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Original Research Article

Integration Modeling for Personalized Therapy Including Current Medical Administration and Traditional Chinese Medication for Lupus Nephritis

Wenqin Li[1], Xiaonan Ying[2], Yan Wang[3], Biaoru Li[4], Hongliang Hu[5]
[1]Department of Chemistry, University of California, Irvine, CA 92697, USA
[2]Candidate for Master of Science in Bioinformatics, Northeastern University, 360 Huntington Ave, Boston, MA 02115, USA
[3]Department of Internal Medicine, China Petroleum Kuerla Hospital, Kuerla, XinJiang, 841000, P.R. China
[4]MD/Ph.D, Department of Pediatrics and GA Cancer Center Children Hospital at GA Augusta, GA 30912, USA
[5]Institute of Traditional Chinese Medicine, Fudan University, 220 Handan Rd, WuJiaoChang, Yangpu Qu, Shanghai Shi, China

***Corresponding author:** Biaoru Li
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Abstract

The damage caused by the lupus nephritis to the patient's kidney was very little studied for treatment module; however, we have the understanding the disease involving in the kidneys by an immune complex glomerulonephritis. Human genomics have been decoded since 2004, it should give clinical scientists and medical doctors a new scenery to develop some new treatment modules to cure these kinds of patients. Here we used a group of genomic data from lupus nephritis to combine the modern medicine knowledge and Traditional Chinese Medicine (TCM) so that an integration module will be subject to the clinical field. The integration model is primarily relied on a comprehensive regulation mechanism of system biology including network, topology and gene-drug interaction database. In this manual we first study the role using genomic expression signature from several databases of clinical lupus nephritis, and then we combine current medications with their immune suppress treatment and TCM with their theory and medication in order that the integration model was eventually established. In near future, we will extend a second-generation model based on the module by using a set of clinical genomic data from different patients such as individual patient genomic data, each patient symptom, laboratory results.

Keywords: Lupus nephritis, gene expression signature, topology, integration medicine, traditional Chinese medicine, personalized therapy.

INTRODUCTION

The lupus nephritis (LN) is a severe kidney disease caused by an immune complex which results in glomerulonephritis [1]. The disease will finally develop renal function failure but very little measurement to control the disease deterioration [2]. Since 2004 when human genomics are decoded, it gives an expectation for clinical scientists and medical doctors to treat the uncured disease suffered by patients. Furthermore, because traditional Chinese medicine (TCM) has several thousand's years practice to treat the uncured disease, it will be possible that recent LN studies have been largely reported by mechanism of "Yin" and "Yang" related to T-cells and cytokines regulation in TCM. Moreover, immune suppress medication has been increasingly studied by their cytokines and gene regulation to treat the disease. Foremost, system biology and gene-drug interaction databases are emerging, an integration model based on genomics will be possible for combination employment of different medication methods in clinics.

Since the integration model is primarily developed by a group of genomic data, here we first studied several genomic databases from LN to develop a module for the integration model. Secondly, some comprehensive pathways are studied to LN network mechanism so that we further set up a network construction by genomic expression signature obtained from public GEO database. Finally, we combine LN networks with their medicine treatment and LN related to cytokine regulation with their TCM medication, and thereby this integration modeling will be a combination to treat Lupus Nephritis (LN) from different mythologies. They should better than lonely method to treat LN such as only immune suppress to treat LN or by only TCM to administer LN. This study will improve our understanding of LN system biology in the uncured disease. The manual purpose will provide a foundation for effective treatment to administer these kinds of uncured diseases. In near future, we will continue to develop second-generation module with a set of clinical genomic data from different patients and their information relied on each patient symptom and

laboratory results. our final purpose is that the feasible module can be used MD to prescribe drugs according to personal genomics information, patient symptom, different lab results.

MATERIALS AND METHODS

Clinical Genomic Sources

There are several public LN genomic databases published in Gene Expression Omnibus (GEO). After these database in GEO are carefully studied (all studies of LN public genomic database were omitted here), we mainly select GSE99967 from GEO for our study model even if combination was used to other information from the LN genomics such as GWAS and other information. The GES99967 have used Affymetrix Human Gene 2.0 ST Array to study LN genomics [3]. Furthermore, these public GEO databases have three advantages and characteristics over than other LN genomic data: (1) RNA was isolated from whole peripheral blood of active SLE patients (systemic *lupus* erythematosus) with their transcriptomic profiling including LN patients; (2) clinical criteria from patients follow up 4 or more of the revised in 1997 by American College of Rheumatology; (3) 38 patients with 17 controls including active patients with and without LN which can be used to identify potential genomic expression signature (GES).

Topology analysis for personalized therapy modeling

After we analyzed the GEO database to combine other information such as GWAS, if we want to study a disease network, as our previous reports [4], we should first study this disease topology model. In details, the specific GES (Supplemental Table-1) was input into Cytoscape to observe abnormal expression from these disease genomic characteristics. Based on our previous publications, we selected three indexes, Betweenness Centrality (BC) which is short pathway between two proteins (node), Connectivity Degree (CD) which is a protein linking other protein number and Cluster Coefficient (CC), which means side-way to a protein. Furthermore, the topology formula selected in the network combined to mTORC pathway (Supplemental Table-2), which is an acute and chronic kidney disease, lay the foundation for the establishment of an operational therapeutic targets.

After we studied the GES topology, the modified gene expression profile is also input into a drug-bank in the Drug Genomic Interaction Database (DGIdb) to define targeted therapeutic drug and the targeting molecule [5]. As our previous researches, we also study an index from each compound with higher BC and lower CC and CD. These targets indicate as a higher targeting for abnormal cells with a lower toxicity for normal cells. Eventually, a list of compounds from drug-bank is established to link genes, especially including FDA-approved drug and molecular therapeutic antibodies and small molecule therapeutics and radiation molecules. This led to the establishment of configuration maps and drug response networks based on the abnormal genome expression characteristics obtained from LN.

Topology analysis for modern medicine treatment

According to several decades efforts from different laboratories, three pathways (Supplemental Table-3) have been discovered for chronic inflammatory response networks, those are, nuclear factor kappa-light-chain-enhancer of activated B cells pathway (NF-κB), hypoxia-inducible factors-1 alpha (HIF-1α) pathway and signal transducer and activator of transcription (STAT) pathway [6]. When patients become chronic inflammation such as LN, the three pathways with their transcriptional factors will become major factors to involve in the diseases.

Moreover, routine clinical health care focus on a corticosteroid (such as prednisone), or suppress immune system such as cyclophosphamide, mycophenolate mofetil or hydroxychloroquine for people who have LN diseases. Because most of LN have high blood pressure, Lupus nephritis can cause high blood pressure in some people. We may need more than one kind of medicine to control patient blood pressure including ACE inhibitors, diuretics, beta blockers or calcium channel blockers. The ACE inhibitors and other drugs may help protect your kidneys, and diuretics help your kidneys remove fluid from your body. Accordingly, all medication related to their molecules and cytokines regarding immune suppress and anti-high-blood pressure were established a linker into the three pathways with their transcriptional factors as described above.

We apply for the list of drugs with targeting genes to combine into the network including three pathways and a list of drugs to administer their treatment. Finally, genes with their drugs still require higher BC with lower CC and CD to establish medication module and drug response networks based on LN.

Topology analysis for traditional Chinese Medicine

Zhuangzi (1020–1078 AD), a famous Chinese philosopher, had interpreted that there are two elements: “Yin” and “Yang” establish a material force in the universe [7]. According to the famous Chinese philosophy: “Yang” and “Yin” interact each other to complete a “Great Ultimate” also called as “Tai-chi diagram”. As current researches, Yang, the “hot” point is inflammation peak (enlargement of yang area) and Yin, “cool” point is regulatory of inflammation (enlargement of yin area). After several decades efforts, inflammation pathways regarding cytokines have been extensively studied in the “Tai-chi diagram” [8] so that we set up topology analysis from inflammation regulation and autoimmune response including cytokines expression in Yin and Yang (Supplemental Table-4).

Moreover, TCM with their treatment will be used for lupus nephritis patients by Chinese Diagnosis Model [9]: A. liver heat (liver fire) which is patient tongue red, the pulse is wiry and rapid; B. spleen-kidney yang deficiency by which patient has night sweats, afternoon fever, chronic fatigue, and pain in the lower back and knees; C. liver-kidney yin deficiency which is face and tongue dark and dull; D. combination with some symptom as above three types. We also apply for a list of traditional drugs with their targeting cytokines as "Tai-chi diagram" from cytokines and T-cells to set up the new network including Yin-Yang pathways and a list of TCM treatment. As topology described above, higher BC with lower CC and CD establish TCM with their treatment including drug response based on Chinese Diagnosis Model.

Topology analysis for integration module

As eventual combination for integration model, we merge all networks from genomic data including their therapeutic targets; three pathways with their immune suppress and symptom such as high blood pressure; "Yin-Yang" as "Tai-chi diagram" related cytokines with their TCM and their medication (all data as supplemental_1_2_3_4).

Support Analysis

In order to support the module of the selected pathways for targeted drugs and a targeted molecule therapy for personalized therapy including current medication and traditional Chinese medication, a python scripts to simulate to assay a drug (Supplemental Table-6). The python scripts were established as our previously reported [10], they are used to simulate the anti-LN drugs to support the module and analyze the matched therapeutic targets including modern medicine and TCM in the LN network for targeted gene expression and the discovered therapeutic molecules. The design principle is that the abnormal inflammation cytokines obtained by network with a dynamic model based on differential equations including qualitative relationships and directed responses as our previous report. The scripts will verify the efficacy of anti-LN drugs for LN patients.

RESULTS

Construction and topology establishment from GES

Recently, therapeutic targeting is going to focus on topology based on GES to discover drug targeting, small molecule targeting, Ab targeting and RNA-interfering therapy. Our laboratory has spent more than a decade to study different topology parameters relied on our experimental assay such as quantitative rtPCR and Western blot [11]. Although most of parameters can be used in different cell-lines, animal and human beings in different lab [12-15], as our previous studies, both BC and DC majorly play an important role in primary cells from clinical specimens while DC is likely to be toxic for normal cells such as normal lymphocytes due to their system-wide influence, thus we firstly study GES (as Supplemental Table-1) with higher BC and low DC/CC from the GEO data. The high BC value indicates a significant targeting node from abnormal cells and low DC and CC means very few branches without their system-wide influence to cause normal cell disfunction [16]. Base on the conception from our long-term data analysis and experimental support, although 21 GES from LN within SEL was obtained from GEO data, we need further refine a construction for feasible therapeutic targets. After we input mTORC (as Supplemental Table-2) and chronic inflammation pathways into Cytoscape, a construction from both LN GES and mTORC/inflammation pathways was established as Fig-1. The uncovered nodes (or genes or proteins) were loaded into the GDIdb to mine drugs, small molecule and other molecular therapy agents. The resulting node and drug candidates with their index (BC, DC and CC) were configured by the construction map as Fig-2. As the Fig-2 shown, hydrochlorothiazide was predicted to inhibit CA1 which can cause renal high pressure although the drug indicates anti-chronic inflammation in the disease GES.

Topology and results of analysis for current medicine treatment

Clinical care for LN have routinely employed prednisone, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine for patients who have LN diseases. Because LN have complex symptoms such as high blood pressure, ACE inhibitors, diuretics, beta blockers or calcium channel blockers may help protect your kidneys and/or diuretics help your kidneys remove fluid from your body. According to chronic inflammatory pathways (as Supplemental Table-3) and drugs targeting genes and cells, we apply for the list of drugs with targeting genes and chronic inflammatory pathways to set up the network for topology constructs. As GES therapeutic targets described above, genes with their drugs require higher BC with lower CC and CD to establish the resulting networks as Fig-3. The results constructs revealed that prednisone inhibiting Cox2, cyclophosphamide, mycophenolate mofetil, hydroxychloroquine blocking T-cells. For example, after block of cyclophosphamide, chronic inflammation will be inhibited in the constructs. In order to study clinical complication for drugs responses in the dynamic network, we also can discover some drugs in the constructed topology with the disease complication as Fig-3.

Topology analysis and results for traditional Chinese Medicine

Traditional Chinese medicine (TCM) for lupus nephritis have a special Chinese Diagnosis Model according to Chinese medication theory: "liver heat", "spleen-kidney yang deficiency", "liver-kidney yin deficiency" and combination with above three types.

"Tai-chi diagram" indicated the "hot" point as Yang is inflammation peak (enlargement of yang area) and "cool" point as Yin is regulatory of inflammation (enlargement of yin area). As Supplemental Table-4 and Fig-4, inflammation pathways including their cytokines and T-cells have been extensively studied in the ""Great Ultimate" so that we set up topology analysis of inflammation regulation and autoimmune response including cytokines expression in Yin and Yang. As topology described above, higher BC with lower CC and CD require traditional Chinese medicine with their treatment including drug response based on Chinese Diagnosis Model. As Fig-5, JSW (金匮肾气丸)can increase "spleen-kidney Yang function" which is constructed by "Great Ultimate" related inflammatory pathways.

Construction and topology analysis for integration model

After we achieved first construct from genomic data with their therapeutic targets, second construct from current LN mechanism with their immune suppress treatment, third construct from TMC mechanism with their treatment, as Fig-6, we merged all nodes within configuration, an integration model with their construction was established as Fig-7. The resulting node and drug candidates with their index (BC, DC and CC) were discovered by the construction map as Supplemental Table-5 and Fig-7. As the Fig-7 shown, if we have a group of GES data, we can predict a comprehensive treatment, including current feasible immune suppress and anti-symptom administration, targeting treatment and traditional Chinses medication, which can block LN with their different complicated symptoms such as renal high pressure and other chronic inflammation.

Python Analysis and Results

In order to support the integration model for these selected pathways and their targeted drugs and a targeted molecule therapy including their current medication and traditional Chinese medication, a python scripts which was established in our lab are used to simulate the anti-LN drugs in the module and analyze their therapeutic targets within modern medication and traditional Chinese medication in the construct network (as Supplemental Table-6). As Fig-8 and Table-1, if genomic data as GES was harvested in the manual, cyclosporin-A is better than cortisone to remodel immune regulation to the therapeutic targets; SJGHDH (参芪桂附地黄汤) is better than other traditional Chinese medication; hydrochlorothiazide is better than ACE inhibitors, beta blockers and calcium channel blockers because this GES data has higher CA1 expression.

An integration modeling and results

name	BetweennessCentrality	DegreeCentriality	ClusteringCoefficient
Cyclosporin_A	5.015625	1	0
CTX	5.015625	1	0
CYCLOTHIAZIDE	5.375	1	0
CHLORTHALIDONE	5.375	1	0
SODIUM_CARBONATE	5.375	1	0
QUINETHAZONE	5.375	1	0
METHYCLOTHIAZIDE	5.375	1	0
HYDROFLUMETHIAZIDE	5.375	1	0
HYDROCHLOROTHIAZIDE	5.375	1	0
DIAZOXIDE	5.375	1	0
BENZTHIAZIDE	5.375	1	0
BENDROFLUMETHIAZIDE	5.375	1	0
SJGHDH	7.203125	2	0
DHY	7.203125	2	0
DBW	7.203125	2	0
SJDH	7.203125	2	0
JJDH	8.1640625	1	0
GZDH	8.1640625	1	0
WZXZ	7.3359375	1	0
JSW	7.3359375	1	0

LEGEND

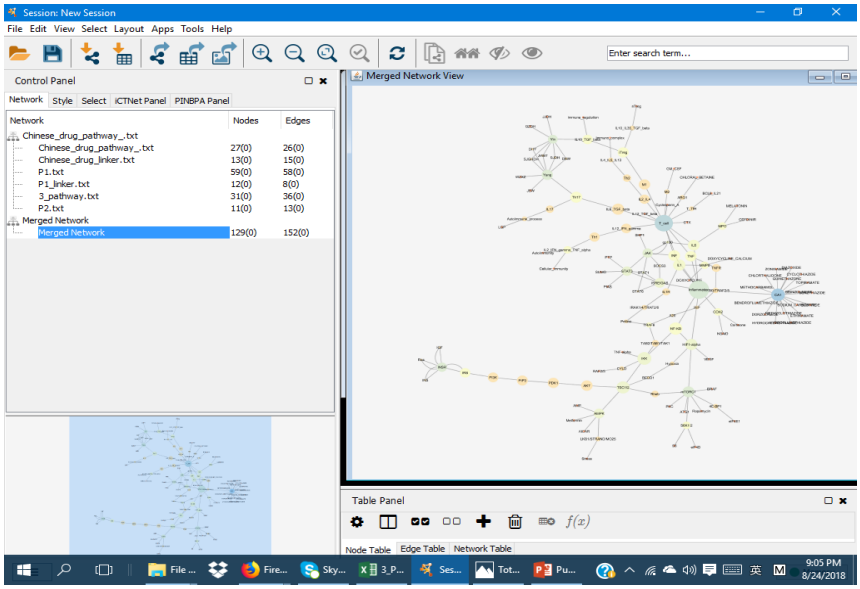

Fig-1: A Cytoscape platform was established by mTORC/inflammation pathways, GES and compounds mined by GDIdb

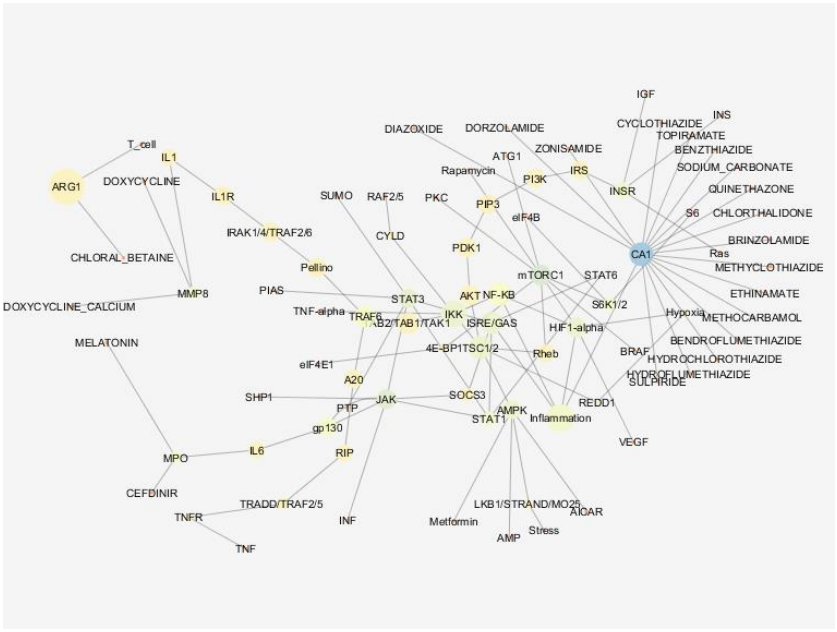

Fig-2: The construction was defined by Cytoscape platform depending on mTORC/inflammation pathways, GES and compounds mined by GDIdb and the configuration were used for the topology analysis such as BC, DC and CC. For example, large node size means larger BC value and DC large means color dark from red, pink, yellow, blue, green to dark

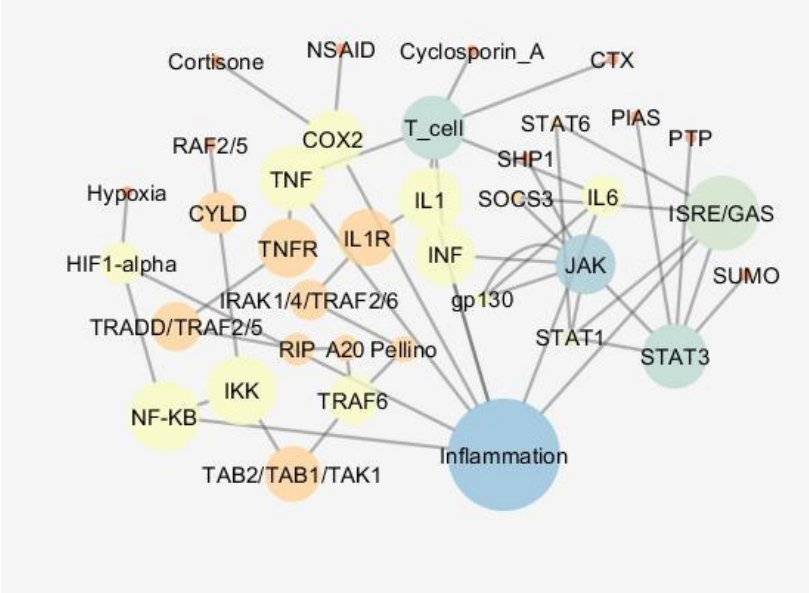

Fig-3: The construction was defined by Cytoscape platform depending on mTORC/inflammation pathways, immune suppress with their compounds mined by GDIdb and they were used for the topology analysis such as BC, DC and CC as Fig-2; the three pathways are activated B cells pathway (NF-κB), hypoxia-inducible factors-1 alpha (HIF-1α) pathway and signal transducer and activator of transcription (STAT) pathway

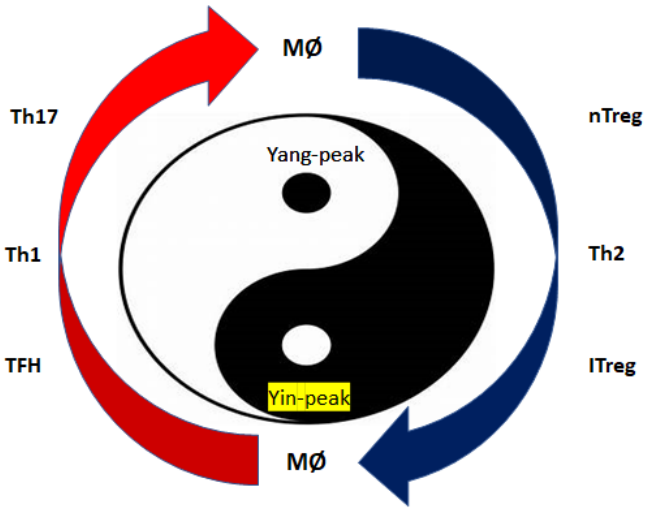

Fig-4: "Tai-chi diagram" indicates Yang, the "hot" point is white from smaller to larger and Yin, "cool" point is dark from regulatory of inflammation (enlargement of yin area) which is 'yang' opposite. Inflammation pathways regarding cytokines from "Tai-chi diagram" were used to study traditional Chinese medication

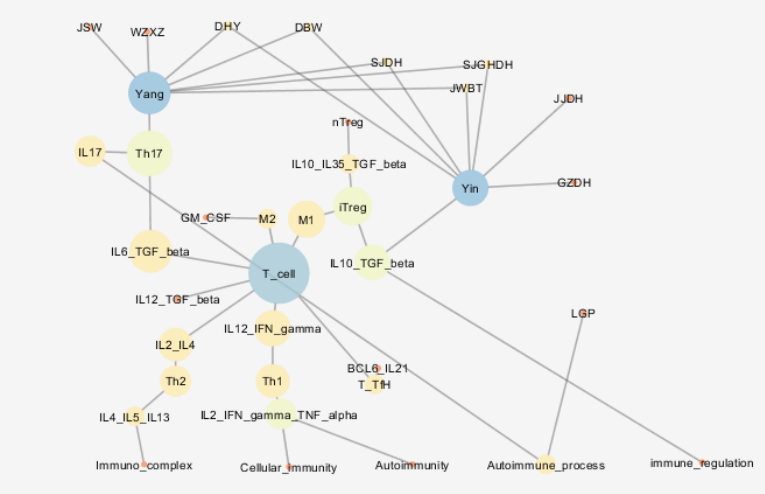

Fig-5: The construction was defined by Cytoscape platform depending on immune regulation and autoimmune pathways including their cytokines and T-cells. They were configured as Yin and Yang including their traditional Chinese mediation. Topology such as BC, DC and CC. were used to study analysis. For example, large node size means larger BC value and DC large means color dark from red, pink, yellow, blue, green to dark

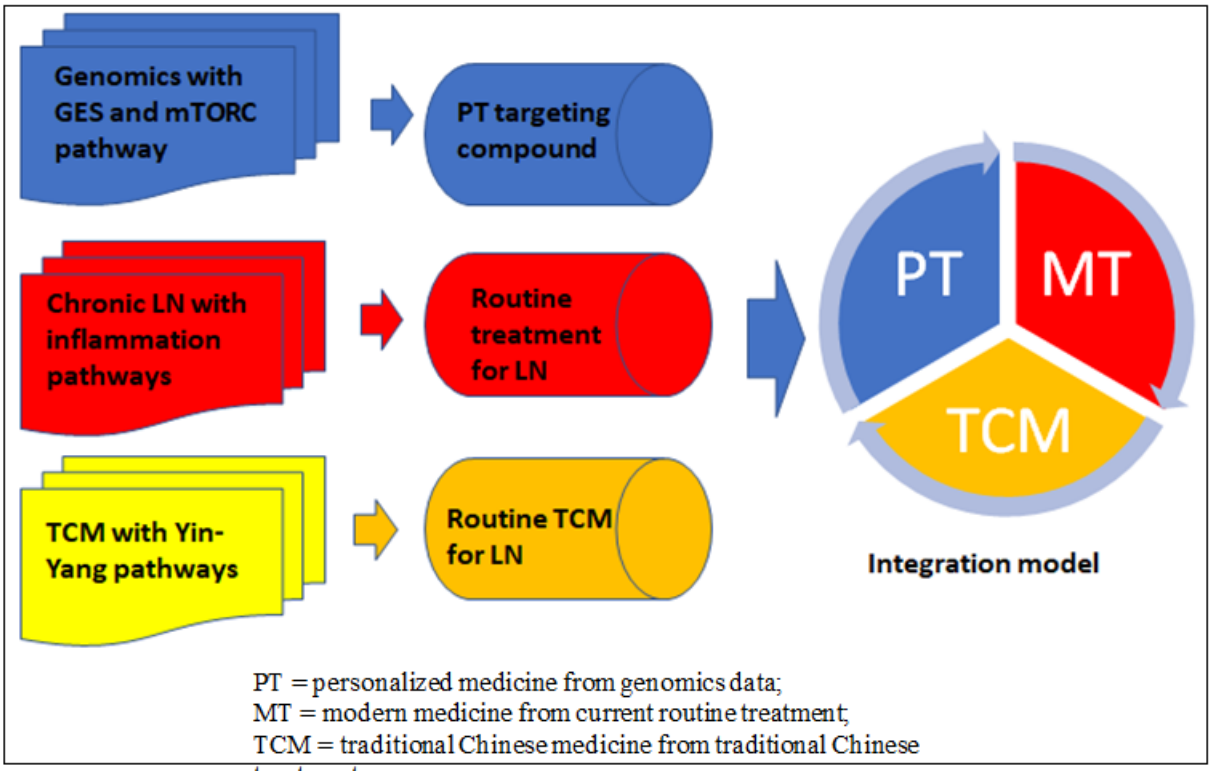

Fig-6: The diagram indicated that an integration process including genomics data with their GES for personalized therapy, chronic LN inflammation with their medication, traditional Chinese medication with Yin and Yang related cytokines and T-cell pathway

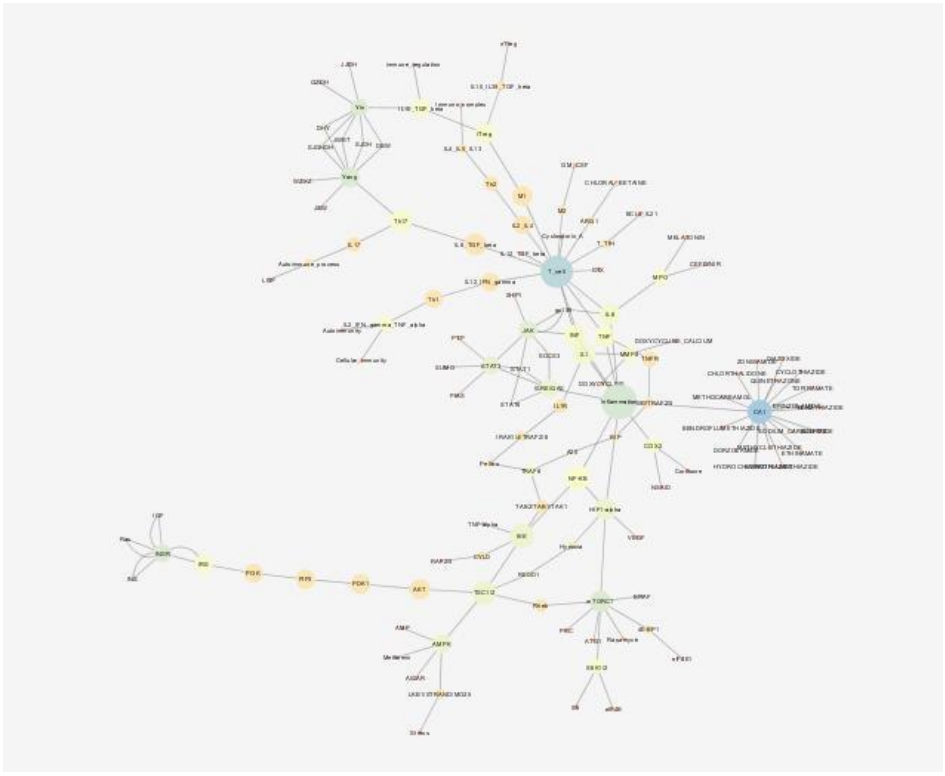

Fig-7: The construction indicated that an integration model including genomics data with their GES for personalized therapy, chronic LN inflammation with their medication and traditional Chinese medication with Yin and Yang related cytokines and T-cell pathway

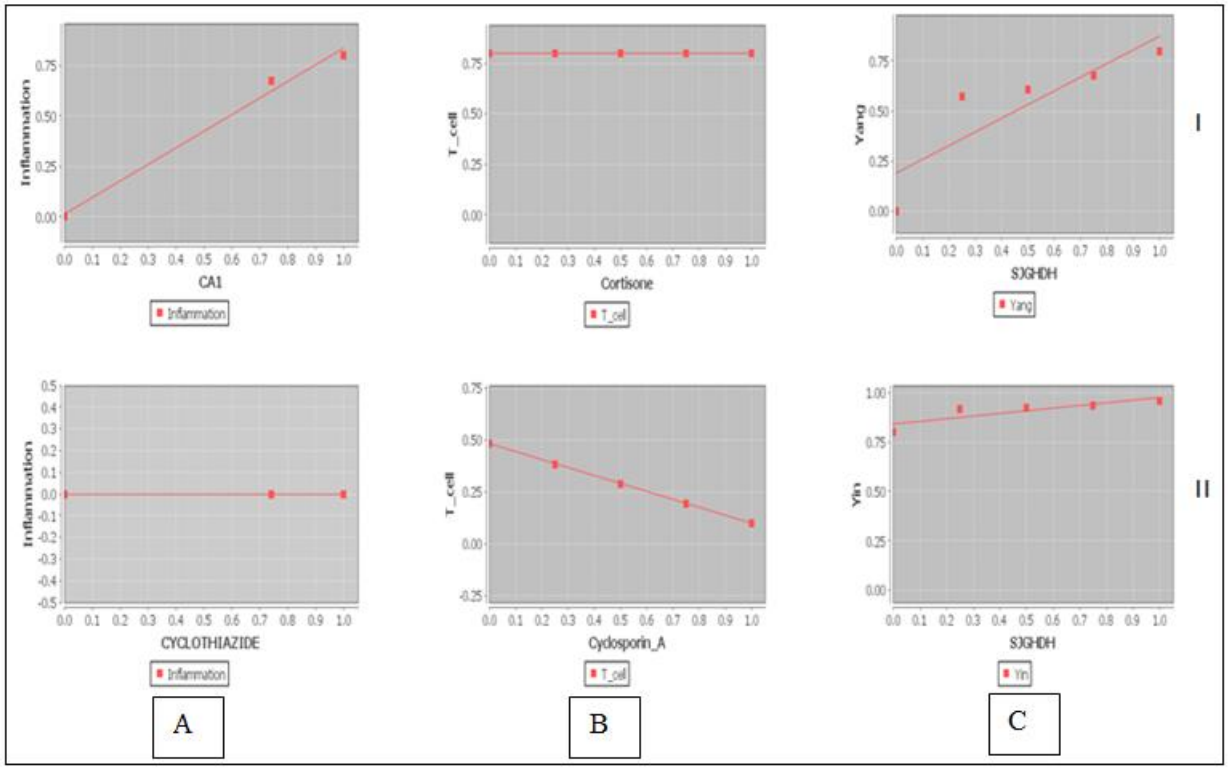

Fig-8: The python analyses support that an integration results such as CA1 will increase inflammation and high blood pressure although cyclothiazide can decrease high blood pressure and also can decrease inflammation (A); cyclosporin-A can inhibit T-cell activity related autoimmune response (B) and SJGHDH can increase Yin and Yang to treat LN related spleen-kidney yin deficiency and yang deficiency (C) from this GES pattern

Supplemental Result

Source	Target	Interaction
INS	INSR	+
INSR	IRS	+
IGF	INSR	+
INSR	IRS	+
IRS	PI3K	+
PI3K	PIP3	+
PIP3	PDK1	+
PDK1	AKT	+
AKT	TSC1/2	-
TSC1/2	Rheb	-
Rheb	mTORC1	+
mTORC1	HIF1-alpha	+
HIF1-alpha	VEGF	+
mTORC1	S6K1/2	+
S6K1/2	elF4B	+
S6K1/2	S6	+
mTORC1	4E-BP1	-
4E-BP1	elF4E1	-
mTORC1	ATG1	-
Rapamycin	mTORC1	-
mTORC1	PKC	+
BRAF	mTORC1	-
Stress	LKB1/STRAND/MO25	+
LKB1/STRAND/MO25	AMPK	+
AMPK	TSC1/2	+
TNF-alpha	IKK	+
IKK	TSC1/2	-
AMP	AMPK	+
Metformin	AMPK	+
AICAR	AMPK	+
Hypoxia	REDD1	+
REDD1	TSC1/2	+
INS	INSR	+
INSR	Ras	+
IGF	INSR	+
INSR	Ras	+
DOXYCYCLINE_CALCIUM	MMP8	-
BENDROFLUMETHIAZIDE	CA1	-
BENZTHIAZIDE	CA1	-
CEFDINIR	MPO	-
CYCLOTHIAZIDE	CA1	-
DIAZOXIDE	CA1	-
ETHINAMATE	CA1	-
HYDROCHLOROTHIAZIDE	CA1	-
HYDROFLUMETHIAZIDE	CA1	-
MELATONIN	MPO	-
METHYCLOTHIAZIDE	CA1	-

QUINETHAZONE	CA1	-
SODIUM_CARBONATE	CA1	-
CHLORTHALIDONE	CA1	-
DORZOLAMIDE	CA1	-
DOXYCYCLINE	MMP8	-
SULPIRIDE	CA1	-
TOPIRAMATE	CA1	-
METHOCARBAMOL	CA1	-
BRINZOLAMIDE	CA1	-
CHLORAL_BETAINE	ARG1	-
ZONISAMIDE	CA1	-
DOXYCYCLINE_CALCIUM	MMP8	-
IL1	MMP8	+
CEFDINIR	MPO	-
IL6	MPO	+
CHLORAL_BETAINE	ARG1	-
T_cell	ARG1	-
CYCLOTHIAZIDE	CA1	-
CA1	Inflammation	+
IL6	gp130	+
gp130	JAK	+
JAK	STAT3	+
STAT3	ISRE/GAS	+
STAT6	ISRE/GAS	+
ISRE/GAS	Inflammation	+
SHP1	JAK	-
JAK	gp130	+
PIAS	STAT3	-
SUMO	STAT3	-
PTP	STAT3	-
ISRE/GAS	SOCS3	+
SOCS3	JAK	-
INF	JAK	+
JAK	STAT1	+
STAT1	ISRE/GAS	+
STAT3	STAT1	+
STAT6	STAT1	+
TNF	TNFR	+
TNFR	TRADD/TRAF2/5	+
TRADD/TRAF2/5	RIP	+
A20	TRAF6	-
A20	RIP	-
CYLD	RAF2/5	-
CYLD	IKK	-
IL1	IL1R	+
IL1R	IRAK1/4/TRAF2/6	+
IRAK1/4/TRAF2/6	Pellino	+
Pellino	TRAF6	+
TRAF6	TAB2/TAB1/TAK1	+
TAB2/TAB1/TAK1	IKK	+

IKK	NF-KB	+
NF-KB	Inflammation	+
Hypoxia	HIF1-alpha	+
HIF1-alpha	NF-KB	-
HIF1-alpha	Inflammation	+
COX2	Inflammation	+
NSAID	COX2	-
Cortisone	COX2	-
CTX	T_cell	-
Cyclosporin_A	T_cell	-
T_cell	IL6	+
T_cell	TNF	+
T_cell	IL1	+
T_cell	INF	+
IL6	Inflammation	+
TNF	Inflammation	+
IL1	Inflammation	+
INF	Inflammation	+
M1	T_cell	+
T_cell	T_TfH	+
T_TfH	BCL6_IL21	+
T_cell	IL12_IFN_gamma	+
IL12_IFN_gamma	Th1	+
Th1	IL2_IFN_gamma_TNF_alpha	+
IL2_IFN_gamma_TNF_alpha	Autoimmunity	+
IL2_IFN_gamma_TNF_alpha	Cellular_immunity	+
T_cell	IL6_TGF_beta	+
IL6_TGF_beta	Th17	+
Th17	IL17	+
IL17	Autoimmune_process	+
Th17	Yang	+
GM_CSF	M2	+
M2	T_cell	+
T_cell	IL12_TGF_beta	+
nTreg	IL10_IL35_TGF_beta	+
T_cell	IL2_IL4	+
IL2_IL4	Th2	+
Th2	IL4_IL5_IL13	+
IL4_IL5_IL13	Immuno_complex	+
IL10_IL35_TGF_beta	iTreg	+
iTreg	M1	+
iTreg	IL10_TGF_beta	+
IL10_TGF_beta	immune_regulation	+
IL10_TGF_beta	Yin	+
JSW	Yang	+
WZXZ	Yang	+
GZDH	Yin	+
JJDH	Yin	+
SJDH	Yang	+
DBW	Yang	+

DHY	Yang	+
SJGHDH	Yang	+
SJDH	Yin	+
DBW	Yin	+
DHY	Yin	+
SJGHDH	Yin	+
JWBT	Yang	-
JWBT	Yin	-
LGP	Autoimmune_process	-

DISCUSSIONS AND CONCLUSION

The lupus nephritis is a severe disease and it will eventually develop into renal function failure. Although current medication including current administration and current Chinese medication can be used to this kind of disease, they still cannot control the disease exacerbation very well. When human genomics have been decoded in 2004, it will produce a new hope for clinical scientists and medical doctors to treat the uncured disease. Here we first studied a group of LN genomic data to set up a construction and then we combined current medication and traditional Chinese Medicine treatment to configure this integration modeling.

Since the integration model is primarily developed by a group of genomic data, some comprehensive network mechanism with their treatment compounds, in the next step, we will further develop second-generation construction with a set of clinical genomic data from patients including patient symptoms, laboratory results and drug priority-order following the first-generation module. Finally, the feasible module will be used by medical doctor to prescribe drugs according to personal genomics information, patient symptom, different lab results. Theoretically, the feasible module should be better than lonely method to treat Lupus Nephritis by only current immune suppress medication or by only traditional Chinese Medication.

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Under the support of Dr. H. D. Preisler, we have set up different methods and models to analyze genomic profiles such as CD3, CD4 and CD8 from immune and tumor diseases related personalized therapy. This clinical application was previously supported by National Cancer Institute IRG-91-022-09, USA (to BL).

Mention of trade names or commercial products in this article is solely for the purpose of providing specific information and does not imply recommendation.

Authors Contributions

WL analyze topology and quantitative network under guidance of BL, XY and BL modify bioinformatics fields including python scripts; YW give us clinical support to some drugs definition; BL conceived and designed the experiments.

Competing Interest Statements

The authors declare no financial interests.

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Table-1

Gene symbol	Gene name	Renal vs Non-renal		Lupus vs Control	
		Fold- Change (Log2)	q value	Fold-Change (Log2)	q value
OLFM4	olfactomedin 4	1.8	0.16	1.19	0.717
CEACAM6	carcinoembryonic antigen-related cell adhesion molecule 6	1.72	0.16	1.04	0.722
CEACAM8	carcinoembryonic antigen-related cell adhesion molecule 8	1.63	0.172	1.22	0.692
MMP8	matrix metallopeptidase 8	1.6	0.184	1.7	0.417
LTF	lactotransferrin	1.58	0.172	1.04	0.773
DEFA4	defensin, alpha 4	1.46	0.16	0.97	0.661
DEFA3/1	defensin, alpha 3/1	1.43	0.238	1.79	0.475
DAAM2	dishevelled associated activator of morphogenesis 2	1.43	0.16	0.04	0.997
CNTNAP3	contactin associated protein-like 3	1.32	0.155	-1.18	0.188
MS4A3	membrane-spanning 4-domains, subfamily A, member 3	1.27	0.165	0.96	0.657
ARG1	arginase 1	1.25	0.17	0.19	0.989
MPO	myeloperoxidase	1.23	0.16	0.57	0.826
ABCA13	ATP-binding cassette, subfamily A, member 13	1.19	0.16	0.84	0.621
CA1	carbonic anhydrase 1	1.13	0.181	0.12	0.996
IFIT1B	interferon-induced protein with tetratricopeptide repeats 1B	1.12	0.178	0.11	0.996
CRISP3	cysteine-rich secretory protein 3	1.12	0.17	0.61	0.835
LCN2	lipocalin 2	1.1	0.181	0.8	0.724
BPI	bactericidal/permeability increasing protein	1.09	0.191	0.61	0.871
XK	X-linked K gene, Kell blood group	1.08	0.167	-0.02	0.999
CNTNAP3B	contactin associated protein-like 3B	1.05	0.155	-0.92	0.229
ARHGEF12	Rho guanine nucleotide exchange factor 12	1	0.16	0.02	0.999

Table-2

source	target	Interaction
INS	INSR	+
INSR	IRS	+
IGF	INSR	+
INSR	IRS	+
IRS	PI3K	+
PIP3	PDK1	+
PDK1	AKT	+
AKT	TSC1/2	-
TSC1/2	Rheb	-
Rheb	mTORC1	+
mTORC1	HIF1-alpha	+
HIF1-alpha	VEGF	+
mTORC1	S6K1/2	+
S6K1/2	elF4B	+
S6K1/2	S6	+
mTORC1	4E-BP1	-
4E-BP1	elF4E1	-
mTORC1	ATG1	-
Rapamycin	mTORC1	-
mTORC1	PKC	+
BRAF	mTORC1	-
Stress	LKB1/STRAND/MO25	+
LKB1/STRAND/MO25	AMPK	+
AMPK	TSC1/2	+
TNF-alpha	IKK	+
IKK	TSC1/2	-
AMP	AMPK	+
Metformin	AMPK	+
AICAR	AMPK	+
Hypoxia	REDD1	+
REDD1	TSC1/2	+
INS	INSR	+
INSR	Ras	+
IGF	INSR	+
INSR	Ras	+

Table-3

source	target	Interaction
IL6	gp130	+
gp130	JAK	+
JAK	STAT3	+
STAT3	ISRE/GAS	+
STAT6	ISRE/GAS	+
ISRE/GAS	Inflammation	+
SHP1	JAK	-
JAK	gp130	+
PIAS	STAT3	-
SUMO	STAT3	-
PTP	STAT3	-
ISRE/GAS	SOCS3	+
SOCS3	JAK	-
INF	JAK	+
JAK	STAT1	+
STAT1	ISRE/GAS	+
STAT3	STAT1	+
STAT6	STAT1	+
TNF	TNFR	+
TNFR	TRADD/TRAF2/5	+
TRADD/TRAF2/5	RIP	+
A20	TRAF6	-
A20	RIP	-
CYLD	RAF2/5	-
CYLD	IKK	-
IL1	IL1R	+
IL1R	IRAK1/4/TRAF2/6	+
IRAK1/4/TRAF2/6	Pellino	+
Pellino	TRAF6	+
TRAF6	TAB2/TAB1/TAK1	+
TAB2/TAB1/TAK1	IKK	+
IKK	NF-KB	+
NF-KB	Inflammation	+
Hypoxia	HIF1-alpha	+
HIF1-alpha	NF-KB	-
HIF1-alpha	Inflammation	+

Table-4

Source	targeting	interaction
M1	T_cell	+
T_cell	T_TfH	+
T_TfH	BCL6_IL21	+
T_cell	IL12_IFN_gamma	+
IL12_IFN_gamma	Th1	+
Th1	IL2_IFN_gamma_TNF_alpha	+
IL2_IFN_gamma_TNF_alpha	Autoimmunity	+
IL2_IFN_gamma_TNF_alpha	Cellular_immunity	+
T_cell	IL6_TGF_beta	+
IL6_TGF_beta	Th17	+
Th17	IL17	+
IL17	Autoimmune_process	+
Th17	Yang	+
GM_CSF	M2	+
M2	T_cell	+
T_cell	IL12_TGF_beta	+
nTreg	IL10_IL35_TGF_beta	+
T_cell	IL2_IL4	+
IL2_IL4	Th2	+
Th2	IL4_IL5_IL13	+
IL4_IL5_IL13	Immuno_complex	+
IL10_IL35_TGF_beta	iTreg	+
iTreg	M1	+
iTreg	IL10_TGF_beta	+
IL10_TGF_beta	immune_regulation	+
IL10_TGF_beta	Yin	+

Table-5

Matching.Attribute	name	AverageShortestPathLength	BetweennessCentrality	ClosenessCentrality	ClusteringCoefficient	Degree	Eccentricity	IsSingleNode	NeighborhoodConnectivity	NumberOfDirectedEdges	NumberOfUndirectedEdges	PartnerOfMultiEdgedNodePairs	Radiality	selected	SelfLoops	shared name	Stress	TopologicalCoefficient
INF	INF	3.921875	0.13575295	0.25498008	0	3	11	FALSE	9.66666667	3	0	0	0.828125	FALSE	0	INF	6080	0.376812
IL1	IL1	3.8984375	0.16459974	0.25651303	0	4	11	FALSE	7	4	0	0	0.829504	FALSE	0	IL1	6582	0.285714
TNF	TNF	3.9453125	0.12457349	0.25346535	0	3	11	FALSE	8.33333333	3	0	0	0.826746	FALSE	0	TNF	5932	0.385965
IL6	IL6	3.9296875	0.13674336	0.25447316	0	4	11	FALSE	7	4	0	0	0.827665	FALSE	0	IL6	6126	0.285714
Cyclosporin_A	Cyclosporin_A	5.015625	0	0.19937695	0	1	13	FALSE	14	1	0	0	0.763787	FALSE	0	Cyclosporin_A	0	0
T_cell	T_cell	4.0234375	0.50869423	0.24854369	0	14	12	FALSE	2.21428571	14	0	0	0.822151	FALSE	0	T_cell	23114	0.086735
CTX	CTX	5.015625	0	0.19937695	0	1	13	FALSE	14	1	0	0	0.763787	FALSE	0	CTX	0	0
Cortisone	Cortisone	5.609375	0	0.17827298	0	1	12	FALSE	3	1	0	0	0.72886	FALSE	0	Cortisone	0	0
NSAID	NSAID	5.609375	0	0.17827298	0	1	12	FALSE	3	1	0	0	0.72886	FALSE	0	NSAID	0	0
Inflammation	Inflammation	3.65625	0.61479454	0.27350427	0.02777778	9	10	FALSE	5.33333333	9	0	0	0.84375	FALSE	0	Inflammation	25032	0.126543
COX2	COX2	4.6171875	0.03112697	0.21658206	0	3	11	FALSE	3.66666667	3	0	0	0.787224	FALSE	0	COX2	1002	0.333333
CA1	CA1	4.3828125	0.24889272	0.22816399	0	18	11	FALSE	1.44444444	18	0	0	0.801011	FALSE	0	CA1	8262	0.055556
CYCLOTHIAZIDE	CYCLOTHIAZIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	CYCLOTHIAZIDE	0	0
ARG1	ARG1	5	0.015625	0.2	0	2	13	FALSE	7.5	2	0	0	0.764706	FALSE	0	ARG1	622	0.5
CHLORAL_BETAINE	CHLORAL_BETAINE	5.9921875	0	0.16688396	0	1	14	FALSE	2	1	0	0	0.706342	FALSE	0	CHLORAL_BETAINE	0	0
MPO	MPO	4.890625	0.03112697	0.20447284	0	3	12	FALSE	2	3	0	0	0.77114	FALSE	0	MPO	586	0.333333
CEFDINIR	CEFDINIR	5.8828125	0	0.16998672	0	1	13	FALSE	3	1	0	0	0.712776	FALSE	0	CEFDINIR	0	0
MMP8	MMP8	4.859375	0.03112697	0.20578778	0	3	12	FALSE	2	3	0	0	0.772978	FALSE	0	MMP8	554	0.333333
DOXYCYCLINE_CALCIUM	DOXYCYCLINE_CALCIUM	5.8515625	0	0.17089453	0	1	13	FALSE	3	1	0	0	0.714614	FALSE	0	DOXYCYCLINE_CALCIUM	0	0
ZONISAMIDE	ZONISAMIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	ZONISAMIDE	0	0
BRINZOLAMIDE	BRINZOLAMIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	BRINZOLAMIDE	0	0
METHOCARBAMOL	METHOCARBAMOL	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	METHOCARBAMOL	0	0
TOPIRAMATE	TOPIRAMATE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	TOPIRAMATE	0	0
SULPIRIDE	SULPIRIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	SULPIRIDE	0	0
DOXYCYCLINE	DOXYCYCLINE	5.8515625	0	0.17089453	0	1	13	FALSE	3	1	0	0	0.714614	FALSE	0	DOXYCYCLINE	0	0
DORZOLAMIDE	DORZOLAMIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	DORZOLAMIDE	0	0
CHLORTHALIDONE	CHLORTHALIDONE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	CHLORTHALIDONE	0	0
SODIUM_CARBONATE	SODIUM_CARBONATE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	SODIUM_CARBONATE	0	0
QUINETHAZONE	QUINETHAZONE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	QUINETHAZONE	0	0
METHYCLOTHIAZIDE	METHYCLOTHIAZIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	METHYCLOTHIAZIDE	0	0

MELATONIN	MELATONIN	5.8828125	0	0.16998672	0	1	13	FALSE	3	1	0	0	0.712776	FALSE	0	MELATONIN	0	0
HYDROFLUMETHIAZIDE	HYDROFLUMETHIAZIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	HYDROFLUMETHIAZIDE	0	0
HYDROCHLOROTHIAZIDE	HYDROCHLOROTHIAZIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	HYDROCHLOROTHIAZIDE	0	0
ETHINAMATE	ETHINAMATE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	ETHINAMATE	0	0
DIAZOXIDE	DIAZOXIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	DIAZOXIDE	0	0
BENZTHIAZIDE	BENZTHIAZIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	BENZTHIAZIDE	0	0
BENDROFLUMETHIAZIDE	BENDROFLUMETHIAZIDE	5.375	0	0.18604651	0	1	12	FALSE	18	1	0	0	0.742647	FALSE	0	BENDROFLUMETHIAZIDE	0	0
Ras	Ras	11.7265625	0	0.08527648	0	2	17	FALSE	4	2	0	1	0.369026	FALSE	0	Ras	0	0
REDD1	REDD1	5.5625	0.00381398	0.17977528	0	2	10	FALSE	3.5	2	0	0	0.731618	FALSE	0	REDD1	114	0.5
Hypoxia	Hypoxia	4.96875	0.01300033	0.20125786	0	2	9	FALSE	3.5	2	0	0	0.766544	FALSE	0	Hypoxia	512	0.5
AICAR	AICAR	7.203125	0	0.13882863	0	1	12	FALSE	5	1	0	0	0.63511	FALSE	0	AICAR	0	0
Metformin	Metformin	7.203125	0	0.13882863	0	1	12	FALSE	5	1	0	0	0.63511	FALSE	0	Metformin	0	0
AMP	AMP	7.203125	0	0.13882863	0	1	12	FALSE	5	1	0	0	0.63511	FALSE	0	AMP	0	0
IKK	IKK	4.7421875	0.25789452	0.21087315	0	5	9	FALSE	2.6	5	0	0	0.779871	FALSE	0	IKK	9404	0.2
TNF-alpha	TNF-alpha	5.734375	0	0.17438692	0	1	10	FALSE	5	1	0	0	0.721507	FALSE	0	TNF-alpha	0	0
AMPK	AMPK	6.2109375	0.07677165	0.16100629	0	5	11	FALSE	2	5	0	0	0.693474	FALSE	0	AMPK	2528	0.2
LKB1/STRAND/MO25	LKB1/STRAND/MO25	7.1875	0.015625	0.13913043	0	2	12	FALSE	3	2	0	0	0.636029	FALSE	0	LKB1/STRAND/MO25	510	0.5
Stress	Stress	8.1796875	0	0.12225406	0	1	13	FALSE	2	1	0	0	0.577665	FALSE	0	Stress	0	0
BRAF	BRAF	5.8203125	0	0.17181208	0	1	10	FALSE	8	1	0	0	0.716452	FALSE	0	BRAF	0	0
PKC	PKC	5.8203125	0	0.17181208	0	1	10	FALSE	8	1	0	0	0.716452	FALSE	0	PKC	0	0
Rapamycin	Rapamycin	5.8203125	0	0.17181208	0	1	10	FALSE	8	1	0	0	0.716452	FALSE	0	Rapamycin	0	0
ATG1	ATG1	5.8203125	0	0.17181208	0	1	10	FALSE	8	1	0	0	0.716452	FALSE	0	ATG1	0	0
eIF4E1	eIF4E1	6.796875	0	0.14712644	0	1	11	FALSE	2	1	0	0	0.659007	FALSE	0	eIF4E1	0	0
4E-BP1	4E-BP1	5.8046875	0.015625	0.17227456	0	2	10	FALSE	4.5	2	0	0	0.717371	FALSE	0	4E-BP1	520	0.5
S6	S6	6.78125	0	0.14746544	0	1	11	FALSE	3	1	0	0	0.659926	FALSE	0	S6	0	0
eIF4B	eIF4B	6.78125	0	0.14746544	0	1	11	FALSE	3	1	0	0	0.659926	FALSE	0	eIF4B	0	0
S6K1/2	S6K1/2	5.7890625	0.03112697	0.17273954	0	3	10	FALSE	3.33333333	3	0	0	0.71829	FALSE	0	S6K1/2	1038	0.333333
VEGF	VEGF	5.234375	0	0.19104478	0	1	11	FALSE	5	1	0	0	0.750919	FALSE	0	VEGF	0	0
HIF1-alpha	HIF1-alpha	4.2421875	0.16662566	0.23572744	0.1	5	10	FALSE	4.6	5	0	0	0.809283	FALSE	0	HIF1-alpha	6340	0.222222
mTORC1	mTORC1	4.828125	0.14815043	0.20711974	0	8	9	FALSE	2	8	0	0	0.774816	FALSE	0	mTORC1	5094	0.125
Rheb	Rheb	5.421875	0.02632874	0.18443804	0	2	10	FALSE	6.5	2	0	0	0.73989	FALSE	0	Rheb	564	0.5
TSC1/2	TSC1/2	5.296875	0.22363025	0.18879056	0	5	10	FALSE	3.2	5	0	0	0.747243	FALSE	0	TSC1/2	7582	0.2
AKT	AKT	6.1640625	0.11811024	0.16223067	0	2	11	FALSE	3.5	2	0	0	0.696232	FALSE	0	AKT	3968	0.5
PDK1	PDK1	7.046875	0.10420768	0.14190687	0	2	12	FALSE	2	2	0	0	0.644301	FALSE	0	PDK1	3486	0.5
PIP3	PIP3	7.9453125	0.09005906	0.12586037	0	2	13	FALSE	2	2	0	0	0.591452	FALSE	0	PIP3	3000	0.5
PI3K	PI3K	8.859375	0.07566437	0.11287478	0	2	14	FALSE	2	2	0	0	0.537684	FALSE	0	PI3K	2510	0.5
IGF	IGF	11.7265625	0	0.08527648	0	2	17	FALSE	4	2	0	1	0.369026	FALSE	0	IGF	0	0
IRS	IRS	9.7890625	0.06102362	0.10215483	0	3	15	FALSE	3	3	0	1	0.482996	FALSE	0	IRS	2016	0.5
INSR	INSR	10.734375	0.04650591	0.09315866	0	8	16	FALSE	1.25	8	0	4	0.42739	FALSE	0	INSR	1524	0.25
INS	INS	11.7265625	0	0.08527648	0	2	17	FALSE	4	2	0	1	0.369026	FALSE	0	INS	0	0
Yin	Yin	7.171875	0.0382628	0.13943355	0	8	16	FALSE	1.875	8	0	0	0.636949	FALSE	0	Yin	1680	0.291667
immune_regulation	immune_regulation	7.3984375	0	0.13516367	0	1	16	FALSE	3	1	0	0	0.623621	FALSE	0	immune_regulation	0	0
IL10_TGF_beta	IL10_TGF_beta	6.40625	0.0601624	0.15609756	0	3	15	FALSE	4	3	0	0	0.681985	FALSE	0	IL10_TGF_beta	2578	0.333333
iTreg	iTreg	5.6328125	0.09830217	0.17753121	0	3	14	FALSE	2.33333333	3	0	0	0.727482	FALSE	0	iTreg	4222	0.333333
Immuno_complex	Immuno_complex	7.8984375	0	0.12660732	0	1	16	FALSE	2	1	0	0	0.59421	FALSE	0	Immuno_complex	0	0
IL4_IL5_IL13	IL4_IL5_IL13	6.90625	0.015625	0.14479638	0	2	15	FALSE	1.5	2	0	0	0.652574	FALSE	0	IL4_IL5_IL13	622	0.5
Th2	Th2	5.9296875	0.03100394	0.16864295	0	2	14	FALSE	2	2	0	0	0.710018	FALSE	0	Th2	1240	0.5
IL2_IL4	IL2_IL4	4.96875	0.04613681	0.20125786	0	2	13	FALSE	8	2	0	0	0.766544	FALSE	0	IL2_IL4	1854	0.5
IL10_IL35_TGF_beta	IL10_IL35_TGF_beta	6.609375	0.015625	0.15130024	0	2	15	FALSE	2	2	0	0	0.670037	FALSE	0	IL10_IL35_TGF_beta	646	0.5
nTreg	nTreg	7.6015625	0	0.1315519	0	1	16	FALSE	2	1	0	0	0.611673	FALSE	0	nTreg	0	0
IL12_TGF_beta	IL12_TGF_beta	5.015625	0	0.19937695	0	1	13	FALSE	14	1	0	0	0.763787	FALSE	0	IL12_TGF_beta	0	0

M2	M2	5	0.015625	0.2	0	2	13	FALSE	7.5	2	0	0	0.764706	FALSE	0	M2	622	0.5
GM_CSF	GM_CSF	5.9921875	0	0.16688396	0	1	14	FALSE	2	1	0	0	0.706342	FALSE	0	GM_CSF	0	0
Yang	Yang	6.34375	0.10346949	0.15763547	0	8	15	FALSE	1.875	8	0	0	0.685662	FALSE	0	Yang	4580	0.291667
Autoimmune_process	Autoimmune_process	7.5	0.015625	0.13333333	0	2	16	FALSE	1.5	2	0	0	0.617647	FALSE	0	Autoimmune_process	662	0.5
IL17	IL17	6.5234375	0.03100394	0.15329341	0	2	15	FALSE	2.5	2	0	0	0.675092	FALSE	0	IL17	1320	0.5
Th17	Th17	5.5625	0.15317421	0.17977528	0	3	14	FALSE	4	3	0	0	0.731618	FALSE	0	Th17	6682	0.333333
IL6_TGF_beta	IL6_TGF_beta	4.8046875	0.16031004	0.20813008	0	2	13	FALSE	8.5	2	0	0	0.776195	FALSE	0	IL6_TGF_beta	7022	0.5
Cellular_immunity	Cellular_immunity	7.8515625	0	0.12736318	0	1	16	FALSE	3	1	0	0	0.596967	FALSE	0	Cellular_immunity	0	0
Autoimmunity	Autoimmunity	7.8515625	0	0.12736318	0	1	16	FALSE	3	1	0	0	0.596967	FALSE	0	Autoimmunity	0	0
IL2_IFN_gamma_TNF_alpha	IL2_IFN_gamma_TNF_alpha	6.859375	0.03112697	0.14578588	0	3	15	FALSE	1.3333333	3	0	0	0.655331	FALSE	0	IL2_IFN_gamma_TNF_alpha	1242	0.333333
Th1	Th1	5.8984375	0.04613681	0.16953642	0	2	14	FALSE	2.5	2	0	0	0.711857	FALSE	0	Th1	1854	0.5
IL12_IFN_gamma	IL12_IFN_gamma	4.953125	0.06102362	0.20189274	0	2	13	FALSE	8	2	0	0	0.767463	FALSE	0	IL12_IFN_gamma	2464	0.5
BCL6_IL21	BCL6_IL21	5.9921875	0	0.16688396	0	1	14	FALSE	2	1	0	0	0.706342	FALSE	0	BCL6_IL21	0	0
T_TfH	T_TfH	5	0.015625	0.2	0	2	13	FALSE	7.5	2	0	0	0.764706	FALSE	0	T_TfH	622	0.5
M1	M1	4.8515625	0.1074065	0.20611916	0	2	13	FALSE	8.5	2	0	0	0.773438	FALSE	0	M1	4690	0.5
LGP	LGP	8.4921875	0	0.11775529	0	1	17	FALSE	2	1	0	0	0.559283	FALSE	0	LGP	0	0
JWBT	JWBT	7.203125	0.0011565	0.13882863	0	2	16	FALSE	8	2	0	0	0.63511	FALSE	0	JWBT	94	0.7
SJGHDH	SJGHDH	7.203125	0.0011565	0.13882863	0	2	16	FALSE	8	2	0	0	0.63511	FALSE	0	SJGHDH	94	0.7
DHY	DHY	7.203125	0.0011565	0.13882863	0	2	16	FALSE	8	2	0	0	0.63511	FALSE	0	DHY	94	0.7
DBW	DBW	7.203125	0.0011565	0.13882863	0	2	16	FALSE	8	2	0	0	0.63511	FALSE	0	DBW	94	0.7
SJDH	SJDH	7.203125	0.0011565	0.13882863	0	2	16	FALSE	8	2	0	0	0.63511	FALSE	0	SJDH	94	0.7
JJDH	JJDH	8.1640625	0	0.12248804	0	1	17	FALSE	8	1	0	0	0.578585	FALSE	0	JJDH	0	0
GZDH	GZDH	8.1640625	0	0.12248804	0	1	17	FALSE	8	1	0	0	0.578585	FALSE	0	GZDH	0	0
WZXZ	WZXZ	7.3359375	0	0.13631523	0	1	16	FALSE	8	1	0	0	0.627298	FALSE	0	WZXZ	0	0
JSW	JSW	7.3359375	0	0.13631523	0	1	16	FALSE	8	1	0	0	0.627298	FALSE	0	JSW	0	0
NF-KB	NF-KB	4.1640625	0.23849656	0.24015009	0.333333333	3	9	FALSE	6.33333333	3	0	0	0.813879	FALSE	0	NF-KB	9242	0.375
TAB2/TAB1/TAK1	TAB2/TAB1/TAK1	5.6328125	0.02620571	0.17753121	0	2	10	FALSE	4	2	0	0	0.727482	FALSE	0	TAB2/TAB1/TAK1	566	0.5
Pellino	Pellino	6.1171875	0.00971949	0.16347382	0	2	11	FALSE	2.5	2	0	0	0.698989	FALSE	0	Pellino	160	0.5
IRAK1/4/TRAF2/6	IRAK1/4/TRAF2/6	5.5625	0.01755249	0.17977528	0	2	12	FALSE	2	2	0	0	0.731618	FALSE	0	IRAK1/4/TRAF2/6	320	0.5
IL1R	IL1R	4.8125	0.02924049	0.20779221	0	2	12	FALSE	3	2	0	0	0.775735	FALSE	0	IL1R	532	0.5
RAF2/5	RAF2/5	6.7109375	0	0.14901048	0	1	11	FALSE	2	1	0	0	0.664063	FALSE	0	RAF2/5	0	0
CYLD	CYLD	5.71875	0.015625	0.17486339	0	2	10	FALSE	3	2	0	0	0.722426	FALSE	0	CYLD	524	0.5
TRAF6	TRAF6	6.1640625	0.01943898	0.16223067	0	3	10	FALSE	2	3	0	0	0.696232	FALSE	0	TRAF6	434	0.333333
A20	A20	6.7734375	0.0054749	0.14763552	0	2	11	FALSE	2.5	2	0	0	0.660386	FALSE	0	A20	112	0.5
RIP	RIP	6.3515625	0.01000656	0.15744157	0	2	12	FALSE	2	2	0	0	0.685202	FALSE	0	RIP	236	0.5
TRADD/TRAF2/5	TRADD/TRAF2/5	5.7734375	0.02027969	0.17320704	0	2	13	FALSE	2	2	0	0	0.71921	FALSE	0	TRADD/TRAF2/5	408	0.5
TNFR	TNFR	4.8671875	0.03338255	0.20545746	0	2	12	FALSE	2.5	2	0	0	0.772518	FALSE	0	TNFR	666	0.5
STAT1	STAT1	5.1015625	0.00179831	0.19601838	0.5	4	12	FALSE	4.75	4	0	0	0.758732	FALSE	0	STAT1	104	0.395833
SOCS3	SOCS3	5.140625	1.13E-04	0.19452888	0	2	12	FALSE	5.5	2	0	0	0.756434	FALSE	0	SOCS3	6	0.642857
PTP	PTP	6.078125	0	0.16452442	0	1	13	FALSE	6	1	0	0	0.701287	FALSE	0	PTP	0	0
SUMO	SUMO	6.078125	0	0.16452442	0	1	13	FALSE	6	1	0	0	0.701287	FALSE	0	SUMO	0	0
PIAS	PIAS	6.078125	0	0.16452442	0	1	13	FALSE	6	1	0	0	0.701287	FALSE	0	PIAS	0	0
SHP1	SHP1	5.7265625	0	0.17462483	0	1	13	FALSE	6	1	0	0	0.721967	FALSE	0	SHP1	0	0
STAT6	STAT6	5.484375	0	0.18233618	1	2	12	FALSE	4.5	2	0	0	0.736213	FALSE	0	STAT6	0	0.75
ISRE/GAS	ISRE/GAS	4.5234375	0.06875	0.22107081	0.2	5	11	FALSE	4.6	5	0	0	0.792739	FALSE	0	ISRE/GAS	1428	0.28
STAT3	STAT3	5.0859375	0.04661868	0.19662058	0.133333333	6	12	FALSE	3	6	0	0	0.759651	FALSE	0	STAT3	804	0.277778
JAK	JAK	4.734375	0.05055979	0.21122112	0.066666667	7	12	FALSE	3	7	0	1	0.780331	FALSE	0	JAK	952	0.233333
gp130	gp130	4.78125	0.00246063	0.20915033	0	3	12	FALSE	5	3	0	1	0.777574	FALSE	0	gp130	64	0.5

Table-6

Source	Target	Interaction
INS	INSR	+
INSR	IRS	+
IGF	INSR	+
INSR	IRS	+
IRS	PI3K	+
PI3K	PIP3	+
PIP3	PDK1	+
PDK1	AKT	+
AKT	TSC1/2	-
TSC1/2	Rheb	-
Rheb	mTORC1	+
mTORC1	HIF1-alpha	+
HIF1-alpha	VEGF	+
mTORC1	S6K1/2	+
S6K1/2	elF4B	+
S6K1/2	S6	+
mTORC1	4E-BP1	-
4E-BP1	elF4E1	-
mTORC1	ATG1	-
Rapamycin	mTORC1	-
mTORC1	PKC	+
BRAF	mTORC1	-
Stress	LKB1/STRAND/MO25	+
LKB1/STRAND/MO25	AMPK	+
AMPK	TSC1/2	+
TNF-alpha	IKK	+
IKK	TSC1/2	-
AMP	AMPK	+
Metformin	AMPK	+
AICAR	AMPK	+
Hypoxia	REDD1	+
REDD1	TSC1/2	+
INS	INSR	+
INSR	Ras	+
IGF	INSR	+
INSR	Ras	+
DOXYCYCLINE_CALCIUM	MMP8	-
BENDROFLUMETHIAZIDE	CA1	-
BENZTHIAZIDE	CA1	-
CEFDINIR	MPO	-
CYCLOTHIAZIDE	CA1	-
DIAZOXIDE	CA1	-
ETHINAMATE	CA1	-
HYDROCHLOROTHIAZIDE	CA1	-
HYDROFLUMETHIAZIDE	CA1	-
MELATONIN	MPO	-

METHYCLOTHIAZIDE	CA1	-
QUINETHAZONE	CA1	-
SODIUM_CARBONATE	CA1	-
CHLORTHALIDONE	CA1	-
DORZOLAMIDE	CA1	-
DOXYCYCLINE	MMP8	-
SULPIRIDE	CA1	-
TOPIRAMATE	CA1	-
METHOCARBAMOL	CA1	-
BRINZOLAMIDE	CA1	-
CHLORAL_BETAINE	ARG1	-
ZONISAMIDE	CA1	-
DOXYCYCLINE_CALCIUM	MMP8	-
IL1	MMP8	+
CEFDINIR	MPO	-
IL6	MPO	+
CHLORAL_BETAINE	ARG1	-
T_cell	ARG1	-
CYCLOTHIAZIDE	CA1	-
CA1	Inflammation	+
IL6	gp130	+
gp130	JAK	+
JAK	STAT3	+
STAT3	ISRE/GAS	+
STAT6	ISRE/GAS	+
ISRE/GAS	Inflammation	+
SHP1	JAK	-
JAK	gp130	+
PIAS	STAT3	-
SUMO	STAT3	-
PTP	STAT3	-
ISRE/GAS	SOCS3	+
SOCS3	JAK	-
INF	JAK	+
JAK	STAT1	+
STAT1	ISRE/GAS	+
STAT3	STAT1	+
STAT6	STAT1	+
TNF	TNFR	+
TNFR	TRADD/TRAF2/5	+
TRADD/TRAF2/5	RIP	+
A20	TRAF6	-
A20	RIP	-
CYLD	RAF2/5	-
CYLD	IKK	-
IL1	IL1R	+
IL1R	IRAK1/4/TRAF2/6	+
IRAK1/4/TRAF2/6	Pellino	+

Pellino	TRAF6	+
TRAF6	TAB2/TAB1/TAK1	+
TAB2/TAB1/TAK1	IKK	+
IKK	NF-KB	+
NF-KB	Inflammation	+
Hypoxia	HIF1-alpha	+
HIF1-alpha	NF-KB	-
HIF1-alpha	Inflammation	+
COX2	Inflammation	+
NSAID	COX2	-
Cortisone	COX2	-
CTX	T_cell	-
Cyclosporin_A	T_cell	-
T_cell	IL6	+
T_cell	TNF	+
T_cell	IL1	+
T_cell	INF	+
IL6	Inflammation	+
TNF	Inflammation	+
IL1	Inflammation	+
INF	Inflammation	+
M1	T_cell	+
T_cell	T_TfH	+
T_TfH	BCL6_IL21	+
T_cell	IL12_IFN_gamma	+
IL12_IFN_gamma	Th1	+
Th1	IL2_IFN_gamma_TNF_alpha	+
IL2_IFN_gamma_TNF_alpha	Autoimmunity	+
IL2_IFN_gamma_TNF_alpha	Cellular_immunity	+
T_cell	IL6_TGF_beta	+
IL6_TGF_beta	Th17	+
Th17	IL17	+
IL17	Autoimmune_process	+
Th17	Yang	+
GM_CSF	M2	+
M2	T_cell	+
T_cell	IL12_TGF_beta	+
nTreg	IL10_IL35_TGF_beta	+
T_cell	IL2_IL4	+
IL2_IL4	Th2	+
Th2	IL4_IL5_IL13	+
IL4_IL5_IL13	Immuno_complex	+
IL10_IL35_TGF_beta	iTreg	+
iTreg	M1	+
iTreg	IL10_TGF_beta	+
IL10_TGF_beta	immune_regulation	+
IL10_TGF_beta	Yin	+
JSW	Yang	+

WZXZ	Yang	+
GZDH	Yin	+
JJDH	Yin	+
SJDH	Yang	+
DBW	Yang	+
DHY	Yang	+
SJGHDH	Yang	+
SJDH	Yin	+
DBW	Yin	+
DHY	Yin	+
SJGHDH	Yin	+
JWBT	Yang	-
JWBT	Yin	-
LGP	Autoimmune_process	-