



Identifying the mechanisms and molecular targets of Hongjingtian injection on treatment of TGF β 1-induced HK-2 cells: coupling network pharmacology with experimental verification

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Background: The study was designed to investigate the mechanism of Hongjingtian injection (HJT) in treating tubulointerstitial fibrosis (TIF) in chronic kidney diseases (CKD) based on network pharmacology and experimental verification.

Methods: First, active ingredients of HJT obtained from literature were screened using the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database and putative targets of active ingredients were predicted using the ChEMMapper, SEA and Swiss Target Prediction database. Subsequently, the “compound-target” network for HJT was established. In addition, TIF disease targets were obtained from the GEO gene chips (accession number GSE20247). The intersecting targets of HJT and TIF obtained through Venny 2.1.0. The key targets and signaling pathways were determined by protein-protein interaction (PPI) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Finally, quantitative polymerase chain reaction (qPCR) and Western blot (WB) were used to validate the predicted five key genes targets (*GAD1*, *SPHK1*, *P4HA2*, *AKR1B1*, *PTGES*). And immunofluorescence, wound healing assay and transwell assay were used to verify the anti-fibrosis effect of HJT on TGF β 1-induced HK-2 cells.

Results: The network pharmacology analysis results showed that there are 36 active compounds and 1,044 putative target genes in HJT. HJT may exert its inhibitory effects against TIF by acting on 79 key targets. Besides, KEGG analysis indicated that the anti-TIF effect of HJT was mediated by multiple pathways, such as the metabolic pathway, pathways in cancer and gap junction. Among them, *GAD1*, *SPHK1*, *P4HA2*, *AKR1B1* and *PTGES* are enriched in the metabolic pathway. *In vitro* induced cell model experiments, the immunofluorescence experience showed that HJT could restore EMT of HK-2 cells. In addition, the qPCR and WB results showed that HJT significantly restored the expression of the *SPHK1* in HK-2 cells induced by TGF- β 1.

Conclusions: This study comprehensively illuminated the active compounds, potential targets, and molecular mechanism of HJT against TIF. HJT treatment of TIF may reverse EMT caused by TGF- β 1 by targeting *SPHK1*.

Keywords: Tubulointerstitial fibrosis (TIF); network pharmacology; HK-2 cells; key targets

Submitted Sep 27, 2022. Accepted for publication Dec 02, 2022.

doi: 10.21037/atm-22-5035

View this article at: <https://dx.doi.org/10.21037/atm-22-5035>

Introduction

Tubulointerstitial fibrosis (TIF) is an irreversible organic change of kidney caused by many pathogenic factors (1). TIF characterized by tubular atrophy, the activation of interstitial fibroblasts and extracellular matrix (ECM) accumulation, is the basic pathological process that chronic kidney diseases (CKD) eventually move towards chronic renal failure (2).

However, due to the complex mechanism of TIF, there are no specific preventive and therapeutic measures in clinical practice. So, it is still a hot research topic to seek effective prevention and treatment measures. Traditional Chinese medicine (TCM) therapy is a unique treatment in China, which has significant clinical efficacy and less side effects. In recent years, many studies have confirmed that TCM has become an effective method to treat TIF through a variety of experimental methods (3,4). TCM injection is a therapeutic drug combining TCM theory and modern scientific means. It is made into a finished product by extracting the pharmaceutical compounds of herb-medicine, which has the characteristics of quick onset and rapid action. The Hongjingtian injection (HJT) is a water-soluble

extract of *Rhodiola*. In China, HJT has been used to treat vascular diseases. Clinical studies have shown that HJT can improve hemorheology, reduce intima-media thickness, and alleviate atherosclerotic inflammatory reaction (5,6). Our previous study has demonstrated that salidroside, the main component of HJT, have renoprotective effects to reduce proteinuria, inhibit renal fibrosis (7).

However, elucidating the pharmacological effects of HJT on TIF is challenging, due to the complex active compounds and unclear mechanism of action. Recently, with the growing understanding of complex diseases, the focus of drug mechanism has shifted from the well-accepted “one target, one compound” model designed toward a single target to a new “multi-target, multi-compound” model aimed at systemically modulating multiple targets. Fully understanding the complex network relationships among diseases, targets, and compounds still remains a big challenge. Fortunately, with the rapid development of systems biology, multidirectional pharmacology, computational biology, network pharmacology has become a new paradigm for clarifying the multivariable interactions of compound-gene-disease system. It provides new scientific and technological support for the mechanism of TCM at the system level, and provides new ideas and directions for experimental research of TCM.

Therefore, in this study, we combined the network pharmacology with the Gene Expression Omnibus (GEO) database to further explore and explain the possible mechanism of HJT in treating TIF. Moreover, the potential mechanism and key target were verified by cell experiments. The flowchart is presented in *Figure 1*. We present the following article in accordance with the MDAR reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5035/rc>).

Methods

Screening and identification of active compounds and potential targets of HJT

A total of 49 compounds of HJT were obtained by searching the literature (8). To identify the active compounds of HJT,

Highlight box

Key findings

- The key finding of the study is that Hongjingtian injection (HJT) may reverse the EMT caused by TGF-β1 to treat Tubulointerstitial fibrosis (TIF) by targeting *SPHK1*.

What is known and what is new?

- TIF is an irreversible organic change of kidney caused by many pathogenic factors. TIF is the basic pathological process that chronic kidney diseases (CKD) eventually move towards chronic renal failure.
- This study comprehensively illuminated the active compounds, potential targets, and molecular mechanism of HJT against TIF.

What is the implication, and what should change now?

- HJT may be an effective measure to prevent and treat CKD. It is necessary to conduct further *in vivo* experimental verification of the potential active ingredients in order to clarify the theoretical prediction.

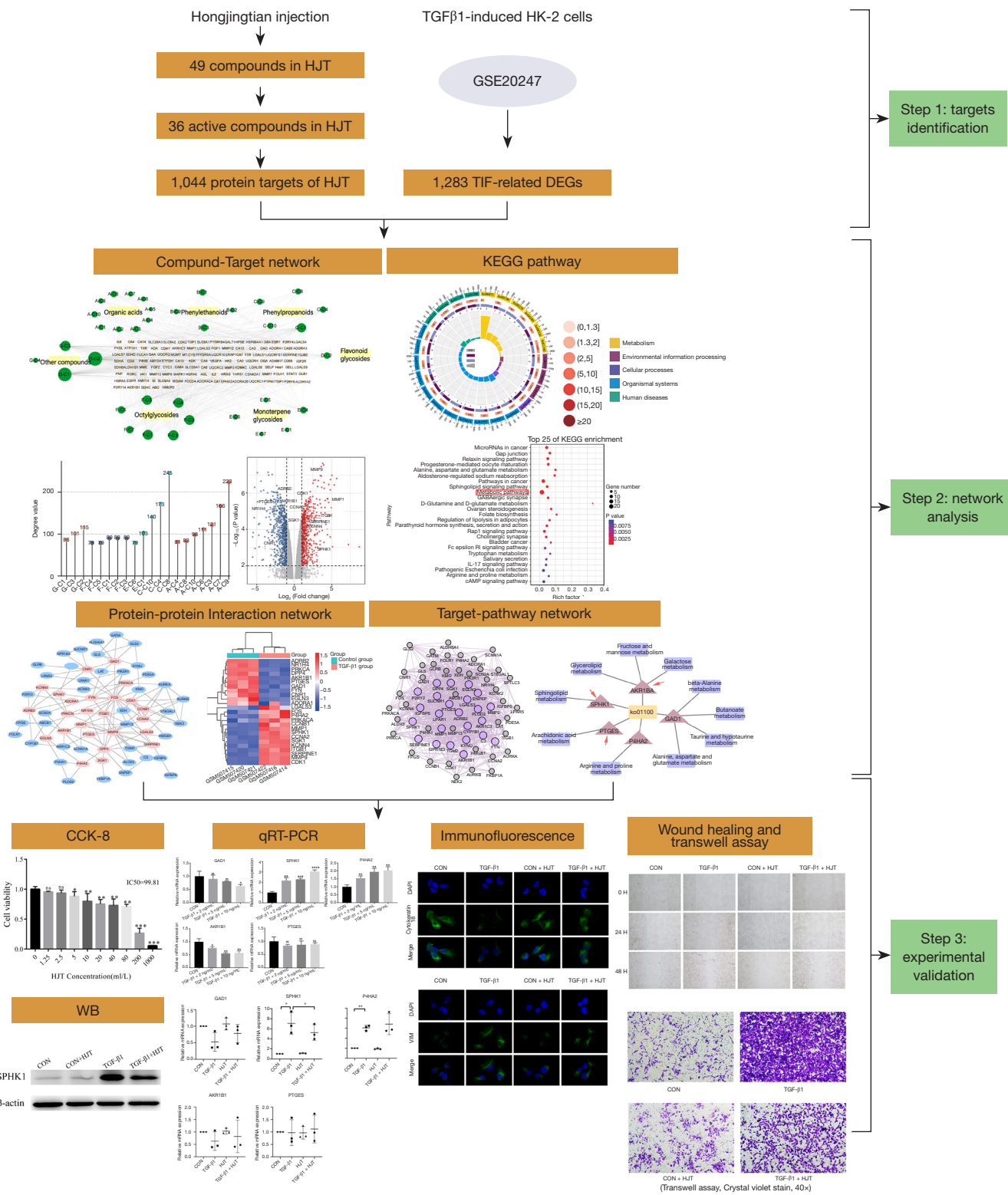


Figure 1 The technical strategy of the current study. HJT, Hongjingtian injection; TIF, treating tubulointerstitial fibrosis; DEG, differentially expressed gene; KEGG, Kyoto Encyclopedia of Genes and Genomes; qRT-PCR, quantitative real-time polymerase chain reaction; WB, Western blot.

the ingredients conforming to the requirements of lipinski, based on the published literature and the information from the SwissADME database (<http://www.swissadme.ch/>). Subsequently, putative targets of these potential compounds were identified from the ChemMapper (<http://lilab.ecust.edu.cn/chemmapper/>), Swiss Target Prediction (<http://www.swisstargetprediction.ch/>) and SEA (<http://sea.bkslab.org>) database. Then, the UniProt database (<https://www.uniprot.org/>) was used to convert targets into official gene symbol. Eventually, all putative targets of HJT were retrieved after removing duplicated targets. In addition, Cytoscape 3.7.2 software was used to establish and visualize the compound-target network of HJT based on the obtained results.

Search, identification, and analysis of differentially expressed gene (DEG)

Expression profiling data from GSE20247 were downloaded from the GEO database (<http://www.ncbi.nlm.nih.gov/geo/>) based on the microarray platform GPL570 (Affymetrix Human Gene Expression Array), which contained 3 samples from healthy individuals and 3 TGF-β1-induced TIF samples. Based on the annotation information in the platform, probe IDs were used to identify the corresponding genes. Genes with an adjusted $P < 0.01$ and $\log_2(\text{fold change}) > 1$ or $\log_2(\text{fold change}) < -1$ were considered significantly differentially expressed and TIF-related targets. Then, these DEGs were visualized using a volcano plot. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Enrichment of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

Based on the above analysis, the Venn diagram that intersects the potential targets of HJT and the DEGs of TIF was drawn by Jvenn (<http://jvenn.toulouse.inra.fr/app/index.html>). Then, with the help of Omicshare information platform (<https://www.omicshare.com/>), we employed the KEGG pathway analysis the gene related signaling pathway (9).

Construction of protein-protein interaction (PPI) network and key targets analysis

The PPI network of these intersection targets was obtained by using the String online tool (<https://string-db.org/>) (10) and visualized using the Cytoscape V3.7.2 (<https://www.cytoscape.org/>). Then, core targets were selected according

to the median values of Degree Centrality (DC), Closeness Centrality (CC), and Betweenness Centrality (BC), which are the three most important parameters for screening the core composite targets (11). Subsequently, the co-expression relationship of genes in the PPI network were analyzed by using the MCODE module in Cytoscape V3.7.2. Ultimately, the key genes enriched in the selected pathway were selected and “key target-signal pathway map” were made using the Cytoscape V3.7.2.

Experimental validation

Reagents and antibodies

TGF-β1 was obtained from novoprotein (CA59, Suzhou, China). HJT was obtained from Tonghua Yusheng Pharmaceutical Co., Ltd. (YBZ11852006, Tonghua, China). Anti-cytokeratin18 was obtained from Boster (A01357-1, Wuhan, China). Anti-Vimentin was obtained from proteintech (10366-1-AP, Wuhan, China). Anti-SPHK1 was obtained from proteintech (10670-1-AP, Wuhan, China).

Cell culture and treatments

The cell lines HK-2 were obtained from Procell (PC-H2022062701, Wuhan, China). The cells were cultured in modified Eagle's medium (SH30024, MEM, HyClone) with 12% fetal bovine serum (Gibco, Thermo Fisher Scientific, USA) and 1% penicillin-streptomycin (J160016, Hyclone, USA). All cells were maintained in 5% CO₂ at 37 °C under a humidified atmosphere. For inducing EMT, cells were treated with different concentrations of TGF-β1 (0, 2, 5 and 10 ng/mL) at 37 °C for 48 h.

Cell Counting Kit-8 (CCK8) assay

A total of 3×10^3 HK-2 cells were plated in 96-well plates and, after a 24 h incubation period, cells were treated with different concentrations of HJT (0, 1.25, 2.5, 5, 10, 20, 40, 80, 200, 1,000 mL/L) at 37 °C for 48 h. Subsequently, 10 μL CCK8 solution (A311-02-AA, Vazyme, China) was added to each well and incubated at 37 °C for a further 2 h, and cell viability was determined by measuring the absorbance at 450 nm on a spectrophotometer.

Quantitative real-time polymerase chain reaction (qRT-PCR) analysis

Total RNA was extracted using a SPARK easy Cell RNA Kit (AC0205, Sparkjade, China,) and cDNA was

synthesized using a SPARK script II RT Plus Kit (AG0304, Sparkjade, China) according to the manufacturer's protocol. Subsequently, the quality of the extracted RNA was detected. The primer sequences were as follows: *SPHK1* (forward) 5'-CTGTCACCCATGAACCTGCTGTC-3' and (reverse) 5'-ACGCCGATACTTCTCACTCTCTAGG-3', *P4HA2* (forward) 5'-CCAGGAACCAAGTACCAGGCAATG-3' and (reverse) 5'-CTGCTCCATCCACAACACCGTATG-3', *GAD1* (forward) 5'-TCCTCCTGGAAGTGGTGGACATAC-3' and (reverse) 5'-AGCAACTGGTGTGGGTGATGAAAG-3', *AKR1B1* (forward) 5'-TGACACCAGAACGCATTGCTGAG-3' and (reverse) 5'-AGACCCTCCAGTTCCTGTTGTAGC-3' and *PTGES* (forward) 5'-TCCTGGGCTTCGTCTACTCCTTTC-3', and (reverse) 5'-TGTAGGTCACGGAGCGGATGG-3' and *GAPDH* (forward) 5'-CCTTCCGTGTCCCCACT-3', and (reverse) 5'-GCCTGCTTCACCACCTTC-3'. Real-time PCR was performed using a SYBR qPCR SuperMix Plus (R311-02, Vazyme, China). The thermocycling conditions were as follows: Initial denaturation at 95 °C for 2 min, followed by 40 amplification cycles at 95 °C for 15 sec and 60 °C for 10 sec. GAPDH was used as the endogenous control for normalization, and the expression was analyzed using the $2^{-\Delta\Delta CT}$ method. The data were extracted from three independent biological experiments with three technical replicates in each experiment.

Western blot (WB) analysis

The total protein in HK-2 cell was collected by RIPA lysis method and the protein concentration was detected by using BCA kit (PC0020, Solarbio, China). Then the proteins were separated using 12% SDS-PAGE (G2037, Servicebio, China) electrophoresis and transferred to PVDF membrane via the electro-blotting at 210 mA for 75 minutes. After taking out the PVDF membrane, wash it three times with TBST for 15 minutes each time. A 5% skimmed milk powder was added and sealed for 2 h. Primary antibody (1:1,000) was put in and cultivated in a refrigerator at 4 °C overnight. The next day, TBST was used for washing three times to remove primary antibody, HRP labeled secondary antibody (1:5,000) was added. After incubation for 2 h, TBST was used for washing three times, with 15 min each time. Finally, ECL luminescence kit (E412-02, Vazyme, China) was used for luminescence and the results of WB analysis were performed by using the software ImageJ. The data were extracted from three independent biological

experiments.

Wound healing assay

HK-2 cells at 10^6 cells/mL were cultured in 6-well plate. A 1,000 μ L pipette was used to create a scratch in the cells. The non-adherent cells were removed by two washes of PBS, and cells in experimental group were intervened with HJT (2.5 mL/L), TGF- β 1 (10 ng/mL) and the TGF- β 1 and HJT (10 ng/mL TGF- β 1+ 2.5 mL/L HJT). Subsequently, the cells were maintained at 37 °C for 48 h. The scratches were photographed at 0, 24 and 48 h respectively by an inverted microscope (XD202, Jiangnan, China). Finally, calculate the relative distance according to the equation $(W_0 - W_t) / W_0 \times 100\%$. The data were extracted from three technical replicates.

Transwell assay

10^5 cells/mL of HK-2 after the intervention were collected and inoculated in the upper chamber, and the cells were cultured in serum-free medium for 12 h. The non-invading cells on the upper chamber were eliminated using a cotton swab. After fixing with 4% paraformaldehyde, the cells on the lower side of the chamber were incubated with crystal violet. The results were counted in three fields randomly selected by a forward microscope (Ni-V, Nikon, Japan). The data were extracted from three technical replicates.

Immunofluorometric assay

First, the treated cells on the round coverslip were fixed with 4% paraformaldehyde for 20 min, penetrated with 0.3% Triton X-100 for 15 min, incubated in a 5% BSA blocking buffer for 2 h at room temperature and then incubated with Vimentin and Cytokeratin-18 antibody (1:200 dilution) overnight at 4 °C. The next day, secondary antibodies labeled with fluorescence (Alexa Fluor 488, Beyotime, 1:1,000) were applied for 1h at room temperature protected from light, followed by incubation with 0.1% DAPI for 10 min. Addition, cells were washed with PBS between each step. Finally, the cells were observed using a forward fluorescence microscope (Ni-V, Nikon, Japan), and photographs were recorded.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software. All the experimental results were expressed as mean \pm standard deviation (SD). The Student's *t*-test was used to analyze the statistical difference between the experimental

and control groups. Moreover, the difference among multiple groups was determined by the one-way analysis of variance (ANOVA) test followed Turkey's posttest. P value <0.05 was considered significant.

Results

Screening of bioactive ingredients and putative targets from HJT

Forty-nine compounds of HJT were found in the literature, and all compounds were identified in the SwissADME database after applying the criteria of lipinski. The molecular names, structures and ADME-related parameters of these compounds are listed in *Table 1*. Finally, 36 bioactive compounds were screened from HJT, including 10 in Organic acids, 4 in Phenylethanoids, 5 in Phenylpropanoids, 1 in Flavonoid glycosides, 5 in Monoterpene glycosides, 7 in Octyl glycosides and 4 in other compounds.

According to the target screening of the bioactive compounds in the Chemmaper, Sea and Swiss database, 1,044 potential target genes were selected for the 36 compounds of HJT after removing duplicate targets (*Table S1*). Moreover, the UniProt database was used to translate the official names of potential targets so that they could be used in network construction for further biological characterization.

Construction of a compound-putative target network of HJT

Chinese herbal compounds can interfere with diseases by regulating a network through binding multiple targets. Therefore, a network of "compound-putative target" was established to predict these targets through the acquisition of detailed information on the bioactive ingredients of HJT. This network consisted of 969 nodes and 3,188 edges (*Figure 2A*), indicating the interactions of chemical compounds and putative targets. As can be seen from the figure, different active compounds corresponded to different targets, which reflected the characteristics of multi-compound, multi-target of HJT. Among them, the degree values of C-C8 (p-Coumaric acid), A-C9 (Ethyl gallate), C-C4((7R,8R)-3-Methoxy-8'-carboxy-7'-en-3',8-epoxy-7,4'-oxyneolignan-4,9-diol), A-C7 (4-Hydroxyphenylacetic acid), C-C10 (6-Feruloyloxyhexanoic acid), A-C3 (Vanillic acid β -glucoside) are the highest, 245, 223, 173, 166, 140 and 121 respectively, which indicated that they were the most

important active compounds in the network (*Figure 2B*).

Identification of TIF-related DEGs

Differential genetic analysis between TIF and healthy individuals was performed with $|\log_2 \text{FC}| > 1$ and $P < 0.01$. Ultimately, 1,283 DEGs were identified. A volcano plot of the distribution of DEGs is shown in *Figure 2C*. Among them, 580 up-regulated genes are represented by red dots, and 703 down-regulated genes are represented by green dots.

Analyses of enrichment of the KEGG pathway

As shown in *Figure 3A*, HJT has 79 genes that act on TIF. *Table 2* lists the specific details. The 79 cross gene were mapped to 218 pathways by KEGG enrichment analysis, the main signaling pathways involved in the treatment of TIF were identified and the first 25 pathways related to TIF and significantly enriched screened were screened (FDR <0.05) (*Table 3*), including Metabolic pathways (ko01100), Pathways in cancer (ko05200), MicroRNAs in cancer (ko05206), Relaxin signaling pathway (ko04926) among others. As the *Figure 3B* shown, the y-axis represents the KEGG pathway and the x-axis indicates the number of genes enriched in that pathway. The redder the color, the smaller the value of P_{adjust} ; it also denotes greater credibility and greater importance. In contrast, the bluer the color, the greater the value of P_{adjust} . Addition, as shown in *Figure 3C*, enrichment of the KEGG pathway could be divided approximately into energy metabolism, environmental information processing, cellular process, organismal systems and human diseases. It is worth noting that the most genes are enriched in metabolic pathways (ko01100). This pathway contains a total of 1,554 genes, of which 24 of the above-mentioned 79 cross genes are included. And it contains 7 up-regulated genes and 17 down-regulated genes.

PPI network and co-expression network construction and analysis

The 79 cross genes were imported into STRING and the PPI network was obtained of which contains 65 nodes and 132 edges (*Figure 4A*). Subsequently, the topological properties of the afore-mentioned merged PPI network were analyzed according to three key parameters: BC, CC, and DC, screened targets above median values of BC,

Table 1 Information for candidate bioactive compounds of HJT

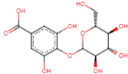
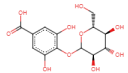
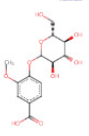




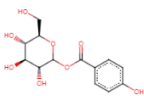
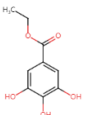
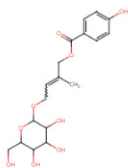
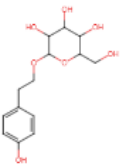
Category	Code name	Structure	Molecule name	Molecular formula	Lipinski	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors
Organic acids	A-C1		4-(β -D-Glucopyranosyloxy)-3,5-dihydroxybenzoic acid or its isomer	C13H16O10	Yes; 1 violation: NHorOH >5	332.26 g/mol	4	10	7
	A-C2		4-(β -D-Glucopyranosyloxy)-3,5-dihydroxybenzoic acid or its isomer	C13H16O10	Yes; 1 violation: NHorOH >5	332.26 g/mol	4	10	7
	A-C3		Vanillic acid β -glucoside	C14H18O9	Yes; 0 violation	330.29 g/mol	5	9	5
	A-C4		Gallic acid	C7H6O5	Yes; 0 violation	170.12 g/mol	1	5	4
	A-C5		Protocatechuic acid	C7H6O4	Yes; 0 violation	154.12 g/mol	1	4	3
	A-C6		4-Hydroxybenzoic acid	C7H6O3	Yes; 0 violation	138.12 g/mol	1	3	2
	A-C7		4-Hydroxyphenylacetic acid	C8H8O3	Yes; 0 violation	152.15 g/mol	2	3	2
	A-C8		p-Hydroxybenzoic acid β -glucoside	C13H16O8	Yes; 0 violation	300.26 g/mol	4	8	5
	A-C9		Ethyl gallate	C9H10O5	Yes; 0 violation	198.17 g/mol	3	5	3
	A-C10		Creoside III	C18H24O9	Yes; 0 violation	384.38 g/mol	8	9	5
Phenylethanoids	B-C1		Salidroside	C14H20O7	Yes; 0 violation	300.30 g/mol	5	7	5

Table 1 (continued)

Table 1 (continued)

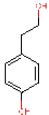
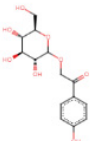
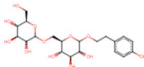
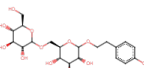
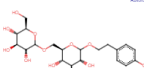
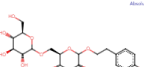
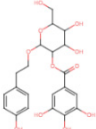
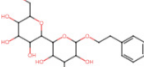
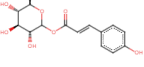
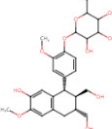
Category	Code name	Structure	Molecule name	Molecular formula	Lipinski	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors
	B-C2		p-Tyrosol	C8H10O2	Yes; 0 violation	138.16 g/mol	2	2	2
	B-C3		2-(β-D-Glucopyranosyloxy)-1-(4-hydroxyphenyl) ethanone	C14H18O8	Yes; 0 violation	314.29 g/mol	5	8	5
	B-C4		2-(4-Hydroxyphenyl)-ethyl-O-β-D-glucopyranoside or its isomer	C20H30O12	No; 2 violations: NorO >10, NHorOH >5	462.45 g/mol	8	12	8
	B-C5		2-(4-Hydroxyphenyl)-ethyl-O-β-D-glucopyranoside or its isomer	C20H30O12	No; 2 violations: NorO >10, NHorOH >5	462.45 g/mol	8	12	8
	B-C6		2-(4-Hydroxyphenyl)-ethyl-O-β-D-glucopyranoside	C20H30O12	No; 2 violations: NorO >10, NHorOH >5	462.45 g/mol	8	12	8
	B-C7		2-(4-Hydroxyphenyl)-ethyl-O-β-D-glucopyranoside or its isomer	C20H30O12	No; 2 violations: NorO >10, NHorOH >5	462.45 g/mol	8	12	8
	B-C8		6''-O-Galloyl-salidroside	C21H24O11	No; 2 violations: NorO >10, NHorOH >5	452.41 g/mol	8	11	7
	B-C9		2-Phenylethyl-6-O-α-L-arabinopyranosyl-β-D-glucopyranoside	C19H28O10	Yes; 1 violation: NHorOH >5	416.42 g/mol	6	10	7
Phenylpropanoids	C-C1		1-O-p-Coumaroyl-β-D-glucopyranose	C15H18O8	Yes; 0 violation	326.30 g/mol	5	8	5
	C-C2		Lariciresinol-4-O-β-D-glucopyranoside	C26H34O11	No; 3 violations: MW >500, NorO >10, NHorOH >5	522.54 g/mol	8	11	7

Table 1 (continued)

Table 1 (continued)

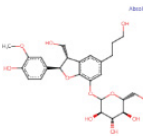
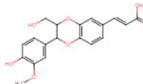
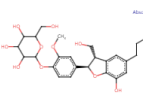
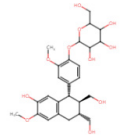
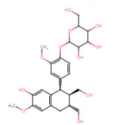
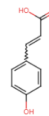
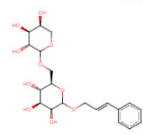
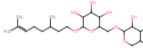
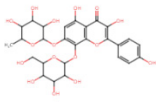
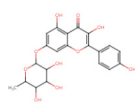
Category	Code name	Structure	Molecule name	Molecular formula	Lipinski	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors
	C-C3		(7R,8S)-Dihydrodehydrodiconiferyl-alcohol-3'-O-β-D-glucopyranoside or (7R,8S)-Dihydrodehydrodiconiferyl-alcohol	C ₂₅ H ₃₂ O ₁₁	No; 3 violations: MW >500, NorO >10, NHorOH >5	508.51 g/mol	9	11	7
	C-C4		(7R,8R)-3-Methoxy-8'-carboxy-7'-en-3',8-epoxy-7,4'-oxyneolignan-4,9-diol	C ₁₉ H ₁₈ O ₇	Yes; 0 violation	358.34 g/mol	5	7	3
	C-C5		(7R,8S)-Dihydrodehydrodiconiferyl-alcohol-4-O-β-D-glucopyranoside	C ₂₅ H ₃₂ O ₁₁	No; 3 violations: MW >500, NorO >10, NHorOH >5	508.51 g/mol	9	11	7
	C-C6		Lariciresinol-4-O-β-D-glucopyranoside	C ₂₆ H ₃₄ O ₁₁	No; 3 violations: MW >500, NorO >10, NHorOH >5	522.54 g/mol	8	11	7
	C-C7		(+)-Isolarisiresinol-4-O-β-D-glucopyranoside	C ₂₆ H ₃₄ O ₁₁	No; 3 violations: MW >500, NorO >10, NHorOH >5	522.54 g/mol	8	11	7
	C-C8		p-Coumaric acid	C ₉ H ₈ O ₃	Yes; 0 violation	164.16 g/mol	2	3	2
	C-C9		Cinnamylalcohol-9-O-(6'-O-α-L-arabinopyranosyl)-β-D-glucopyranoside	C ₂₀ H ₂₈ O ₁₀	Yes; 1 violation: NHorOH >5	428.43 g/mol	7	10	6
	C-C10		6-Feruloyloxyhexanoic acid	C ₁₆ H ₂₀ O ₆	Yes; 0 violation	308.33 g/mol	10	6	2
Flavonoid glycosides	D-C1		Rhodionidin	C ₂₇ H ₃₀ O ₁₆	No; 3 violations: MW >500, NorO >10, NHorOH >5	610.52 g/mol	6	16	10
	D-C2		Kaempferol-7-rhamnoside	C ₂₁ H ₂₀ O ₁₀	Yes; 1 violation: NHorOH >5	432.38 g/mol	3	10	6

Table 1 (continued)

Table 1 (continued)

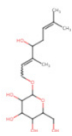
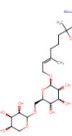
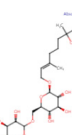
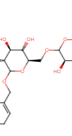
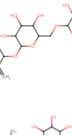
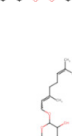
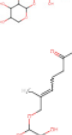
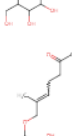
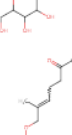

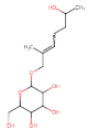
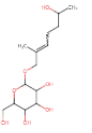
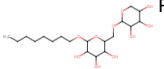
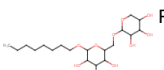
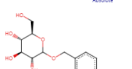
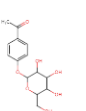
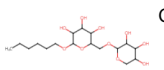

Category	Code name	Structure	Molecule name	Molecular formula	Lipinski	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors
Monoterpene glycosides	E-C1		Rosiridin	C16H28O7	Yes; 0 violation	332.39 g/mol	7	7	5
	E-C2		Sachalose VII	C21H38O11	No; 2 violations: NorO >10, NHorOH >5	466.52 g/mol	10	11	7
	E-C3		Sachalose VIII	C21H38O11	No; 2 violations: NorO >10, NHorOH >5	466.52 g/mol	10	11	7
	E-C4		Sacranoside A	C21H34O10	Yes; 1 violation: NHorOH >5	446.49 g/mol	6	10	6
	E-C5		Sachalose II	C21H34O10	Yes; 1 violation: NHorOH >5	446.49 g/mol	5	10	6
	E-C6		Creoside V	C21H38O10	Yes; 1 violation: NHorOH >5	450.52 g/mol	10	10	6
	E-C7		Kenposide A	C21H36O10	Yes; 1 violation: NHorOH >5	448.50 g/mol	9	10	6
Octylglycosides	F-C1		Creoside I	C14H24O7	Yes; 0 violation	304.34 g/mol	7	7	4
	F-C2		Creoside I	C14H24O7	Yes; 0 violation	304.34 g/mol	7	7	4
	F-C3		Creoside I	C14H24O7	Yes; 0 violation	304.34 g/mol	7	7	4

Table 1 (continued)

Table 1 (continued)

Category	Code name	Structure	Molecule name	Molecular formula	Lipinski	Molecular weight	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors
	F-C4		Creoside II	C14H26O7	Yes; 0 violation	306.35 g/mol	7	7	5
	F-C5		Creoside II	C14H26O7	Yes; 0 violation	306.35 g/mol	7	7	5
	F-C6		Rhodiocyanoside	C19H36O10	Yes; 1 violation: NHorOH >5	424.48 g/mol	11	10	6
	F-C7		Rhodiocyanoside	C19H36O10	Yes; 1 violation: NHorOH >5	424.48 g/mol	11	10	6
Other compounds	G-C1		4-Hydroxybenzyl-β-D-glucopyranoside	C13H18O7	Yes; 0 violation	286.28 g/mol	4	7	5
	G-C2		Picein	C14H18O7	Yes; 0 violation	298.29 g/mol	4	7	4
	G-C3		Creoside IV	C17H32O10	Yes; 1 violation: NHorOH >5	396.43 g/mol	9	10	6
	G-C4		Pyrogallol	C6H6O3	Yes; 0 violation	126.11 g/mol	0	3	3

HJT, Hongjingtian injection;

CC, and DC, thereby selecting the core genes of the TIF-treated effect of HJT. The cutoff value of the screening was $BC > 0.015$, $CC > 0.304$ and $DC > 3$. These 25 core genes are marked in pink. Besides, the heat map of these 25 core genes were listed in *Figures 4B*. Finally, as shown in the *Figure 4C*, co-expression relationships in the PPI network were analyzed and further higher-scoring cluster containing 25 genes were shown in purple. Through the Venn diagram we found that there are 5 key genes enriched in the Metabolic pathway (ko01100), which were AKR1B1 ($\log_2fc = -1.341623$), GAD1 ($\log_2fc = -1.563923$), P4HA2 ($\log_2fc = 1.069761$), SPHK1 ($\log_2fc = 2.22411$) and PTGES ($\log_2fc = -2.268903$). And there were three intersections between these five genes and the sub-network genes of

the co-expression network, *SPHK1*, *AKR1B* and *PTGES*, respectively. These results illustrate that *AKR1B1*, *GAD1*, *P4HA2*, *SPHK1* and *PTGES* may be key genes in HJT to regulate TIF through metabolic pathway, and there may be a co-expression relationship among *SPHK1*, *AKR1B1* and *PTGES*.

TGF affects the expression of AKR1B1, GAD1, P4HA2, SPHK1 and PTGES

We chose TGF-β1 to represent the severity of EMT *in vitro* cell models. In the above network pharmacological analysis, we predicted that *AKR1B1*, *GAD1*, *P4HA2*, *SPHK1* and *PTGES* in the metabolic pathway were key

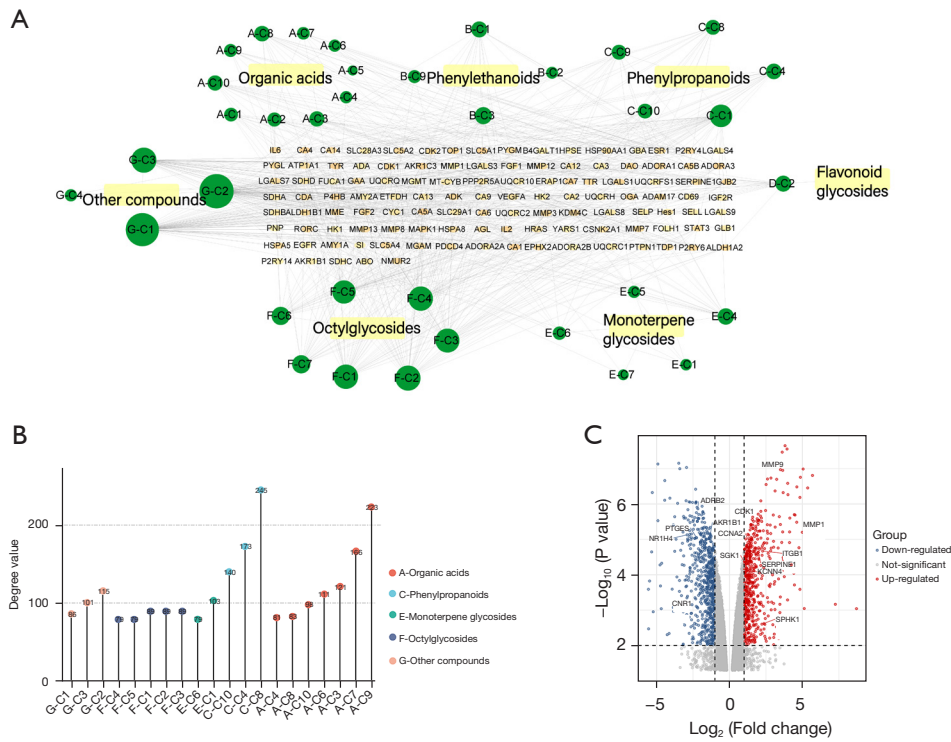


Figure 2 The information of HJT and GSE20247. (A) The compound-target network. The green nodes represent active compounds and the yellow nodes represent potential protein targets. The edges represent the interactions between them and nodes size are proportional to their degree. (B) Top 20 active compounds with degree value. (C) A volcano plot of the distribution of DEGs. HJT, Hongjingtian injection; DEG, differentially expressed gene.

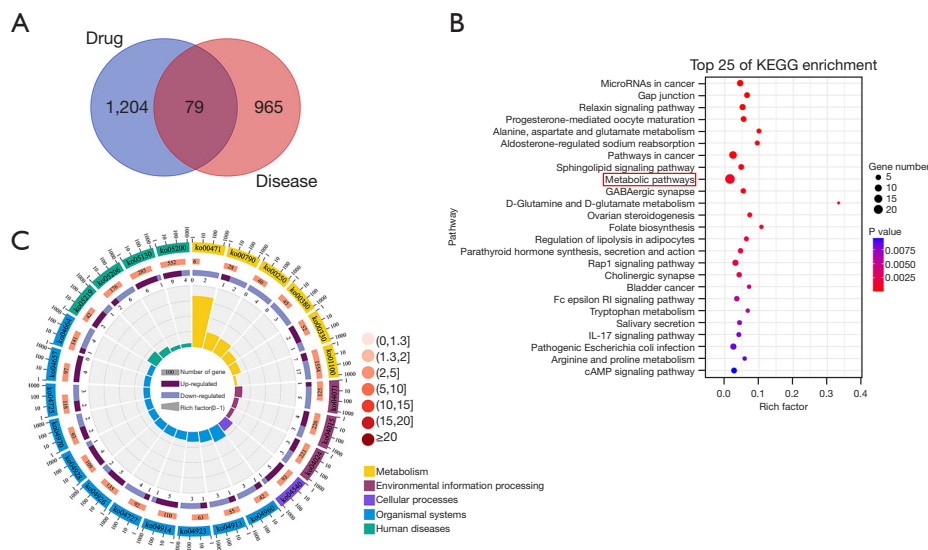


Figure 3 KEGG analysis. (A) 79 overlapping gene symbols between the disease and drug. (B) Top 25 pathways of KEGG enrichment. The y-axis represents the KEGG pathway and the x-axis indicates the number of genes enriched in that pathway. (C) Classification of 25 pathways. KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table 2 Targets of HJT on TIF

Cross gene	Uniport ID	Gene name	LogFC
<i>AKR1B1</i>	P15121	Aldo-keto reductase family 1 member B	-1.34162
<i>LGALS3</i>	P17931	Lectin, galactoside binding soluble 3	1.333141
<i>SERPINE1</i>	P05121	Serpin family E member 1	1.977738
<i>TNNC1</i>	P63316	Troponin C1, slow skeletal and cardiac type	-2.18454
<i>SCNN1A</i>	P37088	Sodium channel epithelial 1 alpha subunit	-5.33779
<i>DPP4</i>	P27487	Dipeptidyl peptidase 4	-1.40641
<i>AKR1C3</i>	P42330	Aldo-keto reductase family 1, member C3	-1.09751
<i>ADORA1</i>	P30542	Adenosine A1 receptor	-1.54902
<i>LPAR5</i>	Q9H1C0	Lysophosphatidic acid receptor 5	4.496225
<i>LPAR1</i>	Q92633	Lysophosphatidic acid receptor 1	1.209421
<i>P2RY2</i>	P41231	Purinergic receptor P2Y2	1.40659
<i>ADRB2</i>	P07550	Adrenoceptor beta 2	-2.16687
<i>P4HA1</i>	P13674	Prolyl 4-hydroxylase subunit alpha 1	1.805188
<i>IGFBP6</i>	P24592	Insulin like growth factor binding protein 6	-1.61997
<i>HMGB1</i>	P09429	High mobility group box 1	1.269433
<i>IGFBP5</i>	P24593	Insulin like growth factor binding protein 5	-2.56708
<i>GLRB</i>	P48167	Glycine receptor beta	-1.04807
<i>ALOX5</i>	P09917	Arachidonate 5-lipoxygenase	-1.54864
<i>PDE5A</i>	O76074	Phosphodiesterase 5A	-2.85102
<i>MMP9</i>	P14780	Matrix metalloproteinase 9	3.495904
<i>PIK3R1</i>	P27986	Phosphoinositide-3-kinase regulatory subunit 1	-1.85214
<i>KYNU</i>	Q16719	Kynureninase	-1.20742
<i>PHYKPL</i>	Q8IUZ5	5-phosphohydroxy-L-lysine phospho-lyase	-1.01669
<i>GAD1</i>	Q8IVA8	Glutamate decarboxylase 1	-1.56392
<i>SPTLC3</i>	Q9NUV7	Serine palmitoyltransferase long chain base subunit 3	-1.72677
<i>FYN</i>	P06241	FYN proto-oncogene, Src family tyrosine kinase	-1.33082
<i>CCNA2</i>	P20248	Cyclin A2	1.395132
<i>CDK1</i>	P06493	Cyclin dependent kinase 1	1.591329
<i>CCNB1</i>	P14635	Cyclin B1	1.153017
<i>MMP1</i>	P03956	Matrix metalloproteinase 1	5.315018
<i>MMP13</i>	P45452	Matrix metalloproteinase 13	4.410247
<i>PRKCA</i>	P17252	Protein kinase C alpha	-1.28924
<i>GATM</i>	P50440	Glycine amidinotransferase	-1.26205
<i>SLC23A1</i>	Q9UHI7	Solute carrier family 23 member 1	-1.71022
<i>PLOD2</i>	O00469	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 2	1.70937

Table 2 (continued)

Table 2 (continued)

Cross gene	Uniport ID	Gene name	LogFC
<i>EGLN3</i>	Q9H6Z9	Egl-9 family hypoxia inducible factor 3	-1.53998
<i>P4HA2</i>	O15460	Prolyl 4-hydroxylase subunit alpha 2	1.069761
<i>SUCNR1</i>	Q9BXA5	Succinate receptor 1	4.608116
<i>ALDH5A1</i>	P51649	Aldehyde dehydrogenase 5 family member A1	-1.95489
<i>ENPEP</i>	Q07075	Glutamyl aminopeptidase	-1.45376
<i>GLS2</i>	Q9UI32	Glutaminase 2	-1.03821
<i>FPGS</i>	Q05932	Folylpolyglutamate synthase	1.304325
<i>GLS</i>	O94925	Glutaminase	-1.27648
<i>NR1H4</i>	Q96RI1	Nuclear receptor subfamily 1 group H member 4	-2.90611
<i>KMO</i>	O15229	Kynurenine 3-monooxygenase (kynurenine 3-hydroxylase)	-3.60623
<i>ESRRG</i>	P62508	Estrogen related receptor gamma	-2.40246
<i>PTGES</i>	O14684	Prostaglandin E synthase	-2.2689
<i>C3</i>	P01024	Complement component 3	-1.83543
<i>CYP26A1</i>	O43174	Cytochrome P450 family 26 subfamily A member 1	-1.25634
<i>KCNN4</i>	O15554	Potassium calcium-activated channel subfamily N member 4	1.292726
<i>Cyp24a1</i>	Q07973	Cytochrome P450 family 24 subfamily A member 1	1.962299
<i>ABCB1</i>	P08183	ATP binding cassette subfamily B member 1	-2.63786
<i>CNR1</i>	P21554	Cannabinoid receptor 1	-2.36452
<i>FOLR1</i>	P15328	Folate receptor 1	-1.27459
<i>ITGB1</i>	P05556	Integrin subunit beta 1	2.271656
<i>CYP1B1</i>	Q16678	Cytochrome P450 family 1 subfamily B member 1	-1.12467
<i>FOS</i>	P01100	Fos proto-oncogene, AP-1 transcription factor subunit	1.069912
<i>KCNK2</i>	O95069	Potassium two pore domain channel subfamily K member 2	-2.09549
<i>Hes1</i>	Q14469	Hes family bHLH transcription factor 1	2.510727
<i>SPHK1</i>	Q9NYA1	Sphingosine kinase 1	2.22411
<i>AURKB</i>	Q96GD4	Aurora kinase B	1.554256
<i>NEK2</i>	P51955	NIMA related kinase 2	1.494727
<i>TUBB4B</i>	P68371	Tubulin beta 4B class IVb	1.123177
<i>GPR183</i>	P32249	G protein-coupled receptor 183	3.13216
<i>TGM2</i>	P21980	Transglutaminase 2	2.387535
<i>TUBA4A</i>	P68366	Tubulin alpha 4a	1.838797
<i>XDH</i>	P47989	Xanthine dehydrogenase	2.158727
<i>CA11</i>	O75493	Carbonic anhydrase 11	-1.2726
<i>PRKACA</i>	P17612	Protein kinase cAMP-activated catalytic subunit alpha	1.079271

Table 2 (continued)

Table 2 (continued)

Cross gene	Uniport ID	Gene name	LogFC
SCN2A	Q99250	Sodium voltage-gated channel alpha subunit 2	-1.45842
EIF4H	Q15056	Eukaryotic translation initiation factor 4H	1.779768
Sgk1	O00141	Serum/glucocorticoid regulated kinase 1	1.012613
DAPK1	P53355	Death associated protein kinase 1	-1.94583
Slc16a7	O60669	Solute carrier family 16 member 7	-1.38307
ST6GAL1	P15907	ST6 beta-galactoside alpha-2,6-sialyltransferase 1	-1.02237
AURKA	O14965	Aurora kinase A	1.16167
LSS	P48449	Lanosterol synthase (2,3-oxidosqualene-lanosterol cyclase)	-1.00177
Lat	O43561	Linker for activation of T-cells	1.492451
FKBP1A	P62942	FK506 binding protein 1A	1.071867

HJT, Hongjingtian injection; TIF, tubulointerstitial fibrosis; FC, fold change.

targets of HJT anti TIF. Thus, we chose these five key genes for further experimental verification. HK-2 cells were pretreated with TGF- β 1 (0, 2, 5, 10 ng/mL) for 48 hours. Real-time polymerase chain reaction analysis results showed that compared with the control group (no TGF- β 1 pretreatment), *AKR1B1*, *GAD1*, *PTGES* were down-regulated and *SPHK1* and *P4HA2* were up-regulated by treatment of 10 ng/mL TGF- β 1 in HK-2 cells (Figure 5).

These results are consistent with the expression trend of the microarray we explored. Finally, we selected TGF- β 1 at 10 ng/mL to further investigate its effects on HJT to the expression of predicted five major gene targets based on the fact that none of the three concentrations of TGF- β 1 inhibited cell activity.

Optimal concentration of HJT

It cannot be ignored that although HJT has a protective effect on HK-2 cells, high dose may cause cell death. In order to explore protective effects of HJT on the HK-2 cells, CCK-8 assay was used to evaluate the survival rate of HK-2 at the doses of 0, 1.25, 2.5, 5, 10, 20, 40, 80, 200, 1,000 mL/L of HJT. As the results showed in Figure 6 that the HJT at the dose within the range of 0–2.5 mL/L has little significant toxicity in HK-2 cell. The half-maximal inhibitory concentration (IC₅₀) of HJT for HK-2 cells was 99.81 mL/L. Therefore, 2.5 mL/L HJT was selected for subsequent experiments.

Effect of HJT on the expression of key targets in TGF- β 1-induced HK-2

qRT-PCR was used to further validate *SPHK1*, *GAD1*, *P4HA2*, *AKR1B1* and *PTGES* for HJT treatment of TIF (Figure 7A). The results showed that HJT could reverse the expression of *SPHK1* with statistical significance ($P < 0.05$). However, the improvement of other genes was not significant ($P > 0.05$). The WB results demonstrated that the expression level of *SPHK1* was promoted in HK-2 ($P < 0.01$). After treatment of HJT, the expression of *SPHK1* was markedly suppressed ($P < 0.05$) (Figure 7B, 7C).

The progression of EMT was promoted by TGF- β 1 but restored by HJT

The immunofluorescence assay showed that TGF- β 1 upregulated Vimentin and downregulated cytokeratin 18 in HK-2 cells. On the contrary, the expression of them was reversed after intervention with HJT (Figure 8A, 8B). Besides, HK-2 migration capacity was measured through wound-healing assay and Transwell assay. As Figure 8C, 8D shown, the first row was the scratch size of control, TGF- β 1, HJT and TGF- β 1 and HJT group at 0 h, which was used as a baseline comparison, while the second and third lines were the scratch size at 24 and 48 h in the corresponding groups, respectively. After 24 hours of intervention, TGF- β 1 showed a 16.7% increase compared with control group

Table 3 Top 25 pathways

KEGG_A_class	KEGG_B_class	Pathway	Out [68]	All (8,312)	P value	Q value	Pathway ID
Human Diseases	Cancer: overview	MicroRNAs in cancer	8	176	0.000086	0.007876	ko05206
Cellular Processes	Cellular community-eukaryotes	Gap junction	6	93	0.000104	0.007876	ko04540
Organismal Systems	Endocrine system	Relaxin signaling pathway	7	135	0.000108	0.007876	ko04926
Organismal Systems	Endocrine system	Progesterone-mediated oocyte maturation	6	110	0.000263	0.013078	ko04914
Metabolism	Amino acid metabolism	Alanine, aspartate and glutamate metabolism	4	40	0.0003	0.013078	ko00250
Organismal Systems	Excretory system	Aldosterone-regulated sodium reabsorption	4	42	0.000363	0.013185	ko04960
Human Diseases	Cancer: overview	Pathways in cancer	13	552	0.00045	0.014012	ko05200
Environmental Information Processing	Signal transduction	Sphingolipid signaling pathway	6	125	0.000524	0.01428	ko04071
Metabolism	Global and overview maps	Metabolic pathways	24	1554	0.000866	0.018547	ko01100
Organismal Systems	Nervous system	GABAergic synapse	5	92	0.000896	0.018547	ko04727
Metabolism	Metabolism of other amino acids	D-Glutamine and D-glutamate metabolism	2	6	0.000969	0.018547	ko00471
Organismal Systems	Endocrine system	Ovarian steroidogenesis	4	55	0.001021	0.018547	ko04913
Metabolism	Metabolism of cofactors and vitamins	Folate biosynthesis	3	28	0.001482	0.024852	ko00790
Organismal Systems	Endocrine system	Regulation of lipolysis in adipocytes	4	63	0.001698	0.026438	ko04923
Organismal Systems	Endocrine system	Parathyroid hormone synthesis, secretion and action	5	109	0.001913	0.027803	ko04928
Environmental Information Processing	Signal transduction	Rap1 signaling pathway	7	226	0.002371	0.032308	ko04015
Organismal Systems	Nervous system	Cholinergic synapse	5	118	0.002708	0.034723	ko04725
Human Diseases	Cancer: specific types	Bladder cancer	3	42	0.004787	0.057971	ko05219
Organismal Systems	Immune system	Fc epsilon RI signaling pathway	5	141	0.005793	0.063375	ko04664
Metabolism	Amino acid metabolism	Tryptophan metabolism	3	45	0.005814	0.063375	ko00380
Organismal Systems	Digestive system	Salivary secretion	4	93	0.00693	0.071942	ko04970
Organismal Systems	Immune system	IL-17 signaling pathway	4	97	0.008026	0.078979	ko04657
Human Diseases	Infectious disease: bacterial	Pathogenic Escherichia coli infection	7	285	0.008397	0.078979	ko05130
Metabolism	Amino acid metabolism	Arginine and proline metabolism	3	52	0.008695	0.078979	ko00330
Environmental Information Processing	Signal transduction	cAMP signaling pathway	6	223	0.009555	0.082423	ko04024

KEGG, Kyoto Encyclopedia of Genes and Genomes; RI, receptor for immunoglobulin E; cAMP, cyclic adenosine monophosphate.

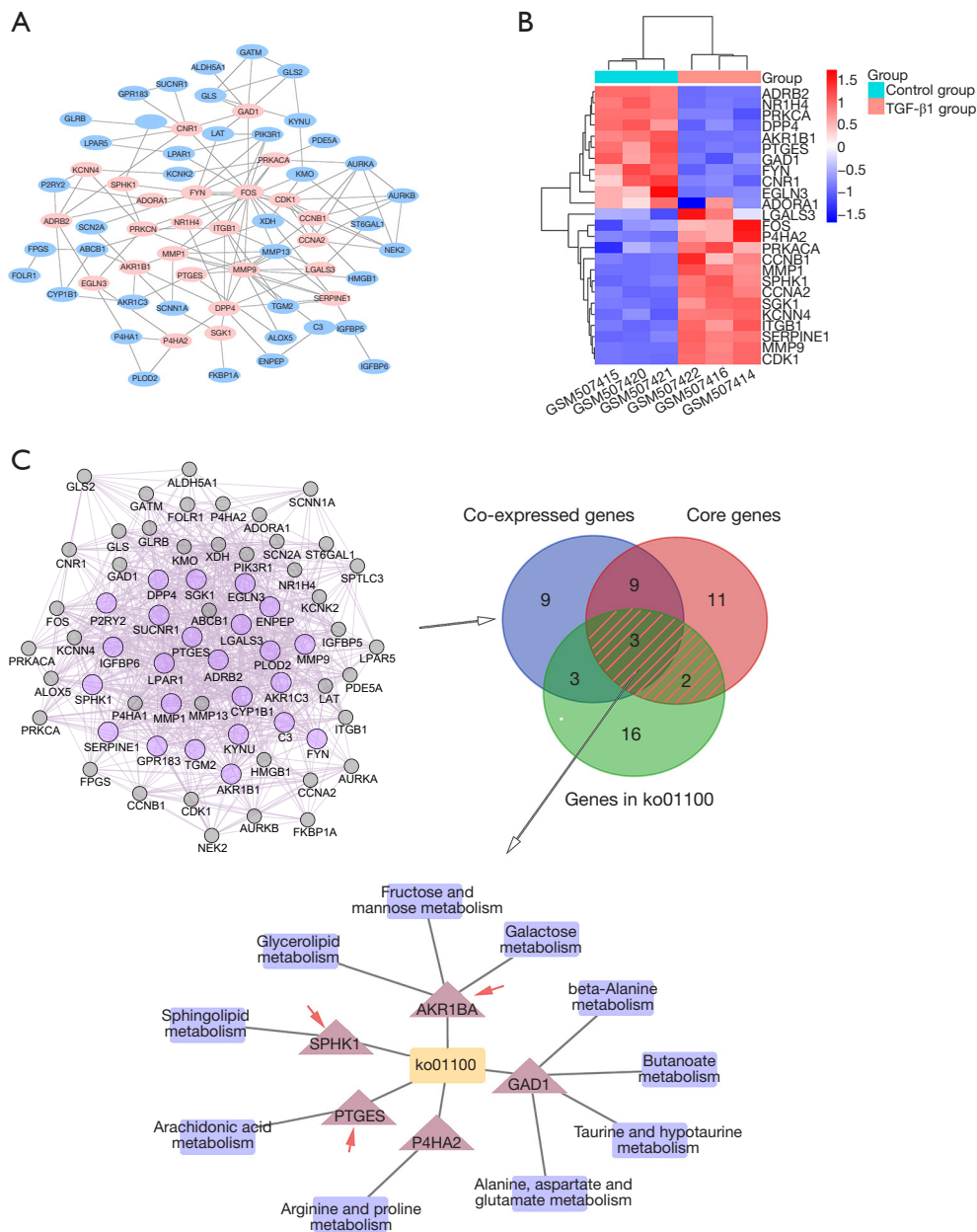


Figure 4 Analysis of PPI and key genes. (A) Protein-protein interaction network of HJT acting on TIF. Network nodes represent proteins, edges represent protein-protein associations. The pink nodes represent 25 core genes. (B) The heatmap of core genes. (C) Co-expression relationships in the PPI network were analyzed and further higher-scoring cluster containing 25 genes were shown in purple. There are 5 key genes enriched in the Metabolic pathway, three of which have co-expression relationship, *SPHK1*, *AKR1B1* and *PTGES*, respectively. PPI, protein-protein interaction; HJT, Hongjingtian injection; TIF, Tubulointerstitial fibrosis.

($P < 0.05$), and 5.6% decrease of TGF- β 1 + HJT to TGF- β 1 ($P > 0.05$). After 48 hours of intervention, TGF- β 1 showed a 21.1% increase compared with control group ($P < 0.05$), and 16.7% decrease of TGF- β 1 + HJT to TGF- β 1 ($P < 0.05$).

To conform the effects on cells migration, Transwell assay was carried out and TGF- β 1 showed a 550.2% increase in comparison with control group ($P < 0.0001$). TGF- β 1 + HJT showed a 44.9% decrease in comparison with TGF- β 1

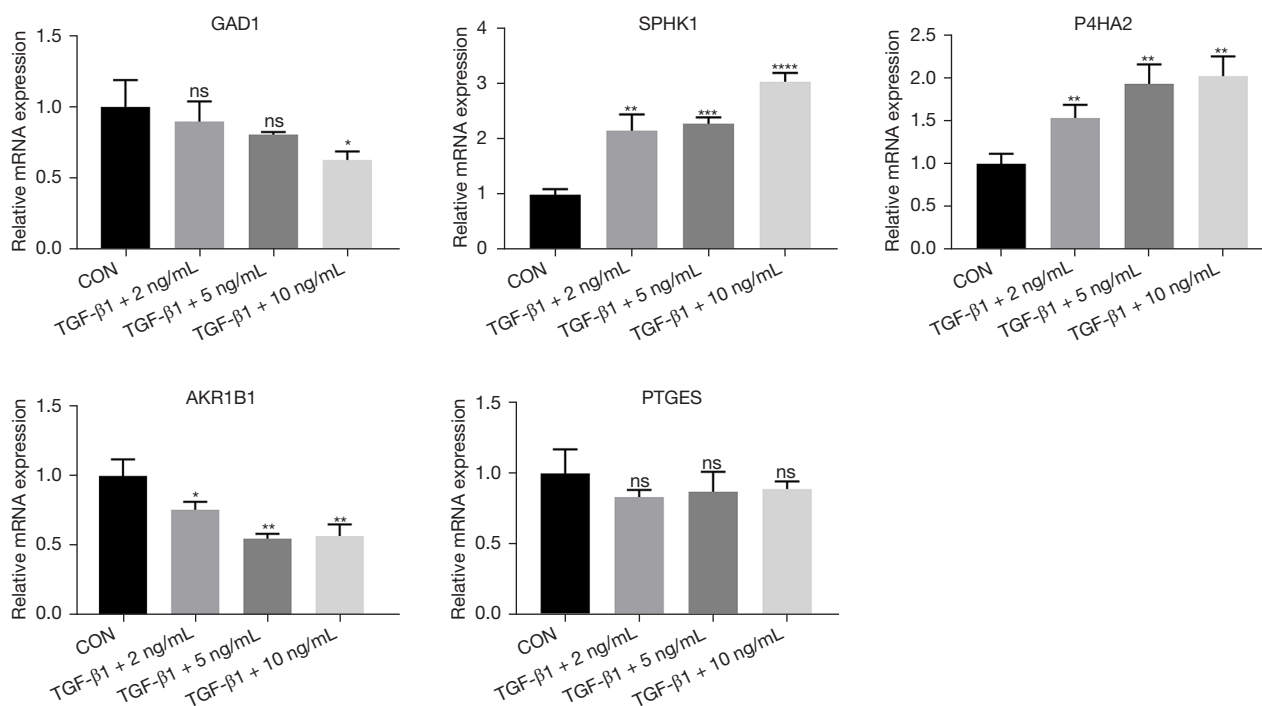


Figure 5 The effect of different concentrations of TGF-β1 on five key genes was determined by qPCR. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$; ns, $P > 0.05$. CON, control group; qPCR, quantitative polymerase chain reaction.

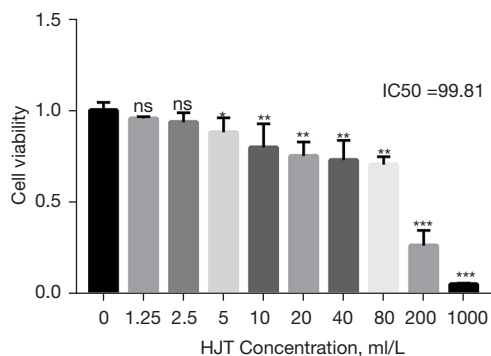


Figure 6 Evaluate the survival rate of HK-2 at the different doses of HJT using CCK-8 assay. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ns, $P > 0.05$. HJT, Hongjingtian injection.

($P < 0.0001$, Figure 8E,8F). Taken together, TGF-β1 could regulate vimentin and cytokeratin 18, and promote the migration of HK-2 cells, consequently accelerated the EMT progression. However, HJT can reverse the phenomenon.

Discussion

TIF is a key and irreversible process in the development of CKD. Existing treatment strategies are insufficient to prevent disease development. Therefore, more effective treatments are needed to delay the progression of TIF. In recent years, traditional Chinese medicine has become popular in western countries due to its reliable efficacy. In TCM theory, TIF is called edema, strangury, consumptive disease and so on. Its pathological mechanism can be roughly summarized as deficiency, blood stasis, phlegm dampness and turbid toxin. Rhodiola, as one of the traditional Tibetan medicines in China, has long existed in the history of medicine. It has the effect of invigorating Qi and promoting blood circulation, clearing the pulse and relieving asthma. In modern pharmacology, Rhodiola has anti-diabetic, anti-inflammatory, anti-cancer, anti-aging, cardio-protective, and neuro-protective effects (12). However, as a preparation extracted from Rhodiola, the mechanism of HJT in treating TIF is still unclear due to the

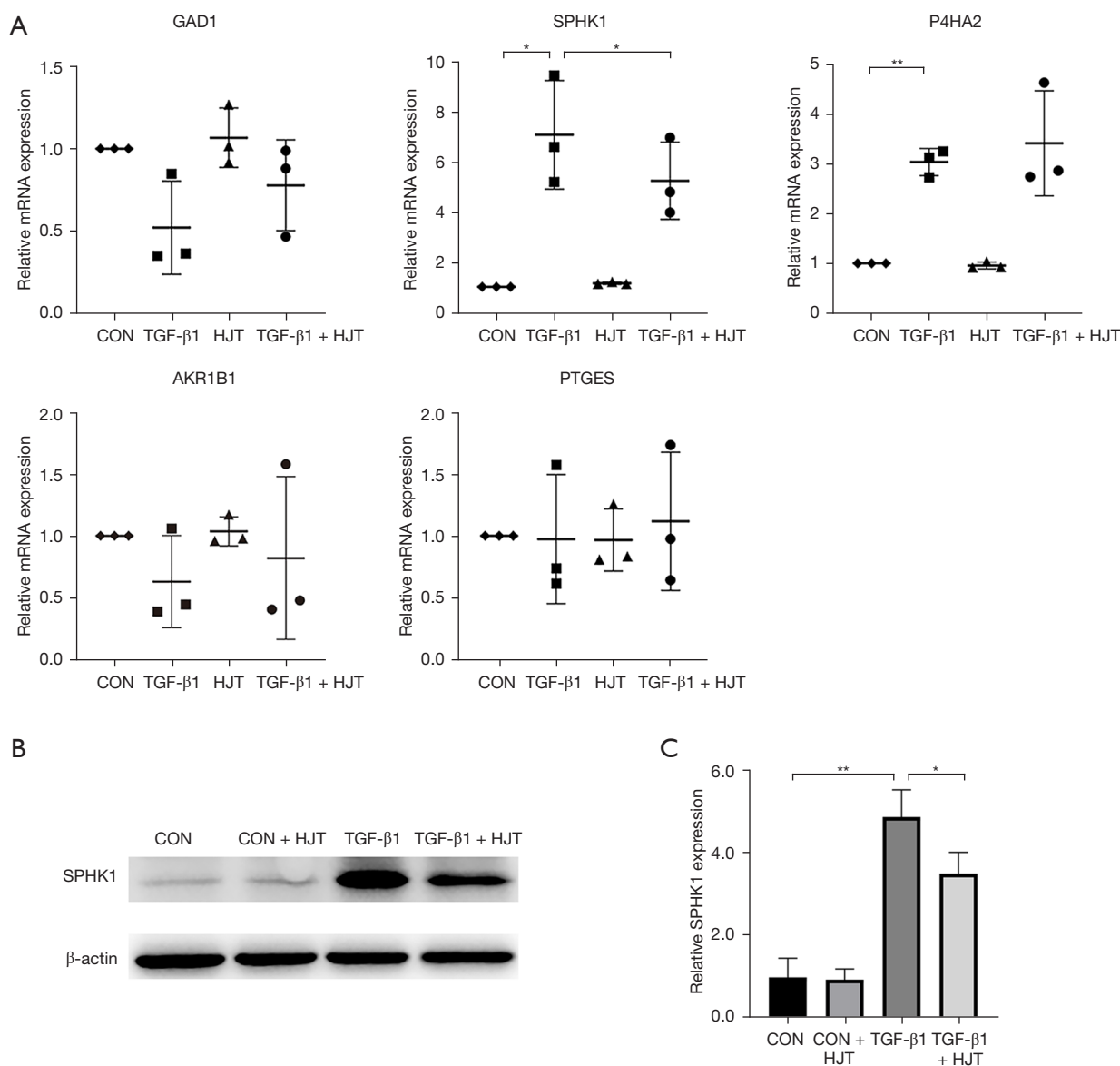


Figure 7 Effect of HJT on five key genes in HK-2 interfered by TGF-β1. (A) Effect of HJT on the expression of key targets in TGF-β1-induced HK-2. *, $P < 0.05$. **, $P < 0.01$. (B,C) The expression level of *SPHK1* was promoted in HK-2 (**, $P < 0.01$). After the treatment of HJT, the expression of *SPHK1* was markedly suppressed (*, $P < 0.05$). HJT, Hongjingtian injection.

complex compounds of traditional Chinese medicine. Thus, this study aimed to clarify the potential mechanism of HJT in the treatment of TIF based on network pharmacology.

We screened out 36 effective active compounds and 1,044 potential targets of HJT. Among the main active compounds of HJT, p-Coumaric acid (p-CA) is a phenolic acid of the hydroxycinnamic acid family (13). Extensive studies have shown that p-CA is related to various bioactivities, including antioxidant, anti-inflammatory, anti-

cancer and antidiabetic (14). Mani *et al.* has revealed that p-CA was found to offer renal protection from oxidative stress by decreasing lipid peroxidation and increasing the activities of antioxidant enzymes in treated diabetic rats (15). Zabad *et al.* also reported that P-CA are able to decrease the fibrotic cytokines and protect against the progression of DKD (16). Ethyl gallate (EG) is a hydroxylated, ethyl ester of benzoic acid. EG has antioxidant, anti-inflammatory and anti-proliferative effects. Cui *et al.* (17) demonstrated

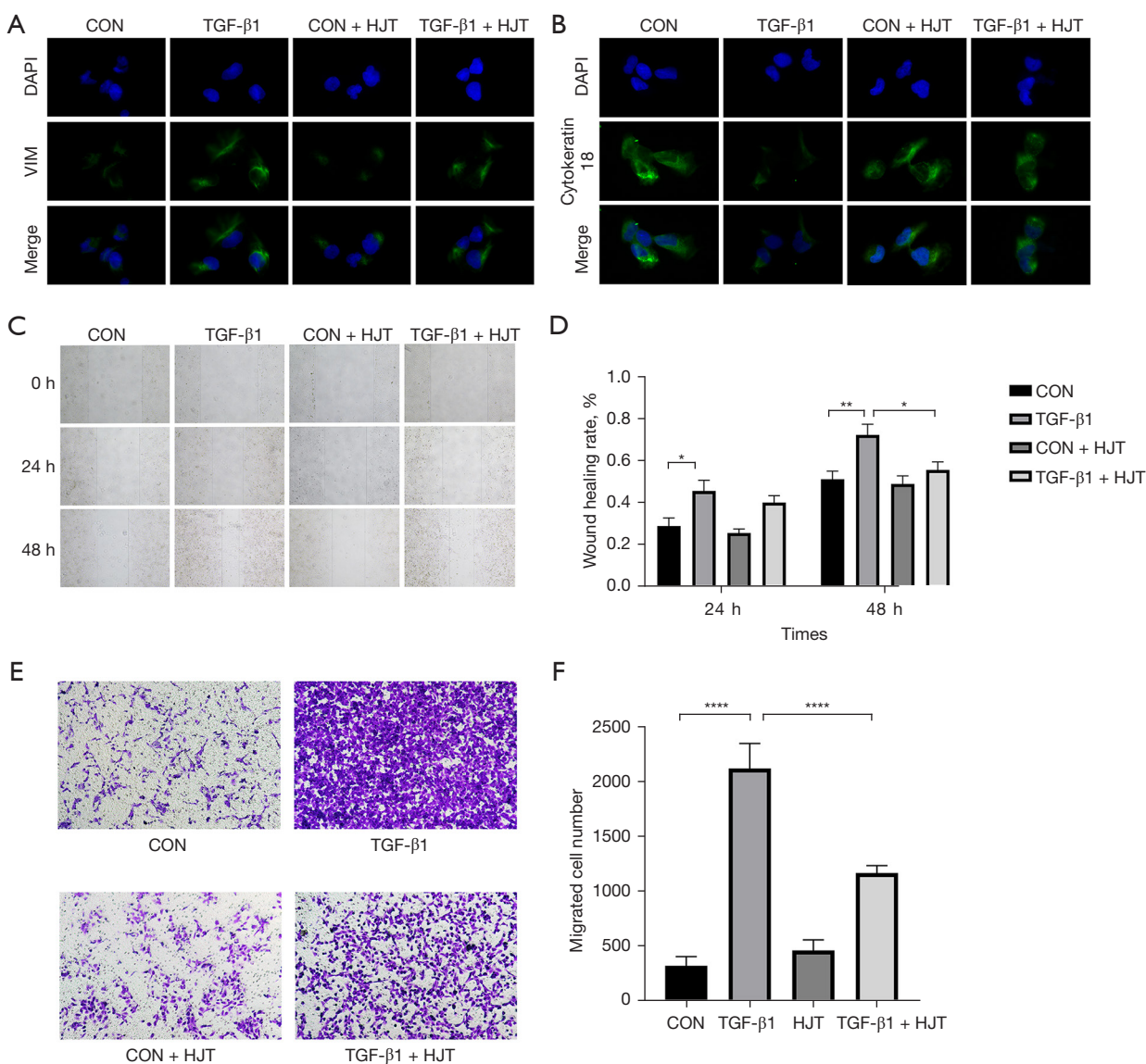


Figure 8 The progression of EMT was promoted by TGF- β 1 but restored by HJT. (A,B) The immunofluorescence assay showed that TGF- β 1 upregulated Vimentin and downregulated cytokeratin18 in HK-2 cells. On the contrary, the expression of them was reversed after intervention with HJT. (40 \times). (C,D) Wound healing assay. The three lines were the scratch size at 0, 24 and 48 h in the corresponding groups, respectively (40 \times). (E,F) Transwell assay (Crystal violet stain, 40 \times). *, $P < 0.05$. **, $P < 0.01$. ****, $P < 0.0001$. HJT, Hongjingtian injection. DAPI, 4',6-diamidino-2-phenylindole, a fluorescent dye with strong binding to DNA. VIM, Vimentin.

that EG suppresses proliferation and invasion in human breast cancer cells by modulating the *PI3K/Akt* pathway, and inhibit downstream targets such as *NF- κ B p-65*, *Bcl-2/Bax*. Ahn *et al.* (18) proposed that EG targeting *PTPN6* and *PPAR γ* exerts an anti-diabetes effect. Crispo *et al.* (19) suggested that EG protects PC12 cells against oxidative stress induction through the *Nrf2* pathway. As such, it

has been proved that EG can protect against diabetes, neuro-degenerative disease, endothelial inflammation and some types of cancer (20). In addition, both 4-Hydroxyphenylacetic acid 4 and Vanillic acid β -glucoside showed potential antioxidant effects (21,22).

Meanwhile, the GSE20247 dataset was downloaded from the GEO database to obtain the gene expression data

of TGF intervention HK-2 cells, and then analyzed the DEGs. In addition, PPI network and functional enrichment analysis were performed on common genes to understand the meaningful pathway between TGF- β 1-induced HK-2 and normal control. Of which, Metabolic pathways is the pathway enriched for the most genes compared to other pathways. We speculated that HJT might participate in the treatment of TIF by regulating metabolic pathways. Therefore, five target genes related to metabolic pathways were selected for further research (*AKR1B1*, *GAD1*, *P4HA2*, *SPHK1* and *PTGES*).

Our result shows that although it was found that the five key genes in HK-2 interfered by TGF- β 1 were consistent with the trend shown by the GSE20247, HJT only had a significant reversal effect on *SPHK1*. The metabolites of sphingolipid include ceramides, sphingosine and sphingosine-1-phosphate (S1P). S1P has a function of cell proliferation and differentiation, while ceramide and sphingosine induced cell growth arrest and apoptosis and migration (23). *SPHK1* is a key metabolic enzyme that catalyzes the synthesis of S1P by sphingosine (24). Fibronectin (FN) is one of ECM components and its accumulation will eventually lead to TIF (25). Chen *et al.* demonstrated that AGEs-RAGE could upregulate FN through regulating *SPHK1* *in vitro* cell experiments (26). Huang *et al.* (27) confirmed the regulatory effect of *SPHK1* on *NF- κ B*-mediated diabetic renal fibrosis *in vivo* and *in vitro* experiments. Compared with diabetic mice, fewer renal fibrotic lesions, FN accumulation and *NF- κ B* nuclear accumulation exhibited in glomeruli of kidneys of *SPHK1*^{-/-} diabetic mice. He *et al.* (28) indicated that the inhibition of *SPHK1* contribute to decrease the EMT by blocking the *NF- κ B* signaling, thereby protecting HK-2 against TIF. Liu *et al.* (29) confirmed that *SPHK1*/S1P signaling upregulates microRNA-21 in renal TECs interfered by TGF- β , thus promoting the overexpression of ECM proteins and TIF. Huang *et al.* (30) reported that the expression of *SPHK1* and S1P were significantly down-regulated by curcumin in diabetic rat kidneys and glomerular mesangial cells (GMCs) with high glucose intervention. Meanwhile, *SPHK1*-S1P-mediated FN and TGF- β 1 were inhibited. In addition, Lan *et al.* (31) also found that berberine exerts renoprotective effects on DKD through *SPHK1*-S1P signaling pathway. S1P is catalytically synthesized by Sphingosine kinases and catabolized by S1P phosphatases and S1P lyase (S1PL). Huang *et al.* (32) suggested that the expressions of *SPHK1* were increased in bleomycin challenged mice. Genetic knockdown of *SPHK1* ameliorated pulmonary fibrosis in

mice while deletion of S1PL potentiated fibrosis. Taken together, the present study *in vitro* and *in vivo* demonstrated that *SPHK1* is closely related to the pathological process of EMT and TIF. Therefore, inhibiting *SPHK1* signaling may be a promising therapeutic strategy in TIF.

During the process of TIF, epithelial cells undergo partial EMT. Partial EMT cells acquire the ability to produce profibrotic cytokines/growth factors while remaining attached to the basement membrane during fibrosis (33). In addition, a study (34) has found that compared with the normal structure of renal tubules in healthy subjects, renal sections of diabetes patients show thickening and hypertrophy of renal tubules. As a key mediator of TIF, TGF- β 1 activates different intracellular signaling pathways during the process of EMT (35), contributing to the secretion of collagen and inducing its deposition, leading to tissue fibrosis (36). Besides, TGF- β 1 is also closely related to hypertrophy of renal tubules (37). Therefore, we established an *in vitro* TIF cell model by intervening HK-2 cells with TGF- β 1. During EMT, epithelial cells lose key phenotypic markers and acquire mesenchymal markers (38). In our results, it was clearly seen that HJT alone did not affect the migration and phenotypic changes of HK-2 without TGF- β 1 intervention. The results of immunofluorescence showed that the expression of cytokeratin 18 decreased and the expression of vimentin increased after TGF- β 1 intervention, and then reversed by HJT. In the wound healing assay and Transwell assay, compared with the control group, the TGF- β 1 experimental group significantly improved the cell migration ability, but the ability decreased after adding HJT. To sum up, HJT has an inhibitory effect on EMT and migration ability. HJT treatment of TIF may reverse EMT caused by TGF- β 1 by targeting *SPHK1*.

Conclusions

In conclusion, HJT treats TIF through multi-component, multi-target and multi-directional. In particular, *SPHK1* may be the most important target of HJT in TIF. Our research revealed the mechanism of HJT in the process of action from a holistic and systematic perspective, which provides a theoretical basis for further research and application of HJT in the future. However, whether HJT is indeed suitable for the prevention and treatment of TIF still needs to be confirmed by future clinical trials. Therefore, *in vivo* experimental validation of potential active ingredients is urgently needed to help further evaluate the therapeutic potential of HJT.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (No. 82105044), the Natural Science Foundation of Shandong Province (No. ZR2020QH310), and Traditional Chinese Medicine Science and Technology Project of Shandong Province (No. M-2022141).

Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5035/rc>

Data Sharing Statement: Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5035/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-5035/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Sun G, Jiao M, Cui Y, Liang X, Liang X, Zhang S, Guo C. Identifying the mechanisms and molecular targets of Hongjingtian injection on treatment of TGF β 1-induced HK-2 cells: coupling network pharmacology with experimental verification. *Ann Transl Med* 2022;10(24):1329. doi: 10.21037/atm-22-5035

Table S1 1,044 potential target genes were selected for the 36 compounds of HJT from the Chemmaper, Sea and Swiss database.

Commonname	Uniprot ID	Target	Database
EPHX2	P34913	Epoxidehydratase	Swiss
SSTR5	P35346	Somatostatinreceptor5	Swiss
SSTR2	P30874	Somatostatinreceptor2	Swiss
SSTR4	P31391	Somatostatinreceptor4	Swiss
SSTR1	P30872	Somatostatinreceptor1	Swiss
SSTR3	P32745	Somatostatinreceptor3	Swiss
PTPN2	P17706	T-cellprotein-tyrosinephosphatase	Swiss
HSP90AA1	P07900	HeatshockproteinHSP90-alpha	Swiss
ADORA3	P0DMS8	AdenosineA3receptor	Swiss
P2RX3	P56373	P2Xpurinoceptor3	Swiss
KDR	P35968	Vascularendothelialgrowthfactorreceptor2	Swiss
LDHB	P07195	L-lactatedehydrogenaseBchain	Swiss
IGF1R	P08069	Insulin-likegrowthfactorIreceptor	Swiss
ALK	Q9UM73	ALKtyrosinekinasereceptor	Swiss
BCL2L1	Q07817	ApoptosisregulatorBcl-X	Swiss
EGFR	P00533	EpidermalgrowthfactorreceptorerbB1	Swiss
PTPN22	Q9Y2R2	Hematopoieticcellprotein-tyrosinephosphatase70Z-PEP	Swiss
TREH	O43280	Trehalase	Swiss
CCNA1	P78396	Cyclin-dependentkinase2/cyclinA	Swiss
CCNA2	P20248	Cyclin-dependentkinase2/cyclinA	Swiss
GRK1	Q15835	Rhodopsinkinase	Swiss
PPP1CC	P36873	Serine/threonineproteinphosphatasePP1-gammacatalyticsubunit	Swiss
PPP2CA	P67775	Serine/threonineproteinphosphatase2A,catalyticsubunit,alphaisoform	Swiss
PPP2R5A	Q15172	Serine/threonineproteinphosphatase2A,56kDaregulatorysubunit,alphaisoform	Swiss
TK1	P04183	Thymidinekinase,cytosolic	Swiss
AHCY	P23526	Adenosylhomocysteinase	Swiss
CDK9	P50750	CDK9/cyclinT1	Swiss
CCNT1	O60563	CDK9/cyclinT1	Swiss
STAT3	P40763	Signaltransducerandactivatoroftranscription3	Swiss
CDK1	P06493	Cyclin-dependentkinase1/cyclinB1	Swiss
CCNB1	P14635	Cyclin-dependentkinase1/cyclinB1	Swiss
RORC	P51449	NuclearreceptorROR-gamma	Swiss
MCL1	Q07820	InducedmyeloidleukemiacelldifferentiationproteinMcl-1	Swiss
MMP3	P08254	Matrixmetalloproteinase3	Swiss
ADAM17	P78536	ADAM17	Swiss
TYMP	P19971	Thymidinephosphorylase	Swiss
IDO1	P14902	Indoleamine2,3-dioxygenase	Swiss
AHCYL1	O43865	Adenosylhomocysteinase2	Swiss
VCP	P55072	TransitionalendoplasmicreticulumATPase	Swiss
MMP13	P45452	Matrixmetalloproteinase13	Swiss
PRKCA	P17252	ProteinkinaseCalpha	Swiss
MMP7	P09237	Matrixmetalloproteinase7	Swiss
MMP8	P22894	Matrixmetalloproteinase8	Swiss
GSK3B	P49841	Glycogensynthasekinase-3beta	Swiss
DTYMK	P23919	Thymidylatekinase	Swiss
PPM1B	O75688	Proteinphosphatase2Cbeta	Swiss
HDAC6	Q9UBN7	Histonedeaetylase6	Swiss
GABRA1	P14867	GABA-Areceptor;alpha-1/beta-2/gamma-2	Swiss
GABRB3	P28472	GABA-Areceptor;alpha-1/beta-3/gamma-2	Swiss
GABBR2	O75899	GABA-Breceptor	Swiss
KCNN4	O15554	Intermediateconductancecalcium-activatedpotassiumchannelprotein4(SK4)(SKCa4)(SKCa4)(IKCa1)(IK1)(KCa3.1)(KCa4) (PutativeGardoschannel)	Swiss
PTGDR2	Q9Y5Y4	ProstaglandinD2receptor2(Chemoattractantreceptor-homologousmoleculeexpressedonTh2cells)(G-proteincoupledreceptor44) (CDantigenCD294)	Swiss
ITGAV	P06756	Integrinalpha-V(Vitronectinreceptor)(Vitronectinreceptorsubunitalpha)(CDantigenCD51)[Cleavedinto:Integrinalpha-Vheavychain;Integrinalpha-Vlightchain]	Swiss
ITGB3	P05106	Integrinbeta-3	Swiss

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
AMPD1	P23109	AMPdeaminase1(EC3.5.4.6)(AMPdeaminaseisoformM)(Myoadenylatedeaminase)	Swiss
CASP1	P29466	Caspase-1(CASP-1)(EC3.4.22.36)(Interleukin-1betaconvertase)(IL-1BC)(Interleukin-1beta-convertingenzyme)(CE)(IL-1beta-convertingenzyme)(p45)[Cleavedinto:Caspase-1subunitp20;Caspase-1subunitp10]	Swiss
CDK4	P11802	Cyclin-dependentkinase4(EC2.7.11.22)(Celldivisionprotein kinase4)(PSK-J3)	Swiss
CDK6	Q00534	Cyclin-dependentkinase6(EC2.7.11.22)(Celldivisionprotein kinase6)(Serine/threonine-protein kinasePLSTIRE)	Swiss
CNR1	P21554	Cannabinoidreceptor1(CB-R)(CB1)(CANN6)	Swiss
CNR2	P34972	Cannabinoidreceptor2(CB-2)(CB2)(hCB2)(CX5)	Swiss
FOLR1	P15328	Folaterceptoralpha(FR-alpha)(Adultfolate-bindingprotein)(FBP)(Folaterceptor1)(Folaterceptor,adult)(KBcellsFBP)(Ovariantumor-associatedantigenMOv18)	Swiss
FOLR2	P14207	Folaterceptorbeta(FR-beta)(Folaterceptor2)(Folaterceptor,fetal/placental)(Placentalfolate-bindingprotein)(FBP)	Swiss
GART	P22102	Trifunctionalpurinebiosyntheticproteinadenosine-3[Includes:Phosphoribosylamine--glycineligase(EC6.3.4.13)(Glycinamideribonucleotidesynthetase)(GARS)(Phosphoribosylglycinamidesynthetase);Phosphoribosylformylglycinamidinercyclo-ligase(EC6.3.3.1)(AIRsynthase)(AIRS)(Phosphoribosyl-aminoimidazolesynthetase);Phosphoribosylglycinamideformyltransferase(EC2.1.2.2)(5'-phosphoribosylglycinamidetransformylase)(GARtransformylase)(GART)]	Swiss
GRK6	P43250	Gprotein-coupledreceptorkinase6(EC2.7.11.16)(Gprotein-coupledreceptorkinaseGRK6)	Swiss
IKKBK	O14920	Inhibitorofnuclearfactorkappa-Bkinasesubunitbeta(l-kappa-B-kinasebeta)(IKK-B)(IKK-beta)(IkKB)(EC2.7.11.10)(l-kappa-Bkinase2)(IKK2)(NuclearfactorNF-kappa-Binhibitor kinasebeta)(NFKBIKB)	Swiss
ITGA2B	P08514	Integrinalpha-IIb(GPAlphallb)(GPIIb)(PlateletmembraneglycoproteinIb)(CDantigenCD41)[Cleavedinto:Integrinalpha-IIbheavychain;Integrinalpha-IIblightchain,form1;Integrinalpha-IIblightchain,form2]	Swiss
ITGB1	P05556	Integrinbeta-1(Fibronectinreceptorsubunitbeta)(GlycoproteinIIa)(GPIIA)(VLA-4subunitbeta)(CDantigenCD29)	Swiss
ITGB5	P18084	Integrinbeta-5	Swiss
PIM2	Q9P1W9	Serine/threonine-protein kinasepim-2(EC2.7.11.1)(Pim-2h)	Swiss
SLC19A1	P41440	Reducedfolatetransporter(FOLT)(Intestinalfolatecarrier1)(IFC-1)(Placentalfolatetransporter)(Reducedfolatecarrierprotein)(RFC)(hRFC)(Reducedfolatetransporter1)(RFT-1)(Solutecarrierfamily19member1)	Swiss
SLC46A1	Q96NT5	Proton-coupledfolatetransporter(G21)(Hemecarrierprotein1)(PCFT/HCP1)(Solutecarrierfamily46member1)	Swiss
TKT	P29401	Transketolase(TK)(EC2.2.1.1)	Swiss
CXCR2	P25025	C-X-Cchemokinerceptortype2(CXC-R2)(CXCR-2)(CDw128b)(GRO/MGSAreceptor)(Highaffinityinterleukin-8receptorB)(IL-8RB)(IL-8receptortype2)(CDantigenCD182)	Swiss
DYRK2	Q92630	Dualspecificitytyrosine-phosphorylation-regulatedkinase2(EC2.7.12.1)	Swiss
FLT1	P17948	Vascularendothelialgrowthfactorreceptor1(VEGFR-1)(EC2.7.10.1)(Fms-liketyrosinekinase1)(FLT-1)(Tyrosine-protein kinaseFRT)(Tyrosine-protein kinase receptorFLT)(FLT)(Vascularpermeabilityfactorreceptor)	Swiss
HSP90AB1	P08238	HeatshockproteinHSP90-beta(HSP90)(Heatshock84kDa)(HSP84)(HSP84)	Swiss
KIT	P10721	Mast/stemcellgrowthfactorreceptorKit(SCFR)(EC2.7.10.1)(Piebaldtraitprotein)(PBT)(Proto-oncogeneKit)(Tyrosine-protein kinaseKit)(p145c-kit)(v-kitHardy-Zuckerman4felinesarcomaviraloncogenehomolog)(CDantigenCD117)	Swiss
LARS	Q9P2J5	Leucine--tRNAligase,cytoplasmic(EC6.1.1.4)(Leucyl-tRNA synthetase)(LeuRS)	Swiss
MAPK10	P53779	Mitogen-activatedprotein kinase10(MAPkinase10)(MAPK10)(EC2.7.11.24)(MAPkinasep493F12)(Stress-activatedprotein kinase1b)(SAPK1b)(Stress-activatedprotein kinaseJNK3)(c-JunN-terminalkinase3)	Swiss
VARS	P26640	Valine--tRNAligase(EC6.1.1.9)(ProteinG7a)(Valyl-tRNA synthetase)(ValRS)	Swiss
APH1A	Q96BI3	Gamma-secretasesubunitAPH-1A(APH-1a)(Aph-1alpha)(Presenilin-stabilizationfactor)	Swiss
APH1B	Q8WW43	Gamma-secretasesubunitAPH-1B(APH-1b)(Aph-1beta)(Presenilin-stabilizationfactor-like)	Swiss
CYP2D6	P10635	CytochromeP4502D6(EC1.14.14.-)(CYPID6)(Cholesterol25-hydroxylase)(CytochromeP450-DB1)(Debrisoquine4-hydroxylase)	Swiss
ECE1	P42892	Endothelin-convertingenzyme1(ECE-1)(EC3.4.24.71)	Swiss
HTR6	P50406	5-hydroxytryptaminereceptor6(5-HT6)(5-HT6)(Serotoninreceptor6)	Swiss
NCSTN	Q92542	Nicastrin	Swiss
NEU2	Q9Y3R4	Sialidase-2(EC3.2.1.18)(Cytosolicsialidase)(N-acetyl-alpha-neuraminidase2)	Swiss
PSEN1	P49768	Presenilin-1(PS-1)(EC3.4.23.-)(ProteinS182)[Cleavedinto:Presenilin-1NTFsubunit;Presenilin-1CTFsubunit;Presenilin-1CTF12(PS1-CTF12)]	Swiss
PSEN2	P49810	Presenilin-2	Swiss
PSENE1	Q9NZ42	Gamma-secretasesubunitPEN-2	Swiss
ADAMTS5	Q9UNA0	Adisintegrinandmetalloproteinasewiththrombospondinmotifs5(ADAM-TS5)(ADAM-TS5)(ADAMTS-5)(EC3.4.24.-)(Adisintegrinandmetalloproteinasewiththrombospondinmotifs1)(ADAM-TS11)(ADAMTS-11)(ADMP-2)(Aggrecanase-2)	Swiss
AURKB	Q96GD4	AurorakinaseB(EC2.7.11.1)(Aurora1)(Aurora-andIPL1-likemidbody-associatedprotein1)(AIM-1)(Aurora/IPL1-relatedkinase2)(ARK-2)(Aurora-relatedkinase2)(STK-1)(Serine/threonine-protein kinase12)(Serine/threonine-protein kinase5)(Serine/threonine-protein kinaseaurora-B)	Swiss
AXL	P30530	Tyrosine-protein kinase receptorUFO(EC2.7.10.1)(AXLoncogene)	Swiss
PTK2	Q05397	Focaladhesionkinase1(FADK1)(EC2.7.10.2)(Focaladhesionkinase-relatednonkinase)(FRNK)(Proteinphosphatase1regulatorysubunit71)(PPP1R71)(Protein-tyrosinekinase2)(p125FAK)(pp125FAK)	Swiss
LCK	P06239	Tyrosine-protein kinaseLck(EC2.7.10.2)(LeukocyteC-terminalSrc kinase)(LSK)(Lymphocytecell-specificprotein-tyrosinekinase)(ProteinYT16)(Proto-oncogeneLck)(Tcell-specificprotein-tyrosinekinase)(p56-LCK)	Swiss

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
NGFR	P08138	Tumornecrosisfactorreceptorsuperfamilymember16(Gp80-LNGFR)(Lowaffinityneurotrophinreceptorp75NTR)(Low-affinitynervegrowthfactorreceptor)(NGFreceptor)(p75ICD)(CDantigenCD271)	Swiss
PGR	P06401	Progesteronereceptor(PR)(Nuclearreceptorsubfamily3groupCmember3)	Swiss
EIF4H	Q15056	Eukaryotictranslationinitiationfactor4H(elf-4H)(Williams-Beurensyndromechromosomalregion1protein)	Swiss
NEU4	Q8WWR8	Sialidase-4(EC3.2.1.18)(N-acetyl-alpha-neuraminidase4)	Swiss
CSNK1D	P48730	Caseinkinaseisoformdelta(CKI-delta)(CKId)(EC2.7.11.1)(Tau-proteinkinaseCSNK1D)(EC2.7.11.26)	Swiss
HSD11B2	P80365	Corticosteroid11-beta-dehydrogenaseisozyme2(EC1.1.1.-)(11-beta-hydroxysteroiddehydrogenasetype2)(11-DH2)(11-beta-HSD2)(11-beta-hydroxysteroiddehydrogenasetypell)(11-HSDtypell)(11-beta-HSDtypell)(NAD-dependent11-beta-hydroxysteroiddehydrogenase)(11-beta-HSD)(Shortchaindehydrogenase/reductasefamily9Cmember3)	Swiss
CD38	P28907	ADP-ribosylcyclase/cyclicADP-ribosehydrolase1(EC3.2.2.6)(2'-phospho-ADP-ribosylcyclase)(2'-phospho-ADP-ribosylcyclase/2'-phospho-cyclic-ADP-ribosetransferase)(EC2.4.99.20)(2'-phospho-cyclic-ADP-ribosetransferase)(ADP-ribosylcyclase1)(ADPRC1)(CyclicADP-ribosehydrolase1)(cADPryhdrolase1)(T10)(CDantigenCD38)	Swiss
AURKA	O14965	AurorakinaseA(EC2.7.11.1)(Aurora2)(Aurora/IPL1-relatedkinase1)(ARK-1)(Aurora-relatedkinase1)(hARK1)(Breasttumor-amplifiedkinase)(Serine/threonine-proteinkinase15)(Serine/threonine-proteinkinase6)(Serine/threonine-proteinkinaseaurora-A)	Swiss
CHRM1	P11229	MuscarinicacetylcholinereceptorM1	Swiss
ERBB2	P04626	Receptortyrosine-proteinkinaseerbB-2(EC2.7.10.1)(Metastaticlymphnodegene19protein)(MLN19)(Proto-oncogeneNeu)(Proto-oncogene-c-erbB-2)(Tyrosinekinase-typecellsurfacereceptorHER2)(p185erbB2)(CDantigenCD340)	Swiss
F7	P08709	CoagulationfactorVII(EC3.4.21.21)(Proconvertin)(Serumprothrombinconversionaccelerator)(SPCA)(Eptacogalfa)[Cleavedinto:FactorVIIlightchain;FactorVIIheavychain]	Swiss
GPR55	Q9Y2T6	G-proteincoupledreceptor55	Swiss
GRB2	P62993	Growthfactorreceptor-boundprotein2(AdapterproteinGRB2)(ProteinAsh)(SH2/SH3adapterGRB2)	Swiss
TACR2	P21452	Substance-Kreceptor(SKRI)(NK-2receptor)(NK-2R)(NeurokininAreceptor)(Tachykininreceptor2)	Swiss
MAP2K1	Q02750	Dualspecificitymitogen-activatedproteinkinasekinase1(MAPkinasekinase1)(MAPKK1)(MKK1)(EC2.7.12.2)(ERKactivatorkinase1)(MAPK/ERKkinase1)(MEK1)	Swiss
NADK	O95544	NADkinase(EC2.7.1.23)(Poly(P)/ATPNADkinase)	Swiss
PIK3CA	P42336	Phosphatidylinositol4,5-bisphosphate3-kinasecatalyticsubunitalphaisoform(PI3-kinasesubunitalpha)(PI3K-alpha)(PI3Kalpha)(PtdIns-3-kinasesubunitalpha)(EC2.7.1.153)(Phosphatidylinositol4,5-bisphosphate3-kinase110kDacatalyticsubunitalpha)(PtdIns-3-kinasesubunitp110-alpha)(p110alpha)(Phosphoinositide-3-kinasecatalyticalphapolypeptide)(Serine/threonineproteinkinasePIK3CA)(EC2.7.11.1)	Swiss
ACLY	P53396	ATP-citrate synthase(EC2.3.3.8)(ATP-citrate(pro-S)-lyase)(ACL)(Citratecleavageenzyme)	Swiss
AKT2	P31751	RAC-beta serine/threonine-proteinkinase(EC2.7.11.1)(ProteinkinaseAkt-2)(ProteinkinaseBbeta)(PKBbeta)(RAC-PK-beta)	Swiss
CLK1	P49759	DualspecificityproteinkinaseCLK1(EC2.7.12.1)(CDC-likekinase1)	Swiss
DYRK1B	Q9Y463	Dualspecificitytyrosine-phosphorylation-regulatedkinase1B(EC2.7.12.1)(Minibrain-relatedkinase)(Mirkproteinkinase)	Swiss
GRM2	Q14416	Metabotropicglutamaterceptor2(mGluR2)	Swiss
GJB2	P29033	Gapjunctionbeta-2protein	Sea
P4HB	P07237	Proteindisulfide-isomerase	Sea
ANTXR2	P58335	Anthraxtoxinreceptor2	Sea
B4GALT1	P15291	Beta-1,4-galactosyltransferase1	Sea
P2RY14	Q15391	P2Ypurinoceptor14	Sea
AMY2A	P04746	Pancreaticalpha-amylase	Sea
UMPS	P11172	Uridine5'-monophosphatesynthase	Sea
ALDH1B1	P30837	AldehydedehydrogenaseX,mitochondrial	Sea
ALDH1A2	O94788	Retinaldehydrogenase2	Sea
CD69	Q07108	EarlyactivationantigenCD69	Sea
SI	P14410	Sucrase-isomaltase,intestinal	Sea
IL6	P05231	Interleukin-6	Sea
ERAP1	Q9NZ08	Endoplasmicreticulumaminopeptidase1	Sea
PDCD4	Q53EL6	Programmedcelldeathprotein4	Sea
P2RY6	Q15077	P2Ypurinoceptor6	Sea
ALPI	P09923	Intestinal-typealkalinephosphatase	Sea
GLB1	P16278	Beta-galactosidase	Sea
HKDC1	Q2TB90	HexokinaseHKDC1	Sea
MGAM	O43451	Maltase-glucoamylase,intestinal	Sea
P2RY4	P51582	P2Ypurinoceptor4	Sea
IGF2R	P11717	Cation-independentmannose-6-phosphatereceptor	Sea
SLC5A11	Q8WWX8	Sodium/myo-inositolcotransporter2	Sea
HEXB	P07686	Beta-hexosaminidasesubunitbeta	Sea
HEXA	P06865	Beta-hexosaminidasesubunitalpha	Sea
GBA2	Q9HCG7	Non-lysosomalglucosylceramidase	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
UGCG	Q16739	Ceramideglucosyltransferase	Sea
SLC5A7	Q9GZV3	Highaffinitycholinetransporter1	Sea
CD22	P20273	B-cellreceptorCD22	Sea
MAG	P20916	Myelin-associatedglycoprotein	Sea
NRAS	P01111	GTPaseNRas	Sea
RARB	P10826	Retinoicacidreceptorbeta	Sea
TNFRSF1A	P19438	Tumornecrosisfactorreceptorsuperfamilymember1A	Sea
RARG	P13631	Retinoicacidreceptorgamma	Sea
RARA	P10276	Retinoicacidreceptoralpha	Sea
PLA2G4B	P0C869	CytosolicphospholipaseA2beta	Sea
GLA	P06280	Alpha-galactosidaseA	Sea
ASF1A	Q9Y294	HistonechaperoneASF1A	Sea
DNPH1	O43598	2'-deoxynucleoside5'-phosphateN-hydrolase1	Sea
LPAR5	Q9H1C0	Lysophosphatidicacidreceptor5	Sea
PLA2G2D	Q9UNK4	GroupIIDsecretoryphospholipaseA2	Sea
PLA2G4A	P47712	CytosolicphospholipaseA2	Sea
TAS2R14	Q9NYV8	Tastereceptortype2member14	Sea
SLC13A5	Q86YT5	Solutecarrierfamily13member5	Sea
SCD	O00767	Acyl-CoAdesaturase	Sea
PTPN12	Q05209	Tyrosine-proteinphosphatase-12	Sea
LPAR1	Q92633	Lysophosphatidicacidreceptor1	Sea
FABP4	P15090	Fattyacid-bindingprotein, adipocyte	Sea
KDM5A	P29375	Lysine-specificdemethylase5A	Sea
PDF	Q9HBH1	Peptidedeformylase, mitochondrial	Sea
MCHR1	Q99705	Melanin-concentratinghormonereceptor1	Sea
CYP26B1	Q9NR63	CytochromeP45026B1	Sea
KLK5	Q9Y337	Kallikrein-5	Sea
PDE4C	Q08493	cAMP-specific3',5'-cyclicphosphodiesterase4C	Sea
PIK3C2G	O75747	Phosphatidylinositol4-phosphate3-kinaseC2domain-containingsubunitgamma	Sea
P2RY2	P41231	P2Ypurinoceptor2	Sea
CXCL12	P48061	Stromalcell-derivedfactor1	Sea
PTPN7	P35236	Tyrosine-proteinphosphatase-7	Sea
PLAA	Q9Y263	PhospholipaseA-2-activatingprotein	Sea
KLF5	Q13887	Kruppel-likefactor5	Sea
TAS1R1	Q7RTX1	Tastereceptortype1member1	Sea
FUT4	P22083	Alpha-(1,3)-fucosyltransferase4	Sea
IGFBP1	P08833	Insulin-likegrowthfactor-bindingprotein1	Sea
IGFBP2	P18065	Insulin-likegrowthfactor-bindingprotein2	Sea
IGFBP4	P22692	Insulin-likegrowthfactor-bindingprotein4	Sea
IGFBP6	P24592	Insulin-likegrowthfactor-bindingprotein6	Sea
HMGB1	P09429	HighmobilitygroupproteinB1	Sea
ST3GAL3	Q11203	CMP-N-acetylneuraminate-beta-1,4-galactosidealpha-2,3-sialyltransferase	Sea
DDO	Q99489	D-aspartateoxidase	Sea
POLI	Q9UNA4	DNApolymeraseiota	Sea
PGAM1	P18669	Phosphoglyceratemutase1	Sea
PGD	P52209	6-phosphogluconatedehydrogenase, decarboxylating	Sea
POLH	Q9Y253	DNApolymeraseeta	Sea
CES2	O00748	Cocaineesterase	Sea
ELAVL3	Q14576	ELAV-likeprotein3	Sea
GLRA3	O75311	Glycinereceptorsubunitalpha-3	Sea
PARP15	Q460N3	Proteinmono-ADP-ribosyltransferasePARP15	Sea
IGFBP5	P24593	Insulin-likegrowthfactor-bindingprotein5	Sea
KDM2A	Q9Y2K7	Lysine-specificdemethylase2A	Sea
GABRB1	P18505	Gamma-aminobutyricacidreceptorsubunitbeta-1	Sea
POLA1	P09884	DNApolymerasealphacatalyticsubunit	Sea
HSD17B14	Q9BPX1	17-beta-hydroxysteroiddehydrogenase14	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
SMAD3	P84022	Mothersagainstdecapentaplegichomolog3	Sea
CES1	P23141	Livercarboxylesterase1	Sea
GLRB	P48167	Glycinereceptorsubunitbeta	Sea
P4HTM	Q9NXG6	Transmembraneproyl4-hydroxylase	Sea
KDM5C	P41229	Lysine-specificdemethylase5C	Sea
CTRC	Q99895	Chymotrypsin-C	Sea
HSPA1A	P0DMV8	Heatshock70kDaprotein1A	Sea
NR4A1	P22736	Nuclearreceptorsubfamily4groupAmember1	Sea
DBH	P09172	Dopaminebeta-hydroxylase	Sea
KAT8	Q9H7Z6	HistoneacetyltransferaseKAT8	Sea
STK38L	Q9Y2H1	Serine/threonine-proteinkinase38-like	Sea
CAMK1G	Q96NX5	Calcium/calmodulin-dependentproteinkinasetype1G	Sea
HSD17B3	P37058	Testosterone17-beta-dehydrogenase3	Sea
SLC37A4	O43826	Glucose-6-phosphateexchangerSLC37A4	Sea
ODC1	P11926	Ornithinedecarboxylase	Sea
PAM	P19021	Peptidyl-glycinealpha-amidatingmonooxygenase	Sea
ALPG	P10696	Alkalinephosphatase,germcelltype	Sea
ERCC1	P07992	DNAexcisionrepairproteinERCC-1	Sea
ERCC4	Q92889	DNArepairendonucleaseXPF	Sea
CYCS	P99999	Cytochromec	Sea
QDPR	P09417	Dihydropteridinereductase	Sea
RXRB	P28702	RetinoicacidreceptorRXR-beta	Sea
MYOC	Q99972	Myocilin	Sea
KDM2B	Q8NHM5	Lysine-specificdemethylase2B	Sea
RXRG	P48443	RetinoicacidreceptorRXR-gamma	Sea
C9	P02748	ComplementcomponentC9	Sea
RXRA	P19793	RetinoicacidreceptorRXR-alpha	Sea
ALPL	P05186	Alkalinephosphatase,tissue-nonspecificisozyme	Sea
APEX1	P27695	DNA-(apurinicorpyrimidinicite)lyase	Sea
MPG	P29372	DNA-3-methyladenineglycosylase	Sea
NSD2	O96028	Histone-lysineN-methyltransferaseNSD2	Sea
ADH5	P11766	Alcoholdehydrogenaseclass-3	Sea
NR1H4	Q96R11	Bileacidreceptor	Sea
HSD17B1	P14061	Estradiol17-beta-dehydrogenase1	Sea
ALOX15	P16050	Arachidonate15-lipoxygenase	Sea
KDM4B	O94953	Lysine-specificdemethylase4B	Sea
HSPE1	P61604	10kDaheatshockprotein,mitochondrial	Sea
HSPD1	P10809	60kDaheatshockprotein,mitochondrial	Sea
HSD17B2	P37059	Estradiol17-beta-dehydrogenase2	Sea
KMO	O15229	Kynurenine3-monooxygenase	Sea
DNM1	Q05193	Dynamin-1	Sea
MEP1B	Q16820	MeprinAsubunitbeta	Sea
CDC25A	P30304	M-phaseinducerphosphatase1	Sea
GFER	P55789	FAD-linkedhydroxyoxidaseALR	Sea
BHMT	Q93088	Betaine--homocysteineS-methyltransferase1	Sea
RPS6KB2	Q9UBS0	RibosomalproteinS6kinasebeta-2	Sea
NR4A2	P43354	Nuclearreceptorsubfamily4groupAmember2	Sea
PLEC	Q15149	Plectin	Sea
ATG4B	Q9Y4P1	CysteineproteaseATG4B	Sea
CSNK2A2	P19784	CaseinkinaseIIsubunitalpha'	Sea
RHOA	P61586	TransformingproteinRhoA	Sea
USP4	Q13107	Ubiquitincarboxyl-terminalhydrolase4	Sea
UQCRB	P14927	Cytochromeb-c1complexsubunit7	Sea
USP5	P45974	Ubiquitincarboxyl-terminalhydrolase5	Sea
MB	P02144	Myoglobin	Sea
PARP10	Q53GL7	Proteinmono-ADP-ribosyltransferasePARP10	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
PARP16	Q8N5Y8	Proteinmono-ADP-ribosyltransferasePARP16	Sea
NLRP1	Q9C000	NACHT,LRRandPYDdomains-containingprotein1	Sea
LIG1	P18858	DNAligase1	Sea
ESRRB	O95718	SteroidhormonereceptorERR2	Sea
CTBP2	P56545	C-terminal-bindingprotein2	Sea
PTPRC	P08575	Receptor-tyrosine-proteinphosphataseC	Sea
HAO1	Q9UJM8	Hydroxyacidoxidase1	Sea
CELA1	Q9UNI1	Chymotrypsin-likeelastasefamilymember1	Sea
RPA1	P27694	ReplicationproteinA70kDaDNA-bindingsubunit	Sea
CYP26A1	O43174	CytochromeP45026A1	Sea
CAMKK2	Q96RR4	Calcium/calmodulin-dependentproteinkinasekinase2	Sea
NAALAD2	Q9Y3Q0	N-acetylated-alpha-linkedacidicdipeptidase2	Sea
TAAR5	O14804	Traceamine-associatedreceptor5	Sea
EZR	P15311	Ezrin	Sea
HTT	P42858	Huntingtin	Sea
PCNA	P12004	Proliferatingcellnuclearantigen	Sea
ELOB	Q15370	Elongin-B	Sea
ELOC	Q15369	Elongin-C	Sea
CALM1	P0DP23	Calmodulin-1	Sea
CBR1	P16152	Carbonylreductase[NADPH]1	Sea
TAAR1	Q96RJ0	Traceamine-associatedreceptor1	Sea
SLC6A5	Q9Y345	Sodium-andchloride-dependentglycinetransporter2	Sea
ACE	P12821	Angiotensin-convertingenzyme(ACE)(EC3.2.1.-(EC3.4.15.1)(Dipeptidylcarboxypeptidase)(KininaseII)(CDantigenCD143) [Cleavedinto:Angiotensin-convertingenzyme,solubleform]	Sea
AGBL2	Q5U5Z8	Cytosoliccarboxypeptidase2(EC3.4.17.-(ATP/GTP-bindingprotein-like2)	Sea
AOC2	O75106	Retina-specificcopperamineoxidase(RAO)(EC1.4.3.21)(Amineoxidase[copper-containing])(Semicarbazide-sensitiveamineoxidase) (SSAO)	Sea
blaIMP-1	Q79MP6	Beta-lactamase	Sea
blm	P54132	Bloomsyndromeprotein(EC3.6.4.12)(DNAhelicase,RecQ-liketype2)(RecQ2)(RecQprotein-like3)	Sea
Ca15	Q99N23	Carbonicanhydrase15	Sea
CAN2	F4IH31	Staphylococcal-likenucleaseCAN2	Sea
CISD1	Q9NZ45	CDGSHiron-sulfurdomain-containingprotein1(MitoNEET)	Sea
CIT2	P08679	Citrate synthase, peroxisomal	Sea
CPA1	P15085	CarboxypeptidaseA1(EC3.4.17.1)	Sea
CPA3	P15088	MastocellcarboxypeptidaseA(MC-CPA)(EC3.4.17.1)(CarboxypeptidaseA3)	Sea
CSK	P41240	Tyrosine-protein kinaseCSK(EC2.7.10.2)(C-Srckinase)(Protein-tyrosine kinaseCYL)	Sea
CTSB	P07858	CathepsinB(EC3.4.22.1)(APPsecretase)(APPS)(CathepsinB1)[Cleavedinto:CathepsinBlightchain;CathepsinBheavychain]	Sea
CTSH	P09668	Pro-cathepsinH[Cleavedinto:CathepsinHminichain;CathepsinH(EC3.4.22.16);CathepsinHheavychain;CathepsinHlightchain]	Sea
Cyp24a1	Q07973	1,25-dihydroxyvitaminD(3)24-hydroxylase, mitochondrial(24-OHase)(VitaminD(3)24-hydroxylase)(EC1.14.15.16) (CytochromeP45024A1)(CytochromeP450-CC24)	Sea
Dhrs9	Q9BPW9	Dehydrogenase/reductaseSDRfamilymember9(EC1.1.1.209)(EC1.1.1.53)(3-alpha-hydroxysteroiddehydrogenase) (3-alpha-HSD)(NADP-dependentretinoldehydrogenase/reductase)(RDH-E2)(RDHL)(Retinoldehydrogenase15) (EC1.1.1.105)(Shortchaindehydrogenase/reductasefamily9Cmember4)(Short-chaindehydrogenase/reductaseretsDR8) (Tracheobronchialepithelialcell-specificretinoldehydrogenase)(RDH-TBE)	Sea
DNTT	P04053	DNA nucleotidylexotransferase(EC2.7.7.31)(Terminaladditionenzyme)(Terminaldeoxynucleotidyltransferase)(Terminaltransferase)	Sea
ENPP2	Q13822	Ectonucleotidepyrophosphatase/phosphodiesterasefamilymember2(E-NPP2)(EC3.1.4.39)(Autotaxin) (ExtracellularlysophospholipaseD)(LysoPLD)	Sea
ERAP2	Q6P179	Endoplasmicreticulumaminopeptidase2(EC3.4.11.-(Leukocyte-derivedarginineaminopeptidase)(L-RAP)	Sea
Fabp1	P07148	Fattyacid-bindingprotein,liver(Fattyacid-bindingprotein1)(Liver-typefattyacid-bindingprotein)(L-FABP)	Sea
FFAR4	Q5NUL3	Freefattyacidreceptor4(G-proteincoupledreceptor120)(G-proteincoupledreceptor129)(G-proteincoupledreceptorGT01) (G-proteincoupledreceptorPGR4)(Omega-3fattyacidreceptor1)	Sea
G6PC	P35575	Glucose-6-phosphatase(G-6-Pase)(G6Pase)(EC3.1.3.9)(Glucose-6-phosphatasealpha)(G6Pase-alpha)	Sea
GLI1	P08151	ZincfingerproteinGLI1(Glioma-associatedoncogene)(OncogeneGLI)	Sea
helD	P15038	DNAhelicaseIV	Sea
HPD	P32754	4-hydroxyphenylpyruvatedioxygenase(EC1.13.11.27)(4-hydroxyphenylpyruvicacidoxidase)(4HPPD)(HPD)(HPPDase)	Sea
IMPA1	P29218	Inositolmonophosphatase1(IMP1)(IMPase1)(EC3.1.3.25)(D-galactose1-phosphatephosphatase)(EC3.1.3.94)(Inositol-1(or4)- monophosphatase1)(Lithium-sensitivemyo-inositolmonophosphataseA1)	Sea
lasB	P14756	Elastase	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
LNPEP	Q9UIQ6	Leucyl-cystinylaminopeptidase(Cystinylaminopeptidase)(EC3.4.11.3)(Insulin-regulatedmembraneaminopeptidase)(Insulin-responsiveaminopeptidase)(IRAP)(Oxytocinase)(OTase)(Placentalleucineaminopeptidase)(P-LAP)[Cleavedinto:Leucyl-cystinylaminopeptidase, pregnancyserumform]	Sea
lpxC	P0A725	UDP-3-O-acyl-N-acetylglucosamine deacetylase	Sea
MDM4	O15151	ProteinMdm4(Doubleminute4protein)(Mdm2-likep53-bindingprotein)(ProteinMdmx)(p53-bindingproteinMdm4)	Sea
MglI	Q99685	Monoglyceridelipase(MGL)(EC3.1.1.23)(HU-K5)(Lysophospholipasehomolog)(Lysophospholipase-like)(Monoacylglycerollipase)(MAGL)	Sea
mgrA	Q2G0B1	HTH-typetranscriptionalregulatorMgrA	Sea
mtcA1	P9WPJ7	Beta-carbonicanhydrase1	Sea
nanA	Q9S4K9	N-acetylneuraminatelyase	Sea
NCE103	Q5AJ71	Carbonicanhydrase	Sea
pobA	Q52185	Phenoxybenzoatedioxygenasesubunitalpha	Sea
PPO2	O42713	Polyphenoloxidase2	Sea
pqsD	P20582	Anthraniloyl-CoAnthraniloyltransferase	Sea
PTGER4	P35408	ProstaglandinE2receptorEP4subtype(PGEreceptorEP4subtype)(PGE2receptorEP4subtype)(ProstanoidEP4receptor)	Sea
Slc15a2	Q16348	Solutecarrierfamily15member2(KidneyH(+)/peptidcotransporter)(Oligopeptidetransporter,kidneyisoform)(Peptidetransporter2)	Sea
SLC22A12	Q96S37	Solutecarrierfamily22member12(Organicaniontransporter4-likeprotein)(Renal-specifictransporter)(RST)(Urateanionexchanger1)	Sea
Slc22a20	Q80UJ1	Solutecarrierfamily22member20	Sea
SLC7A5	Q01650	Largeneutralaminoacidtransportersmallsubunit1(4F2lightchain)(4F2LC)(4F2LC)(CD98lightchain)(IntegralmembraneproteinE16)(E16)(L-typeaminoacidtransporter1)(hLAT1)(Solutecarrierfamily7member5)(y+systemcationicaminoacidtransporter)	Sea
Slco1c1	Q9NYB5	Solutecarrierorganicaniontransporterfamilymember1C1(OrganicaniontransporterF)(OATP-F)(Organicaniontransporterpolypeptide-relatedprotein5)(OAT-RP-5)(OATPRP5)(Organicanion-transportingpolypeptide14)(OATP-14)(Solutecarrierfamily21member14)(Thyroxinetransporter)	Sea
SOAT1	P35610	SterolO-acyltransferase1(EC2.3.1.26)(Acyl-coenzymeA:cholesterolacyltransferase1)(ACAT-1)(Cholesterolacyltransferase1)	Sea
SOAT2	O75908	SterolO-acyltransferase2(EC2.3.1.26)(Acyl-coenzymeA:cholesterolacyltransferase2)(ACAT-2)(Cholesterolacyltransferase2)	Sea
sssIM	P15840	CPGDNA methylase	Sea
Tbxa2r	P21731	ThromboxaneA2receptor(TXA2-R)(ProstanoidTPreceptor)	Sea
Abcb1a	Q3UMH0	Uncharacterizedprotein	Sea
BCHE	P06276	Cholinesterase(EC3.1.1.8)(Acylcholineacylhydrolase)(Butyrylcholineesterase)(CholineesteraseII)(Pseudocholinesterase)	Sea
CYP1A1	P04798	CytochromeP4501A1(CYP1A1)(EC1.14.14.1)(CytochromeP450form6)(CytochromeP450-C)(CytochromeP450-P1)(Hydroperoxyicosatetraenoatedehydratase)(EC4.2.1.152)	Sea
CYP1B1	Q16678	CytochromeP4501B1(EC1.14.14.1)(CYP1B1)(Hydroperoxyicosatetraenoatedehydratase)(EC4.2.1.152)	Sea
cysK1	P9WP55	O-acetylserinesulfhydrylase	Sea
DHCR7	Q9UBM7	7-dehydrocholesterolreductase(7-DHCreductase)(EC1.3.1.21)(Delta7-sterolreductase)(SterolDelta(7)-reductase)(SterolreductaseSR-2)	Sea
EP300	Q09472	Histoneacetyltransferasep300(p300HAT)(EC2.3.1.48)(E1A-associatedproteinp300)(Histonebutyryltransferasep300)(EC2.3.1.-)(Histonecrotonyltransferasep300)(EC2.3.1.-)(Proteinpropionyltransferasep300)(EC2.3.1.-)	Sea
fabI	Q2FZQ3	Enoyl-[acyl-carrier-protein]reductase[NADPH]FabI	Sea
FOS	P01100	Proto-oncogeneFos(CellularoncogeneFos)(G0/G1switchregulatoryprotein7)	Sea
GAPC	P54270	Glyceraldehyde-3-phosphatedehydrogenase, cytosolic	Sea
GLO1	Q04760	Lactoylglutathionelyase(EC4.4.1.5)(Aldoketomutase)(GlyoxalaseI)(GlxI)(Ketone-aldehydemutase)(Methylglyoxalase)(S-D-lactoylglutathionemethylglyoxallyase)	Sea
IKBKG	Q9Y6K9	NF-kappa-Bessentialmodulator(NEMO)(FIP-3)(IkBkinase-associatedprotein1)(IKKAP1)(Inhibitorofnuclearfactorkappa-Bkinasesubunitgamma)(I-kappa-Bkinasesubunitgamma)(IKK-gamma)(IKKG)(IkBkinasesubunitgamma)(NF-kappa-Bessentialmodifier)	Sea
IMA1	P01083	Alpha-amylaseinhibitor0.28	Sea
JUN	P05412	TranscriptionfactorAP-1(Activatorprotein1)(AP1)(Proto-oncogeneJun)(V-junavianarsarcomavirus17oncogenehomolog)(p39)	Sea
KCNK2	O95069	PotassiumchannelsubfamilyKmember2(OutwardrectifyingpotassiumchannelproteinTREK-1)(TREK-1K(+)-channelsubunit)(TwoporedomainpotassiumchannelTREK-1)(TwoporepotassiumchannelTPKC1)	Sea
LOX1.1	P38414	Linoleate9S-lipoxygenase	Sea
MAPT	P10636	Microtubule-associatedproteintau(Neurofibrillarytangleprotein)(Pairedhelicalfilament-tau)(PHF-tau)	Sea
MT-ND1	P03886	NADH-ubiquinoneoxidoreductasechain1(EC7.1.1.2)(NADHdehydrogenasesubunit1)	Sea
MT-ND2	P03891	NADH-ubiquinoneoxidoreductasechain2(EC7.1.1.2)(NADHdehydrogenasesubunit2)	Sea
MT-ND3	P03897	NADH-ubiquinoneoxidoreductasechain3(EC7.1.1.2)(NADHdehydrogenasesubunit3)	Sea
MT-ND4	P03905	NADH-ubiquinoneoxidoreductasechain4(EC7.1.1.2)(NADHdehydrogenasesubunit4)	Sea
MT-ND4L	P03901	NADH-ubiquinoneoxidoreductasechain4L(EC7.1.1.2)(NADHdehydrogenasesubunit4L)	Sea
MT-ND5	P03915	NADH-ubiquinoneoxidoreductasechain5(EC7.1.1.2)(NADHdehydrogenasesubunit5)	Sea
MT-ND6	P03923	NADH-ubiquinoneoxidoreductasechain6(EC7.1.1.2)(NADHdehydrogenasesubunit6)	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
NDUFA1	O15239	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit1(ComplexI-MWFE)(CI-MWFE)(NADH-ubiquinoneoxidoreductaseMWFESubunit)	Sea
NDUFA10	O95299	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit10,mitochondrial(ComplexI-42kD)(CI-42kD)(NADH-ubiquinoneoxidoreductase42kDasubunit)	Sea
NDUFA11	Q86Y39	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit11(ComplexI-B14.7)(CI-B14.7)(NADH-ubiquinoneoxidoreductasesubunitB14.7)	Sea
NDUFA12	Q9UI09	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit12(13kDadifferentiation-associatedprotein)(ComplexI-B17.2)(CI-B17.2)(CIB17.2)(NADH-ubiquinoneoxidoreductasesubunitB17.2)	Sea
NDUFA13	Q9P0J0	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit13(CelldeathregulatoryproteinGRIM-19)(ComplexI-B16.6)(CI-B16.6)(Geneassociatedwithretinoicandinterferon-inducedmortality19protein)(GRIM-19)(GeneassociatedwithretinoicandIFN-inducedmortality19protein)(NADH-ubiquinoneoxidoreductaseB16.6subunit)	Sea
NDUFA2	O43678	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit2(ComplexI-B8)(CI-B8)(NADH-ubiquinoneoxidoreductaseB8subunit)	Sea
NDUFA3	O95167	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit3(ComplexI-B9)(CI-B9)(NADH-ubiquinoneoxidoreductaseB9subunit)	Sea
NDUFA4	O00483	CytochromecoxidasesubunitNDUFA4(ComplexI-MLRQ)(CI-MLRQ)(NADH-ubiquinoneoxidoreductaseMLRQsubunit)	Sea
NDUFA4L2	Q9NRX3	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit4-like2(NADH-ubiquinoneoxidoreductaseMLRQsubunit homolog)(NUOMS)	Sea
NDUFA5	Q16718	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit5(ComplexIsubunitB13)(ComplexI-13kD-B)(CI-13kD-B)(NADH-ubiquinoneoxidoreductase13kDa-Bsubunit)	Sea
NDUFA6	P56556	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit6(ComplexI-B14)(CI-B14)(LYRmotif-containingprotein6)(NADH-ubiquinoneoxidoreductaseB14subunit)	Sea
NDUFA7	O95182	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit7(ComplexI-B14.5a)(CI-B14.5a)(NADH-ubiquinoneoxidoreductasesubunitB14.5a)	Sea
NDUFA8	P51970	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit8(ComplexI-19kD)(CI-19kD)(ComplexI-PGIV)(CI-PGIV)(NADH-ubiquinoneoxidoreductase19kDasubunit)	Sea
NDUFA9	Q16795	NADHdehydrogenase[ubiquinone]1alphasubcomplexsubunit9,mitochondrial(ComplexI-39kD)(CI-39kD)(NADH-ubiquinoneoxidoreductase39kDasubunit)	Sea
NDUFAB1	O14561	Acylcarrierprotein,mitochondrial(ACP)(CI-SDAP)(NADH-ubiquinoneoxidoreductase9.6kDasubunit)	Sea
NDUFAF1	Q9Y375	ComplexIintermediate-associatedprotein30,mitochondrial(NADHdehydrogenase[ubiquinone]1alphasubcomplexassemblyfactor1)	Sea
NDUFAF2	Q8N183	NADHdehydrogenase[ubiquinone]1alphasubcomplexassemblyfactor2(B17.2-like)(B17.2L)(Mimitin)(Myc-inducedmitochondrialprotein)(MMTN)(NDUFA12-likeprotein)	Sea
NDUFAF3	Q9BU61	NADHdehydrogenase[ubiquinone]1alphasubcomplexassemblyfactor3	Sea
NDUFAF4	Q9P032	NADHdehydrogenase[ubiquinone]1alphasubcomplexassemblyfactor4(Hormone-regulatedproliferation-associatedproteinof20kDa)	Sea
NDUFB1	O75438	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit1(ComplexI-MNLL)(CI-MNLL)(NADH-ubiquinoneoxidoreductaseMNLLsubunit)	Sea
NDUFB10	O96000	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit10(ComplexI-PDSW)(CI-PDSW)(NADH-ubiquinoneoxidoreductasePDSWsubunit)	Sea
NDUFB11	Q9NX14	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit11,mitochondrial(ComplexI-ESSS)(CI-ESSS)(NADH-ubiquinoneoxidoreductaseESSSsubunit)(Neuronalprotein17.3)(Np17.3)(p17.3)	Sea
NDUFB2	O95178	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit2,mitochondrial(ComplexI-AGGG)(CI-AGGG)(NADH-ubiquinoneoxidoreductaseAGGGsubunit)	Sea
NDUFB3	O43676	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit3(ComplexI-B12)(CI-B12)(NADH-ubiquinoneoxidoreductaseB12subunit)	Sea
NDUFB4	O95168	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit4(ComplexI-B15)(CI-B15)(NADH-ubiquinoneoxidoreductaseB15subunit)	Sea
NDUFB5	O43674	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit5,mitochondrial(ComplexI-SGDH)(CI-SGDH)(NADH-ubiquinoneoxidoreductaseSGDHsubunit)	Sea
NDUFB6	O95139	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit6(ComplexI-B17)(CI-B17)(NADH-ubiquinoneoxidoreductaseB17subunit)	Sea
NDUFB7	P17568	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit7(CelladhesionproteinSQM1)(ComplexI-B18)(CI-B18)(NADH-ubiquinoneoxidoreductaseB18subunit)	Sea
NDUFB8	O95169	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit8,mitochondrial(ComplexI-ASHI)(CI-ASHI)(NADH-ubiquinoneoxidoreductaseASHIsubunit)	Sea
NDUFB9	Q9Y6M9	NADHdehydrogenase[ubiquinone]1betasubcomplexsubunit9(ComplexI-B22)(CI-B22)(LYRmotif-containingprotein3)(NADH-ubiquinoneoxidoreductaseB22subunit)	Sea
NDUFC1	O43677	NADHdehydrogenase[ubiquinone]1subunitC1,mitochondrial(ComplexI-KFYI)(CI-KFYI)(NADH-ubiquinoneoxidoreductaseKFYIsubunit)	Sea
NDUFC2	O95298	NADHdehydrogenase[ubiquinone]1subunitC2(ComplexI-B14.5b)(CI-B14.5b)(Humanlungcanceroncogene1protein)(HLC-1)(NADH-ubiquinoneoxidoreductasesubunitB14.5b)	Sea
NDUFS1	P28331	NADH-ubiquinoneoxidoreductase75kDasubunit,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(ComplexI-75kD)(CI-75kD)	Sea
NDUFS2	O75306	NADHdehydrogenase[ubiquinone]iron-sulfurprotein2,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(ComplexI-49kD)(CI-49kD)(NADH-ubiquinoneoxidoreductase49kDasubunit)	Sea
NDUFS3	O75489	NADHdehydrogenase[ubiquinone]iron-sulfurprotein3,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(ComplexI-30kD)(CI-30kD)(NADH-ubiquinoneoxidoreductase30kDasubunit)	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
NDUFS4	O43181	NADHdehydrogenase[ubiquinone]iron-sulfurprotein4,mitochondrial(ComplexI-18kDa)(CI-18kDa)(ComplexI-AQDQ)(CI-AQDQ)(NADH-ubiquinoneoxidoreductase18kDasubunit)	Sea
NDUFS5	O43920	NADHdehydrogenase[ubiquinone]iron-sulfurprotein5(ComplexI-15kDa)(CI-15kDa)(NADH-ubiquinoneoxidoreductase15kDasubunit)	Sea
NDUFS6	O75380	NADHdehydrogenase[ubiquinone]iron-sulfurprotein6,mitochondrial(ComplexI-13kD-A)(CI-13kD-A)(NADH-ubiquinoneoxidoreductase13kDa-Asubunit)	Sea
NDUFS7	O75251	NADHdehydrogenase[ubiquinone]iron-sulfurprotein7,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(ComplexI-20kD)(CI-20kD)(NADH-ubiquinoneoxidoreductase20kDasubunit)(PSSSsubunit)	Sea
NDUFS8	O00217	NADHdehydrogenase[ubiquinone]iron-sulfurprotein8,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(ComplexI-23kD)(CI-23kD)(NADH-ubiquinoneoxidoreductase23kDasubunit)(TYKYsubunit)	Sea
NDUFV1	P49821	NADHdehydrogenase[ubiquinone]flavoprotein1,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(ComplexI-51kD)(CI-51kD)(NADHdehydrogenaseflavoprotein1)(NADH-ubiquinoneoxidoreductase51kDasubunit)	Sea
NDUFV2	P19404	NADHdehydrogenase[ubiquinone]flavoprotein2,mitochondrial(EC1.6.99.3)(EC7.1.1.2)(NADH-ubiquinoneoxidoreductase24kDasubunit)	Sea
NDUFV3	P56181	NADHdehydrogenase[ubiquinone]flavoprotein3,mitochondrial(ComplexI-9kD)(CI-9kD)(NADH-ubiquinoneoxidoreductase9kDasubunit)(RenalcarcinomaantigenNY-REN-4)	Sea
NFE2L2	Q16236	Nuclearfactorerythroid2-relatedfactor2(NF-E2-relatedfactor2)(NFE2-relatedfactor2)(HEBP1)(Nuclearfactor,erythroidderived2,like2)	Sea
NFKB1	P19838	NuclearfactorNF-kappa-Bp105subunit(DNA-bindingfactorKBF1)(EBP-1)(NuclearfactorofkappalightpolypeptidegeneenhancerinB-cells1)[Cleavedinto:NuclearfactorNF-kappa-Bp50subunit]	Sea
NR0B2	Q15466	Nuclearreceptorsubfamily0groupBmember2(OrphanuclearreceptorSHP)(Smallheterodimerpartner)	Sea
ptpA	Q15257	Serine/threonine-proteinphosphatase2Activator(EC5.2.1.8)(PP2A,subunitB',PR53isoform)(Phosphotyrosylphosphataseactivator)(PTPA)(Serine/threonine-proteinphosphatase2Regulatorysubunit4)(Serine/threonine-proteinphosphatase2RegulatorysubunitB')	Sea
RELA	Q04206	Transcriptionfactorp65(NuclearfactorNF-kappa-Bp65subunit)(NuclearfactorofkappalightpolypeptidegeneenhancerinB-cells3)	Sea
stxA	Q9FBI2	ShigatoxinsubunitA	Sea
Trpv2	Q9Y5S1	TransientreceptorpotentialcationchannelsubfamilyVmember2(TrpV2)(Osm-9-likeTRPchannel2)(OTRPC2)(Vanilloidreceptor-likeprotein1)(VRL-1)	Sea
TUBB1	Q9H4B7	Tubulinbeta-1chain	Sea
AGL	P35573	Glycogendebanchingenzyme(Glycogendebancher)[Includes:4-alpha-glucanotransferase(EC2.4.1.25)(Oligo-1,4-1,4-glucantransferase);Amylo-alpha-1,6-glucosidase(Amylo-1,6-glucosidase)(EC3.2.1.33)(Dextrin6-alpha-D-glucosidase)]	Sea
env	A0A517FIL8	Envelopeglycoproteingp160	Sea
fimH	P08191	Type1fimbriinD-mannosespecificadhesin	Sea
GGTA1	Q4G0N0	InactiveN-acetyllactosaminidealpha-1,3-galactosyltransferase	Sea
Akt1	P31749	RAC-alpha-serine/threonine-proteinkinase(EC2.7.11.1)(Protein kinaseB)(PKB)(Protein kinaseBalpha)(PKBalpha)(Proto-oncogene-c-Akt)(RAC-PK-alpha)	Sea
GBA3	Q9H227	Cytosolicbeta-glucosidase(EC3.2.1.21)(Cytosolicbeta-glucosidase-likeprotein1)(Cytosolicglycosylceramidase)(CytosolicGCCase)(Glucosidasebetaacid3)(Glucosylceramidasebeta3)(Klotho-relatedprotein)(KLRP)	Sea
GSTM1	P09488	GlutathioneS-transferaseMu1(EC2.5.1.18)(GSTHsubunit4)(GSTclass-mu1)(GSTM1-1)(GSTM1a-1a)(GSTM1b-1b)(GTH4)	Sea
hdaH	Q70I53	Histonedecetylase-likeamidohydrolase	Sea
Hes1	Q14469	TranscriptionfactorHES-1(ClassBbasicelohelix-loop-helixprotein39)(bHLHb39)(Hairyandenhancerofsplit1)(Hairynomolog)(Hairyl-likeprotein)(hHL)	Sea
KCNQ1	P51787	Potassiumvoltage-gatedchannelsubfamilyKQTmember1(IKsproducinglowvoltage-gatedpotassiumchannelsubunitalphaKvLQT1)(KQT-like1)(Voltage-gatedpotassiumchannelsubunitKv7.1)	Sea
Lpar3	Q9UBY5	Lysophosphatidicacidreceptor3(LPAreceptor3)(LPA-3)(LysophosphatidicacidreceptorEdg-7)	Sea
PLCG2	P16885	1-phosphatidylinositol4,5-bisphosphatephosphodiesterasegamma-2(EC3.1.4.11)(PhosphoinositidiphospholipaseC-gamma-2)(PhospholipaseC-IV)(PLC-IV)(PhospholipaseC-gamma-2)(PLC-gamma-2)	Sea
Sis	P01127	Platelet-derivedgrowthfactorsubunitB	Sea
SMPD1	P17405	Sphingomyelinphosphodiesterase(EC3.1.4.12)(Acidsphingomyelinase)(aSMase)	Sea
SPHK1	Q9NYA1	Sphingosinekinase1(SK1)(SPK1)(EC2.7.1.91)(AcetyltransferaseSPHK1)(EC2.3.1.-)	Sea
SPHK2	Q9NRA0	Sphingosinekinase2(SK2)(SPK2)(EC2.7.1.91)	Sea
ACR	P10323	Acrosin(EC3.4.21.10)[Cleavedinto:Acrosinlightchain;Acrosinheavychain]	Sea
Alox15b	O15296	Arachidonate15-lipoxygenaseB(15-LOX-B)(EC1.13.11.33)(15-lipoxygenase2)(15-LOX-2)(Arachidonate15-lipoxygenasetypell)(Linoleate13-lipoxygenase15-LOB)(EC1.13.11.-)	Sea
ATF1	P18846	CyclicAMP-dependenttranscriptionfactorATF-1(cAMP-dependenttranscriptionfactorATF-1)(Activatingtranscriptionfactor1)(ProteinTREB36)	Sea
CACNA1C	Q13936	Voltage-dependentL-typecalciumchannelsubunitalpha-1C(Calciumchannel,Ltype,alpha-1polypeptide,isoform1,cardiacmuscle)(Voltage-gatedcalciumchannelsubunitalphaCav1.2)	Sea
CACNA1D	Q01668	Voltage-dependentL-typecalciumchannelsubunitalpha-1D(Calciumchannel,Ltype,alpha-1polypeptide,isoform2)(Voltage-gatedcalciumchannelsubunitalphaCav1.3)	Sea
CYP1A2	P05177	CytochromeP4501A2(EC1.14.14.1)(CYPIA2)(Cholesterol25-hydroxylase)(CytochromeP(3)450)(CytochromeP4504)(CytochromeP450-P3)(Hydroperoxyicosatetraenoatedehydratase)(EC4.2.1.152)	Sea
DBF4	Q9UBU7	ProteinDBF4homologA(ActivatorofSphasekinase)(ChiffonhomologA)(DBF4-typezincfinger-containingprotein1)	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
EIF2AK3	Q9NZJ5	Eukaryotic translation initiation factor 2-alpha kinase 3 (EC2.7.11.1) (PRKR-like endoplasmic reticulum kinase) (Pancreatic EIF2-alpha kinase) (HsPEK)	Sea
GABRA2	P47869	Gamma-aminobutyric acid receptors subunit alpha-2 (GABA(A) receptors subunit alpha-2)	Sea
GABRA6	Q16445	Gamma-aminobutyric acid receptors subunit alpha-6 (GABA(A) receptors subunit alpha-6)	Sea
GRM6	O15303	Metabotropic glutamate receptor 6 (mGluR6)	Sea
GSTM2	P28161	Glutathione S-transferase Mu2 (EC2.5.1.18) (GST class-mu2) (GSTM2-2)	Sea
KAT2A	Q92830	Histone acetyltransferase KAT2A (EC2.3.1.48) (General control of amino acid synthesis protein 5-like 2) (Histone acetyltransferase GCN5) (hGCN5) (Histone succinyltransferase KAT2A) (EC2.3.1.-) (Lysine acetyltransferase 2A) (STAF97)	Sea
KDM6A	O15550	Lysine-specific demethylase 6A (EC1.14.11.-) (Histone demethylase UTX) (Ubiquitously-transcribed TPR protein on the X chromosome) (Ubiquitously-transcribed X chromosome tetrapeptide repeat protein)	Sea
LOXL2	Q9Y4K0	Lysyl oxidase homolog 2 (EC1.4.3.13) (Lysyl oxidase-like protein 2) (Lysyl oxidase-related protein 2) (Lysyl oxidase-related protein WS9-14)	Sea
NEK6	Q9HC98	Serine/threonine-protein kinase Nek6 (EC2.7.11.1) (Never in mitosis A-related kinase 6) (NimA-related protein kinase 6) (Protein kinase SID6-1512)	Sea
P2RY12	Q9H244	P2Y purinoceptor 12 (P2Y12) (ADP-glucose receptor) (ADPG-R) (P2T(AC)) (P2Y(AC)) (P2Y(cyc)) (P2Y12 platelet ADP receptor) (P2Y(ADP)) (SP1999)	Sea
Parg	Q86W56	Poly(ADP-ribose) glycohydrolase (EC3.2.1.143)	Sea
PHLPP2	Q6ZVD8	PH domain leucine-rich repeat-containing protein phosphatase 2 (EC3.1.3.16) (PH domain leucine-rich repeat-containing protein phosphatase-like) (PHLPP-like)	Sea
PIN4	Q9Y237	Peptidyl-prolyl isomerase NIMA-interacting 4 (EC5.2.1.8) (Parvulin-14) (Par14) (hPar14) (Parvulin-17) (Par17) (hPar17) (Peptidyl-prolyl isomerase Pin4) (PPLase Pin4) (Peptidyl-prolyl isomerase EPVH) (hEPVH) (Rotamase Pin4)	Sea
PLA2G2A	P14555	Phospholipase A2, membrane associated (EC3.1.1.4) (GIIc PLA2) (Group II A phospholipase A2) (Non-pancreatic secretory phospholipase A2) (NPS-PLA2) (Phosphatidylcholine 2-acylhydrolase 2A)	Sea
Pla2g5	P39877	Calcium-dependent phospholipase A2 (EC3.1.1.4) (Group V phospholipase A2) (PLA2-10) (Phosphatidylcholine 2-acylhydrolase 5)	Sea
PRKCH	P24723	Protein kinase C eta type (EC2.7.11.13) (PKC-L) (nPKC-eta)	Sea
PRKCZ	Q05513	Protein kinase C zeta type (EC2.7.11.13) (nPKC-zeta)	Sea
PRNP	F7VJQ1	Alternative prion protein (AltPrP)	Sea
SEN7	Q9BQF6	Sentrin-specific protease 7 (EC3.4.22.-) (SUMO-1-specific protease 2) (Sentrin/SUMO-specific protease SEN7)	Sea
SLC22A2	O15244	Solute carrier family 22 member 2 (Organic cation transporter 2) (hOCT2)	Sea
Slc29a2	Q14542	Equilibrative nucleoside transporter 2 (36 kDa nucleolar protein HNP36) (Delayed-early response protein 12) (Equilibrative nitrobenzyl mercaptopurine riboside-insensitive nucleoside transporter) (Equilibrative NBMPR-insensitive nucleoside transporter) (Hydrophobic nucleolar protein, 36 kDa) (Nucleoside transporter, ei-type) (Solute carrier family 29 member 2)	Sea
STAT1	P42224	Signal transducer and activator of transcription 1-alpha/beta (Transcription factor ISGF-3 component sp91/p84)	Sea
TLR1	Q15399	Toll-like receptor 1 (Toll/interleukin-1 receptor-like protein) (TIL) (CD antigen CD281)	Sea
TLR2	O60603	Toll-like receptor 2 (Toll/interleukin-1 receptor-like protein 4) (CD antigen CD282)	Sea
AHR	P35869	Aryl hydrocarbon receptor (Ah receptor) (AhR) (Class E basic helix-loop-helix protein 76) (bHLHe76)	Sea
CAPN1	P07384	Calpain-1 catalytic subunit (EC3.4.22.52) (Calcium-activated neutral proteinase 1) (CANP1) (Calpain mu-type) (Calpain-1 large subunit) (Cell proliferation-inducing gene 30 protein) (Micromolar-calpain) (muCANP)	Sea
GNB1	P62873	Guanine nucleotide-binding protein G(i)/G(s)/G(t) subunit beta-1 (Transducin beta chain 1)	Sea
GNG2	P59768	Guanine nucleotide-binding protein G(i)/G(s)/G(o) subunit gamma-2 (Ggamma-1)	Sea
GPR183	P32249	G-protein coupled receptor 183 (Epstein-Barr virus-induced G-protein coupled receptor 2) (EBI2) (EBV-induced G-protein coupled receptor 2) (hEBI2)	Sea
HDAC10	Q969S8	Polyamine deacetylase HDAC10 (EC3.5.1.48) (EC3.5.1.62) (Histone deacetylase 10) (HD10)	Sea
HDAC11	Q96DB2	Histone deacetylase 11 (HD11) (EC3.5.1.98)	Sea
HDAC2	Q92769	Histone deacetylase 2 (HD2) (EC3.5.1.98)	Sea
HDAC4	P56524	Histone deacetylase 4 (HD4) (EC3.5.1.98)	Sea
HDAC5	Q9UQL6	Histone deacetylase 5 (HD5) (EC3.5.1.98) (Antigen NY-CO-9)	Sea
HDAC7	Q8WUI4	Histone deacetylase 7 (HD7) (EC3.5.1.98) (Histone deacetylase 7A) (HD7a)	Sea
HDAC9	Q9UKV0	Histone deacetylase 9 (HD9) (EC3.5.1.98) (Histone deacetylase 7B) (HD7) (HD7b) (Histone deacetylase-related protein) (MEF2-interacting transcription repressor MITR)	Sea
LPAR2	Q9HBW0	Lysophosphatidic acid receptor 2 (LPA receptor 2) (LPA-2) (Lysophosphatidic acid receptor Edg-4)	Sea
P2rx1	P51575	P2X purinoceptor 1 (P2X1) (ATP receptor) (Purinergic receptor)	Sea
PTGER2	P43116	Prostaglandin E2 receptor EP2 subtype (PGE receptor EP2 subtype) (PGE2 receptor EP2 subtype) (Prostanoid EP2 receptor)	Sea
PTGER3	P43115	Prostaglandin E2 receptor EP3 subtype (PGE receptor EP3 subtype) (PGE2 receptor EP3 subtype) (PGE2-R) (Prostanoid EP3 receptor)	Sea
PTPN11	Q06124	Tyrosine-protein phosphatase non-receptor type 11 (EC3.1.3.48) (Protein-tyrosine phosphatase 1D) (PTP-1D) (Protein-tyrosine phosphatase 2C) (PTP-2C) (SH-PTP2) (SHP-2) (Shp2) (SH-PTP3)	Sea
RBBP9	O75884	Serine hydrolase RBBP9 (EC3.-.-) (B5T-overexpressed gene protein) (Protein BOG) (Retinoblastoma-binding protein 10) (RBBP-10) (Retinoblastoma-binding protein 9) (RBBP-9)	Sea
SLC12A2	P55011	Solute carrier family 12 member 2 (Basolateral Na-K-Cl symporter) (Bumetanide-sensitive sodium-(potassium)-chloride cotransporter 2)	Sea
Tdo2	P48775	Tryptophan 2,3-dioxygenase (TDO) (EC1.13.11.11) (Tryptamin 2,3-dioxygenase) (Tryptophan oxygenase) (TO) (TRPO) (Tryptophan pyrrolase) (Tryptophanase)	Sea

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
TGM2	P21980	Protein-glutaminegamma-glutamyltransferase2(EC2.3.2.13)(Tissue transglutaminase)(TransglutaminaseC)(TG(C))(TGC)(TGaseC)(TransglutaminaseH)(TGaseH)(Transglutaminase-2)(TGase-2)	Sea
TLR9	Q9NR96	Toll-likereceptor9(CDantigenCD289)	Sea
TRPM2	O94759	TransientreceptorpotentialcationchannelsubfamilyMmember2(Estrogen-responsiveelement-associatedgene1protein)(Longtransientreceptorpotentialchannel2)(LTrpC-2)(LTrpC2)(Transientreceptorpotentialchannel7)(TrpC7)(Transientreceptorpotentialmelastatin2)	Sea
TUBA4A	P68366	Tubulinalpha-4Achain(Alpha-tubulin1)(Testis-specificalpha-tubulin)(TubulinH2-alpha)(Tubulinalpha-1chain)	Sea
FASN	P49327	Fattyacidsynthase(EC2.3.1.85)[Includes:[Acyl-carrier-protein]S-acetyltransferase(EC2.3.1.38);[Acyl-carrier-protein]S-malonyltransferase(EC2.3.1.39);3-oxoacyl-[acyl-carrier-protein]synthase(EC2.3.1.41);3-oxoacyl-[acyl-carrier-protein]reductase(EC1.1.1.100);3-hydroxyacyl-[acyl-carrier-protein]dehydratase(EC4.2.1.59);Enoyl-[acyl-carrier-protein]reductase(EC1.3.1.39);Oleoyl-[acyl-carrier-protein]hydrolase(EC3.1.2.14)]	Sea
IL5	P05113	Interleukin-5(IL-5)(B-celldifferentiationfactor1)(Eosinophildifferentiationfactor)(T-cellreplacingfactor)(TRF)	Sea
Sgk1	O00141	Serine/threonine-protein kinaseSgk1(EC2.7.11.1)(Serum/glucocorticoid-regulatedkinase1)	Sea
CXCR3	P49682	C-X-Cchemokineresceptortype3(CXC-R3)(CXCR-3)(CKR-L2)(Gprotein-coupledreceptor9)(Interferon-inducibleprotein10receptor)(IP-10receptor)(CDantigenCD183)	Sea
Abcc2	Q92887	Canalicularmultispecificorganicaniontransporter1(ATP-bindingcassettesub-familyCmember2)(Canalicularmultidrugresistanceprotein)(Multidrugresistance-associatedprotein2)(EC7.6.2.2)	Sea
Akr1a1	P14550	Aldo-ketoreductasefamily1memberA1(EC1.1.1.2)(EC1.1.1.372)(EC1.1.1.54)(Alcoholdehydrogenase[NADP(+)])(Aldehydereductase)(Glucuronatereductase)(EC1.1.1.19)(Glucuronolactonereductase)(EC1.1.1.20)	Sea
CREB1	P16220	CyclicAMP-responsiveelement-bindingprotein1(CREB-1)(cAMP-responsiveelement-bindingprotein1)	Sea
CYP2C8	P10632	CytochromeP4502C8(EC1.14.14.1)(CYP11C8)(CytochromeP45011C2)(CytochromeP450MP-12)(CytochromeP450MP-20)(CytochromeP450form1)(S-mephenytoin4-hydroxylase)	Sea
DAPK1	P53355	Death-associatedprotein kinase1(DAPkinase1)(EC2.7.11.1)	Sea
ELAVL1	Q15717	ELAV-likeprotein1(Hu-antigenR)(HuR)	Sea
Gusb	P08236	Beta-glucuronidase(EC3.2.1.31)(Beta-G1)	Sea
KCND3	Q9UK17	Potassiumvoltage-gatedchannelsubfamilyDmember3(Voltage-gatedpotassiumchannelsubunitKv4.3)	Sea
LPO	P22079	Lactoperoxidase(LPO)(EC1.11.1.7)(Salivaryperoxidase)(SPO)	Sea
PGF	P49763	Placentagrowthfactor(PIGF)	Sea
PKN1	Q16512	Serine/threonine-protein kinaseN1(EC2.7.11.13)(Protease-activatedkinase1)(PAK-1)(Protein kinaseC-like1)(Protein kinaseC-likePKN)(Protein kinasePKN-alpha)(Protein-kinaseC-relatedkinase1)(Serine-threonineprotein kinaseN)	Sea
PTPRS	Q13332	Receptor-tyrosine-protein phosphataseS(R-PTP-S)(EC3.1.3.48)(Receptor-tyrosine-protein phosphatasesigma)(R-PTP-sigma)	Sea
Slc16a7	O60669	Monocarboxylatetransporter2(MCT2)(Solute carrierfamily16member7)	Sea
ST6GAL1	P15907	Beta-galactosidealpha-2,6-sialyltransferase1(Alpha2,6-ST1)(EC2.4.99.1)(B-cellantigenCD75)(CMP-N-acetylneuramate-beta-galactosamide-alpha-2,6-sialyltransferase1)(ST6GalI)(ST6GalII)(Sialyltransferase1)	Sea
SYN1	P17600	Synapsin-1(Brainprotein4.1)(Synapsin)	Sea
TAS2R31	P59538	Tastereceptortype2member31(T2R31)(Tastereceptortype2member44)(T2R44)(Tastereceptortype2member53)(T2R53)	Sea
LSS	P48449	Lanosterolsynthase(EC5.4.99.7)(2,3-epoxysqualene--lanosterolcyclase)(Oxidosqualene--lanosterolcyclase)(OSC)(hOSC)	Sea
Trpm8	Q7Z2W7	TransientreceptorpotentialcationchannelsubfamilyMmember8(Longtransientreceptorpotentialchannel6)(LTrpC-6)(LTrpC6)(Transientreceptorpotentialp8)(Trp-p8)	Sea
CYSLTR2	Q9NS75	Cysteinyleukotrieneresceptor2(CysLTR2)(G-proteincoupledreceptorGPCR21)(hGPCR21)(G-proteincoupledreceptorHG57)(HPN321)	Sea
EBP	Q15125	3-beta-hydroxysteroid-Delta(8),Delta(7)-isomerase(EC5.3.3.5)(CholesterolDelta-isomerase)(Delta(8)-Delta(7)sterolisomerase)(D8-D7sterolisomerase)(Emopamil-bindingprotein)	Sea
GSR	P00390	Glutathionereductase,mitochondrial(GR)(GRase)(EC1.8.1.7)	Sea
Iat	O43561	LinkerforactivationofT-cellsfamilymember1(36kDaphospho-tyrosineadapterprotein)(pp36)(p36-38)	Sea
NOD2	Q9HC29	Nucleotide-bindingoligomerizationdomain-containingprotein2(Caspaserecruitmentdomain-containingprotein15)(Inflammatoryboweldiseaseprotein1)	Sea
PTPN6	P29350	Tyrosine-protein phosphatase non-receptortype6(EC3.1.3.48)(Hematopoieticcellprotein-tyrosine phosphatase)(Protein-tyrosine phosphatase1C)(PTP-1C)(Protein-tyrosine phosphataseSHP-1)(SH-PTP1)	Sea
SLC22A3	O75751	Solute carrierfamily22member3(Extraneuronalmonoaminetransporter)(EMT)(Organiccationtransporter3)	Sea
Trpv1	Q8NER1	TransientreceptorpotentialcationchannelsubfamilyVmember1(TrpV1)(Capsaicinreceptor)(Osm-9-likeTRPchannel1)(OTRPC1)(Vanilloidreceptor1)	Sea
IFNG	P01579	Interferongamma	Chemmapper
SCNN1A	P37088	Amiloride-sensitivesodiumchannelsubunitalpha	Chemmapper
SCNN1B	P51168	Amiloride-sensitivesodiumchannelsubunitbeta	Chemmapper
SCNN1G	P51170	Amiloride-sensitivesodiumchannelsubunitgamma	Chemmapper
NOS3	P29474	Nitric-oxidesynthase,endothelial	Chemmapper
SULT1A1	P50225	Sulfotransferase1A1	Chemmapper
HBA1	P69905	Hemoglobinsubunitalpha	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
OAT	P04181	Ornithineaminotransferase,mitochondrial	Chemmapper
IGKC	P01834	IgkappachainCregion	Chemmapper
PLA2G1B	P04054	PhospholipaseA2	Chemmapper
AOC3	Q16853	Membranecopperamineoxidase	Chemmapper
IL4I1	Q96RQ9	L-amino-acidoxidase	Chemmapper
EDNRA	P25101	Endothelin-1receptor	Chemmapper
NSF	P46459	Vesicle-fusingATPase	Chemmapper
MBL2	P11226	Mannose-bindingproteinC	Chemmapper
LYZ	P61626	LysozymeC	Chemmapper
CHUK	O15111	InhibitorofnuclearfactorKappa-Bkinasesubunitalpha	Chemmapper
ADRB1	P08588	Beta-1adrenergicreceptor	Chemmapper
DRD5	P21918	D(1B)dopaminereceptor	Chemmapper
PDE4A	P27815	cAMP-specific3',5'-cyclicphosphodiesterase4A	Chemmapper
PDE3A	Q14432	cGMP-inhibited3',5'-cyclicphosphodiesteraseA	Chemmapper
ADRA1B	P35368	Alpha-1Badrenergicreceptor	Chemmapper
PPIF	P30405	Peptidyl-prolylcis-transisomerase,mitochondrial	Chemmapper
PPARG	P37231	Peroxisomeproliferator-activatedreceptorgamma	Chemmapper
PLA2G2E	Q9NZK7	GroupIIsecretoryphospholipaseA2	Chemmapper
PAH	P00439	Phenylalanine-4-hydroxylase	Chemmapper
QPRT	Q15274	Nicotinate-nucleotidepyrophosphorylase[carboxylating]	Chemmapper
DRD4	P21917	D(4)dopaminereceptor	Chemmapper
SLC6A3	Q01959	Sodium-dependentdopaminetransporter	Chemmapper
CACNA2D2	Q9NY47	Voltage-dependentcalciumchannelsubunitalpha-2/delta-2	Chemmapper
CACNA1B	Q00975	Voltage-dependentN-typecalciumchannelsubunitalpha-1B	Chemmapper
DNMT1	P26358	DNA(cytosine-5)-methyltransferase1	Chemmapper
MTAP	Q13126	S-methyl-5-thioadenosinephosphorylase	Chemmapper
PECR	Q9BY49	Peroxisomaltrans-2-enoyl-CoAreductase	Chemmapper
SRPK2	P78362	Serine/threonine-proteinkinaseSRPK2	Chemmapper
ACACB	O00763	Acetyl-CoAcarboxylase2	Chemmapper
APRT	P07741	Adeninephosphoribosyltransferase	Chemmapper
PARP1	P09874	Poly[ADP-ribose]polymerase1	Chemmapper
NFKB2	Q00653	NuclearfactorNF-kappa-Bp100subunit	Chemmapper
CS	O75390	Citrate synthase,mitochondrial	Chemmapper
ME2	P23368	NAD-dependentmalicenzyme,mitochondrial	Chemmapper
PIK3R1	P27986	Phosphatidylinositol3-kinaseregulatorysubunitalpha	Chemmapper
PIK3R2	O00459	Phosphatidylinositol3-kinaseregulatorysubunitbeta	Chemmapper
HTR1D	P28221	5-hydroxytryptamine1Dreceptor	Chemmapper
UCKL1	Q9NWZ5	Uridine-cytidinekinase-like1	Chemmapper
HTR1A	P08908	5-hydroxytryptamine1Areceptor	Chemmapper
DPYD	Q12882	Dihydropyrimidinedehydrogenase[NADP+]	Chemmapper
CALY	Q9NYX4	D1dopaminereceptor-interactingproteinCalcyon	Chemmapper
SLC18A2	Q05940	Synapticvesicularaminetransporter	Chemmapper
SLC6A4	P31645	Sodium-dependentserotonintransporter	Chemmapper
SLC18A1	P54219	Chromaffingranuleaminetransporter	Chemmapper
CSAD	Q9Y600	Cysteinesulfonicaciddecarboxylase	Chemmapper
NFS1	Q9Y697	Cysteinedesulfurase,mitochondrial	Chemmapper
PDXP	Q96GD0	Pyridoxalphosphatephosphatase	Chemmapper
CTH	P32929	Cystathioninegamma-lyase	Chemmapper
GOT1	P17174	Aspartateaminotransferase,cytoplasmic	Chemmapper
DCN	P07585	Decorin	Chemmapper
CANT1	Q8WVQ1	Solublecalcium-activatednucleotidase1	Chemmapper
NEIL1	Q96FI4	EndonucleaseVIII-like1	Chemmapper
PRDX5	P30044	Peroxiredoxin-5,mitochondrial	Chemmapper
RIDA	P52758	RibonucleaseUK114	Chemmapper
RAB9A	P51151	Ras-relatedproteinRab-9	Chemmapper
SLC19A3	Q9BZV2	Thiaminetransporter2	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
CARS2	Q9HA77	ProbablecysteinyI-tRNA synthetase,mitochondrial	Chemmapper
CDO1	Q16878	Cysteinedioxygenasetype1	Chemmapper
GCLM	P48507	Glutamate--cysteineligaseregulatorysubunit	Chemmapper
GCLC	P48506	Glutamate--cysteineligasecatalyticsubunit	Chemmapper
CARS	P49589	CysteinyI-tRNA synthetase,cytoplasmic	Chemmapper
PDXK	O00764	Pyridoxalkinase	Chemmapper
KYNU	Q16719	Kynureninase	Chemmapper
ALAS1	Q5JAM2	Migration-inducingprotein4	Chemmapper
GAD2	Q5VZ30	Glutamatedecarboxylase2	Chemmapper
SHMT2	P34897	SHMT2protein	Chemmapper
PDXDC1	Q6P996	KIAA0251protein	Chemmapper
KYAT3	Q6YP21	Kynurenine--oxoglutaratetransaminase3	Chemmapper
GADL1	Q6ZQY3	CDNAFLJ46802fis,cloneTRACH3032150,moderatelysimilartoCysteinesulfonicaciddecarboxylase	Chemmapper
DKFZp686P09201	Q5HYG8	HypotheticalproteinDKFZp686P09201	Chemmapper
AADAT	Q8N5Z0	Kynurenine/alpha-aminoadipateaminotransferasemitochondrial	Chemmapper
PNPO	Q9NVS9	Pyridoxine-5'-phosphateoxidase	Chemmapper
MOCOS	Q96EN8	Molybdenumcofactorsulfurase	Chemmapper
KYAT1	Q16773	Kynurenine--oxoglutaratetransaminase1	Chemmapper
SRR	Q9GZT4	Serineracemase	Chemmapper
AGXT2	Q9BYV1	Alanine--glyoxylateaminotransferase2,mitochondrial	Chemmapper
AZIN2	Q96A70	Argininedecarboxylase	Chemmapper
SDS	P20132	L-serinedehydratase	Chemmapper
GCAT	O75600	2-amino-3-ketobutyratecoenzymeAIIgase,mitochondrial	Chemmapper
GLDC	P23378	Glycinedehydrogenase[decarboxylating],mitochondrial	Chemmapper
PSAT1	Q9Y617	Phosphoserineaminotransferase	Chemmapper
DDC	Q6IBS8	DDCprotein	Chemmapper
BCAT2	O15382	Branched-chain-amino-acidaminotransferase,mitochondrial	Chemmapper
THNSL1	Q81YQ7	Threoninesynthase-like1	Chemmapper
SCLY	Q96I15	Selenocysteinelyase	Chemmapper
IGSF10	Q6WRI0	Immunoglobulinsuperfamilymember10	Chemmapper
PHYKPL	Q8IUZ5	Alanine--glyoxylateaminotransferase2-like2	Chemmapper
SHMT1	P34896	Serinehydroxymethyltransferase,cytosolic	Chemmapper
ALAS2	P22557	Aminolevulinate,delta-,synthase2	Chemmapper
PLPBP	O94903	Prolinesynthetaseco-transcribedbacterialhomologprotein	Chemmapper
SGPL1	O95470	Sphingosine-1-phosphatylase1	Chemmapper
BCAT1	P54687	Branched-chain-amino-acidaminotransferase,cytosolic	Chemmapper
GOT2	P00505	Aspartateaminotransferase,mitochondrial	Chemmapper
SEPSECS	Q9HD40	O-phosphoseryl-tRNA(Sec)seleniumtransferase	Chemmapper
GAD65	Q9UGI5	Glutamicaciddecarboxylase	Chemmapper
SDSL	Q96GA7	Serinedehydratase-like	Chemmapper
pcap	Q96JQ3	P-selectincytoplasmictail-associatedprotein	Chemmapper
GPT	P24298	Alanineaminotransferase1	Chemmapper
GPT2	Q8TD30	Alanineaminotransferase2	Chemmapper
GAD1	Q8IVA8	Glutamatedecarboxylase1	Chemmapper
AGXT	P21549	Serine--pyruvateaminotransferase	Chemmapper
SPTLC1	O15269	Serinepalmitoyltransferase1	Chemmapper
FTCD	O95954	Formimidoyltransferase-cyclodeaminase	Chemmapper
SPTLC3	Q9NUV7	UncharacterizedproteinC20orf38	Chemmapper
HDC	P19113	Histidinedecarboxylase	Chemmapper
TLH6	Q9UJX1	Alanine-glyoxylateaminotransferasehomolog	Chemmapper
GIG18	Q2TU84	Growth-inhibitingprotein18	Chemmapper
RHO	P08100	Rhodopsin	Chemmapper
UQCR10	Q9UDW1	Cytochromeb-c1complexsubunit9	Chemmapper
SDHA	P31040	Succinatedehydrogenase[ubiquinone]flavoproteinsubunit,mitochondrial	Chemmapper
SDHB	P21912	Succinatedehydrogenase[ubiquinone]iron-sulfursubunit,mitochondrial	Chemmapper
SDHD	O14521	Succinatedehydrogenase[ubiquinone]cytochromebsmallsubunit,mitochondrial	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
ETFDH	Q16134	Electrontransferflavoprotein-ubiquinoneoxidoreductase,mitochondrial	Chemmapper
SDHC	Q99643	Succinatedehydrogenasecytochromeb560subunit,mitochondrial	Chemmapper
ABO	P16442	Histo-bloodgroupABOsystemtransferase	Chemmapper
CYC1	P08574	Cytochromec1,hemeprotein,mitochondrial	Chemmapper
MT-CYB	P00156	Cytochromeb	Chemmapper
UQCRC1	P31930	Ubiquinol-cytochrome-creductasecomplexcoreprotein1,mitochondrial	Chemmapper
UQCRC2	P22695	Cytochromeb-c1complexsubunit2,mitochondrial	Chemmapper
UQCRH	P07919	Cytochromeb-c1complexsubunit6,mitochondrial	Chemmapper
UQCRQ	O14949	Cytochromeb-c1complexsubunit8	Chemmapper
UQCRFS1	P47985	Cytochromeb-c1complexsubunitRieske,mitochondrial	Chemmapper
PTK2B	Q14289	Proteintyrosinekinase2beta	Chemmapper
IGHV1-2	P23083	IgheavychainV-lregionND	Chemmapper
SCN5A	Q14524	Sodiumchannelproteintype5subunitalpha	Chemmapper
GATM	P50440	Glycineamidinotransferase,mitochondrial	Chemmapper
NOS1	P29475	Nitric-oxidesynthase,brain	Chemmapper
ACO2	Q99798	Aconitatehydratase,mitochondrial	Chemmapper
BGLAP	P02818	Osteocalcin	Chemmapper
IDH2	P48735	Isocitratehydrogenase[NADP],mitochondrial	Chemmapper
IDH1	O75874	Isocitratehydrogenase[NADP]cytoplasmic	Chemmapper
KCNJ11	Q14654	ATP-sensitiveinwardrectifierpotassiumchannel11	Chemmapper
GRIA2	P42262	Glutamaterceptor2	Chemmapper
SPR	P35270	Sepiapterinreductase	Chemmapper
GRIN3A	Q8TCU5	Glutamate[NMDA]receptorsubunit3A	Chemmapper
PLOD3	O60568	Procollagen-lysine,2-oxoglutarate5-dioxygenase3	Chemmapper
P3H3	Q8IVL6	Prolyl3-hydroxylase3	Chemmapper
TMLHE	Q9NVH6	Trimethyllysinedioxygenase,mitochondrial	Chemmapper
P3H1	Q32P28	Prolyl3-hydroxylase1	Chemmapper
P3H2	Q8IVL5	Prolyl3-hydroxylase2	Chemmapper
IMPDH1	P20839	Inosine-5'-monophosphatedehydrogenase1	Chemmapper
NT5C2	P49902	Cytosolicpurine5'-nucleotidase	Chemmapper
PLOD1	Q02809	Procollagen-lysine,2-oxoglutarate5-dioxygenase1	Chemmapper
BBOX1	O75936	Gamma-butyrobetainedioxygenase	Chemmapper
ASPH	Q12797	Aspartyl/asparaginylbeta-hydroxylase	Chemmapper
SLC1A1	P43005	Excitatoryaminoacidtransporter3	Chemmapper
ASNS	P08243	Asparaginesynthetase[glutamine-hydrolyzing]	Chemmapper
CHRNA7	Q693P7	Alpha-7nicotiniccholinergicreceptorsubunit	Chemmapper
OPRK1	P41145	Kappa-typeopioidreceptor	Chemmapper
SCNN1D	P51172	Amiloride-sensitivesodiumchannelsubunitdelta	Chemmapper
ASIC2	Q16515	Amiloride-sensitivecationchannel1,neuronal	Chemmapper
ASIC1	P78348	Amiloride-sensitivecationchannel2,neuronal	Chemmapper
AOC1	P19801	Amiloride-sensitiveamineoxidase[copper-containing]	Chemmapper
SLC9A1	P19634	Sodium/hydrogenexchanger1	Chemmapper
TST	Q16762	Thiosulfatesulfurtransferase	Chemmapper
ALKBH3	Q96Q83	Alpha-ketoglutarate-dependentdioxygenasealkBhomolog3	Chemmapper
SLC23A1	Q9UHI7	Solutecarrierfamily23member1	Chemmapper
PLOD2	O00469	Procollagen-lysine,2-oxoglutarate5-dioxygenase2	Chemmapper
PHYH	O14832	Phytanoyl-CoAdioxygenase,peroxisomal	Chemmapper
KDM5D	Q9BY66	Jumonji/ARIDdomain-containingprotein1D	Chemmapper
EGLN3	Q9H6Z9	Eglninehomolog3	Chemmapper
EGLN1	Q9GZT9	Eglninehomolog1	Chemmapper
ALKBH2	Q6NS38	Alpha-ketoglutarate-dependentdioxygenasealkBhomolog2	Chemmapper
OGFOD2	Q6N063	HypotheticalproteinDKFZp686H15154	Chemmapper
LCT	P09848	Lactase-phlorizinhydrolase	Chemmapper
EGLN2	Q96KS0	Eglninehomolog2	Chemmapper
OGFOD1	Q8N543	2-oxoglutarateandiron-dependenttoxygenasedomaincontaining1	Chemmapper
TREM1	Q9NP99	Triggeringreceptorexpressedonmyeloidcells1	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
DDX6	P26196	ProbableATP-dependentRNAhelicaseDDX6	Chemmapper
B3GAT1	Q9P2W7	Galactosylgalactosylxylosylprotein3-beta-glucuronosyltransferase1	Chemmapper
SLC13A1	Q9BZW2	Solutecarrierfamily13member1	Chemmapper
SUCLG2	Q96I99	Succinyl-CoAligase[GDP-forming]beta-chain,mitochondrial	Chemmapper
P4HA2	O15460	Prolyl4-hydroxylasesubunitalpha-2	Chemmapper
SUCLG1	P53597	Succinyl-CoAligase[GDP-forming]subunitalpha,mitochondrial	Chemmapper
OXCT1	P55809	Succinyl-CoA:3-ketoacid-coenzymeAtransferase1,mitochondrial	Chemmapper
SUCNR1	Q9BXA5	Succinate receptor1	Chemmapper
OXCT2	Q9BYC2	Succinyl-CoA:3-ketoacid-coenzymeAtransferase2,mitochondrial	Chemmapper
HSD17B6	O14756	Oxidoreductase	Chemmapper
SUCLA2	Q9P2R7	Succinyl-CoAligase[ADP-forming]beta-chain,mitochondrial	Chemmapper
SLC25A10	Q9UBX3	Mitochondrialdicarboxylatecarrier	Chemmapper
SLC13A2	Q13183	Solutecarrierfamily13member2	Chemmapper
ASS	Q5T6L4	Argininosuccinatesynthase	Chemmapper
ADSSL1	Q8N142	Adenylosuccinatesynthetaseisozyme1	Chemmapper
PAICS	P22234	MultifunctionalproteinADE2[Includes:Phosphoribosylaminoimidazole-succinocarboxamidesynthase	Chemmapper
ACY3	Q96HD9	Aspartoacylase-2	Chemmapper
SLC25A13	Q9UJS0	Calcium-bindingmitochondrialcarrierproteinAralar2	Chemmapper
RNASE1	P07998	Ribonucleasepancreatic	Chemmapper
SLC25A12	O75746	Calcium-bindingmitochondrialcarrierproteinAralar1	Chemmapper
DARS	P14868	Aspartyl-tRNAsynthetase,cytoplasmic	Chemmapper
CAD	P27708	CADprotein[Includes:Glutamine-dependentcarbamoyl-phosphatesynthase	Chemmapper
ADSS	P30520	Adenylosuccinatesynthetaseisozyme2	Chemmapper
DARS2	Q6PI48	Aspartyl-tRNAsynthetase,mitochondrial	Chemmapper
ASPA	P45381	Aspartoacylase	Chemmapper
ASRGL1	Q7L266	ASRGL1 protein	Chemmapper
ASS1	P00966	Argininosuccinatesynthase	Chemmapper
AASS	Q9UDR5	Alpha-aminoadipicsemialdehydesynthase,mitochondrial	Chemmapper
EARS2	Q5JPH6	Probableglutamyl-tRNAsynthetase,mitochondrial	Chemmapper
LGSN	Q5TDP6	Glutamate--ammonialigasedomain-containingprotein1	Chemmapper
SLC1A2	P43004	Excitatoryaminoacidtransporter2	Chemmapper
EPRS	P07814	Bifunctionalaminoacyl-tRNAsynthetase[Includes:Glutamyl-tRNAsynthetase	Chemmapper
GRM1	Q13255	Metabotropicglutamaterceptor1	Chemmapper
GRM7	Q14831	Metabotropicglutamaterceptor7	Chemmapper
NAGS	Q8N159	N-acetylglutamatesynthase,mitochondrial	Chemmapper
SLC25A18	Q9H1K4	Mitochondrialglutamatecarrier2	Chemmapper
GLS2	Q9UI32	Glutaminaseliverisoform,mitochondrial	Chemmapper
DNPEP	Q9ULA0	Aspartylaminopeptidase	Chemmapper
SLC1A3	P43003	Excitatoryaminoacidtransporter1	Chemmapper
CPQ	Q9Y646	Plasmaglutamatecarboxypeptidase	Chemmapper
ALDH18A1	P54886	Delta1-pyrroline-5-carboxylatesynthetase	Chemmapper
OPLAH	O14841	5-oxoprolinase	Chemmapper
GRIK5	Q16478	Glutamaterceptor,ionotropickainate5	Chemmapper
GRIA3	P42263	Glutamaterceptor3	Chemmapper
GRIA1	P42261	Glutamaterceptor1	Chemmapper
GRIN1	Q05586	Glutamate[NMDA]receptorsubunitzeta-1	Chemmapper
GRID1	Q9ULK0	Glutamaterceptordelta-1 subunit	Chemmapper
GRIN2A	Q12879	Glutamate[NMDA]receptorsubunitepsilon-1	Chemmapper
GRIN3B	O60391	Glutamate[NMDA]receptorsubunit3B	Chemmapper
GRIN2D	O15399	Glutamate[NMDA]receptorsubunitepsilon-4	Chemmapper
GRIN2C	Q14957	Glutamate[NMDA]receptorsubunitepsilon-3	Chemmapper
GRID2	O43424	Glutamaterceptordelta-2 subunit	Chemmapper
GRIK1	P39086	Glutamaterceptor,ionotropickainate1	Chemmapper
SLC1A7	O00341	Excitatoryaminoacidtransporter5	Chemmapper
GRM8	O00222	Metabotropicglutamaterceptor8	Chemmapper
GRM4	Q14833	Metabotropicglutamaterceptor4	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
GGCX	P38435	VitaminK-dependentgamma-carboxylase	Chemmapper
GLUL	P15104	Glutaminesynthetase	Chemmapper
GRIK3	Q13003	Glutamaterceptor,ionotropickainate3	Chemmapper
GRIK4	Q16099	Glutamaterceptor,ionotropickainate4	Chemmapper
GATB	O75879	Probableglutamyl-tRNA(Gln)amidotransferasesubunitB,mitochondrial	Chemmapper
GLS	O94925	Glutaminasekidneyisoform,mitochondrial	Chemmapper
SLC25A22	Q9H936	Mitochondrialglutamatecarrier1	Chemmapper
GRIK2	Q13002	Glutamaterceptor,ionotropickainate2	Chemmapper
GRIA4	P48058	Glutamaterceptor4	Chemmapper
NADSYN1	Q6IA69	Glutamine-dependentNAD(+)synthetase	Chemmapper
GMPS	P49915	GMPSynthase[glutamine-hydrolyzing]	Chemmapper
GLUD1	P00367	Glutamatedehydrogenase1,mitochondrial	Chemmapper
GLUD2	P49448	Glutamatedehydrogenase2,mitochondrial	Chemmapper
lacA	P07464	GalactosideO-acetyltransferase	Chemmapper
NPY	P01303	NeuropeptideY	Chemmapper
METAP1	P53582	Methionineaminopeptidase1	Chemmapper
YARS2	Q9Y2Z4	Tyrosyl-tRNAsynthetase,mitochondrial	Chemmapper
SLC22A11	Q9NSA0	Solutecarrierfamily22member11	Chemmapper
OTC	P00480	Ornithinecarbamoyltransferase,mitochondrial	Chemmapper
SLC7A1	P30825	High-affinitycationicaminoacidtransporter1	Chemmapper
SLC25A15	Q9Y619	Mitochondrialornithinetransporter1	Chemmapper
SLC7A3	Q8WY07	Cationicaminoacidtransporter3	Chemmapper
OAZ2	O95190	Ornithinedecarboxylaseantizyme2	Chemmapper
OAZ3	Q9UMX2	Ornithinedecarboxylaseantizyme3	Chemmapper
OAZ1	P54368	Ornithinedecarboxylaseantizyme	Chemmapper
SLC7A2	P52569	Low-affinitycationicaminoacidtransporter2	Chemmapper
SLC25A2	Q9BX12	Mitochondrialornithinetransporter2	Chemmapper
SLC7A4	O43246	Cationicaminoacidtransporter4	Chemmapper
C3	P01024	ComplementC3	Chemmapper
ACAT2	Q9BWD1	Acetyl-CoAacetyltransferase,cytosolic	Chemmapper
GSTP1	P09211	GlutathioneS-transferaseP	Chemmapper
PMP2	P02689	MyelinP2protein	Chemmapper
HTR3A	P46098	5-hydroxytryptamine3receptor	Chemmapper
SCN10A	Q9Y5Y9	Sodiumchannelproteintype10subunitalpha	Chemmapper
CYP19A1	P11511	CytochromeP45019A1	Chemmapper
LTF	P02788	Lactotransferrin	Chemmapper
PTGR1	Q14914	Prostaglandinreductase1	Chemmapper
CCL2	P13500	C-Cmotifchemokine2(HC11)(Monocytechemoattractantprotein1)(Monocytechemotacticandactivatingfactor)(MCAF)(Monocytechemotacticprotein1)(MCP-1)(MonocytesecretoryproteinJE)(Small-induciblecytokineA2)	Chemmapper
ATP5F1A	P25705	ATPSynthasesubunitalpha,mitochondrial(ATPSynthaseF1subunitalpha)	Chemmapper
ATP5F1B	P06576	ATPSynthasesubunitbeta,mitochondrial(EC7.1.2.2)(ATPSynthaseF1subunitbeta)	Chemmapper
NCOA2	Q15596	Nuclearreceptorcoactivator2(NCoA-2)(ClassEbasiceliox-loop-helixprotein75)(bHLHe75)(Transcriptionalintermediaryfactor2)(hTIF2)	Chemmapper
TUBA1A	Q71U36	Tubulinalpha-1Achain(Alpha-tubulin3)(TubulinB-alpha-1)(Tubulinalpha-3chain)[Cleavedinto:Detyrosinatedtubulinalpha-1Achain]	Chemmapper
TUBB4B	P68371	Tubulinbeta-4Bchain(Tubulinbeta-2chain)(Tubulinbeta-2Cchain)	Chemmapper
CA10	Q9NS85	Carbonicanhydrase-relatedprotein10(Carbonicanhydrase-relatedproteinX)(CA-RPX)(CARPX)(Cerebralprotein15)	Chemmapper
CA11	O75493	Carbonicanhydrase-relatedprotein11(CA-RPX1)(CA-XI)(CARPX1)(Carbonicanhydrase-relatedprotein2)(CA-RPII)(CARP-2)	Chemmapper
CA8	P35219	Carbonicanhydrase-relatedprotein(CARP)(CarbonicanhydraseVIII)(CA-VIII)	Chemmapper
CACNA1G	O43497	Voltage-dependentT-typecalciumchannelsubunitalpha-1G(Cav3.1c)(NBR13)(Voltage-gatedcalciumchannelsubunitalphaCav3.1)	Chemmapper
CACNA1H	O95180	Voltage-dependentT-typecalciumchannelsubunitalpha-1H(Low-voltage-activatedcalciumchannelalpha13.2subunit)(Voltage-gatedcalciumchannelsubunitalphaCav3.2)	Chemmapper
CACNA1I	Q9P0X4	Voltage-dependentT-typecalciumchannelsubunitalpha-1I(Voltage-gatedcalciumchannelsubunitalphaCav3.3)(Ca(v)3.3)	Chemmapper
FARS2	O95363	Phenylalanine--tRNAligase,mitochondrial(EC6.1.1.20)(Phenylalanyl-tRNAsynthetase)(PheRS)	Chemmapper
FARSA	Q9Y285	Phenylalanine--tRNAligasealphasubunit(EC6.1.1.20)(CML33)(Phenylalanyl-tRNAsynthetasealphasubunit)(PheRS)	Chemmapper
FARSB	Q9NSD9	Phenylalanine--tRNAligasebetasubunit(EC6.1.1.20)(Phenylalanyl-tRNAsynthetasebetasubunit)(PheRS)	Chemmapper
HCK	P08631	Tyrosine-proteinkinaseHCK(EC2.7.10.2)(Hematopoieticcellkinase)(Hemopoieticcellkinase)(p59-HCK/p60-HCK)(p59Hck)(p61Hck)	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
KCNH2	Q12809	Potassiumvoltage-gatedchannelsubfamilyHmember2(Eaghomolog)(Ether-a-go-go-relatedgenepotassiumchannel1)(ERG-1)(Eag-relatedprotein1)(Ether-a-go-go-relatedprotein1)(H-ERG)(hERG-1)(hERG1)(Voltage-gatedpotassiumchannelsubunitKv11.1)	Chemmapper
MAPKAPK2	P49137	MAPKinase-activatedproteinkinase2(MAPK-activatedproteinkinase2)(MAPKAPkinase2)(MAPKAP-K2)(MAPKAP-2)(MK-2)(MK2)(EC2.7.11.1)	Chemmapper
PKIA	P61925	cAMP-dependentprotein kinaseinhibitoralpha(PKI-alpha)(cAMP-dependentprotein kinaseinhibitor, muscle/brainisoform)	Chemmapper
PRKACA	P17612	cAMP-dependentprotein kinasecatalyticsubunitalpha(PKAC-alpha)(EC2.7.11.11)	Chemmapper
PRSS1	P07477	Trypsin-1(EC3.4.21.4)(Beta-trypsin)(Cationictrypsinogen)(Serineprotease1)(TrypsinI)[Cleavedinto:Alpha-trypsinchain1;Alpha-trypsinchain2]	Chemmapper
RPL10L	Q96L21	60SribosomalproteinL10-like(LargeribosomalsubunitproteinuL16-like)	Chemmapper
RPL11	P62913	60SribosomalproteinL11(CLL-associatedantigenKW-12)(LargeribosomalsubunitproteinuL5)	Chemmapper
RPL13A	P40429	60SribosomalproteinL13a(23kDahighlybasicprotein)(LargeribosomalsubunitproteinuL13)	Chemmapper
RPL15	P61313	60SribosomalproteinL15(LargeribosomalsubunitproteineL15)	Chemmapper
RPL19	P84098	60SribosomalproteinL19(LargeribosomalsubunitproteineL19)	Chemmapper
RPL23	P62829	60SribosomalproteinL23(60SribosomalproteinL17)(LargeribosomalsubunitproteinuL14)	Chemmapper
RPL23A	P62750	60SribosomalproteinL23a(LargeribosomalsubunitproteinuL23)	Chemmapper
RPL26L1	Q9UNX3	60SribosomalproteinL26-like1(LargeribosomalsubunitproteinuL24-like1)	Chemmapper
RPL3	P39023	60SribosomalproteinL3(HIV-1TARRNA-bindingproteinB)(TARBP-B)(LargeribosomalsubunitproteinuL3)	Chemmapper
RPL37	P61927	60SribosomalproteinL37(G1.16)(LargeribosomalsubunitproteineL37)	Chemmapper
RPL8	P62917	60SribosomalproteinL8(LargeribosomalsubunitproteinuL2)	Chemmapper
SCN11A	Q9UI33	Sodiumchannelproteintype11subunitalpha(Peripheralnervesodiumchannel5)(PN5)(Sensoryneuronsodiumchannel2)(SodiumchannelproteintypeXIsubunitalpha)(Voltage-gatedsodiumchannelsubunitalphaNav1.9)(hNaN)	Chemmapper
SCN1A	P35498	Sodiumchannelproteintype1subunitalpha(Sodiumchannelproteinbrainsubunitalpha)(Sodiumchannelproteintypesubunitalpha)(Voltage-gatedsodiumchannelsubunitalphaNav1.1)	Chemmapper
SCN1B	Q07699	Sodiumchannelsubunitbeta-1	Chemmapper
SCN2A	Q99250	Sodiumchannelproteintype2subunitalpha(HBSCII)(SodiumchannelproteinbrainIIsubunitalpha)(Sodiumchannelproteintypesubunitalpha)(Voltage-gatedsodiumchannelsubunitalphaNav1.2)	Chemmapper
SCN3A	Q9NY46	Sodiumchannelproteintype3subunitalpha(SodiumchannelproteinbrainIIIsubunitalpha)(Sodiumchannelproteintypesubunitalpha)(Voltage-gatedsodiumchannelsubunitalphaNav1.3)	Chemmapper
SCN3B	Q9NY72	Sodiumchannelsubunitbeta-3	Chemmapper
SCN4A	P35499	Sodiumchannelproteintype4subunitalpha(SkM1)(Sodiumchannelproteinskeletalmusclesubunitalpha)(Sodiumchannelproteintypesubunitalpha)(Voltage-gatedsodiumchannelsubunitalphaNav1.4)	Chemmapper
SCN4B	Q8IWT1	Sodiumchannelsubunitbeta-4	Chemmapper
SCN9A	Q15858	Sodiumchannelproteintype9subunitalpha(Neuroendocrinesodiumchannel)(hNE-Na)(Peripheralsodiumchannel1)(PN1)(Sodiumchannelproteintypesubunitalpha)(Voltage-gatedsodiumchannelsubunitalphaNav1.7)	Chemmapper
SLC7A8	Q9UHI5	Largeneutralaminoacidtransportersmallsubunit2(L-typeaminoacidtransporter2)(hLAT2)(Solutecarrierfamily7member8)	Chemmapper
SNU13	P55769	NHP2-likeprotein1(Highmobilitygroup-likenuclearprotein2homolog1)(OTK27)(SNU13homolog)(hSNU13)(U4/U6.U5smallnuclearribonucleoproteinSNU13)(U4/U6.U5tri-snRNP15.5kDaprotein)[Cleavedinto:NHP2-likeprotein1,N-terminallyprocessed]	Chemmapper
ATP5F1C	P36542	ATPsynthasesubunitgamma,mitochondrial(ATPsynthaseF1subunitgamma)(F-ATPasegammasubunit)	Chemmapper
PIK3CG	P48736	Phosphatidylinositol4,5-bisphosphate3-kinasecatalyticsubunitgammaisoform(PI3-kinasesubunitgamma)(PI3K-gamma)(PI3Kgamma)(PtdIns-3-kinasesubunitgamma)(EC2.7.1.153)(Phosphatidylinositol4,5-bisphosphate3-kinase110kDacatalyticsubunitgamma)(PtdIns-3-kinasesubunitp110-gamma)(p110gamma)(Phosphoinositide-3-kinasecatalyticgammapolypeptide)(Serine/threonineprotein kinasePIK3CG)(EC2.7.11.1)(p120-PI3K)	Chemmapper
UGT3A1	Q6NUS8	UDP-glucuronosyltransferase3A1(UDPGT3A1)(EC2.4.1.17)	Chemmapper
ABL1	P00519	Tyrosine-protein kinaseABL1(EC2.7.10.2)(Abelsonmurineleukemiaviraloncogenehomolog1)(Abelson tyrosine-protein kinase1)(Proto-oncogene-c-Abl)(p150)	Chemmapper
ARF1	P84077	ADP-ribosylationfactor1	Chemmapper
ARF6	P62330	ADP-ribosylationfactor6	Chemmapper
ECI2	O75521	Enoyl-CoA deltaisomerase2,mitochondrial(EC5.3.3.8)(DRS-1)(Delta(3),delta(2)-enoyl-CoA isomerase)(D3,D2-enoyl-CoA isomerase)(Diazepam-bindinginhibitor-relatedprotein1)(DBI-relatedprotein1)(Dodecenoil-CoA isomerase)(Hepatocellularcarcinoma-associatedantigen88)(Peroxisomal3,2-trans-enoyl-CoA isomerase)(pECI)(Renalcarcinoma antigenNY-REN-1)	Chemmapper
FKBP1A	P62942	Peptidyl-prolylcis-transisomeraseFKBP1A(PPIaseFKBP1A)(EC5.2.1.8)(12kDaFK506-bindingprotein)(12kDaFKBP)(FKBP-12)(Calstabin-1)(FK506-bindingprotein1A)(FKBP-1A)(ImmunophilinFKBP12)(Rotamase)	Chemmapper
GM2A	P17900	GangliosideGM2activator(Cerebrosidesulfateactivatorprotein)(GM2-AP)(Sphingolipidactivatorprotein3)(SAP-3)[Cleavedinto:GangliosideGM2activatorisoformshort]	Chemmapper
GUCA1A	P43080	Guanylylcyclase-activatingprotein1(GCAP1)(Guanylatecyclaseactivator1A)	Chemmapper
INS	P01308	Insulin[Cleavedinto:InsulinBchain;InsulinAchain]	Chemmapper
LY96	Q9Y6Y9	Lymphocyteantigen96(Ly-96)(ESOP-1)(ProteinMD-2)	Chemmapper
PPP3CA	Q08209	Serine/threonine-protein phosphatase2Bcatalyticsubunitalpha isoform(EC3.1.3.16)(CAM-PRPcatalyticsubunit)(Calmodulin-dependent calcineurinA subunitalpha isoform)	Chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
PPP3R1	P63098	CalcineurinsubunitBtype1(Proteinphosphatase2Bregulatorysubunit1)(Proteinphosphatase3regulatorysubunitBalphaisoform1)	Chemmapper
PVR	P15151	Poliovirusreceptor(Nectin-likeprotein5)(NECL-5)(CDantigenCD155)	Chemmapper
RCVRN	P35243	Recoverin(Cancer-associatedretinopathyprotein)(ProteinCAR)	Chemmapper
TRAPPC3	O43617	Traffickingproteinparticlecomplexsubunit3(BET3homolog)	Chemmapper
TDP1	Q9NUW8	Tyrosyl-DNAphosphodiesterase1	Swiss/SEA
AKR1B1	P15121	Aldosereductase(byhomology)	Swiss/SEA
PTPN1	P18031	Protein-tyrosinephosphatase1B	Swiss/SEA
SRD5A1	P18405	Steroid5-alpha-reductase1	Swiss/SEA
TYR	P14679	Tyrosinase	Swiss/SEA
SLC5A2	P31639	Sodium/glucosecotransporter2	Swiss/SEA
LGALS4	P56470	Galectin-4	Swiss/SEA
LGALS8	O00214	Galectin-8	Swiss/SEA
LGALS9	O00182	Galectin-9	Swiss/SEA
SLC28A3	Q9HAS3	Solutecarrierfamily28member3	Swiss/SEA
TPMT	P51580	ThiopurineS-methyltransferase	Swiss/SEA
SLC5A1	P13866	Sodium/glucosecotransporter1	Swiss/SEA
CDA	P32320	Cytidinedeaminase	Swiss/SEA
LGALS3	P17931	Galectin-3	Swiss/SEA
LGALS7	P47929	Galectin-7	Swiss/SEA
LGALS7B	P47929	Galectin-7	Swiss/SEA
FUT7	Q11130	Alpha-(1,3)-fucosyltransferase7	Swiss/SEA
FGF1	P05230	Fibroblastgrowthfactor1	Swiss/SEA
IL2	P60568	Interleukin-2	Swiss/SEA
FGF2	P09038	Fibroblastgrowthfactor2	Swiss/SEA
HK2	P52789	Hexokinase-2	Swiss/SEA
LGALS1	P09382	Galectin-1	Swiss/SEA
HK1	P19367	Hexokinase-1	Swiss/SEA
SELL	P14151	L-selectin	Swiss/SEA
SLC5A4	Q9NY91	Solutecarrierfamily5member4	Swiss/SEA
HRAS	P01112	GTPaseHRas	Swiss/SEA
SELP	P16109	P-selectin	Swiss/SEA
NMUR2	Q9GZQ4	Neuromedin-Ureceptor2	Swiss/SEA
SERPINE1	P05121	Plasminogenactivatorinhibitor1	Swiss/SEA
TNNC1	P63316	TroponinC,slowskeletalandcardiacmuscles	Swiss/SEA
TNNI3	P19429	TroponinI,cardiacmuscle	Swiss/SEA
TNNT2	P45379	TroponinT,cardiacmuscle	Swiss/SEA
HPSE	Q9Y251	Heparanase	Swiss/SEA
F3	P13726	Tissuefactor	Swiss/SEA
POLB	P06746	DNApolymerasebeta	Swiss/SEA
SQLE	Q14534	Squalenemonooxygenase(byhomology)	Swiss/SEA
BACE1	P56817	Beta-secretase1	Swiss/SEA
ADA	P00813	Adenosinedeaminase	Swiss/SEA
ADK	P55263	Adenosinekinase	Swiss/SEA
OGA	O60502	BifunctionalproteinNCOAT	Swiss/SEA
AKR1C3	P42330	Aldo-keto-reductasefamily1memberC3	Swiss/SEA
TOP1	P11387	DNAtopoisomerase1	Swiss/SEA
SLC29A1	Q99808	Equilibrativenucleosidetransporter1	Swiss/SEA
HSPA8	P11142	Heatshockcognate71kDaprotein	Swiss/SEA
HSPA5	P11021	EndoplasmicreticulumchaperoneBiP	Swiss/SEA
SLC28A2	O43868	Sodium/nucleosidecotransporter2	Swiss/SEA
MANBA	O00462	Beta-mannosidase	Swiss/SEA
LTB4R	Q15722	LeukotrieneB4receptor1	Swiss/SEA
NEU3	Q9UQ49	Sialidase-3	Swiss/SEA
KDM4C	Q9H3R0	Lysine-specificdemethylase4C	Swiss/SEA
TTR	P02766	Transthyretin	Swiss/SEA
ABCG2	Q9UNQ0	BroadsubstratespecificityATP-bindingcassettetransporterABCG2	Swiss/SEA

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
KDM5B	Q9UGL1	Lysine-specificdemethylase5B	Swiss/SEA
SRD5A2	P31213	3-oxo-5-alpha-steroid4-dehydrogenase2	Swiss/SEA
KDM4A	O75164	Lysine-specificdemethylase4A	Swiss/SEA
ACHE	P22303	Acetylcholinesterase	Swiss/SEA
KDM3A	Q9Y4C1	Lysine-specificdemethylase3A	Swiss/SEA
GPR35	Q9HC97	G-proteincoupledreceptor35	Swiss/SEA
COMT	P21964	CatecholO-methyltransferase(byhomology)	Swiss/SEA
AKR1C1	Q04828	Aldo-ketoreductasefamily1memberC1	Swiss/SEA
AKR1C2	P52895	Aldo-ketoreductasefamily1memberC2	Swiss/SEA
SELE	P16581	E-selectin	Swiss/SEA
FTO	Q9C0B1	Alpha-ketoglutarate-dependentdioxxygenaseFTO	Swiss/SEA
KDM4E	B2RXH2	Lysine-specificdemethylase4E	Swiss/SEA
ERN1	O75460	Serine/threonine-proteinkinase/endoribonucleaselRE1	Swiss/SEA
IGFBP3	P17936	Insulin-likegrowthfactor-bindingprotein3	Swiss/SEA
KDM4D	Q6B016	Lysine-specificdemethylase4D	Swiss/SEA
FYN	P06241	Tyrosine-proteinkinaseFYN	Swiss/SEA
FUCA1	P04066	Alpha-L-fucosidaseI	Swiss/SEA
GAA	P10253	Lysosomalalpha-glucosidase	Swiss/SEA
HDAC1	Q13547	Histoneacetylase1	Swiss/SEA
MMP1	P03956	Matrixmetalloproteinase1	Swiss/SEA
MME	P08473	Neprilysin	Swiss/SEA
CHIA	Q9BZP6	Acidicmammalianchitinase	Swiss/SEA
MMP12	P39900	Matrixmetalloproteinase12	Swiss/SEA
MMP2	P08253	Matrixmetalloproteinase2	Swiss/SEA
APP	P05067	BetaamyloidA4protein	Swiss/SEA
AKR1B10	O60218	Aldo-ketoreductasefamily1memberB10	Swiss/SEA
AKR1C4	P17516	Aldo-ketoreductasefamily1memberC4	Swiss/SEA
ALB	P02768	Serumalbumin	Swiss/SEA
SNCA	P37840	Alpha-synuclein	Swiss/SEA
KDM6B	O15054	Lysine-specificdemethylase6B	Swiss/SEA
YWHAG	P61981	14-3-3proteingamma	Swiss/SEA
CDC25B	P30305	M-phaseinducerphosphatase2	Swiss/SEA
NOX4	Q9NPH5	NADPHoxidase4	Swiss/SEA
PTGES	O14684	ProstaglandinEsynthase	Swiss/SEA
HDAC8	Q9BY41	Histoneacetylase8	Swiss/SEA
GABRB2	P47870	GABA-Areceptor;alpha-1/beta-2/gamma-2	Swiss/SEA
GABRG2	P18507	GABA-Areceptor;alpha-1/beta-2/gamma-2	Swiss/SEA
SHBG	P04278	Testis-specificandrogen-bindingprotein	Swiss/SEA
CXCL8	P10145	Interleukin-8(IL-8)(C-X-Cmotifchemokine8)(Chemokine(C-X-Cmotif)ligand8)(Emotakin)(Granulocytechemotacticprotein1)(GCP-1)(Monocyte-derivedneutrophilchemotacticfactor)(MDNCF)(Monocyte-derivedneutrophil-activatingpeptide)(MONAP)(Neutrophil-activatingprotein1)(NAP-1)(Protein3-10C)(T-cellchemotacticfactor)[Cleavedinto:MDNCF-a(GCP/IL-8proteinIV)(IL8/NAP1formI);Interleukin-8(Ala-IL-8)77(GCP/IL-8proteinII)(IL-8(1-77))(IL8/NAP1formII)(MDNCF-b);IL-8(5-77);IL-8(6-77)(Ser-IL-8)72(GCP/IL-8proteinI)(IL8/NAP1formIII)(Lymphocyte-derivedneutrophil-activatingfactor)(LYNAP)(MDNCF-c)(Neutrophil-activatingfactor)(NAF);IL-8(7-77)(GCP/IL-8proteinV)(IL8/NAP1formIV);IL-8(8-77)(GCP/IL-8proteinVI)(IL8/NAP1formV);IL-8(9-77)(GCP/IL-8proteinIII)(IL8/NAP1formVI)]	Swiss/SEA
ANPEP	P15144	AminoamidaseN(AP-N)(hAPN)(EC3.4.11.2)(Alanylaminopeptidase)(AminoamidaseM)(AP-M)(Microsomalaminopeptidase)(MyeloidplasmamembraneglycoproteinCD13)(gp150)(CDantigenCD13)	Swiss/SEA
FFAR1	O14842	Freefattyacidreceptor1(G-proteincoupledreceptor40)	Swiss/SEA
LAP3	P28838	Cytosolaminopeptidase(EC3.4.11.1)(Leucineaminopeptidase3)(LAP-3)(Leucylaminopeptidase)(PeptidaseS)(Prolineaminopeptidase)(EC3.4.11.5)(Prolylaminopeptidase)	Swiss/SEA
MET	P08581	HepatocytEGrowthfactorreceptor(HGFReceptor)(EC2.7.10.1)(HGF/SFReceptor)(Proto-oncogeneC-Met)(Scatterfactorreceptor)(SFReceptor)(Tyrosine-proteinkinaseMet)	Swiss/SEA
THRA	P10827	Thyroidhormonereceptoralpha(Nuclearreceptorsubfamily1groupAmember1)(V-erbA-relatedprotein7)(EAR-7)(c-erbA-1)(c-erbA-alpha)	Swiss/SEA
THRB	P10828	Thyroidhormonereceptorbeta(Nuclearreceptorsubfamily1groupAmember2)(c-erbA-2)(c-erbA-beta)	Swiss/SEA
ABCB1	P08183	ATP-dependenttranslocaseABCB1(ATP-bindingcassettesub-familyBmember1)(Multidrugresistanceprotein1)(EC7.6.2.2)(P-glycoprotein1)(PhospholipidtransporterABCB1)(EC7.6.2.1)(CDantigenCD243)	Swiss/SEA

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
ABCC1	P33527	Multidrugresistance-associatedprotein1(EC7.6.2.2)(ATP-bindingcassettesub-familyCmember1)(Glutathione-S-conjugate-translocatingATPaseABCC1)(EC7.6.2.3)(LeukotrieneC(4)transporter)(LTC4transporter)	Swiss/SEA
ALDH2	P05091	Aldehydedehydrogenase,mitochondrial(EC1.2.1.3)(ALDHclass2)(ALDH-E2)(ALDH1)	Swiss/SEA
DHFR	P00374	Dihydrofolatereductase(EC1.5.1.3)	Swiss/SEA
Dyrk1a	Q13627	Dualspecificitytyrosine-phosphorylation-regulatedkinase1A(EC2.7.12.1)(DualspecificityYAK1-relatedkinase)(HP86)(Proteinkinaseinibrainhomolog)(MNBH)(hMNB)	Swiss/SEA
Hsd11b1	P28845	Corticosteroid11-beta-dehydrogenaseisozyme1(EC1.1.1.146)(11-beta-hydroxysteroiddehydrogenase1)(11-DH)(11-beta-HSD1)(Shortchaindehydrogenase/reductasefamily26Cmember1)	Swiss/SEA
PTAFR	P25105	Platelet-activatingfactorreceptor(PAF-R)(PAFr)	Swiss/SEA
ELANE	P08246	Neutrophilelastase(EC3.4.21.37)(Bonemarrowserineprotease)(Elastase-2)(Humanleukocyteelastase)(HLE)(Medullasin)(PMNelastase)	Swiss/SEA
PABPC1	P11940	Polyadenylate-bindingprotein1(PABP-1)(Poly(A)-bindingprotein1)	Swiss/SEA
Trpa1	O75762	TransientreceptorpotentialcationchannelsubfamilyAmember1(Ankyrin-likewithtransmembranedomainsprotein1)(Transformation-sensitiveproteinp120)	Swiss/SEA
XDH	P47989	Xanthinedehydrogenase/oxidase[Includes:Xanthinedehydrogenase(XD)(EC1.17.1.4);Xanthineoxidase(XO)(EC1.17.3.2)(Xanthineoxidoreductase)(XOR)]	Swiss/SEA
RPS6KA3	P51812	RibosomalproteinS6kinasealpha-3(S6K-alpha-3)(EC2.7.11.1)(90kDaribosomalproteinS6kinase3)(p90-RSK3)(p90RSK3)(Insulin-stimulatedproteinkinase1)(SPK-1)(MAPkinase-activatedproteinkinase1b)(MAPK-activatedproteinkinase1b)(MAPKAPkinase1b)(MAPKAPK-1b)(RibosomalS6kinase2)(RSK-2)(pp90RSK2)	Swiss/SEA
YARS1	P54577	Tyrosine--tRNAligase,cytoplasmic	SEA/chemmapper
PDE4D	Q08499	cAMP-specific3',5'-cyclicphosphodiesterase4D	SEA/chemmapper
SPTLC2	O15270	Serinepalmitoyltransferase2	SEA/chemmapper
HCAR3	P49019	Hydroxycarboxylicacidreceptor3	SEA/chemmapper
HNF4A	P41235	Hepatocytenuclearfactor4-alpha	SEA/chemmapper
PDE4B	Q07343	cAMP-specific3',5'-cyclicphosphodiesterase4B	SEA/chemmapper
NOS2	P35228	Nitricoxidesynthase,inducible	SEA/chemmapper
ADRB2	P07550	Beta-2adrenergicreceptor	SEA/chemmapper
P4HA1	P13674	Prolyl4-hydroxylasesubunitalpha-1	SEA/chemmapper
HIF1AN	Q9NWT6	Hypoxia-induciblefactor1-alpha-inhibitor	SEA/chemmapper
SLC7A11	Q9UPY5	Cystine/glutamatetransporter	SEA/chemmapper
ACP1	P24666	Lowmolecularweightphosphotyrosineproteinphosphatase	SEA/chemmapper
SIRT5	Q9NXA8	NAD-dependentdeacetylasesirtuin-5	SEA/chemmapper
ADRB3	P13945	Beta-3adrenergicreceptor	SEA/chemmapper
MAOA	P21397	Amineoxidase[flavin-containing]A	SEA/chemmapper
CBS	P35520	Cystathioninebeta-synthase	SEA/chemmapper
TAT	P17735	Tyrosineaminotransferase	SEA/chemmapper
ABAT	P80404	4-aminobutyrateaminotransferase,mitochondrial	SEA/chemmapper
PYGB	P11216	Glycogenphosphorylase,brainform	SEA/chemmapper
NCOA1	Q15788	Nuclearreceptorcoactivator1	SEA/chemmapper
YARS	P54577	Tyrosyl-tRNA-synthetase,cytoplasmic	SEA/chemmapper
KCNMA1	Q12791	Calcium-activatedpotassiumchannelsubunitalpha1	SEA/chemmapper
DHODH	Q02127	Dihydroorotatedehydrogenase,mitochondrial	SEA/chemmapper
ALDH5A1	P51649	Succinatesemialdehydedehydrogenase,mitochondrial	SEA/chemmapper
SLC1A6	P48664	Excitatoryaminoacidtransporter4	SEA/chemmapper
GRIN2B	Q13224	Glutamate[NMDA]receptorsubunitepsilon-2	SEA/chemmapper
TH	P07101	Tyrosine3-monooxygenase	SEA/chemmapper
GSTA1	P08263	GlutathioneS-transferaseA1	SEA/chemmapper
SLC22A8	Q8TCC7	Solutecarrierfamily22member8	SEA/chemmapper
ARG1	P05089	Arginase-1	SEA/chemmapper
STK17B	O94768	Serine/threonine-proteinkinase17B(EC2.7.11.1)(DAPkinase-relatedapoptosis-inducingproteinkinase2)	SEA/chemmapper
Ncoa3	Q9Y6Q9	Nuclearreceptorcoactivator3(NCoA-3)(EC2.3.1.48)(ACTR)(Amplifiedinbreastcancer1protein)(AIB-1)(CBP-interactingprotein)(pCIP)(ClassEbasichelix-loop-helixprotein42)(bHLHe42)(Receptor-associatedcoactivator3)(RAC-3)(Steroidreceptorcoactivatorprotein3)(SRC-3)(Thyroidhormonereceptoractivator1)(TRAM-1)	SEA/chemmapper
MAPK14	Q16539	Mitogen-activatedproteinkinase14	Swiss/ chemmapper
SLC6A2	P23975	Norepinephrinetransporter	Swiss/ chemmapper
F10	P00742	ThrombinandcoagulationfactorX	Swiss/ chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
ADORA2A	P29274	AdenosineA2areceptor(byhomology)	Swiss/ chemmapper
PNP	P00491	Purinucleosidephosphorylase	Swiss/ chemmapper
DPP4	P27487	DipeptidylpeptidaseIV	Swiss/ chemmapper
MAPK1	P28482	MAPkinaseERK2	Swiss/ chemmapper
ADORA1	P30542	AdenosineA1receptor	Swiss/ chemmapper
ADRA1A	P35348	Alpha-1Aadrenergicreceptor	Swiss/ chemmapper
LDHA	P00338	L-lactatedehydrogenaseAchain	Swiss/ chemmapper
ADRA2B	P18089	Alpha-2Badrenergicreceptor	Swiss/ chemmapper
ADRA2A	P08913	Alpha-2Aadrenergicreceptor	Swiss/ chemmapper
ADRA2C	P18825	Alpha-2Cadrenergicreceptor	Swiss/ chemmapper
DRD1	P21728	D(1A)dopaminereceptor	Swiss/ chemmapper
ADRA1D	P25100	Alpha-1Dadrenergicreceptor	Swiss/ chemmapper
DRD3	P35462	D(3)dopaminereceptor	Swiss/ chemmapper
DRD2	P14416	D(2)dopaminereceptor	Swiss/ chemmapper
CSNK2A1	P68400	CaseinkinaseIIsubunitalpha	Swiss/ chemmapper
ADORA2B	P29275	AdenosineA2breceptor	Swiss/ chemmapper
PDE5A	O76074	cGMP-specific3',5'-cyclicphosphodiesterase	Swiss/ chemmapper
TYMS	P04818	Thymidylatesynthase	Swiss/ chemmapper
TNF	P01375	Tumornecrosisfactor	Swiss/ chemmapper
HTR2C	P28335	5-hydroxytryptamine2Creceptor	Swiss/ chemmapper
HTR1B	P28222	5-hydroxytryptamine1Breceptor	Swiss/ chemmapper
HTR2B	P41595	5-hydroxytryptamine2Breceptor	Swiss/ chemmapper
HTR2A	P28223	5-hydroxytryptamine2Areceptor	Swiss/ chemmapper
CDK2	P24941	Cyclin-dependentkinase2/cyclinA	Swiss/ chemmapper
ATP1A1	P05023	Sodium/potassium-transportingATPasealpha-1chain	Swiss/ chemmapper
F2	P00734	Prothrombin	Swiss/ chemmapper
AR	P10275	Androgenreceptor	Swiss/ chemmapper
FPGS	Q05932	Folypolyglutamatesynthase,mitochondrial	Swiss/ chemmapper
PIN1	Q13526	Peptidyl-prolylcis-transisomeraseNIMA-interacting1	Swiss/ chemmapper
GABBR1	Q9UBS5	GABA-Breceptor	Swiss/ chemmapper
PIM1	P11309	Serine/threonine-proteinkinasepim-1(EC2.7.11.1)	Swiss/ chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
NEK2	P51955	Serine/threonine-protein kinase Nek2 (EC2.7.11.1) (HSPK21) (Never in mitosis A-related kinase 2) (NimA-related protein kinase 2) (NimA-like protein kinase 1)	Swiss/chemmapper
SRC	P12931	Proto-oncogene tyrosine-protein kinase Src (EC2.7.10.2) (Proto-oncogene c-Src) (pp60c-src) (p60-Src)	Swiss/chemmapper
AMY1A	P04745	Alpha-amylase 1	Swiss/SEA/chemmapper
CA14	Q9ULX7	Carbonic anhydrase 14	Swiss/SEA/chemmapper
VEGFA	P15692	Vascular endothelial growth factor A	Swiss/SEA/chemmapper
CA12	O43570	Carbonic anhydrase 12	Swiss/SEA/chemmapper
CA9	Q16790	Carbonic anhydrase 9	Swiss/SEA/chemmapper
CA1	P00915	Carbonic anhydrase 1	Swiss/SEA/chemmapper
CA7	P43166	Carbonic anhydrase 7	Swiss/SEA/chemmapper
CA2	P00918	Carbonic anhydrase 2	Swiss/SEA/chemmapper
CA3	P07451	Carbonic anhydrase 3	Swiss/SEA/chemmapper
CA13	Q8N1Q1	Carbonic anhydrase 13	Swiss/SEA/chemmapper
CA4	P22748	Carbonic anhydrase 4	Swiss/SEA/chemmapper
CA5A	P35218	Carbonic anhydrase 5A, mitochondrial	Swiss/SEA/chemmapper
PYGM	P11217	Glycogen phosphorylase, muscle form	Swiss/SEA/chemmapper
CA6	P23280	Carbonic anhydrase 6	Swiss/SEA/chemmapper
ESR2	Q92731	Estrogen receptor beta	Swiss/SEA/chemmapper
DAO	P14920	D-amino-acid oxidase	Swiss/SEA/chemmapper
MGMT	P16455	Methylated-DNA--protein-cysteine methyltransferase	Swiss/SEA/chemmapper
GBA	P04062	Lysosomal acid glucosylceramidase	Swiss/SEA/chemmapper
GAPDH	P04406	Glyceraldehyde-3-phosphate dehydrogenase	Swiss/SEA/chemmapper
PYGL	P06737	Glycogen phosphorylase, liver form	Swiss/SEA/chemmapper
CA5B	Q9Y2D0	Carbonic anhydrase VB	Swiss/SEA/chemmapper
SLC22A6	Q4U2R8	Solute carrier family 22 member 6	Swiss/SEA/chemmapper
PTGS2	P35354	Prostaglandin G/H synthase 2	Swiss/SEA/chemmapper
PTGS1	P23219	Prostaglandin G/H synthase 1	Swiss/SEA/chemmapper
ALOX5	P09917	Arachidonate 5-lipoxygenase	Swiss/SEA/chemmapper
NQO2	P16083	Ribosyl dihydronicotinamide dehydrogenase [quinone]	Swiss/SEA/chemmapper
HCAR2	Q8TDS4	Nicotinic acid receptor 1	Swiss/SEA/chemmapper
CACNA2D1	P54289	Voltage-dependent calcium channel subunit alpha-2/delta-1	Swiss/SEA/chemmapper
MMP9	P14780	Matrix metalloproteinase-9	Swiss/SEA/chemmapper

Table S1 (Continued)

Table S1 (Continued)

Commonname	Uniprot ID	Target	Database
FOLH1	Q04609	Glutamatecarboxypeptidasell	Swiss/SEA/ chemmapper
ESR1	P03372	Estrogenreceptor	Swiss/SEA/ chemmapper
TOP2A	P11388	DNAtopoisomerase2-alpha	Swiss/SEA/ chemmapper
OPRM1	P35372	Mu-typeopioidreceptor	Swiss/SEA/ chemmapper
OPRD1	P41143	Delta-typeopioidreceptor	Swiss/SEA/ chemmapper
ENPEP	Q07075	Glutamylaminopeptidase	Swiss/SEA/ chemmapper
ESRRG	P62508	Estrogen-relatedreceptorgamma	Swiss/SEA/ chemmapper
MAOB	P27338	Amineoxidase[flavin-containing]B	Swiss/SEA/ chemmapper
MIF	P14174	Macrophagemigrationinhibitoryfactor	Swiss/SEA/ chemmapper
TLR4	O00206	Toll-likereceptor4(hToll)(CDantigenCD284)	Swiss/SEA/ chemmapper

HJT, Hongjingtian injection.