

## METHODS OF TREATMENT USING AN ANTIBODY AGAINST INTERFERON GAMMA

## PRIORITY

This application claims the benefit of US Provisional Application Nos. 61/563,357, 61/616,846, and 61/651,900 filed November 23, 2011, March 28, 2012, and May 25, 2012, respectively, each of which are  
5 incorporated herein in their entirety.

## FIELD

This invention is in the field of methods of patient stratification and methods treatment using an interferon gamma (IFN- $\gamma$ ) inhibitor, as well as uses of IFN- $\gamma$  inhibitors.

## BACKGROUND

10 IFN- $\gamma$  plays an important role in regulating the immune system. It is a cytokine with pleiotropic effects and is thought to play a role in mediating various autoimmune diseases, as well as immune responses to infectious agents and cancer cells. See, e.g., Heremans et al., Develop. Biol. Standard., 71: 113-119, in Symposium on Monoclonal Antibodies for Therapy, Prevention and in vivo diagnosis of human disease, Utrecht, The Netherlands, 1989, S. Karger, Basel, 1990. Comparatively recent analyses of RNA and protein levels have  
15 yielded detailed information concerning the identities of collections of genes that are over- and under-expressed in biological samples from patients suffering from autoimmune diseases. For example, in patients suffering from a variety of autoimmune diseases, type I (i.e., IFN $\alpha$ , IFN $\beta$ , IFN $\omega$ , IFN $\epsilon$ , and IFN $\kappa$ ) and/or type II (i.e., IFN- $\gamma$ ) interferon-induced genes are overexpressed. Baechler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615; Mavragani et al. (2010), Arthr. & Rheum. 62(2): 392-401; Pietrzak et al. (2008), Clinica Chimica Acta 394: 7-21;  
20 van Baarsen et al. (2006), Genes and Immunity 7: 522-531; Reynier et al. (2010), Genes and Immunity 11: 269-278; Fiorentino (2008), Arch. Dermatol. 144(10): 1379-1382. In the case of systemic lupus erythematosus (SLE), overexpression of these genes correlates with clinical and laboratory measures of disease activity. See, e.g., Bauer et al. (2006), PLoS Medicine 3(12): 2274-2284; Bauer et al. (2009), Arthr. & Rheum. 60(10): 3098-3107; Baechler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615. Type I and type II interferons affect  
25 expression of a distinct, but overlapping, set of genes, and such effects may vary depending on the tissue examined. See, e.g., van Baarsen et al. (2006), Genes and Immunity 7: 522-531 and Baechler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615.

Selection of the right patient group and dosage and assessment of patient response to a particular dosage on an ongoing basis can be key factors in the successful use of an IFN- $\gamma$  inhibitor as a therapeutic for the  
30 treatment of autoimmune/inflammatory diseases. Many autoimmune/inflammatory diseases are episodic in nature and have variable clinical manifestations, and possibly also variable etiologies. Some of these diseases have long asymptomatic periods between symptoms or prior to the onset of symptoms. There is a need to determine whether a patient is a candidate for a particular treatment and/or whether an ongoing treatment is having the desired effects. Because of the biological variations between patients who are clinically diagnosed as  
35 having the same disease, it is possible that IFN- $\gamma$  inhibitors may be efficacious for some patients having a particular disease and not for others. Such variations have, for example, been observed in rheumatoid arthritis

patients, some of which respond to TNF inhibitors while others do not. See, e.g., Potter et al. (2010), Ann. Rheum Dis. 69: 1315-1320. Thus, it is highly desirable to distinguish patients for whom inhibition of IFN- $\gamma$  is likely to be helpful from those for whom it is not. Further, the optimal dosage and nature of a particular IFN- $\gamma$  inhibitor are likely to be important factors in the therapeutic suitability of a treatment, given the important role of IFN- $\gamma$  in resistance to infections, among other vital functions. Thus, there is a need to assess the efficacy and safety of various doses and/or frequencies of dosing in asymptomatic, as well as symptomatic, periods of a disease. Methods provided herein utilize current technologies for assessing gene expression at the RNA and protein levels to provide more refined and effective methods of treatment using inhibitors of IFN- $\gamma$ , of identifying optimal doses, and of identifying individuals who are likely to respond to treatment, and/or who are or are not responding to treatment.

#### SUMMARY

In a first aspect, the present invention refers to the use of a monoclonal anti-human interferon gamma (anti-huIFN- $\gamma$ ) antibody in the manufacture of a medicament for treating a patient suffering from an IFN- $\gamma$ -mediated disease, wherein the IFN- $\gamma$ -mediated disease is selected from the group consisting of systemic lupus erythematosus (SLE), lupus nephritis, inflammatory bowel disease, Crohn's disease and ulcerative colitis; and wherein the anti-huIFN- $\gamma$  antibody has a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO:34, a heavy chain complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO:36, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 wherein the monoclonal anti-human interferon gamma (anti-huIFN- $\gamma$ ) antibody is to be administered to the patient at a dose of at least about 20 milligrams to not more than about 200 milligrams. In another aspect the present invention refers to the use of an anti-huIFN- $\gamma$  antibody in the manufacture of a medicament for treating an SLE patient, wherein the anti-huIFN- $\gamma$  antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8 and wherein the monoclonal anti-huIFN- $\gamma$  antibody is to be administered to the patient at a dose of at least about 60 milligrams to not more than about 180 milligrams.

Also described herein are methods of treatment that include administration of an IFN- $\gamma$  inhibitor to a patient and determination of levels of one or more biomarkers in a biological sample from the patient before and/or after administration of the IFN- $\gamma$  inhibitor so as to assess the suitability as a treatment or the biological effects of the IFN- $\gamma$  inhibitor. Such methods can inform decisions as to whether to initiate or continue treatment with an IFN- $\gamma$  inhibitor. Also described are methods for distinguishing patients likely to benefit from treatment with an IFN- $\gamma$  inhibitor from those unlikely to benefit by assessing the levels of one or more biomarkers in a biological sample from a patient as compared to the levels of the same biomarkers in biological samples from a

healthy control group. Further described herein are methods of treatment that include the use of doses of an anti-IFN- $\gamma$  antibody within a specified range and/or at a specified frequency of dosing.

Herein is described a method of treating a patient suffering from an IFN- $\gamma$ -mediated disease comprising administering to the patient a monoclonal anti-human interferon gamma (anti-hulFN- $\gamma$ ) antibody at a dose, which  
5 can be from about 15 mg (mg) to about 300 mg or from about 30, 40, 50, or 60 mg to about 80, 120, 180, 200, 250, 300 or 400 mg, wherein expression at the RNA or protein level of one or more gene(s) listed in Table 1, 2, 4, 5, and/or 6 in a biological sample from the patient taken before the antibody is administered deviates from expression of that gene(s) in a control biological sample in a direction consistent with excess IFN- $\gamma$ . In addition, described herein is a use of a monoclonal anti-hulFN- $\gamma$  antibody as a medicament to treat a patient suffering  
10 from an IFN- $\gamma$ -mediated disease, wherein the dose of the antibody administered is from about 15, 30, 40, 50, or 60 milligrams to about 80, 120, 180, 200, 250, or 300 milligrams and wherein expression at the RNA or protein level of one or more gene(s) listed in Table 1, 2, 4, 5, and/or 6 in a biological sample taken from the patient taken before the antibody is administered deviates from expression of that gene(s) in a control biological sample in a

direction consistent with excess IFN- $\gamma$ . In some examples, the expression of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, or 40 genes listed in Table 1, 2, 4, 5, and/or 6 in the biological sample from the patient deviates from the expression of those genes in the control biological sample in a direction consistent with excess IFN- $\gamma$ . The biological sample from the patient can exhibit expression of one or more of the following human genes at the RNA or protein level that deviates from expression in the control biological sample in a direction consistent with excess IFN- $\gamma$ : indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity Ib, receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), serpin peptidase inhibitor clade B (ovalbumin), member 2 (SERPINB2), matrix metalloproteinase 19 (MMP19), radical S-adenosyl methionine domain containing 2 (RSAD2), heparin sulfate (glucosamine) 3-O-sulfotransferase 1 (HS3ST1), indoleamine 2,3-dioxygenase 2 (IDO2), programmed death ligand-1 (PD-L1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity Ib, receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274. In some examples, the biological sample from the patient can exhibit elevated expression at the RNA or protein level of GBP1 as compared to expression in the control biological sample. The IFN- $\gamma$ -mediated disease can be systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, psoriasis, or an inflammatory bowel disease, including Crohn's disease and ulcerative colitis. The dose of the anti-huIFN- $\gamma$  antibody can be from about 40 mg or 60 mg to about 300 mg, from about 20 mg or 80 mg to about 200 or 250 mg, from about 60 or 100 mg to about 180 mg, or about 40, 50, 60, 70, 80, 90, 100, 120, 150, or 180 mg. The anti-huIFN- $\gamma$  antibody can be administered subcutaneously or intravenously. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another example, described herein is a method for treating a patient having an IFN- $\gamma$ -mediated disease, for example SLE or an inflammatory bowel disease, with an IFN- $\gamma$  inhibitor comprising: (a) determining the level(s) of expression in a biological sample from the patient of one or more genes listed in Tables 1, 2, 4, 5, and/or 6 at the RNA or protein level, wherein level of expression of the same gene(s) in a control biological sample is known or determined; (b) comparing the level(s) of expression of the gene(s) in the biological sample from the patient and in the control biological sample; and (c) if the level(s) of expression of the gene(s) in the biological sample from the patient deviate from the levels of expression of the gene(s) in the control biological sample in a direction consistent with excess IFN- $\gamma$ , administering to the patient a therapeutically effective dose of an IFN- $\gamma$  inhibitor. In addition, described herein is a use of an IFN- $\gamma$  inhibitor as a medicament to treat a patient having an IFN- $\gamma$ -mediated disease, for example SLE or an inflammatory bowel disease, (a) wherein the level(s) of expression in a biological sample from the patient of one or more gene(s) listed in Tables 1, 2, 4, 5, and/or 6 at

the RNA or protein level is determined, (b) wherein the level(s) of expression of the same gene(s) in a control biological sample is known or determined, (c) wherein the level(s) of expression of the same gene(s) in the biological sample from the patient and the control biological sample are compared, and (d) wherein if the level(s) of expression of the gene(s) in the biological sample from the patient deviate from the levels of expression of the gene(s) in the control biological sample in a direction consistent with excess IFN- $\gamma$ , a therapeutically effective

5

dose of the IFN- $\gamma$  inhibitor is administered. The one or more genes listed in Tables 1, 2, 4, 5, and/or 6 of (a) can include at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, or 40 genes. The IFN- $\gamma$  inhibitor can be a human or humanized anti-hulFN- $\gamma$  antibody. The dose of the anti-hulFN- $\gamma$  antibody administered can be from about 15, 30, or 60 mg to about 300 mg, from about 20, 40, or 80 mg to about 250 mg, or from about 40, 50, or 60 mg to about 120, 150, 180 or 200 mg. The patient can have discoid lupus, lupus nephritis, psoriasis, ulcerative colitis, or Crohn's disease. The biological sample from the patient can exhibit expression of one or more of the following genes at the RNA or protein level that deviates from expression in the control biological sample in a direction consistent with excess IFN- $\gamma$ : indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity IgG receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), serpin peptidase inhibitor clade B (ovalbumin), member 2 (SERPINB2), matrix metalloproteinase 19 (MMP19), radical S-adenosyl methionine domain containing 2 (RSAD2), heparin sulfate (glucosamine) 3-O-sulfotransferase 1 (HS3ST1), indoleamine 2,3-dioxygenase 2 (IDO2), programmed death ligand-1 (PD-L1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity IgG receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274. The IFN- $\gamma$  inhibitor can be an anti-hulFN- $\gamma$  antibody that has a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO:34, a heavy chain complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another example, described herein is method for identifying a patient having an IFN- $\gamma$ -mediated disease who can benefit from treatment with an IFN- $\gamma$  inhibitor comprising: (a) determining the level(s) of expression in a biological sample from the patient of one or more of one of the genes listed in Table 1, 2, 4, 5, and/or 6 at the RNA or protein level, wherein level(s) of expression of the same gene(s) in a control biological sample is known or determined; (b) comparing the levels of expression of the gene(s) in the biological sample from the patient and in the control biological sample; and (c) if the level(s) of expression of the gene(s) in the biological sample from the patient deviate from the level(s) in the control biological sample in a direction consistent with excess IFN- $\gamma$ , determining that the patient can benefit from treatment with an IFN- $\gamma$  inhibitor and/or administering a therapeutically effective dose of an IFN- $\gamma$  inhibitor. The one or more genes listed in

Tables 1, 2, 4, 5, and/or 6 of (a) can include at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, or 40 genes. The one or more genes can be from Table 1, 2, 4, 5, or 6. In addition, described herein is a use of an IFN- $\gamma$  inhibitor as a medicament for treating a patient having an IFN- $\gamma$ -mediated disease, wherein the level(s) of expression in a biological sample from the patient of one or more of one of the genes listed in Table 1, 2, 4, 5, and/or 6 is determined at the RNA or protein level, wherein the level(s) of expression of the same gene(s) in a control biological sample is known or determined; wherein the level(s) of expression of the gene(s) in the biological sample from the patient and in the control biological sample are compared; and wherein if the level(s) of expression of the gene(s) in the biological sample from the patient deviate from the level(s) in the control biological sample in a direction consistent with excess IFN- $\gamma$ , determining that the patient can benefit from treatment with an IFN- $\gamma$  inhibitor and/or administering a therapeutically effective dose of an IFN- $\gamma$  inhibitor. The IFN- $\gamma$  inhibitor can be an anti-human IFN- $\gamma$  antibody, for example an antibody comprising the amino acid sequences of SEQ ID NOs: 6 and 8, 10 and 12, 14, and 16, 14 and 31, or 30 and 12. The therapeutically effective dose can be from 60 mg to 500 mg, from 80 mg to 400 mg, from 100 mg to 350 mg, from 60 mg to 180 mg, or from 120 mg to 300 mg. The IFN- $\gamma$ -mediated disease can be SLE including discoid lupus and lupus nephritis, an inflammatory bowel disease including Crohn's disease and ulcerative colitis, or psoriasis, among other IFN- $\gamma$ -mediated diseases disclosed herein. The gene(s) can include one or more of the following genes: indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity IgG, receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), serpin peptidase inhibitor clade B (ovalbumin), member 2 (SERPINB2), matrix metalloproteinase 19 (MMP19), radical S-adenosyl methionine domain containing 2 (RSAD2), heparin sulfate (glucosamine) 3-O-sulfotransferase 1 (HS3ST1), indoleamine 2,3-dioxygenase 2 (INDO2), programmed death ligand-1 (PD-L1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity IgG, receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

Further described herein is a method for treating a patient suffering from an IFN- $\gamma$ -mediated disease comprising: (a) determining the level(s) of expression at the RNA or protein level in a biological sample from the patient of one or more of the genes in Table 1, 2, 4, 5, and/or 6; (b) then administering to the patient a pharmacodynamically effective dose of an IFN- $\gamma$  inhibitor, for example an anti-human IFN- $\gamma$  antibody; (c) then determining the level of expression of the gene(s) of step (a) in a biological sample from the patient; and (d) if the level(s) of expression of the gene(s) determined in step (c), as compared to the level(s) of expression determined in step (a), is modulated in a direction consistent with inhibition of IFN- $\gamma$ , then continuing treatment of the patient

with another pharmacodynamically effective dose of the IFN- $\gamma$  inhibitor. The one or more genes listed in Tables 1, 2, 4, 5, and/or 6 of (a) can include at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, or 40 genes. In addition, described herein is the use of an IFN- $\gamma$  inhibitor antibody, for example an anti-huIFN- $\gamma$  antibody, as a medicament for treating a patient suffering from an IFN- $\gamma$ -mediated disease, wherein (a) the level of expression at the RNA or protein level in a biological sample from the patient of one or more of the genes in Table 1, 2, 4, 5, and/or 6 is determined, (b) then a pharmacodynamically effective dose of the IFN- $\gamma$  inhibitor is administered to the patient, (c) then the level(s) of expression of the gene(s) of step (a) in a biological sample from the patient is determined, and (d) if the level(s) of expression of the gene(s) determined in step (c), as compared to the level(s) of expression determined in step (a), is modulated in a direction consistent with inhibition of IFN- $\gamma$ , then continuing treatment of the patient with another pharmacodynamically effective dose of the IFN- $\gamma$  inhibitor. For an IFN- $\gamma$  inhibitor that is an anti-huIFN- $\gamma$  antibody, the pharmacodynamically effective dose can be from about 15, 30, or 60 mg to about 300 mg, from about 20, 40, or 80 mg to about 250 mg, or from about 60 mg to about 180 or 220 mg. The IFN- $\gamma$ -mediated disease can be selected from the group consisting of SLE, lupus nephritis, discoid lupus, psoriasis, and inflammatory bowel diseases including ulcerative colitis and Crohn's disease. The human genes whose level(s) of expression are determined in (a) and (c) can be selected from the group consisting of: indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity IgG1b, receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), serpin peptidase inhibitor clade B (ovalbumin), member 2 (SERPINB2), matrix metalloproteinase 19 (MMP19), radical S-adenosyl methionine domain containing 2 (RSAD2), heparin sulfate (glucosamine) 3-O-sulfotransferase 1 (HS3ST1), indoleamine 2,3-dioxygenase 2 (IDO2), programmed death ligand-1 (PD-L1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity IgG1b, receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274.

In another example, a method is described for treating a patient suffering from an IFN- $\gamma$ -mediated disease, for example SLE, lupus nephritis, discoid lupus, psoriasis, or an inflammatory bowel disease, with an IFN- $\gamma$  inhibitor, for example an anti-huIFN- $\gamma$  antibody, comprising the following steps: (a) determining the level(s) of expression at the RNA or protein level of one or more genes listed in Tables 1, 2, 4, 5, and/or 6 in a biological sample from the patient; (b) thereafter administering a pharmacodynamically effective dose of the IFN- $\gamma$  inhibitor to the patient; (c) thereafter determining the level(s) of expression of the gene(s) of (a) in a second biological sample from the patient; and (d) if the level(s) of expression of the gene(s) in second biological sample of (c) is substantially the same as that in the biological sample of (a) or if the level of expression of the gene(s) in second biological sample of (c) deviates from the level of expression in the biological sample of (a) in a direction

that is consistent with an excess of IFN- $\gamma$ , then treatment with the IFN- $\gamma$  inhibitor can be discontinued. In another example, described herein is a use of an IFN- $\gamma$  inhibitor, for example an anti-huIFN- $\gamma$  antibody, as a medicament for treating a patient suffering from an IFN- $\gamma$ -mediated disease, wherein (a) the level(s) of expression at the RNA or protein level of one or more genes listed in Tables 1, 2, 4, 5, and/or 6 in a biological sample from the patient

5 can be determined; (b) thereafter a pharmacodynamically effective dose of the IFN- $\gamma$  inhibitor can be administered to the patient; (c) thereafter the level(s) of expression of the gene(s) of (a) in a second biological sample from the patient can be determined; and (d) if the level(s) of expression of the gene(s) in second biological sample of (c) is substantially the same as that in the biological sample of (a) or if the level of expression of the gene(s) in second biological sample of (c) deviates from the level of expression in the biological

10 sample of (a) in a direction that is consistent with an excess of IFN- $\gamma$ , then the treatment with the IFN- $\gamma$  inhibitor can be discontinued. The one or more genes listed in Tables 1, 2, 4, 5, and/or 6 of (a) can include at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 25, 30, 35, or 40 genes. Where the IFN- $\gamma$  inhibitor is an anti-huIFN- $\gamma$  antibody, the pharmacodynamically effective dose can be from about 15, 30, or 60 mg to about 80, 100, 120, 150, 200, 250, or 300 mg, from about 20, 40, or 80 mg to about 90, 100, 120, 150, 180, or 250 mg, or from about

15 60 mg to about 180 or 220 mg. The patient can be suffering from systemic lupus erythematosus, lupus nephritis and/or discoid lupus. The patient can be suffering from psoriasis or an inflammatory bowel disease, including Crohn's disease or ulcerative colitis. The genes whose level(s) of expression are determined in (a) and (c) can be selected from the group consisting of: indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity IgG receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), serpin peptidase inhibitor clade B (ovalbumin), member 2 (SERPINB2), matrix metalloproteinase 19 (MMP19), radical S-adenosyl

20 methionine domain containing 2 (RSAD2), heparin sulfate (glucosamine) 3-O-sulfotransferase 1 (HS3ST1), indoleamine 2,3-dioxygenase 2 (IDO2), programmed death ligand-1 (PD-L1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity IgG receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide,

25 methotrexate, or an anti-malarial can be administered concurrently with the antibody.

30

Any of the methods or uses described above or below that utilize an anti-huIFN- $\gamma$  antibody can utilize an anti-huIFN- $\gamma$  antibody which can have a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the

35 amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid

sequence of SEQ ID NO:43 or SEQ ID NO:44. In specific examples, the heavy chain CDR3 can comprise the amino acid sequence of SEQ ID NO:36, the light chain CDR1 can comprise the amino acid sequence of SEQ ID NO:38, the light chain CDR2 can comprise the amino acid sequence of SEQ ID NO:41, and the light chain CDR3 can comprise the amino acid sequence of SEQ ID NO:43. The heavy chain variable region of the antibody can  
5 comprise the amino acid sequence of SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, or SEQ ID NO:30, and the light chain variable region of the antibody can comprise the amino acid sequence of SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, or SEQ ID NO:31. The heavy chain variable region can comprise the amino acid sequence of SEQ ID NO:6, and the light chain variable region comprises the amino acid sequence of SEQ ID NO:8. The heavy chain variable region can comprise the amino acid sequence of SEQ ID NO:10, and the light  
10 chain variable region can comprise the amino acid sequence of SEQ ID NO:12. The heavy chain variable region can comprise the amino acid sequence of SEQ ID NO:14, and the light chain variable region can comprise the amino acid sequence of SEQ ID NO:16. The heavy chain variable region can comprise the amino acid sequence of SEQ ID NO:30, and the light chain variable region can comprise the amino acid sequence of SEQ ID NO:12. The heavy chain variable region can comprise the amino acid sequence of SEQ ID NO:14, and the light chain  
15 variable region can comprise the amino acid sequence of SEQ ID NO:31. The anti-huIFN- $\gamma$  antibody can be a human, humanized, or chimeric antibody of the IgG, IgM, IgE, IgD, or IgA isotype. The anti-huIFN- $\gamma$  antibody can be an IgG1, IgG2, IgG3, or IgG4 antibody.

In another example, herein is described a method for treating a patient suffering from an IFN- $\gamma$ -mediated disease comprising administering to the patient a dose of an anti-IFN- $\gamma$  antibody such that the  
20 concentration of total IFN- $\gamma$  protein in the patient's serum is maintained at a plateau concentration for at least about two weeks following administration of the antibody, wherein the antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8. The dose can comprise at least about 20, 40, 60, or 80 milligrams and not more than 100, 200, 300, 400, or 500 milligrams of an anti-IFN- $\gamma$  antibody. The plateau concentration can be maintained for at least about 3, 4, 5, 6, or 8 weeks after the antibody is administered. The  
25 plateau concentration of IFN- $\gamma$  protein in the patient's blood can be from about 100 pg/mL to about 2000 pg/mL and/or at least about 200 or 300 pg/mL. The anti-IFN- $\gamma$  antibody can comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light  
30 chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44. The anti-IFN- $\gamma$  antibody can comprise the amino acid sequences of SEQ ID NOs: 6 and 8, SEQ ID NOs: 10 and 12, SEQ ID NOs: 14 and 16, SEQ ID NOs: 30 and 12, or SEQ ID NOs: 14 and 31. The dose of the anti-IFN- $\gamma$  antibody can be at least about 20, 40, 60, 80, 100, 150, 180, 200, 220, or 250 mg and/or not more than 180, 200, 220, 240, 260, 280, 300, 350, 400, 450, or 500  
35 mg and can be administered subcutaneously or intravenously. The level of IFN- $\gamma$  in the patient's serum can remain above about 100, 200, 250, 300, or 350 picograms per milliliter for at least about 14, 16, 18, 20, 25, 30, 35, 40, 45, or 50 days

subsequent to a single dose. The IFN- $\gamma$ -mediated disease can be psoriasis, SLE, lupus nephritis, discoid lupus, or an inflammatory bowel disease such as Crohn's disease or ulcerative colitis. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

Also herein is described a method for identifying a patient that can benefit from treatment with an IFN- $\gamma$  inhibitor comprising the following steps: obtaining a biological sample from the patient; determining the levels of IFN- $\gamma$  protein in the biological sample; and comparing the levels of IFN- $\gamma$  protein in the biological sample from the patient with the levels determined in a control biological sample; wherein if the levels of total IFN- $\gamma$  protein in the biological sample from the patient are higher than those in the control biological sample, then the patient is identified as a patient that may benefit from treatment with an IFN- $\gamma$  inhibitor; and wherein if the levels of IFN- $\gamma$  protein in the biological sample from the patient are lower than or the same as those in the control biological sample, then the patient is identified as a patient that may not benefit from treatment with an IFN- $\gamma$  inhibitor. The levels of IFN- $\gamma$  protein determined can be the levels of total IFN- $\gamma$  protein, meaning the total of free and bound IFN- $\gamma$  protein. The IFN- $\gamma$  inhibitor can be an anti-IFN- $\gamma$  antibody. The anti-IFN- $\gamma$  antibody can comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44. The anti-IFN- $\gamma$  antibody can comprise the amino acid sequences of SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, or SEQ ID NO:30 and SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, or SEQ ID NO:31. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another example, herein is described a method for treating an IFN- $\gamma$ -mediated disease comprising administering a dose of an IFN- $\gamma$  inhibitor such that the concentration of total IFN- $\gamma$  protein in serum is maintained at a plateau concentration for at least about two, three, four, five, six, seven, eight, nine, or ten weeks after administration. The plateau concentration of total IFN- $\gamma$  protein in serum can be from about 200 to about 2000 picograms per milliliter (pg/mL). The plateau concentration of total IFN- $\gamma$  protein in serum can be at least about 250, 300, or 350 pg/mL and/or not more than 600, 800, 1000, or 1500 pg/mL. The IFN- $\gamma$  inhibitor can be a protein that binds to IFN- $\gamma$ , for example, an anti-IFN- $\gamma$  antibody. The anti-IFN- $\gamma$  antibody can comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44. The anti-IFN- $\gamma$  antibody can comprise the amino acid sequences of SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, or

SEQ ID NO:30 and SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, or SEQ ID NO:31. Further doses of the IFN- $\gamma$  inhibitor can be administered at a frequency that maintains a serum concentration of total IFN- $\gamma$  that is at least half of the plateau concentration. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

5 In still another example, herein is described a method of determining a suitable dose of an IFN- $\gamma$  inhibitor for a patient comprising: determining the total IFN- $\gamma$  protein concentration in a biological sample from the patient before dosing; administering the IFN- $\gamma$  inhibitor to the patient at a first dosage amount; and determining the total IFN- $\gamma$  protein concentration in similar biological samples from the patient periodically after dosing; wherein the first dosage amount is not suitable because it is too low if a plateau concentration of total  
10 IFN- $\gamma$  protein lasting at least two weeks is not achieved or wherein the first dosage amount is high enough if a plateau concentration of total IFN- $\gamma$  protein lasting at least two weeks is achieved. If the first dosage amount is high enough, the patient can maintain a plateau concentration of IFN- $\gamma$  protein for at least about two, three, four, five, six, seven, eight, nine, or 10 weeks after dosing. If this is the case, after the concentration of IFN- $\gamma$  protein has fallen below the plateau level, a second, lower dosage amount of the IFN- $\gamma$  inhibitor can be administered and  
15 total IFN- $\gamma$  protein concentrations in similar biological samples from the patient can be determined periodically after dosing at the second, lower dosage amount. If the first dosage amount is too low, a second, higher dosage amount of the IFN- $\gamma$  inhibitor can be subsequently administered and total IFN- $\gamma$  protein concentration in similar biological samples from the patient can be determined periodically after dosing at the second, higher dosage amount. The biological samples can be serum samples or peripheral blood samples. The IFN- $\gamma$  inhibitor can be  
20 a protein that binds to IFN- $\gamma$ , for example an anti-IFN- $\gamma$  antibody, which can be an anti-huIFN- $\gamma$  antibody. Such an anti-IFN- $\gamma$  antibody can comprise a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the  
25 amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44. Such an anti-IFN- $\gamma$  antibody can comprise the amino acid sequences of SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, or SEQ ID NO:30 and SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, or SEQ ID NO:31. The anti-IFN- $\gamma$  antibody can be a human or humanized antibody. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be  
30 administered concurrently with the antibody.

In another example, herein is described a method of treating a patient suffering from an IFN- $\gamma$ -mediated disease, the method comprising: selecting a patient, wherein expression at the RNA or protein level of one or more gene(s) listed in Table(s) 1, 2, 4, 5, and/or 6 in a biological sample taken from the patient before treating the patient deviates from expression of that gene(s) in a control biological sample in a direction consistent with excess IFN- $\gamma$   
35  $\gamma$  pathway activation; and administering to the patient a monoclonal human anti-human interferon

gamma (anti-huIFN- $\gamma$ ) antibody at a dose of from about 20 milligrams to about 300 milligrams, wherein the antibody is an IgG1 antibody and comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8. The IFN- $\gamma$ -mediated disease can be selected from the group consisting of systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, psoriasis, alopecia areata, Sjogren's syndrome, antiphospholipid syndrome, rheumatoid arthritis, multiple sclerosis, polymyositis, dermatomyositis, type I diabetes, sarcoidosis, macrophage activation syndrome (MAS), and hemophagocytic lymphohistiocytosis (HLH). The expression of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, or 50 genes listed in Table(s) 1, 2, 4, 5, and/or 6 in the biological sample from the patient can deviate from the expression of those genes in the control biological sample in a direction consistent with excess IFN- $\gamma$  pathway activation. The biological sample from the patient can exhibit elevated expression at the RNA or protein level as compared to expression in the control biological sample of one or more of the following genes: indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity Ib, receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), and/or programmed death ligand-1 (PD-L1). The dose can be from about 20 milligrams to about 300 milligrams, from about 80 milligrams to about 200, 250, or 300 milligrams, or from about 20 milligrams to about 60, 70, or 80 milligrams. The antibody can comprise the amino acid sequences of SEQ ID NO:17 and SEQ ID NO:18 and can be administered subcutaneously or intravenously. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another example, herein is described a method for treating a patient having an IFN- $\gamma$ -mediated disease with a human anti-huIFN- $\gamma$  antibody comprising: (a) taking a biological sample from the patient before treatment, wherein level(s) of expression of one or more genes listed in Table(s) 1, 2, 4, 5, and/or 6 at the RNA or protein level in the biological sample is determined and wherein level(s) of expression of the same gene(s) in a control biological sample is known or determined; (b) comparing the levels of expression of the gene(s) in the biological sample from the patient and in the control biological sample; and (c) if the level(s) of expression of the gene(s) in the biological sample from the patient deviate from the level(s) of expression of the gene(s) in the control biological sample in a direction consistent with excess IFN- $\gamma$  pathway activation, administering to the patient a therapeutically effective dose of the antibody at a dose of from about 30, 40, 50, 60, or 70 mg to about 80, 100, 120, 150, 180, 250, or 300 mg, wherein the antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8. The IFN- $\gamma$ -mediated disease can be selected from the group consisting of systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, psoriasis, alopecia areata, Sjogren's syndrome, antiphospholipid syndrome, rheumatoid arthritis, multiple sclerosis, polymyositis, dermatomyositis, type I diabetes, sarcoidosis, macrophage activation syndrome (MAS), and hemophagocytic lymphohistiocytosis (HLH). The levels of expression of at least

2, 3, 4, 5, 6, 7, 8, 9, 10, or 50 genes from Table 5 or 6 deviate from the levels of expression of the genes in the control biological sample in a direction consistent with excess IFN- $\gamma$  pathway activation. The biological sample from the patient can exhibit elevated expression at the RNA or protein level as compared to expression in the control biological sample of one or more of the following genes: indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity IgG receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), programmed death ligand-1 (PD-L1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity IgG receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274. The dose administered can be from about 5, 10, 20, or 30 mg to about 60, 70, or 80 mg or can be from about 60, 70, 80, 90, 100, or 120 mg to about 150, 180, 200, or 250 mg. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In a further example, herein is described a method for treating a patient suffering from an IFN- $\gamma$ -mediated disease comprising: (a) taking a biological sample from the patient before administering a human anti-huIFN- $\gamma$  antibody in step (b), wherein the level(s) of expression at the RNA or protein level in the biological sample from the patient of one or more of the genes in Table(s) 1, 2, 4, 5, and/or 6 is determined; (b) administering to the patient a pharmacodynamically effective dose of the human anti-huIFN- $\gamma$  antibody, wherein the antibody has a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44; (c) taking a second biological sample taken from the patient after administration of the antibody, wherein the level(s) of expression of the gene(s) of step (a) in the second biological sample are determined; and (d) if the level(s) of expression of the gene(s) determined in step (c), as compared to the level(s) of expression determined in step (a), is modulated in a direction consistent with inhibition of IFN- $\gamma$ , then continuing treatment of the patient with another pharmacodynamically effective dose of the antibody. The IFN- $\gamma$ -mediated disease can be selected from the group consisting of systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, psoriasis, alopecia areata, Sjogren's syndrome, antiphospholipid syndrome, rheumatoid arthritis, multiple sclerosis, polymyositis, dermatomyositis, type I diabetes, sarcoidosis, macrophage activation syndrome (MAS), and hemophagocytic lymphohistiocytosis (HLH). The pharmacodynamically effective dose can be from about 5, 10, 20, 30, 40, 50, or 60 mg to about 60, 70, 80, 90, or 100 mg or from about 60, 70, 80, 90, or 100 mg to about 120, 150, 180, 200, or 250 mg. The heavy chain

CDR3 can comprise the amino acid sequence of SEQ ID NO:36, the light chain CDR1 comprises the amino acid sequence of SEQ ID NO:38, the light chain CDR2 comprises the amino acid sequence of SEQ ID NO:41, and the light chain CDR3 comprises the amino acid sequence of SEQ ID NO:43. The heavy chain variable region of the antibody can comprise the amino acid sequence of SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, or SEQ ID NO:30, and the light chain variable region of the antibody can comprise the amino acid sequence of SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, or SEQ ID NO:31. The antibody can comprise the amino acid sequences of SEQ ID NOs:6 and 8, 10 and 12, 14 and 16, 30 and 12, or 14 and 31. The level(s) of expression of one or more of the following genes at the protein or RNA level can be determined in steps (a) and (c): indoleamine 2,3-dioxygenase 1 (IDO1), ankyrin repeat domain 22 (ANKRD22), chemokine (C-X-C motif) ligand 9 (CXCL9), family with sequence similarity 26, member F (FAM26F), purinergic receptor P2Y, G-protein coupled, 14 (P2RY14), guanylate binding protein 5 (GBP5), serpin peptidase inhibitor, clade G, member 1 (SERPING1), Fc fragment of IgG, high affinity IgG1, receptor (CD64), guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1), chemokine (C-X-C motif) ligand 10 (CXCL10), ets variant 7 (ETV7), programmed death ligand-1 (PDL1), basic leucine zipper transcription factor, ATF-like 2 (BATF2), Fc fragment of IgG, high affinity IgG2a, receptor (FCGR1B or CD64), activating transcription factor 3 (ATF3), pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4), and/or CD274. A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In still a further example, described is method for treating a patient suffering from an IFN- $\gamma$ -mediated disease with a human anti-huIFN- $\gamma$  antibody comprising the following steps: (a) taking a biological sample from the patient before administering a human anti-huIFN- $\gamma$  antibody in step (b), wherein the level(s) of expression at the RNA or protein level of one or more genes listed in Table(s) 1, 2, 3, 5 and/or 6 in the biological sample are determined; (b) administering to the patient the human anti-human IFN- $\gamma$  antibody, wherein the antibody has a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44; (c) taking a second biological sample taken from the patient taken after administration of the antibody, wherein the level(s) of expression of the gene(s) of (a) are determined in the second biological sample; and (d) if the level(s) of expression of the gene(s) in second biological sample of (c): (i) is modulated in a direction consistent with inhibition of IFN- $\gamma$  as compared to the level(s) of expression in the biological sample determined in (a), then continuing treatment of the patient with another pharmacodynamically effective dose of the antibody; or (ii) is substantially the same as that in the biological sample of (a) or deviates from the level of expression in the biological sample of (a) in a direction that is consistent with an excess of IFN- $\gamma$ , then treatment with the anti-human IFN- $\gamma$  antibody is discontinued. The anti-human IFN- $\gamma$  antibody can be a human or humanized IgG1 antibody. The dose of the antibody administered in (b) can be from about 20, 30, 40, 60, 80, or 100 mg to about

120, 150, 180, 200, 250, or 300 mg or from about 10, 20, or 30 mg to about 80 mg. The dose can be about 30, 40, 50, 60, 70, 80, 100, 120, 150, or 180 mg. The IFN- $\gamma$ -mediated disease can be selected from the group consisting of systemic lupus erythematosus (SLE), discoid lupus, lupus nephritis, inflammatory bowel diseases including Crohn's disease and ulcerative colitis, psoriasis, alopecia areata, Sjogren's syndrome, antiphospholipid syndrome, rheumatoid arthritis, multiple sclerosis, polymyositis, dermatomyositis, type I diabetes, sarcoidosis, macrophage activation syndrome (MAS), and hemophagocytic lymphohistiocytosis (HLH). A glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In still a further example, herein is described a method for treating a patient suffering from SLE, lupus nephritis, discoid lupus, psoriasis, or an inflammatory bowel disease comprising administering to the patient a dose of at least about 15, 20, 30, 40, 50, 60, or 100 milligrams and not more than about 80, 90, 100, 120, 150, 180, 200, 250, or 300 milligrams of an anti-human IFN- $\gamma$  antibody, wherein the anti-human IFN- $\gamma$  antibody comprises a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:34, a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:35, a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43 or SEQ ID NO:44. The anti-IFN- $\gamma$  antibody can comprise the heavy and light chain variable region amino acid sequences of SEQ ID NOs: 6 and 8, SEQ ID NOs: 10 and 12, SEQ ID NOs: 14 and 16, SEQ ID NOs: 30 and 12, or SEQ ID NOs: 14 and 31. Levels of expression of at least 5 genes listed in Table(s) 1, 2, 4, 5, and/or 6 in a biological sample taken from the patient after administration of the antibody can deviate from levels of these genes in a similar biological sample taken from the patient taken at baseline in a direction consistent with inhibition of IFN- $\gamma$ . The dose of the anti-IFN- $\gamma$  antibody can be from about 5, 10, 20, 30, or 40 milligrams to about 60, 70, 80, 90, or 100 milligrams or from about 60, 70, 80, 90, 100, or 120 milligrams to about 125, 150, 180, 200, or 250 milligrams. The dose can be administered subcutaneously or intravenously. The level of total IFN- $\gamma$  protein in the patient's serum can remain above about 200 pg/mL for at least about 2 weeks subsequent to a single dose. A glucocorticoid, optionally prednisone, and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another example, herein is described a method for identifying SLE, psoriasis, or inflammatory bowel disease patients that can benefit from treatment with a human anti-human IFN- $\gamma$  antibody and treating such patients comprising the following steps: (a) obtaining a biological sample from the patient before administration of the antibody, wherein the level of total IFN- $\gamma$  protein in the biological sample is determined; (b) administering to the patient a dose of the antibody; (c) obtaining a second biological sample from the patient after administration of the antibody, wherein the level of total IFN- $\gamma$  protein in the second biological sample is determined; and (d) if the level of total IFN- $\gamma$  protein determined in (c) is higher than the level determined in (a), then continuing treatment with the antibody; wherein the antibody is an IgG1 antibody and comprises the amino

acid sequences of SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, or SEQ ID NO:30 and SEQ ID NO:8, SEQ ID NO:12, SEQ ID NO:16, or SEQ ID NO:31. The antibody can comprise the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8.

In another example, described herein is a method for treating an IFN- $\gamma$ -mediated disease comprising administering to a patient in need thereof a dose of a human anti-human IFN- $\gamma$  antibody comprising the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8 such that the concentration of total IFN- $\gamma$  protein in the patient's serum is maintained at a plateau concentration for at least about two, three, four, five, or six weeks following administration. The plateau concentration of total IFN- $\gamma$  protein in serum can be from about 100, 200, or 300 pg/mL to about 2000 pg/mL.

#### BRIEF DESCRIPTION OF THE FIGURES

**Figure 1:** Volcano plot of expression of an array of genes post- vs. pre-IFN- $\gamma$  stimulation of whole blood from healthy volunteers. The average fold change in RNA expression for each gene is plotted with the associated p-value from an analysis of variance (ANOVA). The circled points have been designated as the top 20 IFN- $\gamma$  regulated genes, which are those with the largest absolute fold change and that have a p-value less than 0.001..

**Figure 2:** Analysis of serum protein levels. Top: Boxplot of interleukin-18 (IL-18), chemokine (C-X-C motif) ligand 10 (CXCL10; also known as interferon gamma inducible protein 10 (IP10)), and chemokine (C-C motif) ligand 2 (CCL2; also known as MCP-1) protein levels in healthy volunteers (HV), SLE, and lupus nephritis (LN) subjects. The y-axis is log-scaled. The horizontal lines are the group medians and the boxes represent the 25<sup>th</sup> and 75<sup>th</sup> percentiles. The whiskers represent the most extreme data point within 1.5 times the inter-quartile range away from the boxes. The black crosses are points outside the whiskers. The numbers above each boxplot, e.g., "n=155," refer to the number of samples from individual subjects that the boxplot represents.

**Figure 3:** IFN-related gene expression in SLE patients treated with AMG 811 compared to patients treated with a placebo. Left: Volcano plot of RNA expression of an array of genes in biological samples from treated subjects at day 15 (described in Example 3) versus samples from untreated/placebo treated subjects. The average fold difference in RNA expression for each gene is plotted with the associated p-value. The top 20 IFN- $\gamma$  signature genes (see Figure 1) are circled. Right: Relationship between AMG 811 serum concentration and guanylate binding protein 1 (GBP1) transcript expression in SLE patients. Samples were taken on Day -1 (pre-dosing; ○) and Day 15 (■) in the clinical trial described in Example 3. The x axis indicates the serum concentration of AMG 811, and the y axis indicates the fold difference in guanylate binding protein 1 (GBP1) RNA expression from that seen in a control group of healthy people.

**Figure 4:** Dose dependent decrease in CXCL10 protein level in response to AMG 811 administration. Symbols are average change from baseline in CXCL10 levels for each dose group by study day of the study described in Example 3. The error bars reflect the 95% confidence interval around the mean. Time points are indicated as follows: ●, day 15 (Dy15) of the study; ■, day 56 (Dy56) of the study; and ◇, end of study (EOS).

**Figure 5:** Mean AMG 811 serum concentration-time profiles following a single subcutaneous or intravenous dose of AMG 811 in systemic lupus erythematosus patients. The x axis indicates the time post-injection, and

the y axis indicates the serum concentration of AMG 811 in nanograms per milliliter (ng/ml). The doses represented by the various symbols and the number of patients dosed (n) are indicated in the legend in the figure.

**Figures 6A and 6B:** Median (6A) and mean (6B) serum total IFN- $\gamma$  protein concentration-time profiles following a single subcutaneous or intravenous dose of AMG 811 in systemic lupus erythematosus patients. The x axis indicates time post-injection, and the y axis indicates the median or mean serum concentration of IFN- $\gamma$ . The doses represented by the various symbols and the number of patients dosed (n) are indicated in the legend in the figure.

**Figure 7:** Average post-dose AMG 811 score in lupus nephritis patients. An "AMG 811 score" was determined as explained in Example 4 for lupus nephritis patients. Diamonds indicate the average score for each dose while vertical lines indicate the 95% confidence interval.

**Figure 8:** Dose dependent decrease in CXCL10 protein level in response to multiple doses of AMG 811 in general SLE patients. Symbols (circles, squares, triangles, etc.) indicate the average fold change from baseline values in CXCL10 levels, and the vertical lines represent the 95% confidence interval. The data are from the study described in Example 4. Each group of seven vertical lines represents data from patient samples taken at, from left to right, day 8 (D8), 16 (D16), 29 (D29), 57 (D57), 86 (D86), 113 (D113), and end of study (EOS), as indicated. The dose of AMG 811 administered is indicated below. A dose of zero indicates that those patients received a placebo.

**Figure 9:** Dose dependent decrease in CXCL10 (IP-10) protein level in response to multiple doses of AMG 811 in lupus nephritis patients. Symbols (circles, squares, triangles, etc.) indicate the average fold change from baseline values in CXCL10 levels, and the vertical lines represent the 95% confidence interval. Each group of seven vertical lines represents data from patient samples taken at, from left to right, day 8 (D8), 16 (D16), 29 (D29), 57 (D57), 86 (D86), 113 (D113), and end of study (EOS) of the study described in Example 4, with the dose of AMG 811 administered indicated below. A dose of zero indicates that those patients received a placebo.

**Figure 10:** Relationship between AMG 811 levels and changes in IP-10 (CXCL10) expression in SLE and lupus nephritis patients. This graph shows the AMG 811 concentration (x axis) in peripheral blood of patients plotted against the fold change in IP-10 concentration from baseline for lupus and lupus nephritis patients involved in the trial described in Example 4 at a variety of time points in the trial, as indicated.

**Figure 11:** Relationship between AMG 811 serum concentration and GBP1 transcript expression in lupus nephritis patients. Blood samples were taken from lupus nephritis patients at baseline and on day 15 in the multi-dose clinical trial described in Example 4. The x axis indicates the serum concentration of AMG 811, and the y axis indicates the fold difference in guanylate binding protein 1 (GBP1) RNA expression from that seen in a control group of healthy people.

**Figure 12:** Blinded data showing the amount of protein detected in 24-hour urine samples from lupus nephritis patients treated with multiple doses of AMG 811 or placebo. This graph show the levels of protein in twenty four hour urine samples from lupus nephritis patients from cohorts 4 (left panel) and 5 (right panel) of the clinical trial described in Example 4. Cohort 4 contained eight patients, two of which received placebo and six of which

received 3 doses of 20 mg of AMG 811. Cohort 5 contained 12 patients, three of which received placebo and nine of which received three doses of 60 mg of AMG 811.

**Figure 13:** Blinded spot urine protein/creatinine ratio (UPCR) in lupus nephritis patients. Blinded data showing the UPCR of patients in cohorts 4 (left panel) and 5 (right panel) at various time points during the clinical trial described in Example 4. Cohort 4 contained eight patients, two of which received placebo and six of which received three doses of 20 mg of AMG 811. Cohort 5 contained 12 patients, three of which received placebo and nine of which received three doses of 60 mg of AMG 811.

**Figure 14:** Blinded data showing PASI scores of psoriasis patients treated with AMG 811 or placebo. This graph shows the PASI scores (y axis) of individual psoriasis patients treated with AMG 811 or placebo at various time points during the trial described in Example 6, as indicated along the x axis. The baseline measurement (B) was taken one to three days prior to the single dose of AMG 811 administered on day 1 of the study.

#### DETAILED DESCRIPTION

Provided herein are methods of treatment using IFN- $\gamma$  inhibitors, methods for identifying patients likely to benefit from such treatment, and methods for determining suitable dosages. The methods utilize techniques for determining levels of proteins and/or RNA transcripts in a biological sample. Using such techniques, overlapping sets of transcripts, the expression of which is modulated by IFN- $\gamma$  *ex vivo* and by AMG 811 *in vivo*, have been defined. Similarly, it has been found that a particular set of transcripts and at least one serum protein is downregulated by an IFN- $\gamma$  inhibitor in human patients *in vivo*, thus making it possible to determine dosages at which these effects are observable and to determine which transcripts in blood cells are regulated by IFN- $\gamma$  *in vivo*. Dosages determined by such methods can be used to treat patients. Similarly, assay of these sets of transcripts can be used to predict which patients are likely to respond to treatment, *i.e.*, those that overexpress genes whose expression can be downregulated by the IFN- $\gamma$  inhibitor and/or those that are up- or down-regulated by activation of the IFN- $\gamma$  pathway. Similarly, these techniques can be used to determine whether a particular dosage of an IFN- $\gamma$  inhibitor is having a biological effect, especially in patients suffering from an episodic disease in which changes in symptoms may not be readily apparent. Further, if an IFN- $\gamma$  inhibitor is not having a biological effect as measured by expression of such biomarkers, treatment with the IFN- $\gamma$  inhibitor can be discontinued and, optionally, a new treatment can be initiated. Alternatively, if an IFN- $\gamma$  inhibitor is having a biological effect as measured by biomarker expression, treatment with the IFN- $\gamma$  inhibitor can be continued.

#### Definitions

An “antibody,” as meant herein, can be a full length antibody containing two full length heavy chains (containing a heavy chain variable region ( $V_H$ ), a first constant domain ( $C_H1$ ), a second constant domain ( $C_H2$ ) and a third constant domain ( $C_H3$ )) and two full length light chains (containing a light chain variable region ( $V_L$ ) and a light chain constant region ( $C_L$ )). Alternatively, an antibody can contain only a single  $V_H$  region or  $V_L$  region, such as the single variable domain antibodies described in, *e.g.*, U.S. Patent 7,563, 443. The portions of this reference describing such antibodies are incorporated herein by reference. An antibody can also be a fragment of a full length antibody that binds to the target antigen, which may also contain other sequences. For

example, an antibody can be an a single chain antibody that comprises  $V_H$  and  $V_L$  regions joined by a peptide linker (i.e., an scFv), a Fab fragment, which may or may not include the hinge region, an scFv-Fc, among many other possible formats. The term "antibody" comprises any protein that includes at least one  $V_H$  or  $V_L$  region.

5 "Baseline," as meant herein, is a timepoint before dosing begins in a clinical trial that can typically be up to about a month before dosing with a test drug or placebo begins.

A "biological sample," as meant herein, is a sample of a liquid, such as blood or cerebrospinal fluid, or a solid piece of tissue, such as a skin biopsy or an excised tumor, taken from a patient. Two biological samples are said to be "similar" if they are taken from similar tissue. For example, two whole blood samples from different patients are similar, as meant herein. Further, two skin biopsies taken from lesions from different  
10 patients are also similar as meant herein.

A drug or treatment is "concurrently" administered with another drug or treatment, as meant herein, if it is administered in the same general time frame as the other drug, optionally, on an ongoing basis. For example, if a patient is taking Drug A once a week on an ongoing basis and Drug B once every six months on an ongoing basis, Drugs A and B are concurrently administered whether or not they are ever administered on the  
15 same day. Similarly, if Drug A is taken once per week on an ongoing basis and Drug B is administered only once or a few times on a daily basis, Drugs A and B are concurrently administered as meant herein. Similarly, if both Drugs A and B are administered for short periods of time either once or multiple times within a one month period, they are administered concurrently as meant herein as long as both drugs are administered within the same month.

20 A "control group," as meant herein, is a group of healthy people to which a patient having a particular disease is compared in some way. For example, expression of certain genes at the protein or RNA level in a biological sample from a patient can be compared to expression of those genes in one or more similar biological samples from people in a control group. In some situations, normal ranges for levels of expression for particular genes can be established by analysis of biological samples from members of a control group. In such a  
25 situation, expression levels in a given sample from a patient having a disease can be compared to these established normal ranges to determine whether expression in the sample from the patient is normal or above or below normal.

A "control biological sample," as meant herein, is (a) a group of biological samples from a "control group" that is compared to a similar biological sample from a patient or (b) a biological sample from non-diseased  
30 tissue from a patient that is compared to a biological sample from diseased tissue from the same patient. For example, a skin biopsy from non-lesional tissue from a discoid lupus patient can be a "control biological sample" for a skin biopsy from lesional tissue from the same discoid lupus patient. Alternatively, a group of skin biopsies from a healthy "control group" can be a "control biological sample" to which a skin biopsy from a discoid lupus patient can be compared. Alternatively, a group of blood samples from healthy people can be a "control  
35 biological sample" to which to compare a blood sample from an SLE patient.

"Determining the level of expression," as meant herein, refers to determining the amount of expression of a gene in a biological sample at either the protein or RNA level. Such levels can be determined in

biological samples from patients suffering from an IFN- $\gamma$ -mediated disease and in control biological samples from healthy people or from non-diseased tissue from the patient (for example in a skin sample not having psoriatic plaques in a psoriasis patient). The comparison between a patient's biological sample from diseased tissue (or blood in a systemic disease) and a control biological sample can provide information as to whether the biomarkers in question are expressed at normal, elevated, or lowered levels. To assay for protein levels in liquid samples, enzyme-linked immunosorbent assay (ELISA) can be used. See, e.g., Berzofsky et al., *Antigen-Antibody Interactions and Monoclonal Antibodies, Chapter 12 in FUNDAMENTAL IMMUNOLOGY, THIRD EDITION*, Paul, ed., Raven Press, New York, 1993, pp. 421-466, at pp. 438-440. Many such assays are commercially available. For solid biological samples, such as, for example, skin samples, immunohistochemistry or immunofluorescence can be used to determine whether and where a particular protein is expressed. Such techniques are well known in the art. See, e.g., *Antigen Retrieval Techniques: Immunohistochemistry and Molecular Morphology*, Shi et al., eds. Eaton Publishing, Natick, Massachusetts, 2000. The portions of this reference that describe techniques of immunohistochemistry and immunofluorescence are incorporated herein by reference. To assay for RNA levels, real time quantitative PCR (for example using a Taqman® kit available from Invitrogen (Carlsbad, California)) or microarrays (such as described, for example, in Chen et al. (1998), *Genomics* 51: 313-324) are generally used.

An "IFN- $\gamma$  inhibitor," as meant herein, is a molecule, which can be a protein or a small molecule, that can inhibit the activity of IFN- $\gamma$  as assayed by the A549 bioassay, which can be performed as follows.

One of the established properties of IFN- $\gamma$  is its anti-proliferative effect on a variety of cell populations. See e.g. Aune and Pogue (1989), *J. Clin. Invest.* 84: 863-875. The human lung cell line A549 has been used frequently in publications describing the bioactivity of IFN- $\gamma$ . See e.g. Aune and Pogue, *supra*; Hill et al. (1993), *Immunology* 79: 236-240. In general, the activity of an inhibitor is tested at a concentration of a stimulating substance, in this case IFN- $\gamma$ , that falls within a part of the dose-response curve where a small change in dose will result in a change in response. One of skill in the art will realize that if an excessive dose of the stimulating substance is used, a very large dose of an inhibitor may be required to observe a change in response. Commonly used concentrations for a stimulating substance are EC<sub>80</sub> and EC<sub>90</sub> (the concentrations at which 80% or 90%, respectively, of the maximum response is achieved).

An IFN- $\gamma$  dose-response curve can be generated to determine the EC<sub>90</sub> for the lung epithelial carcinoma cell line A549. In subsequent experiments, different concentrations of an IFN- $\gamma$ -inhibitor can be mixed with a fixed dose of IFN- $\gamma$ , and the ability of the IFN- $\gamma$ -inhibitor to inhibit the biological activity of the anti-proliferative effect of IFN- $\gamma$  can be determined. The assay can be performed for 5 days, and proliferation can be measured by determining fluorescence generated by the reduction of ALAMARBLUE™ (AccuMed International, Inc., Chicago, Ill.), a dye used to indicate cell growth, by metabolically active, *i.e.*, proliferating, cells. See e.g., de Fries and Mitsuhashi, 1995, *J. Clin. Lab. Analysis* 9(2): 89-95; Ahmed et al., 1994, *J. Immunol. Methods* 170(2): 211-24.

An "IFN- $\gamma$ -mediated disease," as meant herein, is a disease in which evidence from an *in vitro* or a non-human model system or from human patients indicates IFN- $\gamma$  is likely to play a role in driving the course of the disease. Diseases that are included among "IFN- $\gamma$ -mediated diseases" include, for example, diseases in which patient samples display elevated levels of a type I or II IFN or a type I-related "IFN signature" pattern of gene expression. See, e.g., Baechler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615; Bennett et al. (2003), J. Exp. Med. 197(6): 711-723. The portions of these references that describe the IFN signature pattern of gene expression are incorporated herein by reference. IFN- $\gamma$ -mediated diseases include, for example, SLE, discoid lupus, lupus nephritis, alopecia areata, Graves'disease, Sjogren's syndrome, antiphospholipid syndrome, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, dermatomyositis, polymyositis, bacterial septicemia, antigen/antibody complex diseases (Arthus-like syndromes), anaphylactic shock, multiple sclerosis (MS), type I diabetes, thyroiditis, graft versus host disease, transplant rejection, atherosclerosis, immune-mediated hepatic lesions, autoimmune hepatitis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, giant cell arteritis, uveitis, macrophage activation syndrome (MAS), hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), sarcoidosis, and scleroderma.

The term "interferon signature" refers to the characteristic pattern of over- and under-expression of genes observed in response to type I interferons. See, e.g., Bennett et al. (2003), J. Exp. Med. 197(6): 711-723; Baechler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615, the relevant portions of which are incorporated herein by reference.

The expression of a particular gene in a biological sample from a patient is said to "deviate" from the expression of that gene in a control biological sample or in a biological sample from the patient taken at a different time "in a direction consistent with excess IFN- $\gamma$ " or "in a direction consistent with excess IFN- $\gamma$  pathway activation" when it is found to be up- or down-modulated at the RNA or protein level in the same direction as noted in Table 1 below for blood samples stimulated with IFN- $\gamma$ . Table 1 lists the group of genes that are up- or down-regulated in human whole blood from healthy volunteers in response to stimulation with IFN- $\gamma$  *ex vivo*. Thus, for a gene to "deviate" from the expression of that gene in a control biological sample or in a biological sample from the patient taken at a different time "in a direction consistent with excess IFN- $\gamma$ ", it must be listed in Table 1.

Similarly, the expression of a gene can be "modulated in a direction consistent with inhibition of IFN- $\gamma$ " or "modulated in a direction consistent with IFN- $\gamma$  pathway inhibition." This means that the expression of the gene is decreased if the expression of that gene is up-regulated in response to *ex vivo* stimulation with IFN- $\gamma$  as noted in Table 1, and that the expression is increased if the expression of that gene is down-regulated in response to *ex vivo* stimulation with IFN- $\gamma$  as noted in Table 1.

A "monoclonal antibody," as meant herein, is an antibody that specifically binds to an antigen at an epitope, wherein a preparation of the antibody contains substantially only antibodies having the same amino acid sequence, although there may be certain low levels of antibodies that include one or more alteration of certain amino acids or internal, amino-terminal, or carboxyterminal cleavages of the amino acid chain. Such minor

alterations may occur during the production of the antibodies or during storage. In contrast, a preparation of a "polyclonal" antibody contains antibodies having many different amino acid sequences that bind to different epitopes on the same antigen. The term "monoclonal antibody" includes, without limitation, the following kinds of molecules: tetrameric antibodies comprising two heavy and two light chains such as an IgG, IgA, IgD, IgM, or IgE antibody; single chain antibodies (scFv's) containing a V<sub>H</sub> and a V<sub>L</sub> region joined by a peptide linker; variable domain antibodies as described in, for example, U.S. Patent 7,563,443, the relevant portions of which are incorporated herein by reference, that comprise one or more single variable domains, each of which can, by itself, bind specifically to antigen; Fab, Fab', or Fab(ab')<sub>2</sub> fragments; humanized or chimeric antibodies; various kinds of monovalent antibodies, including those described in U.S. Patent Application Publication 2007/0105199, the relevant portions of which are incorporated by reference herein; and bispecific antibodies, including those with mutationally altered constant regions such as those described in, e.g., U.S. Patent Application Publication 2010/0286374 or U.S. Patent Application Publication 2007/0014794; and scFv-Fc molecules.

A "pharmacodynamically effective dose," as meant herein, is a dose of an IFN- $\gamma$  inhibitor that can modulate the expression of a gene "in a direction consistent with inhibition of IFN- $\gamma$ ," as defined herein. Genes regulated by IFN- $\gamma$  *ex vivo* are listed in Table I.

A "plateau concentration," as meant herein, is a concentration of total IFN- $\gamma$  that is observed in a biological sample, such as peripheral blood or serum, taken from a patient after dosing with an IFN- $\gamma$  inhibitor. The plateau concentration is higher than the concentration of total IFN- $\gamma$  protein in a similar biological sample taken from the same patient at baseline, and once it is attained, it is "substantially maintained" for at least about 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks. A concentration is considered to be substantially maintained if it varies by no more than  $\pm 50\%$  of its total value.

A "therapeutically effective dose," as meant herein, is a dose that is effective to decrease one or more observable symptoms of a disease or to delay onset or mitigate the symptoms of a more serious condition that often follows after the condition that a patient is currently experiencing. A therapeutically effective dose may, but need not necessarily, completely eliminate all symptoms of the disease. For example, in lupus nephritis, a lowering of the degree of proteinuria and lowering or stabilization of serum concentration of creatinine would indicate an improvement in kidney function and, thus, an improvement in a symptom of the disease. Hence, a dose of an IFN- $\gamma$  inhibitor that could cause a decrease in proteinuria and lower or stabilize serum creatinine concentration would be both a therapeutically effective dose and a pharmacodynamically effective dose.

### ***Interferons, IFN- $\gamma$ -Mediated Diseases, and Biomarkers***

Interferons were first recognized for their ability to impede viral infections and are now known to also play important roles in mediating host defense against infection by bacteria and other pathogens, as well as in integrating early, innate immune responses and later adaptive immune responses. Decker et al. (2002), J. Clin. Invest. 109(10): 1271-1277. There are at least two types of human and murine interferons: the type I interferons, including primarily a number of IFN $\alpha$  subtypes and IFN $\beta$ , plus IFN $\omega$ , IFN $\epsilon$ , IFN $\delta$ , IFN $\tau$ , and IFN $\kappa$ ; and type II interferon, a class of one member, that is, IFN- $\gamma$ . Sozzani et al. (2010), Autoimmunity 43(3): 196-203.

Type I interferons are produced by most cell types under appropriate conditions and are known to play a role in resisting viral infection, whereas IFN- $\gamma$  is produced by limited cell types, such as NK cells and activated Th1 cells, and is known to strengthen immune responses to unicellular microorganisms, intracellular pathogens, and viruses. In humans, type I and type II interferons bind to distinct receptors, which are, respectively, the interferon alpha/beta receptor (IFNAR, containing IFNAR1 and IFNAR2 chains) and the interferon gamma receptor (IFNGR, containing IFNGR1 and IFNGR2 chains). Both of these receptors are associated with Janus kinases which, along with other intracellular proteins, mediate the transcriptional activation of genes having interferon-stimulated response elements (IFNAR only) and genes having IFN- $\gamma$ -activated site elements (both IFNAR and IFNGR). Decker et al. (2002), J. Clin. Invest. 109(10): 1271-1277; Trinchieri (2010), J. Exp. Med. 207(10): 2053-2063. Thus, although the sets of genes activated by type I and II interferons differ, there is considerable overlap in the two sets. See, e.g., Baechler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615; van Baarsen et al. (2006), Genes and Immunity 7: 522-531. Some differences may be related to different magnitudes of response of a particular gene to a given dose of type I or II interferon. Kariuki et al. (2009), J. Immunol. 182: 34-38

The relationship between the biological activities of type I and II interferons is complex and intertwined and dependent on the expression of other genes. Thus, different cell types can have differing responses to the IFNs. IFN- $\gamma$  is a more potent activator of phagocytic cell and antigen-presenting cell function than type I interferons. Trinchieri (2010), J. Exp. Med. 207(10): 2053-2063. Both type I and II interferons can be produced in the course of an immune response. In some situations, type I interferons can inhibit production of IFN- $\gamma$ , and in other situations, for example, in the absence of STAT1, type I interferons can increase IFN- $\gamma$  production. Nguyen et al. (2000), Nature Immunol. 1(1): 70-76; Brinkman et al. (1993), J. Exp. Med. 178: 1655-1663; Trinchieri (2010), J. Exp. Med. 207(10): 2053-2063. Further, low levels of type I IFN produced during stimulation of dendritic cells are essential for production of IL-12 heterodimer, which induces production of IFN- $\gamma$ . However, in the presence of high levels of type I IFN, production of IL-12 p40 is suppressed, thus limiting the production of IL-12 heterodimer. Thus, the relationship between type I and II interferons is already known to be complex and may be even more complex *in vivo* than is currently understood.

A number of diseases have been associated with changes in gene expression patterns that are thought to reflect elevated activity of IFNs. Some investigators refer to such a gene expression pattern as an "interferon signature," which includes somewhat different groups of genes depending on exactly how the signature is defined. See, e.g., Baehler et al. (2003), Proc. Natl. Acad. Sci. 100(5): 2610-2615; Bennett et al. (2003), J. Exp. Med. 197(6): 711-723. Since IFN- $\gamma$ - and type I IFN-activated genes are overlapping sets, an elevated interferon signature score could implicate elevated activity of IFN- $\gamma$  and/or a type I IFN. In a number of autoimmune and/or inflammatory diseases, many of which characterized by extremely heterogeneous and episodic symptoms, it has been found that a substantial proportion of patients or persons at increased risk of disease have a gene expression pattern reflecting elevated IFN activity and/or have elevated levels of an IFN or a protein whose expression is known to be induced by type I IFN. These diseases include, for example, SLE (Bauer et al. (2006),

PLoS Med. 2(12): 2274-2284; Armañanzas et al. (2009), IEEE Transactions on Inform. Tech. in Biomed. 13(3): 341-350), systemic sclerosis (Sozzani et al. (2010), Autoimmunity 43(3): 196-203), alopecia areata (Ghoreishi et al. (2010), Br. J. Dermatol. 163: 57-62), Graves' disease (Ruiz-Riol et al. (2011), J. Autoimmunity 36: 189-200), Sjogren's syndrome (Sozzani et al. (2010), Autoimmunity 43(3): 196-203; Emamian et al. (2009), Genes Immun. 10: 285-296), antiphospholipid syndrome (Armañanzas et al. (2009), IEEE Transactions on Inform. Tech. in Biomed. 13(3): 341-350), inflammatory bowel diseases including Crohn's disease and ulcerative colitis (see, e.g., U.S. Patent 6,558,661), rheumatoid arthritis (Dawidowicz et al. (2011), Ann. Rheum. Dis. 70: 117-121), psoriasis (Pietrzak et al. (2008), Clin. Chim. Acta 394: 7-21), multiple sclerosis (van Baarsen et al. (2006), Genes and Immunity 7: 522-531), dermatomyositis (Somani et al. (2008), Arch. Dermatol. 145(4): 1341-1349), polymyositis (Sozzani et al. (2010), Autoimmunity 43(3): 196-203), type I diabetes (Reynier et al. (2010), Genes Immun. 11: 269-278), sarcoidosis (Lee et al. 2011, Ann. Dermatol. 23(2): 239-241; Kriegova et al. (2011), Eur. Respir. J. 38: 1136-1144), and hemophagocytic lymphohistiocytosis (HLH; Schmid et al. (2009), EMBO Molec. Med. 1(2): 112-124).

Elevated expression of genes whose expression is induced by IFNs is found in about half of adult SLE patients and the majority of pediatric SLE patients. Baechler et al. (2003), Proc. Natl. Acad. Sci. U.S.A.; 100: 2610-2615; Bennett et al. (2003), J. Exp. Med. 197: 711-723; Kirou et al. (2004), Arthr. & Rheum. 50: 3958-3967. Overexpression of some of these gene products at the protein level, such as CXCL10 (IP-10), CCL2 (MCP-1), and chemokine (C-C motif) ligand 19 (CCL19; also known as (MIP-3B), correlates with disease severity and is predictive of disease flares within a year. Bauer et al. (2009), Arthr. & Rheum 60(10): 3098-3107; Bauer et al. (2006), PLoS. Med. 3: e491; Lit et al. (2006), Ann. Rheum. Dis. 65: 209-215; Narumi et al. (2000), Cytokine 12: 1561-1565; Baechler et al. (2003), Proc. Natl. Acad. Sci 100(5): 2610-2615. Specifically, CXCL10 has been shown to be a major contributor to the overall association of disease with IFN signature and an independent predictor of future disease flare. Bauer et al. (2009), Arthritis & Rheum. 60: 3098-3107; Bauer et al. (2009), Arthritis Rheum. 60:S209.

A variety of other data suggest a pathogenic role for IFN- $\gamma$  in SLE. Studies involving murine models of SLE consistently support the role of IFN- $\gamma$  in the pathogenesis of disease. Balomenos et al. (1998), J. Clin. Invest. 101: 364-371; Jacob et al. (1987), J. Exp. Med. 166: 798-803; Peng et al. (1997), J. Clin. Invest 99: 1936-1946; Hron and Peng (2004), J. Immunol. 173: 2134-2142; Seery et al. (1997), J. Exp. Med. 186: 1451-1459. In addition, lupus-like syndromes have been observed in patients treated for a variety of diseases with IFN- $\gamma$  and/or IFN- $\alpha$ . Wandl et al. (1992), Clin. Immunol. Immunopathol. 65(1): 70-74; Graninger et al. (1991), J. Rheumatol. 18: 1621-1622. A correlation between severity of disease activity and amounts of IFN- $\gamma$  secreted by a patient's peripheral blood mononuclear cells in response to stimulation by lipopolysaccharide and phytohaemagglutinin has been observed. Viillard et al. (1999), Clin. Exp. Immunol. 115: 189-195. Similarly, peripheral blood T cells from SLE patients expressed significantly more IFN- $\gamma$  in response to CD28 costimulation than did T cells from normal controls. Harigai et al. (2008), J. Immunol. 181: 2211-2219. Thus, many different kinds of evidence indicate that IFN- $\gamma$  is likely to play a role in mediating SLE.

SLE is an autoimmune disease of unknown etiology marked by autoreactivity to nuclear self antigens. Its clinical manifestations are so diverse that it is questionable whether it is truly a single disease or a group of related conditions. Kotzin, B.L. 1996. Systemic lupus erythematosus. *Cell* 85:303-306; Rahman, A., and Isenberg, D.A. 2008. Systemic lupus erythematosus. *N. Engl. J. Med.* 358:929-939. Symptoms can include the following: constitutional symptoms such as malaise, fatigue, fevers, anorexia, and weight loss; diverse skin symptoms including acute, transient facial rashes in adults, bullous disease, and chronic and disfiguring rashes of the head and neck; arthritis; muscle pain and/or weakness; cardiovascular symptoms such as mitral valve thickening, vegetations, regurgitation, stenosis, pericarditis, and ischemic heart disease, some of which can culminate in stroke, embolic disease, heart failure, infectious endocarditis, or valve failure; nephritis, which is a major cause of morbidity in SLE; neurological symptoms including cognitive dysfunction, depression, psychosis, coma, seizure disorders, migraine, and other headache syndromes, aseptic meningitis, chorea, stroke, and cranial neuropathies; hematologic symptoms including leucopenia, thrombocytopenia, serositis, anemia, coagulation abnormalities, splenomegaly, and lymphadenopathy; and various gastrointestinal abnormalities. *Id.*; Vratsanos et al., "Systemic Lupus Erythematosus," Chapter 39 in *Samter's Immunological Diseases*, 6<sup>th</sup> Edition, Austen et al., eds., Lippincott Williams & Wilkins, Philadelphia, PA, 2001.

Severity of symptoms varies widely, as does the course of the disease. SLE can be deadly. The disease activity of SLE patients can be rated using an instrument such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), which provides a score for disease activity that takes into consideration the following symptoms, which are weighted according to severity: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, new rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leucopenia. Bombardier et al. (1992), *Arthr. & Rheum.* 35(6): 630-640, the relevant portions of which are incorporated herein by reference. The treatments described herein can be useful in lessening or eliminating symptoms of SLE as measured by SLEDAI.

Another method for assessing disease activity in SLE is the British Isles Lupus Assessment Group (BILAG) index, which is a disease activity assessment system for SLE patients based on the principle of the physician's intention to treat. Stoll et al. (1996), *Ann. Rheum Dis.* 55: 756-760; Hay et al. (1993), *Q. J. Med.* 86: 447-458. The portions of these references describing the BILAG are incorporated herein by reference. A BILAG score is assigned by giving separate numeric or alphabetic disease activity scores in each of eight organ-based systems, general (such as fever and fatigue), mucocutaneous (such as rash and alopecia, among many other symptoms), neurological (such as seizures, migraine headaches, and psychosis, among many other symptoms), musculoskeletal (such as arthritis), cardiorespiratory (such as cardiac failure and decreased pulmonary function), vasculitis and thrombosis, renal (such as nephritis), and hematological. *Id.* The treatments described herein can be useful in lessening or eliminating symptoms of SLE as measured by the BILAG index.

Discoid lupus is a particular form of chronic cutaneous lupus in which the patient has circular lesions that occur most commonly in sun-exposed areas. The lesions can leave disfiguring scars. Up to about 25% of SLE patients develop discoid lupus lesions at some point in the course of their disease. These lesions may

occur in patients that have no other symptoms of SLE. The symptoms that relate specifically to skin in cutaneous forms of lupus can be scored using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), which takes into consideration both disease activity (including erythema, scaling, and hypertrophy of the skin in various areas, as well as mucus membrane lesions and alopecia) and disease-related damage (including dyspigmentation, scarring, atrophy, and panniculitis of the skin as well as scarring of the scalp). Such symptoms can be affected by a treatment for discoid lupus such as an IFN- $\gamma$  inhibitor. The CLASI is described in detail by Albrecht et al. (2005), J. Invest. Dermatol. 125: 889-894. The portions of this article that describe what the CLASI is, what symptoms are included in it, and how to use it are incorporated herein by reference. The treatments described herein can be useful for lessening or eliminating symptoms of discoid lupus as measured by the CLASI.

Another cutaneous disease that can be mediated by IFN- $\gamma$  is psoriasis. Symptoms of psoriasis include itchy, dry skin that can be pink/red in color, thickened and covered with flakes. It is a common condition and is episodic in nature, that is, patients can experience flares and periods of remission. There are five type of psoriasis, erythrodermic, guttate, inverse, plaque, and pustular. Plaque psoriasis is the most common type. Clinical studies with an anti-human IFN- $\gamma$  antibody indicate that inhibition of IFN- $\gamma$  can lessen symptoms of psoriasis as measured by a Psoriasis Area and Severity Index (PASI) score, thus demonstrating that IFN- $\gamma$  plays a role in mediating psoriasis, at least in some patients. International Application Publication WO 2003/097083.

The severity of disease in psoriasis patients can be measured in a variety of ways. One way disease activity is commonly measured in clinical trials the PASI score. A PASI score can range from 0 to 72, with 72 being the most severe disease. For purposes of PASI assessment, the body is considered to consist of four sections, legs, torso (that is, stomach, chest, back, etc.), arms, and head, which are considered to have 40%, 30%, 20%, and 10% of a person's skin, respectively. For each section, the percent of the area of skin affected is estimated and transformed into a grade of from 0 to 6, with 0 being no affected skin and 6 being 90-100% of the skin of the body section in question being affected. The severity of disease is scored by separately considering three features of the affected skin, redness (erythema), scaling, and thickness, and assigning a severity score of from 0 to 4 for each feature for each body section. The sum of the severity scores for all three features for each body section is calculated, and this sum is multiplied by the weight of the respective section as determined by how much of the total skin that body section contains and by the percent of the body section affected. After this number is calculated for each body section, these numbers are added to yield the PASI score. Thus, the PASI score can be expressed as follows:

$$\begin{aligned} \text{PASI} = & 0.1(\text{score for percent of the head affected})(\text{sum of 3 severity scores for the head}) + \\ & 0.2(\text{score for percent of the arms affected})(\text{sum of 3 severity scores for the arms}) + \\ & 0.3(\text{score for percent of the torso affected})(\text{sum of 3 severity scores for the torso}) + \\ & 0.4(\text{score for percent of the legs affected})(\text{sum of 3 severity scores for the legs}) \end{aligned}$$

The descriptions of PASI scores in the following two references are incorporated by reference herein: Feldman and Krueger (2005), *Ann. Rheum. Dis.* 64: 65-68, Langley and Ellis (2004), *J. Am. Acad. Dermatol.* 51(4): 563-69.

Many clinical trials refer to changes in PASI score over the course of the study. For example, a PASI 75 at a particular time point in a clinical trial means that the PASI score of a patient has decreased by 75% as compared to that patient's PASI score at baseline. Similarly a PASI 50 or a PASI 90 denotes a 50% or 90% reduction in PASI score.

Another commonly used measure of psoriasis severity in clinical trials is the static Physicians Global Assessment (sPGA). The sPGA is typically a six category scale rating ranging from 0=none to 5=severe. ENBREL® (etanercept), Package Insert, 2008. A sPGA score of "clear" or "minimal" (sometimes alternately referred to as "almost clear") requires no or minimal elevation of plaques, no or only very faint redness, and no scaling or minimal scaling over <5% of the area of the plaques. ENBREL® (etanercept), Package Insert, 2008. The individual elements of psoriasis plaque morphology or degree of body surface area involvement are not quantified. Nonetheless, sPGA scores correlate to some extent with PASI scores. Langley and Ellis (2004), *J. Am. Acad. Dermatol.* 51(4): 563-69. The methods described herein lessen or eliminate psoriasis symptoms as measured by a PASI or an sPGA score.

Multiple sclerosis (MS) is an autoimmune disease characterized by damage to the myelin sheath that surrounds nerves, which leads to inhibition or total blockage of nerve impulses. The disease is very heterogeneous in clinical presentation, and there is a wide variation in response to treatment as well. van Baarsen et al. (2006), *Genes and Immunity* 7: 522-531. Environmental factors, possibly viral infection, as well as genetic susceptibility, are thought to play a role in causing MS. *Id.* Symptoms can include loss of balance, muscle spasms, tremors, weakness, loss of ability to walk, loss of coordination, various bowel and bladder problems, numbness, pain, tingling, slurred speech, difficulty chewing and swallowing, double vision, loss of vision, uncontrollable eye movements, and depression, among many other possible symptoms. In many patients episodes in which symptoms occur are interspersed with long periods of remission. A subset of MS patients exhibit a pattern of gene expression consistent with high type I IFN activity, although a correlation between this pattern of gene expression and disease severity has not been demonstrated. *Id.* The methods described herein can lessen or eliminate one or more symptoms of MS.

Type I diabetes is an autoimmune disease resulting in the destruction of insulin-producing  $\beta$ -cells in the pancreas, which leads to a lack of insulin. Antibodies against  $\beta$ -cell epitopes are detected in the sera of pre-diabetic patients, suggesting that there is an autoimmune process in progress during a long asymptomatic period that precedes the onset of clinical symptoms. Reynier et al. (2010), *Genes and Immunity* 11: 269-278. The lack of insulin leads to high glucose levels in the blood and urine causing a variety of symptoms including frequent urination, increased hunger and thirst, fatigue, and weight loss. It is generally treated with insulin, a treatment that must be continued indefinitely. The causes of type I diabetes are not completely clear, but are thought to include a genetic component. About thirty percent of non-diabetic siblings of diabetic patients are found to express high levels of RNAs encoded by a group genes activated by type I interferon, although diabetic patients

do not overexpress these RNAs. Reynier et al. (2010), *Genes and Immunity* 11: 269-278. Such overexpression may be an indication of future disease. Since various strategies for inhibiting the progress of the disease are known and may be discovered in the future, it is useful to detect the disease before the onset of clinical symptoms. The methods described herein may be useful to detect and/or treat type I diabetes before and/or  
5 after the onset of clinical symptoms.

Inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis are also IFN- $\gamma$ -mediated diseases as meant herein. Crohn's disease is chronic and debilitating inflammatory bowel disease that is thought to reflect a overly-active T<sub>H</sub>1-mediated immune response to the flora of the gut. The lesions of Crohn's disease can appear anywhere in the bowel and occasionally elsewhere in the gastrointestinal tract.  
10 Ulcerative colitis lesions, on the other hand, usually appear in the colon. The nature of the lesions is also different, but the diseases are sufficiently similar that is sometimes difficult to distinguish them clinically. See, e.g., U.S. Patent 6,558,661.

A variety of evidence indicates that IFN- $\gamma$  plays a role in inflammatory bowel diseases. Results from a clinical study using an anti-human IFN- $\gamma$  antibody in patients with Crohn's disease indicated that the antibody  
15 produced dose dependent, though somewhat marginal, improvements in Crohn's Disease Activity Index (CDAI) scores. International Application Publication WO 2003/097082. The CDAI is described in Best et al. (1976), *Gastroenterology* 70: 439-444. The portions of this reference that describe the CDAI and how to use it are incorporated herein by reference. In addition, data from model systems for inflammatory bowel disease indicate that IFN- $\gamma$  inhibition can be effective in reducing the symptoms of inflammatory bowel diseases. See, e.g., U.S.  
20 Patent 6,558,661, the relevant portions of which are incorporated herein by reference. The methods described herein may be useful for selecting IBD patients to treat, for treating IBD patients, and/or for reducing or eliminating symptoms of IBD.

Sarcoidosis is a systemic granulomatous disease that can affect essentially any tissue, but it primarily affects the lung and lymphatic systems. It is characterized by the presence of noncaseating epithelioid cell  
25 granulomas in more than one organ system. Most commonly the granulomas are found in lung, lymph nodes, skin, liver, and/or spleen, among other possible sites. It can be fatal. For example, fibrosis of the lungs can lead to fatality. Increases in IFN- $\gamma$  levels have been observed in sarcoidosis. Carter and Hunninghake, "Sarcoidosis," Chapter 47 in *Samter's Immunological Diseases*, 6<sup>th</sup> Edition, Austen et al., eds., Lippincott Williams & Wilkins, Philadelphia, PA, 2001. IFN- $\gamma$  plays a crucial role in the pathogenesis of sarcoidosis. See,  
30 e.g., Kriegova et al. (2011), *Eur. Respir. J.* 38: 1136-1143. The methods described herein may be useful for selecting sarcoidosis patients to treat, for treating sarcoidosis patients, and/or for reducing or eliminating symptoms of sarcoidosis.

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal disease having clinical manifestations including fever, hepatosplenomegaly, lymphadenopathy, jaundice and rash. Laboratory findings  
35 associated with HLH include lymphocytosis and histiocytosis and the pathologic finding of hemophagocytosis. Pancytopenia, elevated serum ferritin levels, and abnormal liver enzymes are also frequently present. IFN- $\gamma$  has

been clearly implicated in driving the disease process in a murine model for hemophagocytic anemia. Zoller et al. (2011), J. Exp. Med. 208(6): 1203-1214. The methods described herein may be useful for selecting HLH patients to treat, for treating HLH patients, and/or for reducing or eliminating symptoms of HLH.

For any IFN- $\gamma$ -mediated disease, it would be valuable to have a test to identify patients likely to benefit from a particular treatment. Due to the episodic nature of symptoms in many such diseases, it would also be desirable to be able to evaluate the biological effects of a given treatment without having to wait for the recurrence of symptoms, or lack thereof. Thus, in the methods described herein, expression of one or more biomarkers listed in Table 1, 2, 4, 5, and/or 6 can be measured before treatment begins as a method for determining whether genes regulated by IFN- $\gamma$  are dysregulated in the patient. If so, an IFN- $\gamma$  inhibitor may be an effective treatment. Expression of biomarkers (such as those in Table 1, 2, 4, 5, and/or 6) can also be measured after treatment has begun to determine whether the dosage of the IFN- $\gamma$  inhibitor is having a biological effect. Such information can inform treatment decisions and may be correlated with clinical signs and symptoms of the disease. For example, if the IFN- $\gamma$  inhibitor is not having a biological effect, treatment can be discontinued or a different dosage can be administered. If the IFN- $\gamma$  inhibitor is having a biological effect, then the treatment can be continued. Such information can also be used to determine what doses are having a pharmacodynamic effect, i.e., are modulating the expression of a gene or genes whose expression is regulated by IFN- $\gamma$ .

#### *Interferon Gamma Inhibitors*

Appropriate for use in the methods described herein are inhibitors of human IFN- $\gamma$ , which can be proteins, small molecules, or proteins conjugated to non-protein moieties, such as, for example, a pegylated protein. The capacity of a particular small molecule or protein to inhibit the activity of human IFN- $\gamma$  can be measured by the A549 bioassay described above.

Numerous proteins that are IFN- $\gamma$  inhibitors are known. For example, anti-IFN- $\gamma$  antibodies can inhibit IFN- $\gamma$ . These can be human, humanized, or chimeric antibodies that bind to human IFN- $\gamma$  and/or other mammalian homologs such as rhesus, cynomolgus monkey, chimpanzee, mouse, rabbit, rat, baboon, gorilla, and/or marmoset IFN- $\gamma$ . They can be of the IgG, IgE, IgM, IgA, or IgD isotypes. They can be IgG1, IgG2, IgG3, or IgG4 antibodies. In some embodiments, these antibodies that contain the following pairs of heavy and light chain variable regions: SEQ ID NOs:6 and 8; SEQ ID NOs:10 and 12; SEQ ID NOs: 14 and 16; SEQ ID NOs:14 and 31; and SEQ ID NOs:30 and 12. Further, these antibodies can contain the following pairs of heavy and light chain amino acid sequences: SEQ ID NO:19 and SEQ ID NO:20; SEQ ID NO:17 and SEQ ID NO:18; SEQ ID NO:21 and SEQ ID NO:22; SEQ ID NO:32 and SEQ ID NO:20; or SEQ ID NO:21 and SEQ ID NO:33. These antibodies, which include an antibody called AMG 811 that is used in the clinical trials described in the Examples below, are described in detail in U.S. Patent 7,335,743. The portions of U.S. Patent 7,335,743 that describe these antibodies are incorporated herein by reference. These antibodies can contain a heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising SEQ ID NO:35, a heavy chain CDR3 comprising SEQ ID NO:36 or SEQ ID NO:37, a light chain CDR1 comprising SEQ ID NO:38, SEQ ID NO:39, or SEQ ID NO:40, a light chain CDR2 comprising SEQ ID NO:41 or SEQ ID NO:42, and a light chain CDR3

comprising SEQ ID NO:43 or SEQ ID NO:44. In particular embodiments, the antibody can include the following heavy chain CDR1, CDR2, and CDR3 and light chain CDR1, CDR2, and CDR3, respectively: a) SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:41, and SEQ ID NO:43; b) SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:41, and SEQ ID NO:43; c) SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:41, and SEQ ID NO:43; or d) SEQ ID NO:34, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:40, SEQ ID NO:42, and SEQ ID NO:44.

Other IFN- $\gamma$  inhibitors are also contemplated. Any monoclonal anti-IFN- $\gamma$  antibody capable of inhibiting the activity of human IFN- $\gamma$  can be used. Among these are the humanized anti-IFN- $\gamma$  antibody fontolizumab (HUZAF® PDL Biopharma, Inc.). The sequences of the heavy and light chain variable regions of this antibody are reported in U.S. Patent Application Publication 2002/0091240 as SEQ ID NOs:6 and 8, respectively. These sequences and any other description of this antibody included in U.S. Patent Application Publication 2002/0091240 are incorporated herein by reference. The IFN- $\gamma$  inhibitors described in U.S. Patent 5,451,658 (the relevant portions of which, including the amino acid sequences of the inhibitors, are incorporated herein by reference) are among the

IFN- $\gamma$  inhibitors that can be used to perform the methods described herein. Similarly, IFN- $\gamma$  inhibitors comprising a portion of a naturally occurring human IFN- $\gamma$  receptor, the sequence of which is reported in Aguet et al. (1988), Cell 55: 273-280 (the relevant portions of which are incorporated herein by reference), can be used to practice the methods described herein. One such IFN- $\gamma$  inhibitor is a fusion protein comprising the extracellular region of the human IFN- $\gamma$  receptor fused to a human IgG1 Fc region, which is described in U.S. Patent 6,558,661, the relevant portions of which are incorporated herein by reference. Other such IFN- $\gamma$  inhibitors are the fusion proteins containing part or all of the extracellular regions of IFN- $\gamma$  receptor  $\alpha$  and IFN- $\gamma$  receptor  $\beta$ , as described in U.S. Patent Application Publication 2007/0020283, the relevant portions of which are incorporated herein by reference. Another IFN- $\gamma$  inhibitor is the cytokine which is a specific antagonist of IFN- $\gamma$ , which is described in U.S. Patent 5,612,195, the relevant portions of which are incorporated herein by reference. Still other IFN- $\gamma$  inhibitors are the genetically modified, inactivated protein derivatives of human IFN- $\gamma$  described in U.S. Patent Application Publication 2010/0158865, the relevant portions of which are incorporated herein by reference. Further, a BCRF1 protein, which inhibits production of IFN- $\gamma$ , is an IFN- $\gamma$  inhibitor that can be used to practice the methods described herein. U.S. Patent 5,736,390 describes such BCRF1 proteins, and the portions of U.S. Patent 5,736,390 that describe these proteins and how to make them are incorporated herein by reference.

In addition, various chemical compounds (which are not proteins) are known to inhibit the synthesis of IFN- $\gamma$  and are considered to be IFN- $\gamma$  inhibitors, as meant herein. Among these are the bis phenol or phenoxy compounds and derivatives thereof described in U.S. Patent 5,880,146. The portions of U.S. Patent 5,880,146 that describes such compounds and how to make them are incorporated herein by reference. Similarly, the compounds described in U.S. Patent 5,985,863 that inhibit production of IFN- $\gamma$  by inhibiting production of IFN- $\gamma$  inducing factor or inhibiting interleukin-1 $\beta$  converting enzyme are IFN- $\gamma$  inhibitors that can be used to practice the methods described herein.

### *Methods of Making IFN- $\gamma$ Inhibitors*

With regard to protein inhibitors of IFN- $\gamma$ , these can be made by methods well known in the art. Antibodies, for example, can be made by introducing hybridoma cells that produce the antibody into the peritoneal cavity of a live mouse, a so-called ascites preparation. Hybridoma cells producing an antibody can also be cultured *in vitro*. Other *in vivo* methods of protein production include, for example, protein production in hen eggs, tobacco leaves, and milk. Protein inhibitors of IFN- $\gamma$  can also be made in prokaryotic or eukaryotic host cells, including bacteria such as *Escherichia coli*, various yeasts including *Saccharomyces cerevisiae* and *Pichia pastoris*, and various kinds of mammalian cells including, without limitation, human cells, baby hamster kidney (BHK) cells, Chinese hamster ovary (CHO) cells, VERO, BHK, HeLa, CV1 (including Cos), MDCK, 293, 3T3, myeloma cell lines (e.g., NSO, NS1), PC12, and WI38 cells. Such host cells, into which nucleic acids encoding the desired protein have been introduced, can be cultured in appropriate culture medium, many of which are known in the art, and the desired protein can be recovered from the cell mass or the cell culture medium.

CHO cells are widely used for the production of complex recombinant proteins, e.g. cytokines, clotting factors, and antibodies (Brasel *et al.* (1996), Blood 88:2004-2012; Kaufman *et al.* (1988), J. Biol. Chem. 263:6352-6362; McKinnon *et al.* (1991), J. Mol. Endocrinol. 6:231-239; Wood *et al.* (1990), J. Immunol. 145:3011-3016). The dihydrofolate reductase (DHFR)-deficient mutant cell lines (Urlaub *et al.* (1980), Proc. Natl. Acad. Sci. U.S.A. 77: 4216-4220, which is incorporated by reference), DXB11 and DG-44, are desirable CHO host cell lines because the efficient DHFR selectable and amplifiable gene expression system allows high level recombinant protein expression in these cells (Kaufman R.J. (1990), Meth. Enzymol. 185:537-566, which is incorporated by reference). In addition, these cells are easy to manipulate as adherent or suspension cultures and exhibit relatively good genetic stability. CHO cells and recombinant proteins expressed in them have been extensively characterized and have been approved for use in clinical commercial manufacturing by regulatory agencies. The methods of the invention can also be practiced using hybridoma cell lines that produce an antibody. Methods for making hybridoma lines are well known in the art. See e.g. Berzofsky *et al.* in Paul, ed., *Fundamental Immunology, Second Edition*, pp.315-356, at 347-350, Raven Press Ltd., New York (1989). Cell lines derived from the above-mentioned lines are also suitable for making IFN- $\gamma$  inhibitor proteins.

### *Determining Dosage Using Biomarkers*

Described herein are methods for determining a pharmacodynamically effective dosage of an IFN- $\gamma$  inhibitor for treating an IFN- $\gamma$  mediated disease, as well as methods of treatment using such dosages. The method includes assaying for the expression of one or more genes at either the protein or RNA level both before and after administering an IFN- $\gamma$  inhibitor. The gene(s) can be selected from the genes listed in Table 1 (genes whose expression is modulated in human blood by stimulation with IFN- $\gamma$  *ex vivo*), Table 2 (twenty genes whose expression is modulated in human blood to the greatest extent by IFN- $\gamma$  stimulation *ex vivo*), Table 3 (ten genes whose expression is modulated to the greatest extent by administration of AMG 811 *in vivo*), Table 5 (genes whose expression is modulated by a neutralizing human anti-human IFN- $\gamma$  antibody *in vivo*), and/or Table 6

(genes whose expression is modulated in human blood by stimulation with IFN- $\gamma$  *ex vivo* and whose expression is modulated by a neutralizing human anti-human IFN- $\gamma$  antibody *in vivo*). Those doses that modulate the expression of one or more of these genes in a direction consistent with inhibition of IFN- $\gamma$  can be used to treat an IFN- $\gamma$  mediated disease.

Alternatively or in addition, a pharmacodynamically effective dosage and/or dosing frequency of an IFN- $\gamma$  inhibitor can be determined by the effect of an IFN- $\gamma$  inhibitor on the serum concentration of total IFN- $\gamma$  protein. For example, some doses of an IFN- $\gamma$  inhibitor, for example an IFN- $\gamma$  binding protein such as AMG 811, can cause elevation of the serum levels of total IFN- $\gamma$ . See Figures 6A and 6B below. Presumably, this effect results from protection of IFN- $\gamma$  that is bound by the IFN- $\gamma$  inhibitor from degradation or more rapid clearance. If patients receiving a higher dose of an IFN- $\gamma$  inhibitor (for example, 180 mg SC of AMG 811 in Figure 6A) reach about the same levels of total IFN- $\gamma$  as those attained by patients receiving a somewhat lower dose (for example, 60 mg SC of AMG 811 in Figure 6A), it may be that all available IFN- $\gamma$  is protected at the lower dose. A desirable dose of an IFN- $\gamma$  binding protein, for example AMG 811, would be one that causes patients to achieve a higher-than-baseline level of total IFN- $\gamma$  and to maintain this "plateau" concentration for a time period of, for example, at least about 2, 3, 4, 5, 6, 7, or 8 weeks and/or at least about 1, 2, 3, or 4 months. Based on the data in Figures 6A and 6B for AMG 811, a desirable dose can be greater than about 20 mg SC, at least about 60 mg SC, at least about 180 mg SC, and/or at least about 60 mg IV. Further, using a dose of an IFN- $\gamma$  inhibitor such that the levels of total IFN- $\gamma$  reach and maintain a higher-than-baseline plateau concentration for at least about 2 weeks, dosing frequency can be adjusted such that the levels of total IFN- $\gamma$  do not fall below about 25%, 50%, 60%, 70%, or 80% of this plateau value. Thus, at a lower dose of an IFN- $\gamma$  inhibitor where a plateau value is maintained for a shorter period, dosing can be more frequent, whereas at a higher dose of an IFN- $\gamma$  inhibitor where a plateau value is maintained for a longer period, dosing can be less frequent. For example, based on the data in Figures 6A and 6B, at a dose of 60 mg SC of AMG 811, doses can be administered approximately every 2, 3, 4, or 5 weeks. Similarly, at a dose of AMG 811 of 180 mg SC or 60 mg IV, doses can be administered approximately every 6, 7, 8, 9, 10, 11, or 12 weeks.

In a particular embodiment, at least the lower end of dosage ranges for treating patients having SLE and/or lupus nephritis with a human anti-human IFN- $\gamma$  antibody called AMG 811 have been clarified. See Examples 3 and 4 and Figures 4, 6-9, and 12-14. In that data, the lowest dose at which a clear biological effect was observed was a dose of 20 milligrams, although clearer effects were observed in some cases at a dose of 60 mg.

For any IFN- $\gamma$  inhibitor that contains a protein, for example an anti-huIFN- $\gamma$  antibody such as AMG 811, the dose can be at least about 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, or 250 mg and/or may not exceed 180, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, or 2000 mg. For example, a per-treatment dose of about 15-500, 20-400, 30-300, 60-180, 80-200, or 100-200 milligrams of the antibody can be used to treat an IFN- $\gamma$ -mediated disease.

Alternatively, a per-treatment dose of about 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 220, 240, 260, 270, 290, 300, 350, or 400 milligrams can be used.

Alternatively, a dose can be gauged on the basis of a patient's body weight. For example, a dose of at least about 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, or 5.0 milligrams per kilogram (mg/kg) and/or not more than about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, or 10 mg/kg can be administered. In some embodiments, the dose can be from about 0.2 mg/kg to about 10 mg/kg, from about 0.25 mg/kg to about 8 mg/kg, from about 0.5 mg/kg to about 5 mg/kg, from about 1 mg/kg to about 2 mg/kg, from about 1 mg/kg to about 3 mg/kg, or from about 3 mg/kg to about 5 mg/kg.

Alternatively, a dose can be administered on the basis of the calculated body surface area of a patient. For example, a dose of at least about 4, 6, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 130, 140, 150, 160, 170, 180, or 190 milligrams per square millimeter (mg/mm<sup>2</sup>) and/or not more than 200, 220, 240, 260, 280, 300, 320, 340, 360, or 380 mg/mm<sup>2</sup> can be administered. In some embodiments the dose can be from about 8 mg/mm<sup>2</sup> to about 380 mg/mm<sup>2</sup>, from about 10 mg/mm<sup>2</sup> to about 300 mg/mm<sup>2</sup>, from about 20 mg/mm<sup>2</sup> to about 190 mg/mm<sup>2</sup>, from about 40 mg/mm<sup>2</sup> to about 80 mg/mm<sup>2</sup>, from about 80 mg/mm<sup>2</sup> to about 200 mg/mm<sup>2</sup>.

Since many IFN- $\gamma$ -mediated diseases are chronic and/or recurrent, repeated doses of the IFN- $\gamma$  inhibitor, optionally an anti-huIFN- $\gamma$  antibody, may be required. Repeated doses can be administered, for example, twice per week, once a week, every two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve weeks, or once every one, two, three, four, five, six, seven, eight, nine, ten, eleven, or twelve months.

#### **Patient Stratification**

It is always advantageous for clinicians and patients to be able to predict whether a given treatment will be effective for a particular patient. This is particularly true where the disease commonly includes long asymptomatic periods, either alternating with symptomatic periods or before the onset of symptoms. Provided herein are methods for determining which patients are likely to be successfully treated with an IFN- $\gamma$  inhibitor. As discussed above, there are a number of IFN- $\gamma$  mediated diseases. These include various autoimmune and inflammatory diseases including SLE, including discoid lupus and lupus nephritis, rheumatoid arthritis, type I diabetes, multiple sclerosis, psoriasis, dermatomyositis, sarcoidosis, HLH, and IBDs including Crohn's disease and ulcerative colitis, among a number of others. In the Examples below, it is shown that some genes whose expression was found to be upregulated by IFN- $\gamma$  *ex vivo* are downregulated by an anti-human IFN- $\gamma$  antibody *in vivo*. These genes are listed in Table 6 below.

Provided are methods for identifying patients suffering from an IFN- $\gamma$  mediated disease likely to benefit from treatment with an IFN- $\gamma$  inhibitor comprising determining whether the expression of one or more genes listed in Tables 1, 2, 4, 5, and/or 6 in a biological sample from the patient deviates from the expression of that gene(s) in a control biological sample in a direction consistent with excess IFN- $\gamma$ . If the level of expression of one or more genes mentioned above in the biological sample from the patient deviates from the levels of expression in the control biological sample in a direction consistent with excess IFN- $\gamma$ , it can indicate that the

patient is a candidate for treatment with an IFN- $\gamma$  inhibitor. The IFN- $\gamma$  inhibitor can be an anti-huIFN- $\gamma$  antibody or an IFN- $\gamma$  receptor.

In another aspect, patients likely to benefit from treatment with an IFN- $\gamma$  inhibitor can be identified by determining the levels of total IFN- $\gamma$  in a biological sample from the patient as, for example, described in

5 Example 3. Patients with undetectable or very low levels of total IFN- $\gamma$  may not benefit from therapy with an IFN- $\gamma$  inhibitor, for example an IFN- $\gamma$  binding protein such as an antibody. On the other hand, patients whose biological samples have total IFN- $\gamma$  levels that are substantially higher than those detected in a control biological sample can benefit from therapy with an IFN- $\gamma$  inhibitor, for example an IFN- $\gamma$  binding protein such as an antibody. Thus, determination of total IFN- $\gamma$  levels in a biological sample from a patient can be used to identify patients likely to  
10 benefit from therapy with an IFN- $\gamma$  inhibitor, for example an IFN- $\gamma$  binding protein such as an anti-IFN- $\gamma$  antibody.

#### *Methods for Determining Treatment Efficacy*

The methods provided herein can be useful for patients and clinicians in deciding whether to continue a treatment with an IFN- $\gamma$  inhibitor in a particular patient. In the clinical studies reported in the Examples below, it is reported that the expression of a number of genes is modulated in a statistically significant manner in response  
15 to treatment with an anti-huIFN- $\gamma$  antibody. In a variable and episodic disease such as, for example, SLE or MS, it may be impossible to tell from clinical signs and symptoms whether a treatment is having an effect within a given time period, such as, for example, 1, 2, or 3 weeks or 1, 2, 3, 4, 5, or 6 months. If, however, the expression of a biomarker listed in Table 1, 2, 4, 5, and/or 6 is modulated in a direction consistent with inhibition of IFN- $\gamma$ , then it can be known that the treatment is having a biological effect, even though the patient might not  
20 show immediate changes in signs and symptoms. In such a case, according to the judgment of a clinician, it can be reasonable to continue treatment. However, if the expression of a biomarker listed in Table 1, 2, 4, 5, and/or 6 is not modulated by the IFN- $\gamma$  inhibitor or is modulated in a direction consistent with an excess of IFN- $\gamma$ , and there is not a change in signs and symptoms, it could be reasonably concluded that the patient is not responding to treatment. In such a situation, according to a clinician's judgment, treatment with an IFN- $\gamma$  inhibitor could be  
25 discontinued, and a different treatment could be initiated.

Provided are methods for determining the efficacy of an IFN- $\gamma$  inhibitor such as an anti-huIFN- $\gamma$  antibody. Such an anti-huIFN- $\gamma$  antibody can comprise the amino acid sequence of SEQ ID NO: 6, 10, 14, or 30 and SEQ ID NO: 8, 12, 16, or 31 and/or can comprise a light chain CDR1 comprising SEQ ID NO:38, 39, or 40, a light chain CDR2 comprising SEQ ID NO:41 or 42, a light chain CDR3 comprising SEQ ID NO:43 or 44, a  
30 heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising SEQ ID NO:35, and a heavy chain CDR3 comprising SEQ ID NO:36 or 37. A method for determining the efficacy of an IFN- $\gamma$  inhibitor as a treatment for an IFN- $\gamma$ -mediated disease can comprise the following steps: 1) determining the level of expression of one or more of the genes listed in Table 1, 2, 4, 5, and/or 6 in a biological sample from a patient at the protein or RNA level; 2) determining the level of expression of the same gene(s) in a biological sample from  
35 the patient after administration of the drug; 3) comparing the expression of the gene(s) in biological samples

- from the patient before and after administration of the drug; 4) determining that the drug has shown evidence of efficacy if the level of expression of the gene(s) in the biological sample taken after administration of the drug has been modulated in a direction consistent with inhibition of IFN- $\gamma$ ; and 5) continuing treatment with the drug if it is determined that the drug has shown evidence of efficacy and discontinuing treatment with the drug if it is
- 5 determined that the drug has not shown evidence of efficacy.

### *Combination Therapies*

Treatments exist for most IFN- $\gamma$ -mediated diseases, even though many of these treatments are relatively ineffective, effective for only a subset of patients, and/or have substantial toxicities that limit patient tolerance of treatment. The IFN- $\gamma$  inhibitors described herein can be combined with other existing therapies for

10 IFN- $\gamma$ -mediated diseases.

In particular, an SLE patient can be treated concurrently with another therapy for SLE plus an IFN- $\gamma$  inhibitor such as an anti-IFN- $\gamma$  antibody comprising SEQ ID NO:6 and SEQ ID NO:8 and/or comprising a light chain CDR1 comprising SEQ ID NO:38, a light chain CDR2 comprising SEQ ID NO:41, a light chain CDR3 comprising SEQ ID NO:43, a heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising

15 SEQ ID NO:35, and a heavy chain CDR3 comprising SEQ ID NO:36. Existing therapies for SLE include glucocorticoids such as prednisone, prednisolone, and methylprednisolone, antimalarials such as hydroxychloroquine, quinacrine, and chloroquine, retinoic acid, aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), cyclophosphamide, dehydroepiandrosterone, mycophenolate mofetil, azathioprine,

20 chlorambucil, methotrexate, tacrolimus, dapsone, thalidomide, leflunomide, cyclosporine, anti-CD20 antibodies such as rituximab, BlyS inhibitors such as belimumab, and fusion proteins such as abatacept. Methods of patient stratification and biomarker monitoring concurrently with treatment, as described herein, can be used in patients receiving such combination drug treatments.

In other embodiments a patient suffering from an inflammatory bowel disease (IBD), such as Crohn's disease or ulcerative colitis, can be concurrently treated with a therapy for IBD plus an IFN- $\gamma$  inhibitor, such as an

25 anti-huIFN- $\gamma$  antibody comprising SEQ ID NO:6 and SEQ ID NO:8 and/or comprising a light chain CDR1 comprising SEQ ID NO:38, a light chain CDR2 comprising SEQ ID NO:41, a light chain CDR3 comprising SEQ ID NO:43, a heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising SEQ ID NO:35, and a heavy chain CDR3 comprising SEQ ID NO:36. Existing therapies for IBD include sulfasalazine, 5-aminosalicylic acid and its derivatives (such as olsalazine, balsalazide, and mesalamine), anti-TNF antibodies

30 (including infliximab, adalimumab, golimumab, and certolizumab pegol), corticosteroids for oral or parenteral administration (including prednisone, methylprednisone, budesonide, or hydrocortisone), adrenocorticotrophic hormone, antibiotics (including metronidazole, ciprofloxacin, or rifaximin), azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, and thalidomide. Methods of patient stratification and biomarker monitoring concurrently with treatment, as described herein, can be used in patients receiving such combination

35 drug treatments.

In other embodiments, a patient suffering from rheumatoid arthritis can be concurrently treated with a drug used for RA therapy plus an IFN- $\gamma$  inhibitor, such as an anti-huIFN- $\gamma$  antibody comprising SEQ ID NO:6 and SEQ ID NO:8 and/or comprising a light chain CDR1 comprising SEQ ID NO:38, a light chain CDR2 comprising SEQ ID NO:41, a light chain CDR3 comprising SEQ ID NO:43, a heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising SEQ ID NO:35, and a heavy chain CDR3 comprising SEQ ID NO:36. Therapies for rheumatoid arthritis (RA) include non-steroidal anti-inflammatory drugs (NSAIDs) (such as aspirin and cyclooxygenase-2 (COX-2) inhibitors), disease modifying anti-inflammatory drugs (DMARDs) (such as methotrexate, leflunomide, and sulfasalazine), anti-malarials (such as hydroxychloroquine), cyclophosphamide, D-penicillamine, azathioprine, gold salts, tumor necrosis factor inhibitors (such as etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol), CD20 inhibitors such as rituximab, IL-1 antagonists such as anakinra, IL-6 inhibitors such as tocilizumab, inhibitors of Janus kinases (JAK) (such as tofacitinib), abatacept, and glucocorticoids, among others. Methods of patient stratification and biomarker monitoring concurrently with treatment, as described herein, can be used in patients receiving such combination drug treatments.

In another embodiment, a patient suffering from sarcoidosis can be concurrently treated with a drug used for sarcoidosis therapy plus an IFN- $\gamma$  inhibitor, such as an anti-huIFN- $\gamma$  antibody comprising SEQ ID NO:6 and SEQ ID NO:8 and/or comprising a light chain CDR1 comprising SEQ ID NO:38, a light chain CDR2 comprising SEQ ID NO:41, a light chain CDR3 comprising SEQ ID NO:43, a heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising SEQ ID NO:35, and a heavy chain CDR3 comprising SEQ ID NO:36. Therapies for sarcoidosis include corticosteroids (may be topical or parenteral, depending on symptoms), salicylates (such as aspirin), and colchicine. Methotrexate, cyclophosphamide, azathioprine, and nonsteroidal anti-inflammatory drugs have also been used in sarcoidosis. Various other treatment strategies can be helpful for some of the many different symptoms of sarcoidosis. For example, heart arrhythmias can be treated with antiarrhythmics or a pacemaker. Hypercalcemia can be treated with hydration, reduction in calcium and vitamin D intake, avoidance of sunlight, or ketoconazole. Skin lesions can be treated with chloroquine, hydroxychloroquine, methotrexate, or thalidomide. Methods of patient stratification and biomarker monitoring concurrently with treatment, as described herein, can be used in patients receiving such a combination treatment including an IFN- $\gamma$  inhibitor plus an existing treatment for sarcoidosis.

In another embodiment, a patient suffering from HLH can be concurrently treated with a drug used for HLH therapy plus an IFN- $\gamma$  inhibitor such as an anti-huIFN- $\gamma$  antibody comprising SEQ ID NO:6 and SEQ ID NO:8 and/or comprising a light chain CDR1 comprising SEQ ID NO:38, a light chain CDR2 comprising SEQ ID NO:41, a light chain CDR3 comprising SEQ ID NO:43, a heavy chain CDR1 comprising SEQ ID NO:34, a heavy chain CDR2 comprising SEQ ID NO:35, and a heavy chain CDR3 comprising SEQ ID NO:36. Therapies for HLH include corticosteroids, intravenous immunoglobulin, IL-1 inhibiting agents such as anakinra, VP-16, etoposide, cyclosporine A, dexamethasone, various other chemotherapeutics, bone marrow transplant or stem cell transplant, and antiviral and/or antibacterial agents. Any one or more of these therapies can be combined with an anti-huIFN- $\gamma$  treatment. Further, methods of patient stratification and biomarker monitoring concurrently with

treatment, as described herein, can be used in patients receiving such a combination treatment including an IFN- $\gamma$  inhibitor plus an existing treatment for HLH.

#### *Methods of Administration*

The IFN- $\gamma$  inhibitors and the other disease treatments described herein can be administered by any feasible method. Therapeutics that comprise a protein will ordinarily be administered by injection since oral administration, in the absence of some special formulation or circumstance, would lead to hydrolysis of the protein in the acid environment of the stomach. Subcutaneous, intramuscular, intravenous, intraarterial, intravesical, or peritoneal injection are possible routes of administration. Topical administration is also possible, especially for diseases involving the skin. Alternatively, IFN- $\gamma$  inhibitors, and/or other therapeutics comprising a protein, can be administered through contact with a mucus membrane, for example by intra-nasal, sublingual, vaginal, or rectal administration or as an inhalant. Therapeutics that are small molecules can be administered orally, although the routes of administration mentioned above are also possible.

Having described the invention in general terms above, the following examples are offered by way of illustration and not limitation.

#### EXAMPLES

##### *Example 1: Determining the identity of genes whose expression in blood is modulated by IFN- $\gamma$ ex vivo*

To define a group of genes regulated by IFN- $\gamma$ , blood from healthy volunteers was collected into sodium heparin tubes, and then incubated at 37°C, 5 % CO<sub>2</sub> with or without 294 pM recombinant human IFN- $\gamma$  for 0, 24, or 48 hours. After incubation, the blood was added to PAXGENE® whole blood tubes (Becton Dickinson Catalog # 762165) and processed for RNA purification.

Total RNA was isolated from the PAXGENE® whole blood tubes using the PAXGENE® RNA Kit (Qiagen Catalog # 762164) on the QIACUBE® automated sample prep system. Samples were labeled using the AGILENT® Low RNA Input Linear Amplification Kit PLUS, Two-Color (Agilent Catalog # 5188-5340) per manufacturer's instructions. Briefly, double-stranded cDNA was reverse transcribed from about 300 nanograms of total RNA and acted as template for T7 RNA polymerase in an *in vitro* transcription reaction in which the target material was simultaneously amplified and labeled with cyanine 3- or cyanine 5-CTPs. The resulting fluorescent complementary RNA was hybridized to AGILENT® human whole genome 4x44K (Cat # G4112F) oligonucleotide microarrays per manufacturer's instructions.

Extracted feature intensities for each channel on each array were processed separately by subtracting the lower 0.1<sup>th</sup> percentile from all intensities and then taking the log base 2. The transformed intensities were mapped using a non-linear function to ensure the distribution of the intensities were comparable between arrays

and channels. Arrays were hybridized using a loop-design that allowed estimation and removal of technical bias when averaging the technical repeats.

Samples were processed in batches that roughly corresponded to samples from individual cohorts but with a small number of samples repeated between batches to allow estimation and removal of batch effects.

5 Finally, replicates of any identical sequences on the array were averaged to produce a value we called gene intensities.

In additional to the above processing, a pre-filtering step was applied. Reporters with low levels of expression were removed if 90% of the values fell below the limit of detection, defined as 1.96 standard deviations above mean background. Background was determined by a set of sequences on the array that are  
10 specifically designed to not hybridize with human sequences. Reporters with small dispersion are unlikely to be meaningfully changed, and so, to reduce noise, these were removed. They were defined as those where the fold change between the 5<sup>th</sup> and 95<sup>th</sup> percentile was less than 1.5.

Statistical analysis of the data to identify genes regulated *ex vivo* by IFN- $\gamma$  was performed using a fixed-effects regression model containing factors for donor, time, treatment and all pair wise interactions terms. The  
15 treatment effect was similar at the two post-treatment times of 24 and 48 hours (data not shown), so these data were considered a single group to display the treatment effect. The significance threshold was defined at a false discovery rate of 5% and a fold change of 1.72. See Storey, J.D. 2002. A direct approach to false discovery rates. J. R. Statist. Soc. B. 64: 479-498, the relevant portions of which are incorporated herein by reference. The fold change was selected because we expected about 90% power to detect this fold change at a significance  
20 level of 0.001 assuming a standard deviation of 0.38. The results from this analysis are shown in Figure 1.

In Figure 1 each dot represents the average fold change in expression of an individual gene at the RNA level in blood from a healthy volunteer stimulated *ex vivo* with IFN- $\gamma$  as compared to the same blood pre-stimulation. The x-axis reflects the fold change, and the y-axis represents the p-value of the difference in gene expression in post-stimulation blood as compared to pre-stimulation blood. Generally, a p-value of 0.05 or less  
25 would be considered to indicate statistical significance. The circled dots in Figure 1 correspond to the twenty genes that showed the greatest fold change in expression upon stimulation with IFN- $\gamma$ , where the change had a nominal significance level of 0.001 or less. These data show that a large number of genes are up- and down-regulated by IFN- $\gamma$ . Table 1 below lists genes that were found to be up- or down-regulated by *ex vivo* stimulation with IFN- $\gamma$ . The criteria applied to select these genes from among the tens of thousands of genes on the array  
30 were a false discovery rate of <0.001, powered at 90% to detect an alpha of 0.001.

Table 1: Genes whose expression is modulated by IFN- $\gamma$

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                           | Direction of modulation by IFN- $\gamma$ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|-------------------------------------|------------------------------------------|
| A_23_P112026        | SEQ ID NO:350                                      | INDO           | NM_002164                              | indoleamine-pyrrole 2,3 dioxygenase | up                                       |
| A_23_P161428        | SEQ ID NO:72                                       | ANKRD22        | NM_144590                              | ankyrin repeat domain 22            | up                                       |
| A_23_P18452         | SEQ ID NO:109                                      | CXCL9          | NM_002416                              | chemokine (C-X-C motif) ligand 9    | up                                       |
| A_23_P7827          | SEQ ID NO:83                                       | RP1-93H18.5    | NM_001010919                           | hypothetical protein LOC441168      | up                                       |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                       | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_24_P28722         | SEQ ID NO:351                                      | RSAD2          | NM_080657                              | radical S-adenosyl methionine domain containing 2                                                                               | up                               |
| A_23_P150457        | SEQ ID NO:352                                      | XLKD1          | NM_006691                              | extracellular link domain containing 1                                                                                          | down                             |
| A_24_P165864        | SEQ ID NO:300                                      | P2RY14         | NM_014879                              | purinergic receptor P2Y, G-protein coupled, 14                                                                                  | up                               |
| A_23_P74290         | SEQ ID NO:79                                       | GBP5           | NM_052942                              | guanylate binding protein 5                                                                                                     | up                               |
| A_23_P63390         | SEQ ID NO:73                                       | FCGR1B         | NM_001017986                           | Fc fragment of IgG, high affinity Ib, receptor (CD64)                                                                           | up                               |
| A_24_P245379        | SEQ ID NO:353                                      | SERPINB2       | NM_002575                              | serpin peptidase inhibitor, clade B (ovalbumin), member 2                                                                       | down                             |
| A_24_P316965        | SEQ ID NO:354                                      | RSAD2          | NM_080657                              | radical S-adenosyl methionine domain containing 2                                                                               | up                               |
| A_24_P561165        | SEQ ID NO:322                                      | A_24_P561165   | A_24_P561165                           | Unknown                                                                                                                         | up                               |
| A_23_P121657        | SEQ ID NO:355                                      | HS3ST1         | NM_005114                              | heparan sulfate (glucosamine) 3-O-sulfotransferase 1                                                                            | down                             |
| A_23_P203882        | SEQ ID NO:356                                      | MMP19          | NM_002429                              | matrix metalloproteinase 19                                                                                                     | down                             |
| A_24_P303091        | SEQ ID NO:311                                      | CXCL10         | NM_001565                              | chemokine (C-X-C motif) ligand 10 (IP-10)                                                                                       | up                               |
| A_32_P107372        | SEQ ID NO:76                                       | GBP1           | NM_002053                              | guanylate binding protein 1, interferon-inducible, 67kDa                                                                        | up                               |
| A_23_P62890         | SEQ ID NO:74                                       | GBP1           | NM_002053                              | guanylate binding protein 1, interferon-inducible, 67kDa                                                                        | up                               |
| A_23_P256487        | SEQ ID NO:78                                       | CD274          | ENST00000381577                        | CD274 molecule                                                                                                                  | up                               |
| A_23_P65651         | SEQ ID NO:278                                      | WARS           | NM_004184                              | tryptophanyl-tRNA synthetase                                                                                                    | up                               |
| A_23_P18604         | SEQ ID NO:232                                      | LAP3           | NM_015907                              | leucine aminopeptidase 3                                                                                                        | up                               |
| A_24_P12690         | SEQ ID NO:357                                      | INDOL1         | AK128691                               | indoleamine-pyrrole 2,3 dioxygenase-like 1                                                                                      | up                               |
| A_23_P48513         | SEQ ID NO:269                                      | IFI27          | NM_005532                              | interferon, alpha-inducible protein 27                                                                                          | up                               |
| A_24_P478940        | SEQ ID NO:358                                      | A_24_P478940   | THC2668815                             | Low quality annotation - Q4TBH3_TETNG (Q4TBH3) Chromosome 13 SCAF7124, whole genome shotgun sequence, partial (3%) [THC2668815] | down                             |
| A_23_P103496        | SEQ ID NO:196                                      | GBP4           | NM_052941                              | guanylate binding protein 4                                                                                                     | up                               |
| A_23_P42353         | SEQ ID NO:77                                       | ETV7           | NM_016135                              | ets variant gene 7 (TEL2 oncogene)                                                                                              | up                               |
| A_23_P62115         | SEQ ID NO:359                                      | TIMP1          | NM_003254                              | TIMP metalloproteinase inhibitor 1                                                                                              | down                             |
| A_24_P270460        | SEQ ID NO:309                                      | IFI27          | NM_005532                              | interferon, alpha-inducible protein 27                                                                                          | up                               |
| A_23_P74609         | SEQ ID NO:360                                      | G0S2           | NM_015714                              | G0/G1switch 2                                                                                                                   | up                               |
| A_23_P39840         | SEQ ID NO:163                                      | VAMP5          | NM_006634                              | vesicle-associated membrane protein 5 (myobrevin)                                                                               | up                               |
| A_23_P27306         | SEQ ID NO:361                                      | COLEC12        | NM_030781                              | collectin sub-family member 12                                                                                                  | down                             |
| A_24_P45446         | SEQ ID NO:108                                      | GBP4           | NM_052941                              | guanylate binding protein 4                                                                                                     | up                               |
| A_23_P76386         | SEQ ID NO:362                                      | SLC6A12        | NM_003044                              | solute carrier family 6 (neurotransmitter transporter, betaine/GABA), member 12                                                 | up                               |
| A_23_P121253        | SEQ ID NO:110                                      | TNFSF10        | NM_003810                              | tumor necrosis factor (ligand) superfamily, member 10                                                                           | up                               |
| A_23_P91390         | SEQ ID NO:363                                      | THBD           | NM_000361                              | thrombomodulin                                                                                                                  | down                             |
| A_24_P167642        | SEQ ID NO:301                                      | GCH1           | NM_000161                              | GTP cyclohydrolase 1 (dopa-responsive dystonia)                                                                                 | up                               |
| A_23_P338479        | SEQ ID NO:75                                       | CD274          | NM_014143                              | CD274 molecule                                                                                                                  | up                               |
| A_23_P21485         | SEQ ID NO:364                                      | FLJ20701       | NM_017933                              | hypothetical protein FLJ20701                                                                                                   | down                             |
| A_23_P33723         | SEQ ID NO:365                                      | CD163          | NM_004244                              | CD163 molecule                                                                                                                  | down                             |
| A_23_P420196        | SEQ ID NO:366                                      | SOC31          | NM_003745                              | suppressor of cytokine signaling 1                                                                                              | up                               |
| A_23_P165624        | SEQ ID NO:226                                      | TNFAIP6        | NM_007115                              | tumor necrosis factor, alpha-induced protein 6                                                                                  | up                               |
| A_24_P912985        | SEQ ID NO:326                                      | A_24_P912985   | A_24_P912985                           | Unknown                                                                                                                         | up                               |
| A_24_P15702         | SEQ ID NO:298                                      | LOC389386      | XR_017251                              | similar to leucine aminopeptidase 3                                                                                             | up                               |
| A_23_P156687        | SEQ ID NO:221                                      | CFB            | NM_001710                              | complement factor B                                                                                                             | up                               |
| A_23_P137366        | SEQ ID NO:367                                      | SEQ ID         | NM_000491                              | complement component 1, q subcomponent,                                                                                         | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                   | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------|
|                     |                                                    | NO:100C1 QB    |                                        | B chain                                                                                                                     |                                  |
| A_23_P139123        | SEQ ID NO:210                                      | SERPING1       | NM_000062                              | serpin peptidase inhibitor, clade G (C1 inhibitor), member 1, (angioedema, hereditary)                                      | up                               |
| A_23_P384355        | SEQ ID NO:368                                      | A_23_P384355   | BG547557                               | Low quality annotation - BG547557 602575410F1 NIH_MGC_77 Homo sapiens cDNA clone IMAGE:4703546 5', mRNA sequence [BG547557] | up                               |
| A_23_P55356         | SEQ ID NO:369                                      | VMO1           | NM_182566                              | vitelline membrane outer layer 1 homolog (chicken)                                                                          | down                             |
| A_23_P32500         | SEQ ID NO:370                                      | STAB1          | NM_015136                              | stabilin 1                                                                                                                  | down                             |
| A_32_P171061        | SEQ ID NO:371                                      | ASCL2          | NM_005170                              | achaete-scute complex homolog 2 (Drosophila)                                                                                | up                               |
| A_23_P210763        | SEQ ID NO:238                                      | JAG1           | NM_000214                              | jagged 1 (Alagille syndrome)                                                                                                | up                               |
| A_24_P48204         | SEQ ID NO:320                                      | SECTM1         | NM_003004                              | secreted and transmembrane 1                                                                                                | up                               |
| A_23_P354387        | SEQ ID NO:257                                      | FER1L3         | NM_013451                              | fer-1-like 3, myoferlin (C. elegans)                                                                                        | up                               |
| A_24_P353638        | SEQ ID NO:372                                      | SLAMF7         | NM_021181                              | SLAM family member 7                                                                                                        | up                               |
| A_23_P53891         | SEQ ID NO:270                                      | KLF5           | NM_001730                              | Kruppel-like factor 5 (intestinal)                                                                                          | up                               |
| A_32_P44394         | SEQ ID NO:87                                       | AIM2           | NM_004833                              | absent in melanoma 2                                                                                                        | up                               |
| A_23_P153185        | SEQ ID NO:373                                      | SERPINB2       | ENST00000299502                        | serpin peptidase inhibitor, clade B (ovalbumin), member 2                                                                   | down                             |
| A_23_P200138        | SEQ ID NO:374                                      | SLAMF8         | NM_020125                              | SLAM family member 8                                                                                                        | up                               |
| A_23_P207456        | SEQ ID NO:375                                      | CCL8           | NM_005623                              | chemokine (C-C motif) ligand 8                                                                                              | up                               |
| A_24_P380734        | SEQ ID NO:376                                      | SDC2           | NM_002998                              | syndecan 2 (heparan sulfate proteoglycan 1, cell surface-associated, fibroglycan)                                           | down                             |
| A_23_P370682        | SEQ ID NO:80                                       | BATF2          | NM_138456                              | basic leucine zipper transcription factor, ATF-like 2                                                                       | up                               |
| A_23_P329261        | SEQ ID NO:251                                      | KCNJ2          | NM_000891                              | potassium inwardly-rectifying channel, subfamily J, member 2                                                                | up                               |
| A_24_P383523        | SEQ ID NO:317                                      | SAMD4A         | NM_015589                              | sterile alpha motif domain containing 4A                                                                                    | up                               |
| A_23_P167328        | SEQ ID NO:377                                      | CD38           | NM_001775                              | CD38 molecule                                                                                                               | up                               |
| A_23_P209625        | SEQ ID NO:236                                      | CYP1B1         | NM_000104                              | cytochrome P450, family 1, subfamily B, polypeptide 1                                                                       | down                             |
| A_23_P335661        | SEQ ID NO:253                                      | SAMD4A         | AB028976                               | sterile alpha motif domain containing 4A                                                                                    | up                               |
| A_23_P159325        | SEQ ID NO:378                                      | ANGPTL4        | NM_139314                              | angiopoietin-like 4                                                                                                         | down                             |
| A_23_P2831          | SEQ ID NO:379                                      | EDNRB          | NM_003991                              | endothelin receptor type B                                                                                                  | down                             |
| A_23_P35412         | SEQ ID NO:256                                      | IFIT3          | NM_001549                              | interferon-induced protein with tetratricopeptide repeats 3                                                                 | up                               |
| A_23_P29773         | SEQ ID NO:380                                      | LAMP3          | NM_014398                              | lysosomal-associated membrane protein 3                                                                                     | up                               |
| A_23_P101992        | SEQ ID NO:381                                      | MARCO          | NM_006770                              | macrophage receptor with collagenous structure                                                                              | down                             |
| A_23_P105794        | SEQ ID NO:197                                      | EPST11         | NM_033255                              | epithelial stromal interaction 1 (breast)                                                                                   | up                               |
| A_23_P207507        | SEQ ID NO:382                                      | ABCC3          | NM_003786                              | ATP-binding cassette, sub-family C (CFTR/MRP), member 3                                                                     | down                             |
| A_23_P45871         | SEQ ID NO:383                                      | IFI44L         | NM_006820                              | interferon-induced protein 44-like                                                                                          | up                               |
| A_23_P75430         | SEQ ID NO:285                                      | C11ORF75       | NM_020179                              | chromosome 11 open reading frame 75                                                                                         | up                               |
| A_24_P350686        | SEQ ID NO:106                                      | TIFA           | NM_052864                              | TRAF-interacting protein with a forkhead-associated domain                                                                  | up                               |
| A_23_P57709         | SEQ ID NO:384                                      | PCOLCE2        | NM_013363                              | procollagen C-endopeptidase enhancer 2                                                                                      | down                             |
| A_23_P70095         | SEQ ID NO:385                                      | CD74           | NM_001025158                           | CD74 molecule, major histocompatibility complex, class II invariant chain                                                   | up                               |
| A_32_P56001         | SEQ ID NO:386                                      | CD93           | NM_012072                              | CD93 molecule                                                                                                               | down                             |
| A_24_P943205        | SEQ ID NO:332                                      | EPST11         | ENST00000313624                        | epithelial stromal interaction 1 (breast)                                                                                   | up                               |
| A_24_P305067        | SEQ ID NO:387                                      | HOXB4          | NM_024015                              | homeobox B4                                                                                                                 | up                               |
| A_23_P347541        | SEQ ID NO:99                                       | GRIN3A         | NM_133445                              | glutamate receptor, ionotropic, N-methyl-D-aspartate 3A                                                                     | up                               |
| A_32_P162183        | SEQ ID NO:338                                      | C2             | NM_000063                              | complement component 2                                                                                                      | up                               |
| A_23_P30913         | SEQ ID NO:388                                      | HLA-DPA1       | NM_033554                              | major histocompatibility complex, class II, DP alpha 1                                                                      | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                                                   | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P211445        | SEQ ID NO:240                                      | LIMK2          | NM_016733                              | LIM domain kinase 2                                                                                                                                                                                                                         | up                               |
| A_23_P207905        | SEQ ID NO:389                                      | SECTM1         | NM_003004                              | secreted and transmembrane 1                                                                                                                                                                                                                | up                               |
| A_23_P128050        | SEQ ID NO:390                                      | BCL2L14        | NM_030766                              | BCL2-like 14 (apoptosis facilitator)                                                                                                                                                                                                        | up                               |
| A_23_P41765         | SEQ ID NO:261                                      | IRF1           | NM_002198                              | interferon regulatory factor 1                                                                                                                                                                                                              | up                               |
| A_24_P245815        | SEQ ID NO:306                                      | ASPHD2         | AK097157                               | aspartate beta-hydroxylase domain containing 2                                                                                                                                                                                              | up                               |
| A_23_P86682         | SEQ ID NO:391                                      | FER1L3         | NM_013451                              | fer-1-like 3, myoferlin (C. elegans)                                                                                                                                                                                                        | up                               |
| A_23_P58390         | SEQ ID NO:392                                      | C4ORF32        | NM_152400                              | chromosome 4 open reading frame 32                                                                                                                                                                                                          | up                               |
| A_23_P56630         | SEQ ID NO:89                                       | STAT1          | NM_007315                              | signal transducer and activator of transcription 1, 91kDa                                                                                                                                                                                   | up                               |
| A_23_P25354         | SEQ ID NO:393                                      | P2RX7          | NM_002562                              | purinergic receptor P2X, ligand-gated ion channel, 7                                                                                                                                                                                        | up                               |
| A_23_P358709        | SEQ ID NO:394                                      | AHRR           | NM_020731                              | aryl-hydrocarbon receptor repressor                                                                                                                                                                                                         | down                             |
| A_23_P207003        | SEQ ID NO:395                                      | 40790          | NM_004574                              | sepin 4                                                                                                                                                                                                                                     | up                               |
| A_24_P170136        | SEQ ID NO:396                                      | A_24_P170136   | ENST00000383097                        | Low quality annotation - similar to HLA class II histocompatibility antigen, DP alpha chain precursor (HLA-SB alpha chain) (MHC class II DP3-alpha) (DP(W3)) (DP(W4)) (LOC642043), mRNA [Source:RefSeq_dna;Acc:XR_018078] [ENST00000383097] | up                               |
| A_23_P144959        | SEQ ID NO:397                                      | CSPG2          | NM_004385                              | chondroitin sulfate proteoglycan 2 (versican)                                                                                                                                                                                               | down                             |
| A_23_P163079        | SEQ ID NO:225                                      | GCH1           | NM_000161                              | GTP cyclohydrolase 1 (dopa-responsive dystonia)                                                                                                                                                                                             | up                               |
| A_23_P134176        | SEQ ID NO:398                                      | SOD2           | NM_001024465                           | superoxide dismutase 2, mitochondrial                                                                                                                                                                                                       | up                               |
| A_24_P852756        | SEQ ID NO:399                                      | HLA-DQA2       | NM_020056                              | major histocompatibility complex, class II, DQ alpha 2                                                                                                                                                                                      | up                               |
| A_24_P165423        | SEQ ID NO:400                                      | RBP7           | NM_052960                              | retinol binding protein 7, cellular                                                                                                                                                                                                         | down                             |
| A_32_P9543          | SEQ ID NO:348                                      | APOBEC3A       | NM_145699                              | apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3A                                                                                                                                                                         | up                               |
| A_32_P15169         | SEQ ID NO:336                                      | A_32_P15169    | A_32_P15169                            | Unknown                                                                                                                                                                                                                                     | up                               |
| A_24_P7040          | SEQ ID NO:401                                      | LOC123862      | XR_017225                              | similar to Interferon-induced transmembrane protein 3 (Interferon-inducible protein 1-8U)                                                                                                                                                   | up                               |
| A_24_P378019        | SEQ ID NO:402                                      | IRF7           | NM_004031                              | interferon regulatory factor 7                                                                                                                                                                                                              | up                               |
| A_23_P59005         | SEQ ID NO:113                                      | TAP1           | NM_000593                              | transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)                                                                                                                                                                                 | up                               |
| A_23_P331928        | SEQ ID NO:403                                      | CD109          | NM_133493                              | CD109 molecule                                                                                                                                                                                                                              | down                             |
| A_23_P218928        | SEQ ID NO:243                                      | C4ORF18        | NM_016613                              | chromosome 4 open reading frame 18                                                                                                                                                                                                          | down                             |
| A_23_P8513          | SEQ ID NO:290                                      | SNX10          | NM_013322                              | sorting nexin 10                                                                                                                                                                                                                            | up                               |
| A_24_P54863         | SEQ ID NO:142                                      | C4ORF32        | NM_152400                              | chromosome 4 open reading frame 32                                                                                                                                                                                                          | up                               |
| A_23_P17837         | SEQ ID NO:231                                      | APOL1          | NM_145343                              | apolipoprotein L, 1                                                                                                                                                                                                                         | up                               |
| A_23_P65427         | SEQ ID NO:277                                      | PSME2          | NM_002818                              | proteasome (prosome, macropain) activator subunit 2 (PA28 beta)                                                                                                                                                                             | up                               |
| A_32_P30004         | SEQ ID NO:342                                      | A_32_P30004    | AF086044                               | Low quality annotation - Homo sapiens full length insert cDNA clone YX74D05. [AF086044]                                                                                                                                                     | up                               |
| A_23_P421423        | SEQ ID NO:263                                      | TNFAIP2        | NM_006291                              | tumor necrosis factor, alpha-induced protein 2                                                                                                                                                                                              | up                               |
| A_23_P14174         | SEQ ID NO:213                                      | TNFSF13B       | NM_006573                              | tumor necrosis factor (ligand) superfamily, member 13b                                                                                                                                                                                      | up                               |
| A_23_P29237         | SEQ ID NO:404                                      | APOL3          | NM_145841                              | apolipoprotein L, 3                                                                                                                                                                                                                         | up                               |
| A_23_P64721         | SEQ ID NO:276                                      | GPR109B        | NM_006018                              | G protein-coupled receptor 109B                                                                                                                                                                                                             | up                               |
| A_23_P166633        | SEQ ID NO:405                                      | ITGB5          | NM_002213                              | integrin, beta 5                                                                                                                                                                                                                            | down                             |
| A_24_P98109         | SEQ ID NO:334                                      | SNX10          | NM_013322                              | sorting nexin 10                                                                                                                                                                                                                            | up                               |
| A_24_P243528        | SEQ ID NO:406                                      | HLA-DPA1       | NM_033554                              | major histocompatibility complex, class II, DP alpha 1                                                                                                                                                                                      | up                               |
| A_23_P83098         | SEQ ID NO:289                                      | ALDH1A1        | NM_000689                              | aldehyde dehydrogenase 1 family, member A1                                                                                                                                                                                                  | up                               |
| A_23_P166797        | SEQ ID NO:228                                      | RTP4           | NM_022147                              | receptor (chemosensory) transporter protein 4                                                                                                                                                                                               | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                      | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P214821        | SEQ ID NO:407                                      | EDN1           | NM_001955                              | endothelin 1                                                                                                                   | up                               |
| A_23_P123608        | SEQ ID NO:107                                      | JAK2           | NM_004972                              | Janus kinase 2 (a protein tyrosine kinase)                                                                                     | up                               |
| A_23_P11543         | SEQ ID NO:408                                      | FUCA1          | NM_000147                              | fucosidase, alpha-L- 1, tissue                                                                                                 | down                             |
| A_23_P259901        | SEQ ID NO:409                                      | TKTL1          | NM_012253                              | transketolase-like 1                                                                                                           | down                             |
| A_23_P145874        | SEQ ID NO:215                                      | SAMD9L         | NM_152703                              | sterile alpha motif domain containing 9-like                                                                                   | up                               |
| A_23_P217269        | SEQ ID NO:410                                      | VSIG4          | NM_007268                              | V-set and immunoglobulin domain containing 4                                                                                   | down                             |
| A_23_P33384         | SEQ ID NO:411                                      | CIITA          | NM_000246                              | class II, major histocompatibility complex, transactivator                                                                     | up                               |
| A_23_P85783         | SEQ ID NO:412                                      | PHGDH          | NM_006623                              | phosphoglycerate dehydrogenase                                                                                                 | up                               |
| A_32_P166272        | SEQ ID NO:96                                       | A_32_P166272   | THC2650457                             | Low quality annotation - ALU6_HUMAN (P39193) Alu subfamily SP sequence contamination warning entry, partial (12%) [THC2650457] | up                               |
| A_23_P150768        | SEQ ID NO:413                                      | SLCO2B1        | NM_007256                              | solute carrier organic anion transporter family, member 2B1                                                                    | down                             |
| A_24_P319113        | SEQ ID NO:414                                      | P2RX7          | NM_002562                              | purinergic receptor P2X, ligand-gated ion channel, 7                                                                           | up                               |
| A_23_P206212        | SEQ ID NO:415                                      | THBS1          | NM_003246                              | thrombospondin 1                                                                                                               | down                             |
| A_24_P239731        | SEQ ID NO:416                                      | B4GALT5        | NM_004776                              | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 5                                                               | up                               |
| A_24_P98210         | SEQ ID NO:335                                      | TFEC           | NM_012252                              | transcription factor EC                                                                                                        | up                               |
| A_32_P87697         | SEQ ID NO:417                                      | HLA-DRA        | NM_019111                              | major histocompatibility complex, class II, DR alpha                                                                           | up                               |
| A_23_P417383        | SEQ ID NO:418                                      | SASP           | NM_152792                              | skin aspartic protease                                                                                                         | up                               |
| A_23_P45099         | SEQ ID NO:419                                      | HLA-DRB5       | NM_002125                              | major histocompatibility complex, class II, DR beta 5                                                                          | up                               |
| A_23_P3014          | SEQ ID NO:420                                      | RNASE6         | NM_003615                              | ribonuclease, RNase A family, k6                                                                                               | down                             |
| A_24_P868905        | SEQ ID NO:421                                      | LOC391020      | XR_018907                              | similar to Interferon-induced transmembrane protein 3 (Interferon-inducible protein 1-8U)                                      | up                               |
| A_24_P557479        | SEQ ID NO:422                                      | BIRC4BP        | NM_017523                              | XIAP associated factor-1                                                                                                       | up                               |
| A_24_P196827        | SEQ ID NO:423                                      | HLA-DQA1       | NM_002122                              | major histocompatibility complex, class II, DQ alpha 1                                                                         | up                               |
| A_24_P365469        | SEQ ID NO:424                                      | B4GALT5        | NM_004776                              | UDP-Gal:betaGlcNAc beta 1,4-galactosyltransferase, polypeptide 5                                                               | up                               |
| A_23_P72737         | SEQ ID NO:283                                      | IFITM1         | NM_003641                              | interferon induced transmembrane protein 1 (9-27)                                                                              | up                               |
| A_23_P8108          | SEQ ID NO:425                                      | HLA-DQB1       | NM_002123                              | major histocompatibility complex, class II, DQ beta 1                                                                          | up                               |
| A_24_P322353        | SEQ ID NO:91                                       | PSTPIP2        | NM_024430                              | proline-serine-threonine phosphatase interacting protein 2                                                                     | up                               |
| A_23_P209995        | SEQ ID NO:426                                      | IL1RN          | NM_173842                              | interleukin 1 receptor antagonist                                                                                              | up                               |
| A_23_P23074         | SEQ ID NO:427                                      | IFI44          | NM_006417                              | interferon-induced protein 44                                                                                                  | up                               |
| A_23_P73837         | SEQ ID NO:428                                      | TLR8           | NM_018610                              | toil-like receptor 8                                                                                                           | up                               |
| A_23_P160720        | SEQ ID NO:224                                      | SNFT           | NM_018664                              | Jun dimerization protein p21SNFT                                                                                               | up                               |
| A_32_P184394        | SEQ ID NO:339                                      | TFEC           | NM_012252                              | transcription factor EC                                                                                                        | up                               |
| A_23_P87545         | SEQ ID NO:429                                      | IFITM3         | NM_021034                              | interferon induced transmembrane protein 3 (1-8U)                                                                              | up                               |
| A_23_P48414         | SEQ ID NO:430                                      | CCNA1          | NM_003914                              | cyclin A1                                                                                                                      | up                               |
| A_23_P258769        | SEQ ID NO:431                                      | HLA-DPB1       | NM_002121                              | major histocompatibility complex, class II, DP beta 1                                                                          | up                               |
| A_23_P96556         | SEQ ID NO:94                                       | GK             | NM_203391                              | glycerol kinase                                                                                                                | up                               |
| A_23_P63209         | SEQ ID NO:432                                      | HSD11B1        | NM_181755                              | hydroxysteroid (11-beta) dehydrogenase 1                                                                                       | up                               |
| A_23_P31006         | SEQ ID NO:433                                      | HLA-DRB5       | NM_002125                              | major histocompatibility complex, class II, DR beta 5                                                                          | up                               |
| A_23_P120316        | SEQ ID NO:434                                      | MTHFD2         | NM_001040409                           | methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase                           | up                               |
| A_23_P63896         | SEQ ID NO:92                                       | FAS            | NM_000043                              | Fas (TNF receptor superfamily, member 6)                                                                                       | up                               |
| A_24_P845223        | SEQ ID NO:435                                      | A_24_P845223   | M27126                                 | Low quality annotation - Human lymphocyte antigen (DRw8) mRNA. [M27126]                                                        | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                                                   | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P81698         | SEQ ID NO:288                                      | UBD            | NM_006398                              | ubiquitin D                                                                                                                                                                                                                                 | up                               |
| A_23_P153320        | SEQ ID NO:217                                      | ICAM1          | NM_000201                              | intercellular adhesion molecule 1 (CD54), human rhinovirus receptor                                                                                                                                                                         | up                               |
| A_23_P213102        | SEQ ID NO:436                                      | PALLD          | NM_016081                              | palladin, cytoskeletal associated protein                                                                                                                                                                                                   | down                             |
| A_23_P819           | SEQ ID NO:437                                      | ISG15          | NM_005101                              | ISG15 ubiquitin-like modifier                                                                                                                                                                                                               | up                               |
| A_23_P202029        | SEQ ID NO:438                                      | SPFH1          | NM_006459                              | SPFH domain family, member 1                                                                                                                                                                                                                | up                               |
| A_23_P170719        | SEQ ID NO:439                                      | A_23_P170719   | A_23_P170719                           | Unknown                                                                                                                                                                                                                                     | down                             |
| A_24_P367576        | SEQ ID NO:440                                      | RCBTB2         | AK125170                               | regulator of chromosome condensation (RCC1) and BTB (POZ) domain containing protein 2                                                                                                                                                       | down                             |
| A_23_P69109         | SEQ ID NO:281                                      | PLSCR1         | NM_021105                              | phospholipid scramblase 1                                                                                                                                                                                                                   | up                               |
| A_23_P19510         | SEQ ID NO:441                                      | HLA-DQB2       | NM_182549                              | major histocompatibility complex, class II, DQ beta 2                                                                                                                                                                                       | up                               |
| A_24_P100387        | SEQ ID NO:85                                       | GK             | NM_203391                              | glycerol kinase                                                                                                                                                                                                                             | up                               |
| A_23_P4283          | SEQ ID NO:442                                      | BIRC4BP        | NM_017523                              | XIAP associated factor-1                                                                                                                                                                                                                    | up                               |
| A_24_P288836        | SEQ ID NO:443                                      | HLA-DPB2       | NR_001435                              | major histocompatibility complex, class II, DP beta 2 (pseudogene)                                                                                                                                                                          | up                               |
| A_24_P66027         | SEQ ID NO:324                                      | APOBEC3 B      | NM_004900                              | apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like 3B                                                                                                                                                                         | up                               |
| A_23_P157136        | SEQ ID NO:444                                      | SCIN           | NM_033128                              | scinderin                                                                                                                                                                                                                                   | up                               |
| A_24_P274270        | SEQ ID NO:88                                       | STAT1          | NM_139266                              | signal transducer and activator of transcription 1, 91kDa                                                                                                                                                                                   | up                               |
| A_23_P306148        | SEQ ID NO:445                                      | PML            | NM_002675                              | promyelocytic leukemia                                                                                                                                                                                                                      | up                               |
| A_24_P370472        | SEQ ID NO:446                                      | HLA-DRB4       | NM_021983                              | major histocompatibility complex, class II, DR beta 4                                                                                                                                                                                       | up                               |
| A_23_P218549        | SEQ ID NO:447                                      | EMR3           | NM_032571                              | egf-like module containing, mucin-like, hormone receptor-like 3                                                                                                                                                                             | down                             |
| A_24_P246626        | SEQ ID NO:448                                      | A_24_P246626   | ENST00000308384                        | Low quality annotation - similar to HLA class II histocompatibility antigen, DP alpha chain precursor (HLA-SB alpha chain) (MHC class II DP3-alpha) (DP(W3)) (DP(W4)) (LOC642074), mRNA [Source:RefSeq_dna;Acc:XR_018081] [ENST00000308384] | up                               |
| A_23_P358944        | SEQ ID NO:449                                      | PML            | NM_033244                              | promyelocytic leukemia                                                                                                                                                                                                                      | up                               |
| A_23_P69383         | SEQ ID NO:101                                      | PARP9          | NM_031458                              | poly (ADP-ribose) polymerase family, member 9                                                                                                                                                                                               | up                               |
| A_24_P343929        | SEQ ID NO:450                                      | OAS2           | NM_016817                              | 2'-5'-oligoadenylate synthetase 2, 69/71kDa                                                                                                                                                                                                 | up                               |
| A_24_P354800        | SEQ ID NO:451                                      | HLA-DOA        | NM_002119                              | major histocompatibility complex, class II, DO alpha                                                                                                                                                                                        | up                               |
| A_32_P209960        | SEQ ID NO:452                                      | CIITA          | NM_000246                              | class II, major histocompatibility complex, transactivator                                                                                                                                                                                  | up                               |
| A_24_P118892        | SEQ ID NO:453                                      | IRF7           | NM_004029                              | interferon regulatory factor 7                                                                                                                                                                                                              | up                               |
| A_24_P222655        | SEQ ID NO:305                                      | C1QA           | NM_015991                              | complement component 1, q subcomponent, A chain                                                                                                                                                                                             | up                               |
| A_24_P119745        | SEQ ID NO:454                                      | FN1            | NM_212482                              | fibronectin 1                                                                                                                                                                                                                               | down                             |
| A_23_P34835         | SEQ ID NO:455                                      | LMNA           | NM_005572                              | lamin A/C                                                                                                                                                                                                                                   | down                             |
| A_24_P578437        | SEQ ID NO:456                                      | A_24_P578437   | BE926212                               | Low quality annotation - BE926212 RC5-BN0193-310800-034-A04 BN0193 Homo sapiens cDNA, mRNA sequence [BE926212]                                                                                                                              | up                               |
| A_23_P47955         | SEQ ID NO:457                                      | OAS3           | NM_006187                              | 2'-5'-oligoadenylate synthetase 3, 100kDa                                                                                                                                                                                                   | up                               |
| A_24_P169013        | SEQ ID NO:458                                      | HLA-DRB6       | NR_001298                              | major histocompatibility complex, class II, DR beta 6 (pseudogene)                                                                                                                                                                          | up                               |
| A_23_P76450         | SEQ ID NO:459                                      | PHLDA1         | NM_007350                              | pleckstrin homology-like domain, family A, member 1                                                                                                                                                                                         | down                             |
| A_23_P328740        | SEQ ID NO:460                                      | LINCR          | BC012317                               | likely ortholog of mouse lung-inducible Neutralized-related C3HC4 RING domain protein                                                                                                                                                       | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P380857        | SEQ ID NO:259                                      | APOL4          | NM_030643                              | apolipoprotein L, 4                                                                                                                                                                      | up                               |
| A_24_P299318        | SEQ ID NO:461                                      | FAM101B        | NM_182705                              | family with sequence similarity 101, member B                                                                                                                                            | down                             |
| A_32_P13337         | SEQ ID NO:462                                      | A_32_P13337    | THC2645080                             | Unknown                                                                                                                                                                                  | down                             |
| A_23_P4773          | SEQ ID NO:463                                      | LILRB5         | NM_006840                              | leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 5                                                                                                 | down                             |
| A_32_P108254        | SEQ ID NO:464                                      | FAM20A         | NM_017565                              | family with sequence similarity 20, member A                                                                                                                                             | up                               |
| A_24_P343233        | SEQ ID NO:465                                      | HLA-DRB1       | NM_002124                              | major histocompatibility complex, class II, DR beta 1                                                                                                                                    | up                               |
| A_32_P351968        | SEQ ID NO:466                                      | HLA-DMB        | NM_002118                              | major histocompatibility complex, class II, DM beta                                                                                                                                      | up                               |
| A_23_P145336        | SEQ ID NO:467                                      | HLA-DRB3       | BC106057                               | major histocompatibility complex, class II, DR beta 3                                                                                                                                    | up                               |
| A_24_P325520        | SEQ ID NO:468                                      | SORT1          | NM_002959                              | sortilin 1                                                                                                                                                                               | up                               |
| A_32_P75264         | SEQ ID NO:469                                      | TMEM26         | NM_178505                              | transmembrane protein 26                                                                                                                                                                 | down                             |
| A_23_P39364         | SEQ ID NO:470                                      | HOMER3         | NM_004838                              | homer homolog 3 (Drosophila)                                                                                                                                                             | down                             |
| A_24_P402222        | SEQ ID NO:471                                      | HLA-DRB3       | NM_022555                              | major histocompatibility complex, class II, DR beta 3                                                                                                                                    | up                               |
| A_24_P353300        | SEQ ID NO:472                                      | LIMK2          | NM_001031801                           | LIM domain kinase 2                                                                                                                                                                      | up                               |
| A_32_P167592        | SEQ ID NO:473                                      | A_32_P167592   | ENST00000339867                        | Low quality annotation - similar to Interferon-induced transmembrane protein 3 (Interferon-inducible protein 1-8U) (LOC650205), mRNA [Source:RefSeq_dna;Acc:XR_018421] [ENST00000339867] | up                               |
| A_24_P100382        | SEQ ID NO:474                                      | GK             | NM_203391                              | glycerol kinase                                                                                                                                                                          | up                               |
| A_23_P255444        | SEQ ID NO:100                                      | DAPP1          | NM_014395                              | dual adaptor of phosphotyrosine and 3-phosphoinositides                                                                                                                                  | up                               |
| A_23_P359245        | SEQ ID NO:475                                      | MET            | NM_000245                              | met proto-oncogene (hepatocyte growth factor receptor)                                                                                                                                   | down                             |
| A_32_P78121         | SEQ ID NO:476                                      | A_32_P78121    | CD743044                               | Low quality annotation - CD743044 UI-H-FT1-bjx-e-03-0-UI.s1 NCL CGAP_FT1 Homo sapiens cDNA clone UI-H-FT1-bjx-e-03-0-UI 3', mRNA sequence [CD743044]                                     | up                               |
| A_23_P252106        | SEQ ID NO:166                                      | RIPK2          | NM_003821                              | receptor-interacting serine-threonine kinase 2                                                                                                                                           | up                               |
| A_23_P120883        | SEQ ID NO:477                                      | HMOX1          | NM_002133                              | heme oxygenase (decycling) 1                                                                                                                                                             | down                             |
| A_23_P97064         | SEQ ID NO:296                                      | FBXO6          | NM_018438                              | F-box protein 6                                                                                                                                                                          | up                               |
| A_24_P416997        | SEQ ID NO:478                                      | APOL3          | NM_145641                              | apolipoprotein L, 3                                                                                                                                                                      | up                               |
| A_23_P68155         | SEQ ID NO:279                                      | IFIH1          | NM_022168                              | interferon induced with helicase C domain 1                                                                                                                                              | up                               |
| A_23_P149476        | SEQ ID NO:216                                      | EFCAB2         | NM_032328                              | EF-hand calcium binding domain 2                                                                                                                                                         | up                               |
| A_24_P172481        | SEQ ID NO:302                                      | TRIM22         | NM_006074                              | tripartite motif-containing 22                                                                                                                                                           | up                               |
| A_23_P51487         | SEQ ID NO:93                                       | GBP3           | NM_018284                              | guanylate binding protein 3                                                                                                                                                              | up                               |
| A_23_P30900         | SEQ ID NO:479                                      | HLA-DQA1       | BC008585                               | major histocompatibility complex, class II, DQ alpha 1                                                                                                                                   | up                               |
| A_24_P323148        | SEQ ID NO:313                                      | LYPD5          | NM_182573                              | LY6/PLAUR domain containing 5                                                                                                                                                            | up                               |
| A_24_P928052        | SEQ ID NO:327                                      | NRP1           | NM_003873                              | neuropilin 1                                                                                                                                                                             | down                             |
| A_24_P166443        | SEQ ID NO:480                                      | HLA-DPB1       | NM_002121                              | major histocompatibility complex, class II, DP beta 1                                                                                                                                    | up                               |
| A_24_P16124         | SEQ ID NO:481                                      | IFITM4P        | NR_001590                              | interferon induced transmembrane protein 4 pseudogene                                                                                                                                    | up                               |
| A_23_P136683        | SEQ ID NO:482                                      | HLA-DQB1       | M20432                                 | major histocompatibility complex, class II, DQ beta 1                                                                                                                                    | up                               |
| A_24_P278126        | SEQ ID NO:310                                      | NBN            | NM_001024688                           | nibrin                                                                                                                                                                                   | up                               |
| A_23_P203498        | SEQ ID NO:233                                      | TRIM22         | NM_006074                              | tripartite motif-containing 22                                                                                                                                                           | up                               |
| A_23_P125278        | SEQ ID NO:202                                      | CXCL11         | NM_005409                              | chemokine (C-X-C motif) ligand 11                                                                                                                                                        | up                               |
| A_23_P79518         | SEQ ID NO:287                                      | IL1B           | NM_000576                              | interleukin 1, beta                                                                                                                                                                      | down                             |
| A_24_P923271        | SEQ ID NO:483                                      | A_24_P923      | M15073                                 | Low quality annotation - Human MHC class II                                                                                                                                              | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                             | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
|                     |                                                    | 271            |                                        | HLA-DR-beta-1 chain mRNA (DR4,Dw14), 3' end, clone BIN40c30, [M15073]                                                                                                                                                 |                                  |
| A_23_P209678        | SEQ ID NO:237                                      | PLEK           | NM_002664                              | pleckstrin                                                                                                                                                                                                            | up                               |
| A_23_P258493        | SEQ ID NO:247                                      | LMNB1          | NM_005573                              | lamin B1                                                                                                                                                                                                              | up                               |
| A_23_P146943        | SEQ ID NO:484                                      | ATP1B1         | NM_001677                              | ATPase, Na+/K+ transporting, beta 1 polypeptide                                                                                                                                                                       | up                               |
| A_23_P208119        | SEQ ID NO:84                                       | PSTPIP2        | NM_024430                              | proline-serine-threonine phosphatase interacting protein 2                                                                                                                                                            | up                               |
| A_24_P915692        | SEQ ID NO:485                                      | PHLDA1         | NM_007350                              | pleckstrin homology-like domain, family A, member 1                                                                                                                                                                   | down                             |
| A_23_P259561        | SEQ ID NO:486                                      | A_23_P259561   | THC2632039                             | Low quality annotation - Q8SPE4_9PRIM (Q8SPE4) Major histocompatibility complex (Fragment), partial (85%) [THC2632039]                                                                                                | up                               |
| A_24_P361896        | SEQ ID NO:487                                      | MT2A           | NM_005953                              | metallothionein 2A                                                                                                                                                                                                    | up                               |
| A_23_P106844        | SEQ ID NO:488                                      | MT2A           | NM_005953                              | metallothionein 2A                                                                                                                                                                                                    | up                               |
| A_24_P370702        | SEQ ID NO:126                                      | GBP3           | NM_018284                              | guanylate binding protein 3                                                                                                                                                                                           | up                               |
| A_23_P132388        | SEQ ID NO:205                                      | SCO2           | NM_005138                              | SCO cytochrome oxidase deficient homolog 2 (yeast)                                                                                                                                                                    | up                               |
| A_23_P25155         | SEQ ID NO:489                                      | GPR84          | NM_020370                              | G protein-coupled receptor 84                                                                                                                                                                                         | up                               |
| A_23_P64343         | SEQ ID NO:275                                      | TIMM10         | NM_012456                              | translocase of inner mitochondrial membrane 10 homolog (yeast)                                                                                                                                                        | up                               |
| A_24_P97405         | SEQ ID NO:490                                      | CCRL2          | NM_003965                              | chemokine (C-C motif) receptor-like 2                                                                                                                                                                                 | up                               |
| A_24_P190472        | SEQ ID NO:491                                      | SLPI           | NM_003064                              | secretory leukocyte peptidase inhibitor                                                                                                                                                                               | up                               |
| A_23_P207058        | SEQ ID NO:492                                      | SOCS3          | NM_003955                              | suppressor of cytokine signaling 3                                                                                                                                                                                    | up                               |
| A_24_P52168         | SEQ ID NO:493                                      | A_24_P52168    | A_24_P52168                            | Unknown                                                                                                                                                                                                               | up                               |
| A_23_P29953         | SEQ ID NO:248                                      | IL15           | NM_172174                              | interleukin 15                                                                                                                                                                                                        | up                               |
| A_32_P72351         | SEQ ID NO:494                                      | A_32_P72351    | AK026140                               | Low quality annotation - Homo sapiens cDNA: FLJ22487 fis, clone HRC10931, [AK026140]                                                                                                                                  | down                             |
| A_23_P35912         | SEQ ID NO:129                                      | CASP4          | NM_033306                              | caspase 4, apoptosis-related cysteine peptidase                                                                                                                                                                       | up                               |
| A_23_P252413        | SEQ ID NO:495                                      | MT2A           | ENST00000245185                        | metallothionein 2A                                                                                                                                                                                                    | up                               |
| A_32_P118013        | SEQ ID NO:496                                      | A_32_P118013   | THC2657593                             | Low quality annotation - ALU1_HUMAN (P39188) Alu subfamily J sequence contamination warning entry, partial (7%) [THC2657593]                                                                                          | up                               |
| A_23_P201587        | SEQ ID NO:497                                      | SORT1          | NM_002959                              | sortilin 1                                                                                                                                                                                                            | up                               |
| A_23_P347040        | SEQ ID NO:255                                      | DTX3L          | NM_138287                              | deltex 3-like (Drosophila)                                                                                                                                                                                            | up                               |
| A_23_P47304         | SEQ ID NO:267                                      | CASP5          | NM_004347                              | caspase 5, apoptosis-related cysteine peptidase                                                                                                                                                                       | up                               |
| A_23_P133916        | SEQ ID NO:208                                      | C2             | NM_000063                              | complement component 2                                                                                                                                                                                                | up                               |
| A_23_P94412         | SEQ ID NO:295                                      | PDCD1LG2       | NM_025239                              | programmed cell death 1 ligand 2                                                                                                                                                                                      | up                               |
| A_24_P662177        | SEQ ID NO:498                                      | A_24_P662177   | THC2666469                             | Unknown                                                                                                                                                                                                               | up                               |
| A_23_P85693         | SEQ ID NO:90                                       | GBP2           | NM_004120                              | guanylate binding protein 2, interferon-inducible                                                                                                                                                                     | up                               |
| A_24_P48014         | SEQ ID NO:499                                      | SOCS1          | NM_003745                              | suppressor of cytokine signaling 1                                                                                                                                                                                    | up                               |
| A_32_P56249         | SEQ ID NO:500                                      | A_32_P56249    | THC2670291                             | Low quality annotation - UB30_HUMAN (Q70CQ3) Ubiquitin carboxyl-terminal hydrolase 30 (Ubiquitin thioesterase 30) (Ubiquitin-specific-processing protease 30) (Deubiquitinating enzyme 30), partial (5%) [THC2670291] | up                               |
| A_32_P56759         | SEQ ID NO:344                                      | PARP14         | NM_017554                              | poly (ADP-ribose) polymerase family, member 14                                                                                                                                                                        | up                               |
| A_23_P154235        | SEQ ID NO:102                                      | NMI            | NM_004688                              | N-myc (and STAT) interactor                                                                                                                                                                                           | up                               |
| A_24_P397817        | SEQ ID NO:501                                      | LEP            | NM_000230                              | leptin (obesity homolog, mouse)                                                                                                                                                                                       | down                             |
| A_24_P62530         | SEQ ID NO:502                                      | RHOU           | NM_021205                              | ras homolog gene family, member U                                                                                                                                                                                     | up                               |
| A_23_P156788        | SEQ ID NO:222                                      | STX11          | NM_003764                              | synfadin 11                                                                                                                                                                                                           | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                                 | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_24_P925314        | SEQ ID NO:503                                      | GM2A           | AK127910                               | GM2 ganglioside activator                                                                                                                                                                                                 | up                               |
| A_23_P64828         | SEQ ID NO:504                                      | OAS1           | NM_002534                              | 2',5'-oligoadenylate synthetase 1, 40/46kDa                                                                                                                                                                               | up                               |
| A_23_P128541        | SEQ ID NO:505                                      | TRAFD1         | NM_006700                              | TRAF-type zinc finger domain containing 1                                                                                                                                                                                 | up                               |
| A_23_P42718         | SEQ ID NO:506                                      | NFE2L3         | NM_004289                              | nuclear factor (erythroid-derived 2)-like 3                                                                                                                                                                               | up                               |
| A_24_P89457         | SEQ ID NO:507                                      | CDKN1A         | NM_078467                              | cyclin-dependent kinase inhibitor 1A (p21, Cip1)                                                                                                                                                                          | up                               |
| A_23_P14754         | SEQ ID NO:508                                      | HAPLN3         | NM_178232                              | hyaluronan and proteoglycan link protein 3                                                                                                                                                                                | up                               |
| A_23_P103398        | SEQ ID NO:509                                      | PSEN2          | NM_000447                              | presenilin 2 (Alzheimer disease 4)                                                                                                                                                                                        | up                               |
| A_23_P75741         | SEQ ID NO:286                                      | UBE2L6         | NM_198183                              | ubiquitin-conjugating enzyme E2L 6                                                                                                                                                                                        | up                               |
| A_23_P101434        | SEQ ID NO:510                                      | NLRP12         | NM_033297                              | NLR family, pyrin domain containing 12                                                                                                                                                                                    | down                             |
| A_23_P141362        | SEQ ID NO:511                                      | FZD2           | NM_001466                              | frizzled homolog 2 (Drosophila)                                                                                                                                                                                           | up                               |
| A_24_P287043        | SEQ ID NO:512                                      | IFITM2         | NM_006435                              | interferon induced transmembrane protein 2 (1-8D)                                                                                                                                                                         | up                               |
| A_24_P207139        | SEQ ID NO:513                                      | PML            | NM_033238                              | promyelocytic leukemia                                                                                                                                                                                                    | up                               |
| A_23_P121716        | SEQ ID NO:201                                      | ANXA3          | NM_005139                              | annexin A3                                                                                                                                                                                                                | up                               |
| A_23_P120002        | SEQ ID NO:514                                      | SP110          | NM_004510                              | SP110 nuclear body protein                                                                                                                                                                                                | up                               |
| A_23_P111000        | SEQ ID NO:119                                      | PSMB9          | NM_002800                              | proteasome (prosome, macropain) subunit, beta type, 9 (large multifunctional peptidase 2)                                                                                                                                 | up                               |
| A_32_P356316        | SEQ ID NO:515                                      | HLA-DOA        | NM_002119                              | major histocompatibility complex, class II, DO alpha                                                                                                                                                                      | up                               |
| A_23_P69310         | SEQ ID NO:282                                      | CCRL2          | NM_003965                              | chemokine (C-C motif) receptor-like 2                                                                                                                                                                                     | up                               |
| A_24_P254933        | SEQ ID NO:516                                      | A_24_P254933   | ENST00000270031                        | Low quality annotation - interferon induced transmembrane protein 3 (1-8U) (IFITM3), mRNA<br>[Source:RefSeq_dna;Acc:NM_021034]<br>[ENST00000270031]                                                                       | up                               |
| A_23_P85240         | SEQ ID NO:517                                      | TLR7           | NM_016562                              | toll-like receptor 7                                                                                                                                                                                                      | up                               |
| A_24_P36898         | SEQ ID NO:86                                       | GBP2           | ENST00000294663                        | guanylate binding protein 2, interferon-inducible                                                                                                                                                                         | up                               |
| A_23_P210811        | SEQ ID NO:518                                      | CD93           | NM_012072                              | CD93 molecule                                                                                                                                                                                                             | down                             |
| A_23_P133142        | SEQ ID NO:207                                      | ALPK1          | NM_025144                              | alpha-kinase 1                                                                                                                                                                                                            | up                               |
| A_23_P210465        | SEQ ID NO:519                                      | PI3            | NM_002638                              | peptidase inhibitor 3, skin-derived (SKALP)                                                                                                                                                                               | up                               |
| A_23_P24004         | SEQ ID NO:244                                      | IFIT2          | NM_001547                              | interferon-induced protein with tetratricopeptide repeats 2                                                                                                                                                               | up                               |
| A_24_P48898         | SEQ ID NO:321                                      | APOL2          | NM_145637                              | apolipoprotein L 2                                                                                                                                                                                                        | up                               |
| A_23_P82449         | SEQ ID NO:520                                      | DFNA5          | NM_004403                              | deafness, autosomal dominant 5                                                                                                                                                                                            | down                             |
| A_23_P128447        | SEQ ID NO:203                                      | LRRK2          | NM_198578                              | leucine-rich repeat kinase 2                                                                                                                                                                                              | up                               |
| A_23_P416894        | SEQ ID NO:521                                      | LOC54103       | AK126364                               | hypothetical protein LOC54103                                                                                                                                                                                             | up                               |
| A_23_P57036         | SEQ ID NO:522                                      | CD40           | NM_001250                              | CD40 molecule, TNF receptor superfamily member 5                                                                                                                                                                          | up                               |
| A_24_P403959        | SEQ ID NO:523                                      | RNASE1         | NM_198232                              | ribonuclease, RNase A family, 1 (pancreatic)                                                                                                                                                                              | down                             |
| A_23_P110196        | SEQ ID NO:524                                      | HERC5          | NM_016323                              | hect domain and RLD 5                                                                                                                                                                                                     | up                               |
| A_23_P1962          | SEQ ID NO:525                                      | RARRES3        | NM_004585                              | retinoic acid receptor responder (tazarotene induced) 3                                                                                                                                                                   | up                               |
| A_23_P500614        | SEQ ID NO:526                                      | TNFRSF8        | NM_001243                              | tumor necrosis factor receptor superfamily, member 8                                                                                                                                                                      | down                             |
| A_23_P11201         | SEQ ID NO:527                                      | GPR34          | NM_001033513                           | G protein-coupled receptor 34                                                                                                                                                                                             | down                             |
| A_23_P217258        | SEQ ID NO:528                                      | CYBB           | NM_000397                              | cytochrome b-245, beta polypeptide (chronic granulomatous disease)                                                                                                                                                        | up                               |
| A_32_P71710         | SEQ ID NO:529                                      | A_32_P71710    | AI094165                               | Low quality annotation - AI094165<br>qa29a01.s1 Soares_NhHMPu_S1 Homo sapiens cDNA clone IMAGE:1688136 3' similar to gb:X64532_ma1 INTERLEUKIN-1 RECEPTOR ANTAGONIST PROTEIN PRECURSOR (HUMAN);, mRNA sequence [AI094165] | up                               |
| A_24_P935652        | SEQ ID NO:530                                      | NUB1           | CR606629                               | negative regulator of ubiquitin-like proteins 1                                                                                                                                                                           | up                               |
| A_24_P851254        | SEQ ID NO:531                                      | A_24_P851254   | AK026267                               | Low quality annotation - Homo sapiens cDNA: FLJ22614 fis, clone HSI05089. [AK026267]                                                                                                                                      | down                             |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                 | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P116414        | SEQ ID NO:532                                      | HRASLS3        | NM_007069                              | HRAS-like suppressor 3                                                                                                                                                                                    | up                               |
| A_23_P59210         | SEQ ID NO:533                                      | CDKN1A         | NM_000389                              | cyclin-dependent kinase inhibitor 1A (p21, Cip1)                                                                                                                                                          | up                               |
| A_23_P42969         | SEQ ID NO:266                                      | FGL2           | NM_008682                              | fibrinogen-like 2                                                                                                                                                                                         | up                               |
| A_24_P403417        | SEQ ID NO:534                                      | PTGES          | NM_004878                              | prostaglandin E synthase                                                                                                                                                                                  | down                             |
| A_23_P17655         | SEQ ID NO:230                                      | KCNJ15         | NM_170736                              | potassium inwardly-rectifying channel, subfamily J, member 15                                                                                                                                             | up                               |
| A_23_P91230         | SEQ ID NO:535                                      | SLPI           | NM_003064                              | secretory leukocyte peptidase inhibitor                                                                                                                                                                   | up                               |
| A_23_P152234        | SEQ ID NO:536                                      | CMTM2          | NM_144673                              | CKLF-like MARVEL transmembrane domain containing 2                                                                                                                                                        | down                             |
| A_23_P62932         | SEQ ID NO:537                                      | ATP1B1         | NM_001677                              | ATPase, Na <sup>+</sup> /K <sup>+</sup> transporting, beta 1 polypeptide                                                                                                                                  | up                               |
| A_24_P161018        | SEQ ID NO:299                                      | PARP14         | NM_017554                              | poly (ADP-ribose) polymerase family, member 14                                                                                                                                                            | up                               |
| A_23_P42306         | SEQ ID NO:538                                      | HLA-DMA        | NM_006120                              | major histocompatibility complex, class II, DM alpha                                                                                                                                                      | up                               |
| A_23_P144872        | SEQ ID NO:539                                      | GM2A           | NM_000405                              | GM2 ganglioside activator                                                                                                                                                                                 | up                               |
| A_32_P115555        | SEQ ID NO:540                                      | A_32_P115555   | AA991488                               | Low quality annotation - os91h09.s1 NCI_CGAP_GC3 Homo sapiens cDNA clone IMAGE:1612769 3' similar to gb:J00194 HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DR ALPHA CHAIN (HUMAN);, mRNA sequence [AA991488] | up                               |
| A_23_P91640         | SEQ ID NO:541                                      | ASPHD2         | NM_020437                              | aspartate beta-hydroxylase domain containing 2                                                                                                                                                            | up                               |
| A_23_P140807        | SEQ ID NO:211                                      | PSMB10         | NM_002801                              | proteasome (prosome, macropain) subunit, beta type, 10                                                                                                                                                    | up                               |
| A_23_P378588        | SEQ ID NO:542                                      | ARL5B          | NM_178815                              | ADP-ribosylation factor-like 5B                                                                                                                                                                           | up                               |
| A_23_P104493        | SEQ ID NO:543                                      | PAPSS2         | NM_001015880                           | 3'-phosphoadenosine 5'-phosphosulfate synthase 2                                                                                                                                                          | down                             |
| A_23_P87709         | SEQ ID NO:293                                      | FLJ22662       | NM_024829                              | hypothetical protein FLJ22662                                                                                                                                                                             | up                               |
| A_23_P111804        | SEQ ID NO:544                                      | PARP12         | NM_022750                              | poly (ADP-ribose) polymerase family, member 12                                                                                                                                                            | up                               |
| A_23_P129486        | SEQ ID NO:545                                      | SEPX1          | NM_016332                              | selenoprotein X, 1                                                                                                                                                                                        | up                               |
| A_23_P9232          | SEQ ID NO:294                                      | GCNT1          | NM_001490                              | glucosaminyl (N-acetyl) transferase 1, core 2 (beta-1,6-N-acetylglucosaminyltransferase)                                                                                                                  | up                               |
| A_24_P15502         | SEQ ID NO:546                                      | A_24_P15502    | A_24_P15502                            | Unknown                                                                                                                                                                                                   | up                               |
| A_23_P55998         | SEQ ID NO:547                                      | SLC1A5         | NM_005628                              | solute carrier family 1 (neutral amino acid transporter), member 5                                                                                                                                        | up                               |
| A_23_P15414         | SEQ ID NO:218                                      | SCARF1         | NM_145351                              | scavenger receptor class F, member 1                                                                                                                                                                      | up                               |
| A_23_P100711        | SEQ ID NO:548                                      | PMP22          | NM_000304                              | peripheral myelin protein 22                                                                                                                                                                              | down                             |
| A_24_P11142         | SEQ ID NO:549                                      | KIAA0040       | NM_014656                              | KIAA0040                                                                                                                                                                                                  | up                               |
| A_23_P3221          | SEQ ID NO:250                                      | SQRDL          | NM_021199                              | sulfide quinone reductase-like (yeast)                                                                                                                                                                    | up                               |
| A_23_P39237         | SEQ ID NO:550                                      | ZFP36          | NM_003407                              | zinc finger protein 36, C3H type, homolog (mouse)                                                                                                                                                         | up                               |
| A_23_P353717        | SEQ ID NO:551                                      | C16ORF75       | NM_152308                              | chromosome 16 open reading frame 75                                                                                                                                                                       | up                               |
| A_24_P382319        | SEQ ID NO:316                                      | CEACAM1        | NM_001712                              | carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)                                                                                                                          | up                               |
| A_24_P141214        | SEQ ID NO:552                                      | STOM           | NM_198194                              | stomatin                                                                                                                                                                                                  | up                               |
| A_23_P252062        | SEQ ID NO:553                                      | PPARG          | NM_138711                              | peroxisome proliferator-activated receptor gamma                                                                                                                                                          | down                             |
| A_24_P53051         | SEQ ID NO:128                                      | LACTB          | NM_171846                              | lactamase, beta                                                                                                                                                                                           | up                               |
| A_32_P108277        | SEQ ID NO:554                                      | A_32_P108277   | BQ130147                               | Low quality annotation - BQ130147 ij85d08.x1 Human insulinoma Homo sapiens cDNA clone IMAGE:5778111 3', mRNA sequence [BQ130147]                                                                          | up                               |
| A_32_P95082         | SEQ ID NO:347                                      | C9ORF39        | NM_017738                              | chromosome 9 open reading frame 39                                                                                                                                                                        | up                               |
| A_23_P211488        | SEQ ID NO:241                                      | APOL2          | NM_145637                              | apolipoprotein L, 2                                                                                                                                                                                       | up                               |
| A_23_P56746         | SEQ ID NO:271                                      | FAP            | NM_004460                              | fibroblast activation protein, alpha                                                                                                                                                                      | up                               |
| A_24_P935819        | SEQ ID NO:328                                      | SOD2           | BC016934                               | superoxide dismutase 2, mitochondrial                                                                                                                                                                     | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                      | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|----------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P329870        | SEQ ID NO:252                                      | RHBDF2         | NM_024599                              | rhomboid 5 homolog 2 (Drosophila)                                                                              | up                               |
| A_23_P4821          | SEQ ID NO:268                                      | JUNB           | NM_002229                              | jun B proto-oncogene                                                                                           | up                               |
| A_23_P95172         | SEQ ID NO:555                                      | C17ORF27       | NM_020914                              | chromosome 17 open reading frame 27                                                                            | up                               |
| A_23_P93442         | SEQ ID NO:556                                      | SASH1          | NM_015278                              | SAM and SH3 domain containing 1                                                                                | up                               |
| A_23_P112260        | SEQ ID NO:200                                      | GNG10          | NM_001017998                           | guanine nucleotide binding protein (G protein), gamma 10                                                       | up                               |
| A_24_P260101        | SEQ ID NO:557                                      | MME            | NM_007289                              | membrane metallo-endopeptidase (neutral endopeptidase, enkephalinase)                                          | down                             |
| A_23_P20814         | SEQ ID NO:235                                      | DDX58          | NM_014314                              | DEAD (Asp-Glu-Ala-Asp) box polypeptide 58 (SEQ ID NO:697)                                                      | up                               |
| A_24_P98047         | SEQ ID NO:558                                      | SLC16A10       | NM_018593                              | solute carrier family 16, member 10 (aromatic amino acid transporter)                                          | down                             |
| A_23_P401106        | SEQ ID NO:260                                      | PDE2A          | NM_002599                              | phosphodiesterase 2A, cGMP-stimulated                                                                          | down                             |
| A_23_P142424        | SEQ ID NO:214                                      | TMEM149        | NM_024660                              | transmembrane protein 149                                                                                      | up                               |
| A_23_P216225        | SEQ ID NO:559                                      | EGR3           | NM_004430                              | early growth response 3                                                                                        | up                               |
| A_23_P17663         | SEQ ID NO:560                                      | MX1            | NM_002462                              | myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse)                             | up                               |
| A_23_P26024         | SEQ ID NO:561                                      | C15ORF48       | NM_032413                              | chromosome 15 open reading frame 48                                                                            | up                               |
| A_23_P4286          | SEQ ID NO:562                                      | BIRC4BP        | NM_017523                              | XIAP associated factor-1                                                                                       | up                               |
| A_23_P364024        | SEQ ID NO:563                                      | GLIPR1         | NM_006851                              | GLI pathogenesis-related 1 (glioma)                                                                            | down                             |
| A_23_P166408        | SEQ ID NO:227                                      | OSM            | NM_020530                              | oncostatin M                                                                                                   | up                               |
| A_23_P155049        | SEQ ID NO:219                                      | APOL6          | NM_030641                              | apolipoprotein L, 6                                                                                            | up                               |
| A_23_P141021        | SEQ ID NO:564                                      | AYTL1          | NM_017839                              | acyltransferase like 1                                                                                         | up                               |
| A_24_P47329         | SEQ ID NO:319                                      | A_24_P47329    | BC063641                               | Low quality annotation - Homo sapiens cDNA clone IMAGE:4745832, partial cds. [BC063641]                        | up                               |
| A_23_P44836         | SEQ ID NO:565                                      | NT5DC2         | NM_022908                              | 5'-nucleotidase domain containing 2                                                                            | down                             |
| A_23_P68106         | SEQ ID NO:566                                      | TMSB10         | NM_021103                              | thymosin, beta 10                                                                                              | up                               |
| A_23_P2793          | SEQ ID NO:567                                      | ALOX5AP        | NM_001629                              | arachidonate 5-lipoxygenase-activating protein                                                                 | down                             |
| A_24_P481844        | SEQ ID NO:568                                      | HLA-DMB        | BC035650                               | major histocompatibility complex, class II, DM beta                                                            | up                               |
| A_23_P133133        | SEQ ID NO:206                                      | ALPK1          | NM_025144                              | alpha-kinase 1                                                                                                 | up                               |
| A_24_P315405        | SEQ ID NO:569                                      | A_24_P315405   | A_24_P315405                           | Unknown                                                                                                        | up                               |
| A_23_P251480        | SEQ ID NO:245                                      | NBN            | NM_001024688                           | nibrin                                                                                                         | up                               |
| A_23_P402892        | SEQ ID NO:164                                      | NLRC5          | NM_032206                              | NLR family, CARD domain containing 5                                                                           | up                               |
| A_23_P427703        | SEQ ID NO:570                                      | MT1L           | X97261                                 | metallothionein 1L (pseudogene)                                                                                | up                               |
| A_23_P112251        | SEQ ID NO:199                                      | GNG10          | NM_001017998                           | guanine nucleotide binding protein (G protein), gamma 10                                                       | up                               |
| A_23_P34142         | SEQ ID NO:571                                      | WBP5           | NM_016303                              | VW domain binding protein 5                                                                                    | down                             |
| A_23_P76823         | SEQ ID NO:572                                      | ADSSL1         | NM_199165                              | adenylosuccinate synthase like 1                                                                               | down                             |
| A_23_P161338        | SEQ ID NO:573                                      | PPA1           | NM_021129                              | pyrophosphatase (inorganic) 1                                                                                  | up                               |
| A_32_P156746        | SEQ ID NO:337                                      | A_32_P156746   | BE825944                               | Low quality annotation - BE825944 CM2-EN0014-310500-207-g07 EN0014 Homo sapiens cDNA, mRNA sequence [BE825944] | up                               |
| A_24_P198598        | SEQ ID NO:574                                      | PML            | NM_002675                              | promyelocytic leukemia                                                                                         | up                               |
| A_23_P137856        | SEQ ID NO:575                                      | MUC1           | NM_002456                              | mucin 1, cell surface associated                                                                               | up                               |
| A_24_P940166        | SEQ ID NO:576                                      | PAPSS2         | NM_001015880                           | 3'-phosphoadenosine 5'-phosphosulfate synthase 2                                                               | down                             |
| A_23_P103765        | SEQ ID NO:577                                      | FCER1A         | NM_002001                              | Fc fragment of IgE, high affinity I, receptor for; alpha polypeptide                                           | down                             |
| A_23_P26583         | SEQ ID NO:158                                      | NLRC5          | NM_032206                              | NLR family, CARD domain containing 5                                                                           | up                               |
| A_23_P259692        | SEQ ID NO:578                                      | PSAT1          | NM_058179                              | phosphoserine aminotransferase 1                                                                               | up                               |
| A_23_P111583        | SEQ ID NO:579                                      | CD36           | NM_001001547                           | CD36 molecule (thrombospondin receptor)                                                                        | down                             |
| A_24_P943597        | SEQ ID NO:580                                      | PHLDA1         | NM_007350                              | pleckstrin homology-like domain, family A, member 1                                                            | down                             |
| A_24_P49199         | SEQ ID NO:581                                      | GLDN           | NM_181789                              | gliomedin                                                                                                      | up                               |
| A_24_P941912        | SEQ ID NO:331                                      | DTX3L          | NM_138287                              | deltex 3-like (Drosophila)                                                                                     | up                               |
| A_23_P142697        | SEQ ID NO:582                                      | TTL4           | NM_014640                              | tubulin tyrosine ligase-like family, member 4                                                                  | down                             |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                              | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_23_P256445        | SEQ ID NO:138                                      | VCPIP1         | NM_025054                              | valosin containing protein (p97)/p47 complex interacting protein 1                                                                                                                                                     | up                               |
| A_23_P129492        | SEQ ID NO:204                                      | SEPX1          | NM_016332                              | selenoprotein X, 1                                                                                                                                                                                                     | up                               |
| A_23_P78037         | SEQ ID NO:583                                      | CCL7           | NM_006273                              | chemokine (C-C motif) ligand 7                                                                                                                                                                                         | down                             |
| A_23_P119789        | SEQ ID NO:584                                      | FAM11B         | NR_000034                              | family with sequence similarity 11, member B                                                                                                                                                                           | up                               |
| A_23_P168828        | SEQ ID NO:229                                      | KLF10          | NM_005655                              | Kruppel-like factor 10                                                                                                                                                                                                 | up                               |
| A_24_P273716        | SEQ ID NO:585                                      | ZBTB24         | NM_014797                              | zinc finger and BTB domain containing 24                                                                                                                                                                               | up                               |
| A_23_P137931        | SEQ ID NO:586                                      | ADORA3         | NM_000677                              | adenosine A3 receptor                                                                                                                                                                                                  | down                             |
| A_23_P255263        | SEQ ID NO:587                                      | STOM           | NM_198194                              | stomatin                                                                                                                                                                                                               | up                               |
| A_24_P210406        | SEQ ID NO:588                                      | KLF5           | NM_001730                              | Kruppel-like factor 5 (intestinal)                                                                                                                                                                                     | up                               |
| A_32_P91773         | SEQ ID NO:345                                      | A_32_P91773    | THC2544236                             | Low quality annotation - ALU1_HUMAN (P39188) Alu subfamily J sequence contamination warning entry, partial (10%) [THC2530569]                                                                                          | up                               |
| A_24_P183150        | SEQ ID NO:589                                      | CXCL3          | NM_002090                              | chemokine (C-X-C motif) ligand 3                                                                                                                                                                                       | down                             |
| A_24_P84198         | SEQ ID NO:590                                      | LOC441849      | XR_019057                              | similar to Methionine-R-sulfoxide reductase (Selenoprotein X 1)                                                                                                                                                        | up                               |
| A_24_P88690         | SEQ ID NO:591                                      | SLC11A1        | NM_000578                              | solute carrier family 11 (proton-coupled divalent metal ion transporters), member 1                                                                                                                                    | down                             |
| A_32_P92415         | SEQ ID NO:346                                      | A_32_P92415    | THC2526269                             | Low quality annotation - ALU5_HUMAN (P39192) Alu subfamily SC sequence contamination warning entry, partial (14%) [THC2526269]                                                                                         | up                               |
| A_23_P68851         | SEQ ID NO:280                                      | KREMEN1        | NM_001039570                           | kringle containing transmembrane protein 1                                                                                                                                                                             | up                               |
| A_24_P50245         | SEQ ID NO:592                                      | HLA-DMA        | NM_006120                              | major histocompatibility complex, class II, DM alpha                                                                                                                                                                   | up                               |
| A_24_P935986        | SEQ ID NO:329                                      | BCAT1          | NM_005504                              | branched chain aminotransferase 1, cytosolic                                                                                                                                                                           | down                             |
| A_24_P201360        | SEQ ID NO:593                                      | ACSL5          | NM_203380                              | acyl-CoA synthetase long-chain family member 5                                                                                                                                                                         | up                               |
| A_24_P124624        | SEQ ID NO:594                                      | OLR1           | NM_002543                              | oxidized low density lipoprotein (lectin-like) receptor 1                                                                                                                                                              | down                             |
| A_23_P253145        | SEQ ID NO:595                                      | TAGAP          | NM_054114                              | T-cell activation GTPase activating protein                                                                                                                                                                            | up                               |
| A_24_P354724        | SEQ ID NO:596                                      | TAGAP          | NM_054114                              | T-cell activation GTPase activating protein                                                                                                                                                                            | up                               |
| A_23_P160025        | SEQ ID NO:597                                      | IFI16          | NM_005531                              | interferon, gamma-inducible protein 16                                                                                                                                                                                 | up                               |
| A_23_P161647        | SEQ ID NO:598                                      | PC             | NM_001040716                           | pyruvate carboxylase                                                                                                                                                                                                   | down                             |
| A_23_P8812          | SEQ ID NO:599                                      | A_23_P8812     | W60781                                 | Low quality annotation - W60781 zd26f05.r1 Soares_fetal_heart_NbHH19W Homo sapiens cDNA clone IMAGE:341793 5' similar to gb:J02874 FATTY ACID-BINDING PROTEIN, ADIPOCYTE (HUMAN);, mRNA sequence [W60781]              | down                             |
| A_23_P250245        | SEQ ID NO:600                                      | CD72           | NM_001782                              | CD72 molecule                                                                                                                                                                                                          | up                               |
| A_23_P502520        | SEQ ID NO:601                                      | IL4I1          | NM_172374                              | interleukin 4 induced 1                                                                                                                                                                                                | up                               |
| A_23_P153390        | SEQ ID NO:602                                      | CLEC4G         | NM_198492                              | C-type lectin superfamily 4, member G                                                                                                                                                                                  | up                               |
| A_24_P941167        | SEQ ID NO:330                                      | APOL6          | NM_030641                              | apolipoprotein L, 6                                                                                                                                                                                                    | up                               |
| A_23_P138680        | SEQ ID NO:209                                      | IL15RA         | NM_172200                              | interleukin 15 receptor, alpha                                                                                                                                                                                         | up                               |
| A_32_P191417        | SEQ ID NO:340                                      | A_32_P191417   | AI439246                               | Low quality annotation - AI439246 ti59a08.x1 NCI_CGAP_Lym12 Homo sapiens cDNA clone IMAGE:2134742 3' similar to gb:M81141 HLA CLASS II HISTOCOMPATIBILITY ANTIGEN, DQ(1) BETA CHAIN (HUMAN);, mRNA sequence [AI439246] | up                               |
| A_23_P202978        | SEQ ID NO:603                                      | CASP1          | NM_033292                              | caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)                                                                                                                                      | up                               |
| A_23_P97990         | SEQ ID NO:604                                      | HTRA1          | NM_002775                              | HtrA serine peptidase 1                                                                                                                                                                                                | down                             |
| A_24_P334361        | SEQ ID NO:314                                      | FLJ20035       | NM_017631                              | hypothetical protein FLJ20035                                                                                                                                                                                          | up                               |
| A_23_P114814        | SEQ ID NO:605                                      | RHOJ           | NM_021205                              | ras homolog gene family, member U                                                                                                                                                                                      | up                               |
| A_23_P122924        | SEQ ID NO:606                                      | INHBA          | NM_002192                              | inhibin, beta A (activin A, activin AB alpha                                                                                                                                                                           | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                                                                                                                                           | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
|                     |                                                    |                |                                        | polypeptide)                                                                                                                                                                                                                                        |                                  |
| A_23_P152782        | SEQ ID NO:607                                      | IFI35          | NM_005533                              | interferon-induced protein 35                                                                                                                                                                                                                       | up                               |
| A_24_P212481        | SEQ ID NO:304                                      | MCTP1          | NM_024717                              | multiple C2 domains, transmembrane 1                                                                                                                                                                                                                | up                               |
| A_23_P145965        | SEQ ID NO:608                                      | TPST1          | NM_003596                              | tyrosylprotein sulfotransferase 1                                                                                                                                                                                                                   | down                             |
| A_24_P77008         | SEQ ID NO:609                                      | PTGS2          | NM_000963                              | prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)                                                                                                                                                               | up                               |
| A_23_P37983         | SEQ ID NO:610                                      | MT1B           | NM_005947                              | metallothionein 1B (functional)                                                                                                                                                                                                                     | up                               |
| A_23_P253791        | SEQ ID NO:611                                      | CAMP           | NM_004345                              | cathelicidin antimicrobial peptide                                                                                                                                                                                                                  | down                             |
| A_23_P5273          | SEQ ID NO:612                                      | SBNO2          | NM_014963                              | strawberry notch homolog 2 (Drosophila)                                                                                                                                                                                                             | up                               |
| A_23_P91802         | SEQ ID NO:613                                      | ECGF1          | NM_001953                              | endothelial cell growth factor 1 (platelet-derived)                                                                                                                                                                                                 | up                               |
| A_23_P152548        | SEQ ID NO:614                                      | SCPEP1         | NM_021626                              | serine carboxypeptidase 1                                                                                                                                                                                                                           | up                               |
| A_23_P4662          | SEQ ID NO:615                                      | BCL3           | NM_005178                              | B-cell CLL/lymphoma 3                                                                                                                                                                                                                               | up                               |
| A_32_P222250        | SEQ ID NO:341                                      | A_32_P222250   | AF119908                               | Low quality annotation - Homo sapiens PRO2955 mRNA, complete cds. [AF119908]                                                                                                                                                                        | up                               |
| A_23_P256724        | SEQ ID NO:616                                      | TNFRSF10C      | NM_003841                              | tumor necrosis factor receptor superfamily, member 10c, decoy without an intracellular domain                                                                                                                                                       | down                             |
| A_23_P205489        | SEQ ID NO:617                                      | SLC7A8         | NM_182728                              | solute carrier family 7 (cationic amino acid transporter, y+ system), member 8                                                                                                                                                                      | down                             |
| A_24_P243749        | SEQ ID NO:618                                      | PK4            | NM_002612                              | pyruvate dehydrogenase kinase, isoform 4                                                                                                                                                                                                            | down                             |
| A_24_P272389        | SEQ ID NO:619                                      | LOC285216      | AK092228                               | hypothetical protein LOC285216                                                                                                                                                                                                                      | up                               |
| A_23_P161125        | SEQ ID NO:620                                      | MOV10          | NM_020963                              | Mov10, Moloney leukemia virus 10, homolog (mouse)                                                                                                                                                                                                   | up                               |
| A_24_P659202        | SEQ ID NO:323                                      | A_24_P659202   | THC2527772                             | Low quality annotation - HUMC4AA2 complement component C4A {Homo sapiens} (exp=-1; wgp=0; cg=0), partial (6%) [THC2527772]                                                                                                                          | up                               |
| A_24_P914519        | SEQ ID NO:621                                      | CYBB           | S67289                                 | cytochrome b-245, beta polypeptide (chronic granulomatous disease)                                                                                                                                                                                  | up                               |
| A_24_P304071        | SEQ ID NO:622                                      | IFIT2          | NM_001547                              | interferon-induced protein with tetratricopeptide repeats 2                                                                                                                                                                                         | up                               |
| A_23_P214176        | SEQ ID NO:623                                      | CD109          | NM_133493                              | CD109 molecule                                                                                                                                                                                                                                      | down                             |
| A_23_P127663        | SEQ ID NO:624                                      | PRRG4          | NM_024081                              | proline rich Gla (G-carboxyglutamic acid) 4 (transmembrane)                                                                                                                                                                                         | up                               |
| A_23_P215566        | SEQ ID NO:625                                      | AHR            | NM_001621                              | aryl hydrocarbon receptor                                                                                                                                                                                                                           | down                             |
| A_24_P398130        | SEQ ID NO:626                                      | USP6NL         | ENST00000277575                        | USP6 N-terminal like                                                                                                                                                                                                                                | up                               |
| A_24_P42264         | SEQ ID NO:627                                      | LYZ            | NM_000239                              | lysozyme (renal amyloidosis)                                                                                                                                                                                                                        | up                               |
| A_23_P397293        | SEQ ID NO:628                                      | LY6K           | NM_017527                              | lymphocyte antigen 6 complex, locus K                                                                                                                                                                                                               | down                             |
| A_23_P30243         | SEQ ID NO:629                                      | LRAP           | NM_022350                              | leukocyte-derived arginine aminopeptidase                                                                                                                                                                                                           | up                               |
| A_24_P133542        | SEQ ID NO:630                                      | PML            | NM_002675                              | promyelocytic leukemia                                                                                                                                                                                                                              | up                               |
| A_24_P211106        | SEQ ID NO:631                                      | A_24_P211106   | ENST00000382790                        | Low quality annotation - Tumor necrosis factor receptor superfamily member 11A precursor (Receptor activator of NF-κB) (Osteoclast differentiation factor receptor) (ODFR) (CD265 antigen). [Source:Uniprot/SwissProt;Acc:Q9Y6Q6] [ENST00000382790] | down                             |
| A_24_P7322          | SEQ ID NO:632                                      | A_24_P7322     | A_24_P7322                             | Unknown                                                                                                                                                                                                                                             | up                               |
| A_23_P343837        | SEQ ID NO:254                                      | PARP11         | NM_020367                              | poly (ADP-ribose) polymerase family, member 11                                                                                                                                                                                                      | up                               |
| A_23_P90041         | SEQ ID NO:633                                      | NLRP12         | NM_033297                              | NLR family, pyrin domain containing 12                                                                                                                                                                                                              | down                             |
| A_32_P121978        | SEQ ID NO:634                                      | A_32_P121978   | A_32_P121978                           | Unknown                                                                                                                                                                                                                                             | up                               |
| A_23_P202837        | SEQ ID NO:635                                      | CCND1          | NM_053056                              | cyclin D1                                                                                                                                                                                                                                           | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                                                    | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------|----------------------------------|
| A_24_P136866        | SEQ ID NO:636                                      | SLC8A1         | NM_021097                              | solute carrier family 8 (sodium/calcium exchanger), member 1                                                                 | up                               |
| A_24_P97342         | SEQ ID NO:333                                      | PROK2          | NM_021935                              | prokineticin 2                                                                                                               | down                             |
| A_24_P352952        | SEQ ID NO:637                                      | FAM20A         | NM_017565                              | family with sequence similarity 20, member A                                                                                 | up                               |
| A_23_P32233         | SEQ ID NO:638                                      | KLF4           | NM_004235                              | Kruppel-like factor 4 (gaf)                                                                                                  | up                               |
| A_23_P156327        | SEQ ID NO:639                                      | TGFBI          | NM_000358                              | transforming growth factor, beta-induced, 68kDa                                                                              | down                             |
| A_23_P60933         | SEQ ID NO:640                                      | MT1G           | NM_005950                              | metallothionein 1G                                                                                                           | up                               |
| A_32_P199462        | SEQ ID NO:641                                      | LOC389073      | ENST00000341287                        | similar to RIKEN cDNA D630023F18                                                                                             | up                               |
| A_24_P835388        | SEQ ID NO:642                                      | A_24_P835388   | A_24_P835388                           | Unknown                                                                                                                      | down                             |
| A_23_P217428        | SEQ ID NO:643                                      | ARHGAP6        | NM_001174                              | Rho GTPase activating protein 6                                                                                              | down                             |
| A_23_P571           | SEQ ID NO:272                                      | SLC2A1         | NM_006516                              | solute carrier family 2 (facilitated glucose transporter), member 1                                                          | down                             |
| A_23_P30069         | SEQ ID NO:249                                      | FLJ31033       | AK023743                               | hypothetical protein FLJ31033                                                                                                | up                               |
| A_23_P52219         | SEQ ID NO:644                                      | SPFH1          | NM_006459                              | SPFH domain family, member 1                                                                                                 | up                               |
| A_23_P53763         | SEQ ID NO:645                                      | C13ORF18       | NM_025113                              | chromosome 13 open reading frame 18                                                                                          | down                             |
| A_23_P42302         | SEQ ID NO:265                                      | HLA-DQA2       | NM_020056                              | major histocompatibility complex, class II, DQ alpha 2                                                                       | up                               |
| A_23_P42282         | SEQ ID NO:264                                      | C4B            | NM_001002029                           | complement component 4B (Childo blood group)                                                                                 | up                               |
| A_23_P329353        | SEQ ID NO:646                                      | C2ORF32        | NM_015463                              | chromosome 2 open reading frame 32                                                                                           | down                             |
| A_23_P46936         | SEQ ID NO:647                                      | EGR2           | NM_000399                              | early growth response 2 (Krox-20 homolog, Drosophila)                                                                        | up                               |
| A_23_P74001         | SEQ ID NO:284                                      | S100A12        | NM_005621                              | S100 calcium binding protein A12                                                                                             | down                             |
| A_23_P206724        | SEQ ID NO:648                                      | MT1E           | NM_175617                              | metallothionein 1E (functional)                                                                                              | up                               |
| A_32_P118010        | SEQ ID NO:649                                      | A_32_P118010   | THC2657593                             | Low quality annotation - ALU1_HUMAN (P39188) Alu subfamily J sequence contamination warning entry, partial (7%) [THC2657593] | up                               |
| A_23_P502312        | SEQ ID NO:650                                      | CD97           | NM_078481                              | CD97 molecule                                                                                                                | up                               |
| A_24_P135322        | SEQ ID NO:651                                      | NRP1           | NM_001024629                           | neuropilin 1                                                                                                                 | down                             |
| A_23_P368484        | SEQ ID NO:652                                      | C17ORF76       | NM_207387                              | chromosome 17 open reading frame 76                                                                                          | down                             |
| A_24_P335656        | SEQ ID NO:653                                      | SECTM1         | NM_003004                              | secreted and transmembrane 1                                                                                                 | up                               |
| A_23_P139066        | SEQ ID NO:654                                      | RNF141         | NM_016422                              | ring finger protein 141                                                                                                      | down                             |
| A_23_P138426        | SEQ ID NO:655                                      | USP6NL         | BC042943                               | USP6 N-terminal like                                                                                                         | up                               |
| A_23_P116286        | SEQ ID NO:656                                      | AMPD3          | NM_001025390                           | adenosine monophosphate deaminase (isoform E)                                                                                | down                             |
| A_24_P85539         | SEQ ID NO:657                                      | FN1            | NM_212482                              | fibronectin 1                                                                                                                | down                             |
| A_24_P304154        | SEQ ID NO:312                                      | AMPD3          | NM_001025390                           | adenosine monophosphate deaminase (isoform E)                                                                                | down                             |
| A_23_P41424         | SEQ ID NO:658                                      | SLC39A8        | NM_022154                              | solute carrier family 39 (zinc transporter), member 8                                                                        | down                             |
| A_24_P125096        | SEQ ID NO:659                                      | MT1X           | NM_005952                              | metallothionein 1X                                                                                                           | up                               |
| A_23_P138541        | SEQ ID NO:660                                      | AKR1C3         | NM_003739                              | aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II)                                      | down                             |
| A_24_P372625        | SEQ ID NO:315                                      | RNF141         | NM_016422                              | ring finger protein 141                                                                                                      | down                             |
| A_32_P2605          | SEQ ID NO:661                                      | A_32_P2605     | AV756170                               | Low quality annotation - AV756170 BM Homo sapiens cDNA clone BMFBGA09 5', mRNA sequence [AV756170]                           | up                               |
| A_23_P378298        | SEQ ID NO:662                                      | IKZF4          | BX647761                               | IKAROS family zinc finger 4 (Eos)                                                                                            | up                               |
| A_23_P434919        | SEQ ID NO:663                                      | RAB42          | NM_152304                              | RAB42, member RAS oncogene family                                                                                            | down                             |
| A_23_P55738         | SEQ ID NO:664                                      | CEACAM1        | NM_001024912                           | carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein)                                             | up                               |
| A_23_P414343        | SEQ ID NO:665                                      | MT1H           | NM_005951                              | metallothionein 1H                                                                                                           | up                               |
| A_24_P924010        | SEQ ID NO:666                                      | A_24_P924010   | AW275876                               | NCL CGAP_Lu28 Homo sapiens cDNA clone IMAGE:2753102 3' similar to                                                            | up                               |

| AGILENT® Probe Name | Sequence Listing number of AGILENT® Probe Sequence | Symbol of Gene | NCBI Accession Number of Gene Sequence | Gene Name                                                                                           | Direction of modulation by IFN-γ |
|---------------------|----------------------------------------------------|----------------|----------------------------------------|-----------------------------------------------------------------------------------------------------|----------------------------------|
|                     |                                                    |                |                                        | gb:X57352 INTERFERON-INDUCIBLE PROTEIN 1-8U (HUMAN);, mRNA sequence [AW275876]                      |                                  |
| A_32_P117016        | SEQ ID NO:667                                      | A_32_P117016   | AK094088                               | Low quality annotation - Homo sapiens cDNA FLJ36769 fis, clone ADIPS2000245. [AK094088]             | up                               |
| A_23_P303242        | SEQ ID NO:668                                      | MT1X           | NM_005952                              | metallothionein 1X                                                                                  | up                               |
| A_24_P156490        | SEQ ID NO:133                                      | KCNMA1         | NM_002247                              | potassium large conductance calcium-activated channel, subfamily M, alpha member 1                  | up                               |
| A_32_P103695        | SEQ ID NO:669                                      | FAM92A1        | CR627475                               | family with sequence similarity 92, member A1                                                       | up                               |
| A_24_P335305        | SEQ ID NO:670                                      | OAS3           | NM_006187                              | 2'-5'-oligoadenylate synthetase 3, 100kDa                                                           | up                               |
| A_23_P52266         | SEQ ID NO:671                                      | IFIT1          | NM_001548                              | interferon-induced protein with tetratricopeptide repeats 1                                         | up                               |
| A_23_P24104         | SEQ ID NO:672                                      | PLAU           | NM_002658                              | plasminogen activator, urokinase                                                                    | up                               |
| A_23_P161837        | SEQ ID NO:673                                      | MRV1           | NM_130385                              | murine retrovirus integration site 1 homolog                                                        | down                             |
| A_32_P133090        | SEQ ID NO:674                                      | A_32_P133090   | BG216262                               | Low quality annotation - RST35951 Athersys RAGE Library Homo sapiens cDNA, mRNA sequence [BG216262] | up                               |
| A_24_P306810        | SEQ ID NO:675                                      | KIAA1618       | ENST00000319902                        | KIAA1618                                                                                            | up                               |
| A_32_P200724        | SEQ ID NO:676                                      | A_32_P200724   | AK128013                               | Low quality annotation - Homo sapiens cDNA FLJ46132 fis, clone TEST12051627. [AK128013]             | up                               |
| A_23_P87879         | SEQ ID NO:677                                      | CD69           | NM_001781                              | CD69 molecule                                                                                       | up                               |
| A_23_P41344         | SEQ ID NO:678                                      | EREG           | NM_001432                              | epiregulin                                                                                          | down                             |
| A_23_P48596         | SEQ ID NO:679                                      | RNASE1         | NM_198232                              | ribonuclease, RNase A family, 1 (pancreatic)                                                        | down                             |
| A_23_P135755        | SEQ ID NO:680                                      | IL8RB          | NM_001557                              | interleukin 8 receptor, beta                                                                        | down                             |
| A_23_P132622        | SEQ ID NO:115                                      | XRN1           | NM_019001                              | 5'-3' exoribonuclease 1                                                                             | up                               |
| A_23_P213014        | SEQ ID NO:681                                      | SLC2A9         | NM_001001290                           | solute carrier family 2 (facilitated glucose transporter), member 9                                 | up                               |
| A_32_P399546        | SEQ ID NO:343                                      | ARNTL2         | AF256215                               | aryl hydrocarbon receptor nuclear translocator-like 2                                               | up                               |
| A_24_P62521         | SEQ ID NO:682                                      | PSEN2          | NM_000447                              | presenilin 2 (Alzheimer disease 4)                                                                  | up                               |
| A_24_P277367        | SEQ ID NO:683                                      | CXCL5          | NM_002994                              | chemokine (C-X-C motif) ligand 5                                                                    | down                             |
| A_23_P39925         | SEQ ID NO:684                                      | DYSF           | NM_003494                              | dysferlin, limb girdle muscular dystrophy 2B (autosomal recessive)                                  | up                               |
| A_24_P250922        | SEQ ID NO:307                                      | PTGS2          | NM_000963                              | prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclooxygenase)               | up                               |
| A_23_P163782        | SEQ ID NO:685                                      | LOC645745      | NM_001039954                           | metallothionein 1H-like protein                                                                     | up                               |
| A_23_P216712        | SEQ ID NO:686                                      | TRPM6          | NM_017662                              | transient receptor potential cation channel, subfamily M, member 6                                  | down                             |
| A_23_P69171         | SEQ ID NO:687                                      | SUCNR1         | NM_033050                              | succinate receptor 1                                                                                | up                               |
| A_24_P7594          | SEQ ID NO:688                                      | APOL6          | NM_030641                              | apolipoprotein L, 6                                                                                 | up                               |
| A_23_P373017        | SEQ ID NO:689                                      | CCL3           | NM_002983                              | chemokine (C-C motif) ligand 3                                                                      | up                               |
| A_23_P205200        | SEQ ID NO:234                                      | DHRS12         | NM_024705                              | dehydrogenase/reductase (SDR family) member 12                                                      | up                               |
| A_23_P304356        | SEQ ID NO:690                                      | CLEC5A         | NM_013252                              | C-type lectin domain family 5, member A                                                             | down                             |
| A_23_P217049        | SEQ ID NO:691                                      | FREQ           | NM_014286                              | frequenin homolog (Drosophila)                                                                      | down                             |
| A_23_P157527        | SEQ ID NO:692                                      | LRRCC1         | NM_033402                              | leucine rich repeat and coiled-coil domain containing 1                                             | up                               |
| A_23_P206707        | SEQ ID NO:693                                      | MT1G           | NM_005950                              | metallothionein 1G                                                                                  | up                               |
| A_32_P138348        | SEQ ID NO:694                                      | LY6K           | NM_017527                              | lymphocyte antigen 6 complex, locus K                                                               | down                             |
| A_23_P110204        | SEQ ID NO:695                                      | CXCL5          | NM_002994                              | chemokine (C-X-C motif) ligand 5                                                                    | down                             |
| A_23_P113212        | SEQ ID NO:696                                      | TMEM45A        | NM_018004                              | transmembrane protein 45A                                                                           | up                               |

Amino acid and nucleotide sequences included in publicly available database entries corresponding to the National Center for Biotechnology Information (NCBI) accession numbers listed in Table 1 above are

incorporated herein by reference. Similarly, the sequences of the Agilent® probes are publicly available in the Gene Expression Omnibus (GEO) Database of NCBI. In particular, these sequences are among those disclosed for the Agilent-026652 Whole Human Genome Microarray 4x44K v2 and are incorporated herein by reference.

**Example 2: Serum levels of selected proteins in lupus and lupus nephritis patients compared to healthy volunteers**

Gene dysregulation in SLE was initially examined in a study of 19 healthy volunteers and 39 lupus subjects, which included patients from the clinical trial described in Example 3 as well as other lupus patients. Further, these studies were extended to include patients participating in the clinical trial described in Example 4 below, which included lupus nephritis patients as well as patients having SLE without nephritis. Peripheral blood samples from healthy volunteers and from lupus patients (before dosing) were collected in serum separator tubes (red/black marble top) and processed for serum. Serum CXCL10, CCL2, C-C motif chemokine 5 (CCL5; also known as RANTES), and IL-18 concentrations were determined with commercially available ELISAs according to the manufacturers' instructions (R&D Systems, Minneapolis, MN and Medical & Biological Laboratories Co, Ltd, Des Plaines, IL). Samples were analyzed in triplicate and levels were quantified by interpolation from a standard curve run in parallel on each micro-titer plate. Log ratio of gene expression in lupus subjects relative to healthy subjects along with 95% confidence intervals were estimated using linear regression and expressed as fold change. See Kackar, R.N., and Harville, D.A. 1984. Approximations for Standard Errors of Estimators of Fixed and Random Effects in Mixed Linear-Models. *Journal of the American Statistical Association* 79: 853-862, the relevant portions of which are incorporated herein by reference.

The results are shown in Figure 2. These data indicate that median serum levels of CXCL10, IL-18, and CCL2 were elevated in SLE and lupus nephritis subjects compared to healthy volunteers. Further, median levels observed in lupus nephritis patients were at least numerically higher than levels observed in SLE patients, though differences were statistically significant only for IL-18 expression. No difference in levels of RANTES could be demonstrated (data not shown). As will be shown below, expression of CXCL10 at the RNA and protein levels is decreased *in vivo* in human lupus and lupus nephritis patients in response to treatment with the anti-huIFN- $\gamma$  antibody AMG 811.

Similarly, gene dysregulation in SLE compared to healthy subjects at the RNA level was investigated using microarray analysis performed essentially as described in Example 1 except that the pre-filtering step was omitted. These results are reported in part in Table 2 below. Like the results displayed in Figure 2, data in Table 2 indicate that levels of expression of some genes at the RNA level differ in SLE patients as compared to healthy volunteers.

**Example 3: Single dose escalation study of a neutralizing anti-huIFN- $\gamma$  antibody**

Described below is a phase 1, randomized, double-blind, placebo-controlled, single dose escalation study of an anti-huIFN- $\gamma$  antibody (AMG 811) in subjects with mild, stable SLE. Anti-huIFN- $\gamma$  antibodies, including AMG 811, are described herein (above under the heading "Interferon Gamma Inhibitors") and in U.S. Patent 7,335,743, the relevant portions of which are incorporated herein by reference. Adults aged 18 to 65 with

a diagnosis of SLE (as defined by the American College of Rheumatology classification criteria) of at least 6 months duration were enrolled. Anti-malarials, leflunomide, or methotrexate, and up to 20 mg/day of prednisone (or equivalent) were permitted as concomitant therapies. The subjects had stable disease, that is, symptoms that were constant with no change in therapy for at least 30 days prior to randomization.

Twenty-six subjects with mild, stable SLE were enrolled in this Phase 1, single dose, double blind, randomized, placebo controlled, clinical trial. There were three subjects treated with active drug in each cohort (total of eighteen subjects) and eight subjects in the combined placebo group. The mean age was 43.3 years in the active group and 44.1 in the placebo group. The subjects were predominantly female (92%) and Caucasian (62%). The mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI; see Bombardier et al. (1992), Arthritis & Rheum. 35(6): 630-640, the relevant portions of which are incorporated herein by reference) score was low (2.3 and 3.8 for placebo and AMG 811 groups, respectively). Fifty per cent of placebo subjects and 28% of the subjects receiving AMG 811 were on corticosteroids, receiving mean doses of 10 mg/day and 13.5 mg/day, respectively. Seventy five per cent of placebo subjects and 100% of the subjects receiving AMG 811 were on anti-malarials, while a single subject in the AMG 811 group was on an immunosuppressant (methotrexate).

Each subject was treated with a single dose of AMG 811 (2 milligrams (mg) subcutaneous (SC), 6 mg SC, 20 mg SC, 60 mg SC, 180 mg SC, or 60 mg intravenous (IV)) or placebo (vehicle control) on day 1 of the study. The end of study (EOS) ranged from day 84 to day 196 depending on the dose level. Serum tube and PAXgene® blood RNA tube samples were collected from all cohorts at baseline, that is, on day 1 prior to dosing and at days 15, 56, and EOS after treatment. All samples were collected and included for analysis with the exception of one placebo EOS sample, one EOS sample from the 6 mg treated cohort, and two day 15 samples from the 20 mg cohort. One sample at the day 15 time point (60 mg IV) was subsequently determined to be from an unscheduled day 8 visit. As an actual day 15 sample was not available from this patient, and the expected drug exposure was not anticipated to be very different between day 8 and day 15, this sample was included with the day 15 results.

Total RNA was isolated from each sample and processed and analyzed by hybridization to a microarray as described in Example 1 above, except that the pre-filtering step to remove genes having low levels of expression was not performed.

These results are shown in the left panel of Figure 3, which shows the fold difference in expression of individual genes at the RNA level in day 15 blood samples from patients treated with AMG 811 and baseline or placebo-treated subjects. As in Figure 1, dots represent data from a particular gene sequence. The x-axis shows the fold difference in RNA expression in samples from patients treated with AMG 811 versus in samples from patients treated with placebo. Dots representing the same twenty genes that were circled in Figure 1 are also circled here.

More detailed data on these twenty genes from this experiment, as well as from the ex vivo stimulation experiment described in Example 1 and the comparison of healthy vs. SLE subjects described in Example 2, is shown in Table 2 below.

Table 2: Data from the top 20 IFN- $\gamma$  regulated genes

| Agilent® Probe Designation | Sequence Listing Number of the probe sequence | Symbol, Product(NCBI accession number of cDNA sequence)                            | Sequence Listing Number of cDNA sequence | IFN- $\gamma$ -Stim Fold change (95% CI) | Lupus v. healthy Fold change (95% CI) | D15 treatment effect Fold change (95% CI) | P-value for treatment effect (treated at day 15 vs. baseline) |
|----------------------------|-----------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------|------------------------------------------|---------------------------------------|-------------------------------------------|---------------------------------------------------------------|
| A_23_P112026               | SEQ ID NO:350                                 | INDO1, indoleamine 2,3-dioxygenase 1 (NM_002164)                                   | SEQ ID NO:50                             | 11.3 (10.0,12.8)                         | 1.1 (-1.2, 1.4)                       | -1.4 (-2.0, 1.0)                          | 0.076                                                         |
| A_23_P161428               | SEQ ID NO:72                                  | ANKRD22, ankyrin repeat domain 22 (NM_144590)                                      | SEQ ID NO:51                             | 10.8 (8.8,13.2)                          | 1.3 (-1.0, 1.7)                       | -2.2 (-3.0,-1.6)                          | <0.001                                                        |
| A_23_P18452                | SEQ ID NO:109                                 | CXCL9, chemokine (C-X-C motif) ligand 9 (NM_002416)                                | SEQ ID NO:52                             | 9.8 (8.4,11.4)                           | 1.3 (1.1, 1.5)                        | -1.3 (-1.6,-1.2)                          | <0.001                                                        |
| A_24_P28722                | SEQ ID NO:351                                 | RSAD2, radical S-adenosyl methionine domain containing 2 (NM_080657)               | SEQ ID NO:53                             | 7.7 (5.9,10.1)                           | 5.2 (2.3, 11.5)                       | -1.3 (-1.8, 1.1)                          | 0.184                                                         |
| A_23_P7827                 | SEQ ID NO:83                                  | FAM26F, family with sequence similarity 26, member F (NM_001010919)                | SEQ ID NO:54                             | 7.4 (6.9,8.0)                            | 1.2 (-1.0, 1.5)                       | -1.6 (-1.9,-1.3)                          | <0.001                                                        |
| A_24_P165864               | SEQ ID NO:300                                 | P2RY14, purinergic receptor P2Y, G-protein coupled, 14 (NM_001081455)              | SEQ ID NO:55                             | 7.3 (5.0,10.7)                           | -1.1 (-1.5, 1.2)                      | -1.7 (-2.4,-1.3)                          | 0.001                                                         |
| A_23_P74290                | SEQ ID NO:79                                  | GBP5, guanylate binding protein 5 (NM_052942)                                      | SEQ ID NO:56                             | 7.0 (5.0,9.8)                            | 1.3 (1.0, 1.7)                        | -1.8 (-2.3,-1.5)                          | <0.001                                                        |
| A_24_P561165               | SEQ ID NO:322                                 | SERPINC1, serpin peptidase inhibitor, clade G, member 1 (NM_000062)                | SEQ ID NO:57                             | 6.4 (4.5,8.9)                            | 2.5 (1.7, 3.8)                        | -1.7 (-2.4,-1.3)                          | 0.001                                                         |
| A_23_P63390                | SEQ ID NO:73                                  | FCGR1B or CD64Fc fragment of IgG, high affinity 1b, receptor (NM_001017986)        | SEQ ID NO:58                             | 6.3 (4.8,8.2)                            | 1.2 (-1.1, 1.6)                       | -2.1 (-2.6,-1.6)                          | <0.001                                                        |
| A_23_P150457               | SEQ ID NO:352                                 | LYVE1, lymphatic vessel endothelial hyaluronan receptor 1 (NM_006691)              | SEQ ID NO:59                             | -6.0 (-7.1,5.1)                          | -1.0 (-1.2, 1.1)                      | -1.1 (-1.2, 1.1)                          | 0.367                                                         |
| A_24_P245379               | SEQ ID NO:353                                 | SERPINF2, serpin peptidase inhibitor, clade B (ovalbumin), member 2 (NM_001143818) | SEQ ID NO:60                             | -5.9 (-7.6,4.6)                          | 1.0 (-1.2, 1.2)                       | -1.1 (-1.3, 1.1)                          | 0.536                                                         |
| A_23_P203882               | SEQ ID NO:356                                 | MMP19, matrix metalloproteinase 19 (NM_002429)                                     | SEQ ID NO:61                             | -5.8 (-7.6,-4.4)                         | 1.2 (1.0, 1.4)                        | -1.0 (-1.2, 1.1)                          | 0.699                                                         |
| A_23_P62690                | SEQ ID NO:74                                  | GBP1, guanylate binding protein 1, interferon-inducible, 67kDa (NM_002053)         | SEQ ID NO:62                             | 5.6 (4.0,7.7)                            | 1.6 (1.1, 2.2)                        | -2.0 (-2.4,-1.6)                          | <0.001                                                        |
| A_32_P107372               | SEQ ID NO:76                                  | GBP1, guanylate binding protein 1, interferon-inducible, 67kDa (NM_002053)         | SEQ ID NO:62                             | 5.6 (4.1,7.6)                            | 1.6 (1.2, 2.1)                        | -1.9 (-2.4,-1.5)                          | <0.001                                                        |
| A_24_P303091               | SEQ ID NO:311                                 | CXCL10, chemokine (C-X-C motif) ligand 10 (NM_001565)                              | SEQ ID NO:63                             | 5.4 (4.1,7.1)                            | 1.3 (-1.0, 1.8)                       | -1.6 (-2.2,-1.1)                          | 0.008                                                         |
| A_24_P316965               | SEQ ID NO:354                                 | RSAD2, radical S-adenosyl methionine domain containing 2 (NM_080657)               | SEQ ID NO:53                             | 5.4 (4.6,6.3)                            | 3.6 (2.1, 6.2)                        | -1.2 (-1.7, 1.1)                          | 0.235                                                         |
| A_23_P42353                | SEQ ID NO:77                                  | ETV7, ets variant 7 (NM_016135)                                                    | SEQ ID NO:64                             | 5.2 (3.6,7.5)                            | 1.8 (1.3, 2.6)                        | -1.8 (-2.4,-1.4)                          | <0.001                                                        |

| Agilent® Probe Designation | Sequence Listing Number of the probe sequence | Symbol, Product(NCBI accession number of cDNA sequence)                 | Sequene Listing Number of cDNA sequence | IFN- $\gamma$ Stim Fold change (95% CI) | Lupus v. healthy Fold change (95% CI) | D15 treatment effect Fold change (95% CI) | P-value for treatment effect (treated at day 15 vs. baseline) |
|----------------------------|-----------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------|---------------------------------------|-------------------------------------------|---------------------------------------------------------------|
| A_23_P256487               | SEQ ID NO:78                                  | PD-L1,Programmed Death Ligand-1 (AY254342)                              | SEQ ID NO:65                            | 5.0 (3.9,6.4)                           | 1.2 ( 1.1, 1.4)                       | -1.8 (-2.3,-1.4)                          | <0.001                                                        |
| A_23_P121657               | SEQ ID NO:355                                 | HS3ST1,heparan sulfate (glucosamine) 3-O-sulfotransferase 1 (NM_005114) | SEQ ID NO:66                            | -4.9 (-5.4,4.4)                         | 1.0 (-1.3, 1.3)                       | -1.0 (-1.2, 1.1)                          | 0.892                                                         |
| A_24_P12690                | SEQ ID NO:357                                 | INDO2,indoleamine 2,3-dioxygenase 2 (BC113498)                          | SEQ ID NO:67                            | 4.8 (3.7,6.2)                           | 1.0 (-1.1, 1.2)                       | -1.1 (-1.3, 1.0)                          | 0.126                                                         |

Many of the transcripts that were most impacted by treatment with IFN- $\gamma$  *ex vivo*, which are circled in Figure 1 and the left panel of Figure 3, are downregulated by treatment with AMG 811 *in vivo*. These data provide strong evidence that AMG 811 can inhibit IFN- $\gamma$ -regulated gene expression *in vivo* in SLE patients.

- 5 These data are also reported in more detail Table 5 (described in more detail below) which names a broader set of genes whose expression is modulated by AMG 811 *in vivo*.

An example of the *in vivo* effect of AMG 811 on gene expression at the RNA level is provided by guanylate binding protein 1 (GBP1). Levels of GBP1 RNA observed in individual patients before dosing with AMG 811 on Day -1 and on Day 15 of the study (after dosing) are shown in the right panel of Figure 3. The gene expression levels for the GBP1 transcript were standardized against levels seen in healthy volunteers (y-axis of the figure) and plotted against the serum levels of AMG 811 observed at days -1 and 15, which, of course, varied according to dosage. GBP1 RNA expression decreased at day 15 as compared to day -1 in each patient treated with AMG 811. In samples from patients treated with placebo, considerable change in GBP1 expression was also observed, but the direction of change was not consistent, and the expression was, on average, not different between study days ( $p=0.54$ , data not shown). Since GBP-1 is one of the genes whose expression is upregulated by IFN- $\gamma$  stimulation of blood of healthy volunteers *ex vivo*, these results suggest that inhibition of IFN- $\gamma$  is occurring in every patient treated with AMG 811 in this study.

To determine the effects of various doses of AMG 811 on CXCL10 protein expression, peripheral blood samples were taken and processed for serum, and CXCL10 protein concentrations were determined by ELISA assay. Differences between levels of protein expression at baseline and after a single dose of AMG 811 were estimated by a fixed-effects regression model containing factors for visit and dose, a random factor for subject, and an interaction term for visit and dose. Figure 4 shows the fold change in CXCL10 protein levels at Days 15 and 56 and at the end of study (EOS) as compared to baseline CXCL10 protein levels, with error bars showing the 95% confidence intervals using small sample size correction. Kackar,R.N., and Harville,D.A. 1984. Approximations for Standard Errors of Estimators of Fixed and Random Effects in Mixed Linear-Models. *Journal of the American Statistical Association* 79:853-862. These data indicate that a single dose of AMG 811 greater than 20 mg, that is, 60 mg or 180 mg, decreased levels of serum CXCL10 protein *in vivo* in SLE patients.

Levels of AMG 811 in serum were determined using a validated sandwich immunoassay at Amgen Inc., Thousand Oaks, CA. Study samples were added to a plate coated with a mouse anti-AMG 811 monoclonal antibody. After capture of AMG 811 with the immobilized antibody, unbound materials were removed by a wash step. Biotin conjugated rabbit anti-AMG 811 polyclonal antibody (Amgen Inc., CA) was added to detect the captured AMG 811. After another incubation step with streptavidin-HRP, a tetramethylbenzidine (TMB) peroxide substrate solution (KPL Inc., MD) was added to produce a colorimetric signal, which was proportional to the amount of AMG 811 bound by the capture reagent. The color development was stopped by addition of H<sub>2</sub>SO<sub>4</sub>, and the optical density (OD) signal was measured at 450 nm with reference to 650 nm. The absorbance versus concentration relationship was regressed according to a four-parameter logistic (auto-estimate) regression model with a weighting factor of 1/Y. The lower limit of quantification (LLOQ) was 15.2 ng/mL. Results from the single-dose escalation study are shown in Figure 5. AMG 811 exhibited linear pharmacokinetics (PK), with a mean terminal half-life (t<sub>1/2,z</sub>) ranging from 12 to 21 days. Following a single 60 mg IV dose, the mean area under the curve (AUC) value was approximately 3-fold higher than for the 60 mg SC dose, indicating an approximate 30% bioavailability. Mean AMG 811 PK parameters are presented in Table 3.

**Table 3. Serum PK Parameters for AMG 811**

| Route | Dose (mg)      | AMG 811 PK Parameters               |                                       |                                              |                                       |
|-------|----------------|-------------------------------------|---------------------------------------|----------------------------------------------|---------------------------------------|
|       |                | t <sub>max</sub> <sup>b</sup> (day) | C <sub>max</sub> <sup>c</sup> (µg/mL) | AUC <sub>last</sub> <sup>d</sup> (µg·day/mL) | t <sub>1/2,z</sub> <sup>e</sup> (day) |
| SC    | 2 <sup>a</sup> | 7.1 (7.1-13)                        | 0.143 (0.161)                         | 6.25 (NA)                                    | 21.0 (NA)                             |
|       | 6              | 14 (14-14)                          | 0.323 (0.275)                         | 11.6 (7.61)                                  | 17.0 (2.97)                           |
|       | 20             | 4.0 (4.0-7.0)                       | 1.81 (0.541)                          | 45.0 (9.72)                                  | 15.2 (3.01)                           |
|       | 60             | 4.0 (1.2-7.2)                       | 4.93 (0.705)                          | 117 (38.6)                                   | 12.3 (4.75)                           |
|       | 180            | 4.0 (4.0-14)                        | 17.6 (9.14)                           | 595 (121)                                    | 19.3 (0.667)                          |
| IV    | 60             | 0.04 (0.02,0.04)                    | 25.6 (10.0)                           | 369 (188)                                    | 18.6 (4.61)                           |

<sup>a</sup> One subject in cohort 1 (receiving a dose of 2mg) had only 2 measurable AMG 811 concentrations (data included where applicable)

<sup>b</sup> Time to maximum observed concentration (t<sub>max</sub>) are presented as median (range of values observed)

<sup>c</sup> Mean (standard deviation) maximum serum concentration achieved.

<sup>d</sup> Mean (standard deviation) area under the curve value to last measured time point.

<sup>e</sup> Mean (standard deviation) serum terminal half life.

Levels of total IFN-γ protein in patients dosed with AMG 811 were also determined. The total IFN-γ concentration in human serum was measured using a validated sandwich immunoassay at Amgen Inc., Thousand Oaks, CA. Specifically, study samples were incubated with 25 µg/mL of AMG 811 at 37°C to form IFN-γ-AMG 811 complexes prior to being added to a plate coated with a mouse anti-IFN-γ monoclonal antibody (Hycult Biotechnology, Uden, Netherlands). After capture of IFN-γ-AMG 811 complex with the immobilized anti-IFN-γ monoclonal antibody, unbound materials were removed by a wash step. Biotin conjugated rabbit anti-AMG 811 polyclonal antibody (Amgen Inc., CA) was added for detection of the captured IFN-γ-AMG 811 complex. After another incubation step with streptavidin-HRP, a tetramethylbenzidine (TMB) peroxide substrate solution (KPL Inc., MD) was added to produce a colorimetric signal, which was proportional to the amount of IFN-γ bound by the capture reagent. The color development was stopped by addition of H<sub>2</sub>SO<sub>4</sub>, and the optical density (OD) signal was measured at 450 nm with reference to 650 nm. The absorbance versus concentration relationship

was regressed according to a four-parameter logistic (auto-estimate) regression model with a weighting factor of 1/Y. The LLOQ of the method was 50 pg/mL.

The total IFN- $\gamma$  concentration represents both bound and free endogenous levels. Free IFN- $\gamma$  levels were not assessed separately. An amount of AMG 811 sufficient to saturate all IFN- $\gamma$  was added to the serum samples, and the resulting AMG 811:IFN- $\gamma$  complexes were detected by means of the sandwich immunoassay, as described above. These results are shown in Figures 6A (median levels) and 6B (mean levels). Total IFN- $\gamma$  median levels increased in a dose-dependent manner, then returned to baseline by approximately 6 to 7 months postdose. Figure 6A. The plateau in  $C_{max}$  values at doses of 60 and 180 mg SC and 60 mg IV may indirectly reflect the saturation of circulating, IFN- $\gamma$  levels by AMG 811. These data suggest that 60 mg SC was the lowest dose tested that saturated the available IFN- $\gamma$  in patients. At doses of 180 mg SC or 60 mg IV, the data suggest that this saturation of available IFN- $\gamma$  was maintained for a longer period of time.

In addition, these data suggest that dosing frequency can be adjusted so as to maintain levels of total IFN- $\gamma$  at or near the plateau concentrations observed at the higher doses. For example, at a dose of 60 mg SC, a level of total IFN- $\gamma$  of almost 400 pg/ml is achieved at early timepoints, which starts to drop off at about three or four weeks post-dosing. Dosing repeated about every 3, 4, 5, or 6 weeks could be beneficial at a dose of 60 mg SC. Similarly, at doses of 60 mg IV or 180 SC, levels of total IFN- $\gamma$  of around 400 pg/ml are achieved, but start to drop off at about 8, 9, 10, 11, or 12 weeks post dosing. Dosing repeated about every 4, 6, 8, 9, 10, 11, 12, 13, or 14 weeks could be beneficial at doses of 180 mg SC or 60 mg IV.

These data also have surprising implications about the production and turnover of IFN- $\gamma$ . Generally, IFN- $\gamma$  is undetectable or detectable at only low levels in peripheral blood. The comparatively high levels of total IFN- $\gamma$  detected upon dosing with AMG 811 indicate that IFN- $\gamma$  is likely produced at much higher levels than are generally appreciated and rapidly cleared from circulation. The relatively high levels of IFN- $\gamma$  detected in the presence of AMG 811 may be due to protection of the IFN- $\gamma$  from degradation and/or reduced clearance by binding to AMG 811. This assay allows for a better determination of the total production of IFN- $\gamma$  in an individual and can be useful for determination of dose, dosing frequency, and stratification purposes.

Additionally, although mean total IFN- $\gamma$  levels observed in the 60 mg IV dose group were significantly higher than in other groups (Figure 6B), this may be attributed to one subject with very high baseline levels of total IFN- $\gamma$ . Median profiles (Figure 6A) indicate that the 60 mg IV dose group had similar to IFN- $\gamma$  levels to those observed in the 180 mg SC dose group.

#### *Example 4: Multi-dose clinical trial in SLE patients with and without lupus nephritis*

In addition to the single dose clinical trial described in Example 3, a multi-dose trial was initiated to determine the safety and tolerability of multiple subcutaneous doses of AMG 811 in SLE patients with or without lupus nephritis. Part A of the study included three cohorts, 1, 2, and 3, each containing eight SLE patients

without lupus nephritis. To be eligible for cohorts 1-3, a patient must have been diagnosed with SLE at least 6 months before the start of the study. Prednisone at a dose of  $\leq 20$  mg/day was permitted during the study, as were concurrently administered medications used for treating SLE including mycophenolate mofetil, azathioprine, leflunomide, methotrexate, and anti-malarials. Two of the eight patients in each of cohorts 1-3 received three doses of placebo administered every four weeks, and the other six received three doses AMG 811 (6, 20, or 60 mg for cohorts 1, 2, and 3, respectively) administered every four weeks, that is on days 1, 29, and 57. Part B of the study will include cohorts 4, 5, and 6. Patients in cohorts 4-6 are required to have been diagnosed with SLE at least 6 months before the start of the study and with proliferative glomerulonephritis, as evidenced by a renal biopsy and urine protein/creatinine ratio of  $>1$  or a 24 hour urine protein level of  $> 1$  g/day. These patients were also permitted to take prednisone at a dose of  $\leq 20$  mg/day and to take SLE medications including mycophenolate mofetil, azathioprine, leflunomide, methotrexate, and anti-malarials. Cohorts 4 and 5, for which dosing is now complete, contained eight and twelve SLE patients that had lupus nephritis, respectively. Cohort 6 is to contain eight lupus nephritis patients. Two of the patients in each of cohorts 4 and 6 and three of the twelve patients in cohort 5 will receive (and, in some cases, have received) three doses of placebo administered every four weeks, and the other patients will receive three doses AMG 811 (20, 60, or 120 mg for cohorts 4, 5, and 6, respectively) administered every four weeks, that is, on days 1, 29, and 57. Blood samples will be taken at baseline, *i.e.*, one to three days before dosing, and on days 1 (after dosing), 3, 8, 15, 29, 57, 85, 113, and 197 (which was the end of the study (EOS)) to determine levels of expression of various biomarker genes. Samples will be analyzed for RNA expression by DNA array as described above in Example 3 or for expression of selected proteins by ELISA assay. Blood samples taken at baseline and on days 1 (after dosing), 3, 5, 8, 15, 22, 29 (pre-dosing), 43, 57 (pre- and post-dosing), 59, 61, 64, 71, 78, 85, 113, 141, 169, and 197 will be analyzed to assess a number of laboratory parameters. Twenty four hour urine samples were taken at baseline and on days 15, 29 (pre-dosing), 57 (pre-dosing), 85, 113, 141, 169, and 197 (EOS). Spot urine samples were taken at baseline and on days 3, 8, 15, 22, 29 (pre-dosing), 43, 57 (pre-dosing), 71, 85, 113, 141, 169, and 197 (EOS). Urine samples were analyzed for levels of urine protein using the a dye-binding assay (pyrocatechol violet-ammonium molybdate dye), which was analyzed in a "dry-slide" format using an automated laboratory analyzer such as the Ortho-Clinical VITROS® 5,1 FS Chemistry Analyzer from Ortho Clinical Diagnostics. Creatinine levels in urine samples were assessed by a multi-step coupled enzymatic two-point rate colorimetric assay (creatinine amidohydrolase/creatinine amidohydrolase/sarcosine oxidase/peroxidase) analyzed using a dry-slide format and automated laboratory analyzer. Such an assay is described in, *e.g.*, Guder *et al.* (1986), J. Clin. Chem. Clin Biochem. 24(11): 889-902.

In Table 4 below are listed the ten genes whose expression, as detected at the RNA level, was most significantly correlated with the concentration of AMG 811 in serum as assessed in the single dose clinical trial described in Example 3. Data from the multiple dose clinical trial described in Example 4 showed that the average of the expression levels of these ten genes was responsive to the dosage level of AMG 811.

Table 4: Ten genes whose expression is most affected by AMG 811 concentration in serum

| AGILENT®<br>probe designation | Sequence Listing<br>Number of Agilent Probe<br>Sequence | Gene symbol | NCBI Accession No. of<br>cDNA Sequence | Sequence Listing<br>Number of cDNA<br>Sequence |
|-------------------------------|---------------------------------------------------------|-------------|----------------------------------------|------------------------------------------------|
| A_33_P3407880                 | SEQ ID NO:349                                           | ANKRD22     | NM_144590                              | SEQ ID NO:51                                   |
| A_23_P62690                   | SEQ ID NO:74                                            | GBP1        | NM_002053                              | SEQ ID NO:62                                   |
| A_23_P370682                  | SEQ ID NO:80                                            | BATF2       | NM_138456                              | SEQ ID NO:68                                   |
| A_23_P42353                   | SEQ ID NO:77                                            | ETV7        | NM_016135                              | SEQ ID NO:64                                   |
| A_23_P63390                   | SEQ ID NO:73                                            | FCGR1B      | NM_001017986                           | SEQ ID NO:58                                   |
| A_23_P34915                   | SEQ ID NO:81                                            | ATF3        | NM_001040619                           | SEQ ID NO:69                                   |
| A_23_P139123                  | SEQ ID NO:210                                           | SERPING1    | NM_000062                              | SEQ ID NO:57                                   |
| A_23_P74290                   | SEQ ID NO:79                                            | GBP5        | NM_052942                              | SEQ ID NO:56                                   |
| A_24_P243749                  | SEQ ID NO:82                                            | PKD4        | NM_002612                              | SEQ ID NO:70                                   |
| A_23_P338479                  | SEQ ID NO:75                                            | CD274       | NM_014143                              | SEQ ID NO:71                                   |

Based on average RNA expression of the ten genes listed in Table 4, an "AMG 811 Score" could be assigned to each patient. Figure 7 shows the average AMG 811 Score for the lupus nephritis patients receiving placebo or 20 or 60 mg of AMG 811. The average AMG 811 Score for patients receiving 20 mg or 60 mg was significantly less than the average score for patients receiving placebo. The amount of reduction in the AMG 811 Score was smaller than what was seen in the general SLE population (data not shown), suggesting that the 60 mg doses may not be high enough to achieve the maximal pharmacodynamic effect of AMG 811 in lupus nephritis patients.

Data from cohorts 1-3 was combined to create Figure 8, which shows the fold change from baseline in the expression of CXCL10 at the protein level as measured by ELISA. Figure 9 shows similar data from the lupus nephritis patients in cohorts 4 and 5, who received multiple doses of 20 mg and 60 mg, respectively. These data indicate that the 20 mg and 60 mg multiple dose regimes used were effective to reduce *in vivo* expression of CXCL10 among SLE patients, indicating that these dosage regimes are having a biological effect. These data indicate that the 60 mg multiple dose regime did reduce *in vivo* expression of CXCL10 in lupus nephritis patients at some early time points, although effects were not as clear as those observed in SLE patients without nephritis. Further, lupus nephritis patients dosed with 20 mg of AMG 811 did not exhibit a clear decrease in serum levels of CXCL10. This difference in apparent dosing requirements between SLE and lupus nephritis patients could reflect a generally more highly activated IFN- $\gamma$  pathway in lupus nephritis patients as compared to SLE patients. More highly expressed IL-18, IP-10, and CCL2 proteins (Figure 2) are consistent with this interpretation. Further, these data suggest that expression of biomarkers, for example, CXCL10, IL-18, CCL2, etc., could guide dose selection.

The data in Figure 10 shows serum CXCL10 levels as fold change from baseline plotted against serum concentration of AMG 811 in combined patients with general SLE and with lupus nephritis. Higher levels of AMG 811 correlate with further reduction in CXCL10 levels. This suggests that AMG 811 is reducing CXCL10 levels in these patients.

Data from the single dose clinical trial described above was used to compile a list of genes whose expression is significantly (with a p value < 0.001) modulated (either up- or down-regulated) *in vivo* in SLE patients dosed with AMG 811 as compared to SLE patients dosed with placebo. This list of genes is shown in Table 5 below.

Table 5: Genes whose expression is modulated *in vivo* by AMG 811

| AGILENT® Probe Designation | Sequence Listing Number of Agilent Probe Sequence | Gene Symbol  | NCBI Accession Number of cDNA Sequence | Direction of Modulation by AMG 811 |
|----------------------------|---------------------------------------------------|--------------|----------------------------------------|------------------------------------|
| A_23_P161428               | SEQ ID NO:72                                      | ANKRD22      | NM_144590                              | down                               |
| A_23_P63390                | SEQ ID NO:73                                      | FCGR1B       | NM_001017986                           | down                               |
| A_23_P62890                | SEQ ID NO:74                                      | GBP1         | NM_002053                              | down                               |
| A_23_P338479               | SEQ ID NO:75                                      | CD274        | NM_014143                              | down                               |
| A_32_P107372               | SEQ ID NO:76                                      | GBP1         | NM_002053                              | down                               |
| A_23_P42353                | SEQ ID NO:77                                      | ETV7         | NM_016135                              | down                               |
| A_23_P256487               | SEQ ID NO:78                                      | A_23_P256487 | THC2651085                             | down                               |
| A_23_P74290                | SEQ ID NO:79                                      | GBP5         | NM_052942                              | down                               |
| A_23_P370682               | SEQ ID NO:80                                      | BATF2        | NM_138456                              | down                               |
| A_23_P34915                | SEQ ID NO:81                                      | ATF3         | NM_001040619                           | down                               |
| A_24_P243749               | SEQ ID NO:82                                      | PDK4         | NM_002612                              | down                               |
| A_23_P7827                 | SEQ ID NO:83                                      | FAM26F       | NM_001010919                           | down                               |
| A_23_P208119               | SEQ ID NO:84                                      | PSTPIP2      | NM_024430                              | down                               |
| A_24_P100387               | SEQ ID NO:85                                      | GK           | NM_203391                              | down                               |
| A_24_P36898                | SEQ ID NO:86                                      | A_24_P36898  | AL832451                               | down                               |
| A_32_P44394                | SEQ ID NO:87                                      | AIM2         | NM_004833                              | down                               |
| A_24_P274270               | SEQ ID NO:88                                      | STAT1        | NM_139266                              | down                               |
| A_23_P56630                | SEQ ID NO:89                                      | STAT1        | NM_007315                              | down                               |
| A_23_P85693                | SEQ ID NO:90                                      | GBP2         | NM_004120                              | down                               |
| A_24_P322353               | SEQ ID NO:91                                      | PSTPIP2      | NM_024430                              | down                               |
| A_23_P63896                | SEQ ID NO:92                                      | FAS          | NM_000043                              | down                               |
| A_23_P51487                | SEQ ID NO:93                                      | GBP3         | NM_018284                              | down                               |
| A_23_P96556                | SEQ ID NO:94                                      | GK           | NM_203391                              | down                               |
| A_23_P319792               | SEQ ID NO:95                                      | XRN1         | NM_019001                              | down                               |
| A_32_P166272               | SEQ ID NO:96                                      | STX11        | NM_003764                              | down                               |
| A_24_P196382               | SEQ ID NO:97                                      | ATG3         | BC002830                               | down                               |
| A_24_P33896                | SEQ ID NO:98                                      | ATF3         | NM_001040619                           | down                               |
| A_23_P347541               | SEQ ID NO:99                                      | GRIN3A       | NM_133445                              | down                               |
| A_23_P255444               | SEQ ID NO:100                                     | DAPP1        | NM_014395                              | down                               |
| A_23_P69383                | SEQ ID NO:101                                     | PARP9        | NM_031458                              | down                               |
| A_23_P154235               | SEQ ID NO:102                                     | NMI          | NM_004688                              | down                               |
| A_24_P7594                 | SEQ ID NO:103                                     | APOL6        | NM_030641                              | down                               |
| A_32_P11058                | SEQ ID NO:104                                     | A_32_P11058  | THC2646969                             | down                               |
| A_23_P202978               | SEQ ID NO:105                                     | CASP1        | NM_033292                              | down                               |
| A_24_P350686               | SEQ ID NO:106                                     | TIFA         | NM_052864                              | down                               |
| A_23_P123608               | SEQ ID NO:107                                     | JAK2         | NM_004972                              | down                               |
| A_24_P45446                | SEQ ID NO:108                                     | GBP4         | NM_052941                              | down                               |
| A_23_P18452                | SEQ ID NO:109                                     | CXCL9        | NM_002416                              | down                               |
| A_23_P121253               | SEQ ID NO:110                                     | TNFSF10      | NM_003810                              | down                               |
| A_24_P192805               | SEQ ID NO:111                                     | CARD17       | NM_001007232                           | down                               |
| A_24_P687326               | SEQ ID NO:112                                     | C9ORF109     | NR_024366                              | down                               |
| A_23_P59005                | SEQ ID NO:113                                     | TAP1         | NM_000593                              | down                               |
| A_32_P159254               | SEQ ID NO:114                                     | A_32_P159254 | AK123584                               | down                               |
| A_23_P132822               | SEQ ID NO:115                                     | XRN1         | NM_019001                              | down                               |
| A_23_P64173                | SEQ ID NO:116                                     | CARD16       | NM_001017534                           | down                               |
| A_23_P502797               | SEQ ID NO:117                                     | WDFY1        | NM_020830                              | down                               |
| A_32_P131401               | SEQ ID NO:118                                     | A_32_P131401 | AI276257                               | down                               |
| A_23_P111000               | SEQ ID NO:119                                     | PSMB9        | NM_002800                              | down                               |
| A_32_P34552                | SEQ ID NO:120                                     | POLB         | NM_002690                              | down                               |
| A_23_P102060               | SEQ ID NO:121                                     | SSFA2        | NM_006751                              | down                               |
| A_24_P71938                | SEQ ID NO:122                                     | SMAD1        | NM_005900                              | down                               |
| A_32_P74366                | SEQ ID NO:123                                     | VCPIP1       | ENST00000310421                        | down                               |
| A_23_P213247               | SEQ ID NO:124                                     | FBXL5        | NM_033535                              | down                               |
| A_23_P202199               | SEQ ID NO:125                                     | SLK          | NM_014720                              | down                               |
| A_24_P370702               | SEQ ID NO:126                                     | GBP3         | NM_018284                              | down                               |
| A_24_P937817               | SEQ ID NO:127                                     | A_24_P937817 | AK026195                               | down                               |
| A_24_P53051                | SEQ ID NO:128                                     | LACTB        | NM_171846                              | down                               |
| A_23_P35912                | SEQ ID NO:129                                     | CASP4        | NM_033306                              | down                               |
| A_23_P212706               | SEQ ID NO:130                                     | ATG3         | NM_022488                              | down                               |

| AGILENT® Probe Designation | Sequence Listing Number of Agilent Probe Sequence | Gene Symbol  | NCBI Accession Number of cDNA Sequence | Direction of Modulation by AMG 811 |
|----------------------------|---------------------------------------------------|--------------|----------------------------------------|------------------------------------|
| A_23_P119992               | SEQ ID NO:131                                     | VRK2         | NM_006296                              | down                               |
| A_24_P707156               | SEQ ID NO:132                                     | A_24_P707156 | BG623116                               | down                               |
| A_24_P156490               | SEQ ID NO:133                                     | KCNMA1       | NM_002247                              | down                               |
| A_23_P113263               | SEQ ID NO:134                                     | A_23_P113263 | A_23_P113263                           | down                               |
| A_23_P35906                | SEQ ID NO:135                                     | CASP4        | NM_033306                              | down                               |
| A_24_P393740               | SEQ ID NO:136                                     | FYB          | NM_001465                              | down                               |
| A_24_P239606               | SEQ ID NO:137                                     | GADD45B      | NM_015675                              | down                               |
| A_23_P256445               | SEQ ID NO:138                                     | VCPIP1       | NM_025054                              | down                               |
| A_23_P251962               | SEQ ID NO:139                                     | ZNF273       | BC019234                               | down                               |
| A_23_P83073                | SEQ ID NO:140                                     | HIATL1       | NM_032558                              | down                               |
| A_32_P65804                | SEQ ID NO:141                                     | A_32_P65804  | THC2661836                             | down                               |
| A_24_P54863                | SEQ ID NO:142                                     | C4ORF32      | NM_152400                              | down                               |
| A_23_P356163               | SEQ ID NO:143                                     | WDR49        | NM_178824                              | down                               |
| A_32_P35256                | SEQ ID NO:144                                     | A_32_P35256  | BF436068                               | down                               |
| A_24_P211689               | SEQ ID NO:145                                     | A_24_P211689 | AK021629                               | down                               |
| A_23_P417261               | SEQ ID NO:146                                     | EFHB         | NM_144715                              | down                               |
| A_23_P407090               | SEQ ID NO:147                                     | NFXL1        | NM_152995                              | down                               |
| A_32_P164061               | SEQ ID NO:148                                     | A_32_P164061 | A_32_P164061                           | down                               |
| A_23_P102582               | SEQ ID NO:149                                     | C20ORF24     | NM_018840                              | down                               |
| A_24_P393353               | SEQ ID NO:150                                     | XRN1         | NM_001042604                           | down                               |
| A_24_P50543                | SEQ ID NO:151                                     | TRIM69       | BC031266                               | down                               |
| A_24_P920333               | SEQ ID NO:152                                     | A_24_P920333 | AA748674                               | down                               |
| A_24_P101921               | SEQ ID NO:153                                     | A_24_P101921 | ENST00000391612                        | down                               |
| A_23_P382148               | SEQ ID NO:154                                     | RAB1A        | NM_004161                              | down                               |
| A_24_P43391                | SEQ ID NO:155                                     | TMEM165      | NM_018475                              | down                               |
| A_24_P167473               | SEQ ID NO:156                                     | ARPC3        | NM_005719                              | down                               |
| A_23_P380901               | SEQ ID NO:157                                     | PTH2R        | NM_005048                              | down                               |
| A_23_P26583                | SEQ ID NO:158                                     | NLRC5        | NM_032206                              | down                               |
| A_24_P263623               | SEQ ID NO:159                                     | PTGES3       | NM_006601                              | down                               |
| A_23_P367610               | SEQ ID NO:160                                     | SESTD1       | NM_178123                              | down                               |
| A_24_P372223               | SEQ ID NO:161                                     | MSR1         | NM_138715                              | down                               |
| A_24_P367326               | SEQ ID NO:162                                     | A_24_P367326 | A_24_P367326                           | down                               |
| A_23_P39840                | SEQ ID NO:163                                     | VAMP5        | NM_006634                              | down                               |
| A_23_P402892               | SEQ ID NO:164                                     | NLRC5        | NM_032206                              | down                               |
| A_23_P211080               | SEQ ID NO:165                                     | IFNAR2       | NM_207585                              | down                               |
| A_23_P252106               | SEQ ID NO:166                                     | RIPK2        | NM_003821                              | down                               |
| A_23_P12603                | SEQ ID NO:167                                     | 40607        | NM_017824                              | down                               |
| A_23_P259272               | SEQ ID NO:168                                     | WSB2         | NM_018639                              | down                               |
| A_23_P209805               | SEQ ID NO:169                                     | NAB1         | NM_005966                              | down                               |
| A_23_P79942                | SEQ ID NO:170                                     | PANK2        | NM_153638                              | down                               |
| A_23_P383053               | SEQ ID NO:171                                     | APPBP2       | NM_006380                              | down                               |
| A_23_P147238               | SEQ ID NO:172                                     | WSB2         | NM_018639                              | down                               |
| A_23_P90589                | SEQ ID NO:173                                     | MRPL44       | NM_022915                              | down                               |
| A_23_P250629               | SEQ ID NO:174                                     | PSMB8        | NM_004159                              | down                               |
| A_23_P200560               | SEQ ID NO:175                                     | CDC42        | NM_001039802                           | down                               |
| A_24_P390403               | SEQ ID NO:176                                     | RTF1         | NM_015138                              | down                               |
| A_24_P269619               | SEQ ID NO:177                                     | DECR1        | NM_001359                              | down                               |
| A_23_P71464                | SEQ ID NO:178                                     | DECR1        | NM_001359                              | down                               |
| A_23_P164536               | SEQ ID NO:179                                     | PIK3C3       | NM_002647                              | down                               |
| A_23_P11915                | SEQ ID NO:180                                     | GDAP2        | NM_017686                              | down                               |
| A_23_P74928                | SEQ ID NO:181                                     | MR1          | NM_001531                              | down                               |
| A_24_P206736               | SEQ ID NO:182                                     | ZNF143       | NM_003442                              | down                               |
| A_23_P12920                | SEQ ID NO:183                                     | RAD9A        | NM_004584                              | up                                 |
| A_23_P56188                | SEQ ID NO:184                                     | UBA52        | NM_001033930                           | up                                 |
| A_24_P914134               | SEQ ID NO:185                                     | PRNP         | NM_001080122                           | up                                 |
| A_32_P108870               | SEQ ID NO:186                                     | PMP2         | NM_002677                              | up                                 |
| A_24_P921683               | SEQ ID NO:187                                     | FOXP2        | NM_014491                              | up                                 |
| A_23_P342612               | SEQ ID NO:188                                     | HCN2         | NM_001194                              | up                                 |
| A_24_P227326               | SEQ ID NO:189                                     | RCOR2        | NM_173587                              | up                                 |
| A_23_P111571               | SEQ ID NO:190                                     | HOXA3        | NM_153631                              | up                                 |
| A_23_P55716                | SEQ ID NO:191                                     | BCAM         | NM_005581                              | up                                 |

| AGILENT® Probe Designation | Sequence Listing Number of Agilent Probe Sequence | Gene Symbol  | NCBI Accession Number of cDNA Sequence | Direction of Modulation by AMG 811 |
|----------------------------|---------------------------------------------------|--------------|----------------------------------------|------------------------------------|
| A_23_P397208               | SEQ ID NO:192                                     | GSTM2        | NM_000848                              | up                                 |
| A_23_P150162               | SEQ ID NO:193                                     | DRD4         | NM_000797                              | up                                 |
| A_32_P151317               | SEQ ID NO:194                                     | A_32_P151317 | B1818647                               | up                                 |
| A_24_P142305               | SEQ ID NO:195                                     | HBA2         | NM_000517                              | up                                 |

The amino acid and protein sequences included in the database entries having the accession numbers listed in Table 5 are incorporated herein by reference. In addition, the sequences of the AGILENT® probes are publicly available in GEO database of NCBI website as mentioned above.

These data indicate that administration of AMG 811 affects expression of many genes *in vivo*. Among these are a number of genes whose expression is also modulated by IFN- $\gamma$  *ex vivo* as described in Example 1 and Table 1 above. A group of genes whose expression is modulated by IFN- $\gamma$  *ex vivo* and by AMG 811 *in vivo* (in opposite directions), is listed in Table 6 below. The thresholds for being included in this list included (a) being included in Table 1 and (b) being significantly ( $p < 0.05$ ) modulated *in vivo* in patients receiving AMG 811 as compared to patients receiving placebo. This different cutoff value (as compared to  $p < 0.001$ ) for *in vivo* modulation by AMG 811 is appropriate and was used in view of the fact that this list was selected only from among the genes included in Table 1, rather than from the tens of thousands of genes represented in the array.

Table 6: Genes modulated by IFN- $\gamma$  *ex vivo* and by AMG 811 *in vivo*

| Probe Identifier | Sequence Listing Number of Probe Sequence | Symbol   | Accession No. of Sequence of cDNA | Direction of modulation by AMG 811 |
|------------------|-------------------------------------------|----------|-----------------------------------|------------------------------------|
| A_23_P103496     | SEQ ID NO:196                             | GBP4     | NM_052941                         | down                               |
| A_23_P105794     | SEQ ID NO:197                             | EPSTH1   | NM_033255                         | down                               |
| A_23_P111000     | SEQ ID NO:198                             | PSMB9    | NM_002800                         | down                               |
| A_23_P112251     | SEQ ID NO:199                             | GNG10    | NM_001017998                      | down                               |
| A_23_P112260     | SEQ ID NO:200                             | GNG10    | NM_001017998                      | down                               |
| A_23_P121253     | SEQ ID NO:110                             | TNFSF10  | NM_003810                         | down                               |
| A_23_P121716     | SEQ ID NO:201                             | ANXA3    | NM_005139                         | down                               |
| A_23_P123608     | SEQ ID NO:107                             | JAK2     | NM_004972                         | down                               |
| A_23_P125278     | SEQ ID NO:202                             | CXCL11   | NM_005409                         | down                               |
| A_23_P128447     | SEQ ID NO:203                             | LRRK2    | NM_198578                         | down                               |
| A_23_P129492     | SEQ ID NO:204                             | SEPX1    | NM_016332                         | down                               |
| A_23_P132388     | SEQ ID NO:205                             | SCO2     | NM_005138                         | down                               |
| A_23_P132822     | SEQ ID NO:115                             | XRN1     | NM_019001                         | down                               |
| A_23_P133133     | SEQ ID NO:206                             | ALPK1    | NM_025144                         | down                               |
| A_23_P133142     | SEQ ID NO:207                             | ALPK1    | NM_025144                         | down                               |
| A_23_P133916     | SEQ ID NO:208                             | C2       | NM_000063                         | down                               |
| A_23_P138680     | SEQ ID NO:209                             | IL15RA   | NM_172200                         | down                               |
| A_23_P139123     | SEQ ID NO:210                             | SERPING1 | NM_000062                         | down                               |
| A_23_P140807     | SEQ ID NO:211                             | PSMB10   | NM_002801                         | down                               |
| A_23_P14105      | SEQ ID NO:212                             | RCBTB2   | NM_001268                         | down                               |
| A_23_P14174      | SEQ ID NO:213                             | TNFSF13B | NM_006573                         | down                               |
| A_23_P142424     | SEQ ID NO:214                             | TMEM149  | NM_024660                         | down                               |
| A_23_P145874     | SEQ ID NO:215                             | SAMD9L   | NM_152703                         | down                               |
| A_23_P149476     | SEQ ID NO:216                             | EFCAB2   | NM_032328                         | down                               |
| A_23_P153320     | SEQ ID NO:217                             | ICAM1    | NM_000201                         | down                               |
| A_23_P15414      | SEQ ID NO:218                             | SCARF1   | NM_145351                         | down                               |
| A_23_P154235     | SEQ ID NO:102                             | NMI      | NM_004688                         | down                               |
| A_23_P155049     | SEQ ID NO:219                             | APOL6    | NM_030641                         | down                               |
| A_23_P155052     | SEQ ID NO:220                             | APOL6    | NM_030641                         | down                               |
| A_23_P156687     | SEQ ID NO:221                             | CFB      | NM_001710                         | down                               |
| A_23_P156788     | SEQ ID NO:222                             | STX11    | NM_003764                         | down                               |
| A_23_P160025     | SEQ ID NO:223                             | IFIH6    | NM_005531                         | down                               |
| A_23_P160720     | SEQ ID NO:224                             | BATF3    | NM_018664                         | down                               |

| Probe Identifier | Sequence Listing<br>Number of Probe<br>Sequence | Symbol       | Accession No. of<br>Sequence of cDNA | Direction of modulation by AMG<br>811 |
|------------------|-------------------------------------------------|--------------|--------------------------------------|---------------------------------------|
| A_23_P161428     | SEQ ID NO:72                                    | ANKRD22      | NM_144590                            | down                                  |
| A_23_P163079     | SEQ ID NO:225                                   | GCH1         | NM_000161                            | down                                  |
| A_23_P165624     | SEQ ID NO:226                                   | TNFAIP6      | NM_007115                            | down                                  |
| A_23_P166408     | SEQ ID NO:227                                   | OSM          | NM_020530                            | down                                  |
| A_23_P166797     | SEQ ID NO:228                                   | RTP4         | NM_022147                            | down                                  |
| A_23_P168828     | SEQ ID NO:229                                   | KLF10        | NM_005855                            | down                                  |
| A_23_P17655      | SEQ ID NO:230                                   | KCNJ15       | NM_170736                            | down                                  |
| A_23_P17837      | SEQ ID NO:231                                   | APOL1        | NM_145343                            | down                                  |
| A_23_P18452      | SEQ ID NO:109                                   | CXCL9        | NM_002416                            | down                                  |
| A_23_P18604      | SEQ ID NO:232                                   | LAP3         | NM_015907                            | down                                  |
| A_23_P202978     | SEQ ID NO:105                                   | CASP1        | NM_033292                            | down                                  |
| A_23_P203498     | SEQ ID NO:233                                   | TRIM22       | NM_006074                            | down                                  |
| A_23_P205200     | SEQ ID NO:234                                   | DHRS12       | NM_024705                            | down                                  |
| A_23_P208119     | SEQ ID NO:84                                    | PSTPIP2      | NM_024430                            | down                                  |
| A_23_P20814      | SEQ ID NO:235                                   | DDX58        | NM_014314                            | down                                  |
| A_23_P209625     | SEQ ID NO:236                                   | CYP1B1       | NM_000104                            | down                                  |
| A_23_P209678     | SEQ ID NO:237                                   | PLEK         | NM_002664                            | down                                  |
| A_23_P210763     | SEQ ID NO:238                                   | JAG1         | NM_000214                            | down                                  |
| A_23_P211401     | SEQ ID NO:239                                   | KREMEN1      | NM_001039570                         | down                                  |
| A_23_P211445     | SEQ ID NO:240                                   | LIMK2        | NM_016733                            | down                                  |
| A_23_P211488     | SEQ ID NO:241                                   | APOL2        | NM_145637                            | down                                  |
| A_23_P215154     | SEQ ID NO:242                                   | NUB1         | NM_016118                            | down                                  |
| A_23_P218928     | SEQ ID NO:243                                   | C4ORF18      | NM_016613                            | down                                  |
| A_23_P24004      | SEQ ID NO:244                                   | IFIT2        | NM_001547                            | down                                  |
| A_23_P251480     | SEQ ID NO:245                                   | NBN          | NM_002485                            | down                                  |
| A_23_P252106     | SEQ ID NO:166                                   | RIPK2        | NM_003821                            | down                                  |
| A_23_P255444     | SEQ ID NO:100                                   | DAPP1        | NM_014395                            | down                                  |
| A_23_P256445     | SEQ ID NO:138                                   | VCPIP1       | NM_025054                            | down                                  |
| A_23_P256487     | SEQ ID NO:78                                    | A_23_P256487 | THC2651085                           | down                                  |
| A_23_P257087     | SEQ ID NO:246                                   | PDK4         | NM_002612                            | down                                  |
| A_23_P258493     | SEQ ID NO:247                                   | LMNB1        | NM_005573                            | down                                  |
| A_23_P26583      | SEQ ID NO:158                                   | NLRC5        | NM_032206                            | down                                  |
| A_23_P29953      | SEQ ID NO:248                                   | IL15         | NM_172174                            | down                                  |
| A_23_P30069      | SEQ ID NO:249                                   | DDX60L       | NM_001012967                         | down                                  |
| A_23_P3221       | SEQ ID NO:250                                   | SQRDL        | NM_021199                            | down                                  |
| A_23_P329261     | SEQ ID NO:251                                   | KCNJ2        | NM_000891                            | down                                  |
| A_23_P329870     | SEQ ID NO:252                                   | RHBDF2       | NM_024599                            | down                                  |
| A_23_P335661     | SEQ ID NO:253                                   | SAMD4A       | AB028976                             | down                                  |
| A_23_P338479     | SEQ ID NO:75                                    | CD274        | NM_014143                            | down                                  |
| A_23_P343837     | SEQ ID NO:254                                   | PARP11       | NM_020367                            | down                                  |
| A_23_P347040     | SEQ ID NO:255                                   | DTX3L        | NM_138287                            | down                                  |
| A_23_P347541     | SEQ ID NO:99                                    | GRIN3A       | NM_133445                            | down                                  |
| A_23_P35412      | SEQ ID NO:256                                   | IFIT3        | NM_001549                            | down                                  |
| A_23_P354387     | SEQ ID NO:257                                   | MYOF         | NM_013451                            | down                                  |
| A_23_P358904     | SEQ ID NO:258                                   | IKZF4        | NM_022465                            | up                                    |
| A_23_P35906      | SEQ ID NO:135                                   | CASP4        | NM_033306                            | down                                  |
| A_23_P35912      | SEQ ID NO:129                                   | CASP4        | NM_033306                            | down                                  |
| A_23_P370682     | SEQ ID NO:80                                    | BATF2        | NM_138456                            | down                                  |
| A_23_P380857     | SEQ ID NO:259                                   | APOL4        | NM_030643                            | down                                  |
| A_23_P39840      | SEQ ID NO:163                                   | VAMP5        | NM_006634                            | down                                  |
| A_23_P401106     | SEQ ID NO:260                                   | PDE2A        | NM_002599                            | up                                    |
| A_23_P402892     | SEQ ID NO:164                                   | NLRC5        | NM_032206                            | down                                  |
| A_23_P41765      | SEQ ID NO:261                                   | IRF1         | NM_002198                            | down                                  |
| A_23_P420942     | SEQ ID NO:262                                   | MT1E         | AF495759                             | up                                    |
| A_23_P421423     | SEQ ID NO:263                                   | TNFAIP2      | NM_006291                            | down                                  |
| A_23_P42282      | SEQ ID NO:264                                   | C4B          | NM_001002029                         | up                                    |
| A_23_P42302      | SEQ ID NO:265                                   | HLA-DQA2     | NM_020056                            | up                                    |
| A_23_P42353      | SEQ ID NO:77                                    | ETV7         | NM_016135                            | down                                  |
| A_23_P42969      | SEQ ID NO:266                                   | FGL2         | NM_006682                            | down                                  |
| A_23_P47304      | SEQ ID NO:267                                   | CASP5        | NM_004347                            | down                                  |
| A_23_P4821       | SEQ ID NO:268                                   | JUNB         | NM_002229                            | down                                  |

| Probe Identifier | Sequence Listing Number of Probe Sequence | Symbol    | Accession No. of Sequence of cDNA | Direction of modulation by AMG 811 |
|------------------|-------------------------------------------|-----------|-----------------------------------|------------------------------------|
| A_23_P48513      | SEQ ID NO:269                             | IFI27     | NM_005532                         | up                                 |
| A_23_P51487      | SEQ ID NO:93                              | GBP3      | NM_018284                         | down                               |
| A_23_P53891      | SEQ ID NO:270                             | KLF5      | NM_001730                         | down                               |
| A_23_P56630      | SEQ ID NO:89                              | STAT1     | NM_007315                         | down                               |
| A_23_P56746      | SEQ ID NO:271                             | FAP       | NM_004460                         | down                               |
| A_23_P571        | SEQ ID NO:272                             | SLC2A1    | NM_006516                         | up                                 |
| A_23_P57983      | SEQ ID NO:273                             | PARP14    | AB033094                          | down                               |
| A_23_P58390      | SEQ ID NO:274                             | C4ORF32   | NM_152400                         | down                               |
| A_23_P59005      | SEQ ID NO:113                             | TAP1      | NM_000593                         | down                               |
| A_23_P62890      | SEQ ID NO:74                              | GBP1      | NM_002053                         | down                               |
| A_23_P63390      | SEQ ID NO:73                              | FCGR1B    | NM_001017986                      | down                               |
| A_23_P63896      | SEQ ID NO:92                              | FAS       | NM_000043                         | down                               |
| A_23_P64343      | SEQ ID NO:275                             | TIMM10    | NM_012456                         | down                               |
| A_23_P64721      | SEQ ID NO:276                             | GPR109B   | NM_006018                         | down                               |
| A_23_P65427      | SEQ ID NO:277                             | PSME2     | NM_002818                         | down                               |
| A_23_P65651      | SEQ ID NO:278                             | WARS      | NM_004184                         | down                               |
| A_23_P68155      | SEQ ID NO:279                             | IFIH1     | NM_022168                         | down                               |
| A_23_P68851      | SEQ ID NO:280                             | KREMEN1   | NM_001039570                      | down                               |
| A_23_P69109      | SEQ ID NO:281                             | PLSCR1    | NM_021105                         | down                               |
| A_23_P69310      | SEQ ID NO:282                             | CCRL2     | NM_003965                         | down                               |
| A_23_P69383      | SEQ ID NO:101                             | PARP9     | NM_031458                         | down                               |
| A_23_P72737      | SEQ ID NO:283                             | IFITM1    | NM_003641                         | down                               |
| A_23_P74001      | SEQ ID NO:284                             | S100A12   | NM_005621                         | down                               |
| A_23_P74290      | SEQ ID NO:79                              | GBP5      | NM_052942                         | down                               |
| A_23_P75430      | SEQ ID NO:285                             | C11ORF75  | NM_020179                         | down                               |
| A_23_P75741      | SEQ ID NO:286                             | UBE2L6    | NM_198183                         | down                               |
| A_23_P7827       | SEQ ID NO:83                              | FAM26F    | NM_001010919                      | down                               |
| A_23_P79518      | SEQ ID NO:287                             | IL1B      | NM_000576                         | down                               |
| A_23_P81898      | SEQ ID NO:288                             | UBD       | NM_006398                         | down                               |
| A_23_P83098      | SEQ ID NO:289                             | ALDH1A1   | NM_000689                         | down                               |
| A_23_P8513       | SEQ ID NO:290                             | SNX10     | NM_013322                         | down                               |
| A_23_P85693      | SEQ ID NO:90                              | GBP2      | NM_004120                         | down                               |
| A_23_P85783      | SEQ ID NO:291                             | PHGDH     | NM_006623                         | up                                 |
| A_23_P86390      | SEQ ID NO:292                             | NRP1      | NM_003873                         | up                                 |
| A_23_P87709      | SEQ ID NO:293                             | FLJ22662  | NM_024829                         | down                               |
| A_23_P9232       | SEQ ID NO:294                             | GCNT1     | NM_001490                         | down                               |
| A_23_P94412      | SEQ ID NO:295                             | PDCD1LG2  | NM_025239                         | down                               |
| A_23_P96556      | SEQ ID NO:94                              | GK        | NM_203391                         | down                               |
| A_23_P97064      | SEQ ID NO:296                             | FBXO6     | NM_018438                         | down                               |
| A_24_P100387     | SEQ ID NO:85                              | GK        | NM_203391                         | down                               |
| A_24_P124032     | SEQ ID NO:297                             | RIPK2     | NM_003821                         | down                               |
| A_24_P156490     | SEQ ID NO:133                             | KCNMA1    | NM_002247                         | down                               |
| A_24_P15702      | SEQ ID NO:298                             | LOC389386 | XR_017251                         | down                               |
| A_24_P161018     | SEQ ID NO:299                             | PARP14    | NM_017554                         | down                               |
| A_24_P165864     | SEQ ID NO:300                             | P2RY14    | NM_014879                         | down                               |
| A_24_P167642     | SEQ ID NO:301                             | GCH1      | NM_000161                         | down                               |
| A_24_P172481     | SEQ ID NO:302                             | TRIM22    | NM_006074                         | down                               |
| A_24_P184445     | SEQ ID NO:303                             | MMP19     | NM_002429                         | up                                 |
| A_24_P212481     | SEQ ID NO:304                             | MCTP1     | NM_024717                         | down                               |
| A_24_P222655     | SEQ ID NO:305                             | C1QA      | NM_015991                         | down                               |
| A_24_P243749     | SEQ ID NO:82                              | PKD4      | NM_002612                         | down                               |
| A_24_P245815     | SEQ ID NO:306                             | ASPHD2    | NM_020437                         | down                               |
| A_24_P250922     | SEQ ID NO:307                             | PTGS2     | NM_000963                         | down                               |
| A_24_P251764     | SEQ ID NO:308                             | CXCL3     | NM_002090                         | up                                 |
| A_24_P270460     | SEQ ID NO:309                             | IFI27     | NM_005532                         | up                                 |
| A_24_P274270     | SEQ ID NO:88                              | STAT1     | NM_139266                         | down                               |
| A_24_P278126     | SEQ ID NO:310                             | NBN       | NM_002485                         | down                               |
| A_24_P303091     | SEQ ID NO:311                             | CXCL10    | NM_001565                         | down                               |
| A_24_P304154     | SEQ ID NO:312                             | AMPD3     | NM_001025390                      | down                               |
| A_24_P322353     | SEQ ID NO:91                              | PSTPIP2   | NM_024430                         | down                               |
| A_24_P323148     | SEQ ID NO:313                             | LYPD5     | NM_182573                         | down                               |

| Probe Identifier | Sequence Listing Number of Probe Sequence | Symbol       | Accession No. of Sequence of cDNA | Direction of modulation by AMG 811 |
|------------------|-------------------------------------------|--------------|-----------------------------------|------------------------------------|
| A_24_P334361     | SEQ ID NO:314                             | DDX60        | NM_017631                         | down                               |
| A_24_P350686     | SEQ ID NO:106                             | TIFA         | NM_052864                         | down                               |
| A_24_P36898      | SEQ ID NO:86                              | A_24_P36898  | AL832451                          | down                               |
| A_24_P370702     | SEQ ID NO:126                             | GBP3         | NM_018284                         | down                               |
| A_24_P372625     | SEQ ID NO:315                             | RNF141       | NM_016422                         | down                               |
| A_24_P382319     | SEQ ID NO:316                             | CEACAM1      | NM_001712                         | down                               |
| A_24_P383523     | SEQ ID NO:317                             | SAMD4A       | NM_015589                         | down                               |
| A_24_P393353     | SEQ ID NO:318                             | XRN1         | NM_001042604                      | down                               |
| A_24_P45446      | SEQ ID NO:108                             | GBP4         | NM_052941                         | down                               |
| A_24_P47329      | SEQ ID NO:319                             | A_24_P47329  | BC063641                          | down                               |
| A_24_P48204      | SEQ ID NO:320                             | SECTM1       | NM_003004                         | down                               |
| A_24_P48898      | SEQ ID NO:321                             | APOL2        | NM_145637                         | down                               |
| A_24_P53051      | SEQ ID NO:128                             | LACTB        | NM_171846                         | down                               |
| A_24_P54863      | SEQ ID NO:142                             | C4ORF32      | NM_152400                         | down                               |
| A_24_P561165     | SEQ ID NO:322                             | A_24_P561165 | A_24_P561165                      | down                               |
| A_24_P659202     | SEQ ID NO:323                             | A_24_P659202 | THC2527772                        | up                                 |
| A_24_P66027      | SEQ ID NO:324                             | APOBEC3B     | NM_004900                         | down                               |
| A_24_P7594       | SEQ ID NO:103                             | APOL6        | NM_030641                         | down                               |
| A_24_P87931      | SEQ ID NO:325                             | APOL1        | NM_145343                         | down                               |
| A_24_P912985     | SEQ ID NO:326                             | A_24_P912985 | A_24_P912985                      | down                               |
| A_24_P928052     | SEQ ID NO:327                             | NRP1         | NM_003873                         | down                               |
| A_24_P935819     | SEQ ID NO:328                             | SOD2         | BC016934                          | down                               |
| A_24_P935986     | SEQ ID NO:329                             | BCAT1        | NM_005504                         | down                               |
| A_24_P941167     | SEQ ID NO:330                             | APOL6        | NM_030641                         | down                               |
| A_24_P941912     | SEQ ID NO:331                             | DTX3L        | NM_138287                         | down                               |
| A_24_P943205     | SEQ ID NO:332                             | EPSTH1       | AL831953                          | down                               |
| A_24_P97342      | SEQ ID NO:333                             | PROK2        | NM_021935                         | down                               |
| A_24_P98109      | SEQ ID NO:334                             | SNX10        | NM_013322                         | down                               |
| A_24_P98210      | SEQ ID NO:335                             | TFEC         | NM_012252                         | down                               |
| A_32_P107372     | SEQ ID NO:76                              | GBP1         | NM_002053                         | down                               |
| A_32_P15169      | SEQ ID NO:336                             | A_32_P15169  | A_32_P15169                       | down                               |
| A_32_P156746     | SEQ ID NO:337                             | A_32_P156746 | BE825944                          | down                               |
| A_32_P162183     | SEQ ID NO:338                             | C2           | NM_000063                         | down                               |
| A_32_P166272     | SEQ ID NO:96                              | STX11        | NM_003764                         | down                               |
| A_32_P184394     | SEQ ID NO:339                             | TFEC         | NM_012252                         | down                               |
| A_32_P191417     | SEQ ID NO:340                             | A_32_P191417 | AW276186                          | down                               |
| A_32_P222250     | SEQ ID NO:341                             | A_32_P222250 | AF119908                          | down                               |
| A_32_P30004      | SEQ ID NO:342                             | A_32_P30004  | AF086044                          | down                               |
| A_32_P399546     | SEQ ID NO:343                             | ARNTL2       | AF256215                          | down                               |
| A_32_P44394      | SEQ ID NO:87                              | AIM2         | NM_004833                         | down                               |
| A_32_P56759      | SEQ ID NO:344                             | PARP14       | NM_017554                         | down                               |
| A_32_P91773      | SEQ ID NO:345                             | A_32_P91773  | THC2544236                        | down                               |
| A_32_P92415      | SEQ ID NO:346                             | A_32_P92415  | AA455656                          | down                               |
| A_32_P95082      | SEQ ID NO:347                             | CNTLN        | NM_017738                         | down                               |
| A_32_P9543       | SEQ ID NO:348                             | APOBEC3A     | NM_145699                         | down                               |

Assaying for levels of expression of one or more of the genes in Tables 1, 2, 4, 5, and/or 6 in a biological sample from a diseased patient, optionally an SLE patient, before treatment with an IFN- $\gamma$  inhibitor, such as AMG 811, and comparison to levels of expression in a control biological sample can indicate which patients might benefit from treatment with an IFN- $\gamma$  inhibitor. Patients expressing elevated levels of an RNA or protein that is downregulated *in vivo* by AMG 811 or decreased levels of an RNA or protein that is upregulated by AMG 811 *in vivo* might benefit from treatment with an IFN- $\gamma$  inhibitor. Similarly, patients expressing elevated or lowered levels of an RNA or protein that is up- or down-regulated by IFN- $\gamma$  could also benefit from treatment with an IFN- $\gamma$  inhibitor. Further, comparison of expression levels of one or more of the genes listed in Tables 1, 2, 4,

5, and/or 6 before and after treatment with an IFN- $\gamma$  inhibitor can indicate whether the IFN- $\gamma$  inhibitor is having a biological effect in a particular patient *in vivo*. If so, continuing treatment can be advantageous for that patient. If not, treatment can be discontinued, or the IFN- $\gamma$  inhibitor can be administered at a higher dose or at a greater frequency.

5 In Figure 11, levels of GBP1 transcript versus AMG 811 concentration in serum on days 1 and 15 of the study in lupus nephritis patients are plotted. Comparing Figure 11 to the right panel of Figure 3, which contains similar data from SLE patients, a number of conclusions can be made. First, lupus nephritis patients as a group have higher levels of GBP1 expression at baseline than SLE patients as a group. Further, whereas all SLE patients exhibited a decrease in GBP1 expression upon administration of AMG 811, this was not true for lupus nephritis patients. Also, the magnitude of the decreases observed among general SLE patients was apparently greater than the decreases observed among lupus nephritis patients. Hence, these data indicate that SLE and lupus nephritis patients, as groups, have different responses to AMG 811. These differences may be related to differences in the nature and severity of disease activity in these two groups and may indicate that dosing requirements can differ between these two categories of patients. These data also suggest that expression of biomarkers such as GBP1 could inform dose selection. For example, patients having, for example, higher GBP1 expression could require higher doses of AMG 811, whereas patients with lower GBP1 expression could require lower doses of AMG 811.

Clinical parameters related to kidney function were assessed for patients in cohorts 4 and 5 in this trial. Spot urine protein, spot urine creatinine, 24 hour urine protein, 24 hour urine creatinine, serum creatinine, serum albumin, antibodies against double stranded DNA, and complement factors C3 and C4 were assessed.

Urine protein amounts were determined by a dye-binding assay (pyrocatechol violet-ammonium molybdate dye) analyzed in a "dry slide" format using an automated laboratory analyzer. Samples used were either a collection of all the patient's urine over a 24 hour period (24 hour urine protein) or a single urine sample (spot urine protein). Urine creatinine was assessed by a multi-step coupled enzymatic two-point rate colorimetric assay (creatinine amidohydrolase/creatinine amidohydrolase/sarcosine oxidase/peroxidase) analyzed using a "dry slide" format in an automated laboratory analyzer.

Cohorts 4 and 5 comprised lupus nephritis patients receiving doses of 20 mg or 60 mg AMG 811, respectively, or placebo. Although some results from these cohorts are now available, the results are still blinded. Since only two of eight (cohort 4) and three of twelve (cohort 5) patients received placebo, differences in clinical parameters between cohorts 4 and 5 might indicate dose-dependent responses to AMG 811. Among the various measurements made, the following tests indicated no clear difference between cohorts 4 and 5: spot urine creatinine, 24 hour urine creatinine, serum creatinine, serum albumin, complement factors C3 and C4, and anti-double stranded DNA antibodies. On the other hand, urine protein in a 24 hour urine collection and the ratio of urine protein to urine creatinine (UPCR) clearly differed between cohorts 4 and 5, as shown in Figures 12 and 13. High amounts of urine protein and/or high UPCR indicate impairment of kidney function. Since all but two of the patients in cohort 4 and two or three in cohort 5 received AMG 811, these data suggest that AMG 811 may have a dose-dependent effect on kidney function in lupus nephritis patients. More specifically, these results

suggest that a dose of more than 20 mg of AMG 811 is necessary to have a positive effect on kidney function in lupus nephritis patients.

**Example 5: Single dose trial in discoid lupus**

A phase 1b single dose crossover study in discoid lupus has been enrolled. Sixteen subjects (of twenty  
5 planned subjects) with discoid lupus were dosed with a single dose of 180 milligrams of AMG 811 and a single dose of placebo, each administered subcutaneously, in one of two sequences. Per study protocol, twelve patients were to receive 180 mg SC of AMG 811 on day 1 and a dose of placebo on day 85, and eight patients were to receive a dose of placebo on day 1 and 180 mg SC of AMG 811 on day 85. However, enrollment of the study was stopped after sixteen patients had been enrolled. As primary endpoints of the study, treatment-  
10 emergent adverse events, vital signs, clinical laboratory tests, ECGs, and the incidence of binding and neutralizing antibodies to AMG 811 were monitored. Physical examinations were also to be performed.

In secondary endpoints of the study, the pharmacokinetic profile of AMG 811 is determined, and CLASI scores are determined. Expression of biomarkers in peripheral blood at the RNA level are assessed by hybridization to a DNA array as described above in samples taken at baseline (in the time period from three days  
15 prior to dosing to one day prior to dosing) and on days 15, 29, 57, 85, 99, 113, 141, 169, and 197 (which is the end of study). Analysis of selected biomarkers at the protein level by ELISA may also be performed. In addition, skin samples were taken at baseline and on days 15 and 57 for analysis of biomarker expression at the RNA level by hybridization to a DNA array. Selected biomarkers may also be assayed at the protein level in the skin samples using immunohistochemistry, immunofluorescence, or ELISA. Information available to date indicates  
20 that clinical parameters, such as improvements in the CLASI score, did not correlate clearly with dosing of AMG 811. The results of this trial are still blinded.

**Example 6: Single dose trial in psoriasis**

A phase 1b single dose, double-blind, placebo-controlled study in psoriasis is in progress. Nine subjects with moderate to severe plaque psoriasis (having a PASI score  $\geq 10$  and an affected body surface  
25 area  $\geq 10$ ) were enrolled in the study. The study is still blinded. Proceeding with a study plan that originally included ten, not nine, patients, seven or eight patients will receive drug, and one or two patients will receive placebo. Those that receive drug will receive (or have received) a single dose of 180 milligrams of AMG 811 on study day 1. As primary endpoints of the study, treatment-emergent adverse events, vital signs, clinical laboratory tests, ECGs, and the incidence of binding and neutralizing antibodies to AMG 811 were monitored.  
30 Physical examinations were also performed.

As secondary endpoints, clinicians assessed PASI scores, PGA scores, and target lesions. Photos were taken to document skin lesions. The pharmacokinetic profile of AMG 811 will also be determined. All of these primary and secondary endpoints were assessed at baseline (from three days to one day before dosing) and on days 15, 29, 43, 57, 85, and 113 (which is the end of study). Skin biopsies were taken at baseline and at  
35 baseline and on days 15 and 57 for analysis of biomarker expression at the RNA level as described above. In addition selected biomarkers may be assessed for expression at the protein level by ELISA for serum samples or by immunohistochemistry or immunofluorescence for skin biopsies.

In Figure 14, blinded data showing PASI scores for the nine patients in this trial are displayed. Given the design of the trial, one or two of these patients received placebo, and seven or eight received AMG 811. All but one of these eight patients experienced a decrease, *i.e.*, an improvement, in PASI score at some or all post-dose time points, a result indicating that most patients receiving AMG 811 experienced at least a temporary clinical benefit. However, since the data is blinded and one or two of these patients received placebo, the effects of AMG 811 on PASI scores will be more clear when the data is unblinded.

What is claimed is:

1. Use of a monoclonal anti-human interferon gamma (anti-huIFN- $\gamma$ ) antibody in the manufacture of a medicament for treating a patient suffering from an IFN- $\gamma$ -mediated disease,

wherein the IFN- $\gamma$ -mediated disease is selected from the group consisting of systemic lupus erythematosus (SLE), lupus nephritis, inflammatory bowel disease, Crohn's disease and ulcerative colitis; and

wherein the anti-huIFN- $\gamma$  antibody has a heavy chain complementarity determining region 1 (CDR1) comprising the amino acid sequence of SEQ ID NO:34, a heavy chain complementarity determining region 2 (CDR2) comprising the amino acid sequence of SEQ ID NO:35, a heavy chain complementarity determining region 3 (CDR3) comprising the amino acid sequence of SEQ ID NO:36, a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:38, a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:41, and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:43

wherein the monoclonal anti-human interferon gamma (anti-huIFN- $\gamma$ ) antibody is to be administered to the patient at a dose of at least about 20 milligrams to not more than about 200 milligrams.

2. The use of claim 1, wherein the heavy chain variable region and the light chain variable region comprise, respectively, SEQ ID NO:6 and SEQ ID NO:8.

3. Use of an anti-huIFN- $\gamma$  antibody in the manufacture of a medicament for treating an SLE patient,

wherein the anti-huIFN- $\gamma$  antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8 and wherein the monoclonal anti-huIFN- $\gamma$  antibody is to be administered to the patient at a dose of at least about 60 milligrams to not more than about 180 milligrams.

4. The use of any one of claims 1 to 3, wherein expression at the RNA or protein level of one or more gene(s) listed in Table 1 in a biological sample taken from the patient before use of the medicament deviates from expression of that gene(s) in a control biological sample in a direction consistent with excess IFN- $\gamma$ .

5. The use of any one of claims 1 to 2, wherein the dose is from about 40 milligrams to about 200 milligrams of the monoclonal anti-huIFN- $\gamma$  antibody.

6. The use of any one of claims 1 to 2, wherein the dose is from about 20 milligrams to about 180 milligrams of the monoclonal anti-huIFN- $\gamma$  antibody.

7. The use of any one of claims 1 to 2, wherein the dose is from about 60 milligrams to about 180 milligrams of the monoclonal anti-huIFN- $\gamma$  antibody.

8. The use of any one of claims 1 to 4, wherein the dose is from about 60 milligrams to about 150 milligrams of the monoclonal anti-huIFN- $\gamma$  antibody.

9. The use of any one of claims 1 to 4, wherein the dose is from about 100 milligrams to about 180 milligrams of the monoclonal anti-huIFN- $\gamma$  antibody.

10. The use of any one of claims 1 to 9, wherein the patient concurrently uses a glucocorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial.

11. The use of claim 4, wherein the biological sample from the patient exhibits elevated expression at the RNA or protein level as compared to expression in the control biological sample of one or more of the following genes: indoleamine 2,3-dioxygenase 1 (IDO1); ankyrin repeat domain 22 (ANKRD22); chemokine (C-X-C motif) ligand 9 (CXCL9); purinergic receptor P2Y, G-protein coupled, 14 (P2RY14); guanylate binding protein 5 (GBP5); serpin peptidase inhibitor, clade G, member 1 (SERPING1); guanylate binding protein 1, interferon-inducible, 67 kDa (GBP1); chemokine (C-X-C motif) ligand 10 (CXCL10); ets variant 7 (ETV7); basic leucine zipper transcription factor, ATF-like 2 (BATF2); Fc fragment of IgG, high affinity Ib, receptor (FCGR1B or CD64); pyruvate dehydrogenase kinase, isozyme 4 (nuclear gene encoding mitochondrial protein; PDK4); and/or CD274.

12. The use of claim 11, wherein the biological sample from the patient exhibits elevated expression at the RNA or protein level of GBP1 as compared to expression in the control biological sample.

13. The use of any one of claims 1 to 12, wherein the anti-huIFN- $\gamma$  antibody is a human IgG1 antibody.