

SETD7 is promising druggable target for treating lung neoplasms that controls activity of HNF4A, NFKB1 and TWIST1 transcription factor on promoters of genes encoding enzymes metabolizing given metabolites

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Genome Enhancer release 1.9 (TRANSFAC®, TRANSPATH® and HumanPSD™ release 2020.1)



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) novel biologically 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: HNF4A, NFKB1 and TWIST1. The subsequent network analysis suggested SETD7 as the most promising and druggable molecular targets. Finally, the following drugs were identified as the most promising treatment candidates: S-Adenosyl-L-Homocysteine.

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, new potential small molecular ligands are subsequently predicted for the revealed targets. A general druggability check is performed using a precomputed database of biological activities of chemical compounds from a library of about 13000 pharmaceutically most active compounds. The spectra of biological activities are computed using the program PASS on the basis of a (Q)SAR approach [11-13].

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 analysed 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:

236 genes encoding enzymes, metabolising target metabolites genes were taken for the mapping.

GO (biological process)

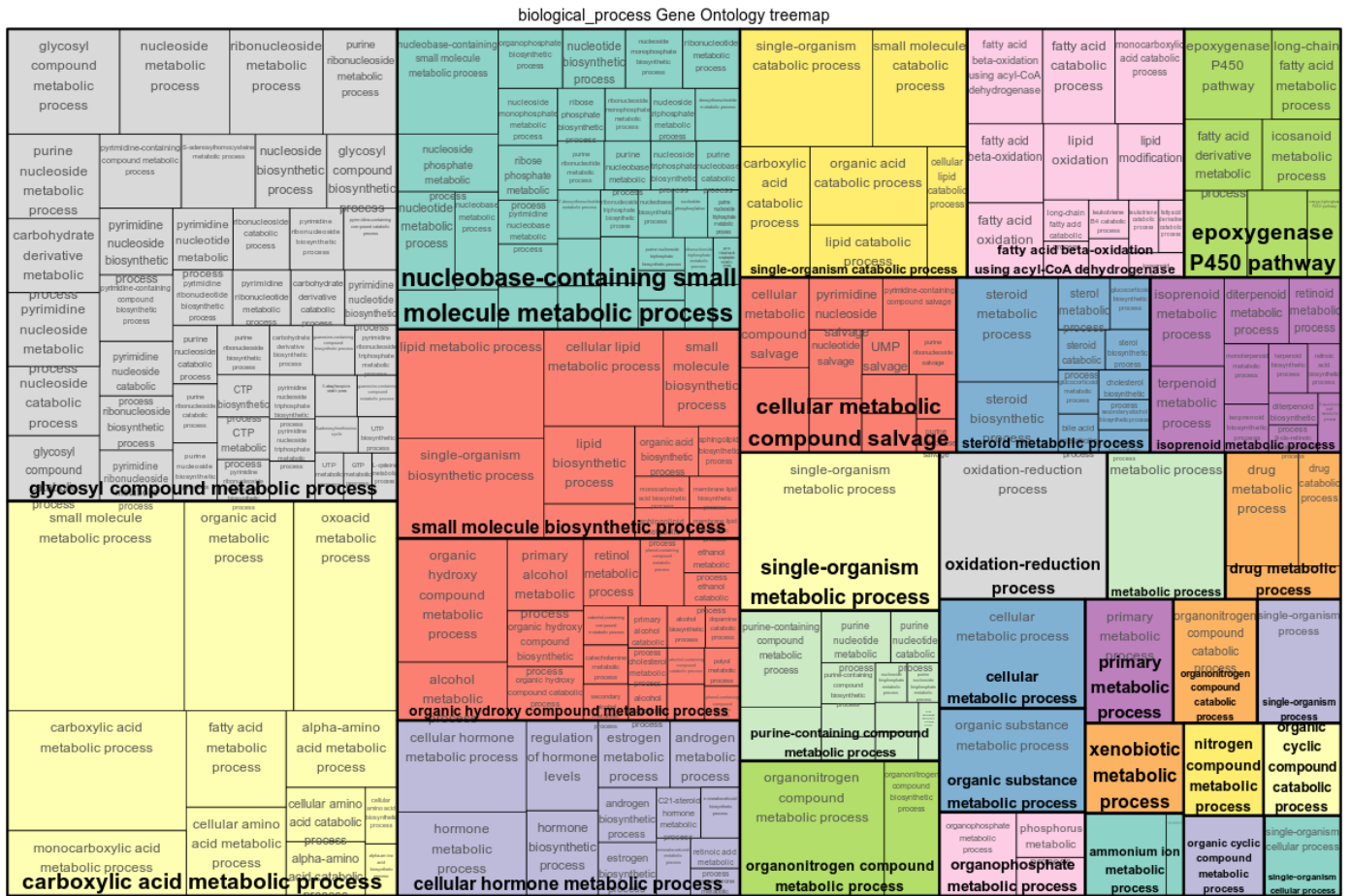


Figure 2. Enriched GO (biological process) of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h.

[Full classification →](#)

TRANSPATH® Pathways (2020.1)

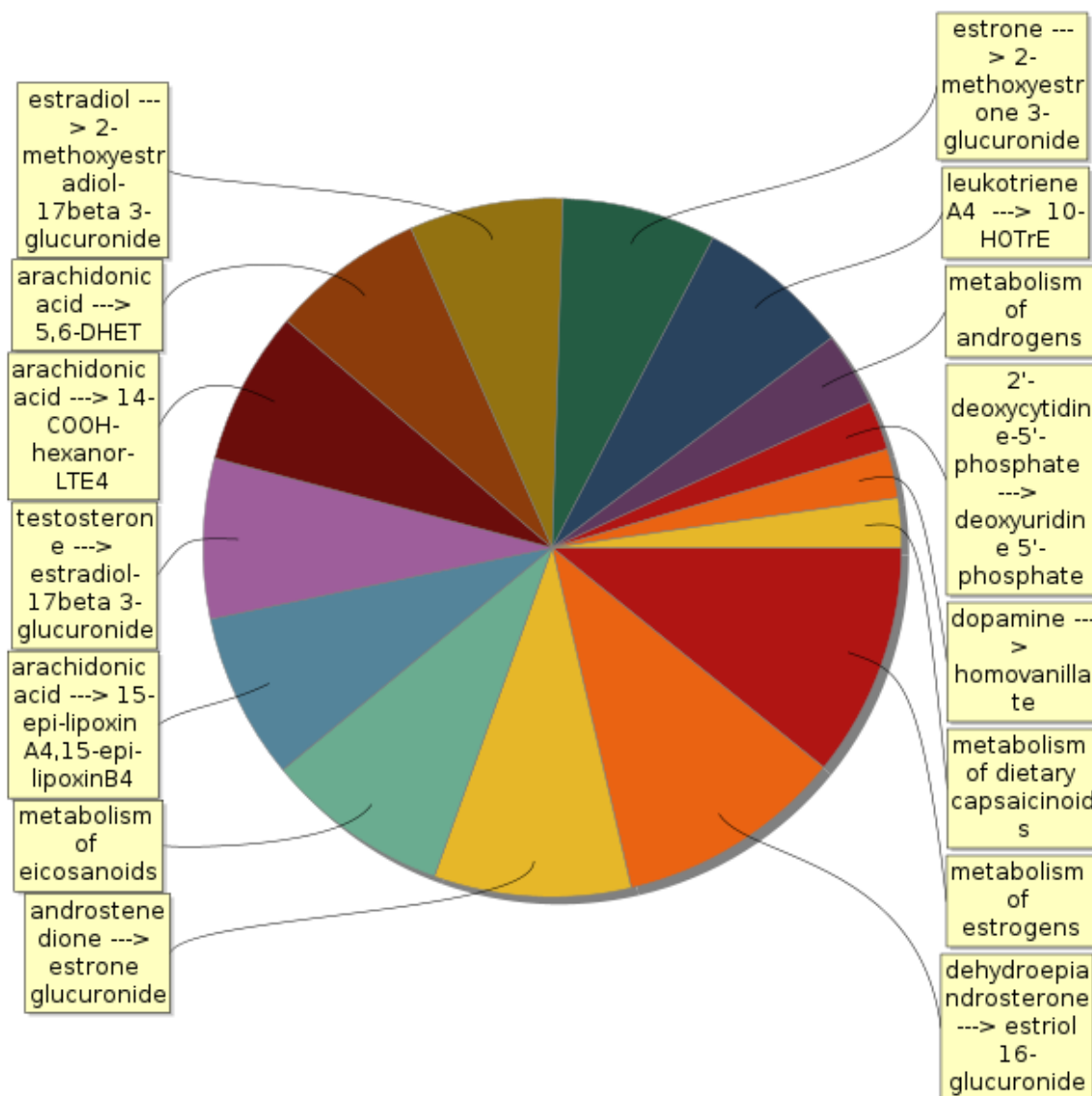


Figure 3. Enriched TRANSPATH® Pathways (2020.1) of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h.

[Full classification →](#)

HumanPSD(TM) disease (2020.1)

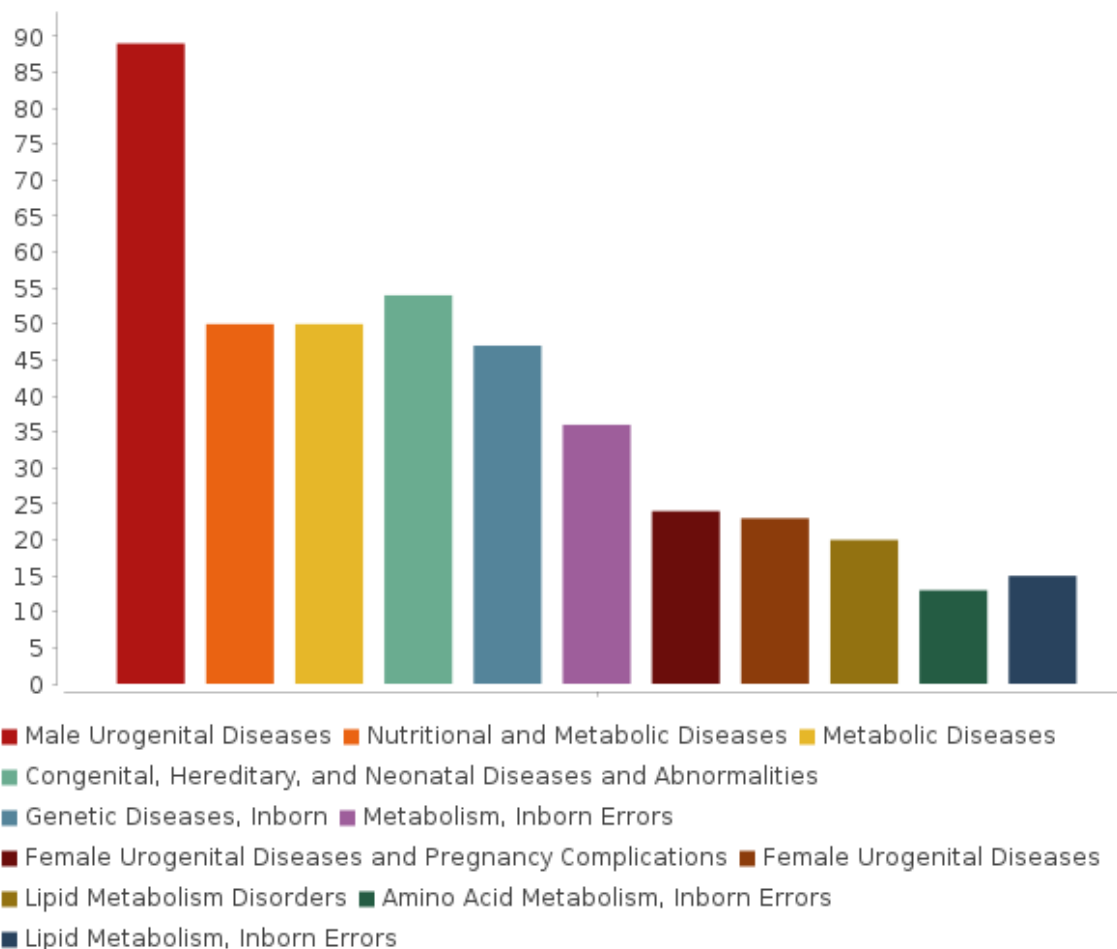


Figure 4. Enriched HumanPSD(TM) disease (2020.1) of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h. The size of the bars correspond to the number of bio-markers of the given disease found among the input set.

[Full classification →](#)

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].

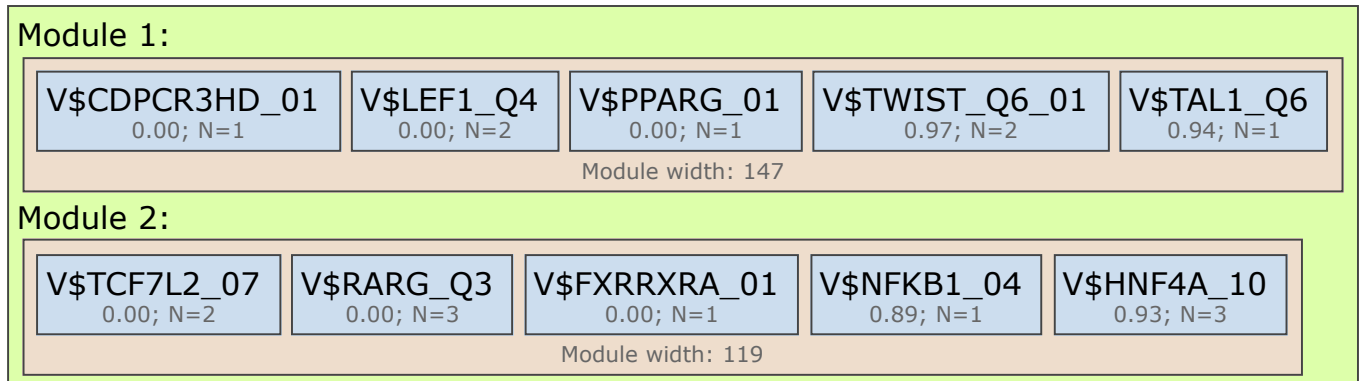
We applied the Composite Module Analyst (CMA) [8] method to detect such potential enhancers, as targets of multiple TFs bound in a cooperative manner to the regulatory regions of the genes of interest. CMA applies a genetic algorithm to construct a generalized model of the enhancers by specifying combinations 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)): 15.02

Wilcoxon p-value (pval): 1.07e-30

Penalty (p): 0.501

Average yes-set score: 4.51

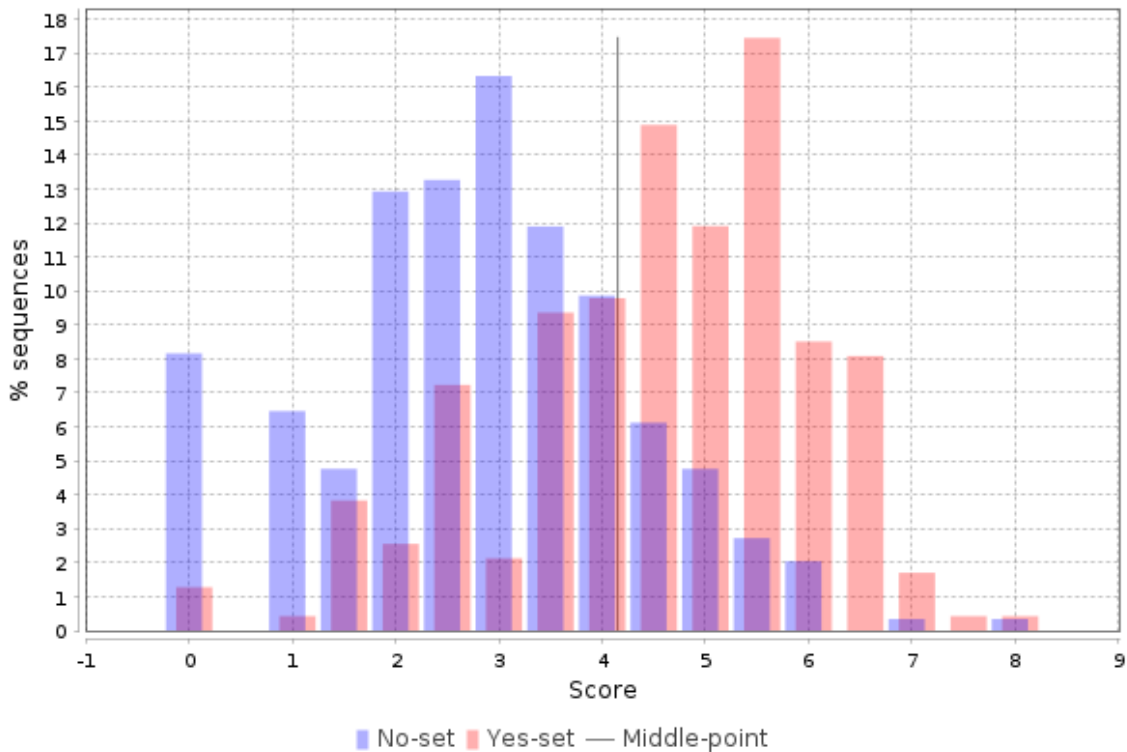
Average no-set score: 2.86

AUC: 0.79

Middle-point: 4.15

False-positive: 17.69%

False-negative: 33.62%



[See model visualization table](#) →

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
ENSG00000135929	CYP27A1	cytochrome P450 family 27 subfamily A member 1	7.8	LEF-1(h), RAR-gamma(h), Tal-1(h), PPARgamma(h), TCF-4(h), CDP(h)
ENSG00000138109	CYP2C9	cytochrome P450 family 2 subfamily C member 9	7.37	RAR-gamma(h), TCF-4(h), Tal-1(h), LEF-1(h), CDP(h), HNF-4alpha(h)
ENSG00000081181	ARG2	arginase 2	7.23	LEF-1(h), CDP(h), TCF-4(h), RAR-gamma(h), Tal-1(h), NF-kappaB1(h)
ENSG00000197506	SLC28A3	solute carrier family 28 member 3	6.84	LEF-1(h), Tal-1(h), TWIST(h), HNF-4alpha(h), NF-kappaB1(h), RAR-gamma(h), CDP(h)...
ENSG00000160868	CYP3A4	cytochrome P450 family 3 subfamily A member 4	6.82	RAR-gamma(h), TCF-4(h), HNF-4alpha(h), CDP(h), Tal-1(h)
ENSG00000197408	CYP2B6	cytochrome P450 family 2 subfamily B member 6	6.8	NF-kappaB1(h), CDP(h), TWIST(h), HNF-4alpha(h), RAR-gamma(h), TCF-4(h), LEF-1(h)
ENSG00000186115	CYP4F2	cytochrome P450 family 4 subfamily F member 2	6.67	PPARGgamma(h), TWIST(h), Tal-1(h), CDP(h), RAR-gamma(h), TCF-4(h)
ENSG00000006534	ALDH3B1	aldehyde dehydrogenase 3 family member B1	6.66	HNF-4alpha(h), CDP(h), RAR-gamma(h), NF-kappaB1(h), Tal-1(h)
ENSG00000186377	CYP4X1	cytochrome P450 family 4 subfamily X member 1	6.65	TCF-4(h), HNF-4alpha(h), NF-kappaB1(h), RAR-gamma(h), Tal-1(h), LEF-1(h)
ENSG00000111732	AICDA	activation induced cytidine deaminase	6.65	RAR-gamma(h), NF-kappaB1(h), TCF-4(h), LEF-1(h), CDP(h)

On the basis of the enhancer models we identified the following transcription factors potentially regulating the **target genes** of our interest. We found 9 transcription factors controlling expression of genes encoding enzymes, metabolising target metabolites (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
MO000027755	HNF4A	hepatocyte nuclear factor 4 alpha	0.72	6.26
MO000019359	NFKB1	nuclear factor kappa B subunit 1	0.58	1.16
MO000028695	TWIST1	twist family bHLH transcription factor 1	0.57	1.47
MO000026882	TCF7L2	transcription factor 7 like 2	0.52	1.57
MO000024708	CUX1	cut like homeobox 1	0.51	1.65
MO000032489	TAL1	TAL bHLH transcription factor 1, erythroid differentiation factor	0.51	1.59
MO000033565	PPARG	peroxisome proliferator activated receptor gamma	0.47	4.38
MO000159782	LEF1	lymphoid enhancer binding factor 1	0.47	2.19
MO000025130	RARG	retinoic acid receptor gamma	0	1.39

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
MO000081811	SUV39H1-isoform1(h)	SUV39H1	suppressor of variegation 3-9 homolog 1	5
MO000094524	G9A-isoform1(h)	EHMT2	euchromatic histone lysine methyltransferase 2	6
MO000065286	G9A(h)	EHMT2	euchromatic histone lysine methyltransferase 2	7
MO000081812	SUV39H1(h)	SUV39H1	suppressor of variegation 3-9 homolog 1	7
MO000334473	Sel-1(h)	DHCR24	24-dehydrocholesterol reductase	7
MO000044865	setd7(h)	SETD7	SET domain containing lysine methyltransferase 7	8

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.

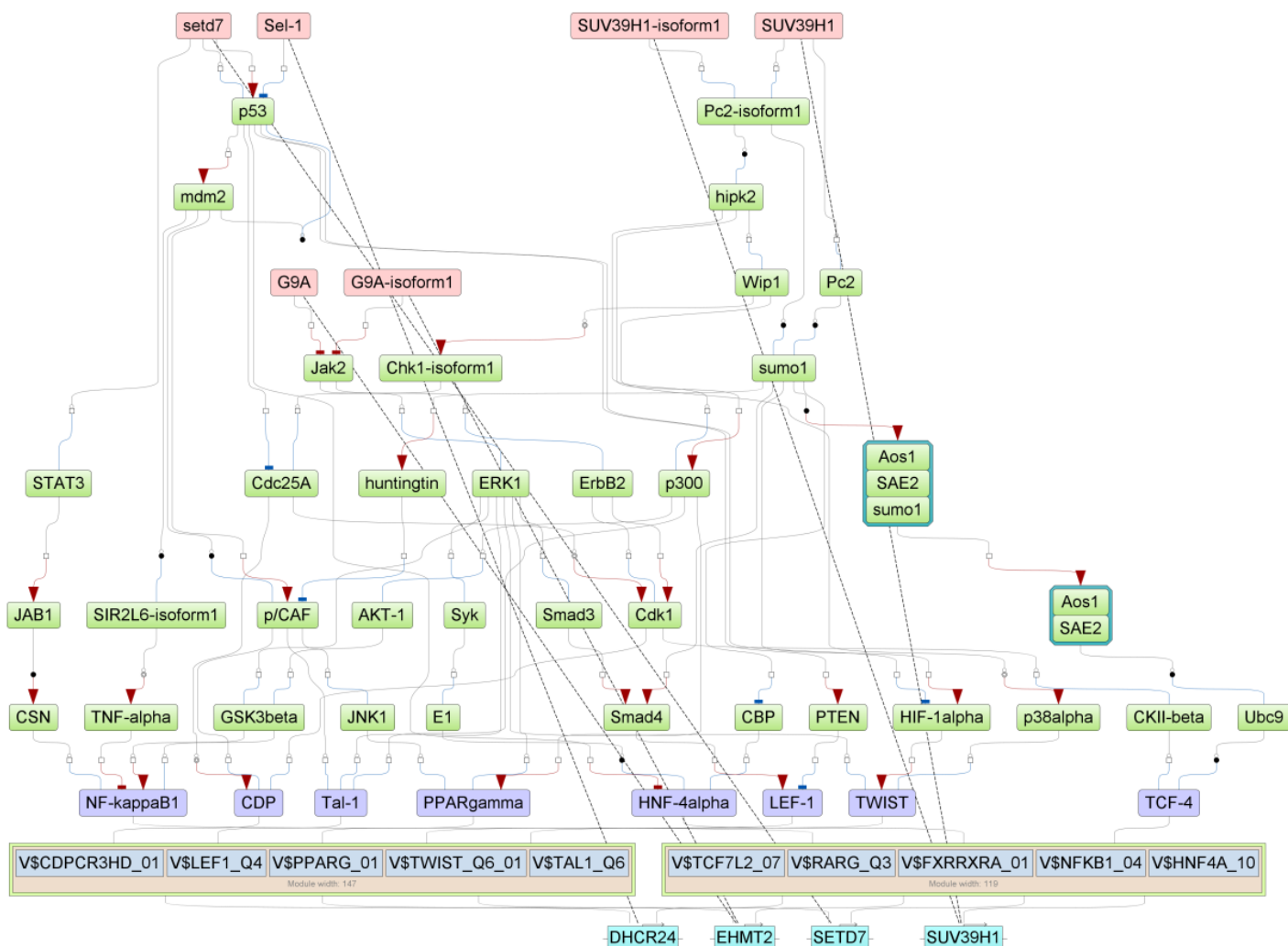


Figure 5. Diagram of intracellular regulatory signal transduction pathways of genes encoding enzymes, metabolising target metabolites in TNF vs NO_TNF 72h. Master regulators are generated by red rectangles, transcription factors are blue rectangles, and green rectangles are intermediate molecules, which 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. Identification of potential drugs

In the last step of the analysis we strived to identify known drugs as well as new potentially active chemical compounds that are potentially suitable for inhibition (or activation) of the identified molecular targets in the context of specified human disease.

First, we identify known drugs using information from HumanPSD™ database [5] about their targets and about clinical trials where the drugs have been tested for the treatment of various human diseases. Table 6 shows the resulting list of druggable master regulators that represent the predicted drug targets of the studied pathology. Table 7 lists chemical compounds and known drugs (from the HumanPSD™ database) potentially acting on corresponding master regulators.

Table 6. Known drug targets for known drugs revealed in this study. The column **Druggability score** contains the number of drugs that are potentially suitable for inhibition (or activation) of the target. **Total rank** is the sum of the ranks of the master molecules sorted by keynode score, CMA score, metabolomics data.

[See full table →](#)

ID	Gene symbol	Gene description	Druggability score	Total rank
ENSG00000145391	SETD7	SET domain containing lysine methyltransferase 7	1	8

Table 7. The list of drugs (from HumanPSD) known to be acting on master regulators revealed in our study that can be proposed as a drug repurposing initiative for the treatment of lung neoplasms. **Target activity score** column contains value of numeric function that depends on ranks of all targets that were found for the drug. **Drug rank** column contains total rank of given drug among all found. See [Methods](#) section for details.

[See full table](#) →

ID	Name	Target names	Target activity score	NA	Phase 1	Phase 2	Phase 3	Phase 4	Drug rank
DB01752	S-Adenosyl-L-Homocysteine	SETD7	1.28E-2						3

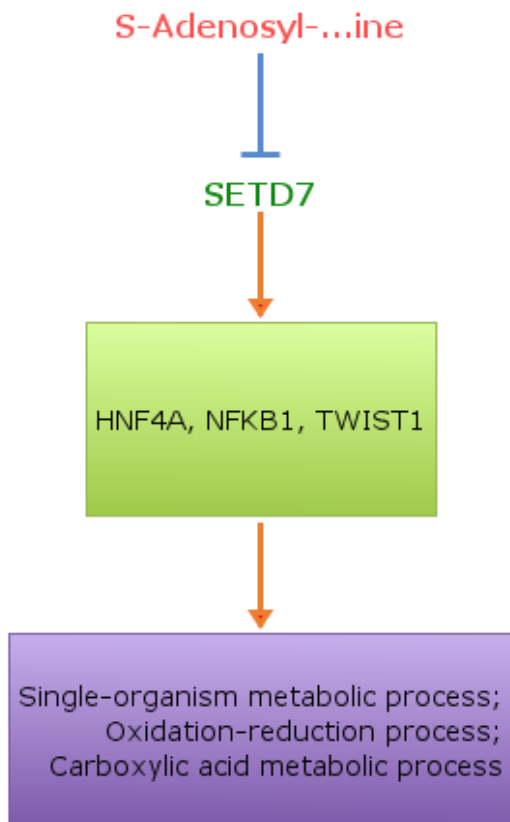
The identified master regulators were scanned through a database of drug-target interactions, constructed on the basis of ligand structures with the use of the (Q)SAR approach [8-10]. Unfortunately this approach has found no compounds capable of inhibiting or activating the identified upregulated and downregulated master activators. Nevertheless, the found master regulators, shown in Table 5 and visualized in Figure 5, represent molecular targets of the studied pathology and their affection can lead to new opportunities for diagnosis and treatment of the disease.

As a result of the drug search we came up with list of chemical compounds potentially applicable to the targets of our interest. This list is based on drugs that are known as ligands for the revealed targets in the context of the diseases in our focus as well as in other disease conditions. Such computational predictions should be taken as mere suggestions and should be used with care in further experiments.

5. 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 schema of how the selected drugs may interfere with the identified target molecules and pathogenic processes discovered by the study reported here.



6. Methods

Databases used in the study

Transcription factor binding sites in promoters and enhancers of differentially expressed genes were analyzed using known DNA-binding motifs described in the **TRANSFAC®** library, release 2020.1 (geneXplain GmbH, Wolfenbüttel, Germany) (<http://genexplain.com/transfac>).

The master regulator search uses the **TRANSPATH®** database (BIOBASE), release 2020.1 (geneXplain GmbH, Wolfenbüttel, Germany) (<http://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 2020.1 (<http://genexplain.com/humanpsd>).

The Ensembl database release Human88.38 (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 sum of three other 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 trials phase.

To calculate clinical trials phase for the given compound we select the maximum phase of all diseases that are known to have clinical trials with this compound. "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, $phase(p,d)$ equals to the phase number if there are known clinical trials for the selected disease on this phase and zero otherwise.

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.

7. References

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Supplementary material

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

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