

TREATMENT OF CARDIOMETABOLIC DISEASE

1 BACKGROUND

[0001] Cardiovascular risk factors, cardiovascular events and subclinical atherosclerosis all occur at a younger age in patients with type I IFN mediated diseases compared with the general population¹. Cardiovascular disease (CVD) resulting from premature atherosclerosis is one of the predominant causes of morbidity and mortality in systemic lupus erythematosus (SLE)^{2,3}. SLE substantially increases the risk of coronary artery disease and myocardial infarction in premenopausal women⁴.

[0002] Traditional cardiometabolic and cardiorespiratory disease risk factors (e.g. smoking, dyslipidemia, diabetes mellitus (DM), hypertension, central obesity and hyperhomocysteinemia) cannot fully account for this enhanced CVD in SLE patients. Immune dysregulation likely contributes to vascular damage in SLE. However, the exact cellular and molecular mechanisms underlying accelerated atherosclerosis and vasculitis in SLE remain unclear.

[0003] Systemic lupus erythematosus (SLE) is a chronic, multisystemic, disabling autoimmune rheumatic disease of unknown aetiology. There is substantial unmet medical need in the treatment of SLE, particularly in subjects with moderate or severe disease. Long-term prognosis remains poor for many subjects.

[0004] A significant problem associated with the treatment of SLE, is the heterogeneous clinical manifestations of SLE⁵. Any organ may be affected in SLE, with the skin, joints, and kidneys being the most commonly involved⁶⁻⁸. Incomplete disease control leads to progressive organ damage, poor quality of life, and increased mortality, with approximately half of all patients with SLE developing organ damage within 10 years of diagnosis^{9,10}. There remains the need for a medical intervention that improves SLE disease activity across multiple systems.

[0005] Clinical manifestations of SLE include, but are not limited to, constitutional symptoms, alopecia, rashes, serositis, arthritis, nephritis, vasculitis, lymphadenopathy, splenomegaly, haemolytic anaemia, cognitive dysfunction and other nervous system involvement. Increased hospitalisations and side effects of medications including chronic oral corticosteroids (OCS) and other immunosuppressive treatments add to disease burden in SLE¹¹⁻¹³.

[0006] All of the therapies currently used for the treatment of SLE have well known adverse effect profiles and there is a medical need to identify new targeted therapies, particularly agents that may reduce the requirement for corticosteroids and cytotoxic agents. There has been only 1 new treatment (belimumab) for SLE approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in the approximately 50 years since hydroxychloroquine was approved for use in discoid lupus and SLE. However, belimumab is not approved everywhere, and the uptake has been modest. Many agents currently used to treat SLE, such as azathioprine, cyclophosphamide, and mycophenolate mofetil/mycophenolic acid, have not been approved for the disease. Furthermore, these drugs all have well-documented safety issues and are not effective in all patients for all manifestations of lupus. Antimalarial agents (e.g. hydroxychloroquine) and corticosteroids may be used to control

arthralgia, arthritis, and rashes. Other treatments include nonsteroidal anti-inflammatory drugs (NSAIDs); analgesics for fever, arthralgia, and arthritis; and topical sunscreens to minimise photosensitivity. It is often difficult to taper subjects with moderate or severe disease completely off corticosteroids, which cause long-term morbidity and may contribute to early cardiovascular mortality^{12,14}. Even small daily doses of 5 to 10 mg prednisone used long-term carry increased risks of side effects such as cataracts, osteoporosis, and coronary artery disease¹².

[0007] Direct measurements of aortic vascular inflammation in patients with CVD can be obtained with positron emission tomography/computed tomography and used as risk markers for CVD progression¹⁵. Short-term changes in arterial inflammation associate with long-term atherosclerosis disease progression, providing validation of measuring subclinical, early stage biomarkers to assess CVD risk. However, these advanced imaging modalities are not accessible to all patients. Furthermore, studying CVD risk in SLE using traditional approaches has low feasibility given disease incidence/prevalence and relatively young age at lupus diagnosis.

[0008] The present invention solves one or more of the above-mentioned problems.

2 SUMMARY

[0009] The invention relates to a method of treating, or reducing the risk for development of, a cardiometabolic disease in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of type I IFN signalling, wherein the patient has a type I IFN mediated disease.

[0010] The invention is supported *inter alia* by data from two phase III, multicenter, multinational, randomized, double-blind, placebo-controlled clinical trials in SLE patients (NCT02446899 and NCT02962960; TULIP I and TULIP II) and a phase II, multinational, multicenter, randomized, double-blind, placebo controlled, parallel-group clinical trial in SLE patients (NCT02962960; MUSE), data analyses of which are presented herein for the first time. These data show that treatment of patients suffering from a type I IFN mediated disease with an inhibitor of type I IFN signalling returns biomarkers of cardiometabolic disease to normal levels. These biomarkers of cardiometabolic disease include GlycA, neutrophil extracellular trap (NET), cholesterol efflux capacity (CEC), TNF- α and/or IL-10.

[0011] The data further show that treatment of patients suffering from a type I IFN mediated disease (e.g. SLE) with an inhibitor of type I IFN signalling (e.g. anifrolumab) treats cardiovascular disease in these patients.

3 BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: BILAG-2004 Index

FIG. 2: Type I IFN pathway and NET complexes elevated in patients with SLE

[0012] **FIG. 2A** shows IFN- α protein levels measured using the quantitative SimoaTM immunoassay in IFNGS test–low (n = 65) and IFNGS test–high (n = 191) patients with moderate to severe SLE. Dashed lines represent the maximum IFN- α level in healthy donors. HD high: 0.53 pg/mL; LLOQ: 0.073 pg/mL.

FIG. 2B shows IFN- α Simoa™ protein level plotted versus 21-IFNGS (n = 256). **FIG. 2C** shows number of neutrophils plotted versus IFN- α protein Simoa™ levels (n = 251). **FIG. 2D** shows levels of the NET complexes CitH3-DNA, MPO-DNA, and NE-DNA measured using capture ELISA in healthy donors (n = 20) and patients with moderate to severe SLE (n = 190). Box and whisker plots represent quartiles of each group. P-values were calculated for **FIG. 2A** and **FIG. 2D** using a 2-tailed Mann–Whitney U test and for **FIG. 2B** and **FIG. 2C** using a 2-tailed Spearman's rank correlation. AUC or Spearman's rank correlation and p-values are above each plot. Abbreviations include: AUC, area under the curve; CitH3, citrullinated histone H3; HD, healthy donors; IFN, interferon; IFNGS, IFN gene signature; LLOQ, lower limit of quantification; MPO, myeloperoxidase; NE, neutrophil elastase; NET, neutrophil extracellular trap; OD, optical density; SLE, systemic lupus erythematosus; WB, whole blood.

FIG. 3: The association of traditional CVD risk factors, IL-10, neutrophil number, TNF- α , and NET complexes with the type I IFN axis in patients with SLE

[0013] Age, BMI, HDL-C, smoking, total cholesterol, CEC, IL-10 protein, neutrophil number per μ L whole blood, TNF- α protein, and circulating NET complexes (CitH3-DNA, MPO-DNA, and NE-DNA) were compared with three measures of the type I IFN pathway: IFN- α protein, 21-IFNGS, and IFNGS test status (IFNGS test–high vs IFNGS test–low). Spearman's rank correlation was used to analyze correlation of parameters with 21-IFNGS and IFN- α protein. Welch's t-test was used to analyze associations of parameters with IFNGS test status, expressed as a Log₂ fold change. Log₂ fold change and Spearman's rank correlation are depicted in forest plots with 95% confidence intervals. Abbreviations include: BMI, body mass index; CitH3, citrullinated histone H3; CEC, cholesterol efflux capacity; CVD, cardiovascular disease; HDL, high-density lipoprotein; IFN, interferon; IFNGS, IFN gene signature; IL, interleukin; MPO, myeloperoxidase; NE, neutrophil elastase; NET, neutrophil extracellular trap; n.s., not significant; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

FIG. 4: Type I IFN pathway inhibition significantly decreased circulating NET complexes after 1 year of treatment

[0014] Levels of the NET complexes CitH3-DNA, MPO-DNA, and NE-DNA were measured using capture ELISA at days 1 and 365 in patients with moderate to severe SLE who received anti-IFNAR1 antibody anifrolumab dosed at 300 mg or placebo. Box and whisker plots represent quartiles of each group. P-values were calculated using a Wilcoxon signed-rank test. *p < 0.05, **p ≤ 0.01. Abbreviations include: CitH3, citrullinated histone H3; ELISA, enzyme-linked immunosorbent assay; IFN, interferon; IFNAR1, IFN alpha and beta receptor subunit 1; MPO, myeloperoxidase; NE, neutrophil elastase; NET, neutrophil extracellular trap; OD, optical density; SLE, systemic lupus erythematosus.

FIG. 5: Serum TNF- α and IL-10 proteins were elevated in patients with SLE at baseline and were reduced after type I IFN pathway inhibition

[0015] **FIG. 5A** shows TNF- α measured using a Simoa™ quantitative immunoassay in IFNGS test-low patients and IFNGS test–high patients with SLE. The healthy donor range is indicated using dashed lines (HD high: 2.9 pg/mL; HD low: 0.68 pg/mL). **FIG. 5B** shows IL-10 protein levels measured using a Simoa™ quantitative immunoassay in healthy donors, IFNGS test–low patients,

and IFNGS test-high patients. For **FIG. 5A** and **FIG. 5B**, box and whisker plots represent quartiles of each group. **FIG. 5C** shows TNF- α protein levels and **FIG. 5D** shows IL-10 protein levels measured at days 1, 85, 169, and 365 in patients who received placebo or anifrolumab 300 mg. TNF- α protein level was measured in 47-58 patients who received placebo and 62-66 patients who received anifrolumab. IL-10 protein was measured in 47-58 patients who received placebo and 61-66 patients who received anifrolumab. For **FIG. 5C** and **FIG. 5D**, percentage change from baseline is plotted with SEM. All p-values were calculated using a 2-tailed Mann-Whitney U test. * $p < 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. Abbreviations include: HD, healthy donor; IFN, interferon; IFNGS, IFN gene signature; IL-10, interleukin-10; SD, standard deviation; SEM, standard error of the mean; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor.

FIG. 6: Impaired CEC at baseline in patients with SLE correlated with NET complex levels and was normalized following type I IFN-signalling inhibition

[0016] **FIG. 6A** shows the CEC of Apo-B depleted plasma samples from healthy donors ($n = 20$), IFNGS test-low patients with SLE ($n = 38$), and IFNGS test-high patients with SLE ($n = 91$). **FIG. 6B** shows the association between CEC and the NET complexes CitH3-DNA, MPO-DNA, and NE-DNA assessed using Spearman's rank correlation in patients with SLE ($n = 123$). **FIG. 6C** shows CEC plotted with SEM in Apo-B-depleted plasma samples from IFNGS test-high patients with moderate to severe SLE with defects in CEC (2SD below HD mean, 0.96) who received placebo ($n = 19$) or anifrolumab dosed at 300 mg ($n = 29$). The CEC at baseline for healthy donors ($n = 20$) is also shown for reference. P-values were calculated using a Wilcoxon signed-rank test. Abbreviations include: CEC, cholesterol efflux capacity; CitH3, citrullinated histone H3; HD, healthy donor; IFN, interferon; IFNGS, IFN gene signature; MPO, myeloperoxidase; NE, neutrophil elastase; NET, neutrophil extracellular trap; OD, optical density; SD, standard deviation; SEM, standard error of the mean; SLE, systemic lupus erythematosus.

FIG. 7: Identification of a CEC defect in patients with SLE

[0017] CEC was measured by liquid scintillation counting to determine radioactive 3H-cholesterol uptake into cellular lipids. CEC percentage distribution is shown for patients who received anifrolumab 300 mg ($n = 72$; purple fill) or placebo ($n = 57$; gray fill) or healthy donors ($n = 20$; black line). The dashed line represents two standard deviations below the healthy donor mean. Abbreviations included: CEC, cholesterol efflux capacity; HD, healthy donor; SD, standard deviation; SLE, systemic lupus erythematosus.

FIG. 8: The greatest CEC increases observed in patients in the lowest quartile of CEC at baseline

[0018] The greatest CEC increases observed in patients in the lowest quartile of CEC at baseline. CEC was measured by liquid scintillation counting to determine the amount of radioactive 3H-cholesterol uptake into cellular lipids. **FIG. 8A** shows CEC distribution in patients with moderate to severe SLE. **FIG. 8B** shows median CEC percentage change on day 365 compared with day 1 in patients with moderate to severe SLE who received anifrolumab. Abbreviations included: CEC, cholesterol efflux capacity; Q, quartile; SLE, systemic lupus erythematosus.

FIG. 9: No effect on CEC of steroid tapering in the placebo group

[0019] CEC was measured by liquid scintillation counting in patients with moderate to severe SLE who received oral corticosteroids dosed at <10 mg/day (n = 12), no oral corticosteroid dosage tapering (n = 24), or oral corticosteroid dosage tapering (n = 8). **FIG. 9A** shows CEC on day 365 compared with day 1 for each patient with SLE. **FIG. 9B** shows CEC for patients with SLE who received oral corticosteroid dosed at <10 mg/day (n = 12), no oral corticosteroid dosage tapering (n = 24), or oral corticosteroid dosage tapering (n = 8), plotted with 95% confidence intervals. The dashed line represents no change in CEC. Abbreviations included: CEC, cholesterol efflux capacity; SLE, systemic lupus erythematosus.

FIG. 10: GlycA was elevated at baseline in patients with SLE and was reduced following type I IFN pathway inhibition

[0020] **FIG. 10A** shows the measurement of baseline GlycA by NMR spectroscopy in healthy donors (n = 10) or IFNGS test-high patients with SLE (n = 50), with AUC indicated. P-value was calculated using a Mann-Whitney U test. **FIG. 10B** shows the measurement of GlycA levels at day 1 and day 365 in IFNGS test-high GlycA-high patients (2SD above HD mean, 500 μ M) who received anifrolumab dosed at 300 mg (right, n = 10), or placebo (left, n = 11). P-values were calculated using a Wilcoxon signed-rank test. Box and whisker plots represent quartiles within each group. Abbreviations include: AUC, area under the curve; CEC, cholesterol efflux capacity; HD, healthy donor; IFN, interferon; IFNGS, IFN gene signature; NMR, nuclear magnetic resonance; n.s., not significant; SD, standard deviation; SLE, systemic lupus erythematosus.

FIG. 11: Type I IFN signalling, neutrophil NET formation, and atherosclerosis pathogenesis in SLE.

[0021] Autoantibody-containing immune complex exposure after type I IFN priming activates neutrophils and induces NET formation; consequently, increased NET formation has been observed in patients with SLE. LDGs, a subset of neutrophils with an enhanced capacity to form NETs, are also elevated in patients with SLE. pDCs and other immune cells are activated by NETs and immune complexes to synthesize increased levels of type I IFNs. The self-nucleic acids released in NET complexes promote loss of immune tolerance, autoantibody production, and immune complex formation in a complex regulatory loop. Components within NET complexes oxidize HDL and impair the process of reverse cholesterol transport. Impaired CEC, a cardiometabolic disease marker, leads to the accumulation of lipid-laden macrophages known as foam cells. Foam cells are hallmarks of early atherosclerotic lesions and secrete the pro-inflammatory cytokine, TNF- α , which is elevated in patients with SLE. Type I IFN also induces endothelial dysfunction to contribute to atherosclerosis. IL-10, which is elevated in a subset of patients with SLE, interferes with endothelial differentiation and enhances the effects of type I IFN on vascular repair in patients with SLE. GlycA, which is a marker of cardiometabolic disease and CVD risk, is elevated in patients with SLE. CVD due to premature atherosclerosis is one of the predominant causes of mortality in patients with SLE. Abbreviations include: CEC, cholesterol efflux capacity; CVD, cardiovascular disease; HDL, high-density lipoprotein; IFN, interferon; IL-10, interleukin 10; LDG, low-density granulocyte; NET, neutrophil extracellular trap; pDC, plasmacytoid dendritic cell; SLE, systemic lupus erythematosus; TNF, tumour necrosis factor.

FIG. 12: CEC, number of neutrophils, and TNF- α levels associated with SLE disease activity

[0022] Log2 fold changes are indicated for age, BMI, HDL-C, smoking, total cholesterol, CEC, IL-10 protein, neutrophil number per μ L whole blood, TNF- α protein, and circulating NET complexes (CitH3-DNA, MPO-DNA, and NE-DNA) compared with two measures of disease activity: SLEDAI and CLASI. Statistical significance was assessed using the Welch's t-test for group comparisons. Abbreviations included: BMI, body mass index; CEC, cholesterol efflux capacity; CitH3, citrullinated histone H3; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein count; IL, interleukin; MPO, myeloperoxidase; NE, neutrophil elastase; NET, neutrophil extracellular trap; n.s., not significant; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index; TNF, tumor necrosis factor.

FIG. 13: A density plot of interferon signature scores for SLE subjects

[0023] Two distributional modes are illustrated, indicating a clear partitioning between the IFN test high and low subpopulations.

FIG. 14: Baseline organ domain involvement assessed using BILAG-2004 and SLEDAI-2K

[0024] Baseline organ domain involvement assessed using BILAG-2004 (**FIG. 8A**) and SLEDAI-2K (**FIG. 8B**) was similar between treatment groups. BILAG-2004, British Isles Lupus Assessment Group-2004; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000. BILAG-2004 scores range from level A (severe/active disease) to E (no current or previous disease). BILAG-2004 organ domain involvement was defined as an A or B score. SLEDAI-2K organ domain involvement was defined as any SLEDAI-2K organ system score.

FIG. 15: BILAG-2004 organ domain responders over time

[0025] Improvements favouring anifrolumab for the mucocutaneous, musculoskeletal and cardiorespiratory BILAG-2004 domains were observed from Week 4, Week 32 and Week 28, respectively. BILAG-2004, British Isles Lupus Assessment Group-2004. BILAG-2004 organ domain responder is defined as a reduction in baseline A or B score at Week 52. Points are estimates. Estimates are calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors as listed in the Methods section. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (based on Cochran–Mantel–Haenszel approach for the comparison of anifrolumab vs placebo).

FIG. 16: SLEDAI-2K organ domain responders over time

[0026] SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score. SLEDAI-2K central nervous system domain is not plotted because there were too few patients in each treatment group. Points are estimates. Estimates are calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors as listed in the Methods section. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (based on Cochran–Mantel–Haenszel approach for the comparison of anifrolumab vs placebo).

FIG. 17. Delivery device

[0027] Anifrolumab is administered by an injection device [1] [9] such as a prefilled syringe (PFS) (FIG. 17A) or an autoinjector (AI) (FIG. 17B).

FIG. 18. Autoinjector

[0028] The autoinjector for administering anifrolumab of the functional variant thereof in exploded view (FIG. 18A), assembled (FIG. 18B) and filled with drug substance (FIG. 18C).

FIG. 19. Accessorized pre-filled syringe

[0029] The accessorized pre-filled syringe (APFS) for anifrolumab of the functional variant thereof. The primary tube is shown in assembled form (FIG. 19A) and in exploded view (FIG. 19B). The APFS with its additional components is shown in assembled form (FIG. 19C) and in exploded view FIG. 19D).

FIG. 20. Packaging for the delivery device

4 DETAILED DESCRIPTION

4.1 Treatment of cardiometabolic disease

[0030] The invention relates to a method of treating or reducing the risk for development of a cardiometabolic disease in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of type I IFN signalling, wherein the patient has a type I IFN mediated disease.

[0031] Pre-treatment with the inhibitor of type I IFN signalling, the patient may have high levels of expression of the one or more cardiometabolic disease markers compared to a healthy subject. Treatment may reduce expression of the one or more cardiometabolic disease markers in the patient from baseline.

[0032] The one or more cardiometabolic disease markers may comprise GlycA. The one or more cardiometabolic disease markers may comprise neutrophil extracellular trap (NET). The one or more cardiometabolic disease markers may comprise TNF- α . The one or more cardiometabolic disease markers may comprise IL-10. The one or more cardiometabolic disease markers may comprise GlycA and NET. The one or more cardiometabolic disease markers may comprise GlycA and TNF- α . The one or more cardiometabolic disease markers may comprise GlycA and IL-10. The one or more cardiometabolic disease markers may comprise GlycA, NET and IL-10. The one or more cardiometabolic disease markers may comprise GlycA, NET and TNF- α . The one or more cardiometabolic disease markers may comprise GlycA, NET, TNF- α and IL-10.

[0033] Pre-treatment with the inhibitor of type I IFN signalling, the patient may have low levels of expression of the one or more cardiometabolic disease markers compared to a healthy subject. Treatment may increase expression of the one or more cardiometabolic disease markers in the patient from baseline. The one or more cardiometabolic disease markers may comprise cholesterol efflux capacity (CEC).

[0034] Pre-treatment the patient may be identified as having a risk of development of a cardiometabolic disease. The method may comprise determining in a sample from the patient the amount of one or more markers; and identifying the patient as having a risk for development of a cardiometabolic disease when the amount of marker is elevated in the patient compared to the amount of the marker in a sample from a healthy subject, wherein the marker is selected from the group consisting of GlycA, TNF- α , IL-10 and combinations thereof. The sample from the patient may comprise blood, plasma, serum, or tissue. GlycA in the sample from the patient may be measured by nuclear magnetic resonance (NMR).

[0035] Pre-treatment with the inhibitor of type I IFN signalling the patient may have elevated serum protein levels of IFN- α compared to a healthy subject, wherein the inhibitor of type I IFN signalling decreases the serum protein levels of IFN- α in the patient from baseline.

[0036] The method of any preceding claim, wherein the cardiometabolic disease is a cardiovascular disease, optionally wherein the cardiovascular disease is myocarditis, arrhythmia, valvular dysfunction, vasculitis, aortitis, atherosclerosis and/or coronary vasculitis. The cardiometabolic disease may be premature atherosclerosis. the premature atherosclerosis may be sub-clinical. The type I IFN mediated disease may be systemic lupus erythematosus (SLE). The patient may have moderate to severe SLE.

[0037] The invention also relates to a pharmaceutical composition for use in any of the methods of the invention, wherein the pharmaceutical composition comprises the inhibitor of type I IFN signalling.

[0038] As utilized in accordance with the present disclosure, unless otherwise indicated, all technical and scientific terms shall be understood to have the same meaning as commonly understood by one of ordinary skill in the art. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0039] In some embodiments, the disclosure provides a method for reducing the risk for development of a cardiometabolic disease in a patient having a risk for development of a cardiometabolic disease, comprising administering a type I interferon receptor inhibitor to the patient, wherein the patient is identified as having a risk for development of a cardiometabolic disease by: determining in a sample from the patient the amount of a marker, wherein the marker is glycoprotein acetylation; and identifying the patient as having a risk for development of a cardiometabolic disease when the amount of glycoprotein acetylation is increased compared to the patient's baseline level.

[0040] In some embodiments, treatment administered to the patient results in a change in expression of a cardiometabolic disease marker from the patient's baseline level. In some embodiments, the treatment results in reduced expression of glycoprotein acetylation from the patient's baseline level.

[0041] In some embodiments, treatment administered to the patient results in a reduction in immune mediators of endothelial dysfunction from the patient's baseline level. In certain embodiments, the immune mediator is one or more of TNF- α and IL-10.

4.2 Inhibitor of type I IFN signalling

[0042] The inhibitor of type I IFN signalling may be a type I IFN receptor inhibitor (IFNAR1). An inhibitor of type I IFN signalling may reduce the IFN- α protein levels in the plasma of a patient having an elevated serum protein levels of IFN- α .

[0043] A “type I interferon receptor inhibitor” refers to a molecule that is antagonistic for the receptor of type I interferon ligands such as interferon- α and interferon- β . Such inhibitors, subsequent to administration to a patient, preferably provide a reduction in the expression of at least 1 (preferably at least 4) pharmacodynamic (PD) marker genes selected from the group consisting of IFI6, RSAD2, IFI44, IFI44L, IFI27, MX1, IFIT1, HERC5, ISG15, LAMP3, OAS3, OAS1, EPST1, IFIT3, LY6E, OAS2, PLSCR1, SIGLEC1, USP18, RTP4, and DNAPTP6. The at least 4 genes may suitably be IFI27, IFI44, IFI44L, and RSAD2. The “type I interferon receptor” is optionally interferon- α/β receptor (IFNAR).

[0044] In one embodiment, the type I interferon receptor inhibitor is a type I interferon receptor-blocking antibody. In one such embodiment, the type I interferon receptor-blocking antibody is anifrolumab. Anifrolumab is a monoclonal antibody that inhibits binding of type I IFN to IFNAR and inhibits the biologic activity of all type I IFNs. Disclosure related to anifrolumab can be found in U.S. Patent No. 7,662,381, which is incorporated herein by reference. The clone 11E2 referenced in U.S. Patent No. 7,662,381 is anifrolumab.

[0045] For example, the type I interferon receptor inhibitor may be an antibody or antigen-binding fragment thereof that inhibits type I IFN activity (by inhibiting the receptor). An example of a suitable antibody or antigen-binding fragment thereof (that inhibits type I IFN activity) is an interferon- α/β receptor (IFNAR) antagonist.

[0046] Additionally or alternatively, the type I interferon receptor inhibitor may be a small molecule inhibitor of a type I interferon receptor (e.g. for pharmacological inhibition of type I interferon receptor activity).

[0047] The type I interferon receptor inhibitor may be an antibody or antigen-binding fragment thereof that inhibits type I IFN activity. A particularly preferred type I interferon receptor inhibitor is the antibody anifrolumab or a functional variant thereof. Anifrolumab is a monoclonal antibody targeting IFNAR1 (the receptor for α , β , and ω interferons). Disclosure related to anifrolumab can be found in U.S. Patent No. 7,662,381 and U.S. Patent No. 9,988,459, which are incorporated herein by reference.

[0048] Thus, in one embodiment the type I interferon receptor inhibitor is anifrolumab or a functional variant thereof.

4.3 Delivery device

[0049] The type I IFN inhibitor may be administered subcutaneously using an accessorized pre-filled syringe (APFS), an autoinjector (AI), or a combination thereof. Such devices have been found to be well-tolerated and reliable for administering subcutaneous doses of an antibody and provide further options for optimizing patient care. Indeed, such devices may reduce the burden of frequent clinic visits for patients. An example of a suitable APFS device is described in Ferguson *et. al.*¹⁶, which is

incorporated herein by reference in its entirety. The delivery device may be single use, disposable system that is designed to enable manual, SC administration of the dose.

[0050] The invention also relates to an injection device comprising the pharmaceutical composition of the invention. The injection device may be a pre-filled syringe (PFS). The injection device may be an accessorized pre-filled syringe (AFPS). The injection device may be an auto-injector.

4.4 Kit

[0051] The invention also relates to a kit comprising the injection device of the invention and instructions for use. The instructions for use may specify that the injection device and/or pharmaceutical composition are for use in the treatment of SLE. The instructions for use may specify that the injection device and/or pharmaceutical composition are for treating a cardiometabolic disease in a patient. The instructions for use may specify any features of the method of the invention or the pharmaceutical composition of the invention. The kit may comprise packaging, wherein the packaging is adapted to hold the injection device and the instructions for use. The instructions for use may be attached to the injection device.

4.5 Type I IFN gene signature (IFNGS)

[0052] The patient may have high interferon gene signature expression compared to a healthy subject, or a subject that is not suffering from a type I IFN mediated disease. The type I interferon gene signature may comprise elevated expression of the genes Interferon Alpha Inducible Protein 27 (IFI27), Interferon Induced Protein 44 (IFI44) interferon induced protein 44 like (IFI44L), and Radical S-Adenosyl Methionine Domain Containing 2 (RSAD2), compared to expression levels in a healthy subject, or a subject that is not suffering from a type I IFN mediated disease. The high interferon gene signature expression may be determined by an increased expression of IFI27, IFI44, IFI44L, and RSAD2 relative to expression of one or more control genes.

[0053] In some embodiments, the disclosure provides a method of treating a cardiometabolic disease in a patient comprising administering to the patient a therapeutically effective amount of a type I interferon receptor inhibitor, wherein the patient has high interferon gene signature expression.

[0054] Direct measurement of type I interferon (IFN) remains a challenge. As such, an IFN gene signature (IFNGS) is used to identify patients with low or high levels of IFN inducible gene expression. In some embodiments, the IFNGS comprises Interferon Alpha Inducible Protein 27 (IFI27), Interferon Induced Protein 44 (IFI44) interferon induced protein 44 like (IFI44L), and Radical S-Adenosyl Methionine Domain Containing 2 (RSAD2). Up regulation or overexpression of the genes comprising the IFNGS can be calculated by well-known methods in the art. For example, the overexpression of the signature is calculated as the difference between the mean Ct (cycle threshold) for IFI27, IFI44, IFI44L, and RSAD2 and the mean Ct of three control genes; 18S, ACTB and GAPDH. The degree of increased expression of the IFNGS permits the identification of a fold change cutoff for identifying IFN-high and IFN-low patients. In one embodiment, the cutoff is at least about 2. In another embodiment, the cutoff is at least about 2.5. In another embodiment, the cutoff is at least about 3. In another

embodiment, the cutoff is at least about 3.5. In another embodiment, the cutoff is at least about 4. In another embodiment, the cutoff is at least about 4.5. In another embodiment, the cutoff is chosen from at least 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, and 4.5. In another embodiment the cutoff is between about 2 and about 8. The degree of increased expression of the IFNGS also permits the identification of a delta Ct cutoff for identifying IFN-high and IFN-low subpopulations.

[0055] Type I IFN is considered to play a central role SLE disease pathogenesis and inhibition of this pathway is targeted by anifrolumab. To understand the relationship between type I IFN expression and response to anti-IFN therapy, it is necessary to know if a subject's disease is driven by type I IFN activation. However, direct measurement of type I IFN remains a challenge. As such, a transcript-based marker was developed to evaluate the effect of over expression of the target protein on a specific set of mRNA markers. The expression of these markers is easily detected in whole blood and demonstrates a correlation with expression in diseased tissue such as skin in SLE. The bimodal distribution of the transcript scores for SLE subjects supports defining an IFN test high and low subpopulation (**FIG. 13**). The type I IFN test is described in WO2011028933 A1, which is incorporated herein by reference in its entirety. The type I IFN gene signature may be used to identify a subject has a type I IFN gene signature (IFNGS)-test high patient or an IFNGS-test low patient. The IFNGS test measures expression of the genes IFI27, IFI44, IFI44L, and RSAD2 compared with 3 reference genes; 18S, ACTB and GAPDH in the whole blood of the subject. The result of the test is a score that is compared with a pre-established cut-off that classifies patients into 2 groups with low or high levels of IFN inducible gene expression (**FIG. 13**).

[0056] The expression of the genes may be measured by RT-PCR. Suitable primers and probes for detection of the genes may be found in WO2011028933. A suitable kit for measuring gene expression for the IFNGS test is the QIAGEN *therascreen*® IFIGx RGQ RT-PCR kit (IFIGx kit), as described in Brohawn et al.¹⁷, which is incorporated herein by reference in its entirety.

4.6 The patient

[0057] The patient may be a human patient. The patient may be an adult. The patient may be a patient with an elevated type I IFN gene signature. The patient may be a type I interferon stimulated gene signature (IFNGS)-test high patient pre-administration with the dose or unit dose. The patient may have elevated of the genes IFI27, IFI44, IFI44L, and RSAD2 in the whole blood. The method may comprise identifying the patient as IFNGS-test high patient pre-treatment with the dose or unit dose. The method may comprise measuring the expression of the genes IFI27, IFI44, IFI44L, and RSAD2 in the whole blood of the patient. The method may comprise measuring the expression of the genes IFI27, IFI44, IFI44L, and RSAD2 in the whole blood of the subject by RT-PCR.

4.7 Formulations

[0058] When used for *in vivo* administration, the formulations of the disclosure should be sterile. The formulations of the disclosure may be sterilized by various sterilization methods, including, for example, sterile filtration or radiation. In one embodiment, the formulation is filter sterilized with a presterilized 0.22-micron filter. Sterile compositions for injection can be formulated according to conventional

pharmaceutical practice as described in "Remington: The Science & Practice of Pharmacy," 21st ed., Lippincott Williams & Wilkins (2005).

[0059] In some embodiments, antibodies can be formulated for particular routes of administration, such as oral, nasal, pulmonary, topical (including buccal and sublingual), rectal, vaginal, and/or parenteral administration. As used herein, the terms "parenteral administration" and "administered parenterally" refer to modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural, and intrasternal injection, and infusion. Formulations of the disclosure that are suitable for topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The antibodies and other actives may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required (see, e.g., U.S. Patent Nos. 7,378,110; 7,258,873; and 7,135,180; U.S. Patent Application Publication Nos. 2004/0042972 and 2004/0042971).

[0060] Stable formulations suitable for administration to subjects and comprising anifrolumab are described in detail in US Patent 10125195 B1, which is incorporated herein in its entirety.

[0061] The Examples that follow are illustrative of specific embodiments of the disclosure, and various uses thereof. They are set forth for explanatory purposes only and should not be construed as limiting the scope of the disclosure in any way.

4.8 Dosage regimes and administration methods

[0062] The method may comprise administering intravenously an intravenous dose of anifrolumab or the functional variant thereof to the subject. The intravenous dose may be ≥ 300 mg anifrolumab or the functional variant thereof. The intravenous dose may be ≤ 1000 mg. The intravenous dose may be about 300 mg or about 1000 mg. The intravenous dose may be 300 mg to 1000 mg. The intravenous dose may be administered every four weeks (Q4W).

[0063] The formulations can be presented in unit dosage form and can be prepared by any method known in the art of pharmacy. Actual dosage levels of the active ingredients in the formulation of the present disclosure may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient (e.g., "a therapeutically effective amount"). Dosages can also be administered via continuous infusion (such as through a pump). The administered dose may also depend on the route of administration. For example, subcutaneous administration may require a higher dosage than intravenous administration.

[0064] The dose of the anifrolumab to be administered to the patient will vary depending, in part, upon the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient.

[0065] In some embodiments, the patient is administered one or more fixed doses of anifrolumab, wherein the dose is 150 mg, 200 mg, 250 mg, 300 mg, or 350 mg. In some embodiments, the patient is administered one or more fixed doses of anifrolumab wherein the dose is 300 mg.

[0066] In some embodiments, anifrolumab is administered over a two-week treatment period, over a four-week treatment period, over a six-week treatment period, over an eight-week treatment period, over a twelve-week treatment period, over a twenty-four-week treatment period, or over a one-year or more treatment period. In some embodiments, anifrolumab is administered over a three-week treatment period, over a six-week treatment period, over a nine-week treatment period, over a twelve-week treatment period, over a twenty-four-week treatment period, or over a one-year or more treatment period. In certain embodiments, anifrolumab is administered for at least 52 weeks.

[0067] In some embodiments, anifrolumab is administered every week, every two weeks, every four weeks, every six weeks, every eight weeks, every ten weeks, or every twelve weeks.

5 Definitions

5.1 Anifrolumab

[0068] Anifrolumab is a monoclonal antibody which binds to IFNAR with high affinity and specificity. The antibody is an IFNAR-blocking (antagonistic) antibody, and blocks the activity of the receptor's ligands, namely type I interferons such as interferon- α and interferon- β . Anifrolumab thus provides for downregulation of IFNAR signalling, and thus suppression of IFN-inducible genes.

Table 5-1: Anifrolumab sequences

Anifrolumab VH (SEQ ID NO: 1)	EVQLVQSGAEVKKPGESLKISCKGSGYIFTNYWIAWVRQMPGKGLKESMGIIYPGDSDI RYSPSFQGGQVTISADKSITAYLQWSSLKASDTAMYYCARHDIEGFDYWGRGTLTV SS
Anifrolumab VL (SEQ ID NO: 2)	EIVLTQSPGTLSLPGERATLSCRASQSVSSSFFAWYQQKPGQAPRLIIYGASSRAT GIPDRLSGSGSGTDFTLTITRLEPEDFAVYYCQQYDSSAITFGQGTRLEIK
HCDR1 (SEQ ID NO: 3)	NYWIA
HCDR2 (SEQ ID NO: 4)	IYPGDSDIRYSPSFQG
HCDR3 (SEQ ID NO: 5)	HDIEGFDY
LCDR1 (SEQ ID NO: 6)	RASQSVSSSFFA
LCDR2 (SEQ ID NO: 7)	GASSRAT
LCDR3 (SEQ ID NO: 8)	QQYDSSAIT
Light chain constant region (SEQ ID NO: 9)	RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYFPREAKVQWKVDNALQSGNSQESV TEQDSKDSITYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
Heavy chain constant region (SEQ ID NO: 10)	ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHFFP AVLQSSGLYSLSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPA PEFEGGSPVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAK TKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPASEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGS FFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
Heavy chain (SEQ ID NO: 11)	EVQLVQSGAEVKKPGESLKISCKGSGYIFTNYWIAWVRQMPGKGLKESMGIIYPGDSDI RYSPSFQGGQVTISADKSITAYLQWSSLKASDTAMYYCARHDIEGFDYWGRGTLTV SSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTWNSGALTSKVHFFP AVLQSSGLYSLSVTVPSSSLGTQTYICNVNHKPSNTKVDKRVPEPKSCDKTHTCPPCPA PEFEGGSPVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP

	SIEKTISKAK GQPPEPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN NYKTTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYT QKS LSLSPGK
Light chain (SEQ ID NO: 12)	EIVLTQSPGTLSPGERATLSCRASQSVS SSFFAWYQQK PGQAPRLLIY GASSRATGIPDRLSGSGSGT DFTLTITRLE PEDFAVYYCQ QYDSSAITFG QGTRLEIKRTVAAPSVFIFPPSDEQLKSGT ASVVCLLNNF YPREAKVQWK VDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTH QGLSSPVTKSFNRGEC

[0069] Thus, “anifrolumab” is an antibody comprising an HCDR1, HCDR2 and HCDR3 of SEQ ID NO: 3, SEQ ID NO: 4, and SEQ ID NO: 5, respectively (or functional variant thereof); and an LCDR1, LCDR2 and LCDR3 of SEQ ID NO: 6, SEQ ID NO: 7, and SEQ ID NO: 8, respectively (or functional variant thereof). In more detail, anifrolumab as referred to herein is an antibody comprising a VH of SEQ ID NO: 1 and a VL of SEQ ID NO: 2 (or functional variant thereof).

[0070] The constant region of anifrolumab has been modified such that anifrolumab exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody. Anifrolumab is a modified IgG class monoclonal antibody specific for IFNAR1 comprising in the Fc region an amino acid substitution of L234F, as numbered by the EU index as set forth in Kabat (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). Anifrolumab is a modified IgG class monoclonal antibody specific for IFNAR1 comprising in the Fc region an amino acid substitution of L234F, L235E and/or P331S, as numbered by the EU index as set forth in Kabat (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). Anifrolumab is an antibody comprising a light chain constant region of SEQ ID NO: 9. Anifrolumab is an antibody comprising a heavy chain constant region of SEQ ID NO: 10. Anifrolumab is an antibody comprising a light chain constant region of SEQ ID NO: 9 and a heavy chain constant region of SEQ ID NO: 10. Anifrolumab is an antibody comprising a heavy chain of SEQ ID NO: 11. Anifrolumab is an antibody comprising a light chain of SEQ ID NO: 12. Anifrolumab is an antibody comprising a heavy chain of SEQ ID NO: 11 and a light chain of SEQ ID NO: 12.

[0071] The present invention encompasses the antibodies defined herein having the recited CDR sequences or variable heavy and variable light chain sequences (reference (anifrolumab) antibodies), as well as functional variants thereof. A “functional variant” binds to the same target antigen as the reference (anifrolumab) antibody. The functional variants may have a different affinity for the target antigen when compared to the reference antibody, but substantially the same affinity is preferred. Functional variants of anifrolumab are sequence variants that perform the same function as anifrolumab. Functional variants of anifrolumab are variants that bind the same target as anifrolumab and have the same effector function as anifrolumab. Functional anifrolumab variants include antigen-binding fragments of anifrolumab and antibody and immunoglobulin derivatives of anifrolumab. Functional variants include biosimilars and interchangeable products. The terms biosimilar and interchangeable product are defined by the FDA and EMA. The term biosimilar refers to a biological product that is highly similar to an approved (e.g. FDA approved) biological product (reference product, e.g. anifrolumab) in terms of structure and has no clinically meaningful differences in terms of

pharmacokinetics, safety and efficacy from the reference product. The presence of clinically meaningful differences of a biosimilar may be assessed in human pharmacokinetic (exposure) and pharmacodynamic (response) studies and an assessment of clinical immunogenicity. An interchangeable product is a biosimilar that is expected to produce the same clinical result as the reference product in any given patient.

[0072] Functional variants of a reference (anifrolumab) antibody may show sequence variation at one or more CDRs when compared to corresponding reference CDR sequences. Thus, a functional antibody variant may comprise a functional variant of a CDR. Where the term “functional variant” is used in the context of a CDR sequence, this means that the CDR has at most 2, preferably at most 1 amino acid differences when compared to a corresponding reference CDR sequence, and when combined with the remaining 5 CDRs (or variants thereof) enables the variant antibody to bind to the same target antigen as the reference (anifrolumab) antibody, and preferably to exhibit the same affinity for the target antigen as the reference (anifrolumab) antibody.

[0073] Without wishing to be bound by theory, since anifrolumab targets (e.g. blocks or antagonizes) IFNAR, it is believed that anifrolumab treats a disease (such as lupus nephritis) by blocking signalling initiated by type I interferons (IFNs). Type I IFNs are known to be important drivers of inflammation (e.g. by coordinating the type I interferon response), and thus play a pivotal role in the immune system. However, dysregulation of type I IFN-signalling can lead to aberrant (e.g. aberrantly high) levels of inflammation, and autoimmunity. Such dysregulation of type I IFN interferons has been reported in numerous autoimmune diseases.

[0074] A variant of the reference (anifrolumab) antibody may comprise: a heavy chain CDR1 having at most 2 amino acid differences when compared to SEQ ID NO: 3; a heavy chain CDR2 having at most 2 amino acid differences when compared to SEQ ID NO: 4; a heavy chain CDR3 having at most 2 amino acid differences when compared to SEQ ID NO: 5; a light chain CDR1 having at most 2 amino acid differences when compared to SEQ ID NO: 6; a light chain CDR2 having at most 2 amino acid differences when compared to SEQ ID NO: 7; and a light chain CDR3 having at most 2 amino acid differences when compared to SEQ ID NO: 8; wherein the variant antibody binds to the target of anifrolumab (e.g. IFNAR) and preferably with the same affinity.

[0075] A variant of the reference (anifrolumab) antibody may comprise: a heavy chain CDR1 having at most 1 amino acid difference when compared to SEQ ID NO: 3; a heavy chain CDR2 having at most 1 amino acid difference when compared to SEQ ID NO: 4; a heavy chain CDR3 having at most 1 amino acid difference when compared to SEQ ID NO: 5; a light chain CDR1 having at most 1 amino acid differences when compared to SEQ ID NO: 6; a light chain CDR2 having at most 1 amino acid difference when compared to SEQ ID NO: 7; and a light chain CDR3 having at most 1 amino acid difference when compared to SEQ ID NO: 8; wherein the variant antibody binds to the target of anifrolumab (e.g. IFNAR) optionally with the same affinity.

[0076] A variant antibody may have at most 5, 4 or 3 amino acid differences total in the CDRs thereof when compared to a corresponding reference (anifrolumab) antibody, with the proviso that there is at

most 2 (optionally at most 1) amino acid differences per CDR. A variant antibody may have at most 2 (optionally at most 1) amino acid differences total in the CDRs thereof when compared to a corresponding reference (anifrolumab) antibody, with the proviso that there is at most 2 amino acid differences per CDR. A variant antibody may have at most 2 (optionally at most 1) amino acid differences total in the CDRs thereof when compared to a corresponding reference (anifrolumab) antibody, with the proviso that there is at most 1 amino acid difference per CDR.

[0077] The amino acid difference may be an amino acid substitution, insertion or deletion. The amino acid difference may be a conservative amino acid substitution as described herein.

[0078] A variant antibody may have at most 5, 4 or 3 amino acid differences total in the framework regions thereof when compared to a corresponding reference (anifrolumab) antibody, with the proviso that there is at most 2 (optionally at most 1) amino acid differences per framework region. Optionally a variant antibody has at most 2 (optionally at most 1) amino acid differences total in the framework regions thereof when compared to a corresponding reference (anifrolumab) antibody, with the proviso that there is at most 2 amino acid differences per framework region. Optionally a variant antibody has at most 2 (optionally at most 1) amino acid differences total in the framework regions thereof when compared to a corresponding reference (anifrolumab) antibody, with the proviso that there is at most 1 amino acid difference per framework region.

[0079] Thus, a variant antibody may comprise a variable heavy chain and a variable light chain as described herein, wherein: the heavy chain has at most 14 amino acid differences (at most 2 amino acid differences in each CDR and at most 2 amino acid differences in each framework region) when compared to a heavy chain sequence herein; and the light chain has at most 14 amino acid differences (at most 2 amino acid differences in each CDR and at most 2 amino acid differences in each framework region) when compared to a light chain sequence herein; wherein the variant antibody binds to the same target antigen as the reference (anifrolumab) antibody (e.g. IFNAR) and preferably with the same affinity.

[0080] The variant heavy or light chains may be referred to as “functional equivalents” of the reference heavy or light chains. A variant antibody may comprise a variable heavy chain and a variable light chain as described herein, wherein: the heavy chain has at most 7 amino acid differences (at most 1 amino acid difference in each CDR and at most 1 amino acid difference in each framework region) when compared to a heavy chain sequence herein; and the light chain has at most 7 amino acid differences (at most 1 amino acid difference in each CDR and at most 1 amino acid difference in each framework region) when compared to a light chain sequence herein; wherein the variant antibody binds to the same target antigen as the reference (anifrolumab) antibody (e.g. IFNAR) and preferably with the same affinity.

[0081] The term “anifrolumab” preferably encompasses an antigen binding fragment thereof. The term “antigen-binding fragment”, refers to one or more fragments of anifrolumab that retain(s) the ability to specifically bind to the antigen for anifrolumab (IFNAR). Examples of antigen-binding fragments include

the following: Fab fragment, F(ab')₂ fragment, Fd fragment, Fv fragment, dAb fragment, as well as a scFv.

5.2 Cardiometabolic disease

[0082] As used herein, a "cardiometabolic disease" refers to a disease of the cardiac and/or metabolic systems. In some embodiments, the cardiometabolic disease is cardiovascular disease, atherosclerosis, vasculopathy, insulin resistance, impaired glucose tolerance, dyslipidemia, hypertension, or central adiposity.

[0083] As used herein, "baseline level" refers to the level in the patient pre-treatment or before treatment.

5.3 Clinical trials

5.3.1 Phase 2/Phase II/pivotal studies

[0084] Phase II studies gather preliminary data on effectiveness. In Phase 2 studies, researchers administer the drug to a group of patients with the disease or condition for which the drug is being developed. Typically involving a few hundred patients, these studies aren't large enough to show whether the drug will be beneficial. Instead, Phase 2 studies provide researchers with additional safety data. Researchers use these data to refine research questions, develop research methods, and design new Phase 3 research protocols.

5.3.2 Phase 3/Phase III/pivotal studies or trials

[0085] Researchers design Phase 3 studies to demonstrate whether or not a product offers a treatment benefit to a specific population. Sometimes known as pivotal studies, these studies involve 300 to 3,000 participants. Phase 3 studies provide most of the safety data. In previous studies, it is possible that less common side effects might have gone undetected. Because these studies are larger and longer in duration, the results are more likely to show long-term or rare side effects. Regulatory bodies such as the EMA and FDA usually require a phase III clinical trial demonstrating that the product is safe and at least as effective (if not better) than available medications, before approving a new medication. Phase III clinical trials usually fail, even if they follow a successful a phase II clinical trial.

5.4 End points

5.4.1 BILAG-2004 (British Isles Lupus Assessment Group-2004)

[0086] The BILAG-2004 is a translational index with 9 organ systems (General, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic, Renal and Haematology) that is able to capture changing severity of clinical manifestations (**FIG. 1**). It has ordinal scales by design and does not have a global score; rather it records disease activity across the different organ systems at a glance by comparing the immediate past 4 weeks to the 4 weeks preceding them. It is based on the principle of physicians' intention to treat and categorises disease activity into 5 different levels from A to E:

- Grade A represents very active disease requiring immunosuppressive drugs and/or a prednisone dose of >20 mg/day or equivalent
- Grade B represents moderate disease activity requiring a lower dose of corticosteroids, topical steroids, topical immunosuppressives, antimalarials, or NSAIDs
- Grade C indicates mild stable disease
- Grade D implies no disease activity but the system has previously been affected
- Grade E indicates no current or previous disease activity

[0087] Although the BILAG-2004 was developed based on the principle of intention to treat, the treatment has no bearing on the scoring index. Only the presence of active manifestations influences the scoring.

[0088] In the Cardio-respiratory domain score, the BILAG-2004 Index records myocarditis – mild; myocarditis/endocarditis + cardiac failure; arrhythmia; new valvular dysfunction, pleurisy/pericarditis, cardiac tamponade, pleural effusion with dyspnoea, pulmonary haemorrhage/vasculitis, interstitial alveolitis/pneumonitis, shrinking lung syndrome, aortitis and coronary vasculitis (**FIG. 1**), as defined in **Table 5-2**.

Table 5-2 – BILAG-2004 Cardiorespiratory organ domain

Mild myocarditis	inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction
Cardiac failure	cardiac failure due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)
	cardiac failure due to myocarditis is defined by left ventricular ejection fraction $\leq 40\%$ & pulmonary oedema or peripheral oedema
	cardiac failure due to acute valvular regurgitation (from endocarditis) can be associated with normal left ventricular ejection fraction
	diastolic heart failure is not included
Arrhythmia	arrhythmia (except sinus tachycardia) due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)
	confirmation by electrocardiogram required (history of palpitations alone inadequate)
New valvular dysfunction	new cardiac valvular dysfunction due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis)
	supportive imaging required
Pleurisy/Pericarditis	convincing history &/or physical findings that you would consider treating in absence of cardiac tamponade or pleural effusion with dyspnoea
	do not score if you are unsure whether or not it is pleurisy/pericarditis
Cardiac tamponade	supportive imaging required
Pleural effusion with dyspnoea	supportive imaging required
Pulmonary haemorrhage/vasculitis	inflammation of pulmonary vasculature with haemoptysis &/or dyspnoea &/or pulmonary hypertension
Interstitial alveolitis/pneumonitis	radiological features of alveolar infiltration not due to infection or haemorrhage required for diagnosis
	corrected gas transfer Kco reduced to < 70% normal or fall of > 20% if previously abnormal
	on-going activity would be determined by clinical findings and lung function tests, and repeated imaging may be required in those with deterioration (clinically or lung function tests) or failure to respond to therapy
Shrinking lung syndrome	acute reduction (> 20% if previous measurement available) in lung volumes (to < 70% predicted)

	in the presence of normal corrected gas transfer (Kco) & dysfunctional diaphragmatic movements
Aortitis	inflammation of aorta (with or without dissection) with supportive imaging abnormalities
	accompanied by > 10 mm Hg difference in BP between arms &/or claudication of extremities &/or vascular bruits
	repeated imaging would be required to determine on-going activity in those with clinical deterioration or failure to respond to therapy
Coronary vasculitis	inflammation of coronary vessels with radiographic evidence of non-atheromatous narrowing, obstruction or aneurysmal changes

5.4.2 BICLA (BILAG-Based Composite Lupus Assessment)

[0089] BICLA is a composite index that was originally derived by expert consensus of disease activity indices. BICLA response is defined as (1) at least one gradation of improvement in baseline BILAG scores in all body systems with moderate or severe disease activity at entry (e.g., all A (severe disease) scores falling to B (moderate), C (mild), or D (no activity) and all B scores falling to C or D); (2) no new BILAG A or more than one new BILAG B scores; (3) no worsening of total SLEDAI score from baseline; (4) no significant deterioration ($\leq 10\%$) in physicians global assessment; and (5) no treatment failure (initiation of non-protocol treatment).

[0090] Particularly, a subject is a BICLA responder if the following criteria are met:

- Reduction of all baseline BILAG-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by 1 new BILAG-2004 A or more than 1 new BILAG-2004 B item;
- No worsening from baseline in SLEDAI-2K as defined as an increase from baseline of >0 points in SLEDAI-2K;
- No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA VAS;
- No discontinuation of investigational product or use of restricted medications beyond the protocol-allowed threshold before assessment

5.4.3 CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index)

[0091] The CLASI is a validated index used for assessing the cutaneous lesions of SLE and consists of 2 separate scores: the first summarizes the inflammatory activity of the disease; the second is a measure of the damage done by the disease. The activity score takes into account erythema, scale/hypertrophy, mucous membrane lesions, recent hair loss, and nonscarring alopecia. The damage score represents dyspigmentation, scarring/atrophy/panniculitis, and scarring of the scalp. Subjects are asked if their dyspigmentation lasted 12 months or longer, in which case the dyspigmentation score is doubled. Each of the above parameters is measured in 13 different anatomical locations, included specifically because they are most often involved in cutaneous lupus erythematosus (CLE). The most severe lesion in each area is measured.

5.4.4 SRI (Systemic Lupus Erythematosus Responder Index of ≥ 4)

[0092] A subject achieves SRI(4) if all of the following criteria are met:

- Reduction from baseline of ≥ 4 points in the SLEDAI-2K;
- No new organ system affected as defined by 1 or more BILAG-2004 A or 2 or more
- BILAG-2004 B items compared to baseline using BILAG-2004;
- No worsening from baseline in the subjects' lupus disease activity defined by an increase ≥ 0.30 points on a 3-point PGA VAS.

[0093] SRI(X) (X=5, 6, 7, or 8) is defined by the proportion of subjects who meet the following criteria:

- Reduction from baseline of $\geq X$ points in the SLEDAI-2K;
- No new organ systems affected as defined by 1 or more BILAG-2004 A or 2 or
- more BILAG-2004 B items compared to baseline using BILAG-2004;
- No worsening from baseline in the subjects' lupus disease activity defined by an
- increase ≥ 0.30 points on a 3-point PGA VAS

5.4.5 SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index 2000)

[0094] The SLEDAI-2K disease activity index consists of a list of organ manifestations, each with a definition. A certified Investigator or designated physician will complete the SLEDAI-2K assessment and decide whether each manifestation is "present" or "absent" in the last 4 weeks. The assessment also includes the collection of blood and urine for assessment of the laboratory categories of the SLEDAI-2K.

[0095] The SLEDAI-2K assessment consists of 24 lupus-related items. It is a weighted instrument, in which descriptors are multiplied by a particular organ's "weight". For example, renal descriptors are multiplied by 4 and central nervous descriptors by 8 and these weighted organ manifestations are totaled into the final score. The SLEDAI-2K score range is 0 to 105 points with 0 indicating inactive disease. The SLEDAI-2K scores are valid, reliable, and sensitive clinical assessments of lupus disease activity. The SLEDAI-2K calculated using a timeframe of 30 days prior to a visit for clinical and laboratory values has been shown to be similar to the SLEDAI-2K with a 10-day window¹⁸.

5.5 Treatment

[0096] As used herein, the terms "treatment" or "treat" refer to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include patients having a cardiometabolic disease as well as those prone to having cardiometabolic disease or those in which cardiometabolic disease is to be prevented. In some embodiments, the methods disclosed herein can be used to treat cardiometabolic disease. The present disclosure may be applied to other diseases in addition to cardiometabolic diseases such as diseases affiliated with cardiometabolic diseases.

5.6 Administration

[0097] As used herein, the terms "administration" or "administering" refer to providing, contacting, and/or delivering a compound or compounds by any appropriate route to achieve the desired effect.

Administration may include, but is not limited to, oral, sublingual, parenteral (e.g., intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection), transdermal, topical, buccal, rectal, vaginal, nasal, ophthalmic, via inhalation, and implants.

5.7 Biomarkers

5.7.1 Cholesterol efflux capacity (CEC)

[0098] Cholesterol efflux capacity (CEC) measures the ability of an individual's HDL to promote cholesterol efflux from cholesterol donor cells such as macrophages. Impaired CEC promotes accumulation of lipid-laden macrophages in atherosclerotic lesions, which secrete pro-inflammatory cytokines and are a hallmark of atherosclerosis. In some embodiments, treatment administered to the patient results in an increase in cholesterol efflux capacity from the patient's baseline level.

5.7.2 Neutrophils release neutrophil extracellular traps (NETs)

[0099] Neutrophils release neutrophil extracellular traps (NETs) in a cell death-associated process, and this phenomenon has proatherogenic effects. Immune complexes containing NET autoantigens induce plasmacytoid dendritic cells and other innate immune cells to aberrantly enhance type I IFN synthesis. In some embodiments, treatment administered to the patient results in a reduction in neutrophil extracellular trap formation from the patient's baseline level.

5.7.3 Glycoprotein Acetylation (GlycA)

[0100] Glycoprotein Acetylation (GlycA) is a biomarker of systemic inflammation. GlycA is associated with incident cardiovascular disease (CVD)^{19,20}, particularly atherosclerosis^{21,22}, and cardiometabolic (CM) disease²³. GlycA is a nuclear magnetic resonance (NMR) signal, measured in the blood serum or plasma, and reflects mainly the glycosylation of acute-phase proteins α 1-acid glycoprotein, haptoglobin, α 1antitrypsin, α 1antichymotrypsin and transferrin²².

5.8 Steroids

[0101] Steroids, particularly oral corticosteroids (OCS, glucocorticoids) include prednisone, cortisone, hydrocortisone, methylprednisolone, prednisolone and triamcinolone. Examples of equivalent doses of oral prednisone are shown in **Table 5-3**.

Table 5-3: Examples of equivalent doses of oral prednisone

Oral Prednisone and Equivalents	Equivalent Dose				
Oral Prednisone	7.5 mg	10 mg	20 mg	30 mg	40 mg
Cortisone	37.5 mg	50 mg	100 mg	150 mg	200 mg
Hydrocortisone	30 mg	40 mg	80 mg	120 mg	160 mg
Methylprednisolone	6 mg	8 mg	16 mg	24 mg	32 mg
Prednisolone	7.5 mg	10 mg	20 mg	30 mg	40 mg
Triamcinolone	6 mg	8 mg	16 mg	24 mg	32 mg

[0102] The Examples that follow are illustrative of specific embodiments of the disclosure, and various uses thereof. They are set forth for explanatory purposes only and should not be construed as limiting the scope of the disclosure in any way.

6 EXAMPLE 1: Anifrolumab in the clinic

[0103] Anifrolumab safety has been evaluated in 8 blinded or open-label intravenous (IV) and subcutaneous (SC) studies: 6 studies in patients with SLE (Study 05, Study 04, Study 1013, Study 1145, and Study 08), 1 study in patients with systemic sclerosis (SSc) (Study MI-CP180), and 1 study in healthy volunteers (Study 06) (**Table 6-1**). Of these studies, two (Studies 08 and 06) employed SC anifrolumab administration. Two studies are ongoing: 1 study in patients with SLE (Study 09) and 1 study in patients with lupus nephritis (LN) (Study 07).

Table 6-1: Anifrolumab clinical studies

Phase III studies		Subjects	Admin.	Anifro Dose	CT.gov
Study 05	TULIP II	SLE patients	IV	300 mg Q4W	NCT02446899
Study 04	TULIP I	SLE patients	IV	300 mg Q4W	NCT02962960
Study 09	Long-term extension	SLE patients	IV	300 mg	
Phase II studies					
Study 1013	MUSE	SLE patients	IV	300mg or 1000 mg Q4W	NCT01438489
Study 1145	MUSE OLE		IV	300 mg	NCT01753193
Study 08		SLE patients	SC		NCT02962960
Study 07		LN patients			NCT02547922
Phase I					
Study MI-CP180		Scleroderma patients	IV		
Study 06 ²⁴		Healthy volunteers	IV and SC	300mg, SC, 300 mg IV or 600 mg SC	NCT02601625

[0104] Study 1013 is described in further detail in Furie et al. 2017²⁵, which is incorporated herein by reference in its entirety. Study 04 is described in further detail in Furie et al. 2019²⁶, which is incorporated herein by reference in its entirety. The results of Study 05 are presented in Morand et al. 2020²⁷, herein incorporated by reference in its entirety. A full summary of the evidence for intravenous anifrolumab

clinical efficacy in SLE is provided in Tanaka et al., 2020²⁸, which is incorporated herein by reference in its entirety.

7 EXAMPLE 2: Modulation of cardiometabolic disease markers by inhibition of type I IFN signalling in SLE

7.1 Introduction

[0105] The inventors evaluated the ability of anifrolumab, a type I IFN receptor-blocking antibody, to reduce neutrophil extracellular trap (NET) formation and modulate cardiometabolic disease markers in comparison to placebo.

7.2 Materials and Methods

7.2.1 Patients and sample collection

[0106] Blood samples were obtained from adults aged 18–65 years with moderate to severe systemic lupus erythematosus (SLE) as assessed by SLE Disease Activity Index 2000 (SLEDAI-2K), enrolled in the phase 2b MUSE randomized, double-blind study (NCT01438489)²⁹. Patients were randomized 1:1:1 to receive intravenous infusions of anifrolumab 300 mg (n = 99), anifrolumab 1,000 mg (n = 104), or placebo (n = 102) every 4 weeks alongside standard therapy, with the final dose administered at 48 weeks. Plasma/sera from fasting patients were collected at days 0, 169, and 365 of the MUSE study. Interferon gene signature (IFNGS) test status was measured prior to randomization, and oral corticosteroid tapering was allowed after randomization (Furie et al., 2017). Details on the inclusion and exclusion criteria and patient demographics for the MUSE trial have been published (Furie et al., 2017).

7.2.2 Measurement of neutrophil number

[0107] Blood samples from patients were collected pre-dose on day 1, and neutrophil number was derived from complete blood count with differential, performed using validated methods (Casey *et al.*, *Lupus Sci. Med.* 5(1): e000286 (2018)).

7.2.3 IFN target gene expression

[0108] For the IFNGS test an analytically validated four-gene (*IFI27*, *IFI44*, *IFI44L*, and *RSAD2*) IFNGS test was conducted in whole blood by quantitative polymerase chain reaction (qPCR) as previously published (Furie *et al.*, 2017) to determine IFNGS test status. Patients were segregated into IFNGS test-high and IFNGS test-low categories at baseline using a predetermined ΔCt -based cutoff point in the trough of the bimodal distribution (**FIG. 13**).

[0109] The 21-IFNGS was generated using a 21-gene qPCR assay to measure the extent of type I interferon (IFN) signaling dysregulation in patients with SLE as previously described (Yao *et al.*, *Hum. Genomics Proteomics* pii: 374312 (2009)).

7.2.4 Measurement of neutrophil extracellular trap (NET) complexes

[0110] NET remnants in patient sera were quantified using capture enzyme-linked immunosorbent assays (ELISAs) that detect complexes of myeloperoxidase (MPO)-DNA, neutrophil elastase (NE)-

DNA, or citrullinated histone H3(CitH3)-DNA, as published previously (Lood *et al.*, *Nat. Med.* 22(2): 146–53 (2016)). For detection of MPO-DNA, high-binding, 96-well ELISA plates were incubated overnight with a mouse anti-human MPO antibody (clone 4A4; AbD Serotec) at 4°C in Cell Death Detection kit (Roche) coating buffer. Nonspecific binding sites were blocked in 1% bovine serum albumin, and plasma samples diluted in blocking buffer were incubated overnight at 4°C. After washing, anti-DNA-peroxidase (Roche) detection antibody was incubated for 1.5 hours at room temperature. 3,3',5,5'-Tetramethylbenzidine substrate (Sigma) was added, before stopping reagent (Sigma), and absorbance was measured at 450 nm. Similarly, NE-DNA and CitH3-DNA were detected using rabbit anti-human NE (Calbiochem) or rabbit anti-human CitH3 (Abcam ab5103) capture antibodies, respectively, followed by 1 hour incubations with the monoclonal mouse anti-double-stranded DNA primary antibody (Millipore) and anti-mouse immunoglobulin G horseradish peroxidase (Bio-Rad) secondary antibody.

7.2.5 LDG gene signature analysis

[0111] PAXgene whole-blood RNA tubes were stored at –80°C prior to shipment for RNA sequencing (Covance Genomics Laboratory). After RNA extraction using standard RNA preparation procedures, samples with an RNA integrity number score >5.0, as measured using an Agilent Bioanalyzer, were selected for downstream application. Globin messenger RNA (mRNA) was depleted using a GLOBINclear™ kit (Ambion) prior to mRNA selection and library preparation using the Illumina TruSeq Stranded mRNA kit. High-throughput sequencing was performed using an Illumina HiSeq 4000. Sequence-read qualities were assessed by FastQC and adapter primers were trimmed with Trimmomatic v0.32 (Bolger *et al.*, *Bioinformatics* 30(15): 2114–20 (2014)). Paired-end reads were mapped to human genome GRCh38 using STAR 2.5 (Dobin *et al.*, *Bioinformatics* 29(1): 15–21 (2013)) and read numbers were counted using HTSeq-count-0.6.1 (Anders *et al.*, *Bioinformatics* 31(2): 166–69 (2015)). Genes were included for assessment if they had >50 mapped reads across all included samples. Differentially expressed genes were selected by DESeq2 (Love *et al.*, *Genome Biol.* 15: 550 (2014)), which was also used alongside custom scripts to calculate fragments per kilobase exon per million fragments mapped. A composite LDG gene signature was calculated as a Z-score from the reads per kilobase million values of AZU1, MPO, CTSG, PRTN3, ELANE, and DEFA3 as previously described¹⁵. LDG gene signature³⁰ changes were obtained by comparing matched Z-scores at day 365 with day 1 in patients with Z-score > median Z-score at baseline.

7.2.6 Serum protein measurements

[0112] Serum samples were stored at –80°C before shipment to Myriad RBM (Austin, TX, USA). Serum IFN-α, IFN-β, IFN-γ, IL-10, and tumour necrosis factor alpha (TNF-α) were quantified using a Simoa™ immunoassay (Myriad RBM, Ultrasensitive Immunoassays developed by Myriad RBM based on the Simoa™ technology, 2018 (available from myriadrbm.com/products-services/ultrasensitive-immunoassays)). All other serum proteins were measured using Luminex quantitative immunoassay according to standard procedures.

7.2.7 Measurement of cholesterol efflux capacity (CEC)

[0113] High-density lipoprotein (HDL) CEC assays were performed based on published methods using J774 cells derived from a murine macrophage cell line (Mehta *et al.*, *Atherosclerosis* 224(1): 218–21 (2012)). Briefly, 3×10^5 J774 cells/well were plated and radiolabeled with 2 μ Ci of 3H-cholesterol/mL. ATP-binding cassette transporter A1 was upregulated by means of a 16-hour incubation with 0.3 mM of 8-(4-chlorophenylthio)-cAMP. Apolipoprotein B (ApoB)-depleted plasma (2.8%) was added to the efflux medium for 4 hours. Liquid scintillation counting was used to quantify the efflux of radioactive cholesterol from the cells. Efflux was calculated using the following formula: (μ Ci of 3H-cholesterol in media containing 2.8% apoB-depleted subject plasma – μ Ci of 3H-cholesterol in plasma-free media / μ Ci of 3H-cholesterol in media containing 2.8% apoB-depleted pooled control plasma – μ Ci of 3H-cholesterol in pooled control plasma-free media). A CEC defect was identified based on values that were two standard deviations below the mean CEC in plasma obtained from five healthy adult volunteers (FIG. 7). All assays were performed in duplicate.

7.2.8 GlycA and LipoProfile® nuclear magnetic resonance (NMR) spectroscopy

[0114] As per Otvos *et al.*, *Clin. Chem.* 61(5): 714–23 (2015), plasma was adjusted to a density of 1.22 g/mL in sodium bromide and centrifuged to separate the lipoprotein and protein fractions (84,000 g, 48 hours at 4°C). The two fractions were dialyzed against NMR diluent (50 mM sodium phosphate, 120 mM KCl, 5 mM Na₂EDTA, 1 mM CaCl₂, pH 7.4) and concentration-adjusted before centrifugal passage through a 10-kDa Centricon ultrafilter (Merck Millipore) to yield the desired molecular weight fraction. A standard 0.01-M *N*-acetylglucosamine sample was prepared in NMR diluent. GlycA and other lipid parameters were measured in plasma by NMR spectroscopy (LabCorp) using the NMR LipoProfile test spectrum (Otvos *et al.*, 2015; LabCorp, GlycA TEST: 123850, 2018, available from labcorp.com/test-menu/26131/glyca). GlycA high and lipid cutoffs were determined as two standard deviations from the median value in healthy donors.

7.2.9 Insulin resistance

[0115] Serum insulin concentrations were determined using an Insulin Human ELISA Kit (Thermo Fisher, #KAQ1251). Serum glucose concentrations were determined via an enzymatic assay as part of a clinical, validated chemistry panel performed by LabCorp (LabCorp, Glucose Test: 001032, 2019 ; available from www.labcorp.com/test-menu/26026/glucose). Insulin resistance (IR) was calculated from insulin and glucose concentrations using the HOMA2 Calculator (Diabetes Trials Unit, University of Oxford, HOMA2 Calculator; available from www.dtu.ox.ac.uk/homacalculator/).

7.2.10 Statistics

[0116] A 2-tailed Mann–Whitney U test was used to analyze CEC, GlycA, IL-10, IR, neutrophil number, NET complexes, and TNF- α in patients with SLE compared with healthy donors and comparison of anifrolumab 300 mg versus placebo. Spearman's rank correlation was used to analyze associations of vascular inflammatory markers, neutrophil number, and NET complexes with 21-IFNGS analyses and IFN- α protein measurements. Welch's t-test for group comparisons was used to analyze associations of vascular inflammatory markers, neutrophil number, and NET complexes with IFNGS test status, SLEDAI score, and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) score.

Signed-rank tests were used to compare changes from baseline in the aforementioned markers after treatment with anifrolumab 300 mg or placebo. RStudio 1.1.383 was used to perform all statistical analyses.

7.3 Results

7.3.1 Association of IFN- α with IFNGS in SLE patients

[0117] Using ultrasensitive immunoassays, the association of serum protein levels of IFN- α and IFN- β with type I IFNGS was analyzed. IFN- α was quantifiable in baseline serum samples in the majority of patients (80.1%, 205/256), including 96.3% (184/191) who were IFNGS test-high and 32.3% (21/65) who were IFNGS test-low (**FIG. 2A**). In contrast, IFN- β was quantifiable in only 2.0% (5/256) of patients, indicating IFN- α is the dominant type I IFN protein in circulation in lupus.

[0118] IFNGS test-high patients had significantly higher serum IFN- α protein concentrations than IFNGS test-low patients (area under the curve (AUC) = 0.92, $p < 0.001$). Median IFN- α protein level in IFNGS test-high patients was greater than the maximum level of healthy donors (**FIG. 2A**). While the 4-gene IFNGS test categorizes patients into two distinct subgroups, a 21-gene IFNGS panel (21-IFNGS) generates a continuous 21-IFNGS score. Serum IFN- α protein levels correlated with whole blood 21-IFNGS in SLE (Spearman's rank correlation [R] = 0.81, $p < 0.001$; **FIG. 2B**), supporting a direct contribution of IFN- α to lupus IFN gene signatures.

[0119] Proteins that significantly correlated with both IFN- α protein and the 21-IFNGS included many atherosclerosis- and vascular dysfunction-associated proteins including tumour necrosis factor alpha (TNF- α), interleukin (IL)-10, angiopoietin 2, VCAM-1, MIP-3 β , MCP-1, progranulin, IP-10, and von Willebrand factor (**Table 7-1**).

Table 7-1: Serum analytes that correlate with both IFN- α and IFN 21-gene signature expression

	Analyte ^a	IFN- α				21-IFNGS			
		N	Rho	P-value	FDR	n	Rho	P-value	FDR
IFN and IFN-Inducible Cytokines	21-IFNGS	255	0.82	< E-14	< E-14	NA	NA	NA	NA
	IFN- α	NA	NA	NA	NA	255	0.82	< E-14	< E-14
	MCP-2	256	0.65	< E-14	< E-14	301	0.67	< E-14	< E-14
	IP-10	256	0.63	< E-14	< E-14	301	0.63	< E-14	< E-14
	BAFF	256	0.62	< E-14	< E-14	301	0.57	< E-14	< E-14
	MIP-3 β	256	0.60	< E-14	< E-14	301	0.63	< E-14	< E-14
	ITAC	256	0.59	< E-14	< E-14	301	0.56	< E-14	< E-14
	BLC	256	0.43	3.49E-13	2.48E-12	301	0.43	4.44E-15	3.61E-14
	MCP-1	256	0.37	7.48E-10	4.03E-9	301	0.34	1.54E-9	7.93E-9
	Eotaxin 2	256	-0.23	1.88E-4	6.21E-4	301	-0.21	1.84E-4	6.10E-4
Vascular Damage/ Lipid Dysregulation	TNF- α	254	0.62	< E-14	< E-14	253	0.61	< E-14	< E-14
	IL-10	254	0.55	< E-14	< E-14	253	0.51	< E-14	< E-14
	Angiopoietin 2	256	0.52	< E-14	< E-14	301	0.47	< E-14	< E-14
	VCAM-1	256	0.49	< E-14	< E-14	301	0.47	< E-14	< E-14
	vWF	255	0.32	1.42E-7	6.35E-7	300	0.33	6.37E-9	3.15E-8
	ApoA 1	50	-0.33	0.021	0.044	50	-0.37	0.009	0.021
	Medium cHDL	50	-0.34	0.015	0.032	50	-0.36	0.010	0.023
	LDL	50	-0.37	0.009	0.020	50	-0.41	0.003	0.009
	Total cholesterol	50	-0.39	0.005	0.013	50	-0.39	0.005	0.012
	H3P	50	-0.50	2.07E-4	6.81E-4	50	-0.46	8.69E-4	0.003
Neutrophil Dysregulation	Progranulin	256	0.62	< E-14	< E-14	301	0.57	< E-14	< E-14
	CitH3-DNA	185	0.23	0.001	0.004	188	0.22	0.002	0.006
	MPO-DNA	185	0.19	0.008	0.020	188	0.21	0.003	0.009
	Neutrophil number	251	-0.29	2.13E-6	8.89E-6	296	-0.18	0.002	0.005
Immune Dysregulation/Other	B-2 microglobulin	255	0.52	< E-14	< E-14	300	0.52	< E-14	< E-14
	Ficolin 3	256	0.45	3.02E-14	2.28E-13	301	0.48	< E-14	< E-14
	IL-2	253	0.43	6.89E-13	4.75E-12	252	0.40	2.37E-11	1.44E-10
	IFN- γ	256	0.42	1.67E-12	1.08E-11	255	0.46	1.04E-14	8.17E-14
	IgE	256	0.37	1.22E-9	6.40E-9	301	0.33	6.37E-9	3.15E-8
	TRAIL-R3	256	-0.22	5.11E-4	0.002	301	-0.24	2.20E-5	8.08E-5
	IL-1R2	256	-0.36	4.08E-9	2.05E-8	301	-0.29	4.09E-7	1.80E-6
	Leukocyte number	251	-0.41	7.62E-12	4.79E-11	296	-0.33	9.53E-9	4.63E-8
	Lymphocyte number	251	-0.48	1.33E-15	1.09E-14	296	-0.49	< E-14	< E-14

^a Includes analytes measured with a p-value < 0.05 and an FDR < 0.05. ApoA 1, apolipoprotein A1; BAFF, B-cell-activating factor; BLC, B-cell lymphoma 2; cHDL, high-density lipoprotein particle count; CitH3, citrullinated histone H3; FDR, false discovery rate; HDL, high density lipoprotein count; IFN, interferon; IgE, immunoglobulin E; IL-2, interleukin 2; IL-1R2, interleukin 1 receptor type 2; IP-10, interferon gamma-induced protein 10; ITAC, interferon-inducible T-cell alpha chemoattractant; MCP-1, monocyte chemoattractant protein; MIP-3 β , macrophage inflammatory protein 3-beta; MPO, myeloperoxidase; Rho, Spearman's rho; TNF, tumor necrosis factor, TRAIL-R3, TNF-related apoptosis-inducing ligand receptor 3; VCAM-1, vascular cell adhesion molecule 1; vWF, von Willebrand factor.

[0121] EXAMPLE 2: Inhibition of type I IFN signalling modulates NET levels in SLE

[0122] To understand the relationship between type I IFN signalling, neutrophil dysregulation, and associated biology, the correlation of IFN- α protein and the 21-IFNGS was assessed with other analytes

in sera (**Table 7-2**). Whole blood neutrophil numbers negatively correlated with serum IFN- α protein levels ($R = -0.29$, $p < 0.001$; **FIG. 2C**) and with 21-IFNGS, while IFNGS test-high patients had significantly fewer neutrophils compared with IFNGS test-low patients. These results support a direct association between neutrophils and multiple measures of type I IFN pathway activity.

[0123] Levels of circulating NET complexes (citrullinated histone H3 [CitH3]-, MPO-, and neutrophil elastase [NE]-DNA) were elevated in SLE compared with healthy donors (**FIG. 2D**) and negatively correlated with neutrophil numbers (**Table 7-2**). IFNGS test-high patients had significantly elevated CitH3-DNA NET remnants compared with IFNGS test-low patients ($p = 0.030$), and there was a correlation between CitH3-DNA and 21-IFNGS and IFN- α protein (**Table 7-2**). Similar associations were also observed between assessments of the other NET remnants (MPO-DNA and NE-DNA) and type I IFN measures. Thus, increased circulating NETs in SLE are associated with reduced neutrophil numbers and elevated type I IFN activity.

[0124] Statistical correlations of the type I IFN pathway with NETs and neutrophils are shown in **FIG. 3**. Associations with lupus disease activity are in **FIG. 7**. Patients with increased SLEDAI scores had significantly decreased CEC, reduced neutrophil numbers, and increased TNF- α compared with patients with lower SLEDAI scores (CEC: $p = 0.03066$; neutrophil number: $p = 0.000224$; TNF- α : $p = 8.27E-4$). Patients with increased CLASI scores also had reduced neutrophil numbers and increased TNF- α compared with patients with lower CLASI scores (neutrophil numbers: $p = 0.00533$; TNF- α : $p = 0.002$). Patients with increased SLEDAI scores were also significantly older and had increased HDL counts compared with patients who had lower SLEDAI scores (age: $p = 6.66E-5$; HDL: $p = 0.0421$). There were no significant associations between NET complexes or GlycA with SLE disease activity. Together, these results demonstrate associations of NET complexes with the type I IFN pathway, but not to degree of SLE disease activity.

[0125] Given the association between NETs and the type I IFN pathway, NET complexes at days 1 and 365 in patients who received the anti-IFNAR1 antibody anifrolumab or placebo were investigated (**FIG. 4**). Notably, median NET complex levels were significantly decreased at day 365 in patients receiving anifrolumab. Placebo patients had increased CitH3-DNA levels (but not the other NET complexes) at day 365 ($p = 0.006$). There were no changes in LDG-associated gene signature¹⁵ in patients who received anifrolumab. These results demonstrate that type I IFN pathway inhibition significantly reduced circulating NETs without an apparent reduction in circulating LDGs, although it is possible that the LDG signature may have been diluted by other neutrophils.

Table 7-2: The correlation between analyte pairs was analyzed using Spearman's rank correlation. Analyte pairs with a false-discovery rate (FDR) of <0.05 are indicated by bold text.

Analyte	Analyte	n	rho	P value	FDR
21-IFNGS	Lymphocyte count	296	-4.944E-01	<E-14	<E-14
21-IFNGS	ANG2	301	4.667E-01	<E-14	<E-14
21-IFNGS	VCAM1	301	4.669E-01	<E-14	<E-14
21-IFNGS	Ficolin 3	301	4.765E-01	<E-14	<E-14
21-IFNGS	IL-10	253	5.063E-01	<E-14	<E-14
21-IFNGS	B2M	300	5.159E-01	<E-14	<E-14
21-IFNGS	ITAC	301	5.622E-01	<E-14	<E-14

21-IFNGS	Progranulin	301	5.699E-01	<E-14	<E-14
21-IFNGS	BAFF	301	5.700E-01	<E-14	<E-14
21-IFNGS	TNF- α	253	6.089E-01	<E-14	<E-14
21-IFNGS	IP-10	301	6.266E-01	<E-14	<E-14
21-IFNGS	MIP3- β	301	6.270E-01	<E-14	<E-14
21-IFNGS	MCP2	301	6.674E-01	<E-14	<E-14
21-IFNGS	IFN- α protein (pg/mL)	255	8.181E-01	<E-14	<E-14
21-IFNGS	BLC	301	4.314E-01	<E-14	3.610E-14
21-IFNGS	IFN- γ	255	4.592E-01	1.044E-14	8.170E-14
21-IFNGS	IL-2	252	4.047E-01	2.368E-11	1.440E-10
21-IFNGS	MCP1	301	3.392E-01	1.539E-09	7.930E-09
21-IFNGS	IgE	301	3.268E-01	6.374E-09	3.150E-08
21-IFNGS	von Willebrand factor	300	3.273E-01	6.365E-09	3.150E-08
21-IFNGS	Leukocyte count	296	-3.258E-01	9.527E-09	4.630E-08
21-IFNGS	IL1RII	301	-2.870E-01	4.092E-07	1.800E-06
21-IFNGS	TRAILR3	301	-2.420E-01	2.197E-05	8.080E-05
21-IFNGS	Eotaxin-2	301	-2.140E-01	1.836E-04	6.100E-04
21-IFNGS	HDL in the H3P size range (μ M)	50	-4.562E-01	8.692E-04	2.608E-03
21-IFNGS	Neutrophil number	296	-1.823E-01	1.634E-03	4.675E-03
21-IFNGS	CitH3-DNA	188	2.218E-01	2.219E-03	6.164E-03
21-IFNGS	HDLC (mg/dL)	50	-4.073E-01	3.330E-03	8.877E-03
21-IFNGS	MPO-DNA	188	2.120E-01	3.492E-03	9.195E-03
21-IFNGS	NE-DNA	188	2.052E-01	4.724E-03	1.169E-02
21-IFNGS	Total cholesterol (mg/dL)	50	-3.902E-01	5.084E-03	1.244E-02
21-IFNGS	Ferritin	301	1.515E-01	8.486E-03	1.964E-02
21-IFNGS	Apolipoprotein A1 (mg/dL)	50	-3.655E-01	9.044E-03	2.062E-02
21-IFNGS	Medium cHDLP (μ M)	50	-3.597E-01	1.031E-02	2.294E-02
21-IFNGS	cHDLP (μ M)	50	-2.277E-01	1.118E-01	1.796E-01
21-IFNGS	CEC	129	-1.211E-01	1.716E-01	2.620E-01
21-IFNGS	Medium TRLP (nM)	50	1.813E-01	2.077E-01	3.079E-01
21-IFNGS	IR	121	1.063E-01	2.458E-01	3.504E-01
21-IFNGS	Very Small TRLP (nM)	50	1.234E-01	3.932E-01	5.031E-01
21-IFNGS	GlycA	50	-1.005E-01	4.875E-01	5.924E-01
21-IFNGS	Very Large TRLP (nM)	50	-3.916E-02	7.872E-01	8.440E-01
IFN- α protein (pg/mL)	ANG2	256	5.181E-01	<E-14	<E-14
IFN- α protein (pg/mL)	B2M	255	5.246E-01	<E-14	<E-14
IFN- α protein (pg/mL)	BAFF	256	6.193E-01	<E-14	<E-14
IFN- α protein (pg/mL)	Ficolin 3	256	4.513E-01	3.020E-14	2.280E-13
IFN- α protein (pg/mL)	BLC	256	4.340E-01	3.491E-13	2.480E-12
IFN- α protein (pg/mL)	IgE	256	3.682E-01	1.219E-09	6.400E-09
IFN- α protein (pg/mL)	Eotaxin-2	256	-2.313E-01	1.884E-04	6.214E-04
IFN- α protein (pg/mL)	HDL in the H3P size range (μ M)	50	-5.015E-01	2.072E-04	6.810E-04
IFN- α protein (pg/mL)	CitH3-DNA	185	2.318E-01	1.498E-03	4.357E-03
IFN- α protein (pg/mL)	HDLC (mg/dL)	50	-3.666E-01	8.836E-03	2.034E-02
IFN- α protein (pg/mL)	Apolipoprotein A1 (mg/dL)	50	-3.254E-01	2.113E-02	4.426E-02
IFN- α protein (pg/mL)	NE-DNA	185	1.575E-01	3.231E-02	6.367E-02
IFN- α protein (pg/mL)	Ferritin	256	1.191E-01	5.704E-02	1.030E-01
IFN- α protein (pg/mL)	CEC	127	-1.401E-01	1.162E-01	1.862E-01
IFN- α protein (pg/mL)	cHDLP (μ M)	50	-1.915E-01	1.828E-01	2.766E-01
IFN- α protein (pg/mL)	IR	106	9.313E-02	3.424E-01	4.487E-01
IFN- α protein (pg/mL)	GlycA	50	-1.023E-01	4.795E-01	5.881E-01
CitH3-DNA	ANG2	190	2.337E-01	1.176E-03	3.479E-03
CitH3-DNA	CEC	123	-2.850E-01	1.397E-03	4.104E-03
CitH3-DNA	BLC	190	1.417E-01	5.108E-02	9.378E-02
CitH3-DNA	Apolipoprotein A1 (mg/dL)	48	-2.362E-01	1.061E-01	1.742E-01
CitH3-DNA	cHDLP (μ M)	48	-1.416E-01	3.372E-01	4.446E-01
CitH3-DNA	B2M	189	5.637E-02	4.410E-01	5.480E-01
CitH3-DNA	BAFF	190	5.095E-02	4.851E-01	5.916E-01
MPO-DNA	NE-DNA	190	4.851E-01	1.319E-12	8.740E-12
MPO-DNA	CitH3-DNA	190	4.002E-01	1.061E-08	5.130E-08
MPO-DNA	ITAC	190	2.412E-01	8.008E-04	2.433E-03
MPO-DNA	Eotaxin-2	190	-2.399E-01	8.579E-04	2.583E-03
MPO-DNA	ANG2	190	2.220E-01	2.078E-03	5.829E-03
MPO-DNA	CEC	123	-2.613E-01	3.512E-03	9.214E-03
MPO-DNA	IL1RII	190	-2.107E-01	3.531E-03	9.214E-03
MPO-DNA	IgE	190	2.042E-01	4.718E-03	1.169E-02
MPO-DNA	Ficolin 3	190	2.035E-01	4.868E-03	1.197E-02

MPO-DNA	IFN- α protein (pg/mL)	185	1.930E-01	8.482E-03	1.964E-02
MPO-DNA	MCP2	190	1.547E-01	3.304E-02	6.451E-02
MPO-DNA	BLC	190	1.422E-01	5.027E-02	9.268E-02
MPO-DNA	MIP3- β	190	1.324E-01	6.853E-02	1.192E-01
MPO-DNA	GlycA	48	-2.278E-01	1.194E-01	1.907E-01
MPO-DNA	Lymphocyte count	184	-8.838E-02	2.329E-01	3.364E-01
MPO-DNA	IL-2	182	8.366E-02	2.615E-01	3.697E-01
MPO-DNA	Medium TRLP (nM)	48	1.619E-01	2.715E-01	3.792E-01
MPO-DNA	BAFF	190	7.978E-02	2.739E-01	3.809E-01
MPO-DNA	HDL in the H3P size range (μ M)	48	-1.499E-01	3.091E-01	4.165E-01
MPO-DNA	IP-10	190	6.977E-02	3.388E-01	4.461E-01
MPO-DNA	Medium cHDLP (μ M)	48	-1.304E-01	3.768E-01	4.872E-01
MPO-DNA	B2M	189	6.253E-02	3.926E-01	5.031E-01
MPO-DNA	IR	76	-7.167E-02	5.384E-01	6.350E-01
MPO-DNA	IFN- γ	185	4.009E-02	5.880E-01	6.804E-01
MPO-DNA	HDLC (mg/dL)	48	-6.501E-02	6.606E-01	7.465E-01
MPO-DNA	Apolipoprotein A1 (mg/dL)	48	-5.931E-02	6.888E-01	7.682E-01
MPO-DNA	IL-10	183	-2.567E-02	7.301E-01	8.028E-01
MPO-DNA	cHDLP (μ M)	48	4.773E-02	7.473E-01	8.145E-01
MPO-DNA	MCP1	190	-2.208E-02	7.624E-01	8.236E-01
MPO-DNA	Ferritin	190	-3.934E-03	9.570E-01	9.671E-01
MPO-DNA	MPO-DNA	190		1.000E+00	
NE-DNA	CitH3-DNA	190	7.106E-01	<E-14	<E-14
NE-DNA	Eotaxin-2	190	-2.071E-01	4.141E-03	1.052E-02
NE-DNA	ANG2	190	1.629E-01	2.470E-02	5.004E-02
NE-DNA	CEC	123	-1.953E-01	3.042E-02	6.021E-02
NE-DNA	Ficolin 3	190	1.315E-01	7.058E-02	1.220E-01
NE-DNA	BLC	190	1.090E-01	1.344E-01	2.093E-01
NE-DNA	HDL in the H3P size range (μ M)	48	-1.457E-01	3.230E-01	4.305E-01
NE-DNA	B2M	189	5.800E-02	4.279E-01	5.339E-01
NE-DNA	BAFF	190	3.634E-02	6.187E-01	7.102E-01
NE-DNA	HDLC (mg/dL)	48	-7.077E-02	6.327E-01	7.234E-01
NE-DNA	Ferritin	190	-3.322E-02	6.491E-01	7.354E-01
NE-DNA	cHDLP (μ M)	48	-4.062E-02	7.840E-01	8.427E-01
NE-DNA	Apolipoprotein A1 (mg/dL)	48	-3.536E-02	8.114E-01	8.625E-01
NE-DNA	GlycA	48	1.211E-02	9.349E-01	9.532E-01
NE-DNA	NE-DNA	190		1.000E+00	
IL-10	BLC	254	4.905E-01	<E-14	<E-14
IL-10	IFN- α protein (pg/mL)	254	5.486E-01	<E-14	<E-14
IL-10	B2M	253	5.959E-01	<E-14	<E-14
IL-10	IP-10	254	6.689E-01	<E-14	<E-14
IL-10	ITAC	254	4.775E-01	<E-14	<E-14
IL-10	BAFF	254	4.620E-01	<E-14	6.250E-14
IL-10	IFN- γ	254	4.601E-01	1.021E-14	8.070E-14
IL-10	ANG2	254	4.558E-01	1.954E-14	1.490E-13
IL-10	Ficolin 3	254	2.639E-01	2.029E-05	7.530E-05
IL-10	cHDLP (μ M)	50	-4.470E-01	1.138E-03	3.377E-03
IL-10	IgE	254	1.902E-01	2.332E-03	6.437E-03
IL-10	IR	105	2.835E-01	3.386E-03	8.989E-03
IL-10	IL1RII	254	-1.817E-01	3.658E-03	9.482E-03
IL-10	GlycA	50	3.746E-01	7.364E-03	1.737E-02
IL-10	Apolipoprotein A1 (mg/dL)	50	-3.365E-01	1.689E-02	3.573E-02
IL-10	HDLC (mg/dL)	50	-3.220E-01	2.260E-02	4.712E-02
IL-10	Ferritin	254	1.418E-01	2.385E-02	4.890E-02
IL-10	HDL in the H3P size range (μ M)	50	-1.432E-01	3.211E-01	4.293E-01
IL-10	CitH3-DNA	183	6.972E-02	3.484E-01	4.558E-01
IL-10	CEC	125	-7.410E-02	4.115E-01	5.193E-01
IL-10	NE-DNA	183	5.199E-02	4.846E-01	5.916E-01
IL-10	Eotaxin-2	254	-9.713E-03	8.776E-01	9.159E-01
IL-10	IL-10	254		1.000E+00	
TNF- α	MCP1	254	4.939E-01	<E-14	<E-14
TNF- α	ANG2	254	5.323E-01	<E-14	<E-14
TNF- α	IFN- γ	254	5.361E-01	<E-14	<E-14
TNF- α	BAFF	254	5.682E-01	<E-14	<E-14
TNF- α	Progranulin	254	5.700E-01	<E-14	<E-14
TNF- α	ITAC	254	5.831E-01	<E-14	<E-14

TNF- α	MCP2	254	5.983E-01	<E-14	<E-14
TNF- α	IFN- α protein (pg/mL)	254	6.172E-01	<E-14	<E-14
TNF- α	IL-2	252	6.262E-01	<E-14	<E-14
TNF- α	MIP3- β	254	6.899E-01	<E-14	<E-14
TNF- α	B2M	253	7.086E-01	<E-14	<E-14
TNF- α	IP-10	254	7.222E-01	<E-14	<E-14
TNF- α	IL-10	253	7.324E-01	<E-14	<E-14
TNF- α	BLC	254	4.297E-01	7.807E-13	5.330E-12
TNF- α	Lymphocyte count	249	-3.186E-01	2.800E-07	1.240E-06
TNF- α	IL1RII	254	-2.957E-01	1.606E-06	6.780E-06
TNF- α	IgE	254	2.355E-01	1.517E-04	5.162E-04
TNF- α	Ficolin 3	254	2.305E-01	2.112E-04	6.915E-04
TNF- α	HDLC (mg/dL)	50	-4.609E-01	7.554E-04	2.306E-03
TNF- α	Neutrophil number	249	-1.949E-01	2.008E-03	5.669E-03
TNF- α	Apolipoprotein A1 (mg/dL)	50	-4.184E-01	2.497E-03	6.826E-03
TNF- α	cHDLp (μ M)	50	-3.883E-01	5.331E-03	1.297E-02
TNF- α	Medium cHDLp (μ M)	50	-3.416E-01	1.520E-02	3.246E-02
TNF- α	HDL in the H3P size range (μ M)	50	-3.398E-01	1.577E-02	3.352E-02
TNF- α	Eotaxin-2	254	-1.383E-01	2.754E-02	5.489E-02
TNF- α	CEC	126	-1.962E-01	2.771E-02	5.510E-02
TNF- α	Total cholesterol (mg/dL)	50	-2.919E-01	3.971E-02	7.548E-02
TNF- α	Ferritin	254	1.202E-01	5.578E-02	1.011E-01
TNF- α	CitH3-DNA	183	1.185E-01	1.102E-01	1.777E-01
TNF- α	NE-DNA	183	1.039E-01	1.618E-01	2.483E-01
TNF- α	MPO-DNA	183	7.888E-02	2.885E-01	3.949E-01
TNF- α	Medium TRLP (nM)	50	1.407E-01	3.297E-01	4.367E-01
TNF- α	IR	106	9.146E-02	3.511E-01	4.587E-01
TNF- α	TRAILR3	254	-4.429E-02	4.822E-01	5.904E-01
TNF- α	GlycA	50	2.381E-02	8.696E-01	9.098E-01
GlycA	BAFF	50	-2.471E-01	8.364E-02	1.415E-01
GlycA	Eotaxin-2	50	2.409E-01	9.188E-02	1.536E-01
GlycA	BLC	50	1.916E-01	1.825E-01	2.766E-01
GlycA	CitH3-DNA	48	-1.288E-01	3.829E-01	4.928E-01
GlycA	cHDLp (μ M)	50	-1.172E-01	4.178E-01	5.244E-01
GlycA	Apolipoprotein A1 (mg/dL)	50	-8.643E-02	5.506E-01	6.459E-01
GlycA	B2M	49	-8.382E-02	5.669E-01	6.605E-01
GlycA	Ficolin 3	50	5.595E-02	6.996E-01	7.762E-01
GlycA	CEC	50	-4.466E-02	7.581E-01	8.221E-01
GlycA	Ferritin	50	-3.667E-02	8.004E-01	8.549E-01
GlycA	ANG2	50	-5.693E-03	9.687E-01	9.768E-01
CEC	Apolipoprotein A1 (mg/dL)	50	4.846E-01	3.625E-04	1.156E-03
CEC	BAFF	129	-2.266E-01	9.824E-03	2.191E-02
CEC	ANG2	129	-2.152E-01	1.430E-02	3.078E-02
CEC	B2M	128	-1.862E-01	3.536E-02	6.827E-02
CEC	BLC	129	-7.015E-02	4.296E-01	5.353E-01
Leukocyte count	Lymphocyte count	298	4.622E-01	<E-14	<E-14
Leukocyte count	Neutrophil number	297	9.381E-01	<E-14	<E-14
Leukocyte count	Progranulin	295	-3.929E-01	2.513E-12	1.600E-11
Leukocyte count	IFN- α protein (pg/mL)	251	-4.146E-01	7.620E-12	4.790E-11
Leukocyte count	IP-10	295	-3.479E-01	8.067E-10	4.290E-09
Leukocyte count	TRAILR3	295	3.464E-01	9.658E-10	5.100E-09
Leukocyte count	MIP3- β	295	-3.322E-01	4.974E-09	2.490E-08
Leukocyte count	MCP2	295	-3.267E-01	9.195E-09	4.500E-08
Leukocyte count	ITAC	295	-3.098E-01	5.580E-08	2.600E-07
Leukocyte count	IL1RII	295	3.013E-01	1.316E-07	6.000E-07
Leukocyte count	BAFF	295	-3.012E-01	1.329E-07	6.020E-07
Leukocyte count	B2M	294	-2.911E-01	3.758E-07	1.660E-06
Leukocyte count	VCAM1	295	-2.839E-01	7.107E-07	3.070E-06
Leukocyte count	IL-2	248	-2.950E-01	2.266E-06	9.430E-06
Leukocyte count	Eotaxin-2	295	2.683E-01	2.951E-06	1.210E-05
Leukocyte count	TNF- α	249	-2.859E-01	4.542E-06	1.820E-05
Leukocyte count	IFN- γ	251	-2.552E-01	4.309E-05	1.539E-04
Leukocyte count	ANG2	295	-2.246E-01	9.960E-05	3.430E-04
Leukocyte count	Total cholesterol (mg/dL)	50	4.890E-01	3.142E-04	1.009E-03
Leukocyte count	Ficolin 3	295	-2.007E-01	5.239E-04	1.628E-03
Leukocyte count	BLC	295	-1.850E-01	1.414E-03	4.126E-03

Leukocyte count	Very Large TRLP (nM)	50	4.359E-01	1.555E-03	4.492E-03
Leukocyte count	IgE	295	-1.687E-01	3.667E-03	9.482E-03
Leukocyte count	von Willebrand factor	294	-1.540E-01	8.153E-03	1.908E-02
Leukocyte count	MPO-DNA	184	-1.919E-01	9.053E-03	2.062E-02
Leukocyte count	CitH3-DNA	184	-1.878E-01	1.067E-02	2.361E-02
Leukocyte count	NE-DNA	184	-1.658E-01	2.452E-02	4.991E-02
Leukocyte count	HDL in the H3P size range (μM)	50	2.690E-01	5.889E-02	1.059E-01
Leukocyte count	MCP1	295	-1.091E-01	6.127E-02	1.090E-01
Leukocyte count	cHDLP (μM)	50	2.614E-01	6.668E-02	1.165E-01
Leukocyte count	Apolipoprotein A1 (mg/dL)	50	2.551E-01	7.375E-02	1.273E-01
Leukocyte count	IL-10	249	-1.129E-01	7.539E-02	1.293E-01
Leukocyte count	HDLC (mg/dL)	50	2.363E-01	9.849E-02	1.634E-01
Leukocyte count	GlycA	50	2.308E-01	1.068E-01	1.742E-01
Leukocyte count	Medium TRLP (nM)	50	2.219E-01	1.214E-01	1.922E-01
Leukocyte count	IR	121	1.404E-01	1.245E-01	1.960E-01
Leukocyte count	CEC	128	1.177E-01	1.857E-01	2.800E-01
Leukocyte count	Ferritin	295	-6.562E-02	2.612E-01	3.697E-01
Leukocyte count	Medium cHDLP (μM)	50	1.002E-01	4.885E-01	5.924E-01
Leukocyte count	Very Small TRLP (nM)	50	4.953E-02	7.327E-01	8.046E-01
Leukocyte count	Leukocyte count	298		1.000E+00	
von Willebrand factor	VCAM1	302	5.206E-01	<E-14	<E-14
von Willebrand factor	B2M	302	4.025E-01	3.459E-13	2.480E-12
von Willebrand factor	TNF-α	253	4.268E-01	1.277E-12	8.590E-12
von Willebrand factor	IP-10	302	3.630E-01	7.752E-11	4.540E-10
von Willebrand factor	IL-10	253	3.939E-01	8.073E-11	4.700E-10
von Willebrand factor	MCP2	302	3.538E-01	2.486E-10	1.380E-09
von Willebrand factor	Progranulin	302	3.150E-01	2.204E-08	1.050E-07
von Willebrand factor	IFN-α protein (pg/mL)	255	3.223E-01	1.417E-07	6.350E-07
von Willebrand factor	BLC	302	2.966E-01	1.513E-07	6.750E-07
von Willebrand factor	Ferritin	302	2.765E-01	1.056E-06	4.530E-06
von Willebrand factor	ITAC	302	2.719E-01	1.617E-06	6.790E-06
von Willebrand factor	MIP3-β	302	2.629E-01	3.641E-06	1.480E-05
von Willebrand factor	BAFF	302	2.602E-01	4.614E-06	1.840E-05
von Willebrand factor	MCP1	302	2.492E-01	1.176E-05	4.540E-05
von Willebrand factor	Ficolin 3	302	2.469E-01	1.418E-05	5.430E-05
von Willebrand factor	ANG2	302	2.452E-01	1.633E-05	6.200E-05
von Willebrand factor	IL-2	252	2.659E-01	1.887E-05	7.090E-05
von Willebrand factor	Lymphocyte count	294	-2.369E-01	4.087E-05	1.472E-04
von Willebrand factor	IFN-γ	255	1.861E-01	2.847E-03	7.685E-03
von Willebrand factor	Very Small TRLP (nM)	49	2.319E-01	1.089E-01	1.762E-01
von Willebrand factor	MPO-DNA	189	-1.021E-01	1.621E-01	2.483E-01
von Willebrand factor	TRAILR3	302	-7.787E-02	1.771E-01	2.690E-01
von Willebrand factor	cHDLP (μM)	49	-1.830E-01	2.082E-01	3.080E-01
von Willebrand factor	Neutrophil number	294	-7.097E-02	2.251E-01	3.268E-01
von Willebrand factor	IL1RII	302	-6.234E-02	2.802E-01	3.860E-01
von Willebrand factor	Very Large TRLP (nM)	49	-1.508E-01	3.010E-01	4.100E-01
von Willebrand factor	Eotaxin-2	302	5.890E-02	3.076E-01	4.158E-01
von Willebrand factor	CEC	128	7.140E-02	4.232E-01	5.288E-01
von Willebrand factor	GlycA	49	6.935E-02	6.359E-01	7.242E-01
von Willebrand factor	HDLC (mg/dL)	49	-6.381E-02	6.631E-01	7.476E-01
von Willebrand factor	Medium TRLP (nM)	49	6.377E-02	6.634E-01	7.476E-01
von Willebrand factor	Apolipoprotein A1 (mg/dL)	49	-5.765E-02	6.940E-01	7.710E-01
von Willebrand factor	Medium cHDLP (μM)	49	-5.431E-02	7.109E-01	7.857E-01
von Willebrand factor	NE-DNA	189	-2.424E-02	7.406E-01	8.092E-01
von Willebrand factor	CitH3-DNA	189	-1.054E-02	8.856E-01	9.198E-01
von Willebrand factor	IR	118	-1.245E-02	8.936E-01	9.269E-01
von Willebrand factor	IgE	302	7.378E-03	8.984E-01	9.308E-01
von Willebrand factor	HDL in the H3P size range (μM)	49	-3.626E-03	9.803E-01	9.837E-01
von Willebrand factor	Total cholesterol (mg/dL)	49	2.731E-03	9.851E-01	9.863E-01
Very Small TRLP (nM)	BAFF	50	4.007E-01	3.932E-03	1.008E-02
Very Small TRLP (nM)	TNF-α	50	3.671E-01	8.740E-03	2.017E-02
Very Small TRLP (nM)	B2M	49	2.906E-01	4.284E-02	8.071E-02
Very Small TRLP (nM)	HDLC (mg/dL)	50	-2.730E-01	5.508E-02	1.003E-01
Very Small TRLP (nM)	VCAM1	50	2.658E-01	6.207E-02	1.098E-01
Very Small TRLP (nM)	ANG2	50	2.539E-01	7.515E-02	1.293E-01
Very Small TRLP (nM)	IL-10	50	2.524E-01	7.700E-02	1.318E-01
Very Small TRLP (nM)	ITAC	50	2.145E-01	1.347E-01	2.094E-01

Very Small TRLP (nM)	IFN- γ	50	2.025E-01	1.585E-01	2.437E-01
Very Small TRLP (nM)	IL-2	49	1.977E-01	1.732E-01	2.640E-01
Very Small TRLP (nM)	Apolipoprotein A1 (mg/dL)	50	-1.912E-01	1.835E-01	2.772E-01
Very Small TRLP (nM)	MCP1	50	1.870E-01	1.935E-01	2.892E-01
Very Small TRLP (nM)	MIP3- β	50	1.853E-01	1.977E-01	2.950E-01
Very Small TRLP (nM)	cHDLP (μ M)	50	-1.748E-01	2.246E-01	3.267E-01
Very Small TRLP (nM)	Ferritin	50	1.582E-01	2.726E-01	3.798E-01
Very Small TRLP (nM)	Medium cHDLP (μ M)	50	-1.565E-01	2.779E-01	3.840E-01
Very Small TRLP (nM)	IFN- α protein (pg/mL)	50	1.488E-01	3.024E-01	4.113E-01
Very Small TRLP (nM)	HDL in the H3P size range (μ M)	50	-1.452E-01	3.142E-01	4.214E-01
Very Small TRLP (nM)	Progranulin	50	1.378E-01	3.399E-01	4.461E-01
Very Small TRLP (nM)	Ficolin 3	50	1.267E-01	3.805E-01	4.904E-01
Very Small TRLP (nM)	IP-10	50	1.187E-01	4.118E-01	5.193E-01
Very Small TRLP (nM)	Medium TRLP (nM)	50	1.167E-01	4.197E-01	5.252E-01
Very Small TRLP (nM)	MCP2	50	1.128E-01	4.354E-01	5.417E-01
Very Small TRLP (nM)	Total cholesterol (mg/dL)	50	1.087E-01	4.525E-01	5.598E-01
Very Small TRLP (nM)	BLC	50	-1.003E-01	4.882E-01	5.924E-01
Very Small TRLP (nM)	Eotaxin-2	50	-9.795E-02	4.986E-01	6.021E-01
Very Small TRLP (nM)	Neutrophil number	50	8.363E-02	5.637E-01	6.576E-01
Very Small TRLP (nM)	GlycA	50	6.948E-02	6.316E-01	7.232E-01
Very Small TRLP (nM)	Very Large TRLP (nM)	50	4.752E-02	7.431E-01	8.109E-01
Very Small TRLP (nM)	CEC	50	-4.121E-02	7.763E-01	8.355E-01
Very Small TRLP (nM)	IR	34	-4.482E-02	8.013E-01	8.549E-01
Very Small TRLP (nM)	IgE	50	2.850E-02	8.442E-01	8.923E-01
Very Small TRLP (nM)	IL1RII	50	-2.209E-02	8.790E-01	9.162E-01
Very Small TRLP (nM)	CitH3-DNA	48	1.630E-02	9.124E-01	9.428E-01
Very Small TRLP (nM)	MPO-DNA	48	-1.353E-02	9.273E-01	9.516E-01
Very Small TRLP (nM)	Lymphocyte count	50	-1.197E-02	9.342E-01	9.532E-01
Very Small TRLP (nM)	TRAILR3	50	1.005E-02	9.448E-01	9.578E-01
Very Small TRLP (nM)	NE-DNA	48	8.747E-03	9.529E-01	9.641E-01
Very Small TRLP (nM)	Very Small TRLP (nM)	50		1.000E+00	
Very Large TRLP (nM)	cHDLP (μ M)	50	5.339E-01	6.517E-05	2.290E-04
Very Large TRLP (nM)	Total cholesterol (mg/dL)	50	4.824E-01	3.887E-04	1.226E-03
Very Large TRLP (nM)	Apolipoprotein A1 (mg/dL)	50	4.658E-01	6.531E-04	2.001E-03
Very Large TRLP (nM)	Neutrophil number	50	4.022E-01	3.787E-03	9.733E-03
Very Large TRLP (nM)	IR	34	4.804E-01	4.034E-03	1.028E-02
Very Large TRLP (nM)	HDL in the H3P size range (μ M)	50	3.810E-01	6.337E-03	1.516E-02
Very Large TRLP (nM)	IL1RII	50	3.657E-01	9.016E-03	2.062E-02
Very Large TRLP (nM)	HDLC (mg/dL)	50	3.622E-01	9.742E-03	2.179E-02
Very Large TRLP (nM)	B2M	49	-3.228E-01	2.370E-02	4.883E-02
Very Large TRLP (nM)	Medium cHDLP (μ M)	50	2.976E-01	3.584E-02	6.903E-02
Very Large TRLP (nM)	VCAM1	50	-2.815E-01	4.763E-02	8.857E-02
Very Large TRLP (nM)	MIP3- β	50	-2.583E-01	7.015E-02	1.215E-01
Very Large TRLP (nM)	Progranulin	50	-2.310E-01	1.065E-01	1.742E-01
Very Large TRLP (nM)	CEC	50	2.299E-01	1.082E-01	1.757E-01
Very Large TRLP (nM)	TRAILR3	50	2.219E-01	1.215E-01	1.922E-01
Very Large TRLP (nM)	BAFF	50	-2.177E-01	1.289E-01	2.014E-01
Very Large TRLP (nM)	Ferritin	50	-1.808E-01	2.089E-01	3.086E-01
Very Large TRLP (nM)	IP-10	50	-1.792E-01	2.131E-01	3.136E-01
Very Large TRLP (nM)	TNF- α	50	-1.785E-01	2.148E-01	3.151E-01
Very Large TRLP (nM)	IL-10	50	-1.672E-01	2.458E-01	3.504E-01
Very Large TRLP (nM)	Lymphocyte count	50	1.601E-01	2.668E-01	3.753E-01
Very Large TRLP (nM)	ANG2	50	-1.569E-01	2.765E-01	3.840E-01
Very Large TRLP (nM)	Medium TRLP (nM)	50	1.474E-01	3.070E-01	4.158E-01
Very Large TRLP (nM)	IgE	50	1.409E-01	3.289E-01	4.367E-01
Very Large TRLP (nM)	MCP1	50	1.173E-01	4.172E-01	5.244E-01
Very Large TRLP (nM)	Eotaxin-2	50	1.033E-01	4.754E-01	5.847E-01
Very Large TRLP (nM)	IFN- α protein (pg/mL)	50	-9.687E-02	5.033E-01	6.061E-01
Very Large TRLP (nM)	IL-2	49	-9.369E-02	5.220E-01	6.224E-01
Very Large TRLP (nM)	GlycA	50	7.964E-02	5.825E-01	6.750E-01
Very Large TRLP (nM)	IFN- γ	50	-6.757E-02	6.411E-01	7.272E-01
Very Large TRLP (nM)	NE-DNA	48	-6.026E-02	6.841E-01	7.640E-01
Very Large TRLP (nM)	Ficolin 3	50	4.509E-02	7.559E-01	8.207E-01
Very Large TRLP (nM)	MPO-DNA	48	-4.480E-02	7.624E-01	8.236E-01
Very Large TRLP (nM)	CitH3-DNA	48	-4.015E-02	7.864E-01	8.440E-01
Very Large TRLP (nM)	MCP2	50	3.532E-02	8.076E-01	8.595E-01

Very Large TRLP (nM)	ITAC	50	-2.831E-02	8.453E-01	8.923E-01
Very Large TRLP (nM)	BLC	50	-4.225E-03	9.768E-01	9.813E-01
VCAM1	BLC	303	4.577E-01	<E-14	<E-14
VCAM1	MCP2	303	4.590E-01	<E-14	<E-14
VCAM1	ANG2	303	4.630E-01	<E-14	<E-14
VCAM1	ITAC	303	4.671E-01	<E-14	<E-14
VCAM1	BAFF	303	4.683E-01	<E-14	<E-14
VCAM1	IFN- α protein (pg/mL)	256	4.946E-01	<E-14	<E-14
VCAM1	Progranulin	303	5.128E-01	<E-14	<E-14
VCAM1	MIP3- β	303	5.304E-01	<E-14	<E-14
VCAM1	IP-10	303	5.431E-01	<E-14	<E-14
VCAM1	B2M	302	6.078E-01	<E-14	<E-14
VCAM1	IL-10	254	6.128E-01	<E-14	<E-14
VCAM1	TNF- α	254	6.843E-01	<E-14	<E-14
VCAM1	IL-2	253	4.359E-01	3.733E-13	2.610E-12
VCAM1	IFN- γ	256	4.032E-01	2.005E-11	1.220E-10
VCAM1	Lymphocyte count	295	-3.609E-01	1.673E-10	9.670E-10
VCAM1	MCP1	303	3.017E-01	8.544E-08	3.910E-07
VCAM1	Ficolin 3	303	2.429E-01	1.908E-05	7.140E-05
VCAM1	Neutrophil number	295	-1.686E-01	3.678E-03	9.482E-03
VCAM1	Ferritin	303	1.626E-01	4.546E-03	1.135E-02
VCAM1	IL1RII	303	-1.537E-01	7.353E-03	1.737E-02
VCAM1	cHDLp (μ M)	50	-3.522E-01	1.214E-02	2.646E-02
VCAM1	HDLC (mg/dL)	50	-3.293E-01	1.954E-02	4.124E-02
VCAM1	Total cholesterol (mg/dL)	50	-3.216E-01	2.278E-02	4.738E-02
VCAM1	IgE	303	1.191E-01	3.832E-02	7.316E-02
VCAM1	Apolipoprotein A1 (mg/dL)	50	-2.925E-01	3.930E-02	7.486E-02
VCAM1	Medium cHDLp (μ M)	50	-2.834E-01	4.610E-02	8.621E-02
VCAM1	HDL in the H3P size range (μ M)	50	-2.630E-01	6.496E-02	1.141E-01
VCAM1	CEC	129	-1.350E-01	1.271E-01	1.990E-01
VCAM1	CitH3-DNA	190	7.692E-02	2.915E-01	3.978E-01
VCAM1	IR	119	6.989E-02	4.501E-01	5.576E-01
VCAM1	NE-DNA	190	5.172E-02	4.785E-01	5.877E-01
VCAM1	MPO-DNA	190	4.944E-02	4.981E-01	6.021E-01
VCAM1	GlycA	50	8.964E-02	5.359E-01	6.338E-01
VCAM1	Medium TRLP (nM)	50	6.984E-02	6.299E-01	7.221E-01
VCAM1	TRAILR3	303	-9.001E-03	8.760E-01	9.153E-01
VCAM1	Eotaxin-2	303	-4.492E-03	9.379E-01	9.546E-01
VCAM1	VCAM1	303		1.000E+00	
TRAILR3	Neutrophil number	295	3.352E-01	3.548E-09	1.810E-08
TRAILR3	IL1RII	303	2.255E-01	7.508E-05	2.617E-04
TRAILR3	Eotaxin-2	303	2.132E-01	1.842E-04	6.100E-04
TRAILR3	IFN- α protein (pg/mL)	256	-2.157E-01	5.114E-04	1.601E-03
TRAILR3	Ficolin 3	303	-1.487E-01	9.516E-03	2.150E-02
TRAILR3	IFN- γ	256	-1.421E-01	2.298E-02	4.767E-02
TRAILR3	Lymphocyte count	295	1.265E-01	2.990E-02	5.932E-02
TRAILR3	Progranulin	303	-1.214E-01	3.467E-02	6.707E-02
TRAILR3	IL-2	253	-1.191E-01	5.863E-02	1.056E-01
TRAILR3	GlycA	50	2.419E-01	9.060E-02	1.518E-01
TRAILR3	B2M	302	9.448E-02	1.013E-01	1.670E-01
TRAILR3	BLC	303	-8.897E-02	1.223E-01	1.931E-01
TRAILR3	ANG2	303	7.157E-02	2.141E-01	3.146E-01
TRAILR3	CitH3-DNA	190	-8.013E-02	2.718E-01	3.792E-01
TRAILR3	IgE	303	5.921E-02	3.043E-01	4.132E-01
TRAILR3	HDL in the H3P size range (μ M)	50	1.431E-01	3.216E-01	4.294E-01
TRAILR3	IP-10	303	-5.618E-02	3.297E-01	4.367E-01
TRAILR3	Total cholesterol (mg/dL)	50	1.273E-01	3.785E-01	4.885E-01
TRAILR3	MCP1	303	-3.887E-02	5.002E-01	6.032E-01
TRAILR3	MPO-DNA	190	-4.874E-02	5.043E-01	6.064E-01
TRAILR3	IL-10	254	-4.103E-02	5.151E-01	6.160E-01
TRAILR3	BAFF	303	2.927E-02	6.119E-01	7.043E-01
TRAILR3	NE-DNA	190	-2.970E-02	6.842E-01	7.640E-01
TRAILR3	Apolipoprotein A1 (mg/dL)	50	5.749E-02	6.917E-01	7.704E-01
TRAILR3	MCP2	303	-1.811E-02	7.536E-01	8.193E-01
TRAILR3	Medium TRLP (nM)	50	4.206E-02	7.718E-01	8.327E-01
TRAILR3	Ferritin	303	1.469E-02	7.989E-01	8.545E-01
TRAILR3	HDLC (mg/dL)	50	3.195E-02	8.257E-01	8.755E-01

TRAILR3	CEC	129	-1.520E-02	8.643E-01	9.075E-01
TRAILR3	MIP3-β	303	6.143E-03	9.152E-01	9.437E-01
TRAILR3	ITAC	303	-5.800E-03	9.199E-01	9.463E-01
TRAILR3	cHDLP (μM)	50	1.247E-02	9.315E-01	9.532E-01
TRAILR3	IR	119	2.967E-03	9.745E-01	9.812E-01
TRAILR3	Medium cHDLP (μM)	50	2.763E-03	9.848E-01	9.863E-01
TRAILR3	TRAILR3	303		1.000E+00	
Total cholesterol (mg/dL)	cHDLP (μM)	50	5.077E-01	1.677E-04	5.664E-04
Total cholesterol (mg/dL)	Apolipoprotein A1 (mg/dL)	50	4.963E-01	2.465E-04	7.980E-04
Total cholesterol (mg/dL)	HDLC (mg/dL)	50	4.702E-01	5.707E-04	1.761E-03
Total cholesterol (mg/dL)	HDL in the H3P size range (μM)	50	4.684E-01	6.029E-04	1.854E-03
Total cholesterol (mg/dL)	Lymphocyte count	50	4.218E-01	2.282E-03	6.318E-03
Total cholesterol (mg/dL)	Progranulin	50	-4.123E-01	2.930E-03	7.882E-03
Total cholesterol (mg/dL)	BAFF	50	-3.965E-01	4.359E-03	1.094E-02
Total cholesterol (mg/dL)	Neutrophil number	50	3.935E-01	4.698E-03	1.169E-02
Total cholesterol (mg/dL)	IFN-α protein (pg/mL)	50	-3.878E-01	5.386E-03	1.306E-02
Total cholesterol (mg/dL)	IL-2	49	-3.860E-01	6.162E-03	1.482E-02
Total cholesterol (mg/dL)	Medium cHDLP (μM)	50	3.648E-01	9.205E-03	2.091E-02
Total cholesterol (mg/dL)	MCP2	50	-3.415E-01	1.523E-02	3.246E-02
Total cholesterol (mg/dL)	IL1RII	50	3.180E-01	2.444E-02	4.986E-02
Total cholesterol (mg/dL)	Eotaxin-2	50	3.141E-01	2.633E-02	5.293E-02
Total cholesterol (mg/dL)	GlycA	50	2.994E-01	3.465E-02	6.707E-02
Total cholesterol (mg/dL)	MIP3-β	50	-2.466E-01	8.424E-02	1.422E-01
Total cholesterol (mg/dL)	B2M	49	-2.379E-01	9.976E-02	1.649E-01
Total cholesterol (mg/dL)	Medium TRLP (nM)	50	2.355E-01	9.974E-02	1.649E-01
Total cholesterol (mg/dL)	IP-10	50	-2.308E-01	1.068E-01	1.742E-01
Total cholesterol (mg/dL)	CEC	50	2.301E-01	1.079E-01	1.756E-01
Total cholesterol (mg/dL)	IFN-γ	50	-2.230E-01	1.196E-01	1.907E-01
Total cholesterol (mg/dL)	ANG2	50	-2.079E-01	1.473E-01	2.282E-01
Total cholesterol (mg/dL)	IR	34	2.310E-01	1.888E-01	2.841E-01
Total cholesterol (mg/dL)	CitH3-DNA	48	-1.927E-01	1.894E-01	2.846E-01
Total cholesterol (mg/dL)	IL-10	50	-1.379E-01	3.396E-01	4.461E-01
Total cholesterol (mg/dL)	ITAC	50	-1.231E-01	3.946E-01	5.040E-01
Total cholesterol (mg/dL)	BLC	50	-8.912E-02	5.382E-01	6.350E-01
Total cholesterol (mg/dL)	MCP1	50	-5.384E-02	7.104E-01	7.857E-01
Total cholesterol (mg/dL)	MPO-DNA	48	4.278E-02	7.728E-01	8.328E-01
Total cholesterol (mg/dL)	IgE	50	-3.330E-02	8.184E-01	8.689E-01
Total cholesterol (mg/dL)	NE-DNA	48	2.443E-02	8.691E-01	9.098E-01
Total cholesterol (mg/dL)	Ficolin 3	50	1.089E-02	9.402E-01	9.546E-01
Total cholesterol (mg/dL)	Ferritin	50	-5.668E-03	9.688E-01	9.768E-01
Progranulin	ANG2	303	4.719E-01	<E-14	<E-14
Progranulin	IL-2	253	4.918E-01	<E-14	<E-14
Progranulin	BAFF	303	4.956E-01	<E-14	<E-14
Progranulin	IL-10	254	5.378E-01	<E-14	<E-14
Progranulin	ITAC	303	5.448E-01	<E-14	<E-14
Progranulin	B2M	302	5.482E-01	<E-14	<E-14
Progranulin	MCP2	303	5.713E-01	<E-14	<E-14
Progranulin	IP-10	303	5.936E-01	<E-14	<E-14
Progranulin	IFN-α protein (pg/mL)	256	6.208E-01	<E-14	<E-14
Progranulin	MIP3-β	303	6.291E-01	<E-14	<E-14
Progranulin	IFN-γ	256	4.835E-01	<E-14	<E-14
Progranulin	Ficolin 3	303	3.686E-01	3.478E-11	2.070E-10
Progranulin	BLC	303	3.667E-01	4.454E-11	2.630E-10
Progranulin	MCP1	303	3.440E-01	7.635E-10	4.080E-09
Progranulin	Lymphocyte count	295	-3.199E-01	1.925E-08	9.260E-08
Progranulin	Neutrophil number	295	-3.155E-01	3.047E-08	1.450E-07
Progranulin	IgE	303	3.101E-01	3.537E-08	1.660E-07
Progranulin	IL1RII	303	-2.270E-01	6.701E-05	2.345E-04
Progranulin	Ferritin	303	1.983E-01	5.173E-04	1.614E-03
Progranulin	HDL in the H3P size range (μM)	50	-4.356E-01	1.568E-03	4.514E-03
Progranulin	Eotaxin-2	303	-1.556E-01	6.650E-03	1.582E-02
Progranulin	MPO-DNA	190	1.629E-01	2.469E-02	5.004E-02
Progranulin	CitH3-DNA	190	1.611E-01	2.643E-02	5.293E-02
Progranulin	NE-DNA	190	1.557E-01	3.197E-02	6.313E-02
Progranulin	Apolipoprotein A1 (mg/dL)	50	-2.833E-01	4.616E-02	8.621E-02
Progranulin	HDLC (mg/dL)	50	-2.673E-01	6.054E-02	1.079E-01
Progranulin	cHDLP (μM)	50	-2.393E-01	9.424E-02	1.572E-01

Progranulin	Medium cHDLP (μM)	50	-1.945E-01	1.760E-01	2.677E-01
Progranulin	GlycA	50	-9.944E-02	4.920E-01	5.958E-01
Progranulin	Medium TRLP (nM)	50	-9.632E-02	5.058E-01	6.074E-01
Progranulin	CEC	129	-5.719E-02	5.197E-01	6.206E-01
Progranulin	IR	119	1.759E-02	8.494E-01	8.940E-01
Progranulin	Progranulin	303		1.000E+00	
Neutrophil number	Eotaxin-2	295	2.804E-01	9.877E-07	4.250E-06
Neutrophil number	IFN-α protein (pg/mL)	251	-2.941E-01	2.128E-06	8.890E-06
Neutrophil number	IL1RII	295	2.573E-01	7.603E-06	2.980E-05
Neutrophil number	MIP3-β	295	-2.519E-01	1.195E-05	4.590E-05
Neutrophil number	IP-10	295	-2.321E-01	5.716E-05	2.017E-04
Neutrophil number	MCP2	295	-2.251E-01	9.639E-05	3.346E-04
Neutrophil number	ITAC	295	-2.249E-01	9.733E-05	3.366E-04
Neutrophil number	IL-2	248	-2.310E-01	2.440E-04	7.928E-04
Neutrophil number	B2M	294	-1.893E-01	1.108E-03	3.301E-03
Neutrophil number	BAFF	295	-1.792E-01	2.001E-03	5.666E-03
Neutrophil number	IFN-γ	251	-1.898E-01	2.538E-03	6.917E-03
Neutrophil number	Lymphocyte count	297	1.691E-01	3.472E-03	9.170E-03
Neutrophil number	CitH3-DNA	184	-1.937E-01	8.431E-03	1.962E-02
Neutrophil number	MPO-DNA	184	-1.908E-01	9.493E-03	2.150E-02
Neutrophil number	NE-DNA	184	-1.886E-01	1.037E-02	2.301E-02
Neutrophil number	GlycA	50	3.519E-01	1.220E-02	2.652E-02
Neutrophil number	ANG2	295	-1.428E-01	1.410E-02	3.043E-02
Neutrophil number	Ficolin 3	295	-1.320E-01	2.337E-02	4.825E-02
Neutrophil number	IgE	295	-1.316E-01	2.384E-02	4.890E-02
Neutrophil number	IR	121	1.623E-01	7.538E-02	1.293E-01
Neutrophil number	Medium TRLP (nM)	50	2.169E-01	1.302E-01	2.031E-01
Neutrophil number	CEC	128	1.076E-01	2.266E-01	3.285E-01
Neutrophil number	HDL in the H3P size range (μM)	50	1.689E-01	2.408E-01	3.456E-01
Neutrophil number	Apolipoprotein A1 (mg/dL)	50	1.591E-01	2.698E-01	3.784E-01
Neutrophil number	cHDLP (μM)	50	1.586E-01	2.712E-01	3.792E-01
Neutrophil number	HDLC (mg/dL)	50	1.330E-01	3.572E-01	4.639E-01
Neutrophil number	BLC	295	-4.842E-02	4.074E-01	5.158E-01
Neutrophil number	MCP1	295	-4.377E-02	4.539E-01	5.607E-01
Neutrophil number	Ferritin	295	-3.650E-02	5.323E-01	6.323E-01
Neutrophil number	IL-10	249	3.693E-02	5.619E-01	6.567E-01
Neutrophil number	Medium cHDLP (μM)	50	1.581E-02	9.132E-01	9.428E-01
MCP2	IFN-γ	256	4.875E-01	<E-14	<E-14
MCP2	IL-2	253	5.008E-01	<E-14	<E-14
MCP2	ANG2	303	5.069E-01	<E-14	<E-14
MCP2	IL-10	254	5.161E-01	<E-14	<E-14
MCP2	MCP1	303	5.330E-01	<E-14	<E-14
MCP2	BAFF	303	5.652E-01	<E-14	<E-14
MCP2	B2M	302	5.932E-01	<E-14	<E-14
MCP2	ITAC	303	6.108E-01	<E-14	<E-14
MCP2	IFN-α protein (pg/mL)	256	6.514E-01	<E-14	<E-14
MCP2	MIP3-β	303	6.585E-01	<E-14	<E-14
MCP2	IP-10	303	7.476E-01	<E-14	<E-14
MCP2	Ficolin 3	303	3.905E-01	1.770E-12	1.140E-11
MCP2	IgE	303	3.747E-01	1.559E-11	9.660E-11
MCP2	BLC	303	3.735E-01	1.827E-11	1.120E-10
MCP2	Lymphocyte count	295	-3.601E-01	1.847E-10	1.060E-09
MCP2	Ferritin	303	2.150E-01	1.628E-04	5.518E-04
MCP2	HDLC (mg/dL)	50	-4.950E-01	2.581E-04	8.322E-04
MCP2	CitH3-DNA	190	2.550E-01	3.841E-04	1.220E-03
MCP2	Apolipoprotein A1 (mg/dL)	50	-4.482E-01	1.097E-03	3.279E-03
MCP2	cHDLP (μM)	50	-4.361E-01	1.546E-03	4.481E-03
MCP2	IL1RII	303	-1.564E-01	6.383E-03	1.522E-02
MCP2	Eotaxin-2	303	-1.485E-01	9.617E-03	2.168E-02
MCP2	NE-DNA	190	1.873E-01	9.677E-03	2.171E-02
MCP2	HDL in the H3P size range (μM)	50	-2.729E-01	5.522E-02	1.003E-01
MCP2	CEC	129	-1.516E-01	8.634E-02	1.455E-01
MCP2	Medium cHDLP (μM)	50	-2.309E-01	1.067E-01	1.742E-01
MCP2	GlycA	50	-1.175E-01	4.163E-01	5.240E-01
MCP2	IR	119	5.233E-02	5.719E-01	6.654E-01
MCP2	Medium TRLP (nM)	50	-6.501E-02	6.538E-01	7.397E-01
MCP1	IP-10	303	4.637E-01	<E-14	<E-14

MCP1	B2M	302	3.934E-01	1.289E-12	8.600E-12
MCP1	IL-10	254	4.245E-01	1.556E-12	1.010E-11
MCP1	MIP3-β	303	3.534E-01	2.429E-10	1.360E-09
MCP1	IL-2	253	3.792E-01	4.492E-10	2.460E-09
MCP1	IFN-α protein (pg/mL)	256	3.726E-01	7.481E-10	4.030E-09
MCP1	IFN-γ	256	3.664E-01	1.489E-09	7.730E-09
MCP1	BAFF	303	3.243E-01	7.541E-09	3.710E-08
MCP1	ANG2	303	3.025E-01	7.907E-08	3.660E-07
MCP1	ITAC	303	2.651E-01	2.871E-06	1.180E-05
MCP1	BLC	303	2.427E-01	1.938E-05	7.220E-05
MCP1	Ficolin 3	303	2.332E-01	4.154E-05	1.490E-04
MCP1	Lymphocyte count	295	-1.536E-01	8.230E-03	1.920E-02
MCP1	Ferritin	303	1.501E-01	8.886E-03	2.040E-02
MCP1	HDLC (mg/dL)	50	-3.205E-01	2.327E-02	4.816E-02
MCP1	Medium cHDLP (μM)	50	-3.150E-01	2.589E-02	5.220E-02
MCP1	Eotaxin-2	303	1.140E-01	4.734E-02	8.822E-02
MCP1	Apolipoprotein A1 (mg/dL)	50	-2.803E-01	4.866E-02	9.030E-02
MCP1	CEC	129	-1.645E-01	6.242E-02	1.101E-01
MCP1	IgE	303	1.046E-01	6.906E-02	1.199E-01
MCP1	cHDLP (μM)	50	-2.487E-01	8.159E-02	1.388E-01
MCP1	HDL in the H3P size range (μM)	50	-2.280E-01	1.113E-01	1.791E-01
MCP1	IL1RII	303	-6.735E-02	2.425E-01	3.474E-01
MCP1	Medium TRLP (nM)	50	1.613E-01	2.630E-01	3.713E-01
MCP1	GlycA	50	9.456E-02	5.136E-01	6.151E-01
MCP1	IR	119	5.596E-02	5.456E-01	6.417E-01
MCP1	NE-DNA	190	-3.739E-02	6.085E-01	7.023E-01
MCP1	CitH3-DNA	190	-2.308E-02	7.519E-01	8.184E-01
MCP1	MCP1	303		1.000E+00	
Medium TRLP (nM)	IgE	50	-3.493E-01	1.291E-02	2.801E-02
Medium TRLP (nM)	IL-2	49	-3.520E-01	1.314E-02	2.842E-02
Medium TRLP (nM)	CitH3-DNA	48	-2.429E-01	9.616E-02	1.601E-01
Medium TRLP (nM)	IR	34	-2.714E-01	1.205E-01	1.915E-01
Medium TRLP (nM)	Eotaxin-2	50	2.089E-01	1.455E-01	2.257E-01
Medium TRLP (nM)	Medium cHDLP (μM)	50	-1.813E-01	2.078E-01	3.079E-01
Medium TRLP (nM)	ANG2	50	-1.566E-01	2.774E-01	3.840E-01
Medium TRLP (nM)	NE-DNA	48	-1.486E-01	3.133E-01	4.213E-01
Medium TRLP (nM)	GlycA	50	1.397E-01	3.333E-01	4.402E-01
Medium TRLP (nM)	Lymphocyte count	50	1.297E-01	3.692E-01	4.788E-01
Medium TRLP (nM)	Ficolin 3	50	1.288E-01	3.728E-01	4.826E-01
Medium TRLP (nM)	cHDLP (μM)	50	1.224E-01	3.972E-01	5.063E-01
Medium TRLP (nM)	MIP3-β	50	1.221E-01	3.983E-01	5.066E-01
Medium TRLP (nM)	ITAC	50	1.111E-01	4.424E-01	5.489E-01
Medium TRLP (nM)	B2M	49	9.137E-02	5.324E-01	6.323E-01
Medium TRLP (nM)	IP-10	50	-8.998E-02	5.343E-01	6.331E-01
Medium TRLP (nM)	IL1RII	50	8.504E-02	5.571E-01	6.526E-01
Medium TRLP (nM)	Ferritin	50	7.971E-02	5.821E-01	6.750E-01
Medium TRLP (nM)	IFN-α protein (pg/mL)	50	6.873E-02	6.353E-01	7.242E-01
Medium TRLP (nM)	IFN-γ	50	-6.767E-02	6.406E-01	7.272E-01
Medium TRLP (nM)	IL-10	50	6.156E-02	6.711E-01	7.553E-01
Medium TRLP (nM)	BAFF	50	-6.133E-02	6.722E-01	7.556E-01
Medium TRLP (nM)	BLC	50	-2.805E-02	8.467E-01	8.923E-01
Medium TRLP (nM)	HDL in the H3P size range (μM)	50	-2.119E-02	8.839E-01	9.198E-01
Medium TRLP (nM)	CEC	50	1.369E-02	9.248E-01	9.502E-01
Medium TRLP (nM)	Apolipoprotein A1 (mg/dL)	50	1.175E-02	9.354E-01	9.532E-01
Medium TRLP (nM)	HDLC (mg/dL)	50	-9.902E-03	9.456E-01	9.578E-01
Medium cHDLP (μM)	HDL in the H3P size range (μM)	50	8.236E-01	2.078E-13	1.500E-12
Medium cHDLP (μM)	Apolipoprotein A1 (mg/dL)	50	6.058E-01	3.142E-06	1.280E-05
Medium cHDLP (μM)	HDLC (mg/dL)	50	6.015E-01	3.844E-06	1.550E-05
Medium cHDLP (μM)	cHDLP (μM)	50	5.537E-01	3.028E-05	1.100E-04
Medium cHDLP (μM)	CEC	50	4.757E-01	4.799E-04	1.508E-03
Medium cHDLP (μM)	BAFF	50	-4.589E-01	8.027E-04	2.433E-03
Medium cHDLP (μM)	IFN-α protein (pg/mL)	50	-3.430E-01	1.476E-02	3.162E-02
Medium cHDLP (μM)	MIP3-β	50	-2.951E-01	3.745E-02	7.166E-02
Medium cHDLP (μM)	B2M	49	-2.710E-01	5.967E-02	1.068E-01
Medium cHDLP (μM)	IP-10	50	-2.498E-01	8.018E-02	1.370E-01
Medium cHDLP (μM)	Ficolin 3	50	2.200E-01	1.248E-01	1.961E-01
Medium cHDLP (μM)	ANG2	50	-2.034E-01	1.566E-01	2.412E-01

Medium cHDLP (μM)	GlycA	50	1.780E-01	2.163E-01	3.168E-01
Medium cHDLP (μM)	IL-10	50	-1.757E-01	2.223E-01	3.240E-01
Medium cHDLP (μM)	IL1RII	50	1.757E-01	2.224E-01	3.240E-01
Medium cHDLP (μM)	BLC	50	-1.565E-01	2.777E-01	3.840E-01
Medium cHDLP (μM)	IR	34	1.797E-01	3.091E-01	4.165E-01
Medium cHDLP (μM)	IL-2	49	-1.454E-01	3.189E-01	4.270E-01
Medium cHDLP (μM)	IgE	50	1.331E-01	3.567E-01	4.639E-01
Medium cHDLP (μM)	CitH3-DNA	48	-1.284E-01	3.843E-01	4.939E-01
Medium cHDLP (μM)	Lymphocyte count	50	1.186E-01	4.119E-01	5.193E-01
Medium cHDLP (μM)	ITAC	50	-6.896E-02	6.342E-01	7.242E-01
Medium cHDLP (μM)	Ferritin	50	-6.845E-02	6.367E-01	7.242E-01
Medium cHDLP (μM)	NE-DNA	48	-5.431E-02	7.139E-01	7.880E-01
Medium cHDLP (μM)	IFN-γ	50	-4.443E-02	7.593E-01	8.224E-01
Medium cHDLP (μM)	Eotaxin-2	50	1.196E-02	9.343E-01	9.532E-01
Medium cHDLP (μM)	Medium cHDLP (μM)	50	1.000E+00		
MIP3-β	ANG2	303	5.214E-01	<E-14	<E-14
MIP3-β	IL-10	254	5.853E-01	<E-14	<E-14
MIP3-β	BAFF	303	5.928E-01	<E-14	<E-14
MIP3-β	IFN-α protein (pg/mL)	256	6.010E-01	<E-14	<E-14
MIP3-β	B2M	302	6.184E-01	<E-14	<E-14
MIP3-β	ITAC	303	6.191E-01	<E-14	<E-14
MIP3-β	IP-10	303	6.658E-01	<E-14	<E-14
MIP3-β	IL-2	253	4.819E-01	<E-14	<E-14
MIP3-β	IFN-γ	256	4.451E-01	7.327E-14	5.440E-13
MIP3-β	BLC	303	4.016E-01	3.568E-13	2.520E-12
MIP3-β	Ficolin 3	303	3.552E-01	1.946E-10	1.100E-09
MIP3-β	Lymphocyte count	295	-3.136E-01	3.746E-08	1.750E-07
MIP3-β	IgE	303	2.971E-01	1.363E-07	6.140E-07
MIP3-β	IL1RII	303	-2.385E-01	2.723E-05	9.940E-05
MIP3-β	HDLC (mg/dL)	50	-4.251E-01	2.091E-03	5.846E-03
MIP3-β	cHDLP (μM)	50	-4.119E-01	2.956E-03	7.928E-03
MIP3-β	Ferritin	303	1.678E-01	3.393E-03	8.989E-03
MIP3-β	HDL in the H3P size range (μM)	50	-4.049E-01	3.534E-03	9.214E-03
MIP3-β	Apolipoprotein A1 (mg/dL)	50	-3.964E-01	4.376E-03	1.095E-02
MIP3-β	NE-DNA	190	1.427E-01	4.953E-02	9.151E-02
MIP3-β	CEC	129	-1.706E-01	5.322E-02	9.728E-02
MIP3-β	CitH3-DNA	190	1.265E-01	8.194E-02	1.391E-01
MIP3-β	Eotaxin-2	303	-6.681E-02	2.463E-01	3.505E-01
MIP3-β	GlycA	50	-8.395E-02	5.622E-01	6.567E-01
MIP3-β	IR	119	1.557E-02	8.665E-01	9.087E-01
Lymphocyte count	IFN-α protein (pg/mL)	251	-4.754E-01	<E-14	1.090E-14
Lymphocyte count	BLC	295	-4.307E-01	<E-14	7.430E-14
Lymphocyte count	IL-10	249	-4.603E-01	1.821E-14	1.400E-13
Lymphocyte count	BAFF	295	-4.210E-01	4.219E-14	3.160E-13
Lymphocyte count	IP-10	295	-3.986E-01	1.119E-12	7.580E-12
Lymphocyte count	B2M	294	-3.443E-01	1.327E-09	6.920E-09
Lymphocyte count	ITAC	295	-3.145E-01	3.397E-08	1.610E-07
Lymphocyte count	Ficolin 3	295	-2.691E-01	2.740E-06	1.130E-05
Lymphocyte count	IFN-γ	251	-2.796E-01	6.865E-06	2.710E-05
Lymphocyte count	IL-2	248	-2.809E-01	7.062E-06	2.780E-05
Lymphocyte count	ANG2	295	-2.470E-01	1.781E-05	6.730E-05
Lymphocyte count	IL1RII	295	1.855E-01	1.373E-03	4.050E-03
Lymphocyte count	IgE	295	-1.472E-01	1.136E-02	2.508E-02
Lymphocyte count	cHDLP (μM)	50	2.227E-01	1.200E-01	1.910E-01
Lymphocyte count	HDL in the H3P size range (μM)	50	1.872E-01	1.929E-01	2.888E-01
Lymphocyte count	GlycA	50	-1.777E-01	2.169E-01	3.171E-01
Lymphocyte count	HDLC (mg/dL)	50	1.731E-01	2.292E-01	3.317E-01
Lymphocyte count	Ferritin	295	-6.942E-02	2.345E-01	3.382E-01
Lymphocyte count	Apolipoprotein A1 (mg/dL)	50	1.691E-01	2.405E-01	3.456E-01
Lymphocyte count	IR	121	-1.066E-01	2.444E-01	3.496E-01
Lymphocyte count	Eotaxin-2	295	6.683E-02	2.525E-01	3.582E-01
Lymphocyte count	CitH3-DNA	184	-4.686E-02	5.276E-01	6.283E-01
Lymphocyte count	CEC	128	2.956E-02	7.405E-01	8.092E-01
Lymphocyte count	NE-DNA	184	-1.583E-02	8.311E-01	8.802E-01
Lymphocyte count	Lymphocyte count	298	1.000E+00		
IL-2	B2M	252	4.884E-01	<E-14	<E-14

IL-2	IL-10	253	5.185E-01	<E-14	<E-14
IL-2	IP-10	253	5.577E-01	<E-14	<E-14
IL-2	IFN- γ	253	5.654E-01	<E-14	<E-14
IL-2	ITAC	253	4.813E-01	<E-14	<E-14
IL-2	IFN- α protein (pg/mL)	253	4.314E-01	6.892E-13	4.750E-12
IL-2	BAFF	253	4.199E-01	3.149E-12	1.990E-11
IL-2	BLC	253	3.806E-01	3.810E-10	2.100E-09
IL-2	ANG2	253	3.604E-01	3.561E-09	1.810E-08
IL-2	IL1RII	253	-2.335E-01	1.786E-04	5.961E-04
IL-2	Eotaxin-2	253	-1.965E-01	1.685E-03	4.804E-03
IL-2	Ficolin 3	253	1.805E-01	3.979E-03	1.017E-02
IL-2	IgE	253	1.672E-01	7.706E-03	1.813E-02
IL-2	CitH3-DNA	182	1.868E-01	1.155E-02	2.544E-02
IL-2	IR	105	2.441E-01	1.209E-02	2.643E-02
IL-2	cHDLP (μ M)	49	-3.035E-01	3.404E-02	6.616E-02
IL-2	CEC	124	-1.827E-01	4.228E-02	7.984E-02
IL-2	HDL in the H3P size range (μ M)	49	-2.791E-01	5.211E-02	9.547E-02
IL-2	Apolipoprotein A1 (mg/dL)	49	-2.760E-01	5.495E-02	1.002E-01
IL-2	NE-DNA	182	1.396E-01	6.018E-02	1.075E-01
IL-2	HDLC (mg/dL)	49	-2.685E-01	6.208E-02	1.098E-01
IL-2	GlycA	49	-1.351E-01	3.547E-01	4.620E-01
IL-2	Ferritin	253	9.104E-03	8.854E-01	9.198E-01
IL1RII	IFN- α protein (pg/mL)	256	-3.571E-01	4.077E-09	2.050E-08
IL1RII	Eotaxin-2	303	2.414E-01	2.152E-05	7.950E-05
IL1RII	IP-10	303	-2.352E-01	3.535E-05	1.279E-04
IL1RII	IFN- γ	256	-1.961E-01	1.613E-03	4.631E-03
IL1RII	ITAC	303	-1.767E-01	2.019E-03	5.680E-03
IL1RII	CEC	129	2.448E-01	5.176E-03	1.263E-02
IL1RII	BAFF	303	-1.585E-01	5.687E-03	1.376E-02
IL1RII	HDL in the H3P size range (μ M)	50	3.764E-01	7.052E-03	1.673E-02
IL1RII	NE-DNA	190	-1.921E-01	7.920E-03	1.858E-02
IL1RII	CitH3-DNA	190	-1.823E-01	1.183E-02	2.598E-02
IL1RII	ANG2	303	-1.443E-01	1.192E-02	2.611E-02
IL1RII	Apolipoprotein A1 (mg/dL)	50	3.022E-01	3.293E-02	6.444E-02
IL1RII	cHDLP (μ M)	50	2.955E-01	3.724E-02	7.141E-02
IL1RII	IR	119	1.708E-01	6.334E-02	1.115E-01
IL1RII	HDLC (mg/dL)	50	2.496E-01	8.050E-02	1.372E-01
IL1RII	BLC	303	-9.741E-02	9.054E-02	1.518E-01
IL1RII	B2M	302	-8.861E-02	1.244E-01	1.960E-01
IL1RII	Ficolin 3	303	-7.378E-02	2.003E-01	2.984E-01
IL1RII	GlycA	50	1.562E-01	2.786E-01	3.844E-01
IL1RII	IgE	303	-5.886E-02	3.071E-01	4.158E-01
IL1RII	Ferritin	303	4.362E-03	9.397E-01	9.546E-01
ITAC	IgE	303	4.832E-01	<E-14	<E-14
ITAC	BAFF	303	5.209E-01	<E-14	<E-14
ITAC	ANG2	303	5.710E-01	<E-14	<E-14
ITAC	B2M	302	5.804E-01	<E-14	<E-14
ITAC	IFN- α protein (pg/mL)	256	5.922E-01	<E-14	<E-14
ITAC	IP-10	303	7.055E-01	<E-14	<E-14
ITAC	IFN- γ	256	4.568E-01	1.332E-14	1.030E-13
ITAC	BLC	303	4.116E-01	8.127E-14	5.980E-13
ITAC	Ficolin 3	303	3.447E-01	7.015E-10	3.800E-09
ITAC	CitH3-DNA	190	2.747E-01	1.255E-04	4.304E-04
ITAC	Eotaxin-2	303	-1.670E-01	3.542E-03	9.214E-03
ITAC	NE-DNA	190	1.980E-01	6.187E-03	1.484E-02
ITAC	CEC	129	-1.955E-01	2.641E-02	5.293E-02
ITAC	HDLC (mg/dL)	50	-2.682E-01	5.966E-02	1.068E-01
ITAC	Apolipoprotein A1 (mg/dL)	50	-2.293E-01	1.093E-01	1.765E-01
ITAC	cHDLP (μ M)	50	-2.197E-01	1.253E-01	1.965E-01
ITAC	Ferritin	303	7.916E-02	1.693E-01	2.590E-01
ITAC	HDL in the H3P size range (μ M)	50	-1.401E-01	3.317E-01	4.387E-01
ITAC	GlycA	50	8.993E-02	5.346E-01	6.331E-01
ITAC	IR	119	3.070E-02	7.403E-01	8.092E-01
ITAC	ITAC	303		1.000E+00	
IFN- γ	IP-10	256	5.626E-01	<E-14	<E-14
IFN- γ	IFN- α protein (pg/mL)	256	4.224E-01	1.673E-12	1.080E-11
IFN- γ	B2M	255	4.020E-01	2.538E-11	1.530E-10

IFN- γ	BAFF	256	3.274E-01	8.275E-08	3.810E-07
IFN- γ	BLC	256	2.991E-01	1.093E-06	4.660E-06
IFN- γ	ANG2	256	2.518E-01	4.600E-05	1.637E-04
IFN- γ	Eotaxin-2	256	-2.323E-01	1.763E-04	5.906E-04
IFN- γ	IgE	256	2.142E-01	5.599E-04	1.734E-03
IFN- γ	Ficolin 3	256	1.891E-01	2.377E-03	6.538E-03
IFN- γ	CitH3-DNA	185	1.898E-01	9.682E-03	2.171E-02
IFN- γ	NE-DNA	185	1.686E-01	2.179E-02	4.555E-02
IFN- γ	cHDLP (μ M)	50	-2.872E-01	4.318E-02	8.118E-02
IFN- γ	Apolipoprotein A1 (mg/dL)	50	-1.545E-01	2.840E-01	3.900E-01
IFN- γ	Ferritin	256	6.190E-02	3.239E-01	4.310E-01
IFN- γ	IR	106	8.302E-02	3.975E-01	5.063E-01
IFN- γ	HDLC (mg/dL)	50	-1.218E-01	3.994E-01	5.072E-01
IFN- γ	HDL in the H3P size range (μ M)	50	-8.834E-02	5.418E-01	6.382E-01
IFN- γ	CEC	127	-3.366E-02	7.072E-01	7.836E-01
IFN- γ	GlycA	50	-3.757E-02	7.956E-01	8.520E-01
IP-10	BLC	303	4.661E-01	<E-14	<E-14
IP-10	ANG2	303	5.811E-01	<E-14	<E-14
IP-10	BAFF	303	5.878E-01	<E-14	<E-14
IP-10	B2M	302	6.266E-01	<E-14	<E-14
IP-10	IFN- α protein (pg/mL)	256	6.268E-01	<E-14	<E-14
IP-10	IgE	303	3.997E-01	4.712E-13	3.270E-12
IP-10	Ficolin 3	303	2.824E-01	5.792E-07	2.520E-06
IP-10	cHDLP (μ M)	50	-5.577E-01	2.583E-05	9.470E-05
IP-10	Apolipoprotein A1 (mg/dL)	50	-5.112E-01	1.482E-04	5.065E-04
IP-10	HDLC (mg/dL)	50	-4.995E-01	2.218E-04	7.235E-04
IP-10	Eotaxin-2	303	-1.738E-01	2.392E-03	6.558E-03
IP-10	Ferritin	303	1.613E-01	4.880E-03	1.197E-02
IP-10	NE-DNA	190	1.749E-01	1.582E-02	3.355E-02
IP-10	CEC	129	-1.983E-01	2.430E-02	4.969E-02
IP-10	CitH3-DNA	190	1.548E-01	3.293E-02	6.444E-02
IP-10	HDL in the H3P size range (μ M)	50	-2.960E-01	3.688E-02	7.088E-02
IP-10	IR	119	1.093E-01	2.368E-01	3.409E-01
IP-10	GlycA	50	1.071E-01	4.589E-01	5.661E-01
IP-10	IP-10	303		1.000E+00	
IgE	ANG2	303	4.074E-01	1.519E-13	1.110E-12
IgE	B2M	302	3.694E-01	3.363E-11	2.010E-10
IgE	BAFF	303	2.567E-01	6.027E-06	2.390E-05
IgE	Ficolin 3	303	2.448E-01	1.631E-05	6.200E-05
IgE	NE-DNA	190	2.301E-01	1.402E-03	4.105E-03
IgE	Eotaxin-2	303	-1.640E-01	4.213E-03	1.064E-02
IgE	CitH3-DNA	190	2.037E-01	4.824E-03	1.190E-02
IgE	BLC	303	1.404E-01	1.447E-02	3.107E-02
IgE	CEC	129	-2.038E-01	2.053E-02	4.311E-02
IgE	Ferritin	303	6.664E-02	2.475E-01	3.517E-01
IgE	IR	119	4.844E-02	6.009E-01	6.945E-01
IgE	cHDLP (μ M)	50	-7.381E-02	6.105E-01	7.036E-01
IgE	GlycA	50	5.030E-02	7.287E-01	8.023E-01
IgE	HDL in the H3P size range (μ M)	50	-1.629E-02	9.106E-01	9.424E-01
IgE	Apolipoprotein A1 (mg/dL)	50	-1.282E-02	9.296E-01	9.528E-01
IgE	HDLC (mg/dL)	50	4.455E-03	9.755E-01	9.812E-01
IgE	IgE	303		1.000E+00	
IR	Ficolin 3	119	1.697E-01	6.506E-02	1.141E-01
IR	CEC	79	-2.083E-01	6.547E-02	1.146E-01
IR	Eotaxin-2	119	-1.478E-01	1.086E-01	1.761E-01
IR	GlycA	34	2.727E-01	1.187E-01	1.900E-01
IR	HDL in the H3P size range (μ M)	34	2.242E-01	2.024E-01	3.009E-01
IR	BLC	119	9.916E-02	2.833E-01	3.896E-01
IR	Apolipoprotein A1 (mg/dL)	34	1.643E-01	3.531E-01	4.607E-01
IR	Ferritin	119	-7.918E-02	3.920E-01	5.030E-01
IR	CitH3-DNA	76	9.392E-02	4.196E-01	5.252E-01
IR	BAFF	119	-6.795E-02	4.628E-01	5.700E-01
IR	cHDLP (μ M)	34	1.246E-01	4.828E-01	5.904E-01
IR	NE-DNA	76	5.870E-02	6.145E-01	7.064E-01
IR	ANG2	119	-3.768E-02	6.841E-01	7.640E-01
IR	B2M	118	3.278E-02	7.245E-01	7.987E-01

IR	HDLC (mg/dL)	34	4.339E-02	8.075E-01	8.595E-01
HDLC (mg/dL)	Apolipoprotein A1 (mg/dL)	50	9.651E-01	<E-14	<E-14
HDLC (mg/dL)	cHDLP (μM)	50	8.071E-01	1.456E-12	9.570E-12
HDLC (mg/dL)	HDL in the H3P size range (μM)	50	5.788E-01	1.068E-05	4.140E-05
HDLC (mg/dL)	CEC	50	5.073E-01	1.698E-04	5.709E-04
HDLC (mg/dL)	ANG2	50	-4.289E-01	1.883E-03	5.352E-03
HDLC (mg/dL)	BAFF	50	-4.156E-01	2.690E-03	7.284E-03
HDLC (mg/dL)	Eotaxin-2	50	3.156E-01	2.559E-02	5.172E-02
HDLC (mg/dL)	Ferritin	50	-2.910E-01	4.032E-02	7.647E-02
HDLC (mg/dL)	CitH3-DNA	48	-2.856E-01	4.907E-02	9.086E-02
HDLC (mg/dL)	BLC	50	-2.325E-01	1.042E-01	1.715E-01
HDLC (mg/dL)	B2M	49	-1.470E-01	3.136E-01	4.213E-01
HDLC (mg/dL)	GlycA	50	-8.003E-02	5.806E-01	6.746E-01
HDLC (mg/dL)	Ficolin 3	50	-5.727E-02	6.928E-01	7.707E-01
HDL in the H3P size range (μM)	Apolipoprotein A1 (mg/dL)	50	6.216E-01	1.450E-06	6.150E-06
HDL in the H3P size range (μM)	cHDLP (μM)	50	5.397E-01	5.240E-05	1.857E-04
HDL in the H3P size range (μM)	BAFF	50	-4.888E-01	3.158E-04	1.011E-03
HDL in the H3P size range (μM)	CEC	50	4.233E-01	2.193E-03	6.111E-03
HDL in the H3P size range (μM)	ANG2	50	-2.718E-01	5.618E-02	1.016E-01
HDL in the H3P size range (μM)	GlycA	50	2.600E-01	6.825E-02	1.190E-01
HDL in the H3P size range (μM)	BLC	50	-2.053E-01	1.527E-01	2.361E-01
HDL in the H3P size range (μM)	B2M	49	-1.899E-01	1.912E-01	2.868E-01
HDL in the H3P size range (μM)	Eotaxin-2	50	1.593E-01	2.690E-01	3.779E-01
HDL in the H3P size range (μM)	CitH3-DNA	48	-1.570E-01	2.865E-01	3.928E-01
HDL in the H3P size range (μM)	Ficolin 3	50	1.003E-01	4.882E-01	5.924E-01
HDL in the H3P size range (μM)	Ferritin	50	-1.525E-02	9.163E-01	9.437E-01
HDL in the H3P size range (μM)	HDL in the H3P size range (μM)	50		1.000E+00	
Ficolin 3	B2M	302	3.544E-01	2.292E-10	1.290E-09
Ficolin 3	Ferritin	303	3.304E-01	3.770E-09	1.910E-08
Ficolin 3	BAFF	303	2.844E-01	4.781E-07	2.090E-06
Ficolin 3	ANG2	303	2.534E-01	7.975E-06	3.110E-05
Ficolin 3	BLC	303	2.026E-01	3.875E-04	1.226E-03
Ficolin 3	Eotaxin-2	303	-7.217E-02	2.103E-01	3.101E-01
Ficolin 3	CitH3-DNA	190	7.733E-02	2.889E-01	3.949E-01
Ficolin 3	cHDLP (μM)	50	8.726E-02	5.468E-01	6.423E-01
Ficolin 3	CEC	129	-1.722E-02	8.464E-01	8.923E-01
Ficolin 3	Apolipoprotein A1 (mg/dL)	50	9.864E-04	9.946E-01	9.946E-01
Ficolin 3	Ficolin 3	303		1.000E+00	
Ferritin	B2M	302	2.612E-01	4.226E-06	1.700E-05
Ferritin	ANG2	303	1.724E-01	2.601E-03	7.064E-03
Ferritin	Apolipoprotein A1 (mg/dL)	50	-3.016E-01	3.330E-02	6.486E-02
Ferritin	cHDLP (μM)	50	-2.897E-01	4.128E-02	7.811E-02
Ferritin	BAFF	303	1.160E-01	4.356E-02	8.171E-02
Ferritin	CitH3-DNA	190	-2.981E-02	6.831E-01	7.640E-01
Ferritin	BLC	303	2.369E-02	6.813E-01	7.640E-01
Ferritin	Eotaxin-2	303	1.957E-02	7.344E-01	8.055E-01
Ferritin	CEC	129	1.675E-02	8.505E-01	8.942E-01
Eotaxin-2	CitH3-DNA	190	-2.406E-01	8.283E-04	2.502E-03
Eotaxin-2	Apolipoprotein A1 (mg/dL)	50	3.136E-01	2.656E-02	5.305E-02
Eotaxin-2	cHDLP (μM)	50	2.782E-01	5.044E-02	9.281E-02
Eotaxin-2	CEC	129	1.650E-01	6.171E-02	1.096E-01
Eotaxin-2	ANG2	303	-9.977E-02	8.295E-02	1.406E-01
Eotaxin-2	BAFF	303	-8.212E-02	1.539E-01	2.375E-01
Eotaxin-2	B2M	302	4.808E-02	4.051E-01	5.137E-01
Eotaxin-2	BLC	303	-3.804E-02	5.095E-01	6.110E-01
Eotaxin-2	Eotaxin-2	303		1.000E+00	
cHDLP (μM)	Apolipoprotein A1 (mg/dL)	50	8.885E-01	<E-14	<E-14
cHDLP (μM)	BAFF	50	-3.982E-01	4.183E-03	1.059E-02
cHDLP (μM)	CEC	50	3.833E-01	6.002E-03	1.448E-02
cHDLP (μM)	ANG2	50	-3.270E-01	2.046E-02	4.307E-02
cHDLP (μM)	B2M	49	-3.059E-01	3.253E-02	6.394E-02
cHDLP (μM)	BLC	50	-2.377E-01	9.651E-02	1.604E-01
cHDLP (μM)	cHDLP (μM)	50		1.000E+00	
B2M	ANG2	302	5.034E-01	<E-14	<E-14
B2M	BAFF	302	5.400E-01	<E-14	<E-14
B2M	BLC	302	3.458E-01	6.604E-10	3.600E-09

B2M	Apolipoprotein A1 (mg/dL)	49	-1.627E-01	2.640E-01	3.720E-01
B2M	B2M	302		1.000E+00	
BLC	ANG2	303	3.772E-01	1.106E-11	6.900E-11
BLC	BAFF	303	3.552E-01	1.946E-10	1.100E-09
BLC	Apolipoprotein A1 (mg/dL)	50	-2.438E-01	8.803E-02	1.480E-01
BAFF	ANG2	303	5.373E-01	<E-14	<E-14
BAFF	Apolipoprotein A1 (mg/dL)	50	-4.085E-01	3.232E-03	8.641E-03
BAFF	BAFF	303		1.000E+00	
Apolipoprotein A1 (mg/dL)	ANG2	50	-3.968E-01	4.335E-03	1.091E-02
ANG2	ANG2	303		1.000E+00	

7.3.2 Cytokines associated with vascular dysfunction are modulated by anifrolumab

[0126] Type I IFN signalling and NET formation directly impact the vasculature and were upregulated in SLE. Serum TNF- α was elevated in IFNGS test-high patients compared with IFNGS test-low patients ($p < 0.001$; **FIG. 5A**). The median TNF- α concentration in IFNGS test-high patients was above the range of healthy donors, but not in IFNGS test-low patients. TNF- α , 21-IFNGS, and IFN- α protein significantly correlated in SLE (**FIG. 3, Table 7-2**). IFNGS test-high patients had elevated IL-10 compared with those who were IFNGS test-low ($p = 4.4E-10$; **FIG. 5B**). Similar to TNF- α , serum IL-10 levels correlated with 21-IFNGS ($R = 0.506$, $p < E-14$) and serum IFN- α protein levels ($R = 0.549$, $p < E-14$; **FIG. 3, Table 7-2**). TNF- α and IL-10 levels were correlated ($R = 0.732$, $p < E-14$; **Table 7-2**). Together, these results demonstrate an association between TNF- α , IL-10, and type I IFN signalling, three putative key mediators of vascular dysfunction in SLE.

[0127] TNF- α and IL-10 significantly decreased in IFNGS test-high patients after anifrolumab compared with placebo at various timepoints (**FIG. 5C-D**). In IFNGS test-high patients, but not in IFNGS test-low patients, IL-10 levels decreased with anifrolumab compared with placebo at days 169 ($p = 0.037$) and 365 ($p = 0.016$). Overall, anifrolumab significantly decreased TNF- α and IL-10 levels.

7.3.3 Inhibition of type I IFN signalling modulates cardiometabolic disease markers

[0128] Given that NETs can oxidize HDL and impact CEC, the impact of NET inhibition with anifrolumab on these parameters was assessed. Baseline CEC values were significantly reduced in SLE compared with healthy donors in both IFNGS test-low and test-high patients, suggesting proatherogenic dysregulation of HDL function (**FIG. 6A**). While multiple proinflammatory and proatherogenic proteins associated with the type I IFN pathway (**Table 7-1**), no association between CEC and IFNGS test status was found, serum IFN- α , or 21-IFNGS in this cohort (**FIG. 3, Table 7-2**). In contrast, a significant negative correlation between CEC and circulating NET complex levels was observed (**FIG. 6B**) consistent with aberrant HDL function resulting from neutrophil-mediated oxidation.

[0129] To investigate whether anifrolumab could improve impaired (≥ 2 standard deviations [SD] below healthy donor mean) CEC, CEC levels of those patients were measured before and after treatment (**FIG. 7**). In IFNGS test-high patients receiving anifrolumab, and not in the IFNGS test-low or placebo groups, CEC increased significantly (17.3%) at day 365 compared with baseline ($p < 0.001$; **FIG. 6C**). This effect was more pronounced in patients with highest CEC impairments at baseline (**FIG. 8**). CEC was not altered by corticosteroid tapering alone (**FIG. 9**).

[0130] Lipoprotein levels were quantified (including particle count and size) by NMR in IFNGS test–high SLE. HDL cholesterol (HDL-C), HDL in the H3P size range, HDL particle count (cHDLP), medium cHDLP, apolipoprotein A-1, and very large triglyceride-rich lipoprotein particles (TRLP) were significantly lower in SLE patients than in healthy donors, whereas medium TRLP was significantly higher (**Table 7-3**). Statistical significance was assessed using a Mann–Whitney U test; parameters above the thick line indicate $p < 0.05$.

Table 7-3: Baseline lipid parameters in patients with SLE

Analyte	AUC	P-value	FDR
H3P (μmol/L)	0.15	5.56E–04	1.83E–02
Medium high-density lipoprotein (HDL) particle count (cHDLP) (μmol/L)	0.18	1.45E–03	2.39E–02
Medium triglyceride-rich lipoprotein particle (TRLP) (nmol/L)	0.76	1.11E–02	1.05E–01
Apolipoprotein A-1 (mg/dL)	0.25	1.35E–02	1.05E–01
Very large TRLP (nmol/L)	0.28	1.58E–02	1.05E–01
HDL count (HDL-C) (mg/dL)	0.28	2.76E–02	1.52E–01
cHDLP (μmol/L)	0.29	4.20E–02	1.98E–01
Very small TRLP (nmol/L)	0.31	6.35E–02	2.33E–01
Total cholesterol (TC) (mg/dL)	0.31	6.36E–02	2.33E–01
Small cHDLP (μmol/L)	0.66	1.15E–01	3.79E–01
Low-density lipoprotein (LDL) count (LDLC) (mg/dL)	0.36	1.56E–01	4.29E–01
LDL particle (LDLP) count (cLDLP) (nmol/L)	0.36	1.56E–01	4.29E–01
Triglyceride-rich lipoprotein (TRL)-triglyceride (TRLTG) (mg/dL)	0.64	1.84E–01	4.66E–01
Large cHDLP (μmol/L)	0.37	2.11E–01	4.98E–01
H6P (μmol/L)	0.38	2.37E–01	5.21E–01
Triglycerides (TG) (mg/dL)	0.61	2.89E–01	5.34E–01
H1P (μmol/L)	0.60	3.25E–01	5.34E–01
H2P (μmol/L)	0.59	3.56E–01	5.34E–01
Apolipoprotein B (mg/dL)	0.41	3.72E–01	5.34E–01
Medium cLDLP (nmol/L)	0.41	3.76E–01	5.34E–01
H123 (μmol/L)	0.41	3.77E–01	5.34E–01
H5P (μmol/L)	0.41	3.87E–01	5.34E–01
Small TRLP (nmol/L)	0.59	3.94E–01	5.34E–01
HDL size (nm)	0.42	4.03E–01	5.34E–01
TRL count (TRLC) (mg/dL)	0.59	4.04E–01	5.34E–01
Large cLDLP (nmol/L)	0.43	5.06E–01	6.43E–01
H7P (μmol/L)	0.56	5.57E–01	6.72E–01
LDL size (nm)	0.44	5.70E–01	6.72E–01
Small cLDLP (nmol/L)	0.45	6.13E–01	6.94E–01
Large TRLP (nmol/L)	0.55	6.31E–01	6.94E–01
H4P (μmol/L)	0.52	8.35E–01	8.89E–01
TRLP (nmol/L)	0.52	8.82E–01	9.09E–01
TRL size (nm)	0.49	9.13E–01	9.13E–01

[0131] The correlations between HDL-C and total cholesterol with IFN-α protein were assessed using 21-IFNGS, and IFNGS test. IFNGS test–high patients had reduced levels of total cholesterol and HDL-C compared with IFNGS test–low patients (**FIG. 3**). Total cholesterol and HDL-C negatively correlated with 21-IFNGS and IFN-α. Traditional CVD risk factors like body mass index (BMI) and age also inversely associated with type I IFN measures. Patients who were IFNGS test–high had significantly decreased body mass index (BMIs) compared with those who were IFNGS test–low ($p = 0.000136$). BMI also negatively correlated with IFN 21-gene signature and IFN-α protein (IFN 21-gene signature: $R = -0.17303$, $p = 0.002508$; IFN-α: $R = -0.14517$, $p = 0.0144$). Patients who were IFNGS test–high were younger than patients who were IFNGS–test low, and age also negatively correlated with IFN 21-gene signature and IFN-α protein (IFNGS test-status: $p = 0.00527$; IFN 21-gene signature: $R = -$

0.25517, $p = 6.86\text{E-}6$; IFN- α : $R = -0.2918$, $p = 0.000179$). There was no association between smoking status and the type I IFN measures. These results indicate that, although IFNGS test-high patients had reduced traditional CVD risk factors (age, BMI, total cholesterol) compared with IFNGS test-low patients, they had increased immune markers of vascular dysfunction and neutrophil dysregulation and lower levels of HDL-C, supporting elevated CVD risk that is not predicted by traditional CVD risk factors alone.

[0132] To further examine the association between lipoprotein/lipid parameters and type I IFN pathway, the effect of anifrolumab on lipid parameters were evaluated for which there were ≥ 10 patients with baseline lipid defects (measurements ≥ 2 SD from healthy donor mean; **Table 5-1**). Lipid parameters were assessed by NMR LipoProfile® in patients with SLE to calculate median change at day 365 compared with day 1. A signed-rank test was used to compare longitudinal median changes. In patients with reduced baseline HDL in the H3P size range, H3P levels significantly increased from baseline after anifrolumab ($p = 0.0223$) but not placebo. There were no significant, treatment-specific changes in medium, small, or very small TRLP.

Table 7-4: Longitudinal changes in lipid NMR measurements after type I IFN inhibition in patients with SLE with a baseline NMR defect^a

Median change Signed rank test p -value Lipid analyte ($n = \text{placebo, anifrolumab}$)	Placebo	Anifrolumab 300 mg	Placebo	Anifrolumab 300 mg
Medium TRLP ($n = 13, 7$)	-6.10	-18.20	4.79E-2	3.13E-2
Small TRLP ($n = 7, 6$)	-41.90	-30.90	5.78E-1	9.38E-2
Very small TRLP ($n = 9, 4$)	16.10	29.50	3.46E-2	2.50E-1
H3P ($n = 7, 7$)	0.70	1.50	2.71E-1	2.23E-2

^a Lipid analytes were included in the assessment if ≥ 10 patients had a defect at baseline compared with healthy donors, with a defect defined as a lipid measurement outside the bounds of two standard deviations from the mean of the healthy donors. IFN, interferon; NMR, nuclear magnetic resonance; SLE, systemic lupus erythematosus; TRLP, triglyceride-rich lipoprotein.

[0133] It was analysed whether IR correlated with type I IFN measures at baseline. Analysis of all patients, regardless of IR status, showed no significant difference in IR between those who were IFNGS test-high or test-low. No correlation was detected between IR and IFN- α or 21-IFNGS (**Table 7-1**). However, among the few patients who had early IR (>1.9 [49]), IFNGS test-high patients had greater IR than IFNGS test-low patients ($p = 0.046$). There was no reduction in percentage IR change from baseline after anifrolumab compared with placebo, even in patients in the upper quartile of IR ($\text{IR} \geq 3.9$). Overall, these results do not support a role for type I IFN pathway inhibition in modulation of IR in SLE, although there may be value in examining this relationship in a cohort further enriched for IR.

[0134] GlycA levels were significantly elevated in IFNGS test-high patients compared with healthy donors ($\text{AUC} = 0.84$, $p < 0.001$; **FIG. 10A**). The effect of anifrolumab treatment on GlycA levels in IFNGS test-high patients who had increased GlycA at baseline were investigated. Surprisingly GlycA levels significantly decreased by day 365 with anifrolumab ($n = 10$, $p = 0.006$), but not with placebo ($n = 11$; **FIG. 10B**). These results demonstrate that type I IFN-signalling inhibition in SLE significantly normalized GlycA toward healthy donor levels.

[0135] Similar to the observed normalization of CEC, it was found that type I IFN pathway inhibition decreased GlycA levels in SLE. GlycA was previously associated with neutrophil gene networks, and the major protein contributors to the GlycA NMR signal (α 1-acid glycoprotein and haptoglobin) can be synthesized and secreted from neutrophil granules³¹. These observations support a model centred on pathogenic neutrophil effector functions leading to aberrant type I IFN production, cardiometabolic dysregulation, and vascular damage in SLE (FIG. 11). These findings further support a model where vascular damage occurs through multiple mechanisms driven by the downstream effects of unabated IFN- α signalling.

[0136] Studying CVD risk in SLE using traditional approaches has low feasibility given disease incidence/prevalence and relatively young age at lupus diagnosis. Identification of meaningful biomarkers of CVD risk to select patients for intervention is a promising approach to address such challenges. The present disclosure advantageously demonstrates that several subclinical markers with direct physiological links to SLE-associated CVD risk (enhanced NET formation, impaired CEC, and elevated GlycA) are significantly modulated by anifrolumab, which have the potential to be practical tools to facilitate earlier CVD detection and improved symptom monitoring of CVD risk and vasculopathy.

8 EXAMPLE 4: Efficacy of Anifrolumab in treating cardiovascular disease in SLE patients

8.1 Introduction

[0137] The similarity in design of the TULIP-1 and TULIP-2 trials facilitated pooling of data for assessment of individual organ systems with greater statistical power than possible with individual trials alone. In this post hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials, we assessed the effects of anifrolumab on individual SLE organ domain disease activity.

8.2 Methods

8.2.1 Patients and study design

[0138] This was a *post hoc* analysis of pooled data from the 52-week TULIP-1 and TULIP-2 trials, in which patients who had moderate to severe SLE despite standard therapy with oral glucocorticoids, antimalarials, and/or immunosuppressants were randomized to receive anifrolumab 300 mg or placebo intravenously every 4 weeks for 48 weeks.

[0139] The study design and methods have been described in detail previously^{26,27}. In brief, all patients were aged 18 to 70 years and fulfilled the American College of Rheumatology classification criteria for SLE. Patients with active severe neuropsychiatric SLE or severe lupus nephritis were excluded. Mandatory attempts to taper oral glucocorticoids to ≤ 7.5 mg/day between Week 8 and Week 40 were required for patients receiving prednisone or equivalent ≥ 10 mg/day at baseline; tapering was also permitted for patients receiving lower doses at baseline. In all patients, glucocorticoid doses were required to be stable from Week 40 through Week 52.

8.2.2 Study endpoints and assessments

[0140] Organ domain involvement was assessed using BILAG-2004¹⁷ and SLEDAI-2K.¹⁸ BILAG-2004 response was defined as a reduction from A (severe disease) at baseline to B (moderate), C (mild), or D (no current disease), or from B at baseline to C or D. The proportions of patients who improved 1 step (eg, from A to B or B to C), 2 steps (eg, from A to C or B to D), and up to 3 steps (ie, from A to D) in a given organ domain from baseline to Week 52 were evaluated. SLEDAI-2K improvement was defined as a reduction in domain scores in patients with baseline scores >0. For both BILAG-2004 and SLEDAI-2K, patients who were treated with restricted medication beyond protocol-allowed thresholds or who discontinued investigational product were classified as nonresponders.

[0141] In addition to changes in mean hematologic and serologic values, the percentages of patients with abnormal (low or high) values at baseline who converted to normal values at Week 52 were evaluated. Patients who discontinued study treatments or had missing Week 52 data were assumed not to have normalized.

8.2.3 Statistical analyses

[0142] The similar TULIP-1 and TULIP-2 trial designs allowed for the results to be pooled. BILAG-2004 and SLEDAI-2K organ domain responder rates, SLEDAI-2K organ domain responders over time, CLASI-A responders over time, and ≥50% reductions in joint counts from baseline were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors (matching those in the TULIP studies) of SLEDAI-2K score at screening, type I IFN gene signature test status at screening, and Day 1 oral glucocorticoid dose. The reported 2-sided P-values and 95% confidence intervals (CIs) are based on this approach. All reported P-values are nominal. For assessment of pooled TULIP data, TULIP-1 data were analysed according to the TULIP-2–revised restricted medication analytic rules. Missing data were imputed using the last observation carried forward for the first visit with missing data; subsequent visits with missing data were not imputed.

8.3 Results

8.3.1 Baseline characteristics

[0143] Data were pooled for 726 patients; 360 received anifrolumab 300 mg (180 patients in each trial), and 366 received placebo (184 and 182 patients in TULIP-1 and TULIP-2, respectively). Baseline demographics and background treatment for SLE were comparable between groups (**Table 8-1**).

Table 8-1: Baseline patient demographics, disease characteristics, and SLE medications of patients enrolled in TULIP-1 and TULIP-2 (pooled data)

Characteristics	Placebo (n=366)	Anifrolumab 300 mg (n=360)
Age, mean (SD), years	41.0 (11.9)	42.6 (12.0)
Female, n (%)	341 (93.2)	333 (92.5)
Race, n (%)		
White	244 (66.7)	235 (65.3)
Black	48 (13.1)	46 (12.8)
Asian	35 (9.6)	41 (11.4)
Other	31 (8.5)	30 (8.3)
Time from initial SLE diagnosis to randomization, median (range), months	78.5 (4–503)	91.0 (0–555)

BILAG-2004, n (%)		
≥1 A item	179 (48.9)	174 (48.3)
No A items and ≥2 B items	162 (44.3)	170 (47.2)
SLEDAI-2K		
Mean (SD)	11.5 (3.7)	11.4 (3.8)
≥10, n (%)	266 (72.7)	254 (70.6)
PGA, mean (SD)	1.8 (0.4)	1.8 (0.4)
CLASI-A	7.8 (7.2)	8.4 (7.6)
Mean (SD)	7.8 (7.2)	8.4 (7.6)
≥10, n (%)	4 (25.7)	107 (29.7)
SDI, mean (SD)	0.6 (0.9)	0.6 (1.0)
Number of swollen joints, mean (SD)	7.2 (5.7)	6.8 (5.8)
Number of tender joints, mean (SD)	10.8 (7.5)	10.3 (7.4)
Baseline treatment for SLE, n (%)		
Oral glucocorticoid use ^a	304 (83.1)	291 (80.8)
<10 mg/day	181 (49.5)	170 (47.2)
≥10 mg/day	185 (50.5)	190 (52.8)
Antimalarial	267 (73.0)	243 (67.5)
Immunosuppressant ^b	177 (48.4)	173 (48.1)

BILAG-2004, British Isles Lupus Assessment Group-2004; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLASI-A, CLASI activity score; PGA, Physician's Global Assessment; SD, standard deviation; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLE, systemic lupus erythematosus; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000. ^aOral glucocorticoids contains prednisone or equivalent; ^bImmunosuppressant: azathioprine, methotrexate, mycophenolate mofetil, mycophenolic acid, and mizoribine.

[0144] Of the 726 patients enrolled, the mean age was 41.8 years; 92.8% were women, and 66.0% were white. At baseline, 82.0% (595/726) of patients were receiving oral glucocorticoids, of whom 52.8% (190/360) of the anifrolumab group and 50.5% (185/366) of the placebo group were receiving ≥10 mg/day (prednisone or equivalent). Baseline disease activity levels, measured with BILAG and SLEDAI-2K, were similar between the pooled treatment arms (**Table 8-1**), with a mean SLEDAI-2K of approximately 11 and approximately half of all patients having at least one BILAG A domain score.

[0145] Baseline organ domain involvement assessed using BILAG-2004 and SLEDAI-2K was similar between treatment groups (**FIG. 14A** and **FIG. 14B**). The most commonly affected organ domains at baseline were mucocutaneous (BILAG-2004 86.4% [627/726]; SLEDAI-2K 96.3% [699/726]) and musculoskeletal (BILAG-2004 88.8% [645/726]; SLEDAI-2K 94.2% [684/726]) **FIG. 14A** and **FIG. 14B**). In the most commonly affected BILAG-2004 domains, musculoskeletal and mucocutaneous, the majority of patients had severe or moderate disease activity at baseline as shown by the overall frequency of BILAG A (musculoskeletal 31.5% [229/726], mucocutaneous 21.9% [159/726]) or BILAG B (musculoskeletal 57.3% [416/726]; mucocutaneous 64.5% [468/726]) scores.

8.3.2 Efficacy in BILAG-2004 cardiorespiratory organ domain

[0146] Improvements favouring anifrolumab for the mucocutaneous, musculoskeletal and cardiorespiratory BILAG-2004 domains were observed from Week 4, Week 32 and Week 28, respectively (**FIG. 15**).

8.3.3 Efficacy in SLEDAI-2K cardiorespiratory and vascular organ domain

At Week 52, significantly more anifrolumab-treated than placebo-receiving patients had improvements in the SLEDAI-2K organ domains most frequently affected at baseline: mucocutaneous (54.7%

[190/348] vs 39.4% [138/351]; nominal $P < 0.001$), musculoskeletal (48.8% [164/335] vs 40.4% [141/349]; nominal $P < 0.05$), nominal $P < 0.05$) (**FIG. 16**). Greater proportions of patients receiving anifrolumab versus placebo had improvements at Week 52 for vascular and cardiorespiratory SLEDAI-2K domains (**FIG. 16**).

8.3.4 Laboratory markers – hematology and serology

[0147] Patients in the anifrolumab and placebo groups had similar mean hematology values at baseline (**Table 8-2**).

Table 8-2 Changes in hematologic measures from baseline to Week 52

	Placebo (n=365) ^a	Anifrolumab 300 mg (n=360)
Hemoglobin		
Baseline mean (SD), g/L	126.0 (15.2)	125.0 (14.8)
Change from baseline, mean (SD), g/L	-2.7 (11.33)	0.5 (10.59)
Normalization at Week 52 in patients with abnormal hemoglobin at baseline, n (%) ^b	0 (0)	0 (0)
Hematocrit		
Baseline mean (SD)	0.4 (0.04)	0.4 (0.04)
Change from baseline, mean (SD)	-0.005 (0.03)	0.005 (0.03)
Normalization at Week 52 in patients with abnormal hematocrit at baseline, n (%) ^b	0 (0)	0 (0)
Lymphocytes		
Baseline mean (SD), 10 ⁹ /L	1.3 (0.6)	1.3 (0.6)
Change from baseline, mean (SD), 10 ⁹ /L	-0.03 (0.5)	0.3 (0.6)
Normalization at Week 52 in patients with abnormal lymphocytes at baseline, n (%) ^b	11 (3.0)	23 (6.4)
Neutrophils		
Baseline mean (SD), 10 ⁹ /L	4.0 (2.1)	3.8 (1.8)
Change from baseline, mean (SD), 10 ⁹ /L	0.1 (2.0)	0.7 (1.8)
Normalization at Week 52 in patients with abnormal neutrophils at baseline, n (%) ^b	0 (0)	1 (0.3)
Platelets		
Baseline mean (SD), 10 ⁹ /L	250.2 (79.8)	239.9 (78.2)
Change from baseline, mean (SD), 10 ⁹ /L	3.2 (49.8)	24.3 (58.2)
Normalization at Week 52 in patients with abnormal platelets at baseline, n (%) ^b	1 (0.3)	0 (0.0)

SD, standard deviation. ^a1 patient was removed from the analysis after study completion; ^bRange of normal values for hemoglobin (>60 to <200 g/L), hematocrit (>0.18 to <0.64), lymphocytes (>0.5 to <10.0 10⁹/L), neutrophils (>0.5 to <20.0 10⁹/L), and platelets (>20 to <600 10⁹/L).

[0148] At Week 52, treatment effects favouring anifrolumab versus placebo were seen for mean (SD) increase in haemoglobin (0.5 [10.59] vs -2.7 [11.33] g/L) and platelets (24.3 [58.2] vs 3.2 [49.8] x10⁹/L). In the anifrolumab group, 6.4% (23/360) of patients with leukopenia at baseline demonstrated normalization, versus 3.0% (11/366) of patients receiving placebo.

[0149] Among patients who were anti-dsDNA positive at baseline, mean (SD) levels of anti-dsDNA antibodies decreased with anifrolumab treatment, compared with an increase for placebo (-25.0 [238.4] vs 28.0 [498.5] U/mL; **Table 3**). Accordingly, 7.8% (13/167) of patients receiving anifrolumab versus 5.8% (9/155) of patients receiving placebo converted to anti-dsDNA negative by Week 52 (**Table 8-3**).

[0150] At Week 52, greater improvements from baseline in mean (SD) complement C3 levels were observed with anifrolumab (0.13 [0.18]) versus placebo (0.04 [0.16] U/mL) (**Table 8-3**). In patients with low C3 at baseline, normalization was observed in 16.2% (21/130) of anifrolumab-treated and 9.5%

(13/137) of placebo-treated patients. Similarly, normalization of low baseline C4 occurred in more patients receiving anifrolumab versus placebo (22.6% [19/84] vs 7.1% [6/85]).

Table 8-3: Change in laboratory markers from baseline to Week 52

	Placebo (n=366)	Anifrolumab 300 mg (n=360)
Anti-dsDNA^{a,b}		
Anti-dsDNA positive at baseline, n (%)	155 (42.3)	167 (43.4)
Mean (SD), U/mL	211.95 (549.65)	129.34 (261.40)
Change from baseline, mean (SD), U/mL	27.96 (498.47)	-24.98 (238.39)
Normalization at Week 52 in patients with abnormal anti-dsDNA at baseline, n (%)	9 (5.8%)	13 (7.8%)
C3^{a,c}		
Abnormal C3 at baseline, n (%)	137 (37.4)	130 (36.1)
Mean (SD), U/mL	0.70 (0.14)	0.69 (0.15)
Change from baseline, mean (SD), U/mL	0.04 (0.16)	0.13 (0.18)
Normalization at Week 52 in patients with abnormal C3 at baseline, n (%)	13 (9.5)	21 (16.2)
C4^{a,d}		
Abnormal C4 at baseline, n (%)	85 (23.2)	84 (23.3)
Mean (SD), U/mL	0.07 (0.02)	0.07 (0.02)
Change from baseline, mean (SD), U/mL	0.02 (0.04)	0.02 (0.03)
Normalization at Week 52 in patients with abnormal C4 at baseline, n (%)	6 (7.1)	19 (22.6)

anti-dsDNA, anti-double-stranded DNA; C3, complement 3; C4, complement 4; SD, standard deviation.

^aOnly patients with baseline positive anti-dsDNA or low C3 or C4 are included in the summary statistics for the respective variables; ^bAnti-dsDNA antibody "positive" defined as a result of >15 U/mL; ^cComplement C3 "abnormal" levels defined as a result of <0.9 g/L; ^dComplement C4 "abnormal" levels defined as a result of <0.1 g/L.

8.4 Discussion

[0151] In this *post hoc* analysis of pooled data from the TULIP-1 and TULIP-2 trials, compared with placebo, anifrolumab treatment was associated with greater improvement in the cardiorespiratory and vascular organ domains of patients with moderate to severe SLE. Anifrolumab treatment also resulted in greater frequency of hematologic and serologic normalization compared with placebo.

[0152] Results of the TULIP-1 and TULIP-2 trials previously demonstrated that patients treated with anifrolumab had higher BICLA responder rates compared with patients receiving placebo. The present analyses also surprisingly demonstrate consistency between BILAG-2004 and SLEDAI-2K activity assessments in the cardiorespiratory and cardiovascular organ domains.

[0153] Serologic activity is indicative of immune system activation and is typically associated with SLE disease activity. More anifrolumab-treated patients were able to normalize anti-dsDNA antibodies and complement C3 and C4 levels compared with placebo-treated patients. These results suggest that the effects of anifrolumab on serologic markers are consistent with the greater improvements observed in those treated with anifrolumab compared with placebo in the SLEDAI-2K immunologic domain.

[0154] In conclusion, in pooled data from the phase 3 TULIP-1 and TULIP-2 trials, compared with placebo, anifrolumab treatment in patients with moderate to severe SLE was associated with improvements across cardiovascular and cardiorespiratory organ systems, as measured by BILAG-2004 and SLEDAI-2K domain scores. These data thus surprisingly demonstrate the inhibition of type I IFN signalling treats cardiovascular disease in SLE patients.

9 EXAMPLE 5: Injection device

[0155] Anifrolumab is administered by an injection device [1] [9] such as a prefilled syringe (PFS) (FIG. 17A) or an autoinjector (AI) (FIG. 17B).

9.1 Autoinjector

[0156] Anifrolumab may be administered by an autoinjector [1]. The autoinjector is shown in exploded view (FIG. 18A) and in an assembled form (FIG. 18B). A label [4] is wrapped around and attached to the autoinjector [1] (FIG. 18C). The autoinjector has an autoinjector housing [3], cap and cap remover [2] and drive unit [5]. The liquid anifrolumab formulation unit dose [6] is contained in the autoinjector housing [3]. The unit dose [6] can be viewed through the viewing window [7].

9.2 Accessorized pre-filled syringe

[0157] Anifrolumab may be administered by accessorized pre-filled syringe (APFS) [8]. The APFS [8] includes the unit dose of anifrolumab [6] contained in a primary container [9] shown in an assembled state in FIG. 19A and in an exploded view in FIG. 19B. The primary container [9] has a plunger stopper [16]. The primary container has a nominal fill volume [17] of 0.8 ml but may contain slightly more than 0.8 ml. The remainder of the space in the primary container [9] is taken up by an air bubble [18]. The air bubble [18] may have a size of 3-5mm, optionally, 4 mm. The primary container [9] has a defined stopper position [19].

[0158] The accessorized pre-filled syringe (APFS) primary container [9] is provided in a PFS assembly [8] including a needle guard [12], a finger flange [11] and a plunger rod [13] (FIG. 19C, FIG. 19D). A label [14] is provided with the primary container [9] in the PFS assembly [8]. The label [14] is wrapped around the syringe [9] in the label placement position [15].

9.3 Packaging

[0159] The injection device [1] [8] is provided in a kit [20] (FIG. 20). A label [4] [14] is provided with the APFS or autoinjector in the packaging. The label includes instruction for the use of the injection device [1], [8]. The packaging includes a tamper seal.

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CLAIMS

1. A method of treating or reducing the risk for development of a cardiometabolic disease in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of an inhibitor of type I IFN signalling, wherein the patient has a type I IFN mediated disease.
2. The method of any preceding claim, wherein, pre-treatment with the inhibitor of type I IFN signalling, the patient has high levels of expression of the one or more cardiometabolic disease markers compared to a healthy subject, and wherein treatment reduces expression of the one or more cardiometabolic disease markers in the patient from baseline.
3. The method of claim 2, wherein the one or more cardiometabolic disease markers comprise GlycA.
4. The method of claim 2 or 3, wherein the one or more cardiometabolic disease markers comprise neutrophil extracellular trap (NET).
5. The method of any of claims 2 to 4, wherein the one or more cardiometabolic disease markers comprise TNF- α and/or IL-10.
6. The method of any preceding claim, wherein, pre-treatment with the inhibitor of type I IFN signalling, the patient has low levels of expression of the one or more cardiometabolic disease markers compared to a healthy subject, and wherein treatment increases expression of the one or more cardiometabolic disease markers in the patient from baseline.
7. The method of claim 6, wherein the one or more cardiometabolic disease markers comprise cholesterol efflux capacity (CEC).
8. The method of any preceding claim, wherein pre-treatment the patient is identified as having a risk of development of a cardiometabolic disease.
9. The method of claim 8, comprising:
 - a) determining in a sample from the patient the amount of one or more markers; and
 - b) identifying the patient as having a risk for development of a cardiometabolic disease when the amount of marker is elevated in the patient compared to the amount of the marker in a sample from a healthy subject,wherein the marker is selected from the group consisting of GlycA, TNF- α , IL-10 and combinations thereof.
10. The method of claim 9, wherein the sample from the patient comprises blood, plasma, serum, or tissue.
11. The method of claim 9 or 10, wherein GlycA in the sample from the patient is measured by nuclear magnetic resonance (NMR).

12. The method of any preceding claim, wherein pre-treatment with the inhibitor of type I IFN signalling the patient has elevated serum protein levels of IFN- α compared to a healthy subject, and wherein the inhibitor of type I IFN signalling decreases the serum protein levels of IFN- α in the patient from baseline.
13. The method of any preceding claim wherein the inhibitor of type I IFN signalling is a type I IFN receptor inhibitor (IFNAR1).
14. The method of claim 13, wherein the IFNAR1 inhibitor is a human monoclonal antibody specific for IFNAR1, optionally a modified IgG1 class human monoclonal antibody.
15. The method of claim 14, wherein the antibody comprises:
 - a) a heavy chain variable region complementarity determining region 1 (HCDR1) comprising the amino acid sequence of SEQ ID NO: 3;
 - b) a heavy chain variable region complementarity determining region 2 (HCDR2) comprising the amino acid sequence of SEQ ID NO: 4;
 - c) a heavy chain variable region complementarity determining region 3 (HCDR3) comprising the amino acid sequence of SEQ ID NO: 5;
 - d) a light chain variable region complementarity determining region 1 (LCDR1) comprising the amino acid sequence SEQ ID NO: 6;
 - e) a light chain variable region complementarity determining region 2 (LCDR2) comprising the amino acid sequence SEQ ID NO: 7; and
 - f) a light chain variable region complementarity determining region 3 (LCDR3) comprising the amino acid sequence SEQ ID NO: 8.
16. The method of claim 14 or 15, wherein the antibody comprises: (a) a human heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 1; (b) a human light chain variable region comprising the amino acid sequence of SEQ ID NO: 2; (c) a human light chain constant region comprising the amino acid sequence of SEQ ID NO: 9; and (d) a human heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 10.
17. The method of any of claims 14 to 16, wherein the antibody comprises in the Fc region an amino acid substitution of L234F, as numbered by the EU index as set forth in Kabat and wherein said antibody exhibits reduced affinity for at least one Fc ligand compared to an unmodified antibody.
18. The method of any of claims 14 to 17, wherein the antibody comprises: (a) a human heavy chain comprising the amino acid sequence of SEQ ID NO: 11; and (b) a human light chain comprising the amino acid sequence of SEQ ID NO: 12.

19. The method of any preceding claim, wherein the inhibitor of type I IFN signalling is anifrolumab or a functional variant thereof.
20. The method of claim 19, comprising administering intravenously an intravenous dose of anifrolumab or the functional variant thereof to the subject.
21. The method of claim 20, wherein the intravenous dose is ≥ 300 mg anifrolumab or the functional variant thereof.
22. The method of claim 20 or 21, wherein the intravenous dose is ≤ 1000 mg.
23. The method of claim 21, wherein the intravenous dose is about 300 mg or about 1000 mg.
24. The method of any of claims 20 to 23, wherein the intravenous dose is administered every four weeks (Q4W).
25. The method of any preceding claim, wherein the patient has high interferon gene signature expression compared to a healthy subject.
26. The method of claim 25, wherein the type I interferon gene signature comprises elevated expression of the genes Interferon Alpha Inducible Protein 27 (IFI27), Interferon Induced Protein 44 (IFI44) interferon induced protein 44 like (IFI44L), and Radical S-Adenosyl Methionine Domain Containing 2 (RSAD2) compared to a healthy subject.
27. The method of claim 25 or 26, wherein the high interferon gene signature expression is determined by an increased expression of IFI27, IFI44, IFI44L, and RSAD2 relative to expression of one or more control genes.
28. The method of any preceding claim, wherein the cardiometabolic disease is a cardiovascular disease, optionally wherein the cardiovascular disease comprises myocarditis, arrhythmia, valvular dysfunction, vasculitis, aortitis, atherosclerosis and/or coronary vasculitis.
29. The method of any preceding claim, wherein the cardiometabolic disease is premature atherosclerosis.
30. The method of claim 29, wherein the premature atherosclerosis is sub-clinical.
31. The method of any preceding claim, wherein the type I IFN mediated disease is systemic lupus erythematosus (SLE).
32. The method of claim 31, the type I IFN mediated disease is moderate to severe SLE.
33. A pharmaceutical composition for use in any of the methods of claims 1-32, comprising the inhibitor of type I IFN signalling.
34. An injection device comprising the pharmaceutical composition of claim 33.
35. The injection device of claim 34, wherein the injection device is a pre-filled syringe (PFS).

36. The injection device of claim 35, wherein the injection device is an accessorized pre-filled syringe (AFPS).
37. The injection device of claim 35, wherein the injection device is an auto-injector.
38. A kit comprising the injection device of any of claims 34 to 37, and instructions for use.
39. The kit of claim 38, wherein the instructions for use comprise instructions for subcutaneous administration of the pharmaceutical composition or unit dose to the patient.
40. The kit of claim 35 or 39, wherein the instructions for use specify that the injection device and/or pharmaceutical composition are for use in the treatment of SLE.
41. The kit of any of claims 35-40, wherein the instructions for use specify that the injection device and/or pharmaceutical composition are for treating a cardiometabolic disease.
42. The kit of any of claims 35 to 41, comprising packaging, wherein the packaging is adapted to hold the injection device and the instructions for use.
43. The kit of any of claims 35 to 42, wherein the instructions for use are attached to the injection device.