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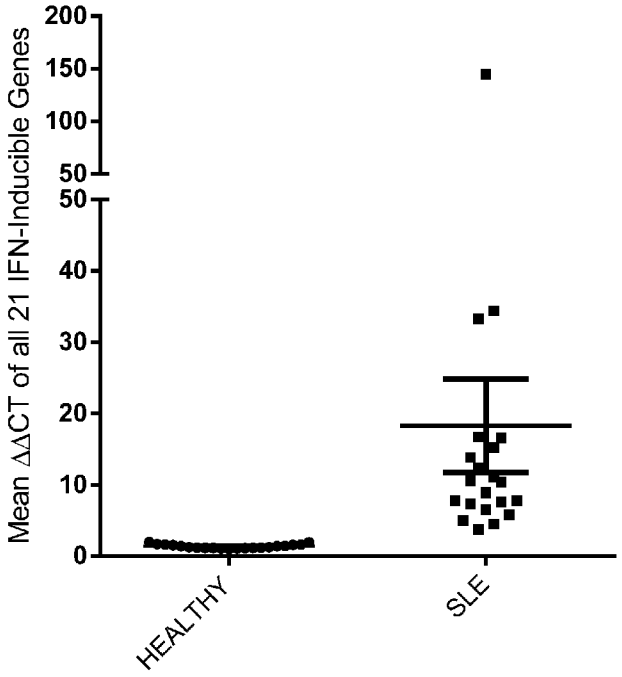
(54) Title: TYPE I INTERFERON SIGNATURES AND METHODS OF USE

FIG. 1A



(57) Abstract: Type I interferon (IFN-I) signatures are useful in methods of diagnosing whether a subject (or patient) with IFN-I mediated disease will be responsive to treatment with an IFN-I inhibitor and treating or refraining from treating the subjects.

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[Continued on next page]

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Type I Interferon Signatures and Methods of Use

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on October 17, 2019, is named JBI6021USNP1_ST25.txt and is 63 kilobytes in size.

Field

The disclosure is directed to Type I interferon signatures and methods of using them.

Background

Type I interferon (IFN-I) may exhibit protective or deleterious effects depending on the disease setting. For example, recombinant IFN-I has been utilized as a treatment for a variety of cancers (Medrano *et al,. Oncotarget 8:71249-84, 2017)*, chronic hepatitis (Woo *et al., Annals of Translational Medicine 5:159, 2017*), and multiple sclerosis (Zettl *et al., Expert Review of Clinical Immunology 14:137-53, 2018*), while many autoimmune disorders may benefit from blockade of this pathway (Muskardin and Niewold, *Nature Reviews Rheumatology 14:214-28, 2018*). Evaluation of IFN-Iinducible transcripts (e.g., IFN-I signature) can facilitate assessment of disease status and/or efficacy of treatment in established disease or preventive interventions within early onset diseases in which IFN-I plays a role. Therefore, there is a need to develop sensitive means to detect IFN-I signatures.

Summary of the disclosure

The disclosure provides a method of diagnosing and treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease that is responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor.

The disclosure also provides a method of treating a subject suspected to have or having a type I interferon (IFN-I) mediated disease with an IFN-I inhibitor, comprising

determining that the subject has an elevated IFN-I signature by

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining that the subject has the elevated IFN-I signature when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject determined to have the elevated IFN-I signature to treat the IFN-I mediated disease.

The disclosure also provides a method of detecting an elevated type I interferon (IFN-I) signature in a subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

detecting the elevated IFN-I signature in the subject when the combined expression value is equal to or higher than a threshold value.

The disclosure also provides a method of detecting a baseline type I interferon (IFN-I) signature in a subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

detecting the baseline IFN-I signature in the subject when the combined expression value is less than a threshold value.

The disclosure also provides a method of diagnosing and treating a subject having a type I interferon (IFN-I) mediated disease, comprising:

obtaining a biological sample from a subject suspected to have or having a type I interferon (IFN-I) mediated disease;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value; and

treating the subject suspected to have or having IFN-I mediated disease by administering a therapeutically effective amount of an IFN-I inhibitor to the subject.

The disclosure also provides an *in vitro* method for predicting and/or diagnosing that a subject has an IFN-I mediated disease, comprising:

obtaining a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

predicting and/or diagnosingthat the subject has the IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value.

The disclosure also provides a method of diagnosing and treating a subject with type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2($2^{\wedge -ddCT}$)); or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2($2^{\wedge -ddCT}$)| (Formula I); or any combination thereof;

diagnosing the subject with IFN-I mediated disease that is responsive to treatment with the IFN-I inhibitor when SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2($2^{\wedge\text{-ddCT}}$) value is equal to or higher than a threshold SUMlog2($2^{\wedge\text{-ddCT}}$) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor.

The disclosure also provides a method of determining whether a subject having a type I interferon (IFN-I) mediated disease is responsive to treatment with an IFN-I inhibitor and deciding whether to treat the subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease as responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value or diagnosing the subject with the IFN-I mediated disease as non-responsive to treatment with the IFN-I inhibitor when the combined expression value is less than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor or refraining from administering the IFN-I inhibitor to the subject diagnosed as non-responsive to treatment with the IFN-I inhibitor.

Brief Description of the Drawings

FIG. 1A shows comparison of the mean fold change (ΔΔCT) and standard error of the mean (SEM) of 21 IFN-inducible genes in blood from a healthy and SLE cohort.

FIG. 1B shows the process of identifying a 10-gene set (POISE) used for assessing Type I interferon (IFN-I) signature expression.

FIG. 2 shows a curve of simulation correlating the POISE score to false positive and true positive IFN-I signature samples. POISE score of 35 (arrow) correlated to 90% true positive.

FIG. 3 shows the correlation between subject specific POISE Score and subject specific SUMΔCT.

FIG. 4 shows the distribution of POISE Score in SLE and Healthy subjects (HC) calculated on qPCR samples. A POISE score of 35 correctly discriminated 2 populations of SLE subjects; one

having elevated IFN-I in comparison with the majority of healthy controls and one with an elevated IFN-I signature.

FIG. 5 shows the correlation of the POISE Score with serum IFN-α protein concentrations (log(pg/mL)) indicating that the POISE Score (x-axis) detects elevated IFN-I signature before IFN-α protein concentration (y-axis) reaches assay detectable levels in the serum of lupus patients or healthy control subjects.

FIG. 6 shows the distribution of POISE scores at the time of screening for JNJ-55920839 phase 1 study. in SLE and healthy subjects based on site geography. POISE score of >35 was considered IFN-I positive and required for enrollment of part B of trial.

FIG. 7 shows the asessment of the POISE scores at baseline by response status (non-responders: n = 10; responders: n = 5; placebo: n = 8). Response status was based on SRI-4 at day 100.

FIG. 8 shows the clinical responses at day 100 of four secondary descriptive endpoints in placebo (left column in each group) and JNJ-55920839 (right column in each group) treated subjects. PGA, Physician's Global Assessment of Disease Activity; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI, Systemic Lupus Erythematosus Responder Index; SRI-4, 4 point or greater improvement in SRI; SRI-50, 50% response rate for improvement in SLEDAI.

FIG. 9 shows RNA-Seq assessment of the POISE scores in JNJ-55920839 responders and non-responders after the dosing period. Longitudinal IFN-I median score gene assessment using GSVA analysis. Error bars represent the MAD. Response status based on SRI-4 at day 100.

Detailed Description of the Disclosure

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as though fully set forth.

It is to be understood that the terminology used herein is for the purpose of describing embodiments only and is not intended to be limiting. 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 the disclosure pertains.

Although any methods and materials similar or equivalent to those described herein may be used in the practice for testing of the present disclosure, exemplary materials and methods are described herein. In describing and claiming the present disclosure, the following terminology will be used.

As used herein and in the claims, the singular forms "a," "and," and "the" include plural reference unless the context clearly dictates otherwise.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

"Diagnosing" or "diagnosis" refers to methods to determine if a subject is suffering from a given disease or condition or may develop a given disease or condition in the future. Diagnosis is typically performed by a physician based on the general guidelines for the disease to be diagnosed.

"**Treat**" or "**treatment**" refers 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 complications due to a chronic inflammatory disease or an autoimmune disease. Beneficial or desired clinical results include 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. 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.

"**Subject**" includes any human or nonhuman animal. "**Nonhuman animal**" includes all vertebrates, *e.g.*, mammals and non-mammals, such as nonhuman primates, sheep, dogs, cats, horses, cows, chickens, amphibians, reptiles, etc. The terms "subject" and "patient" can be used interchangeably herein.

"Type I interferon" or "IFN-I" refers to all native subtypes of human interferon-α (IFNα) and one subtype of interferon-β (IFNβ), interferon-ε (IFNε), interferon-ω (IFNω) and interferon-κ (IFNκ) which bind to a common heterodimeric interferon receptor IFNAR comprising of IFNAR1 and IFNAR2. The amino acid sequences of the various IFN-I proteins, IFNAR1 and IFNAR2 are well known are retrievable from from example UNIPROT or Genbank. An exemplary amino acid sequence if IFN-I is that of human IFNω of SEQ ID NO: 15.

SEQ ID NO: 15

CDLPQNHGLLSRNTLVLLHQMRRISPFLCLKDRRDFRFPQEMVKGSQLQKAHVMSVLHEM
LQQIFSLFHTERSSAAWNMTLLDQLHTGLHQQLQHLETCLLQVVGEGESAGAISSPALTLRR
YFQGIRVYLKEKKYSDCAWEVVRMEIMKSLFLSTNMQERLRSKDRDLGSS

"Type I interferon (IFN-I) mediated disease" refers to a disease that is at least partially characterized by overexpression of IFN-I inducible gene transcripts and/or elevated IFN-I in blood or tissue.

"Responsive", "responsiveness" or **"likely to respond"** refers to any kind of improvement or positive response, such as alleviation or amelioration of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread 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.

"IFN-I inhibitor", "**inhibitor**" or "**antagonist**" is a molecule having the ability to inhibit IFN-I biological activity or reduce IFN-I signature in blood or tissue, or both. Inhibition may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, or a statistically significant inhibition when compared to a control. Upon receptor binding, IFN-I initiates a signaling cascade through activation of JAK1 and TYK2 leading to the phosphorylation of several STAT family members including STATs 1-6. STAT1 and STAT2 activation leads to the formation of a complex with IFN-regulatory factor 9 (IRF9) and this complex, also known as the IFN-stimulated gene factor 3 (ISGF3) complex, binds to IFN-stimulated response elements (ISREs) in the nucleus resulting in the transcription of many interferon-stimulated genes (ISGs) including IRF7 and CXCL10 (IP-10). IFN-I also modulates cellular function through other pathways including the v-crk sarcoma virus CT10 oncogene homolog (avian)-like (CRKL), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), and through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ). IFN-I inhibitor, for example Jak1 or Tyk2 inhibitor, may inhibit one or more of the above mentioned signaling cascades. IFN-I inhibitor may also reduce disease characteristics in animal models of autoimmune disease, such as NZB/NZW F1 mice that exhibit a time-dependent and female-biased disease with several features of human lupus including glomerulonephritis. Inhibitors of IFN-I also encompass modulators of plasmacytoid dendritic cell survival or function and modulators of innate immune sentinals capable of triggering IFN-I production such as Toll-like receptors TLR3, TLR7, TLR8, TLR9 or modulators of the the cGAS-cGAMP-STING pathway.

"**IFN-I inducer**", "**inducer**" or "**agonist**" is a molecule having the ability to potentiate IFN-I biological activity or elevate IFN-I signature in blood or tissue, or both. Potentiation may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, or a statistically significant inhibition when compared to a control. Such agonists may be Jak1 or Tyk2 agonists.

"**Type I interferon signature**" or "IFN-I signature" refers to the upregulation of a subset of genes that are modulated by IFN-I. Various IFN-I signatures are known, ranging from a handful to several hundred genes and including the gene set described herein. These signatures may be utilized for example as pharmacodynamic markers to assess target engagement of IFN-I inhibitors for

treatment of IFN-I mediated diseases such as Systemic Lupus Erythematosus (SLE) and for purpose of SLE patient stratification or to assess disease activity or progression in any disease or therapeutic efficacy of drugs in which IFN-I may play a role, such as type 1 diabetes, multiple sclerosis, cancers or infectious diseases.

"**Baseline IFN-I signature**" refers to a signature of interferon inducible genes having the mean fold change across the entire population equal or less than 1.5.

"**Gene expression signature**" or "**signature**" as used herein refers to a group of genes, the expression of which indicates a particular status of a cell, tissue, organ, organism or tumor. The genes making up this signature can be expressed, for example, in a specific cell lineage, stage of differentiation, during a particular biological response or in a disease or particular subtype thereof. "IFN-I signature" is encompassed withn "gene expression signature".

"**Biological sample**" refers to a collection of similar fluids, cells, or tissues isolated from a subject, as well as fluids, cells, or tissues present within a subject. Exemplary samples are biological fluids such as blood, serum and serosal fluids, plasma, lymph, urine, saliva, cystic fluid, tear drops, feces, sputum, mucosal secretions of the secretory tissues and organs, vaginal secretions, ascites fluids, fluids of the pleural, pericardial, peritoneal, abdominal and other body cavities, fluids collected by bronchial lavage, synovial fluid, liquid solutions contacted with a subject or biological source, for example, cell and organ culture medium including cell or organ conditioned medium, lavage fluids and the like, tissue biopsies, fine needle aspirations, surgically resected tissue, organ cultures or cell cultures.

"**Gene expression**" refers to translation of information encoded in a gene into a gene product (e.g., RNA, protein). Expressed genes include genes that are transcribed into RNA (e.g., mRNA) that is subsequently translated into protein as well as genes that are transcribed into non-coding functional RNAs that are not translated into protein (e.g., miRNA, tRNA, rRNA, ribozymes etc.).

"**Combined expression value**" refers to a value or mathematical representation of the level of expression of a combination of test genes, such as a combination of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L.

"**Level of gene expression**" or "**expression level**" refers to the level (e.g., amount) of one or more products (e.g. RNA, protein) encoded by a given gene in a sample or reference standard. The expression level can be relative or absolute.

"Overexpression", "overexpressed", "upregulation", "upregulated", "increased", "increase", "enhance", "enhanced" and "elevated" are all used herein to generally mean an increased expression of one or more genes or a combination of genes (e.g. gene expression signature) in a test

sample vs a reference sample by a statically significant amount, or above a pre-identified threshold value. A 1.5-fold increase in the expression level of a gene is indicative of "overexpression".

"**Threshold value**" refers to a value obtained for the combined expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L that differentiates subjects having elevated IFN-I signature vs. subjects having baseline IFN-I signature with high accuracy. Threshold value may be expressd by various ways depending on the methods of analyzing gene expression. The threshold value may for example be obtained from a population of subjects that are substantially healthy (e.g. subjects who display a baseline IFN-I signature). The threshold value may be stored as a value(s) on a computer or PDA device to permit comparison with a value obtained from a subject using the methods described herein. The threshold value may also be obtained from the same subject e.g., at an earlier time point prior to onset of an IFN-Imediated disease, or prior to initiation of treatment with an IFN-I inhibitor. One of skill in the art can determine an appropriate reference sample for use with the methods described herein.

"**Normalizing**" refers to a manipulation of discrete expression level data wherein the expression level of one or more test genes is expressed relative to the expression level of one or more control genes, such as one or more housekeeping genes. For example, numerical expression level value one or more housekeeping genes may be deducted from the numerical expression level value of one or more test genes thereby permitting comparison of normalized marker values among a plurality of samples or to a reference.

"**Housekeeping gene**" refers to a gene encoding a transcript and/or protein that is constitutively expressed and is necessary for basic maintenance and essential cellular functions. A housekeeping gene generally is not expressed in a cell- or tissue- dependent manner, most often being expressed by all cells in a given organism. Some examples of housekeeping proteins include B2M, TFRC, YWHAZ, RPLO, 18S, GUSB, UBC, TBP, GAPDH, PPIA, POLR2A, ACTB, PGK1, HPRT1, IPO8 or HMBS, among others.

"**Therapeutically effective amount**" refers to an amount effective, at doses and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount may vary depending on factors such as the disease state, age, sex, and weight of the individual, and the ability of a therapeutic or a combination of therapeutics to elicit a desired response in the individual. Exemplary indicators of an effective therapeutic or combination of therapeutics that include, for example, improved well-being of the patient or reduction of IFN-I signature in a subject.

"**About**" means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Unless explicitly stated otherwise

within the Examples or elsewhere in the Specification in the context of a particular assay, result or embodiment, "about" means within one standard deviation per the practice in the art, or a range of up to 5%, whichever is larger.

"**Polynucleotide**" refers to a synthetic molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. cDNA is an exemplary synthetic polynucleotide.

"Differential expression" refers to a change in expression level of one or more genes or a combination of genes (e.g. gene expression signature) in a test sample vs a reference sample by a statistically significant amount, or above a pre-identified threshold value. A 1.5-fold change in the expression level of a gene is indicative of "differential expression".

"Blocks" or **"blocking"** refers to a molecule that inhibits interaction of IFN-I and IFNAR. The inhibition may be 60%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, or a statistically significant inhibition when compared to a control.

"**Placebo effect**" refers to an improvement in a disease state, such as alleviation or amelioration of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread 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 in a subject who is enrolled into a clinical trial and is not receiving the study drug.

"**Once in two weeks**" refers refers to an approximate number, and can include once every 14 days±two days, i.e., every 12 days to every 16 days.

"DHX58" refers to human DExH-box helicase 58 gene that produces a transript comprising the polynucleotide sequence of NM_024119 (**SEQ ID NO: 1).** In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 1

agtttcagtttccatttctgatttctgctctctgcgctgagcacagcggcaccaggctgagctaagcagggccgccttgggcaggcctacgtggtg
gtgcaggcgagacccaggctgggcaaggcgcagtttcagtttccatcttgggtctctgagctgagcagagtggcaccaggctgagttaagtggg
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atcacgacattccttccctaccaaggccacttctatttttgaggctcctcataaaaataaatgaaaaaatgggatagaaaaaaaaaaaaaaaaa

"**EIF2AK2**" refers to human eukaryotic translation initiation factor 2 alpha kinase 2 gene that that produces a transript comprising the polynucleotide sequence of NM_001135651 (**SEQ ID NO: 2**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 2

agcagacgagggcttgtgcgagaggggccgggcggctgcagggaaggcggagtccaaggggaaaacgaaactgagaaccagctctccc
gaagccgcgggtctccggccggcggcggcggcggcggcggcggcgcagtttctggagcaaattcagtttgccttcctggatttgtaaattg
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"**HERC5**" refers to human HECT and RLD domain containing E3 ubiquitin protein ligase 5) gene that produces a transript comprising the polynucleotide sequence of NM_016323.3 (**SEQ ID NO: 3**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 3

tcagtagctgaggctgcggttccccgacgccacgcagctgcgcgcagctggttcccgctctgcagcgcaacgcctgaggcagtgggcgcgct
cagtcccgggaccaggcgttctctcctctcgcctctgggcctgggaccccgcaaagcggcgatggagcggaggtcgcggaggaagtcgcgg
cgcaacgggcgctcgaccgcgggcaaggccgccgcgacccagcccgcgaagtctccgggcgcacagctctggctctttcccagcgccgcg
ggcctccaccgcgcgctgctccggagggtggaggtgacgcgccaactctgctgctcgccggggcgcctcgcggtcttggaacgcggcgggg
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acccgtgactgtattctctcccttggataccctatgcctacatcatattccttacctcttttgggaaatatttttcaaaaataaaataaccgaaaaattaa
cataaaa

"**IFI44**" refers to interferon induced protein 44 gene that produces a transript comprising the polynucleotide sequence of NM_006417.4 (**SEQ ID NO: 4**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 4

tctttgaagcttcaaggctgctgaataatttccttctcccattttgtgcctgcctagctatccagacagagcagctaccctcagctctagctgatactac
agacagtacaacagatcaagaagtatggcagtgacaactcgtttgacatggttgcacgaaaagatcctgcaaaatcattttggagggaagcggctt
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tgttctgtatctgtgaaaaaataaatttcttataaaactcgggtctaaaaaaaaaaaaaaaaaa

"**IFI44L**" refers to interferon induced protein 44 like gene that produces a transript comprising the polynucleotide sequence of NM_006820.3 (**SEQ ID NO: 5**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 5

aaagttagtggcagttggcatgctgccagctgagtttttttgctgctttgagtctcagttttctttctttcctagagtctctgaagccacagatctcttaaga
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catttgacccaacatcctttaggagcataaatgttgacactaagttatccctttgtgctaaaatggacagtattggcaaaatgataccacaacttcttat
tctctggctctatattgctttggaaacacttaaacatcaaatggagttaaatacatatttgaaatttaggttaggaaatattggtgaggaggcctcaaaa
agggggaaacatctttgtctgggaggatattttccattttgtggatttccctgatctttttctaccaccctgaggggtggtgggaattatcattttgctac
attttagaggtcatccaggatttttgaaactttacattctttacggttaagcaagatgtacagctcagtcaaagacactaaattcttcttagaaaaatagt
gctaaggagtatagcagatgacctatatgtgtgttggctgggagaatatcatcttaaagtgagagtgatgttgtggagacagttgaaatgtcaatgct
agagcctctgtggtgtgaatgggcacgttaggttgttgcattagaaagtgactgtttctgacagaaatttgtagctttgtgcaaactcacccaccatct
acctcaataaaatatagagaaaagaaaaatagagcagtttgagttctatgaggtatgcaggcccagagagacataagtatgttcctttagtcttgctt
cctgtgtgccacactgcccctccacaaccatagctgggggcaattgtttaaagtcattttgttcccgactagctgccttgcacattatcttcatttttcctg
gaatttgatacagagagcaatttatagccaattgatagcttatgctgtttcaatgtaaattcgtggtaaataacttaggaactgcctcttctttt
tctttgaaaacctacttataactgttgctaataagaatgtgtattgttcaggacaacttgtctccatacagttgggttgtaaccctcatgcttggcccaaat
aaactctctacttatatcagtttttcctacacttcttccttttaggtcaacaataccaagaggggttactgtgctgggtaatgtgtaaacttgtgtcttgttta
gaaagataaatttaaagactatcacattgctttttcataaaacaagacaggtctacaattaatttatttttgacgcaaattgataggggggccaagtaagc
cccatatgcttaatgatcagctgatgaataatcatctcctagcaacataactcaatctaatgctaaggtacccacaagatggcaaggctgatcaaagt
cgtcatggaatcctgcaaccaaaagccatgggaatttggaagccctcaaatcccattcctaatctgatgagtctatggaccaatttgtggaggacag
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tgggccagtgagatcatggatatagaagtacagtcaatgttcagctgtaccctcccacaatcccacttccttcctcaacacaattcaaacaaatagac
tcagactgtttcaggctccaggacaggaagtgcagtgtaggcaaaattgcaaaaattgagggcacaggggtggaggtgggggggttgaataac
aagctgtgctaaataattacgtgtaaatatatttttttcatttttaaaaattgatttcttttgcacattccatgacaatatatgtcacatttttaaaataaatgcaa
agaagcatacatccaaaaaaaaaaaaaaaa

"**IFI6**" refers to interferon alpha inducible protein 6 gene that produces a transript comprising the polynucleotide sequence of NM_022873.2 (**SEQ ID NO: 6**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 6

ccagccttcagccggagaaccgtttactcgctgctgtgcccatctatcagcaggctccgggctgaagattgcttctcttctctcctccaaggtctagt
gacggagcccgcgcgcggcgccaccatgcggcagaaggcggtatcgcttttcttgtgctacctgctgctcttcacttgcagtggggtggaggca
ggtgagaatgcgggtaaggatgcaggtaagaaaaagtgctcggagagctcggacagcggctccgggttctggaaggccctgaccttcatggc
cgtcggaggaggactcgcagtcgccgggctgcccgcgctgggcttcaccggcgccggcatcgcggccaactcggtggctgcctcgctgatg
agctggtctgcgatcctgaatgggggcggcgtgcccgccgggggggctagtggccacgctgcagagcctcggggctggtggcagcagcgtcg
tcataggtaatattggtgccctgatgggctacgccacccacaagtatctcgatagtgaggaggatgaggagtagccagcagctcccagaacctct
tcttccttcttggcctaactcttccagttaggatctagaactttgccttttttttttttttttttttttgagatgggttctcactatattgtccaggctagagtgca
gtggctattcacagatgcgaacatagtacactgcagcctccaactcctagcctcaagtgatcctcctgtctcaacctcccaagtaggattacaagca
tgcgccgacgatgcccagaatccagaactttgtctatcactctccccaacaacctagatgtgaaaacagaataaacttcacccagaaaacactt

"**IRF7**" refers to interferon regulatory factor 7 gene that produces a transript comprising the polynucleotide sequence of NM_004031.3 (**SEQ ID NO: 7**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 7

gagacgaaacttcccgtcccggcggctctggcacccagggtccggcctgcgccttcccgccaggcctggacactggttcaacacctgtgacttc
atgtgtgcgcgccggccacacctgcagtcacacctgtagcccccctctgccaagagatccataccgaggcagcgtcggtggctacaagccctca
gtccacacctgtggacacctgtgacacctggccacacgacctgtggccgcggcctggcgtctgctgcgacaggagcccttacctcccctgttata
acacctgaccgccacctaactgcccctgcagaaggagcaatggccttggctcctgagaggtaagagcccggcccacccctctccagatgccagt
ccccgagcgccctgcagccggccctgactctccgcggccgggcacccgcagggcagccccacgcgtgctgttcggagagtggctccttgga
gagatcagcagcggctgctatgaggggctgcagtggctggacgaggcccgcacctgtttccgcgtgccctggaagcacttcgcgcgcaagga
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cgaggctgagactgcggagcgcgccggctggaaaaccaacttccgctgcgcactgcgcagcacgcgtcgcttcgtgatgctgcgggataact
cgggggacccggccgacccgcacaaggtgtacgcgctcagccgggagctgtgctggcgagaaggcccaggcacggaccagactgaggca
gaggcccccgcagctgtcccaccaccacagggtgggcccccagggccattcctggcacacacacatgctggactccaagccccaggccccc
tccctgccccagctggtgacaaggggacctcctgctccaggcagtgcaacagagctgcctggcagaccatctgctgacagcgtcatggggg
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ggaggaactgctgcggcacgtggcccctgggttgcacctggagcttcgggggccacagctgtgggcccggcgcatgggcaagtgcaaggtg

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gagtcttcttccaagagctggtggaattccgggcacggcagcgccgtggctccccacgctataccatctacctgggcttcgggcaggacctgtca
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tgtcttccctggatagcagcagcctcagcctctgcctgtccagcgccaacagcctctatgacgacatcgagtgcttccttatggagctggagcagc
ccgcctagaacccagtctaatgagaactccagaaagctggagcagcccacctagagctggccgcggccgcccagtctaataaaaagaactcc
agaacacgta

"**PARP9**" refers to poly(ADP-ribose) polymerase family member 9 that produces a transript comprising the polynucleotide sequence of NM_001146102.1 (**SEQ ID NO: 8**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 8

agagccgcttccccctcctccctgtgctgtctgcaccgaggagagcggcctgccggaagtgggccaccatatctggaaactacagtctatgcttt
gaagcgcaaaagggaataaacatttaaagactcccccggggacctggaggatggacttttccatggtggccggagcagcagcttacaatgaaa
aatcaggtaggattacctcgctctcactcttgtttcagaaagtctttgctcagatctttcctcagtggagaaaggggaatacagaagaatgtctcccct
acaagtgctcagagactggtgctcttggagaaaactatagttggcaaattcccattaaccacaatgacttcaaaattttaaaaaataatgagcgtcag
ctgtgtgaagtcctccagaataagtttggctgtatctctaccctggtctctccagttcaggaaggcaacagcaaatctctgcaagtgttcagaaaaat
gctgactcctaggatagagttatcagtctggaaagatgacctcaccacacatgctgttgatgctgtggtgaatgcagccaatgaagatcttctgcat
gggggaggcctggccctggccctggtaaaagctggtggatttgaaatccaagaagagagcaaacagtttgttgccagatatggtaaagtgtcag
ctggtgagatagctgtcacgggagcagggaggcttccctgcaaacagatcatccatgctgttgggcctcggtggatggaatgggataaacagg
gatgtactggaaagctgcagagggccattgtaagtattctgaattatgtcatctataaaaatactcacattaagacagtagcaattccagccttgagct
ctgggatttttcagttccctctgaatttgtgtacaaagactattgtagagactatccgggttagtttgcaagggaagccaatgatgagtaatttgaaag
aaattcacctggtgagcaatgaggaccctactgttgctgcctttaaagctgcttcagaattcatcctagggaagagtgagctgggacaagaaacca
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aaagaaggaaacagcagcagagattttgtttgatgaagttttaacatttgccaaagaccatgtaaaacaccagttaactgtaaaatttgtgatctttcc
aacagatttggagatatataaggctttcagttctgaaatggcaaagaggtccaagatgctgagtttgaacaattacagtgtcccccagtcaaccaga
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tccaaagaatcctgagtctccagaaccaccacatcattgagaataatcatattctgtaccttgggagaaaggaacatgacattttgtctcagcttcag
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gaacattgaagatatgctttgtaaagtacaggaggaaatggcaaggaaaaaggagcgaggcctttggcgctcgttaggacagtggactattcag
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aaaaatgtggtttgcaggttctaaaggtggagaagatagacaatgaggtccttatggctgcctttcaaagaaagaagaaaatgatggaagaaaaa
ctgcacaggcaacctgtgagccataggctgtttcagcaagtcccataccagttctgcaatgtggtatgcagagttggctttcaaagaatgtactcga
caccttgcgatccaaaatacggagctggcatatacttcaccaagaacctcaaaaacctggcagagaaggccaagaaaatctctgctgcagataa
gctgatctatgtgtttgaggctgaagtactcacaggcttcttctgccagggacatccgttaaatattgttcccccaccactgagtcctggagctataga
tggtcatgacagtgtggttgacaatgtctccagccctgaaacctttgttatttttagtggcatgcaggctatacctcagtatttgtggacatgcacccag
gaatatgtacagtcacaagattactcatcaggaccaatgagacccctttgcacagcatccttggaggggattcgcaagtggcagccctgttgattaat
ctctacatcattttaacagctggtatggccttaccttgggtgaactaaccaaataatgaccatcgatggctcaaagagtggcttgaatatatcccatgg
gttatctgtatggactgactgggttattgaaaggactagccacatactagcatcttagtgcctttatctgtctttatgtcttggggttggggtaggtagat
accaaatgaaacactttcaggaccttccttcctcttgcagttgttctttaatctcctttactagaggagataaatattttgcatataatgaagaaatttttcta
gtatataacgcaggccttttatttttctaaaatgatgatagtataaaaatgttaggataacagaatgattttagattttccagagaatattataaagtgcttta
ggtatgaaaataaatcatctttgtctgattaactggctctgaaaaaaaaaaaaaaaaaa

"**PLSCR1**" refers to phospholipid scramblase 1 gene that produces a transript comprising the polynucleotide sequence of NM_021105.2 (**SEQ ID NO: 9**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 9

caccggacaaacgtctctggagtctctccaatgagcaagaaagcaagtcgggggtaggggaggggcctcacaccaggggtgggcgcagtc
cctcctccagctccttcaccctccagtagtctcgtgggtccccgagcgccagcgcgggaaccgggaaaaggaaaccgtgttgtgtacgtaagat
tcaggaaacgaaaccaggagccgcgggtgttggcgcaaaggttactcccagacccttttccggctgacttctgagaaggttgcgcagcagctgt
gcccggcagtctagaggcgcagaagaggaagccatcgcctggccccggctctctggaccttgtctcgctcgggagcggaaacagcggcagc
cagagaactgttttaatcatggacaaacaaaactcacagatgaatgcttctcacccggaaacaaacttgccagttgggtatcctcctcagtatccac
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cagctggctttcctgtcccaaatcagccagtgtataatcagccagtatataatcagccagttggagctgcaggggtaccatggatgccagcgcca
cagcctccattaaactgtccacctggattagaatatttaagtcagatagatcagatactgattcatcagcaaattgaacttctggaagttttaacaggtt
ttgaaactaataacaaatatgaaattaagaacagctttggacagagggtttactttgcagcggaagatactgattgctgtacccgaaattgctgtggg
ccatctagacctttttaccttgaggattattgataatatgggtcaagaagtcataactctggagagaccactaagatgtagcagctgttgttgtccctgc
tgccttcaggagatagaaatccaagctcctcctggtgtaccaataggttatgttattcagacttggcacccatgtctaccaaagtttacaattcaaaat
gagaaaagagaggatgtactaaaaataagtggtccatgtgttgtgtgcagctgttgtggagatgttgattttgagattaaatctcttgatgaacagtgt
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gttgtatacttttgcttttcaaattatagtttatcttctgtataactgatttataaaggtttttgtacatttttttaatactcattgtcaatttgagaaaaaggacata
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ctagaagctaatctataccataatattttcatattcacaagatattaaattaccaattttcaaattattgttagtaaagaacaaaatgattctctcccaaaga
aagacacattttaaatactccttcactctaaaactctggtattataacttttgaaagttaatatttctacatgaaatgtttagctcttacactctatccttccta
gaaaatggtaattgagattactcagatattaattaaatacaatatcatatatatattcacagagtataaacctaaataatgatctattagattcaaatatttg
aaataaaaacttgatttttttgtaaaaaaaaaaaaaaaaaaa

"**SAMD9L**" refers to sterile alpha motif domain containing 9 like gene that produces a transript comprising the polynucleotide sequence of NM_152703.4 (**SEQ ID NO: 10**). In the sequence, thymine (t) may be substituted for uracil (u).

SEQ ID NO: 10

gcttctcaactggcactctgacacaccctcagaaagtcagagtactgggagaacagaagacttcacaatttaatgcctcagtttttaaaaaaggatc
cttacacttcatgtctcctagccatcagaagaggaatgagacagcaaaagttcaaatggcctgtttcaagtttctgatataaaacgatgacattttcag
gaaaatcctgcatttccagagagagactggctggttaaatttctgaaagaggacaccagctaaaagaaggtattgcatctcacccgagcagactgt
gtctgtggaaagtgtaagccccttgccagaagagcagcttcccagcaaaggcagagggtgaaaacagcaaaggtcttaagacactggggacct
agagtcaaaagggacctcctccagggaaaacgctgtgtgagaaatggcctcattcggtgactgtgagtgacacagcagaaagttgggtcattcc
ggctgctttttgagaagtccctgaagagatcaataacagcaagagggaacctggcaaggaagctattcctataatccaggaaagagatgagga
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ttcagctcactccctttttccacaaagaaaatgaattatccaaaaaacatatggtgcaatttttatcaggaaagtggaccattcctcctgatcccagaa
atgaatgttatttggctcttagcaagttcacatcccacctaaaaaatttacaatcagatctgaaaaggtgctttgacttttttattgattatatggttcttctg
aaaatgaggtatacccaaaaagaaattgcagaaatcatgttaagcaagaaagtcagtcgttgtttcaggaaatacacagaacttttctgtcatttgga
tccatgtctattacaaagtaaagagagtcaattactccaggaggagaattgcaggaaaaagctagaagctctgagagcagataggtttgctggact
cttggaatatcttaatccaaactacaaagatgctaccaccatggaaagtatagtgaatgaatatgccttcctactgcagcaaaactcaaaaaagccc
atgacaaatgagaaacaaaattccattttggccaacattattctgagttgtctaaagcccaactccaagttaattcaaccacttaccacgctaaaaaaa

caactccgagaggtcttgcaatttgtaggactaagtcatcaatatccaggtccttatttcttggcctgcctcctgttctggccagaaaatcaagagcta
gatcaagattccaaactaatagaaaagtatgtttcatccttaaatagatccttcaggggacagtacaagcgcatgtgcaggtccaagcaggcaagc
acacttttctatctgggcaaaaggaagggtctaaacagtattgttcacaaggccaaaatagagcagtactttgataaagcacaaaatacaaattccc
tctggcacagtggggatgtgtggaaaaaaaatgaagtcaaagacctcctgcgtcgtctaactggtcaggctgaaggcaagctaatctctgtagaa
tatggaacagaggaaaaaataaaaataccagtaatatctgtttattcaggtccactcagaagtggtaggaacatagaaagagtgtctttctacctag
gattttccattgaaggccctctggcatatgatatagaagtaatttaagacaatacatcacctgtagttcaaatacgtttatttatatctttatgattttattctc
tctctctattctcatggcactttcataacattatggctaacctctaattacagattttgcttttgcctccctgaatgaattacaagccttttttaagatatgaaa
tatgcctacccgcagagcttggcacaaagtggagtcaatcttttaatgttttaaatatgcattttcagactcaaataattaagaagtttcattgatatcca
ctggtcacatcataactgtctatagggcaataaaatctgtgttaaactcaattgcttttataagttttctaaattatttcttcactgtgacagcaaagattta
aataagatgaatgtaaaagagaaagcttattggactcaaacccacagatccacaccagagttctatttacctcatcttggtatcaataaaaacttatgt
ggaaggtaaatatattgttccccatccaccacataacactctccccaacacacacacacacacacacacacacacacacacacactcct
tgtacccccttgcccttctcccagctcattgctccaggagagagaagagttcaaaaaataaagtaatcataaacttgaactctctccattctcttgttccc
atttacaggtgaatctcttcctttaagccatttttgtctcctgtgaatacagccttatctccacctgtttcttagatcccatctcccctggcttatttttttccatt
cattaccctctttgttccctttacttctcaacctgtgctatatacatgctgttctctctgttgagattgccttatttccatctaacattctctctcctgctattctg
atttgtcattcacaactgatttcaagagtcaccttcaccaggaagtcttccttgaccaccatcattcctgcctgattagagggcttcctcatggtaatat
gtgttctcaagttttcagtgtcaaggaatgccatcccagaagctcattctcagatgcacaacagccagaacagtctcaagcagcattctagagcttg
gaatttaagaactacgcattgcctataaagtgaaacataggctaatatagattaaattgaatattgaataaaaaatatatttatttatccaca

The disclosure provides new means to detect type I interferon (IFN-I) signature utilizing POISE (Profile of Interferon Signature Expression) and methods and uses of POISE. The disclosure is based, at least in part, on the identification of a gene signature comprised of ten genes that can be used to differentate between baseline and elevated IFN-I signature in a subject utilizing expression threshold values developed herein. The developed IFN-I signature can be utilized in a broad spectrum of applications, such as assessing IFN-I downstream activation, assessing therapeutic efficacy of administered IFN-I agonists or antagonists by evaluating baseline and post-administration IFN-I signature, identifying clinically asymptomatic subject with pre-onset or early onset disease based on elevated IFN-I signature, or methods of diagnosing and treating subjects having or suspected to have an elevated IFN-I signature.

The disclosure provides a solution to the challenge of reliably identifying patients having an elevated IFN-I signature, which may greatly increase the probability of success to achieve meaningful efficacy with an IFN-I inhibitor therapy while also minimizing exposure to patients that may not benefit from such a therapy. The disclosure also provides a solution to a challenge of early detection and identification of subjects who would benefit from IFN-I inhibitor therapy prior to onset of full clinical symptomology. The disclosure also provides a sensitive detection of IFN-I

signature prior to the ability to directly detect IFN-I protein elevation, which may facilitate therapeutic and preventive interventions within early onset and pre-onset patients with IFN-I mediated disease.

Autoimmune and chronic inflammatory disorders involve abnormal immune response of the body targeting substances and tissues that are normally and/or chronically present in the body resulting in development of pathological symptoms. Examples of relatively common autoimmune and chronic inflammatory disorders include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), psoriatic arthritis (PA), and Sjögren's syndrome (SS).

It is widely believed that many autoimmune and chronic inflammatory disorders exhibit an onset that substantially precedes clinically-observable symptoms. Importantly, changes in biomarker profiles typically occur early in this cascade of events and thus may enable the detection of this progression before disease onset. For example, it has been reported that IFN-I is elevated in preclinical SLE (Lu *et al., J Autoimmun 74:182-93, 2016).*

Many autoimmune and chronic inflammatory disorders are characterized by an upregulation of IFN-I inducible transcripts, (i.e. IFN-I signature), however the degree and presence of IFN-I signature in patients is heterogenous. For example, approximately half of adult SLE patients exhibit an upregulation of IFN-I inducible transcripts in the blood and/or tissue *(*Baechler *et al., Proc Natl Acad Sci U S A 100:2610-15, 2003;* Bennett *et al., J Exp Med 197:711-23, 2003;* Dall'era *et al., Annals of the Rheumatic Diseases 64:1692-97, 2005).*

Many therapeutic agents are known to be efficacious for treating patients afflicted with autoimmune and chronic inflammatory disorders, and at least some of the therapeutic effects of those agents are believed to be attributable to the ability of the agents to decrease IFN-I production, or response to IFN-I. However, the therapeutic and IFN-I production-modulating effects of these agents have been observed mainly in patients who have already presented with clinical manifestations of autoimmune and chronic inflammatory disorders, including IFN-I overproduction.

For example, in a Phase 2 trial of moderate-to-severe SLE patients, anifrolumab (anti-IFN receptor chain 1 antibody) improved disease outcomes across multiple clinical endpoints (Furie *et al., Arthritis & Rheumatology 69:376-86, 2017*), however post hoc analysis of data from this trial indicated that efficacy responses were greater in patients with high baseline expression of IFN-I signature versus low signature.

Therefore, the ability to identify patients having an elevated IFN-I signature may greatly increase the probability of success to achieve meaningful efficacy with an IFN-I modulating therapy while also minimizing exposure to patients that may not benefit from such a therapy.

The disclosure provides a method of diagnosing and treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease that is responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor.

The disclosure also provides a method of treating a subject suspected to have or having a type I interferon (IFN-I) mediated disease with an IFN-I inhibitor, comprising:

determining that the subject has an elevated IFN-I signature by

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining that the subject has the elevated IFN-I signature when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject determined to have the elevated IFN-I signature to treat the IFN-I mediated disease.

The disclosure also provides a method of detecting an elevated type I interferon (IFN-I) signature in a subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

detecting the elevated IFN-I signature in the subject when the combined expression value is equal to or higher than a threshold value.

The disclosure also provides a method of detecting a baseline type I interferon (IFN-I) signature in a subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

detecting the baseline IFN-I signature in the subject when the combined expression value is less than a threshold value.

The disclosure also provides a method of identifying a subject having elevated type I interferon (IFN-I) signature, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

identifying the subject having elevated IFN-I signature when the combined expression value is equal to or higher than a threshold value.

The disclosure also provides a method of determining whether a subject having a type I interferon (IFN-I) mediated disease is responsive to treatment with an IFN-I inhibitor and deciding whether to treat the subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease as responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value or

diagnosing the subject with the IFN-I mediated disease as non-responsive to treatment with the IFN-I inhibitor when the combined expression value is less than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor or refraining from administering the IFN-I inhibitor to the subject diagnosed as non-responsive to treatment with the IFN-I inhibitor.

The disclosure also provides an *in vitro* method for predicting and/or diagnosing that a subject has an IFN-I mediated disease,

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

predicting and/or diagnosing that the subject has the IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value.

The disclosure also provides a method of reducing placebo effect in a clinical trial, comprising

providing a biological sample from a subject considred to be enrolled into a clinical trial;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

enrolling the subject into the clinical trial when the combined expression value is equal to or higher than a threshold value and refraining to enroll the subject into the clinical trial when the combined expression value is less than the threshold value, thereby reducing the placebo effect

In the clinical study described in the Examples no placebo response was observed. By not wihing to be boudn by any particular theory, his observation suggests that SLE subjects with high IFN-I signature at baseline are less responsive to standard of care therapy which the placebo subjects continue to receive during the clinical trila Thus, enriching for participants having elevated IFN-I signature at baseline may be a strategy to minimize placebo responses in SLE trials.

In some embodiments, the subject has an IFN-I mediated disease.

In some embodiments, the subject has a family history of the IFN-I mediated disease.

In some embodiments, the subject has one or more clinical symptoms of the IFN-I mediated disease but is ineligible for treatment with an IFN-I inhibitor.

In some embodiments, the subject has an autoimmune disease.

In some embodiments, the subject has cancer.

In some embodiments, the subject has been treated with a cancer therapeutic.

In some embodiments, the subject has an infectious disease.

In some embodiments, the subject has been treated with a drug against the infectious diseases.

The disclosure also provides a method of treating a subject suspected to have or having a type I interferon (IFN-I) mediated disease with an IFN-I inhibitor, comprising:

determining that the subject has an elevated IFN-I signature by

providng a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining that the subject has the elevated IFN-I signature when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject determined to have the elevated IFN-I signature to treat the IFN-I mediated disease.

The disclosure also provides a method of diagnosing and treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from a subject suspected to have or having a type I interferon (IFN-I) mediated disease;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value; and

treating the subject suspected to have or having the IFN-I mediated disease by administering a therapeutically effective amount of an IFN-I inhibitor to the subject.

The disclosure also provides a method of predicting response of a subject having a type I interferon (IFN-I) mediated disease to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

predicting the subject as a responder when the combined expression value is equal to or higher than a threshold value and predicting the subject as a responder when the combined expression value is lower than the threshold value.

The disclosure also provides a method of treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

treating the subject with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value.

The disclosure also provides a method of determining whether a subject having a type I interferon (IFN-I) mediated disease is responsive to treatment with an IFN-I inhibitor and deciding whether to treat the subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease as responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value or diagnosing the subject with the IFN-I mediated disease as non-responsive to treatment with the IFN-I inhibitor when the combined expression value is less than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor or refraining from administering the IFN-I inhibitor to the subject diagnosed as non-responsive to treatment with the IFN-I inhibitor.

The disclosure also provides a method of treating a subject with an IFN-I inhibitor, wherein the subject has a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, the method comprising the steps of:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2(2^{-ddCT})); and/or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2(2^{-ddCT})| (Formula I); or any combination thereof;

treating the subject with the IFN-I mediated disease with the IFN-I inhibitor when SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2(2^{-ddCT}) value is equal to or higher than a threshold SUMlog2(2^{-ddCT}) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof.

The disclosure also provides a method of predicting response of a subject having a type I interferon (IFN-I) mediated disease to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2(2^{-ddCT})); and/or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2(2^{-ddCT})| (Formula I); or any combination thereof;

predicting the subject as a responder when the SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2(2^{-ddCT}) value is equal to or higher than a threshold SUMlog2(2^{-ddCT}) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof.

The disclosure also provides a method of treating a subject with an antagonistic antibody that binds Type I interferon comprising a heavy chain variable region 1 (HCDR1), a HCDR2, a

HCDR3, a light chain variable region 1 (LCDR1), a LCDR2 and a LCDR3 of SEQ ID NOs: 11, 12, 13, 14, 15 and 16, respectively, such as a heavy chain variable region (VH) of SEQ ID NO: 17 and a light chain variable region (VL) of SEQ ID NO: 18, for example a heavy chain (HC) of SEQ ID NO: 19 and a light chain (LC) of SEQ ID NO: 20, wherein the subject has Type I interferon (IFN-I) mediated disease that is responsive to treatment with the antibody, the method comprising the steps of:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2($2^{\wedge-ddCT}$)); and/or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2($2^{\wedge-ddCT}$)| (Formula I); or any combination thereof;

treating the subject with the IFN-I mediated disease with the IFN-I inhibitor when SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2($2^{\wedge-ddCT}$) value is equal to or higher than a threshold SUMlog2($2^{\wedge-ddCT}$) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof.

The disclosure also provides a method of predicting response of a subject having Type I interferon (INF-I) mediated disease to treatment with an antagonistic antibody that binds Type I interferon comprising a heavy chain variable region 1 (HCDR1), a HCDR2, a HCDR3, a light chain variable region 1 (LCDR1), a LCDR2 and a LCDR3 of SEQ ID NOs: 11, 12, 13, 14, 15 and 16, respectively, such as a heavy chain variable region (VH) of SEQ ID NO: 17 and a light chain variable region (VL) of SEQ ID NO: 18, for example a heavy chain (HC) of SEQ ID NO: 19 and a light chain (LC) of SEQ ID NO: 20, wherein the subject has IFN-I mediated disease that is responsive to treatment with the antibody, the method comprising the steps of:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2(2^{-ddCT})); and/or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2(2^{-ddCT})| (Formula I); or any combination thereof;

predicting the subject as a responder when the SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2(2^{-ddCT}) value is equal to or higher than a threshold SUMlog2(2^{-ddCT}) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof.

In some embodiments, the methods of the disclosure comprise a step of normalizing gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L to the expression level of a control gene.

In some embodiments, the control gene is a housekeeping gene.

In some embodiments, the housekeeping gene is B2M, TFRC, YWHAZ, RPLO, 18S, GUSB, UBC, TBP, GAPDH, PPIA, POLR2A, ACTB, PGK1, HPRT1, IPO8 or HMBS.

In some embodiments, the housekeeping gene comprises ACTB, B2M and GAPDH.

In some embodiments, the combined expression value is a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L.

In some embodiments, the threshold value is SUMΔCT of 57.474.

In some embodiments, the combined expression value is a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2(2^-ddCT)).

In some embodiments, the threshold value is SUMlog2(2^-ddCT) of 8.725.

In some embodiments, the combined expression value is a POISE Score of Formula I:

POISE Score = 70- |43.7251664- SUMlog2(2^{-ddCT})| (Formula I)

In some embodiments, the reference value is the POISE Score of between 30 and 40.

In some embodiments, the the reference value is the POISE score of 35.

In some embodiments, the sensitivity and false positive rate of detecting the elevated IFN-I signature is about 90% about 15%, respectively.

In some embodiments, the sensitivity and false positive rate of detecting the elevated IFN-I signature is about 82% about 10%, respectively.

In some embodiments, the sensitivity and false positive rate of detecting the elevated IFN-I signature is about 98% about 30%, respectively.

The disclosure also provides a method of diagnosing and treating a subject with a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more helthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2(2^{-ddCT})); or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2(2^{-ddCT})| (Formula I); or any combination thereof;

diagnosing the subject with the IFN-I mediated disease that is responsive to treatment with the IFN-I inhibitor when SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2(2^{-ddCT}) value is equal to or higher than a threshold SUMlog2(2^{-ddCT}) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor.

In some embodiments, the biological sample is a blood sample or a tissue sample.

In some embodiments, gene expression is assayed using quantitative Polymerase Chain Reaction (qPCR) or microarray, or both.

In some embodiments, gene expression is measured at the mRNA level.

In some embodiments, gene expression is measured one ore more days after the subject has been administered the IFN-I inhibitor.

In some embodimetns, gene expression is measured 2, 3, 4, 5,, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days after the subject has been administered the IFN-I inhibitor.

In some embodiments, gene expression is measured one ore more days after the subject has been administered the IFN-I inhibitor for the first time.

In some embodiments, gene expression is measured 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or more days after the subject has been administered the IFN-I inhibitor for the first time.

In some embodiments, the IFN-I mediated disease is SLE, type I diabetes, psoriasis, primary Sjögren's disease, systemic sclerosis, rheumatoid arthritis, transplant rejection, dermatomyositis, polymyositis, Aicardi-Goutières syndrome, Sting associated vasculopathy with onset in infancy (SAVI) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

In some embodiments, the IFN-I mediated disease is SLE. In some embodiments, the IFN-I mediated disease is type I diabetes. In some embodiments, the IFN-I mediated disease is primary Sjögren's disease. In some embodiments, the IFN-I mediated disease is systemic sclerosis. In some embodiments, the IFN-I mediated disease is rheumatoid arthritis. In some embodiments, the IFN-I mediated disease is dermatomyositis. In some embodiments, the IFN-I mediated disease is polymyositis. In some embodiments, the IFN-I mediated disease is Aicardi-Goutières syndrome. In some embodiments, the IFN-I mediated disease is Sting associated vasculopathy with onset in infancy (SAVI). In some embodiments, the IFN-I mediated disease is chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

In some embodiments, SLE is lupus nephritis, cutaneous lupus or lupus with central nervous system (CNS) manifestations.

In some embodiments, the IFN-I inhibitor is a molecule that blocks interaction of IFN-I with IFNAR, an antagonistic antibody that binds Type I interferon, an antagonistic antibody that binds IFNAR, an inhibitor of Tyk2, Jak1, TLR3, TLR7, TLR8, TLR9, STING a modulator or depletor of plasmacytoid dendritic cells; or an agent that degrades nucleic acids.

In some embodiments, the Type I interferon is IFN-α, IFN-β, IFN-ε, IFN-ω or IFN-κ.

In some embodiments, the modulator or depletor of plasmacytoid dendritic cells is an antibody that binds BDCA2, CD123 or ILT7/FcεRIγ complex.

In some embodiments, the anti-BDCA2 antibody is BIIB059.

In some embodiments, the anti-CD123 antibody is SL-501, SL-101, IMGN-632, IM-23, CSL-362 (talacotuzumab) or SM-401.

In some embodiments, the anti-ILT7 antibody such as MEDI7734,

In some embodiments, the agent that degrades nucleic acids is a recombinant nuclease.

In some embodiments, the antagonistic antibody that binds IFN-I comprises a heavy chain variable region 1 (HCDR1) of SEQ ID NO: 11, a HCDR2 of SEQ ID NO: 12, a HCDR3 of SEQ ID NO: 13, a light chain variable region 1 (LCDR1) of SEQ ID NO: 14, a LCDR2 comprising the amino acid sequence GAS and a LCDR3 of SEQ ID NO: 16;
a heavy chain variable region (VH) of SEQ ID NO: 17 and a light chain variable region (VL) of SEQ ID NO: 18; or
a heavy chain (HC) of SEQ ID NO: 19 and a light chain (LC) of SEQ ID NO: 20, or any combination thereof. GAS refers to the amino acids glycine, alanine and serine as is well-known.

In some embodiments, the antagonistic antibody that binds IFN-I is administered at a dose of about 10 mg/kg.

In some embodiments, the antagonistic antibody that binds IFN-I is administered at a dose of about 10 mg/kg once every two weeks.

In some embodiments, the antagonistic antibody that binds IFN-I is PF 06823859.

In some embodiments, the antagonistic antibody that binds IFN-I is AGS-009.

In some embodiments, the antagonistic antibody that binds IFN-I is rontalizumab.

In some embodiments, the antagonistic antibody that binds IFNAR comprises a heavy chain variable region 1 (HCDR1), a HCDR2, a HCDR3, a light chain variable region 1 (LCDR1), a LCDR2 and a LCDR3 of SEQ ID NOs: 21, 22, 23, 24, 25 and 26, respectively;
a heavy chain variable region (VH) of SEQ ID NO: 27 and a light chain variable region (VL) of SEQ ID NO: 28; and/or
a heavy chain (HC) of SEQ ID NO: 29 and a light chain (LC) of SEQ ID NO: 30. (anifrolumab).

HCDR1 (SEQ ID NO: 11)
GYSFTSYW

HCDR2 (SEQ ID NO: 12)
IDPSDSDT

HCDR3 (SEQ ID NO: 13)
ARHPGLNWAPDFDY

LCDR1 (SEQ ID NO: 14)
QSIDNSY

LCDR2
GAS

LCDR3 (SEQ ID NO: 16)
QQGYDFPLT

SEQ ID NO: 17
EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPSDSDTRYS
PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARHPGLNWAPDFDYWGQGTLVTVSS

SEQ ID NO: 18
DIQMTQSPSSLSASVGDRVTITCRASQSIDNSYLNWYQQKPGKAPKLLIYGASSLQSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQQGYDFPLTFGQGTKVEIK

SEQ ID NO: 19
EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGIIDPSDSDTRYS
PSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCARHPGLNWAPDFDYWGQGTLVTVSS
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL
YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVF
LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR
VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVF
SCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 20

DIQMTQSPSSLSASVGDRVTITCRASQSIDNSYLNWYQQKPGKAPKLLIYGASSLQSGVPSRF
SGSGSGTDFTLTISSLQPEDFATYYCQQGYDFPLTFGQGTKVEIKRTVAAPSVFIFPPSDEQLK
SGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYE
KHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 21
NYWIA

SEQ ID NO: 22
IIYPGDSDIRYSPSFQG

SEQ ID NO: 23
HDIEGFDY

SEQ ID NO: 24
RASQSVSSSFFA

SEQ ID NO: 25
GASSRAT

SEQ ID NO: 26
QQYDSSAIT

SEQ ID NO: 27
EVQLVQSGAEVKKPGESLKISCKGSGYIFTNYWIAWVRQMPGKGLESMGI
IYPGDSDIRYSPSFQGQVTISADKSITTAYLQWSSLKASDTAMYYCARHD
IEGFDYWGRGTLVTVSS

SEQ ID NO: 28
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFFAWYQQKPGQAPRLLIY
GASSRATGIPDRLSGSGSGTDFTLTITRLEPEDFAVYYCQQYDSSAITFG
QGTRLEIK

SEQ ID NO: 29

EVQLVQSGAEVKKPGESLKISCKGSGYIFTNYWIAWVRQMPGKGLESMGI
IYPGDSDIRYSPSFQGQVTISADKSITTAYLQWSSLKASDTAMYYCARHD
IEGFDYWGRGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF
PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC
NVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPEFEGGPSVFLFPPKPKDT
LMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPASIEKTISKAKGQPREPQVYT
LPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 30
EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFFAWYQQKPGQAPRLLIY
GASSRATGIPDRLSGSGSGTDFTLTITRLEPEDFAVYYCQQYDSSAITFG
QGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK
VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQ
GLSSPVTKSFNRGEC

In some embodiments, Tyk2 inhibitor is PF-06263276, SGI-1252, ARYY-111, UR-67767, TD-1473, PF-06826647, PF-06700841, PF-04965842, BMS-986165, SAR-20347, OST-246 or OST-122.

In some embodiments, Jak1 inhibitor is ATI-50001, LAS194046, TD-1473, ruxolitinib, BMT-1438, GLPG-0555, PF-04965842. Baricitinib, GSK-899, filgotinib maleate, INCB-47986, SGI-1252, ATI-50002, VR-588, tofacitinib, R-256, solcitinib, itacitinib, INCB-054707, tofacitinib, INCB-16562, SHR-0302, NIP-565, momelotinib, peficitinib, upadacitinib, CT-15300, BS-HH-002, SAR-20347, PF-06700841, PF-06263276, ABBV-599 or INCB-052793.

In some embodiments, TLR7 inhibitor is JB-6121, IMO-8400, IMO-9200, CPG-52364, IRS-954, DV-1079, DV-1179, E-6742 or E-6887.

In some embodiments, TLR8 inhibitor is JB-6121, VTX-763, IMO-8400, IMO-9200, CPG-52364, IMO-3100, E-6742 or E-6887.

In some embodiments, TLR9 inhibitor is E-6446, JB-6121, GNKS-356, IMO-9200, IMO-8400, CPG-52364, IMO-3100, IRS-954, DV-1079, DV-1179 or alicaforsen.

Type I IFN and IFN-I signature

In humans, IFN-I is composed of 12 IFN-α protein subtypes and single functional proteins for IFN-β, IFN-ε, IFN-κ, and IFN-ω. IFN-I induction occurs in response to both sterile and microbial ligands and this family of cytokines all signal through a ubiquitously expressed heterodimeric receptor (IFNAR) resulting in antiviral, antiproliferative and immunomodulatory effects. Thus, recombinant IFN-Is have been utilized in the clinic to treat both infectious and oncologic indications and more recently approaches to anatagonize this pathway are in development for autoimmune indications. Exposure of cells to IFN-I induces the expression of hundreds of IFN-I inducible transcripts ultimately encoding gene products responsible for these pleotrophic effects.

Given the broad diversity of transcripts induced by IFN-I several transcriptional signatures have been reported in the literature and have been utilized as a surrogate for direct dectection of multiple IFN-I ligands. An exemplary IFN-I signature consisting of 21 upreguated genes is described in Yao *et al.,. Human Genomics and Proteomics : HGP 2009.* Other exemplary IFN-I signatures are described in Tcherepanova *et al., Annals of the Rheumatic Diseases* 71(Suppl3) (2012) and Richardson *et al., ACR/ARHP 2012 Annual Meeting Abstract 620 (2012).*

The identification of additional sets of IFN-I inducible transcripts and their application to sensitively quantify elevated IFN-I signature in human blood or tissue samples would enable an improvement in the current state of the art and enable a more precise approach to select for patients having a disease mediated by IFN-I and thus minimize exposure to agents modulating this pathway that may not have an IFN-I mediated disease as well as facilitate preventive interventions in pre-onset autoimmune subjects. This is of particular importance for autoimmune disease such as lupus where there is high unmet need and substantial heterogeneity as reflected by the long list of clinical trial failures seen in this disease.

The disclosure provides a novel IFN-I signature identified using human patient samples and machine learning and further describe its application to quantify IFN-I signature in human patient samples. The generated IFN-I signature was demonstrated to be more sensitive than direct detection of IFN-I protein in patient sera, thereby enabling identification of still asymptomatic or partially symptomatic subjects.

Methods of measuring gene expression

Gene expression levels may be measured at the RNA level using known methods. Total RNAand/or mRNA may be isolated from a biological sample, such as blood using well-known methods.

Methods of analyzing gene expression are well-known and include methods based on hybridization of polynucleotides, methods based on sequencing of polynucleotides, and proteomics-based methods. mRNA expression in a sample may be quantified using northern blotting or in situ hybridization, RNAse protection assays, microarrays or PCR-based methods, such as reverse transcription polymerase chain reaction (RT-PCR) optionally followed by quantitative PCR (qPCR). RT-PCR step is typically primed using specific primers, random hexamers, or oligo-dT primers, depending on the circumstances and the goal of expression profiling. For example, extracted RNA can be reverse-transcribed using a GeneAmp RNA PCR kit (Perkin Elmer, Calif., USA), following the manufacturer's instructions. The generated cDNA can then be used as a template in the subsequent qPCR reaction. In an exemplary method, total RNA is isolated from a blood sample of a subject using PAXgene Blood RNA tubes and RNA isolation kit from Qiagen, followed by reverse transcription into cDNA using commercial kits such as one from Qiagen. Gene expression profiling may be conducted using custom or off-the-shelf RT^2 Profiler PCR arrays commercially available from Qiagen, the arrays incorporating elements for RNA sample quality, data normalization and genomic DNA contamination detection.

To minimize errors and the effect of sample-to-sample variation, qPCR may be performed using an internal standard expressed at a constant level across various tissues. RNAs commonly used to normalize patterns of gene expression are mRNAs for one or more housekeeping genees, such as ACTB, B2M and GAPDH.

Data analyses of qPCR results may be based on the ΔCT or ΔΔCT methods, normalizing the raw data of a test gene in a test sample to the expression of one ore more housekeeping gene(s) within the test sample (ΔCT) and/or comparing the normalized expression of the test gene in the test sample to the normalized expression of the same test gene in a control sample (ΔΔCT). In some instances, level of gene expression may be expressed as fold change in a test sample vs. control sample (e.g. $2^{\wedge-\Delta\Delta CT}$), of alternatively, as log2 fold changes (e.g. $\log2(2^{\wedge-ddCT})$). In some instances, when expression levels of a combination of genes is analyzed, a sum of the various expression values may be analyzed (e.g. SUMΔCT; SUMΔΔCT; $SUM2^{\wedge-\Delta\Delta CT}$ and/or SUM $\log2(2^{\wedge-ddCT})$.

Level of gene expression may also be analyzed using microarrays using commercially available platforms such as those from Affymetrix, Illumina and Agilent.

Generating threshold values

The disclosure described herein provides a new 10-gene gene set comprising genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L that is capable of differentiating subjects having elevated IFN-I signature vs. subjects having baseline IFN-I signature

with high accuracy. This combinantion of genes and threshold was empirically derived using machine learning methods and internal data sets to best classify healthy versus SLE subjects from a larger set of 84 IFN-I inducible genes described herein.

Threshold values utilizing the 10-gene signature may be developed by analyzing pooled biological samples obtained from healthy subjects having verified baseline IFN-I signature and subjects having verified elevated IFN-I signature for differential expression of the 10 genes. Threshold values may be then identified that stratify subjects to those having elevated IFN-I signature and those with baseline IFN-I signature.

Utilizing the methodologies described herein and in Example 1, a POISE (Profile of Interferon Signature Expression) Score threshold and a subject specific POISE score can be generated which can differentiate subjects having elevated IFN-I signature from those having baseline IFN-I signature using Formula I. POISE refers to a measurement of the expression levels of IFN-I response genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L. POISE may be determined at baseline, i.e., prior to any treatment or at any time after administration of the treatment.

Formula I:

POISE Score(subject): 70- |43.72516641664- SUMlog2(2^-ddCT)(subject)|;

wherein SUMlog2(2^-ddCT) is a sum of log2 fold chages of expression of the combination of the 10 genes in a biological sample from the subject when compared to the expression levels of the 10 genes in the control sample.

Subjects having a POISE Score of equal to or over 35 are identified as having an elevated IFN-I signature with about 90% sensitivity and a false positive rate of about 15%. Subjects having a POISE Score of equal to or over 30 are identified as having an elevated IFN-I signature with about 82% sensitivity and a false positive reate of about 20%. Subjects having a POISE Score of equal to or over 40 are identified as having an elevated IFN-I signature with about 98% sensitivity and a false positive rate of about 30%.

"**Threshold POISE Score**" refers to the POISE Score of between 30 and 40. In some embodiments, threshold POISE Score is 30. In some embodiments, threshold POISE Score is 35. In some embodiments, thershold POISE Score is 40.

With the identification of the threshold POISE Score, a threshold SUMlog2($2^{\text{-ddCT}}$)" value of 8.725 and a threshold SUMΔCT value of 57.474 can be derived which correspond to the POISE Score of 35.

Treatment and Administration

Any subject identified to have an elevated IFN-I signature using the 10-gene signature developed herein may be treated with the IFN-I inhibitor as described herein. Such subjects include initially those suspected to have a IFN-I mediated disease and those diagnosed with the IFN-I mediated disease. Such disease include SLE, including specific organ manifestations such as lupus nephritis, cutaneous lupus, and CNS manifestations, type I diabetes, psoriasis, primary Sjögren's disease, systemic sclerosis, rheumatoid arthritis, transplant rejection, dermatomyositis, polymyositis, Aicardi-Goutières syndrome, Sting associated vasculopathy with onset in infancy (SAVI) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

For example, IFN-I signature has been reported to positively correlate with both clinical and serological features of lupus (Baechler *et al., Proc Natl Acad Sci U S A 100:2610-15, 2003;* Bennett *et al., J Exp Med 197:711-23, 2003;* Dall'era *et al., Annals of the Rheumatic Diseases 64:1692-97, 2005;* Karageorgas *et al., J Biomed Biotechnol 273907, 2011; Niewold et al., Genes Immun 8: 492-502, 2007).*

The IFN-I inhibitor may be administered as a pharmaceutical composition containing a therapeutically effective amount of the IFN-I inhibitor and a pharmaceutically acceptable carrier. "Carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the IFN-I inhibitor is administered. Such vehicles may be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. For example, 0.4% saline and 0.3% glycine may be used. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening, lubricating and coloring agents, etc. Suitable vehicles and formulations, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in e.g. Remington: The Science and Practice of Pharmacy, 21st Edition, Troy, D.B. ed., Lipincott Williams and Wilkins, Philadelphia, PA 2006, Part 5, Pharmaceutical Manufacturing pp 691-1092, See especially pp. 958-989.

The mode of administration of the IFN-I inhibitor be any suitable route that delivers the antibody to a subject, such as parenteral administration, e.g., intradermal, intramuscular, intraperitoneal, intravenous or subcutaneous, pulmonary, transmucosal (oral, intranasal, intravaginal, rectal), using a formulation in a tablet, capsule, solution, powder, gel, particle; and contained in a syringe, an implanted device, osmotic pump, cartridge, micropump; or other means appreciated by

the skilled artisan, as well known in the art. Site specific administration may be achieved by for example intratumoral, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intracardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravascular, intravesical, intralesional, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery.

The IFN-I inhibitor may also be administered prophylactically in order to reduce the risk of developing a IFN-I mediated disease and/or delay the onset of the symptoms.

Further embodiments of the invention

Set out below are certain further embodiments of the invention according to the disclosures elsewhere herein. Features from embodiments of the invention set out above described as relating to the invention disclosed herein also relate to each and every one of these further numbered embodiments.

Embodiment 1. A method of diagnosing and treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease that is responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor.

Embodiment 2. A method of treating a subject suspected to have or having a type I interferon (IFN-I) mediated disease with an IFN-I inhibitor, comprising:

determining that the subject has an elevated IFN-I signature by:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining that the subject has an elevated IFN-I signature when the combined expression value is equal to or higher than a threshold value; and

administering the IFN-I inhibitor to the subject determined to have the elevated IFN-I signature to treat the IFN-I mediated disease.

Embodiment 3. A method of detecting an elevated type I interferon (IFN-I) signature in a subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

detecting the elevated IFN-I signature in the subject when the combined expression value is equal to or higher than a threshold value.

Embodiment 4. A method of diagnosing and treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising

providing a biological sample from a subject suspected to have or having a type I interferon (IFN-I) mediated disease;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value; and

treating the subject suspected to have or having the IFN-I mediated disease by administering a therapeutically effective amount of an IFN-I inhibitor to the subject.

Embodiment 5. A method of predicting response of a subject having a type I interferon (IFN-I) mediated disease to treatment with an IFN-I inhibitor, comprising

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

predicting the subject as a responder when the combined expression value is equal to or higher than a threshold value and predicting the subject as a responder when the combined expression value is lower than the threshold value.

Embodiment 6. A method of treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

treating the subject with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value.

Embodiment 7. A method of determining whether a subject having a type I interferon (IFN-I) mediated disease is responsive to treatment with an IFN-I inhibitor and deciding whether to treat the subject, comprising:

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

diagnosing the subject with the IFN-I mediated disease as responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value or

diagnosing the subject with the IFN-I mediated disease as non-responsive to treatment with the IFN-I inhibitor when the combined expression value is less than a threshold value; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor or refraining from administering the IFN-I inhibitor to the subject diagnosed as non-responsive to treatment with the IFN-I inhibitor.

Embodiment 8. An *in vitro* method for predicting and/or diagnosing that a subject has an IFN-I mediated disease, comprising

providing a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

predicting and/or diagnosing that the subject has the IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value.

Embodiment 9. The method of any one of embodiments 1-8, comprising a step of normalizing gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L to the expression level of a control gene.

Embodiment 10. The method of any one of embodiments 1-9, wherein the control gene is a housekeeping gene.

Embodiment 11. The method of any one of embodiments 1-10, wherein the housekeeping gene comprises B2M, TFRC, YWHAZ, RPLO, 18S, GUSB, UBC, TBP, GAPDH, PPIA, POLR2A, ACTB, PGK1, HPRT1, IPO8 or HMBS.

Embodiment 12. The method any one of embodiments 1-11, wherein the housekeeping gene comprises ACTB, B2M and GAPDH.

Embodiment 13. The method of any one of embodiments 1-12, wherein the combined expression value is a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L.

Embodiment 14. The method of any one of embodiments 1-13, wherein the threshold value is SUMΔCT of 57.474.

Embodiment 15. The method of any one of embodiments 1-12, wherein the combined expression value is a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L ((SUMlog2(2^-ddCT)).

Embodiment 16. The method of embodiment 15, wherein the threshold value is SUMlog2(2^-ddCT) of 8.725.

Embodiment 17. The method of any one of embodiments1-12, wherein the combined expression value is a POISE Score of Formula I:

$$\text{POISE Score} = 70 - |43.7251664 - \text{SUMlog2}(2^{\wedge -ddCT})| \quad \text{(Formula I)}$$

Embodiment 18. The method of embodiment 17, wherein the reference value is the POISE Score of between 30 and 40.

Embodiment 19. The method of embodiment18, wherein the reference value is the POISE score of 35.

Embodiment 20. The method of any one of embodiments 1-19, wherein sensitivity and false positive rate of detecting the elevated IFN-I signature is about 90% and about 15%, respectively.

Embodiment 21. A method of diagnosing and treating a subject with a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising

obtaining a biological sample from the subject;

assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

determining

a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L;

a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more helthy controls of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L (SUMlog2($2^{\wedge -ddCT}$)); or

a POISE score calculated according to a formula I:

POISE Score = 70- |43.7251664- SUMlog2($2^{\wedge-ddCT}$)| (Formula I); or any combination thereof;

diagnosing the subject with the IFN-I mediated disease that is responsive to treatment with the IFN-I inhibitor when SUMΔCT is equal to or higher than a threshold SUMΔCT value of 57.474, the SUMlog2($2^{\wedge-ddCT}$) value is equal to or higher than a threshold SUMlog2($2^{\wedge-ddCT}$) value of 8.725 or the POISE score is equal to or higher than a threshold POISE score of 35; or any combination thereof; and

administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor.

Embodiment 22. The method of embodiment 21, wherein sensitivity and false positive rate of detecting the elevated IFN-I signature is about 90% and about 15%, respectively.

Embodiment 23. The method of any one of embodiments 1-22, wherein the biological sample is a blood sample or a tissue sample.

Embodiment 24. The method of any one of embodiments 1-23, wherein gene expression is assayed using quantitative Polymerase Chain Reaction (qPCR) or microarray, or both.

Embodiment 25. The method of any one of embodiments 1-24, wherein gene expression is measured at the mRNA level.

Embodiment 26. The method of any one of embodiments 1-25, wherein the IFN-I mediated disease is systemic lupus erythematosus (SLE), type I diabetes, psoriasis, primary Sjögren's disease, systemic sclerosis, rheumatoid arthritis, transplant rejection, dermatomyositis, polymyositis, Aicardi-Goutières syndrome, Sting associated vasculopathy with onset in infancy (SAVI) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

Embodiment 27. The method of embodiment 26, wherein SLE comprises lupus nephrits, cutaneous lupus or lupus with central nervous system (CNS) manifestations.

Embodiment 28. The method of any one of embodiments 1-27, wherein the IFN-I inhibitor is a molecule that blocks interaction of IFN-I with IFNAR, an antagonistic antibody that binds IFN-I, an antagonistic antibody that binds IFNAR, an inhibitor of Tyk2, Jak1, TLR7, TLR8, TLR9 or STING, a modulator or depletor of plasmacytoid dendritic cells; or an agent that degrades nucleic acids.

Embodiment 29. The method of any one of enbodiments 1-28, wherein the IFN-I is IFN-α, IFN-β, IFN-ε, IFN-ω or IFN-κ.

Embodiment 30. The method of embodiment 28 or 29, wherein the modulator or depletor of plasmacytoid dendritic cells is an antibody that binds BDCA2, CD123 or ILT7/FcεRIγ complex.

Embodiment 31. The method of any one of embodiments 28-30, wherein the agent that degrades nucleic acids is a recombinant nuclease.

Embodiment 32. The method of any one of embodiments 1-32, wherein the antagonistic antibody that binds IFN-I comprises:

a heavy chain variable region 1 (HCDR1) of SEQ ID NO: 11, a HCDR2 of SEQ ID NO: 12, a HCDR3 of SEQ ID NO: 13, a light chain variable region 1 (LCDR1) of SEQ ID NO: 14, a LCDR2 comprising the amino acid sequence GAS and a LCDR3 of SEQ ID NO: 16;

a heavy chain variable region (VH) of SEQ ID NO: 17 and a light chain variable region (VL) of SEQ ID NO: 18; and/or

a heavy chain (HC) of SEQ ID NO: 19 and a light chain (LC) of SEQ ID NO: 20. (JNJ-839).

Embodiment 33. The method of any oen of embodiments 28-31, wherein the antagonistic antibody that binds IFNAR comprises:

a heavy chain variable region 1 (HCDR1), a HCDR2, a HCDR3, a light chain variable region 1 (LCDR1), a LCDR2 and a LCDR3 of SEQ ID NOs: 21, 22, 23, 24, 25 and 26, respectively;

a heavy chain variable region (VH) of SEQ ID NO: 27 and a light chain variable region (VL) of SEQ ID NO: 28; and/or

a heavy chain (HC) of SEQ ID NO: 29 and a light chain (LC) of SEQ ID NO: 30. (anifrolumab).

Embodiment 34. The method of embodiment 28, wherein the antagonistic antibody that binds IFN-I is PF 06823859, AGS-009 or rontalizumab.

While having described the disclosure in general terms, the embodiments of the disclosure will be further disclosed in the following examples that should not be construed as limiting the scope of the claims.

Example 1 Generation of Profile of Interferon Signature Expression (POISE) and POISE score

POISE is a 10-gene quantitative PCR (qPCR) based method developed to quantify IFN-I signature in subjects. POISE score is a calculated value that differentiates subjects having elevated

IFN-I signature and subjects having baseline IFN-I signature utilizing expression profiling information from blood samples of healthy donors and SLE patients.

Materials

A) SLE and healthy donor PAXgene Blood RNA tubes, (Provided by Temple University, Biological Specialty Corporation, Bioserve Biotechnologies, and Bioreclamation all under informed consent)

B) PAXgene Blood RNA kit (QIAGEN, Cat# 762164)

C) RT^2 First Strand kit (QIAGEN, Cat# 330404)

D) Custom RT^{2}RNA PCR Array (QIAGEN, Cat# CAPH13527)

E) RT^2 Sybr® Green qPCR Mastermix (QIAGEN, Cat# 330529)

Methods and Results

Design and validation of RT^2 qPCR Array

84 interferon-inducible genes and eleven controls per array were initially selected and printed onto a 96x4 format RT^2 qPCR array. The IFN-inducible genes were either known IFN-inducible transcripts (Yao, *et al. Human genomics and proteomics : HGP 2009; 2009)* or transcripts which were identified through internal RNA-Seq analysis of SLE donor blood samples.

A pooled healthy control total RNA sample was generated to standardize normalization of healthy versus each individual SLE sample to enable the establishment of a quantitative threshold for IFN-I dysregulation relative to healthy subjects. Healthy donor PAXgene blood RNA tubes were purchased from Biological Specialty Corporation and Bioserve. RNA was extracted using the PAXgene Blood RNA kit (QIAGEN) according to manufacturer's instructions. RNA yields of each sample were determined using a QIAxpert instrument (QIAGEN). 25 of the healthy PAXgene samples obtained had sufficient yield to begin reverse transcription into cDNA starting from 200ng of total RNA from each sample. cDNA synthesis was performed using the RT^2 First Strand kit (QIAGEN) and then added to the RT^2 Sybr® Green qPCR Mastermix (QIAGEN) according to manufacturer's instructions. As a positive control, several SLE donor PAXgene tubes (29 total donors) were processed the same way. Samples were loaded onto custom qPCR arrays and qPCR data was obtained using the Viia™ 7 Real-Time PCR Instrument (Thermo Fisher Scientific). After instrument run completion, data was exported into Excel for analysis. To calculate the relative gene expression ($\Delta\Delta$CT) changes amongst each of the samples, the following formulas were utilized:

1) Formula 1 = CT Target gene - average CT of endogenous controls = Value A (endogenous controls included housekeeping genes ACTB, GAPDH, and B2M)

2) Formula 2 = mean of Value A's from untreated (or healthy donor) control group = Mean Value A
3) Formula 3 = Value A SLE donor - Mean Value A control group = ΔΔCT
4) Formula 4 = 2^-ΔΔCT = Fold Change

To determine what extent the healthy cohort showed baseline expression of IFN-inducible genes, samples from healthy donors were evaluated using an 21-gene IFN-I signature which included genes IFI27, IFI6, RSAD2, IFI44, IFI44L, USP18, LY6E, OAS1, SIGLEC1, ISG15, IFIT1, OAS3, HERC5, MX1, LAMP3, EPSTI1, IFIT3, OAS2, RTP4, PLSCR1, and DNAPTP6 (Yao, *et al. Human genomics and proteomics : HGP 2009; 2009).* The mean fold change of all 21 genes across each individual healthy donor versus the mean of the healthy group overall was 1.36. In contrast, the mean of the SLE donors versus the mean of the healthy group overall was 18.29 (**FIG. 1A**). As the baseline IFN-I signature across healthy donors varies slightly, the population was to be considered **"baseline"** signature when the mean fold change across the entire population was equal or less than 1.5.

Because there was little variability overall within the healthy cohort examined, all 25 donors were selected for creating the pooled healthy RNA preparation to be used as a normalization control on each of the custom qPCR arrays. To create this pooled preparation, 600ng of each healthy donor's total RNA was combined into a single tube and frozen. 20 additional healthy donor PAXgene tubes were also evaluated for IFN-I signature to expand the pooled healthy RNA pool. There was a high correlation (R^2=0.9797; p<0.0001) between the 21-gene panel IFN inducible gene expression between the additional and original donors and hence all healthy donor samples were pooled and stored at -80°C.

29 PAXgene tubes from SLE donors were obtained for evaluation of expression profiles of the selected 84 IFN-inducible genes. All sample processing methods were followed identically to that described above except that the instrument used to generate the data was the 7900HT Real-Time PCR system (Applied Biosystems). On each qPCR array, the first position was designated for the pooled healthy control sample, while the remaining 3 positions were for SLE samples. Data were analyzed and each SLE sample's fold change over the healthy control was assessed to understand the heterogeneity in gene expression in subjects with SLE.

Using a machine learning approach on the qPCR dataset, a Random Forest (RF) classifier was designed to distinguish SLE versus healthy donor gene expression. The classifier was run on the qPCR ΔΔCT (log2 of fold change) data table in a 10 x 5-fold cross-validation setting as previously described (Zhang *et al., Genome Biol.* 2015, 16:14). Genes were ranked by their RF significance,

expressed by the Gini index. The Matthews Correlation Coefficient (MCC) (Baldi *et al.*, Assessing *Bioinformatics* 16:412-24, 2000) was used for performance assessment. A model build on the 20 top-ranked genes (qPCR-20) achieved a MCC=0.76. Next, an independent training data set from a separate RNA-Seq study was used to validate these results. This step was performed to identify the most robust set of transcripts agnostic of the gene expression platform utilized which would increase the utility of this assay. These data were converted to fold change to match the qPCR data. Using this dataset, the 84 genes contained on the qPCR array were evaluated using an RF classifier on the data set in a 10 x 5-fold CV setting enabling another model to be built which contained 40 genes ranked at highest significance (RNASEQ-40). After running the performance assessment, the achieved MCC value was 0.70. After comparing the qPCR-20 versus the RNA-Seq 40 gene lists, 10 IFN-inducible genes were identified in common: DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1, and SAMD9L. To confirm the accuracy of these 10 genes to correctly classify SLE versus healthy donors, random forest analysis was repeated using only these 10 genes and once again, this gene list could distinguish healthy vs SLE donors with similar accuracy (MCC=0.76). The 10 genes were hence selected for subsequent analyses to assess IFN-I signature status in subjects moving forward (e.g. POISE). **FIG. 1B** shows the outline of the process of identifying the 10 genes for IFN-I signature.

POISE Score Derivation

Determining threshold POISE Score and threshold log2(2^-ddCT) values

The log2 fold changes of differential expression (e.g. log2(2^-ΔΔCT)) for each SLE donor (n=29) vs. the healthy donor pool were determined across the 10 selected genes. The highest fold change for each of the genes across all donors was identified. The sum of the highest log2 fold changes for each of the 10 genes across all 29 SLE donors was then calculated [sum(GenesFC_SLE_Best)]. This score was designated as "SLE_Best" and was calculated to be 43.7251664. In other words, the value represented a hypothetical "best case scenario" of an SLE subject with an elevated IFN-I signature. This number was then used as the benchmark IFN-I signature for SLE subject comparison. To this end, each unknown SLE sample to be scored was treated similarly in that the sum of the log2 fold changes (e.g. log2($2^{\text{-ddCT}}$)) of the same 10 genes was calculated [sum(GenesFC_SLE)] to generate a secondary "SLE subject-specific" score. Next, the absolute value of the distance between the benchmark "SLE_Best" score and the "SLE subject-specific" score was determined. This value was a precursor value of the POISE score. To make the POISE score value more intuitive aka higher score = higher IFN-I signature, the precursor value of

the POISE score was subtracted from a score of 70 (which equals to twice the threshold POISE Score of 35 determined below) to generate the POISE score.

POISE Score = 70- |sum(GenesFC_SLE_best)-sum(GenesFC_SLE)|;

The subject specific POISE Score can thus be calculated as:

POISE Score(subject) = 70- |43.7251664- SUMlog2($2^{\wedge -ddCT}$)(subject)|

POISE score calculation also allows for the possibility of encountering an SLE subject with an even greater elevated IFN-I signature than that determined as "SLE_Best". In this scenario, the sum of the fold changes from the individual SLE subject would be greater than the "SLE_Best" resulting in a negative inverse POISE score value. When this negative value is subtracted from 70, the resulting POISE score would be a value even greater than 70 and therefore also above the threshold POISE Score of 35.

To identify a threshold POISE Score to classify a subject as having an elevated IFN-I signature a simulation with different cutoffs was performed and the fraction of False Positives and the fraction of True Positives (sensitivity) were calculated for each cutoff. From this analysis, a threshold POISE Score of 35 was chosen as an appropriate threshold value to classify subjects (**FIG. 2**) because it was the threshold at which true IFN-I signature positive subjects could be identified accurately approximately 90% of the time and the false positive rate was about 15%.

Other threshold POISE Scores could also be used with alternative sensitivity and false positive values:

Threshold POISE Score of 30: Utilizing ths threshold the false positive rate dropped to 10% and the true positive rate decreased to about 82% indicating that in about 20% of assessments, subjects with an elevated IFN-I signature were misclassified as having baseline IFN-I signature.

Threshold POISE Score of 40: Utilizing ths threshold the false positive rate increased to about 30% and the true positive rate increased to about 98%.

To this end, a cutoff of 35 was determined to be the best compromise between the false and true positive fractions.

Threshold POISE Score of 35 or greater would require a minimum sum of log2 fold change SUMlog2($2^{\wedge -ddCT}$) for all 10 genes to be greater than or equal to 8.725. Subjects having SUMlog2($2^{\wedge -ddCT}$) under 8.725 would be considered to have baseline IFN-I signature.

Calculating POISE Score and threshold expression values without normalizing to healthy donor control sample(s)

Initial inclusion of healthy donor scores enabled the determination of a threshold cutoff distinguishing IFN-I signature levels in healthy subjects versus SLE subjects. To eliminate the need for inclusion of a benchmark pooled healthy control sample a methodology was developed to derive the POISE Score a without normalizing gene expression to the healthy donor pool.

To accomplish this, gene expression of the 10 selected genes was normalized to the expression level of the three housekeeping genes within each analyzed sample for which sample specific POISE Score was available. For each sample, the average expression level of the three houseskeeping genes (ACTB, GAPDH, and B2M) was substracted from the expression level of each of the 10 genes in the same sample, after which the sum of the normalized expression for each of the 10 genes was calculated (nSum)

nSum= SUM(Genes-Average(Housekeeping genes))

nSum = SUM(CT(genes) – Average CT(housekeeping genes) = SUMΔCT

Sample specific POISE Scores were then correlated with the obtained sample specific nSum values (e.g. SUMΔCT) and a formula was extrapolated that facilitated conversion of SUMΔCT into the POISE Score. To obtain the POISE Score, the following formula was applied:

Y= X - 27.474; wherein

Y is the POISE Score and X is nSum (e.g. SUMΔCT)

FIG. 3 shows the correlation of the subject specific POISE Score and subject specific SUMΔCT.

A threshold SUMΔCT of 57.474 was determined to correlate with the threshold POISE Score of 35, i.e. subjects with SUMΔCT of 57.474 or more can be identified as having elevated IFN-I signature.

Example 2. A Phase 1, Randomized, Double-blind, Placebo-controlled, Single Ascending Dose Study in Healthy Subjects and Multiple Dose Study of JNJ-55920839 in Subjects with Mild to Moderate Systemic Lupus Erythematosus (NCT02609789)

JNJ-55920839 is a monoclonal antibody (mAb) targeting type I interferons (IFN-I). JNJ-55920839 broadly binds and neutralizes 11 of the 12 human interferon alpha (IFN-α) subtypes and human interferon omega (IFN-ω) with high affinity, but does not neutralize interferon beta (IFN-β) or IFN-α subtype D/1.

The primary objectives of this study are to assess the safety and tolerability of JNJ-55920839 following single ascending IV or subcutaneous administration in healthy subjects (Part A) and assess the safety and tolerability of JNJ-55920839 following multiple IV dose administrations in subjects with mild to moderate SLE (Part B).

Secondary Objectives of the study are to assess the pharmacokinetics (PK) and immunogenicity of JNJ-55920839 following ascending IV or subcutaneous administration in healthy subjects (Part A), and following multiple IV dose administrations in subjects with mild to moderate SLE (Part B), to evaluate pharmacodynamic (PD) effects and clinical responses following a IV or SC dose of JNJ-55920839 in healthy subjects (Part A), and evaluate PD and clinical response following multiple IV doses of JNJ-55920839 in subjects with mild to moderate SLE (Part B).

Exploratory Objectives are to evaluate biomarkers following a single IV or SC dose of JNJ-55920839 in healthy subjects (Part A), and following multiple IV doses of JNJ-55920839 in subjects with mild to moderate SLE (Part B), to evaluate the level of dysregulation of interferon signaling and how this dysregulation correlates with changes in other biomarkers and clinical response measures to administration of study agent, to explore the variability of interferon signatures across different racial/ethnic populations and its potential impact on clinical response associated with exposure to study agent and to explore PK/PD relationships of JNJ-55920839 through analysis of biomarkers, PD markers, and clinical response.

Inclusion and exclusion criteria for subjects with SLE can be found at ClinicalTrials website, as service for the U.S. National instutites of Health, under trial NCT02609789. Among other requirements, subjects eligible for enrollment in this study must have an elevated IFN-I signature as assessed by the POISE Score during screening (prior to randomization).

All subjects will be dosed based on their Day-1 body weight. In Part A, single ascending IV doses ranging from 0.3 to 15.0 mg/kg of JNJ-55920839 or placebo will be administered to sequential cohorts of healthy subjects as an IV infusion of at least 30 minutes. The infusion duration may be increased to approximately 60 minutes if issues of tolerability are encountered in prior cohorts. One additional cohort will receive a single 1 mg/kg SC administration of JNJ-55920839 or placebo. In Part B, 6 doses of up to 10 mg/kg JNJ-55920839 or placebo will be administered every 2 weeks as an IV infusion of at least 30 minutes. Based on the safety information observed in Part A, a dose lower than the planned 10 mg/kg dose may be selected in Part B.

Sterile 0.9% Saline for Injection, USP will be used for dilution of study agent and will also serve as placebo.

Subject eligibility

Subject eligibility to the study was assessed in part by determining elevated IFN-I signature using the POISE score.

Two PAXgene tubes per subject were collected and one tube was sent to a centralized service core for analyses. RNA extraction was conducted utilizing QIAGEN PAXgene blood RNA extraction kit per manufacturer's instructions. RNA samples with >25 µg/ml, 260/280 ratio >1.8 and lack of degradation observed using Agilent® 2200 Tapestation using a RNA ScreenTape or Agilent® 2100 Bioanalyzer using an RNA 6000 Nano-Chip were proceeded to expression analysis using RT2 Prolifer PCR array (Qiagen) according to manufacturer's instruction using 200 ng of total RNA as starting material. The samples were amplified usingViiA 7 Real-Time PCR System (Thermo Fisher Scientific). Expression of DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1, and SAMD9L and housekeeping genes ACTB, GAPDH and B2M genes were assessed. The POISE Score was calculated as described in Example 1.

Table 1 and **Table 2** show the results of the RT^2 Proflier PCR array showing ΔCT (target – mean endogenous control), ΔΔCT ((ΔCT of diseased sample vs ΔCT healthy control)), $2^{\wedge-\Delta\Delta CT}$ (exprssion fold change) and log2 ($2^{\wedge-\Delta\Delta CT}$) (log2 of expression fold change) values for the pool of health controls and five subjects seeking enrollement to the clinical trial. The sum of log2 ($2^{\wedge-\Delta\Delta CT}$) for the 10 tested genes, callucated POISE score and inverse POISE score are shown in Table 3.

Table 1.

Sample Name	Gene	CT	ΔCT	ΔΔCT	$2^{\wedge-\Delta\Delta CT}$	log2($2^{\wedge-\Delta\Delta CT}$)
Healthy Control*	ACTB	18.65				
Subject 1**	ACTB	19.75				
Subject 2***	ACTB	18.01				
Healthy Control	B2M	19.84				
Subject 1	B2M	20.02				
Subject 2	B2M	19.13				
Healthy Control	GAPDH	23.72				
Subject 1	GAPDH	24.21				
Subject 2	GAPDH	22.99				
Healthy Control	DHX58	29.57	8.84	0.00	1.00	0.00
Subject 1	DHX58	28.37	7.04	-1.80	3.49	1.80
Subject 2	DHX58	29.78	9.73	0.89	0.54	-0.89
Healthy Control	EIF2AK2	26.71	5.97	0.00	1.00	0.00
Subject 1	EIF2AK2	24.82	3.49	-2.49	5.61	2.49
Subject 2	EIF2AK2	25.48	5.44	-0.54	1.45	0.54
Healthy Control	HERC5	28.68	7.95	0.00	1.00	0.00
Subject 1	HERC5	26.08	4.75	-3.19	9.14	3.19

Sample Name	Gene	CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta CT}$	$\log2(2^{-\Delta\Delta CT})$
Subject 2	HERC5	28.07	8.02	0.08	0.95	-0.08
Healthy Control	IFI44	27.07	6.34	0.00	1.00	0.00
Subject 1	IFI44	23.14	1.81	-4.53	23.07	4.53
Subject 2	IFI44	27.21	7.17	0.83	0.56	-0.83
Healthy Control	IFI44L	29.25	8.51	0.00	1.00	0.00
Subject 1	IFI44L	23.74	2.41	-6.10	68.67	6.10
Subject 2	IFI44L	29.56	9.52	1.01	0.50	-1.01
Healthy Control	IFI6	26.78	6.05	0.00	1.00	0.00
Subject 1	IFI6	24.07	2.74	-3.31	9.92	3.31
Subject 2	IFI6	26.00	5.96	-0.09	1.06	0.09
Healthy Control	IRF7	29.96	9.23	0.00	1.00	0.00
Subject 1	IRF7	29.00	7.67	-1.56	2.95	1.56
Subject 2	IRF7	29.35	9.30	0.08	0.95	-0.08
Healthy Control	PARP9	25.52	4.79	0.00	1.00	0.00
Subject 1	PARP9	24.42	3.09	-1.69	3.24	1.69
Subject 2	PARP9	24.12	4.08	-0.71	1.64	0.71
Healthy Control	PLSCR1	25.89	5.16	0.00	1.00	0.00
Subject 1	PLSCR1	24.08	2.76	-2.40	5.29	2.40
Subject 2	PLSCR1	24.15	4.11	-1.05	2.07	1.05
Healthy Control	SAMD9L	27.35	6.62	0.00	1.00	0.00
Subject 1	SAMD9L	24.75	3.43	-3.19	9.16	3.19
Subject 2	SAMD9L	26.27	6.22	-0.40	1.32	0.40
* mean CT of housekeeping genes: 20.74						
**Mean CT of housekeeing genes: 21.33						
***Mean CT of housekeeping genes: 20.04						

Table 2.

Sample Name	Target Name	CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta CT}$	$\log2(2^{-\Delta\Delta CT})$
Healthy Control	ACTB	18.43				
Subject 3	ACTB	17.14				
Subject 4	ACTB	17.04				
Subject 5	ACTB	17.73				
Healthy Control	B2M	19.76				
Subject 3	B2M	18.61				
Subject 4	B2M	18.42				
Subject 5	B2M	20.13				
Healthy Control	GAPDH	23.73				
Subject 3	GAPDH	22.41				
Subject 4	GAPDH	22.09				
Subject 5	GAPDH	22.97				

Sample Name	Target Name	CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta CT}$	$\log2(2^{-\Delta\Delta CT})$
Healthy Control	DHX58	29.22	8.58	0.00	1.00	0.00
Subject 3	DHX58	28.95	9.56	0.98	0.51	-0.98
Subject 4	DHX58	26.15	6.96	-1.62	3.07	1.62
Subject 5	DHX58	29.13	8.85	0.28	0.83	-0.28
Healthy Control	EIF2AK2	26.58	5.93	0.00	1.00	0.00
Subject 3	EIF2AK2	25.44	6.06	0.12	0.92	-0.12
Subject 4	EIF2AK2	23.28	4.09	-1.84	3.58	1.84
Subject 5	EIF2AK2	26.98	6.70	0.77	0.59	-0.77
Healthy Control	HERC5	28.43	7.79	0.00	1.00	0.00
Subject 3	HERC5	27.88	8.49	0.70	0.62	-0.70
Subject 4	HERC5	23.94	4.76	-3.03	8.18	3.03
Subject 5	HERC5	28.95	8.67	0.88	0.54	-0.88
Healthy Control	IFI44	26.98	6.34	0.00	1.00	0.00
Subject 3	IFI44	26.65	7.27	0.92	0.53	-0.92
Subject 4	IFI44	21.75	2.57	-3.77	13.66	3.77
Subject 5	IFI44	27.22	6.95	0.60	0.66	-0.60
Healthy Control	IFI44L	28.68	8.04	0.00	1.00	0.00
Subject 3	IFI44L	30.18	10.79	2.75	0.15	-2.75
Subject 4	IFI44L	23.10	3.91	-4.12	17.43	4.12
Subject 5	IFI44L	30.14	9.87	1.83	0.28	-1.83
Healthy Control	IFI6	26.51	5.87	0.00	1.00	0.00
Subject 3	IFI6	26.40	7.01	1.15	0.45	-1.15
Subject 4	IFI6	22.19	3.01	-2.86	7.27	2.86
Subject 5	IFI6	27.31	7.03	1.17	0.45	-1.17
Healthy Control	IRF7	30.06	9.42	0.00	1.00	0.00
Subject 3	IRF7	29.26	9.87	0.45	0.73	-0.45
Subject 4	IRF7	27.08	7.89	-1.53	2.89	1.53
Subject 5	IRF7	30.07	9.79	0.37	0.77	-0.37
Healthy Control	PARP9	25.66	5.02	0.00	1.00	0.00
Subject 3	PARP9	24.23	4.84	-0.18	1.13	0.18
Subject 4	PARP9	23.06	3.88	-1.15	2.21	1.15
Subject 5	PARP9	25.77	5.49	0.47	0.72	-0.47
Healthy Control	PLSCR1	26.14	5.49	0.00	1.00	0.00
Subject 3	PLSCR1	24.05	4.66	-0.83	1.78	0.83
Subject 4	PLSCR1	21.97	2.78	-2.71	6.56	2.71
Subject 5	PLSCR1	25.67	5.39	-0.11	1.08	0.11
Healthy Control	SAMD9L	27.10	6.46	0.00	1.00	0.00
Subject 3	SAMD9L	25.98	6.59	0.14	0.91	-0.14
Subject 4	SAMD9L	24.17	4.99	-1.47	2.77	1.47
Subject 5	SAMD9L	26.98	6.70	0.24	0.85	-0.24
Healthy Control mean CT of housekeeping genes: 20.64						
Subject 1 mean CT of housekeeping genes: 19.39						

Sample Name	Target Name	CT	ΔCT	ΔΔCT	$2^{-\Delta\Delta CT}$	$\log2(2^{-\Delta\Delta CT})$
Subject 2 mean CT of housekeeping genes: 19.19						
Subject 3 mean CT of housekeeping genes: 20.28						

Table 3.

	Sum of log2 fold changes ($SUMlog2(2^{-ddCT})$)	Precursor POISE score	POISE score
Subject 1	30.26	13	57
Subject 2	-0.10	44	26
Subject 3	-6.20	50	20
Subject 4	24.10	20	50
Subject 5	-6.51	50	20

The POISE Scores derived from the expression profiling were 57 for Subject 1, 26 for Subject 2, 20 for Subject 3, 50 for Subject 4 and 20 for Subject 5. Subjects with POISE score of 35 or more (e.g. subjects 1 and 4) were defined as having elevated IFN-I signature and eligible to participate to the clinical trial.

Subject eligibility to participate to the clinical trial could also be assessed utilizing thrshold $SUMlog2(2^{-ddCT})$ of 8.725. Utilizing this threshold, subjects 1 and 4 would be eligible to participate to the clincal trial.

FIG. 4 shows the distribution of determined POISE scores from healthy control (HC) subjects and SLE donors determined to have baseline or elevated IFN-I signature based on the threshold POISE Score of 35. Subjects with POISE score of equal to 35 or greater were eligible to be enrolled to the study provided other eligilibity requirements were met.

Example 3. Automation of generation and collection of the POISE Score

Creating the Validated Spreadsheet to Generate the POISE Score

An Excel spreadsheet was designed to automatically generate a POISE score from the exported Viia7 qPCR instrument raw data file with minimal user interface. To begin, sheet 1 of the Excel spreadsheet contained a designated space in which the user copied the raw qPCR data into. On sheet 2, all calculations utilized to arrive at the log2 fold changes were automatically populated

for the 10 genes of interest after qPCR raw data was copied into sheet 1. Calculations were as follows:

1) The mean CT value was determined for the following housekeeping genes: ACTB, B2M, and GAPDH.
2) The delta CT (ΔCT) was determined by subtracting the mean of the housekeeping genes from the CT of each of the 10 target genes.
3) The ΔCT of the pooled healthy sample was subtracted from the ΔCT of each SLE sample to determine the delta delta CT (ΔΔCT).
4) The fold change between the pooled healthy control and each SLE sample was determined by calculating $2^{-\Delta\Delta CT}$.
5) The base 2 logarithm of the $2^{-\Delta\Delta CT}$ fold change was determined.

Sheet 3 of the spreadsheet contains the POISE score calculation formula for each SLE sample run on the array. The end user submitted this number into the IWRS system which was relayed back to the clinical sites and indicated whether the subject met IFN-I signature inclusion criteria. This spreadsheet was validated as an approved tool to generate the POISE score.

Example 4. POISE IFN-I signature analysis is more sensitive than direct detection of IFN-I by ELISA

Healthy control and SLE patient samples were examined to determine the relationship between the POISE score from RNA isolated from the blood of patients versus the direct level of IFN-α protein in the serum from the same patient collected at the same time. A highly sensitive single molecule array platform (Simoa) was utilized to accomplish protein quantification. The POISE assay enabled quantification of IFN-I activity in samples before direct detection by ELISA using this highly sensitive platform enabling healthy donor levels of IFN-I activity to be distinguished between donors. As IFN-α became detectable by ELISA the POISE scores and IFN-α levels were positively correlated reaffirming the specificity of the POISE as a marker of IFN-I pathway activation. This data indicated that the POISE is a highly sensitive means to quantify IFN-I levels even in healthy human subjects which would also enable robust measurement of pharmacodynamic responses in SLE patients undergoing treatment with IFN-I inhibitor treatment. **FIG. 5** shows the correlation of the POISE Score and plasma IFN-α concentration (log(pg/ml)) in healthy (black dots) or SLE subjects (gray dots).

Example 5. Safety, tolerability and clinical response in healty volunteers and participants with midl-to-moderate systemic lupus erythematosus (NCT0260978)

The clinical study design is described in Example 2 and in this Example. In this first-in-human Phase I, 2-part, randomized, double-blind, placebo-controlled, multicenter design study, a single-ascending intravenous (IV) dose of 0.3 mg/kg to 15 mg/kg or a single subcutaneous dose of 1 mg/kg was administered to healthy volunteers (Part A) and multiple IV doses of 10 mg/kg were administered to participants with mild-to-moderate systemic lupus erythematosus (SLE) (Part B).

Summary of the results*:* The pharmacokinetic profile of JNJ-55920839 was generally similar in healthy volunteers and participants with SLE. Bioavailability of JNJ-55920839 was approximately 80% in healthy volunteers. No antidrug antibodies were detected. In participants with SLE, JNJ-55920839 treatment appeared to associate with clinical responses measured by the Systemic Lupus Erythematosus Responder Index, Systemic Lupus Erythematosus Disease Activity Index 2000, and Physician's Global Assessment relative to placebo. Infections were the most common adverse events reported in both parts of the study with numerically increased rate in exposed over placebo; in 2 participants with SLE, locally disseminated herpes zoster of the skin was reported.
Conclusion: The JNJ-55920839 pharmacokinetic profile was similar to other monoclonal antibodies and was well tolerated and safe in healthy volunteers and participants with SLE. Clinical responses and dysregulation of IFN-I signature were improved in JNJ-55920839 treated participants compared with placebo.

Significance of the study

- JNJ-55920839 was found to be safe and well tolerated in healthy volunteers and participants with mild-to-moderate SLE exhibiting an elevated IFN-I at screening.
- Improvements in SRI responses, SLEDAI-2K responses, and Physician's Global Assessment were observed after six 10 mg/kg IV doses of JNJ-55920839 in participants with mild-to-moderate SLE.
- POISE expression signature was utilized for participant inclusion and to assess PD effects of JNJ-55920839 in part B of this trial.
- JNJ-55920839 treated participants exhibited a pronounced and intended temporal PD effect on IFN-I signature expression in whole blood compared with the placebo population.
- Infection events appeared to associate with exposure to study agent. Additional research is needed to optimize the dosing regimen and further characterize safety for SLE participants.

Inclusion criteria for healthy volunteers (Part A) included men or women aged 18 to 55 years, inclusive; body weight of 50 to 90 kg, inclusive; and body mass index of 18 to 30 kg/m^2, inclusive. Female volunteers were required to be postmenopausal or surgically sterile and have a negative pregnancy test at screening. General inclusion criteria for participants with mild-to-moderate SLE (Part B) were similar to those for healthy volunteers, except that body weight could go down to 40 kg and up to 100 kg, inclusive. Concomitant medications were limited by dosage or number: if on oral corticosteroids, participant must be on stable dose equivalent to an average dose of ≤7.5 mg daily prednisone for 6 weeks prior to first dose; if on antimalarial (eg, chloroquine and hydroxychloroquine), participant must be on stable dose for 6 weeks prior to first dose; and participants were limited to 1 immunosuppressive drug without exceeding dose levels specified for each drug (methotrexate ≤20 mg/week, azathioprine/mercaptopurine ≤2 mg/kg/day, or mycophenolate mofetil/mycophenolic acid equivalent ≤2 g/day). Participants with lupus nephritis were also required to exhibit an active extrarenal feature of lupus at the time of entry. Additionally, participants had to meet the following key criteria at enrollment: Systemic Lupus International Collaborating Clinics modification of the criteria from the American College of Rheumatology (Petri *et al., Arthritis Rheum* 64: 2677-86, 2012) for diagnosis of lupus with at least 1 Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)-defined nonserologic clinical activity within 3 months prior to first dose of study drug. In addition to meeting criteria from the Systemic Lupus International Collaborating Clinics, the participant must be serologically defined as positive within 2 months prior to first dose or at screening by a positive antinuclear antibody titer of ≥1:80 or a positive anti-double-stranded deoxyribonucleic acid test or a positive anti-Smith antibody, positive anti-ribonucleoprotein antibody and/or anti-Ro antibody, and in addition to at least one of the above, a positive lupus IFN-I signature score at screening as assessed using the POISE score.

For both parts of the study, subjects were excluded if they had a serious infection within 4 months prior to the screening visit, had a coexisting medical condition or past history that was concerning to the investigator, or had active or latent tuberculosis.

Part A of the study assessed the safety, tolerability, PK, and immunogenicity of a single administration of JNJ-55920839 or placebo in healthy volunteers. A computer-generated randomization schedule was used to randomly assign volunteers to a treatment group. Single-ascending IV doses ranging from 0.3 mg/kg to 15.0 mg/kg of JNJ-55920839 or placebo were administered to sequential cohorts of healthy volunteers as an IV infusion. An additional cohort received a single 1 mg/kg SC administration of JNJ-55920839.

Part B of the study explored the safety, tolerability, clinical response, PK, PD using the POISE score, and immunogenicity in participants with SLE. Six doses of 10 mg/kg JNJ-55920839

or placebo were administered every 2 weeks as an IV infusion. Randomization was stratified by racial/ethnic subpopulation (Asian/non-Asian) and elevated level of serologic disease activity (present [antinuclear antibody ≥1:160 titer or presence of lupus autoantibodies] or absent [antinuclear antibody absent or <1:160 titer and no lupus autoantibodies]), and participants were assigned based on a computer-generated randomization schedule.

Study subjects were involved for approximately 13 weeks for Part A and 22 weeks for Part B, including a screening visit up to 28 days before administration of study drug. Healthy volunteers stayed at the study site for 6 days and 5 nights. All subjects received study drug on Day 1, and participants with mild-to-moderate SLE received additional doses on Days 15, 29, 43, 57, and 71.

Blood Sampling and Bioanalysis

Blood samples for all Part A cohorts were collected prior to study drug administration and at various timepoints up to 63 days after dosing. For Part B, blood samples were collected predose and at various timepoints up to 129 days after first study drug administration. Serum samples were analyzed to determine concentrations of JNJ-55920839 using a validated, immunoassay method with a lower limit of quantification of 0.06 µg/mL. In addition, serum samples were used to evaluate antibodies to JNJ-55920839 using a validated assay method.

IFN-I Signature Score (POISE Score)

A whole-blood quantitative polymerase chain reaction-based 10 gene IFN-I gene signature was developed to enable enrollment of participants based on IFN-I signature levels at screening. Generation of the signature threshold was calculated based on the following genes: DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1, and SAMD9L. This combination of genes and threshold was empirically derived using machine learning methods and internal data sets to best classify healthy volunteers versus SLE participants. This IFN-I gene signature was also quantified by RNA-sequencing of longitudinally collected blood samples in the study to assess the PD of JNJ-55920839 and the stability of the signature over time in the placebo arm.

Noncompartmental PK Analysis

Noncompartmental PK analysis was performed using Phoenix™ WinNonlin® (version 6.2.1; Tripos LP, USA). Mean terminal elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda z$, with λz being the apparent terminal elimination rate-constant, estimated by linear regression using the

terminal log-linear phase of the logarithmic transformed concentration versus time curve. A bsolute bioavailability after SC administration was calculated from the ratio of area under the serum concentration-time curve following SC and IV administration of the same dose of JNJ-55920839.

Safety and Clinical Response Evaluations

Safety and tolerability were evaluated until Day 64 for healthy volunteers (Part A) and Day 130 for participants with mild-to-moderate SLE (Part B). The safety population included any subjects who received any administration of JNJ-55920839 or placebo. Evaluations included adverse event (AE) assessments, vital sign measurements, electrocardiogram measurements, clinical laboratory tests, and physical examinations. Treatment-emergent adverse events (TEAEs) were coded in accordance with the Medical Dictionary for Regulatory Activities versions 18.1 (Part A) and 21.0 (Part B).

Response evaluations and patient-reported quality of life measures included SLEDAI-2K/SLEDAI-2K Responder Index (S2K RI-50), British Isles Lupus Assessment Group (22), Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), Physician's Global Assessment (PGA) of Disease Activity, Short-form-36 questionnaire (SF-36), EuroQol – 5 dimensions – 5 levels (EQ-5D-5L) Patient Diary, and Joint Assessment. All evaluations were completed predose on Days 1, 15, 29, 57, 71, and 100.

Results

Study Populations and Disposition

For Part A, 48 healthy volunteers from a single site in Belgium were randomized to receive single-ascending IV (n=30) or SC (n=6) doses of JNJ-55920839 or placebo (n=12; **Table 4**). There were more male (40 [83.3%]) than female (8 [16.7%]) volunteers. The mean age of the study population in Part A was 40.4 years (standard deviation [SD]=11.37), and the mean body mass index and baseline weight were 25.27 kg/m^2 (SD=2.61) and 78.77 kg (SD=9.97), respectively. Demographics and disposition of placebo and JNJ-55920839 volunteers were similar (**Table 4**).

Table 4.

		JNJ-55920839 (mg/kg)							
	Placebo (n=12)	IV 0.3 (n=6)	IV 1 (n=6)	IV 3 (n=6)	IV 10 (n=6)	IV 15 (n=6)	SC 1 (n=6)	Combined (n=36)	Total (n=48)
Age (years)									

Mean (SD)	41.3 (9.81)	42 (10.28)	38 (13.08)	51.2 (4.88)	35.5 (11.61)	41.2 (11.84)	32.5 (13.13)	40.1 (11.95)	40.4 (11.37)
Sex, n (%)									
Female	3 (25)	0	1 (16.7)	2 (33.3)	0	1 (16.7)	1 (16.7)	5 (13.9)	8 (16.7)
Male	9 (75)	6 (100)	5 (83.3)	4 (66.7)	6 (100)	5 (83.3)	5 (83.3)	31 (86.1)	40 (83.3)
Race, n (%)									
Black/African American	0	0	0	0	0	0	1 (16.7)	1 (2.8)	1 (2.1)
White	12 (100)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	5 (83.3)	35 (97.2)	47 (97.9)
Weight (kg)									
Mean (SD)	82.7 (9.157)	79.87 (8.709)	75.58 (7.639)	79.85 (6.775)	81.25 (4.819)	77.87 (14.578)	70.32 (13.722)	77.46 (10.006)	78.77 (9.972)
BMI (kg/m^2)									
Mean (SD)	26.22 (2.829)	25.02 (2.807)	24.88 (2.278)	26.57 (1.269)	24.42 (1.537)	25.65 (2.604)	23.22 (3.455)	24.96 (2.491)	25.27 (2.607)
BMI, body mass index; IV, intravenous; SC, subcutaneous; SD, standard deviation									

For Part B, 28 participants with mild-to-moderate SLE from 19 sites in 7 countries were randomized to receive study drug (n=20; 10 mg/kg IV) or placebo (n=8; **Table 5**). There were more female (27 [96.4%]) than male (1 [3.6%]) participants. Of these, 15 (53.6%) participants were self-described as Asian, 2 (7.1%) were black/African American, and 11 (39.3%) were white. The mean age of the study population was 35.9 years (SD=9.30), mean body mass index was 22.5 kg/m^2 (SD=3.42), and mean baseline weight was 58.4 kg (SD=8.77). The baseline characteristics (disease, criteria from the Systemic Lupus International Collaborating Clinics, and lupus nephritis classification) and demographics were well balanced between the study drug and placebo cohorts (**Table 5**). Overall use of selected prior medications (methotrexate, systemic corticosteroids, and chloroquine/hydroxychloroquine) and concomitant medications at baseline was balanced between both placebo and study drug cohorts.

Table 5.

	Placebo (n=8)	JNJ-55920839 10 mg/kg IV (n=20)	Total (n=28)
Age (years)			
Mean (SD)	39.5 (8.00)	34.5 (9.58)	35.9 (9.30)
Sex, n (%)			
Female	8 (100.0%)	19 (95.0%)	27 (96.4%)
Male	0	1 (5.0%)	1 (3.6%)
Race, n (%)			
Black/African American	0 (0%)	2 (10.0%)	2 (7.1%)
Asian	4 (50.0%)	11 (55.0%)	15 (53.6%)
White	4 (50.0%)	7 (35.0%)	11 (39.3%)
Weight (kg)			
Mean (SD)	56.3 (6.90)	59.2 (9.45)	58.4 (8.77)
BMI (kg/m^2)			
Mean (SD)	22.1 (3.48)	22.6 (3.47)	22.5 (3.42)
Baseline SLEDAI -2K (0 - 105)			
Mean (SD)	9.5 (3.16)	9.0 (3.63)	9.1 (3.45)
Baseline PGA (VAS 0 - 10 cm)			
Mean (SD)	3.0 (1.41)	2.9 (1.32)	2.9 (1.32)
Baseline Joints with Pain and Inflammation			
Mean (SD)	2.8 (2.71)	1.2 (0.89)	1.6 (1.73)
Anti-RNP			
Positive	2 (25.0%)	11 (55.0%)	13 (46.4%)
Negative	6 (75.0%)	9 (45.0%)	15 (53.6%)
Anti-Smith			
Positive	2 (25.0%)	5 (25.0%)	7 (25.0%)
Negative	6 (75.0%)	14 (70.0%)	20 (71.4%)
Anti-SSA/Ro			
Positive	3 (37.5%)	15 (75.0%)	18 (64.3%)
Negative	5 (62.5%)	4 (20.0%)	9 (32.1%)

Antinuclear Antibodies			
Mean (SD)	580.0 (832.21)	1130.0 (1178.88)[a]	946.7 (1089.63)[b]
Anti-Double-Stranded DNA			
Mean (SD)	85.0 (107.17)	126.7 (173.17)[c]	113.8 (154.90)[d]

BMI, body mass index; IV, intravenous; PGA, Physician's Global Assessment of Disease Activity; RNP, ribonucleoprotein; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SSA/Ro, SSA/Ro antigen; VAS, visual analogue scale.
a. n=16
b. n=24
c. n=18
d. n=26

A total of 46 healthy volunteers completed Part A, and 25 participants completed Part B of the study. Two volunteers from the study drug cohort did not complete Part A; reasons included an AE of myringitis bullous and an elective withdrawal from the study. Both volunteers completed the early termination visit. A total of 3 participants did not complete Part B of the study; reasons for terminating participation included AE (n=1, groin pain: lymphadenopathy) and "other reasons" (n=2; participants were randomized, but not dosed due to exclusionary electrocardiogram abnormalities prior to dosing).

POISE Scores at Screening

One of the primary goals in this study was to assess the impact of JNJ-55920839 on the IFN-I signature in participants with an elevated IFN-I signature score at screening. IFN-I signature was assessed using POISE. The POISE scores from the screened SLE participants revealed both a separation between healthy control samples and the SLE population as well as a bimodal distribution of The POISE scores within the SLE population **(FIG. 6)**. The screening scores also revealed predominantly POISE scores above the threshold in the cohort of participants from Taiwan relative to the other cohorts.

Although not reaching statistical significance, baseline POISE scores were slightly higher in the JNJ-55920839 responder population than in the non-responder population **(FIG. 7)**. One participant presented as negative at baseline despite being IFN-I positive at screening. This participant remained below the IFN-I signature cutoff for the remainder of the study.

Pharmacokinetics

After a single IV infusion of JNJ-55920839 across the dose range of 0.3 mg/kg to 15 mg/kg, there was an approximately dose-dependent and dose-proportional increase in maximum PK concentration and area under the serum concentration-time curve. Mean $t_{1/2}$ was similar after IV infusion (20.7 days to 24.6 days) and SC injection (24.6 days) in healthy volunteers. The absolute bioavailability of JNJ-55920839 administered as an SC injection, based on the comparison with an IV infusion at the same dose, was estimated at approximately 80%.

PK profile following the first dose was similar in participants with mild-to-moderate SLE compared with those in healthy volunteers, with a biphasic disposition. For participants with SLE following multiple IV infusions of JNJ-55920839 (10 mg/kg), steady state was achieved within 43 days of treatment (Dose 4). Mean $t_{1/2}$ after Dose 6 was 14.8 days.

Immunogenicity

No subject developed antibodies to JNJ-55920839 following single administration of JNJ-55920839 IV between 0.3 mg/kg to 15 mg/kg or SC at 1 mg/kg in healthy volunteers or multiple administrations of JNJ-55920839 IV at 10 mg/kg in participants with mild-to-moderate SLE.

Clinical Response in Participants with SLE

Overall Systemic Lupus Erythematosus Responder Index with a 4-point or greater improvement (SRI-4) response data at Day 100 shows that participants receiving JNJ-55920839 had a numerically greater response rate than those who received placebo (31.3% vs 0%, respectively; **FIG. 8**). The JNJ-55920839 cohort showed a greater reduction than the placebo cohort for SLEDAI-2K and S2K RI-50. Mean percentage change from baseline at Day 100 for SLEDAI-2K was a decrease of 23.74 (SD=27.06) vs 8.93 (SD=13.14), respectively; mean percentage change from baseline at Day 100 for S2K RI-50 was a decrease of 51.77 (SD=24.76) vs 25.84 (SD=22.16), respectively. Mean percentage change from baseline to Day 100 in PGA was greater for the JNJ-55920839 cohort than the placebo cohort (decrease of 19.60 [SD=36.25] vs 6.09 [SD=29.15], respectively).

In addition, the JNJ-55920839 cohort exhibited a numerically smaller number of swollen joints than the placebo cohort. There was no difference between JNJ-55920839 and placebo for overall CLASI activity (-27.3% vs -20.4%, respectively), but baseline activity was low. For several clinical and patient-reported outcomes, no changes were observed between treatment cohorts from baseline to after treatment (no new A or 2B shifts per British Isles Lupus Assessment Group, number of time to SLEDAI flare from Day 1 through Day 100, and overall scores or individual domains of EQ-5D-5L and SF-36).

Pharmacodynamics

RNA-Sequence analysis indicated that temporal suppression of the IFN-I signature as measured using the POISE score in the blood was rapid and largely comparable between JNJ-55920839 responders and non-responders (SRI-4 at Day 100) throughout the dosing period from Day 1 through Day 71 with signature levels approaching the cut-off score for enrollment inclusion. The placebo group, by contrast, did not exhibit significant changes in the POISE scores over time **(FIG. 9)**. After the last dose at Day 71, JNJ-55920839 responders exhibited sustained POISE score suppression through Day 86 reaching placebo levels at Day 130, whereas JNJ-55920839 non-responder signature levels rapidly reached placebo levels at Day 79 **(FIG. 9)**.

Safety and Tolerability

During Part A, 39 of 48 healthy volunteers (81.3%) reported experiencing 1 or more TEAEs. The most common TEAE was reported in the system organ class (SOC) of Infections and Infestations (12/48 [25%]) with a higher percentage of volunteers who were exposed to JNJ-55920839 experiencing infections than those exposed to placebo (27.8% vs 16.7%, respectively; **Table 6**). There was a possible association between increasing dose of study drug and the percentage of volunteers who experienced infections. All TEAEs of infections were nonserious.

One infection in a healthy volunteer treated with JNJ-55920839 resulted in discontinuation at their own discretion; this volunteer experienced myringitis bullous that responded to conventional therapy. Additional infections/infestations were observed, primarily upper respiratory, and were not serious; no cases of herpes zoster were noted.

During Part B of the study, similar rates of TEAEs were observed in both cohorts, and a total of 20 participants reported experiencing 1 or more TEAEs. Similar to Part A, the most common TEAE reported was in the SOC of Infections and Infestations (10 [38.5%] participants). However, there was a higher rate in the JNJ-55920839 treatment cohort compared with the placebo cohort (50% vs 12.5%, respectively; **Table 7**). The infections observed in the JNJ-55920839 cohort included common bacterial and viral infections as well as 2 serious adverse events of locally disseminated herpes zoster. A higher rate of events in the SOC of Gastrointestinal Disorders was also reported in the JNJ-55920839 cohort compared with the placebo cohort (16.7% vs 0% participants, respectively). However, these TEAEs were all symptoms rather than a specific diagnosis.

Serious TEAEs were reported by 2 (7.7%) participants from the JNJ-55920839 cohort including 2 cases of herpes zoster (7.7%) and premature labor in 1 participant (3.8%). No serious TEAEs were reported in the placebo cohort. One participant treated with JNJ-55920839 10 mg/kg IV discontinued participation because of a nonserious TEAE of groin pain (lymphadenopathy),

which was considered as possibly related to the study drug by the investigator and eventually resolved. The cases of herpes zoster were considered as related to the study drug. As a result, study enrollment was suspended, and inclusion/exclusion criteria were amended to exclude any participants who had already shown at any point in their medical history a predisposition to developing disseminated forms of zoster. No action was taken with regard to these participants because both had received all planned doses prior to the onset of events. The participant with the serious TEAE of premature labor delivered a healthy baby, and the delivery was within 2 days of 37 weeks (full-term pregnancy). No other issues were reported related to the participant or baby, and this was considered not related to the study drug by the study investigator.

No infusion reacti ons were reported, and no local injection site reactivity was attributed to study drug. There were no clinically meaningful increases in postbaseline chemistry or hematology values for subjects treated with JNJ-55920839.

Table 6.

		JNJ-55920839 (mg/kg)							
	Placebo (n=12)	IV 0.3 (n=6)	IV 1 (n=6)	IV 3 (n=6)	IV 10 (n=6)	IV 15 (n=6)	SC 1 (n=6)	Combined (n=36)	Total (n=48)
Average duration of follow-up (weeks)	12.4	13.2	10.4	15.2	13.8	11	10.8	12.4	12.4
Subjects with 1 or more treatment-emergent adverse events, n (%)	2 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)	1 (16.7)	1 (16.7)	10 (27.8)	12 (25)
System organ class/Preferred term, n (%)									
Infections and Infestations	2 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)	1 (16.7)	1 (16.7)	10 (27.8)	12 (25)
Rhinitis	0	0	2 (33.3)	1 (16.7)	2 (33.3)	0	0	5 (13.9)	5 (10.4)
Nasopharyngitis	0	0	0	0	1 (16.7)	1 (16.7)	1 (16.7)	3 (8.3)	3 (6.3)
Enterobiasis	1 (8.3)	0	0	0	0	0	0	0	1 (2.1)
Gastroenteritis	1 (8.3)	0	0	0	0	0	0	0	1 (2.1)

Myringitis bullous	0	1 (16.7)	0	0	0	0	0	1 (2.8)	1 (2.1)
Viral infection	0	0	0	0	1 (16.7)	0	0	1 (2.8)	1 (2.1)
Note: Percentage was calculated with the number of randomized, treated subjects in each study phase as the denominator. Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events. Adverse events are coded using MedDRA version 18.1. IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; SC, subcutaneous.									

Table 7.

	Placebo (n=8)	JNJ-55920839 10 mg/kg IV (n=18)	Total (n=26)
Average duration of follow-up (weeks)	18.7	18.7	18.7
Subjects with 1 or more treatment emergent adverse events, n (%)	1 (12.5)	9 (50.0)	10 (38.5)
System organ class/Preferred term, n (%)			
Infections and Infestations	1 (12.5)	9 (50.0)	10 (38.5)
Nasopharyngitis	1 (12.5)	5 (27.8)	6 (23.1)
Urinary tract infection	0	3 (16.7)	3 (11.5)
Herpes zoster	0	2 (11.1)	2 (7.7)
Vulvovaginitis	0	2 (11.1)	2 (7.7)
Pharyngitis	0	1 (5.6)	1 (3.8)
Upper respiratory tract infection	0	1 (5.6)	1 (3.8)
Vaginal infection	1 (12.5)	0	1 (3.8)
Note: Percentage was calculated with the number of randomized, treated subjects in each treatment group as the denominator. Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events. Adverse events are coded using MedDRA version 21.0. IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities.			

5

Discussion

JNJ-55920839, a fully human immunoglobulin G1 kappa monoclonal antibody targeting multiple IFN-α subtypes and IFN-ω, was developed to explore the clinical benefits of specifically

neutralizing the activity of these IFNs in participants with SLE having an elevated IFN-I signature. This Phase I study was the first study of the safety, tolerability, PK, immunogenicity, PD, and clinical response in humans following both IV and SC administration. JNJ-55920839 showed linear PK across the IV dose range of 0.3 mg/kg to 15 mg/kg and had similar mean $t_{1/2}$ between IV and SC administration. Similar PK profiles were observed in healthy volunteers and participants with mild-to-moderate SLE, despite the slightly lower clearance observed in these participants. No treatment-induced antidrug antibody to JNJ-55920839 was observed in this first-in-human study. This may not be representative of repeated administrations in the intended patient population.

Overall, JNJ-55920839 at a dose of 10 mg/kg every 2 weeks (6 doses) was associated with numerically better clinical response than placebo, as judged by SRI-4 responses, SLEDAI-2K responses, and PGA. Joint counts showed significant baseline differences across placebo and JNJ-55920839 cohorts, rendering comparisons difficult, but the JNJ-55920839 cohort did show a numerically greater reduction in the number of swollen joints. Few participants had significant CLASI activity at baseline, which made comparisons difficult for this evaluation measurement; however, no difference was seen between JNJ-55920839 and placebo. No improvements were noted in patient-reported outcome measures (SF-36 and EQ-5D-5L). The clinical responses measured by clinical evaluation tools are encouraging as the study was not powered to detect clinical efficacy responses. Additional dose-finding studies that are adequately powered can further optimize the dosing regimen for JNJ-55920839 for clinical responses.

JNJ-55920839 was overall well tolerated among healthy volunteers following a single dose. No infusion reactions occurred, and no local injection site reactivity was attributed to study drug. No serious AEs occurred in Part A of the study. Infections were the most common AE and showed a possible dose response. One infection in a healthy volunteer treated with JNJ-55920839 resulted in discontinuation at their own discretion. This volunteer experienced myringitis bullous requiring antibiotic therapy that responded in an expected time course. Additional infections/infestations were observed, but these were not serious nor did they impact participation in the study. No cases of herpes zoster were noted in the healthy volunteers.

In Part B, 2 cases of locally disseminated herpes zoster infection were observed in participants with mild-to-moderate SLE exposed to the full course of JNJ-55920839 treatment. Both cases resolved without sequelae following conventional therapy. Reactivation of zoster is known to increase with concomitant therapy and SLE and has been reported with other agents that block IFN-I (Furie *et al., Arthritis & Rheumatology* 69:376-86, 2017; Khamashta *et al., Ann Rheum Dis* 75:1909-16, 2016). There was no evidence for broader dissemination of zoster or other specific viral infections in this study. The serious TEAE of premature labor is not considered clinically significant

as the participant was within 2 days of carrying the pregnancy to term. No clinically significant changes from baseline were observed for laboratory parameters, vital signs, physical examination, or electrocardiogram findings. Increased rates of infection in both parts of the study require additional investigation to understand whether the risk of infection is increased with JNJ-55920839. No notable study limitations were identified.

JNJ-55920839 was well tolerated in both healthy volunteers and participants with mild-to-moderate SLE. The clinical measures showed that responders clustered to the JNJ-55920839 cohort. The safety profile of JNJ-55920839 was acceptable with minor concern for development of infections as AEs. The screening strategy used in this study to include an IFN-I signature using the POISE score may be helpful for future studies.

Longitudinal blood samples from participants treated with JNJ-55920839 indicated a clear PD effect versus placebo. These data also indicated that JNJ-55920839 responders did not achieve a deeper level of suppression of the IFN-I signature versus non-responders during the dosing period (Day 1 through Day 71). Despite this observation, using the POISE score for participant enrollment would be expected to enrich for responders to IFN-I inhibition as indicated by the anifrolumab Phase 2 study results (Furie *et al., Arthritis & Rheumatology* 69:376-86, 2017). It is interesting to note that, in this study, no placebo response was observed. This is consistent with data from the ustekinumab Phase 2 analysis, which indicated that lower placebo response rates were observed in subjects having higher IFN-I signature levels at baseline (van Vollenhoven *et al., Lancet* 392: 1330-9, 2018). This observation suggests that SLE subjects with high IFN-I signature at baseline are less responsive to standard-of-care therapy. Thus, enriching for participants having elevated IFN-I signature at baseline could potentially be a strategy to minimize placebo responses in SLE trials. Strikingly, there were PD differences observed after the final dose between Days 72 and 100 between JNJ-55920839 responders and non-responders, where JNJ-55920839 responders consistently exhibited suppression of the IFN-I signature and non-responders reached similar levels to placebo by Day 79. It is currently unclear why non-responders failed to exhibit similar levels of IFN-I signature suppression during this time period after dosing because the levels of suppression were largely similar during the dosing period. Serum samples from this study did not reveal antidrug antibodies in these non-responder participants. Although there are clear limitations to this study due to the sample size, these data indicate the possibility of using this post-dosing assessment in an adaptive trial setting where participants who failed to maintain suppression of the signature during this time period would be discontinued from the study or switched into another study.

Another interesting observation from this study was that the greatest level of IFN-I signature suppression was seen immediately after the first dose of JNJ-55920839. Given the clean

immunogenicity findings from this study, it is unclear why this initial rapid suppression was not maintained after subsequent doses. It is possible that compensatory factors may have been induced to compensate for the immediate suppression of IFN-I signaling after the first dose, but no such factors have been identified. It is also interesting that the IFN-I suppression seen after the last dose, peaking at Day 79 (approximately 1 week after final dose), was the second greatest level of IFN-I suppression observed in this study and only occurred in the JNJ-55920839 responder group. In either case, levels of IFN-I signature never durably reached the levels observed in the healthy control group, which is consistent with data from other trials including those with the anti-IFNR activity, such as anifrolumab (Furie *et al., Arthritis & Rheumatology* 69:376-86, 2017). Despite the lack of complete suppression of the IFN-I signature to levels observed in healthy controls, responders were identified in this study and other SLE trials using IFN-I inhibitors indicating that complete normalization of the IFN-I signature is not required to achieve clinical benefit using the SRI-4 instrument.

Based on these observations, additional study of JNJ-55920839 including dose and regimen for the treatment of SLE is warranted.

We claim

1) A method of treating a subject having a type I interferon (IFN-I) mediated disease that is responsive to treatment with an IFN-I inhibitor, comprising:

   a) providing a biological sample from the subject;

   b) assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

   c) determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

   d) treating the subject with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value.

2) The method of claim 2, wherein the combined expression value is a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9 and the threshold value is SUMΔCT of 57.474.

3) The method of claim 1, wherein the combined expression value is a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls (SUMlog2(2^-ddCT)) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L and the threshold value is SUMlog2(2^-ddCT) of 8.725.

4) The method of claim 1, wherein the combined expression value is a POISE Score of Formula I:

   POISE Score = 70- |43.7251664- SUMlog2($2^{\wedge -ddCT}$)| (Formula I) and the threshold value is the POISE Score of between 30 and 40.

5) The method of claim 4, wherein the threshold value is the POISE score of 35.

6) The method of claim 1, wherein the biological sample is a blood sample or a tissue sample.

7) The method of claim 1, wherein the IFN-I mediated disease is systemic lupus erythematosus (SLE), type I diabetes, psoriasis, primary Sjögren's disease, systemic sclerosis, rheumatoid arthritis, transplant rejection, dermatomyositis, polymyositis, Aicardi-Goutières syndrome, Sting associated vasculopathy with onset in infancy (SAVI) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

8) The method of claim 7, wherein SLE comprises lupus nephrits, cutaneous lupus or lupus with central nervous system (CNS) manifestations.

9) The method of claim 1, wherein the IFN-I inhibitor is a molecule that blocks interaction of IFN-I with IFNAR, an antagonistic antibody that binds IFN-I, an antagonistic antibody that binds IFNAR, an inhibitor of Tyk2, Jak1, TLR7, TLR8, TLR9 or STING, a modulator or depletor of plasmacytoid dendritic cells; or an agent that degrades nucleic acids.

10) The method of claim 9, wherein the antagonistic antibody that binds IFN-I comprises:

a) a heavy chain variable region 1 (HCDR1) of SEQ ID NO: 11, a HCDR2 of SEQ ID NO: 12, a HCDR3 of SEQ ID NO: 13, a light chain variable region 1 (LCDR1) of SEQ ID NO: 14, a LCDR2 comprising the amino acid sequence GAS and a LCDR3 of SEQ ID NO: 16;

b) a heavy chain variable region (VH) of SEQ ID NO: 17 and a light chain variable region (VL) of SEQ ID NO: 18; or

c) a heavy chain (HC) of SEQ ID NO: 19 and a light chain (LC) of SEQ ID NO: 20, or any combination thereof.

11) The method of claim 10, wherein the antagonistic antibody that binds IFN-I is administered at a dose of about 10 mg/kg.

12) The method of claim 11, wherein the antagonistic antibody that binds IFN-I is administered at a dose of about 10 mg/kg once every two weeks.

13) A method of determining whether a subject having a type I interferon (IFN-I) mediated disease is responsive to treatment with an IFN-I inhibitor and deciding whether to treat the subject, comprising:

a) providing a biological sample from the subject;

b) assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

c) determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

d) diagnosing the subject with the IFN-I mediated disease as responsive to treatment with the IFN-I inhibitor when the combined expression value is equal to or higher than a threshold value or diagnosing the subject with the IFN-I mediated disease as non-responsive to

treatment with the IFN-I inhibitor when the combined expression value is less than a threshold value; and

e) administering the IFN-I inhibitor to the subject diagnosed as responsive to treatment with the IFN-I inhibitor or refraining from administering the IFN-I inhibitor to the subject diagnosed as non-responsive to treatment with the IFN-I inhibitor.

14) The method of claim 13, wherein the combined expression value is a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L and the threshold value is SUMΔCT of 57.474.

15) The method of claim 13, wherein the combined expression value is a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls (SUMlog2(2^-ddCT)) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L and the threshold value is SUMlog2(2^-ddCT) of 8.725.

16) The method of claim 13, wherein the combined expression value is a POISE Score of Formula I:

POISE Score = 70- |43.7251664- SUMlog2($2^{\wedge -ddCT}$)| (Formula I) and the threshold value is the POISE Score of between 30 and 40.

17) The method of claim 16, wherein the threshold value is the POISE score of 35.

18) The method of claim 13, wherein the biological sample is a blood sample or a tissue sample.

19) The method of claim 13, wherein the IFN-I mediated disease is systemic lupus erythematosus (SLE), type I diabetes, psoriasis, primary Sjögren's disease, systemic sclerosis, rheumatoid arthritis, transplant rejection, dermatomyositis, polymyositis, Aicardi-Goutières syndrome, Sting associated vasculopathy with onset in infancy (SAVI) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

20) The method of claim 19, wherein SLE comprises lupus nephrits, cutaneous lupus or lupus with central nervous system (CNS) manifestations.

21) The method of claim 13, wherein the IFN-I inhibitor is a molecule that blocks interaction of IFN-I with IFNAR, an antagonistic antibody that binds IFN-I, an antagonistic antibody that binds IFNAR, an inhibitor of Tyk2, Jak1, TLR7, TLR8, TLR9 or STING, a modulator or depletor of plasmacytoid dendritic cells; or an agent that degrades nucleic acids.

22) The method of claim 21, wherein the antagonistic antibody that binds IFN-I comprises:

a) a heavy chain variable region 1 (HCDR1) of SEQ ID NO: 11, a HCDR2 of SEQ ID NO: 12, a HCDR3 of SEQ ID NO: 13, a light chain variable region 1 (LCDR1) of SEQ ID NO: 14, a LCDR2 comprising the amino acid sequence GAS and a LCDR3 of SEQ ID NO: 16;

b) a heavy chain variable region (VH) of SEQ ID NO: 17 and a light chain variable region (VL) of SEQ ID NO: 18; or

c) a heavy chain (HC) of SEQ ID NO: 19 and a light chain (LC) of SEQ ID NO: 20, or any combinations thereof.

23) The method of claim 22, wherein the antagonistic antibody that binds IFN-I is administered at a dose of about 10 mg/kg.

24) The method of claim 23, wherein the antagonistic antibody that binds IFN-I is administered at a dose of about 10 mg/kg once every two weeks.

25) An *in vitro* method for predicting and/or diagnosing that a subject has an IFN-I mediated disease, comprising

a) providing a biological sample from the subject;

b) assaying gene expression of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample;

c) determining a combined expression value of the genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L in the biological sample; and

d) predicting and/or diagnosing that the subject has the IFN-I mediated disease when the combined expression value is equal to or higher than a threshold value.

26) The method of claim 25, wherein the combined expression value is a sum of normalized threshold cycle (CT) values (SUMΔCT) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L and the threshold value is SUMΔCT of 57.474.

27) The method of claim 25, wherein the combined expression value is a sum of log2 fold changes of normalized differential expression between the biological sample and a biological sample obtained from one or more healthy controls (SUMlog2(2^-ddCT)) of genes DHX58, EIF2AK2, HERC5, IFI44, IFI44L, IFI6, IRF7, PARP9, PLSCR1 and SAMD9L and the threshold value is SUMlog2(2^-ddCT) of 8.725.

28) The method of claim 25, wherein the combined expression value is a POISE Score of Formula I:

POISE Score = 70- |43.7251664- SUMlog2($2^{\wedge -ddCT}$)| (Formula I) and the reference value is the POISE Score of between 30 and 40.

29) The method of claim 28, wherein the reference value is the POISE score of 35.

30) The method of claim 25, wherein the biological sample is a blood sample or a tissue sample.

31) The method of claim 30, wherein gene expression is assayed using quantitative Polymerase Chain Reaction (qPCR) or microarray, or both.

32) The method of claim 31, wherein gene expression is measured at the mRNA level.

33) The method of claim 25, wherein the IFN-I mediated disease is systemic lupus erythematosus (SLE), type I diabetes, psoriasis, primary Sjögren's disease, systemic sclerosis, rheumatoid arthritis, transplant rejection, dermatomyositis, polymyositis, Aicardi-Goutières syndrome, Sting associated vasculopathy with onset in infancy (SAVI) or chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE).

FIG. 1A

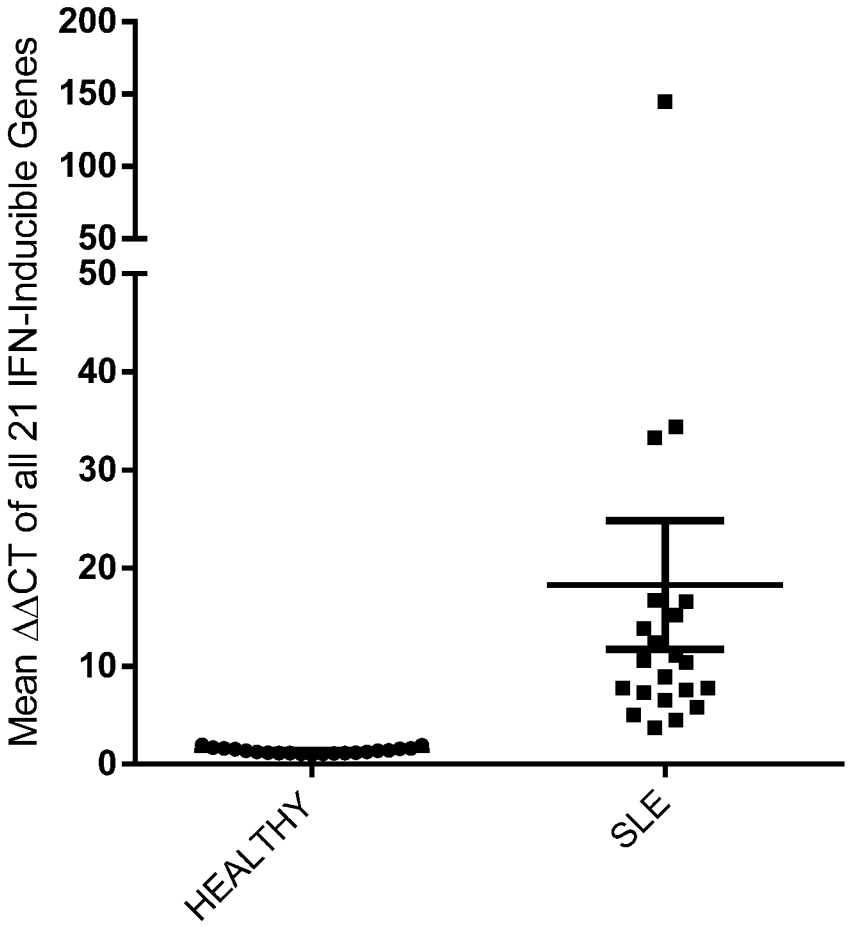

Mean ΔΔCT of all 21 IFN-Inducible Genes
200
150
100
50
50
40
30
20
10
0
HEALTHY
SLE

FIG. 1B

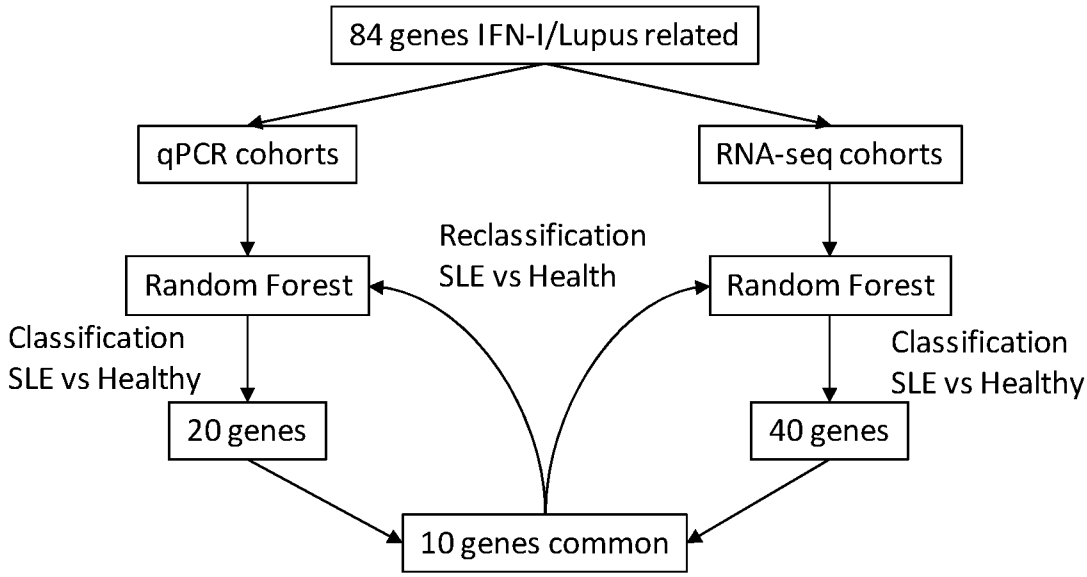

84 genes IFN-I/Lupus related
qPCR cohorts
RNA-seq cohorts
Reclassification
SLE vs Health
Random Forest
Random Forest
Classification
SLE vs Healthy
Classification
SLE vs Healthy
20 genes
40 genes
10 genes common

FIG. 2

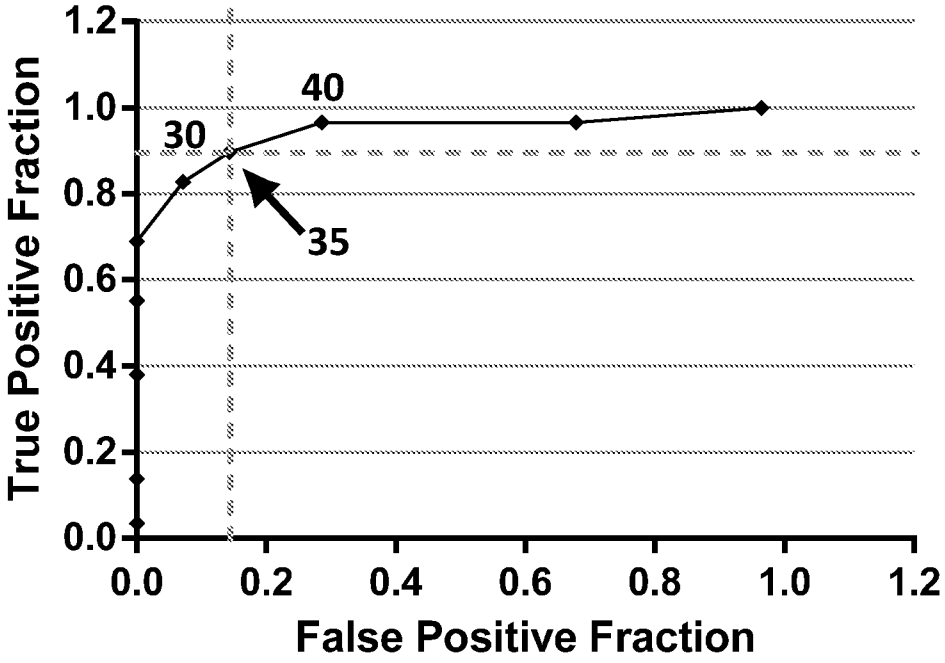

True Positive Fraction
False Positive Fraction
0.0
0.2
0.4
0.6
0.8
1.0
1.2
30
35
40

FIG. 3

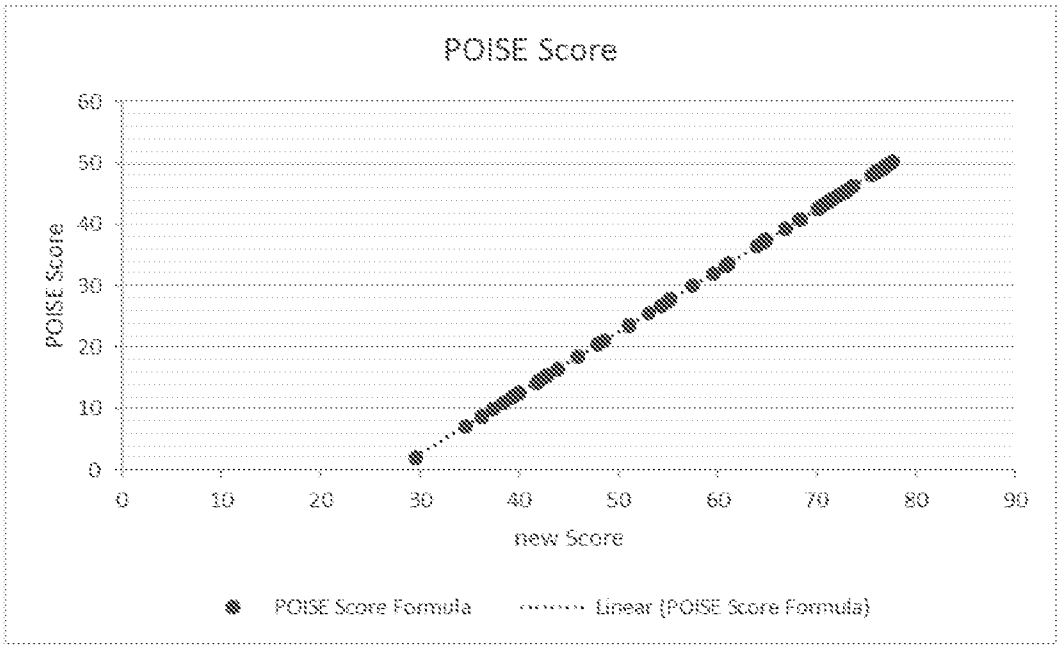

POISE Score
POISE Score
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
new Score
POISE Score Formula
Linear (POISE Score Formula)

FIG. 4

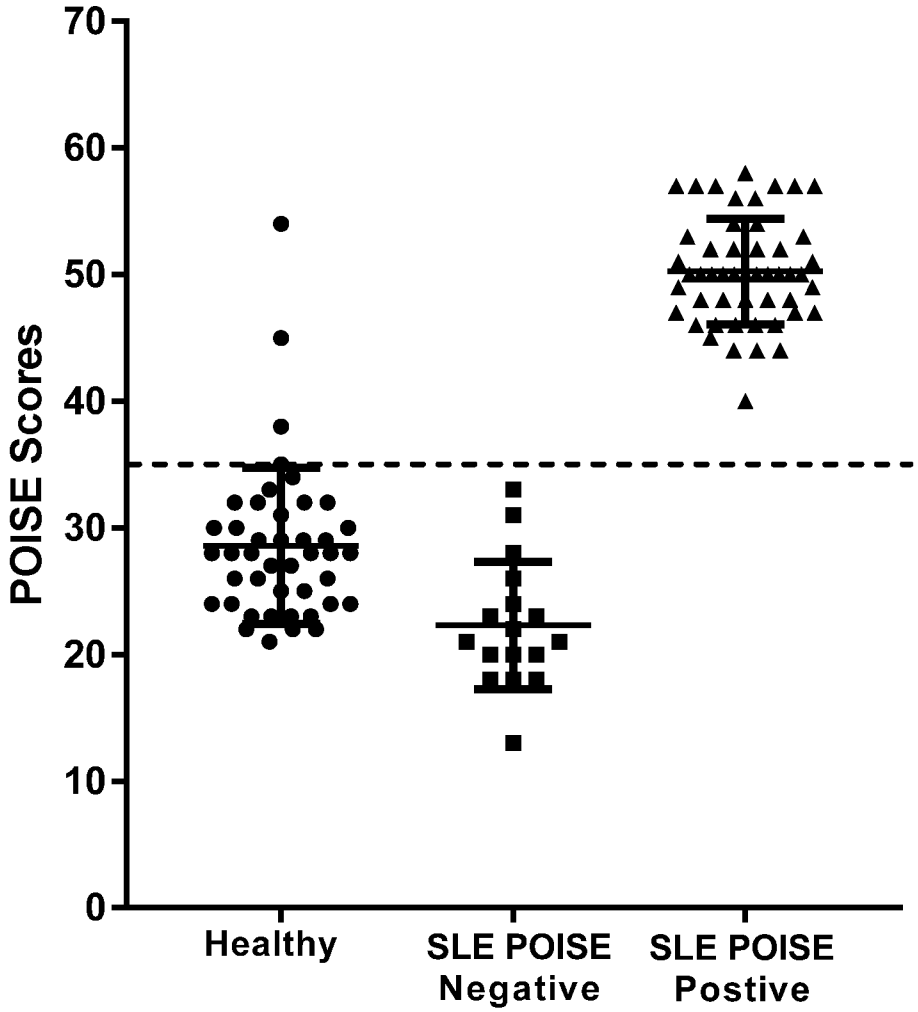

70
60
50
40
30
20
10
0
POISE Scores
Healthy
SLE POISE Negative
SLE POISE Postive

FIG. 5

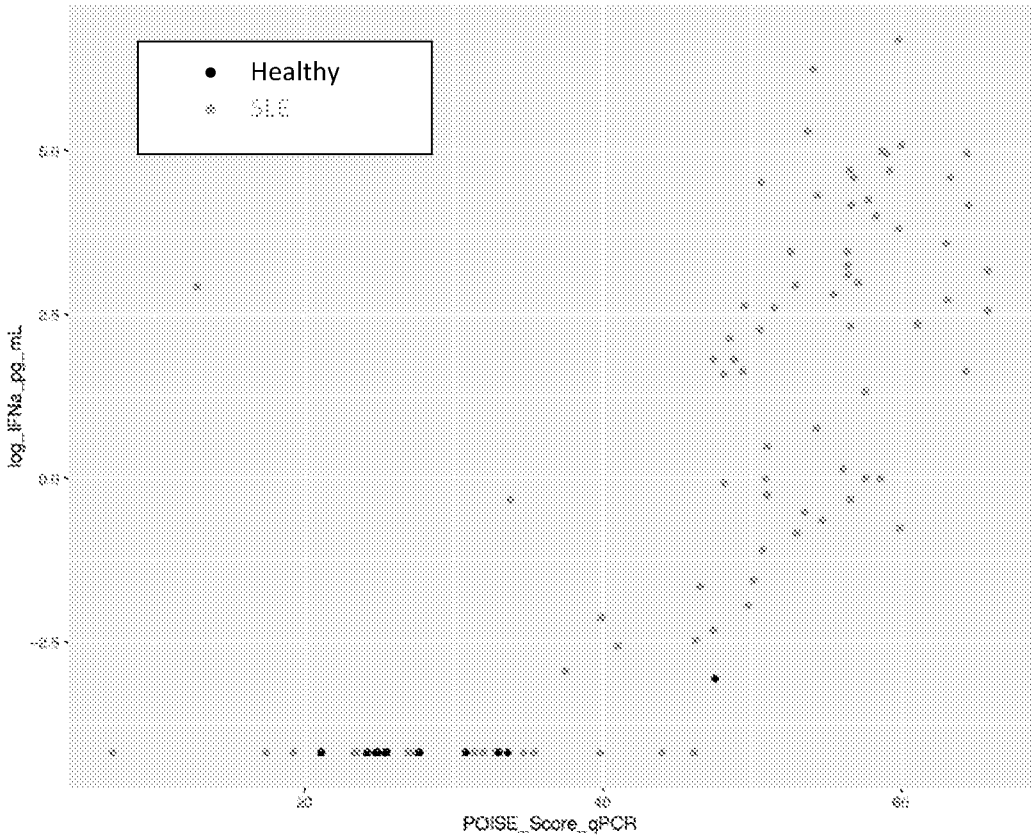


FIG. 6

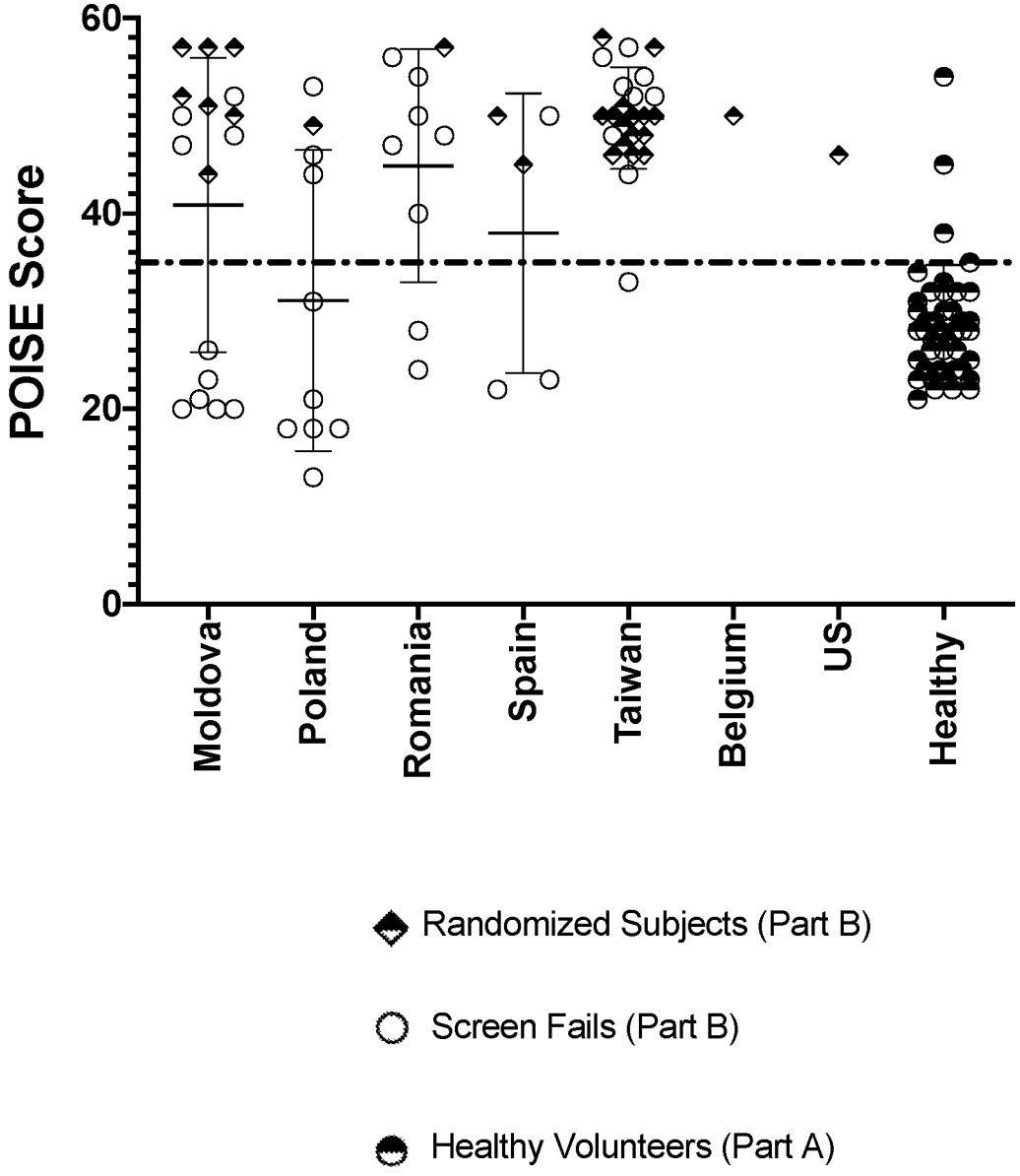

POISE Score
60
40
20
0
Moldova
Poland
Romania
Spain
Taiwan
Belgium
US
Healthy
Randomized Subjects (Part B)
Screen Fails (Part B)
Healthy Volunteers (Part A)

FIG. 7

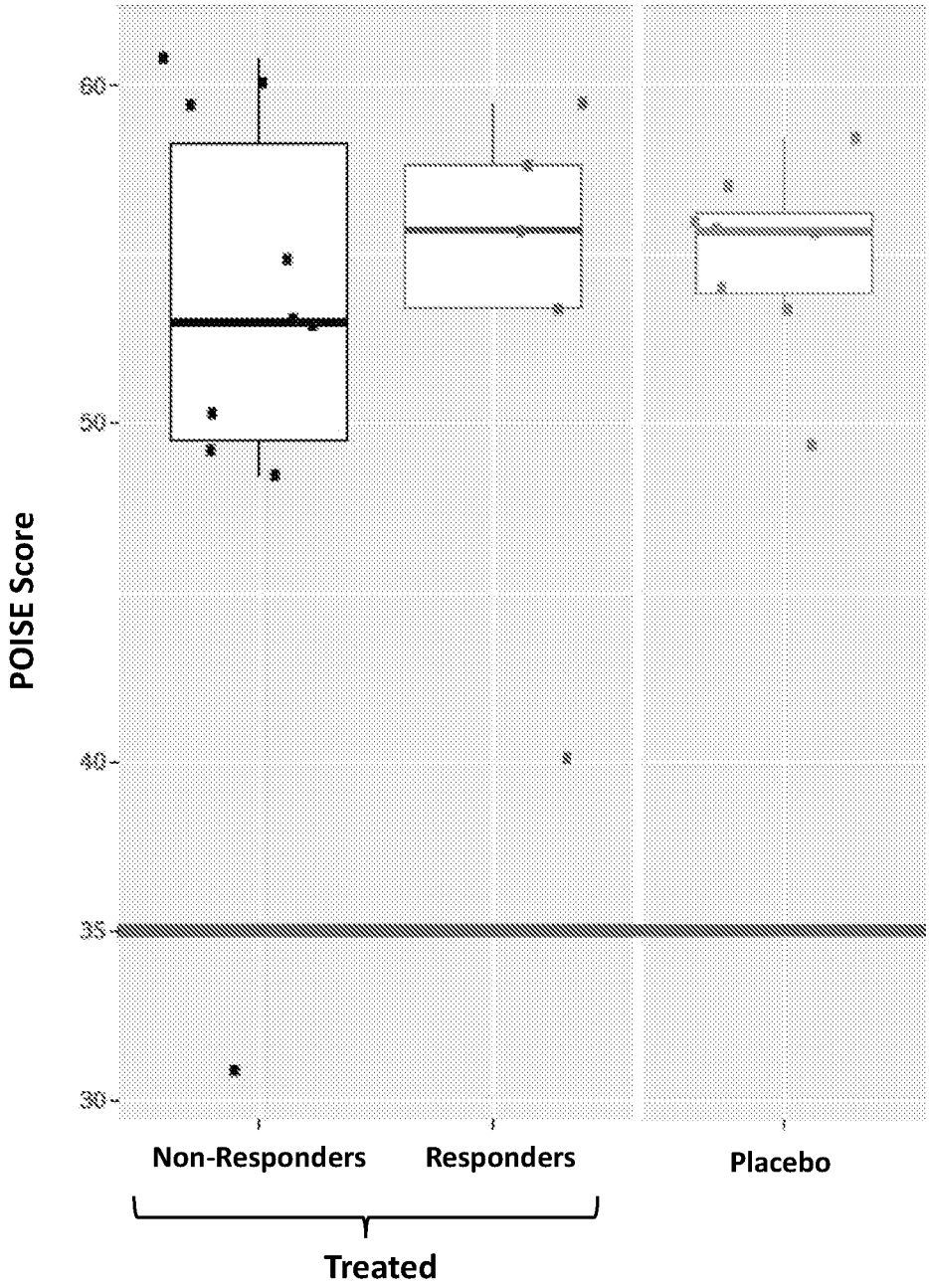

POISE Score
60
50
40
35
30
Non-Responders
Responders
Placebo
Treated

FIG. 8

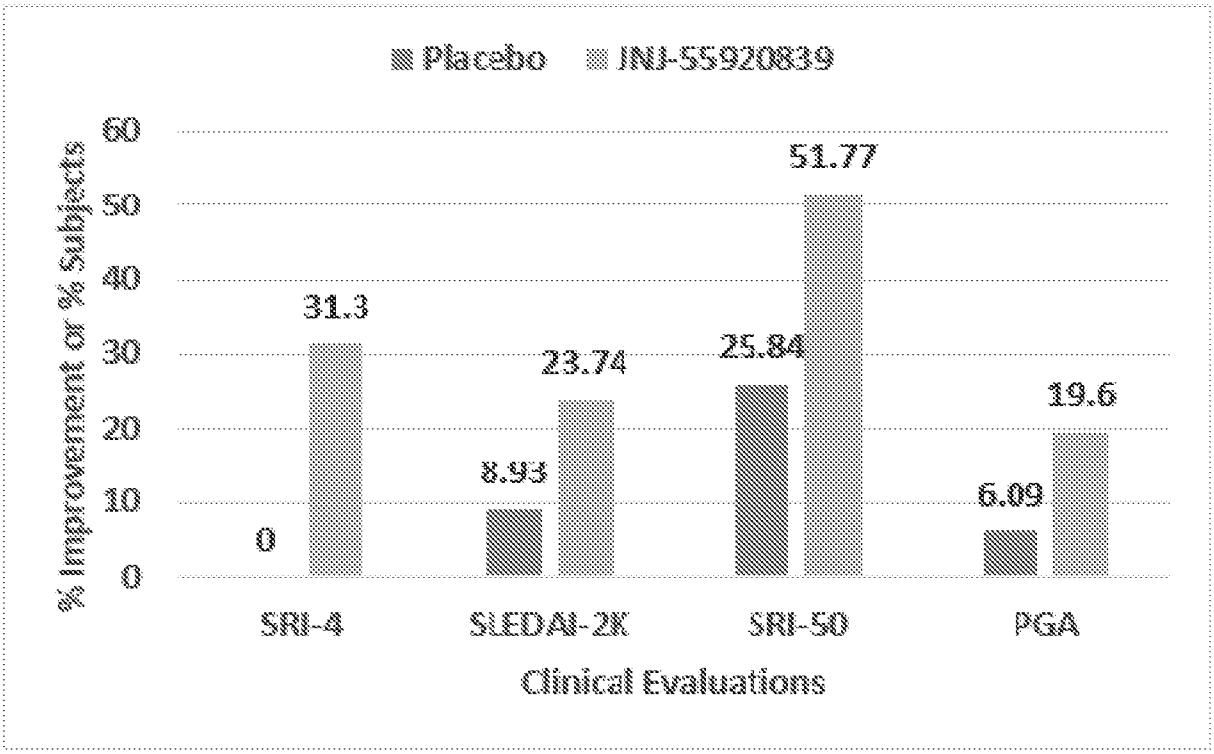
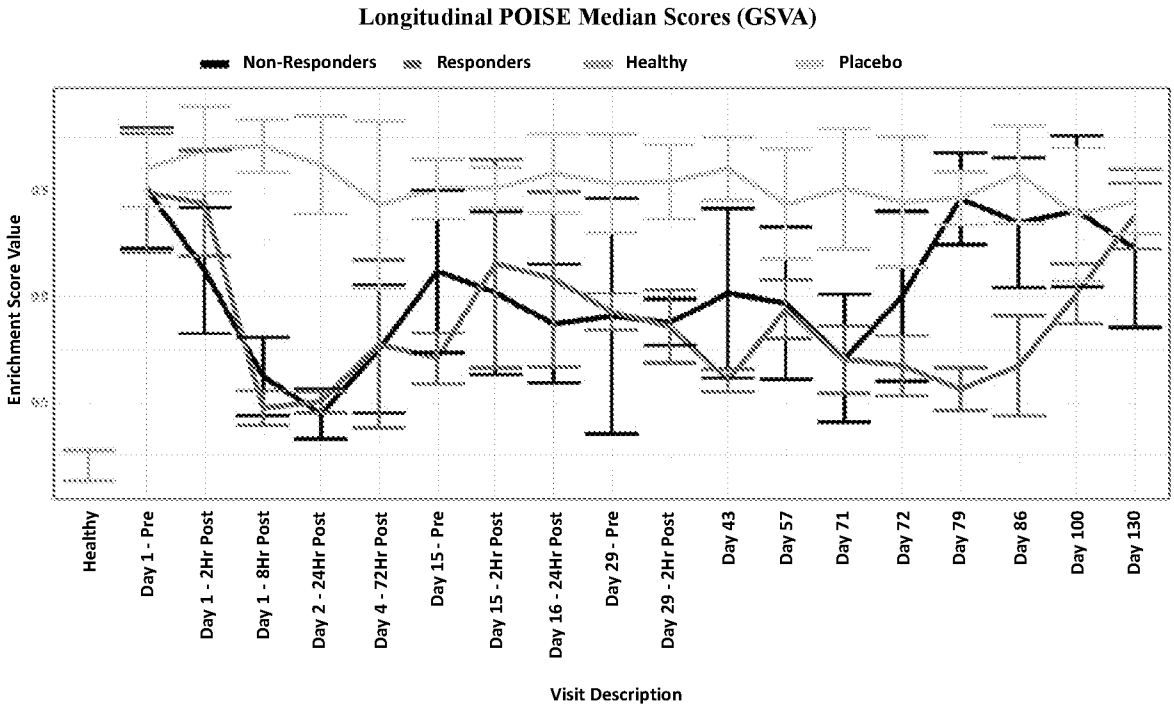

Placebo
INJ-55920839
% Improvement or % Subjects
60
50
40
30
20
10
0
0
31.3
8.93
23.74
25.84
51.77
6.09
19.6
SRI-4
SLEDAI-2K
SRI-50
PGA
Clinical Evaluations

FIG. 9


Longitudinal POISE Median Scores (GSVA)
Non-Responders
Responders
Healthy
Placebo
Enrichment Score Value
Healthy
Day 1 - Pre
Day 1 - 2Hr Post
Day 1 - 8Hr Post
Day 2 - 24Hr Post
Day 4 - 72Hr Post
Day 15 - Pre
Day 15 - 2Hr Post
Day 16 - 24Hr Post
Day 29 - Pre
Day 29 - 2Hr Post
Day 43
Day 57
Day 71
Day 72
Day 79
Day 86
Day 100
Day 130
Visit Description

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB19/59178

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 39/395, 38/21; C07K 16/24; C12Q 1/68 (2020.01)

CPC - A61K 39/395, 38/21, 39/001141; C07K 16/24; C12Q 1/68

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)
See Search History document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/200165 A1 (JANSSEN BIOTECH, INC.) 30 December 2015; page 119, paragraph 2; claims 1, 38	1-33
A	WO 2008/070137 A2 (MEDIMMUNE, INC.) 12 June 2008; page 98, table 21; claims 1, 24, 28-29	1-33
A	WO 2010/120759 A1 (SCHERING CORPORATION) 21 October 2010; claims 4-5	1-33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"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
22 January 2020 (22.01.2020)	19 FEB 2020
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. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300