Sepsis is a syndrome with hyperactivity of TH17-like innate immunity and hypoactivity of adaptive immunity

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Abstract

Currently, there are two major theories for the pathogenesis of sepsis: hyperimmune and hypoimmune. Hyperimmune theory suggests that cytokine storm causes the symptoms of sepsis. On the contrary, hypoimmune theory suggests that immunosuppression causes the manifestations of sepsis. By using microarray study, this study implies that hyperactivity of TH17-like innate immunity and failure of adaptive immunity are noted in sepsis patients. Thus, both hyperimmune and hypoimmune play important roles in the pathophysiology of sepsis.

Introduction

Despite of the discovery of antibiotics, mortality rate of sepsis is still very high. Most important of all, the exact pathophysiology of sepsis is still unclear. Currently, there are two dominant theory to explain the etiology of sepsis: hyperimmune theory and hypoimmune theory. However, these two theories are contrary with each other. Hyperimmune theory was proposed by Dr. Lewis Thomas. In his classical paper in NEJM 1972, he proposed that hyperactivation of proinflammatory cytokines, the cytokine storm, is the actual cause of sepsis symptoms. These uncontrolled cytokines destruct and cause multiple organ failure. His theory is the mainstream theory of sepsis etiology. Based on this theory, therapeutic strategy such as antibody neutralizing TNFα was tested in septic patients in clinical trials. However, these antibodies did not improve the survival rate of septic patients. Further, anti-TNFα increased the mortality rate of septic patients in several clinical trials. That makes people to doubt the hyperimmune theory. Thus, another theory-hypoimmune theory emerges. Based on the observation that immunosuppressive patients are prone to get sepsis, hypoimmune status was suggested to be the etiology of sepsis. However, the hypoimmune theory cannot successfully explain the proinflmmatory cytokines storm noted in sepsis. Both hyperimmune theory and hypoimmune theory have clinical and experimental evidences. However, they are contrary with each other. Here, I use the microarray study of whole blood of septic patients to propose a new theory: Sepsis is a syndrome of hyperactivity of innate immunity and hypoactivity of adaptive immunity. This new theory solves the above controversy.

Material and Methods

Microarray dataset

According to Dr. J. A. Howrylak's research in Physiol Genomics 2009, he collected total RNA from whole blood in sepsis and sepsis induced ARDS patients.[1] He tried to find out molecular signature of ARDS compared to sepsis patients. His dataset is available in Gene Expression Omnibus (GEO) www.ncbi.nlm.nih.gov/geo (assession

number GSE 10474). I use his samples of sepsis patients from this dataset to do the further microarray analysis. The sample size is 21 patients with 35% mortality rate. The second dataset is from GSE20189 of Gene Expression Omnibus. This dataset was collected by Dr. Melissa Rotunno in Cancer Prevention Research 2011.[2] Molecular signature of early stage of lung adenocarcinoma was studied by microarray. I use the healthy control (sample size 21)whole blood RNA from this dataset to compare the septic patients. In this study, I perform further analysis to study peripheral leukocyte gene expression profiles of sepsis compared to those of healthy controls.

Statistical analysis

Affymetrix HG-U133A 2.0 genechip was used in both samples. RMA express software(UC Berkeley, Board Institute) is used to do normalization and to rule out the outliners of the above dataset. I rule out the potential outliners of samples due to the following criteria:

1. Remove samples which have strong deviation in NUSE plot

2. Remove samples which have broad spectrum in RLE value plot

3. Remove samples which have strong deviation in RLE-NUSE mutiplot

4. Remove samples which exceed 99% line in RLE-NUSE T2 plot

Then, Genespring XI software was done to analysis the significant expressed genes between ARDS and healthy control leukocytes. P value cut-off point is less than 0.05. Fold changecut-off point is >2.0 fold change. Benjamini-hochberg corrected false discovery rate was used during the analysis. Totally, a genelist of 3277 genes was generated from the HGU133A2.0 chip with 18400 transcripts including 14500 well-characterized human genes.

RT-PCR confirmation

Dr. J. A. Howrylak performed real time PCR for selected transcripts (cip1, kip2) by using TaqMan Gene Expression Assays (Applied Biosystems, Foster City, CA). In the second dataset, Dr. Melissa Rotunno also performed qRT-PCR test to validate the microarray results. RNA quantity and quality was determined by using RNA 600 LabChip-Aligent 2100 Bioanalyzer. RNA purification was done by the reagents from Qiagen Inc. All real-time PCRs were conducted by using an ABI Prism 7000 Sequence Detection System with the designed primers and probes for target genes and an internal control gene-GAPDH. This confirms that their microarray results are convincing compared to RT-PCR results.

Results

RMA analysis of whole blood from healthy normal control

The RMA analysis was performed for RNA samples from whole blood of healthy control of the lung adenocarcinoma dataset. Raw boxplot, NUSE plot, RLE value plot, RLE-NUSE multiplot, and RLE-NUSE T2 plot were generated. Then, sample was included and excluded by using these graphs(Figure 1A, 1B, 1C, 1D, 1E). Because of the strong deviation in the T2 plot, the sample GSM506435 was removed for the further analysis.

RMA analysis of whole blood from septic patients

The RMA analysis was performed for RNA samples from whole blood of sepsis patients dataset. Raw boxplot, NUSE plot, RLE value plot, RLE-NUSE multiplot, and RLE-NUSE T2 plot were generated. Then, sample was included and excluded by using these graphs(Figure 2A, 2B, 2C, 2D, 2E)

Figure legends

Figure 1. RMA express plot for selecting samples in normal healthy controls.

1-A NUSE boxplot for normal control

1-B RLE boxplot for normal control

1-C RLE-NUSE multiplot for normal control

1-D RLE-NUSE T2 plot for normal control

1-E Raw data Boxpolt for normal control

Figure 2. RMA express plot for selecting samples in septic patients.

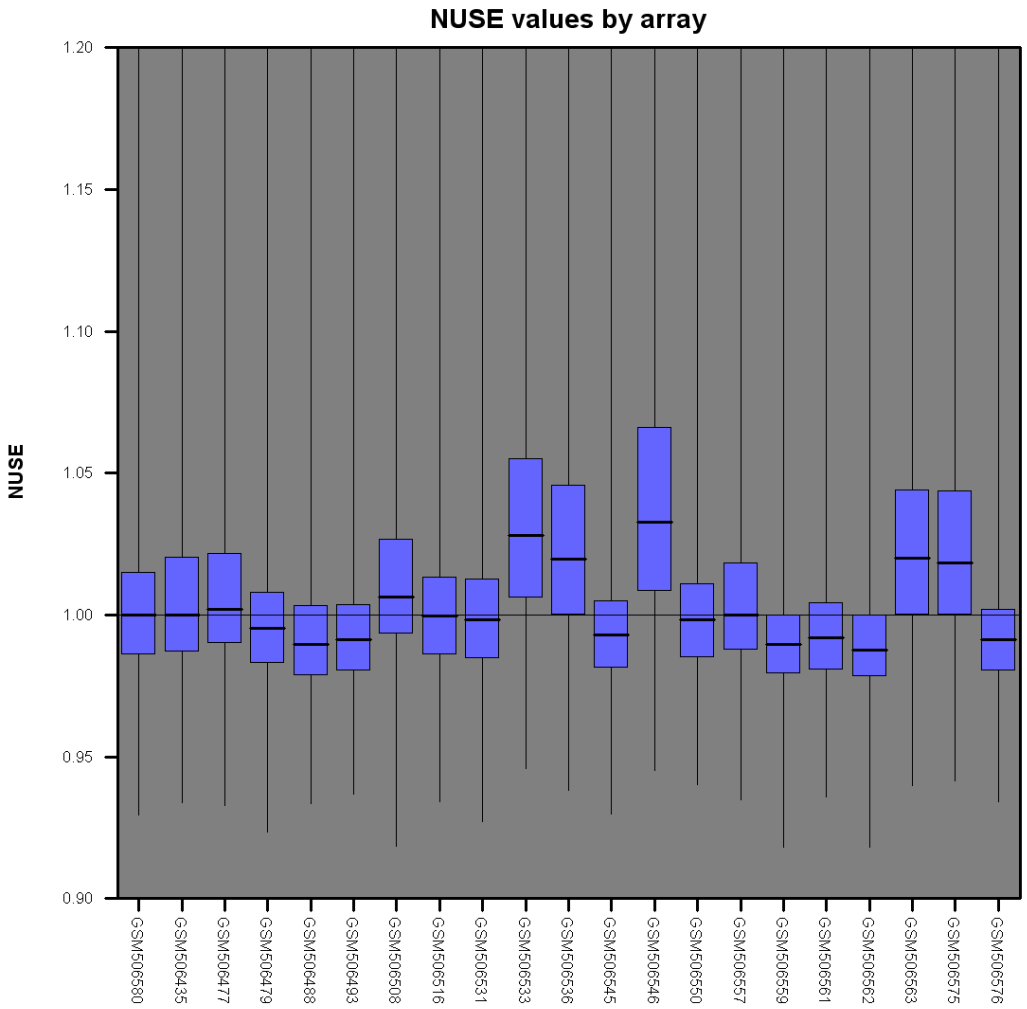
2-A NUSE boxplot for septic patients

2-B RLE boxplot for septic patients

2-C RLE-NUSE multiplot for septic patients

2-D RLE-NUSE T2 plot for septic patients

2-E Raw data Boxplot for septic patients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GSM506488
GSM506493
GSM506508
GSM506516
GSM506531
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GSM506546
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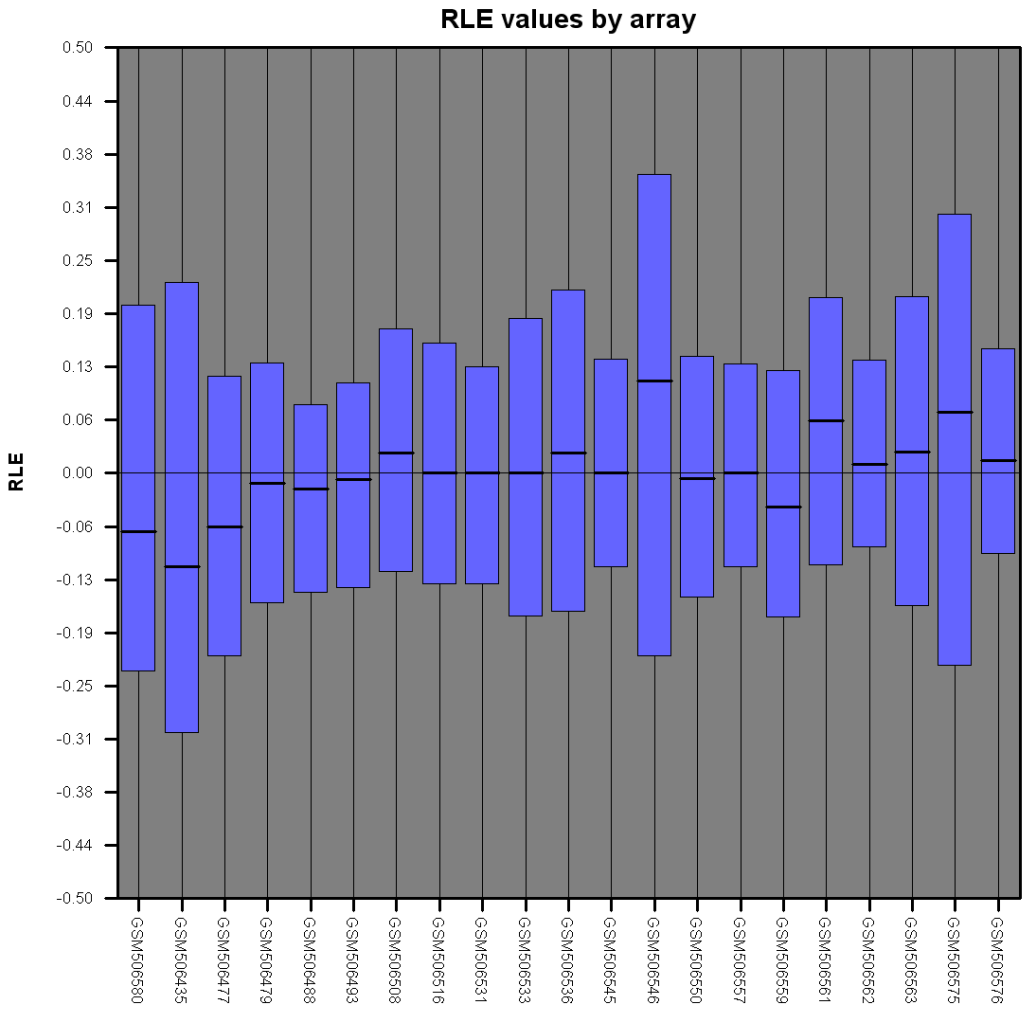
GSM506576

Figure 1A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0.31
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0.13
0.06
0.00
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-0.13
-0.19
-0.25
-0.31
-0.38
-0.44
-0.50
GSM506580
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GSM506479
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GSM506546
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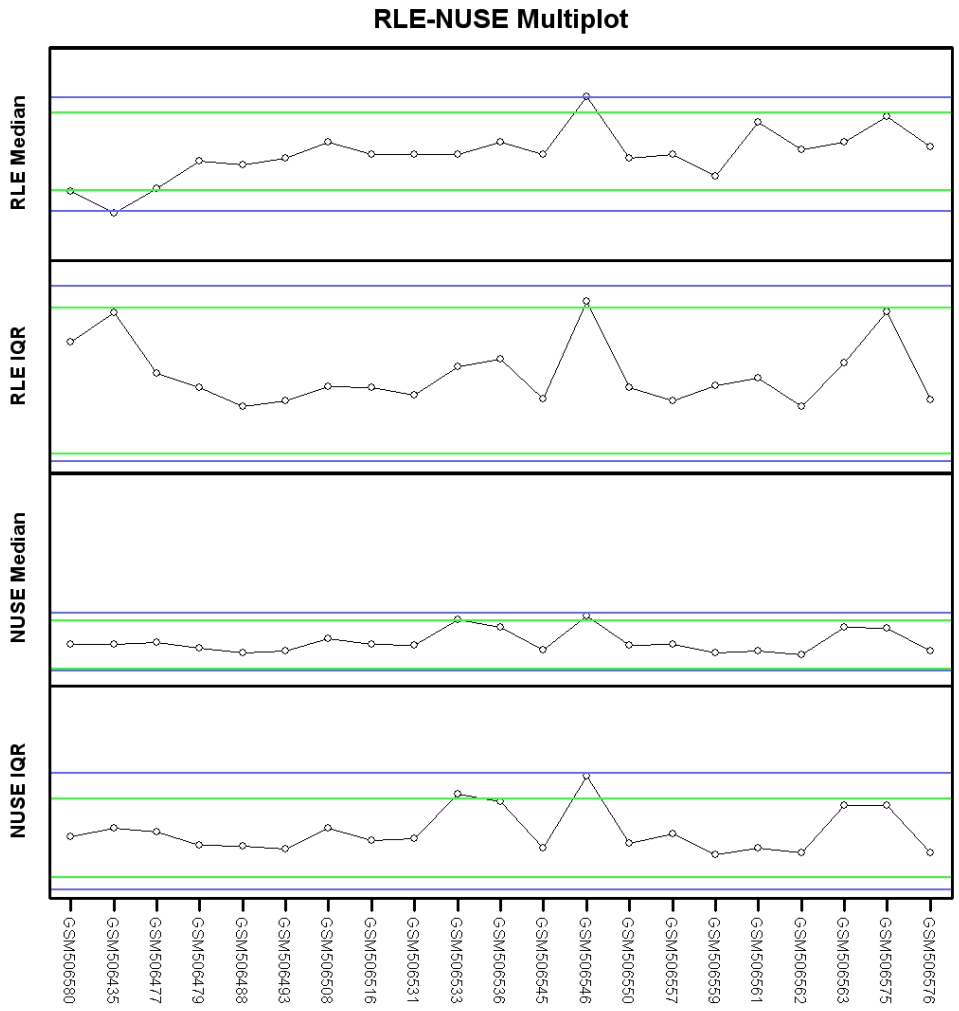
Figure 1-B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RLE Median
RLE IQR
NUSE Median
NUSE IQR
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Figure 1-C

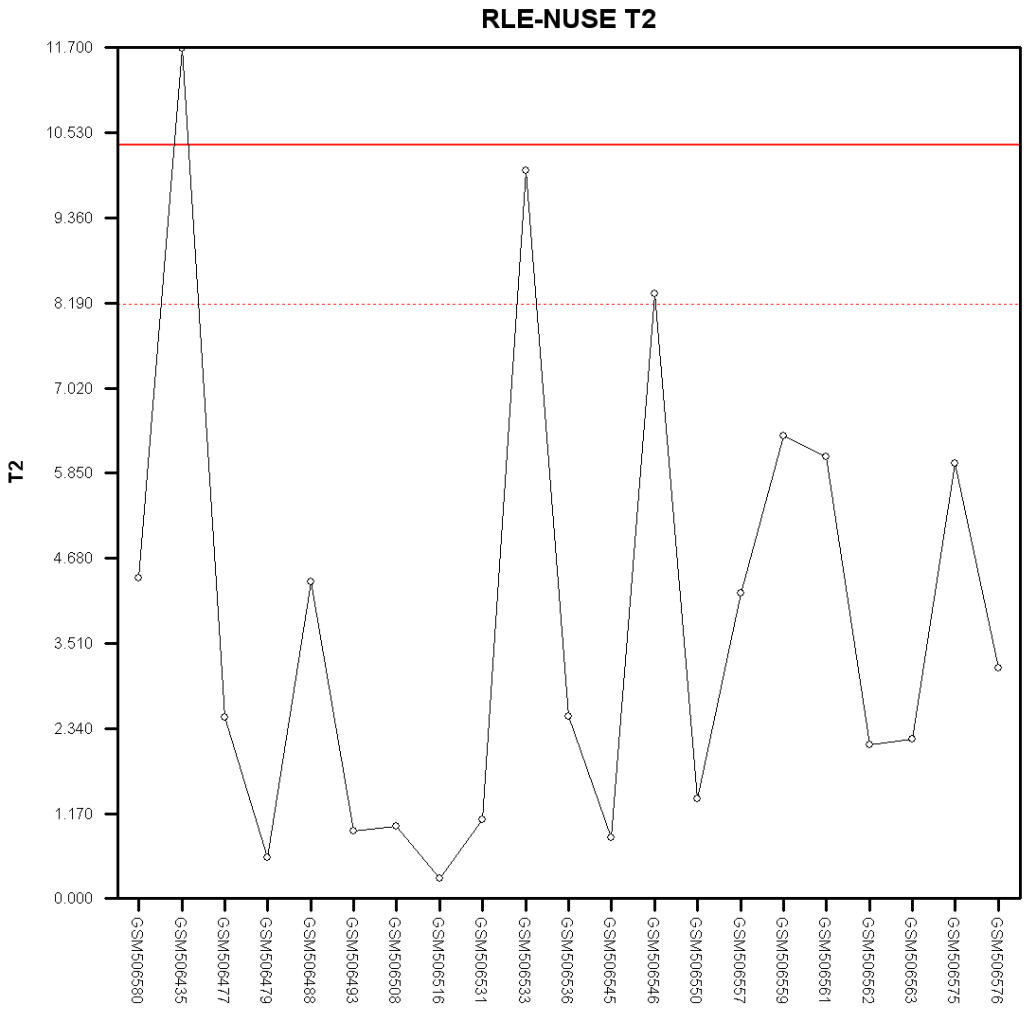
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Figure 1-D

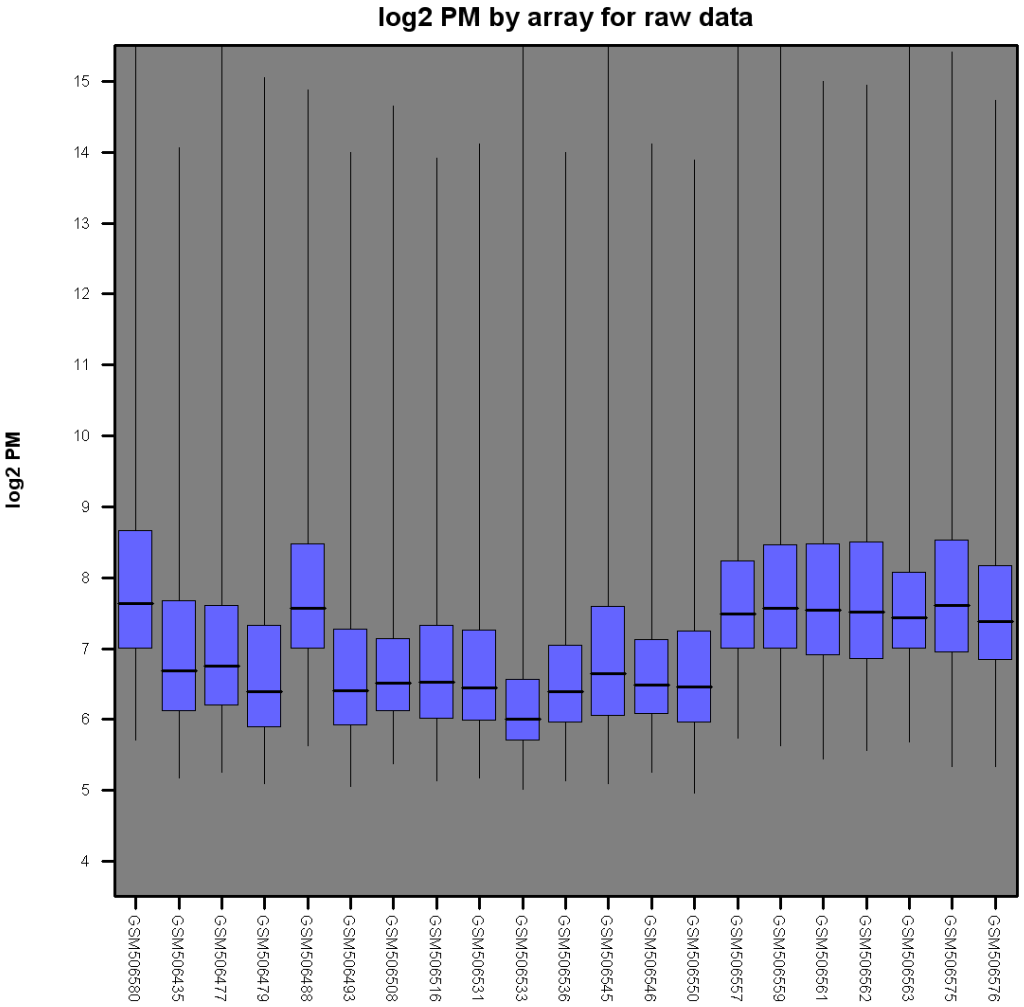
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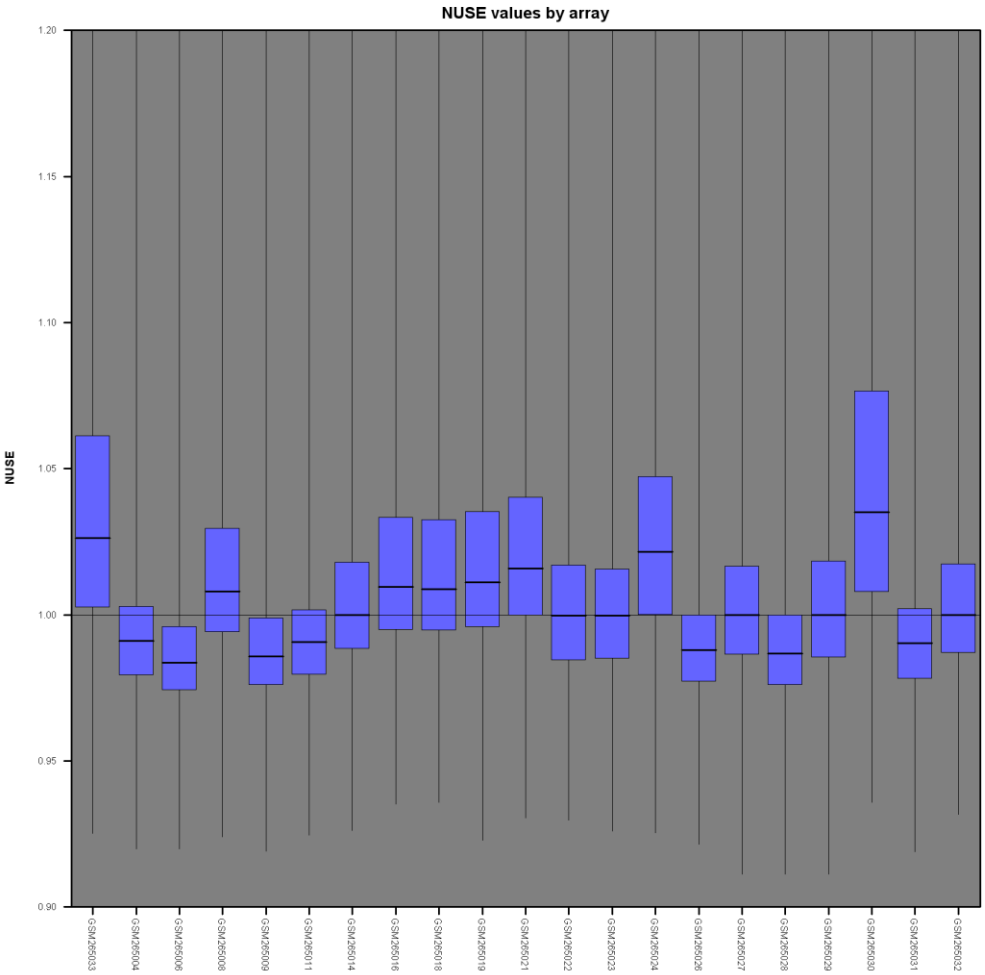
Figure 1-E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1.10
1.05
1.00
0.95
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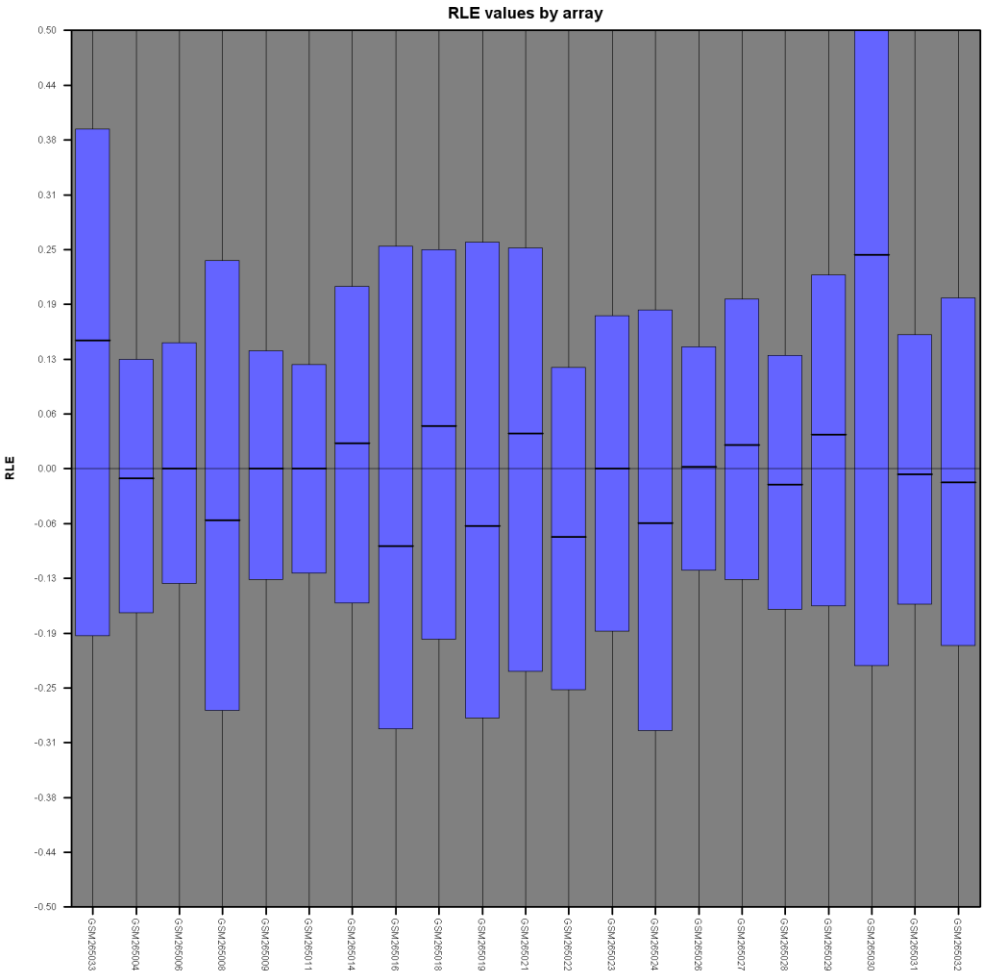
Figure 2-A


RLE values by array
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0.44
0.38
0.31
0.25
0.19
0.13
0.06
0.00
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-0.13
-0.19
-0.25
-0.31
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-0.44
-0.50
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Figure 2-B

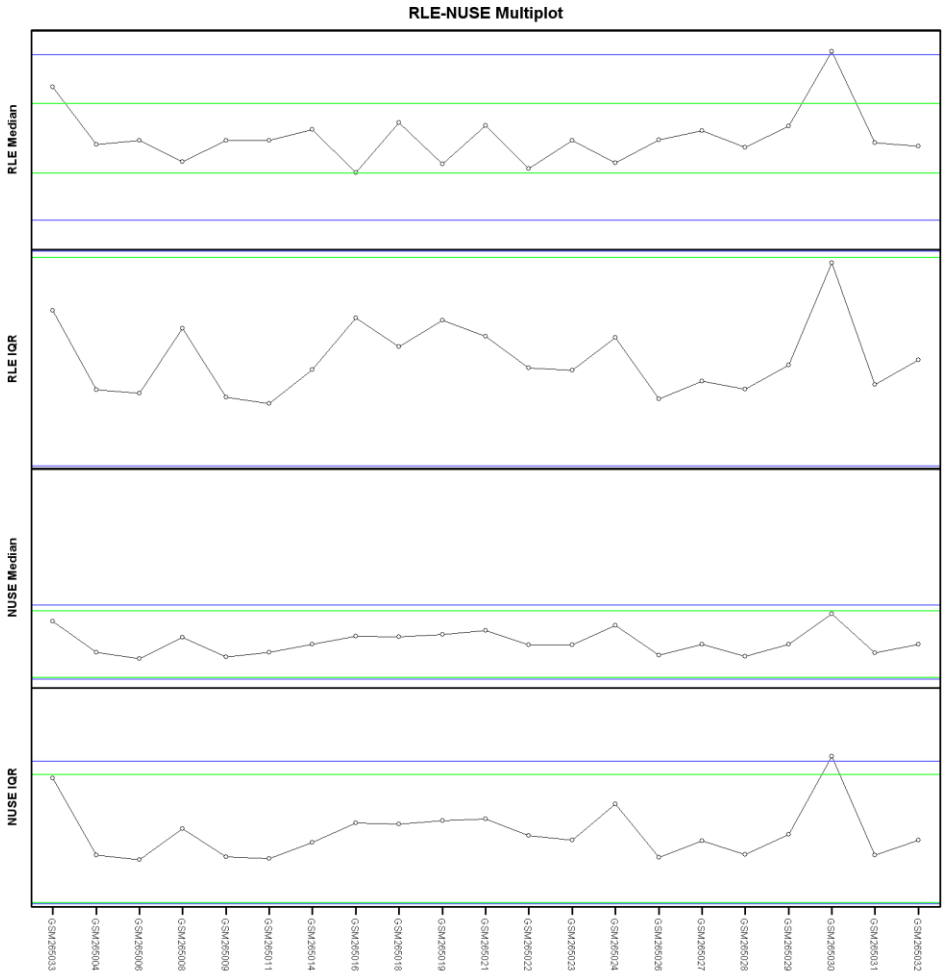
RLE-NUSE Multiplot
RLE Median
RLE IQR
NUSE Median
NUSE IQR
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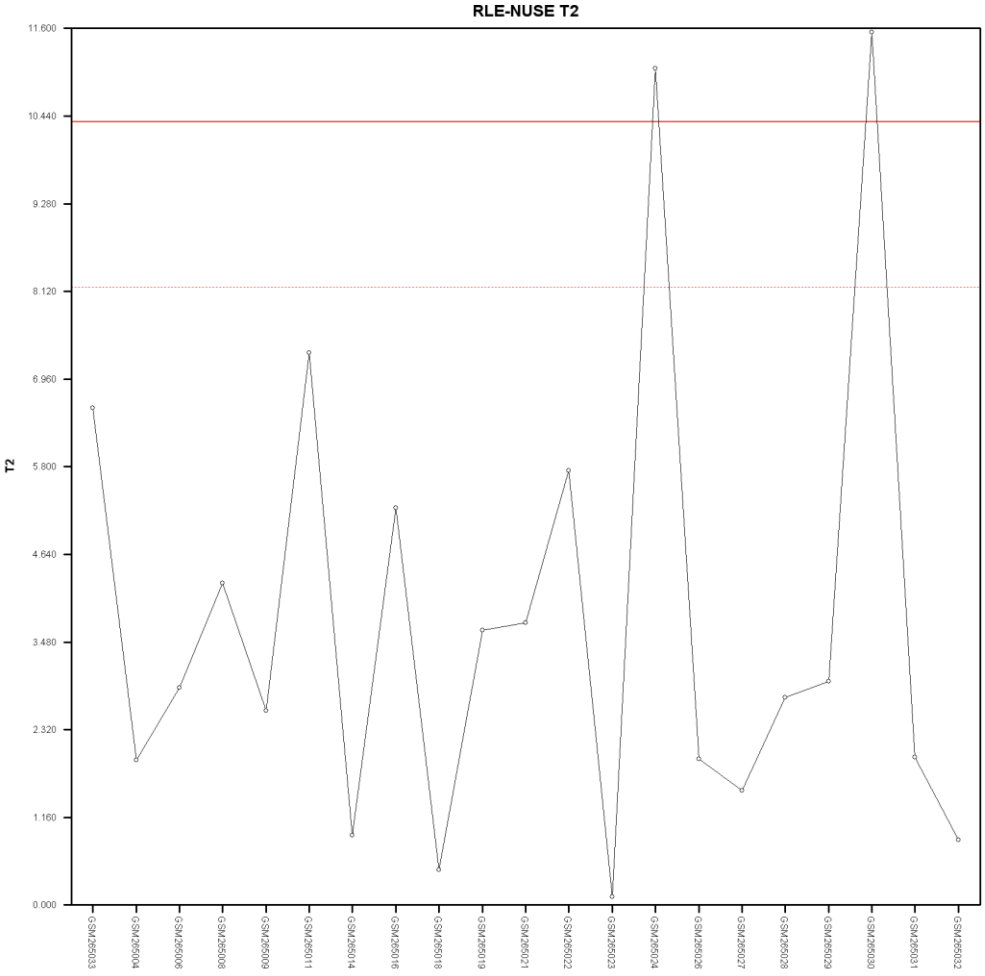
Figure 2-C


RLE-NUSE T2
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9.280
8.120
6.960
5.800
4.640
3.480
2.320
1.160
0.000
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Figure 2-D

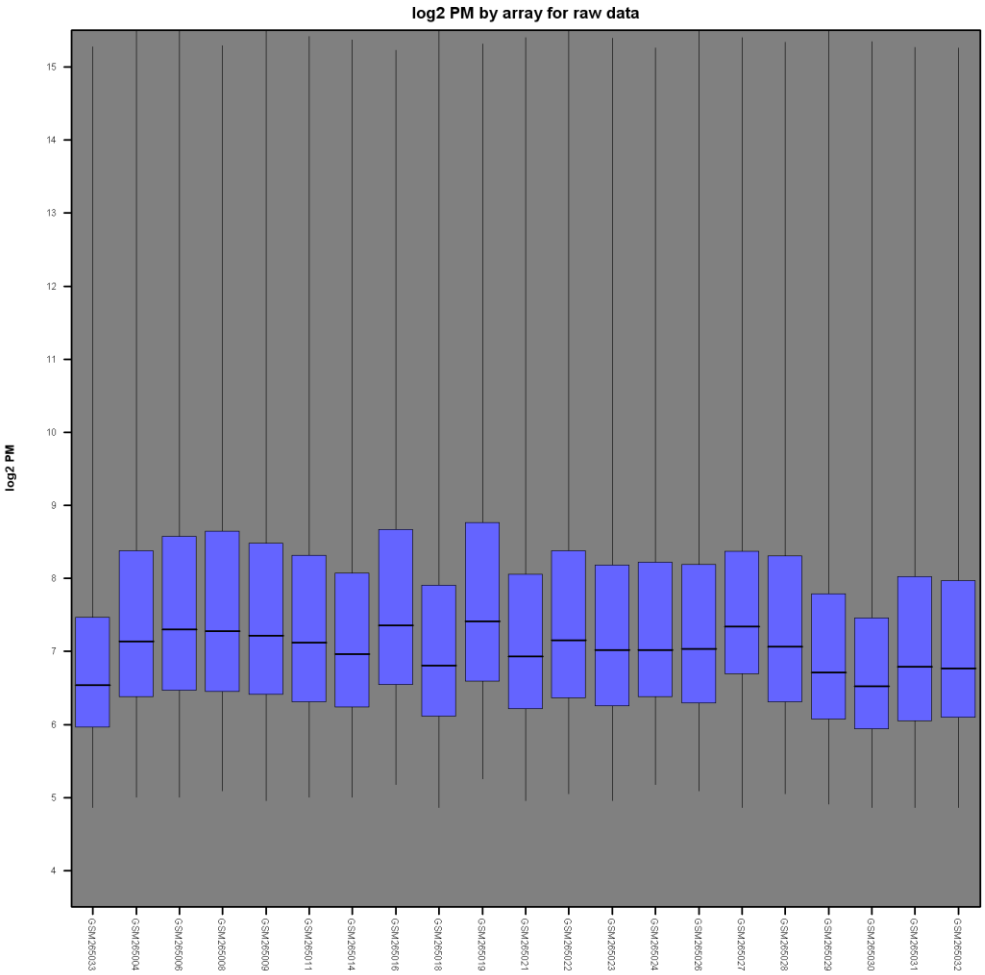
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Figure 2-E

Table 1. TLR

Probe ID	Pvalue	Arrow	Fold	Gene
201743_at	1.37E-04	up	2.176301	CD14
204924_at	1.45E-10	up	3.380896	TLR2
210166_at	9.16E-08	up	2.395743	TLR5
210176_at	0.001131	up	2.073326	TLR1
213817_at	3.14E-13	up	21.0364	IRAK3
219618_at	1.89E-09	up	2.692996	IRAK4
220832_at	4.76E-09	up	5.164016	TLR8
221060_s_at	6.62E-07	up	3.331681	TLR4
212184_s_at	2.03E-05	up	2.61743	TAB2
221705_s_at	8.46E-10	down	2.07506	SIKE1

Table 2. HSP

Probe ID	Pvalue	Arrow	Fold	Gene
200598_s_at	4.02E-04	down	2.112279	HSP90B1
200599_s_at	6.27E-04	up	2.143909	HSP90B1
200800_s_at	8.98E-09	up	2.664816	HSPA1A /1B
200941_at	1.29E-10	up	2.175182	HSBP1
200942_s_at	7.06E-08	up	2.197023	HSBP1
202557_at	1.10E-05	up	2.82175	HSPA13
202558_s_at	7.12E-05	up	2.112017	HSPA13
202581_at	1.98E-14	up	7.20045	HSPA1A/1B
202842_s_at	6.81E-06	up	2.73954	DNAJB9
202843_at	8.03E-07	up	2.087716	DNAJB9
206782_s_at	1.21E-09	up	2.374709	DNAJC4
208810_at	3.57E-04	up	2.196654	DNAJB6
209015_s_at	9.66E-09	up	2.548422	DNAJB6
209157_at	1.97E-10	up	2.893105	DNAJA2
210338_s_at	1.85E-05	down	2.06926	HSPA8
211936_at	1.05E-07	up	2.110743	HSPA5
211969_at	3.39E-17	down	13.51482	HSP90AA1
212467_at	1.01E-07	up	3.702917	DNAJC13
212911_at	1.88E-13	up	3.009307	DNAJC16
219237_s_at	2.18E-04	down	2.275608	DNAJB14

Table 3. Cathepsin

Probe ID	Pvalue	Arrow	Fold	Gene
200661_at	6.28E-10	up	2.550876	CTSA
200766_at	3.53E-12	up	3.746886	CTSD
201487_at	7.15E-06	up	2.584763	CTSC
203758_at	4.23E-08	down	2.3372	CTSO
205653_at	1.36E-04	up	3.234722	CTSG
210042_s_at	2.94E-07	up	3.044302	CTSZ
214450_at	2.16E-06	down	2.202781	CTSW

Table 4. Proteasome

Probe ID	Pvalue	Arrow	Fold	Gene
201052_s_at	8.16E-06	down	2.218188	PSMF1
201067_at	3.68E-20	down	4.692738	PSMC2
201232_s_at	5.58E-11	up	2.577756	PSMD13
201699_at	2.88E-08	up	4.61153	PSMC6
202352_s_at	1.45E-08	up	2.49783	PSMD12
202353_s_at	1.04E-07	up	2.4536	PSMD12
202753_at	6.55E-08	up	2.001992	PSMD6
203447_at	1.23E-10	up	2.450336	PSMD5
208805_at	6.04E-05	up	2.094127	PSMA6
208827_at	4.41E-09	up	2.513269	PSMB6
212220_at	1.31E-09	down	3.309962	PSME4
219485_s_at	1.85E-07	up	2.271658	PSMD10

Table 5. MHC

Probe ID	Pvalue	Arrow	Fold	Gene
201137_s_at	5.80E-04	down	2.085101	HLA-DPB1
203290_at	2.56E-08	down	5.193201	HLA-DQA1
204670_x_at	6.77E-08	down	2.848446	HLA-DRB1/B4
205671_s_at	1.27E-04	down	2.016965	HLA-DOB
208306_x_at	1.53E-06	down	2.437791	HLA-DRB1
208894_at	8.06E-07	down	2.762713	HLA-DRA
209312_x_at	1.24E-06	down	2.674953	HLA-DRB1/B4/B5
209823_x_at	8.65E-04	down	2.083243	HLA-DQB1
210294_at	7.08E-10	down	2.247553	TAPBP
210528_at	1.28E-05	down	2.565486	MR1
210982_s_at	4.46E-05	down	2.140575	HLA-DRA
211944_at	5.60E-22	down	7.377162	BAT2L2
211947_s_at	9.14E-14	down	4.692785	BAT2L2
211948_x_at	3.66E-28	down	11.74736	BAT2L2
211990_at	5.10E-06	down	3.188215	HLA-DPA1
211991_s_at	1.47E-05	down	2.428313	HLA-DPA1
212384_at	8.83E-15	down	2.983359	HLABAT1
212671_s_at	0.002545	down	2.265915	HLA-DQA1/A2
213537_at	7.83E-05	down	2.338689	HLA-DPA1
214052_x_at	4.45E-14	down	2.404988	BAT2L2
214055_x_at	1.16E-24	down	9.415468	BAT2L2
215193_x_at	2.90E-06	down	2.522364	HLA-DRB1/B3/B4
221491_x_at	1.50E-06	down	2.247077	HLA-DRB1/B3/B4/B5

Table 6. Transcription factor

Probe ID	Pvalue	Arrow	Fold	Gene
M97935_MA_at	1.92E-04	down	2.010955	STAT1
201473_at	3.65E-09	up	2.459731	JUNB
201502_s_at	9.16E-07	down	2.364327	NFKBIA
202527_s_at	5.77E-09	up	3.237444	SMAD4
203075_at	3.46E-06	up	2.133481	SMAD2
203077_s_at	4.90E-07	up	2.370214	SMAD2
203574_at	4.37E-10	up	5.176725	NFIL3
204039_at	4.62E-08	up	2.059098	CEBPA
204203_at	9.92E-07	up	2.172468	CEBPG
205026_at	1.66E-09	up	2.20184	STAT5B
205841_at	1.02E-13	up	4.655113	JAK2
205842_s_at	6.01E-07	up	2.878639	JAK2
206035_at	7.43E-10	down	2.106359	REL
206036_s_at	8.46E-12	down	4.746634	REL
206359_at	3.22E-07	up	2.092249	SOCS3
206363_at	9.68E-06	down	2.261549	MAF
208991_at	1.49E-13	down	3.223685	STAT3
209604_s_at	2.74E-19	down	6.546836	GATA3
209969_s_at	2.12E-08	down	4.748202	STAT1
210426_x_at	1.14E-12	down	6.358444	RORA
210479_s_at	5.21E-15	down	7.850211	RORA
212501_at	1.73E-07	up	2.169912	CEBPB
212549_at	7.00E-12	up	2.369991	STAT5B
212550_at	7.19E-10	up	2.522143	STAT5B
213006_at	6.03E-10	up	4.206962	CEBPD
218221_at	1.49E-11	up	2.349603	ARNT
218559_s_at	9.49E-07	up	3.354582	MAFB
218880_at	5.34E-11	up	3.750719	FOSL2

Table 7. Cytokine

Probe ID	Pvalue	Arrow	Fold	Gene
201108_s_at	2.84E-06	up	2.858913	THBS1
201109_s_at	3.87E-05	up	3.674066	THBS1
201110_s_at	2.02E-09	up	8.271206	THBS1
203085_s_at	1.57E-08	up	2.327314	TGFB1
203828_s_at	7.88E-05	down	2.130993	IL32
205016_at	8.33E-10	up	4.855893	TGFA
205992_s_at	4.40E-06	up	3.5756	IL15
208114_s_at	7.75E-20	down	5.849659	ISG20L2
208200_at	3.06E-11	down	4.80094	IL1A
212195_at	3.90E-06	up	2.667476	IL6ST
206488_s_at	1.04E-04	up	2.926877	CD36
209555_s_at	2.87E-05	up	3.18128	CD36
212657_s_at	2.96E-07	up	2.31195	IL1RN

Table 8. Cytokine receptor

Probe ID	Pvalue	Arrow	Fold	Gene
201642_at	1.42E-09	up	2.315	IFNGR2
202727_s_at	1.44E-08	up	3.323753	IFNGR1
202948_at	5.77E-10	up	6.463163	IL1R1
203233_at	2.36E-10	up	3.270304	IL4R
204191_at	2.98E-07	up	2.05704	IFNAR1
204731_at	7.48E-21	down	11.93166	TGFBR3
204786_s_at	5.23E-19	down	6.864011	IFNAR2
205227_at	2.89E-05	up	2.68359	IL1RAP
205291_at	2.89E-08	down	2.442178	IL2RB
205403_at	1.87E-08	up	6.689801	IL1R2
205707_at	1.73E-09	down	2.408515	IL17RA
205798_at	2.48E-24	down	31.78504	IL7R
205926_at	1.06E-09	down	2.187688	IL27RA
205945_at	1.49E-22	down	16.68902	IL6R
206618_at	4.70E-09	up	12.92154	IL18R1
207072_at	5.22E-08	up	4.927116	IL18RAP
211372_s_at	1.76E-08	up	10.6815	IL1R2
211676_s_at	6.66E-09	up	4.607373	IFNGR1
217489_s_at	2.79E-14	down	3.546462	IL6R

Table 9. CSF

Probe ID	Pvalue	Arrow	Fold	Gene
205159_at	1.17E-06	up	2.511396	CSF2RB
210340_s_at	4.36E-10	up	2.295372	CSF2RA

Table 10. TNF

Probe ID	Pvalue	Arrow	Fold	Gene
202509_s_at	1.99E-12	down	2.4938	TNFAIP2
206026_s_at	7.48E-06	up	3.620447	TNFAIP6
206222_at	1.55E-06	down	2.076582	TNFRSF10C
207536_s_at	5.06E-07	down	2.86682	TNFRSF9
207643_s_at	3.72E-12	up	2.681254	TNFRSF1A
207907_at	9.40E-17	down	3.895788	TNFSF14
208296_x_at	2.21E-05	up	2.431529	TNFAIP8
210260_s_at	4.11E-05	up	2.505209	TNFAIP8
214329_x_at	1.19E-04	up	2.324046	TNFSF10

Table 11. Chemokine

Probe ID	Pvalue	Arrow	Fold	Gene
200660_at	9.23E-12	up	2.053883	S100A11
202917_s_at	2.79E-12	up	2.617102	S100A8
203535_at	3.98E-16	up	2.584441	S100A9
204103_at	3.51E-09	down	2.364728	CCL4
204351_at	7.20E-04	up	2.155134	S100P
205099_s_at	6.98E-05	down	2.455516	CCR1
205118_at	1.05E-10	down	7.612908	FPR1
205863_at	7.49E-14	up	4.166398	S100A12
205898_at	6.76E-04	down	2.496165	CX3CR1
206337_at	5.73E-08	down	5.099034	CCR7
206366_x_at	1.36E-09	down	3.847104	XCL1
206978_at	7.29E-05	up	2.362277	CCR2
207165_at	6.52E-05	up	2.285972	HMMR
208304_at	4.88E-05	down	3.621386	CCR3
210772_at	2.06E-08	up	4.776773	FPR2
210773_s_at	2.95E-06	up	4.516464	FPR2
214370_at	5.04E-06	down	2.084171	S100A8
214567_s_at	8.06E-08	down	2.902829	XCL1 /// XCL2
221058_s_at	1.49E-09	up	2.15809	CKLF

Table 12. AcuteResponseProtein

Probe ID	Pvalue	Arrow	Fold	Gene
200602_at	3.75E-12	up	4.384286	APP
206157_at	8.31E-08	up	3.272863	PTX3
208248_x_at	2.42E-09	up	2.54326	APLP2
208691_at	0.001264	up	2.485756	TFRC
208702_x_at	7.55E-09	up	2.826174	APLP2
208703_s_at	1.26E-07	up	3.047052	APLP2
208704_x_at	1.61E-08	up	2.435629	APLP2
211404_s_at	4.34E-10	up	2.927751	APLP2
214875_x_at	1.32E-08	up	2.761566	APLP2
214953_s_at	8.93E-05	up	2.120433	APP
219890_at	1.43E-12	up	7.827181	CLEC5A
220496_at	2.59E-07	up	3.327139	CLEC1B
205033_s_at	1.17E-05	up	4.788064	DEFA1/A1B/A3
207269_at	2.87E-05	up	6.665461	DEFA4

Table 13. Complement

Probe ID	Pvalue	Arrow	Fold	Gene
200983_x_at	7.97E-09	up	3.370908	CD59
200984_s_at	9.06E-10	up	3.891589	CD59
200985_s_at	4.85E-11	up	6.593943	CD59
201925_s_at	2.14E-07	up	5.613841	CD55
201926_s_at	6.74E-09	up	3.830297	CD55
202953_at	7.01E-06	up	2.526228	C1QB
205786_s_at	5.02E-13	up	4.053864	ITGAM
206244_at	6.06E-12	up	6.759067	CR1
208783_s_at	0.004769	up	2.21095	CD46
209906_at	7.48E-09	up	4.336492	C3AR1
210184_at	1.17E-06	up	2.086657	ITGAX
212463_at	2.34E-09	up	2.845059	CD59
217552_x_at	5.04E-10	up	3.57143	CR1
218232_at	1.52E-08	up	3.972673	C1QA
218983_at	7.83E-08	up	2.636687	C1RL
220088_at	9.13E-08	up	2.491036	C5AR1
202910_s_at	3.42E-07	up	2.255245	CD97

Table 14. NO/ NADPH oxidase

Probe ID	Pvalue	Arrow	Fold	Gene
201940_at	9.58E-11	up	5.886338	CPD
201941_at	1.14E-09	up	5.264568	CPD
201942_s_at	6.35E-08	up	3.362135	CPD
201943_s_at	7.91E-12	up	6.937615	CPD
204961_s_at	7.26E-08	up	2.016737	NCF1/1B/1C
207677_s_at	5.88E-10	up	2.661943	NCF4
214084_x_at	1.31E-08	up	2.251172	NCF1C

Table 15. MMP

Probe ID	Pvalue	Arrow	Fold	Gene
203167_at	1.02E-13	up	3.135463	TIMP2
203936_s_at	2.89E-16	up	10.59129	MMP9
206871_at	1.04E-06	up	5.3948	ELANE
207329_at	3.41E-11	up	32.06008	MMP8
207890_s_at	1.30E-11	up	3.108211	MMP25
202833_s_at	2.83E-09	up	2.778271	SERPINA1
204614_at	5.64E-08	up	3.074429	SERPINB2
212268_at	8.64E-11	up	5.643009	SERPINB1
213572_s_at	7.52E-11	up	5.130388	SERPINB1

Table 16. Caspase

Probe ID	Pvalue	Arrow	Fold	Gene
202763_at	1.22E-06	up	2.523658	CASP3
204780_s_at	1.71E-04	up	2.524168	FAS
207500_at	4.39E-06	up	2.385929	CASP5
208485_x_at	1.73E-08	down	2.568559	CFLAR
209508_x_at	1.14E-10	down	2.749778	CFLAR
210564_x_at	1.77E-07	down	2.357083	CFLAR
210907_s_at	7.22E-06	up	2.816621	PDCD10
211316_x_at	3.60E-13	down	3.914512	CFLAR
211317_s_at	1.10E-07	down	2.657199	CFLAR
211367_s_at	7.39E-06	up	2.2941	CASP1
211862_x_at	3.34E-08	down	2.575973	CFLAR
213596_at	4.92E-09	up	3.013394	CASP4
214486_x_at	3.71E-08	down	2.177017	CFLAR
215719_x_at	2.24E-06	up	3.678086	FAS
221601_s_at	1.49E-09	down	4.178467	FAIM3
221602_s_at	2.73E-12	down	3.899111	FAIM3

Table 17. Fc receptor

Probe ID	Pvalue	Arrow	Fold	Gene
203561_at	6.67E-09	up	2.023942	FCGR2A
204232_at	8.21E-11	up	2.713677	FCER1G
207674_at	8.78E-08	up	6.420722	FCAR
210992_x_at	1.24E-07	up	2.313229	FCGR2C
211307_s_at	8.29E-08	up	4.563443	FCAR
211395_x_at	1.20E-06	up	2.139768	FCGR2C
211734_s_at	3.84E-05	down	3.85882	FCER1A
211816_x_at	3.58E-05	up	2.405171	FCAR
214511_x_at	2.07E-05	up	3.075548	FCGR1B
216950_s_at	5.51E-08	up	5.08392	FCGR1A/1C

Table 18. PGD LTX

Probe ID	Pvalue	Arrow	Fold	Gene
203913_s_at	1.26E-08	up	16.54476	HPGD
203914_x_at	3.77E-08	up	14.66064	HPGD
204445_s_at	2.84E-06	up	2.076126	ALOX5
204446_s_at	1.01E-07	up	2.0434	ALOX5
204748_at	0.019719	up	2.109052	PTGS2
205128_x_at	5.85E-07	up	2.664767	PTGS1
207206_s_at	1.59E-04	up	2.531166	ALOX12
209533_s_at	3.14E-10	up	2.619734	PLAA
210128_s_at	9.02E-10	up	2.505719	LTB4R
210145_at	1.51E-12	up	3.476688	PLA2G4A
211548_s_at	4.38E-08	up	12.3211	HPGD
211549_s_at	3.53E-04	up	2.6726	HPGD
211748_x_at	1.56E-06	down	2.033312	PTGDS
214366_s_at	5.17E-10	up	3.681805	ALOX5
215813_s_at	1.01E-08	up	3.363031	PTGS1
215894_at	2.35E-14	down	10.40363	PTGDR
216388_s_at	9.35E-07	up	2.104241	LTB4R

Table 19. CD molecule

Probe ID	Pvalue	Arrow	Fold	Gene
200663_at	7.97E-10	up	2.446524	CD63
201005_at	4.83E-08	up	4.230153	CD9
202351_at	5.59E-10	up	3.163429	ITGAV
202638_s_at	7.74E-08	up	2.891012	ICAM1
202878_s_at	8.07E-06	up	2.265542	CD93
202910_s_at	3.42E-07	up	2.255245	CD97
203645_s_at	2.02E-09	up	9.129274	CD163
204306_s_at	2.48E-06	up	2.098005	CD151
204489_s_at	2.80E-09	up	2.832196	CD44
204490_s_at	3.30E-09	up	2.773283	CD44
204661_at	2.08E-04	down	2.102266	CD52
205173_x_at	8.14E-08	up	3.565981	CD58
205789_at	6.34E-06	up	3.14233	CD1D
205831_at	4.40E-10	down	3.924635	CD2
205988_at	3.64E-19	down	5.606748	CD84
206488_s_at	1.04E-04	up	2.926877	CD36
206761_at	5.72E-06	down	2.026305	CD96
208405_s_at	5.16E-06	up	2.167749	CD164
208650_s_at	7.29E-08	up	4.591438	CD24
208651_x_at	5.17E-10	up	3.761404	CD24
208653_s_at	1.98E-11	up	4.511797	CD164
208654_s_at	3.10E-07	up	5.153189	CD164
209555_s_at	2.87E-05	up	3.18128	CD36
209771_x_at	1.91E-08	up	4.956121	CD24
209835_x_at	3.82E-07	up	2.377499	CD44
210031_at	4.04E-09	down	3.14224	CD247
211744_s_at	7.96E-09	up	3.998247	CD58
211900_x_at	3.47E-14	down	2.437045	CD6
211945_s_at	2.07E-06	up	2.577267	ITGB1
212014_x_at	4.13E-07	up	2.48835	CD44
212063_at	5.59E-07	up	2.205469	CD44
213958_at	2.29E-08	down	2.119745	CD6
215049_x_at	6.80E-09	up	8.964883	CD163
216233_at	3.21E-06	up	4.34145	CD163
216379_x_at	6.81E-09	up	5.765379	CD24
216942_s_at	4.88E-06	up	3.031317	CD58

217523_at	4.41E-13	down	6.665958 CD44
219669_at	1.40E-13	up	34.68958 CD177
222061_at	6.85E-09	up	3.64802 CD58
222292_at	7.05E-11	down	2.150798 CD40
266_s_at	1.78E-10	up	6.956197 CD24

Table 20. Coagulation

Probe ID	Pvalue	Arrow	Fold	Gene
203305_at	2.16E-04	up	2.180403	F13A1
204714_s_at	1.87E-08	up	3.933558	F5
205756_s_at	2.79E-05	up	2.08411	F8
205871_at	7.54E-07	down	3.123419	PLGLA/B1/B2
206655_s_at	2.25E-08	up	5.369561	GP1BB/SEPT5
207808_s_at	6.30E-08	up	2.883896	PROS1
210845_s_at	2.55E-07	up	2.502571	PLAUR
211924_s_at	5.53E-07	up	2.325629	PLAUR
212245_at	6.18E-07	up	2.301938	MCFD2
213258_at	1.07E-06	up	2.352817	TFPI
213506_at	0.002877	up	2.349815	F2RL1
214415_at	1.30E-09	down	5.536361	PLGLB1/B2
214866_at	5.37E-10	up	2.031086	PLAUR
216956_s_at	4.64E-05	up	2.39087	ITGA2B
218718_at	2.79E-10	up	9.385749	PDGFC
204627_s_at	1.30E-06	up	4.180416	ITGB3
203887_s_at	8.66E-09	up	4.530585	THBD
203888_at	4.42E-08	up	2.810682	THBD

Table 21. Glycolysis

Probe ID	Pvalue	Arrow	Fold	Gene
200650_s_at	2.02E-09	up	2.710678	LDHA
200737_at	2.94E-11	up	3.17309	PGK1
201030_x_at	9.45E-05	down	2.016562	LDHB
201251_at	2.51E-10	up	2.67251	PKM2
202464_s_at	6.45E-09	up	7.300454	PFKFB3
202934_at	9.80E-14	up	4.768903	HK2
202990_at	2.15E-12	up	4.196534	PYGL
203502_at	1.24E-04	up	3.670577	BPGM
205936_s_at	5.17E-12	up	4.987516	HK3
206348_s_at	9.53E-11	up	2.597892	PDK3
208308_s_at	3.92E-09	up	2.215685	GPI
209992_at	3.99E-09	up	11.77066	PFKFB2
213453_x_at	2.13E-12	up	2.175151	GAPDH
217294_s_at	3.28E-06	up	2.62132	ENO1
217356_s_at	4.20E-08	up	2.028929	PGK1
218273_s_at	1.01E-07	down	2.250674	PDP1

Table 22. H-ATPase

Probe ID	Pvalue	Arrow	Fold	Gene
200078_s_at	6.15E-13	up	2.530917	ATP6V0B
201171_at	4.49E-10	up	2.484021	ATP6V0E1
201443_s_at	5.84E-06	up	2.32877	ATP6AP2
201971_s_at	4.45E-13	down	5.207561	ATP6V1A
202872_at	1.95E-10	up	6.183733	ATP6V1C1
202874_s_at	6.99E-10	up	5.718367	ATP6V1C1
204158_s_at	5.14E-08	up	2.068726	TCIRG1
208898_at	2.66E-09	up	2.413653	ATP6V1D
213587_s_at	1.13E-08	down	2.067119	ATP6V0E2
206208_at	1.00E-11	up	3.51149	CA4
206209_s_at	4.18E-15	up	7.982899	CA4
209301_at	2.78E-06	up	3.422036	CA2
212536_at	4.38E-09	up	4.21056	ATP11B
213582_at	1.89E-08	up	2.241957	ATP11A

Table 23. Vasodilator

Probe ID	Pvalue	Arrow	Fold	Gene
201494_at	1.01E-08	up	2.190291	PRCP
202912_at	1.20E-08	up	4.330455	ADM
212741_at	0.004196	up	2.027247	MAOA

Table 24. NK cell

Probe ID	Pvalue	Arrow	Fold	Gene
202379_s_at	2.01E-30	down	26.43984	NKTR
205821_at	1.39E-12	down	3.985353	KLRK1
207509_s_at	7.71E-10	down	2.948439	LAIR2
207795_s_at	1.01E-09	down	3.216148	KLRD1
210288_at	1.62E-11	down	5.382525	KLRG1
210606_x_at	1.91E-09	down	3.341239	KLRD1
214470_at	1.11E-04	down	2.103258	KLRB1
215338_s_at	1.06E-24	down	14.54682	NKTR
220646_s_at	1.34E-04	down	2.386466	KLRF1
205488_at	1.01E-05	down	2.867692	GZMA
206666_at	1.84E-07	down	3.446082	GZMK
207460_at	3.78E-09	down	2.502287	GZMM
210164_at	8.91E-09	down	3.75597	GZMB
210321_at	8.94E-10	down	5.800327	GZMH
214617_at	2.22E-06	down	2.646147	PRF1

Table 25. T cell

Probe ID	Pvalue	Arrow	Fold	Gene
205039_s_at	2.79E-08	down	2.22558	IKZF1
205255_x_at	3.09E-08	down	2.955244	TCF7
205456_at	5.31E-08	down	2.877146	CD3E
205488_at	1.01E-05	down	2.867692	GZMA
205495_s_at	5.33E-10	down	4.378694	GNLY
205758_at	1.20E-07	down	3.258815	CD8A
206666_at	1.84E-07	down	3.446082	GZMK
206804_at	1.10E-15	down	5.118528	CD3G
207460_at	3.78E-09	down	2.502287	GZMM
208003_s_at	5.52E-18	down	12.03963	NFAT5
209670_at	5.21E-06	down	2.475029	TRAC
209671_x_at	3.58E-08	down	2.774547	TRAC
209813_x_at	1.49E-09	down	4.424708	TARP
210164_at	8.91E-09	down	3.75597	GZMB
210321_at	8.94E-10	down	5.800327	GZMH
210370_s_at	1.34E-07	down	2.482685	LY9
210555_s_at	1.02E-07	down	2.476832	NFATC3
210556_at	4.68E-08	down	2.850907	NFATC3
210915_x_at	6.23E-06	down	2.847533	TRBC1
210972_x_at	1.78E-07	down	2.875805	TRAC/J17/V20
211144_x_at	5.76E-08	down	3.696107	TARP/TRGC2
211796_s_at	6.35E-06	down	2.926207	TRBC1/C2
211902_x_at	8.99E-07	down	2.286838	TRD@
212759_s_at	3.98E-16	down	3.926594	TCF7L2
212762_s_at	2.70E-09	down	2.376013	TCF7L2
212808_at	1.21E-21	down	5.549449	NFATC2IP
213193_x_at	2.53E-06	down	2.918569	TRBC1
213539_at	1.00E-08	down	3.193378	CD3D
213830_at	5.93E-08	down	3.51036	TRD@
214617_at	2.22E-06	down	2.646147	PRF1
215092_s_at	1.36E-09	down	2.475134	NFAT5
215806_x_at	1.02E-08	down	4.078028	TARP/TRGC2
216191_s_at	4.71E-07	down	4.762182	TRDV3
216920_s_at	2.28E-10	down	5.341667	TARP/TRGC2
217143_s_at	1.26E-08	down	6.055404	TRD@
217526_at	1.43E-12	down	3.846013	NFATC2IP

217527_s_at	2.12E-13	down	5.801224	NFATC2IP
220684_at	7.39E-09	down	2.077709	TBX21
220704_at	2.15E-10	down	5.686157	IKZF1
37145_at	9.67E-10	down	4.340701	GNLY
214032_at	6.60E-08	down	2.523588	ZAP70
204890_s_at	1.65E-07	down	2.638662	LCK
204891_s_at	4.58E-08	down	3.313788	LCK
205831_at	4.40E-10	down	3.924635	CD2
201565_s_at	8.13E-13	down	4.167651	ID2
213931_at	7.33E-08	down	3.546731	ID2/2B

Table 26. B cell

Probe ID	Pvalue	Arrow	Fold	Gene
221969_at	9.96E-13	down	4.199424	PAX5
203140_at	3.09E-10	up	3.687249	BCL6
210105_s_at	9.37E-10	down	3.319013	FYN
210754_s_at	2.98E-10	down	3.545109	LYN
205039_s_at	2.79E-08	down	2.22558	IKZF1
211430_s_at	0.015735	up	2.830679	IGHG1/G2
211643_x_at	0.024398	up	2.10616	IGK
212592_at	0.017267	up	2.569312	IGJ
212827_at	0.008027	down	2.240154	IGHM
214677_x_at	0.031357	up	2.035694	IGLV1-44
214768_x_at	0.006798	up	2.374888	IGKV1-5
217022_s_at	5.28E-05	up	5.197489	IGHA1 /A2
210970_s_at	2.98E-06	up	2.298244	IBTK