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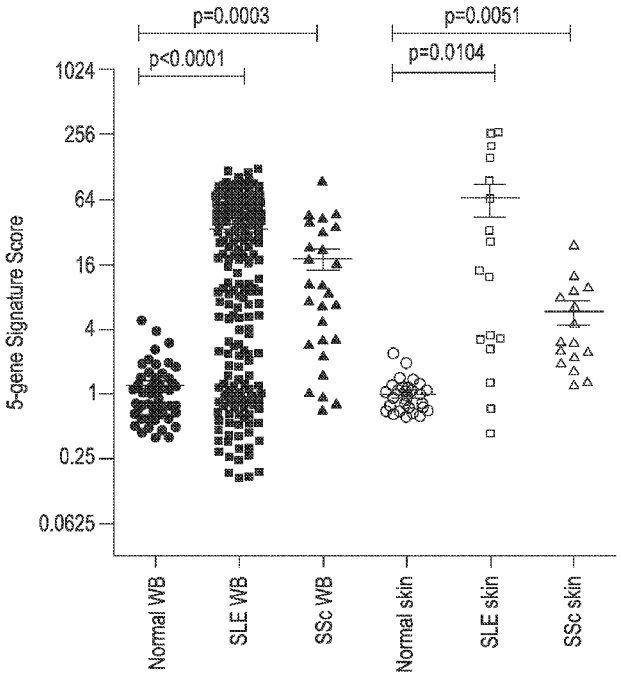
(54) Title: FIXED DOSAGE REGIMENS FOR ANTI-TYPE I INTERFERON RECEPTOR (IFNAR) ANTIBODIES

FIG. 1



(57) Abstract: The disclosure provides methods for treating a subject having a type I IFN-mediated disease or disorder comprising administration of a fixed dose of an anti-interferon alpha receptor antibody. The disclosure also provides methods for suppressing a type I interferon (IFN) gene signature (GS) in a subject. In addition, the disclosure provides methods of prognosing or monitoring disease progression in a subject having a type I IFN-mediated disease or disorder, methods of predicting a dosage regimen, methods of identifying a candidate therapeutic agent, methods of identifying a patient as a candidate for a therapeutic agent, and methods of designing a personalized therapy.

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FIXED DOSAGE REGIMENS FOR ANTI-TYPE I INTERFERON RECEPTOR (IFNAR) ANTIBODIES

BACKGROUND OF THE DISCLOSURE

FIELD OF THE DISCLOSURE

[0001] The present disclosure provides methods for the treatment of autoimmune diseases such as systemic lupus erythematosus, scleroderma, lupus nephritis, and myositis with fixed doses of anti-interferon receptor antibodies.

BACKGROUND ART

[0002] Type I interferons (IFNs) are a family of cytokines including 14 IFN-α subtypes, IFN-β, -ω, and –κ, all of which are involved in antiviral or antitumor function. A potential role for type I IFNs in the disease pathogenesis of several autoimmune disorders including systemic sclerosis (SSc, scleroderma), systemic lupus erythematous (SLE), primary Sjögren's, rheumatoid arthritis, as well as myositis.

[0003] SLE is a chronic rheumatic disease characterized by autoreactive antibodies targeting a variety of self-antigens resulting in inflammation, tissue and organ damage. The role of type I IFNs has been implicated in the development of SLE. SSc is a rheumatic disease of the connective tissue, affecting multiple systems including skin, muscle, and internal organs. Like SLE, increased type I IFN activity plays a role in the pathogenesis of SSc, as confirmed by the over-expression of type I IFN-inducible genes and the enrichment of plasmacytoid dendritic cells in skin and/or blood of SSc patients (Fleming et al., PLoS One 3:e1452 (2008); Coelho et al., Arch. Dermatol. Res. 299:259-262 (2007); Tan et al., Rheumatology (Oxford) 45:694-702 (2006); Duan et al., Arthritis Rheum. 58:1465-1474 (2008)). These observations along with other data including animal model studies have suggested type I IFN signaling as a viable therapeutic target in both SLE and SSc (Tan et al., Rheumatology (Oxford) 45:694-702 (2006); 28. Crow, Rheum. Dis. Clin. North Am. 36:173-186 (2010); York et al., Arthritis Rheum. 56:1010-1020 (2007)).

[0004] Type I IFNs in serum or plasma are not easily measured. On the other hand, type I IFN inducible genes can be conveniently measured improved sensitivity and specificity (Bengtsson et al., Lupus 9:664-671 (2000); Dall'era et al., Ann. Rheum. Dis. 64:1692-1697 (2005); Kirou et al., Arthritis Rheum. 50:3958-3967 (2004)). Several well defined type I IFN

signatures have been used to correlate type I IFN activity with SLE or SSc disease pathogenesis (Eloranta et al., Ann. Rheum. Dis. 69:1396-1402 (2010)), disease activity (Bilgic et al., Arthritis Rheum. 60:3436-3446 (2009)), as well as assessing the drug-target interaction (*i.e.*, pharmacodynamics, PD) of an anti-IFN-α therapy in SLE (Yao et al., Arthritis Rheum. 60:1785-1796 (2009); Yao et al., Hum. Genomics Proteomics 2009:374312 (2009); Yao et al., Arthritis Res. Ther. 12 (Suppl 1):S6 (2010)). The development of a type I IFN signature to identify subpopulations showing both activation and concordance of the type I IFN pathway between the peripheral blood and disease-affected tissues in both SLE and SSc (Higgs et al., Ann. Rheum. Dis. 70:2029-2036 (2011)) has demonstrated the potential utility of using a type I IFN signature as a PD marker in both diseases.

[0005] The clinical development of a new drug is a lengthy and costly process with low odds of success, and contrary to common impression, the clinical development of biotherapeutics, especially monoclonal antibodies, is not quicker or cheaper than small molecule drugs (DiMasi *et al.*, Clin. Pharmacol. Ther. 87:272-277 (2010)). The early clinical development of biotherapeutics, in particular Phase 1 is much lengthier than for small molecules. Absent definitive efficacy signal from early phase studies in patients, a sensitive, disease-relevant and robust biomarker can greatly aid the interpretation of clinical results.

[0006] Type I IFN-mediated diseases such as SLE present diverse disease manifestations and highly variable disease progression, flares and remissions. Due to this heterogeneity, it is crucial to identify patients with similar pathway activation parameters to designate the most appropriate therapies for the different patient subsets. To expedite the clinical development and improve the odds of success, a relevant, sensitive and robust set of PD markers that can be easily tracked or monitored in patients is of great value for dose finding at the early clinical development stage. Methods of applying this set of PD markers would be highly valuable tools to account for differences in target expression and pathway activation in different diseases, and to facilitate bridging between clinical trials in different indications.

BRIEF SUMMARY OF THE DISCLOSURE

[0007] The present disclosure provides method for treating a subject having a type I IFN-mediated disease or disorder comprising administration of a fixed dose of an anti-interferon alpha receptor antibody. The disclosure also provides methods for suppressing a type I interferon (IFN) gene signature (GS) in a subject. In addition, the disclosure provides

methods of prognosing and monitoring disease progression in a subject having a type I IFN-mediated disease or disorder, methods of predicting a dosage regimen, methods of identifying a candidate therapeutic agent, methods of identifying a patient as a candidate for a therapeutic agent, and methods of designing a personalized therapy. Also disclosed are dosage regimens and personalized therapies selected according to these methods.

[0008] In some aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) measuring a type I Interferon Gene Signature (type I IFN GS) score in a sample taken from a patient having a type I IFN-mediated disease or disorder, relative to a baseline type I IFN GS score; and (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

[0009] In other aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) administering to a patient having a type I IFN- mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) measuring the patient's type I IFN GS score relative to a baseline type I IFN GS score; and (c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0010] In certain aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score; (b) determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, (c) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

[0011] In some aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) submitting a sample taken from the patient for measurement of a type I IFN GS score; (c) determining from the results

of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, (d) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0012] In other aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

[0013] In certain aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) submitting a sample taken from the patient for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and (c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0014] In some aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) measuring a type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder; (b) determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; (c) instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

[0015] In other aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising (a) obtaining a sample from a patient having a type I IFN- mediated disease or disorder, where the patent has received a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) measuring a type I IFN GS score from the sample; (c) determining whether the

patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; (d) instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0016] In certain aspects, the present disclosure provides a method of suppressing an type I IFN GS in a patient comprising (a) measuring the type I IFN GS score in a sample taken from a patient having a type I IFN- mediated disease or disorder, relative to a baseline type I IFN GS score; and (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0017] In some aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) measuring the patient's type I IFN GS score relative to a baseline type I IFN GS score; and (c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0018] In other aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score; (b)determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, (c) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0019] In certain aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) submitting a sample taken from the patient for measurement of a type I IFN GS score; (c) determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS

score; and, (d) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0020] In some aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0021] In other aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) administering to a patient having a type I IFN- mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) submitting a sample taken from the patient for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and (c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0022] In certain aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) measuring a type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder; (b) determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; (c) instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0023] In some aspects, the present disclosure provides a method of suppressing a type I IFN GS in a patient comprising (a) obtaining a sample from a patient having a type I IFN-mediated disease or disorder, where the patent has received a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (b) measuring a type I IFN GS score from the sample; (c) determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; (d) instructing a healthcare provider to

increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0024] In other aspects, the present disclosure provides a method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprising (a) measuring a first type I IFN GS score in a sample taken from a patient having a type I IFN- mediated disease or disorder; (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (c) measuring a second type I IFN GS score in a sample taken from the patient following antibody administration; and (d) comparing the second type I IFN GS score to the first type I IFN GS score; wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

[0025] In certain aspects, the present disclosure provides a method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprising (a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a first type I IFN GS score; (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (c) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a second type I IFN GS score; and (d) comparing the second type I IFN GS score to the first typ I IFN GS score; wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

[0026] In some aspects, the present disclosure provides a method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprising (a) measuring a first type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder; (b) instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; (c) measuring a second type I IFN GS score in a sample taken from the patient following antibody administration; and (d) comparing the second type I IFN GS score

to the first type I IFN GS score; wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

[0027] In other aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise measuring the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier IFN GS score, or both, after the administration of the fixed dose. In some aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise measuring the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of a subsequent fixed dose.

[0028] In certain aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise submitting a sample from the patient for measurement of the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of the fixed dose. In some aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise submitting a sample from the patient for measurement of the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of a subsequent fixed dose.

[0029] In some aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise increasing the amount or frequency of subsequent fixed doses if the patent's type I IFN GS score remains elevated. In other aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patent's type I IFN GS score remains elevated. In yet other aspects, the method of treating a patient having a type I IFN-mediated disease or disorder, and the method of suppressing a type I IFN GS in a patient further comprise increasing the amount or frequency of subsequent fixed doses if the patent's type I IFN GS score remains elevated.

[0030] The present disclosure also provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising administering a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity, wherein the fixed dose is effective to treat the disorder.

[0031] In some aspects, the type I IFN activity is IFN-alpha activity. In some aspects, the type I IFN GS comprises up-regulated expression or activity of at least 4 pharmacodynamic (PD) marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In other aspects, the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2. In some aspects, the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

[0032] In some aspects, the antibody or antigen-binding fragment thereof that modulates type I IFN activity specifically binds to an IFN receptor. In other aspects, the IFN receptor is an IFN alpha receptor. In some aspects, the IFN alpha receptor is IFNAR1. In other aspects, the antibody or antigen binding fragment thereof specifically binds to subunit 1 of IFNAR1. In some aspects, the antibody or antigen-binding fragment thereof is monoclonal. In other aspects, the antibody or antigen-binding fragment thereof comprises an immunoglobulin IgG Fc region. In specific aspects, the antibody is MEDI-546 or an antigen-binding fragment thereof. In some aspects, the antibody or antigen-binding fragment thereof suppresses the type I IFN GS in disease tissue.

[0033] In some aspects, the fixed dose ranges from about 300 mg to about 1000 mg. In other aspects, the fixed dosage is lower than about 300 mg. In other aspects, the fixed dose is about 100 mg. In certain aspects, the fixed dose is selected from the group consisting of about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800, about 900 mg and about 1000 mg.

[0034] In some aspects, the disease tissue is skin. In some aspects, the antibody or antigen-binding fragment thereof suppresses the type I IFN GS in peripheral blood. In other aspects, the suppression is full suppression. In certain aspects, the suppression is partial suppression.

[0035] In some aspects, the antibody or antigen-binding fragment thereof is administered in two or more doses. In some aspects, the therapeutic agent is administered monthly. In

some aspects, the therapeutic agent is administered intravenously, intramuscularly, subcutaneously, or a combination thereof. In some aspects, the disease is an autoimmune disease. In some aspects, the autoimmune disease is systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, or lupus nephritis.

[0036] In some aspects, the antibody or antigen-binding fragment thereof suppresses the type I IFN GS by at least 10%, at least 20%, at least 30% or at least 40% as compared to the type I IFN GS of the subject prior to the administration of the fixed dose of the antibody or antigen-binding fragment thereof. In some aspects, the therapeutic agent suppresses the type I IFN GS by at least 10%, at least 20%, at least 30% or at least 40% as compared to the average type I IFN GS signature in a population.

[0037] The present disclosure also provides a kit for detecting a type I IFN genetic signature (IFN GS) common to two diseases whose pathogeneses are mediated by type I IFN comprising a set of diagnostic assays capable of measuring differentially regulated pharmacodynamic (PD) marker genes in a patient sample, wherein the type I IFN GS is suppressed by the administration of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity. In some aspects, the type I IFN GS comprises up-regulated expression or activity of at least four PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In other aspects, the type I IFN GS comprises up-regulated expression or activity of at least five of the PD marker genes. In some aspects, the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2. In some aspects, the type I IFN GS further comprises up-regulated expression or activity of gene IFI6. In some aspects, the patient sample is blood or a fraction thereof, muscle, skin, or a combination thereof. In other aspects, the diagnostic assays comprise nucleic acid probes which hybridize to mRNA in the patient sample.

[0038] The present disclosure also provides a computer-implemented method for predicting an optimal dosage regimen with an antibody or antigen-binding fragment thereof that modulates type I IFN activity. This method comprises (a) inputting PK/PD data from a second type I IFN-mediated disease or disorder into a computer system comprising a pharmacokinetic-pharmacodynamic (PK/PD) stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PK/PD

data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model; (b) applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder; and, (c) identifying an optimal dosage of the antibody or antigen-binding fragment thereof that modulates type I IFN activity for the second type I IFN-mediated disease or disorder from the output of the adjusted PK/PD stochastic model.

[0039] The present disclosure also provides a computer-implemented method of identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating a type I IFN-mediated disease or disorder. This method comprises (a) inputting PD/PK data from a second type I IFN-mediated disease or disorder into a computer system comprising a PK/PD stochastic model based on PK/PD values corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PD/PK data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model; (b) applying the adjusted PK/PD stochastic model to the inputted data from the second type I IFN-mediated disease or disorder; and, (c) identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating the second type I IFN-mediated disease or disorder from the output of the adjusted PK/PD stochastic model.

[0040] The present disclosure also provides a computer-implemented method of identifying a patient as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity. This method comprises (a) inputting PD/PK data from a second type I IFN-mediated disease or disorder into a computer system comprising a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PD/PK data from the second type I IFN-mediated disease is used to adjust the PK/PD stochastic model; applying the adjusted PK/PD stochastic model to the inputted PD/PK data from the second type I IFN-mediated disease or disorder; and, identifying a patient with the second disease as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity for the second type I IFN-mediated disease from the output of the adjusted PK/PD stochastic model.

[0041] The present disclosure also provides a computer-implemented method of designing a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity. This

method comprises (a) inputting PD/PK data from a second type I IFN-mediated disease or disorder into a computer system comprising a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model; (b) applying the adjusted PK/PD stochastic model to the inputted PD/PK data from the second type I IFN-mediated disease or disorder; and, (c) identifying a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity for the second type I IFN-mediated disease or disorder from the output of the adjusted PK/PD stochastic model.

[0042] In some aspects, the type I IFN activity in the computer-implemented method is IFN-α activity. In some aspects, the first and second type I IFN-mediated disease or disorder in the computer-implemented method share a common type I IFN GS. In some aspects, the type I IFN GS in the computer-implemented method is differentially regulated.

[0043] In some aspects, the type I IFN GS in the computer-implemented method comprises up-regulated expression or activity of at least 4 PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In some aspects, the type I IFN GS in the computer-implemented method comprises up-regulated expression or activity of at least 5 PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In some aspects, the type I IFN GS in the computer-implemented method comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2. In some aspects, the type I IFN GS in the computer-implemented method further comprises up-regulated expression or activity of gene IFI6.

[0044] In some aspects, the antibody or antigen binding fragment thereof in the computer-implemented method specifically binds to an IFN receptor. In other aspects, the IFN receptor in the computer-implemented method is an IFN alpha receptor. In other aspects, the IFN alpha receptor in the computer-implemented method is IFNAR1. In other aspects, the antibody or antigen binding fragment thereof in the computer-implemented method specifically binds to subunit 1 of IFNAR1. In other aspects, the antibody or antigen binding fragment thereof in the computer-implemented method is monoclonal.

[0045] In some aspects, the antibody or antigen binding fragment thereof in the computer-implemented method comprises an immunoglobulin IgG Fc region. In other aspects, the antibody in the computer-implemented method is MEDI-546. In some aspects, the first and the second type I IFN-mediated disease or disorder in the computer-implemented method are autoimmune diseases. In some other aspects, the autoimmune diseases in the computer-implemented method are rheumatic diseases. In some aspects, the rheumatic diseases in the computer-implemented method are selected from the group consisting of systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, and lupus nephritis.

[0046] In some aspects, the first type I IFN-mediated disease or disorder in the computer-implemented method is SSc and the second type I IFN-mediated disease or disorder is SLE. In some aspects, the first type I IFN-mediated disease or disorder in the computer-implemented method is SSc and the second type I IFN-mediated disease or disorder is myositis. In some aspects, the first type I IFN-mediated disease or disorder in the computer-implemented method is SSc and the second type I IFN-mediated disease or disorder is lupus nephritis.

[0047] In other aspects, the PK/PD data in the computer-implemented method corresponding to the first or second type I IFN-mediated disease or disorder comprises binding affinity data. In some aspects, the binding affinity data in the computer-implemented method corresponds to the binding of an antibody or antigen binding fragment thereof to an IFN receptor. In other aspects, the antibody or antigen binding fragment thereof in the computer-implemented method is MEDI-546. In some aspects, the IFN receptor in the computer-implemented method is IFNAR1.

[0048] In some aspects, the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder in the computer-implemented method comprises kinetics data. In other aspects, the kinetics data corresponds to internalization kinetics of an antigen-antibody complex by cells. In some aspects, the antigen in the computer-implemented method is IFNAR1. In other aspects, the antibody in the computer-implemented method is MEDI-546. In some aspects, the cells in the computer-implemented method are THP-1 cells.

[0049] In some aspects, the PK/PD data corresponding to the first or second type I IFN-mediated disease or disorder in the computer-implemented method comprises type I IFN GS suppression data. In some aspects, the type I IFN GS suppression in the computer-implemented method is full suppression. In some aspects, the type I IFN GS suppression in

the computer-implemented method is partial suppression. In some aspects, the type I IFN GS in the computer-implemented method comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, RSAD2, and IFI6.

[0050] In some aspects, the PK/PD stochastic model comprises two compartments. In some aspects, the two compartments in the PK/PD stochastic model are a central compartment and a peripheral compartment. In some aspects, the PK/PD stochastic model further comprises a skin compartment. In some aspects, the PK/PD stochastic model comprises two elimination pathways. In some aspects, the two elimination pathways are a clearance pathway and a target-mediated disposition pathway. In one specific aspect, the clearance pathway in the PK/PD stochastic model is a reticuloendothelial system pathway.

[0051] The present disclosure also provides a computer-readable medium containing program instructions for predicting an optimal dosage regimen with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of (a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder; (b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and, (c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder; wherein the output of the simulation identifies an optimal dosage of the antibody or antigen-binding fragment thereof that modulates type I IFN activity in the second type I IFN-mediated disease or disorder.

[0052] The present disclosure also provides a computer-readable medium containing program instructions for identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating a type I IFN-mediated disease or disorder, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of (a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder; (b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and, (c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated

disease or disorder; wherein the output of the simulation identifies an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating the second type I IFN-mediated disease or disorder.

[0053] The present disclosure also provides a computer-readable medium containing program instructions for identifying a patient as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of (a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder; (b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and, (c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder; wherein the output of the simulation identifies a patient with the second type I IFN-mediated disease as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity.

[0054] The present disclosure also provides a computer-readable medium containing program instructions for designing a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of (a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder; (b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and, (c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder; wherein the output of the simulation identifies a personalized therapy for treating the second type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity. In some aspects of the computer-readable medium, the type I IFN activity is IFN-α activity. In other aspects of the computer-readable medium, the first and second type I IFN-mediated disease or disorder share a common IFN GS. In some aspects of the computer-readable medium, the type I IFN GS is differentially regulated.

[0055] In some aspects of the computer-readable medium, the type I IFN GS comprises up-regulated expression or activity of at least 4 PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In some aspects of the computer-readable medium, the type I IFN GS comprises up-regulated expression or activity of at least 5 PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In some aspects of the computer-readable medium, the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2. In some aspects of the computer-readable medium, the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

[0056] In some aspects of the computer-readable medium, the antibody or antigen binding fragment thereof specifically binds to an IFN receptor. In some aspects of the computer-readable medium, the IFN receptor is an IFN alpha receptor. In some aspects of the computer-readable medium, the IFN alpha receptor is IFNAR1. In some aspects of the computer-readable medium, the antibody or antigen binding fragment thereof specifically binds to subunit 1 of IFNAR1. In some aspects of the computer-readable medium, the antibody or antigen binding fragment thereof is monoclonal. In some aspects of the computer-readable medium, the antibody or antigen binding fragment thereof comprises an immunoglobulin IgG Fc region. In some aspects of the computer-readable medium, the antibody is MEDI-546.

[0057] In some aspects of the computer-readable medium, the first and the second type I IFN-mediated disease or disorder are autoimmune diseases. In some aspects of the computer-readable medium, the autoimmune diseases are rheumatic diseases. In some aspects of the computer-readable medium, the rheumatic diseases are selected from the group consisting of systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, and lupus nephritis. In some aspects of the computer-readable medium, the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is SLE. In some aspects of the computer-readable medium, the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is myositis. In some aspects of

the computer-readable medium, the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is lupus nephritis.

[0058] In some aspects of the computer-readable medium, the PK/PD data corresponding to the first or second type I IFN-mediated disease or disorder comprise binding affinity data. In some aspects of the computer-readable medium, the binding affinity data corresponds to the binding of an antibody or antigen binding fragment thereof to an IFN receptor. In some aspects of the computer-readable medium, the antibody or antigen binding fragment thereof is MEDI-546. In some aspects of the computer-readable medium, the IFN receptor is IFNAR1.

[0059] In some aspects of the computer-readable medium, the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise kinetics data. In some aspects of the computer-readable medium, the kinetics data is corresponds to internalization kinetics of an antigen-antibody complex by cells. In some aspects of the computer-readable medium, the antigen is IFNAR1. In some aspects of the computer-readable medium, the antibody is MEDI-546. In some aspects of the computer-readable medium, the cells are THP-1 cells.

[0060] In some aspects of the computer-readable medium, the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise type I IFN GS suppression data. In some aspects of the computer-readable medium, the type I IFN GS suppression is full suppression. In some aspects of the computer-readable medium, the type I IFN GS suppression is partial suppression. In some aspects of the computer-readable medium, the IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, RSAD2, and IFI6.

[0061] In some aspects of the computer-readable medium, the PK/PD stochastic model comprises two compartments. In some aspects of the computer-readable medium, the two compartments in the PK/PD stochastic model are a central compartment and a peripheral compartment. In some aspects of the computer-readable medium, the PK/PD stochastic model further comprises a skin compartment. In some aspects of the computer-readable medium, the PK/PD stochastic model comprises two elimination pathways. In some aspects of the computer-readable medium, the two elimination pathways in the PK/PD stochastic model are a clearance pathway and a target-mediated disposition pathway. In some aspects of

the computer-readable medium, the clearance pathway in the PK/PD stochastic model is a reticuloendothelial system pathway.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0062] FIG. 1 shows baseline type I IFN Gene Signature (type I IFN GS) scores for SLE (whole blood, WB: 262, skin: 17), SSc (whole blood, WB: 28, skin: 16), and healthy control patients (whole blood, WB: 54, skin: 30) in both blood and skin specimens. Horizontal summary lines indicate the mean and standard error for each distribution of type I IFN GS scores.

[0063] FIGS. 2A to 2D shows median type I IFN GS profiles (FIG. 2A and FIG. 2B) and percent remaining type I IFN GS (FIG. 2C and FIG. 2D) in diffuse SSc patients following single or multiple IV administrations of MEDI-546 in whole blood specimens (FIG. A and FIG. 2C) or skin specimens (FIG. 2B and FIG. 2D) from MI-CP180 trial. For each pair of plots, the single and multiple dose treatment cohorts have been separated into their respective graph. X-axis represents time from the start of the study in days, where day 0 is pre treatment. Target modulation for each dose cohort is reported as a percentage from starting values of 100%, so each point post treatment for each cohort indicates the median percentage of remaining GS. Only baseline positive GS_0 score SSc patients were plotted. The minimum and average GS score among the pool of normal healthy controls are shown as the black dashed line and grey dashed line respectively (FIG. 2A and FIG. 2B).

[0064] FIG. 3 shows the measurement of MEDI-546 internalization rate in THP-1 cells by confocal fluorescence imaging studies. Cells were stained with CFSE (cytosol) and MEDI-546-Alexa647. Internalization was initiated by transferring cells from ice to 37°C. Overlays of CFSE and MEDI-546-Alexa647 fluorescent images are shown before (FIG. 3A) and 40 min after the start of internalization (FIG. 3B). MEDI-546-Alexa647 fluorescence signals in cytoplasm were normalized to total fluorescence and plotted versus time (FIG. 3C). Each data point represents the average of triplicates in an experiment. The graph combined data obtained from four independent experiments.

[0065] FIG. 4 shows the MEDI-546 PK-PD model structure. Ab, Ab_p and Ab_{skin} are MEDI-546 in the central, peripheral and skin compartments, respectively. Q is the inter-compartmental clearance. The partitioning of MEDI-546 from blood (serum) to skin is represented by k_{bs} and k_{sb}. CL_{RES} represents the clearance by the reticuloendothelial system.

MEDI-546 (Ab) binds to IFNAR1 (R) and the complex (Ab.R) is subsequently internalized and degraded inside the cells. $GS_{IFN,wb}$ and $GS_{IFN,skin}$ represent type I IFN GS in the whole blood and skin, respectively. I_{max} is the maximum fractional extent of inhibition of type I IFN GS production by MEDI-546, and IC_{50} is potency (MEDI-546 concentration corresponding to half maximum inhibition of type I IFN GS production). k_{in} and k_{out} are the production rate and elimination rate constant of IFN genes. The inclusion of the skin compartment is for simulation purpose only. There is no MEDI-546 mass loss from the central compartment due to the partitioning to the skin tissues.

[0066] FIGS. 5A to 5D show representative individual MEDI-546 PK and type I IFN GS profiles in diffuse SSc patients from the MI-CP180 clinical trial. FIGS. 5A and 5B correspond to PK and PD of single-dose phase, respectively. FIGS. 5C and 5D correspond to PK and PD of multiple-dose phase, respectively. Two patients were selected for each dose phase, one from a lower dose group and the other from a high dose group. Patients in the multiple-dose cohorts received four weekly intravenous administrations of MEDI-546; the last dose was given on Day 28. Open circles represent observed serum concentration of MEDI-546 or type I GS in peripheral blood. Grey lines are the population predictions while the black lines are individual predictions by the population PK-PD model. SD: single dose regimen, MD: multiple dose regimen, SID: subject ID.

[0067] FIGS. 6A and 6B show simulated type I IFN GS profiles in peripheral blood (FIG. 6A) and skin tissue (FIG. 6B) of SLE patients upon multiple IV administrations of MEDI-546 (fixed dose) once every four weeks. The solid lines represent the medians of 1,000 simulated profiles while dotted lines represent the lower or upper quartiles. The observed upper boundary (mean + 2 standard deviations) of the type I IFN GS in the blood and skin of healthy donors were 2.9 and 1.8, respectively.

[0068] FIG. 7 shows the target modulation profiles in the blood of seven SSc patients with baseline GS_0 >13 from the MI-CP180 clinical trial. Black and grey lines represent single dose (0.3, 1, 10 or 20 mg/kg) or multiple dose (1 mg/kg) regimens respectively; the grey dashed line represents the average value of type I IFN GS score (1.1) of the pool of normal healthy controls. Mpk = mg/kg.

[0069] FIG. 8 shows the specific binding of MEDI-546 to THP-1 cells. Cells were stained with CFSE (cytosol) and either IgG-Alexa647 (A) or MEDI-546-Alexa647 (B).

Overlays of CFSE and Alexa647 fluorescent images are shown from a representative experiment.

[0070] FIGS. 9A and 9B show observed and model-predicted MEDI-546 PK profiles in diffuse SSc patients. Patients enrolled in the multiple-dose cohorts received four weekly IV administrations of MEDI-546. Symbols represent observed values. The grey solid lines are the population predictions and the black solid lines are the individual predictions. SD: single-dose, MD: multiple-dose, SID: subject ID. X-axes represent days. Y-axes represent MEDI-546 concentrations (μg/mL).

[0071] FIGS. 10A and 10B show observed and model-predicted blood type I IFN GS profiles in diffuse SSc patients. Patients enrolled in the multiple-dose cohorts received four weekly IV administrations of MEDI-546. Symbols represent observed values. The grey solid lines are the population predictions and the black solid lines are the individual predictions. SD: single-dose, MD: multiple-dose, SID: subject ID. X-axes represent days. Y-axes represent type I IFN GS scores.

[0072] FIG. 11A and 11B show observed and model-predicted Target Modulation in peripheral blood from diffuse SSc patients. Patients enrolled in the multiple-dose cohorts received four weekly IV administrations of MEDI-546. Symbols represent observed values. The grey solid lines are the population predictions and the black solid lines are the individual predictions. SD: single-dose, MD: multiple-dose, SID: subject ID. X-axes represent days. Y-axes represent (100% - Target Modulation) (%).

[0073] FIG. 12 shows visual predictive checks of MEDI-546 PK profiles in adult SSc patients. Symbols represent observed serum concentrations of MEDI-546. The solid lines are medians of 1,000 simulated replicates. The dashed lines represent 5th/95th or 10th/90th percentiles from 1,000 simulations using the population PK-PD model.

[0074] FIG. 13 shows visual predictive checks of type I IFN GS responses in adult SSc patients following MEDI-546 administration. Symbols represent observed type I IFN GS in peripheral blood. The solid lines are medians of 1,000 simulated replicates. The dashed lines represent 5th/95th or 10th/90th percentiles from 1,000 simulations using the population PK-PD model.

[0075] FIG. 14 shows observed and simulated type I IFN GS scores in skin tissues from SSc patients enrolled in the FTIH study for MEDI-546. Baseline (FIG. 14A) and post-dose

scores (FIG. 14B) are shown. The skin type I IFN GS data were not modeled (no curve-fitting was performed).

DETAILED DESCRIPTION OF THE INVENTION

[0076] The present disclosure provides methods of identifying, diagnosing, treating and monitoring disease progression in patients. MEDI-546 (see U.S. 2011-0059078, herein incorporated by reference in its entirety), a fully human IgG_1 kappa monoclonal antibody directed against subunit 1 of IFNAR1 that blocks all type I IFNs, was tested in a first-time-in-human trial (FTIH) in diffuse systemic sclerosis (SSc). A type I IFN Gene Signature (type I IFN GS) shared by systemic lupus erythematous (SLE) and SSc was developed to evaluate the pharmacodynamics, and potentially to predict clinical benefit of MEDI-546.

Definitions

[0077] It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more," and "at least one" can be used interchangeably herein.

[0078] Furthermore, “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following embodiments: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0079] It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0080] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And

Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0081] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Unless otherwise indicated, amino acid sequences are written left to right in amino to carboxy orientation. The headings provided herein are not limitations of the various aspects or embodiments of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety. Amino acids are referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical Nomenclature Commission. Nucleotides, likewise, are referred to by their commonly accepted single-letter codes.

[0082] As used herein, the term "autoimmune disease" refers to a disorder, disease state or condition associated with the formation of autoantibodies reactive with the patient's own cells to form antigen-antibody complexes. The term "autoimmune disease" includes conditions such as, *e.g.*, systemic lupus erythematosus, as well as those disorders which are triggered by a specific external agent, *e.g.*, acute rheumatic fever. Examples of autoimmune disorders include, but are not limited to, autoimmune hemolytic anemia, autoimmune hepatitis, Berger's disease, chronic fatigue syndrome, Crohn's disease, dermatomyositis, fibromyalgia, Graves' disease, Hashimoto's thyroiditis, idiopathic thrombocytopenia purpura, lichen planus, multiple sclerosis, myasthenia gravis, psoriasis, rheumatic fever, rheumatoid arthritis, scleroderma, Sjogren's syndrome, systemic lupus erythematosus, type 1 diabetes, ulcerative colitis, and vitiligo. In specific aspects, the autoimmune disease is systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, or lupus nephritis.

[0083] The terms "Interferon alpha receptor-1," "IFNAR1," and "IFNAR" are used interchangeably, and include variants, isoforms, species homologs of human IFNAR1, and analogs having at least one common epitope with IFNAR1. See, e.g., de Weerd et al., J. Biol. Chem. 282:20053-20057 (2007). Accordingly, human antibodies specific for human IFNAR1, in certain cases, cross-react with IFNAR1 from species other than human, or other proteins which are structurally related to human IFNAR1 (*e.g.*, human IFNAR1 homologs). In other cases, the antibodies can be completely specific for human IFNAR1 and not exhibit

species or other types of cross-reactivity. The complete eDNA sequence of human IFNAR1 has the Genbank accession number NM_000629.

[0084] The terms "type I interferon" or “type I IFN” as used herein refer to members of the type I interferon family of molecules that are ligands for IFNAR1 (i.e., members of the type I interferon family of molecules that are capable of binding IFNAR1). Examples of type I interferon ligands are interferon alpha 1, 2a, 2b, 4, 5, 6, 7, S, 10, 14, 16, 17, 21, interferon beta and interferon omega.

[0085] The term “type I IFN-mediated disease or disorder” refers to any type I IFN or IFNα inducible disease, disorder, or condition that exhibits a type I IFN PD marker expression profile or gene signature (type I IFN GS). A PD marker expression profile and a gene signature will be understood to be equivalent. These diseases, disorders, or conditions include those with an autoimmune component such as systemic lupus erythematosus (SLE), scleroderma, lupus nephritis, o myosotis. A type I IFN-mediated disease or disorder can be treated by administering a small molecule or a biological agent, *e.g.*, an antibody or an antigen binding fragment thereof. If the therapeutic agent is a biological agent, it may be an antibody specific for any subtype(s) of type I IFN or IFNα. For instance, the antibody may be specific for any one of IFNαl, IFNα2, IFNα4, IFNα5, IFNαó, IFNα7, IFNα8, IFNαlO, IFNαl4, IFNα 17, IFNα21, IFNβ, or IFNω. Alternatively, the antibody may be specific for any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, any eleven, any twelve type I IFN of IFNα subtypes. If the antibody is specific for more than one type I IFN subtype, the antibody may be specific for IFNαl, IFNα2, IFN α4, IFNα5, IFNα8, IFNαlO, and IFNα21; or it may be specific for IFNαl, IFNα2, IFNα4, IFNα5, IFNα8, and IFNαlO; or it may be specific for IFNαl, IFNα2, IFNα4, IFNα5, IFNα8, and IFNα21; or it may be specific for IFNαl, IFNα2, IFNα4, IFNα5, IFNαlO, and IFNα21. A therapeutic agent that modulates IFNα activity may neutralize IFNα activity. A type I IFN-mediated disease or disorder can also be treated with antibodies specific for a type I IFN receptor, *e.g.*, IFNAR1. In some aspects, anti-IFNAR1 antibodies can cross-react with IFNAR1 from species other than human. In other aspects, the anti-IFNAR1 antibodies can be specific for IFNAR1 only and not exhibit species or other types of cross-reactivity. In some aspects, the anti-IFNAR1 antibodies exhibit reduced binding affinities for FC ligands and have reduced or ablated effector function (ADCC and/or CDC), reduced or ablated binding to Fc ligands, or reduced or ablated toxicities as compared to an unmodified antibody.

[0086] The term “MEDI-546” refers to an Fc-modified version of the anti-IFNAR 9D4 antibody described in U.S. Patent No. 7,662,381. The sequence of MEDI-546 is described in U.S. 2011-0059078. MEDI-546 comprises a combination of three mutations: L234F, L235E, and P331S, wherein the numbering is according to the EU index as set forth in Kabat, introduced into the lower hinge and CH2 domain of human IgG1, which cause a decrease in their binding to human FcγRI (CD64), FcγRIIA (CD32A), FcγRIII (CD16) and C1q. See, *e.g.*, US 2011/0059078 and Oganesyan *et al.* Acta Crystallographica D 64:700-704 (2008), which are hereby incorporated by reference in their entireties. The VH and Vk sequences of MEDI-546 are shown in TABLE 1.

TABLE 1

MEDI-546 VH (SEQ ID NO:1)	EVQLVQSGAEVKKPGESLKISCKGSGYIFTNYWIAWVRQMPGKC LESMGIIYPGDSDIRYSPSFQGQVTISADKSITTAYLQWSSLKAS DTAMYYCARHDIEGFDYWGRGTLVTVSS
MEDI-546 Vκ (SEQ ID NO:2)	EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFFAWYQQKPGQAPR LLIYGASSRATGIPDRLSGSGSGTDFTLTITRLEPEDFAVYYCQ QYDSSAITFGQGTRLEIK

[0087] The term “antibody or antigen-binding fragment thereof that modulates type I IFN activity” refers to an antibody (see *infra*) in its broadest sense capable of modulating type I IFN activity in a patient. The term “modulating” as used herein includes the inhibition or suppression of a type I IFN activity as well as the induction or enhancement of a type I IFN activity. In specific aspects, the type I IFN activity is IFNα activity. In some aspects, the suppression of a type IFN GS is a suppression of a type I IFN activity. In some aspects, the antibody or antigen-binding fragment thereof is monoclonal. In specific aspects, the antibody or antigen-binding fragment thereof that modulates type I IFN activity specifically binds to a type I IFN receptor such as IFNAR1. In some specific aspects, the antibody or antigen-binding fragment thereof specifically binds to subunit 1 of IFNAR1.

[0088] The term "antibody" is used herein in its broadest sense and includes, *e.g.*, monoclonal antibodies, polyclonal antibodies, multivalent antibodies, multispecific antibodies, chimeric antibodies, and humanized antibodies. The term "antibody" includes whole antibodies. The term "antibody" also refers to a protein comprising at least two

immunoglobulin heavy (H) chains and two immunoglobulin light (L) chains inter-connected by disulfide bonds, or an antigen binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies can mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (*e.g.*, effector cells) and the first component (C1q) of the classical complement system.

[0089] The term “antigen-binding fragment” refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (*e.g.*, IFNAR). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward *et al.*, (1989) Nature 341:544-546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see *e.g.*, Bird *et al.* (1988) Science 242:423-426; and Huston *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding fragment" of an antibody. These antibody fragments are

obtained using conventional techniques known to those with skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

[0090] An "isolated antibody," as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (*e.g.*, an isolated antibody that specifically binds IFNAR is substantially free of antibodies that specifically bind antigens other than IFNAR). An isolated antibody that specifically binds IFNAR can, however, have cross-reactivity to other antigens, such as IFNAR molecules from other species. Moreover, an isolated antibody can be substantially free of other cellular material and/or chemicals.

[0091] The term "monoclonal antibody" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody displays a single binding specificity and affinity for a particular epitope.

[0092] The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the disclosure can include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0093] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, *e.g.*, a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0094] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic or transchromosomal for

human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, *e.g.*, from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0095] The term “antibody” as used herein also includes "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567; and Morrison *et al, Proc. Natl. Acad. Sci. USA 81*:6851-6855 (1984)).

[0096] Basic antibody structures in vertebrate systems are relatively well understood. See, *e.g.*, Harlow *et al.* (1988) Antibodies: A Laboratory Manual (2nd ed.; Cold Spring Harbor Laboratory Press).

[0097] In the case where there are two or more definitions of a term that is used and/or accepted within the art, the definition of the term as used herein is intended to include all such meanings unless explicitly stated to the contrary. A specific example is the use of the term "complementarity determining region" ("CDR") to describe the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. This particular region has been described by Kabat *et al.* (1983) U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" and by Chothia and Lesk, *J. Mol. Biol. 196*:901-917 (1987), which are incorporated herein by reference, where

the definitions include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues that encompass the CDRs as defined by each of the above cited references are set forth below in TABLE 2 as a comparison. The exact residue numbers that encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

TABLE 2

CDR Definitions[1]

	Kabat	Chothia
VH CDR1	31-35	26-32
VH CDR2	50-65	52-58
VH CDR3	95-102	95-102
VL CDR1	24-34	26-32
VL CDR2	50-56	50-52
VL CDR3	89-97	91-96

[1]Numbering of all CDR definitions in Table 1 is according to the numbering conventions set forth by Kabat *et al.* (see below).

[0098] Kabat *et al.* also defined a numbering system for variable domain sequences that is applicable to any antibody. One of ordinary skill in the art can unambiguously assign this system of "Kabat numbering" to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. As used herein, "Kabat numbering" refers to the numbering system set forth by Kabat *et al.* (1983) U.S. Dept. of Health and Human Services, "Sequence of Proteins of Immunological Interest." Unless otherwise specified, references to the numbering of specific amino acid residue positions in an anti-IFNAR antibody or antigen-binding fragment, variant, or derivative thereof of the present disclosure are according to the Kabat numbering system.

[0100] As used herein, the terms "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the progression of an autoimmune condition, *e.g.*, a rheumatic condition. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression,

amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[0101] The terms "effective amount" or "amount effective to" or "therapeutically effective amount" includes reference to a dosage of a therapeutic agent sufficient to produce a desired result.

[0102] By "subject" or "patient" is meant any subject, particularly a mammalian subject, for whom diagnosis, prognosis, or therapy is desired. As used herein, the terms "subject" or "patient" include any human or nonhuman animal. The term "nonhuman animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, bears, chickens, amphibians, reptiles, etc. As used herein, phrases such as "a patient having a type I IFN-mediated disease or disorder" includes subjects, such as mammalian subjects, that would benefit from the administration of an antibody or antigen-binding fragment thereof that modulates type I IFN activity, *e.g.*, for detection, imaging, or other diagnostic procedure, and/or from treatment, *i.e.*, palliation or prevention of a disease, with such antibody or antigen-binding thereof.

[0103] Terms such as "treating" or "treatment" or "to treat" refer to both (1) therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder and (2) prophylactic or preventative measures that prevent and/or slow the development of a targeted pathologic condition or disorder. Thus, those in need of treatment include those already with the disorder; those prone to have the disorder; and those in whom the disorder is to be prevented.

Pharmacokinetic Model and Translational Application

[0104] In a Phase 1 trial (MI-CP180; ClinicalTrials.gov Identifier: NCT00930683) treatment with MEDI-546 resulted in complete neutralization of the type I IFN GS in peripheral blood and skin biopsies from SSc patients in a dose-dependent manner. To our knowledge, this is the first study demonstrating normalization of the type I IFN GS in the peripheral blood and disease tissue where type I IFN is involved in the pathogenesis of the disease.

[0105] To rapidly bridge clinical indications to SLE for a Phase 2 trial, a translational model was developed that incorporated (1) the pharmacokinetics (PK) and pharmacodynamics (PD) of MEDI-546 in SSc patients, (2) the internalization kinetics of the MEDI-546/IFNAR complex as determined from confocal imaging studies, and (3) the magnitude of differences in the type I IFN GS in blood and skin between SSc and SLE patients. This model was first used to characterize the disposition properties of MEDI-546 and the suppression of the type I IFN signature in SSc patients, for which clinical data was available. Afterwards, the PK/PD model was adjusted to account for the magnitude of differences in the type I IFN GS between SSc and SLE patients, and stochastic PK-PD simulations were performed to predict type I IFN GS responses in blood and skin specimens upon multiple MEDI-546 administrations in virtual SLE patients. This approach facilitated a rapid progression of MEDI-546 clinical development and the optimal design of a Phase 2 study in SLE. Stochastic simulations predicted that once-every-four-week intravenous administrations of MEDI-546 at 100mg, 300mg or 1000mg fixed doses could suppress the type I IFN GS in the blood of SLE patients to the level of healthy normal subjects (mean ± 2 standard).

[0106] Thus, the present disclosure provides a pharmacokinetic/pharmacodynamic (PK/PD) stochastic model for type I IFN-mediated diseases or disorders. In some aspects, the PK/PD stochastic model comprises two compartments. These two compartments can be a central compartment and a peripheral compartment. In certain aspects, the PK/PD stochastic model can comprises additional compartments, *e.g.*, a skin compartment. The PK/PD stochastic model comprises can also comprise at least one elimination pathway. In some aspects, the PK/PD stochastic model comprises two elimination pathways. In some aspects, the two elimination pathways are a clearance pathway and a target-mediated disposition pathway. In some aspects, the clearance pathway in the PK/PD stochastic model is a reticuloendothelial system pathway.

[0107] The PK/PD stochastic model can be used, for example for translational purposes. In this respect, PK/PD data corresponding a first type I IFN-mediated disease or disorder can be used to generate the PK/PD stochastic model, and then the PK/PD stochastic model can be adjusted using inputted PK/PD data from the second type I IFN-mediated disease or disorder. This adjusted model can be used in turn to conduct simulation and infer information corresponding to the second type I IFN-mediated disease or disorder such as determining

optimal dosage regimens, determining whether a candidate therapeutic agent should be selected to treat a patient, select a candidate patient for therapy, or design a personalized therapy. In some aspects, the adjusted model can be used, for example, to select candidate subjects for a clinical study.

[0108] The PK/PD data for the first or second type I IFN-mediated disease or disorder can comprise binding affinity data. For example, the binding affinity data can correspond to the binding of an antibody or antigen binding fragment thereof to a type I IFN receptor. In some aspects, the antibody or antigen binding fragment thereof is MEDI-546. In some aspects, the type I IFN receptor is IFNAR1.

[0109] In some aspects, the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is SLE. In some other aspects, the first type I IFN-mediated disease or disorder SSc and the second type I IFN-mediated disease or disorder is myositis. In some aspects, the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is lupus nephritis. In general, the first and second type I IFN-mediated diseases or disorders can be rheumatic diseases. One skilled in the art will appreciate that other pairs of type I IFN-mediated related diseases or disorders can be used.

[0110] In some aspects, the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise kinetics data, *e.g.*, internalization kinetics of an antigen-antibody complex by cells. In some aspects, the antigen is IFNAR1. In other aspects, the antibody is MEDI-546. In some aspects, the cells are THP-1 cells. One skilled in the art would appreciate that different antibodies, antigens, and cell lines can be used.

[0111] In some aspects, the PK/PD data corresponding to the first or second type I IFN-mediated disease or disorder comprise type I IFN GS suppression data (*e.g.*, full suppression or partial suppression). In some aspects, the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2. In some aspects, the type I IFN GS further comprises IFI6. One skilled in the art would appreciate that other type I IFN GS can be used, as discussed below.

Fixed Dose Administration

[0112] The present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising administering a fixed dose of an antibody or antibody fragment thereof that modulates type I IFN activity, wherein the dose is effective to

treat the disorder. In some aspects, the antibody is an anti IFNAR antibody. In some specific aspects, the antibody is an anti-IFNAR1 antibody, *e.g.*, MEDI-546.

[0113] A "fixed dose" as used herein refers to a dose that is administered to a patient without regard for the weight (WT) or body surface area (BSA) of the patient. The fixed dose of antibody or antibody fragment thereof that modulates type I IFN activity, *e.g.*, MEDI-546, is therefore not provided as a mg/kg dose or mg/m2 dose, but rather as an absolute amount of the therapeutic agent.

[0114] In some aspects, an antibody or antibody fragment thereof that modulates type I IFN activity is administered as a fixed dose ranging from about 100 mg to about 1000 mg. In other aspects, the fixed dose is from about 300 mg to about 1000 mg. In some aspects, the fixed dose is lower than about 300 mg. In some specific aspects, the antibody or antibody fragment thereof that modulates type I IFN activity is MEDI-546.

[0115] In some aspects, an antibody or antibody fragment thereof that modulates type I IFN activity is administered at a fixed dose of about 10 mg, or about 20 mg, or about 30 mg, or about 40 mg, or about 50 mg, or about 60 mg, or about 70 mg, or about 80 mg, or about 90 mg, or about 100 mg. In other aspects, an antibody or antibody fragment thereof that modulates type I IFN activity is administered at a fixed dose of about 100 mg, or about 150 mg, about 200 mg, or about 300 mg, or about 400 mg, or about 500 mg, or about 600 mg, or about 700 mg, or about 800 mg, or about 900 mg, or about 1000 mg, or about 1100 mg, or about 1200 mg, or about 1300 mg, or about 1400 mg, or about 1500 mg, or about 1600 mg, or about 1700 mg, or about 1800 mg, or about 1900 mg, or about 2000 mg. In certain aspects, the fixed dose is about 100 mg. In other specific aspects, the fixed dose is about 300 mg. In yet another aspect, the fixed dose is about 1000 mg.

[0116] In some aspects, the antibody or antibody fragment thereof that modulates type I IFN activity can be administered intravenously, intramuscularly, subcutaneously, or a combination thereof. The antibody or antibody fragment thereof that modulates type I IFN activity can also be administered by any means known in the art. In specific aspects, the antibody or antibody fragment thereof that modulates type I IFN activity is administered intravenously at a fixed dosage about 100 mg, or about 300 mg, or about 1000 mg. In a specific aspect, the antibody or antibody fragment thereof that modulates type I IFN activity is administered subcutaneously at a fixed dosage of about 100 mg, or about 300 mg, or about 1000 mg.

[0117] In some aspects, a loading dose of the antibody or antibody fragment thereof that modulates type I IFN activity is administered. In a specific aspect, the antibody or antibody fragment thereof that modulates type I IFN activity is administered intravenously at a fixed dosage about 100 mg, or about 300 mg, or about 1000 mg once per month. In some aspects, the antibody or antibody fragment thereof that modulates type I IFN activity can be administered subcutaneously.

[0118] When a series of fixed doses of an antibody or antibody fragment thereof that modulates type I IFN activity are administered, these doses can, for example, be administered approximately every week, approximately every 2 weeks, approximately every 3, or about every 4 weeks. In some aspects, fixed doses of an antibody or antibody fragment thereof that modulates type I IFN activity are administered approximately every day, approximately every two days, approximately every three days, approximately every 4 days, approximately every 5 days, approximately every 6 days, or approximately every seven days.

[0119] In a specific aspect, the fixed dose of antibody or antibody fragment thereof that modulates type I IFN activity is a 100 mg dose administered monthly. In another specific aspect, the fixed dose of antibody or antibody fragment thereof that modulates type I IFN activity is a 300 mg dose administered monthly. In a specific aspect, the fixed dose of antibody or antibody fragment thereof that modulates type I IFN activity is a 1000 mg dose administered monthly. In specific aspects, the fixed dose of antibody or antibody fragment thereof that modulates type I IFN activity is a 100 mg, 300 mg, or 1000 mg monthly dose of MEDI-546.

[0120] In specific aspects, fixed doses of antibody or antibody fragment thereof that modulates type I IFN activity can be administered every month. Successive doses can be administered in successive months. These fixed doses can be administered, for example, for about 1 month, or about 2 months, or about 3 months, or about 4 months, or about 5 months, or about 6 months. Such fixed doses can, for example, continue to be administered until disease progression, adverse event, or other parameter occurs as determined by a healthcare provider, *e.g.*, suppression or lack of suppression of a type I IFN GS.

[0121] In some embodiments, patients can be administered at least one, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14 or at least 15 fixed doses of antibody or antibody fragment thereof that modulates type I IFN activity. In some aspects, fixed doses of antibody or antibody

fragment thereof that modulates type I IFN activity are administered at equal time intervals. In other embodiment, fixed doses of antibody or antibody fragment thereof that modulates type I IFN activity are administered at varying intervals. In some aspects, all administered fixed doses are essentially identical. In other aspects, at least one fixed dose is different with respect to the other doses, *e.g.*, in volume, concentration, route of administration, formulation, etc.

[0122] For the prevention or treatment of autoimmune diseases, *e.g.*, SLE, SSc, myositis, or lupus nephritis the fixed dose of antibody or antibody fragment thereof that modulates type I IFN activity, *e.g.*, MEDI-546, will depend, for example, on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician.

[0123] In a specific embodiment, the disclosure provides a method of treating a type I IFN-mediated disease or disorder, such as an autoimmune disorder (*e.g.*, SLE, SSc, lupus nephritis, myositis) in a patient comprising administering at least one intravenous or subcutaneous fixed dose of an anti-IFNAR antibody such as MEDI-546 to the patient, wherein the fixed dose is about 100 mg, about 300 mg, or about 1000 mg.

Type I Interferon Gene Signature (IFN GS)

[0124] The present disclosure also provides a type I Interferon Gene Signature (type I IFN GS) that can be specifically suppressed when a patient suffering from a type I IFN-mediated disease or disorder is treated with a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity.

[0125] In one aspect, the type I IFN GS that can be suppressed with a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity is a subset of the 21 genes used as pharmacodynamics (PD) markers for sifalimumab, an anti-IFN-α monoclonal therapy in SLE described previously (Yao *et al.*, Arthritis Rheum. 60:1785-1796 (2009); Yao *et al.*, Hum. Genomics Proteomics 2009:374312 (2009); Yao *et al.*, Arthritis Res. Ther. 12 (Suppl 1):S6 (2010)).

[0126] In some aspects, these 21 genes (see TABLE 3) are: IFI27 (interferon alpha inducible protein 27) (SEQ ID NO:3), IFI44 (interferon-induced protein 44) (SEQ ID NO:4), IFI44L (interferon induced protein 44, like) (SEQ ID NO:5), RSAD2 (radical S-adenosyl

methionine domain containing 2) (SEQ ID NO:6), IFI6 (interferon, alpha inducible protein 6) (SEQ ID NO:7), MX1 (myxovirus (influenza virus) resistance 1, interferon-inducible protein p78) (SEQ ID NO:8), IFIT1 (interferon-induced protein with tetratricopeptide repeats 1) (SEQ ID NO:9), HERC5 (hect domain and RLD 5) (SEQ ID NO:10), ISG15 (ISG15 ubiquitin-like modifier) (SEQ ID NO:11), LAMP3 (lysosomal-associated membrane protein 3) (SEQ ID NO:12), OAS3 (2'-5'-oligoadenylate synthetase 3, 100kDa) (SEQ ID NO:13), OAS1 (2'-5'-oligoadenylate synthetase 1, 40/60kDa) (SEQ ID NO:14), EPST1 (epithelial stromal interaction 1 (breast)) (SEQ ID NO:15), IFIT3 (interferon-induced protein with tetratricopeptide repeats 3) (SEQ ID NO:16), LY6E (lymphocyte antigen 6 complex, locus E) (SEQ ID NO:17), OAS2 (2'-5'-oligoadenylate synthetase 2, 69/71kDa) (SEQ ID NO:18), PLSCR1 (phospholipid scramblase 1) (SEQ ID NO:19), SIGLEC1 (sialic acid binding Ig-like lectin 1, sialoadhesin) (SEQ ID NO:20), USP18 (ubiquitin specific peptidase 18) (SEQ ID NO:21), RTP4 (receptor (chemosensory) transporter protein 4) (SEQ ID NO:22), and DNAPTP6 (DNA polymerase-transactivated protein 6) (SEQ ID NO:23). See PCT Publ. No. WO 2008/070137, which is incorporated herein by reference in its entirety.

TABLE 3

IFI27 (SEQ ID NO:3)	sp|P40305|IFI27_HUMAN Interferon alpha-inducible protein 27	MEASALTSSAVTSVAKVVRVASGSAVVLPLARIATVVIGGVVA VPMVLSAMGFTAAGIASSSIAAKMMSAAAIANGGGVASGS LVATLQSLGATGLSGLTKFILGSIGSAIAAVIARFY
IFI44 (SEQ ID NO:4)	sp|Q8TCB0|IFI44_HUMAN Interferon-induced protein 44	MAVTTRLTWLHEKILQNHFGGKRLSLLYKGSVHGFRNGVLLDR CCNQGPTLTVIYSEDHIIGAYAEESYQEGKYASIILFALQ DTKISEWKLGLCTPETLFCCDVTKYNSPTNFQIDGRNRKV IMDLKTMENLGLAQNCTISIQDYEVFRCEDSLDERKIKGV IELRKSLLSALRTYEPYGSLVQQIRILLLGPIGAGKSSFF NSVRSVFQGHVTHQALVGTNTTGISEKYRTYSIRDGKDGK YLPFILCDSLGLSEKEGGLCRDDIFYILNGNIRDRYQFNP MESIKLNHHDYIDSPSLKDRIHCVAFVFDASSIQYFSSQM IVKIKRIRRELVNAGVVHVALLTHVDSMDLITKGDLIEIE RCEPVRSKLEEVQRKLGFALSDISVVSNYSSEWELDPVKD VLILSALRRMLWAADDFLEDLPFEQIGNLREEIINCAQGK K
IFI44L (SEQ ID NO:5)	sp|Q53G44|IF44L_HUMAN Interferon-induced protein 44-like	MEVTTRLTWNDENHLRKLLGNVSLSLLYKSSVHGGSIEDMVER CSRQGCTITMAYIDYNMIVAFMLGNYINLHESSTEPNDSL WFSLQKKNDTTEIETLLLNTAPKIIDEQLVCRLSKTDIFI ICRDNKIYLDKMITRNLKLRFYGHRQYLECEVFRVEGIKD NLDDIKRIIKAREHRNRLLADIRDYRPYADLVSEIRILLV GPVGSGKSSFFNSVKSIFHGHVTGQAVVGSDITSITERYR IYSVKDGKNGKSLPFMLCDTMGLDGAEGAGLCMDDIPHIL KGCMPDRYQFNSRKPITPEHSTFITSPSLKDRIHCVAYVL DINSIDNLYSKMLAKVKQVHKEVLNCGIAYVALLTKVDDC SEVLQDNFLNMSRSMTSQSRVMNVHKMLGIPISNILMVGN YASDLELDPMKDILILSALRQMLRAADDFLEDLPLEETGA IERALQPCI

RSAD2 (SEQ ID NO:6)	sp|Q8WXG1|RSAD2_HUMAN Radical S-adenosyl methionine domain-containing protein 2	MWVLTPAAFAGKLLSVFRQPLSSLWRSLVPLFCWLRATFWLLA TKRRKQQLVLRGPDETKEEEEDPPLPTTPTSVNYHFTRQC NYKCGFCFHTAKTSFVLPLEEAKRGLLLLKEAGMEKINFS GGEPFLQDRGEYLGKLVRFCKVELRLPSVSIVSNGSLIRE RWFQNYGEYLDILAISCDSFDEEVNVLIGRGQGKKNHVEN LQKLRRWCRDYRVAFKINSVINRFNVEEDMTEQIKALNPV RWKVFQCLLIEGENCGEDALREAERFVIGDEEFERFLERH KEVSCLVPESNQKMKDSYLILDEYMRFLNCRKGRKDPSKS ILDVGVEEAIKFSGFDEKMFLKRGGKYIWSKADLKLDW
IFI6 (SEQ ID NO:7)	sp|P09912|IFI6_HUMAN Interferon alpha-inducible protein 6	MRQKAVSLFLCYLLLFTCSGVEAGKKKCSESSDSGSGFWKALT FMAVGGGLAVAGLPALGFTGAGIAANSVAASLMSWSAILN GGGVPAGGLVATLQSLGAGGSSVVIGNIGALMGYATHKYL DSEEDEE
MX1 (SEQ ID NO:8)	gi|295842578|ref|NP_001171517.1| interferon-induced GTP-binding protein Mx1 [Homo sapiens]	MVVSEVDIAKADPAAASHPLLLNGDATVAQKNPGSVAENNLCS QYEEKVRPCIDLIDSLRALGVEQDLAL PAIAVIGDQSSGKSSVLEALSGVALPRGSGIVTRCPLVLKLKK LVNEDKWRGKVSYQDYEIEISDASEVE KEINKAQNAIAGEGMGISHELITLEISSRDVPDLTLIDLPGIT RVAVGNQPADIGYKIKTLIKKYIQRQE TISLVVVPSNVDIATTEALSMAQEVDPEGDRTIGILTKPDLVD KGTEDKVVDVVRNLVFHLKKGYMIVKC RGQQEIQDQLSLSEALQREKIFFENHPYFRDLLEEGKATVPCL AEKLTSELITHICKSLPLLENQIKETH QRITEELQKYGVDIPEDENEKMFFLIDKVNAFNQDITALMQGE ETVGEEDIRLFTRLRHEFHKWSTIIEN NFQEGHKILSRKIQKFENQYRGRELPGFVNYRTFETIVKQQIK ALEEPAVDMLHTVTDMVRLAFTDVSIK NFEEFFNLHRTAKSKIEDIRAEQEREGEKLIRLHFQMEQIVYC QDQVYRGALQKVREKELEEEKKKKSWD FGAFQSSSATDSSMEEIFQHLMAYHQEASKRISSHIPLIIQFF MLQTYGQQLQKAMLQLLQDKDTYSWLL KERSDTSDKRKFLKERLARLTQARRRLAQFPG
IFIT1 (SEQ ID NO:9)	gi|116534937|ref|NP_001539.3| interferon-induced protein with tetratricopeptide repeats 1 [Homo sapiens]	MSTNGDDHQVKDSLEQLRCHFTWELSIDDDEMPDLENRVLDQI EFLDTKYSVGIHNLLAYVKHLKGQNEE ALKSLKEAENLMQEEHDNQANVRSLVTWGNFAWMYYHMGRLAE AQTYLDKVENICKKLSNPFRYRMECPE IDCEEGWALLKCGGKNYERAKACFEKVLEVDPENPESSAGYAI SAYRLDGFKLATKNHKPFSLLPLRQAV RLNPDNGYIKVLLALKLQDEGQEAEGEKYIEEALANMSSQTYV FRYAAKFYRRKGSVDKALELLKKALQE TPTSVLLHHQIGLCYKAQMIQIKEATKGQPRGQNREKLDKMIR SAIFHFESAVEKKPTFEVAHLDLARMY IEAGNHRKAEENFQKLLCMKPVVEETMQDIHFHYGRFQEFQKK SDVNAIIHYLKAIKIEQASLTRDKSIN SLKKLVLRKLRRKALDLESLSLLGFVYKLEGNMNEALEYYERA LRLAADFENSVRQGP
HERC5 (SEQ ID NO:10)	gi|110825982|ref|NP_057407.2| E3 ISG15--protein ligase HERC5 [Homo sapiens]	MERRSRRKSRRNGRSTAGKAAATQPAKSPGAQLWLFPSAAGLH RALLRRVEVTRQLCCSPGRLAVLERGG AGVQVHQLLAGSGGARTPKCIKLGKNMKIHSVDQGAEHMLILS SDGKPFEYDNYSMKHLRFESILQEKKI IQITCGDYHSLALSKGGELFAWGQNLHGQLGVGRKFPSTTTPQ IVEHLAGVPLAQISAGEAHSMALSMSG NIYSWGKNECGQLGLGHTESKDDPSLIEGLDNQKVEFVACGGS HSALLTQDGLLFTFGAGKHGQLGHNST

		QNELRPCLVAELVGYRVTQIACGRWHTLAYVSDLGKVFSFGSG KDGQLGNGGTRDQLMPLPVKVSSSEEL KLESHTSEKELIMIAGGNQSILLWIKKENSYVNLKRTIPTLNE GTVKRWIADVETKRWQSTKREIQEIFS SPACLTGSFLRKRRTTEMMPVYLDLNKARNIFKELTQKDWITN MITTCLKDNLLKRLPFHSPPQEALEIF FLLPECPMMHISNNWESLVVPFAKVVCKMSDQSSLVLEEYWAT LQESTFSKLVQMFKTAVICQLDYWDES AEENGNVQALLEMLKKLHRVNQVKCQLPESIFQVDELLHRLNF FVEVCRRYLWKMTVDASENVQCCVIFS HFPFIFNNLSKIKLLHTDTLLKIESKKHKAYLRSAAIEEERES EFALRPTFDLTVRRNHLIEDVLNQLSQ FENEDLRKELWVSFSGEIGYDLGGVKKEFFYCLFAEMIQPEYG MFMYPEGASCMWFPVKPKFEKKRYFFF GVLCGLSLFNCNVANLPFPLALFKKLLDQMPSLEDLKELSPDL GKNLQTLLDDEGDNFEEVFYIHFNVHW DRNDTNLIPNGSSITVNQTNKRDYVSKYINYIFNDSVKAVYEE FRRGFYKMCDEDIIKLFHPEELKDVIV GNTDYDWKTFEKNARYEPGYNSSHPTIVMFWKAFHKLTLEEKK KFLVFLTGTDRLQMKDLNNMKITFCCP ESWNERDPIRALTCFSVLFLPKYSTMETVEEALQEAINNNRGF G
ISG15 (SEQ ID NO:11)	gi|4826774|ref|NP_ 005092.1| ubiquitin-like protein ISG15 precursor [Homo sapiens]	MGWDLTVKMLAGNEFQVSLSSSMSVSELKAQITQKIGVHAFQQ RLAVHPSGVALQDRVPLASQGLGPGST VLLVVDKCDEPLSILVRNNKGRSSTYEVRLTQTVAHLKQQVSG LEGVQDDLFWLTFEGKPLEDQLPLGEY GLKPLSTVFMNLRLRGGGTEPGGRS
LAMP3 (SEQ ID NO:12)	gi|38455385|ref|NP _055213.2| lysosome- associated membrane glycoprotein 3 precursor [Homo sapiens]	MPRQLSAAAALFASLAVILHDGSQMRAKAFPETRDYSQPTAAA TVQDIKKPVQQPAKQAPHQTLAARFMD GHITFQTAATVKIPTTTPATTKNTATTSPITYTLVTTQATPNN SHTAPPVTEVTVGPSLAPYSLPPTITP PAHTTGTSSSTVSHTTGNTTQPSNQTTLPATLSIALHKSTTGQ KPVQPTHAPGTTAAAHNTTRTAAPAST VPGPTLAPQPSSVKTGIYQVLNGSRLCIKAEMGIQLIVQDKES VFSPRRYFNIDPNATQASGNCGTRKSN LLLNFQGGFVNLTFTKDEESYYISEVGAYLTVSDPETIYQGIK HAVVMFQTAVGHSFKCVSEQSLQLSAH LQVKTTDVQLQAFDFEDDHFGNVDECSSDYTIVLPVIGAIVVG LCLMGMGVYKIRLRCQSSGYQRI
OAS3 (SEQ ID NO:13)	gi|45007007|ref|NP _006178.2| 2'-5'- oligoadenylate synthase 3 [Homo sapiens]	MDLYSTPAAALDRFVARRLQPRKEFVEKARRALGALAAALRER GGRLGAAAPRVLKTVKGGSSGRGTALK GGCDSELVIFLDCFKSYVDQRARRAEILSEMRASLESWWQNPV PGLRLTFPEQSVPGALQFRLTSVDLED WMDVSLVPAFNVLGQAGSGVKPKPQVYSTLLNSGCQGGEHAAC FTELRRNFVNIRPAKLKNLILLVKHWY HQVCLQGLWKETLPPVYALELLTIFAWEQGCKKDAFSLAEGLR TVLGLIQQHQHLCVFWTVNYGFEDPAV GQFLQRQLKRPRPVILDPADPTWDLGNGAAWHWDLLAQEAASC YDHPCFLRGMGDPVQSWKGPGLPRAGC SGLGHPIQLDPNQKTPENSKSLNAVYPRAGSKPPSCPAPGPTG AASIVPSVPGMALDLSQIPTKELDRFI QDHLKPSPQFQEQVKKAIDIILRCLHENCVHKASRVSKGGSFG

		RGTDLRDGCDVELIIFLNCFTDYKDQG PRRAEILDEMRAQLESWWQDQVPSLSLQFPEQNVPEALQFQLV STALKSWTDVSLLPAFDAVGQLSSGTK PNPQVYSRLLTSGCQEGEHKACFAELRRNFMNIRPVKLKNLIL LVKHWYRQVAAQNKGKGPAPASLPPAY ALELLTIFAWEQGCRQDCFNMAQGFRTVLGLVQQHQQLCVYWT VNYSTEDPAMRMHLLGQLRKPRPLVLD PADPTWNVGHGSWELLAQEAAALGMQACFLSRDGTSVQPWDVM PALLYQTPAGDLDKFISEFLQPNRQFL AQVNKAVDTICSFLKENCFRNSPIKVIKVVKGGSSAKGTALRG RSDADLVVFLSCFSQFTEQGNKRAEII SEIRAQLEACQQERQFEVKFEVSKWENPRVLSFSLTSQTMLDQ SVDFDVLPAFDALGQLVSGSRPSSQVY VDLIHSYSNAGEYSTCFTELQRDFIISRPTKLKSLIRLVKHWY QQCTKISKGRGSLPPQHGLELLTVYAW EQGGKDSQFNMAEGFRTVLELVTQYRQLCIYWTINYNAKDKTV GDFLKQQLQKPRPIILDPADPTGNLGH NARWDLLAKEAAACTSALCCMGRNGIPIQPWPVKAAV
OAS1 (SEQ ID NO:14)	gi|74229013|ref|NP_058132.2| 2'-5'-oligoadenylate synthase 1 isoform 1 [Homo sapiens]	MMDLRNTPAKSLDKFIEDYLLPDTCFRMQINHAIDIICGFLKE RCFRGSSYPVCVSKVVKGGSSGKGTTL RGRSDADLVVFLSPLTTFQDQLNRRGEFIQEIRRQLEACQRER AFSVKFEVQAPRWGNPRALSFVLSSLQ LGEGVEFDVLPAFDALGQLTGGYKPNPQIYVKLIEECTDLQKE GEFSTCFTELQRDFLKQRPTKLKSLIR LVKHWYQNCKKKLGKLPPQYALELLTVYAWERGSMKTHFNTAQ GFRTVLELVINYQQLCIYWTKYYDFKN PIIEKYLRRQLTKPRPVILDPADPTGNLGGGDPKGWRQLAQEA EAWLNYPCFKNWDGSPVSSWILLAESN SADDETDDPRRYQKYGYIGTHEYPHFSHRPSTLQAASTPQAEE DWTCTIL
EPSTI1 (SEQ ID NO:15)	gi|50428917|ref|NP_001002264.1| epithelial-stromal interaction protein 1 isoform 1 [Homo sapiens]	MNTRNRVVNSGLGASPASRPTRDPQDPSGRQGELSPVEDQREG LEAAPKGPSRESVVHAGQRRTSAYTLI APNINRRNEIQRIAEQELANLEKWKEQNRAKPVHLVPRRLGGS QSETEVRQKQQLQLMQSKYKQKLKREE SVRIKKEAEEAELQKMKAIQREKSNKLEEKKRLQENLRREAFR EHQQYKTAEFLSKLNTESPDRSACQSA VCGPQSSTWKLPILPRDHSWARSWAYRDSLKAEENRKLQKMKD EQHQKSELLELKRQQQEQERAKIHQTE HRRVNNAFLDRLQGKSQPGGLEQSGGCWNMNSGNSWGSLLVFS RHLRVYEKILTPIWPSSTDLEKPHEML FLNVILFSLTVFTLISTAHTLDRAVRSDWLLLVLIYACLEELI PELIFNLYCQGNATLFF
IFIT3 (SEQ ID NO:16)	gi|31542980|ref|NP_001540.2| interferon-induced protein with tetratricopeptide repeats 3 [Homo sapiens]	MSEVTKNSLEKILPQLKCHFTWNLFKEDSVSRDLEDRVCNQIE FLNTEFKATMYNLLAYIKHLDGNNEAA LECLRQAEELIQQEHADQAEIRSLVTWGNYAWVYYHLGRLSDA QIYVDKVKQTCKKFSNPYSIEYSELDC EEGWTQLKCGRNERAKVCFEKALEEKPNNPEFSSGLAIAMYHL DNHPEKQFSTDVLKQAIELSPDNQYVK VLLGLKLQKMNKEAEGEQFVEEALEKSPCQTDVLRSAAKFYRR KGDLDKAIELFQRVLESTPNNGYLYHQ IGCCYKAKVRQMQNTGESEASGNKEMIEALKQYAMDYSNKALE KGLNPLNAYSDLAEFLETECYQTPFNK EVPDAEKQQSHQRYCNLQKYNGKSEDTAVQHGLEGLSISKKST

		DKEEIKDQPQNVSENLLPQNAPNYWYL QGLIHKQNGDLLQAAKCYEKELGRLLRDAPSGIGSIFLSASEL EDGSEEMGQGAVSSSPRELLSNSEQLN
LY6E (SEQ ID NO:17)	gi|119602691|gb|EAW82285.1| lymphocyte antigen 6 complex, locus E, isoform CRA_a [Homo sapiens]	MKIFLPVLLAALLGVERASSLMCFSCLNQKSNLYCLKPTICSD QDNYCVTVSASAGIGNLVTFGHSLSKT CSPACPIPEGVNVAAS
OAS2 (SEQ ID NO:18)	gi|74229021|ref|NP_001027903.1| 2'-5'-oligoadenylate synthase 2 isoform 3 [Homo sapiens]	MGNGESQLSSVPAQKLGWFIQEYLKPYEECQTLIDEMVNTICD VLQEPEQFPLVQGVAIGGSYGRKTVLR GNSDGTLVLFFSDLKQFQDQKRSQRDILDKTGDKLKFCLFTKW LKNNFEIQKSLDGFTIQVFTKNQRISF EVLAAFNALSKHCWVSGEKSQRSGCQTALCNL
PLSCR1 (SEQ ID NO:19)	gi|10863877|ref|NP_066928.1| phospholipid scramblase 1 [Homo sapiens]	MDKQNSQMNASHPETNLPVGYPPQYPPTAFQGPPGYSGYPGPQ VSYPPPPAGHSGPGPAGFPVPNQPVYN QPVYNQPVGAAGVPWMPAPQPPLNCPPGLEYLSQIDQILIHQQ IELLEVLTGFETNNKYEIKNSFGQRVY FAAEDTDCCTRNCCGPSRPFTLRIIDNMGQEVITLERPLRCSS CCCPCCLQEIEIQAPPGVPIGYVIQTW HPCLPKFTIQNEKREDVLKISGPCVVCSCCGDVDFEIKSLDEQ CVVGKISKHWTGILREAFTDADNFGIQ FPLDLDVKMKAVMIGACFLIDFMFFESTGSQEQKSGVW
SIGLEC1 (SEQ ID NO:20)	gi|146424342|gb|AAI41885.1| SIGLEC1 protein [Homo sapiens]	MGFLPKLLLLASFFPAGQASWGVSSPQDVQGVKGSCLLIPCIF SFPADVEVPDGITAIWYYDYSGQRQVV SHSADPKLVEARFRGRTEFMGNPEHRVCNLLLKDLQPEDSGSY NFRFEISEVNRWSDVKGTLVTVTEEPR VPTIASPVELLEGTEVDFNCSTPYVCLQEQVRLQWQGQDPARS VTFNSQKFEPTGVGHLETLHMAMSWQD HGRILRCQLSMANHRAQSEIHLQVKYAPRGVKILLSPSGRNIL PGELVTLTCQVNSSYPAVSSIKWLKDG VRLQTKTGVLHLPQAAWSDAGVYTCQAENGVGSLVSPPISLHI FMAEVQVSPAGPILENQTVTLVCNTPN EAPSDLRYSWYKNHVLLEDAHSHTLRLHLATRADTGFYFCEVQ NVHGSERSGPVSVVVNHPPLTPVLTAF LETQAGLVGILHCSVVSEPLATLVLSHGGHILASTSGDSDHSP RFSGTSGPNSLRLEIRDLEETDSGEYK CSATNSLGNATSTLDFHANAARLLISPAAEVVEGQAVTLSCRS GLSPTPDARFSWYLNGALLHEGPGSSL LLPAASSTDAGSYHCRARDGHSASGPSSPAVLTVLYPPRQPTF TTRLDLDAAGAGAGRRGLLLCRVDSDP PARLQLLHKDRVVATSLPSGGGCSTCGGCSPRMKVTKAPNLLR VEIHNPLLEEEGLYLCEASNALGNAST SATFNGQATVLAIAPSHTLQEGTEANLTCNVSREAAGSPANFS WFRNGVLWAQGPLETVTLLPVARTDAA LYACRILTEAGAQLSTPVLLSVLYPPDRPKLSALLDMGQGHMA LFICTVDSRPLALLALFHGEHLLATSL GPQVPSHGRFQAKAEANSLKLEVRELGLGDSGSYRCEATNVLG SSNTSLFFQVRGAWVQVSPSPELQEGQ AVVLSCQVPTGVPEGTSYRWYRDGQPLQESTSATLRFAAITLT QAGAYHCQAQAPGSATTSLAVPISLHV SYAPRHVTLTTLMDTGPGRLGLLLCRVDSDPPAQLRLLHGDRL

		VASTLQGVGGPEGSSPRLHVAVAPNTL RLEIHGAMLEDEGVYICEASNTLGQASASADFDAQAVNVQVWP GATVREGQLVNLTCLVWTTHPAQLTYT WYQDGQQRLDAHSIPLPNVTVRDATSYRCGVGPPGRAPRLSRP ITLDVLYAPRNLRLTYLLESHGGQLAL VLCTVDSRPPAQLALSHAGRLLASSTAASVPNTLRLELRGPQP RDEGFYSCSARSPLGQANTSLELRLEG VRVILAPEAAVPEGAPITVTCADPAAHAPTLYTWYHNGRWLQE GPAASLSFLVATRAHAGAYSCQAQDAQ GTRSSRPAALQVLYAPQDAVLSSFRDSRARSMAVIQCTVDSEP PAELALSHDGKVLATSSGVHSLASGTG HVQVARNALRLQVQDVPAGDDTYVCTAQNLLGSISTIGRLQVE GARVVAEPGLDVPEGAALNLSCRLLGG PGPVGNSTFAWFWNDRRLHAEPVPTLAFTHVARAQAGMYHCLA ELPTGAAASAPVMLRVLYPPKTPTMMV FVEPEGGLRGILDCRVDSEPLASLTLHLGSRLVASSQPQGAPA EPHIHVLASPNALRVDIEALRPSDQGE YICSASNVLGSASTSTYFGVRALHRLHQFQQLLWVLGLLVGLL LLLLGLGACYTWSSLILMQPHVRPQPV PHPWAEVI
USP18 (SEQ ID NO:21)	gi|48146549|emb|CA G33497.1| USP18 [Homo sapiens]	MSKAFGLLRQICQSILAESSQSPADLEEKKEEDSNMKREQPRE RPRAWDYPHGLVGLHNIGQTCCLNSLI QVFVMNVDFTRILKRITVPRGADEQRRSVPFQMLLLLEKMQDS RQKAVRPLELAYCLQKCNVPLFVQHDA AQLYLKLWNLIKDQITDVHLVERLQALYMIRVKDSLICVDCAM ESSRNSSMLTLPLSLFDVDSKPLKTLE DALHCFFQPRELSSKSKCFCENCGKKTRGKQVLKLTHLPQTLT IHLMRFSIRNSQTRKICHSLYFPQSLD FSQILPMKRESCDAEEQSGGQYELFAVIAHVGMADSGHYCVYI RNAVDGKWFCFNDSNICLVSWEDIQCT YGNPNYHWQETAYLLVYMKMEC
RTP4 (SEQ ID NO:22)	gi|54607029|ref|NP _071430.2| receptor- transporting protein 4 [Homo sapiens]	MVVDFWTWEQTFQELIQEAKPRATWTLKLDGNLQLDCLAQGWK QYQQRAFGWFRCSSCQRSWASAQVQIL CHTYWEHWTSQGQVRMRLFGQRCQKCSWSQYEMPEFSSDSTMR ILSNLVQHILKKYYGNGTRKSPEMPVI LEVSLEGSHDTANCEACTLGICGQGLKSCMTKPSKSLLPHLKT GNSSPGIGAVYLANQAKNQSAEAKEAK GSGYEKLGPSRDPDPLNICVFILLLVFIVVKCFTSE
DNAPTP6 (SEQ ID NO:23)	gi|154426310|ref|N P_056350.2| SPATS2-like protein isoform a [Homo sapiens]	MAELNTHVNVKEKIYAVRSVVPNKSNNEIVLVLQQFDFNVDKA VQAFVDGSAIQVLKEWNMTGKKKNNKR KRSKSKQHQGNKDAKDKVERPEAGPLQPQPPQIQNGPMNGCEK DSSSTDSANEKPALIPREKKISILEEP SKALRGVTEGNRLLQQKLSLDGNPKPIHGTTERSDGLQWSAEQ PCNPSKPKAKTSPVKSNTPAAHLEIKP DELAKKRGPNIEKSVKDLQRCTVSLTRYRVMIKEEVDSSVKKI KAAFAELHNCIIDKEVSLMAEMDKVKE EAMEILTARQKKAEELKRLTDLASQMAEMQLAELRAEIKHFVS ERKYDEELGKAARFSCDIEQLKAQIML CGEITHPKNNYSSRTPCSSLLPLLNAHAATSGKQSNFSRKSST HNKPSEGKAANPKMVSSLPSTADPSHQ TMPANKQNGSSNQRRRFNPQYHNNRLNGPAKSQGSGNEAEPLG KGNSRHEHRRQPHNGFRPKNKGGAKNQ EASLGMKTPEAPAHSEKPRRRQHAADTSEARPFRGSVGRVSQC

		NLCPTRIEVSTDAAVLSVPAVTLVA

[0127] In some aspects, the type I IFN GS that can be suppressed with a fixed dose of of an antibody or antigen-binding fragment thereof that modulates type I IFN activity comprises up-regulated expression or activity of at least 4 PD markers. In some aspects, the type I IFN GS comprises up-regulated expression or activity of at least 5 PD markers. In some aspects, the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2. In some aspects, the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

[0128] In some aspects, the genes in a type I IFN GS that can be suppressed with a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity are selected based on three primary criteria: (i) prevalence and magnitude of over-expression in patients compared to healthy controls; (ii) ability to be induced in whole blood from healthy donors *ex vivo* by type I IFN; and, (iii) the ability to be substantially suppressed by an antibody or antigen-binding fragment thereof that modulates type I IFN activity, *e.g.*, MEDI-546 *ex vivo* in healthy donor peripheral blood mononuclear cells after stimulation by SLE serum (see. *e.g.*, Yao *et al.*, Hum. Genomics Proteomics 2009:374312 (2009)).

[0129] In some aspects, a type I IFN GS score corresponding to up-regulated expression of the type I IFN GS in blood and lesional skin of patients can be calculated from the expression level of the genes in the type I IFN GS. The type I IFN GS score and its suppression after treatment can be measured, for example, in whole blood (*e.g.*, in peripheral blood) or skin samples from a patient.

[0130] A fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity can suppress or neutralize a type I IFN GS of the present disclosure. This suppression can be a reduction in the expression levels in at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21 up-regulated genes in the type I IFN GS. In some specific aspects, the suppression is a reduction in the expression levels of 4 up-regulated genes in the type I IFN GS. In other specific aspects, the suppression is a reduction in the expression levels of 5 up-regulated genes in the type I IFN GS. Suppression can be partial suppression or full suppression of the expression of the genes in the type I IFN GS.

[0131] Suppression of the up-regulated expression of the type I IFN GS can be a reduction of at least 2%, at least 3%, at least 4%, at least 5%, at least 7%, at least 8%, at least 10%, at least 15%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, or at least 90% of any of the at least one, at least two, at least three, at least five, at least seven, at least eight, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21 up-regulated genes in a type I IFN GS.

[0132] Alternatively, suppression of the up-regulated expression of the type I IFN GS refers to a reduction of expression levels of at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 16, at least 17, at least 18, at least 19, at least 20 or at least 21 genes, of at most 50%, at most 45%, at most 40%, at most 35%, at most 30%, at most 25%, at most 20%, at most 15%, at most 10%, at most 5%, at most 4%, at most 3%, at most 2%, or at most 1% of the expression levels of those genes in a control or reference. In some aspects, the antibody or antigen-binding fragment thereof that modulates type I IFN activity, *e.g.*, an anti-IFNAR antibody such as MEDI-546 can neutralize the type I IFN GS at fixed doses of about 100 mg, about 300 mg, or about 1000 mg.

[0133] A number of controls or reference samples can be used to determine the degree of suppression of a type I IFN GS prior to treatment or after treatment with a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity. For example, a type I IFN GS after treatment with a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity agent can be compared to the type I IFN GS of the subject prior to the administration of the fixed dose. In other aspects, during a succession of treatment administrations, a type I IFN GS after treatment with a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity can be compared to the type I IFN GS of the patient analyzed prior to the administration of the fixed dose. In other aspects, other references such as the average type I IFN GS in a population, the type I IFN GS in a non-responsive patient, or the type I IFN GS in a relapsed patient can be used for comparison.

[0134] Up- or down-regulation of gene expression or activity of PD markers in a type I IFN GS can be determined by any means known in the art. For example, up- or down-regulation of gene expression can be detected by determining mRNA levels. mRNA

expression may be determined, for exampler, by northern blotting, slot blotting, quantitative reverse transcriptase polymerase chain reaction, or gene chip hybridization techniques. See, *e.g.*, U.S. Pat. Nos. 5,744,305 and 5,143,854 for examples of making nucleic acid arrays for gene chip hybridization techniques. See also Hrovat *et al.*, Cell. Mol. Biol. Lett. 1: 55-69 (2010), Svec *et al.*, Int. J. Exp. Pathol. 1: 44-53 (2010), and Kurokawa *et al.*, Cancer Chemother. Pharmacol. 3: 427-436 (2010), for examples of how to use the TAQMAN® method for measuring gene expression.

[0135] Primers that selectively bind to targets in polymerase chain reactions (PCR) can be chosen based on empirically determining primers that hybridize in a PCR reaction and produce sufficient signal to detect the target over background, or can be predicted using the melting temperature of the primer:target duplex as described in Maniatis *et al.* Molecular Cloning, Second Edition, Section 11.46 (1989). Similarly, nucleic acid probes for detecting PCR products in a TAQMAN® or related method can be empirically chosen or predicted. Such nucleic acid primers and probes (collectively "oligonucleotides") may be between 10 and 30 nucleotides or greater in length.

[0136] Up- or down-regulation of gene expression or activity of PD markers in a type I IFN GS can also be determined by detecting protein levels. Methods for detecting protein expression levels include, for example, immuno-based assays such as enzyme-linked immunosorbant assays, western blotting, protein arrays, and silver staining. Up- or down-regulation of gene expression or activity of the PD markers in the type I IFN GS can be also determined by detecting activity of proteins including, but not limited to, detectable phosphorylation activity, de-phosphorylation activity, or cleavage activity. Furthermore, up- or down-regulation of gene expression or activity of PD markers in the type I IFN GS may be determined by detecting any combination of these gene expression levels or activities. Any combination of decreased number and decrease level of PD markers in the type I IFN GS can indicate efficacy.

[0137] The present disclosure provides specific methods of suppressing a type I IFN GS in a patient. For example, a type I IFN GS can be suppressed by measuring the type I IFN GS score in a sample taken from a patient having a type I IFN-mediated disease or disorder, relative to a baseline type I IFN GS score; and, subsequently administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN

activity if the patient's type I IFN GS score is elevated, wherein the administration of the antibody or antigen-binding fragment thereof suppresses the IFN GS of the patient.

[0138] A type I IFN GS can also be suppressed by administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; measuring the patient's type I IFN GS score relative to a baseline IFN GS score; and, then increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the IFN GS of the patient.

[0139] In some aspects, a type I IFN GS can be suppressed by submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of an type I IFN GS score; determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the IFN GS of the patient.

[0140] Another way of suppressing a type I IFN GS in a patient comprises administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; submitting a sample taken from the patient for measurement of a type I IFN GS score; determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0141] In other aspect, a type I IFN GS can be suppressed by submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0142] In certain aspects, a type I IFN GS can be suppressed by administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-

binding fragment thereof that modulates type I IFN activity; submitting a sample taken from the patient for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and, increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0143] In another aspect, a method of suppressing a type I IFN GS in a patient comprises measuring a type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder; determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient. In a certain aspect, a method of suppressing a type I IFN GS in a patient comprises obtaining a sample from a patient having a type I IFN- mediated disease or disorder, where the patent has received a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; measuring an type I IFN GS score from the sample; determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

[0144] One skilled in the art will appreciate, for example, that samples can be obtained by different methods known in the art, that the samples can be obtained from different tissues, that samples can be obtained at different times, and that different individuals and entities can perform the different steps in the methods disclosed above, as it is discussed in the following sections.

Methods of Treatment, Monitoring, and Prognosing

[0145] The present disclosure also provides methods of treatment with an antibody or antigen-binding fragment thereof that modulates type I IFN activity and can suppress a type I IFN GS at fixed doses, thus resulting in a decrease in one or more symptoms of the type I IFN-mediated disease or disorder.

[0146] Treatment with the antibody or antigen-binding fragment thereof that modulates type I IFN activity can result in fewer flare-ups related to the type I IFN-mediated disease or disorder, improve prognosis for the patient having the type I IFN-mediated disease or disorder, provide a higher quality of life for the patient, alleviate the need to co-administer second therapeutic agents (*e.g.*, steroids), lessen the dosage of administration of a second agent to the patient, or reduces the number of hospitalizations of the patient that are related to the type I IFN-mediated disease or disorder.

[0147] In order to treat a patient, samples from the patient can be obtained before or after the administration of an antibody or antigen-binding fragment thereof that modulates type I IFN activity. In some cases, successive samples can be obtained from the patient after treatment has commenced or after treatment has ceased. Samples can, *e.g.*, be requested by a healthcare provider (*e.g.*, a doctor) or healthcare benefits provider, obtained and/or processed by the same or a different healthcare provider (*e.g.*, a nurse, a hospital) or a clinical laboratory, and after processing, the results can be forwarded to yet another healthcare provider, healthcare benefits provider or the patient. Similarly, the measuring/determination of type I IFN GS scores, comparisons between type IFN GS scores can be, evaluation of the type I IFN GS scores and treatment decisions can be performed by one or more healthcare providers, healthcare benefits providers, and/or clinical laboratories.

[0148] As used herein, the term "healthcare provider" refers individuals or institutions which directly interact and administer to living subjects, *e.g.*, human patients. Non-limiting examples of healthcare providers include doctors, nurses, technicians, therapist, pharmacists, counselors, alternative medicine practitioners, medical facilities, doctor's offices, hospitals, emergency rooms, clinics, urgent care centers, alternative medicine clinics/facilities, and any other entity providing general and/or specialized treatment, assessment, maintenance, therapy, medication, and/or advice relating to all, or any portion of, a patient's state of health, including but not limited to general medical, specialized medical, surgical, and/or any other type of treatment, assessment, maintenance, therapy, medication and/or advice.

[0149] As used herein, the term "clinical laboratory" refers to a facility for the examination or processing of materials derived from a living subject, *e.g.*, a human being. Non-limiting examples of processing include biological, biochemical, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, genetic, or other examination of materials derived from the human body for the purpose of providing

information, *e.g.*, for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of living subjects, *e.g.*, human beings. These examinations can also include procedures to collect or otherwise obtain a sample, prepare, determine, measure, or otherwise describe the presence or absence of various substances in the body of a living subject, *e.g.*, a human being, or a sample obtained from the body of a living subject, *e.g.*, a human being.

[0150] As used herein, the term "healthcare benefits provider" encompasses individual parties, organizations, or groups providing, presenting, offering, paying for in whole or in part, or being otherwise associated with giving a patient access to one or more healthcare benefits, benefit plans, health insurance, and/or healthcare expense account programs.

[0151] In some aspects, a healthcare provider can administer or instruct another healthcare provider to administer an antibody or antigen-binding fragment thereof that modulates type I IFN activity. A healthcare provider can implement or instruct another healthcare provider or patient to perform the following actions: obtain a sample, process a sample, submit a sample, receive a sample, transfer a sample, analyze or measure a sample, quantify a sample, provide the results obtained after analyzing/measuring/quantifying a sample, receive the results obtained after analyzing/measuring/quantifying a sample, compare/score the results obtained after analyzing/measuring/quantifying one or more samples, provide the comparison/score from one or more samples, obtain the comparison/score from one or more samples, administer a therapeutic agent (*e.g.*, an antibody or antigen-binding fragment thereof that modulates type I IFN activity), commence the administration of a therapeutic agent, cease the administration of a therapeutic agent, continue the administration of a therapeutic agent, temporarily interrupt the administration of a therapeutic agent, increase the amount of administered therapeutic agent, decrease the amount of administered therapeutic agent, continue the administration of an amount of a therapeutic agent, increase the frequency of administration of a therapeutic agent, decrease the frequency of administration of a therapeutic agent, maintain the same dosing frequency on a therapeutic agent, replace a therapeutic agent by at least another therapeutic agent, combine a therapeutic agent with at least another treatment or additional therapeutic agent.

[0152] In some aspects, a healthcare benefits provider can authorize or deny, for example, collection of a sample, processing of a sample, submission of a sample, receipt of a sample, transfer of a sample, analysis or measurement a sample, quantification a sample,

provision of results obtained after analyzing/measuring/quantifying a sample, transfer of results obtained after analyzing/measuring/quantifying a sample, comparison/scoring of results obtained after analyzing/measuring/quantifying one or more samples, transfer of the comparison/score from one or more samples, administration a therapeutic agent, commencement of the administration of a therapeutic agent, cessation of the administration of a therapeutic agent, continuation of the administration of a therapeutic agent, temporary interruption of the administration of a therapeutic agent, increase of the amount of administered therapeutic agent, decrease of the amount of administered therapeutic agent, continuation of the administration of an amount of a therapeutic agent, increase in the frequency of administration of a therapeutic agent, decrease in the frequency of administration of a therapeutic agent, maintain the same dosing frequency on a therapeutic agent, replace a therapeutic agent by at least another therapeutic agent, or combine a therapeutic agent with at least another treatment or additional therapeutic agent. In addition a healthcare benefits provides can, *e.g.*, authorize or deny the prescription of a therapy, authorize or deny coverage for therapy, authorize or deny reimbursement for the cost of therapy, determine or deny eligibility for therapy, etc.

[0153] In some aspects, a clinical laboratory can, for example, collect or obtain a sample, process a sample, submit a sample, receive a sample, transfer a sample, analyze or measure a sample, quantify a sample, provide the results obtained after analyzing/measuring/quantifying a sample, receive the results obtained after analyzing/measuring/quantifying a sample, compare/score the results obtained after analyzing/measuring/quantifying one or more samples, provide the comparison/score from one or more samples, obtain the comparison/score from one or more samples,

[0154] The above enumerated actions can be performed by a healthcare provider, healthcare benefits provider, or patient automatically using a computer-implemented method (*e.g.*, via a web service or stand-alone computer system).

[0155] Patient samples include any biological fluid or issue, such as whole blood, serum, muscle, saliva, Samples include any biological fluid or tissue, such as whole blood, serum, muscle, saliva, urine, synovial fluid, bone marrow, cerebrospinal fluid, nasal secretions, sputum, amniotic fluid, bronchoalveolar lavage fluid, peripheral blood mononuclear cells, total white blood cells, lymph node cells, spleen cells, tonsil cells, or skin. In some specific

aspects, that patient sample is blood or a fraction thereof, muscle, skin, or a combination thereof. Patient samples can be obtained by any means known in the art.

[0156] Accordingly, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising measuring a type I IFN GS score in a sample taken from a patient having a type I IFN- mediated disease or disorder, relative to a baseline IFN GS score; and administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder. Also provided is a method of treating a patient having a type I IFN-mediated disease or disorder comprising administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; measuring the patient's type I IFN GS score relative to a baseline IFN GS score; and increasing the amount or frequency of subsequent fixed doses if the patient's IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0157] In some aspects, the present disclosure provides a method of treating a patient having a type I IFN-mediated disease or disorder comprising: submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score; determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

[0158] In other aspects, a method of treating a patient having a type I IFN-mediated disease or disorder comprises administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; submitting a sample taken from the patient for measurement of an IFN GS score; determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and, increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0159] In some aspects, the method of treating a patient having a type I IFN-mediated disease or disorder comprises submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score and comparison to a baseline IFN GS score; and administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder. In other aspects, the method of treating a patient having a type I IFN-mediated disease or disorder comprises administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; submitting a sample taken from the patient for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0160] In some aspects, the method of treating a patient having a type I IFN-mediated disease or disorder comprises measuring a type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder; determining whether the patient's IFN GS score is elevated relative to a baseline type I IFN GS score; instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated; wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder. In some aspects, the method of treating a patient having a type I IFN-mediated disease or disorder comprises obtaining a sample from a patient having a type I IFN- mediated disease or disorder, where the patent has received a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; measuring a type I IFN GS score from the sample; determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated; wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

[0161] In methods of monitoring or prognosing disease progression of a patient having a type I IFN-mediated disease or disorder, samples from the patient may be obtained before or after administration of a therapeutic agent. In some cases, the therapeutic agent can be a

different antibody or other biologic (*e.g.*, fusion protein or conjugate) or small molecule. In this respect, the methods provided in the present disclosure can be applied to a patient undergoing a first therapy, determining a type I IFN GS score, and determining according to that type I IFN GS score whether to continue or discontinue the first therapy. The methods provided in the present disclosure can be applied to a patient undergoing a first therapy, determining a type I IFN GS score, and determining according to that type I IFN GS score whether to replace or combine the first therapy with the administration of a fixed dose of an antibody or antigen-binding fragment thereof or small molecule that modulates type I IFN activity.

[0162] The sample obtained from the patient may be obtained prior to a first administration of a therapeutic agent, *e.g.*, antibody or antigen-binding fragment thereof or small molecule that modulates type I IFN activity. In this situation, the patient is naïve to the antibody or antigen-binding fragment thereof that modulates type I IFN activity. Alternatively, the sample obtained from the patient can occur after administration of a fixed dose of the antibody or antigen-binding fragment thereof that modulates type I IFN activity in the course of treatment. For example, the therapeutic agent can be administered prior to the initiation of the monitoring protocol. Following administration a fixed dose of the antibody or antigen-binding fragment thereof that modulates type I IFN activity, additional samples can be obtained from the patient and type I IFN GS measurement be compared. The samples can be of the same type or of a different type. For example, each sample obtained can be a blood sample, or each sample obtained can be a skin or muscle sample. The type I IFN GS detected in each sample can be the same, can overlap substantially, or can be similar.

[0163] The sample can be obtained at any time before or after the administration of a fixed dose of the antibody or antigen-binding fragment thereof that modulates type I IFN activity. The sample obtained after the administration of the fixed dose of the antibody or antigen-binding fragment thereof that modulates type I IFN activity can be obtained at least 2, at least 3, at least 4, at least 5, at least 7, at least 8, at least 9, at least 10, at least 12, or at least 14 days after administration.

[0164] The sample obtained after administration of the fixed dose of antibody or antigen-binding fragment thereof that modulates type I IFN activity can be obtained at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, or at least 8 weeks after administration. The sample obtained after administration of the fixed dose of antibody or antigen-binding

fragment thereof that modulates type I IFN activity can be obtained at least 2, at least 3, at least 4, at least 5, or at least 6 months following administration.

[0165] Additional samples can be obtained from the patient following administration of a fixed dose of the antibody or antigen-binding fragment thereof that modulates type I IFN activity. At least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 12, at least 15, at least 20, at least 25 samples can be obtained from the patient to monitor progression or regression of the type I IFN-mediated disease or disorder over time. Progression of the type I IFN-mediated disease or disorder can be monitored over a time period of at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, at least 5 years, at least 10 years, or over the lifetime of the patient.

[0166] Additional samples can be obtained from the patient at regular intervals such as at monthly, bi-monthly, once a quarter year, twice a year, or yearly intervals. The samples can be obtained from the patient following administration of a fixed dose of the antibody or antigen-binding fragment thereof that modulates type I IFN activity at regular intervals. For instance, the samples can be obtained from the patient at one week, or at two weeks, or at three weeks, or at one month, or at two months following each administration of the fixed dose of antibody or antigen-binding fragment thereof that modulates type I IFN activity. Alternatively, multiple samples may be obtained from the patient following each administration.

[0167] Disease progression in a patient can similarly be monitored in the absence of administration of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity. Samples can periodically be obtained from the patient having the disease or disorder. Disease progression can be identified if the type I IFN GS score increases in a later-obtained sample relative to an earlier obtained sample. The type I IFN GS score can increase by at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10. Disease progression can be identified if the type IFN GS score increases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. Disease progression may be identified if level of any given PD marker in the type I IFN GS increases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%,

at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. The number of up-regulated PD markers in the type I IFN GS with increased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, or at least 20. Any combination of increased number and increased level of up-regulated in the type I IFN GS can indicate disease progression.

[0168] Disease regression can also be identified in a patient having a disease or disorder, not treated by a therapeutic agent. In this instance, regression can be identified if the type I IFN GS score decreases in a later-obtained sample relative to an earlier obtained sample. Disease regression can be identified if the level of any given up-regulated PD marker in the type I IFN GS decreases by at least 10%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 95%. The number of up-regulated PD markers in the type I IFN GS with decreased levels may be at least 1, at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, or at least 20. Disease progression or disease regression can be monitored by obtaining samples over any period of time and at any interval.

[0169] Disease progression or disease regression can be monitored by obtaining samples over the course of at least 1 week, at least 2 weeks, at least 3 weeks, at least 4 weeks, at least 5 weeks, at least 6 weeks, at least 7 weeks, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 1 year, at least 2 years, at least 3 years, at least 4 years, at least 5 years, at least 10 years, or over the lifetime of the patient. Disease progression or disease regression can be monitored by obtaining samples at least monthly, bi-monthly, once a quarter year, twice a year, or yearly. The samples need not be obtained at strict intervals.

[0170] Variance in the type I IFN GS scores among the samples after administration of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity can guide treatment strategy of the type I IFN-mediated disease or disorder. Treatment strategy can be, for example, increase or decrease in dosage of a particular therapeutic, increase or decrease the frequency of administration of a particular therapeutic, removal or addition of particular therapeutics administered to a patient, commencement or suspension or treatment, etc. Accordingly, the present disclosure provides specific methods to monitor therapeutic efficacy of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder.

In some aspects, the method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprises measuring a first type I IFN GS score in a sample taken from a patient having a type I IFN-mediated disease or disorder; administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; measuring a second type I IFN GS score in a sample taken from the patient following antibody administration; and comparing the second type I IFN GS score to the first type I IFN GS score; wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

[0171] In one aspect, the method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprises submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a first type I IFN GS score; administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a second type I IFN GS score; and comparing the second type I IFN GS score to the first type I IFN GS score; wherein a decrease between the first and second IFN GS scores indicates efficacy or good prognosis. In another aspect, the method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprises measuring a first type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder; instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity; measuring a second type I IFN GS score in a sample taken from the patient following antibody administration; and comparing the second type I IFN GS score to the first type I IFN GS score; wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

[0172] In some specific aspects, the method of monitoring therapeutic efficacy further comprises, for example:

(a) measuring the patient's type I IFN GS score relative to a baseline IFN GS score, relative to the patient's earlier IFN GS score, or both, after the administration of the fixed dose;

(b) measuring the patient's type I IFN GS score relative to a baseline IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of a subsequent fixed dose;

(c) submitting a sample from the patient for measurement of the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of the fixed dose;

(d) submitting a sample from the patient for measurement of the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of a subsequent fixed dose;

(e) a combination of two or more of the steps above.

[0173] In other aspect, the method of monitoring therapeutic efficacy further comprises, for example:

(a) increasing/decreasing the amount or frequency of subsequent fixed doses if the patent's IFN GS score remains elevated;

(b) increasing/decreasing the amount or frequency of subsequent fixed doses if the patent's IFN GS score remains elevated;

(c) increasing/decreasing the amount or frequency of subsequent fixed doses if the patent's IFN GS score remains elevated;

(d) a combination of two or more of the steps above.

Kits

[0174] Also provided in the present disclosure is a kit for detecting a type I IFN genetic signature (IFN GS) common to two diseases whose pathogeneses are mediated by type I IFN. The kit can comprise containers filled with nucleic acid probes (e.g., oligonucleotides) capable of hybridizing nucleic acids (*e.g.*, mRNA) encoding the PD markers disclosed herein or fragments thereof. Specifically, the present disclosure provides a kit for detecting a type I IFN genetic signature (type I IFN GS) common to two diseases, *e.g.*, SSc and SLE, whose pathogeneses are mediated by type I IFN comprising a set of diagnostic assays capable of measuring differentially regulated pharmacodynamic (PD) marker genes in a patient sample,

wherein the type I IFN GS is suppressed by the administration of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity.

[0175] In some aspects, the kit comprises oligonucleotide probes for at least one PD marker gene selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. In other aspects, the kit can comprise 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 21 oligonucleotide probes capable of detecting the PD marker genes described above. In some aspects, a PD marker genes can be detected by two or more oligonucleotide probes. Oligonucleotide probes can be labeled by any method known in the art, *e.g.*, using fluorescent or radioactive labels. Oligonucleotide probes in the kit can be unlabeled. In some aspects, the kit also contains controls and/or calibration standards.

[0176] In other aspects, the kit comprises oligonucleotide probes for at least five of the PD marker genes, *e.g.*, IFI27, IFI44, IFI44L, and RSAD2. In some aspects, the kit also comprises oligonucleotide probes for IFI6.

[0177] In some aspects, the kit can be used for diagnostic or investigational purposes on patient samples such as blood or a fraction thereof, muscle, skin, or a combination thereof. The kit can comprise oligonucleotide capable of hybridizing to DNA and/or RNA. Such DNA and/or RNA can be a full gene nucleic acid, or correspond to a fragment or degradation product. In some aspects, the kit can be used the PD markers disclosed herein or fragments thereof, preferably in a purified form.

[0178] Optionally associated with the kit's container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Computer Implemented Methods and Computer-Readable Media

[0179] The present disclosure also provides computer-implemented a method for predicting an optimal dosage regimen with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, a method for identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating a type I IFN-mediated disease or disorder, a method for identifying a patient as a

candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, and a method of designing a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity.

[0180] In these methods, PK/PD data from a second type I IFN-mediated disease or disorder is inputted into a computer system comprising a pharmacokinetic-pharmacodynamic (PK/PD) stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PK/PD data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model. The adjusted PK/PD stochastic model can be applied to the inputted PK/PD data from the second type I IFN-mediated disease or disorder. Based on the application of the adjusted PK/PD stochastic model to the inputted PK/PD from the second type I IFN-mediated disease or disorder, an optimal dosage regimen, a candidate therapeutic agent, a candidate patient for therapy, or a personalized therapy can be identified.

[0181] The present disclosure also provides a computer-readable medium containing program instructions for predicting an optimal dosage regimen with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, program instructions for identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating a type I IFN-mediated disease or disorder, instructions for identifying a patient as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, and instructions for designing a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity. The execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of (a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder; (b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and, (c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder. The output of the simulation identifies, *e.g.*, an optimal dosage of the antibody or antigen-binding fragment thereof that modulates type I IFN activity in the second type I IFN-mediated disease or

disorder, an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating the second type I IFN-mediated disease or disorder, a patient with the second type I IFN-mediated disease as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, or a personalized therapy for treating the second type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity.

[0182] The computer implemented methods and computer-readable media disclosed herein can be implemented as a tool to be used by healthcare providers, either as a stand-alone tool or via a server. The tool can include computer-readable components, an input/output system, and one or more processing units. The input/output system can be any suitable interface between user and computer system, for input and output of data and other information, and for operable interaction with the one or more processing units. In one aspect, data to be inputted into the tool can be derived from *in vitro* or *in vivo* sources. In some aspects, the user can evaluate alternatives by changing one or more of the parameters and constants of the system. In a forward mode of operation, the user can predict absorption, individual parameters of absorption, as well as one or more other bioavailability parameters of a compound from relatively few input variables. Additionally, the user can evaluate alternatives by changing any of the parameters and constants of the system, and observe the ripple effect of the change in one or more parameters on all other parameters. For instance, the user can evaluate alternative absorption profiles using "What if" analysis with any parameter of the system.

[0183] In a backward mode of operation, the user can specify one or more objective parameters of a formulation of interest and the tool and method of the disclosure would generate alternatives to satisfy the objective. The user can also vary input dosing and formulation parameters for "What if" analysis. Simulated absorption profiles can then be utilized for preparing suitable formulations and/or dosing regimens. Solubility, permeability, bioavailability, doses and the like also may be estimated in the backward mode of operation.

[0184] In some aspects, the input/output system may provide direct input form measuring equipment. The input/output system preferably provides an interface for a standalone computer or integrated multi-component computer system having a data processor, a memory, and a display. Data may be entered numerically, as a mathematical expression or as a graph that represents a physiological or pharmacokinetic parameter.

[0185] All patents and publications referred to herein are expressly incorporated by reference in their entireties.

Examples

MATERIALS AND METHODS

Patient Population and Study Design.

[0186] An open-label, cohort dose-escalation Phase 1 study in adult patients with diffuse scleroderma (SSc) (ClinicalTrials.gov identifier NCT00930683) was conducted in accordance with the Declaration of Helsinki (1996), the International Conference on Harmonisation Guidelines for Good Clinical Practice (Topic E6), Institutional Review Boards (21 CFR Part 56) and Investigational New Drug Application (21 CFR Part 312), to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity and pharmacodynamics (PD) of single and multiple intravenous doses of MEDI-546, a fully human monoclonal antibody directed against subunit 1 of the type I Interferon Receptor. The protocol was reviewed and approved by the Institutional Review Board or Independent Ethics Committee of each participating center prior to study initiation. Written informed consent was obtained from each participant before the conduct of any protocol-specific activity or study entry.

[0187] A total of 34 adult diffuse SSc patients who had skin thickening in an area suitable for repeat biopsy were enrolled to receive single (0.1, 0.3, 1.0, 3.0, 10.0, or 20.0 mg/kg) or multiple doses (0.3, 1.0, or 5.0 mg/kg weekly × 4) of MEDI-546, which was administered as an intravenous (IV) infusion over at least 30 minutes. The starting dose of 0.1 mg/kg was based on the human equivalence dose (HED) of primate pharmacologically active dose (PAD) and the predicted short duration of IFNAR occupancy by MEDI-546 in humans from translational simulations. Cohort designation, patient demographics, and baseline type I IFN GS status are summarized in TABLE 4.

TABLE 4. Summary of Patient Demographics for MEDI-546 First Time in Human (FTIH) Study in Adult Patients with SSc. Values are shown as median (range) or count (percentage).

	N	**Age, y**	**Weight, kg**	**Gender,**	**Race,**	**GS_{IFN}**	**GS_{IFN}**

				Female	**white**	**Blood, Positive**	**Skin, Positive**
Single-Dose (mg/kg)							
0.1	1	41 (41-41)	64 (64-64)	1 (100%)	1 (100%)	0 (0%)	0 (0%)
0.3	4	59.5 (45-69)	60 (50-61)	3 (75%)	3 (75%)	4 (100%)	2 (50%)
1	4	44 (38-54)	71 (42-103)	4 (100%)	2 (50%)	2 (50%)	2 (50%)
3	4	34.5 (19-44)	66 (48-112)	3 (75%)	2 (50%)	3 (75%)	1 (25%)
10	4	46 (35-65)	65 (50-114)	4 (100%)	2 (50%)	3 (75%)	2 (50%)
20	4	46.5 (35-54)	70 (54-81)	3 (75%)	3 (75%)	3 (75%)	1 (25%)
Multiple-Dose (mg/kg, QWx4)							
0.3	4	46 (27-51)	86 (78-102)	2 (50%)	4 (100%)	1 (25%)	0 (0%)
1.0	4	46.5 (42-62)	65 (50-124)	3 (75%)	4 (100%)	3 (75%)	2 (50%)
5.0	4	55 (43-77)	66 (48-107)	4 (80%)	4 (80%)	3 (60%)	1 (20%)
Total	**34**	**46 (19-77)**	**65 (42-124)**	**27 (79%)**	**25 (74%)**	**22 (65%)**	**11 (32%)**

PK Sample Collection and Bioanalytical Assays.

[0188] Serum PK samples were obtained from all patients pre-dose and at pre-designated timepoints up to Day 84 (single-dose cohorts) or Day 105 (multiple-dose cohorts) for the measurement of MEDI-546 concentrations using a validated electrochemiluminescence (ECL) assay on the Meso Scale Discovery (MSD) platform. In brief, MEDI-546 was captured by biotinylated soluble interferon alpha receptor (sIFNAR1) bound to streptavidin-coated MSD plates. The captured MEDI-546 was detected with a sulfo-TAG labeled monoclonal antibody specifically targeting distinct amino acids within the Fc region of MEDI-546, which was mutated to eliminate antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). An MSD read buffer was added and the plates were placed on a MSD Sector™ Imager Model 6000 reader for the generation

and measurement of ECL signals. The assay had a measurement range of 20 to 1,280 ng/mL of MEDI-546 in human serum.

Total RNA Extraction and Microarray Processing.

[0189] Whole blood samples were collected from all patients at screening and pre-designated PK visits to determine levels of mRNA for type I IFN-inducible genes. Skin biopsies were also collected pre-dose (Day 0) and on Day 7 (single-dose) or Day 28 (multiple-dose). The Human Genome U133 Plus 2.0 array platform (Affymetrix, Santa Clara, CA) was used to evaluate the effects of MEDI-546 in whole blood and in lesional skin from matched SSc patient specimens from whom skin biopsy samples were collected. The general procedures for sample processing and data analysis for microarray studies have been described previously (Yao et al., Hum. Genomics Proteomics 2009:374312 (2009); Yao et al., PLoS One 3:e2737 (2008)).

Calculation of the type I Interferon (IFN) Gene Signature (GS).

[0190] The type I IFN GS score, a quantity used to express the amount of type I IFN activity present in an individual, was measured in the whole blood or skin. The type I IFN GS score was calculated using a set of five genes (IFI27, IFI44, IFI44L, RSAD2, and IFI6) for each subject. On a log2 scale, the arithmetic means were calculated for each gene in a set of 24 normal control samples and the difference for each gene was calculated between each individual disease subject and the mean vector of the normal control samples.

[0191] The five type I IFN-inducible genes were used to generate subsets of the fold change (FC) data matrix calculated above (dimensions = X * *n*, where *n* was the number of total subject samples). The median value across the five genes for each subject was calculated as the FC score. The FC values were then transposed to a linear scale using the formula 2^{FC}, and denoted as the type I IFN GS score. For each subject, the type I IFN GS score was calculated at both baseline and each time point post dose. Then the median type I IFN GS scores for each dose cohort were plotted across time to indicate the degree of suppression of type I IFN activity at different dosage levels.

[0192] Target modulation was then calculated as the ratio of the type I IFN GS score post dose to the type I IFN GS score pre-dose (GS_0). This quantity was represented as a percentage and for each dose cohort, scaled to the GS_0 value. Then this quantity was

subtracted from 100% to indicate the remaining percentage of type I IFN GS, so all patients at day 0 (pre-dose) started with 100% target modulation.

[0193] Only patients with a positive type I IFN GS score at baseline had PD data calculated using both methods described above. The distribution of type I IFN GS scores at baseline varied for different disease indications and specimen source. For example, the baseline median type I IFN GS scores for SLE patient blood specimens were higher than those of SSc patients (FIG. 1). This same pattern was reinforced in the skin specimens of these two diseases. In SLE patients, the median baseline type I IFN GS scores in skin were slightly higher than in blood specimens. In SSc patients, the median type I IFN GS scores in blood were higher than those in skin specimens. As compared to normal healthy controls, the type I IFN GS scores were higher in both disease and specimen source distributions.

Receptor Internalization Kinetics.

[0194] The internalization of MEDI-546 upon binding to IFNAR1 was assessed using live-cell confocal fluorescent imaging technology. MEDI-546 and an isotype control IgG were fluorescently tagged with Alexa647 using a dye-conjugation kit (A-20186) from Invitrogen (Life Technologies Corp, Carlsbad, CA). Reaction mixtures were purified from unincorporated fluorescent molecules using size-exclusion mini-columns provided in the kit. IFNAR1-expressing THP-1 cells were maintained in suspension using RPMI growth medium containing 10% FBS, and seeded in a fresh growth medium at 2x105 cells/mL overnight prior to the experiments. On the day of experiments, THP-1 cells were washed and resuspended to a concentration of $3x10^6$ cells/mL.

[0195] Cell suspensions were first stained for 10-20 min with cytosol dye, CFSE, from Invitrogen (Life Technologies Corp, Carlsbad, CA) in a CO_2 incubator at 37°C. Excess CFSE was removed by two washes with 1xPBS. Cells were then pre-chilled, blocked with FcR blockers to prevent FcR-mediated binding, and stained on ice with 1 μg/mL of MEDI-546-Alexa647 or IgG-Alexa647 for 1-2 hours. Following the removal of unincorporated antibodies by centrifugation, cells were resuspended to initial volumes, and dispensed into the wells of 384-well imaging plates.

[0196] Cells were then transferred to the environmental control chamber (37°C, 5% CO2 and 70% humidity) of the confocal fluorescent imager, Opera (Perkin Elmer, Waltham, MA), where fluorescence images were acquired using a 40x objective lens with a numerical

aperture of 0.9 at designated time points to monitor the kinetics of MEDI-546-Alexa647 internalization. The acquired kinetic images were analyzed using an internally-developed algorithm that quantifies fluorescence intensity in the membrane and cytoplasmic compartments of the cells. Accumulation of MEDI-546-Alexa647 fluorescence in the cytoplasm region over time was normalized by the total fluorescence (membrane plus cytoplasm) and the normalized data was used for the assessment of the internalization rate.

PK-PD Model Structure

[0197] A 2-compartment PK model with parallel first-order and IFNAR-mediated elimination pathways was developed to describe the observed serum concentration profiles of MEDI-546 in SSc patients (FIG. 4). The first-order elimination pathway represented the clearance of MEDI-546 by the reticulo-endothelial system (CLres), in the same way as for an endogenous IgG. The nonlinear elimination pathway was presumably associated with the IFNAR-mediated clearance (antigen-sink effect). R represented the target receptor (IFNAR1) and AbR was the antibody-receptor complex.

[0198] MEDI-546 bound to the receptor (k_{on}, k_{off}), and the antibody-receptor complex was subsequently internalized and degraded (k_{int}) inside the cells. Parameters k_{syn} and k_{deg} represented the endogenous production and degradation of IFNAR1, respectively.

[0199] The 2 compartmental PK model with first-order elimination and target-mediated drug disposition with quasi-steady-state approximation was described by the following set of differential equations:

$$k_{on}C \cdot R - (k_{off} + k_{int})RC = 0 \quad \text{(Equation 1)}$$

$$\frac{C \cdot R}{RC} = \frac{k_{off} + k_{int}}{k_{on}} = K_D + \frac{k_{int}}{k_{on}} = K_s \quad \text{(Equation 2)}$$

$$C = \frac{1}{2}[(C_{tot} - R_{tot} - K_{ss}) + \sqrt{(C_{tot} - R_{tot} - K_s)^2 + 4K_s C_{tot}}] \quad \text{(Equation 3)}$$

$$RC = \frac{R_{tot}C}{K_s + C}; C_{tot} = \frac{R_{tot}C}{K_s + C} + C \quad \text{(Equation 4)}$$

$$\frac{dC_{tot}}{dt} = \frac{input}{V} - k_{el}C - k_{int}RC - k_{SerumTissue}C + \frac{k_{TissueSerum}A_{Tissue}}{V} \quad \text{(Equation 5)}$$

$$\frac{dC}{dt} = -\frac{\frac{input}{V} + k_{el}C - k_{\text{int}}\frac{R_{tot}C}{K_s + C} - k_{SerumTissue}C + \frac{k_{TissueSerum}A_{Tissue}}{V}}{1 + R_{tot}\frac{K_s}{(C + K_s)^2}} \quad \text{(Equation 6)}$$

$$\frac{dA_{Tissue}}{dt} = k_{SerumTissue}C \cdot V - k_{TissueSerum}A_{Tissue} \quad \text{(Equation 7)}$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{\text{deg}}R_{tot} - (k_{\text{int}} - k_{\text{deg}})(\frac{R_{tot}C}{K_s + C}) \quad \text{(Equation 8)}$$

whereas,

A_{Tissue} = amount of MEDI-546 in the peripheral tissue compartment;

C = concentration of the free (unbound MEDI-546) in the central compartment;

C_{tot} = total (free and bound) MEDI-546 in the central compartment;

RC = concentration of the drug-receptor complex (Ab·R);

R_{tot} = concentration of the total (free and bound) receptors, R + Ab·R;

k_{el} = first-order elimination constant;

k_{int} = internalization (elimination of the complex) rate constant;

k_{deg} = degradation (elimination of the free receptor) rate constant;

k_{syn} = receptor production rate;

k_{on} = binding rate constant;

k_{off} = dissociation rate constant;

K_s = steady-state rate constant;

$k_{SerumTissue}$, $k_{TissueSerum}$ = rate constant for inter-compartmental transfer between central serum compartment and peripheral tissue compartment;

Input = intravenous infusion rate; and,

V= central distribution volume of MEDI-546.

[0200] Change of free drug concentrations in central and peripheral compartments over time was expressed by Equations 6 and 7. Equation 8 expressed the change of total receptor concentration over time in terms of free drug and R_{tot}.

[0201] To avoid model over-parameterization, rate constants k_{deg} and k_{int} were assumed the same and fixed to a value experimentally determined by confocal imaging studies.

[0202] The initial conditions for each compartment were as follows:

$C(0) = D/V$;

$A_{Tissue}(0) = 0$;

$RC(0) = 0$;

$R(0) = k_{syn} / k_{deg}$; and,

$GS(0) = k_{in} / k_{out}$

[0203] For translational simulation purposes an additional compartment representing the skin tissues was included in the PK-PD model (FIG. 4). The partitioning of MEDI-546 to the skin compartment was described by the following equation:

$$\frac{dC_{skin}}{dt} = k_{bs} \cdot C - k_{sb} \cdot C_{skin} \qquad \text{(Equation 9)}$$

[0204] The partitioning of MEDI-546 from the central compartment to skin was characterized by a skin-to-blood rate constant (k_{sb}) of 0.27 d^{-1}, which corresponds to the estimated absorption rate of CAT-354, a monoclonal antibody against IL-13, in healthy volunteers (Oh et al., Br. J. Clin. Pharmacol. 69:645-655 (2010)), and a distribution rate constant (blood to skin, k_{bs}) of $0.25 \cdot k_{sb}$. The k_{bs} rate constant was scaled to reflect a 0.25 skin:serum MEDI-546 concentration ratio at equilibrium. In this model, no mass loss in the central compartment was assumed due to MEDI-546 partitioning to the skin.

[0205] MEDI-546 blocked the interaction of interferons with IFNAR1 and inhibited the production of type I IFN genes (k_{in}) according to the formula:

$$\frac{dGS}{dt} = k_{in} * \left(1 - \frac{I_{max} * C_1}{IC50 + C_1}\right) - k_{out} * GS$$

where:

GS = Type I IFN gene signature score;

I_{max} = Maximum fractional extent of inhibition;

IC_{50} = Potency, MEDI-546 concentration corresponding to half-maximum inhibition of GS production;

k_{in} = Endogenous GS production rate; and,

k_{out} = GS elimination rate constant.

[0206] The initial condition at time zero for the PD compartment (GS in peripheral blood) was $GS(0)=k_{in}/k_{out}$.

[0207] To simulate the type I IFN GS response in skin tissues, it was assumed that type I IFN genes were locally produced and suppressed by MEDI-546 in a similar manner. The production rate of skin IFN gene signature ($k_{in,skin}$) was adjusted to reflect a baseline value lower than or equal to the type I IFN GS in whole blood.

Population PK-PD Modeling of MEDI-546 in SSc Patients.

[0208] Data analysis was performed using a pharmacostatistical software package NONMEM (Version 7.1, ICON Development Solutions, Elliott City, Maryland). The model development was based on the NONMEM objective function value (-2 times the log of the likelihood) and the randomness of weighted residuals. The first-order conditional estimation with interaction (FOCEI) method was used for model development.

[0209] The total dose that each subject received (mg) was calculated according to the weight-based dosage (mg/kg) and recorded body weight of that subject. Interindividual variability was modeled as a multiplicative random effect: $\theta \cdot \exp(\eta)$, where θ represented a typical value of a structural parameter and η was an individual-specific normally distributed random effect. The residual variability was modeled as:

$$Y = F+F*\varepsilon_{proportional} + \varepsilon_{additive},$$

where Y was a PK or PD observation and F was the corresponding model predicted value.

[0210] The residual error ε was assumed to be normally distributed with mean 0 and unknown variances to be estimated. An exploratory covariate analysis was performed to evaluate the effects of body weight on CL_{res} and V_c. Both parameters were allometrically scaled to a typical body weight of 70 kg, $(\text{body weight}/70)^{\theta}$, where θ represented the power coefficient.

[0211] Model stability and performance were assessed by a visual predictive check procedure (Holford, in 14th meeting of the Population Approach Group in Europe. (Pamplona, Spain, 2005)) and bootstrap resampling technique (Ette, J. Clin. Pharmacol. 37:486-495 (1997)) using the PsN-Toolkit (Lindbom *et al.*, Comput Methods Programs Biomed. 79:241-257 (2005)). For VPC, the final fixed- and random-effect model parameters,

along with original dataset as the simulation template, were used to generate the 90% intervals of 1,000 simulated profiles. Median, 5th, 10th, 90th, and 95th percentiles of the simulated concentrations at each time point were calculated and plotted.

[0212] Graphical comparison was made between the observed data and prediction intervals derived from the simulated profiles. The bootstrap resampling technique was used to validate parameter estimates. This model evaluation consisted of repeatedly fitting the model to 1,000 bootstrap replicates of the dataset. The datasets were replicated by randomly sampling the patient data with replacement up to the total number of patients in the original dataset. The median of the 1,000 parameter estimates was compared with the estimates obtained with the original dataset. The 95% confidence interval (CI) of each parameter was computed as the 2.5 to 97.5 percentile range of the bootstrapped parameter estimates.

Stochastic Simulations for MEDI-546 in SLE Patients

[0213] The PK-PD model developed for SSc was subsequently used to simulate type I IFN GS and target modulation profiles in SLE patients upon multiple MEDI-546 administrations. An additional compartment representing the skin tissue was added to the PK-PD model. It was assumed that PK of MEDI-546 in patients with SLE was the same as in SSc patients. The production rate (kin) of IFN-related GS score was increased for SLE patients to reflect a higher baseline value than in SSc patients. Stochastic simulations were performed using resampled actual observed baseline GS scores and body weight of patients with SLE enrolled in a prior clinical study for an anti-IFNα mAb (Higgs et al., Ann. Rheum. Dis. 70:2029-2036 (2011); Yao et al., Arthritis Rheum. 60:1785-1796 (2009); Yao et al., PLoS One 3:e2737 (2008); Yao et al., Hum. Genomics Proteomics 2009:374312 (2009); Yao et al., Arthritis Res. Ther. 12 (Suppl 1):S6 (2010); Merrill et al., Ann. Rheum. Dis. 70:1905-1913 (2011)). To simulate skin tissue GS scores, the partition of the MEDI-546 from serum to tissues was assumed to be 25% (Paquet et al., Exp. Dermatol. 15:381-386 (2006)).

Example 1

Type I IFN Signature as a PD Marker

[0214] A composite PD biomarker was developed using a five gene type I IFN GS shared by SLE and SSc, both in blood and in disease tissue (skin). The five gene type I IFN GS is a

reliable surrogate of type I IFN activity in the blood as well as a correlate with baseline disease activity in SLE and SSc. There is also a strong concordance in this GS score between blood and skin specimens from SLE or SSc patients (Higgs *et al.*, Ann. Rheum. Dis. 70:2029-2036 (2011), allowing the use of this type I IFN signature in blood as a PD biomarker to measure pharmacological effect of MEDI-546.

[0215] The five type I IFN-inducible genes (IFI27, IFI44, IFI44L, RSAD2, and IFI6) used to measure the PD of MEDI-546 are a subset of the 21 genes used as PD markers for sifalimumab, an anti-IFN-α mAb therapy in SLE described previously (Yao *et al.*, Arthritis Rheum. 60:1785-1796 (2009); Yao *et al.*, Hum. Genomics Proteomics 2009:374312 (2009); Yao *et al.*, Arthritis Res. Ther. 12 (Suppl 1):S6 (2010)). These 21 genes are: IFI6 (interferon, alpha inducible protein 6), RSAD2 (radical S-adenosyl methionine domain containing 2), IFI44 (interferon-induced protein 44), IFI44L (interferon induced protein 44, like), IFI27 (interferon alpha inducible protein 27), MX1 (myxovirus (influenza virus) resistance 1, interferon-inducible protein p78), IFIT1 (interferon-induced protein with tetratricopeptide repeats 1), HERC5 (hect domain and RLD 5), ISG15 (ISG15 ubiquitin-like modifier), LAMP3 (lysosomal-associated membrane protein 3), OAS3 (2'-5'-oligoadenylate synthetase 3, 100kDa), OAS1 (2'-5'-oligoadenylate synthetase 1, 40/60kDa), EPST1 (epithelial stromal interaction 1 (breast)), IFIT3 (interferon-induced protein with tetratricopeptide repeats 3), LY6E (lymphocyte antigen 6 complex, locus E), OAS2 (2'-5'-oligoadenylate synthetase 2, 69/71kDa), PLSCR1 (phospholipid scramblase 1), SIGLEC1 (sialic acid binding Ig-like lectin 1, sialoadhesin), USP18 (ubiquitin specific peptidase 18), RTP4 (receptor (chemosensory) transporter protein 4), and DNAPTP6 (DNA polymerase-transactivated protein 6) (see PCT Publ. No. WO 2008/070137, which is incorporated herein by reference in its entirety).

[0216] The 21 type I IFN gene signature (GS) was shown to be neutralized in a dose-dependent manner following treatment with sifalimumab in mild-to-moderate SLE patients in a Phase 1a clinical trial (Yao *et al.*, Arthritis Rheum. 60:1785-1796 (2009); Merrill *et al.*, Ann. Rheum. Dis. 70:1905-1913 (2011)). There was a strong correlation between the five and 21 gene type I IFN gene signatures in SLE (Higgs *et al.*, Ann. Rheum. Dis. 70:2029-2036 (2011)). While both type I IFN gene signatures were suitable PD markers for MEDI-546 in SLE, the five gene PD markers were used in the MEDI-546 trial in SSc.

[0217] Briefly, the five genes in the type I IFN GS were selected based on three primary criteria:

(1) prevalence and magnitude of over-expression in SSc and SLE patients compared to healthy controls;

(2) ability to be induced in whole blood from healthy donors *ex vivo* by type I IFN; and,

(3) the ability to be substantially suppressed by MEDI-546 *ex vivo* in healthy donor peripheral blood mononuclear cells after stimulation by SLE serum (Yao *et al.*, Hum. Genomics Proteomics 2009:374312 (2009)).

[0218] The magnitude of overexpression of the type I IFN GS score in blood and lesional skin of SLE and SSc patients was calculated by the expression level of the five genes described (statistically significant in all cases) (FIG. 1). Baseline levels of the type I IFN GS score were concordant between blood and lesional skin in both SSc and SLE patients (see, e.g., Higgs et al., Ann. Rheum. Dis. 70:2029-2036 (2011)).

Example 2

MEDI-546 Completely Suppressed the Type I IFN Signature in SSc Patients in a Dose-dependent Manner

[0219] The type I IFN GS described above was used in a FTIH study for MEDI-546 in SSc. Besides observing a dosing dependent PD effect, this study showed for the first time that an antibody that targets the type I IFN signaling pathway had the ability to normalize the type I IFN signature in both blood and disease tissue in a disease where type I IFN might play a role in the disease pathogenesis. Furthermore, for several SSc patients that had comparable level of the type I IFN signature with that in SLE, a near complete suppression of the type I IFN signature (duration of suppression varied in response to difference in dosing) was observed following MEDI-546 treatment.

[0220] TABLE 4, *supra*, shows the summaries of baseline demographic and type I IFN GS status as determined by type I IFN GS score for SSc patients enrolled in the FTIH study (MI-CP180) before they received MEDI-546 treatment (GS_0; baseline; pretreatment). The cutoffs for type I IFN GS positivity in blood and skin of SSc patients were $GS_0>2.9$ and $GS_0>1.8$, respectively. These type I IFN GS thresholds represented the upper boundary of mean ± 2 standard deviations of the distribution of the type I IFN GS in the blood and skin of

54 and 30 healthy donors (1.2 ± 1.7 in blood, 1.0 ± 0.8 in skin; FIG. 1). The median observed type I IFN GS score for each single- or multiple-dose cohort was calculated and plotted across time for all SSc patients that were positive for type I IFN GS score at baseline in both blood and skin (FIG. 2). Those dose cohorts with type I IFN GS modulated to or below values of mean for blood and skin in healthy donors respectively during the study period achieved complete suppression of the type I IFN GS.

[0221] Durable and nearly complete modulation of the type I IFN GS in SSc patients was observed in blood in three high exposure cohorts: 20.0 mg/kg single dose, 1.0 mg/kg and 5.0 mg/kg multiple doses. Complete suppression of type I IFN GS in skin was observed in two cohorts: 20.0 mg/kg single dose and 1.0 mg/kg multiple doses. The 5.0 mg/kg multi-dose cohort contained only a single GS_0 positive patient. The small sample size in this cohort likely was not able to provide an accurate evaluation of the PD effect, although the percentage of type I IFN GS suppression represented in FIG. 2D for this patient was consistent with the overall trend.

[0222] The minimum type I IFN GS score among this pool of healthy controls shown as the dashed line (FIGS. 2A and 2B) indicated the lowest boundary of type I IFN GS values in the healthy control population, of which no type I IFN GS positive patients in the MEDI-546 treated cohort went below. Overall, a dose-dependent target modulation (see Methods, *supra*) of the type I IFN GS with MEDI-546 (*i.e.*, PD effect) in SSc patients was observed in both whole blood and skin.

[0223] With the exception of the 0.3 mg/kg (both single and multi-dose) cohorts, a normalization of the type I IFN GS up to two weeks was observed in blood in all other cohorts. As mentioned above, the three highest exposure dose cohorts provided more durable PD effect. It should be noted that several SSc patients in the trial had high baseline type I IFN GS that is comparable to that of SLE patients. A near complete target modulation following MEDI-546 treatment was observed in these patients following initial dosing, and the duration of response varied based on dosing schedules (FIG. 7).

Example 3

Receptor Internalization Kinetics

[0224] Kinetics of MEDI-546 internalization in IFNAR1 expressing THP-1 cells was assessed quantitatively using live-cell confocal fluorescent imaging technology (FIG. 3). Fluorescently labeled MEDI-546 (MEDI-546-Alexa647) bound to THP-1 cells, while no binding of IgG-Alexa647, the isotype control of MEDI-546, was observed. This result demonstrated specific binding to THP-1 cells by MEDI-546 (FIG. 8). The translocation of MEDI-546-Alexa647 from the cell surface to the cytoplasm was monitored over time using a confocal fluorescent imager. Overlays of fluorescence images for cytoplasm (CFSE) and antibody (Alexa647) signals prior to and after the internalization of MEDI-546-*Alexa647* are shown in FIGS. 3A and 3B, respectively.

[0225] While initially MEDI-546-associated fluorescence was predominantly localized on the cell surface (FIG. 3A), at 40 min, MEDI-546-Alexa647 signals were seen in punctuated spots located in the cytoplasm (FIG. 3B). Kinetic images recorded over the time course were analyzed using a quantitative algorithm. A time course of MEDI-546-Alexa647 internalization into cytoplasm was constructed from the data obtained from four independent experiments (FIG. 3C). The internalization half-life was estimated to be 12.9 ± 1.2 (standard deviations) minutes.

Example 4

Population PK-PD Modeling of MEDI-546 in SSc Patients

[0226] The PD biomarker data and the target receptor internalization kinetics as determined from confocal imaging studies, along with prior knowledge from a previous clinical study evaluating an anti-IFN-α mAb in SLE (Yao et al., Arthritis Rheum. 60:1785-1796 (2009); Merrill et al., Ann. Rheum. Dis. 70:1905-1913 (2011)) were integrated into a PK-PD model for the population analysis of MEDI-546 SSc data and stochastic simulations for SLE.

[0227] A mechanistic PK-PD model for MEDI-546 was generated (see FIG. 4). According to this model, following intravenous (IV) administration, MEDI-546 (Ab) bound to IFNAR1 (R) and the antibody-receptor complex was subsequently internalized and degraded (k_{int}) inside the cells. The PD of MEDI-546 (type I IFN GS score) was best described by an indirect response model, in which the type I IFN-inducible gene production (k_{in}) was inhibited by MEDI-546. A total of 202 quantifiable PK observations from all 34

patients receiving MEDI-546 and 147 type I IFN GS score observations in peripheral blood from 22 type I IFN GS positive patients were included in the modeling dataset. Four outlier PD observations from different patients, identified during the model development with exaggerated weight residual values (absolute value greater than 5), were excluded from the final analysis.

[0228] The estimated PK-PD structural and variance parameters are summarized in TABLE 5.

TABLE 5. Summary of estimated population PK-PD parameters, interindividual and residual error variance of MEDI-546 in SSc patients following single IV administration.

Parameter	Original Estimates (RSE, %)[a]	Bootstrap (n = 1,000)	
		Median	95% CI
Fixed effect			
CL_{RES} (L/d)	0.198 (14)	0.192	0.141 – 0.234
V_c (L)	3.46 (8.3)	3.46	3.19 – 3.83
Q (L/d)	0.926 (16)	0.919	0.327 – 1.18
V_p (L)	2.52 (18)	2.54	2.18 – 3.24
K_{ss} (nM)	1.17 (16)	1.30	0.555 – 3.08
R_0 (nM)	0.0882 (10)	0.0907	0.0758 – 0.107
k_{int} (d^{-1})	77.4 Fixed (NA)	N.E.	N.E.
I_{max}	0.939 (1.3)	0.938	0.920 - 0.966
IC_{50} (nM)	0.978 (52)	0.772	0.248 - 1.96
GS_0	7.30 (21)	7.66	5.96 - 10.1
k_{GS} (d^{-1})	1.92 (9.4)	2.00	1.65 - 2.57
GS_{FLOOR}	0.764 (4.4)	0.746	0.521 - 0.874
Interindividual variability [b]			
η_{CLRES}	29.1 (23)	27.8	12.6 – 64.0
η_{Vc}	19.6 (16)	18.7	12.6– 24.4
η_{R0}	18.9 (28)	17.6	7.21 – 39.5

η_{IC50}	93.8 (48)	98.6	85.5 – 270
η_{GS0}	55.8 (3.6)	51.2	29.8 – 58.6
Residual variability			
PK proportional error (%CV)	15.6 (12)	15.2	11.4 - 18.3
PK additive error (SD, µg/mL)	0.0263 SD (10)	0.0257	0.0023 - 0.0305
PD proportional error (%CV)	40.5 (4.5)	39.0	32.7 - 46.8

[a] Relative standard error of the parameter estimate [b] Expressed as percent coefficient of variation (CV%). NA = not available; and N.E. = not estimated.

[0229] The parameters included in the table are: CL_{RES} = MEDI-546 clearance corresponding to the first-order elimination pathway; V_c = central distribution volume; Q = inter-compartmental clearance corresponding to the transfer of mavrilimumab between central serum compartment and peripheral tissue compartment; V_p = peripheral distribution volume; K_{ss} = steady-state constant, apparent equilibrium dissociation constant; R_0 = baseline IFNAR1 level; k_{int} = internalization rate constant; I_{max} = maximum fractional extent of inhibition; IC_{50} = Potency, MEDI-546 concentration corresponding to half-maximum inhibition of GS production; GS_0 = baseline type I IFN GS; k_{GS} = GS elimination (degradation) rate constant; and GS_{FLOOR} = theoretical lower limit of GS measurement.

[0230] The first-order clearance (CL_{RES}, 0.198 L/d) was close to that of an endogenous IgG not subject to the antigen-sink effect. The central distribution volume (V_c, 3.46 L) was slightly greater than the serum volume in humans, while the smaller peripheral distribution volume (V_p, 2.52 L) suggested restricted extravascular distribution of MEDI-546, as expected for a monoclonal antibody. The internalization rate of the MEDI-546/IFNAR1 complex (k_{int}) was fixed to a value determined from *in vitro* confocal imaging experiments. The population baseline type I IFN GS in peripheral blood, GS_0, was 7.30 with an IC_{50} (potency) of 0.978 nM. The elimination constant of type I IFN GS score (k_{out}) was 1.92 d^{-1}, corresponding to a

half-life of 8.7 hours for IFNAR-associated mRNAs in whole blood. The floor parameter f_{GS} (0.764) represented the theoretical analytical lower boundary of the PD assay.

[0231] Interindividual PK variability was moderate in SSc patients following IV administration. Both CL_{RES} and V_c increased with body weight. From a pharmacostatistical assessment, the covariate effect of weight on PK was not significantly different from the typical value for IgG, thus in the final PK model, the exponents corresponding to the body weight effect were fixed to the default values of 0.75 (CL_{RES}) and 1.0 (V_c). When body weight effect was incorporated, interindividual variability decreased from 54.1% to 29.1% for CL_{RES}, and from 35.1% to 19.6% for V_c. The estimated variance of proportional error for MEDI-546 concentrations was 0.0242, which corresponds to an assay precision of 15.6% CV. The estimated standard error of the additive residual component was 0.0263 μg/mL, close to the assay lower limit of quantitation (0.02 μg/mL).

[0232] Comparing with MEDI-546 PK, the type I IFN GS data was more variable. The interindividual variability (%CV) was 93.8% for IC50 and 55.8% for baseline GS score. The estimated proportional residual error for the PD assay was 40.5% CV.

[0233] The PK and PD profiles from four representative patients (two from the single-dose cohorts and two from the multiple-dose cohorts) are presented in FIG. 5. The solid circles represent PK or type I IFN GS scores observed in peripheral blood, while the solid lines represent the population (gray line) and individual (black line) model predictions, respectively. All the observed and model-predicted individual PK and PD profiles are shown in FIGS. 9A, 9B, 10A and 10B. Target modulation was calculated from model-predicted type I IFN GS scores, and compared with the observed values (FIGS. 11A and 11B). Doses greater than or equal to 1.0 mg/kg achieved complete target modulation in SSc patients. The duration of target modulation response was dose-dependent: higher doses prolonged the duration of complete target modulation.

[0234] The performance of the PK-PD model was evaluated by visual predictive check, in which the observations were overlaid with the simulated profiles from 1,000 replicates (FIGS. 12 and 13). Most observations centered around the medians of the simulated profiles and were encapsulated within the 5th and 95th percentiles, demonstrating that the pharmacostatistical model sufficiently captured the PK and PD properties of MEDI-546 and interindividual variabilities

[0235] In the MI-CP180 clinical trial skin biopsies were only collected pre-dose and at one time point post dosing (Day 7 for single-dose cohorts and Day 28 for multiple-dose cohorts). Given the limited information of the type I IFN signature in skin, its GS scores were not modeled for this Phase 1 study in SSc patients. These data were used to assess the utility of the PK-PD model in predicting the GS response in skin tissues after MEDI-546 treatment. The skin GS predictions were made by assuming a 25% tissue:serum ratio distribution of IgG (Paquet *et al.*, Exp. Dermatol. 15:381-386 (2006)) and a skin-to-blood rate constant of 0.27 d^{-1}, which is typical for the absorption of subcutaneously administered IgG from the dosing site (Oh et al., Br. J. Clin. Pharmacol. 69:645-655 (2010)).

[0236] In patients with toxic epidermal necrolysis the median IgG concentration in cutaneous blister fluid was approximately 24% of that in serum (Paquet *et al.*, Exp. Dermatol. 15:381-386 (2006)). The subcutaneous absorption rate of an IgG was well characterized in a Phase 1 study in heathy volunteers with intensive PK sampling schedule (Oh *et al.*, Br. J. Clin. Pharmacol. 69:645-655 (2010)). When both assumptions were incorporated in the mechanistic model, the trend and magnitude of observed skin GS response in SSc patients after MEDI-546 administration were adequately captured by the model.

[0237] No regression or curve-fitting was conducted, and the primary interest was to evaluae whether the PK-PD model sufficiently captured the trend and range of the type I GS response in skin tissues (FIG. 14).

[0238] Although the baseline skin GS data were highly variable, following MEDI-546 treatment the simulated type I GS in skin were close to the actual observations, especially for doses ≥ 1 mg/kg, for SSc patients. One subject in Cohort 2 (0.3 mg/kg, SID=2) had a relatively high baseline type I IFN GS in peripheral blood, resulting in a higher projected skin type I IFN GS score in this subject. The trend and extent of skin type I IFN GS responses in SSc patients following MEDI-546 administration were adequately projected by the PK-PD model, especially for doses ≥ 1 mg/kg (SID≥6). This provided additional evidence of the applicability of the PK-PD model to simulate and predict the skin IFN GS response in SLE patients upon multiple MEDI-546 administrations. Accordingly, the pharmacostatistical model was subsequently used to simulate the PK and PD profiles of MEDI-546 in SLE. In healthy donors (n=30) the observed upper boundary (mean + 2 standard deviations) of type I IFN GS was 1.8 in skin.

[0239] The antigen of MEDI-546 is a cell-membrane associated receptor (IFNAR1), which is widely expressed on most nucleated cells. From *in vitro* confocal imaging studies, upon MEDI-546 binding to IFNAR1 the antibody-receptor complex was rapidly internalized with a typical half-life of 12.9 minutes (FIG. 3). Therefore the PK of MEDI-546 was subject to the target-receptor mediated clearance, or the antigen-sink effect (more rapid drug clearance at lower concentration levels). The estimated distribution volumes and the first-order clearance by the reticuloendothelial system were typical for IgG not subject to the antigen sink effect (Oh *et al.*, Br. J. Clin. Pharmacol. 69:645-655 (2010); Tabrizi *et al.*, Inflamm. Allergy Drug Targets 9:229-237 (2010)).

[0240] Despite the small sample size of this Phase 1 study, both CL_{RES} and Vc were found to increase with body weight as observed with other IgGs. The systemic expression level of IFNAR1 in SSc patients was 88 pM. Overall the model appeared robust as the PK parameter estimates were close to the median of bootstrap replicates shown in TABLE 5.

Example 5

Stochastic Simulations for SLE Patients

[0241] To support the program transition from a FTIH study in SSc patients to a large Proof- of-Concept (PoC) study in SLE, we used translational simulations to bridge across the two patient populations in lieu of an additional Phase 1 trial in SLE. The recorded SLE patient body weight and baseline type I IFN GS from a clinical study of sifalimumab were used as the basis for a simulation of type I IFN GS responses in virtual SLE patients upon multiple MEDI-546 administrations.

[0242] To ease the dose preparation and reduce theoretical dosing error for the PoC study in SLE patients, MEDI-546 dosing was switched from weight-based (mg/kg) to fixed-dose (mg) based on translational simulations. Although from stochastic simulations a 300 mg monthly fixed-dose could maintain the suppression of peripheral-blood GS to the normal level ($\leq$2.9) in a typical SLE subject (FIG. 6A, median), a higher dose (1000 mg) was also recommended for the PoC trial to ensure adequate drug exposure and GS suppression in skin especially for SLE patients with substantially elevated type I IFN GS at baseline.

[0243] In addition, the 1000 mg dose would insure against potential divergence of the SLE simulation assumptions (*e.g.*, the potency and efficacy of MEDI-546 in SLE could be different from in SSc). Suboptimal doses lower than 300 mg were not recommended for the

PoC trial, as it would be unlikely for SLE patients to receive much MEDI-546 treatment benefits assuming that substantial target modulation is essential for observing clinical benefit. On the other hand, the improvement in efficacy was predicted to be incremental at doses greater than 1000 mg. Based on above considerations, both 300 and 1000 mg monthly doses were recommended for the PoC trial in SLE.

[0244] Accordingly, the modulation of the type I IFN GS in whole blood (FIG. 6A) and skin tissues (FIG. 6B) were simulated in virtual SLE patients (n=1,200 for each dose) following repeated every-four-week IV administrations of MEDI-546 at 300- or 1,000-mg fixed dose level.

[0245] The virtual SLE patients were generated by repetitive sampling from recorded type I IFN GS at baseline and body weight of SLE patients previously enrolled in a study for sifalimumab, an anti-IFNα mAb. The median baseline whole blood GS score was 37 in SLE patients (GS_0 range: 3 to 86; FIG. 1). The median body weight of SLE patients was 74 kg, with a range of 39.4 to 141 kg. FIGS. 6A and 6B show the median (solid line), lower and upper quartiles (dotted lines) of simulated type I IFN GS responses in these patients.

[0246] According to the simulations, the whole-blood type I IFN GS scores in SLE patients could be neutralized to the range of 1 to 5 (median 2 to 3) with monthly MEDI-546 dosing. This represented approximately 94% suppression of the type I IFN signature from the baseline level at steady-state of MEDI-546 treatment. The higher dose (1,000 mg) would allow for increased MEDI-546 tissue exposure, resulting in more substantial type I IFN GS suppression in skin tissues than the lower dose (300 mg). In addition, the simulated type I IFN GS responses in both whole blood and skin tissues fluctuated with the 300 mg monthly dose administration, while remaining relatively flat for the 1000 mg dose during the treatment period.

[0247] More SLE patients were simulated (n=12,000 for each dose level) for the calculation of overall target modulation after 6 months of MEDI-546 treatment. In peripheral blood, type I IFN GS was suppressed to the level of that of healthy normal patients (≤2.9, the upper boundary of mean ± 2 standard deviations from 54 normal controls as described above) in 68% of the simulated SLE patients dosed at 1000 mg (53% at 300 mg level). In skin tissues the projected percentage of SLE patients with over 90% IFN GS suppression were 20% and 30% for the 300 and 1000 mg dose levels, respectively.

Example 6

Treatment of SLE, Myositis, and Lupus Nephritis Patients with Fixed Dosage Regimens Determined Using Translational Simulations

[0248] Translational simulations are used to identify effective dosages and to design dosage regimens to treat SLE, myositis or lupus nephritis patients based on SSc clinical data. Type I IFN GS signatures are identified that are common to SSc and SLE, SSc and myositis, or SSc and lupus nephritis. PK/PD models based on SSc data are generated as described above and adjusted based on PK/PD data corresponding to SLE, myositis, or lupus nephritis. Stochastic simulations on virtual patients are conducted on the adjusted SSc/SLE, SSc/myositis, or SSc/lupus nephritis PK/PD models.

[0249] Fixed doses predicted to suppress the type I IFN GS in the virtual patients are identified through the simulations. The fixed dose amounts of therapeutic agents identified in the simulations are administered to actual SLE, myosotis, or lupus nephritis patients. The administration of the fixed dose of therapeutic agent effectively suppresses the type I IFN GS in the actual patients and effectively treats SLE, myosotis, or lupus nephritis.

[0250] The foregoing description of the specific aspects will so fully reveal the general nature of the disclosure that others can, by applying knowledge within the skill of the art, readily modify and/or adapt for various applications such specific aspects, without undue experimentation, without departing from the general concepts provided. Therefore, such adaptations and modifications are intended to be within the meaning and range of equivalents of the disclosed aspects, based on the teaching and guidance presented herein. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation, such that the terminology or phraseology of the present specification is to be interpreted by the skilled artisan in light of the teachings and guidance.

[0251] The breadth and scope of the present disclosure should not be limited by any of the above-described exemplary aspects, but should be defined only in accordance with the following claims and their equivalents.

WHAT IS CLAIMED IS:

1. A method of treating a patient having a type I IFN-mediated disease or disorder comprising administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

2. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

   (a) measuring a type I Interferon Gene Signature (IFN GS) score in a sample taken from a patient having a type I IFN- mediated disease or disorder, relative to a baseline type I IFN GS score; and,

   (b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

   wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

3. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

   (a) administering to a patient having a type I IFN- mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

   (b) measuring the patient's type I IFN GS score relative to a baseline type I IFN GS score; and,

   (c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

4. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

(a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score;

(b) determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(c) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

5. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

(a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) submitting a sample taken from the patient for measurement of a type I IFN GS score;

(c) determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(d) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

6. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

(a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and,

(b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

7. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

(a) administering to a patient having a type I IFN- mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) submitting a sample taken from the patient for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and,

(c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

8. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

(a) measuring a type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder;

(b) determining whether the patient's type I IFN GS score is elevated relative to a baseline IFN GS score; and,

(c) instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the fixed dose of the antibody or fragment thereof effectively treats the disease or disorder.

9. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

(a) obtaining a sample from a patient having a type I IFN- mediated disease or disorder, where the patent has received a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) measuring a type I IFN GS score from the sample;

(c) determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(d) instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein suppression of the type I IFN GS of the patient is indicative of treatment efficacy.

10. A method of suppressing a type I IFN GS in a patient comprising:

(a) measuring the type I IFN GS score in a sample taken from a patient having a type I IFN- mediated disease or disorder, relative to a baseline type I IFN GS score; and,

(b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

11. A method of suppressing an type I IFN GS in a patient comprising:

(a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) measuring the patient's type I IFN GS score relative to a baseline type IFN GS score; and,

(c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type IFN GS of the patient.

12. A method of suppressing an IFN GS in a patient comprising:

(a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of an IFN GS score;

(b) determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(c) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

13. A method of suppressing an IFN GS in a patient comprising:

(a) administering to a patient having a type I IFN-mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) submitting a sample taken from the patient for measurement of a type I IFN GS score;

(c) determining from the results of the measurement whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(d) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

14. A method of suppressing a type I IFN GS in a patient comprising:

(a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and

(b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

15. A method of suppressing a type I IFN GS in a patient comprising:

(a) administering to a patient having a type I IFN- mediated disease or disorder a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) submitting a sample taken from the patient for measurement of a type I IFN GS score and comparison to a baseline type I IFN GS score; and,

(c) increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

16. A method of suppressing a type I IFN GS in a patient comprising:

(a) measuring a type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder;

(b) determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(c) instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

17. A method of suppressing a type I IFN GS in a patient comprising:

(a) obtaining a sample from a patient having a type I IFN- mediated disease or disorder, where the patent has received a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(b) measuring a type I IFN GS score from the sample;

(c) determining whether the patient's type I IFN GS score is elevated relative to a baseline type I IFN GS score; and,

(d) instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score is elevated;

wherein the administration of the antibody or antigen-binding fragment thereof suppresses the type I IFN GS of the patient.

18. A method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprising:

(a) measuring a first type I IFN GS score in a sample taken from a patient having a type I IFN- mediated disease or disorder;

(b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(c) measuring a second type I IFN GS score in a sample taken from the patient following antibody administration; and,

(d) comparing the second type I IFN GS score to the first type I IFN GS score;

wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

19. A method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprising:

(a) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a first type I IFN GS score;

(b) administering to the patient a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(c) submitting a sample taken from a patient with a type I IFN-mediated disease or disorder for measurement of a second type I IFN GS score; and,

(d) comparing the second type I IFN GS score to the first type I IFN GS score;

wherein a decrease between the first and second IFN GS scores indicates efficacy or good prognosis.

20. A method of monitoring therapeutic efficacy of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity in a patient having a type I IFN-mediated disease or disorder comprising:

(a) measuring a first type I IFN GS score from a sample taken from a patient having a type I IFN-mediated disease or disorder;

(b) instructing a healthcare provider to administer a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

(c) measuring a second type I IFN GS score in a sample taken from the patient following antibody administration; and,

(d) comparing the second type I IFN GS score to the first type I IFN GS score;

wherein a decrease between the first and second type I IFN GS scores indicates efficacy or good prognosis.

21. The method of claim 1, 7, 9, or 16, further comprising measuring the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of the fixed dose.

22. The method of claim 2, 8, 10, or 17, further comprising measuring the patient's type IIFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of a subsequent fixed dose.

23. The method of claim 3, 5, 11, or 14, further comprising submitting a sample from the patient for measurement of the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of the fixed dose.

24. The method of claim 4, 6, 12, or 15, further comprising submitting a sample from the patient for measurement of the patient's type I IFN GS score relative to a baseline type I IFN GS score, relative to the patient's earlier type I IFN GS score, or both, after the administration of a subsequent fixed dose.

25. The method of claim 21, further comprising increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score remains elevated.

26. The method of claim 23, further comprising instructing a healthcare provider to increase the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score remains elevated.

27. The method of claim 23, further comprising increasing the amount or frequency of subsequent fixed doses if the patient's type I IFN GS score remains elevated.

28. A method of treating a patient having a type I IFN-mediated disease or disorder comprising:

administering a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity;

wherein the fixed dose is effective to treat the disorder.

29. The method of any one of claims 1 to 28, wherein the type I IFN activity is IFN-alpha activity.

30. The method of any one of claims 1 to 29, wherein the type I IFN GS comprises up-regulated expression or activity of at least 4 pharmacodynamic (PD) marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6.

31. The method of claim 30, wherein the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2.

32. The method of claim 31 wherein the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

33. The method any one of claims 1 to 32, wherein the antibody or antigen-binding fragment thereof that modulates type I IFN activity specifically binds to an IFN receptor.

34. The method of claim 33, wherein the IFN receptor is an IFN alpha receptor.

35. The method of claim 34, wherein the IFN alpha receptor is IFNAR1.

36. The method of claim 35, wherein the antibody or antigen binding fragment thereof specifically binds to subunit 1 of IFNAR1.

37. The method of any one of claims 1 to 36, wherein the antibody or antigen-binding fragment thereof is monoclonal.

38. The method of claim 37, where the antibody or antigen-binding fragment thereof comprises an immunoglobulin IgG Fc region.

39. The method of claim any one of claims 1 to 38, wherein the antibody is MEDI-546 or an antigen-binding fragment thereof.

40. The method any one of claims 1 to 39, wherein the fixed dose ranges from about 300 mg. to about 1000 mg.

41. The method of any one of claims 1 to 39, wherein the fixed dose is lower than about 300 mg.

42. The method of any of one claims 1 to 39, wherein the fixed dose is about 100 mg.

43. The method of any one of claims 1 to 39, wherein the fixed dose is selected from the group consisting of about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800, about 900 mg and about 1000 mg.

44. The method of any one of claims 1 to 43, wherein the antibody or antigen-binding fragment thereof suppresses the type I IFN GS in disease tissue.

45. The method of claim 44, wherein the disease tissue is skin.

46. The method of any one of claims 1 to 44, wherein the herein the antibody or antigen-binding fragment thereof suppresses the type I IFN GS in peripheral blood.

47. The method of any one of claims 1 to 46, wherein the suppression is full suppression.

48. The method of any one of claims 1 to 46, wherein the suppression is partial suppression.

49. The method of any one of claims 1 to 48, wherein the antibody or antigen-binding fragment thereof is administered in two or more doses.

50. The method of any one of claims 1 to 49, wherein the antibody or antigen-binding fragment thereof is administered monthly.

51. The method of any one of claims 1 to 50, wherein the antibody or antigen-binding fragment thereof is administered intravenously, intramuscularly, subcutaneously, or a combination thereof.

52. The method of any one of claims 1 to 51, wherein the disease is an autoimmune disease.

53. The method of claim 52, wherein the autoimmune disease is systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, or lupus nephritis.

54. The method of any one of claims 1 to 53, wherein the antibody or antigen-binding fragment thereof suppresses the type I IFN GS by at least 10%, at least 20%, at least 30% or at least 40% as compared to the type I IFN GS of the subject prior to the administration of the fixed dose of the antibody or antigen-binding fragment thereof.

55. The method of any one of claims 1 to 54, wherein the antibody or antigen-binding fragment thereof suppresses the type I IFN GS by at least 10%, at least 20%, at least 30% or at least 40% as compared to the average type I IFN GS signature in a population.

56. A kit for detecting a type I IFN genetic signature (IFN GS) common to two diseases whose pathogeneses are mediated by type I IFN comprising a set of diagnostic assays capable of measuring differentially regulated pharmacodynamic (PD) marker genes in a patient sample, wherein the type I IFN GS is suppressed by the administration of a fixed dose of an antibody or antigen-binding fragment thereof that modulates type I IFN activity.

57. The kit of claim 56, wherein the type I IFN GS comprises up-regulated expression or activity of at least four PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6.

58. The kit of claim 57, wherein the type I IFN GS comprises up-regulated expression or activity of at least five of the PD marker genes.

59. The kit of any one of claims 56 to 58, wherein the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2.

60. The kit of claim 59, wherein the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

61. The kit of any one of claims 56 to 60, wherein the patient sample is blood or a fraction thereof, muscle, skin, or a combination thereof

62. The kit of any one of claims 56 to 61, wherein the diagnostic assays comprise nucleic acid probes which hybridize to mRNA in the patient sample.

63. A computer-implemented method for predicting an optimal dosage regimen with an antibody or antigen-binding fragment thereof that modulates type I IFN activity comprising:

(a) inputting PK/PD data from a second type I IFN-mediated disease or disorder into a computer system comprising a pharmacokinetic-pharmacodynamic (PK/PD) stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PK/PD data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model;

(b) applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder; and,

(c) identifying an optimal dosage of the antibody or antigen-binding fragment thereof that modulates type I IFN activity for the second type I IFN-mediated disease or disorder from the output of the adjusted PK/PD stochastic model.

64. A computer-implemented method of identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating a type I IFN-mediated disease or disorder comprising:

(a) inputting PD/PK data from a second type I IFN-mediated disease or disorder into a computer system comprising a PK/PD stochastic model based on PK/PD values

corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PD/PK data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model;

(b) applying the adjusted PK/PD stochastic model to the inputted data from the second type I IFN-mediated disease or disorder; and,

(c) identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating the second type I IFN-mediated disease or disorder from the output of the adjusted PK/PD stochastic model.

65. A computer-implemented method of identifying a patient as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity comprising:

(a) inputting PD/PK data from a second type I IFN-mediated disease or disorder into a computer system comprising a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted PD/PK data from the second type I IFN-mediated disease is used to adjust the PK/PD stochastic model;

(b) applying the adjusted PK/PD stochastic model to the inputted PD/PK data from the second type I IFN-mediated disease or disorder; and,

(c) identifying a patient with the second disease as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity for the second type I IFN-mediated disease from the output of the adjusted PK/PD stochastic model.

66. A computer-implemented method of designing a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity comprising:

(a) inputting PD/PK data from a second type I IFN-mediated disease or disorder into a computer system comprising a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder, wherein the inputted data from the second type I IFN-mediated disease or disorder is used to adjust the PK/PD stochastic model;

(b) applying the adjusted PK/PD stochastic model to the inputted PD/PK data from the second type I IFN-mediated disease or disorder; and,

(c) identifying a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity for the second type I IFN-mediated disease or disorder from the output of the adjusted PK/PD stochastic model.

67. The computer-implemented method of any one of claims 63-66, wherein the type I IFN activity is IFN-α activity.

68. The computer-implemented method of any one claims 63-66, wherein the first and second type I IFN-mediated disease or disorder share a common type I IFN GS.

69. The computer-implemented method of claim 68, wherein the type I IFN GS is differentially regulated.

70. The computer-implemented method of any one of claims 68 or 69, wherein the type I IFN GS comprises up-regulated expression or activity of at least 4 pharmacodynamic (PD) marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27,

MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6.

71. The computer-implemented method of claim 68 or 69, wherein the type I IFN GS comprises up-regulated expression or activity of at least 5 PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6.

72. The computer-implemented method of any one of claims 70 or 71, wherein the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2.

73. The computer-implemented method of claim 72, wherein the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

74. The computer-implemented method of any one of claims 63-66, wherein the antibody or antigen binding fragment thereof specifically binds to an IFN receptor.

75. The computer-implemented method of claim 74, wherein the IFN receptor is an IFN alpha receptor.

76. The computer-implemented method of claim 75, wherein the IFN alpha receptor is IFNAR1.

77. The computer-implemented method of claim 76, wherein the antibody or antigen binding fragment thereof specifically binds to subunit 1 of IFNAR1.

78. The computer-implemented method of any one of claims 73-77, wherein the antibody or antigen binding fragment thereof is monoclonal.

79. The computer-implemented method of claim 78, wherein the antibody or antigen binding fragment thereof comprises an immunoglobulin IgG Fc region.

80. The computer-implemented method of any one of claims 63-66, wherein the antibody is MEDI-546.

81. The computer-implemented method of any one of claims 63-66, wherein the first and the second type I IFN-mediated disease or disorder are autoimmune diseases.

82. The computer-implemented method of claim 81, wherein the autoimmune diseases are rheumatic diseases.

83. The computer-implemented method of claim 82, wherein the rheumatic diseases are selected from the group consisting of systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, and lupus nephritis.

84. The computer-implemented method of any one of claims 63-66, wherein the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is SLE.

85. The computer-implemented method of any one of claims 63-66, wherein the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is myositis.

86. The computer-implemented method of any one of claims 63-66, wherein the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is lupus nephritis.

87. The computer-implemented method of any one of claims 63-66, wherein the PK/PD data corresponding to the first or second type I IFN-mediated disease or disorder comprise binding affinity data.

88. The computer-implemented method of claim 87, wherein the binding affinity data corresponds to the binding of an antibody or antigen binding fragment thereof to an IFN receptor.

89. The computer-implemented method of claim 88, wherein the antibody or antigen binding fragment thereof is MEDI-546.

90. The computer-implemented method of claim 88, wherein the IFN receptor is IFNAR1.

91. The computer-implemented method of any one of claims 63-66, wherein the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise kinetics data.

92. The computer-implemented method of claim 91, wherein the kinetics data corresponds to internalization kinetics of an antigen-antibody complex by cells.

93. The computer-implemented method of claim 92, wherein the antigen is IFNAR1.

94. The computer-implemented method of claim 92, wherein the antibody is MEDI-546.

95. The computer-implemented method of claim 92, wherein the cells are THP-1 cells.

96. The computer-implemented method of any one of claims 63-66, wherein the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise type I IFN GS suppression data.

97. The computer-implemented method of claim 96, wherein the type I IFN GS suppression is full suppression.

98. The computer-implemented method of claim 96, wherein the type I IFN GS suppression is partial suppression.

99. The computer-implemented method of any one of claims 96-98, wherein the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, RSAD2, and IFI6.

100. The computer-implemented method of any one of claims 63-66, wherein the PK/PD stochastic model comprises two compartments.

101. The computer-implemented method of claim 100, wherein the two compartments are a central compartment and a peripheral compartment.

102. The computer-implemented method of claim 100, further comprising a skin compartment.

103. The computer-implemented method of any one of claims 63-66, wherein the PK/PD stochastic model comprises two elimination pathways.

104. The computer-implemented method of claim 103, wherein the two elimination pathways are a clearance pathway and a target-mediated disposition pathway.

105. The computer-implemented method of claim 104, wherein the clearance pathway is a reticuloendothelial system pathway.

106. A computer-readable medium containing program instructions for predicting an optimal dosage regimen with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of:

(a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder;

(b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and,

(c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder;

wherein the output of the simulation identifies an optimal dosage of the antibody or antigen-binding fragment thereof that modulates type I IFN activity in the second type I IFN-mediated disease or disorder.

107. A computer-readable medium containing program instructions for identifying an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating a type I IFN-mediated disease or disorder, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of:

(a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder;

(b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and,

(c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder;

wherein the output of the simulation identifies an antibody or antigen-binding fragment thereof that modulates type I IFN activity as a candidate therapeutic agent for treating the second type I IFN-mediated disease or disorder.

108. A computer-readable medium containing program instructions for identifying a patient as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of:

(a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder;

(b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and,

(c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder;

wherein the output of the simulation identifies a patient with the second type I IFN-mediated disease as a candidate for therapy with an antibody or antigen-binding fragment thereof that modulates type I IFN activity.

109. A computer-readable medium containing program instructions for designing a personalized therapy for treating a type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity, wherein execution of the program instructions by one or more processors of a computer system causes the one or more processors to carry out the steps of:

(a) processing inputted PK/PD data from a second type I IFN-mediated disease or disorder:

(b) adjusting a PK/PD stochastic model based on PK/PD data corresponding a first type I IFN-mediated disease or disorder with the processed PK/PD data from the second type I IFN-mediated disease or disorder; and,

(c) executing a stochastic simulation applying the adjusted PK/PD stochastic model to the inputted PK/PD data from the second type I IFN-mediated disease or disorder;

wherein the output of the simulation identifies a personalized therapy for treating the second type I IFN-mediated disease or disorder with an antibody or antigen binding fragment thereof that modulates type I IFN activity.

110. The computer-readable medium of any one of claims 106-109, wherein the type I IFN activity is IFN-α activity.

111. The computer-readable medium of any one claims 106-110, wherein the first and second type I IFN-mediated disease or disorder share a common type I IFN GS.

112. The computer-readable medium of claim 111, wherein the type I IFN GS is differentially regulated.

113. The computer-readable medium of any one of claims 111 or 112, wherein the type I IFN GS comprises up-regulated expression or activity of at least 4 pharmacodynamic (PD) marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6.

114. The computer-readable medium of claim 111 or 112, wherein the type I IFN GS comprises up-regulated expression or activity of at least 5 PD marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6.

115. The computer-readable medium of any one of claims 113 or 114, wherein the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, and RSAD2.

116. The computer-readable medium of claim 115, wherein the type I IFN GS further comprises up-regulated expression or activity of gene IFI6.

117. The computer-readable medium of any one of claims 106-116, wherein the antibody or antigen binding fragment thereof specifically binds to an IFN receptor.

118. The computer-readable medium of claim 117, wherein the IFN receptor is an IFN alpha receptor.

119. The computer-readable medium of claim 118, wherein the IFN alpha receptor is IFNAR1.

120. The computer-readable medium of claim 119, wherein the antibody or antigen binding fragment thereof specifically binds to subunit 1 of IFNAR1.

121. The computer-readable medium of any one of claims 106-120, wherein the antibody or antigen binding fragment thereof is monoclonal.

122. The computer-readable medium of claim 121, wherein the antibody or antigen binding fragment thereof comprises an immunoglobulin IgG Fc region.

123. The computer-readable medium of any one of claims 106-119, wherein the antibody is MEDI-546.

124. The computer-readable medium of any one of claims 106-109, wherein the first and the second type I IFN-mediated disease or disorder are autoimmune diseases.

125. The computer-readable medium of claim 124, wherein the autoimmune diseases are rheumatic diseases.

126. The computer-readable medium of claim 125, wherein the rheumatic diseases are selected from the group consisting of systemic lupus erythematosus (SLE), scleroderma (SSc), myositis, and lupus nephritis.

127. The computer-readable medium of any one of claims 106-109, wherein the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is SLE.

128. The computer-readable medium of any one of claims 106-109, wherein the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is myositis.

129. The computer-readable medium of any one of claims 106-109, wherein the first type I IFN-mediated disease or disorder is SSc and the second type I IFN-mediated disease or disorder is lupus nephritis.

130. The computer-readable medium of any one of claims 106-109, wherein the PK/PD data corresponding to the first or second type I IFN-mediated disease or disorder comprise binding affinity data.

131. The computer-readable medium of claim 130, wherein the binding affinity data corresponds to the binding of an antibody or antigen binding fragment thereof to an IFN receptor.

132. The computer-readable medium of claim 131, wherein the antibody or antigen binding fragment thereof is MEDI-546.

133. The computer-readable medium of claim 131, wherein the IFN receptor is IFNAR1.

134. The computer-readable medium of any one of claims 106-109, wherein the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise kinetics data.

135. The computer-readable medium of claim 134, wherein the kinetics data is corresponds to internalization kinetics of an antigen-antibody complex by cells.

136. The computer-readable medium of claim 135, wherein the antigen is IFNAR1.

137. The computer-readable medium of claim 135, wherein the antibody is MEDI-546.

138. The computer-readable medium of claim 135, wherein the cells are THP-1 cells.

139. The computer-readable medium of any one of claims 106-109, wherein the PK/PD data corresponding the first or second type I IFN-mediated disease or disorder comprise type I IFN GS suppression data.

140. The computer-readable medium of claim 139, wherein the type I IFN GS suppression is full suppression.

141. The computer-readable medium of claim 139, wherein the type I IFN GS suppression is partial suppression.

142. The computer-readable medium of any one of claims 139-141, wherein the type I IFN GS comprises up-regulated expression or activity of genes IFI27, IFI44, IFI44L, RSAD2, and IFI6.

143. The computer-readable medium of any one of claims 106-109, wherein the PK/PD stochastic model comprises two compartments.

144. The computer-readable medium of claim 143, wherein the two compartments are a central compartment and a peripheral compartment.

145. The computer-readable medium of claim 144, further comprising a skin compartment.

146. The computer-readable medium of any one of claims 106-109, wherein the PK/PD stochastic model comprises two elimination pathways.

147. The computer-readable medium of claim 146, wherein the two elimination pathways are a clearance pathway and a target-mediated disposition pathway.

148. The computer-readable medium method of claim 147, wherein the clearance pathway is a reticuloendothelial system pathway.

FIG. 1

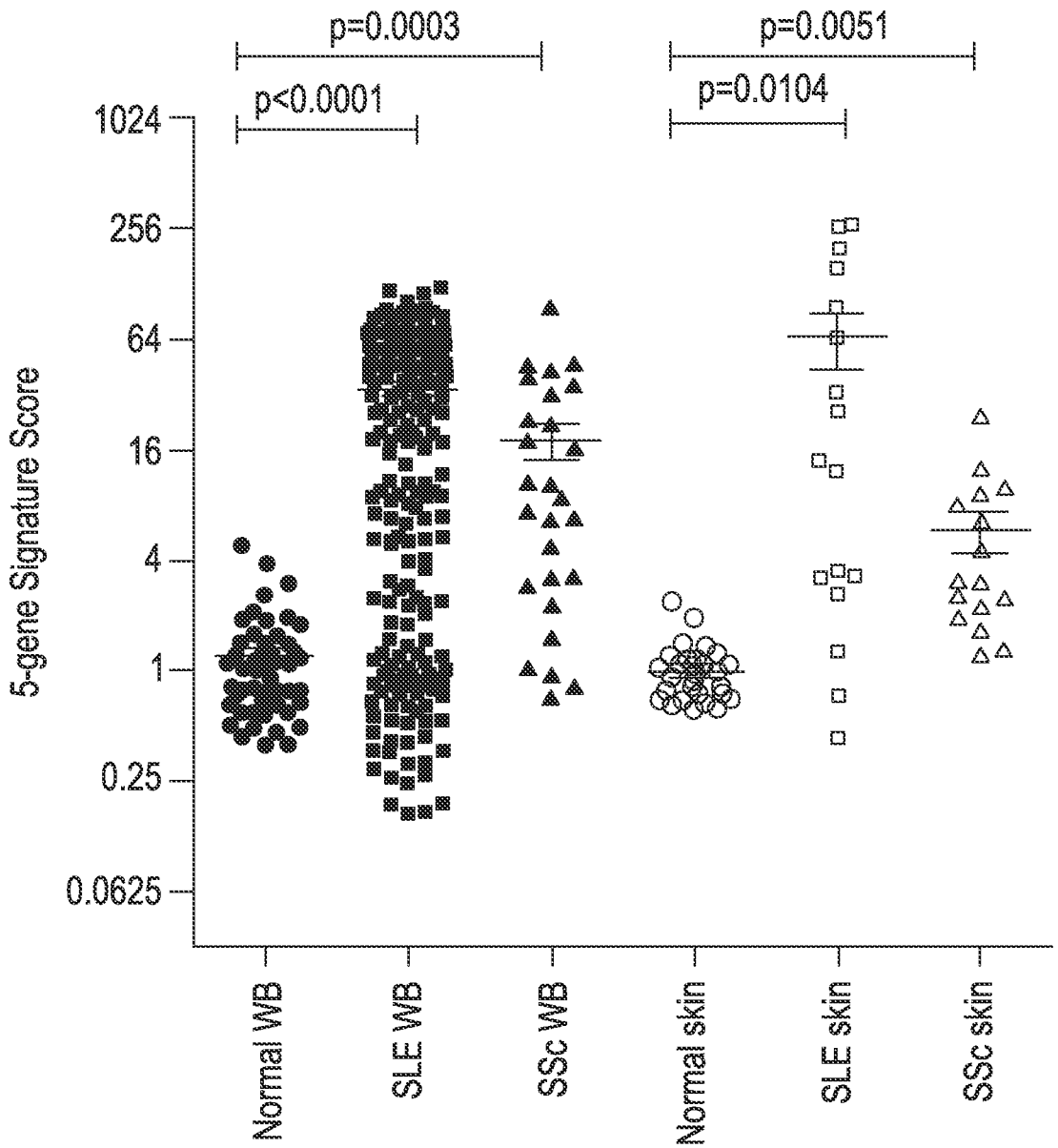

p=0.0003
p<0.0001
p=0.0051
p=0.0104
1024
256
64
16
4
1
0.25
0.0625
5-gene Signature Score
Normal WB
SLE WB
SSc WB
Normal skin
SLE skin
SSc skin

FIG. 2A

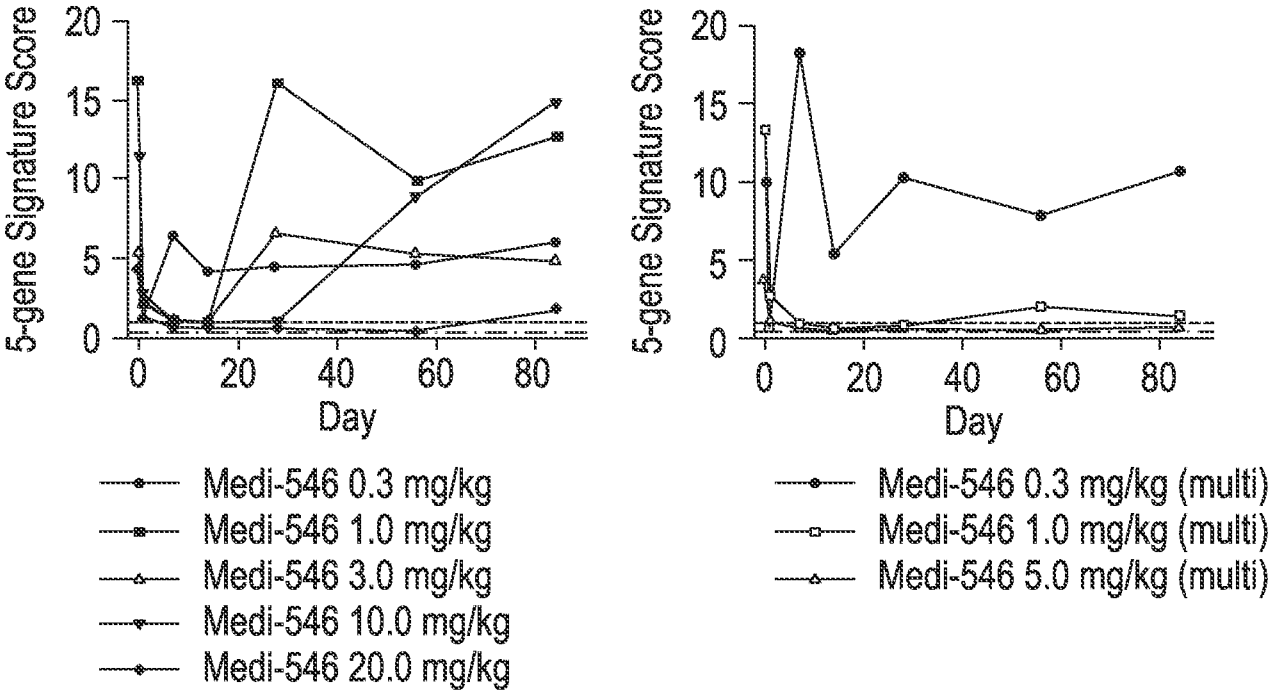

5-gene Signature Score
20
15
10
5
0
0
20
40
60
80
Day
Medi-546 0.3 mg/kg
Medi-546 1.0 mg/kg
Medi-546 3.0 mg/kg
Medi-546 10.0 mg/kg
Medi-546 20.0 mg/kg
5-gene Signature Score
20
15
10
5
0
0
20
40
60
80
Day
Medi-546 0.3 mg/kg (multi)
Medi-546 1.0 mg/kg (multi)
Medi-546 5.0 mg/kg (multi)

FIG. 2B

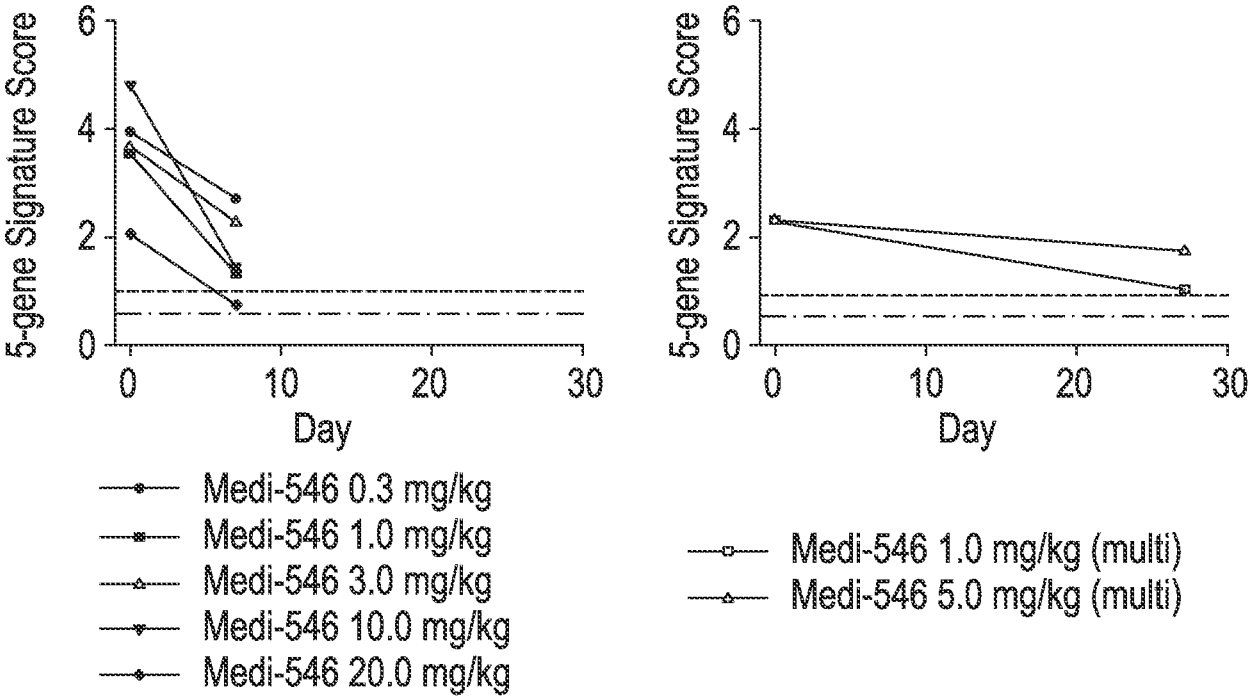

5-gene Signature Score
6
4
2
0
0
10
20
30
Day
Medi-546 0.3 mg/kg
Medi-546 1.0 mg/kg
Medi-546 3.0 mg/kg
Medi-546 10.0 mg/kg
Medi-546 20.0 mg/kg
5-gene Signature Score
6
4
2
0
0
10
20
30
Day
Medi-546 1.0 mg/kg (multi)
Medi-546 5.0 mg/kg (multi)

FIG. 2C

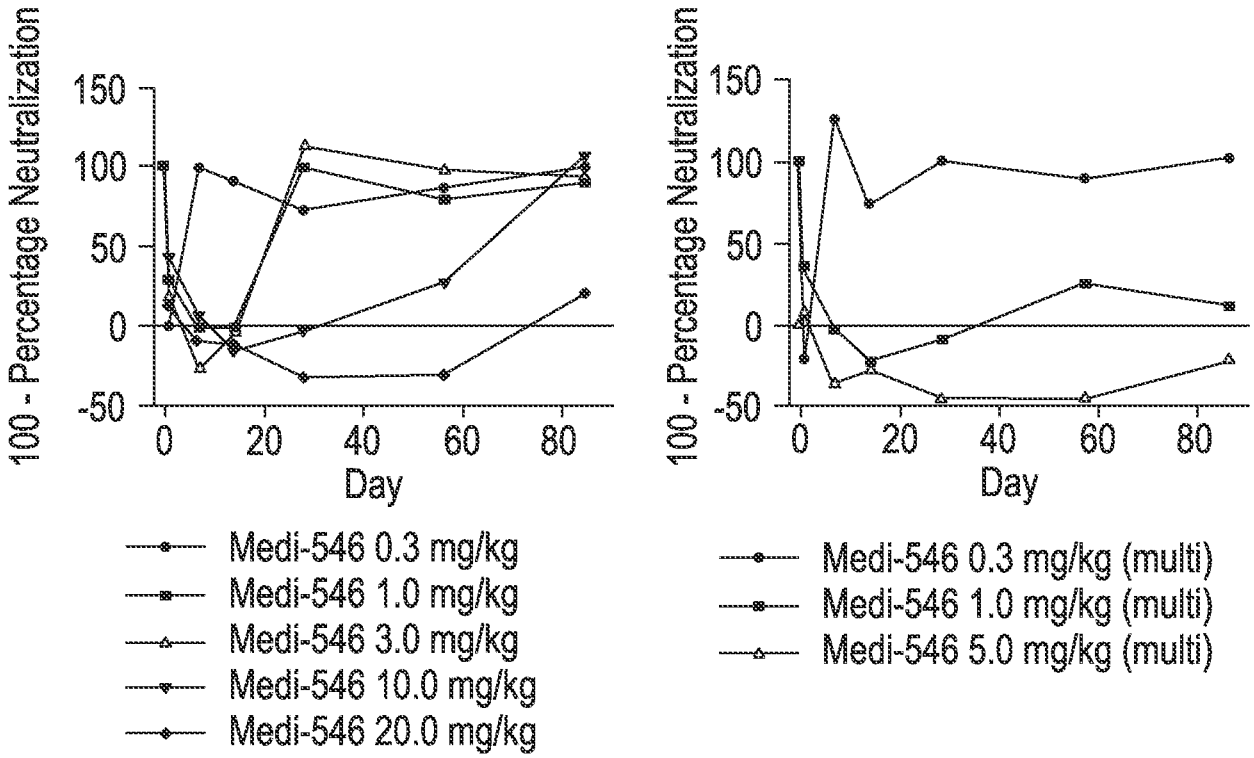

100 - Percentage Neutralization
150
100
50
0
-50
0
20
40
60
80
Day
Medi-546 0.3 mg/kg
Medi-546 1.0 mg/kg
Medi-546 3.0 mg/kg
Medi-546 10.0 mg/kg
Medi-546 20.0 mg/kg
100 - Percentage Neutralization
150
100
50
0
-50
0
20
40
60
80
Day
Medi-546 0.3 mg/kg (multi)
Medi-546 1.0 mg/kg (multi)
Medi-546 5.0 mg/kg (multi)

FIG. 2D

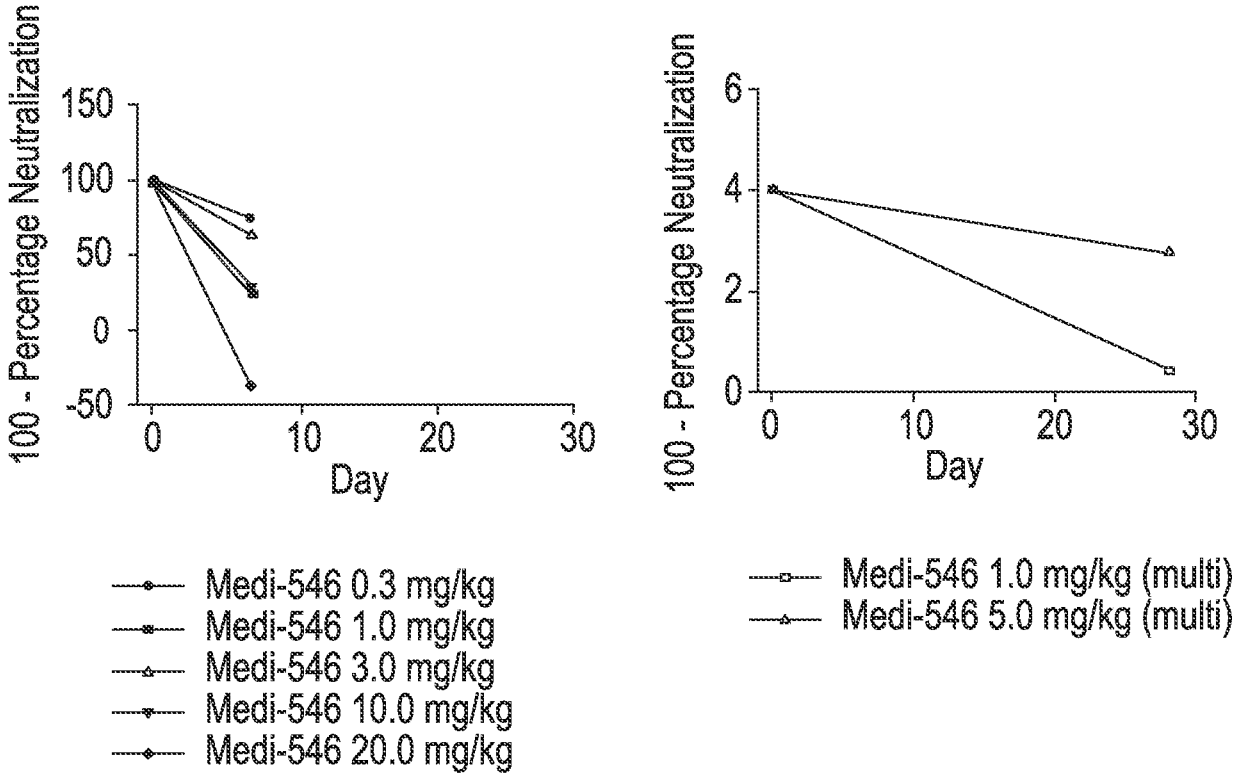

100 - Percentage Neutralization
150
100
50
0
-50
0
10
20
30
Day
Medi-546 0.3 mg/kg
Medi-546 1.0 mg/kg
Medi-546 3.0 mg/kg
Medi-546 10.0 mg/kg
Medi-546 20.0 mg/kg
100 - Percentage Neutralization
6
4
2
0
0
10
20
30
Day
Medi-546 1.0 mg/kg (multi)
Medi-546 5.0 mg/kg (multi)

FIG. 3A

(t=0 min)

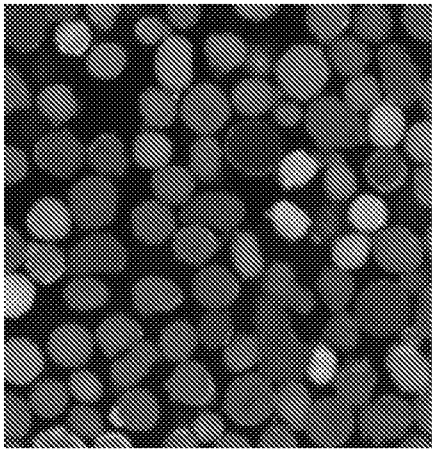


FIG. 3B

(t=40 min)

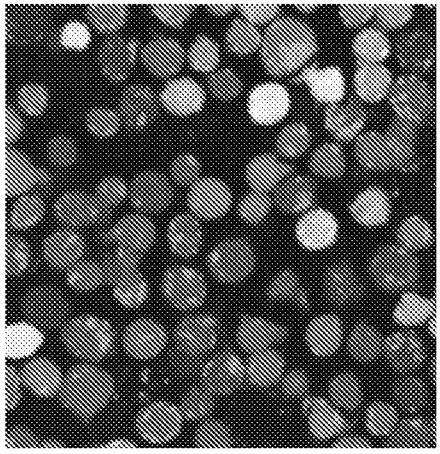


FIG. 3C

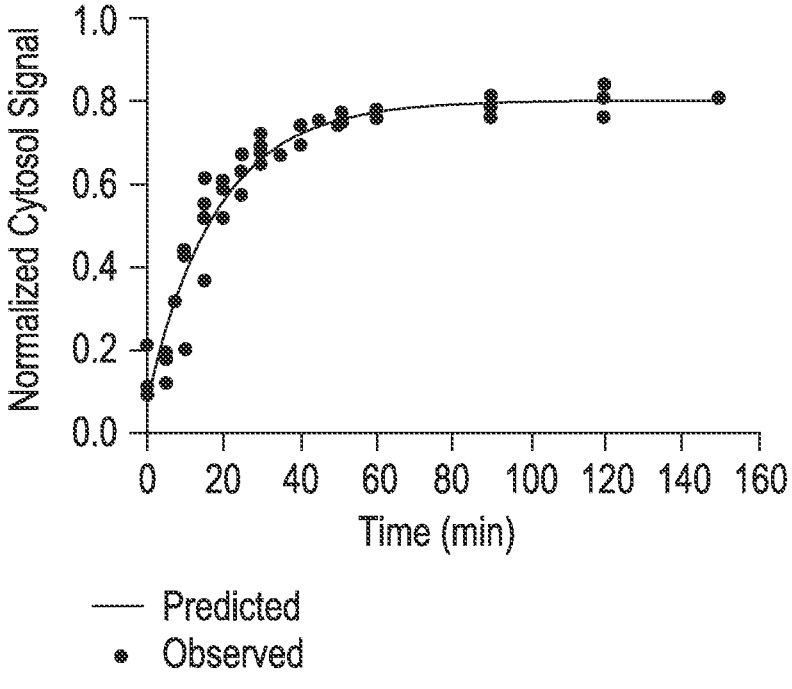


FIG. 4

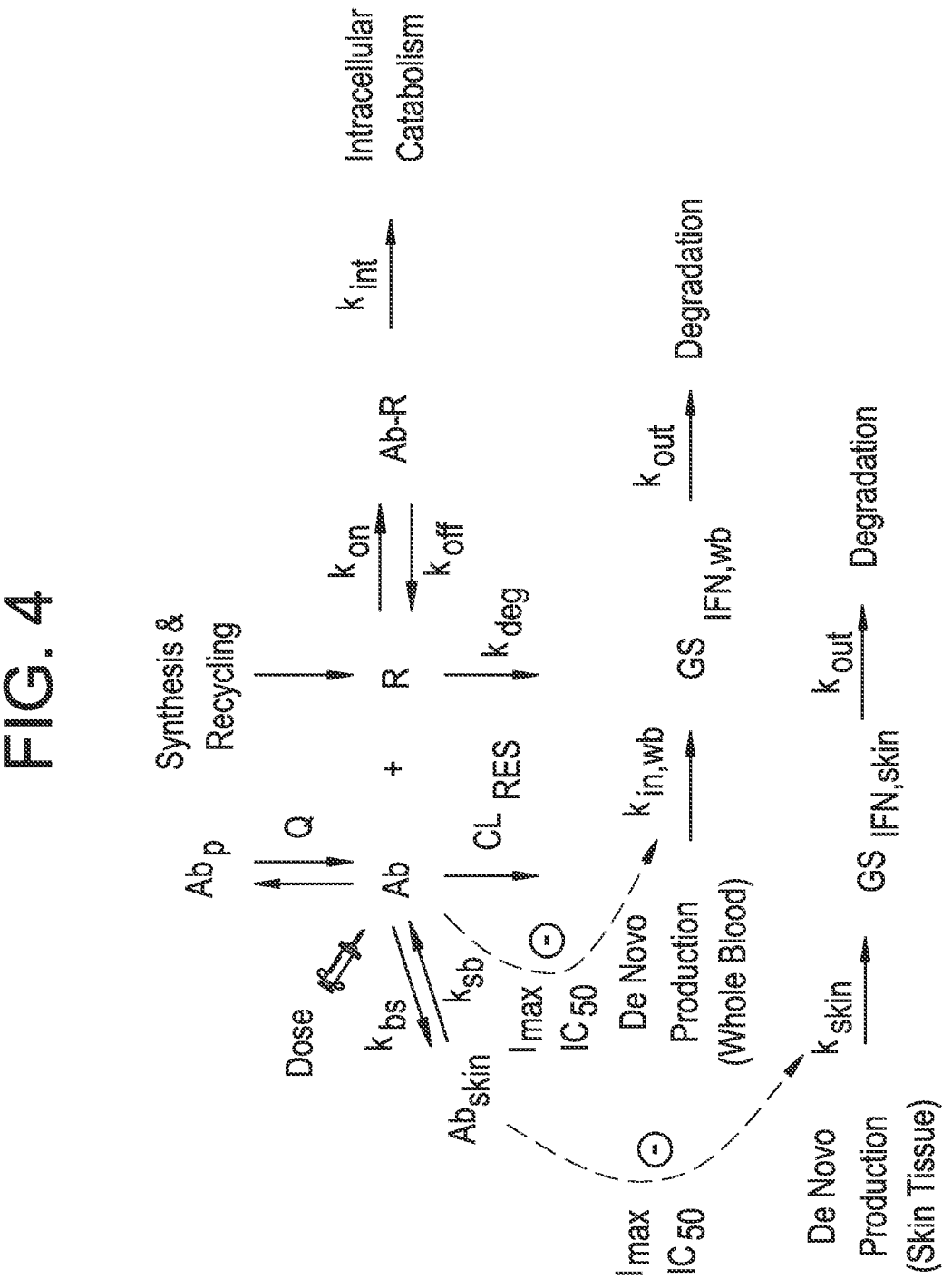

Synthesis &
Recycling
Intracellular
Catabolism
Ab p
Q
Dose
k on
k off
k int
Ab
+
R
Ab-R
k bs
k sb
CL RES
k deg
Ab skin
Imax
IC 50
De Novo
Production
(Whole Blood)
k in,wb
GS IFN,wb
k out
Degradation
Imax
IC 50
De Novo
Production
(Skin Tissue)
k skin
GS IFN,skin
k out
Degradation

FIG. 5A

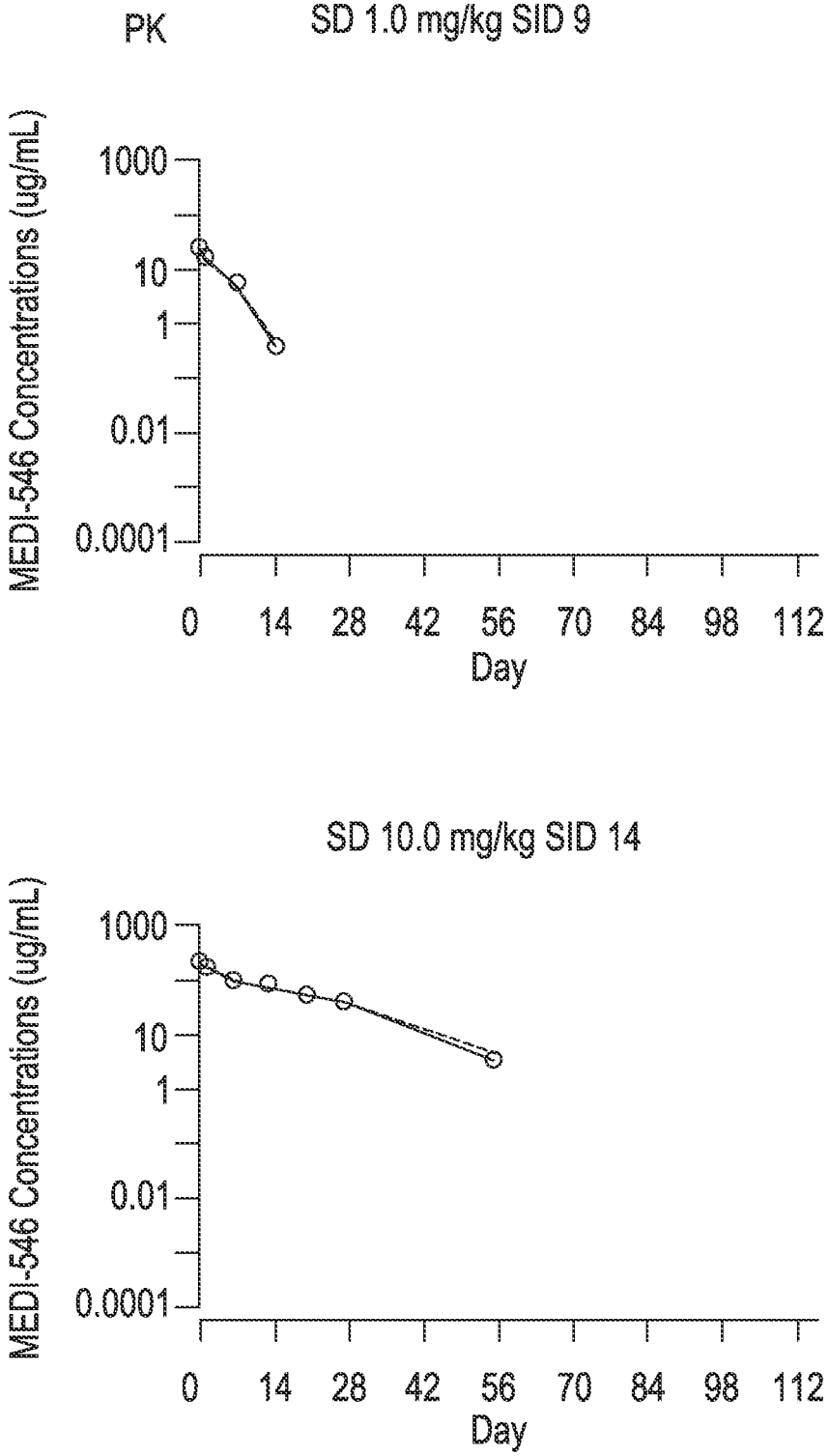

PK
SD 1.0 mg/kg SID 9
MEDI-546 Concentrations (ug/mL)
1000
10
1
0.01
0.0001
0
14
28
42
56
70
84
98
112
Day
SD 10.0 mg/kg SID 14
MEDI-546 Concentrations (ug/mL)
1000
10
1
0.01
0.0001
0
14
28
42
56
70
84
98
112
Day

FIG. 5B

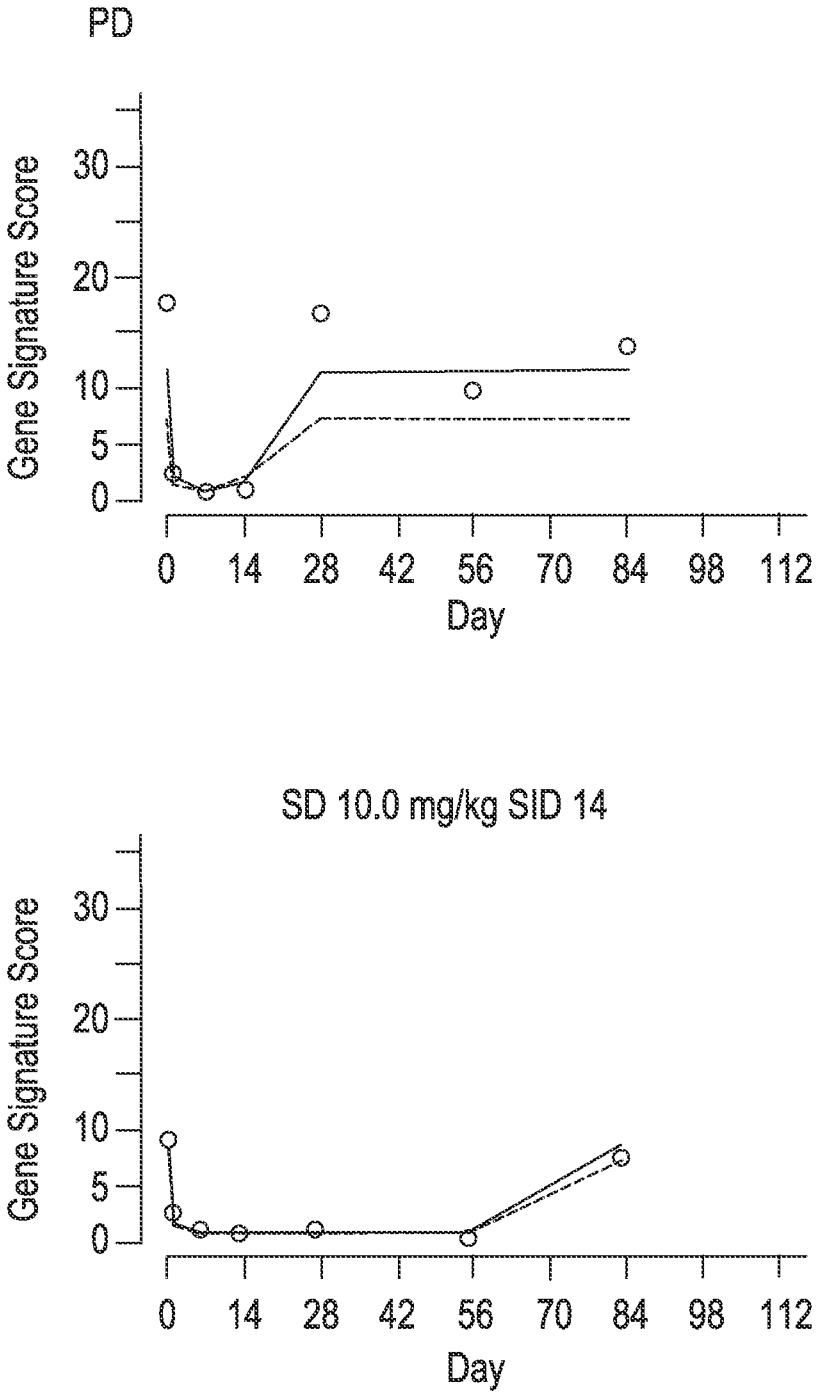

SD 1.0 mg/kg SID 9
PD
Gene Signature Score
30
20
10
5
0
0
14
28
42
56
70
84
98
112
Day
SD 10.0 mg/kg SID 14
Gene Signature Score
30
20
10
5
0
0
14
28
42
56
70
84
98
112
Day

FIG. 5C

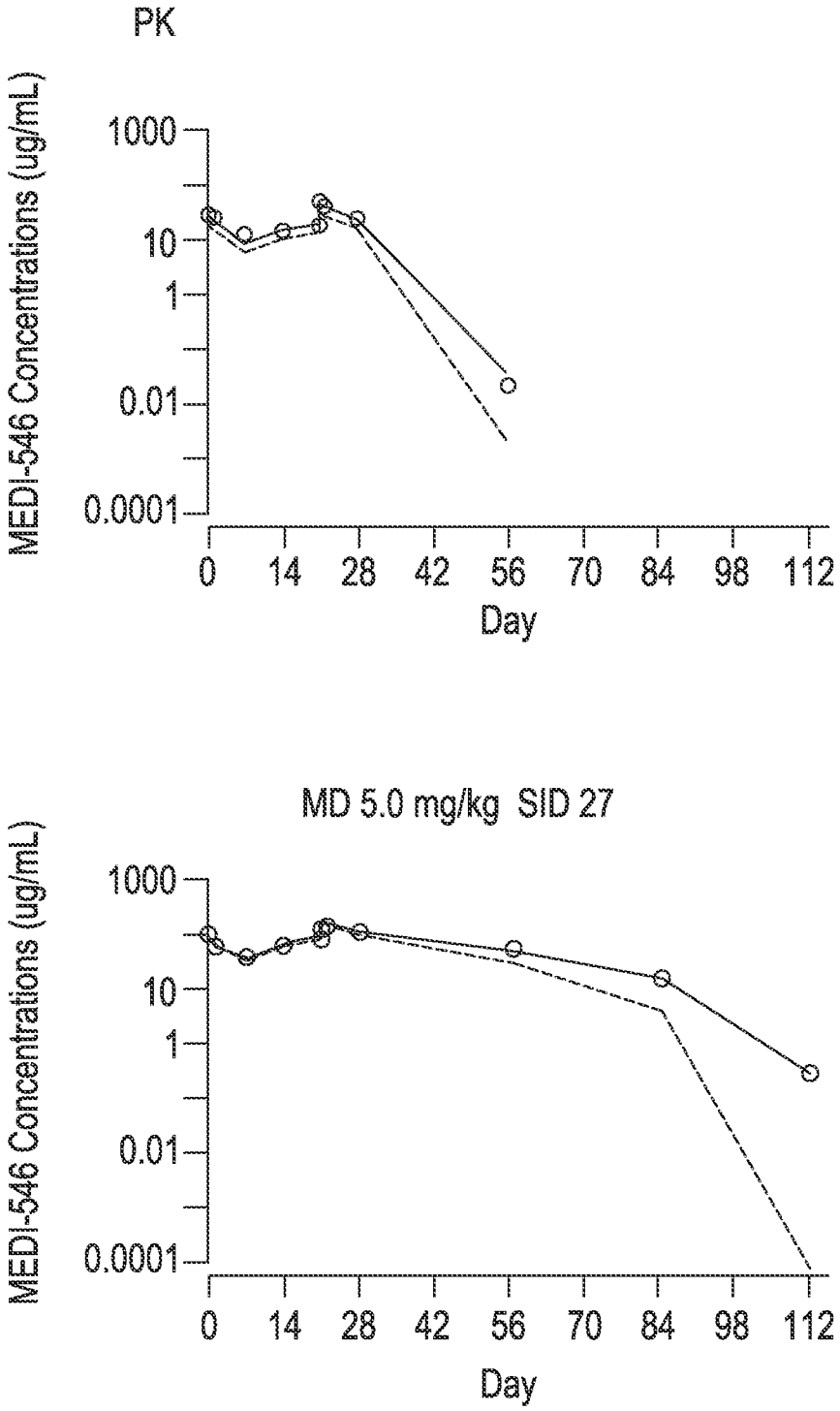

MD 1.0 mg/kg SID 24
PK
MEDI-546 Concentrations (ug/mL)
1000
10
1
0.01
0.0001
0
14
28
42
56
70
84
98
112
Day
MD 5.0 mg/kg SID 27
MEDI-546 Concentrations (ug/mL)
1000
10
1
0.01
0.0001
0
14
28
42
56
70
84
98
112
Day

FIG. 5D

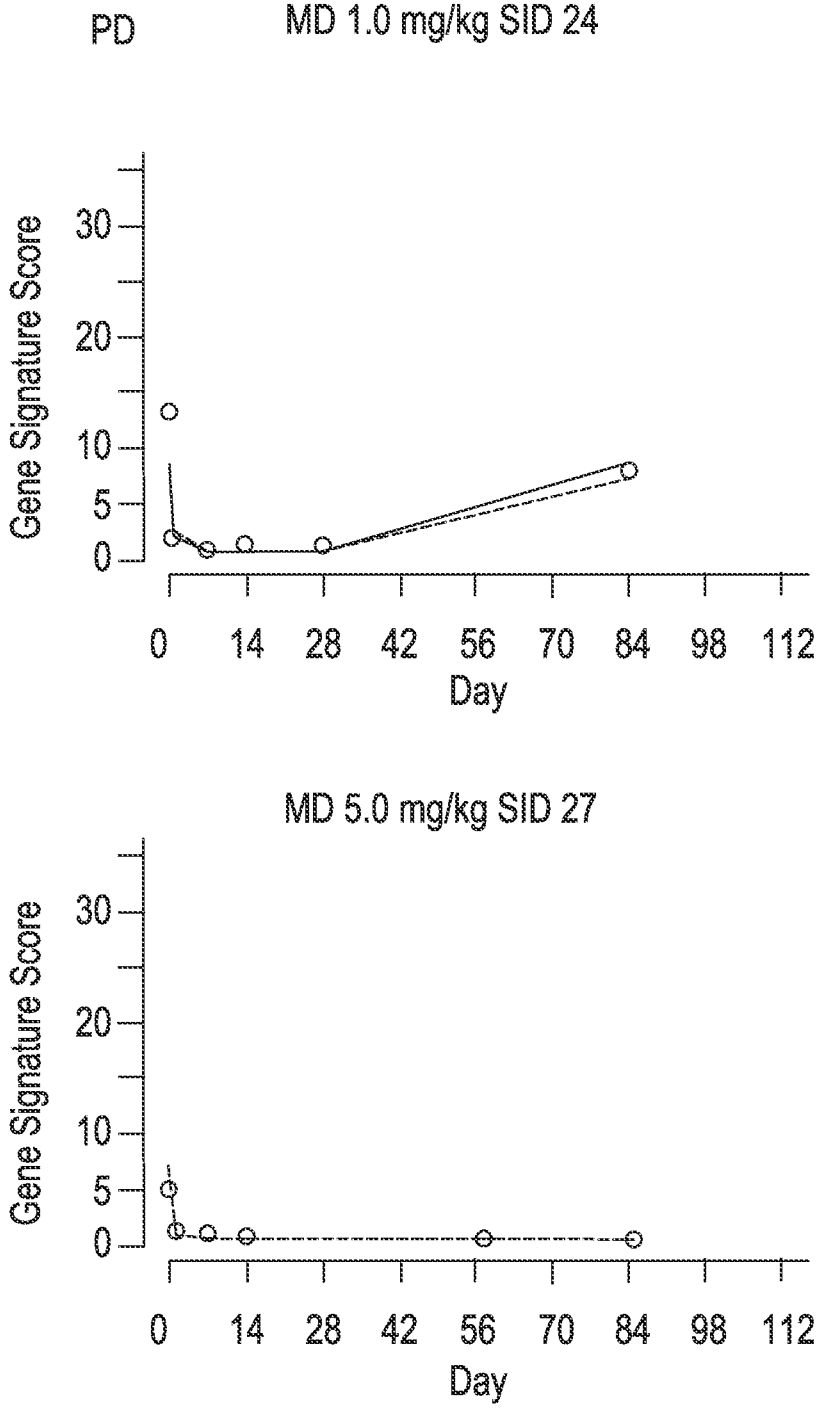

PD
MD 1.0 mg/kg SID 24
Gene Signature Score
30
20
10
5
0
0
14
28
42
56
70
84
98
112
Day
MD 5.0 mg/kg SID 27
Gene Signature Score
30
20
10
5
0
0
14
28
42
56
70
84
98
112
Day

FIG. 6A

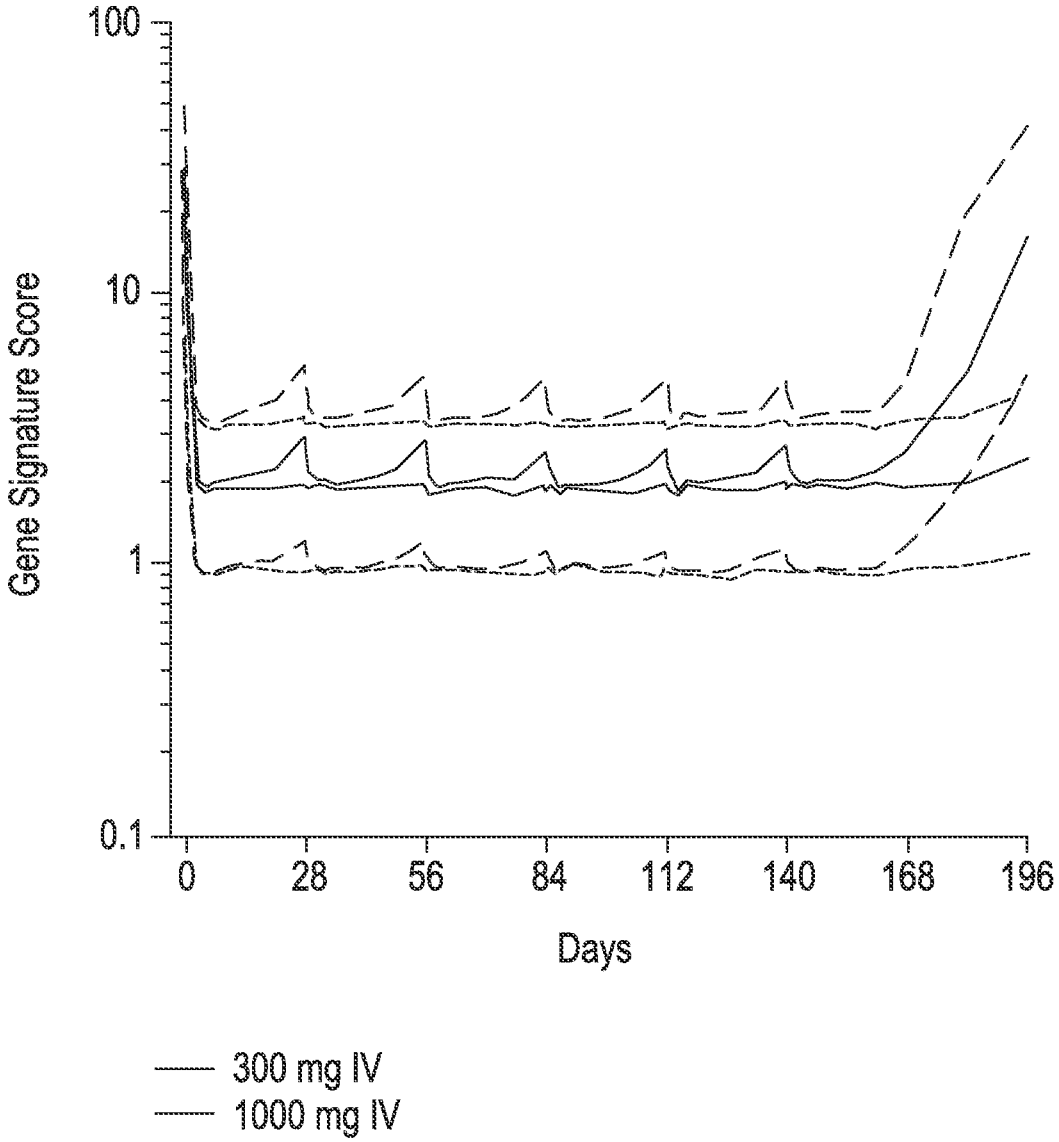

100
10
1
0.1
Gene Signature Score
0
28
56
84
112
140
168
196
Days
300 mg IV
1000 mg IV

FIG. 6B

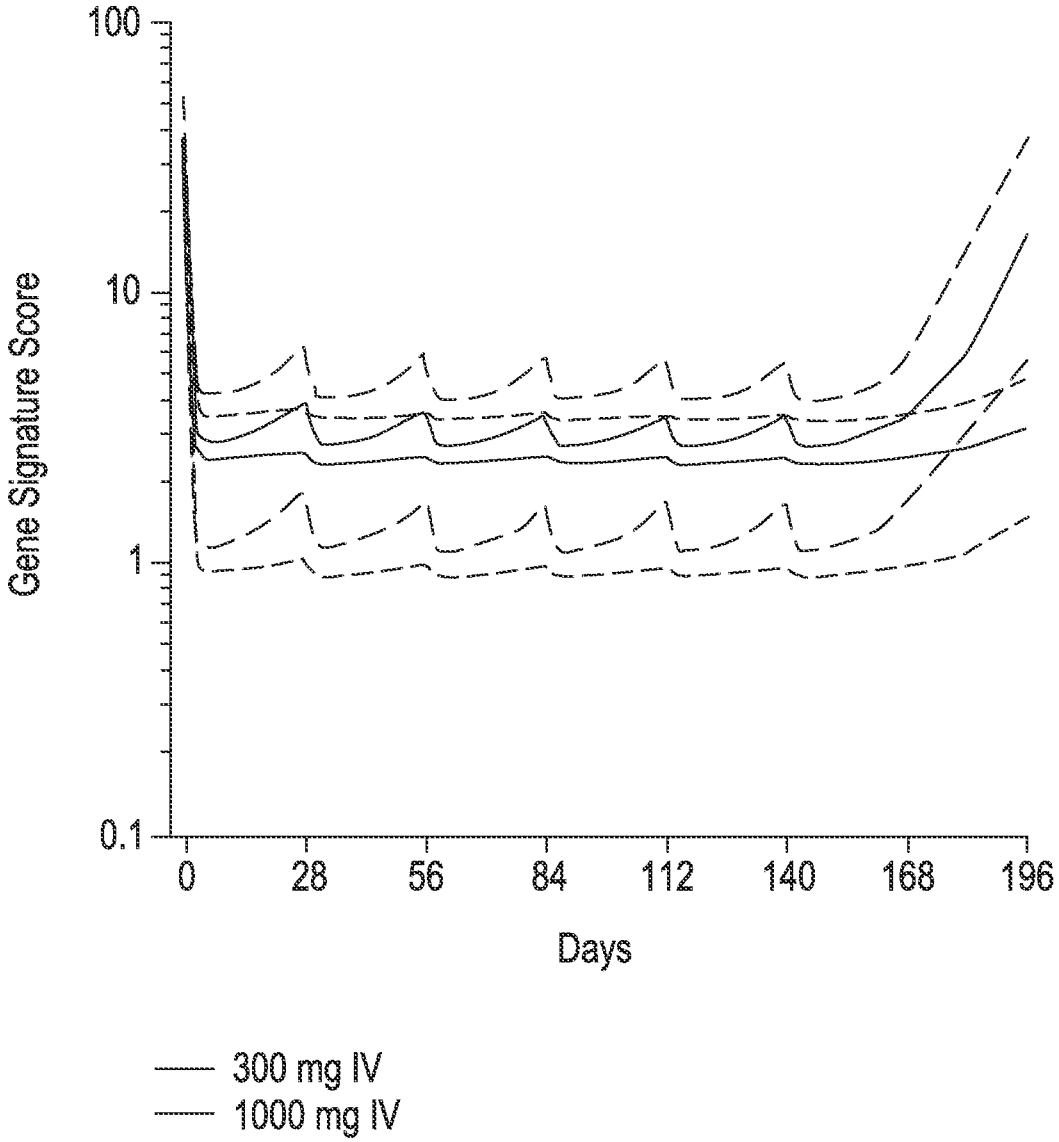

100
10
1
0.1
Gene Signature Score
0
28
56
84
112
140
168
196
Days
300 mg IV
1000 mg IV

FIG. 7

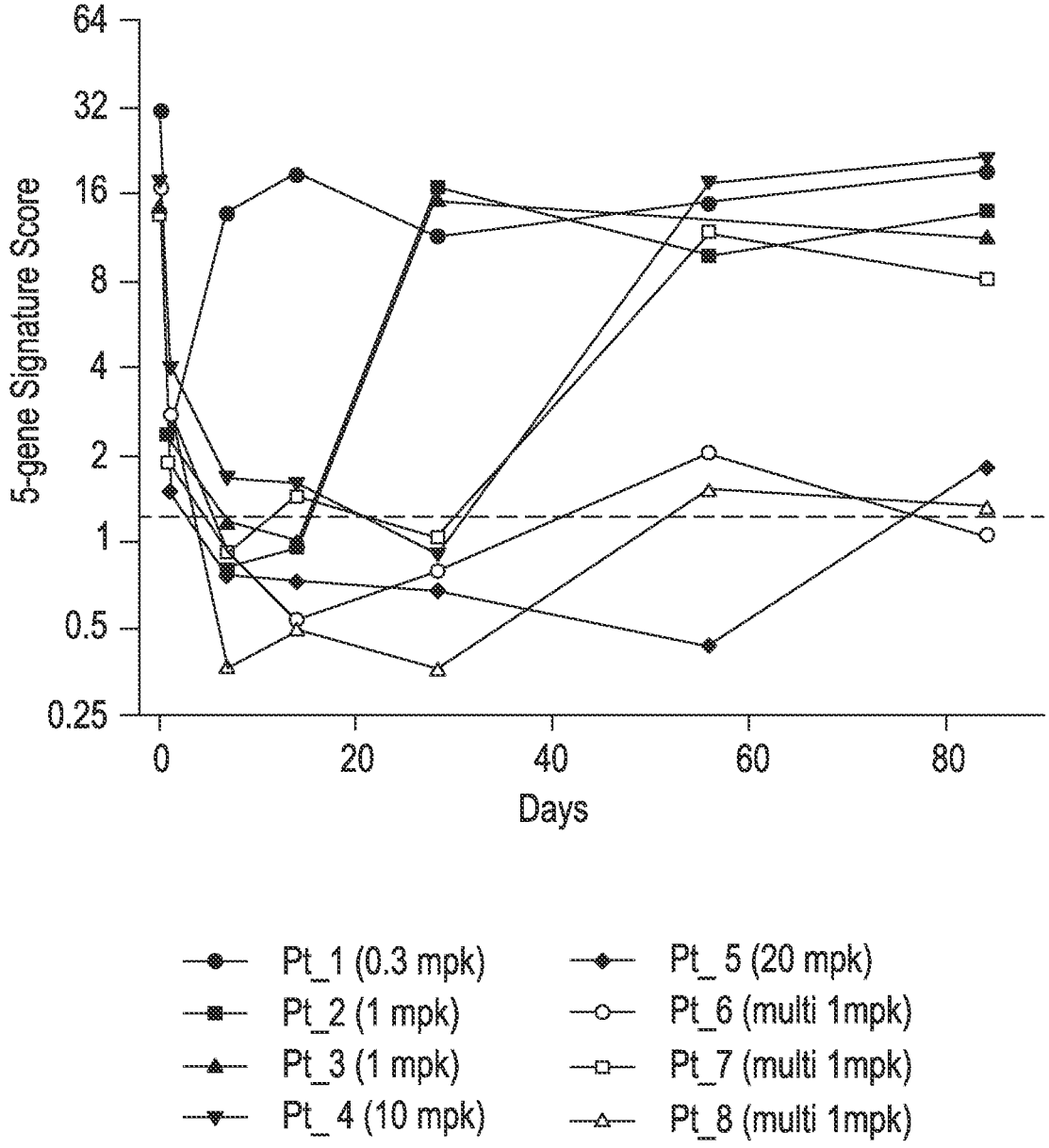

64
32
16
8
4
2
1
0.5
0.25
5-gene Signature Score
0
20
40
60
80
Days
Pt_1 (0.3 mpk)
Pt_2 (1 mpk)
Pt_3 (1 mpk)
Pt_ 4 (10 mpk)
Pt_ 5 (20 mpk)
Pt_6 (multi 1mpk)
Pt_7 (multi 1mpk)
Pt_8 (multi 1mpk)

FIG. 8A

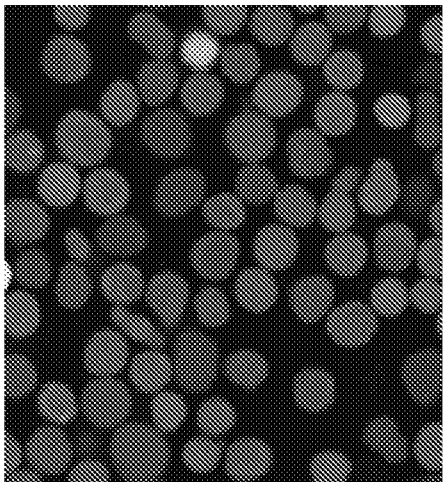


FIG. 8B

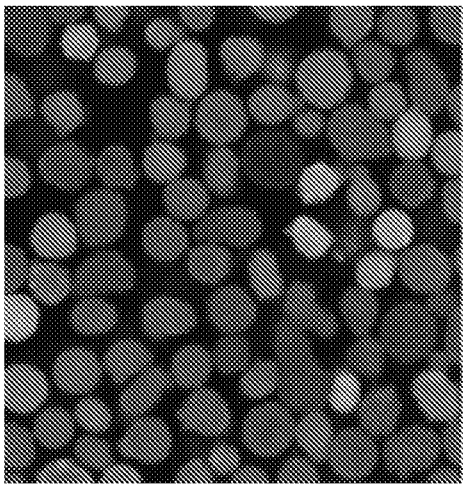


FIG. 9A

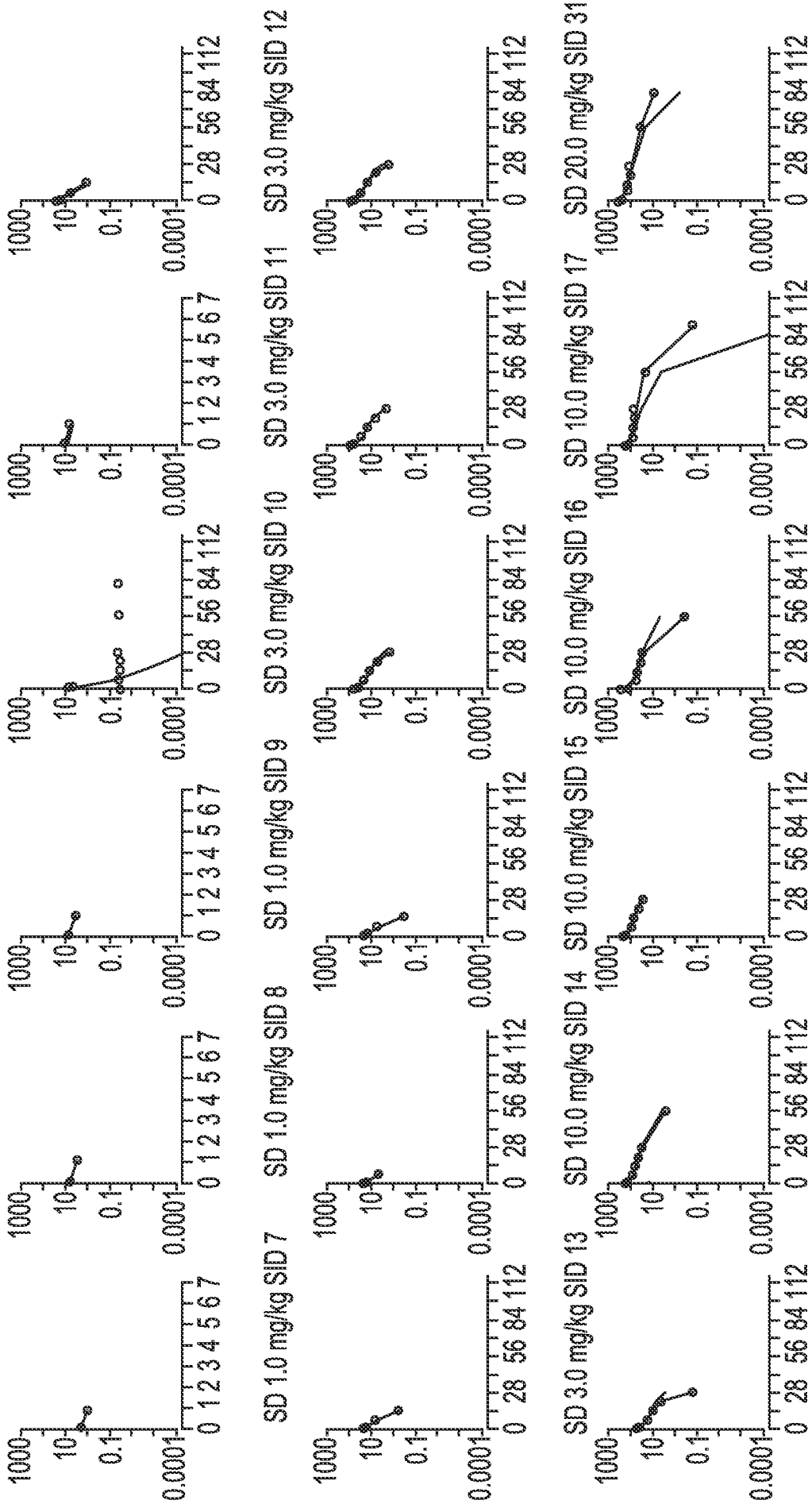

SD 0.1 mg/kg SID 1
SD 0.3 mg/kg SID 2
SD 0.3mg/kg SID 3
SD 0.3 mg/kg SID 4
SD 3.0 mg/kg SID 5
SD 1.0 mg/kg SID 6
SD 1.0 mg/kg SID 7
SD 1.0 mg/kg SID 8
SD 1.0 mg/kg SID 9
SD 3.0 mg/kg SID 10
SD 3.0 mg/kg SID 11
SD 3.0 mg/kg SID 12
SD 3.0 mg/kg SID 13
SD 10.0 mg/kg SID 14
SD 10.0 mg/kg SID 15
SD 10.0 mg/kg SID 16
SD 10.0 mg/kg SID 17
SD 20.0 mg/kg SID 31
1000
10
0.1
0.0001
0 1 2 3 4 5 6 7
0 28 56 84 112

FIG. 9B

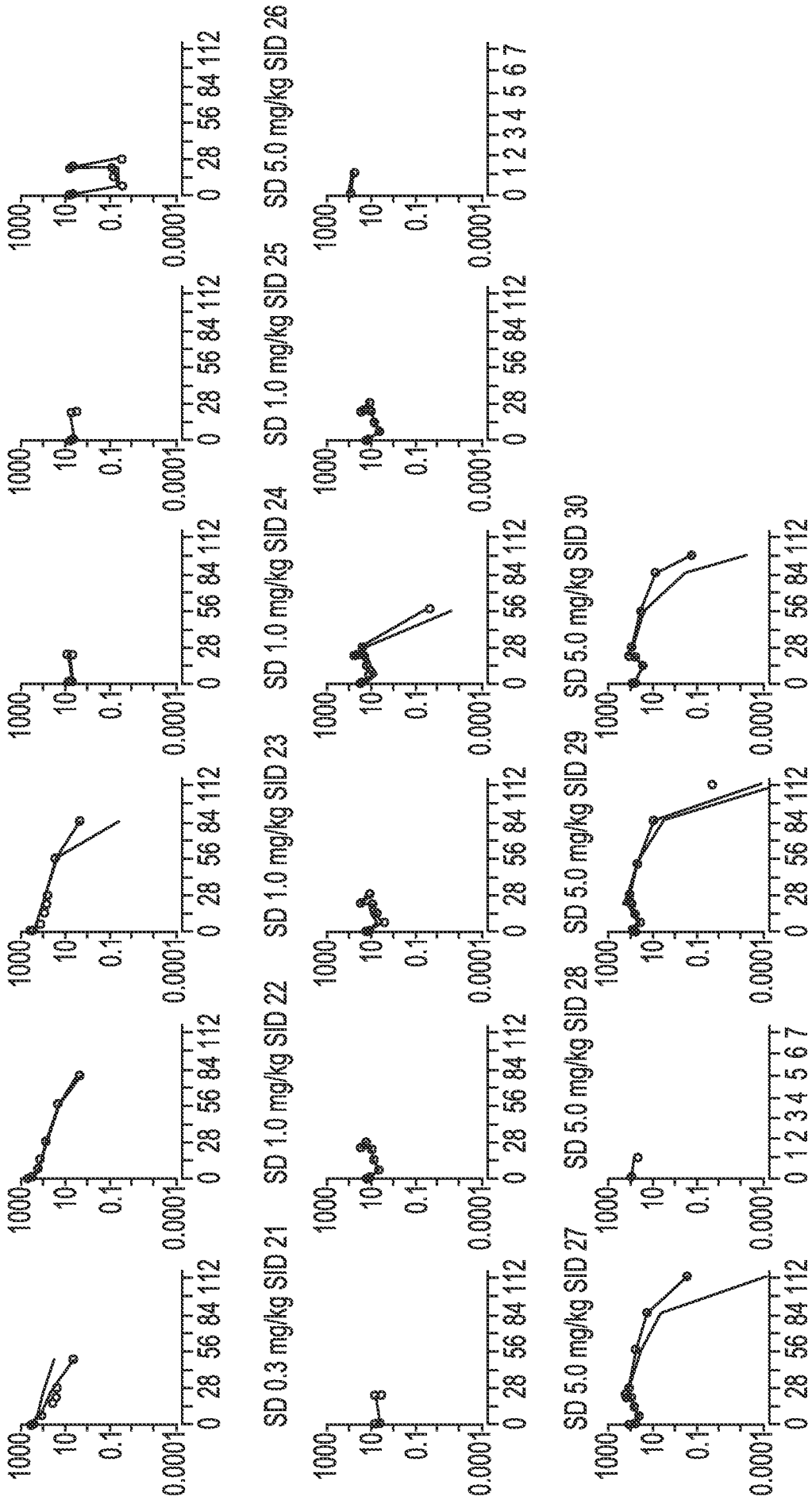

SD 20.0 mg/kg SID 32
SD 20.0 mg/kg SID 33
SD 20.0 mg/kg SID 34
SD 0.3 mg/kg SID 18
SD 0.3 mg/kg SID 19
SD 0.3 mg/kg SID 20
SD 0.3 mg/kg SID 21
SD 1.0 mg/kg SID 22
SD 1.0 mg/kg SID 23
SD 1.0 mg/kg SID 24
SD 1.0 mg/kg SID 25
SD 5.0 mg/kg SID 26
SD 5.0 mg/kg SID 27
SD 5.0 mg/kg SID 28
SD 5.0 mg/kg SID 29
SD 5.0 mg/kg SID 30
1000
10
0.1
0.0001
0 28 56 84 112
0 1 2 3 4 5 6 7

FIG. 10A

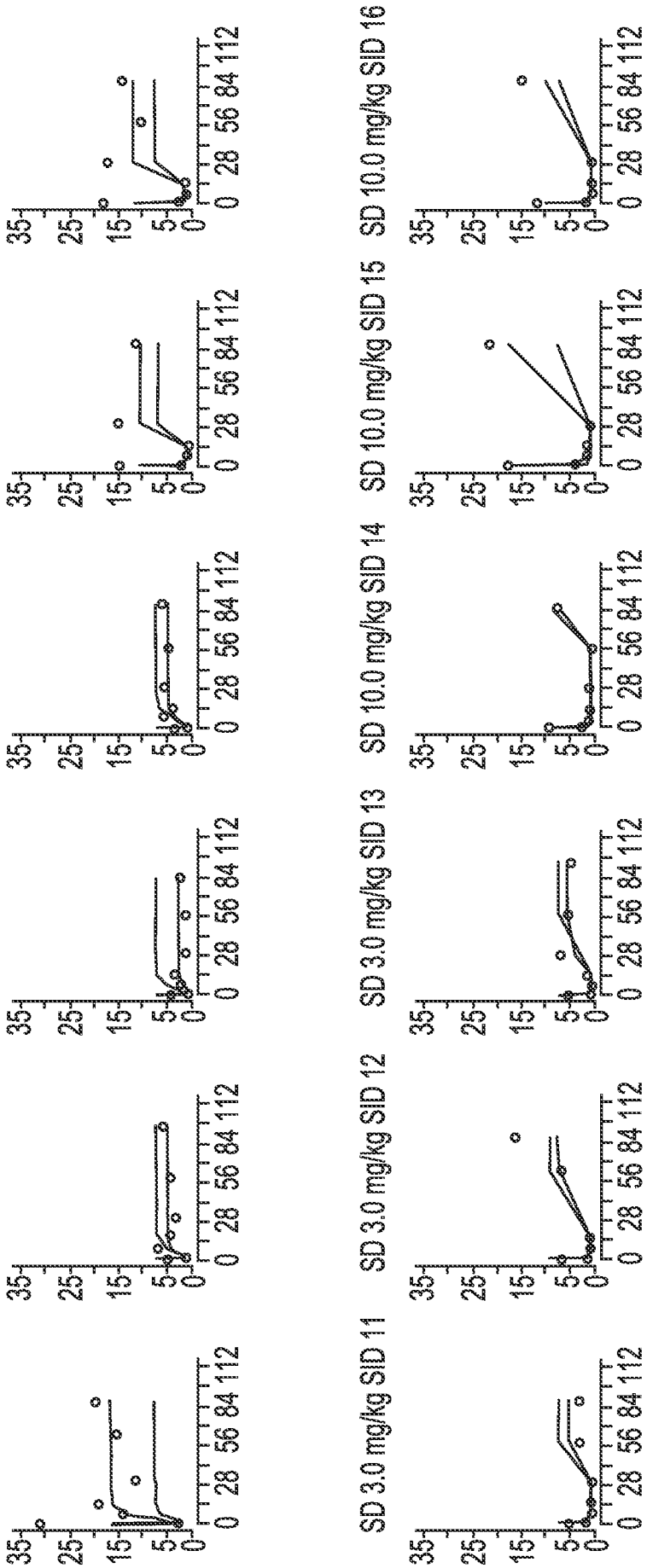

SD 0.3 mg/kg SID 2
SD 0.3 mg/kg SID 3
SD 0.3 mg/kg SID 4
SD 0.3 mg/kg SID 5
SD 1.0 mg/kg SID 6
SD 1.0 mg/kg SID 9
SD 3.0 mg/kg SID 11
SD 3.0 mg/kg SID 12
SD 3.0 mg/kg SID 13
SD 10.0 mg/kg SID 14
SD 10.0 mg/kg SID 15
SD 10.0 mg/kg SID 16
0 5 15 25 35
0 28 56 84 112

FIG. 10B

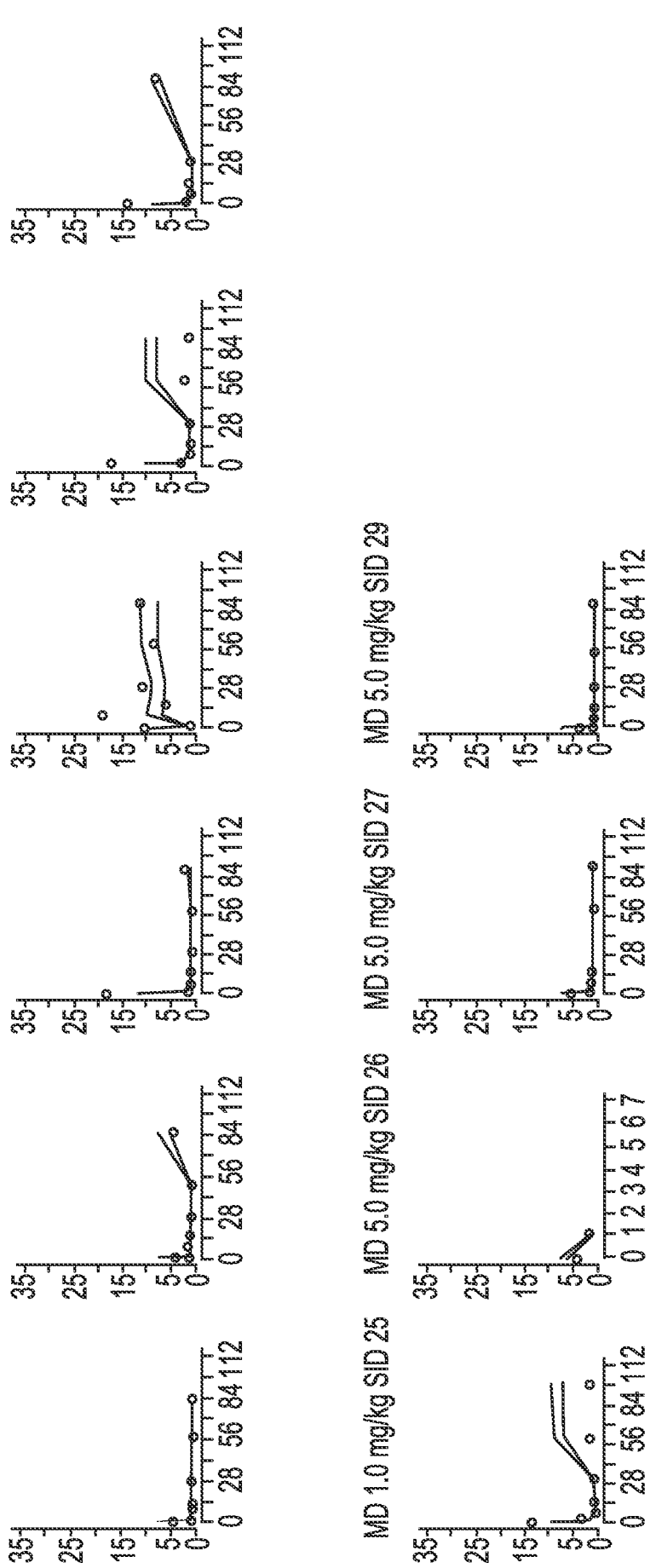

SD 20.0 mg/kg SID 31
SD 20.0 mg/kg SID 32
SD 20.0 mg/kg SID 34
MD 0.3 mg/kg SID 19
MD 1.0 mg/kg SID 23
MD 1.0 mg/kg SID 24
MD 1.0 mg/kg SID 25
MD 5.0 mg/kg SID 26
MD 5.0 mg/kg SID 27
MD 5.0 mg/kg SID 29
0 28 56 84 112
0 1 2 3 4 5 6 7

FIG. 11A

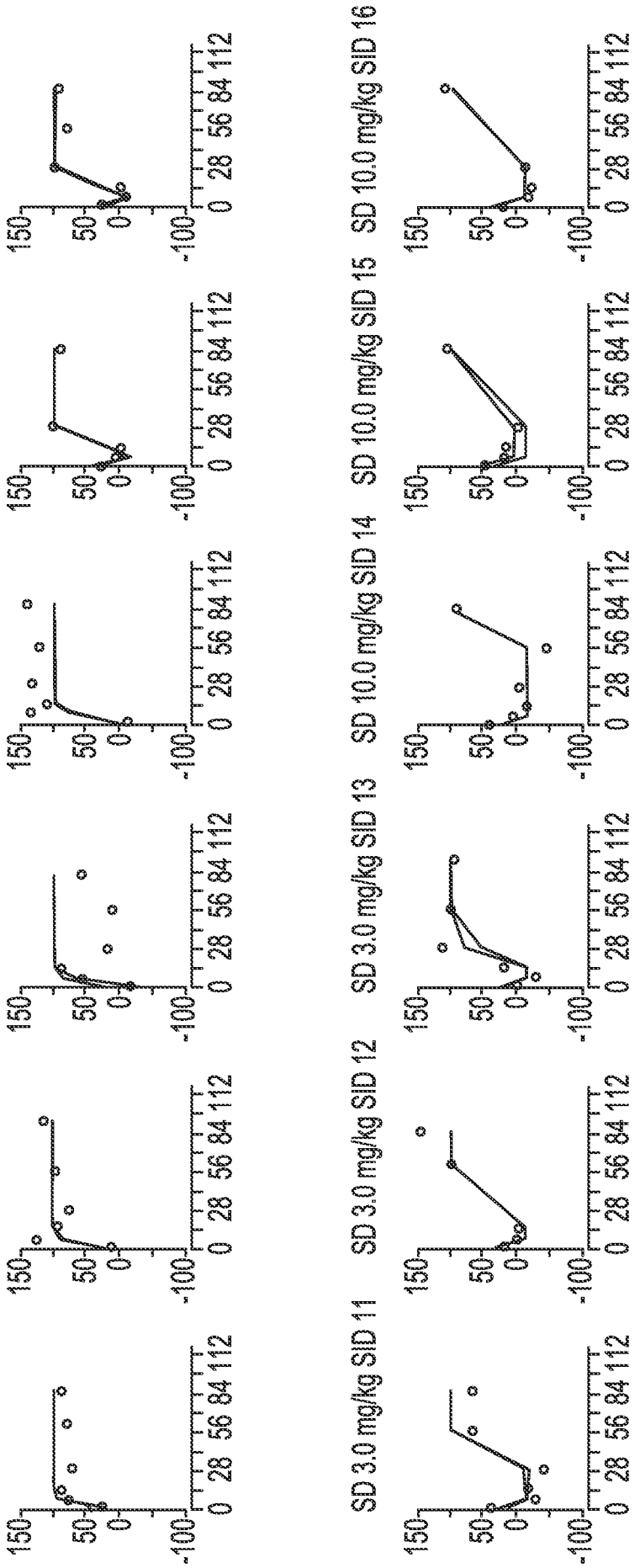

SD 0.3 mg/kg SID 2
SD 0.3 mg/kg SID 3
SD 0.3 mg/kg SID 4
SD 0.3 mg/kg SID 5
SD 1.0 mg/kg SID 6
SD 1.0 mg/kg SID 9
SD 3.0 mg/kg SID 11
SD 3.0 mg/kg SID 12
SD 3.0 mg/kg SID 13
SD 10.0 mg/kg SID 14
SD 10.0 mg/kg SID 15
SD 10.0 mg/kg SID 16
150
50
0
-100
0 28 56 84 112

FIG. 11B

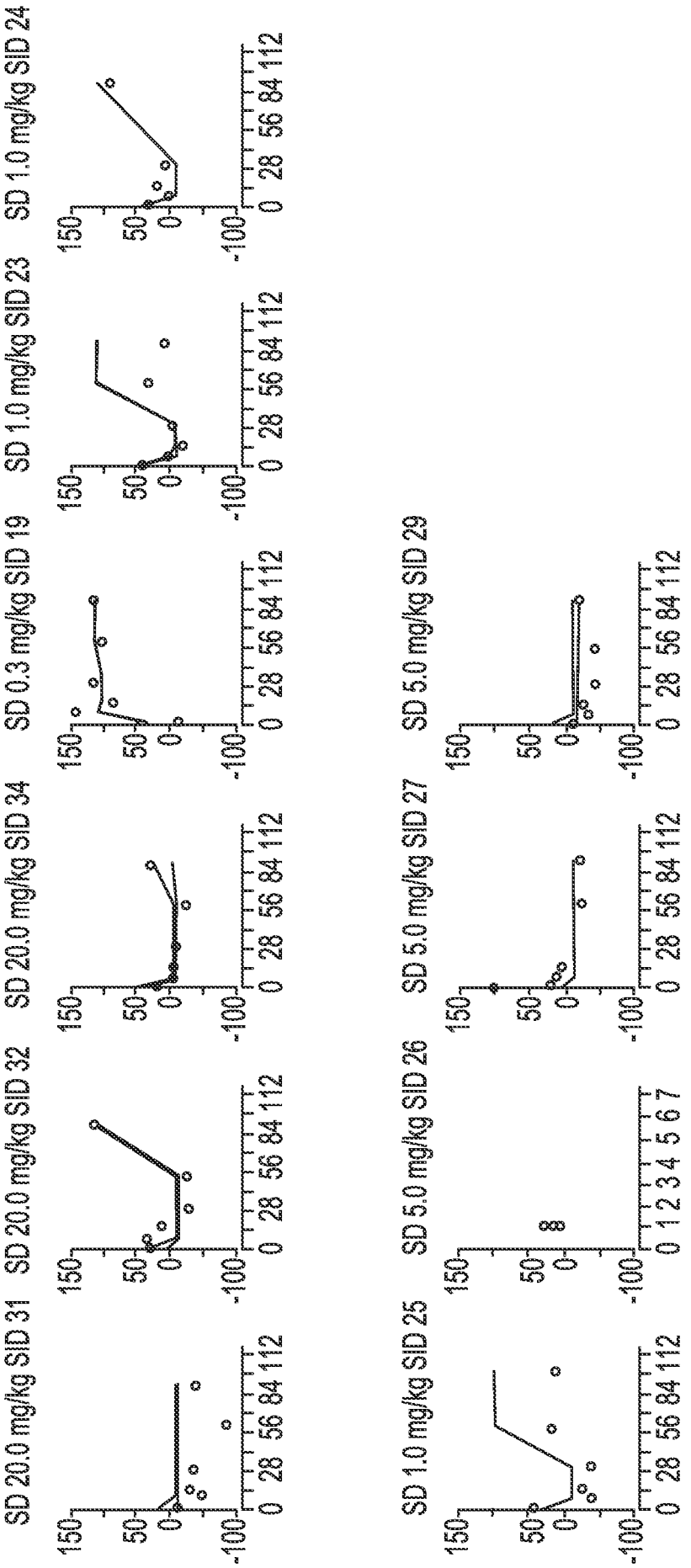

SD 20.0 mg/kg SID 31
SD 20.0 mg/kg SID 32
SD 20.0 mg/kg SID 34
SD 0.3 mg/kg SID 19
SD 1.0 mg/kg SID 23
SD 1.0 mg/kg SID 24
SD 1.0 mg/kg SID 25
SD 5.0 mg/kg SID 26
SD 5.0 mg/kg SID 27
SD 5.0 mg/kg SID 29
150
50
0
-100
0 28 56 84 112
0 1 2 3 4 5 6 7
8

FIG. 12

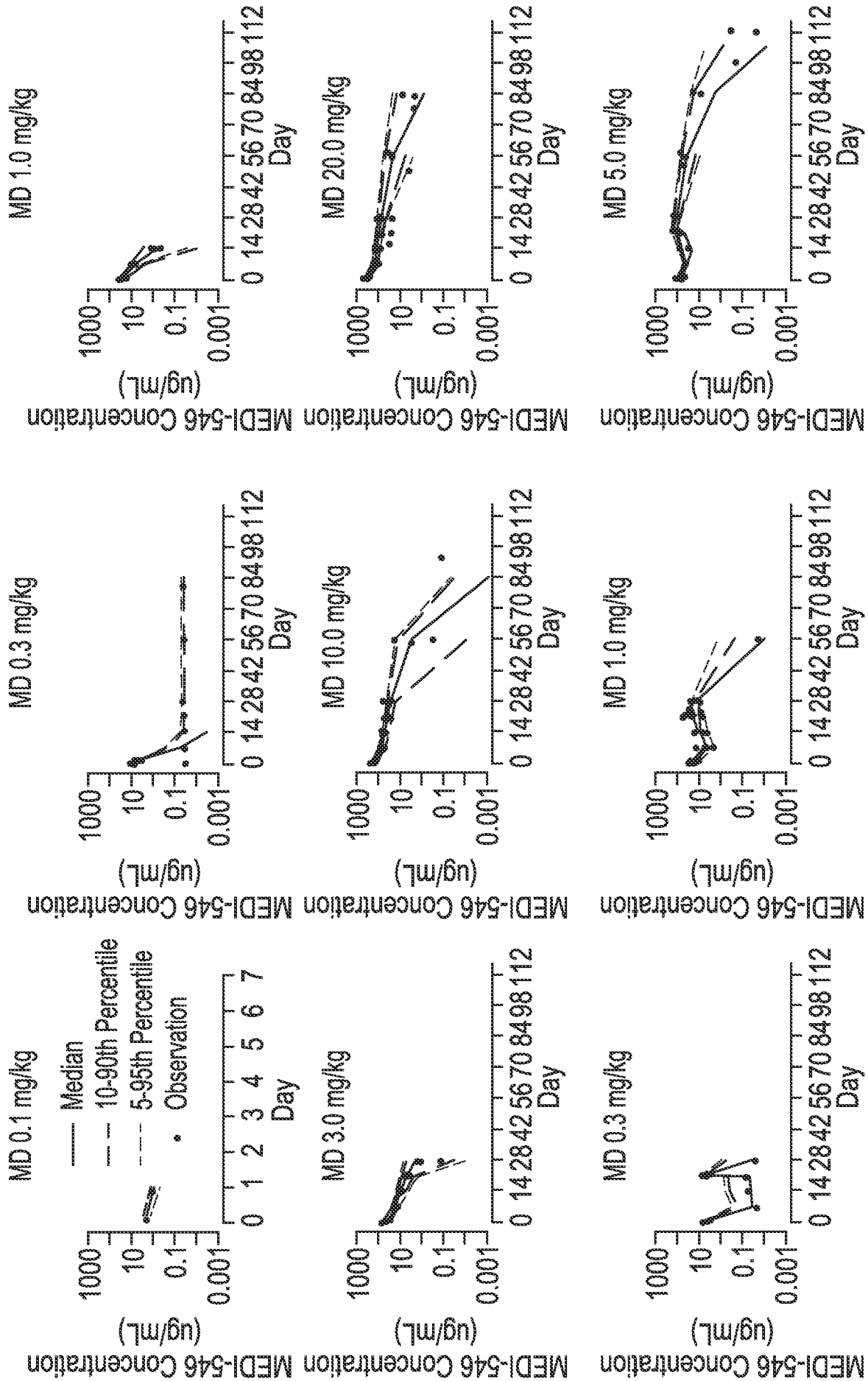

MD 0.1 mg/kg
MD 0.3 mg/kg
MD 1.0 mg/kg
MD 3.0 mg/kg
MD 10.0 mg/kg
MD 20.0 mg/kg
MD 5.0 mg/kg
Median
10-90th Percentile
5-95th Percentile
Observation
MEDI-546 Concentration (ug/mL)
1000
10
0.1
0.001
Day
0 1 2 3 4 5 6 7
0 14 28 42 56 70 84 98 112

FIG. 13

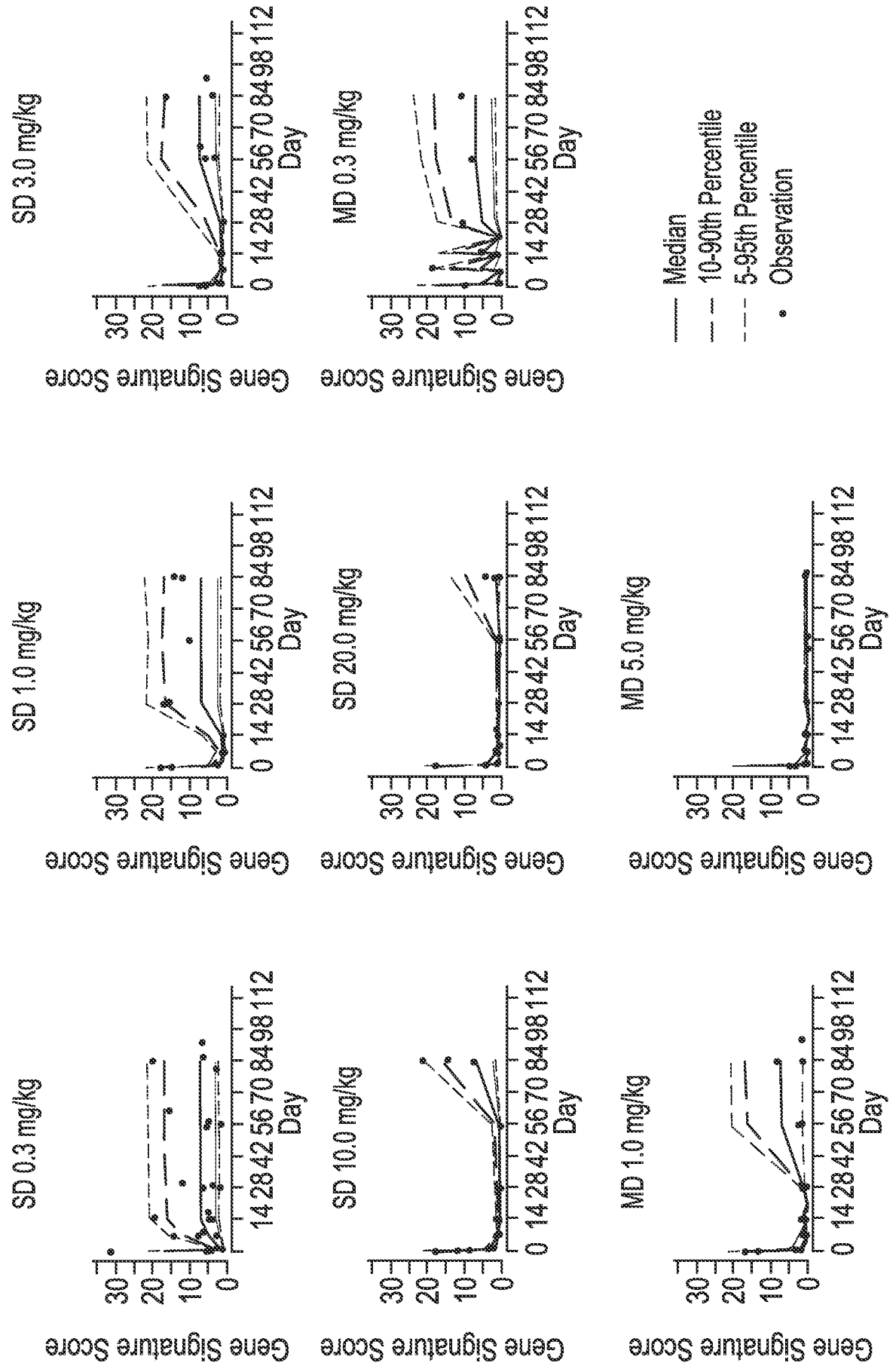

SD 0.3 mg/kg
SD 1.0 mg/kg
SD 3.0 mg/kg
MD 0.3 mg/kg
MD 1.0 mg/kg
SD 10.0 mg/kg
SD 20.0 mg/kg
MD 5.0 mg/kg
Gene Signature Score
Day
0 14 28 42 56 70 84 98 112
0 10 20 30
Median
10-90th Percentile
5-95th Percentile
Observation

FIG. 14A

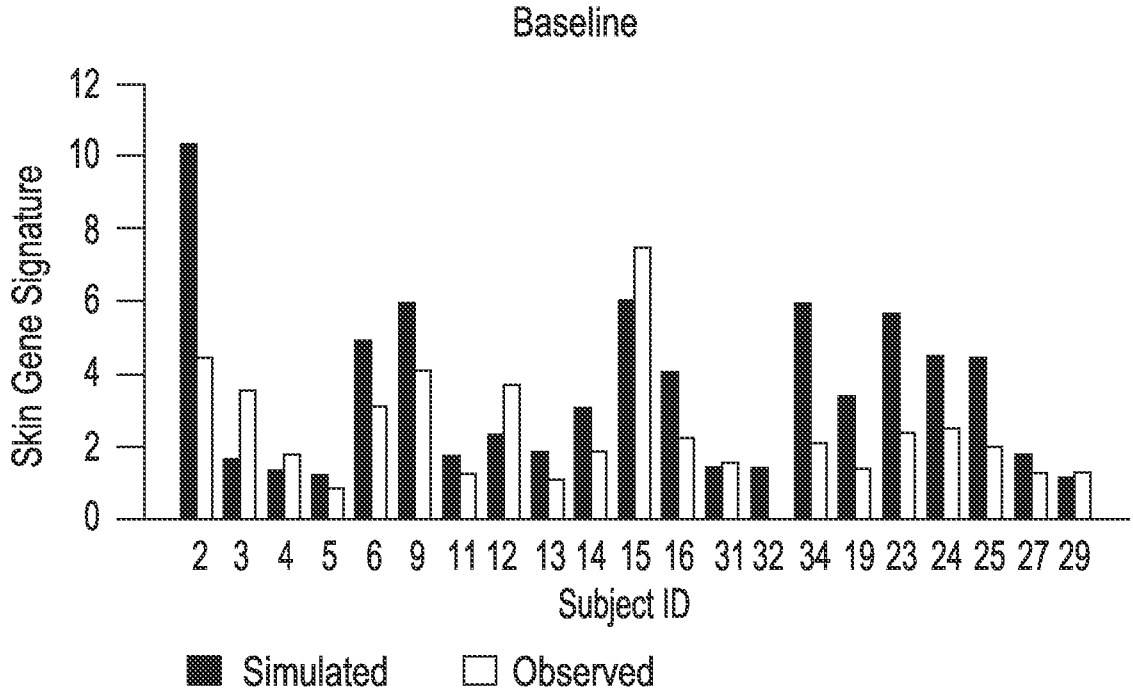
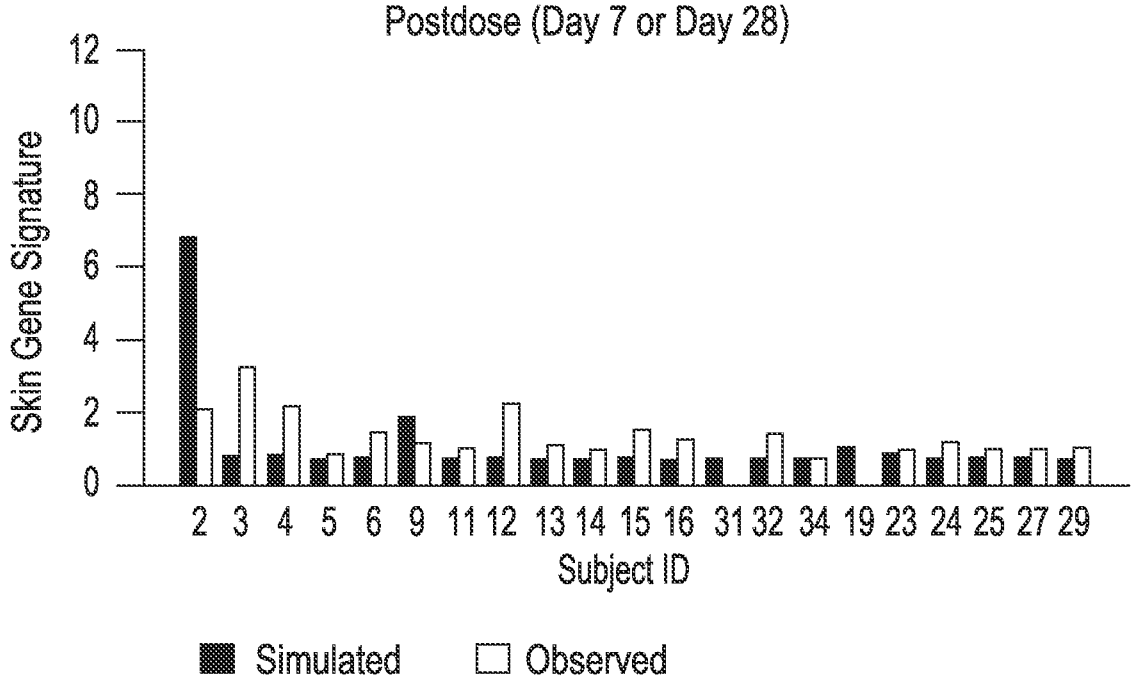


FIG. 14B



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/45327

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07K 16/249, 16/00; A61K 39/395 (2013.01)
USPC - 424/145.1, 141.1, 158.1, 130.1, 142.1, 143.1; 530/389.2, 388.2, 388.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): C07K 16/249, 16/00; A61K 38/395 (2013.01)
USPC: 424/145.1, 141.1, 158.1, 130.1, 142.1, 143.1; 530/389.2, 388.2, 388.1, 387.1, 386

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Micropatent (US-G, US-A, EP-A, EP-B, WO, JP-bib, DE-C,B, DE-A, DE-T, DE-U, GB-A, FR-A; USPTO Web Page; PCT Patentscope; DialogPRO, Google Scholar; Elsevier Science Direct; 'IFN-alpha,' 'autoimmune disease,' dosage, antibody, 'marker signature,' 'baseline level,' 'monitoring therapy,' prognosis, treatment, 'computer-readable medium,' pharmacodynamics, pharmacokinetics

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0287022 A1 (YAO, Y et al.) November 24, 2011; abstract; figure 60; paragraphs [0003], [0004], [0008], [0009], [0046], [0076], [0095], [0107], [0110], [0111], [0121], [0125], [0129], [0132], [0137], [0139], [0181]-[0184], [0186], [0204], [0320], [0323], [0324]-[0329], [0592], [0544]-[0548], [0666], [0707]	1-28, 56-60, 63-69, 74-77, 80-98, 100-110, 124-141, 143-148
Y	US 2011/0008365 A1 (COYLE, A) January 13, 2011; paragraphs [0002], [0010], [0022], [0047], [0054], [0058], [0061], [0062]	1-28, 56-60
Y	US 2011/0159513 A1 (SCHOEBERL, B et al.) June 30, 2011; paragraphs [0012], [0015], [0019], [0062], [0067], [0070], [0191]	63-69, 74-77, 80-98, 100-110, 124-141, 143-148
Y	WO 2011/028933 A1 (HIGGS, B et al.) March 10, 2011; paragraphs [0003], [0006], [0029]	84-86, 127-129
Y	US 2011/083866 A1 (CLARKE, MF et al.) July 28, 2011; abstract; paragraphs [0003], [0020], [0086], [0131], [0246]	87-90, 97/96/63-66, 98/96/63-66, 130-133, 140/139/106-109, 141/139/106-109
Y	US 2008/0113011 A1 (QUAY, SC et al.) May 15, 2008; paragraphs [0014], [0015], [0017], [0019], [0023]-[0025], [0030], [0034], [0037], [0045], [0292], [0301], [0400], [0408]	92-95, 100-105, 135-138, 143-148
Y	US 2011/0250168 A1 (NAUWYNCK, H et al.) October 13, 2011; abstract; paragraphs [0006], [0016], [0023], [0025]	95/92/91/63-66, 138/135/134/106-109

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
04 November 2013 (04.11.2013)	12 NOV 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/45327

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 29-55, 61, 62, 70-73, 78, 79, 99, 111-123, 142
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

摘要

本公开内容提供了用于治疗患有一种I型IFN介导的疾病或失调的受试者方法，该方法包括给予一种固定剂量的抗干扰素α受体抗体。本公开内容还提供了用于抑制受试者体内的一种I型干扰素(IFN)基因特征标记(GS)的方法。此外，本公开内容提供了对患有一种I型IFN介导的疾病或失调的受试者体内的疾病进展进行预后或监测的方法、预测一种给药方案的方法、鉴别一种候选治疗剂的方法、针对一种治疗剂鉴别一位患者作为一名候选者的方法、以及设计一种个体化治疗的方法。