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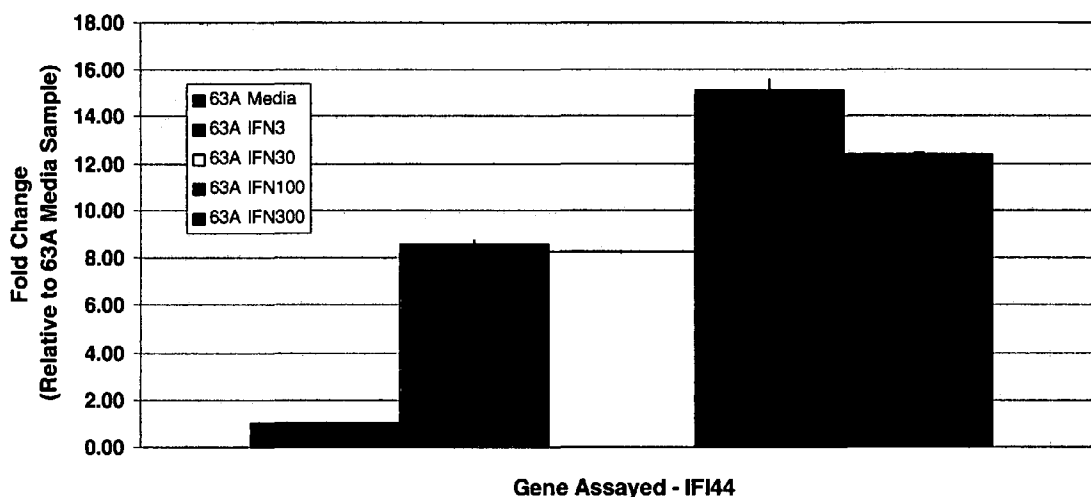
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(54) Title: INTERFERON ALPHA-INDUCED PHARMACODYNAMIC MARKERS

63A IFN Study - TaqMan (IFI44)

(57) Abstract: The present invention encompasses type-I IFN and IFN α -induced PD marker expression profiles, kits, and methods for identifying such IFN α -induced PD marker expression profiles. The type-I IFN and IFN α -induced PD marker expression profiles may also be used in, for example, methods of treating patients having a type-I IFN or IFN α -mediated disorder, methods of monitoring disease progression of patients receiving treatment with a therapeutic agent that binds to and modulates IFN α activity, identifying patients as candidates to receive a therapeutic that binds to and neutralizes IFN α activity, and in diagnosing or providing a prognosis to patients having IFN α -induced disorders.

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INTERFERON ALPHA-INDUCED PHARMACODYNAMIC MARKERS

FIELD OF THE INVENTION

The present invention relates to pharmacodynamic (PD) markers inducible by interferon (IFN) alpha, probes and kits that detect the PD markers, and methods employing the same.

BACKGROUND OF THE INVENTION

The present invention encompasses PD markers that are induced by IFN α . The PD markers can be used in methods of treating patients with a therapeutic agent that binds to and modulates IFN α activity, methods that identify patients as candidates for a therapeutic agent that binds to and modulates IFN α activity, methods of diagnosing a patient as having a disorder associated with increased IFN α levels, methods of monitoring disease progression of a patient receiving treatment with a therapeutic agent that binds to and modulates IFN α activity, and methods of identifying a candidate therapeutic for treating IFN α -mediated disorders

SUMMARY OF THE INVENTION

One embodiment of the invention encompasses a method of identifying a patient as a candidate for a therapeutic agent that binds to and modulates IFN α activity. Presence or absence of an IFN α -inducible PD marker expression profile is detected in a sample from the patient.

Another embodiment of the invention encompasses a method of treating a patient having a type I IFN or IFN α -mediated disease or disorder. An agent that binds to and modulates type I IFN or IFN α activity is administered to the patient. The agent neutralizes a type I IFN or IFN α -inducible PD marker expression profile of the patient.

Yet another embodiment of the invention encompasses a method of treating an autoimmune disease patient comprising a moderate or strong type I IFN or an IFN α PD marker profile. An agent that binds to and modulates type I IFN or IFN α activity is administered to the patient. The agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.

A further embodiment of the invention encompasses a method of neutralizing a type I IFN or IFN α -inducible PD marker expression profile in a patient in need thereof. An agent

that binds to and modulates type I IFN or IFN α activity is administered to the patient. The agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Another embodiment of the invention encompasses a method of diagnosing a patient as having a disorder associated with increased IFN α levels. Presence or absence of an IFN α -inducible PD marker expression profile is detected in a sample from the patient.

A further embodiment of the invention encompasses a method of monitoring disease progression of a patient receiving treatment with a therapeutic agent that binds to and modulates IFN α activity. A first IFN α -inducible PD marker expression profile is obtained in a first sample from the patient. A therapeutic agent that binds to and modulates IFN α activity is administered to the patient. A second IFN α -inducible PD marker expression profile is obtained from a second sample from the patient. The first and the second IFN α -inducible PD marker expression profiles are compared.

Yet another embodiment of the invention encompasses a method of identifying a candidate therapeutic for treating IFN α -mediated disorders. Cells comprising an IFN α -inducible PD marker expression profile are contacted with an agent. Presence or absence of a change in the IFN α -induced PD marker expression profile of the cells is detected.

A further embodiment of the invention encompasses a set of probes.

Yet a further embodiment of the invention encompasses kits that comprise the probes.

Another embodiment of the invention encompasses a method of detecting IFN activity in a sample. Cells comprising a polynucleotide sequence comprising a reporter gene under the control of an IFN-stimulated response element are incubated with a sample. Expression of the reporter gene is detected.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1: TaqMan qPCR IFI44 gene expression analysis of IFN α -stimulated whole blood of healthy donors.

Figure 2: TaqMan qPCR IRF2 gene expression analysis of IFN α -stimulated whole blood of healthy donors.

Figure 3: TaqMan qPCR RSAD2 gene expression analysis of IFN α -stimulated whole blood of healthy donors.

Figure 4: TaqMan qPCR G1P3 gene expression analysis of IFN α -stimulated whole blood of healthy donors.

Figure 5: TaqMan qPCR HERC5 gene expression analysis of IFN α -stimulated whole blood of healthy donors.

Figure 6: MEDI-545 neutralization of RAB8B gene expression induced by IFN- α in whole blood of healthy donors.

Figure 7: MEDI-545 neutralization of IRF7 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 8: MEDI-545 neutralization of MARCKS gene expression induced by IFN- α in whole blood of healthy donors.

Figure 9: MEDI-545 neutralization of IL6ST gene expression induced by IFN- α in whole blood of healthy donors.

Figure 10: MEDI-545 neutralization of Ly6E gene expression induced by IFN- α in whole blood of healthy donors.

Figure 11: MEDI-545 neutralization of IFIT3 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 12: MEDI-545 neutralization of IFIT1 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 13: MEDI-545 neutralization of HERC5 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 14: MEDI-545 neutralization of OAS1 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 15: MEDI-545 neutralization of OAS3 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 16: MEDI-545 neutralization of RSAD2 gene expression induced by IFN- α in whole blood of healthy donors.

Figure 17: Ex vivo stimulation in whole blood identifies genes inducible by type I IFN.

Figure 18: MEDI-545 neutralization of top 25 type I IFN inducible genes in individual lupus patients' whole blood.

Figure 19: Heatmap of target modulation and PCA plot using top 25 up-regulated type I IFN inducible probe sets in whole blood of patient 1541 before and after MEDI-545 treatment.

Figure 20: Heatmap of target modulation and PCA plot based on 25 most up-regulated type I IFN inducible genes in whole blood of patient 1449 before and after MEDI-545 treatment.

Figure 21: Heatmap of target modulation calculated based on 165 type I IFN inducible genes up-regulated in whole blood of one patient treated with 0.3 mg/kg MEDI-545.

Figure 22: PCA using 169 probe sets that are type I IFN inducible - 24/35 SLE patients have statistically significant type I IFN signature in whole blood.

Figure 23: MEDI-545 neutralizes the top 25 most upregulated type I IFN inducible probe sets of lupus patients. Target neutralization of the top 25 most upregulated type I IFN inducible genes was measured at days 1, 4, 7, 14, 28, and 84 for each patient. Dose range was from 1 (placebo) to 3 mg/kg Medl 545.

Figure 24: MEDI-545 neutralizes the top 25 most upregulated type I IFN inducible probe sets of lupus patients. Target neutralization of the top 25 most upregulated type I IFN inducible genes was measured at days 1, 4, 7, 14, and 28 for each patient. Dose range was from 0 (placebo) to 30 mg/kg MEDI-545.

Figure 25a and b: Heatmap (a) and PCA (b) showing neutralization of the top 25 type I IFN inducible probe sets in whole blood of a SLE patient treated with 30 mg/kg MEDI-545 at 0, 1, 4, 7, and 14 days post-dosing.

Figure 26a and b: PCA plots of lupus patient before (a) and after (b) dosing with placebo control show no trend in the change of type I IFN inducible gene signature. The 25 most upregulated type I IFN inducible probe sets were used to perform the PCA analysis.

Figure 27: Type-I IFN α subtypes are upregulated in the whole blood of individual lupus patients.

Figure 28: Distribution of average fold-change of top 25 type I IFN inducible probe sets in whole blood of individual lupus patients.

Figure 29a-c: Pair-wise fold change ranking test proves MEDI-545 neutralizes type I IFN genes in a clinical trial. Top genes neutralized are shown for (a) SLE patients having a type I IFN gene signature at 14 days following MEDI-545 treatment; (b) SLE patients not having a type I IFN gene signature at 14 days following MEDI-545 treatment; and (c) SLE patients 14

days following treatment with placebo. Genes highlighted in yellow are genes identified as having a type-I IFN signature.

Figure 30: Hierarchical clustering of 1384 probe sets differentially regulated by IFN α subtypes, IFN β , IFN γ , and TNF α in *ex vivo* stimulated whole blood. Each row corresponds to a single probe set, while each column corresponds to a single sample. The branch lengths indicate the correlation with which probe sets/samples are joined, with a longer branch indicating a weaker correlation. Color represents relative expression level of individual probe sets as compared to the average expression of the no treatment controls. Red indicates up-regulation versus control; green indicates down-regulation versus control; black indicates no change.

Figure 31a-31b: a. Hierarchical clustering of the relative expression of the top 25 most overexpressed type-I IFN inducible probe sets in whole blood *ex vivo* challenged with a variety of IFN α subtypes, IFN β , IFN γ , and TNF α . b. Heatmap of the relative expression of the same 25 probe sets compared to no-treatment control in keratinocyte *ex vivo* challenged with IFN α 2a, IFN β , IFN γ , and TNF α . Red indicates upregulated gene expression relative to no treatment control, green indicates downregulated gene expression relative to no treatment control, black indicates no significant change in gene expression of challenged samples relative to control.

Figure 32a-32c: The distribution of the average (a) and median (b) fold change of the top 25 most overexpressed type-I IFN inducible probe sets in 26 pairs of lesional skin compared to non-lesional skin. (c) the average of the average and median fold change of the top 25 most overexpressed type-I IFN inducible probe sets in 26 pairs of lesional and non-lesional skin.

Figure 33a-33d: Relative expression of selected type-I IFN inducible genes ((a)HPSE, (b) OASL, and (c) HERC6) and non type-IFN inducible genes ((d) SERPINB4) in lesional skin (LS) compared to non-lesional skin (NS), and non-lesional skin compared to normal skin (NN) in psoriatic patients based on microarray data. The fold change of these genes in LS is compared to its paired NS, while NS is compared to the average of 21 normal skin controls. The *p* value for HPSE, OASL, HERC6, and SERPINB4 is a comparison between NS and NN, between LS and NS are (listed in pairs): 0.468, <0.00001; 0.376, <0.00001; 0.03, <0.00001; 0.0002, <0.00001.

Figure 34a-34b: (a) Hierarchical clustering of all psoriasis samples profiled (21 normal (blue bars)) 26 paired non lesional (black bars) and lesional skin (red bars) from 24 psoriatic

patients, and 3 lesional skin (red bars) from 3 psoriatic patients whose paired non lesional skin either did not yield sufficient cRNA for hybridization or scanned arrays had scaling factors that were more than 3 times the average) using the 164 upregulated type-I IFN inducible probe sets in lesional skin compared to those in mostly paired non-lesional skin. Each row corresponds to a single probe set, while each column corresponds to a single sample. The branch lengths indicate the degree of correlation with which samples are joined, with a longer branch indicating a weaker correlation. Color represents relative expression level of individual probe set as compared to the average expression of the 21 normals. Red represents upregulation vs. control and green represents downregulation vs. control. (b) PCA of all psoriasis samples profiled using the 164 upregulated type-I IFN inducible probe sets in lesional skin compared to those in mostly paired non-lesional skin. (PCA is calculated and data is visualized in Spotfire). Each circle represents one sample (blue circles = normal skin; black circles = non-lesional skin; red circles = lesional skin).

Figure 35: Overexpression of selected type-I IFN inducible genes in 18 pairs of lesional and non-lesional skin from 18 psoriatic patients based on taqMan QRT-PCR assays using Fluidigm's BioMark™ 48.48 dynamic array.

Figure 36a-36b: Correlation coefficient distribution of overexpressed genes in lesional skin of psoriatic patients between taqMan and array results. The genes are grouped based on correlation coefficient between taqMan QRT-PCR and microarray measurement. (a) correlation coefficient distribution of all 40 upregulated genes in lesional skin that are validated by taqMan QRT-PCR; (b) correlation coefficient distribution of 29 type-IFN inducible genes.

Figure 37a-37d: Comparison of taqMan QRT-PCR based assay using BioMark™ 48.48 dynamic array and Affymetrix® genechip results for selected type-I IFN inducible genes ISG15 and MX1.

Figure 38: TaqMan QRT-PCR validation of Affymetrix® genechip results of overexpression of type-I IFN inducible genes IFI27 and CXCL10.

Figure 39a-39f: *Ex vivo* stimulation of normal keratinocytes with leukocyte IFN and IFN α 2a and dose-dependent neutralization of type-I IFN induced genes by IFN α antibody. (a) neutralization of ISG15 overexpression in response to 350 I.U./mL IFN α 2a, (b) neutralization of ISG15 overexpression in response to 150 I.U./mL leukocyte IFN, (c) neutralization of USP18 overexpression in response to 350 I.U./mL IFN α 2a, (d) neutralization of USP18

overexpression in response to 150 I.U./mL leukocyte IFN, (e) neutralization of IFIT2 overexpression in response to 350 I.U./mL IFN α 2a, and (f) neutralization of IFIT2 overexpression in response to 150 I.U./mL leukocyte IFN. Each dose titration curve is generated on three technical replicates. The overexpression of individual genes with no IFN α antibody is normalized to 1.

Figure 40a-40c: Relative expression of mRNA and median fold changes of type-I IFN α subtypes (Figure 40a), other members of the type-I IFNs (Figure 40b), and IFN α receptors (Figure 40c) in the lesional skin (LS) or the non-lesional skin (NS) compared to skin from healthy normal controls (NN). The averages of the relative mRNA levels of these cytokines and their receptors in the normal skin of two healthy donors were scaled to be 1 based on taqMan QRT-PCR assays using TLDA from Applied Biosciences. Black: the relative fold change of mRNA in the non-lesional skin compared to normal skin (NS/NN); Red: the relative fold change of mRNA in the lesional skin compared to normal skin (LS/NS). The *p* values for the overexpression of these individual genes in the non-lesional skin or lesional skin compared to healthy normal skin (listed in pairs) are as follows: IFN α 1, 0.303, <0.001; IFN α 2, 0.389, 0.072; IFN α 5, <0.001, 0.002; IFN α 6, 0.664, 0.093; IFN α 7, 0.586, 0.077; IFN α 8, 0.430, 0.049; IFN α 14, 0.224, 0.049; IFN α 17, 0.552, 0.0203; IFN α 21, 0.113, 0.003; IFN β , 0.255, 0.022; IFN κ , 0.03, <0.001; IFN ω , 0.516, 0.049; IFNAR1, 0.192, <0.001; IFNAR2, <0.001, <0.001, respectively.

Figure 41: Relative expression of mRNA and median fold changes of IFN γ , TNF α , and IFN γ receptors in the lesional skin (LS), or the non-lesional skin (NS) compared to skin from healthy normal controls (NN). The averages of the relative mRNA levels of these cytokines and their receptors in the normal skin of two healthy donors were scaled to be 1 based on taqMan QRT-PCR assays using TLDA from Applied Biosciences. Black: the relative fold change of mRNA in the non-lesional skin compared to normal skin; Red: the relative fold change of mRNA in the lesional skin compared to normal skin. The *p* values for the overexpression of these individual genes in the non-lesional skin or lesional skin compared to healthy normal skin (listed in pairs) are as follows: IFN γ , 0.02, <0.001; IFNGR1, <0.001, <0.001; IFNGR2, <0.001, <0.001; TNF α , <0.001, <0.001, respectively.

Figure 42: A Venn diagram illustrating both the number of probe sets that are altered by type I IFN, IFN γ , and TNF α during *ex vivo* stimulation, and probe sets that are altered in the lesional skin compared to non-lesional skin. Red numbers: probe sets that show increased expression with cytokine treatment or compared to non-lesional skin baseline; Green

numbers: probe sets that show decreased expression with cytokine treatment or compared to non-lesional skin baseline. The intersecting regions represent the probe sets that are common to both comparisons.

Figure 43a and 43b: Co-overexpression type-I IFN, type-II IFN, and TNF-inducible genes in lesional/non-lesional skin of psoriatic patients based on Affymetrix genechip® results. The type-I IFN, type-II IFN, and TNF α inducible genes were selected based on *ex vivo* stimulation experiments (Examples 10 and 16). A probe set with an at least 2-fold change from non-lesional to lesion skin was considered overexpressed. (a) the number of up-regulated type I IFN, IFN γ , and TNF α inducible genes in the lesional skin shows strong correlation. (b) the number of type I IFN, IFN γ , and TNF α inducible genes in the lesional skin were significantly different amongst pairwise comparisons.

Figure 44: Immunohistochemical analysis of biopsies from psoriatic skin, non-lesional skin and skin from normal donors. BDCA2 is a specific marker for pDCs which are present at greater numbers in lesional skin compared to non-lesional skin, and not at all in normal skin. CD83 is a marker for mDCs, CD4 is present on T cells and dendritic cells. STAT1 protein staining was observed in the epidermis of lesional skin (both nuclear and cytoplasmic) and dermal mononuclear inflammatory cells, but not in non-lesional or normal skin. ISG15 protein increase was observed in psoriatic skin and to a lesser extent in non-lesional skin, but was not detected in normal skin.

Figure 45: A Venn diagram illustrating the number of probe sets that show altered expression at mRNA level in the lesional skin compared to non-lesional skin, or in the non-lesional skin compared to normal skin of psoriatic patients. Values shaded in red indicate the number of probe sets significantly upregulated while those values shaded in green indicate the number of probe sets significantly downregulated. The intersecting region represents probe sets that are common to both comparisons.

Figure 46: Graphic representation of type-IFN signaling pathway that is activated in the lesional skin of psoriatic patients. Pathway image was generated with GeneGo's MetaCore integrated software suite. Individual symbols within the image represent well characterized proteins or protein complexes. Arrows linking the proteins represent the stimulatory, inhibitory, or interactive effect of the protein on the target protein. Thermometers adjacent to the individual symbols represent relative expression levels (red indicates overexpression,

while green indicates underexpression) of transcripts that comprise the protein (or protein complex) within the particular pathway.

Figure 47a and 47b: Table providing fold change (fc; log2 transformed) and q value (calculated by FDR) of the top 100 probe sets upregulated in the lesional skin compared to non-lesional skin in psoriasis. Also listed are the log2 transformed fold change and q values of these genes when comparing non-lesional skin with healthy normal skin controls. Type I IFN inducible genes are listed in bold font.

Figure 48: Distinctive separation of the lesional skin from non-lesional skin and normal skin – hierarchical clustering of all samples using transcript profiles of all genes on a whole genome (Affymetrix whole genome U133 plus v2.0 array) array.

Figure 49: Probe sets identified as IFN γ inducible by overlap in Figure 42.

Figure 50: Probe sets identified as TNF α inducible by overlap in Figure 42.

Figure 51: Probe sets identified as type I IFN inducible by overlap in Figure 42.

Figure 52: Immunohistochemical analysis of biopsies from skin lesions of a placebo-treated SLE patient to detect pDC, mDC, and T cell infiltrates.

Figure 53: Immunohistochemical analysis of biopsies from skin lesions of a placebo-treated SLE patient to detect HERC5, ISG15, and IP10 proteins, proteins expressed from type I IFN-induced genes.

Figure 54: Immunohistochemical analysis of biopsies from skin lesions of an SLE patient treated with 10 mg/kg MEDI-545 to detect pDC, mDC, and T cell infiltrates.

Figure 55: Immunohistochemical analysis of biopsies from skin lesions of an SLE patient treated with 10 mg/kg MEDI-545 to detect HERC5, ISG15, and IP10 proteins, proteins expressed from type I IFN-induced genes.

Figure 56: Immunohistochemical analysis of biopsies from skin lesions of an SLE patient treated with 10 mg/kg MEDI-545 to detect pDC, mDC, and T cell infiltrates.

Figure 57: Immunohistochemical analysis of biopsies from skin lesions of an SLE patient treated with 10 mg/kg MEDI-545 to detect HERC5, ISG15, and IP10 proteins, proteins expressed from type I IFN-induced genes.

Figure 58a and 58b: Heatmap (a) and PCA (b) showing neutralization of the top 25 type I IFN inducible genes in a skin biopsy of an SLE patient treated with 10 mg/kg MEDI-545 at 0 and 7 days post-dosing.

Figure 59a-d: Detection of type I and type II IFN activity in an IFN bioassay.

Figure 60a and 60b: Detection of MEDI-545 (a) and MEDI-546 (b)-mediated neutralization of IFN α activity in the IFN bioassay.

Figure 61: Detection of anti-IFN γ -mediated neutralization of IFN γ activity in the IFN bioassay.

Figure 62: Detection of anti-IFN ω -mediated neutralization of IFN ω activity in the IFN bioassay.

Figure 63: Detection of anti-IFN β -mediated neutralization of IFN β activity in the IFN bioassay.

Figure 64: Heat map showing modulation of gene expression in whole blood from healthy donors *ex vivo* stimulated with IFN γ , TNF α , or IFN α/β . Negative control (NT).

Figure 65: Type I IFN-inducible genes were among the most upregulated genes in whole blood of SLE patients.

Figure 66: IFN γ , IFN ω , IFNAR1 and IFNAR2 mRNAs are upregulated in whole blood of lupus patients.

Figure 67: Heat map showing modulation of gene expression in healthy donor PBMCs *ex vivo* stimulated with lupus patient serum.

Figure 68a and 68b: (A) PCA plot showing lupus patients having a strong/moderate type I IFN inducible signature (approximately 66% in this sampling) cluster together. (b) Table providing the 25 genes used for PCA analysis.

Figure 69: Confirmation of overexpression of selected type-I IFN inducible genes in lupus patients based on taqMan QRT-PCR assays using Fluidigm's BioMarkTM 48.48 dynamic array.

Figure 70a and 70b: (a) Ability of four different SLE patient serum samples to induce type I IFN activity in a reporter gene assay. (b) Number of transcripts induced at least 3-fold in healthy human PBMCs by each of the four different SLE patient serum samples following 4 hour co-incubation.

Figure 71a and 71b: The majority of genes neutralized by an anti-IFN α Ab 4 hours post co-incubation of SLE patient serum and healthy human PBMCs are type I IFN genes, while the majority of genes neutralized by the anti-IFN α Ab 18 hours post co-incubation of SLE patient serum and healthy human PBMCs are non-type I IFN genes as shown by (a) heatmap analysis and represented (b) in bar graphs.

Figure 72a and 71b: Provides the (a) type I IFN genes and (b) non-type I IFN genes that were upregulated and neutralized by an anti-IFN α Ab 18 hours post co-incubation of SLE patient serum and healthy human PBMCs, but that were not upregulated 4 hours post co-incubation of SLE patient serum and healthy human PBMCs.

Figure 73: Provides pathways and cell processes neutralized by an anti-IFN α Ab 18 hours following co-incubation of SLE patient serum and healthy human PBMCs.

Figure 74a and 74b: Detection of (a) increased and (b) decreased levels of specific proteins in serum of lupus patients.

Figure 75: QuantiGenePlex 1.0 analysis of IFN-inducible gene signatures from whole blood of 5 healthy donors stimulated with 20 IU/mL IFN α 2b.

Figure 76: Dose-dependent changes in gene expression in blood from a single healthy donor treated with multiple concentrations of IFN α 2b.

Figure 77: Detection of IFN-inducible transcripts in PAXgene-preserved whole blood samples from SLE subjects with and without detectable serum IFN α activity.

Figure 78: Correlation between QuantiGenePlex and Fluidigm technologies in SLE PAXgene-preserved whole blood samples.

Figure 79: Longitudinal testing of SLE samples following administration of an anti-IFN α monoclonal antibody: comparison of QuantiGenePlex 2.0 and Fluidigm technologies.

Figure 80: Representative heat map visualizing the (in descending order) overexpression of type I IFN gene signature; overexpression of granulocyte signature; underexpression of T-cell signature, underexpression of NK-cell signature, and underexpression of B-cell signature, in whole blood from 46 SLE patients (indicated by red bar under the heat map) compared with

whole blood from 24 healthy donors (indicated by blue bar under the heat map) IFN=interferon; SLE=systemic lupus erythematosus.

Figure 81a-81c: Type I IFN-inducible genes in whole blood of SLE patients can be used to separate SLE patients with a type I IFN gene signature from healthy normal controls. (a) Three-dimensional PCA plot of whole blood from 46 SLE samples using a 114 type I IFN-inducible probe sets upregulated in whole blood of SLE patients compared with those from 24 healthy donors. (b) PCA plot of whole blood from 54 SLE patients in the prospective study using the 114 upregulated type I IFN-inducible probe set confirmed the overexpression of type I IFN gene signatures in SLE patients. (c) PCA plot of whole blood from 100 SLE samples in both discovery and prospective study using 21 upregulated type I IFN-inducible gene panel in SLE patients compared with 24 healthy donors. Each point represents one sample (blue dots, healthy normals; red dots, SLE patients). IFN=interferon; PCA=principal components analysis; SLE=systemic lupus erythematosus.

Figure 82: Relative expression of mRNAs and median fold changes (horizontal bars) of TNF- α , IFN- γ , and IFN- γ receptors in whole blood of SLE patients compared with healthy controls ($P < 0.05$ for all). Averages of relative mRNA levels of these cytokines and their receptors in whole blood from 24 healthy donors were scaled to 1 based on TaqMan QRT-PCR assays. IFN=interferon; QRT-PCR=quantitative real-time reverse transcriptase polymerase chain reaction; SLE=systemic lupus erythematosus; TNF=tumor necrosis factor.

Figure 83a-83c: TaqMan QRT-PCR confirmed the overexpression of type I IFN-inducible genes in whole blood of SLE patients. (a) Relative fold changes of 15 type I IFN-inducible genes (generically labeled 1–15) in SLE patients were compared with healthy donors ($p < 0.05$ for all). Averages of relative mRNA levels of genes in the pooled RNA from 24 healthy donors were scaled to 1 based on TaqMan QRT-PCR assays. Horizontal bars represent average fold change. (b and c) TaqMan QRT-PCR validation of overexpression of the 21-gene panel of type I IFN-inducible genes in whole blood of SLE patients as determined by whole genome array. The relative overexpression of 21 type I IFN-inducible genes in 2 SLE patients is shown via microarray (left) and TaqMan (right) assays. Correlation coefficients between TaqMan QRT-PCR and microarray were 0.9861 and 0.9888 for patient X and Y, respectively. IFN=interferon; QRT-PCR=quantitative real-time reverse transcriptase polymerase chain reaction; SLE=systemic lupus erythematosus.

Figure 84: Magnitude of overexpression of type I IFN gene signature in whole blood of SLE patients as measured by the median fold change of the 25 most overexpressed type I IFN-inducible genes or type I IFN gene signature score in individual SLE patients. The horizontal bars represent the median values. Patients whose type I IFN gene signature score was ≥ 10 were considered to have strong type I IFN gene signatures; those with scores between 4 and 10 were considered to have moderate type I IFN gene signatures, whereas those with scores ≤ 4 were considered to have weak type I IFN gene signatures. IFN=interferon; SLE=systemic lupus erythematosus.

Figure 85a-85c: Stratification of 35 SLE patients into groups of low (a; green), moderate (b; gray), and high (c; red) type I IFN gene signature based on median fold change across the 21-gene panel of type I IFN-inducible genes. Densities for each SLE patient are calculated and graphed using the fold change for each of the 21 genes from each SLE patient on the $\log_2$ scale to provide a representation of the distribution of 21 genes fold change values. The vertical dashed lines partition the 3 classes of signature scores: 7 patients with a weak type I IFN gene signature = median fold change < 1.91 (0.93 on $\log_2$ scale), 8 patients with a moderate type I IFN gene signature = median fold change between 1.91 and 5.53, and 20 patients with a strong type I IFN gene signature = median fold change > 5.53 (2.47 on $\log_2$ scale). IFN=interferon; SLE=systemic lupus erythematosus.

Figure 86: Dose-dependent neutralization of 21 upregulated IFN- α/β -inducible genes in SLE patients by MEDI-545.

Figure 87a and 87b: Heatmap (a) and PCA (b) showing neutralization of 21 upregulated IFN- α/β -inducible genes in whole blood of an SLE patient treated with 30 mg/kg MEDI-545 (0, 1, 4, 7, and 14 days post-dose).

Figure 88a and 88b: PCA plots prepared using the 21 upregulated IFN- α/β -inducible probe sets do not show IFN signature neutralization in placebo-treated patients.

Figure 89: Neutralization of the 21 upregulated IFN- α/β -inducible probe sets in patients treated with 0.3, 1.0, 3.0, 10.0, and 30.0 mg/kg MEDI-545.

Figure 90: Methodology for calculating target neutralization for Figure 89.

DETAILED DESCRIPTION

The invention encompasses methods of identifying, diagnosing, treating, and monitoring disease progression in patients. Patients include any animal having a type I IFN or an IFN α -inducible disease, disorder, or condition. The patient may have the disease, disorder, or condition as a result of experimental research, *e.g.*, it may be an experimental model developed for the disease, disorder, or condition. Alternatively, the patient may have the disease, disorder, or condition in the absence of experimental manipulation. Patients include humans, mice, rats, horses, pigs, cats, dogs, and any animal used for research.

The patient may comprise a type I IFN or IFN α -inducible PD marker expression profile. The type I IFN or IFN α -inducible PD marker expression profile may be a strong profile, a moderate profile, or a weak profile. The type I IFN or IFN α -inducible PD marker expression profile can readily be designated as strong, moderate, or weak by determining the fold dysregulation of the type I IFN or IFN α -inducible PD marker expression profile of the patient, (*e.g.*, the fold increase in expression of upregulated type I IFN or IFN α -inducible PD markers in the patient), relative to a control sample(s) or control patient(s) and comparing the patient's fold dysregulation to that of other patients having a type I IFN or IFN α -inducible PD marker expression profile. Fold dysregulation can be calculated by well known methods in the art as can the comparing. See, *e.g.*, Example 8.

The type I IFN or IFN α -inducible PD marker expression profile may comprise ~~upregulation of any group of genes or group of genes detected by the probes identified in~~ Tables 19, 20, 21, 22, 23, 24, 26, 28, or 30. The group of genes or group of genes detected by the probes identified in Tables 19, 20, 21, 22, 23, 24, 26, 28 or 30 may include any at least 2, any at least 3, any at least 4, any at least 5, any at least 6, any at least 7, any at least 8, any at least 9, any at least 10, any at least 11, any at least 12, any at least 13, any at least 14, any at least 15, any at least 16, any at least 17, any at least 18, any at least 19, any at least 20, any at least 21, any at least 22, any at least 23, any at least 24, any at least 25, any at least 26, any at least 27, any at least 28, any at least 29, any at least 30, any at least 40, or any at least 50 of the genes or genes detected by the probes identified in the Tables.

The group of genes that may be included in the type I IFN or IFN α -inducible PD marker expression profile of the patient may be MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RASD2, and IFI44. The genes or genes detected by the probes may include IFI44, IFI27, IFI44L, DNAPTP6, LAMP3, LY6E, RSAD2, HERC5, IFI6, ISG15, OAS3, SIGLEC1, OAS2, USP18, RTP4, IFIT1, MX1, OAS1, EPSTI1, PLSCR1, and IFRG28.

The genes may include any at least 2, any at least 3, any at least 4, any at least 5, any at least 6, any at least 7, any at least 8, any at least 9, any at least 10, or any at least 11, or any at least 12, or any at least 13, or any at least 14, or any at least 15, or any at least 16, or any at least 17, or any at least 18, or any at least 19, or at least 20, or any at least 21, or any at least 22, or any at least 23, or any at least 24, or any least 25, or any at least 26, or any at least 27, or any at least 28, or any at least 29, or any at least 30 of LAMP3, DNAPTP6, FLJ31033, HERC6, SERPING1, EPSTI1, RTP4, OASL, FBXO6, IFIT2, IFI44, OAS3, BATF2, ISG15, IRF7, RSAD2, IFI35, OAS1, LAP3, IFIT1, IFIT5, PLSCR1, IFI44L, MS4A4A, GALM, UBE2L6, TOR1B, SAMD9L, HERC5, TDRD7, TREX1, PARP12, and AXUD1.

The type I IFN or IFN α -inducible PD marker expression profile may contain upregulation of the entire group of genes or group of genes detected by the probes identified in one of Table 19, or Table 20, or Table 21, or Table 22, or Table 23, or Table 24, or Table 26, or Table 28, or Table 30 or may be any one or more of the genes identified in Figure 72. The type I IFN or IFN α -inducible PD marker expression profile may include upregulation of all the genes identified in Table 24. The type I IFN or IFN α -inducible PD marker expression profile may include upregulation of the genes identified in figure 72 A or figure 72b, or figure 72a and figure 72b.

The patient comprising the type I IFN or IFN α -inducible PD marker expression profile may further comprise downregulated type I IFN or IFN α PD marker(s). The downregulated PD markers may include any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, any 15, any 20, any 25, any 30, any 35, any 40, any 45, or any 50 of the genes in Table 31 or any of CYP1B1, TGST1, RRAGD, IRS2, MGST1, TGFBR3, and RGS2.

The patient comprising the type I IFN or IFN α -inducible PD marker expression profile may further comprise upregulation of expression of any number of IFN α or type-I IFN subtypes. The IFN α or type-I IFN subtypes may include any more than one, more than two, more than three, more than four, more than five, more than six, more than seven, more than eight, more than nine, or more than ten IFN α or type-I IFN subtypes. These subtypes may include IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 6, IFN α 7, IFN α 8, IFN α 10, IFN α 14, IFN α 17, IFN α 21, IFN β , or IFN ω . The patient may comprise upregulation of expression of IFN subtypes IFN α 1, IFN α 2, IFN α 8, and IFN α 14.

Alternatively, a patient treated in the methods encompassed by the invention may simply be one identified as comprising a gene expression profile with upregulation of expression of any number of IFN α or type-I IFN subtypes. The IFN α or type-I IFN subtypes

may include any more than one, more than two, more than three, more than four, more than five, more than six, more than seven, more than eight, more than nine, or more than ten IFN α or type-I IFN subtypes. These subtypes may include IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 6, IFN α 7, IFN α 8, IFN α 10, IFN α 14, IFN α 17, IFN α 21, IFN β , or IFN ω . These subtypes may include IFN α 1, IFN α 2, IFN α 8, and IFN α 14.

The patient comprising the type I IFN or IFN α -inducible PD marker expression profile may further comprise upregulation of expression of IFN α receptors, either IFNAR1 or IFNAR2, or both, or TNF α , or IFN γ , or IFN γ receptors (either IFNGR1, IFNGR2, or both IFNGR1 and IFNGR2). The patient may simply be identified as one who comprises upregulation of expression of IFN α receptors, either IFNAR1 or IFNAR2, or both, or TNF α , or IFN γ , or IFN γ receptors (either IFNGR1, IFNGR2, or both IFNGR1 and IFNGR2).

The upregulation or downregulation of the type I IFN or IFN α -inducible PD markers in the patient's expression profile may be by any degree relative to that of a sample from a control (which may be from a sample that is not disease tissue of the patient (e.g., non-lesional skin of a psoriasis patient) or from a healthy person not afflicted with the disease or disorder). The degree upregulation or downregulation may be at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, at least 100%, at least 125%, at least 150%, or at least 200%, or at least 300%, or at least 400%, or at least 500% that of the control or control sample.

Furthermore, the patient may overexpress or have a tissue that overexpresses a type I IFN subtype at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, at least 100%, at least 125%, at least 150%, or at least 200%, or at least 300%, or at least 400%, or at least 500% that of the control. The type I IFN subtype may be any one of IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 6, IFN α 7, IFN α 8, IFN α 10, IFN α 14, IFN α 17, IFN α 21, IFN β , or IFN ω . The type I IFN subtypes may include all of IFN α 1, IFN α 2, IFN α 8, and IFN α 14.

The patient may further comprise or alternatively comprise alterations in levels of proteins in serum. The patient may have increased serum levels of proteins such as adiponectin, alpha-fetoprotein, apolipoprotein CIII, beta-2 microglobulin, cancer antigen 125, cancer antigen 19-9, eotaxin, FABP, factor VII, ferritin, IL-10, IL-12p70, IL-16, IL-18, IL-1ra, IL-3, MCP-1, MMP-3, myoglobin, SGOT, tissue factor, TIMP-1, TNF RII, TNF-alpha, VCAM-1, or vWF. The patient may have increased serum levels of any 1, 2, 3, 4, 5, 6, 7, 8,

9, 10, 11, 12, 13 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, or 26 of these proteins in serum. The increased level may be at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, at least 100%, at least 125%, at least 150%, or at least 200%, or at least 300%, or at least 400%, or at least 500% that of a control, e.g., a healthy subject. The alteration may be a decrease in serum levels of proteins such as BDNK, complement 3, CD40 ligand, EGF, ENA-78, EN-RAGE, IGF-1, MDC, myeloperoxidase, RANTES, or thrombopoietin. The patient may have decreased serum levels of any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 of these proteins. The decreased level may be at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 90%, or at least 100% that of a control, e.g., a healthy subject. The PD marker profile may comprise one or more of these increased or decreased serum levels of proteins.

The patient may further comprise auto-antibodies that bind to any one of the following auto-antigens: (a) Myxovirus (influenza virus) resistance 1, interferon-inducible protein p78; (b) surfactant protein 5, transcript variant c; (c) proteasome (prosome, macropain) activator subunit 3 (PA28 gamma; Ki) trans; (d) retinoic acid receptor, alpha; (e) Heat shock 10 kDa protein 1 (chaperonin 10); (f) tropomyosin 3; (g) pleckstrin homology-like domain, family A, member 1; (h) cytoskeleton-associated protein 1; (i) Sjogren syndrome antigen A2 (60 kDa, ribonucleoprotein auto-antigen SS-A/Ro); (j) NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex 1, 8 kDa; (k) NudE nuclear distribution gene E homolog 1 (A. nidulans); (l) MutL homolog 1, colon cancer, nonpolyposis type 2 (E. coli); (m) leucine rich repeat (in FLII) interacting protein 2; (n) tropomyosin 1 (alpha); (o) spastic paraplegia 20, spartin (Troyer syndrome); (p) preimplantation protein, transcript variant 1; (r) mitochondrial ribosomal protein L45; (s) Lin-28 homolog (C. elegans); (t) heat shock 90 kDa protein 1, alpha; (u) dom-3 homolog Z (C. elegans); (v) dynein, cytoplasmic, light intermediate polypeptide 2; (w) Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein); (x) synovial sarcoma, X breakpoint 2, transcript variant 2; (y) moesin; (z) homer homolog (Drosophila), transcript variant 1; (aa) GCN5 general control of amino-acid synthesis 5-like 2 (yeast); (bb) eukaryotic translation elongation factor 1 gamma; (cc) eukaryotic translation elongation factor 1, delta; (dd) DNA-damage-inducible transcript 3; (ee) CCAAT/enhancer binding protein (C/EBP) gamma; and any other auto-antigen described in provisional application entitled "Auto-antibody markers of autoimmune disease" filed May 3, 2007 or in provisional application entitled "Auto-antibody markers of autoimmune disease" to be filed November 6, 2007 (for example, but not limited to, those

described on Tables 2, 4, 5, and 9). The patient may comprise auto-antibodies that bind to any number of these auto-antigens, *e.g.*, any at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9 at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25.

A type I IFN or an IFN α -inducible disease, disorder, or condition is any that exhibits a type I IFN or an IFN α PD marker expression profile or gene signature. A PD marker expression profile and a gene signature will be understood to be equivalent. These diseases, disorders, or conditions include those with an autoimmune component such as systemic lupus erythematosus, insulin dependent diabetes mellitus, inflammatory bowel disease (including Crohn's disease, ulcerative colitis, and Celiac's disease), multiple sclerosis, psoriasis, autoimmune thyroiditis, rheumatoid arthritis, glomerulonephritis, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, dermatomyositis, polymyositis, and sarcoidosis. Other diseases, disorders, or conditions include graft versus host disease and transplant rejection.

The patients may also exhibit any of a number of symptoms as discussed in, *e.g.*, provisional patent application Methods of Treating Systemic Lupus Erythematosus filed April 16, 2007, or may have a clinical SLEDAI score or BILAG score as discussed in the same. These symptoms may include fatigue, organ damage, malar rash, and alopecia. The patient may be scored using a known clinical scoring system, *e.g.*, SLEDAI which is an index of SLE disease activity as measured and evaluated within the last 10 days (Bombardier C, Gladman D D, Urowitz M B, Caron D, Chang C H and the Committee on Prognosis Studies in SLE: Derivation of the SLEDAI for Lupus Patients. *Arthritis Rheum* 35:630-640, 1992.). Disease activity under the SLEDAI scoring system can range from 0 to 105. The following categories of SLEDAI activity have been defined: no activity (SLEDAI = 0); mild activity (SLEDAI = 1-5); moderate activity (SLEDAI = 6-10); high activity (SLEDAI = 11-19); very high activity (SLEDAI = 20 or higher). (Griffiths, et al., Assessment of Patients with Systemic Lupus Erythematosus and the use of Lupus Disease Activity Indices). Another disease scoring index is the BILAG index which is an activity index of SLE that is based on specific clinical manifestations in eight organ systems: general, mucocutaneous, neurological, musculoskeletal, cardiovascular, respiratory, renal, and hematology results. Scoring is based on a letter system, but weighted numerical scores can also be assigned to each letter, making it possible to calculate a BILAG score in the range of 0-72. (Griffiths, et al., Assessment of Patients with Systemic Lupus Erythematosus and the use of Lupus Disease Activity Indices). Other scoring indices include the PGA score, the composite responder index (CRI), and the

ANAM4™ test. The methods described herein, *e.g.*, of treating an autoimmune disorder, may be used for any subject identified as having any activity level of disease activity as measured by any classification methodology known in the art, *e.g.*, mild, moderate, high, or very high. The methods described herein, *e.g.*, of treating an autoimmune disorder, may result in a decrease in a patient's symptoms or may result in an improvement in a score of disease for the patient's type I IFN or an IFN α -inducible disease, disorder, or condition.

A therapeutic agent may be administered to a patient or a patient may be identified as a candidate for administration of an agent or a therapeutic agent. A therapeutic agent is any molecule that binds to and modulates type I IFN or IFN α activity. The therapeutic agent may be a small molecule or a biological agent. If the therapeutic agent is a small molecule it may be synthesized or identified and isolated from a natural source.

If the therapeutic agent is a biological agent, it may be an antibody specific for any subtype(s) of type I IFN or IFN α . For instance, the antibody may be specific for any one of IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 6, IFN α 7, IFN α 8, IFN α 10, IFN α 14, IFN α 17, IFN α 21, IFN β , or IFN ω . Alternatively, the antibody may be specific for any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, any eleven, any twelve type I IFN or IFN α subtypes. If the antibody is specific for more than one type I IFN subtype, the antibody may be specific for IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 8, IFN α 10, and IFN α 21; or it may be specific for IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 8, and IFN α 10; or it may be specific for IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 8, and IFN α 21; or it may be specific for IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 10, and IFN α 21. Antibodies specific for type I IFN or IFN α include MEDI-545, any biologic or antibody other than MEDI-545, antibodies described in U.S. patent applications 11/009,410 filed December 10, 2004 and 11/157,494 filed June 20, 2005, 9F3 and other antibodies described in U.S. Patent No. 7,087,726 (Example 1 and Example 2, those disclosed in Table 3 and Table 4, and/or those disclosed in the table entitled "Deposit of Material" on lines 25-54, column 56), NK-2 and YOK5/19 (WO 84/03105), LO-22 (U.S. Patent 4,902,618), 144 BS (U.S. Patent 4,885,166), and EBI-1, EBI-2, and EBI-3 (EP 119476). A therapeutic agent that modulates IFN α activity may neutralize IFN α activity. One of skill in the art is well aware of preparation and formulation of such biological agents and methods of their administration.

The antibody may be a synthetic antibody, a monoclonal antibody, polyclonal antibodies, a recombinantly produced antibody, an intrabody, a multispecific antibody (including bi-specific antibodies), a human antibody, a humanized antibody, a chimeric antibody, a single-chain Fv (scFv) (including bi-specific scFv), a BiTE molecule, a single

chain antibody, a Fab fragments, a F(ab') fragment, a disulfide-linked Fv (sdFv), or an epitope-binding fragment of any of the above. The antibody may be any of an immunoglobulin molecule or immunologically active portion of an immunoglobulin molecule. Furthermore, the antibody may be of any isotype. For example, it may be any of isotypes IgG1, IgG2, IgG3 or IgG4. The antibody may be a full-length antibody comprising variable and constant regions, or an antigen-binding fragment thereof, such as a single chain antibody, or a Fab or Fab'2 fragment. The antibody may also be conjugated or linked to a therapeutic agent, such as a cytotoxin or a radioactive isotope.

In the methods of treatment a second agent other than the agent that binds to modulates IFN α activity may be administered to the patient. Second agents include, but are not limited to non-steroidal anti-inflammatory drugs such as ibuprofen, naproxen, sulindac, diclofenac, piroxicam, ketoprofen, diflunisal, nabumetone, etodolac, and oxaprozin, indomethacin; anti-malarial drugs such as hydroxychloroquine; corticosteroid hormones, such as prednisone, hydrocortisone, methylprednisolone, and dexamethasone; methotrexate; immunosuppressive agents, such as azathioprine and cyclophosphamide; and biologic agents that, *e.g.*, target T cells such as Alefacept and Efalizumab, or target TNF α , such as, Enbrel, Remicade, and Humira.

Treatment with the agent may result in neutralization of the type I IFN or IFN α -inducible profile. Treatment with the agent may result in a decrease in one or more symptoms of the type I IFN or an IFN α -mediated disease or disorder. Treatment with the agent may result in fewer flare-ups related to the type I IFN or an IFN α -mediated disease or disorder. Treatment with the agent may result in improved prognosis for the patient having the type I IFN or an IFN α -mediated disease or disorder. Treatment with the agent may result in a higher quality of life for the patient. Treatment with the agent may alleviate the need to co-administer second agents or may lessen the dosage of administration of the second agent to the patient. Treatment with the agent may reduce the number of hospitalizations of the patient that are related to the type I IFN or an IFN α -mediated disease or disorder.

The agent that binds to and modulates type I IFN or IFN α activity may neutralize a type I IFN or IFN α -inducible profile. Neutralization of the type I IFN or IFN α -inducible profile may be a reduction in at least one, at least two, at least three, at least five, at least seven, at least eight, at least ten, at least twelve, at least fifteen, at least twenty, at least twenty five, at least thirty, at least thirty five, at least forty, at least forty five, or at least fifty genes up-regulated by type I IFN or IFN α . The genes upregulated by type I IFN or IFN α may be any group of genes in Tables 19, 20, 21, 22, 23, 24, 26, 28, or 30 as discussed above.

Neutralization of the type I IFN or IFN α -inducible profile is a reduction of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% of any of the at least one, at least two, at least three, at least five, at least seven, at least eight, at least ten, at least twelve, at least fifteen, at least twenty, at least twenty five, at least thirty, at least thirty five, at least forty, at least forty five, or at least fifty genes up-regulated in any type I IFN or IFN α -inducible profile. Alternatively, neutralization of the type I IFN or IFN α -inducible profile refers to a reduction of expression of up-regulated type I IFN or IFN α -inducible genes that is within at most 50%, at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 5%, at most 4%, at most 3%, at most 2%, or at most 1% of expression levels of those type I IFN or IFN α -inducible genes in a control sample. If the agent that binds to and modulates type I IFN or IFN α activity is a biologic agent, such as an antibody, the agent may neutralize the type I IFN or IFN α profile at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg.

Neutralization of the type I IFN or IFN α -inducible profile may be increased expression of at least one, at least two, at least three, at least five, at least seven, at least eight, at least ten, at least twelve, at least fifteen, at least twenty, at least twenty five, at least thirty, at least thirty five, at least forty, at least forty five, or at least fifty genes whose expression is reduced by type I IFN or IFN α . The genes whose expression is reduced by type I IFN or IFN α may be any group of genes in Table 30. Neutralization of down-regulated genes in a type I IFN or IFN α -inducible profile is an increase of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90%, or at least 100%, or at least 125%, or at least 130%, or at least 140%, or at least 150%, or at least 175%, or at least 200%, or at least 250%, or at least 300%, or at least 500% of any of the at least one, at least two, at least three, at least five, at least seven, at least eight, at least ten, at least twelve, at least fifteen, at least twenty, or at least twenty five genes whose expression is downregulated in any type I IFN or IFN α -inducible profile. Alternatively, neutralization of the type I IFN or IFN α -inducible profile refers to an increase in expression of type I IFN or IFN α -inducible genes to within at most 50%, at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 5%, at most 4%, at most 3%, at most 2%, or at most 1% of expression

levels of those type I IFN or IFN α -inducible (downregulated) genes in a control sample. If the agent that binds to and modulates type I IFN or IFN α activity is a biologic agent, such as an antibody, the agent may neutralize the type I IFN or IFN α profile at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg.

The agent that binds to and modulates type I IFN or IFN α activity may further or alternatively neutralize expression of one or more type I IFN or IFN α subtypes. The IFN α or type-I IFN subtypes may include any more than one, more than two, more than three, more than four, more than five, more than six, more than seven, more than eight, more than nine, or more than ten IFN α or type-I IFN subtypes. These subtypes may include IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 6, IFN α 7, IFN α 8, IFN α 10, IFN α 14, IFN α 17, IFN α 21, IFN β , or IFN ω . These subtypes may include all of IFN α 1, IFN α 2, IFN α 8, and IFN α 14. Alternatively, these subtypes may include IFN α 1, IFN α 2, IFN α 4, IFN α 5, IFN α 8, IFN α 10, IFN α 21. Neutralization of the IFN α or type-I IFN subtypes may be a reduction of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% of any of the at least one, at least two, at least three, at least five, at least seven, at least eight, or at least ten of the subtypes. Neutralization of the IFN α or type-I IFN subtypes may be a reduction in expression of IFN α or type-I IFN subtype genes that is within at most 50%, at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 5%, at most 4%, at most 3%, at most 2%, or at most 1% of expression levels of those IFN α or type I IFN subtypes in a control sample. If the agent that binds to and modulates IFN α activity or type I IFN activity is a biologic agent, such as an antibody, the agent may neutralize the IFN α or type I IFN subtypes at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg.

The agent that binds to and modulates type I IFN or IFN α activity may further or alternatively neutralize expression of IFN α receptors, either IFNAR1 or IFNAR2, or both, or TNF α , or IFN γ , or IFN γ receptors (either IFNGR1, IFNGR2, or both IFNGR1 and IFNGR2). Neutralization of expression of IFN α receptors, either IFNAR1 or IFNAR2, or both, or TNF α , or IFN γ , or IFN γ receptors (either IFNGR1, IFNGR2, or both IFNGR1 and IFNGR2) may be a reduction of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least

8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% of any of the at least one, at least two, at least three, at least five, or at least six of these genes. Neutralization of expression of IFN α receptors, either IFNAR1 or IFNAR2, or TNF α , or IFN γ , or IFN γ receptors (either IFNGR1, IFNGR2, or both IFNGR1 and IFNGR2) is a reduction of expression of at most 50%, at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 5%, at most 4%, at most 3%, at most 2%, or at most 1% of expression levels of these genes in a control sample. If the agent that binds to and modulates type I IFN or IFN α activity is a biologic agent, such as an antibody, the agent may neutralize expression of IFN α receptors IFNAR1 or IFNAR2, or TNF α , or IFN γ , or IFN γ receptors IFNGR1 or IFNGR2 at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg.

The agent that binds to and modulates type I IFN or IFN α activity may further or alternatively neutralize alterations of levels of proteins in serum, *e.g.*, increase levels of those proteins whose serum levels are downregulated or decrease levels of those proteins whose serum levels are upregulated to levels closer to those of control subjects. Neutralization of expression of proteins in serum, such as adiponectin, alpha-fetoprotein, apolipoprotein CIII, beta-2 microglobulin, cancer antigen 125, cancer antigen 19-9, eotaxin, FABP, factor VII, ferritin, IL-10, IL-12p70, IL-16, IL-18, IL-1ra, IL-3, MCP-1, MMP-3, myoglobin, SGOT, tissue factor, TIMP-1, TNF RII, TNF-alpha, VCAM-1, vWF, BDNK, complement 3, CD40 ligand, EGF, ENA-78, EN-RAGE, IGF-1, MDC, myeloperoxidase, RANTES, or thrombopoietin may be by bringing the level of at least one, at least two, at least three, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least twelve, at least fifteen, at least twenty, or at least 25 of these proteins to within at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% levels of the protein in serum of a healthy subject. If the agent that binds to and modulates type I IFN or IFN α activity is a biologic agent, such as an antibody, the agent may neutralize levels of the serum proteins, *e.g.*, adiponectin, alpha-fetoprotein, apolipoprotein CIII, beta-2 microglobulin, cancer antigen 125, cancer antigen 19-9, eotaxin, FABP, factor VII, ferritin, IL-10, IL-12p70, IL-16, IL-18, IL-1ra, IL-3, MCP-1, MMP-3, myoglobin, SGOT, tissue factor, TIMP-1, TNF RII, TNF-alpha, VCAM-1, vWF,

BDNF, complement 3, CD40 ligand, EGF, ENA-78, EN-RAGE, IGF-1, MDC, myeloperoxidase, RANTES, or thrombopoietin, at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg.

The agent that binds to and modulates type I IFN or IFN α activity may further or alternatively reduce number or level of auto-antibodies that bind to any one, any at least 2, any at least 3, any at least 4, any at least 5, any at least 6, any at least 7, any at least 8, any at least 9, any at least 10, any at least 15, or any at least 20 of the following auto-antigens: (a) Myxovirus (influenza virus) resistance 1, interferon-inducible protein p78; (b) surfait 5, transcript variant c; (c) proteasome (posome, macropain) activator subunit 3 (PA28 gamma; Ki) trans; (d) retinoic acid receptor, alpha; (e) Heat shock 10 kDa protein 1 (chaperonin 10); (f) tropomyosin 3; (g) pleckstrin homology-like domain, family A, member 1; (h) cytoskeleton-associated protein 1; (i) Sjogren syndrome antigen A2 (60 kDa, ribonucleoprotein auto-antigen SS-A/Ro); (j) NADH dehydrogenase (ubiquinone) 1, alpha/beta subcomplex 1, 8 kDa; (k) NudE nuclear distribution gene E homolog 1 (*A. nidulans*); (l) MutL homolog 1, colon cancer, nonpolyposis type 2 (*E. coli*); (m) leucine rich repeat (in FLII) interacting protein 2; (n) tropomyosin 1 (alpha); (o) spastic paraplegia 20, spartin (Troyer syndrome); (p) preimplantation protein, transcript variant 1; (r) mitochondrial ribosomal protein L45; (s) Lin-28 homolog (*C. elegans*); (t) heat shock 90 kDa protein 1, alpha; (u) dom-3 homolog Z (*C. elegans*); (v) dynein, cytoplasmic, light intermediate polypeptide 2; (w) Ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein); (x) synovial sarcoma, X breakpoint 2, transcript variant 2; (y) moesin; (z) homer homolog (*Drosophila*), transcript variant 1; (aa) GCN5 general control of amino-acid synthesis 5-like 2 (yeast); (bb) eukaryotic translation elongation factor 1 gamma; (cc) eukaryotic translation elongation factor 1, delta; (dd) DNA-damage-inducible transcript 3; (ee) CCAAT/enhancer binding protein (C/EBP) gamma; and any other auto-antigen described in provisional application entitled "Auto-antibody markers of autoimmune disease" filed May 3, 2007; and any other auto-antigen described in provisional application entitled "Auto-antibody markers of autoimmune disease" filed November 6, 2007 (for example, but not limited to, those described on Tables 2, 4, 5, and 9). Reduction in level of auto-antibody may be a reduction of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% in presence of any of the auto-antibodies. If the agent that binds to and modulates type I IFN or

IFN α activity is a biologic agent, such as an antibody, the agent may reduce number or level or auto-antibodies at doses of 0.3 to 30 mg/kg, 0.3 to 10 mg/kg, 0.3 to 3 mg/kg, 0.3 to 1 mg/kg, 1 to 30 mg/kg, 3 to 30 mg/kg, 5 to 30 mg/kg, 10 to 30 mg/kg, 1 to 10 mg/kg, 3 to 10 mg/kg, or 1 to 5 mg/kg.

The agent that binds to and modulates type I IFN or IFN α activity may not neutralize expression of genes that are not included in an interferon-inducible signature or PD marker profile.

Samples may also be obtained from patients in the methods of the invention. Samples include any biological fluid or tissue, such as whole blood, saliva, urine, synovial fluid, bone marrow, cerebrospinal fluid, nasal secretions, sputum, amniotic fluid, bronchoalveolar lavage fluid, peripheral blood mononuclear cells, total white blood cells, lymph node cells, spleen cells, tonsil cells, or skin. The samples may be obtained by any means known in the art.

IFN α -inducible PD marker expression profiles may include up-regulated expression or activity of genes in cells exposed to elevated IFN α levels relative to baseline. Up-regulated expression or activity of genes includes an increase in expression of mRNA from a gene, an increase in expression of a protein encoded by a gene, or an increase in activity of a protein encoded by a gene. The expression or activity of the genes may be up-regulated as a direct or indirect response to IFN α .

The up-regulated expression or activity of any gene detected in a sample, by probes, or by probes in kits in an IFN α -inducible PD marker expression profile may be at least 1.2-fold, at least 1.25-fold, at least 1.3-fold, at least 1.4-fold, at least 1.5-fold, at least 2.0-fold, at least 2.25-fold, at least 2.5-fold, at least 2.75-fold, at least 3.0-fold, at least 3.5-fold, at least 4.0-fold, at least 4.5-fold, at least 5.0-fold, at least 6.0-fold, at least 7.0-fold, at least 8.0-fold, at least 9.0-fold, at least 10.0-fold, at least 15.0-fold, at least 20.0-fold, at least 25.0-fold, or at least 50.0-fold relative to baseline levels of control cells, *e.g.*, cells of healthy volunteers or cells of control animals or cells not exposed to IFN α in culture. All of the genes in the IFN α -inducible PD marker expression profile may have up-regulated expression or activity at the same fold increase. Alternatively, the genes in the PD marker expression profile may have varying levels of up-regulated expression or activity.

The down-regulated expression or activity of any gene detected in a sample, by probes, or by probes in kits in an IFN α -inducible PD marker expression profile may be at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at

least 98%, or at least 99% relative to baseline levels of control cells, *e.g.*, cells of healthy volunteers or cells of control animals or cells not exposed to IFN α in culture. All of the genes in the IFN α -inducible PD marker expression profile may have down-regulated expression or activity at the same fold decrease. Alternatively, the genes in the PD marker expression profile may have varying levels of down-regulated expression or activity.

The number of genes included in IFN α -inducible PD marker expression profile may be at least 2, at least 3, at least 4, at least 5, at least 10, at least 20, at least 25 at least 30, at least 50, at least 75, at least 100, at least 150, at least 200, at least 250, at least 300, at least 400, at least 500, at least 750, at least 1000, at least 1500, at least 2000, at least 2500, at least 5000, at least 10000, or at least 15000 genes. These genes may include those listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30 and/or 31 and/or any of the genes identified in Figures 72, 74, 75, or 77. The genes included in IFN α -inducible PD marker expression profile may be up-regulated genes, down-regulated genes, or a combination of up- and down-regulated genes.

The genes included in the IFN α -inducible PD marker expression profile may be the genes provided in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30 and/or 31 and/or any of the genes identified in Figures 72, 74, 75, or 77. The genes included in the IFN α -inducible PD marker expression profile may consist of or comprise at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 75%, at least 80%, at least 85% at least 90%, at least 95%, or at least 100% of the genes provided in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30 and/or 31 and/or any of the genes identified in Figures 72, 74, 75, or 77.

The IFN α -inducible PD markers in an expression profile may include any at least 5 genes such as, for example: MX1, LLY6E, IFI27, OAS1, IFIT1; or MX1, LLY6E, IFI27, OAS1, IFI6; or MX1, LLY6E, IFI27, OAS1, IFI44L; or MX1, LLY6E, IFI27, OAS1, ISG15; or MX1, LLY6E, IFI27, OAS1, LAMP3; or MX1, LLY6E, IFI27, OAS1, OASL; or MX1, LLY6E, IFI27, OAS1, RSAD2; or MX1, LLY6E, IFI27, OAS1, IFI44; or MX1, LLY6E, IFI27, OAS1, IFIT2; or MX1, LLY6E, IFI27, OAS1, OAS3; or MX1, LLY6E, IFI27, OAS1, USP18; or MX1, LLY6E, IFI27, OAS1, SIGLEC1; or MX1, LLY6E, IFI27, OAS1, HERC5; or MX1, LLY6E, IFI27, OAS1, DNAPTP6; or MX1, LLY6E, IFI27, OAS1, LOC129607; or MX1, LLY6E, IFI27, OAS1, EPSTI1; or MX1, LLY6E, IFI27, OAS1, BIRC4BP; or MX1, LLY6E, IFI27, OAS1, SIGLEC1; or MX1, LLY6E, IFI27, OAS1, gene detected by probe 229450_at; or MX1, LLY6E, IFI27, OAS1, gene detected by probe 235276_at; or LLY6E,

IFI27, OAS1, IFIT1, IFI6; or LLY6E, IFI27, OAS1, IFIT1, IFI44L; or LLY6E, IFI27, OAS1, IFIT1, ISG15; or LLY6E, IFI27, OAS1, IFIT1, LAMP3; or LLY6E, IFI27, OAS1, IFIT1, OASL; or LLY6E, IFI27, OAS1, IFIT1, RSAD2; or LLY6E, IFI27, OAS1, IFIT1, IFI44; or LLY6E, IFI27, OAS1, IFIT1, IFIT2; or LLY6E, IFI27, OAS1, IFIT1, OAS3; or LLY6E, IFI27, OAS1, IFIT1, USP18; or LLY6E, IFI27, OAS1, IFIT1, SIGLEC1; or LLY6E, IFI27, OAS1, IFIT1, HERC5; or LLY6E, IFI27, OAS1, IFIT1, DNAPTP6; or LLY6E, IFI27, OAS1, IFIT1, LOC129607; or LLY6E, IFI27, OAS1, IFIT1, EPSTI1; or LLY6E, IFI27, OAS1, IFIT1, BIRC4BP; or LLY6E, IFI27, OAS1, IFIT1, SIGLEC1; or LLY6E, IFI27, OAS1, IFIT1, gene detected by probe 229450_at; or LLY6E, IFI27, OAS1, IFIT1, gene detected by probe 235276_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15; or IFI27, OAS1, IFIT1, IFI6, LAMP3; or IFI27, OAS1, IFIT1, IFI6, OASL; or IFI27, OAS1, IFIT1, IFI6, RSAD2; or IFI27, OAS1, IFIT1, IFI6, IFI44; or IFI27, OAS1, IFIT1, IFI6, IFIT2; or IFI27, OAS1, IFIT1, IFI6, OAS3; or IFI27, OAS1, IFIT1, IFI6, USP18; or IFI27, OAS1, IFIT1, IFI6, SIGLEC1; or IFI27, OAS1, IFIT1, IFI6, HERC5; or IFI27, OAS1, IFIT1, IFI6, DNAPTP6; or IFI27, OAS1, IFIT1, IFI6, LOC129607; or IFI27, OAS1, IFIT1, IFI6, EPSTI1; or IFI27, OAS1, IFIT1, IFI6, BIRC4BP; or IFI27, OAS1, IFIT1, IFI6, SIGLEC1; or IFI27, OAS1, IFIT1, IFI6, gene detected by probe 229450_at; or IFI27, OAS1, IFIT1, IFI6, gene detected by probe 235276_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15; or OAS1, IFIT1, IFI6, IFI44L, LAMP3; or OAS1, IFIT1, IFI6, IFI44L, OASL; or OAS1, IFIT1, IFI6, IFI44L, RSAD2; or OAS1, IFIT1, IFI6, IFI44L, IFI44; or OAS1, IFIT1, IFI6, IFI44L, IFIT2; or OAS1, IFIT1, IFI6, IFI44L, OAS3; or OAS1, IFIT1, IFI6, IFI44L, USP18; or OAS1, IFIT1, IFI6, IFI44L, SIGLEC1; or OAS1, IFIT1, IFI6, IFI44L, HERC5; or OAS1, IFIT1, IFI6, IFI44L, DNAPTP6; or OAS1, IFIT1, IFI6, IFI44L, LOC129607; or OAS1, IFIT1, IFI6, IFI44L, EPSTI1; or OAS1, IFIT1, IFI6, IFI44L, BIRC4BP; or OAS1, IFIT1, IFI6, IFI44L, SIGLEC1; or OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 229450_at; or OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 235276_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3; or IFIT1, IFI6, IFI44L, ISG15, OASL; or IFIT1, IFI6, IFI44L, ISG15, RSAD2; or IFIT1, IFI6, IFI44L, ISG15, IFI44; or IFIT1, IFI6, IFI44L, ISG15, IFIT2 or IFIT1, IFI6, IFI44L, ISG15, OAS3; or IFIT1, IFI6, IFI44L, ISG15, USP18; or IFIT1, IFI6, IFI44L, ISG15, SIGLEC1; or IFIT1, IFI6, IFI44L, ISG15, HERC5; or IFIT1, IFI6, IFI44L, ISG15, DNAPTP6; or IFIT1, IFI6, IFI44L, ISG15, LOC129607; or IFIT1, IFI6, IFI44L, ISG15, EPSTI1; or IFIT1, IFI6, IFI44L, ISG15, BIRC4BP; or IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 229450_at; or IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 235276_at; or IFI6, IFI44L, ISG15, LAMP3, HERC5; or IFI6, IFI44L, ISG15, LAMP3,

DNAPTP6; or IFI6, IFI44L, ISG15, LAMP3, LOC129607; or IFI6, IFI44L, ISG15, LAMP3, EPSTI1; or IFI6, IFI44L, ISG15, LAMP3, BIRC4BP; or IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 229450_at; or IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 235276_at; or IFI6, IFI44L, ISG15, LAMP3, SIGLEC1; or IFI6, IFI44L, ISG15, LAMP3, USP18; or IFI6, IFI44L, ISG15, LAMP3, OAS3; or IFI6, IFI44L, ISG15, LAMP3, IFIT2; or IFI6, IFI44L, ISG15, LAMP3, IFI44; or IFI6, IFI44L, ISG15, LAMP3, RSAD2; or IFI6, IFI44L, ISG15, LAMP3, OASL; or IFI44L, ISG15, LAMP3, OASL, RSAD2; or IFI44L, ISG15, LAMP3, OASL, IFI44; or IFI44L, ISG15, LAMP3, OASL, IFIT2; or IFI44L, ISG15, LAMP3, OASL, OAS3; or IFI44L, ISG15, LAMP3, OASL, USP18; or IFI44L, ISG15, LAMP3, OASL, SIGLEC1; or IFI44L, ISG15, LAMP3, OASL, HERC5; or IFI44L, ISG15, LAMP3, OASL, DNAPTP6; or IFI44L, ISG15, LAMP3, OASL, LOC129607; or IFI44L, ISG15, LAMP3, OASL, EPSTI1; or IFI44L, ISG15, LAMP3, OASL, BIRC4BP; or IFI44L, ISG15, LAMP3, OASL, gene detected by probe 229450_at; or IFI44L, ISG15, LAMP3, OASL, gene detected by probe 235276_at; or ISG15, LAMP3, OASL, RSAD2, IFI44; or ISG15, LAMP3, OASL, RSAD2, IFIT2; or ISG15, LAMP3, OASL, RSAD2, OAS3; or ISG15, LAMP3, OASL, RSAD2, USP18; or ISG15, LAMP3, OASL, RSAD2, SIGLEC1; or ISG15, LAMP3, OASL, RSAD2, HERC5; or ISG15, LAMP3, OASL, RSAD2, DNAPTP6; or ISG15, LAMP3, OASL, RSAD2, LOC129607; or ISG15, LAMP3, OASL, RSAD2, EPSTI1; or ISG15, LAMP3, OASL, RSAD2, BIRC4BP; or ISG15, LAMP3, OASL, RSAD2, gene detected by probe 229450_at; or ISG15, LAMP3, OASL, RSAD2, gene detected by probe 235276_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2; or LAMP3, OASL, RSAD2, IFI44, OAS3; or LAMP3, OASL, RSAD2, IFI44, USP18; or LAMP3, OASL, RSAD2, IFI44, SIGLEC1; or LAMP3, OASL, RSAD2, IFI44, HERC5; or LAMP3, OASL, RSAD2, IFI44, DNAPTP6; or LAMP3, OASL, RSAD2, IFI44, LOC129607; or LAMP3, OASL, RSAD2, IFI44, EPSTI1; or LAMP3, OASL, RSAD2, IFI44, BIRC4BP; or LAMP3, OASL, RSAD2, IFI44, gene detected by probe 229450_at; or LAMP3, OASL, RSAD2, IFI44, gene detected by probe 235276_at; or OASL, RSAD2, IFI44, IFIT2, OAS3; or OASL, RSAD2, IFI44, IFIT2, USP18; or OASL, RSAD2, IFI44, IFIT2, SIGLEC1; or OASL, RSAD2, IFI44, IFIT2, HERC5; or OASL, RSAD2, IFI44, IFIT2, DNAPTP6; or OASL, RSAD2, IFI44, IFIT2, LOC129607; or OASL, RSAD2, IFI44, IFIT2, EPSTI1; or OASL, RSAD2, IFI44, IFIT2, BIRC4BP; or OASL, RSAD2, IFI44, IFIT2, gene detected by probe 229450_at; or OASL, RSAD2, IFI44, IFIT2, gene detected by probe 235276_at; or RSAD2, IFI44, IFIT2, OAS3, USP18; or RSAD2, IFI44, IFIT2, OAS3, SIGLEC1; or RSAD2, IFI44, IFIT2, OAS3, HERC5; or RSAD2, IFI44, IFIT2, OAS3, DNAPTP6; or RSAD2, IFI44, IFIT2, OAS3,

LOC129607; or RSAD2, IFI44, IFIT2, OAS3, EPSTI1; or RSAD2, IFI44, IFIT2, OAS3, BIRC4BP; or RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 229450_at; or RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 235276_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1; or IFI44, IFIT2, OAS3, USP18, HERC5; or IFI44, IFIT2, OAS3, USP18, DNAPTP6; or IFI44, IFIT2, OAS3, USP18, LOC129607; or IFI44, IFIT2, OAS3, USP18, EPSTI1; or IFI44, IFIT2, OAS3, USP18, BIRC4BP; or IFI44, IFIT2, OAS3, USP18, gene detected by probe 229450_at; or IFI44, IFIT2, OAS3, USP18, gene detected by probe 235276_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5; or IFIT2, OAS3, USP18, SIGLEC1, DNAPTP6; or IFIT2, OAS3, USP18, SIGLEC1, LOC129607; or IFIT2, OAS3, USP18, SIGLEC1, EPSTI1; or IFIT2, OAS3, USP18, SIGLEC1, BIRC4BP; or IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 229450_at; or IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 235276_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6; or OAS3, USP18, SIGLEC1, HERC5, LOC129607; or OAS3, USP18, SIGLEC1, HERC5, EPSTI1; or OAS3, USP18, SIGLEC1, HERC5, BIRC4BP; or OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 229450_at; or OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 235276_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607; or USP18, SIGLEC1, HERC5, DNAPTP6, EPSTI1; or USP18, SIGLEC1, HERC5, DNAPTP6, BIRC4BP; or USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 229450_at; or USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 235276_at; or SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1; or SIGLEC1, HERC5, DNAPTP6, LOC129607, BIRC4BP; or SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 229450_at; or SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 235276_at; or HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP; or HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 229450_at; or HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 235276_at; or DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at; or DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 235276_at; or LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at, gene detected by probe 235276_at. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include any at least 6 genes such as, for example: MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI44L; or MX1, LLY6E, IFI27, OAS1, IFIT1, ISG15; or MX1, LLY6E, IFI27, OAS1, IFIT1, LAMP3; or MX1, LLY6E, IFI27, OAS1, IFIT1, OASL; or

MX1, LLY6E, IFI27, OAS1, IFIT1, RSAD2; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI44; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFIT2; or MX1, LLY6E, IFI27, OAS1, IFIT1, OAS3; or MX1, LLY6E, IFI27, OAS1, IFIT1, USP18; or MX1, LLY6E, IFI27, OAS1, IFIT1, SIGLEC1; or MX1, LLY6E, IFI27, OAS1, IFIT1, HERC5; or MX1, LLY6E, IFI27, OAS1, IFIT1, DNAPTP6; or MX1, LLY6E, IFI27, OAS1, IFIT1, LOC129607; or MX1, LLY6E, IFI27, OAS1, IFIT1, EPSTI1; or MX1, LLY6E, IFI27, OAS1, IFIT1, BIRC4BP; or MX1, LLY6E, IFI27, OAS1, IFIT1, gene detected by probe 229450_at; or MX1, LLY6E, IFI27, OAS1, IFIT1, gene detected by probe 235276_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L; or LLY6E, IFI27, OAS1, IFIT1, IFI6, ISG15; or LLY6E, IFI27, OAS1, IFIT1, IFI6, LAMP3; or LLY6E, IFI27, OAS1, IFIT1, IFI6, OASL; or LLY6E, IFI27, OAS1, IFIT1, IFI6, RSAD2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFIT2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, OAS3; or LLY6E, IFI27, OAS1, IFIT1, IFI6, USP18; or LLY6E, IFI27, OAS1, IFIT1, IFI6, SIGLEC1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, HERC5; or LLY6E, IFI27, OAS1, IFIT1, IFI6, DNAPTP6; or LLY6E, IFI27, OAS1, IFIT1, IFI6, LOC129607; or LLY6E, IFI27, OAS1, IFIT1, IFI6, EPSTI1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, BIRC4BP; or LLY6E, IFI27, OAS1, IFIT1, IFI6, gene detected by probe 229450_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, gene detected by probe 235276_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15; or IFI27, OAS1, IFIT1, IFI6, IFI44L, LAMP3; or IFI27, OAS1, IFIT1, IFI6, IFI44L, OASL; or IFI27, OAS1, IFIT1, IFI6, IFI44L, RSAD2; or IFI27, OAS1, IFIT1, IFI6, IFI44L, IFI44; or IFI27, OAS1, IFIT1, IFI6, IFI44L, IFIT2; or IFI27, OAS1, IFIT1, IFI6, IFI44L, OAS3; or IFI27, OAS1, IFIT1, IFI6, IFI44L, USP18; or IFI27, OAS1, IFIT1, IFI6, IFI44L, SIGLEC1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, HERC5; or IFI27, OAS1, IFIT1, IFI6, IFI44L, DNAPTP6; or IFI27, OAS1, IFIT1, IFI6, IFI44L, LOC129607; or IFI27, OAS1, IFIT1, IFI6, IFI44L, EPSTI1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, BIRC4BP; or IFI27, OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 229450_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 235276_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3; or OAS1, IFIT1, IFI6, IFI44L, ISG15, OASL; or OAS1, IFIT1, IFI6, IFI44L, ISG15, RSAD2; or OAS1, IFIT1, IFI6, IFI44L, ISG15, IFI44; or OAS1, IFIT1, IFI6, IFI44L, ISG15, IFIT2; or OAS1, IFIT1, IFI6, IFI44L, ISG15, OAS3; or OAS1, IFIT1, IFI6, IFI44L, ISG15, USP18; or OAS1, IFIT1, IFI6, IFI44L, ISG15, SIGLEC1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, HERC5; or OAS1, IFIT1, IFI6, IFI44L, ISG15, DNAPTP6; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LOC129607; or OAS1, IFIT1, IFI6, IFI44L, ISG15, EPSTI1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, BIRC4BP; or OAS1, IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 229450_at; or OAS1, IFIT1, IFI6, IFI44L,

ISG15, gene detected by probe 235276_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, RSAD2; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, IFI44; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, IFIT2; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OAS3; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, USP18; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, SIGLEC1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, HERC5; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, DNAPTP6; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, LOC129607; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, EPSTI1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, BIRC4BP; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 229450_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 235276_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2; or IFI6, IFI44L, ISG15, LAMP3, OASL, IFI44; or IFI6, IFI44L, ISG15, LAMP3, OASL, IFIT2; or IFI6, IFI44L, ISG15, LAMP3, OASL, OAS3; or IFI6, IFI44L, ISG15, LAMP3, OASL, USP18; or IFI6, IFI44L, ISG15, LAMP3, OASL, SIGLEC1; or IFI6, IFI44L, ISG15, LAMP3, OASL, HERC5; or IFI6, IFI44L, ISG15, LAMP3, OASL, DNAPTP6; or IFI6, IFI44L, ISG15, LAMP3, OASL, LOC129607; or IFI6, IFI44L, ISG15, LAMP3, OASL, EPSTI1; or IFI6, IFI44L, ISG15, LAMP3, OASL, BIRC4BP; or IFI6, IFI44L, ISG15, LAMP3, OASL, gene detected by probe 229450_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, gene detected by probe 235276_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFIT2; or IFI44L, ISG15, LAMP3, OASL, RSAD2, OAS3; or IFI44L, ISG15, LAMP3, OASL, RSAD2, USP18; or IFI44L, ISG15, LAMP3, OASL, RSAD2, SIGLEC1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, HERC5; or IFI44L, ISG15, LAMP3, OASL, RSAD2, DNAPTP6; or IFI44L, ISG15, LAMP3, OASL, RSAD2, LOC129607; or IFI44L, ISG15, LAMP3, OASL, RSAD2, EPSTI1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, BIRC4BP; or IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 229450_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 235276_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2; or ISG15, LAMP3, OASL, RSAD2, IFI44, OAS3; or ISG15, LAMP3, OASL, RSAD2, IFI44, USP18; or ISG15, LAMP3, OASL, RSAD2, IFI44, SIGLEC1; or ISG15, LAMP3, OASL, RSAD2, IFI44, HERC5; or ISG15, LAMP3, OASL, RSAD2, IFI44, DNAPTP6; or ISG15, LAMP3, OASL, RSAD2, IFI44, LOC129607; or ISG15, LAMP3, OASL, RSAD2, IFI44, EPSTI1; or ISG15, LAMP3, OASL, RSAD2, IFI44, BIRC4BP; or ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 229450_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 235276_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3; or LAMP3, OASL, RSAD2, IFI44, IFIT2, USP18; or LAMP3, OASL, RSAD2, IFI44, IFIT2, SIGLEC1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, HERC5;

or LAMP3, OASL, RSAD2, IFI44, IFIT2, DNAPTP6; or LAMP3, OASL, RSAD2, IFI44, IFIT2, LOC129607; or LAMP3, OASL, RSAD2, IFI44, IFIT2, EPSTI1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, BIRC4BP; or LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 229450_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 235276_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18; or OASL, RSAD2, IFI44, IFIT2, OAS3, SIGLEC1; or OASL, RSAD2, IFI44, IFIT2, OAS3, HERC5; or OASL, RSAD2, IFI44, IFIT2, OAS3, DNAPTP6; or OASL, RSAD2, IFI44, IFIT2, OAS3, LOC129607; or OASL, RSAD2, IFI44, IFIT2, OAS3, EPSTI1; or OASL, RSAD2, IFI44, IFIT2, OAS3, BIRC4BP; or OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 229450_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 235276_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1; or RSAD2, IFI44, IFIT2, OAS3, USP18, HERC5; or RSAD2, IFI44, IFIT2, OAS3, USP18, DNAPTP6; or RSAD2, IFI44, IFIT2, OAS3, USP18, LOC129607; or RSAD2, IFI44, IFIT2, OAS3, USP18, EPSTI1; or RSAD2, IFI44, IFIT2, OAS3, USP18, BIRC4BP; or RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 229450_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 235276_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, DNAPTP6; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, LOC129607; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, EPSTI1; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, BIRC4BP; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 229450_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 235276_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, LOC129607; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, EPSTI1; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, BIRC4BP; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 229450_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 235276_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, EPSTI1; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, BIRC4BP; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 229450_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 235276_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, BIRC4BP; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 229450_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 235276_at; or SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP; or SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 229450_at; or

SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 235276_at ; or HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at; or HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 235276_at; or DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at, gene detected by probe 235276_at. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include any at least 7 genes such as, for example: MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, ISG15; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, LAMP3; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, OASL; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, RSAD2; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFIT2; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, OAS3; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, USP18; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, SIGLEC1; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, HERC5; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, DNAPTP6; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, LOC129607; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, EPSTI1; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, BIRC4BP; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, gene detected by probe 229450_at; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, gene detected by probe 235276_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, LAMP3; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, OASL; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, RSAD2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, IFI44; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, IFIT2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, OAS3; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, USP18; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, SIGLEC1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, HERC5; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, DNAPTP6; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, LOC129607; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, EPSTI1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, BIRC4BP; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 229450_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 235276_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, OASL; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, RSAD2; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, IFI44; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, IFIT2; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, OAS3; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, USP18; or IFI27, OAS1, IFIT1,

IFI6, IFI44L, ISG15, SIGLEC1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, HERC5; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, DNAPTP6; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LOC129607; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, EPSTI1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, BIRC4BP; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 229450_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 235276_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, RSAD2; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, IFI44; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, IFIT2; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OAS3; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, USP18; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, SIGLEC1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, HERC5; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, DNAPTP6; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, LOC129607; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, EPSTI1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, BIRC4BP; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 229450_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 235276_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, IFI44; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, IFIT2; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, OAS3; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, USP18; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, SIGLEC1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, HERC5; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, DNAPTP6; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, LOC129607; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, EPSTI1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, BIRC4BP; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, gene detected by probe 229450_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, gene detected by probe 235276_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFIT2; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, OAS3; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, USP18; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, SIGLEC1; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, HERC5; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, DNAPTP6; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, LOC129607; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, EPSTI1; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, BIRC4BP; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 229450_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 235276_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, OAS3; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44,

USP18; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, SIGLEC1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, HERC5; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, DNAPTP6; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, LOC129607; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, EPSTI1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, BIRC4BP; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 229450_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 235276_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, USP18; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, SIGLEC1; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, HERC5; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, DNAPTP6; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, LOC129607; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, EPSTI1; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, BIRC4BP; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 229450_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 235276_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, SIGLEC1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, HERC5; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, DNAPTP6; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, LOC129607; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, EPSTI1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, BIRC4BP; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 229450_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 235276_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, HERC5; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, DNAPTP6; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, LOC129607; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, EPSTI1; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, BIRC4BP; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 229450_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 235276_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, DNAPTP6; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, LOC129607; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, EPSTI1; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, BIRC4BP; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 229450_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 235276_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, LOC129607; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, EPSTI1; or IFI44, IFIT2,

OAS3, USP18, SIGLEC1, HERC5, BIRC4BP; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 229450_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 235276_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, EPSTI1; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, BIRC4BP; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 229450_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 235276_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, BIRC4BP; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 229450_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 235276_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 229450_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 235276_at; or SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at; or SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 235276_at; or HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at, gene detected by probe 235276_at. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include any at least 8 genes such as, for example: MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, LAMP3; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, OASL; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, RSAD2; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, IFI44; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, IFIT2; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, OAS3; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, USP18; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, SIGLEC1; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, HERC5; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, DNAPTP6; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, LOC129607; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, EPSTI1; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, BIRC4BP; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 229450_at; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, gene detected by probe 235276_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3; or LLY6E, IFI27, OAS1, IFIT1, IFI6,

IFI44L, ISG15, OASL; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, RSAD2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, IFI44; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, IFIT2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, OAS3; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, USP18; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, SIGLEC1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, HERC5; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, DNAPTP6; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LOC129607; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, EPSTI1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, BIRC4BP; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 229450_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, gene detected by probe 235276_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, RSAD2; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, IFI44; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, IFIT2; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OAS3; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, USP18; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, SIGLEC1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, HERC5; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, DNAPTP6; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, LOC129607; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, EPSTI1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 229450_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, BIRC4BP; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, gene detected by probe 235276_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, IFI44; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, IFIT2; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, OAS3; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, USP18; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, SIGLEC1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, HERC5; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, DNAPTP6; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, LOC129607; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, EPSTI1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, BIRC4BP; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, gene detected by probe 229450_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, gene detected by probe 235276_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFIT2; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, OAS3; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, USP18; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, SIGLEC1;

or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, HERC5; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, DNAPTP6; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, LOC129607; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, EPSTI1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, BIRC4BP; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 229450_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 235276_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, OAS3; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, USP18; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, SIGLEC1; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, HERC5; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, DNAPTP6; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, LOC129607; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, EPSTI1; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, BIRC4BP; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 229450_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 235276_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, USP18; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, SIGLEC1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, HERC5; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, DNAPTP6; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, LOC129607; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, EPSTI1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, BIRC4BP; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 229450_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 235276_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, SIGLEC1; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, HERC5; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, DNAPTP6; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, LOC129607; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, EPSTI1; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, BIRC4BP; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 229450_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 235276_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, HERC5; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, DNAPTP6; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, LOC129607; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3,

USP18, EPSTI1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, BIRC4BP; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 229450_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 235276_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, DNAPTP6; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, LOC129607; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, EPSTI1; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, BIRC4BP; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 229450_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 235276_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, LOC129607; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, EPSTI1; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 229450_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, BIRC4BP; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 235276_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, EPSTI1; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, BIRC4BP; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 229450_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 235276_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, BIRC4BP; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 229450_at; or IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 235276_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 229450_at; or OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 235276_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at; or USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 235276_at; or SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at, gene detected by probe 235276_at. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include any at least 12 genes such as, for example: MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFIT2; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, OAS3; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, USP18; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, SIGLEC1; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, HERC5; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, DNAPTP6; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, LOC129607; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, EPSTI1; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, BIRC4BP; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 229450_at; or MX1, LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, gene detected by probe 235276_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, OAS3; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, USP18; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, SIGLEC1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, HERC5; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, DNAPTP6; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, LOC129607; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, EPSTI1; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, BIRC4BP; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 229450_at; or LLY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, gene detected by probe 235276_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, USP18; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, SIGLEC1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, HERC5; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, DNAPTP6; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, LOC129607; or IFI27, OAS1, IFIT1, IFI6,

IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, EPSTI1; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, BIRC4BP; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 229450_at; or IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, gene detected by probe 235276_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, SIGLEC1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, HERC5; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, DNAPTP6; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, LOC129607; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, EPSTI1; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, BIRC4BP; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 229450_at; or OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, gene detected by probe 235276_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, HERC5; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, DNAPTP6; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, LOC129607; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, EPSTI1; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, BIRC4BP; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 229450_at; or IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, gene detected by probe 235276_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, DNAPTP6; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, LOC129607; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, EPSTI1; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, BIRC4BP; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 229450_at; or IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, gene detected by probe 235276_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6; or IFI44L, ISG15, LAMP3,

OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, LOC129607; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, EPSTI1; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, BIRC4BP; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 229450_at; or IFI44L, ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, gene detected by probe 235276_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, EPSTI1; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, BIRC4BP; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 229450_at; or ISG15, LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, gene detected by probe 235276_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, BIRC4BP; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 229450_at; or LAMP3, OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, gene detected by probe 235276_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 229450_at; or OASL, RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, gene detected by probe 235276_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at; or RSAD2, IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at; or IFI44, IFIT2, OAS3, USP18, SIGLEC1, HERC5, DNAPTP6, LOC129607, EPSTI1, BIRC4BP, gene detected by probe 229450_at gene detected by probe 235276_at. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL,

CCL2, HERC5, OAS1. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28, and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, EPSTI1, and RSAD2. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes BCL2, BAK1, BAD, BAX, and BCL2L1. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, GIP3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and

IFI27. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30. •

The IFN α -inducible PD markers in an expression profile may include at least genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, LY6E, SIGLEC1, and USP18. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, and IFIT1. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFI6, RSAD2, IFI44, IFI44L, and IFI27. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes IFI27, IL-121R beta2, IL-15R alpha, IL-15, suppressor of cytokine signaling 1 (SOCS1), janus kinase 2, CXCL11 (T-TAC), TNFSF13B (BAFF), TRAF-type domain 1 (TRAFD1), SERPING1, CD274 (PD1-L), indoleamine 2,3 dioxygenase (INDO), lymphocyte-activation gene 3 (LAG3), and caspase 5. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include at least genes complement factor B, insulin-like growth factor (IGF2BP3), cyclin A1, neuropilin 2, complement 1qB, complement 1qC, CD80, CD47, MMP14, toll-like receptor 3 (TLR3), TLR adaptor molecule 2 (TICAM2), macrophage scavenger receptor-1 (MSR1), desmoplakin, PDGR receptor, CCL13 (MCP-4), CXCL13 (BCA-1), CCL19 (CCR7), IL-1 family 5, purinergic receptor P2X7, IRS1, caspase 3, and cyclin-dependent kinase-like 1 (CDKL1). The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include alterations in any one or more of serum protein levels of adiponectin, alpha-fetoprotein, apolipoprotein CIII, beta-2 microglobulin, cancer antigen 125, cancer antigen 19-9, eotaxin, FABP, factor VII, ferritin, IL-10, IL-12p70, IL-16, IL-18, IL-1ra, IL-3, MCP-1, MMP-3, myoglobin, SGOT, tissue factor, TIMP-1, TNF RII, TNF-alpha, VCAM-1, vWF, BDNK, complement 3, CD40 ligand, EGF, ENA-78, EN-RAGE, IGF-1, MDC, myeloperoxidase, RANTES, or thrombopoietin.

The IFN α -inducible PD markers in an expression profile may include alterations in any one or more of serum protein levels of adiponectin, alpha-fetoprotein, apolipoprotein CIII, beta-2 microglobulin, cancer antigen 125, cancer antigen 19-9, eotaxin, FABP, factor VII, ferritin, IL-10, IL-12p70, IL-16, IL-18, IL-1ra, IL-3, MCP-1, MMP-3, myoglobin, SGOT, tissue factor, TIMP-1, TNF RII, TNF-alpha, VCAM-1, or vWF. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed

in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

The IFN α -inducible PD markers in an expression profile may include alterations in any one or more of serum protein levels of BDNK, complement 3, CD40 ligand, EGF, ENA-78, EN-RAGE, IGF-1, MDC, myeloperoxidase, RANTES, or thrombopoietin. The IFN α -inducible PD markers in such an expression profile may further include at least one or more gene listed in Table 19 and/or 20 and/or 21, and/or 22, and/or 23, and/or 24, and/or 26, and/or 28 and/or 30.

An IFN α -inducible PD marker expression profile may further include genes whose expression or activity is down-regulated in cells exposed to non-baseline IFN α levels. The genes whose expression or activity is down-regulated may be any of the genes that are identified in Table 31. The genes may include any one or more of SLC4A1, PRSS33, FCER1A, BACH2, KLRB1, D4S234E, T cell receptor alpha locus/T cell receptor delta locus, FEZ1, AFF3, CD160, ABCB1, PTCH1, OR2W3, IGHD, NOG, NR3C2, TNS1, PDZK1IP1, SH2D1B, STRBP, ZMYND11, TMOD1, FCRLA, DKFZp761P0423, EPB42, NR6A1, LOC341333, MS4A1, IGHM, SIGLECP3, KIR2DS2, PKIA, BLR1, C5orf4, MYLK, LOC283663, MAD1L1, CXCL5, D4S234E, FCRLA, KRT1, c16orf74, ABCB4, or GPRASP1. Any number of these genes may serve as PD markers in an IFN α -inducible PD marker expression profile. For example, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12 at least 15, at least 20, at least 25, at least 30, at least 35, at least 40, at least 45, or at least 50 down-regulated genes may be included in the IFN α -inducible PD marker expression profile. The IFN α -inducible PD marker expression profile may further include genes listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28.

The IFN α -inducible PD marker expression profile may include gene FEZ1, or may include genes FEZ1 and NOG, or may include gene NOG, or may include genes FEZ1, NOG, and SLC4A1, or may include gene SLC4A1, or may include genes NOG and SLC4A1, or may include genes FEZ1, NOG, SLC4A1, and D4S234E, or may include genes FEZ1, NOG, SLC4A1, D4S234E, and PRSS33. The IFN α -inducible PD marker expression profile may further include genes listed in Tables 19 and/or 20 and/or 21 and/or 22 and/or 23 and/or 24 and/or 26 and/or 28 and/or 30, and/or 31.

Down-regulated genes may have down-regulated expression or activity of at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%,

at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% that of control cells, *e.g.*, cells of healthy volunteers or cells of control animals or cells not exposed to IFN α in culture.

Up- or down-regulation of gene expression or activity of IFN α -inducible PD markers may be determined by any means known in the art. For example, up- or down-regulation of gene expression may be detected by determining mRNA levels. mRNA expression may be determined by northern blotting, slot blotting, quantitative reverse transcriptase polymerase chain reaction, or gene chip hybridization techniques. See U.S. Pat. Nos. 5,744,305 and 5,143,854 for examples of making nucleic acid arrays for gene chip hybridization techniques.

Up- or down-regulation of gene expression or activity of IFN α -inducible PD markers may be determined by detecting protein levels. The up- or down-regulated gene whose protein levels are detected may be any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, any twelve, any fifteen, any twenty, any twenty five, any thirty, any thirty five, or more of adiponectin, alpha-fetoprotein, apolipoprotein CIII, beta-2 microglobulin, cancer antigen 125, cancer antigen 19-9, eotaxin, FABP, factor VII, ferritin, IL-10, IL-12p70, IL-16, IL-18, IL-1ra, IL-3, MCP-1, MMP-3, myoglobin, SGOT, tissue factor, TIMP-1, TNF RII, TNF-alpha, VCAM-1, vWF, BDNK, complement 3, CD40 ligand, EGF, ENA-78, EN-RAGE, IGF-1, MDC, myeloperoxidase, RANTES, or thrombopoietin. Methods for detecting protein expression levels include immuno-based assays such as enzyme-linked immunosorbant assays, western blotting, protein arrays, and silver staining.

An IFN α -inducible PD marker expression profile may comprise a profile of protein activity. Up- or down-regulation of gene expression or activity of IFN α -inducible PD markers may be determined by detecting activity of proteins including, but not limited to, detectable phosphorylation activity, de-phosphorylation activity, or cleavage activity. Furthermore, up- or down-regulation of gene expression or activity of IFN α -inducible PD markers may be determined by detecting any combination of these gene expression levels or activities.

A candidate therapeutic for treating IFN α -mediated disorders may be identified by the methods encompassed by the invention. Candidate therapeutics may be any type of molecule including a small molecule or a biological agent. A candidate therapeutic identified by the methods encompassed by the invention may immediately be identified as useful as a therapeutic for a disease, disorder, or condition. Alternatively, a candidate therapeutic identified by the methods encompassed by the invention may need to be further tested and/or

modified before selection for treating patients. Alternatively, a candidate therapeutic identified by the methods encompassed by the invention may, after further testing, be de-selected as a molecule for treating patients.

In methods that identify candidate therapeutics, cells comprising an IFN α -inducible PD marker expression profile are contacted with an agent. The cells may be any type of cells, such as commercially available immortalized cell lines that comprise an IFN α -inducible PD marker expression profile, commercially available immortalized cell lines that have been treated with IFN α to induce an IFN α -inducible PD marker expression profile, cells isolated from a patient having an IFN α -inducible PD marker expression profile, or cells isolated from a healthy patient and treated with IFN α to induce an IFN α -inducible PD marker expression profile.

Presence or absence of a change in the IFN α -inducible PD marker expression profile of the cells is detected following contacting the cells with the agent. Presence of change may be any change in IFN α -inducible PD marker expression profile including at least a 10% decrease in up-regulated expression or activity of at least 1 gene in the IFN α -inducible PD marker expression profile, at least a 20% decrease of the at least 1 up-regulated gene, at least a 30% decrease of the at least up-regulated 1 gene, at least a 40% decrease of the at least 1 up-regulated gene, at least a 50% decrease of the at least 1 up-regulated gene, at least a 60% decrease of the at least 1 up-regulated gene, at least a 70% decrease of the at least 1 up-regulated gene, at least a 75% decrease of the at least 1 up-regulated gene, at least an 80% decrease of the at least 1 up-regulated gene, at least an 85% decrease of the at least 1 up-regulated gene, at least a 90% decrease of the at least 1 up-regulated gene, at least a 95% decrease of the at least 1 up-regulated gene, at least a 96% decrease of the at least 1 up-regulated gene, at least a 97% decrease of the at least 1 up-regulated gene, at least a 98% decrease of the at least 1 up-regulated gene, at least a 99% decrease of the at least 1 up-regulated gene, or a 100% decrease of the at least 1 up-regulated gene. Alternatively, or in addition, presence of change may be any change in IFN α -inducible PD marker expression profile including at least a 10% increase in expression or activity of at least 1 down-regulated gene in the IFN α -inducible PD marker expression profile, at least a 20% increase of the at least 1 down-regulated gene, at least a 30% increase of the at least 1 down-regulated gene, at least a 40% increase of the at least 1 down-regulated gene, at least a 50% increase of the at least 1 down-regulated gene, at least a 60% increase of the at least 1 down-regulated gene, at least a 70% increase of the at least 1 down-regulated gene, at least a 75% increase of the at least 1 down-regulated gene, at least an 80% increase of the at least 1 down-regulated gene, at

least an 85% increase of the at least 1 down-regulated gene, at least a 90% increase of the at least 1 down-regulated gene, at least a 95% increase of the at least 1 down-regulated gene, at least a 96% increase of the at least 1 down-regulated gene, at least a 97% increase of the at least 1 down-regulated gene, at least a 98% increase of the at least 1 down-regulated gene, at least a 99% increase of the at least 1 down-regulated gene, or a 100% increase of the at least 1 down-regulated gene.

In methods of monitoring disease progression of a patient samples from the patient may be obtained before and after administration of an agent, *e.g.*, an agent that binds to and modulates type I IFN or IFN α activity, or an agent that binds to and does not modulate type I IFN or IFN α activity, or a combination of agents that may or may not include an agent that binds to and modulates type I IFN or IFN α activity. Type I IFN or IFN α inducible PD marker expression profiles are obtained in the (before and after agent administration) samples. The type I IFN or IFN α inducible PD marker expression profiles in the samples are compared. Comparison may be of the number of type I IFN or IFN α inducible PD markers present in the samples or may be of the quantity of type I IFN or IFN α inducible PD markers present in the samples, or any combination thereof. Variance indicating efficacy of the therapeutic agent may be indicated if the number or level (or any combination thereof) of up-regulated type I IFN or IFN α inducible PD markers decreases in the sample obtained after administration of the therapeutic agent relative to the sample obtained before administration of the therapeutic agent. The number of up-regulated type I IFN or IFN α inducible PD markers may decrease by at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10. The level of any given up-regulated type I IFN or IFN α inducible PD marker may decrease by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. The number of up-regulated type I IFN or IFN α inducible PD markers with decreased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35. Any combination of decreased number and decreased level of up-regulated type I IFN or IFN α inducible PD markers may indicate efficacy. Variance indicating efficacy of the therapeutic agent may be indicated if the number or level (or any combination thereof) of down-regulated type I IFN or IFN α inducible PD markers decreases in the sample obtained after administration of the therapeutic agent relative to the sample obtained before administration of the therapeutic agent. The number of down-regulated type I IFN or IFN α inducible PD markers may decrease by at least 1, at least 2, at least 3, at least 4, at least 5, at

least 6, at least 7, at least 8, at least 9, or at least 10. The level of any given down-regulated type I IFN or IFN α inducible PD marker may increase by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. The number of down-regulated type I IFN or IFN α inducible PD markers with increased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35. Any combination of decreased number and increased level of down-regulated type I IFN or IFN α inducible PD markers may indicate efficacy.

The sample obtained from the patient may be obtained prior to a first administration of the agent, *i.e.*, the patient is naïve to the agent. Alternatively, the sample obtained from the patient may occur after administration of the agent in the course of treatment. For example, the agent may have been administered prior to the initiation of the monitoring protocol. Following administration of the agent an additional samples may be obtained from the patient and type I IFN or IFN α inducible PD markers in the samples are compared. The samples may be of the same or different type, *e.g.*, each sample obtained may be a blood sample, or each sample obtained may be a serum sample. The type I IFN or IFN α inducible PD markers detected in each sample may be the same, may overlap substantially, or may be similar.

The samples may be obtained at any time before and after the administration of the therapeutic agent. The sample obtained after administration of the therapeutic agent may be obtained at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, or at least 14 days after administration of the therapeutic agent. The sample obtained after administration of the therapeutic agent may be obtained at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 weeks after administration of the therapeutic agent. The sample obtained after administration of the therapeutic agent may be obtained at least 2, at least 3, at least 4, at least 5, or at least 6 months following administration of the therapeutic agent.

Additional samples may be obtained from the patient following administration of the therapeutic agent. At least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 15, at least 20, at least 25 samples may be obtained from the patient to monitor progression or regression of the disease or disorder over time. Disease progression may be monitored over a time period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, at least 5 years, at least 10 years, or

over the lifetime of the patient. Additional samples may be obtained from the patient at regular intervals such as at monthly, bi-monthly, once a quarter year, twice a year, or yearly intervals. The samples may be obtained from the patient following administration of the agent at regular intervals. For instance, the samples may be obtained from the patient at one week following each administration of the agent, or at two weeks following each administration of the agent, or at three weeks following each administration of the agent, or at one month following each administration of the agent, or at two months following each administration of the agent. Alternatively, multiple samples may be obtained from the patient following an or each administration of the agent.

Disease progression in a patient may similarly be monitored in the absence of administration of an agent. Samples may periodically be obtained from the patient having the disease or disorder. Disease progression may be identified if the number of type I IFN or IFN α inducible PD markers increases in a later-obtained sample relative to an earlier obtained sample. The number of type I IFN or IFN α inducible PD markers may increase by at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10. Disease progression may be identified if level of any given up-regulated type I IFN or IFN α inducible PD marker increases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. Disease progression may be identified if level of any given down-regulated type I IFN or IFN α inducible PD marker decreases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. The number of up-regulated type I IFN or IFN α inducible PD markers with increased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35. The number of down-regulated type I IFN or IFN α inducible PD markers with decreased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35. Any combination of increased number and increased level of up-regulated type I IFN or IFN α inducible PD marker may indicate disease progression. Alternatively, or in combination, any combination of decreased number and decreased level of down-regulated type I IFN or IFN α inducible PD marker may indicate disease progression. Disease regression may also be identified in a patient having a disease or disorder, not treated by an agent. In this instance, regression may be identified if the number of type I IFN or IFN α inducible PD markers decreases in a later-obtained sample relative to an earlier obtained

sample. The number of type I IFN or IFN α inducible PD markers may decrease by at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10. Disease regression may be identified if level of any given up-regulated type I IFN or IFN α inducible PD marker decreases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. Disease regression may be identified if level of any given down-regulated type I IFN or IFN α inducible PD marker increases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. The number of up-regulated type I IFN or IFN α inducible PD markers with decreased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35. The number of down-regulated type I IFN or IFN α inducible PD markers with increased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20, at least 25, at least 30, or at least 35. Disease progression or disease regression may be monitored by obtaining samples over any period of time and at any interval. Disease progression or disease regression may be monitored by obtaining samples over the course of at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, at least 5 years, at least 10 years, or over the lifetime of the patient. Disease progression or disease regression may be monitored by obtaining samples at least monthly, bi-monthly, once a quarter year, twice a year, or yearly. The samples need not be obtained at strict intervals.

The invention also encompasses kits and probes. The probes may be any molecule that detects any expression or activity of any gene that may be included in an IFN α -inducible PD marker expression profile.

The invention also encompasses methods of detecting IFN activity. These methods may employ cells comprising a polynucleotide sequence comprising a reporter gene under the control of an interferon-stimulated response element. The cells comprising the polynucleotide sequence may be any cells amenable to transfection or transformation with a polynucleotide sequence and that can be maintained in culture. These cells include animal cells, bacterial cells, yeast cells, insect cells, or plant cells. These cells may be adherent or may grow in suspension. If the cells are animal cells, they may be from a known cell line such as HeLa, COS, NIH3T3, AGS, 293, CHO, Huh-7, HUVEC, MCF-7, C6, BHK-21, BNL

CL 2, C2C12, HepG2, and ATDC5. Countless other cell lines are known and can be obtained by those of skill in the art. The cells may alternatively be primary cells that have or have not been immortalized.

The cells may comprise a polynucleotide sequence comprising a reporter gene under the control of an interferon-stimulated response element. The polynucleotide sequence may be stably integrated in the DNA of the cell or may be an extrachromosomal element that is stably or transiently in the cell. The polynucleotide may have been introduced to the cell as a naked polynucleotide molecule, a polynucleotide molecule complexed with lipids or other molecules, or a polynucleotide in a virus particle.

If the polynucleotide was introduced as a naked polynucleotide molecule, the polynucleotide may have been a linear or a circular molecule. Non-limiting examples of circular polynucleotide molecules include plasmids, and artificial chromosomes. These vectors may be cleaved with enzymes, for example, to generate linear polynucleotide molecules.

Furthermore, if the polynucleotide was introduced as a naked polynucleotide it may have been introduced into the cells by any of many well known techniques in the art. These techniques include, but are not limited to, electroporation, microinjection, and biolistic particle delivery. See, also, *e.g.*, Loeffler and Behr, 1993, *Meth. Enzymol.* 217:599-618; Cohen *et al.*, 1993, *Meth. Enzymol.* 217:618-644; *Clin. Pharma. Ther.* 29:69-92 (1985), Sambrook, *et al. Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989 and Ausubel *et al.*, ed. *Current Protocols in Molecular Biology*, John Wiley & Sons, Inc., N.Y., N.Y. (1987-2001).

If the polynucleotide was introduced as a complex with lipids or liposomes, it too may have been introduced by one of many known techniques to the skilled artisan. Lipids or liposomes comprise a mixture of fat particles or lipids which bind to DNA or RNA to provide a hydrophobic coated delivery vehicle. Suitable liposomes may comprise any of the conventional synthetic or natural phospholipid liposome materials including phospholipids from natural sources such as egg, plant or animal sources such as phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, sphingomyelin, phosphatidylserine or phosphatidylinositol. Synthetic phospholipids also may be used, *e.g.*, dimyristoylphosphatidylcholine, dioleoylphosphatidylcholine, dioleoylphosphatidylcholine and corresponding synthetic phosphatidylethanolamines and phosphatidylglycerols. Lipids

or liposomes that may be conjugated with the vector are also commercially available to the skilled artisan. Examples of commercially available lipid or liposome transfection reagents known to those of skill in the art include LIPOFECTAMINE™ (Invitrogen), GENEJUICE® (Novagen), GENEJAMMER® (Stratagene), FUGENE® HD (Roche), MEGAFECTIN™ (Qbiogene), SUPERFECT® (Qiagen), and EFFECTENE® (Qiagen).

If the polynucleotide was introduced as a complex with other molecules it may have been compacted or in a nanosphere. Compacted polynucleotide complexes are described in U.S. Patents 5,972,901, 6,008,336, and 6,077,835. Nanospheres are described in U.S. Patent Nos. 5,718,905 and 6,207,195. These compacted polynucleotide complexes and nanospheres that complex nucleic acids utilize polymeric cations. Typical polymeric cations include gelatin, poly-L-lysine, and chitosan. Alternatively, the polynucleotide may have been complexed with DEAE-dextran, or transfected using techniques such as calcium phosphate coprecipitation, or calcium chloride coprecipitation.

If the polynucleotide was introduced associated with a virus, the virus may have been any well known suitable virus for polynucleotide delivery. Example viruses that may be used as vectors include adenovirus, adeno-associated virus, lentivirus, retrovirus, herpes virus (*e.g.* herpes simplex virus), vaccinia virus, papovirus, Sendai virus, SV40 virus, respiratory syncytial virus, etc.

The polynucleotide sequence may include a reporter gene and an interferon-stimulated response element. The reporter gene may be any one of luciferase, chloramphenicol acetyl transferase, β -galactosidase, green fluorescent protein, β -glucuronidase, or secreted placental alkaline phosphatase. Variations of many of these reporter genes, *e.g.*, green fluorescent protein and luciferase, are known and can be readily identified and/or produced by those of skill in the art. Other reporter genes in addition to those listed will also be known to those of skill in the art and are readily available. Interferon-stimulated response elements are also known to those of skill in the art. They may be obtained from commercial vendors such as Stratagene, Clontech, and Biomyx. They have also been reported in, for instance, Alcantara *et al.* (*Nuc. Acid. Res.* 30 (2002):2068-2075 and Kirchhoff *et al.* (*Oncogene* 18 (1999):3725-3736).

The cells employed in the assay may be incubated with a sample. The sample may be obtained from a patient, from a vendor with patient samples, or a control sample used for calibration or as a control. If the sample is obtained from a patient it may be any biological fluid or tissue, such as whole blood, saliva, urine, synovial fluid, bone marrow, cerebrospinal

fluid, nasal secretions, sputum, amniotic fluid, bronchoalveolar lavage fluid, peripheral blood mononuclear cells, total white blood cells, lymph node cells, spleen cells, tonsil cells, or skin.

Expression of the reporter gene is detected by any well known means in the art. The expression, even if "0" indicates IFN activity in the sample. One of skill in the art may further quantitate any level of expression of the reporter gene which may then correlate to level of IFN activity in the sample.

Applicants provide a set of non-limiting embodiments to describe some of the aspects of the invention.

Embodiments

Embodiment 1. A method of treating a patient having a type I IFN or an IFN α -mediated disease or disorder comprising:

administering an agent that binds to and modulates type I IFN or IFN α activity;
wherein the patient comprises a type I IFN or IFN α -inducible PD marker expression profile;
and wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Embodiment 2. The method of 1 further comprising detecting neutralization of the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Embodiment 3. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1 IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

Embodiment 4. The method of embodiment 1 wherein the agent is a biologic agent.

Embodiment 5. The method of embodiment 4 wherein the agent is an antibody.

Embodiment 6. The method of embodiment 5 wherein the antibody is MEDI-545.

Embodiment 7. The method of embodiment 5 wherein the antibody is specific for one or more type I IFN or IFN α subtype but is not MEDI-545.

Embodiment 8. The method of embodiment 1 wherein the administering the agent alleviates one or more symptoms of the disease or disorder.

Embodiment 9. The method of embodiment 5 wherein the antibody is administered at a dose between approximately .03 and 30 mg/kg.

Embodiment 10. The method of embodiment 9 wherein the antibody is administered at a dose between 0.3 and 3 mg/kg.

Embodiment 11. The method of embodiment 10 wherein the antibody is administered at a dose between .03 and 1 mg/kg.

Embodiment 12. The method of any one of embodiments 9-11 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 10%.

Embodiment 13. The method of embodiment 12 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 20%.

Embodiment 14. The method of embodiment 13 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 30%.

Embodiment 15. The method of embodiment 14 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 40%.

Embodiment 16. The method of embodiment 15 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 50%.

Embodiment 17. The method of embodiment 1 wherein the type I IFN or an IFN α -mediated disease or disorder is one of lupus, psoriasis, vasculitis, sarcoidosis, Sjogren's syndrome, or idiopathic inflammatory myositis.

Embodiment 18. The method of embodiment 17 wherein the type I IFN or an IFN α -mediated disease or disorder is lupus.

Embodiment 19. The method of embodiment 17 wherein the type I IFN or an IFN α -mediated disease or disorder is psoriasis.

Embodiment 20. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of at least IFN α subtypes 1, 2, 8, and 14.

Embodiment 21. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises transcripts of PD marker genes.

Embodiment 22. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises polypeptides expressed from PD marker genes.

Embodiment 23. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27,

SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1

Embodiment 24. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2

Embodiment 25. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 26. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 27. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 28. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 29. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPPI, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 30. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 31. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 32. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

Embodiment 33. The method of embodiment 32 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes MX1 and IFIT1.

Embodiment 34. The method of embodiment 33 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes OAS2 and OAS1.

Embodiment 35. The method of any one of embodiments 3 or 23-33 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

Embodiment 36. The method of embodiment 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

Embodiment 37. The method of embodiment 22 wherein the polypeptides are detected at increased levels in serum.

Embodiment 38. The method of embodiment 37 wherein polypeptides include cancer antigen 125, ferritin, tissue factor, and MMP-3.

Embodiment 39. The method of embodiment 22 wherein the polypeptides are detected at decreased levels in serum.

Embodiment 40. The method of embodiment 39 wherein the polypeptides include EGF, thrombopoietin, and CD40 ligand.

Embodiment 41. A method of treating an autoimmune disease patient comprising a moderate or strong type I IFN or an IFN α PD marker profile comprising:

administering an agent that binds to and modulates type I IFN or IFN α activity;

wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Embodiment 42. The method of 41 further comprising detecting neutralization of the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Embodiment 43. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

Embodiment 44. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1

Embodiment 45. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2

Embodiment 46. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 47. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 48. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 49. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 50. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 51. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 52. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 53. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, and IFI27.

Embodiment 54. The method of embodiment 53 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes MX1 and IFIT1.

Embodiment 55. The method of embodiment 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of at least IFN α subtypes 1, 2, 8, and 14.

Embodiment 56. The method of embodiment 41 wherein the agent is a biologic agent.

Embodiment 57. The method of embodiment 41 wherein the agent is an antibody.

Embodiment 58. The method of embodiment 57 wherein the antibody is MEDI-545.

Embodiment 59. The method of embodiment 57 wherein the antibody is specific for one or more type I IFN or IFN α subtype but is not MEDI-545.

Embodiment 60. The method of embodiment 41 wherein the administering the agent alleviates one or more symptoms of the disease or disorder.

Embodiment 61. The method of embodiment 57 wherein the antibody is administered at a dose between approximately .03 and 30 mg/kg.

Embodiment 62. The method of embodiment 57 wherein the antibody is administered at a dose between 0.3 and 3 mg/kg.

Embodiment 63. The method of embodiment 57 wherein the antibody is administered at a dose between .03 and 1 mg/kg.

Embodiment 64. The method of embodiment 41 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 10%.

Embodiment 65. The method of embodiment 64 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 20%.

Embodiment 66. The method of embodiment 65 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 30%.

Embodiment 67. The method of embodiment 66 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 40%.

Embodiment 68. The method of embodiment 67 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 50%.

Embodiment 69. The method of embodiment 41 wherein the autoimmune disease patient is a lupus, psoriasis, vasculitis, sarcoidosis, Sjogren's syndrome, or idiopathic inflammatory myositis patient.

Embodiment 70. The method of embodiment 69 wherein the patient is a lupus patient.

Embodiment 71. The method of embodiment 69 wherein the patient is a psoriasis patient.

Embodiment 72. A method of neutralizing a type I IFN or IFN α -inducible PD marker expression profile in a patient in need thereof, comprising:

administering an agent that binds to and modulates type I IFN or IFN α activity to the patient;

wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Embodiment 73. The method of 72 further comprising detecting neutralization of the type I IFN or IFN α -inducible PD marker expression profile of the patient.

Embodiment 74. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1 IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

Embodiment 75. The method of embodiment 72 wherein the agent is a biologic agent.

Embodiment 76. The method of embodiment 75 wherein the agent is an antibody.

Embodiment 77. The method of embodiment 76 wherein the antibody is MEDI-545.

Embodiment 78. The method of embodiment 76 wherein the antibody is specific for one or more type I IFN or IFN α subtype but is not MEDI-545.

Embodiment 79. The method of embodiment 72 wherein the administering the agent alleviates one or more symptoms of the disease or disorder.

Embodiment 80. The method of embodiment 76 wherein the antibody is administered at a dose between approximately .03 and 30 mg/kg.

Embodiment 81. The method of embodiment 80 wherein the antibody is administered at a dose between 0.3 and 3 mg/kg.

Embodiment 82. The method of embodiment 81 wherein the antibody is administered at a dose between .03 and 1 mg/kg.

Embodiment 83. The method of any one of embodiments 80-82 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 10%.

Embodiment 84. The method of embodiment 83 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 20%.

Embodiment 85. The method of embodiment 84 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient at least 30%.

Embodiment 86. The method of embodiment 85 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient at least 40%.

Embodiment 87. The method of embodiment 86 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient at least 50%.

Embodiment 88. The method of embodiment 72 wherein the patient is a lupus, psoriasis, vasculitis, sarcoidosis, Sjogren's syndrome, or idiopathic inflammatory myositis patient.

Embodiment 89. The method of embodiment 88 wherein the patient is a lupus patient.

Embodiment 90. The method of embodiment 88 wherein the patient is a psoriasis patient.

Embodiment 91. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of at least IFN α subtypes 1, 2, 8, and 14.

Embodiment 92. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises transcripts of PD marker genes.

Embodiment 93. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises polypeptides expressed from PD marker genes.

Embodiment 94. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

Embodiment 95. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

Embodiment 96. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 97. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, GIP3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 98. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes

LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 99. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 100. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 101. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 102. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 103. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

Embodiment 104. The method of embodiment 103 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes MX1 and IFIT1.

Embodiment 105. The method of any one of embodiments 74 or 94-104 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

Embodiment 106. The method of embodiment 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

Embodiment 107. The method of embodiment 93 wherein the polypeptides are detected at increased levels in serum.

Embodiment 108. The method of embodiment 107 wherein polypeptides include cancer antigen 125, ferritin, tissue factor, and MMP-3.

Embodiment 109. The method of embodiment 93 wherein the polypeptides are detected at decreased levels in serum.

Embodiment 110. The method of embodiment 109 wherein the polypeptides include EGF, thrombopoietin, and CD40 ligand.

Embodiment 111. A method of monitoring or prognosing autoimmune disease progression of a patient comprising:

obtaining a first IFN α -inducible PD marker expression profile in a first sample from a patient.

Embodiment 112. The method of embodiment 111 wherein the first IFN α -inducible PD marker expression profile is a strong profile and the patient prognosis is disease progression.

Embodiment 113. The method of embodiment 112 wherein the autoimmune disease is SLE and the progression is an SLE flare.

Embodiment 114. The method of embodiment 111 wherein the first IFN α -inducible PD marker expression profile is a weak profile and the patient prognosis is disease regression.

Embodiment 115. The method of embodiment 111 further comprising:

obtaining a second IFN α -inducible PD marker expression profile in a second sample from a patient;

wherein an increase in number or level of type I IFN or IFN α inducible PD markers in the second relative to the first expression profile prognoses disease progression; or

wherein a decrease in number or level of type I IFN or IFN α inducible PD markers in the second relative to the first expression profile prognoses disease regression.

Embodiment 116. A method of monitoring disease progression of a patient receiving treatment with a therapeutic agent that binds to and modulates IFN α activity comprising:

obtaining a first IFN α -inducible PD marker expression profile in a first sample from the patient;

administering a therapeutic agent that binds to and modulates IFN α activity;

obtaining a second IFN α -inducible PD marker expression profile in a second sample from the patient; and

comparing the first and the second IFN α -inducible PD marker expression profiles,

wherein a variance in the first and the second IFN α -inducible PD marker expression profiles indicates a level of efficacy of the therapeutic agent that binds to and modulates IFN α activity.

Embodiment 117. The method of embodiment 116 wherein the first IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44

Embodiment 118. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

Embodiment 119. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

Embodiment 120. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 121. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 122. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1,

MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 123. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 124. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 125. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 126. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 127. The method of embodiment 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

Embodiment 128. The method of embodiment 116 wherein the variance is a decrease in up-regulated expression or activity levels of the genes.

Embodiment 129. The method of embodiment 116 wherein the disease is lupus, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, sarcoidosis, and psoriasis.

Embodiment 130. The method of embodiment 131 wherein the disease is lupus.

Embodiment 131. The method of embodiment 116 wherein the therapeutic agent is a small molecule or a biologic agent.

Embodiment 132. The method of embodiment 131 wherein the biologic agent is an antibody.

Embodiment 133. The method of embodiment 132 wherein the antibody is MEDI-545.

Embodiment 134. The method of embodiment 116 wherein the first IFN α -inducible PD marker expression profile is obtained prior to administration of the therapeutic agent.

Embodiment 135. The method of embodiment 116 wherein the first IFN α -inducible PD marker expression profile is obtained at the time of administration of the therapeutic agent.

Embodiment 136. The method of embodiment 116 wherein the first and the second sample are whole blood or serum.

Embodiment 137. The method of embodiment 116 further comprising obtaining a third IFN α -inducible PD marker expression profile in a third sample from the patient.

Embodiment 138. The method of 137 further comprising obtaining a fourth IFN α -inducible PD marker expression profile in a fourth sample from the patient.

Embodiment 139. The method of 138 further comprising obtaining a fifth IFN α -inducible PD marker expression profile in a fifth sample from the patient.

Embodiment 140. The method of 139 further comprising obtaining a sixth IFN α -inducible PD marker expression profile in a sixth sample from the patient.

Embodiment 141. The method of 116 wherein the second sample is obtained at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following administration of the therapeutic agent.

Embodiment 142. The method of 137 wherein the third sample is obtained at least 2 days, at least 5 days, at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following obtaining the second sample.

Embodiment 143. The method of 138 wherein the fourth sample is obtained at least 2 days, at least 5 days, at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following obtaining the third sample.

Embodiment 144. The method of 139 wherein the fifth sample is obtained at least 2 days, at least 5 days, at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following obtaining the fourth sample.

Embodiment 145. The method of embodiment 116 wherein variance is a decrease in up-regulated expression or activity of the gene.

Embodiment 146. The method of embodiment 145 wherein the decrease is at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%.

Embodiment 147. A method of identifying a patient as a candidate for a therapeutic agent that binds to and modulates IFN α activity comprising:

detecting presence or absence of an IFN α -inducible PD marker expression profile in a sample from the patient,

wherein detecting presence of the IFN α -induced PD marker expression profile identifies the patient as a candidate for the therapeutic agent that binds to and modulates IFN α activity.

Embodiment 148. The method of embodiment 147 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

Embodiment 149. The method of embodiment 147 wherein type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

Embodiment 150. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

Embodiment 151. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 152. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, GIP3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 153. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 154. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 155. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 156. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 157. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 158. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

Embodiment 159. The method of embodiment 147 wherein the patient has been diagnosed as having a disorder selected from the group consisting of lupus, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, sarcoidosis, and psoriasis.

Embodiment 160. The method of embodiment 159 wherein the disorder is lupus.

Embodiment 161. The method of embodiment 147 wherein the therapeutic agent is a small molecule or a biologic agent.

Embodiment 162. The method of embodiment 161 wherein the biologic agent is an antibody.

Embodiment 163. The method of embodiment 162 wherein the antibody is MEDI-545.

Embodiment 164. The method of any one of embodiments 148-158 wherein the up-regulated expression or activity comprises at least a 2-fold increase in expression of one or more of the genes.

Embodiment 165. The method of any one of embodiments 148-158 wherein the up-regulated expression or activity comprises at least a 3-fold increase in expression of one or more of the genes.

Embodiment 166. The method of any one of embodiments 148-158 wherein the up-regulated expression or activity comprises an increase in mRNA levels of one or more of the genes.

Embodiment 167. The method of any one of embodiments 148-158 wherein the up-regulated expression or activity comprises an increase in protein levels of one or more of the genes.

Embodiment 168. The method of any one of embodiments 148-158 wherein the up-regulated expression or activity comprises an increase in enzymatic activity of a protein expressed from one or more of the genes.

Embodiment 169. The method of embodiment 147 wherein the sample is whole blood.

Embodiment 170. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

Embodiment 171. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises increased serum levels of polypeptides cancer antigen 125, ferritin, tissue factor, and MMP-3.

Embodiment 172. The method of embodiment 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises decreased serum levels of polypeptides EGF, thrombopoietin, and CD40 ligand.

Embodiment 173. A method of diagnosing a patient as having a disorder associated with increased IFN α levels comprising:

detecting presence or absence of an IFN α -inducible PD marker expression profile in a sample from the patient,

wherein detecting presence of the IFN α -induced PD marker expression profile identifies the patient as having a disorder associated with increased IFN α levels.

Embodiment 174. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

Embodiment 175. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

Embodiment 176. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

Embodiment 177 The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 178. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 179. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 180. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 181. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 182. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 183. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 184. The method of embodiment 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

Embodiment 185. The method of embodiment 173 wherein the disorder is lupus, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, sarcoidosis, or psoriasis.

Embodiment 186. The method of embodiment 185 wherein the disorder is lupus.

Embodiment 187. The method of any one of embodiments 174-184 wherein the up-regulated expression or activity comprises at least a 2-fold increase in expression or activity of one or more of the genes.

Embodiment 188. The method of embodiment 187 wherein the up-regulated expression or activity comprises at least a 3-fold increase in expression or activity of one or more of the genes.

Embodiment 189. The method of any one of embodiments 174-184 wherein the up-regulated expression or activity comprises an increase in mRNA levels of one or more of the genes.

Embodiment 190. The method of any one of embodiments 174-184 wherein the up-regulated expression or activity comprises an increase in protein levels of one or more of the genes.

Embodiment 191. The method of any one of embodiments 174-184 wherein the up-regulated expression or activity comprises an increase in enzymatic activity of a protein expressed from one or more of the genes.

Embodiment 192. The method of any one of embodiments 174-184 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOGSLC4A1, PRSS33, and FEZ1.

Embodiment 193. The method any one of embodiments 174-184 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises increased serum levels of polypeptides cancer antigen 125, ferritin, tissue factor, and MMP-3.

Embodiment 194. The method of any one of embodiments 174-184 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises decreased serum levels of polypeptides EGF, thrombopoietin, and CD40 ligand.

Embodiment 195. A method of identifying a candidate therapeutic for treating IFN α -mediated disorders comprising:

contacting cells comprising an IFN α -inducible PD marker expression profile with an agent; and

detecting presence or absence of a change in the IFN α -induced PD marker expression profile of the cells,

wherein the presence of a change comprising a reduction in the up-regulation of the genes of the IFN α -inducible PD marker expression profile indicates the agent is a candidate therapeutic agent.

Embodiment 196. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

Embodiment 197. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, and OAS1.

Embodiment 198. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

Embodiment 199 The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

Embodiment 200. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

Embodiment 201. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

Embodiment 202. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

Embodiment 203. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 204. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

Embodiment 205. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

Embodiment 206. The method of embodiment 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

Embodiment 207. The method of embodiment 195 wherein the cells obtained from a patient comprising a disorder associated with increased IFN α levels.

Embodiment 208. The method of embodiment 195 wherein the cells are cells treated with IFN α to induce the IFN α -inducible PD marker expression profile.

Embodiment 209. The method of embodiment 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile is at least a 2-fold increase in expression of one or more of the genes of the profile.

Embodiment 210. The method of embodiment 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile is at least a 3-fold increase in expression of one or more of the genes of the IFN α -inducible PD marker expression profile.

Embodiment 211. The method of embodiment 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile comprises an increase in mRNA levels of one or more of the genes of the IFN α -inducible PD marker expression profile.

Embodiment 212. The method of embodiment 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile comprises an increase in protein levels of one or more of the genes of the IFN α -inducible PD marker expression profile.

Embodiment 213. The method of embodiment 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile comprises an increase in enzymatic activity of a protein expressed from one or more of the genes of the IFN α -inducible PD marker expression profile.

Embodiment 214. The method of any one of embodiments 196-206 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOGSLC4A1, PRSS33, and FEZ1; and

wherein the presence of a change comprising an increase in expression or activity of the down-regulated genes indicates the agent is a candidate therapeutic agent.

Embodiment 215. The method of any one of embodiments 196-206 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises increased serum levels of polypeptides cancer antigen 125, ferritin, tissue factor, and MMP-3; and

wherein the presence of a change comprising a decrease in serum levels of the polypeptide indicates the agent is a candidate therapeutic agent.

Embodiment 216. The method of any one of embodiments 196-206 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises decreased serum levels of polypeptides EGF, thrombopoietin, and CD40 ligand

wherein the presence of a change comprising an increase in serum levels of the polypeptide indicates the agent is a candidate therapeutic agent.

Embodiment 217. A set of probes comprising:

polynucleotides that specifically detect expression of any one of the sets of genes:

- (a) MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44; or
- (b) IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1; or
- (c) IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2; or
- (d) SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1; or
- (e) RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15; or
- (f) LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27; or
- (g) DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18; or
- (h) SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1; or
- (i) SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1; or
- (j) IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18; or
- (k) IFI6, RSAD2, IFI44, IFI44L, and IFI27; or
- (l) NOGSLC4A1, PRSS33, and FEZ1.

Embodiment 218. A kit comprising any of the set of probes recited in embodiment 217.

Embodiment 219. A method of detecting IFN activity in a sample comprising:

incubating cells comprising a polynucleotide sequence comprising a reporter gene under the control of an interferon-stimulated response element with a sample; and
detecting expression of the reporter gene,
wherein expression of the reporter gene indicates IFN activity in the sample.

Embodiment 220. The method of embodiment 219 wherein cells are HEK293H cells.

Embodiment 221. The method of embodiment 219 wherein the reporter gene is luciferase, chloramphenicol acetyl transferase, β -galactosidase, green fluorescent protein, β -glucuronidase, or secreted placental alkaline phosphatase.

Embodiment 222. The method of embodiment 221 wherein the reporter gene is luciferase.

Embodiment 223. The method of embodiment 222 wherein the luciferase is *Gaussia princeps* luciferase.

Embodiment 224. The method of embodiment 219 further comprising quantitating level of expression of the reporter gene.

Embodiment 225. The method of embodiment 224 further comprising correlating the level of expression of the reporter gene to level of IFN activity in the sample.

All publications, patents and patent applications mentioned in this specification are herein incorporated by reference into the specification to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference.

This application claims the benefit of priority of U.S. Provisional Application Serial No. 60/873,008 filed December 6, 2006, U.S. Provisional Application Serial No. 60/907,762 filed April 16, 2007, U.S. Provisional Application Serial No. 60/924,219 filed May 3, 2007, U.S. Provisional Application Serial No. 60/924,584 filed May 21, 2007, U.S. Provisional Application Serial No. 60/960,187 filed September 19, 2007, and U.S. Provisional Application Serial No. 60/996,176 filed November 5, 2007, herein incorporated by reference for all purposes. This application also claims the benefit of priority of U.S. Provisional Application Serial No. 60/924,220 filed May 3, 2007, U.S. Provisional Application entitled "Auto-Antibody Markers of Autoimmune Disease" filed November 6, 2007 (Attorney docket no. 1A201P2), and U.S. Provisional Application entitled "Auto-Antibody Markers of Autoimmune Disease" filed December 6, 2007 (Attorney docket no. 1A201P3), herein incorporated by reference for all purposes. This application further claims the benefit of

priority of U.S. Provisional Application Serial No. 60/907,767 filed April 16, 2007, U.S. Provisional Application Serial No. 60/996,174 filed November 5, 2007, and PCT application entitled "Methods of Treating Systemic Lupus Erythematosus", filed December 6, 2007 (Attorney docket no. IA210PCT), herein incorporated by reference for all purposes.

The set of examples that follow are provided for the purpose of illustration only and the invention should in no way be construed as being limited to these examples.

EXAMPLES

Example 1a: Initial Identification of Up-Regulated Genes in Lupus Patients

Gene expression in whole blood of 5 (2 cutaneous and 3 severe) lupus patients and 5 healthy volunteers was profiled using Affymetrix whole genome array technology and qPCR validation. Gene expression fold-change values were determined by calculating the $\log_2$ signal intensity difference between individual lupus patient samples and the mean $\log_2$ signal intensity for the 5 healthy donor samples. 118 genes were identified as up-regulated by at least 2-fold in whole blood of all 5 lupus patients relative to the healthy volunteers.

Table 1 provides a summary for 71 of the 118 annotated genes identified as up-regulated by at least 2-fold in all 5 lupus patients. Table 2 provides the fold-up-regulation in gene expression for a subset of the 118 genes for each of the five lupus patients relative to the healthy volunteers. Table 2 also provides a comparison between fold-change values determined on two unique platforms (Affy GeneChip and TaqMan (i.e. qPCR)).

Table 1: Genes Identified as Up-Regulated at Least 2-Fold in Whole Blood of Lupus Patients

Probe_ID	UniGene	Gene Title	Gene Sym	Gene Ontology	Bi	Gene Ontic	Gene Ontic Pathway	Avg. Norma	Avg. SLE	LE	Avg. t	p value	35SRH	Avg. 199R	Avg. 26CR	Avg. 33XR	Avg.
223674_s	222065	CDC42 small effector 1	CDC42SE	7165 // signal tran	5886 // pla	5095 // GT	---	2.355	6.012	3.657	1.20E-05	2.787	4.166	4.429	3.165	3.737	
204415_at	523847	interferon, alpha-inducible G1P3	6955 // immune re	16021 // in	---	---	---	6.515	9.733	3.218	0.018746	1.626	1.102	2.325	5.854	5.183	
228220_at	165762	FCH domain only 2	FCHO2	---	---	---	---	4.381	7.361	2.980	0.023153	4.085	2.810	1.084	2.995	3.928	
226312_at	407926	TORC2-specific protein A'AVO3	---	---	---	5488 // bin	---	7.034	9.818	2.784	0.025167	3.163	2.487	1.045	3.274	3.953	
215245_x	103183	fragile X mental retardatio	FMR1	6397 // mRNA pro	5625 // coi	3723 // RN	---	8.070	8.828	2.758	0.032436	3.156	2.255	1.234	3.377	3.767	
202194_at	482873	transmembrane, emp24 p	TMED5	6886 // intracellule	5783 // en	6320 // pro	---	6.365	9.084	2.699	0.065615	3.433	2.392	1.051	2.553	4.064	
226641_at	432706	Ankyrin repeat domain 44	LOC91526	---	---	---	---	7.476	10.170	2.694	0.030007	3.184	2.337	1.070	2.878	4.001	
212585_at	430849	oxysterol binding protein-	OSBPL8	6869 // lipid trans	---	---	---	8.182	10.818	2.636	0.028512	3.093	2.358	1.163	2.445	4.120	
201237_at	446123	capping protein (actin fila	CAPZA2	6461 // protein coi	8290 // F-	3779 // act	---	6.438	9.060	2.622	0.026777	3.338	2.289	1.004	2.644	3.836	
226934_at	369606	Cleavage and polyadenyl	CPSF6	6397 // mRNA pro	5634 // nuc	166 // nuc	---	5.619	8.241	2.622	0.007781	2.441	2.553	1.672	2.505	3.940	
203983_at	96247	translin-associated factor	TSNAX	---	5634 // nuc	3677 // DN	---	5.522	8.141	2.619	0.018885	2.958	2.306	1.051	2.878	3.900	
221428_s	439970	transducin (beta)-like 1X	ITBL1XR1	6350 // transcripti	5634 // nuc	---	---	5.859	8.427	2.568	0.017844	3.004	2.258	1.524	2.398	3.654	
215838_at	512233	leukocyte immunoglobulin	LILRA5	---	---	---	---	6.847	9.190	2.543	0.000349	2.071	2.399	2.263	2.840	3.144	
209884_s	250072	solute carrier family 4, so	SLC4A7	6820 // anion tran	16020 // m	5452 // ino	---	4.525	7.088	2.543	0.006683	2.579	2.292	1.432	2.495	3.918	
222605_at	356399	REST corepressor 3	RCOR3	45449 // regulatio	5634 // nuc	3677 // DN	---	5.249	7.775	2.526	0.032918	2.965	1.850	1.330	2.689	3.796	
202304_at	508010	fibronectin type III domain	FNDC3A	---	---	---	---	4.793	7.288	2.475	0.014487	3.070	2.013	1.088	2.686	3.510	
212579_at	8118	structural maintenance of	SMCHD1	51276 // chromos	5694 // chi	5515 // pro	---	8.996	11.436	2.440	0.014165	2.930	2.037	1.088	3.002	3.143	
208783_s	510402	membrane cofactor protein	MCP	6955 // immune re	5886 // pla	4872 // rec	---	8.996	11.431	2.435	0.033522	3.161	2.327	1.100	2.518	3.068	
1555643_s	512233	leukocyte immunoglobulin	LILRA5	---	---	---	---	6.942	9.367	2.426	0.001163	2.004	2.163	1.967	2.854	3.140	
226617_at	470233	ADP-ribosylation factor-1	ARL5	6886 // intracellule	---	166 // nuc	---	4.385	6.781	2.395	0.07287	2.903	1.994	1.025	2.486	3.570	
229584_at	187636	leucine-rich repeat kinase	LRRK2	6468 // protein am	---	4672 // pro	---	8.541	10.926	2.385	0.008927	2.872	1.812	1.216	2.938	3.087	
211967_at	503705	pro-oncogene receptor indu	PORIN1	---	16021 // in	4872 // rec	---	8.522	10.735	2.383	0.032836	2.049	1.805	1.025	2.397	3.640	
212192_at	109438	potassium channel tetran	KCTD12	6813 // potassium	8076 // volt	5249 // volt	---	8.386	10.763	2.377	0.040801	2.993	1.615	1.076	2.365	3.838	
208719_s	528305	DEAD (Asp-Glu-Ala-Asp)	DDX17	6396 // RNA proc	5634 // nuc	186 // nuc	---	4.196	6.546	2.349	0.009291	1.614	4.874	1.826	2.018	1.416	
209884_s	250072	myristoylated alanine-rich	MARCKS	6928 // cell motil	5886 // pla	5516 // cal	---	8.155	10.888	2.333	0.007603	2.738	2.177	1.128	3.141	2.479	
222572_at	22265	protein phosphatase 2C	PPM2C	6470 // protein am	5739 // mit	287 // mag	Krebs-TCA	5.335	7.684	2.329	0.069262	2.681	1.957	1.016	2.279	3.712	
212195_at	532082	Interleukin 6 signal trans	IL6ST	6955 // immune re	5886 // pla	4872 // rec	Ribosomal	8.733	11.015	2.382	0.006803	2.104	2.242	1.440	2.020	3.605	
226711_at	458478	human T-cell leukemia vir	HTLF	6350 // transcripti	5634 // nuc	3700 // tra	---	7.581	8.959	2.278	0.016463	2.791	1.734	1.043	2.440	3.384	
222846_at	389733	RAB8B, member RAS on	RAB8B	6886 // intracellule	---	166 // nuc	---	5.584	7.857	2.273	0.044318	2.897	1.665	1.193	2.829	2.779	
203566_s	904	lamylo-1, 6-glucosidase,	LAGL	5975 // carbohydi	43033 // is	4134 // 4-g	Glycogen	4.862	7.131	2.269	0.041967	2.283	1.758	1.057	2.579	3.668	
203564_x	405410	O-linked N-acetylglucosa	OGT	6493 // protein am	5634 // nuc	3677 // sin	---	6.919	9.156	2.236	0.004017	2.212	2.086	1.479	2.355	3.048	
219237_s	512743	DnaJ (Hsp40) homolog,	DNABJ14	6457 // protein fol	---	31072 // hi	---	6.022	8.229	2.207	0.004813	2.454	1.832	1.172	2.322	3.253	
214403_at	567255	far upstream element (FUF)	UBP1	6350 // transcripti	5634 // nuc	3677 // sin	---	5.205	7.403	2.198	0.007941	1.994	1.644	1.199	2.491	3.661	
218589_at	123464	purinergic receptor P2Y,	P2RY5	7165 // signal tran	16021 // in	1584 // the	GPCRDB	6.422	8.576	2.154	0.011493	2.263	1.396	1.174	1.868	4.067	
217941_s	519346	erbB2 interacting protein	ERBB2IP	7049 // cell cycle	5634 // nuc	5176 // Eit	---	7.497	9.837	2.140	0.020564	2.313	2.026	1.112	2.354	2.895	
203603_s	34871	zinc finger homeobox 1b	ZFXH1B	6355 // regulation	5634 // nuc	3700 // tra	TGF_Beta	4.781	6.915	2.134	0.021477	2.750	1.278	1.039	2.257	3.346	
213111_at	173939	phosphatidylinositol-3-ph	PIP5K3	7242 // intracellule	45121 // li	5515 // pro	---	5.914	8.033	2.119	0.013802	2.394	1.869	1.048	2.315	2.968	
213070_at	175343	Phosphoinositide-3-kinas	PIK3C2A	6661 // phosphati	5634 // nuc	3700 // tra	Inositol ph	4.886	6.996	2.111	0.043279	2.405	1.654	1.103	1.921	3.472	
218041_x	221847	solute carrier family 38, s	SLC38A2	6865 // amino acid	16020 // m	5279 // am	---	7.527	9.629	2.102	0.023894	2.417	1.890	1.140	1.927	3.136	
202033_s	196102	RB1-inducible coiled-coil	RB1CC1	6350 // transcripti	5634 // nuc	16301 // ki	---	7.096	9.178	2.082	0.018164	2.798	1.406	1.272	2.225	2.709	
200603_at	280342	protein kinase, cAMP-de	PRKAR1A	6357 // regulation	5952 // ca	166 // nuc	G-Protein	9.293	11.373	2.080	0.030496	2.651	2.062	1.004	2.031	2.653	
228996_at	495097	ring finger and CCHC-tyr	RC3H1	16567 // protein ut	151 // ubiq	3723 // RN	---	4.366	6.436	2.070	0.004022	3.253	1.738	1.435	1.897	2.026	
1554479_s	446146	caspase recruitment dom	CARD8	42981 // regulatio	5634 // nuc	5515 // pro	---	7.947	10.012	2.065	0.023092	2.558	1.733	1.054	2.133	2.848	
203031_at	492120	inositol(myo)- (for 4-mo)	IMPA1	5975 // carbohydi	---	287 // mag	Sireptomyl	5.383	7.442	2.059	0.043964	2.487	1.447	1.001	2.187	3.173	
223940_x	187199	metastasis associated li	MALAT1	---	---	---	---	4.166	6.212	2.046	0.003564	2.139	1.026	1.120	2.671	3.273	
222317_at	445711	Phosphodiesterase 3B, c	PDE3B	7165 // signal tran	16020 // m	4119 // cG	---	4.840	6.865	2.025	0.021022	2.593	1.664	1.155	1.901	2.812	
228157_at	500775	zinc finger protein 207	ZNF207	6355 // regulation	5634 // nuc	3700 // tra	---	6.352	8.371	2.019	0.043641	2.300	1.363	1.074	2.263	3.094	
221505_at	385913	acidic (leucine-rich) nucle	ANP32E	---	5634 // nuc	19212 // pl	---	7.489	9.501	2.012	0.057164	2.070	1.656	1.053	2.251	3.028	
1554472_s	304362	PHD finger protein 20-like	PHF20L1	6355 // regulation	---	5515 // pro	---	4.062	6.074	2.012	0.000292	2.270	1.460	1.355	2.254	2.718	
226345_at	25362	ADP-ribosylation factor-1	ARL8	6886 // intracellule	---	166 // nuc	---	5.050	7.057	2.007	0.034947	2.308	1.707	1.169	1.898	2.953	
224862_at	269782	Guanine nucleotide bindi	GNAO1	6471 // protein am	5737 // cyt	166 // nuc	G-Protein	6.663	8.665	2.002	0.046272	2.679	1.850	1.194	1.605	2.682	
207387_s	1466	glycerol kinase	GK	5975 // carbohydi	5737 // cyt	166 // nuc	Glycerolip	6.577	8.565	1.987	0.00655	2.663	1.071	1.146	2.292	2.765	
222633_at	438970	transducin (beta)-like 1X	ITBL1XR1	6350 // transcripti	5634 // nuc	---	---	5.358	7.324	1.968	3.89E-05	2.171	1.460	1.799	1.689	2.711	
236224_at	491234	Ras-like without CAAX 1	RIT1	6886 // intracellule	5886 // pla	166 // nuc	---	5.105	7.064	1.960	0.018708	2.825	2.017	1.110	2.178	1.669	
203080_s	470369	bromodomain adjacent to	BAZ2B	6350 // transcripti	5634 // nuc	3677 // DN	---	7.254	9.212	1.959	0.008344	2.597	1.166	1.051	2.058	2.921	
222587_s	127407	UDP-N-acetyl-alpha-D-ga	GALNT7	5975 // carbohydi	5795 // Go	4653 // pol	O-Glycan	4.095	6.038	1.944	0.006624	2.585	1.283	1.121	2.393	2.336	
235057_at	472505	itchy homolog E3 ubiquit	ITCH	1558 // regulation	5634 // nuc	3677 // DN	---	3.238	5.161	1.923	0.001003	1.885	1.781	1.343	1.272	3.337	
1554154_s	310809	ganglioside induced differ	GDAP2	---	---	---	---	4.572	6.484	1.922	0.001031	2.092	1.729	1.615	1.761	2.413	
226444_at	413434	Solute carrier family 39 (z	SLC39A10	300001 // metal ion	5634 // nuc	3676 // nuc	---	5.668	7.583	1.915	0.024435	1.542	1.861	1.070	1.880	3.221	
204646_at	335034	dihydropyrimidine dehydro	DPYD	6118 // electron tr	5737 // cyt	4152 // di	Pyrimidine	7.632	9.545	1.913	0.049699	2.268	1.489	1.263	1.806	2.719	
205321_at	539684	eukaryotic translation init	EIF2S3	6412 // protein bio	5843 // cyt	166 // nuc	Translation	6.682	8.563	1.881	0.030696	2.094	2.213	1.758	1.309	2.030	
202165_at	535731	protein phosphatase 1, re	PPP1R2	5975 // carbohydi	---	4865 // typ	---	5.590	7.464	1.874	0.064575	2.078	1.532	1.055	1.763	2.943	
201668_x	519909	myristoylated alanine-rich	MARCKS	6928 // cell motil	5886 // pla	5515 // cal	---	4.137	5.987	1.850	0.001437	2.370	1.760	1.413	2.538	1.170	
213701_at	494204	hypothetical protein DKF	DKFZp434	---	---	---	---	3.954	5.802	1.848	0.044061	1.883	1.388	1.137	1.485	3.345	
201110_s	164226	thrombospondin 1	THBS1	6928 // cell motil	5576 // ext	4866 // enr	TGF_Beta	4.265	6.106	1.841	0.000653	1.953	1.964	1.018	2.122	2.149	
224800_at	368359	WD repeat and FYVE do	WDFY1	---	5634 // nuc	5545 // ph	---	6.372	8.193	1.820	0.027641	2.080	1.251	1.067	2.247	2.457	
2183																	

Table 2: Up-Regulation in Gene Expression for a Set of Genes for each of Five Lupus Patients

Probe_ID	Gene Symbol	I29KHR.SLE (TaqMan)	I29KHR.S LE (Affy)	RH33XR.SLE (TaqMan)	RH33XR.S LE (Affy)	J9SSR (Ta	OJ9SSR (A	4499R (Ta	4499R (A	I26CR(Ta	I26CR(A
228220_at	FCHO2	3.24	39.86	3.30	76.15	33.05	84.86	22.36	35.07	17.77	10.61
205483_s_at	G1P3	86.13	146.74	80.55	92.15	4.45	7.83	2.90	5.45	5.06	12.71
212195_at	IL6ST	3.87	9.18	3.63	27.52	6.60	9.73	4.95	10.70	2.35	6.14
203275_at	IRF2	8.10	6.46	5.00	4.80	5.07	6.54	4.12	4.32	2.44	4.66
1555643_s_at	LILRA5	16.43	12.00	27.25	14.64	11.22	6.66	6.82	7.44	4.86	6.49
205170_at	STAT2	11.55	8.67	9.74	2.25	8.08	2.16	6.37	2.92	4.12	2.62

Example 1a: Validation of Genes Identified as Up-Regulated Genes in Lupus Patients

To further identify candidate PD markers for anti-IFN- α mAb clinical trials in SLE, the Affymetrix Human Genome U133 Plus 2.0 GeneChip[®] array platform was used to profile WB from 46 SLE patients and WB from 24 age- and sex-matched healthy donors. It was observed that 245 and 77 probe sets were upregulated and downregulated, respectively, in WB of SLE patients compared with that from healthy control donors.

Of the 245 probe sets upregulated in WB of SLE patients, 114 were type I IFN inducible. Table 30 lists the 50 most upregulated probe sets in WB of these SLE patients; 76% of them are type I IFN inducible. Table 30 also lists the prevalence of the overexpression of these genes in WB of SLE patients. The majority of these genes are overexpressed by at least 2-fold in 65% to 80% of the patients profiled. The robust and prevalent overexpression of a large number of type I IFN-inducible genes in SLE patients suggests that they might be suitable PD markers for clinical trials that investigate an anti-IFN- α mAb therapy for SLE.

Table 30: 50 most upregulated probe sets in whole blood of SLE patients

Probe ID	Gene Title	Gene Symbol	log ₂ fc	q Value (FDR)	Prevalence
202411_at	interferon, alpha-inducible protein 27	IFI27	4.60	8.41E-07	73.91
219519_s_at	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1	3.52	7.28E-07	65.22
214059_at	Interferon-induced protein 44	IFI44	3.51	8.04E-07	73.91
213797_at	radical S-adenosyl methionine domain containing 2	RSAD2	3.29	9.86E-06	71.74
204415_at	interferon, alpha-inducible protein 6	IFI6	3.21	2.25E-09	82.61
242625_at	radical S-adenosyl methionine domain containing 2	RSAD2	3.19	1.55E-06	69.57
204439_at	interferon-induced protein 44-like	IFI44L	3.14	4.99E-06	71.74
219211_at	ubiquitin specific peptidase 18	USP18	2.84	2.23E-06	67.39
214453_s_at	interferon-induced protein 44	IFI44	2.72	1.07E-05	71.74
202145_at	lymphocyte antigen 6 complex, locus E	LY6E	2.53	7.28E-07	63.04
207329_at	matrix metalloproteinase 8 (neutrophil collagenase)	MMP8	2.51	0.00111	60.87
202869_at	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	2.33	1.66E-06	69.57
222154_s_at	DNA polymerase-transactivated protein 6	DNAPT6	2.32	1.14E-05	65.22
44673_at	sialic acid binding Ig-like lectin 1,	SIGLEC1	2.31	2.23E-06	58.70

	sialoadhesin				
242234_at	XIAP associated factor-1	BIRC4BP	2.31	8.41E-07	65.22
203153_at	interferon-induced protein with tetratricopeptide repeats 1	IFIT1	2.25	9.53E-05	67.39
218400_at	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	2.24	1.23E-05	67.39
212768_s_at	olfactomedin 4	OLFM4	2.23	0.00608	60.87
241869_at	apolipoprotein L, 6	APOL6	2.22	0.00045	80.43
235643_at	sterile alpha motif domain containing 9-like	SAMD9L	2.22	1.37E-06	84.78
231688_at	Transcribed locus	---	2.22	0.00248	63.04
208470_s_at	haptoglobin /// haptoglobin-related protein	HP /// HPR	2.20	2.48E-05	80.43
239979_at	Epithelial stromal interaction 1 (breast)	EPSTI1	2.20	5.44E-06	65.22
206697_s_at	haptoglobin	HP	2.19	2.96E-05	73.91
205552_s_at	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	2.18	4.98E-07	65.22
205483_s_at	ISG15 ubiquitin-like modifier	ISG15	2.16	2.73E-06	65.22
227609_at	epithelial stromal interaction 1 (breast)	EPSTI1	2.15	4.99E-06	67.39
1555643_s_at	leukocyte immunoglobulin-like receptor, subfamily A	LILRA5	2.14	8.41E-07	76.09
222816_s_at	zinc finger, CCHC domain containing 2	ZCCHC2	2.09	5.43E-05	80.43
205569_at	lysosomal-associated membrane protein 3	LAMP3	2.08	2.74E-06	65.22
226702_at	hypothetical protein LOC129607	LOC129607	2.07	5.96E-05	67.39
215838_at	leukocyte immunoglobulin-like receptor, subfamily A	LILRA5	2.07	1.87E-05	71.74
219863_at	hect domain and RLD 5	HERC5	2.03	1.53E-05	67.39
204747_at	interferon-induced protein with tetratricopeptide repeats 3	IFIT3	2.01	1.55E-06	67.39
200986_at	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	SERPING1	1.98	0.00013	67.39
224225_s_at	ets variant gene 7 (TEL2 oncogene)	ETV7	1.98	2.48E-05	58.70
219684_at	receptor (chemosensory) transporter protein 4	RTP4	1.96	2.74E-06	63.04
206133_at	XIAP associated factor-1	BIRC4BP	1.96	7.28E-07	65.22
206871_at	elastase 2, neutrophil	ELA2	1.95	0.00316	54.35
217502_at	interferon-induced protein with tetratricopeptide repeats 2	IFIT2	1.95	4.86E-06	71.74
237340_at	solute carrier family 26, member 8	SLC26A8	1.93	6.68E-06	60.87
235276_at	---	---	1.93	6.44E-06	65.22
203757_s_at	carcinoembryonic antigen-related cell adhesion molecule 6	CEACAM6	1.91	0.00124	47.83
202086_at	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse) /// myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1	1.90	2.66E-05	67.39
241916_at	Phospholipid scramblase 1	PLSCR1	1.89	4.86E-06	73.91
203595_s_at	interferon-induced protein with tetratricopeptide repeats 5	IFIT5	1.89	2.81E-08	69.57
205660_at	2'-5'-oligoadenylate synthetase-like	OASL	1.89	1.94E-05	65.22
219352_at	hect domain and RLD 6	HERC6	1.87	9.79E-06	63.04
211657_at	carcinoembryonic antigen-related cell adhesion molecule 6	CEACAM6	1.86	0.00667	60.87
228439_at	basic leucine zipper transcription factor, ATF-like 2	BATF2	1.86	2.63E-05	63.04

Data were generated from 46 SLE patients and 24 healthy controls using SAM and FDR in R (see Methods). Type I IFN-inducible genes are highlighted in bold. FDR=false discovery rate; SAM=significance analysis of microarrays; SLE=systemic lupus erythematosus; WB=whole blood.

Figure 80 (top panel) shows a heat map of the expression of the 114 upregulated type I IFN-inducible probe sets in SLE patients and healthy controls. A total of 32/46 of the SLE patients profiled showed significant overexpression of the type I IFN gene signature. To confirm the observation that type I IFN-inducible genes are overexpressed in WB of SLE patients, WB was procured from 54 SLE patients in a prospective study. Figure 81A shows the PCA plot of the 46 SLE patients in the first study using the 114 overexpressed type I IFN-inducible probes. A clear difference was observed between SLE patients that had distinct overexpression of type I IFN gene signature from healthy donors and SLE patients that had weak or nondetectable type I IFN gene signature in WB. Figure 81B shows the PCA plot from the 54 SLE patients in the prospective study using the same 114 type I IFN-inducible probe sets identified. A similar separation of SLE patients was observed based on type I IFN gene signature as in Figure 81A. The distribution of the type I IFN gene signature scores in the prospective study was also similar to that of the first study (data not shown). The ability to use the overexpressed type I IFN-inducible genes identified to segregate SLE patients into 2 distinct groups—patients with or without type I IFN gene signature—validated the accurate identification of overexpression in the type I IFN gene signature in WB of SLE patients.

In addition to the overexpression of a type I IFN gene signature, the overexpression of a gene signature that is indicative of granulocyte activation in WB of SLE patients was observed. The granulocyte gene signature included (but was not limited to) the following genes: AZU, DEFA1, DEFA4, ELA2, MMP8, MMP9, RNAS2, MPO, CAMP, FCAR, and CYBB (Figure 80, second panel). The granulocyte gene signature was present in about 50% of the SLE patients profiled.

The 50 most downregulated probe sets observed in WB of SLE patients are shown in Table 31. The downregulation of T, NK, and B cell gene signatures was observed in WB of SLE patients (Figure 80, panels three, four, and five, respectively); this is in agreement with the observation of lymphopenia in SLE patients previously reported in the literature (Bennett L, Palucka AK, Arce E *et al.*: Interferon and granulopoiesis signatures in systemic lupus erythematosus blood. *J Exp Med.* 197(6), 711-723 (2003), Rivero SJ, Diaz-Jouanen E and Alarcon-Segovia D: Lymphopenia in systemic lupus erythematosus. Clinical, diagnostic, and prognostic significance. *Arthritis Rheum.* 21(3), 295-305 (1978).

Table 31: Top 50 most downregulated transcripts in whole blood of SLE patients

Probe ID	Gene Title	Gene Symbol	log ₂ fc	q Value (FDR)	Prevalence
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1552713_a_at	solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)	SLC4A1	-1.82	0.00021	69.57
1552348_at	protease, serine, 33	PRSS33	-1.71	0.00046	63.04
211734_s_at	Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide /// Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide	FCER1A	-1.59	0.00083	54.35
236307_at	BTB and CNC homology 1, basic leucine zipper transcription factor 2	BACH2	-1.51	0.00012	54.35
214470_at	killer cell lectin-like receptor subfamily B, member 1 /// killer cell lectin-like receptor subfamily B, member 1	KLRB1	-1.50	0.00000	58.70
209570_s_at	DNA segment on chromosome 4 (unique) 234 expressed sequence	D4S234E	-1.46	0.00000	65.22
217143_s_at	T cell receptor alpha locus /// T cell receptor delta locus	TRA@ /// TRD@	-1.38	0.00001	58.70
203562_at	fasciculation and elongation protein zeta 1 (zygin I)	FEZ1	-1.36	0.00028	89.13
227198_at	AF4/FMR2 family, member 3	AFF3	-1.35	0.00046	45.65
207840_at	CD160 molecule	CD160	-1.34	0.00079	47.83
232286_at	AF4/FMR2 family, member 3	AFF3	-1.34	0.00003	56.52
209993_at	ATP-binding cassette, sub-family B (MDR/TAP), member 1	ABCB1	-1.32	0.00002	63.04
209815_at	patched homolog 1 (Drosophila)	PTCH1	-1.29	0.00003	54.35
241881_at	olfactory receptor, family 2, subfamily W, member 3	OR2W3	-1.29	0.01736	50.00
213674_x_at	immunoglobulin heavy constant delta	IGHD	-1.29	0.01801	50.00
231798_at	Noggin	NOG	-1.28	0.00234	73.91
239673_at	Nuclear receptor subfamily 3, group C, member 2	NR3C2	-1.27	0.00004	56.52
221748_s_at	tensin 1 /// tensin 1	TNS1	-1.23	0.00953	50.00
218864_at	tensin 1	TNS1	-1.22	0.00718	50.00
219630_at	PDZK1 interacting protein 1	PDZK1IP1	-1.20	0.00528	56.52
1553177_at	SH2 domain containing 1B	SH2D1B	-1.20	0.00187	47.83
229513_at	Spermatid perinuclear RNA binding protein	STRBP	-1.20	0.00017	58.70
243054_at	Zinc finger, MYND domain containing 11	ZMYND11	-1.20	0.00101	60.87
236796_at	BTB and CNC homology 1, basic leucine zipper transcription factor 2	BACH2	-1.20	0.00004	56.52
203661_s_at	tropomodulin 1	TMOD1	-1.19	0.00675	50.00
239278_at	CDNA clone IMAGE:5301129	---	-1.17	0.00002	65.22
235400_at	Fc receptor-like A	FCRLA	-1.17	0.00099	52.17
240690_at	Homolog of rat pragma of Rnd2	DKFZp761P0423	-1.17	0.00012	52.17
210746_s_at	erythrocyte membrane protein band 4.2 /// erythrocyte membrane protein band 4.2	EPB42	-1.16	0.00552	45.65
232478_at	Nuclear receptor subfamily 6, group	NR6A1	-1.15	0.00004	47.83

	A, member 1				
243810_at	Similar to Heterogeneous nuclear ribonucleoprotein A1 (Helix-destabilizing protein) (Single-strand RNA-binding protein) (hnRNP core protein A1)	LOC341333	-1.15	0.00014	47.83
228599_at	membrane-spanning 4-domains, subfamily A, member 1	MS4A1	-1.14	0.00454	45.65
212827_at	immunoglobulin heavy constant mu /// immunoglobulin heavy constant mu	IGHM	-1.14	0.00324	45.65
1552349_a_at	protease, serine, 33	PRSS33	-1.13	0.02357	47.83
216191_s_at	T cell receptor alpha locus /// T cell receptor delta locus /// B-cell CLL/lymphoma 11B (zinc finger protein)	TRA@ /// TRD@ /// BCL11B	-1.12	0.01073	50.00
232686_at	sialic acid binding Ig-like lectin, pseudogene 3	SIGLECP3	-1.12	0.00003	58.70
211532_x_at	killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 2	KIR2DS2	-1.10	0.04011	54.35
1563217_at	Protein kinase (cAMP-dependent, catalytic) inhibitor alpha	PKIA	-1.10	0.00024	58.70
243798_at	Burkitt lymphoma receptor 1, GTP binding protein (chemokine (C-X-C motif) receptor 5)	BLR1	-1.10	0.00044	54.35
220751_s_at	chromosome 5 open reading frame 4	C5orf4	-1.09	0.00531	50.00
202555_s_at	myosin, light chain kinase /// myosin, light chain kinase	MYLK	-1.09	0.00149	52.17
230245_s_at	hypothetical protein LOC283663	LOC283663	-1.09	0.00977	47.83
233921_s_at	MAD1 mitotic arrest deficient-like 1 (yeast)	MAD1L1	-1.08	0.00001	41.30
214974_x_at	chemokine (C-X-C motif) ligand 5	CXCL5	-1.08	0.00717	54.35
209569_x_at	DNA segment on chromosome 4 (unique) 234 expressed sequence	D4S234E	-1.08	0.00005	58.70
235401_s_at	Fc receptor-like A	FCRLA	-1.08	0.00173	50.00
205900_at	keratin 1 (epidermolytic hyperkeratosis)	KRT1	-1.08	0.04518	43.48
242509_at	Chromosome 16 open reading frame 74	C16orf74	-1.08	0.00016	47.83
209994_s_at	ATP-binding cassette, sub-family B (MDR/TAP), member 1 /// ATP-binding cassette, sub-family B (MDR/TAP), member 4	ABCB1 /// ABCB4	-1.08	0.00000	56.52
204793_at	G protein-coupled receptor associated sorting protein 1	GPRASP1	-1.08	0.00026	45.65

Data were generated from 46 SLE patients and 24 healthy controls using SAM and FDR in R (see Methods). FDR=false discovery rate; SLE=systemic lupus erythematosus; SAM=significance analysis of microarrays; WB=whole blood.

To further confirm the observation of overexpression of the type I IFN and granulocyte signatures and to identify other signaling pathways that may be altered in SLE, a pathway and network analysis was carried out with GeneGo software (see Methods). Overall, for SLE, this pathway analysis confirmed the activation of the type I IFN pathway, along

with the activation of a granulocyte signature, and the underexpression of the T-cell signaling pathway. Additionally, in the patients profiled, the activation of the IL-10 signaling pathway was among the other notable pathways found to be altered. This may suggest B cell activation and be indicative of the abnormal apoptosis of T-cell subsets observed in SLE patients. (Diaz-Alderete A, Crispin JC, Vargas-Rojas MI and Alcocer-Varela J: IL-10 production in B cells is confined to CD154+ cells in patients with systemic lupus erythematosus. *J Autoimmun.* 23(4), 379-383 (2004), Wang H, Xu J, Ji X *et al.*: The abnormal apoptosis of T cell subsets and possible involvement of IL-10 in systemic lupus erythematosus. *Cell Immunol.* 235(2), 117-121 (2005)).

Confirmation of overexpression of type I IFN-inducible genes: To confirm the overexpression of type I IFN-inducible genes in SLE that were observed in the microarray analyses, a BioMark™ 48.48 dynamic array was used to perform high throughput (HTP) TaqMan QRT-PCR on 40 of the type I IFN-inducible genes (selected based on their magnitude and prevalence of overexpression in whole blood of SLE patients). TaqMan QRT-PCR assays confirmed the overexpression of all 40 genes in whole blood of 35 of the originally profiled 46 SLE patients. The overexpression of 15 of the 40 type I IFN-inducible genes using TaqMan assays is shown in Figure 83A. These genes were upregulated by an average of 8- to 92-fold, and all were significantly overexpressed ($P < 0.05$). These observations provide evidence that type I IFN-inducible genes are significantly overexpressed in SLE patients. The consistency of the results among microarray and TaqMan assays and the strong correlation (correlation coefficient > 0.98) between microarray and TaqMan assays for 21 IFN-inducible genes in 2 example SLE patients (Figures 83B and 4C) argues for their potential as PD and diagnostic markers in clinical trials that investigate anti-IFN- α approaches in the treatment of SLE.

Example 2: Potential PD Markers Selected from Genes Up-Regulated in Lupus Patients

Using the whole genome profiling data described in Example 1a, a group of candidate PD markers were selected. These candidate markers are provided in Table 3.

Table 3: Candidate PD markers

Probe_ID	Gene Symbol	Group
204415_at	HERC5	1
202411_at	IFI27	1
214453_s_at	IFI44	1
229450_at	IFIT3	1
1555643_s_at	LILRA5	1
205483_s_at	G1P2	1
204439_at	IFI44L	1
203153_at	IFIT1	1
202145_at	LY6E	1
202869_at	OAS1	1
218400_at	OAS3	1
242625_at	RSAD2	1
228220_at	FCHO2	2
205483_s_at	G1P3	2
212195_at	IL6ST	2
203275_at	IRF2	2
1555643_s_at	LILRA5	2
205170_at	STAT2	2
208436_s_at	IRF7	3
211967_at	PORIMIN	3
226312_at	AVO3	3
201669_s_at	MARCKS	3
222846_at	RAB8B	3

Example 3: Candidate PD Markers Exhibit Minimal Variation in Healthy Donors

qPCR was conducted for a selected group of candidate PD markers to determine whether they exhibited variation at baseline in the whole blood of healthy volunteers. qPCR indicated that baseline variation was minimal. See Table 4, which provides the baseline qPCR data (healthy volunteers shown in shaded columns).

Table 4: Baseline Variation of Candidate PD Markers

Gene	102-PAX	129-PAX	129KHR-SLE	RH33XR-SLE
CDC42SE1	0.589	1.000	2.622	1.996
FCHO2	0.872	1.000	3.235	3.298
GIP3	2.059	1.000	86.130	80.545
HERC5	3.638	1.000	638.073	159.621
IFI27	0.246	1.000	508.346	14.012
IFI44	5.194	1.000	636.965	338.921
IFIT3	1.413	1.000	104.166	59.344
IL6ST	0.337	1.000	3.873	3.628
IRF2	1.486	1.000	8.096	4.998
LILRA5	1.48177	1.000	16.433182	27.248745
BAFF	0.433	1.000	2.478	4.679
GIP2	0.571	1.000	22.168	13.634
IFI44L	2.581	1.000	407.035	259.517
IFIT1	4.018	1.000	128.164	151.301
LY6E	0.442	1.000	10.095	5.181
OAS1	0.817	1.000	16.650	10.379
OAS3	2.517	1.000	75.542	32.355
RSAD2	2.425	1.000	310.575	217.885
STAT2	1.526	1.000	11.551	9.735

Example 4. IFN α Stimulates Up-Regulation in Expression of Candidate PD Markers in Whole Blood of Healthy Volunteers

A study was performed to determine whether IFN α could stimulate expression of candidate PD markers in whole blood of healthy volunteers. Whole blood of healthy volunteers was collected in heparinized tubes, transferred to the appropriate wells of 6-well culture plates, and incubated with leukocyte IFN doses of 3, 30, 100, and 300 I.U. and then incubated for 4 hours at 37°C, 5% CO₂. Fold-induction of expression of candidate PD markers for genes IFI44, IRF2, RSAD2, GIP3, and HERC5 was determined using RNA isolated from PBMCs (Peripheral Blood Mononuclear Cells) with Qiagen's RNeasy kit. As shown in Table 5 (IFI44 and IRF2), Table 6 (RSAD2), and Table 7 (GIP3 and HERC5) leukocyte IFN causes up-regulation in expression of each of these candidate PD markers. See also Figure 1 (IFI44), Figure 2 (IRF2), Figure 3 (RSAD2), Figure 4 (GIP3), and Figure 5 (HERC5) for a graphical analysis of these candidate PD marker expression results.

A summary hierarchical clustering of all samples using 1384 genes differentially regulated by IFN type 1, IFN type 2, or TNF α obtained from a separate experiment is shown in Figure 17. A heat map with a summary hierarchical clustering is also provided for 689 type I IFN inducible probe sets used on whole blood samples from healthy donors *ex vivo* stimulated with IFN type 1, IFN type 2, or TNF α . See figure 64.

Table 5: Induced IFI44 and IRF2 Expression Following Leukocyte IFN Stimulation of Healthy Volunteer's Whole Blood

Sample	Gene	Average FC	StDev
63A Media	IFI44	1.00	
63A IFN3	IFI44	8.58	0.16
63A IFN30	IFI44	8.27	0.07
63A IFN100	IFI44	15.12	0.50
63A IFN300	IFI44	12.42	0.04
Sample	Gene	Average FC	StDev
63A Media	IRF2	1.00	
63A IFN3	IRF2	2.25	0.08
63A IFN30	IRF2	1.96	0.06
63A IFN100	IRF2	2.19	0.06
63A IFN300	IRF2	3.75	0.10

Table 6: Induced RSAD2 Expression Following Leukocyte IFN Stimulation of Healthy Volunteer's Whole Blood

Sample	Gene	Average FC	StDev
63A Media	RSAD2	1.00	
63A IFN3	RSAD2	10.88	0.11
63A IFN30	RSAD2	11.14	0.21
63A IFN100	RSAD2	14.96	0.12
63A IFN300	RSAD2	25.50	0.50

Table 7: Induced G1P3 and HERC5 Expression Following Leukocyte IFN Stimulation of Healthy Volunteer's Whole Blood

Sample	Gene	Average FC	StDev
63A Media	G1P3	1.00	
63A IFN3	G1P3	42.88	1.03
63A IFN30	G1P3	25.76	0.10
63A IFN100	G1P3	21.72	0.48
63A IFN300	G1P3	16.02	0.06
Sample	Gene	Average FC	StDev
63A Media	HERC5	1.00	
63A IFN3	HERC5	14.17	0.12
63A IFN30	HERC5	13.74	0.12
63A IFN100	HERC5	18.51	0.58
63A IFN300	HERC5	23.55	0.54

Example 5. IFN α Ab Neutralizes IFN α -Induced Candidate PD Marker Expression in Healthy Volunteers' Whole Blood

Source of Interferon= IFN α 2a

Because IFN α treatment of healthy volunteers' whole blood induced expression of candidate PD markers, it was determined whether IFN α Ab, MEDI-545, could neutralize the induction of expression of these markers.

Blood was drawn from each of three donors into heparin tubes. Aliquots of 2.5 ml of drawn blood were added to each of 4 wells of 6- or 24-well treatment plates. The 4 wells were designated for treatment as follows: (a) blood + vehicle, (b) blood + 100 IU IFN α 2a, (c) blood + 100 IU IFN α 2a + MEDI-545 (IFN α Ab), and (d) blood + 100 IU IFN α 2a + R347 (control Ab).

Wells containing blood to be treated with Ab were first incubated with either MEDI-545 (IFN α Ab; well (c)) or R347 (control Ab; well (d)) for 30 minutes. Following Ab treatment, vehicle (well (a)) or IFN α 2a (wells (b), (c), and (d)) was added to the appropriate wells and was then incubated for an additional 4 hours at 37°C, 5% CO₂. The samples were then transferred to PAXgene tubes and incubated at room temperature for 2 hr. Following the 2 hr incubation the tubes were transferred to -80 °C for storage.

Following, at least, an overnight incubation at -80°C the total RNA of the cells was prepared according to the PAXgene protocol. First and second strand cDNA was prepared via Affy GRP methods and TaqMan was conducted on the cDNA samples.

Expression of at least 11 candidate PD markers, previously identified as up-regulated in lupus patients, could be neutralized by MEDI-545 in the IFN α 2a-stimulated whole blood. See Table 8 (RAB8B), Table 9 (IRF7), Table 10 (MARCKS), Table 11 (IL6ST), Table 12 (LY6E), Table 13 (IFIT3), Table 14 (IFIT1), Table 15 (HERC5), Table 16 (OAS1), Table 17 (OAS3), and Table 18 (RSAD2), which provide quantitative gene expression analysis for each of these 11 genes in the whole blood of each of the 3 healthy volunteers.

Table 8: IFN α 2a-Induced RAB8B Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	RAB8B	1.00	
107 IFN	RAB8B	3.45	0.31
107 IFN+545	RAB8B	1.30	0.04
107 IFN+R347	RAB8B	3.15	0.03
163 VEH	RAB8B	0.70	0.01
163 IFN	RAB8B	2.20	0.04
163 IFN+545	RAB8B	1.18	0.01
163 IFN+R3437	RAB8B	3.71	0.02
175 VEH	RAB8B	0.64	0.01
175 IFN	RAB8B	2.63	0.04
175 IFN+545	RAB8B	1.15	0.02
175 IFN+R347	RAB8B	2.51	0.05

Table 9: IFN α 2a-Induced IRF7 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	IRF7	1.00	
107 IFN	IRF7	18.53	3.32
107 IFN+545	IRF7	3.42	0.33
107 IFN+R347	IRF7	19.48	1.67
163 VEH	IRF7	0.91	0.02
163 IFN	IRF7	17.16	1.39
163 IFN +545	IRF7	2.92	0.22
163 IFN+R3437	IRF7	23.28	1.46
175 VEH	IRF7	1.25	0.10
175 IFN	IRF7	24.65	0.80
175 IFN+545	IRF7	2.43	0.08
175 IFN+R347	IRF7	26.34	8.61

Table 10: IFN α 2a-Induced MARCKS Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	MARCKS	1.00	
107 IFN	MARCKS	3.97	0.09
107 IFN+545	MARCKS	1.30	0.08
107 IFN+R347	MARCKS	2.99	0.10
163 VEH	MARCKS	0.56	0.01
163 IFN	MARCKS	2.59	0.12
163 IFN +545	MARCKS	1.55	0.05
163 IFN+R3437	MARCKS	4.42	0.07
175 VEH	MARCKS	0.41	0.01
175 IFN	MARCKS	2.59	0.06
175 IFN+545	MARCKS	0.55	0.02
175 IFN+R347	MARCKS	3.38	0.05

Table 11: IFN α 2a-Induced IL6ST Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	IL6ST	1.00	
107 IFN	IL6ST	3.54	0.60
107 IFN+545	IL6ST	2.62	0.16
107 IFN+R347	IL6ST	8.19	0.54
163 VEH	IL6ST	2.50	0.58
163 IFN	IL6ST	7.69	0.47
163 IFN +545	IL6ST	4.18	0.44
163 IFN+R3437	IL6ST	13.24	0.12
175 VEH	IL6ST	1.37	0.09
175 IFN	IL6ST	7.62	0.56
175 IFN+545	IL6ST	2.95	0.38
175 IFN+R347	IL6ST	23.91	2.77

Table 12: IFN α 2a-Induced LY6E Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	LY6E	1.00	
107 IFN	LY6E	19.09	0.03
107 IFN+545	LY6E	3.50	0.15
107 IFN+R347	LY6E	12.54	0.20
163 VEH	LY6E	1.02	0.04
163 IFN	LY6E	13.52	0.35
163 IFN +545	LY6E	4.80	0.18
163 IFN+R3437	LY6E	22.56	0.35
175 VEH	LY6E	1.61	0.15
175 IFN	LY6E	19.32	0.68
175 IFN+545	LY6E	3.74	0.00
175 IFN+R347	LY6E	15.57	0.44

Table 13: IFN α 2a-Induced IFIT3 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	IFIT3	1.00	
107 IFN	IFIT3	38.43	0.78
107 IFN+545	IFIT3	6.78	0.14
107 IFN+R347	IFIT3	42.59	0.75
163 VEH	IFIT3	0.62	0.01
163 IFN	IFIT3	25.94	0.57
163 IFN+545	IFIT3	4.58	0.08
163 IFN+R3437	IFIT3	44.83	0.44
175 VEH	IFIT3	1.32	0.02
175 IFN	IFIT3	35.02	0.48
175 IFN+545	IFIT3	5.28	0.05
175 IFN+R347	IFIT3	29.71	0.79

Table 14: IFN α 2a-Induced IFIT1 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	IFIT1	1.00	
107 IFN	IFIT1	80.21	3.44
107 IFN+545	IFIT1	13.14	0.02
107 IFN+R347	IFIT1	86.44	0.57
163 VEH	IFIT1	0.92	0.03
163 IFN	IFIT1	51.65	1.21
163 IFN+545	IFIT1	7.60	0.05
163 IFN+R3437	IFIT1	86.63	2.67
175 VEH	IFIT1	1.47	0.17
175 IFN	IFIT1	82.98	2.94
175 IFN+545	IFIT1	8.40	0.24
175 IFN+R347	IFIT1	58.50	1.47

Table 15: IFN α 2a-Induced HERC5 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	HERC5	1.00	
107 IFN	HERC5	41.12	2.87
107 IFN+545	HERC5	6.29	0.49
107 IFN+R347	HERC5	55.04	0.69
163 VEH	HERC5	1.05	0.07
163 IFN	HERC5	75.81	0.50
163 IFN+545	HERC5	7.83	0.00
163 IFN+R3437	HERC5	95.44	7.79
175 VEH	HERC5	1.19	0.06
175 IFN	HERC5	74.58	5.79
175 IFN+545	HERC5	6.89	0.13
175 IFN+R347	HERC5	98.15	19.40

Table 16: IFN α 2a-Induced OAS1 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	OAS1	1.00	
107 IFN	OAS1	15.11	4.27
107 IFN+545	OAS1	3.45	1.03
107 IFN+R347	OAS1	17.82	3.93
163 VEH	OAS1	0.77	0.22
163 IFN	OAS1	14.19	3.14
163 IFN +545	OAS1	3.05	0.75
163 IFN+R3437	OAS1	22.44	3.49
175 VEH	OAS1	1.62	0.38
175 IFN	OAS1	22.09	0.97
175 IFN+545	OAS1	4.04	0.45
175 IFN+R347	OAS1	15.22	4.48

Table 17: IFN α 2a-Induced OAS3 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	OAS3	1.00	
107 IFN	OAS3	49.04	13.74
107 IFN+545	OAS3	7.03	0.84
107 IFN+R347	OAS3	76.88	13.69
163 VEH	OAS3	0.49	0.06
163 IFN	OAS3	42.01	10.01
163 IFN +545	OAS3	14.60	4.53
163 IFN+R3437	OAS3	52.60	7.04
175 VEH	OAS3	1.27	0.14
175 IFN	OAS3	37.87	3.57
175 IFN+545	OAS3	3.92	0.06
175 IFN+R347	OAS3	34.91	2.07

Table 18: IFN α 2a-Induced RSAD2 Gene Expression is Neutralized by MEDI-545

Sample	Gene	Average	StDev
107 VEH	RSAD2	1.00	
107 IFN	RSAD2	109.64	36.65
107 IFN+545	RSAD2	9.88	0.32
107 IFN+R347	RSAD2	107.32	35.38
163 VEH	RSAD2	0.56	0.11
163 IFN	RSAD2	71.47	21.17
163 IFN +545	RSAD2	4.39	0.60
163 IFN+R3437	RSAD2	114.51	28.63
175 VEH	RSAD2	1.88	0.43
175 IFN	RSAD2	126.27	22.95
175 IFN+545	RSAD2	8.43	0.36
175 IFN+R347	RSAD2	90.97	7.42

See also Figure 6 (RAB8B), Figure 7 (IRF7), Figure 8 (MARCKS), Figure 9 (IL6ST), Figure 10 (LY6E), Figure 11 (IFIT3), Figure 12 (IFIT1), Figure 13, (HERC5), Figure 14 (OAS1), Figure 15 (OAS3), and Figure 16 (RSAD2) for graphical representations of the gene expression data for each of the 11 genes.

Source of Interferon=SLE patient serum

(a) Neutralization of type I IFN-induced genes by MEDI-545 could also be observed in whole blood of healthy volunteers that had been stimulated with serum obtained from lupus patients. Serum samples were obtained from SLE patients that had been tested in an IFN bioassay. Whole blood was collected from healthy donors in heparinized vacutainer tubes and PBMC were isolated using Ficoll gradient centrifugation method. PBMC were resuspended at 1×10^7 cells/mL in RPMI media with 10% fetal bovine serum (FBS) and 125 μ L of cells were aliquoted into each well of a 24 well flat bottom plate (1.25×10^6 cells/well). Serum from SLE patients was preincubated for one hour with MEDI-545 (0.1, 1, 10 μ g/mL), anti-IFN- γ antibody (1 μ g/mL) or control antibody (10 μ g/mL). SLE serum was added to the PBMC at a final concentration 25% (62.5 μ L per well). Additional volume of RPMI + 10% FBS was added to the wells to obtain a final volume of 250 μ L per well. Plates were incubated at 37°C for either 4 or 18 hours. Following the incubation, RNA was harvested by adding 750 μ L of Trizol LS to each well. Samples were frozen at -70°C until the time of RNA isolation. Table 21 provides the MEDI-545 blockade of 74 type I IFN genes in healthy volunteers' whole blood stimulated *ex vivo* with SLE patient serum.

Table 21: MEDI-545 blocks overexpression of type I IFN genes in whole blood of healthy volunteers stimulated *ex vivo* with lupus patient serum

Probe ID	D1_002_545.10	D1_004_545.10	D1_17021_545.10	UniGene.ID	Gene.Symbol
219211_at	-3.1949	-4.9995	-4.0543	Hs.38260	USP18
217502_at	-3.1886	-4.2648	-3.0247	Hs.437609	IFIT2
218400_at	-3.1235	-4.3204	-3.9594	Hs.528634	OAS3
213797_at	-3.0752	-3.3250	-2.5795	Hs.17518	RSAD2
203153_at	-2.8862	-4.6545	-4.7890	Hs.20315	IFIT1
242625_at	-2.8104	-2.9506	-2.2214	Hs.17518	RSAD2
204747_at	-2.7900	-3.6590	-2.9676	Hs.47338	IFIT3
205483_s_at	-2.5237	-2.9955	-3.1566	Hs.458485	ISG15
204439_at	-2.5133	-3.5887	-3.5926	Hs.389724	IFI44L
202145_at	-2.4809	-3.0198	-3.5950	Hs.521903	LY6E
202869_at	-2.4582	-3.5402	-3.2304	Hs.524760	OAS1
235643_at	-2.4535	-3.3586	-2.9115	Hs.489118	SAMD9L
219352_at	-2.4496	-3.5983	-3.8692	Hs.529317	HERC6
204415_at	-2.4417	-2.5228	-2.3149	Hs.523847	IFI6
219684_at	-2.4167	-2.8965	-2.1421	Hs.43388	RTP4
236156_at	-2.4160	-2.5440	-2.8885	Hs.127445	LIPA
205552_s_at	-2.3880	-3.3679	-2.7561	Hs.524760	OAS1
206133_at	-2.3139	-3.0772	-2.4787	Hs.441975	BIRC4BP
214453_s_at	-2.2965	-3.1707	-3.3204	Hs.82316	IFI44
1556643_at	-2.2666	-2.0429	-1.7120	Hs.515243	LOC93343
228607_at	-2.2597	-2.1659	-2.3234	Hs.414332	OAS2
218943_s_at	-2.2563	-2.4118	-2.6600	Hs.190622	DDX58
242020_s_at	-2.2542	-2.6436	-1.7975	Hs.302123	ZBP1
204959_at	-2.2501	-1.3731	-1.5559	Hs.153837	MNDA
226757_at	-2.2481	-2.9288	-2.3984	Hs.437609	IFIT2
219863_at	-2.2465	-3.0980	-3.8114	Hs.26663	HERC5
229450_at	-2.2281	-3.2200	-2.2151	---	---
214059_at	---	-3.2929	-3.5281	Hs.82316	IFI44
232517_s_at	-2.1925	-2.2750	-2.4569	Hs.517180	PRIC285
232666_at	-2.1925	-1.9206	-1.4938	Hs.528634	OAS3
230036_at	-2.1654	-3.0256	-2.4879	Hs.489118	SAMD9L
227609_at	-2.1548	-2.5608	-1.1577	Hs.546467	EPSTI1
226702_at	-2.1420	-3.0150	-3.0155	Hs.7155	LOC129607
226603_at	-2.1183	-2.8672	-2.4103	Hs.489118	SAMD9L
210397_at	-2.1095	-0.5687	-2.0322	Hs.32949	DEFB1
204994_at	-2.0685	-3.2727	-3.6132	Hs.926	MX2
202086_at	-2.0661	-3.2741	-3.6406	Hs.517307	MX1
228617_at	-2.0596	-2.5832	-2.3139	Hs.441975	BIRC4BP
219364_at	-2.0583	-2.3774	-2.4651	Hs.55918	LGP2
209417_s_at	-2.0364	-2.5262	-2.4132	Hs.632258	IFI35
222154_s_at	-2.0330	-2.4542	-2.6425	Hs.120323	DNAPT6
228230_at	-2.0323	-2.9621	-3.0255	Hs.517180	PRIC285
242234_at	-2.0161	-3.0047	-3.1633	Hs.441975	BIRC4BP
219519_s_at	-2.0077	-0.2596	-3.1621	Hs.31869	SIGLEC1
207713_s_at	-1.9940	-1.0134	-1.6345	Hs.247280	C20orf18
218974_at	-1.8904	-2.5122	-2.5244	Hs.445244	FLJ10159
1552309_a_at	-1.8820	-2.4284	-2.7221	Hs.632387	NEXN
210873_x_at	-1.8424	-1.2891	-1.2710	Hs.348983	APOBEC3A
243271_at	-1.8388	-2.2657	-2.0595	Hs.489118	SAMD9L
202411_at	-1.8385	-0.1345	-2.4757	Hs.532634	IFI27
222793_at	-1.8137	-2.4540	-2.6576	Hs.190622	DDX58
235276_at	-1.8007	-2.6121	-1.4780	---	---
203236_s_at	-1.7926	-1.9069	-2.6425	Hs.81337	LGALS9
225291_at	-1.7801	-2.0167	-2.4613	Hs.388733	PNPT1
44673_at	-1.7547	-0.1337	-2.3913	Hs.31869	SIGLEC1
213294_at	-1.7361	-2.4393	-2.5907	Hs.546523	---
211122_s_at	-1.7296	-3.0816	-1.5743	Hs.632592	CXCL11
224701_at	-1.6827	-1.7880	-1.2356	Hs.583792	PARP14
230314_at	-1.6795	-2.2159	-2.3476	Hs.112420	---
218986_s_at	-1.6648	-2.1615	-2.0204	Hs.591710	FLJ20035
205569_at	-1.6647	-2.5741	-2.6878	Hs.518448	LAMP3
219691_at	-1.6420	-1.8434	-1.8310	Hs.65641	SAMD9
204211_x_at	-1.6244	-2.0612	-2.3379	Hs.131431	EIF2AK2
220146_at	-1.6033	-2.7419	-1.7471	Hs.443036	TLR7
241916_at	-1.6026	-1.5906	-1.3802	Hs.130759	PLSCR1
229350_x_at	-1.5906	-1.7395	-1.3577	Hs.348609	PARP10
1555464_at	-1.5866	-1.7397	-1.3101	Hs.163173	IFIH1
204972_at	-1.5822	-2.8402	-2.8355	Hs.414332	OAS2
204698_at	-1.5277	-1.5978	-1.6553	Hs.459265	ISG20
203595_s_at	-1.4853	-1.8724	-1.5442	Hs.252839	IFIT5
220576_at	-1.4834	-1.7834	-1.0040	Hs.229988	PGAP1
1555491_a_at	-1.4739	-1.0165	-1.4991	---	FLJ11286
1565752_at	-1.4418	-0.0040	-1.0835	Hs.509664	FGD2
203596_s_at	-1.4389	-2.0356	-1.9284	Hs.252839	IFIT5

Analysis of the genes uniquely activated at the 18 hour time point revealed upregulation of genes involved in the innate immune response (TLR, NF κ B), adaptive immune response (NFAT, IL-1/IL-6), complement activation as well as leukocyte chemotaxis and adhesion. It is possible that neutralization of the type IFN pathway has the potential to modify downstream pathways that may significantly impact the pathogenesis of SLE.

Heatmap analysis was also performed to examine induction of a type I IFN signature in PBMCs of a healthy donor by serum of an SLE patient and neutralization of the type I IFN signature by MEDI-545. See Figure 67. The anti-IFN- α mAb treatment (lanes 4–6) demonstrated strong neutralization of a large number of genes stimulated with the serum of an SLE patient. Furthermore, neutralization by the anti-IFN- α mAb was dose-dependent, which suggests that these genes could be good candidates for PD. The reference mAb itself inhibited the overexpression of some of the genes upregulated when challenged with SLE patient sera; some of these were identified as type I IFN-inducible genes. However, the effect of anti-IFN- α mAb was much broader, with strong neutralization observed in a large number of genes of which neither the reference mAb nor anti-IFN- γ mAb had any significant effect (lane 2; lanes 4–6). It should be noted that treatment with anti-IFN- α R mAb (lane 7) induced more neutralization than anti-IFN- α mAb, which suggests the presence of other type I IFN family members in the serum of the SLE patients, in addition to IFN- α .

(b) Further investigation was conducted to identify early and late transcriptional responses in healthy donor PBMCs stimulated with SLE patient serum. In this study, four SLE patient serum samples, with varying levels of IFN α activity, were used to stimulate PBMCs isolated from a healthy donor. The varying levels of IFN α activity in the four SLE serum samples were determined in a luciferase reporter gene assay as described in Example 20. Briefly, HEK293H cells were stably transfected with a luciferase construct (*Gaussia princeps*) under the control of the IFN-stimulated response element (ISRE). Transfected cells were incubated with 50% patient sera and luciferase activity was detected in the culture supernatants 24 h later. Samples generating a signal greater than 1.5X negative control wells (normal human serum) were considered positive. To determine which class of type I IFN was responsible for the positive response, cells were treated with anti-type I and anti-type II IFN mAbs. Figure 70a shows the range of levels of type I IFN activity in each of the four SLE patient serum samples.

Each of the four SLE patient serum samples was co-incubated with PBMCs isolated from a healthy volunteer. The PBMCs from the healthy volunteer (previously determined to be IFN-signature negative) were isolated using Ficoll gradient centrifugation. Isolated PBMCs were incubated with 25% SLE patient serum or with 25% autologous patient serum (as a negative control). Following the incubation, cells were harvested with Trizol LS and stored at -70°C for RNA isolation. Total RNA was extracted and RNA purity and concentration were determined spectrophotometrically (260/280>1.9). The generation and hybridization of biotin-labeled amplified complementary RNA (cRNA) were conducted

according to manufacturer's instructions (Affymetrix, Santa Clara, CA). Data was generated by implementing a 3-fold (up-regulation) expression cutoff between SLE serum stimulation compared to autologous serum control samples (q value ≤ 0.05). Figure 70b shows the number of probes detected as 3-fold or more upregulated in the healthy volunteer PBMCs by each of the four SLE patient serum samples. The number of probes detected as 3-fold or more upregulated by an SLE patient serum sample correspondingly increased with the level of type I IFN activity detected in the SLE serum sample.

The role of type I IFNs in inducing the 3-fold or more upregulation of probes by the SLE patient serum samples was next investigated. PBMCs isolated from a healthy volunteer, discussed above, were incubated with 25% SLE patient serum in the presence or absence of neutralizing antibodies against IFN- α , or irrelevant mAb, for 4 or 18 hours. As a negative control, PBMC were incubated with 25% of autologous patient serum. Following the incubation, cells were harvested with Trizol LS and stored at -70°C for RNA isolation. Total RNA was extracted and RNA purity and concentration were determined spectrophotometrically ($260/280 > 1.9$). The generation and hybridization of biotin-labeled amplified complementary RNA (cRNA) were conducted according to manufacturer's instructions (Affymetrix, Santa Clara, CA). ArrayAssist® Lite software was used to calculate probe-level summaries from the array cell intensity files and R packages were used to identify differentially regulated genes (3-fold or greater upregulation in expression between SLE serum stimulation compared to autologous serum control samples (q value ≤ 0.05); R Development Core Team, New Zealand). Percent neutralization was then determined by calculating the percent change for each upregulated probe treated with and without anti-IFN α antibody. Figure 71a provides heat maps showing the percent neutralization of probes that were identified as upregulated following anti-IFN α treatment for type I IFN genes (689 probes) and non-type I IFN genes (probes induced by SLE serum outside of type I IFN gene list) 4 and 18 h post incubation. Figure 71b shows, for each of the four SLE patient serum samples, the percentage of type I IFN gene signature or non-type I IFN gene signature probes that were neutralized by the anti-IFN α treatment following both the 4 and 18 hour incubations. It appears that the majority of genes neutralized by anti-IFN α treatment of SLE serum-treated healthy volunteer's PBMCs 4 hours post-incubation were type I IFN genes, while the majority of genes neutralized by anti-IFN α treatment of SLE serum-treated healthy volunteer's PBMCs 18 hours post-incubation were non-type I IFN genes.

Genes, whether type I IFN genes or non-type I IFN genes, that were both upregulated and neutralized by anti-IFN α treatment at 18 hours, but that were not upregulated at 4 hours (i.e., “unique genes”) were identified for each SLE patient serum sample. Figure 72 provides the (a) type I IFN genes and (b) non-type I IFN genes that were identified as unique genes. Shaded areas indicate greater than 50% neutralization by anti-IFN α in that patient sample.

Cell pathways and processes neutralized by anti-IFN α treatment at the 18 hr time point are involved in cytokine and chemokine signaling pathways, immune regulation, cell adhesion, and cell survival. See Figure 73, which provides a table showing the pathway analysis of altered genes and proteins at the 18 hr time point. Pathways highlighted in yellow were also significantly altered in SLE serum samples. The cell pathways and processes neutralized by anti-IFN α treatment at the 18 hr time point were analyzed with the MetaCore integrated software suite from GeneGo, Inc. using the identified unique genes. Only pathways with p-values ≤ 0.05 were considered significant. The pathways shown were altered in at least 2 out of 4 SLE serum samples.

Example 6: Administering MEDI-545 to Lupus Patients Neutralizes the IFN α -Inducible Candidate PD Marker Expression Pattern

Whole blood of lupus patients receiving placebo, 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg MEDI-545 were analyzed for expression of IFN α -inducible PD markers over the course of 28 days. Whole blood (~2.5 mL) was drawn into PAXgene RNA tubes and processed as outlined above. With increasing doses of MEDI-545, up-regulated expression of the top 25 PD markers was neutralized. See Figure 18, Figure 23, and Figure 24 which provide graphical representations of neutralization of these top 25 PD markers following administration of varying concentrations of the MEDI-545 IFN α Ab over various lengths of time. The top 25 PD markers measured in this study are provided in Table 19.

Table 19: Top 25 IFN-Induced PD Markers in Lupus Patients

Probe ID	UniGene ID	Gene Title	Gene Symbol
202086_at	Hs.517307	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse) /// myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1
202145_at	Hs.521903	lymphocyte antigen 6 complex, locus E	LY6E
202411_at	Hs.532634	interferon, alpha-inducible protein 27	IFI27
202869_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1
203153_at	Hs.20315	interferon-induced protein with tetratricopeptide repeats 1 /// interferon-induced protein with tetratricopeptide repeats 1	IFIT1

204415_at	Hs.523847	interferon, alpha-inducible protein 6	IFI6
204439_at	Hs.389724	interferon-induced protein 44-like	IFI44L
205483_s_at	Hs.458485	ISG15 ubiquitin-like modifier	ISG15
205569_at	Hs.518448	lysosomal-associated membrane protein 3	LAMP3
205660_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL
213797_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2
214059_at	Hs.82316	Interferon-induced protein 44	IFI44
217502_at	Hs.437609	interferon-induced protein with tetratricopeptide repeats 2	IFIT2
218400_at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3
219211_at	Hs.38260	ubiquitin specific peptidase 18	USP18
219519_s_at	Hs.31869	sialic acid binding Ig-like lectin 1, sialoadhesin /// sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1
219863_at	Hs.26663	hect domain and RLD 5	HERC5
222154_s_at	Hs.120323	DNA polymerase-transactivated protein 6	DNAPTP6
226702_at	Hs.7155	hypothetical protein LOC129607	LOC129607
227609_at	Hs.546467	epithelial stromal interaction 1 (breast)	EPSTI1
229450_at	---	---	---
235276_at	---	---	---
239979_at	Hs.546467	Epithelial stromal interaction 1 (breast)	EPSTI1
242234_at	Hs.441975	XIAP associated factor-1	BIRC4BP
44673_at	Hs.31869	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1

The neutralization of IFN-induced PD markers by MEDI-545 for several individual lupus patients was examined and is presented in Figures 19-21. Figures 19 and 20 are heatmaps showing the neutralization of the top 25 PD markers (see Table 19) for two individual lupus patients (Figure 19, patient 1541; and Figure 20, patient 1449). Each of these lupus patients received 3 mg/kg MEDI-545. Each exhibited neutralization of the top 25 inducible PD markers at 7 and 14 days post-MEDI-545 treatment.

Neutralization of the top 25 type I IFN inducible genes in whole blood of an SLE patient treated with high dose (30 mg/kg) MEDI-545 was also examined. A heatmap of neutralization of the top 25 type I IFN inducible genes at 1, 4, 7, and 14 days following administration of MEDI-545 is presented in Figure 25(a). Neutralization of all genes can be seen following administration of MEDI-545. Figure 25(b) is a PCA of target modulation based on the top 25 type I IFN inducible genes. The PCA diagram shows the progression of the treated SLE patient from a position directly opposite that of normal healthy donors prior to administration of MEDI-545 to a position where it clusters with the healthy donors after administration of MEDI-545.

The neutralization of 165 PD markers by MEDI-545 was examined in a further lupus patient dosed with a lower, 0.3 mg/kg dose, of Ab. See Figure 21. MEDI-545 neutralized most of the 165 candidate PD markers in this lupus patient. The 165 candidate PD markers are shown as the first 165 entries of Table 20.

The neutralization of type I IFN inducible probes sets was not observed in SLE patients treated with placebo control. Compare PCA plots of SLE patients before (a) and after (b) dosing with placebo in Figure 26. Thus, the neutralization of the type-I IFN PD markers was due to the MEDI-545 antibody.

Table 22 provides a list of the 63 type I IFN inducible probes upregulated in whole blood of lupus patients and neutralized by MEDI-545 or placebo by at least 30% at day 7, day 14, or day 28 post administration. Each set of columns provides neutralization data for each of the indicated genes at 7, 14, and 28 days post-administration. The first set of columns provides percentage neutralization of each of the indicated genes for lupus patients having a type I IFN signature and that were treated with MEDI-545. It can be noted that for each of the indicated genes, neutralization ranged from 30% to 68% at day 7 post-administration. Meanwhile, at day 7 in the placebo treated group, neutralization of the same genes ranged from 0% to 27%.

Table 22: Neutralization of 63 Type I IFN Inducible Probes in Whole Blood of Lupus by MEDI-545

Gene	Lupus Samples With IFN	ALL Lupus Samples, (+)Medi					Lupus Samples Without an IFN					Samples Receiving Placebo		
		Day.7_Sig	Day.14_Sig	Day.28_Sig	Day.7_All	Day.14_All	Day.28_All	Day.7_NoSig	Day.14_NoSig	Day.28_NoSig	Day.7_Placebo	Day.14_Placebo	Day.28_Placebo	
IFI44	214059_at	0.6871	0.6276	0.5047	0.3433	0.2657	0.2357	-0.0799	-0.2278	-0.0088	-0.1325	-1.91*	-0.4185	
IFI44L	204439_at	0.6621	0.6193	0.5515	0.6662	0.5561	0.492	0.6713	0.4698	0.4379	0.007	-2.1816	0.0035	
RSAD2	213797_at	0.6547	0.631	0.5213	0.6023	0.4611	0.4464	0.5377	0.2294	0.3783	-0.2332	-5.0172	-0.9617	
G1P2	205483_s_at	0.6395	0.5954	0.5703	0.5404	0.4781	0.4148	0.4185	0.3181	0.2734	0.0423	-0.944	0.1706	
RSAD2	242625_at	0.6359	0.6123	0.4946	0.5607	0.541	0.3443	0.4681	0.4437	0.2077	-0.3537	-2.7176	-0.2632	
USP18	219211_at	0.6305	0.6269	0.5577	0.4322	0.4423	0.4082	0.1882	0.1907	0.2723	-0.4424	-2.4219	-0.4972	
IFI44	214453_s_at	0.626	0.5875	0.4223	0.4956	0.2741	0.2298	0.3352	-0.1532	0.0547	-0.2833	-1.0524	-2.4005	
IFIT1	203153_at	0.6224	0.6093	0.5376	0.5442	0.4586	0.4182	0.448	0.2532	0.3097	-0.1604	-1.1565	-0.436	
IFIT3	204747_at	0.6213	0.5676	0.5638	0.5212	0.4174	0.3854	0.398	0.2124	0.2232	-5.9101	-9.7543	-7.4011	
SERPING1	200986_at	0.617	0.6214	0.5974	0.4617	0.4294	0.3673	0.2706	0.1676	0.1582	-0.5973	-2.7824	-0.4193	
HERC6	219352_at	0.5996	0.531	0.5352	0.3581	0.3678	0.4335	0.0609	0.1452	0.341	-0.9901	-4.4468	-1.6832	
DNAPT6	222154_s_at	0.5973	0.6223	0.5016	0.345	0.3819	0.2244	0.0345	0.0543	-0.0276	0.028	-1.947	0.007	
OASL	210797_s_at	0.5968	0.5529	0.5815	0.4715	0.3853	0.4208	0.3174	0.1569	0.2748	-0.1014	-1.6808	-0.1344	
HERC5	219863_at	0.5948	0.5552	0.4997	0.4651	0.4521	0.3816	0.3054	0.3115	0.2742	-0.0955	-0.9446	-0.1306	
OAS3	218400_at	0.589	0.5792	0.5062	0.4846		0.4039	0.3562	0.3065	0.311	-0.0945	-1.1786	-0.1744	
IFRG28	219684_at	0.581	0.5218	0.4955	0.3014	0.3035	0.2441	-0.0427	0.0058	0.0155	-2.1401	-2.8445	-3.3644	
MX1	202086_at	0.5807	0.5329	0.5073	0.512	0.4831	0.4001	0.4273	0.4152	0.3026	-0.0951	-0.7789	0.01	
OAS1	202869_at	0.5761	0.5148	0.5652	0.4345	0.429	0.4373	0.2603	0.3119	0.3211	0.0389	-0.6246	0.0692	
OASL	205660_at	0.5681	0.5549	0.5494	0.4814	0.4415	0.4046	0.3746	0.2868	0.2729	-0.0675	-0.9765	0.0773	
OAS1	205552_s_at	0.5678	0.5193	0.56	0.4796	0.4115	0.4196	0.3711	0.2644	0.292	-0.1562	-1.7918	-0.395	
LAMP3	205569_at	0.5531	0.6796	0.4871	0.3427	0.4182	0.2854	0.0838	0.0618	0.1021	0.007	-1.4332	0.045	
MGC20410	228439_at	0.535	0.5085	0.5093	0.359	0.2949	0.332	0.1424	0.0036	0.1709	-1.1629	-2.0558	-0.5523	
SN	219519_s_at	0.5321	0.5639	0.5307	0.307	0.3711	0.212	0.03	0.1081	-0.0778	-0.1736	-4.8297	0.1133	
HSXIAPAF1	228617_at	0.5317	0.503	0.4707	0.3942	0.3604	0.266	0.2249	0.1659	0.0799	-0.2206	-0.7607	-0.1053	
IFIT5	203596_s_at	0.5257	0.4922	0.3314	0.3004	0.1997	0.0723	0.023	-0.1991	-0.1633	0.0791	-0.2048	-0.1939	
IRF7	208436_s_at	0.5183	0.494	0.4717	0.4318	0.3509	0.301	0.3253	0.1557	0.1459	0.1162	-0.2791	0.2159	
EPST11	227609_at	0.517	0.5298	0.4999	0.3142	0.2662	0.2798	0.0646	-0.0932	0.0797	0.0161	-1.0185	-0.1578	
EPST11	239979_at	0.5074	0.4803	0.553	0.3738	0.3527	0.3674	0.2093	0.1786	0.1987	-0.6502	-1.8449	-0.4975	
ETV7	224225_s_at	0.5057	0.5101	0.3596	0.2965	0.2389	0.0985	0.039	-0.1308	-0.1389	-0.5808	-1.3814	-0.6834	
IFIT5	203595_s_at	0.5056	0.4731	0.2902	0.2482	0.2263	0.028	-0.0685	-0.1102	-0.2105	-0.1956	-0.4059	-0.6195	
HES4	227347_x_at	0.4998	0.4746	0.4266	0.3377	0.3141	0.2703	0.1383	0.0953	0.1283	0.0775	-0.3688	0.2619	
ZC3HDC1	218543_s_at	0.4812	0.4274	0.4076	0.3058	0.2935	0.2109	0.0898	0.1109	0.0321	0.055	-0.1726	0.1826	
C7orf6	230036_at	0.4636	0.4665	0.4025	0.3114	0.2848	0.2299	0.1241	0.037	0.073	0.0287	-0.4023	-0.002	
C7orf6	226603_at	0.4578	0.4242	0.3425	0.264	0.1555	0.1794	0.0253	-0.211	0.0312	-0.2153	-0.8023	-0.4988	
OAS3	232666_at	0.4557	0.3628	0.4828	0.3165	0.2457	0.3356	0.1452	0.086	0.2018	-0.3754	-1.0637	-0.0014	
OAS2	204972_at	0.4532	0.4503	0.3889	0.2963	0.3106	0.2084	0.1032	0.1202	0.0444	-0.1067	-0.9025	-0.1084	
IFIT2	217502_at	0.4514	0.4519	0.1899	0.0857	-0.039	-0.4306	-0.3643	-0.7083	-0.9948	-0.7316	-0.9653	-4.4123	
CXCL10	204533_at	0.4476	0.4647	0.262	0.1834	0.1911	0.1282	-0.1418	-0.1819	0.0066	-0.1664	-0.9562	-0.1939	
LY6E	202145_at	0.4463	0.4582	0.4113	0.3404	0.3294	0.2612	0.21	0.1536	0.1247	-0.4715	-1.729	-0.5955	
HERC6	239988_at	0.4449	0.3726	0.3596	0.2951	0.2402	0.2433	0.1108	0.0596	0.1376	0.2771	-0.098	0.0584	
G1P3	204415_at	0.4421	0.3914	0.1018	0.152	0.3129	-0.3045	-0.205	0.2058	-0.6738	-0.3862	-0.3826	-0.4763	
C7orf6	243271_at	0.4419	0.4279	0.401	0.2663	0.2445	0.2165	0.0501	-0.0055	0.0488	1.00E-04	-0.2487	0.116	
OAS2	206553_at	0.4377	0.3721	0.2965	0.3008	0.2379	0.1882	0.1323	0.0548	0.0897	-0.0861	-1.1845	-0.2322	
APOL6	241869_at	0.4264	0.063	0.4352	-0.0787	-0.5482	-0.2042	-0.7003	-1.3816	-0.7855	-1.0548	-2.225	0.0949	
ZBP1	242020_s_at	0.4232	0.406	0.3729	0.0761	0.1281	0.2718	-0.3512	-0.2508	0.1799	0.0954	-0.6879	-0.0275	
PLSCR1	202446_s_at	0.4022	0.3948	0.2996	0.1919	0.1973	0.1063	-0.0668	-0.0719	-0.0694	0.0049	-0.5041	-0.1826	
OAS2	228607_at	0.3989	0.3655	0.3374	0.2712	0.2174	0.1639	0.114	0.0155	0.0061	-0.026	-0.5978	-0.0611	
TRIM6	223599_at	0.3896	0.3464	0.2669	0.2285	0.1987	0.1119	0.0303	-0.0027	-0.0289	-0.4333	-1.2181	-0.76	
ZCCHC2	233425_at	0.3891	0.4249	0.3925	0.2541	0.2965	0.2822	0.088	0.1213	0.182	-0.1376	-0.4844	-0.075	
PLSCR1	202430_s_at	0.3847	0.3858	0.2706	-0.2032	-0.0283	-0.1714	-0.9268*	-0.5931	-0.5733	-0.091	-0.5114	-0.3841	
CLEC4D	1552773_at	0.3782	0.2012	0.1293	-0.5127	-0.9029	-0.5568	-1.6091	-2.4085	-1.1806	-0.0151	-0.298	-0.9965	
ECGF1	204858_s_at	0.3778	0.2403	0.2971	0.3178	0.1699	0.0019	0.244	0.0741	-0.2665	0.0637	-0.2711	0.1519	
C17orf27	233880_at	0.3658	0.3508	0.2804	0.2913	0.2599	0.108	0.1996	0.136	-0.0488	-0.4266	-0.7606	-0.4247	
SN	44673_at	0.3642	0.3373	0.3736	0.2344	0.2522	0.1405	0.0747	0.1362	-0.0714	-0.321	-1.2105	0.1766	
PRIC285	228230_at	0.3636	0.4131	0.3363	0.2701	0.2731	0.1074	0.155	0.0822	-0.1008	-0.5711	-0.6313	-0.1671	
PARP14	224701_at	0.3611	0.3765	0.3718	0.2737	0.2855	0.2267	0.1662	0.1614	0.0947	-0.0715	-0.3247	0.0835	
DNAPT6	241812_at	0.3448	0.3672	0.2896	0.2048	0.2134	0.108	0.0325	0.0037	-0.0571	-0.134	-0.5147	0.0613	
HSXIAPAF1	242234_at	0.3371	0.3793	0.1084	0.1586	0.1796	-0.2285	-0.0612	-0.0927	-0.5347	-0.4102	-0.7359	0.0295	
TNFAIP6	206025_s_at	0.336	0.3559	0.3269	0.1913	0.1909	0.1164	0.0133	-0.034	-0.0751	-0.3457	-0.7114	-0.2343	
LGALS3BP	200923_at	0.3331	0.27	0.2644	-0.0457	0.1764	0.1032	-0.512	0.0487	-0.0434	0.111	-0.2857	0.3187	
CKS2	204170_s_at	0.3215	0.0604	0.0634	-0.2323	-0.5787	-1.1884	-0.914	-1.4502	-2.3265	-0.3697	0.1034	-1.5141	
STAT2	205170_at	0.3176	0.1781	0.1852	0.1643	-0.0318	-0.051	-0.0245	-0.318	-0.2657	0.0708	-0.6738	-0.8915	
EIF2AK2	204211_x_at	0.3094	0.3621	0.2577	0.2165	0.286	0.1441	0.1021	0.1822	0.0408	-0.2044	-0.3038	-0.2554	

Table 33 provides the results of a separate study which determined the top 50 genes neutralized in SLE patient whole blood 7 days after MEDI-545 treatment. Only three genes of the 50 genes, ZCCHC2, REC8L1, and GCLM, were not IFN- α/β -inducible

Table 33: Top 50 probes neutralized 7 days post-dose in SLE patients receiving MEDI-545 treatment

Probe ID	UniGene ID	Gene Title	Gene Symbol	Avg Probe Rank (By % Neutralization)	Final Probe Rank
52 at	Hs.529317	hect domain and RLD 6	HERC6	2277.0	1
36 s at	Hs.166120	interferon regulatory factor 7	IRF7	2497.5	2
17 s at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	2708.2	3
33 s at	Hs.458485	ISG15 ubiquitin-like modifier	ISG15	2735.7	4
39 at	Hs.389724	interferon-induced protein 44-like	IFI44L	3194.9	5
11 at	Hs.38260	ubiquitin specific peptidase 18	USP18	3458.6	6
13 s at	Hs.12646	poly (ADP-ribose) polymerase family, member 12	PARP12	3472.3	7
11 at	Hs.567405	SCO cytochrome oxidase deficient homolog 2 (yeast)	SCO2	3825.7	8
17 at	Hs.47338	interferon-induced protein with tetra-ricopeptide repeats 3	IFIT3	3987.2	9
9 s at	Hs.31869	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1	4207.2	10
30 at	Hs.517180	peroxisomal proliferator-activated receptor A interacting complex 285	PRIC285	4373.1	11
16 at	---	---	---	4438.7	12
39 at	Hs.82316	Interferon-induced protein 44	IFI44	4477.4	13
14 s at	Hs.120323	DNA polymerase-transactivated protein 6	DNAPTP6	4531.3	14
15 at	Hs.521903	lymphocyte antigen 6 complex, locus E	LY6E	4618.6	15
9 s at	Hs.514941	Mov10, Moloney leukemia virus 10, homolog (mouse)	MOV10	4691.0	16
14 at	Hs.55918	likely ortholog of mouse D11lqp2	LGP2	4717.4	17
13 s at	Hs.114191	zinc finger, CCHC domain containing 2	ZCCHC2	4926.5	18
17 at	Hs.441975	XIAP associated factor-1	BIRC4BP	4942.0	19
1 at	---	hypothetical protein FLJ11286	FLJ11286	5046.2	20
30 at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	5136.7	21
18 at	Hs.526464	promyelocytic leukemia	PML	5328.7	22
35 at	Hs.514554	KIAA1618	KIAA1618	5344.5	23
36 at	Hs.517307	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1	5484.4	24
25 at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	5522.4	25
17 s at	Hs.632258	interferon-induced protein 35	IFI35	5529.4	26
39 at	Hs.124840	basic leucine zipper transcription factor, ATF-like 2	BATF2	5563.0	27
36 s at	Hs.10784	family with sequence similarity 46, member A	FAM46A	5607.1	28
16 s at	Hs.130759	phospholipid scramblase 1	PLSCR1	5911.3	29
30 at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	6001.3	30
15 s at	Hs.344812	three prime repair exonuclease 1	TREX1	6062.0	31
1 at	Hs.344812	three prime repair exonuclease 1	TREX1	6097.0	32
39 at	Hs.524760	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	6101.5	33
33 s at	Hs.82316	interferon-induced protein 44	IFI44	6210.4	34
191 a at	---	hypothetical protein FLJ11286	FLJ11286	6235.7	35
36 at	Hs.489118	sterile alpha motif domain containing 9-like	SAMD9L	6254.1	36
17 s at	Hs.438723	solute carrier family 27 (fatty acid transporter), member 3	SLC27A3	6257.9	37
11 at	Hs.118110	bone marrow stromal cell antigen 2	BST2	6371.4	38
39 at	Hs.419259	REC8-like 1 (yeast)	REC8L1	6423.3	39
17 at	Hs.531314	glutamate-cysteine ligase, modifier subunit	GCLM	6500.4	40
11 at	Hs.388733	polynucleotide nucleotidyltransferase 1	PNPT1	6537.6	41
11 x at	Hs.374950	metallothionein 1X	MT1X	6541.4	42
30 at	Hs.520102	KIAA0082	KIAA0082	6547.1	43
17 x at	Hs.154029	hairy and enhancer of split 4 (Drosophila)	HES4	6557.3	44
16 at	Hs.257352	apolipoprotein L, 6	APOL6	6571.1	45
39 at	Hs.464419	F-box protein 6	FBXO6	6683.0	46
36 at	Hs.384598	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)	SERPING1	6688.7	47
1 at	Hs.459265	interferon stimulated exonuclease gene 20kDa	ISG20	6853.8	48
3 s at	Hs.252682	torsin family 1, member B (torsin B)	TOR1B	6866.4	49
17 s at	Hs.352018	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	TAP1	6909.0	50

Example 7: The Majority of Lupus Patients Exhibit a Type I IFN-Inducible PD Marker Expression Pattern

Using 169 probe sets to detect expression of a number of PD markers, gene expression in whole blood samples of 35 lupus patients was analyzed using PCA (Principal Component Analysis). Principal component analysis is a statistical technique for simplifying a dataset, by reducing multidimensional datasets to lower dimensions for analysis. PCA was conducted on the filtered data set (169 probe sets) using the Spotfire statistical tool. The PCA determined that 24/35 of the lupus patients had a statistically significant PD marker signature. See Figure 22 for PCA analysis results. The 169 probe sets used for this PCA analysis are provided in Table 20.

Table 20: Gene Expression Detected by 169 Probe Sets in 35 SLE Patients

Probe ID	UniGene ID	Gene Title	Gene Symbol
1552772_at	Hs.351811	C-type lectin domain family 4, member D	CLEC4D
1554343_a_at	Hs.435579	BCR downstream signaling 1	BRDG1
1555464_at	Hs.163173	interferon induced with helicase C domain 1 membrane-spanning 4-domains, subfamily A, member 4	IFIH1
1555728_a_at	Hs.325960		MS4A4A
1556643_at	Hs.515243	Hypothetical protein BC011840	LOC93343
1557236_at	Hs.257352	apolipoprotein L, 6	APOL6
1559585_at	Hs.535011	hypothetical protein FLJ31033	FLJ31033
200887_s_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1
200923_at	Hs.514535	lectin, galactoside-binding, soluble, 3 binding protein	LGALS3BP
200986_at	Hs.384598	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)	SERPING1
201015_s_at	Hs.514174	junction plakoglobin	JUP
201324_at	Hs.436298	epithelial membrane protein 1	EMPI
201641_at	Hs.118110	bone marrow stromal cell antigen 2	BST2
201646_at	Hs.349656	scavenger receptor class B, member 2 methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	SCARB2
201761_at	Hs.469030	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse) ///	MTHFD2
202086_at	Hs.517307	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1
202145_at	Hs.521903	lymphocyte antigen 6 complex, locus E guanylate binding protein 1, interferon-inducible, 67kDa ///	LY6E
202270_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1
202411_at	Hs.532634	interferon, alpha-inducible protein 27	IFI27
202430_s_at	Hs.130759	phospholipid scramblase 1	PLSCR1
202446_s_at	Hs.130759	phospholipid scramblase 1	PLSCR1 AKAP2 ///
202759_s_at	Hs.591908	A kinase (PRKA) anchor protein 2 ///	PALM2- AKAP2
202863_at	Hs.369056	SP100 nuclear antigen	SP100
202869_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa interferon-induced protein with tetratricopeptide repeats 1 ///	OAS1
203153_at	Hs.20315	interferon-induced protein with tetratricopeptide repeats 1	IFIT1
203595_s_at	Hs.252839	interferon-induced protein with tetratricopeptide repeats 5	IFIT5
203596_s_at	Hs.252839	interferon-induced protein with tetratricopeptide repeats 5	IFIT5
203771_s_at	Hs.488143	biliverdin reductase A	BLVRA
204211_x_at	Hs.131431	eukaryotic translation initiation factor 2-alpha kinase 2	EIF2AK2
204224_s_at	Hs.86724	GTP cyclohydrolase 1 (dopa-responsive dystonia)	GCH1
204326_x_at	Hs.374950	metallothionein 1X	MT1X
204415_at	Hs.523847	interferon, alpha-inducible protein 6	IFI6
204439_at	Hs.389724	interferon-induced protein 44-like	IFI44L
204533_at	Hs.632586	chemokine (C-X-C motif) ligand 10 interferon-induced protein with tetratricopeptide repeats 3	CXCL10
204747_at	Hs.47338		IFIT3
204972_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2
204994_at	Hs.926	myxovirus (influenza virus) resistance 2 (mouse)	MX2
205098_at	Hs.301921	chemokine (C-C motif) receptor 1	CCR1
205099_s_at	Hs.301921	chemokine (C-C motif) receptor 1	CCR1
205170_at	Hs.530595	signal transducer and activator of transcription 2, 113kDa	STAT2
205241_at	Hs.567405	SCO cytochrome oxidase deficient homolog 2 (yeast)	SCO2
205483_s_at	Hs.458485	ISG15 ubiquitin-like modifier	ISG15

205552_s_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1
205569_at	Hs.518448	lysosomal-associated membrane protein 3	LAMP3
205660_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL
206025_s_at	Hs.437322	tumor necrosis factor, alpha-induced protein 6	TNFAIP6
206026_s_at	Hs.437322	tumor necrosis factor, alpha-induced protein 6	TNFAIP6
206133_at	Hs.441975	XIAP associated factor-1	BIRC4BP
206332_s_at	---	interferon, gamma-inducible protein 16	IFI16
206513_at	Hs.281898	absent in melanoma 2	AIM2
206553_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2
206576_s_at	Hs.512682	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	CEACAM1
206715_at	Hs.125962	transcription factor EC	TFEC
208087_s_at	Hs.302123	Z-DNA binding protein 1 /// Z-DNA binding protein 1	ZBP1
208436_s_at	Hs.166120	interferon regulatory factor 7	IRF7
208581_x_at	Hs.374950	metallothionein 1X	MT1X
208653_s_at	Hs.591335	CD164 molecule, sialomucin	CD164
208966_x_at	---	interferon, gamma-inducible protein 16	IFI16
209417_s_at	Hs.632258	interferon-induced protein 35	IFI35
209498_at	Hs.512682	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	CEACAM1
209593_s_at	Hs.252682	torsin family 1, member B (torsin B)	TOR1B
210001_s_at	Hs.50640	suppressor of cytokine signaling 1	SOCS1
210705_s_at	Hs.370515	tripartite motif-containing 5	TRIM5
210797_s_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL
210873_x_at	Hs.348983	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A	APOBEC3A
210985_s_at	Hs.369056	SP100 nuclear antigen	SP100
			PML ///
		promyelocytic leukemia /// hypothetical protein	LOC161527
		LOC161527 /// similar to promyelocytic leukemia	///
		protein isoform 9	LOC652671
211012_s_at	Hs.498345	hypothetical protein LOC650610	LOC650610
211456_x_at	---	carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)	CEACAM1
211889_x_at	Hs.512682	metallothionein 2A	MT2A
212185_x_at	Hs.534330	interleukin 1 receptor antagonist	IL1RN
212657_s_at	Hs.81134	interleukin 1 receptor antagonist	IL1RN
212659_s_at	Hs.81134	sterile alpha motif domain containing 4A	SAMD4A
212845_at	Hs.98259	tripartite motif-containing 22	TRIM22
213293_s_at	Hs.501778	Full-length cDNA clone CS0DK002YF13 of HeLa cells Cot 25-normalized of Homo sapiens (human)	---
213294_at	Hs.546523	tudor domain containing 7	TDRD7
213361_at	Hs.193842	GPI deacylase	PGAP1
213469_at	Hs.229988	radical S-adenosyl methionine domain containing 2	RSAD2
213797_at	Hs.17518	Interferon-induced protein 44	IFI44
214059_at	Hs.82316	tumor necrosis factor (ligand) superfamily, member 10 /// tumor necrosis factor (ligand) superfamily, member 10	TNFSF10
214329_x_at	Hs.478275	interferon-induced protein 44	IFI44
214453_s_at	Hs.82316	Fc fragment of IgG, high affinity Ia, receptor (CD64) /// Fc-gamma receptor I B2 /// similar to Fc-gamma receptor I B2 isoform b	FCGR1A /// LOC440607 /// LOC652758
214511_x_at	Hs.534956	interleukin 1 receptor antagonist	IL1RN
216243_s_at	Hs.81134	chemokine (C-C motif) ligand 2	CCL2
216598_s_at	Hs.303649	metallothionein 1F (functional)	MT1F
217165_x_at	Hs.513626	interferon-induced protein with tetratricopeptide repeats 2	IFIT2
217502_at	Hs.437609	leucine aminopeptidase 3	LAP3
217933_s_at	Hs.570791	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3
218400_at	Hs.528634		

218543_s_at	Hs.12646	poly (ADP-ribose) polymerase family, member 12	PARP12
218943_s_at	Hs.190622	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	DDX58
218986_s_at	Hs.591710	hypothetical protein FLJ20035	FLJ20035
219062_s_at	Hs.631682	zinc finger, CCHC domain containing 2	ZCCHC2
219209_at	Hs.163173	interferon induced with helicase C domain 1	IFIH1
219211_at	Hs.38260	ubiquitin specific peptidase 18	USP18
219352_at	Hs.529317	hect domain and RLD 6	HERC6
219364_at	Hs.55918	likely ortholog of mouse D11lgp2	LGP2
219519_s_at	Hs.31869	sialic acid binding Ig-like lectin 1, sialoadhesin ///	SIGLEC1
219607_s_at	Hs.325960	sialic acid binding Ig-like lectin 1, sialoadhesin membrane-spanning 4-domains, subfamily A, member 4	MS4A4A
219684_at	Hs.43388	receptor transporter protein 4	RTP4
219691_at	Hs.65641	sterile alpha motif domain containing 9	SAMD9
219863_at	Hs.26663	hect domain and RLD 5	HERC5
219885_at	---	schlafen family member 12	SLFN12
220059_at	Hs.435579	BCR downstream signaling 1	BRDG1
220576_at	Hs.229988	GPI deacylase	PGAP1
221680_s_at	Hs.272398	ets variant gene 7 (TEL2 oncogene)	ETV7
221816_s_at	Hs.369039	PHD finger protein 11	PHF11
222154_s_at	Hs.120323	DNA polymerase-transactivated protein 6	DNATP6
222631_at	Hs.443733	phosphatidylinositol 4-kinase type 2 beta	PI4K2B
222793_at	Hs.190622	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	DDX58
222816_s_at	Hs.631682	zinc finger, CCHC domain containing 2	ZCCHC2
223167_s_at	Hs.473370	ubiquitin specific peptidase 25	USP25
223220_s_at	Hs.518200	poly (ADP-ribose) polymerase family, member 9	PARP9
223434_at	---	guanylate binding protein 3	GBP3
223501_at	---	---	---
223849_s_at	Hs.514941	Mov10, Moloney leukemia virus 10, homolog (mouse)	MOV10
224225_s_at	Hs.272398	ets variant gene 7 (TEL2 oncogene)	ETV7
224701_at	Hs.583792	poly (ADP-ribose) polymerase family, member 14	PARP14
225291_at	Hs.388733	polyribonucleotide nucleotidyltransferase 1	PNPT1
225415_at	Hs.518201	deltex 3-like (Drosophila)	DTX3L
225636_at	Hs.530595	signal transducer and activator of transcription 2, 113kDa	STAT2 LOC652689
		hypothetical protein LOC652689 /// family with sequence similarity 72, member A /// similar to family with sequence similarity 72, member A ///	/// FAM72A /// LOC653594 /// LOC653820
225834_at	Hs.599880	unc-93 homolog B1 (C. elegans)	UNC93B1
225869_s_at	Hs.502989	nexilin (F actin binding protein)	NEXN
226103_at	Hs.632387	sterile alpha motif domain containing 9-like	SAMD9L
226603_at	Hs.489118	hypothetical protein LOC129607	LOC129607
226702_at	Hs.7155	interferon-induced protein with tetratricopeptide repeats 2	IFIT2
226757_at	Hs.437609	---	---
227458_at	---	---	---
227609_at	Hs.546467	epithelial stromal interaction 1 (breast)	EPSTI1
227697_at	Hs.527973	suppressor of cytokine signaling 3	SOCS3
228152_s_at	Hs.535011	hypothetical protein FLJ31033	FLJ31033
228230_at	Hs.517180	peroxisomal proliferator-activated receptor A interacting complex 285	PRIC285
228439_at	Hs.124840	basic leucine zipper transcription factor, ATF-like 2	BATF2
228531_at	Hs.65641	sterile alpha motif domain containing 9	SAMD9
228607_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2
228617_at	Hs.441975	XIAP associated factor-1	BIRC4BP
229450_at	---	---	---

230036_at	Hs.489118	sterile alpha motif domain containing 9-like Transcribed locus, strongly similar to XP_511805.1 PREDICTED: hypothetical protein XP_511805 [Pan troglodytes]	SAMD9L
230314_at	Hs.112420		---
231769_at	Hs.464419	F-box protein 6	FBXO6
232034_at	Hs.599821	hypothetical protein LOC203274	LOC203274
232155_at	Hs.514554	KIAA1618	KIAA1618
232375_at	Hs.565365	Signal transducer and activator of transcription 1, 91kDa	STAT1
232666_at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3
233425_at	Hs.631682	zinc finger, CCHC domain containing 2	ZCCHC2
233880_at	Hs.195642	chromosome 17 open reading frame 27	C17orf27
235061_at	Hs.291000	protein phosphatase 1K (PP2C domain containing)	PPM1K
235112_at	Hs.533491	KIAA1958	KIAA1958
235157_at	Hs.583792	Poly (ADP-ribose) polymerase family, member 14	PARP14
235276_at	---	---	---
235643_at	Hs.489118	sterile alpha motif domain containing 9-like lipase A, lysosomal acid, cholesterol esterase (Wolman disease)	SAMD9L
236156_at	Hs.127445		LIPA
236692_at	---	---	---
238439_at	Hs.217484	ankyrin repeat domain 22	ANKRD22
238581_at	Hs.513726	Guanylate binding protein 5 Full-length cDNA clone CS0DK002YF13 of HeLa cells Cot 25-normalized of Homo sapiens (human)	GBP5
238743_at	Hs.546523		---
239196_at	Hs.217484	ankyrin repeat domain 22	ANKRD22
239277_at	---	---	---
239979_at	Hs.546467	Epithelial stromal interaction 1 (breast)	EPSTI1
241812_at	Hs.120323	DNA polymerase-transactivated protein 6	DNATP6
241916_at	Hs.130759	Phospholipid scramblase 1	PLSCR1
242020_s_at	Hs.302123	Z-DNA binding protein 1	ZBP1
242234_at	Hs.441975	XIAP associated factor-1	BIRC4BP
242625_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2
242898_at	---	---	---
243271_at	Hs.489118	Sterile alpha motif domain containing 9-like	SAMD9L
44673_at	Hs.31869	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1
AFFX- HUMISGF3A/M97935_3_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1
AFFX- HUMISGF3A/M97935_5_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1
AFFX- HUMISGF3A/M97935_MB_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1

Similarly, using 25 highly upregulated IFN-inducible genes, expression in whole blood samples of lupus patients and normal healthy donors was analyzed using PCA (Principal Component Analysis). The PCA determined that approximately 66% of the lupus patients had a strong/moderate type I IFN inducible signature. See Figure 68a for PCA analysis results and 68b for 25 genes used in the PCA analysis.

The overexpression of type I IFN genes in SLE patient whole blood for a larger number of patients, determined using an Affymetrix whole genome array, is provided in Table 23. Table 23 and Figure 65 provide further evidence that a high percentage of SLE patients share at least 2-fold overexpression of each individual type I IFN genes.

Table 23: Overexpressed Type-I IFN Genes in Whole Blood of Lupus Patients

Probe.ID	Gene.Title	Gene.Symbol	Number Of Samples Displaying A Fold-Change ≥ 2	% of Samples	Average log2 Fold- Change
222816 s at	zinc finger, CCHC domain containing 2	ZCCHC2	70	79.55	2.124
204415 at	interferon, alpha-inducible protein 6	IFI6	67	76.14	3.007
217502 at	interferon-induced protein with tetratricopeptide repeats 2	IFIT2	65	73.86	1.913
235643 at	sterile alpha motif domain containing 9-like	SAMD9L	65	73.86	2.020
213797 at	radical S-adenosyl methionine domain containing 2	RSAD2	62	70.45	2.978
214059 at	Interferon-induced protein 44	IFI44	61	69.32	3.050
202411 at	interferon, alpha-inducible protein 27	IFI27	60	68.18	3.937
204439 at	interferon-induced protein 44-like	IFI44L	60	68.18	2.847
242625 at	radical S-adenosyl methionine domain containing 2	RSAD2	59	67.05	2.861
214453 s at	interferon-induced protein 44	IFI44	59	67.05	2.463
203153 at	interferon-induced protein with tetratricopeptide repeats 1 /// in	IFIT1	59	67.05	2.034
242234 at	XIAP associated factor-1	BIRC4BP	59	67.05	2.066
203595 s at	interferon-induced protein with tetratricopeptide repeats 5	IFIT5	59	67.05	1.603
202086 at	myxovirus (influenza virus) resistance 1, interferon-inducible p	MX1	58	65.91	1.777
206133 at	XIAP associated factor-1	BIRC4BP	58	65.91	1.803
216243 s at	interleukin 1 receptor antagonist	IL1RN	58	65.91	1.278
219863 at	hect domain and RLD 5	HERC5	57	64.77	1.795
202869 at	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	56	63.64	2.057
226702 at	hypothetical protein LOC129607	LOC129607	56	63.64	1.797
205483 s at	ISG15 ubiquitin-like modifier	ISG15	56	63.64	1.979
204747 at	interferon-induced protein with tetratricopeptide repeats 3	IFIT3	56	63.64	1.675
1555464 at	interferon induced with helicase C domain 1	IFIH1	56	63.64	1.532
218400 at	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	55	62.50	1.932
227609 at	epithelial stromal interaction 1 (breast)	EPSTI1	55	62.50	1.788
200986 at	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (a	SERPING1	55	62.50	1.503
202145 at	lymphocyte antigen 6 complex, locus E	LY6E	54	61.36	2.242
239979 at	Epithelial stromal interaction 1 (breast)	EPSTI1	54	61.36	1.895
205552 s at	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	54	61.36	1.945
225929 s at	chromosome 17 open reading frame 27	C17orf27	54	61.36	1.054
222154 s at	DNA polymerase-transactivated protein 6	DNAPT6	53	60.23	2.030
205569 at	lysosomal-associated membrane protein 3	LAMP3	53	60.23	1.813
205660 at	2'-5'-oligoadenylate synthetase-like	OASL	53	60.23	1.677
219352 at	hect domain and RLD 6	HERC6	52	59.09	1.663
210797 s at	2'-5'-oligoadenylate synthetase-like	OASL	52	59.09	1.548
241916 at	Phospholipid scramblase 1	PLSCR1	52	59.09	1.396
208087 s at	Z-DNA binding protein 1 /// Z-DNA binding protein 1	ZBP1	52	59.09	1.438
243271 at	Sterile alpha motif domain containing 9-like	SAMD9L	52	59.09	1.126
219519 s at	sialic acid binding Ig-like lectin 1, sialoadhesin /// sialic acid bin	SIGLEC1	51	57.95	3.019
228617 at	XIAP associated factor-1	BIRC4BP	51	57.95	1.473
202446 s at	phospholipid scramblase 1	PLSCR1	51	57.95	1.307
232095 at	SLIT-ROBO Rho GTPase activating protein 2	SRGAP2	50	56.82	1.155
232666 at	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	49	55.68	1.862
204972 at	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	49	55.68	1.642
202430 s at	phospholipid scramblase 1	PLSCR1	49	55.68	1.209
224701 at	poly (ADP-ribose) polymerase family, member 14	PARP14	49	55.68	1.098
219211 at	ubiquitin specific peptidase 18	USP18	48	54.55	2.365
206553 at	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	48	54.55	1.582
219684 at	receptor transporter protein 4	RTP4	48	54.55	1.534
230000 at	chromosome 17 open reading frame 27	C17orf27	47	53.41	0.936
44673 at	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1	47	53.41	1.975
203596 s at	interferon-induced protein with tetratricopeptide repeats 5	IFIT5	47	53.41	1.327
218986 s at	hypothetical protein FLJ20035	FLJ20035	47	53.41	1.091
242020 s at	Z-DNA binding protein 1	ZBP1	47	53.41	1.195
212659 s at	interleukin 1 receptor antagonist	IL1RN	47	53.41	1.196
228439 at	basic leucine zipper transcription factor, ATF-like 2	BATF2	46	52.27	1.180
226757 at	interferon-induced protein with tetratricopeptide repeats 2	IFIT2	46	52.27	0.882
225291 at	polynucleotide nucleotidyltransferase 1	PNPT1	46	52.27	0.957
206026 s at	tumor necrosis factor, alpha-induced protein 6	TNFAIP6	46	52.27	0.942
222858 s at	dual adaptor of phosphotyrosine and 3-phosphoinositides	DAPP1	46	52.27	1.055
208436 s at	interferon regulatory factor 7	IRF7	45	51.14	1.146
217933 s at	leucine aminopeptidase 3	LAP3	45	51.14	0.807
228152 s at	hypothetical protein FLJ31033	FLJ31033	45	51.14	0.834
230036 at	sterile alpha motif domain containing 9-like	SAMD9L	44	50.00	1.097
228607 at	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	44	50.00	1.113
218543 s at	poly (ADP-ribose) polymerase family, member 12	PARP12	44	50.00	1.111
226603 at	sterile alpha motif domain containing 9-like	SAMD9L	44	50.00	1.033
204211 x at	eukaryotic translation initiation factor 2-alpha kinase 2	EIF2AK2	44	50.00	1.050
235157 at	Poly (ADP-ribose) polymerase family, member 14	PARP14	44	50.00	0.940
209417 s at	interferon-induced protein 35	IFI35	44	50.00	0.957

Based on the observations of different overexpressed type I IFN genes in SLE patients, described above, a set of 21 type I IFN genes in whole blood of lupus patients was identified as potentially useful. See Table 24.

Table 24: Twenty one potential overexpressed type I IFN genes useful as PD markers

le	IFI44	IFI27	IFI44L	DNAPTP6	LAMP3	LY6E	RSAD2	HERC5	IFI6	ISG15	OAS3	SIGLEC1	OAS2	USP18	RTP4	IFIT1	MX1	OAS1	EPSTH1	PLSCR1	IFRG28
29	23.67	3.34	23.45	7.63	6.75	7.25	28.21	8.12	5.53	7.47	4.82	5.16	5.22	7.14	3.94	15.26	4.98	7.75	6.57	3.69	3.71
30	5.31	4.33	6.28	2.80	4.23	1.44	8.14	2.76	2.39	3.44	3.48	2.26	2.63	2.12	1.82	4.83	2.77	2.06	2.48	3.65	2.17
43	10.70	1.41	10.31	2.51	2.23	2.94	11.76	2.52	1.25	1.97	2.63	0.96	2.38	2.85	2.73	7.39	2.82	3.78	2.97	2.12	2.89
45	37.55	30.71	28.86	5.28	3.94	4.30	35.61	1.88	1.85	3.73	2.26	0.92	3.03	2.54	3.70	21.92	2.66	4.51	10.06	2.48	3.92
50	10.72	4.62	7.36	2.42	1.34	3.38	14.35	2.07	3.34	2.46	2.55	2.81	2.17	2.01	1.12	13.79	2.32	2.30	3.51	1.40	1.29
51	4.19	0.83	5.32	2.51	4.13	1.27	7.01	3.64	4.67	3.08	4.16	6.38	2.97	2.43	1.46	4.55	2.40	2.02	2.40	2.43	1.41
55	24.79	8.25	26.45	15.76	18.11	11.33	54.51	13.72	15.37	16.02	10.79	10.33	8.85	9.57	7.07	23.56	8.22	11.56	16.51	5.93	7.49
73	0.88	0.96	0.53	0.63	0.65	0.85	0.27	0.39	0.48	0.70	0.25	0.26	0.50	0.96	1.35	0.31	0.77	0.68	0.59	1.45	1.48
75	0.85	0.17	0.67	0.89	0.14	0.36	0.36	0.32	0.18	0.27	0.42	0.12	0.73	0.43	0.69	0.32	0.23	0.92	0.50	2.97	0.82
76	1.25	4.20	0.83	2.71	2.19	2.82	0.95	1.97	0.70	1.78	0.93	0.45	2.15	2.94	4.70	0.49	1.76	1.54	1.01	7.92	4.96
77	0.78	17.78	0.54	0.37	0.40	2.26	0.11	0.28	0.65	1.99	0.28	0.57	0.35	1.18	3.44	0.23	0.96	1.65	0.51	2.05	3.50
78	1.53	5.56	0.98	1.90	2.24	1.89	0.82	1.65	0.71	2.89	0.50	1.00	1.64	1.86	4.20	0.39	1.73	2.40	1.23	8.18	4.51
1	8.93	162.67	16.29	41.43	4.13	35.49	14.75	10.03	5.34	31.98	5.95	13.14	6.35	15.81	13.08	0.65	18.84	10.75	9.42	8.16	14.58
2	30.64	135.38	53.11	15.25	6.78	7.33	20.98	4.88	6.52	8.78	6.28	6.49	5.58	23.17	6.56	15.64	6.73	9.22	7.10	3.62	6.68
4	25.99	220.81	71.18	18.13	8.48	9.94	51.74	8.77	4.32	12.04	7.00	6.60	7.87	32.60	11.21	21.06	9.69	8.07	11.63	7.62	10.31
5	11.39	324.78	63.12	44.63	6.71	14.93	50.68	11.58	7.46	22.37	11.03	23.05	11.90	63.56	10.70	19.74	17.43	14.42	9.62	5.59	9.02
ib	0.48	0.57	0.47	0.55	0.25	0.73	0.27	0.33	1.20	0.70	0.21	0.31	0.34	0.38	0.81	0.33	0.38	0.52	0.60	0.37	0.67
7	63.08	498.86	71.47	31.25	9.75	25.15	124.43	17.26	12.01	30.68	4.98	4.88	11.92	37.94	14.21	32.73	13.92	12.20	14.28	14.35	11.18
9	30.12	209.75	46.29	15.45	6.63	11.07	32.35	8.07	4.71	10.17	6.77	8.67	9.57	21.00	8.07	14.25	9.04	9.53	8.01	7.83	7.49
0	24.31	85.83	42.22	21.61	10.78	15.14	49.98	12.94	7.29	19.29	10.90	7.34	10.34	18.34	7.80	12.47	8.32	11.58	12.30	7.21	7.03
1	26.17	160.53	30.34	57.41	32.45	29.58	45.36	35.18	2.66	14.93	44.32	25.28	27.10	51.74	26.85	9.19	15.63	17.96	15.00	19.29	28.84
2	48.84	131.90	85.63	15.28	7.85	10.17	57.95	8.19	5.21	8.71	7.76	4.55	10.17	31.27	10.46	27.35	8.32	7.66	12.35	6.33	9.08
3	3.14	2.21	4.97	1.84	1.79	0.73	6.65	2.66	1.34	1.02	1.85	0.74	1.41	2.45	2.69	3.55	2.14	1.32	3.19	2.30	2.31
7	21.09	256.30	48.34	18.49	5.74	9.18	35.38	7.79	4.91	13.13	6.54	4.77	6.67	16.58	4.91	18.66	5.69	10.37	8.29	5.62	5.43
8	71.14	177.60	97.17	41.72	11.95	28.82	98.76	16.75	10.97	27.33	18.71	9.84	16.48	75.02	18.41	44.09	23.41	12.66	18.71	12.52	15.63
9	75.89	362.67	158.96	30.47	16.33	17.58	113.44	17.70	16.63	29.09	7.39	5.29	15.13	61.50	21.00	22.61	21.25	19.06	18.93	12.46	19.78
0	49.27	149.00	96.50	40.29	13.89	23.41	77.48	16.52	10.21	30.40	6.26	5.92	11.57	48.59	13.57	34.76	13.99	11.76	13.89	8.63	13.38
21	100.31	153.10	123.21	46.69	25.19	19.63	95.12	17.61	8.08	42.37	3.38	8.45	14.21	58.15	12.60	20.80	14.95	20.32	23.72	13.22	13.85
22	7.05	3.09	4.15	2.50	3.07	1.82	2.62	1.75	0.61	1.29	0.40	0.58	1.55	5.30	1.56	3.31	1.98	1.87	4.22	3.40	1.54
14	49.92	189.36	47.56	32.63	11.84	24.45	50.62	15.98	15.19	50.39	12.14	6.27	13.98	26.94	12.80	33.17	10.47	17.41	16.85	8.43	13.63
71	32.06	8.24	26.46	13.54	9.78	6.63	41.14	12.40	5.23	10.87	7.65	8.53	8.22	12.46	5.35	25.74	11.90	5.68	8.13	6.33	5.56
53	77.48	163.43	90.25	236.52	162.67	30.05	73.47	26.40	25.86	193.45	35.73	130.31	28.23	71.63	23.96	33.26	13.14	20.71	25.62	12.29	27.39
11	5.39	0.81	2.19	1.36	0.54	1.08	1.15	0.79	1.05	1.42	0.17	0.30	0.88	1.08	2.50	1.43	1.29	2.19	2.02	2.20	2.80
77	16.15	7.55	19.03	7.33	3.59	6.35	14.39	3.88	1.82	4.88	3.85	3.76	4.75	7.64	3.43	7.76	4.15	3.10	6.32	2.90	3.76
71	86.57	51.95	89.42	96.06	18.37	28.43	110.34	24.75	12.09	45.54	24.29	12.46	25.62	54.29	17.10	51.00	13.86	21.64	25.98	14.28	17.42
in	23.67	30.71	26.46	15.25	6.63	7.33	32.35	8.07	4.71	8.78	4.98	5.16	6.35	12.16	5.35	14.25	6.73	7.75	8.13	5.93	5.56
3e	28.22	101.10	40.00	25.02	12.14	11.37	38.03	9.19	5.94	18.76	7.62	9.39	8.07	22.10	8.17	15.62	7.95	8.32	9.27	6.55	8.16
le	IFI44	IFI27	IFI44L	DNAPTP6	LAMP3	LY6E	RSAD2	HERC5	IFI6	ISG15	OAS3	SIGLEC1	OAS2	USP18	RTP4	IFIT1	MX1	OAS1	EPSTH1	PLSCR1	IFRG28

Overexpression of these genes, as detected initially using the Affymetrix arrays, was confirmed by Fluidigm dynamic array, validating their overexpression. See Figure 69.

Example 8: MEDI-545 Considerably Neutralizes the Type I IFN Gene Signature of SLE Patients Having a Strong to Moderate Type I IFN Gene Signature

Patients in a clinical trial were identified as having a strong/moderate type I IFN gene, a weak type I IFN gene signature, or no type I IFN gene signature. These patients were designated into one of these groups based on 149 genes. Table 25 shows the number of lupus patients in the clinical trial that were designated in each of these three groups and indicates the treatment protocol they received.

Table 25: Patient distribution based on type-I IFN gene signature prior to treatment

Group	Strong & moderate signature	Weak signature	No signature
PBO	10	5	2
0.3 mpk	5	0	1
1 mpk	2	2	2
3 mpk	3	2	1
10 mpk	4	3	0
30 mpk	3	2	1
Total	27	14	7

The SLE patients that were designated as having strong and moderate type-I IFN gene signatures all had: an average 4-fold increase in expression of the top 25 most upregulated type I IFN genes; an average 2-fold increase in expression of the top 50 most upregulated type I IFN genes; and a percentage of total examined disease genes being type I IFN inducible of 3.8. The average fold increase in the top 25 type I IFN inducible genes for each patient having a strong/moderate type I IFN signature or a weak signature in the trial is provided in Figure 28.

Treatment of these different SLE patient groups provided evidence that neutralization of the type I IFN gene signature by MEDI-545 is drug specific. Figure 29(a) shows that in a group of SLE patients having a type-I IFN gene signature, virtually all of the top 39 genes neutralized 14 days post-MEDI-545 treatment are type I IFN signature genes (see yellow highlighted genes; percentage inhibition of the type I IFN signature genes ranged from 30.5-64.7). By contrast, none of the top 39 neutralized genes in SLE patients who received placebo were type I IFN signature genes. See Figure 29(c). The SLE patients who lacked a type I IFN signature and were treated with MEDI-545 displayed an intermediate neutralization pattern, with some type I IFN signature genes neutralized. (See Figure 29(b); yellow highlighting indicates type I IFN signature genes, which were neutralized from 19%-44.9%).

Further break down of SLE patients into strong, moderate, and weak type-I IFN gene signatures was conducted. Briefly, the 25 most highly overexpressed type I IFN-inducible

genes in individual SLE patients generated from the ex vivo stimulation of healthy donor WB with SLE patient sera study were selected and the median fold change of these 25 genes was used to construct a type I IFN gene signature score for each SLE patient. Figure 84 shows the distribution of the type I IFN gene signature scores of the 46 SLE patients profiled. The SLE patients were profiled into 3 groups based on their type I IFN gene signature score: high type I IFN gene signature (score >10); moderate type I IFN gene signature (score 4–10); and weak type I IFN gene signature (score <4).

Selection of a panel of 21 type I IFN-inducible genes in WB of SLE patients

To select a small, robust panel of type I IFN-inducible genes that could be developed into an HTP assay, the gene panel was narrowed to 21 genes. To identify the 21 potential PD and diagnostic markers, 807 IFN- α/β -inducible probes identified by ex vivo stimulation of healthy donor WB with 10 IFN- α subtypes (2a, 4b, 5, 6, 7, 8, 10, 14, 16, and 17) and IFN- β were used as a candidate marker starting point. The WB samples from a total of 46 SLE patients procured from commercial vendors and 24 healthy normal controls were used to determine the type I IFN-inducible probes that are upregulated in WB of SLE patients. 114 overexpressed probes ($q \leq 0.05$; fold change ≥ 2) were identified in WB of SLE patients were type I IFN-inducible using SAM and FDR.

To investigate whether these overexpressed type I IFN-inducible genes in WB of SLE patients were neutralizable by an anti-IFN- α mAb, one healthy donor PBMC was stimulated ex vivo with sera from six individual SLE patients. The healthy donor was prescreened to exclude those donors that might have viral infection. 161 type I IFN-inducible probes were upregulated by ≥ 2 -fold in the PBMC of the healthy donor following stimulation with ≥ 1 SLE patient serum in which the overexpression of these genes was suppressed by $\geq 50\%$ and $\geq 70\%$ by an anti-IFN- α mAb and an anti-IFN- α R mAb, respectively.

The intersection between this list of 161 probes and previously determined list of 114 probes was 80 probes. Each of these 80 probes was ranked by both the average fold change magnitude across all SLE patients and the percentage of patients displaying a change ≥ 2 -fold. Generally, the 21 most prevalently overexpressed type I IFN-inducible genes (that represent unique genes using the NetAffx annotation file for the Affymetrix U133 2.0 plus array; ESTs were excluded) from this ranking were retained for a static list of probes used to measure PD. The type I IFN signature score was then defined by the median of these 21 genes.

With these 21 genes, it was necessary to recalculate the thresholds that had been previously identified for partitioning SLE patients into type I IFN gene signature responses of

strong, moderate, or weak (based on the Affymetrix platform) for a lower density platform (TaqMan-based assay). A scaling method was required to convert the type I IFN signature score based on the top 25 differentially expressed genes (independent for each SLE patient) on the Affymetrix platform to the type I IFN signature score based on the 21 genes selected for the TaqMan-based assay. This method was implemented to compensate for 3 primary differences between the 2 platforms: (1) the number of probes used for the type I IFN signature (25 genes dynamically determined for each patient on the Affymetrix platform versus a 21 static gene list on the TaqMan-based assay), (2) the differences in sensitivity between the 2 platforms, and (3) the scales of the dynamic ranges within each platform. First, the fold change values were calculated (on a $\log_2$ scale) for the 155 type I-inducible probes between the 35 randomly selected SLE patients and the average of a set of normal healthy controls. The genes with the top 25-fold change values were determined for each patient on the Affymetrix platform (this gene set is allowed to vary from patient to patient depending on which type I IFN-inducible genes are most highly expressed). Next, the median fold change was calculated from the top 25 genes for each SLE patient. The same calculation was conducted across the same patients using the static 21 gene set on the TaqMan-based assay. This gene set was identical for each patient and the median fold change was calculated based on 21 genes, rather than 25 dynamic genes, as was conducted for the Affymetrix platform. A simple regression model was then computed using these 2 vectors of equal length (35 median fold change values), and the coefficients from the model were used to calculate the conversion factor (from the Affymetrix platform to the TaqMan-based assay) for the response threshold values to partition the SLE patients into a type I IFN gene signature category of strong (>10 on Affymetrix; >5.53 on TaqMan), moderate (between 4 and 10 on Affymetrix; between 1.91 and 5.53 on TaqMan), or weak (<4 on Affymetrix; <1.91 on TaqMan). Using these scaled threshold values, for the purpose of stratifying SLE patients, the signature (ie, median fold change) that was calculated on the 21 genes from the TaqMan-based assay was comparable to that from the top 25 upregulated type I IFN-inducible genes.

The prevalence and fold change ($\log_2$ based) of the 21 IFN α/β -inducible genes in whole blood of 111 SLE patients is provided in Table 32, below.

Table 32: Prevalence and fold change in expression of 21 IFN α/β -inducible genes in SLE patient whole blood

Probe	Q value	Fold	Prevalence	Gene name	Gene symbol
204415 at	$qv < 1e-16$	9.38	78.20	interferon, alpha-inducible protein 6	IFI6
213797 at	2.67E-12	8.27	71.80	radical S-adenosyl methionine domain	RSAD2

				containing 2	
214059_at	7.18E-14	7.93	70.90	Interferon-induced protein 44	IFI44
204439_at	5.85E-12	6.45	69.10	interferon-induced protein 44-like	IFI44L
202411_at	6.35E-12	14.42	67.30	interferon, alpha-inducible protein 27	IFI27
202086_at	1.09E-09	3.26	66.40	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1
203153_at	3.90E-07	3.52	65.50	interferon-induced protein with tetratricopeptide repeats 1	IFIT1
219863_at	8.05E-11	3.27	64.50	hect domain and RLD 5	HERC5
205483_s at	1.23E-13	3.71	63.60	ISG15 ubiquitin-like modifier	ISG15
205569_at	qv<1e-16	3.91	62.70	lysosomal-associated membrane protein 3	LAMP3
218400_at	1.01E-10	3.65	62.70	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3
202869_at	4.95E-11	3.77	61.80	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1
227609_at	7.41E-10	3.16	60.90	epithelial stromal interaction 1 (breast)	EPSTI1
204747_at	9.78E-11	3.04	60.90	interferon-induced protein with tetratricopeptide repeats 3	IFIT3
202145_at	qv<1e-16	4.65	60.90	lymphocyte antigen 6 complex, locus E	LY6E
204972_at	qv<1e-16	3.06	58.20	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2
241916_at	6.29E-07	2.46	56.40	Phospholipid scramblase 1	PLSCR1
44673_at	qv<1e-16	3.91	55.50	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1
219211_at	2.54E-13	4.83	55.50	ubiquitin specific peptidase 18	USP18
219684_at	2.75E-07	2.47	50.00	receptor (chemosensory) transporter protein 4	RTP4
241812_at	5.25E-07	1.84	38.20	DNA polymerase-transactivated protein 6	DNAPTP6

These 21 genes were neutralized in a dose-dependent dependent fashion by MEDI-545. See Figure 86 and 89. Heatmap (Figure 87a) and PCA calculations (Figure 87b) using these 21 genes showed neutralization of the-upregulated IFN α/β gene signature in an SLE patient treated with 30 mg/kg MEDI-545, but not in placebo-treated SLE patients (Figure 88). Thus, it is evident that these genes could be used as a PD marker set.

Stratification of 35 patients, by strength of type I IFN gene signature using the 21 genes

Figure 85 shows the stratification of 35 SLE patients into groups of high (20 patients), moderate (8 patients), and weak (7 patients) type I IFN gene signatures based on the distribution of fold change values ($\log_2$ scale) of all 21 type I IFN-inducible genes and partitioned into each group by the median fold change of this distribution of 21 genes for each patient (vertical dashed lines), as measured by the dynamic array from Fluidigm. From figure 85, it is apparent that each patient distribution exhibits slight differences in skewness and basic shape/form, as this indicates the diversity in the various severity levels of SLE, based on the 21 type IFN-inducible gene selected. In a PCA plot for all SLE patients profiled in this study (n=100) and for the 24 healthy control samples using the 21 type I IFN-inducible genes, a clear distinction between SLE patients with an overexpressed type I IFN

gene signature and those with weak or nondetectable type I IFN gene signatures is observed (Figure 82C). Furthermore, the SLE patients with weak or nondetectable type I IFN gene signatures were clustered together with healthy donors. Importantly, the partitioning between these groups using the 21-gene panel of type I IFN-inducible genes was similar to that observed with the larger 114-gene set (Figures 81A and 81B).

Example 9: Multiple Type-I IFN Subtypes are Up-Regulated in Whole Blood of SLE Patients

To identify the type-I IFN subtypes responsible for the induction of the type-I IFN signature of SLE patients, mRNA levels of type-I IFN genes in SLE patient whole blood were measured.

Gene expression analysis was performed using a TaqMan Low Density Array (TLDA) from Applied Biosystems. Expression of type-I IFN α subtypes 1, 2, 5, 6, 7, 8, 14, 17, and 21 was monitored and compared in whole blood of SLE patients relative to healthy volunteers.

Double-stranded cDNA for each patient sample was pre-amplified using the TaqMan PreAmp Master Mix kit (Applied Biosystems). cDNA was pre-amplified by conducting 10 cycles of PCR on each patient sample using a pooled solution of primers, a pair for each gene analyzed on the array. The pre-amplified cDNA were diluted 1:5 with TE. A 50 μ L volume of the diluted pre-amplified cDNA was added to a 50 μ L volume of 2x TaqMan Universal PCR Master Mix (Applied Biosystems) and mixed. The array was loaded with the mixture using standard procedures and the loaded array was run on a 7900HT Fast Real-Time PCR System (Applied Biosystems). Data analysis of the resulting Ct values was conducted with the SDSv2.2.2 software tool (Applied Biosystems).

Figure 27 shows the relative overexpression of mRNA of nine IFN α subtypes in the whole blood of lupus patients relative to healthy volunteers. Many of these IFN α subtypes were upregulated at the mRNA level in the whole blood of SLE patients.

Figure 66 shows that IFN β , IFN ω and IFNAR1 and IFNAR2 genes are also overexpressed in whole blood of lupus patients relative to healthy volunteers.

Figure 82 shows that TNF- α , IFN- γ , IFN- γ R1, and IFN- γ R2 transcripts were also upregulated in WB of SLE patients (Figure 82). However, the relative magnitude of overexpression of these transcripts was less than that of the type I IFN family members, especially the IFN- α subtypes.

Example 10: *Ex vivo* IFN-stimulated whole blood and keratinocytes of healthy individuals identifies a panel of type I IFN-inducible genes relevant to psoriasis

To identify type-I IFN inducible genes over-expressed in keratinocytes of lesions of psoriatic patients, whole blood and keratinocytes of healthy donors were stimulated *ex vivo* with a panel of IFN α subtypes, as well as IFN β , IFN γ , and TNF α .

Whole blood

Whole blood was collected from healthy donors in heparinized tubes. The total blood volume collected from each donor was pooled into a single culture flask and 3 mL of the total volume was aliquoted into a single well of a 6-well culture plate. Individual wells of blood were then exposed to a variety of treatments, including: vehicle (1x PBS), a panel of IFN α subtypes (IFN α 2a, -4b, -5, -6, -7, -8, -10, -16, -17), IFN β , IFN ω , IFN λ , IFN γ , leukocyte IFN, or TNF α . Following exposure, the blood was gently mixed by pipetting and incubated at 37°C, 5% CO₂ for 4 hrs (TNF α treatment was conducted for both 2hrs and 4hrs). Following the incubation period, 2.5 mL of blood was transferred to a PAXgene RNA tube and inverted 8-10 times. The PAXgene tubes were incubated at room temperature for two hours and then frozen (-20°C overnight, -70°C for long term storage) until further processing was required. Induction of gene expression by exposure to each of the treatment conditions was performed using Affymetrix GeneChip[®] human genome U133 plus v2.0 arrays.

The various IFN α subtypes and IFN β up-regulated 900-1200 probe sets by at least 2 fold. Of these, 689 probe sets (approximately 1.3% of all probe sets on the Affymetrix human genome U133 plus v2.0 array) were uniformly up-regulated by at least 2 fold in all donors by all ten IFN α subtypes and IFN β . Using the same approach, 336 probe sets were identified as down-regulated by IFN α / β in the *ex vivo* stimulated whole blood.

Alterations in gene expression in healthy patient whole blood stimulated with TNF α were also observed at both the two and four hour time points. In all, 234 and 72 probe sets were up-regulated and down-regulated, respectively, by at least 2 fold in all donors. Furthermore, IFN γ challenge of whole blood for 4 hrs induced up-regulation of 304 probe sets and down-regulation of 52 probe sets by at least 2 fold. Little overlap was observed in the probe sets up-regulated by IFN α / β and TNF α (40 probes). By contrast, greater overlap was observed in the probe sets up-regulated by IFN α / β and IFN γ . 198 probes were up-regulated by at least 2-fold by both IFN α / β and IFN γ . Of the 198 probes up-regulated by at least 2-fold by both IFN α / β and IFN γ , the magnitude of up-regulation by IFN α / β was greater for about 2/3 of these probes (*p* value less than 0.05) than IFN γ .

Figure 30 provides the hierarchical clustering of 1384 probe sets differentially regulated by either IFN α/β , or IFN γ , or TNF α in *ex vivo* stimulated whole blood. From this hierarchical clustering the similar response of whole blood to challenge with IFN α subtypes and IFN β can easily be observed, as can the similar but distinctly different effect of IFN γ from IFN α/β , and the drastically different effect of TNF α from IFN α/β .

Figure 31a provides the hierarchical clustering of the relative expression of only the top 25 type-I IFN inducible probe sets identified in the *ex vivo* stimulated whole blood.

Keratinocytes

Normal human keratinocytes (EpiDerm system, MatTek, Inc.) were grown under serum-free conditions according to the manufacturers instructions. Briefly, keratinocytes were maintained on tissue culture inserts at the air-liquid interface to maintain a multilayered, fully differentiated epithelial phenotype. Keratinocytes were stimulated with human leukocyte IFN (15, 50, 150, IU/mL, PBL Biomedical Labs), human IFN α 2a (15-350 IU/ml, PBL Biomedical Labs), recombinant human TNF α (0.1 ng/ml, R+D Systems) or recombinant human IFN γ (3 ng/ml, R+D Systems). Epidermal cultures were harvested at 2, 4, or 18 hours post treatment for transcript analysis. Over 100 probe sets were identified as overexpressed in keratinocytes cultures stimulated with human IFN α 2a and leukocyte IFN.

Figure 31b provides the hierarchical clustering of the relative expression of 25 type-I IFN inducible genes in *ex vivo* stimulated keratinocytes. The 25 type-I IFN inducible probe sets used to prepare the hierarchical clustering are the top 25 type-I IFN inducible probes identified in the *ex vivo* stimulated whole blood (those shown in Figure 31a). Many of the top 25 type-I IFN inducible probe sets in *ex vivo* stimulated whole blood are also induced in *ex vivo* stimulated keratinocytes. See, *e.g.*, MX1, IFI27, OAS1, IFI6, IFI44L, etc.

In addition, many of these genes were among those most overexpressed in the lesional skin of psoriasis patients. See discussion in Example 11, below.

Example 11: Whole genome array profiling identified IFN α/β signaling pathway as the most significantly activated pathway in lesional skin of psoriasis patients

A comparison of gene expression profiles of skin samples from healthy donors and paired non-lesional/lesional skin samples from psoriasis patients was performed to identify a type-I interferon induced gene expression signature associated with psoriatic skin lesions. Briefly, skin samples of 21 normal healthy control donors (5 samples obtained from Biochain, 14 from ILSbio, and 2 from Dr. James Krueger's lab) and 26 paired non-lesional/lesional skin samples of 24 psoriatic patients (21 pairs obtained from Asterand, and 5

from Dr. James Krueger's lab) were obtained. Three additional lesional skin samples from 3 psoriatic patients were obtained. These 3 additional lesional skin samples lacked a paired non-lesional skin sample because the non-lesional skin sample either did not yield sufficient cRNA for hybridization or the scanned array for the non-lesional skin sample had high scaling factors that were more than 3-fold of average.

Total RNA from the samples was extracted using the Qiagen RNeasy-Mini kit (Hilden, Germany). The purity and concentration of the extracted RNA were determined spectrophotometrically ($260/280 > 1.9$). RNA quality was assessed on an Agilent 2100 Bioanalyzer using the RNA 6000 Nano LabChip[®]. Generation of biotin-labeled amplified cRNA, from 2 µg of total RNA, was accomplished using the Affymetrix GeneChip[®] One-Cycle cDNA Synthesis kit and the Affymetrix GeneChip[®] IVT Labeling kit. Concentration and purity of the cRNA product were determined spectrophotometrically.

Twenty micrograms of each biotin-labeled cRNA was fragmented for hybridization on Affymetrix GeneChip[®] human genome U133 plus v2.0 arrays. Fragmented cRNA was prepared for hybridization as outlined in the Affymetrix GeneChip[®] manual. Hybridization was conducted overnight in a model 320 rotating hybridization oven set at 45°C. All GeneChip[®] wash and staining procedures were performed on an Affymetrix Model 450 Fluidics station. Arrays were scanned on an Affymetrix GeneChip[®] Scanner 3000. Data capture and initial array quality assessment were performed with the GeneChip Operating Software (GCOS) tool.

Stratagene's (La Jolla, CA) ArrayAssist[®] Lite software was used to calculate probe-level summaries (GC-RMA normalization algorithm) from the array CEL files. R packages (R development core team) samr & qvalue were used to generate differentially regulated genes. PCA and hierarchical clustering analyses were performed in both SpotFire and R (R Development Core Team). SAM & FDR were used to select differentially regulated genes (pairwise comparison between lesional and non-lesional skin, lesional and normal skin, and non-lesional and normal skin). Probe sets with a fold-change of at least 2 and q value less than or equal to 0.05 were considered to be differentially regulated. PCA and hierarchical clustering were performed in both SpotFire and bioconductor R.

Overall, 1408 probe sets were up-regulated and 1465 probe sets were down-regulated in lesional skin compared to non-lesional skin. Although the downregulated genes outnumbered the upregulated genes in the lesional skin, the magnitude of differential regulation of the upregulated genes was much greater as a whole. For example, 318 probe sets were upregulated by at least four fold in the lesional skin, while only 84 probe sets were

downregulated by at least four fold in the lesional skin. Among them, 96 probe sets were upregulated by at least eight fold in the lesional skin, while only six probe sets were downregulated by at least eight fold.

463 probe sets were also up-regulated and 489 probe sets were down-regulated in non-lesional skin compared to normal skin. Figure 45 provides a Venn diagram of the probe sets both upregulated (downregulated) in lesional skin and non-lesional skin relative to normal healthy skin. Only 70 of the 1408 upregulated probe sets in the lesional skin were also upregulated in non-lesional skin. Meanwhile, only 43 of the 1465 probe sets downregulated in the lesional skin were also downregulated in the non-lesional skin. These data suggested that the molecular events and biological changes from the non-lesional skin to lesional skin were quite different from those from the normal skin to the non-lesional skin.

To identify the most statistically significant signaling pathways altered in psoriasis, the list of differentially regulated genes were submitted to GeneGo for pathway and network analysis. Briefly, the pathway and network analysis was conducted with the MetaCore™ integrated software suite from GeneGo, Inc. (St. Joseph, MI). The significance, given a particular pathway or network, is approximated by a hypergeometric distribution where the *p*-value essentially represents the probability of a particular gene set mapping arising by chance, given the numbers of genes in the set of all genes on pathway maps, genes on a particular pathway map and genes in the experiment.

Fifty seven signaling pathways were significantly altered in lesional skin compared to non-lesional skin, a majority of which were involved in immune response and cell cycle. The IFN α / β signaling pathway was the most significantly altered in lesional skin with a *p* value of 3.8×10^{-13} . IFN α / β signaling pathway members such as IFN α , IFN β , IFNAR1, IFNAR2, STAT1, IRF1, MPL, ISG15, IFI6 were all significantly overexpressed in lesional skin compared to uninvolved skin.

Overall, 22 signaling pathways were activated and 37 signaling pathways were inhibited (*p*<0.05) in the lesional skin compared to non-lesional skin. All the putative signaling pathways activated were either cytokine and chemokine mediated signaling pathways or were involved in immune responses. For example, IFN γ , TNF α and oncostatin M signaling pathways were activated in the lesional skin of psoriatic patients. Of all the signaling pathways altered in lesional and non-lesional skin, IFN α / β signaling pathway topped the list with a *p* value of 6.6×10^{-26} (Figure 46). Components of the pathway like IFN α subtypes, IFN β , IFNAR1, IFNAR2, STAT1, IRF1, MPL, ISG15, IFI6 were all significantly overexpressed in lesional skin compared to non-lesional skin of psoriatic patients.

Using the list of probe sets identified to be type-I IFN inducible in the whole blood and keratinocyte *ex vivo* stimulation studies (Example 10), 164 of the 1408 (approximately 11.7%) probe sets upregulated in lesional relative to non-lesional skin were identified as type-I IFN inducible. Fisher's exact test calculated a *p* value (one-tailed *t* test) less than 0.0001, suggesting that the observed overexpression of type-I IFN genes in lesional skin of psoriatic patients was statistically significant. The type-I IFN induced genes were also many of the most highly upregulated genes in the lesional relative to non-lesional psoriatic skin. Nineteen percent of the top 100 and 200 most upregulated probe sets in lesional skin relative to non-lesional skin were type-I IFN genes. See Figure 47a and b for the top 100 upregulated probe sets in lesional skin. These genes included STAT1, a key component in forming the ISGF3 complex; IRF7, a master regulator of the IFN α/β mediated immune response; MYD88, which governs the induction of CD8⁺ T-cell responses with IRF7; IRF1, a transcriptional activator for the type-I IFN genes; OAS family members OAS1, OAS2, OAS3, mediators of resistance to virus infection; ISG15, a ubiquitin-like protein that becomes conjugated to many cellular proteins upon activation by IFN α/β ; and members of the ISG15 signaling pathways such as USP18, UBE2L6, and HERC5. This enrichment of type I IFN genes indicated them as the most overexpressed genes in lesional skin of psoriatic patients.

Table 26 lists, in descending order, the top 50 IFN induced probes in lesional skin compared to non-lesional skin of psoriasis patients. Table 26 not only compares the log₂-based fold change (log₂ fc) and *q* value for each of the 50 most upregulated type I IFN inducible genes in lesional relative to non-lesional skin of psoriasis patients, it also compares the log₂-based fold change and *q* value for these 50 genes in non-lesional skin of psoriasis patients relative to healthy control patients.

Table 26: The frequency of upregulation of the top 50 type-I IFN induced probes in lesional relative to non-lesional skin in psoriasis patients

Probe ID	Unigene ID	Gene Title	Gene Symbol	Lesional vs. Non-lesional		Non-lesional vs. Normal	
				log2 fc	q value	log2 fc	q value
219403_s_at	Hs.44227	heparanase	HPSE	4.598	4.46E-22	0.226	0.23589
204972_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	4.098	8.57E-14	0.096	0.28896
205660_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	4.030	1.34E-12	0.029	0.20341
227609_at	Hs.546467	epithelial stromal interaction 1 (breast)	EPSTI1	4.002	1.14E-14	-0.254	0.10796
227458_at	---	---	---	3.859	9.31E-14	-0.591	0.05449
219352_at	Hs.529317	hect domain and RLD 6	HERC6	3.842	9.49E-16	-0.460	0.04810
216834_at	Hs.75256	regulator of G-protein signalling 1	RGS1	3.809	2.47E-17	-5.269	0.00000
204533_at	Hs.632586	chemokine (C-X-C motif) ligand 10	CXCL10	3.697	2.97E-12	0.338	0.13024
226702_at	Hs.7155	hypothetical protein LOC129607	LOC129607	3.572	2.37E-16	-0.156	0.26500
242625_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	3.403	1.65E-12	-0.070	0.31309
213797_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	3.243	3.36E-10	0.004	0.36209
202086_at	Hs.517307	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1	3.235	5.28E-14	0.050	0.33453
205552_s_at	Hs.524760	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	3.222	2.41E-14	0.328	0.13669
210797_s_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	3.216	1.63E-09	0.005	0.34940
204439_at	Hs.389724	interferon-induced protein 44-like	IFI44L	3.205	4.73E-13	0.120	0.30073
202411_at	Hs.532634	interferon, alpha-inducible protein 27	IFI27	3.165	4.81E-12	-0.154	0.26878
202869_at	Hs.524760	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	3.150	2.47E-14	0.248	0.21403
205483_s_at	Hs.458485	ISG15 ubiquitin-like modifier	ISG15	3.088	4.73E-13	-0.273	0.11013
209969_s_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	2.993	7.95E-17	0.199	0.20072
228531_at	Hs.65641	sterile alpha motif domain containing 9	SAMD9	2.846	5.42E-14	-0.033	0.35359
204415_at	Hs.523847	interferon, alpha-inducible protein 6	IFI6	2.769	7.23E-09	-0.045	0.29074
214453_s_at	Hs.82316	interferon-induced protein 44	IFI44	2.679	1.94E-12	0.086	0.32618
222838_at	Hs.517265	SLAM family member 7	SLAMF7	2.659	1.60E-16	-0.046	0.31222
219684_at	Hs.43388	receptor transporter protein 4	RTP4	2.649	3.73E-11	0.497	0.04912
203127_s_at	Hs.435661	serine palmitoyltransferase, long chain base subunit 2	SPTLC2	2.628	1.04E-20	-1.016	0.00017
205569_at	Hs.518448	lysosomal-associated membrane protein 3	LAMP3	2.589	2.64E-09	0.293	0.22865
219691_at	Hs.65641	sterile alpha motif domain containing 9	SAMD9	2.559	1.30E-13	0.011	0.37349
223220_s_at	Hs.518200	poly (ADP-ribose) polymerase family, member 9	PARP9	2.553	1.08E-15	0.069	0.31416
AFFX-HUMISG	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	2.525	1.64E-10	0.706	0.03338
212268_at	Hs.381167	serpin peptidase inhibitor, clade B (ovalbumin), member 1	SERPINF1	2.510	3.02E-15	-0.605	0.07749
216202_s_at	Hs.435661	serine palmitoyltransferase, long chain base subunit 2	SPTLC2	2.507	1.17E-13	-0.682	0.01693
229450_at	---	---	---	2.492	1.50E-14	0.224	0.20674
208436_s_at	Hs.166120	interferon regulatory factor 7	IRF7	2.448	6.90E-15	-0.578	0.01612
AFFX-HUMISG	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	2.444	3.03E-10	0.516	0.05854
204747_at	Hs.47338	interferon-induced protein with tetratricopeptide repeats 3	IFIT3	2.424	2.15E-14	0.365	0.07219
229390_at	Hs.381220	hypothetical protein LOC441168	RP1-93H18.5	2.400	2.59E-12	-0.369	0.11426
218400_at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	2.397	3.83E-14	0.179	0.11631
235276_at	---	---	---	2.386	3.61E-15	0.057	0.32771
203153_at	Hs.20315	interferon-induced protein with tetratricopeptide repeats 1	IFIT1	2.351	1.17E-10	0.054	0.34454
210873_x_at	Hs.348983	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A	APOBEC3A	2.348	1.35E-07	-0.048	0.30119
204698_at	Hs.459265	interferon stimulated exonuclease gene 20kDa	ISG20	2.337	1.50E-12	-0.644	0.05052
232666_at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	2.236	4.50E-10	0.077	0.04816
222881_at	Hs.44227	heparanase	HPSE	2.230	3.47E-15	0.221	0.17127
205241_at	Hs.567405	SCO cytochrome oxidase deficient homolog 2 (yeast)	SCO2	2.208	1.90E-17	-0.285	0.08517
AFFX-HUMISG	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	2.205	5.29E-10	0.397	0.10218
206553_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	2.183	1.34E-09	0.043	0.14755
207387_s_at	Hs.1466	glycerol kinase	GK	2.160	9.38E-14	0.014	0.37488
219716_at	Hs.257352	apolipoprotein L, 6	APOL6	2.123	3.03E-11	-0.126	0.19251
202270_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	2.113	4.67E-14	-0.053	0.31367

Removal of ESTs, hypothetical proteins, and duplications of genes due to identification by multiple probe sets produced Table 27. Table 27 provides, in descending order, the top 50 most upregulated type-I IFN genes in lesional skin compared to non-lesional skin. For genes identified by more than one probe set, only the probe set detected as most upregulated is provided.

Table 27: Top 50 type-I IFN induced genes in lesional relative to non-lesional skin in psoriasis patients

Probe.ID	Unigene.ID	Gene.Title	Gene.Symbol	log2.fc	q.value(fdr)	% Prevalence
219403 s at	Hs.44227	heparanase	HPSE	4.60	4.46E-22	100.00
204972 at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	4.10	8.57E-14	96.15
205660 at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	4.03	1.34E-12	96.15
227609 at	Hs.546467	epithelial stromal interaction 1 (breast)	EPSTI1	4.00	1.14E-14	92.31
219352 at	Hs.529317	hect domain and RLD 6	HERC6	3.84	9.49E-16	96.15
216834 at	Hs.75256	regulator of G-protein signalling 1	RGS1	3.81	2.47E-17	100.00
204533 at	Hs.632586	chemokine (C-X-C motif) ligand 10	CXCL10	3.70	2.97E-12	100.00
242625 at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	3.40	1.65E-12	88.46
202086 at	Hs.517307	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)	MX1	3.24	5.28E-14	92.31
205552 s at	Hs.524760	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	3.22	2.41E-14	96.15
204439 at	Hs.389724	interferon-induced protein 44-like	IFI44L	3.21	4.73E-13	88.46
202411 at	Hs.532634	interferon, alpha-inducible protein 27	IFI27	3.17	4.81E-12	92.31
205483 s at	Hs.458485	ISG15 ubiquitin-like modifier	ISG15	3.09	4.73E-13	92.31
209969 s at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	2.99	7.95E-17	96.15
228531 at	Hs.65641	sterile alpha motif domain containing 9	SAMD9	2.85	5.42E-14	92.31
204415 at	Hs.523847	interferon, alpha-inducible protein 6	IFI6	2.77	7.23E-09	84.62
214453 s at	Hs.82316	interferon-induced protein 44	IFI44	2.68	1.94E-12	92.31
222838 at	Hs.517265	SLAMF family member 7	SLAMF7	2.66	1.60E-16	92.31
219684 at	Hs.43388	receptor transporter protein 4	RTP4	2.65	3.73E-11	88.46
203127 s at	Hs.435661	serine palmitoyltransferase, long chain base subunit 2	SPTLC2	2.63	1.04E-20	100.00
205569 at	Hs.518448	lysosomal-associated membrane protein 3	LAMP3	2.57	2.64E-09	96.15
223220 s at	Hs.518200	poly (ADP-ribose) polymerase family, member 9	PARP9	2.55	1.08E-15	88.46
212268 at	Hs.381167	serpin peptidase inhibitor, clade B (ovalbumin), member 1	SERPINF1	2.51	3.02E-15	88.46
208436 s at	Hs.166120	interferon regulatory factor 7	IRF7	2.45	6.90E-15	96.15
204747 at	Hs.47338	interferon-induced protein with tetratricopeptide repeats 3	IFIT3	2.42	2.15E-14	92.31
218400 at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	2.40	3.83E-14	100.00
203153 at	Hs.20315	interferon-induced protein with tetratricopeptide repeats 1	IFIT1	2.35	1.17E-10	84.62
210873 x at	Hs.348983	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A	APOBEC3A	2.35	1.35E-07	80.77
204698 at	Hs.459265	interferon stimulated exonuclease gene 20kDa	ISG20	2.34	1.50E-12	92.31
205241 at	Hs.567405	SCO cytochrome oxidase deficient homolog 2 (yeast)	SCO2	2.21	1.90E-17	96.15
207387 s at	Hs.1466	glycerol kinase	GK	2.16	9.38E-14	92.31
219716 at	Hs.257352	apolipoprotein L, 6	APOL6	2.12	3.03E-11	92.31
202270 at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	2.11	4.67E-14	92.31
229625 at	Hs.513726	Guanylate binding protein 5	GBP5	2.07	7.52E-10	88.46
228617 at	Hs.441975	XIAP associated factor-1	BIRC4BP	2.05	3.41E-12	84.62
206513 at	Hs.281898	absent in melanoma 2	AIM2	2.04	2.32E-08	76.92
218943 s at	Hs.190622	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	DDX58	2.00	1.39E-10	88.46
203148 s at	Hs.575631	tripartite motif-containing 14	TRIM14	1.94	2.17E-17	96.15
213293 s at	Hs.501778	tripartite motif-containing 22	TRIM22	1.89	1.36E-12	88.46
214838 at	---	SFT2 domain containing 2	SFT2D2	1.88	5.30E-17	92.31
231769 at	Hs.464419	F-box protein 6	FBXO6	1.86	6.34E-14	88.46
227697 at	Hs.527973	suppressor of cytokine signaling 3	SOCS3	1.82	4.55E-10	88.46
206632 s at	Hs.226307	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	APOBEC3B	1.81	9.42E-10	92.31
201649 at	Hs.425777	ubiquitin-conjugating enzyme E2L 6	UBE2L6	1.81	2.15E-13	84.62
204702 s at	Hs.404741	nuclear factor (erythroid-derived 2)-like 3	NFE2L3	1.80	1.71E-16	96.15
202531 at	Hs.436061	interferon regulatory factor 1	IRF1	1.79	2.13E-13	80.77
204994 at	Hs.926	myxovirus (influenza virus) resistance 2 (mouse)	MX2	1.75	7.99E-09	69.23
215966 x at	---	glycerol kinase pseudogene 3	GKP3	1.73	3.33E-11	80.77
207655 s at	Hs.444049	B-cell linker	BLNK	1.71	2.28E-14	96.15
216598 s at	Hs.303649	chemokine (C-C motif) ligand 2	CCL2	1.71	4.80E-07	65.38

The fold changes (log2 fc) were calculated based on relative transcript level between paired lesional skin and non-lesional skin. Q values were calculated based on FDR. Prevalence tabulated the percentage of the 26 paired lesional and non-lesional skin that had at least 2-fold overexpression of the genes listed in the table.

These top 50 type-I IFN induced genes in lesional relative to non-lesional skin in psoriasis patients were overexpressed, on average, 3.2-fold (CCL2 and BLNK) to 24-fold (HPSE) more in the lesional skin. In addition, all of the genes in the table, except CCL2 and AIM2, were upregulated in at least 84% of the paired lesional/non-lesional skin biopsies (23 of the 26 pairs) of the psoriasis patients. This robust upregulation of a large panel of type-I IFN genes across lesional versus non-lesional skin samples of psoriasis patients provided a strong rationale for their use as PD markers.

As briefly alluded to, above, upregulation of type-I interferon inducible genes was consistently observed across psoriasis patients. Table 28 provides the average and median fold change of the top 25 most upregulated type-I IFN probe sets for each paired lesional/non-lesional skin sample. The top 25 most upregulated type-I IFN probe sets were consistently observed to detect elevated gene expression in the lesional relative to non-lesional skin of each individual psoriasis patient.

Table 28: Average and median fold change of the top 25 most upregulated type-I IFN inducible genes in 26 pairs of lesional skin compared to lesional skin

Probe ID	Unigene ID	Gene Symbol	Pair 1	Pair 2	Pair 3	Pair 4	Pair 5	Pair 6	Pair 7	Pair 8	Pair 9	Pair 10	Pair 11	Pair 12	Pair 13	Pair 14	Pair 15	Pair 16	Pair 17	Pair 18	Pair 19	Pair 20	Pair 21	Pair 22	Pair 23	Pair 24	Pair 25	Pair 26
219405 s at	Hs 44237	HPSE	67.78	24.31	35.28	27.94	37.31	26.55	126.24	128.77	10.28	7.12	19.62	25.78	30.21	24.01	56.60	10.70	35.20	11.42	5.66	12.73	25.78	30.81	32.25	24.58	48.50	105.13
204972 s at	Hs 414332	OAS2	12.60	21.22	1.19	2.44	49.33	48.03	33.22	43.96	13.92	71.36	76.17	4.04	24.63	79.34	15.84	96.99	10.27	30.28	9.26	30.11	16.38	24.27	60.43	25.32	132.09	9.07
205660 s at	Hs 118633	OASL	7.19	13.48	4.51	9.03	62.19	50.23	31.12	54.05	9.72	9.94	1.10	2.31	24.75	44.70	11.91	45.96	17.46	14.66	33.60	17.27	84.97	24.22	92.12	46.44	54.96	39.66
227609 s at	Hs 546467	EPSTI1	11.25	20.34	-1.43	1.38	57.01	32.14	14.40	23.42	10.53	55.80	32.87	8.86	59.54	47.71	33.84	78.12	14.34	25.86	33.41	12.06	19.24	17.86	28.12	22.43	78.03	10.90
227458 s at	---	---	16.69	10.94	19.35	3.11	54.31	23.30	30.76	10.59	3.25	40.43	41.37	6.70	26.83	23.19	37.88	70.78	75.98	18.04	26.19	49.50	5.43	24.89	24.13	11.45	26.05	9.87
219352 s at	Hs 529317	HERC6	7.86	15.70	2.38	1.46	49.25	51.01	11.64	19.63	20.95	21.72	15.84	5.82	10.58	23.06	30.42	113.47	11.03	26.94	9.90	16.46	19.06	33.32	27.98	19.08	26.56	8.66
216834 s at	Hs 75256	RGS1	27.92	8.50	17.90	6.81	58.42	16.25	4.97	20.52	10.02	24.32	19.50	9.91	94.41	14.83	23.00	15.64	13.95	31.80	100.03	8.02	2.44	13.49	15.83	22.64	29.15	14.83
204533 s at	Hs 632506	CXCL10	3.92	3.01	8.72	3.91	249.00	13.12	13.37	15.14	4.75	68.66	56.31	22.30	12.75	8.30	16.61	26.11	12.95	30.79	66.10	17.72	11.89	12.12	41.27	10.90	30.14	5.96
226702 s at	Hs 7156	LOC129607	3.59	5.77	3.10	1.27	60.00	12.76	14.72	22.00	9.53	58.99	27.55	2.99	5.99	39.75	25.66	125.99	19.79	30.96	4.88	45.30	14.42	7.91	32.87	14.50	19.85	3.13
242025 s at	Hs 17518	RSAD2	4.57	6.19	1.79	1.24	66.13	51.91	19.28	23.36	4.02	32.04	8.80	1.76	5.64	16.36	15.97	94.85	9.47	14.58	4.64	33.67	16.26	10.67	68.96	20.21	40.67	5.99
213797 s at	Hs 17518	RSAD2	8.33	7.37	1.16	1.00	78.64	33.08	11.98	25.13	1.86	21.73	8.43	2.73	3.23	31.91	12.04	49.52	8.11	12.61	11.92	24.02	25.00	10.04	75.04	17.36	29.33	6.29
202066 s at	Hs 517307	MX1	5.03	9.17	1.25	1.08	20.97	39.08	14.63	23.54	11.33	18.56	11.71	5.08	8.93	20.03	8.68	86.72	11.04	19.60	7.24	4.00	12.06	10.53	28.80	11.08	27.74	5.88
205652 s at	Hs 524780	OAS1	5.93	11.05	1.19	2.76	21.03	29.00	11.76	27.37	7.71	19.23	20.14	3.49	2.82	37.85	21.91	39.43	6.13	24.10	5.86	2.63	4.18	13.46	21.42	9.30	32.15	16.09
210797 s at	Hs 118633	OASL	2.04	6.30	1.32	1.34	45.94	31.06	16.86	66.61	9.25	1.89	1.73	1.20	19.00	23.73	1.62	43.86	11.71	10.30	26.36	2.77	78.51	15.88	65.78	33.47	35.32	18.92
204439 s at	Hs 389724	IFM4L	4.52	6.71	-3.59	-1.06	14.49	58.16	9.25	32.21	6.68	37.49	31.62	3.96	19.43	16.66	23.81	253.56	6.81	20.34	3.18	17.90	12.16	7.60	18.42	4.52	25.93	1.12
202411 s at	Hs 532634	IFD7	10.97	15.52	1.94	2.66	12.02	38.87	14.83	27.63	17.02	17.72	17.69	5.81	9.36	26.00	15.85	38.94	2.01	30.69	4.59	-4.73	3.46	10.59	22.17	7.00	50.18	7.37
202869 s at	Hs 524760	OAS1	5.34	7.99	2.04	2.09	16.23	32.48	13.29	30.47	12.75	49.00	10.15	5.52	2.31	18.94	19.52	36.57	4.58	16.19	4.81	8.96	4.73	11.05	11.67	7.13	18.20	7.30
205483 s at	Hs 458485	ISG15	5.64	4.37	1.65	1.10	19.82	40.24	8.30	13.89	7.00	12.18	14.49	4.47	6.78	19.24	10.65	57.01	3.67	12.65	2.96	2.57	11.30	5.71	34.41	18.06	30.48	5.07
209909 s at	Hs 565365	STAT1	6.14	6.12	2.85	2.00	38.30	16.50	10.35	7.10	12.90	17.32	12.41	3.77	14.31	7.49	25.00	18.73	5.45	9.63	9.18	17.30	7.10	9.27	11.03	10.91	12.19	4.37
228531 s at	Hs 65641	SAMD9	5.07	5.24	2.52	1.79	12.56	12.67	5.76	15.63	9.88	12.94	20.65	1.97	4.70	24.24	15.22	20.12	10.49	10.39	5.60	14.30	6.80	6.38	16.24	12.46	13.49	6.75
204415 s at	Hs 523847	IF6	1.52	6.53	-2.01	1.00	13.90	25.74	5.59	16.88	4.66	11.65	6.45	3.30	5.43	30.76	3.29	38.93	4.08	20.01	2.08	1.00	49.45	16.05	58.43	12.95	52.57	6.96
214453 s at	Hs 82316	IF44	2.60	6.23	-2.89	1.22	14.76	10.55	4.43	9.99	2.67	12.32	25.67	3.66	8.26	18.22	2.57	61.65	6.49	20.83	8.32	10.75	4.93	5.66	13.27	8.02	26.71	2.03
222036 s at	Hs 517205	SLAMF7	5.26	7.36	1.70	1.97	19.55	6.75	5.56	9.97	6.78	10.62	15.91	5.44	19.09	5.39	14.93	6.86	10.10	8.69	15.42	7.59	4.69	5.06	5.52	5.61	11.22	9.01
219684 s at	Hs 43388	RTF4	13.11	13.02	-3.07	-1.11	13.35	18.00	6.50	10.68	3.48	30.25	23.69	8.93	6.66	16.47	10.97	18.65	3.40	17.36	5.96	1.92	5.90	8.90	4.55	4.92	28.75	3.91
203127 s at	Hs 436661	SPILC2	6.06	5.07	-4.11	3.50	8.18	5.50	11.49	8.25	2.73	4.53	6.24	5.57	5.61	11.30	8.25	7.73	10.82	7.32	4.82	3.64	9.24	5.35	9.32	13.11	11.00	12.69
Average fold change			10.04	9.92	4.12	3.20	43.40	29.08	22.41	27.45	8.55	26.73	19.14	6.13	17.23	25.18	18.49	63.16	13.82	19.99	16.49	14.30	18.21	13.65	32.82	15.54	25.61	13.97
Median fold change			5.93	7.37	1.79	1.79	37.31	29.00	11.98	22.00	9.25	19.23	17.69	4.01	9.36	23.06	15.85	43.88	10.27	19.04	7.24	12.06	11.89	10.67	27.98	13.11	28.75	7.37

Figure 32 provides a graphic of the distribution of the average and median fold changes among the different pairs of lesional and non-lesional skin. The prevalent and uniform upregulation of the most overexpressed type-I IFN genes in lesional skin of psoriatic patients verified their usefulness as PD markers.

Seventeen probe sets were also observed as underexpressed in lesional skin that were also down-regulated by IFN α/β in the *ex vivo* stimulation studies described in Example 10. These genes include CYP1B1, TGST1, RRAGD, IRS2, MGST1, TGFBR3, and RGS2.

Example 12: Expression of type-I IFN genes is not significantly altered in normal skin relative to non-lesional skin of psoriatic patients

Although the array data obtained in Example 11 identified overexpression of numerous type-I IFN-inducible genes in lesional relative to non-lesional skin, it identified only 5 probe sets overexpressed in non-lesional skin relative to normal control skin. The p value of Fisher's exact test (two-tailed t -test) was 0.581, which suggested that the overexpression of the type-I IFN genes is not statistically significant in the non-lesional skin of the psoriasis patients over normal skin.

As shown in Table 26 (Example 11), most of the genes identified as being top 50 type-I IFN-induced genes in lesional relative to non-lesional skin were comparably expressed in non-lesional skin relative to normal skin controls (several genes, *e.g.*, RGS1, SPTLC2, are downregulated in the non-lesional skin compared to normal skin). Figure 33 provides a graphical representation of the relative expression of 3 type-I IFN inducible genes (HPSE, OASL, and HERC6; included as top 50 type-I IFN-induced probe sets in lesional relative to non-lesional skin), and 1 non type-I IFN inducible gene (SERPINB4) in both (a) lesional skin compared to non-lesional skin and (b) non-lesional skin compared to normal skin. The overexpression of genes HPSE, OASL, and HERC6 in lesional skin compared to non-lesional skin is both statistically significant (as evidenced by the very small p value) and large in scale (between 12-250 fold overexpression on average). SERPINB4 is overexpressed in non-lesional skin by about 3-4 fold compared to normal skin, but upregulated by well over 200 fold in lesional skin compared to non-lesional skin.

Analysis of normal healthy, lesional psoriasis, and non-lesional psoriasis skin samples using the 164 probe sets identified in Example 11 as type-I IFN inducible, showed a clustering of lesional psoriasis samples and a clustering of non-lesional psoriasis and normal healthy skin samples. Figure 34a provides heatmap of unsupervised hierarchical clustering of all lesional, non-lesional, and normal skin samples profiled using the 164 type-I IFN-inducible probe sets in lesional skin compared to non-lesional skin of psoriasis patients. It can be observed that nearly all (all but three) of the lesional skin samples clustered together, while nearly all of the non-lesional and normal skin samples clustered together. Figure 34b provides a PCA plot of the skin samples using the same 164 upregulated type-I IFN inducible probe sets. Again, the normal skin samples and the non-lesional skin samples mostly clustered together, indicating similar levels of expression of the 164 genes. Also, the majority of the lesional skin samples were separated from the normal and non-lesional skin samples, indicating that the lesional samples exhibited a distinct overexpression of the type-I

IFN inducible genes that was separable from the gene expression levels of the normal and non-lesional skin samples.

These observations were further confirmed by gene pathway analysis. GeneGo analysis showed that the possibility of an alteration in the IFN α/β signaling pathway of non-lesional skin of psoriasis patients relative to normal skin had a *p* value close to 1. A distinctive separation of lesional skin samples from non-lesional skin samples and normal skin samples was even observed when clustering samples based on the transcript profile of an entire genome array. See Figure 47.

Example 13: Validation of type-I IFN-inducible gene up-regulation in psoriatic lesional skin using taqMan-based assays

A BioMark™ 48.48 dynamic array (taqMan-based assay) from Fluidigm was used to validate the results of the Affymetrix GeneChip® human genome U133 plus v2.0 arrays, results indicating that type-I IFN genes are up-regulated in lesional psoriatic relative to non-lesional psoriatic or normal skin samples.

Eighteen pairs of lesional and non-lesional skin samples from 18 psoriasis patients were used for the gene expression analysis. Twenty nine of these genes were type-I IFN inducible genes while 11 were highly upregulated in lesional skin but were not IFN-inducible genes, *e.g.*, S100A9, S100A12, SERPINGB4, and KLK13. Each of these genes was selected based on prevalence and significance of overexpression in lesional skin. The overexpression of all genes in the lesional skin was confirmed by taqMan qRT-PCR, the majority of which showed very good correlation between microarray and taqMan assays. Figure 35 provides taqMan data showing overexpression of each of ten (OAS2, OASL, EPSTI1, MX1, IFI44L, IFI44, HERC6, HPSE, ISG15, and STAT1) type-I IFN-inducible genes in lesional skin in the 18 paired lesional/non-lesional samples.

Overall, the taqMan-based assay and Affymetrix array results correlated well, validating the selected genes as overexpressed type-I IFN-induced genes in lesional psoriatic skin. The distribution of correlation coefficients between the taqMan-based assay and the Affymetrix array for the 40 overexpressed genes is provided in Figure 36a. Nineteen of the overexpressed genes had correlation coefficients greater than 0.85, indicating excellent correlation between the microarray and taqMan-based assay. Another 17 genes had high correlation coefficients between the microarray and taqMan-based assay of 0.5 - 0.85. Figure 36b provides the distribution of correlation coefficients between the taqMan-based assay and the Affymetrix array for the 29 type-I IFN-induced genes of the 18 psoriasis patients. Again,

many of the genes had high correlation coefficients, greater than 0.90. These genes include, *inter alia*, IFI27, CXCL10, ISG15, and MX1.

Figures 37a - 37d and 38 provide detailed gene expression data obtained from the microarray and taqMan-based assays for several type-I IFN-inducible genes in the paired lesional/non-lesional samples. These data evidence that similar levels of overexpression of type-I IFN-induced genes in lesional psoriatic skin is detected between the taqMan and array assays, and thus the high correlation coefficients discussed above. Figure 37a and 37b show similar overexpression of ISG15 in each of the 18 paired lesional/non-lesional skin samples as determined by taqMan (37a) and microarray (37b) analysis. Figure 37c and 37d show similar overexpression of MX1 in each of the 18 paired lesional/non-lesional skin samples as determined by taqMan (37c) and microarray (37d) analysis. The correlation coefficient between the taqMan and microarray was 0.9735 for ISG15 and 0.9836 for MX1. Figure 38 shows measurement of similar overexpression of type-I IFN-inducible genes IFI27 and CXCL10 by taqMan and microarray analysis in each of the 18 paired lesional/non-lesional skin samples. The correlation coefficient between the taqMan and microarray results for IFI27 and CXCL10 was 0.9456 and 0.9455, respectively.

Example 14: IFN α Ab neutralizes type-I IFN α -induced gene expression in *ex vivo* stimulated keratinocytes of healthy volunteers

Keratinocytes of healthy volunteers were isolated and stimulated *ex vivo* with escalating doses of IFN α 2a and leukocyte IFN to induce an escalating type I IFN α -induced gene expression pattern. Anti-IFN α antibody was able to neutralize the type I IFN α -induced gene expression pattern in a dose-dependent manner.

Normal human keratinocytes (EpiDerm system, MatTek, Inc.) were grown under serum-free conditions according to manufacturer's instructions. Briefly, keratinocytes were maintained on tissue culture inserts at the air-liquid interface to maintain a multilayered, fully differentiated epithelial phenotype. Keratinocytes were stimulated with human leukocyte IFN (15-150 IU/ml, PBL Biomedical Labs) and human IFN α 2a (15-350 IU/ml, PBL Biomedical Labs). In some wells a humanized anti-human IFN α monoclonal antibody (0.01-100 μ g/ml; MEDI-545, MedImmune, Inc) or isotype matched control antibody of irrelevant specificity (R347, MedImmune, Inc) was added simultaneously with cytokine stimulus. Epidermal cultures were harvested at 2, 4, or 18 hours post treatment for transcript analysis. Expression of type-I IFN-induced genes was measured using a BioMark™ 48.48 dynamic array.

Expression of a majority of type-I IFN-induced genes was upregulated in the IFN α 2a and leukocyte interferon stimulated keratinocytes in a dose-dependent manner. This upregulation of type-I IFN-induced genes, by either IFN α 2a or leukocyte interferon, was likewise inhibited in a dose-dependent manner by IFN α monoclonal antibody (MEDI-545). Control antibody, R347, did not have a significant effect on neutralization of the type-I IFN-induced genes.

Dose-dependent neutralization of three type-I IFN-induced genes (ISG15, USP18, and IFIT2) by MEDI-545 in IFN α 2a or leukocyte IFN stimulated keratinocytes is provided in Figure 39. Figure 39 (a), (c), and (e) show that MEDI-545 neutralizes overexpression of type-I IFN induced genes ISG15, USP18, and IFIT2, respectively, in keratinocytes stimulated with 350 IU/mL IFN α 2a. Each of these genes was neutralized 100% by MEDI-545. Figure 39 (b), (d), and (f), show that MEDI-545 neutralizes overexpression of type-I IFN induced genes ISG15, USP18, and IFIT2, respectively, in keratinocytes stimulated with 150 I.U./mL leukocyte IFN. Neutralization of these genes by MEDI-545 was between 70 and 100%, which is not surprising because leukocyte IFN contains both IFN α and IFN β . MEDI-545 neutralizes a majority of IFN α subtypes efficiently, but not IFN β . These neutralization data provide further evidence that the type-I IFN-inducible genes identified in *ex vivo* stimulated whole blood and keratinocytes (Example 10) are type-I IFN-inducible genes. It also provides further support that upregulated expression of these genes in lesional psoriatic skin relative to non-lesional skin due to type-I IFN induction.

Example 15: Multiple type-I IFN subtypes are up-regulated in lesional skin of psoriasis patients

To identify the type-I IFN subtypes responsible for the induction of the type-I IFN signature in lesional skin of psoriasis patients, mRNA levels of type-I IFN genes in psoriatic lesions were measured.

Gene expression analysis was performed using a TaqMan Low Density Array (TLDA) from Applied Biosystems. Expression of 23 genes, including type-I IFN α subtypes 1, 2, 5, 6, 7, 8, 14, 17, and 21; type-I IFNs IFN β , κ , and ω ; IFN γ ; IFN α receptors IFNAR1 and IFNAR2; IFN γ receptors IFNGR1 and IFNGR2; type-I IFN α inducible genes RSAD2, OAS3, IFI44, MX1, and CXCL10; and TNF α was monitored and compared in paired lesional and non-lesional skin of 18 psoriasis patients.

Double-stranded cDNA for each patient sample was pre-amplified using the TaqMan PreAmp Master Mix kit (Applied Biosystems). cDNA was pre-amplified by conducting 10

cycles of PCR on each patient sample using a pooled solution of primers, a pair for each gene analyzed on the array. The pre-amplified cDNA were diluted 1:5 with TE. A 50 μ L volume of the diluted pre-amplified cDNA was added to a 50 μ L volume of 2x TaqMan Universal PCR Master Mix (Applied Biosystems) and mixed. The array was loaded with the mixture using standard procedures and the loaded array was run on a 7900HT Fast Real-Time PCR System (Applied Biosystems). Data analysis of the resulting Ct values was conducted with the SDSv2.2.2 software tool (Applied Biosystems).

Figure 40a shows the relative overexpression of mRNA of nine IFN α subtypes in the lesional skin compared to either non-lesional skin or normal skin. With the exception of IFN α 5 (upregulated by about 4.6 fold; median fold change, $p < 0.001$), none of the IFN α subtypes were significantly altered at the mRNA level in the non-lesional skin compared to that in the normal skin ($p < 0.05$). However, all of these IFN α subtypes were upregulated at the mRNA level in the lesional skin compared to that in the normal skin (or non-lesional skin), with the overexpression of IFN α 1, IFN α 5, IFN α 8, IFN α 14, IFN α 17, IFN α 21 being statistically significant ($p < 0.05$). Figure 40b shows that the overexpression of other members of type I IFN family members, IFN β , - κ , and - ω mRNA in the lesional skin compared to either non-lesional skin or normal skin. The alterations of IFN β and IFN ω mRNAs in the non-lesional skin were not significant. However, the upregulation of these mRNAs were significant in the lesional skin compared to normal skin (p values of 0.022 and 0.049 respectively). IFN κ mRNA was upregulated by about 1.6 fold (median fold change, $p = 0.03$) in the non-lesional skin, and was sharply upregulated by 62.6 fold (median fold change) in the lesional skin compared to normal skin ($p < 0.001$). Additionally, the receptors for type I IFN, IFNAR1 and IFNAR2 were also significantly overexpressed in the lesional skin of psoriatic patients at transcript level (p values < 0.001 ; Figure 40c). While IFNAR2 upregulation was significant in the non-lesional skin, IFNAR1 was not (Figure 40c). Collectively, these data provided strong evidence that mRNA levels of type I IFN family members were comparable between the non-lesional skin and healthy normal skin (with the exception of IFN α 5 and IFN κ), and were uniformly overexpressed in the lesional skin of psoriatic patients.

Table 29, lists the correlation coefficients of the overexpression of type-I IFN family member (type-I IFN α subtypes 1, 2, 5, 6, 7, 8, 14, 17, and 21; and IFN β , IFN κ , and IFN ω) mRNAs in lesional skin compared to non-lesional skin of psoriatic patients. Of the 12 type-I IFN family members measured, overexpression of IFN α 1, 2, 8, and 14 in lesional skin correlated most consistently with overexpression of other members in the type-I IFN family,

with the exception of IFN α 5 which showed the weakest correlation with other type-I IFN family members.

Table 29: Correlation coefficient of overexpression of type-I IFN family members in lesional skin of psoriasis patients

	IFNA1	IFNA2	IFNA5	IFNA6	IFNA7	IFNA8	IFNA14	IFNA17	IFNA21	IFNB1	IFNK	IFNW1
IFNA1	1											
IFNA2	0.66	1										
IFNA5	0.11	0.20	1									
IFNA6	0.45	0.47	-0.01	1								
IFNA7	0.77	0.79	0.09	0.68	1							
IFNA8	0.64	0.99	0.19	0.49	0.84	1						
IFNA14	0.84	0.94	0.28	0.44	0.72	0.94	1					
IFNA17	1.00	0.96	0.15	0.07	0.77	0.97	0.94	1				
IFNA21	0.71	0.49	0.50	0.42	0.81	0.49	0.61	0.75	1			
IFNB1	0.54	0.86	0.28	0.33	0.69	0.96	0.80	0.93	0.54	1		
IFNK	0.78	0.73	0.09	0.59	0.27	0.73	0.77	0.03	0.22	0.54	1	
IFNW1	0.73	0.72	0.44	0.22	0.75	0.70	0.77	0.93	0.90	0.73	0.26	1

Example 16: Co-overexpression of type-I IFN, type-II IFN, and TNF α and their gene signatures in lesional skin of psoriasis patients

The involvement of IFN γ and TNF α mRNA signaling pathways was also evaluated in the paired lesional/non-lesional psoriasis and normal skin samples. As discussed in Example 15, above, TLDA from Applied Biosciences was used to measure IFN γ , IFNGR1 and IFNGR2, and TNF α mRNA in lesional and non-lesional skin of psoriasis patients and in normal healthy skin.

Unlike the observations for type-I IFN mRNA expression levels, IFN γ , IFNGR1, IFNGR2, and TNF α mRNAs were significantly overexpressed in non-lesional skin compared to healthy normal skin (Figure 41; p values of 0.02, <0.001, <0.001 and <0.001 respectively). TNF α mRNA was upregulated by about 5.7 fold, while IFN γ , IFNGR1 and IFNGR2 mRNAs were upregulated by about 1.5, 2.2, and 2.8 fold compared to that in the normal skin (median fold change; Figure 41). However, like the type I IFNs, these genes were upregulated in the lesional skin compared to either non-lesional skin (p values of 0.04, 0.01, 0.001 and 0.007 respectively) or normal skin (p values <0.001 for all of them; Figure 41). TNF α , IFN γ , IFNGR1 and IFNGR2 mRNAs were upregulated by about 33.5, 116.7, 11.6, and 8.4 fold in the lesional skin compared to that in the normal skin. These observations indicated that the mRNA expression patterns for IFN γ and TNF α are different from those of type I IFN family members, which were comparable between healthy skin and non-lesional skin (with the exception of IFN α 5 and IFN κ), but upregulated in the lesional skin compared to non-lesional skin of psoriasis patients.

Example 17: Identification genes induced by type II IFN and TNF α in *ex vivo* stimulated whole blood and which are induced in skin lesions of psoriasis patients

As described in Example 10, whole blood of healthy donors was stimulated *ex vivo* with a panel of IFN α subtypes, as well as IFN β , IFN γ , and TNF α . Stimulating whole blood *ex vivo* with IFN γ or TNF α identified probe sets associated with potential IFN γ - or TNF α -inducible genes. Three hundred four probe sets were identified as at least 2-fold upregulated by IFN γ four hours post-stimulation. Two hundred thirty four probe sets were identified as at least 2-fold upregulated by TNF α both 2 and 4 hours post-stimulation.

The probe sets identified as associated with *ex vivo* IFN γ or TNF α induction were compared with the total 1408 probe sets (Example 11) found to be upregulated in lesional skin relative to non-lesional skin of psoriasis patients. Using this method, 106 and 35 of the probe sets included in the total 1408 upregulated in lesional skin were identified as IFN γ or TNF α inducible, respectively (Figure 42). The 106 probe sets identified as IFN γ inducible are provided in Figure 49. The 35 probe sets identified as TNF α inducible are provided in Figure 50. The 164 probes sets shown in Figure 42 as identified as type-I IFN inducible are provided in Figure 51. The Fisher's exact test indicated that the *p* values (one-tailed t-test) of the overexpression of IFN γ or TNF α inducible genes in lesional skin were both less than 0.0001. The overexpression of IFN γ and TNF α inducible genes was significant.

Also using the list of probe sets identified to be type I IFN, IFN γ and TNF α inducible from the *ex vivo* studies, type I IFN, IFN γ and TNF α inducible genes upregulated at least 2-fold in each of the lesional relative to non-lesional skin sample were identified. Figure 43 shows the number of type I IFN, IFN γ and TNF α inducible genes upregulated in each of the 26 paired lesional and non-lesional skin. The larger the number of type I IFN inducible genes upregulated in a particular lesional skin biopsy usually gave rise to the overexpression of larger numbers of IFN γ and TNF α inducible genes in the same lesional skin biopsy. This observation was confirmed by the strong correlation in the co-activation of these three sets of genes with correlation coefficients of 0.9811, 0.9179 and 0.9372 using two-tail paired t-test to compare the upregulation of type I IFN and IFN γ , type I IFN and TNF α , and IFN γ and TNF α inducible genes in lesional skin compared to non-lesional skin (Figure 43a).

Similar analysis was carried out for the downregulated genes in the lesional skin compared to the non-lesional skin of psoriatic patients (Figure 42). Of the 1465 total probe sets downregulated in lesional relative to non-lesional skin, only 17, 5, and 5 of them were type I IFN, IFN γ and TNF α inducible.

Although IFN γ and TNF α mRNAs were found to be upregulated in the non-lesional skin of psoriatic patients when compared to healthy normal skin, IFN γ and TNF α inducible genes did not appear to be significantly overexpressed in the non-lesional skin (Figure 42).

The absence of type I IFN, IFN γ and TNF α inducible gene signatures in the non-lesional skin compared to normal skin, even when IFN γ and TNF α mRNAs are overexpressed in the non-lesional skin, suggested that either IFN γ and TNF α proteins were not made in the non-lesional skin, or other signaling molecules might have inhibitory effect on the IFN γ and TNF α pathways in the non-lesional skin of psoriatic patients.

Example 18: Immunohistochemical analysis of biopsies from lesional psoriatic skin, non-lesional psoriatic skin, and skin from normal donors shows increased protein levels of type I IFN-induced genes

To determine whether some of the highly overexpressed type I IFN inducible genes in psoriatic skin gave rise to similar changes in the expression of the proteins, immunohistochemical analyses were carried out to assess the presence of STAT1 and ISG15 protein in the skin. Furthermore, analysis of the cellular infiltrates (pDCs, mDCs and CD4-positive cells) was carried to compare the number of IFN-producing cell types and inflammatory cells in the biopsies of the lesional vs. non-lesional and normal skin.

Snap-frozen lesional psoriatic, non-lesional psoriatic, and normal skin biopsies were divided in half. One-half of each sample was embedded in O.C.T., sectioned at 5 μ M, placed on a “plus” slide, and fixed in cold acetone. The sectioned samples were incubated with primary antibodies (specific for BDCA2, CD83, CD4, STAT1, and ISG15) for 4 hours and washed with TBS. The slides were then incubated with peroxidase-labeled polymer conjugated to goat anti-mouse immunoglobulin antibody (Envision+; Dakocytomation, Carpinteria, CA) for 30 minutes and washed with Tris-buffered saline, pH 7.2. Detection was performed with 3,3'-diaminobenzidine tetrahydrochloride (DAB+; DakoCytomation) as the chromogen. Slides were washed with dH₂O), counterstained with hematoxylin, dehydrated and coverslipped.

In all psoriasis patients for which paired lesional/non-lesional samples could be evaluated, lesional skin contained increased numbers of pDCs, and/or mDCs, increased numbers of CD4+ cells, as well as the significant upregulation of STAT-1 and ISG15 protein in the epidermis and dermis compared to non-lesional biopsies. By contrast, skin biopsies from normal donors did not contain appreciable numbers of pDCs, mDCs or staining for STAT-1 and ISG15. See Figure 44 for example immunohistochemistry slides.

Example 19: Immunohistochemical and gene expression analysis of biopsies from SLE patient skin lesions show reduced expression of type I IFN-induced genes at the protein and transcript level following treatment with MEDI-545

To determine whether transcripts of the top 25 type I IFN inducible genes in skin lesions of an SLE patient were neutralized by MEDI-545, biopsies from patients treated with 10mg/kg MEDI-545 were examined. A heatmap of neutralization of the top 25 type I IFN inducible genes in skin lesions at 0 and 14 days post-treatment is provided in Figure 58(a). All of the top 25 genes are neutralized 14 days following administration of MEDI-545. A PCA diagram of target modulation based on these top 25 type I IFN-inducible genes is provided in Figure 58(b). The PCA diagram shows the progression of the treated SLE patient from a position directly opposite that of normal healthy donors prior to administration of MEDI-545 to a position nearing that of the healthy donors 14 days after administration of MEDI-545.

To determine whether levels of some of the proteins expressed from these highly overexpressed type I IFN inducible genes were also reduced by treatment with 10 mg/kg MEDI-545, immunohistochemical analyses were carried out to detect HERC5, ISG15, and IP10 protein in SLE skin lesions of patients treated with MEDI-545 and placebo. Furthermore, analysis of the cellular infiltrates (pDCs, mDCs and CD4-positive cells) was carried out to compare the number of IFN-producing cell types and inflammatory cells in the biopsies of the SLE skin lesions of MEDI-545 treated patients and placebo treated controls.

Snap-frozen skin lesion samples of MEDI-545 treated SLE patients and placebo treated SLE patients were divided in half. One-half of each sample was embedded in O.C.T., sectioned at 5 μ M, placed on a "plus" slide, and fixed in cold acetone. The sectioned samples were incubated with primary antibodies (specific for BDCA2, CD83, CD4, IP10, and ISG15) for 4 hours and washed with TBS. The slides were then incubated with peroxidase-labeled polymer conjugated to goat anti-mouse immunoglobulin antibody (Envision+; Dakocytomation, Carpinteria, CA) for 30 minutes and washed with Tris-buffered saline, pH 7.2. Detection was performed with 3,3'-diaminobenzidine tetrahydrochloride (DAB+; DakoCytomation) as the chromogen. Slides were washed with dH₂O), counterstained with hematoxylin, dehydrated and coverslipped.

In placebo-treated SLE patients both cellular infiltrates and levels of proteins expressed from overexpressed type I IFN inducible genes increased (or worsened) over the course of 14 days. See Figure 52 which shows an increase in (worsening of) mDC (CD83 staining) and T cell (CD4 staining) infiltration in skin lesions. Figure 52 also shows no change in pDC (BDCA2 staining) infiltration in the placebo-treated SLE patient skin lesions over the 14 days. See also Figure 53 which shows an increase in staining for proteins

expressed from overexpressed type I IFN inducible genes HERC and IP10. No change in staining for ISG15 was observed.

By contrast, in patients treated with 10 mg/kg MEDI-545 levels of infiltrates and proteins expressed from overexpressed type I IFN inducible genes were decreased by varying degrees. See Figures 54 and 55, which provide immunohistochemical data from a first SLE patient treated with MEDI-545 and Figures 56 and 57, which provide immunohistochemical data from a second SLE patient treated with MEDI-545.

Example 20: Assay for sensitive detection of type I and type II IFNs

To devise an assay to sensitively detect type I and type II IFNs a construct containing the gene for a luciferase enzyme isolated from the marine organism *Gaussia princeps* (Targeting Systems; Santee, CA) under the control of an interferon-stimulated response element (ISRE) (TAGTTTCACTTTCCC)₅; Biomyx; San Diego, CA) was cloned. HEK293H cells were stably transfected with the construct and these cells were used for the IFN detection assays.

25,000 of the stably transfected HEK293H cells were seeded per assay well in 50uL of cell culture medium overnight in a CO₂ incubator. The following day, patient serum samples (or normal pooled human serum spiked with the various sub-types of IFN alpha or IFN-beta, IFN-omega, IFN-gamma) were screened for detection of the various subtypes of IFN by adding 50uL of undiluted patient or spiked serum to the assay wells containing the seeded cells (final concentration of 50% patient sera in the wells for 24 hours). IFN-induced luciferase activity was detected the following day, by observing chemiluminescence in the culture supernatants. Chemiluminescence was observed by transferring 50uL of supernatant from the wells to a B&W Isoplate, adding 50uL of chemiluminescent substrate, and detecting luminescence at 6 minutes. Samples generating a signal greater than 1.5-times the Negative Control wells on each assay plate are classified as Positive for IFN activity. See Figure 59 a-d, which provide detected levels of type I and type II IFN activity in the IFN bioassay for different plates of cells treated with patient serum and spiked control serum. Each of panels a-d show that increased dose of IFN in the assay results in increased detection of IFN activity.

In samples where IFN activity is detected, antibodies that specifically neutralize various Type I and Type II IFNs can then be used to determine which IFN was responsible for the positive response. Anti-IFN-type specific antibodies are pre-incubated with either the

positive serum sample(s) (in the case of MEDI 545, anti-IFN beta, anti-IFN gamma and anti-IFN omega that bind to the IFN ligand itself) or with the cells (in the case of MEDI 546 that binds to the Type I interferon receptor on the HEK293H cells) followed by addition of the samples to the cells and chemiluminescence determination as above. Spiked samples that demonstrate lower chemiluminescence following specific antibody treatment are considered to be positive for the presence of the particular IFN(s) that is neutralized by the IFN-specific antibodies.

Figure 60(a) shows that increasing dose of MEDI-545 in the treated wells increasingly neutralizes IFN activity as does increasing dose of MEDI-546 (Figure 60(b)). Figures 61-63 show that IFN γ , IFN ω , and IFN β , respectively, are neutralized by antibodies specific for IFN γ , IFN ω , and IFN β , as expected.

Example 21: Alterations of Levels of Soluble Proteins in Serum of Lupus Patients

Serum was collected from SLE (n=40) and CLE (n=5) patients that had a history of at least 4 of 11 positive ACR classification criteria and demonstrated active disease manifestations at the time of sample collection. Ninety-five percent were female, with mean $\pm$ SD age of 41 $\pm$ 15 years. Seventy-six percent were currently receiving oral corticosteroids in doses ranging from 1 mg/d to 30 mg/d prednisone, with 2 SLE patients also receiving pulse intravenous steroids. Fifty-nine percent were receiving at least 1 potential disease-modifying medication other than corticosteroids. Luminex xMAP technology was used to detect changes in 89 analytes and was performed by Rules Based Medicine (see the world wide web at domain name rulesbasedmedicine . com). Results for each analyte were compared to the mean of a panel of normal human serum (n=17) and significance was determined using a paired t-test. Figure 74 shows analytes whose levels were significantly (a) increased or (b) decreased from the mean of the normal serum (p value $\geq$ 0.05). Significant alterations in levels of cytokines chemokines, metabolic proteins, and other soluble mediators were detected in serum of lupus patients.

Example 22: Alternative Assay, Panomics QuantiGenePlex Assay, Verifies IFN-Induced Gene Expression Analysis Results

The QuantiGenePlex assay was first performed to assess the ability of QuantiGenePlex to detect 22 IFN-inducible transcripts in whole blood stimulated with IFN α 2b. The 22 IFN-inducible transcripts detected by this initial QuantiGenePlex assay

were selected based on their consistent up-regulation in SLE patients and are shown on the x-axis of the graphs shown in Figures 75 and 76.

Stimulation of the whole blood was performed by incubating freshly drawn Na-EDTA whole blood from 5 healthy donors with 20 IU/mL IFN α 2b for 4 hours. Following this incubation, 2.5 mL of the stimulated whole blood was added to PAXgene tubes, mixed, and held overnight at room temperature. After overnight incubation, the samples were frozen at -80°C. These sample-handling procedures were selected to mimic those to be used during clinical trials.

PAXgene blood was analyzed for expression levels of the IFN-inducible transcripts. PAXgene blood (500 μ L) was pelleted and then lysed in 139 μ L of buffer according to the QuantiGenePlex PAXgene Blood Lysis Protocol. Processed blood from each donor was split into duplicate wells and hybridized overnight with a multiplex probe set for the 22 IFN-inducible genes. Gene expression was assessed the following day using a Luminex 100 instrument with BioRad BioPlex software. Fold changes were assessed for each individual based on the increase in signal observed between IFN-stimulated and PBS-stimulated control wells. Figure 75 shows the fold-change in expression of each of the 22 IFN-inducible genes following IFN stimulation of each of the 5 healthy volunteer whole blood samples. The dashed line indicates a 2-fold change over PBS-stimulated control samples.

Whole blood of a single volunteer was further stimulated over a dose range of 0.2 to 200 IU/mL IFN α 2b to determine whether upregulation of the IFN-inducible genes by IFN α 2b was dose-dependent and could be detected by the QuantiGenePlex assay. For each of the 22 transcripts, a dose-dependent induction was observed. See Figure 76, which provides the fold change in expression for each of the 22 transcripts at each IFN α 2b dosage. Maximal transcript induction of nearly 100-fold was observed for RSAD2, IFIT3, and MX1. Using a 2-fold increase over baseline as a cutoff criterion, 19/22 genes were detected in samples spiked with 2 IU/mL of IFN and 5/22 were detected in samples spiked with 0.2 IU/mL IFN. Expression of SIGLEC1, LY6E, SERPING1, OAS3 and IFI27 transcripts were poorly induced by IFN α 2b stimulation. These low levels of induction may indicate a lack of sensitivity of the assay to these targets or differences in gene expression between actual SLE disease (from which this panel of transcripts was chosen) and *ex vivo* stimulation with a single IFN α subtype, IFN α 2b. Dashed line indicates a 2-fold change over PBS-stimulated control samples.

Next, the QuantiGenePlex assay was used to detect levels of IFN-inducible transcripts in whole blood of SLE patients. Twenty of the 22 probes from the original QuantiGenePlex kit, probes identified in Figures 75 and 76, were retained in the QuantiGenePlex assay used for this data analysis. Two probes, HSXIAPAF1 and GIP3, were substituted with different probes, XAF1 and IFI6. Using this panel of 22 probes, a baseline gene signature was established based on whole blood samples of ten healthy donors (blue bars in each panel). The baseline gene signature, based on the whole blood samples of the healthy donors, was compared to (1) the gene signature of an SLE patient that had detectable IFN serum activity and (2) the gene signature of an SLE patient that did not have detectable IFN serum activity. IFN serum activity was detected in the SLE patient serum samples using the assay described in Example 20. Figure 77a shows a comparison of the gene signature of an SLE patient (red bars) having no detectable serum IFN α activity (i.e. serum IFN activity <2.5 IU/mL) relative to the baseline gene signature (blue bars). With the exception of LAMP3, all transcript levels were detected as elevated in blood from the SLE patient with no IFN serum activity. Figure 77b shows a comparison of the gene signature of an SLE patient with high levels of serum IFN α activity (red bars) relative to the baseline gene signature (blue bars). All transcripts were elevated at least 2-fold in the blood of the patient with high IFN serum activity, with maximal inductions of nearly 80-fold for IFI27.

The data obtained from the QuantiGenePlex assay was next evaluated for its comparability to data obtained from a Fluidigm Real-Time PCR assay. QuantiGenePlex and Fluidigm methods were each used to analyze and compare transcript levels in PAXgene-preserved whole blood samples from 16 SLE patients participating in a Phase I clinical trial (of a monoclonal antibody against IFN α) relative to a composite median gene score from 10 healthy donors. Fluidigm analyses were carried out using a mixture of TaqMan Gene Expression assays, including 4 reference control genes prepared using the TaqMan PreAmp Master Mix Kit (Applied Biosystems). Dynamic arrays were loaded using a NanoFlex 4-IFC Controller (Fluidigm Corp) and real-time reactions were performed using a BioMark Real-Time PCR System. Results were analyzed using BioMark Real-Time PCR Analysis software. Delta-delta Cts (DDCt) were calculated using the mean of 4 reference genes (GAPDH, TFRC, b2M, and 18S) and a calibrator sample. The results obtained using whole blood samples from SLE patients demonstrated a high degree of correlation between QuantiGenePlex and Real-Time PCR approaches to detect disease-related gene expression profiles. Figure 78 shows the (a) composite median and (b) mean-fold changes of all genes

in the panels that were calculated and compared by Pearson's correlation analysis. Significant correlation was observed between QuantiGenePlex and Fluidigm when median ($p=0.0002$) and mean ($p<0.0001$) fold changes were compared for the panel of genes.

Data obtained from the QuantiGenePlex and Fluidigm Real-Time PCR assays were further compared in their ability to detect changes in transcript levels in SLE patient samples over the course of treatment in a clinical trial. For this comparison, SLE patient samples were collected directly into PAXgene tubes on Day 0 (pre-dose) and multiple subsequent time points following administration of a single dose of an anti-IFN α monoclonal antibody or placebo. For each sample, an aggregate median fold-change was calculated from the panel of 22 genes and compared to the pre-dose sample for that patient. Figure 79a shows the changes in gene signature for placebo- or antibody-treated SLE patients using Fluidigm technology. Figure 79b shows the changes in gene signature of the placebo- or antibody-treated SLE patients using QuantiGenePlex technology. For each non-placebo subject, a decrease in IFN gene signature is observed within 24 hours following drug administration and is consistent between Fluidigm and QuantiGenePlex. Subsequent changes in transcript levels post-administration were also highly similar between QuantiGenePlex and Fluidigm technologies.

WE CLAIM:

1. A method of treating a patient having a type I IFN or an IFN α -mediated disease or disorder comprising:
 - administering an agent that binds to and modulates type I IFN or IFN α activity;
 - wherein the patient comprises a type I IFN or IFN α -inducible PD marker expression profile;
 - and wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.
2. The method of 1 further comprising detecting neutralization of the type I IFN or IFN α -inducible PD marker expression profile of the patient.
3. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.
4. The method of claim 1 wherein the agent is a biologic agent.
5. The method of claim 4 wherein the agent is an antibody.
6. The method of claim 5 wherein the antibody is MEDI-545.
7. The method of claim 5 wherein the antibody is specific for one or more type I IFN or IFN α subtype but is not MEDI-545.
8. The method of claim 1 wherein the administering the agent alleviates one or more symptoms of the disease or disorder.
9. The method of claim 5 wherein the antibody is administered at a dose between approximately .03 and 30 mg/kg.
10. The method of claim 9 wherein the antibody is administered at a dose between 0.3 and 3 mg/kg.
11. The method of claim 10 wherein the antibody is administered at a dose between .03 and 1 mg/kg.
12. The method of any one of claims 9-11 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 10%.
13. The method of claim 12 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 20%.

14. The method of claim 13 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 30%.
15. The method of claim 14 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 40%.
16. The method of claim 15 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 50%.
17. The method of claim 1 wherein the type I IFN or an IFN α -mediated disease or disorder is one of lupus, psoriasis, vasculitis, sarcoidosis, Sjogren's syndrome, or idiopathic inflammatory myositis.
18. The method of claim 17 wherein the type I IFN or an IFN α -mediated disease or disorder is lupus.
19. The method of claim 17 wherein the type I IFN or an IFN α -mediated disease or disorder is psoriasis.
20. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of at least IFN α subtypes 1, 2, 8, and 14.
21. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises transcripts of PD marker genes.
22. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises polypeptides expressed from PD marker genes.
23. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1
24. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2
25. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3,

IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

26. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

27. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

28. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

29. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

30. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

31. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

32. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

33. The method of claim 32 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes MX1 and IFIT1.

34. The method of claim 33 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes OAS2 and OAS1.
35. The method of any one of claims 3 or 23-33 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.
36. The method of claim 1 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.
37. The method of claim 22 wherein the polypeptides are detected at increased levels in serum.
38. The method of claim 37 wherein polypeptides include cancer antigen 125, ferritin, tissue factor, and MMP-3.
39. The method of claim 22 wherein the polypeptides are detected at decreased levels in serum.
40. The method of claim 39 wherein the polypeptides include EGF, thrombopoietin, and CD40 ligand.
41. A method of treating an autoimmune disease patient comprising a moderate or strong type I IFN or an IFN α PD marker profile comprising:
- administering an agent that binds to and modulates type I IFN or IFN α activity;
 - wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.
42. The method of 41 further comprising detecting neutralization of the type I IFN or IFN α -inducible PD marker expression profile of the patient.
43. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.
44. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1

45. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2
46. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.
47. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.
48. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.
49. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.
50. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.
51. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.
52. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

53. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, and IFI27.
54. The method of claim 53 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes MX1 and IFIT1.
55. The method of claim 41 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of at least IFN α subtypes 1, 2, 8, and 14.
56. The method of claim 41 wherein the agent is a biologic agent.
57. The method of claim 41 wherein the agent is an antibody.
58. The method of claim 57 wherein the antibody is MEDI-545.
59. The method of claim 57 wherein the antibody is specific for one or more type I IFN or IFN α subtype but is not MEDI-545.
60. The method of claim 41 wherein the administering the agent alleviates one or more symptoms of the disease or disorder.
61. The method of claim 57 wherein the antibody is administered at a dose between approximately .03 and 30 mg/kg.
62. The method of claim 57 wherein the antibody is administered at a dose between 0.3 and 3 mg/kg.
63. The method of claim 57 wherein the antibody is administered at a dose between .03 and 1 mg/kg.
64. The method of claim 41 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 10%.
65. The method of claim 64 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 20%.
66. The method of claim 65 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 30%.
67. The method of claim 66 wherein the wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 40%.

68. The method of claim 67 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile by at least 50%.
69. The method of claim 41 wherein the autoimmune disease patient is a lupus, psoriasis, vasculitis, sarcoidosis, Sjogren's syndrome, or idiopathic inflammatory myositis patient.
70. The method of claim 69 wherein the patient is a lupus patient.
71. The method of claim 69 wherein the patient is a psoriasis patient.
72. A method of neutralizing a type I IFN or IFN α -inducible PD marker expression profile in a patient in need thereof, comprising:
- administering an agent that binds to and modulates type I IFN or IFN α activity to the patient;
 - wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient.
73. The method of 72 further comprising detecting neutralization of the type I IFN or IFN α -inducible PD marker expression profile of the patient.
74. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.
75. The method of claim 72 wherein the agent is a biologic agent.
76. The method of claim 75 wherein the agent is an antibody.
77. The method of claim 76 wherein the antibody is MEDI-545.
78. The method of claim 76 wherein the antibody is specific for one or more type I IFN or IFN α subtype but is not MEDI-545.
79. The method of claim 72 wherein the administering the agent alleviates one or more symptoms of the disease or disorder.
80. The method of claim 76 wherein the antibody is administered at a dose between approximately .03 and 30 mg/kg.
81. The method of claim 80 wherein the antibody is administered at a dose between 0.3 and 3 mg/kg.

82. The method of claim 81 wherein the antibody is administered at a dose between .03 and 1 mg/kg.
83. The method of any one of claims 80-82 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 10%.
84. The method of claim 83 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient by at least 20%.
85. The method of claim 84 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient at least 30%.
86. The method of claim 85 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient at least 40%.
87. The method of claim 86 wherein the agent neutralizes the type I IFN or IFN α -inducible PD marker expression profile of the patient at least 50%.
88. The method of claim 72 wherein the patient is a lupus, psoriasis, vasculitis, sarcoidosis, Sjogren's syndrome, or idiopathic inflammatory myositis patient.
89. The method of claim 88 wherein the patient is a lupus patient.
90. The method of claim 88 wherein the patient is a psoriasis patient.
91. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of at least IFN α subtypes 1, 2, 8, and 14.
92. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises transcripts of PD marker genes.
93. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises polypeptides expressed from PD marker genes.
94. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.
95. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6,

IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

96. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

97. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

98. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

99. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

100. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

101. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

102. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

103. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

104. The method of claim 103 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises up-regulated expression or activity of genes MX1 and IFIT1.

105. The method of any one of claims 74 or 94-104 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

106. The method of claim 72 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.

107. The method of claim 93 wherein the polypeptides are detected at increased levels in serum.

108. The method of claim 107 wherein polypeptides include cancer antigen 125, ferritin, tissue factor, and MMP-3.

109. The method of claim 93 wherein the polypeptides are detected at decreased levels in serum.

110. The method of claim 109 wherein the polypeptides include EGF, thrombopoietin, and CD40 ligand.

111. A method of monitoring or prognosing autoimmune disease progression of a patient comprising:

obtaining a first IFN α -inducible PD marker expression profile in a first sample from a patient.

112. The method of claim 111 wherein the first IFN α -inducible PD marker expression profile is a strong profile and the patient prognosis is disease progression.

113. The method of claim 112 wherein the autoimmune disease is SLE and the progression is an SLE flare.

114. The method of claim 111 wherein the first IFN α -inducible PD marker expression profile is a weak profile and the patient prognosis is disease regression.

115. The method of claim 111 further comprising:

obtaining a second IFN α -inducible PD marker expression profile in a second sample from a patient;

wherein an increase in number or level of type I IFN or IFN α inducible PD markers in the second relative to the first expression profile prognoses disease progression; or

wherein a decrease in number or level of type I IFN or IFN α inducible PD markers in the second relative to the first expression profile prognoses disease regression.

116. A method of monitoring disease progression of a patient receiving treatment with a therapeutic agent that binds to and modulates IFN α activity comprising:

obtaining a first IFN α -inducible PD marker expression profile in a first sample from the patient;

administering a therapeutic agent that binds to and modulates IFN α activity;

obtaining a second IFN α -inducible PD marker expression profile in a second sample from the patient; and

comparing the first and the second IFN α -inducible PD marker expression profiles,

wherein a variance in the first and the second IFN α -inducible PD marker expression profiles indicates a level of efficacy of the therapeutic agent that binds to and modulates IFN α activity.

117. The method of claim 116 wherein the first IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44

118. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

119. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

120. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2,

IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

121. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

122. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

123. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

124. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPP1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

125. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

126. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

127. The method of claim 116 wherein the first type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

128. The method of claim 116 wherein the variance is a decrease in up-regulated expression of activity levels of the genes.

129. The method of claim 116 wherein the disease is lupus, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, sarcoidosis, and psoriasis.
130. The method of claim 131 wherein the disease is lupus.
131. The method of claim 116 wherein the therapeutic agent is a small molecule or a biologic agent.
132. The method of claim 131 wherein the biologic agent is an antibody.
133. The method of claim 132 wherein the antibody is MEDI-545.
134. The method of claim 116 wherein the first IFN α -inducible PD marker expression profile is obtained prior to administration of the therapeutic agent.
135. The method of claim 116 wherein the first IFN α -inducible PD marker expression profile is obtained at the time of administration of the therapeutic agent.
136. The method of claim 116 wherein the first and the second sample are whole blood or serum.
137. The method of claim 116 further comprising obtaining a third IFN α -inducible PD marker expression profile in a third sample from the patient.
138. The method of 137 further comprising obtaining a fourth IFN α -inducible PD marker expression profile in a fourth sample from the patient.
139. The method of 138 further comprising obtaining a fifth IFN α -inducible PD marker expression profile in a fifth sample from the patient.
140. The method of 139 further comprising obtaining a sixth IFN α -inducible PD marker expression profile in a sixth sample from the patient.
141. The method of 116 wherein the second sample is obtained at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following administration of the therapeutic agent.
142. The method of 137 wherein the third sample is obtained at least 2 days, at least 5 days, at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following obtaining the second sample.

143. The method of 138 wherein the fourth sample is obtained at least 2 days, at least 5 days, at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following obtaining the third sample.

144. The method of 139 wherein the fifth sample is obtained at least 2 days, at least 5 days, at least one week, at least 2 weeks, at least three weeks, at least one month or at least two months following obtaining the fourth sample.

145. The method of claim 116 wherein variance is a decrease in up-regulated expression or activity of the gene.

146. The method of claim 145 wherein the decrease is at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%.

147. A method of identifying a patient as a candidate for a therapeutic agent that binds to and modulates IFN α activity comprising:

detecting presence or absence of an IFN α -inducible PD marker expression profile in a sample from the patient,

wherein detecting presence of the IFN α -induced PD marker expression profile identifies the patient as a candidate for the therapeutic agent that binds to and modulates IFN α activity.

148. The method of claim 147 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

149. The method of claim 147 wherein type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

150. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

151. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

152. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

153. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

154. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

155. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPPI, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

156. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

157. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

158. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

159. The method of claim 147 wherein the patient has been diagnosed as having a disorder selected from the group consisting of lupus, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, sarcoidosis, and psoriasis.
160. The method of claim 159 wherein the disorder is lupus.
161. The method of claim 147 wherein the therapeutic agent is a small molecule or a biologic agent.
162. The method of claim 161 wherein the biologic agent is an antibody.
163. The method of claim 162 wherein the antibody is MEDI-545.
164. The method of any one of claims 148-158 wherein the up-regulated expression or activity comprises at least a 2-fold increase in expression of one or more of the genes.
165. The method of any one of claims 148-158 wherein the up-regulated expression or activity comprises at least a 3-fold increase in expression of one or more of the genes.
166. The method of any one of claims 148-158 wherein the up-regulated expression or activity comprises an increase in mRNA levels of one or more of the genes.
167. The method of any one of claims 148-158 wherein the up-regulated expression or activity comprises an increase in protein levels of one or more of the genes.
168. The method of any one of claims 148-158 wherein the up-regulated expression or activity comprises an increase in enzymatic activity of a protein expressed from one or more of the genes.
169. The method of claim 147 wherein the sample is whole blood.
170. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises down-regulated expression or activity of genes NOG, SLC4A1, PRSS33, and FEZ1.
171. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises increased serum levels of polypeptides cancer antigen 125, ferritin, tissue factor, and MMP-3.
172. The method of claim 147 wherein the type I IFN or IFN α -inducible PD marker expression profile comprises decreased serum levels of polypeptides EGF, thrombopoietin, and CD40 ligand.

173. A method of diagnosing a patient as having a disorder associated with increased IFN α levels comprising:

detecting presence or absence of an IFN α -inducible PD marker expression profile in a sample from the patient,

wherein detecting presence of the IFN α -induced PD marker expression profile identifies the patient as having a disorder associated with increased IFN α levels.

174. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

175. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1.

176. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

177. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

178. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

179. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

180. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27,

IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

181. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPPI, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

182. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

183. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

184. The method of claim 173 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

185. The method of claim 173 wherein the disorder is lupus, idiopathic inflammatory myositis, Sjogren's syndrome, vasculitis, sarcoidosis, or psoriasis.

186. The method of claim 185 wherein the disorder is lupus.

187. The method of any one of claims 174-184 wherein the up-regulated expression or activity comprises at least a 2-fold increase in expression or activity of one or more of the genes.

188. The method of claim 187 wherein the up-regulated expression or activity comprises at least a 3-fold increase in expression or activity of one or more of the genes.

189. The method of any one of claims 174-184 wherein the up-regulated expression or activity comprises an increase in mRNA levels of one or more of the genes.

190. The method of any one of claims 174-184 wherein the up-regulated expression or activity comprises an increase in protein levels of one or more of the genes.

191. The method of any one of claims 174-184 wherein the up-regulated expression or activity comprises an increase in enzymatic activity of a protein expressed from one or more of the genes.

192. The method of any one of claims 174-184 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOGSLC4A1, PRSS33, and FEZ1.

193. The method any one of claims 174-184 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises increased serum levels of polypeptides cancer antigen 125, ferritin, tissue factor, and MMP-3.

194. The method of any one of claims 174-184 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises decreased serum levels of polypeptides EGF, thrombopoietin, and CD40 ligand.

195. A method of identifying a candidate therapeutic for treating IFN α -mediated disorders comprising:

- contacting cells comprising an IFN α -inducible PD marker expression profile with an agent; and

- detecting presence or absence of a change in the IFN α -induced PD marker expression profile of the cells,

- wherein the presence of a change comprising a reduction in the up-regulation of the genes of the IFN α -inducible PD marker expression profile indicates the agent is a candidate therapeutic agent.

196. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44.

197. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, and OAS1.

198. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2.

199 The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SERPING1, IFIT2, IFIT3, IFI6,

LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1.

200. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15.

201. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27.

202. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18.

203. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPPI1, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

204. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1.

205. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18.

206. The method of claim 195 wherein the IFN α -inducible PD marker expression profile comprises up-regulated expression or activity of genes IFI6, RSAD2, IFI44, IFI44L, and IFI27.

207. The method of claim 195 wherein the cells obtained from a patient comprising a disorder associated with increased IFN α levels.

208. The method of claim 195 wherein the cells are cells treated with IFN α to induce the IFN α -inducible PD marker expression profile.

209. The method of claim 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile is at least a 2-fold increase in expression of one or more of the genes of the profile.

210. The method of claim 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile is at least a 3-fold increase in expression of one or more of the genes of the IFN α -inducible PD marker expression profile.

211. The method of claim 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile comprises an increase in mRNA levels of one or more of the genes of the IFN α -inducible PD marker expression profile.

212. The method of claim 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile comprises an increase in protein levels of one or more of the genes of the IFN α -inducible PD marker expression profile.

213. The method of claim 195 wherein the up-regulation of the genes of the IFN α -inducible PD marker expression profile comprises an increase in enzymatic activity of a protein expressed from one or more of the genes of the IFN α -inducible PD marker expression profile.

214. The method of any one of claims 196-206 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises down-regulated expression or activity of genes NOGSLC4A1, PRSS33, and FEZ1; and

wherein the presence of a change comprising an increase in expression or activity of the down-regulated genes indicates the agent is a candidate therapeutic agent.

215. The method of any one of claims 196-206 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises increased serum levels of polypeptides cancer antigen 125, ferritin, tissue factor, and MMP-3; and

wherein the presence of a change comprising a decrease in serum levels of the polypeptide indicates the agent is a candidate therapeutic agent.

216. The method of any one of claims 196-206 wherein the type I IFN or IFN α -inducible PD marker expression profile further comprises decreased serum levels of polypeptides EGF, thrombopoietin, and CD40 ligand

wherein the presence of a change comprising an increase in serum levels of the polypeptide indicates the agent is a candidate therapeutic agent.

217. A set of probes comprising:

polynucleotides that specifically detect expression of any one of the sets of genes:

- (a) MX1, LY6E, IFI27, OAS1, IFIT1, IFI6, IFI44L, ISG15, LAMP3, OASL, RSAD2, and IFI44; or
- (b) IFI27, SIGLEC1, RSAD2, IFI6, IFI44L, IFI44, USP18, IFIT2, SAMD9L, BIRC4BP, DNAPTP6, OAS3, LY6E, IFIT1, LIPA, LOC129607, ISG15, PARP14, MX1, OAS2, OASL, CCL2, HERC5, OAS1; or
- (c) IFIT1, IFIT3, IRF7, IFI6, IL6ST, IRF2, LY6E, MARCKS, MX1, MX2, OAS1, EIF2AK2, ISG15, STAT2, OAS3, IFI44, IFI44L, HERC5, RAB8B, LILRA5, RSAD2, and FCHO2; or
- (d) SERPING1, IFIT2, IFIT3, IFI6, LY6E, MX1, OAS1, ISG15, IFI27, OAS3, IFI44, LAMP3, DNAPTP6, ETV7, HERC5, OAS2, USP18, XAF1, RTP4, SIGLEC1, and EPSTI1; or
- (e) RTP4, RSAD2, HERC5, SIGLEC1, USP18, LY6E, ETV7, SERPING1, IFIT3, OAS1, HSXIAPAF1, G1P3, MX1, OAS3, IFI27, DNAPTP6, LAMP3, EPSTI1, IFI44, OAS2, IFIT2, and ISG15; or
- (f) LAMP3, SIGLEC1, DNAPTP6, IFIT2, ETV7, RTP4, SERPING1, HERC5, XAF1, MX1, EPSTI1, OAS2, OAS1, OAS3, IFIT3, IFI6, USP18, RSAD2, IFI44, LY6E, ISG15, and IFI27; or
- (g) DNAPTP6, EPSTI1, HERC5, IFI27, IFI44, IFI44L, IFI6, IFIT1, IFIT3, ISG15, LAMP3, LY6E, MX1, OAS1, OAS2, OAS3, PLSCR1, RSAD2, RTP4, SIGLEC1, and USP18; or
- (h) SAMD9L, IFI6, IFI44, IFIT2, ZC3HAV1, ETV6, DAPPI, IL1RN, CEACAM1, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1; or
- (i) SAMD9L, IFI6, IFI44, IFIT2, OAS1, IFI27, OAS3, IFI44L, HERC5, IFIT1, EPSTI1, ISG15, SERPING1, OASL, GBP1, and MX1; or
- (j) IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, ISG15, LAMP3, OAS3, OAS1, EPSTI1, IFIT3, OAS2, SIGLEC1, and USP18; or
- (k) IFI6, RSAD2, IFI44, IFI44L, and IFI27; or
- (l) NOGSLC4A1, PRSS33, and FEZ1.

218. A kit comprising any of the set of probes recited in claim 217.

219. A method of detecting IFN activity in a sample comprising:

incubating cells comprising a polynucleotide sequence comprising a reporter gene under the control of an interferon-stimulated response element with a sample; and
detecting expression of the reporter gene,
wherein expression of the reporter gene indicates IFN activity in the sample.

220. The method of claim 219 wherein cells are HEK293H cells.

221. The method of claim 219 wherein the reporter gene is luciferase, chloramphenicol acetyl transferase, β -galactosidase, green fluorescent protein, β -glucuronidase, or secreted placental alkaline phosphatase.

222. The method of claim 221 wherein the reporter gene is luciferase.

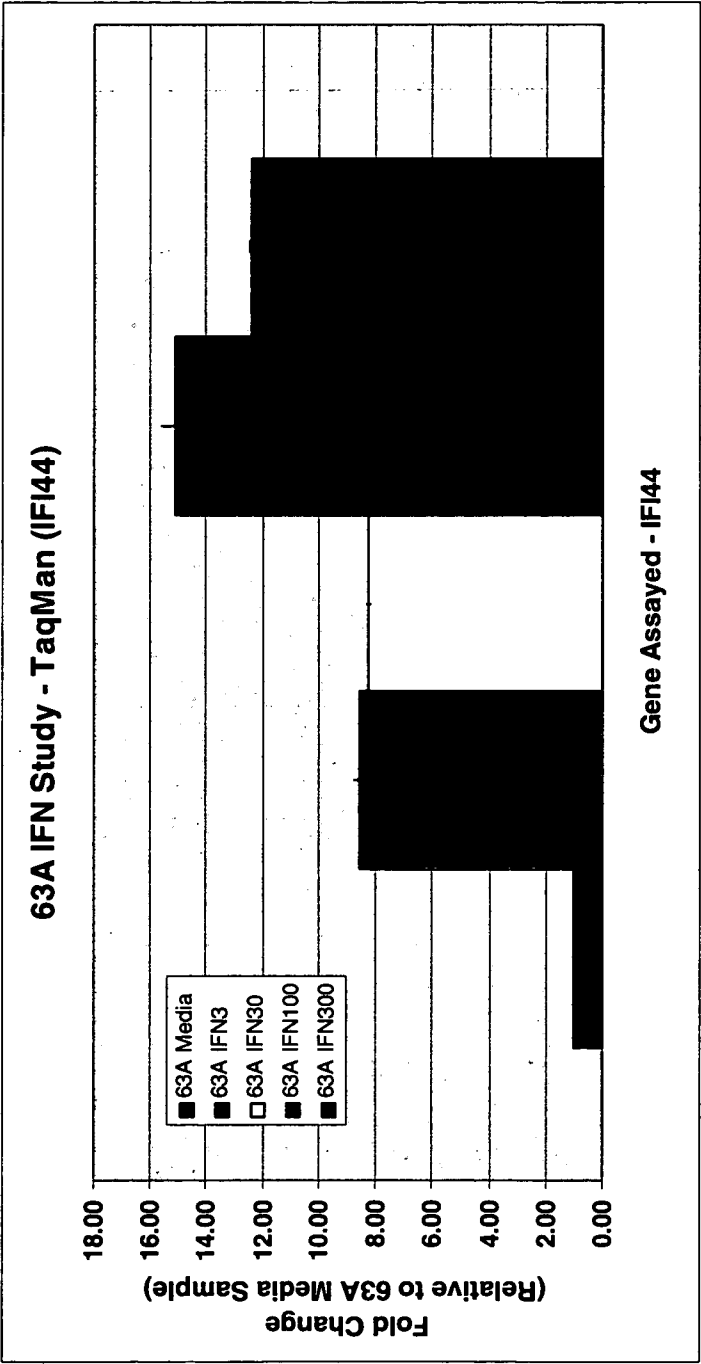
223. The method of claim 222 wherein the luciferase is *Gaussia princeps* luciferase.

224. The method of claim 219 further comprising quantitating level of expression of the reporter gene.

225. The method of claim 224 further comprising correlating the level of expression of the reporter gene to level of IFN activity in the sample.

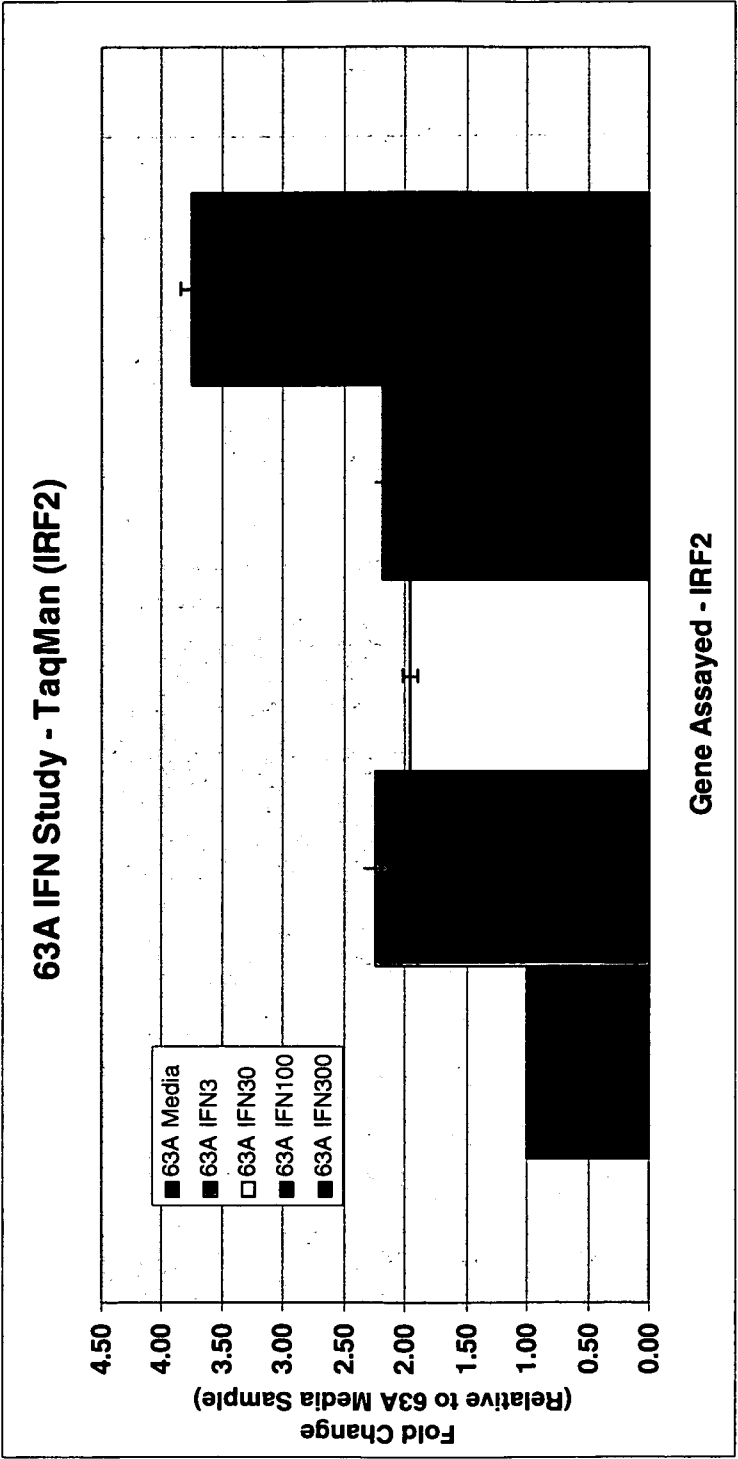
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Figure 1



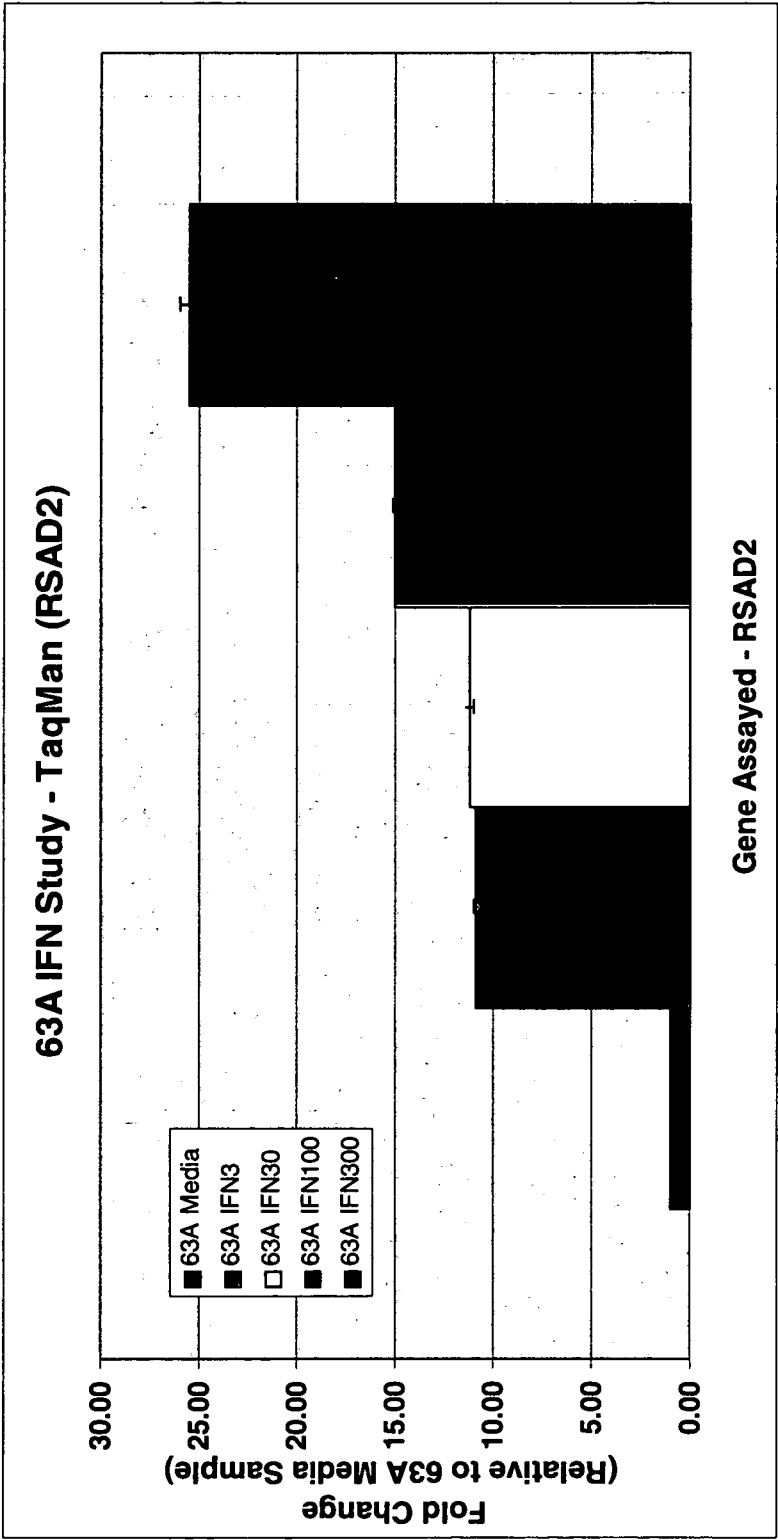
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Figure 2



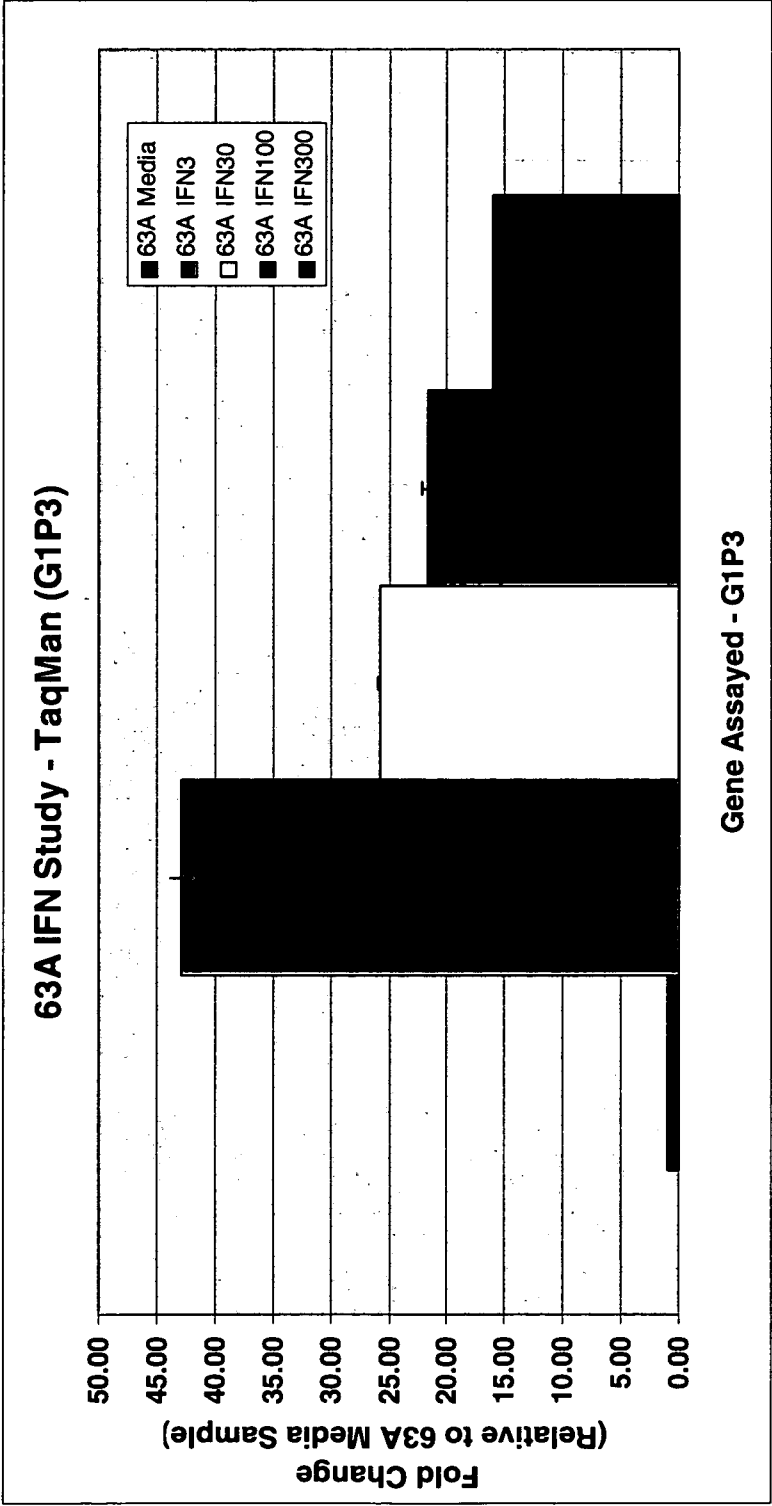
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Figure 3



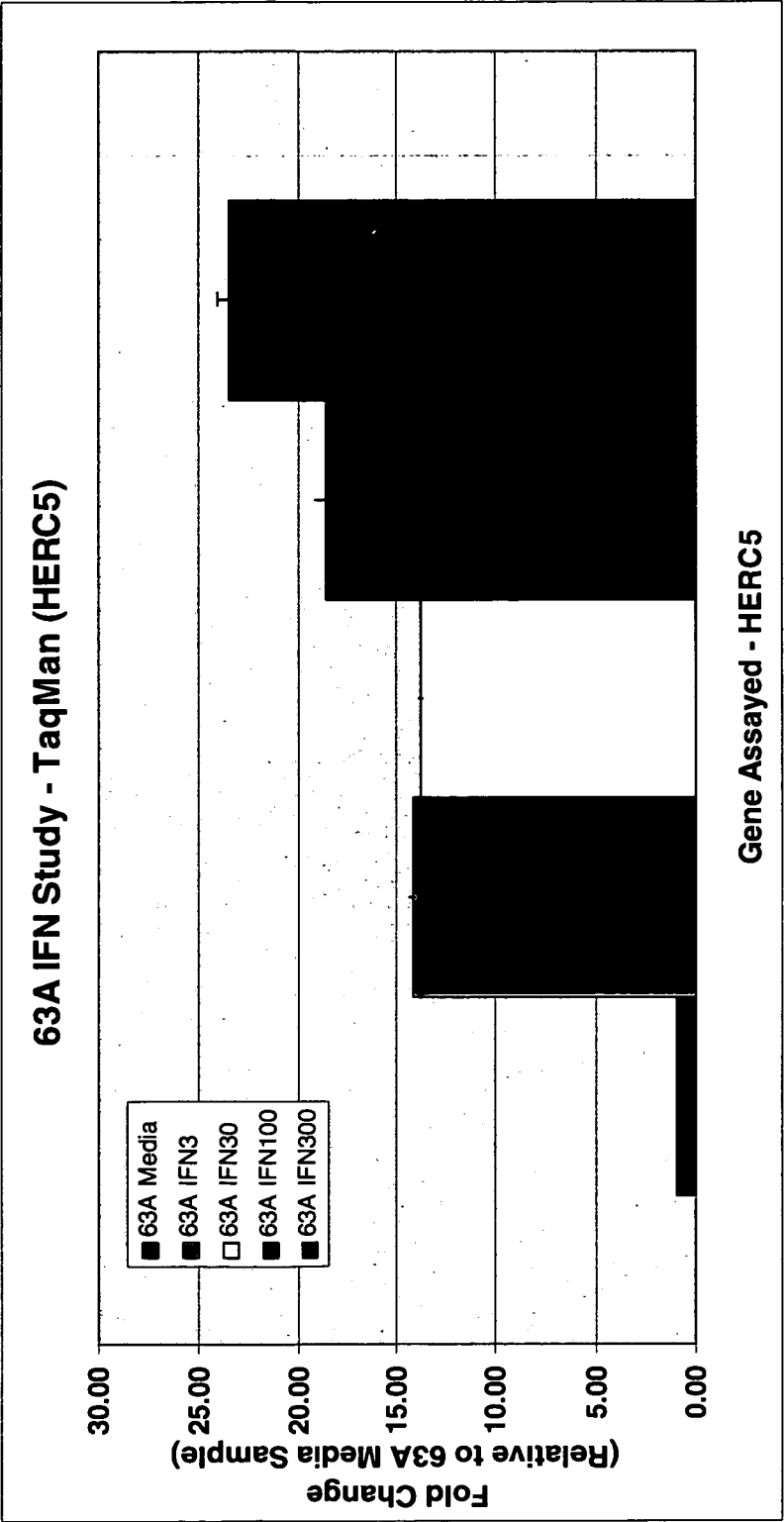
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Figure 4



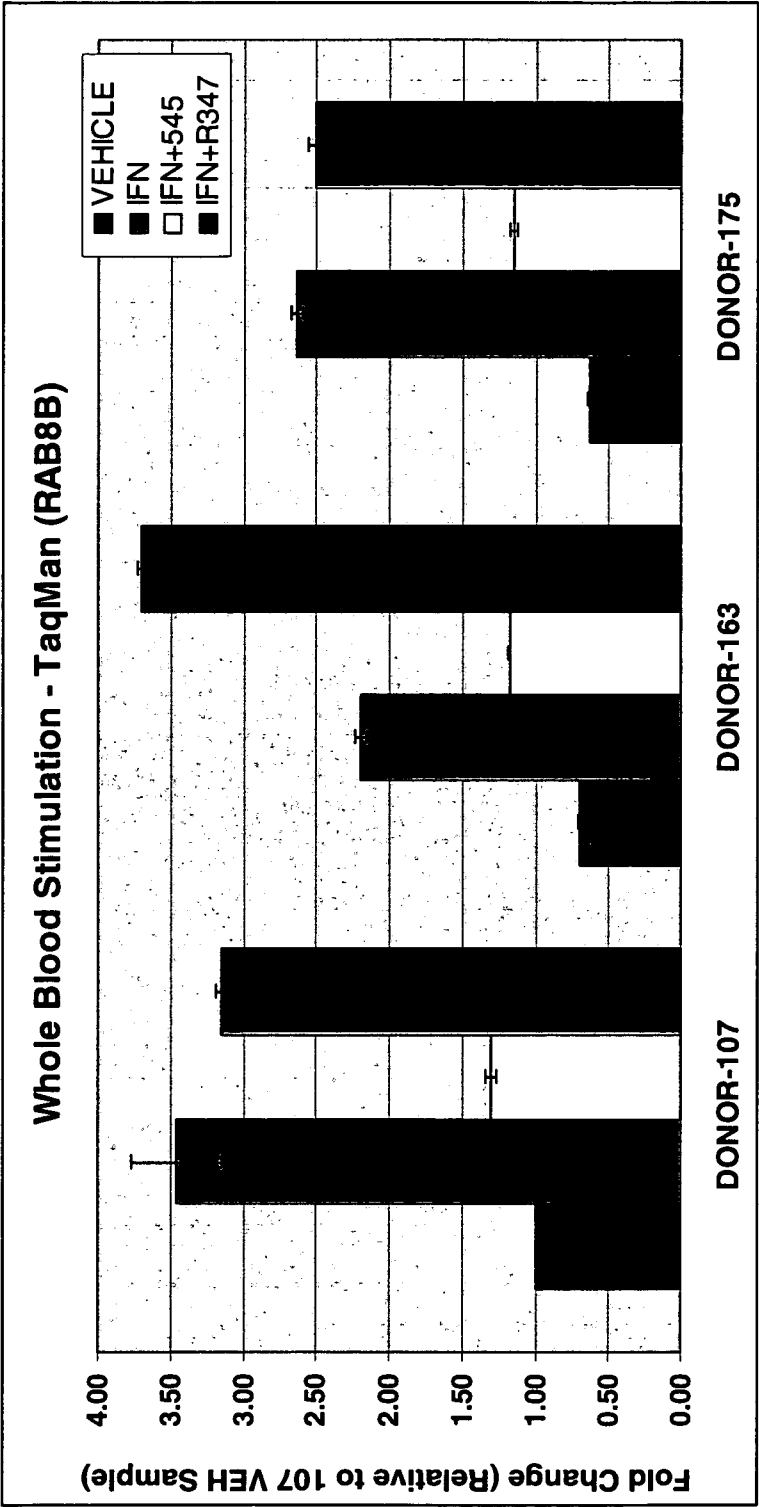
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Figure 5



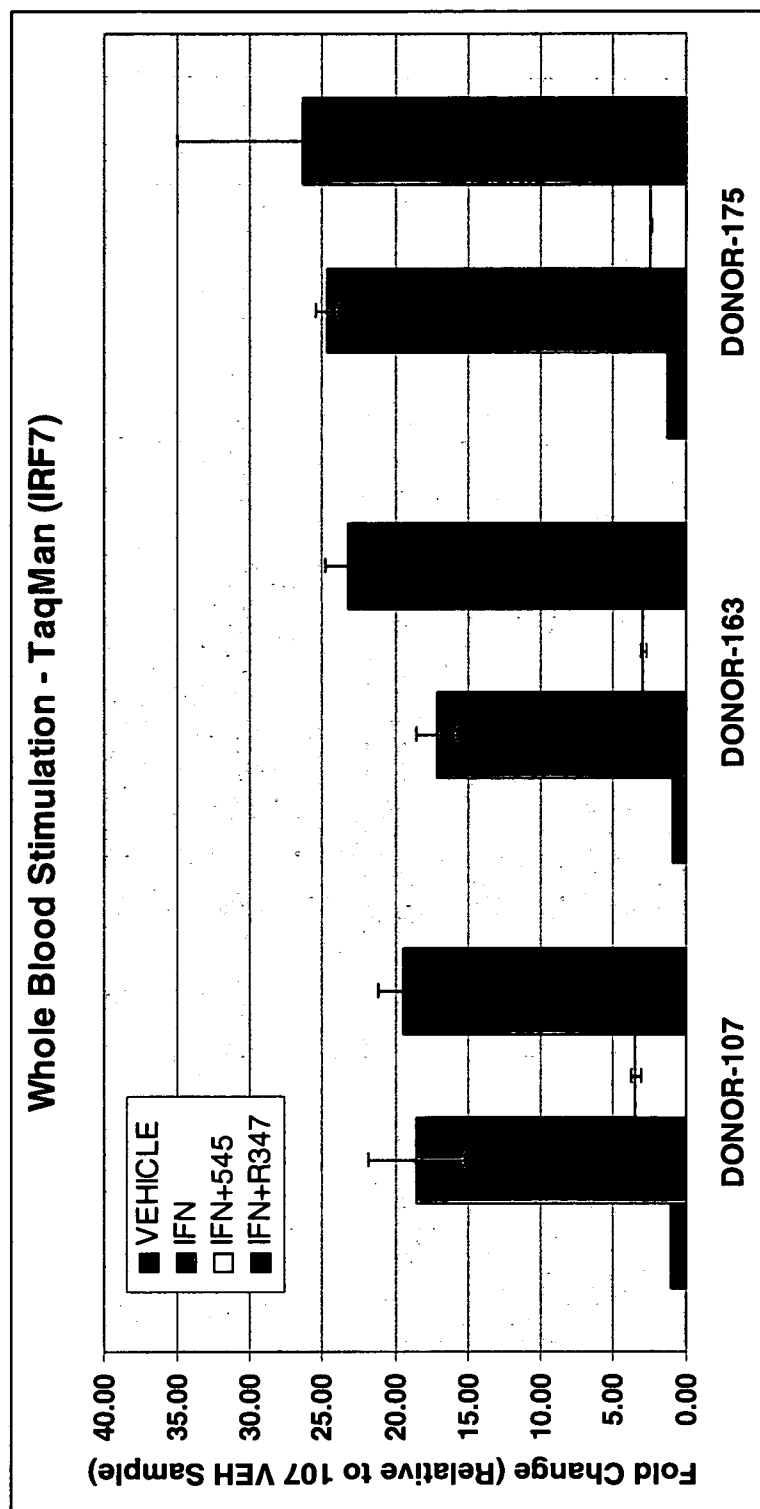
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Figure 6



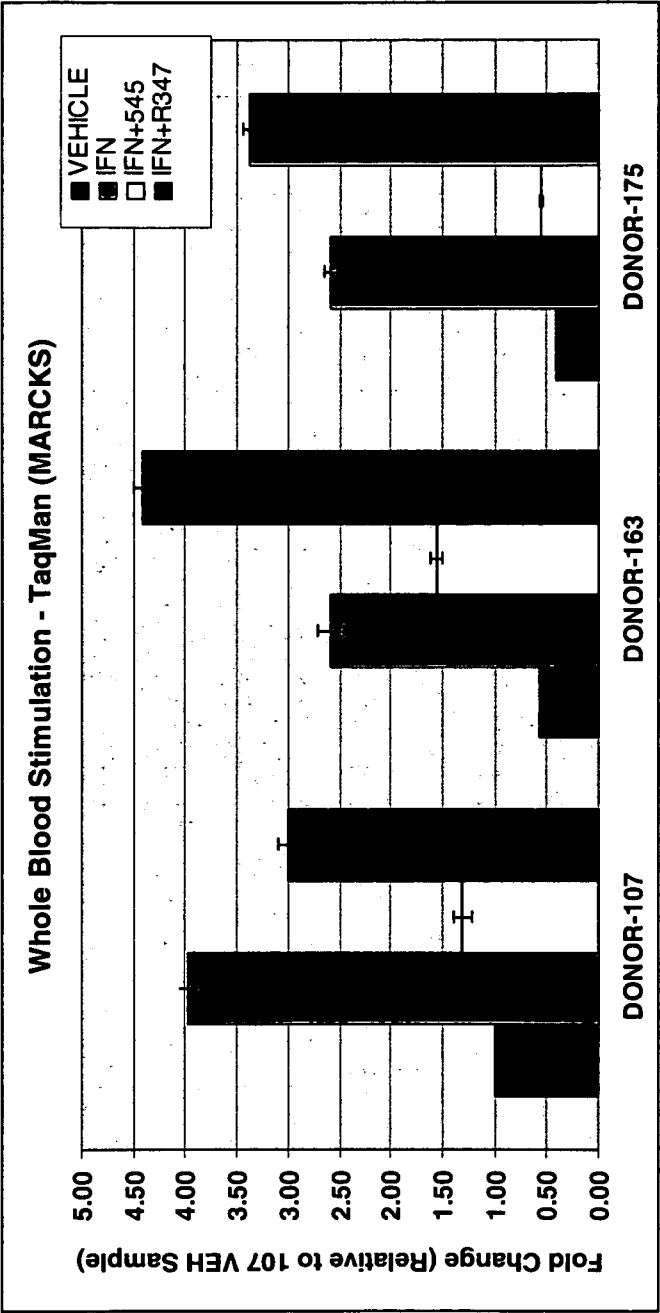
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Figure 7



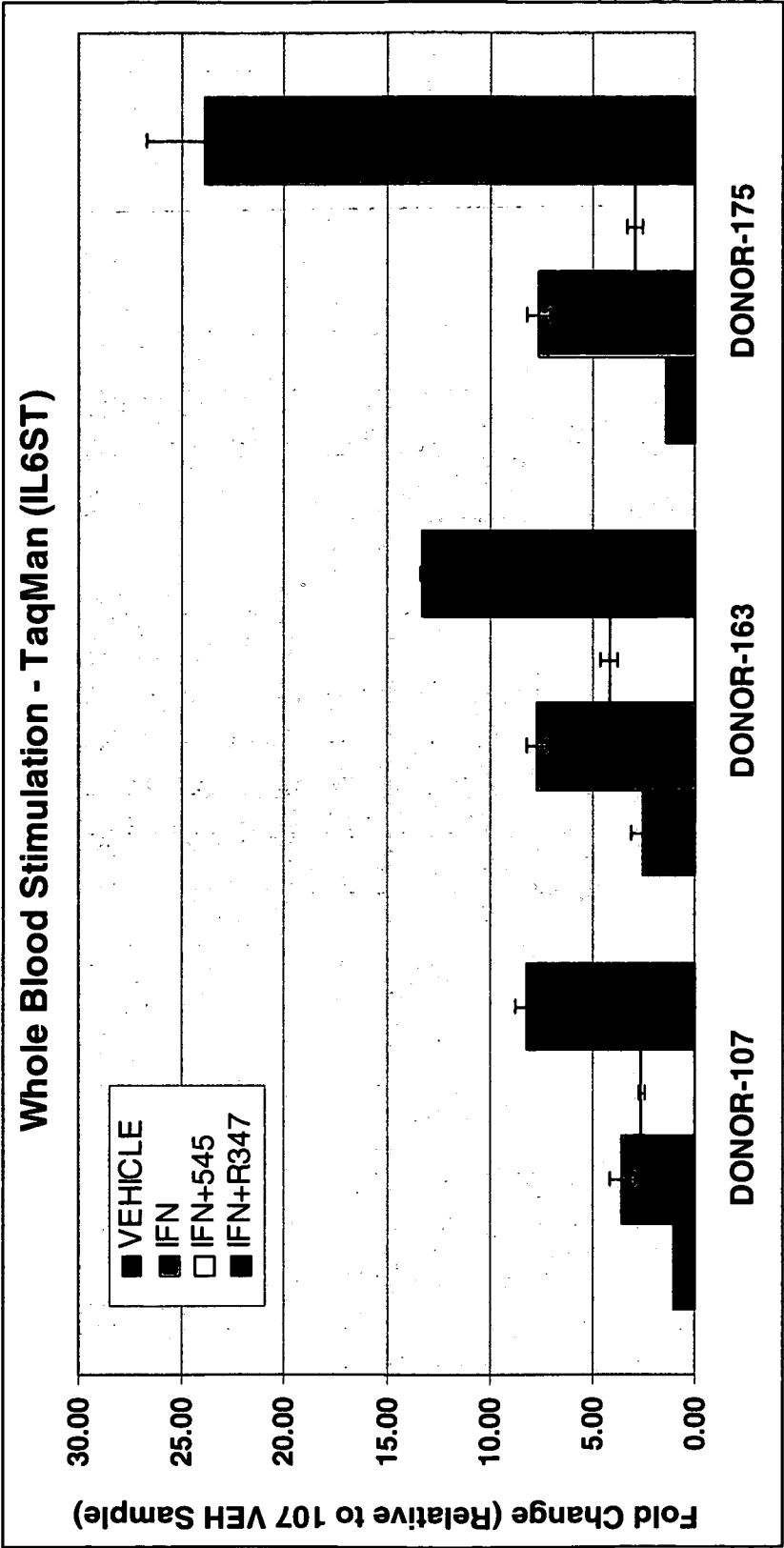
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Figure 8



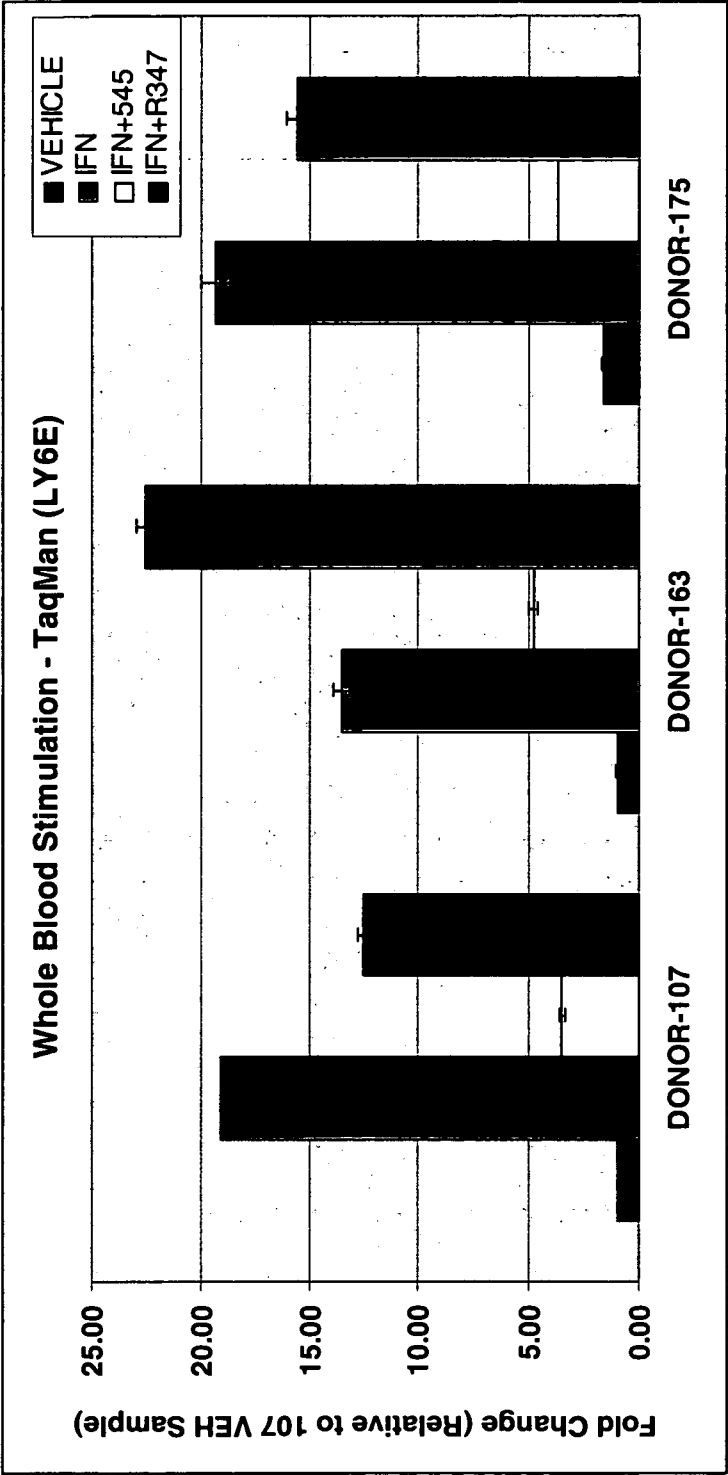
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Figure 9



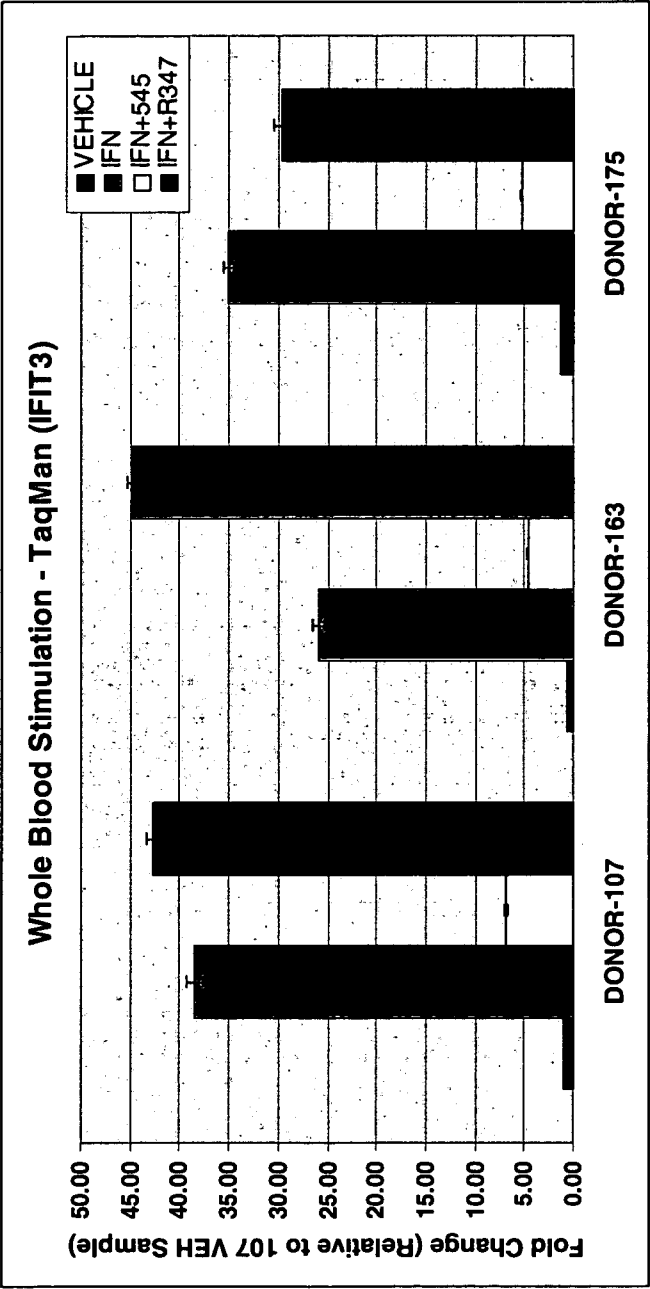
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Figure 10



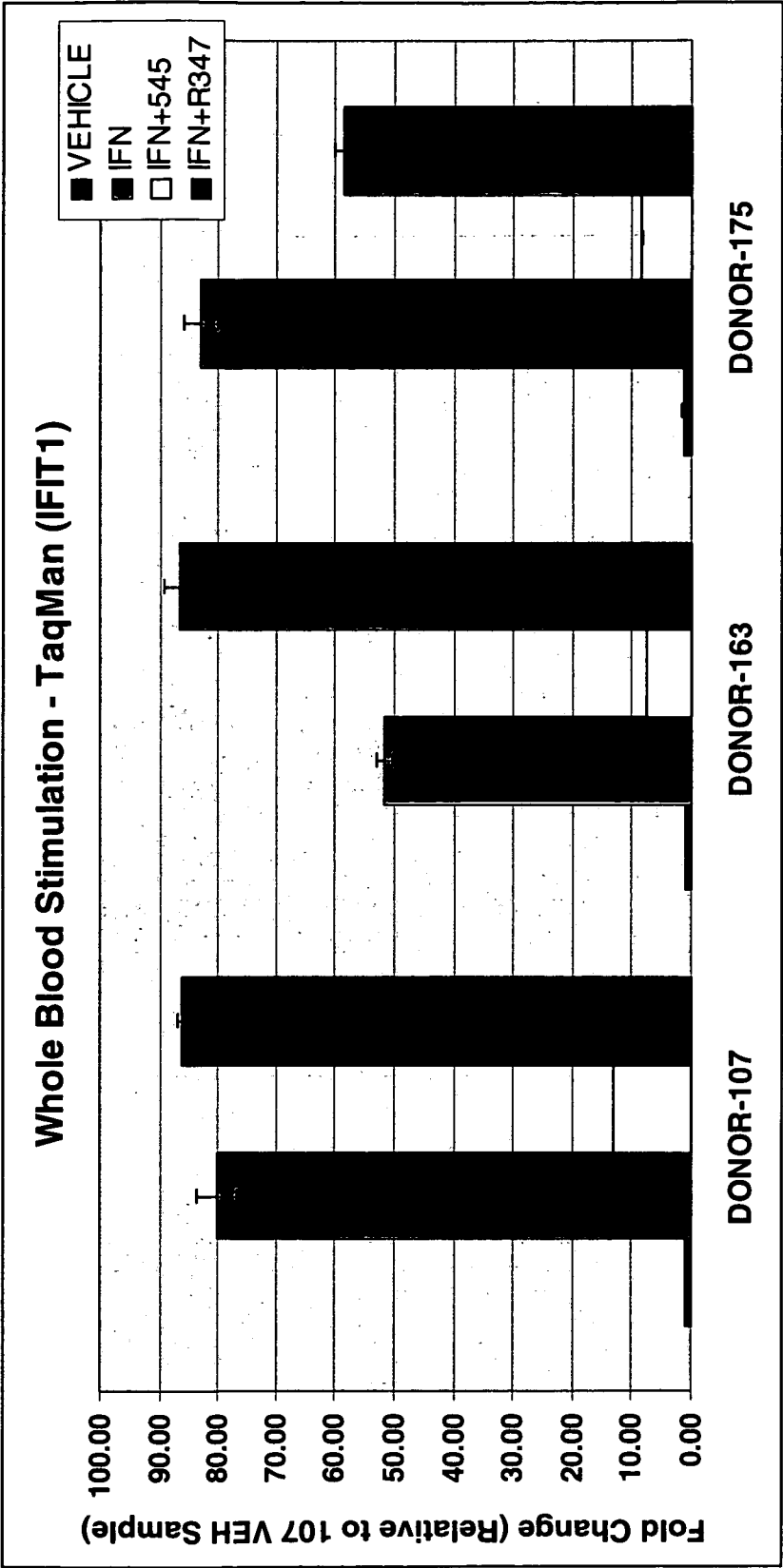
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Figure 11



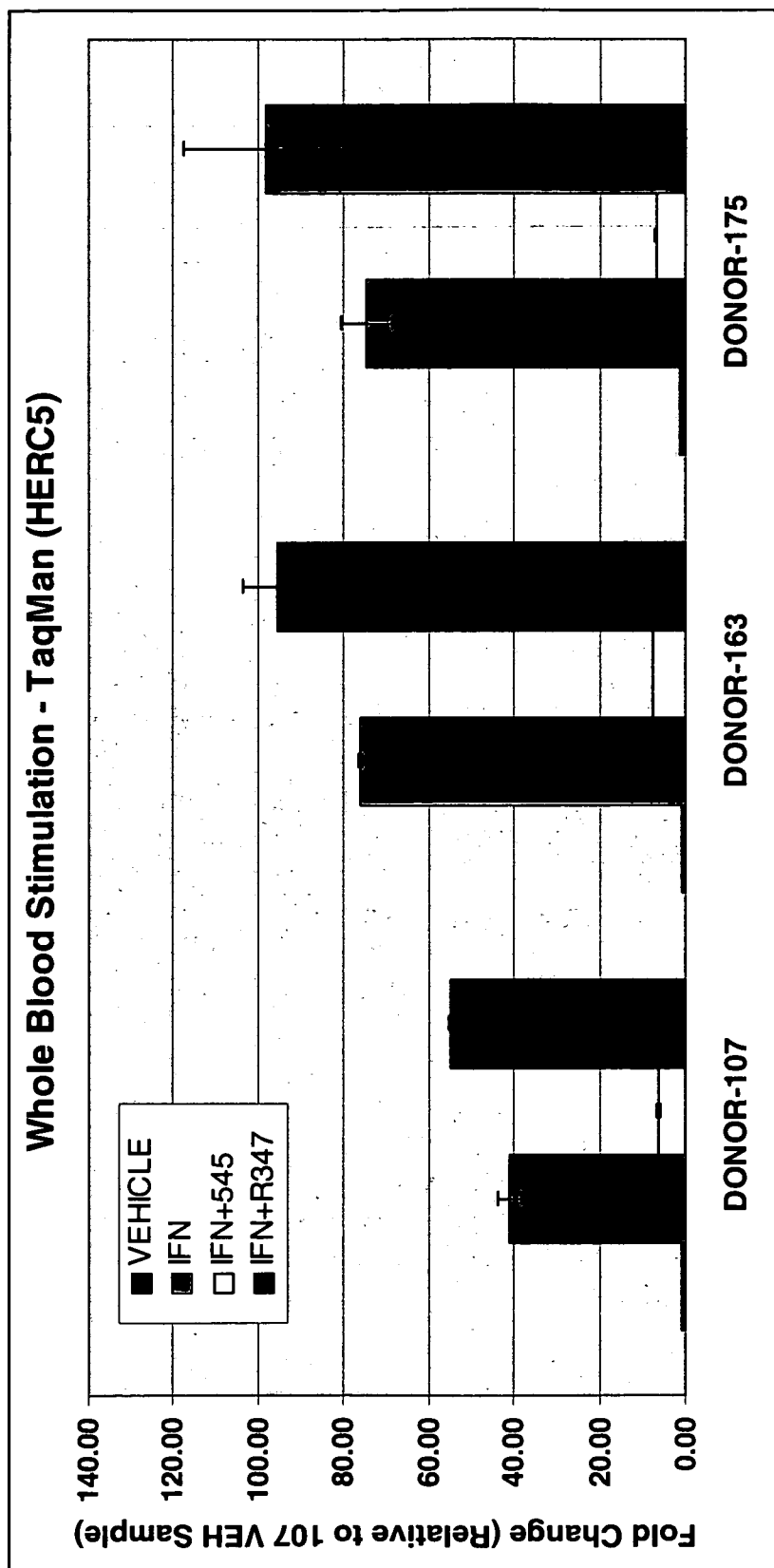
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Figure 12



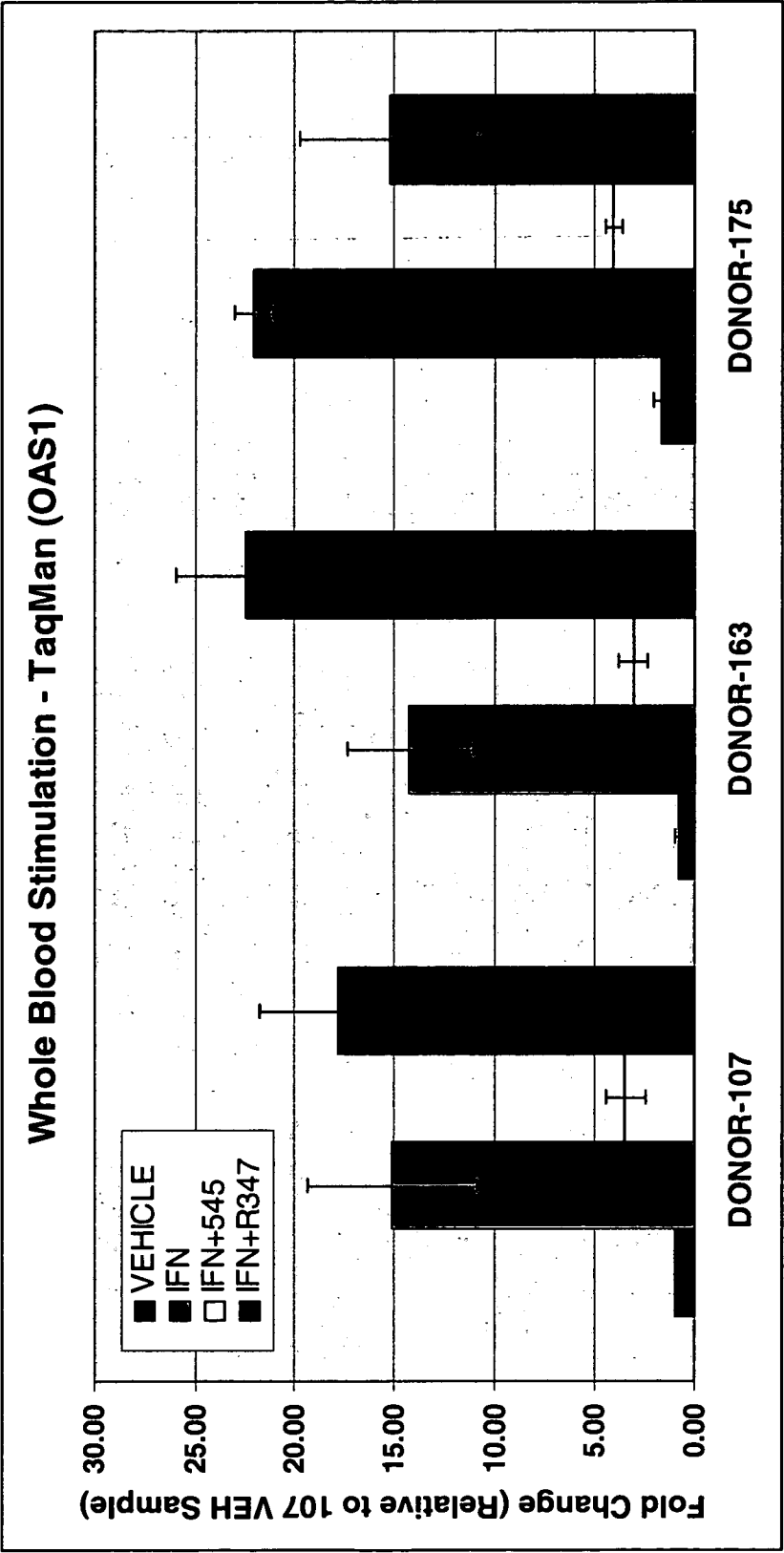
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Figure 13



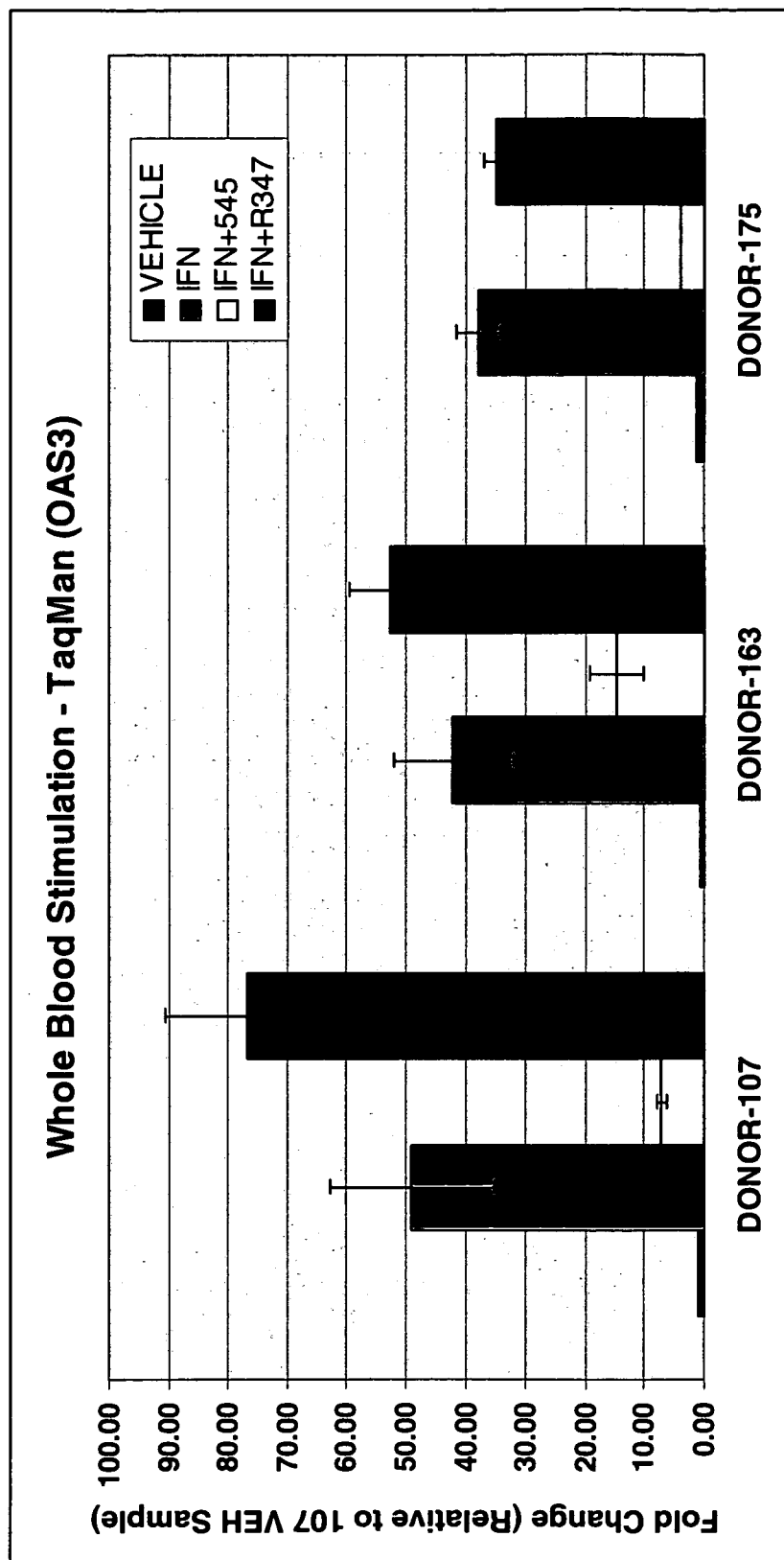
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Figure 14



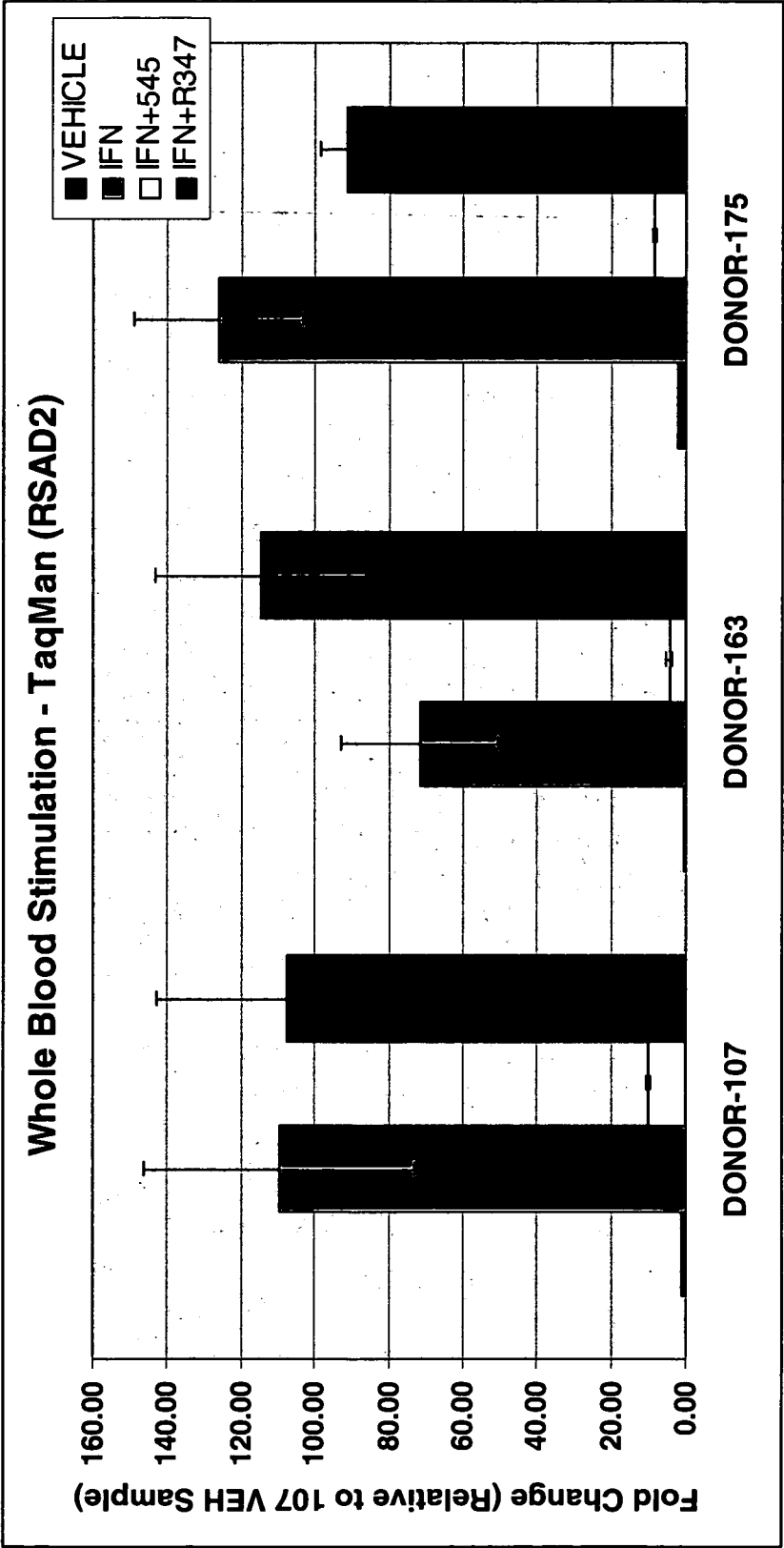
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Figure 15

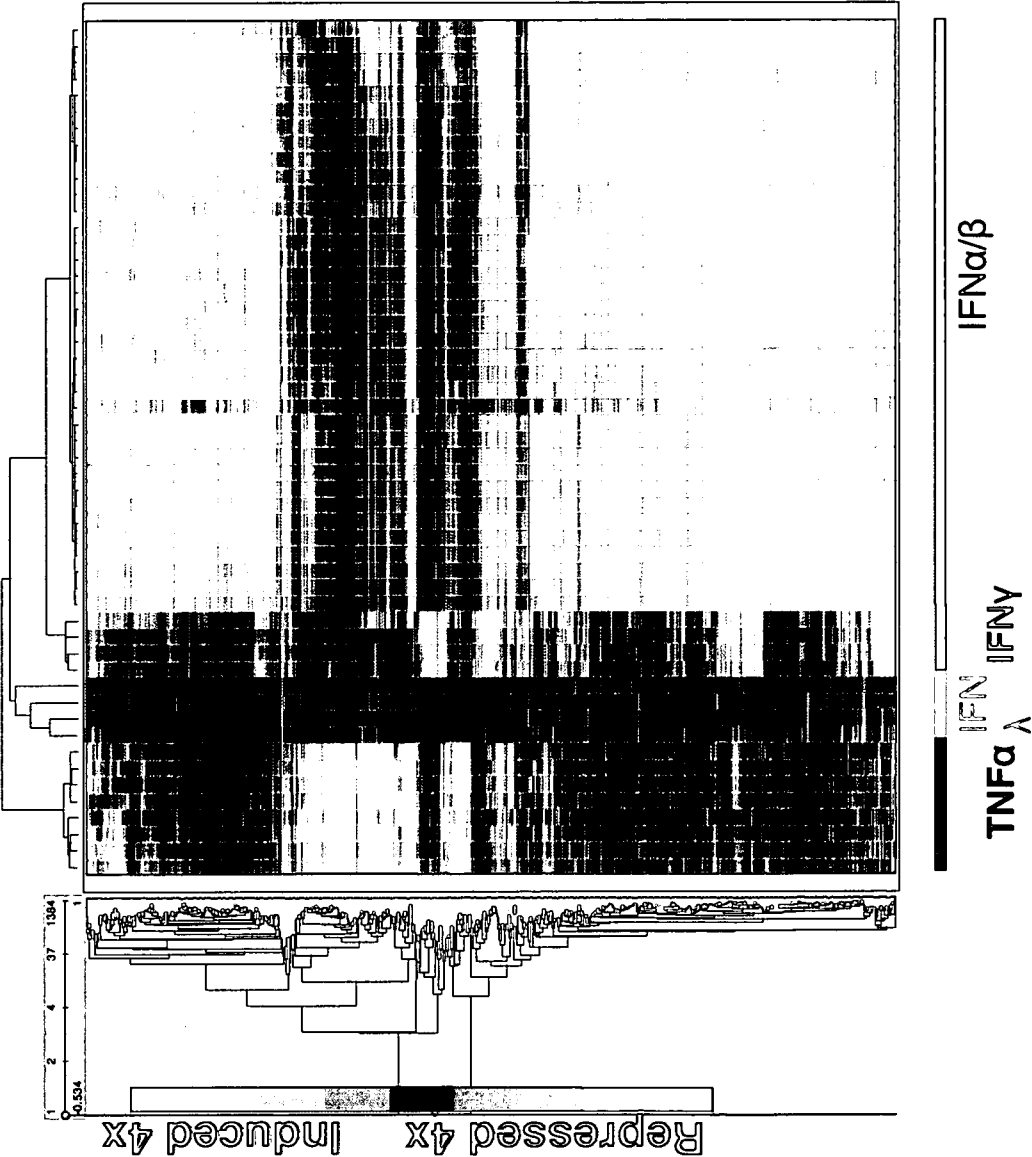


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Figure 16

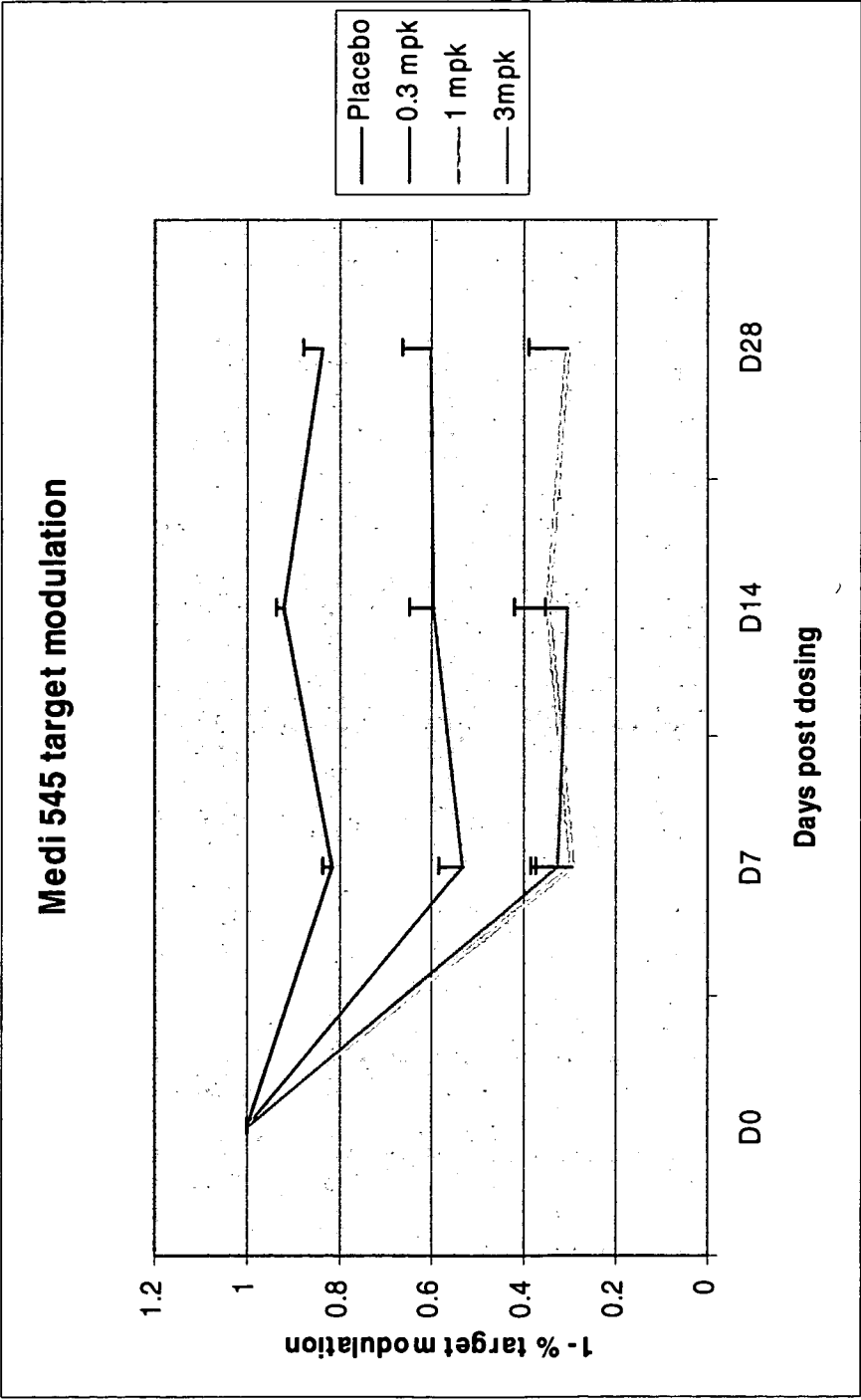


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Figure 17



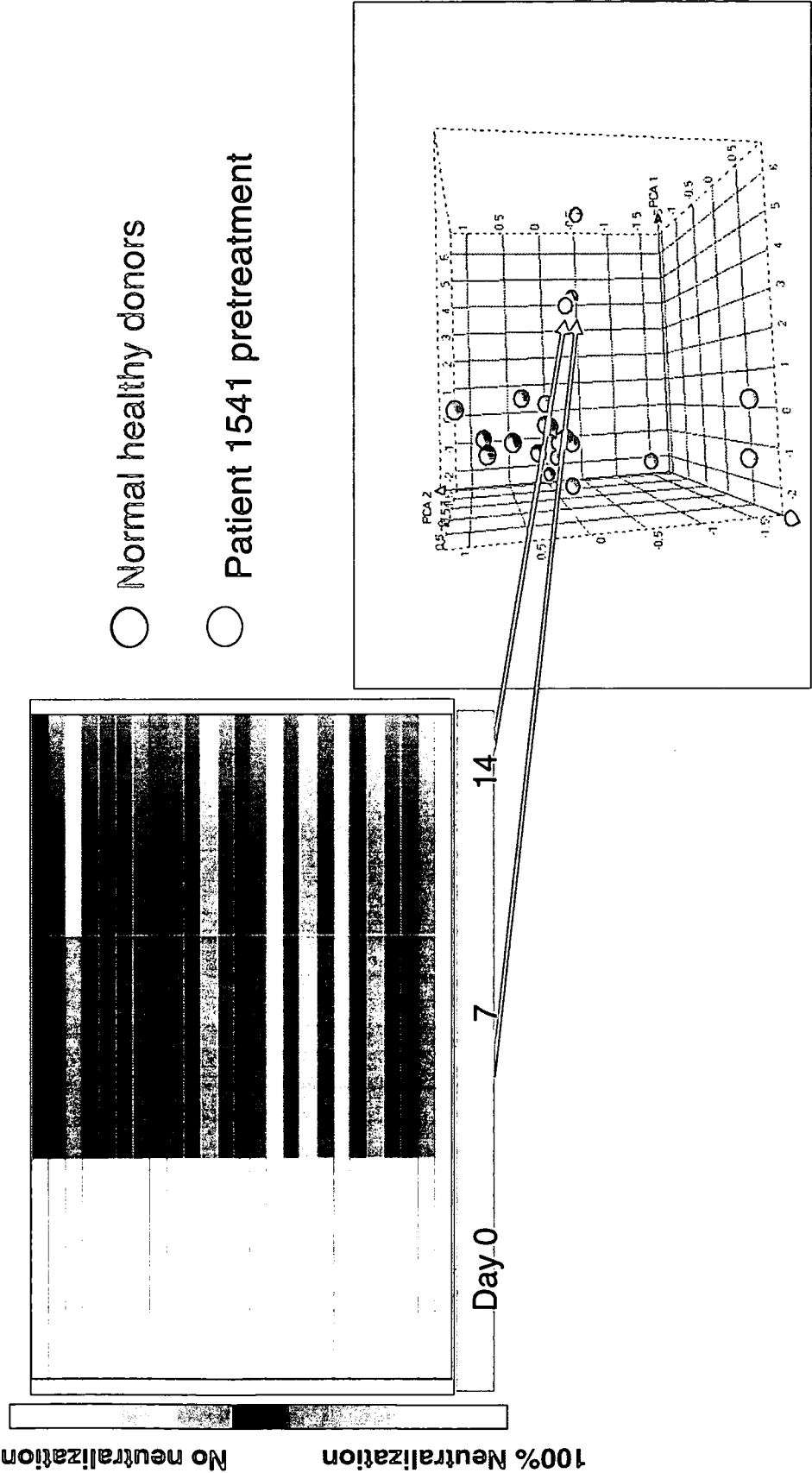
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Figure 18



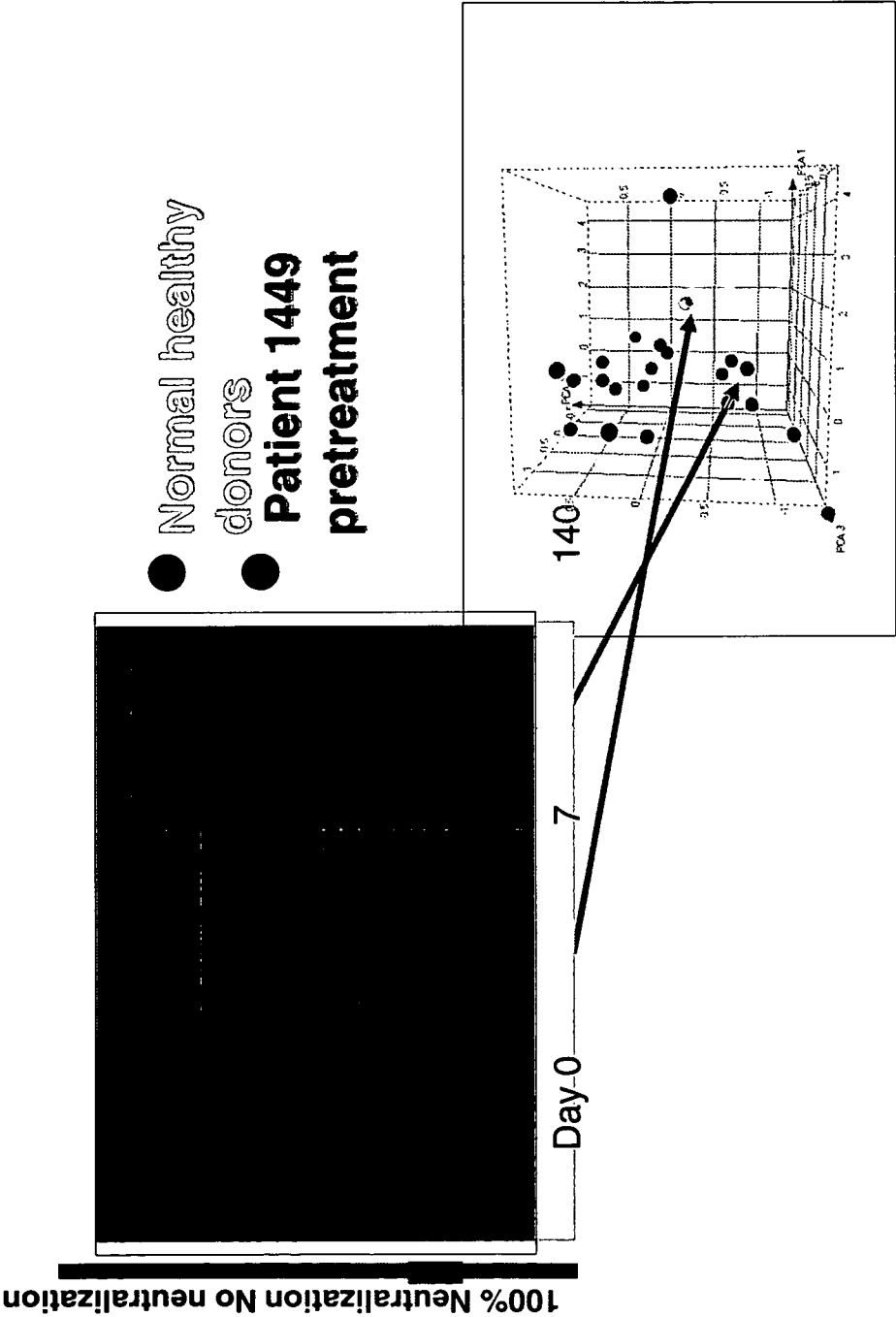
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Figure 19

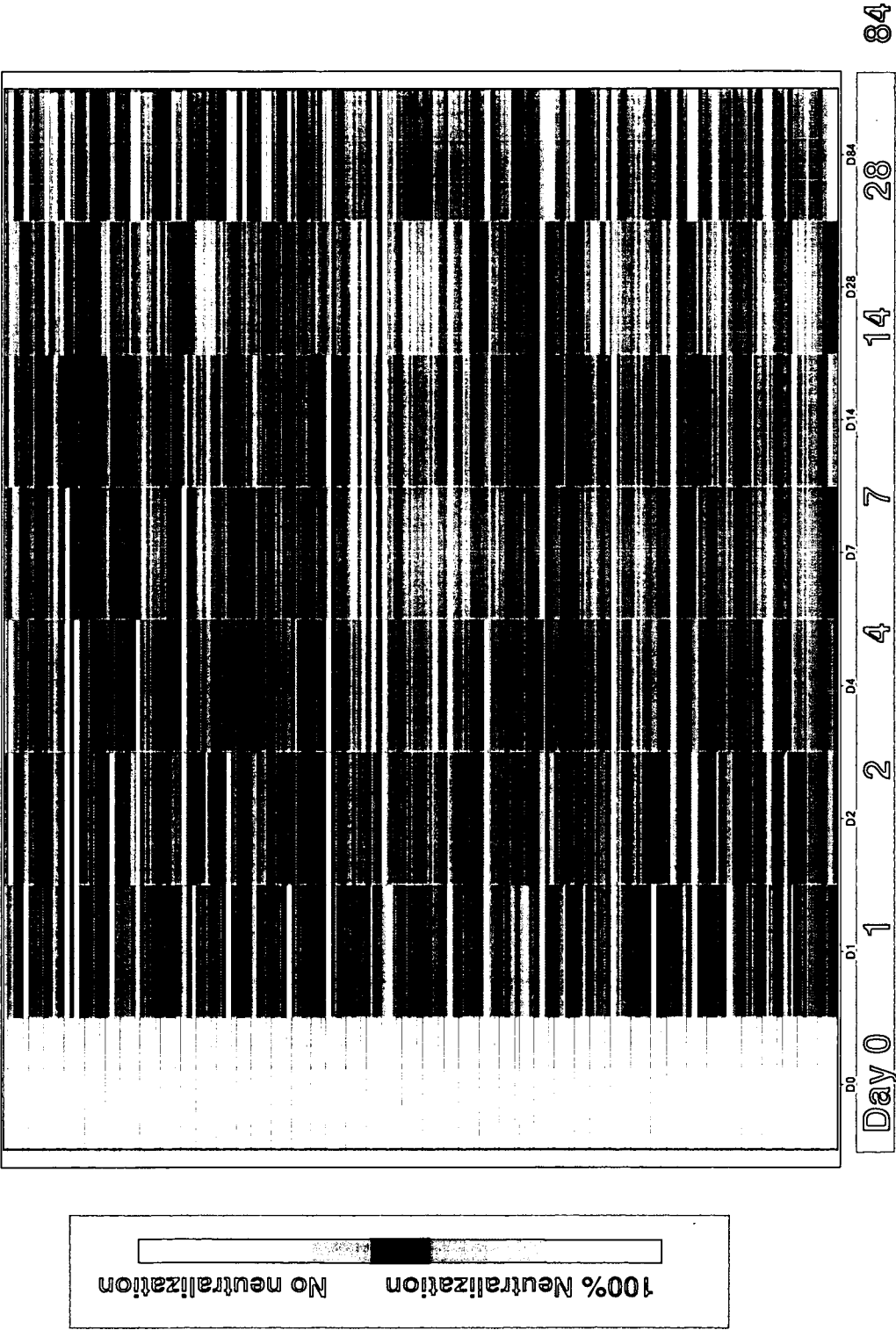


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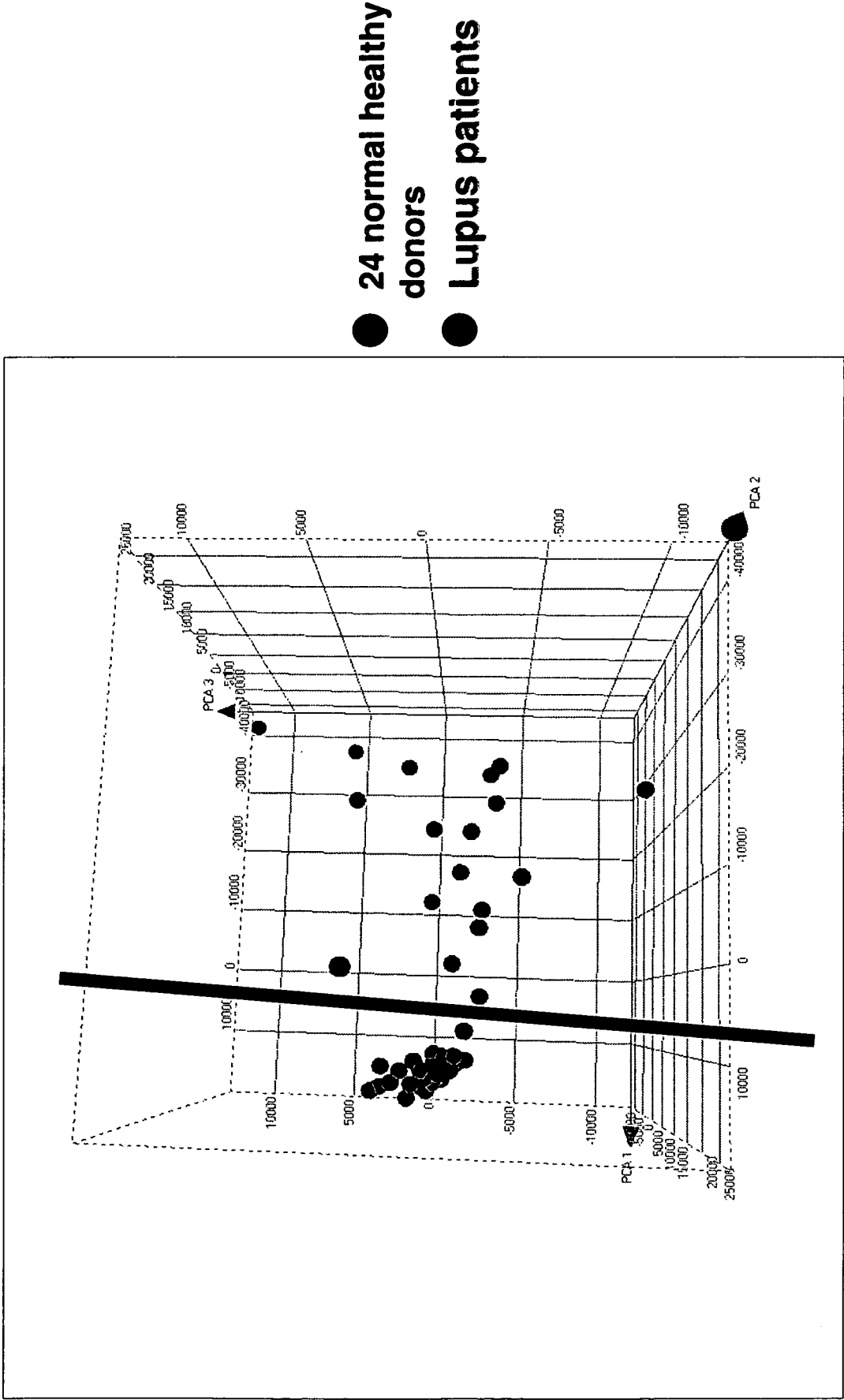
Figure 20



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Figure 21

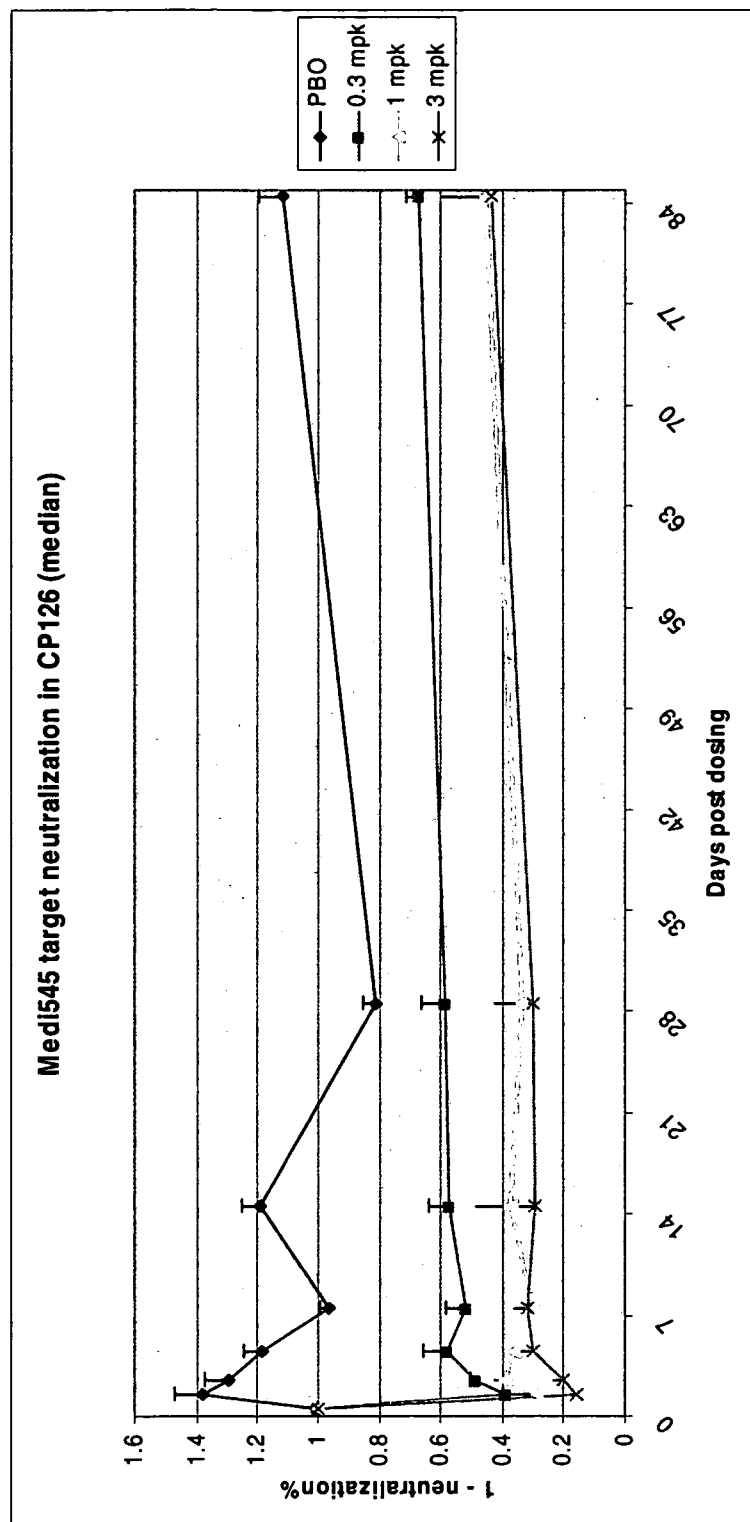


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Figure 22

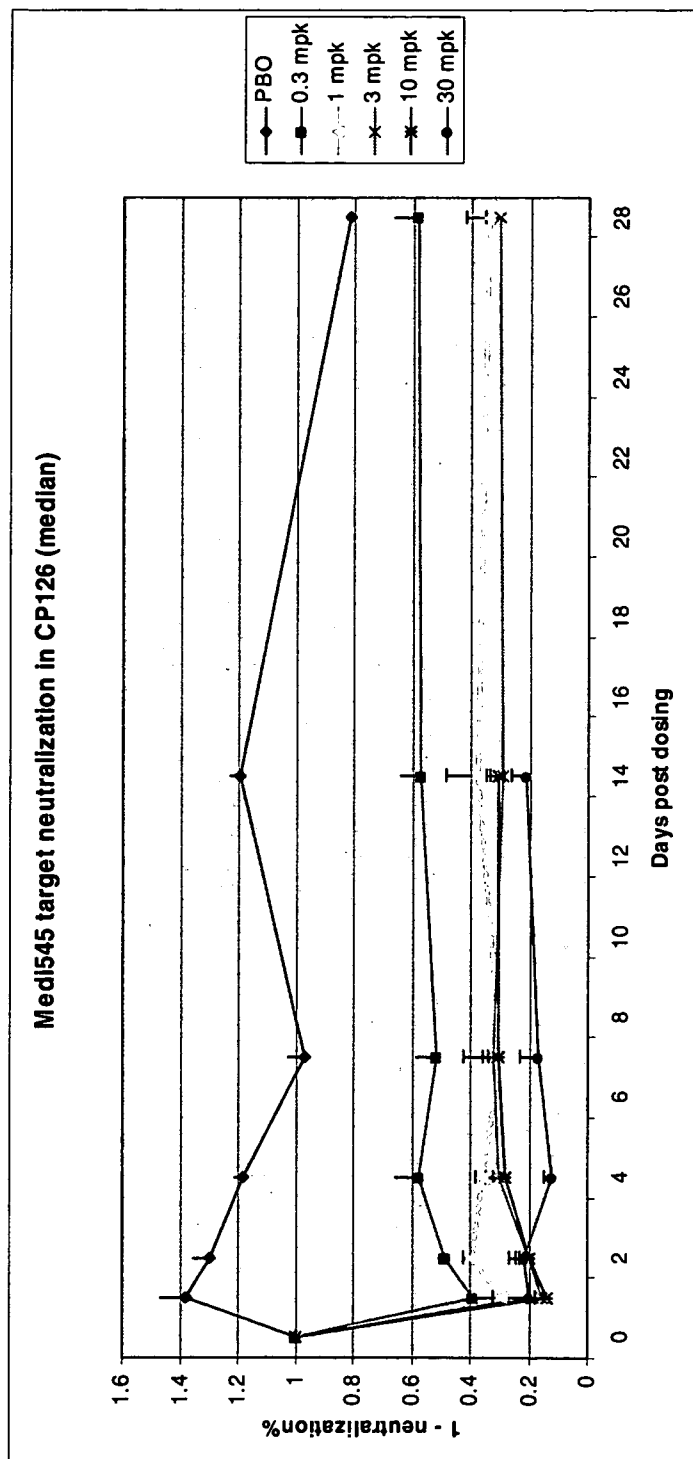


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Figure 23

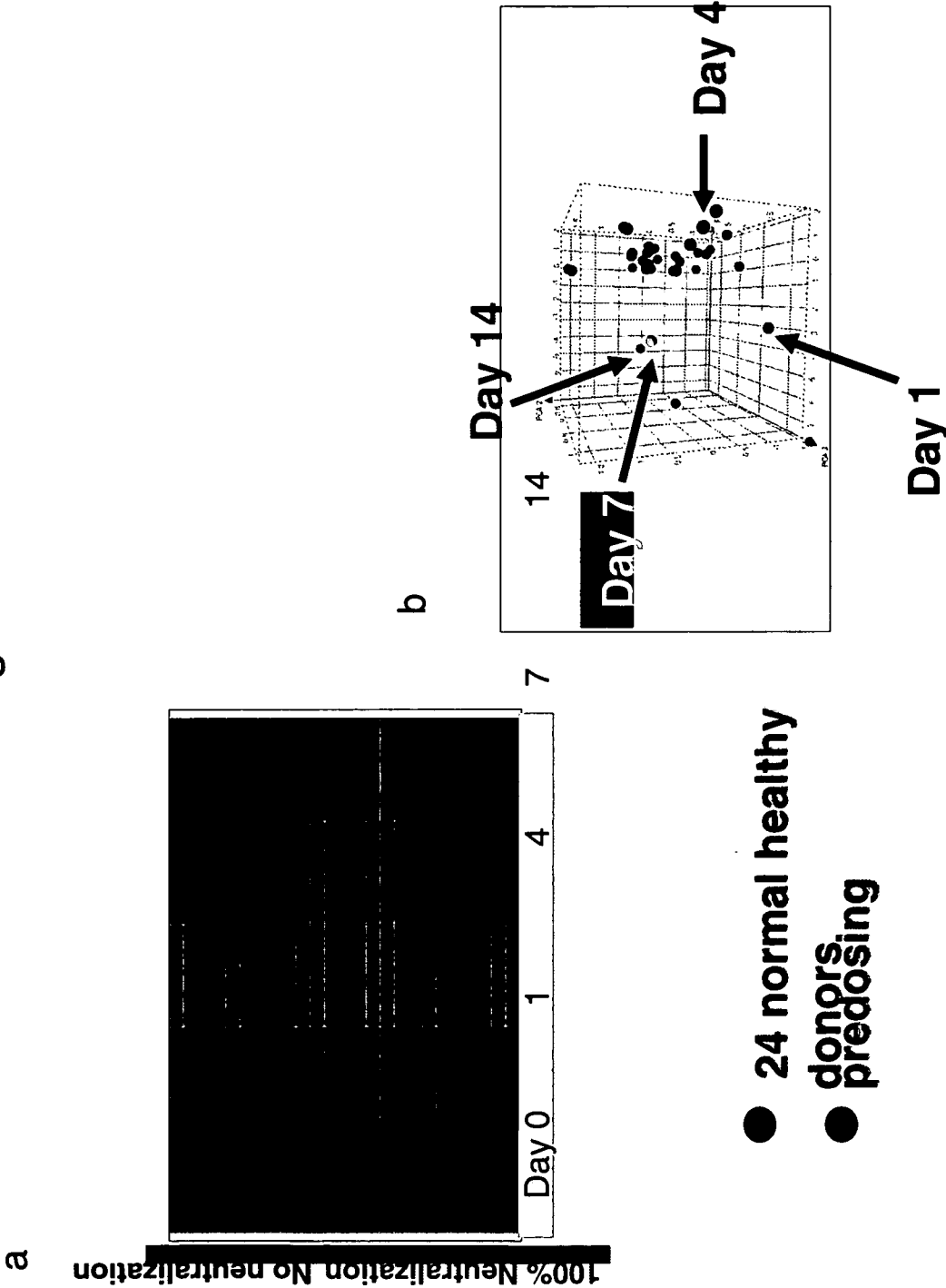


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Figure 24

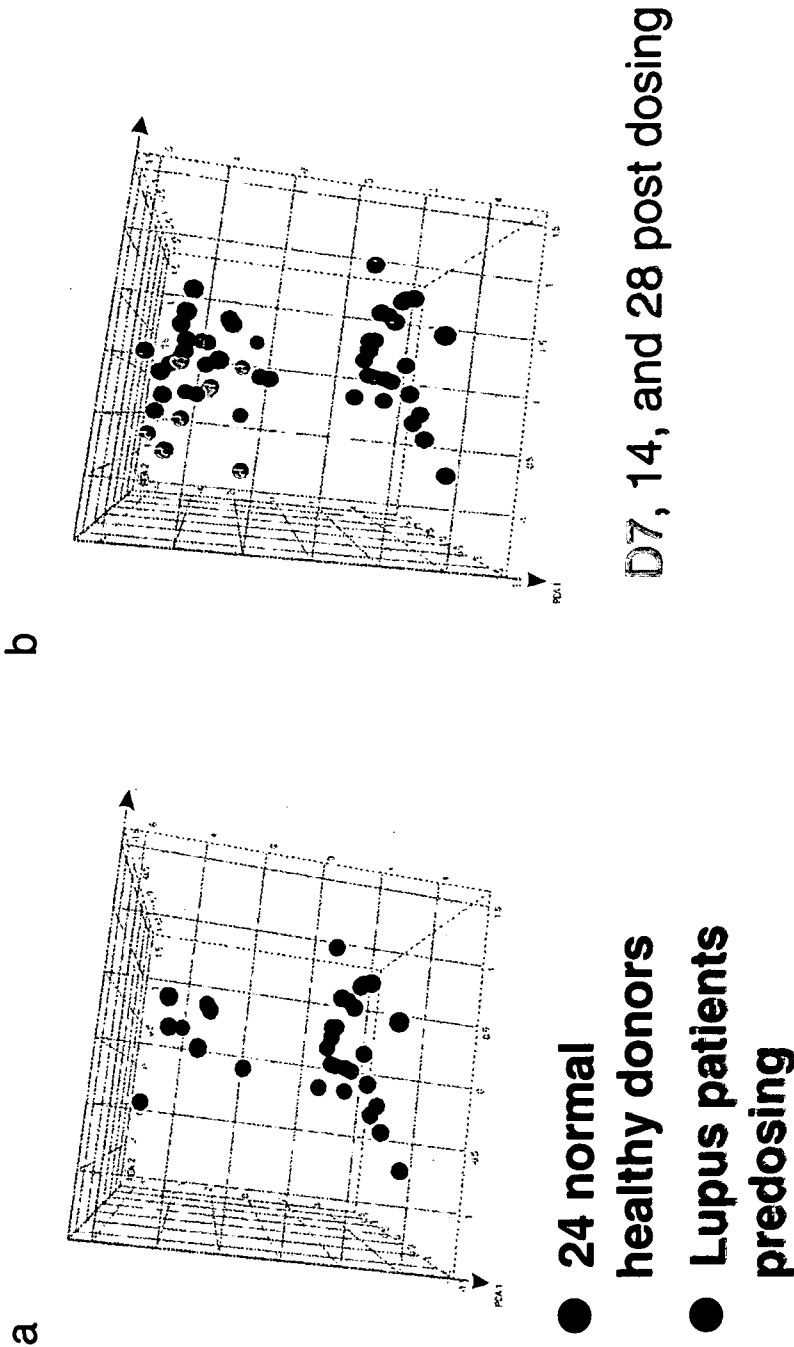


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Figure 25

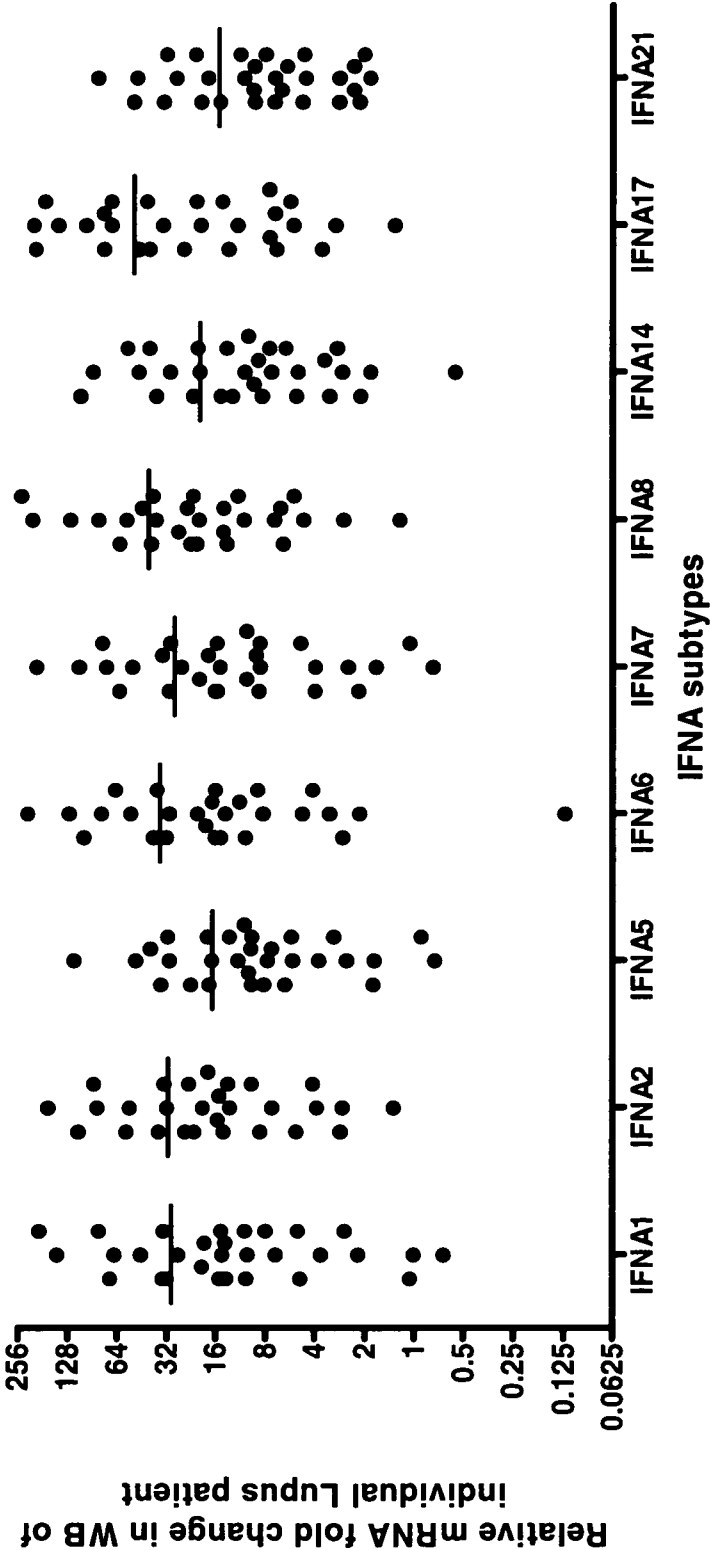


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Figure 26

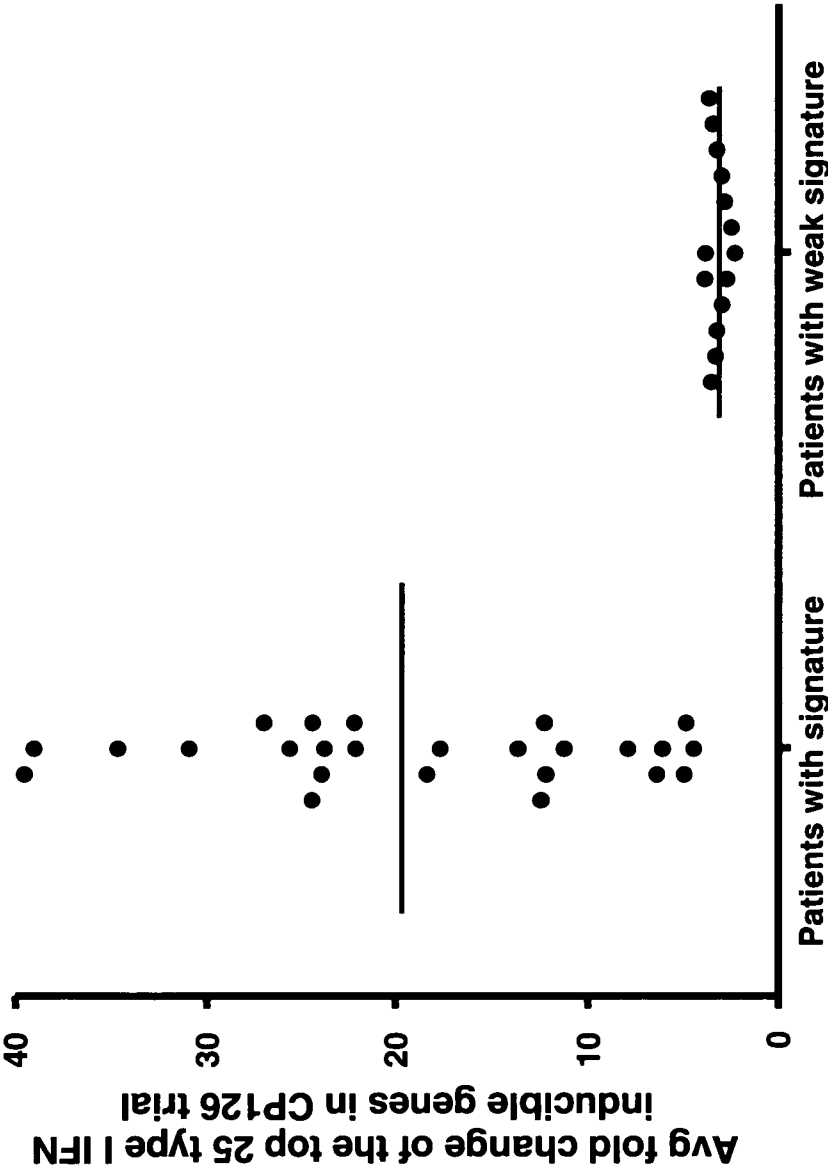


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Figure 27



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Figure 28



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Figure 29

Gene ID	Gene Symbol	Description	Avg	Gene Rank	Gene	Avg % Inhibition
27074	LAMP3	lysosomal-associated men	279.7	1	1	0.647
26010	DNAH10	DNA polymerase-transac	435.4	2	2	0.562
91351	FLJ1033	hypothetical protein FLJ1033	451	3	3	0.496
55008	HERC6	hect domain and RLD 6	457.6	4	4	0.505
710	SERPINC1	serpin peptidase inhibitor, cl	559	5	5	0.602
94240	EPSTN1	epithelial stromal interacto	568.3	6	6	0.486
64108	RTP4	receptor transporter protein	685.2	8	8	0.491
8638	OASL	2'-5'-oligoadenylate synthet	779.7	9	9	0.528
26270	FBXO6	F-box protein 6	794.8	10	10	0.445
3433	IFIT2	interferon-induced protein v	797.8	11	11	0.503
10561	IFI44	interferon-induced protein 4	851.1	13	13	0.521
4940	OAS3	2'-5'-oligoadenylate synthet	899.6	15	15	0.521
116071	BAITF2	basic leucine zipper transc	931.4	16	16	0.561
9636	ISG15	ISG15 ubiquitin-like modifi	948.5	17	17	0.516
3665	IRF7	interferon regulatory factor	1013.2	18	18	0.481
91543	RSAD2	radical S-adenosyl methior	1056.2	19	19	0.563
3430	IFI35	interferon-induced protein 3	1067.3	20	20	0.444
4938	OAS1	2'-5'-oligoadenylate synthet	1075.8	21	21	0.466
51056	LAP3	leucine aminopeptidase 3	1087.1	22	22	0.384
3434	IFIT1	interferon-induced protein v	1105.7	24	24	0.558
24138	IFIT5	interferon-induced protein v	1143	25	25	0.440
5359	PLSCR1	phospholipid scramblase 1	1156.9	26	26	0.399
10964	IFI44L	interferon-induced protein 4	1169.7	27	27	0.538
51338	MSA4A	membrane-spanning 4-dom	1255.6	28	28	0.404
130589	GALM	galactose mutarotase (aldc	1255.7	29	29	0.341
9246	UBE2L6	ubiquitin-conjugating enzyr	1297.9	30	30	0.327
27348	TOR1B	torin family 1, member B	1313.9	31	31	0.352
219285	SAMD9L	sterile alpha motif domain	1327	32	32	0.384
51191	HERC5	hect domain and RLD 5	1474	34	34	0.487
23424	TDRD7	tudor domain containing 7	1516.9	35	35	0.323
11277	TREX1	three prime repair exonucit	1566.5	37	37	0.305
64761	PARP12	poly (ADP-ribose) polymer	1573.6	38	38	0.381
64651	AXUD1	AXIN1 up-regulated 1	1592.5	39	39	0.307
647384	LOC647384	region containing cell divi	702.25	1	1	0.377
4599	MX1	myxovirus (influenza virus)	773.75	2	2	0.418
9638	ISG15	ISG15 ubiquitin-like modifi	866.375	3	3	0.355
91543	RSAD2	radical S-adenosyl methior	1234.875	4	4	0.400
5266	PI3	peptidase inhibitor 3, st	1284.375	5	5	0.324
1978	EIF4EBP1	eukaryotic translation init	1295.5	6	6	0.336
645238	LOC645238	hypothetical protein LOC64	1310.875	7	7	0.445
10410	IFITM3	interferon induced transme	1404.125	8	8	0.312
55331	PHCA	phytocearidase, alk-alime	1438	9	9	0.314
10954	IFI44L	interferon-induced protein 4	1458.25	10	10	0.449
646870	LOC646870	hypothetical protein LOC64	1478.125	11	11	0.332
51191	HERC5	hect domain and RLD 5	1561.75	12	12	0.342
79796	ALG9	asparagine-linked glycosyl	1586	13	13	0.283
51101	C8orf70	chromosome 8 open readin	1552.25	14	14	0.276
3434	IFIT1	interferon-induced protein v	1821.375	15	15	0.348
4938	OAS1	2'-5'-oligoadenylate synthet	1918.5	16	16	0.266
1796	DPAGT1	dolichyl-phosphate (UDP-4	2033.25	17	17	0.264
55072	RNF31	ring finger protein 31	2033.375	18	18	0.271
10211	NOXA1	NADPH oxidase activator	2052.875	19	19	0.291
5598	MAPK7	mitogen-activated protein k	2130.5	20	20	0.227
55603	FAM46A	family with sequence simil	2131.125	21	21	0.229
80262	C16orf70	chromosome 16 open read	2150.5	22	22	0.259
553156	FLJ11903	similar to hypothetical prot	2215.25	23	23	0.423
11277	TREX1	three prime repair exonucit	2231	24	24	0.200
64121	RRAGC	Ras-related GTP binding C	2235.625	25	25	0.262
3692	ITGB4BP	integrin beta 4 binding prot	2324.375	26	26	0.190
6468	FBXW4	F-box and WD-40 domain	2327	27	27	0.213
9896	KIAA0274	KIAA0274	2335.125	28	28	0.235
8536	CANX1	calcium/calmodulin-depen	2419.875	29	29	0.228
2769	GNA15	guanine nucleotide binding	2448	30	30	0.233
146540	FLJ32130	hypothetical protein FLJ32	2448.25	31	31	0.288
2678	GGT1	gamma-glutamyltransferas	2491.75	32	32	0.394
51253	MRPL37	mitochondrial ribosomal pr	2529.75	33	33	0.210
83343	LOC83343	hypothetical protein BC011	2539.375	34	34	0.190
9973	CDC	copper chaperone for supe	2546	35	35	0.209
148022	TICAM1	tol-like receptor adaptor m	2547.75	36	36	0.201
553115	PEF1	pena-EF-hand domain con	2556.125	37	37	0.204
4064	CD180	CD180 molecule	2551.875	38	38	0.210
7106	TSPAN4	tetraspanin 4	2579.5	39	39	0.200
275	AMT	aminomethyltransferase	2580.375	40	40	0.297

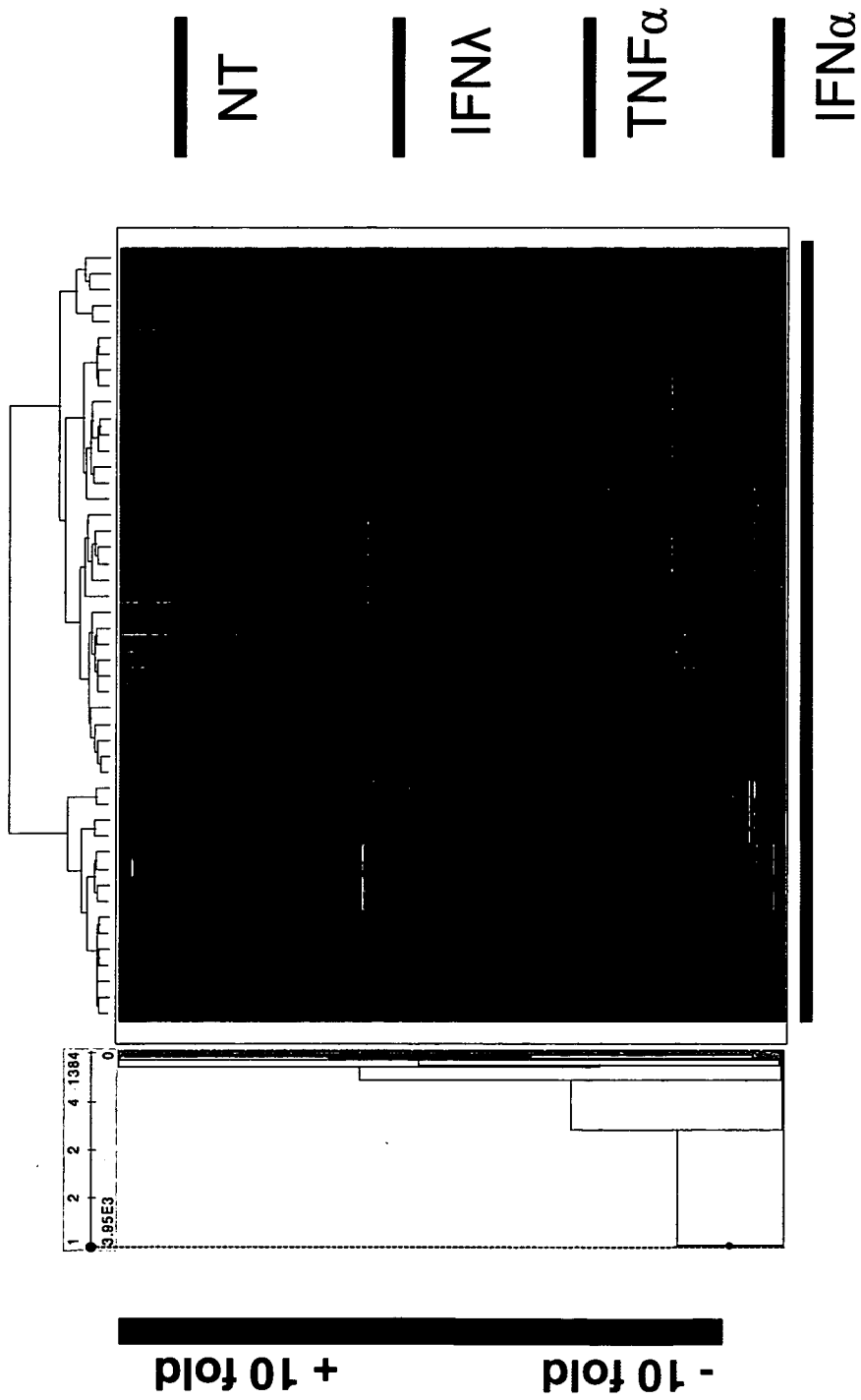
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Figure 29

Gene ID	Gene Symbol	Description	Avg. Gene Rank	Gene	Avg. % Inhibition
54958	TMEM160	transmembrane protein 160	1131.125	1	0.428
55759	WDR12	WD repeat domain 12	1161	2	0.417
84650	EBPL	emopamil binding protein-like	1196.125	3	0.438
91978	C19orf20	chromosome 19 open reading frame 20	1213.25	4	0.447
440	ASNS	asparagine synthetase	1391	5	0.376
83707	TRPT1	tRNA phosphotransferase	1678	6	0.324
1178	CLC	Charcot-Leyden crystal protein	1686.875	7	0.426
79612	NARG1L	NMDA receptor regulated 1	1691.125	8	0.338
84524	ZC3H8	zinc finger CCH-type containing 8	1698.25	9	0.343
60561	RINT1	RAD50 interactor 1	1703.375	10	0.324
10572	SIVA	CD27-binding (Siv) protein	1763.875	11	0.328
2272	FHIT	fragile histidine triad gene	1764.5	12	0.316
10207	INADL	InaD-like (Drosophila)	1784.625	13	0.326
9790	BMS1L	BMS1-like, ribosome associated	1790.5	14	0.303
9533	POLR1C	polymyrase (RNA) I polypeptide	1826.75	15	0.324
163087	ZNF383	zinc finger protein 383	1835.125	16	0.403
9657	IOCB1	IO motif containing B1	1870.125	17	0.324
91949	COG7	component of oligomeric GTPase	1880	18	0.327
29922	NME7	non-metastatic cells 7, protein	1881.25	19	0.381
11266	DUSP12	dual specificity phosphatase 12	1891.25	20	0.293
61119	RPA3	replication protein A3, 14kDa	1940	21	0.323
257218	SHPRH	SNF2 histone linker PHD finger	1953.25	22	0.360
93081	RP11-484f6.3	hypothetical protein BC015	1956.75	23	0.372
23155	CLGC1	chloride channel CLC-like 1	1982	24	0.304
9014	TAF1B	TAF box binding protein 1	1999.125	25	0.363
55657	ZNF692	zinc finger protein 692	2045.5	26	0.306
55352	C17orf79	chromosome 17 open reading frame 79	2051.375	27	0.311
84284	C1orf57	chromosome 1 open reading frame 57	2059.625	28	0.296
839	CASP6	caspase 6, apoptosis-related	2069.25	29	0.303
440498	LOC440498	hypothetical gene support	2077.125	30	0.280
619435	C8orf61	chromosome 8 open reading frame 61	2110.375	31	0.320
8464	SUPT3H	suppressor of Ty 3 homolog	2126.875	32	0.364
199857	ALG14	asparagine-linked glycosyl transferase 14	2148	33	0.472
28642	TRAV39	T cell receptor alpha variable region 39	2157.125	34	0.401
5189	PEX1	peroxisome biogenesis factor 1	2158.625	35	0.297
130916	MTERFD2	MTERF domain containing 2	2162.375	36	0.278
79921	TCEAL4	transcription elongation factor 4	2205.75	37	0.285
928	CD9	CD9 molecule	2236.75	38	0.286
54344	DPM3	dolichyl-phosphate mannosyl transferase 3	2276.375	39	0.326
54914	KIAA1797	KIAA1797	2277	40	0.271

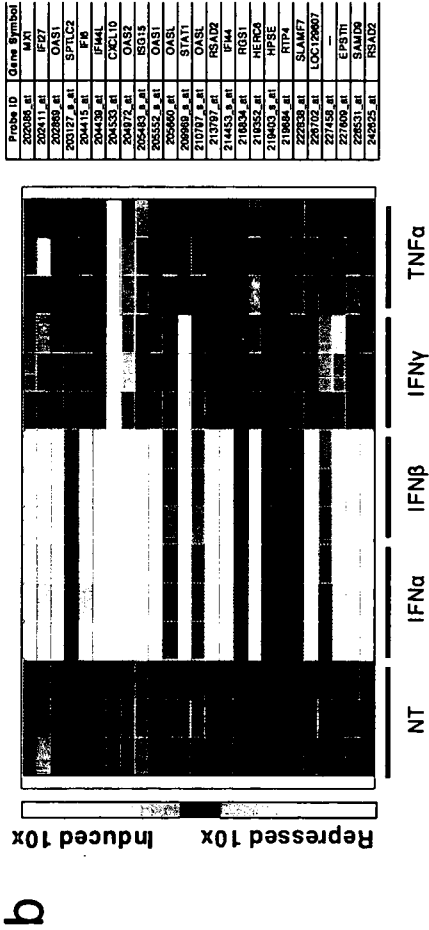
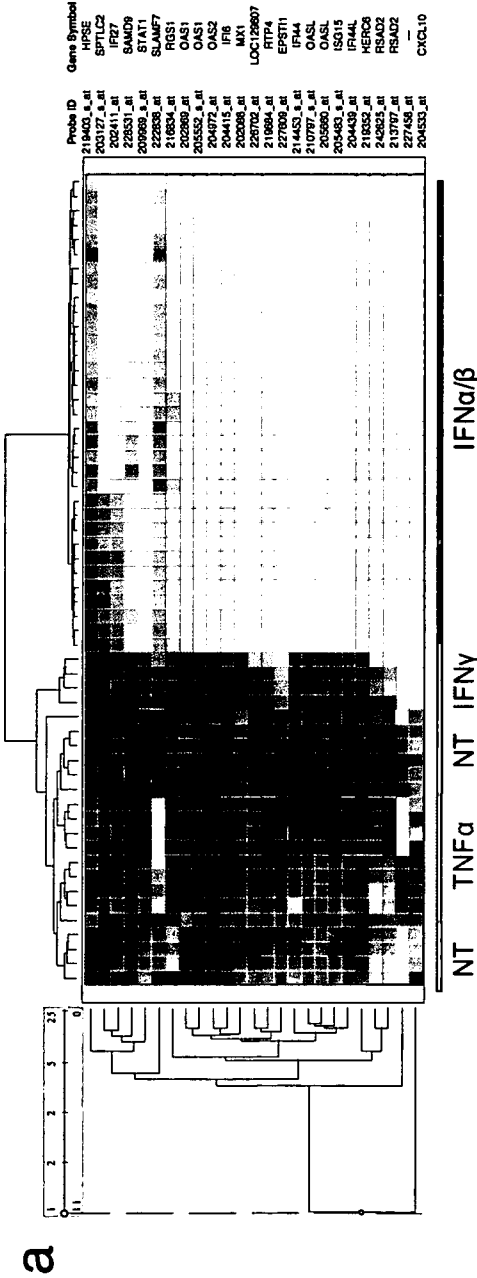
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Figure 30

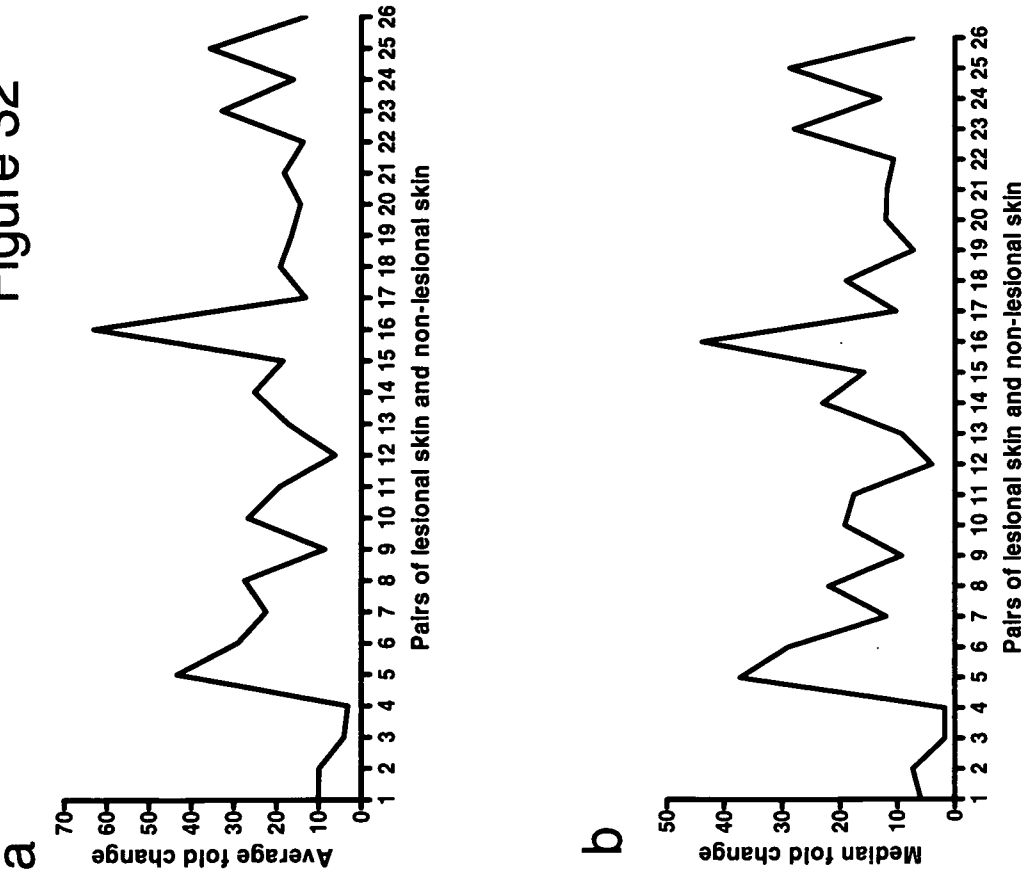


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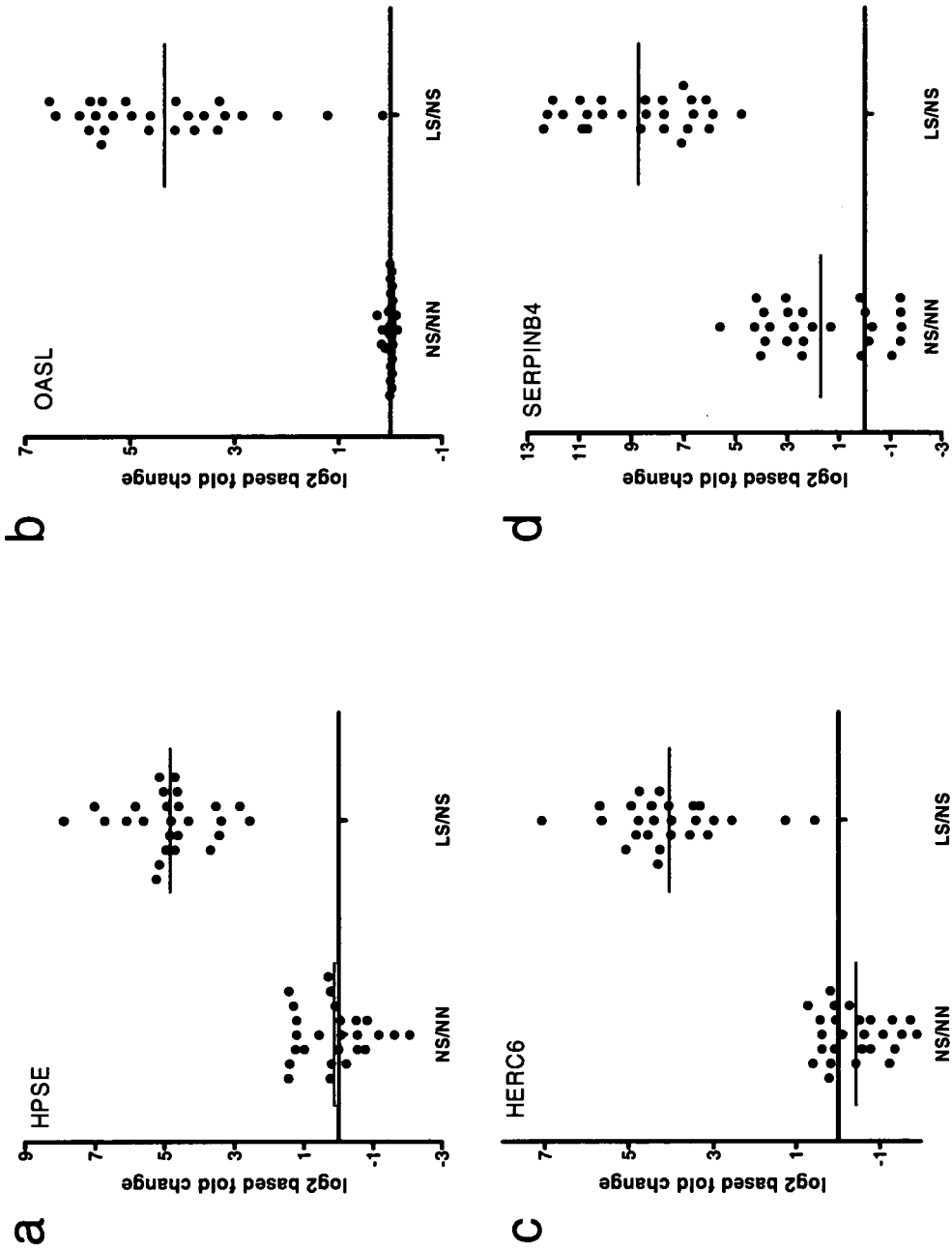
Figure 31



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Figure 32

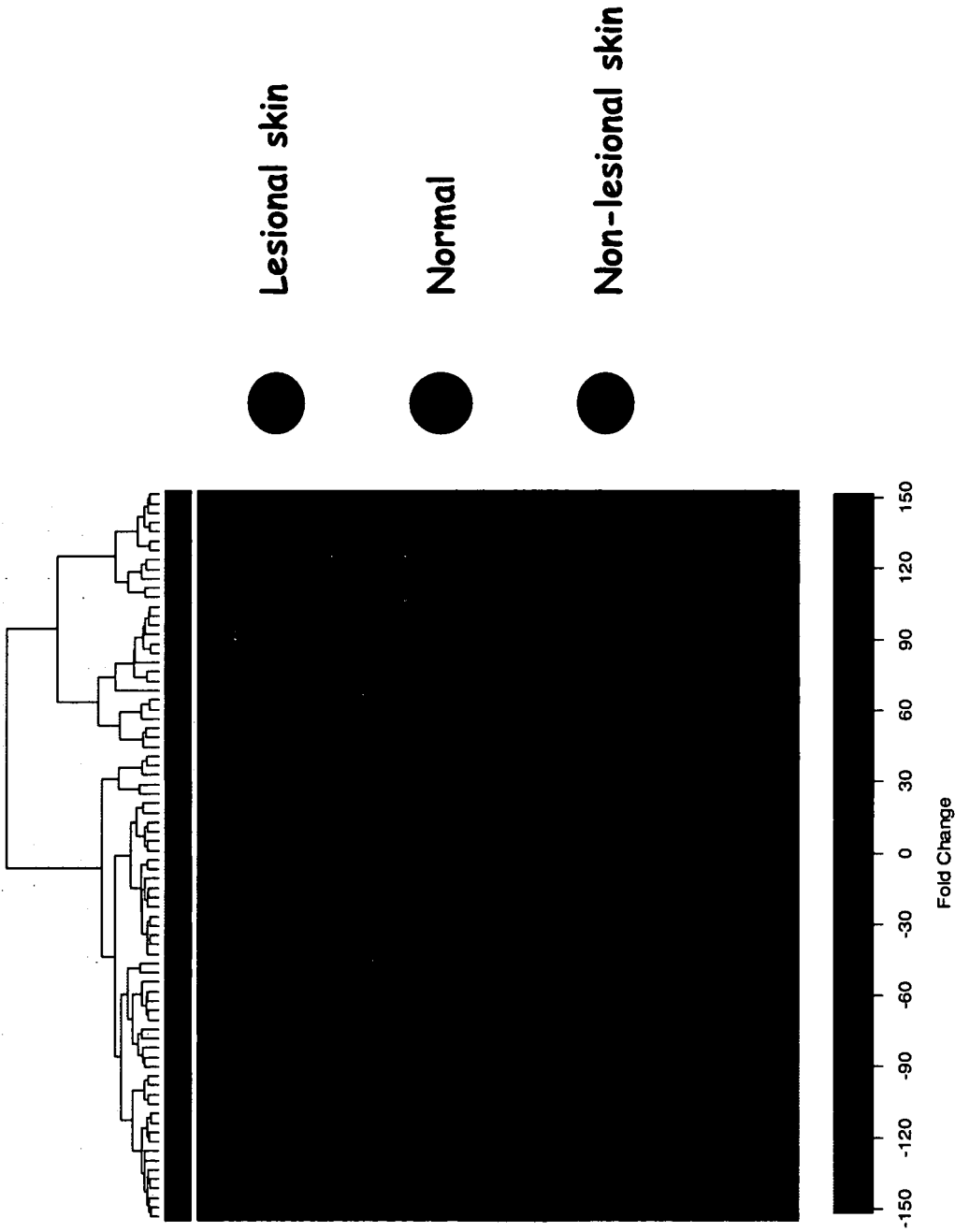


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Figure 33



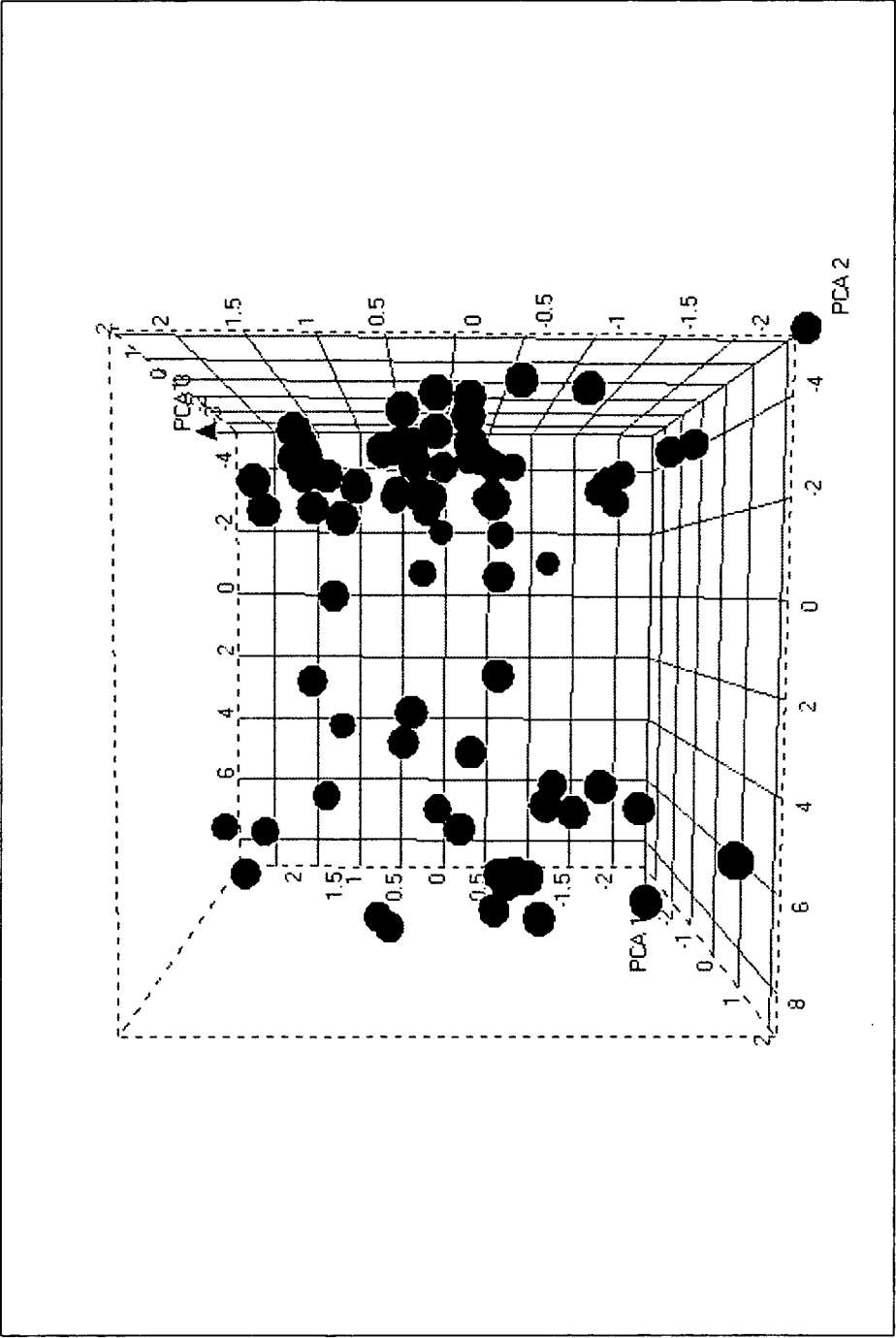
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Figure 34a

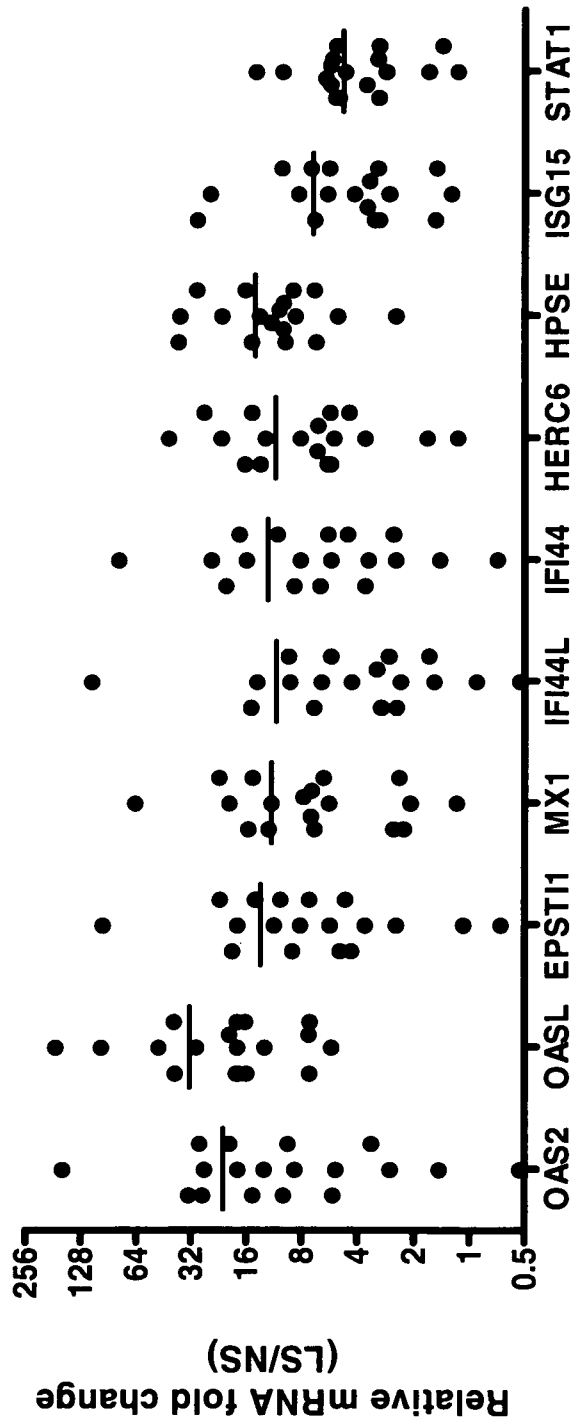


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Figure 34b



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Figure 35

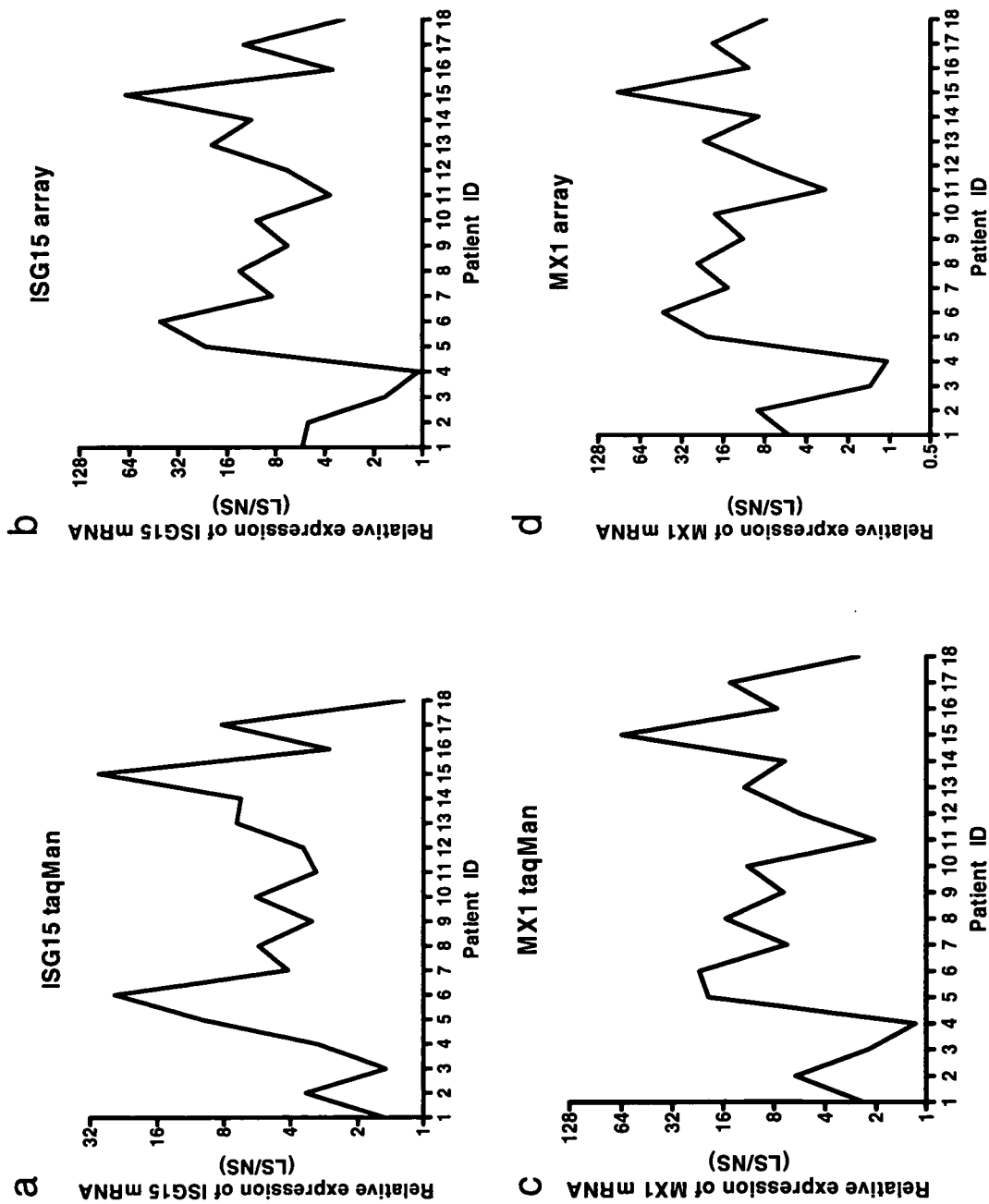


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Figure 36

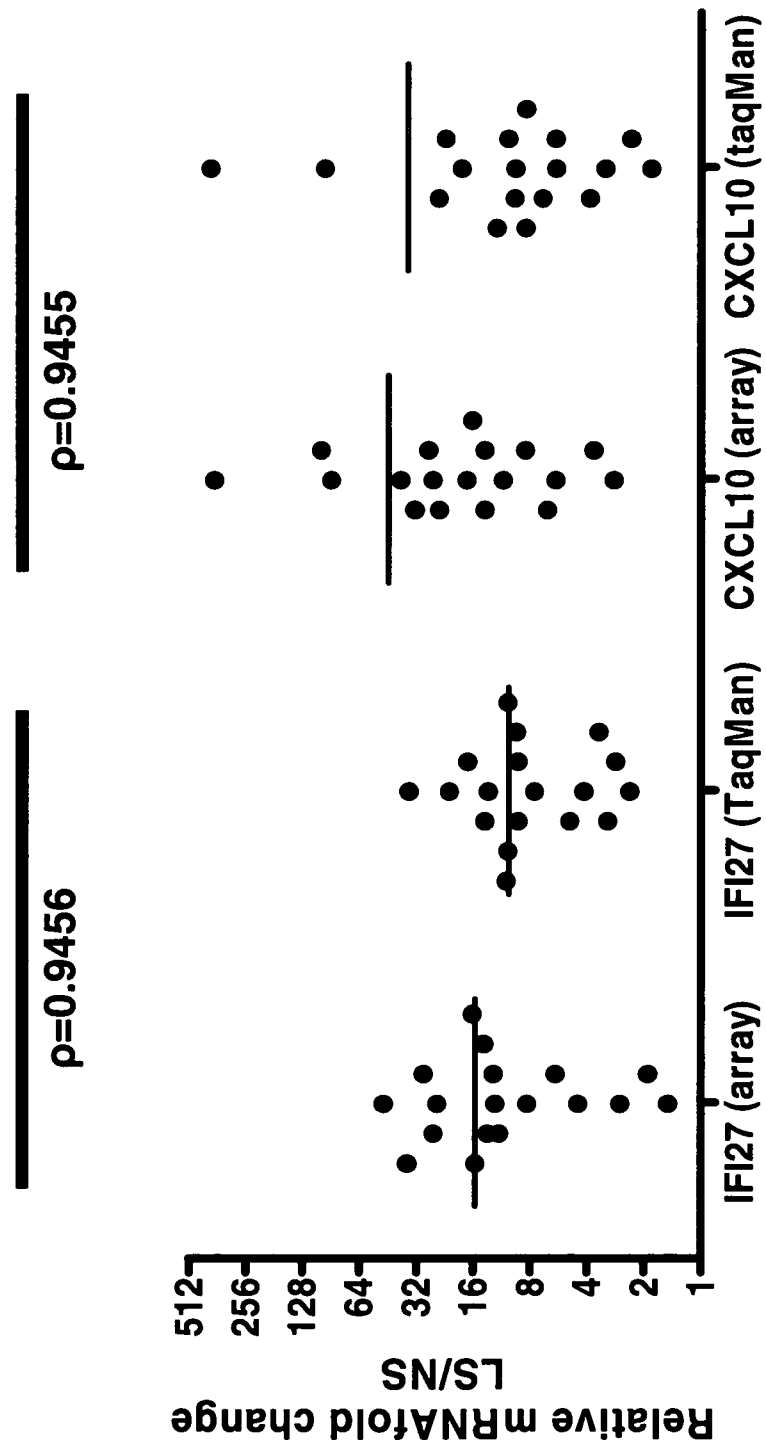


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Figure 37

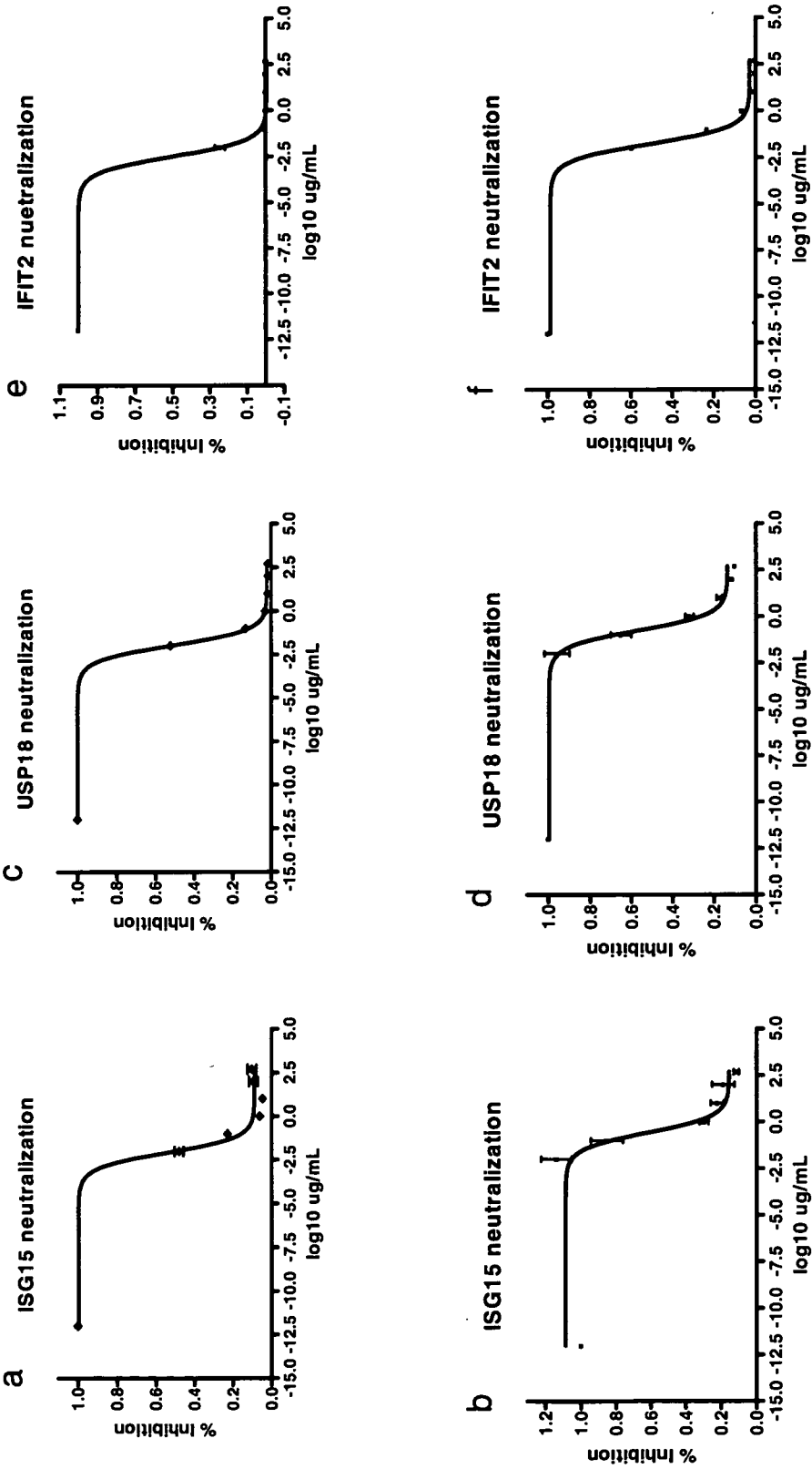


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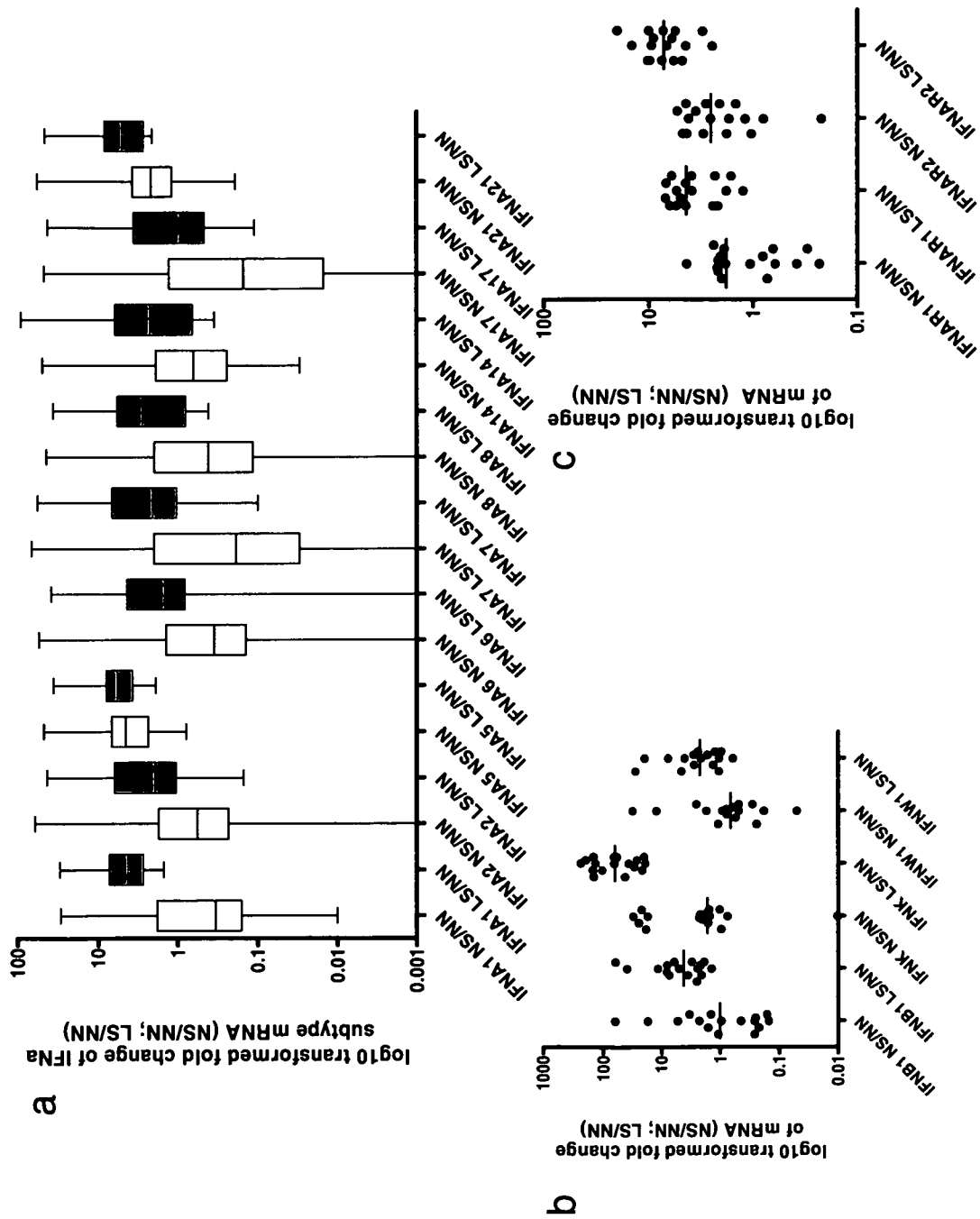
Figure 38



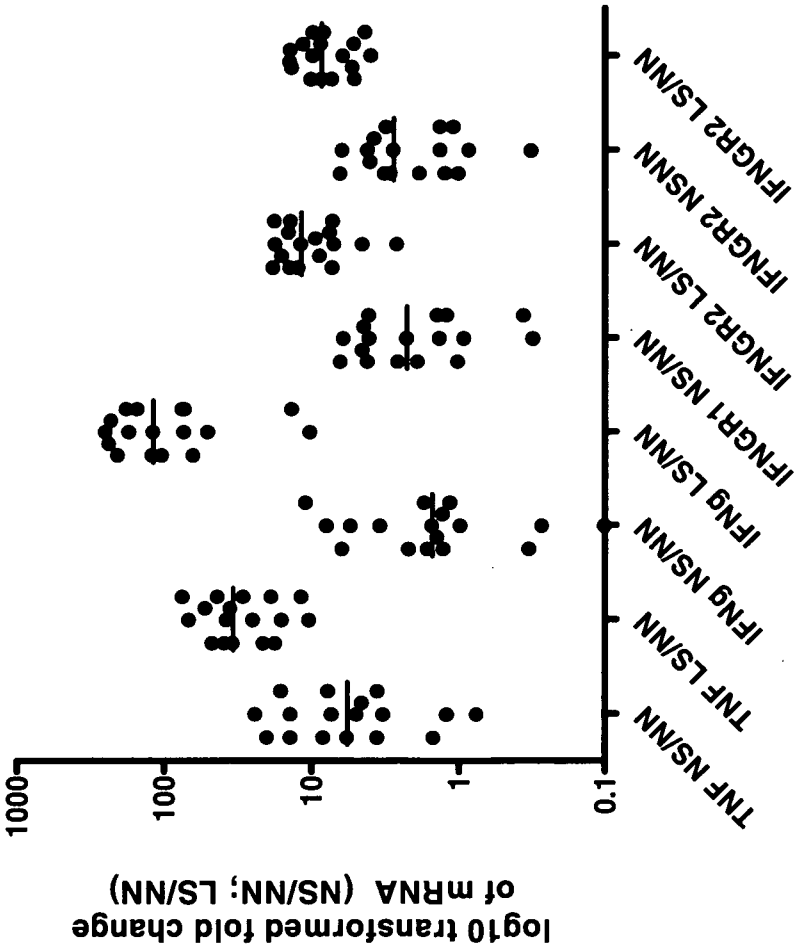
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Figure 39



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Figure 40

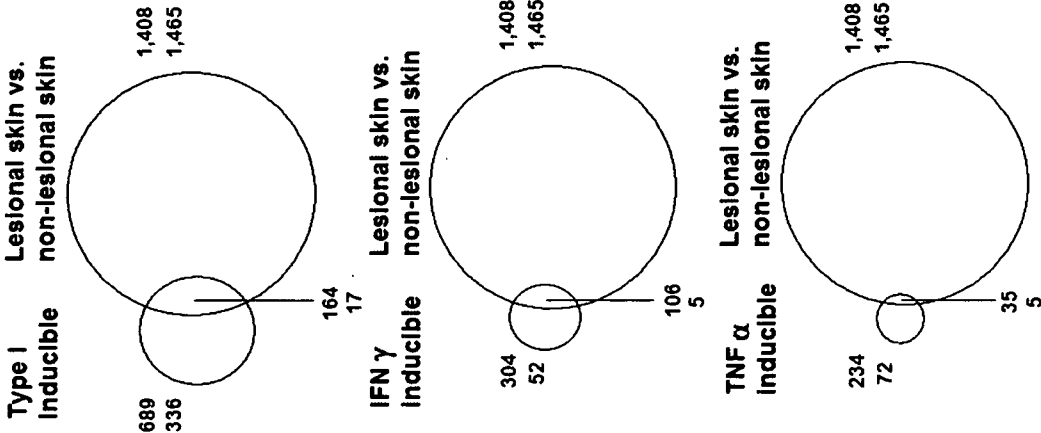


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Figure 41



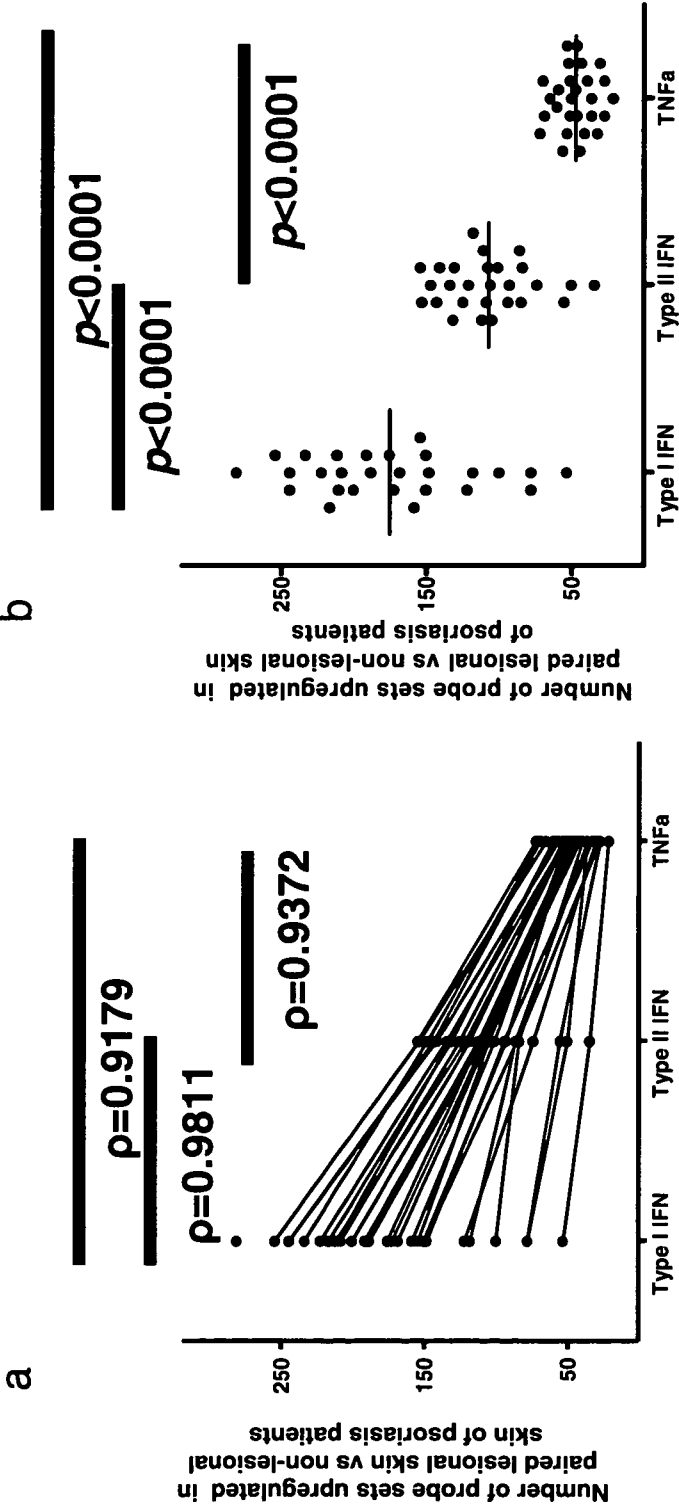
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Figure 42



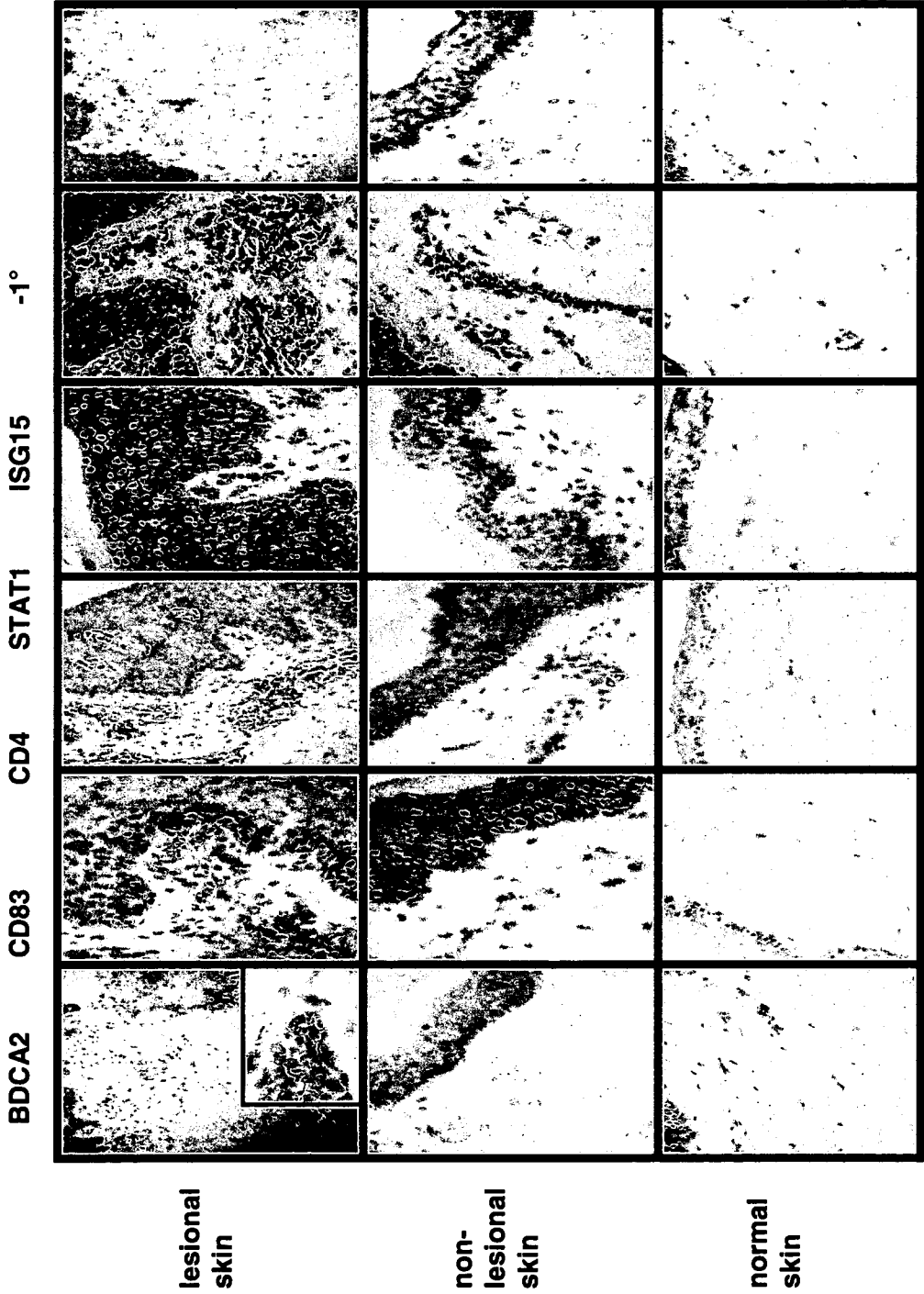
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Figure 43



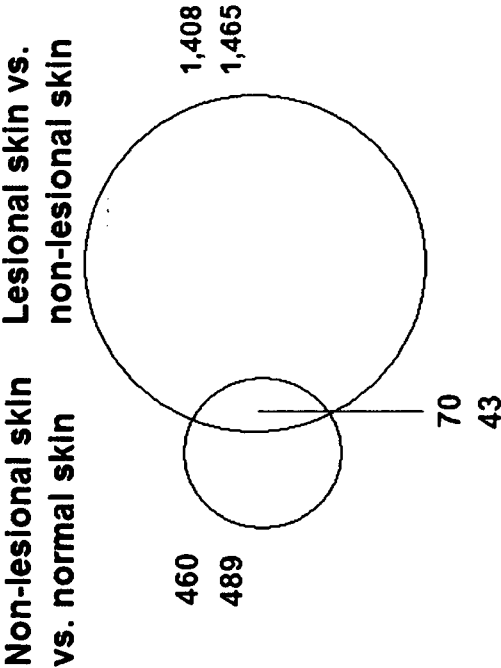
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Figure 44



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Figure 45



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Figure 47a

ProbeID	Gene Title	Gene Symbol	Lesional vs. Non-lesional	Non-lesional vs. Normal
22170_at	Unigenes.1	Unigenes.1	p value	q value
22170_at	Unigenes.1	Unigenes.1	log2 fc	q value
211908_s_at	Unigenes.1	Unigenes.1	p value	q value
356_at	Unigenes.1	Unigenes.1	log2 fc	q value
513_at	Unigenes.1	Unigenes.1	p value	q value
469_at	Unigenes.1	Unigenes.1	log2 fc	q value
491_at	Unigenes.1	Unigenes.1	p value	q value
13_x_at	Unigenes.1	Unigenes.1	log2 fc	q value
393_at	Unigenes.1	Unigenes.1	p value	q value
664_at	Unigenes.1	Unigenes.1	log2 fc	q value
19_x_at	Unigenes.1	Unigenes.1	p value	q value
227848	Unigenes.1	Unigenes.1	log2 fc	q value
203535_s_at	Unigenes.1	Unigenes.1	p value	q value
202018_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
212531_at	Unigenes.1	Unigenes.1	p value	q value
205581_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
205539_s_at	Unigenes.1	Unigenes.1	p value	q value
217388_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
207367_at	Unigenes.1	Unigenes.1	p value	q value
239430_at	Unigenes.1	Unigenes.1	log2 fc	q value
219554_at	Unigenes.1	Unigenes.1	p value	q value
213060_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
204735_at	Unigenes.1	Unigenes.1	p value	q value
202922_at	Unigenes.1	Unigenes.1	log2 fc	q value
202859_s_at	Unigenes.1	Unigenes.1	p value	q value
224328_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
219403_at	Unigenes.1	Unigenes.1	p value	q value
209800_at	Unigenes.1	Unigenes.1	log2 fc	q value
227735_s_at	Unigenes.1	Unigenes.1	p value	q value
220602_at	Unigenes.1	Unigenes.1	log2 fc	q value
210683_s_at	Unigenes.1	Unigenes.1	p value	q value
204580_at	Unigenes.1	Unigenes.1	log2 fc	q value
227736_at	Unigenes.1	Unigenes.1	p value	q value
220074_at	Unigenes.1	Unigenes.1	log2 fc	q value
204972_at	Unigenes.1	Unigenes.1	p value	q value
219765_at	Unigenes.1	Unigenes.1	log2 fc	q value
221033_at	Unigenes.1	Unigenes.1	p value	q value
205660_at	Unigenes.1	Unigenes.1	log2 fc	q value
227609_at	Unigenes.1	Unigenes.1	p value	q value
205783_at	Unigenes.1	Unigenes.1	log2 fc	q value
227458_at	Unigenes.1	Unigenes.1	p value	q value
155756_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
219352_at	Unigenes.1	Unigenes.1	p value	q value
203915_at	Unigenes.1	Unigenes.1	log2 fc	q value
204858_s_at	Unigenes.1	Unigenes.1	p value	q value
216834_at	Unigenes.1	Unigenes.1	log2 fc	q value
206134_at	Unigenes.1	Unigenes.1	p value	q value
218810_at	Unigenes.1	Unigenes.1	log2 fc	q value
232082_x_at	Unigenes.1	Unigenes.1	p value	q value
204533_at	Unigenes.1	Unigenes.1	log2 fc	q value
205476_at	Unigenes.1	Unigenes.1	p value	q value
228702_at	Unigenes.1	Unigenes.1	log2 fc	q value
232378_at	Unigenes.1	Unigenes.1	p value	q value
224209_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
205916_at	Unigenes.1	Unigenes.1	p value	q value
243754_at	Unigenes.1	Unigenes.1	log2 fc	q value
203772_s_at	Unigenes.1	Unigenes.1	p value	q value
202817_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
242625_at	Unigenes.1	Unigenes.1	p value	q value
211788_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
211362_s_at	Unigenes.1	Unigenes.1	p value	q value
214580_x_at	Unigenes.1	Unigenes.1	log2 fc	q value
204385_at	Unigenes.1	Unigenes.1	p value	q value
214490_at	Unigenes.1	Unigenes.1	log2 fc	q value
218257_at	Unigenes.1	Unigenes.1	p value	q value
206628_at	Unigenes.1	Unigenes.1	log2 fc	q value
210138_at	Unigenes.1	Unigenes.1	p value	q value
213797_at	Unigenes.1	Unigenes.1	log2 fc	q value
220686_at	Unigenes.1	Unigenes.1	p value	q value
220658_s_at	Unigenes.1	Unigenes.1	log2 fc	q value
205552_s_at	Unigenes.1	Unigenes.1	p value	q value

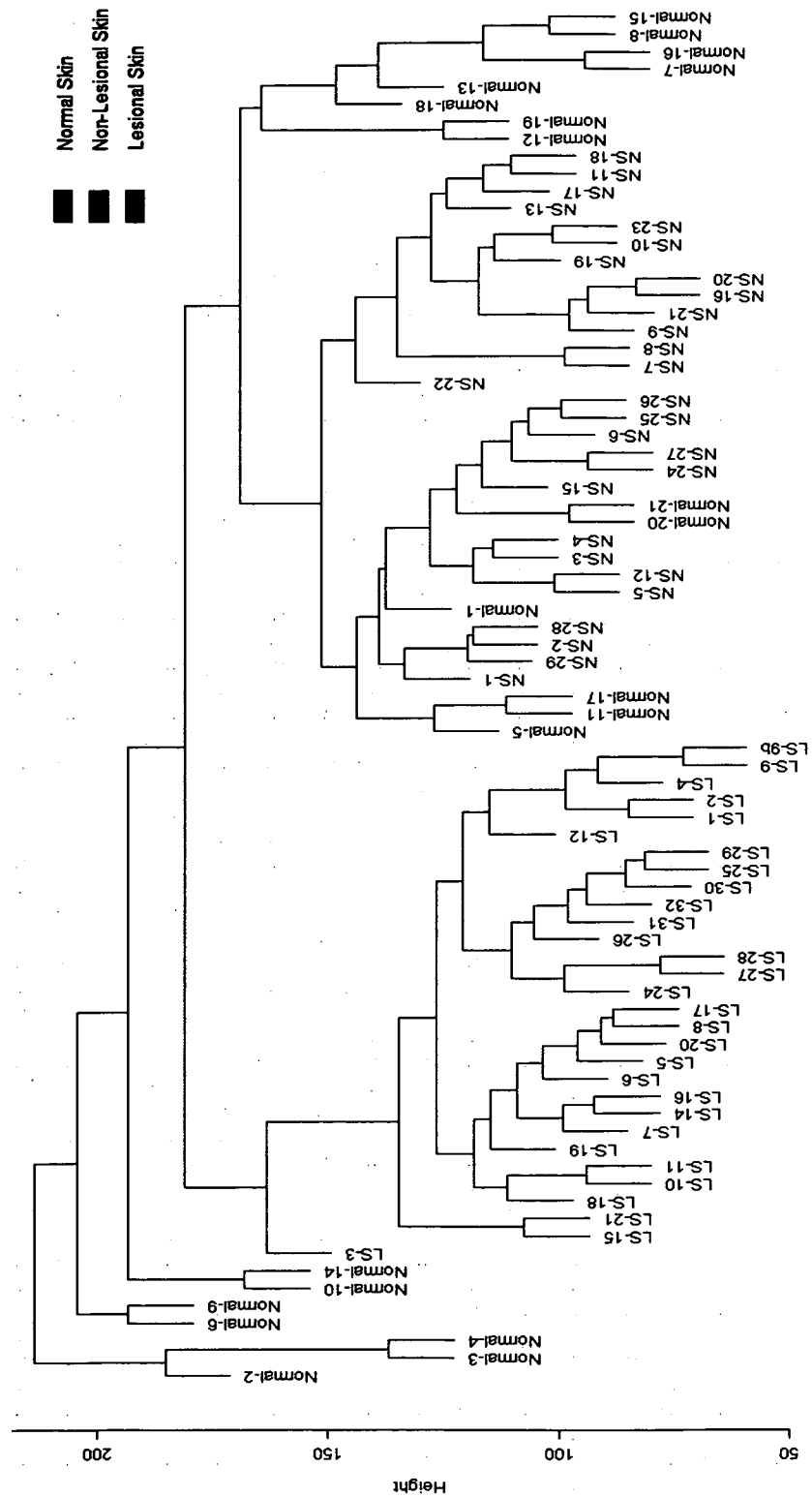
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Figure 47b

210797_s_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	3.23E-10	3.21E-10	1.63E-09	0.005	0.3484
209125_at	---	keratin 6A	KRT6A	1.28E-16	3.20E-16	5.42E-15	0.444	0.1822
204439_at	Hs.389724	Interferon-induced protein 44-like	IFI44L	2.77E-14	3.20E-14	4.73E-13	0.120	0.3007
214549_x_at	Hs.46320	small proline-rich protein 1A	SPRR1A	3.46E-13	3.20E-13	4.18E-12	0.880	0.0579
210164_at	Hs.1051	granzyme B	GZMB	4.50E-14	3.20E-13	2.31E-13	-0.379	0.0324
202411_at	Hs.632634	Interferon, alpha-inducible protein 27	IFI27	4.08E-13	3.16E-13	4.81E-12	-0.154	0.2688
221698_s_at	Hs.143929	C-type lectin domain family 7, member A	CLEC7A	3.35E-20	3.16E-13	3.98E-18	0.278	0.1921
202689_at	Hs.624760	2'-5'-oligoadenylate synthetase 1, 40/48kDa	OAS1	7.81E-16	3.15E-10	2.47E-14	0.246	0.2140
209773_s_at	Hs.226390	ribonucleotide reductase M2 polypeptide	RRM2	5.02E-13	3.13E-12	5.71E-12	0.922	0.0664
208850_s_at	Hs.375108	CD24 molecule	CD24	1.56E-20	3.11E-22	3.04E-18	0.112	0.3046
217272_s_at	Hs.241407	serpin peptidase inhibitor, clade B (ovalbumin), member 13	SERPINF13	3.01E-23	3.08E-23	3.18E-20	0.678	0.0760
228848_at	Hs.515079	leucine-rich alpha-2-glycoprotein 1	LRG1	1.90E-15	3.08E-15	2.52E-14	-0.615	0.0859
206483_s_at	Hs.459485	ISG15 ubiquitin-like modifier	ISG15	2.77E-14	3.08E-14	2.37E-10	-0.273	0.1101
32178_at	Hs.143961	chemokine (C-C motif) ligand 18	CCL18	8.19E-09	3.07E-14	2.87E-08	-0.290	0.2388
206008_at	Hs.508950	transglutaminase 1	TGM1	1.70E-19	3.06E-13	2.22E-17	0.102	0.2978
209924_at	Hs.143981	chemokine (C-C motif) ligand 18	CCL18	3.59E-09	3.05E-15	1.39E-08	-0.060	0.3811
220249_at	Hs.28673	hyaluronoglucosaminidase 4	HYAL4	1.07E-16	3.03E-13	4.73E-15	0.141	0.1043
226898_at	Hs.591257	FCH and double SH3 domains 1	FCHSD1	9.34E-20	3.03E-13	1.34E-17	0.809	0.0002
241894_at	Hs.250	xanthine dehydrogenase	XDH	5.96E-16	3.03E-13	3.19E-14	0.217	0.2494
211361_s_at	Hs.241407	serpin peptidase inhibitor, clade B (ovalbumin), member 13	SERPINF13	7.42E-25	3.01E-13	9.27E-22	0.322	0.1823
205844_at	Hs.12114	vanin 1	VNN1	7.56E-14	3.01E-13	4.11E-12	0.085	0.2701
221107_at	Hs.272278	cholinergic receptor, nicotinic, alpha 9	CHRNA9	5.31E-17	3.00E-13	2.75E-15	0.262	0.0385
154406_s_at	Hs.143929	C-type lectin domain family 7, member A	CLEC7A	1.34E-22	2.99E-13	3.96E-20	0.255	0.1288
220528_at	Hs.183656	vanin 3	VNN3	2.69E-12	2.98E-13	2.44E-11	0.006	0.3008
209869_s_at	Hs.665365	signal transducer and activator of transcription 1, 91kDa	STAT1	8.40E-19	2.89E-13	7.85E-17	0.189	0.2007
215223_s_at	Hs.487046	superoxide dismutase 2, mitochondrial	SOD2	2.63E-19	2.89E-13	3.13E-17	-1.089	0.0401
226218_at	Hs.382807	siRNA; cDNA DKFZp667P0610 (from clone DKFZp667P0610)	---	1.24E-14	2.88E-13	2.45E-13	-0.860	0.0210

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Figure 48



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Figure 49a

Probe.ID	Unigene.ID	Gene.Title	Gene.Symbol	p.value	log2.fc	q.value
205660_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	9.22E-14	4.03	1.34E-12
227609_at	Hs.546467	epithelial stromal interaction 1 (breast)	EPSTI1	3.10E-16	4.002	1.14E-14
227458_at	---	---	---	3.94E-15	3.859	9.31E-14
203915_at	Hs.77367	chemokine (C-X-C motif) ligand 9	CXCL9	2.49E-12	3.84	2.27E-11
204533_at	Hs.632586	chemokine (C-X-C motif) ligand 10	CXCL10	2.35E-13	3.697	2.97E-12
226702_at	Hs.7155	hypothetical protein LOC129607	LOC129607	3.09E-18	3.572	2.37E-16
242625_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	1.19E-13	3.403	1.65E-12
213797_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	5.47E-11	3.243	3.36E-10
205552_s_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	7.58E-16	3.222	2.41E-14
202869_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa signal transducer and activator of transcription 1, 91kDa	OAS1	7.81E-16	3.15	2.47E-14
209969_s_at	Hs.565365	SLAM family member 7	STAT1	8.40E-19	2.993	7.95E-17
222838_at	Hs.517265	receptor transporter protein 4	SLAMF7	1.92E-18	2.659	1.60E-16
219684_at	Hs.43388	lysosomal-associated membrane protein 3	RTP4	4.37E-12	2.649	3.73E-11
205569_at	Hs.518448	hypothetical LOC440731	LAMP3	5.57E-10	2.569	2.64E-09
237563_s_at	Hs.181156	signal transducer and activator of transcription 1, 91kDa	LOC440731	6.99E-17	2.553	3.40E-15
AFFX-						
HUMISGF3A/M97935_MA_at	Hs.565365	chromosome 14 open reading frame 58	STAT1	2.40E-11	2.525	1.64E-10
229450_at	---	interferon regulatory factor 7	---	4.33E-16	2.492	1.50E-14
222866_s_at	Hs.509966	signal transducer and activator of transcription 1, 91kDa	C14orf58	1.45E-16	2.479	5.98E-15
208436_s_at	Hs.166120	interferon-induced protein with tetratricopeptide repeats 3	IRF7	1.71E-16	2.448	6.90E-15
AFFX-						
HUMISGF3A/M97935_5_at	Hs.565365	hypothetical protein LOC441168	STAT1	4.88E-11	2.444	3.03E-10
204747_at	Hs.47338	repeats 3	IFIT3	6.58E-16	2.424	2.15E-14
			RPI-			
229390_at	Hs.381220	hypothetical protein LOC441168	93H18.5	1.99E-13	2.4	2.59E-12
235276_at	---	---	---	7.67E-17	2.386	3.61E-15

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Figure 49b

AFFX- HUMISGF3A/M97935_MB_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	9.17E-11	2.205	5.29E-10
	207387_s_at	glycerol kinase	GK	4.00E-15	2.16	9.38E-14
	219716_at	apolipoprotein L, 6	APOL6	3.45E-12	2.123	3.03E-11
AFFX- HUMISGF3A/M97935_3_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	1.67E-15	2.113	4.67E-14
	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	3.56E-19	2.11	3.93E-17
	Hs.546467	Epithelial stromal interaction 1 (breast)	EPSTI1	1.06E-16	2.091	4.73E-15
AFFX- HUMISGF3A/M97935_3_at	Hs.513726	Guanylate binding protein 5	GBP5	1.37E-10	2.074	7.52E-10
	Hs.1466	glycerol kinase	GK	1.03E-10	2.06	5.86E-10
	Hs.441975	XIAP associated factor-1	BIRC4BP	2.76E-13	2.045	3.41E-12
AFFX- HUMISGF3A/M97935_3_at	Hs.281898	absent in melanoma 2	AIM2	6.42E-09	2.043	2.32E-08
	Hs.592072	caspase recruitment domain family, member 15	CARD15	7.29E-20	2.012	1.11E-17
	Hs.190622	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	DDX58	1.97E-11	2	1.39E-10
AFFX- HUMISGF3A/M97935_3_at	Hs.436023	PR domain containing 1, with ZNF domain	PRDM1	4.94E-14	1.999	7.73E-13
	Hs.438683	SLAM family member 8	SLAMF8	2.11E-11	1.934	1.47E-10
AFFX- HUMISGF3A/M97935_3_at	Hs.381220	hypothetical protein LOC441168	RPI-			
	229391_s_at		93H18.5	3.62E-11	1.932	2.34E-10
	214838_at	SFT2 domain containing 2	SFT2D2	5.17E-19	1.881	5.30E-17
AFFX- HUMISGF3A/M97935_3_at	Hs.441975	XIAP associated factor-1	BIRC4BP	8.74E-11	1.881	5.08E-10
	Hs.464419	F-box protein 6	FBXO6	2.38E-15	1.861	6.34E-14
	238725_at	---	---	3.13E-15	1.842	7.84E-14
AFFX- HUMISGF3A/M97935_3_at	Hs.441975	XIAP associated factor-1	BIRC4BP	1.70E-10	1.823	9.14E-10
	Hs.527973	suppressor of cytokine signaling 3	SOCS3	7.71E-11	1.819	4.55E-10
	Hs.425777	ubiquitin-conjugating enzyme E2L 6	UBE2L6	1.06E-14	1.814	2.15E-13
AFFX- HUMISGF3A/M97935_3_at	Hs.436061	interferon regulatory factor 1	IRF1	1.04E-14	1.791	2.13E-13
	Hs.1466	glycerol kinase	GK	2.13E-13	1.789	2.75E-12
	Hs.131933	Hypothetical protein FLJ22662	FLJ22662	4.03E-08	1.774	1.18E-07
AFFX- HUMISGF3A/M97935_3_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	5.81E-13	1.733	6.47E-12
	---	glycerol kinase pseudogene 3	GKP3	3.84E-12	1.732	3.33E-11
	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	9.15E-13	1.721	9.62E-12
AFFX- HUMISGF3A/M97935_3_at	Hs.460777	Selectin ligand interactor cytoplasmic-1	SLIC1	2.16E-13	1.717	2.78E-12

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Figure 49c

16598_s_at	Hs.303649	chemokine (C-C motif) ligand 2	CCL2	1.94E-07	1.711	4.80E-07
223502_s_at	Hs.525157	tumor necrosis factor (ligand) superfamily, member 13b	TNFSF13B	7.02E-06	1.706	1.18E-05
204057_at	Hs.137427	interferon regulatory factor 8	IRF8	7.30E-10	1.705	3.37E-09
217167_x_at	Hs.1466	glycerol kinase	GK	6.00E-11	1.701	3.64E-10
209546_s_at	Hs.114309	apolipoprotein L, 1	APOL1	3.98E-09	1.63	1.52E-08
220187_at	Hs.521008	STEAP family member 4	STEAP4	2.64E-07	1.603	6.34E-07
200629_at	Hs.497599	tryptophanyl-tRNA synthetase	WARS	1.75E-13	1.593	2.32E-12
200628_s_at	Hs.497599	tryptophanyl-tRNA synthetase	WARS	1.56E-10	1.582	8.48E-10
214038_at	Hs.271387	chemokine (C-C motif) ligand 8	CCL8	1.69E-07	1.569	4.25E-07
238581_at	Hs.513726	Guanylate binding protein 5	GBP5	3.49E-09	1.564	1.35E-08
210029_at	Hs.840	indoleamine-pyrrrole 2,3 dioxygenase	INDO	5.15E-07	1.531	1.15E-06
235157_at	Hs.583792	Poly (ADP-ribose) polymerase family, member 14	PARP14	2.93E-08	1.519	8.92E-08
232375_at	Hs.565365	Signal transducer and activator of transcription 1, 91kDa	STAT1	6.86E-11	1.483	4.11E-10
216316_x_at	Hs.1466	glycerol kinase	GK /// GKP3	2.02E-09	1.461	8.34E-09
202446_s_at	Hs.130759	phospholipid scramblase 1	PLSCR1	6.94E-13	1.435	7.55E-12
227807_at	Hs.518200	poly (ADP-ribose) polymerase family, member 9	PARP9	2.40E-11	1.422	1.64E-10
202687_s_at	Hs.478275	tumor necrosis factor (ligand) superfamily, member 10	TNFSF10	3.17E-14	1.407	5.28E-13
202688_at	Hs.478275	tumor necrosis factor (ligand) superfamily, member 10	TNFSF10	3.18E-15	1.363	7.91E-14
209762_x_at	Hs.145150	SP110 nuclear body protein	SP110	9.20E-14	1.357	1.34E-12
214329_x_at	Hs.478275	tumor necrosis factor (ligand) superfamily, member 10	TNFSF10	5.39E-14	1.336	8.39E-13
204166_at	Hs.408708	KIAA0963	KIAA0963	5.87E-14	1.325	9.02E-13
225987_at	Hs.521008	STEAP family member 4	STEAP4	3.56E-08	1.325	1.06E-07
225415_at	Hs.518201	deltex 3-like (Drosophila)	DTX3L	2.24E-16	1.299	8.67E-15
205992_s_at	Hs.168132	interleukin 15	IL15	1.73E-08	1.285	5.61E-08
238025_at	Hs.119878	mixed lineage kinase domain-like	MLKL	1.27E-16	1.274	5.40E-15
205220_at	Hs.458425	G protein-coupled receptor 109B	GPR109B	8.30E-08	1.266	2.25E-07
227556_at	---	non-metastatic cells 7, protein expressed in (nucleoside-diphosphate kinase)	NME7	3.38E-04	1.26	3.74E-04
229723_at	Hs.529984	T-cell activation GTPase activating protein	TAGAP	1.16E-07	1.243	3.02E-07
1557236_at	Hs.257352	apolipoprotein L, 6	APOL6	2.29E-09	1.24	9.29E-09

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Figure 49d

208012_x_at	Hs.145150	SP110 nuclear body protein	SP110	2.18E-13	1.234	2.79E-12
209417_s_at	Hs.632258	interferon-induced protein 35	IFI35	5.68E-08	1.23	1.60E-07
226603_at	Hs.489118	sterile alpha motif domain containing 9-like lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	SAMD9L	1.53E-07	1.227	3.90E-07
205270_s_at	Hs.304475	apolipoprotein L, 6	LCP2	1.23E-06	1.202	2.49E-06
1557116_at	Hs.257352	GTP cyclohydrolase 1 (dopa-responsive dystonia)	APOL6	7.14E-10	1.192	3.30E-09
204224_s_at	Hs.86724	promyelocytic leukemia	GCH1	4.95E-16	1.191	1.69E-14
206503_x_at	Hs.526464	guanylate binding protein 3	PML	5.06E-11	1.184	3.14E-10
223434_at	---	promyelocytic leukemia	GBP3	4.41E-06	1.184	7.75E-06
211013_x_at	Hs.526464	poly (ADP-ribose) polymerase family, member 14	PML	1.89E-11	1.172	1.34E-10
224701_at	Hs.583792	ankyrin repeat domain 22	PARP14	5.35E-09	1.159	1.98E-08
238439_at	Hs.217484	lectin, galactoside-binding, soluble, 8 (galectin 8)	ANKRD22	1.01E-08	1.15	3.45E-08
208934_s_at	Hs.4082	Cullin 1	LGALS8	5.87E-12	1.147	4.83E-11
228899_at	Hs.146806	2'-5'-oligoadenylate synthetase 2, 69/71kDa	CUL1	1.68E-17	1.138	1.02E-15
228607_at	Hs.414332	family with sequence similarity 11, member B	OAS2	9.30E-10	1.133	4.19E-09
219253_at	Hs.376722	suppressor of cytokine signaling 1	FAM11B	1.28E-10	1.123	7.09E-10
210001_s_at	Hs.50640	ankyrin repeat domain 22	SOCS1	7.53E-08	1.108	2.06E-07
239196_at	Hs.217484	hect domain and RLD 5	ANKRD22	4.12E-11	1.103	2.61E-10
219863_at	Hs.26663	caspase 7, apoptosis-related cysteine peptidase	HERC5	6.50E-11	1.102	3.92E-10
207181_s_at	Hs.9216	sterile alpha motif domain containing 9-like lactamase, beta	CASP7	6.40E-14	1.093	9.73E-13
230036_at	Hs.489118	chromosome 11 open reading frame 75	SAMD9L	2.77E-06	1.075	5.13E-06
1552485_at	Hs.410388	interferon, gamma-inducible protein 16	LACTB	1.83E-10	1.075	9.76E-10
219806_s_at	---	interferon induced with helicase C domain 1	C11orf75	7.33E-09	1.069	2.61E-08
208966_x_at	---	SLAM family member 7	IFI16	3.38E-14	1.055	5.58E-13
1555464_at	Hs.163173		IFIH1	7.78E-08	1.047	2.12E-07
219159_s_at	Hs.517265		SLAMF7	2.87E-09	1.023	1.14E-08

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Figure 50a

Probe.ID	Unigene.ID	Gene.Title	Gene.Symbol	p.value	log2.fc	q.value
41469_at	Hs.112341	peptidase inhibitor 3, skin-derived (SKALP)	PI3	7.04E-27	7.145	4.40E-23
203691_at	Hs.112341	peptidase inhibitor 3, skin-derived (SKALP)	PI3	1.23E-28	7.007	1.54E-24
217388_s_at	Hs.470126	kynureninase (L-kynurenine hydrolase)	KYNU	3.66E-25	5.354	5.07E-22
227458_at	---	---	---	3.94E-15	3.859	9.31E-14
220330_s_at	Hs.570423	SAM domain, SH3 domain and nuclear localisation signals, 1	SAMSN1	1.95E-17	2.919	1.16E-15
223484_at	Hs.112242	chromosome 15 open reading frame 48	C15orf48	5.70E-13	2.814	6.37E-12
222838_at	Hs.517265	SLAM family member 7	SLAMF7	1.92E-18	2.659	1.60E-16
216841_s_at	Hs.487046	superoxide dismutase 2, mitochondrial	SOD2	6.14E-18	2.417	4.26E-16
215977_x_at	Hs.1466	glycerol kinase	GK	1.03E-10	2.06	5.86E-10
231779_at	Hs.449207	interleukin-1 receptor-associated kinase 2	IRAK2	2.66E-18	1.981	2.07E-16
204702_s_at	Hs.404741	nuclear factor (erythroid-derived 2)-like 3	NFE2L3	2.09E-18	1.803	1.71E-16
202269_x_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	5.81E-13	1.733	6.47E-12
231577_s_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	9.15E-13	1.721	9.62E-12
201195_s_at	Hs.513797	solute carrier family 7 (cationic amino acid transporter, y+ system), member 5	SLC7A5	5.07E-10	1.61	2.43E-09
204440_at	Hs.484703	CD83 molecule	CD83	2.98E-13	1.554	3.64E-12
211661_x_at	---	platelet-activating factor receptor	PTAFR	1.51E-15	1.512	4.32E-14
203471_s_at	Hs.468840	pleckstrin	PLEK	9.93E-10	1.508	4.45E-09
204601_at	Hs.511839	Nedd4 binding protein 1	N4BP1	3.29E-17	1.406	1.83E-15
1555638_a_at	Hs.570423	SAM domain, SH3 domain and nuclear localisation signals, 1	SAMSN1	2.34E-07	1.26	5.69E-07
32069_at	Hs.511839	Nedd4 binding protein 1	N4BP1	1.46E-15	1.228	4.19E-14
230966_at	---	interleukin 4 induced 1	IL4I1	1.06E-07	1.219	2.81E-07
204224_s_at	Hs.86724	GTP cyclohydrolase 1 (dopa-responsive dystonia)	GCH1	4.95E-16	1.191	1.69E-14
210538_s_at	Hs.127799	baculoviral IAP repeat-containing 3	BIRC3	1.22E-07	1.169	3.17E-07

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Figure 50b

212902_at	Hs.595540	SEC24 related gene family, member A (S. cerevisiae)	SEC24A	4.43E-16	1.151	1.52E-14
209037_s_at	Hs.523774	EH-domain containing 1	EHD1	3.61E-11	1.126	2.33E-10
205205_at	Hs.307905	v-rel reticuloendotheliosis viral oncogene homolog B, nuclear factor of kappa light polypeptide gene enhancer in B-cells 3 (avian)	RELB	1.17E-08	1.112	3.95E-08
231513_at	Hs.597550	Transcribed locus	---	1.60E-05	1.104	2.46E-05
200999_s_at	Hs.74368	cytoskeleton-associated protein 4	CKAP4	6.41E-18	1.096	4.38E-16
200998_s_at	Hs.74368	cytoskeleton-associated protein 4	CKAP4	3.95E-11	1.093	2.52E-10
			CCL3 ///			
			CCL3L1 ///			
			CCL3L3 ///			
205114_s_at	Hs.514107	chemokine (C-C motif) ligand 3	LOC643930	3.67E-05	1.073	5.16E-05
226121_at	Hs.631760	hypothetical protein MGC23280	MGC23280	7.86E-11	1.051	4.64E-10
203470_s_at	Hs.468840	pleckstrin	PLEK	3.31E-07	1.049	7.74E-07
1555464_at	Hs.163173	interferon induced with helicase C domain 1	IFIH1	7.78E-08	1.047	2.12E-07
219159_s_at	Hs.517265	SLAM family member 7	SLAMF7	2.87E-09	1.023	1.14E-08
201564_s_at	Hs.118400	fascin homolog 1, actin-bundling protein (Strongylocentrotus purpuratus)	FSCN1	2.61E-08	1.013	8.03E-08

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Figure 51a

Probe.ID	Unigene.ID	Gene.Title	Gene.Symbol	p.value	log2.fc	q.value
219403_s_at	Hs.44227	heparanase	HPSE	2.85E-25	4.598	4.46E-22
204972_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	3.52E-15	4.098	8.57E-14
205660_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	9.22E-14	4.03	1.34E-12
227609_at	Hs.546467	epithelial stromal interaction 1 (breast)	EPST11	3.10E-16	4.002	1.14E-14
227458_at	---	---	---	3.94E-15	3.859	9.31E-14
219352_at	Hs.529317	hect domain and RLD 6	HERC6	1.55E-17	3.842	9.49E-16
216834_at	Hs.75256	regulator of G-protein signalling 1	RGS1	1.97E-19	3.809	2.47E-17
204533_at	Hs.632586	chemokine (C-X-C motif) ligand 10	CXCL10	2.35E-13	3.697	2.97E-12
226702_at	Hs.7155	hypothetical protein LOC129607	LOC129607	3.09E-18	3.572	2.37E-16
242625_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	1.19E-13	3.403	1.65E-12
213797_at	Hs.17518	radical S-adenosyl methionine domain containing 2	RSAD2	5.47E-11	3.243	3.36E-10
202086_at	Hs.517307	myxovirus (influenza virus) resistance 1	MX1	1.92E-15	3.235	5.28E-14
205552_s_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	7.58E-16	3.222	2.41E-14
210797_s_at	Hs.118633	2'-5'-oligoadenylate synthetase-like	OASL	3.23E-10	3.216	1.63E-09
204439_at	Hs.389724	interferon-induced protein 44-like	IFI44L	2.77E-14	3.205	4.73E-13
202411_at	Hs.532634	interferon, alpha-inducible protein 27	IFI27	4.08E-13	3.165	4.81E-12
202869_at	Hs.524760	2',5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	7.81E-16	3.15	2.47E-14
205483_s_at	Hs.458485	ISG15 ubiquitin-like modifier	ISG15	2.77E-14	3.088	4.73E-13
209969_s_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	8.40E-19	2.993	7.95E-17
228531_at	Hs.65641	sterile alpha motif domain containing 9	SAMD9	1.99E-15	2.846	5.42E-14
204415_at	Hs.523847	interferon, alpha-inducible protein 6	IFI6	1.72E-09	2.769	7.23E-09
214453_s_at	Hs.82316	interferon-induced protein 44	IFI44	1.42E-13	2.679	1.94E-12
222838_at	Hs.517265	SLAM family member 7	SLAMF7	1.92E-18	2.659	1.60E-16
219684_at	Hs.43388	receptor transporter protein 4	RTP4	4.37E-12	2.649	3.73E-11
203127_s_at	Hs.435661	serine palmitoyltransferase, long chain base subunit 2	SPTLC2	1.33E-23	2.628	1.04E-20
205569_at	Hs.518448	lysosomal-associated membrane protein 3	LAMP3	5.57E-10	2.569	2.64E-09

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Figure 51b

219691_at	Hs.65641	sterile alpha motif domain containing 9	SAMD9	5.92E-15	2.559	1.30E-13
223220_s_at	Hs.518200	poly (ADP-ribose) polymerase family, member 9	PARP9	1.77E-17	2.553	1.08E-15
AFFX- HUMISGF3A/M97935_MA_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	2.40E-11	2.525	1.64E-10
212268_at	Hs.381167	serpin peptidase inhibitor, clade B (ovalbumin), member 1	SERPINB1	6.03E-17	2.51	3.02E-15
216202_s_at	Hs.435661	serine palmitoyltransferase, long chain base subunit 2	SPTLC2	5.17E-15	2.507	1.17E-13
229450_at	---	---	---	4.33E-16	2.492	1.50E-14
208436_s_at	Hs.166120	interferon regulatory factor 7	IRF7	1.71E-16	2.448	6.90E-15
AFFX- HUMISGF3A/M97935_5_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	4.88E-11	2.444	3.03E-10
204747_at	Hs.47338	interferon-induced protein with tetratricopeptide repeats 3	IFIT3	6.58E-16	2.424	2.15E-14
229390_at	Hs.381220	hypothetical protein LOC441168	RP1-93H18.5	1.99E-13	2.4	2.59E-12
218400_at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	1.32E-15	2.397	3.83E-14
235276_at	---	---	---	7.67E-17	2.386	3.61E-15
203153_at	Hs.20315	interferon-induced protein with tetratricopeptide repeats 1	IFIT1	1.61E-11	2.351	1.17E-10
210873_x_at	Hs.348983	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A	APOBEC3A	4.69E-08	2.348	1.35E-07
204698_at	Hs.459265	interferon stimulated exonuclease gene 20kDa	ISG20	1.05E-13	2.337	1.50E-12
232666_at	Hs.528634	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	7.60E-11	2.236	4.50E-10
222881_at	Hs.44227	heparanase	HPSE	7.17E-17	2.23	3.47E-15
205241_at	Hs.567405	SCO cytochrome oxidase deficient homolog 2 (yeast)	SCO2	1.37E-19	2.208	1.90E-17
AFFX- HUMISGF3A/M97935_MB_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	9.17E-11	2.205	5.29E-10
206553_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/71kDa	OAS2	2.60E-10	2.183	1.34E-09
207387_s_at	Hs.1466	glycerol kinase	GK	4.00E-15	2.16	9.38E-14
219716_at	Hs.257352	apolipoprotein L, 6	APOL6	3.45E-12	2.123	3.03E-11
202270_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	1.67E-15	2.113	4.67E-14
AFFX- HUMISGF3A/M97935_3_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	3.56E-19	2.11	3.93E-17
239979_at	Hs.546467	Epithelial stromal interaction 1 (breast)	EPSTI1	1.06E-16	2.091	4.73E-15

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229625_at	Hs.513726	Guanylate binding protein 5	GBP5	1.37E-10	2.074	7.52E-10
215977_x_at	Hs.1466	glycerol kinase	GK	1.03E-10	2.06	5.86E-10
228617_at	Hs.441975	XIAP associated factor-1	BIRC4BP	2.76E-13	2.045	3.41E-12
206513_at	Hs.281898	absent in melanoma 2	AIM2	6.42E-09	2.043	2.32E-08
228152_s_at	Hs.535011	hypothetical protein FLJ31033	FLJ31033	2.23E-15	2.016	6.02E-14
218943_s_at	Hs.190622	DEAD (Asp-Glu-Ala-Asp) box polypeptide 58	DDX58	1.97E-11	2	1.39E-10
214059_at	Hs.82316	Interferon-induced protein 44	IFI44	1.00E-09	1.996	4.49E-09
200887_s_at	Hs.565365	signal transducer and activator of transcription 1, 91kDa	STAT1	1.39E-18	1.987	1.21E-16
203148_s_at	Hs.575631	tripartite motif-containing 14	TRIM14	1.61E-19	1.944	2.17E-17
213572_s_at	Hs.381167	serpin peptidase inhibitor, clade B (ovalbumin), member 1	SERPINB1	2.34E-14	1.934	4.13E-13
229391_s_at	Hs.381220	hypothetical protein LOC441168	RP1-93H18.5	3.62E-11	1.932	2.34E-10
213293_s_at	Hs.501778	tripartite motif-containing 22	TRIM22	9.36E-14	1.892	1.36E-12
214838_at	---	SFT2 domain containing 2	SFT2D2	5.17E-19	1.881	5.30E-17
206133_at	Hs.441975	XIAP associated factor-1	BIRC4BP	8.74E-11	1.881	5.08E-10
231769_at	Hs.464419	F-box protein 6	FBXO6	2.38E-15	1.861	6.34E-14
238725_at	---	---	---	3.13E-15	1.842	7.84E-14
242234_at	Hs.441975	XIAP associated factor-1	BIRC4BP	1.70E-10	1.823	9.14E-10
227697_at	Hs.527973	suppressor of cytokine signaling 3	SOCS3	7.71E-11	1.819	4.55E-10
206632_s_at	Hs.226307	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B	APOBEC3B	1.76E-10	1.815	9.42E-10
201649_at	Hs.425777	ubiquitin-conjugating enzyme E2L 6	UBE2L6	1.06E-14	1.814	2.15E-13
204702_s_at	Hs.404741	nuclear factor (erythroid-derived 2)-like 3	NFE2L3	2.09E-18	1.803	1.71E-16
202531_at	Hs.436061	interferon regulatory factor 1	IRF1	1.04E-14	1.791	2.13E-13
214681_at	Hs.1466	glycerol kinase	GK	2.13E-13	1.789	2.75E-12
204994_at	Hs.926	myxovirus (influenza virus) resistance 2 (mouse)	MX2	1.92E-09	1.75	7.99E-09
202269_x_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	5.81E-13	1.733	6.47E-12
215966_x_at	---	glycerol kinase pseudogene 3	GKP3	3.84E-12	1.732	3.33E-11
231577_s_at	Hs.62661	guanylate binding protein 1, interferon-inducible, 67kDa	GBP1	9.15E-13	1.721	9.62E-12
33304_at	Hs.459265	interferon stimulated exonuclease gene 20kDa	ISG20	2.38E-12	1.72	2.19E-11
207655_s_at	Hs.444049	B-cell linker	BLNK	7.04E-16	1.712	2.28E-14

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Figure 51d

216598_s_at	Hs.303649	chemokine (C-C motif) ligand 2	CCL2	1.94E-07	1.711	4.80E-07
223502_s_at	Hs.525157	tumor necrosis factor (ligand) superfamily, member 13b	TNFSF13B	7.02E-06	1.706	1.18E-05
217167_x_at	Hs.1466	glycerol kinase	GK	6.00E-11	1.701	3.64E-10
200923_at	Hs.514535	lectin, galactoside-binding, soluble, 3 binding protein	LGALS3BP	3.70E-09	1.684	1.43E-08
219209_at	Hs.163173	interferon induced with helicase C domain 1	IFIH1	1.45E-13	1.674	1.97E-12
228230_at	Hs.517180	peroxisomal proliferator-activated receptor A interacting complex 285	PRIC285	3.34E-11	1.644	2.18E-10
209546_s_at	Hs.114309	apolipoprotein L, 1	APOL1	3.98E-09	1.63	1.52E-08
200629_at	Hs.497599	tryptophanyl-tRNA synthetase	WARS	1.75E-13	1.593	2.32E-12
218986_s_at	Hs.591710	hypothetical protein FLJ20035	FLJ20035	3.44E-11	1.592	2.23E-10
200628_s_at	Hs.497599	tryptophanyl-tRNA synthetase	WARS	1.56E-10	1.582	8.48E-10
214038_at	Hs.271387	chemokine (C-C motif) ligand 8	CCL8	1.69E-07	1.569	4.25E-07
238581_at	Hs.513726	Guanylate binding protein 5	GBP5	3.49E-09	1.564	1.35E-08
204205_at	---	apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3G	APOBEC3G	1.10E-08	1.541	3.73E-08
210029_at	Hs.840	indoleamine-pyrrole 2,3 dioxygenase	INDO	5.15E-07	1.531	1.15E-06
235157_at	Hs.583792	Poly (ADP-ribose) polymerase family, member 14	PARP14	2.93E-08	1.519	8.92E-08
239648_at	Hs.101007	DCN1, defective in cullin neddylation 1, domain containing 3 (S. cerevisiae)	DCUN1D3	2.96E-14	1.51	4.99E-13
223298_s_at	Hs.487933	5'-nucleotidase, cytosolic III	NT5C3	5.36E-16	1.497	1.81E-14
232375_at	Hs.565365	Signal transducer and activator of transcription 1, 91kDa	STAT1	6.86E-11	1.483	4.11E-10
203964_at	Hs.54483	N-myc (and STAT) interactor	NMI	6.43E-19	1.47	6.37E-17
216316_x_at	Hs.1466	glycerol kinase	GK /// GKP3	2.02E-09	1.461	8.34E-09
219211_at	Hs.38260	ubiquitin specific peptidase 18	USP18	5.29E-08	1.45	1.51E-07
202779_s_at	Hs.396393	ubiquitin-conjugating enzyme E2S	UBE2S ///	5.19E-08	1.442	1.48E-07
202446_s_at	Hs.130759	phospholipid scramblase 1	LOC651816	6.94E-13	1.435	7.55E-12
202430_s_at	Hs.130759	phospholipid scramblase 1	PLSCR1	5.46E-13	1.427	6.14E-12
227807_at	Hs.518200	poly (ADP-ribose) polymerase family, member 9	PLSCR1	2.40E-11	1.422	1.64E-10
202687_s_at	Hs.478275	tumor necrosis factor (ligand) superfamily, member 10	PARP9	3.17E-14	1.407	5.28E-13
			TNFSF10			

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204601_at	Hs.511839	Nedd4 binding protein 1	N4BP1	3.29E-17	1.406	1.83E-15
211122_s_at	Hs.632592	chemokine (C-X-C motif) ligand 11	CXCL11	0.000205024	1.364	0.000241
202688_at	Hs.478275	tumor necrosis factor (ligand) superfamily, member 10	TNFSF10	3.18E-15	1.363	7.91E-14
209762_x_at	Hs.145150	SP110 nuclear body protein	SP110	9.20E-14	1.357	1.34E-12
214329_x_at	Hs.478275	tumor necrosis factor (ligand) superfamily, member 10	TNFSF10	5.39E-14	1.336	8.39E-13
206999_at	Hs.479347	interleukin 12 receptor, beta 2	IL12RB2	6.07E-11	1.333	3.68E-10
202087_s_at	Hs.418123	cathepsin L	CTSL	2.53E-11	1.332	1.72E-10
225415_at	Hs.518201	deltex 3-like (Drosophila)	DTX3L	2.24E-16	1.299	8.67E-15
205992_s_at	Hs.168132	interleukin 15	IL15	1.73E-08	1.285	5.61E-08
204770_at	Hs.502	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	TAP2	3.30E-07	1.281	7.71E-07
238025_at	Hs.119878	mixed lineage kinase domain-like	MLKL	1.27E-16	1.274	5.40E-15
223501_at	---	---	---	1.05E-05	1.274	1.68E-05
204279_at	Hs.132682	proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)	PSMB9	5.85E-06	1.267	9.98E-06
225344_at	Hs.171426	nuclear receptor coactivator 7	NCOA7	5.66E-15	1.253	1.26E-13
229723_at	Hs.529984	T-cell activation GTPase activating protein	TAGAP	1.16E-07	1.243	3.02E-07
1557236_at	Hs.257352	apolipoprotein L, 6	APOL6	2.29E-09	1.24	9.29E-09
208012_x_at	Hs.145150	SP110 nuclear body protein	SP110	2.18E-13	1.234	2.79E-12
209417_s_at	Hs.632258	interferon-induced protein 35	IFI35	5.68E-08	1.23	1.60E-07
226603_at	Hs.489118	sterile alpha motif domain containing 9-like	SAMD9L	1.53E-07	1.227	3.90E-07
230966_at	---	interleukin 4 induced 1	IL4I1	1.06E-07	1.219	2.81E-07
217995_at	Hs.511251	sulfide quinone reductase-like (yeast)	SQRDL	1.84E-20	1.213	3.52E-18
210163_at	Hs.632592	chemokine (C-X-C motif) ligand 11	CXCL11	0.000158403	1.197	0.000191
1557116_at	Hs.257352	apolipoprotein L, 6	APOL6	7.14E-10	1.192	3.30E-09
204224_s_at	Hs.86724	GTP cyclohydrolase 1 (dopa-responsive dystonia)	GCH1	4.95E-16	1.191	1.69E-14
219759_at	Hs.591249	leukocyte-derived arginine aminopeptidase	LRAP	0.002962889	1.189	0.002449
206503_x_at	Hs.526464	promyelocytic leukemia	PML	5.06E-11	1.184	3.14E-10
223434_at	---	guanylate binding protein 3	GBP3	4.41E-06	1.184	7.75E-06
211013_x_at	Hs.526464	promyelocytic leukemia	PML	1.89E-11	1.172	1.34E-10
224701_at	Hs.583792	poly (ADP-ribose) polymerase family, member 14	PARP14	5.35E-09	1.159	1.98E-08

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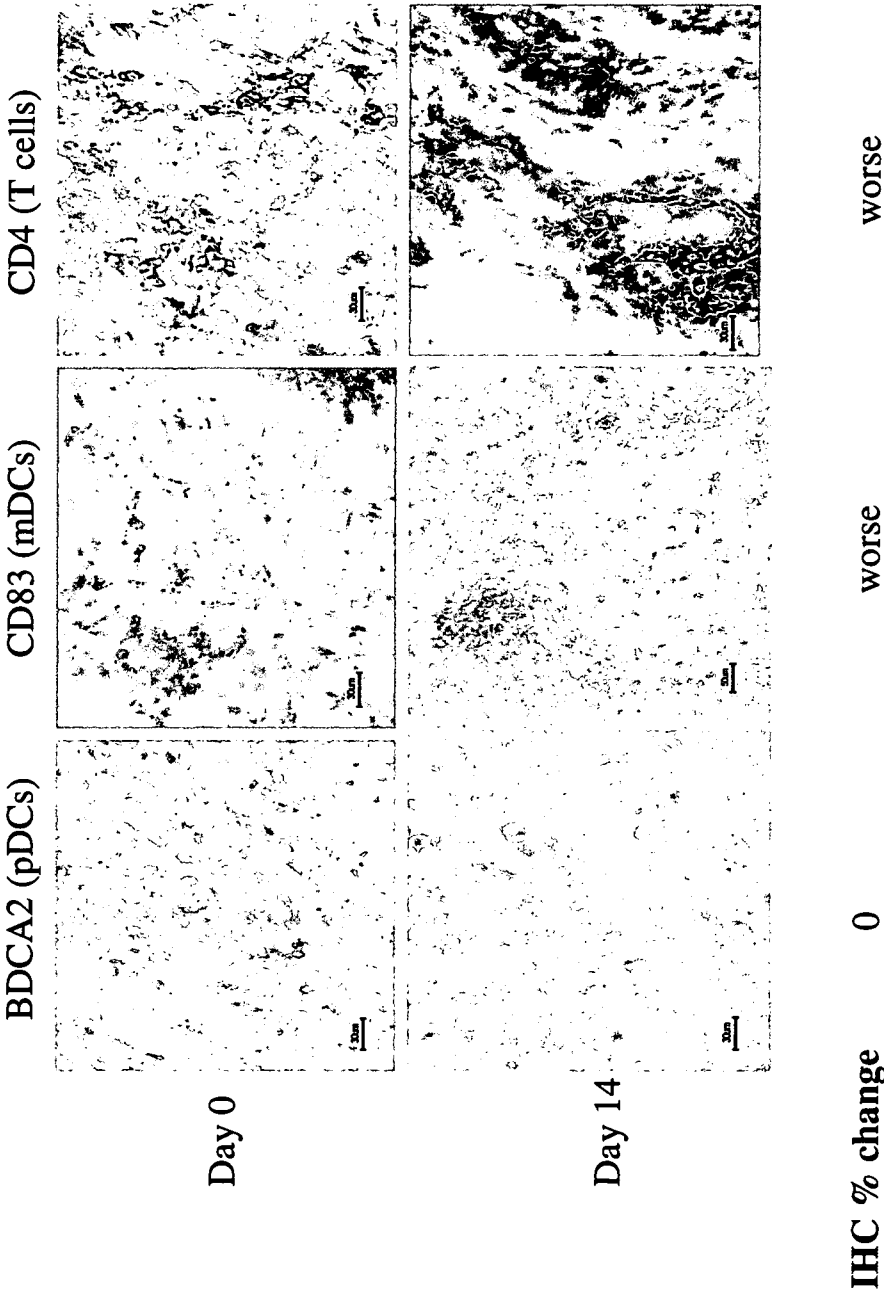
238439_at	Hs.217484	ankyrin repeat domain 22	ANKRD22	1.01E-08	1.15	3.45E-08
206247_at	Hs.211580	MHC class I polypeptide-related sequence B lectin, galactoside-binding, soluble, 8 (galectin 8)	MICB	5.09E-08	1.148	1.46E-07
208934_s_at	Hs.4082		LGALS8	5.87E-12	1.147	4.83E-11
228607_at	Hs.414332	2'-5'-oligoadenylate synthetase 2, 69/7 kDa	OAS2	9.30E-10	1.133	4.19E-09
219253_at	Hs.376722	family with sequence similarity 11, member B	FAM11B	1.28E-10	1.123	7.09E-10
222262_s_at	Hs.29464	ethanolamine kinase 1	ETNK1	1.69E-12	1.123	1.63E-11
214791_at	---	hypothetical protein BC004921	LOC93349	3.31E-09	1.109	1.29E-08
225973_at	Hs.502	transporter 2, ATP-binding cassette, sub-family B (MDR/TAP)	TAP2	1.03E-10	1.108	5.86E-10
210001_s_at	Hs.50640	suppressor of cytokine signaling 1	SOCS1	7.53E-08	1.108	2.06E-07
239196_at	Hs.217484	ankyrin repeat domain 22	ANKRD22	4.12E-11	1.103	2.61E-10
219863_at	Hs.26663	hect domain and RLD 5	HERC5	6.50E-11	1.102	3.92E-10
53720_at	---	hypothetical protein FLJ11286	FLJ11286	4.01E-18	1.094	2.96E-16
207181_s_at	Hs.9216	caspase 7, apoptosis-related cysteine peptidase	CASP7	6.40E-14	1.093	9.73E-13
219017_at	Hs.29464	ethanolamine kinase 1	ETNK1	7.57E-12	1.085	6.02E-11
210732_s_at	Hs.4082	lectin, galactoside-binding, soluble, 8 (galectin 8)	LGALS8	1.57E-06	1.085	3.08E-06
214617_at	Hs.2200	perforin 1 (pore forming protein)	PRF1	6.88E-11	1.081	4.12E-10
230036_at	Hs.489118	sterile alpha motif domain containing 9-like	SAMD9L	2.77E-06	1.075	5.13E-06
1552485_at	Hs.410388	lactamase, beta	LACTB	1.83E-10	1.075	9.76E-10
			CCL3 ///			
			CCL3L1 ///			
			CCL3L3 ///			
205114_s_at	Hs.514107	chemokine (C-C motif) ligand 3	LOC643930	3.67E-05	1.073	5.16E-05
227868_at	Hs.532236	hypothetical protein LOC154761	LOC154761	4.63E-11	1.061	2.89E-10
209795_at	Hs.208854	CD69 molecule	CD69	3.46E-06	1.058	6.24E-06
208966_x_at	---	interferon, gamma-inducible protein 16	IFI16	3.38E-14	1.055	5.58E-13
203147_s_at	Hs.575631	tripartite motif-containing 14	TRIM14	3.16E-08	1.055	9.55E-08
209310_s_at	Hs.138378	caspase 4, apoptosis-related cysteine peptidase	CASP4	1.89E-14	1.052	3.46E-13
1555464_at	Hs.163173	interferon induced with helicase C domain 1	IFIH1	7.78E-08	1.047	2.12E-07
230110_at	Hs.591446	mucopolip 2	MCOLN2	3.04E-07	1.03	7.16E-07
220941_s_at	Hs.293811	chromosome 21 open reading frame 91	C21orf91	5.37E-07	1.025	1.19E-06
219159_s_at	Hs.517265	SLAM family member 7	SLAMF7	2.87E-09	1.023	1.14E-08

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218429_s_at	---	hypothetical protein FLJ11286	FLJ11286	4.50E-17
				1.014
				2.36E-15

Figure 51g

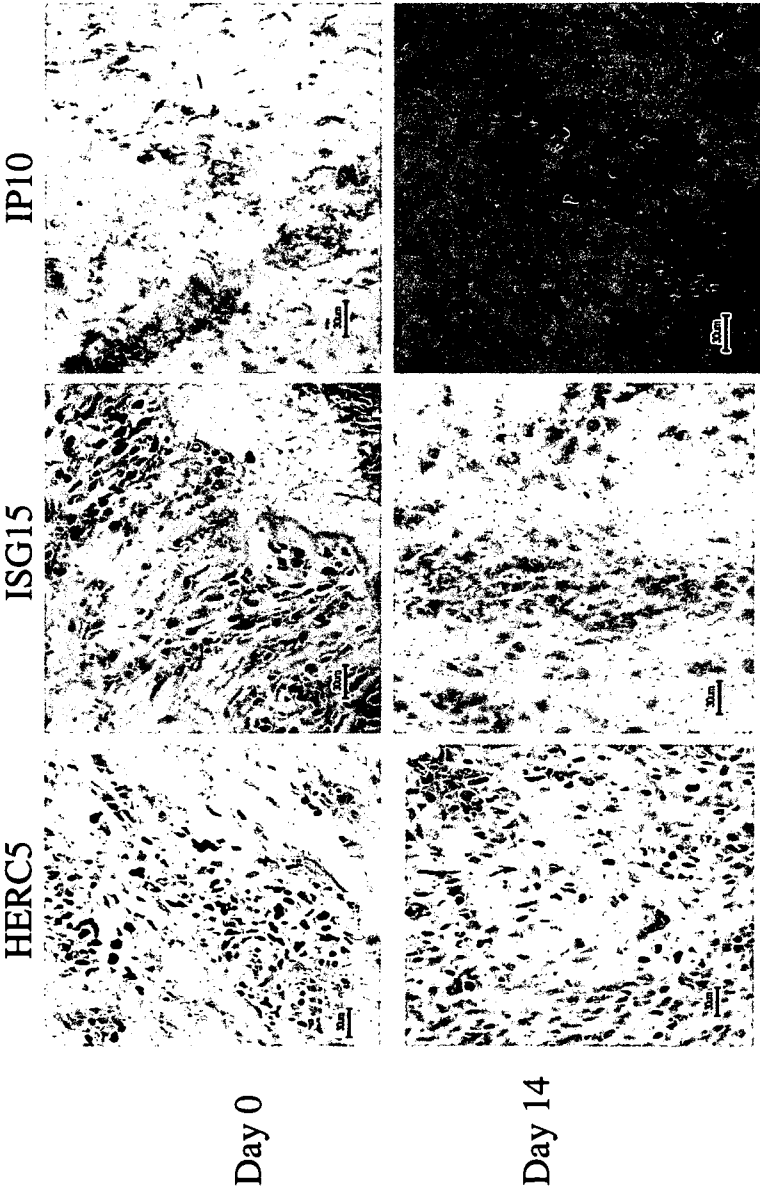
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Figure 52

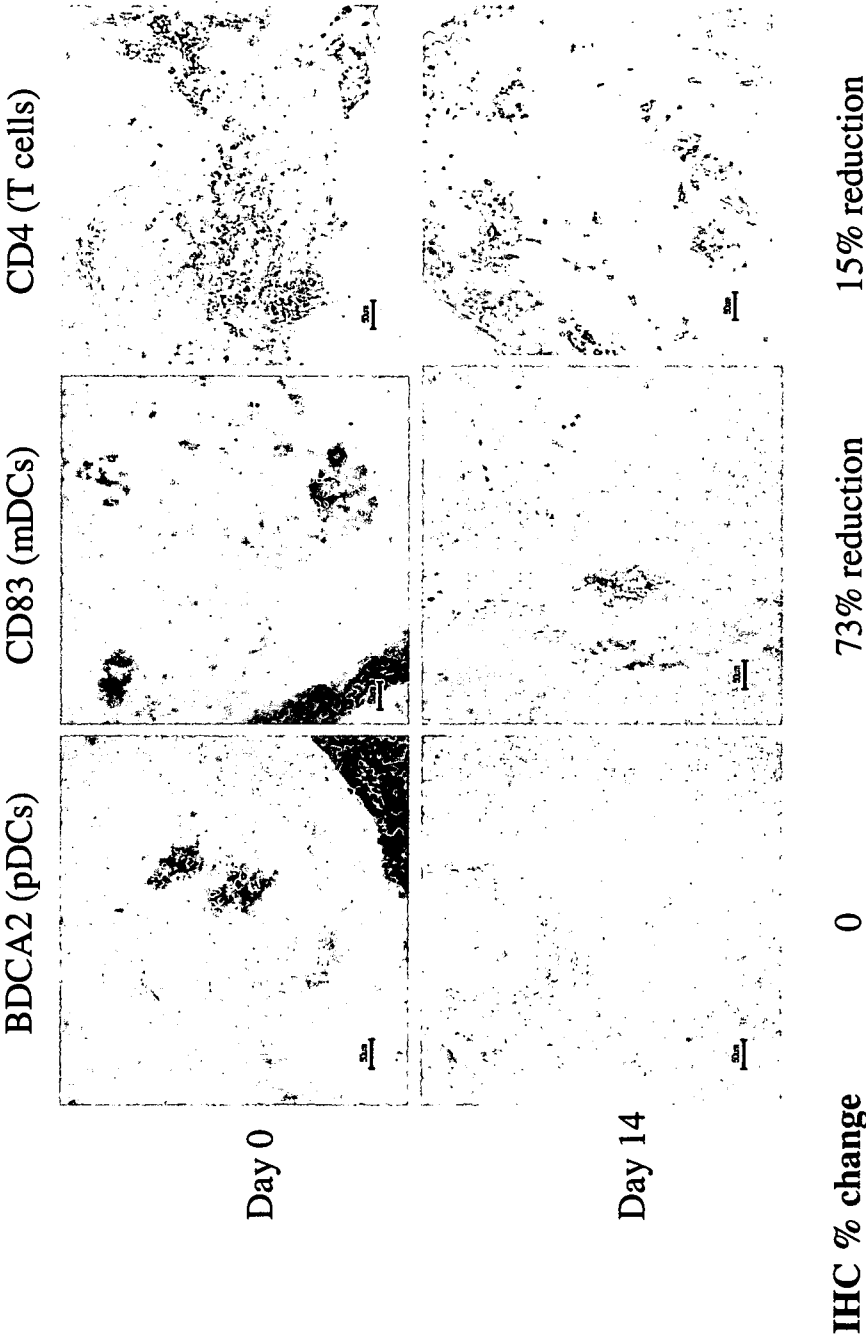


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Figure 53

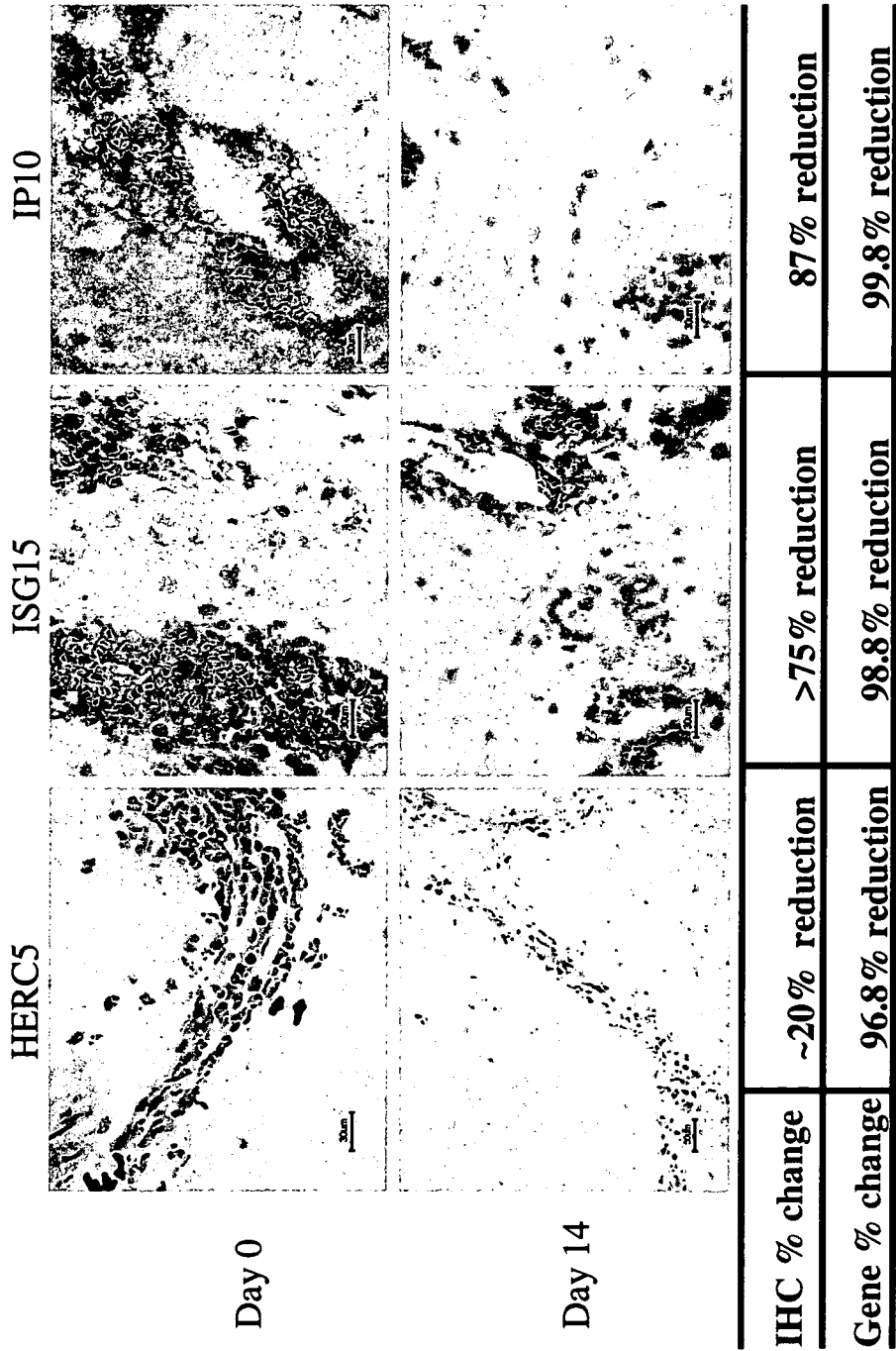


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Figure 54

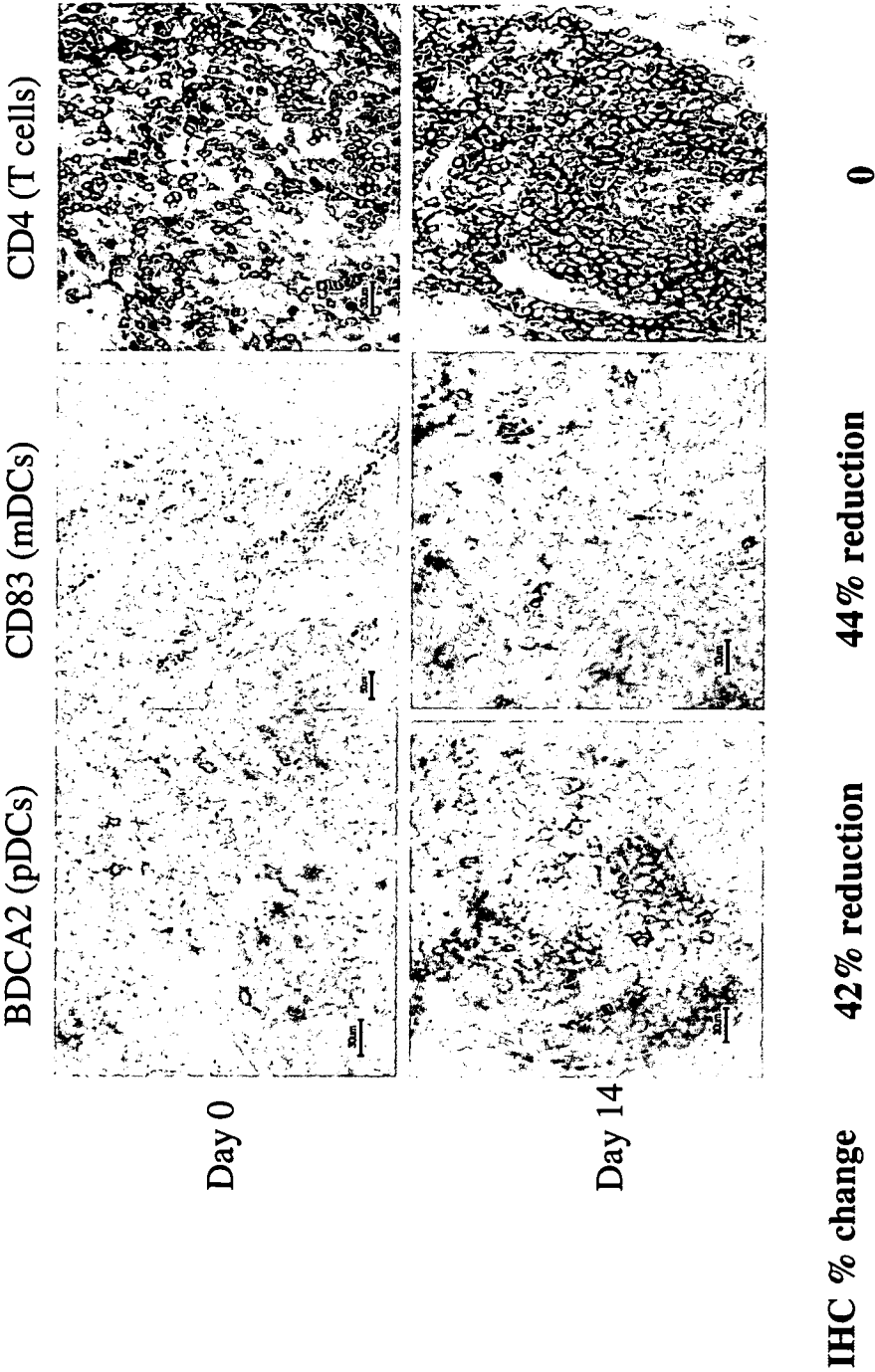


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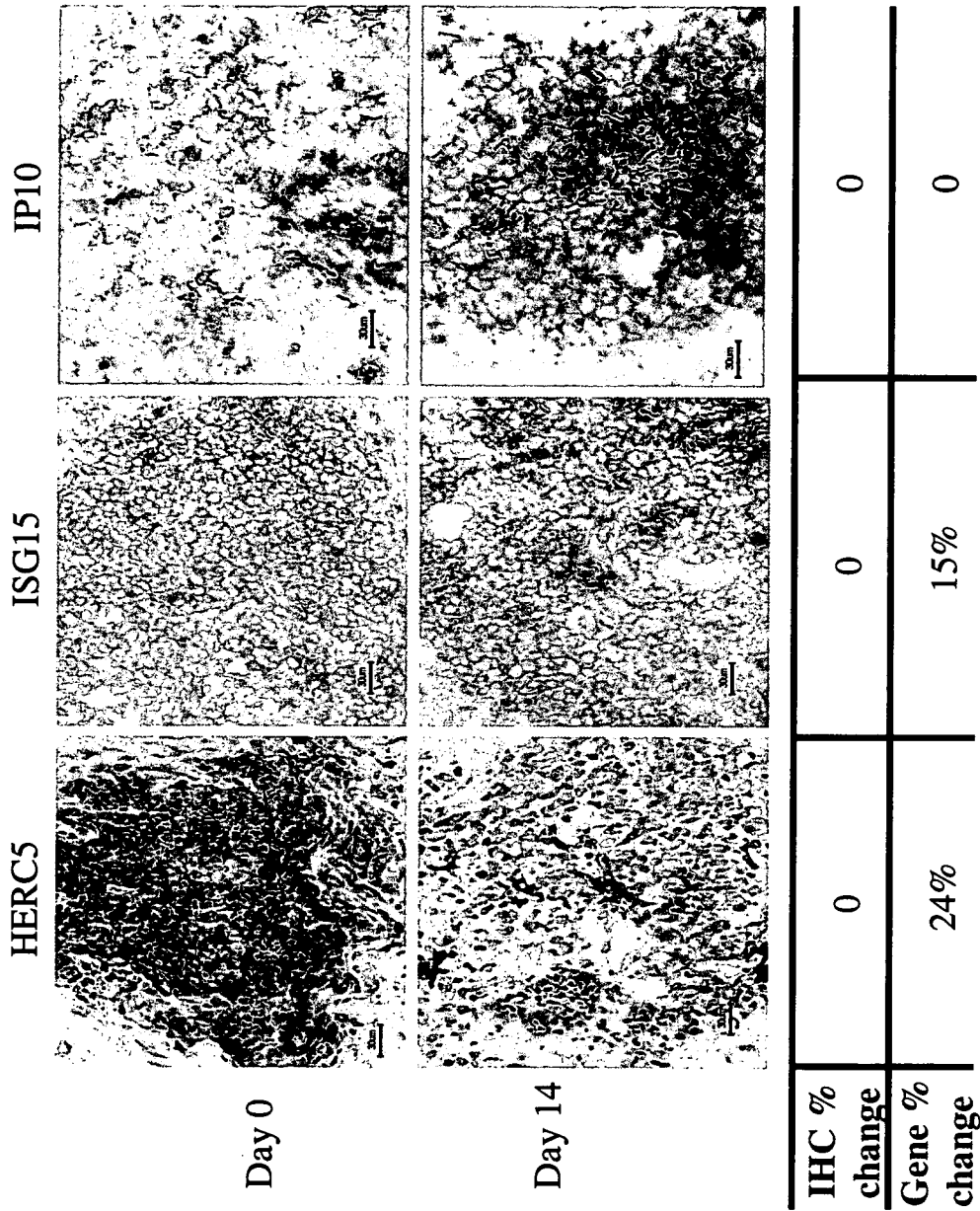
Figure 55



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Figure 56

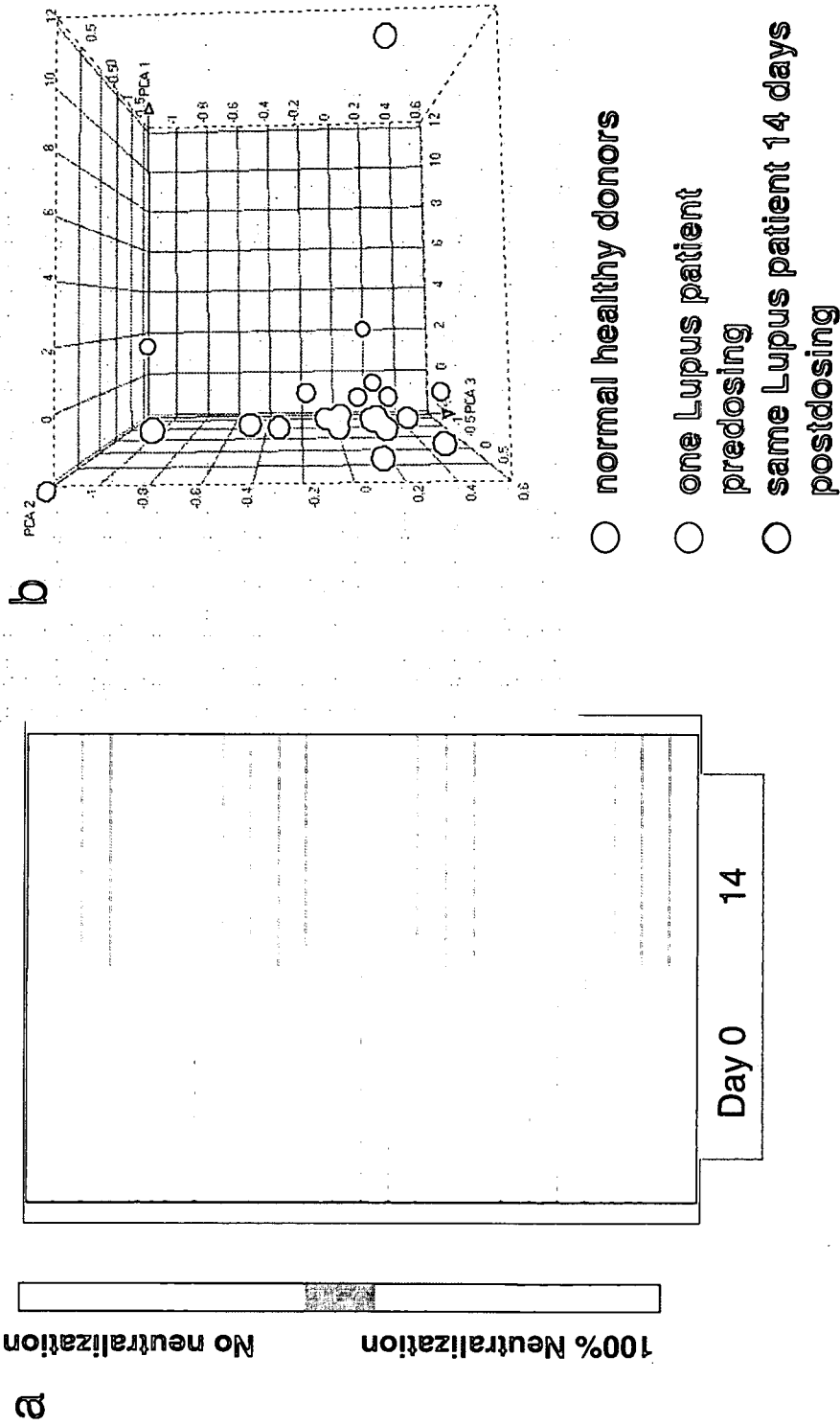


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Figure 57



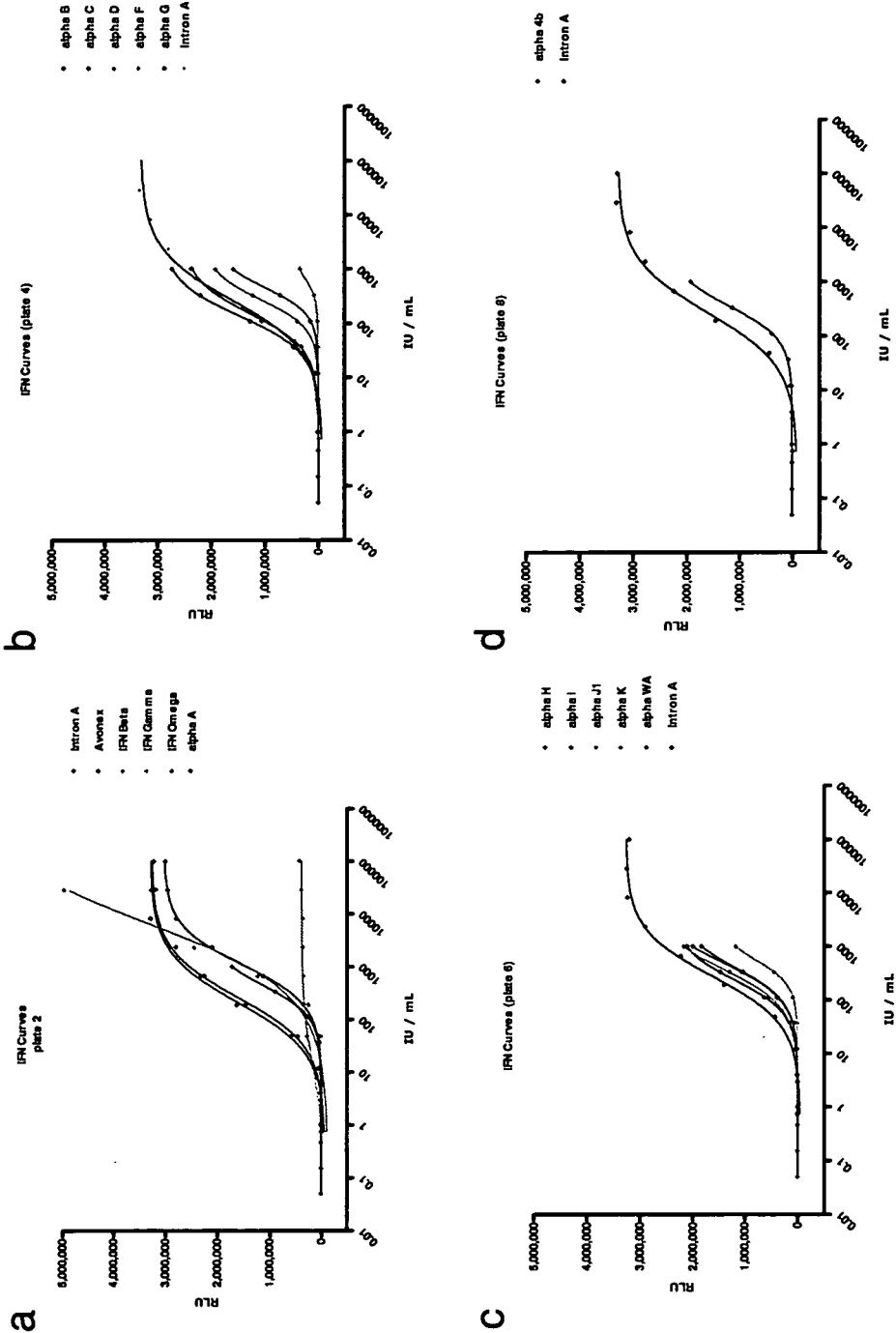
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Figure 58

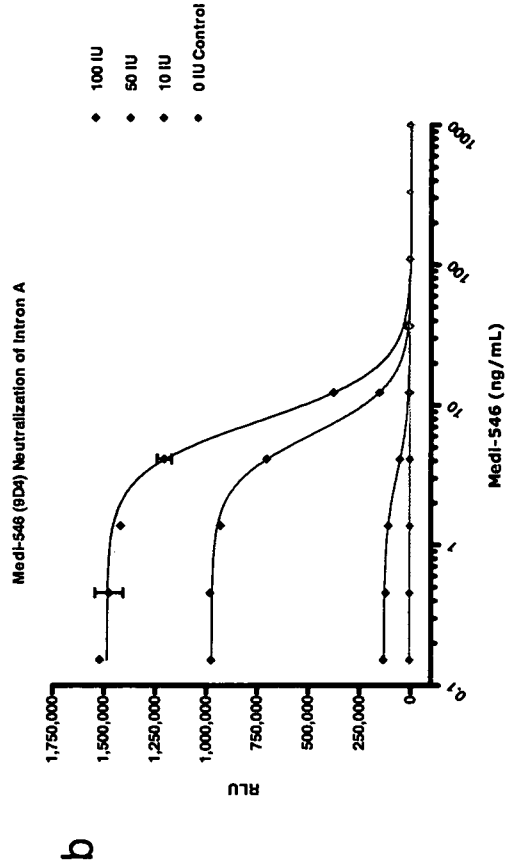
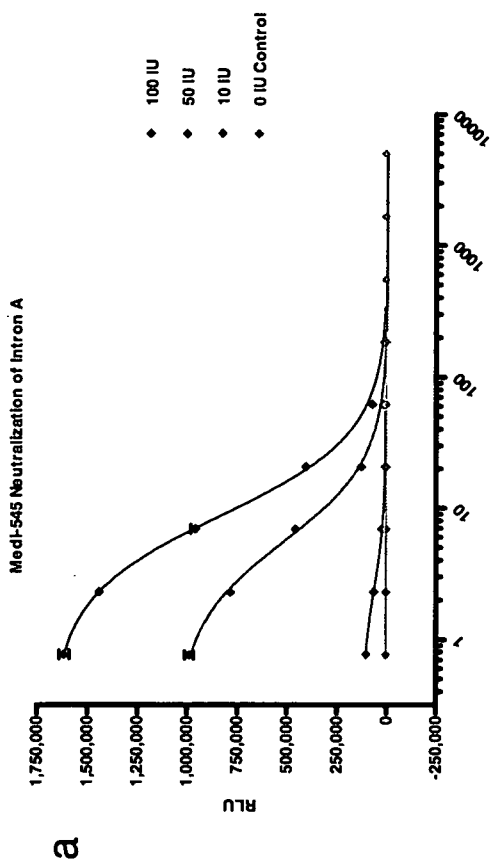


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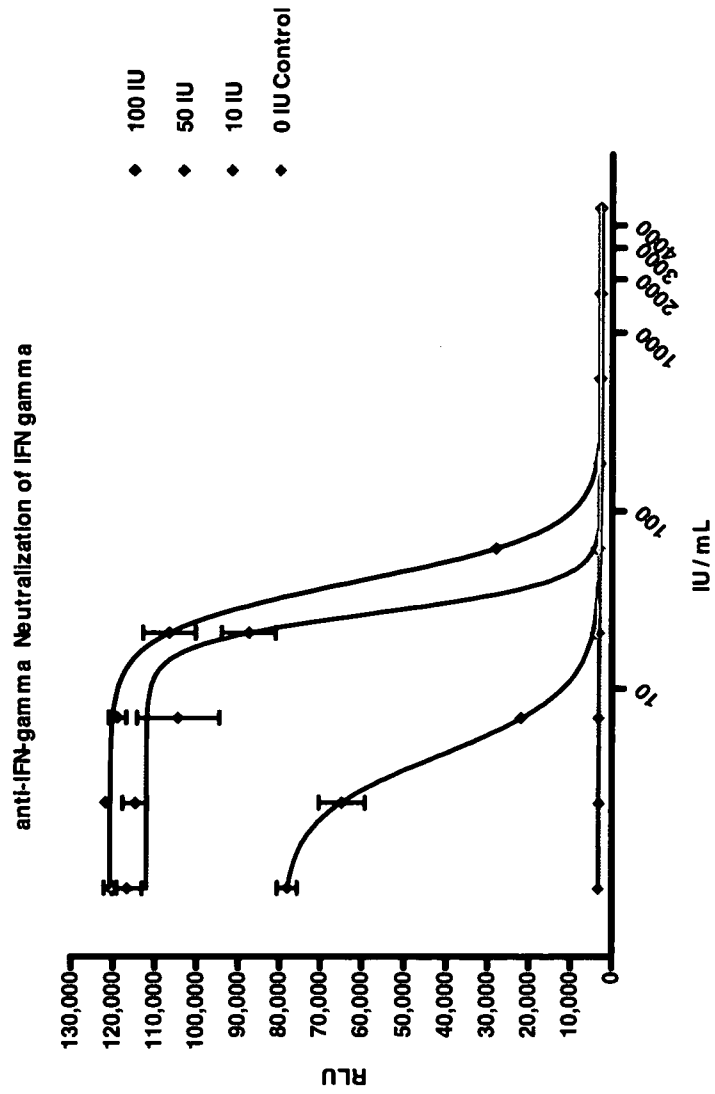
Figure 59



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Figure 60

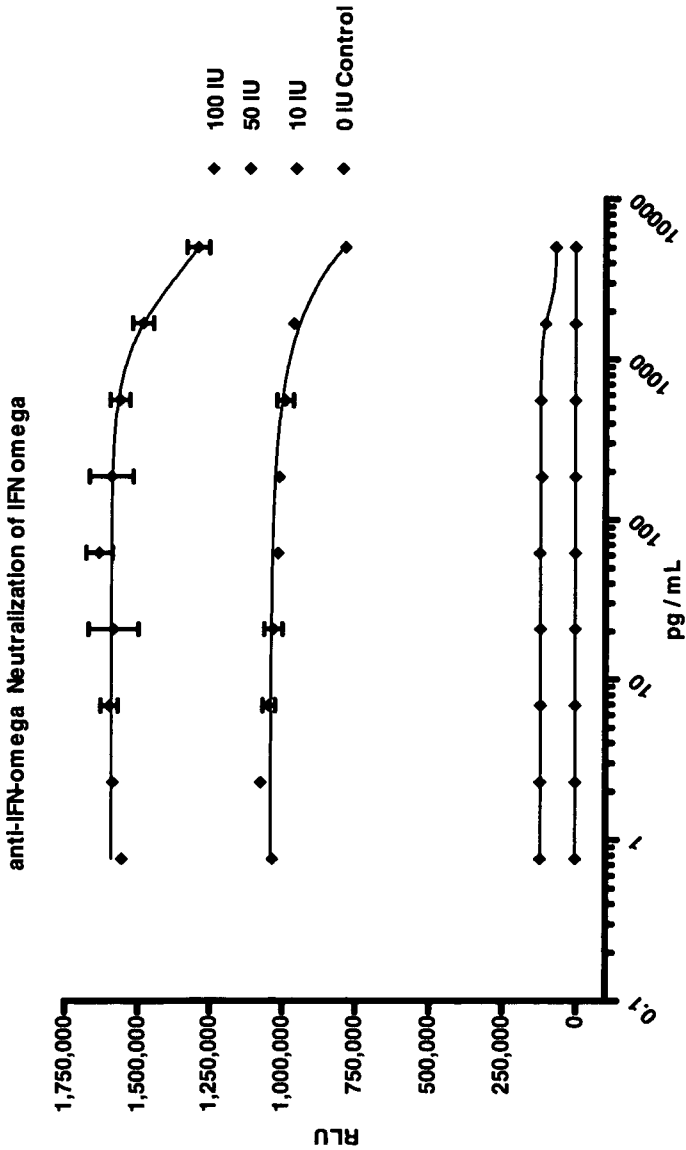


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Figure 61

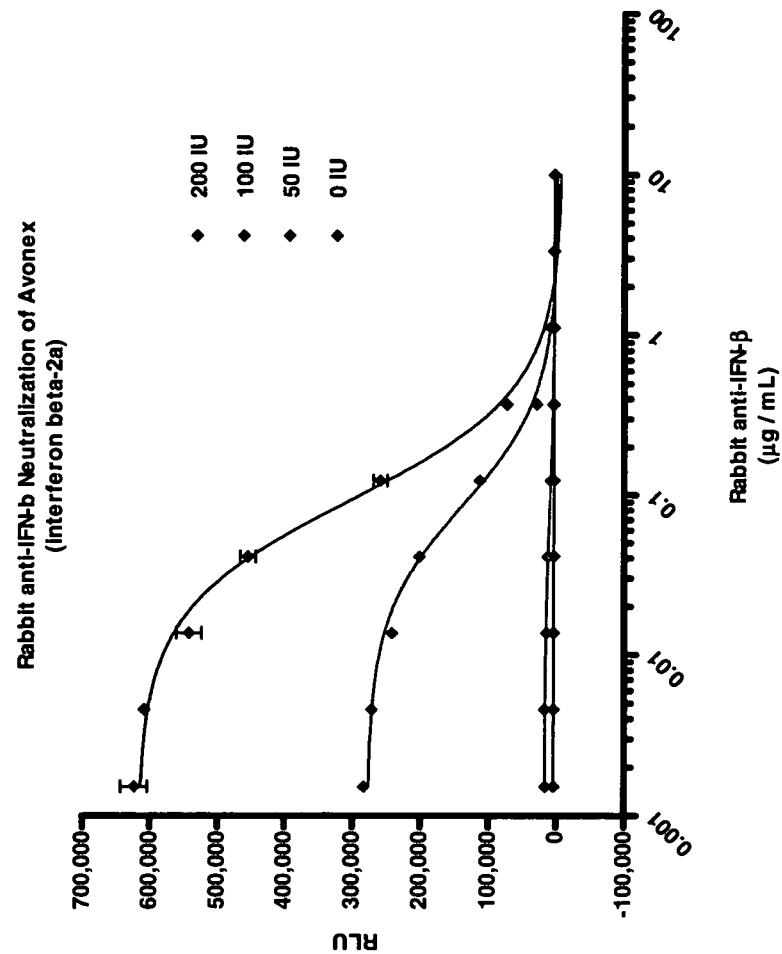


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Figure 62

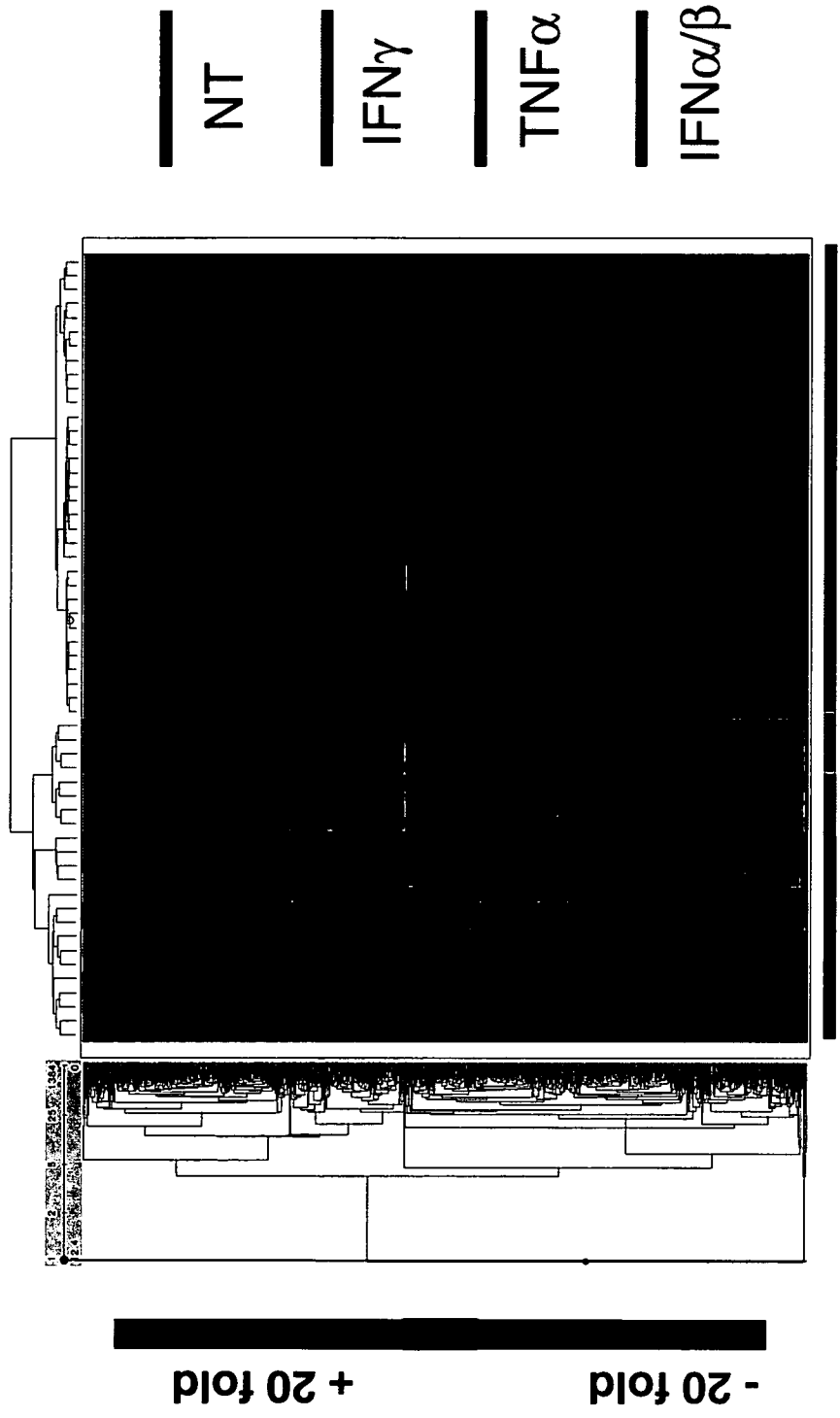


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Figure 63



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Figure 64



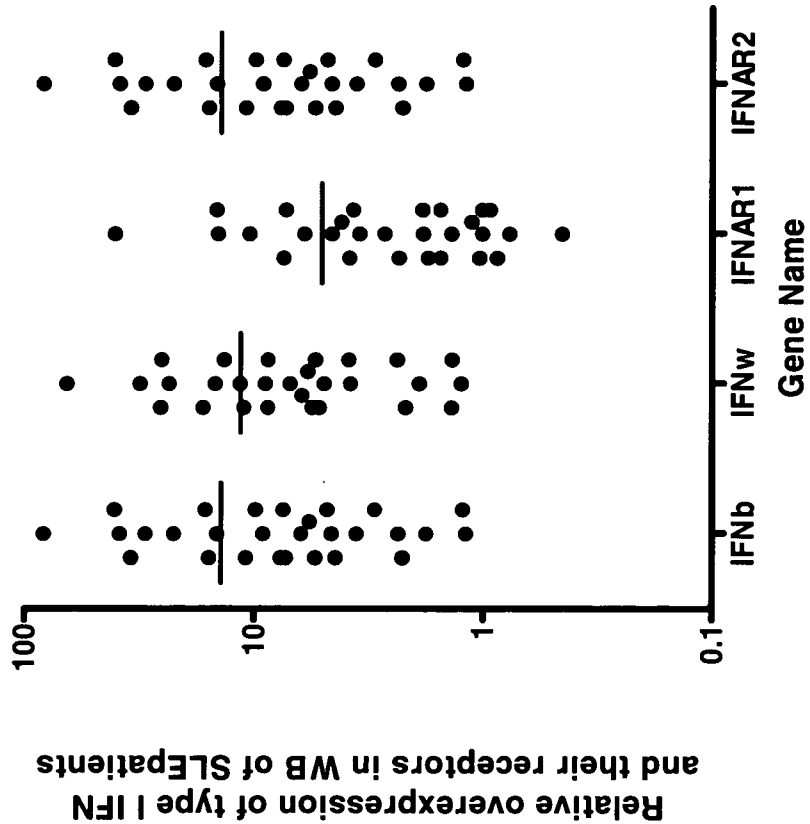
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Figure 65

Probe ID	Gene Title	Gene Symbol	log2.fc	q.value(tdr)	Samples with FC>=2	Percentage of Samples (Prevalence)	IFN Inducible Probe
202411_at	interferon, alpha-inducible protein 27	IFI27	4.601	8.41E-07	34	73.91	Y
219519_s_at	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1	3.524	7.28E-07	30	65.22	Y
214059_at	Interferon-induced protein 44	IFI44	3.509	8.04E-07	34	73.91	Y
213797_at	radical S-adenosyl methionine domain containing 2	RSAD2	3.286	9.86E-06	33	71.74	Y
204415_at	interferon, alpha-inducible protein 6	IFI6	3.207	2.25E-09	38	82.61	Y
242625_at	radical S-adenosyl methionine domain containing 2	RSAD2	3.191	1.55E-06	32	69.57	Y
204439_at	interferon-induced protein 44-like	IFI44L	3.140	4.99E-06	33	71.74	Y
219211_at	ubiquitin specific peptidase 18	USP18	2.839	2.23E-06	31	67.39	Y
214453_s_at	interferon-induced protein 44	IFI44	2.721	1.07E-05	33	71.74	Y
202145_at	lymphocyte antigen 6 complex, locus E	LY6E	2.530	7.28E-07	29	63.04	Y
207329_at	matrix metalloproteinase 8 (neutrophil collagenase)	MMP8	2.508	0.001106918	28	60.87	N
202869_at	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	2.328	1.66E-06	32	69.57	Y
222154_s_at	DNA polymerase-transactivated protein 6	DNAPT6	2.324	1.14E-05	30	65.22	Y
44673_at	sialic acid binding Ig-like lectin 1, sialoadhesin	SIGLEC1	2.310	2.23E-06	27	58.70	Y
242234_at	XIAP associated factor-1	BIRC4BP	2.306	8.41E-07	30	65.22	Y
203153_at	interferon-induced protein with tetratricopeptide repeats 1	IFIT1	2.252	9.53E-05	31	67.39	Y
218400_at	2'-5'-oligoadenylate synthetase 3, 100kDa	OAS3	2.235	1.23E-05	31	67.39	Y
212768_s_at	olfactomedin 4	OLFM4	2.225	0.006082542	28	60.87	N
241869_at	apolipoprotein L, 6	APOL6	2.222	0.000453671	37	80.43	N
235643_at	sterile alpha motif domain containing 9-like	SAMD9L	2.221	1.37E-06	39	84.78	Y
231688_at	Transcribed locus	---	2.216	0.002484265	29	63.04	N
208470_s_at	haptoglobin /// haptoglobin-related protein	HP /// HPR	2.199	2.48E-05	37	80.43	N
239979_at	Epithelial stromal interaction 1 (breast)	EPSTI1	2.196	5.44E-06	30	65.22	Y
206697_s_at	haptoglobin	HP	2.186	2.96E-05	34	73.91	N
205552_s_at	2'-5'-oligoadenylate synthetase 1, 40/46kDa	OAS1	2.184	4.98E-07	30	65.22	Y
205483_s_at	ISG15 ubiquitin-like modifier	ISG15	2.161	2.73E-06	30	65.22	Y
227609_at	epithelial stromal interaction 1 (breast)	EPSTI1	2.147	4.99E-06	31	67.39	Y
1555643_s_at	leukocyte immunoglobulin-like receptor, subfamily A	LILRA5	2.138	8.41E-07	35	76.09	N
222816_s_at	zinc finger, CCHC domain containing 2	ZCCHC2	2.095	5.43E-05	37	80.43	Y
205569_at	lysosomal-associated membrane protein 3	LAMP3	2.085	2.74E-06	30	65.22	Y
226702_at	hypothetical protein LOC129607	LOC129607	2.065	5.96E-05	31	67.39	Y
215838_at	leukocyte immunoglobulin-like receptor, subfamily A	LILRA5	2.065	1.87E-05	33	71.74	N
219863_at	hect domain and RLD 5	HERC5	2.032	1.53E-05	31	67.39	Y
204747_at	interferon-induced protein with tetratricopeptide repeats 3	IFIT3	2.015	1.55E-06	31	67.39	Y
200986_at	serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	SERPING1	1.984	0.000130143	31	67.39	Y
224225_s_at	ets variant gene 7 (TEL2 oncogene)	ETV7	1.983	2.48E-05	27	58.70	Y
219684_at	receptor (chemosensory) transporter protein 4	RTP4	1.960	2.74E-06	29	63.04	Y
206133_at	XIAP associated factor-1	BIRC4BP	1.955	7.28E-07	30	65.22	Y
206871_at	elastase 2, neutrophil	ELA2	1.953	0.003161604	25	54.35	N
217502_at	interferon-induced protein with tetratricopeptide repeats 2	IFIT2	1.949	4.86E-06	33	71.74	Y

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Figure 66



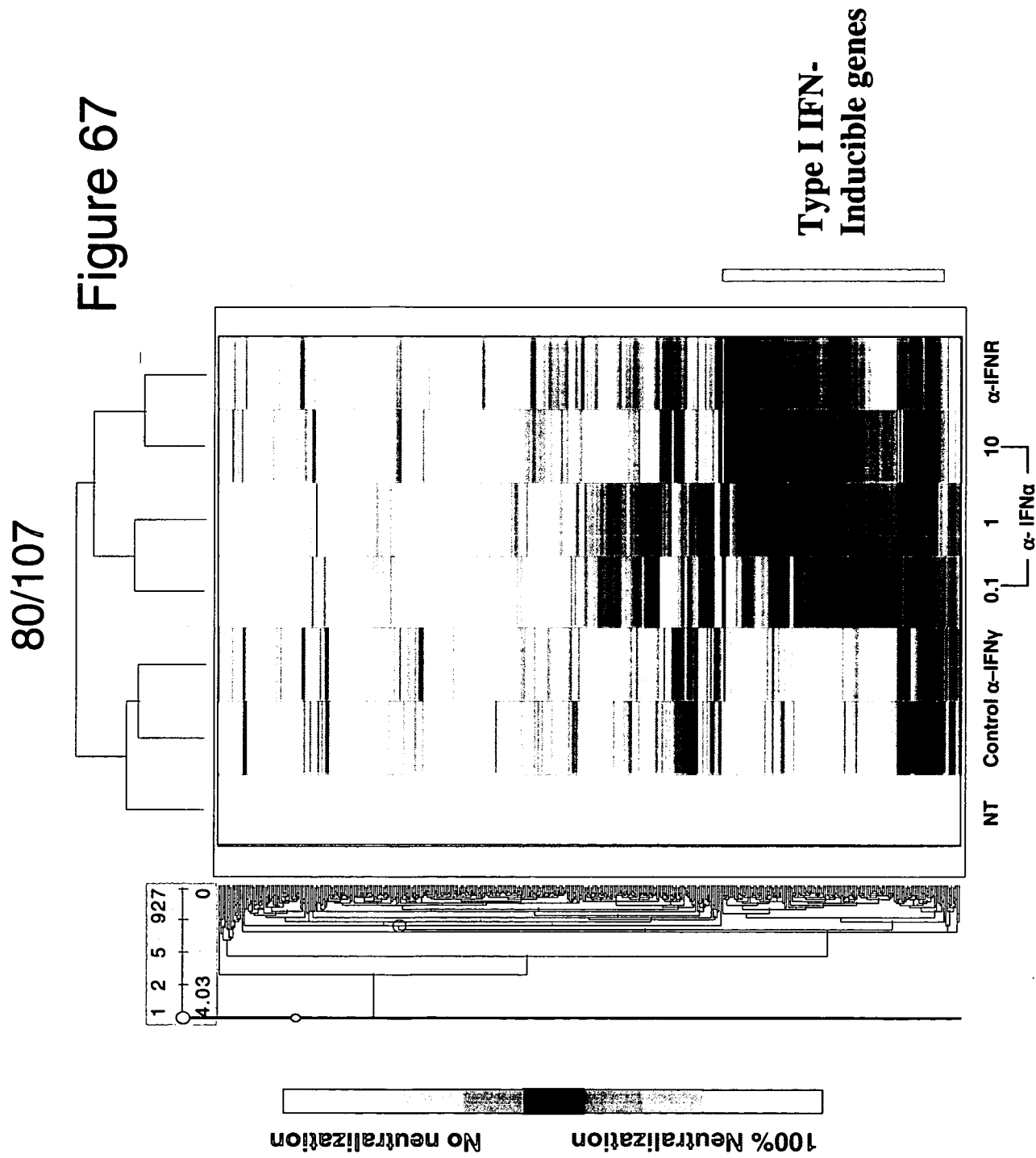
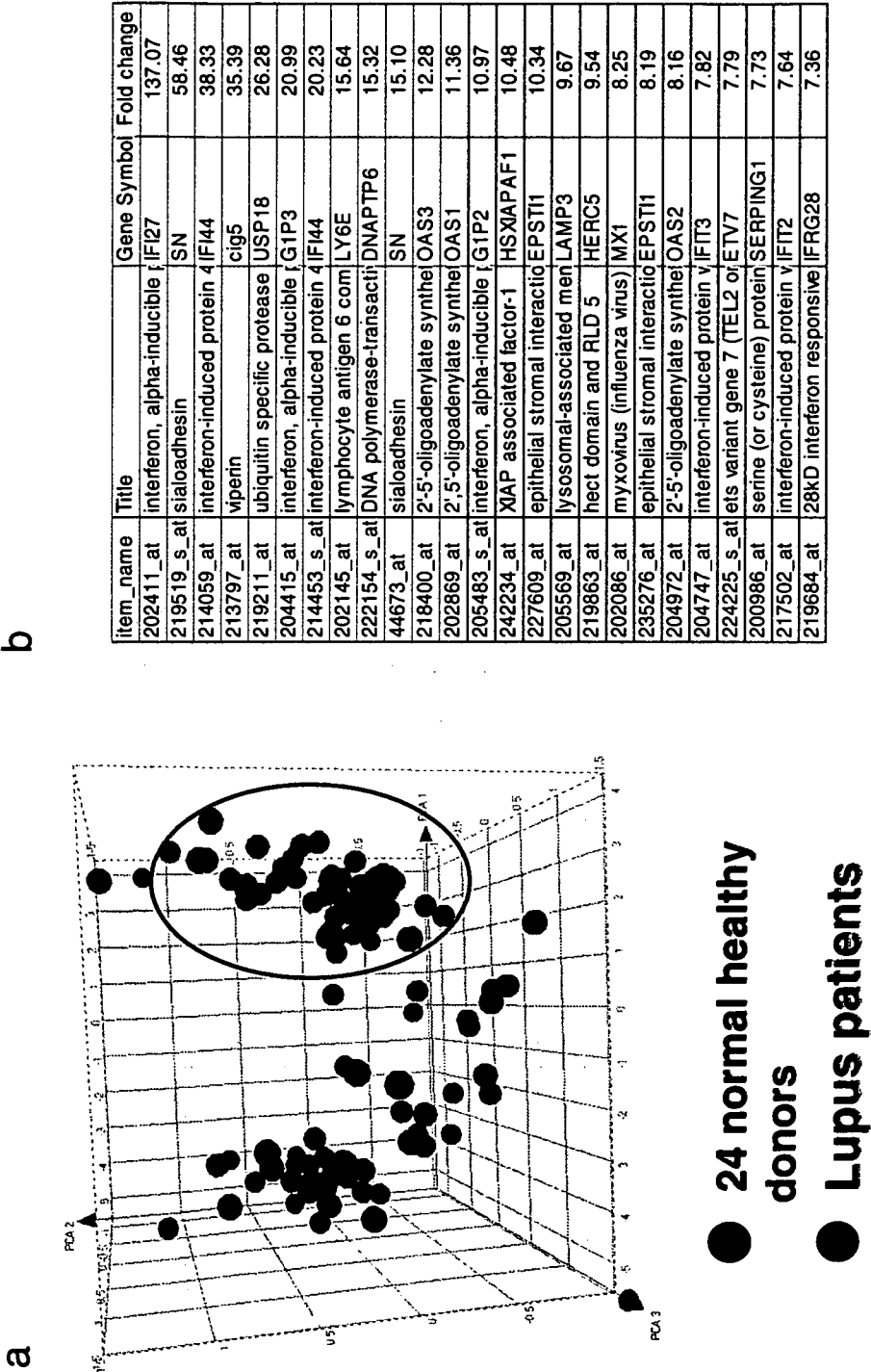
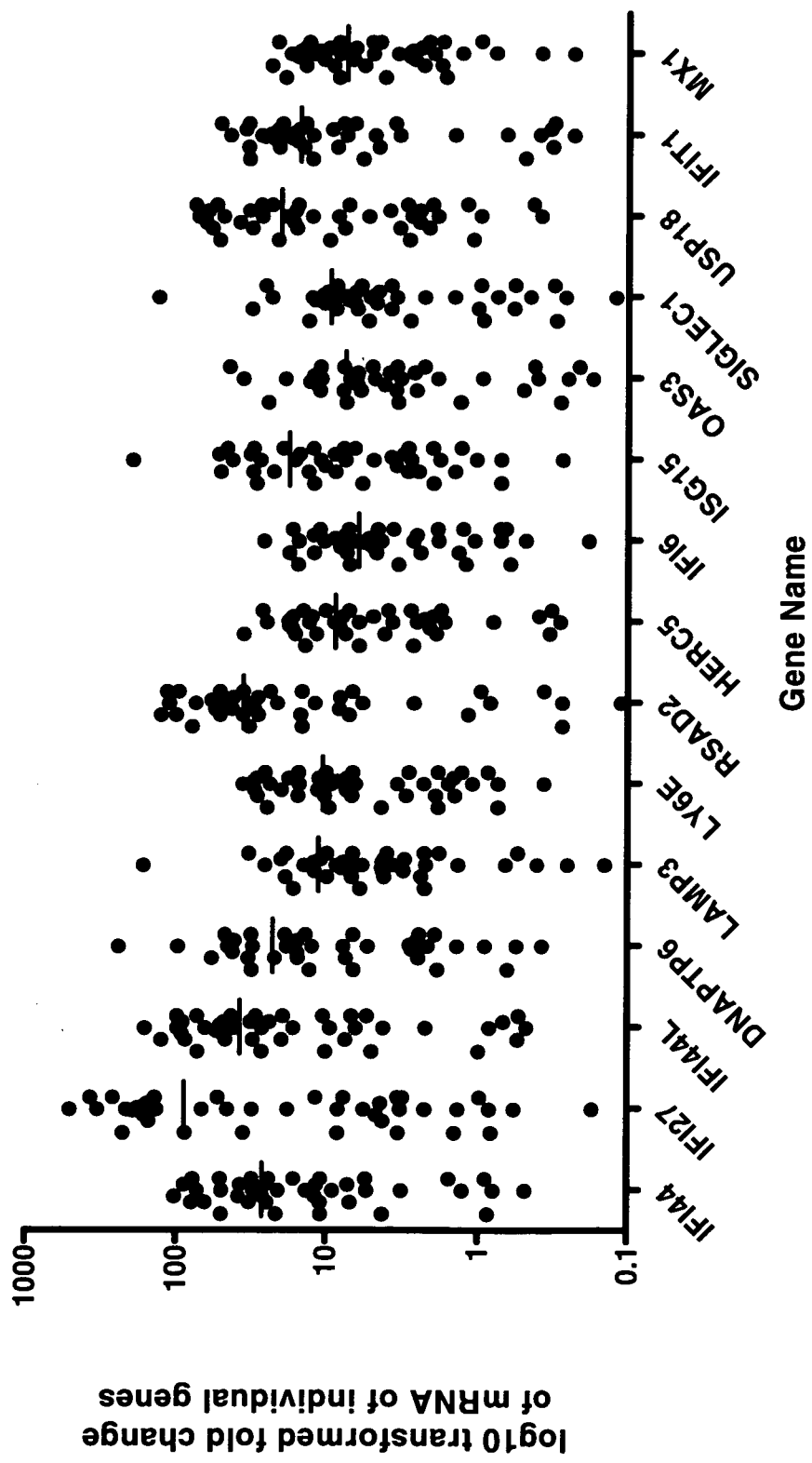


Figure 68



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Figure 69

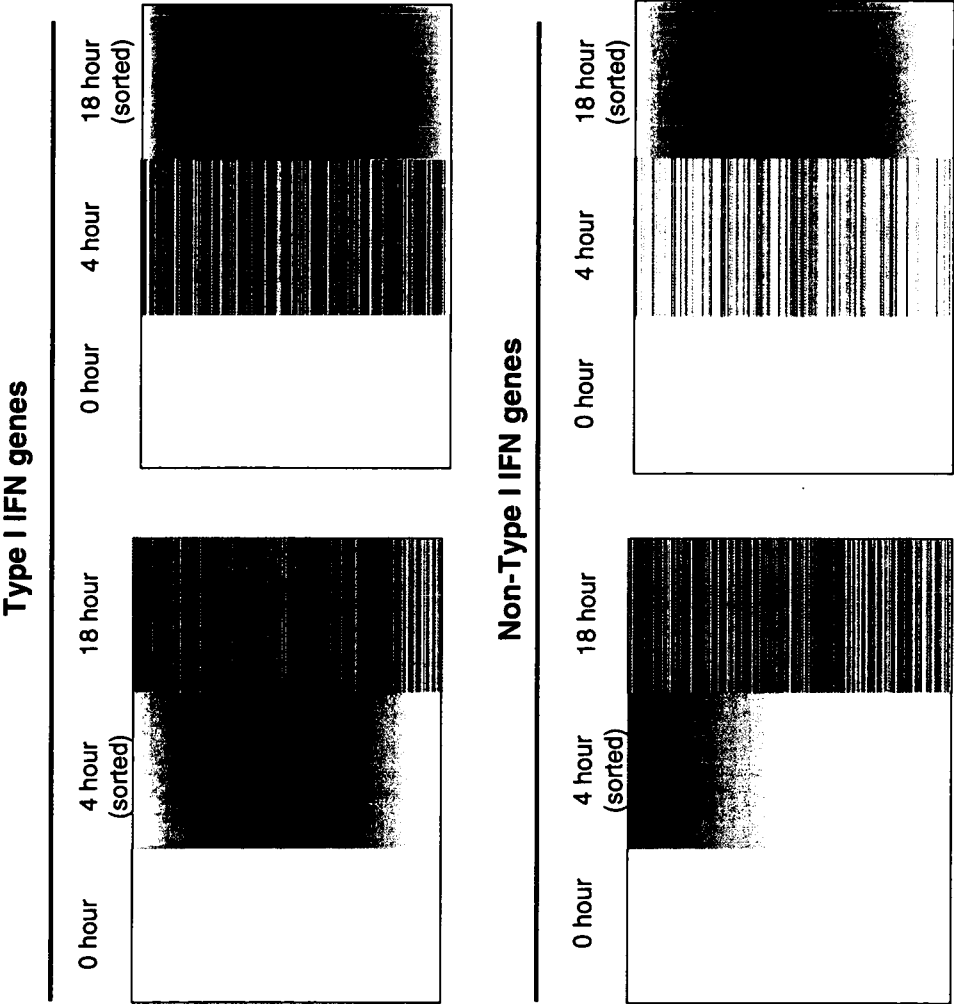


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Figure 70

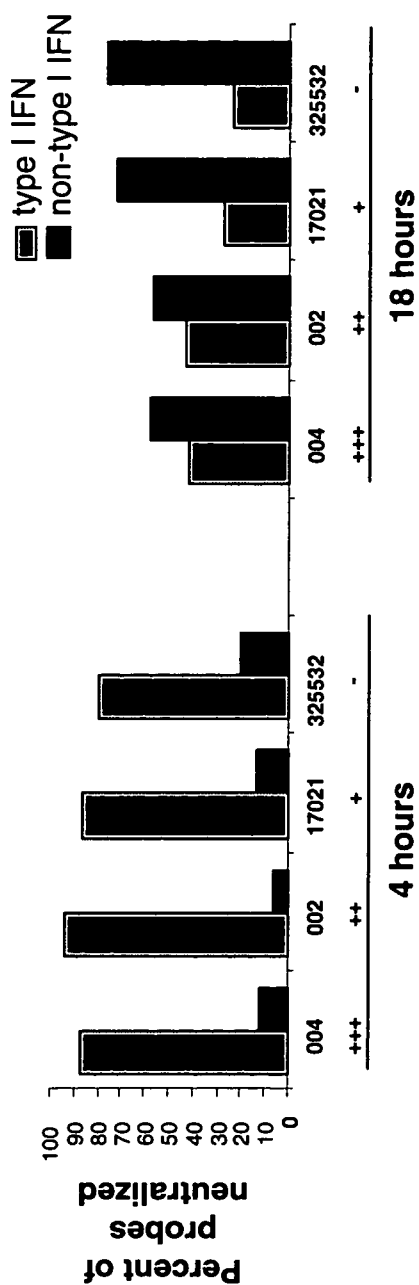


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Figure 71a



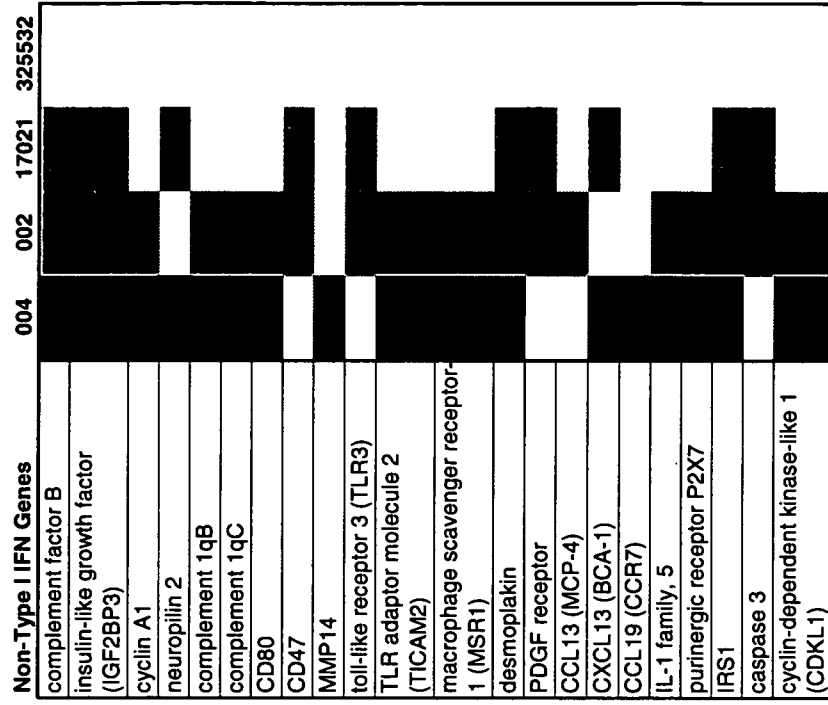
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Figure 71b

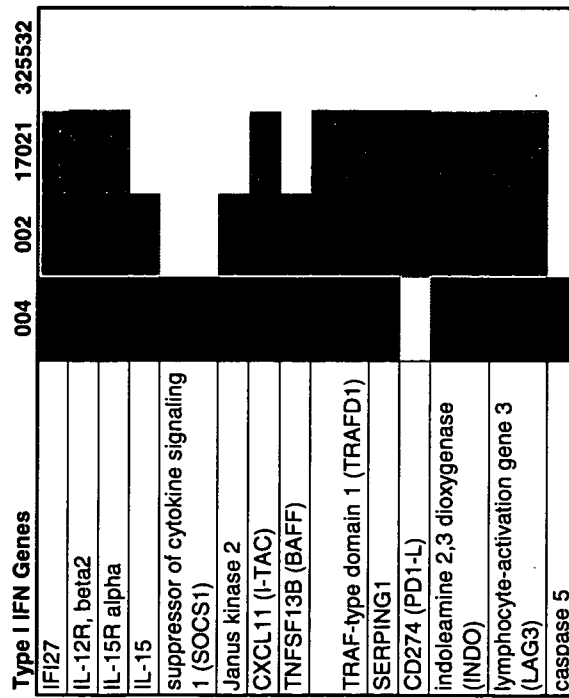


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Figure 72

b



a

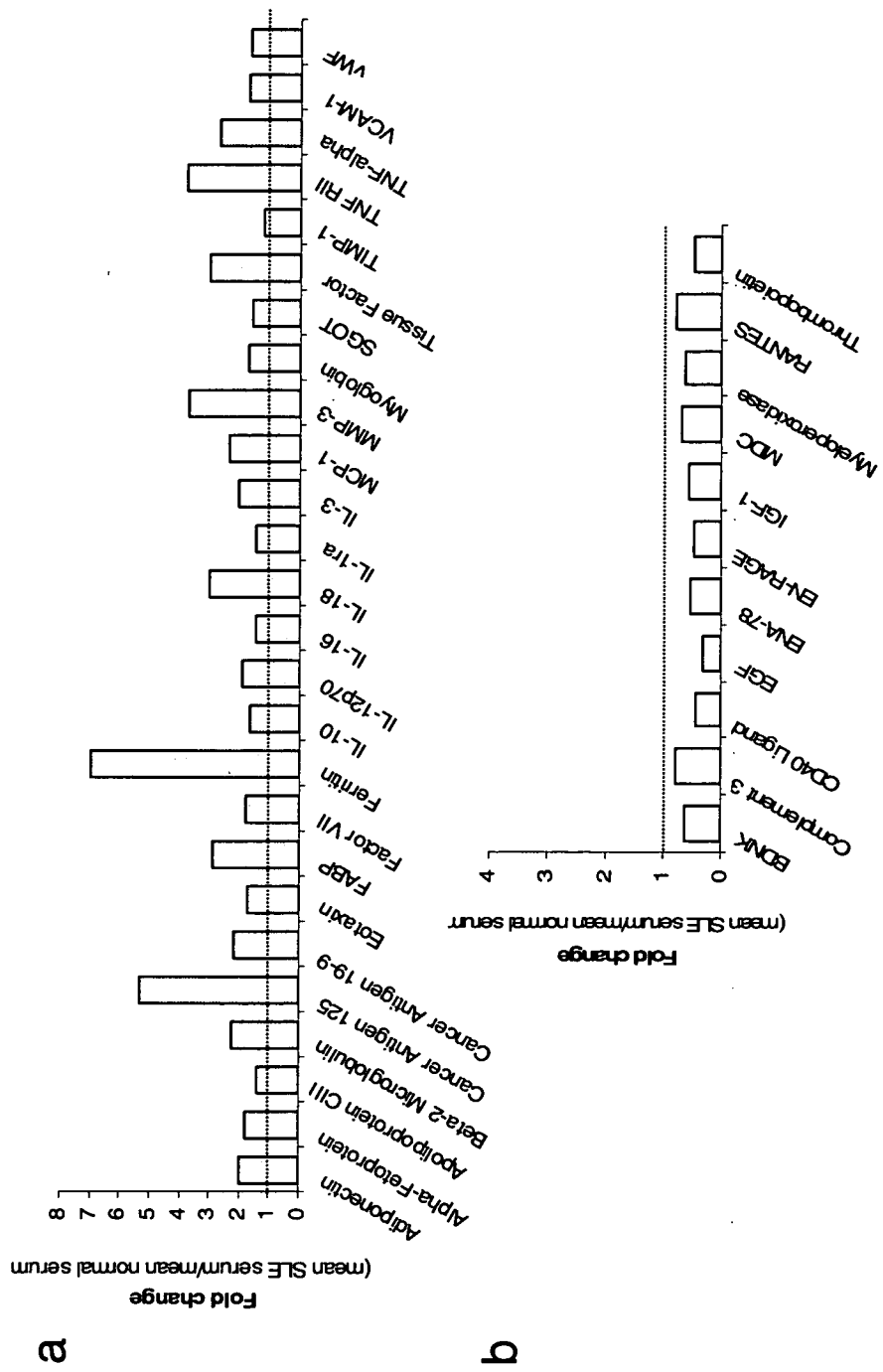


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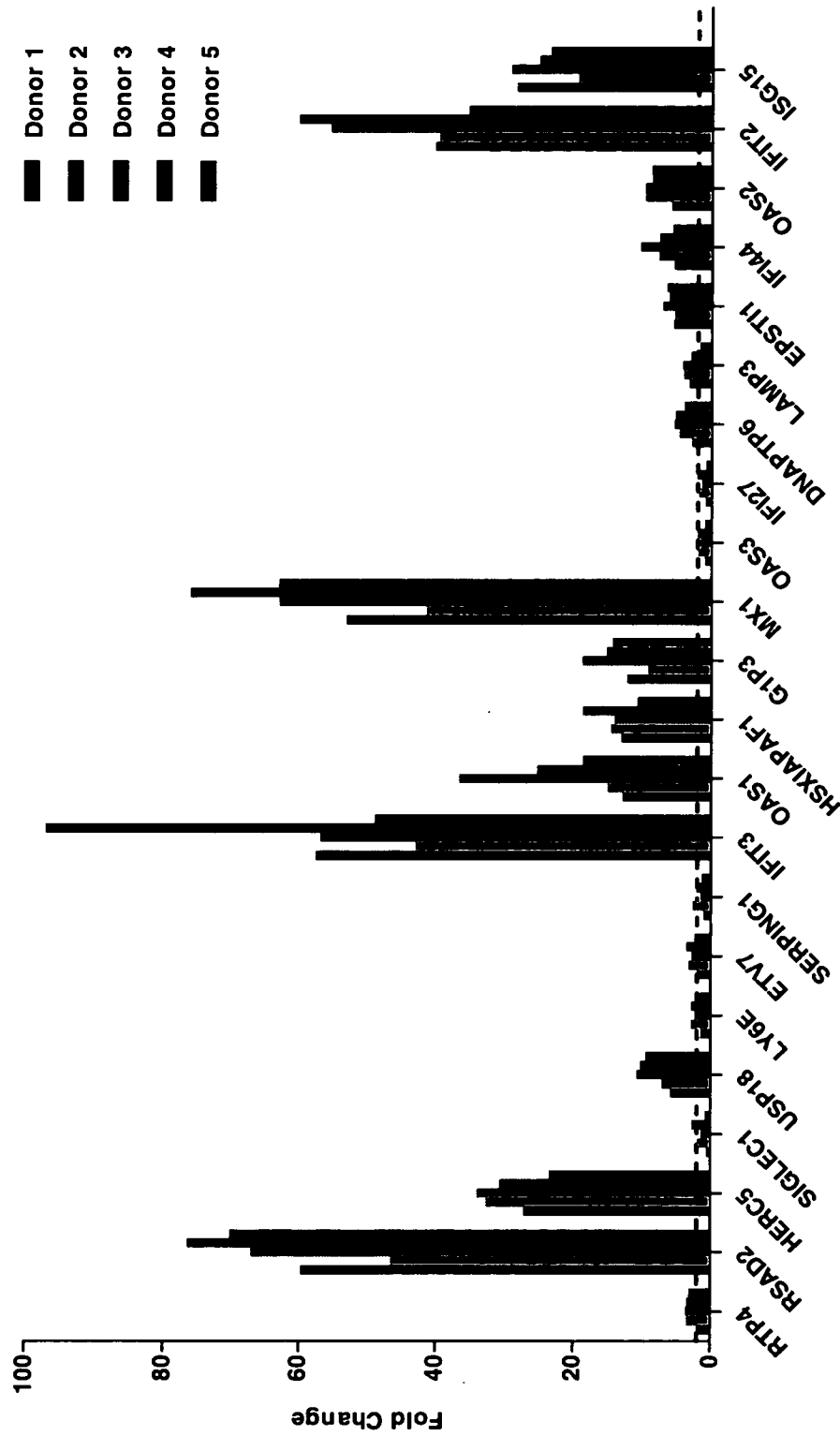
Figure 73

Pathway Map	Cell Process	# Genes
Caspases cascade	apoptosis and survival	3
Lymphotoxin-beta receptor signaling	apoptosis and survival	3
Leukocyte chemotaxis	cell adhesion	5
Endothelial cell contacts by junctional mechanisms	cell adhesion	2
Gap junctions	cell adhesion	6
IFN alpha/beta signaling pathway	cytokine and chemokine mediated signaling pathway	2
NF-AT signaling and leukocyte interactions	cytokine and chemokine mediated signaling pathway	5
NF-AT signaling in Cardiac Hypertrophy	disease	5
Alternative complement pathway	immune response	2
Antiviral actions of Interferons	immune response	3
MIF in innate immunity response	immune response	4
PGE2-induced pain processing	immune response	3
Classic complement pathway	immune response	3
Role of TLRs 3 and 4 in cell antiviral response	immune response	3
MIF-mediated glucocorticoid regulation	immune response	2
Leptin signaling via JAK/STAT and MAPK cascades	response to hormone stimulus	3
Role of AP-1 in regulation of cellular metabolism	transcription	3
Regulation of lipid metabolism via PPAR, RXR and VDR	transcription	2

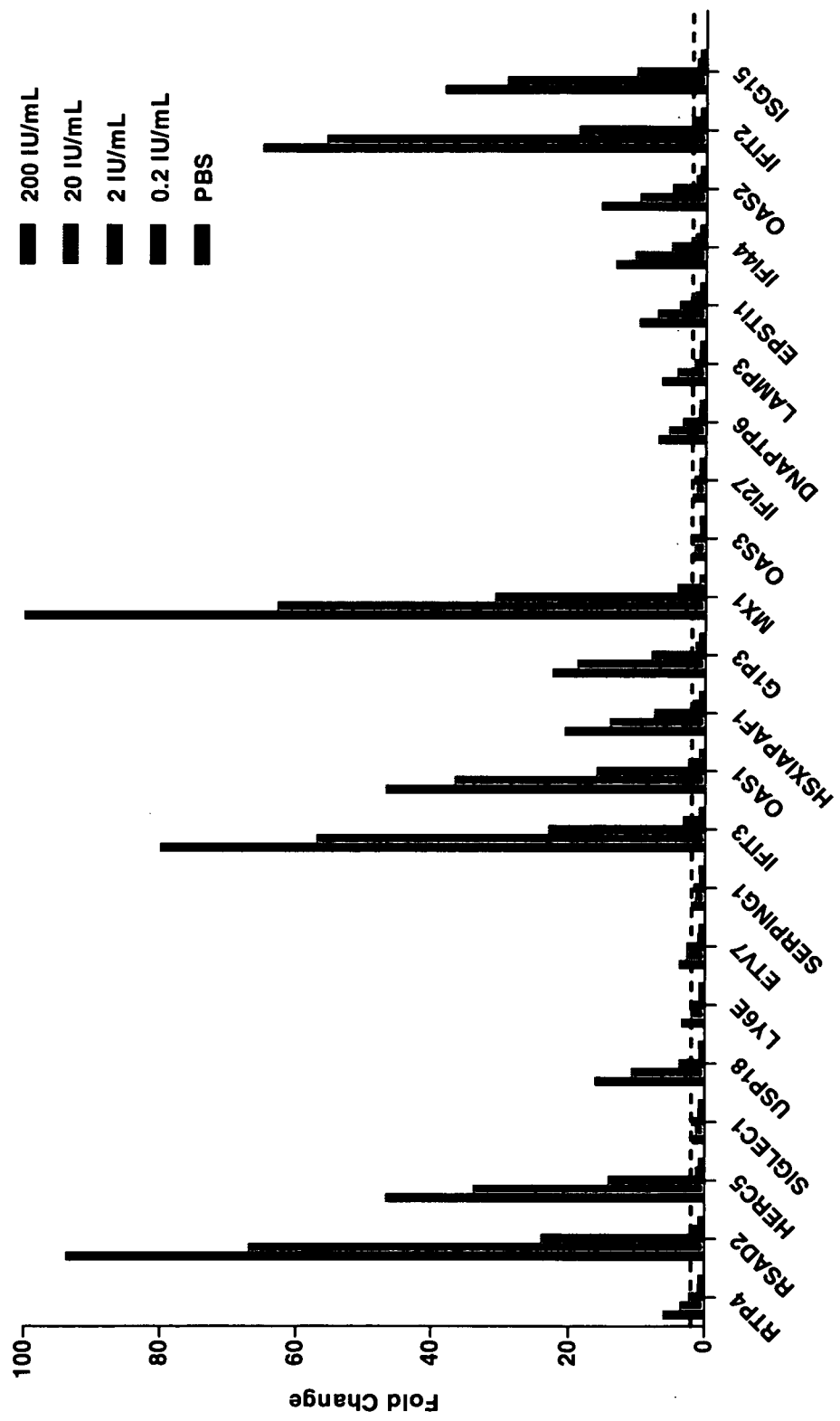
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Figure 74



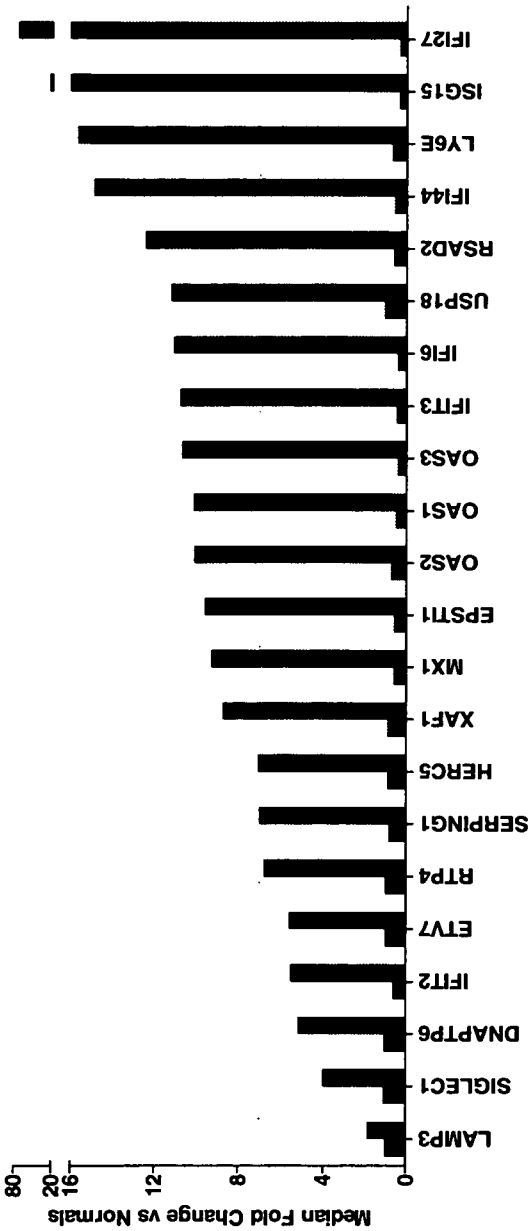
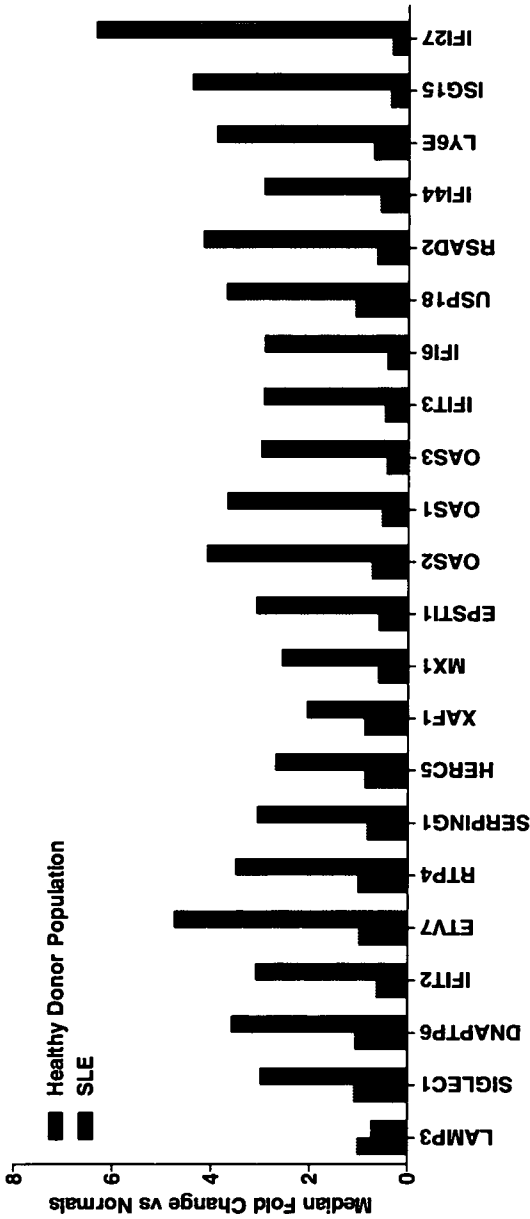
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Figure 75



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Figure 76

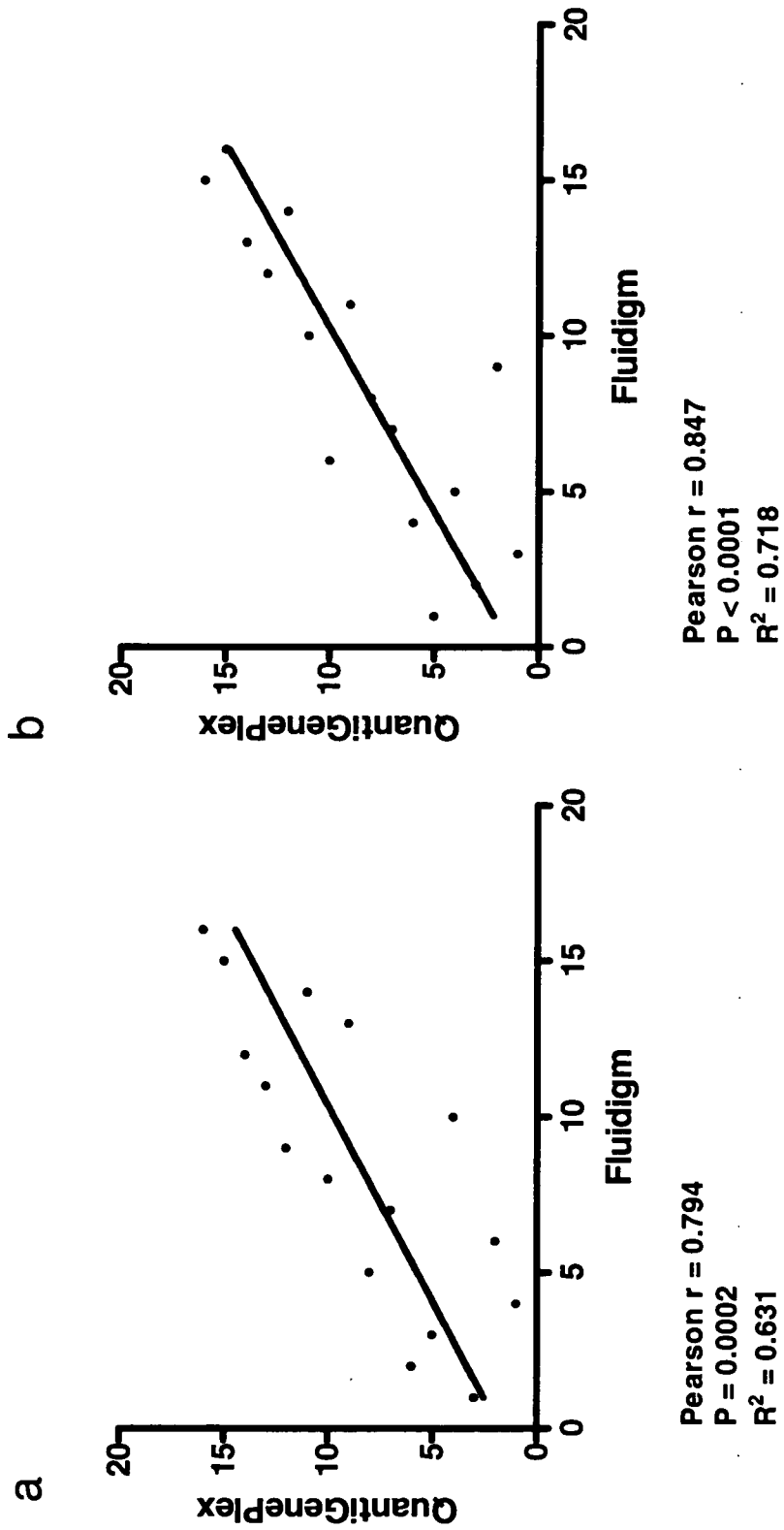


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Figure 77

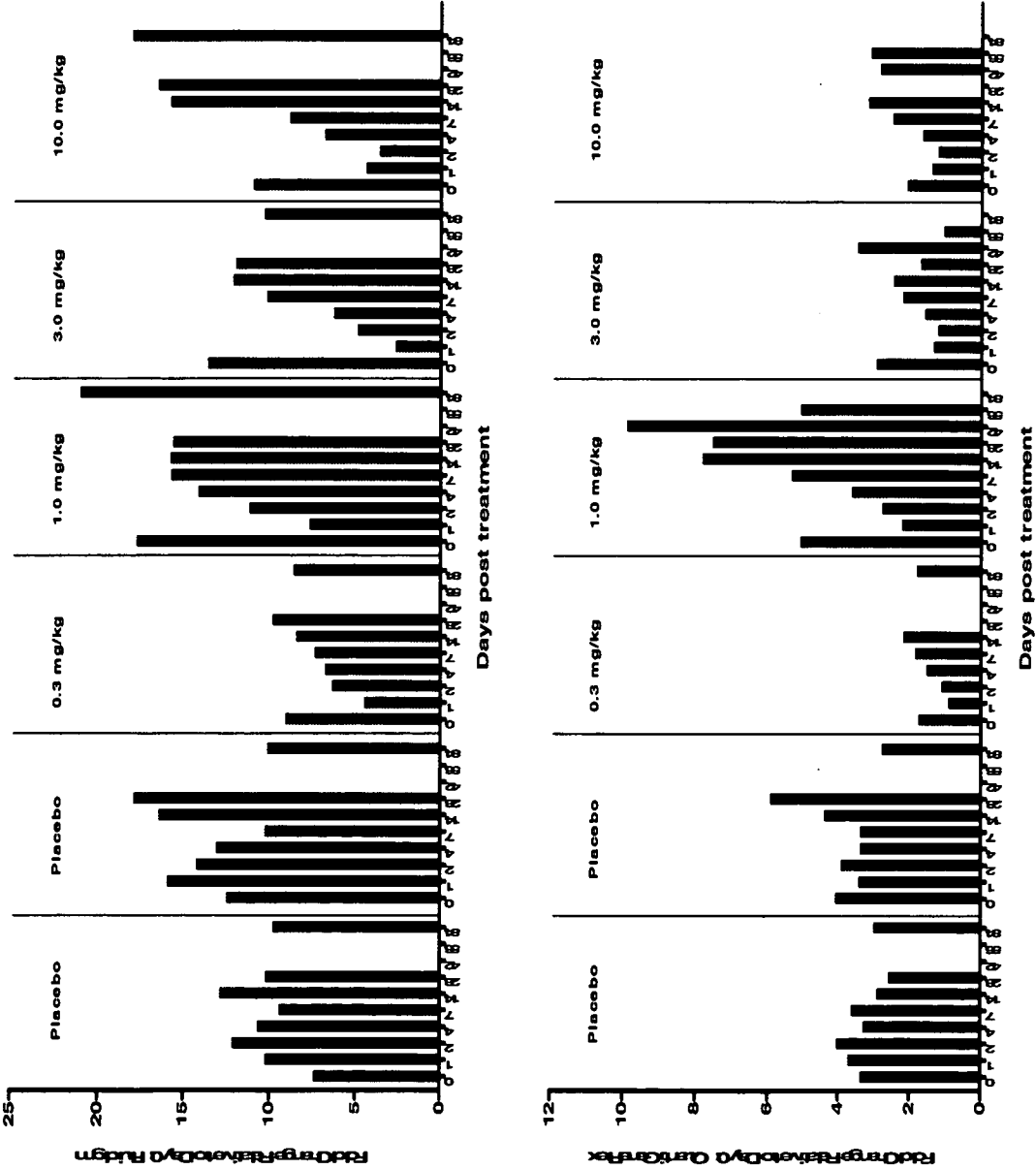


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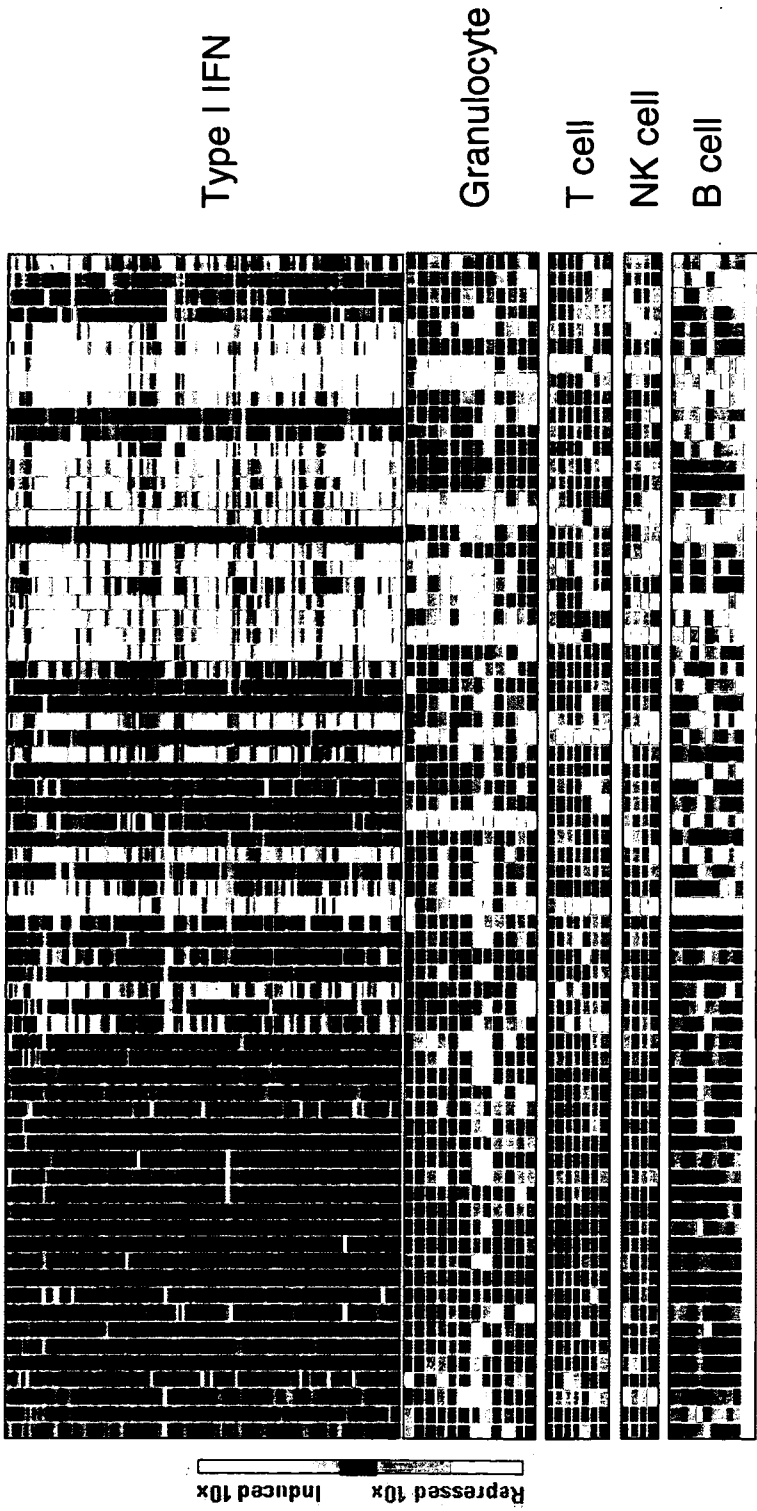
Figure 78



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Figure 79

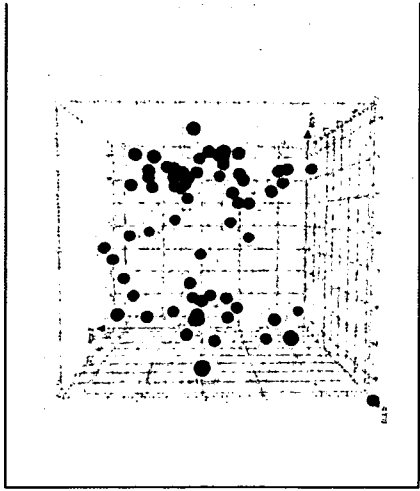


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Figure 80

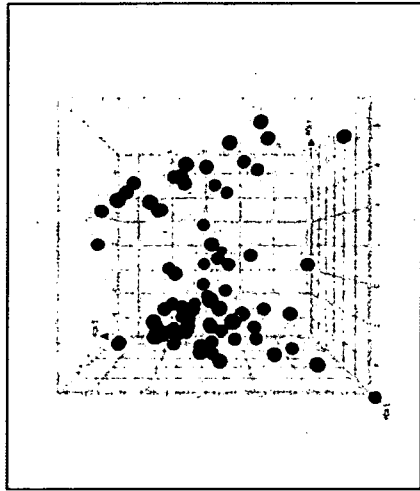


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Figure 81

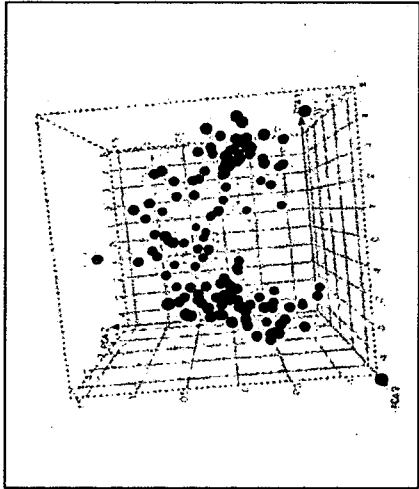
A.



B.

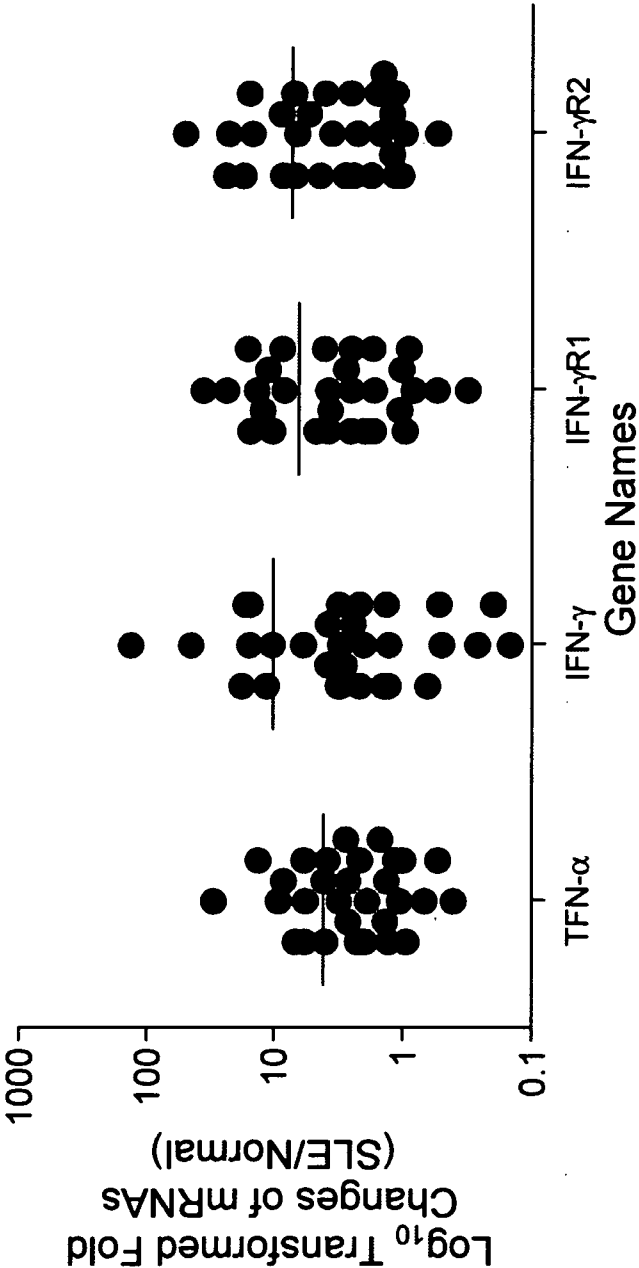


C.



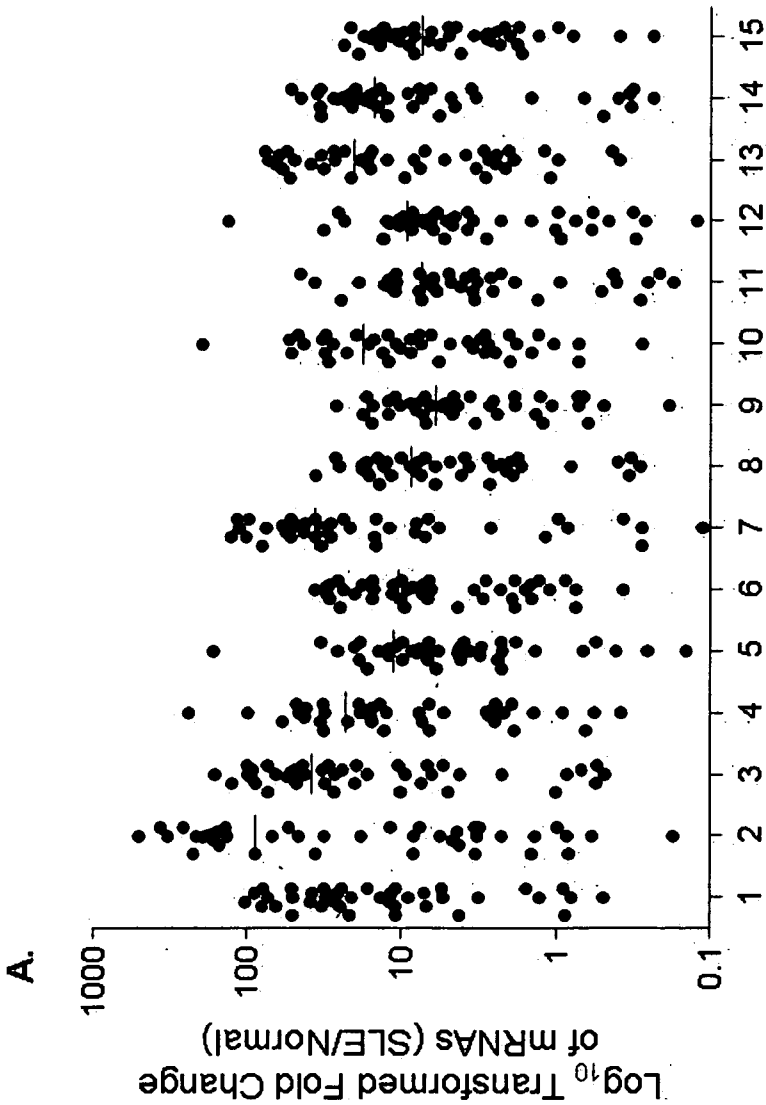
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Figure 82



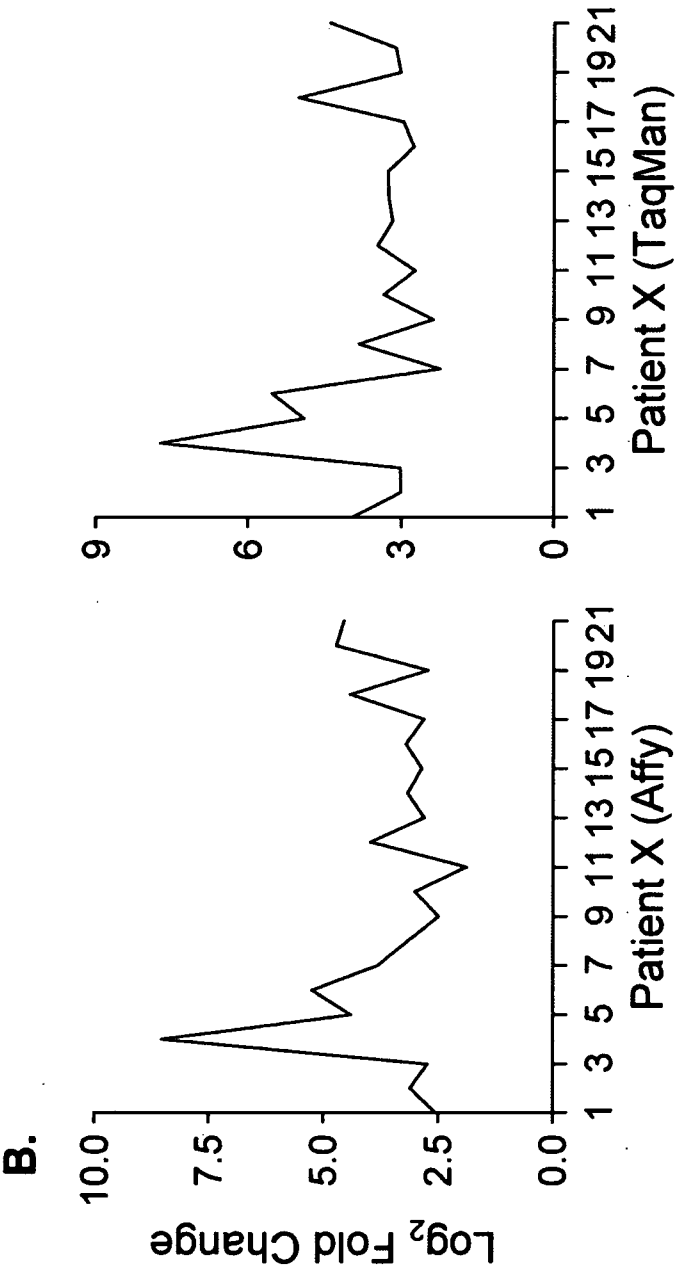
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Figure 83



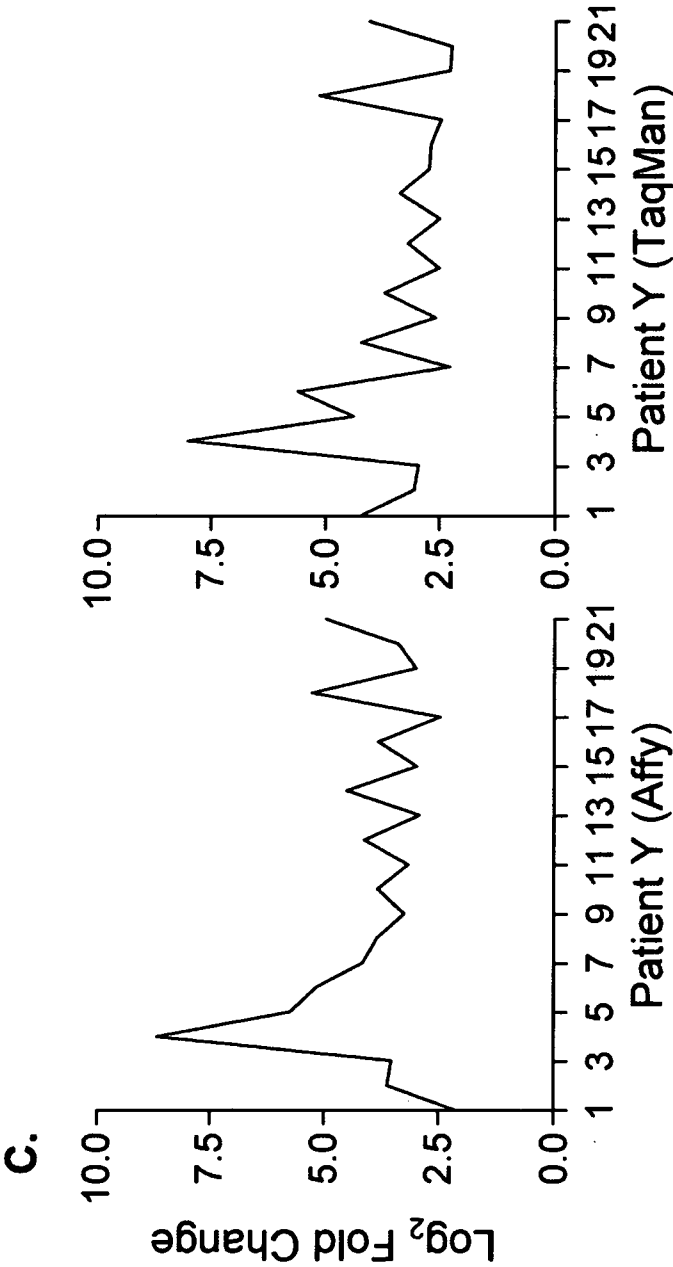
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Figure 83

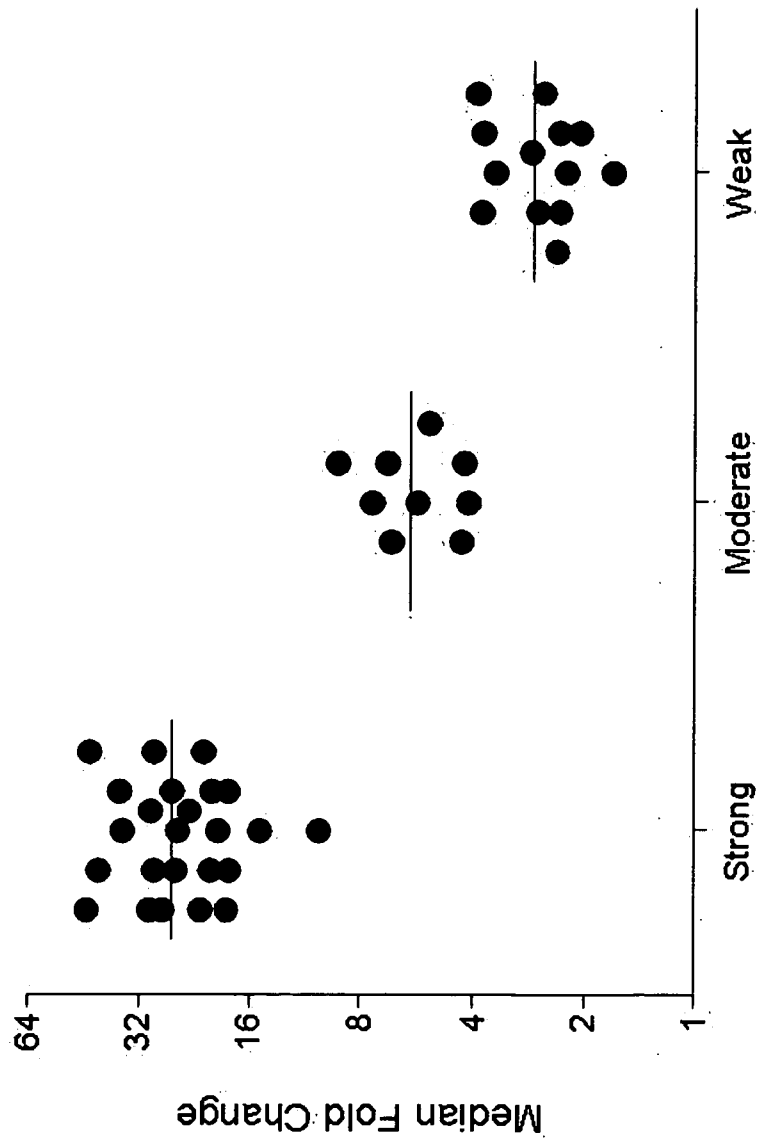


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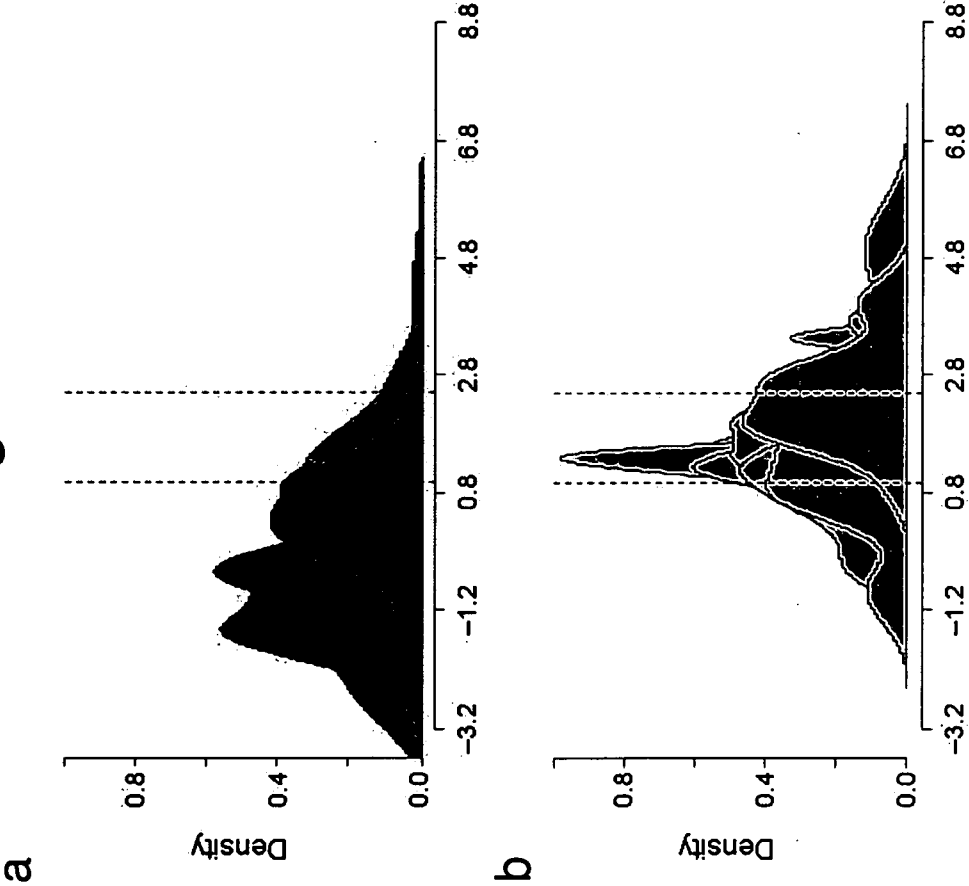
Figure 83



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Figure 84

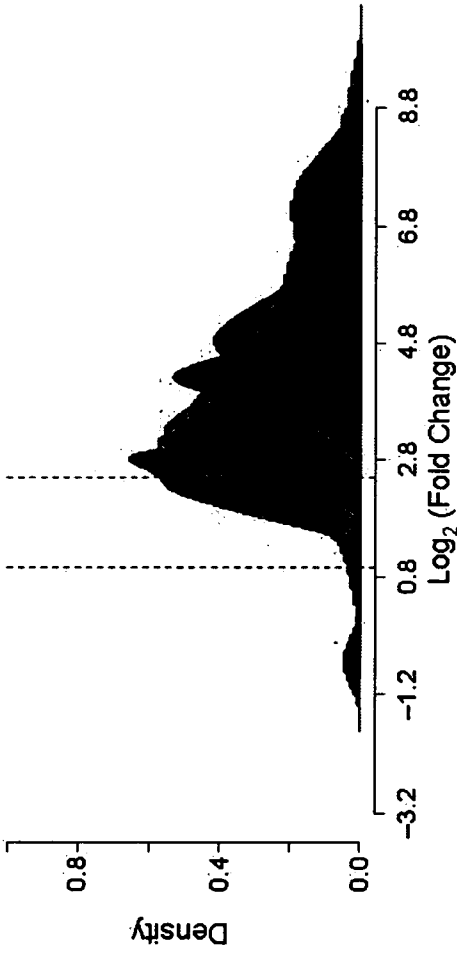


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Figure 85

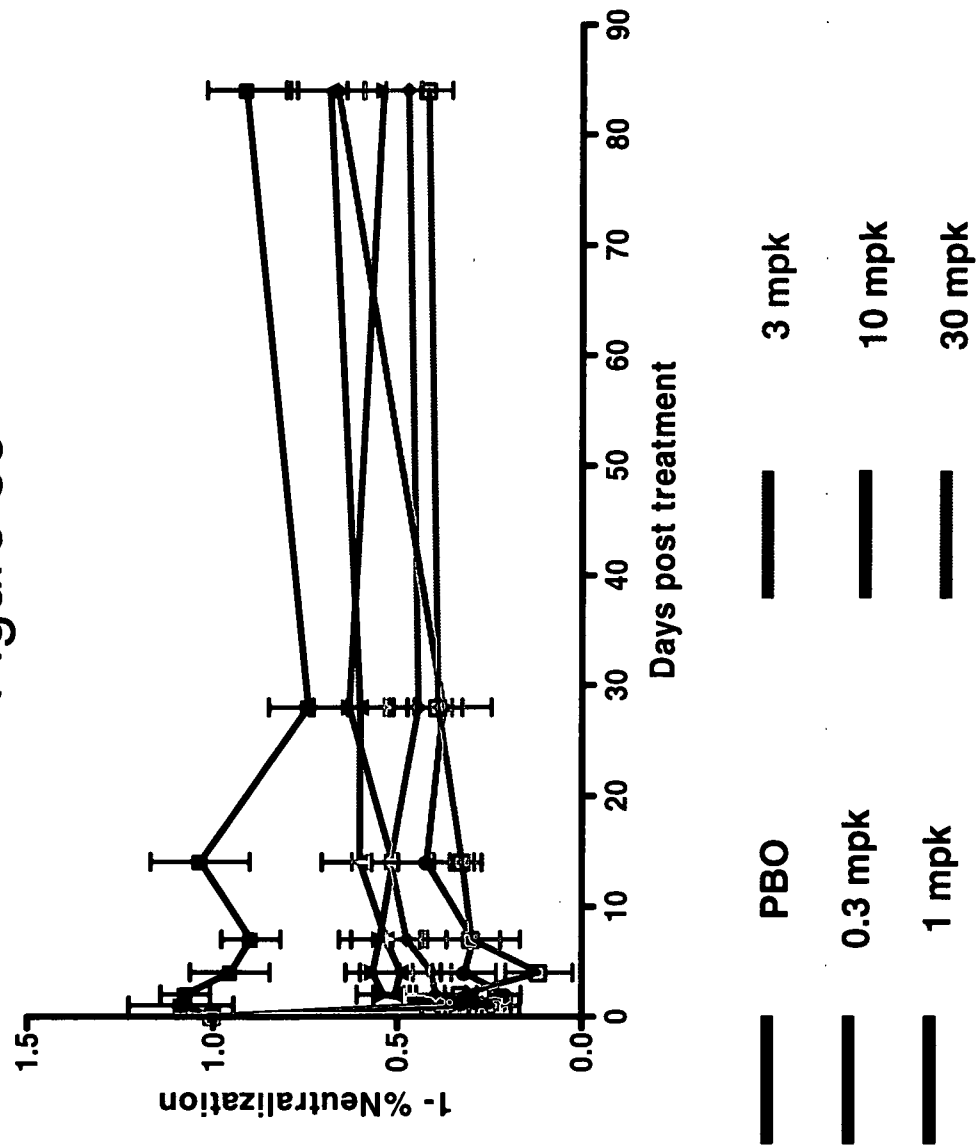


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Figure 85

C



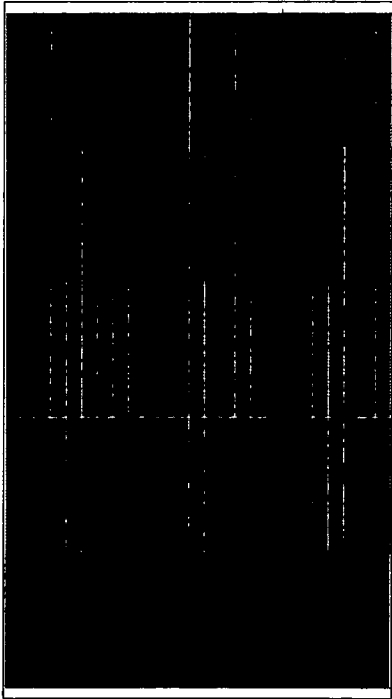
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Figure 86



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Figure 87

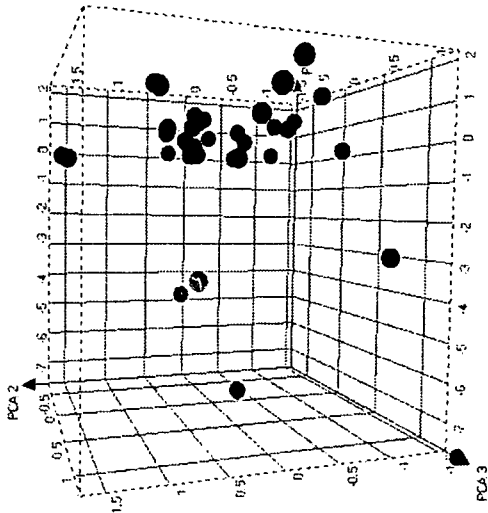
a



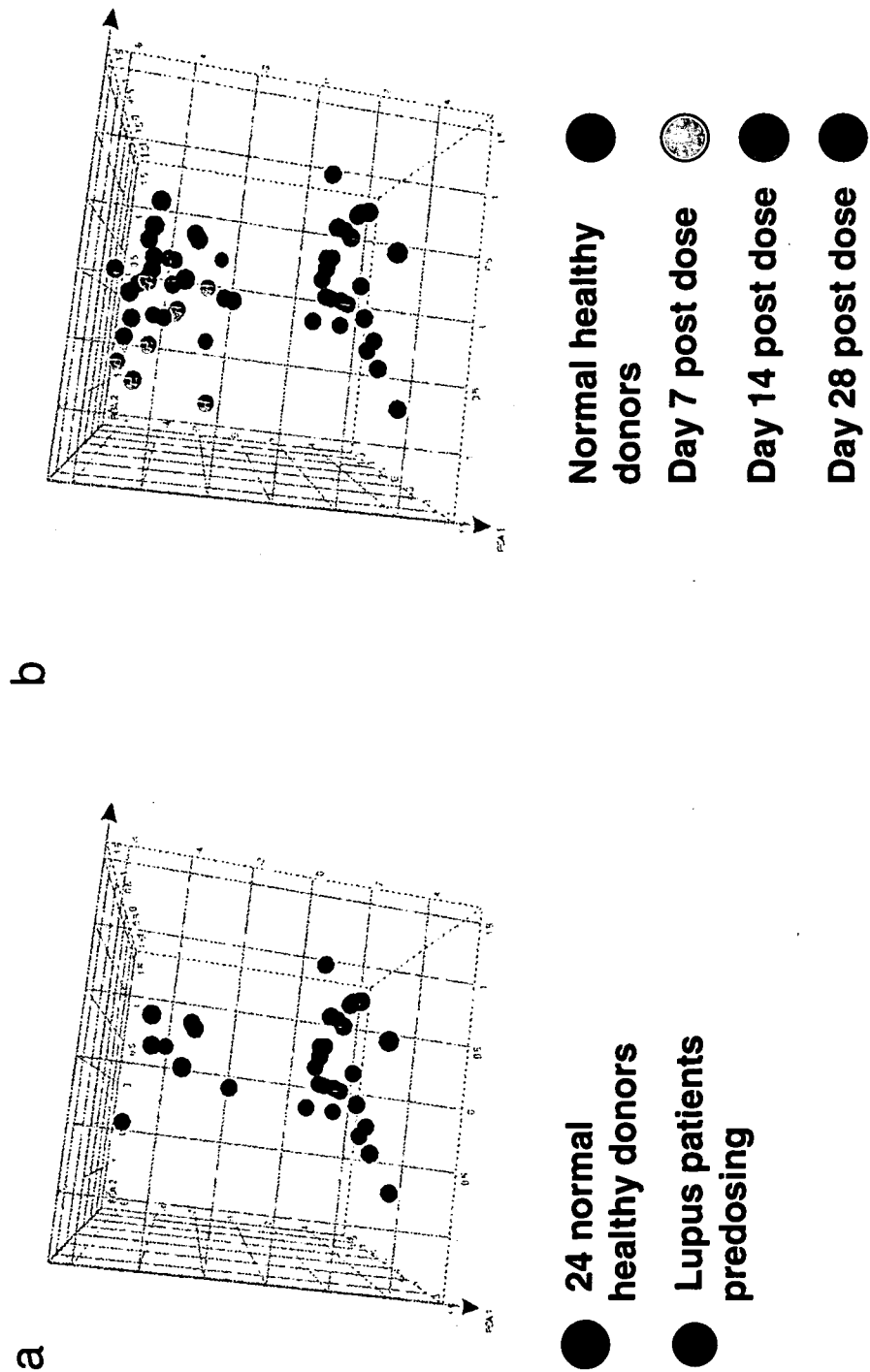
Day 0 1 4 7 14

100% Neutralization No neutralization

b



- Normal healthy donors
- Predosing
- Day 4
- Day 7
- Day 14
- Day 84



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Figure 89

	Day 1 (post dose)	Day 2 (post dose)	Day 4 (post dose)	Day 7 (post dose)	Day 14 (post dose)	Day 28 (post dose)	Day 84 (post dose)
	-1.06	-1.24	-0.81	-0.49	-0.73	-0.50	-0.60
	-2.49	-1.59	-1.18	-1.37	-1.58	-0.43	-1.54
	-0.07	0.01	-0.08	0.43	0.45	0.41	0.32
4144104	-0.31	-0.23	-0.09	0.02	-0.17	-0.28	0.03
4188204	0.14	-0.08	0.16	0.43	0.08	0.54	0.09
9475208	-0.25	-0.29	-0.05	0.04	-0.67	-0.22	-0.07
4141307	0.22	0.05	0.03	0.20	0.06	0.07	0.23
4144311	0.01	0.14	0.07	0.02	-0.01	0.89	0.13
4144408	-0.07	-0.04	0.06	-0.05	0.32	0.07	0.02
mean	-0.43	-0.36	-0.21	-0.09	-0.25	0.06	-0.16
SE	0.29	0.21	0.15	0.19	0.21	0.16	0.19
9635102	0.59	0.56	0.72	0.78	0.76	0.87	0.62
4144103	0.67	0.50	NA	0.49	0.46	0.36	0.30
4144107	0.53	0.30	0.22	0.32	0.20	0.24	0.13
4144110	0.47	0.52	0.57	0.09	0.20	0.24	0.10
9078105	0.56	0.46	0.35	0.38	0.19	0.10	0.10
mean	-0.57	-0.46	-0.47	-0.41	-0.36	-0.36	-0.25
SE	0.03	0.05	0.11	0.11	0.11	0.13	0.10
4141209	0.57	0.53	0.58	0.78	0.79	0.71	0.63
4169604	0.72	0.72	0.54	0.55	0.43	0.33	0.18
9642601	0.70	0.24	0.26	0.32	0.23	0.22	0.13
9642602	0.65	0.37	0.17	0.10	0.69	0.12	0.69
4142606	0.54	0.36	0.09	0.05	-0.12	0.01	-0.23
mean	0.63	0.44	0.33	0.36	0.40	0.28	0.28
SE	0.04	0.08	0.10	0.14	0.16	0.12	0.17
9475306	0.87	0.73	0.72	0.55	0.44	0.49	0.33
9649312	0.83	0.67	0.64	0.65	0.68	0.51	0.93
4144702	0.83	0.68	0.57	0.33	0.27	0.20	0.23
mean	0.84	0.69	0.64	0.51	0.46	0.40	0.50
SE	0.01	0.02	0.03	0.10	0.12	0.10	0.12
4140406	0.86	NA	NA	0.72	0.79	0.78	-0.03
4142409	0.81	0.74	0.61	0.48	0.43	NA	0.40
4142802	0.59	0.68	0.40	0.22	-0.41	-0.55	-0.66
4188803	0.77	0.77	0.83	0.80	0.71	0.45	0.33
4188804	0.82	0.84	0.84	0.81	0.71	0.70	0.34
mean	0.77	0.76	0.67	0.61	0.45	0.34	0.08
SE	0.05	0.03	0.11	0.11	0.22	0.31	0.20
4140504	0.77	0.72	0.97	0.82	0.68	0.58	0.57
4141903	0.81	0.74	0.54	0.29	0.29	0.61	NA
4144901	0.89	0.91	0.93	0.91	0.92	0.92	NA
mean	0.82	0.79	0.81	0.87	0.83	0.79	0.57
SE	0.03	0.03	0.03	0.03	0.03	0.03	0.03

Placebo

0.3 mg/kg 1 mg/kg

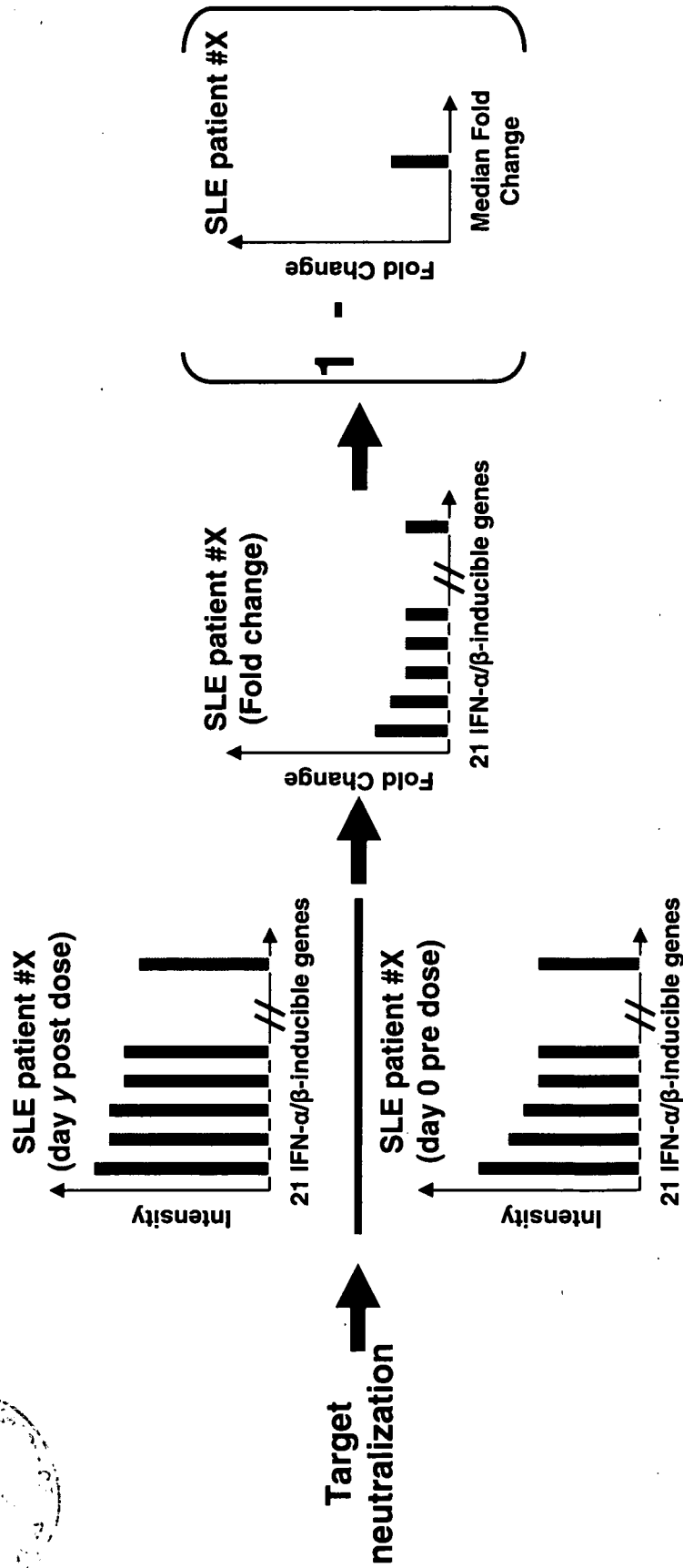
3 mg/kg

10 mg/kg

30 mg/kg

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Figure 90



median(1 - Day y/Day 0), where y is 1, 2, 4, 7, 14, 28, and 84 days.