#### Alcohol 48 (2014) 603-610



Contents lists available at ScienceDirect

# Alcohol

journal homepage: http://www.alcoholjournal.org/

# Ethanol treatment of lymphoblastoid cell lines from alcoholics and non-alcoholics causes many subtle changes in gene expression



LCOHOL

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Keywords: Alcoholism Gene expression Lymphoblastoid cell lines NFkappaB Cytokines TNF

## ABSTRACT

To elucidate the effects of a controlled exposure to ethanol on gene expression, we studied lymphoblastoid cell lines (LCLs) from 21 alcoholics and 21 controls. We cultured each cell line for 24 h with and without 75 mM ethanol and measured gene expression using microarrays. Differences in expression between LCLs from alcoholics and controls included 13 genes previously identified as associated with alcoholism or related traits, including *KCNA3*, *DICER1*, *ZNF415*, *CAT*, *SLC9A9*, and *PPARGC1B*. The paired design allowed us to detect very small changes due to ethanol treatment: ethanol altered the expression of 37% of the probe sets (51% of the unique named genes) expressed in these LCLs, most by modest amounts. Ninety-nine percent of the named genes expressed in the LCLs were also expressed in brain. Key pathways affected by ethanol include cytokine, TNF, and NFkB signaling. Among the genes affected by ethanol were *ANK3*, *EPHB1*, *SLC1A1*, *SLC9A9*, *NRD1*, and *SH3BP5*, which were reported to be associated with alcoholism or related phenotypes in 2 genome-wide association studies. Genes that either differed in expression between alcoholics and controls or were affected by ethanol exposure are candidates for further study.

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# Introduction

Alcoholism is a major health problem around the world (World Health Organization, 2011). It is a complex disease with both genetic and environmental contributions to risk, and the interplay between genes and environment is likely to be important (Edenberg & Foroud, 2006; Enoch, 2012; Meyers & Dick, 2010; Rietschel & Treutlein, 2013). Alcoholism and alcoholic organ damage are consequences of repeated exposures to high levels of ethanol over long periods (Koob & Le Moal, 2005; Laakso et al., 2000; Parry, Patra, & Rehm, 2011). Understanding how cells and organs are affected by ethanol can provide clues about mechanisms of toxicity and protection. Studies of gene expression can also complement linkage and association studies, by pointing to genes that differ in basal expression between alcoholics and controls and also to genes whose expression is altered temporarily or permanently by ethanol exposure. Nicolae et al. (2010) showed that

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trait-associated single nucleotide polymorphisms (SNPs) are more likely to affect gene expression in LCLs (i.e., to be expression quantitative trait loci [QTLs]), and that application of this information can enhance discovery of trait-associated SNPs for complex phenotypes.

Gene expression has been profiled in post-mortem human brain from alcoholics and controls (Flatscher-Bader et al., 2005; Iwamoto et al., 2004; Liu, Lewohl, Harris, Dodd, & Mayfield, 2007; Liu et al., 2006; Mayfield et al., 2002; McClintick et al., 2013). Those data, while important, do not allow one to disentangle the effects of longterm alcohol exposure and pre-existing expression differences. Animal models have been used to detect both innate differences in gene expression (Edenberg et al., 2005; Kimpel et al., 2007) and differences due to alcohol consumption (Rodd et al., 2008). However, for studies of living humans an accessible tissue such as blood or a cell culture surrogate such as Epstein-Barr virus (EBV) transformed LCLs can be of great value. Thibault, Hassan, and Miles (2005) concluded that in vitro assays in human cell lines are valuable for identifying changes in expression profiles upon exposure to ethanol and other drugs of addiction. Gene expression profiles of LCLs are most like the B cells from which they were derived (Min et al., 2010). They can provide insights into immune response

<sup>0741-8329/\$ –</sup> see front matter © 2014 Elsevier Inc. All rights reserved. http://dx.doi.org/10.1016/j.alcohol.2014.07.004

mechanisms that play an important role in alcoholism and its effects on the brain (Crews, Zou, & Qin, 2011; Mayfield, Ferguson, & Harris, 2013; McClintick et al., 2013). A recent study has shown substantial overlap in expression between blood and many tissues, including many regions of the brain (Sullivan, Fan, & Perou, 2006; Wright et al., 2014), suggesting they also provide a window on many otherwise inaccessible processes. LCLs have been used in the study of other complex diseases, including autism. Nishimura et al. (2007) used expression profiling of LCLs from patients affected with autism and compared the results to controls to find different sets of dysregulated genes for 2 different subtypes of autism.

We have analyzed both basal gene expression and the effects of ethanol on gene expression in LCLs from 21 alcoholics and 21 controls. We have detected differences in gene expression between LCLs from alcoholics and controls and differences caused by the ethanol exposure. Most of the effects of ethanol were modest, but the effects highlighted pathways that have changes in many genes. We have also examined the overlap between the differences we detect in LCL gene expression and the results of expression studies in brain and with data from genome-wide association studies (GWAS) to identify and prioritize promising candidate genes for association and functional studies.

### Methods

## Cell growth

Immortalized lymphoblastoid cell lines (LCLs) were created from peripheral blood mononuclear cells isolated from subjects recruited as part of the Collaborative Study on the Genetics of Alcoholism (Begleiter et al., 1995; Bierut et al., 2010; Edenberg & Foroud, 2006). Immortalization was by transformation with Epstein–Barr virus and early passage (>12) cultures were used. In a test of the effects of ethanol on cell growth,  $2 \times 10^6$  LCLs from each of 3 individuals were cultured in the presence of 0, 50, 75, or 100 mM ethanol in 10 mL RPMI1640 medium supplemented with 15% FBS, 2 mM glutamine, 50 U/mL penicillin, and 50 µg/mL streptomycin at 37 °C. For each treatment (cell line and ethanol concentration), 5 identical parallel flasks were seeded. At a given time, cells in 1 flask were counted twice, and the average number was used to calculate a growth curve and doubling time for each individual.

## Microarray analysis of LCLs

For the microarray experiment,  $2 \times 10^6$  LCLs from each of 21 alcoholics and 21 non-alcoholics were seeded in 10 mL of RPMI1640 medium supplemented with 15% FBS, 2 mM glutamine, 50 U/mL penicillin, and 50 µg/mL streptomycin. Cultures were maintained in tightly capped flasks to minimize evaporation. Alcoholics were defined as meeting DSM-IV criteria for alcohol dependence (American Psychiatric Association, 1994) at age 18 years or younger. Non-alcoholics were defined as having taken at least 1 drink of alcohol and not meeting any of 4 definitions of alcohol dependence: DSM-IV (American Psychiatric Association, 1994), DSM-IIIR (American Psychiatric Association, 1987), ICD-10 (World Health Organization, 1993), or Feighner definite alcoholism (Feighner et al., 1972); none was dependent on any illicit drug. Each phenotypic group (alcoholic or non-alcoholic) contained 12 males and 9 females. Growth of ethanol-treated and untreated cells was parallel by 22 h even up to 100 mM ethanol; we chose 75 mM to be within this range and to offer a good possibility of discerning effects. Cells were cultured in the absence or presence of 75 mM ethanol for 24 h, at which time cells were harvested and lysed with buffer RLT, supplied in the Qiagen RNeasy kit, and RNA extractions were conducted per the manufacturer's protocol.

Reverse transcription and labeling used the Affymetrix 3' IVT labeling kit and protocols (GeneChip<sup>®</sup> Expression Analysis Technical Manual, Affymetrix, Santa Clara, CA). Samples were labeled in groups balanced by sex and phenotype to the extent possible; pairs of treated and untreated samples from the same individual were labeled and hybridized at the same time. Samples were hybridized to Affymetrix HG U133 Plus 2 GeneChips<sup>®</sup> for 17 h, then washed and stained using the standard Affymetrix protocols. GeneChips<sup>®</sup> were scanned using an Affymetrix Model 3000 scanner controlled by GCOS software (Affymetrix, Santa Clara, CA). MAS5 signals and detection calls were generated by GCOS. Data are available from NCBI GEO, Accession number GSE52553.

To avoid analyzing genes that were not expressed, only probe sets that were called "present" in at least 33% of the arrays in at least 1 experimental group (phenotype, treatment, sex) were selected for analysis (McClintick & Edenberg, 2006). Using these criteria, 31,528 of the 54,675 probe sets on the GeneChips were retained for analvsis. The MAS5 data were imported into Partek Genomics Suite (Partek Inc., St. Louis, Mo.). Because we expected cell lines from different individuals to differ, analysis was done using a general linear method with repeated measures for 0 and 75 mM ethanol; the main effects factors were ethanol treatment, phenotype (alcoholic vs. non-alcoholic), sex, and labeling batch. Addition of the 3 interaction terms (sex\*treatment, sex\*phenotype, and phenotype\*treatment) to the model did not improve the results; none of the interaction terms reached significance after correcting for multiple testing. Therefore, we present the data from the simpler model with main effects only. The *p* values for each factor tested were imported into R to compute false discovery rate (FDR) using the Storey qvalue package (Storey & Tibshirani, 2003). Partek Genomics Suite was used for hierarchical clustering of the arrays using Euclidean distance and average linkage.

Genes that were differentially expressed either by alcohol treatment or by phenotype were analyzed using Ingenuity Pathway Analysis (Ingenuity<sup>®</sup> Systems, spring 2013 release). Duplicate probe sets were eliminated by selecting the entry with the best *p* value. Parameters were set to use the Ingenuity knowledge base as the reference set. Due to the large number of genes that were differentially expressed after ethanol treatment, we limited the analysis to those genes with FDR  $\leq$  0.05 and minimum absolute fold change  $\geq$ 1.2; for phenotype, FDR was set at  $\leq$ 0.36 with no minimum fold change. We used the canonical pathway analysis to identify modified pathways and the upstream regulator analysis to identify putative factors responsible for the changes in expression. The upstream regulator analysis looks for transcription factors, cytokines, hormones, vitamins, and other signaling molecules that may be responsible for a portion of the differential expression. IPA uses its knowledge base of causal effects and the list of differentially expressed genes to predict whether a particular regulator could be activated. The activation z-score sign  $(\pm)$  indicates whether the upstream 'factor' is activated or less active in either the LCLs treated with ethanol or from alcoholics.

#### Measurement of gene expression by real time PCR

Two micrograms of total RNA (from the same RNA used for microarrays) was reverse-transcribed using the TaqMan Reverse Transcription Reagent kit (Applied Biosystems, Foster City, CA). An aliquot of the cDNA was amplified for 40 cycles on a GeneAmp 7900HT Sequence Detection System with gene-specific primers designed using the Primer Express software (Applied Biosystems). Sybr Green was used for signal detection. All analyses were carried out in triplicate, and no-template controls and dissociation curves were used to ensure specific amplification. For each primer pair, serial dilutions of a control cDNA were used to determine standard

curves, and curves with  $R^2 > 0.98$  were then used to determine the mRNA levels in individual samples. The expression levels were calculated as a ratio of the mRNA level for a given gene relative to the mRNA level for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) in the same cDNA.

## Microarray analysis of brain tissues

Samples from 9 different regions of the brains of each of 4 individuals (2 male and 2 female; an alcoholic and a control of each sex) were obtained from the NIAAA-supported brain bank at the Tissue Resource Center located in the Neuropathology Unit of the Department of Pathology, University of Sydney, Australia. We extracted total RNA from each of the 9 regions of each individual brain: prefrontal cortex, cerebral cortex, thalamus, visual cortex, hippocampus, amygdala, caudate nucleus, putamen, and cerebellum. RNA was extracted using Trizol (Invitrogen), with a higher ratio of Trizol to tissue to improve yield and purity (Edenberg et al., 2005), and further purified using RNeasy mini-columns (Qiagen, Valencia, CA). Samples were labeled using the Affymetrix Whole-Transcript labeling protocol starting with 100 ng of total RNA. The labeled samples were hybridized to Human Gene 1.0 ST arrays, then washed, stained, and scanned as described above.

Partek Genomics Suite was used to generate robust multichip average (RMA) (Bolstad, Irizarry, Astrand, & Speed, 2003; Irizarry et al., 2003) data for each of the arrays from brain samples. The average and standard deviation of RMA values were generated for the core probe sets in each brain region. The mean RMA values ranged from 4 to 21,734 (median = 106). Genes with expression levels at or near background (RMA < 16) were excluded from analyses (McClintick & Edenberg, 2006). When multiple probe sets represented 1 gene, the probe set with the largest mean expression was selected. If the mean RMA value was above 16 in at least 1 region, we considered the gene expressed in brain. In supplementary data, we show relative expression as the mean RMA value in the region in which it was highest.

To determine which genes were expressed both in the LCLs and in the brain, we matched gene symbols associated with the probe sets on the 2 different arrays. We were able to match 24,668 of the 26,814 genes that were detectably expressed in at least 1 group of LCL samples (on the Affymetrix HG U133 Plus 2 GeneChips<sup>®</sup>) with genes on the Human Gene 1.0 ST arrays on which the brain samples were analyzed.

#### Cross comparison with GWAS and human gene expression results

We compared the LCL results with results from 14 recent genome-wide association studies (GWAS) for alcohol dependence or related phenotypes (Bierut et al., 2010; Edenberg et al., 2010; Foroud et al., 2007; Gelernter et al., 2014; Hack et al., 2011; Johnson, Drgon, Walther, & Uhl, 2011; Kapoor et al., 2013; Kendler et al., 2011; Lind et al., 2010; Treutlein et al., 2009; Wang et al., 2013; Xuei et al., 2006; Zlojutro et al., 2011; Zuo, Gelernter, et al., 2012). These studies used alcohol dependence and/or 1 or more related phenotypes: age of onset of DSM-IV alcohol dependence, DSM-IV symptom count, initial sensitivity to alcohol, alcohol tolerance, withdrawal, craving, and maximum number of drinks within a 24-h period (maxdrinks). Gene symbols were matched to gene names reported by the various groups, which frequently represented genes within a given distance from the SNP.

We also compared the LCL results to a list of genes identified as differentially expressed by 1 or more of 11 post-mortem gene expression studies in humans (Flatscher-Bader, Harrison, Matsumoto, & Wilce, 2010; Flatscher-Bader et al., 2005; Iwamoto et al., 2004; Kryger & Wilce, 2010; Lewohl et al., 2000; Liu et al., 2007, 2006; Mayfield et al., 2002; McClintick et al., 2013; Sokolov, Jiang, Trivedi, & Aston, 2003; Zhou, Yuan, Mash, & Goldman, 2011).

#### Results

#### Effects of ethanol treatment on cell growth

To select ethanol concentrations that would not be toxic over the 24-h course of the experiment, the response of 3 LCLs to increasing concentrations of ethanol up to 100 mM were examined. The 3 LCLs differed in their rates of doubling in the absence of ethanol (22, 28, and 35 h). Ethanol prolonged the lag phase before LCLs began logarithmic growth, but in the period from 22 to 70 h after ethanol was added, LCLs treated with 0, 50, 75, or 100 mM ethanol were in log phase. A plot of log<sub>10</sub> (cell number) vs. time during this period fit a linear regression with  $r^2 \ge 0.98$  for all LCLs with all concentrations of ethanol. The average doubling time in the absence of ethanol was 27.4 h, and it was 27.7 h in 75 mM ethanol (Supplementary Fig. 1). Thus at the time studied, the cells were growing exponentially. Based upon these data, we chose to examine gene expression with and without 24 h exposure to 75 mM ethanol.

#### Effects of ethanol on gene expression

For a global picture of differential gene expression, we used hierarchical clustering of the arrays. The differences between individuals were greater than the differences due to either ethanol treatment or phenotype: the ethanol-treated and untreated samples from each person invariably clustered together, whether using all 31,522 probe sets expressed or the 5000 most variable probe sets (those with the largest coefficient of variation; data not shown). Although between-person effects were large, the paired design in which ethanol-treated and untreated LCLs from each of 42 individuals were used as repeated measures allowed us to detect the widespread effects of ethanol on gene expression, even when differences were small; each individual cell line acted as its own control, reducing the noise due to inter-individual differences.

Ethanol treatment significantly affected the expression of 11,734 probe sets (37% of the expressed probe sets), representing 7183 unique, named genes, at a stringent Storey FDR  $\leq$  5% (nominal *p* value  $\leq$  0.039). Most of the expression differences, however, were small (Fig. 1). There were 1393 named genes with absolute fold changes  $\geq$ 1.2, of which 165 had an absolute fold change  $\geq$ 1.4.



**Fig. 1.** Genes affected by ethanol exposure. The number of unique, named genes that significantly differed between ethanol-treated and untreated cells is plotted as a function of fold change. 1 = 1.01 - 1.099, 1.1 = 1.10 - 1.199, etc. Some genes did not map to the Gene 1.0 ST array used for comparison to brain.

Twenty-three histone genes were all decreased, more than half with absolute fold changes larger than 1.5-fold. A large number of heat shock proteins were affected by ethanol treatment. A list of differentially expressed genes with fold changes  $\geq$ 1.1 can be found in Supplementary Table 1.

There were 567 probe sets, representing 478 unique named genes, that differed in expression between cell lines derived from alcoholics and cell lines from non-alcoholics (at an FDR  $\leq$  36%, nominal *p* value  $\leq$  0.0076; Fig. 2). Sixty-four percent of the genes that differed by phenotype were also affected by ethanol treatment (305 genes), compared to 51% of named genes being affected by ethanol. Supplementary Table 2 lists the genes differentially expressed between alcoholics and controls.

Not unexpectedly, sex had a significant effect on gene expression: 122 probe sets, associated with 58 unique named genes, were expressed differently in cells from males than in cells from females, FDR  $\leq$ 0.05 (nominal *p* value  $\leq 2 \times 10^{-4}$ ). This list includes genes such as *XIST* and *EIF1AX*, which are not detectably expressed in males, and *EIF1AY*, DDX3Y, and NLGN4Y, which are not detectably expressed in females. Of these 58 loci, 48 mapped to either the X or Y chromosome.

#### Pathway analysis

The 1393 genes affected by ethanol treatment with an absolute fold change  $\geq$  1.2 were used for Ingenuity Pathway Analysis. Fortyone pathways were significantly affected by ethanol treatment (Table 1). Among these were several inflammatory pathways, including IL-6 signaling, dendritic cell maturation, CD40 signaling, IL-10, and IL-9 signaling. TNFR2 (tumor necrosis factor receptor 2) signaling showed mostly increased expression. Four NFkB-related genes (NFKB2, NFKBIA, NFKBIE, and IKBKE), all with increased expression, are collectively found in 28 of these pathways, including the NFkB pathway itself. The results from the upstream regulator analysis, shown in Supplementary Table 3, reinforce these findings. NFkB was identified as the most significantly activated upstream regulator. TNF signaling also appears activated; TNFa, which has increased expression, is found in 17 of the pathways. Also affected were 45 cytokines, including IL6 and IL1β. All were activated except 3, 2 of which, IL10 and IL1RN, have known



**Fig. 2.** Genes that differed between alcoholics and controls. The number of unique, named genes that significantly differed between cells from alcoholics and controls is plotted as a function of fold change. 1 = 1.01-1.099, 1.1 = 1.10-1.199, etc. Some genes did not map to the Gene 1.0 ST array used for comparison to brain.

anti-inflammatory effects. Other harbingers of inflammation were seen: activation of interferons and Toll-like receptors.

The pathways that differed between cells from alcoholics and controls included phospholipase C signaling, G beta gamma signaling, RAN signaling, signaling by Rho family GTPases, androgen signaling, hypoxia signaling in the cardiovascular system, RhoGDI signaling, netrin signaling, tec kinase signaling, paxillin signaling, telomerase signaling, and ephrin B signaling (Table 2). *RAC1, GNG2, GNA11,* and *RHOT2,* with decreased expression in alcoholics, were common to several pathways. *GNA13, SOS2, PRKCE,* and *RHOQ,* with increased expression, were also common to multiple pathways. The upstream regulator analysis of the phenotype differences (Supplementary Table 4) shows increased signaling due to retinoic acid, vitamin D, *TP53,* and *APP.* The growth factor receptor), along with transcription factors MYC and MAX, are less active in the alcoholics.

Protein ubiquitination pathway and hypoxia signaling in the cardiovascular system were the only 2 pathways in common for treatment and phenotype. The only affected gene common to these 2 pathways is *UBE2Q*, a ubiquitin-conjugating enzyme, which was decreased in alcoholics and because of treatment by ethanol.

## Comparison to brain expression

We detected 20,165 unique genes expressed in at least 1 brain region. Ninety-nine percent of the genes expressed in the LCLs that could be mapped to the Gene 1.0 ST arrays were expressed in at least 1 of the 9 brain regions (Supplementary Tables 1 & 2).

#### Confirmation by qRT-PCR

qRT-PCR was used to confirm microarray results. Genes that were previously identified by animal or human studies or related to stress or inflammatory response were selected for testing. Of the 22 genes selected for qRT-PCR based on different expression after treatment with ethanol, 20 were confirmed with a *p* value <0.05, and 1 (*FOXP1*) had a similar fold and direction but with *p* = 0.09 (Supplementary Table 5, Sections A & B). SRSF11, which was not confirmed, was measured on the array by 2 non-overlapping probe sets with different results, reflecting different splice variants; the differentially expressed variant contained a longer 3' UTR that was not captured by the qRT-PCR. The 11 genes selected based on differential expression between alcoholics and controls (8 overlapped with the set affected by ethanol) were confirmed with *p* < 0.05 (Supplementary Table 5, Sections B & C).

## Discussion

Analyzing the effects of a 24-h exposure to ethanol on lymphoblastoid cell lines (LCLs) under identical culture conditions allowed us to focus on the direct effects of ethanol on gene expression in a single cell type without complications of organismal environmental variables such as hormonal and nutritional status or different distributions of cell types. The differences in gene expression among individuals were large, but since each individual cell line was its own control, the effects of ethanol could be isolated and measured. Ethanol at 75 mM altered the expression of 37% of the probe sets expressed in LCLs, representing 51% of the unique named genes, which is remarkable, but most changes were small in magnitude (Fig. 1). This concentration, corresponding to a blood level of 0.345 mg%, is within the range seen after heavy drinking by alcoholics (Adachi et al., 1991; Lindblad & Olsson, 1976). Almost all of these genes were also expressed in brain. Given that one cannot sample brain from living subjects, LCLs offer a well-controlled, living cell alternative that can be examined for genes affected by

Tuble 1	
Pathways affected by ethanol exposure	e.

Type I Dabetes mellitus signaling         44.6.07         MARZIKO, HLA-MA, SOCJ, SOCJ, ALCA, INTERE, SOCZ, SOCK, HLA-DQAL, MAPRS, SOCJ, ARGKE, ILRI, NREZ, FAS, NREZ, HLA, SOL, SOCJ, ALCA, INTER, SOCZ, SOCK, HLA-DQAL, MAPRS, SOCJ, SOCJ, MARZIK, ISL, ALCA, DOL, DOB, TYF           Lie signaling         506-66         MARZIK, SOCJ, SOCJ, ALCE, ILL, ALCZ, TINAREN, NREZ, ILL, MARZI, TRASH, TANK, SOCJ, KOKLA, ILCZ, NR.           Dendritic cell maturation         128-65         ILL, CAMI, PRAN, INREZ, FARL, CORS, NREAN, TANK, NREZ, FARL, MAPRS, COSJ, ALCE, THE, TANK, CLU, ALK, TANK, TUR, SOCJ, SOCJ, ALK, ALK, TYR, SOCK, SOCJ, SOCJ, ALK, ALK, TYR, SOCK, SOCJ, SOCJ, ALK, ALK, TYR, SOKK, ALK, TYR, THAT, JUNN, INREZ, FARL, TANK, ULLZ, WREAL, TANK, TANKI, CORM, AMAPIS, CDSG, RAK, TANK, THAT, JUNN, ALK, TANK, ALK, TANK, THAT, JUNN, ALK, TANK, ALK, TANK, ALK, TANK, THAT, JUNN, ALK, TANK, ALK, TANK,	Canonical pathways	p value	Molecules
<ul> <li>NERBA CLEDB, MAPSE, 1128, LTZ, CADJ, CDBS, TM<sup>2</sup></li> <li>G Sagnaling</li> <li>L Sagnaling</li> <li>L Sagnaling</li> <li>L Sagnaling, ALER, K. S. COSS, S. COS, L. RADE, JLA, ALCJ, TM<sup>2</sup></li> <li>Dendritic cell maturation</li> <li>L Sagnaling</li> <li>L Marker, Contr. J. Netton, L. T. Netton, L. T. Netton, L. T. Netton, C Dag, C. Das, TNR - Netton, L Dag, C Das, TNR - Netton, L Dag, C Das, TNR - Netton, L Dag, C Das, TNR - Netton, L Das, Netton, L Das, C Das, TNR - Netton, L Das, C Das, TNR - Netton, L Das, Netton, Netton, L Das, Netton, L Das, Netton, Netton, L Das, Netton, Netton, L Das, Netton, Ne</li></ul>	Type I Diabetes mellitus signaling	4.4E-07	MAP2K6, HLA-DMA, SOCS1, SOCS3, ICA1, NFKBIE, SOCS2, SOCS6, HLA-DQA1, MAPK9, SOCS4, IKBKE, IL1R1, NFKB2, FAS,
<ul> <li>G. Segaling</li> <li>S. Guo, G. MAPZK, SUCSJ, SOCSJ, ARCH, LIN, AKTZ, INNARS, MERGE, MAPKE, INER, LIN, NURZE, STATJ, ILLE, WEGA, COLAI, NYRRE, Coll and Status</li> <li>Dendritic cell maturation</li> <li>L. Z. G. MAPZK, SUCSJ, SOCSJ, ARCH, LYN, AKTZ, NYRRE, MAPKE, DAM, AKTZ, REE, MAPKE, OSA, IKAKE, NYRRE, YARAN, SOCS, NYRRE, YARAN, SOCS, IKAKE, NYRRE, YARAN, SOCS, NYRRE, YARAN, SOCS, YARA, AKTZ, REEK, NYRRE, YARAN, SOCS, YARA, AKTZ, REEK, NYRRE, YARAN, SOCS, YARA, YARAN, YARA</li></ul>			NFKBIA, CD80, MAP3K7, IL12B, LTA, GAD1, CD86, TNF
Dendritic cell maturation       12-6       11.4       10-8	IL-6 signaling	5.0E-06	MAP2K6, SOCS3, SOCS1, ABCB1, IL1A, AKT2, TNFAIP6, NFKBIE, MAPK9, IKBKE, IL1R1, NFKB2, STAT3, IL1R2, VEGFA, COLIA1,
CREBS STATA COLLAI, COBR, CARA, HURLE, TAN, SCHW, COBR, THE, HUNRI, CORR, CARA, MARSAR, PARZ, RUSCI, LTA, TRAFI COMO signaling 24:10-03 NRBAR, CLAIN, NRBBE, TRAPIN, BANKO, LOBES, TATA, STRESS, NRBBA, CAMA, MAPSK, FIKAS, CLAIL, TARFI MERCE, STATA, COLLAI, COBR, CARA, NREE, STATA, SUCKS, MISER, STATA, STRESS, NRBBA, CAMA, MAPSK, FIKAS, CLAIL, ATAR Stress, CLAIL, CARA, CHAN, NRBBE, TINAPITZ, MRREE, STRAT, STRESS, NRBBA, CAMA, MAPSK, FIKAS, CLAIL, TAFF, TARFI CrossTable Networe dendritic cells and natural Miller Miller and natural Miller cells and natural Miller cells and natural Miller dells and natural Miller dells and natural Miller Miller Miller Miller Miller Miller Miller Miller Miller and natural Miller Miller and natural Miller Miller and natural Miller Miller Miller Miller Miller Miller Miller Miller and natural Miller Miller Miller and natural Miller Miller and natural Miller Miller Miller Miller Miller and natural Miller Miller Miller Miller Miller Acute multipation pathway and natural Miller Miller Miller Miller Miller Miller Miller Miller Miller and natural Miller Mil	Dendritic cell maturation	1 2F-05	INFKBIA, IMAPSK7, PIKSCS, CSINKZAT, AKTS, INF II 1A TCAM1 PDIA3 NEKRIE HLA-DOA1 CD83 NEKRIA PIK3C3 AKT3 HLA-DMA AKT2 RELR MAPK9 CD58 IKRKE NEKR2
CP40 signaling         42.6         M24266, CAM, NIKEL, TMARING, MKRK, MKR2, NIKEL, TMARIN, CAM, MARCH, CAM, MKRA, LTA, RIKZ, S. REL, TARAF, AKT3, IKRE, NIKEZ, INTEAH           Cymphotosin f) receptor signaling         21.6         AKT2, VCAM, INKRAL LTA, NKRAL LTA, KNRZ, RKS, TKARA, KAT3, IKRE, NIKEZ, TMARI           Cymolon signaling         24.6         AKT2, VCAM, INKRAL LTA, RKRZ, AKT3, IKRE, NIKEZ, SILL, TA, SKNI, COZE, CD86, CD85, CD87, CD87, LI2R, CD9, CD90, LI2R, LTA, SKNI, CD27, LI2R, ILAR, CMM, CMMAR, PMAR, NIKEL, MARCH, CM2, MARSH, CC9, MARA, TC71, LISRI, MYC, LI2Z, VKGAF, TE40, NIKEL           Cymolon signaling         28.6-04         MAPKS, SOCS3, SOCS1, SILL, LA, KAMI, CMAR, PMAR, NKRBH, CSNK, MATT3, LILR, TC73, LISRI, MYC, LIZZ, VKGAF, TE40, NIKEL           Cymolon signaling         49.6-04         MAPKS, SOCS3, SOCS1, SILL, LA, KAMI, CMAR, PMAR, AND, NCRBE, CSNKBA, TAT3, LILR, TC73, LISRI, MICC, LITZ, MARCH, CD40, CD80, LIZR, LITA, RKLB, TLRB, HAR, MKRC, MKRZ, TMF, AKAT, TC74, LISRI, MARCH, SANKA, MARCH, CSNKBA, TAT3, LILR, TC74, CAMI, Includes           Anter woold indevina signaling         49.6-04         MAPKS, SOCS3, SOCS1, LILA, KAMI, CMAR, PMAR, AKAT, CBRE, NCRB, TAT3, MKRC, LILR, MKRC, MKRZ, TMF, TH100, TMAR, PMAR, MARCH, MARCH, SANKA, MKRZ, MKRR, TKRS, LILRA, MKRZ, TKRS, TKRS, AKATA, TC74, MKC3, KKRZ, TKRS, TKRS, AKATA, TKRS, LILRA, MKRZ, TKRS, TKRS, AKATA, TKRS, LILRA, MKRZ, TKRS, TKRS, AKATA, TKRS, LILRA, MKRZ, TKRS, TKRS	Denantie cen maturation	1.22-05	CREB5, STAT4, COL1A1, CD80, CD40, IL12B, LTA, FSCN1, CD86, TNF, IFNAR1, CCR7
<ul> <li>TINPEZ signaling</li> <li>466-69</li> <li>NEKRIA, LTA, NRKIE, TINALTE, NRKE, NRKE, NRKE, NRKE, NRKE, NRKE, NRKE, TATS I</li> <li>LIFO4 AKT, NKRE, CALL, CAMI, NRKIE, LIAL, KICA, KIC, SKRE, NRKE, NRKE, NRKE, NRKE, TATS I</li> <li>LIFO4 AKT, NKRE, CALL, CAMI, NRKIE, LIAL, KOM, LIZR, LTA, FSCHI, CD22, CD86, TNF, CC7, IL2R</li> <li>Ad natural killer cells</li> <li>Cadotchial cerls in meunatod</li> <li>Cadotchial cerls in meunatod</li> <li>See-04</li> <li>MARZE, SINTA, ACCS, SOCS, SOCS,</li></ul>	CD40 signaling	4.2E-05	MAP2K6, ICAM1, NFKBIE, TNFAIP3, MAPK9, IKBKE, STAT3, NFKB2, NFKBIA, CD40, MAP3K7, PIK3C3, LTA, TRAF1
<ul> <li>Jumphotoxin Ji receptor signaling</li> <li>21.64</li> <li>AKZ, VCAMI, NRBIA, LTA, JRKCZ, REB, TRAFA, AKT3, IRBE, F.NRBZ, NTAFI, CTAP, ICCE, ILZB</li> <li>and tatural killer cells</li> <li>Robe of JAKZ In hormone-like</li> <li>24.6-04</li> <li>AKZ, VCAMI, NRBIA, LTA, JRKCZ, REB, TRAFA, AKT3, IRBE, SIRPA</li> <li>Cytokine signaling</li> <li>Robe of JAKZ In hormone-like</li> <li>24.6-04</li> <li>AKZ, VCAMI, NRBIA, LTA, JRKCZ, REB, STAT3, PRLR, SIRPA</li> <li>Cytokine signaling</li> <li>Constant between signaling</li> <li>And Parko, SOC3, SOC3, SOC3, JLLA, ICAMI, CAMKA, PDIA3, NRBIE, CSNKIA1, TCF7, ILTB1, MYC, ILTB2, VEGFA, TLF10, NFKBIA, MAPPIC, FIGCA, AKT3, IRK1, VCAMI, AKZ3, IRK1, VCAMI, AKZ3, MAPR, CAM, CS, RMBE, STAT3, JLR11, TCF3, CREBS, ILT, CAMI (includes arbtristis)</li> <li>In hormatodia</li> <l< td=""><td>TNFR2 signaling</td><td>4.6E-05</td><td>NFKBIA, LTA, NFKBIE, TNFAIP3, IKBKE, NFKB2, BIRC3, TNF, TRAF1</td></l<></ul>	TNFR2 signaling	4.6E-05	NFKBIA, LTA, NFKBIE, TNFAIP3, IKBKE, NFKB2, BIRC3, TNF, TRAF1
<ul> <li>Crosstan between dendmine cells</li> <li>Z4E-04</li> <li>ILRAN CLEM, CLEM,</li></ul>	Lymphotoxin $\beta$ receptor signaling	2.1E-04	AKT2, VCAM1, NFKBIA, LTA, PIK3C3, RELB, TRAF4, AKT3, IKBKE, NFKB2, TNFSF14, TRAF1
Role of JAC In hormone-like cytokine signaling       2.4E-04       SOCS1, SOCS3, STATSA, SOCS6, SOCS2, SOCS4, STAT3, PRLR, SIRPA cytokine signaling         Role of macrophages, Binohasts and archtrikis       2.4E-04       MCRXE, SOCS3, SOCS1, ILI, I. (CMI, CAMKE, DIDA3, NERRE, CSK MLI, TCF7, ILI8R1, MCC, LI IR2, VEGA, TLEID, NERMA, ACITE myloid leukema signaling         Acter myloid leukema signaling in rheumatoid arthritis       40E-04       MARZKS, STATSA, ARTS, STAT3, NERZ, TCF7, TCF7, MCC, BARC, CSE2R, AAR, RAA, PIRSC3, RATSA HAL-D04, TLR0, ILIA, SLMMFI, CD40, CD80, ILI2R, LIA, RELE, TL86, HLA-DQAI, CD86, NRK2, TNF, FAS         TREMI signaling       42E-04       STATSA, TRIO, ARTZ, ICAMI, CD40, CD80, ILI2R, ILIA, RELE, TL86, HLA-DQAI, CD86, NRK2, TNF, FAS         Thelper cell differentiation       5.1E-04       STATA, HLA-DMA, CD40, CD80, ILI2R, ILIZR, HLA-DQAI, CD86, ILIZR, NLR2, TNF         Thelper cell differentiation       5.1E-04       STATA, HLA-DMA, CD40, CD80, ILIZR, ILIZR, HLA-DQAI, CD86, ILIZR, NLR2, TNF         Protein ubiquitination pathway       7.8E-04       SIFA4, HLA-DMA, CD40, CD80, ILIZR, ILIZR, HLA-DQAI, CD80, ILIZR, ILIZR, SITATS, MFCE, IKRE, IK	crosstaik between dendritic cells	2.4E-04	IL3KA, CD69, CD83, NFKB2, FAS, CSF2KB, CD40, CD80, IL12B, L1A, FSCN1, CD226, CD86, 1NF, CCK7, IL2KB
<ul> <li>cytofine signaling</li> <li>2.8E-04</li> <li>MAP2KG SOC33, SOC31, ILIA, ICAMI, CAMKA, PDIA3, NYRBIE, CSNKIAI, TCF7, ILISRI, MYC, ILIR2, VEGA, TREJO, NYRBIA</li> <li>endorbeial cells in rheumatoid arthritis</li> <li>Acute myeloid leukemia signaling</li> <li>ACUE myeloid leukemia signaling</li> <li>ALE-04</li> <li>MAP2KG, TKAFA, AKT3, TKAFA, KAT3, TKAFA, VCAMI, AKT2, MAPK9, CS, IKOKE, STAT3, ILIRI, TCF3, CREBS, IL7, CALMI (includes others), ILAT. ILRG, DEGS, INF, WYR5A</li> <li>ACUE myeloid leukemia signaling</li> <li>ALE-04</li> <li>ALE-04</li> <li>MAP2KG, TKAFA, AKT2, STAT3A, NKRE, TCF7, TCF7, MYC, BRAC, CSERA, AKRE, RAAR, RAKA, PIKSC3, AKT3</li> <li>ALE-04</li> <li>HAPAM, TRIJO, ILIA, SLMMFI, CD40, CD80, ILIZ, ILA, REIB, TIRB, HLA-DQAI, CD86, INFA</li> <li>ALE-04</li> <li>HAPAM, TRIJO, ILIA, SLMMFI, CD40, CD80, ILIZ, ILIA, REIB, TIRB, HLA-DQAI, CD86, ISRA</li> <li>LI-05 signaling</li> <li>SLE-04</li> <li>FIAA-DMA, TRIJO, ILIA, ACPATS, ABHDS, PMP2A, LPCAT2, MD0AT2, ACPAT3, LEOVIG</li> <li>Theore signaling</li> <li>SLE-04</li> <li>HA-DMA, TRIJO, ILIA, SLAMFI, CD40, CD80, ILIZ, ILIA, BLUZ, ILIA, SLAMFI, CD40, CD80, ILIZ, ILIA, ILIZ, SLAT3, TNF</li> <li>Protein ubiquitination pathway</li> <li>VE-64</li> <li>SLE-04</li> <li>HA-DMA, CD80, CD40, HLA-DQAI, CD86, ILICH, ILIZ, ILIA, SLAMFI, UBE2QI, ULHS, SUBAY, SLESZI, ULHS, SLESZI, SLESZI, ULHS, SLESZI,</li></ul>	Role of IAK2 in hormone-like	2.4E-04	SOCS1, SOCS3, STAT5A, SOCS6, SOCS2, SOCS4, STAT3, PRLR, SIRPA
<ul> <li>Role of macrophages, Broblasts and 2.8E-04 MAP2K6, SOC3, SOC3, LILA, ICAM, CAMIKA, PD/A3, NRKBE, CANICAL, TCF, ILISRI, MYC, ILIRZ, VEGPA, TIRIO, MAPSK, OPCA, TRIO, MAPSK, DEVA, MAPSK, TRIO, TAT, TRIO, MAPSK, DEVA, TRIO, TRIO, MAPSK, DEVA, TRIO, TRIO, MAPSK, DEVA, TRIO, TRIO, TRIO, MAPSK, DEVA, TRIO, TRIO, TRIO, MAPSK, DEVA, TRIO, TRIO,</li></ul>	cytokine signaling		
endothelial cells in therumatoi arthritis Acute mycloid leukenia signaling Acute mycloid leukenia signaling Bieloid leukenia signaling Bieloid leukenia signaling Bieloid leukenia signaling Bieloid Hint-DAM, AIRIO, KMR2, IKAN, AKR2, KMRA, MARAKE, MARER, IKARE, AKR3, TKAH, AKR2, KMRA, MARA, KB, KARA, JU, AKR3, TKAH, AKR2, KMRA, Bieloid Link, Simpan, Charlo, Simpan, Bieloid Link, Akr2, KMRA, Bieloid Link, Akr2, KMRA, Bieloid Link, Akr3, TKAH, Akr2, KMRA, Charl, Charl, AKR3, TKAH, Akr2, KMRA, Bieloid Link, Akr3, TKAH, Ak	Role of macrophages, fibroblasts and	2.8E-04	MAP2K6, SOCS3, SOCS1, IL1A, ICAM1, CAMK4, PDIA3, NFKBIE, CSNK1A1, TCF7, IL18R1, MYC, IL1R2, VEGFA, TLR10, NFKBIA,
artmitis ones, Lux, Luce, Lub, In, Winson, Acure myeloid leukemia signaling differentiation arthritis signaling differentiation arthritis signaling differentiation spatial spatial signaling differentiation spatial spatia spatial spatia spatial spatial spatial spatia s	endothelial cells in rheumatoid		MAP3K7, PIK3C3, TRAF4, AKT3, TRAF1, VCAM1, AKT2, MAPK9, C5, IKBKE, STAT3, IL1R1, TCF3, CREB5, IL7, CALM1 (includes
<ul> <li>Hatered T. et al. and B. cell signaling</li> <li>Hatered T. et al. a</li></ul>	arthritis Acute myeloid leukemia signaling	4 0E-04	OTHERS), LIA, ILKO, FZDO, INF, WNI5A MADDKG STATSA AKTO STATO NEKRO TCEO TCEO MYC RDAE CSEORR ARAE RADA DIKOCO AKTO
in theumatoid arthritis 5 FREM signaling 4.2E-04 STATSA, TREIO, AKT2, ICAMI, CD40, TRE6, AKT3, CD86, CD83, STATS, INFRE2, INF Triacytglycerol biosynthesis 45:04 PPAPCUER, <i>ACPAT5, BAHDS, IPAP2A, LPCAT4, DCAT2, MEDAT2, ACPAT3, ACPAT3, ACPAT3, LEVIE</i> Thelper cell differentiation 5 1E-04 STAT4, HA-DAM, CD40, CD80, IL72, IL72, MAT2K, ACPAT3, ACPAT3, ACPAT3, TFR, IL18R1 1E-10 signaling in the cell differentiation pathway Frotein ubiquitination Frotein	Altered T cell and B cell signaling	4.0E-04 4.1E-04	MIA-DNA, TIRTIO, MILA, SIAMST, MINDA, TCTS, TCT, MIC, DIAT, CJERD, ANAT, MIN, MINSC, AND SA
TREM       42E-04       STATSA T.RTIO. AKT2, ICAMI. CD40, TRE6, AKT3, CD86, COSS, STAT3, NFKB2, TVF         Trickyglycore biosynthesis       43E-04       STATA, HLA-DMA, CD40, CD80, ILI2B, ILI2B, HLA-DQA1, LD68, ILZRA, ILI2B, STAT3, TNF, ILIRI         1-10 signaling       6.9E-04       STATA, HLA-DMA, CD40, CD80, ILI2B, ILI2B, HLA-DQA1, CD86, ILZRA, ILIZBR, STAT3, TNF, ILIRI         1-10 signaling       6.9E-04       ULR2, MPXES, SOS3, ILIA, NFKBI, IMPXER, INREAP, INREQ, INREQ, INSTAT, TNF         Protein ubiquitination pathway       7.8E-04       ULR2, MPXES, SOS3, ILIA, NFKBI, IMPXES, INREQ, INREQ, INSTA, TNF         B cell development       8.1E-04       HLA-DMA, CD80, CD40, ILIA-DQA1, CD86, IGHM, ILI7, IGHD         Small cell lung cancer signaling       8.1E-04       HHT, AKT2, MC24, NFKBIL, IRNE, NFKB2, PIKSC3, TRAF4, AKT3, TRAF1         Hypoxia signaling in the       1.0E-03       RPL22, AKT2, EIF3H, RPS28, EIF1, RPJ37, PPP1CB, EIF4A, 2RT23, RPL36, RPS23, EIF3M, RPL15, EIF3A, EIF3         FIF3 signaling       1.0E-03       RPL22, KT2, EIF3H, RPS28, EIF1, RPJ37, PPP1CB, EIF4A, 2RT23, RPL36A, RPS23, EIF3M, RPL15, EIF3A, LST2, RPL36, RPS23, EIF3A, LST3, RPL37, RPL35, RPS23, EIF3A, LST3, RPL37, RPL35, RPL36, RPS23, EIF3A, LST3, RPL37, RPL35, RPL36, RPS33, EIF3, LST3, RPL37, RPL37	in rheumatoid arthritis		
Triacylgvcrol biosynthesis       43E-04       PPAPPC1B, ACPATS, PAP2A, LPCAT4, DCAT2, MORDZ, ACPAT9, ACPAT3, ELOVI6         Thelper cell differentiation       51E-04       PATAF, HLA-DAM, CD40, CD80, LD28, L12R, L12R, HLA-DAM, LD28A, LD2RA, LD2R	TREM1 signaling	4.2E-04	STAT5A, TLR10, AKT2, ICAM1, CD40, TLR6, AKT3, CD86, CD83, STAT3, NFKB2, TNF
1 helper cell differentiation       5.11-04       S1.14, HLA-DUM, CUB0, (L120, L121, HLA, HLA, HLA, HLA, HLA, HLA, HLA, HLA	Triacylglycerol biosynthesis	4.3E-04	PPAPDC1B, AGPAT5, ABHD5, PPAP2A, LPCAT4, DGAT2, MBOAT2, AGPAT9, AGPAT3, ELOVL6
<ul> <li>Le 10 signaling</li> <li>GSZ-94</li> <li>Li La, MUZRO SDS, Li Li, MURDA, MURSA, TEEJ, ANARCI, SULIN, JUNEZ, LIN, JUNEZ, J</li></ul>	Thelper cell differentiation	5.1E-04	SIA14, HLA-DMA, CD40, CD80, IL12B, IL21B, HLA-DQA1, CD86, IL2KRA, IL12KB2, SIA13, INF, IL18K1
<ul> <li>Hoelen despinstering (Hells, DNAJE30, PSMC2, BIRC3, HSP86, HSPA4L, UBE201, DNAJC27, USP9X, UBE202, PSMD11, UBE213, USP32, PSMA5, UBE203, UBE21</li> <li>B cell development</li> <li>Sinel cell tung cancer signaling</li> <li>HIA, JMA, CB00, CD40, HLA-DQA1, CD86, IGHM, IL7, IGHD</li> <li>Small cell tung cancer signaling</li> <li>HIA, JMA, CB00, CD40, HLA-DQA1, CD86, IGHM, IL7, IGHD</li> <li>Singaling</li> <li>Lie-04</li> <li>HIA, JMA, CB00, CD40, HLA-DQA1, CD86, IGHM, IL7, IGHD</li> <li>Singaling</li> <li>Lie-05</li> <li>RPL22, AKT2, IEI3H, RPS28, EIF1, RP137, PPPICB, EIF4A2, RP123, RP125A, RP233, EIF3M, RP115, EIF252, EIF3B, EIF1AX, PKS26, ART3, RP520, RP515A, RP113</li> <li>NF-κB signaling</li> <li>Lie-03</li> <li>MAP2K6, AZ2, LILA, AKT2, RELB, NRKBE, TNFR29, XIR1, MALT1, ILIR2, TLR10, NFKBIA, CD40, MAP3K7, PIK3C3, LTA, TR66, CMXCA1, IGF1R, AKT3, TNF</li> <li>Signaling</li> <li>LiE-03</li> <li>MAP2K6, AZ2, LILA, AKT2, RELB, NRKBE, TNFA27, SIRTS</li> <li>Signaling</li> <li>LiSe-03</li> <li>MAP2K6, AZZ, LILA, AKT3, TNF</li> <li>Signaling in osteoclasts</li> <li>LiSe-03</li> <li>MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, JIBR1, SMURF1, ILIR2, NFKBIA, IGF1, MAP3K7, PIK3C3, AKT3, BIRC3, AKT3, BIRC3</li> <li>AKT2, MAPK9, IKBKE, ILIR1, TCF3, IL7, CAMK1, MAP3K13, NFKBIE, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3, AKT3, PP2R5E</li> <li>POSSGK signaling</li> <li>Theore cells</li> <li>LiE-03</li> <li>MAP2K6, AKT2, CAMK4, NFKBIE, HIA-DQA1, MAPS, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, OR50, SOC3, STAT5A, AKT3, PP2R5E</li> <li>POS signaling in Thelper cells</li> <li>LiA-03, AKT2, CAMK4, NFKBIE, HIA-DQA1, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IPP2R5E</li> <li>HIA-DWA, AKT2, CAMK4, NFKBE, HIA-DQA1, IKBKE, MAR50, ITKAF1</li> <li>HIA-DWA, AKT2, CAMK4, NFKBE, HIA-DQA1,</li></ul>	Protein ubiquitination pathway	0.9E-04 7 8F-04	ILIRZ, WHYZAO, SUCSS, ILIR, NYKOBIA, WHYSAY, DUVKA, NYKOBE, INKNE, NYKOZ, ILIKI, SIAIS, INY ISPAS HSPATA/HSPATR DNACIS HSPAST TCFRI ANAPCI SMIIRFI IISPS HSPAA PANZ ISPZ IISPZ IISPZ IISPZ7 IIRF2DA
Peell development       8,1E-04       HLA-DMA, CD80, CD40, HLA-DQA1, CD86, IGHM, IL7, IGHD         Small cell lung cancer signaling       8,9E-04       FHIT, AKT2, PA2C4, NFKBIE, IKBKE, NFKB2, PTEN, MYC, NFKBIA, NKR2A, CREDS, UBE2D3, PTEN, UBE21         cardiovascular system       1.0E-03       UBE2C2, VECFA, UBE2L3, NFKBIA, UBE2Q1, SUMOL, UBE2Q3, RPL3SA, RPS23, EF3M, RPL15, EF2S2, EF3F, EF3B, EF1AX, PKR3E, Signaling         10F-03       RPL22, AKT2, EF3B, FF3A, AKT3, RPS2 RF15A, RPL37, PPP1CB, EF4A2, RPL23, RPL3SA, RPS23, EF3M, RPL15, EF2S2, EF3F, EF3B, EFF1AX, PKR3E, TSF5A, RPL13         NF-x6 signaling       1.1E-03       MAP2K6, AZI2, LLIA, AKT2, RELB, NFKBE, TNFAP23, NFKB2, ILTR1, MALT1, ILTR2, TLR10, NFKB1A, CD40, MAP3K7, PIK3C3, AKT3, BFC7         Role of osceoblasts, osteoclasts       1.5E-03       MAP2K6, AZI2, CLINA, NFKBIE, CSNK1A1, TCF7, ITC63, ILTSR1, SMURF1, ILTR2, NFKBIA, IGF1, MAP3K7, PIK3C3, AKT3, BFC3, and chordrocytes in rheumatoid arthritis       AKT2, MAP4N9, IKK8E, ILTR1, TCF1, ITC7, ITC7, ITC63, ILTSR1, SMURF1, ILTR2, NFKBIA, MAP3K7, PIK3C3, AKT3, BFC3, BFC3         Regulation of eF4 and       2.1E-03       MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, CD86, AKT3         CD28 signaling in Thelper cells       2.1E-03       HAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, CD86, AKT3         CD35 signaling in Thelper cells       2.1E-03       HAP2K6, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, CD80, CD40, PIK	rotem abiquitmation pathway	7.02 01	UCHL5, DNAJB1, DNAJC30, PSMC2, BIRC3, HSPB6, HSPA4L, UBE201, DNAJC27, USP3X, UBE2C2, PSMD11, UBE213, USP32,
B cell development       5.1E-04       HLA-DMA, CD80, CD40, HLA-DQA1, CD86, IGHN, IZ, ICHD         Small cell lung cancer signaling       B.6-04       HHZ, ATXZ, PAZCA, NERRE, IXKER, NERRE, PTEN, MYC, NERREA, ZHZ, ATXZ, RELP, SNERRE, PTEN, MYC, NERREA, PTEN, TEN, WNTSA         11-9 signaling       1.5E-03       MAP2K6, AKT2, CAMK4, NERRE, PTEN, CALMI (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BPRC3, PTESCA, PTSOSK signaling       1.5E-03       MAP2K6, AKT2, CAMK4, MP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALMI (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, PP22R5C, PTSOS, MISSA, PP22R5C         Regulation of elF4 and pten cells       2.1E-03       AKT2, EP3P, PFP2CA, RFS28, EIF1, EIF4A2, RFS23, EIF3A, EIF3A, EIF3A, EIF3A, EIF3A, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PP22G, PTSOS, PTSOSA, PP22R5C			PSMA5, UBE2D3, UBE2I
Small cell lung cancer signaling       895-04       FHIT, AKT2, PAZC4, NFKBE, IKBKE, NFKB2, PTEN, WYC, NFKBIA, MYC, NFKBIA, UB2C3, TKAF4, AKT3, TKAF1         Hypoxia signaling in the cardiovascular system       1.06-03 <i>UBE2C3, VECFA, UBE2L3, NFKBIA, UBE2L3, SUMO1, NFKBIE, UBE2D4, CREBS, UBE2D3, PTEN, UBE21</i> EIF2 signaling       1.06-03 <i>RPL22, AKT2, EIF3H, RPS28, EIF1, RPL37, PYP1CB, EIF4A2, RPL33, RPL35A, RPS23, EIF3M, RPL15, EIF2S2, EIF3F, EIF3B, EIF1AX, PK153C, STAT5A, AKT2, RELB, NFKBE, TNFAP13, NFKB2, LILRI, MALT1, IL1R2, TLR10, NFKBIA, CD40, MAP3K7, PIK3C3, TATA, TK86, CNZ4, LILR, AKT3, TFF         NF-kB signaling       1.16-03       MAP2K6, AZ2, LILA, AKT2, RPL24, RKS13, NFKB2, LILRI, MALT1, IL1R2, NFKBIA, CD40, MAP3K7, PIK3C3, AKT3, BIRC3, and chordrocytes in rheumatoid arthritis         Rank signaling in osteoclasts       1.6E-03       MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3, MAP2K6, Signaling in T helper cells         CD28 signaling in T helper cells       2.1E-03       AKT2, CAMK4, NFKBIE, HIA-DQA1, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, NFKBIA, CD80, CD40, PIK3C3, AKT3, SIRC3, AKT3, SIRC3, AKT3, SIRC3, AKT3, SIRC3, AKT3, SIRC3, AKT3, SIRC3, CD55, AKT3, SIRC3, CALS3, Signaling in T helper cells       2.1E-03       AKT2, CAMK4, NFKBIE, HIA-DQA1, MAPK9, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, SIRC3, CD55, AKT3, SIRC3, CD55, AKT3, SIRC3, CD55, SIRC31, SIRC4, SIRC</i>	B cell development	8.1E-04	HLA-DMA, CD80, CD40, HLA-DQA1, CD86, IGHM, IL7, IGHD
Hypotok signaling       10E-03       OB2L2, VLM, OB2L3, VRMA, OB2L3, VRMA, OB2L3, VRMA, OB2L4, VLMA, ILRA, VLMA, OB2L4, VLMA, ARD, RES, RPL3,	Small cell lung cancer signaling	8.9E-04	FHIT, AKT2, PA2G4, NFKBIE, IKBKE, NFKB2, PTEN, MYC, NFKBIA, PIK3C3, TRAF4, AKT3, TRAF1
<ul> <li>LiB2 signaling</li> <li>L0E-03</li> <li>RPL22, AKT2, EIF3H, RPS28, EIF1, RPL37, PPP1CB, EIF4A2, RPL23, RPL35A, RPS23, EIF3M, RPL15, EIF2S2, EIF3F, EIF3B, EIF1AX, PIK3CC3, EIF2B5, EIF3A, AKT3, RPS20, RPI53A, RPL3</li> <li>PS-kB signaling</li> <li>L1E-03</li> <li>MAPZK6, AZZ, L1A, AKT2, RELB, NFKBE, TNFAIP3, NFKB2, JL1R1, MALT1, IL1R2, TLR10, NFKBIA, CD40, MAP3K7, PIK3C3, LTA, TLR6, CSNRCA1, ICF1R, AKT3, RPS</li> <li>NESCO of osteoblasts, osteoclasts</li> <li>AKT2, MAPK9, IKBKE, IL1R1, AKT2, RELB, NFKBE, TNFAIP3, NFKB2, JL1R1, MALT1, IL1R2, NFKBIA, CD40, MAP3K7, PIK3C3, AKT3, BIRC3, and chondrocytes in rheumatoid arthritis</li> <li>Rank signaling in osteoclasts</li> <li>L6E-03</li> <li>MAP2K6, AKT2, CAMK4, NFKBIE, CSNK1A1, TCF7, TGB3, IL18R1, SMURF1, IL1R2, NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3, AKT2, MAPK9, IKBKE, IL1R1, TCF3, IL7, CALM1 (includes others), OL1A1, FZD6, TNF, WNT5A</li> <li>AKT2, MAPK9, IKBKE, IL1R1, TCF3, IL7, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3</li> <li>Regulation of eIF4 and</li> <li>P16-03</li> <li>AKT2, EIF3H, PPP2CA, RPS28, EIF1, EIF4A2, RPS23, EIF3M, EIF2S2, EIF3E, EIF1AX, PIK3C3, EIF2B5, EIF3A, AKT3, PP2RSC</li> <li>P70S6K signaling</li> <li>CD-63</li> <li>CD-64</li> <li>CD-60</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P16-74</li> <li>P176-74</li> <li>P16-74</li> <li>P176-74</li> <li>P176-74</li> <li>P178-74</li> <li>P17</li></ul>	cardiovascular system	1.0E-03	UBEZGZ, VEGRA, UBEZLS, NIRKBIA, UBEZQI, SUNIOI, NIRKBIE, UBEZD4, CREBS, UBEZD3, PIEN, UBEZI
PIK3C3, EIP2B5, EIF3A, AKT3, RPS20, RPS13A, RPL13         NF-kB signaling       1.1E-03       MAP2K6, AZI2, LILA, AKT2, REJB, NFKBE, TNFAIP3, NFKB2, ILIR1, MALT1, IL1R2, TLR10, NFKBIA, CD40, MAP3K7, PIK3C3, LTA, TLR6, SNIXCA1, ICF1R, AKT3, TNF         Role of osteoblasts, osteoclasts       1.3E-03       SOCS3, STAT5A, ILSP, IRX2C3, SOCS2, STAT3, NFKB2, TNF         Role of osteoblasts, osteoclasts       1.5E-03       MAP2K6, IL1A, CAMK4, NFKBIE, CSNIKA1, TCF3, ILT2, NLR18, SMURF1, IL1R2, NFKBIA, IGF1, MAP3K7, PIK3C3, AKT3, BIRC3, and chondrocytes in rheumatoid arthritis         Rank signaling in osteoclasts       1.6E-03       MAP2K6, RIX2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3, BIRG3         Regulation of eIF4 and       2.1E-03       AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, CARS2, OR PS15A, PP02RSE         CD28 signaling in Thelper cells       2.1E-03       HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, CD80, PIK3C3, CD86, AKT3         rCOS-iCOSL signaling in Thelper cells       2.4E-03       HLA-DMA, AKT2, GAML4B, JMY, FAS, TP3BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDD         rDil-like receptor signaling       2.7E-03       WTI, PMAIP1, AKT2, GADD45B, JMY, FAS, TP3BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDD         rDil-like receptor signaling       3.2E-03       TNFKSP9, NFKBIA, MAP3K7, TIK3C3, NFKBIE, KAT3, MAPS9, IKBKE, TATA7, MAFS9, IKBKE, TATA7, MAFS9, IKBKE, TATA7, MAFS9, IKBKE, MAR2	EIF2 signaling	1.0E-03	RPL22, AKT2, EIF3H, RPS28, EIF1, RPL37, PPP1CB, EIF4A2, RPL23, RPL35A, RPS23, EIF3M, RPL15, EIF2S2, EIF3F, EIF3B, EIF1AX,
<ul> <li>NF-kB signaling</li> <li>1.1E-03</li> <li>MAP2KG, AZI2, ILIA, AKT2, RELB, NFKBIE, TNFAIP3, NFKB2, ILIR1, MALT1, ILIR2, TLR10, NFKBIA, CD40, MAP3K7, PIK3C3, LTA, TLR6, CNK2AT, IGF1R, AKT3, TNF</li> <li>il-9 signaling</li> <li>1.3E-03</li> <li>SOCS3, STAT5A, IJSP, PIK3C3, SOCS2, STAT3, NFKB2, TNF</li> <li>SOCS3, STAT5A, LIPA, PIK3C3, SOCS2, STAT3, NFKB2, TNF</li> <li>MAP2KG, AKT2, CAMK4, MAP3K13, NFKBIE, CNK1A1, TC7, TGB3, ILIRR1, SMURF1, ILIR2, NFKBIA, IGF1, MAP3K7, PIK3C3, AKT3, BIRC3, AKT2, MAPK6, IKBKE, ILIR1, TC73, IL7, ALM1 (includes others), OLIA1, FZDG, TNF, WNT5A</li> <li>Regulation of elF4 and</li> <li>PS0 (D28 signaling in T helper cells</li> <li>CD28 signaling in T helper cells</li> <li>L1E-03</li> <li>HL2-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, NFKBIA, CD80, PIK3C3, CD86, AKT3</li> <li>COS-iCOSL signaling in T helper cells</li> <li>L1E-03</li> <li>HL3-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, NFKBIA, CD80, PIK3C3, CD86, AKT3</li> <li>COS-iCOSL signaling in T helper cells</li> <li>L2E-03</li> <li>HL3-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, NFKBIA, CD80, PIK3C3, AKT3, NFKBIA, CD80, PIK3C3, AKT3, NFKBIA, CD80, PIK3C3, CD86, AKT3</li> <li>COS-iCOSL signaling in T helper cells</li> <li>L2E-03</li> <li>HL3-DMA, AKT2, CAMK4, NFKBIE, MAP4, TRKB, NFKBE, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, NFKBIA, MPK9, TR44, TR6, TNFAIP3, NFKB2, PTEN, CD80, PIK3C3, AKT3, NFKBIA, MPK9, TTA4, TLR6, TNFAIP3, NFKB2, TRAF1</li> <li>L1-17A signaling in T lymphocytes</li> <li>L2-25 signaling in T lymphocytes</li> <li>L3E-03</li> <li>AKT2, NFKBIA, MAP3K7, PIK3C3, NK5BIE, MAPK9, IKBKE, STAT3, NFKB2, PTEN</li> <li>L3-24 Signaling</li> <li>AKT2, NFKBIA, MAP3K</li></ul>			PIK3C3, EIF2B5, EIF3A, AKT3, RPS20, RPS15A, RPL13
<ul> <li>TLR6, CSNR2A1, IGF1R, AKT3, TNF</li> <li>TLR6, CSNR2A1, IGF1R, AKT3, TNF</li> <li>Seros SOC33, STAT5A, IJ98, PIK3C3, SOC2, STAT3, NFKB2, TNF</li> <li>Role of osteoblasts, osteoclasts and chondrocytes in rheumatoid arthritis</li> <li>Rank signaling in osteoclasts</li> <li>L5E-03 MAP2K6, IL1A, CAMK4, NFKBIE, CSNK1A1, TCF7, ITGB3, IL18R1, SMURF1, IL1R2, NFKBIA, IGF1, MAP3K7, PIK3C3, AKT3, BIRC3, AKT2, MAPK9, IKBKE, IL1R1, TCF3, IL7, CALM1 (includes others), COL1A1, FZD6, TNF, WNT5A</li> <li>Rank signaling in osteoclasts</li> <li>L6E-03 MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3</li> <li>Regulation of elF4 and p7056K signaling</li> <li>CD28 signaling in T helper cells</li> <li>L1E-03 HLA-DMA, AKT2, CAMK4, NFKBIE, HIA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, OB90, PIK3C3, CD86, AKT3</li> <li>COS-iCOSL signaling in T helper cells</li> <li>L1E-03 HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, CD80, CD40, PIK3C3, AKT3, IZPA, IL2PA, IL2PA</li> <li>CD28 signaling in T helper cells</li> <li>L1E-03 HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IZPA, IL2PA, IL2PA, IL2PA</li> <li>L2PA IL2PA, IL2PA</li> <li>TOIl-like receptor signaling</li> <li>J0E-03 PPARA, MAP2K6, TLR10, NFKBIE, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF1</li> <li>L-17A signaling in T lymphocytes</li> <li>J3E-03 AKT2, NFKBIE, MAPK9, IKBKE, NFKB2, TAF41</li> <li>L-17A signaling</li> <li>J3E-03 TAT2, NFCKBIE, MAPK9, IKBKE, NFKB2, TLR1, AFK3, SOC54, STAT3, SOC5</li></ul>	NF-ĸB signaling	1.1E-03	MAP2K6, AZI2, IL1A, AKT2, RELB, NFKBIE, TNFAIP3, NFKB2, IL1R1, MALT1, IL1R2, TLR10, NFKBIA, CD40, MAP3K7, PIK3C3, LTA,
<ul> <li>In-Signaling (1): 15-03 SUCSS, SIATSA, ILSP, PLASCS, SUCSS, JATSS, MARSA, ILSP, PLASCS, SUCSS, JATSS, MARSA, ILSP, PLASCS, IDESS, PLASCS, JATSS, MARSA, ILSP, PLASCS, PLASCS, JATSS, MARSA, ILSP, PLASCS, PLASCS,</li></ul>	il O signalia a	1 25 02	TLR6, CSNK2A1, IGF1R, AKT3, TNF
<ul> <li>Kord outcome and chondrocytes in rheumatoid arthritis</li> <li>Rank signaling in osteoclasts</li> <li>LoE-03</li> <li>AKT2, MAPK9, IKBKE, LLTR1, TCF3, LL7, CALM1 (includes others), COL1A1, FZD6, TNF, WNT5A</li> <li>AKT2, MAPK9, IKBKE, LLTR1, TCF3, LL7, CALM1 (includes others), COL1A1, FZD6, TNF, WNT5A</li> <li>BiRC3</li> <li>Regulation of elF4 and p7056K signaling</li> <li>CD28 signaling in T helper cells</li> <li>CD28 signaling in T helper cells</li> <li>CD5-0</li> <li>HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), NFKBIA, ACTR3, NFKBIA, CD80, PIX3C3, CD86, AKT3</li> <li>CD5-10SL signaling in T helper cells</li> <li>CD6-10S PVRAR, MAP2K6, TLR10, NFKBIA, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, LZR4, LZR8</li> <li>P53 signaling in in invov cells</li> <li>3.E-03</li> <li>SDC-03</li> <li>PFARA, MAP2K6, TLR10, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF1</li> <li>L-17A signaling in airway cells</li> <li>3.E-03</li> <li>SAF14, SOCS1, SOCS3, STAT5A, AKT2, AKT3, MAPK9, IKBKE, STAT3, NFKB2, CLAR, BIRC3, TNF, FAS</li> <li>P418B signaling in airway cells</li> <li>3.E-03</li> <li></li></ul>	Role of osteoblasts, osteoclasts	1.3E-03 1.5E-03	SUCS3, STATSA, IL9K, PIK3C3, SUCS2, STAT3, NFKB2, TNF MAP2K6 II 1A CAMK4 NFKRIF CSNK1A1 TCF7 ITCR3 II 18R1 SMIIRF1 II 1R2 NFKRIA ICF1 MAP3K7 PIK3C3 AKT3 BIRC3
arthritisRank signaling in osteoclasts1.6E-03MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3Regulation of elF4 and p7056K signaling2.1E-03AKT2, EIF3H, PPP2CA, RPS28, EIF1, EIF4A2, RPS23, EIF3M, EIF2S2, EIF3F, EIF3B, EIF1AX, PIK3C3, EIF2B5, EIF3A, AKT3, PPP2R5C, RPS20, RPS15A, PPP2R5ECD28 signaling in T helper cells2.1E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, CD80, PIK3C3, CD86, AKT3iCOS-iCOSL signaling in T helper cells2.4E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IL2RA, IL2RBp53 signaling to1l-like receptor signaling 4-1BB signaling in T lymphocytes3.2E-03WT1, PMAIP1, AKT2, GADD45B, JMY, FAS, TP53BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDD10l-like receptor signaling 1L-22 signaling 1AK/Sta signaling3.6E-03SOCS3, STAT5A, AKT2, NFKBIA, NFKBIE, MAPK9, IKBKE, NFKB2, TRAF11L-22 signaling 1L-22 signaling 1AK (Sta signaling 1B aste-03SITAT4, SOCS1, SOCS3, SITAT5A, AKT2, PIK3C3, SITA5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3Death receptor signaling 1Potati signaling 1Potati signaling3.9E-03NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, CILAR, BIRC3, TNF, FASHepatic fibrosis/hepatic stellate cell activation4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, CILAR, BIRC3, TNF, FASInduction of apoptosis by HIV1 1Pot-1 signaling Production of nitric oxide and reactive oxygen species in macrophagesNFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1	and chondrocytes in rheumatoid	1.52 05	AKT2, MAPK9, IKBKE, IL1R1, TCF3, IL7, CALM1 (includes others), COL1A1, FZD6, TNF, WNT5A
Rank signaling in osteoclasts1.6E-03MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3, BIRC3Regulation of elF4 and p70S6K signaling2.1E-03AKT2, EIF3H, PPP2CA, RPS28, EIF1, EIF4A2, RPS23, EIF3M, EIF2S2, EIF3F, EIF3B, EIF1AX, PIK3C3, EIF2B5, EIF3A, AKT3, PPP2R5C, RPS20, RPS15A, PPP2R5ECD28 signaling in T helper cells2.1E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, CD80, PIK3C3, CD86, AKT3iCOS-iCOSL signaling in T helper cells2.4E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IL2RA, IL2RBp53 signaling2.7E-03WT1, PMAIP1, AKT2, GADD45B, JMY, FAS, TP53BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDDToll-like receptor signaling3.0E-03SOC3, STAT5A, AKT2, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF11L-122 signaling in airway cells3.3E-03AKT2, NFKBIA, MAP3K7, PIK3C3, NFKBIE, MAT9, NFKB2, TRAF11L-22 signaling3.0E-03SOC3, STAT5A, AKT2, PTS15, NFKB2, CFLAR, BIRC3, TNF, FASHepatic fibrosis/hepatic stellate cell activation4.0E-03SNAD2, IGEP4, VCAM1, IL1A, ICAM1, CXC19, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1IGF-1 signaling4.8E-03ICFBP4, SOCS3, SOC51, AKT2, IFKB2, MFKB2, RHOF, TNF, SIRPAProduction of nitric oxide and reactive oxygen species in macrophagesNFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03ICFBP4, SOCS1, SOCS1, SOCS1, SOCS2, CSNC24, IL1R1, AKT3, SOCS4, STAT3, SFNProduc	arthritis		
BIRC3Regulation of elF4 and p70S6K signaling2.1E-03AKT2, EIF3H, PPP2CA, RPS28, EIF1, EIF4A2, RPS23, EIF3M, EIF2S2, EIF3F, EIF3B, EIF1AX, PIK3C3, EIF2B5, EIF3A, AKT3, PPP2R5CCD28 signaling in T helper cells2.1E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, CD80, PIK3C3, CD86, AKT3iCOS-iCOSL signaling in T helper cells2.4E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, ILZRA, ILZRAp53 signaling2.7E-03WT1, PMAIP1, AKT2, GADD45B, JMY, FAS, TP53BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDDToll-like receptor signaling3.0E-03PPARA, MAP2K6, TLR10, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF11-17A signaling in T lymphocytes3.3E-03AKT2, NFKBIA, NFKBIE, MAPSW, IKBKE, NFKB2, TRAF11-128 signaling3.6E-03SOCS3, STAT5A, AKT2, PIK3C3, NFKBIE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTEN1L-22 signaling3.6E-03SOCS3, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3Death receptor signaling3.9E-03NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, CFLAR, BIRC3, TNF, FASHepatic fibrosis/hepatic stellate cell activation4.0E-03SMAD2, IGFBP4, VCAM1, IL1A, ICAM1, CXCL9, NFKB2, BIRC3, TNF, FAS, SOCS4, STAT3, SOCS4, STAT3, SFNHepatic fibrosis/bepatic stellate cell activation4.8E-03IFBRA, NFKBIE, MAPK9, IKBKE, MTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03IGFBP4, SOCS3, SOCS1, AKT2, CF1, PIK3C3, SOCS6, SOCS2, CSNC2A1, IGF1R, AKT3, SOCS4, STAT3, SFNProduction of nitric oxide and ractive oxygen species in<	Rank signaling in osteoclasts	1.6E-03	MAP2K6, AKT2, CAMK4, MAP3K13, NFKBIE, MAPK9, IKBKE, NFKB2, CALM1 (includes others), NFKBIA, MAP3K7, PIK3C3, AKT3,
Regulation of elf4 and p7056K signaling2.1E-03ART2, EIF3H, PP2CPC, RF323, EIF1, EIF4A2, RF323, EIF3H, EIF3B, EIF1AA, PIK3C3, EIF2B5, EIF3A, ART3, PIP2RSECD28 signaling in T helper cells2.1E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA, CD80, PIK3C3, CD86, AKT3iCOS-iCOSL signaling in T helper cells2.1E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IL2RA, IL2RAp53 signaling2.7E-03WT1, PMAIP1, AKT2, GADD45B, JMY, FAS, TP53BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDDToll-like receptor signaling3.0E-03PPARA, MAP2K6, TLR10, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF14-1BB signaling in T lymphocytes3.2E-03TNFRSF9, NFKBIA, NFKBIE, MAPK9, IKBKE, NFKB2, RAF11L-17A signaling3.6E-03SOCS3, STAT5A, AKT2, AKT3, MAPK9, STAT3JAK/Stat signaling3.8E-03STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3JAK/Stat signaling3.9E-03NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1 cell activationInduction of apoptosis by HIV14.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF1-1 signaling4.9E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF2-1 signaling4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF1-1 signaling4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF2-1 signaling4.5E-03NFKB	Description of oIC4 and	2 15 02	BIRC3
Droom signalingIntract, on Start, TheoremCD28 signaling in T helper cells2.1E-03ICOS-iCOSL signaling in T helper cells2.4E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, CD86, AKT3iCOS-iCOSL signaling in T helper cells2.4E-03HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IL2RA, IL2RAp53 signaling2.7E-03TOIL-like receptor signaling3.0E-03PPARA, MAP2K6, TLR10, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF11-17A signaling in airway cells3.3E-03AKT2, NFKBIA, NFKBIE, MAPS, NFKBE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTENIL-22 signaling3.6E-03SOC3, STAT5A, AKT2, AKT3, MAPK9, STAT3JAK/Stat signaling3.8E-03STAT4, SOC51, SOC53, STAT5A, AKT2, NFKB2, CFLAR, BIRC3, TNF, FASHepatic fibrosis/hepatic stellate4.0E-03cell activation4.5E-03Induction of apoptosis by HIV14.5E-03IGF-1 signaling4.8E-03IGF2H signaling4.8E-03IGF2H signaling4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF2H signaling4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF2H signaling4.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF2H signaling4.5E-03NFKBIA, N	n70S6K signaling	2.1E-03	AN 12, EIF3H, PP2ZA, NE328, EIF1, EIF4A2, NE323, EIF3M, EIF232, EIF3F, EIF3B, EIF1AA, PIK3C3, EIF2B3, EIF3A, AK13, PPP2K3C, R053A, P0515A, P072F5
<ul> <li>CD80, PIK3C3, CD86, AKT3</li> <li>iCOS-iCOSL signaling in T helper cells</li> <li>2.4E-03</li> <li>HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, Signaling</li> <li>2.7E-03</li> <li>WT1, PMAIP1, AKT2, GADD45B, JMY, FAS, TP53BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDD</li> <li>TOIL-like receptor signaling</li> <li>3.2E-03</li> <li>TNFRSF9, NFKBIA, NFKBIE, MAPK9, IKBKE, NFKB2, TRAF1</li> <li>IL-17A signaling in airway cells</li> <li>3.3E-03</li> <li>AKT2, NFKBIA, MAP3K7, PIK3C3, NFKBIE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTEN</li> <li>IL-22 signaling</li> <li>3.6E-03</li> <li>SOC33, STAT5A, AKT2, AKT3, MAPK9, STAT3</li> <li>JAK/Stat signaling</li> <li>3.8E-03</li> <li>STAT4, SOCS1, SOC35, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3</li> <li>Death receptor signaling</li> <li>3.8E-03</li> <li>STAT4, SOCS1, SOC35, STAT54, AKT2, NFKB2, CTLAR, BIRC3, TNF, FAS</li> <li>Hepatic fibrosis/hepatic stellate cell activation</li> <li>Induction of apoptosis by HIV1</li> <li>4.5E-03</li> <li>NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1</li> <li>IGF-1 signaling</li> <li>YAEB-03</li> <li>NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1</li> <li>IGFP4, SOCS3, SOCS1, AKT2, AKT2, IFK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN</li> <li>YPARA, AKT2, APOM, PPP2CA, NFKBIE, MAPK9, IKBKE, MAPK9, IKBKE, NFKB2, RAP14, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP1CB, MAPK9, IKBKE, NFKB2, RAP14, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA</li> </ul>	CD28 signaling in T helper cells	2.1E-03	HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, MAPK9, IKBKE, MALT1, NFKB2, CALM1 (includes others), PAK1, ACTR3, NFKBIA,
<ul> <li>iCOS-iCOSL signaling in T helper cells</li> <li>2.4E-03</li> <li>HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3, AKT3, IL2RA, IL2RB</li> <li>p53 signaling</li> <li>2.7E-03</li> <li>WT1, PMAIP1, AKT2, GADD45B, JMY, FAS, TP53BP2, PTEN, CHEK1, CCND2, PIK3C3, AKT3, SFN, PIDD</li> <li>Yoll-like receptor signaling</li> <li>3.0E-03</li> <li>PPARA, MAP2K6, TLR10, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAIP3, NFKB2, TRAF1</li> <li>L-17A signaling in airway cells</li> <li>3.3E-03</li> <li>AKT2, NFKBIA, MAP3K7, PIK3C3, NFKBE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTEN</li> <li>IL-22 signaling</li> <li>3.6E-03</li> <li>SOCS3, STAT5A, AKT2, AKT3, MAPK9, STAT3</li> <li>JAK/Stat signaling</li> <li>3.8E-03</li> <li>STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIKS15, NFKB2, CFLAR, BIRC3, TNF, FAS</li> <li>Hepatic fibrosis/hepatic stellate cell activation</li> <li>Induction of apoptosis by HIV1</li> <li>IGF-1 signaling</li> <li>YoFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1</li> <li>IGFP4, SOCS3, SOCS1, AKT2, ICF1, PIK3C3, SOCS6, SOCS2, CNX2A1, ICF1R, AKT3, SOCS4, STAT3, SFN</li> <li>Production of nitric oxide and reactive oxygen species in macrophages</li> </ul>			CD80, PIK3C3, CD86, AKT3
AKT3, IL2RA, IL2RBp53 signaling2.7E-03Toll-like receptor signaling3.0E-034-1BB signaling in T lymphocytes3.2E-03IL-17A signaling in airway cells3.3E-03AKT2, NFKBIA, MAP3K7, PIK3C3, NFKBI2, NFKB2, TRAF1IL-22 signaling3.6E-03JAK/Stat signaling3.6E-03SOCS3, STAT5A, AKT2, AKT3, MAPK9, IKBKE, NFKB2, NFKB2, STAT3, NFKB2, PTENIL-22 signaling3.8E-03JAK/Stat signaling3.8E-03STAT4, SOCS1, SOCS3, STAT5A, AKT2, NFKBIE, AKT3, MAPK9, IKBKE, STAT3, SOCS4, STAT3Death receptor signaling3.9E-03NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, CFLAR, BIRC3, TNF, FASHepatic fibrosis/hepatic stellate cell activation4.0E-03Induction of apoptosis by HIV14.5E-03IGF-1 signaling4.8E-03ICFBP4, SOCS3, SOCS1, AKT2, IFKBIA, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03ICFBP4, SOCS3, SOCS1, AKT2, IFKBIA, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03ICFBP4, SOCS3, SOCS1, AKT2, IFKBIA, MFKBIE, MAPK9, IKBKE, MTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03ICFBP4, SOCS3, SOCS1, AKT2, IFKBIA, MFKBIE, MAPK9, IKBKE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPAmacrophagesVPARA, AKT2, APOM, PPP2CA, NFKBIE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA	iCOS-iCOSL signaling in T helper cells	2.4E-03	HLA-DMA, AKT2, CAMK4, NFKBIE, HLA-DQA1, IKBKE, NFKB2, PTEN, CALM1 (includes others), NFKBIA, CD80, CD40, PIK3C3,
<ul> <li>b) Signaling 2, 7E-03 W11, PMAIP1, AK12, GADD458, JMT, PAS, IPSBP2, PEN, CHEKT, CCND2, PIK3C3, AK13, SPN, PDD</li> <li>c) 2,7E-03 W11, PMAIP1, AK12, GADD458, JMT, PAS, IPSBP2, PEN, CHEKT, CCND2, PIK3C3, AK13, SPN, PDD</li> <li>c) 3,0E-03 PPARA, MAP2K6, TLR10, NFKBIA, MAP3K7, TRAF4, TLR6, TNFAB13, NFKB2, TRAF1</li> <li>a) 3,0E-03 AK12, NFKBIA, MFKBIE, MAPK9, IKBKE, NFKB2, TRAF1</li> <li>c) 3,3E-03 AK12, NFKBIA, MAP3K7, PIK3C3, NFKBE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTEN</li> <li>c) 3,3E-03 SOCS3, STAT5A, AKT2, AKT3, MAPK9, STAT3</li> <li>c) 3,8E-03 STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIK3C3, NFKB2, CFLAR, BIRC3, TNF, FAS</li> <li>c) activation</li> <li>c) activation</li> <li>c) activation</li> <li>c) AKED4, NFKBIE, MAPK9, IKBKE, HTRA2, TNFSF15, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1</li> <li>c) activation</li> <li>c) NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS</li> <li>c) NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1</li> <li>l) GF-1 signaling</li> <li>e) AKE2.</li> <li>e) NFKBIA, NFKBIE, MAPK9, IKBKE, MTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1</li> <li>l) CFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CNN2A1, IGF1R, AKT3, SOCS4, STAT3, SFN</li> <li>e) PPARA, AKT2, APOM, PPP2CA, NFKBIE, MAPK9, IKBKE, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA</li> </ul>		2 75 02	AKT3, ILZRA, ILZRA
<ul> <li>Hard Receptor Signaling</li> <li>Sole of ThrRSP, MRHS, MAPS, STATS, SCH, MRHS, MR</li></ul>	Toll-like recentor signaling	2.7E-03 3.0F-03	WTT, PWAIPT, AKTZ, GADD45B, JWY, FAS, TP33BP2, PTEN, CHEKT, CCND2, PIK3C3, AKT3, SPN, PIDD PPARA MAP2K6 TERTO NEKRIA MAP3K7 TRAE4 TER6 TNEAIP3 NEKR2 TRAE1
IL-17A signaling in airway cells3.3E-03AKT2, NFKBIA, MAP3K7, PIK3C3, NFKBIE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTENIL-22 signaling3.6E-03SOCS3, STAT5A, AKT2, AKT3, MAPK9, STAT3JAK/Stat signaling3.8E-03STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3Death receptor signaling3.9E-03NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, CFLAR, BIRC3, TNF, FASHepatic fibrosis/hepatic stellate cell activationSMAD2, IGFBP4, VCAM1, IL1A, ICAM1, CXCL9, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1Induction of apoptosis by HIV14.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFNProduction of nitric oxide and reactive oxygen species in macrophages4.9E-03NFKBIA, NFKBIE, MAPK9, IKBKE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA	4-1BB signaling in T lymphocytes	3.2E-03	THERSES, NEKBIA, NEKBIE, MAPKS, IKBKE, NEKB2, TRAF1
IL-22 signaling       3.6E-03       SOCS3, STAT5A, AKT2, AKT3, MAPK9, STAT3         JAK/Stat signaling       3.8E-03       STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3         Death receptor signaling       3.9E-03       NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, CFLAR, BIRC3, TNF, FAS         Hepatic fibrosis/hepatic stellate cell activation       4.0E-03       SMAD2, IGFBP4, VCAM1, IL1A, ICAM1, CXCL9, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1         Induction of apoptosis by HIV1       4.5E-03       NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1         IGF-1 signaling       4.8E-03       IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN         Production of nitric oxide and reactive oxygen species in macrophages       NPARA, AKT2, APOM, PPP2CA, NFKBIE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA	IL-17A signaling in airway cells	3.3E-03	AKT2, NFKBIA, MAP3K7, PIK3C3, NFKBIE, AKT3, MAPK9, IKBKE, STAT3, NFKB2, PTEN
JAK/Stat signaling       3.8E-03       STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3         Death receptor signaling       3.9E-03       NFKBIA, NFKBIE, IKBKE, HTRA2, TNFSF15, NFKB2, CFLAR, BIRC3, TNF, FAS         Hepatic fibrosis/hepatic stellate cell activation       4.0E-03       SMAD2, IGFBP4, VCAM1, IL1A, ICAM1, CXCL9, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1         Induction of apoptosis by HIV1       4.5E-03       NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1         IGF-1 signaling       4.8E-03       IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN         Production of nitric oxide and reactive oxygen species in macrophages       NCF2, AKT3, PPP2CSC, PPP2R5E, RHOF, TNF, SIRPA	IL-22 signaling	3.6E-03	SOCS3, STAT5A, AKT2, AKT3, MAPK9, STAT3
Detail receptor signating       5.5E-03       NRKBIA, NRKBIE, INKRE, HTKAZ, INRSE/3, NRKBZ, CELAR, BIKCS, TNF, FAS         Hepatic fibrosis/hepatic stellate cell activation       4.0E-03       SMAD2, IGFBP4, VCAM1, IL1A, ICAM1, CXCL9, NFKB2, IL1R1, FAS, VEGFA, IL1R2, COL1A1, IGF1, CD40, IGF1R, TNF, CCR7, IFNAR1         Induction of apoptosis by HIV1       4.5E-03       NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1         IGF-1 signaling       4.8E-03       IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN         Production of nitric oxide and reactive oxygen species in macrophages       PPARA, AKT2, APOM, PPP2CA, NFKBIE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA	JAK/Stat signaling	3.8E-03	STAT4, SOCS1, SOCS3, STAT5A, AKT2, PIK3C3, SOCS6, SOCS2, AKT3, SOCS4, STAT3
<ul> <li>Induction of apoptosis by HIV1</li> <li>IGF-1 signaling</li> <li>Production of nitric oxide and reactive oxygen species in macrophages</li> <li>INDUCTION PROFESSION (CONTROL OF CONTROL OF CONTROL</li></ul>	Henatic fibrosis/benatic stellate	3.9E-03	INFORM, INFORME, INDRE, HIRZE, HIRSELS, INFORCE, CHARA, BICS, HIRF, FAS SMADD JGERRE VCMMI HIRA ICAMI COXIG NEKR2 HIRI FAS VECEA HIRZ COLIAI IGEI CDAD IGEIR THE CCR7 IENARI
Induction of apoptosis by HIV14.5E-03NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1IGF-1 signaling4.8E-03IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFNProduction of nitric oxide and reactive oxygen species in macrophages4.9E-03NFKBIA, NFKBIE, MAPK9, IKBKE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA	cell activation	1.02 05	
IGF-1 signaling       4.8E-03       IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN         Production of nitric oxide and reactive oxygen species in macrophages       4.9E-03       IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN	Induction of apoptosis by HIV1	4.5E-03	NFKBIA, NFKBIE, MAPK9, IKBKE, HTRA2, NFKB2, BIRC3, TNF, FAS, TRAF1
Production of nitric oxide and reactive oxygen species in macrophages       4.9E-03       PPAKA, AK12, APOM, PPP2CA, NFKBIE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCF2, AKT3, PPP2R5C, PPP2R5E, RHOF, TNF, SIRPA	IGF-1 signaling	4.8E-03	IGFBP4, SOCS3, SOCS1, AKT2, IGF1, PIK3C3, SOCS6, SOCS2, CSNK2A1, IGF1R, AKT3, SOCS4, STAT3, SFN
macrophages	Production of nitric oxide and	4.9E-03	PPAKA, AK12, APUM, PPP2CA, NFKBIE, MAP3K13, PPP1CB, MAPK9, IKBKE, NFKB2, RAP1A, APOL1, NFKBIA, MAP3K7, PIK3C3, NCC2 AVT2 DDD2D5C DD2D5C DD205C
	macrophages		וינויב, מדוש, דררבאשנ, צרצעשב, דחטר, וויר, שוגרא
AIM signaling 5.0E-03 GADD45B, NFKBIA, H2AFX, MAPK9, TDP1, CBX5, CREB5, CHEK1, CCNB1, SMC1A	ATM signaling	5.0E-03	GADD45B, NFKBIA, H2AFX, MAPK9, TDP1, CBX5, CREB5, CHEK1, CCNB1, SMC1A

Genes with FDR  $\leq$  0.05 and absolute fold change  $\geq$  1.2 were used for Ingenuity<sup>®</sup> pathway analysis. In cases where there are multiple probe sets for the same gene, the lowest *p* value was used.

ethanol, and can help in prioritizing findings from genetic studies and biomarker studies of expression in the more complex mixture of blood cells.

## Gene expression affected by ethanol

Ethanol activated many pathways related to inflammation (Table 1, Supplementary Tables 1 & 3). The NF $\kappa$ B and TNF $\alpha$  pathways

are central to inflammatory responses and alcoholic liver disease (Roh & Seki, 2013; Wang, Gao, Zakhari, & Nagy, 2012). These pathways showed strong increases in expression of many genes, including TNF $\alpha$ , 15 TNF receptors or TNF-associated genes, and 5 NF $\kappa$ B related genes (*NFKB1, NFKB2, NFKBIA or NFKBIE, IKBKE*). It is notable that *NFKB1* was found to be associated with risk for alcoholism (Edenberg et al., 2010). Seventy-seven genes downstream of NF $\kappa$ B and 151 downstream of TNF $\alpha$  were affected, as were

Table	2
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Pathways that differ between alcoholics and controls.

Ingenuity canonical pathways	p value	Molecules
Molecular mechanisms of cancer	9.8E-04	RAP2B, JAK1, GNA11, RHOT2, SOS2, RAC1, RALBP1, NBN, RHOQ, MAX, PRKAR1B, PRKCE, ARHGEF2, GNA13,
		ARHGEF3, CTNNB1, BCL2L11
Actin nucleation by ARP-WASP complex	1.0E-03	ARPC1A, RHOQ, RHOT2, SOS2, RAC1, NCK1
Protein ubiquitination pathway	1.0E-03	UCHL3, USP14, UBE2Q1, PSMD13, SKP1, HSPA8, PSMB7, UBE2J1, HSP90AB1, PSMB2, UBE2G1, HSPE1, PSMA4,
		PSMB1
Phospholipase C signaling	1.6E-03	CALM1 (includes others), RHOQ, HDAC7, GNG2, SOS2, RHOT2, RAC1, PRKCE, ARHGEF2, MEF2C, GNA13, ARHGEF3, LCP2
Breast cancer regulation by Stathmin1	2.9E-03	CALM1 (includes others), TUBB3, SOS2, GNG2, RAC1, PRKAR1B, PRKCE, PPP1R11, ARHGEF2, ARHGEF3, GNA13
G Beta Gamma signaling	4.4E-03	KCNJ5, SOS2, GNG2, GNA11, PRKAR1B, PRKCE, GNA13
RAN signaling	6.6E-03	KPNA2, TNPO1, RAN
Signaling by Rho family GTPases	8.9E-03	ARFIP2, ARPC1A, RHOQ, DIAPH3, RHOT2, GNG2, GNA11, RAC1, ARHGEF2, ARHGEF3, GNA13
Androgen signaling	9.8E-03	CALM1 (includes others), GNG2, GNA11, PRKAR1B, PRKCE, POLR2B, GNA13
Hypoxia signaling in the cardiovascular system	1.1E-02	UBE2J1, UBE2Q1, HSP90AB1, UBE2G1, CSNK1D
RhoGDI signaling	1.2E-02	ARPC1A, RHOQ, RHOT2, GNG2, GNA11, RAC1, ARHGEF2, ARHGEF3, GNA13
Netrin signaling	1.3E-02	RAC1, PRKAR1B, NCK1, ABLIM1
Fcγ receptor-mediated phagocytosis in macrophages and monocytes	1.6E-02	ARPC1A, RAC1, PRKCE, RAB11A, NCK1, LCP2
Tec Kinase signaling	1.7E-02	JAK1, RHOQ, RHOT2, GNG2, GNA11, PRKCE, GNA13, TNFRSF10A
Paxillin signaling	1.8E-02	ITGB2, ARFIP2, SOS2, RAC1, NCK1, ITGAL
Telomerase signaling	1.8E-02	ELF2, HSP90AB1, SOS2, HDAC7, PTGES3, ELF1
Ephrin B signaling	2.0E-02	GNG2, GNA11, RAC1, GNA13, CTNNB1
Acetyl-CoA biosynthesis I (Pyruvate Dehydrogenase	2.0E-02	DLAT, DLD
Complex)		
Huntington's disease signaling	2.1E-02	HSPA8, ARFIP2, BDNF, SOS2, HDAC7, GNG2, GNA11, PRKCE, CASP4, POLR2B
Integrin signaling	2.1E-02	RAP2B, ITGB2, ARPC1A, RHOQ, RHOT2, SOS2, RAC1, NCK1, ITGAL
Semaphorin signaling in neurons	2.2E-02	SEMA4D, RHOQ, RHOT2, RAC1
Cholecystokinin/Gastrin-mediated signaling	2.2E-02	RHOQ, RHOT2, SOS2, PRKCE, MEF2C, GNA13
Cleavage and Polyadenylation of Pre-mRNA	2.5E-02	PABPN1, CPSF4
Role of NFAT in regulation of the immune response	3.1E-02	CALM1 (includes others), SOS2, GNG2, GNA11, CSNK1D, MEF2C, GNA13, LCP2
CREB signaling in neurons	3.6E-02	CALM1 (includes others), SOS2, GNG2, GNA11, PRKAR1B, PRKCE, POLR2B, GNA13
Sertoli Cell-Sertoli cell junction signaling	3.8E-02	TUBB3, TJAP1, PPAP2B, RAC1, PRKAR1B, MLLT4, YBX3, CTNNB1
Tight Junction signaling	3.9E-02	RAC1, PRKAR1B, MLLT4, YBX3, ARHGEF2, CTNNB1, CPSF4
ERK5 signaling	4.5E-02	YWHAG, YWHAE, MEF2C, GNA13
ERK/MAPK signaling	4.6E-02	ELF2, YWHAG, SOS2, RAC1, PRKAR1B, PRKCE, PPP1R11, ELF1
Germ Cell-Sertoli cell junction signaling	4.7E-02	TUBB3, RHOQ, PPAP2B, RHOT2, RAC1, MLLT4, CTNNB1
PI3K/AKT signaling	4.9E-02	YWHAG, JAK1, YWHAE, HSP90AB1, SOS2, CTNNB1
CXCR4 signaling	4.9E-02	RHOQ, RHOT2, GNG2, GNA11, RAC1, PRKCE, GNA13

Genes with FDR  $\leq$  0.36 were used for Ingenuity<sup>®</sup> pathway analysis. In cases where there are multiple probe sets for the same gene, the lowest *p* value was used.

numerous genes downstream of the activated cytokines and more than 120 downstream of the interferons. The Toll-like receptors are also activated by ethanol. TXNIP (thioredoxin interacting protein; 1.5-fold higher in LCL from alcoholics) is also increased 10% by ethanol treatment. TXNIP, which functionally links ER stress to the inflammasome and activation of NFkB, was found to be 1.7-fold higher in the hippocampus of alcoholics (McClintick et al., 2013). Recently, neuroinflammation has been linked to alcoholism and may play a role in the addiction process (Crews et al., 2011; Mayfield et al., 2013). It has been hypothesized that lipopolysaccharides (LPS) introduced into circulation from the gut may be responsible for neuroinflammation (Mayfield et al., 2013) by activating peripheral TLR4 receptors to produce circulating cytokines that can cross the blood-brain barrier. Others have shown that a robust inflammatory response to ethanol does not require lipopolysaccharides from the gut-liver axis, and that a direct effect of ethanol on Toll-like receptor 4 can initiate neuroinflammation (Fernandez-Lizarbe, Montesinos, & Guerri, 2013). Our data show that a 24-h exposure to ethanol was sufficient to initiate this inflammatory response in LCLs without exposure to LPS.

Among the LCL genes differentially expressed upon exposure to ethanol, 1043 were differentially expressed in brain in 1 or more of 11 post-mortem gene expression studies, 58 of which also differed between alcoholics and controls (Supplementary Table 1). Most GWAS findings are in the non-protein coding portion of the genome, and are thought to influence gene expression. Traitassociated SNPs are more likely to be expression quantitative trait loci (Nicolae et al., 2010). We therefore examined the overlap between genes whose expression in LCLs was altered by ethanol and genes reported in GWAS studies. Two hundred eighty-four were identified by at least 1 GWAS (Supplementary Table 1, GWAS references therein), including 8 that also differed between alcoholics and controls (Supplementary Tables 1 & 2). Among the 284 genes, 12 were reported by 2 GWAS, including 2 genes associated with glutamate uptake. SLC9A9 (cation proton antiporter 9) is associated with alcohol dependence (Kendler et al., 2011) and alcohol dependence symptom count (Wang et al., 2013); it was also associated with smoking (Vink et al., 2009) and ADHD (Kondapalli et al., 2013). SLC9A9 expression was also altered in the frontal cortex of alcoholics (Liu et al., 2006; Wang et al., 2013). SLC1A1 (high affinity glutamate transporter) is associated with alcohol dependence (Edenberg et al., 2010; Kendler et al., 2011); it was also associated with obsessive-compulsive disorder (Wendland et al., 2009) and schizophrenia (Horiuchi et al., 2012). Three SNPs in or near SLC1A1 are correlated with gene expression levels in LCLs (Wendland et al., 2009), and are associated with increased expression in postmortem prefrontal cortex (Horiuchi et al., 2012). ANK3 (ankyrin 3, node of Ranvier) is associated with alcoholism (Kendler et al., 2011) and alcohol plus illegal substance dependence (Johnson et al., 2011), and also with posttraumatic stress disorder and externalizing behavior (Logue et al., 2013), bipolar disorder especially associated with stress (Leussis et al., 2013), and autism susceptibility (Bi et al., 2012). EPHB1 (ephrin receptor B1) is associated with alcoholism (Edenberg et al., 2010; Kendler et al., 2011) and also shown to differ in expression in the frontal cortex of alcoholics (Liu et al., 2007). SH3BP5, which was also differentially expressed in

alcoholics compared to controls, was identified in 2 GWAS related to alcohol dependence (Bierut et al., 2010; Johnson et al., 2011) and has been replicated recently in alcohol and nicotine co-dependence (Zuo, Zhang, et al., 2012).

#### Gene expression in alcoholics vs. controls

Genes that differ between alcoholics and controls were harder to detect, given the relatively high level of expression heterogeneity observed among all subjects. Such differences could reflect genomic variation between subjects including gene expression differences and gene product variations that contribute to risk, effects of repeated exposure to ethanol in the subject from whom the cells were derived, or gene  $\times$  environment interactions. Most of the pathways that exhibited expression differences between LCLs from alcoholics and controls are signaling pathways, including ones associated with brain functions (Table 2). *PRKCE* is known to affect ethanol consumption (Olive, Mehmert, Messing, & Hodge, 2000).

Thirteen genes differentially expressed in the alcoholics were associated with alcoholism in at least 1 of 14 GWAS (Supplementary Table 2; references therein). *ZNF415* (Zinc finger 415, a transcriptional regulator) had the largest fold difference between alcoholics and controls (1.9-fold increase) and was previously identified by post-mortem expression (Sokolov et al., 2003) and GWAS (Kendler et al., 2011).

We did not detect significant interaction between alcoholic status and ethanol exposure. After correction of the interaction term for multiple testing, only 1 probe set for an unknown transcript had an FDR <0.95. This may be an issue of power, given the relatively small number of genes detected as differentially expressed between the alcoholics and controls. There was substantial heterogeneity between LCL from different subjects, which reduces power to detect differences between alcoholics and controls but did not greatly interfere with detection of the effects of ethanol because of our paired design.

We have identified genes and pathways that differ in expression between alcoholics and controls, and genes that are affected by ethanol treatment. In a complex disease such as alcoholism, both pre-existing genetic risk factors that might influence gene expression, and expression differences that result from heavy drinking, can contribute to the disease. LCLs are an accessible tissue model, and 99% of the genes differentially expressed in LCLs treated with ethanol that could be mapped to the Gene 1.0 ST array are also expressed in at least 1 part of the brain. Many were also identified in studies of post-mortem brain. These data can be used to prioritize genes reported by GWAS at sub-genome-wide levels.

### Acknowledgments

Microarray studies were carried out using the facilities of the Center for Medical Genomics at Indiana University School of Medicine, which is supported in part by the Indiana Genomics Initiative of Indiana University (INGEN<sup>®</sup>); INGEN is supported in part by The Lilly Endowment, Inc.

The Collaborative Study on the Genetics of Alcoholism (COGA), Principal Investigators B. Porjesz, V. Hesselbrock, H. Edenberg, L. Bierut, includes 10 different centers: University of Connecticut (V. Hesselbrock); Indiana University (H.J. Edenberg, J. Nurnberger Jr., T. Foroud); University of Iowa (S. Kuperman, J. Kramer); SUNY Downstate (B. Porjesz); Washington University in St. Louis (L. Bierut, A. Goate, J. Rice, K. Bucholz); University of California at San Diego (M. Schuckit); Rutgers University (J. Tischfield); Southwest Foundation (L. Almasy); Howard University (R. Taylor); and Virginia Commonwealth University (D. Dick). Other COGA collaborators include: L. Bauer (University of Connecticut); D. Koller, S. O'Connor, L. Wetherill, X. Xuei (Indiana University); Grace Chan (University of Iowa); N. Manz, M. Rangaswamy (SUNY Downstate); A. Hinrichs, J. Rohrbaugh, JC Wang (Washington University in St. Louis); A. Brooks (Rutgers University); and F. Aliev (Virginia Commonwealth University). A. Parsian and M. Reilly are the NIAAA Staff Collaborators. We continue to be inspired by our memories of Henri Begleiter and Theodore Reich, founding PI and Co-PI of COGA, and also owe a debt of gratitude to other past organizers of COGA, including TingKai Li (currently a consultant with COGA), P. Michael Conneally, Raymond Crowe, and Wendy Reich, for their critical contributions. This national collaborative study is supported by National Institutes of Health Grant U10AA008401 from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA).

The LCLs are stored at RUDCR Infinite Biologics at Rutgers, the State University of New Jersey and are made available to qualified scientists. Brain tissues were received from the New South Wales Tissue Resource Centre, which is supported by the National Health and Medical Research Council of Australia, The University of Sydney, Prince of Wales Medical Research Institute, Neuroscience Institute of Schizophrenia and Allied Disorders, National Institute of Alcohol Abuse and Alcoholism (Grant R01 AA12725) and NSW Department of Health.

#### Appendix. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.alcohol.2014.07.004.

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