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-γ is likely to be helpful from those for whom it is not. Further, the optimal dosage and nature of a particular IFN-γ inhibitor are likely to be important factors in the therapeutic suitability of a treatment, given the important role of IFN-γ 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-γ, 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-γ) antibody in the manufacture of a medicament for treating a patient suffering from an IFN-γ-mediated disease, wherein the IFN-γ-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-γ 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-γ) 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-γ antibody in the manufacture of a medicament for treating an SLE patient, wherein the anti-huIFN-γ antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8 and wherein the monoclonal anti-huIFN-γ 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 dDescribed herein are methods of treatment that include administration of an IFN-γ 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-γ inhibitor so as to assess the suitability as a treatment or the biological effects of the IFN-γ inhibitor. Such methods can inform decisions as to whether to initiate or continue treatment with an IFN-γ inhibitor. Also described are methods for distinguishing patients likely to benefit from treatment with an IFN-γ 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-γ 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-γ-mediated disease comprising administering to the patient a monoclonal anti-human interferon gamma (anti-huIFN-γ) antibody at a dose, which 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-γ. In addition, described herein is a use of a monoclonal anti-huIFN-γ antibody as a medicament to treat a patient suffering from an IFN-γ-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-γ. In some ~~embodiments~~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-γ. 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-γ: 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 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 metallopeptidase 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 ~~embodiments~~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-γ-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-hulFN-γ 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-hulFN-γ antibody can be administered subcutaneously or intravenously. A gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another ~~aspect~~example, described herein is a method for treating a patient having an IFN-γ-mediated disease, for example SLE or an inflammatory bowel disease, with an IFN-γ 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-γ, administering to the patient a therapeutically effective dose of an IFN-γ inhibitor. In addition, described herein is a use of an IFN-γ inhibitor as a medicament to treat a patient having an IFN-γ-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-γ, a therapeutically effective

dose of the IFN-γ 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-γ inhibitor can be a human or humanized anti-huIFN-γ antibody. The dose of the anti-huIFN-γ 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-γ: 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 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 metallopeptidase 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. The IFN-γ inhibitor can be an anti-huIFN-γ 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 gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another ~~aspect~~example, described herein is method for identifying a patient having an IFN-γ-mediated disease who can benefit from treatment with an IFN-γ 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-γ, determining that the patient can benefit from treatment with an IFN-γ inhibitor and/or administering a therapeutically effective dose of an IFN-γ inhibitor. The one or more genes listed in

with another pharmacodynamically effective dose of the IFN-γ 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-γ inhibitor antibody, for example an anti-huIFN-γ antibody, as a medicament for treating a patient suffering from an IFN-γ-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-γ 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-γ, then continuing treatment of the patient with another pharmacodynamically effective dose of the IFN-γ inhibitor. For an IFN-γ inhibitor that is an anti-huIFN-γ 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-γ-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 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 metallopeptidase 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 another ~~aspect~~example, a method is described for treating a patient suffering from an IFN-γ-mediated disease, for example SLE, lupus nephritis, discoid lupus, psoriasis, or an inflammatory bowel disease, with an IFN-γ inhibitor, for example an anti-huIFN-γ 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-γ 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-γ, then treatment with the IFN-γ inhibitor can be discontinued. In another ~~aspect~~example, described herein is a use of an IFN-γ inhibitor, for example an anti-huIFN-γ antibody, as a medicament for treating a patient suffering from an IFN-γ-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 can be determined; (b) thereafter a pharmacodynamically effective dose of the IFN-γ 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 sample of (a) in a direction that is consistent with an excess of IFN-γ, then the treatment with the IFN-γ 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-γ inhibitor is an anti-huIFN-γ 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 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 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 metallopeptidase 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. A gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

Any of the methods or uses described above or below that utilize an anti-huIFN-γ antibody can utilize an anti-huIFN-γ 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 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 ~~embodiment~~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 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 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 variable region can comprise the amino acid sequence of SEQ ID NO:31. The anti-huIFN-γ antibody can be a human, humanized, or chimeric antibody of the IgG, IgM, IgE, IgD, or IgA isotype. The anti-huIFN-γ antibody can be an IgG1, IgG2, IgG3, or IgG4 antibody.

In another ~~aspect~~example, herein is described a method for treating a patient suffering from an IFN-γ-mediated disease comprising administering to the patient a dose of an anti-IFN-γ antibody such that the concentration of total IFN-γ 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-γ antibody. The plateau concentration can be maintained for at least about 3, 4, 5, 6, or 8 weeks after the antibody is administered. The plateau concentration of IFN-γ 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-γ 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-γ 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-γ 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 mg and can be administered subcutaneously or intravenously. The level of IFN-γ 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-γ-mediated disease can be psoriasis, SLE, lupus nephritis, discoid lupus, or an inflammatory bowel disease such as Crohn's disease or ulcerative colitis. A gluococorticoid 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-γ inhibitor comprising the following steps: obtaining a biological sample from the patient; determining the levels of IFN-γ protein in the biological sample; and comparing the levels of IFN-γ protein in the biological sample from the patient with the levels determined in a control biological sample; wherein if the levels of total IFN-γ 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-γ inhibitor; and wherein if the levels of IFN-γ 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-γ inhibitor. The levels of IFN-γ protein determined can be the levels of total IFN-γ protein, meaning the total of free and bound IFN-γ protein . The IFN-γ inhibitor can be an anti-IFN-γ antibody. The anti-IFN-γ 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-γ 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 gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another ~~embodiment~~example, herein is described a method for treating an IFN-γ–mediated disease comprising administering a dose of an IFN-γ inhibitor such that the concentration of total IFN-γ 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-γ protein in serum can be from about 200 to about 2000 picograms per milliliter (pg/mL). The plateau concentration of total IFN-γ 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-γ inhibitor can be a protein that binds to IFN-γ, for example, an anti-IFN-γ antibody. The anti-IFN-γ 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-γ 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-γ inhibitor can be administered at a frequency that maintains a serum concentration of total IFN-γ that is at least half of the plateau concentration. A gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In still another ~~aspect~~example, herein is described a method of determining a suitable dose of an IFN-γ inhibitor for a patient comprising: determining the total IFN-γ protein concentration in a biological sample from the patient before dosing; administering the IFN-γ inhibitor to the patient at a first dosage amount; and determining the total IFN-γ 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 IFN-γ 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-γ 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-γ 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-γ protein has fallen below the plateau level, a second, lower dosage amount of the IFN-γ inhibitor can be administered and total IFN-γ 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-γ inhibitor can be subsequently administered and total IFN-γ 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-γ inhibitor can be a protein that binds to IFN-γ, for example an anti-IFN-γ antibody, which can be an anti-huIFN-γ antibody. Such an anti-IFN-γ 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. Such an anti-IFN-γ 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-γ antibody can be a human or humanized antibody. A gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another ~~aspect~~example, herein is described a method of treating a patient suffering from an IFN-γ-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-γ pathway activation; and administering to the patient a monoclonal human anti-human interferon

gamma (anti-huIFN-γ) 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-γ-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-γ 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 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 gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another ~~embodiment~~example, herein is described a method for treating a patient having an IFN-γ-mediated disease with a human anti-huIFN-γ 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-γ 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-γ-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-γ 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 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), 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. 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 about150, 180, 200, or 250 mg. A gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In a further ~~aspect~~example, herein is described a method for treating a patient suffering from an IFN-γ-mediated disease comprising: (a) taking a biological sample from the patient before administering a human anti-hulFN-γ 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-hulFN-γ 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-γ, then continuing treatment of the patient with another pharmacodynamically effective dose of the antibody. The IFN-γ-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 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), 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. A gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In still a further ~~aspect~~example, ~~provided~~ described is method for treating a patient suffering from an IFN-γ-mediated disease with a human anti-huIFN-γ antibody comprising the following steps: (a) taking a biological sample from the patient before administering a human anti-huIFN-γ 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-γ 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-γ 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-γ, then treatment with the anti-human IFN-γ antibody is discontinued. The anti-human IFN-γ 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-γ-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 gluococorticoid and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In still a further ~~aspect~~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-γ antibody, wherein the anti-human IFN-γ 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-γ 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-γ. The dose of the anti-IFN-γ 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-γ 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 gluococorticoid, optionally prednisone, and/or mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial can be administered concurrently with the antibody.

In another ~~embodiment~~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-γ 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-γ 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-γ protein in the second biological sample is determined; and (d) if the level of total IFN-γ 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 ~~aspect~~example, ~~provided~~ described herein is a method for treating an IFN-γ–mediated disease comprising administering to a patient in need thereof a dose of a human anti-human IFN-γ antibody comprising the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8 such that the concentration of total IFN-γ 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-γ 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-γ 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-γ 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 25th and 75th 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-γ 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

What is claimed is:

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

wherein the IFN-γ-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-γ 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-γ) 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-γ antibody in the manufacture of a medicament for treating an SLE patient,

wherein the anti-huIFN-γ antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8 and wherein the monoclonal anti-huIFN-γ 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-γ.

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-γ 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-γ 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-γ 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-γ 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-γ 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 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-γ antibody is a human IgG1 antibody.

What is claimed is:

1. Use of a pharmaceutical composition comprising from about 15 milligrams to about 200 milligrams of a monoclonal anti-human interferon gamma (anti-huIFN-γ) antibody in the manufacture of a medicament for treating a patient suffering from an IFN-γ-mediated disease,

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

wherein the anti-huIFN-γ 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 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.

2. The use of claim 1, wherein the heavy chain CDR3 comprises 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.

3. The use of claim 3, wherein the heavy chain variable region and the light chain variable region comprise, respectively, SEQ ID NO:6 and SEQ ID NO:8, SEQ ID NO:10 and SEQ ID NO:12, SEQ ID NO:14 and SEQ ID NO:16, SEQ ID NO:30 and SEQ ID NO:12, or SEQ ID NO:14 and SEQ ID NO:31.

4. Use of a pharmaceutical composition comprising at least about 60 milligrams and not more than about 180 milligrams of an anti-huIFN-γ antibody in the manufacture of a medicament for treating an SLE patient,

wherein the anti-huIFN-γ antibody comprises the amino acid sequences of SEQ ID NO:6 and SEQ ID NO:8.

5. The use of any one of claims 1 to 4, wherein expression at the RNA or protein level of one or more gene(s) listed in Table(s) 2, 4, 5, and/or 6 in a biological sample taken from the patient before use of the pharmaceutical composition deviates from expression of that gene(s) in a control biological sample in a direction consistent with excess IFN-γ pathway activation.

6. The use of any one of claims 1 to 5, wherein the pharmaceutical composition comprises from about 40 milligrams to about 200 milligrams, from about 60 milligrams to about 150 milligrams, or from about 100 milligrams to about 180 milligrams of the monoclonal anti-huIFN-γ antibody.

7. The use of any one of claims 1 to 6, wherein the patient concurrently uses a glucocorticoid, mycophenolate mofetil, azathioprine, leflunomide, methotrexate, or an anti-malarial.

8. The use of claim 5, 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); family with sequence similarity 26, member F (FAM26F); purinergic receptor P2Y, G-protein coupled, 14 (P2RY14); guanylate binding 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); 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.

9. The use of claim 8, 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.

10. The use of any one of claims 1 to 9, wherein the anti-huIFN-γ antibody is a human IgG1 antibody.