Pharmacogenomic Responses of Rat Liver to Methylprednisolone: An Approach to Mining a Rich Microarray Time Series

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ABSTRACT

A data set was generated to examine global changes in gene expression in rat liver over time in response to a single bolus dose of methylprednisolone. Four control animals and 43 drug-treated animals were humanely killed at 16 different time points following drug administration. Total RNA preparations from the livers of these animals were hybridized to 47 individual Affymetrix RU34A gene chips, generating data for 8799 different probe sets for each chip. Data mining techniques that are applicable to gene array time series data sets in order to identify drug-regulated changes in gene expression were applied to this data set. A series of 4 sequentially applied filters were developed that were designed to eliminate probe sets that were not expressed in the tissue, were not regulated by the drug treatment, or did not meet defined quality control standards. These filters eliminated 7287 probe sets of the 8799 total (82%) from further consideration. Application of judiciously chosen filters is an effective tool for data mining of time series data sets. The remaining data can then be further analyzed by clustering and mathematical modeling techniques.

KEYWORDS: Data mining, gene arrays, glucocorticoids, mathematical modeling, pharmacogenomics

INTRODUCTION

Corticosteroids are widely used therapeutically to suppress inflammatory/immune responses. However, this class of drugs has a low therapeutic index owing to their extensive effects on many tissues.[1-4] Corticosteroids produce most of their effects either by altering transcription of specific genes directly, or by indirectly altering the expression of transcription factors that subsequently alter the expression of downstream genes. Changes in the expression of genes in the liver are important to both the efficacious and the adverse effects of corticosteroids.

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Microarrays can provide a method of high throughput data collection that is necessary for constructing comprehensive information on the transcriptional basis of polygenic phenomena. When microarrays are used in a rich in vivo time series, they yield temporal patterns of changes in gene expression that illustrate the cascade of molecular events that cause broad systemic responses. Mechanism-based pharmacokinetic/pharmacodynamic (PK/PD) models provide a tool for constructing testable hypotheses using these temporal patterns.

Previously we described the mining and cluster analysis of a microarray time series, illustrating the response of liver to the corticosteroid methylprednisolone (MPL).[5] This time series included individual chips from multiple control animals as well as multiple animals at each of 16 times over a 72-hour period following bolus dosing with MPL. Our first approach to analyzing this data set combined the processes of data mining and clustering and relied on 2 clustering methods, self-organizing maps (SOM) and K-means, followed by correlation coefficients between the probe sets in clusters. The result of that analysis was elaboration of 196 regulated probe sets coding for 143 individual genes. These probe sets were divided into 6 clusters of probe sets with similar temporal signatures. Mechanism-based PK/PD models were then developed for each of the 6 clusters. However, on further consideration of the data set using extensive pathway analysis, it became apparent that the initial analysis of this data set eliminated many biologically relevant regulated probe sets.

Mining a time series data set presents uniquely different problems from those encountered when microarrays are used to distinguish one group from another (eg, cancerous vs noncancerous tissues).[6-8] For those applications an attempt is made to define a pattern or fingerprint that distinguishes with very high probability one group from another and need not include all differentially regulated genes. In these cases, it is the distinguishing pattern of gene expression rather than the relationship between the genes that is the important focus. In the present application of microarrays, the problem is sorting through the vast amount of data to identify probe sets with temporal patterns of change in expression that indicate that the gene is regulated in response to the drug. In this case, the mechanistic relationships between the genes whose expression is

changing in response to the drug are of paramount importance. For example, the drug may change the expression of a particular transcription factor that in turn alters the expression of downstream genes. For this application, the most important aspect of the initial data mining is to avoid discarding valuable data. This is of particular importance because each gene that is identified as being potentially regulated becomes the subject of extensive literature searches to allow placement into a temporal context of all other regulated genes. The purpose of the endeavor is to use PK/PD modeling to develop a ''motion picture'' of the polygenic response to the drug.

In the present report, we describe a new approach to analysis of this data set that focuses on the process of data mining (identifying regulated probes). We took advantage of the inherent redundancy of this rich time series, which contains many time points and multiple measurements per time point, to develop a sequence of filters that identified and removed probe sets that did not meet explicitly defined criteria. These filters eliminated more than 7000 of the 8799 probe sets from the data set. Using this procedure, the remaining 1512 probe sets can then become the focus of more intense scrutiny by other methods including temporal clustering, functional clustering, and PK/PD modeling, which provide additional ways of organizing and limiting the number of probes and genes of interest.

MATERIALS AND METHODS

Experimental Design

Liver samples were obtained from a previously performed animal study in our laboratory.[9] All procedures involving experimental animals adhered to the National Institutes of Health (NIH) principles of laboratory animal care and were reviewed by our institution's institutional animal care and use committee (IACUC). Male adrenalectomized (ADX) Wistar rats (*Rattus rattus*) weighing 225 to 250 g were obtained from Harlan Sprague-Dawley (Indianapolis, IN). One day prior to the study, all rats were subjected to right external jugular vein cannulation under light ether anesthesia. Four animals were designated as controls (ie, zero time samples) and received vehicle only. All remaining animals received a single 50-mg/kg dose of MPL sodium succinate (Pharmacia-Upjohn Co, Kalamazoo, MI) via the cannula over 30 seconds. Three rats were killed by exsanguination under anesthesia at the following time points: 0.25, 0.5, 0.75, 1, 4, 5.5, 6, 7, 8, 18, and 48 hours after dosing. Because of loss during the course of the experiment, only 2 rats were killed at 2, 5, 12, 30, and 72 hours after dosing. The sampling time points were selected based on previous studies describing glucocorticoid receptor (GR) dynamics and enzyme induction in liver and skeletal muscle.[9-11] The use of vehicle-treated animals as controls was based on extensive experimentation and PK/PD modeling by our laboratories. That work and attendant modeling demonstrated that, using this experimental construct and ADX animals, regulated mRNAs and protein deviate from a vehicle control–defined baseline and return to that baseline within a 72-hour period.[5]

Microarrays

Liver powder (100 mg) from each individual animal was added to 1 mL of prechilled Trizol reagent (Invitrogen, Carlsbad, CA), and total RNA extractions were performed according to manufacturer's directions. Extracted RNAs were further purified by passage through RNAeasy minicolumns (QIAGEN, Valencia, CA) according to manufacturer's protocols for RNA cleanup. Final RNA preparations were resuspended in RNase-free water and stored at –80°C. The RNAs were quantified spectrophotometrically, and purity and integrity were assessed by agarose gel electrophoresis.

Isolated RNA from each individual liver was used to prepare target according to manufacturer's protocols. The biotinylated cRNAs were hybridized to 47 individual Affymetrix GeneChips Rat Genome U34A (Affymetrix Inc, Santa Clara, CA), which contained 8799 probe sets. Unlike the cDNA arrays used in a previous study,[12] the high reproducibility of in situ synthesis of oligonucleotide chips allows accurate comparison of signals generated by samples hybridized to separate arrays. This entire data set has been submitted to the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus database (GSE490) and is also available online at www.pepr.cnmcresearch.org.

Data Analysis

The Affymetrix oligonucleotide microarrays use sequence information and photolithograpy-directed combinatorial chemical synthesis to develop probe sets for the genes of interest. Each probe set consisted of a series of short oligonucleotide sequences and an identical partner sequence, except for a single base mismatch in the center. The mismatch sequence provides a unique background for each sequence in the series. Affymetrix Microarray Suite 5.0 (Affymetrix) was used for initial data acquisition and basic analysis. In this first step, a ''call'' of present (P), absent (A), or marginal (M) was determined for each probe set on each chip based on the comparison of the matched and mismatched pairs for the gene sequence. The results were normalized for each chip using a distribution of all genes around the 50th percentile. The results from the first step were inputted to the program, GeneSpring 6.1 (Silicon Genetics, Redwood City, CA).

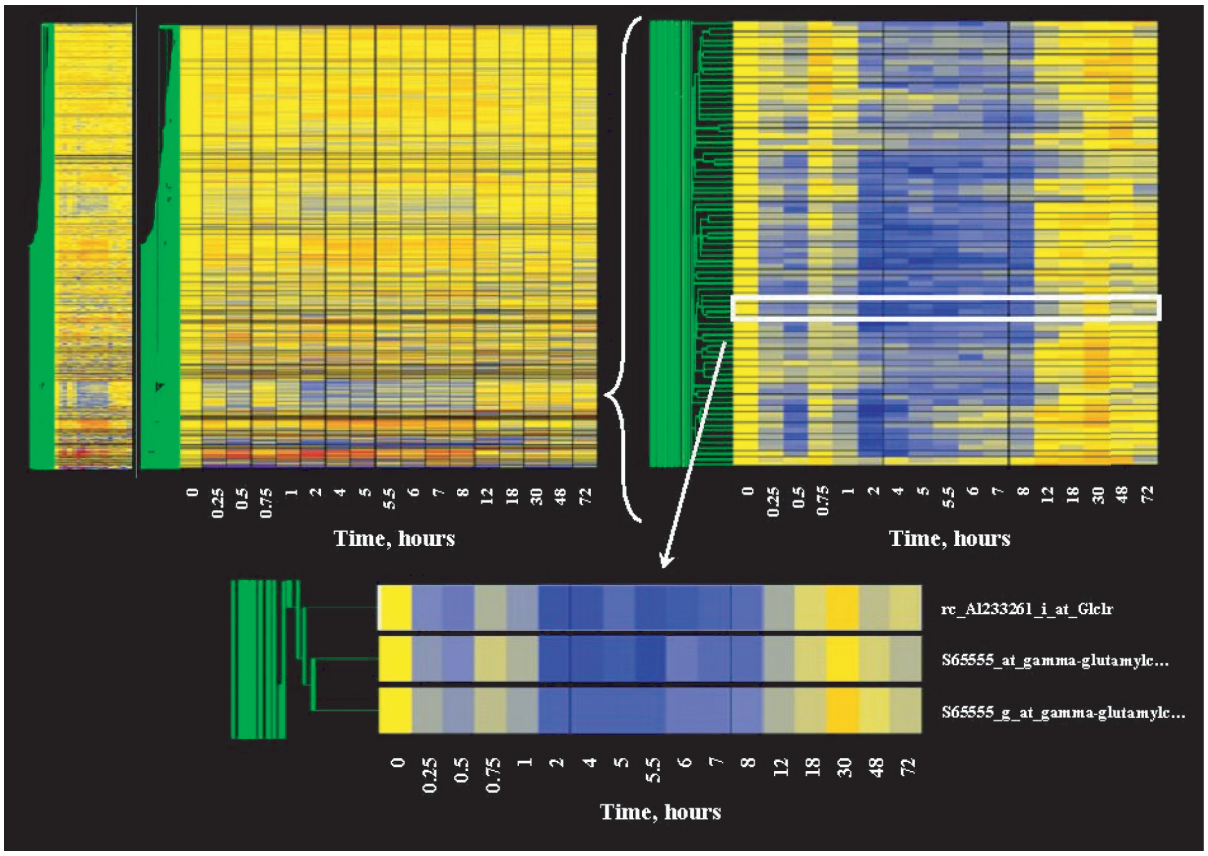

Figure 1. Gene tree representation of entire data set of mRNA expression in liver as a function of time following MPL treatment. The gene tree represents the averaged normalized values of each of 8799 probe sets at 17 different time points following MPL treatment, grouped by pattern similarities. The y-axis represents individual probe sets, with color representing relative intensities (yellow represents no change from control, progression toward red indicates increased expression, and progression toward blue represents decreased expression vs control values). The x-axis ranks the samples in sequence of time following MPL treatment. The top left panel represents the entire data set, while the top right and bottom panels present successive zoom in views of the areas highlighted.

RESULTS

The approach to data mining was developed based on our use of gene arrays as a technique for high throughput data collection within the context of a rigidly controlled time series paradigm. The initial step in the data mining analysis was to transform the data so that the values for all probe sets were within the same range. To accomplish this, values for each individual probe set on each chip were expressed as a ratio to the mean of the 4 control values for that gene, which we refer to as ''normalized intensity.'' Thus, the average of each probe set has a value of 1 at zero time and either decreases, increases, or remains not different from controls over the time series. To monitor the progression of the mining, we used the gene tree tool developed by Eisen et al.[13] This algorithm can be used to construct a dendrogram of genes with similar patterns. A negative aspect of this tool, and most clustering algorithms when applied to time series data, is the assumption that the points in the time series are equally spaced. Notwithstanding this drawback, gene trees provide an excellent method of visualizing the progression of the data analysis.

Figure 1 (top left) shows the gene tree derived from the GeneSpring program for the entire data set (8799 probe sets at 17 time points). The x-axis presents the 17 time points (including zero time controls) studied in rank order from left to right. Vehicle controls are nominally referred to as time zero. As indicated above, with this visualization tool each time point is equally spaced and therefore does not represent the actual temporal relationship between points. The y-axis presents the mean of the normalized value at each time point for each of the individual probe sets, represented by color and clustered by similarity. In this view, the color yellow represents a value of ''1''; progression toward red represents values that exceed ''1''; and progression toward blue represents values that decline toward zero. The intensity of the color reflects the intensity of the original signal. To the left of the figure is a schematic tree of the relationship of all probe sets to each other based on expression pattern similarity (represented in green). On the left side of the figure, but spatially separated, is what is referred to as a ''marquee view'' in the GeneSpring software. This marquee view can be used to

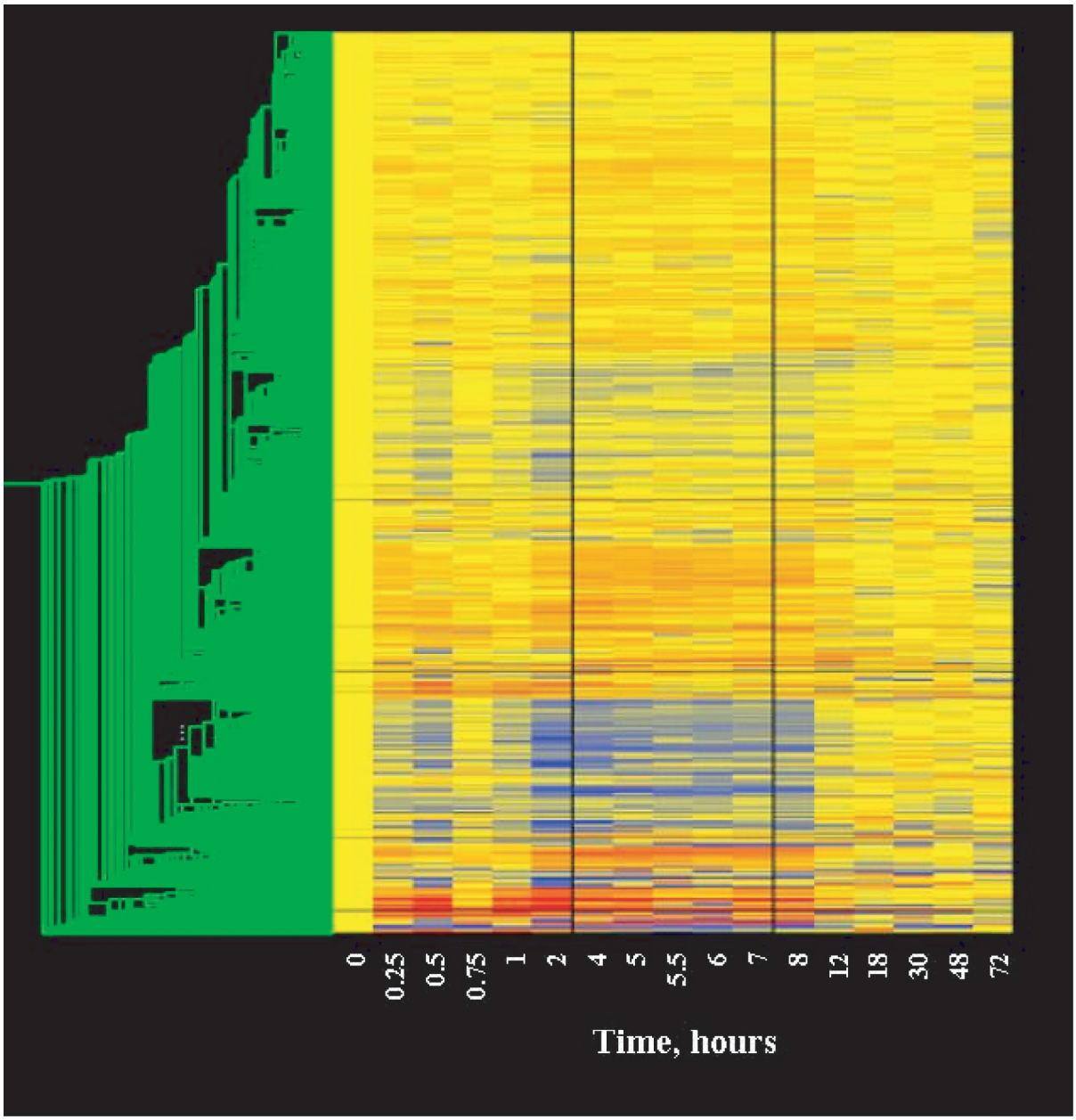

Figure 2. Gene tree of the 4373 probe sets remaining after filtering to remove probe sets not expressed in liver regardless of drug treatment, as described in the text. The gene tree is as described in Figure 1.

navigate the view of the tree on the right. Although the gene tree representation of the entire data set is of limited value for examining individual gene patterns of regulation, it does illustrate 2 points. First, within the entire data set are a vast number of genes represented by black (no expression in liver regardless of treatment) or by the color yellow across the entire time frame studied. This latter group of genes exhibits no temporal regulation by the drug (ie, their expression does not deviate from control value following drug dosing) and represents probe sets that we wish to filter from the data set. Second, it does reflect segregation of similarly regulated genes and demonstrates that similar patterns of regulation do exist. For example, groups of intense red or blue represent clusters of genes with similar up- or down-regulation respectively. Figure 1 (top right) provides a zoom-in view of one such clustering of probe sets with apparent down-regulation. The location of this group of probe sets within the entire data set is indicated by brackets. Figure 1 (bottom) shows an even closer zoom-in on 3 probe sets in this grouping with similar patterns. All 3 of these probe sets are for glutamate cysteine ligase, which is involved in cysteine metabolism and glutathione biosynthesis. The fact that these down-regulated probe sets reside together on the gene tree illustrates both the high

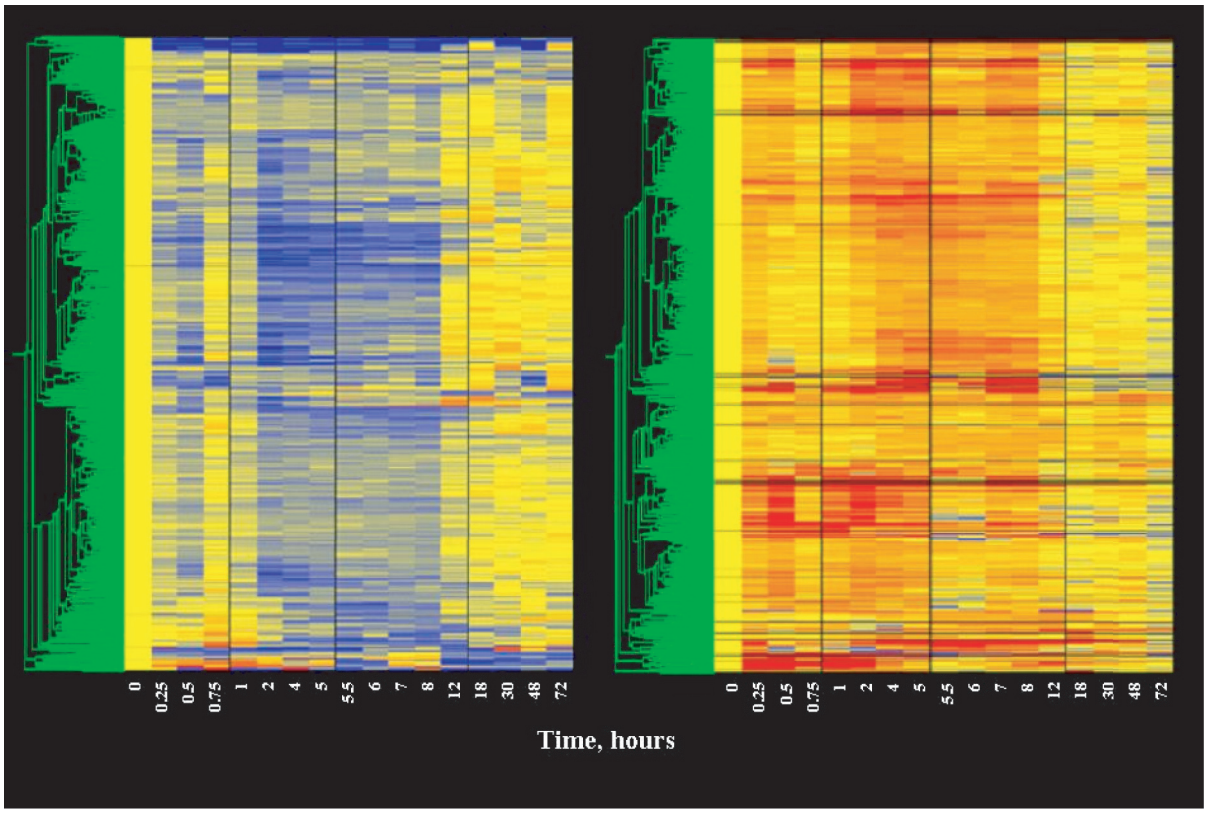

Figure 3. Gene tree of probe sets remaining following filtering for non–drug-regulated probe sets. The left panel presents the 829 probe sets remaining after filtering out probe sets not exhibiting repressed expression as described in the text. The right panel presents the 817 probe sets remaining after filtering out probe sets not exhibiting enhanced expression as described in the text. A description of the gene tree is provided in Figure 1.

reproducibility of the Affymetrix gene chips and the ideal functioning of the Eisen et al approach to grouping genes.[13]

A series of ''filtering'' steps were applied to the data in an attempt to eliminate probe sets that were not of further interest. The first level of filtering was designed to eliminate probe sets not expressed in liver, and used the Affymetrix ''call'' feature. This first filter required that the probe set for the gene have a call of P on at least 4 of the 47 chips. This filter eliminated 4426 probe sets from the data set. Figure 2 provides a gene tree of the 4373 probe sets not eliminated by this first filter. The gene tree also demonstrates that as probe sets are eliminated there is a more intense concentration of probe sets with contiguous strings of red and blue.

The second level of filtering that we applied was designed to eliminate probe sets that could not meet the basic criterion of a regulated probe. Specifically, this filter was designed to eliminate probe sets whose average did not deviate from baseline by a certain value for a reasonable number of time points. After exploring a variety of filtering values and number of conditions using gene trees in the manner described in the previous paragraph, we developed 2 filters that were designed to eliminate probe sets that were neither down- nor up-regulated. The first of these filters eliminated probe sets that could not meet a minimal criterion for down-regulation. Starting with the 4P filtered list, we eliminated all probe sets that did not have average values below 0.65 in at least 4 conditions (time points). Figure 3 (left) shows a gene tree of the 829 probe sets that were not eliminated by this filter. Most of these probe sets clearly contain a sustained run of time points represented by the color blue, as expected of down-regulated probe sets. The next filter was designed to eliminate probe sets that could not meet a minimal criterion for up-regulation. Starting with the 4P filtered list, we eliminated all probe sets that did not have average values above 1.5 in at least 4 conditions (time points). Figure 3 (right) shows a gene tree of the 817 probe sets that were not eliminated by this filter. Most of these probe sets clearly contain a sustained run of red time points as expected of up-regulated probe sets. There were a small number of probe sets that were not eliminated by either filter indicating both up- and down-regulation. These probe sets suggest biphasic regulation, a phenomenon we have previously described.[5] Thus, using 3 straightforward filters we were able to eliminate all but 18% of the probe sets present in the original data set.

The last filter we applied addressed the quality of the data. For this quality control filter we eliminated probe sets that

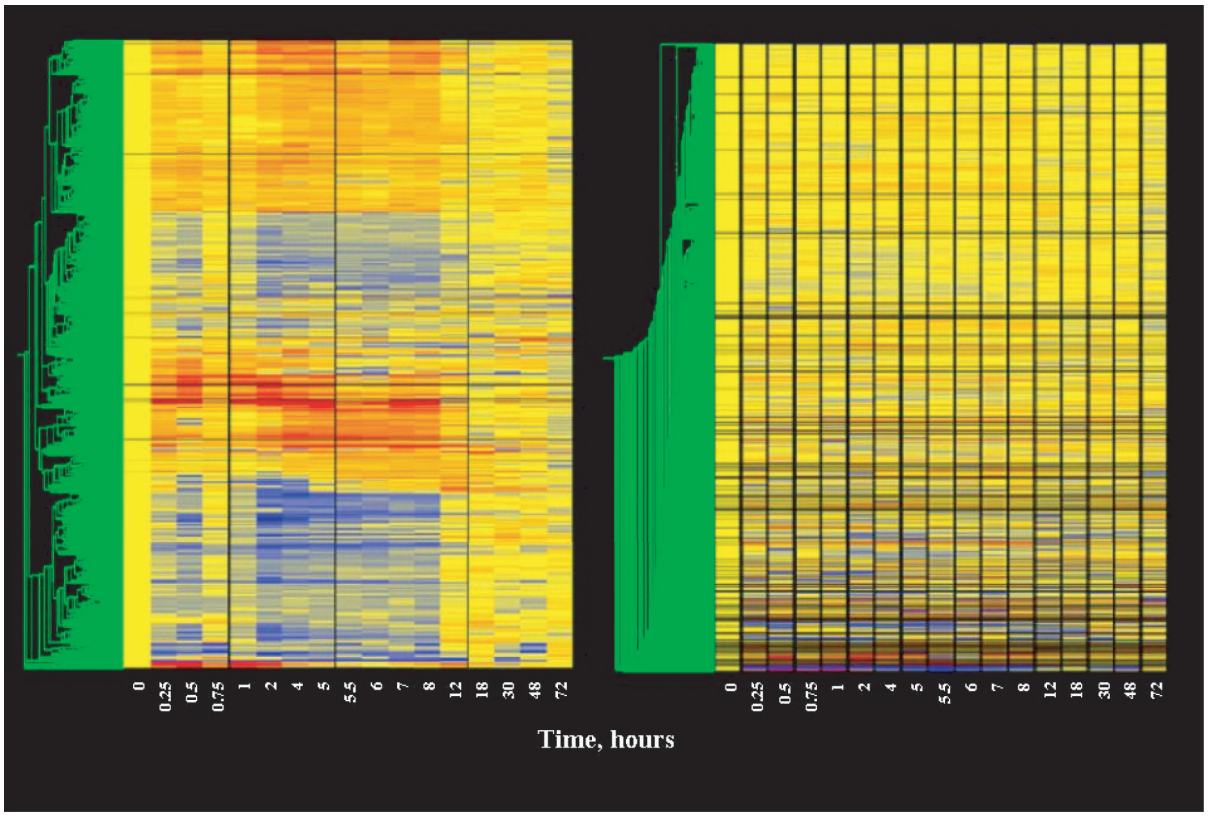

Figure 4. Gene trees of the 1512 probe sets remaining after completion of all filtering steps described in the text (left panel), and of the 7287 eliminated probe sets (right panel). Gene trees are as described in Figure 1.

did not meet 2 conditions. The first condition focused on the control chips. As indicated above, our initial operation was to divide the value of each individual probe set on each chip by the mean of the values for that probe set on the 4 control chips. Therefore, the quality of the control data for each particular probe set is of unique importance in defining regulation by the drug. This filter eliminated probe sets whose control values exhibited coefficients of variation (CV) of greater than 50%. The second condition focused on the remaining 16 time points. This filter also eliminated probe sets that had CVs for more than 8 of the remaining 16 time points exceeding 50%. For the 11 points for which we had 3 samples, the CV was calculated using the SD of the mean. For the 5 points for which we only had 2 samples, a quasi-CV was calculated using the difference between the 2 values divided by the average. This quality control filter eliminated an additional 103 probe sets. Figure 4 (left) provides a gene tree of the 1512 probe sets that were not eliminated by the entire series of filters. Figure 4 (right) shows the 7287 probe sets that were filtered out by the entire set of filters. Comparing Figure 1 (top left) with Figure 4 (right) demonstrates that probes with apparent regulation are no longer present in the eliminated data set. The single exception to this observation is a small group of intensely blue probe sets at the bottom of the figure. Although they all were eliminated by the last filter owing to highly variable data, they do warrant noting. For all of these probe sets, the normalized value dropped from 1 in the controls to virtually zero and remained at zero throughout most of the time course. One of these probes, metallothionein, was one of the most highly expressed and up-regulated genes observed in an earlier gene array experiment on MPL-treated liver using a spotted array.[12] In discussions with Affymetrix, we learned that very intense signals can desensitize the photomultiplier tube (PMT) and yield a value of zero. Because of this limitation in the Affymetrix technology, some regulated probe sets cannot be captured in our studies and are eliminated from further analysis. The 1512 probe sets remaining after filtering the total data set (Figure 4 left) are the product of this approach to data mining and thus become the focus of temporal clustering, functional clustering, and PK/PD modeling.

A previous very stringent analysis of this data set, which combined data mining with clustering, yielded only 197 regulated probe sets.[5] Those probe sets are a subset of those identified here. However, that analysis demonstrated that variations on 3 basic temporal signatures of regulation can be expected following single bolus dosing by MPL of a population of ADX rats that have a stable baseline. These 3 signatures indicate up-regulation, down-regulation, and biphasic regulation. Figure 5 (top left, 738 probe sets; top right, 739 probe sets; and bottom, 23 probe sets) provides gene trees for probe sets that fall into these 3 categories. Tables 1, 2, and 3 list the corresponding probe sets.

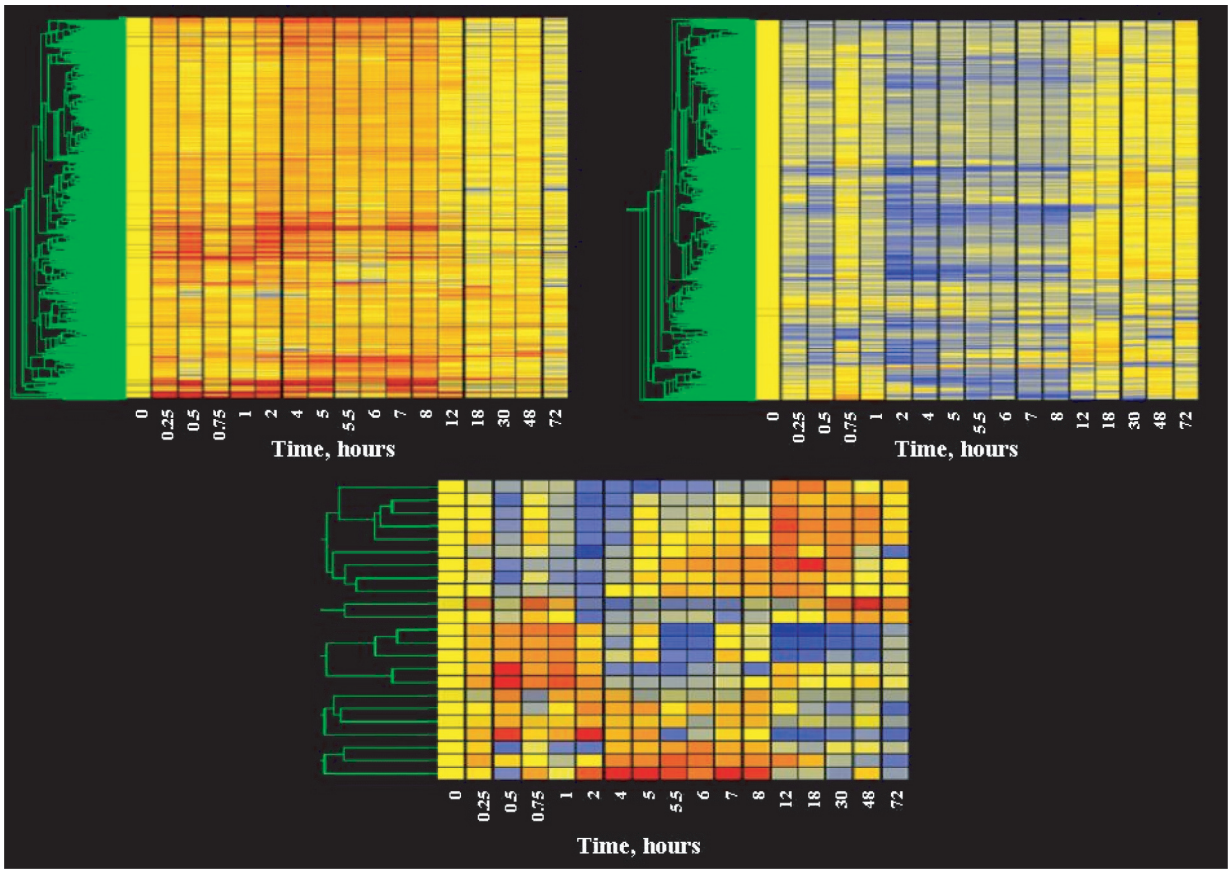

Figure 5. Gene trees of probe sets representing up-regulation (top left), down-regulation (top right), and biphasic regulation (bottom) in liver as a function of time following MPL administration. Gene trees are as described in Figure 1.

The purpose of developing this data set was to generate data that can be used to model the cascade of transcriptional events initiated in liver by MPL. Figure 6 (left) presents plasma MPL concentrations in these same animals, along with liver receptor densities (right). Figure 7 shows the parent model that uses kinetics as the driving force for the formation of the drug receptor complex (DR), which is translocated into the nucleus to become DR(N), which is the driving force for transcriptional changes. Models for the 3 general signatures are also provided in this figure. These models were derived from our initial analysis of this data set.[5] The first model is for direct stimulation of transcription, which is typified by the response of the acute phase protein α_2-macroglobulin. The second model is for direct inhibition of transcription, which is typified by dihydropyrimidinase. The last model is for a biphasic regulation of transcription. This model is for arginase, whose mRNA first declines and later is enhanced. The biphasic nature of the curve suggests that 2 mechanistic processes are involved. This model describes the initial decline as DR stimulating the degradation of the mRNA and the later increase as DR(N) stimulating the synthesis of a biosignal (BS) that, following translation into protein, stimulates the production of mRNA. There is strong evidence that in this case the BS is CCAAT-enhancer binding protein beta (CEBPβ), whose expression is enhanced by MPL.[14] Figure 8A shows the fitting of 4 probe sets for α_2-macroglobulin using the direct stimulation model. Figure 8B shows the fitting of 2 probe sets for dihydropyrimidinase using the direct inhibition model. Figure 8C shows the fitting of a probe set for arginase using the biphasic model.

DISCUSSION

A population of ADX male Wistar rats was injected with a single bolus dose of MPL; groups of animals were killed at 16 time points over a 72-hour period; and MPL-treated liver samples were compared with vehicle-treated controls. ADX animals were used to eliminate the circadian oscillation of corticosterone and provide a stable baseline.[9-11,15-17] This allowed us to identify gene transcripts that deviate from the baseline in response to MPL and determine the duration of time it takes to return to that baseline. The times of killing over the 72-hour period were chosen based on previous experiments indicating that the effect of the drug was most significant at the early times following dosing, but full recovery required in some cases as long as 72 hours.

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
D45252_s_at	2,3-oxidosqualene: lanosterol cyclase
U31352_at	2,3-oxidosqualene: lanosterol cyclase
X55286_at	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
X55286_g_at	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
D89514_at	5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP
J04197_i_at	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1
X15580complete_seq_s_at	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 1
rc_AA891920_at	Ntf2-like domain of Tap-P15 Mrna nuclear export factor
AJ012603UTR#1_g_at	a disintegrin and metalloproteinase domain 17
U01914_at	A kinase anchor protein 8
rc_AA894086_g_at	Ac1133 mRNA, complete cds
rc_AI104567_at	actin alpha cardiac 1
rc_AI104567_g_at	actin alpha cardiac 1
rc_H31144_at	activated p21cdc42Hs kinase [Homo sapiens]
rc_H31144_g_at	activated p21cdc42Hs kinase [Homo sapiens]
M63282_at	activating transcription factor 3
rc_AA799779_at	acyl-CoA:dihydroxyacetonephosphate acyltransferase
rc_AA799779_g_at	acyl-CoA:dihydroxyacetonephosphate acyltransferase
U18942_at	adenosine deaminase, RNA-specific
X77235_at	ADP-ribosylation-like 4
M12919mRNA#2_at	aldolase A
M12919mRNA#2_g_at	aldolase A
rc_AA924326_s_at	aldolase A
J03572_i_at	alkaline phosphatase, tissue-nonspecific
rc_AA900582_at	alpha-2-macroglobulin
rc_AI113046_at	alpha-2-macroglobulin
X13983mRNA_at	alpha-2-macroglobulin
J00797cds_s_at	alpha-tubulin
rc_AA892333_at	alpha-tubulin
J03190_at	aminolevulinic acid synthase 1
J03190_g_at	aminolevulinic acid synthase 1
X07648cds_g_at	amyloid beta (A4) precursor protein
rc_AI171962_s_at	annexin 1
S57478cds_s_at	annexin 1
D64061_at	annexin V binding protein ABP-7
D44495_s_at	apurinic/apyrimidinic endonuclease 1
rc_AI104781_at	arachidonate 5-lipoxygenase activating protein
X52196cds_at	arachidonate 5-lipoxygenase activating protein
X12459_at	arginosuccinate synthetase
U08986_s_at	aryl hydrocarbon receptor nuclear translocator
U61184_at	aryl hydrocarbon receptor nuclear translocator
AF015953_at	aryl hydrocarbon receptor nuclear translocator-like
D49434_at	arylsulfatase B
rc_AI230614_s_at	ATPase Na^+/K+ transporting beta 1 polypeptide
J04024_at	ATPase, Ca^{2+} transporting, cardiac muscle, slow twitch 2
Y12635_at	ATPase, H^+ transporting, lysosomal (vacuolar proton pump), beta 56/58 kd, isoform 2
D84450_at	ATPase, Na^+/K+ transporting, beta 3 polypeptide
M74494_g_at	ATPase, Na^+K+ transporting, alpha 1
AF019628_at	ATP binding cassette, sub-family C (CFTR/MRP), member 9
rc_AA799744_at	B chain B, *E coli* (Lacz) beta-galactosidase in complex with D-galctopyranosyl-1-On

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
L26268_at	B cell translocation gene 1
L26268_g_at	B cell translocation gene 1
M60921_at	B cell translocation gene 2, antiproliferative
rc_AA944156_s_at	B cell translocation gene 2, antiproliferative
AF087037_at	B cell translocation gene 3
AF087037_g_at	B cell translocation gene 3
rc_AA859938_at	Bcl2/adenovirus E1B 19 kd-interacting protein 3-like
S78284_s_at	Bcl2-like 1
U34963_s_at	Bcl2-like 1
U72350_at	Bcl2-like 1
Y07704_at	Best5 protein
Y07704_g_at	Best5 protein
D17809_at	beta-4N-acetylgalactosaminyltransferase
rc_AA859722_at	BGAL_ECOLI Beta-galactosidase (Lactase)
rc_AA860049_at	BGAL_ECOLI Beta-galactosidase (Lactase)
rc_AA894188_at	BGAL_ECOLI Beta-galactosidase (Lactase)
D49955_at	bone marrow stromal cell antigen 1
D14441_at	brain acidic membrane protein
X13933_s_at	Calmodulin 1
L13039_s_at	calpactin I heavy chain
rc_AA944422_at	calponin 3, acidic
U78517_at	cAMP-regulated guanine nucleotide exchange factor II
M11710cds_s_at	Carbamoyl-phosphate synthetase 1
S68245_g_at	carbonic anhydrase 4
AB010635_s_at	carboxylesterase 2 (intestine, liver)
L15619_at	casein kinase II beta subunit
L15618_at	casein kinase II, alpha 1 polypeptide
M60753_s_at	catechol-O-methyltransferase
rc_AA891917_at	CAZ1_HUMAN F-actin capping protein alpha-1 subunit (CapZ alpha-1)
rc_AA900476_at	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2
rc_AA900476_g_at	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2
rc_AI014091_at	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2
S77528cds_s_at	CCAAT/enhancer binding protein (C/EBP), beta
X60769mRNA_at	CCAAT/enhancer binding protein (C/EBP), beta
M65149_at	CCAAT/enhancerbinding protein (C/EBP), delta
rc_AI045030_s_at	CCAAT/enhancerbinding protein (C/EBP), delta
rc_AA875047_at	CCT (chaperonin containing TCP-1) zeta subunit (LOC303526), mRNA
AF087943_s_at	CD14 antigen
AF087944mRNA_s_at	CD14 antigen
rc_AI171462_s_at	CD24 antigen
U49062_at	CD24 antigen
AB005743_at	cd36 antigen
AF072411_at	cd36 antigen
AF072411_g_at	cd36 antigen
rc_AA799326_s_at	cd36 antigen
rc_AA946368_at	cd36 antigen
D29646_at	CD38 antigen
M61875_s_at	CD44 antigen
X13044_at	CD74 antigen
rc_AA859920_at	cDNA clone MGC:72278 IMAGE:5598632, complete cds

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
rc_AA875537_at	cDNA clone MGC:73009 IMAGE:6889746, complete cds
rc_AA800243_at	cell death activator CIDE-A (LOC291541), mRNA
rc_AA799330_at	CGI-17 protein; pelota (*Drosophila*) homolog [*Homo sapiens*]
rc_AA800566_at	CGI-78 protein [*Homo sapiens*]
rc_AA799545_at	Chaperonin CCT gamma chain - human S61529
U22414_at	Chemokine (C-C motif) ligand 3
AF030358_g_at	chemokine (C-X3-C motif) ligand 1
U45965_at	chemokine (C-X-C motif) ligand 2
rc_AA894234_at	chromosome 20 open reading frame 169 (LOC296359), mRNA
U07619_at	coagulation factor 3
D28557_s_at	cold shock domain protein A
S79263_s_at	colony-stimulating factor 2 receptor, beta 1, low-affinity (granulocyte-macrophage)
rc_AI178135_at	complement component 1, q subcomponent binding protein
AF001417_s_at	core promoter element binding protein
rc_AA892506_at	coronin, actin binding protein 1A
M55534mRNA_s_at	crystallin, alpha B
L16532_at	cyclic nucleotide phosphodiesterase 1
D16309_at	cyclin D3
D16309_g_at	cyclin D3
X70871_at	cyclin G1
AF030091UTR#1_at	cyclin L
AF030091UTR#1_g_at	cyclin L
U41164_at	Cys2/His2 zinc finger protein (rKr1)
rc_AI232256_at	cytochrome b5, outer mitochondrial membrane isoform
Y12517cds_at	cytochrome b5, outer mitochondrial membrane isoform
rc_AA924591_at	cytochrome P450 4A3
L00320cds_f_at	cytochrome P450, 2b19
U36992_at	cytochrome P450, subfamily 7B, polypeptide 1
AF065161_at	cytokine inducible SH2-containing protein
X67877_at	cytosolic resiniferatoxin binding protein
X67877_g_at	cytosolic resiniferatoxin binding protein
rc_AA892042_at	DEAD-box protein 3 (helicase-like protein 2) (HLP2)
rc_AI639233_s_at	Decorin
X59859_r_at	Decorin
U24282_at	deiodinase, iodothyronine, type III
rc_AA686164_at	dendritic cell protein [*Homo sapiens*]
rc_AA892485_at	dihydrolipoamide acetyltransferase
rc_AA891107_at	diphosphoinositol polyphosphate phosphohydolase type II
U95001UTR#1_s_at	diphosphoinositol polyphosphate phosphohydolase type II
U95178_s_at	disabled homolog 2, mitogen-responsive phosphoprotein (*Drosophila*)
rc_AI639475_at	DKFZP564O1863 protein (LOC362463), mRNA
J02776_s_at	DNA polymerase beta
rc_AA957640_s_at	DNA polymerase beta
U67994_at	DNA primase, p49 subunit
AA848218_at	DNA topoisomerase I
rc_AI170685_at	DnaJ (Hsp40) homolog, subfamily A, member 2
U95727_at	DnaJ (Hsp40) homolog, subfamily A, member 2
rc_AI011998_at	dnaJ homolog, subfamily b, member 9
Y16774_at	Dri 27/ZnT4 protein
L25605_at	dynamin 2

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
U39044_at	dynein, cytoplasmic, intermediate polypeptide 2
rc_AI009806_at	dynein, cytoplasmic, light chain 1
rc_H31847_at	dynein, cytoplasmic, light intermediate chain 1
rc_AA892562_at	dyskeratosis congenita 1, dyskerin
rc_AA892562_g_at	dyskeratosis congenita 1, dyskerin
U31668_at	E2F transcription factor 5
rc_AA800739_at	EG:39E1.2 gene product [*Drosophila melanogaster*]
U06713_at	EGL nine homolog 3 (*C elegans*)
U36482_at	endoplasmic reticulum protein 29
AA685903_at	endoplasmin precursor – human A35954
AB016931_s_at	endothelial differentiation, sphingolipid G-protein-coupled receptor, 5
U10699_at	endothelial differentiation, sphingolipid G-protein-coupled receptor, 5
M64711_at	endothelin 1
D29683_at	endothelin converting enzyme 1
rc_AA956930_s_at	endothelin converting enzyme 1
rc_AA818970_s_at	endothelin receptor type B
S65355_g_at	endothelin receptor type B
S79797_at	enzymatic glycosylation-regulating gene
U38253_at	eukaryotic translation initiation factor 2B, subunit 3 (gamma, 58 kd)
U38253_g_at	eukaryotic translation initiation factor 2B, subunit 3 (gamma, 58 kd)
rc_AA891553_at	eukaryotic translation initiation factor 3, subunit 7 (zeta, 66/67 kd) [*Homo sapiens*]
rc_AA875205_at	eukaryotic translation initiation factor 3, subunit 9 (eta, 116 kd) [*Homo sapiens*]
rc_AA875205_g_at	eukaryotic translation initiation factor 3, subunit 9 (eta, 116 kd) [*Homo sapiens*]
X83399_at	eukaryotic translation initiation factor 4E
U05014_at	eukaryotic translation initiation factor 4E binding protein 1
rc_AI013194_at	eukaryotic translation initiation factor 5 (eIF-5) (LOC295660), mRNA
rc_AA866482_at	faciogenital dysplasia-associated protein FGD1 - human A55380
S69874_s_at	fatty acid binding protein 5, epidermal
rc_AA892550_at	F-box only protein 22; hypothetical protein FLJ13986; F-box protein Fbx22
rc_AA892550_g_at	F-box only protein 22; hypothetical protein FLJ13986; F-box protein Fbx22
M32062_at	Fc receptor, IgG, low affinity III
M32062_g_at	Fc receptor, IgG, low affinity III
X57018_at	FGR
Z35138cds_s_at	fibroblast growth factor receptor 2
M28259cds_at	fibronectin 1
U82612cds_at	fibronectin 1
U82612cds_g_at	fibronectin 1
X05831cds_at	fibronectin 1
rc_AA946251_at	G protein-coupled receptor kinase 5
rc_AI228669_at	GABA transporter protein
D87991_at	galactose transporter
rc_H31692_at	GERp95
X07467_at	glucose-6-phosphate dehydrogenase
AF087431_at	glucosidase 1
AF087431_g_at	glucosidase 1
J04171_at	glutamate oxaloacetate transaminase 1
rc_AA800587_at	glutathione peroxidase 2
X53428cds_s_at	glycogen synthase kinase 3 beta
M34097_at	granzyme B
L32591mRNA_at	growth arrest and DNA-damage-inducible 45 alpha

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
L32591mRNA_g_at	growth arrest and DNA-damage-inducible 45 alpha
rc_AI070295_at	growth arrest and DNA-damage-inducible 45 alpha
rc_AI070295_g_at	growth arrest and DNA-damage-inducible 45 alpha
D30735_at	growth factor, erv1 –like
L13619_at	growth response protein (CL-6)
L13619_g_at	growth response protein (CL-6)
rc_H31287_at	GS3955 protein [*Homo sapiens*]
E03424cds_s_at	GTP cyclohydrolase 1
U53475_at	GTPase Rab8b
rc_AA875225_at	GTP binding protein (G-alpha-i2)
rc_AA859837_at	guanine deaminase
rc_AA859837_g_at	guanine deaminase
M17527_at	guanine nucleotide binding protein, alpha inhibiting 1
AF022083_s_at	guanine nucleotide binding protein, beta 1
U88324_at	guanine nucleotide binding protein, beta 1
U03390_at	guanine nucleotide binding protein, beta polypeptide 2-like 1
M80367_at	guanylate binding protein 2, interferon-inducible
M55636_at	guanylate cyclase 2C
rc_AI177503_at	H3 histone, family 3B
rc_AA946439_at	H4 histone family, member I [*Homo sapiens*]
rc_AI170613_g_at	heat shock 10 kd protein 1
rc_AI176658_s_at	heat shock 27 kd protein 1
AF077354_at	heat shock 70 kd protein 4
L16764_s_at	heat shock 70 kd protein 1A
Z27118cds_s_at	heat shock 70 kd protein 1A
U68562mRNA#2_s_at	heat shock protein 60 (liver)
rc_AA944397_at	heat shock protein 86
rc_AI176546_at	heat shock protein 86
rc_AI236601_at	Heat-shock protein 105 kd (Heat shock 110 kd protein)
J02722cds_at	heme oxygenase 1
rc_AI179610_at	heme oxygenase 1
S74141_s_at	hemopoietic cell kinase
rc_AA799893_at	heterogeneous nuclear ribonucleoprotein A1
rc_AA799511_g_at	heterogeneous nuclear ribonucleoprotein B1 - human B34504
U60882_at	heterogeneous nuclear ribonucleoproteins methyltransferase-like 2 (*S cerevisiae*)
AFFX_Rat_Hexokinase_3_at	hexokinase 1
rc_AI012593_at	hexokinase 1
rc_AA891535_at	hippocampus abundant gene transcript 1; tetracycline transporter-like protein
rc_AA892014_s_at	HLA-B-associated transcript 1A
L13201_at	HNF-3/forkhead homolog-1
AB017140_g_at	homer, neuronal immediate early gene, 1
AF093267_s_at	homer, neuronal immediate early gene, 1
AF036537_g_at	homocysteine respondent protein HCYP2
rc_AA892779_at	HSPC039 protein [*Homo sapiens*]
D37951UTR#1_at	human immunodeficiency virus type 1 enhancer binding protein 2
M65251_s_at	human immunodeficiency virus type 1 enhancer binding protein 2
X54249mRNA_s_at	human immunodeficiency virus type 1 enhancer binding protein 2
X54250mRNA_at	human immunodeficiency virus type I enhancer binding protein 1
AF034218_at	hyaluronidase 2
AF034218_g_at	hyaluronidase 2

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
rc_AA925752_at	hypothetical gene supported by NM_031561 (LOC360376), mRNA
rc_AA893667_g_at	hypothetical protein DKFZp434E229; hypothetical protein FLJ14846 [*Homo sapiens*]
rc_AI639411_at	hypothetical protein DKFZp434I1614.1 - human (fragment) T46344
rc_H31976_at	hypothetical protein FLJ10439 [*Homo sapiens*]
rc_AI177404_at	hypothetical protein FLJ13340, isoform 1; putative N-acetyltransferase [*Homo sapiens*]
rc_AA799531_at	hypothetical protein FLJ20752 [*Homo sapiens*]
rc_AA799531_g_at	hypothetical protein FLJ20752 [*Homo sapiens*]
rc_AI013993_at	Hypothetical protein KIAA0182 Y182_HUMAN
rc_AA893708_at	hypothetical protein KIAA0560 - human T00333
rc_AI639012_at	hypothetical protein MGC2601 [*Homo sapiens*]
rc_AA891749_at	hypothetical protein MGC5560 (LOC290573), mRNA
rc_AI639342_at	Hypothetical protein S164 YS64_HUMAN
U21718mRNA_at	hypothetical RNA binding protein RDA288
Y09507_at	hypoxia inducible factor 1, alpha subunit
U17254_at	immediate early gene transcription factor NGFI-B
AJ223184_at	immunoglobulin superfamily, member 6
AJ223184_g_at	immunoglobulin superfamily, member 6
L23148_g_at	Inhibitor of DNA binding 1, helix–loop–helix protein (splice variation)
J05510_at	inositol 1,4,5-triphosphate receptor 1
X52140_at	integrin alpha 1
D00913_at	intercellular adhesion molecule 1
D00913_g_at	intercellular adhesion molecule 1
U68272_at	interferon gamma receptor
M34253_at	interferon regulatory factor 1
M34253_g_at	interferon regulatory factor 1
rc_AA799861_at	interferon regulatory factor 7 isoform d [*Homo sapiens*]
rc_AA799861_g_at	interferon regulatory factor 7 isoform d [*Homo sapiens*]
rc_AI014163_at	interferon-related developmental regulator 1
E01884cds_s_at	interleukin 1 beta
M98820_at	interleukin 1 beta
M95578_g_at	interleukin 1 receptor, type I
U14010_g_at	interleukin 1 receptor, type I
Z22812_at	interleukin 1 receptor, type II
X60675_at	interleukin 10
M26744_at	interleukin 6
M58587_at	interleukin 6 receptor
M92340_at	interleukin 6 signal transducer
L20900_at	islet cell autoantigen 1, 69 kd
AF003835_at	isopentenyl-diphosphate delta isomerase
AJ000557cds_s_at	Janus kinase 2
U13396_g_at	Janus kinase 2
rc_AI178267_g_at	JC7185 chromosome 1 C1orf9 protein - human
rc_AI236597_at	JC7185 chromosome 1 C1orf9 protein - human
rc_AA799766_at	Jtv1-pending protein (LOC288480), mRNA
rc_AA891041_at	Jun-B oncogene
X54686cds_at	Jun-B oncogene
rc_AA799457_at	K07H8.2a.p [*C elegans*]
rc_AA799537_at	KIAA0652 gene product [*Homo sapiens*]
U09793_at	Kirsten rat sarcoma viral oncogene homolog 2 (active)
M14369exon#2_at	K-kininogen, differential splicing leads to HMW Kngk

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
D12769_at	Kruppel-like factor 9
D12769_g_at	Kruppel-like factor 9
U07181_at	lactate dehydrogenase B
U07181_g_at	lactate dehydrogenase B
rc_AI145490_at	lamin B receptor
U19614_g_at	lamina-associated polypeptide 1C
X94551_at	laminin, gamma 1
L21711_s_at	lectin, galactose binding, soluble 5
U72741_at	lectin, galactose binding, soluble 9
U72741_g_at	lectin, galactose binding, soluble 9
D31874_at	LIM motif-containing protein kinase 2
X02309_at	lingual lipase
L32132_at	lipopolysaccharide binding protein
L03294_at	lipoprotein lipase
L03294_g_at	lipoprotein lipase
rc_AI237731_s_at	lipoprotein lipase
M13506_at	liver UDP-glucuronosyltransferase, phenobarbital-inducible form
AB009463_at	low density lipoprotein receptor-related protein 3
rc_AA891695_f_at	Ly6-B antigen gene (LOC362935), mRNA
M30691_at	Ly6-C antigen gene
rc_AA946044_s_at	lyn protein nonreceptor kinase
AF100421_at	LYRIC
rc_AA892775_at	Lysozyme
E13732cds_at	macrophage inflammatory protein-1 alpha receptor gene
U09870_at	major vault protein
U21662_at	mannosyl (alpha-1,6-)-glycoprotein beta-1,2-N-acetylglucosaminyltransferase
rc_AA799814_at	MAP kinase-activated protein kinase 2
rc_AI012030_at	matrix Gla protein
D14448_s_at	Max
J05571_s_at	methionine adenosyltransferase II, alpha
L10652_g_at	methionine aminopeptidase 2
U75920_at	microtubule-associated protein, RP/EB family, member 1
U05784_s_at	microtubule-associated proteins 1A/1B light chain 3
rc_AA799656_at	mitochondrial ribosomal protein S31; imogen 38 [*Homo sapiens*]
rc_AA799656_g_at	mitochondrial ribosomal protein S31; imogen 38 [*Homo sapiens*]
rc_AA799369_at	mitochondrial ribosomal protein S4 [Homo sapiens]
rc_AA924542_s_at	Mitogen-activated protein kinase 14
rc_AI137862_s_at	Mitogen-activated protein kinase 14
rc_AI171630_s_at	Mitogen-activated protein kinase 14
U73142_at	Mitogen-activated protein kinase 14
U73142_g_at	Mitogen-activated protein kinase 14
U91847_s_at	Mitogen-activated protein kinase 14
M64301_at	Mitogen-activated protein kinase 6
M64301_g_at	Mitogen-activated protein kinase 6
M94454_at	Mitogen-activated protein kinase kinase kinase 8
U87627_at	monocarboxylate transporter
rc_AI111401_s_at	Multiple inositol polyphosphate histidine phosphatase 1
rc_AI229637_at	MYB binding protein 1a
rc_AI237258_at	MYB binding protein 1a
AF020618_at	Myeloid differentiation primary response gene 116

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
AF020618_g_at	Myeloid differentiation primary response gene 116
X68199_at	myosin Ib
U50185_g_at	myosin phosphatase, target subunit 1
rc_AA859896_at	myristoylated alanine rich protein kinase C substrate
rc_AA899253_at	myristoylated alanine rich protein kinase C substrate
rc_AA925762_at	myristoylated alanine-rich C-kinase substrate (MARCKS) (LOC294446), mRNA
rc_AA955167_s_at	myristoylated alanine-rich C-kinase substrate (MARCKS) (LOC294446), mRNA
X52711_at	myxovirus (influenza virus) resistance
U17260_s_at	N-acetyltransferase 1 (arylamine N-acetyltransferase)
rc_AI071866_s_at	Nclone10 mRNA
U31866_at	Nclone10 mRNA
AB006461_at	Neurochondrin
M15880_at	neuropeptide Y
D44591_s_at	nitric oxide synthase 2, inducible
U03699complete_seq_at	nitric oxide synthase 2, inducible
rc_AI112173_at	NME7
AF036335_at	NonO/p54nrb homolog
AF036335_g_at	NonO/p54nrb homolog
AF069782_at	Nopp140 associated protein
rc_AA799539_at	NS1 binding protein [*Homo sapiens*]
L26267_at	nuclear factor kappa B p105 subunit
X63594cds_at	nuclear factor of kappa light chain gene enhancer in B cells inhibitor, alpha
X63594cds_g_at	nuclear factor of kappa light chain gene enhancer in B cells inhibitor, alpha
U10995_at	nuclear receptor subfamily 2, group F, member 1
rc_AI176710_at	nuclear receptor subfamily 4, group A, member 3
AF063447_at	nuclear RNA helicase, DECD variant of DEAD box family
D13309_s_at	nuclease sensitive element binding protein 1
M94287_at	nucleolar phosphoprotein p130
rc_AA998882_s_at	nucleolar phosphoprotein p130
M55015cds_s_at	Nucleolin
J03969_at	nucleophosmin 1
J04943_at	nucleophosmin 1
Z21780_at	nucleoporin 155kd
AF000901_s_at	nucleoporin p58
U63839_at	nucleoporin p58
AF062594_at	nucleosome assembly protein 1-like 1
rc_AA866472_at	nucleosome assembly protein 1-like 1
rc_AA892598_at	Nucleostemin
rc_AA892598_g_at	Nucleostemin
AF091563_i_at	olfactory receptor
J04791_s_at	ornithine decarboxylase 1
J04792_at	ornithine decarboxylase 1
rc_AI043631_s_at	ornithine decarboxylase antizyme inhibitor
D63411_s_at	outer mitochondrial membrane receptor rTOM20
U21871_at	outer mitochondrial membrane receptor rTOM20
U89280_at	oxidative 17 beta hydroxysteroid dehydrogenase type 6
rc_AI071531_s_at	oxidized low density lipoprotein (lectin-like) receptor 1
E01524cds_s_at	P450 (cytochrome) oxidoreductase
M10068mRNA_s_at	P450 (cytochrome) oxidoreductase
rc_AI137856_s_at	P450 (cytochrome) oxidoreductase

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
AF000899_g_at	P58/p45 [*Rattus norvegicus*], mRNA sequence
L20869_at	pancreatitis-associated protein 3
rc_AA892298_at	peptidylprolyl cis-trans isomerase-like protein 3
AJ224120_at	peroxisomal membrane protein Pmp26p (Peroxin-11)
rc_AA892128_at	peroxisomal membrane protein Pmp26p (Peroxin-11)
rc_AA893267_at	PEST phosphatase interacting protein (LOC300732), mRNA
D50580_at	phenobarbital-inducible carboxylesterase (liver)
rc_AA925887_at	phosphate cytidylyltransferase 1, choline, alpha isoform
D88666_at	phosphatidylserine-specific phospholipase A1
M25350_s_at	phosphodiesterase 4B
X58865mRNA_at	phosphofructokinase, liver, B-type
U20195_s_at	phosphoglucomutase 1
rc_AI169417_s_at	phosphoglycerate mutase 1
U17901_at	phospholipase A2, activating protein
X51529_at	phospholipase A2, group IIA (platelets, synovial fluid)
X16554_at	phosphoribosyl pyrophosphate synthetase 1
D21132_at	phosphotidylinositol transfer protein, beta
rc_AA998446_s_at	phosphotidylinositol transfer protein, beta
rc_AA799461_at	Pincher
M23697_at	plasminogen activator, tissue
rc_AI169104_at	Platelet factor 4 precursor (PF-4) (Oncostatin A) (Iroplact) PLF4_HUMAN
rc_AA799323_at	pleckstrin (LOC364206), mRNA
rc_AI102795_at	Pleiotrophin
rc_AI639353_at	pleiotropic regulator 1
rc_AA892950_at	polymerase (DNA directed), gamma 2
X74565cds_at	polypyrimidine tract binding protein
X74565cds_g_at	polypyrimidine tract binding protein
D42145_at	potassium inwardly-rectifying channel, subfamily J, member 8
D82363_s_at	presenilin 1
U05989_at	PRKC, apoptosis, WT1, regulator
rc_AA875602_at	probable phenylalanine-tRNA ligase (EC 6.1.1.20) [imported] - human T45074
AF016503_s_at	procollagen C-proteinase enhancer protein
rc_AA892897_at	procollagen lysine, 2-oxoglutarate 5-dioxygenase 2
L48060_s_at	prolactin receptor
U61729_at	proline rich 2
D45250_s_at	protease (prosome, macropain) 28 subunit, beta
rc_AA858879_at	proteasome (prosome, macropain) 26S subunit, non-ATPase
AB017188_at	proteasome (prosome, macropain) 26S subunit, non-ATPase,4
E03358cds_at	proteasome (prosome, macropain) subunit, alpha type 2
D10755_s_at	proteasome (prosome, macropain) subunit, alpha type 6
D30804_g_at	proteasome (prosome, macropain) subunit, alpha type 7
rc_AA849722_at	proteasome (prosome, macropain) subunit, beta type 1
AF059530_at	protein arginine N-methyltransferase 3(hnRNP methyltransferase S cerevisiae)-like 3
E13644cds_s_at	protein carrying the RING-H2 sequence motif
rc_AA894089_s_at	protein carrying the RING-H2 sequence motif
M15523_s_at	protein kinase C, epsilon
M18332_s_at	protein kinase C, zeta
L29281_at	protein kinase, interferon-inducible double-stranded RNA dependent
S78218_g_at	protein phosphatase 1, catalytic subunit, beta isoform
rc_AI012595_at	protein phosphatase 2a, catalytic subunit, alpha isoform

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
X16043cds_at	protein phosphatase 2a, catalytic subunit, alpha isoform
rc_AA891537_at	protein predicted by clone 23733 [*Homo sapiens*]
L27843_s_at	protein tyrosine phosphatase 4a1
M33962_at	protein tyrosine phosphatase, nonreceptor type 1
M33962_g_at	protein tyrosine phosphatase, nonreceptor type 1
rc_AI113289_s_at	protein tyrosine phosphatase, nonreceptor type 1
rc_AI180145_s_at	protein tyrosine phosphatase, nonreceptor type 1
S74351_s_at	protein tyrosine phosphatase, nonreceptor type 16
S81478_s_at	protein tyrosine phosphatase, nonreceptor type 16
U02553cds_s_at	protein tyrosine phosphatase, nonreceptor type 16
X58828_at	protein tyrosine phosphatase, nonreceptor type 2
D85183_s_at	protein tyrosine phosphatase, nonreceptor type substrate 1
M10072mRNA_s_at	protein tyrosine phosphatase, receptor type, C
U40790_at	protein tyrosine phosphatase, receptor type, J
rc_AA799812_at	protein tyrosine phosphatase (EC 3.1.3.48), nonreceptor type 3 - human A41109
rc_AA818894_at	proteoglycan peptide core protein
rc_AI070277_s_at	proteolipid protein
D10757_g_at	proteosome (prosome, macropain) subunit, beta type 9
U56839_at	purinergic receptor P2Y, G-protein coupled 2
AF040954_at	putative protein phosphatase 1 nuclear targeting subunit
AF062740_at	pyruvate dehydrogenase phosphatase isoenzyme 1
rc_AA818951_at	pyruvate kinase, muscle
L07925_g_at	ral guanine nucleotide dissociation stimulator
U82623_g_at	RalA binding protein 1
rc_AA892554_at	Ras-GTPase-activating protein binding protein 2 (GAP SH3-domain binding protein 2)
rc_AA892554_g_at	Ras-GTPase-activating protein binding protein 2 (GAP SH3-domain binding protein 2)
rc_AA894119_at	Ras-GTPase-activating protein binding protein 2 (GAP SH3-domain binding protein 2)
rc_AA800305_at	Ras-related protein Rab-5A RB5A_HUMAN
M33329_f_at	rat senescence marker protein 2A gene, exons 1 and 2
rc_AA945050_f_at	rat senescence marker protein 2A gene, exons 1 and 2
U21719mRNA_s_at	Clone D920 intestinal epithelium proliferating cell-associated
E01983cds_s_at	regenerating islet-derived 1
U92279_at	regulator of G-protein signaling 14
AJ001929_s_at	Reticulocalbin
U15734_at	reticulocalbin 2
rc_AA875563_at	reticulocalbin precursor - human JC4173
U33500_at	retinol dehydrogenase type II mRNA, complete cds
U33500_g_at	retinol dehydrogenase type II mRNA, complete cds
U18762_at	retinol dehydrogenase type III
rc_AA900505_at	rhoB gene
AB022209_s_at	ribonucleoprotein F
rc_AA891713_at	ribosomal protein L13A
rc_AA799672_s_at	ribosomal protein L6
M89646_at	ribosomal protein S24
rc_AA891580_at	ribosomal protein S3a
AF100470_at	ribosome associated membrane protein 4
rc_AA859848_at	RIKEN cDNA 0610038L10 gene (LOC311241), mRNA
rc_AA891689_g_at	RIKEN cDNA 4733401F03 [*Mus musculus*]
AF022081_at	ring finger protein 4
U16025_at	RT1 class Ib gene, locus M3

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
L35271_at	runt related transcription factor 1
AB002406_at	RuvB-like protein 1
X06916_at	S100 calcium binding protein A4
L18948_at	S100 calcium binding protein A9 (calgranulin B)
J03627_at	S-100 related protein, clone 42C
rc_AA800808_at	S12207 hypothetical protein (B2 element) - mouse
M15185_s_at	S-adenosylhomocysteine hydrolase
rc_AI008131_s_at	S-adenosylmethionine decarboxylase 1
X59132_at	secretin receptor
M93669_at	secretogranin 2
rc_AI073164_at	secretory carrier membrane protein 1
S79523_at	selectin, lymphocyte
L23088_at	selectin, platelet
rc_AA799700_at	selenide, water dikinase 2 (selenophosphate synthetase 2) (selenium donor protein 2)
M24067_at	serine (or cysteine) proteinase inhibitor, member 1
X69834_at	serine protease inhibitor 2.4
AF086624_s_at	serine threonine kinase pim3
AJ001529cds_at	serine/threonine kinase 3
L01624_at	serum/glucocorticoid regulated kinase
rc_AA800686_at	SH2-domain protein Grb-IR - human I39175
rc_AA892553_at	signal transducer and activator of transcription 1
X91810_at	signal transducer and activator of transcription 3
X67859_at	Sjogren syndrome antigen B
AB017170_s_at	slit homolog 1 (*Drosophila*)
U47312_s_at	Smad ubiquitination regulatory factor 1 (Ubiquitin-protein ligase SMURF1)
X17053cds_s_at	small inducible cytokine A2
X17053mRNA_s_at	small inducible cytokine A2
U06434_at	small inducible cytokine A4
AF053312_s_at	small inducible cytokine subfamily A20
M29295_at	small nuclear ribonucleoprotein polypeptides B and B1
rc_AA799526_at	small nuclear ribonucleoprotein Sm D3 (snRNP core protein D3) (Sm-D3) SMD3_HUMAN
rc_AA900769_s_at	smooth muscle alpha-actin
U81186_at	smooth muscle-specific 17 beta-hydroxysteroid dehydrogenase type 3
U81186_g_at	smooth muscle-specific 17 beta-hydroxysteroid dehydrogenase type 3
S59158_at	solute carrier family 1, member 3
U07183_at	solute carrier family 10, member 2
AF008439_at	solute carrier family 11, member 2
AF008439_g_at	solute carrier family 11, member 2
rc_AA892390_s_at	solute carrier family 11, member 2
AF051561_s_at	solute carrier family 12, member 2
M13979_at	solute carrier family 2, member 1
S68135_s_at	solute carrier family 2, member 1
AB015433_s_at	solute carrier family 3, member 2
X89225cds_s_at	solute carrier family 3, member 2
AF004017_at	solute carrier family 4, member 4
AJ001290cds_at	solute carrier family 5 (inositol transporters), member 3
M96601_at	solute carrier family 6, member 6
rc_AA957917_s_at	solute carrier family 7, member 1
U70476_at	solute carrier family 7, member 1
U53927_at	solute carrier family 7, member 3

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
U04738_at	somatostatin receptor 4
rc_AA874928_at	sorting nexin 4 SNX4_HUMAN
rc_AA874928_g_at	sorting nexin 4 SNX4_HUMAN
D78303_at	splicing factor YT521-B
D37920_at	squalene epoxidase
U75404UTR#1_s_at	Ssecks 322 mRNA, 3′ untranslated region, partial sequence
M81639_at	Stannin
AF006617_at	stress 70 protein chaperone, microsome-associated, 60kD human homolog
Y15068_at	stress-induced-phosphoprotein 1 (Hsp70/Hsp90-organizing protein)
D31854_s_at	Subtilisin-like endoprotease
rc_AI230712_at	Subtilisin-like endoprotease
Y00497_s_at	superoxide dismutase 2
rc_AI171166_at	suppression of tumorigenicity 13 (colon carcinoma) Hsp70-interacting protein
AF044910_g_at	survival motor neuron
U90312_at	synaptojanin 2
S61868_at	syndecan 4
rc_AA892373_at	Syntenin
rc_AI639447_at	TANK binding kinase 1; NF-kB-activating kinase [*Homo sapiens*]
rc_AA891286_at	thioredoxin reductase 1
rc_AA891694_at	thioredoxin-like (32 kd)
U90121_at	Thrombomodulin
rc_AI169327_at	tissue inhibitor of metalloproteinase 1
U27201_at	tissue inhibitor of metalloproteinase 3
L14463_at	transducin-like enhancer of split 4, E(spl) homolog (Drosophila)
M58040_at	transferrin receptor
rc_AI639058_s_at	transmembrane, prostate androgen induced RNA; PMEPA1 protein [*Homo sapiens*]
X57523_g_at	transporter 1, ATP binding cassette, sub-family B (MDR/TAP)
Z14030_at	TRAP-complex gamma subunit
AF036255_at	tripartite motif protein 3
J02780_at	tropomyosin 4
rc_AA945143_at	tryptophan 2,3-dioxygenase
E02468cds_s_at	tumor necrosis factor superfamily, member 2
X13058_at	tumor protein p53
L12025_at	tumor-associated antigen 1
S55305_s_at	tyrosine 3-monooxygenase/tryptophan 5-monooxgenase activation protein
D17445_at	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein
rc_AI104389_g_at	tyrosine hydroxylase
M62388_at	ubiquitin conjugating enzyme
M62388_g_at	ubiquitin conjugating enzyme
rc_AA799612_at	ubiquitin conjugating enzyme
U13176_at	ubiquitin conjugating enzyme E2D 2
AF048687_s_at	UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 6
AF047707_at	UDP-glucose:ceramide glycosyltransferase
U07683_at	UDP-glucuronosyltransferase 8
rc_AA891681_at	UNR-interacting protein (serine-threonine kinase receptor-associated protein)
rc_AA859954_at	vacuole membrane protein 1
M98327_at	Valyl-tRNA synthetase 2
M84488_at	vascular cell adhesion molecule 1
X63722cds_s_at	vascular cell adhesion molecule 1
L20913_s_at	vascular endothelial growth factor

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
X67788_at	Villin 2
X62952_at	vimentin
rc_AA944014_at	v-jun sarcoma virus 17 oncogene homolog (avian)
U56241_at	v-maf musculoaponeurotic fibrosarcoma oncogene family, protein B (avian)
U14746_at	von Hippel-Lindau syndrome homolog
rc_AI172247_at	xanthine dehydrogenase
rc_AA893584_at	Y73B6BL.30.p [*C elegans*]
rc_AA893860_at	YSHUT threonine–tRNA ligase (EC 6.1.1.3) - human
AF079873_at	zinc finger protein 162
rc_AI170608_at	zinc finger protein 265
M96548_at	zinc finger protein 354A
rc_AA800613_at	zinc finger protein 36
X63369cds_at	zinc finger protein 36
AA108277_at	—
AB000717exons#1–8_s_at	—
AB005540_at	—
AF034900mRNA_i_at	—
AF055292mRNA_at	—
D13623_at	—
D13623_g_at	—
D17521_at	—
D38066exon_s_at	—
D87991_g_at	—
D88461_at	—
E02315cds_f_at	—
L00370cds_s_at	—
L00981mRNA#2_at	—
M12112mRNA#3_s_at	—
M13100cds#1_g_at	—
M13100cds#4_f_at	—
M22670cds_at	—
M27886exon_g_at	—
M55017exon_s_at	—
M91234_f_at	—
rc_AA799529_at	—
rc_AA799726_at	—
rc_AA799804_at	—
rc_AA799991_at	—
rc_AA800017_at	—
rc_AA800186_at	—
rc_AA800597_at	—
rc_AA800626_at	—
rc_AA800753_at	—
rc_AA800840_at	—
rc_AA800908_at	—
rc_AA859536_at	—
rc_AA859585_at	—
rc_AA859725_at	—
rc_AA859966_s_at	—
rc_AA874803_at	—

Table 1. Up-regulated Probe Sets

Probe Set ID	Gene Name
rc_AA874875_at	—
rc_AA874889_g_at	—
rc_AA875032_at	—
rc_AA875126_at	—
rc_AA875126_g_at	—
rc_AA875620_at	—
rc_AA891220_at	—
rc_AA891233_at	—
rc_AA891475_at	—
rc_AA891542_at	—
rc_AA891931_at	—
rc_AA892083_at	—
rc_AA892146_f_at	—
rc_AA892238_at	—
rc_AA892257_at	—
rc_AA892273_at	—
rc_AA892414_at	—
rc_AA892541_g_at	—
rc_AA892570_at	—
rc_AA892750_at	—
rc_AA892754_at	—
rc_AA892774_at	—
rc_AA892851_at	—
rc_AA892851_g_at	—
rc_AA893088_at	—
rc_AA893105_at	—
rc_AA893172_at	—
rc_AA893603_at	—
rc_AA893743_at	—
rc_AA894029_at	—
rc_AA894340_at	—
rc_AA925880_at	—
rc_AI010580_s_at	—
rc_AI230228_at	—
rc_AI638995_at	—
rc_AI638998_at	—
rc_AI639029_s_at	—
rc_AI639042_at	—
rc_AI639106_at	—
rc_AI639141_at	—
rc_AI639149_s_at	—
rc_AI639246_at	—
rc_AI639312_at	—
rc_AI639331_at	—
rc_AI639338_at	—
rc_AI639405_at	—
rc_AI639438_at	—
rc_AI639471_r_at	—
rc_AI639474_at	—
rc_H31732_at	—
rc_H31955_at	—
rc_H33619_at	—
S58528_at	—
S63233_g_at	—
S63521_r_at	—
S68589_s_at	—
S70011_at	—
S70011_g_at	—
S71021_s_at	—
S78556_at	—
S81025_at	—
S82649_s_at	—
U20643mRNA#2_f_at	—
X03347cds_g_at	—
X05472cds#3_f_at	—
X06769cds_g_at	—
X07686cds_s_at	—
X07944exon#1—12_s_at	—
X16038exon_s_at	—
X51615_at	—
X51615_g_at	—
X59864mRNA_g_at	—
X62950mRNA_f_at	—
X62951mRNA_s_at	—
X96437mRNA_g_at	—
Y00396mRNA_g_at	—
Z15123exon#5_s_at	—

Affymetrix RU34A chips were used to examine the temporal profile of changes in global gene expression in liver in response to this single bolus dose of MPL. RNA samples from each individual animal were applied to a separate chip to preserve interanimal variation. Because this chip contains 8799 probe sets, the major problem was identifying the relatively small percentage of the probe sets that are regulated by corticosteroids. In a previous study, we used cluster analysis tools and correlation coefficients to concurrently address the problems of data mining and temporal clustering with this data set.[5] Those tools did identify 6 clusters of regulated probe sets with different temporal signatures. However, while examining genes in pathways we were prompted to visually inspect the results for genes that ''should'' have been regulated based on the literature. The results of the visual inspection of individual genes demonstrated to us that the initial very stringent approach that we employed eliminated probe sets that were clearly regulated. There are 2 reasons for this deficit. First, we approached data mining (identifying regulated probe sets) and clustering (grouping probe sets with simi-

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
M76704_s_at	0–6-methylguanine-DNA methyltransferase
M59861_at	10-formyltetrahydrofolate dehydrogenase
D00569_at	2,4-dienoyl CoA reductase 1, mitochondrial
L32601_s_at	20-alpha-hydroxysteroid dehydrogenase
AF044574_at	2–4-dienoyl-Coenzyme A reductase 2, peroxisomal
AF044574_g_at	2–4-dienoyl-Coenzyme A reductase 2, peroxisomal
rc_AA893239_at	2-hydroxyphytanoyl-CoA lyase
rc_AA859975_at	2-oxoglutarate carrier
U84727_at	2-oxoglutarate carrier
rc_AI177004_s_at	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1
X52625_at	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1
M33648_at	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2
M33648_g_at	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2
D28339_s_at	3-hydroxyanthranilate 3,4-dioxygenase
D44494_at	3-hydroxyanthranilate 3,4-dioxygenase
rc_AA817846_at	3-hydroxybutyrate dehydrogenase precursor; (R)-3-hydroxybutyrate dehydrogenase
D87839_at	4-aminobutyrate aminotransferase
D87839_g_at	4-aminobutyrate aminotransferase
U70825_at	5-oxoprolinase (ATP-hydrolysing)
M83740_s_at	6-pyruvoyl-tetrahydropterin synthase
AB016800_at	7-dehydrocholesterol reductase
rc_AA891922_at	Ab1–152 mRNA, complete cds
rc_AA892916_at	Ab2–305 mRNA, complete cds
rc_AA893212_at	Ac1054 mRNA, complete cds
rc_AI639504_at	Ac2–202 (LOC307858), mRNA
D00512_g_at	acetyl-Coenzyme A acetyltransferase 1
D13921_s_at	acetyl-Coenzyme A acetyltransferase 1
J02749_at	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)
J02749_g_at	acetyl-Coenzyme A acyltransferase 1 (peroxisomal 3-oxoacyl-Coenzyme A thiolase)
X05341_at	acetyl-Coenzyme A acyltransferase 2 (mitochondrial 3-oxoacyl-Coenzyme A thiolase)
J05029_s_at	acetyl-Coenzyme A dehydrogenase, long-chain
J02791_at	acetyl-Coenzyme A dehydrogenase, medium chain
D32209_at	acidic nuclear phosphoprotein 32 family, member A
rc_AA945171_at	ACL (LOC292698), mRNA
rc_AI179012_s_at	Actin, beta
AF089825_at	activin beta E
X95189_at	acyl-Coenzyme A oxidase 2, branched chain
rc_AA891812_at	adducin 1, alpha
rc_AI176052_at	adenylate kinase 3
L01115_at	adenylyl cyclase 6
rc_AA874941_at	adipose differentiation-related protein
rc_AA893280_at	adipose differentiation-related protein
U12568_at	ADP-ribosylation-like 3
M60655_at	adrenergic receptor, alpha 1b
AF045464_s_at	aflatoxin B1 aldehyde reductase
M25073_at	alanyl (membrane) aminopeptidase
rc_AA866237_s_at	albumin
M15327_at	alcohol dehydrogenase 1
X72792cds_s_at	alcohol dehydrogenase 1
rc_AA874874_at	alcohol dehydrogenase 4 (class II), pi polypeptide

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
X90710_at	alcohol dehydrogenase 4 (class II), pi polypeptide
rc_AA893658_at	alcohol dehydrogenase PAN1B-like protein (LOC305150), mRNA
AF001898_at	aldehyde dehydrogenase family 1, member A1
M23995_g_at	aldehyde dehydrogenase family 1, subfamily A4
M73714_at	aldehyde dehydrogenase family 3, subfamily A2
rc_AA996484_g_at	aldehyde dehydrogenase family 3, subfamily A2
L34821_at	aldehyde dehydrogenase family 5, subfamily A1
D17309_at	aldo-keto reductase family 1, member D1 (delta 4–3-ketosteroid-5-beta-reductase)
S80431_s_at	aldo-keto reductase family 1, member D1 (delta 4–3-ketosteroid-5-beta-reductase)
rc_AA892821_at	aldo-keto reductase family 7, member A2 (aflatoxin aldehyde reductase)
rc_AA892821_g_at	aldo-keto reductase family 7, member A2 (aflatoxin aldehyde reductase)
rc_AA892395_s_at	aldolase B
X02284_at	aldolase B
S87544_at	Alpha 1 microglobulin/bikunin
S87544_g_at	Alpha 1 microglobulin/bikunin
M22359mRNA_s_at	Alpha(1)-inhibitor 3, variant I
M22360_s_at	Alpha(1)-inhibitor 3, variant I
rc_AA859899_at	Alpha-2 antiplasmin
X63446_at	Alpha-2-HS-glycoprotein
M27434_s_at	Alpha-2u globulin PGCL1
X02361_g_at	Alpha-fetoprotein
U89905_at	Alpha-methylacyl-CoA racemase
rc_AA800745_at	aminolevulinate, delta-, dehydratase
L14462_g_at	amino-terminal enhancer of split
M74054_s_at	angiotensin II receptor, type 1 (AT1A)
X03468_at	apolipoprotein A-II
M00002_at	apolipoprotein A-IV
L07114_at	apolipoprotein B editing complex 1
X15512_at	apolipoprotein C-I
rc_AI169758_at	apolipoprotein C-III
U90829_at	APP binding protein 1
AB005547_at	aquaporin 8
U04733_s_at	arachidonic acid epoxygenase
rc_AA891194_s_at	Arg/Abl-interacting protein ArgBP2
rc_AA892251_at	arginine vasopressin receptor 1A
D13978_s_at	argininosuccinate lyase
X07636_at	asialoglycoprotein receptor 2
J05210_at	ATP citrate lyase
L19927_at	ATP synthase, H+ transporting, mitochondrial F1 complex, gamma polypeptide 1
D13127_g_at	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit
D13122_f_at	ATPase inhibitor
AF106563_s_at	ATP binding cassette, sub-family B (MDR/TAP), member 6
D86086_s_at	ATP binding cassette, sub-family C (CFTR/MRP), member 2
rc_AA946532_at	ATP binding cassette, sub-family D (ALD), member 3
rc_AA859645_at	attractin
rc_AA800678_g_at	AW046014 protein (LOC363328), mRNA
rc_AA891739_at	BC021608 (LOC300676), mRNA
AB001347_s_at	beta-spectrin 3
rc_AA859994_at	BGAL_ECOLI Beta-galactosidase (Lactase)
rc_AA891944_at	BGAL_ECOLI Beta-galactosidase (Lactase)

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
rc_AA892522_at	BGAL_ECOLI Beta-galactosidase (Lactase)
rc_AA892778_at	BGAL_ECOLI Beta-galactosidase (Lactase)
rc_AA893032_at	BGAL_ECOLI Beta-galactosidase (Lactase)
rc_AA894193_at	BGAL_ECOLI Beta-galactosidase (Lactase)
D43964_at	bile acid-Coenzyme A: amino acid N-acyltransferase
AA684963_at	binding protein (LOC293702), mRNA
J02827_g_at	branched chain keto acid dehydrogenase subunit E1, alpha polypeptide
rc_AA891576_i_at	C1HUQC complement subcomponent C1q chain C precursor - human
AF097593_at	cadherin 2
AF097593_g_at	cadherin 2
AF061947_at	Cain
L27487_at	calcitonin receptor-like
AF063102_g_at	calcium-independent alpha-latrotoxin receptor homolog 2
rc_AI180288_s_at	caldesmon 1
rc_AA892382_at	camello-like 1
S66024_at	cAMP responsive element modulator
AF037072_at	carbonic anhydrase 3
U12268_at	carbonic anhydrase 5
X81395_at	carboxylesterase 1
X65296cds_s_at	carboxylesterase 3
rc_AI237825_at	carboxypeptidase B1
J04963_at	carcinoembryonic antigen-related cell adhesion molecule 1
J02844_s_at	carnitine O-octanoyltransferase
U26033_at	carnitine O-octanoyltransferase
L07736_at	carnitine palmitoyltransferase 1, liver
AF025670_g_at	caspase 6
M11670_at	catalase
rc_AA926149_g_at	catalase
D90404_at	cathepsin C
D90404_g_at	cathepsin C
AB000199_at	CCA2 protein
D26439_at	CD1d1 antigen
rc_AA818025_g_at	CD59 antigen
rc_AA874943_at	CDC42 effector protein (Rho GTPase binding) 3 (LOC313838), mRNA
X60767mRNA_s_at	cell division cycle 2 homolog A (*S pombe*)
U66471_at	cell growth regulatory with ring finger domain
rc_AA858607_at	cellular repressor of E1A-stimulated genes CREG (LOC289185), mRNA
rc_AI639381_at	checkpoint suppressor 1 (LOC314367), mRNA
rc_AI232194_at	chimerin (chimaerin) 2
D10262_at	choline kinase
M74067_at	claudin 3
U02506UTR#1_s_at	clone 15 polymeric immunoglobulin receptor mRNA, 3′UTR microsatellite repeats
U75405UTR#1_f_at	collagen, type 1, alpha 1
M29866_s_at	complement component 3
X52477_at	complement component 3
U86379_at	complement component 3a receptor 1
U52948_at	complement component 9
rc_AA893495_at	corticosteroid binding globulin precursor (CBG) (Transcortin) (LOC299270), mRNA
D17370_at	CTL target antigen
rc_AA875598_at	Cul2 protein (LOC361258), mRNA

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
AJ224680_at	cyclic nucleotide-gated channel beta subunit 1
D14013_at	cyclin C
D14014_at	cyclin D1
D14014_g_at	cyclin D1
X75207_s_at	cyclin D1
rc_AA899106_at	cyclin D2
rc_AI231292_g_at	cystatin C
M64755_at	cysteine-sulfinate decarboxylase
J03786_s_at	cytochrom P450 15-beta gene
AF007107_s_at	cytochrome b5
rc_AA818226_s_at	cytochrome c oxidase, subunit 4a
rc_AI008815_s_at	cytochrome c, somatic
rc_AA945573_f_at	cytochrome P450 2C17 - human (fragment) G38462
U46118_at	cytochrome P450 3A9
U39206_at	cytochrome P450 4F4
U39208_at	cytochrome P450 4F6
J02669_s_at	cytochrome P450 IIA1 (hepatic steroid hydroxylase IIA1) gene
K01721mRNA_s_at	cytochrome P450, 2b19
M18335_f_at	cytochrome P450, 2c39
M31031mRNA_f_at	cytochrome P450, 2c39
D38381_s_at	cytochrome P450, 3a18
J04187_at	cytochrome P450, subfamily 2A, polypeptide 1
AF056333_s_at	cytochrome P450, subfamily 2E, polypeptide 1
AF017393_at	cytochrome P450, subfamily 2F, polypeptide 1
J02657_s_at	cytochrome P450, subfamily IIC (mephenytoin 4-hydroxylase)
AB008423_s_at	cytochrome P450, subfamily IID2
AB008424_s_at	cytochrome P450, subfamily IID3
M94548_at	cytochrome P450, subfamily IVF, polypeptide 14 (leukotriene B4 omega hydroxylase)
J02869mRNA_s_at	cytochrome P450CMF1b
rc_AI169735_g_at	cytochrome P450IIB3
X81448cds_at	cytokeratin (LOC294853), mRNA
X60328_g_at	cytosolic epoxide hydrolase
X65083cds_at	cytosolic epoxide hydrolase
J03179_at	D site albumin promoter binding protein
rc_AA799488_at	D330021B20 protein (LOC316685), mRNA
Z36980_at	D-dopachrome tautomerase
Z36980_g_at	D-dopachrome tautomerase
rc_AI639418_at	deiodinase, iodothyronine, type I
X57999cds_at	deiodinase, iodothyronine, type I
U75689_s_at	deoxyribonuclease I-like 3
U64030_at	deoxyuridinetriphosphatase (dUTPase)
rc_AI012275_at	developmentally regulated protein TPO1
D78588_at	diacylglycerol kinase zeta
D00636cds_s_at	diaphorase 1
D00636Poly_A_Site#1_s_at	diaphorase 1
J03867_s_at	diaphorase 1
rc_AA963839_s_at	diaphorase 1
rc_AA900413_at	dihydrofolate reductase
D63704_at	Dihydropyrimidinase
D63704_g_at	Dihydropyrimidinase

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
rc_AI058941_s_at	dimethylarginine dimethylaminohydrolase 1
rc_AA892345_at	dimethylglycine dehydrogenase precursor
M95768_at	di-N-acetylchitobiase
J04591_at	dipeptidylpeptidase 4
rc_AA892069_s_at	dipeptidylpeptidase 4
U66322_at	dithiolethione-inducible gene-1
D00729_at	dodecenoyl-Coenzyme A delta isomerase
rc_AI170568_s_at	dodecenoyl-Coenzyme A delta isomerase
D89375_s_at	dopa/tyrosine sulfotransferase
U42627_at	dual specificity phosphatase 6
X94185cds_s_at	dual specificity phosphatase 6
D28560_at	ectonucleotide pyrophosphatase/phosphodiesterase 2
L00117_at	elastase 1
rc_AI237007_at	electron-transferring-flavoprotein dehydrogenase
U08976_at	enoyl-Coenzyme A hydratase 1
K03249_at	enoyl-Coenzyme A, hydratase/3-hydroxyacyl Coenzyme A dehydrogenase
D38056_at	ephrin A1
rc_AA892417_at	ephrin A1
U04842_at	epidermal growth factor
L20823_at	Epimorphin
M26125_at	epoxide hydrolase 1
D00362_s_at	esterase 2
M20629_s_at	esterase 2
rc_AA875050_at	ethanolamine kinase-like protein EKI2 (FLJ10761) (LOC360843), mRNA
rc_AA819500_at	expressed sequence AU040575 (LOC288003), mRNA
M95591_at	farnesyl diphosphate farnesyl transferase 1
M95591_g_at	farnesyl diphosphate farnesyl transferase 1
U72497_at	fatty acid amide hydrolase
V01235_at	fatty acid binding protein 1
U02096_at	fatty acid binding protein 7
D90109_at	fatty acid Coenzyme A ligase, long chain 2
rc_AA893242_at	fatty acid Coenzyme A ligase, long chain 2
rc_AA893242_g_at	fatty acid Coenzyme A ligase, long chain 2
rc_AI044900_s_at	fatty acid Coenzyme A ligase, long chain 2
AB012933_at	fatty acid Coenzyme A ligase, long chain 5
rc_AA892832_at	fatty acid elongase 1
M76767_s_at	fatty acid synthase
X13527cds_s_at	fatty acid synthase
M21622_at	Fc receptor, IgE, high affinity I, alpha polypeptide
X14323cds_g_at	Fc receptor, IgG, alpha chain transporter
D50436_at	ferredoxin 1
rc_AI044488_at	ferredoxin 1
U57715_at	FGF receptor activating protein 1
M35601_at	fibrinogen, alpha polypeptide
M35601_g_at	fibrinogen, alpha polypeptide
U05675_at	fibrinogen, beta polypeptide
rc_AI136977_at	FK506 binding protein 4 (59 kDa)
rc_AI136977_g_at	FK506 binding protein 4 (59 kDa)
rc_AA859885_at	follistatin-like
AF061242_s_at	fractured callus expressed transcript 1

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
X16145_at	fucosidase, alpha-L- 1, tissue
M77694_at	fumarylacetoacetate hydrolase
U76206_at	G protein-coupled receptor 105
AF061443_at	G protein-coupled receptor 48
rc_AA893235_at	G0S2-like protein (LOC289388), mRNA
rc_AI639017_at	G9a protein - human S30385
AB003515_at	GABA(A) receptor-associated protein like 2
L05541_at	Galactose-1-phosphate uridylyltransferase (Gal-1-P uridylyltransferase)
U38379_at	gamma-glutamyl hydrolase
X04070_at	gap junction membrane channel protein beta 1
rc_AA800786_at	GATA binding protein 6
M96674_at	glucagon receptor
X53588_at	Glucokinase
rc_AA945442_at	glucokinase regulatory protein
L37333_s_at	glucose-6-phosphatase, catalytic
AF080468_at	glucose-6-phosphatase, transport protein 1
M13962mRNA#2_at	glucuronidase, beta
rc_AI233261_i_at	glutamate cysteine ligase, modifier subunit
S65555_at	glutamate cysteine ligase, modifier subunit
rc_AI233216_at	glutamate dehydrogenase 1
J05181_at	glutamate-cysteine ligase catalytic subunit
L24896_s_at	glutathione peroxidase 4
rc_AA893189_at	glutathione reductase
U73174_at	glutathione reductase
U73174_g_at	glutathione reductase
K01932_f_at	glutathione S-transferase, alpha 1
X78848cds_f_at	glutathione S-transferase, alpha 1
X67654_at	glutathione S-transferase, theta 1
D10026_s_at	glutathione S-transferase, theta 2
rc_AI138143_at	glutathione S-transferase, theta 2
K00136mRNA_at	glutathione S-transferase, alpha type2
rc_AA945082_at	glutathione S-transferase, alpha type2
rc_AI235747_at	glutathione S-transferase, alpha type2
AB002558_at	glycerol 3-phosphate dehydrogenase
D16102_at	glycerol kinase
U36772_at	glycerol-3-phosphate acyltransferase, mitochondrial
X78593_g_at	glycerol-3-phosphate dehydrogenase 2
U07971_at	glycine amidinotransferase (L-arginine:glycine amidinotransferase)
rc_AA893219_at	glycine methyltransferase
X06150cds_at	glycine methyltransferase
J05446_at	glycogen synthase 2
rc_AA892799_s_at	glyoxylate reductase/hydroxypyruvate reductase (LOC298085), mRNA
M12450_at	group specific component
AF076619_at	growth factor receptor bound protein 14
Z83757mRNA_at	growth hormone receptor
Z83757mRNA_g_at	growth hormone receptor
U85512_s_at	GTP cyclohydrolase I feedback regulatory protein
J03588_at	guanidinoacetate methyltransferase
rc_AA849036_at	guanylate cyclase 1, soluble, alpha 3
rc_AI233225_at	guanylate cyclase 1, soluble, beta 3

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
M57507_at	guanylate cyclase, soluble, beta 2
K01933_at	Haptoglobin
AF008587_s_at	Hemochromatosis
X55955_at	hepatocyte nuclear factor 3, alpha
L09647_at	hepatocyte nuclear factor 3, beta
X57133mRNA_g_at	hepatocyte nuclear factor 4, alpha
X70900_at	Hepsin
AB016536_s_at	heterogeneous nuclear ribonucleoprotein A/B
D84418_s_at	high mobility group box 2
AB002393_g_at	histidine ammonia lyase
M58308_at	histidine ammonia lyase
rc_AA892470_at	histone H2A.F/Z variant isoform 1; purine-rich binding element protein B
rc_AA893035_s_at	HP33
rc_AA799891_g_at	HSPCO34 protein [*Homo sapiens*]
rc_AI232087_at	hydroxyacid oxidase (glycolate oxidase) 3
rc_AI012802_at	hydroxyacyl glutathione hydrolase
D16478_g_at	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A
M67465_at	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase
X06827_at	hydroxymethylbilane synthase
rc_AA945583_at	hydroxysteroid (17-beta) dehydrogenase 10
rc_AA799442_at	hypothetical LOC293114 (LOC293114), mRNA
rc_AA891423_at	hypothetical protein FLJ12118 (LOC361184), mRNA
rc_AA891978_at	hypothetical protein FLJ20487 (LOC361726), mRNA
rc_AI234939_at	hypothetical protein FLJ21827 (LOC300675), mRNA
rc_AA893237_at	hypothetical protein MGC18837 (LOC300441), mRNA
rc_AA859931_g_at	hypothetical protein MGC2749 [Homo sapiens]
rc_AA875639_at	hypothetical protein MGC45594 (LOC291403), mRNA
rc_AI234828_g_at	immunoglobulin alpha heavy chain (partial), complete constant region
AF000942_at	inhibitor of DNA binding 3, dominant negative helix–loop–helix protein
rc_AI171268_at	inhibitor of DNA binding 3, dominant negative helix–loop–helix protein
X06107_i_at	insulin-like growth factor 1
X06107_r_at	insulin-like growth factor 1
X16703_i_at	insulin-like growth factor 2
J04486_at	insulin-like growth factor binding protein 2
rc_AA924289_s_at	insulin-like growth factor binding protein, acid labile subunit
X65036_g_at	integrin alpha 7
X74293_s_at	integrin alpha 7
AF020046_s_at	integrin alpha E1, epithelial-associated
Y11283_at	inter alpha-trypsin inhibitor, heavy chain 4
D26178_at	intestinal cell kinase
rc_AA892314_at	isocitrate dehydrogenase 1
rc_AI045395_at	isopentenyl-diphosphate delta isomerase
J05031_at	isovaleryl coenzyme A dehydrogenase
rc_AA892545_at	ITM (LOC309131), mRNA
rc_AA900503_at	jagged 1
U58858_at	junction plakoglobin
M30282_at	kallikrein B, plasma 1
rc_AA893552_at	Kallistatin
M86235_at	Ketohexokinase
U93306_at	kinase insert domain protein receptor

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
L26292_g_at	Kruppel-like factor 4 (gut)
M55532_at	Kupffer cell receptor
U68168_at	kynureninase (L-kynurenine hydrolase)
AF056031_at	kynurenine 3-hydroxylase
rc_AA799676_at	Lactamase, beta 2 (LOC297768), mRNA
X66870_at	lamin A
rc_AA946108_at	laminin 5 alpha 3
rc_AI232691_at	lectin, galactose binding, soluble 8
X74549_at	leuserpin-2
AF090134_at	lin-7-Ba
AF090134_g_at	lin-7-Ba
AF090135_at	lin-7-Ba
rc_AA874784_s_at	lipase A, lysosomal acid
S81497_i_at	lipase A, lysosomal acid
S81497_s_at	lipase A, lysosomal acid
M16235_at	lipase, hepatic
J05499_at	liver mitochondrial glutaminase
AB010466_s_at	liver multidrug resistance-associated protein 6
X13722_at	low density lipoprotein receptor
L34049_g_at	low density lipoprotein receptor-related protein 2
Z11995cds_at	low density lipoprotein receptor-related protein associated protein 1
rc_AA800220_at	lysophospholipase 1
U97146_at	lysophospholipase 1
rc_AI234060_s_at	lysyl oxidase
M26594_at	malic enzyme 1
rc_AI008020_at	malic enzyme 1
rc_AI171506_at	malic enzyme 1
X05023_at	mannose binding protein C (liver)
M64862_at	matrin F/G 1
rc_AA800797_at	matrin F/G 1
D50564_at	mercaptopyruvate sulfurtransferase
Z17223_at	mesenchyme homeo box 2
rc_AI102562_at	metallothionein
rc_AI176456_at	METALLOTHIONEIN-IE (MT-1E) MT1E_HUMAN
M29472_at	mevalonate kinase
rc_AA924198_s_at	mevalonate kinase
AF095741_at	Mg87 protein
AF095741_g_at	Mg87 protein
AF029240_at	MHC class Ib RT1.S3
J03752_at	microsomal glutathione S-transferase 1
rc_AA892234_at	microsomal glutathione S-transferase 3 (LOC289197), mRNA
rc_AI008638_at	milk fat globule-EGF factor 8 protein
rc_AI639082_s_at	mini chromosome maintenance deficient 6 (S cerevisiae)
AB000098_g_at	MIPP65 protein
Y09333_at	mitochondrial acyl-CoA thioesterase 1
M96633_at	mitochondrial intermediate peptidase
U48596_g_at	mitogen activated protein kinase kinase kinase 1
D49785_at	mitogen activated protein kinase kinase kinase 12
rc_AA892500_at	mKIAA0623 protein (LOC303206), mRNA
M23601_at	monoamine oxidase B

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
AJ001320_at	multiple PDZ domain protein
rc_AI229497_at	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 10
rc_AI112237_at	NADH dehydrogenase (ubiquinone) 1 beta subcomplex, 2 (LOC362344), mRNA
rc_AI104679_s_at	NADH dehydrogenase (ubiquinone) 1, subcomplex unknown, 1 (6kD, KFYI)
rc_AA875268_at	NADH dehydrogenase (ubiquinone) Fe-S protein 7 (LOC362837), mRNA
rc_AI229440_s_at	NADH-cytochrome b5 reductase (B5R) NC5R_HUMAN
rc_AA891785_at	NADP+-specific isocitrate dehydrogenase (LOC293043), mRNA
AF016296_at	Neuropilin
rc_AI177161_at	NF-E2-related factor 2
rc_AA799560_at	N-myc downstream-regulated gene 2
D78018_s_at	nuclear factor I/A
X13167cds_s_at	nuclear factor I/A
AF014503_at	nuclear protein 1
D86580_at	nuclear receptor subfamily 0, group B, member 2
M25804_g_at	nuclear receptor subfamily 1, group D, member 1
U11685_at	nuclear receptor subfamily 1, group H, member 3
U18374_at	nuclear receptor subfamily 1, group H, member 4
M14053_at	nuclear receptor subfamily 3, group C, member 1
M36074_at	nuclear receptor subfamily 3, group C, member 2
rc_AA850885_s_at	nucleolar protein 3 (apoptosis repressor with CARD domain)
rc_AI638971_g_at	occluding
AF079864_at	olfactory receptor 78
AF004218_s_at	opioid receptor, sigma 1
rc_AA893325_at	ornithine aminotransferase
M11266_at	ornithine transcarbamylase
V01216_at	orosomucoid 1
U42719_at	palmitoyl-protein thioesterase 2
rc_AA817964_s_at	paraoxonase 1
U94856_at	paraoxonase 1
U94856_g_at	paraoxonase 1
M33025_s_at	Parathymosin
X16481_r_at	Parathymosin
rc_AA892993_at	PDZ-domain protein Gipc3 (LOC362825), mRNA
D63673_g_at	peroxisomal biogenesis factor 6
rc_AI013834_s_at	peroxisomal multifunctional enzyme type II
rc_AI101743_s_at	peroxisomal multifunctional enzyme type II
rc_AI176021_at	phosphatase and tensin homolog
AF080568_at	phosphate cytidylyltransferase 2, ethanolamine
AF040261_s_at	phosphatidylcholine transfer protein
L14441_at	phosphatidylethanolamine N-methyltransferase
AB009636_at	phosphatidylinositol 3-kinase, C2 domain containing, gamma polypeptide
Z22867_at	phosphodiesterase 3B
L14323_at	phospholipase C, beta 1
J03806_at	phospholipase C, gamma 1
D85435_at	PKC-delta binding protein
D85435_g_at	PKC-delta binding protein
M62832_at	Plasminogen
X70706cds_at	plastin 3 (T-isoform)
rc_AA891735_at	poliovirus receptor-related 1 (herpesvirus entry mediator C; nectin)
AB017711_at	polymerase II

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
rc_AA818069_f_at	Polyubiquitin
X62839mRNA_s_at	potassium voltage gated channel, Shaw-related sub-family, member 2
rc_AA945569_at	pregnancy-zone protein
M27156_at	Probasin
rc_AA892112_g_at	proline dehydrogenase (oxidase) 2 (LOC361538), mRNA
rc_AA799448_g_at	proline-rich proteoglycan 2 precursor, parotid - rat
X64336_at	protein C
X95577_at	protein kinase, AMP-activated, beta 1 noncatalytic subunit
D14421_at	protein phosphatase 2 (formerly 2A), regulatory subunit B (PR 52), beta isoform
rc_AI639479_at	protein RAKb (LOC361266), mRNA
U06230_s_at	protein S
rc_AA894258_at	protein tyrosine phosphatase, nonreceptor type 3 (protein-tyrosine phosphatase H1)
U28356_at	protein-tyrosine phosphatase, nonreceptor type 7
rc_AA859700_g_at	protoporphyrinogen oxidase (LOC289219), mRNA
Z36944cds_at	putative chloride channel (similar to Mm Clcn4–2)
U82591_at	putative c-Myc-responsive
rc_AA799691_at	putative potassium-chloride cotransporter-4; KCC4 (LOC308069), mRNA
U32314_at	pyruvate carboxylase
U32314_g_at	pyruvate carboxylase
L22294_at	pyruvate dehydrogenase kinase 1
U10357_at	pyruvate dehydrogenase kinase 2
U10357_g_at	pyruvate dehydrogenase kinase 2
AF062741_g_at	pyruvate dehydrogenase phosphatase isoenzyme 2
X05684_at	pyruvate kinase, liver and RBC
rc_AA892796_at	QIL1 (LOC301124), mRNA
J03481mRNA_at	quinoid dihydropteridine reductase
J03481mRNA_g_at	quinoid dihydropteridine reductase
M83678_at	RAB13
M94043_at	Rab38, member of RAS oncogene family
D85844_at	rabaptin 5
rc_H31588_at	Ral-A exchange factor RalGPS2 (LOC304887), mRNA
rc_AA800671_at	Ras GTPase-activating-like protein IQGAP2
X60212_i_at	Rat amino acid starvation-induced protein mRNA, 3′ end
rc_AA892675_at	*Rattus norvegicus* similar to RIKEN cDNA 0710008A13 (LOC305895), mRNA
L24907_at	Regulator of G-protein signaling 19
U17604_at	reticulon 1
D25233cds_at	retinoblastoma 1
D25233UTR#1_g_at	retinoblastoma 1
rc_AI227715_at	retinoblastoma-like 2
AF016387_at	retinoid X receptor gamma
AF016387_g_at	retinoid X receptor gamma
AF041066_at	ribonuclease, RNase A family 4
rc_AA965264_at	ribosomal protein S29
X59051cds_s_at	ribosomal protein S29
rc_AA892888_at	RIKEN cDNA 0610006F02 (LOC366792), mRNA
rc_AA891800_at	RIKEN cDNA 1110013G13 (LOC310856), mRNA
rc_AA891800_g_at	RIKEN cDNA 1110013G13 (LOC310856), mRNA
rc_AA892353_at	RIKEN cDNA 1110038M16 (LOC313529), mRNA
rc_AA891774_at	RIKEN cDNA 1810013B01 (LOC300983), mRNA
rc_AA891950_at	RIKEN cDNA 1810021J13 (LOC300516), mRNA

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
rc_AA894277_at	RIKEN cDNA 2010107G23 (LOC294499), mRNA
rc_AA859663_at	RIKEN cDNA 2310067G05 [*Mus musculus*]
rc_AI639157_at	RIKEN cDNA 2410002K23 (LOC287069), mRNA
rc_AA892861_at	RIKEN cDNA 2610528J11 (LOC362576), mRNA
rc_AA799762_g_at	RIKEN cDNA 2700038C09 (LOC296470), mRNA
rc_AA799472_g_at	RIKEN cDNA 2900091E11 (LOC299707), mRNA
rc_AA892561_at	RIKEN cDNA 4931406C07 (LOC363016), mRNA
rc_AI639155_at	RIKEN cDNA 5330414D10 (LOC311726), mRNA
rc_AA893260_at	RIKEN cDNA 5830411J07 [*Mus musculus*]
rc_AA892986_at	RIKEN cDNA 9230117N10 (LOC361749), mRNA
rc_AA892572_g_at	RIKEN cDNA D130059P03 gene (LOC312248), mRNA
rc_AA800197_at	RIKEN cDNA E430026E19 (LOC314683), mRNA
M11071_f_at	RT1 class Ib gene(Aw2)
U75928UTR#1_s_at	secreted acidic cysteine rich glycoprotein
M14656_at	secreted phosphoprotein 1
rc_AA893080_at	selenocysteine lyase SCLY (LOC363285), mRNA
M63991_at	serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin)
X16273cds_at	serine (or cysteine) proteinase inhibitor, clade A, member 1
D00752_at	serine protease inhibitor
D00753_at	serine protease inhibitor
rc_AA945128_at	serine protease inhibitor
M35299_s_at	serine protease inhibitor, Kazal type 1
rc_AA893793_at	smooth muscle myosin heavy chain 11 isoform SM1-like (LOC362697), mRNA
M77479_at	solute carrier family 10, member 1
rc_AA892616_at	solute carrier family 13 (sodium-dependent dicarboxylate transporter), member 3
rc_AA859652_at	solute carrier family 16 (monocarboxylic acid transporters), member 6
U62316_at	solute carrier family 16, member 7
rc_AA892920_at	solute carrier family 17 (vesicular glutamate transporter), member 1
U28504_g_at	solute carrier family 17 (vesicular glutamate transporter), member 1
L28135_at	solute carrier family 2, member 2
U88036_at	solute carrier family 21 (organic anion transporter), member 5
L27651_at	solute carrier family 22 (organic anion transporter), member 7
L27651_g_at	solute carrier family 22 (organic anion transporter), member 7
U76379_s_at	solute carrier family 22, member 1
X78855_s_at	solute carrier family 22, member 1
AJ223355_at	solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10
AJ223355_g_at	solute carrier family 25 (mitochondrial carrier; dicarboxylate transporter), member 10
L23413_at	solute carrier family 26 (sulfate transporter), member 1
D85100_at	solute carrier family 27 (fatty acid transporter), member 32
AF015304_at	solute carrier family 29, member 1
U17133_at	solute carrier family 30, member 1
U76714_at	solute carrier family 39 (iron-regulated transporter), member 1
U76714_g_at	solute carrier family 39 (iron-regulated transporter), member 1
rc_AI030175_s_at	sorbitol dehydrogenase
X74593_at	sorbitol dehydrogenase
rc_AA875037_at	SPI6 (LOC361241), mRNA
rc_AA858573_s_at	spp-24 precursor
U19485_at	spp-24 precursor
rc_AA891810_at	Sprague-Dawley liver r-goliath mRNA, complete cds
rc_AI231821_at	stathmin 1

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
J02585_at	stearoyl-Coenzyme A desaturase 1
J05035_g_at	steroid 5 alpha-reductase 1
M62763complete_seq_at	sterol carrier protein 2
L27112_s_at	stress-activated protein kinase alpha II
rc_AI231354_at	stress-activated protein kinase alpha II
U75393_s_at	succinate-CoA ligase, GDP-forming, alpha subunit
rc_AA891738_at	sulfite oxidase
rc_AA926193_at	sulfotransferase 1C1 (SULT1C#1) (ST1C2) (humSULTC2) S1C1_HUMAN
L22339_at	sulfotransferase family 1A, member 2
L22339_g_at	sulfotransferase family 1A, member 2
M86758_at	sulfotransferase, estrogen preferring
Z24721_at	superoxide dismutase 3
S45663_at	synaptic glycoprotein SC2
S45663_g_at	synaptic glycoprotein SC2
S61865_s_at	syndecan 1
X60651mRNA_s_at	syndecan 1
X75856_at	testis-enhanced gene transcript
rc_AA893905_at	testis-abundant finger protein (LOC309591), mRNA
rc_AA893529_at	TF3A_HUMAN transcription factor IIIA (Factor A) (TFIIIA)
rc_AI071299_at	TGFB inducible early growth response
X56228_g_at	thiosulfate sulfurtransferase
rc_AA818982_at	Thymopoietin
J03819_at	thyroid hormone receptor beta
U75916_at	tight junction protein 2
S72594_s_at	tissue inhibitor of metalloproteinase 2
K02814_at	T-kininogen
rc_AA899854_at	topoisomerase (DNA) 2 alpha
L25785_at	transforming growth factor beta 1 induced transcript 4
rc_AI059508_s_at	Transketolase
U09256_at	Transketolase
M60666_s_at	tropomyosin 1, alpha
rc_AA800948_at	tubulin alpha-4 chain (Alpha-tubulin 4) (LOC316531), mRNA
rc_AI230748_at	tumor protein, translationally-controlled 1
rc_AA891834_at	type IV collagen alpha 5 chain (LOC300276), mRNA
rc_AA818888_at	ubiquitin A-52 residue ribosomal protein fusion product 1
rc_AI639241_at	Ubiquitin carboxyl-terminal hydrolase 12 (Ubiquitin thiolesterase 12)
J02589mRNA#2_at	UDP glycosyltransferase 2 family, polypeptide B
M33747_at	UDP-glucuronosyltransferase 2 family, member 5
rc_AI145931_at	UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase
X13098cds_s_at	urate oxidase
M97662_at	Ureidopropionase, beta
rc_AI105463_at	V-1 protein
D30040_at	v-akt murine thymoma viral oncogene homolog 1
AF054826_at	vesicle-associated membrane protein 5
U44845_at	Vitronectin
rc_AA891614_at	voltage-gated Ca channel
AF037272_at	wap 4-disulfide core domain 1
rc_AI112516_at	zinc finger protein 36, C3H type-like 1
rc_AI136891_at	zinc finger protein 36, C3H type-like 1
U67082_at	zinc finger protein 386 (Kruppel-like)

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
AF052042_s_at	zinc finger protein Y1 (RLZF-Y)
AB012944cds_s_at	—
AB013112_s_at	—
AF053988_at	—
AF080507_g_at	—
AFFX-DapX-M_at	—
AJ011656cds_s_at	—
D14564cds_s_at	—
D16339_at	—
D31662exon#4_s_at	—
D38061exon_s_at	—
D38069exon_s_at	—
D86745cds_s_at	—
D86745exon_s_at	—
E01184cds_s_at	—
E01415cds_s_at	—
E03190cds_s_at	—
E04239cds_s_at	—
E06822cds_s_at	—
E07296cds_s_at	—
E12625cds_at	—
E13557cds_s_at	—
J00728cds_f_at	—
J01435cds#4_s_at	—
J02596cds_at	—
J03914cds_s_at	—
K00996mRNA_s_at	—
K03041mRNA_s_at	—
K03045cds_r_at	—
K03241cds_s_at	—
K03243mRNA_s_at	—
L11587_at	—
L13025UTR#1_f_at	—
L15079mRNA_s_at	—
L16995_at	—
L31394exon_s_at	—
M12981cds_f_at	—
M13234cds_f_at	—
M14775_s_at	—
M14776_f_at	—
M15474cds_s_at	—
M18363cds_s_at	—
M22993cds_s_at	—
M23566exon_s_at	—
M24239cds#2_f_at	—
M33312cds_s_at	—
M33550cds_s_at	—
M64733mRNA_s_at	—
M86912exon_at	—
M86912exon_g_at	—
M91595exon_s_at	—
M93297cds_at	—
rc_AA799396_at	—
rc_AA799396_g_at	—
rc_AA800202_at	—
rc_AA800290_g_at	—
rc_AA800456_at	—
rc_AA800768_at	—
rc_AA800790_at	—
rc_AA800930_at	—
rc_AA858620_at	—
rc_AA859597_at	—
rc_AA866240_f_at	—
rc_AA866426_at	—
rc_AA874873_g_at	—
rc_AA875495_at	—
rc_AA891737_at	—
rc_AA891916_at	—
rc_AA891916_g_at	—
rc_AA891949_at	—
rc_AA892027_at	—
rc_AA892300_at	—
rc_AA892538_at	—
rc_AA892805_g_at	—
rc_AA892818_at	—
rc_AA893436_at	—
rc_AA893453_at	—
rc_AA893485_at	—
rc_AA893485_g_at	—
rc_AA894316_at	—
rc_AA945152_s_at	—
rc_AI014135_at	—
rc_AI179150_s_at	—
rc_AI638982_at	—
rc_AI639043_at	—
rc_AI639056_at	—
rc_AI639102_g_at	—
rc_AI639103_s_at	—
rc_AI639108_at	—
rc_AI639200_at	—
rc_AI639343_at	—
rc_AI639361_at	—
rc_AI639417_at	—
rc_AI639457_at	—
rc_AI639457_g_at	—
rc_AI639470_g_at	—
rc_AI639501_s_at	—
rc_H31897_at	—
rc_H31914_at	—
rc_H33426_at	—

Table 2. Down-regulated Probe Sets

Probe Set ID	Gene Name
rc_H33426_g_at	—
S45812_s_at	—
S46785_at	—
S46785_g_at	—
S48325_s_at	—
S49003_s_at	—
S50461_s_at	—
S56936_s_at	—
S56937_s_at	—
S62516_s_at	—
S66184_s_at	—
S70364_at	—
S72505_f_at	—
S72506_s_at	—
S76779_s_at	—
S77494_s_at	—
S82820mRNA_s_at	—
S87522_at	—
U11071_f_at	—
U33540exon_f_at	—
U39609_s_at	—
U75397UTR#1_s_at	—
V01225mRNA_s_at	—
X02291exon_s_at	—
X05861exon#1—6_s_at	—
X07551cds_s_at	—
X08056cds_s_at	—
X62086mRNA_s_at	—
X62660mRNA_g_at	—
X76456cds_at	—

lar temporal signatures) as a single process. Second, we applied clustering algorithms based on Euclidian distance and correlation coefficients. Neither Euclidian distance nor correlation coefficients incorporate time interval, in that they treat all time domains as equal in magnitude. In our time series design, 9 of the 16 points are within the first 6 hours, and 12 of the 16 points are within the first 12 hours following drug dosing. The interval between time domains ranged from 0.25 hours in the beginning to 24 hours at the end. The assumption that these time domains are equal greatly impairs the effectiveness of most current mathematical tools for mining and clustering biologically relevant time series data.

We therefore developed a new approach to data mining that is based on a series of filters designed to eliminate probe sets that do not meet certain explicit criteria. This series of filters produces a remainder of a relatively small percentage of the total probe sets that then can become the focus of temporal and functional clustering. For example, we have identified in the data set probe sets for a group of more than 20 genes involved in nitrogen disposal in the liver. These probe sets reflect several different temporal signatures but constitute a functional cluster that can be used for PK/PD modeling. Two of the genes in this functional cluster are C/EBPδ and arginase 1 discussed above. Other functional clusters identified in the data set relate to lipid metabolism, gluconeogenesis, and immunosuppression. Such functional clustering based on text mining of the literature will provide an additional filtering process prior to the application of mechanism-based PK/PD modeling. Since we have previously published data on expression changes of small groups of genes measured individually by other methods in conjunction with PK/PD modeling of that data, the drug kinetics and receptor dynamics for this data set have been published.[9]

The foundation of this new approach is filtering the data based on specific characteristics of the probe sets to be eliminated. The first filter we applied was designed to eliminate all probe sets that were not expressed in the liver. This filter reduced the number of probe sets under consideration from 8799 to 4373. The second filter we applied was designed to identify and eliminate a group of probe sets that do not meet the minimal criteria of down-regulation. This filter eliminated all but 829 probe sets. Similarly, we filtered for those that did not meet the minimal criteria for up-regulation. This filter eliminated all but 817 probe sets. We then combined the 2 lists of probe sets that had not been eliminated and filtered that list of 1615 probe sets on data quality. The results of the entire set of filters is that 7287 probe sets of the original 8799 probe sets were eliminated from further consideration. This left a remainder of 1512 probe sets for further consideration with respect to temporal clustering, functional clustering, and PK/PD modeling.

In a previous report[5] in which we handled data mining and clustering as a single screening process we separated these liver probe sets into six clusters. Probe sets in the six clusters were identified by correlation with exemplars. Two of those clusters (4 and 6) were designated as biphasic with differing but strongly evident temporal patterns and were used for modeling purposes. Cluster 4 contained 66 probe sets and cluster 6 contained 68 probe sets. Twenty-seven of the 134 probe sets in those clusters failed the present quality control filter and are not included in this report. We presently have placed only 27 probe sets in the biphasic group. As detailed above, these probe sets were sequestered in this group because they passed both the filter of 0.65 in four conditions and the 1.5 filter in four conditions. The remaining probes in the previously described clusters 4 and 6 only passed one of these two filters and are

Table 3. Biphasic Probe Sets

Probe Set ID	Gene Name
rc_AA866302_at	4-hydroxyphenylpyruvic acid dioxygenase
rc_AI169695_f_at	alcohol sulfotransferase (hydroxysteroid sulfotransferase) (ST) (ST-60)
J02720_at	arginase 1
U35774_at	branched chain aminotransferase 1, cytosolic
rc_AI169735_at	cytochrome P450IIB3
rc_AA891842_at	death receptor 6 (LOC316256), mRNA
AF023087_s_at	early growth response 1
M18416_at	early growth response 1
rc_AI176662_s_at	early growth response 1
D10354_s_at	glutamic-pyruvate transaminase (alanine aminotransferase)
D14989_f_at	hydroxysteroid sulfotransferase subunit, complete cds
U26397_at	inositol polyphosphate-4-phosphatase, type 1
D00403_at	interleukin 1 alpha
M55049_at	interleukin 2 receptor, alpha chain
rc_AA892680_at	peptidylprolyl cis-trans isomerase-like protein 3
AB016532_at	period homolog 2
rc_AA799729_at	phosphodiesterase 4B
M34083_at	prolactin receptor
M74152_s_at	prolactin receptor
X63410cds_f_at	Rat senescence marker protein 2A gene, exons 1 and 2
L19998_at	sulfotransferase family 1A, phenol-preferring, member 1
D14988_f_at	sulfotransferase, hydroxysteroid preferring 2
D14987_f_at	sulfotransferase, hydroxysteroid preferring 2
M31363mRNA_f_at	sulfotransferase, hydroxysteroid preferring 2
rc_AA817987_f_at	sulfotransferase, hydroxysteroid preferring 2
rc_AA818122_f_at	sulfotransferase, hydroxysteroid preferring 2
E05489cds_s_at	—

contained in either the up- or down-regulated tables. This may be due to too few data points beyond 12 hours. These differences in resolution of patterns are indicative of the difficult problem of finding both computationally and biologically meaningful approaches to clustering of gene array profiles.

CONCLUSION

The use of a rich time series and microarrays as a high throughput method of data collection provides a means for obtaining the mRNA expression profiles necessary for developing PK/PD models for complex polygenic phenomena such as nitrogen, carbohydrate, and lipid metabolism.

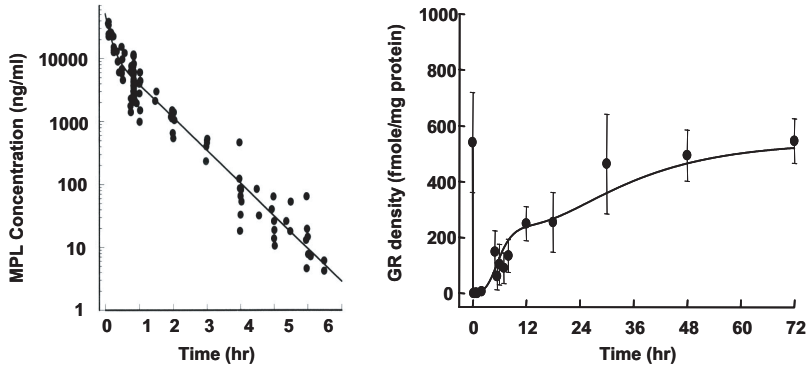

Figure 6. Plasma concentrations of methylprednisolone (left) and liver glucocorticoid receptor density (right) following a 50 mg/kg IV bolus dose in rats[9].

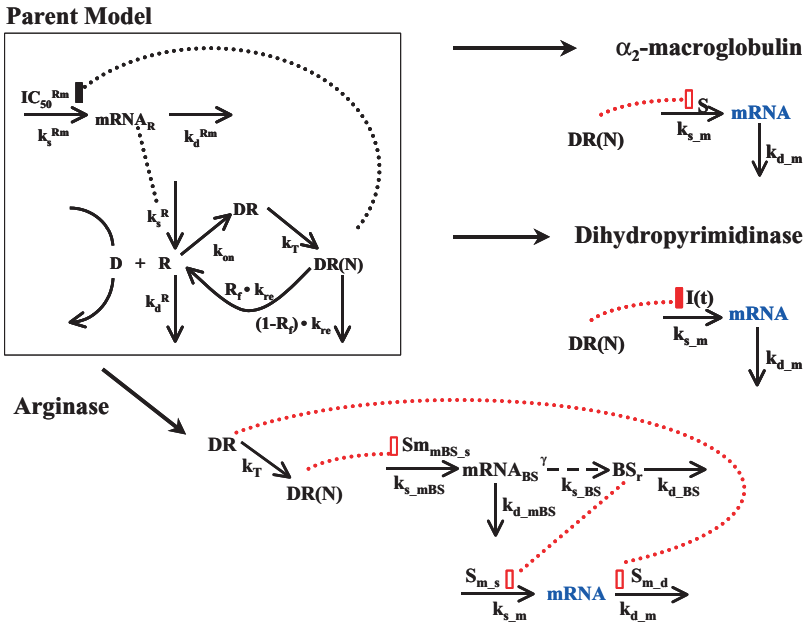

Figure 7. The proposed general model for corticosteroid-induced pharmacogenomic effects, and 3 specific models describing direct stimulation of transcription, direct inhibition of transcription, and biphasic regulation. DR indicates drug-receptor complex in cytosol; DR(N), drug-receptor complex in nucleus; mRNA, target mRNA level; k_{s_m}, zero-order rate of the target mRNA synthesis; k_{d_m}, first-order rate of the target mRNA degradation; S, linear stimulation factor; $mRNA^0$, baseline mRNA level; $mRNA_{BS}$, the message level of the intermediate regulator BS (normalized as ratio to 0-hour control); BS_r, the protein level of the BS (normalized); k_T, first-order rate of the drug-receptor complex translocation into the nucleus; k_{s_BSm}, zero-order rate of BS mRNA synthesis; k_{d_BSm}, first-order rate of BS mRNA degradation; k_{s_BS}, first-order rate of BS translation to protein; k_{d_BS}, first-order rate of BS protein degradation; S_{BSm}, linear stimulation of k_{s_BSm} by DR(N); S_{m_s}, linear stimulation of k_{s_m} by BS_r; S_{m_d}, linear stimulation of k_{d_m} by DR; $mRNA_{BS}^0$, baseline BS mRNA level; BS_r^0, baseline BS protein level; and $mRNA^0$, baseline target mRNA level.

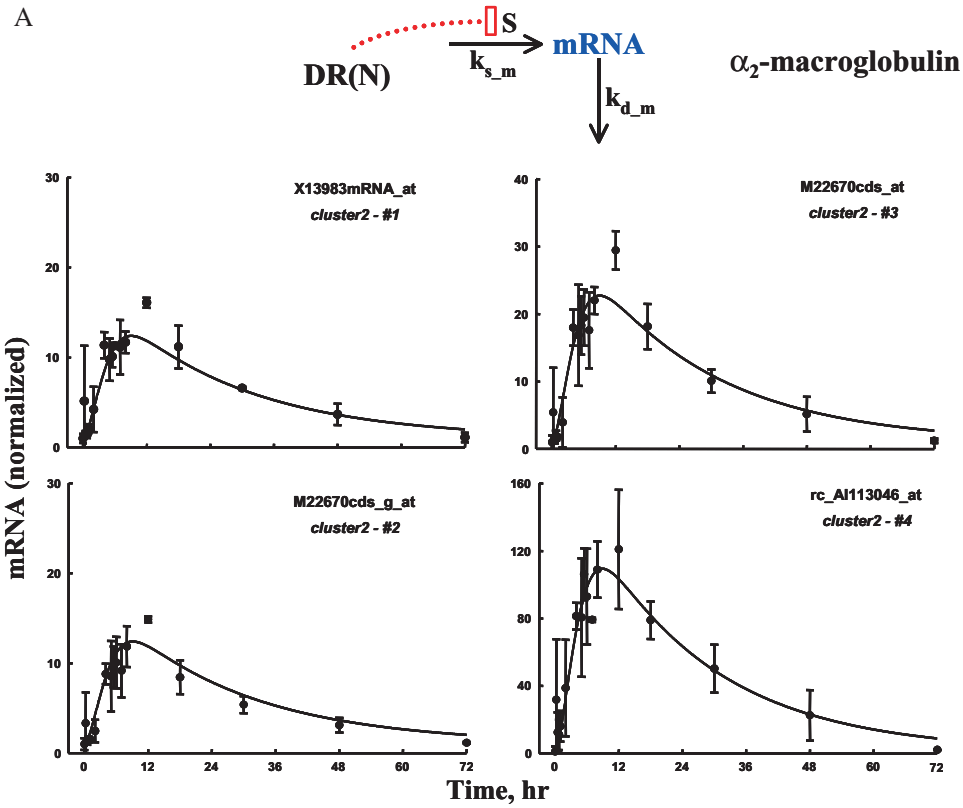

Figure 8. Continued.

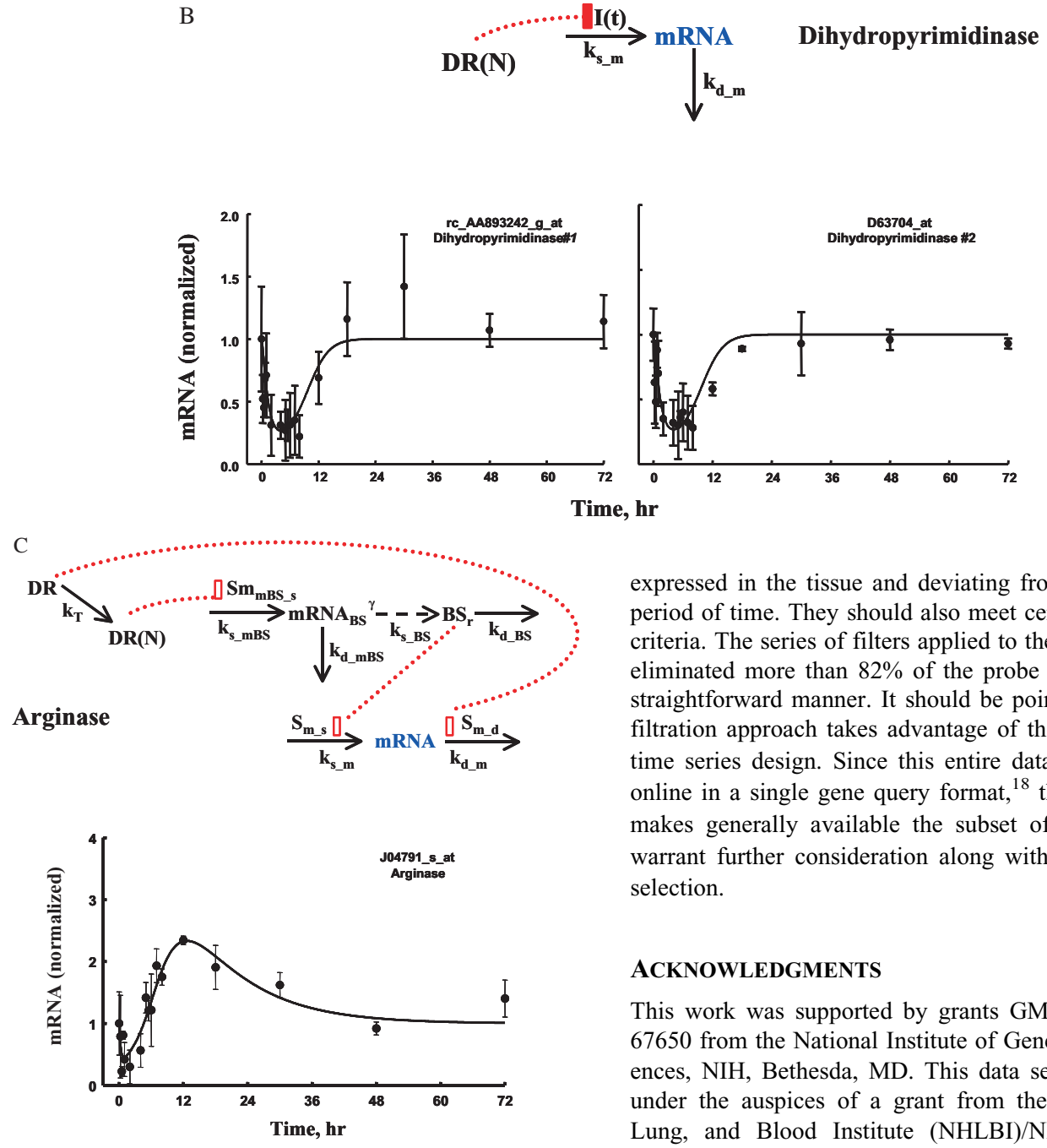

Figure 8. Representative fittings of (A) 4 probe sets for α_2-macroglobulin (direct stimulation of transcription), (B) 2 probe sets for dihydropyrimidinase (direct inhibition of transcription), and (C) arginase (biphasic regulation of transcription). Solid circles are the mean gene array data and bars are the standard deviations. Solid lines are fittings with the proposed model for each individual gene. Model abbreviations are as defined in Figure 7.

The initial problem presented by this approach is to focus attention on a small percentage of regulated genes out of the thousands measured by gene arrays. Probes that fit this category should meet minimal requirements such as being expressed in the tissue and deviating from baseline for a period of time. They should also meet certain data quality criteria. The series of filters applied to the present data set eliminated more than 82% of the probe sets in a simple, straightforward manner. It should be pointed out that this filtration approach takes advantage of the richness of the time series design. Since this entire data set is available online in a single gene query format,[18] the present report makes generally available the subset of probe sets that warrant further consideration along with their criteria of selection.

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