	-
Temozolomide	Astrocytoma Nervous System Neoplasms	28
Temsirolimus	Carcinoma, Renal Cell	83
Teniposide	Precursor Cell Lymphoblastic Leukemia-Lymphoma	43
Thalidomide	Brain Abscess Immune System Diseases Multiple Myeloma Neoplasms, Plasma Cell	55
Tivozanib	Carcinoma, Renal Cell	83
Tocilizumab	Arthritis Arthritis, Juvenile Arthritis, Rheumatoid Behavior Cytokine Release Syndrome Giant Cell Arteritis Neurobehavioral Manifestations Oral Manifestations Psychotic Disorders Schizophrenia Tic Disorders	-
Topotecan	Small Cell Lung Carcinoma	34
Toremifene	Breast Neoplasms	19
Trabectedin	Leiomyosarcoma Liposarcoma	-
Trametinib	Carcinoma, Non-Small-Cell Lung Melanoma	87
Trastuzumab	Breast Neoplasms Neoplasms	70
Tretinoin	Lentigo	75
Triptorelin	Fatty Liver Hypogonadism Infertility, Female Prostatic Neoplasms	76
Tucatinib	Breast Neoplasms	88
Valrubicin	Urinary Bladder Neoplasms	-
Vandetanib	Thyroid Neoplasms	91
Vemurafenib	Melanoma	79
Venetoclax	Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Myeloid, Acute	-
Vinblastine	Glioma	39
Vincristine	Precursor Cell Lymphoblastic Leukemia-Lymphoma	27
Vinorelbine	Carcinoma, Non-Small-Cell Lung	48
Vismodegib	Carcinoma, Basal Cell	-
Vorinostat	Lymphoma, T-Cell, Cutaneous	73
Zoledronate	Arthritis Bone Marrow Diseases Brain Abscess Chronic Kidney Disease-Mineral and Bone Disorder Chronic Periodontitis HIV Infections Hypersensitivity Infections Kidney Diseases Metabolic	-

6. Conclusion

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

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



Vatalanib, seliciclib, Camptothecin and Iodophenyl

These drugs were selected for acting on the following targets: DYRK1B, HIF1A and MTOR, 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:



Jak1, PML, MKK3:Dyrk1B:PHS 2:HNF-1alpha and 26S proteasome

These potential drug targets should be considered as a prospective research initiative for further drug repurposing and drug development purposes. The following drugs were predicted as, matching those drug targets: 2,6-Dihydroanthra/1,9-Cd/Pyrazol-6-One, Tazarotene, CA4P, Uracil mustard, seliciclib, Vatalanib and uab-30. These drugs should be considered with special caution for research purposes only.

In this study, we came up with a detailed signal transduction network regulating genes carrying sequence variations in the studied pathology. In this network we have revealed the following top master regulators (signaling proteins and their complexes) that play a crucial role in the molecular mechanism of the studied pathology, which can be proposed as the most promising molecular targets for further drug repurposing and drug development initiatives.

- Jak1
- PML
- MKK3:Dyrk1B:PHS 2:HNF-1alpha
- 26S proteasome

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

7. Methods

Databases used in the study

Transcription factor binding sites in promoters and enhancers of genes carrying sequence variations were analyzed using known DNA-binding motifs described in the [TRANSFAC®](https://genexplain.com/transfac) library, release 2023.2 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transfac>). The master regulator search uses the [TRANSPATH®](https://genexplain.com/transpath) database (BIOBASE), release 2023.2 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transpath>). A comprehensive signal transduction network of human cells is built by the software on the basis of reactions annotated in [TRANSPATH®](https://genexplain.com/transpath).

The information about drugs corresponding to identified drug targets and clinical trials references were extracted from [HumanPSD™](https://genexplain.com/humanpsd) database, release 2023.2 (<https://genexplain.com/humanpsd>).

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

Genomic data processing

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

$w_1 = 0.7$ for variations in exon area

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

$w_1 = 1.0$ for variations in other locations.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Methods for finding master regulators in networks

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

Methods for analysis of pharmaceutical compounds

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

Method for analysis of known pharmaceutical compounds

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

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

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

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

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

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

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

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

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

Method for prediction of pharmaceutical compounds

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

We selected compounds that satisfied the following conditions:

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

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

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

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 $G(m)$; $\text{optWeight}(g)$ 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" ($D\text{-score}$) is calculated as follows:

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

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

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Supplementary material

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

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

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

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

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