

DNMT3B and DNMT1 are promising druggable targets for treating Lung Neoplasms that control activity of NR3C1, RXRA and TAL1 transcription factor on promoters of genes encoding enzymes metabolizing given metabolites

Demo User

geneXplain GmbH

info@genexplain.com

Data received on 06/09/2019 ; Run on 29/06/2024 ; Report generated on 29/06/2024

Genome Enhancer release 3.4 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2024.1)



Abstract

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

From the data set analyzed in this study, we found the following TFs to be potentially involved in the regulation of the genes encoding enzymes metabolizing given metabolites: NR3C1, RXRA and TAL1. The subsequent network analysis suggested

- DNMT3B
- DNMT1

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: tariquidar, Raltegravir and UBIQUINONE-1.

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 encoding enzymes metabolizing given metabolites 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 |
|------------------------|--------------|
| TGF_72h vs. NO_TGF_72h | Metabolomics |



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: TNF vs NO_TNF 72h.

3.1. Identification of target genes

In the first step of the analysis **target genes** were identified from the uploaded experimental data. The metabolites were mapped to Recon2 database. Then, genes encoding enzymes, which are involved in synthesis, degradation or modification of these metabolites were identified in Recon2 database. These genes (**target genes**) were then used for further upstream analysis.

Table 2. Top ten genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h.

[See full table](#) →

| ID | Gene description | Gene symbol | Recon2 ID | Title | logFC |
|---------------------------------|-------------------------------------|-------------|--------------------|---|-------|
| ENSG00000109107 | aldolase, fructose-bisphosphate C | ALDOC | M_pmtcrn | L-palmitoylcarnitine | 12.21 |
| ENSG00000110090 | carnitine palmitoyltransferase 1A | CPT1A | M_dgsn,M_pmtcrn | Deoxyguanosine,L-palmitoylcarnitine | 12.21 |
| ENSG00000136872 | aldolase, fructose-bisphosphate B | ALDOB | M_pmtcrn | L-palmitoylcarnitine | 12.21 |
| ENSG00000149925 | aldolase, fructose-bisphosphate A | ALDOA | M_pmtcrn | L-palmitoylcarnitine | 12.21 |
| ENSG00000157184 | carnitine palmitoyltransferase 2 | CPT2 | M_dgsn,M_pmtcrn | Deoxyguanosine,L-palmitoylcarnitine | 12.21 |
| ENSG00000169169 | carnitine palmitoyltransferase 1C | CPT1C | M_dgsn,M_pmtcrn | Deoxyguanosine,L-palmitoylcarnitine | 12.21 |
| ENSG00000178537 | solute carrier family 25 member 20 | SLC25A20 | M_pmtcrn | L-palmitoylcarnitine | 12.21 |
| ENSG00000205560 | carnitine palmitoyltransferase 1B | CPT1B | M_dgsn,M_pmtcrn | Deoxyguanosine,L-palmitoylcarnitine | 12.21 |
| ENSG00000129673 | aralkylamine N-acetyltransferase | AANAT | M_Nacsertn | N-acetylserotonin | 11.77 |
| ENSG00000196433 | acetylserotonin O-methyltransferase | ASMT | M_Nacsertn,M_ahcys | N-acetylserotonin,S-Adenosyl-L-homocysteine | 11.77 |

3.2. Functional classification of genes

A functional analysis of genes encoding enzymes metabolizing given metabolites 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.

Genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h:

237 genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h genes were taken for the mapping.

TRANSPATH® Pathways (2024.1)

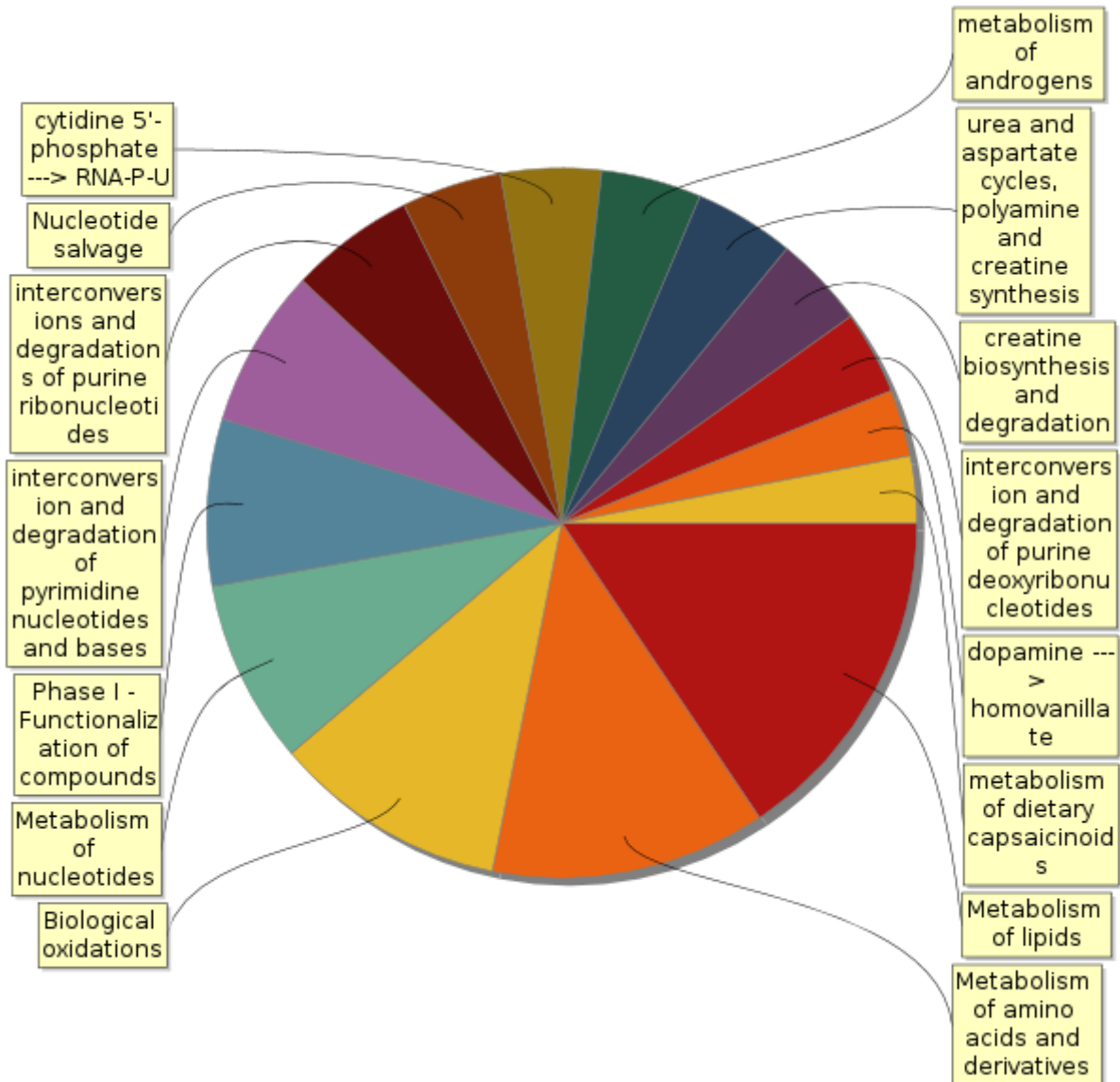
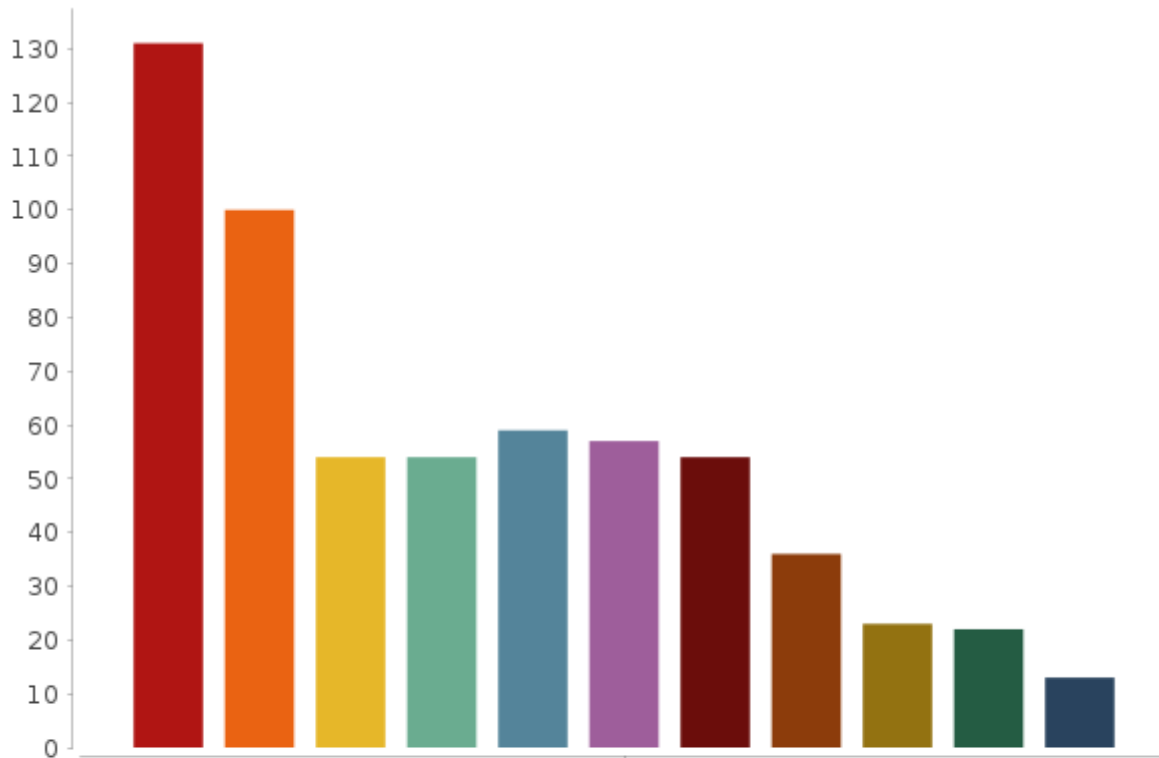


Figure 3. Enriched TRANSPATH® Pathways (2024.1) of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h.

[Full classification](#) →

HumanPSD(TM) disease (2024.1)

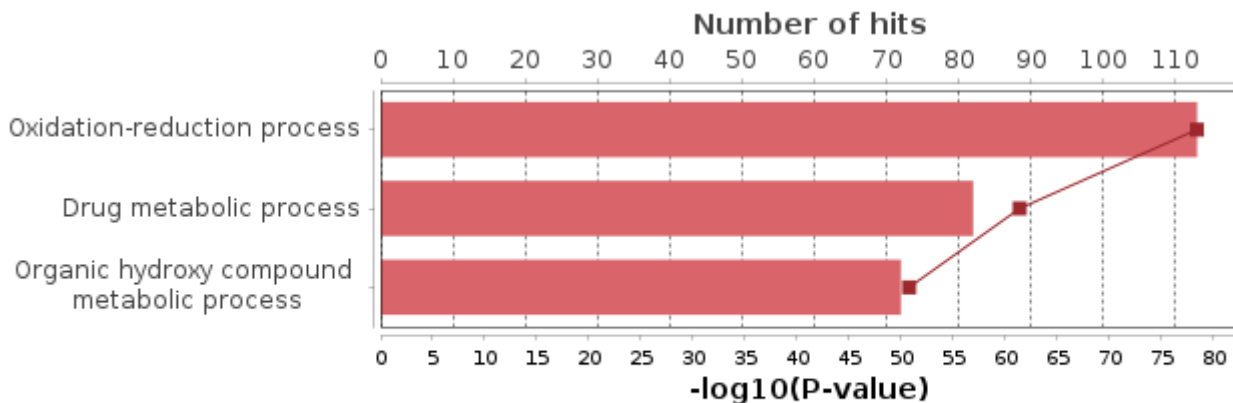


- Urogenital Diseases
- Male Urogenital Diseases
- Metabolic Diseases
- Nutritional and Metabolic Diseases
- Genital Neoplasms, Male
- Prostatic Neoplasms
- Congenital, Hereditary, and Neonatal Diseases and Abnormalities
- Metabolism, Inborn Errors
- Female Urogenital Diseases and Pregnancy Complications
- Female Urogenital Diseases
- Amino Acid Metabolism, Inborn Errors

Figure 4. Enriched HumanPSD(TM) disease (2024.1) of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h. 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 encoding enzymes metabolizing given metabolites of the studied pathology can be summarized by the following diagram, revealing the most significant functional categories overrepresented among the observed (genes encoding enzymes metabolizing given metabolites):



- Genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h hits
- Genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h $-\log_{10}(P\text{-value})$

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

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

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

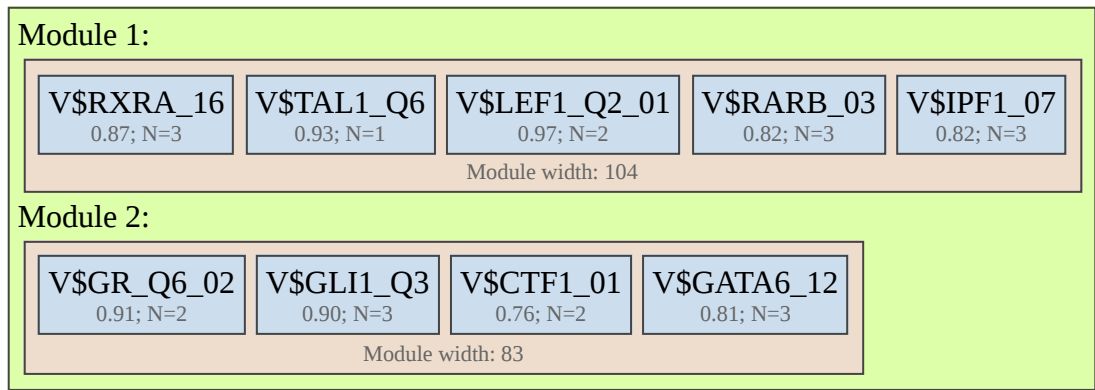
We applied the Composite Module Analyst (CMA) [8] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the enhancers by specifying combinations 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 (genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h).

To build the most specific composite modules we choose genes as the input of CMA algorithm.

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

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



Model score (-p*log10(pval)): 14.79

Wilcoxon p-value (pval): 2.53e-29

Penalty (p): 0.517

Average yes-set score: 7.60

Average no-set score: 5.91

AUC: 0.78

Separation point: 7.06

False-positive: 20.76%

False-negative: 32.49%

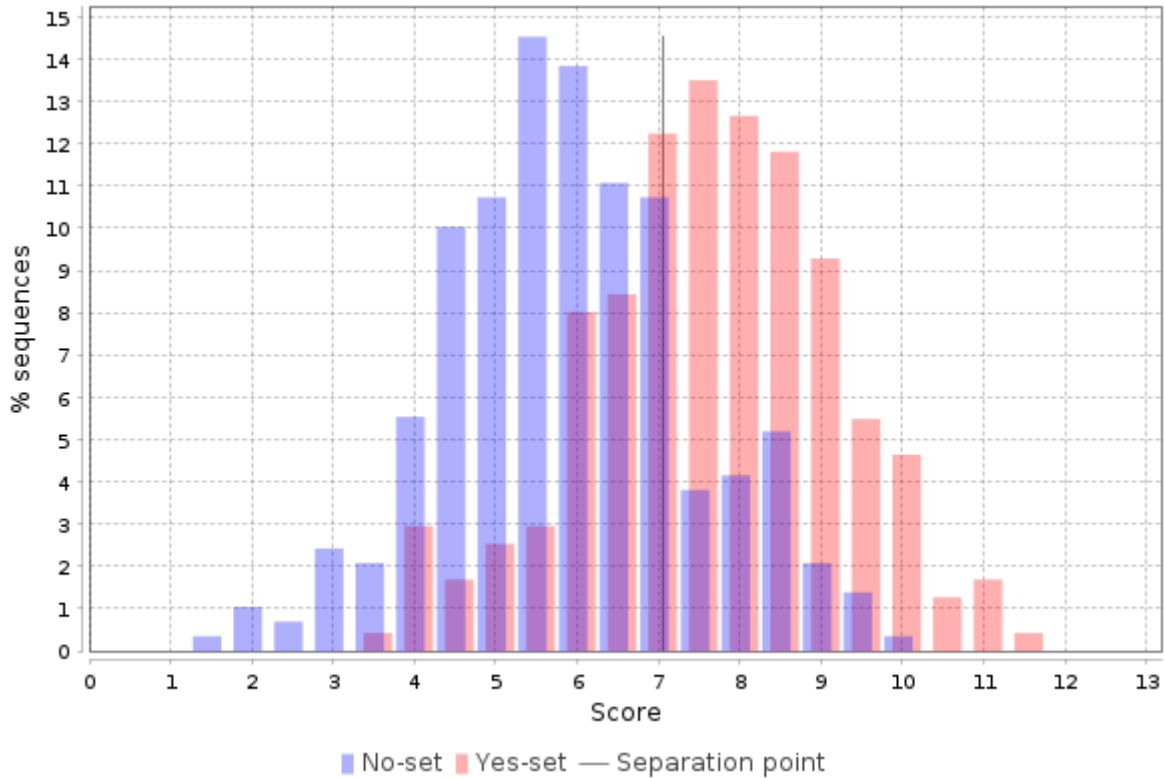


Table 3. List of top ten genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h with identified enhancers in their regulatory regions. **CMA score** - the score of the CMA model of the enhancer identified in the regulatory region.

[See full table](#) →

| Ensembl IDs | Gene symbol | Gene description | CMA score | Factor names |
|-----------------|-------------|--|-----------|---|
| ENSG00000093010 | COMT | catechol-O-methyltransferase | 11.55 | GLI1(h), GATA-6(h), GR(h), RXRalpha(h), PDX-1(h), RAR-beta(h), LEF-1(h)... |
| ENSG00000184254 | ALDH1A3 | aldehyde dehydrogenase 1 family member A3 | 11.09 | GLI1(h), GATA-6(h), GR(h), NF-1C(h), RXRalpha(h), RAR-beta(h), LEF-1(h) |
| ENSG00000160439 | RDH13 | retinol dehydrogenase 13 | 10.97 | NF-1C(h), GR(h), GLI1(h), GATA-6(h), Tal-1(h), PDX-1(h), RXRalpha(h)... |
| ENSG00000138109 | CYP2C9 | cytochrome P450 family 2 subfamily C member 9 | 10.85 | PDX-1(h), Tal-1(h), RXRalpha(h), GR(h), RAR-beta(h), GATA-6(h), LEF-1(h) |
| ENSG00000160688 | FLAD1 | flavin adenine dinucleotide synthetase 1 | 10.85 | GATA-6(h), NF-1C(h), GLI1(h), PDX-1(h), GR(h), RXRalpha(h), LEF-1(h)... |
| ENSG00000156222 | SLC28A1 | solute carrier family 28 member 1 | 10.61 | RXRalpha(h), RAR-beta(h), GR(h), Tal-1(h), PDX-1(h), GLI1(h), NF-1C(h) |
| ENSG00000203857 | HSD3B1 | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1 | 10.43 | PDX-1(h), RXRalpha(h), RAR-beta(h), Tal-1(h), GR(h), GATA-6(h), LEF-1(h)... |
| ENSG00000197446 | CYP2F1 | cytochrome P450 family 2 subfamily F member 1 | 10.26 | RXRalpha(h), RAR-beta(h), PDX-1(h), Tal-1(h), GLI1(h), NF-1C(h), GR(h) |
| ENSG00000100170 | SLC5A1 | solute carrier family 5 member 1 | 10.14 | RXRalpha(h), RAR-beta(h), GLI1(h), GR(h), GATA-6(h), PDX-1(h), NF-1C(h)... |
| ENSG00000131480 | AOC2 | amine oxidase copper containing 2 | 10.11 | GATA-6(h), NF-1C(h), Tal-1(h), PDX-1(h), GLI1(h), RXRalpha(h), RAR-beta(h)... |

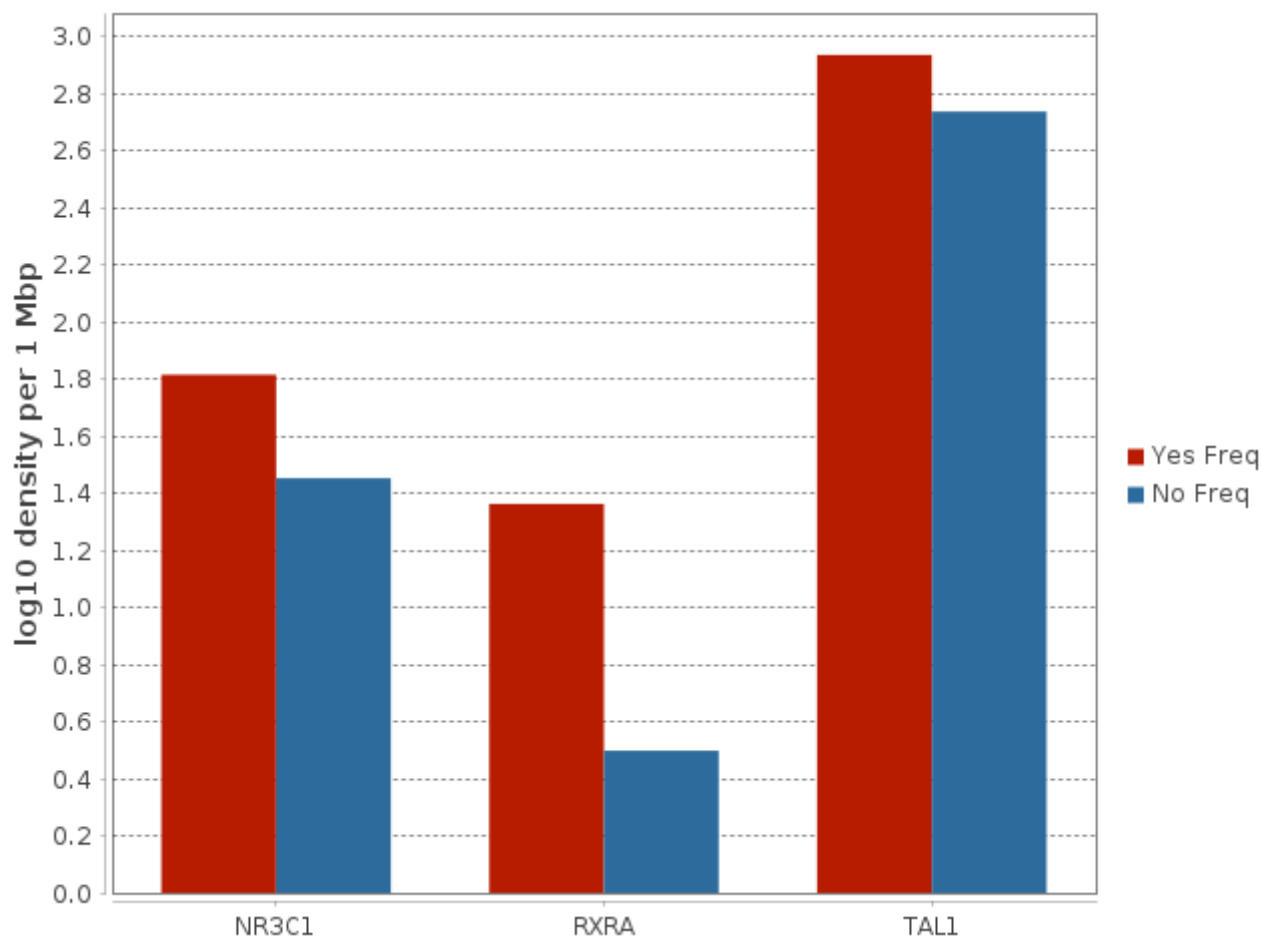
On the basis of the enhancer models we identified transcription factors potentially regulating the **target genes** of our interest. We found 9 transcription factors controlling expression of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h (see Table 4).

Table 4. Transcription factors of the predicted enhancer model potentially regulating the genes encoding enzymes metabolizing given metabolites (genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h). **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 |
|--------------|-------------|---|------------------|--------------|
| MO000031266 | NR3C1 | nuclear receptor subfamily 3 group C member 1 | 2.86 | 2.3 |
| MO000019619 | RXRA | retinoid X receptor alpha | 2.71 | 7.32 |
| MO000032489 | TAL1 | TAL bHLH transcription factor 1, erythroid differentiation factor | 2.14 | 1.58 |
| MO000019117 | GLI1 | GLI family zinc finger 1 | 2.03 | 1.28 |
| MO0000159782 | LEF1 | lymphoid enhancer binding factor 1 | 2.03 | 2.1 |
| MO000007664 | PDX1 | pancreatic and duodenal homeobox 1 | 1.59 | 1.65 |
| MO000019618 | RARB | retinoic acid receptor beta | 1.59 | 1.64 |
| MO000024750 | NFIC | nuclear factor I C | 1.08 | 1.52 |
| MO000026665 | GATA6 | GATA binding protein 6 | 0.4 | 1.66 |

The following diagram represents the key transcription factors, which were predicted to be potentially regulating genes encoding enzymes metabolizing given metabolites in the analyzed pathology: NR3C1, RXRA and TAL1.



3.4. Finding master regulators in networks

In the second step of the upstream analysis common regulators of the revealed TFs were identified. These master regulators appear to be the key candidates for therapeutic targets as they have a master effect on regulation of intracellular pathways that activate the pathological process of our study. The identified master regulators are shown in Table 5.

Table 5. Master regulators that may govern the regulation of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, metabolomics data.

[See full table](#) →

| ID | Master molecule name | Gene symbol | Gene description | Total rank |
|-------------|----------------------|-------------|------------------------------|------------|
| MO000093731 | DNMT3B-isoform1(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000093733 | DNMT3B-isoform2(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000093734 | DNMT3B-isoform3(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000093736 | DNMT3B-isoform4(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000093737 | DNMT3B-isoform5(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000093738 | DNMT3B-isoform6(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000286251 | DNMT3B-isoform7(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000286252 | DNMT3B-isoform8(h) | DNMT3B | DNA methyltransferase 3 beta | 27 |
| MO000093732 | DNMT3B(h) | DNMT3B | DNA methyltransferase 3 beta | 38 |
| MO000054397 | DNMT1(h) | DNMT1 | DNA methyltransferase 1 | 72 |

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 encoding enzymes metabolizing given metabolites, and selected master regulators, which are responsible for the regulation of these TFs.

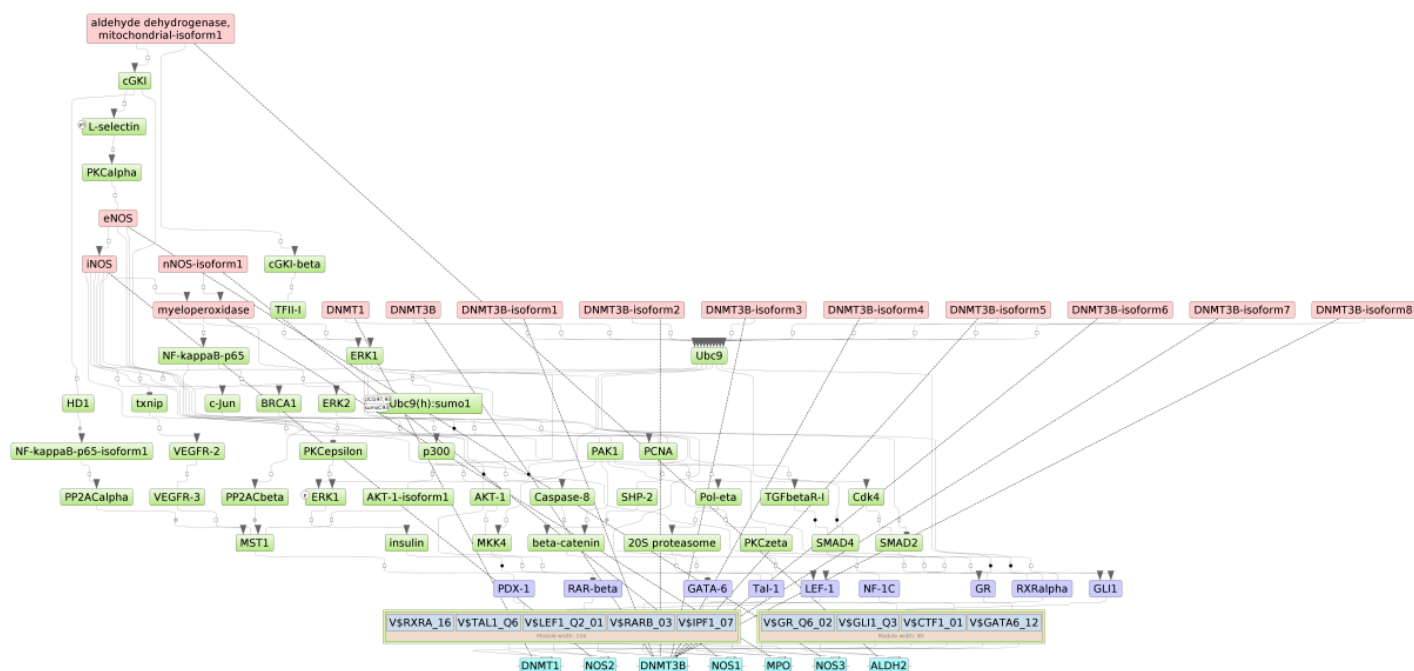


Figure 5. Diagram of intracellular regulatory signal transduction pathways of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h. Master regulators are indicated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which have been added to the network during the search for master regulators from selected TFs. Orange and blue frames highlight molecules that are encoded by up- and downregulated genes, resp.

[See full diagram](#) →

4. Finding prospective drug targets

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

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

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

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



Table 6. 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 |
|-------------|---|--------------------|------------|
| DNMT3B | DNA methyltransferase 3 beta | 6 | 38 |
| DNMT1 | DNA methyltransferase 1 | 18 | 72 |
| ARG2 | arginase 2 | 2 | 98 |
| CYP2J2 | cytochrome P450 family 2 subfamily J member 2 | 1 | 98 |
| SLC7A2 | solute carrier family 7 member 2 | 2 | 112 |
| CYP1B1 | cytochrome P450 family 1 subfamily B member 1 | 11 | 125 |



Table 7. 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.

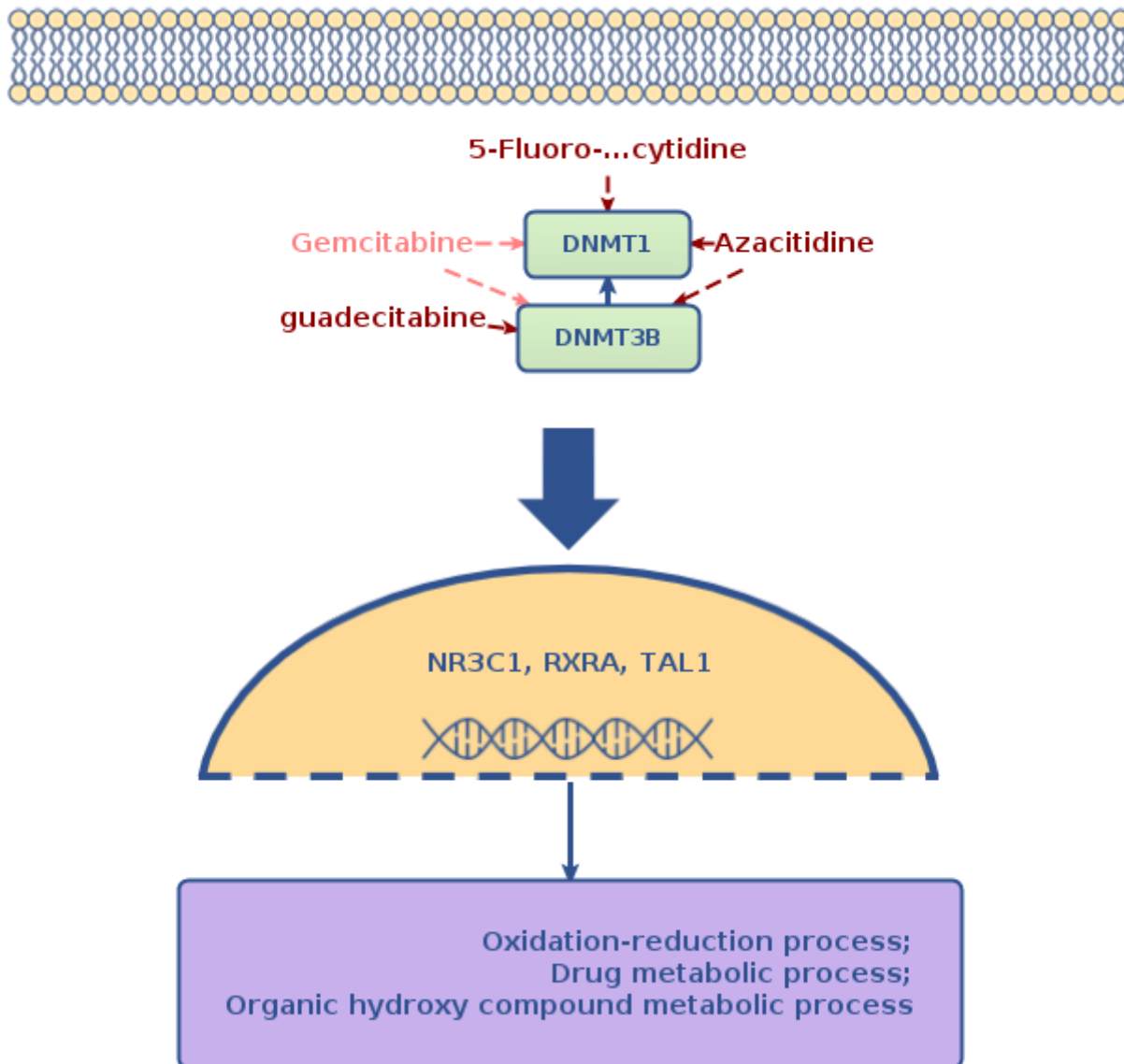
[See full table](#) →

| Gene symbol | Gene Description | Druggability score | Total rank |
|-------------|---|--------------------|------------|
| DNMT3B | DNA methyltransferase 3 beta | 14.35 | 38 |
| DNMT1 | DNA methyltransferase 1 | 16.64 | 72 |
| CYP2J2 | cytochrome P450 family 2 subfamily J member 2 | 12.28 | 98 |
| CYP1B1 | cytochrome P450 family 1 subfamily B member 1 | 12.28 | 125 |
| MPO | myeloperoxidase | 96.88 | 128 |
| DNMT3A | DNA methyltransferase 3 alpha | 14.35 | 136 |

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:

- DNMT3B
- DNMT1

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: Gemcitabine, Azacitidine, guadecitabine and 5-Fluoro-2'-deoxycytidine, 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 8 and 9), reflects the number of the highest clinical trials phase on which the drug was tested for any pathology).

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

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

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

Drugs approved in clinical trials



Table 8. FDA approved drugs or 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 |
|-----------------------------|--|------------|------------------------|--|
| tariquidar | CYP2B6, CYP3A4, CYP1A2, CYP2E1, CYP2C9, CYP2C8, CYP2D6 | 94 | 2 | Phase 2: Lung Neoplasms, Adrenal Cortex Neoplasms, Adrenocortical Carcinoma, Kidney Neoplasms, Neoplasms, Ovarian Neoplasms, Uterine Cervical Neoplasms |
| Azacitidine | DNMT3B, DNMT1, DNMT3A | 94 | 3 | Phase 2: Lung Neoplasms, Acute Disease, Anemia, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Blast Crisis, Brain Abscess, Breast Neoplasms, Carcinoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Renal Cell, Carcinoma, Transitional Cell, Chromosome Aberrations, Chromosome Disorders, Cytopenia, Enteropathy-Associated T-Cell Lymphoma, Fibroma, Gastrointestinal Stromal Tumors, Glioma, Head and Neck Neoplasms, Hematologic Diseases, Hematologic Neoplasms, Hodgkin Disease, Hypereosinophilic Syndrome, Immunoblastic Lymphadenopathy, Kidney Neoplasms, Leukemia, Leukemia, Erythroblastic, Acute, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative, Leukemia, Myelomonocytic, Acute, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Leukemia, Neutrophilic, Chronic, Lymphadenopathy, Lymphatic Diseases, Lymphoma, Lymphoma, Non-Hodgkin, Lymphoma, T-Cell, Lymphoma, T-Cell, Peripheral, Melanoma, Multiple Myeloma, Myelodysplastic Syndromes, Myelodysplastic-Myeloproliferative Diseases, Myeloproliferative Disorders, Nasopharyngeal Carcinoma, Nasopharyngeal Neoplasms, Neoplasm, Residual, Neoplasms, Neoplasms, Plasma Cell, Neurofibroma, Neurofibromatoses, Neurofibromatosis 1, Osteosarcoma, Paraganglioma, Pharyngeal Neoplasms, Pheochromocytoma, Pica, Plasmacytoma, Polycythemia, Polycythemia Vera, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Prostatic Neoplasms, Recurrence, Sarcoma, Syndrome, Thalassemia, Thrombocytopenia, Essential, Thrombocytopenia, Thrombocytosis, Tuberculosis, Tuberculosis, Pulmonary, Urinary Bladder Neoplasms, alpha-Thalassemia, beta-Thalassemia |
| Decitabine | DNMT3B, DNMT1, DNMT3A | 94 | 3 | Phase 2: Lung Neoplasms, Anemia, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Anemia, Sickle Cell, Blast Crisis, Bone Marrow Failure Disorders, Breast Neoplasms, COVID-19, Carcinoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Congenital Bone Marrow Failure Syndromes, Cytopenia, Esophageal Neoplasms, Esophageal Squamous Cell Carcinoma, Extranodal Extension, Glioma, Leukemia, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Myelomonocytic, Chronic, Leukemia, Myelomonocytic, Juvenile, Lymphoma, Lymphoma, B-Cell, Lymphoma, Large B-Cell, Diffuse, Medulloblastoma, Mesothelioma, Mesothelioma, Malignant, Myelodysplastic Syndromes, Myelodysplastic-Myeloproliferative Diseases, Myeloproliferative Disorders, Nasopharyngeal Carcinoma, Neoplasm, Residual, Neoplasms, Neuroectodermal Tumors, Neuroectodermal Tumors, Primitive, Neutropenia, Pancytopenia, Pneumonia, Polycythemia, Polycythemia Vera, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Preleukemia, Primary Myelofibrosis, Recurrence, Severe Acute Respiratory Syndrome, Syndrome, Thalassemia, Thrombocytopenia, Essential, Thrombocytopenia, Thrombocytosis, Urinary Bladder Neoplasms, alpha-Thalassemia, beta-Thalassemia |

| | | | | |
|-----------------------------|------------------------|----|---|--|
| tilarginine | NOS1, NOS3, NOS2 | 88 | 1 | Phase 1: Lung Neoplasms, Carcinoma, Carcinoma, Non-Small-Cell Lung, Carcinoma, Squamous Cell, Carcinoma, Transitional Cell, Cerebral Arterial Diseases, Cysts, DNA Repair-Deficiency Disorders, Endotoxemia, Essential Hypertension, Fibrosis, Glomerulonephritis, Hodgkin Disease, Hypercapnia, Hypertension, Hypoxia, Insulin Resistance, Kidney Diseases, Kidney Diseases, Cystic, Liver Cirrhosis, Lymphoma, Melanoma, Neoplasms, Nephritis, Obesity, Polycystic Kidney Diseases, Polycystic Kidney, Autosomal Dominant, Sarcopenia, Squamous Cell Carcinoma of Head and Neck, Toxemia, Urinary Bladder Neoplasms |
| Allopurinol | HPRT1, XDH | 87 | 3 | Phase 2: Lung Neoplasms, Anemia, Anemia, Refractory, Anemia, Refractory, with Excess of Blasts, Apnea, Arthritis, Arthritis, Gouty, Ascites, Bipolar Disorder, Brain Abscess, Brain Diseases, Burkitt Lymphoma, Carcinoma, Small Cell, Cardiomyopathies, Cardiomyopathy, Dilated, Cardiovascular Diseases, Diabetes Mellitus, Diabetes Mellitus, Type 2, Essential Hypertension, Fibrosis, Gout, Hand-Foot Syndrome, Heart Diseases, Heart Failure, Hematologic Diseases, Hepatic Encephalopathy, Hypertension, Hyperuricemia, Kidney Diseases, Leishmaniasis, Leishmaniasis, Cutaneous, Leukemia, Leukemia, Biphenotypic, Acute, Leukemia, Lymphocytic, Chronic, B-Cell, Leukemia, Lymphoid, Leukemia, Myelogenous, Chronic, BCR-ABL Positive, Leukemia, Myeloid, Leukemia, Myeloid, Acute, Leukemia, Plasma Cell, Leukemia, Prolymphocytic, Liver Cirrhosis, Lymphoma, Lymphoma, Mantle-Cell, Mania, Metabolic Diseases, Multiple Myeloma, Muscular Diseases, Myelodysplastic Syndromes, Myeloproliferative Disorders, Neoplasms, Neoplasms, Plasma Cell, Peritonitis, Plasmacytoma, Precursor Cell Lymphoblastic Leukemia-Lymphoma, Prehypertension, Preleukemia, Renal Insufficiency, Renal Insufficiency, Chronic, Sleep Apnea Syndromes, Sleep Apnea, Obstructive, Small Cell Lung Carcinoma, Syndrome, Vascular Diseases, Waldenstrom Macroglobulinemia |

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

Repurposing drugs



Table 9. 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 |
|-------------------------------|---|------------|---|
| Raltegravir | CYP3A4, CYP1A2, CYP2C9, CYP2D6 | 92 | Phase 4: Acquired Immunodeficiency Syndrome, Bone Diseases, Bone Diseases, Metabolic, Cardiovascular Diseases, Communicable Diseases, Drug Misuse, Fatty Liver, Fatty Liver, Alcoholic, HIV Infections, HIV Seropositivity, Hepatitis, Hepatitis A, Hepatitis C, Hepatitis C, Chronic, Immunologic Deficiency Syndromes, Infections, Inflammation, Liver Diseases, Metabolic Diseases, Non-alcoholic Fatty Liver Disease, Osteoporosis, Syndrome, Tuberculosis, Vascular Diseases |
| Nitroarginine | NOS1, NOS3, NOS2 | 91 | Phase 1: Cardiovascular Diseases, Vascular Diseases |
| gw-274150 | NOS1, NOS3, NOS2 | 91 | Phase 2: Arthritis, Arthritis, Rheumatoid, Migraine Disorders |
| filibuvir | CYP3A4, CYP1A2, CYP2C9, CYP2C8 | 91 | Phase 2: Hepatitis, Hepatitis A, Hepatitis C |
| rsv-604 | CYP3A4, CYP1A2, CYP2C9, CYP2D6 | 91 | Phase 2: Communicable Diseases, Infections, Respiratory Syncytial Virus Infections, Virus Diseases |

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



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



Table 10. 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 |
|--------------|--|------------|-----------------------|
| UBIQUINONE-1 | CYP2B6, CYP3A4, ALDH1A2, CYP1B1, CYP1A2, CYP2J2, NOS3, CYP2E1, CYP2C9, CYP2C8, CYP2D6, CYP1A1 | 95 | 0.44 |
| Gemcitabine | NT5E, DNMT3B, DNMT1, ASS1, NT5C, TK1, DNMT3A, NT5C3A, NT5M, TK2 | 86 | 0.22 |
| Bisoxatin | CYP2B6, CYP3A4, CYP1B1, CYP1A2, CYP2J2, CYP2E1, CYP2C9, CYP2C8, CYP2D6, CYP1A1 | 85 | 0.51 |
| Hesperetin | CYP3A4, TPO, CYP1A2, CYP2J2, XDH, CYP2C9, CYP2C8, CYP2B6, MAOA, MPO, CYP1B1, CKB, NOS3, CYP2E1, CYP2D6, CYP1A1 | 84 | 0.74 |
| Floxuridine | NT5E, DNMT3B, TYMP, NOS3, DNMT1, ASS1, NT5C, NT5C3A, TK1, DNMT3A, NT5M, TK2 | 83 | 0.42 |

As the result of drug search we propose the following drugs as most promising candidates for treating the pathology under study: tariquidar, Raltegravir and UBIQUINONE-1. These drugs were selected for acting on the following targets: CYP3A4 and CYP2J2, 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 11. Supplementary drug info: extended list of drugs used for treatment of neoplasms with respective drug scores predicted for the studied pathology.

| Drug | Disease | Predicted Drug Score |
|---------------------------|--|----------------------|
| Abarelix | Prostatic Neoplasms | - |
| Abemaciclib | Breast Neoplasms | - |
| Abiraterone | Prostatic Neoplasms, Castration-Resistant | 81 |
| Abiraterone acetate | Prostatic Neoplasms, Castration-Resistant | - |
| Acalabrutinib | Lymphoma, Mantle-Cell | - |
| Acitretin | Psoriasis | - |
| Ado-trastuzumab emtansine | Breast Neoplasms Neoplasms | - |
| Afatinib | Carcinoma, Non-Small-Cell Lung | - |
| Aflibercept | Colorectal Neoplasms Diabetic Retinopathy Edema Vascular Diseases Wet Macular Degeneration | 48 |
| Alectinib | Carcinoma, Non-Small-Cell Lung | 20 |

| | | |
|---------------------|---|----|
| 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 | Keratosis Keratosis, Actinic | - |
| Anagrelide | Thrombocythemia, Essential Thrombocytosis | - |
| Anastrozole | Breast Neoplasms Hypersensitivity Obesity Obesity, Morbid Recurrence Weight Loss | 66 |
| Apalutamide | Prostatic Neoplasms, Castration-Resistant | - |
| Aprepitant | Nausea Neoplasms Postoperative Nausea and Vomiting | 52 |
| Arsenic trioxide | Leukemia, Promyelocytic, Acute | - |
| 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 | 24 |
| Azacitidine | Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes Preleukemia Syndrome | 94 |
| Belinostat | Lymphoma, T-Cell, Peripheral | - |
| Bendamustine | Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Lymphoid | - |
| Bevacizumab | Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms Corneal Neovascularization Diabetic Retinopathy Dilatation, Pathologic Edema Epistaxis Glaucoma Hemorrhage Macular Degeneration Macular Edema Neoplasm Metastasis Neoplasms Neovascularization, Pathologic Optic Nerve Diseases Pterygium Rectal Neoplasms Retinal Detachment Retinal Diseases Retinal Vein Occlusion Telangiectasia, Hereditary Hemorrhagic Telangiectasis Vitreous Hemorrhage | - |
| Bexarotene | Lymphoma, T-Cell Lymphoma, T-Cell, Cutaneous | - |
| Bicalutamide | Prostatic Neoplasms | 9 |
| Binimetinib | Melanoma | - |
| Blinatumomab | Precursor B-Cell Lymphoblastic Leukemia-Lymphoma | - |
| Bortezomib | Brain Abscess Glomerulonephritis Glomerulonephritis, IGA Kidney Diseases Multiple Myeloma Neoplasms, Plasma Cell Nephritis Renal Insufficiency | - |
| Bosutinib | Leukemia, Myelogenous, Chronic, BCR-ABL Positive | - |
| Brentuximab vedotin | Hodgkin Disease Lymphoma Lymphoma, Large-Cell, Anaplastic Lymphoma, T-Cell, Peripheral | - |
| Brigatinib | Carcinoma, Non-Small-Cell Lung | - |
| Buserelin | Prostatic Neoplasms | - |
| Cabazitaxel | Prostatic Neoplasms, Castration-Resistant | - |
| Cabergoline | Drug-Related Side Effects and Adverse Reactions Pituitary Neoplasms | - |
| Cabozantinib | Thyroid Neoplasms | - |
| Capecitabine | Breast Neoplasms Colonic Neoplasms Colorectal Neoplasms | - |
| Carboplatin | Carcinoma, Non-Small-Cell Lung Lung Neoplasms Neoplasms Neuroendocrine Tumors Ovarian Neoplasms Retinoblastoma | - |
| Carfilzomib | Multiple Myeloma | - |
| Carmustine | Astrocytoma Glioblastoma Hodgkin Disease Medulloblastoma Multiple Myeloma Neoplasms | - |
| Ceritinib | Carcinoma, Non-Small-Cell Lung | - |
| Cetuximab | Colorectal Neoplasms | - |
| Cinacalcet | Anemia Calcinosis Cardiovascular Diseases Hyperparathyroidism Hyperparathyroidism, Secondary Kidney Diseases Kidney Failure, Chronic Neoplasm Metastasis Neoplasms Parathyroid Neoplasms Renal Insufficiency Vascular Calcification Vascular Diseases Vision Disorders | - |

| | | |
|-------------------------|--|----|
| Cisplatin | Carcinoma, Squamous Cell Neoplasms Uterine Cervical Neoplasms Carcinoma, Non-Small-Cell Lung Esophageal Neoplasms Carcinoma | 28 |
| Cladribine | Leukemia, Hairy Cell | 5 |
| Clofarabine | Precursor Cell Lymphoblastic Leukemia-Lymphoma | 50 |
| Cobimetinib | Melanoma | - |
| Copanlisib | Lymphoma, Follicular | - |
| Crizotinib | Carcinoma, Non-Small-Cell Lung | - |
| Cyproterone acetate | Prostatic Neoplasms | - |
| Dabrafenib | Melanoma | - |
| Dacomitinib | Carcinoma, Non-Small-Cell Lung | - |
| Daratumumab | Multiple Myeloma | - |
| Dasatinib | Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid, Chronic-Phase Precursor Cell Lymphoblastic Leukemia-Lymphoma | - |
| Decitabine | Anemia, Refractory Anemia, Refractory, with Excess of Blasts Leukemia, Myelomonocytic, Chronic Myelodysplastic Syndromes | 94 |
| Degarelix | Cardiovascular Diseases Prostatic Neoplasms Vascular Diseases | - |
| Denosumab | Arthritis, Rheumatoid Bone Diseases Bone Diseases, Metabolic Breast Neoplasms Hyperparathyroidism Hyperparathyroidism, Primary Metabolic Diseases Neoplasm Metastasis Neoplasms Osteoporosis Osteoporosis, Postmenopausal Prostatic Neoplasms | - |
| Dexrazoxane | Breast Neoplasms Cardiomyopathies | - |
| Dienogest | Menorrhagia | - |
| Dinutuximab | Neuroblastoma | - |
| Docetaxel | Breast Neoplasms Carcinoma, Non-Small-Cell Lung Prostatic Neoplasms Squamous Cell Carcinoma of Head and Neck Stomach Neoplasms | - |
| Doxorubicin | Neoplasms Multiple Myeloma Carcinoma, Ovarian Epithelial Ovarian Neoplasms Leukemia, Lymphoid Breast Neoplasms Lymphoma, Follicular Thyroid Neoplasms Triple Negative Breast Neoplasms Glioma | 49 |
| Durvalumab | Carcinoma, Non-Small-Cell Lung Carcinoma, Transitional Cell | - |
| Dutasteride | Alcoholism Hyperplasia Hypertrophy Neoplasms Prostatic Hyperplasia | - |
| Duvelisib | Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular | - |
| Elotuzumab | Multiple Myeloma | - |
| Enasidenib | Leukemia, Myeloid, Acute | - |
| Encorafenib | Colorectal Neoplasms Melanoma | - |
| Enfortumab vedotin | Carcinoma, Transitional Cell Neoplasms | - |
| Entrectinib | Carcinoma, Non-Small-Cell Lung | - |
| Enzalutamide | Prostatic Neoplasms Prostatic Neoplasms, Castration-Resistant | - |
| Epirubicin | Breast Neoplasms | - |
| Erdafitinib | Urinary Bladder Neoplasms | - |
| Eribulin | Breast Neoplasms Drug-Related Side Effects and Adverse Reactions Neoplasms | - |
| Erlotinib | Carcinoma, Non-Small-Cell Lung Neoplasms Pancreatic Neoplasms | - |
| Erlotinib hydrochloride | Carcinoma, Non-Small-Cell Lung Gastrointestinal Stromal Tumors | - |
| Estramustine | Prostatic Neoplasms | - |
| Ethinyl Estradiol | Acne Vulgaris Neoplasms | 9 |
| 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 | - |
| Exemestane | Breast Neoplasms | 72 |
| Fedratinib | Primary Myelofibrosis | - |
| Finasteride | Hyperplasia Neoplasms Prostatic Hyperplasia | - |
| Flavopiridol | Leukemia, Lymphocytic, Chronic, B-Cell | - |
| Fluorouracil | Skin Neoplasms Neoplasms, Basal Cell Neoplasms, Second Primary Neoplasms, Squamous Cell Neoplasms Colorectal Neoplasms Pancreatic Neoplasms | 25 |
| Fluoxymesterone | Breast Neoplasms Hypogonadism Puberty, Delayed | - |

| | | |
|-----------------------------|--|----|
| Flutamide | Premenstrual Dysphoric Disorder Premenstrual Syndrome Prostatic Neoplasms | 28 |
| Fulvestrant | Breast Neoplasms | 69 |
| Gefitinib | Carcinoma, Non-Small-Cell Lung | - |
| Gemcitabine | Breast Neoplasms Carcinoma, Non-Small-Cell Lung Ovarian Neoplasms Pancreatic Neoplasms | - |
| Gemtuzumab ozogamicin | Leukemia, Myeloid, Acute | - |
| Gilteritinib | Leukemia, Myeloid, Acute | - |
| 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 | - |
| Ibritumomab | Lymphoma, B-Cell Lymphoma, Follicular | - |
| Ibrutinib | Graft vs Host Disease Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, B-Cell, Marginal Zone Lymphoma, Mantle-Cell Waldenstrom Macroglobulinemia | - |
| Idarubicin | Leukemia, Myeloid, Acute | - |
| Idelalisib | Leukemia, Lymphocytic, Chronic, B-Cell Lymphoma, Follicular | - |
| Ifosfamide | Neoplasms | 77 |
| Imatinib | Leukemia, Myelogenous, Chronic, BCR-ABL Positive Mastocytosis, Systemic Neoplasms | 1 |
| Inotuzumab ozogamicin | Precursor B-Cell Lymphoblastic Leukemia-Lymphoma | - |
| Ipilimumab | Carcinoma, Renal Cell Melanoma | - |
| Irinotecan | Colorectal Neoplasms | 23 |
| Ivosidenib | Leukemia, Myeloid, Acute | - |
| Ixabepilone | Breast Neoplasms | - |
| Ixazomib | Multiple Myeloma | - |
| Lapatinib | Breast Neoplasms | - |
| Larotrectinib | Neoplasm Metastasis | - |
| Lenalidomide | Brain Abscess Lupus Erythematosus, Cutaneous Myelodysplastic Syndromes Neoplasms, Plasma Cell | - |
| Lenvatinib | Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms | - |
| Letrozole | Breast Neoplasms Cysts Fibroma Myofibroma Myoma Ovarian Cysts Syndrome | 66 |
| Leuprolide | Hot Flashes Ovarian Hyperstimulation Syndrome Prostatic Neoplasms Puberty, Precocious | - |
| Levamisole | Ascariasis Colonic Neoplasms Helminthiasis | - |
| Levonorgestrel | Epilepsy Hyperplasia Menorrhagia | - |
| Lomustine | Brain Neoplasms Hodgkin Disease | - |
| Lonafarnib | Breast Neoplasms Carcinoma, Non-Small-Cell Lung Central Nervous System Neoplasms Colorectal Neoplasms Gliosarcoma Head and Neck Neoplasms Leukemia, Myelomonocytic, Chronic Liver Neoplasms Lymphoma Myelodysplastic Syndromes Ovarian Neoplasms Urethral Neoplasms Urinary Bladder Neoplasms | - |
| Lorlatinib | Carcinoma, Non-Small-Cell Lung | - |
| Masoprocol | Keratosi, Actinic | - |
| Medroxyprogesterone Acetate | Depression Depression, Postpartum Depressive Disorder Metrorrhagia Neoplasms Uterine Hemorrhage | 43 |
| 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 | - |
| Methyltestosterone | Breast Neoplasms Hypogonadism Puberty, Delayed | 72 |
| Midostaurin | Leukemia, Mast-Cell Leukemia, Myeloid, Acute Mastocytosis, Systemic | - |
| Mitotane | Adrenocortical Carcinoma | 65 |
| Mitoxantrone | Autoimmune Diseases Autoimmune Diseases of the Nervous System Demyelinating Autoimmune Diseases, CNS Immune System | 78 |

| | | |
|--------------------------|--|----|
| | Diseases Leukemia, Myeloid, Acute Multiple Sclerosis Myelitis Myelitis, Transverse Nervous System Diseases Neuromyelitis Optica Prostatic Neoplasms, Castration-Resistant | |
| Mogamulizumab | Mycosis Fungoides Neoplasms Sezary Syndrome | - |
| Moxetumomab pasudotox | Leukemia, Hairy Cell Neoplasms | - |
| Necitumumab | Carcinoma, Non-Small-Cell Lung Neoplasms | - |
| Nelarabine | Precursor T-Cell Lymphoblastic Leukemia-Lymphoma | - |
| Neratinib | Breast Neoplasms | - |
| Nilotinib | Blast Crisis Leukemia, Myelogenous, Chronic, BCR-ABL Positive Leukemia, Myeloid, Chronic-Phase | - |
| Nilutamide | Prostatic Neoplasms | - |
| Nintedanib | Fibrosis Idiopathic Pulmonary Fibrosis | - |
| Niraparib | Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms | - |
| Nivolumab | Carcinoma, Non-Small-Cell Lung Kidney Neoplasms Neoplasms Lung Neoplasms Melanoma | - |
| Obinutuzumab | Leukemia, Lymphocytic, Chronic, B-Cell | - |
| Octreotide | Acromegaly Adenoma Ascites Carcinoid Tumor Fistula Pancreatic Fistula Pituitary Diseases Renal Insufficiency Vipoma | 30 |
| Ofatumumab | Leukemia, Lymphocytic, Chronic, B-Cell | - |
| Olaparib | Breast Neoplasms Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Ovarian Neoplasms Pancreatic Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant | - |
| Olaratumab | Sarcoma | - |
| Osimertinib | Carcinoma, Non-Small-Cell Lung | - |
| Oxaliplatin | Colonic Neoplasms Colorectal Neoplasms Neoplasms Rectal Neoplasms | - |
| 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 | 12 |
| Palbociclib | Breast Neoplasms | - |
| Panitumumab | Colorectal Neoplasms | - |
| Panobinostat | Multiple Myeloma | - |
| Pazopanib | Carcinoma Carcinoma, Renal Cell Sarcoma | - |
| Pembrolizumab | Carcinoma, Hepatocellular Carcinoma, Merkel Cell Carcinoma, Non-Small-Cell Lung Carcinoma, Renal Cell Carcinoma, Transitional Cell Hodgkin Disease Melanoma Neoplasms Stomach Neoplasms | - |
| Pemetrexed | Carcinoma, Non-Small-Cell Lung Mesothelioma | - |
| Pentostatin | Leukemia, Hairy Cell | - |
| Pertuzumab | Breast Neoplasms | - |
| Pomalidomide | Multiple Myeloma | - |
| Ponatinib | Leukemia, Myelogenous, Chronic, BCR-ABL Positive Precursor Cell Lymphoblastic Leukemia-Lymphoma | - |
| 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 | - |
| Relugolix | Prostatic Neoplasms | - |
| Ribociclib | Breast Neoplasms | - |
| Rituximab | Arthritis Arthritis, Rheumatoid Granulomatosis with Polyangiitis Leukemia Leukemia, Lymphoid Lymphoma Lymphoma, B-Cell Lymphoma, Follicular Lymphoma, Non-Hodgkin Myelitis Neuromyelitis Optica Purpura Purpura, Thrombocytopenic Purpura, Thrombocytopenic, Idiopathic Thrombocytopenia | - |
| Romidepsin | Lymphoma, T-Cell, Cutaneous | - |

| | | |
|--------------|--|----|
| Rucaparib | Carcinoma, Ovarian Epithelial Fallopian Tube Neoplasms Peritoneal Neoplasms Prostatic Neoplasms, Castration-Resistant | - |
| Ruxolitinib | Graft vs Host Disease Polycythemia Polycythemia Vera Primary Myelofibrosis Thrombocytosis | - |
| Selinexor | Multiple Myeloma | - |
| Selumetinib | Neurofibromatosis 1 | - |
| Siltuximab | Giant Lymph Node Hyperplasia | - |
| Sirolimus | Angiomyolipoma Constriction, Pathologic Coronary Restenosis Eye Diseases Immune System Diseases Kidney Failure, Chronic Lipoma Tuberous Sclerosis | 19 |
| Sonidegib | Carcinoma, Basal Cell | - |
| Sorafenib | Carcinoma, Hepatocellular Carcinoma, Renal Cell Thyroid Neoplasms | - |
| Sunitinib | Adenoma Carcinoma, Renal Cell Digestive System Neoplasms Gastrointestinal Neoplasms Gastrointestinal Stromal Tumors Intestinal Neoplasms | - |
| Talazoparib | Breast Neoplasms | - |
| Tamoxifen | Breast Diseases Cystic Fibrosis Cysts Fibroadenoma Fibrocystic Breast Disease Hemorrhage Menorrhagia Menstruation Disturbances Metrorrhagia Neoplasms | 3 |
| Tamsulosin | Calculi Coronary Artery Disease Heart Diseases Hernia Hernia, Inguinal Inflammation Ischemia Lithiasis Lower Urinary Tract Symptoms Myocardial Ischemia Prostatic Hyperplasia Ureteral Calculi Urinary Calculi Urolithiasis Urologic Diseases | - |
| Temozolomide | Astrocytoma Nervous System Neoplasms | - |
| Temsirolimus | Carcinoma, Renal Cell | - |
| Teniposide | Precursor Cell Lymphoblastic Leukemia-Lymphoma | - |
| Thalidomide | Brain Abscess Immune System Diseases Multiple Myeloma Neoplasms, Plasma Cell | - |
| Tivozanib | Carcinoma, Renal Cell | - |
| 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 | - |
| Toremifene | Breast Neoplasms | 75 |
| Trabectedin | Leiomyosarcoma Liposarcoma | - |
| Trametinib | Carcinoma, Non-Small-Cell Lung Melanoma | - |
| Trastuzumab | Breast Neoplasms Neoplasms | - |
| Tretinoin | Lentigo | 33 |
| Triptorelin | Fatty Liver Hypogonadism Infertility, Female Prostatic Neoplasms | - |
| Tucatinib | Breast Neoplasms | - |
| Valrubicin | Urinary Bladder Neoplasms | - |
| Vandetanib | Thyroid Neoplasms | - |
| Vemurafenib | Melanoma | - |
| Venetoclax | Leukemia, Lymphocytic, Chronic, B-Cell Leukemia, Myeloid, Acute | - |
| Vinblastine | Glioma | 28 |
| Vincristine | Precursor Cell Lymphoblastic Leukemia-Lymphoma | - |
| Vinorelbine | Carcinoma, Non-Small-Cell Lung | - |
| Vismodegib | Carcinoma, Basal Cell | - |
| Vorinostat | Lymphoma, T-Cell, Cutaneous | - |
| Zoledronate | Arthritis Bone Marrow Diseases Brain Abscess Chronic Kidney Disease-Mineral and Bone Disorder Chronic Periodontitis HIV Infections Hypersensitivity Infections Kidney Diseases Metabolic Diseases Multiple Myeloma Neoplasms Neoplasms, Plasma Cell Neoplasms, Second Primary Osteitis Osteoarthritis Periodontitis Pleural Effusion, Malignant Prostatic Neoplasms Renal Insufficiency, Chronic Thalassemia Wounds and Injuries | - |

6. Conclusion

We applied the software package "Genome Enhancer" to a data set that contains *metabolomics* data. The study is done in the context of *Lung Neoplasms*. The data were pre-processed, statistically analyzed and genes encoding enzymes metabolizing given metabolites were identified. Also checked was the enrichment of GO or disease categories among the studied gene sets.

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



These drugs were selected for acting on the following targets: CYP3A4 and CYP2J2, which were predicted to be involved in the molecular mechanism of the pathology under study.

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



These potential drug targets should be considered as a prospective research initiative for further drug repurposing and drug development purposes. The following drugs were predicted as, matching those drug targets: Gemcitabine, Azacitidine, guadecitabine and 5-Fluoro-2'-deoxycytidine. 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 encoding enzymes metabolizing given metabolites 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.

- DNMT3B
- DNMT1

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 encoding enzymes metabolizing given metabolites were analyzed using known DNA-binding motifs described in the **TRANSFAC®** library, release 2024.1 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transfac>).

The master regulator search uses the **TRANSPATH®** database (BIOBASE), release 2024.1 (geneXplain GmbH, Wolfenbüttel, Germany) (<https://genexplain.com/transpath>). A comprehensive signal transduction network of human cells is built by the software on the basis of reactions annotated in **TRANSPATH®**.

The information about drugs corresponding to identified drug targets and clinical trials references were extracted from **HumanPSD™** database, release 2024.1 (<https://genexplain.com/humanpsd>).

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

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

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

We search for transcription factor binding sites (TFBS) that are enriched in the promoters and enhancers under study as compared to a background sequence set such as promoters of genes that were not differentially regulated under the condition of the experiment. We denote study and background sets briefly as Yes and No sets. In the current work we used a workflow considering promoter sequences of a standard length of 1100 bp (-1000 to +100). The error rate in this part of the pipeline is controlled by estimating the adjusted p-value (using the Benjamini-Hochberg procedure) in comparison to the TFBS frequency found in randomly selected regions of the human genome (adj.p-value < 0.01).

We have applied the CMA algorithm (Composite Module Analyst) for searching composite modules [7] in the promoters and enhancers of the Yes and No sets. We searched for a composite module consisting of a cluster of 10 TFs in a sliding window of 200-300 bp that statistically significantly separates sequences in the Yes and No sets (minimizing Wilcoxon p-value).

Methods for finding master regulators in networks

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

Methods for analysis of pharmaceutical compounds

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

Method for analysis of known pharmaceutical compounds

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

1. ranking by "Target activity score" ($T\text{-score}_{PSD}$),
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, $\maxRank(T)$ equals $\max(rank(t))$ for all targets t in T .

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

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

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, $phase(p, d)$ equals to the phase number if there are known clinical trials for the selected disease on this phase and zero otherwise.

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

Method for prediction of pharmaceutical compounds

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

We selected compounds that satisfied the following conditions:

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

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

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

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

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

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

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

8. References

1. Kel A, Voss N, Jauregui R, Kel-Margoulis O, Wingender E. Beyond microarrays: Finding key transcription factors controlling signal transduction pathways. *BMC Bioinformatics*. **2006**;7(S2), S13. doi:10.1186/1471-2105-7-s2-s13
2. Stegmaier P, Voss N, Meier T, Kel A, Wingender E, Borlak J. Advanced Computational Biology Methods Identify Molecular Switches for Malignancy in an EGF Mouse Model of Liver Cancer. *PLoS ONE*. **2011**;6(3):e17738. doi:10.1371/journal.pone.0017738

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

Thank you for using the Genome Enhancer!

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

Supplementary material

- [Supplementary table 1 - Detailed report. Composite modules and master regulators \(genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h\).](#)
- [Supplementary table 2 - Detailed report. Pharmaceutical compounds and drug targets.](#)

Disclaimer

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

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

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

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

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

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